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Effects of Pulsatile Subcutaneous Injections of Insulin Lispro on Plasma Insulin Concentration Levels

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Abstract

Background:
Most insulin pumps used for the treatment of diabetes perform subcutaneous insulin injections by pulses. The purpose of this work is to analyze the effects of pulsatile injections of modern insulins on plasma insulin levels compared with a continuous insulin infusion.

Method:
We simulate pulsatile implementations of a basal rate profile over a day on a type 1 diabetes mellitus patient using insulin lispro. Pulse periods were varied between 1 and 60 min, and random pump errors were included, modeled as white noise, 1/f noise, or $1/f^2$ noise with relative standard deviations up to 10% of the pump output.

Results:
Oscillations in plasma insulin caused by the pulsatile injections were not significant with respect to the global variations for pulse periods below 15 min. This cutoff period was found to be robust to random pump errors with standard deviations up to 10% of the pump output and hence solely determined by the insulin kinetics. Additionally, we showed that the pulse period achieving the best implementation of a continuous profile is an increasing function of the error variance for a given type of noise.

Conclusions:
Our findings support that continuous insulin infusion can be implemented by a pulsatile injection of insulin as infrequent as a pulse every 15 min without significant effects on plasma insulin levels. If clinically confirmed, this result would have important consequences on the design and *in silico* testing of automated insulin treatment strategies, as increased delivery intervals imply higher accuracy of insulin delivery and facilitated implementations of closed-loop control algorithms.

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (MDI) multiple daily injections, (T1DM) type 1 diabetes mellitus

Keywords: pulsatile insulin injection, pump errors, subcutaneous insulin absorption

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Introduction

Patients suffering from type 1 diabetes mellitus (T1DM) usually inject exogenous insulin multiple times a day to maintain safe levels of blood glucose.[1,2] An alternative solution to multiple daily injections (MDI) is the use of insulin pumps that, by delivering insulin in smaller amounts but more frequently throughout the day, approximate physiological insulin secretion patterns, thereby achieving better glucose control than episodic insulin injections. There is evidence supporting the idea that normoglycemia prevents later complications to diabetes, and studies have shown a better control of blood glucose levels with continuous subcutaneous insulin infusion (CSII) over MDI.[3,4] Improved blood glucose control has been observed in patients under CSII for periods as short as 5 weeks to periods longer than 12 months.[5–8] A decreased rate of severe hypoglycemia, lower hemoglobin A1c, and no change in diabetic ketoacidosis usually follow insulin pump therapy, whether regular or lispro insulin was used.[9–11]

Most commercial pumps deliver insulin by pulses. This means that the pumps are actually not delivering a continuous flow of insulin, but rather a discrete sequence of insulin pulses aimed at approximating a continuous infusion. For instance, the Deltec Cozmo® insulin pump (Smiths Medical, St. Paul, MN) injects insulin by means of pulses every 3 min, whereas the OmniPod® insulin pump (Insulet Corporation, Bedford, MA) adapts its injection period to the insulin dose. A few clinical experiments have previously been run to assess the effects of the frequency of insulin injections on plasma insulin and blood glucose levels. Levy-Marchal *et al*. compared glycemic control with pulsed injections of regular insulin versus continuous subcutaneous infusion on T1DM subjects. Pulsatile injections every 30, 60, or 120 min in the six subjects led to no significant variations of the plasma glucose.[12] Later, Hildebrandt *et al*. used ^{125}I-labeled insulin to compare the depot size and insulin absorption rate on eight subjects and found no significant difference between 6- and 60-min pulses. Both studies therefore concluded that intermittent insulin injections, administered as infrequently as every 120 min, yield similar plasma glucose concentrations as a CSII.[13]

Through the use of labeled insulin, Hildebrandt *et al*. reduced the time interval for data collection to 15 min, but such a large time interval, inherent to clinical experiments, still does not enable a fine analysis of insulin concentration variations induced by pulsatile injections. Several studies[14–20] indicate that insulin kinetics may be fast enough to induce significant differences in plasma insulin levels between a 1 min and a 60 min pulsatile insulin injection. Modern modeling techniques and the available literature allow for detailed investigation of the influence of pulsatile insulin delivery using simulation and a mathematical model of insulin kinetics.

Several models have been developed to describe the pharmacokinetics of subcutaneously injected insulin and most acknowledge the presence of multimeric forms of insulin at the depot site—dimeric, hexameric, and bound insulin, among which only the dimeric form is assumed capable of penetrating the capillary membrane, resulting in a slow absorption at the injection site. Whereas degradation of insulin at the subcutaneous depot is not always accounted for, plasma insulin is represented by most authors as a single compartment, based on considerations relative to transport timing in major subcutaneous tissues versus in blood vessels.[14,21–24] More recent models have included the use of insulin analogs such as the rapid-acting lispro, which offers faster subcutaneous absorption and earlier and greater insulin peaks compared with regular insulin.[25,26]

Using a four compartment model, Mosekilde *et al*.[21] confirmed the clinical experiments presented by Levy-Marchal *et al*.,[12] and showed that insulin could be injected as infrequently as 30 min without a significant difference from the continuous infusion. Nonetheless, these results do not include new understandings of insulin kinetics as well as the appearance of faster modern insulins (e.g., lispro).[25–28]

The purpose of this work is to continue the study of the effects of pulsatile injections of modern fast-acting insulins on plasma insulin concentration levels and to determine the significance of the oscillations caused by the pulsatile injections with respect to the overall plasma insulin variations. Implementation of a basal rate with various pulse periods was simulated on a T1DM patient over one day, and the threshold at which injecting insulin by pulses can be confounded with a continuous infusion was determined. Random pump errors modeled by white noise, 1/f noise, and $1/f^2$ noise with relative standard deviations were included, and their effects on plasma insulin concentration levels were analyzed.

Methodology

Based on the work of Dalla Man and colleagues,[29–30] the insulin absorption model depicted in **Figure 1** was considered.

The model is composed of two submodels: one describing the transport of insulin in the blood and one describing the insulin kinetics in T1DM subjects. The model of insulin transport comprises two compartments, I_1 and I_2, expressing a slow absorption rate, and assumes that insulin is injected in the first compartment. k_d, k_{a1}, and k_{a2} are the rates at which insulin moves from the first compartment to the second compartment and is transported in the blood from both compartments, respectively. The model of insulin kinetics has two compartments representing insulin masses in plasma, I_P, and liver, I_L. m_1 and m_2 are the rates at which insulin moves between the two compartments, and m_3 and m_4 are the rates of liver and plasma insulin degradation, respectively. The plasma insulin concentration I is equal to I_p divided by the volume of insulin distribution, V_I. The model is described by the following equations:

$$\begin{cases} I_1 = -(k_d + k_{a1})I_1 + S \\ I_2 = k_d I_1 - k_{a2} I_2 \\ I_P = -(m_2 + m_4)I_P + m_1 I_L + k_{a1} I_1 + k_{a2} I_2. \\ I_L = -(m_1 + m_3)I_L + m_2 I_P \\ I = \dfrac{I_p}{V_I} \end{cases}$$

Spectral Analysis

Consider the model of insulin transport only. Rewriting the equations of the model in the frequency domain and rearranging the equations yield a transfer function that is a sum of a first- and second-order low-pass filter:

$$\frac{IRa(\omega)}{S(\omega)} = \frac{K_1}{1 + j\dfrac{\omega}{\omega_c}} + \frac{K_2}{\left(\dfrac{\omega}{\omega_0}\right)^2 - j\dfrac{\omega}{\omega_0 Q} - 1}, \text{ where}$$

$$K_1 = \frac{k_{a1}}{k_d + k_{a1}}$$

$$\omega_c = k_d + k_{a1}$$

$$K_2 = -\frac{k_d}{k_d + k_{a1}}$$

$$\omega_0^2 = k_{a2}(k_d + k_{a1})$$

$$Q = \frac{\omega_0}{k_d + k_{a1} + k_{a2}}.$$

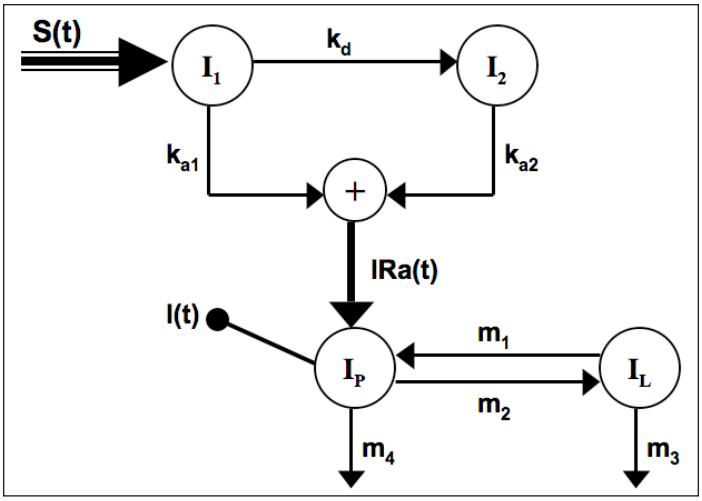

Figure 1. Subcutaneous insulin absorption model.

Consequently, the insulin transport system filters out most high-frequency variations and only carries on information contained in the low frequencies. Thus fast-changing characteristics of the secretion profile will be filtered out in the insulin rate of appearance by the frequency threshold determined in the next subsection.

Determination of the Cutoff Pulse Period

We simulated pulsatile implementations of a basal insulin injection profile over one day using the model described earlier. Population parameters for the injection of fast-acting insulin, such as lispro, were used in the model, and the basal insulin injection profile over 24 h for a T1DM patient was considered: 1.2 IU/h from midnight to 3 a.m., 1.3 IU/h from 3 a.m. to 6 a.m., 1.425 IU/h from 6 a.m. to noon, 1.4 IU/h from noon to 6 p.m., and 1.325 IU/h from 6 p.m. to midnight. Pulse periods were varied in the range of 1 to 60 min. **Figure 2** shows different pulsatile basal implementations delivering the same total amount of insulin (i.e., the longer the pulse period, the larger the insulin bolus at each pulse).

Statistical Analysis

The oscillations of plasma insulin resulting from the pulsatile injections were measured with respect to the insulin concentration profile resulting from a continuous insulin infusion. Consequently, the conclusions drawn will not be exclusive to the basal rate used in our analysis. We define the coefficient of determination R^2 as

$$R^2 = \frac{\sum\left(I_{\text{cont}}(i) - \bar{I}_{\text{cont}}\right)^2}{\sum\left(I_{\text{puls}}(i) - I_{\text{cont}}(i)\right)^2 + \left(I_{\text{cont}}(i) - \bar{I}_{\text{cont}}\right)^2},$$

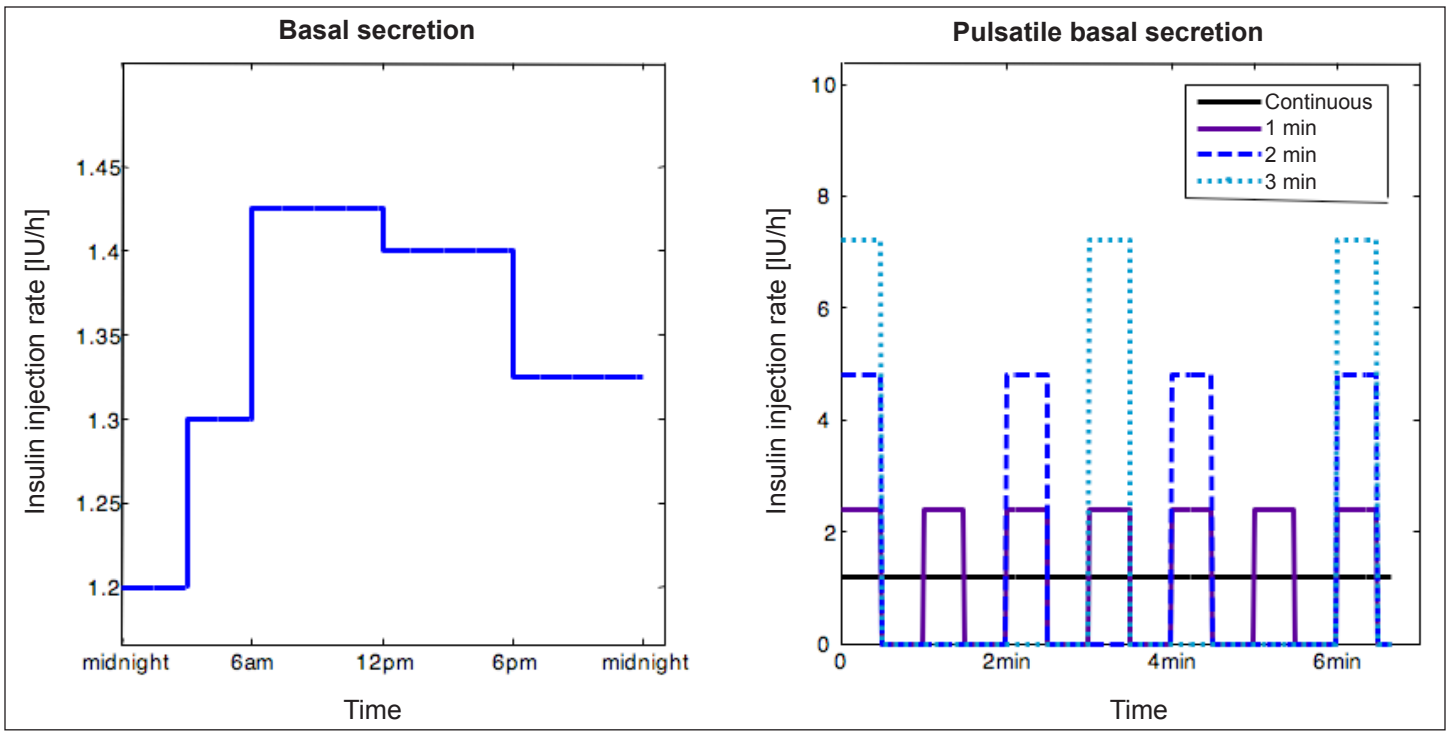

Figure 2. (**Left**) Basal rate profile over 24h. (**Right**) Pulsatile implementations of the basal rate plotted for the first 6 min.

where I_{cont} and I_{puls} are the plasma insulin concentrations after continuous infusion and pulsatile injection, respectively, and $\bar{I}_{cont}$ is the mean value of I_{cont}. The numerator represents the global variation of the insulin concentration under continuous infusion, and the denominator expresses the deviations of insulin concentration under pulsatile injection from the continuous-injection curve. When no deviation is observed, R^2 is equal to 1. As pulsatile injections yield variations in insulin concentration, R^2 decreases as the inverse of the sum of its squared deviations from the continuous-infusion concentration levels. We considered nonsignificant differences between pulsatile injection and continuous insulin infusion for R^2 greater than 0.99, i.e., for pulsatile injection resulting in variations of plasma insulin within 1% of the continuous infusion.

To assess the effects of pulsatile insulin injections on plasma insulin concentrations, Mosekilde *et al.*[21] used the peak-to-peak variation in insulin concentration over the mean concentration. For comparison purposes, we also computed this ratio.

Effects of Random Pump Errors on the Cutoff Pulse Period

To examine the effects of random pump errors on plasma insulin levels, we considered the addition of three types of noise on the pump output: white noise, 1/f noise (or pink noise), and $1/f^2$ noise (or Brownian noise). These noises are characterized by their power spectral density. White noise has a flat power spectral density and thus has constant energy at all frequencies. Conversely, 1/f noise has a power spectral density decreasing at the rate of the inverse of the frequency and has constant energy per constant percentage bandwidth. Lower frequencies thus contain more energy than higher ones. Similarly, $1/f^2$ noise has a power spectral density proportional to the inverse of the squared frequency and therefore has even more energy at lower frequencies than 1/f noise. 1/f and $1/f^2$ noises (and more generally, any type of noise other than white noise) are correlated over short time scales. However, $1/f^2$ noise exhibits stronger correlation over time than 1/f noise. Random errors are assumed to be positively correlated with pump output, which translates into an increased potential error with the amount of insulin injected. The error is modeled as a zero mean signal with relative standard deviation. One hundred simulations were performed for each pulse period, and the value of the relative standard deviation varied between 1 and 10% of the pump output value.

Statistical analysis

We determined the significance of the plasma insulin oscillations due to the pulsatile implementation with added random pump errors using the previously defined coefficient of determination R^2. Pulsatile implementation

of the basal rate is deemed to have nonsignificant effects on plasma insulin variations with respect to the global variations for R^2>0.99.

Furthermore, to measure the simultaneous effects of the pulse periods and errors, we introduced another index F, defined as the ratio of the sum of squared differences between the pulsatile plasma insulin and the mean continuous plasma insulin over the sum of squared differences between the continuous and pulsatile plasma insulin:

$$F = \frac{\sum\left(I_{\text{puls}} - \bar{I}_{\text{cont}}\right)^2}{\sum\left(I_{\text{cont}} - I_{\text{puls}}\right)^2}.$$

This index assesses how close the pulsatile response is from the continuous one. The larger the value of F, the closer the plasma insulin concentration resulting from the pulsatile injection is to the continuous response. The period yielding the maximum value of F represents the optimal injection period.

Results

Cutoff Pulse Period for Noise-Free Pumps

We studied the effects of pulsatile implementations of a continuous basal rate on plasma insulin concentrations at a scale down to 1 min. Using a validated and commonly accepted model of insulin kinetics, we simulated different pulsatile implementations of a continuous basal rate over one day on a T1DM patient. The population parameters of the model used to simulate insulin lispro are k_{a1}=0.002 min^{-1}, k_{a2}=0.0211 min^{-1}, k_d=0.0166 min^{-1}, m_1=0.2057 min^{-1}, m_2=0.3098 min^{-1}, m_3=0.3086 min^{-1}, m_4=0.1236 min^{-1}, and V_I=0.05 liter/kg. The plasma insulin concentration profiles resulting from a continuous insulin infusion of the basal rate and its pulsatile implementations are presented in **Figure 3**, and the values of the coefficient of determination R^2 obtained for pulses ranging from 1 to 60 min are plotted in **Figure 4**. The largest pulse period such that R^2>0.99 is 15 min, hence oscillations due to the pulses are not significant compared with continuous-infusion variations for discrete pulses up to every 15 min. The rapid changes in the injections are smoothed out by the transport system, which then produces a concentration profile comparable with continuous infusion. This is physiologically explained by the buffering role of the injection depot where insulin accumulates due to polymerization, resulting in slow absorption.

Our results show that implementations of a continuous basal rate with pulses as infrequent as 4/h can be done without a significant difference in plasma insulin concentrations. This updates the results obtained by Mosekilde *et al.* who simulated oscillations in plasma insulin concentration and found that the variations represented less than 1% of the continuous infusion for pulse periods less than 30 min. Using the same statistic for our simulations, we obtained nonsignificant oscillations for pulse periods less than 12 min,

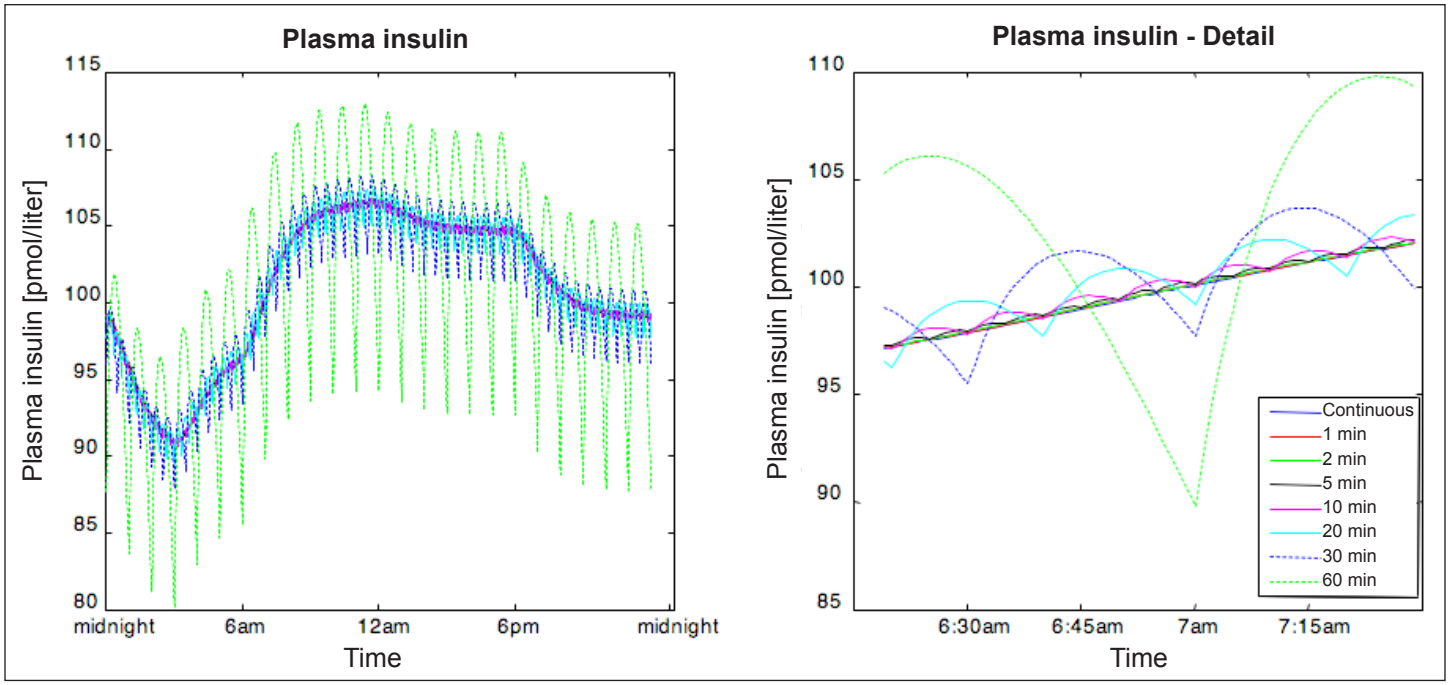

Figure 3. Effects of pulsatile insulin injections. Plasma insulin levels over 24h (**left**) and over 1h (**right**).

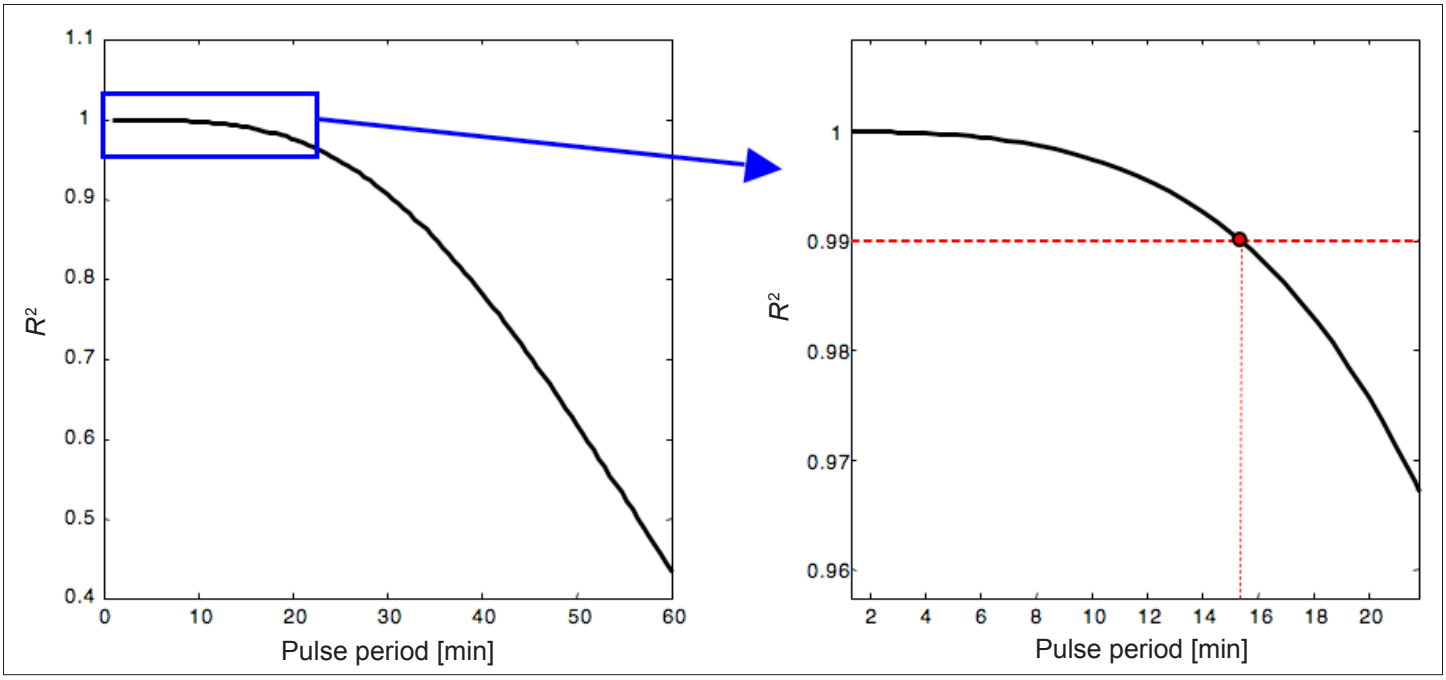

Figure 4. Cutoff pulse period at a 99% significance level.

approximately half the threshold previously obtained (**Figure 5**). This is concordant with the type of insulin used at the time; since insulin lispro is approximately twice as fast as regular insulin in terms of subcutaneous absorption, insulin peaks and postpeaks decrease, and it is natural to expect the cutoff pulse period to shorten.

Cutoff Pulse Periods with Random Pump Errors

We accounted for the effects of random pump errors on plasma insulin concentration levels by adding either white noise, 1/f noise, or $1/f^2$ noise on the pump output values. The greatest pulse period such that $R^2>0.99$ is robust to all three types of noise considered up to 10% relative standard deviation and remains equal to 15 min as shown in **Figure 6**. On the other hand, random pump errors do affect the smallest pulse period for which $R^2>0.99$. In the error-free case, all pulse periods below the cutoff value of 15 min yield an R^2 value above 0.99, meaning that a pulsatile implementation of the continuous infusion with any pulse period between 1 and 15 min results in negligible oscillations of plasma insulin compared with the main variations. With 1/f and $1/f^2$ noises, higher noise amplitude results in a higher lower bound of acceptable pulse periods, with a more pronounced effect for $1/f^2$ noise than for 1/f noise. The range of acceptable pulse periods does not change with the addition of white noise at all values of standard deviation up to 10% relative standard deviation. The robustness of the cutoff value to pump errors containing

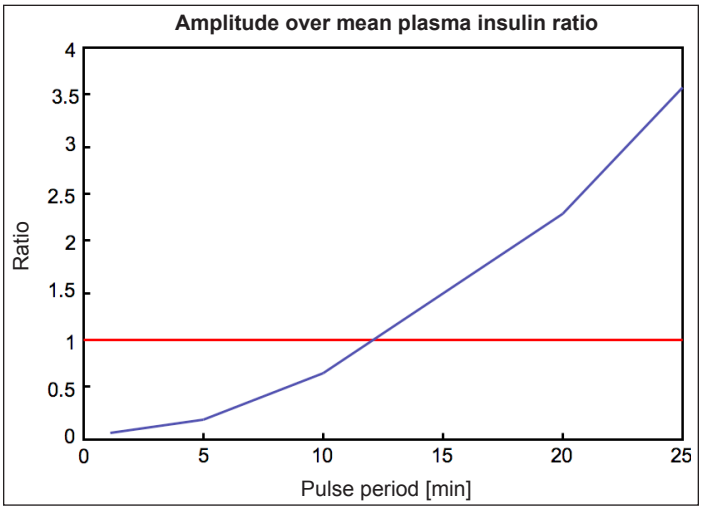

Figure 5. Ratio of the oscillations amplitude in plasma insulin over the mean plasma insulin concentration.

a high amount of low-frequencies and the low-pass nature of the insulin system provide strong basis to state that the 15 min cutoff is robust to most types of pump noise. The insulin system entirely determines the cutoff pulse period independent of insulin pump noise considerations.

Among all pulse periods yielding smooth plasma insulin levels, there exists an optimal period that achieves the closest insulin levels to continuous-infusion ones. The optimal pulse period for a given type of pump noise

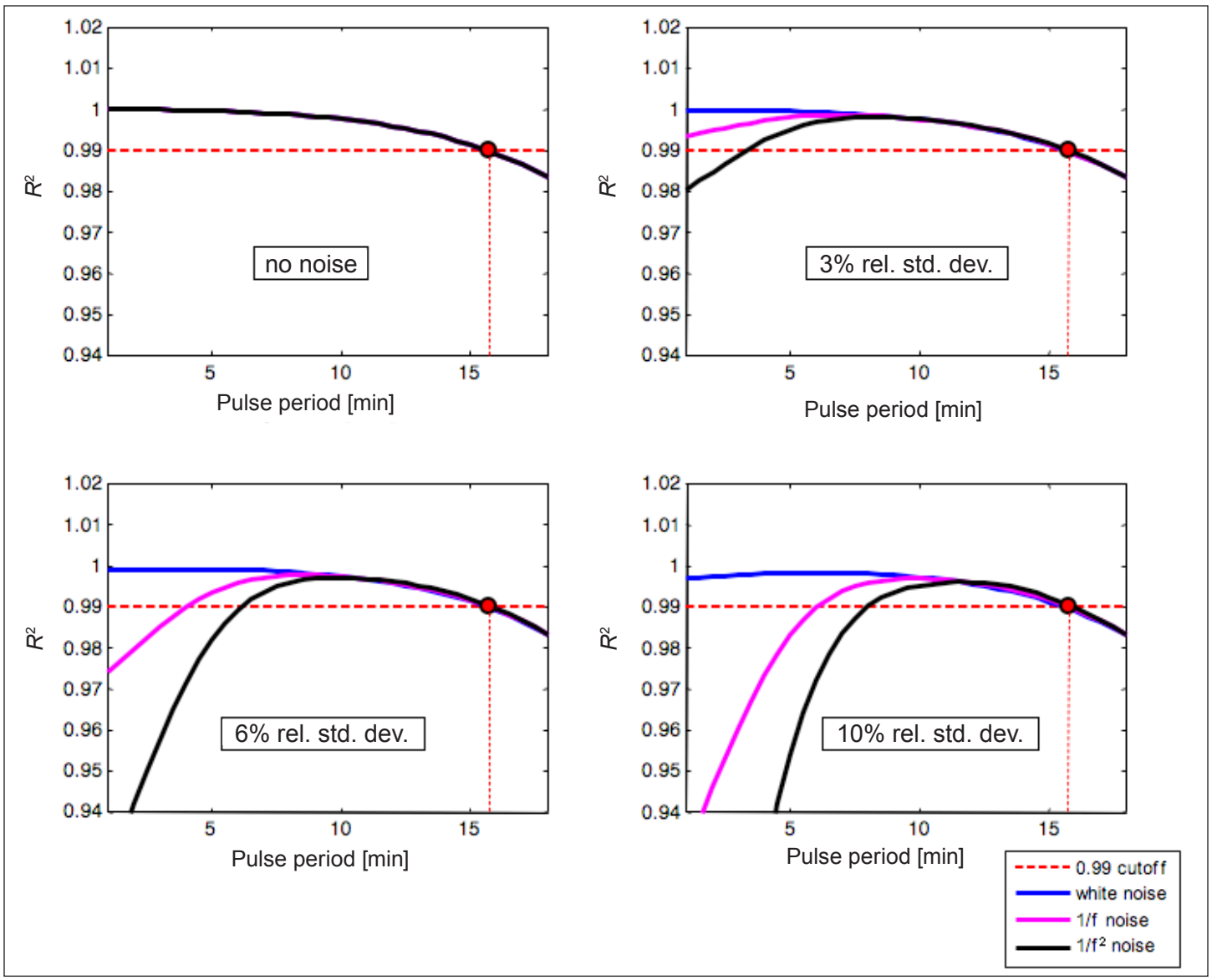

Figure 6. Effects of random pump errors on the cutoff pulse period. The R^2 values are plotted against pulse periods for different pump noise with relative variance.

is assessed by the F index. **Figure 7** (**left**) shows the F index against the pulse period for different values of the standard deviation under a white noise assumption. The curves have been normalized to obtain a maximum value equal to 1. **Figure 7** (**right**) shows the optimal injection pulse period as a function of the noise standard deviation. Similar trends are observed for the other two pump errors.

Conclusion

This study analyzes the effects of pulsatile subcutaneous insulin delivery and random errors of insulin pumps on plasma insulin levels *in silico*. We simulated plasma insulin oscillations resulting from pulsatile implementations of a daily basal injection profile with pulse periods varying from 1 to 60 min, three types of noise (white, 1/f, and $1/f^2$), and noise levels up to 10%. The oscillations created by the pulsatile insulin injection represented less than 1% of the total insulin variations for pulse periods up to 15 min. Random pump errors did not affect this cutoff pulse period.

The addition of noise did, nonetheless, reveal the existence of a pulse period threshold below which the oscillations in plasma insulin are not negligible with respect to the global variations. Whereas the 15 min cutoff pulse period is solely dependent upon the insulin system and is robust to all three types of pump noise considered up to 10% relative standard deviation, the minimum pulse

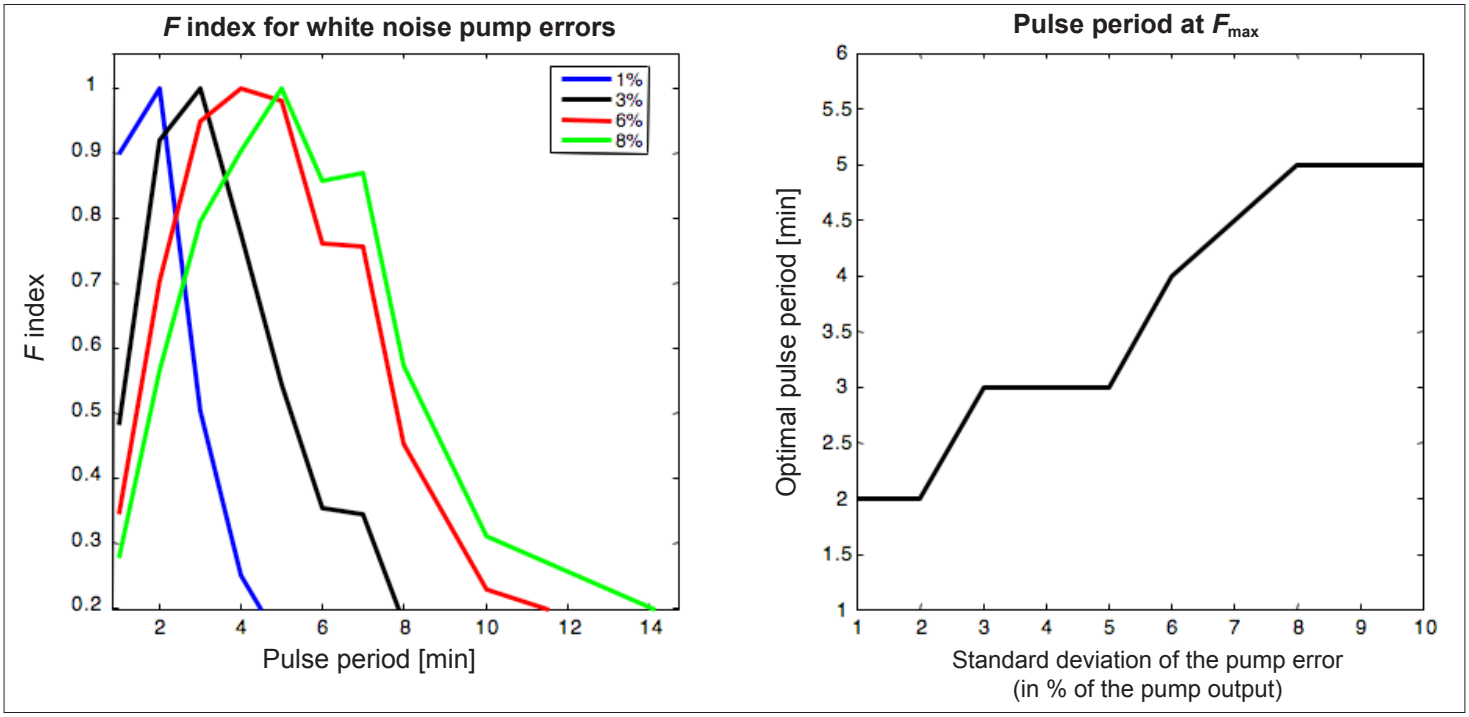

Figure 7. White noise random pump error case. (**Left**) *F* index for different values of the relative standard deviation of the pump error. (**Right**) Optimal pulse period plotted against the pump error relative standard deviation.

period yielding nonsignificant plasma insulin oscillations varies greatly with the type and amplitude of noise.

Consequently, for moderate unbiased random errors up to 10% relative standard deviation, discrete subcutaneous insulin deliveries with injection frequencies of approximately 4 pulses/h are equivalent to a continuous infusion. These results have implications for T1DM treatment, particularly in automated insulin delivery, as they indicate that discrete delivery and moderate random errors associated with most commercial insulin pumps approximate continuous infusion as long as the same amount of insulin is delivered on average. For example, the 3 min pulse interval and 3% pump error of the Deltec Cozmo pump closely reproduces a continuous infusion but would be considered suboptimal.

Furthermore, we have demonstrated that continuous insulin infusion can be implemented by pulsatile injection of insulin as infrequent as a pulse every 15 min without significant effects on plasma insulin levels similar. These results are derived from model analysis and computer simulations and still have to be verified *in vivo*. If clinically confirmed, these findings would have important consequences on the design and *in silico* testing of automated insulin treatment strategies, as it facilitates implementations of closed-loop control algorithms while still yielding smooth plasma insulin levels.

In addition, higher accuracy in insulin delivery can potentially be achieved by increasing the insulin delivery interval to its maximum when implementing continuous infusion, i.e., 15 min for insulin lispro. In effect, the standard deviation of pump errors may not be relative to the pump output exclusively but more likely to a combination of a constant and a relative component. The effects of random pump errors with constant standard deviation were assessed by repeating this analysis under a constant noise variance assumption and yielded very similar results: a very robust 15 min cutoff pulse period and a noise-dependent lower bound.

These results are not specific to the subcutaneous insulin transport model used to perform the simulations but are rather general and provide updated insights to pulsatile injections of rapid-acting insulins. The model used is based on the buffer role of the insulin depot, smoothing out the high variations of pulsatile insulin injections, which we modeled with a two-compartment model; another low-pass equivalent model of the insulin transport would yield the same results.

Finally, because implementations of continuous insulin infusion with insulin lispro, whose action time is twice as fast as regular insulin, yielded a cutoff pulse period twice as low as with regular insulin, it is then expected that with the use of more modern insulins (e.g., Viaject™,

approximately twice as fast as insulin lispro), the cutoff value will be again divided by two. More details on the action of this new insulin would be needed to evaluate the new parameters of the subcutaneous absorption model, to repeat the analysis, and to determine the new pulse thresholds.

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