Anticipating Meals with Behavioral Profiles in an Artificial Pancreas System - An Informed Multistage Model Predictive Control Approach

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Abstract: This contribution presents an individualized multistage model predictive control (MS-MPC) algorithm for blood glucose (BG) stabilization and improved postprandial BG control for people with type 1 diabetes (T1D) with consistent meal patterns. The multistage formulation utilizes different meal patterns as disturbance realizations entering the glucose-insulin system, then assesses the best possible control input among all of the probable scenarios. The disturbance realizations, in the form of glucose rate of appearance traces, are estimated by using meal records (time and carbohydrate amount) as the input into an individualized oral model. Meal signatures are then clustered with the k-medoids algorithm to obtain meal patterns. Two approaches, a hybrid closed-loop (HCL) and fully closed-loop (FCL) MS-MPC were tested and compared with their respective control treatments (hybrid and fully automated MPC, respectively) using the complete in silico adult cohort of the FDA-accepted UVA/Padova metabolic simulator. Results confirm an improvement in both postprandial and overall percent time in 70-180 mg/dL. 85.2 ± 15.5 vs. 89.6 ± 12.2 and 94.1 ± 6.3 vs. 95.7 ± 5.0, respectively, using the HCL approach, and 37.8 ± 15.7 vs. 63.4 ± 16.6 and 65.8 ± 12.7 vs. 82.2 ± 9.2, using the FCL approach.

Keywords: Artificial Pancreas, Type 1 Diabetes, Behavioral Profiling, Postprandial Glucose Control

1. INTRODUCTION

In health, the pancreas regulates the production of insulin, which allows for glucose to clear from plasma, and glucagon, which stimulates the liver to release glucose into the blood. In T1D, this precise feedback process is dysregulated. The pancreas does not produce insulin, leading to high blood glucose (BG), also known as hyperglycemia. To prevent this, exogenous insulin must be administered for life to maintain plasma glucose levels within a safe range.

Treatment guidelines suggest that people with T1D calculate an insulin dose at meal times based on carbohydrate counting (CC) and their insulin therapy parameters American Diabetes Association (2016); Tascini et al. (2018). Furthermore, to minimize the effect of ingested carbohydrates on glucose levels, insulin should be ideally administered 15-20 minutes before food Slattery et al. (2018). Results related to how accurate people with T1D are at CC vary from study to study, but there is a consensus that errors in CC are common in real-life. Deeb et al. reported that children and adolescents are only able to make accurate carbohydrate estimations for 67% of meals Deeb et al. (2017). Another study showed that adults with T1D were only able to estimate the carbohydrate content of foods within a 5 gram range of the true amount 44% of the time Meade and Rushton (2016). A survey by Lancaster et al. reported that adolescents with T1D consider CC as a barrier to achieving glycemic control Lancaster et al. (2010)

Postprandial glucose management remains a challenge for artificial pancreas systems (APS). In a hybrid closed-loop (HCL) approach, inaccurate CC and parameters such as carbohydrate ratio (CR) and insulin-to-carbohydrate correction factor (ICF) have a meaningful impact on glucose control since insulin underdose/overdose may arise Bally et al. (2017); Kovatchev et al. (2017). Although promising results regarding fully closed-loop (FCL) systems have been reported, balancing the controller’s aggressiveness to mitigate meal-related glucose excursions without increasing the risk of late hypoglycemia remains an open challenge Dassau et al. (2013); Turksoy et al. (2016); Bally et al. (2017); Colmegna et al. (2018); Sánchez-Peña et al. (2018).

Meal anticipation could further improve APS postprandial control for both HCL and FCL systems. For example, Hughes et al. approached the issue of the delay between subcutaneous BG measurements and the effect of insulin action, by anticipating meals using a random meal profile Hughes et al. (2011). In silico results from this paper showed that the HCL approach that used meal anticipation and insulin boluses for announced carbohydrates resulted in an attenuated postprandial BG excursion when compared to open-loop control with meal boluses. The action of the controller was regulated by the probability

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of the user skipping a meal causing the controller to be more aggressive if there wasless of a chance that the user chose not to eat during one of the three meal windows (breakfast, lunch, and dinner).

In Cameron et al. (2012), a methodology to detect and reject meal disturbances is presented using a multiple hypothesis approach. This control framework uses multiple models to predict BG values depending on the detected scenario. Each model has different assumed inputs and current measurements are used as a way of assessing which model’s input disturbances describe the observed measurements most accurately. Prior probabilities of the disturbance timing and magnitude are calculated based on observation data of people’s eating habits. This information allows for meals to be anticipated and detected more readily. The authors showed 45% and 18% reduction in the 2 hour prediction error (BG) when compared to an algorithm without meal detection and with meal detection, respectively.

This work presents the following contributions:

1. A method for creating individualized meal disturbance profiles that can be used within the context of a MS-MPC controller to anticipate the occurrence of meals.

2. In silico results that illustrate how the use of anticipatory disturbance profiles can mitigate postprandial hyperglycemia and achieve better glycemic outcomes overall for people with T1D that exhibit consistent eating behavior.

2. METHODS

2.1 Physiological model

In this work, we use the double triangular subcutaneous oral glucose minimal model (dSOGMM), which is the original SOGMM as presented by Patek et al. (2016), but with the additions of triangular meal and insulin sub-systems. These nonlinear dynamics can be represented as follows:

\[ G(t) = -S_p[G(t) - G_0] - S_i X(t) G(t) + R_a(t) \]  
(1)

\[ X(t) = -p_2 X(t) + p_2 I(t) - I_0 \]  
(2)

\[ Q_1(t) = -(k_{m1} + k_{m2})Q_1(t) + m(t) \]  
(3)

\[ Q_2(t) = -k_{m2}Q_2(t) + k_{m2}Q_1(t) \]  
(4)

\[ I_{sc1}(t) = -(k_1 + k_2)I_{sc1}(t) + u(t) \]  
(5)

\[ I_{sc2}(t) = -k_{sc1}I_{sc1}(t) + k_{sc2}I_{sc1}(t) \]  
(6)

\[ I(t) = -n I(t) + IR_a(t) \]  
(7)

with

\[ R_a(t) = \frac{I_{sc1}(t) + I_{sc2}(t)}{V_I \cdot BW} \]  
(8)

\[ R_a(t) = \frac{k_1 I_{sc1}(t) + k_2 I_{sc2}(t)}{V_I \cdot BW} \]  
(9)

where \( G \) is the plasma glucose concentration (mg/dL), \( X \) is the proportion of insulin in the remote compartment (mU/L), \( Q_1 \) and \( Q_2 \) are the glucose masses in the stomach and gut (mg), \( I_{sc1} \) and \( I_{sc2} \) are the amounts of nonmonomeric and monomeric insulin in the subcutaneous space (mU), \( I \) is the amount of plasma insulin (mU/L), \( m \) is the input rate of mixed-meal carbohydrate absorption (mg/min), and \( u \) is the exogenous insulin input (mU/min). Model parameters are defined in Table 1, indicating which ones are fixed to population-level values, and which ones are estimated from collected data. Concerning the latter, the model is individualized following a similar procedure as detailed in Garcia-Tirado et al. (2018).

2.2 Subject-specific Meal Disturbance Profiles

Meal disturbance profiles are generated based on the recorded meal activity of a given individual. To create 24-hour behavioral \( R_a \) signals, \( R_{a,ant} \), the meal records for a given day are used to generate a single trace that represents the rate of appearance of the meals recorded by the patient. The glucose rate of appearance over time defined in equation (9) is calculated using the timing of meals and the carbohydrate content recorded by the patient as an input, \( m \), to equation (3). These daily signals are grouped using the k-medoids clustering algorithm Kaufman and Rousseweu (2009). The value of \( k \) for each individual is chosen based on what number of clusters, between 1 and 7, produces the highest silhouette score Rousseweu (1987). A profile trace is then found by taking the average of the grouped disturbance signals in a particular cluster at each point in time during the day. The probability of a particular cluster, \( p_i \), is found based on the cluster membership using the following formula,

\[ p_i = \frac{n_i}{\sum_{j=1} n_j} \]  
(10)

where \( n_i \) is the number of daily signals in cluster \( i \) and similarly \( n_j \) is the number of signals in cluster \( j \). Figure 1 shows an example of a what the meal profiles may look like for a particular individual. It can be seen here that on the days considered to generate these profiles the subject regularly had 3 large meals at roughly around 9 a.m., 1 p.m., and 7 p.m. Each of the 5 profiles for this subject has an associated probability of occurrence ranging from 12.7 to 29.1%.

2.3 MS-MPC for the AP System

MS-MPC was introduced by Lucia et al. (2013) as a robust formulation of the MPC problem to deal with uncertain model predictions. In the case of an APS, MS-MPC has already been proven successful in mitigating exercise-related hypoglycemia Garcia-Tirado et al. (2019a,b). Here, we propose to use the same framework, but to inform the controller about likely future meal disturbances. To this end, Equation (1) is modified as follows:

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Table 1. Model parameters.

| Symbol | Meaning | Value [Units] |
|--------|---------|--------------|
| \( S_p \) | Fractional glucose effectiveness | Estimated [min\(^{-1}\)] |
| \( G_0 \) | Basal glucose | 120 [mg/dL] |
| \( D_p \) | Mean insulin basal rate | Subject-specific [mU/min] |
| \( I_s \) | Basal insulin | \( \mu \cdot \beta \cdot V_I \cdot BW \) [mU/L] |
| \( V_I \) | Distribution volume of glucose | 1.7 [dL/kg] |
| \( S_I \) | Insulin sensitivity | Estimated [min\(^{-1}\) per mU/L] |
| \( p_2 \) | Rate constant | 0.02 [min\(^{-1}\)] |
| \( k_{m1} \) | Rate constant | 0.02 [min\(^{-1}\)] |
| \( k_{m2} \) | Rate constant | 0.01 [min\(^{-1}\)] |
| \( k_{sc1} \) | Rate constant | Estimated [min\(^{-1}\)] |
| \( k_1 \) | Rate constant | 0.02 [min\(^{-1}\)] |
| \( k_2 \) | Rate constant | 0.02 [min\(^{-1}\)] |
| \( k_d \) | Rate constant | Estimated [min\(^{-1}\)] |
| \( n \) | Rate constant | 0.178 [min\(^{-1}\)] |
| \( V_I \) | Distribution volume of insulin | Estimated [L·kg\(^{-1}\)] |
| \( BW \) | Body weight | Subject-specific [kg] |
| \( f \) | Fraction of intestinal absorption | 0.9 |
where the additive term $R_{a,\text{amp}}$ is a meal signature built upon the subject’s eating behavior, and $\rho$ is an activation coefficient to avoid the potential double counting effect of $R_a$ and $R_{a,\text{amp}}$, as it will be shown later. In this regard, we formulate every meal occurrence as a part of a scenario tree that appears in the upcoming horizon. The scenario tree considered in this work assumes robust horizon $N_r = 1$, meaning that the uncertainty only branches at the beginning. In order to embed model (2)-(11) into the MPC design, it is first linearized at $(u_{\text{op}}, y_{\text{op}}) = (\bar{z}_0, 120)$, and later discretized with a sampling period of 5 minutes. Thus, the following realization is obtained:

$$
\begin{align*}
    x_k^{l+1} &= A x_k^{l} + B u_k^{l} + B_d d_k^{l}, \\
    y_k^{l} &= C x_k^{l} + y_k^{l}(1)
\end{align*}
$$

where $x_k^{l} = \delta(G, X, Q_1, Q_2, I_{\text{lc}}, I_{\text{tc}}, I)$ $\in \mathbb{R}^7$ is the model state vector, $A, B_1, B_2, C$ are the matrices of the discrete-time linear system (12)-(13) with corresponding dimensions, $u_k^{l}, y_k^{l} \in \mathbb{R}$ are the insulin and glucose deviations from steady-state, and $d_k^{l} = R_{a,\text{amp}} \in \mathbb{R}$ is the corresponding disturbance realization of the uncertainty at stage $k$, with $R_{a,\text{amp}}$ being the $i$-th realization of the anticipatory meal signature for a given subject.

Bearing the above in mind, we formulate the following MS-MPC problem that is solved at each step $k$:

$$
\begin{align*}
    \min_{u_k^{l}} & \quad \phi^{\text{ms}} \\
    \text{s.t.} & \quad x_k^{l+1} = A x_k^{l} + B u_k^{l} + B_d d_k^{l}, \\
    & \quad y_k^{l} = C x_k^{l} + y_k^{l}(1) \\
    & \quad u_{\text{min}} \leq u_k^{l} \leq u_{\text{max}}, \\
    & \quad \Delta u_{\text{min}} \leq \Delta u_k^{l} \leq \Delta u_{\text{max}}, \\
    & \quad y_{\text{min}} - y_k^{l} \leq y_k^{l}, \\
    & \quad r_{\text{amp}}^{l} \frac{I_{\text{tc}}}{I_{\text{lc}}} > 0, \\
    & \quad u_k^{l} = u_k^{l}, \text{ with } i \neq l
\end{align*}
$$

where $\phi^{\text{ms}} = \frac{1}{2} \sum_{i=1}^{N_p} p_i$:

$$
\begin{align*}
    \sum_{j=0}^{N_p-1} (y_k^{l+j} - r_k^{l+j})^T Q_2 (y_k^{l+j} - r_k^{l+j}) + \kappa (\eta_k^{l+j})^T (\eta_k^{l+j}) + \sum_{j=0}^{N_p-1} \lambda (\Delta u_k^{l+j})^T (\Delta u_k^{l+j})
\end{align*}
$$

where $\lambda = 350/\bar{z}_0$ and $\kappa = 100$ are weights to prevent an aggressive change in the control action and to avoid hypoglycemic, respectively, and $Q_2$, the weight on the difference between model prediction $y$ and the evolution of the controller’s reference $r$, is defined as:

$$
\begin{align*}
    Q_2(\text{IOB}) = \begin{cases}
    Q_0 & \text{if IOB} < 0 \\
    m \cdot \text{IOB} + Q_0 & \text{if IOB} \in [0, \text{TDI}/\alpha] \\
    Q_0/\beta & \text{if IOB} > \text{TDI}/\alpha
\end{cases}
\end{align*}
$$

where $m = \alpha \cdot (1 - \beta) \cdot Q_0/(\beta \cdot \text{TDI})$, IOB is the amount of insulin on board, TDI is the subject-specific total daily insulin, $Q_0 = 10$ is the value of $Q_2$ at basal insulin on board (IOB), and $\alpha = 20$ and $\beta = 1000$ are tuning parameters. In this way, the controller is de-tuned at high IOB values to prevent controller-induced insulin overdosing. This behavior is particularly desired in a HCL approach where an insulin bolus is manually administered at meal times to fully account for the meal content. To enhance the safety of the algorithm, the reference, $r$, is defined as the following asymmetric time-varying exponential signal Boiroux et al. (2018); Garcia-Tirado et al. (2019b):

$$
\begin{align*}
    r_{k+j+1} = \begin{cases}
    y_k - y_{kp} \cdot e^{-(q_{k+j+1}-y_k)/\tau_r}, & y_k \geq y_{kp} \\
    0, & y_k < y_{kp}
\end{cases}
\end{align*}
$$

where $\tau_r = 10, y_{kp} = 120 \text{ mg/dL}$ is the BG target, and $t_k$ is the discrete time. In this way, we enforce fast (from hypoglycemia) and smooth (from hyperglycemia) returns to the desired glucose concentration. Finally, in order to avoid the double counting effect of meals in a HCL approach, we designed an activation coefficient for $R_{a,\text{amp}}$, namely $\rho$. This coefficient will not emphasize the anticipatory pattern when a meal is occurring. To this end, the coefficient is built as a function $Q_1$ and $Q_2$ as follows:

$$
\begin{align*}
    \rho(Q_1, Q_2) = e^{-(Q_1+Q_2)}
\end{align*}
$$

where $\gamma = \beta_2 \cdot \ln(100)/\text{TDI}$, TDC is the subject-specific total daily carbohydrate, and $\beta_2 = 20$ is a parameter to regulate the decay constant of $\rho$.

3. IN SILICO STUDIES

3.1 Experimental Design

We performed two closed-loop experiments using all 100 adults in the UVA/Padova simulator Visentin et al. (2018) with a meal behavior extracted from a representative real subject. In the first experiment, the in silico subjects administered a bolus at meal times using their subject-specific carbohydrate to insulin ratio (HCL). In the second experiment, the subjects did not announce meals to the controller and no meal boluses were delivered (FCL). The MS-MPC controller was compared to a regular Model Predictive Control (rMPC) that was not informed by the meal disturbance profiles.
Table 2. Glucose metric results from the HCL experiment.

|                  | rMPC Mean BG (mg/dL) | Overall Mean BG (mg/dL) | p-value | rMPC Mean BG (mg/dL) | Postprandial Mean BG (mg/dL) | p-value |
|------------------|----------------------|-------------------------|---------|----------------------|-----------------------------|---------|
| BG Standard Deviation (mg/dL) | 25.7±(8.6)           | 24.3±(8.3)              | <0.01   | 25.6±(7.8)           | 25.6±(8.1)                  | 0.94    |
| Time <54 mg/dL (%) | 0.0±(0.0)            | 0.0±(0.0)               | 0.57    | 0.0±(0.0)            | 0.0±(0.0)                   | -       |
| Time <70 mg/dL (%) | 0.3±(0.5)            | 0.4±(0.6)               | <0.01   | 0.1±(0.1)            | 0.1±(0.1)                   | 0.02    |
| Time 70-140 mg/dL (%) | 75.9±(9.9)          | 81.3±(9.4)              | <0.01   | 44.2±(19.1)          | 56.6±(19.4)                 | <0.01   |
| Time 70-180 mg/dL (%) | 94.1±(6.3)          | 95.7±(5.0)              | <0.01   | 85.2±(15.5)          | 89.1±(12.2)                 | <0.01   |
| Time >180 mg/dL (%) | 5.6±(6.0)            | 3.9±(4.6)               | <0.01   | 14.7±(15.5)          | 10.3±(12.2)                 | <0.01   |
| Time >250 mg/dL (%) | 0.2±(0.6)            | 0.1±(0.4)               | 0.04    | 0.5±(1.6)            | 0.4±(1.1)                   | 0.04    |

Table 3. Glucose metric results from the FCL experiment.

|                  | rMPC Mean BG (mg/dL) | Overall Mean BG (mg/dL) | p-value | rMPC Mean BG (mg/dL) | Postprandial Mean BG (mg/dL) | p-value |
|------------------|----------------------|-------------------------|---------|----------------------|-----------------------------|---------|
| BG Standard Deviation (mg/dL) | 165.8±(19.4)        | 140.7±(11.2)            | <0.01   | 202.1±(24.9)         | 170.6±(18.4)                | <0.01   |
| Time <54 mg/dL (%) | 0.0±(0.0)            | 0.0±(0.0)               | -       | 0.0±(0.0)            | 0.0±(0.0)                   | -       |
| Time <70 mg/dL (%) | 0.0±(0.0)            | 0.3±(0.4)               | <0.01   | 0.0±(0.0)            | 0.1±(0.1)                   | <0.01   |
| Time 70-140 mg/dL (%) | 43.9±(10.7)          | 60.8±(8.7)              | <0.01   | 11.1±(4.7)           | 27.4±(10.0)                 | <0.01   |
| Time 70-180 mg/dL (%) | 65.8±(12.7)          | 82.2±(9.2)              | <0.01   | 37.8±(15.7)          | 63.4±(16.6)                 | <0.01   |
| Time >180 mg/dL (%) | 34.2±(12.7)          | 17.5±(9.1)              | <0.01   | 62.2±(15.7)          | 36.5±(16.6)                 | <0.01   |
| Time >250 mg/dL (%) | 8.8±(8.7)            | 2.7±(3.4)               | <0.01   | 17.7±(15.2)          | 6.3±(7.6)                   | <0.01   |

In both experiments, the meal record for the representative real subject was split into training (75%) and testing data (25%), i.e., 55 days for training and 18 days for testing, randomly selected for every test subject. Meal disturbance profiles and probabilities were generated using the meal record from the training data and individualized oral glucose model described in Section 2.

The patient records from the testing days defined the meal regimen that was used in the simulation experiment. The meal amounts for the test meals were scaled based on the in silico subject’s body weight. For the HCL experiment, meal boluses were calculated based on the estimated carbohydrate amounts, subject to estimation error, of a given meal and the in silico subject’s personalized carbohydrate ratio. Carbohydrate estimation error was uniformly distributed and ranged ±25% of the true value, and hypoglycemia treatments of 15 grams of carbohydrates were administered every 15 minutes when BG was below 70 mg/dL. The carbohydrate estimation error and timing was the same for meals used as the input for the simulation for both control and experimental controllers.

To compare the performance of the MS-MPC (HCL and FCL) with the rMPC, glucose metrics defined in Danne et al. (2017) were considered for all of the testing data as well as the 3 hour period after each meal (postprandial period). Additionally, the mean number of hypoglycemic events where BG was < 70 mg/dL and peak BG following meals were computed. Statistical significance was determined from the paired t-test.

### 3.2 Results

**HCL Overall** For all of the data, there were significant differences in the rMPC and the MS-MPC in terms of all of the metrics considered except for percent time spent below 54 mg/dL. The effectiveness of the MS-MPC is largely shown in the 5.4% increase in the percent time spent greater than 70 and less than 140 and the reduction in mean BG from 127.2 ± 6.7 to 121.8 ± 6.1 mg/dL. There was a modest (1.6%) increase in the percentage of time where BG was greater than 70, but less than 180 mg/dL. There was also a reduction in the percentage of time when BG was greater than 180 from 5.6% to 3.9%. There was a significant increase in the number of hypoglycemic events between the two controllers, with the rMPC averaging 0.07 per day whereas the MS-MPC had a mean of 0.45 hypoglycemic events per day. The overall results from the HCL experiment are shown in Table 2.

**FCL Overall** When meals were not announced in the FCL experiment there was a more noticeable difference in the performance of the rMPC and MS-MPC overall. During this experiment, all metrics considered were significant except for percent time when BG was less than 54 mg/dL. Mean BG was 25.1 mg/dL lower when the meal disturbance profiles were used (140.7 ± 11.2 vs. 165.8 ± 19.4 mg/dL). The MS-MPC also demonstrated an improved percentage of time spent in the 70 to 140 and 70 to 180 mg/dL ranges. This can largely be attributed to the 16.7% reduction in the amount of time when BG was greater than 180 mg/dL. On average a subject using the MS-MPC would experience 0.33 hypoglycemic events per day versus none if they were to use the rMPC. The overall results from the FCL experiment are shown in Table 3.
In silico

In the postprandial period, the differences between the two controllers is even more pronounced. In the 3 hours following the meals all metrics, except for percent time spent less than 54 mg/dL, were significant. The MS-MPC had a mean postprandial BG of 170.6 ± 18.4 compared to 202.1 ± 24.9 mg/dL when the rMPC was used. Here, there was also a 5.1 mg/dL reduction in the mean standard deviation of the BG values that the in silico subjects experienced. When the percent time spent in the 70 to 140 mg/dL range was considered, the MS-MPC had a percent time in range of 27.24% whereas the subjects were only in this range 11.1% when the rMPC was used. There was also a 25.6% increase in the percentage of time where BG was greater than 70 and less than 180 mg/dL. This can be attributed to the similar (25.7%) decrease in the amount of time that subjects’ BG was above 180 mg/dL. When the subjects used the MS-MPC they had a reduction of peak postprandial BG from 329.6 to 292.6 mg/dL. The results from the postprandial glucose excursion in the FCL experiment are presented in Table 3.

Box-plots comparing the percentage of time in the 70-180 mg/dL range obtained with each of the analyzed strategies (i.e. FCL and HCL) with and without anticipation, is depicted in Figure 2. Figure 3 shows an example of BG values and insulin delivery for a representative virtual subject. It can be seen here that BG is controlled the best when MS-MPC is used with meal announcements and the worst when no meal announcements were made to the rMPC controller.

4. CONCLUSION & FUTURE WORK

The MS-MPC strategy outlined in this work was able improve glycemic control compared to our standard MPC strategy with...
and without meal announcements. Though this approach did lead to a slight, but statistically significant, increase in the percent time where BG values were less than 70 mg/dL and produced more hypoglycemic events on a daily basis that required treatment. The HCL with and without meal profiles outperformed the FCL system with the meal profiles, but requires the user to input carbohydrate amounts at each meal which is burdensome and could result in consequences related to inaccurate carbohydrate counting.

In future work, we intend on expanding the number of scenarios that this strategy is tested under to include a broader range of eating behaviors and variations in insulin sensitivity. Additionally, we will evaluate how exercise should be considered and what safeguards need to be put into place to ensure user safety. Furthermore, we will develop a more sophisticated strategy to determine the probabilities of each profile that uses current information of dynamically shift the likelihood of a particular disturbance.

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