# Benchtop to Bedside to Worldwide: Implementing Model-Based Glycemic Control in Intensive Care

**Aaron J. Le Compte[*], Geoffrey M. Shaw[**], J. Geoffrey Chase[*]**

** Department of Mechanical Engineering, University of Canterbury*
*New Zealand (phone: +64-3-364-2987, e-mail: aaron.lecompte@canterbury.ac.nz)*
*** Department of Intensive Care, Christchurch Hospital, New Zealand*

Abstract: Hyperglycaemia is a common physiological response in critically ill patients, and reflects the perturbed metabolic state associated with severe illness. Regulating blood glucose (BG) levels to pre-ICU concentrations may provide patients with a greater chance of survival and reduced complications. However, despite the potential benefits there is still no universally adopted method for regulating BG levels in the ICU, and several large trials have failed to provide a consistent level of BG regulation across multiple centers. Models of the glucose regulatory system together with specialized controllers can assist clinical staff in therapy decisions by optimizing insulin and nutrition dosing. These systems can be readily implemented using existing or commodity equipment. This article presents experiences in implementing such model-based BG control in eight studies across four clinical units in three countries and highlights challenges faced when translating control systems from design and simulation environments to daily bedside clinical usage. Several practical issues need to be addressed for successful clinical implementation. Patient response to glucose and insulin inputs needs to be characterized, and it has been observed that level of insulin response varies significantly between patients and within patients over time. Clinically desired target ranges for BG control often vary by clinic and by year, and thus control schemes are required to adapt. Finally, the design of the system interface plays an important role in merging with local clinical practices and achieving nursing support for the system. Considerable variation exists, not only in the types of patients and observed responses to treatment, but also in the provision of clinical treatment. Thus a balance is required between flexibility and complexity to reduce training time and costs, improve transparency and promote independent clinical uptake.

*Keywords:* Biomedical computing, clinical trial, forecasting, stochastic approximation**,** glycemic control

## 1. INTRODUCTION

Stress-induced hyperglycemia is a significant issue in critical care. Up to 30-50% of adult intensive care unit (ICU) patients and 32-86% of very low birth-weight neonatal ICU (NICU) patients are affected. Links to increased morbidity and mortality (McCowen et al., 2001, Krinsley, 2004, Hays et al., 2006) have been established, and potentially benefits of regulating blood glucose (BG) levels have been observed (Chase et al., 2008b, Van den Berghe et al., 2001). Controlling glycemia has proved difficult due to the associated risk of hypoglycemia when highly dynamic patients are treated with exogenous insulin (Griesdale et al., 2009). Both high and low glycemic extremes, as well as glycemic variability, have been independently linked to increased morbidity and mortality (Bagshaw et al., 2009, Egi et al., 2006, Krinsley, 2008). Accurate glycemic control (AGC) has proven difficult to achieve safely and consistently (Casaer et al., 2011), with increased hypoglycemia a common consequence of control attempts in many studies (Preiser et al., 2009, Beardsall et al., 2008).

However, the higher nursing workloads due to high density glucose readings are impractical in many units (Mackenzie et al., 2005, Aragon, 2006). Hand-held glucometers are easier for measurement, but their larger errors can add additional difficulty for some AGC protocols. Finally, clinical compliance determines much of the efficacy of any AGC method, with quality of glycemic control thus also limited by the confidence and compliance of nursing staff (Aragon, 2006, Chase et al., 2008a). All of these issues interact with the inherent inter- and intra- patient metabolic variability (Chase et al., 2011) to exacerbate the difficulty of achieving good control. Hence, glycemic control targets are often raised to mitigate these factors and avoid hypoglycemia as a best outcome compromise, despite the physiological and clinical evidence on the negative impact of even moderate hyperglycemia (McCowen et al., 2001, Krinsley, 2004).

Three aspects of clinical implementation are covered in this article: a) Patient characteristics; b) Controller targets; and c) Clinical integration. Examples are provided of modifications and additions to the BG control system as it is transitioned from simulation environments to daily clinical usage.

## 2. GLUCOSE CONTROL CLINICAL STUDIES

Table I summarizes several clinical implementation studies of model-based decision support systems for glucose control that were performed between 2005 and 2012. These studies include both adult and neonatal cohorts, and several are on-going. The studies presented in Table I range from 24-hour pilot trials to full clinical practice change.

Several modifications to the control system to comply with local clinical practices are shown in Table I. Target ranges for

TABLE I
SPRINT AND STAR CLINICAL TRIALS AND IMPLEMENTATIONS

| Study details: | SPRINT | SPRINT-Gyula | STAR-Chch | STAR-Belgium-1 | STAR-Belgium-2 | STAR-Gyula | NICU: short-term | NICU: long-term |
|---|---|---|---|---|---|---|---|---|
| Location | Christchurch, NZ | Gyula, Hungary | Christchurch, NZ | Liege, Belgium | Liege, Belgium | Gyula, Hungary | Christchurch, NZ | Christchurch, NZ |
| ICU type | Adult | Adult | Adult | Adult | Adult | Adult | Neonatal | Neonatal |
| No. patient episodes | 371 | 12 | 19 | 9 | 9 | 14 | 8 | 27 |
| Target BG range (mmol/L) | 4.0 - 6.1 | 4.0 - 6.1 | 4.4 - 8.0 | 4.4 - 7.8 (target of 6.9) | 5.6 - 7.8 | 4.4 - 8.0 | 4.0 - 7.0 | 4.0 - 7.0 |
| Nutrition modulation | Yes | Yes | Yes | No | No | Yes | No | No |
| Insulin delivery | Bolus | Infusion | Bolus + infusion | Infusion | Infusion | Infusion | Infusion | Infusion |
| BG measurement frequency | 1 - 2 hours | 1 -2 hours | 1 - 3 hours | 1 - 2 hours | 2 - 3 hours | 1 - 3 hours | 2 hours | 2 - 4 hours |
| Primary BG measurement device | Glucometer | Glucometer | Glucometer | Glucometer and blood-gas | Blood-gas | Glucometer | Blood-gas | Blood-gas |
| User interface | Paper-based | Paper-based | Tablet-based | Computer-based | Computer-based | Tablet-based | Computer-based | Computer-based |
| Control results: | | | | | | | | |
| Average control duration | 121 hours | 91 hours | 149 hours | 24 hours | 24 hours | 83 hours | 24 hours | 117 hours |
| BG in target range | 59.1% | 42.2% | 83.9% | 54.2% | 54.9% | 75.6% | 40.9% | 53.7% |
| # patients < 2.2 mmol/L | 8 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| BG below target | 2.8% | 1.9% | 3.8% | 0.5% | 3.3% | 4.5% | 0.9% | 4.0% |
| BG median (mmol/L) | 5.7 | 6.3 | 6.1 | 7.6 | 7.4 | 6.1 | 7.4 | 6.6 |
| BG IQR (mmol/L) | [5.0 - 6.4] | [5.5 - 7.5] | [5.5 - 6.8] | [6.8 - 8.8] | [6.5 - 8.4] | [5.4 - 7.4] | [6.2 - 9.4] | [5.5 - 8.2] |
| Insulin median [IQR] (U/hr) | 2.6 [2.1 – 3.3] | 3.0 [2.2 – 5.0] | 3.0 [1.5 - 4.5] | 1.5 [0.5 - 3.4] | 2.0 [1.0 - 2.5] | 2.3 [1.0 - 4.3] | 0.058 U/kg/hr | 0.033 U/kg/hr |
| Carb intake median [IQR] (g/hour) | 3.9 [2.3 – 5.2] | 7.4 [4.4 – 9.7] | 4.9 [0.0 - 6.9] | 7.4 [2.0 - 11.2] | 0.0 [0.0 - 5.4] | 6.6 [4.7 - 8.6] | 8.2 mg/kg/min | 7.9 mg/kg/min |

control were based on local clinical guidelines and clinician preferences. SPRINT and STAR were both designed to incorporate nutrition modulation into control therapy. However some units preferred to leave nutrition unchanged, and thus control for these units was via insulin modulation only. Where nutrition modulation was allowed goal feeding rates varied between units in accordance with local practices. Bolus-based insulin delivery was used at Christchurch adult ICU implementations for patient safety and potential efficacy, with other hospitals opting for insulin infusions. The controller implementation vehicle was also customized for each hospital, with SPRINT using a unique paper-based form, and STAR software developed for either computers/laptops or tablets and generally translated to the local language of the unit (English, French or Hungarian).

BG measurement and controller intervention frequency balanced the desire for frequent re-evaluation of patient metabolic state for therapy adjustment and clinical workload, and varied between studies. Additionally, neonatal care has further restrictions on measurement frequency due to limited blood volumes in pre-term infants (Le Compte et al., 2011a). Glucometers or blood gas analysers were used for BG measurement depending on the unit, with the latter generally having higher measurement accuracy.

All relevant changes to controller parameters were evaluated in simulation prior to clinical usage (Lonergan et al., 2006b) using virtual patient simulated clinical trials. This stage allowed potential issues to be identified and communicated to clinical staff prior to trial commencement.

The BG control results in Table 1 show a generally consistent level of control across the studies despite numerous implementation differences. Percentage of BG within target bands tended to be lower for the short-term 24-hour trials as a higher proportion of time is spent initially decreasing BG from hyperglycemic levels compared to the longer term studies. The width of target bands varied between studies from 2.1 mmol/L to 3.6 mmol/L, where wider target bands showed more BG measurement within target. However, the IQR width is relatively consistent, suggesting BG variability was controlled in all cases. Median BG reflected a balance between target BG range and nutrition practices of local units, where those units feeding more carbohydrates showed elevated median BG results. Insulin usage was also generally higher for units with higher carbohydrate nutrition regimes as expected to balance glycemic load.

## 2. QUANTIFYING PATIENT RESPONSE

The insulin sensitivity (SI) metric is used as the main driver for BG control in this system (Chase et al., 2011). This quantity is either explicitly evaluated in the case of STAR or implicitly determined in the SPRINT table format. Thus,

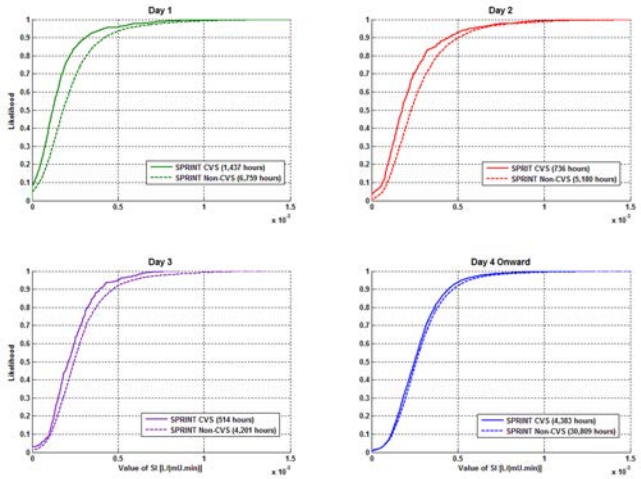


Fig 1. Cumulative Density Functions (CDFs) of cohort SI evolution over first four days of ICU stay for cardiac-surgery patients compared to other diagnoses. Cardiac surgery patients initially show lower SI with differences decreasing over subsequent days.

knowledge of how SI varies between patients and temporally is important for real-time BG control. Not only identifying patients that may be more resistant to insulin, but also tracking changes in response to insulin over time may be important (Le Compte et al., 2011b).

SI may cover not only physical response, but other artefacts such as modelling error (Chase et al., 2010), measurement device noise and pump errors. Thus even though SI may be numerically evaluated, it is often interpreted cautiously and limits are often placed on controller actions to limit potential harm if a rapid SI change was due to noise rather than a treatment or physiological change (Le Compte et al., 2011a). Frequent SI re-evaluation could also limit the impact of spurious measurements, particularly when used with glucometers (Lonergan et al., 2006a). Often strategies for dealing with missing, imprecise, error-prone information is a major component of creating a reliable system for a typical ICU. Thus identification of state is influenced by device noise and suggests that practical controllers should be aware of such limitations during development.

Differences in patient demographics influence observed evolution of SI. Adults and neonates show marked differences in the relationship between inter- vs intra-variability (Le Compte et al., 2011b), suggesting neonates show larger difference between patients, but lower variability within individuals compared to adults. Data from a single unit of the European Glucontrol study suggested similarities between Belgian and New Zealand patients (Suhaimi et al., 2010), and subsequent analysis of BG control trials showed modest improvements could be obtained by using stochastic model customised to a specific target group (Penning et al., 2011).

Thus, incorporating more baseline patient information may potentially improve forecasting by segregating patients into groups that show similar responses. Cardiac surgery patients are a subgroup of ICU population that have shown benefit of TGC. This population was also observed to have a tendency towards lower and more variable SI as a cohort compared to patients with other medical diagnoses, as shown in Fig. 1. However this *a-priori* information is not completely specific, and a particular cardiac surgery patient may easily oppose the trend and exhibit higher and/or less variable SI than a typical ICU patient. Diabetic patients also show similar trends during initial ICU stay as presented in Fig 2. However, such baseline information may not be completely reliable as it is estimated the prevalence of undiagnosed diabetes is significant (Cowie et al., 2006).

Figure 3 shows SI distributions grouped by several major diagnosis categories. Although some trends and shifts are numerically evident, there is also large overlap with little separation between groups. Knowledge of diagnosis, for example, could instruct a controller of a tendency towards lower SI, but would not be strong at this stage to solely drive therapy. Thus, this reinforces the utility of timely re-evaluation of SI for tracking patient response.

## 3. CLINICAL THERAPY TARGETS

The range of clinical BG targets amongst the studies shown in Table I reflects the range of targets encountered between units and changing opinions of BG control over time. The seminal 2001 Leuven study (Van den Berghe et al., 2001) encouraged many units to adopt low tight BG targets of around 4 – 6 mmol/L. Later studies that showed high degrees of hypoglycemia tempered this approach, and the latest ADA recommendations called for BG targets of 7.8-10.0 mmol/L (Moghissi et al., 2009).

Neonatal units also have a wide variation in desired glucose targets (Alsweiler et al., 2007), and the 4.0 – 7.0 mmol/L target chosen in the studies presented in Table 1 reflects adult targets in the absence of detailed studies in the neonatal population.

Computerized model-based approaches such as STAR offer the ability to alter targets in real-time, whereas paper-based approaches such as SPRINT are inflexible in this regard. Differences in patient response over the first days in ICU may dictate different target ranges per day. Additionally, new evidence suggesting diabetic patients may show greater benefit from higher BG targets compared to non-diabetic patients (Egi et al., 2011) suggests BG targets may also become patient-specific. Thus, it is possible control schemes need to be flexible with respect to chosen BG target to handle

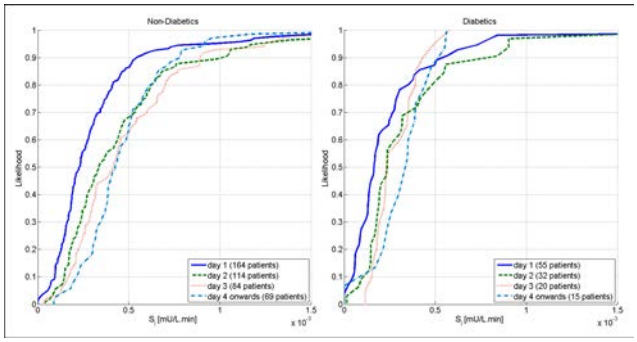


Fig 2. Cumulative Density Functions (CDFs) of cohort SI evolution over first four days of ICU stay for diagnosed diabetic patients (left panel) compared to non-diagnosed diabetics (right panel).

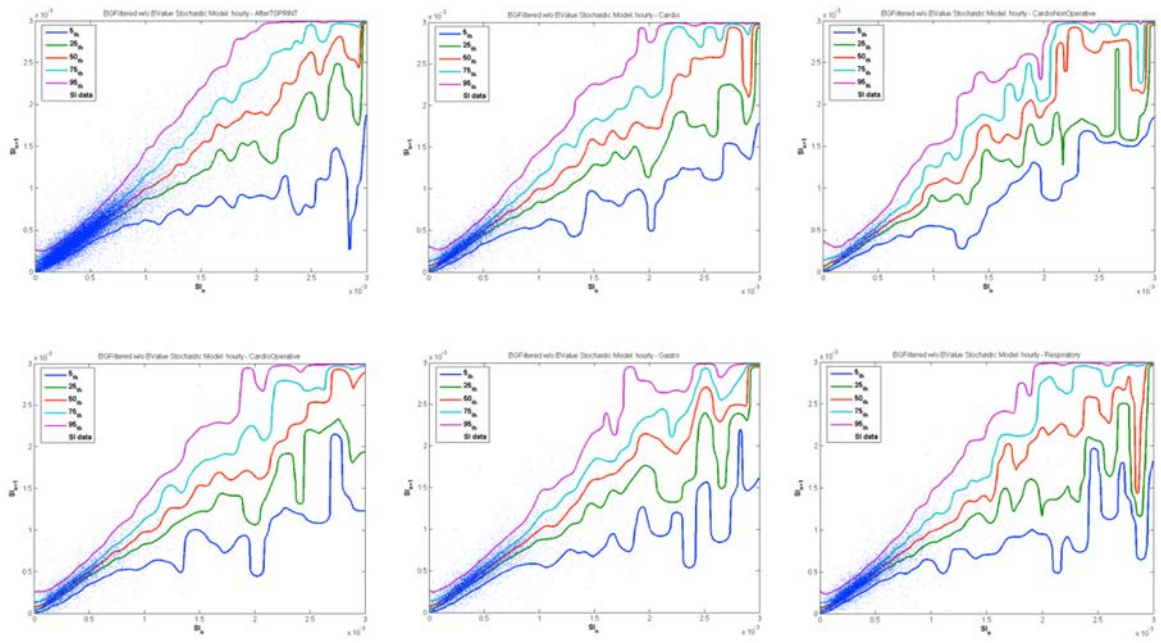

Fig 3. Stochastic model fits separated by clinical diagnostic category. Clockwise from top-left: whole-cohort, cardiovascular (all), cardiovascular (non-surgical), respiratory, gastrointestinal, cardiovascular (surgical).

these clinical scenarios.

Similarly, nutritional targets in ICU are also under debate (Peake et al., 2011). STAR and SPRINT recommend reducing nutritional intake in cases of excessive hyperglycemia and/or patients with particularly low sensitivity to insulin. Whether rigorously meeting daily caloric goals is required in ICU patients is presently debatable, with some studies showing improved outcomes with mildly hypo-caloric feeding regimens (Krishnan et al., 2003). Furthermore, it is not yet known whether maintaining caloric intake or regulated glycemia is the stronger driver for improved outcomes in cases where insulin resistance is very high. Thus, control schemes are likely required to be adapted over time as results from future studies influence ICU feeding practices.

Furthermore, even amongst units presented in Table I that modulated nutrition there was substantial variation in total carbohydrates administered and reflects local goal-feeding practices. Christchurch ICU tends to prescribe a low-carbohydrate enteral feeding formula for hyperglycaemic patients, whereas Gyula Hospital uses higher-carbohydrate formulas and makes extensive use of parenteral feeding routes.

## 4. DEVICE IMPLEMENTATION

The model-based studies presented in Table I were implemented on three platforms. SPRINT is a paper-based design that imitates model-based control (Lonergan et al., 2006b). Its low-cost format is readily implementable and has been used continuously since 2005. STAR is implemented either on desktop/laptop hardware or in tablet-based form (Evans et al., 2011), depending on the computing requirements of the target clinical unit.

Flexibility around measurement timing, BG targets, nutritional targets, baseline patient data and insulin administration choices require balance between flexibility allowed to nursing staff and ability to meet clinical requirements. Accurate data entry is crucial to accurate control. Mistyped entries can be a significant source of error, and tablet versions of STAR utilize a custom-designed keypads, shown in Fig 4, that have been shown to reduce incidence of mis-entered information (Ward et al., 2012). Increased communication with hospital information systems

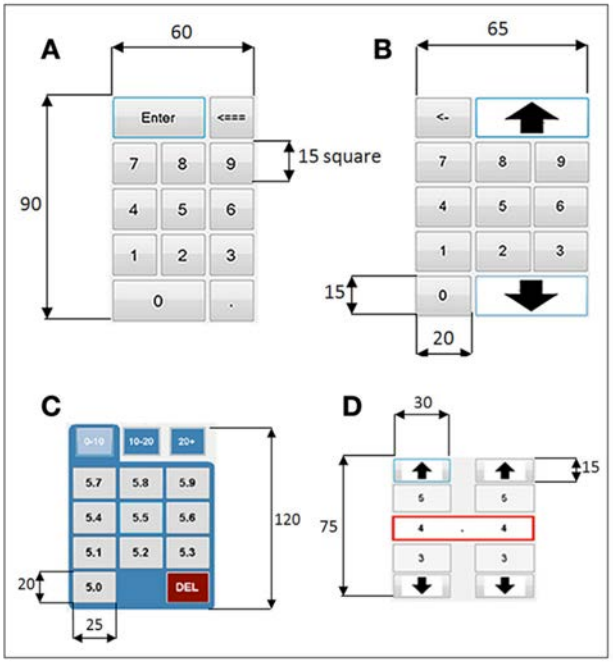


Fig 4. Numerical input methods tested to evaluate speed and accuracy performance when applied to tablet-based BG control systems.

and individual devices may also assist in limiting the amount of data entry and improve accuracy.

Finally, the BG control system needs to be trusted by frontline clinical staff, or recommendations may be overridden. The paper-based design of SPRINT is relatively transparent in that all possible insulin/nutrition combinations can be seen directly. More complex systems such as STAR typically hide many mathematical complexities involved in generating recommendations. Thus, it is important to communicate concepts such as sensitivity to insulin and model-based BG forecasting to staff to build awareness of motivation behind sometimes unintuitive therapy choices, and prevent protocol violations which can hamper studies (Preiser et al., 2009). For example, STAR graphically presents model-generate BG forecast bands to the user to communicate the expected outcome of a therapy selection, and the uncertainties in BG prediction due to patient condition.

## 4. CONCLUSIONS

The experience of the research work presented here is aimed at decision support systems. However, many of the issues still hold for full closed loop control systems. Patient variation in response to insulin must be handled by any control system. Although there are links between baseline conditions and SI evolution, few so far have appeared specific enough to strongly drive controller behaviour. Thus, re-evaluating SI appears to be important for safe control.

Targets for BG and nutrition differ between units, are may potentially change over time as further research is performed. Thus, control is likely required to be dynamic and personalized, and thus require flexibility in control laws. Finally, integrating with end users requires limits on complexity to assist for implementation including training, limiting data entry errors and utilizing available equipment in the ICU.

## 6. REFERENCES


ALSWEILER, J. M., KUSCHEL, C. A. & BLOOMFIELD, F. H. 2007. Survey of the management of neonatal hyperglycaemia in Australasia. *Journal of Paediatrics and Child Health,* 43**,** 632-635.

ARAGON, D. 2006. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. *Am J Crit Care,* 15**,** 370-7.

BAGSHAW, S., BELLOMO, R., JACKA, M., EGI, M., HART, G., GEORGE, C. & COMMITTEE, T. A. C. M. 2009. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Critical Care,* 13**,** R91.

BEARDSALL, K., VANHAESEBROUCK, S., OGILVY-STUART, A. L., VANHOLE, C., PALMER, C. R., VAN WEISSENBRUCH, M., MIDGLEY, P., THOMPSON, M., THIO, M., CORNETTE, L., OSSUETTA, I., IGLESIAS, I., THEYSKENS, C., DE JONG, M., AHLUWALIA, J. S., DE ZEGHER, F. & DUNGER, D. B. 2008. Early Insulin Therapy in Very-Low-Birth-Weight Infants. *N Engl J Med,* 359**,** 1873-1884.

CASAER, M. P., MESOTTEN, D., HERMANS, G., WOUTERS, P. J., SCHETZ, M., MEYFROIDT, G., VAN CROMPHAUT, S., INGELS, C., MEERSSEMAN, P., MULLER, J., VLASSELAERS, D., DEBAVEYE, Y., DESMET, L., DUBOIS, J., VAN ASSCHE, A., VANDERHEYDEN, S., WILMER, A. & VAN DEN BERGHE, G. 2011. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med,* 365**,** 506-17.

CHASE, J. G., ANDREASSEN, S., JENSEN, K. & SHAW, G. M. 2008a. Impact of Human Factors on Clinical Protocol Performance: A Proposed Assessment Framework and Case Examples. *Journal of Diabetes Science and Technology,* 2**,** 409-416.

CHASE, J. G., LE COMPTE, A. J., SUHAIMI, F., SHAW, G. M., LYNN, A., LIN, J., PRETTY, C. G., RAZAK, N., PARENTE, J. D., HANN, C. E., PREISER, J.-C. & DESAIVE, T. 2011. Tight glycemic control in critical care - The leading role of insulin sensitivity and patient variability: A review and model-based analysis. *Computer Methods and Programs in Biomedicine,* 102**,** 156-171.

CHASE, J. G., SHAW, G., LE COMPTE, A., LONERGAN, T., WILLACY, M., WONG, X.-W., LIN, J., LOTZ, T., LEE, D. & HANN, C. 2008b. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. *Critical Care,* 12**,** R49.

CHASE, J. G., SUHAIMI, F., PENNING, S., PREISER, J. C., LE COMPTE, A. J., LIN, J., PRETTY, C. G., SHAW, G. M., MOORHEAD, K. T. & DESAIVE, T. 2010. Validation of a model-based virtual trials method for tight glycemic control in intensive care. *Biomed Eng Online,* 9**,** 84.

COWIE, C. C., RUST, K. F., BYRD-HOLT, D. D., EBERHARDT, M. S., FLEGAL, K. M., ENGELGAU, M. M., SAYDAH, S. H., WILLIAMS, D. E., GEISS, L. S. & GREGG, E. W. 2006. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. *Diabetes Care,* 29**,** 1263-8.

EGI, M., BELLOMO, R., STACHOWSKI, E., FRENCH, C. J. & HART, G. 2006. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology,* 105**,** 244-52.

EGI, M., BELLOMO, R., STACHOWSKI, E., FRENCH, C. J., HART, G. K., TAORI, G., HEGARTY, C. & BAILEY, M. 2011. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med,* 39**,** 105-11.

EVANS, A., SHAW, G. M., LE COMPTE, A., TAN, C. S., WARD, L., STEEL, J., PRETTY, C. G., PFEIFER, L., PENNING, S., SUHAIMI, F., SIGNAL, M., DESAIVE, T. & CHASE, J. G. 2011. Pilot proof of concept clinical trials of Stochastic Targeted (STAR) glycemic control. *Ann Intensive Care,* 1**,** 38.

GRIESDALE, D. E., DE SOUZA, R. J., VAN DAM, R. M., HEYLAND, D. K., COOK, D. J., MALHOTRA, A., DHALIWAL, R., HENDERSON, W. R., CHITTOCK, D. R., FINFER, S. & TALMOR, D. 2009. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ,* 180**,** 821-7.

HAYS, S. P., SMITH, B. & SUNEHAG, A. L. 2006. Hyperglycemia Is a Risk Factor for Early Death and Morbidity in Extremely Low Birth-Weight Infants. *Pediatrics,* 118**,** 1811-1818.

KRINSLEY, J. S. 2004. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc,* 79**,** 992-1000.

KRINSLEY, J. S. 2008. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med,* 36**,** 3008-13.

KRISHNAN, J. A., PARCE, P. B., MARTINEZ, A., DIETTE, G. B. & BROWER, R. G. 2003. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest,* 124**,** 297-305.

LE COMPTE, A. J., CHASE, J. G., LYNN, A., HANN, C. E., SHAW, G. M. & LIN, J. 2011a. Development of blood glucose control for extremely premature infants. *Comput Methods Programs Biomed,* 102**,** 181-91.

LE COMPTE, A. J., PRETTY, C. G., LIN, J., SHAW, G. M., LYNN, A. & CHASE, J. G. 2011b. Impact of variation in patient response on model-based control of glycaemia in critically ill patients. *Comput Methods Programs Biomed*.

LONERGAN, T., LE COMPTE, A., WILLACY, M., CHASE, J. G., SHAW, G. M., HANN, C. E., LOTZ, T., LIN, J. & WONG, X. W. 2006a. A pilot study of the SPRINT protocol for tight glycemic control in critically Ill patients. *Diabetes Technol Ther,* 8**,** 449-62.

LONERGAN, T., LECOMPTE, A., WILLACY, M., CHASE, J. G., SHAW, G. M., WONG, X. W., LOTZ, T., LIN, J. & HANN, C. E. 2006b. A simple insulin-nutrition protocol for tight glycemic control in critical illness: development and protocol comparison. *Diabetes Technol Ther,* 8**,** 191-206.

MACKENZIE, I., INGLE, S., ZAIDI, S. & BUCZASKI, S. 2005. Tight glycaemic control: a survey of intensive care practice in large English hospitals. *Intensive Care Med,* 31**,** 1136.

MCCOWEN, K. C., MALHOTRA, A. & BISTRIAN, B. R. 2001. Stress-induced hyperglycemia. *Crit Care Clin,* 17**,** 107-124.

MOGHISSI, E. S., KORYTKOWSKI, M. T., DINARDO, M., EINHORN, D., HELLMAN, R., HIRSCH, I. B., INZUCCHI, S. E., ISMAIL-BEIGI, F., KIRKMAN, M. S. & UMPIERREZ, G. E. 2009. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care,* 32**,** 1119-31.

PEAKE, S., RIDLEY, E. & CHAPMAN, M. 2011. Energy Goals in the Critically Ill Adult. *In:* VINCENT, J. L. (ed.) *Annual Update in Intensive Care Medicine 2011*. Springer Science + Business.

PENNING, S., LE COMPTE, A. J., MOORHEAD, K. T., DESAIVE, T., MASSION, P., PREISER, J. C., SHAW, G. M. & CHASE, J. G. 2011. First pilot trial of the STAR-Liege protocol for tight glycemic control in critically ill patients. *Comput Methods Programs Biomed*.

PREISER, J. C., DEVOS, P., RUIZ-SANTANA, S., MELOT, C., ANNANE, D., GROENEVELD, J., IAPICHINO, G., LEVERVE, X., NITENBERG, G., SINGER, P., WERNERMAN, J., JOANNIDIS, M., STECHER, A. & CHIOLERO, R. 2009. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med,* 35**,** 1738-48.

SUHAIMI, F., LE COMPTE, A., PREISER, J. C., SHAW, G. M., MASSION, P., RADERMECKER, R., PRETTY, C. G., LIN, J., DESAIVE, T. & CHASE, J. G. 2010. What makes tight glycemic control tight? The impact of variability and nutrition in two clinical studies. *J Diabetes Sci Technol,* 4**,** 284-98.

VAN DEN BERGHE, G., WOUTERS, P., WEEKERS, F., VERWAEST, C., BRUYNINCKX, F., SCHETZ, M., VLASSELAERS, D., FERDINANDE, P., LAUWERS, P. & BOUILLON, R. 2001. Intensive insulin therapy in the critically ill patients. *N Engl J Med,* 345**,** 1359-1367.

WARD, L., STEEL, J., LE COMPTE, A., EVANS, A., TAN, C. S., PENNING, S., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2012. Data entry errors and design for model-based tight glycemic control in critical care. *J Diabetes Sci Technol,* 6**,** 135-43.