Review of: "Reduced Blood to Brain Glucose Transport as The Cause For Hyperglycemia: a Model That Resolves Multiple Anomalies in Type 2 Diabetes"

M. C. Palumbo[1]

1 Italian National Research Council

Potential competing interests: No potential competing interests to declare.

In this research, the authors present an interesting alternative possibility to describe the cause of hyperglycaemia, as strictly linked to neuronal involvement and considering the reduced rate of blood-to-brain transportation of glucose and insulin.

Other works can describe the metabolic changes that happens in the brain, the authors should take them into consideration when revising the literature. The one by Palumbo et at (A computational model of the effects of macronutrients absorption and physical exercise on hormonal regulation and metabolic homeostasis', 2023) describes the metabolic and hormonal changes due to everyday life stimuli such as food intake and exercise at the whole body level and in the organs (brain, liver, skeletal muscle, heart, gut, adipose tissue). Also Kurata elaborated a model comprehending the brain (Kurata, 2021, 'Virtual metabolic human dynamic model for pathological analysis and therapy design for diabetes'). Other two works are related only to exercise, describing the metabolic and hormonal changes due to physical activity at the whole body level and in the organs, as aforementioned (Kim et al, 2007, 'Multiscale computational model of fuel homeostasis during exercise: effects of hormonal control'; Palumbo et al, 2018, 'Personalising physical exercise in a computational model of fuel homeostasis').

In the keywords, the authors should include a term considering the brain.

Please, introduce the acronym CSF (line 199) and BBB (line 270).

Line 203: FG and FI are in italic, I the following line they are not in italic.

Line 265: 'Plasma glucose levels are only a means to'. Perhaps there is an extra 's' after 'mean'.

Line 448: the 4 in K4 should be a subscript.

Line 474. The variable Gt (also in Eq 1) is not listed in Table 1. Please consider it and check all the variables and the parameters. What is the value for Gt used to simulate the food intake? It is interesting to see what happens in case of different doses of Gt.

The authors use both the terms 'steady state' and 'steady-state'. Please, use only one.

Table 1. It is not clear what the 's no' means in the first column, first row. If some values/ranges are taken from the literature, please add the reference.

In some part of the paper the patterns are cited without square brackets, in other parts they are cited with square brackets. Please use only one format.

In the section Results, as well as in the Discussion, the authors should justify their sentences by citing the figures that show the behaviours they are describing. As an example, the first sentence of the Results says "We observe that the steady-state solutions and the autonomic iteration simulations match well in the end results except when the limits of L and K4 are reached". The authors should cite the figures they refer to. This is only an example, the sections Results and Discussion should be entirely revised in this way. Moreover, for the sake of readability, the authors should also cite the equations they refer to, not only the parameters they change.

For what concerns the figures:
1) please cite in the text the equations the figures refer to;
2) always insert the units on the axes;
3) use similar dimensions for the fonts used;
4) the authors must not insert comments regarding the results in the citations (comments should go in the text of the sections Results or Discussion);

Figure 1. A: do not use 'Y' or 'X', but 'Brain glucose level' or 'Plasma glucose level'. B and C are overlapped, it is difficult to understand their meaning.

Line 766. Perhaps the authors intended to say 'By incorporating'.

In the sections Results and Discussion the authors explaining how their model fulfills all the 18 patterns, but the pattern 10 is never cited. Is there a particular reason? How obese or prediabetic subjects are modelled?