DIP AND BUFFERING IN A FAST-SLOW SYSTEM ASSOCIATED TO BRAIN LACTATE KINETICS

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Abstract. High-dimensional compartmental dynamical systems have been introduced to model brain metabolism. In this article, an approach is proposed to their mathematical analysis. Reductions of these models are obtained by replacing several compartments by a control term. The analysis focuses here on lactate kinetics. A mathematical analysis of the initial dip of lactate, observed under stimulation, and of the periodic buffering, underlying the response to a repetitive sequence of identical stimuli, can be proposed. This mathematical analysis relies on asymptotics techniques of time multi-scaled dynamical systems such as averaging along slow manifolds.

1. Introduction

Several mathematical compartmental models have been recently developed to represent the metabolism of neurons and astrocytes \[1,2,3,4,5,7\]. Such models involve too many variables to be accessible to mathematical analysis and until now they were only discussed via numerical simulations. The viewpoint adopted here is to reduce several compartments contributions into a control, keeping very few dynamical variables, and characterize the controls which are compatible with the observations. We first discuss a two-dimensional controlled system and then move to a four-dimensional system which allows to distinguish between neurons and astrocytes. We focus on these two cases in the understanding of two important phenomena observed in experiments. One is the initial dip in the extracellular lactate concentration, first reported \textit{in vivo} by Hu and Wilson \[9\] using an enzyme-based lactate microsensor on rat brain hippocampus after an electrical stimulation of the perforant pathway. The other is a periodic buffering response to the application of a periodic sequence of stimuli, also observed by Hu and Wilson, and further discussed by Aubert-Costalat-Magistretti-Pellerin \[3\], on the basis of numerical simulations of the Aubert-Costalat system. More precisely, the initial dip can be well explained, in the setting of fast-slow dynamics, by the theorem of existence of slow manifold, when the critical manifold is transversally attractive. The periodic buffering is mathematically justified using both averaging theory on a slow manifold and a theorem of Flatto-Levinson \[8\]. To make the article self-contained a short proof of this theorem is included and the full verifications of the hypothesis required for its application are provided.
Let us consider a (fast-slow) dynamical system equipped with a slow control \( J(t, x) \) and an input \( F(t) \):

\[
\begin{align*}
\frac{dx}{dt} &= \epsilon' [J(t, x)] - C\left(\frac{x}{k+x} - \frac{y}{k'+y}\right), \\
\frac{dy}{dt} &= F(t)(L - y) + C\left(\frac{x}{k+x} - \frac{y}{k'+y}\right).
\end{align*}
\]

The two variables \( x \) and \( y \) stand for the lactate concentration in an interstitial (extracellular) domain, respectively in a capillary domain. The experimental context refers to Hu and Wilson [9] where an electrical stimulus is applied and is represented by the impulsive term \( F(t) \). In mathematical terms, \( F(t) \) is an input function that we assume continuous piecewise linear: \( F(0) = F_0 > 0, F(t) = F_1, t \in [t_0, t_1] \), \( F(t) = F_0, t \in [t_f, T] \). The time scales \( \epsilon, \epsilon' \) are assumed to be small enough within the domain of validity of asymptotics methods of fast-slow systems.

The term \( C\left(\frac{x}{k+x} - \frac{y}{k'+y}\right) \) stands for a cotransport through the brain-blood-boundary. Justifications for such an expression can be found, for instance, in [10].

The full justification of the model stands on several previous articles [3], [11], [12], [13] related to physiology and to physiopathology where emerged gradually the pertinence of the time multi-scaled approach. Finally the interaction with a third intracellular compartment (which includes both neurons and astrocytes) is embodied in a control term \( J(t, x) \). The aim of this modeling is to characterize the control terms compatible with the observation of the transients (and asymptotics) of the solutions \((x(t), y(t))\). Of course, such a controlled dynamical system could be applied in a wide variety of context (not necessarily lactate kinetics) which would encompass capillary and bbb transport (or transport through cellular membrane). Note finally that \( T, k, k' \) are seen as fixed parameters.

In a second part of the article, we further discuss a natural extension of the system where the intracellular compartment splits into neurons and astrocytes and which includes transports through cell membranes. Following the choice made in [2], a direct transport from capillary to intracellular astrocytes is included. The input \( F(t) \) is kept and we add to the control \( J_0(t, x, u, v) \), still applied to the intracellular compartment, two other independent controls \( J_1(t, x, u, v) \) and \( J_2(t, x, u, v) \) (resp.) responsible for the intracellular lactate dynamics inside the neurons (resp.) astrocytes. This yields a 4-dimensional fast-slow dynamics with slow control:

\[
\begin{align*}
\frac{dx}{dt} &= \epsilon' [J_0(t, x, u, v)] + C_1\left(\frac{u}{k_a+u} - \frac{x}{x+k}\right) + C_2\left(\frac{w}{k_a+w} - \frac{x}{x+k}\right) - C\left(\frac{x}{k+x} - \frac{y}{k'+y}\right), \\
\frac{dy}{dt} &= \epsilon' [J_1(t, x, u, v)] - C_1\left(\frac{u}{k_a+u} - \frac{x}{x+k}\right), \\
\frac{du}{dt} &= \epsilon' [J_2(t, x, u, v)] - C_2\left(\frac{w}{k_a+w} - \frac{x}{x+k}\right) - C_u\left(\frac{w}{k_a+w} - \frac{y}{k'+y}\right), \\
\frac{dw}{dt} &= F(t)(L - y) + C\left(\frac{x}{k+x} - \frac{y}{k'+y}\right) + C_a\left(\frac{w}{k_a+w} - \frac{y}{k'+y}\right).
\end{align*}
\]

The same analysis can be extended to this 4-dimensional system and further new possibilities offered by this extension are discussed using a quasi-stationary approximation.

2. Dip and buffering in the 2-dimensional system

2.1. Qualitative analysis of the system with fixed controls: stationary point and slow manifold. Recall shortly the local analysis of the 2-dimensional system obtained by freezing the input and the control term:
\[
\begin{align*}
\frac{dx}{dt} &= \epsilon' [J - C(x_k - k' - y)] \\
\epsilon \frac{dy}{dt} &= F(L - y) + C(x_k - k' - y).
\end{align*}
\]

Theorem 1. The system (3) displays a unique stationary point which is of node type.

Proof. Solving the system:
\[
\begin{align*}
0 &= J - C(x_k - k' - y) \\
0 &= F(L - y) + C(x_k - k' - y),
\end{align*}
\]
yields
\[
y = L + \frac{J}{F} = y_0,
\]
which is always positive. This displays:
\[
x = \frac{k \left( \frac{J}{C} + \frac{y_0}{k' + y_0} \right)}{1 - \left( \frac{J}{C} + \frac{y_0}{k' + y_0} \right)} = x_0.
\]
There is, thus, a unique stationary point \((x_0, y_0)\) and we further discuss its nature.

The eigenvalues \(\lambda_{\pm}\) of the Jacobian of the vector field solve the equation:
\[
(A + \lambda)(\frac{B + F}{\epsilon} + \lambda) - \frac{AB}{\epsilon} = 0,
\]
with
\[
A = \frac{kC}{(k + x)^2}, \quad B = \frac{k'C}{(k' + y)^2}.
\]
The eigenvalues are so that:
\[
\lambda_{+} + \lambda_{-} = -(A + \frac{B + F}{\epsilon}) < 0, \\
\lambda_{+} \lambda_{-} = AF/\epsilon > 0,
\]
hence the stationary point is stable. Furthermore,
\[
\Delta = (A + \frac{B + F}{\epsilon})^2 - 4\frac{AF}{\epsilon} = \\
A^2 + 2A\left(\frac{B + F}{\epsilon}\right) + \left(\frac{B + F}{\epsilon}\right)^2 - 4\frac{AF}{\epsilon} > \\
A^2 - 2A\left(\frac{B + F}{\epsilon}\right) + \left(\frac{B + F}{\epsilon}\right)^2 \geq 0,
\]
hence this unique stationary point is a node. \(\square\)

Next, we use the fast-slow nature of the system to analyse its global phase portrait. The full phase portrait (for any values of \(x\) and \(y\)) requires some attention because the vector field is rational and displays poles. But we can note that the vector field is entrant on the boundary of the "meaningful domain" where \(x \geq 0, y \geq 0\) represents concentrations.

Theorem 2. For \(\epsilon\) small enough, the system (3) displays a slow attractive invariant manifold which is a graph (parabola) over the \(y\)-axis and a globally attractive stationary point in restriction to the positive quadrant.
Proof. The critical manifold of (3) is given by the equation:

\[ \Phi(x, y) = F(L - y) + C\left(\frac{x}{k + x} - \frac{y}{k' + y}\right) = 0. \]

Given \( y = y_0 \), there exists a single solution \( x = x_0 \) to the equation \( \Phi(x, y_0) = 0 \). Indeed, write

\[ B(y_0) = \frac{Cy_0}{k' + y_0} - F(L - y_0), \]

yields

\[ x = x_0 := \frac{kB(y_0)}{C - B(y_0)}. \]

Given \( x = x_0 \), there are two solutions \( y \) to the equation \( \Phi(x_0, y) = 0 \) obtained by solving

\[ y^2 - \left[ F(L - k') - \frac{Ck}{k + x_0}\right]y - \left(\frac{k'Cx_0}{k + x_0} + FLk'\right) = 0. \]

Note that for \( x_0 > 0 \) the product of the two roots is \( -\left(\frac{k'Cx_0}{k + x_0} + FLk'\right) < 0 \). Hence the parabola \( \Phi(x, y) = 0 \) intersects the \( y \)-axis in one positive and one negative value of \( y \). This shows that the critical manifold is also a graph over the \( x \)-axis in restriction to the positive quadrant \( x \geq 0, y \geq 0 \).

Note now that

\[ \Phi_y'(x, y) = -F - \frac{Ck'}{(k' + y)^2} < 0, \]

hence the critical manifold is attractive. Usual techniques of study of fast-slow systems can be used. In particular, Tikhonov theorem can be applied \(^{17}\) (For a discussion of the Tikhonov theorem see \(^{18}\)). In restriction to the positive quadrants, for \( \epsilon \) small enough, all orbits of the flow display a fast attraction to a slow manifold which is \( \epsilon \)-close to the critical manifold. Along this slow manifold, the flow is conjugated to the restriction of the slow flow on the critical manifold and it converges to the stable stationary point. \( \square \)

2.2. Geometrical explanation for the dip. Let us consider now the impulsive dynamics defined in the introduction by the piecewise constant function \( F(t) \). For fixed value \( F(t) = F_0, F(t) = F_1 \), we can apply the preceding results. As \( F(t) \) switches from one value to the other, the critical manifold jumps from one level to another level. We can now interpret geometrically the numerical result of the article \(^{3}\). The authors choose a trapezoidal function \( F(t) \), which varies linearly from \( F(0) = F_0 \) to \( F(t_i) = (1 + \alpha_F)F_0 \), then remains constant \( = (1 + \alpha_F)F_0 \) between \( t_i \) and \( t_f \) and then decreases linearly back to \( F_0 \) between \( t_f \) and \( t_f + t_i \).

Before the imput, a generic solution of the system approaches rapidly the slow manifold and then slowly moves to the stationary point. After this transient, we can assume that the initial data is the stationary point. Then, the imput is applied. The main effect is that the slow manifold is moved to a lower position and as a consequence, the solution moves quickly toward the slow manifold which is now below. Then it moves slowly to the new stationary point which is slightly displaced on the left. If the control \( J(t, x) \) is applied, it pushes the slow nullcline farther left.
Then the solution goes farther left as well in pursuit of the stationary point. This initiates a notable dip of the extracellular lactate concentration $x$. Of course, if the control $J(t, x)$ is turn off, the solution goes back to the initial stationary point.

Although, this is not quite the experimental situation observed by Hu and Wilson. Indeed, they observed that the initial dip is followed by an augmentation of the extracellular lactate concentration $x$ before returning back to the equilibria. This motivates [3] the choice of a plausible control $J(t, x)$. For some initial time $t_0$, $J(t)$ is linearly increased from $J_0$ to some level $J_1$ where it remains constant for a while and the system displays the dip. Then $J(t)$ is decreased below the equilibrium level $J_0$ to $J_{-1}$. As a consequence, the slow nullcline is now moved to the right, and the extracellular concentration $x$ increases as observed. After some time where $J(t)$ is kept constant at this lower level, it is then removed back to its equilibrium $J(0)$.

2.3. Geometrical analysis of the buffering: frequency locking in a forced fast-slow system. In the same experimental conditions, Hu and Wilson considered also the feedback to a sequence of repeated stimuli. They observed a buffering of the interstitial lactate concentration which tends rather quickly to an asymptotically frequency locking response. Latter, in the article [3], this was confirmed by numerical simulations. We show indeed, by averaging theory on a slow manifold, that the impulsive system with a periodic input $F(t)$ of period $T$ displays, for some large choice of $T$-periodic controls $J(t, x)$, an attractive periodic orbit, in the limit where $\epsilon'$ and $\epsilon$ are small enough. This is the main theorem involved:

**Theorem 3.** Let us consider a fast-slow $(p, q)$ system in balanced form:

$$
\frac{dx}{dt} = \epsilon' f(x, y, t) \\
\epsilon \frac{dy}{dt} = g(x, y, t),
$$

where $f, g$ are $T$-periodic in $t$. Assume that

a- The equation $g(x, y, t) = 0$ is solved by $y = \phi(x, t)$ which is an asymptotically stable solution of the equation:

$$
\frac{dy}{d\tau} = g(x, y),
$$

uniformly in $x \in D$ and $\tau \in \mathbb{R}_+$ (i.e. there exists a $\mu$, uniform in $x, \tau$ such that $\text{Re}(A(g(y))) \leq -\mu < 0$).

Let $A(t)$ be the $T$-periodic matrix defined as

$$
A(t) = f_x(x, \phi(x, t), t) - f_y g_y^{-1} g_x(x, \phi(x, t), t).
$$

b-Assume that the linear equation:

$$
\frac{d\xi}{dt} = A(t)\xi,
$$

displays no other $T$-periodic solution than $\xi = 0$.

c-There exists an isolated solution $x_0$ to the equation:

$$
\frac{1}{T} \int_0^T g(x, \phi(t, x))dt = 0.
$$

Then the fast-slow system displays a $T$ periodic solution with initial data $x_0, y_0 = \phi(0, x_0)$ up to $O(\epsilon\epsilon')$. 

This is typically a situation of averaging in a slow manifold (cf. for instance in [19]). Indeed the theorem follows from the usual averaging theorem (see for instance [16], [18]) and a theorem of [8]. For sake of completeness we include a proof here which follows the lines of the article [8]:

**Proof.** 1-Assume that the slow limit of the equation:

$$\frac{dx}{dt} = f(x, y, t)$$
$$\dot{0} = g(x, y, t)$$

displays a $T$-periodic solution $x = \theta(t), y = \phi(t)$. Change first variable: $\xi = x - \theta(t), \eta = y - \phi(t)$ and get:

$$\frac{d\xi}{dt} = f(x, y, t) + F,$$
$$\epsilon \frac{d\eta}{dt} = g(x, y, t) + S.$$

Then eliminate the term $g_x \xi$ by changing $\xi$ into $w$ so that $w = y - \phi(t) + U \xi$, $U = g_y^{-1} g_x$, this yields:

$$\frac{dw}{dt} = (f_x - f_y U) \xi + f_y w + F$$
$$\epsilon \frac{dw}{dt} = g_y w + G.$$

2- Consider first equation $\epsilon \frac{dw}{dt} = g_y w$. The fundamental matrix (or Green function) $\Phi(s, t)$ of

$$\epsilon \frac{dw}{dt} = Q(t)w, \Re(\Lambda(Q(t))) \leq -\mu,$$

satisfies $|\Phi(s, t, \epsilon)| \leq K e^{-\mu (t-s)/\epsilon}$.

3-Write $A(t) = f_x - f_y U$, assumption is the only $T$-periodic solution of

$$\frac{d\xi}{dt} = A(t)\xi$$

is $\xi = 0$. Write $\Psi(s, t)$ the Green function of this linear homogeneous equation. Assumption implies that for any ($T$-periodic) $b(t)$ the only $T$-periodic solution of the linear non-homogeneous equation:

$$\frac{d\xi}{dt} = A(t)\xi + b(t),$$

writes

$$\xi(t) = \int_0^T \Psi(t, s)b(s)ds.$$  

The equation

$$\frac{d\xi}{dt} = (f_x - f_y U)\xi + f_y w + F$$
$$\epsilon \frac{dw}{dt} = g_y w + G.$$

displays a $T$-periodic solution if and only if the integral equation:

$$\xi(t) = \int_0^T \Phi(t, s)[f_y(s)w(s) + H(s, \xi(s), w(s))]ds$$
$$w(t) = \Psi(t, 0)[I - \Phi(T, 0)]^{-1} \frac{1}{\epsilon} \int_0^T \Phi(T, s)G(s)ds + \frac{1}{\epsilon} \int_0^t \Phi(t, s)G(s)ds,$$

has a solution. To prove that this integral equation has a solution, we apply iterative method. The Lipschitz constant might be very high by the presence of $\frac{1}{\epsilon}$ but this factor is killed by the flat estimate $|\Phi(s, t, \epsilon)| \leq K e^{-\mu (t-s)/\epsilon}$. Note that the convergence to the periodic orbit is very fast.
4-If there exists an isolated solution $x_0$ to the equation:

$$\frac{1}{T} \int_0^T f(x, \phi(t, x), t) dt = 0. $$

then, by the usual averaging theorem, the system

$$\frac{dx}{dt} = f(x, y, t)$$
$$\frac{dy}{dt} = g(x, y, t)$$

displays a $T$-periodic solution for $\epsilon'$ small enough and we can apply what precedes. □

To conclude this part, we have to check the conditions of application of the previous theorem to the system (1).

a- The computations made on paragraph 2 are still valid when $F = F(t)$ is time-dependent. We have seen that the equation

$$g(x, y, t) = F(t)(L - y) + C\left(\frac{x}{k + x} - \frac{y}{k' + y}\right) = 0,$$

equivalent to:

$$y^2 + y[k' + \frac{Ck}{(k + x)F(t)}] - L - k'L - k'\frac{Cx}{(k + x)F(t)} = 0,$$

solves into

$$y = \phi(x, t) = \frac{1}{2}[-k' - \frac{Ck}{(k + x)F(t)}] + L + \sqrt{\Delta(t)},$$

with

$$\Delta(t) = [k' + \frac{Ck}{(k + x)F(t)}] - L]^2 + 4k'L + 4k'\frac{Cx}{(k + x)F(t)} > 0.$$

The only point to be checked is that

$$g_y'(x, y, t) = -F(t) - C\frac{k'}{(k'+ y)^2} \leq -\mu = -\text{Min} F(t) - \frac{C}{k'} < 0.$$

b- The matrix $A(t)$ is in our case a scalar function which writes:

$$A(t) = \epsilon'\left[ J_x - \frac{kC}{(k + x)^2} F(t) + \frac{k'C}{(k' + y)^2} \right].$$

At this point, if we consider the special case $J(t, x) = J(t)$ as in the article [3], we can check the condition as $A(t) < 0$. In general, it looks natural to impose $J_x \leq 0$.

c- This yields the slow equation in the standard form (for averaging theory):

$$\frac{dx}{dt} = \epsilon' F(x, t, \epsilon) = \epsilon' \{J(t) + F(t)[L(t) - \phi(x, t)]\} + O(\epsilon^2).$$

Denote:

$$\mathcal{J}(x) = \frac{1}{T} \int_0^T J(t, x) dt,$$
$$\mathcal{T} = \frac{1}{T} \int_0^T F(t) dt,$$
the averaging of the impulse \( F(t) \) and of the periodic control \( J(t, x) \). The averaging equation writes:

\[
\frac{dx}{dt} = \epsilon' \mathcal{J}(x),
\]

\[
\mathcal{J}(x) = \mathcal{J}(x) + LF - \frac{1}{\epsilon} \int_0^T F(t) \phi(t, x) dt.
\]

This makes the averaging condition \( \mathcal{J}(x) = 0 \) quite practical to compute for piecewise linear impulse and controls in our case.

### 3. Extension to the 4-dimensional system

An important issue expected of the large compartmental models ([11, 12, 13, 14]) is to represent the subtle metabolic balance between neurons and astrocytes ([20, 21, 22, 23, 24]). It seems tempting to push further the reduced model to include two more compartments (intracellular neurons and intracellular astrocytes). We keep focusing on lactates and use the same rules of co-transports. Following these lines, we find the 4-dimensional system:

\(
\frac{dx}{dt} = \epsilon' [J_0(t, x, u, v) + C_1(\frac{u}{k_a + u} - \frac{x}{x+k}) + C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C(\frac{x}{k+z} - \frac{y}{k+y})]
\)

\(
\frac{du}{dt} = \epsilon' [J_1(t, x, u, v) - C_1(\frac{u}{k_a + u} - \frac{x}{x+k})]
\)

\(
\frac{dv}{dt} = \epsilon' [J_2(t, x, u, v) - C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C_a(\frac{v}{k_a + v} - \frac{y}{k+y})]
\)

\(
\epsilon \frac{dy}{dt} = F(t)(L - y) + C(\frac{x}{k+z} - \frac{y}{k+y}) + C_a(\frac{v}{k_a + v} - \frac{y}{k+y}).
\)

The extracellular lactate concentration is still denoted \( x \), as well as the intracapillar concentration \( u \). We denote \( u \) the intra-neuron concentration and \( v \) the intra-astrocyte concentration.

#### 3.1. System with fixed controls, stationary point
We consider first the system obtained by freezing the input \( F(t) \) and the three controls \( J_i(t, x, u, v), i = 0, 1, 2 \):

\[
\frac{dx}{dt} = \epsilon' [J_0 + C_1(\frac{u}{k_a + u} - \frac{x}{x+k}) + C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C(\frac{x}{k+z} - \frac{y}{k+y})]
\]

\[
\frac{du}{dt} = \epsilon' [J_1 - C_1(\frac{u}{k_a + u} - \frac{x}{x+k})]
\]

\[
\frac{dv}{dt} = \epsilon' [J_2 - C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C_a(\frac{v}{k_a + v} - \frac{y}{k+y})]
\]

\[
\epsilon \frac{dy}{dt} = F(L - y) + C(\frac{x}{k+z} - \frac{y}{k+y}) + C_a(\frac{v}{k_a + v} - \frac{y}{k+y}).
\]

**Theorem 4.** The system \((42)\) displays a unique stationary point.

**Proof.** The equations for the stationary point display:

\[
0 = [J_0 + C_1(\frac{u}{k_a + u} - \frac{x}{x+k}) + C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C(\frac{x}{k+z} - \frac{y}{k+y})]
\]

\[
0 = [J_1 - C_1(\frac{u}{k_a + u} - \frac{x}{x+k})]
\]

\[
0 = [J_2 - C_2(\frac{v}{k_a + v} - \frac{x}{x+k}) - C_a(\frac{v}{k_a + v} - \frac{y}{k+y})]
\]

\[
0 = F(L - y) + C(\frac{x}{k+z} - \frac{y}{k+y}) + C_a(\frac{v}{k_a + v} - \frac{y}{k+y}).
\]

Summing up the 4 equations yields:

\[
y = y_0 = L + \frac{J_0 + J_1 + J_2}{F}.
\]
Next, the last two equations display:

\begin{equation}
-(C_2 + C_a) \frac{v}{v+k_a} + C_2 \frac{x}{x+k} = J_2 - C_a \frac{y_0}{k'+y_0}
\end{equation}

This last system can be easily solved into:

\begin{equation}
v = v_0 = \frac{k_a \left[ C_2 J_2 + C_a (J_0 + J_1 + J_2) \right]}{k' + y_0}
\end{equation}

\begin{equation}
x = x_0 = \frac{k \left[ C_a J_2 - (C_2 + C_a) (J_0 + J_1 + J_2) \right]}{k' + y_0}
\end{equation}

Lastly, the second equation yields:

\begin{equation}
\frac{u}{k_n + u} = \frac{J_1}{F_1} + \frac{x_0}{x_0 + k'}
\end{equation}

and thus:

\begin{equation}
u = u_0 = \frac{k_n \left[ C_2 J_2 + C_a (J_0 + J_1 + J_2) \right]}{k' + y_0}
\end{equation}

It seems difficult to discuss the question of the stability of this stationary point. But it is quite easy to check that the critical manifold given by the equation:

\begin{equation}
g(y, x, v) = F(L - y) + C \left( \frac{x}{k' + y} - \frac{y}{k + x} \right) + C_a \left( \frac{v}{k_a + v} - \frac{y}{k' + y} \right) = 0,
\end{equation}

again defines a branch of hypersurface of equation

\begin{equation}
y = \phi(x, v), y \geq 0
\end{equation}

obtained explicitly by solving a quadratic equation. This branch is again attractive because:

\begin{equation}
g_y'(y, v, x) = -F - (C + C_a) \frac{k'}{(k' + x)^2} < 0.
\end{equation}

A similar analysis for the dip can be made. It is also possible to use the previous theorem provided that the technical condition b is fulfilled. This yields again to the possibility of a periodic buffering.

The ANLSH (astrocyte-neuron lactate shuttle hypothesis) posed by L. Pellerin and P.J. Magistretti in 1994 (see [20, 21, 22, 7]) emphasizes that astrocytes act as a syncitium to distribute energy substrates such as lactate to active neurons. In relation with this astrocyte-neuron metabolic cooperation, it may be interesting to notice that the system [22] allows for a simple quasi-stationary analysis. In particular, we can see from the explicit formula obtained above for the equilibrium
value \( u = u_0 \), the influence of the controls term on an increase of \( u_0 \) which would correspond to a consumption by neurons of extracellular lactate. More precisely:

If \( J_0 + J_1 + J_2 \) is decreased then \( y_0 \) drops. If

\[
\frac{C_a J_2 - (C_2 + C_a)(J_0 + J_1 + J_2)}{CC_a + C_2 C_a}
\]

(53)

decreases then \( x_0 \) decreases. Furthermore if \( J_1 \) is increased then \( u_0 \) increases and if

\[
\frac{C J_2 + C_2(J_0 + J_1 + J_2)}{CC_a + C_2 C_a}
\]

(54)

increases then \( v_0 \) decreases.

From the mathematical point of view, it seems interesting to see a rather unusual setting of periodic control theory. Indeed previous references of periodic control theory display examples where non-periodic control is used to approach to a given periodic trajectory (like in satellites dynamics see for instance [13], [15]). Here, the periodic orbit is built by the control (or forcing term) \( J(t) \). Also there are more mathematical perspectives to develop about the asymptotics related with averaging in a slow manifold.

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