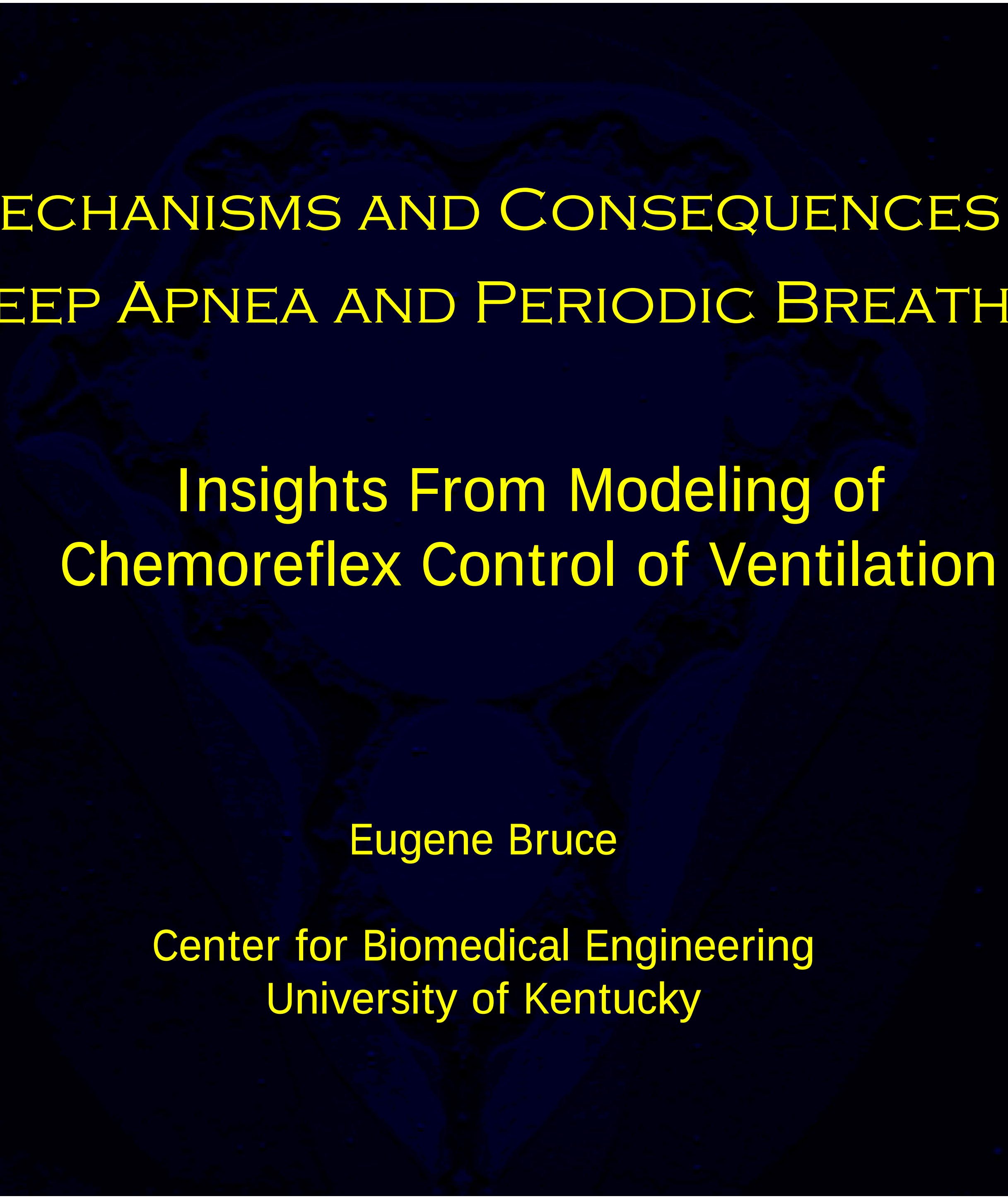


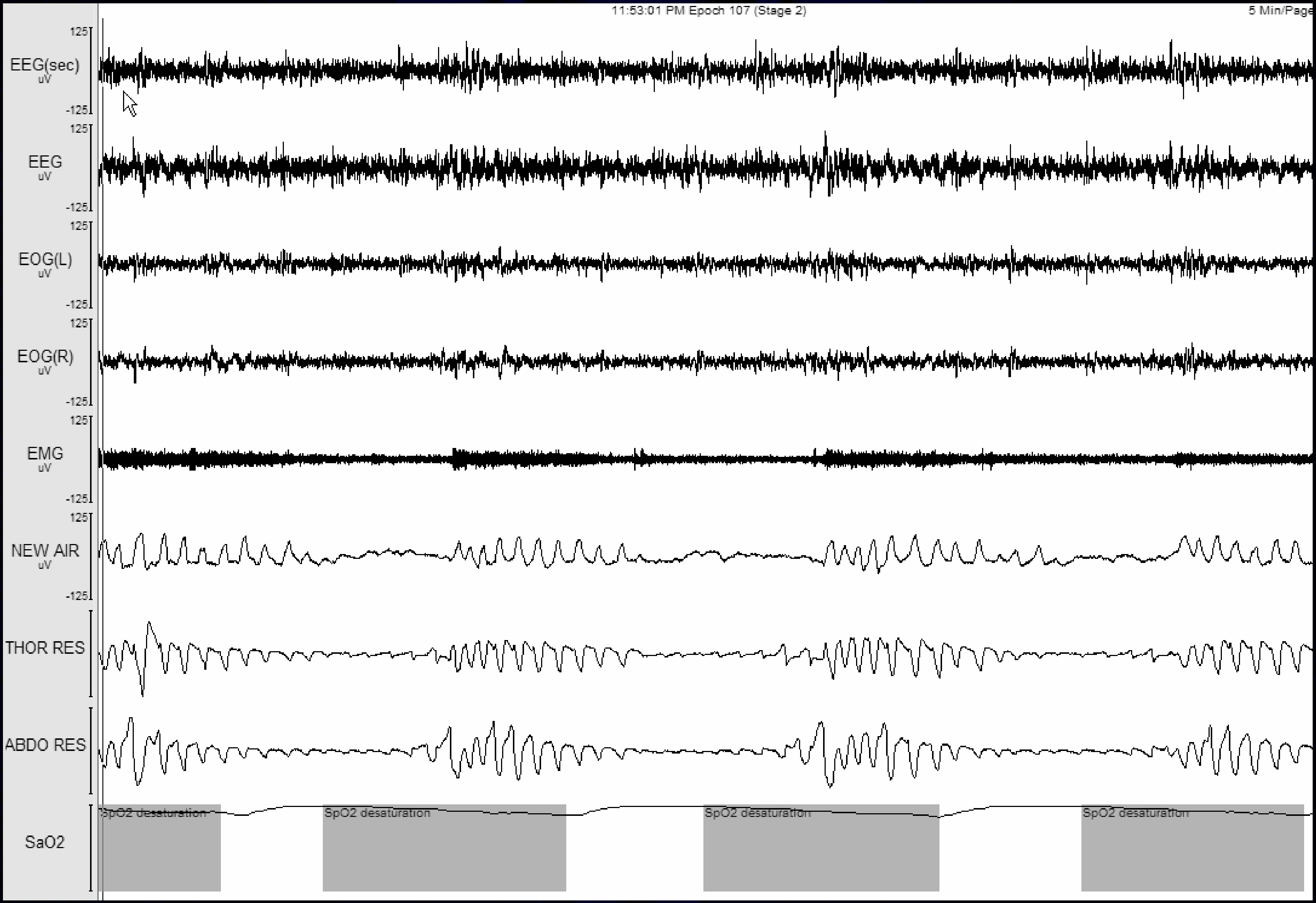
Mechanisms and Consequences of Sleep Apnea and Periodic Breathing:

Insights From Modeling of Chemoreflex Control of Ventilation

Eugene Bruce

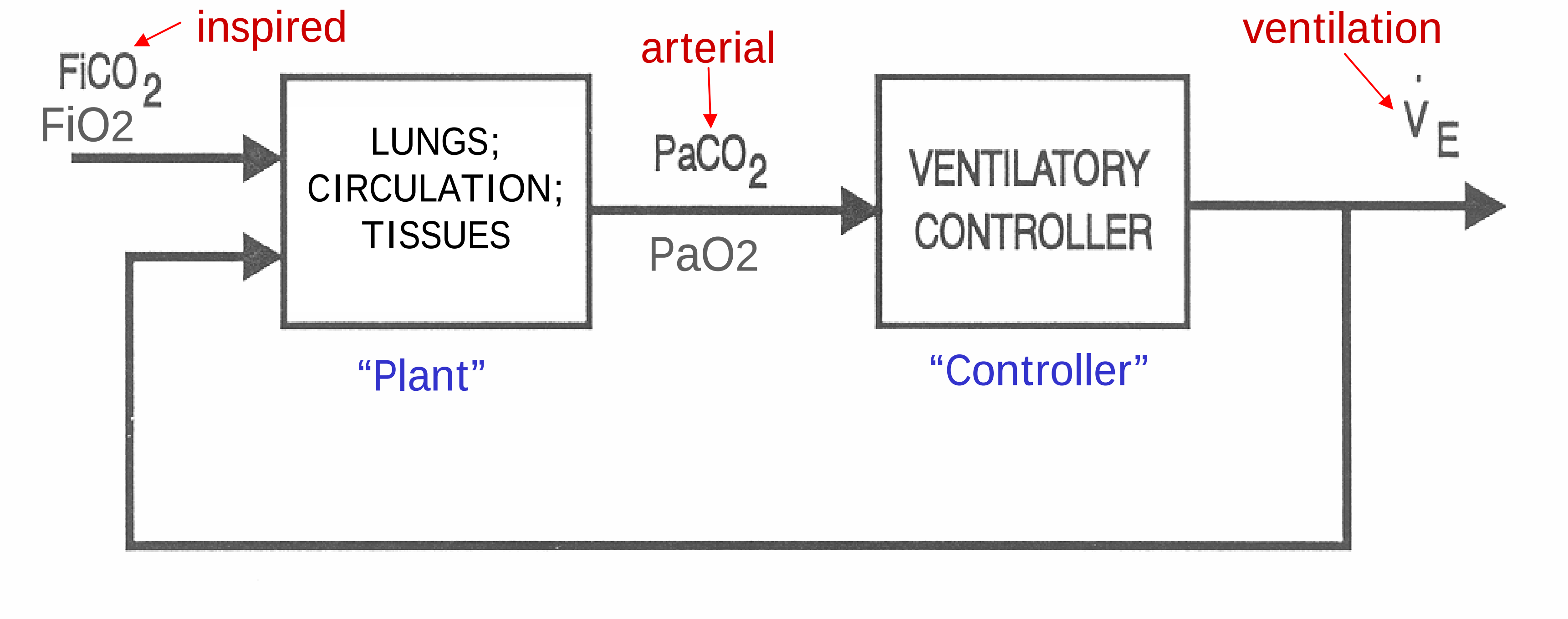
Center for Biomedical Engineering
University of Kentucky

Abnormal Oscillation in Ventilation: Periodic Breathing



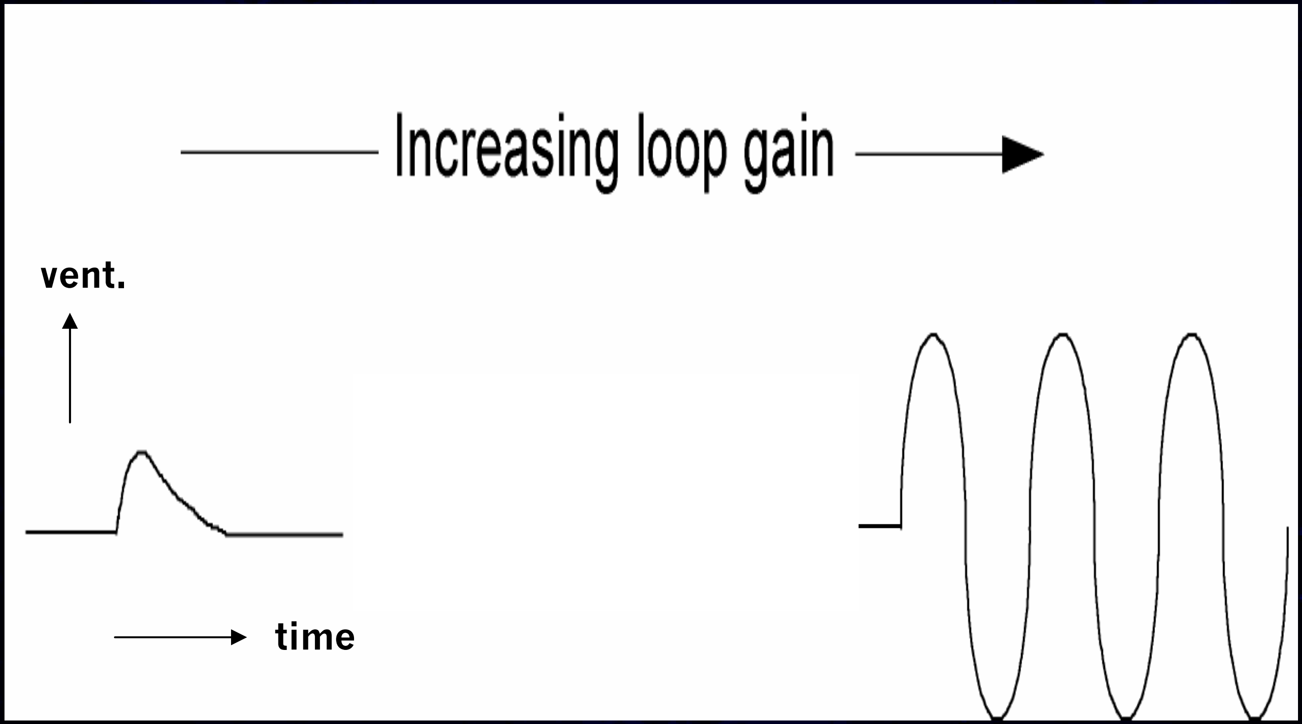
Sleep Heart Health Study: female, age 75

Chemoreflex Feedback Control of Ventilation

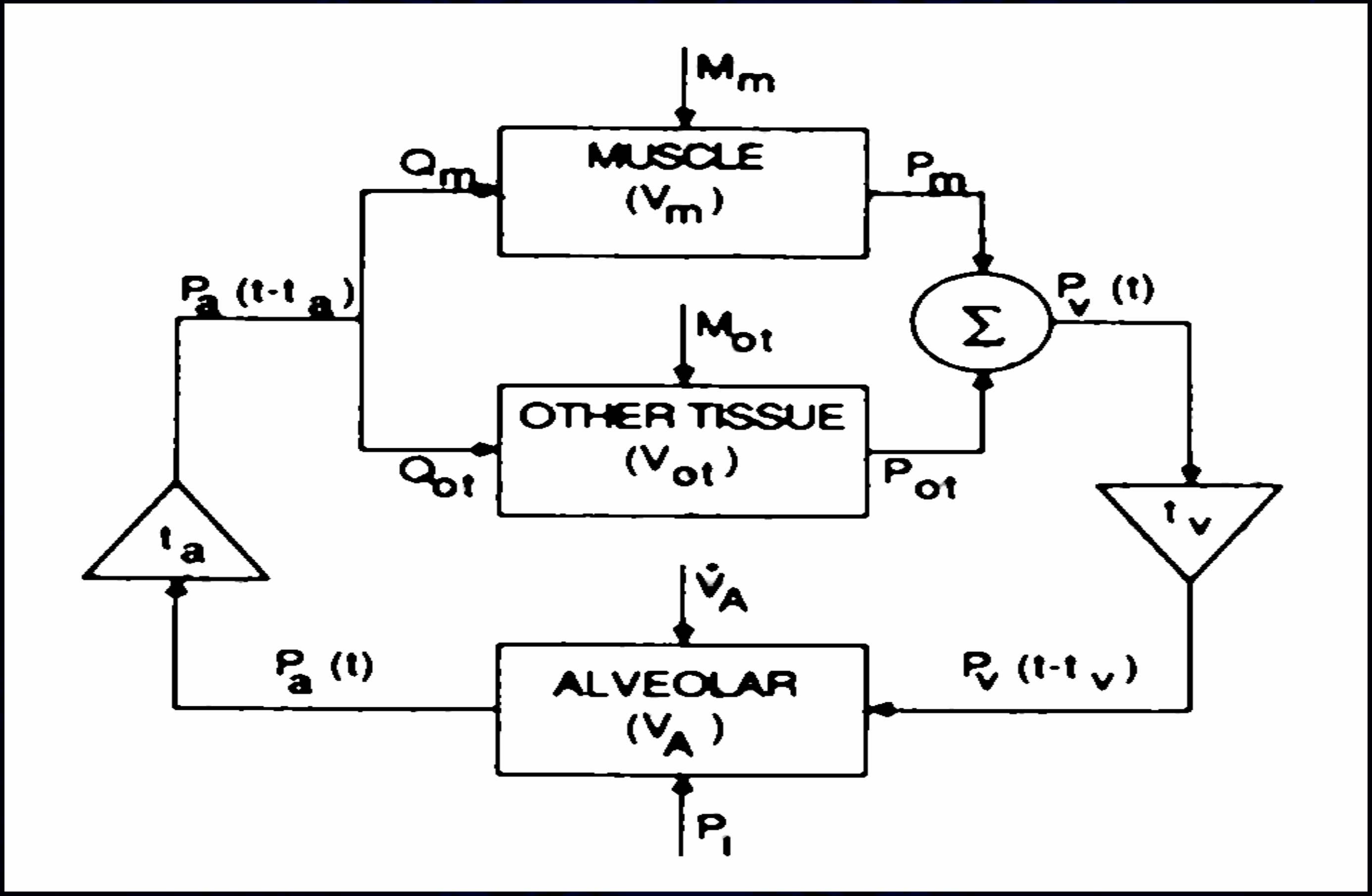


The Central Dogma of Periodic Breathing

Ventilatory response to a brief disturbance to $PaCO_2$ becomes oscillatory when chemoreflex loop gain is “large enough”



3-Compartment "Plant" Model for CO2



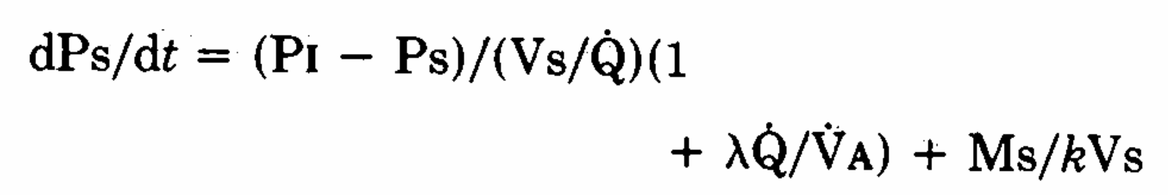
$$V_A\,dP_A/dt = \dot{V}_A(P_I - P_A) + \lambda Q[P_v^* - P_a]$$

$$V_m\,dP_m/dt = M_m/k + Q_m[P_a^* - P_m]$$

$$V_{ot}\,dP_{ot}/dt = M_{ot}/k + Q_{ot}[P_a^* - P_{ot}].$$

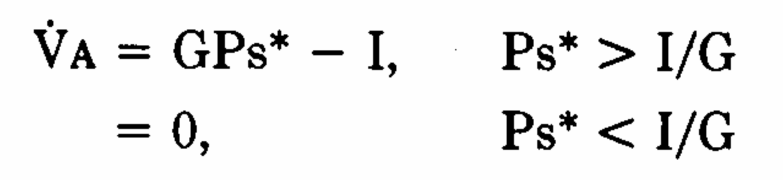
El Hefnawy, et al., Annals BME 16:445, 1988

Reduced Model (6 Parameters)



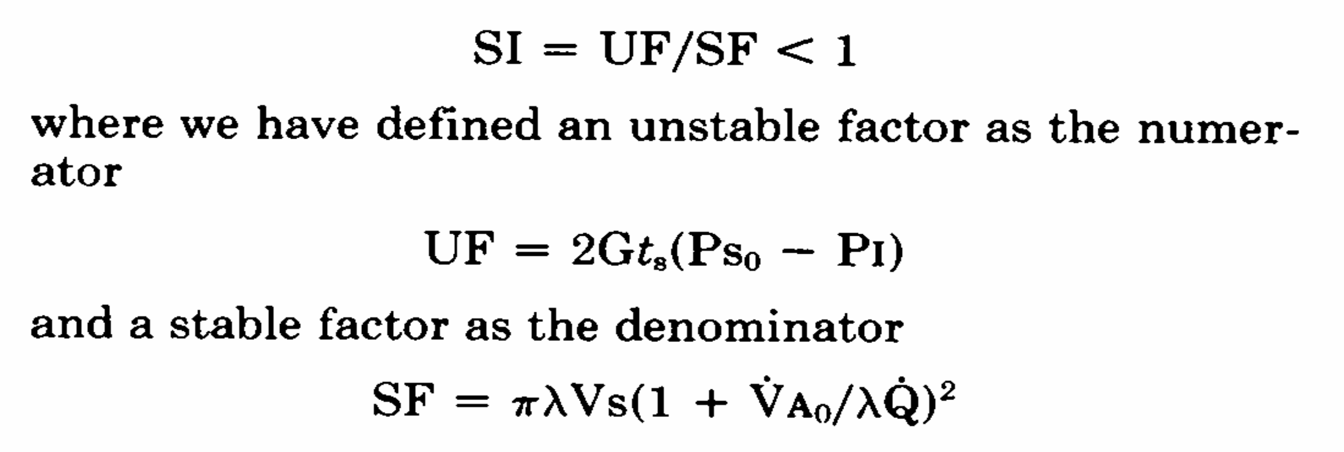
$$dP_S/dt = (P_I - P_S)/(V_S/\dot{Q})(1 + \lambda\dot{Q}/\dot{V}_A) + M_S/kV_S$$

Controlled System



$$\begin{aligned} \dot{V}_A &= GP_S^* - I, && P_S^* > I/G \\ &= 0, && P_S^* < I/G \end{aligned}$$

Ventilation Controller



$$SI = UF/SF < 1$$

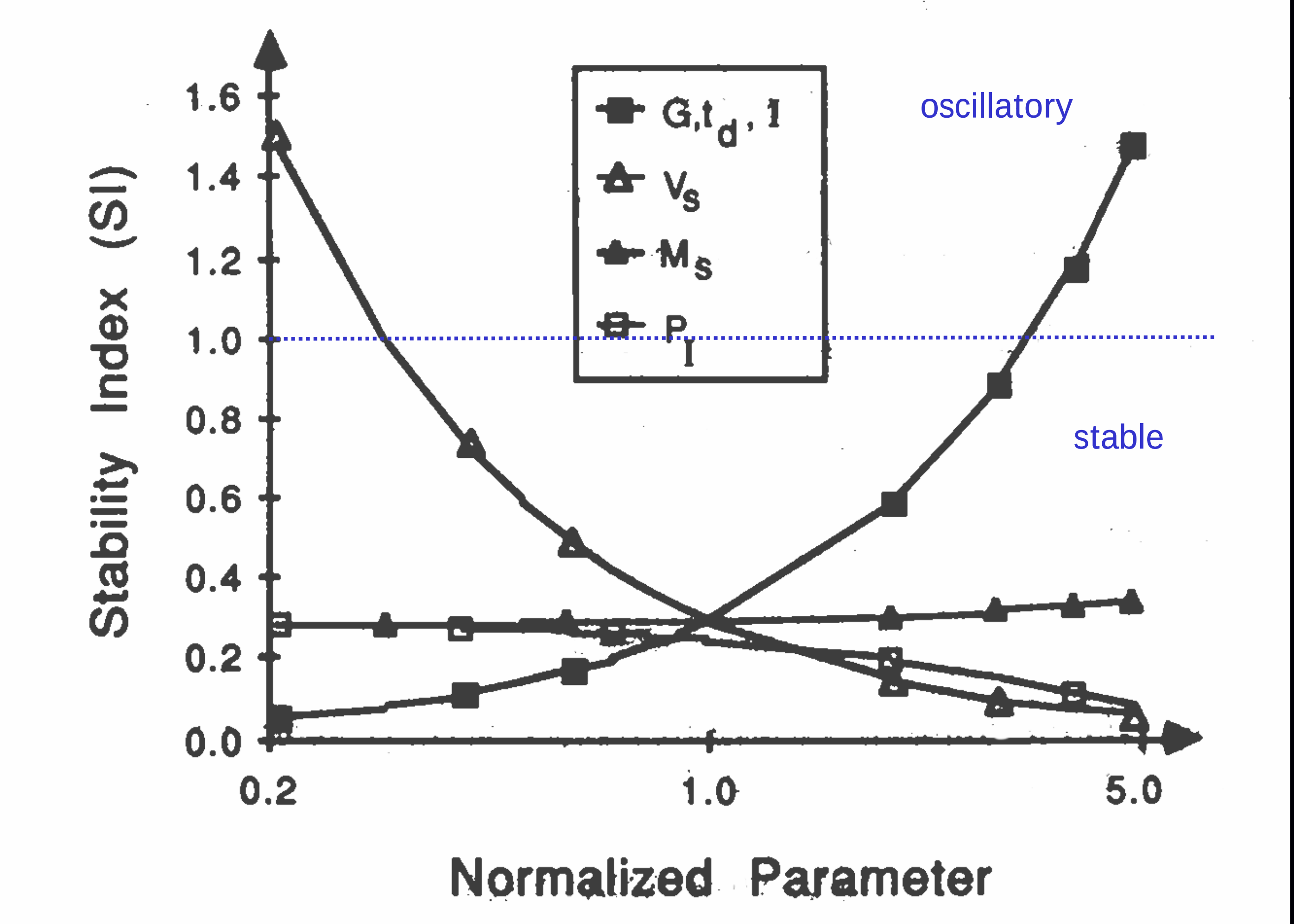
where we have defined an unstable factor as the numerator

$$UF = 2Gt_s(P_{S_0} - P_I)$$

and a stable factor as the denominator

$$SF = \pi\lambda V_S(1 + \dot{V}_{A_0}/\lambda\dot{Q})^2$$

Parameter Dependence of Ventilatory Oscillations: Reduced Model



El Hefnawy, et al., Annals BME 16:445, 1988

Conclusions

The model is qualitatively correct, but. . .

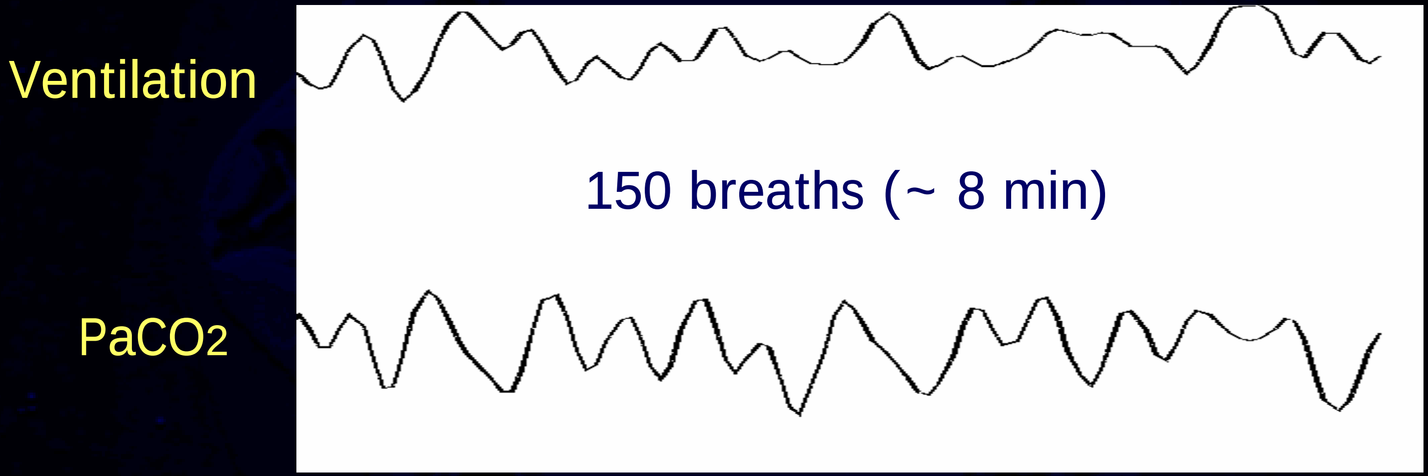
. . . the quantitative errors are significant (errors in plant model may be magnified by model reduction), and . . .

. . . one cannot easily evaluate even these 6 parameters in individual subjects.

Therefore, this approach (reducing a complex model) is most suitable for illustrating general principles.

Experimental Observation

Ventilation normally exhibits low-amplitude, irregular oscillations.



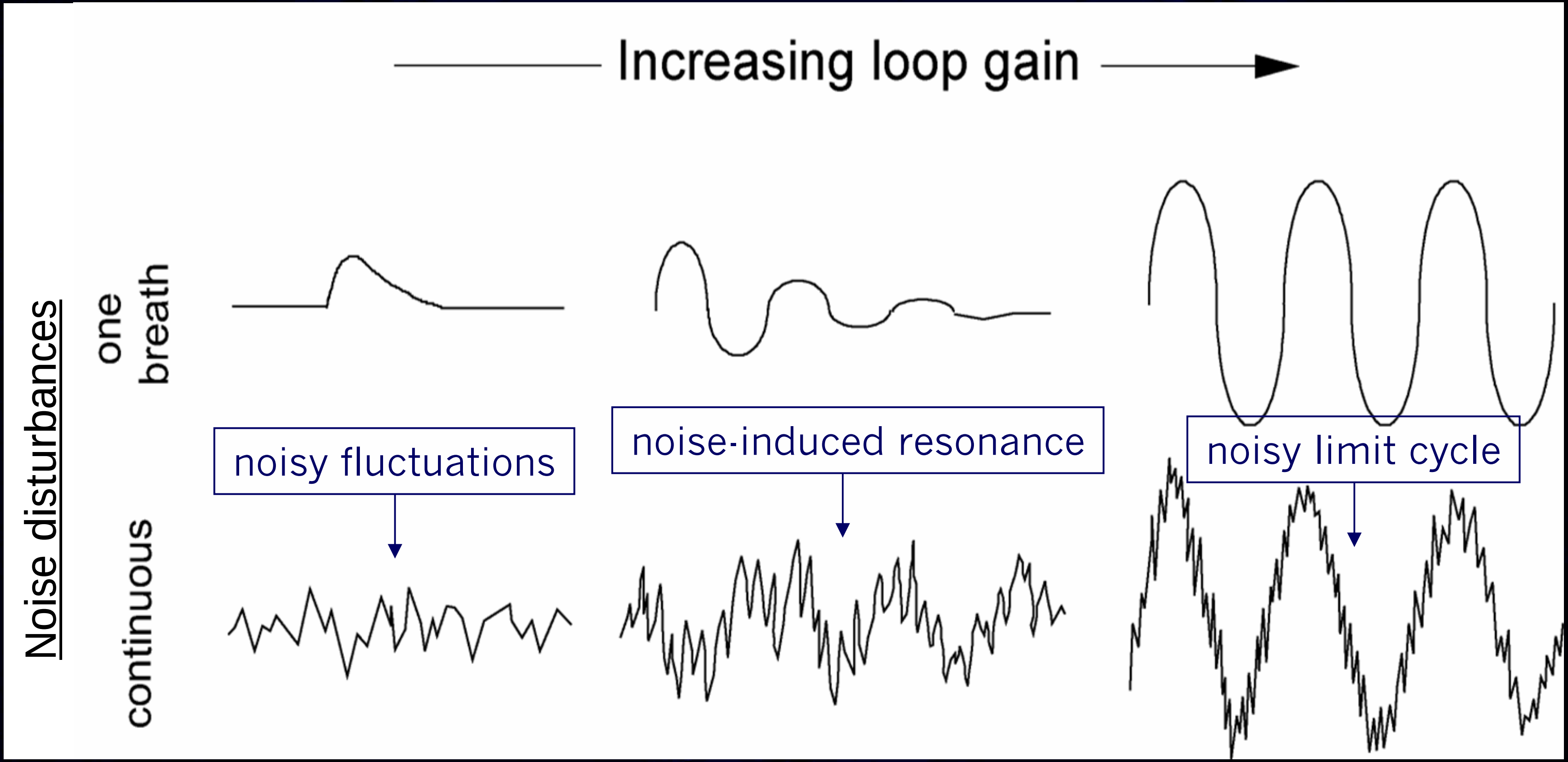
Fundamental Question

Do low-amplitude oscillations in ventilation represent an early stage of disease before frank periodic breathing occurs?

The (Expanded) Central Dogma of Periodic Breathing

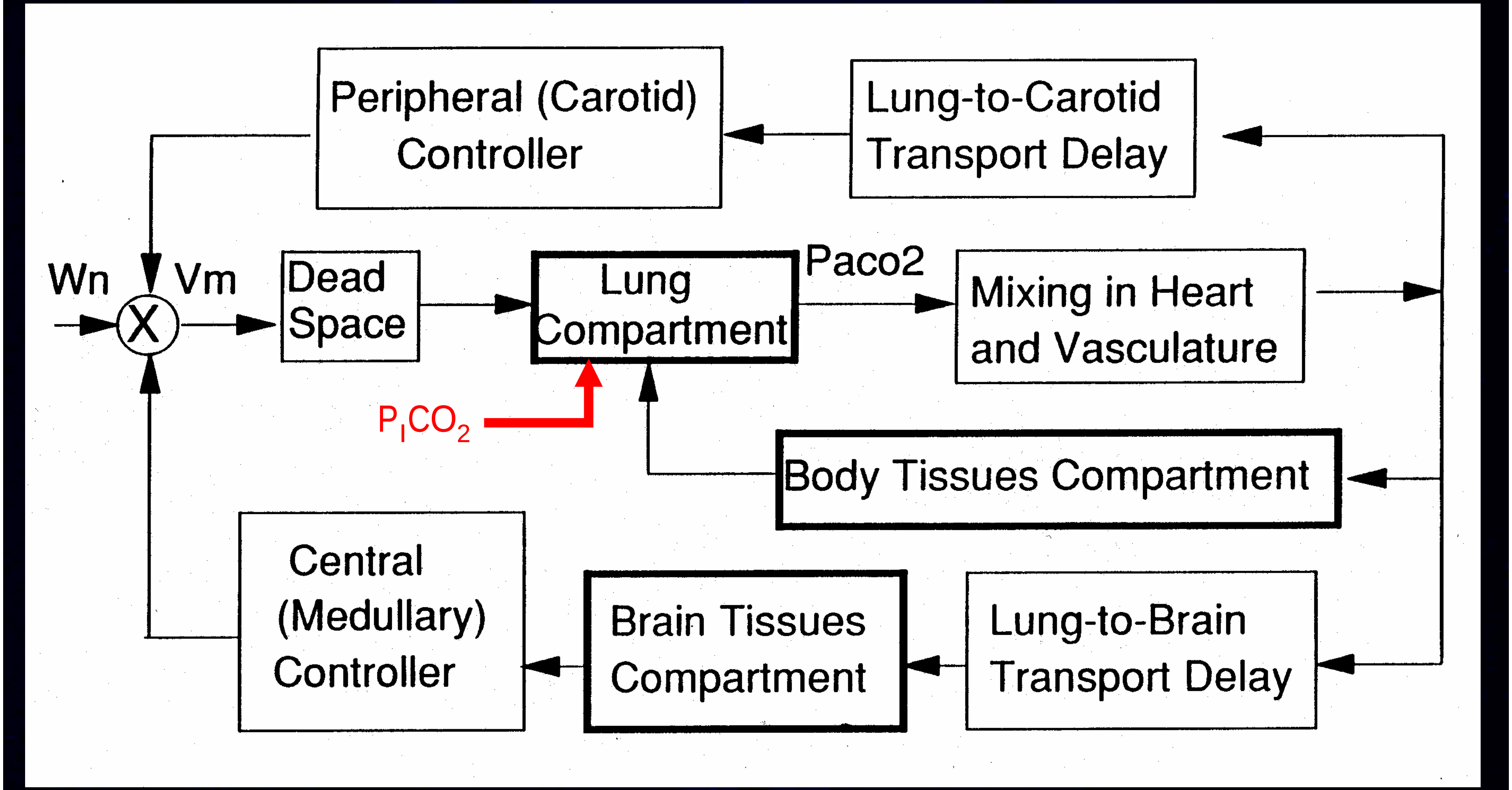
Ventilatory response to a brief disturbance to PaCO2 becomes oscillatory when chemoreflex loop gain is "large enough", and . . .

. . . small amplitude oscillations can be due to noise-induced resonance



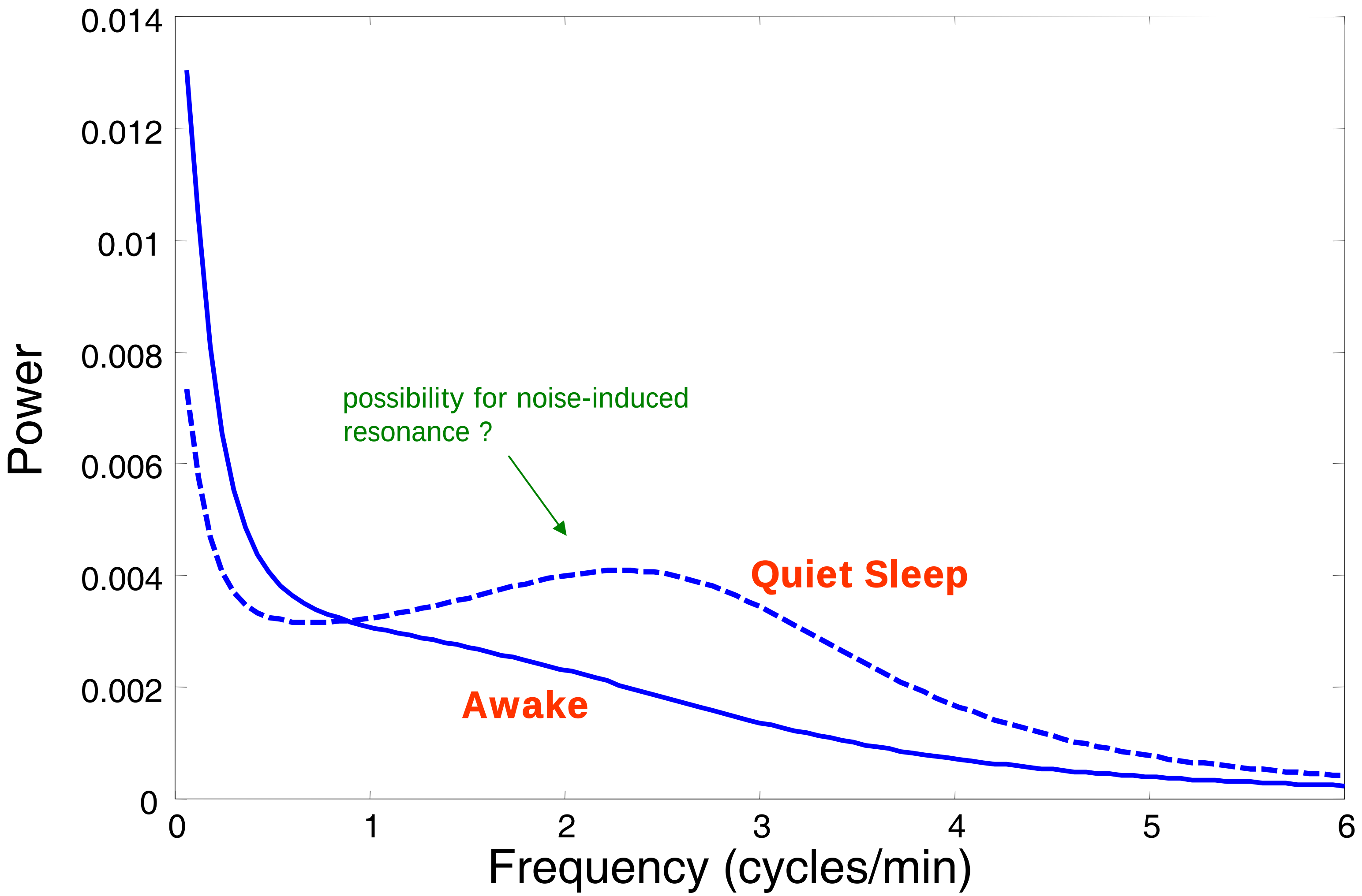
Can one characterize the ventilatory stability of individual subjects based on their ventilatory responses to noise?

Feasibility Studies: Noise-Induced Ventilatory "Oscillations" in a Model of Chemoreflex Control of Breathing



COMPUTATIONAL PREDICTIONS

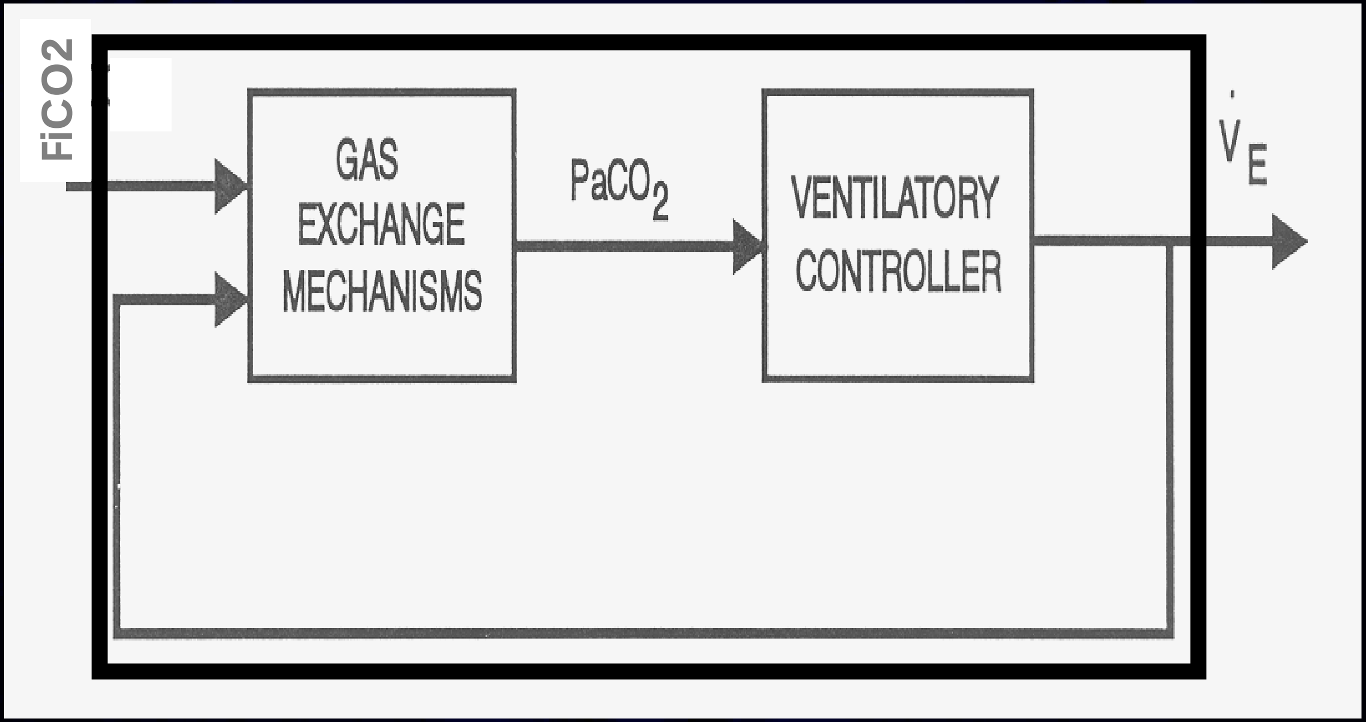
Spectrum of V_A Awake and in Quiet Sleep:
P_ICO_2 = Unit-Variance White Noise



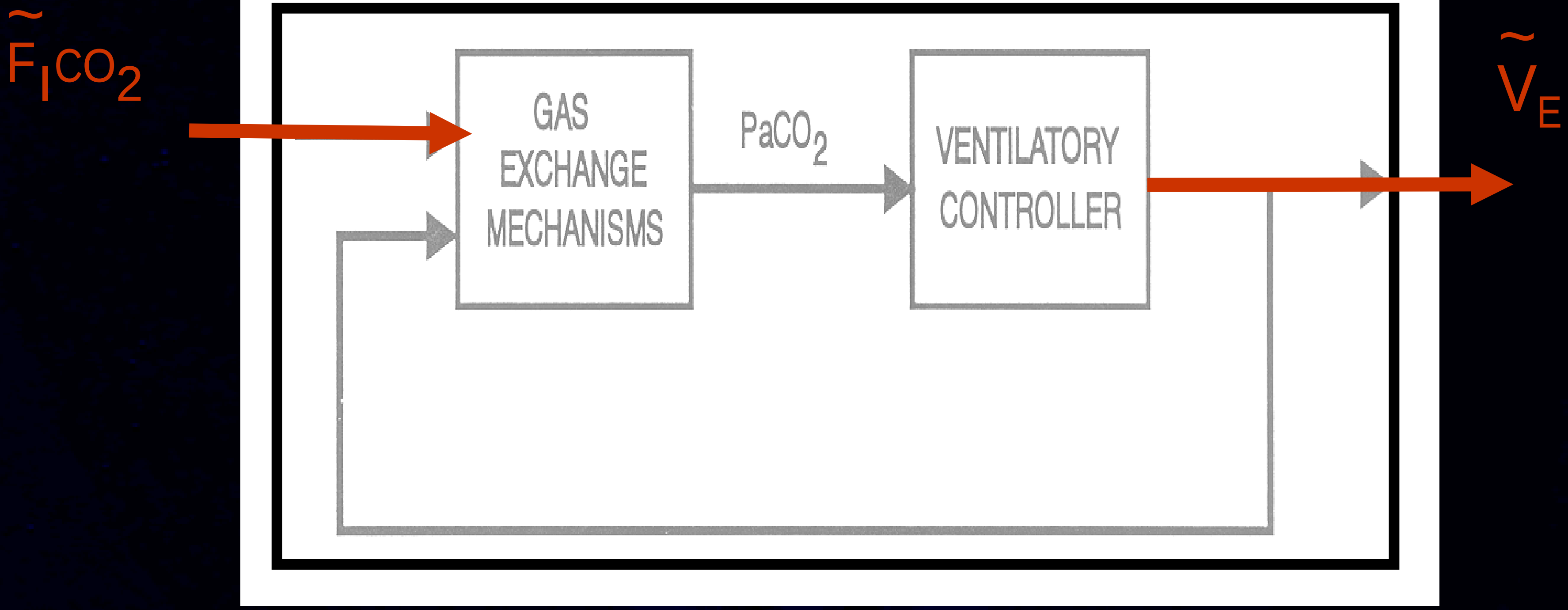
possibility for noise-induced resonance ?

Concern: Is the shape of the power spectrum determined only by our applied stimulus?

A “black box” modeling approach will relate the ventilatory response to the applied CO_2 stimulus

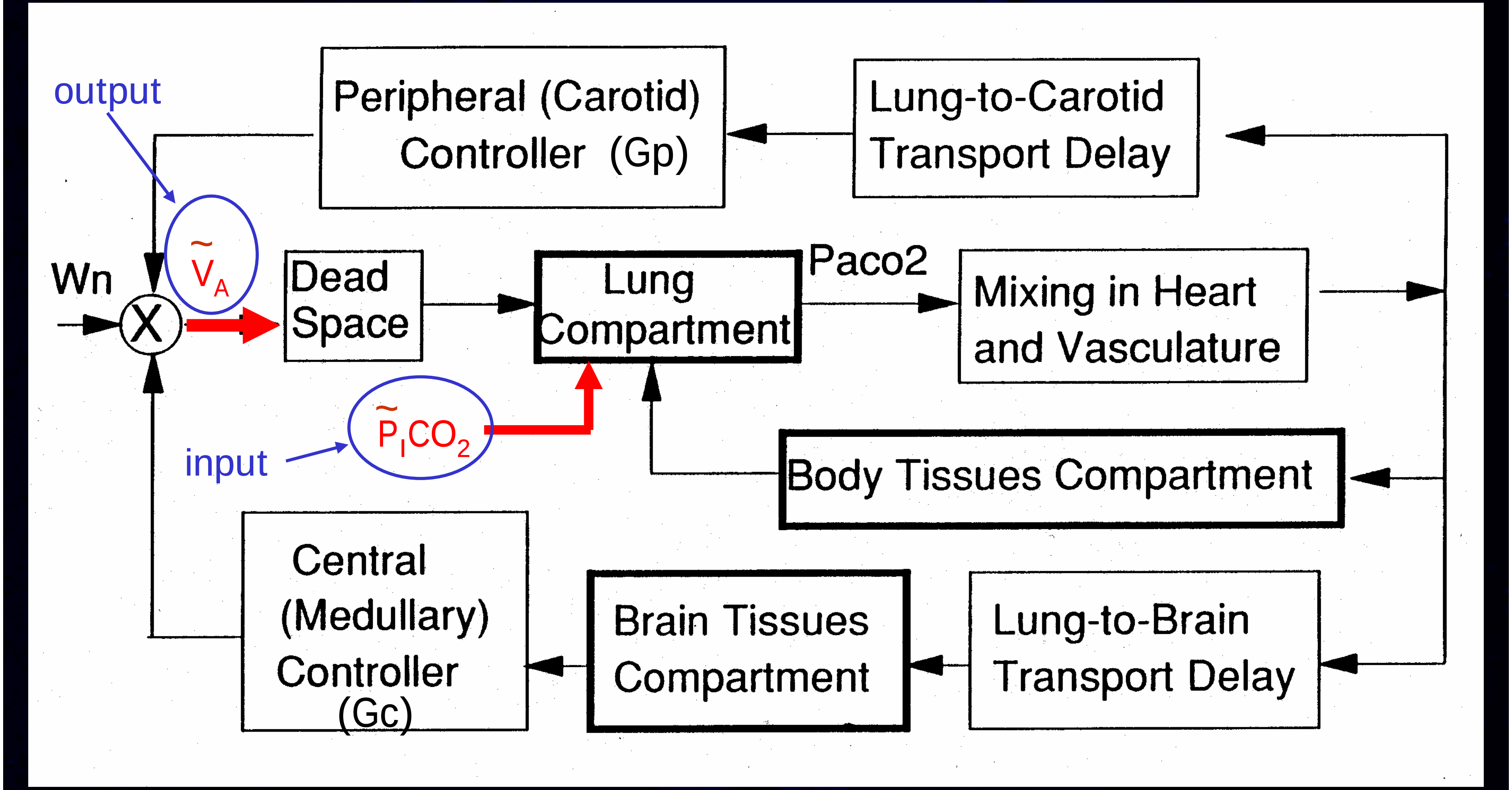


This approach provides a means of assessing stability of feedback control of ventilation in individual subjects

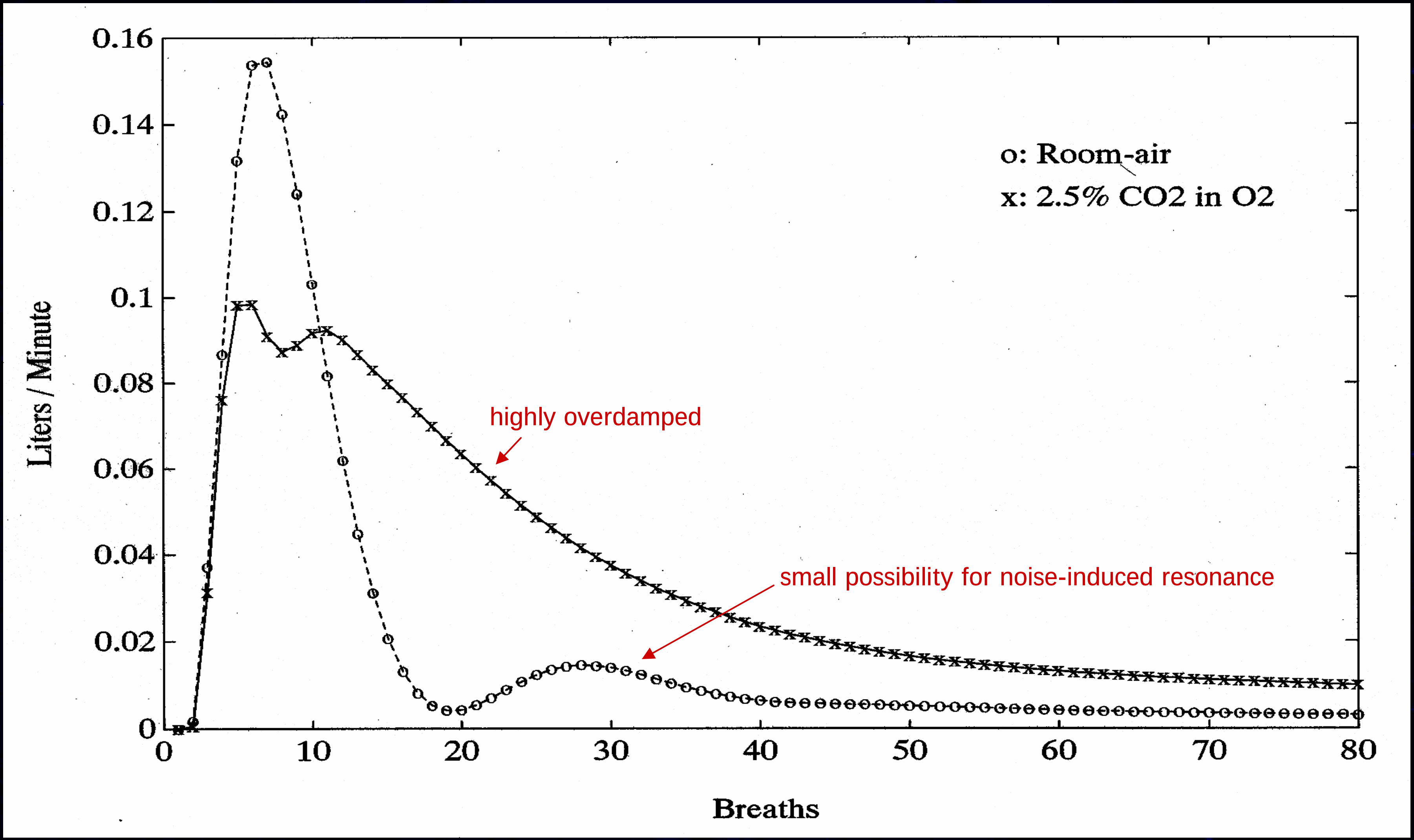


Apply $\tilde{F}_I CO_2$, measure resulting $\tilde{V}_E$, and estimate transfer function (or impulse response) of the “black box”.

Simulation Studies of Feasibility Using a Mechanistic Model



Impulse Responses of Ventilation: Model-based Predictions (Random PICO2 Stimulus)

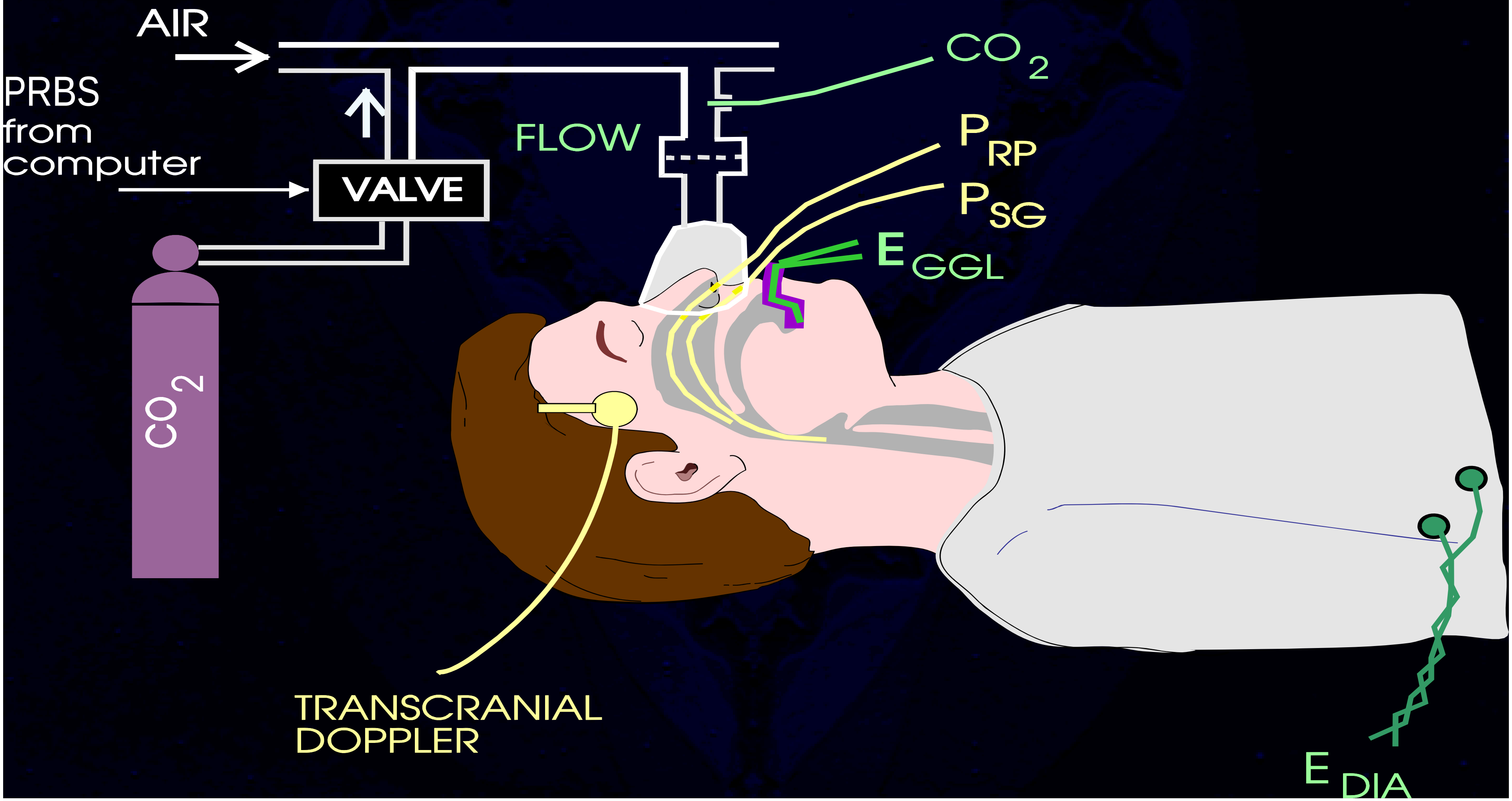


highly overdamped

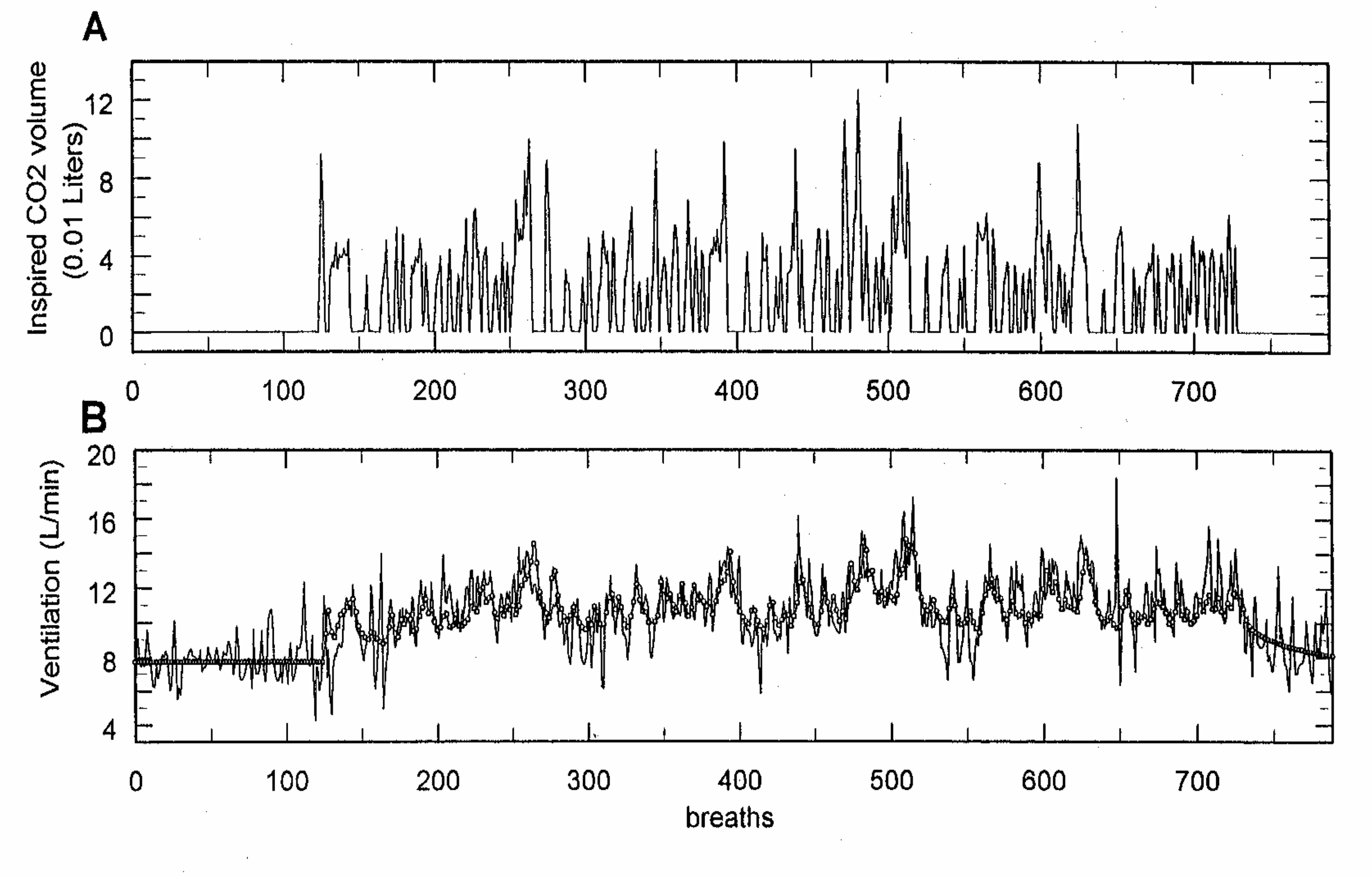
small possibility for noise-induced resonance

Modarreszadeh, M., and Bruce. *J. Appl. Physiol.*, 72: 242, 1992

Assessing Stability of Feedback Control of Ventilation Using Pseudorandom Variations in Inspired CO2

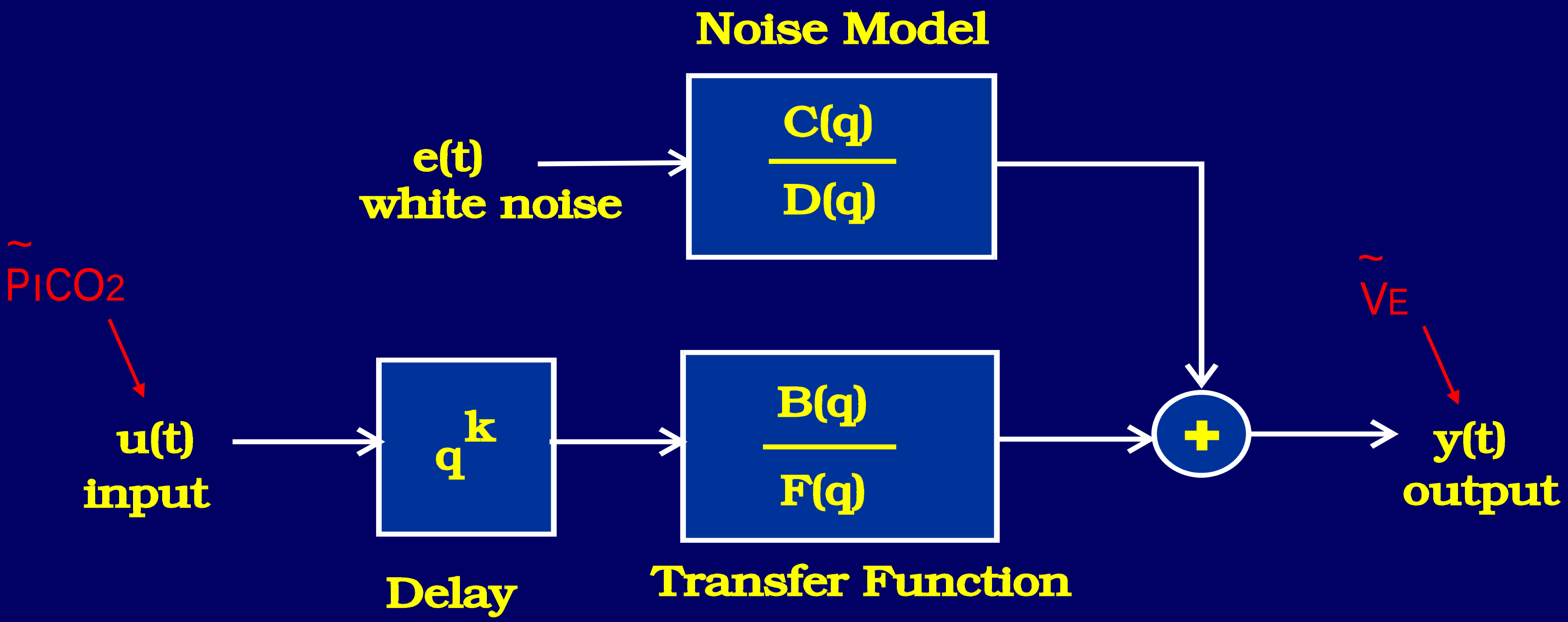


Example Data: Human, PRBS CO2 Stimulation



Lai and Bruce, *J. Appl. Physiol.* 83: 466, 1997

Box-Jenkins Model Structure for Transfer Function Estimation



Noise Model

e(t)
white noise

$\frac{C(q)}{D(q)}$

$\tilde{P}_{ICO_2}$

u(t)
input

q^k

Delay

$\frac{B(q)}{F(q)}$

Transfer Function

+

$\tilde{V}_E$

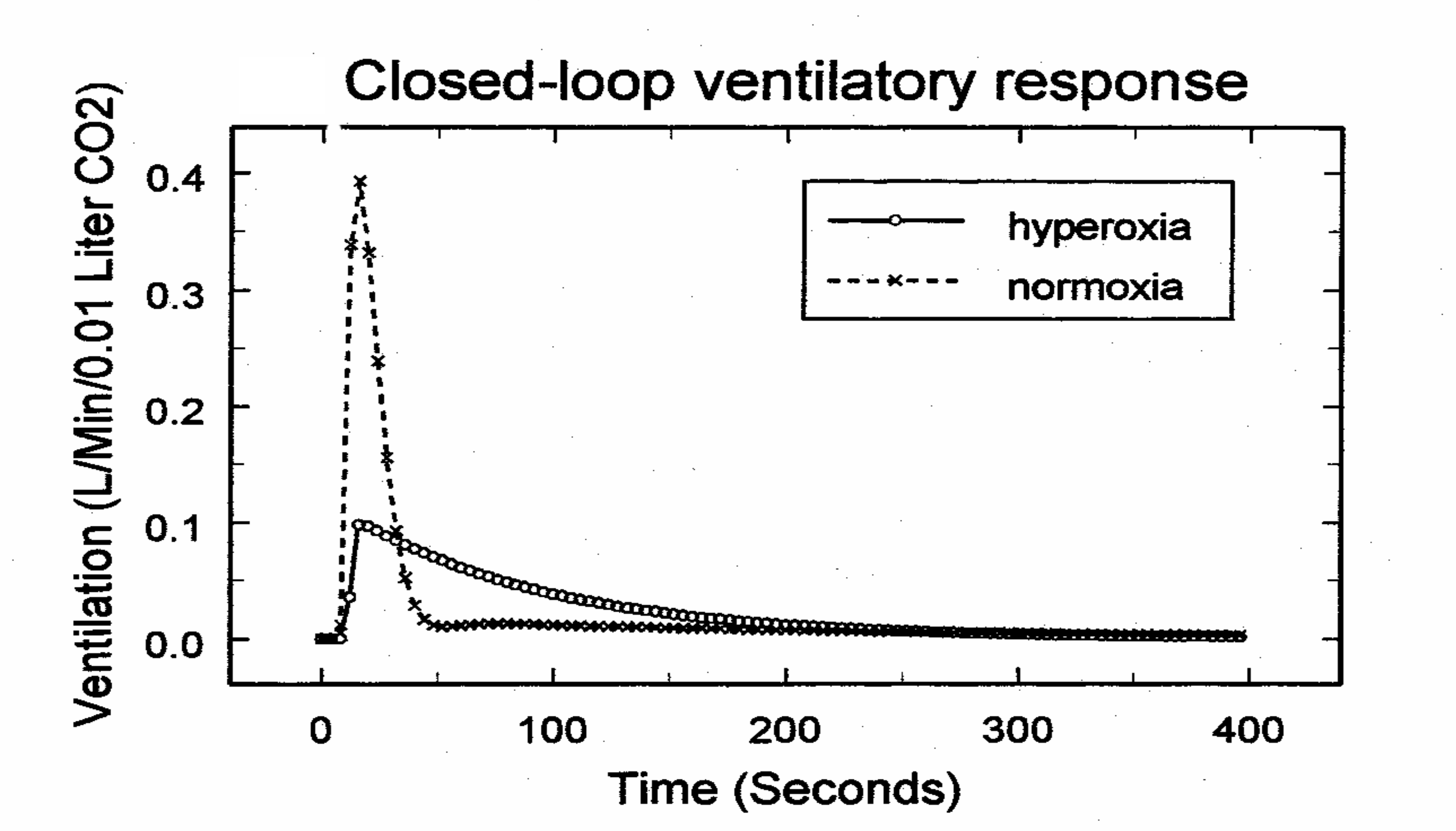
y(t)
output

Prediction equation:

$$y(t) = [B(q)/F(q)] * u(t-k) + [C(q)/D(q)] * e(t)$$

EXPERIMENTAL DATA (NORMAL SUBJECTS)

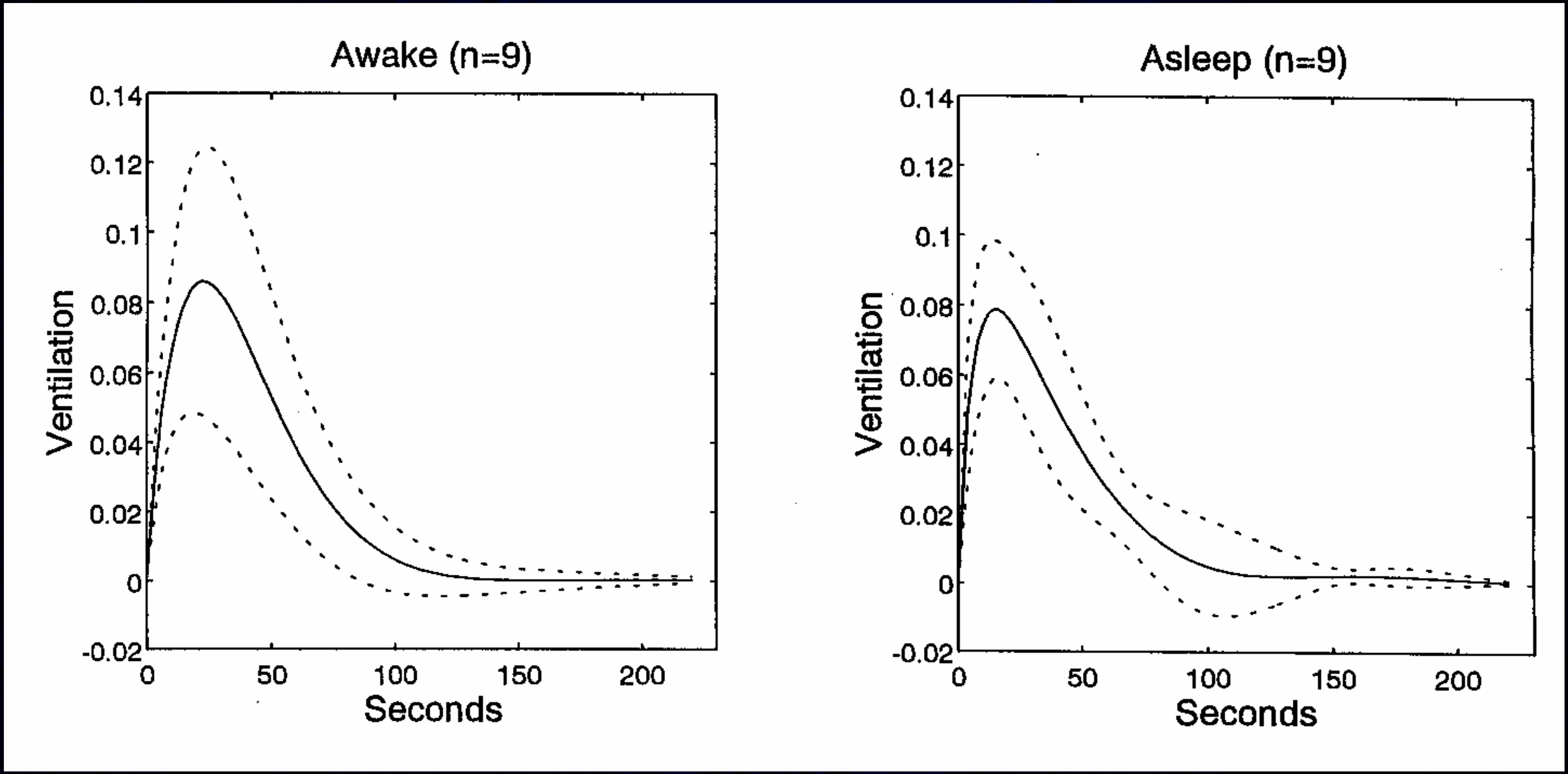
Impulse Responses of Ventilation Estimated from PRBS CO2 Data: Room Air and Hyperoxia



Lai and Bruce, *J. Appl. Physiol.* 83: 466, 1997

EXPERIMENTAL DATA (NORMAL SUBJECTS)

Ventilation Impulse Responses to CO2 Awake and in Quiet Sleep

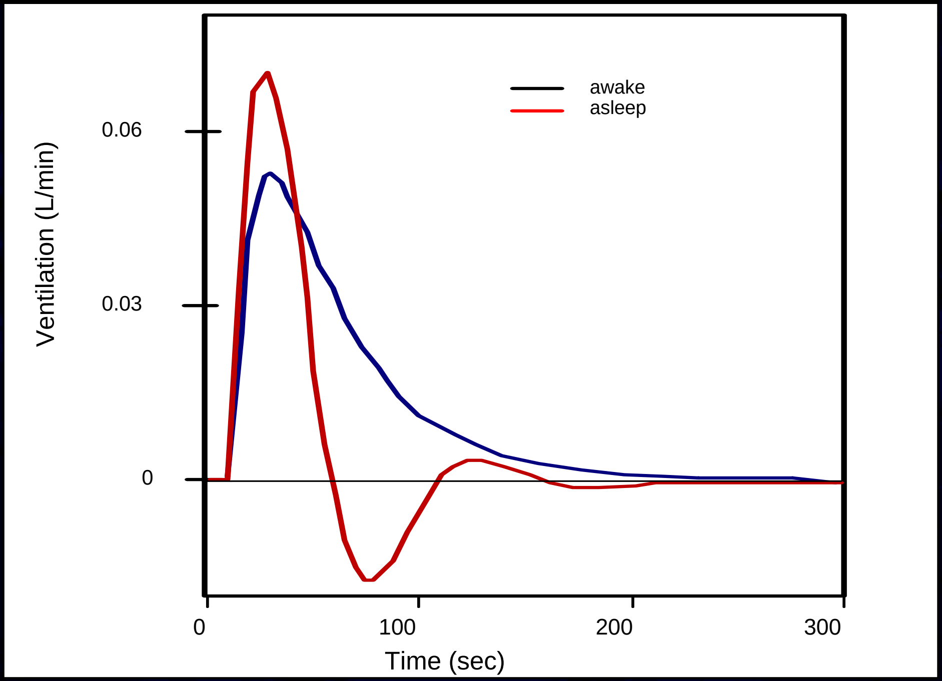


Conclusions: (1) No evidence for noise-induced oscillations in ventilation in QS.

(2) Changes in the plant in sleep must offset changes in the controller.

Modarreszadeh, et al., *J. Appl. Physiol.* 79: 1071, 1995

Ventilation Impulse Response to CO2: Elderly Subject



The impulse response to hyperoxic CO_2 stimulation in humans is more oscillatory in:

1. Awake COPD patients than in normal subjects
2. Awake CHF patients than in normal subjects
3. Sleeping elderly normals than in young normals

Conclusion: Mechanistic models of ventilatory control should carefully consider details of the “plant” mechanisms.

The Need to Improve Modeling of Oxygen Transport and Storage in Ventilatory Control Models

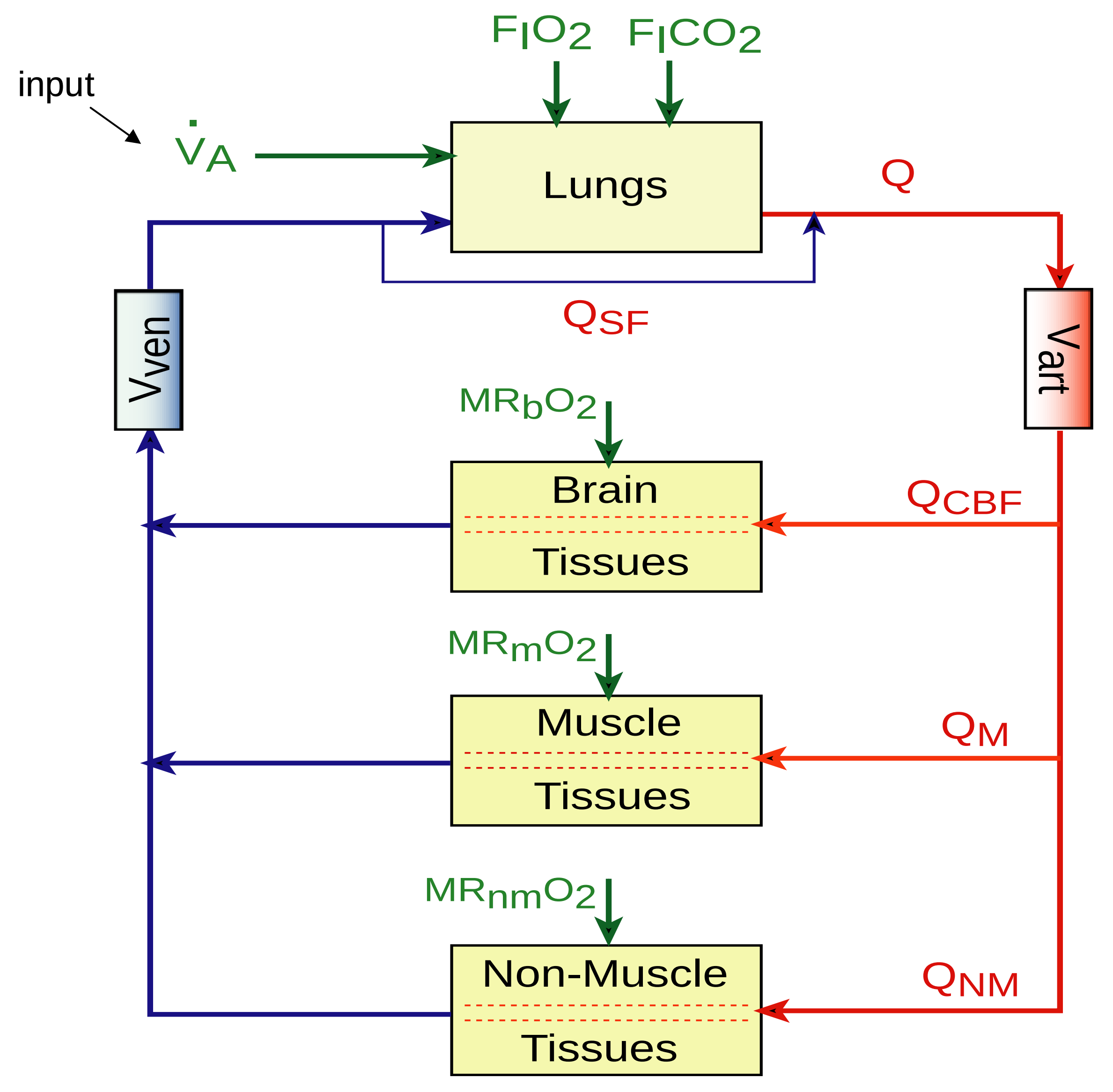
- Ventilatory stability is strongly dependent on the size and accessibility of O_2 stores

  Lungs: ~300 ml (less during hypoventilation)
  HbO2: ~450 ml @75% Sat (~300 ml readily accessible)
  MbO2: ~90 ml

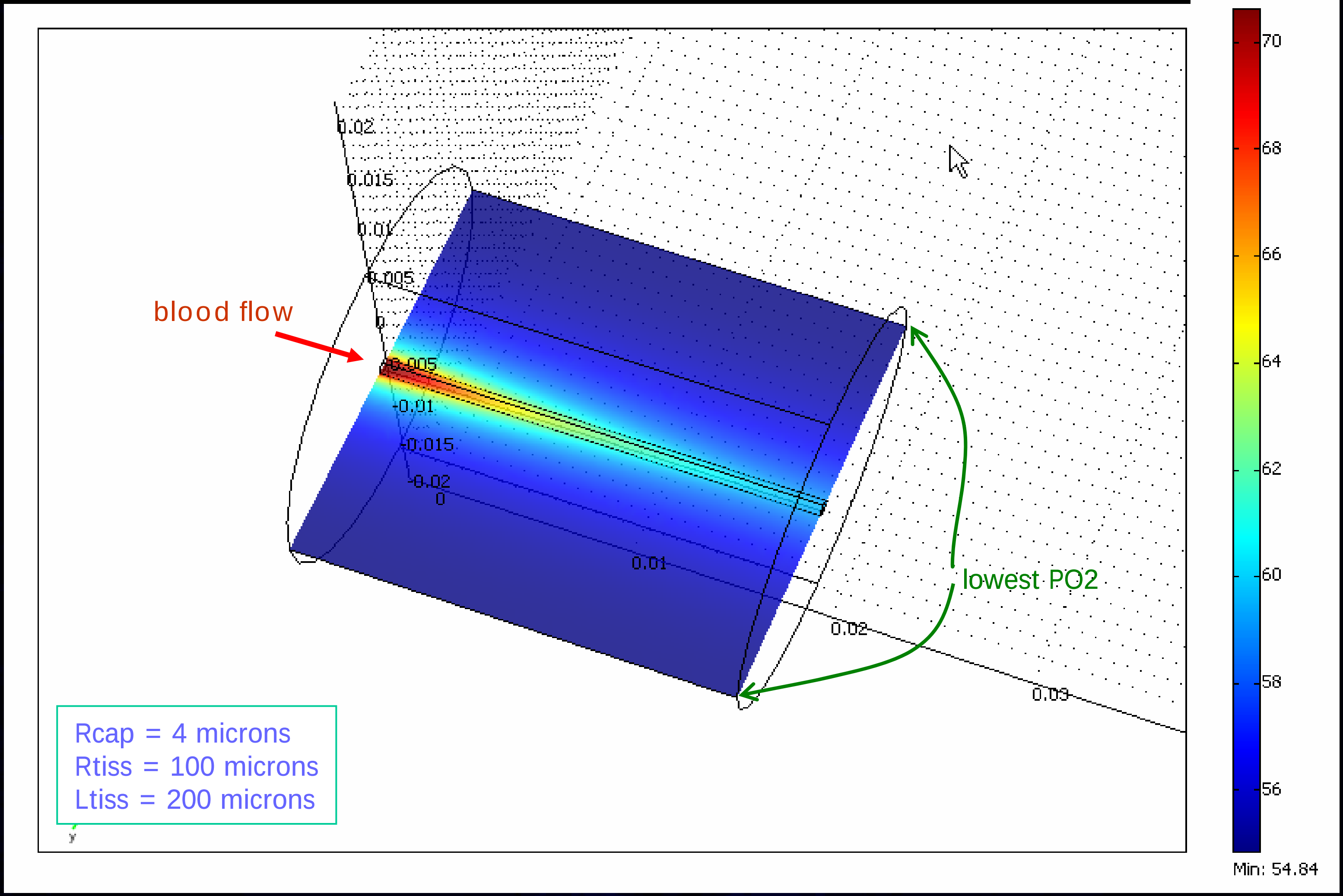
- Ventilatory control (and other neural functions) can be modulated by brain hypoxia

- In order to model and predict brain O_2 level, we need to model uptake and storage of O_2 in muscle correctly

Prediction of Oxygen Delivery to the Brain and Other Tissues: Physiological Structure of "Plant" Model



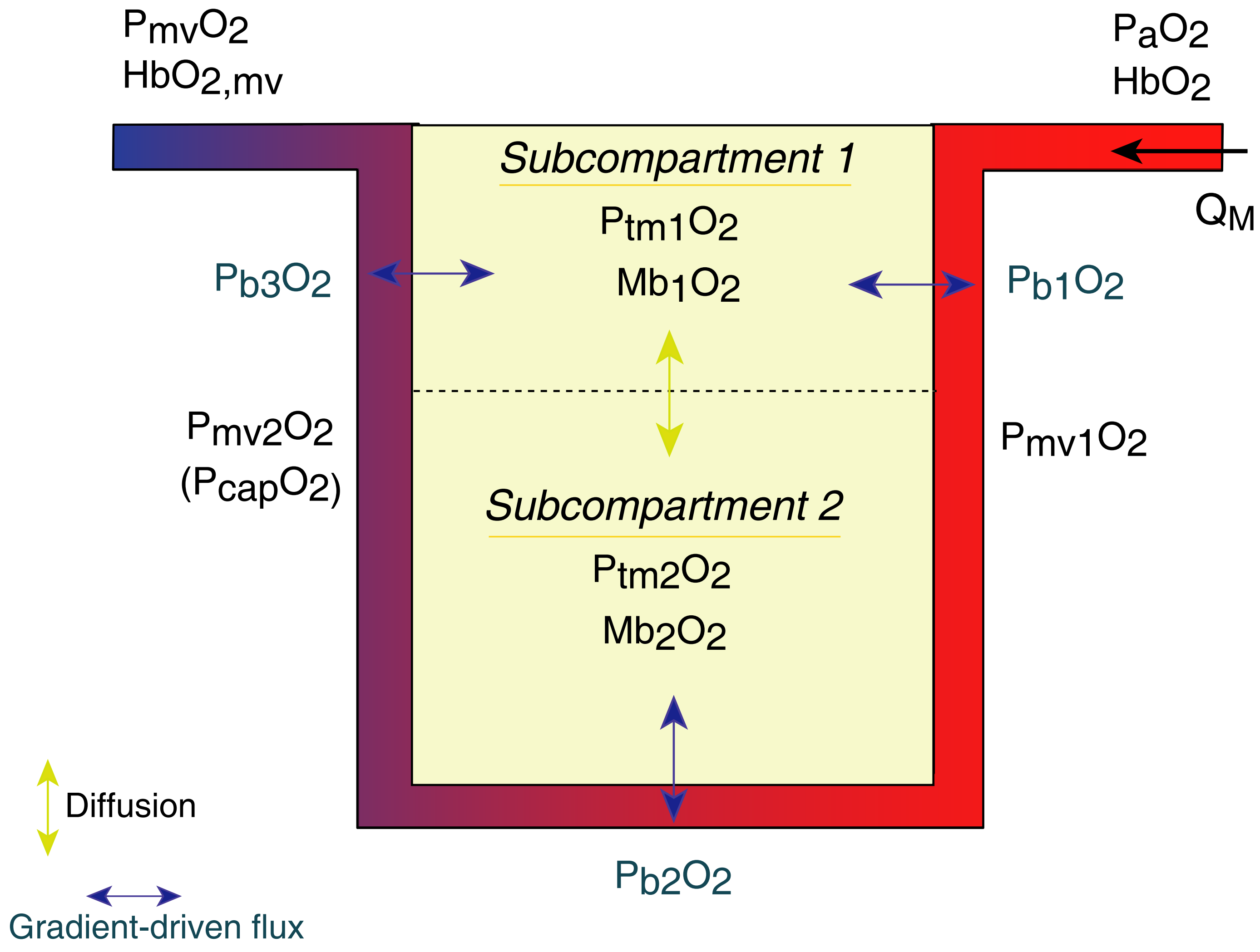
Finite-Element Solution of 3-D Krogh Cylinder Model of Muscle Tissue: Diffusion Within the Tissue Is Important



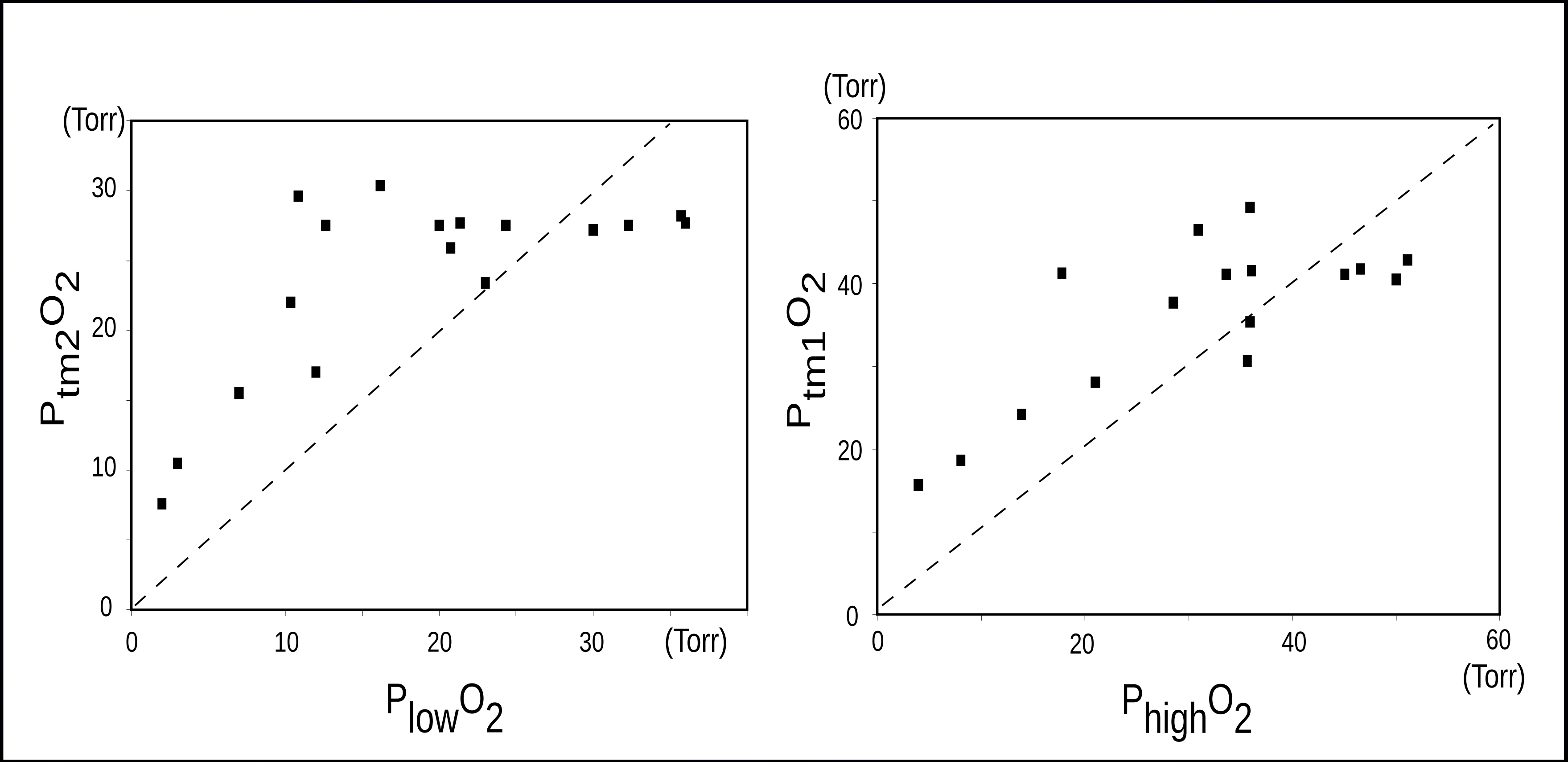
Rcap = 4 microns
Rtiss = 100 microns
Ltiss = 200 microns

Limitations: (i) vascular geometry is more complex; (ii) gas exchange with arterioles/venules not represented

Muscle Tissue Model With 2 Subcompartments



Comparison of Muscle PO2 from Model (Ptm1O2, Ptm2O2) with Experimental Data

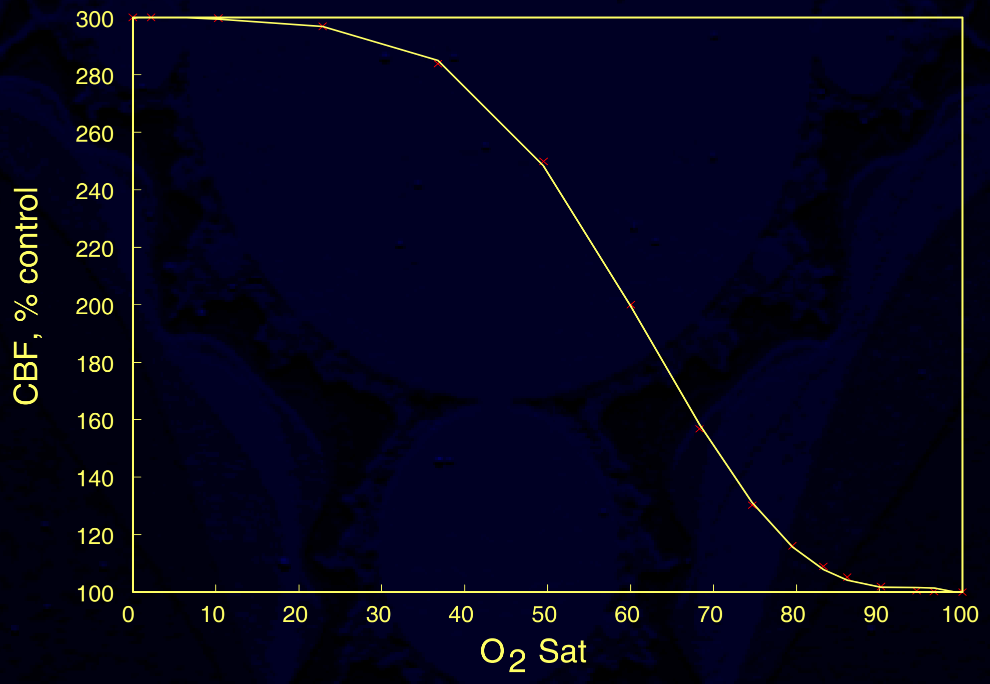


Brain Tissue Compartment With 2 Subcompartments

	UNITS	MEASURED	MODEL
MRO2 (GM)	ml O2/min/100 gm	5.7, 5.9	5.0
CBF (GM)	ml/min/100 gm	61, 69, 65.3, 62.0, 66.5	75
MRO2 (WM)	ml O2/min/100 gm	1.8, 1.43	
CBF (WM)	ml/min/100 gm	19, 21.4, 22.2	
MRO2 (G+W)	ml O2/min/100 gm	3.65, 3.2	
CBF (G+W)	ml/min/100 gm	55, 53.5	
PtO2 (GM)	Torr	5-15, 42, 7-42 (mean 23)	18, 32
PcapO2 (GM)	Torr		37.0
PtO2 (G+W)	Torr	10-40, 27-47, 12-48	
PvenuleO2 (G+W)	Torr	37.9, 40.9	
PvenuleO2 (GM)	Torr		31.5
PsagO2 (G+W)	Torr	43.5, 44-60	
PsagO2 (GM)	Torr		31.6
%HbO2, sag. (G+W)		68, 71.5	
%HbO2, sag. (GM)			63.4

Brain Tissue Compartment With 2 Subcompartments

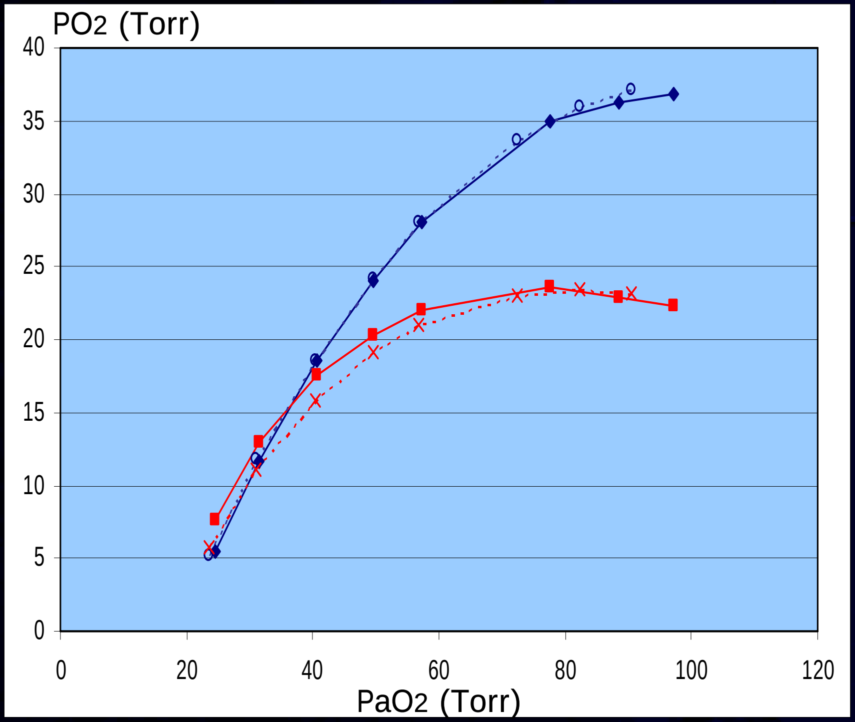
Cerebral blood flow dependence on arterial oxygen saturation



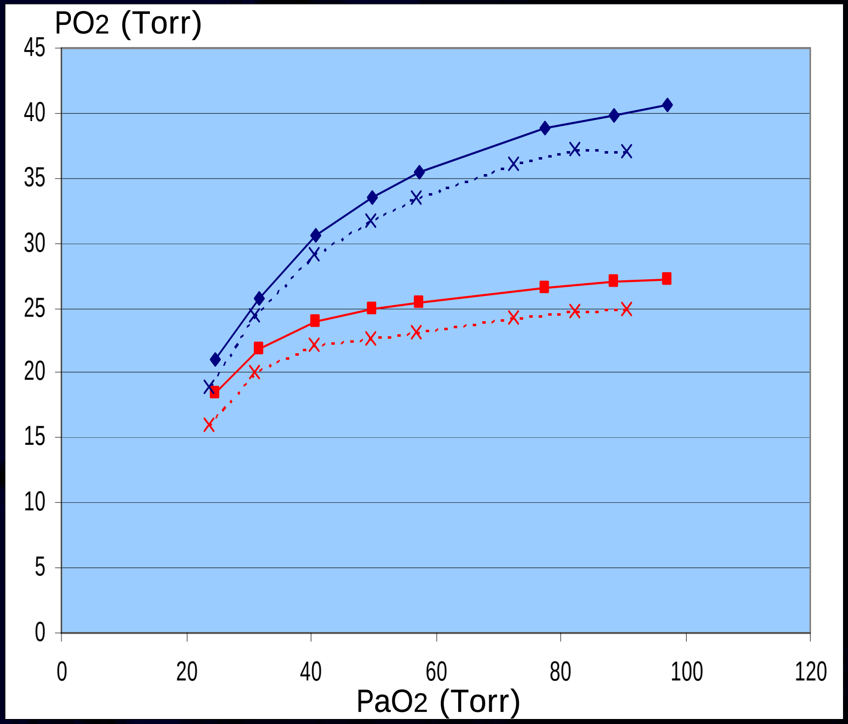
Brain MRO2, CBF, CBF dependence on O2 Sat and PaCO2, all decrease in sleep

Steady-state Effects of Hypoventilation on Brain and (Resting) Muscle Tissue PO2 Levels

Brain

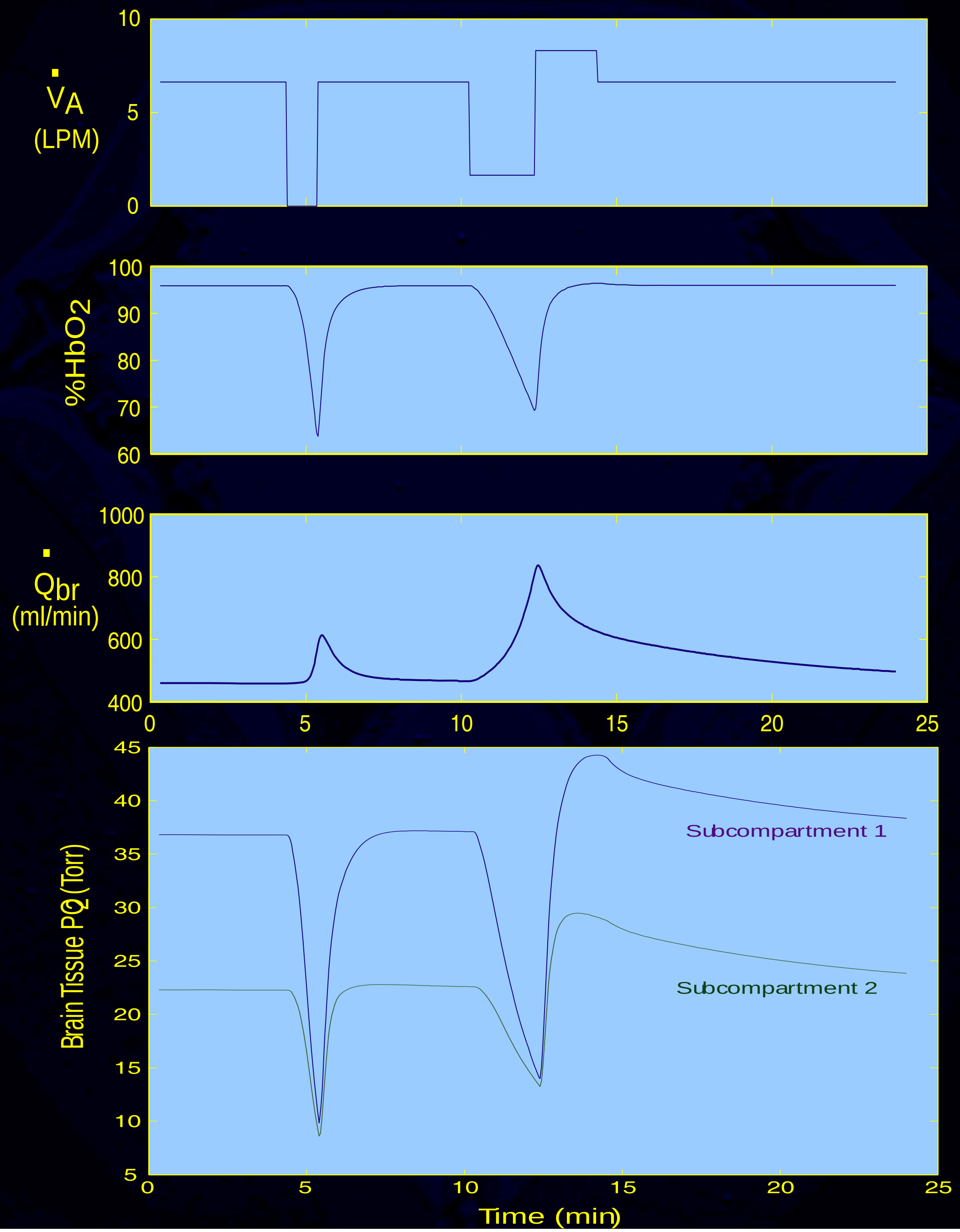


Muscle

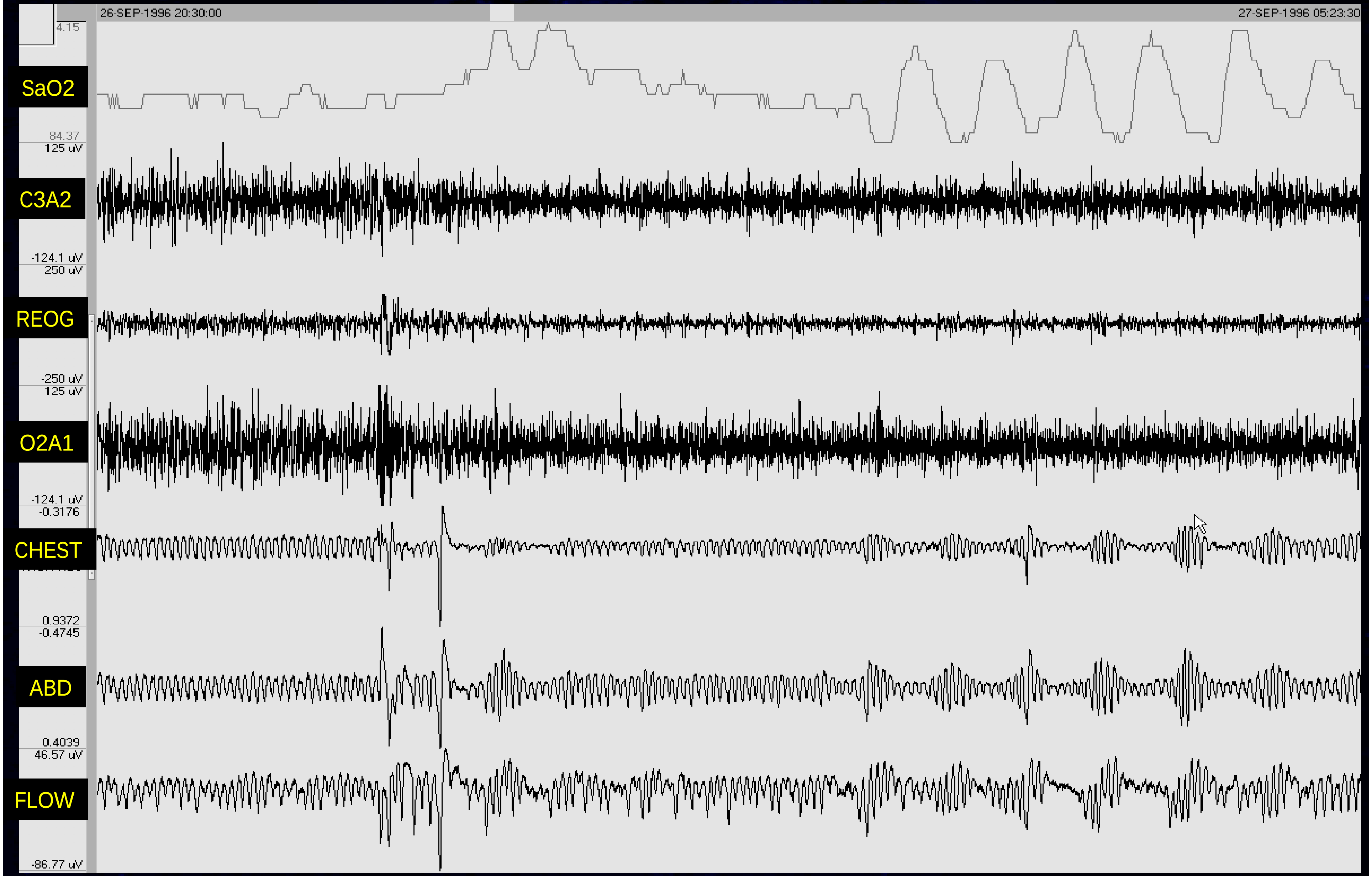


KEY	Wake	NREM
Subcompartment 1	———	- - -
Subcompartment 2	———	- - -

Response of Model to a Test Ventilatory Pattern

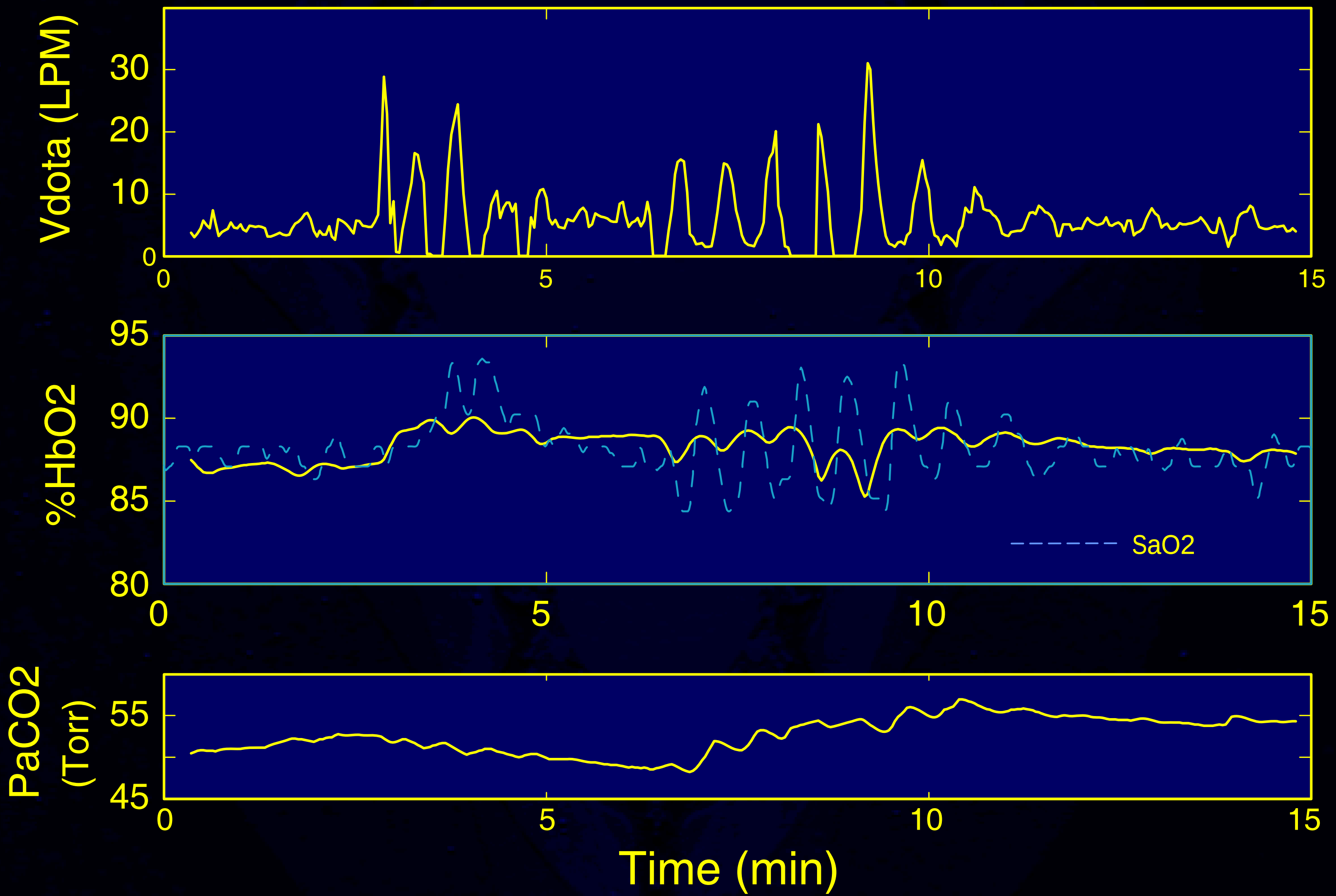


Periodic Breathing in Stage 2 Sleep

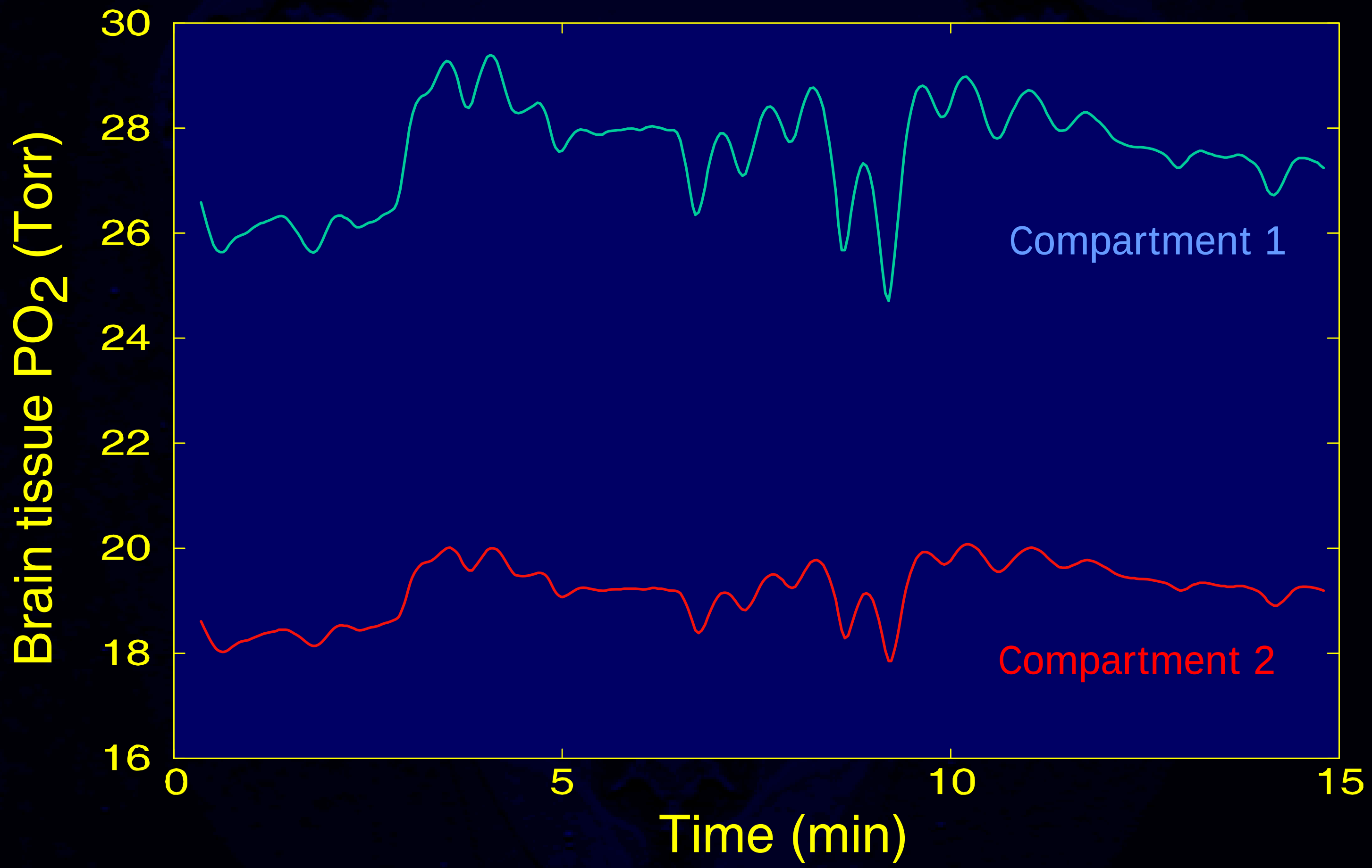


Sleep Heart Health Study: female, age 75

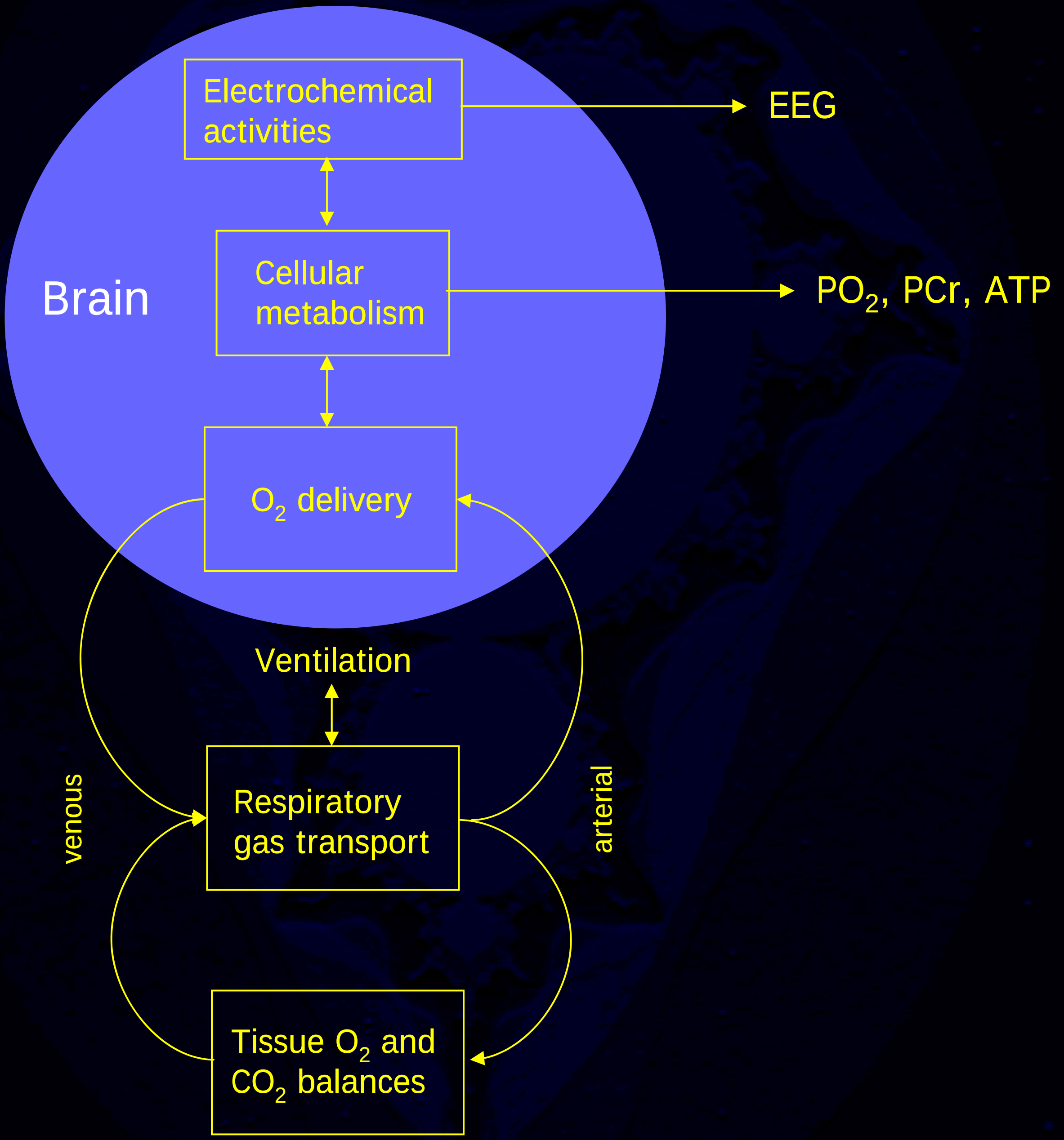
Arterial O2 and CO2 Levels Computed by Model When Driven by Subject's Measured Ventilation (Vdota, calculated from ABD/CHEST Signals)



Brain Tissue PO2 Levels Computed by Model When Driven by Subject's Measured Ventilation



Future Directions: Validation of Predicted Brain Hypoxia



Brain

Electrochemical activities → EEG

Cellular metabolism → PO_2, PCr, ATP

O_2 delivery

Ventilation

venous

arterial

Respiratory gas transport

Tissue O_2 and CO_2 balances