Supplementary Material

1 DATA

Our retrospective evaluation methodology required including patients who experienced at least one adverse event (either hypoglycemia or hyperglycemia), which resulted in 23 patients. However, the original dataset included 106 patients who required IV insulin administration and fed through an enteral tube. It is important to note that 20 out of the 106 patients required only bolus insulin which was delivered intravenously. The remaining 86 patients required either only continuous IV insulin or bolus IV insulin in addition to continuous IV insulin. Here, we provide detailed information about all of the 106 patients in Table S1. Since the current version of the methodology provides decision support for continuous IV insulin delivery, we provide the length of continuous IV insulin delivery statistics only for the 86 patients.

Table S1. Demographic and ICU stay-related health record information of patients who required IV insulin administration and fed through an enteral tube in the real-world dataset. These patients did not necessarily experience an adverse event (hypoglycemia or hyperglycemia). (* indicates that the reported statistics represent 86 patients who required continuous IV insulin administration. The remaining 20 patient were delivered only bolus IV insulin.)

	mean	**stdev**	**min**	**median**	**max**
Age (years)	55.6	13.9	25.0	56.0	81.0
Length of ICU stays that contain an interval meeting the inclusion criteria (days)	16.3	15.2	3.4	10.8	72.9
Total number of BG measurements	89.1	75.3	4	72.5	462
Length of tube feed administration (hours)	194.7	154.9	73.3	142.8	875
***Length of IV insulin administration (hours)**	96.7	82.8	1.5	84.5	444.0
Race	American Indian and Alaska Native: 2 Asian: 4 Black or African American: 12 Multiple Race: 1 Other: 6 White or Caucasian: 81				
Ethnicity	Hispanic: 12 Non-Hispanic: 94				
Sex	Female: 36 Male: 70				

2 SIMULATIONS OF BLOOD GLUCOSE LEVELS RESULTING FROM THE MODEL-BASED CONTROLLER AND PROTOCOL USED IN CLINICAL PRACTICE

We show the simulations of resulting BG values with the LQG controller-suggested and protocol-suggested IV insulin rates for a detailed explanation of the developed methodology. In Fig. 1, the top panels show simulated BG values, representing a virtual patient's response to the IV insulin rate shown in the middle panels. The nutrition rates (lower panels) are the same in each subfigure.

We used the ICUMM to create virtual patient profiles and to represent those virtual patients' glycemic response to LQG-suggested and protocol-suggested IV insulin rates. In this sense, ICUMM is a representation of reality. We used the MSG model in our control-theoretical framework to *learn* the patients' BG dynamics and estimate the optimal amount of IV insulin rate for GM. This figure demonstrates potential GM performance given a perfect representation of BG dynamics with a mechanistic model. The

target value for the LQG controller is the upper limit of the respective protocol's target range (180 mg/dL) to avoid hypoglycemia. The BG values simulated with the MSG model hover around that target value, with occasional lower values due to nutrition rate changes shifting the system equilibrium. However, the LQG controller quickly identifies the IV insulin rate to shift the equilibrium to the target value of 180 mg/dL.

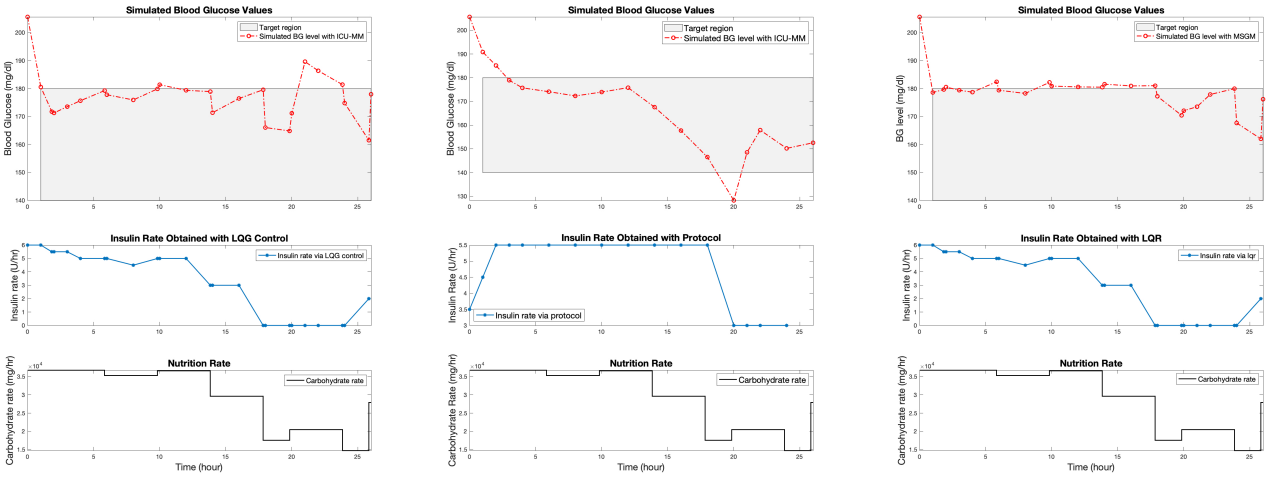

Figure 1a. LQG — ICUMM **Figure 1b.** Protocol — ICUMM **Figure 1c.** LQG - MSGM

Figure 1. Tthe upper panels show the BG values simulated by the model shown in the respective legend in response to the IV insulin rate plotted in the middle panels. The nutrition rates are identical in all subfigures since we do not change nutrition rate. Panels **(A)** and **(B)** represent a virtual patient's response to LQG-suggested and protocol-suggested IV insulin rates. Panel **(C)** shows a possible GM result if we had a BG model that could represent the real BG dynamics of ICU patients perfectly.

We included nutrition change times as intervention times for the LQG controller in addition to the intervention times of a protocol. We see the positive effect of this strategy by comparing the BG values between 15-20 hours. Since the protocol does not account for nutrition amount changes, it continually suggested higher IV insulin rates while the LQG controller suggested lower rates due to reduced nutrition amounts over that time interval. This difference shows the importance of accounting for nutritional changes in developing BG control strategies.

Figure 1c shows simulated BG values by the MSG model in response to LQG-suggested IV insulin rate. This figure demonstrates potential GM performance given a perfect representation of BG dynamics with a physiology-based mechanistic model. Our target value for the LQG controller is the upper limit of the respective protocol's target range (180 mg/dl in Figure 1) to avoid hypoglycemia. The BG values simulated with the MSG model hover around that target value, with occasional lower values due to nutrition rate changes shifting the system equilibrium. However, the LQG controller quickly identifies the IV insulin rate to shift the equilibrium to the target value of 180 mg/dl. Therefore, one way to develop an effective model-based BG controller is to use a model that accurately represents BG dynamics. However, such models do not exist and might not be useful in control frameworks because of their complexity and real-world data limitations. Hence, we aim to develop controllers using simpler models accounting for the system's dynamic behavior and real-world data limitations through novel techniques (such as introducing resolvable stochasticity into the model) rather than increasing model complexity.