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Lactate's behavioral switch in the brain: an *in-silico* model

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Abstract

It is well known that glucose serves as the main energy substrate for the brain, and emerging evidence emphasizes its involvement in both physiological processes and disease (traumatic brain injury, memory, epilepsy, etc.). Furthermore, the usefulness of mathematical modeling in deciphering underlying dynamics of the brain to investigate lactate roles and mechanisms of action has been well established. Here, we analyze a novel mathematical model of brain lactate exchanges between four

compartments: neurons, astrocytes, capillaries, and extracellular space. A system of four ordinary differential equations is proposed to explain interactions between these compartments. We first optimize the model's parameters under normal, resting state conditions, and then use it to simulate changes linked to elevated arterial lactate. Our results show that even though increased arterial lactate results in increased uptake by astrocytes and release to the extracellular space, it cannot strongly recover the initial drop in neuronal lactate concentration. Also, we show that the direction of lactate transport between the compartments is influenced by the maximum astrocyte production rate and the transport rate between astrocytes and extracellular space.

Keywords:

Astrocytes, Brain Metabolism, Lactate, Mathematical Modeling, Optimization

1. Introduction

While it has been shown that lactate plays a significant role as a substrate for energy production in the brain, there are still unanswered questions about the mechanisms regulating its distribution and use across different brain compartments (Roosterman and Cottrell, 2020; Huang et al., 2021). Lactate's role as a metabolite involved in brain energetics has been extensively studied (Mahan, 2021), and it has been proposed to have a neuroprotective role in the brain (Glenn et al., 2015). It is also a central component of the astrocytic-neuronal-lactate-shuttle (ANLS) hypothesis. The ANLS framework was first proposed by Pellerin et al. (Pellerin and Magistretti, 1994; Pellerin et al., 1998), who posited that after neuronal synaptic release of glutamate, its effect was stopped by astrocytic uptake of the transmitter, supported by their aerobic glycolysis of glucose, resulting in lactate formation and release followed by neuronal uptake. Many experiments have supported this hypothesis (Pierre and Pellerin, 2005; O'Brien et al., 2007; Machler et al., 2016) with different types of analyses, as depicted in Table 2 in Gladden (2004) and more recent reviews (Pellerin and Magistretti, 2012; Mason, 2017; Brooks, 2018; Powell et al., 2020; Beard et al., 2022). There is evidence that lactate shuttling mechanism also exists intracellularly (Hashimoto et al., 2008).

However, a certain number of authors positioned themselves against the ANLS hypothesis, concluding that time delays are incompatible with this hypothesis (Fillenz, 2005; Korf, 2006) or that astrocytes participate only very moderately to the lactate used by neurons (Gjedde and Marrett, 2001; Gandhi et al., 2009; Mangia et al., 2009; Díaz-García et al., 2017).

In addition to the intra-cerebral astrocytes-neurons exchanges of lactate, exchanges with other organs are also of interest. For instance, muscles can produce significant quantities of lactate, in particular during exercise (Andersen et al., 2013; Riske et al., 2017), which can then be transported into the brain (Quistorff et al., 2008; Rasmussen et al., 2011; Felipe et al., 2017; Matsui et al., 2017). These exchanges take place across the blood-brain-barrier (BBB) through astrocytes end-feet (Gonçalves et al., 2019). In general, neurons do not come in direct contact with vessels, although direct synaptic appositions are also present (Jukkola and Gu, 2015).

In addition to experimental work which has provided us with crucial elements to understand lactate use and exchanges in the brain, authors have explored this metabolite role using mathematical models. These models were developed at different levels of complexity, including more compartments and variables depending on the measures at hand (Patsatzis et al., 2019; Perrillat-Mercerot et al., 2019; Raad et al., 2023). Such approaches are particularly useful when actual experimental measurements cannot be easily obtained, especially in humans (Powell et al., 2020).

These models explicitly analyze the hypothetical nevertheless plausible mechanistic impact of physiological parameters, such as the glucose uptake ratio between neurons and astrocytes on the change of lactate transport direction or the neuronal firing duration on brain metabolism (Capo Rangel et al., 2019).

In the case of the ANLS hypothesis, multiple models have been proposed to assess its validity. Even though a number of models provided support for ANLS (Aubert and Costalat, 2005; Aubert et al., 2005; Bouzier-Sore et al., 2006; Cloutier et al., 2009; Jolivet et al., 2015), a few simulations predicted lactate flow in the opposite direction, neuronal-astrocytic-lactate-shuttle (NALS) (Simpson et al., 2007; Mangia et al., 2009; Occhipinti et al., 2009) or concluded that results are highly sensitive to parameters selection (Jolivet et al., 2010; Somersalo et al., 2012; Massucci et al., 2013).

In this work, we proposed a new mathematical model at the mesoscopic level based on the recent physiological data comprising neuronal, extracellular space, astrocytic and capillary compartments with a simplified version of lactate consumption/production within each of those, as depicted in Fig. 1.

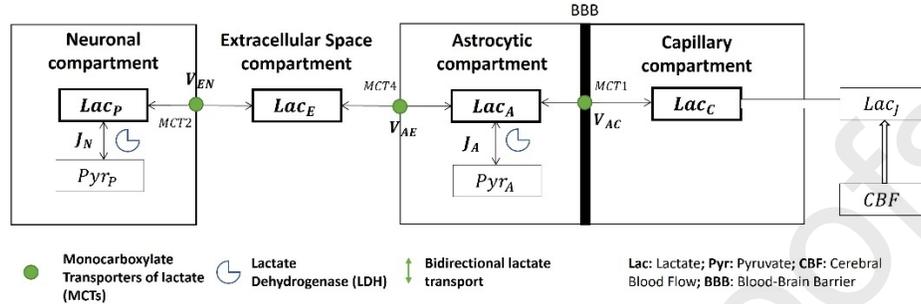


Figure 1- Schematic representation of the model. It includes four compartments: neurons, astrocytes, capillaries and extracellular space. Green circles represent monocarboxylate transporters (MCTs) of lactate. Simple arrows represent bidirectional transport and the double arrow represents two different transports (see Model description). Lactate dehydrogenase enzyme, converting lactate to pyruvate and vice versa is represented by the three-quarter circle. Corresponding lactate exchange rates and net production are shown in the interfaces.

The goal of this paper is to assess lactate repartition and transfer across compartments under physiological conditions. Consistent with the literature, we assume possible bidirectional transport at all interfaces to prevent biases in model implementation regarding the direction of lactate transport (Gladden, 2004; Takata et al., 2004; Nehlig and Coles, 2007; Pellerin, 2008; Castro et al., 2009; Genc et al., 2011; Bergersen, 2015; Beland-Millar et al., 2017). This makes it possible for the model to account for potential regulatory functions of astrocytes, including their ability to buffer excessive extracellular lactate increases caused by neuronal release or by vascular to brain transfer. We also include pyruvate in neurons and astrocytes in order to indirectly control changes in the glucose uptake.

We specifically attempt to simulate potential behavioral regimes that the model can generate in the physiological range of parameters by optimizing the model in resting state and identifying potential parameter settings that satisfy specific constraints. In particular, we explore the system in two situations: resting and active states. First, in the resting state, we mainly investigate how a switch between ANLS and NALS can occur and the parameters it depends on. Additionally, we investigate interactions between capillary and brain tissue as well as resting concentration variations. We are particularly interested in estimating the contribution of the lactate shuttle at the neuronal compartment. By perturbing resting state, we aim at evaluating if elevated artery lactate contributes to a drop in neuronal lactate. This situation resembles physical exercise, during which there is an increase in arterial lactate concentration, as discussed in the previous paragraphs.

In comparison to other modelling efforts (Aubert and Costalat, 2005; Simpson et al., 2007), we attempted to reduce the biases that may arise from basing the results on a specific parameter set at the parameter selection level. To represent a broader range of potential behaviors, we investigated the model's response using several sets of parameters, obtained by mathematical optimization techniques (Atashpaz-Gargari and Lucas, 2007; Soltanzadeh, 2021), in addition to fixing some parameters from the physiological literature (Kuhr et al., 1988; Dimmer et al., 2000; Aubert and Costalat, 2005; Atlante et al., 2007; O'Brien et al., 2007; Ramírez et al., 2007; Gandhi et al., 2009; Boumezbeur et al., 2010; Rasmussen et al., 2011; Jolivet et al., 2015), as shown in Table 1.

2. Materials and methods

The model of Fig. 1 is developed to include four compartments: neurons, extracellular space, astrocytes, and capillaries. Production and consumption of lactate occur inside astrocytes and neurons. Another source of lactate is the delivery of lactate produced in other organs via arteries. Lactate can also be exchanged between compartments via monocarboxylate transporters (MCTs) (Bélanger et al., 2011; Hertz et al., 2014). There exists various types of MCTs in the brain depending on the interface they are transporting lactate through (Pierre and Pellerin, 2005). In the following, we briefly review MCTs and explain our selection of transporters for each interface in the model.

2.1. Localization of the MCTs in the brain

The main lactate transporters in the brain are MCT1, MCT2 and MCT4 (Hertz, 2004; Pierre and Pellerin, 2005; Bergersen, 2007). Differences across species and in experimental settings reveal localization discrepancies (Bergersen, 2015). Anatomical expression of these transporters has been reviewed by Pierre et al., Bergersen (2007), Vijay and Morris (2014), Lauritzen et al. (2015):

- Some studies localize MCT4 transporters specifically in astrocytes,
- MCT1 transporters have an important role in capillaries exchanges across the blood brain barrier (BBB),
- MCT2 transporters are primarily localized in neurons.

Despite some variations in transporters localization as illustrated in Fig. 1 from Simpson et al. (2007), we chose MCT1, MCT2, and MCT4 (Pellerin and Magistretti, 2012) to be represented in our model, as also summarized in Table 2 of Castro et al. (2009).

2.2. Model description

Physiologically, all MCTs are bidirectional (Barros and Deitmer, 2010; Hertz et al., 2014). Contrary to the model of Simpson et al. (2007) using a representation including H^+ concentration, we use the simple and well-known Michaelis-Menten forms (double and reversible) to model lactate exchanges, because we have access to the (V_m, K_m) parameters in most of the experimental studies (see Table 1). Aubert et al. (2005) showed little contribution of pH on the extracellular lactate dynamics. Hence, our model does not include a variable for $[H^+]$ to tackle the impact of pH).

In the following sections, \mathbf{Lac}_x , $x = N, E, A, C$ refers to the lactate concentration inside neurons, extracellular space, astrocytes, and capillaries, respectively. We keep these states in bold-italic format to distinguish them from other parameters in the model. Lac_j is the symbol of artery lactate concentration.

2.2.1. Neuronal Compartment

This compartment interacts with the extracellular space via a bidirectional pathway (MCT2 representation), allowing them to uptake or release lactate. We model this process as a reversible enzymatic reaction with a rate given by V_{EN} :

$$V_{EN} = \frac{V_{EN}^m (\mathbf{Lac}_E - \mathbf{Lac}_N)}{K_{EN}^m + \mathbf{Lac}_N + \mathbf{Lac}_E} \quad (1)$$

with V_{EN}^m being the saturation rate of the transport between the neurons and extracellular space and K_{EN}^m being the Michaelis constant. We keep the same notation for the other compartments.

Additionally, in the last step of glycolysis, lactate is reversibly produced from pyruvate lactate dehydrogenase (LDH) (Schurr, 2018). There exist five isoforms of LDH with different kinetic properties. LDH1, called heart-type LDH, favors lactate consumption and is more found in the neurons, while LDH5 which favors lactate production is called muscle-type

LDH and is more expressed in the astrocytes (O'Brien et al., 2007). Pyruvate then enters the tricarboxylic acid cycle (TCA cycle) and produces energy. In our model, lactate production represents the formation of lactate from pyruvate and lactate consumption is the opposite.

We assumed Michaelis-Menten equations for the production and consumption kinetics, introduced in Eq. (2):

$$J_N = \text{Prod}_N - \text{Cons}_N = \frac{V_N^{\text{prod}} \text{Pyr}_N}{K_N^{\text{prod}} + \text{Pyr}_N} - \frac{V_N^{\text{cons}} \text{Lac}_N}{K_N^{\text{cons}} + \text{Lac}_N} \quad (2)$$

Pyr_N is the pyruvate concentration inside neurons, $V_N^{\text{prod/cons}}$ is the maximum rate, and $K_N^{\text{prod/cons}}$ is the Michaelis constant for the LDH reaction of the neuronal compartment. In our computational model, pyruvate concentration, Pyr_N of Eq. (2) inside neuronal and astrocytic compartments controls the lactate production and is an input to the system. For resting state simulations, pyruvate concentration is chosen so that $\text{Pyr}_N^{\text{SS}} = \frac{\text{Lac}_N^{\text{SS}}}{18}$, which is based on the model proposed by Aubert and Costalat (2005) and for temporal simulations the following piecewise trapezoid function model is used:

$$S(t) = \begin{cases} S_0, & 0 < t < t_1 \text{ and } t_{\text{end}} < t < L \\ S_0 + (S_1 - S_0)(t - t_1)/t_d, & t_1 < t \leq t_1 + t_d \\ S_1, & t_1 + t_d < t \leq t_{\text{end}} \\ S_1 + (S_1 - S_0)(t - t_{\text{end}})/t_d, & t_{\text{end}} < t < t_{\text{end}} + t_d \end{cases} \quad (3)$$

Where S represents either Pyr_N , Pyr_A or Lac_j and S_0 is their resting concentration. t_1 and t_{end} are the onset and end of perturbation, while L is the end of simulation time. Figure 3 (a) shows how $S(t)$ looks like. Considering Eqs. (1)-(2), the time derivative of lactate concentration inside neurons is written as:

$$\frac{dLac_N}{dt} = V_{EN} + J_N \quad (4)$$

2.2.2. Astrocytic Compartment.

Astrocytes play the role of an interface between capillaries and brain tissue (through MCT1 expression) as shown in Fig. 1. It has been shown that astrocytes' end-feet encircle capillaries and trade lactate via two unidirectional routes (Jukkola and Gu, 2015). We model the dynamics of these two transport pathways by an irreversible Michaelis-Menten equation expressed in Eq. (5):

$$V_{AC} = V_{AC}^m \frac{Lac_A}{K_{AC}^m + Lac_A} - V_{CA}^m \frac{Lac_C}{K_{CA}^m + Lac_C} \quad (5)$$

On the other hand, they release into and uptake lactate from extracellular space through a bidirectional pathway (MCT4 representation) given by:

$$V_{AE} = V_{AE}^m \frac{(Lac_A - Lac_E)}{K_{AE}^m + Lac_A + Lac_E} \quad (6)$$

Like neurons, astrocytes produce lactate from pyruvate but usually at a higher rate (Sotelo-Hitschfeld et al., 2015). To model lactate production and consumption inside astrocytes, we can write:

$$J_A = Prod_A - Cons_A = \frac{V_A^{prod} Pyr_A}{K_A^{prod} + Pyr_A} - \frac{V_A^{cons} Lac_A}{K_A^{cons} + Lac_A} \quad (7)$$

For the resting state, we choose pyruvate concentration to be a hundred times of the lactate concentration inside astrocytes and in order to simulate resting state perturbations, we use the same model introduced in Eq. (3). Consequently, the dynamics of astrocyte lactate concentrations is determined by:

$$\frac{d\text{Lac}_A}{dt} = -V_{AE} - V_{AC} + J_A \quad (8)$$

2.2.3. Extracellular space

Lactate is exchanged between neurons and astrocytes by releasing it to, and internalizing it from, the extracellular compartment. According to Eqs. (1) and (6), the time derivative of extracellular space lactate concentration can be written as:

$$\frac{d\text{Lac}_E}{dt} = -\frac{V_{EN}}{r_{EN}} + \frac{V_{AE}}{r_{AE}} \quad (9)$$

where $r_{EN} = \frac{V_E}{V_N}$ and $r_{AE} = \frac{V_A}{V_E}$ are called volume fraction and are equal to the ratio of the volume occupied by the compartments (Capo Rangel et al., 2019).

2.2.4. Capillary

Additionally, although most computational models take lactate exchanges through the Blood Brain Barrier (BBB) into account, they frequently only include one direction (from tissue to blood) and contribution of elevated blood lactate is not investigated (Cloutier et al., 2009; DiNuzzo et al., 2009; Massucci et al., 2013; Jolivet et al., 2015; Winter et al., 2017). As we discussed in the introduction, it is possible for lactate to cross the BBB and be transported between blood and brain tissue.

According to the previous models proposed for the lactate (Aubert and Costalat, 2005; Cloutier et al., 2009), the effect of arterial lactate concentration on the capillary lactate is modeled as:

$$V_{\text{cap}} = \frac{2\text{CBF}}{V_C}(\text{Lac}_j - \text{Lac}_c), \quad (10)$$

In which Lac_j refers to the arterial lactate and V_C represents the capillary volume. Increases in neuronal activity in the brain are reliably accompanied by changes in local blood flow (Vlassenko et al., 2006). Here, we model the temporal dynamics of cerebral blood flow (CBF) by a double exponential model as proposed by Jolivet et al. (2015):

$$\text{CBF}(t) = \begin{cases} \text{CBF}_0, & t < t_1 \\ \text{CBF}_0 \pm \text{CBF}_1 \left(\exp\left(-\frac{t-t_1}{\tau_1}\right) - \exp\left(-\frac{t-t_1}{\tau_2}\right) \right), & t_1 \leq t \leq t_{\text{end}} \\ \text{CBF}_0 \left(1 + ((\text{CBF}(t_{\text{end}}) - \text{CBF}_0) \exp\left(\frac{t_{\text{end}}-t}{\tau_3}\right)) \right), & t_{\text{end}} < t < L \end{cases} \quad (11)$$

Where CBF_0 and CBF_1 are the values of CBF in resting and elevated activity, respectively. t_1 , t_{end} are the onset and end time of the increase and τ_1 and τ_2 are the rise and decay time constants. In some scenarios such as during exercise, it has been shown that lactate is transported to the brain as the artery lactate concentration increases dramatically (Quistorff et al., 2008). In our simulations, we use Eq. (3) to model dynamics of the artery lactate over time. Considering the interaction of capillaries with astrocytes modeled in Eq. (5), we end up with the following equation:

$$\frac{d\text{Lac}_c}{dt} = V_{\text{cap}} + \frac{1}{r_{\text{CA}}}(V_{\text{AC}} - V_{\text{CA}}) \quad (12)$$

Where $r_{\text{CA}} = \frac{V_C}{V_A}$ is the volume fraction of capillary volume and astrocyte volume. Eqs. (4), (8), (9) and (12) build our system of ODEs. Fig.1 shows the corresponding lactate exchange rates (V_{ij}) and net production (J_x) in each interface.

2.3. Parameter estimation

Parameter values in a computational model are very often difficult to determine as they are rarely directly measured in experimental studies. In our model we have two types of parameters. First are the ones that we chose following an extensive experimental literature review on Michaelis-Menten parameters of MCT1, MCT2, and MCT4 transporters as reported in Table 1. We then converted all the values to the same dimension (mM and mM/min) as explained in the legend of Table 1. From these conversions we derived physiological ranges for maximum rates and affinities, except for V_{AE}^m as explained in the *Results* section.

On the other hand, second type of parameters include the ones that their ranges were not clearly defined (no available data), in particular for parameters inside neuronal and astrocytic compartments (LDH reaction fluxes). To tackle this issue, we solved a steady state optimization problem in resting-state aiming at determining distribution of unknown parameters for the LDH equations. In this study, resting state refers to a situation in which the brain functions normally and concentration of lactate in each compartment is at equilibrium.

Because Eqs. (4), (8), (9), and (12) form a non-linear system of ODEs with a number of parameters greater than the number of equations, there is no single solution to this problem. Therefore, multiple parameter sets can result in a steady state. By running the optimization algorithm a sufficient number of times (1500), we were able to define multiple parameter sets that satisfy the condition of the steady state, enabling us to examine the system's average behavior using all possible parameter sets and prevent the optimization solutions from being trapped in local minima.

As a result, we will have a subset of optimized parameters ($\Theta_s \in \Theta$) that satisfy all the conditions and could be a candidate for the system. The whole procedure is summarized in Fig. S1 in the supplementary materials. Finally, the whole model with fixed and optimized parameters is simulated and analyzed in MATLAB (The MathWorks, Natick MA, USA). during steady-state and activation. We used the MATLAB built-in function *ode15s*, to numerically solve ODEs.

Table 1- Parameter values and intervals

| | Parameter | Value | Unit | Optimized/ fixed | Description |
|-----------------------|---|-----------------------------------|--|---------------------|---|
| MCT Parameters | (V_{EN}^m, K_{EN}^m) | $(1, 2.2)^1$ | (mM/min, mM) | Fixed | Maximum rate and Michaelis constant of lactate transport between neuron and extracellular |
| | $(V_{CA}^m, K_{CA}^m),$ (V_{AC}^m, K_{AC}^m) | $(0.4, 5.1)^2,$ $(0.5, 5.1)_2$ | (mM/min, mM) | Fixed | Maximum rate and Michaelis constant of lactate transport between astrocyte and capillary |
| | K_{AE}^m | 28^3 | mM | Fixed | Michaelis constant of astrocyte and extracellular interface |
| | V_{AE}^m | 0.1 to $8^2,$ $_{3,4}$ | mM/min | Fixed* | Maximum transport rate of astrocyte and extracellular interface |
| LDH Parameter | V_A^{prod} | 1876^{5**} 0.5 to 70 | $\mu\text{mol/min/mg.}$ protein mM/min | Optimized | Maximum lactate production rate in astrocyte |

| | | | | | |
|--|----------------------------|--|--|-----------|---|
| | K_A^{prod} | 0.084 ⁵ | mM | Fixed | Michaelis constant for lactate production in astrocyte |
| | (V_A^{cons}, K_A^{cons}) | (0.08, 1) ⁶ | (mM/min, mM) | Fixed | Maximum rate and Michaelis constant for lactate consumption in astrocytes |
| | (V_N^{prod}, K_N^{prod}) | (56.26, 0.07) ⁷ (1163, 0.029) ^{5**} | (mM/min, mM) (μ mol/min/mg. protein, mM) | Optimized | Maximum rate and Michaelis constant for lactate production in neurons |
| | (V_N^{cons}, K_N^{cons}) | (28.6, 4,9) ⁷ (0.24, 0,3) ⁶ (0.31, 8,5) ⁶ (128, 1,73) ^{5**} (268, 7,77) ^{5**} | (mM/min, mM) (mM/min, mM) (mM/min, mM) (μ mol/mn/mg prot, mM) (μ mol/mn/mg prot, mM) | Optimized | Maximum rate and Michaelis constant for lactate consumption in neurons |

| | | | | | |
|----------------------------|--------------------------|--------------------------------------|-------------------|-------|--|
| Volume Fractions | r_{EN}, r_{EA}, r_{CA} | 0.8, 0.444, 0.022 ⁸ | - | Fixed | Ratio of extracellular space, neuronal, astrocytic and capillary compartments volume |
| Blood | Lac_j | 0.7 ⁹ | mM | Fixed | Artery lactate |
| | V_C | 0.0055 ⁸ | - | Fixed | Capillary volume |
| | CBF_0 | 0.012 ⁸ | min ⁻¹ | Fixed | Cerebral blood flow |
| Lac/Pyr ratio | $\frac{Lac_N}{Pyr_N}$ | 18 ⁸ | - | Fixed | Neuronal lactate/pyruvate ratio |
| | $\frac{Lac_A}{Pyr_A}$ | 100 ⁸ | - | Fixed | Astrocytic lactate/pyruvate ratio |
| Temporal Parameters | t_1, t_{end} | 3, 6 ¹⁰ | min | Fixed | Resting perturbation start and end time |
| | t_d | 0.1 ¹⁰ | min | Fixed | Pyruvate decay time delay |

| | | | | | |
|--|--------------------------|--------------------------|-----|-------|-----------------------------------|
| | τ_1, τ_2, τ_3 | 2, 0.1, 20 ¹¹ | min | Fixed | CBF rise and decay time constants |
| | L | 24 | min | Fixed | Total simulation time |

¹(Kuhr et al., 1988); ²(Boumezbeur et al., 2010); ³(Gandhi et al., 2009); ⁴(Dimmer et al., 2000); ⁵(O'Brien et al., 2007); ⁶(Ramírez et al., 2007); ⁷(Atlante et al., 2007); ⁸(Aubert and Costalat, 2005); ⁹(Rasmussen et al., 2011); ¹⁰(Rangel, 2019); ¹¹(Jolivet et al., 2015)

* In each optimization round V_{AE}^m is fixed.

** Conversion of values taken from the O'Brien et al. (2007) resulted in unacceptable rates. So we mentioned their values in their original unit.

3. Results

3.1. Resting State

To explore contribution of lactate transporters at the interface of astrocytes and extracellular space (MCT4) to the lactate shuttling between neurons and astrocytes, we repeat the optimization procedure explained in the Materials and Methods section for 20 values of V_{AE}^m ranging from 0.1 to 8 mM/min. For each value of V_{AE}^m , we calculated resting state lactate exchange rates as well as LDH activity rates using all realizations of the parameters in the optimization procedure. It was done because of the relay role of astrocytes in our central inquiry to understand the effect of blood lactate on the diminished neuronal lactate. Distribution of resting state rates and their mean are shown in Fig. 2 as a function of V_{AE}^m . It should be noted that in resting state, V_{AE} and V_{EN} have the same sign according to Eq. (9), therefore only V_{EN} is shown.

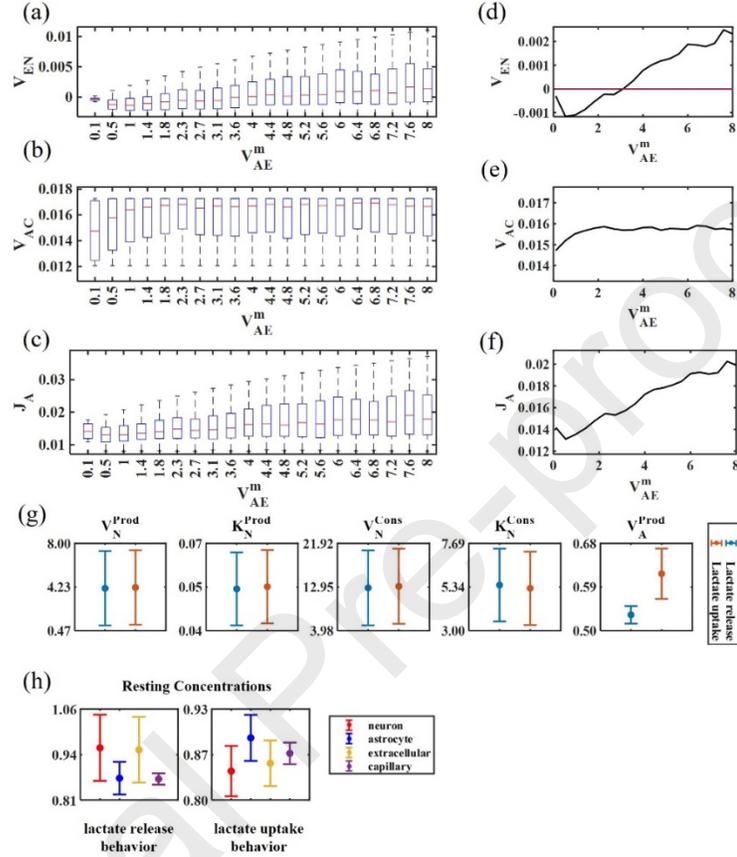


Figure 2-Resting state results. (a-c) Distribution of resting state rates is shown for each value of V_{AE}^m ranging from 0.1 to 8 mM/min. Red line marks the median of distributions and each box includes 25th and 75th percentiles of the distribution. (d-f) Mean value of the rates are shown as a function of V_{AE}^m . Red line marks the border between release and uptake behaviors. (g) distribution of optimized parameters separated based on the sign of V_{EN} showing release or uptake of lactate by the neurons in resting. (h) Optimized resting state concentrations for all the compartments framing both behavior regimes.

3.1.1. Behavior switch between ANLS and NALS.

From Fig. 2(a)-(c), it can be seen that by increasing the maximum transport rate between astrocyte and extracellular compartments (V_{AE}^m), instead of lactate release by the neurons to

the extracellular space and uptake by the astrocytes ($V_{EN} < 0, V_{AE} < 0$), neurons tend to capture lactate ($V_{EN} > 0, V_{AE} > 0$). In fact, parameter values are important to determine the emergent behaviour of the model and switches from NALS to ANLS depending on those. This behavioral switch happens around $V_{AE}^m = 3.5$ mM/min based on the fixed parameters value described in Table 1. This tendency to have lactate uptake by the neurons, is clearer in Fig. 2(d)-(f). However, according to Fig. 3(a), even though in resting state by increasing V_{AE}^m , the average behavior of the model will converge to lactate shuttling toward neurons, the variance of the lactate exchange rates will also allow the model to operate in different behavioral regimes at equilibrium for the same value of V_{AE}^m , depending on other optimized parameters.

To delineate what parameters are more effective in determining the V_{EN} 's sign, we combined all the optimized parameters for all the values of V_{AE}^m (denoted by Θ_s in Materials and Methods section) and classified them into two groups. First, the group generating lactate uptake by the neurons ($V_{EN} > 0$) and second, the parameter group reproducing lactate release by the neurons ($V_{EN} < 0$). This is equivalent to the neurons switching from net lactate producers to net lactate consumers. As shown in Fig. 2(g), we see that compared to other parameters, it is V_A^{Prod} that differs the most between uptake and release regime in steady state. This parameter determines maximum lactate production rate inside astrocytes.

Additionally, as shown in Fig. 2(b) and 2(e), V_{AC} is positive meaning that lactate is released to the capillary during resting state. Except for the low values of V_{AE}^m , release to the capillary remains constant when varying V_{AE}^m .

Fig. 2(h) shows that the optimized resting concentration of lactate in neurons is significantly higher than in astrocytes when neurons release lactate and lower in the uptake regime of behavior. Also, astrocyte lactate concentration is higher compared to the extracellular space and neuronal compartments concentration when lactate is transported to the neurons.

3.2. *Perturbation of resting state*

In this section, we evaluate the model's response as a result of perturbation in neuronal lactate production and artery lactate. Here, we reduce the pyruvate concentration of neurons by 20% for a 3-minute interval to impose a temporary reduction in the lactate production.

This pyruvate reduction indirectly signals the model about higher energy demand during activation, which can result in glucose reduction and consequently pyruvate decrease. We keep astrocytic pyruvate constant based on studies showing constant or slightly decreased Pyr_A (Machler et al., 2016). At the same time, with the elevated CBF, we increase the artery lactate, which resembles transport of lactate to the brain due to physical exercise. This elevated arterial lactate will contribute to brain tissue lactate through at the capillary compartment level. Then, after setting up these inputs in the model, we can investigate the possibility of the transported arterial lactate being shuttled to the neurons under physiological circumstances. One example of such simulations is shown in Fig. 3. Simulation results of another parameters set that qualitatively match the experimental recordings of extracellular lactate (Lac_E) by Hu and Wilson (1997), is shown in Fig. S2.

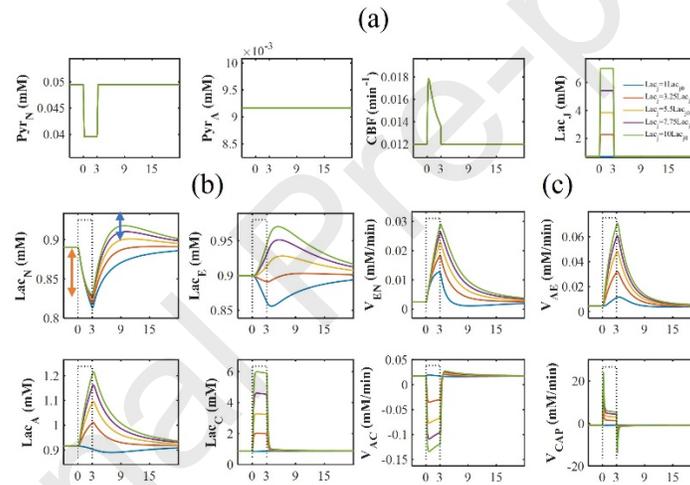


Figure 3- Temporal simulation example. (a) Inputs used to stimulate the model in temporal simulation. (b) Concentration of lactate in all compartments and (c) transport rates of lactate between compartments are shown for different values of artery lactate (Lac_j). Orange arrow on Lac_N shows the undershoot as a result of drop in Pyr_N and blue arrow indicates an overshoot.

3.2.1. Blood lactate contribution to the lactate drop in neurons

According to Fig. 3(b), an undershoot is predicted due to the decreased lactate production and an overshoot because of the elevated arterial lactate. It can be observed that these undershoot and overshoot are affected by the level of Lac_j . Also, as mentioned in previous sections, we obtained multiple parameters sets. Therefore, we explore changes in the

overshoot and undershoot when artery lactate is at baseline and when it is elevated to 10 times its baseline. In this case, we sampled 500 sets of parameters and simulated the model using the inputs similar to Fig. 3(a). We group these parameters into uptake and release resting based on the V_{EN} 's sign in resting. Therefore, it enables us to investigate the effect of resting state behavior on the response to a perturbation.

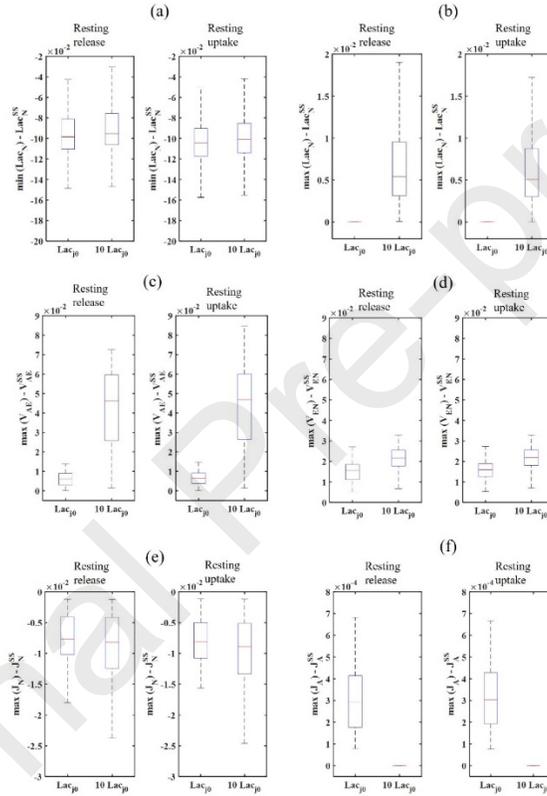


Figure 4-lactate dynamics distribution in elevated lactate scenario. Distribution of (a-b) changes in the minimum and maximum of neuronal lactate, (c-d) difference between the maximum of V_{AE} and V_{EN} and their resting state values, and (e-f) changes in the lactate production/consumption in neurons and astrocytes. In each figure, first and second boxplots show the results of simulations when artery lactate is kept at the baseline and when it is elevated until ten times its baseline, respectively. For all the rates and concentrations, we separated results of parameters in uptake and release resting regimes.

Fig. 4 illustrates distribution of V_{EN} , V_{AE} , J_N , J_A and minimum and maximum of Lac_N , for all the sampled parameters divided into two predefined regimes (Resting uptake and release)

to also visualize the effect of resting state. We can see that compared to other states and exchange rates, the neuronal lactate undershoot is not significantly affected by the arterial lactate increase, as shown in Fig. 4(a). In fact, contribution of arterial lactate is more evident in the intraneuronal lactate maximum that occurs with a delay after the perturbation ends.

Fig. 4(c) shows that upon stimulation, V_{AE} jumps to higher values compared to resting meaning that more lactate is released by the astrocytes to the extracellular space upon the introduction of a drop in lactate production in the neurons. As shown in Fig. 4(d), the same happens to V_{EN} except for the fact that when the arterial lactate level is elevated, V_{AE} increases more significantly.

Figs. 4(a)-4(d) could reflect two competing explanations. One asserts that the elevated artery lactate enters the brain but cannot reach the neurons. The other possibility is that the surplus lactate acts as an alternative for the lactate produced in the astrocytes and is transported to the extracellular space and reaches the neurons. Fig. 4(e) and Fig. 4(f) show that the lactate production in astrocytes dramatically decreases in response to the flow of lactate from the capillary compartment.

Additionally, in all the dynamics shown in Fig. 4, the baseline direction is not effective in changing the direction of lactate transport when resting state is perturbed. Altogether, we see that even though the astrocytes release lactate to extracellular space, neurons do not import this excess amount of lactate. This suggests that the neuronal lactate uptake capacity might be limited.

4. Discussion

While there is an increasing amount of evidence supporting ANLS hypothesis (Powell et al., 2020), there are also experiments suggesting that astrocytes take up the lactate released by the neurons or at least demonstrate that the direction of lactate transport in the brain may be circumstance dependent (Díaz-García et al., 2017). Since the introduction of ANLS hypothesis, computational models have been employed to explore the existence and strength of lactate shuttling between neurons and astrocytes. However, one of the common challenges has been parameter estimation and its effect on physiological conclusions. This issue has specifically been mentioned in the context of mathematical models for lactate dynamics (Pellerin and Magistretti, 2012). For example, Jolivet et al. (2010) suggested that the differences between the results obtained by Simpson et al. (2007) and Aubert et al. (2005) were due to variations in glucose uptake ratios in the models. Furthermore, Somersalo et al.

(2012) studied a metabolic model of the brain and demonstrated that glucose compartmentalization is a crucial factor in determining lactate uptake direction in the models. In this paper, we put forward a mathematical model for the exchange of lactate in the brain and examined how its predictions are affected in the physiological range of parameter values. To prevent our conclusions from being reliant on a single set of parameters, we analyzed multiple parameter realizations that were obtained through optimization and analyzed distribution of possible behaviors. We specifically investigated the existence of ANLS in the proposed model in the resting state and during perturbation of lactate production.

In general, modeling results support a situation-dependent existence of lactate shuttling from astrocytes to neurons (Genc et al., 2011; Neves et al., 2012; Patsatzis et al., 2019), higher lactate production in the astrocytes (Hyder et al., 2006; O'Brien et al., 2007; Sotelo-Hitschfeld et al., 2015) and lactate release by the astrocytes upon activation (Pellerin et al., 1998; Morland et al., 2015). When increasing capacity of lactate release by the astrocytes, distribution of resting state parameters, on average, converge to lactate shuttling at equilibrium. However, the analysis shown in Fig. 2 emphasizes the fact that both export capacity and production rate of lactate inside astrocytes influence the expression of the ANLS during resting conditions. Furthermore, when the system transitions to the ANLS behavior at rest, the baseline concentration of lactate within astrocytes is significantly higher than that of neurons. This difference in the resting lactate concentration between neurons and astrocytes is supported by experimental findings, such as those by Machler et al. (2016) and has been cited as evidence for the ANLS.

On the other hand, from Fig. 4, the model does not support strong reliance of the neurons on the lactate provided by the astrocytes during an artificial lactate drop in the neuronal compartment. Our results propose that in the event of interrupted lactate production, even though increased artery lactate causes astrocytes to switch from lactate exporter under resting conditions to importer from the capillary compartment and lactate to be shuttled to the neurons, this cannot compensate the observed undershoot in the Lac_N . The possibility of lactate uptake by the brain has been shown using arterio-venous measurements post-exercise and using fluorescent sensors during lactate injection (Rasmussen et al., 2011; Machler et al., 2016). These studies suggest that brain lactate levels increase post-exercise, and the latter suggest that lactate injection in animals could increase lactate levels inside neurons and astrocytes. We also showed that peripheral lactate provided by systemic arteries causes reduced lactate production inside the astrocytic compartment. The explanation discussed here is summarized in Fig. 5.

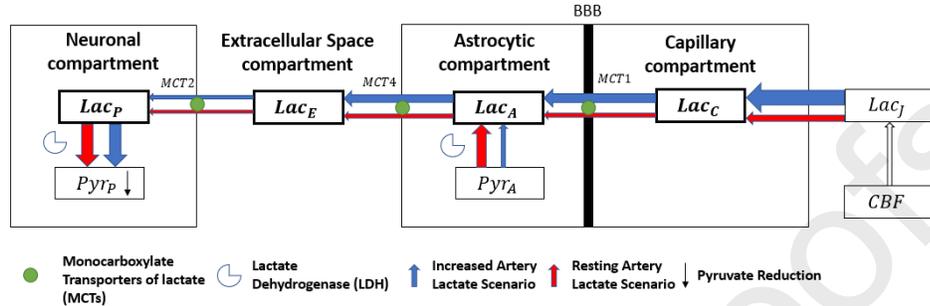


Figure 5-Model of lactate distribution. This represents that according to the model, excessive transported lactate from the blood will be uptaken by the brain tissue and will be transported to the neurons but due to the transporter properties in neurons, it does not significantly affect the drop in lactate levels. This figure shows that the pool of lactate narrows than as it reaches neuronal compartment.

The ability of neurons to be net lactate producers rather than net consumers is shown in the results from experimental studies such as one by Baeza-Lehnert et al. (2019) where they illustrated that by blocking MCTs in a culture of neurons, lactate concentration declined in 60% of them while it continued to increase or remained constant in other cells. This might imply different transporter properties in neurons underlying behavior switch.

As expected, an increase in V_{AE}^m generally results in a greater efflux of lactate from astrocytes but when sufficient intracellular lactate is produced. In addition, according to Figs. 3 and S2, the model's dynamics are qualitatively in agreement with the experimental recordings in terms of initial dip due to the neuronal energy demand and recovery time after the onset of the perturbation (Hu and Wilson, 1997).

In this study, we perturbed lactate production indirectly by manipulating pyruvate concentration and this might alter our conclusions. Therefore, as an extension to this model it would be useful to also include glucose metabolism to compare a possible switch between these two metabolites as energy substrates. Extending this model will enable us to answer more questions regarding glycolysis and oxidative metabolism. Moreover, we investigated the possibility of blood lactate contributing to neuronal energy demand. We showed that despite the uptake by astrocytes, blood lactate cannot strongly contribute to lactate concentration in the neuronal compartment in the model. Our conclusions are limited to the chosen mesoscopic scale model and making the model more detailed or coarse might affect

the conclusions. In our model, CBF and arterial lactate follow fixed dynamic functions. However, these dynamics could be captured by another system of differential equations. Future research is needed to shed light on the direct impact of physical exercise lactate on neuronal energy generation. This might emerge as an energy substrate or, as proposed in recent years, a signaling molecule activating certain receptors (Sotelo-Hitschfeld et al., 2015; Magistretti and Allaman, 2018; Xue et al., 2022).

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Competing interests

The authors declare no competing interests.

Supplementary information

A supplementary document is available.

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Highlights

- Blood lactate does not strongly contribute to the initial dip in neuronal lactate
- Astrocyte-neuron lactate shuttle conditionally provides lactate to the neurons
- Existence and strength of lactate shuttle depends on transporter properties
- Lactate shuttling also depends on the astrocytic lactate production

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