

Peer Review

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

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1. Independent researcher

I believe the authors entered in a very important endeavor, and with its correspondent challenges. During my PhD, I have entered similar endeavor, but instead of focusing on the brain, I have focused on other components, which I have called the web of hormones. The excess of focus on insulin for explaining glucose dynamics, according to my research, is due to not taking into account other hormones; whereas for the authors, it is due to lacking to take into account the brain contribution to the equations. I have a guess that we may need both. We need to take into account other players, and also the contribution of neural circuitry, as the authors nicely bring to attention of the scientific community, something to praise.

It became a trend in bioinformatics to use stochastic models. This stochastic approach may backfire, and the authors bring to attention one possible way it may happen. Once we start to accept randomness, we may neglect factors that we could model, such as the contributions of the brain to the dynamics, and also the contributions of other hormones. All this together may be hidden on stochasticity, that we now tend to model proudly; whereas it is a weakness of our models, and the authors nicely bring that to attention.

“the role of the brain in glucose homeostasis was revealed by experiments in which damage to the fourth cerebral ventricle was shown to impair homeostatic control (Bernard, 1859). ”

Concerned if this book should be cited since medicine changes so fast. Maybe in a history of science book, but in a paper about mathematical modeling, not sure it is a good idea to use this book to support a novel model.

“The success of insulin was so spectacular that all other mechanisms of glucose regulation were almost forgotten (Lundqvist et al., 2019). ”

Indeed, totally agree and it is a risky movie from the scientific community.

“fasting insulin and fasting glucose are poorly correlated ”

Very interesting!

“A common set of assumptions is shared by most of the models that fasting glucose is the steady state achieved by a balance between glucose uptake by tissues and glucose production by the liver. ”

I have found out it very interesting that the authors are building the model questioning basic assumptions generally done. It is precisely the way of making medicine and biology more like physics. We cannot leave any stone unturned.

Common assumption: “A common assumption is that insulin resistance reduces glucose uptake ”

“Compatibility with empirical findings cannot be taken as proof or validation of the model, but if a model directly contradicts one or more of the empirical findings, it becomes serious grounds for rejecting the model. ”

Therefore, would not be enough for a model to explain datasets?

“The focus of the field is so much on the peripheral mechanism that the review by Mari et al. (2020) does not even cite the models incorporating the role of the brain. ”

Please define CSS models and TSS models on section 1.2. Peripheral models of glucose homeostasis

“It is quite well known that a number of neuronal mechanisms in the brain are involved in energy homeostasis. Nevertheless, for some reason, they do not occupy a central stage in the mainstream thinking in T2DM and glucose regulation models. ” that is a good question. I have the feeling that it happens because we tend to build models on top of other. Once a set of models gain respect, rarely someone will risk building new models, it is risky. Nice work on questioning this, it is indeed a good question for starting such a model.

“we prefer qualitative predictions over quantitative ones. ” Thus, the authors are centered on qualitative behaviors.

Since it seems the authors is trying to defy current standard model, and I do applaud it, I do support their effort.

I feel this section is very important, and should be explained better. I had to use chatGPT to support me to understand.

“We test whether the model is able to predict the pattern observed empirically under some set of parameters. The ability to predict a given pattern is not proof of the validity of the model, but the inability to predict an observed phenomenon at any set of parameters in a realistic range is a strong reason to call the model either inadequate or wrong. If an additional consideration compatible with the model is able to explain a pattern not explained by the main model, the model can be called inadequate but not falsified. However, if the model outcome directly contradicts a consistent and reproducible empirical finding, it can be considered falsifying evidence. We emphasize the need to evaluate our model in comparison with classical models on these lines. ”

My suggestion is: either explain is better or create supplementary material. See it does not mean the work is bad, just that the authors may have taken as granted that everyone would understand, a common mistake we make when we understand very well something.

As an example how chatGPT can support on that.

Please, explain this sentence: "if the model outcome directly contradicts a consistent and reproducible empirical finding, it can be considered falsifying evidence."

“This sentence is discussing the relationship between a model's predictions or outcomes and empirical evidence in the context of scientific research. Let's break it down:

Model Outcome: Refers to the result or prediction generated by a model. This could be the output of a mathematical or computational model used to simulate or represent a real-world phenomenon.

Consistent and Reproducible Empirical Finding: Refers to a result or observation obtained through direct experimentation or observation in the real world. "Consistent" implies that the finding is in agreement with other similar observations, and "reproducible" means that the experiment or observation can be repeated by other researchers to obtain similar results.

Contradicts: Indicates a conflict or opposition between the model outcome and the empirical finding. In this context, if the model predicts something that is in direct opposition to a well-established and consistently observed phenomenon in the real world, there is a contradiction.

Falsifying Evidence: Suggests that the model's outcome, in this case, could be considered as evidence that contradicts or disproves a particular hypothesis or understanding. In scientific terms, if a model consistently produces results that go against well-established empirical findings, it might be a signal that the model is flawed or incorrect.

In summary, the sentence is highlighting that if a model consistently predicts outcomes that are directly at odds with well-established and reproducible real-world observations, it could be seen as providing evidence that the model is not accurate or valid in representing the phenomenon it is supposed to simulate. This is an important consideration in scientific research, as models are expected to align with empirical evidence to be considered reliable tools for understanding and predicting real-world phenomena.

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With this explanation, it makes sense. The authors can simply ask chatGPT to explain, and double-check the outcome.

Hope that helps! :)

Model

On Table 1. outcome variables: the same variables designate different phenomena, PI and PG, not sure it makes sense. How do we know which version of the variable is active. Just add a S to steady-state, such as SPI is for steady-state plasma insulin.

The model is a deterministic dynamical system with nonlinearity, with saturation and thresholds.

“Since the brain forms only about 3 % of total body mass, we assume plasma glucose diffused to the brain is a negligible fraction of total plasma glucose.” not sure it is correct, the brain consumes 20% of the energy, even being so small(*).

Final remarks

I did my best to read the article, nonetheless, I suggest caution when using on your own research. Once I have tried to replicate a paper on my PhD, from a famous journal, from a famous university: it had negative behaviors where it should not. Thus, my review is merely saying the paper is worth-reading and considering, I am not saying it is correct; replicating a paper and finding bugs takes time, and it should be done by the researcher interested on the research, not the reviewers. Which as a reviewer I cannot do.

The paper is good, sounds well-written, therefore, should gain the scientific community for further scrutiny. The most important part is the criticism they have on the current models that do not account for the brain as an important player on glucose dynamics, that is what we should focus on. The model most likely will have to be improved, it is a process that may require several hands.

I have taken a look at the current reviews, and seem to address points that I have not, but equally important to be considered.

Nice work!

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Talking to chatGPT

“Since the brain forms only about 3 % of total body mass, we assume plasma glucose diffused to the brain is a negligible fraction of total plasma glucose. ” not sure it is correct, the brain consumes 20% of the energy, even being so small.

You are correct that the brain consumes a significant amount of energy. According to a [source](#), the brain consumes roughly 20% of the body’s energy each day. This is equivalent to 260 calories per day¹.

Regarding the statement you mentioned, it is true that the brain only forms about 3% of the total body mass². However, the statement is not implying that the brain consumes a negligible fraction of total plasma glucose. Instead, it is suggesting that the amount of plasma glucose that diffuses to the brain is negligible compared to the total plasma glucose in the body. This is because the brain has a **blood-brain barrier** that regulates the movement of substances between the blood and the brain².

I hope this clarifies your doubts. Let me know if you have any further questions!

“I have the feeling that the amount of energy consumed is proportional to glucose. Therefore, would not that require more glucose as a consequence?

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You are correct that the brain consumes a significant amount of energy. According to a [source](#), the brain consumes roughly 20% of the body’s energy each day. This is equivalent to 260 calories per day¹.

The brain primarily uses glucose as its energy source²³. The amount of glucose required by the brain depends on various factors such as the level of activity, age, and health status¹². However, it is true that the brain requires more glucose when it is more active².

Therefore, it is reasonable to assume that the brain would require more glucose when it is more active, such as during periods of intense mental activity¹².

I hope this answers your question. Let me know if you have any further doubts!

Declarations

Potential competing interests: No potential competing interests to declare.