Review of "Model Based Learning and Optimization for Personalized Heparin Dosing"

In this paper, the authors consider optimizing personalized heparin doses with a predictive model. They utilize the model to develop a scenario generation based approach so that patient safety are ensured. A set of numerical experiments are also conducted to validate the performance of the paper.

After reading the paper, I have the following major comments regarding paper:

- **Modeling:** Regarding the definitions in θ_y and θ_x, can the authors please provide evidences to show that these are all the parameters should be considered in the problem?

- **Linear Approximation:** This might be one of the most important comments. As far as I could understand, the linear approximation in equation (4) tries to give an approximation to the function $g(\cdot, \cdot, \cdot)$ and the authors plot figure 1 to show the approximation error. There are thus two critical problems here.

  First, what exactly is the approximation error here? I suppose it depends on the values of α and k. To argue that this is a valid approximation (especially such an approximation is new as suggested by the authors), the authors should give an upper bound on the approximation error and discuss what are the implications for carrying such an error.

  Next, the motivation of this particular linear approximation is in fact not solid. So far, the authors seem to want the model to fit into a specific optimization framework. This does not seem to be a valid reason. Given the existing approximations, which appear to be widely accepted, I would suggest we find an optimization framework that works for them rather than fixing the optimization framework ahead.

  Alternatively, the authors should at least show a set of results, which include the followings: 1) It is impossible (either statistically or computationally) to use the existing approximations to solve the problem; and 2) Given the above, the current linear approximation works well.

  Since this paper is motivated by practice and it aims at guiding practice, it is of fundamental importance to make sure the model is precise and accurate.

- **Assumptions:** I would encourage the authors to provide more evidences to support Assumptions 1 and 2. In the current version, only the first half of Assumption 1 can be

supported by the problem of interest. I would suggest the authors to use real-world data to show that the rest of the assumptions can be satisfied in the heparin dosing scenario.

Similar comments apply to the subsequent assumptions (Assumptions 3, 4, and 6).

- **Clarification of Novelty:** I would also encourage the authors to clearly state the technical and/or modeling novelties of the work. When reading through the paper, the presentation seems to suggest that the methods developed in this paper are adopted (after some modifications) from prior works. To make the contributions clear, it would be helpful for the authors to clearly distinguish this work from previous ones. Here, I would suggest we focus more on the difference compared to existing techniques as Section 1.3 has done a good job in summarizing what are the techniques used in this paper.
- **Optimality Criterion:** In Section 4, the authors show the asymptotic optmality of the proposed policy, but I am curious why not using the standard notion of (finite time) regret as the optimality measure? If the latter is possible, I would encourage the authors to do so.

Some minor comments:

- What is $x(t)$ in equation (3)?
- Some of the sentences after equation (1) is pretty complex and hard to understand, I would suggest the authors to split them into multiple short sentences.

Given the above, I humbly think that the paper is somewhat at the borderline. Given the benefit of doubts, I thus recommend Major Revision for the current submission.