Patient-Specific Metabolic Variability and Precision Glycaemic Control in Critical Care

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Patient-Specific Metabolic Variability and Precision Glycaemic Control in Critical Care

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Abstract

Critically ill patients often experience stress-induced hyperglycaemia. Elevated blood glucose levels are associated with increased morbidity and mortality. Glycaemic control demonstrated improved outcomes for these patients. However, other studies failed to replicate the results, primarily blaming the increased risk of hypoglycaemia and glycaemic variability, both associated with worse outcomes. These confounding outcomes have resulted in acceptance of hyperglycaemia and reduced outcomes, causing ongoing debate on glycaemic control.

The goal of the thesis is to define what makes glycaemic control hard to achieve safely, prove safe, effective control impacts patient outcome, and demonstrate it is possible to achieve safe, effective control for all patients, despite targeting lower glycaemic ranges.

Metabolic variability is the main factor making glycaemic control hard to achieve safely. More specifically, sudden changes in patient-specific response to insulin (intra-patient variability) can lead to severe hyper- and hypo-glycaemia. Novel analysis of model-based insulin sensitivity and its variability clearly showed while inter-patient variability can be significantly different across patients, intra-patient variability is equivalent. Therefore, no patient is harder nor easier to control, and thus all patients should be able to benefit from similar quality of control. In turn, conclusions on glycaemic control from studies failing to do so may be biased due to poor protocol design, rather than physiological factors related to severity and outcome.

Intra-patient variability is still very large, and it is not possible to discriminate more and less variable patients, reducing the quality of control deliverable in practical clinical scenarios. This research developed a novel 3D stochastic model to optimally segregate more and less variable patients based on prior behaviours. This approach enabled significantly improved, and tighter prediction of risks associated with a given insulin and/or nutrition intervention. Clinical trial results in NZ have shown improved control and safety using this new 3D stochastic model.

To demonstrate these outcomes, a clinical trial using STAR, a model-based, patient-specific glycaemic control framework, was designed and implemented at the University Hospital of Liège. Results showed STAR succeeded in providing safe, effective control to virtually all patients, despite targeting lower target bands associated with better outcomes. However, increased workload compared to the standard protocol was identified as a limitation.

Finally, this thesis develops a means to dramatically increase the STAR measurement interval from 1-3 hourly to 1-6 hourly without significantly degrading performance or safety. Virtual trials clearly defined the risk and reward trade-off between control performance, patient safety, workload, and nutrition. This result allows clinical staff to choose from a far wider range of options and approaches to provide safe, effective control, with clearly defined risk trade-offs.

Overall, a series of analyses and clinical trials have shown safe, effective control is necessary to improve outcomes, and can be achieved for all patients. These outcomes are possible using patient-specific, model-based glycaemic control protocols developed in this thesis, which directly account for both intra- and inter-patient variability and reduce workload.
Résumé

Le stress et l'inflammation chez les patients critiques déclenchent une cascade de réactions ayant pour effet une production endogène de glucose anormalement élevée et une résistance accrue à l'insuline, provoquant de l'hyperglycémie. L'insulinothérapie est donc prescrite chez ces patients, dans le but de réduire ces niveaux anormalement élevés de glycémie, associés à des comorbidités multiples. Plusieurs études ont mis en évidence les bénéfices liés au contrôle strict de la glycémie, mais l'augmentation importante des risques d'hypoglycémie et de la variabilité glycémique, tous deux indépendamment associés à des complications sévères, ont ouvert un débat quant aux effets positifs ou néfastes liés à ce contrôle. En effet, bien que des glycémies normales soient davantage bénéfiques pour les patients, des glycémies légèrement plus hautes permettent de minimiser les risques d'hypoglycémie.

Cette thèse tente d'identifier les facteurs impactant la qualité et la sécurité du contrôle de la glycémie, ainsi que de démontrer qu'il est possible d'offrir un contrôle de qualité pour tous les patients.

Un des facteurs principaux rendant le contrôle difficile est la variabilité de la sensibilité à l'insuline. La sensibilité varie d'un individu à l'autre, évolue avec le temps, et est directement responsable des risques potentiels d'hypoglycémie. Dans cette thèse, il est montré qu'alors que la sensibilité à l'insuline entre les patients est différente, la variabilité temporelle est équivalente. Il en résulte que la qualité du contrôle de la glycémie doit être similaire chez tous les patients, et qu'un protocole mal adapté ne permet pas de s'en assurer.

Caractériser la variabilité de la sensibilité à l'insuline est donc primordial dans le contrôle de la glycémie. Dans STAR, un protocole de contrôle de glycémie, cette variabilité est prise en compte grâce à un modèle mathématique, déterminant la sensibilité à l'insuline spécifique du patient, ainsi qu'un modèle stochastique pour en évaluer sa variabilité. Un nouveau modèle stochastique 3D est développé pour améliorer la prédiction de l'évolution de la sensibilité à l'insuline. Il se base sur l'évolution antérieure de cette variable, et permet de mieux quantifier les risques d'hypoglycémie liés à un traitement spécifique. Un essai clinique en Nouvelle-Zélande a pu montrer une amélioration de la sécurité du contrôle de la glycémie grâce à ce nouveau modèle.

STAR a également été implémenté dans un essai clinique en Belgique, afin de montrer une fois encore qu'un protocole adapté, prenant en compte la variabilité métabolique des patients, peut contrôler la glycémie de manière sécurisée et efficace. Cet essai clinique quantifie également, pour la première fois, l'impact du contrôle de la nutrition, en plus de l'insuline, aux soins intensifs. Les résultats de l'étude montrent une nouvelle fois une augmentation significative de la qualité de contrôle, et un apport nutritionnel beaucoup plus adapté que lorsque la nutrition est laissée à l'appréciation du staff médical.

Enfin, au vu de l'augmentation de la charge de travail induite par des mesures cliniques plus fréquentes demandées par STAR, cette thèse évalue également l'impact lié à l'utilisation d'intervalles de mesure plus longs sur le contrôle de la glycémie. Au travers de simulations, le compromis entre les risques et les bénéfices lié à un suivi moins régulier de la glycémie sont clairement définis, donnant des pistes de réflexion concernant la meilleure stratégie à adopter.

Cette thèse démontre, au travers d'analyses in-silico et d'essais cliniques, qu'un contrôle strict, sécurisé, et efficace de la glycémie est non seulement possible, mais indispensable pour tous les patients, puisque la variabilité métabolique est identique et indépendante de leur état.
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## Nomenclature

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<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>%ΔSI</td>
<td>Hour-to-hour percentage change in SI</td>
</tr>
<tr>
<td>AIR</td>
<td>Acute immune response</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>BG</td>
<td>Blood Glucose</td>
</tr>
<tr>
<td>CDF</td>
<td>Cumulative Distribution Function</td>
</tr>
<tr>
<td>CHO</td>
<td>Carbohydrate</td>
</tr>
<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>EGP</td>
<td>Endogenous Glucose Production</td>
</tr>
<tr>
<td>GC</td>
<td>Glycaemic Control</td>
</tr>
<tr>
<td>GF</td>
<td>Goal Feed</td>
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<tr>
<td>ICING</td>
<td>Intensive Control Insulin-Nutrition-Glucose</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IIT</td>
<td>Intensive Insulin Therapy</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>LOS</td>
<td>Length of Stay</td>
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<td>NICE-SUGAR</td>
<td>Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation</td>
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<tr>
<td>RCT</td>
<td>Randomised Clinical Trial</td>
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<td>Rule of Thumb</td>
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