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THE STABILITY ANALYSIS OF BRAIN LACTATE KINETICS

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Abstract. Our aim in this article is to study properties of a generalized dynamical system modeling brain lactate kinetics, with N neuron compartments and A astrocyte compartments. In particular, we prove the uniqueness of the stationary point and its asymptotic stability. Furthermore, we check that the system is positive and cooperative.

1. **Introduction.**

The system of ODE's

$$\begin{aligned} \frac{dx}{dt} &= J - T\left(\frac{x}{k+x} - \frac{y}{k'+y}\right), \quad T,\ k,\ k',\ J > 0, \\ \epsilon\frac{dy}{dt} &= F(L-y) - T\left(\frac{y}{k'+y} - \frac{x}{k+x}\right), \quad \epsilon,\ F,\ L > 0, \end{aligned} \tag{1}$$

where ϵ is a small parameter, was proposed and studied as a model for brain lactate kinetics (see [3, 6, 7, 8]). In this context, $x = x(t)$ and $y = y(t)$ correspond to the lactate concentrations in an interstitial (i.e., extra-cellular) domain and in a capillary domain, respectively. Furthermore, the nonlinear term $T(\frac{x}{k+x} - \frac{y}{k'+y})$ stands for a co-transport through the brain-blood boundary (see [5]). Finally, J and F are forcing and input terms, respectively, assumed frozen. The model has a unique stationary point which is asymptotically stable. Recently, in [10, 4], a PDE's system obtained by adding diffusion of lactate was introduced. The authors proved existence and uniqueneness of nonnegative solutions and obtained linear stability results. A more general ODE's model for brain lactate kinetics, where the intracellular compartment splits into neuron and astrocyte, was considered in [6, 7]. It displays

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$$\begin{aligned}
\frac{dx}{dt} &= J_0 + T_1(-\frac{x}{k+x} + \frac{u}{k_n+u}) + T_2(-\frac{x}{k+x} + \frac{v}{k_a+v}) - T(\frac{x}{k+x} - \frac{y}{k'+y})\\
\frac{du}{dt} &= J_1 - T_1(-\frac{x}{k+x} + \frac{u}{k_n+u})\\
\frac{dv}{dt} &= J_2 - T_2(-\frac{x}{k+x} + \frac{v}{k_a+v}) - T_a(\frac{v}{k_a+v} - \frac{y}{k'+y})\\
\epsilon\frac{dy}{dt} &= F(L-y) + T(\frac{x}{k+x} - \frac{y}{k'+y}) + T_a(\frac{v}{k_a+v} - \frac{y}{k'+y})
\end{aligned} \tag{2}$$

where all the constants are nonnegative. It also includes transports through cell membranes and a direct transport from capillary to intracellular astrocyte. It was proved in [6, 7] that this 4-dimensional system displays a unique stationary point but its nature was left open. The stability of the unique stationary point is an important issue as it relates with therapeutic protocols developped in the references [6, 7]. Another important issue is the boundedness of the lactate concentrations related with the viability domain (cf. [6, 7]). We can in fact consider a natural extension of this system into a more general $N + A + 2$ system. For this generalized system, we prove both uniqueness and asymptotic stability of the stationary point. In this article we do not consider fast-slow limits and absorb ϵ in the parameters.

2. Extension to N neuron compartments and A astrocyte compartments.

2.1. Introduction of the system and its positivity. Let us consider a dynamical system equipped with forcing terms $J_i > 0, i = 0, 1, \ldots, N+A$, and input $F > 0$ and all parameters $C, C_n, D_a, E_a > 0$ with $n \in \{1, \ldots, N\}$, $a \in \{1, \ldots, A\}$:

$$\begin{aligned}
\frac{dx}{dt} &= J_0 + \sum_{n=1}^{N} C_n(\frac{u_n}{k_n+u_n} - \frac{x}{k+x}) + \sum_{a=1}^{A} D_a(\frac{v_a}{k_{N+a}+v_a} - \frac{x}{k+x})\\
&\quad -C(\frac{x}{k+x} - \frac{y}{k'+y})\\
\frac{du_1}{dt} &= J_1 - C_1(\frac{u_1}{kn_1+u_1} - \frac{x}{k+x})\\
&\vdots\\
\frac{du_N}{dt} &= J_N - C_N(\frac{u_N}{kn_N+u_N} - \frac{x}{k+x})\\
\frac{dv_1}{dt} &= J_{N+1} - D_1(\frac{v_1}{ka_1+v_1} - \frac{x}{k+x}) - E_1(\frac{v_1}{ka_1+v_1} - \frac{y}{k'+y})\\
&\vdots\\
\frac{dv_A}{dt} &= J_{N+A} - D_A(\frac{v_A}{ka_A+v_A} - \frac{x}{k+x}) - E_A(\frac{v_A}{ka_A+v_A} - \frac{y}{k'+y})\\
\frac{dy}{dt} &= F(L-y) + C(\frac{x}{k+x} - \frac{y}{k'+y}) + \sum_{a=1}^{A} E_a(\frac{v_a}{ka_a+v_a} - \frac{y}{k'+y}).
\end{aligned} \tag{3}$$

For $N = A = 1$, this system coincides with the 4-dimensional system considered in ([6, 7]). It can be considered as a model of brain lactate kinetics with co-transports (intracellular-extracellular) through the N neuron membranes and (intracellular-extracellular) through the astrocytes membranes and direct crossing (intracellular-capillary) from astrocyte to capillary. Variable x stands for the extracellular concentration. Variables $u_n, n = 1, \dots, N$ stand for the intracellular concentration inside neurons. Variables $v_a, a = 1, \dots, A$ represent the intracellular concentration in astrocytes. Variable y represents the concentration in capillary. For convenience, we denote as W the set of variables $W = (x, u_n, v_a, y) \in \mathbb{R}^d, d = N+A+2$.

Recall that an autonomous continuous dynamical system associated with a vector field:

$$\frac{dW_i}{dt} = f_i(W), \quad i = 1, \dots, d \tag{4}$$

is said to be positive if and only if: $\forall i \in 1, \dots, d$

$$\dot{W}_i = f_i(W_1 \geq 0, \dots, W_i = 0, \dots, W_d \geq 0) \geq 0 \tag{5}$$

It is easy to check that the vector field defined by system (3) is positive. The geometrical meaning of this property is that the flow of the vector field can be restricted to the convex set $\Omega = \mathbb{R}^d_+$.

2.2. **Uniqueness of the stationary point.**

Theorem 2.1. *The system (3) displays a unique stationary point denoted as s^*.*

Proof. The equations for finding a stationary point yield:

$$\begin{aligned}
0 &= J_0 + \sum_{n=1}^{N} C_n\left(\tfrac{u_n}{kn_n+u_n} - \tfrac{x}{x+k}\right) + \sum_{a=1}^{A} D_a\left(\tfrac{v_a}{ka_a+v_a} - \tfrac{x}{x+k}\right) - C\left(\tfrac{x}{k+x} - \tfrac{y}{k'+y}\right)\\
0 &= J_1 - C_1\left(\tfrac{u_1}{kn_1+u_1} - \tfrac{x}{x+k}\right)\\
&\vdots\\
0 &= J_n - C_n\left(\tfrac{u_n}{kn_n+u_n} - \tfrac{x}{x+k}\right)\\
&\vdots\\
0 &= J_N - C_N\left(\tfrac{u_N}{kn_N+u_N} - \tfrac{x}{x+k}\right)\\
0 &= J_{N+1} - D_1\left(\tfrac{v_1}{ka_1+v_1} - \tfrac{x}{x+k}\right) - E_1\left(\tfrac{v_1}{ka_1+v_1} - \tfrac{y}{k'+y}\right)\\
&\vdots\\
0 &= J_{N+a} - D_a\left(\tfrac{v_a}{ka_a+v_a} - \tfrac{x}{x+k}\right) - E_a\left(\tfrac{v_a}{ka_a+v_a} - \tfrac{y}{k'+y}\right)\\
&\vdots\\
0 &= J_{N+A} - D_A\left(\tfrac{v_a}{ka_A+v_A} - \tfrac{x}{x+k}\right) - E_A\left(\tfrac{v_A}{ka_A+v_A} - \tfrac{y}{k'+y}\right)\\
0 &= F(L-y) + C\left(\tfrac{x}{k+x} - \tfrac{y}{k'+y}\right) + \sum_{a=1}^{A} E_a\left(\tfrac{v_a}{ka_a+v_a} - \tfrac{y}{k'+y}\right)
\end{aligned} \tag{6}$$

Consider the following change of variable:

$$X = \frac{x}{k+x}, Y = \frac{y}{k'+y}, U_n = \frac{u_n}{kn_n+u_n}, V_a = \frac{v_a}{ka_a+v_a} \tag{7}$$

for $n \in \{1, \dots, N\}$ and $a \in \{1, \dots, A\}$. So we can write the system in a matrix equation:

$$Ms = b \tag{8}$$

where $M \in \mathbb{R}^{d \times d}$ displays:

$$M = \left(\begin{array}{ccc|ccc|c|c}
C_1 & & & & & & -C_1 & \\
& \ddots & & & 0 & & \vdots & 0 \\
& & C_N & & & & -C_N & \\
\hline
& & & D_1+E_1 & & & -D_1 & -E_1 \\
& 0 & & & \ddots & & \vdots & \vdots \\
& & & & & D_A+E_A & -D_A & -E_A \\
\hline
-C_1 & \dots & -C_N & -D_1 & \dots & -D_A & \sum_{n=1}^{N} C_n + \sum_{a=1}^{A} D_a + C & -C \\
\hline
& 0 & & -E_1 & \dots & -E_A & -C & \sum_{a=1}^{A} E_a + C
\end{array}\right)$$

$$s = \begin{pmatrix} U_1 \\ \vdots \\ U_N \\ V_1 \\ \vdots \\ V_A \\ X \\ Y \end{pmatrix} \in \mathbb{R}^d \qquad b = \begin{pmatrix} J_1 \\ \vdots \\ J_N \\ J_{N+1} \\ \vdots \\ J_{N+A} \\ J_0 \\ F(L-y) \end{pmatrix} \in \mathbb{R}^d$$

After summing up the d equations, this yields:

$$y = y^* = L + \frac{J_0 + J_1 + \cdots + J_{N+A}}{F}. \tag{9}$$

So we have a unique solution for y. In this case we can reduce equation (8) into a new matrix equation of dimension $d-1$ denoted:

$$M's' = b' \tag{10}$$

where

$$M' = \left(\begin{array}{ccc|ccc|c}
C_1 & & & & & & -C_1 \\
& \ddots & & & 0 & & \vdots \\
& & C_N & & & & -C_N \\
\hline
& & & D_1+E_1 & & & -D_1 \\
& 0 & & & \ddots & & \vdots \\
& & & & & D_A+E_A & -D_A \\
\hline
-C_1 & \dots & -C_N & -D_1 & \dots & -D_A & \sum_{n=1}^{N} C_n + \sum_{a=1}^{A} D_a + C
\end{array}\right)$$

$$s' = \begin{pmatrix} U_1 \\ \vdots \\ U_N \\ V_1 \\ \vdots \\ V_A \\ X \end{pmatrix} \in \mathbb{R}^{d-1} \qquad b' = \begin{pmatrix} J_1 \\ \vdots \\ J_N \\ J_{N+1} + E_1 \frac{y^*}{k'+y^*} \\ \vdots \\ J_{N+A} + E_A \frac{y^*}{k'+y^*} \\ J_0 + Cy^* \end{pmatrix} \in \mathbb{R}^{d-1}$$

We can write a block decomposition of the matrix M' as follows:

$$M' = \begin{pmatrix} M_1 & M_2 \\ M_3 & M_4 \end{pmatrix}$$

so

$$M_1 = \left(\begin{array}{ccc|ccc} C_1 & & & & & \\ & \ddots & & & 0 & \\ & & C_N & & & \\ \hline & & & D_1 + E_1 & & \\ & 0 & & & \ddots & \\ & & & & & D_A + E_A \end{array}\right) \in \mathbb{R}^{(d-2)\times(d-2)}$$

$$M_2 = \begin{pmatrix} -C_1 & \dots & -C_N & -D_1 & \cdots & -D_A \end{pmatrix}^T \in \mathbb{R}^{(d-2)\times 1}$$

$$M_3 = \begin{pmatrix} -C_1 & \dots & -C_N & -D_1 & \cdots & -D_A \end{pmatrix} \in \mathbb{R}^{1\times(d-2)}$$

$$M_4 = \sum_{n=1}^{N} C_n + \sum_{a=1}^{A} D_a + C \in \mathbb{R}$$

As M_1 is an invertible square matrix, we can write:

$$\det(M') = \det \begin{pmatrix} M_1 & M_2 \\ M_3 & M_4 \end{pmatrix} = \det(M_1)\det(M_4 - M_3 {M_1}^{-1} M_2).$$

The determinant of M_1 writes $\det(M_1) = \prod_{n=1}^{N} C_n \prod_{a=1}^{A} (D_a + E_a) > 0$.

Direct computation of the Matrix $(M_4 - M_3 {M_1}^{-1} M_2)$, which is a real number, yields:

$$\begin{aligned} \det(M_4 - M_3 {M_1}^{-1} M_2) &= \sum_{n=1}^{N} C_n + \sum_{a=1}^{A} D_a + C - (\sum_{n=1}^{N} C_n + \sum_{a=1}^{A} \frac{{D_a}^2}{(D_a + E_a)}) \\ &= \sum_{a=1}^{A} D_a + C - \sum_{a=1}^{A} \frac{{D_a}^2}{(D_a + E_a)} \\ &= \sum_{a=1}^{A} D_a (1 - \frac{{D_a}^2}{D_a + E_a}) + C \\ &= \sum_{a=1}^{A} \frac{D_a E_a}{D_a + E_a} + C > 0. \end{aligned}$$

Computation yields $\det(M') \neq 0$ and the equation (10) displays a unique solution s' which is as $s' = {M'}^{-1} b'$. With the change of variable (7), there is a unique solution for system (6) denoted as s'':

$$s'' = (x^*, u_1^*, \cdots, u_N^*, v_1^*, \cdots, v_A^*).$$

This proves the uniqueness of the stationary point $s^* = (s'', y^*)$ of system (3). In the next subsection, we discuss the positivity of this stationary point. □

2.3. **Conditions for the positivity of the stationary point.** The stationary point $s^* = (s'', y^*)$ does not belong necessarily to $\mathbb{R}^d_+$ as it was observed already for the 2-dimensional system in [6, 3]. Following the notations of equation (1), the stationary point belongs to $\mathbb{R}^2_+$ if and only if:

$$T > J[1 + \frac{1}{k'}(L + \frac{J}{F})]. \tag{11}$$

Similar explicit conditions can be given for the 4-dimensional system as shown in [6, 7]. In any dimension d, even if these conditions are not easily obtained explicitly, they read, with vector $e = (1, 1, ..1)$, $0 \leq M'^{-1}b' \leq e$.

3. **Asymptotic stability of the stationary point, cooperative dynamics and boundedness.** It is useful to introduce some more notations and definitions.

Definition 3.1. Let A and B be two $d \times d$ matrices, we denote:
$A \gg B \quad \Longleftrightarrow \quad a_{ij} > b_{ij}$ for all i,j $\in \{1, \ldots, n\}$,
$A > B \quad \Longleftrightarrow \quad a_{ij} \geq b_{ij}$ for all i,j $\in \{1, \ldots, n\}$ and $A \neq B$,
$A \geq B \quad \Longleftrightarrow \quad a_{ij} \geq b_{ij}$ for all i,j $\in \{1, \ldots, n\}$.

Definition 3.2. Given a $d \times d$ matrix, the spectral radius of A, denoted by $\rho(A)$ is: $\rho(A)$:=max$\{|\lambda| : \lambda \in \sigma(A)\}$ where $\sigma(A)$ is the set of all eigenvalues (spectrum) of the matrix A.

Definition 3.3. Given a $d \times d$ matrix, the spectral abscissa of A denoted by $\mu(A)$ is: $\mu(A)$:=max$\{Re(\lambda) : \lambda \in \sigma(A)\}$

Definition 3.4. A Matrix A is said to be reducible when there exists a permutation matrix P such that

$$P^T A P = \begin{pmatrix} X & Y \\ 0 & Z \end{pmatrix}$$

where X and Z are both square matrices.

In other terms, a matrix A is irreducible if and only if it is not equivalent to a block upper triangular matrix by permutations of row and columns.

Definition 3.5. The graph of a $d \times d$ matrix A denoted by $G(A)$ is the directed graph on d nodes $\{N_1, N_2, \ldots, N_d\}$, in which there is a directed edge leading from N_i to N_j if and only if $a_{ij} \neq 0$.

The graph $G(A)$ is said strongly connected if for each pair of nodes (N_i, N_j), there is a sequence of directed edges leading from N_i to N_j, where $i, j \in \{1, \ldots, d\}$.

Recall that A is an irreducible matrix if and only if its graph is strongly connected (cf. [9]).

We compute the Jacobian matrix of the vector field (3):
$J_F =$

$$\begin{pmatrix}
-(\sum\limits_{n=1}^{N} C_n + \sum\limits_{a=1}^{A} D_a + C)\frac{k}{(x+k)^2} & C_1\frac{kn_1}{(u_1+kn_1)^2} & \cdots & C_N\frac{kn_N}{(u_N+kn_N)^2} & D_1\frac{ka_1}{(v_1+ka_1)^2} & \cdots & D_A\frac{ka_A}{(v_A+ka_A)^2} & C\frac{k'}{(y+k')^2} \\
C_1\frac{k}{(x+k)^2} & -C_1\frac{kn_1}{(u_1+kn_1)^2} & & & & & & \\
\vdots & & \ddots & & & & & \\
C_N\frac{k}{(x+k)^2} & & & -C_N\frac{kn_N}{(u_N+kn_N)^2} & & & & \\
D_1\frac{k}{(x+k)^2} & & & & -(D_1+E_1)\frac{ka_1}{(v_1+ka_1)^2} & & & E_1\frac{k'}{(y+k')^2} \\
\vdots & & & & & \ddots & & \vdots \\
D_A\frac{k}{(x+k)^2} & & & & & & -(D_A+E_A)\frac{ka_A}{(v_A+ka_A)^2} & E_A\frac{k'}{(y+k')^2} \\
C\frac{k}{(x+k)^2} & & & & E_1\frac{ka_1}{(v_1+ka_1)^2} & \cdots & E_A\frac{ka_A}{(v_A+ka_A)^2} & -F-(C+\sum\limits_{a=1}^{A} E_a)\frac{k'}{(y+k')^2}
\end{pmatrix}$$

Denote J_0 the Jacobian matrix J_F for the input $F = 0$. All off-diagonal elements of the matrix J_F (and of J_0) are nonnegative. Following [12], such matrices are called Metzler matrices.

Let us recall the theorem due to Hal.L. Smith which applies to the Metzler matrices:

Theorem 3.6 (Smith[12]). *Let $A \in \mathbb{R}^{d\times d}$ be a Metzler matrix, then $\mu(A)$ is an eigenvalue of A and there is a corresponding eigenvector $v > 0$. Moreover $Re(\lambda) < \mu(A)$ for all other eigenvalue of A.*

In addition, if A is irreducible then:
i): $\mu(A)$ is an algebraically simple eigenvalue of A;
ii): $v \gg 0$ and any eigenvector $w > 0$ of A is a positive multiple of v;
iii): If B is a matrix satisfying $B > A$, then $\mu(B) > \mu(A)$.

We now prove the following theorem:

Theorem 3.7. *The stationary point of system (3) is asymptotically stable.*

Proof. As we can see, there are no zero elements at the first row and the first column in matrix J_F (and J_0). This means that in the graph associated to the matrix, there is a sequence of directed edges leading from N_i to N_j for all $i, j \in (1, 2..., d)$. Hence, $G(J_F)$ is strongly connected, so J_F (and J_0) is an irreducible matrix. Note that the strictly positive vector $w \in \mathbb{R}^d$:

$$\begin{aligned} w = \Big(&\frac{(x+k)^2}{k}, \frac{(u_1+kn_1)^2}{kn_1}, \cdots, \frac{(u_N+kn_N)^2}{kn_N}, \frac{(v_1+ka_1)^2}{ka_1}, \cdots \\ &\cdots, \frac{(v_A+ka_A)^2}{ka_A}, \frac{(y+k')^2}{k'}\Big)^T \end{aligned} \tag{12}$$

solves $J_0 w = 0$.

By (ii) in theorem (3.6), the vector w is necessarily proportional to the positive eigenvector v which corresponds to the spectral abscissa. Hence, we obtain that $\mu(J_0) = 0$.

By (iii) in theorem (3.6), $\mu(J_F) < \mu(J_0) = 0$.

This shows that all the real parts of eigenvalues of the Jacobian matrix J_F are negative, which means that the stationary point of system (3) is asymptotically stable. ☐

Recall now the following

Definition 3.8. A continuous dynamical system defined on the convex set $\Omega = \mathbb{R}^d_+$ by the equations:

$$\frac{dX_i}{dt} = f_i(X), \quad i = 1, ..., d \tag{13}$$

is said to be cooperative if the Jacobian matrix $\dfrac{\partial f_i}{\partial X_j}(X, t)$ is a Metzler matrix.

In particular the d-dimensional system (3) is cooperative. Such a cooperative system displays the so-called Kamke property (consequence of the fundamental theorem of differential calculus):

Proposition 1. *Given a continuous dynamical system defined on the convex set $\Omega = \mathbb{R}^d_+$ by the equations:*

$$\frac{dX_i}{dt} = f_i(X), \quad i = 1, ..., d \tag{14}$$

for any pair of points $b \geq a \in \Omega$, then $f(b) \geq f(a)$.

Proposition 2. *Given a continuous dynamical system defined on the convex set $\Omega = \mathbb{R}^d_+$ which displays the Kamke property and two points x_0 and y_0 in Ω so that $x_0 \leq y_0$, then if the solutions $\phi_t(x_0)$ and $\phi_t(y_0)$ (ϕ_t is the flow at time t of the vector field) are defined then $\phi_t(x_0) \leq \phi_t(y_0)$.*

Such tools are useful to discuss the other important issue of boundedness of the lactate concentrations in relation with the viability domain (cf.[3, 6, 7, 8]).

Consider first the reduced 2-dimensional system. Assume that the condition $T > J[1 + \frac{1}{k'}(L + \frac{J}{F})]$ is not fullfilled. The domain Ω is invariant by the positive flow. Consider any initial point x_0 in Ω and assume that the closure of its orbit is contained in a compact set. Consider its ω limit set $\omega(x_0)$. By the Poincaré-Bendixson theorem it is either a stationary point, a periodic orbit or a polycyle (union of stationary point connected by heteroclinic connexions). All these cases are ruled out by the fact that the system does not display a stationary point inside the domain Ω. This shows that there is no bounded orbit inside the domain.

Consider now the d-dimensional system which distinguishes the neuron and astrocyte compartments. Assume that the positivity conditions for the unique stationary point are fullfilled. Then in that case, the basin of attraction of the stationary point provides a positive invariant set of non-empty interior of solutions which are bounded and positive. Although it is not easy to proceed with explicit computations and we focus on the case $d = 4$.

Theorem 3.9. *There is a non-empty set of entries (J_0, J_1, J_2, L, F) so that the system (2) displays a full open set of solutions which are positive and bounded.*

Proof. It is enough to check that there are conditions on the entries so that the system (2) displays a positive stationary point. This yields:

$$
\begin{aligned}
x^* &= \frac{k\big(T_a(J_0+J_1) + T_2(J_0+J_1+J_2) + (TT_2 + TT_a + T_2T_a)\dfrac{y^*}{k'+y^*}\big)}{-T_a(J_0+J_1) - T_2(J_0+J_1+J_2) + (TT_2 + TT_a + T_2T_a)\dfrac{k'}{k'+y^*}}, \\
u^* &= \frac{k_n\big(\dfrac{J_1}{T_1} + \dfrac{T_a(J_0+J_1)+T_2(J_0+J_1+J_2)}{TT_2+TT_a+T_2T_a} + \dfrac{y^*}{k'+y^*}\big)}{1 - \big(\dfrac{J_1}{T_1} + \dfrac{T_a(J_0+J_1)+T_2(J_0+J_1+J_2)}{TT_2+TT_a+T_2T_a} + \dfrac{y^*}{k'+y^*}\big)}, \\
v^* &= \frac{k_a\big(TJ_2 + T_2(J_0+J_1+J_2) + (TT_2 + TT_a + T_2T_a)\dfrac{y^*}{k'+y^*}\big)}{-TJ_2 - T_2(J_0+J_1+J_2) + (TT_2 + TT_a + T_2T_a)\dfrac{k'}{k'+y^*}}, \\
y^* &= L + \frac{J_0+J_1+J_2}{F}.
\end{aligned}
\tag{15}
$$

Note that, for instance in the limit where $J = (J_0, J_1, J_2) = O(\eta)$ is small, then $y^* = \frac{L}{k'+L} + O(\eta)$ and we check that the other coordinates are also positive. □

4. **Remarks and perspectives.** 1- A natural question (for instance for the 4-dimensional system) is whether the conditions on the non-existence of stationary point inside the domain Ω implies that there is no bounded positive solutions.

2- There is a non-autonomous version of the Brain Lactate Dynamics for which the entries $J(t)$ and the forcing term $F(t)$ are time dependent. Further studies on the cooperative nature of these dynamics will be developed.

3- It should be interesting to analyse the reaction-diffusion PDE system obtained by adding diffusion to the 4-dimensional system (2) from the viewpoint of cooperative systems.

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