MECHANISTIC MODELLING OF ASTROCYTIC METABOLISM IN PHYSIOLOGICAL GEOMETRIES REVEALS SPATIOTEMPORAL EFFECTS POTENTIALLY DRIVING NEURODEGENERATION

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AIM AND SCOPE

Astrocytes, the most abundant cell in the central nervous system, have many tasks one of which is to be a metabolic mediator between neurons and blood vessels. Metabolic dysfunctions have been noticed in the presence of many neurodegenerative diseases. Moreover their morphological changes can give insights about the status of the cell.

Figure 1 The complex morphology of an astrocyte from a human post mortem sample obtained by fluorescent (GFAP) super-resolution light microscopy and reconstructed by the machine learning based tool MicMac [1].

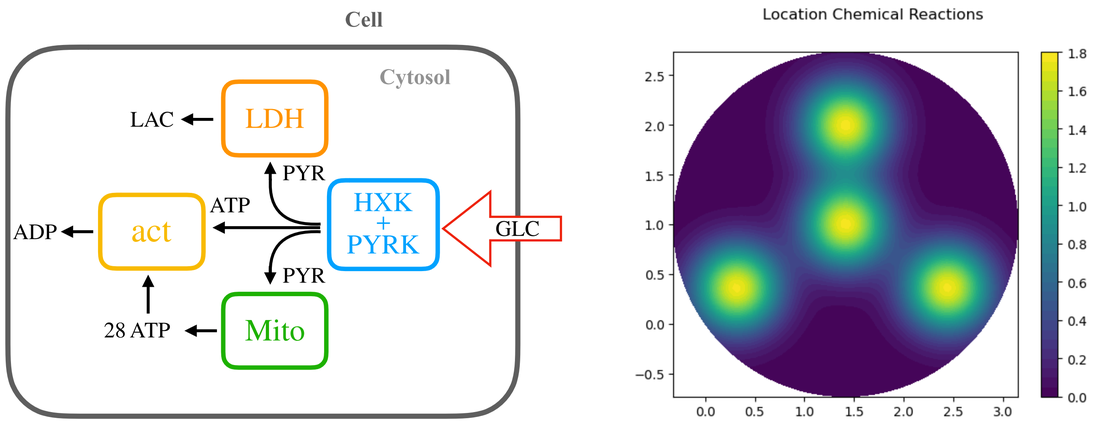
Computational models are complementary to biological investigation: they can simplify the reality giving access to information previously inaccessible. Despite the importance of the cell morphology, few models have tried to incorporate it due to the higher complexity.

The goal of this project is to describe the energy metabolism of an astrocyte through a computational model including the 3D real morphology allowing us to investigate the spatial organization of the cell in healthy and unhealhty conditions.

SIMPLIFIED MODEL

The main pathways we consider in our Simplified Model of Energy Metabolism of a cell are presented by the following five reactions and sketched in **Figure 2B**:

$$\begin{aligned} \mathrm{HXK} &: \mathrm{GLC} + 2\,\mathrm{ATP} \rightarrow 2\,\mathrm{ADP} + 2\,\mathrm{GLY} \\ \mathrm{PYRK} &: \mathrm{GLY} + 2\,\mathrm{ADP} \rightarrow 2\,\mathrm{ATP} + \mathrm{PYR} \\ \mathrm{LDH} &: \mathrm{PYR} \rightarrow \mathrm{LAC} \\ \mathrm{Mito} &: \mathrm{PYR} + 28\,\mathrm{ADP} \rightarrow 28\,\mathrm{ATP} \\ \mathrm{act} &: \mathrm{ATP} \rightarrow \mathrm{ADP} \end{aligned}$$



A **B**

Figure 2 A- GLC enters the cell into the cytosol and takes part in glycolysis composed of the two reactions HXK and PYRK. The products of glycolysis are then consumed in LDH reaction, that generates LAC, in act reaction, that describes the cellular activity, and in mitochondria where the reaction denoted Mito happens. Mito reaction represents the contributions of the Krebs cycle and oxidative phosphorylation [2]. **B-** We use gaussian functions to locate the chemical reactions in our domain.

MATHEMATICAL MODEL

The simplified model is described mathematically using a reaction diffusion system. Generally, in a bounded domain Ω, we want to find $c(x,t) : \Omega \times I \rightarrow \mathbb{R}$ where $I \subset \mathbb{R}$ such that:

$$\frac{\partial c(x,t)}{\partial t} = D\Delta c(x,t) + R(c)$$

where D is the diffusion coefficient and $R(c)$ is a function depending on $c(x,t)$.

METHODOLOGY

- The real morphology of astrocytes is imaged in collaboration with Luxembourg Centre of Systems Biomedicine (LCSB) based on [1] (see **Figure 1**).
- The numerical method chosen to solve the reaction diffusion system is Cut Finite Element Method. The strength of CutFEM is that it allow us to work easily with complex domains disentangling the cell morphology from its discretisation while retaining the accuracy and robustness of a standard finite element method [3].

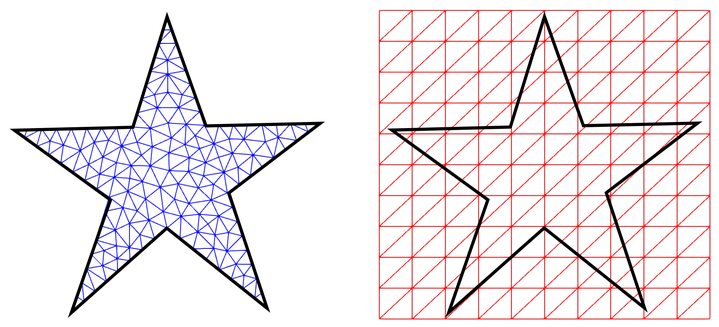


Figure 3 Classic FEM requires to fit the mesh to the boundary of the domain, while CutFEM embeds the domain in a background mesh.

RESULTS

In order to study the spatial organization of the cell, we locate the chemical reactions following **Figure 2B**, permuting the reactions lead to twelve possible locations. Our findings are shown in **Figure 4**.

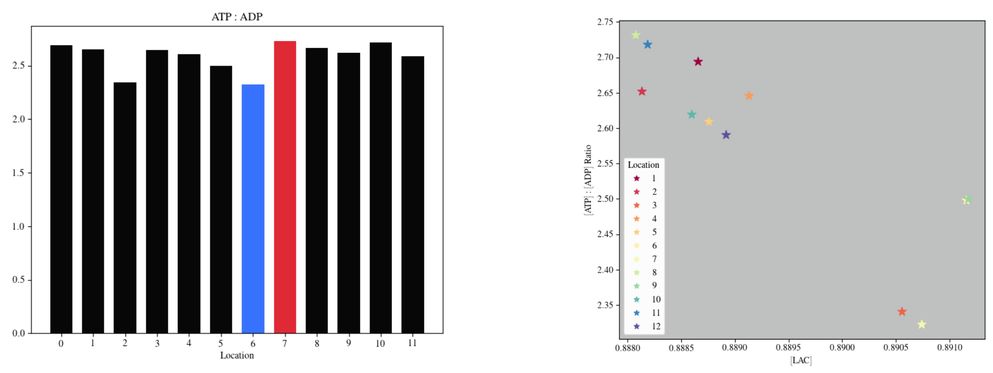


Figure 4 Different locations lead to different values of $\mathrm{ATP} : \mathrm{ADP}$ ratio and LAC.

CONCLUSION

In [2] we propose, test and verify CutFEM to solve our simplified model of metabolic pathways in domains of increasing complexity from two to three dimensions. Our findings highlight CutFEM as a valuable approach to deal with biological problems with arbitrarily complex cell morphologies.

The preliminary results presented in the previous section suggest the central role of the spatial organization inside the cell.

Our next steps will be to use data from healthy and pathological astrocytes to calibrate our 3D simulations. In **Figure 5** we can see some preliminary results.

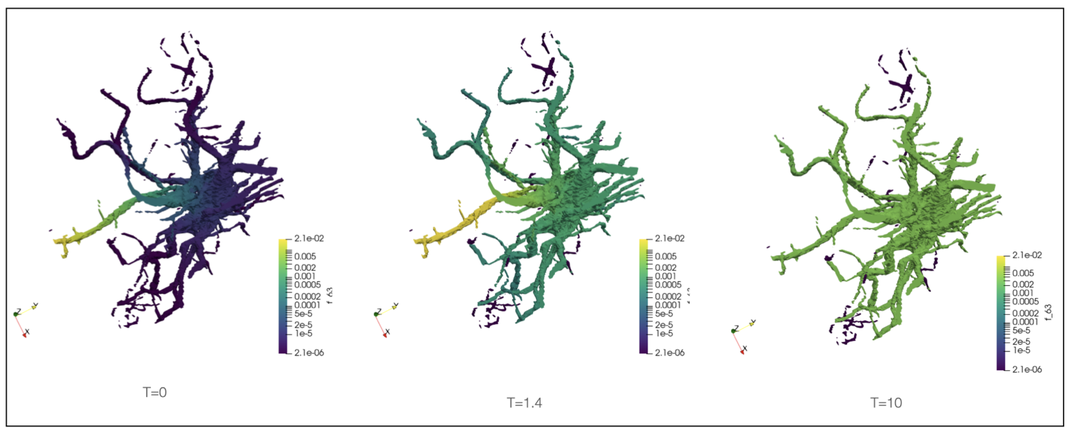


Figure 5 Preliminary results of our energy metabolism model solved using CutFEM. The figure shows GLC diffusing inside a 3D astrocyte shape.

ACKNOWLEDGEMENT

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