Towards a refined bi-compartmental model of brain metabolism using bonded cumomers analysis of ^{13}C MRS spectra

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TARGET AUDIENCE: Those interested in metabolic modeling and ^{13}C MRS spectra analysis using isotopomers.

PURPOSE:

This work aims to develop a bi-compartmental model that best explains isotopomer data on the basis of biologically sound hypotheses.

METHODS:

^{13}C MRS Data: Data used in this work were published in 2003 [1]. Briefly, spectra were collected in the rat brain at 9.4 T using an ISIS-DEPT sequence during a 7-hour infusion of [1,6-$^{13}C_2$]glucose. Spectra were analyzed in terms of the different multiplets reflecting isotopomers (or more precisely, the bonded cumomers [2]) using LCModel, and concentration values were scaled using brain extracts analysed with ultra-high field NMR.

Initial observations: To rapidly generate the differential equations describing the formation of bonded cumomers [2]), an automatic approach was used [3]. Fitting multiplet data with the traditional bi-compartment model [4] yields high discrepancies between the data and fit. The most striking ones are observed for glutamate, singly-labeled in positions 2 and 4 (GLUC2S and GLUC4S) and doubly labeled (GLU2D23 and GLU4D34 for labeled positions 2-3 and 3-4 respectively) for which the rapid rise is followed by a much faster consumption than predicted. This suggests the lack of a buffer step in the model where glutamate would be stored before undergoing a second labeling. The initial fit also shows an inability to explain the linear rise of total glutamate (and glutamine) labeling suggesting higher ^{13}C accumulation than predicted by the model. This additional influx could be explained by additional labeled pyruvate dilution. Three models are compared: Model 1- The classical bi-compartment model introduced in 2001[4], Model 2- Added vesicular neuronal glutamate (in red in Fig.1) and Model 3- Added vesicular glutamate as well as separate pyruvate dilution in glial and neuronal compartments (in blue on Fig.1) whereas Model 1 and 2 only includes a single pyruvate dilution.

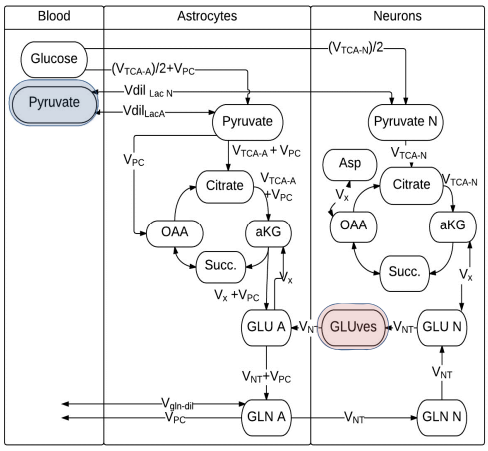

Figure 1: Bi-compartment model (Model 1) with added vesicular glutamate (Model 2) pyruvate dilution (Model 3)

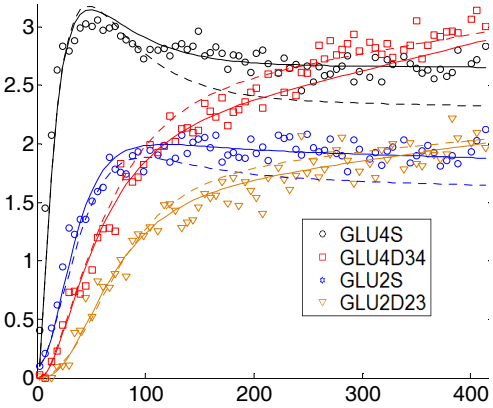

Figure 2: Bonded cumomers fits for Glu4 and Glu2 with Model 1 (dotted line) and Model 2 (solid line) in mM vs time (min)

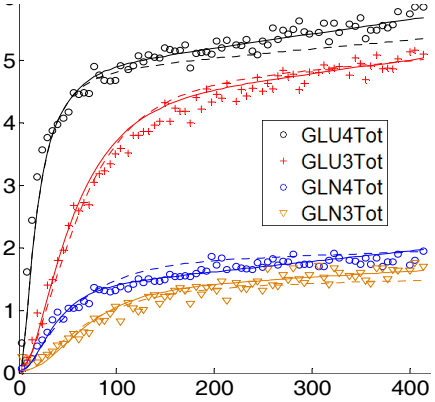

Figure 3: Total Glutamate and Glutamine fits for position 3 and 4 using Model 1 (dotted line) and Model 3 (solid line) in mM vs time (min)

RESULTS AND DISCUSSION:

Vesicular glutamate: Model 2 fitted the data better than Model 1 (this is particularly evident for GLUC2S, GLUC4S, GLUC2D23 and GLUC4D43). Furthermore, the size of the glutamate vesicular pool can be estimated when added as a free parameter and affects the shape of the GLU4S dynamic curve. Using this approach the size of this pool was estimated to 1.5 mM. This implies that the model depends on the correct assumption of each pool size for correct flux estimation.

Labeled pyruvate dilution: An improvement can be observed at later times when comparing the fit of the total signal curves for GLU3, GLU4, GLN3 and GLN4 (total glutamate and glutamine labeled in positions 3 and 4) between fits obtained from model 1 and model 3.

These results reinforce the idea that vesicular glutamate together with pyruvate dilutions are key pools that have to be considered in the modeling of brain metabolism. We observe that the refined model seems to attribute a much higher dilution rate to astrocytes than neurons[5]. This is consistent with the relative position of the compartments inside the brain; astrocytes are wrapped around capillaries while neurons have limited access to capillaries for substrate intake from the blood.

Estimated values for metabolic fluxes were consistent with previously published values, with TCA cycle rates being 5 to 7 times greater in neurons than astrocytes, and pyruvate carboxylase accounting for less than 20% of the total carbon catabolism in the neurons. The glutamine dilution flux added to stabilize the model in conventional bi-compartment model seems to be unnecessary here, with its value close to 0 (Model 3)

Table 1

	V_{TCA-N}	V_{TCA-A}	V_{PC}	V_X	V_{NT}	$V_{gln-dil}$	Vdil $_{Lac\ N}$	Vdil $_{Lac\ A}$
Model 1	0.54±0.01	0.13±0.01	0.02±0.00	4.88±1.43	0.08±0.00	0.03±0.00	0.25±0.01	
Model 3	0.59±0.01	0.11±0.01	0.06±0.00	1.60±0.12	0.17±0.01	0.01±0.00	0.09±0.01	0.80±0.16

CONCLUSION:

Using bonded cumomers analysis on high quality data over 7 hours of acquisition helped refine the bi-compartment model to best explain data variations otherwise invisible to a traditional approach (positional analysis and shorter glucose infusion).The new model includes vesicular glutamate as well as a double pyruvate dilution to explain early and late labelling.

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