TECHNISCHE UNIVERSITÄT MÜNCHEN

Buhl-Strohmaier-Stiftung

STIFTUNG WÜRTH

Viability Approach to Autoregulation of Cerebral Blood Flow in Preterm Infants

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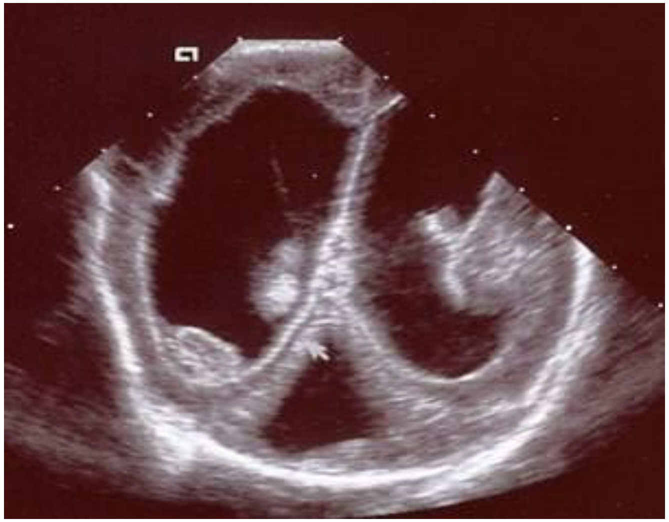
Motivation

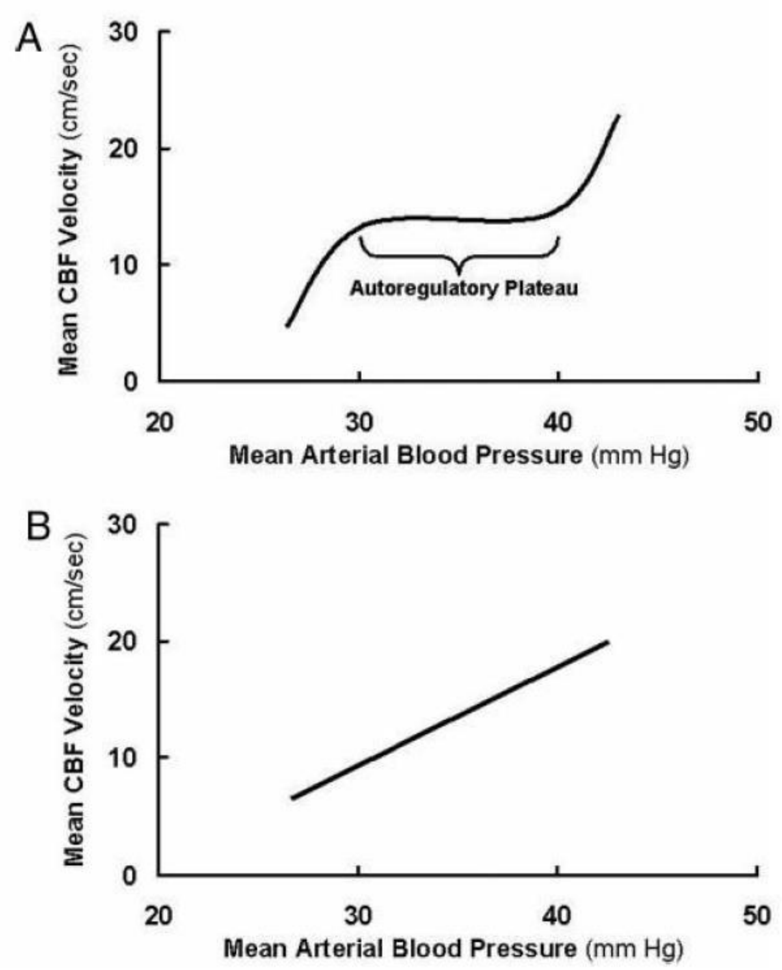
Incidence of intracranial hemorrhages in newborns weighting less than 1500 gm dropped to 20%

Ultrasonic image showing intraventricular bleeding in a preterm newborn



The cause of brain bleeding is the **germinal matrix** of the immature brain!

Cerebral autoregulation



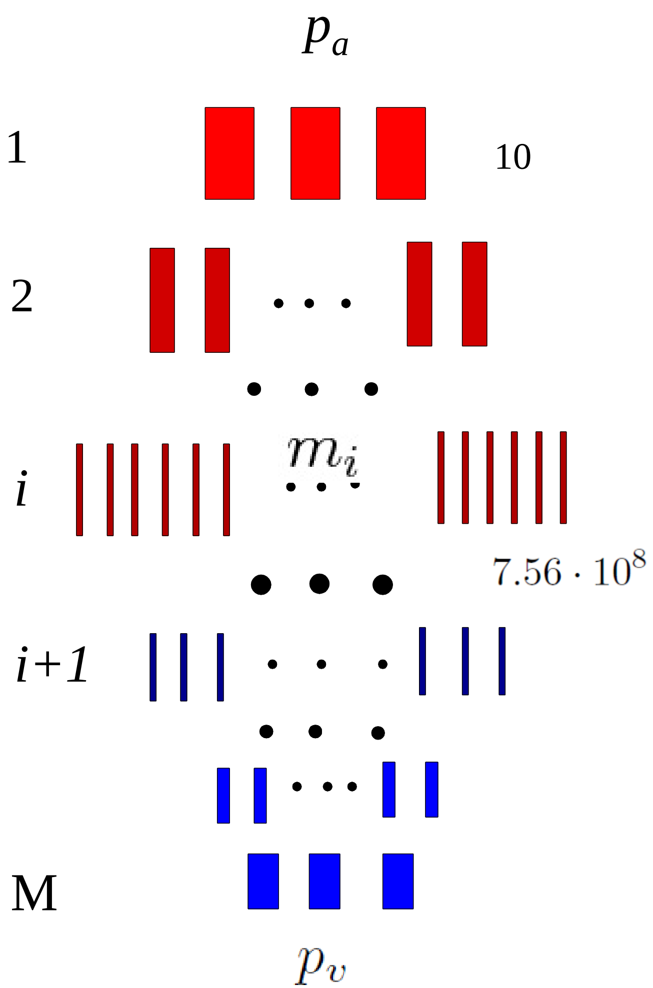
Intact autoregulation

Impaired autoregulation

M. van de Bor, F.J. Walther. Cerebral blood fow velocity regulation in preterm infants. Biol. Neonate 59, 1991.

H.C.Lou, N.A.Lassen, B. Friis-Hansen. Impaired autoregulationopf cerebral blood flow in the distressed newborn infant. J. Pediatri. 94, 1979.

Cerebral blood flow



$$CBF = (p_a - p_{ic})\left(\sum_{i=1}^{M} \frac{R_i}{m_i}\right)^{-1}$$

p_a the mean arterial pressure

p_{ic} the intracranial pressure (constant)

M the number of levels

m_i the number of vessels at i_{th} level

R_i the resistance of each vessel at i_{th} level

$R_i = 8\mu l_i / \pi r_i^4$ in the case of Poiseuille flow

l_i, r_i the length and radius of vessels at i_{th} level

$r_i = r_i^0 \cdot \lambda \cdot (1 + c_i \cdot pCO_2)$

r_i^0 the reference radius

λ modifier due to the vascular volume change

c_i, pCO_2 the reactivity and partial CO_2 pressure

S.K.Piechnik, P.A.Chiarelli, P. Jezzard,
Modelling vascular reactivity to investigate the basis of the relationship between cerebral blood volume and flow under CO2 manipulation.
NeuroImage 39, 2008.

Micropolar field equations for incompressible viscous fluids

$$-(\nu + \nu_r)\Delta\vec{v} + \nabla p = 2\nu_r \operatorname{rot}\vec{\omega}$$

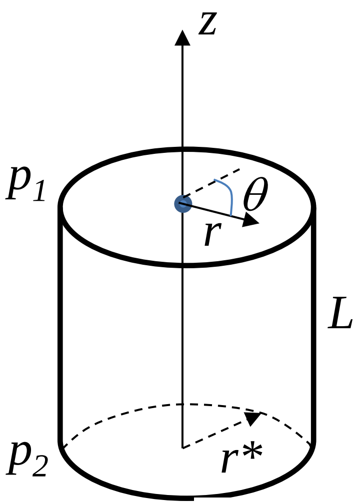
$$-(c_a + c_d)\Delta\vec{\omega} - (c_0 + c_d - c_a)\nabla \operatorname{div}\vec{\omega} + 4\,\nu_r\,\vec{\omega} = 2\,\nu_r \operatorname{rot}\vec{v}$$

$$\operatorname{div}\vec{v} = 0$$

$\vec{v}$	the velocity field
$\vec{\omega}$	the micro-rotation field
p	the hydrostatic pressure
ν	the classical viscosity coefficient
ν_r	the vortex viscosity coefficient
$c_a,\ c_d,\ c_0$	the spin gradient viscosity coefficients

G. Lukaszewicz. Micropolar fluids: Theory and applications. Birkhäuser: Boston, 1999.

Micropolar field equations in cylindrical coordinate system



Assumptions: $v_r = v_\theta = 0,\ v_z = u(r)$

$$\omega_r = 0,\ \omega_\theta = \omega(r),\ \omega_z = 0$$

$$(\nu + \nu_r)\left(u'' + \frac{1}{r}\ u'\right) + 2\nu_r \frac{(r\omega)'}{r} = \frac{dp}{dz} \tag{1}$$

$$(c_d + c_a)\left(\omega'' + \frac{1}{r}\omega' - \frac{1}{r^2}\omega\right) - 2\nu_r u' - 4\nu_r \omega = 0 \tag{2}$$

Boundary conditions: $u|_{r=r^*} = 0,\ u'|_{r=r^*} = -(2+s)\omega$ (Parameter s is a measure of suspension concentration)

+ uniformity conditions on $r=0$

Solutions have the form: $u = u(I_0(r), I_1(r)),\ \omega = \omega(I_1(r))$

I_0 , I_1 are the modified Bessel functions

M.E.Erdoğan. Polar effects in apparent viscosity of a suspension. Rheol. Acta 9, 1970.

Computation of solution using power-series expansion

Note that $\dfrac{dp}{dz} = const \Longrightarrow p = (p_1 - p_2)/L$

Integrate equation (1) and express ω through u to obtain

$$\omega = -\frac{\nu + \nu_r}{2\nu_r} u' + \frac{p\, r}{4\, \nu_r}$$

Plug ω in equation (2) and denote $w = u'$:

$$r^2\, w'' + r\, w' - a\, r^2\, w - w + b\, r^3 = 0,$$

where $a = \dfrac{4\, \nu\, \nu_r}{(\nu + \nu_r)(c_a + c_d)}$; $b = \dfrac{2\, \nu_r\, p}{(\nu + \nu_r)(c_a + c_d)}$ (set $p = 1$)

Boundary conditions

$$w(0) = 0; \;\; w(r^*) = \frac{p\, r^*}{2[\nu + (1 - \alpha)\nu_r]} = d$$ (set $p = 1$)

Computation of solution using power-series expansion

Searching for the solution in the form

$$w = a_0 + a_1\, r + a_2\, r^2 + a_3\, r^3 + a_4\, r^4 + a_5\, r^5$$

1) $w(0) = 0 \;\; \Rightarrow a_0 = 0$

2) $S(r^1) = 0 \;\; \Rightarrow 0 = 0$

3) $S(r^2) = 0 \;\; \Rightarrow 3\, a_2 - a \cdot a_0 = 0$

4) $S(r^3) = 0 \;\; \Rightarrow 8\, a_3 - a \cdot a_1 + b = 0$

5) $S(r^4) = 0 \;\; \Rightarrow 15\, a_4 - a \cdot a_2 = 0$

6) $S(r^5) = 0 \;\; \Rightarrow 24\, a_5 - a \cdot a_3 = 0$

7) $w(r^*) = d \;\; \Rightarrow a_0 + a_1\, r^* + a_2\, r^{*2} + a_3\, r^{*3} + a_4\, r^{*4} + a_5\, r^{*5} = d$

Flow $\quad \mathcal{Q} = \overbrace{-2\pi \int_0^{r^*} u(r)\, r\, dr}^{\mathcal{Q}_1} \cdot \left(\dfrac{p_1 - p_2}{L}\right)$

Velocity $\quad u(r) = \displaystyle\int_0^{r} w(\eta)\, d\eta - \int_0^{r^*} w(\eta) d\eta\,,$ $\qquad$ Resistance $\quad R^{mp} = \dfrac{L}{\mathcal{Q}_1}$

CBF and *Resistance* computed with Maple software

$(R := r^*)$

$$
\begin{aligned}
Q := {} & \frac{1}{48} \frac{a\,(a\,d - b\,R)\,R^7}{192 + 24\,R^2\,a + R^4\,a^2} \\
& + \frac{(a\,d - b\,R)\,R^5}{192 + 24\,R^2\,a + R^4\,a^2} \\
& + \frac{1}{8} \frac{\left(192\,d + 24\,R^3\,b + R^5\,a\,b\right)\,R^3}{192 + 24\,R^2\,a + R^4\,a^2} + \frac{1}{2} \Bigg(\\
& - \frac{6\,(a\,d - b\,R)\,R^3}{192 + 24\,R^2\,a + R^4\,a^2} \\
& - \frac{1}{6} \frac{a\,(a\,d - b\,R)\,R^5}{192 + 24\,R^2\,a + R^4\,a^2} \\
& - \frac{1}{2} \frac{\left(192\,d + 24\,R^3\,b + R^5\,a\,b\right)\,R}{192 + 24\,R^2\,a + R^4\,a^2} \Bigg) R^2
\end{aligned}
$$

$(R := r^*)$

$$
\begin{aligned}
Res := {} & \frac{1}{2} L \Bigg/ \Bigg(\pi \Bigg(\frac{1}{48} \frac{a\,(a\,d - b\,R)\,R^7}{192 + 24\,R^2\,a + R^4\,a^2} \\
& + \frac{(a\,d - b\,R)\,R^5}{192 + 24\,R^2\,a + R^4\,a^2} \\
& + \frac{1}{8} \frac{\left(192\,d + 24\,R^3\,b + R^5\,a\,b\right)\,R^3}{192 + 24\,R^2\,a + R^4\,a^2} + \frac{1}{2} \Bigg(\\
& - \frac{6\,(a\,d - b\,R)\,R^3}{192 + 24\,R^2\,a + R^4\,a^2} \\
& - \frac{1}{6} \frac{a\,(a\,d - b\,R)\,R^5}{192 + 24\,R^2\,a + R^4\,a^2} \\
& - \frac{1}{2} \frac{\left(192\,d + 24\,R^3\,b + R^5\,a\,b\right)\,R}{192 + 24\,R^2\,a + R^4\,a^2} \Bigg) R^2 \Bigg) \Bigg)
\end{aligned}
$$

Thus, we have in the case of a micropolar fluid:

$$CBF = (p_a - p_{ic})\Big(\sum_{i=1}^{M} \frac{R_i^{mp}}{m_i}\Big)^{-1}$$

Here R_i^{mp} are computed as above with $r^* := r_i$, where, as before,

$$r_i = r_i^0 \cdot \lambda \cdot (1 + c_i \cdot pCO_2)$$

r_i^0 the reference radius of vessels at i_{th} level

λ modifier due to the vascular volume change

c_i, pCO_2 the reactivity and partial CO_2 pressure, respectively

Finally, we have in both Newtonian and micropolar fluid cases:

$$CBF = q(p_a, \lambda, pCO_2),$$

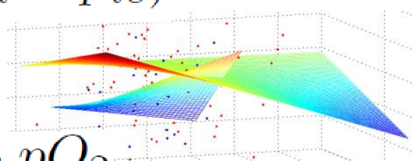
where q is a quickly computable function.

Model equations

Dynamic equations
$$\frac{dC_a}{dt} = \frac{1}{\tau}\left[F\left(\frac{q(p_a, \lambda, pCO_2) - q_0}{q_0}\right) - C_a\right] + u$$
$$\frac{d}{dt}pCO_2 = -k_1(pCO_2 - v_1)$$
$$\frac{d}{dt}pO_2 = -k_2(pO_2 - v_2)$$

Additional dependencies $\lambda = \alpha\sqrt{V_a}\,,\quad V_a = C_a(p_a - p_{ic})$

Quasilinear regression model for arterial pressure



$$p_a = \alpha_0 + \alpha_1 \cdot pCO_2 + \alpha_2 \cdot pO_2 + \alpha_{12} \cdot pCO_2 \cdot pO_2$$

(based on experimental data collected from premature babies (Newborns Intensive Station of the Children Clinic of the Technical University of Munich in the Women Clinic of the Clinic „rechts der Isar“)

Constraints on control and disturbances

$$\underline{\nu}_1 \le v_1 \le \overline{\nu}_1 \quad \underline{\nu}_2 \le v_2 \le \overline{\nu}_2 \quad |u| \le \mu$$

State constraints $\underline{q} \le q(p_a, \lambda, pCO_2) \le \overline{q}$

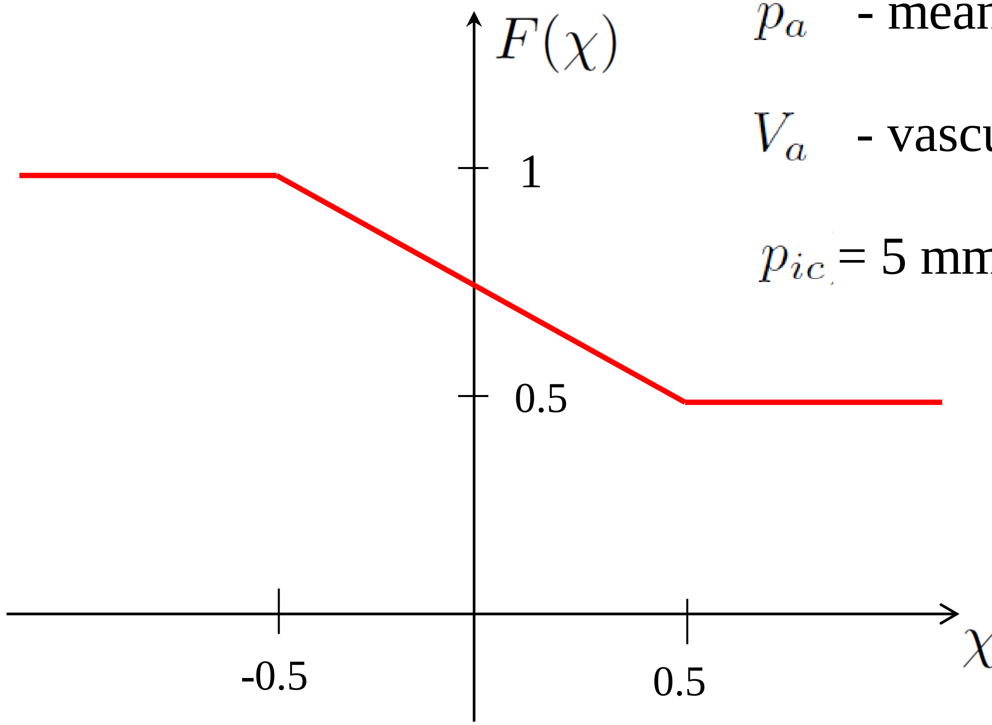
$$\underline{C}_a \le C_a \le \overline{C}_a \quad \underline{pCO}_2 \le pCO_2 \le \overline{pCO}_2 \quad \underline{pO}_2 \le pO_2 \le \overline{pO}_2$$

Variables, constants, parameters

Numerical values of parameters	
τ	0.5
α	0.1
α_0	27.3071
α_1	0.1789
α_2	0.0714
α_{12}	-0.0031
k_1	1
k_2	1
$\underline{\nu}_1$	30
$\overline{\nu}_1$	80
$\underline{\nu}_2$	25
$\overline{\nu}_2$	85
μ	2
$\underline{q}$	10
$\overline{q}$	15
$\underline{C}_a$	0.2
$\overline{C}_a$	1.8
$\underline{pCO_2}$	29
$\overline{pCO_2}$	81
$\underline{pO_2}$	24
$\overline{pO_2}$	86

State variables:

- C_a - compliance (ability of vessels to distend with increasing pressure)
- pCO_2 - partial carbon dioxide pressure
- pO_2 - partial oxygen pressure



p_a - mean arterial pressure

V_a - vascular volume

p_{ic} = 5 mmHg - intracranial pressure

M. Ursino, C.A. Lodi, A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics, J. Appl. Physiol. 82(4), 1997.

Viability kernel

Differential game

$$\dot{x} = f(x, u, v), \; x \in R^n, \; u \in P \subset R^p, \; v \in Q \subset R^q$$

Consider a family of state constraints: $G_\lambda = \{x \in R^n, g(x) \leq \lambda\}$

Find a function V such that: $Viab(G_\lambda) = \{x \in R^n, V(x) \leq \lambda\}$

Grid method for finding viability kernels

Let $\delta > 0$ be a time step,

$h := (h_1, ..., h_n)$ space sampling with $|h| = \max\limits_{1 \le i \le n} h_i$

Operator acting on grid functions:

$$\Pi^*[\delta, h; \phi](x) = \phi(x) + \delta \min_{u \in P} \max_{v \in Q} \sum_{i=1}^{n} (p_i^{\text{right}} f_i^{+} + p_i^{\text{left}} f_i^{-})$$

$$a^{+} = \max\{a, 0\}, \quad a^{-} = \min\{a, 0\},$$

$$p_i^{\text{right}} = [\phi(x_1, ..., x_i + h_i, ..., x_n) - \phi(x_1, ..., x_i, ..., x_n)]/h_i,$$

$$p_i^{\text{left}} = [\phi(x_1, ..., x_i, ..., x_n) - \phi(x_1, ..., x_i - h_i, ..., x_n)]/h_i.$$

Let a sequence $\{\delta_\ell\}$ is chosen as: $\delta_\ell \to 0$, $\sum_{\ell=0}^{\infty} \delta_\ell = \infty$.

Denote $\mathcal{V}^h(x_{i_1}, ..., x_{i_n}) = \mathcal{V}(i_1 h_1, ..., i_n h_n)$

$$g^h(x_{i_1}, ..., x_{i_n}) = g(i_1 h_1, ..., i_n h_n)$$

Grid scheme

$$\mathcal{V}_{\ell+1}^h = \max\{\Pi^*[\delta, h; \mathcal{V}_\ell^h], g^h\}, \ \mathcal{V}_0^h = g^h, \quad \ell = 0, 1, ...$$

Proposition. Let $B = \sup\{|f| : x \in R^n, u \in P, v \in Q\}$ and

$\delta_\ell / |h| \leq (B\sqrt{n})^{-1}$, then $\mathcal{V}_\ell^h \nearrow V^h$ as $\ell \to \infty$. **(Botkin & T., Proc. Inst. Math. Mech 21(2), 2015)**

With $|V^h - V| \leq k\sqrt{|h|}$ (**Botkin, Hoffmann, Mayer, & T., Analysis 31, 2011; Botkin &T., Mathematics 2, 2014) ,**

we obtain that $\mathcal{V}_\ell^h$ approximates V if ℓ is large and $|h|$ is small.

Criterion of the accuracy: $\sup\limits_{overgrid} |\mathcal{V}_{\ell+1}^h - \mathcal{V}_\ell^h| \leq \varepsilon$

Control design

$$u_{i_1,i_2\dots i_n} = \arg_u \min_{u\in P} \max_{v\in Q} \sum_{i=1}^{n} (p_i^{\text{right}} f_i^{+} + p_i^{\text{left}} f_i^{-})$$

Feedback strategy of the first player

$$u(x) = \mathcal{L}_h[u_{i_1,i_2,\dots,i_n}](x)$$

Here $\mathcal{L}_h$ is an interpolation operator.

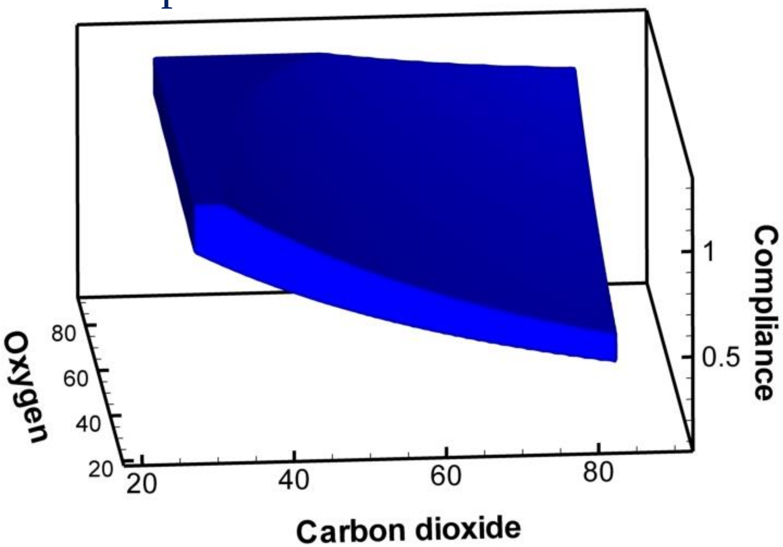
Feedback strategy of the second player

$$v_{i_1,i_2\dots i_n} = \arg \max_{v\in Q} \min_{u\in P} \sum_{i=1}^{n} (p_i^{\text{right}} f_i^{+} + p_i^{\text{left}} f_i^{-})$$

$$v(x) = \mathcal{L}_h[v_{i_1,i_2\dots i_n}](x)$$

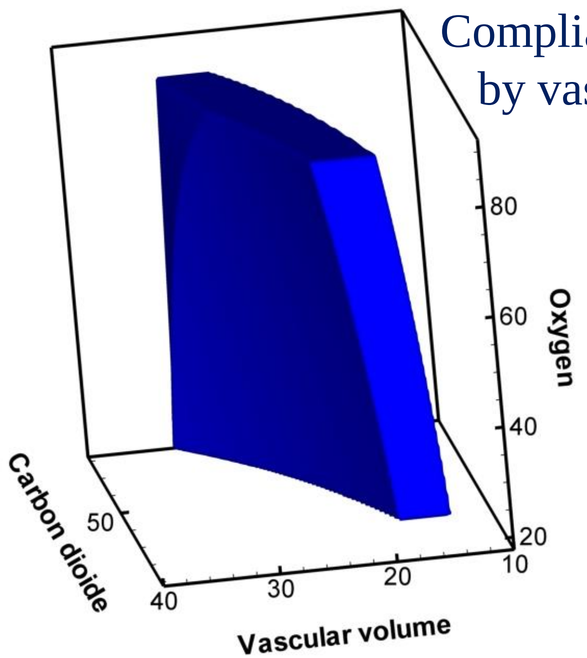
Application to the blood flow model

The space of state variables

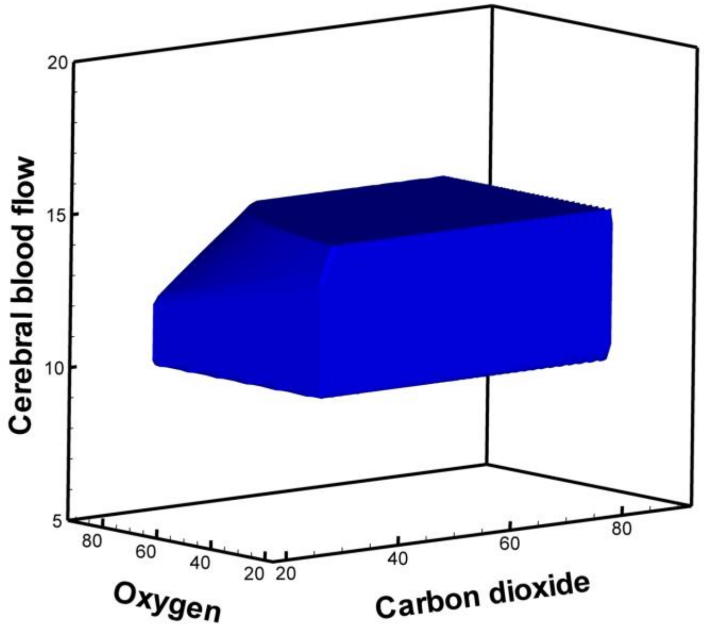


Blood is modeled as usual Newtonian fluid. The viability kernel is shown in different axes

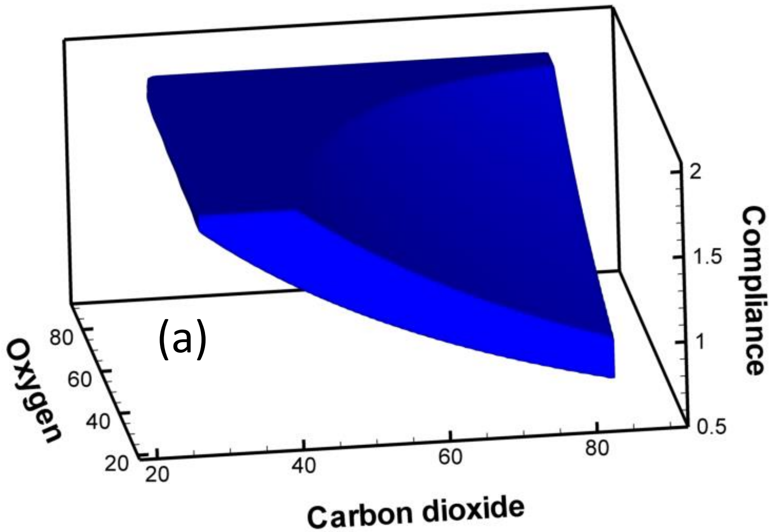
Compliance is replaced by vascular volume



Compliance is replaced by cerebral blood flow

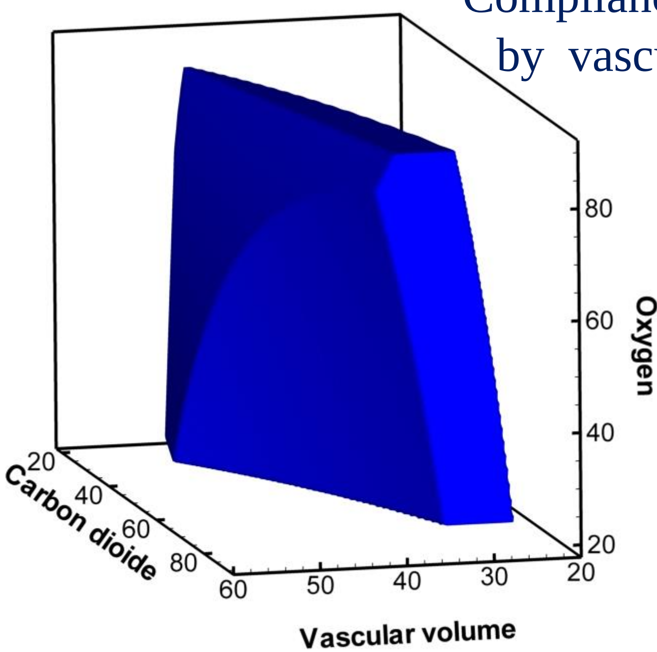


The space of state variables

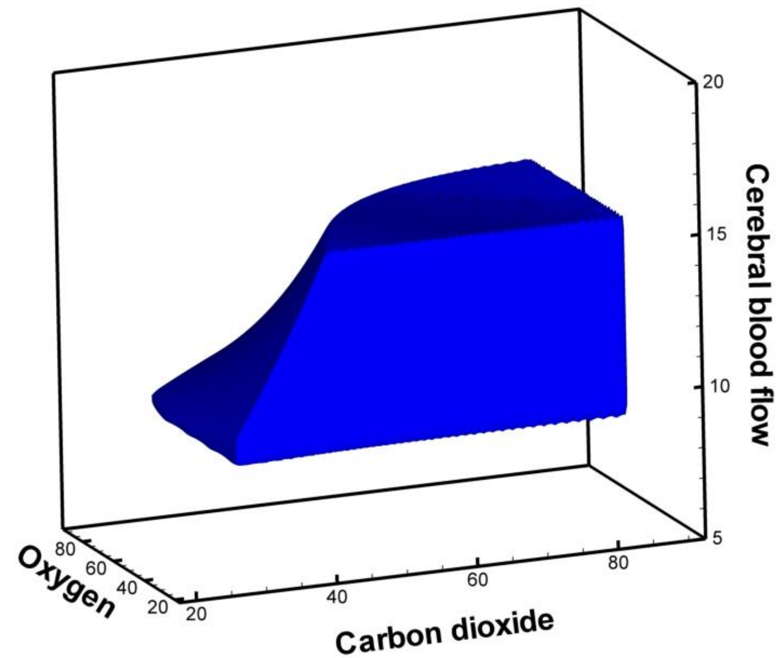


Blood is modeled as a micropolar fluid. The viability kernel is shown in different axes

Compliance is replaced by vascular volume

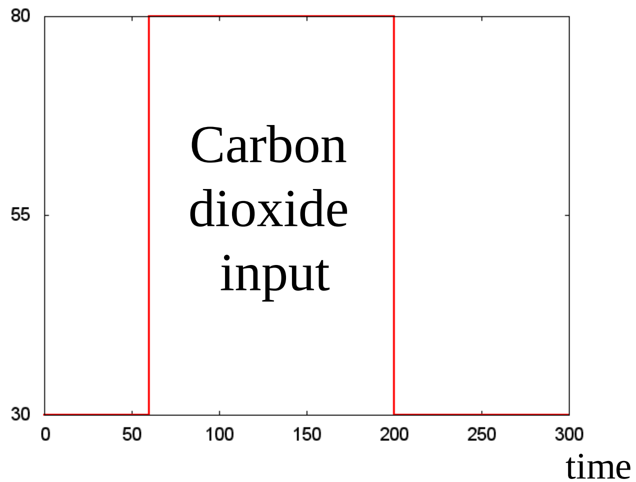


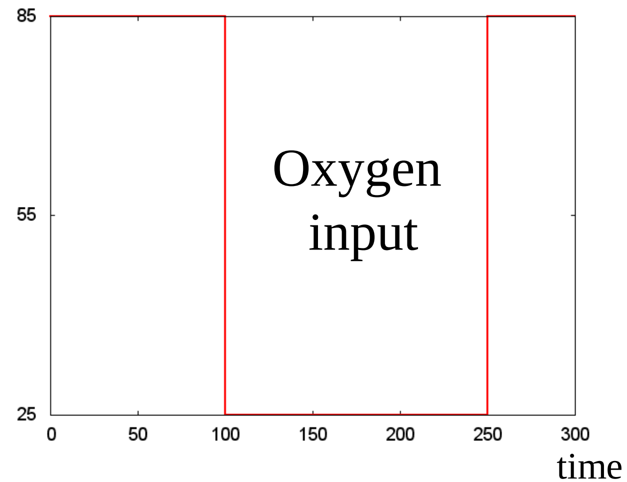
Compliance is replaced by cerebral blood flow



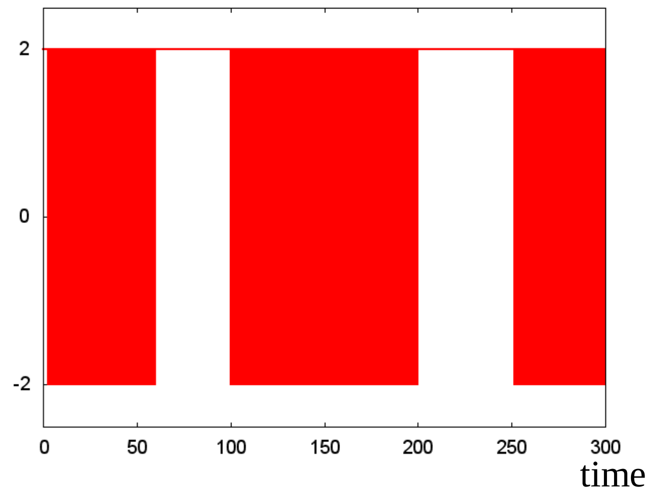
Simulation of trajectories

Optimal feedback control plays against step shaped disturbances

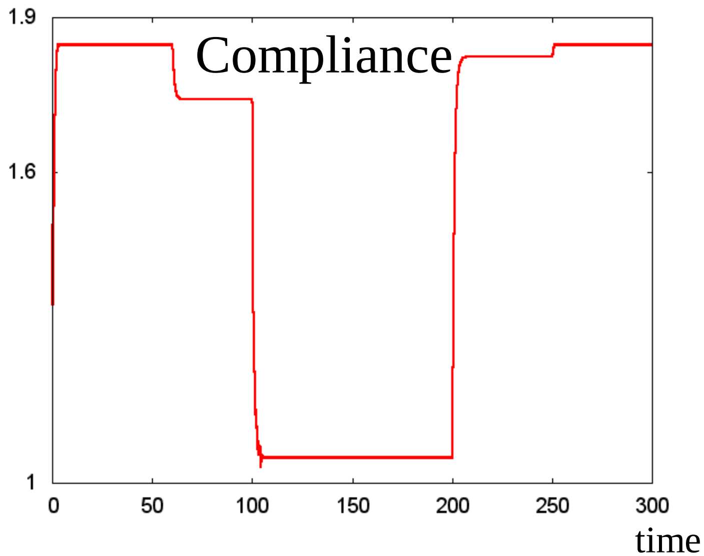


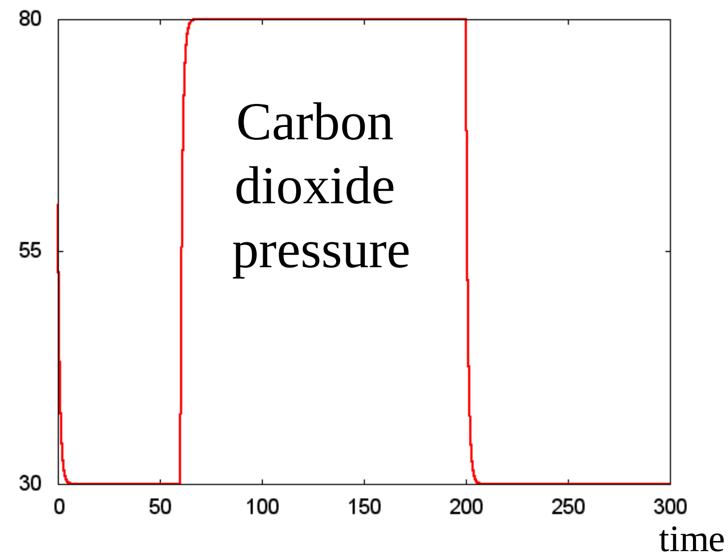


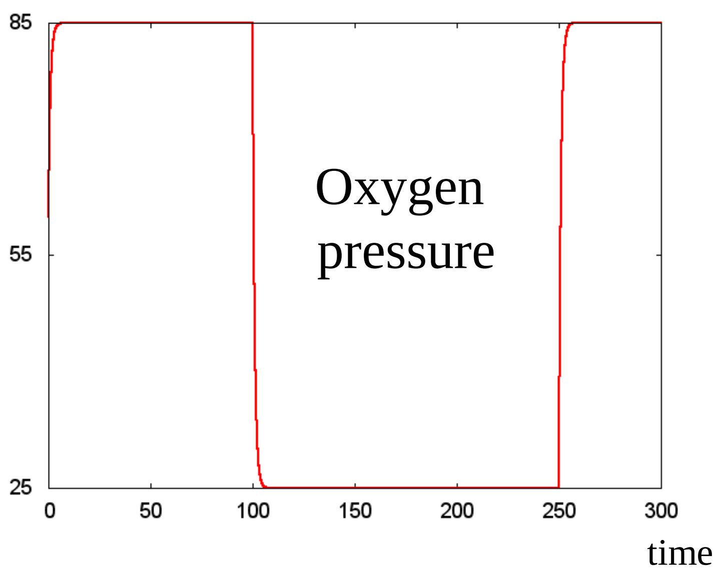
Control produced by the optimal feedback strategy

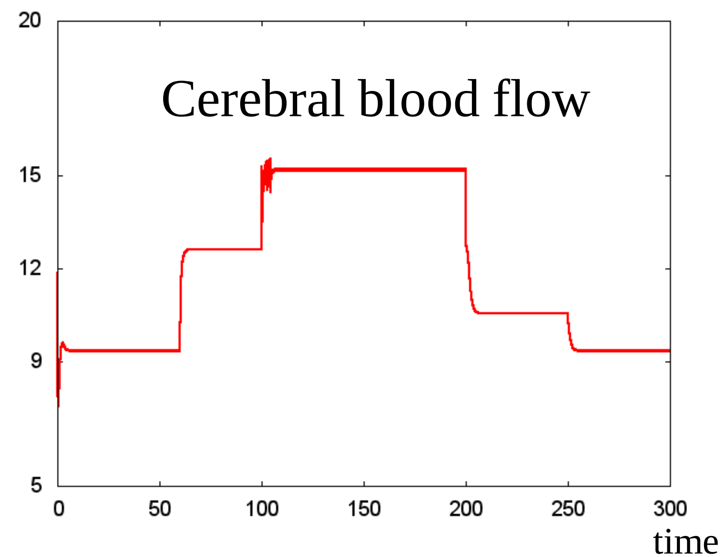


All state constraints are kept, but the chattering control is not physically implementable!









A simple feedback strategy

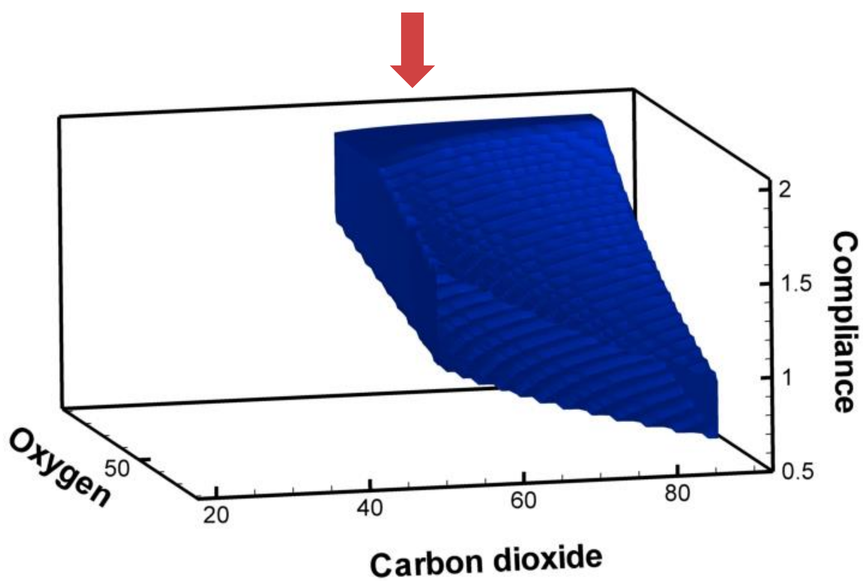
$$u = -2\left[q(p_a, \alpha\sqrt{V_a}, pCO_2) - q_0\right]$$

1. Put this strategy into the model

2. Compute the viability kernel for the resulting system. In the case, the grid algorithm contains only maximizations over the disturbances.

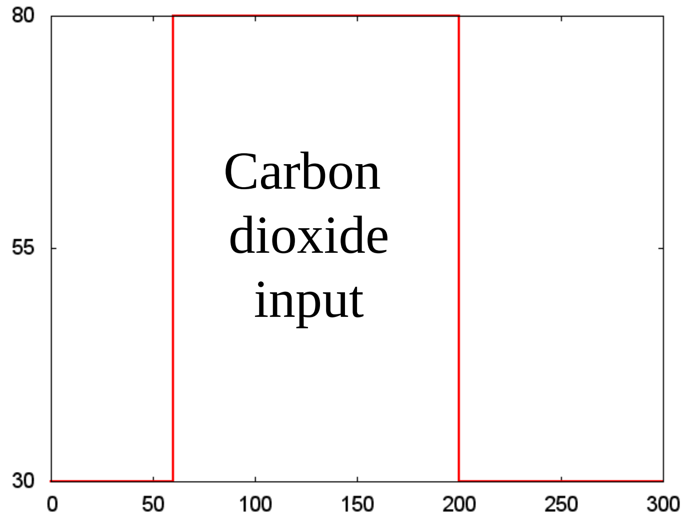
3. If such a viability kernel is nonempty, the above control strategy is classified as acceptable.

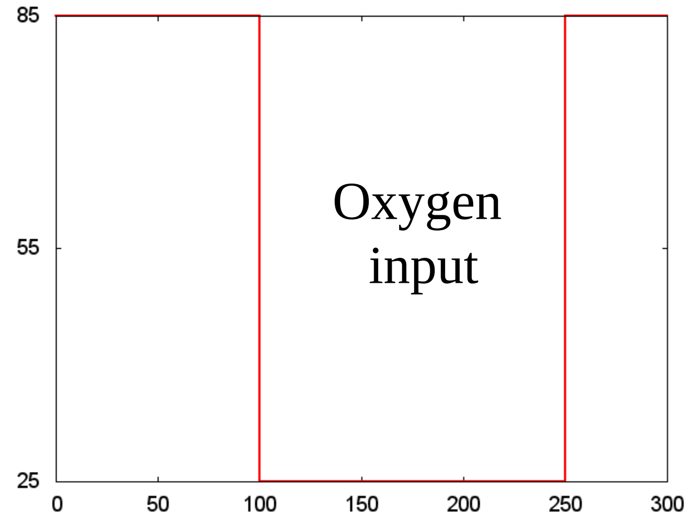
Result



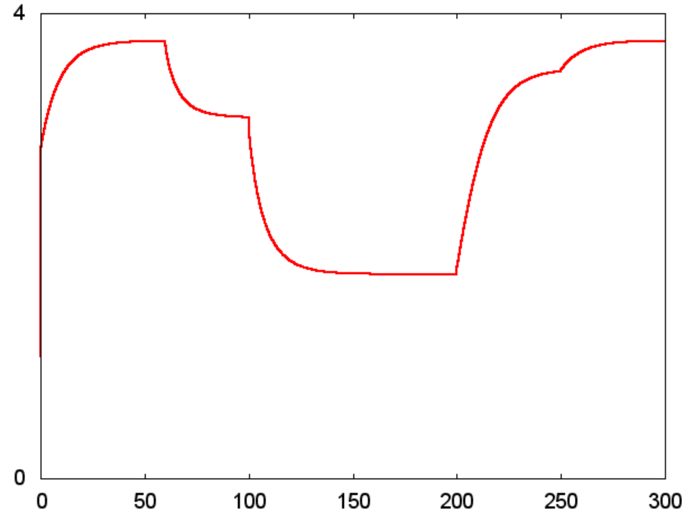
M.N.Kim et al. Noninvasive measurement of cerebral blood flow and blood oxygenation using near-infrared and diffuse correlation spectroscopies in critically brain-injured adults. Neurocrit. Care 12(2), 2010.

The simple feedback control plays against step shaped disturbances



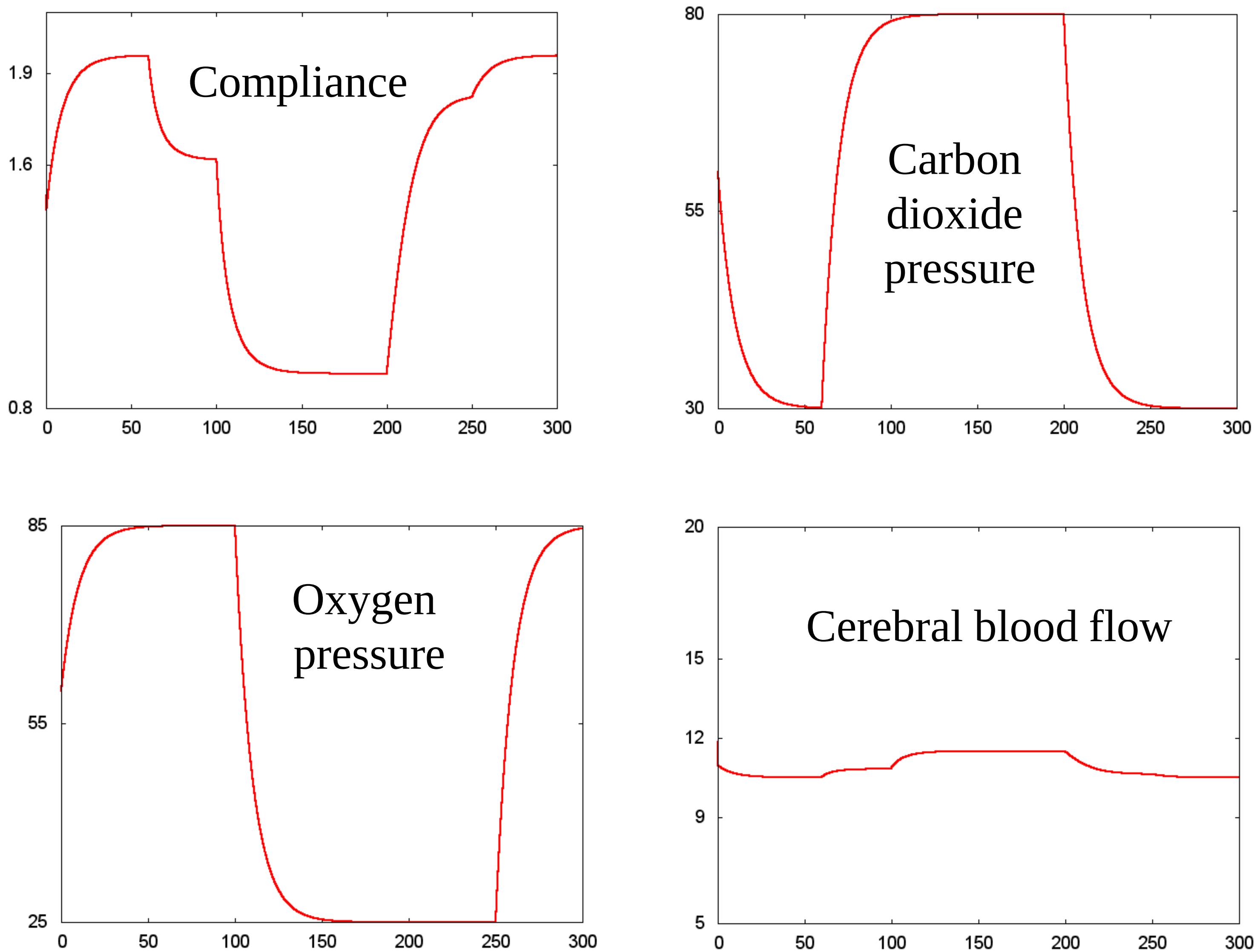


Control produced by the simple feedback strategy



is acceptably bounded and smooth

All state constraints are acceptably kept



Computation details

Grid parameters:

C_a : [0.1, 2] /100, pCO_2 : [20, 90]/140, pO_2 : [20, 90]/120

Time-step width 0.0005, accuracy $\varepsilon = 10^{-6}$

Linux SMP-computer with 8xQuad-Core AMD Opteron processors (Model 8384, 2.7 GHz) and shared 64 Gb memory.

The programming language C with OpenMP (Open Multi-Processing) support. The efficiency of the parallelization is up to 80%.

Computation time for viability set ca. 15 min

Outlook

- Evaluation of therapy strategies
- Taking into account other factors
- More realistic models of cerebral blood vessel system
- More experimental data

Project funded by Klaus Tschira-Stiftung just started:
“Mathematical modelling of cerebral blood circulation in premature infants with accounting for germinal matrix”

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Klaus Tschira Stiftung

Thank you!