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# Optimization study of a new computational model for brain lactate exchanges at rest

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## INTRODUCTION

- **Background:** Our aim is to understand underlying mechanisms of local lactate metabolism by means of a new mathematical model (introduced in poster#2318 for OHBM 2020), in particular in terms of the different sources of lactate production/consumption and exchanges between the different cells types at a local level. Model parameter estimation is an important step in defining a model's capacity in terms of reproducing physiologically reasonable behavior. The proposed models is non-linear and non-convex, making most optimization techniques return local minima while we are interested in the global minima.
- **Motivation:** We are interested in finding some parameters for the proposed computational model for lactate exchanges by optimizing the equations with respect to resting state data. In particular, the parameters related to the LDH-catalyzed reactions are hard to determine experimentally and there is no consensus on their values in the literature.
- **Objective:** To compare three global optimization techniques including Multi Start (MS), Global Search (GS) and imperialist competitive algorithm (ICA) in order to find parameter values that better reproduce resting lactate concentrations reported in [1] and reasonable physiological behavior.
- **Problem formulation**

$$\begin{cases} 0 = \frac{dx_1}{dt} = f_1(x_1, x_2, V_m^{+P}, K_m^{+P}, V_m^{-P}, K_m^{-P}) \\ 0 = \frac{dx_2}{dt} = f_2(x_1, x_2, x_3) \\ 0 = \frac{dx_3}{dt} = f_3(x_2, x_3, x_4, V_m^{+A}) \\ 0 = \frac{dx_4}{dt} = f_4(x_3, x_4) \end{cases}$$

• Optimization of  $f_{objective} = \sum_{i=1}^4 f_i^2$ ,

$$s. t \begin{cases} V_{upper} < V < V_{lower} \\ V_{upper} < K < K_{lower} \\ V_m^{+A} > V_m^{+P} \end{cases}$$

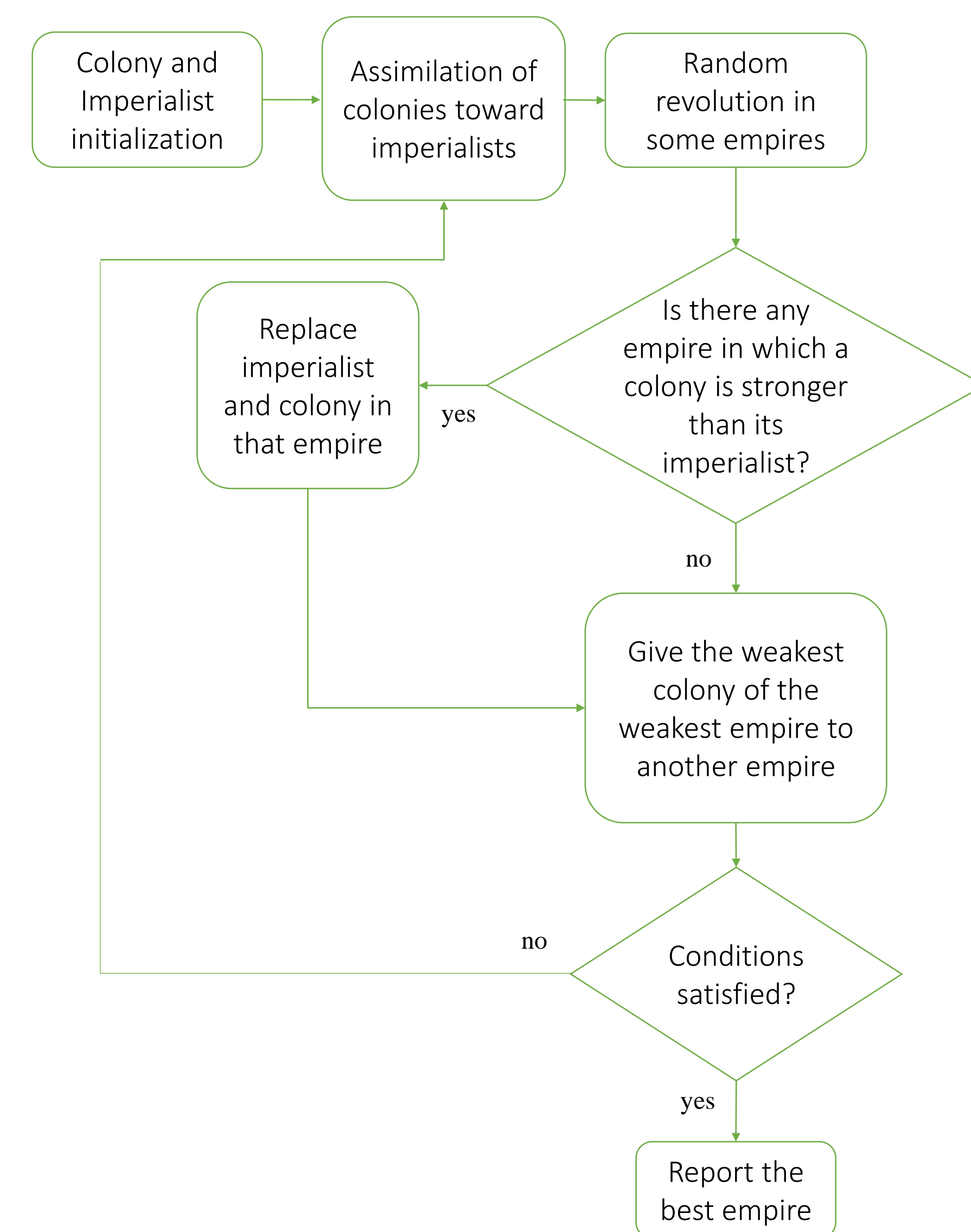
- Where  $\mathbf{K}, \mathbf{V}$  are vectors containing maximum rates and Michaelis constants,
- Lower and upper bound values are derived from our extensive literature review.

## METHOD

- We applied several local and global optimization techniques like particle swarm, genetic algorithm, etc. but MS, GS, ICA returned best results. Now we want to compare these three algorithms together.
- MS, GS search as much as possible the whole space defined by the constraints to find global minima.
- We used implementation of MS and GS in Global Optimization Toolbox in Matlab.
- ICA implementation is quite different from MS, GS and is available online [2].
- **Multi Start (MS):**
  - Chooses random multiple start points.
  - Runs local optimum solver on the start points and outputs a vector of converged solutions.
  - We set the number of points to start from as 50.
- **Global Search (GS)**
  - It runs the local solver on the start point provided by the user and based on its convergence generate a group of start points.
  - It then picks the best start points from this generated set of points and runs the local solver on them.
  - It creates a vector of solutions that satisfy the specified conditions.
- **Imperialist Competitive Algorithm (ICA)**
  - A heuristic algorithm like genetic algorithm based on the socio-political metaphor of Imperialistic competition [3].
  - Each colony is a set of variables resulting in the larger cost compared to its imperialist.
  - In the process of assimilation, colonies move toward their imperialists i.e. changing variables in order to

- find global minima in between.
- After finishing each iteration, imperialists take the best solutions ever find.
- We choose maximum number of iterations as termination condition.

### ICA flowchart:



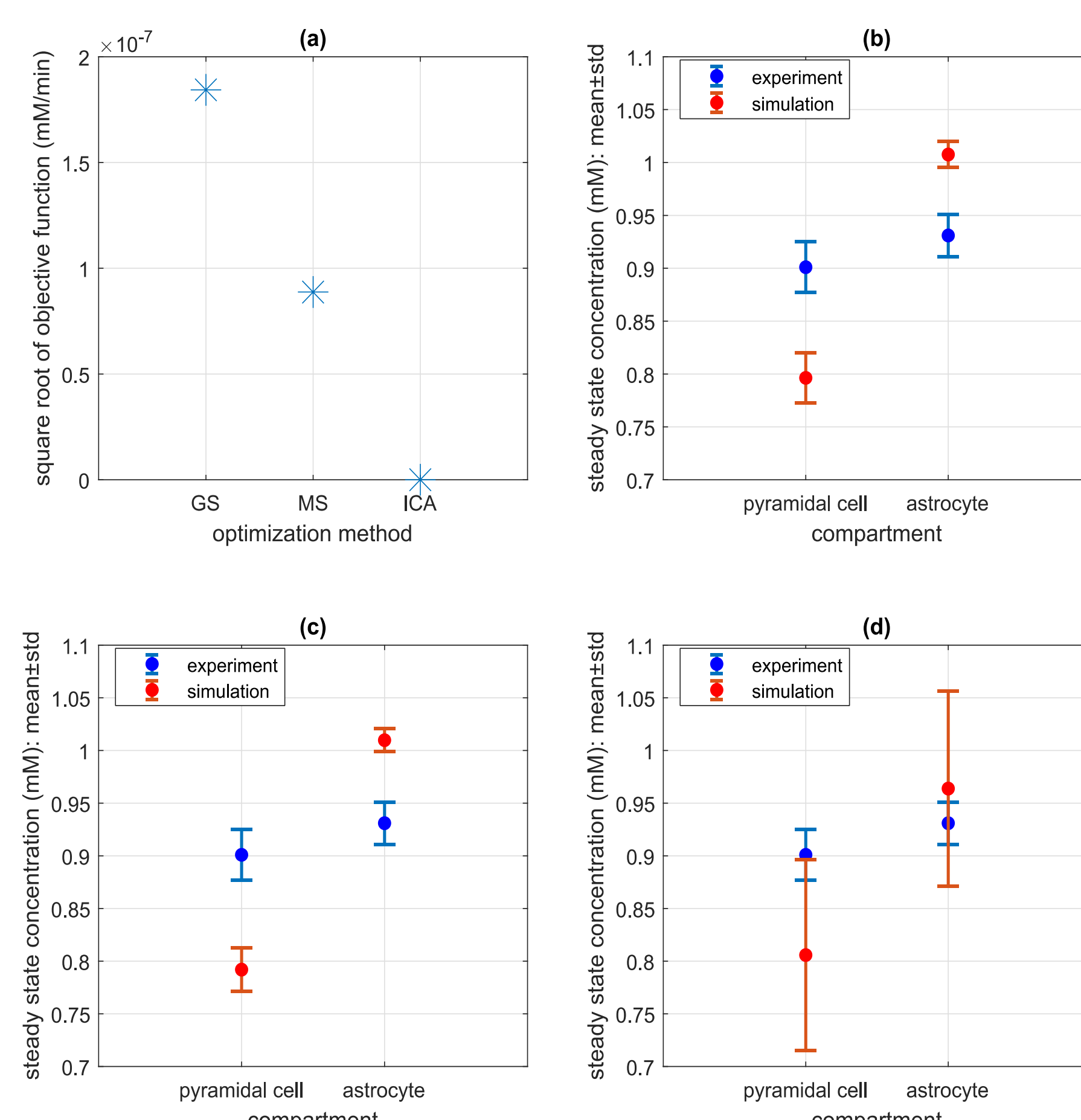
## RESULTS

- To prevent algorithms from trapping in a local minimum, we pick start points randomly and also run the whole optimization for 1000 times.
- Each algorithm returns 1000 possible solutions for this non-linear optimization problem, which means that we have to choose the best algorithm and the best set of parameters it returns.

Parameter Method	$V_m^{+P}$	$K_m^{+P}$	$V_m^{-P}$	$K_m^{-P}$	$V_m^{+A}$
MS	15.32± 0.21	0.67± 0.00	7.00± 1.46	4.50± 0.67	32.24± 4.94
GS	14.72± 0.12	0.64± 0.00	6.85± 1.55	4.40± 0.46	31.19± 5.70
ICA	8.49± 2.69	16.84± 1.75	4.09± 3.78	5.50± 1.84	23.32± 12.13

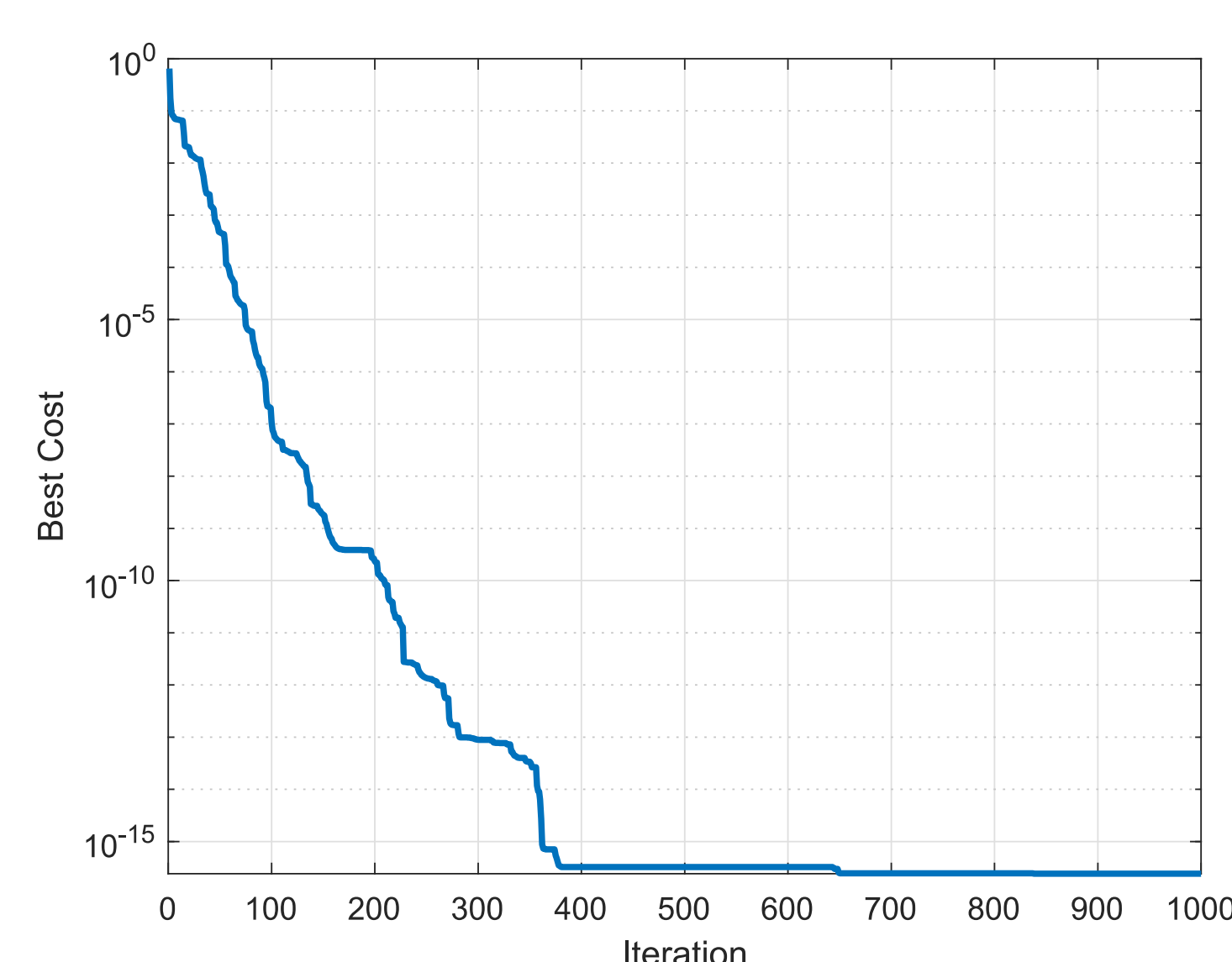
**Table 1. Mean value of optimized parameters.**

This table includes values of optimized parameters (mean±std) for all three methods. According to the standard deviation of the parameters found by ICA it covers a wide range of values for each parameter.  $V_m^{\pm P}, V_m^{+A}$  are expressed in  $mM/min$  and  $K_m^{\pm P}$  is in  $mM$ .



**Figure 1. Comparison of optimization methods.** (a) For each method, shows the square root of the objective function (mean). (b) It visualizes how obtained resting state values using GS are distributed compared to the measurements, plotted in blue, by Mächler et al. (2016). (c) It illustrates the results for MS. (d) Finally, it depicts the distribution of concentrations acquired using ICA.

- We test following criteria to choose between algorithms:
  - Value of the objective function
  - Distributions of resulted resting states compared the experimental data by Mächler et al. (2016).
- According to the results, ICA shows a better performance



**Figure 2. Convergence plot for ICA.**

This figure shows how the square root of cost function decrease and approaches its minimum in each iteration of ICA.

- It is observable that ICA can converge to the values not significantly different from measurements. Meaning that we can have parameters set that can reproduce close values to the experiments.
- More details about the model's behavior and resting lactate concentrations obtained by using values in table 2 are explained in poster#2318 submitted to OHBM.

$V_m^{+P}$	$K_m^{+P}$	$V_m^{-P}$	$K_m^{-P}$	$V_m^{+A}$
2.77	1.60	1.00	7.61	5.15

**Table 2. Optimized parameter values.**

This table includes the best parameters obtained for the maximum rates and Michaelis constants for the Michaelis-Menten equations of LDH-catalyzed reactions happen in the neurons and astrocytes. These parameters will force the model to stay in resting state with resting lactate concentrations close to the experiments.

## DISCUSSION

- Fig. 1(a) shows that ICA returns the lowest minimum value for the objective function while MS, GS could not pave their way to a comparable minimum. It seems that MS works a little bit better than GS in terms of objective function's value.
- Fig. 1(b)-(c) indicate that the parameters returned by MS, GS cannot converge to the resting state concentrations proposed experimentally.
- According to fig. 1(d), ICA can better approach the desired steady states as the distribution of its solutions cover experimental values.
- So according to these results, ICA outperforms MS, GS in terms of converging toward the global minimum and finding lactate model's missing parameters.
- We were finally able to determine unknown parameter values from the outputs of ICA. Table 2 shows the values.
- Model's general behavior has been shown in poster#2318 to be similar for the wide range of parameters achieved using ICA.

## CONCLUSION

- In this study we compared performance of three optimization techniques in order to find missing parameters for LDH activity equations of a new computational model for brain lactate exchanges which is presented in another poster in OHBM 2020.
- ICA seems to be the best algorithm in terms of reaching global optimum and it enables our model to be physiologically reasonable and coherent.
- Future work will include optimization of model's parameters with respect to dynamical behavior of the system.