A Physiologically Based Digital Twin for Alcohol Consumption – Predicting Real-life Drinking Responses and Long-term Plasma PEth

Henrik Podéus[†,1] (0000-0002-7501-4031), Christian Simonsson[†,1,2] (0000-0003-3805-1674), Patrik Nasr[3] (0000-0002-2928-4188), Mattias Ekstedt[2, 3] (0000-0002-5590-8601), Stergios Kechagias[3] (0000-0001-7614-739X), Peter Lundberg[2,4] (0000-0001-8661-2232), William Lövfors[†,1,5] (0000-0002-9058-7049), Gunnar Cedersund (0000-0001-9386-0568) [1,2,5 *]

[1.] *Department of Biomedical Engineering (IMT), Linköping University, Linköping, Sweden*

[2.] *Center for Medicine Imaging and Visualization Science (CMIV), Linköping University, Linköping, Sweden*

[3] *Department of Health, Medicine, and Caring Sciences, Linköping University, Linköping, Sweden*

[4] *Department of Radiation Physics, Radiology, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden*

[5] *School of Medical Sciences and Inflammatory Response and Infection Susceptibility Centre (iRiSC), Faculty of Medicine and Health, Örebro University, Örebro, Sweden*

† Authors contributed equally.

***** Corresponding author: Gunnar Cedersund, Email: gunnar.cedersund@liu.se

Address: Department of Biomedical Engineering, Linköping University, 58185 Linköping, Sweden. Phone: +4613-28 67 26

Abstract

Alcohol consumption is associated with a wide variety of preventable health complications and is a major risk factor for all-cause mortality in the age group 15-47 years. To reduce dangerous drinking behavior, eHealth applications have shown promise. The most advanced such eHealth applications make use of underlying predictive models. However, existing mathematical models do not consider real-life situations, such as combined intake of meals and beverages, and also do not connect drinking to clinical markers, such as *phosphatidylethanol* (PEth). Herein, we present such a model. More specifically, we have developed a new sub-model for gastric emptying, which depends on all food and beverages consumed. The new model can accurately describe both training data and independent validation data, not used for training. The model can also be personalized using e.g. anthropometric data from a specific individual and can thus be used as a physiologically based digital twin. This twin is also able to connect short-term consumption of alcohol to the long-term dynamics of plasma PEth. We illustrate how this connection allows for a new way to determine patient alcohol consumption from PEth levels, which has the potential to improve upon traditionally used self-reporting forms. Finally, the new model is integrated into a new eHealth app, which also could help guide individual users or clinicians to help reduce dangerous drinking.

Abbreviations

PEth - *Phosphatidylethanol*

ODE – *Ordinary differential equation*

CYP2E1 - *Cytochrome P450 2E1*

ADH – *Alcohol dehydrogenase*

BAC – *Blood alcohol concentration*

BrAC – *Breath alcohol concentration*

eBAC – Estimated *blood alcohol concentration*

SEM – Standard *error of the mean*

AUDIT-C – *Alcohol Use Disorders Identification Test*

ALD – *Alcohol related liver disease*

Introduction

Alcohol consumption causes around five percent of deaths worldwide and contributes to numerous societal health issues (1). How one consumes alcohol, *i.e.,* one's personal drinking habits (2), might contribute to both short-term and long-term effects on personal health. One common type of drinking habit is 'binge drinking', or heavy episodic drinking, which is more prevalent in adolescents and young adults. Binge drinking can cause major health problems, contributing to both acute injuries (*e.g.,* accidents) and long-term negative effects (3). Furthermore, during 'heavy drinking', the ability to judge your own intoxication level is decreased (4). For these reasons, it is important to determine and control the amount of alcohol consumed. One way to obtain such reductions could be to use eHealth applications (5–7).

Many of the available eHealth applications lack proper scientific based ethanol dynamics and predictive capabilities (8). Predictive capabilities would be useful for preventive and educational purposes and have the potential to help individuals make more informed decisions. Currently, predictive capabilities in eHealth applications are lacking. One way to introduce predictive capabilities is to make use of mathematical models which have strong predictive capabilities (Fig. 1A). However, no suitable mathematical model does yet exist for use in an eHealth application.

Mathematical modelling has for a long time been used in interpreting dynamics of plasma ethanol, and there exist a variety of models. The first example is the minimal plasma ethanol models from the field of forensic science, used for determining kinetic parameters of ethanol dynamics (9,10). While these minimal models can be used to estimate the *blood alcohol concentration* (BAC) they are not useful when handling varying and combined ingestion of drinks and food. In contrast to the minimal plasma ethanol models, physiological-based models which include more detailed descriptions of physiology, have also been created. Recently, in studies by Zhu *et al.* and Toroghi *et al.* (11,12) comprehensive dynamic models describing ethanol in a whole-body context are presented. While the models describe the whole-body context, they do not include a mechanistic description of gastric emptying and food consumption which influences ethanol dynamics. Such a description would be beneficial when describing real-life drinking behaviors, including consumption of various types of meals. Another recent model presented by Moore *et al.* (13) does include the dynamics of ethanol absorption in combination with a meal, but in primates and not humans. Also, the model by Moore *et al.* does not consider the caloric content of the beverage, or the foodstuff, which is of importance for the rate of gastric emptying. Overall, these models lack the ability to describe several important factors impacting ethanol dynamics during a real-life scenario, i.e., how food interacts with ethanol gut absorption.

A model able to explain the dynamics of ethanol in real life drinking scenarios should include a set of mechanisms: the rate of gastric emptying and the impact of different drinks and meals, differences in phenotypes and genetic variations of ethanol metabolism, and general anthropometric parameters. We will here go through these mechanisms and models describing the mechanisms briefly. Firstly, various studies have shown the importance of several factors influencing gastric emptying such as: consumed beverage volume, caloric content of the beverage, caloric type of the beverage, and the influence of simultaneous consumption of food (14–19). There exist simple mathematical models for gastric emptying (20–22), although no model is connected to the appearance of ethanol in plasma. Thus, there is a need for a model

that includes all factors as well as the connection to ethanol. Secondly, different enzyme expressions and phenotypes present in the liver will impact the ethanol plasma dynamics. The breakdown of ethanol is primarily controlled by enzymes such as *alcohol dehydrogenase* (ADH) and *Cytochrome P450 2E1* (CYP2E1). There exist mathematical models describing the expression of CYP2E1 (23), and the enzyme kinetics is well-known. Furthermore, enzyme expression can be highly diverse in a population, and is thus an important aspect for model personalization. Lastly, anthropometric parameters, such as heigh, weight and sex impact the blood volume which directly effects the plasma ethanol concentration and are thus also an important aspect for model personalization. In summary, a dynamic model with a high-level of personalization, also referred to as a physiologically based digital twin, opens a wide avenue of usages if connected to clinically relevant biomarkers.

eHealth applications based on physiologically based digital twins have the possibility of providing users with more information in real-time, by simulating and predicting the levels of plasma ethanol during different real-life drinking scenarios. Digital twins could also connect short-term and long-term dynamics of alcohol consumption, and relevant clinical biomarkers such as blood *phosphatidylethanol* (PEth), a product of non-oxidative ethanol breakdown. PEth has shown great promise as a long-term marker for alcohol misuse (24,25). Thus, by also including breakdown of ethanol into PEth, a digital twin could connect short-term drinking habits to dynamics of long-term outcome. Which would make it possible to approximate alcohol consumption based on a given PEth value, and other patient-specific parameters. A digital twin-based eHealth application could thus help clinicians identify incorrectly self-reported consumption, especially among heavy drinkers (4). To our knowledge no mathematical model of PEth plasma dynamics exists, and furthermore, no model connecting ethanol consumption to long-term PEth trajectories exist.

Therefore, we have herein created a mathematical model (also referred to as a physiologically based digital twin) incorporating several aspects of plasma ethanol dynamics after alcohol consumption not present in other models: 1) factors impacting gastric emptying, and 2) ethanol break-down into PEth.

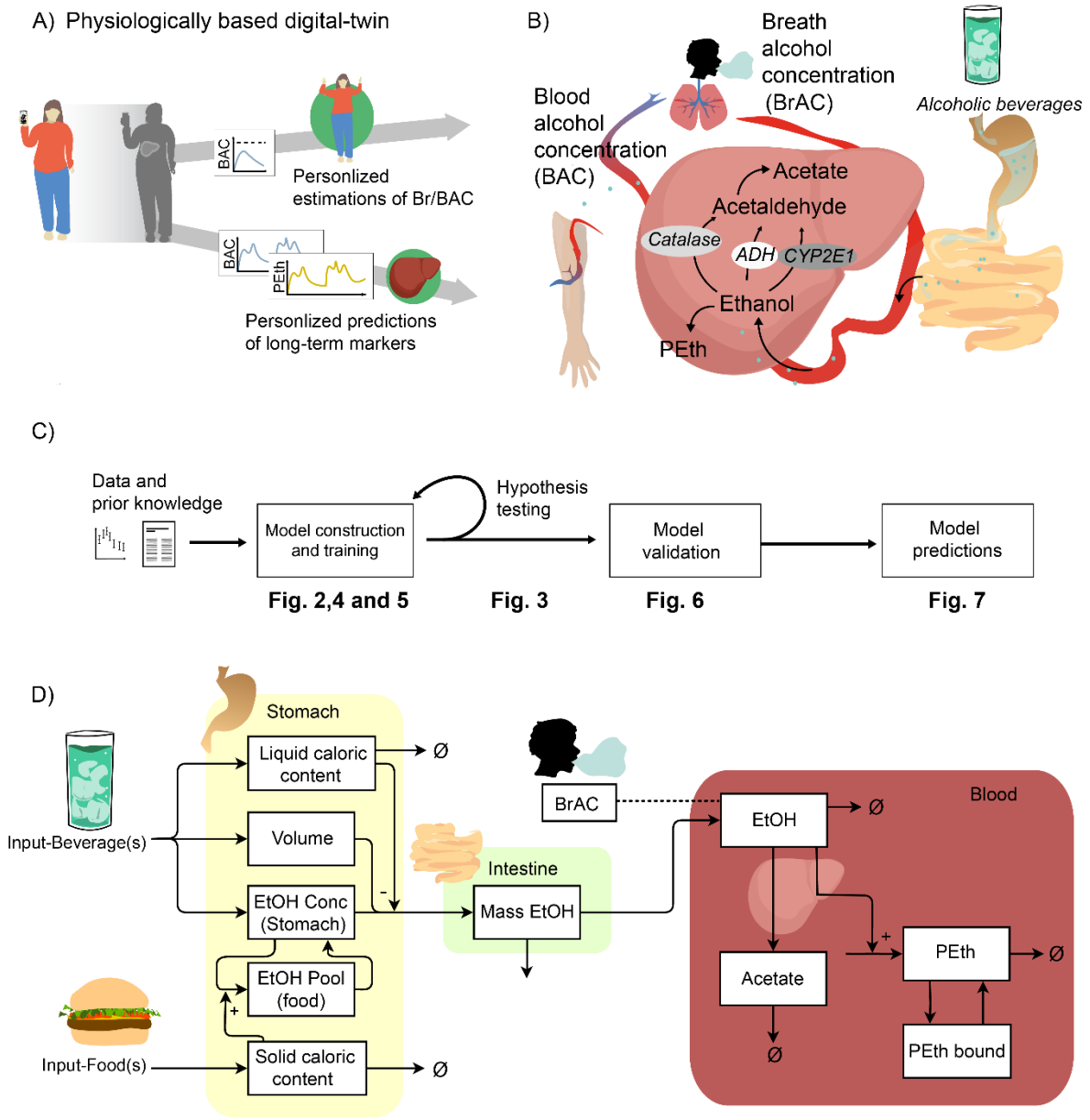

Figure. 1: *Graphical abstract and modelling framework.* **A)** Herrin, we present a physiologically based mechanistic model capable of describing ethanol plasma concentration in a variety of scenarios. The model has a high degree of personalization and can be denoted as a physiologically based digital-twin. The model can produce personalized predictions for short-term alcohol-consumption, including the effect of non-alcoholic beverages, and effect of solid food-stuff intake. The model is also capable of predicting the long-term result of different drinking schedules on e.g., PEth levels. **B)** Short overview of the physiological process which the model describes. Ethanol enters the body via the stomach, where already a small amount can enter plasma. Via the stomach emptying the ethanol enters the intestine. Here, most of the ethanol is taken up via absorption. Most of the ethanol is metabolized in the liver, and a small amount is excreted via renal pathways. In the liver, ethanol is converted into acetaldehyde via three oxidative pathways governed by the enzymes: *Alcohol dehydrogenases* (ADH), catalase, and CYP2E1. Acetaldehyde is further converted into acetate and then acetyl-COA. There also exist non-oxidative pathways, responsible for a miniscule amount of ethanol breakdown, e.g., into PEth. Alcohol concentration is then either measured in the blood (BAC), or in the breath (BrAC). **C)** Schematic over the modelling approach. **D)** Schematic showing the model structure, for a detailed description see material and methods.

Results

The mechanistic model, *i.e.*, the physiologically based digital twin was trained and validated on various published experimental data (14,15,25–32). The model could simultaneously find agreement to all data included in the training dataset using one set of parameters (Fig. 2, 4-5). Additionally, the model can predict independent validation data using the same parameter values (Fig. 6). The model agreement to data was evaluated using a χ^2-test on the residuals (see methods section). The χ^2-test cutoff value was chosen using a confidence level $\alpha = 0.05$, with degrees of freedom being the number of data-points included in the training dataset (193). For the best model agreement, the χ^2 test statistic was 187.0 which was lower than the cutoff ($T_{\chi 2} = 226.4$). The model prediction of the validation data (using the parameter values that gave the best agreement to training data) also passes a χ^2-test with a confidence level of $\alpha = 0.05$. The χ^2 test statistic was 70.8 which was lower than the cutoff ($T_{\chi 2} = 93.5$, for 73 degrees of freedom). Furthermore, we used the modelling framework to test different hypotheses for the effect of meals on the plasma ethanol dynamics (Fig. 3). Lastly, Fig. 7 shows the long-term model behavior for daily drinking and how it can be used to predict PEth levels.

The model can find agreement to gastric emptying data describing different types of interventions.

In this section we will show the model agreement for our gastric emptying module to experimental data from three studies published by Okabe *et al.* (14,15,26). In one of the studies by Okabe *et al.* (14), the study participants drank beverages with the same volume but different caloric content. The data from the study indicates that there is no significant effect of the calorie type on the rate of gastric emptying. The model agreement to this data is shown (Fig. 2A-E). In the second study by Okabe *et al.* (26), participants ingested an alcoholic beverage, whiskey based drink (8.0 %), and the gastric volume was measured. The model agreement to this data is shown in Fig. 2F. In the third study by Okabe *et al*. (15), experimental data indicates that caloric density is not of importance for the gastric emptying, rather the total caloric content is the most significant factor (15). Model agreement to these data is shown in Fig. 2G-H. In summary, our gastric module can find agreement to a range of experimental data and captures fundamental mechanisms shown in the data.

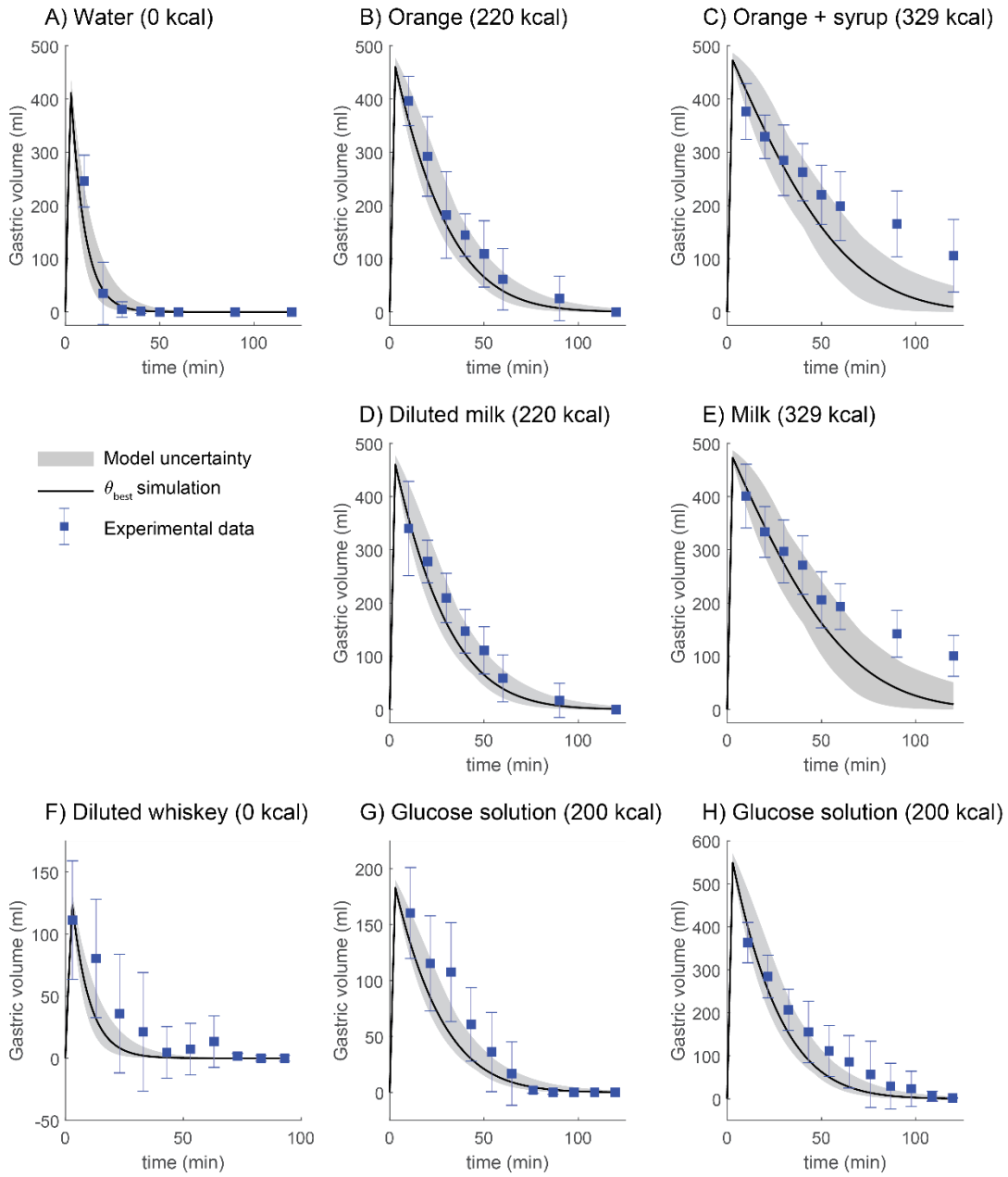

Figure 2: *Model agreement to gastric emptying data.* The solid line is the best model fit, the shaded area is the model uncertainty, the blue boxes are the mean experimental data value with the error bars indicating the standard error of the mean (SEM). The model (solid lines) describes the clearance of different beverages from the stomach (blue markers with error bars). In all experiments the beverage was consumed over 3 minutes and was constituted of the following: **A)** 500 mL containing 0 kcal, **B)** 500 mL containing 220 kcal, **C)** 500 mL containing 329 kcal, **D)** 500 mL containing 220 kcal, **E)** 500 mL containing 329 kcal, **F)** 150 mL containing 0 non-ethanol kcal, **G)** 200 mL containing 200 kcal, and **H)** 600 mL containing 200 kcal. The important factors in controlling the gastric emptying are: 1) total caloric content of the beverage such as sugar and fat do not show a significant difference **B**&**D** vs **C**&**E**, and 2) the total caloric content is important rather than the concentration of calories **G**-**H**.

Investigation of the meal effect on plasma ethanol dynamics

The process of the model formulation governing the meal effect on plasma ethanol is showcased here (Fig. 3). Four different hypotheses (H1-H4) of the interaction between ethanol and the food were formulated based on known interactions (27,33–36). These are illustrated in Fig. 3A, as the following: H1) alcohol is encapsulated by food and released when the food is degraded, H2) the food slows down the passing of liquid to the intestines, H3) in addition to slower passing of liquid to the intestines, gastric alcohol dehydrogenase is present and the activity is upregulated by the food, and H4) processing of the food increases blood flow, and by extension the enzyme effect in the liver. All these hypotheses describe the rate of gastric emptying of foodstuff as reported by Gervais *et al.* (37). These hypotheses were evaluated against the estimation data and only H1 could sufficiently describe data, both quantitatively, and qualitatively (Fig. 3B). Thus, the final model formulation includes the meal effect on plasma ethanol as described by H1.

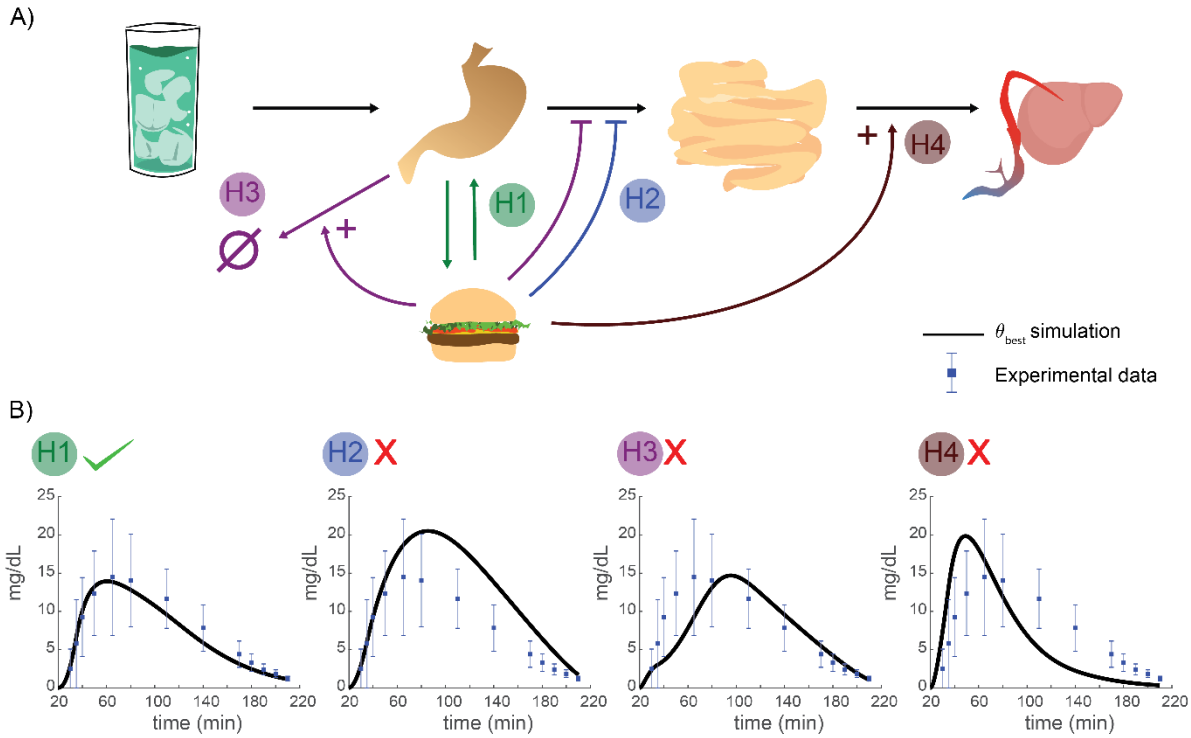

Figure 3: *Investigation of the meal effect on plasma ethanol dynamics.* **A)** Four different hypotheses were designed that could be explained to describe the meal effect on plasma ethanol dynamics. H1: food can encapsulate ethanol while present in the stomach. As the food is processed ethanol can also be released back into the stomach. H2: the contents of the stomach (including the liquid) are held longer due to the food needing to be processed. H3: gastric alcohol dehydrogenase is introduced and is upregulated by food in addition to the contents of the stomach being held longer. H4: the processing of the food recruits more blood to the gastric area and therefore the alcohol is transported more actively to the liver – increasing the activity of liver alcohol dehydrogenase. **B)** The different model hypothesis was implemented and fitted to the estimation data. Here, the simulation of the models is showed for the experimental data from Jones *et al.* (27). When taking all the estimation data into account – only H1 is describing the experimental data sufficiently well.

The model can describe plasma ethanol data from a wide range of real-life drinking scenarios

In addition to describing the stomach emptying data, the model can simultaneously describe plasma ethanol from a wide variety of experimental studies (27–30,38). The studies included in the model training dataset introduced different types of perturbations. We will now go through each one. Firstly, the study by Mitchell *et al.* (28) present the plasma ethanol dynamics after consumption of three different beverages (Beer 5.1, Wine 12, and Spirit 20 v/v %) with different volumes (1.0, 0.42, 0.26 L) resulting in the same total alcoholic content. The model agreement to the Mitchell *et al.* data is shown (Fig. 4A-C). Secondly, the model can fit both data from BAC and *breath alcohol concentration* (BrAC). The model agrees to the BAC data from Jones *et al*. and Kechagias *et al*. in fasting subjects (27,29) (Fig. 4D-E) and in a fed state (Fig. 4G-H). Lastly, Fig. 4F shows model agreement to BrAC data from a study by Javors *et al*. (12). In summary, the model is capable of describing several different types of real-life drinking scenarios.

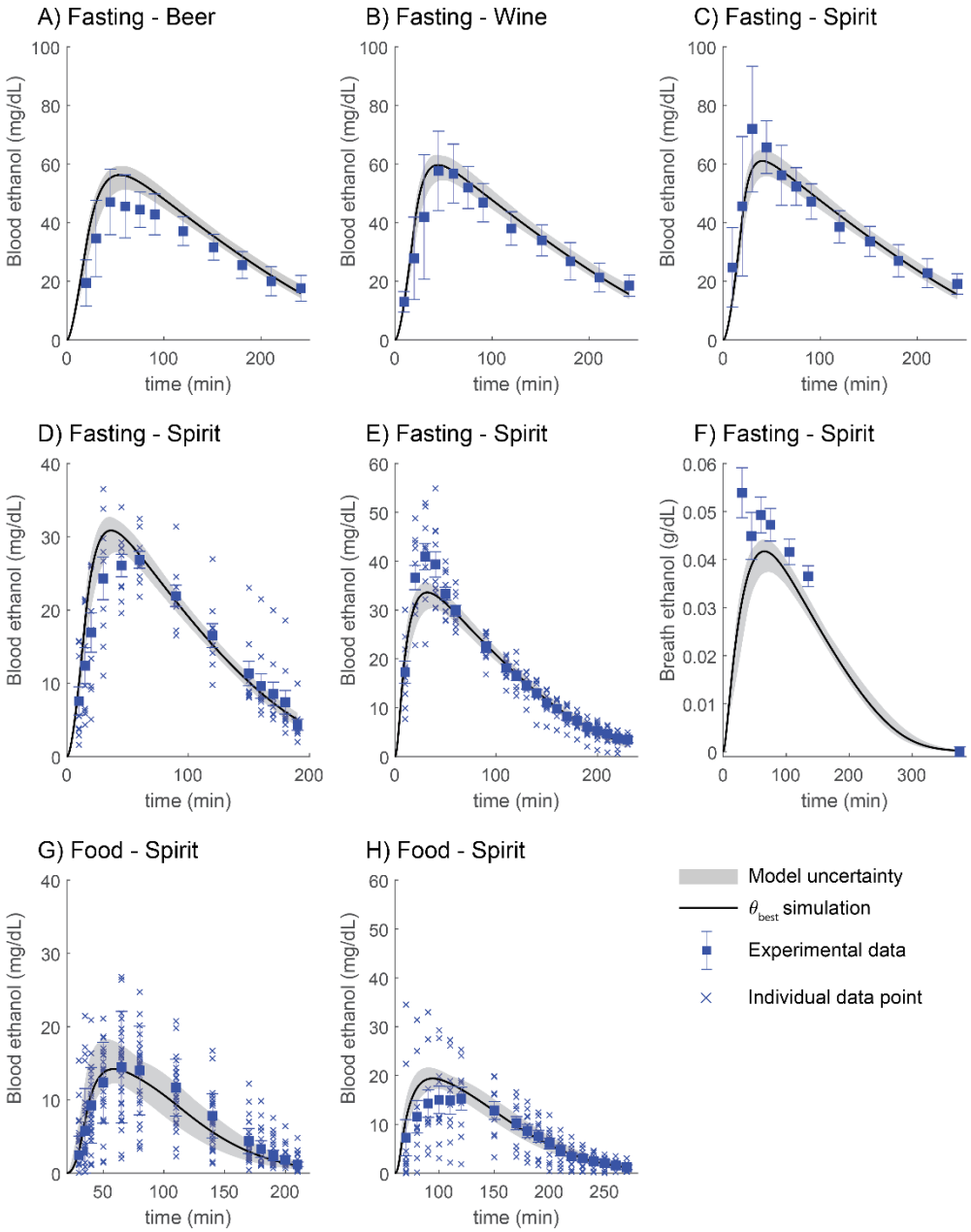

Figure 4: *Model agreement to ethanol data for various interventions*. The solid line is the best model fit, the shaded area the model uncertainty, the white boxes the mean experimental data value with the error bars indicating the standard error of the mean (SEM), individual data points are marked with a x. The alcohol was consumed orally through different beverages in various alterations **A)** 1L of 5.1 v/v % beer (133 kcal) was consumed over 20 min, **B)** 0.42L of 12.5 v/v % wine (56 kcal) was consumed over 20 min, **C)** 0.26L of 20 v/v % spirit blend (43 kcal) was consumed over 20 min, **D)** 0.14L of 20.0 v/v % spirit blend (51 kcal) over 15 min, **E)** 0.15L of 20 v/v % spirit blend (53 kcal) was consumed over 5 min, **F)** 0.71L of 6.5 v/v % spirit blend (247 kcal) was consumed over 15 min, **G)** 0.14L of 20.0 v/v % spirit blend (51 kcal) over 15 min after a meal constituted of 700 kcal, **H)** 0.15L of 20 v/v % spirit blend (53 kcal) was consumed over 5 min after eating a meal constituted of 760 kcal. In **A-F** the beverage was consumed in a fasting state. In **A-E** and **G-H** absolute change of BAC was measured and in **F** absolute change in BrAC was measured.

The model can describe products from hepatic ethanol metabolism

Included in the training dataset was experimental data describing the plasma concentrations of derivatives of oxidative and non-oxidative ethanol breakdown pathways (Fig. 5A). The data used to represent the oxidative pathways was plasma acetate levels after beverage consumption presented by Sarkola *et al.* . The model agreement to the acetate data is shown (Fig. 5B). To represent the non-oxidative breakdown, data describing plasma PEth from a study by Javors *et al.* (30) was included in the training data set; which included both short-term and long-term data of PEth concentration changes. Firstly, for the short-term, the model agrees to data showing PEth levels, presented as relative change, directly after beverage consumption (Fig. 5C). Secondly, for the long-term, the model describes the fast PEth plasma dynamics directly after beverage consumption (Fig. 5D, left), and subsequent slower long-term breakdown over several days (Fig. 5D, right). For the long-term data set Javors *et al*. presented the absolute PEth plasma concentration (ng/mL) (Fig. 5D).

In summary, the model is capable of simultaneously describing data from different ethanol derivatives, in addition to the already shown agreement to gastric-emptying and plasma ethanol dynamics. We will now use the model to make predictions of scenarios not present in the training dataset.

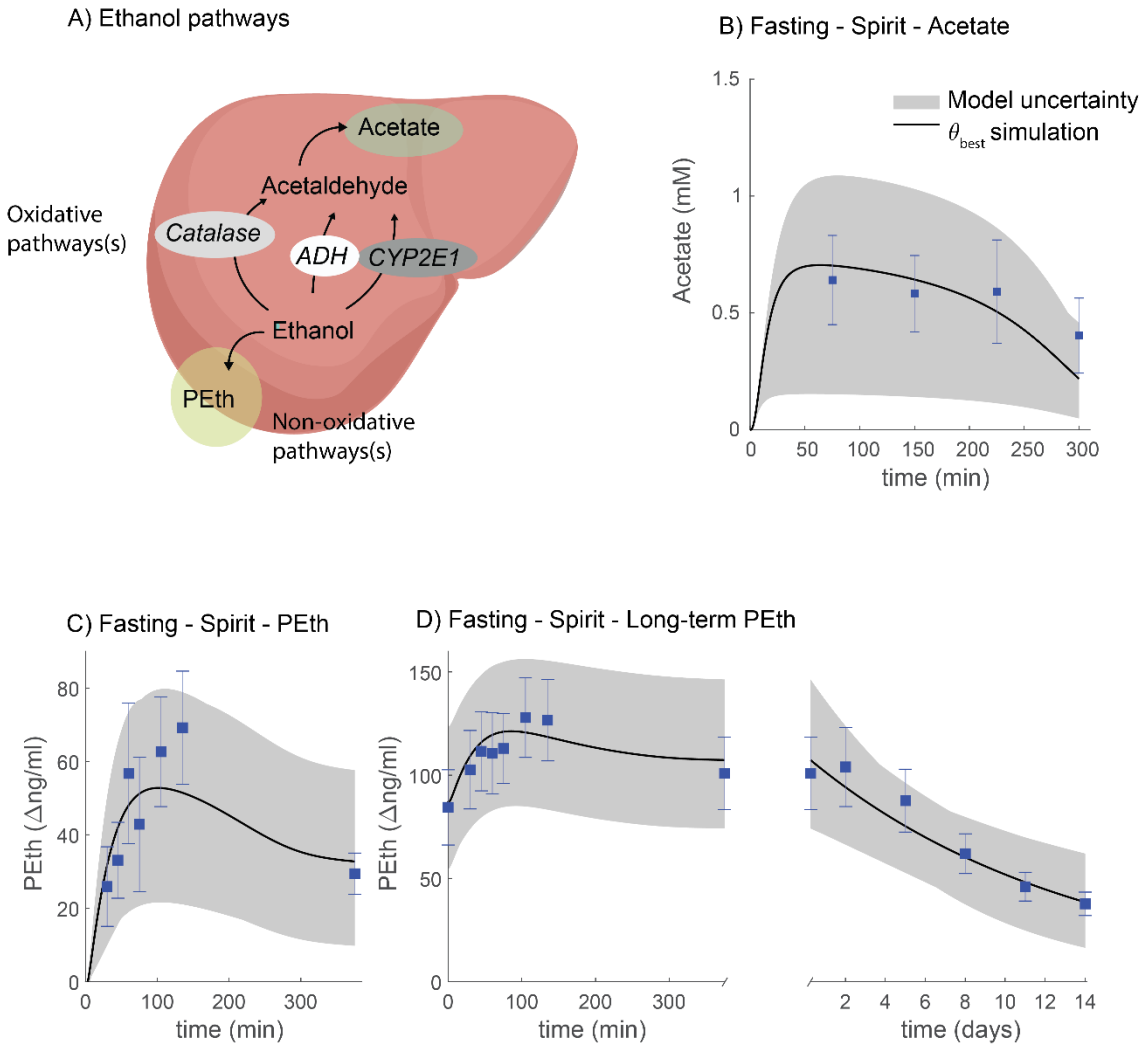

Figure 5: *Model agreement to derivatives of oxidative and non-oxidative ethanol breakdown data for various interventions*. The solid line is the best model fit, the shaded area is the model uncertainty, the blue boxes are the mean experimental data values with the error bars indicating the standard error of the mean (SEM). The alcohol was consumed orally through different beverages. **A)** Schematic of the oxidative and non-oxidative breakdown pathways. **B)** Estimated acetate from consumption of 0.28L of 12.4 v/v % spirit blend (85 kcal) was consumed over 15 min. **C)** Estimated relative change of PEth from consumption of 0.71L of 6.5 v/v % spirit blend (247 kcal) over 15 min. **D)** Weighted mean behavior PEth from two groups consuming different beverages. Group 1 (n=16) consumed 0.72L of 3.25 v/v % spirit blend (251 kcal) over 15 min. Group 2 (n=11) consumed 0.71L of 6.5 v/v % spirit blend (247 kcal) over 15 min. The combined PEth is the mean behavior for both groups.

The model can predict independent validation data

The model was used to make predictions of the behavior of different attributes, and these predictions were validated against experimental data not used during model training (Fig. 6). The model predicts the gastric emptying rate following consumption of; 150 ml water (Fig. 6A), 150 ml glucose liquid containing 67 kcal (Fig. 6B), and 400 ml glucose liquid containing 200 kcal (Fig. 6C). Data presented by Okabe *et al*. (15,26). Predictions of plasma ethanol following consumption of an alcoholic beverage are compared with experimental data from Sarkola *et al*. (31)(Fig. 6D). The model can also predict data from a study by Javors *et al*. (30). In Fig. 6E model predictions of the behavior of BrAC are shown. In Fig. 6F relative PEth levels following consumption of an alcoholic beverage in shown. Furthermore, the model can also predict experimental data from Frezza *et al*. (32). Shown in Fig. 6G-H are model predictions of the influence of a meal and sex differences on the BAC level. The model agreement to data for women (Fig. 6G) and corresponding agreement to data for men (Fig. 6H). In these data the study participants consumed the same alcoholic contents per body weight.

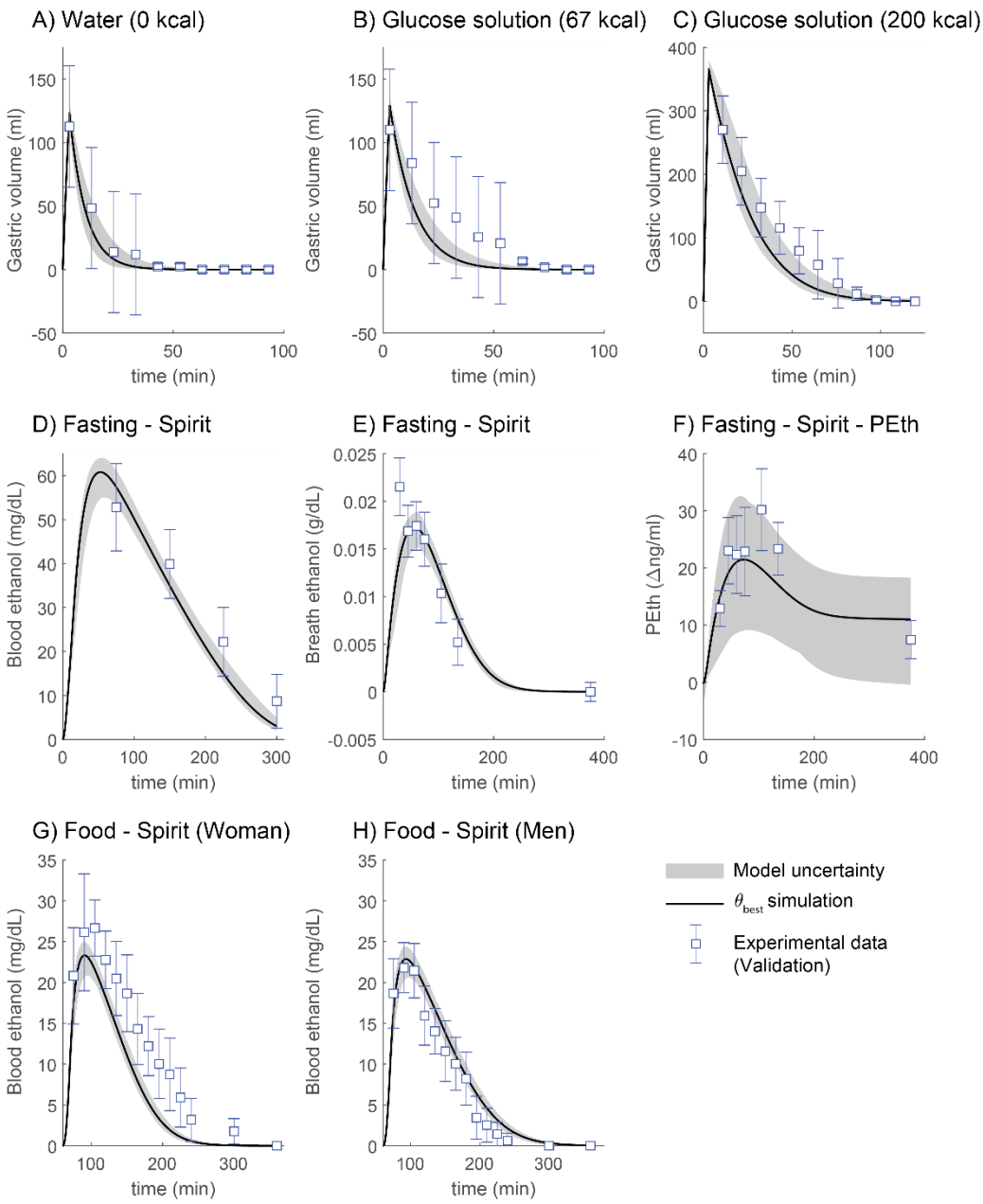

Figure 6: *Model predictions compared to data for various interventions*. The solid line is the best model fit, the shaded area the model uncertainty, the white boxes are the mean experimental data values with the error bars indicating the standard error of the mean (SEM) – the white box indicated that the data was used for model validation. **A)** gastric emptying of 150 mL water, **B)** gastric emptying of 150 mL glucose liquid containing 67 kcal, **C)** gastric emptying of 400 ml glucose liquid containing 200 kcal, **D)** plasma ethanol levels from consumption of 0.48L of 10.0 v/v % spirit blend (149 kcal) over 15 min, **E)** breath ethanol levels from consumption of 0.72L of 3.25 v/v % spirit blend (251 kcal) over 15 min, **F)** relative change of PEth levels from consumption of 0.72L of 3.25 v/v % spirit blend (251 kcal) over 15 min, **G)** plasma ethanol levels in women after consumption of 0.20L of 12 v/v % spirit blend (36 kcal) over 10 min after eating a meal constituted of 555 kcal, **H)** plasma ethanol levels in men after consumption of 0.24L of 12 v/v % spirit blend (43 kcal) over 10 min after eating a meal constituted of 555 kcal.

The model can be used to predict the effect of long-term alcohol use on PEth and differences in alcohol patterns.

To highlight model usability, we used the validated model to highlight two different areas of use. The first example was to show how the short-term drinking habits affect the long-term values of the alcohol consumption marker PEth (Fig. 7B, D). The second examples were to highlight model personalization and how sex-specific anthropometric difference effect plasma ethanol dynamics in different drinking scenarios (Fig. 7A, C).

To investigate how well the model could assess the effect of long-term drinking on PEth levels, the model was used to simulate the PEth study presented by Kechagias *et al.* (25). In the study, 44 participants drank wine (13.5-14%v/v) every evening (16.0-16.5 g, 1.3 standard drinks for women, and 32-33g, 2.7 standard drinks for men) for 3 months and their PEth levels were measured after 3 months. In Fig. 7A, we show the model prediction of plasma ethanol after the study specified daily dosage, one glass of wine for females, for five females with different anthropometrics (BMI 18, 22.5, 25, 28.5, and 32). The wine was consumed together with a dinner containing 920 kcal (40% of recommended daily intake for a medium active young adult female, in Sweden). In Fig. 7C, we show the model prediction of plasma ethanol after the study specified daily dosage, two glasses of wine for males, for five males with different anthropometrics (BMI 18, 22.5, 25, 28.5, and 32). The wine was consumed together with a dinner containing 1120 kcal (40% of recommended daily intake for a medium active young adult male, in Sweden) Using the model, we simulated the 3-month long study intervention and compared the model predicted PEth values with the PEth range presented by Kechagias *et al*. The model predicted PEth values for all subjects, with different anthropometrics, to be within the reported range of the Kechagias *et al*. measured values (0.007-0.17 $\mu mol/L$).

To illustrate the personalization capabilities of the model we have made simulations of either male (Fig. 7A) or female (Fig. 7C) anthropometrics, with varying BMI 18-32. The consumption of one glass of wine, by females, yields a plasma ethanol level (11 mg/dL, BMI 18), which is less than half of that of men consuming 2 glasses of wine (27 mg/dL, BMI 18). This is explained by the relative higher ability of the meal (920 kcal for females and 1120 kcal for men) to lower the plasma ethanol for females. As men consumes double the volume of wine the only slightly bigger meal cannot slow down the appearance of ethanol in plasma as effectively as in the case for the females, resulting in a higher response. For both females and men, we observe a lower peak value with increasing body size (BMI value).

As proof of concept, we also showcase the model capability of predicting weekly alcohol-consumption and the corresponding PEth levels (Fig. 7E-F). For a specific individual, defined via sex and BMI, the model can predict the long-term PEth levels for continuous drinking of various drinking schedules, corresponding to different amounts of weekly intake (g/week) (Fig. 7E). Using this approach, the model can predict a trajectory (gradient area) of what range of PEth levels correspond to which weekly consumption. Clinically, such a trajectory could be compared to a reported value (Fig. 7F, yellow dot), giving an indication if patients fail to self-report consumption (Fig. 7F). In Fig. 7G we show as a concept, the further integration into an easy-to use eHealth application, which we will create in the future.

In summary, our validated model can simulate long-term alcohol consumption and predict clinically relevant levels of PEth. Using the model, we could also simulate highly personalized

predictions based on anthropometry and show the effect on different types of drinking habits. The model could thus be used in a wide variety of applications to assess the level of alcohol consumption e.g., to validate reported consumption via an *Alcohol Use Disorders Identification Test* (AUDIT-C).

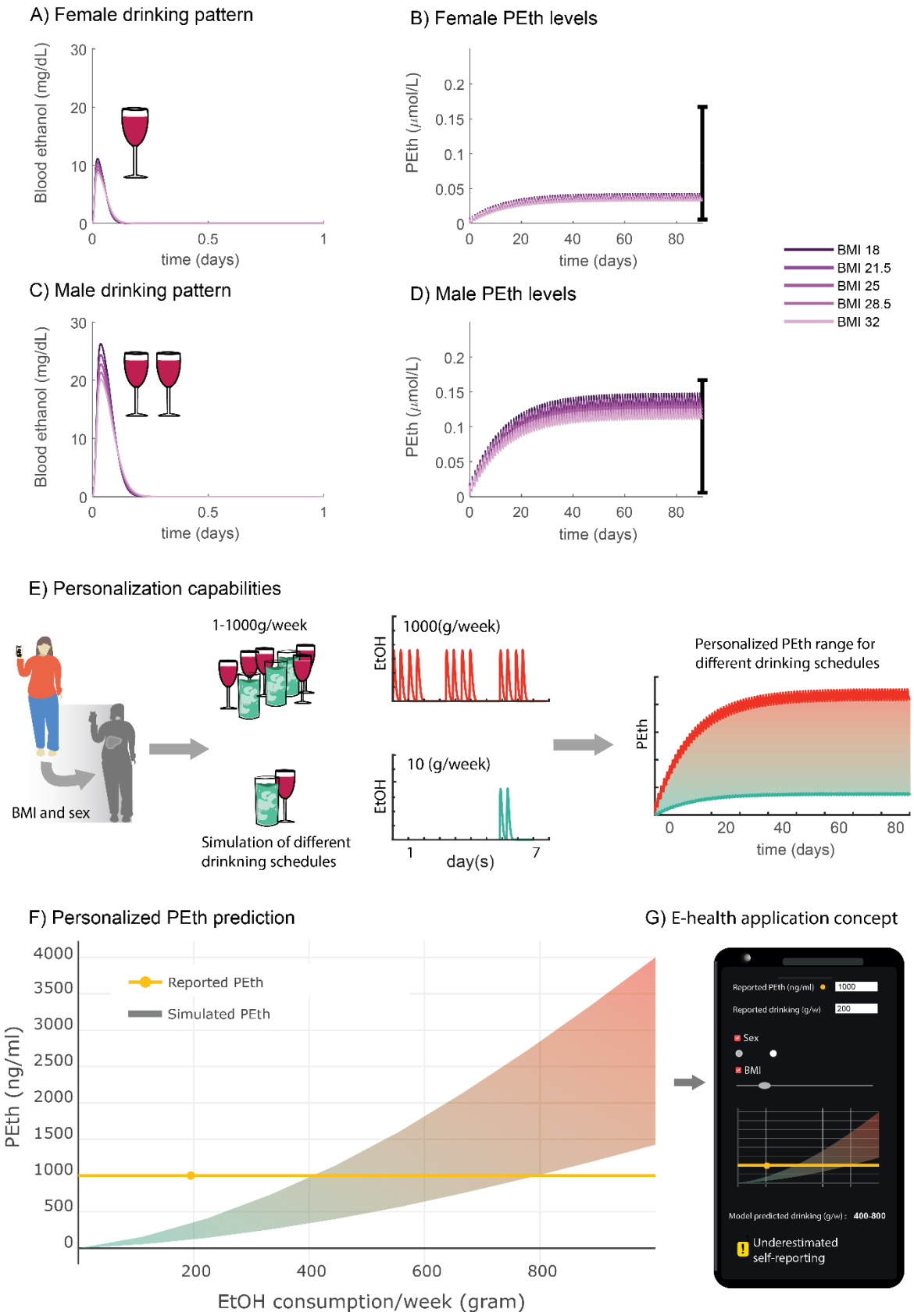

Figure 7: *Model simulations of long-term plasma ethanol dynamics.* We here show model simulations of the short-term ethanol dynamics with corresponding long-term progression of PEth levels for two different drinking patterns, one for male and one for female, in the three month long drinking intervention presented in Kechagias *et al.* (25). We also show a simulation approach for determining alcohol consumption. **A)** Model simulated ethanol

dynamics during consumption of one standard glass of wine (15 cl, 13.5 v/v %) %) together with a meal consisting of 920 kcal by the female participants. The simulations were done for participants with different BMIs (18-32, light-to-dark purple lines). **B)** Model simulation of PEth for females consuming one standard glass of wine every day for 90 days and for the five different body sizes, BMI 18-28. The error bar represent the PEth range reported in Kechagias *et al*. (25). **C)** Model simulated ethanol dynamics during consumption of two standard glasses of wine (30 cl, 13.5 v/v %), in one sitting, together with a meal consisting of 1120 kcal., by the male participants. **D)** The corresponding model simulation of PEth progression for males consuming two standard glasses of wine every day for 90 days and for the five different body sizes, BMI 18-32. The error bar represent the reported PEth range by Kechagias *et al*. (25). **E)** We here show our simulation approach for determining alcohol consumption based on a given PEth level. For a specific individual, defined via sex and BMI, the model also allows for simulations of different drinking patterns which can correspond to different amounts of alcohol consumed per week (1 to 1000g/week). The weekly consumption can then be simulated for a longer time so that the steady-state PEth levels for the specific drinking schedule can be acquired. **F)** Using this approach for different amounts of consumption, the model can predict a trajectory for what weekly consumption corresponds to which PEth level range. The simulated trajectory is shown as the gradient area. The yellow line is an example of a predicted miss-match in self-reporting and model simulated alcohol consumption, for a specific PEth level. **G)** As a concept we show the future aim to integrate the physiologically based digital twin into an eHealth application, with possible use in clinics to motivate treatment compliance for patients with heavy drinking problems.

Discussion

Herein, we have presented a mathematical model that can be personalized into a physiologically based digital twin for alcohol consumption capable of simulating real-life drinking scenarios. The model could simultaneously find agreement to: gastric emptying data for beverages with different volume and caloric content (Fig. 2), plasma ethanol in response to various drinking challenges (with and without food consumed) from different individuals (Fig. 4), and lastly data for markers of metabolized ethanol (Fig. 5). Furthermore, the model could make validated predictions of gastric emptying, BAC, BrAC, and PEth (Fig. 6). We also tested four hypothesis of meal effects on plasma ethanol (Fig. 3), where only one hypothesis agreed with the experimental data. The validated model was then used to investigate the effect of anthropometric differences on the short-term plasma ethanol dynamics (Fig. 7). Lastly, the model predicts the long-term dynamics of PEth in response to daily consumption of alcohol (Fig. 7). These long-term predictions accurately describe the 90-day end of trail PEth range reported by Kechagias *et al*. (25).

The model can accurately describe short-term ethanol dynamics.

The model was trained and validated to a total of 10 different study datasets, which include different conditions, such as; different beverage volumes, ethanol content, food consumption or fasting, and sex-specific parameters (Fig. 2, 4-6) (14,15,25–32). The model could explain all training and validation data for both ethanol and PEth to a satisfactory level (Fig. 4&6). Furthermore, the model also describes the plasma acetate level following an alcoholic drink (Fig. 5B), with data from Sarkola *et al*. (31). While the model passes a χ^2-test for all estimation data, it is worth pointing out some aspects of the data that the model does not fully capture. Most notably, the model does not describe the observed amplitude in BAC data for some data sets. For instance, from the studies by Kechagias *et al*. and Jones *et al*., different BAC dynamics where reported for the same consumption of 0.3 g ethanol/kg bodyweight for subjects with similar anthropometrics (27,29). As all the drinking challenges presented to the model are fitted with the same set of parameter values the model is not able to account for differences in BAC behavior for similar drinking challenges (Fig. 4D-E). We also observe that the model does not quite capture the dynamics of the peak in the data for beer and spirit consumption (Fig. 4 A,C) from Mitchell *et al.* (28). This could be due to us estimating the caloric content falsely (see supplementary material, S2. Model input estimation), making the gastric emptying rate of beer to fast and spirit to slow. Also, in the case of the beer data (Fig. 4A), the potential effect of carbonation on the rate of gastric emptying (39–41) could potentially influence the gastric emptying to allow better plasma ethanol dynamics for the beer data .

Unlike previous models, our model has integrated gastric emptying dynamics to account for the influence of the caloric content, drink volume, and meal effect on gastric emptying (10,42–44). While newer models have been developed to include dynamics of the stomach, they are limited to only considering alcoholic drinks (11,13) and not consumption of drinks paired with food. This makes them less usable when describing a real-life setting, where alcoholic drinks are often mixed with non-alcoholic drinks and food.

Mechanistic model for the meal effect on plasma ethanol dynamics

We tested several hypotheses regarding the meal effect on gastric emptying. The effect of meals on plasma ethanol dynamics has been discussed in various studies (27,33–36) and the literature

is not unanimous on the underlying mechanism. Therefore, we formulated four different hypotheses (H1-H4) of the meal effect (Fig. 3A). In the first hypothesis (H1) food can encapsulate ethanol while present in the stomach (27). As the food is processed ethanol can be released back into the stomach and thus again become available for future absorption in the intestines. In the second hypothesis (H2) the contents of the stomach (including the liquid) are held longer in the stomach, due to the need for the food to be processed. In the third hypothesis (H3), H2 is extended to also include gastric ADH (27). In the final hypothesis (H4) the processing of the food recruits more blood to the gastric area which leads to both a faster uptake of alcohol and clearance due to increased activity of liver ADH (33,35,36). We tested these hypotheses by evaluating their best agreement to the experimental data. We found that only H1 was able to have acceptable agreement to data, and H2-H4 had to be rejected (Fig. 3B).

While the rejected hypotheses show that the corresponding mechanisms were not sufficient in explaining the available experimental data, the mechanisms might still be there. For example, studies have shown that eating a meal reduces the amplitude and increases the clearance of plasma ethanol when ethanol is administrated intravenously (33,36). In this situation, additional mechanisms like the ones in H4 might be needed. This is because food consumed will have limited interaction with alcohol in the stomach, likely meaning that the processing of the food recruits more blood to the liver. However, intravenous infusion of alcohol is outside of the scope for normal drinking, which the model is aimed at describing. Since these mechanisms were not needed for describing the training data, we have not included the mechanisms from H4 in the final model. Furthermore, there is a consensus that ADH is present in the stomach (35,45–47). Again, these mechanisms were not able nor needed to describe the experimental data and were therefore not included in the final model. The final model corresponds to H1 and can describe all the available experimental data sufficiently well.

Caloric content as a model input is enough to describe differences in gastric emptying

In line with the reported work of Okabe *et al.* (14,15), we choose the total beverage caloric amount as the driving factor for gastric emptying. This concept is further illustrated in other studies (17,48,49). Although this has previously been debated since other factors are thought to be important such as; viscosity, osmolality, and nutrient composition (19,49,50). However, the effect of these factors seems to be outweighed by the total amount of non-ethanol calories, which was the only effect included in the model driving the liquid gastric emptying.

We also had to make some simplifications of the gastric emptying rate of foodstuff. Firstly, we have opted to not differentiate between the caloric density for the different macronutrients (carbohydrates, protein, and fat). There are reported cases of macronutrients affecting the plasma ethanol level differently (27,34), although there is no major difference. Due to the small difference and macronutrient information not being consistently reported in studies, we left it out from our framework. Secondly, there are more variables describing the meal that were not included in the model. One such variable is the viscosity of foodstuff. The caloric content has been shown to have a larger impact than the viscosity on the gastric emptying (51), we therefore choose the caloric content to be the driving factor. Thirdly, another simplification is the foodstuffs ability to hinder ethanol absorption after consumption. The exact timing of the highest effect of food on the absorption is not known, which was reported by Franke *et al.* (52). Although the effect is reported, we do not have enough data on the mechanisms to quantify the

effect on the plasma ethanol rate of appearance. Lastly, an additional measure that could be considered is the fiber contents of a meal. Including the fiber content in the model would allow for distinguishing between liquid and solid meals, and by extension the rate of gastric emptying of solids (16,53). However, it is reported that the emptying rate of liquids remains mostly unaffected in the presence of foodstuff (18,54). The fiber contents have not been reported to influence the ethanol rate of appearance in plasma, and thus we did not include such a description. In summary, there are a lot of reported mechanisms in literature, but more data would be needed to include them in our digital twin.

Predicting the long-term PEth outcome based on short-term drinking habits

Simulation-based models, such as a physiologically based digital twins have not yet been explored in the context of eHealth application aimed at reducing dangerous drinking habits. A variety of eHealth and smartphone applications have shown tentative promise as tools for reducing alcohol consumption (7,55–58). These applications mainly focus on either supporting, altering, or educating individuals about their drinking habits. An eHealth application similar to our simulation-based model is evaluated in a study by Gajceki *et al.* (59). In the study, a smartphone application showing real time assessment of *estimated blood alcohol concentration* (eBAC) and simulations of predicted eBAC during a future drinking event was tested in a cohort of university students. The use of these apps did not impact alcohol consumption in the study group. One critical element we believe is needed for such applications to have an impact is to connect the short-term drinking to long-term consequences, which our physiologically based digital twin can provide.

Our validated model could tentatively predict PEth levels based on short-term consumption habits (Fig. 7B, D). The use of plasma PEth as biomarker for alcohol consumption is widely used in clinical practice, sometimes as a validation to self-reporting systems (such as AUDIT-C) (60,61). As a proof-of-concept, we provide simulations of long-term PEth levels in response to different drinking patterns and anthropometrics (Fig. 7 B, D), as well as provide a tool to evaluate self-reported weekly drinking in combination with measured PEth levels (Fig. 7 E-G). In the future, having a personalized model capable of predicting the long-term PEth trajectories given short-term drinking habit might prove useful for patients, where distinguishing between moderate, and heavy drinking is important, e.g., liver-transplant patients. In the future we would like to further validate the long-term PEth model predictions, as well as expand the ethanol degradation pathways in model. With the intention to show how long-term exposure might lead to dysregulated metabolism and *alcohol related liver disease* (ALD).

Limitations and delimitation

There are some model limitations and delimitations that should be discussed. We will begin by discussing limitations in the data. All data used in this project was acquired via digitalization, thus a negligible difference from the actual data might exist. However, the qualitative information in the dataset is the same. In addition to this, some of the studies did not report anthropometrical data of the subjects or details regarding several aspects of the experimental setup e.g., reported drinking time. Also, for some datasets mean values were calculated in a mixed cohort including both female and male participants (30,31). To take this into consideration we opted to estimate the mean blood volume based on the sex distribution. Also,

for some studies the caloric content was not reported, leading to some assumptions regarding the consumed beverage. The caloric content is of importance as the gastric emptying module is the major contributor to the ethanol rate of appearance in plasma. For details regarding assumptions see supplementary material, S2. Model input estimation.

Conclusion

We herein present a physiologically based digital twin, including a gastric emptying module, capable of describing plasma ethanol dynamics for a wide variety of drinking scenarios. The twin also connects short-term alcohol consumption to long-term progression of the clinical marker PEth. We hope that the digital twin, with further validation and integration of more personalization (such as genetic variations in enzyme expression), could serve as a clinical tool to e.g., test reported alcohol consumption in an AUDIT questionnaire. This digital twin could function as a first simulation-based eHealth application for alcohol consumption, with the goal of educating people about their alcohol drinking habits and their long-term effects.

Method

Model description

Here we will briefly go through the model equations. The full description of model equations and simulation approach can be found in the supplemental material (supplementary material, S1. Model formulation). Additionally, a summary of all the model inputs assembled from all the studies and derived model inputs can be found in the supplementary (supplementary material, S2. Model input estimation).

Data availability

In this work, experimental data was collected from a wide variety of different published studies and used for model estimation and validation. This section will detail information about the studies included.

Gastric emptying

Three studies were included concerning the gastric emptying of liquids, all being works of Okabe *et al*. The first study describes the emptying rate of 500 ml liquids containing different amount of calories (14). The second study investigated how the total volume affects the emptying of isocaloric beverages (15). The third study investigates how calories from ethanol compares to non-alcoholic calories in isometric volume beverages.

Blood alcohol concentration

A variety of studies observing the BAC levels were included, some including the impact of a meal in combination with an alcoholic beverage. Mitchell *et al.* investigated the effect of consuming different alcoholic beverages with the same total alcoholic content (28). Sarkola *et al.* investigated an additional variant of alcoholic beverage (31). Kechagias *et al.* and Jones *et al.* both compared the BAC levels after consumption of an alcoholic beverage, with and without having a meal (27,29). Lastly, the work of Frezza *et al.* presents sex specific differences in the BAC levels after consumption of an alcoholic beverage, where the ethanol contents were determined on the subjects body weight, in combination with a meal (32).

Blood alcohol derivates

We also included several studies measuring either acetate or PEth after ingestion of alcohol. Firstly, in a study by Sarkola *et al.* the appearance of blood acetate after consumption of a single alcoholic drink (31) was reported. Secondly, time series of BrAC and PEth were published by Javors *et al*. for two drinks with different alcoholic content (30). Javors *et al.* also presented PEth measurements over a two-week period. Lastly, Kechagias *et al.* presented a study where PEth level were measured before and after a 30 day period of daily consumption of wine (25).

Parameter estimation

All model analysis and simulation were performed in both MATLAB 2022b and Python 3 using the system biology toolbox (62). For model parameter estimation the extended scatter search (ESS) algorithm implemented in the MEIGO toolbox was used (63).

Parameter estimation was done by quantifying the model performance, using the model output ŷ to calculate the traditional weighted least squares cost function defined as

$$V(\theta) = \sum_i \sum_k \sum_j \left(\frac{y_{i,k,j}(t_{i,k,j}) - \hat{y}_{i,k,j}(t_{i,k,j},\theta)}{SEM_{i,k,j}(t_{i,k,j})} \right)^2 \quad \text{(Eq. 1)}$$

$$SEM_{i,k,j} = \frac{\sigma_{i,k,j}(t_{i,k,j})}{\sqrt{n_{i,k,j}(t_{i,k,j})}} \quad \text{(Eq. 2)}$$

where, θ is the model parameters; $y_{i,k,j}(t_{i,k,j})$ is the measured data from a study *i*, and from on type of measure *k*, at time point *j*; $\hat{y}_{i,k,j}(t_{i,k,j},\theta)$ is the simulation value for a given experiment setup *i*, type of measure *k*, and time point *j*. SEM is the standard error of the mean, which is the sample standard deviation, $\sigma_{i,k,j}(t_{i,k,j})$ divided with the square root of the number of repeats, $n_{i,k,j}(t_{i,k,j})$ at each time point. The value of the cost function, $V(\theta)$, is then minimized by tuning the values of the parameters, typically referred to as parameter estimation.

To evaluate the new model, we performed a χ^2-test for the size of the residuals, with the null hypothesis that the experimental data have been generated by the model, and that the experimental noise is additive and normally distributed. In practice the cost function value was compared to a χ^2 test statistic, $T^o_{\chi 2}$. The test statisticχ^2 cumulative density function,

$$T^o_{\chi 2} = \mathcal{F}^{\text{cdf-inv}}_{\chi 2}(1-\alpha, v) \quad \text{(Eq. 3)}$$

where $\mathcal{F}^{\text{cdf-inv}}_{\chi 2}$ is the inverse density function; and α is the significance level (α = 0.05, was used) and *v* is the degrees of freedom, which was equal to the number of data points in the training dataset (193 in total, all timepoints over all experiments). In practice, the model is rejected if the model cost is larger than the χ^2-threshold ($T^o_{\chi 2}$).

Uncertainty estimation

The model simulation uncertainty was gathered as proposed in (64). The model uncertainty is estimated by dividing the problem into multiple optimization problems, with one problem per model property ($\hat{p}$). In this work, the property $\hat{p}$ corresponds to either a simulation at a specific time point *j*, $\hat{y}(t_{j,}\theta)$, or a parameter value $\hat{\theta}_m$. Each problem is solved by maximizing and minimizing the property value, while satisfying that the cost ($V(\theta)$) is below the χ^2-threshold ($T^o_{\chi 2}$). By identifying the maximal and minimal value of the model property ($\hat{p}_{max}$ and $\hat{p}_{min}$), we get the boundary values of the property uncertainty area. Mathematically, this operation for the parameter values is formulated as,

$$minimize\ \hat{\theta}_m \quad \text{(Eq. 4a)}$$

$$subject\ to\ V(\theta) < T^o_{\chi 2} \quad \text{(Eq. 4b)}$$

where $\hat{\theta}_m$ is minimized to find the lower value of the parameter, while also satisfying that the cost ($V(\theta)$) is below the χ^2-threshold ($T^o_{\chi 2}$). To find the upper bound of the uncertainty area

the problem is maximized instead. In practice, the constraint (Eq 4b) can be relaxed into the objective function as a L1 penalty term with an offset if $V(\theta) > T_{\chi 2}^{o}$.

$$minimize\ \hat{\theta}_m + penalty \qquad \text{(Eq. 5a)}$$

$$where\ penalty = \begin{cases} |\hat{\theta}_m| + |\hat{\theta}_{m,0}| * \left(1 + \left(V(\theta) - T_{\chi 2}^{o}\right)\right), if\ V(\theta) > T_{\chi 2}^{o} \\ 0, \qquad otherwise \end{cases} \qquad \text{(Eq. 5b)}$$

Here, the penalty is scaled with the initial value of the parameter, $\hat{\theta}_{m,0}$ and the offset between the cost and the χ^2-threshold ($V(\theta) - T_{\chi 2}^{o}$). To maximize the parameter $\hat{\theta}$, and thus finding the upper bound of the uncertainty area, we solve the problem as a minimization problem. This is done by substituting $\hat{\theta}_m$ with $-\hat{\theta}_m$ in the objective function. To solve the problem for the model simulation at a specific time point, $\hat{y}(t_j, \theta)$, we formulate the problem as follows,

$$minimize\ \hat{y}(t_j, \theta) + penalty \qquad \text{(Eq. 6a)}$$

$$where\ penalty = \begin{cases} |\hat{y}(t_j, \theta)| + |\hat{y}(t_j, \theta)_0| * \left(1 + \left(V(\theta) - T_{\chi 2}^{o}\right)\right), if\ V(\theta) > T_{\chi 2}^{o} \\ 0, \qquad otherwise \end{cases} \qquad \text{(Eq. 6b)}$$

Here, the penalty is scaled with the initial value of the parameter, $\hat{y}(t_j, \theta)_0$, and the offset between the cost and the χ^2-threshold ($V(\theta) - T_{\chi 2}^{o}$). To maximize the model simulation at time point *j*, ($\hat{y}(t_j, \theta)$, and thus finding the upper bound of the uncertainty area, we solve the problem as a minimization problem. This is done by substituting $\hat{y}(t_j, \theta)$ with $-\hat{y}(t_j, \theta)$ in the objective function.

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