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Computational Modeling of the Respiratory Network

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Synonyms

Respiratory network; respiratory central pattern generator; respiratory CPG

Definition

►Respiratory network is a neural circuitry in the mammalian ►brainstem that generates the ►respiratory rhythm and complex pattern of neuronal activity controlling movement of respiratory muscles that provide ►lung ventilation and perform the vitally important function of ►breathing. Computational modeling of the respiratory network is a powerful tool for theoretical investigations aimed at increasing our understanding of the complex neural mechanisms involved in generation and control of the respiratory rhythm and motor pattern.

Characteristics

Generation of the Respiratory Rhythm: Concepts, Mechanisms and Computational Models

Respiratory Network: Location, Types of Neurons, and the Respiratory Pattern

The motor pattern observed during normal breathing (►eupnea) consists of three phases: ►inspiration (I), ►postinspiration (pI or E1), and late ►expiration (E2), which can be recognized in the integrated activity of the ►phrenic nerve and ►cranial nerves. This pattern originates within a bilateral column of neurons, called the ►ventral respiratory column (VRC), located in the ►ventrolateral medulla, and is controlled by inputs from other medullary and pontine regions. The VRC includes

several compartments arranged in the rostro-caudal direction: ▶Bötzinger Complex (BötC), ▶pre-Bötzinger Complex (pre-BötC), and rostral (rVRG) and caudal (cVRG) subregions of the ▶ventral respiratory group (VRG). Respiratory neurons in these compartments are classified based on their temporal firing pattern (e.g., decrementing, augmenting) and the phase of activity relative to the breathing cycle, such as: early-inspiratory (early-I or I-DEC), i.e., ▶inspiratory neurons with a decrementing discharge pattern; ramp-inspiratory (ramp-I or I-AUG), i.e., inspiratory neurons with an augmenting firing pattern; ▶post-inspiratory neurons (post-I or E-DEC), i.e., neurons with a decrementing pattern during expiration; augmenting or stage II expiratory (aug-E or E-AUG or E-2), i.e., ▶expiratory neurons with an augmenting pattern; ▶pre-inspiratory neurons (pre-I or I-E/I) whose activity starts before the onset of inspiration and continues during inspiration. The BötC, with predominately post-I and aug-E neurons, is considered a major source of expiratory activity. The adjacent, more caudal compartment, the pre-BötC, contains circuitry essential for generating inspiratory activity. The activity of bulbospinal inspiratory (ramp-I or E-AUG) neurons of the rVRG, projecting to the phrenic motoneurons, is driven by the pre-BötC and inhibited by the inhibitory expiratory neurons of BötC and cVRG. The pontine respiratory regions include the ▶Kölliker-Fuse (K-F) nucleus and ▶parabrachial (PB) complex in the ▶dorsolateral pons and several areas in the ▶ventrolateral pons. Neurons in these areas exhibit phasic or tonic activity with inspiratory, expiratory or phase-spanning modulation and are involved in control of the respiratory pattern. Mechanosensory feedback from lungs provides strong modulation of the respiratory rhythm and pattern by controlling the timing of phase transitions and durations of inspiration and expiration. Specifically, lung inflation activates ▶pulmonary stretch receptors (PSRs) that project to the ▶pump (P) cells in the ▶nucleus tractus solitarii (NTS), which transmit information on lung inflation to the VRC and pontine nuclei. This feedback provides the ▶Hering–Breuer reflex consisting of shortening (advanced termination) of inspiration and prolongation of expiration.

Network Mechanisms for Respiratory Rhythm and Pattern Generation and Network Models

Computational models of the respiratory network have been in development for several decades. Early computational models focused on the network interactions between different types of respiratory neurons and did not consider possible contributions of the intrinsic, biophysical properties of neurons. Generation of the respiratory rhythm in these models was based on a network concept suggesting that the respiratory rhythm results from sequential phase switchings, such as an inspiratory off-switch (IOS, transition from inspiration to expiration) and an expiratory off-switch (EOS, transition from expiration to inspiration). These phase switchings were proposed to result from the reciprocal (mostly inhibitory) interactions among different types of respiratory neuron populations. The early network models employed relatively simple activity-based models of single neurons in which the output neuronal (or population) activity was described by single continuous variables representing the neuronal firing rate. For example, Duffin [1] proposed a model of the respiratory network consisting of two inhibitory (I-DEC and E-BÖT) and one excitatory (I-AUG) neurons, that generated two-phase (inspiration–expiration) oscillations based upon mutual inhibition between the I-DEC and E-BÖT neurons. Both phase switching mechanisms (IOS and EOS) in this model were based on the adaptive properties of the I-DEC neuron and the reciprocal interactions between the two inhibitory neurons.

A series of three-phase network models were developed based on a conceptual schematic proposed by Richter et al. [2] that postulated that the respiratory cycle consists of three phases: inspiration, postinspiration, and late expiration. The IOS mechanism in these models involved late-I neurons that started firing by the end of inspiration, reached peak activity at the transition from inspiration to expiration, and provided the initial inhibition of inspiratory neurons. The early three-phase models usually used the activity-based models of units for simulating single neurons or neural populations. The model proposed by Botros and Bruce [3] included five neuron populations: I (inspiratory with a ramp-I pattern); early-I; late-I, post-I and E (expiratory). The interconnections among these populations were assigned in accordance with the Richter scheme [2]. The model generated a stable respiratory rhythm and reproduced realistic activity profiles of all five neuron populations incorporated. Some effects of pulmonary mechanosensory feedback on the respiratory pattern were also reproduced.

Balis et al. [4] developed the first model of the respiratory network based on interacting populations of respiratory neurons using simplified, "spiking", ▶integrate-and-fire models of single neurons. Their network model contained six neuron populations: one excitatory (I-AUG type), four inhibitory (I-DEC, E-AUG, E-SYM, and E-DEC), and an additional I-E/I (pre-I) population. Some key connections in the model were assigned from a spike-train analysis of multiple recordings performed by the same group. Interestingly, depending on the model parameters the respiratory pattern could be generated with or without an involvement of the I-E/I population.

Rybak et al. [5] built a series of network models with more complicated, ▶conductance-based models of single neurons and analyzed possible roles of intrinsic

neuronal properties in the genesis of the respiratory rhythm. Several distinct network schematics were comparatively investigated. One version of this model is shown in Fig. 1. The model includes six respiratory neurons: early-I, ramp-I, late-I, post-I, aug-E (or E2), and pre-I. The IOS mechanism operates via the late-I neuron as proposed by the Richter scheme [2]. The EOS mechanism involves the pre-I neuron, which is inhibited during expiration, but when released from inhibition provides an initial activation of early-I and ramp-I neurons; the early-I neuron then inhibits post-I and aug-E neurons, hence completing the switch to inspiration.

This model includes a simplified model of the lungs and PSRs that provide pulmonary feedback to the respiratory network (Fig. 1a). This feedback is excitatory to the late-I and post-I neurons and inhibitory to the early-I neuron, allowing the expression of the Hering–Breuer reflex. Disconnecting the vagal feedback ("▶vagotomy") causes a prolongation of inspiration and an increase in the amplitude of integrated phrenic discharges (Fig. 1b).

The model generates a realistic respiratory pattern, reproduces membrane potential trajectories of individual respiratory neurons (Fig. 1b), and shows proper changes in the respiratory pattern and firing activities of individual respiratory neurons under different conditions, including vagotomy and application of various stimuli activating afferent nerves. At the same time, this model (as well as other network models, such as those described above) failed to reproduce some important behaviors obtained from in vitro studies of the neonatal rodent system, specifically the persistence of rhythmic activity after inhibition in the network was blocked (see below).

Pre-Bötzinger Complex and Rhythm Generation In Vitro
A fundamentally distinct concept of respiratory rhythm generation was derived from the neonatal in vitro studies. The important discovery has been that a subregion of the VRC, called the pre-Bötzinger Complex (pre-BötC), contains a population of excitatory interneurons that can intrinsically generate an inspiratory-like rhythm [6]. This rhythm was shown to persist after blockade of synaptic inhibition, indicating that the pre-BötC may contain special cells with intrinsic ▶bursting properties. Butera et al. [2] developed and analyzed a series of computational models of ▶bursting pacemaker neurons and populations of these neurons with mutual excitatory connections. In these models, the intrinsic bursting activity was based on a subthreshold activating, slowly inactivating ▶persistent sodium current (I_{NaP}) as the essential burst-generating, inward cationic current. The rhythmic bursting cycle in these models was controlled by the slow kinetics of inactivation and recovery from inactivation of I_{NaP}. This kinetics was shown sufficient to generate

voltage-dependent oscillations with the frequency spanning the range of bursting frequencies observed experimentally. Simulations performed have shown that the excitatory synaptic interactions coupled with I_{NaP} activation can readily synchronize cellular bursts and produce population bursting (Fig. 2a, b). Generation of this rhythm does not require inhibitory interactions; this can explain the persistence of the in vitro oscillations after inhibitory synaptic transmission was blocked. It was also shown that even a small fraction of intrinsically bursting cells (5–10%) can produce a synchronized bursting activity of the entire population. Moreover, synchronized population rhythms may occur even if none of the cells are in the intrinsic bursting state [7]. Elevation of tonic drive to the population reduces burst duration and increases burst frequency (see Fig. 2c) and, finally, switches population activity from bursting to a regime of sustained asynchronous activity (Fig. 2d).

This and a series of other related models were able to reproduce many characteristics of the pre-BötC activity in vitro, including multiple modes of activity (silence, bursting, and tonic) and a voltage-dependency of burst frequency.

Network-Based Versus Pacemaker-Driven Mechanisms for Respiratory Rhythmogenesis and a Hybrid Pacemaker-Network Model
As described above, network models where able to reproduce many characteristics of the respiratory ▶CPG including the generation of a realistic respiratory motor pattern and its alteration under different conditions. However, these models have failed to reproduce some characteristic behaviors observed in the reduced in vitro preparations and, specifically, the maintenance of the respiratory rhythm after blockade of synaptic inhibition. Alternatively, the pacemaker-based models, developed to fit to in vitro data, could not explain many behaviors observed in vivo, such as the Hering–Breuer and other respiratory reflexes, and independent regulation of the duration of each respiratory phase. For example, the pacemaker-based model could not reproduce ▶apneusis, a breathing pattern characterized by a significantly prolonged inspiration (up to several seconds) alternating with short expiratory intervals. Moreover, the pattern of rhythmic inspiratory discharges obtained from the reduced in vitro preparations and reproduced by the pacemaker-based models was characterized by a decrementing shape of inspiratory discharges (see Fig. 2), which differed from the augmenting shape of phrenic discharges observed during eupneic breathing in vivo and rather resembled the decrementing bursts observed during ▶gasping in vivo.

The contradiction between the network-based and pacemaker-based concepts and models can be resolved by postulating that: (i) the pre-BötC, while capable of bursting intrinsically when isolated, is embedded in the

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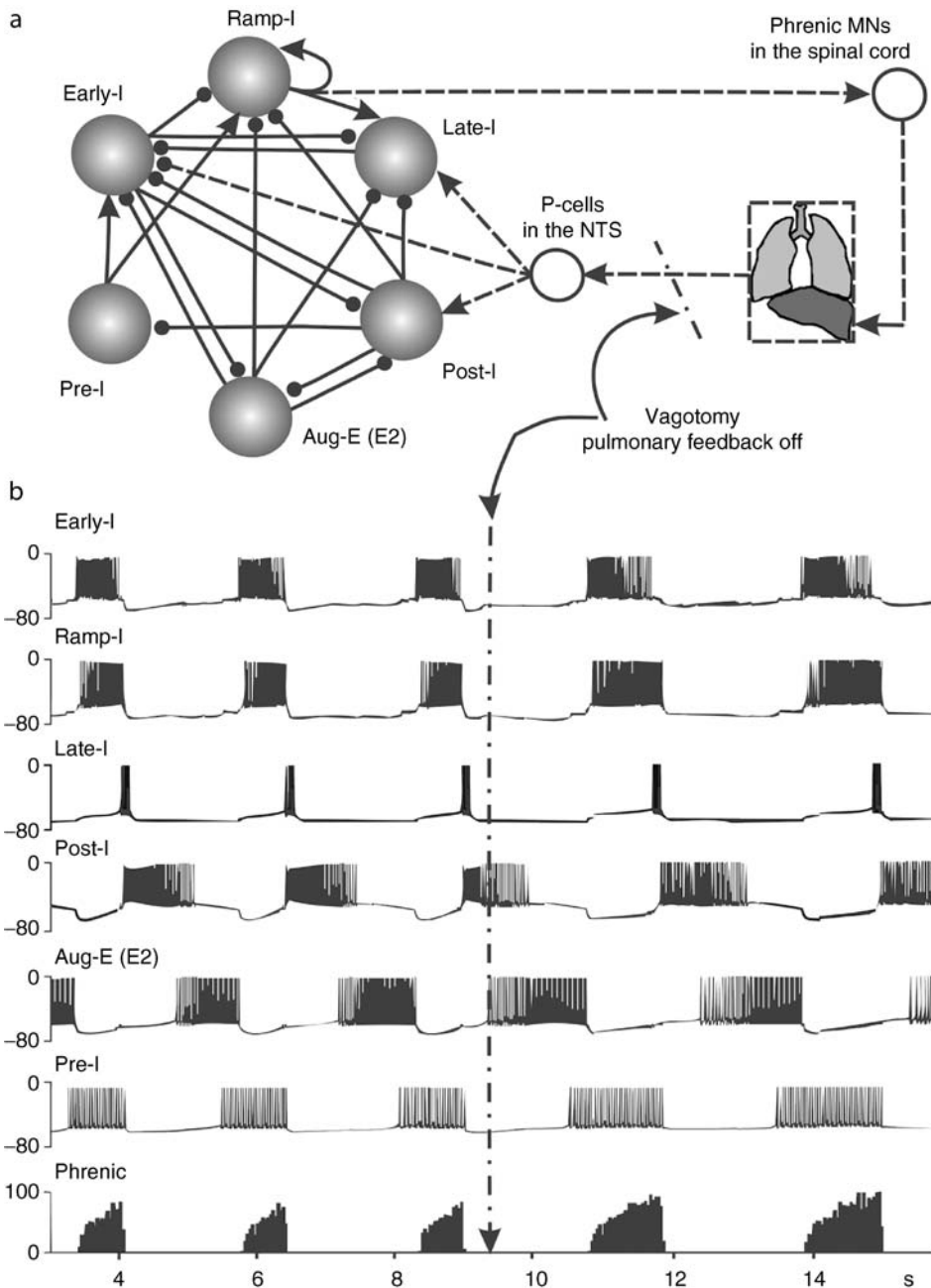
Computational Modeling of the Respiratory Network. Figure 1 A network model of the respiratory CPG. (a) The schematic of a network model. Large spheres represent different respiratory neuron types. Excitatory and inhibitory synaptic connections are shown by arrows and small circles respectively. Each neuron also receives external excitatory drive (not shown). The pulmonary feedback loop that includes the lungs is shown by *dash lines*. (b) Model performance. All traces, except the bottom one, show membrane potential trajectory of particular respiratory neurons (indicated at *left*); the *bottom trace* shows the integrated phrenic activity. The *dash-dot line* indicates the moment of vagal feedback disconnection ("vagotomy"). Modified from [5] with permission.

larger brainstem respiratory network and its behavior as a part of the network becomes dependent on the interactions with other respiratory neural populations and (ii) the respiratory rhythmogenesis per se is state dependent, and therefore the rhythm may be generated by either a network-based or pacemaker-driven mechanisms, or their specific combinations depending on the conditions [8–10].
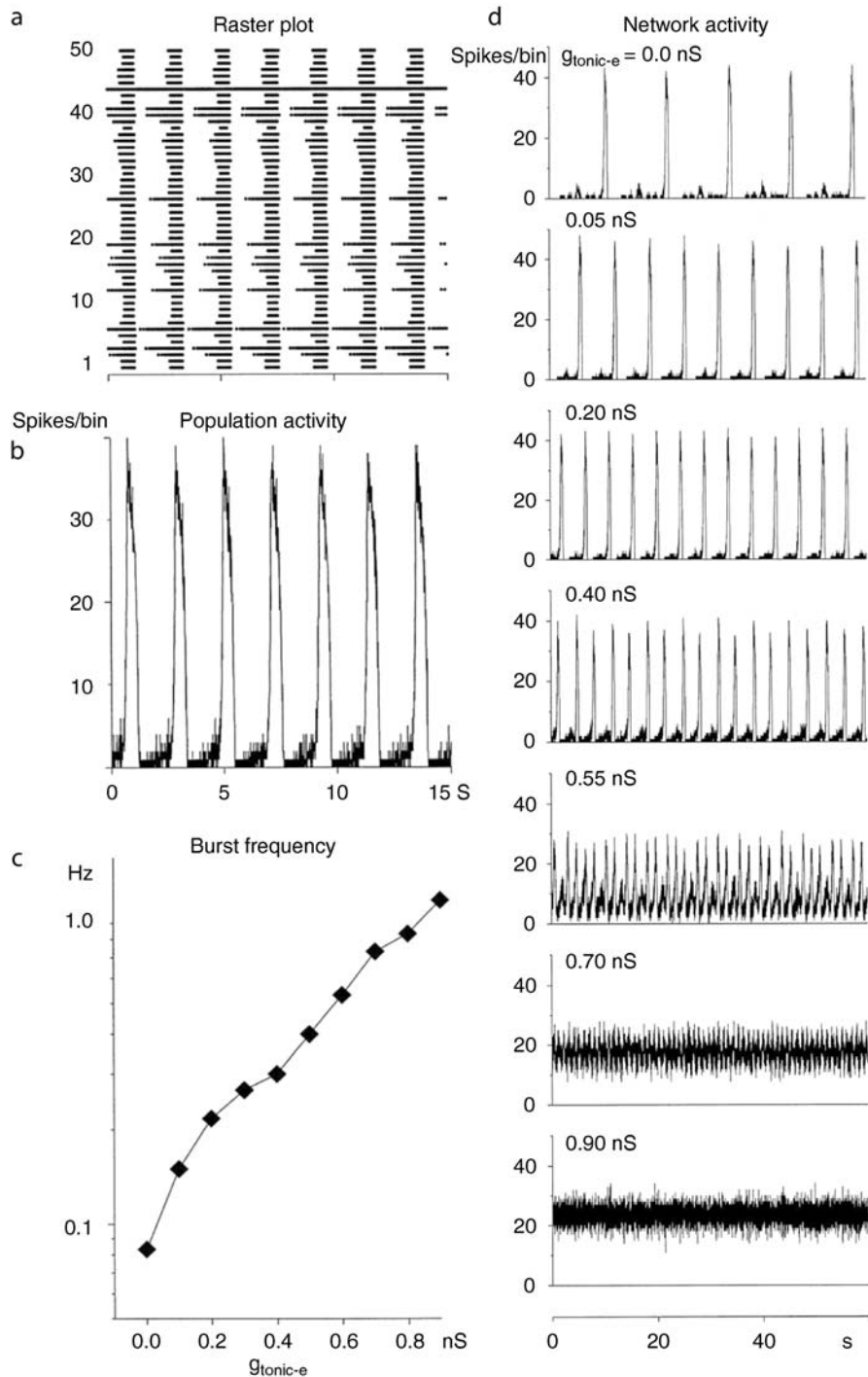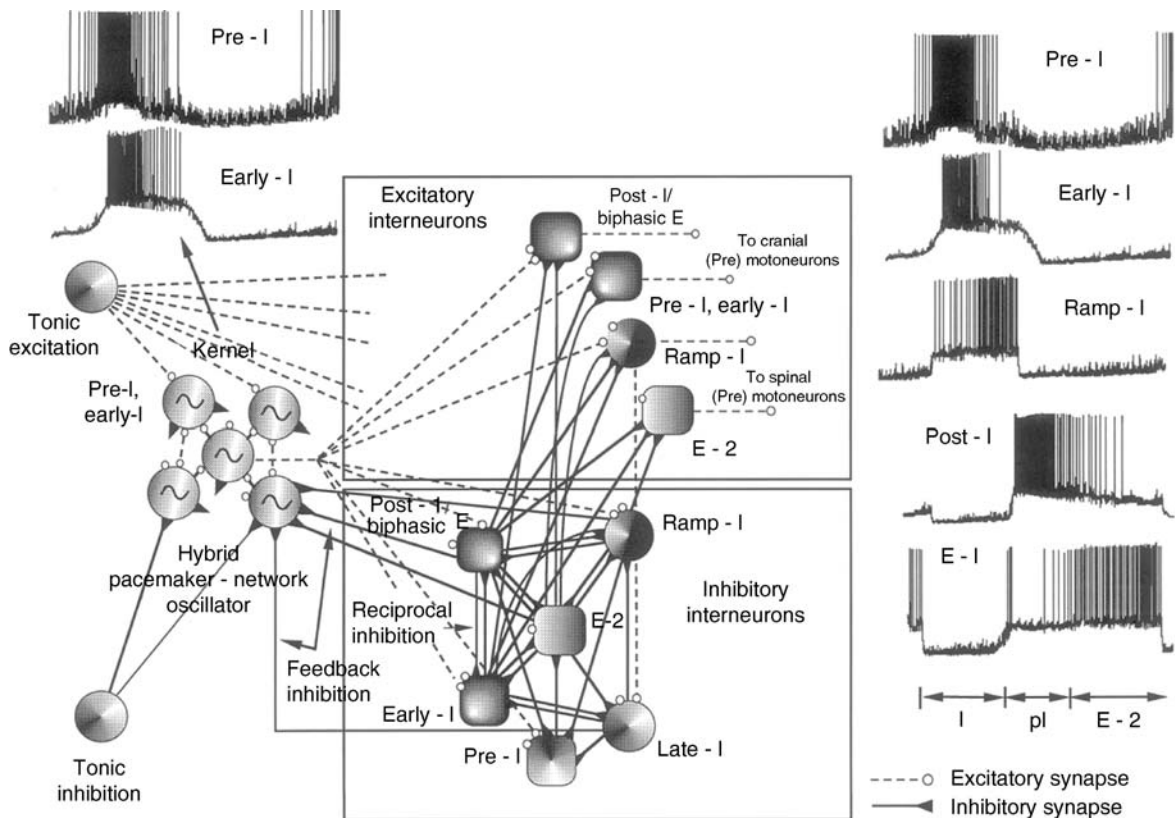
Computational Modeling of the Respiratory Network. Figure 2 Modeling the intrinsic bursting activity of the pre-Bötzinger Complex in vitro. Simulations are shown for a heterogeneous population of 50 voltage-dependent bursting neurons (see raster plot at *left* in a) coupled by fast excitatory synaptic connections. All neurons incorporate the persistent (slowly inactivating) sodium current (I_{NaP}). The population receives excitatory tonic drive. Heterogeneity and the cells' voltage-dependent properties result in temporal dispersion of spiking within the pre-BötC population. Population oscillations (b) generated by the model are similar to those recorded from the isolated pre-BötC in vitro. Population activity was obtained by calculating histograms (10 ms bins) of spike times across the 50 neurons. Control of pre-BötC population bursting frequency by tonic excitatory synaptic input ($g_{tonic-e}$) is shown in (c) and (d). Elevation of this input (from *top to bottom* in d) increases burst frequency and, finally, switches the population activity from bursting to sustained asynchronous activity. Modified from [7] with permission.

Based on these ideas, Smith at al. [10] proposed a hybrid pacemaker-network model in which the pre-BötC excitatory kernel, with I_{NaP}-dependent bursting pacemaker properties, was embedded into an inhibitory network. The schematic of this model is shown in Fig. 3. The network model contains several populations of inspiratory and expiratory neurons (pre-I, early-I, ramp- I, late-I, post-I/biphasic-E, and late-E (aug-E or E-2)) simulated using populations of conductance-based single neuron models. It was shown that this model can operate in multiple rhythm-generating regimes depending on the expression of voltage-dependent pacemaker properties in the kernel cells and on the inhibitory network interactions. In the pacemaker (kernel)-driven mode, the inspiratory bursting activity in the pre-BötC results from the interactions between the pacemaker properties and tonic and phasic excitatory and inhibitory inputs. With the system operating in this mode, oscillation frequency is controlled by tonic excitation/inhibition as in the isolated pre-BötC in vitro. In the network-driven mode, the kernel pacemaker neurons operate in the regime of sustained activity. In this state, the network feedback inhibition is required for ►inspiratory phase termination. The inhibitory hyperpolarization resets I_{NaP} in the pre-BötC cells, allowing recovery from current inactivation, and the next inspiration is initiated when the inhibition declines. Analysis of the model has demonstrated that this hybrid model can be transformed dynamically between the above modes with specific changes in model parameters.

State-Dependent Generation of the Respiratory Rhythm: The Ponto-Medullary Model

As described above, the functional state of the pre-BötC neurons with I_{NaP}-dependent bursting properties can be controlled by excitatory tonic drive and phasic synaptic inhibition (see also in [7]). Specifically, a relatively high excitatory drive can depolarize these neurons producing

Computational Modeling of the Respiratory Network. Figure 3 The hybrid pacemaker-network model. The respiratory network consists of interacting populations of different excitatory and inhibitory interneurons and incorporates the excitatory pacemaker-driven "kernel", representing the pre-BötC that includes the populations of neurons (pre-I and early-I types) with I_{NaP} current (their activity is shown at the *top left*). Follower excitatory interneurons (see examples of activity patterns at the *top right*) generate synaptic drive via parallel transmission pathways to cranial and spinal (pre)motoneurons. Interconnected inhibitory interneurons generate temporal patterns of synaptic inhibition that project to the pre-BötC via feedback connections and the to the follower excitatory populations to sculpt pre-motor output activity. Modified from [10] with permission.

inactivation of I_{NaP} and putting these neurons to the state of tonic spiking. In addition, phasic inhibition can entrain a rhythmic rebound bursting resulting from the periodical disinhibition of pacemaker neurons. Hence tonic drive from supramedullary centers (e.g., from the ►pons) may control the functional state of the pre-BötC directly, via excitatory drive to the pre-BötC, as well as indirectly through the activation of post-I neurons providing phasic inhibition to the pre-BötC. As a result, pontine inputs to both the pre-BötC and BötC may change the operating rhythmogenesis mechanism via alteration of the functional state of pre-BötC neurons.

Rybak et al. [9] developed a model of the ponto-medullary respiratory network that employed the above state switching mechanism. Fig. 4 shows the schematic of this model and its performance under different conditions. The model consists of interacting populations of neurons modeled using conductance-based single neuron models. An attempt has been made to integrate known cellular-, network-, and system-level mechanisms contributing to respiratory rhythm generation and control, and accumulate all advantages of the previous models. Also in contrast to the previous models, this model has considered a spatial organization of "respiratory" compartments in the ►medulla (VRC) and pons by incorporating spatially separate compartments, such as rVRG, pre-BötC, BötC (all in VRC) as well as rostral (rPons) and caudal (cPons) parts of the pons. Each compartment includes neural populations known to be dominantly present in this region. Synaptic connections between neural populations within the VRC (i.e., between the ramp-I, early-I, late-I, post-I, aug-E and pre-I populations) define the basic circuitry for IOS and EOS mechanisms, which were similar to those operating in the network model shown in Fig. 1. At the same time, the pre-I population of the pre-BötC contains neurons with I_{NaP}-dependent pacemaker properties. Reciprocal excitatory connections between the medullary ramp-I and the pontine I-mod and IE-mod populations, and between the medullary post-I and the pontine IE-mod and E-mod populations, provide I-, IE- or E-modulation of the activity of the corresponding pontine populations. The model suggests that reticular neurons from the caudal pons (the tonic population) provide excitatory tonic drive to the majority of medullary respiratory neurons. Similar to the network model shown in Fig. 1, pulmonary mechanosensory feedback controls the activity of the key neural populations involved in IOS and EOS mechanisms (via activation of the late-I, post-I and ramp-I populations and inhibition of the early-I population) and hence contributes to regulation of the durations of respiratory phases through the Hering–Breuer reflex. In addition, this feedback suppresses the activity of the pontine neural populations that receive excitation from the medullary populations (I-mod, IE-mod, E-mod). Importantly, the IOS and EOS mechanisms in this model operate under control of both pontine input and pulmonary feedback, which both are excitatory to the late-I, ramp-I and post-I populations.

The performance of the model under different conditions is shown in Fig. 4b–e. With pons intact, the model generates a stable "eupneic" respiratory rhythm and exhibits realistic firing patterns and membrane potential trajectories of respiratory neurons (see Fig. 4b). Specifically, the bursts of ramp-I neurons as well as phrenic discharges exhibit augmenting patterns. The pulmonary feedback to the medulla provides the Hering–Breuer reflex, so that disconnecting this feedback ("vagotomy") produces an increase in the amplitude and duration of phrenic discharges (Fig. 4c) reflecting the loss of the Hering–Breuer reflex.

Disconnection of vagal feedback also eliminates the suppressing influence of vagal afferents upon the pontine I-mod, IE-mod and E-mod populations (Fig. 4a) and hence increases the role of these pontine populations in the control of respiratory phase switching. This control is provided via the same medullary IOS and EOS circuits that are controlled by pulmonary vagal feedback when the latter is intact.

As shown previously in cats and rats, a removal of the rostral pons or chemical blockade of respiration-related structures within this region produces apneusis, and a complete removal of the pons and rostral medullary structures in vivo can produce gasping-like phrenic bursts with decrementing phrenic discharges. Similarly, a removal of rPons in this model converts the normal breathing pattern to apneusis (Fig. 4d), and a complete removal of the pons (additional removal of cPons) produces gasping-like (or in vitro-like) oscillations characterized by a decrementing phrenic discharges (Fig. 4e). More recent versions also consider the regulatory role of inputs from rostral medullary neurons such as ►retrotrapezoid nucleus neurons, which have been proposed to convey tonic input related to chemosensory function.

This model (as well as the hybrid model described above) suggests that the operating rhythm-generating mechanism (network-based, pacemaker-driven or hybrid), particular that is engaged and expressed under conditions, depends on the functional states of the pre-BötC and other VRC compartments (e.g., BötC), which in turn are controlled by multiple network interactions within the medulla as well as by various supramedullary (e.g., pontine) and afferent (mechano- and chemosensory) inputs carrying information on the functional state and metabolic needs of the system.

Synopsis

Although many cellular and network properties involved in respiratory rhythm and pattern generation remain unknown, there is an emerging understanding

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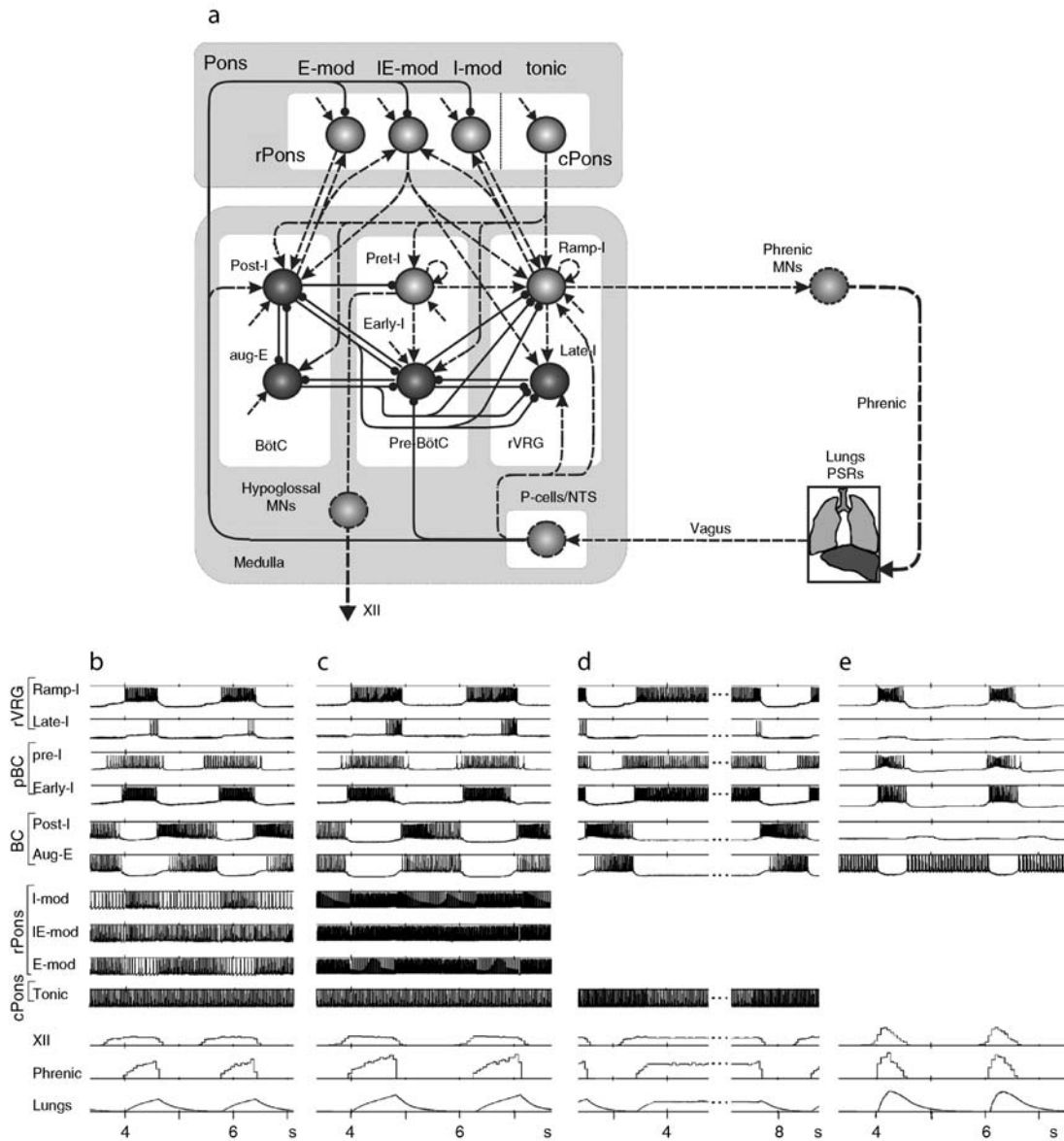
Computational Modeling of the Respiratory Network. Figure 4 The ponto-medullary model of the respiratory CPG. (a) Model schematic. Each sphere represents a population of 50 neurons. *Dark and light large spheres* are excitatory and inhibitory populations respectively. *Dashed lines with arrows* represent excitatory synaptic connections and *solid lines* ended with small circles show inhibitory connections. *Additional arrows* at the population circles indicate external excitatory tonic drive to each population. (b–e) Model performance under different conditions. The *top traces* (except the bottom three) show membrane potential trajectory of one, randomly selected neuron from each population; the three *bottom traces* show integrated hypoglossal (XII) and phrenic activities and lung volume (the *bottom trace*). (b) The performance of the intact network ("eupnea"). (c) "Vagotomy" – the vagal feedback in the model is disconnected. (d) "Apneusis" produced by removal of rPons. (e) Complete removal of the pons switches the system to the state in which the rhythm in the network is completely driven by bursting pacemaker activity originating in the pre-BötC. Modified from [9] with permission.

that the operating neural mechanisms involved are state-dependent and entail complex cross-level interactions between multiple cellular-, network-, and system-level processes. Computational modeling at all levels of complexity is expected to play an increasing role in analyzing the complex mechanisms underlying respiratory network function and the neural control of breathing.

References

1. Duffin J (1991) A model of respiratory rhythm generation. Neuroreport 2:623–626
2. Richter D, Ballantyne D, Remmers JE (1986) How is the respiratory rhythm generated? A model. News Physiol Sci 1:109–112
3. Botros SM, Bruce EN (1990) Neural network implementation of the three-phase model of respiratory rhythm generation. Biol Cybern 63:143–153
4. Balis UJ, Morris KF, Koleski J, Lindsey BG (1994) Simulations of a ventrolateral medullary neural network for respiratory rhythmogenesis inferred spike train cross-correlation. Biol Cybern 70:311–327
5. Rybak IA, Paton JFR, Schwaber JS (1997) Modeling neural mechanisms for genesis of respiratory rhythm and pattern: II. Network models of the central respiratory pattern generator. J Neurophysiol 77:2007–2026
6. Smith JC, Ellenberger H, Ballanyi K, Richter DW, Feldman JL (1991) Pre-Bötzinger complex: a brain stem region that may generate respiratory rhythm in mammals. Science 254:726–729
7. Butera RJ, Rinzel JR, Smith JC (1999) Models of respiratory rhythm generation in the pre-Bötzinger complex: II. Populations of coupled pacemaker neurons. J Neurophysiol 82:398–415
8. Rybak IA, Paton JFR, Rogers RF, St.-John WM (2002) Generation of the respiratory rhythm: state-dependency and switching. Neurocomputing 44–46:603–612
9. Rybak IA, Shevtsova NA, Paton JFR, Dick TE, St.-John WM, Mörschel M, Dutschmann M (2004) Modeling the ponto-medullary respiratory network. Respir Physiol Neurobiol 143:307–319
10. Smith JC, Butera RJ, Koshiya N, Del Negro C, Wilson CG, Johnson SM (2000) Respiratory rhythm generation in neonatal and adult mammals: the hybrid pacemaker-network model. Respir Physiol 122:131–147