Supplementary Material

1 Deviation Analysis: Technical Details

Before a new control strategy is tested in a clinical trial, it has become common practice to evaluate and adjust this new therapy scheme in simulation studies. Detailed physiological models of the glucose dynamics of diabetic patients like the UVA/Padova [1] or the Cambridge simulator [2] have become indispensable tools for this purpose and numerous publications over the last couple of years show evaluations of new control strategies using those models (e.g. [3, 4, 5]).

Even though these detailed physiological models have proven to be very valuable for the testing of new insulin dosing schemes, there are some drawbacks of using them for the performance evaluation. Most models show a time-invariant behavior[1] and are (usually) restricted to insulin and meal carbohydrates as only system inputs. This is of course a simplification of reality, where there are lots of other influencing factors that also affect the glucose level of diabetic patients (stress, sports, daytime, mixed-meal composition, etc.). Testing a new control strategy using a standard physiological model can thus lead to a significant overestimation of performance.

What is often done by users is to enhance the time-invariant models by incorporating some additional variability and/or stochastic effects in order to make the control task more challenging (see e.g. [7] or [8]). However, it is difficult to estimate the magnitude and mode of action of those additional effects from standard data, which is why those model enhancements are to some extend arbitrary and just try to imitate phenomena observed in real patient data.

Recently, several new methodologies for the testing of insulin dosing strategies have been proposed that try to combine real measurement data, i.e. continuous glucose monitoring (CGM) data and insulin injections (dose and timing) with simple (often linear) models in order to create a test environment that also incorporates the complex phenomena of real-life glucose dynamics in diabetic patients. The methodologies differ slightly, however, the basic idea is always the same: A simple model of insulin action is used together with the assumption that the effect of insulin on the glucose level can be separated from all other effects. In order to test a new control strategy the effect of the recorded insulin injections is then subtracted from the CGM data using the assumed model of insulin action and the effect of a different insulin amount (determined by the newly proposed control algorithm) is calculated using the same model of insulin action and added to the glucose data.

In this paper these methodologies are referred with the term "Deviation Analysis". As already discussed, the basic idea behind all Deviation Analysis strategies that have so far been proposed is the same. The corresponding workflow can be seen in Fig. 1: A simple model of insulin action $G_2(s)$ (in Fig. 1 assumed to be linear) is used to subtract the effect of the original insulin dosing (Ins) from the recorded glucose data (CGM) and to determine the new glucose traces ($\mathrm{CGM}_{\mathrm{mod}}$) for an alternative dosing scheme ($\mathrm{Ins}_{\mathrm{mod}}$). Assuming a linear model G_2 he new glucose trace can thus be calculated in the Laplace domain as:

$$\mathrm{CGM}_{\mathrm{mod}}(s) = \mathrm{CGM}(s) - G_2(s) \cdot \mathrm{Ins} + G_2(s) \cdot \mathrm{Ins}_{\mathrm{mod}} \tag{1}$$

The oldest paper we are aware of in which such a strategy has been proposed is [9]. In the newer publications [10] and [11] similar approaches have been presented. Recently, there have also been first publications in which evaluation results for insulin dosing strategies using Deviation Analysis are presented - most notably [12], which gained a lot of attention in the technical diabetes community, [13] (these two papers most probably use a modified version of the method presented in [11], unfortunately the papers do not give details about the Deviation Analysis strategy), as well as [14] and [15] (which use the model from [16] to describe insulin action).

[1] This is not true anymore for the Cambridge simulator [2] and the newest version of the UVA/Padova simulator [6], which include some level of *intraday variability* in selected model parameters.

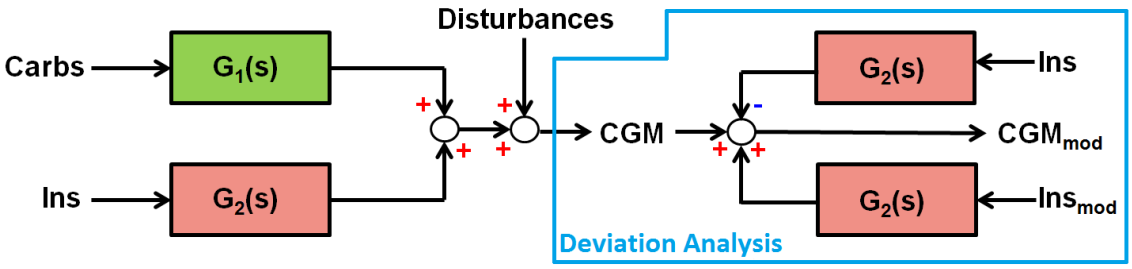

Figure 1: Deviation Analysis - Workflow for obtaining simulation results.

However, even though these Deviation Analysis strategies are rather similar, there are some significant differences, especially regarding the model used for describing insulin action (model structure and parameter values). For the current work the method described in [10] has been chosen.

In [10] the model for insulin action corresponds to a population mean pharmacodynamic profile for rapid-acting insulin scaled by a patient-specific insulin sensitivity factor (ISF). It was found that the pharmacodynamic profile in [10] can be approximated very well with a simple transfer function of third order. Scaling it in order to get a minimum in the impulse response of magnitude ISF, it reads as follows:

$$G_2(s) = \frac{-\exp(2) \cdot \mathrm{ISF}_{\mathrm{DS}} \cdot T_{\mathrm{DS}}}{2 \cdot (1 + T_{\mathrm{DS}} \cdot s)^3} \tag{2}$$

T_{DS} was determined from the plot with the assumed pharmacodynamics profile supplied in [10] to be 38.19 min. $\mathrm{ISF}_{\mathrm{DS}}$ is computed from the total daily dose (TDD) in Insulin Units (IU) using the standard 1800-rule:

$$\mathrm{ISF}_{\mathrm{DS}}\ (\text{in mg/dl/IU}) = \frac{1800}{\mathrm{TDD}} \tag{3}$$

Applying this method for the performance assessment of insulin dosing methods in T2D relies upon a couple of assumptions and simplifications:

- The effect of insulin can be separated from all other influencing factors.
- The effect of insulin on BG is assumed to be linear. As a consequence insulin works the same independently of the BG concentration and independently of the injected quantity.
- Insulin pharamcodynamics are comparable between type 2 diabetes (T2D) and type 1 diabetes (T1D) patients.

The first two assumption are inherent to almost all Deviation Analysis methods (exceptions are the nonlinear approaches proposed in [17, 18], for which the second assumption is not made). The third one is specific to [10] and is due to the fact that the insulin action profile is derived based on T1D data. Basically all three assumptions are not 100% correct from a physiological point of view, but in case of small differences compared to the recorded data the resulting error is expected to be small. The bigger the difference to the recorded data on the other hand, the bigger also the error made in the Deviation Analyses (see *e.g.* the comparison between the UVA/Padova simulator and the used Deviation Analysis approach in [10]).

2 Treatment Options: Technical Details

2.1 Pen & SMBG and Pen & CGM

For the two analyzed treatment options "Pen & SMBG" and "Pen & CGM" the basal insulin was left unchanged compared to the recorded data in the Deviation Analyses and only the bolus amount has been modified. Both considered options rely upon Advanced Carbohydrate Counting for computing the required amount of bolus insulin at each meal, which is computed according to the following formula:

$$\mathrm{BI} = \frac{\mathrm{CHO}}{\mathrm{CIR}} + \frac{\mathrm{BG_{pre}} - \mathrm{BG_{target}}}{\mathrm{ISF}} - \mathrm{IOB} \tag{4}$$

In (4) BI corresponds to the bolus insulin needs, CHO is the carbohydrate content of the meal, $\mathrm{BG_{pre}}$ is the pre-prandial BG, $\mathrm{BG_{target}}$ describes the target value for the post-prandial BG and IOB stands for insulin-on-board, *i.e.* the bolus insulin from previous injections that is still active in the body. The first term in (4) is used for counteracting the effect of the meal intake on the BG, whereas the second term is used for BG corrections. Crucial parameters for calculating the bolus needs are the proportionality factors CIR, the carbohydrate-to-insulin ratio, and ISF, the insulin sensitivity factor. CIR represents the amount of a meal's carbohydrates (in grams) whose effect is counteracted per injected insulin unit (IU) of bolus insulin, whereas ISF describes by how many mg/dl the BG level will decrease per injected IU. For these two considered treatment options patient and mealtime specific estimates for CIR and ISF have been computed using the Adaptive Bolus Calculator (ABC) approach described in the next subchapter, but have been manually re-tuned based on the Deviation Analysis results where deemed necessary. Furthermore, the identified average patient-specific T_2 values for the ABC approach are used together with the assumed model of insulin action from the ABC approach in order to compute IOB for both options.

In the Deviation Analyses the target BG value was set to 110 mg/dl. Meal boluses were computed according to (4) and were injected at the time of the meal as in the recorded data. Additionally, correction boluses have been considered. For the option "Pen & SMBG" a correction bolus was only injected (calculated according to (4) with CHO = 0) at the points in time where there was really a correction bolus in the recorded data, whereas as for option "Pen & CGM" it was assumed that patients inject additional correction boluses based on the hyperglycemia alarm of the CGM. It was therefore assumed for this option that patients inject correction bolus when the glucose concentration indicated by the CGM is above 200 mg/dl and there was no previous bolus injection within the last 60 minutes.

For the option "Pen & CGM" it is furthermore assumed that the patients use the hypoglycemia alarm of the CGM device in order to ingest rescue carbohydrates if necessary. In case the glucose concentration drops below 80 mg/dl and there was no previous carbohydrate ingestion within the last 60 minutes, an ingestion of 5 g of rescue carbohydrates was simulated in the Deviation Analyses. In the option "Pen & SMBG" on the other hand no rescue carbohydrates were considered in the Deviation Analyses.

2.2 The ABC Approach for Estimating CIR and ISF

Recently [19, 20], the ABC method has been proposed to compute estimates of CIR and ISF using methods from continuous time system identification. This method has been derived for T1D patients, but is applied in the current work in order to obtain estimates for CIR and ISF for T2D patients that are then applied when computing the required bolus insulin amount according to (4).

For describing the BG dynamics in response to meal intakes and insulin injections, the control oriented model from [21] is used:

$$\mathrm{BG}(s) = \frac{K_1}{(1+s{\cdot}T_1)^2{\cdot}s}{\cdot}D(s) + \frac{K_2}{(1+s{\cdot}T_2)^2{\cdot}s}{\cdot}U(s) \tag{5}$$

In this formula, BG(s) describes the BG level, $D(s)$ the meal intakes and $U(s)$ the bolus insulin injections, all in the Laplace domain. The meal intakes and insulin injections are represented by impulses in the time domain.

The physiological interpretation of this formula is very similar to the interpretation of the bolus calculator formula (4): A carbohydrate intake of 1 g increases the BG by factor K_1, whereas the injection of 1 IU of bolus insulin decreases the BG by factor K_2. Therefore, K_2 has the same meaning as ISF and K_2/K_1 corresponds to CIR.

In order to account for diurnal variations in K_1 and K_2 (and therefore also in CIR and ISF) these factors were assumed to be described by second order polynomials as a function of daytime:

$$\begin{aligned} K_{1,i} &= K_{11} + K_{12}{\cdot}t_i + K_{13}{\cdot}t_i^2 \\ K_{2,j} &= K_{21} + K_{22}{\cdot}t_j + K_{23}{\cdot}t_j^2 \end{aligned} \tag{6}$$

It should be noted that a specific K_1 and K_2 is calculated for each (impulse-shaped) meal input i and insulin input j separately based on (6) and the corresponding times of the inputs (t_i and t_j). The values are then kept constant for calculating the system response following a specific input.

Additional constraints are introduced in order to limit the intra-patient variability of the profiles of K_1 and K_2 to a reasonable value. Additionally, the values of K_2 were imposed not to vary too much from some predefined reference ISF values. In the ABC approach the rule of thumb for calculating ISF according to [22] is used for this purpose:

$$\mathrm{ISF}_{King}(mg/dl/IU) = 12 + 1076/\,\mathrm{TDD}(IU) \tag{7}$$

It is of course possible to use some other reference ISF instead or to impose such a condition on K_1 (using a formula that specifies by which value the BG should rise after carbohydrate intakes, *e.g.* as a function of body weight, see [23]).

The additional constraints result in the optimization problem (8). In this problem $\mathbf{BG_{meas}}$ is the vector of measured BG values, whereas $\mathbf{BG_{model}}$ corresponds to a vector of calculated BGs (model outputs at the times of the measurements). The entries in $\mathbf{BG_{model}}$ depend on the values of the model parameters $K_{1k,l}$, $K_{2k,l}$, $T_{1,l}$ and $T_{2,l}$ with indexes k (index to describe the three parameters in the quadratic equations for K_1 and K_2) and l (index describing each day for the ABC approach, N days in total).

The minimum and maximum allowed values for K_1, K_2, K_2/K_1, T_1, T_2 and T_2/T_1 in the optimization can be found in Tab. 1. These were chosen in accordance with scientific literature (see e.g. [23]) in order to represent a physiologically relevant parameter space. The day-to-day variability of T_1 and T_2 was restricted to 25 % ($\Delta_T = 0.25$) and the day-to-day variations of the profiles of K_1 and K_2 were limited to 30 % ($\Delta_K = 0.30$) which were assumed to be reasonable values (see e.g. [24] for the intra-patient variability of insulin absorption and insulin action). The maximum allowed deviation between K_2 and ISF_{King} (calculated according to (7)) was set to 25 % ($\Delta_{\mathrm{ISF}} = 0.25$).

In order to obtain patient and mealtime specific CIR and ISF estimates the following workflow has to be performed:

- CGM data is collected with information about bolus injections and meal intakes over N days (in our case $N = 4$).
- The methodology described in this subsection is applied to this dataset and diurnal profiles for K_2/K_1 and K_2 are identified.
- The combined profiles for K_2/K_1 and K_2 of all days are used to compute an average profile for CIR and ISF as a function of daytime.
- Based on the identified values of T_2 a value for the duration of insulin action (DIA) can be estimated for computing IOB.

- The CIR, ISF and DIA values can be applied in a standard bolus calculator using equation (4).

$$
\begin{aligned}
(K^*_{1k,l},\ K^*_{2k,l},\ T^*_{1,l},\ T^*_{2,l}) = & \underset{K_{1k,l},K_{2k,l},T_{1,l},T_{2,l}}{\operatorname{argmin}} (\underline{BG}_{model} - \underline{BG}_{meas})^\top \cdot (\underline{BG}_{model} - \underline{BG}_{meas}) \qquad (8)\\
\text{subject to}: \ & K_{1,min} < K_{11,l} + K_{12,l}{\cdot}t + K_{13,l}{\cdot}t^2 < K_{1,max} \text{ for } t \in [t_{min}, t_{max}]\\
& K_{2,min} < K_{21,l} + K_{22,l}{\cdot}t + K_{23,l}{\cdot}t^2 < K_{2,max} \text{ for } t \in [t_{min}, t_{max}]\\
& \mathrm{CIR}_{min} < \frac{K_{21,l} + K_{22,l}{\cdot}t + K_{23,l}{\cdot}t^2}{K_{11,l} + K_{12,l}{\cdot}t + K_{13,l}{\cdot}t^2} < \mathrm{CIR}_{max} \text{ for } t \in [t_{min}, t_{max}]\\
& 1-\Delta_K < \frac{K_{11,l} + K_{12,l}{\cdot}t + K_{13,l}{\cdot}t^2}{\frac{1}{N}\sum_{m=1}^{N}(K_{11,m} + K_{12,m}{\cdot}t + K_{13,m}{\cdot}t^2)} < 1+\Delta_K \text{ for } t \in [t_{min}, t_{max}]\\
& 1-\Delta_K < \frac{K_{21,l} + K_{22,l}{\cdot}t + K_{23,l}{\cdot}t^2}{\frac{1}{N}\sum_{m=1}^{N}(K_{21,m} + K_{22,m}{\cdot}t + K_{23,m}{\cdot}t^2)} < 1+\Delta_K \text{ for } t \in [t_{min}, t_{max}]\\
& 1-\Delta_{\mathrm{ISF}} < \frac{K_{21,l} + K_{22,l}{\cdot}t + K_{23,l}{\cdot}t^2}{-\mathrm{ISF}_{King}} < 1+\Delta_{\mathrm{ISF}} \text{ for } t \in [t_{min}, t_{max}]\\
& T_{1,min} < T_{1,l} < T_{1,max};\ T_{2,min} < T_{2,l} < T_{2,max};\ T_{21,min} < \frac{T_{2,l}}{T_{1,l}} < T_{21,max}\\
& 1-\Delta_T < \frac{T_{1,l}}{\frac{1}{N}\sum_{m=1}^{N} T_{1,m}} < 1+\Delta_T;\ 1-\Delta_T < \frac{T_{2,l}}{\frac{1}{N}\sum_{m=1}^{N} T_{2,m}} < 1+\Delta_T\\
\text{with}: \quad & k = 1,2,3 \quad l = 1,2,...,N
\end{aligned}
$$

One key assumption behind the ABC method is that the basal rates of the patients are well adjusted and keep the glucose level more or less constant in the absence of challenges to the glucose metabolism (like meals). In [19] and [20] the CIR and ISF values computed with the ABC approach were compared to values optimized by medical doctors for patients with T1D and a good agreement was found. Furthermore, the performance of the ABC settings was demonstrated for T1D patients in Deviation Analyses in [25].

2.3 Pump & SMBG – Optimization of Basal Rates

For the treatment option "Pump & SMBG" the bolus insulin injections are left unchanged as compared to the recorded data and only the basal insulin is modified in the Deviation Analyses. In order to subtract the

Table 1: Max. and min. parameter values for the ABC Method for inequality constraints of (8).

	Minimum	Maximum
K_1 [mg/dl/g CHO]	2	8
K_2 [mg/dl/IU]	-100	-10
K_2/K_1 [g CHO/IU]	2	100
T_1 [min]	10	60
T_2 [min]	25	150
T_2/T_1 [-]	1	10

effect of the basal insulin in the Deviation Analyses it is assumed that the injected basal insulin leads to a roughly constant plasma concentration of the basal insulin analogue and that this analogue is metabolized at a more or less constant rate during a 24 hour period. After subtracting the effect of the original basal insulin dosing the use of an insulin pump for continuous subcutaneous insulin infusion (CSII) is simulated.

In this work it was assumed that each patient uses four different basal rates for four different times of the day: overnight (0:00 till 4:00), morning (4:00 till 10:00), during day (10:00 till 18:00) and evening (18:00 till 24:00). The basal rates within each of those time periods is assumed to be constant. The basal rate for each time period is optimized using Deviation Analysis results of the 4 days available for analysis. This optimization is performed using a run-to-run approach in which the basal rate is modified based on the value a cost function (determined based on the Deviation Analysis results):

$$\text{BasalRate}_{k+1} = \text{BasalRate}_k + R_1 \cdot (\overline{BG} - BG_{\text{target}}) + R_2 \cdot (T_{\text{Hypo}}) \tag{9}$$

In (9) BasalRate_k corresponds to the setting for the basal rate in iteration k, whereas BasalRate_{k+1} is the computed basal rate for the next iteration. $\overline{BG}$ corresponds to the average glucose concentration as from the Deviation Analysis results, BG_{target} is the target BG concentration (set to 100 mg/dl for this application) and T_{Hypo} is the time of hypoglycemia (defined as time below 80 mg/dl for this purpose). The cost thus consists of two terms, one for the difference between the average glucose from the Deviation Analyses and a target value and one for time in hypoglycemia, with weighting coefficients R_1 and R_2.

The optimization of the basal rates is thus performed using the following workflow:

1. Start with an initial guess for the basal rates.
2. Perform Deviation Analysis computations with the chosen basal rates.
3. Compute $\overline{BG}$ and T_{Hypo} from the Deviation Analysis results.
4. Update the basal rate according to (9).
5. If the difference between BasalRate_k and BasalRate_{k+1} is small enough the run-to-run optimization is stopped, otherwise go back to point 2.

The run-to-run approach is used in this work to retrospectively optimize the basal rate settings of an insulin pump based on Deviation Analysis results. Other successful applications of run-to-run control for insulin dosing can *e.g.* be found in [26, 27, 28, 29].

2.4 Artificial Pancreas (AP) with Model Predictive Control (MPC) Algorithm

For this option both the basal insulin, as well as the bolus insulin injections are modified in the Deviation Analyses as compared to the recorded data. The Artificial Pancreas (AP) algorithm used for this work is a standards model predictive control (MPC) algorithm with reference tracking. The model used inside the MPC uses rapid acting insulin and meal carbohydrates as an input and the subcutaneous glucose concentration as measured output and can be described by the following trasnfer function model:

$$\text{BG}(s) = \frac{K_1^{MPC} \cdot T_1^{MPC}}{(1 + s \cdot T_1^{MPC})^2} \cdot D(s) + \frac{K_2^{MPC} \cdot T_2^{MPC}}{(1 + s \cdot T_2^{MPC})^2} \cdot U(s) \tag{10}$$

with T_1^{MPC} fixed to 60 minutes, T_2^{MPC} fixed to 76.4 minutes, and K_1^{MPC} and K_2^{MPC} estimated based on the following correlations:

$$K_1^{MPC}(\text{mg/dl/g CHO}) = 1000/\text{BW} \tag{11}$$

$$K_2^{MPC}(\text{mg/dl/IU}) = -ISF_{DS} \cdot \exp(1) \tag{12}$$

with BW, the patient's body weight (in kg) and ISF_{DS} the ISF estimated according to the 1800-rule (3). The rapid acting insulin corresponds to the control input, whereas the meal carbohydrates are treated as a measured disturbance. The settings of the MPC were chosen to follow the recommendations as from [30] as closely as possible. The MPC formulation used here looks as follows:

$$J_k = \min_{\Delta I_{k+i|k}} \sum_{i=0}^{n_{\mathrm{PH}}-1} Q \cdot (y_{k+i|k} - BG_{\mathrm{ref}})^2 + R \cdot (I_{k+i|k})^2 + S \cdot (\Delta I_{k+i|k})^2 \tag{13}$$

subject to

$$\underline{x}_{k+i+1|k} = \underline{\underline{A}}_k \underline{x}_{k+i|k} + \underline{\underline{B}}_k \underline{u}_{k+i|k} \tag{14}$$

$$y_{k+i|k} = \underline{\underline{C}}\ \underline{x}_{k+i|k} + \underline{\underline{D}}\ \underline{u}_{k+i|k} \tag{15}$$

$$\forall i \in \{0, \ldots, n_{\mathrm{PH}} - 1\} \tag{16}$$

In (13) $y_{k+i|k}$ corresponds to the predicted glucose concentration, whereas $I_{k+i|k}$ is the corresponding insulin amount and $\Delta I_{k+i|k}$ is the change in insulin as compared to the infusion rate one time step earlier. Q, R and S are weights for the three terms in the cost function, whereas BG_{ref} corresponds to the reference BG value and was set to 112.5 mg/dl in this work. Equations (14) and (15) correspond to the model (10) transformed to a state space representation, meaning that the future glucose concentration is predicted using model (10). In this MPC formulation the prediction horizon n_{PH} was set to 200 minutes, whereas the control horizon n_{CH} was set to 50 minutes.

3 Data Analysis in the Frequency Domain

Any given signal with a constant sampling time can be analyzed in the frequency domain after calculating the Fourier transform of the signal. In this transformation the signal is (roughly speaking) approximated by a sum of sinus signals, each with a different frequency ω_i. The transformation consists of determining the weights that are assigned to each specific sinus function, the so-called Fourier coefficients. A high weight means that a certain frequency is common to be observed in the signals, whereas frequencies that appear less in the signal obtain a lower weight.

Given a vector of equidistant blood glucose (BG) measurements from a continuous glucose monitoring (CGM) device with N elements

$$\vec{cgm} = [cgm_0, cgm_1, \ldots, cgm_{N-1}] \tag{17}$$

and sampling time T_s, the Fourier coefficients can be calculated according to

$$CGM_k = \sum_{n=0}^{N-1} cgm_n e^{-\frac{2\pi j}{N} nk} \quad k = 0, \ldots, 2n-1. \tag{18}$$

The result is a sequence of Fourier coefficients CGM_k and one can also write

$$\vec{cgm} \circ\!\!-\!\!\bullet\ \vec{CGM}. \tag{19}$$

The domain of $\vec{CGM}$ is $[0, N-1]$, but we consider only the right half of the transformed sequence, which correspond to the entries $k = 0 \ldots N/2$. In a frequency spectrum the resulting Fourier coefficients are plotted for a frequency range from 0 to π radians per sampling time T_s. Using $F_s = 1/T_S$, the x-axis can be scaled as

$$0, \frac{k}{N} F_s, \ldots, \frac{1}{2} F_s \tag{20}$$

in Hertz, or

$$\infty, \frac{N}{k} T_s, \ldots, 2T_s \tag{21}$$

in seconds.

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