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Degeneracy as a Substrate for Respiratory Regulation

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Abstract

Recent studies in vivo and in vitro suggest that both respiratory rhythmogenesis and its central chemosensory modulation arise from multiple, mechanistically and/or anatomically distinct networks whose outputs are similar. These observations are consistent with degeneracy, defined as the ability of structurally distinct elements to generate similar function. This review argues that degeneracy is an essential feature of respiratory networks, ensuring the survival of the individual organism over the course of development, and accounting for the transformation of respiratory biomechanics over evolutionary time. At faster timescales, respiration must adapt continuously and rapidly to changes in metabolic demand and ambient conditions to maintain blood-gas homeostasis. Control theory, which formalizes homeostasis, states axiomatically that rapid responsiveness can only be achieved with high gain, but high gain comes at the cost of instability. Homeostatic systems displaying highly optimized tolerance (HOT) mitigate the instability accompanying high gain by incorporating regulatory mechanisms that provide protection against expected perturbations, yet these systems remain fragile to catastrophic failure in response to rare events. Because the multiple mechanisms that are conjectured to mediate respiratory rhythmogenesis and chemosensation have distinct ranges of activity and responses to modulatory input, they provide a richer substrate for respiratory regulation than than those of any single mechanism. Respiration, though robust, remains fragile to rare perturbations, matching a key feature of HOT. These observations support the conclusion that degeneracy provides the substrate for respiratory regulation, and that the resulting regulatory system conforms to HOT.

1 Overview

The central focus of in vitro studies of respiratory networks has been the identification of the minimal substrate necessary and sufficient for respiratory rhythm generation, conceived as a feed-forward motor pattern. This research program has its origin in Flourens' postulate that the brainstem constituted a "*nœud vital*" dedicated to controlling vital functions such as breathing (Flourens, 1824). In its modern form, this kernel hypothesis for respiratory rhythm generation (Feldman et al., 1990; Rekling and Feldman, 1998) has been elaborated using the neonate rodent transverse slice preparation (Smith et al., 1991a), which isolates the pre-Bötzinger Complex (preBötC). A central claim of this hypothesis is that the preBötC is both necessary and sufficient for inspiratory rhythm generation.

This review posits that to understand the organization of respiratory networks in the ventrolateral medulla, it is more useful to ask how these networks integrate and appropriately respond to feedback, rather than how they solve the feed-forward problem of rhythm

generation. We will argue that as a byproduct of evolution, parallel, functionally similar, structurally distinct (degenerate) circuits and processes (Tononi et al., 1999; Edelman and Gally, 2001) have evolved to generate and regulate respiratory rhythm. To provide support for this claim, we will discuss how rhythmogenic and central chemosensory processing embody degeneracy. Finally, we will propose that the existence of functionally duplicative structures and mechanisms provides the neural substrate for the regulatory networks that manage the critical and difficult problem of maintaining blood-gas homeostasis.

2 Degeneracy of rhythmogenic and chemosensory networks

Over evolutionary time, vertebrate respiratory biomechanics have undergone substantial transformation. In cyclostomes, respiration involves active expiration / passive inspiration (Johansen and Strahan, 1963). In bony fish and amphibian larvae aquatic respiration involves active inspiration / active expiration, while aerial respiration involves active inflation / passive deflation (McMahon, 1969; Brainerd and Owerkowicz, 2006). In birds respiration involves active inspiration / active expiration (Bouverot, 1963). Finally, in mammals respiration consists of active inspiration / passive expiration (Gans, 1970), though during periods of intense activity both inspiration and expiration are active. Because transitions between biomechanical modes was gradual, and gas exchange had to be maintained without disruption, respiratory mechanisms were necessarily duplicative so that one system could undergo evolutionary change, while the other maintained blood-gas homeostasis. This duplicative organization is apparent at the base of the vertebrate lineage: in the lamprey, two distinct, coupled medullary networks produce respiratory rhythm (Martel et al., 2007). In the bullfrog, two coupled respiratory *behaviors* involving distinct anatomical structures coexist: buccal ventilation, and lung ventilation (Gans et al., 1969). These behaviors are regulated by two distinct medullary networks (Wilson et al., 2002): the buccal rhythm-generating network just rostral to the hypoglossal nerve and the lung rhythm-generating network just caudal to the vestibulocochlear nerve.

In rodents, gas exchange occurs via the lungs alone, and at rest, respiration is only active during inspiration. Based on a variety of in vitro and in vivo studies, it has been proposed that the preBötC is the source of eupneic rhythm (Smith et al., 1991a). This view was challenged by others who argued that networks at the level of the facial nucleus (VIIn) generated inspiratory bursts (Onimaru and Homma, 1987; Onimaru and Homma, 2003). Evidence that this second network could determine inspiratory burst times was inferred from differences in the response to opioids between the transverse slice preparation, which slows continuously in response to opioids, and the more intact en bloc brainstem-spinal cord preparation or juvenile vagotomized rat, both of which slow to integer multiples of control period (Mellen et al., 2003). The existence of two anatomically distinct respiratory networks was validated via optical recordings from the en bloc preparation; the more rostral structure was named the parafacial respiratory group (pFRG) (Onimaru and Homma, 2003). Recently, the ontogeny of rhythmogenic networks at the level of the preBötC (Thoby-Brisson et al., 2005) and pFRG (Thoby-Brisson et al., 2009) have been described. These groundbreaking studies establish that each rhythmogenic network arises independently of the other, has distinct biophysical properties, and the systems-level properties of each differs from those observed when both are coupled. Independent of degeneracy, the idea that different neuronal subnetworks contribute to respiratory rhythmogenesis in a state-dependent manner has been proposed elsewhere (Hilaire and Duron, 1999).

A similar proliferation of functionally duplicative mechanisms and networks is seen in the context of detection of hypercapnia / acidosis. In mammals hypercapnia sensing is mediated peripherally, by the carotid bodies (Lahiri, 1994; Forster et al., 2008; Blain et al., 2009) and centrally, by a variety of networks that are pH-sensitive (Nattie, 2001; Putnam et al., 2004;

Nattie and Li, 2010). While the existence of widely distributed chemosensory regions is compatible with degeneracy, our discussion will be limited to two regions that have been shown to have an important chemosensory role, in order to illustrate the applicability of the concept of degeneracy to respiratory regulation. The first of these is the Raphé Nucleus in central and medial medulla (Richerson et al., 2001); the second is the retrotrapezoid nucleus (RTN), lying ventral to the VIIn (Guyenet, 2008) and overlapping with the pFRG (Onimaru and Homma, 2003).

Raphé neurons are typically activated by artificial cerebrospinal fluid (aCSF) acidification (Wang et al., 1998) in vitro, or systemic acidosis (Veasey et al., 1995; Hodges et al., 2004) in vivo. These neurons have processes that surround arterial vasculature, and thus are optimally suited to sense systemic blood-gases (Bradley et al., 2002). They also project to respiratory networks, including the RTN (Mulkey et al., 2007), the preBötC, and phrenic motoneurons (Lindsay and Feldman, 1993). Raphe neurons release serotonin, which has been shown to have powerful modulatory effects on both inspiratory burst amplitude and frequency, and when serotonergic transmission is blocked, respiratory rhythmogenesis in the slice is disrupted (Ptak et al., 2009). In addition, peptides Substance-P (SP) and Thyrotropin-Releasing Hormone (TRH), both co-released with serotonin by Raphé neurons, up-regulate chemosensory and rhythmogenic function (Talley and Bayliss, 2000; Pena and Ramirez, 2002; Richter et al., 2003). Finally, a transgenic mouse lacking serotonergic neurons show blunted chemosensory responses (Hodges et al., 2008).

Neurons of the RTN are located at the ventral surface of the medulla and respond to acidification of the surrounding parenchyma. These cells show a consistent and robust response to central acidosis both in vivo (Nattie and Li, 2008) and in vitro following synaptic blockade (Mulkey et al., 2004). In addition, they fire briskly during carotid chemoreceptor stimulation (Takakura et al., 2006), indicating that they also integrate peripheral chemosensory drive. RTN neurons show respiratory modulation (Guyenet et al., 2005), are glutamatergic, and project to preBötC respiratory networks, thus likely provide excitatory drive to the preBötC (Mulkey et al., 2004). Recently, a constituent phenotype of the RTN has been identified, which is glutamatergic, non-cholinergic, non-aminergic, and expresses the *Phox2b* transcription factor, (ccRTN; (Lazarenko et al., 2009). These neurons have been classified into two groups based on their pH sensitivity, consistent with central chemosensory function. The importance of *phox2b*-expressing neurons in human central chemosensation is supported by blunted central chemosensation observed in congenital central hypoventilation syndrome (CCHS) patients, caused by *Phox2b* transcription factor mutations (Amiel et al., 2003). This deficit is matched in the $Phox2b^{27Ala/+}$ transgenic mouse analog (Dubreuil et al., 2008).

Although the existence of more than one rhythmogenic and central chemosensory mechanism or network provides support for degeneracy, closer scrutiny of emerging data illustrate a more complicated story that points to important differences between degeneracy and redundance. A key component of the degeneracy concept is that while members of a degenerate set can each generate similar outputs, their functional role is state-dependent, so that degenerate elements can participate in other functions and behaviors (Tononi et al., 1999). This feature is exemplified by the functional overlap between the pFRG and the RTN (Onimaru et al., 2009; Guyenet and Mulkey, 2010). Anatomically, these two structures overlap. While both are heterogeneous, each contain ccRTN neurons as constituents (Onimaru et al., 2008; Lazarenko et al., 2009). In late embryonic mice, $phox2b^{+}$ neurons within RTN/pFRG were found to have endogenous bursting properties, to synchronize via gap-junction coupling, and to increase the frequency of the preBötC generated-rhythm (Thoby-Brisson et al., 2009). In a subsequent study in which conditional $phox2b^{+}$ mutants lacking oscillatory parafacial networks were studied, a dramatically slower respiratory rhythm that was insensitive to acidotic challenge was observed (Dubreuil et al., 2009). Together, these studies provide support for a dual rhythmogenic and

chemosensory function for *phox2b*$^{+}$ neurons, which overlap with, and likely match ccRTN neurons.

Another hypothesized role for pFRG networks is their contribution to expiratory rhythm generation, driving thoracic expiratory muscles during periods of elevated physical activity (Janczewski and Feldman, 2006; Abdala et al., 2009). This activity is lost in vitro when the rostral 30% of the VIIn is removed (Ruangkittisakul et al., 2007; Giraudin et al., 2008). The conditional recruitment of expiratory networks with increased effort in rodents is analogous to what is seen in frogs: at rest, blood-gas homeostasis is maintained by continuous buccal breathing, but episodic cycles of lung breathing coupled to the buccal rhythm are triggered by hypercapnia (Kinkead and Milsom, 1994). The functional analogy between the frog lung oscillator and the putative rodent expiratory oscillatory is supported by their similar anatomical location: the pFRG in rodents originates from rhombomeres 3 or 5 (Thoby-Brisson et al., 2009). Because adult frogs preserve rhombomeric organization (Straka et al., 2002, 2006), the anatomical location of lung rhythm-generating networks in adult frog indicates that they arise out of rhombomeres 3 or 4.

Taken together, these different lines of research indicate that the RTN/ pFRG plays an important role in chemosensation -- except during sleep (Nattie, 2001). In addition, it appears to determine inspiratory burst times under conditions of opioid-induced depression. Finally, it may function as an expiratory rhythm generator during periods of intense physical exertion. Qualitatively, the RTN/pFRG contributes to both respiratory rhythmogenesis and chemosensation in a state-dependent manner. The observation that a constituent of a degenerate system can play more than one functional role, depending on conditions of the larger system in which it is embedded is an essential feature of degeneracy (Tononi et al., 1999), and is incompatible with redundancy.

Multiple studies provide support for the hypothesis that the preBötC plays an obligatory role in respiratory rhythmogenesis. On one hand, minimal in vitro preparations establish that the isolated PBC is sufficient to generate a rhythm (Johnson et al., 2001; Ruangkittisakul et al., 2008). On the other, highly specific in vivo lesions to preBötC constituents suggest that the preBötC is also necessary for normal breathing (Gray et al., 2001b; Tan et al., 2008). In both of these lesion studies however, neuronal ablation or silencing was relatively rapid. In a recent in vivo study in goats, when similar focal lesions were induced over a period of weeks resulting in near total preBötC ablation, respiratory rhythm during both sleep and wakefulness was unaffected (Krause et al., 2009). Because rapidly induced smaller lesions to the same region in goats led to the fatal disruption of eupneic breathing (Wenninger et al., 2004), these findings indicate that medullary networks are resilient to preBötC ablation if time is allowed for neuronal compensatory plasticity. Thus, these findings indicate that other networks can be recruited to replace the rhythmogenic function of preBötC, consistent with degeneracy.

3 Degeneracy and development

Degenerate organization of respiratory rhythmogenic and regulatory networks may be of particular relevance in the perinatal period. The observation that mice lacking the pFRG die at birth, but can be rescued by μ-opiate receptor antagonist naloxone administration in the perinatal period (del Toro et al., 2001) has been interpreted as evidence that pFRG networks maintain respiratory patency in the perinatal period (Feldman and Del Negro, 2006). In addition, subunit switches in $GABA_A$ (Liu and Wong-Riley, 2006), and AMPA receptors (Liu and Wong-Riley, 2005) over the first two weeks of life across the CNS – and in particular in the brainstem – have the net effect of reducing excitatory drive and increasing inhibitory drive (Wong-Riley and Liu, 2008). Strikingly, with the exception of lability at P13, these and other changes in subunit expression (Singer et al., 1998) and receptor subtype expression (Volgin et

al., 2003) in brainstem are accompanied by minimal changes in respiratory pattern, rhythm, or response to hypoxic challenge (Liu et al., 2006). Moreover, responses to hypoxia in the perinatal period remain stable even as chemoreceptive mechanisms shift from mainly central (in the neonate) to both central and peripheral (in adults) (Saetta and Mortola, 1987). During the post-natal period, variation in hypercapnic responses between rat strains is large (Davis et al., 2006), as is animal-to-animal variability (Stunden et al., 2001), thus consistent developmental changes in CO2 sensitivity have as yet not been identified.

Developmental changes are likely to impact functionally similar subnetworks differently, due to the different transduction mechanisms and/or signallng pathways in each. So long as at least one subnetwork remains functional, the animal remains resilient to transient disruptions in the functional contribution of subnetworks impacted by developmental changes. While this account is admittedly speculative, it is consistent with experimental data (del Toro et al., 2001), which support the conjecture that opioid-insensitive pFRG network maintain inspiratory rhythm during post-natal opiate-induced depression of preBötC neurons. Furthermore, in the absence of degeneracy, one is required to account for how blood-gas homeostasis could be maintained in a system with a single chemosensory / rhythmogenic mechanism, while its biophysical and pharmacological properties undergo substantial change. This is analogous to building a ship while at sea.

4 Highly optimized tolerance as a solution to homeostatic regulation

Qualitatively, degeneracy implies a many-to-one mapping between inputs and outputs. A direct consequence of this is robustness: the existence of multiple ways of implementing a function protects that function against failure of any one mechanism, particularly because the function is implemented in mechanistically distinct ways (Noppeney et al., 2004). This is critical with respect to a basic behavior such as breathing because even transient interruption is life-threatening.

While robustness is a necessary feature of the neural substrate for respiration, equally important is adaptiveness: breathing is continuously modulated in rate and amplitude to maintain blood-gas homeostasis. Several factors make this homeostatic regulation a difficult problem. First, metabolic demand is highly variable: O_2 consumption ranges from 250 ml/min at rest to 800 ml/min during light exercise (Feldman and Del Negro, 2006). Second, there is a lag between when blood gas mixtures move towards hypercapnia/hypoxia, and when chemosensors in the carotid body and ventral medulla detect these changes, due to circulatory delay (Khoo, 2001). Similarly, movement of O_2 and CO_2 between bronchi and alveoli occurs via diffusion, thus steep increases in respiratory rate do not immediately lead to equilibration of blood gases (West, 2004). These lags are problematic because feedback circuits that contain them will be prone to oscillatory responses.

Homeostatic circuits have been formalized within control theory (Zhou and Doyle, 1998), whose basic components are a reference signal, which is compared to a feedback signal to generate a command signal that determines the output. A fundamental contribution of control theory to our understanding of homeostatic function is that there is a hard trade-off: homeostatic regulation with low gain is stable but responds slowly to perturbations or changes in command signals, while a high-gain system adjusts rapidly to perturbations or command signals, but is unstable. Generically, for closed-loop feedback systems, there exists a sinusoidal perturbation whose period matches time-lags in the loop such that feedback increases exponentially. This instability can only be prevented by incorporating regulatory mechanisms that will guard against a limited set of destabilizing input signals. These regulatory mechanisms cannot eliminate the instability associated with high gain, but can protect the system against perturbations it is likely to encounter, leaving it vulnerable to rarely encountered events for

which appropriate regulatory mechanisms are lacking. As a consequence, high-gain homeostatic systems acquire robustness at the cost of spiraling complexity (Csete and Doyle, 2002), while remaining fragile to rare events.

Systems where robustness and adaptiveness are both achieved by accretion of regulatory networks are described as examples of “highly optimized tolerance” (HOT) (Carlson and Doyle, 1999), which share the attributes of “highly structured, nongeneric, self-dissimilar internal configurations” (Carlson and Doyle, 2002). Thus, structures displaying HOT will have low redundance because its constituents are nongeneric and self-dissimilar. In an effort to formalize degeneracy and to provide methods for its quantification, the distinction between degeneracy and redundance has been developed in an information-theoretic context (Tononi et al., 1999). In a system composed of identical components, redundancy will be high and degeneracy absent; thus, the entropy of the system will be the same as the entropy of any one component. In a multi-component system whose elements are all structurally and functionally different, both redundancy and degeneracy will be absent; thus, the entropy of the system as a whole will equal the sum of the entropies of the components. Finally, in a multi-component system whose elements are functionally similar but structurally and/or mechanistically different, degeneracy will be high, redundance will be low, and the entropy of the system as a whole will be less than the sum of the entropies of its components (Tononi et al., 1999). Thus, both HOT and degenerate systems have low redundance.

We hypothesize that degeneracy provides the substrate for homeostatic regulatory systems that display HOT. Importantly, while degeneracy has been developed as a purely descriptive concept (Edelman and Gally, 2001), HOT has been defined functionally, as a necessary attribute of systems that must operate robustly and adaptively in a variable and unpredictable environment (Carlson and Doyle, 2002). As stipulated by the developers of the concept, HOT appears to have broad applicability to biology. Although robustness to a variable and uncertain environment is both a feature of biological systems and systems that display HOT, this robustness hardly proves that biological systems embody HOT. A key idea of HOT is that, while systems can be optimized to deal with a range of expected perturbations, they remain fragile to rare perturbations, which can lead to catastrophic failure. Thus, stronger proof that biological systems embody HOT can be obtained by analyzing how they fail. Using this approach, age-related immune system deterioration has been proposed to be a consequence of HOT (Stromberg and Carlson, 2006), and fragilities predicted by HOT have been identified in cell-cycle regulatory pathways as targets for drug development (Nayak et al., 2008).

Existing studies support the hypothesis that respiratory networks display HOT. On one hand, respiratory networks are robust to widespread bilateral chemical and electrical lesions (Speck and Feldman, 1982), as well as pharmacological disruption (Ramirez et al., 1998), observations consistent with the existence of spatially distributed functionally similar networks. On the other hand, respiratory networks cannot guard against cascading disregulation that ensues as a result of chronic intermittent hypoxia (CIH). This disregulation is manifest first as phrenic (Baker and Mitchell, 2000) and carotid body (Peng et al., 2003) long-term facilitation (i.e., increase in both feedback gain and the amplitude of actuator output). These facilitatory mechanisms adaptively improve airway patency (Mahamed and Mitchell, 2007). If CIH persists, these adaptive responses lead to increased production of reactive oxygen species (MacFarlane and Mitchell, 2008), which cause widespread transcription factor expression changes due to upregulation of hypoxia-inducible-factor 1 (Nanduri et al., 2008). These transcription factor changes have been implicated in cardio-respiratory disregulation (Prabhakar et al., 2005; Kumar et al., 2006). Importantly, chronic hypoxia, which accompanies a variety of common disease states, does not trigger these changes in transcription factor expression (Peng and Prabhakar, 2004). CIH-induced disregulation is clinically important, as it is found in patients suffering from obstructive sleep apnea (OSA), which is growing more common due to the

epidemic of obesity (Cameron and Zimmet, 2008). Because obesity is rare in nature, HOT would predict that regulatory circuits would be vulnerable to obesity-induced OSA, as their regulatory networks are only tailored to "expected" perturbations.

An essential feature of degeneracy is robustness to insult (Noppeney et al., 2004). This is also an attribute of HOT systems: the basic behavior is expected to be robust to insult, but adaptive regulation of that behavior is fragile (Carlson and Doyle, 2002). This combination of core function robustness but regulatory fragility is apparent in a highly selective lesioning study carried out on respiratory networks in vivo. Bilateral injections into the preBötC of the neurokinin-1 receptor agonist Substance-P, conjugated to the neurotoxin saporin led, after 5 days, to near-complete destruction of the preBötC (Gray et al., 2001a). Although these animals generated ataxic breathing patterns and were moderately hypercapnic, hypoxic and acidotic, they survived in room air. By contrast, if treated animals were exposed to hyperoxic, hypoxic, hypercapnic gas mixtures, or underwent mild anesthesia, grossly abnormal ventilatory responses ensued, and unless the animals were artificially ventilated, they died. Thus, as predicted by HOT, while lesioned rodents remained viable in room air, their ability to respond adaptively to perturbations was lost.

5 Degeneracy and regulatory function

Respiratory rhythmogenic and regulatory networks appear to manifest the robustness / fragility characteristics of HOT systems, but this would arguably be the case for any responsive homeostatic system, regardless of how it was realized, and does not imply that degeneracy contributes to regulation. The claim that degeneracy provides the substrate for homeostatic regulation finds support in specific examples at the level of mechanism. One example is provided by an elegant study of how individual medullary neurons transduce pH. The problem that motivated this study was the observation that pH-sensitive neurons increase their rate of firing in a graded manner that accurately reflects pH over a wide range of values; this graded response was hypothesized to be mediated by K^+ channels (Dean et al., 1989; Bayliss et al., 2001). While a variety of K^+ channels are modulated by pH over distinct ranges, no individual K^+ channel had the dynamic range of pH-sensitivity seen in these neurons. Using dissociated brainstem neurons cultured on microelectrode arrays, cells whose firing rates were an accurate reflection of extracellular pH over a wide range were probed using selective K^+ channel blockers (Su et al., 2007). Many distinct K+ channels show pH sensitivity over different ranges, including the ubiquitously-expressed family of inward rectifying K^+ channels (K_{IR}) (Katz, 1949; Kubo et al., 2005) and TWIK-related acid-sensitive potassium channels (TASK1 and TASK3) (Ketchum et al., 1995). K_{IR} channels are pH-sensitive over a narrow range near pH 7.4, while TASK channels show graded firing over a broad range (pH 6.9-7.5), but are relatively insensitive to small changes in pH near 7.4. It was demonstrated that in cells with broad and accurate pH-responsiveness, that response to severe hypercapnia/acidosis was lost if TASK1 channels were blocked. In the same cells response to hypocapnia and mild hypercapnia was lost when K_{IR} was selectively blocked. Thus, this study suggests that broad pH-responsiveness is mediated by two distinct mechanisms, consistent with degeneracy.

Analogously, a modeling study demonstrated that, while a network devoid of endogenous bursters was capable of maintaining stable rhythmic output, the range of parameters over which the network remained rhythmic as well as the range of frequencies it could generate were both narrower than the same network after the addition of endogenous bursters (Purvis et al., 2007), suggesting that a network combining network- and burster-based rhythmogenic menchanisms would be more robust and dynamic than a network containing only one rhythmogenic mechanism. Within the preBötC, bursters are themselves heterogeneous. Bursting can be generated by a persistent Na+ conductance (I_{NaP}), or by non-specific cation conductance (I_{CAN}) (Thoby-Brisson and Ramirez, 2001). It has been shown that these two types

of bursters differ in their response to the respiratory neuromodulator norepinephrine (Viemari and Ramirez, 2006), and it has been argued that a network containing both burster types is endowed with a broader repertoire of behaviors in response to synaptic or neuromodulatory inputs than a network containing only one (Doi and Ramirez, 2008). The distinct biophysical properties of these bursters may also have implications for networks containing both: I_{NaP}-based bursters vary their frequency over a wide range in response to applied bias currents and reset their phase in response to transient stimuli, while the frequency range of I_{CAN} –based bursters is narrower, and bursting phase is not reset by stimuli (Thoby-Brisson and Ramirez, 2001). The wide dynamic range and steep voltage-dependence of I_{NaP}-based burst-ers may provide the responsiveness required of a high-gain feedback system, with the accompanying instability, while the narrow dynamic range and insensitivity to resetting stimuli of I_{CAN}-based bursters are compatible with low-gain feedback systems. A network containing both types of bursters might have the responsiveness of a high-gain system (mediated by I_{NaP}-based bursters), yet would be stabilized by the presence of the less dynamic I_{CAN}-based bursters.

6 Conclusion

Accumulating data suggest that rhythmogenesis and chemosensation in ventrolateral medulla are carried out by functionally duplicative, anatomically distinct structures, consistent with degeneracy. We have argued that the regulatory system that maintains blood-gas homeostasis displays the robustness and fragility characteristic of HOT, and that the computational complexity of HOT is realized by degeneracy. This conjecture is supported by examples of how degeneracy at the level of the biophysical mechanisms for pH sensitivity and rhythmogenesis give rise to a wider range of responses than would be possible if only one mechanism were present. This framework may offer a way to reconcile opposing views regarding loci (Smith et al., 1991b; Onimaru and Homma, 2003) and/or mechanisms (Del Negro et al., 2002; Paton and St-John, 2007; Ramirez and Garcia, 2007; Koizumi and Smith, 2008) for respiratory rhythm generation and central chemosensation (Richerson et al., 2001; Guyenet et al., 2008; Nattie and Li, 2010), and may support new interpretations of experimental data.

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