Assessing Performances of Glucose Control Algorithms on a Set of Virtual ICU Patients

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INTRODUCTION : The 2001 van den Berghe et al. study showed that intensive glucose control reduced mortality. Subsequent large randomized controlled trials of tight glucose control have failed to show a mortality benefit. Consequently, considerable controversy has emerged as to whether tight glucose control is warranted in all critically ill adults. Differences between studies have been explained by the expertness of medical staff. Therefore, with non expert nurses, glucose control is solely based on algorithm performance. Rather than an educational simulation program of insulin dosage and dietary adjustment (AIDA [1]), we provided physicians with a tool to score algorithm performance using realistic virtual ICU patients before actual trials. Our simulation was conducted using two recent algorithms as examples: the NICE-SUGAR algorithm [2] and the one used in the ongoing CGAO-REA study [3], which has been developed using our tool. Our main objective was to add a validation step ahead of trials in a real environment setting by verifying the algorithm manages to control virtual ICU patients.

METHODS : The set of virtual patients was built using real data coming from Chartres Hospital patients using a non-linear pharmaco-dynamic glucose-insulin system model [4] where patients' endogenous glucose clearance and insulin-sensitivity were time dependent parameters. Algorithm robustness was then tested on ten diabetic and non-diabetic virtual patients by simulating the ICU environment: 1) delays were implemented by generating random numbers using the delays distribution law observed in Chartres Hospital, while 2) inaccuracy of glucose meters was used as perturbation. Then, recommendations computed by each tested algorithm were applied to the virtual patients and the overall performance over the whole stay was assessed according to standard scores (e.g. time spent in the target range) and indexes (e.g. variability index).

RESULTS : For highly insulin-sensitive patients or patients with high variation of insulin sensitivity, scores obtained using NICE-SUGAR algorithm were very low. The percentage of time in the target range (4.4-6.1 mmol/L) was lower than 50% for almost all patients and the frequency of hypoglycemia was high. With insulin-sensitive patients, glucose fluctuations and sometimes severe hypoglycemia (see Fig.1) were induced by the algorithm. The mean percentage of time in the target range using CGAO system was about 60% and the variability index calculated in this case was significantly lower than with NICE-SUGAR. NICE-SUGAR control showed random behavior considering delays and noise and no trend was highlighted whereas CGAO system was robust to noise and delays in all cases.

DISCUSSION : NICE-SUGAR outcome has cast doubt on whether tight glucose control is beneficial and a new target range has been suggested subsequent to its publication. However, control algorithms are at the forefront of blood glucose target achievement problems and thus, a target range without a proper algorithm to achieve it is useless. The purpose of this study is to demonstrate that preliminary trials, such as numerical testing, enable the invalidation of low-scored algorithms and consequently, avoid target overlay between groups. Numerical simulations of the NICE-SUGAR algorithm agreed with the post-analysis by revealing relatively high glucose variability outside the target range in some cases, which increases the risk of hypoglycemia. In contrast, scores obtained using the CGAO-REA algorithm were encouraging and further tests were performed on real ICU patients prior to the start of the CGAO-REA study. Finally, although the effect of non respect of insulin flow recommendations have not been investigated, it is likely that this factor played an important role in glucose control.

REFERENCES :

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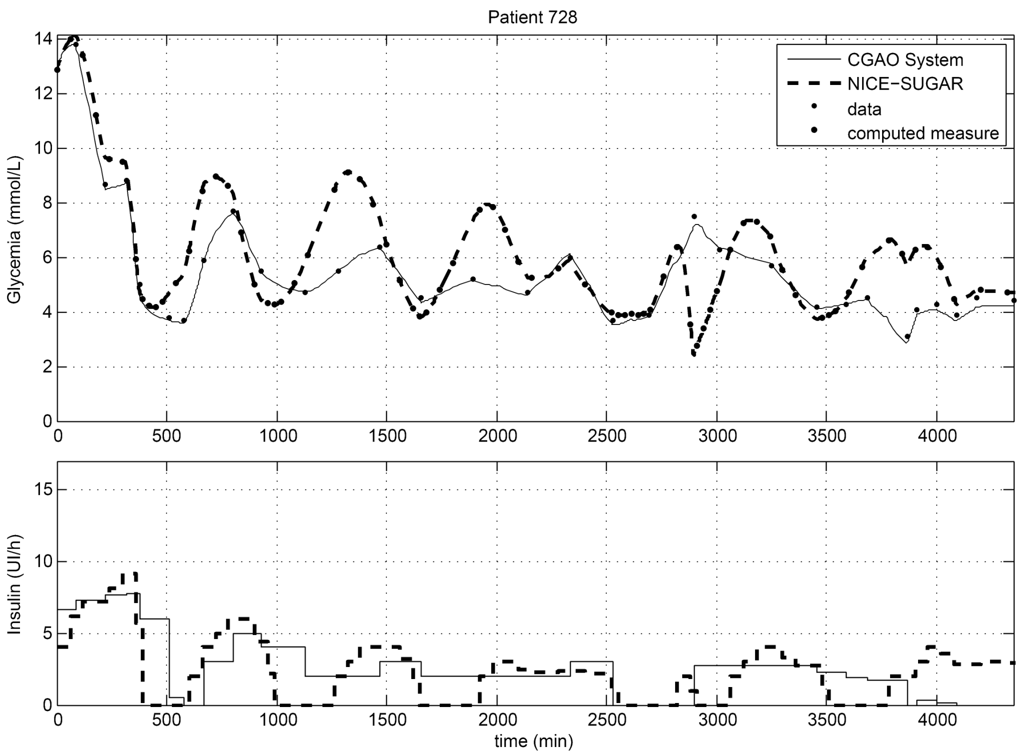

Figure 1