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Modeling and simulation of cerebral blood flow autoregulation considered as an output regulation control problem

A mathematical model of cerebral blood flow in the form of a system of nonlinear ordinary differential equations is studied. The cerebral blood flow autoregulation modeling problem is formulated as an output regulation automatic control problem. The nonlinear dynamics inversion based approach is applied to reveal the controllability properties of the model and construct the feedback control laws which describe mathematics behind the cerebrovascular autoregulation mechanism.

Key words: *intracranial hemodynamics, cerebral autoregulation, nonlinear control, dynamics inversion, output regulation.*

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Introduction and problem statement

In recent years, cerebral blood circulation and autoregulation modeling has become very popular (see, e.g. [1–4]). Understanding mathematics behind the cerebral autoregulation is of great clinical importance. It could help us prevent various brain disorders, e.g. intracranial hemorrhages in preterm newborns [2], by reproducing the autoregulation mechanisms of healthy humans, for instance, using medicaments which dilate or constrict the blood vessels.

In this paper, we study the cerebral hemodynamics model suggested in [1] and written in the form [4]:

$$\begin{aligned} \dot{V}_a &= \frac{1}{1+k_E P_{ic} C_a}\left(-k_E P_{ic} C_a\left(\frac{P_c-P_{ic}}{R_f}-\frac{P_{ic}-P_{vs}}{R_o}+I_i\right)+(P_a-P_{ic})\dot{C}_a\right), \\ \dot{P}_{ic} &= \frac{k_E P_{ic}}{1+k_E P_{ic} C_a}\left(\frac{P_c-P_{ic}}{R_f}-\frac{P_{ic}-P_{vs}}{R_o}+I_i+(P_a-P_{ic})\dot{C}_a\right), \end{aligned} \tag{1}$$

where V_a is the arterial-arteriolar blood volume variable, P_{ic} stands for the intracranial pressure variable, C_a is the arterial-arteriolar compliance variable, P_a denotes the systemic arterial pressure, P_c is the capillary pressure variable, the constant values P_{vs}, R_f,

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R_o, I_i, k_E stand for the venous sinus pressure, the cerebrospinal fluid production and reabsorption hydraulic resistances, the rate of possible mock cerebrospinal fluid injection and the craniospinal compartment elastance coefficient, respectively. The capillary pressure P_c and the arterial-arteriolar compliance C_a quantities in the right-hand side of the system (1) can be represented as functions of the system state variables V_a and P_{ic} [4].

The cerebral blood flow autoregulation mechanism is described in terms of the arterial-arteriolar compliance C_a time behavior. Vasodilation or vasoconstriction of the arterioles are modeled through positive or negative values of the compliance rate $\dot{C}_a$, respectively. In the current work, we consider the arterial-arteriolar compliance rate $\dot{C}_a$ as a control input u, i.e. $\dot{C}_a = u$.

Further in the paper, let us suppose that the arterial blood pressure dynamics are in a steady state, i.e. $\dot{P}_a \equiv 0$, and the arterial pressure P_a has a constant value which is possibly different from the basal one of a healthy human.

The arterial-arteriolar blood flow rate q is considered as a system output function and is written as the following function of the system state variables V_a and P_{ic} [4]:

$$q = q(V_a, P_{ic}) = \frac{(R_{pv} + R_f)(P_a - P_{ic})V_a^2}{k'_R(R_{pv} + R_f) + R_f R_{pv} V_a^2}, \tag{2}$$

where k'_R is a coefficient of the arterial-arteriolar hydraulic resistance R_a inverse proportionality to the square of the V_a variable.

The cerebral blood flow autoregulation modeling problem is formulated as an asymptotic output regulation control problem for the nonlinear dynamical system (1), i.e. it is required to find a feedback control law $u = u(V_a, P_{ic})$ such that

$$|q(V_a(t), P_{ic}(t)) - q_n| \to 0 \ \text{ as } \ t \to +\infty \tag{3}$$

for all reasonable initial values $V_a(0) = V_{a0}$, $P_{ic}(0) = P_{ic0}$ of the system state variables. Here, q_n denotes a basal value of the cerebral blood flow required for tissue metabolism.

In this paper, we analyze controllability properties of the cerebral blood flow model (1). It is shown that the control singularity set doesn't have any considerable influence on the controllability of the dynamical system (1). Then, the nonlinear dynamics inversion based approach is applied to construct the feedback control laws which model the cerebral autoregulation performance.

1 Controllability of cerebral hemodynamics

The change of the state variables [4]

$$\begin{gathered} z_1 = \varphi_1(V_a, P_{ic}) = k_E V_a - \ln P_{ic}, \\ z_2 = \varphi_2(V_a, P_{ic}) = \frac{-k_E R_{pv}}{R_{pv} + R_f} q + \frac{k_E}{R_o} P_{ic} - k_E \left(\frac{P_{vs}}{R_o} + I_i \right) \end{gathered} \tag{4}$$

transforms the system (1) into the form

$$\dot{z}_1 = z_2, \quad \dot{z}_2 = \widetilde{f}(z_1, z_2) + \widetilde{g}(z_1, z_2)u, \tag{5}$$

where $\widetilde{f}(\cdot)$ and $\widetilde{g}(\cdot)$ are corresponding functions of their arguments [4].

One can check that the relations (4) can be considered as a diffeomorphism $z = \Phi(V_a, P_{ic})$, where $z = (z_1, z_2)^{\mathrm{T}}$, $\Phi(V_a, P_{ic}) = (\varphi_1(V_a, P_{ic}), \varphi_2(V_a, P_{ic}))^{\mathrm{T}}$, defined for all values of the variables V_a and P_{ic} such that the inequality

$$\begin{aligned} P_{ic} \neq \big(&2P_a R_o V_a k'_R R_{pv}^2 + 2P_a R_o R_f V_a k'_R R_{pv}\big) / \big(2k_E R_f R_{pv} {k'_R}^2 + k_E R_{pv}^2 {k'_R}^2 + \\ &+2k_E R_f^2 R_{pv} V_a^2 k'_R + 2k_E R_f R_{pv}^2 V_a^2 k'_R + R_o k_E R_f R_{pv} V_a^2 k_R + 2R_o R_f R_{pv} V_a k'_R + \\ &+R_o k_E R_{pv}^2 V_a^2 k'_R + 2R_o R_{pv}^2 V_a k'_R + k_E R_f^2 R_{pv}^2 V_a^4 + R_o k_E R_f R_{pv}^2 V_a^4 + k_E R_f^2 {k'_R}^2\big) \end{aligned} \tag{6}$$

is satisfied. Then, it can be shown that the condition $\widetilde{g}(z_1, z_2) \neq 0$ at a point $z_1 = \varphi_1(V_a, P_{ic})$, $z_2 = \varphi_2(V_a, P_{ic})$ is equivalent to the condition (6) which is an outcome of a general theory of nonlinear state space transformations of dynamical systems presented in [5].

It is well-known that controllability properties of a dynamical system of the form (5) drastically depend on the system trajectories behavior in the control singularity set

$$N = \big\{(z_1, z_2)^{\mathrm{T}} \in \mathbb{R}^2 \;\big|\; \widetilde{g}(z_1, z_2) = 0\big\}$$

which in its turn is determined by the unforced system dynamics vector field $\Big(z_2, \widetilde{f}(z_1, z_2)\Big)^{\mathrm{T}}$ orientation on N.

Notice that the medically plausible intervals for the system (1) state variables are $V_a(t) \in [9, 20]$ ml and $P_{ic}(t) \in [5, 15]$ mmHg for all $t \geq 0$ [1, 6]. Hence, the admissible state set of the system (1) is as below

$$\Omega = \big\{(V_a, P_{ic})^{\mathrm{T}} \in \mathbb{R}^2 \;\big|\; 9 \leq V_a \leq 20, 5 \leq P_{ic} \leq 15\big\}.$$

Figure 1 shows the curves $\widetilde{g}(z_1, z_2) = 0$ on the phase plane (V_a, P_{ic}) for different values of the arterial pressure P_a within the autoregulatory range $P_a \in [60, 160]$ mmHg and the model parameter values taken from [1]. From figure 1 follows that for the arterial pressure values lower than the approximate value $P_a = 125$ mmHg the set of admissible states Ω doesn't contain any control singularities, i.e. points (V_a, P_{ic}) such that $\widetilde{g}(z_1, z_2) = 0$ holds.

Figure 2 demonstrates the set of admissible states $\Phi(\Omega)$ and the control singularity set N on the phase plane (z_1, z_2) for model parameter values taken from [1]. Then, in view of the vector field $(z_2, \widetilde{f}(z_1, z_2))^{\mathrm{T}}$ orientation on N and the position of the set N on the phase plane (z_1, z_2) one can conclude that the control singularity set N doesn't have any considerable influence on the controllability [5] of the system (5) in the set $\Phi(\Omega)$. Let us recall that due to the relation $z_2 = \dot{z}_1$ the motion in the upper ($z_2 > 0$) and lower ($z_2 < 0$) parts of the phase plane (z_1, z_2) is possible from the left-hand side to the right-hand side and from the right-hand side to the left-hand side, respectively.

2 Cerebral blood flow autoregulation control design

To guarantee the cerebral blood flow autoregulation (3) let us first find constant reference values $V_a = V_{ar} = \text{const}$ and $P_{ic} = P_{icr} = \text{const}$ such that the condition $q(V_{ar}, P_{icr}) = q_n$ holds [4]. Then, the control strategy will be to force the differences $V_a(t) - V_{ar}$ and $P_{ic}(t) - P_{icr}$ to zero as $t \to +\infty$ in a controllable way by the choice of a state feedback $u = u(V_a, P_{ic})$.

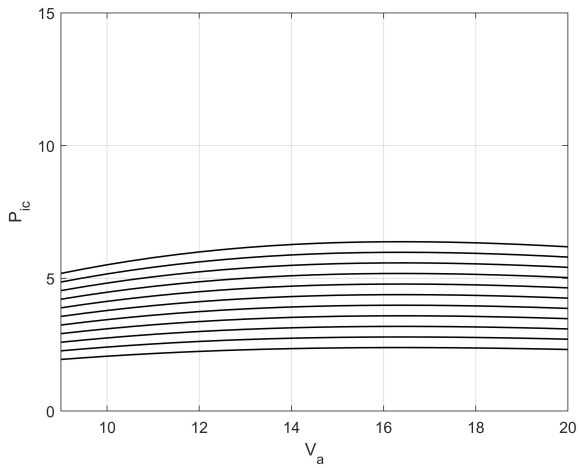

Fig. 1: The control singularity set N on the phase plane (V_a, P_{ic}) for different values of the arterial pressure P_a within the autoregulatory range $P_a \in [60, 160]$ mmHg. The lower curve corresponds to $P_a = 60$ mmHg. The upper curve stands for $P_a = 160$ mmHg. The intermediate curves correspond to P_a values consistently increased with a step size of 10 mmHg, respectively.

Next, due to the relationships (4) one takes

$$z_{1r} = k_E V_{ar} - \ln P_{icr}, \quad z_{2r} = \frac{-k_E R_{pv}}{R_{pv} + R_f} q_n + \frac{k_E}{R_o} P_{icr} - k_E \left(\frac{P_{vs}}{R_o} + I_i \right)$$

as reference values of the z_1 and z_2 state variables, respectively. To guarantee that the transient from an admissible initial state $z_1(0) = z_{10}$, $z_2(0) = z_{20}$ to the desired final state $z_1(T) = z_{1r}$, $z_2(T) = z_{2r}$ lies entirely in the admissible state set $\Phi(\Omega)$, we use the considerations suggested in [7]. To connect the points (z_{10}, z_{20}) and (z_{1r}, z_{2r}) on the phase plane (z_1, z_2), we employ phase graphic $\bar{p}(t) = (p(t), \dot{p}(t))$, $t \in [0, T]$, of the polynomial

$$p(t) = z_{10} + z_{20} t + c_1 t^2 + c_2 t^3, \tag{7}$$

with the coefficients c_1, c_2 being found from the conditions $p(T) = z_{1r}$, $\dot{p}(T) = z_{2r}$ and written as (see, e.g., [7])

$$c_1 = -\big((2z_{20} + z_{2r})T + 3(z_{10} - z_{1r})\big)/T^2, \quad c_2 = \big((z_{20} + z_{2r})T + 2(z_{10} - z_{1r})\big)/T^3.$$

Notice that one way to guarantee the boundedness property $|p(t)| \le M_1$, $|\dot{p}(t)| \le M_2$ for all $t \in [0, T]$ with some relevant bounds M_1, M_2 is to provide the monotonicity property of the functions $p(t)$ and $\dot{p}(t)$ on the interval $t \in [0, T]$. One can show that the final time value selection

$$T = \min \left\{ \frac{3(z_{1r} - z_{10})}{2z_{20} + z_{2r}}, \frac{3(z_{1r} - z_{10})}{z_{20} + 2z_{2r}} \right\}$$

results in the monotonicity property of the polynomial (7) and its time derivative on the interval $t \in [0, T]$ (see [7]).

Introduce the tracking error variables $e_{z1} = z_1 - p(t)$, $e_{z2} = z_2 - \dot{p}(t)$ and rewrite the system (5) as

$$\dot{e}_{z1} = e_{z2}, \quad \dot{e}_{z2} = \widetilde{f}(z_1, z_2) + \widetilde{g}(z_1, z_2)u - \ddot{p}(t).$$

Then, the nonlinear dynamics inversion based control

$$u = \frac{1}{\widetilde{g}(z_1, z_2)} \left(-\widetilde{f}(z_1, z_2) + \ddot{p}(t) - c_1 e_{z1} - c_2 e_{z2} \right) \tag{8}$$

yields the tracking error dynamics

$$\dot{e}_{z1} = e_{z2}, \quad \dot{e}_{z2} = -c_1 e_{z1} - c_2 e_{z2}. \tag{9}$$

Moreover, for any positive gain coefficients $c_1 > 0$ and $c_2 > 0$ the equilibrium point $e_{z1} = 0$, $e_{z2} = 0$ of the system (9) is (globally) asymptotically stable. Notice that the control law (8) and, hence, the resultant closed-loop dynamics (9) are defined whenever the control coefficient $\widetilde{g}(z_1, z_2)$ in (5) is not zero.

Figure 2 suggests that one can always choose the reference values $V_a = V_{ar}$, $P_{ic} = P_{icr}$ of the arterial-arteriolar blood volume and intracranial pressure variables, respectively, such that the condition $\widetilde{g}(z_{1r}, z_{2r}) \neq 0$ holds for the autoregulatory range $P_a \in [60, 160]$ mmHg. Hence, due to the continuity property of the function $\widetilde{g}(\cdot)$ the inequality $\widetilde{g}(z_1, z_2) \neq 0$ is satisfied at least in some neighborhood of the point $z_1 = z_{1r}$, $z_2 = z_{2r}$ of the phase plane (z_1, z_2).

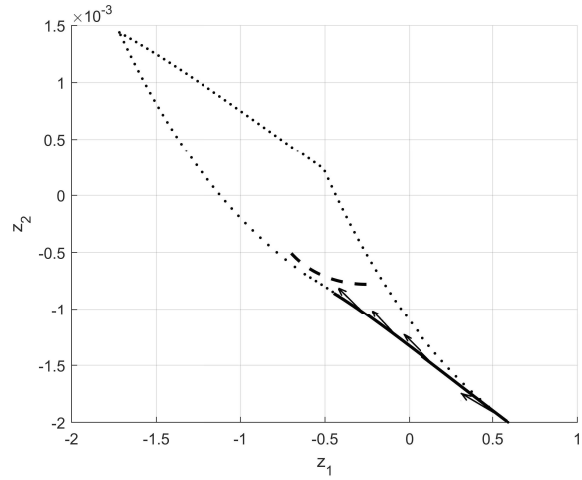

Fig. 2: The autoregulation response (trajectory of the system (5) under control (8)) (dashed line), the admissible state set $\Phi(\Omega)$ (dotted lines indicate the set boundaries) and the control singularity set N (solid line) on the phase plane (z_1, z_2) for $P_a = 130$ mmHg. The arrows show the vector field $(z_2, \widetilde{f}(z_1, z_2))^{\mathrm{T}}$ orientation on N.

Simulation results, namely, a trajectory of the system (5) under control (8) on the phase plane (z_1, z_2), are shown in figure 2 for $V_a(0) = 18.085$ ml, $P_{ic}(0) = 9.432$ mmHg, $V_a(T) = 11.33$ ml, $P_{ic}(T) = 7$ mmHg, $T = 646$ s, $c_1 = 4$, $c_2 = 4$ under model parameter values taken from [1].

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АННОТАЦИЯ

Исследуется математическая модель мозгового кровообращения, имеющая вид системы обыкновенных дифференциальных уравнений. Задача моделирования механизма авторегулирования мозгового кровотока рассматривается как задача автоматического управления, заключающаяся в отслеживании заданного выходного сигнала. Для синтеза стабилизирующих законов управления и исследования свойств управляемости модели кровотока используется метод обратных задач динамики.

Ключевые слова: *биомеханическая система, мозговое кровообращение, авторегулирование, нелинейное управление, стабилизация.*