

# Modeling the variability of insulin sensitivity during the menstrual cycle in women with type 1 diabetes to adjust open-loop insulin therapy

Jenny L. Diaz C.<sup>1</sup>, Eda Cengiz<sup>2</sup>, Marc D. Breton<sup>1</sup> and Chiara Fabris<sup>1</sup>

**Abstract**—Women with type 1 diabetes (T1D) typically experience a decrease in insulin sensitivity (SI) during the second half of their menstrual cycle (or the luteal phase (LP)), which oftentimes is not properly addressed by insulin therapy, therefore leading to increased exposure to hyperglycemia. This study proposes a suitable way to model SI variability due to the menstrual cycle in the FDA-accepted University of Virginia (UVA)/Padova T1D Simulator, to determine to what extent the inclusion of menstrual cycle information to fine-tune insulin therapy could help improve glycemic control in the LP of the menstrual cycle. In-silico tests were performed considering different simulation scenarios, and the obtained results show that hyperglycemic excursions can be largely reduced when SI variability is taken into account for planning insulin therapy, without a relevant increase in hypoglycemic events.

## I. INTRODUCTION

Type 1 Diabetes (T1D) is a chronic disease characterized by the autoimmune destruction of pancreatic  $\beta$ -cells, resulting in absolute insulin deficiency [1]. As a consequence, individuals with T1D require life-long insulin replacement therapy, that needs to account for time-varying insulin requirements driven by multiple metabolic and psycho-behavioral factors. Incorrect insulin dosing not accurately reflecting individual insulin needs is an outstanding problem in the management of T1D, as it can lead to hypoglycemia and/or sustained hyperglycemia, which are associated to various short- and long-term health complications.

Among these factors, the menstrual cycle has been documented to complicate insulin dosing in women with T1D [2], [3]. Phases of the menstrual cycle are determined based on menses dates and can vary among individuals; usually, the follicular phase (FP) refers to the first-half of the cycle prior to ovulation while the luteal phase (LP) follows ovulation [4]. Several studies have shown that insulin requirements for women with T1D change across the menstrual cycle, with an increase in average blood glucose (BG) levels during LP as a result of decreased insulin sensitivity (SI) not correctly accounted for by insulin therapy [5], [2], [3]. These data support the need to include information about the menstrual cycle in the design of insulin therapies to correct suboptimal insulin dosing and prevent undesired hyperglycemic events as women transition to the LP of their cycle.

<sup>1</sup> Jenny Diaz, Marc Breton and Chiara Fabris are with the Center for Diabetes Technology, University of Virginia, Charlottesville, VA, USA {mut4vm, mb6nt, cf9qe}@virginia.edu

<sup>2</sup>Eda Cengiz is with the Division of Pediatric Endocrinology and Diabetes, Yale University School of Medicine, New Haven, CT, USA b.d.researcher@ieee.org

In this study, an in-silico analysis was performed to determine to what extent including menstrual cycle information to tune insulin therapy could help maintain BG at desired levels throughout the menstrual cycle, in women with T1D on open-loop insulin therapy based on continuous subcutaneous insulin infusion (CSII). For this purpose, the FDA-accepted University of Virginia (UVA)/Padova T1D Simulator [6] was deployed, which consists of a fully-identified maximal model of glucose metabolism in T1D and a virtual population of 100 adult subjects displaying key metabolic behaviors observed in the general population of individuals with T1D. The simulation platform was modified to include a monthly SI variability profile modeled based on real-world data from euglycemic clamps performed in the FP and LP of the menstrual cycle in women with T1D. Relying on this modified environment, the analysis compared glycemic control obtained across the menstrual cycle using standard open-loop insulin therapy and open-loop insulin therapy informed by menstrual cycle-related SI variability, showing that the latter approach improves glycemic outcomes in simulation.

## II. METHOD

### A. Clinical Data

Clinical data used in this work were collected during 5-hour euglycemic clamp experiments conducted in 14 women with T1D at the Yale-New Haven Hospital Research Unit (New Haven, CT, USA). The clamp experiment was performed twice for each study participant, once during the FP of the menstrual cycle and once during the LP. Subjects were admitted on the evening before the clamp to monitor BG levels, and fasted overnight and throughout the clamp study. At the beginning of the clamp, subjects received a bolus of rapid-acting insulin analog (insulin aspart or lispro) at 0.2 U/kg of body weight via their insulin pump; simultaneously, basal insulin infusion was suspended. During the clamp, BG levels were measured every five minutes and were used to adjust the 20% dextrose infusion to maintain BG levels between 90 and 110 mg/dL; this variable glucose infusion rate (GIR) was recorded every time an adjustment was made. In addition, plasma insulin levels were measured every 10 minutes. As GIR represents the amount of glucose a person needs to maintain euglycemia in response to an insulin load, its values are indicative of the level of a person's SI.

### B. Reproducing Clinical Data in Simulation

The clamp experiments were reproduced within the UVA/Padova T1D Simulator following the same protocol used in the study. GIRs capable of generating BG traces

matching the experimental data were simulated for both phases of the menstrual cycle. These GIR signals were then compared to the GIR data from the study, to assess whether the overall SI of the virtual population matched more closely the SI levels observed in the FP or in the LP.

To reproduce the clamp studies, the distributions of BG levels at the beginning of the experiments were described using ad-hoc probability density functions (PDFs); distributions characterized by the identified PDFs were then randomly sampled to assign an initial BG value to each virtual subject for each clamp experiment. Similarly, for each subject, a BG setpoint was randomly selected from a uniform distribution with support 90-110 mg/dL. Then, to compute GIR every five minutes, a proportional-integral (PI) controller was tuned for each phase of the cycle. Based on the difference between BG setpoint ( $SP_{BG}$ ) and current BG measurement ( $M_{BG}$ ), GIR was adjusted every five minutes according to:

$$GIR(k) = K_p e(k) + K_i \sum_{j=1}^k e(j) t_s, \quad (1)$$

where  $k \in \mathbb{Z}_{\geq 0}$  is the discrete-time index,  $e(k) = SP_{BG}(k) - M_{BG}(k)$ ,  $t_s = 5$  min is the sampling time, and  $K_p$  and  $K_i$  are the proportional and integral gains of the controller, respectively. The controller gains were determined to fit the experimental data, by solving an optimization problem that matches the distribution of the simulation results ( $\bar{y}$ ) to the distribution of the BG traces collected during the clamps ( $y$ ):

$$\begin{aligned} \min_{K_p, K_i} \quad & w_1 (\Delta \bar{y}_M)^2 + w_2 (\Delta \bar{y}_{25})^2 + w_3 (\Delta \bar{y}_{75})^2 + w_4 \Delta GIR^2 \\ \text{s.t.} \quad & K_p, K_i \in [0 \ 5], \end{aligned} \quad (2)$$

where  $\Delta \bar{y}_i = \bar{y}_i - y_i$ , subscripts  $M$ ,  $25$ , and  $75$  indicate the across-subject median,  $25^{th}$  and  $75^{th}$  percentiles of BG traces,  $\Delta GIR$  is the first-order differences of GIR penalized to reduce oscillations in the control action, and  $w_i$  are weights defined to penalize deviations from the median more heavily than deviations from the percentiles.

### C. Modeling SI Variability Due to the Menstrual Cycle in the UVA/Padova Simulator

SI variability across menstrual cycle was determined based on the GIR data from the clamp experiments. Specifically, the average area under the GIR curve (AUGIR) was considered for both phases of the cycle to compute the relative variation in SI ( $RV_{SI}$ ) from one phase to the other as:

$$RV_{SI} = \frac{AUC_{Ph2}}{AUC_{Ph1}}. \quad (3)$$

Once the virtual population in the simulator is determined to be representative of a certain phase of the menstrual cycle, this phase is set as the baseline phase (i.e.,  $Ph1$ ) to model SI variability within the UVA/Padova Simulator. Thus, a profile starting with no modulation during  $Ph1$  and then modulating by  $RV_{SI}$  in  $Ph2$ , is generated and embedded within the simulation environment to multiply the SI-related model parameters. These parameters in the UVA/Padova Simulator relate to insulin action on the liver, and insulin-dependent glucose utilization for both fasting and postprandial states.

For the design of the SI variability profile, suitable values for the length of the menstrual cycle and its phases, the transition day between phases, and the number of ovulation days, were determined based on the literature [2]. Transitions between phases and cycles in the profile were modeled using sigmoid functions with the day of the menstrual cycle as the independent variable and a return value between 1 and  $RV_{SI}$ . The inter-phase transition (four days) was set from the late FP to the early LP encompassing the ovulation days; the inter-cycle transition (five days) was defined during the LP.

### D. In-Silico Studies

In-silico studies were designed to assess the ability of open-loop insulin therapy based on CSII to handle SI variability due to the menstrual cycle. CSII therapy includes basal and bolus insulin. Basal insulin is supplied in the form of a continuous infusion (basal rate ( $BR$ )) to cover overnight and fasting periods. Bolus insulin is given when food is consumed to minimize postprandial glucose excursions, in the form of a meal bolus ( $MB$ ) to cover for meal carbohydrates and correction bolus ( $CB$ ) to correct for glucose deviating from the desired target BG ( $BG_{Tg}$ ).  $MB$  and  $CB$  are computed as  $MB = \frac{CHO}{CR}$  and  $CB = \frac{BG - BG_{Tg}}{CF}$ , where  $CHO$  is the amount of meal carbohydrates, and  $CR$  and  $CF$  are the carbohydrate-to-insulin ratio and the correction factor parameters used to calculate the insulin dose.  $BR$ ,  $CR$ , and  $CF$  are daily profiles providing individual insulin dosing parameters, which are periodically tuned by the health care provider based on the retrospective analysis of BG, insulin, and food intake data.

Two simulation studies were performed: 1) including variability in SI driven by the menstrual cycle; 2) including variability driven by the menstrual cycle and adding Dawn phenomenon, and circadian intra- and inter-day SI variability according to real-world data [6]. For each study, three simulation scenarios were performed, differing based on how insulin was dosed. In the first scenario (SS-1),  $BR$ ,  $CR$ , and  $CF$  were not modified to account for menstrual cycle-related SI variability, and the dosing parameters built in the simulator for each subject were used throughout the study. In the second scenario (SS-2), SI variability across the menstrual cycle was used to inform insulin therapy, by modifying  $BR$ ,  $CR$ , and  $CF$  during  $Ph2$  as follows:

$$CR_{Ph2} = CR_{Ph1} RV_{SI}, \quad (4)$$

$$CF_{Ph2} = CF_{Ph1} RV_{SI}, \quad (5)$$

$$BR_{Ph2} = BR_{Ph1} \frac{1}{RV_{SI}}, \quad (6)$$

where  $BR_{Ph1}$ ,  $CR_{Ph1}$ , and  $CF_{Ph1}$  are the dosing parameters built in the simulator, and  $BR_{Ph2}$ ,  $CR_{Ph2}$ , and  $CF_{Ph2}$  are modified according to the SI changes observed from one phase to the other summarized by  $RV_{SI}$ . Finally, in the third scenario (SS-3), insulin dosing was informed by the SI variability as in SS-2, but, in this case, the modulation of the dosing parameters was not predetermined according to  $RV_{SI}$ , while it was optimized to achieve desired glycemic outcomes. To this end, the virtual population was divided into

training (15 subjects) and testing (85 subjects) sets. Then, an  $\alpha$  factor that corrects  $RV_{SI}$  defining  $RV_{SI}^{Opt} = \alpha RV_{SI}$ , was determined by solving the following optimization problem:

$$\begin{aligned} \min_{\alpha} \quad & \beta TBR + TAR \\ \text{s.t.} \quad & \alpha \in [0.7 \ 2]. \end{aligned} \quad (7)$$

The optimization problem in (7) was solved by an iterative process in which the  $\beta$  factor was increased until an optimal  $\alpha$  was achieved that yielded similar TBR values for both FP and LP. For this purpose, the  $\beta$  factor was initialized as the ratio between TAR and TBR obtained in SS-2 and, variations of 0.5 above and below the initial value were tested.

All simulations were performed over four menstrual cycles (112 days). Three meals per day were included in the simulations, with amounts randomly selected from a uniform distribution in the range [40 70] grams of CHO, and timing selected from uniform distributions in the range [06:00 09:00], [12:00 14:00], and [18:00 20:00] for breakfast, lunch, and dinner, respectively. For each subject, meals were different across days but were the same for all the scenarios and studies. In addition, hypoglycemia treatments were administered any time BG levels fell below 60 mg/dL.

### E. Glycemic Outcomes

All glycemic outcomes were computed based on the simulated BG. Established metrics quantifying the quality of glycemic control were calculated, including: percent time spent in the target range of 70-180 mg/dl (TIR), percent time spent in hyperglycemia  $>180$  mg/dL (TAR), and percent time spent in hypoglycemia  $<70$  mg/dL (TBR). Additional outcomes are average of BG levels, time spent in 70-140 mg/dL,  $<50$  mg/dL, and  $>250$  mg/dL, and the number of given hypoglycemia treatments. All results are presented as mean value  $\pm$  standard deviation (SD).

## III. RESULTS

### A. SI Variability Due to the Menstrual Cycle

A comparison between clamp data and results obtained by reproducing the clamp experiments in simulation is presented in Figure 1. As visible, the envelope of GIR traces required to maintain BG levels during the clamp for the virtual subjects, matches well the experimental GIR data in the FP, while it is not a good representation of the LP data. Based on this, the virtual population was assessed to show SI levels comparable to those observed in the FP, the FP was set as the baseline phase (i.e.,  $Ph1$ ) for the following computations, and the SI was modeled to adequately represent the behavior during LP.

From the data,  $AUCGIR_{Ph2} = 46.146$  and  $AUCGIR_{Ph1} = 74.821$ ; therefore, according to (3),  $RV_{SI} = 0.617$ . This result means that during the LP, SI decreases by about 40% as a result of hormonal changes during the menstrual cycle. Based on these results, the profile of SI variability throughout a menstrual cycle is designed starting in the FP with a value of 1. Then, from the late FP to the early LP, the profile gradually reduces to reach  $RV_{SI} = 0.617$  in the LP. Finally, during the late LP, the profile gradually increases to go back to no modulation in the FP (see Figure 2).

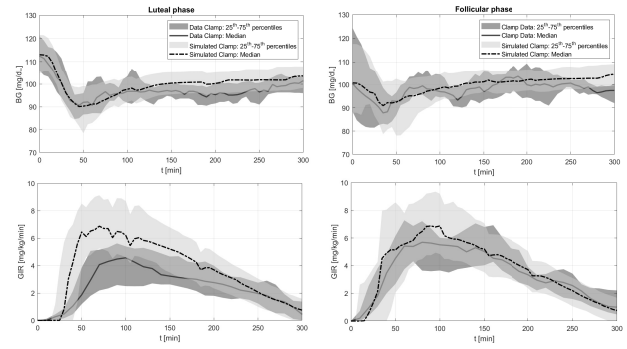


Fig. 1: Comparison between clamp data and results obtained by reproducing the clamp experiments in simulation.

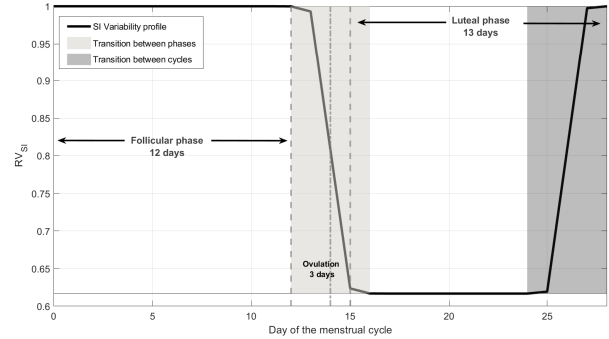


Fig. 2: SI variability profile across the menstrual cycle.

### B. In-Silico Study 1: Insulin Therapy with Menstrual Cycle SI Variability

Optimal  $\beta$  for SS-3 resulted to be 4, which led to  $\alpha = 1.077$ . Thus, optimal modulation of insulin therapy to be deployed in SS-3 was computed as  $RV_{SI}^{Opt} = \alpha RV_{SI} = 0.664$ . Glycemic outcomes obtained in Study 1, for all simulation scenarios, are presented in Table I. The following comparisons describe SS-1 vs. SS-2 vs. SS-3, unless otherwise specified, and focus on the LP (insulin therapy during the FP was the same across all scenarios). TIR was higher in SS-2 and SS-3 than in SS-1 ( $52.1\% \pm 19.8\%$  vs.  $88.8\% \pm 11.9\%$  vs.  $87.5\% \pm 13.3\%$ ). TAR was lower in SS-2 and SS-3 than in SS-1 ( $47.8\% \pm 19.8\%$  vs.  $8.7\% \pm 12.1\%$  vs.  $11.8\% \pm 13.3\%$ ). TBR was lower in SS-1 than in SS-2 and SS-3 ( $0.1\% \pm 0.2\%$  vs.  $2.4\% \pm 3.3\%$  vs.  $0.7\% \pm 1.3\%$ ). Differences in TIR and TAR between FP and LP were lower in SS-2 and SS-3 than in SS-1 ( $39.4\% \pm 0.2\%$  vs.  $3.2\% \pm 0.1\%$  vs.  $4.6\% \pm 0.1\%$  and  $-40.1\% \pm 0.2\%$  vs.  $-1.5\% \pm 0.1\%$  vs.  $-4.7\% \pm 0.1\%$ ). The difference in TBR between FP and LP was the lowest in SS-3 ( $0.7\% \pm 0.03\%$  vs.  $-1.7\% \pm 0.07\%$  vs.  $0.01\% \pm 0.03\%$ ).

### C. In-Silico Study 2: Insulin Therapy with Menstrual Cycle and Circadian SI Variability

When Dawn phenomenon and circadian variability in SI parameters is considered, by using  $\beta = 3.5$ ,  $\alpha = 1.130$  was obtained by solving the optimization problem in (7). Glycemic outcomes obtained in Study 2, for the three simulation scenarios, are presented in Table II. Similarly to Study

TABLE I. Glycemic outcomes for in-silico study 1.

	SS-1 - 100 subj			SS-2 - 100 subj			SS-3 - 85 subj		
	Overall	FP	LP	Overall	FP	LP	Overall	FP	LP
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Glucose mg/dL	155.13 (47.78)	128.39 (33.18)	181.88 (45.11)	128.27 (34.12)	127.58 (32.75)	128.97 (35.41)	132.19 (34.15)	127.45 (32.63)	136.94 (34.97)
% time <50 mg/dL	0.00 (0)	0.00 (0)	0.00 (0)	0 (0.01)	0.00 (0)	0 (0.03)	0.00 (0)	0.00 (0)	0.00 (0)
% time <70 mg/dL	0.39 (0.93)	0.72 (1.83)	0.05 (0.21)	1.58 (2.27)	0.75 (1.85)	2.42 (3.33)	0.7 (1.33)	0.71 (1.69)	0.7 (1.28)
% time [70 140] mg/dL	41.79 (10.73)	65.7 (13.16)	17.89 (12.69)	65.23 (13.83)	66.74 (13.53)	63.72 (14.62)	62.06 (13.09)	66.79 (13.66)	57.33 (13.4)
% time [70 180] mg/dL	71.86 (13.21)	91.58 (10.63)	52.13 (19.83)	90.43 (11.03)	92.01 (10.43)	88.84 (11.93)	89.82 (11.72)	92.14 (10.43)	87.5 (13.33)
% time >180 mg/dL	27.76 (13.01)	7.7 (10.48)	47.81 (19.8)	7.99 (11.09)	7.24 (10.29)	8.74 (12.06)	9.48 (11.6)	7.14 (10.23)	11.81 (13.28)
% time >250 mg/dL	3.74 (5.9)	0.18 (0.83)	7.31 (11.27)	0.26 (1.2)	0.16 (0.76)	0.36 (1.66)	0.29 (1.11)	0.12 (0.52)	0.46 (1.76)
Num Hypo Treat	1 (6)	0 (1)	0 (1)	14 (26)	0 (2)	0 (2)	4 (10)	0 (1)	0 (1)

TABLE II. Glycemic outcomes for in-silico study 2.

	SS-1 - 100 subj			SS-2 - 100 subj			SS-3 - 85 subj		
	Overall	FP	LP	Overall	FP	LP	Overall	FP	LP
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Glucose mg/dL	165.88 (53.27)	138.9 (38.78)	192.85 (52.11)	140.84 (41.93)	138.12 (38.55)	143.57 (44.89)	144.44 (42.31)	138.43 (38.49)	155.12 (45.42)
% time <50 mg/dL	0.02 (0.06)	0.04 (0.12)	0.01 (0.03)	0.14 (0.24)	0.05 (0.14)	0.22 (0.4)	0.09 (0.19)	0.05 (0.14)	0.07 (0.19)
% time <70 mg/dL	0.77 (1.06)	1.39 (1.96)	0.15 (0.31)	2.1 (2.3)	1.46 (2)	2.74 (2.92)	1.58 (2.14)	1.45 (2.07)	1.31 (2.13)
% time [70 140] mg/dL	35.48 (10.19)	56.28 (13.3)	14.67 (10.36)	53.18 (13.64)	57.05 (13.45)	49.3 (14.61)	50.36 (13.2)	56.8 (13.27)	40.05 (13.85)
% time [70 180] mg/dL	63.73 (13.97)	83.47 (12.67)	43.99 (19.36)	80.88 (13.25)	83.89 (12.56)	77.88 (14.34)	79.51 (13.45)	83.78 (12.6)	72.67 (15.23)
% time >180 mg/dL	35.5 (13.66)	15.14 (12.07)	55.85 (19.32)	17.02 (12.67)	14.65 (11.93)	19.38 (13.81)	18.91 (12.73)	14.77 (11.88)	26.02 (14.65)
% time >250 mg/dL	7.46 (8.03)	0.83 (2.76)	14.1 (14.38)	1.45 (3.67)	0.78 (2.67)	2.11 (4.88)	1.76 (3.98)	0.81 (2.8)	3.33 (5.91)
Num Hypo Treat	12 (21)	2 (5)	2 (5)	41 (55)	3 (5)	3 (5)	30 (48)	3 (5)	3 (5)

1, TIR was higher in SS-2 and SS-3 than in SS-1 ( $43.99\% \pm 19.4\%$  vs.  $77.8\% \pm 14.3\%$  vs.  $75.2\% \pm 14.8\%$ ); TAR was lower in SS-2 and SS-3 than in SS-1 ( $55.8\% \pm 19.3\%$  vs.  $19.4\% \pm 13.8\%$  vs.  $23.1\% \pm 14.1\%$ ); and TBR was lower in SS-1 than in SS-2 and SS-3 ( $0.2\% \pm 0.3\%$  vs.  $2.7\% \pm 2.9\%$  vs.  $1.7\% \pm 2.4\%$ ). Differences in TIR and TAR between FP and LP were lower in SS-2 and SS-3 than in SS-1 ( $39.5\% \pm 0.3\%$  vs.  $6.1\% \pm 0.3\%$  vs.  $11.1\% \pm 0.4\%$  and  $-40.7\% \pm 0.2\%$  vs.  $-4.7\% \pm 0.2\%$  vs.  $-11.3\% \pm 0.3\%$ ). The difference in TBR between FP and LP was again the lowest in SS-3 ( $1.2\% \pm 0.9\%$  vs.  $-1.3\% \pm 0.1\%$  vs.  $0.14\% \pm 0.1\%$ ).

#### IV. DISCUSSION

Dosing insulin across phases of the menstrual cycle is a difficult task for women with T1D, due to decreased SI levels during the LP. As a consequence, the LP of the menstrual cycle is usually characterized by sustained hyperglycemia because of improper insulin replacement therapy. Based on the results obtained in this study, it appears that glycemic control can be improved during the LP of the menstrual cycle, when changes in SI are taken into account for planning insulin therapy. This translates into modulating insulin dosing parameters according to SI levels quantified through clamp studies performed in women with T1D in both FP and LP, to properly increase the aggressiveness of insulin therapy during the LP to compensate for the changing insulin requirements.

According to our preliminary analyses, modulating insulin therapy exactly based on the observed SI variability from FP to LP (i.e., by using  $RV_{SI}$ ) does not seem to be the best strategy, as it may increase hypoglycemic excursions during the LP. However, when insulin therapy is informed by means of the  $\alpha$  factor, the quality of glycemic control achieved in the LP becomes similar to the glycemic control shown in the FP, which can be considered as a reference as not impacted by menstrual cycle-related SI fluctuations. In this case, similar values for TIR, TBR, and TAR could be obtained for both phases.

Of note, the FP was taken as a reference to determine the  $\alpha$  factor in SS-3, rather than considering the entire

simulation in SS-1, because in the latter case glucose metrics are biased towards hyperglycemia due to the variability of SI parameters introduced in the simulator, without appropriate therapy adjustment. This explains why the TBR is lower in SS-1 (overall and in the LP) than in SS-2 and SS-3, and the TAR is higher in SS-1 than in SS-2 and SS-3.

#### V. CONCLUSIONS

By properly adjusting insulin therapy to account for SI variability due to the menstrual cycle, hyperglycemic excursions during the LP can be minimized and, therefore, the risk for long-term chronic complications can be mitigated in women with T1D. Future work will include assessing whether the proposed approach can improve glycemic outcomes also in the presence of closed-loop insulin therapy (i.e., the artificial pancreas). In addition, customization of the SI variability profile to take into account the specific characteristics of each subject could be investigated to develop individualized and adaptive insulin replacement strategies to be tested in future clinical trials.

#### REFERENCES

- [1] ADA, "Diagnosis and classification of diabetes mellitus," *Diabetes Care*, vol. 33, no. Supplement 1, pp. S62–S69, 2010.
- [2] S. A. Brown, B. Jiang, M. McElwee-Malloy, C. Wakeman, and M. D. Breton, "Fluctuations of hyperglycemia and insulin sensitivity are linked to menstrual cycle phases in women with t1d," *Journal of Diabetes Science and Technology*, vol. 9, no. 6, pp. 1192–1199, Oct. 2015.
- [3] L. Herranz, L. S. de Ibarra, N. Hillman, R. Gaspar, and L. F. Pallardo, "Glycemic changes during menstrual cycles in women with type 1 diabetes," *Medicina Clínica (English Edition)*, vol. 146, no. 7, pp. 287–291, 2016.
- [4] R. J. Fehring, M. Schneider, and K. Raviele, "Variability in the phases of the menstrual cycle," *Journal of Obstetric, Gynecologic & Neonatal Nursing*, vol. 35, no. 3, pp. 376–384, 2006.
- [5] D. S. Barata, L. F. Adan, E. M. Netto, and A. C. Ramalho, "The effect of the menstrual cycle on glucose control in women with type 1 diabetes evaluated using a continuous glucose monitoring system," *Diabetes Care*, vol. 36, no. 5, pp. e70–e70, Apr. 2013.
- [6] R. Visentin, E. Campos-Náñez, M. Schiavon, D. Lv, M. Vettoretti, M. Breton, B. P. Kovatchev, C. D. Man, and C. Cobelli, "The uva/padova type 1 diabetes simulator goes from single meal to single day," *Journal of Diabetes Science and Technology*, vol. 12, no. 2, pp. 273–281, 2018.