Models of Cheyne-Stokes Respiration with Cardiovascular Pathologies

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THE HUMAN CARDIO-VASCULAR SYSTEM

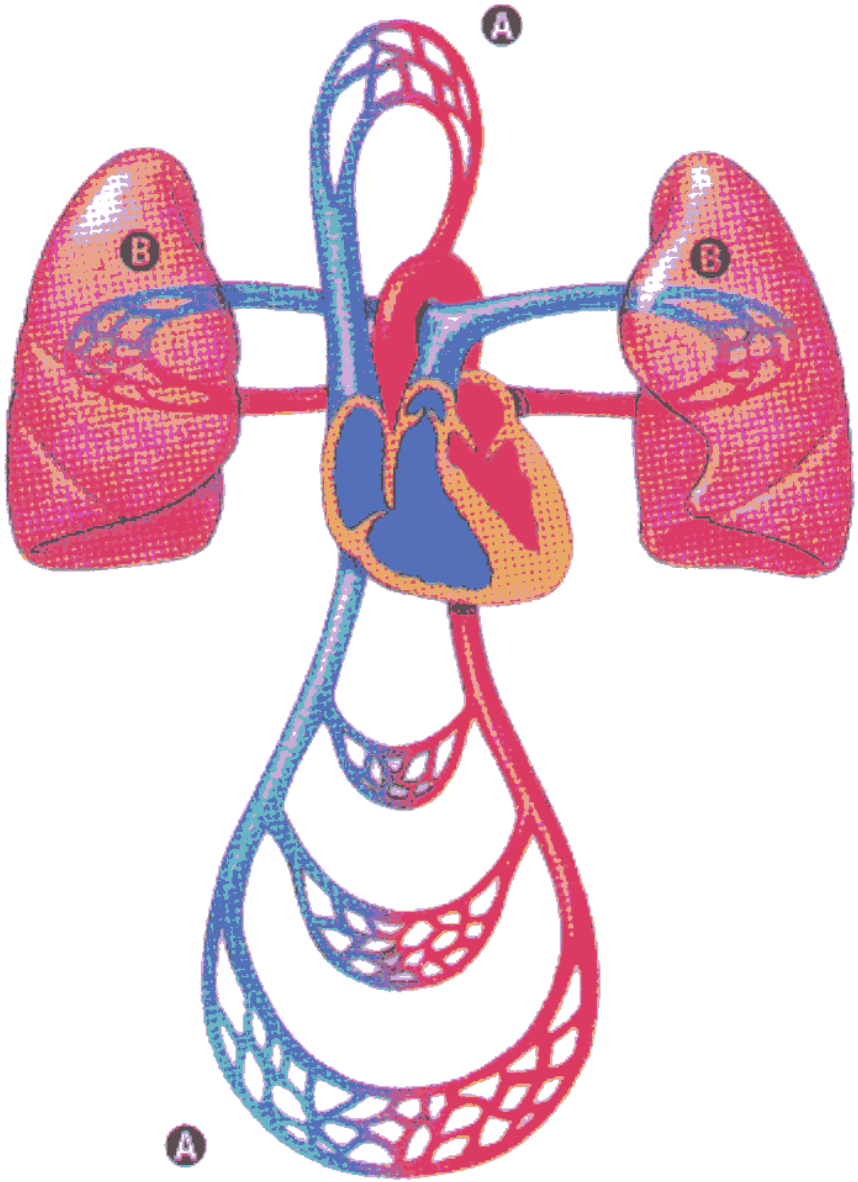
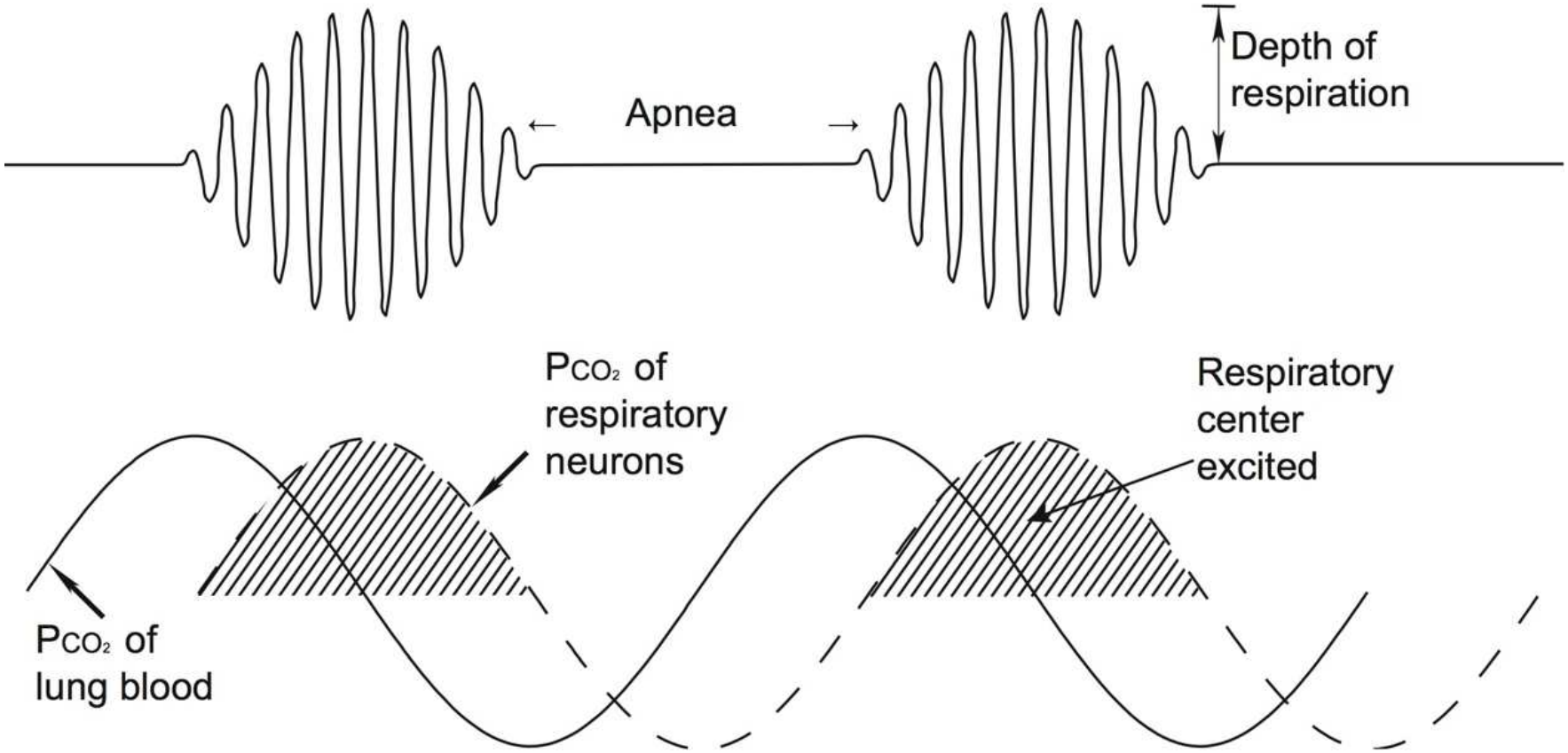


FIGURE General plan of circulation. Ⓐ Systemic circulation. Ⓑ Pulmonary circulation.

CHEYNE-STOKES RESPIRATION (CSR)

- A periodic breathing pattern.
- Intervals of little or no breathing (apnea) alternate with very heavy breathing (hyperpnea).
- This cycle repeats every minute or less.
- Blood carbon dioxide levels fluctuate with the same rhythm.
- Believed to be neurological in origin, not to be confused with *obstructive sleep apnea.*

CHEYNE-STOKES RESPIRATION (CSR)



Breathing pattern is *in phase* with PCO_2 of neurons, but *delayed* from PCO_2 of lungs. [A.C. Guyton and J.E. Hall, *Textbook of Medical Physiology*, Saunders Publ. 1996].

Conditions FAVOURING CSR in Humans

- Sleep
  - person periodically stops breathing (Apnea)
- Low CO_2 in blood (Hypocapnea)
  - may be induced by:
    - hyperventilation
    - high altitudes
- Cardiac disease (reduced blood flow)
  - increases lung-to-brain transport time
- Encephalitis
  - impedes blood flow in the head

LABORATORY EXPERIMENTS

A. Guyton [*Amer. J. Physiol.* 1956] caused Cheyne-Stokes respiration to occur in a dog, by inserting a circulatory time delay between the heart and the brain of the dog.

Mackey-Glass Model

Guyton's experiments led Mackey and Glass [*Science* 1977] to consider a simple delay-equation model:

$$\frac{dx}{dt} = \lambda - \alpha x \left[\frac{x_\tau^n}{1 + x_\tau^n} \right]$$

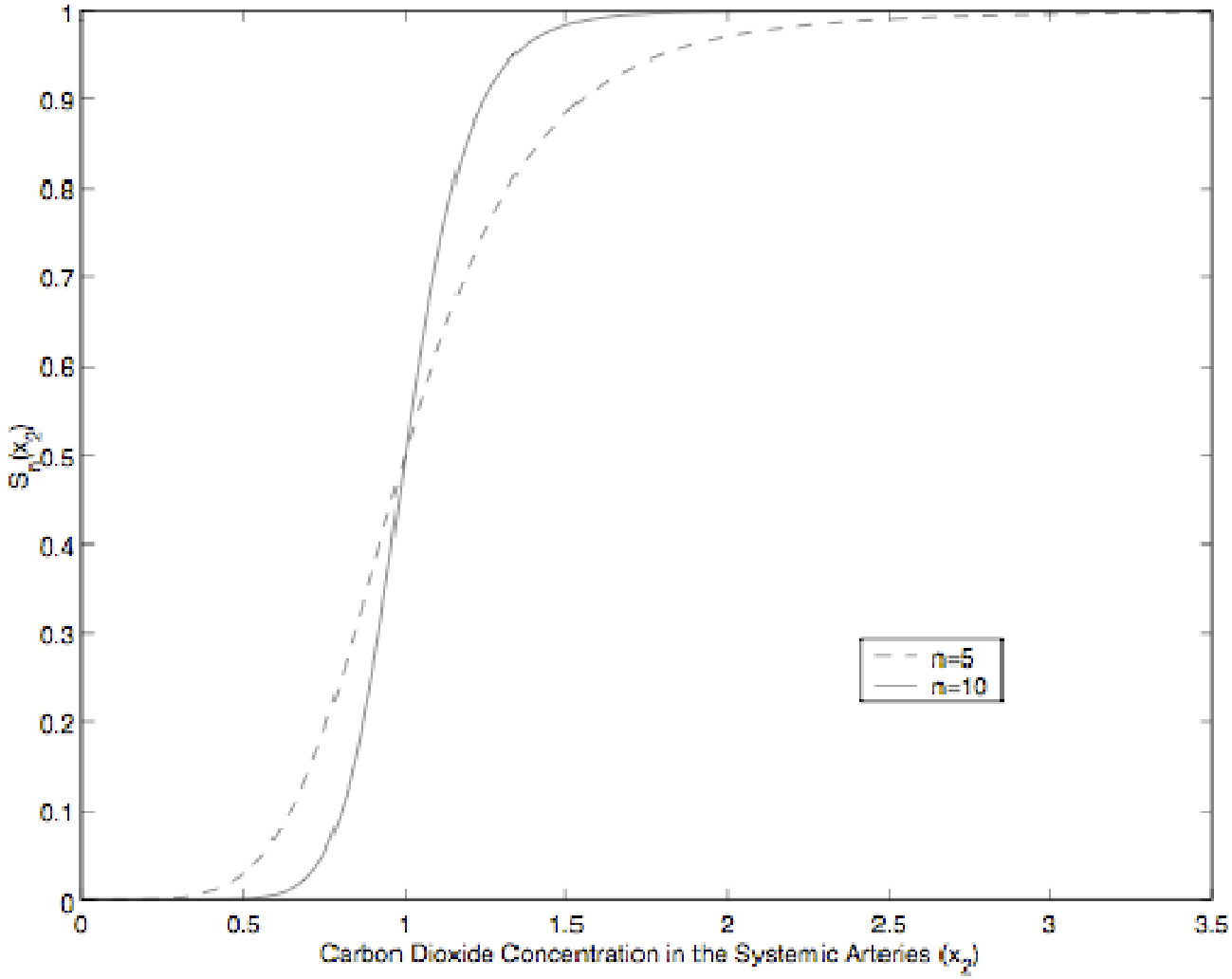
where τ is the time delay: $x_\tau \equiv x(t - \tau)$.

They found oscillations when $\mu\tau > \frac{\pi\alpha}{\lambda}$

and $\mu = n/4$ is the gain (slope) of the *Hill function*.

HILL FUNCTION

$$S_n(x) \equiv \frac{x^n}{1+x^n}$$

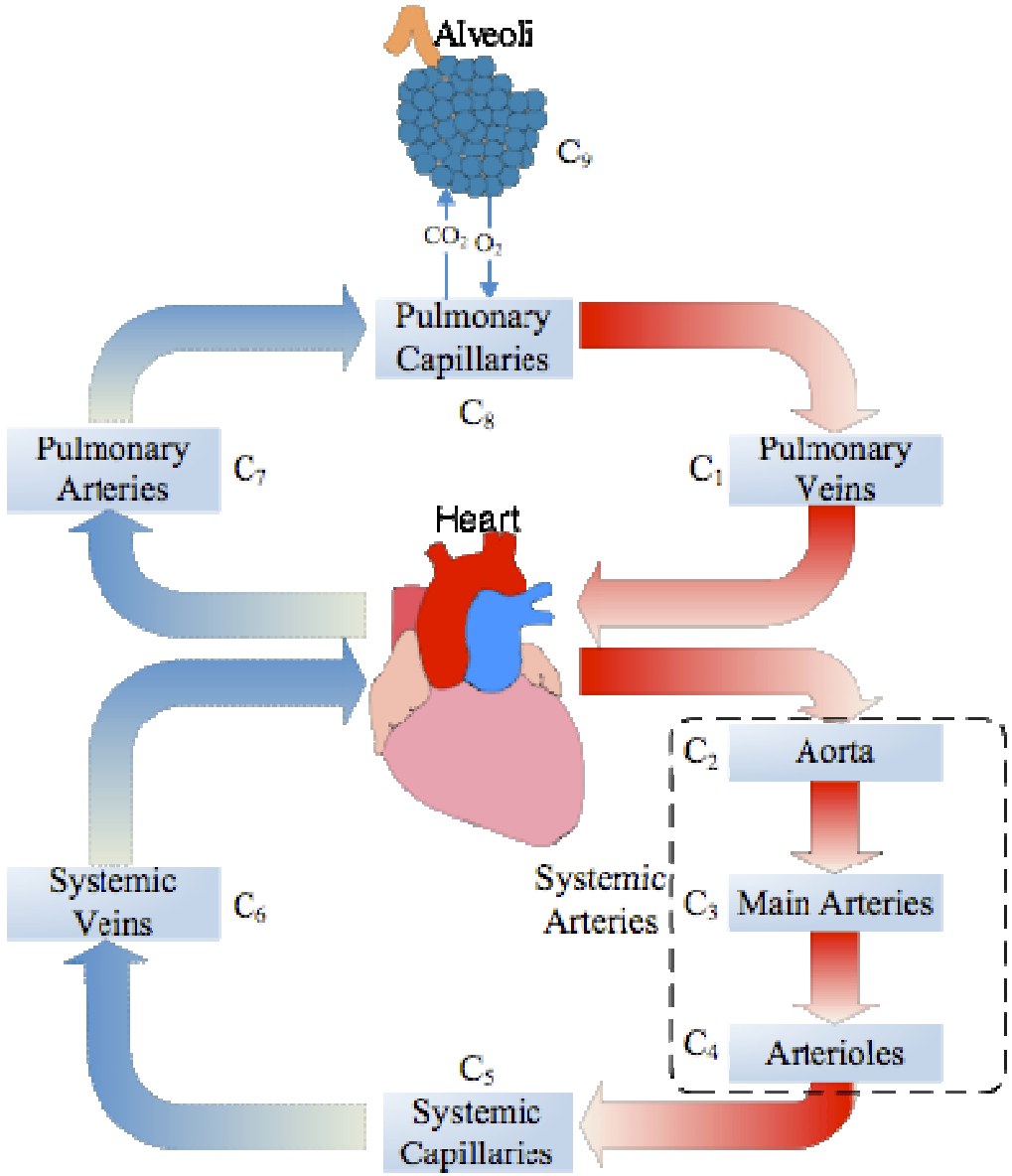


$S_n(x)$ approaches a step function as $n \to \infty$.

THE MATHEMATICAL MODEL

COMPARTMENTAL MODEL OF CARDIO-RESPIRATORY SYSTEM

Separate the system into n compartments, and let $C_j(t)$ represent the concentration of O_2 in compartment j.



Although the blood transports both *oxygen* from the lungs to tissues and *carbon dioxide* from tissues to lungs, only *carbon dioxide* is included in this model.

This choice is justified by clinical research.

Ref. Lorenzi-Filho, Rankin, Bies and Bradley (1999), *Am. J. Respir. Crit. Care Med.* Vol. 159, pp. 1490-1498.

EQUATIONS FOR CO_2 IN THE CARDIOVASCULAR SYSTEM

RATE CONSTANTS

Rate of blood flow pumped by heart:

$$\dot{F} \approx 5 \text{ L/min}$$

Rate of production of CO_2 by metabolism:

$$\dot{P} \approx 200 \text{ mL/min}$$

Rate of removal of CO_2 by respiration:

$$\dot{R} \approx 200 \text{ mL/min}$$

CONSERVATION LAW

The total CO_2 in each compartment j of the cardiovascular system is governed by:

$$\frac{d(v_j c_j)}{dt} = \dot{F} \cdot (c_{j-1} - c_j) \pm [\text{source or sink}]$$

where v_j is volume of compartment j.

For the systemic capillaries ($j = 6$),

$$v_6 \frac{dc_6}{dt} = \dot{F}(c_5 - c_6) + \dot{P}$$

PULMONARY BLOOD FLOW

$$v_8 \frac{dc_8}{dt} = \dot{F}(c_7 - c_8) - \dot{R}$$

where

$$\dot{R} = d_1 \dot{F}(p_8 - p_9)$$

$$d_1 = 8 \ \frac{\mathrm{mL}}{\mathrm{L} \cdot \mathrm{mmHg}}$$

$p_8,\ p_9 =$ partial pressures of CO_2 in pulmonary blood and air

and

$$p_8 = \frac{c_8}{8} - 20$$

THE RESPIRATORY SYSTEM

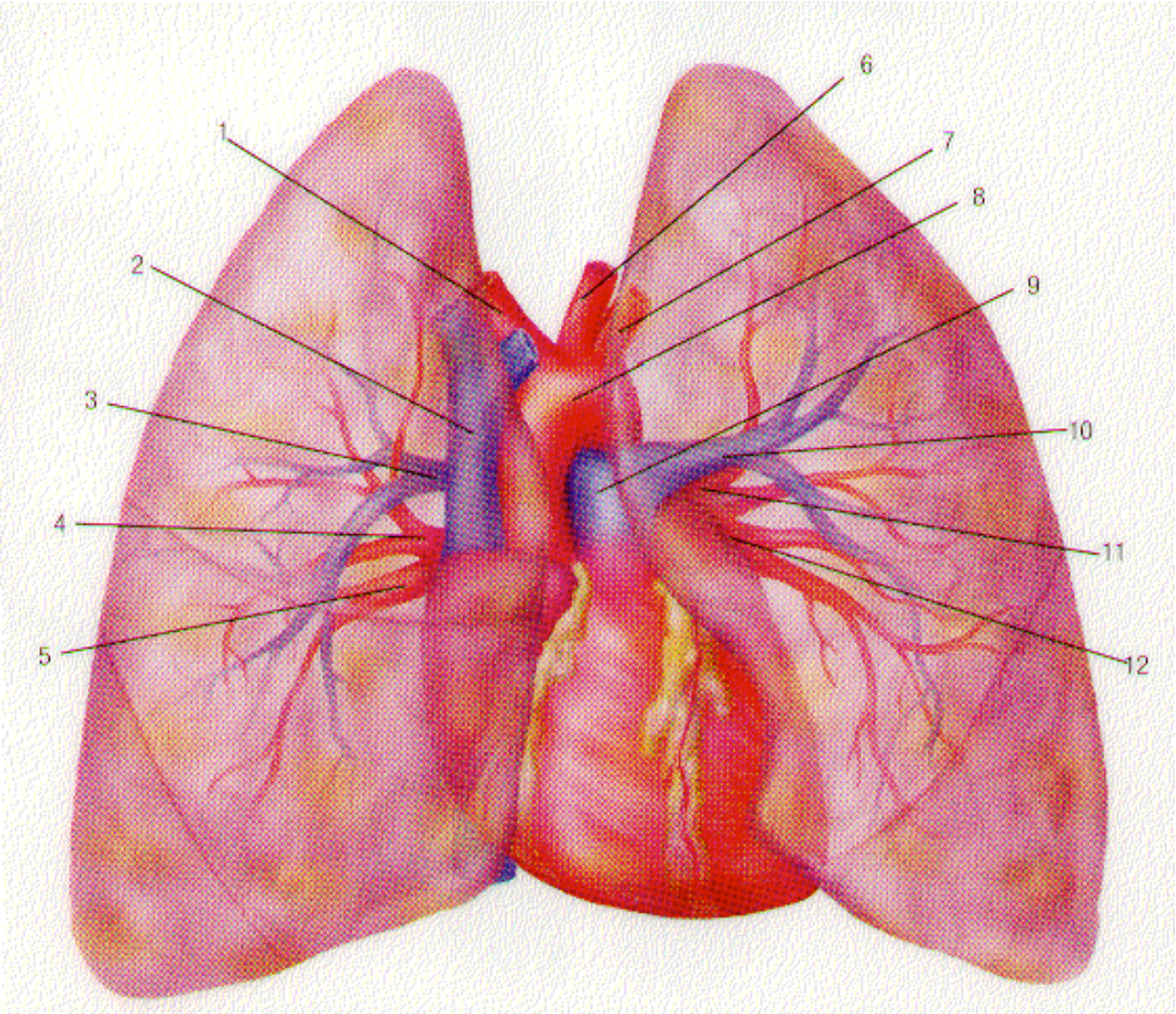


Figure	Heart and Lungs
1	Brachiocephalic trunk
2	Superior vena cava
3	Right pulmonary a.
4	Right superior pulmonary v.
5	Right inferior pulmonary v.
6	Left common carotid a.
7	Left subclavian a.
8	Aortic arch
9	Pulmonary trunk
10	Left pulmonary a.
11	Left superior pulmonary v.
12	Left inferior pulmonary v.

EXPIRATION OF CO_2 TO THE ATMOSPHERE

CO_2 is removed from the lungs by breathing, at a rate proportional to the difference in partial pressures between the alveoli and the atmosphere, and proportional to the ventilation rate

$$\frac{dp_9}{dt} = \frac{\dot{V}}{v_A}(p_9 - p_I) + d_2\dot{F}(p_8 - p_9)$$

where

$v_A \approx 3.5$ L (alveolar volume)

$p_I \approx 0.3$ mmHg [CO_2 atmos. press.]

FEEDBACK CONTROL SYSTEM

The model assumes that the peripheral chemoreceptors (at the carotid bodies) monitor CO_2 concentration in arterial blood (indirectly through pH of carbonic acid). [Ref. Lorenzi-Filho et al. (1999)]

If the CO_2 level increases, the brain stimulates an increase in the ventilation rate $\dot{V}$ (and similarly for a CO_2 decrease in).

Following Mackey and Glass (1977), we model this feedback control by a *Hill function.*

The pulmonary ventilation rate is

$$\dot{V}_\mu(c_5) = 2\bar{\dot{V}}\left[\frac{c_5^n}{a^n + c_5^n}\right]$$

where

$c_5 = CO_2$ concentration in blood to brain

$a =$ normal value of c_5

$\bar{\dot{V}} =$ normal ventilation rate

$$\mu = \frac{d}{dx}S_n(a) = \frac{n}{4a} = \mathrm{GAIN}$$

NON-DIMENSIONALIZED EQUATIONS

In each compartment $j = 1, 2, 3, 4, 5, \ , 7,$

$$\frac{dy_j}{ds} = \frac{1}{\hat{v}_6}(y_{j-1} - y_j)$$

In the systemic capillaries

$$\frac{dy_6}{ds} = \frac{1}{\hat{v}_6}(y_5 - y_6 + \frac{m}{a})$$

In the lung alveoli

$$\frac{dy_8}{ds} = \hat{d}(y_7 - y_8) - \left[\frac{\dot{V}}{\dot{F}}\right] \frac{2}{\hat{v}_9} \frac{y_5^n}{1 + y_5^n} \left(y_8 - \frac{160 + 8p_I}{a}\right)$$

TWO CRITICAL RATIOS

In the non-dimensionalized equations, the ventilation rate $\dot{\bar{V}}$, blood flow (perfusion) rate $\dot{F}$ and metabolic rate $\dot{P}$ appear ONLY in the ratios

Ventilation-Perfusion Ratio: $r = \frac{\dot{\bar{V}}}{\dot{F}}$

Cardiovascular Efficiency Ratio: $m = \frac{\dot{P}}{\dot{F}}$

ANALYSIS OF THE MODEL

- Determine the unique equilibrium steady-state of the system, for physiologically-valid parameters.
- Linearize the system at this equilibrium and compute eigenvalues of the Jacobian matrix.
- Find parameter values for which a complex-conjugate pair of eigenvalues crosses the imaginary axis.
- Study the resulting Hopf Bifurcation to a periodic oscillation: *stability, period, phases*.
- How does the Hopf bifurcation vary with gain

THE HOPF BIFURCATION THEOREM

- This is the mathematically generic mechanism for a change in behaviour of a system, from a stable steady-state to a periodic oscillation.
- It is detected mathematically by a change of sign of the real part of complex eigenvalues.
- Hopf bifurcation in the model corresponds to the onset of CSR oscillations.

THE STANDARD MODEL:

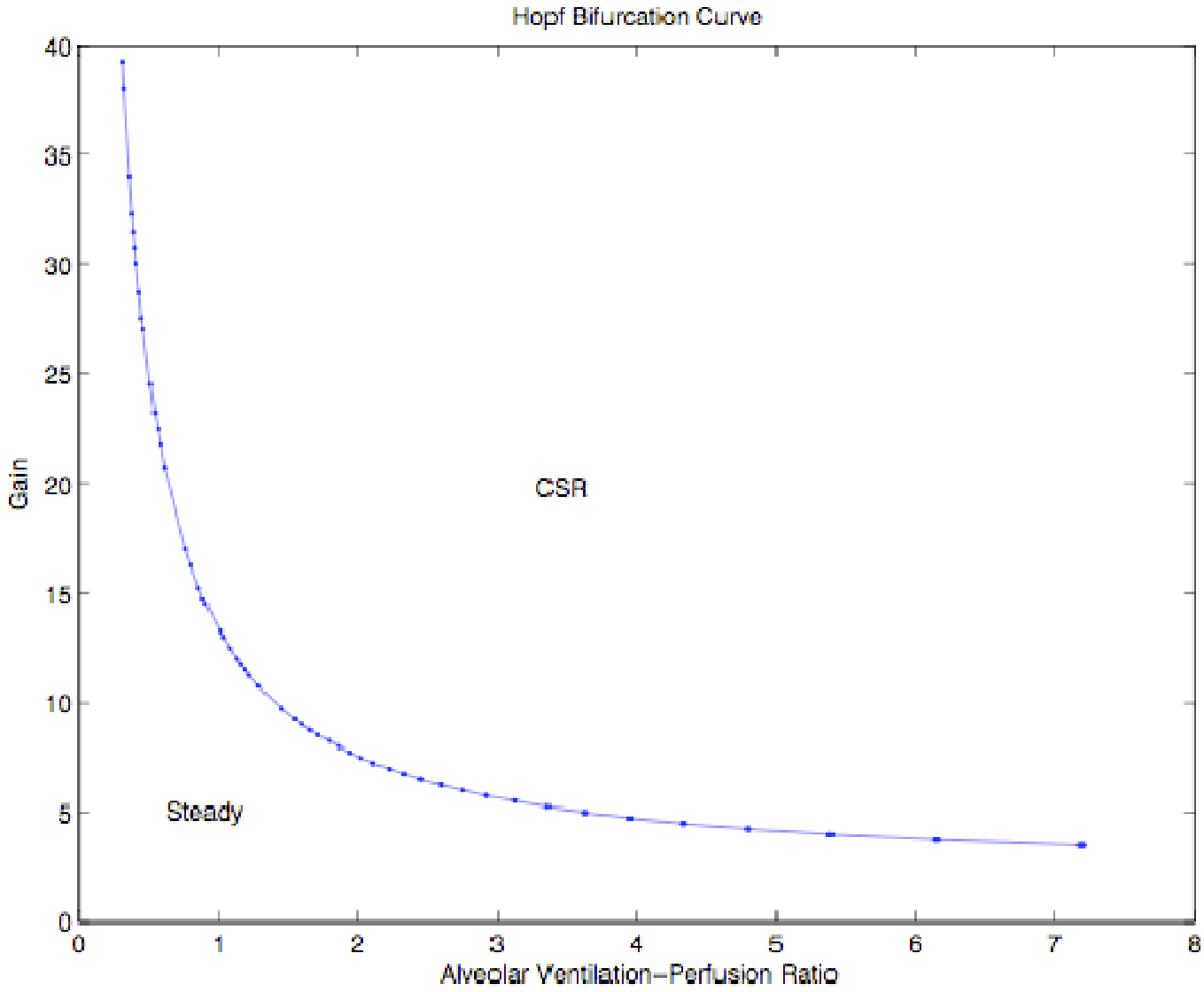
Choose normal parameter values, then vary the gain μ and the ventilation-perfusion ratio r

Model Parameters from the Medical Literature

Table 1 Parameters in the mathematical model

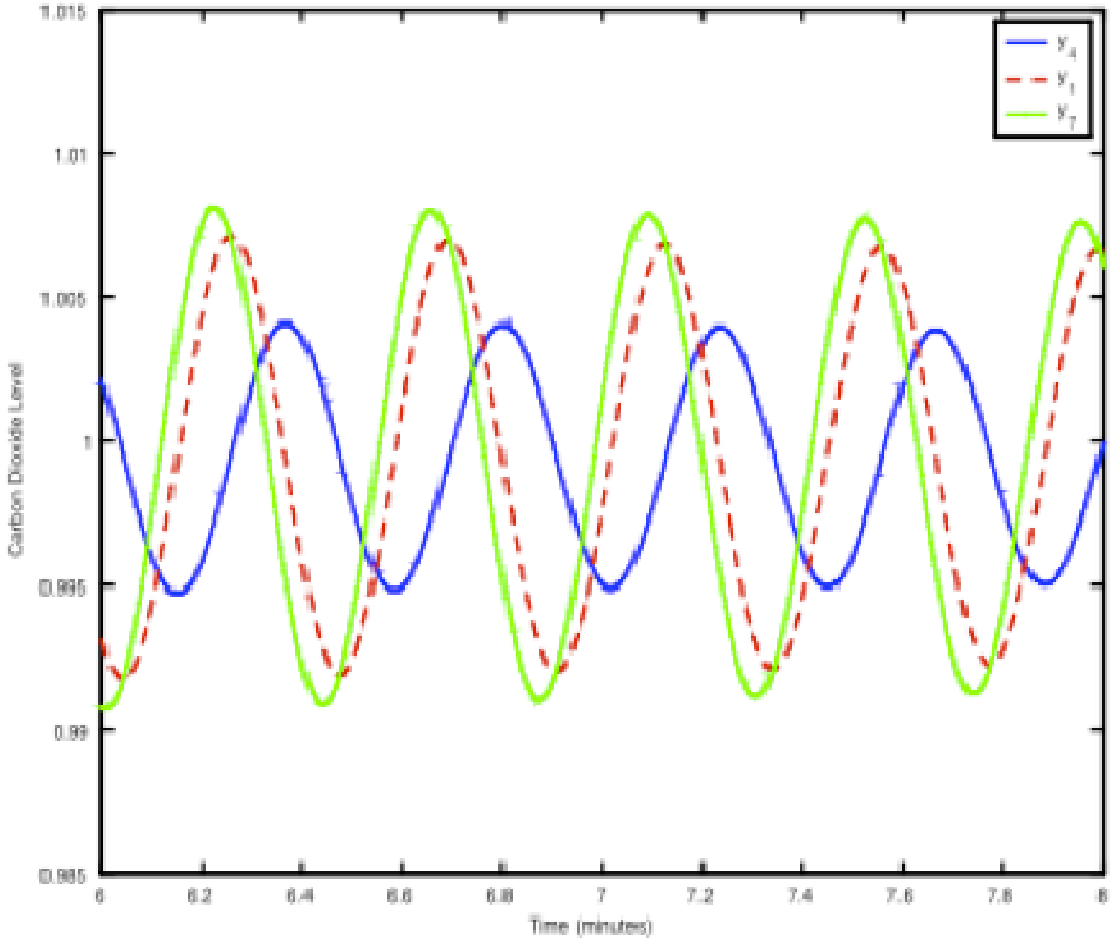
Quantity	Typical value	References
Blood flow rate at rest	$\dot{Q}$ — 5 L/min	[3,11,25,28]
Breathing rate at rest	f — 12–15 breaths/min	[11,28]
Tidal volume per breath	V_T — 500 mL	[11,25,28]
Dead space volume	V_D — 150 mL	[11,25,28]
Alveolar ventilation rate at rest	$\bar{V}_A$ — 4–5 L/min	[11,14,25,28]
Alveolar gas volume	V_9 — 3 L	[11,28]
Inspired CO_2 partial pressure	p_I — 0.3 mmHg	[11,26,28]
Alveolar CO_2 partial pressure at rest	p_9 — 40 mmHg	[11,14,25,28]
Metabolic CO_2 production at rest	$\dot{M}$ — 200 mL/min	[3,19,25,26]
Total volume of blood in body	v_T — 5.0 L	[11,12,14]
Pulmonary veins volume	v_1 — 0.25 L	[11,12]
Left heart volume	v_2 — 0.15 L	[11,14]
Aorta volume	v_3 — 0.3 L	[11,14]
Main arteries volume	v_4 — 0.5 L	[11,14]
Arterioles volume	v_5 — 0.2 L	[11,14]
Systemic capillaries volume	v_6 — 0.2 L	[11,14]
Systemic veins, pulmonary arteries and right heart volume	v_7 — 3.3 L	[11,12,14]
Pulmonary capillaries volume	v_8 — 0.1 L	[11,14]
Arterial CO_2 concentration at rest	c_5^* — 480 mL/L	[11,25,28]
Venous CO_2 concentration at rest	c_7^* — 520 mL/L	[11,25,28]
Arterial CO_2 partial pressure at rest	p_5^* — 40 mmHg	[11,14,28]
Venous CO_2 partial pressure at rest	p_7^* — 45 mmHg	[11,14,28]
Perfusion constant (Appendix B)	d — 0.28767 mmHg/mL	[2]
Ventilation–perfusion ratio $\bar{V}_A/\dot{Q}$	r — 0.9	[2]
Cardiovascular efficiency $\dot{M}/\dot{Q}$	m — 40 mL/L	

HOPF BIFURCATION CURVE: Standard Model



Cheyne-Stokes Respiration occurs above the Hopf bifurcation curve.

Oscillations in Standard Model



y_1 = CO_2 leaving Lungs

y_4 = CO_2 in Arteries (to brain)

y_7 = CO_2 returning to Lungs

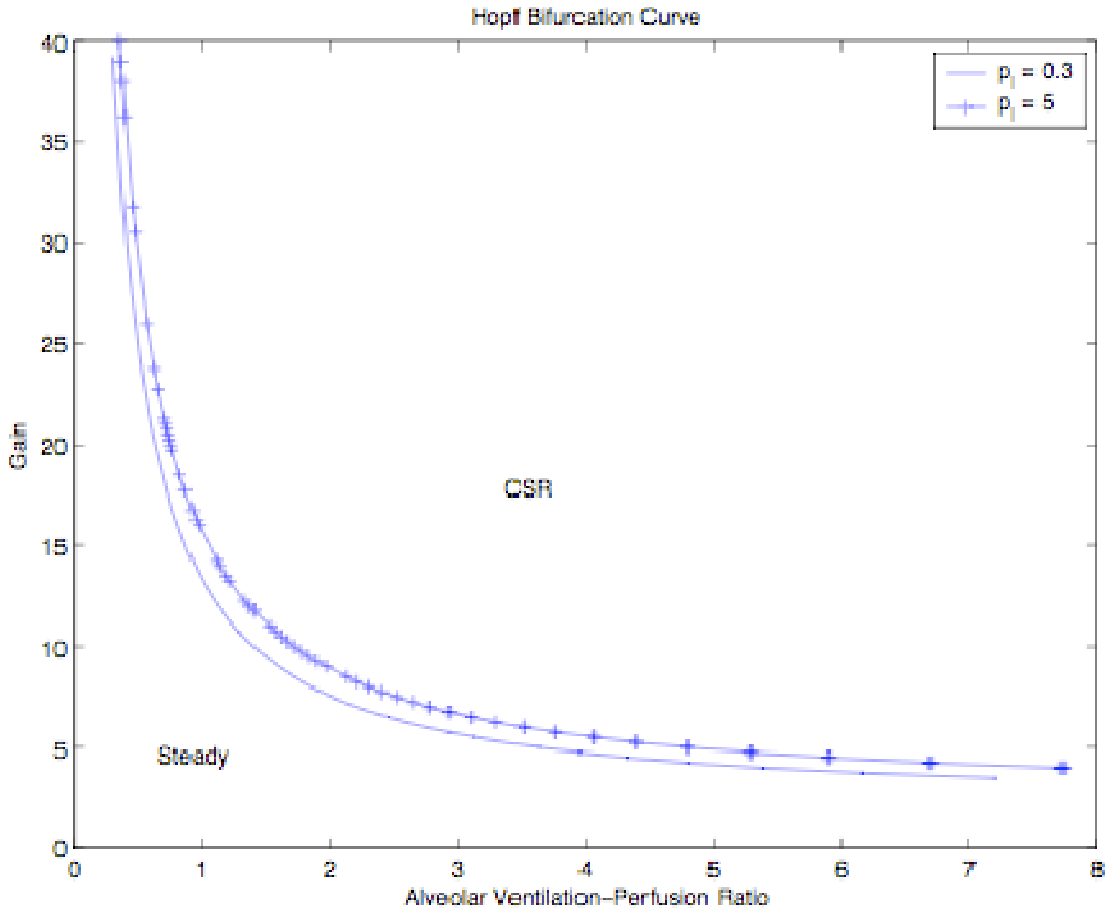
Note: Same phase relationship as in the figure of Guyton (1996).

The Standard Model reproduces the essential features of CSR onset including: period of oscillation, flow rates, concentrations and phase relationships.

CARDIOVASCULAR PATHOLOGIES:

STUDY THE EFFECTS OF CHANGES IN THE PARAMETERS

Effect of Increasing Inhaled CO_2 Pressure:

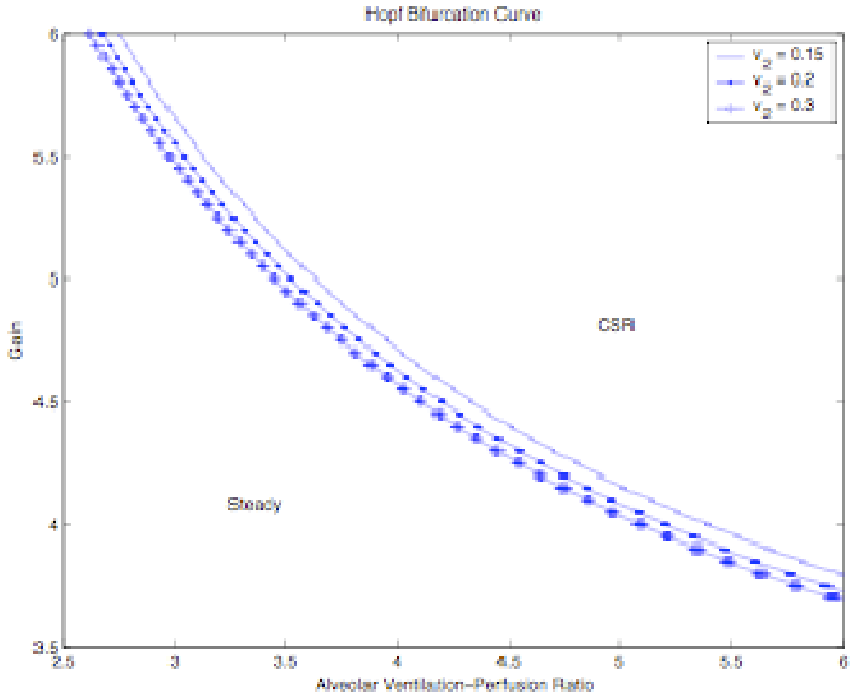


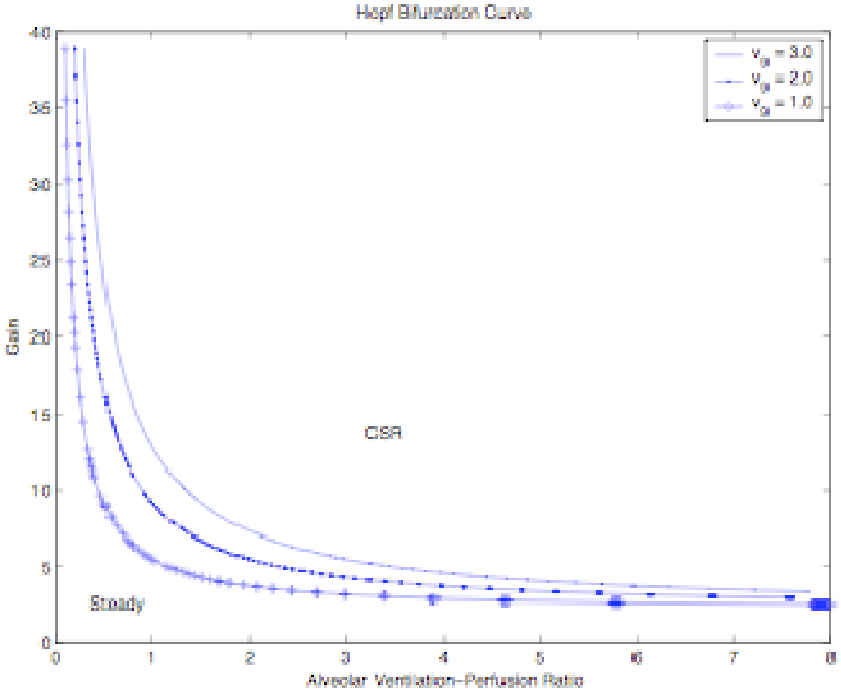
Cheyne-Stokes Respiration is inhibited.

CHRONIC HEART FAILURE

- "Chronic Heart Failure" (CHF) refers to a weakening of the heart muscles (from a variety of causes), a loss of pumping efficiency and a swelling of the heart with blood. It may lead to fluid buildup, especially in the lungs, and is then called "Congestive Heart Failure".
- It is frequently fatal.
- Cheyne-Stokes respiration is observed more often during CHF and results in elevated mortality. [Bradley and Floras (2003)]
- CHF may cause enlargement of the left heart to "tremendous size". [Guyton and Hall (1996)]
- We conjecture that an increase in either of the left heart volume or congestion in the lungs, may cause Cheyne-Stokes Respiration.

EFFECTS OF CONGESTIVE HEART FAILURE





v_2 = left heart blood volume

CSR increases with v_2

V_9 = alveolar gas volume

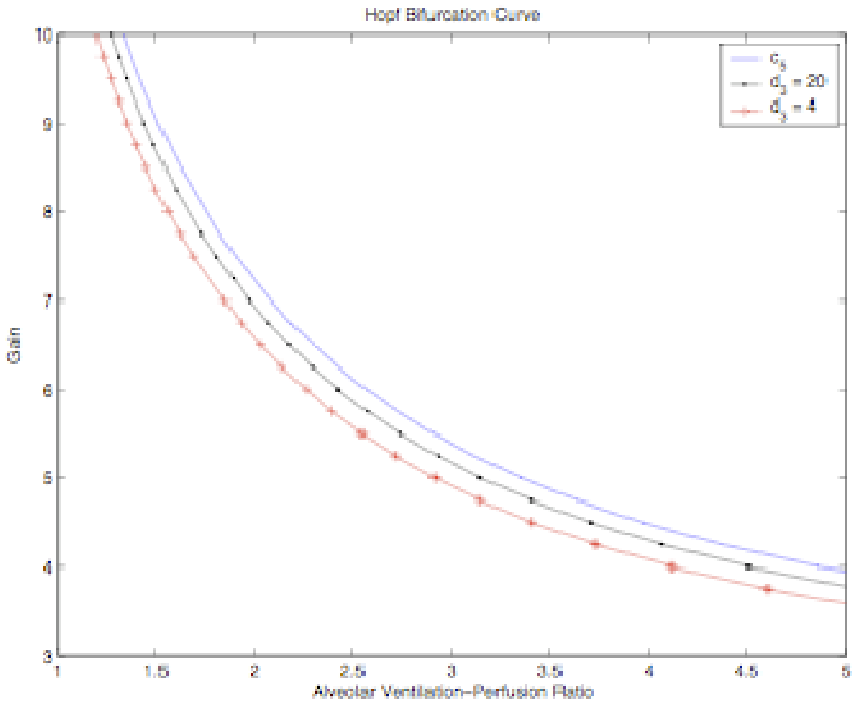
CSR decreases with V_9

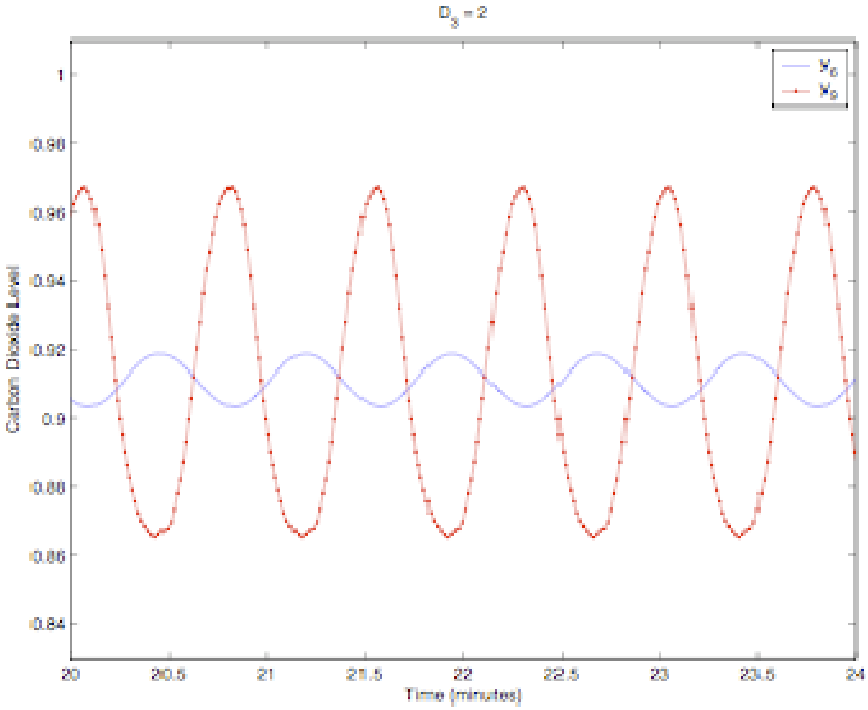
ENCEPHALITIS

- *"Encephalitis"* is an inflammation of the brain, most often caused by an infectious organism, usually a virus, but sometimes by chemicals. It may cause irreparable brain damage and is sometimes fatal.
- Cheyne-Stokes respiration often occurs during encephalitis.
- Encephalitis causes obstruction of the normal flow of blood through the brain, increasing the concentration of carbon dioxide, and this may interfere with the operation of the respiratory control center.
- We conjecture that poor circulation of blood in the brain may be a cause of Cheyne-Stokes respiration during encephalitis.

ENCEPHALITIS MODEL

Add a new compartment to the model, representing the chemoreceptors and brain. Assume diffusive coupling of this compartment to the arterial blood, with an adjustable diffusion coefficient.





CSR increases with decreasing diffusion coefficient.

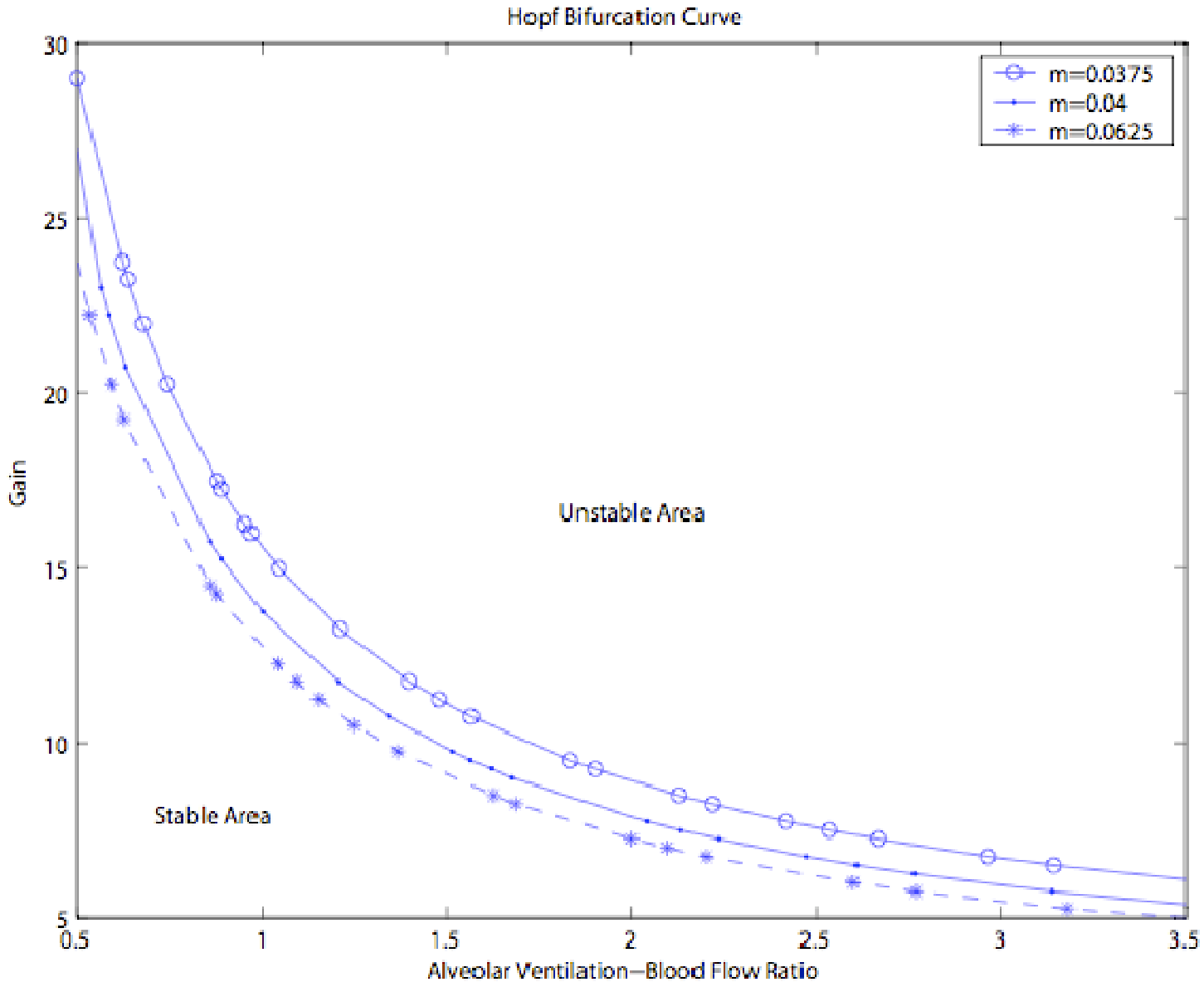
Nearly 180° phase shift between lungs and chemoreceptors.

CARDIOVASCULAR EFFICIENCY

Recall the *cardiovascular efficiency ratio:*

$$\eta_c = \frac{\dot{P}}{\dot{F}}$$

A higher value of this ratio implies a more efficient cardiovascular system.



CSR becomes *more likely* as the cardiovascular efficiency *increases*.

DISCUSSION

1. The model confirms that onset of CSR oscillations results from increasing any of:
   - Feedback control gain μ
   - Ventilation-Perfusion ratio V/F
   - Transport time from lungs to brain T
   - Cardiovascular efficiency m

   or decreasing:
   - Alveolar lung volume V_g

2. The model agrees with observations of CSR in humans under wide conditions:
   - Sleep apnea – V/F increased
   - High altitude – V/F increased
   - Congestive HF – T increased and V_g decreased
   - Encephalitis – T increased
   - High fitness – μ, m increased

FURTHER WORK

- Compare occurrence of CSR for parameter values typical of males and of females.
- Study possible link between CSR and Sudden Infant Death Syndrome (SIDS).
- Refine the model to serve as a predictive tool in clinical settings.
- Computer models can be used to perform experiments that would be harmful to human subjects.

Thank you!

Reference: F. Dong and W. F. Langford (2008), Models of Cheyne-Stokes respiration with cardiovascular pathologies, *J. Math. Biol.* Vol. 57, pp. 497-519.

For reprints or further information:

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