



Computational modeling of the regulatory effects to the transport of respiratory gases in the body

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Motivation



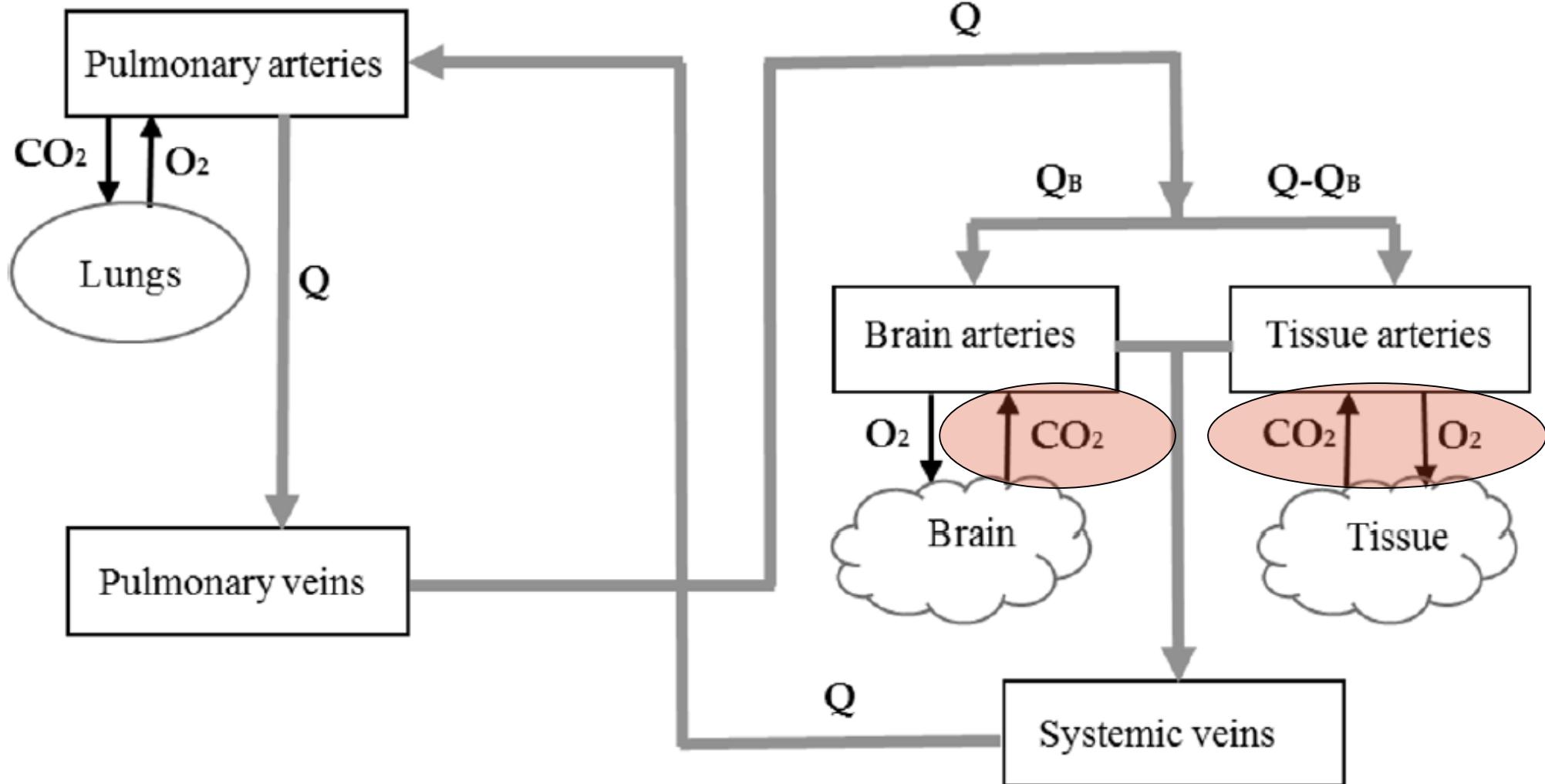
Oxygen and/or **carbon dioxide** variations in the blood may cause irreversible pathological changes: **Hypoxia** and ischemic events (oxygen decrease), **Hypercapnia** (carbon dioxide increase) and acidosis or alkalosis (acid-base balance variations), etc.

Possible reasons:

- Pathological breathing patterns
- Improper mechanical ventilation
- Asthma attack
- High performance physical activity



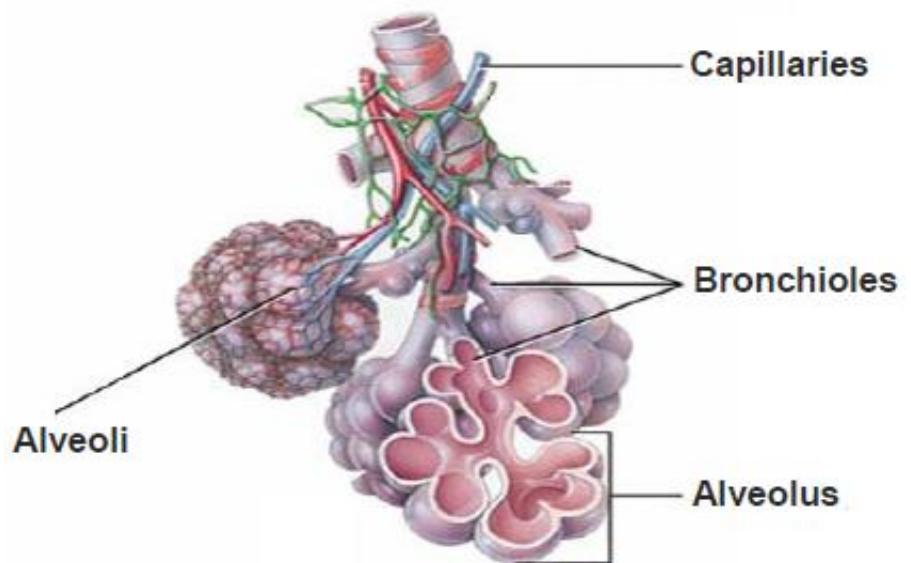
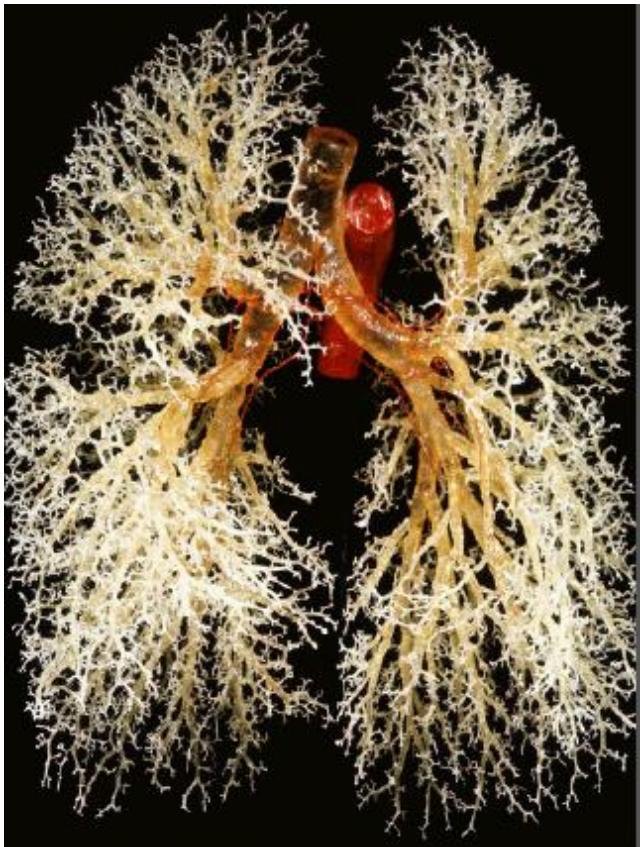
Compartment decomposition of the respiratory and the cardiovascular systems



Regulation: minute blood flow, respiratory rate, tidal volume



The respiratory system

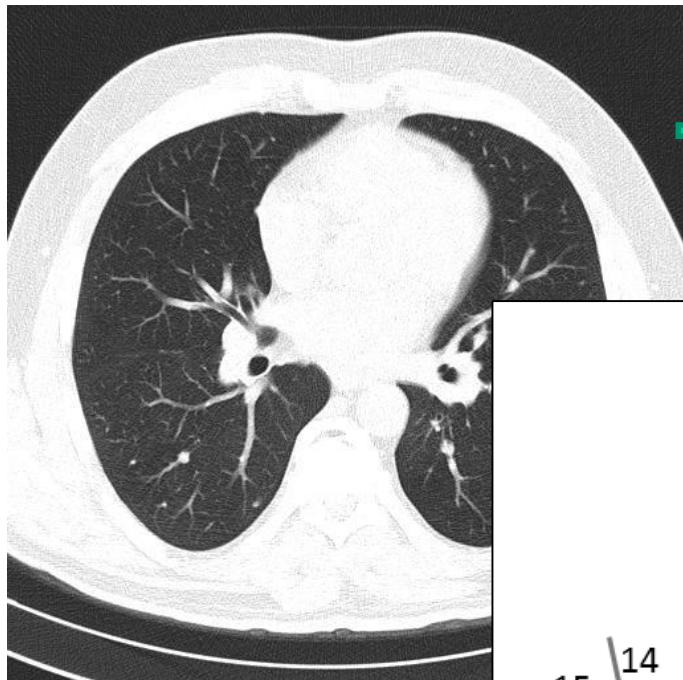


Trachea-bronchial tree

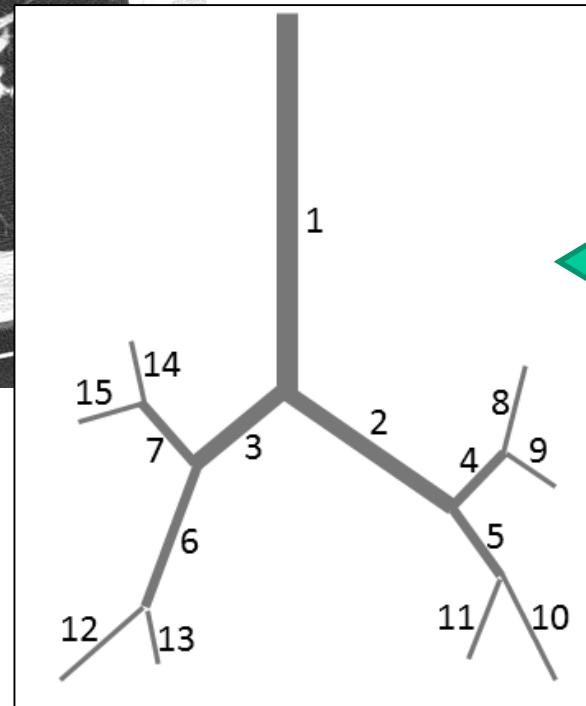
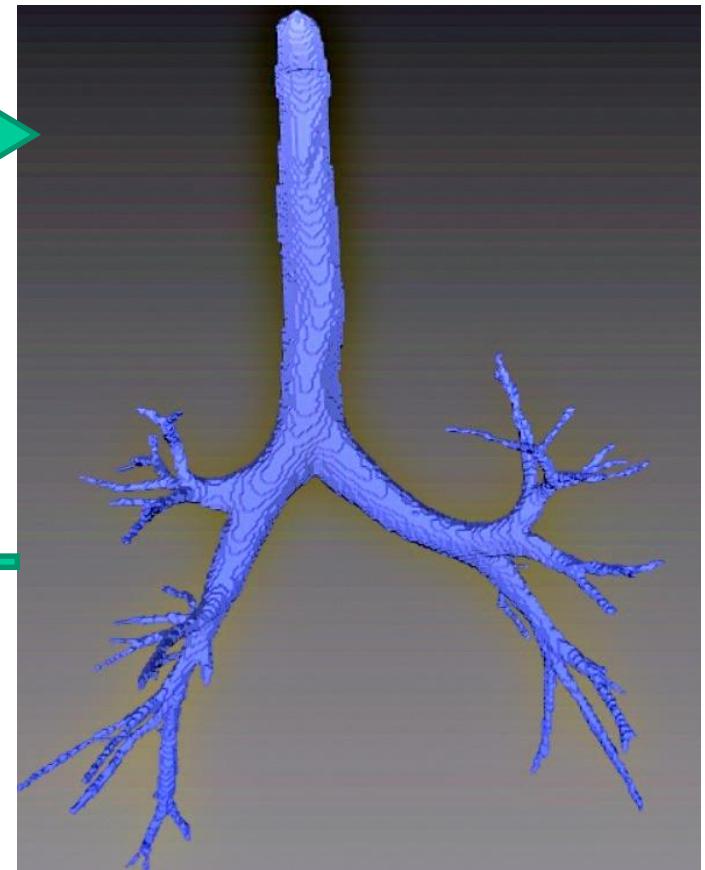


The conducting zone

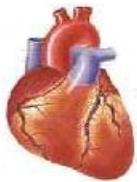
CT – data of the trachea-bronchial tree



The 3D structure



The 1D network structure



The conducting zone (1D-model)

1) The mass conservation

$$\frac{\partial S_k}{\partial t} + \frac{\partial (S_k u_k)}{\partial x} = 0$$

2) The momentum conservation

$$\frac{\partial u_k}{\partial t} + \frac{\partial}{\partial x} \left(\frac{u_k^2}{2} + \frac{p_k(S_k)}{\rho} \right) = 0$$

3) The bronchial tubes elasticity

$$p_k(S_k) = \rho c_{0k}^2 \left(\frac{S_k}{S_{0k}} - 1 \right)$$

4) The input to the nasopharynx region

$$p_1(S_1(t, 0)) = p_{atm} = const$$



The conducting zone (1D Model, boundary condition)



- All bifurcation are dichotomous

1) The mass conservation condition

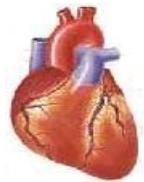
$$S_{k_1^m}(t, L_{k_1^m}) u_{k_1^m}(t, L_{k_1^m}) - S_{k_2^m}(t, 0) u_{k_2^m}(t, 0) - S_{k_3^m}(t, 0) u_{k_3^m}(t, 0) = 0$$

2) The Bernoulli's theorem

$$\frac{p_{k_i}(S_{k_i}(t, \tilde{x}_{k_i}))}{\rho} + \frac{u_{k_i}^2(t, \tilde{x}_{k_i})}{2} = I_m(t), i = 1 \div 3,$$

3) Compatibility conditions along characteristics

$$\mathbf{w}_{ki} \cdot \left(\frac{d\mathbf{V}_k}{dt} \right)_i = \mathbf{w}_{ki} \cdot \left(\frac{\partial \mathbf{V}_k}{\partial t} + \lambda_{ki} \frac{\partial \mathbf{V}_k}{\partial x} \right) = \mathbf{0},$$



The smaller airways and alveoli (Lumped model)



1) Alveolar compartment

$$R_a^k \frac{dV_a^k}{dt} + E_a^k (V_a^k - V_{0a}^k) = p_a^k - p_{pl}(t),$$

2) Pleural pressure

$$p_{pl}(t) = p_g \sin(\nu t)$$

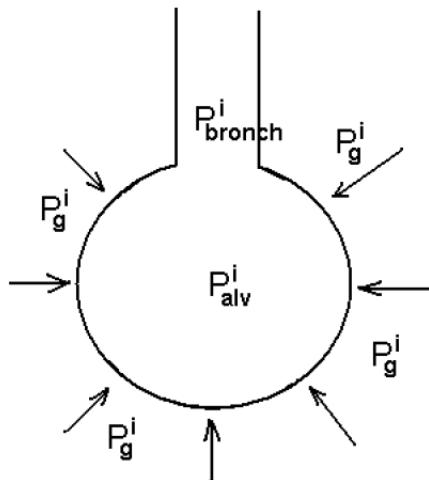
3) Poiseuille's law for the tube

$$R_a = \frac{8\eta l_{ef}}{\pi r_{ef}^4}$$

4) The alveolar volume-equivalence

$$V_a \approx \pi r_{ef}^2 l_{ef} \approx \frac{4\pi r_{ef}^3}{3}$$

$$R_a = \frac{128\eta}{9\pi^2 V_a}$$





1D model and Lumped model coupling



The mass conservation and pressure continuity

$$\frac{dV_{ak}}{dt} = S_k(t, L_k) u_k(t, L_k)$$

$$p_{ak} = p_k(t, L_k)$$

Implicit Euler method

$$V_a^{n+1} = V_a^n + \tau S_J^{n+1} u_J^{n+1}$$

=> The fourth – order polynomial equation

$$\frac{128\eta}{9\pi^2(V_a^n + \tau S_J^{n+1} u_J^{n+1})} S_J^{n+1} u_J^{n+1} + E_a(V_a^n + \tau S_J^{n+1} u_J^{n+1} - V_{0a}) = \rho c_0^2 \left(\frac{S_J^{n+1}}{S_0} - 1 \right) - p_{pl}^{n+1}$$



The transport of oxygen and carbon dioxide (the conducting zone)



The mass transport along the bronchial tubes

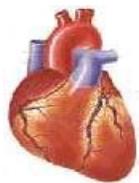
$$\frac{\partial C_{k,m}}{\partial t} + u_k \frac{\partial C_{k,m}}{\partial x} = 0$$

The input to the nasopharynx during inspiration

$$C_{1,O_2}(t, 0) = C_{O_2}^{atm} \quad C_{1,CO_2}(t, 0) = C_{CO_2}^{atm}$$

The junction of the bronchial tubes

$$\begin{aligned} C_{k_1^n, m}(t, L_{k_1^n}) S_{k_1^n}(t, L_{k_1^n}) u_{k_1^n}(t, L_{k_1^n}) &= \\ &= C_{k_2^n, m}(t, 0) S_{k_2^n}(t, 0) u_{k_2^n}(t, 0) + C_{k_3^n, m}(t, 0) S_{k_3^n}(t, 0) u_{k_3^n}(t, 0) \end{aligned}$$



The transport of oxygen and carbon dioxide



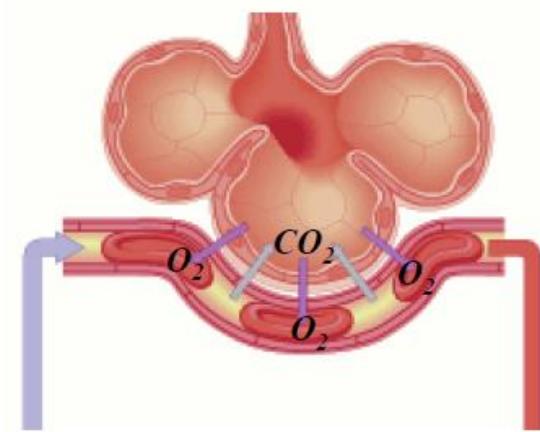
The alveolar volume

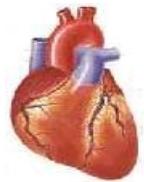
$$\frac{d(C_{a,m}^k V_a^k)}{dt} = C_{k,m} S_k(t, L_k) u_k(t, L_k) + D_m S_k^a (C_m^b - C_{a,m}^k)$$

The blood compartment

$$\frac{dC_m^b}{dt} = \frac{Q_m^b}{V^b} + D_m \sum_k \frac{S_k^a}{V^b} (C_{a,m}^k - C_m^b)$$

$$S_a^k = \sqrt[3]{36\pi (V_a^k)^2}$$





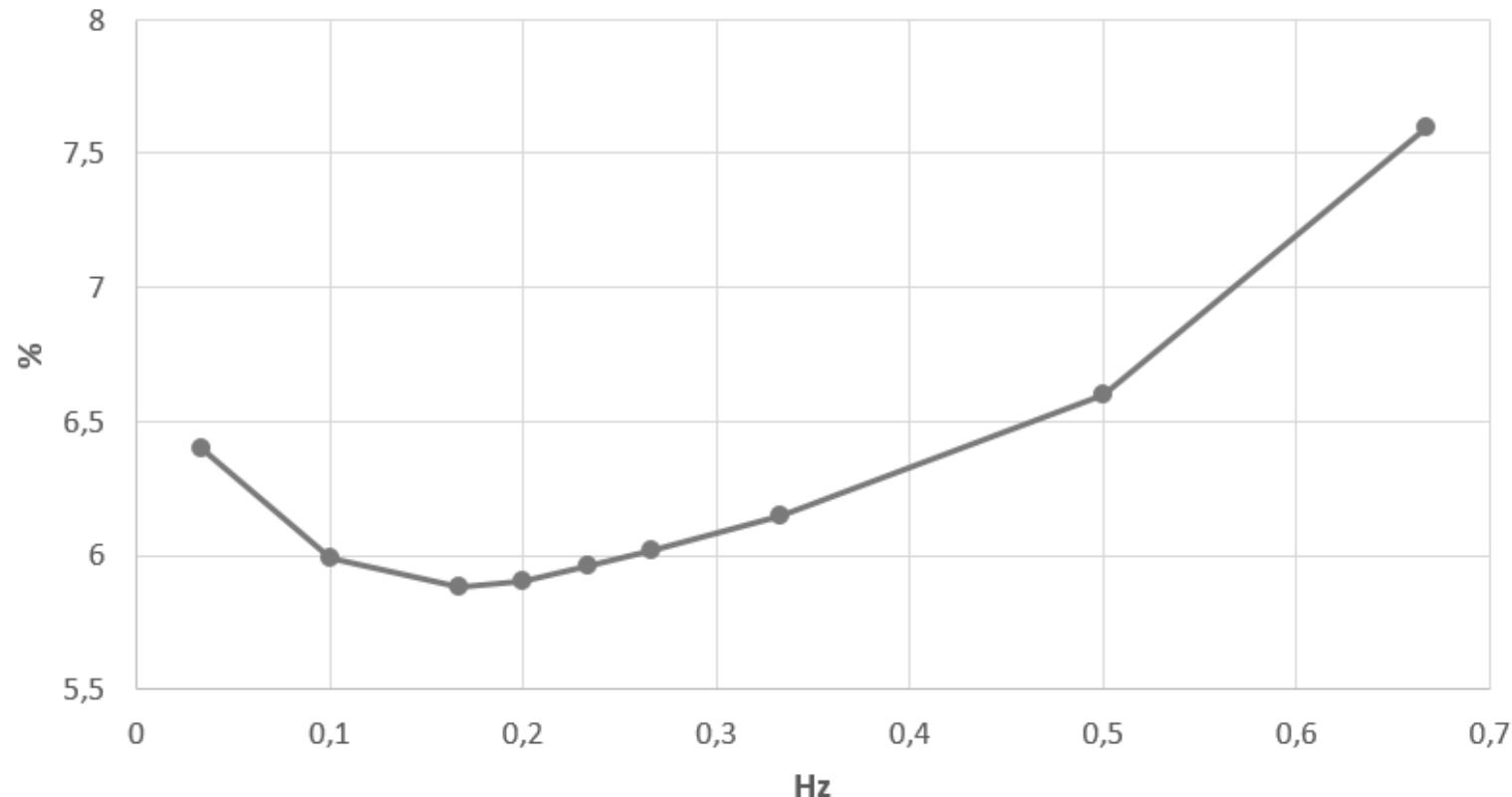
The efficiency of carbon dioxide elimination during mechanical ventilation

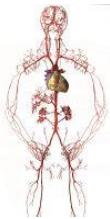


Boundary conditions

$$60V_{td} \nu_{ARR} = V_{minute} = const \quad S_1(t, 0) u_1(t, 0) = Q_{td} \sin(2\pi\nu_{ARR}t), Q_{td} = \frac{V_{td}}{\pi\nu_{ARR}}$$

Alveolar concentration of CO₂ from the ARR



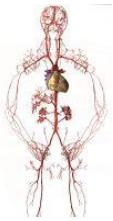
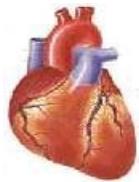


The Biot's breathing pattern

The constant amplitude of the frequency and
the depth, long term pauses

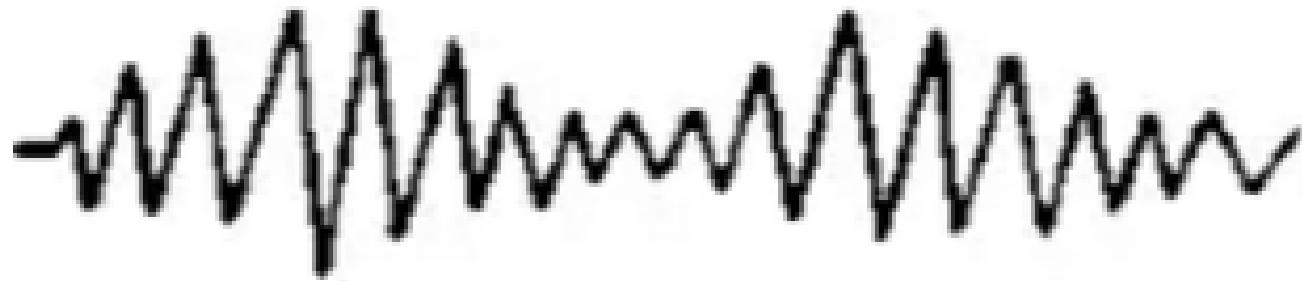


$$p_{pl}(t) = \begin{cases} 2p_g \sin(vt), & 0 \leq t < 0.5T_{pt} \\ 0, & 0.5T_{pt} \leq t < T_{pt} \end{cases}$$



The Cheyne-Stokes breathing pattern

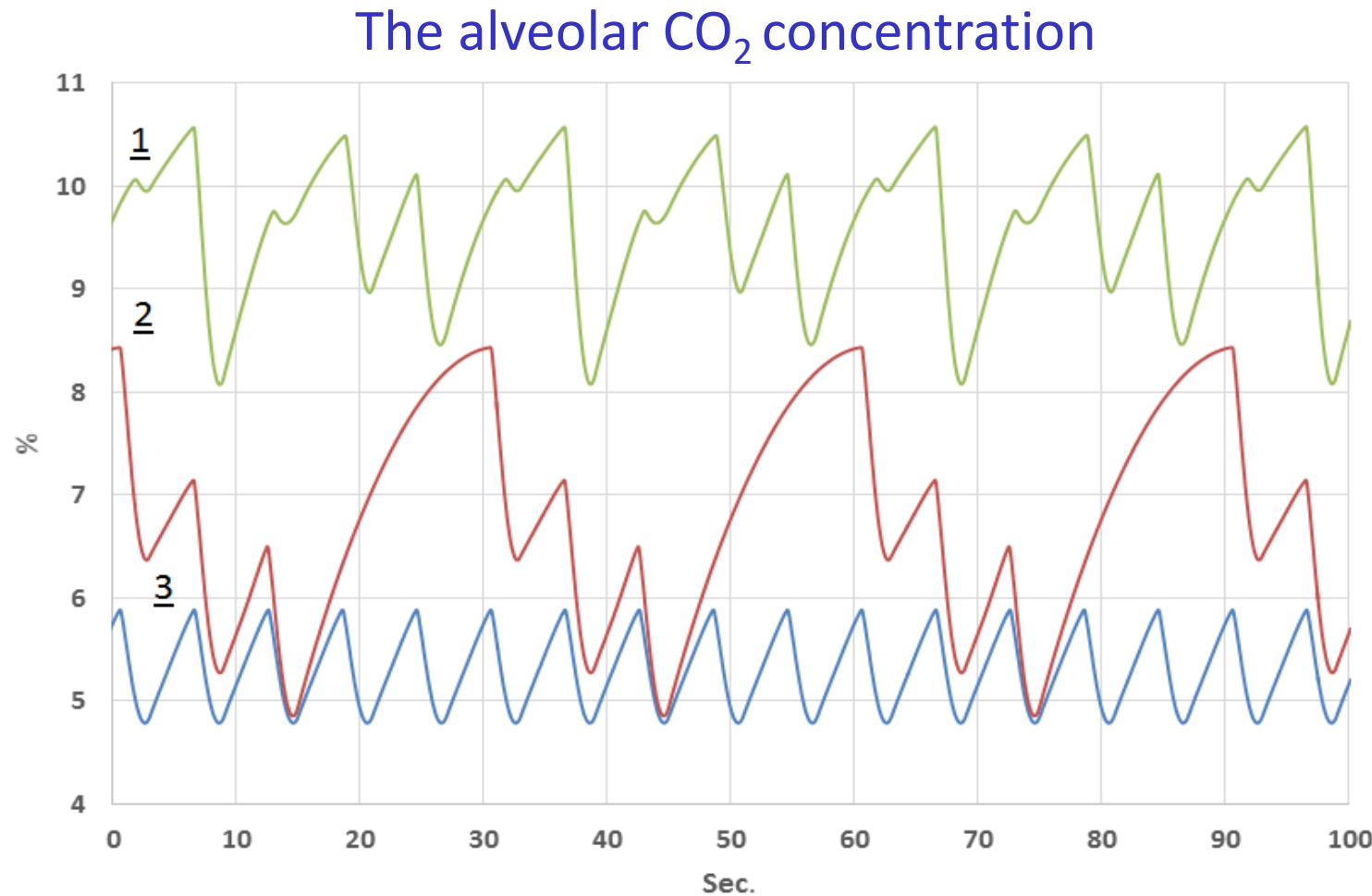
The weak shallow breathing with increase and decrease of the depth



$$p_{pl}(t) = \begin{cases} 2p_g \sin(vt) \sin(5vt), & 0 \leq t < 0.75T_{pt} \\ 0.1p_g \sin(vt), & 0.75T_{pt} \leq t < T_{pt} \end{cases}$$



The Cheyne-Stokes and the Biot's Breathing numerical modeling

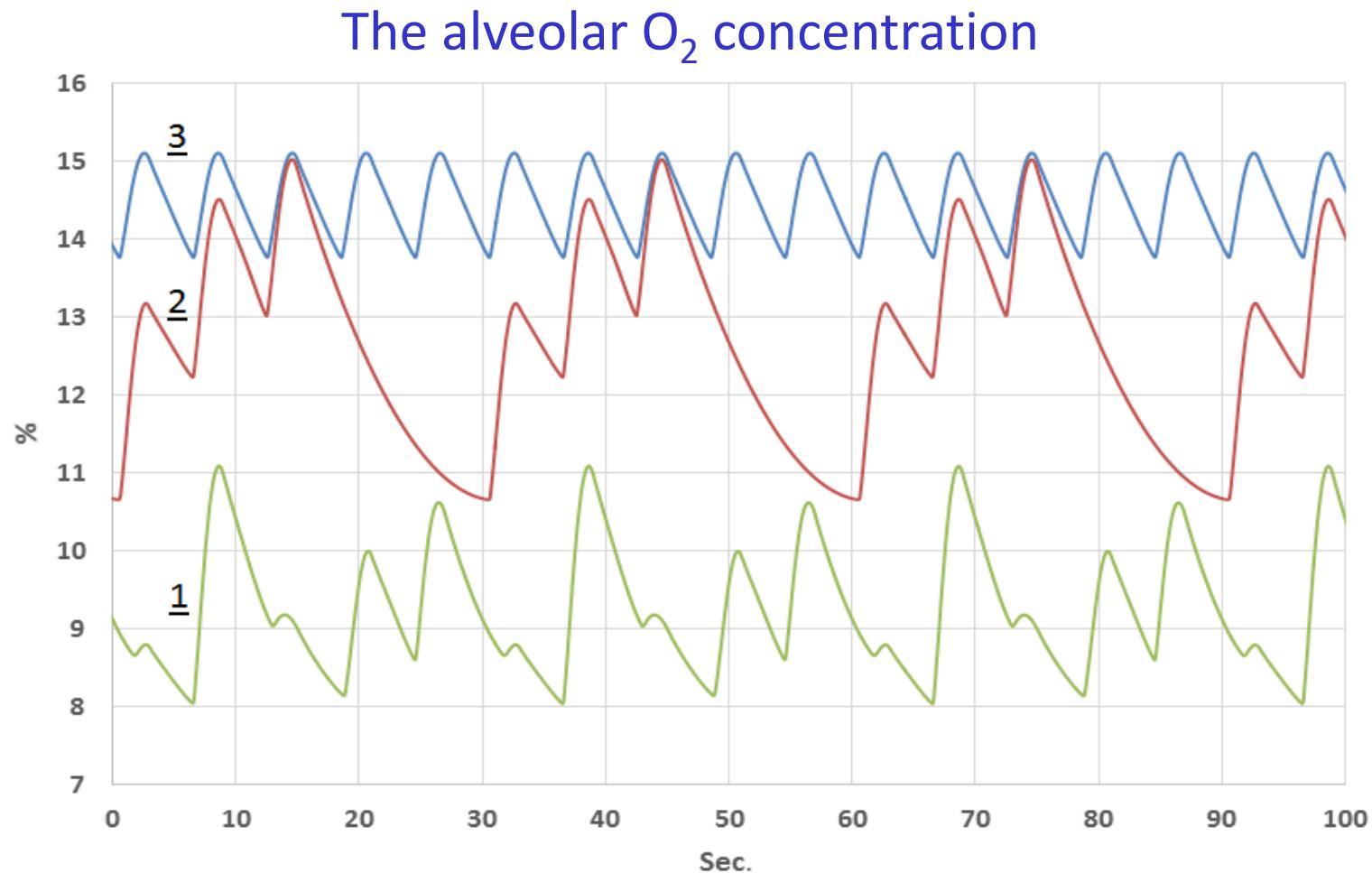


1) Cheyne-Stokes breathing 2) Biot's breathing

3) Normal sinusoidal breathing



The Cheyne-Stokes and the Biot's Breathing numerical simulations



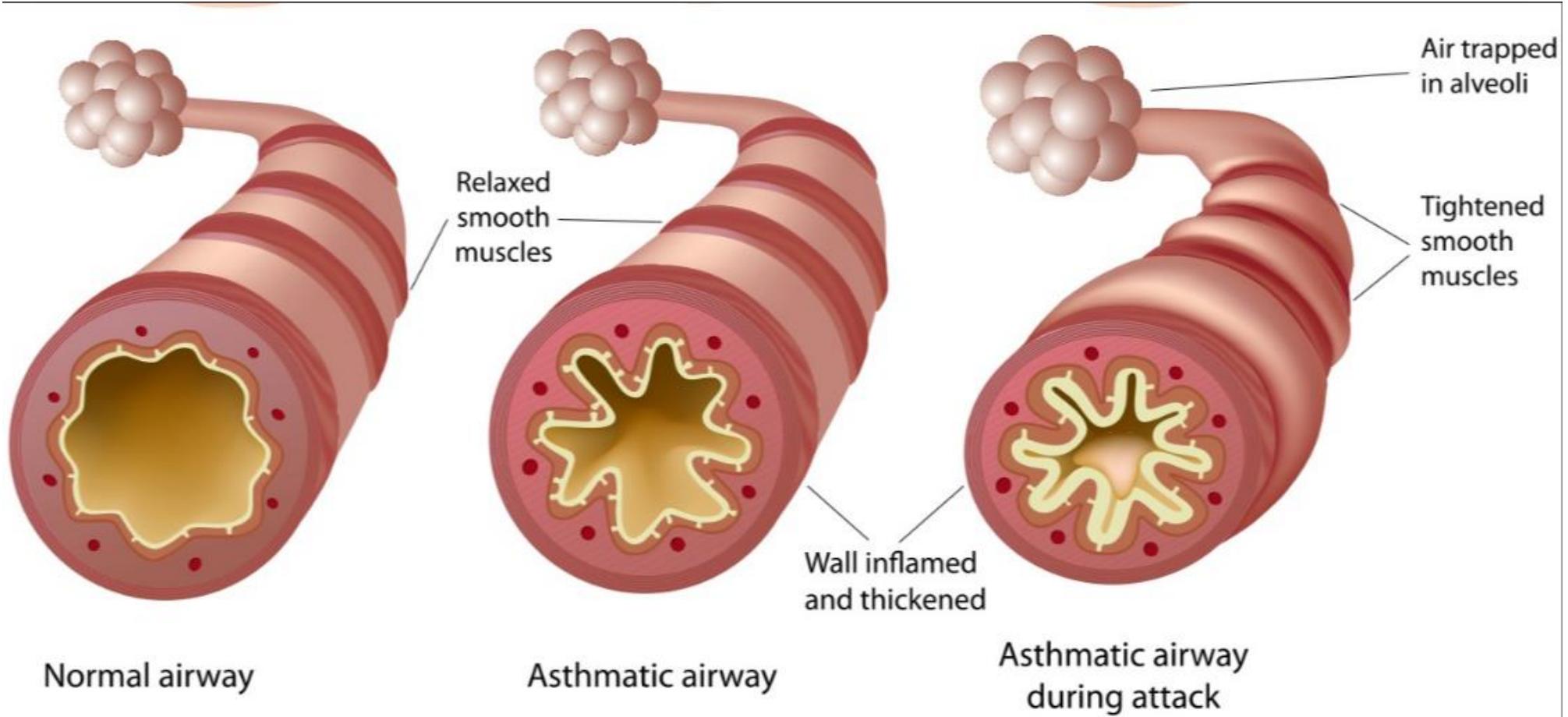
1) Cheyne-Stokes breathing 2) Biot's breathing

3) Normal sinusoidal breathing



Asthma

Bronchial obstruction

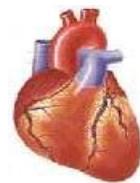


Normal airway

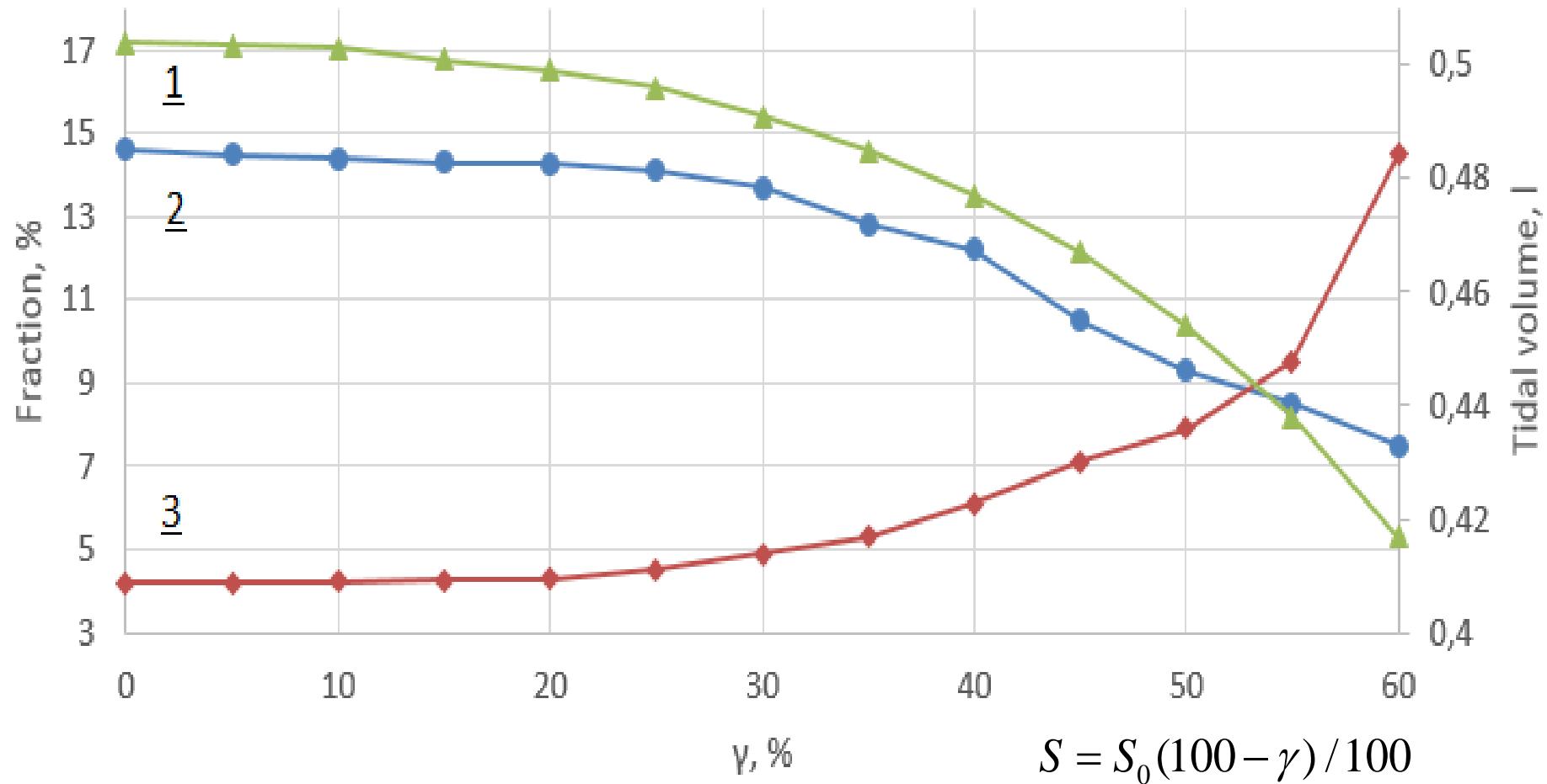
Asthmatic airway

Asthmatic airway
during attack

$$S = S_0(100 - \gamma) / 100$$



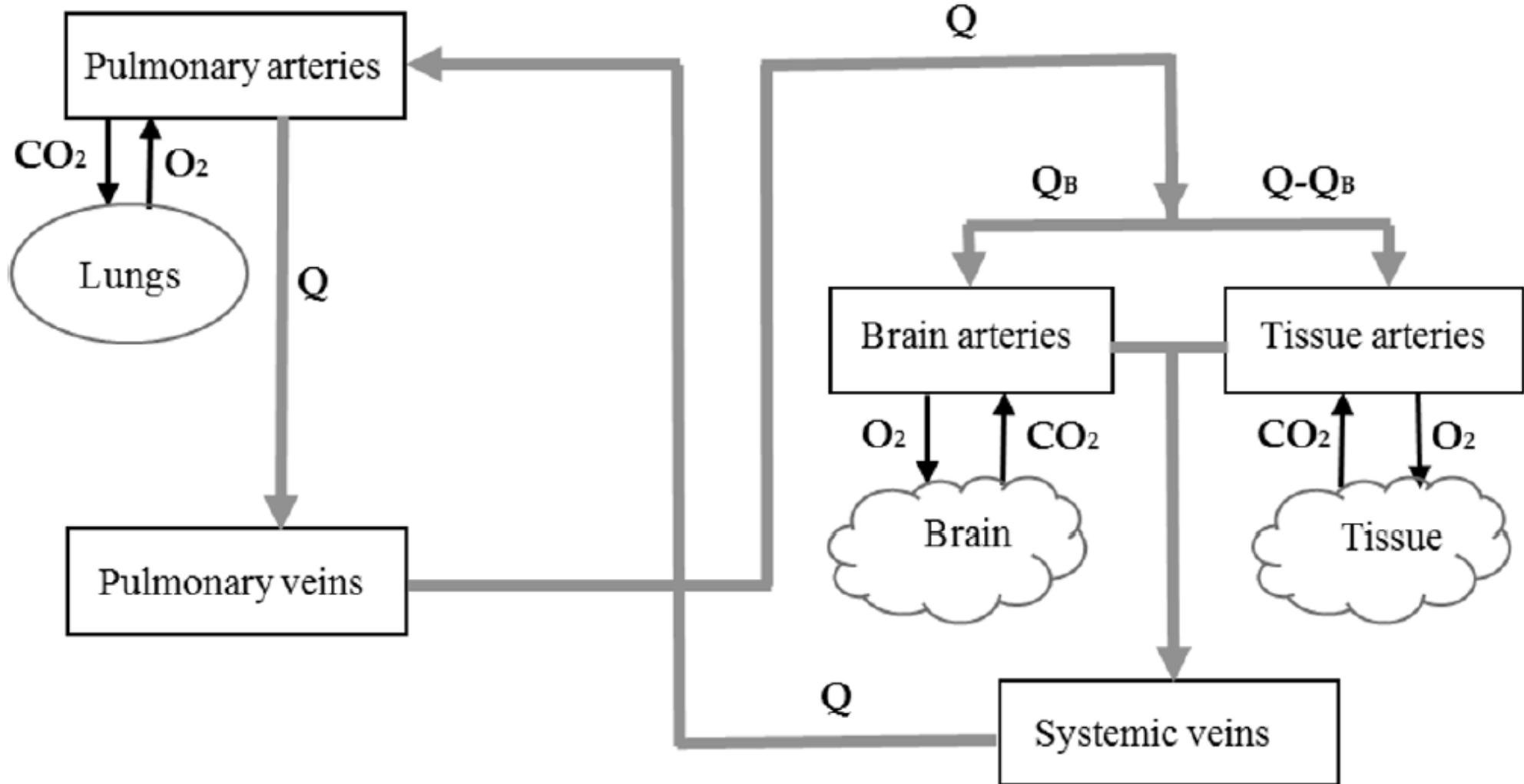
Asthma numerical simulations



1) Tidal volume 2) Alveolar O₂ fraction 3) Alveolar CO₂ fraction



Compartment decomposition of the respiratory and the cardiovascular systems

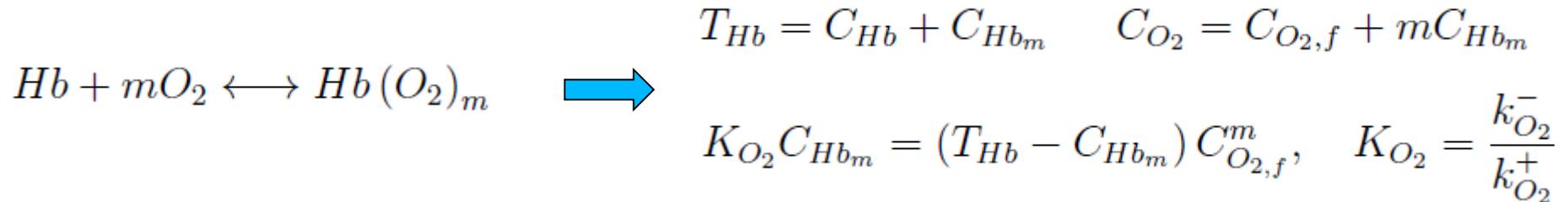




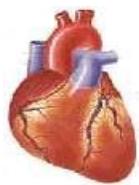
Balance of oxygen and carbon dioxide in the blood



Oxyhemoglobin balance



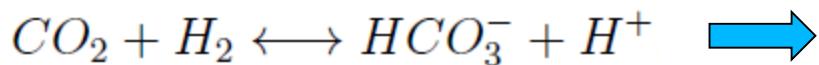
$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\xi_{O_2}(\mathbf{x}) + \chi_{O_2}(\mathbf{x}),$$
$$\xi_{O_2}(\mathbf{x})_i = \frac{x_i + \frac{mT_{Hb}x_i^m}{K_{O_2} + x_i^m}}{S_{O_2}(x_i)}$$
$$S_{O_2}(x_i) = 1 + \frac{m^2 K_{O_2} T_{Hb} x_i^{m-1}}{(K_{O_2} + x_i^m)^2},$$
$$\chi_{O_2}(\mathbf{x}) = \begin{pmatrix} \frac{D_{O_2} S}{V_1 S_{O_2}(x_1)} \left(P_{O_2,alv} - \frac{x_1}{\sigma_{O_2}} \right) \\ 0 \\ 0 \\ -\frac{\dot{V}_{O_2,B}}{V_4 S_{O_2}(x_4)} \\ -\frac{\dot{V}_{O_2,T}}{V_5 S_{O_2}(x_5)} \end{pmatrix},$$



Balance of oxygen and carbon dioxide in the blood



Carbon dioxide balance



$$C_{CO_2} = C_{CO_{2,f}} + C_{HCO_3^-}$$

$$C_{HCO_3^-} = K_{CO_2} \frac{C_{CO_{2,f}}}{C_{H^+}}, \quad K_{CO_2} = \frac{k_{CO_2}^-}{k_{CO_2}^+}$$

$$\frac{d\mathbf{y}}{dt} = \mathbf{A}\xi_{CO_2}(\mathbf{y}) + \chi_{CO_2}(\mathbf{y})$$

$$\xi_{CO_2}(\mathbf{y})_i = \frac{y_i^2 + (K_{CO_2} - Hc_i)y_i}{S_{CO_2}(y_i)K_{CO_2}}$$

$$S_{CO_2}(y_i) = \frac{K_{CO_2} - Hc_i + 2y_i}{K_{CO_2}}$$

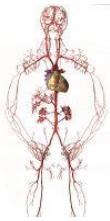
$$\chi_{CO_2}(\mathbf{y}) = \begin{pmatrix} \frac{D_{CO_2}S}{V_1 S_{CO_2}(y_1)} \left(P_{CO_2,alv} - \frac{y_1^2 - y_1 Hc_1}{K_{CO_2} \sigma_{CO_2}} \right) \\ 0 \\ 0 \\ \frac{\dot{V}_{CO_2,B}}{V_4 S_{CO_2}(y_4)} \\ \frac{\dot{V}_{CO_2,T}}{V_5 S_{CO_2}(y_5)} \end{pmatrix}$$



Connectivity matrix



$$\mathbf{A} = \begin{pmatrix} -\frac{Q_0}{V_1} & 0 & \frac{Q_0}{V_1} & 0 & 0 \\ \frac{Q_0}{V_2} & -\frac{Q_0}{V_2} & 0 & 0 & 0 \\ 0 & 0 & -\frac{Q_0}{V_3} & \frac{Q_B}{V_3} & \frac{Q_0-Q_B}{V_3} \\ 0 & \frac{Q_B}{V_4} & 0 & -\frac{Q_B}{V_4} & 0 \\ 0 & \frac{Q_0-Q_B}{V_5} & 0 & 0 & -\frac{Q_0-Q_B}{V_5} \end{pmatrix}$$



Cardiac regulation

The minute cardiac output

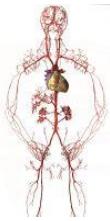
$$Q_0 = Q_{MCO} \left(0.937 + \frac{0.817}{1 + \left(\frac{P_{O_2,SA}}{47.2} \right)^{3.41}} \right) I(P_{CO_2,SA})$$

$$I(P_{CO_2,SA}) = \begin{cases} 1 + 0.03(P_{CO_2,SA} - 40), & N_{CO_2,SA} \leq 1 \\ 1 - 0.025(P_{CO_2,SA} - 40), & N_{CO_2,SA} > 1 \end{cases}$$

$$N_{CO_2,SA} = \frac{P_{CO_2,SA}}{P_{CO_2,SA,0}}$$

The minute cerebral blood flow

$$Q_B = Q_{MCBF} \left(1.014 + \frac{0.734}{1 + \left(\frac{P_{CO_2,SA}}{41.4} \right)^{16.6}} \right) \left(0.43 + \frac{1.91}{1 + 10.6e^{-5.25\log_{10}P_{CO_2,SA}}} \right)$$



Respiratory regulation

The minute lungs ventilation

$$V_E = V_{SS} + (V_C + V_P)$$

$$V_C = K_{cCO_2} (P_{cCO_2} - T_{cCO_2}), V_C \geq 0,$$

$$V_P = K_{pCO_2} (P_{pCO_2} - T_{pCO_2}) + \left(\frac{570}{P_{pO_2} - 26.2} - 8.05 \right) F(CO_2), V_P \geq 0,$$

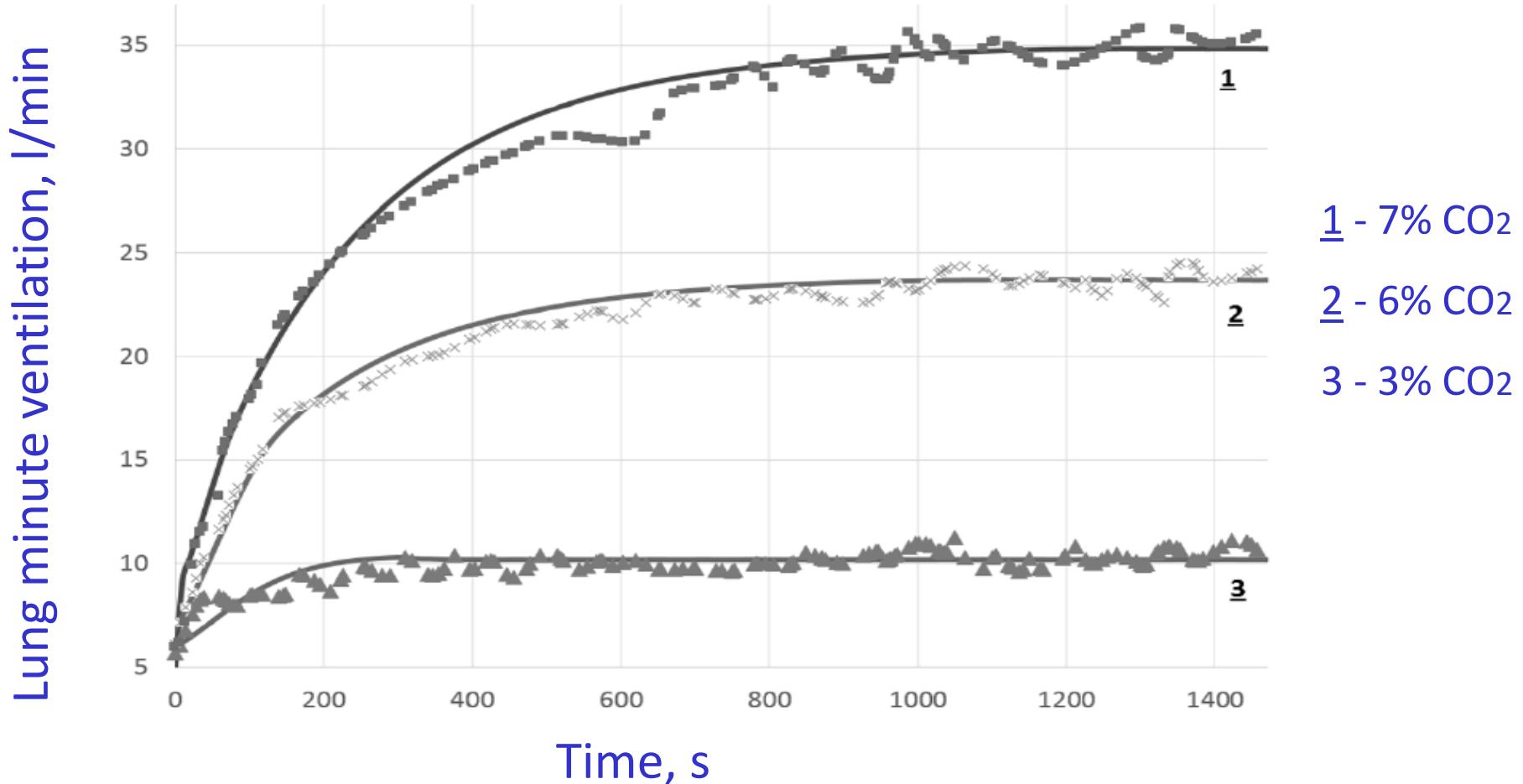
$$F(CO_2) = \begin{cases} (5 - 4N_{pCO_2}^4)^{-1}, & N_{pCO_2} \leq 1 \\ N_{pCO_2}^3, & N_{pCO_2} > 1 \end{cases}, N_{pCO_2} = \frac{P_{pCO_2}}{P_{pCO_2}^0}$$

The minute lungs ventilation, the tidal volume and the ventilation rate dependence

$$V_E = nV_T \quad \begin{cases} n = n_0, \quad V_T = \frac{V_E}{n_0}; & V_E \leq V_{E,T} \\ V_T = \alpha V_E^\beta, \quad n = \frac{V_E}{V_T}; & V_E > V_{E,T} \end{cases}$$



Respiratory regulation during hypercapnia

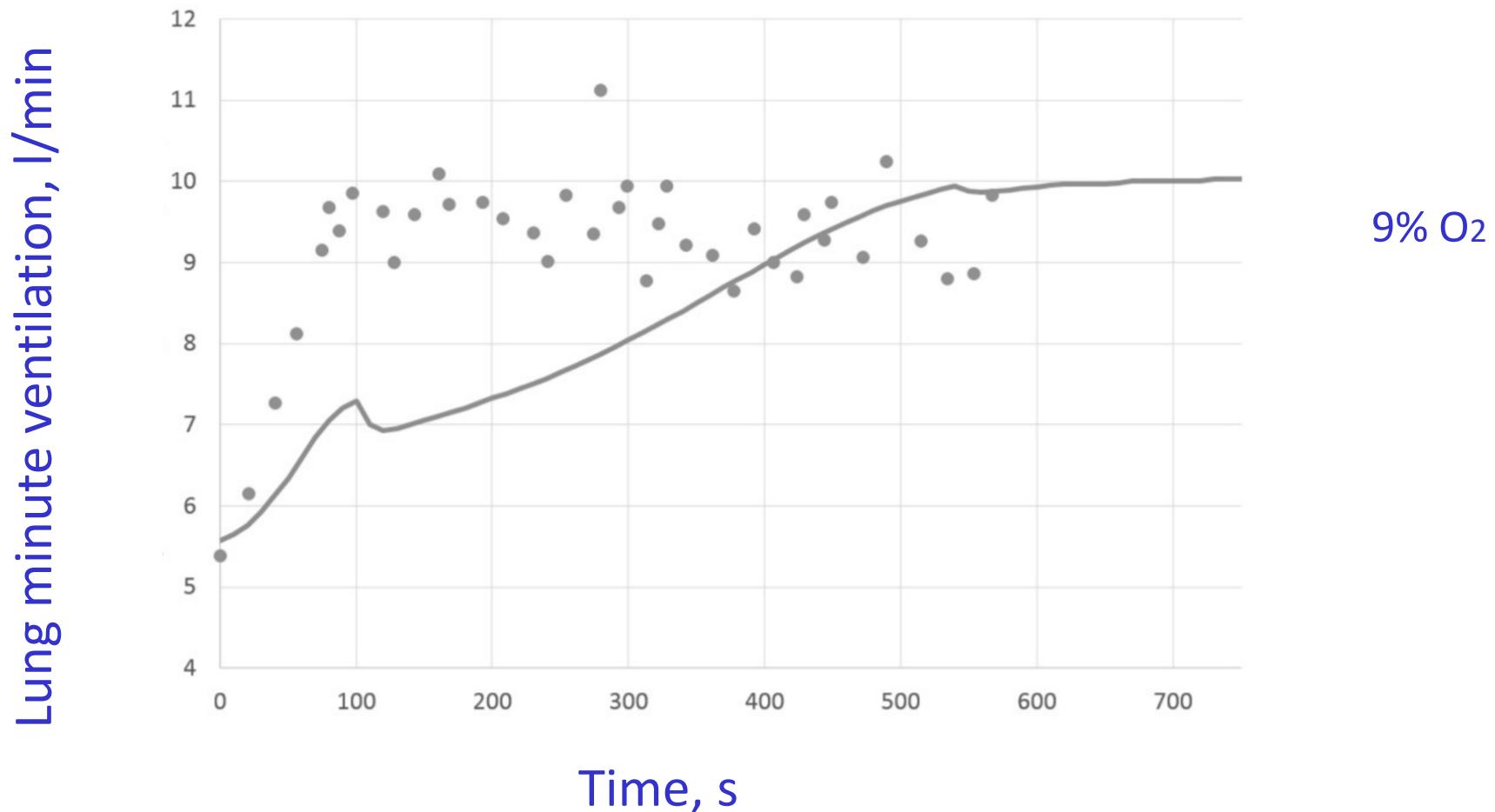


The experiment: Reynolds W. J., Milhorn H. T., Holloman G. H. Transient ventilatory response to graded hypercapnia in man. Journal of applied physiology. 1972. Vol. 33, No. 1. PP. 47-54.

Golov, A. V., Simakov S. S. Mathematical model of respiratory regulation during hypoxia and hypercapnia. Computer research and modeling. 2017; Vol. 2(9). pp.297–310



Respiratory regulation during hypoxia



The experiment: Reynolds W. J., Milhorn H. T., Holloman G. H. Transient ventilatory response to hypoxia with and without controlled alveolar PCO₂. //Journal of applied physiology. —1973. —Vol. 35, No. 2. — PP. 187-196.

Golov, A. V., Simakov S. S. Mathematical model of respiratory regulation during hypoxia and hypercapnia. Computer research and modeling. 2017; Vol. 2(9). pp.297–310



The treadmill load test



**The Center of Innovative Technologies
in Sport and Training of the
Representative Teams, Moscow**

Treadmill parameters

Initial speed: 7 km/h

Increased by 0.1 km/h every 10 sec

Measured data $W = Mgv \sin 5^\circ$

Athlete	H, m	M, kg	RQ	$\dot{V}_{O_2,T}$, l/min	$\dot{V}_{O_2,B}$, l/min	$C_{la,0}$, mM	W_{LT} , w	V_E , l/min	n_0
S1	1.66	61.7	0.84	0.232	0.058	2.1	255	14.9	17.3
S2	1.80	70.8	0.94	0.224	0.060	1.8	324	19.6	20.8
S3	1.92	85.7	0.90	0.288	0.072	1.5	392	21.2	16.9
S4	1.88	73.0	0.83	0.192	0.048	3.0	294	15.2	14.3
S5	1.71	50.9	0.82	0.216	0.054	1.8	205	11.1	14.6
S6	1.76	74.0	0.88	0.160	0.040	2.1	435	11.7	18.1
S7	1.82	70.5	0.89	0.224	0.056	0.9	308	18.0	22.5
S8	1.85	74.6	0.89	0.176	0.044	0.7	395	21.4	18.5
S9	1.79	75.3	0.85	0.248	0.062	1.2	344	18.2	22.3
S10	1.81	71.4	0.90	0.256	0.064	1.7	332	16.8	24.9
Avg	1.80	70.8	0.87	0.224	0.056	1.7	328	16.8	19.0



Muscle metabolism model

The physical work (sum of aerobic and anaerobic parts)

$$W = W_a + W_{an}$$

$$W_a = e_a \dot{V}_{O_2,M}$$

$\dot{V}_{O_2,M}$ - muscles request

$$W_{an} = e_{la} \dot{V}_{la}$$

$$e_{la} = \frac{3M}{V_{blood}} e_a \quad (\text{energy equivalence})$$

$$\dot{V}_{la,u} = \begin{cases} u_{la} (C_{la} - C_{la,0}), & C_{la} \geq C_{la,0} \\ 0, & C_{la} < C_{la,0} \end{cases}$$

Aerobic work fraction

$$\sigma(W) = W_a/W = 1 - \beta e^{\alpha(W - W_{LT})}$$



Update of the balance of oxygen and carbon dioxide in the blood



$$\chi_{O_2}(\mathbf{x}) = \begin{pmatrix} \frac{D_{O_2}S}{V_1 S_{O_2}(x_1)} \left(P_{O_2,alv} - \frac{x_1}{\sigma_{O_2}} \right) \\ 0 \\ 0 \\ -\frac{\dot{V}_{O_2,B}}{V_4 S_{O_2}(x_4)} \\ -\frac{1}{V_5 S_{O_2}(x_5)} \left(\dot{V}_{O_2,T} + \dot{V}_{O_2,M} \right) \end{pmatrix}$$

$$\chi_{CO_2}(\mathbf{y}) = \begin{pmatrix} \frac{D_{CO_2}S}{V_1 S_{CO_2}(y_1)} \left(P_{CO_2,alv} - \frac{y_1^2 - Hc_1 y_1}{K_{CO_2} \sigma_{CO_2}} \right) \\ 0 \\ 0 \\ \frac{\dot{V}_{CO_2,B}}{V_4 S_{CO_2}(y_4)} \\ \frac{1}{V_5 S_{CO_2}(y_5)} \left(\dot{V}_{CO_2,T} + \dot{V}_{O_2,M} RQ + \kappa_{CO_2} (z_5 - C_{la,0}) \right) \end{pmatrix}$$



Muscle efficiency model



$$\eta = \frac{e_a}{e_{O_2}}.$$

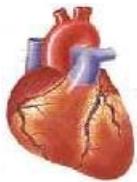
- Efficiency of the chemical to the mechanical energy transformation

$$\begin{cases} \gamma_C + 0.7\gamma_F = RQ \\ \gamma_C + \gamma_F = 1 \end{cases}$$

$RQ = 0.7$ - fat metabolism
 $RQ = 1$ - carbohydrate metabolism
 $\gamma_{C,F}$ - fraction of fats and carbohydrates

$$e_{O_2} = 20.9\gamma_C + 19.5\gamma_F \approx 4.7RQ + 16.23$$

$$\eta = \frac{3Me_{la}}{V_{blood}(4.7RQ + 16.23)}$$



Parameters identification

Unknown parameters: e_a , u_{la} , κ_{CO_2} , β , α

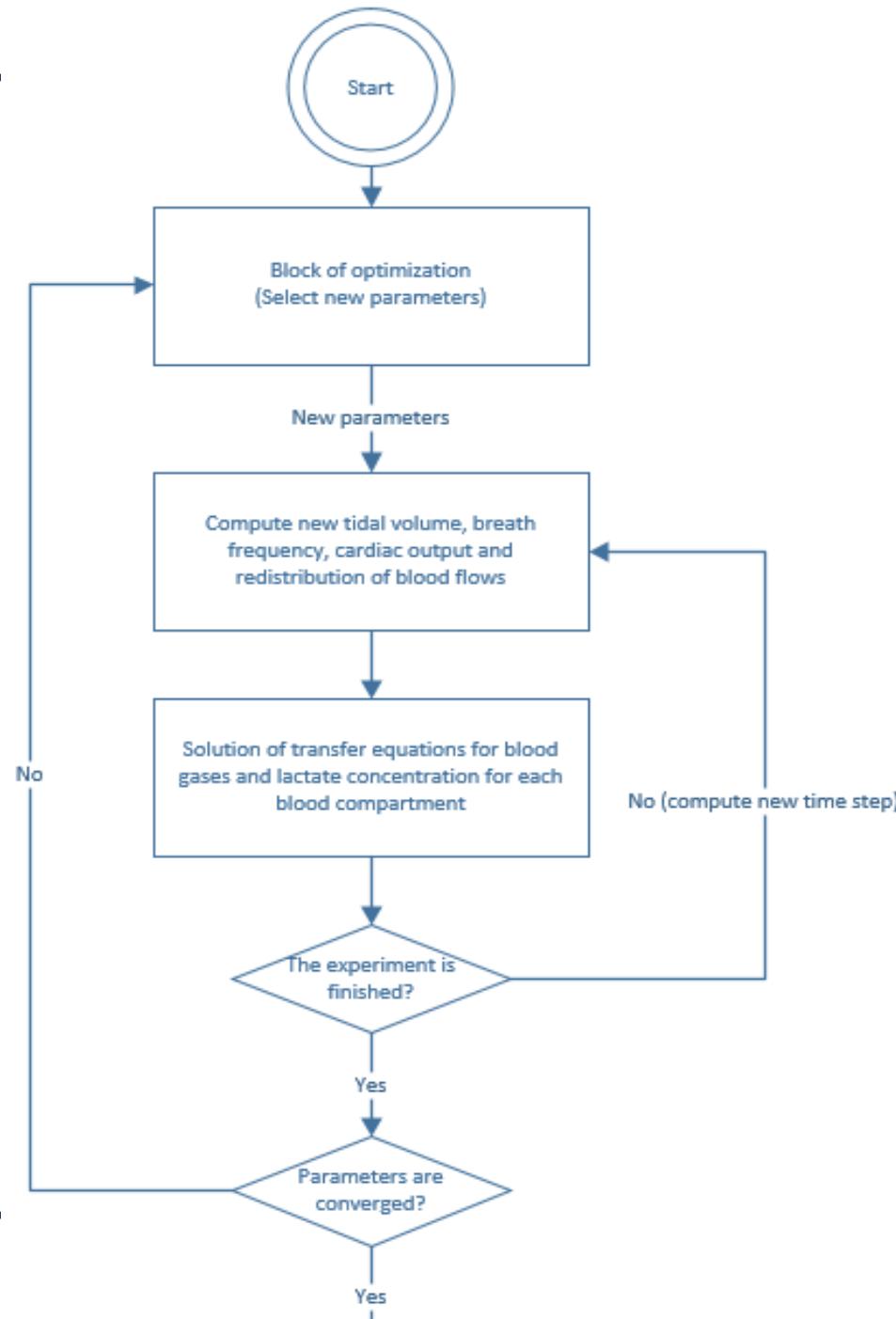
$$\Phi = \sum_{M \in \{O_2, CO_2, V_E, LA\}} \left(\frac{1}{N_M} \sum_{i=1}^{N_M} \text{huber}(\Delta_{M,i}) \right),$$

$$\text{huber}(\Delta) = \begin{cases} \frac{1}{2}\Delta^2, & |\Delta| \leq \delta \\ \delta(|\Delta| - \frac{1}{2}\delta), & |\Delta| > \delta \end{cases}, \Delta_{M,i} = \frac{x_{M,i}^{\text{exp}} - x_{M,i}^{\text{num}}}{x_{M,i}^{\text{exp}}}, \delta_M = 1.5 \sqrt{\frac{1}{N_M} \sum_{i=1}^{N_M} \Delta_{M,i}^2}$$

Differential evolution stochastic method was used for optimization

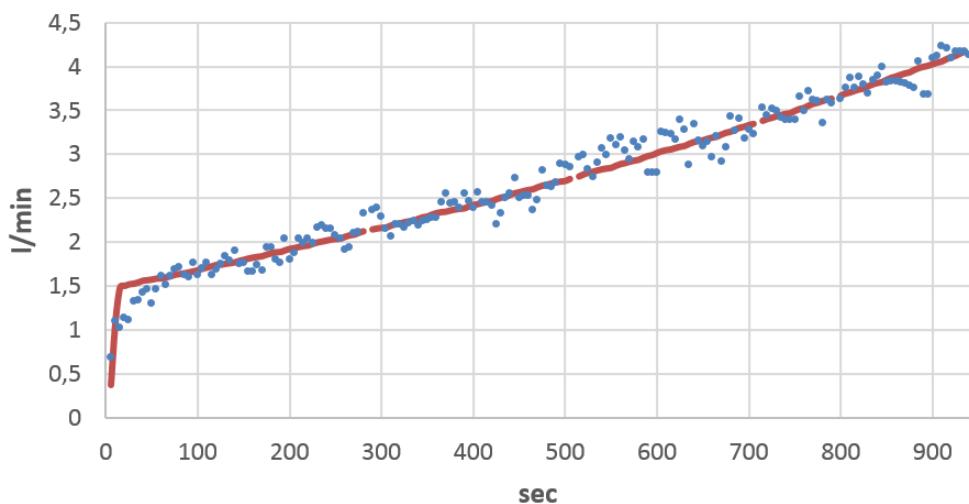


Parameters identification

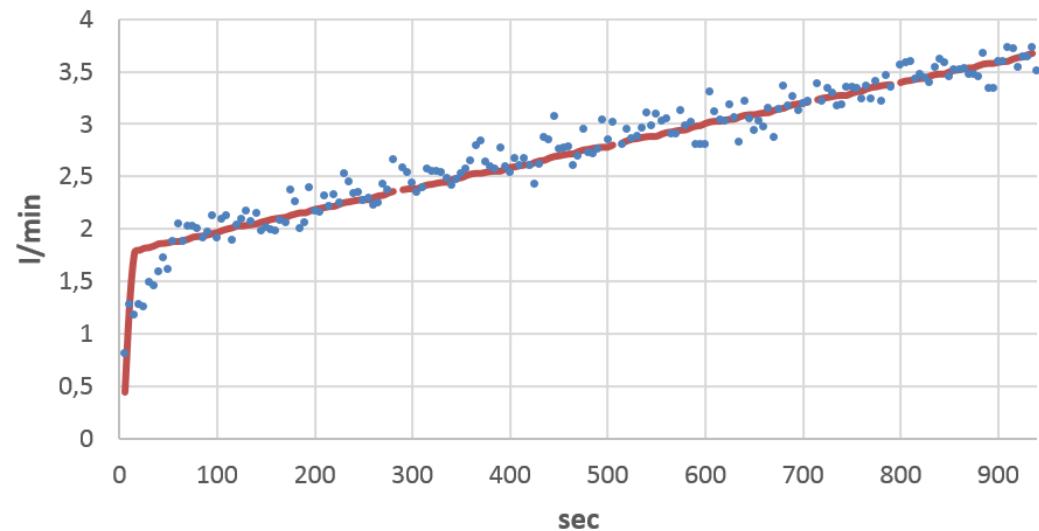




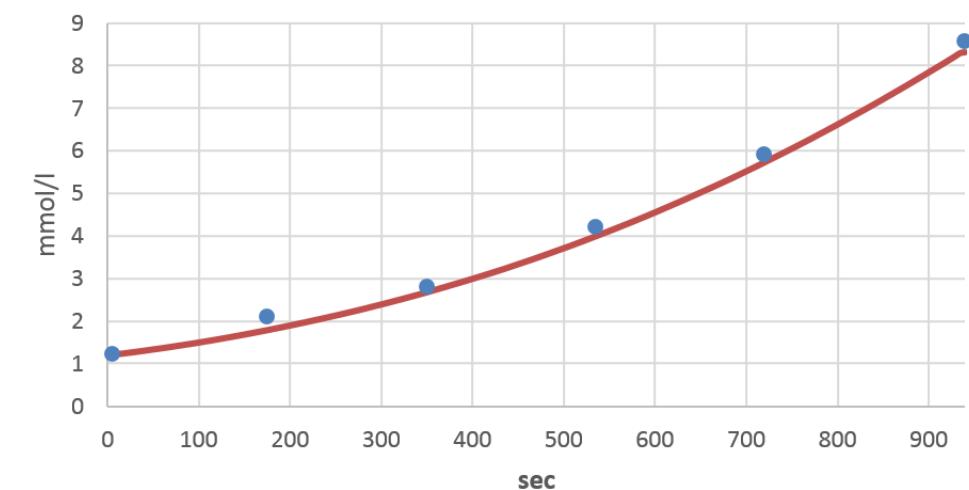
Parameter identification



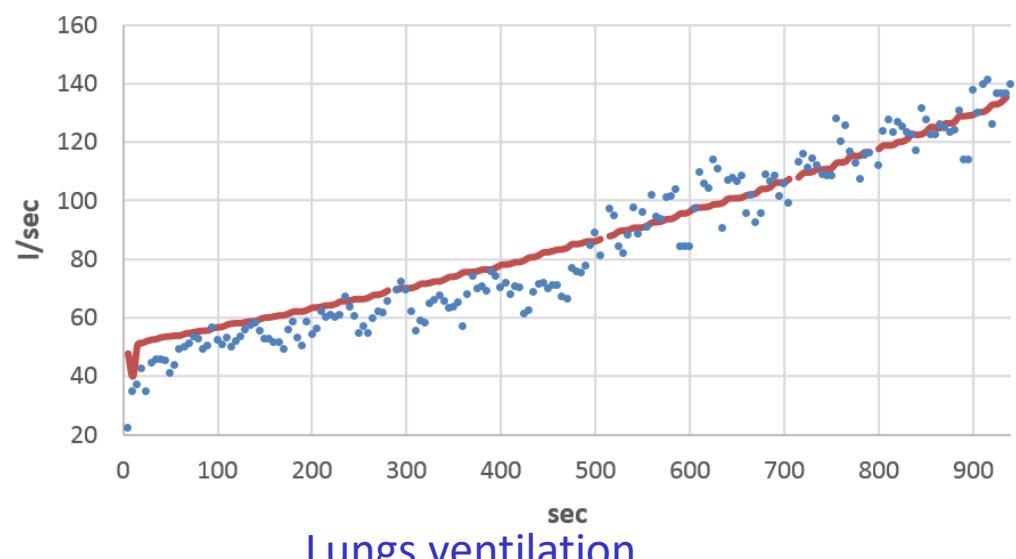
Minute CO_2 production



Minute O_2 consumption



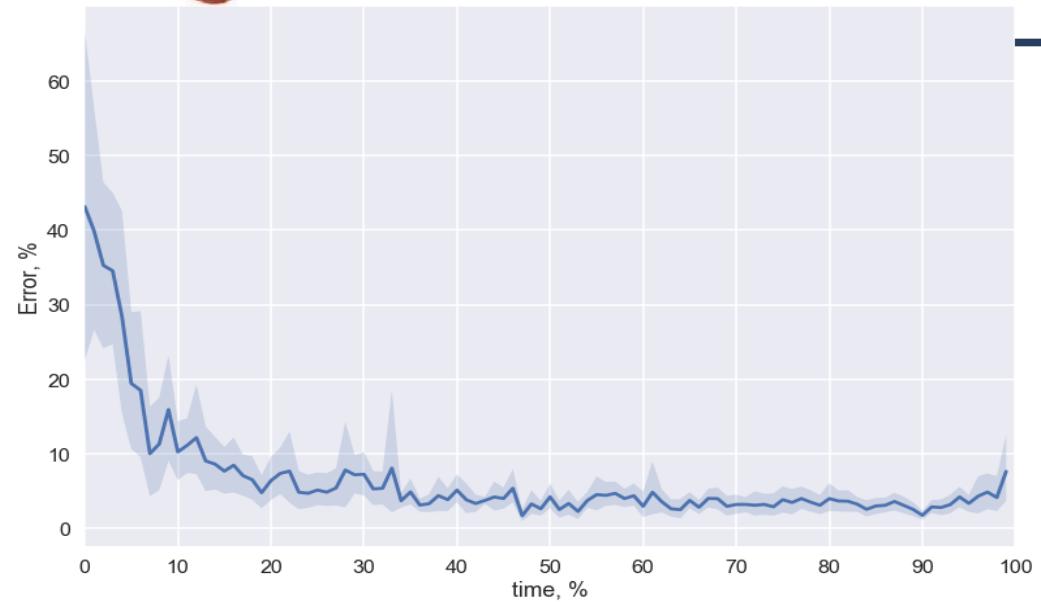
Lactate concentration in blood



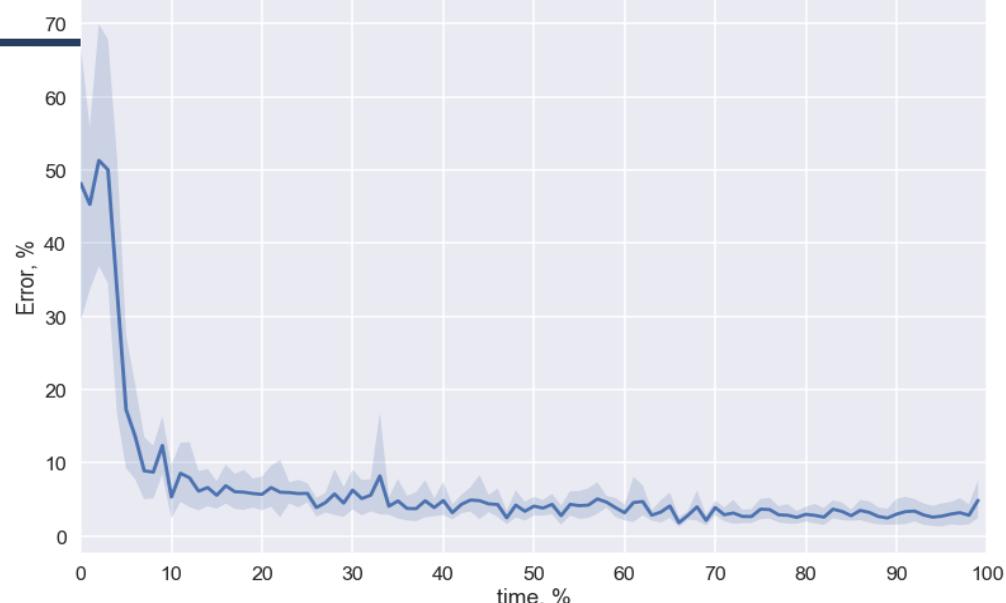
Lungs ventilation



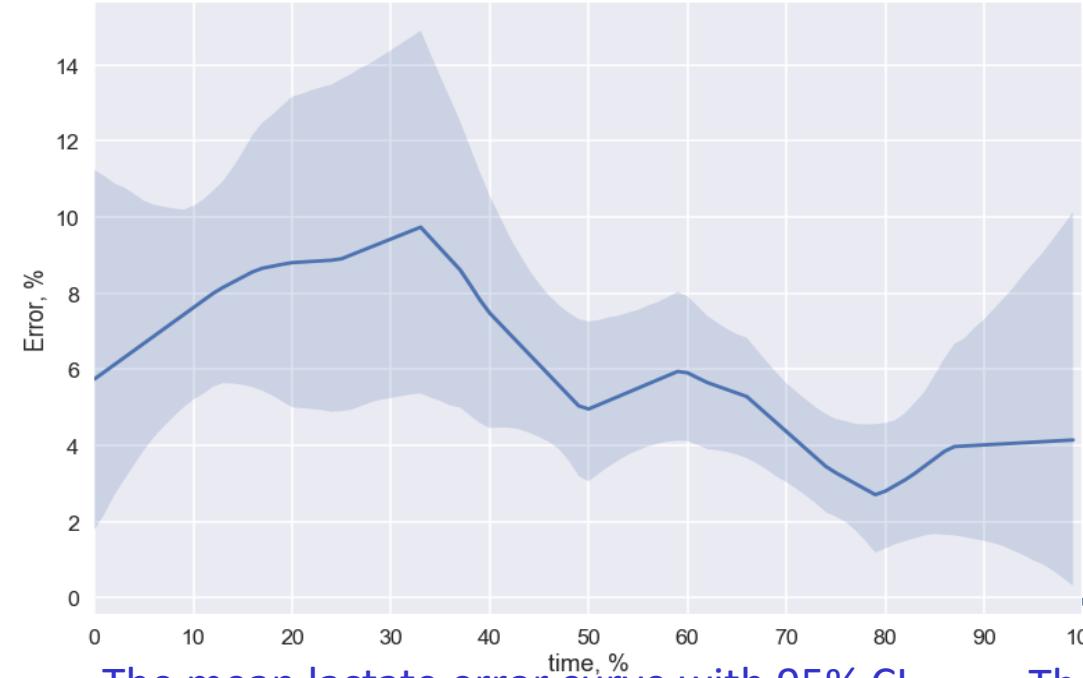
The relative modeling error



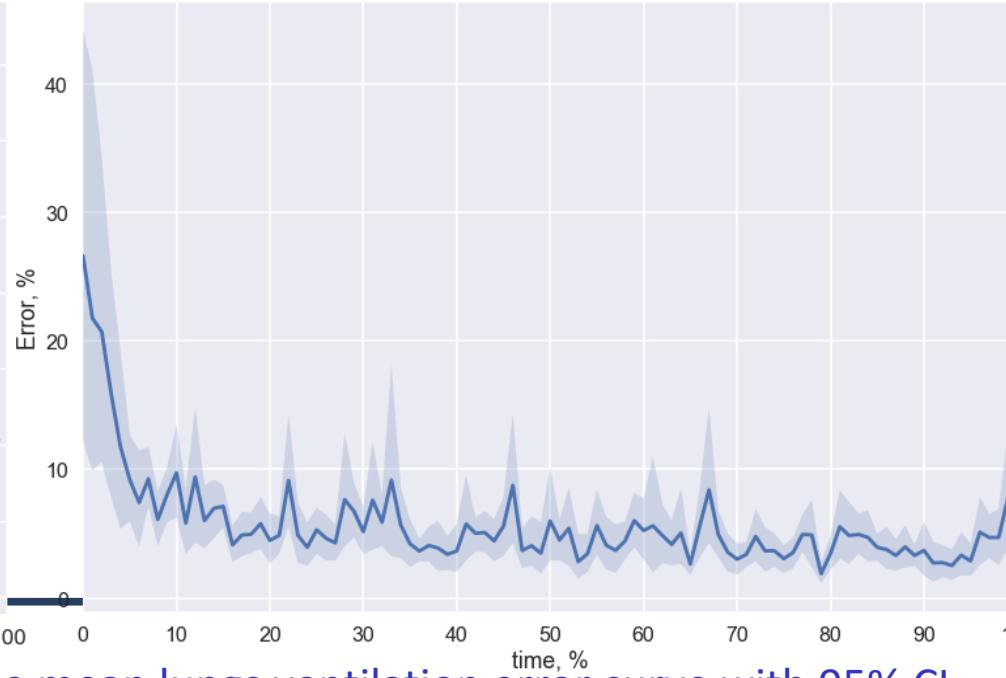
The mean CO₂ error curve with 95% CI



The mean O₂ error curve with 95% CI



The mean lactate error curve with 95% CI

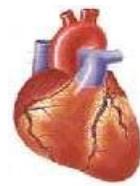


The mean lungs ventilation error curve with 95% CI



The relative modeling error

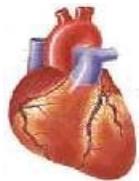
Sportsmen	$\sigma_{err,O_2}, \%$	$\sigma_{err,CO_2}, \%$	$\sigma_{err,VE}, \%$	$\sigma_{err,LA}, \%$
S1	2.3	3.5	2.5	4.8
S2	4.1	3.0	3.8	6.6
S3	4.5	3.6	3.8	4.6
S4	3.2	3.7	4.3	7.2
S5	3.3	3.5	5.2	3.4
S6	6.3	7.1	10.3	4.6
S7	3.5	4.0	4.3	3.3
S8	3.1	2.9	3.9	9.0
S9	3.6	4.7	6.6	12.2
S10	4.5	4.3	5.9	3.4
Avg	4.3	4.5	5.4	6.4



Identified parameters



	e_a , kJ/l	u_{la} , $10^{-3} s^{-1}$	κ_{CO_2} , s^{-1}	β , 10^{-2}	α , 10^{-2}
S1	4.87 ± 0.05	1.6 ± 0.18	3.78 ± 0.54	1.92 ± 0.04	7.88 ± 0.18
S2	4.42 ± 0.07	0.88 ± 0.09	2.11 ± 0.55	0.8 ± 0.02	7.3 ± 0.04
S3	3.96 ± 0.04	1.4 ± 0.07	1.79 ± 0.52	1.32 ± 0.02	9.8 ± 0.11
S4	3.92 ± 0.06	1.23 ± 0.1	1.63 ± 0.26	0.7 ± 0.01	6.62 ± 0.1
S5	4.88 ± 0.02	1.25 ± 0.12	2.02 ± 0.04	1.6 ± 0.02	10.36 ± 0.08
S6	4.97 ± 0.03	1.75 ± 0.06	7.04 ± 0.38	0.69 ± 0.0	7.6 ± 0.02
S7	4.08 ± 0.04	1.66 ± 0.28	2.66 ± 0.18	0.4 ± 0.01	8.84 ± 0.02
S8	4.94 ± 0.02	5.42 ± 0.97	4.87 ± 0.28	2.29 ± 0.16	3.97 ± 0.03
S9	4.69 ± 0.09	8.75 ± 0.73	1.45 ± 0.19	4.58 ± 0.2	3.91 ± 0.01
S10	4.71 ± 0.09	2.03 ± 0.1	4.81 ± 0.58	1.1 ± 0.02	7.75 ± 0.05



Mechanical effectiveness



Sportsmen	$\eta, \%$	Sportsmen	$\eta, \%$
S1	23.3 ± 0.2	S6	24.1 ± 0.1
S2	22.0 ± 0.3	S7	19.9 ± 0.2
S3	19.4 ± 0.2	S8	24.2 ± 0.1
S4	19.0 ± 0.3	S9	22.9 ± 0.4
S5	23.5 ± 0.1	S10	22.8 ± 0.4

$$\eta = \frac{e_a}{e_{O_2}}.$$



Thank you

