Eupnea, tachypnea, and autoresuscitation in a closed-loop respiratory control model

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MOTIVATION:

Incorporation of sensory feedback is essential to guide the timing of rhythmic motor processes. How sensory information influences the dynamics of a central pattern generating circuit varies from system to system, and general principles for understanding this aspect of rhythmic motor control are lacking. It has been realized for sometime, however, that the mechanism underlying rhythm generation in a central circuit when considered in isolation may be different from the mechanism underlying rhythmicity in the intact organism [1].

MAIN RESULTS:

We developed a minimal model incorporating a central pattern generator (CPG) in a respiratory control loop [2]

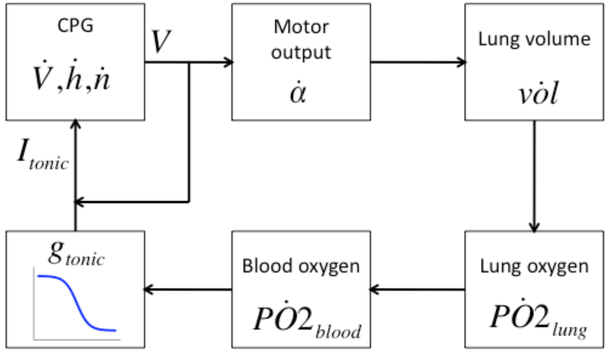
• The closed-loop system has bistability corresponding to coexistence of a eupneic-like breathing rhythm with normal minute ventilation and blood oxygen level, and a tachypneic-like state with pathologically reduced minute ventilation and critically low blood oxygen.

• An artificially imposed bout of hypoxia can cause the system to leave the basin of attraction for the eupneic-like state and enter the basin of attraction for the tachypneic-like state.

• Oscillations in the intact (closed-loop) and isolated CPG (open-loop) systems appear to arise from two distinct mechanisms.

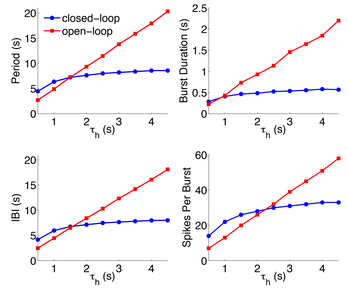
• Conductances endogenous to the Butera-Rinzel-Smith model of the respiratory CPG [3] can lead to spontaneous autoresuscitation after short or mild bouts of hypoxia.

Respiratory control model



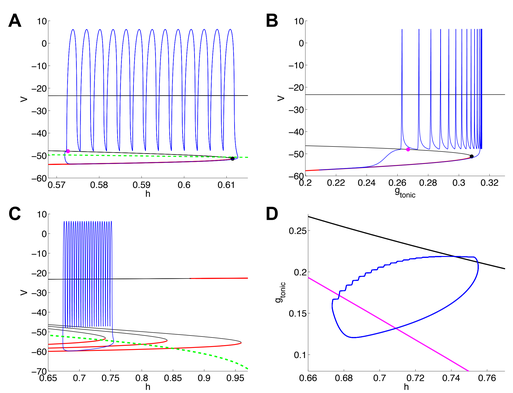
Minimal model of respiratory control. The Butera-Rinzel-Smith respiratory CPG model is embedded in a closed-loop system that includes simplified representation of lung mechanics, gas exchange, metabolic consumption of oxygen, and chemosensation.

Bursting mechanism in closed vs. open-loop models

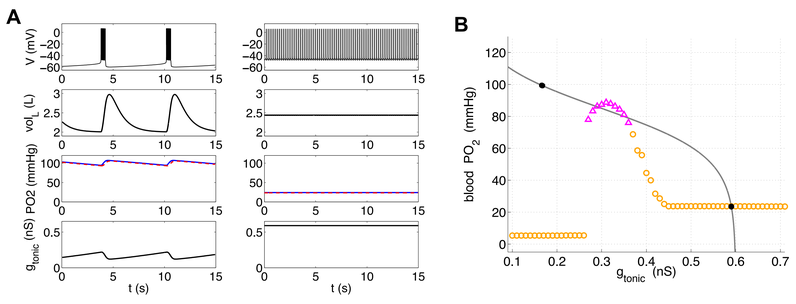


Bursting properties are different in open and closed-loop versions of the model. Burst duration, interburst interval, and the number of spikers per burst are less sensitive to changes in the time constant of INaP inactivation (τ_h) in closed-loop than open-loop. *Bursting can still occur in closed-loop model even with h set at a constant value (not shown).*

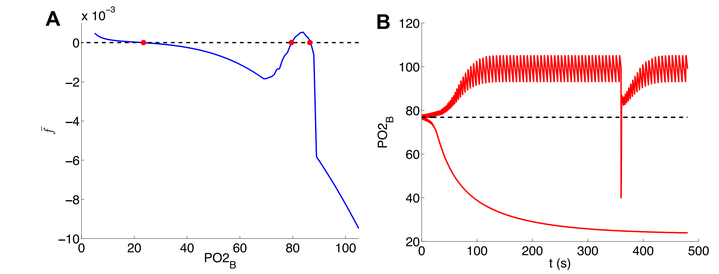
(A) Bursting dynamics in original BRS model (constant gtonic) with *h* as bifurcation parameter. Initiation and termination of spiking are through saddle-node and homoclinic bifurcations respectively. (B) BRS model with constant *h* and *gtonic* as bifurcation parameter. (C) BRS model with variable gtonic and h as bifurcation parameter. The curve of fast system steady states shifts as gtonic varies. During the silent phase, the cell still moves slowly to the right along the lower branch of fixed points as h increases. However gtonic is increasing as well (since PO2B is dropping), which shifts the lower knee to the left, causing the cell to jump up and start spiking at a gtonic value that would give quiescence in the original BRS model. (D) Two-parameter bifurcation diagram showing the location of the saddle-node (black) and homoclinic bifurcations (magenta).

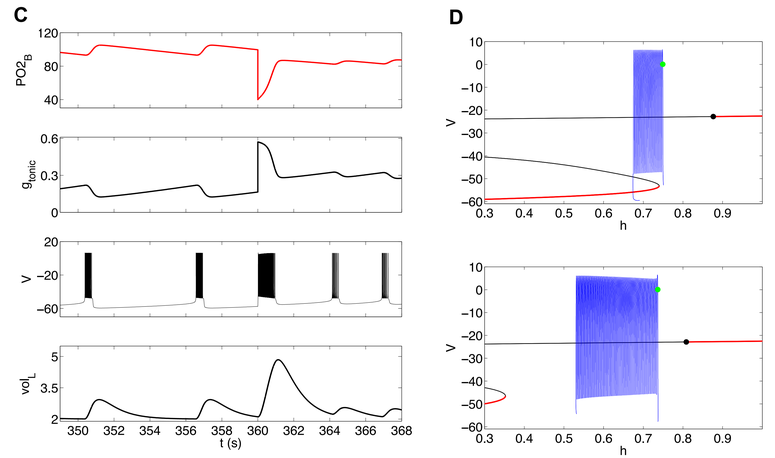


Bistability in closed-loop model



Autoresuscitation





Model equations

$$C\frac{dV}{dt} = -I_{NaP} - I_{Na} - I_K - I_L - I_{tonic}$$
$$\frac{dh}{dt} = (h_\infty(v) - h)/\tau_h(v)$$
$$\frac{dn}{dt} = (n_\infty(v) - n)/\tau_n(v)$$
$$\frac{d\alpha}{dt} = r[T](1-\alpha) - r\alpha$$

$$\frac{d}{dt}(vol_{lung}) = -E_1(vol_{lung} - Vol_0) + E_2\alpha$$
$$\frac{d}{dt}(PO2_{lung}) = \frac{PO2_{ext} - PO2_{lung}}{vol_{lung}}\left[\frac{d}{dt}(vol_{lung})\right]_+ - \frac{PO2_{lung} - PO2_{blood}}{\tau_{LB}}$$
$$\frac{d}{dt}(PO2_{blood}) = \frac{J_{LB} - J_{BT}}{\gamma\left(\beta O2 + \eta\frac{\partial SaO2}{\partial PO2}\right)}$$

$$J_{LB} = \left(\frac{PO2_{lung} - PO2_{blood}}{\tau_{LB}}\right)\left(\frac{vol_{lung}}{RT}\right)$$
$$J_{BT} = M\left(\eta SaO2 + \beta O2 \times PO2_{blood}\right)\gamma$$
$$SaO2 = \frac{PO2^n_{blood}}{PO2^n_{blood} + K^n}$$

$$\frac{\partial SaO2}{\partial PO2_{blood}} = nPO2^{n-1}_{blood}\left(\frac{1}{PO2^n_{blood} + K^n} - \frac{PO2^n_{blood}}{(PO2^n_{blood} + K^n)^2}\right)$$
$$\eta = [Hb] \times \left(\frac{1.36 \text{ mL } O_2}{\text{gm Hb}}\right)$$
$$\gamma = vol_{blood} \times \left(\frac{\text{mole } O_2}{22{,}400 \text{ mL } O_2}\right)$$
$$g_{tonic} = 0.3\left(1 - \tanh\left(\frac{PO2_{blood} - 100}{30}\right)\right)$$

References:

[1] Bassler, *Biol Cybern* **54**: 65-69 (1986)

[2] Diekman, Wilson, and Thomas, *Conf Proc IEEE Eng Med Biol Soc*, 6669-72 (2012)

[3] Butera, Rinzel, and Smith, *J. Neurophysiol.* **82:** 382–397 (1999)

Funding:

NSF DMS 0931642, 1010434, 1412877

NIH HD064830