



A physiologically-based computational model to study brain lactate exchanges

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INTRODUCTION

Background

- Lactate had long been considered as a waste product but this view has been changed over the last decades. For instance there are evidences that show its effect on memory [1] and even proved to be neuroprotective in pathologies such as epilepsy while inhibited [2] and traumatic brain energy when administered [3].
- Role of lactate as an alternative energy substrate in some conditions has also been proposed [4].
- Considering the fact that during exercise lactate concentration increases in the artery, there might be a link between exercise benefits and lactate.
- Current debates about lactate include: role of astrocytes as lactate provider for neurons, lactate as the end product of glycolysis, and lactate as a signaling molecule.
- Lack of direct access to the interactions inside brain, has motivated researchers to propose mathematical models for lactate kinetics.

Objective

- Our aim is to understand underlying mechanisms of local lactate metabolism by means of a new mathematical model, in particular in terms of the different sources of lactate production/consumption and exchanges between the different cells types at this local level.
- The model's description and equations are based on an extensive literature on lactate transport and exchanges.
- A parameter estimation was done by using imperialist competitive algorithm which is described in more details in another poster presented at OHBM 2020.

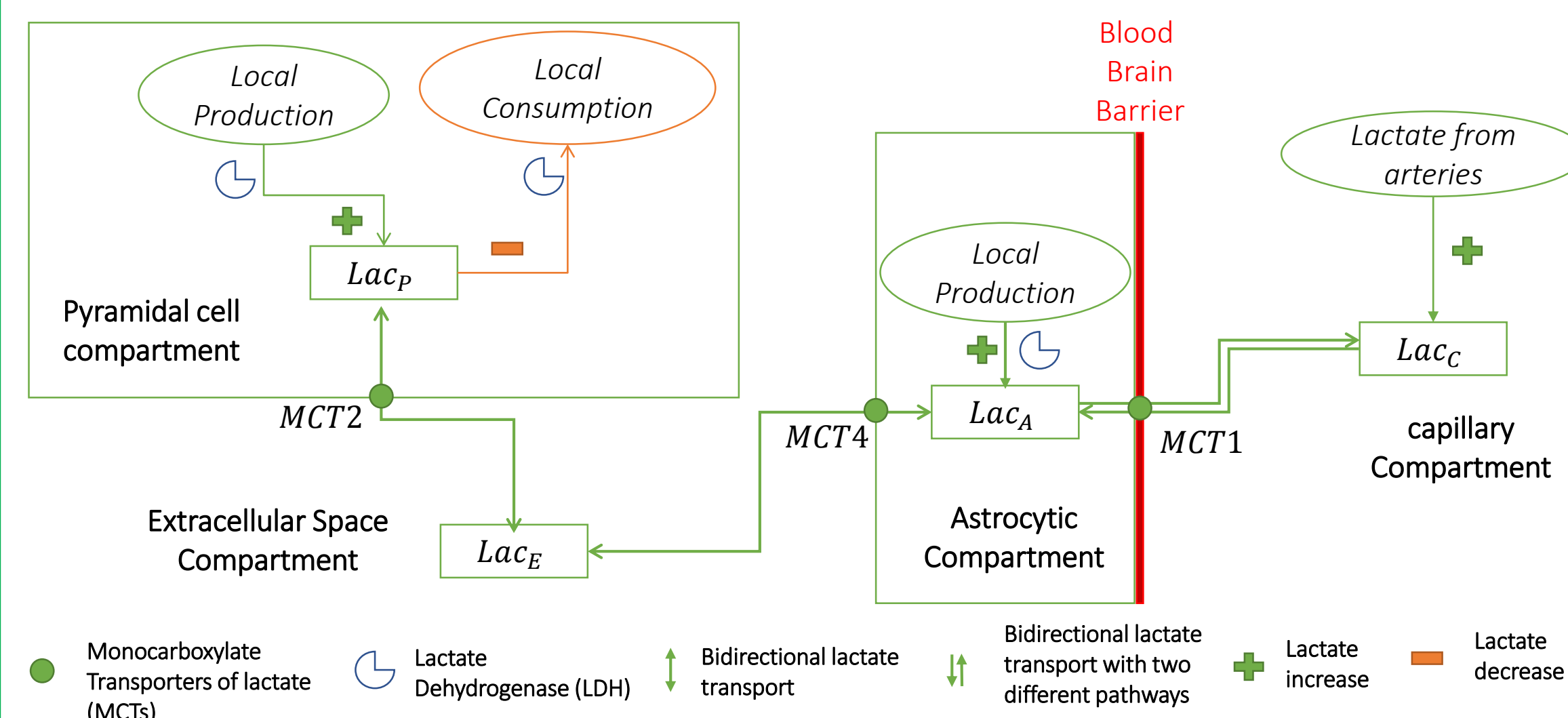
METHOD

General description of the model

- We propose a model with two main sources of lactate: (1) local production inside pyramidal cell and astrocytic compartment, and (2) lactate coming from arteries, both consumed by the pyramidal cell.
- Astrocytic compartment works like a gate for exchanging lactate with the capillary and this lactate uptake from the capillary increases during exercise or due to injection.
- MCTs carry lactate across the cell membrane and can be found in different isoforms including MCT1, MCT2 and MCT4.

More details about the interactions

- Exchange of lactate between compartments (V_{xy})**
 - Lactate exchanges between pyramidal cells, extracellular space and astrocytes are modeled as reversible bidirectional transports based on the existing literature [5].



- Lactate transport between capillaries and astrocytes are assumed to be reversible but in two different directions. According to this assumption, we modeled this using two Michaelis-Menten equations.
- Parameters are determined using experiments from literature.

LDH activity (V_{prod}^x, V_{cons}^x)

- Pyruvate is formed from glucose in the process of glycolysis and then it is converted to lactate and vice versa [4].
- LDH is an enzyme that contributes to the reaction of lactate/pyruvate production (we refer to the latter as lactate consumption):
 $(Lactate + NAD^+ \xrightarrow{\text{Lactate Dehydrogenase (LDH)}} Pyruvate + NADH + H^+)$
- Value of pyruvate concentration is fixed from the literature in order to calculate LDH activity
- Due to sparse values in the literature, we optimized the model to find LDH equation's parameters for both compartments

Balloon model

- A model for effect of artery lactate on capillaries [6]

Figure 1. Model Representation. Lac_x ($x = P$: pyramidal cell, E : extracellular space, A : astrocyte, C : Capillary) denotes the lactate concentration in each compartment expressed in mmol per unit volume (mM).

RESULTS

ODE system

$$\begin{cases} \frac{dLac_P}{dt} = V_{prod}^P - V_{cons}^P + V_{EP} \\ \frac{dLac_E}{dt} = -\frac{V_{EP}}{r_{EP}} + \frac{V_{AE}}{r_{AE}} \\ \frac{dLac_A}{dt} = V_{prod}^A - V_{AE} - V_{AC} \\ \frac{dLac_C}{dt} = V_{cap} + \frac{V_{AC}}{r_{CA}} \end{cases}$$

Transport equations

$$V_{xy} = \frac{V_m^{xy}(Lac_x - Lac_y)}{K_m^{xy} + Lac_x + Lac_y}, \quad x, y = P, E, A$$

$$V_{AC} = \frac{V_m^{AC} Lac_A}{K_m^{AC} + Lac_A} - \frac{V_m^{CA} Lac_C}{K_m^{CA} + Lac_C}$$

- Negative sign in these equations corresponds to the transport of lactate is from y to x .

LDH rate

$$V_{prod}^x = \frac{V_m^{+x} Pyr_x}{K_m^{+x} + Pyr_x}, \quad x = A, P$$

$$V_{cons}^x = \frac{V_m^{-x} Lac_x}{K_m^{-x} + Lac_x}, \quad x = P$$

- Lactate consumption inside astrocytes is negligible compare to the production [7]

Balloon model

$$V_{cap} = \frac{2CBF(t)(Lac_{artery} - Lac_C)}{v_C}$$

$$CBF = \text{Cerebral Blood Flow}$$

Volume fractions

$$r_{EP} = \frac{v_E}{v_P}$$

$$r_{AE} = \frac{v_A}{v_E}$$

$$r_{CA} = \frac{v_C}{v_A}$$

Analysis

- Running optimization for 1000 times, we obtained 1000 possible sets of parameters each results in a series of fixed points (More details about optimization procedure can be found in poster#1058)

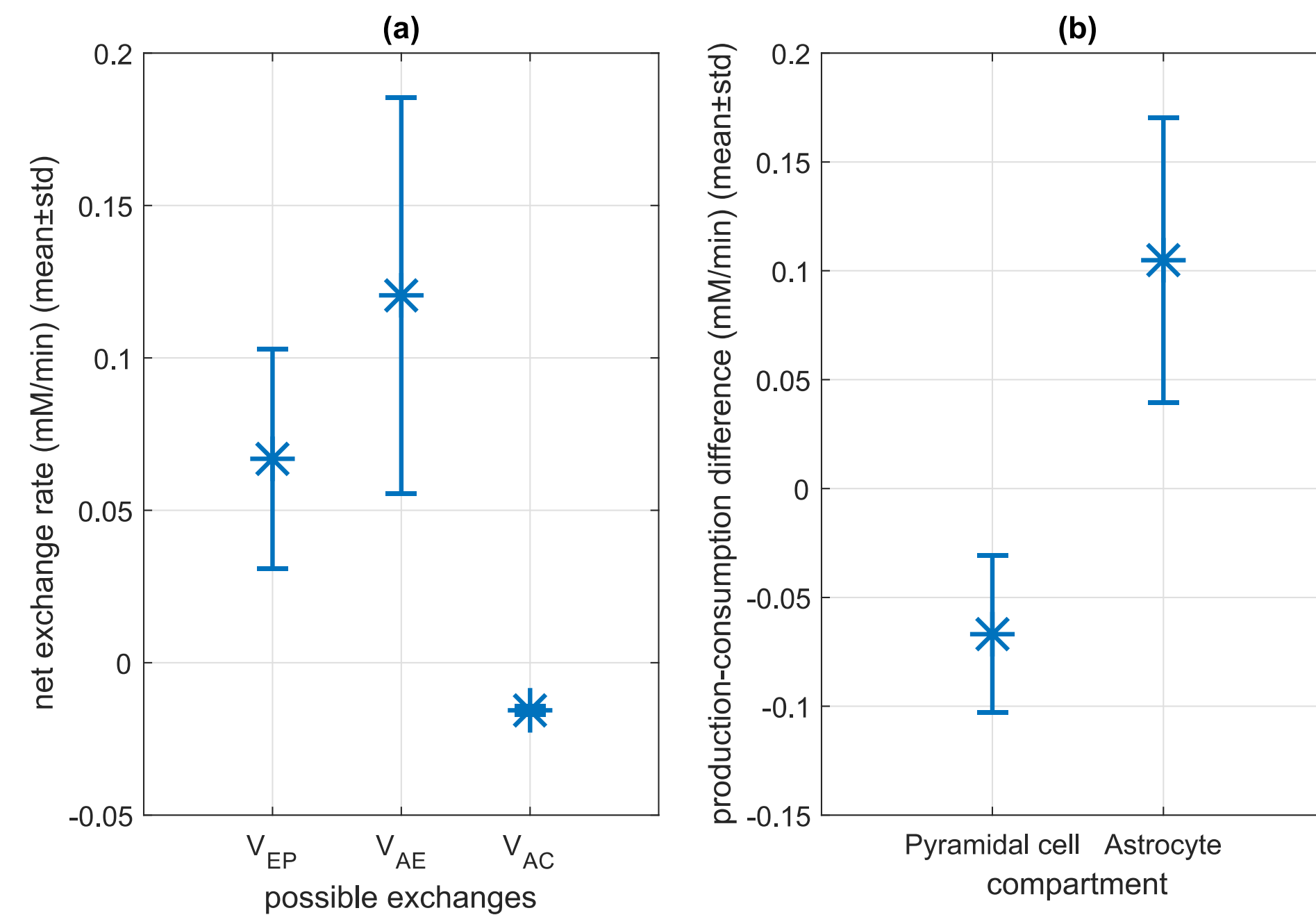


Figure 2. Rates of lactate exchange and LDH activity.

(a) This figure shows the sign and value of exchange rates and LDH activity. According to these values and their standard deviation, lactate is uptaken by astrocytes from capillaries ($V_{AC} < 0$) and is delivered to the neurons through the extracellular space ($V_{AE} > 0, V_{EP} > 0$). (b) This figure illustrates the difference between lactate production and consumption in pyramidal cell (left) and Lactate production in the astrocyte compartment (right). The negative sign for the pyramidal cell, denotes that lactate is more consumed by this compartment.

Table 1. Summary of resting lactate concentrations

State	Resting value (mM)	
	simulation	experiments
Lac_P	0.901	0.901
Lac_E	0.934	N/A
Lac_A	0.992	0.931
Lac_C	0.721	N/A

Parameter selection

- Parameters are chosen based on:
 - How much their resulted fixed points are close to the resting state concentrations in [8].
 - Local stability of the fixed points based on the Jacobian matrix of the linearized functions.
 - The parameters should also reproduce reasonable results in terms of temporal dynamics.

DISCUSSION

- From physiological point of view, our results show that in the range of optimized parameters behavior of the system is the same.
- Results indicate that in the resting state, lactate is not only provided by the astrocyte production but also through uptake from the capillaries.
- We showed that in the physiological range of parameters, pyramidal cells are lactate consumers which is in accordance with the experimental results in [7]
- Astrocyte neuron lactate shuttle (ANLS), first proposed by Pellerin et al. (1998) and is still debated among researchers, indicates that there is this so called shuttle between astrocytes and neurons that provide lactate for the neurons. Our results suggest that, at least in resting state, ANLS using a wide range of physiological parameters. Further investigation is needed to determine its existence during activation.

CONCLUSION

- In this work a new computational model to study lactate kinetics was proposed.
- Resting state concentrations, transport rates and LHD rates are physiologically coherent with the information derived from the experiments exist in the literature.
- Future work will include analysis of the temporal dynamics of the model and then it enables us to use it in a general neuro-glia-vascular model and study effect of lactate accumulation or depletion on the brain activity.