35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

A Model-Based Control Protocol for Transition from ICU to HDU: Robustness Analysis

Normy N. Razak, J. Geoffrey Chase, Fatanah M. Suhaimi, Geoffrey M. Shaw, Ummu Jamaluddin.

Abstract— **The robustness of a model-based control protocol as a less intensive TGC protocol using insulin Glargine for provision of basal insulin is simulated in this study. To quantify the performance and robustness of the protocol to errors, namely physiological variability and sensor errors, an in-silico Monte Carlo analysis is performed. Actual patient data from Christchurch Hospital, New Zealand were used as virtual trial patients.**

Keywords-model-based protocol; less critical patients; Monte Carlo; tight glycaemic control;

I. INTRODUCTION

There is a pressing need for insulin delivery protocols that can be successfully implemented with minimal clinical effort, burden and resources. Based on current evidence from critically ill and surgical patients, it is logical to expect that maintenance of normoglycaemia within less critical patients such in high dependency units (HDU) would limit potential complications associated with elevated blood glucose levels. This assumption is not unreasonable as patients in the ICU and within HDU share an accelerated catabolic, hyperglycaemic state that also reduces the immune response. The challenge is to find and implement glycaemic goals with a standardized, safe and effective protocol.

The SPRINT-1U+Glargine protocol was developed to simulate a less intensive TGC protocol to support the transition of patients from ICU to less acute wards. Glargine is injected 1-2x/day, so it can potentially reduce the workload to match clinical resources. The protocol uses an integrated pharmaco-kinetics/dynamic model of insulin Glargine intravenous insulin and glucose from [1] and [2]. To quantify the performance and robustness of the protocol to errors, namely physiological variability and sensor errors, an in-silico Monte Carlo analysis is performed. The main assessments taken into account are accuracy and repeatability.

II. SYSTEM MODEL

A four compartment description of subcutaneous insulin kinetics is presented, where Glargine is modelled to appear in its precipitate, hexameric, dimeric / monomeric, and (local) interstitium states. The underlying structure of this pharmacokinetics model is adopted from [1]. The model describes the pharmacokinetics processes following subcutaneous administration of Glargine:

Insulin Glargine Compartmental Model.

Precipitate State:

$$\dot{p}_{gla}(t) = \frac{-k_{prep,gla}\,p_{gla}(t)}{1+\dfrac{k_{prep,gla}}{r_{dis,\max}\,p_{gla}(t)}} + u_{p,gla}(t) \quad (1)$$

Hexameric State:

$$\dot{x}_{h,gla}(t) = -(k_{1,gla}+k_d)x_{h,gla}(t) + k_{prep,gla}\,p_{gla}(t)\frac{k_{prep,gla}\,p_{gla}(t)}{1+\dfrac{k_{prep,gla}}{r_{dis,\max}\,p_{gla}(t)}} + u_{h,gla(t)} \quad (2)$$

Dimeric/ Monomeric State:

$$\dot{x}_{dm}(t) = -(k_2+k_d)x_{dm}(t) + k_{1,gla}\,x_{h,gla}(t) + u_{m,gla}(t) \quad (3)$$

Interstitium:

$$\dot{x}_i(t) = -(k_3+k_{d,i})x_i(t) + k_2\,x_{dm}(t) \quad (4)$$

where all variables in Equations (1)-(4) are defined in Table 1

Table 1: Description of Glargine Model Parameters.

Parameter	Description
$x_{h,gla}(t)$	Mass in glargine hexameric compt. [mU]
$p_{gla}(t)$	Mass in glargine precipitate compt. [mU]
$x_{dm}(t)$	Mass in dimer/monomer compartment [mU]
$x_i(t)$	Mass in the interstitium compartment [mU]
$r_{dis,max}$	Max glargine precip. dissolution rate [mU/min]
$u_{total,gla}(t)$	Insulin glargine input [mU/min]
$u_{p,gla}(t)$	Glargine precipitate state insulin input [mU/min]
$u_{h,gla}(t)$	Glargine hexamer state insulin input [mU/min]
n	Decay rate of insulin from plasma [1/min]
α_I	Saturation of plasma insulin disappearance [L/mU]
u_{ex}	Exogenous insulin input [mU/min]
$k_{prep,gla}$	Glargine precipitate dissolution rate [min-1]
k_1	Hexamer dissociation rate [min-1]

$k_{1,gla}$	Glargine hexamer dissociation rate [min-1]
k_2	Dimeric/monomeric insulin transport rate into interstitium [min-1]
k_3	Interstitium transport rate into plasma [min-1]
k_{d1}	Rate of loss from interstitium [min-1]
kd	Rate of diffusive loss from hexameric and dimeric
$u_{m,gla}(t)$	Glargine dimer/monomer state insulin input
m_b	Body Mass [kg]

Insulin-Glucose Model:

$$\dot{I}(t) = \frac{-nI(t)}{1+\alpha_I I(t)} + \frac{k_{di}x_i(t)}{m_b V_{xi}} + \frac{u_{ex}(t)}{V_i} \quad (5)$$

$$\dot{Q}(t) = -kQ(t) + kI(t) \quad (6)$$

$$\dot{P}1 = -d_1 P1 + D(t) \quad (7)$$

$$\dot{P}2 = -\min(d_2 P2; P\max) + d_1 P1 \quad (8)$$

$$P(t) = \min(d_2 P1, P\max) \quad (9)$$

$$\dot{G}(t) = -p_G G(t) - S_I G(t)\frac{Q(t)}{1+\alpha_G Q(t)} + \frac{EGP - CNS + d_2 P2(t)}{V_G} \quad (10)$$

where all variables in Equations (5)-(10) are defined in Table 2:

Table 2: Description of Insulin-Glucose Model Parameters.

G	Total plasma glucose [mmol/L]
I	Plasma insulin [mmol/L]
Q	Interstitial insulin [mU/L]
EGP	Endogenous glucose production [mmol/min]
pG	Glucose clearance [1/min]
S_I	Insulin sensitivity [L/(mU.min)],
u_{ex}	Exogenous insulin input [mU/min]
D	Enteral dextrose infusion
$P1$	Represents stomach [mmol/min]
$P2$	Represents gut [mmol/min]
P	Glucose appearance [mmol/min]
n	Decay rate of insulin from plasma [1/min]
k	Effective life of insulin in the system
d_1	Transport rate [1/min]
d_2	Transport rate [1/min]
α_G	Saturation of insulin-dependent glucose clearance [L/mU]
α_I	Saturation of plasma insulin disappearance [L/mU]
V_G	Glucose distribution volume [L]
V_I	insulin distribution volume [L]

III. METHOD

Table 3 shows the details for 30 patients chosen from the SPRINT cohort [3]. Males are 70% of patients. Median age of these patients is 53.5 [IQR: 44,73] years old. Median APACHE II score is 18 with IQR=[12,19]. The average length of stay is 6.6 days (Range: 5.6-10 days). Mortality is 0 for the selected patients. The effectiveness of Glargine for blood glucose control is assessed in silico.

Glargine is intended for patients recovering from critical illness, for whom metabolic homeostasis had been regained. Patients selected for simulation are those who exhibit metabolic stability within 30 hours of ICU admission. Metabolic stability is defined:

- Hourly insulin boluses ≤ 3U for at least 12 hours.
- Hourly feed rate of ≥60% of individual patient's goal feed rate.

Time-varying insulin sensitivity, SI was fitted hourly to clinical patient data using Equations (5)-(11) and an integral fitting method [4]. Constraints are placed on SI to ensure a physiologically valid range. The resulting time-varying SI profiles represent time-varying metabolic status for individual patients. Thus, these profiles of SI can act as clinically validated virtual patients for testing different glycaemic control protocols [5].

Table 3: Long-term virtual trial patient cohort (N=30, 4,420 total hours equivalent to 184.2 day)

Patient ID	Length of Stay (hr)	Medical Group	APACHE 11 Score	Age	Sex
5006	161	Respiratory	23	44	F
5013	90	Respiratory	18	56	F
5033	100	Trauma	29	66	F
5054	158	Respiratory	18	75	M
5060	271	Gastrointestinal	15	79	M
5061	140	Trauma	16	22	M
5071	107	Trauma	12	49	M
5076	240	Gastrointestinal	12	32	M
5086	127	Respiratory	32	64	M
5101	280	Neurological	19	50	M
5104	113	Trauma	18	18	M
5122	159	Trauma	19	73	M
5124	147	Respiratory	16	74	M
5149	325	Surgical	21	60	M
5158	103	Neurological	22	68	F
5173	295	Respiratory	19	67	F
5188	129	Trauma	14	73	F
5207	155	Respiratory	19	42	F
5233	39	Gastrointestinal	16	76	M
5276	87	Septic Shock	18	18	M
5279	85	Trauma	18	45	M
5280	141	Trauma	18	45	M
5288	77	Meningococcus	23	21	F
5299	103	Respiratory	20	56	F
5310	34	Neurological	19	60	F
5315	196	Respiratory	18	19	M
5317	136	Toxicology	19	23	M
5322	136	Respiratory	15	72	F
5351	166	Respiratory	12	76	M
5376	120	Surgical	16	56	F

Virtual trials are performed using SPRINT with daily (24 hours) doses of Glargine, where the first dose is given 12 hours after ICU admission. The initial Glargine bolus is the sum of SPRINT insulin boluses administered during the previous 12 hours. The following Glargine boluses are calculated as being half

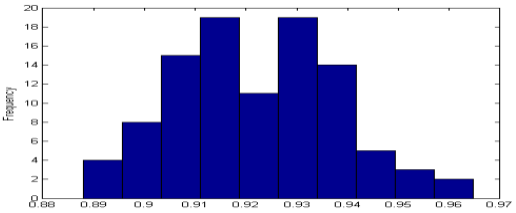
of the total daily insulin (IV boluses + Glargine) from the previous day. Each bolus is capped at 40U for safety against hypoglycaemia.

The SPRINT-1U+Glargine protocol seeks to use Glargine, gradually replacing intravenous insulin. As noted, it is a first step and protocol towards developing a complete, more final solution.

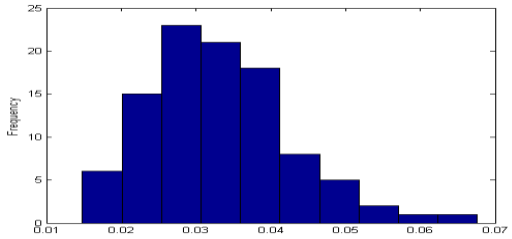
A. Monte Carlo Error

For each patient, 100 simulations were performed to generate statistics on performance. Each virtual trial had added sensor noise simulated to be normally distributed with a standard deviation of 5%, and max error of ±4 standard deviations, with a saturated max of ±20%. The latest generation of glucose meters is more advanced with greater accuracy [6]. In addition, subcutaneous Glargine absorption variability was added. Hence, the error simulated is typical of today's devices or slightly larger.

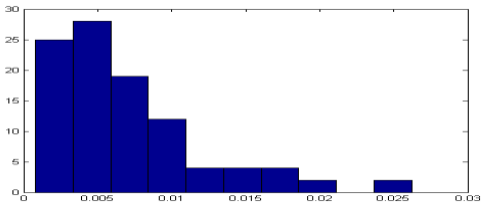
The parameters , $k_{prep,gla}$, $k1gla$, and αgla are Glargine pharmacokinetics parameters varied to generate a range of valid possible values of maximal plasma insulin concentration, Cmax and time to maximal plasma insulin, Tmax, as reported in literature. Using a lognormal distribution in the Glargine model parameters eliminates non-physiological negative values, as shown in Fig. 2.



(a) α_{gla}



(b) $k_{prep,gla}$



(c) $k_{1,gla}$

Figure 2: Histogram plot of the actual variability of Glargine pharmacokinetics parameters, $k_{prep,gla}$, $k1gla$, and αgla, and the frequency they occurred in the 100 Monte Carlo simulations for Patient 5376.

This work is sponsored in part by UNITEN.

Thus, variability is accounted for in Glargine PK parameters and glucose sensor error. There are 3000 simulations in total (30 patients X 100 simulations), each being unique due to different random errors generated. Simulated error reflects the clinical variability, which gives a realistic feature to assess the model based control protocol. The main assessments taken into account are accuracy and repeatability. Safety and performance are the two primary criteria of the controller, evaluated by avoidance of hypoglycaemia (<2.2mmol/L), median and IQR of blood glucose measurements, percentage in desired band (4.0-6.1mmol/L, 4.0-7.0mmol/L), amount of insulin prescribed (IV boluses+Glargine), amount of nutrition given, and nursing effort intensity based on the number of interventions required.

IV. RESULTS

Table 3 shows the results of Monte Carlo simulations for the 30 patients' cohort. The result of each MC performance measurement is almost similar to the non error simulations. The primary overall result is that the variations and errors considered do not appear to have any great impact on the protocol design or its ability to manage patient's variability. It is important to note that median (IQR) results in Table 3 show the middle, much more likely the, 50% of the results. Hence, this result should hold as a general trend across a wide range of possibilities. This Monte Carlo virtual analysis result is parallel with Monte Carlo analysis of SPRINT and other protocols using clinically validated virtual patients, which revealed little difference with added measurement error. Overall, it can be concluded that the robustness of the SPRINT-1U+Glargine protocol in a noisy clinical environment is validated with this Monte Carlo analysis.

Table 3: Per-patient performance measurement with and without Monte Carlo

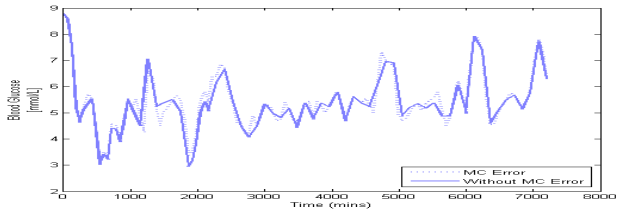
Performance	MC Error	Without MC Error
BG mmol/L	5.65 [IQR:5.27-6.16]	5.62 [IQR:5.12,6.28]
% Time band 4-6.1	65 [IQR:55.12,72.72]	66.12 [IQR:57.14,74.21]
% Time Band 4-7.0	87.19 [IQR:81.39,89.84]	86.46 [IQR:83.88,90.65]
Nursing Effort	36 [IQR:34,38]	36 [IQR:34,38]
Total Insulin U/day	70.8 [IQR:61.67,74.47]	71.2 [IQR:62.5,75.07]
Glargine Daily U\day	35.84 [IQR:32.03,36.81]	35.91 [IQR:32.11,36.84]
IV Daily U/day	37.23 [IQR:28.41,40.11]	35.20 [IQR:29.11,40.97]
Feed Gram/day	109.87 [88.29,145.19]	109 [IQR:78.45,125]
Hypo	0	0

Figure 3 is the BG profile comparison for a sample patient with median of 100 MC simulations against the simulations without introduced error. This sample

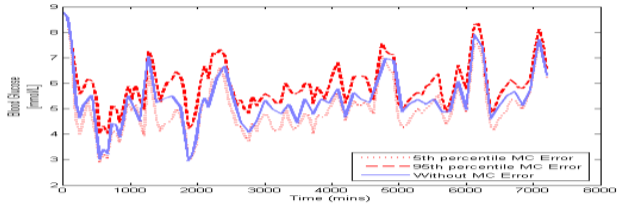
patient is representative of the cohort. Both resulting BG profiles are almost similar as expected, since the median would be expected to be as similar as possible to the actual profile overall possible random variations and errors. The largest differences would be seen at the 5th and 95th percentile. Hence, an upper and lower envelope representing the 5th and 95th percentile of all possible blood glucose concentration is shown in Figure 3(b). The 5th and 95th percentile range are quite tight particularly towards the end of Patient 5376's stay from 6000 to 7500 mins. The results also show that BG values are more varied between the values of 3-6 mmol/L, where the biggest difference between the 95th percentile range and median MC simulations could be seen around 1500-5500 mins.

V. DISCUSSION

Monte Carlo simulations allow sensor errors to be generated in the data, as well as adding valid physiological variances. Both are instrumental in portraying the real and potentially quite different physiological conditions of patients, which mix with sensor errors to yield the glycaemic variability observed clinically. In particular, in any clinical environment, a validated in silico virtual patient environment offers the ability to include the effect of parameter uncertainty and sensor error in the virtual simulations. The specific Monte Carlo results presented confirm the robustness of SPRINT-1U+Glargine protocol to realistic, physiological variations and sensor errors. The results clearly define, quantitatively the impact of variability across the cohort and for individual patients. Finally, the results provide a qualitative measure robustness and confidence in the developed protocol.



(a) Median MC Error



(b) Without MC Error

Figure 3. Comparison of BG profile for Patient 5376 simulated 100 runs with and without error. Figure 7.3(a) compares the actual BG profile in solid blue line, (-) against median of 100 MC error runs shown as blue dotted line, (⋯). Figure 7.3(b) compares the actual BG profile depicted in solid blue line (-) against the 5th and 95th percentile of 100 MC error. The 5th percentile error is shown in red dotted line, (⋯) while 95th percentile error is in red dashed line (- -).

VI. CONCLUSION

An effective, robust and safe subcutaneous transition protocol is presented. In-silico analysis accurately quantified nursing effort and performance. Monte Carlo analysis was used to test the robustness of the control protocol and robustness is achieved with the ability of the control protocol accounting for possible BG concentrations and variations of Glargine absorption. In particular, the middle 50% of likely outcomes indicates that there is no change of clinical significance in control quality and nursing effort. The 5-95% range shows that safety and acceptable control quality are guaranteed. Overall, the results meet the primary goal of the analysis to justify a clinical pilot study to validate these in-silico results.

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