Predicting the macronutrient composition of mixed meals from dietary biomarkers in blood

Anurag Das, Bobak Mortazavi, Seyedhooman Sajjadi, Theodora Chaspari, Laura E. Ruebush, Nicolaas E. Deutz, Gerard L. Cote, Ricardo Gutierrez-Osuna

***Abstract*— Diet monitoring is an essential intervention component for a number of diseases, from type 2 diabetes to cardiovascular diseases. However, current methods for diet monitoring are burdensome and often inaccurate. In prior work, we showed that continuous glucose monitors (CGMs) may be used to predict the macronutrients in a meal (e.g., carbohydrates, protein, and fat) by analyzing the shape of the post-prandial glucose response. The objective of this new study was to examine a number of additional dietary biomarkers in blood by their ability to improve the prediction of meal macronutrients, compared to using CGMs alone. As our experimental method, we conducted a nutritional study where (*n=10*) participants consumed nine different mixed meals with varied but known macronutrient amounts, and we analyzed the concentration of 33 dietary biomarkers (including amino acids and their combinations, insulin, triglycerides, and 3 independent measures of glucose) at various times post-prandially. As our computational method, we built machine learning models to predict the macronutrient amounts from (1) individual biomarkers and (2) their combinations. The major result from this work is that the additional blood biomarkers provide complementary information, and more importantly, achieve higher prediction performance for the three macronutrients in terms of normalized root mean squared error (carbohydrates: 22.9%; protein: 23.4%; fat: 32.3%) than CGMs alone (carbohydrates: 28.9%, $t(18)=1.64, p=0.060$; protein: 46.4%, $t(18)=5.38, p<0.001$; fat: 40.0%, $t(18)=2.09,\ p=0.025$). Our main conclusion is that augmenting CGMs to measure these additional dietary biomarkers improves macronutrient prediction performance, and may ultimately lead to the development of automated methods to monitor monitor nutritional intake. This work is significant to biomedical research as it provides a potential solution to the long-standing problem of diet monitoring, facilitating new interventions for a number of diseases.**

***Index Terms*— Continuous glucose monitors, biomarkers, diet monitoring, macronutrients, machine learning**

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A. Das, B. Mortazavi, S. Sajjadi, T. Chaspari and R. Gutierrez-Osuna are with the Department of Computer Science and Engineering, Texas A&M University. L. E. Ruebush and N. E. Deutz are with the Center for Translational Research in Aging and Longevity, Texas A&M University. G. L. Cote is with the Department of Biomedical Engineering, Texas A&M University

I. Introduction

POOR diet is a major contributor to the development of chronic diseases, from type 2 diabetes to heart disease [1]. Thus, monitoring and modifying food intake is an essential component of many clinical interventions. However, conventional methods for diet monitoring rely on self-report tools (e.g., food diaries, 24-hour recall), which are problematic. For example, food diaries require manual input, which is burdensome [2] and often leads to low adherence rates [3]. Further, 24-hour records suffer from memory recall, which can lead to severe over and under-reporting [4]. To address this issue, various wearable sensing techniques (e.g., microphones, accelerometers) are being explored to detect eating behaviors such as hand-to-mouth movements and chewing/swallowing [5]–[7]. These approaches can be used to detect moments of food intake, but have limited ability to estimate the nutritional content of foods. The latter requires measuring dietary biomarkers associated with consumption of various nutrients.

As a first step in this direction, in recent work [8], [9] we proposed using continuous glucose monitors (CGMs) to monitor food intake. CGMs generally consist of a small electrode inserted under the skin to measure glucose in the interstitial fluid, and a transmitter that sends the information to a monitoring device. Our rationale for using CGMs for diet monitoring was based on the observation that changes in blood glucose levels after a meal, also known as the post-prandial glucose response (PPGR), depend on the meal macronutrients (e.g., carbohydrates, protein, fat). Though the major determinant of post-prandial glucose is the amount of carbohydrates (CHO), adding protein or fat to a meal generally yields smaller spikes and lengthier responses [10], [11]. To test this rationale, we conducted a study in which 15 healthy participants consumed nine different meals over the course of 2-3 weeks while wearing a CGM. Each meal had a different but known amount of CHO, protein, and fat. Then, we trained several machine learning models to predict the macronutrient amounts (i.e., grams of CHO and protein, and milliliters of fat) from the PPGRs. The best performing models were able to predict the macronutrient amounts with a normalized root mean squared error (NRMSE) of 22% for CHO, 47% for protein and 40% for fat, a promising result given the large inter-individual differences in food metabolism [12].

As a logical next step, the aim of this work was to examine whether measuring additional blood biomarkers would improve prediction performance for the three macronutrients,

when compared to using only glucose measurements from CGMs. To answer this question, for 10 of the participants in the abovementioned study, we also analyzed blood samples at various times during the post-prandial period to measure the plasma concentration of three additional types of biomarkers: insulin, triglycerides, and amino acids. Further, since CGMs measure glucose in interstitial fluid, we collected two additional glucose measures in venous blood for comparison, via liquid chromatography (LC) and fingerstick blood glucose measurement. Our working hypothesis was that the addition of amino acids and triglycerides would primarily improve the prediction performance for protein and fat, respectively. Using extreme gradient boosted decision trees (XGBoost) [13] as the underlying prediction model, we performed a series of computational analyses to predict meal macronutrients. These analyses consistently indicate that the additional blood biomarkers provide complementary information to each other and, more importantly, achieve higher prediction accuracy for the three macronutrients (CHO: 22.9%; protein: 23.4%; fat: 32.3%) than CGMs alone (CHO: 28.9%, $t(18)=1.64, p=0.060$; protein: 46.4%, $t(18)=5.38, p<0.001$; fat: 40.0%, $t(18)=2.09, p=0.025$; one-tailed t-test).

This work is novel in several respects. First, to our knowledge, the problem of predicting meal macronutrients from blood biomarkers has never been examined, with the exception of our recent prior work [8], [9]. However, our prior work focused on glucose responses from CGMs, whereas the present work evaluates 32 additional biomarkers by their ability to predict macronutrients. Second, through a series of complementary analyses, we identify (1) the most relevant individual biomarkers, (2) the most relevant combinations of biomarkers, and (3) the most relevant regions in the postprandial response of these biomarkers. Third, our work is related to (but distinct from) research on the artificial pancreas (AP) [14]. In both cases, the goal is to infer food intake. In the artificial pancreas, this information is used to control an insulin pump, which administers doses of insulin according to a pre-established insulin-to-carb ratio. Thus, the artificial pancreas is concerned with estimating the amount of CHO. In contrast, our work aims to estimate not only CHO, but also fat and protein. In addition, being a control problem, the artificial pancreas is very sensitive to delays and lags: to prevent large glucose responses after a meal, an AP must make a decision based on the early part of the glucose response. In contrast, our work can afford to exploit information in the entire glucose response curve to predict the full macronutrient composition of a meal. Finally, our work is related to (but also distinct from) the personalized-nutrition project of Zeevi et al. [12], which used machine-learning models to predict the post-prandial glucose response of different meals; see section II-A. In contrast, we aim to solve the inverse problem: predicting meal macronutrients from post-prandial responses.

Results from this work suggest that expanding the sensing capabilities of existing indwelling or implantable CGMs [15] to measure these additional dietary biomarkers would make it possible to monitor nutritional intake in an automated fashion, removing burden from participants while providing a wealth of nutritional and behavioral information to them and their healthcare providers. Towards this end, our group has proposed an implantable barcode-like sensor the size of a grain of rice that, once inserted, could be probed optically with a watch-type device and used to noninvasively monitor not only glucose but other dietary biomarkers such as the ones presented here in free living conditions [16]. These data could then be analyzed on the watch, or transmitted to a mobile device or to the cloud, to detect moments of meal intake and predict macronutrient composition of those meals.

Note that measuring these biomarkers using current standard methods is complicated as it requires extraction of the fluid, such as either a blood draw and centrifugation to get plasma, or dialysis membrane extraction for interstitial fluid, followed by the use of well-established but relatively sophisticated bench-top analytical instruments. Though the future barcode sensor would facilitate the measurement of these biomarkers, development of the sensor itself is nontrivial as both the recognition elements (e.g. aptamers, antibodies) and transduction methods through tissue (e.g. fluorescence, phosphorescence lifetime) need to be determined and optimized for each biomarker.

II. Related work

A. Effect of macronutrients on postprandial glucose

A number of studies have examined the effect of meal macronutrient amount and composition on PPGRs. The main determinant of postprandial glucose is the amount and type of CHO. However, other macronutrients that are present in mixed meals also contribute to the glucose response. Specifically, adding protein, fat or dietary fiber to a meal reduces and/or slows down the glucose response [10], [11], typically due to gastric emptying or endogenous secretion of insulin [17]–[19]. More recent work has focused on understanding individual differences in food metabolism. In a landmark study, Zeevi et al. [12] used CGMs to track the glucose response of 800 participants while participants kept detailed records of their diet. The authors found high inter-personal variability in the glucose response to identical meals, which puts into question the utility of universal dietary recommendations. To address this issue, the authors developed a machine-learning model that could predict the glucose response of a meal for each participant by accounting for individual factors (e.g., anthropometric variables, blood panels, gut microbiota). When tested on an independent cohort of 100 participants, the model was able to generate personalized diets that led to reduced postprandial hyper-glycemia.

B. Diet monitoring technology

Technology may enable automatic monitoring of food intake, reducing participant burden and avoiding errors due to manual food tracking. Three broad types of technologies have been used for monitoring food intake: wearable sensors, smart utensils and computer vision. As an example, food intake can be captured by recording chewing sounds with a microphone and then performing acoustic analysis [5], [20]. Piezoelectric sensors have also been used for detecting food intake from chewing [6]. After chewing, swallowing is the next step of food consumption, and a number of wearable sensors have been used for detecting swallowing sounds based on acoustic

analysis [21]. Finally, a few studies have attempted to detect food intake from both chewing and swallowing sounds [22], [23]. A number of smart devices, such as smart watches and smart utensils, have also been used to detect food types and the amount of food consumed [7], [24]. The advantage to using smart watches with inertial sensing is that they do not interfere with user privacy, compared to other approaches such as microphones embedded in earbuds [25]. Smart utensils (e.g., smart forks) have also been used for identifying foods consumed [26], and commercial products also exist (e.g., HAPIfork). Finally, computer vision techniques have been developed to classify foods, predict food constituents and estimate food portions from images [27]–[29]. Further, a growing number of commercial apps are using computer vision techniques to estimate nutrition from food photographs, e.g., Lose It!, CalorieMama, Snaq, Undermyfork, gocarb, and several software libraries for food image recognition are available for integration with mobile apps, e.g., bite.ai, FoodAI.

C. Dietary biomarkers

Various dietary biomarkers have been associated with macronutrients, foods and dietary components. Sugars such as glucose or fructose are associated with CHO and contribute to energy intake. Unfortunately, sugar can be introduced through a number of processed foods and hidden sources, which makes accounting for the amount of sugar consumed challenging. Instead, a biomarker that could estimate the amount of sugar in food would be more useful. To this end, urinary sucrose and fructose have been identified as dietary biomarkers for sugar intake [30]. For the consumption of saturated fats, blood lipids such as low density cholesterol (LDL) and high density cholesterol (HDL) have been identified as predictive biomarkers [31]. Plasma cholesterol and triglyceride (TG) levels may also be associated with dietary fiber intake; however, some studies reveal conflicting results. Specific fatty acids such as mono-unsaturated (MUFA), poly-unsaturated (PUFA) and saturated fatty acids (SFA) are hard to capture and current methods of estimation are costly and time-consuming [32]. To measure dietary protein intake, urinary nitrogen has been identified as a potential biomarker [33]. Other potential biomarkers of protein intake include creatinine, taurine, 1-methlyhistidine and 3-methylhistidine [34]. These biomarkers are specific to meat intake and are excreted via urine.

III. Methods

This section describes the experimental dataset used for the study, and the data preprocessing techniques to extract information from postprandial responses and reduce individual differences. Further, we describe the prediction model (XGBoost) that was used throughout all subsequent analyses, to answer this study's overarching question: to what extent do additional biomarkers (i.e., beyond interstitial glucose from CGMs) improve prediction of meal macronutrients?

A. Dietary study dataset

To assess the influence of meal macronutrients on postprandial responses for glucose and other biomarkers, we recruited 15 healthy participants (not diagnosed with pre-diabetes or type 2 diabetes) between the ages of 60-85 and Body Mass Index (BMI) in the range of 25-35. Each participant took part in nine study days where they consumed a predefined meal on each day based on a randomized design. The participant was asked to follow the same protocol on each day and the only difference between any two days was the macronutrients of the meal consumed. The meal was prepared as a liquid drink mixed with a pudding base (Jell-O Vanilla, Kraft Food, IL, USA) containing 0.75 g CHO and with different levels of protein, CHO and fat; see Table I . In what follows, we use the notation CxPxFx to denote the amount of macronutrients in a meal, where x can take values 1 (low), 2 (medium) and 3 (high). Whey protein (BiPro, Agropur, MN, USA) was used as the protein nutrient, maltodextrin (Polycose, Abbott Nutrition, IL, USA) as the CHO nutrient, and sunflower oil (Great Value, Wal-mart, AZ, USA) as the fat nutrient. Meals were prepared early on each study day. The protein hydrolysates and maltodextrin were dissolved in 250 ml water, mixed with the pudding base, and then thoroughly mixed with sunflower oil within 30 minutes of ingestion. Each participant was asked to fast for eight hours before consuming the meal, so that the first reading captured would be their fasting biomarker levels. After consuming the meal, the participant remained in a sedentary state for the next eight hours, so that there was no effect of physical activity on postprandial responses. Informed consent was obtained from all participants involved in the study. This study was approved by the Texas A&M Institutional Review Board (IRB #2017-0886F; approval date 12/06/2017).

TABLE I: Macronutrient amounts of the 9 meals in the study

Meal	CHO (g)	Protein (g)	Fat (ml)
C1P1F1	52	15	13
C1P2F2	52	30	26
C2P2F1	95	30	13
C2P1F2	95	15	26
C2P2F2	95	30	26
C2P2F3	95	30	52
C2P3F2	95	60	26
C3P2F2	180	30	26
C3P3F3	180	60	52

On the first day of the study, an Abbott Freestyle Libre Pro CGM was placed on the participant's upper arm, and was replaced as needed. This CGM device takes glucose readings every 15 minutes for up to 14 days. The concentration of the remaining biomarkers was measured by first extracting blood samples via venipuncture at intervals of 15 minutes for the first hour, 30 minutes for the second hour and 60 minutes for the remainder of the study day. However, due to budgetary constraints, blood samples were analyzed for only 10 subjects. Additionally, the response of three meals were missing due to experimental errors or CGM malfunction, leading to a total of data from 87 meals for analysis across the 10 subjects. Table II provides a list of all biomarkers measured in the study. The first 24 biomarkers are individual amino acids. Biomarkers 25-27 represent different combinations of amino acids commonly used in nutritional studies. Biomarkers 31-33 represent three independent measures of glucose from venipuncture (LC-glucose), fingerstick (Stick-glucose) and interstitial fluid (CGM-glucose).

TABLE II: List of biomarkers measured in the study

#	Name	Abbreviation
1	Aspartate	ASP
2	Glutamate	GLU
3	HydroxyProline	hPRO
4	Asparagine	ASN
5	Glutamine	GLN
6	Citrulline	CIT
7	Serine	SER
8	Glycine	GLY
9	Arginine	ARG
10	Threonine	THR
11	tauMethylHistidine	tauMEH
12	Alanine	ALA
13	Taurine	TAU
14	Proline	PRO
15	Valine	VAL
16	Methionine	MET
17	Isoleucine	ILE
18	Leucine	LEU
19	Tryptophan	TRP
20	Phenylalanine	PHE
21	Ornithine	ORN
22	Histidine	HIS
23	Lysine	LYS
24	Tyrosine	TYR
25	Branched Chain Amino Acids[1]	BCAA
26	Essential Amino Acids[2]	EAA
27	Non-Essential Amino Acids[3]	NEAA
28	Sum Amino Acids[4]	SUMAA
29	Liquid Chromatography (LC) insulin	LC-insulin
30	LC triglycerides	LC-TG
31	LC glucose (venous blood)	LC-glucose
32	Finger stick glucose (venous blood)	Stick-glucose
33	CGM glucose (interstitial fluid)	CGM-glucose

Venipuncture blood samples were collected in pre-chilled, EDTA or li-heparinized tubes (Becton Dickinson Vacutainer system, Franklin Lakes, NJ, USA) and kept on ice. Plasma was obtained by centrifugation of whole blood at 4°C for 10 min at 3120 g, and was aliquoted with vortexing to tubes containing either 0.1 vol of 33% (w/w) trichloroacetic acid or the residue after evaporation of 0.17 vol of 33% (w/w) 5-sulfosalicylic dihydrate to denature proteins. All samples were frozen in liquid nitrogen and stored at -80°C until analysis. All venipuncture biomarker analyses were performed in plasma. Insulin was measured with an electrochemiluminescent immunoassay, and glucose and triglycerides with standardized enzymatic assays, all assessed by LabCORP. The fingerstick glucose readings were analysed using using reagent test strips and a point of care testing glucometer (Accu-Chek® Aviva, Roche). Plasma amino acids were analyzed batchwise with liquid chromatography with tandem mass spectrometry (LC/MS/MS), as previously described [35].

B. Feature extraction

A prototypical biomarker response is shown in Figure 1; it features an initial rise, reaches a peak and then finally returns to baseline. Actual biomarker responses are illustrated later –see Figure 3. To capture the shape of the response, we place a family of Gaussian kernels uniformly over time, as shown in Figure 1. Using these kernels, we then calculate the area under the curve (AUC) of the biomarker response, which we refer to as Gaussian area-under-the-curve (gAUC) as:

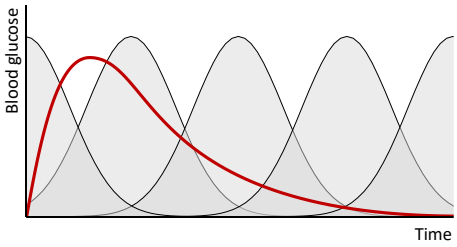

Fig. 1: gAUC features extracted using 5 Gaussian kernels. The red curve represents the post-prandial response of a biomarker, and the shaded curves represent a family of Gaussian kernels. Each gAUC feature is the weighted average of the biomarker concentration at a given time period, weighted by the kernel.

$$x(k) = \int_0^T [b(t) - b(0)] \frac{1}{\sqrt{2\pi}\sigma_k} \exp \frac{(t - T_k)^2}{2\sigma_k^2} \qquad (1)$$

where $b(t)$ is the biomarker response over time, $x(k)$ is the k-th gAUC feature computed from $b(t)$, T is the duration of postprandial period (8 hours in our study), and T_k represents the time at which the Gaussian kernel is centered with a spread of σ_k^2. These gAUC features capture information related to the initial time to peak, duration of elevated glucose level and time of return to baseline level. For consistency with our prior work [9], we use a combination of 3 and 5 kernels to extract features from the biomarker responses, as we found this combination led to the best performance[5]. As a final pre-processing step, and following our prior work [9], we normalize the gAUC features of each participant using z-score normalization, i.e., we subtract the mean from each gAUC feature and divide by its standard deviation. Note that we also subtract the biomarker reading prior to consuming a meal $b(t = 0)$ from the postprandial biomarker response of the meal. The rationale behind using a baseline correction step is that two individuals may have different responses to the same meal owing to their different fasting levels. A baseline correction step ensures that there is no effect of fasting level on the overall response. The biomarker response is therefore represented as relative to the fasting level instead of an absolute value.

C. Macronutrient prediction model

Once the gAUC features are generated, we predict the amount of each macronutrient by means of eXtreme Gradient Boosting (XGBoost) [13], a machine learning algorithm that has achieved state-of-the-art results on a number of domains, such as web text classification, customer behavior prediction

[1]Branched chain amino acids are the sum of LEU, ILE and VAL.

[2]Essential amino acids are defined as the sum of HIS, ILE, LEU, LYS, MET, PHE, THR, TRP and VAL.

[3]Non-essential amino acids are defined as ASP, GLU, hPRO, ASN, GLN, CIT, SER, GLY, ARG, t-MHIS, ALA, TAU, PRO, ORN and TYR.

[4]Sum amino acids (SUMAA) is the sum of all amino acids in Table II

[5]Gaussian centers are placed evenly across the 8-hour period following meal intake, i.e., $T_k = \{0h, 4h, 8h\}$ for the 3-Gaussian family, and $T_k = \{0h, 2h, 4h, 6h, 8h\}$ for the 5-Gaussian family. To ensure that the 95% confidence interval of the Gaussian kernel aligns with these time intervals, we set the standard deviation of the Gaussian to $\sigma_k = \sigma = 8/n/1.96$, where n is the number of kernels. This results in $\sigma = 82min$ for the 3-Gaussian family and $\sigma = 49min$ for the 5-Gaussian family.

and product categorization. XGBoost uses an ensemble of weak learners (regression trees) to obtain a strong learner using an iterative process. Starting with one regression tree trained to model the entire data, XGBoost iteratively adds one more regression tree to the ensemble in order to reduce the residual obtained from the previous set of trees using gradient descent. Following [13], XGBoost generates a prediction by adding the outputs from all the trees in the ensemble:

$$\hat{y}_i = \sum_{k=1}^{K} f_k(x_i) \tag{2}$$

where $\hat{y}_i$ is the prediction for input x_i, and f_k is the $k-$th regression tree in the ensemble. The model is trained to optimize the objective function:

$$L = \sum_i l(y_i, \hat{y}_i) + \sum_k \Omega(f_k) \tag{3}$$

where l is the loss function between the ground truth y_i and the prediction $\hat{y}_i$, and Ω is a regularization term that penalizes the weights of the model from becoming very large, and therefore prevents overfitting:

$$\Omega(f_k) = \gamma T + \frac{1}{2}\lambda ||w||^2 \tag{4}$$

where T is the number of leaves in the tree, $||w||$ represents the scores of the leaves, and γ and λ are regularization parameters. At each iteration t, a new regression tree f_t is added to reduce the loss:

$$L^{(t)} = \sum_i l(y_i, (\hat{y_i}^{(t-1)} + f_t(x_i))) + \Omega(f_t) \tag{5}$$

We use XGBoost for all the experiments in the manuscript. Because XGBoost is based upon decision trees, the impact of the features provided have easy-to-interpret relationships with the predicted regression values. We train a separate model to predict each of the macronutrients (CHO, protein, fat). To further avoid overfitting and assess the generalization capabilities of the model, we use a leave-one-subject-out procedure to evaluate the model, i.e. we train on data from 9 subjects, then test on the 10th subject. To report the performance of the model, we use normalized root mean squared error (NRMSE) between the predicted and ground truth macronutrients:

$$NRMSE = (\frac{1}{N}\sum (y - \hat{y})^2 / y^2)^{\frac{1}{2}} \tag{6}$$

For hyperparameter tuning[6], we use the following cross-validation procedure: given a total of 10 subjects, we use 8 subjects for training, the 9th subject for validation and the 10th subject for testing. A model is trained on 8 subjects and then tested on the validation subject using all combinations of hyperparameters. Keeping the test subject fixed, we repeat this process for all combinations of train and validation subjects and all hyperparameter combinations. The set of hyperparameters that have the lowest NRMSE across all validation subjects is then chosen for testing. In our experiments, we optimize two hyperparameters, the maximum depth of tree $(n = 2, 3)$ and the maximum number of trees $(m = 20, 30)$, and set the learning rate to $\eta = 0.1$. We limited the depth of the trees and number of trees to prevent overfitting, relative to the number of features extracted for each meal and number of meals.

[6]We used the XGBoost (https://xgboost.readthedocs.io) package implemented in Python. For hyperparameter tuning, we wrote our own code using nested for loops instead of using existing packages

IV. Results

A. Impact of macronutrients' amounts on biomarker concentrations

In a first analysis, we examine how increasing amounts of macronutrients affect the postprandial response for the different biomarkers. Results are summarized in Figure 2. The first row shows the average AUC for venipuncture blood glucose (LC-glucose) as we increase the amount of CHO, protein, and fat. We observe a marked increase in the AUC as the amount of CHO increases (a correlation coefficient r = 0.65), and a smaller increase for proteins and fats (r = 0.24 and r = 0.03, respectively), a result that is consistent with our earlier studies showing predicting macronutrients from CGMs is easier for CHO than for fat and protein, in that order [8], [9]. This result also confirms that LC-glucose responds maximally to increases in consumption of CHO, as one might expect. The second row in Figure 2 illustrates the corresponding effect for amino acids, in this case using Leucine (LEU) as an example. The greatest increase in AUC arises from consuming meals with increasing amounts of protein (a correlation coefficient r = 0.68), which suggests that the postprandial levels of LEU are mostly affected by intake of protein, as we had hypothesized, and only minimally by intake of CHO and fats (r = 0.21 and r = 0.24, respectively). The third row of Figure 2 illustrates the average AUC of triglycerides after consuming meals with different amounts of macronutrients. In this case, we note that the postprandial levels of triglycerides are associated mainly with fat intake (r = 0.55), but also with the amount of CHO (r = 0.28) and protein (r = 0.35). However, the largest increase is seen for fats, which suggests that fat content in a meal is the most important determinant of post-prandial triglycerides, as we had also hypothesized. Finally, the fourth row in Figure 2 shows the average AUC for insulin as a function of the macronutrients. The three macronutrients have a marked effect, with CHO showing the strongest influence (as one might also expect). Altogether, these results suggest that the four biomarkers provide information that is complementary about the amount of macronutrients in the meal, which provides support for the main objective of this work.

Next, we analyze the shape of the post-prandial biomarker response for different amounts of macronutrients. Figure 3(a) shows the LC-glucose response (averaged across subjects) for meals with low, medium and high amount of CHO. We observe that the corresponding increases in the AUC are largely due to an increase in the time to return to baseline, but that the peak of the response does not change significantly. Figure 3(b) shows the average response for Leucine as the amount of protein is increased. In contrast with LC-glucose, the corresponding increases in the AUC are due to the combined effect of increases in the peak of the response and in the time to return to baseline. Similar results are obtained for triglycerides with respect to increases in fat –see Figure 3(c), and for insulin with

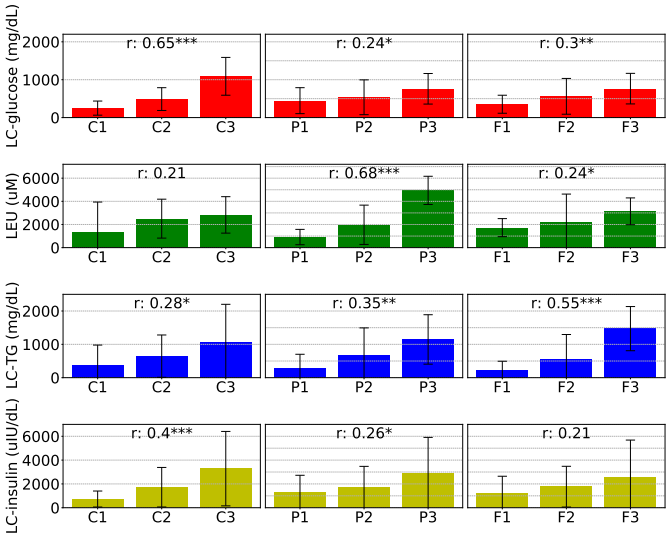

Fig. 2: Area under the curve of three biomarker responses (blood glucose, Leucine, and triglycerides) for meals with different amounts of macronutrients. Error bars indicate standard deviation, measured by aggregating individual AUCs from all subjects for the corresponding meals. ***: $p < 0.001$, **: $0.001 \leq p \leq 0.01$, *: $0.01 \leq p < 0.05$.

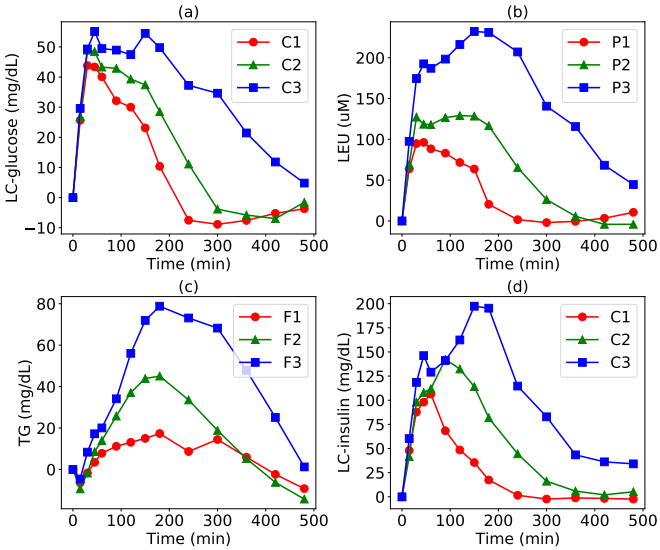

Fig. 3: Average shape of the postprandial biomarker response for different amount of macronutrients. For each biomarker, only the most influential macronutrient is shown (e.g., CHO for LC-glucose and insulin, protein for Leucine, and fat for triglycerides)

respect to increases in CHO –see Figure 3(d). Notice that the shape of the response is markedly different for LC-glucose, Leucine and insulin, the three of which show rapid increases in concentration shortly after consumption of the meal, as compared to triglycerides, for which the response is much slower. Thus, the shape of these postprandial responses appears to provide critical information that may help the prediction model (XGBoost) estimate the amounts of macronutrients in the meal, which further justifies our use of the gAUC features.

B. Quantifying the performance of individual biomarkers

In the next experiment, we evaluate the ability of individual biomarkers to predict each one of the three macronutrients. For this purpose, we built a separate XGBoost model using gAUC features from each individual biomarker as the only inputs, and then examined the NRMSE of the predictions. Results for CHO are shown in Figure 4(a), where biomarkers have been arranged by increasing order of NRMSE. The most predictive biomarker is insulin, with an NRMSE of 23.5%. This is an expected result, since insulin is released by the pancreas in response to glucose levels increasing in the bloodstream for normal subjects. The next three biomarkers in the list are the three independent measures of glucose in the study (LC-glucose, CGM and finger stick). Of interest, we observe a sharp increase in NRMSE between insulin and the three glucose measures, one of which (CGM-glucose) was the biomarker used in our original studies [8], [9], but the difference is not statistically significant ($t(18) = 1.49, p = 0.076$). Additional increases in NRMSE as we move towards the least informative biomarkers appear marginal, but overall there is a significant difference in performance between the most predictive biomarker (insulin; 23.5%) and the least predictive one (GLY; 47.3%; $t(18) = 7.15, p < 0.001$).

Results for the prediction of protein are shown in Figure 4(b). The most predictive biomarker is LYS, with an NRMSE of 23.6%. We observe a significant increase in NRMSE for the amino acids PRO and ASN. Inspection of the amino acid content of the whey protein used in the study (data not shown) indicates that the majority of the amino acids before these sharp increases are those that appear at higher concentrations in whey protein (e.g., LYS, LEU, TYR), or are combinations of multiple amino acids (e.g., EAA, BCAA, SUMAA), which explains the result. Comparison between the best biomarker for protein (LYS; 23.6%) and CGM-glucose (46.4%) –the biomarker used in our previous studies [8], [9], shows a statistically significant improvement in the prediction of protein ($t(18) = 4.29, p < 0.001$).

Results for the prediction of fat are shown in Figure4(c). As one might expect, the most predictive biomarker is triglycerides, with an NRMSE of 35.2%. In contrast with CHO and protein, however, we do not observe an elbow in the distribution of NRMSEs across biomarkers, but a graded response. Further, unlike in the case of protein, the most predictive biomarker (triglycerides) is only slightly more predictive of fat content in the meal than the biomarker in our original study (CGM-glucose, 40.0%, $t(18) = 0.94, p = 0.177$).

Finally, we performed one-tailed t-tests between the best performing biomarker and each of the remaining ones.The first biomarkers for which there is a statistically significant difference ($p < 0.05$) with respect to the best performing biomarker are LYS for CHO, PRO for protein, and ASN for fat.

C. Identifying the optimal combination of biomarkers

Next, we perform a study to identify which combinations of individual biomarkers is most predictive of the macronutrients in the meal. Given the relatively large number of biomarkers (a total of 33 in Table II), exhaustive evaluation of each possible

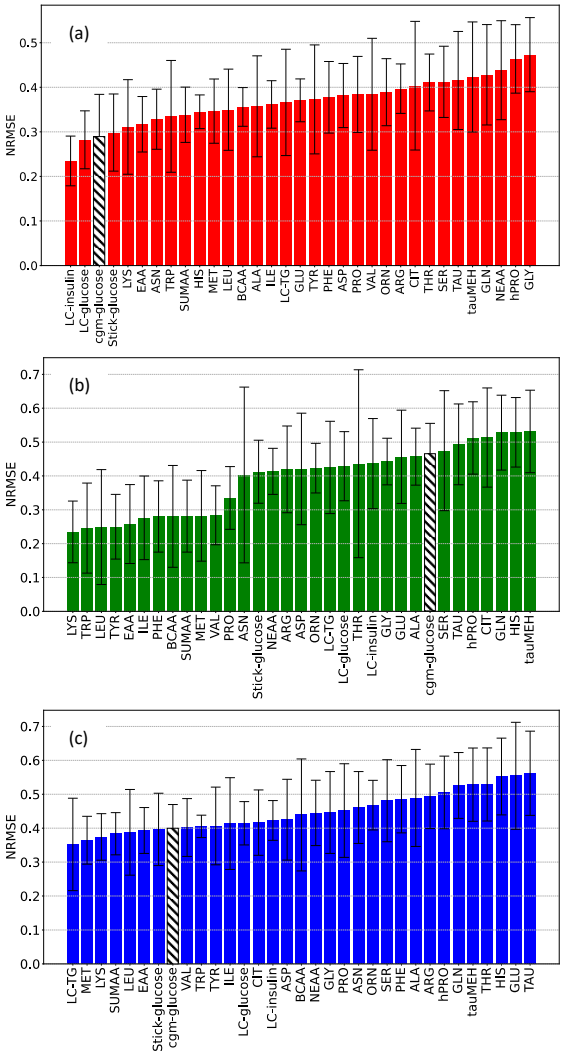

Fig. 4: Prediction performance of an XGBoost model trained to predict the amount of (a) CHO, (b) protein, and (c) fat in the meal from each individual biomarker. Highlighted in black and white stripes is CGM-glucose, the biomarker used in our original studies [8], [9], as a reference. Error bars represent standard deviations.

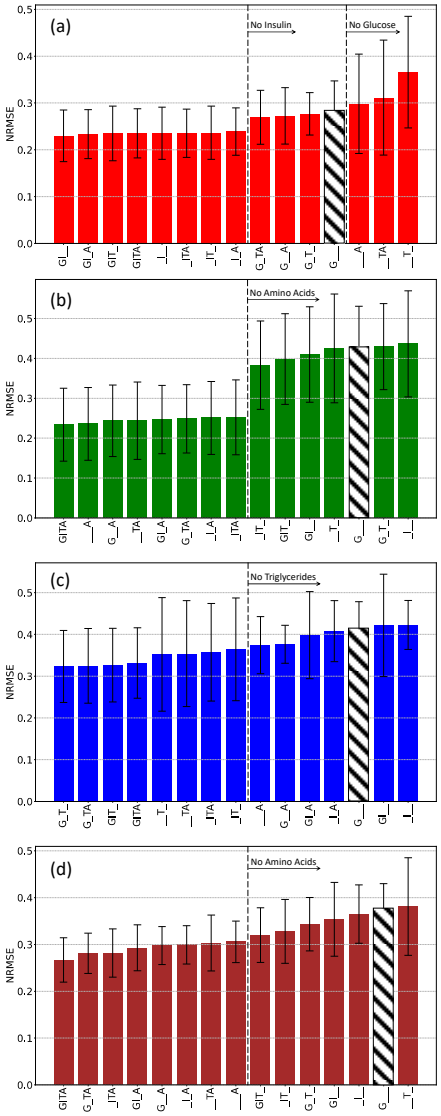

Fig. 5: Ranking all feature combinations of four biomarkers: glucose (G), insulin (I), triglycerides (T) and amino acids (A) for the prediction of (a) CHO, (b) protein, (c) fat, and (d) the combined prediction of the three macronutrients.

combination is impractical (over 8 billion combinations). Further, the limited dataset in our nutritional study also precludes us from building models with a high number of input features. For this reason, we decide to pre-select the most important biomarkers identified in the previous section: (1) insulin and (2) LC-glucose for CHO, (3) Lysine for protein, and (4) LC-triglycerides for fat. This allows us to perform exhaustive search (15 possible combinations of biomarkers, or $2^4 - 1$) on this reduced feature set, which is computationally feasible and also avoids issues associated with data sparsity.

Results for CHO are shown in Figure 5(a), ranked from the most predictive feature subset to the least predictive. The feature subsets cluster into three distinct areas. The first eight subsets correspond to all combinations that contain insulin as a feature. The feature subset that only includes insulin is ranked in position #5, but its performance is not statistically different from the other seven subsets, indicating that insulin is the only necessary biomarker for prediction of CHO. The next four combinations consist of all subsets that include glucose (but not insulin), and we find that the difference in NRMSE between subset (_I_A) and (G_TA) is not statistically significant ($t(18) = 1.19, p = 0.124$). The last three combinations are feature subsets that do not include insulin or glucose. Notice that for these last 3 feature subsets there is a high degree of individual variability, as indicated by the error bars.

Results for protein are shown in Figure 5(b), again ranked from most to least informative. We find two distinct clusters. The first eight combinations represent subsets that include amino acids as a feature. As shown in the figure, they all perform similarly, suggesting that amino acids are the only biomarkers needed in order to predict protein. Removing the amino acid from the feature subset results in a statistically significant degradation in prediction performance ($t(18) = 2.77, p = 0.006$).

Results for fat are shown in Figure 5(c). In this case, we still find an intuitive ordering of the feature subsets, but the clustering is less prominent than in the case of CHO and

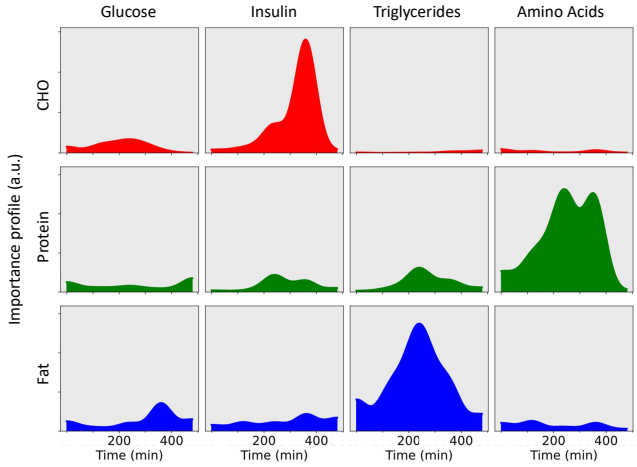

Fig. 6: Importance profile of the post-prandial response of each biomarker for predicting macronutrients

protein. The first eight combinations represent all subsets that contain triglycerides, and the first four combinations contain triglycerides and glucose. In contrast with the previous two cases, where a single biomarker was sufficient (e.g., insulin for CHO, amino acids for protein), in the case of fat, two biomarkers appear to be critical: triglycerides and glucose.

In a final analysis, we evaluate the 15 feature subsets in terms of the average NRMSE across the three macronutrients. Results are shown in Figure 5(d). As with fats, there is no clustering of feature subsets, though the subsets are ordered such that the first eight combinations are those containing amino acids. We also find that the optimal subset is the one containing the four types of biomarkers: glucose, insulin, amino acids and triglycerides, with an average NRMSE of 26.7% across the three macronutrients. It is interesting to note that removing insulin from the subset (#2 combination) does not result in a statistically significant increase in NRMSE ($t(18) = 0.63, p = 0.267$). This finding can have practical implications since insulin is a relatively large molecule that may be more difficult to detect in interstitial fluid –a likely target of implantable or indwelling biosensors for nutrition monitoring [16]. Finally, we find that the optimum subset (GITA; 26.7%) is significantly more predictive than the biomarker in our original study (CGM-glucose; 38.5%; $t(18) = 5.45, p < 0.001$).

D. Understanding the prediction models

Next, we examine whether it is possible to identify particular regions in the biomarker postprandial response that are used preferentially by the prediction model. To answer this question, we use one measure of feature importance returned by XGBoost that represents the average gain (in information) of splits in the decision trees that use each feature. Namely, we trained XGBoost models for each macronutrient that used the four types of biomarkers as inputs (glucose, insulin, amino acid, triglycerides), and then generated an importance profile for each biomarker as:

$$i(t) = \sum_{k=1}^{K} G_k \frac{1}{\sqrt{2\pi}\sigma_k} \exp \frac{(t - T_k)^2}{2\sigma_k^2} \qquad (7)$$

where T_k and σ_k are the mean (i.e., time location) and variance (i.e., spread) of the k-th Gaussian kernel (see Figure

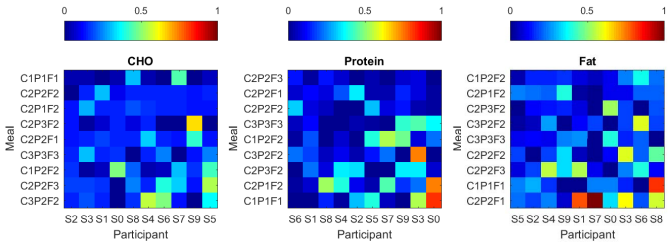

Fig. 7: Distribution of prediction errors across meals for all participants. For each macronutrient, meals (top to bottom) and participants (left to right) were ordered by increasing order of NRMSE. Colorbar on top shows NRMSE scale.

1), K is the number of Gaussian kernels used (8 for each biomarker, 32 in total), and G_k is the gain returned by XGBoost for the k-th input feature. Results are shown in Figure 6. The first row shows that the carbohydrate model relies primarily on a narrow time window (centered at 6 hours after meal intake) in the insulin postprandial response, with only a minor contribution from a broader region (centered on 4 hours after meal intake) in the glucose postprandial response. This result agrees with those reported in section IV-C, which showed that the best feature subsets are those that contain insulin, and that the combination of glucose and insulin was optimal, though only by a narrow margin (see Figure 5(a)). The second row in Figure 6 indicates that the protein model relies primarily on the amino acid postprandial response, but in this case on a broad time window between 3-7 hours after meal intake. Again, this overall result is consistent with section IV-C, which showed that the best feature combinations were those that contained amino acids. Finally, the third row in Figure 6 shows that the fat model mainly uses information from the triglyceride postprandial response, in this case around 4 hours after meal intake. As before, this result is consistent with those in section IV-C, which showed that the best feature combinations are those that contain triglycerides. It is also interesting to note that the peak in the importance profile is closely aligned with the peak of the triglyceride postprandial response in Figure 3, something that does not occur for the other three biomarkers.

E. prediction errors

In a final step, we analyzed the distribution of prediction errors for each meal across participants. Results are shown in Figure 7. For each macronutrient, and for ease of interpretation, meals (top to bottom) and subjects (left to right) have been sorted by increasing order of the corresponding NRMSE. Thus, the bottom right corner of each heatmap tends to have higher errors. To analyze these results, we performed 2-way ANOVA on the carbohydrate NRMSE, with meal and gender as independent factors. We find a marginally significant effect for meal type ($F(8, 72) = 2.06, p = 0.051$), indicating that the prediction errors vary across meals, and a significant interaction between the two factors ($F(8, 72) = 2.96, p = 0.006$), indicating that the errors are not uniformly distributed across participants. Repeating the analysis on protein NRMSE yields a significant effect for gender ($F(1, 72) = 4.71, p = 0.033$),), indicating that the average error was higher for females (0.24) than for males (0.16), and meal type ($F(8, 72) = 3.19, p =$

0.004), but no interaction. Finally, the same analysis on fat NRMSE yields a significant effect for meal type ($F(8, 72) = 2.66, p = 0.013$) and a significant interaction ($F(8, 72) = 2.72, p = 0.011$).

V. Discussion

In prior work [8], [9], we had shown that CGMs can be used to monitor diet by analyzing the shape of the postprandial glucose response, which depends not only on the amount of CHO in a meal but also on the protein and fat content. In the present study, we sought to determine if other blood biomarkers, namely amino acids, insulin and triglycerides, could provide additional information to the prediction model. Results from four types of analysis consistently show that they do, and that the information provided by the four biomarkers is largely complementary.

In a first analysis (section IV-A), we showed that increasing the macronutrients in a meal leads to measurable changes in the concentration of the four types of biomarkers post-prandially: adding CHO increases glucose and insulin concentration rapidly, adding protein increases amino acids (also rapidly), and adding fat increases triglycerides, though at a slower rate. In a second analysis (section IV-B), we compared biomarkers individually by their ability to predict the three macronutrients. For CHO, we find that insulin is the most predictive biomarker, followed by the three independent measures of glucose in our study. In the case of protein, we find that the most informative amino acids are those that appear at higher concentration in the protein source used in our dietary study. This could be viewed as problematic, since different protein sources have different amino acid content. Fortunately, we find that overall measures of amino acid content that are likely to generalize across a variety of protein sources, such as Branched Chain Amino Acids (BCAA) and Essential Amino Acids (EAA) also perform well, as shown in Figure 4(b). Finally, in the case of fat, we find that the most informative biomarker is triglyceride. In a third analysis (IV-C), we preselected the four key biomarkers identified in the previous analysis, and performed an exhaustive search for the optimal combination of biomarkers for each macronutrient. Results reinforce with the earlier two analyses, showing that insulin (and glucose to a lesser extent) is the most critical biomarker for CHO prediction, amino acid for protein prediction, and triglycerides for fat prediction. In a fourth analysis (section IV-D), we sought to determine if there are specific regions in the postprandial response of each biomarker that are important for prediction. We find that the prediction models use a relatively narrow time window in the latter part of the postprandial glucose response to predict CHO, a very broad analysis window in the postprandial amino acid response to predict protein, and also a broad region halfway through the postprandial triglyceride response to predict fat. While it could be argued that these four sets of analysis are somewhat redundant, we view the overwhelming agreement between them as evidence of the robustness of our results.

We performed three types of statistical analyses to derive these conclusions. First, we used pairwise t-tests to compare the performance of models that employed different biomarkers as inputs. Second, we used Pearson's correlation to test the relationship between macronutrients amounts and the area-under-the-curve for various biomarkers. Finally, we used 2-way ANOVA to analyze the distribution of prediction errors across participants and meals.

While our results are promising, it is important to highlight the limitations of this work. First, participants were asked to consume liquid meals with single-source macronutrients (maltodextrin, whey protein and sunflower oil), so our findings must be validated when participants consume solid meals with a more complex mixture of macronutrients that may lead to different digestion patterns and thus postprandial responses. Second, participants were asked to rest for 8 hours following consumption of the meal, whereas in practical settings participants will likely engage in some form of physical activity following meal intake (e.g., walking), which is known to affect postprandial glucose [36]. A further limitation in the study is that the machine-learning model uses an 8-hour prediction window during which it is assumed that no other meal is consumed. To address these issues, in a forthcoming study we will have participants (n=100) consume not only liquid meals (as in the study reported here) but also complex meals in free-living conditions. This will allow us to examine the extent to which models trained on liquid meals generalize to solid meals, and also account for post-prandial physical activity. Further, while the forthcoming study will still impose an eating restriction following each meal, this restriction will be limited to a more realistic 3 hours rather than the 8 hours used here. This will allow us to examine the compounding effects of multiple meals taken within a short period.

A. Future work

Additional features may be extracted from postprandial responses, including features derived from the time derivative, time to peak concentration, number of local peaks, and other local variations. This would likely require using a smoothing filter prior to feature extraction, since postprandial responses tend to be rather noisy, particularly for CGMs. Future analyses will also examine whether limiting feature extraction to the early part of the postprandial response (e.g., 2-3 hours after food intake) would affect prediction performance. The average postprandial responses in Figure 3 suggest that sufficient discriminatory information is contained in the first 2-3 hours, so predicting macronutrients based on this information seems plausible. Additional machine-learning models could also be used for macronutrient prediction. As an example, recurrent neural networks such as Long Short-Term Memories (LSTMs) may be used to process the raw postprandial responses directly, avoiding the need to perform feature extraction and any potential loss of information in the process. Finally, data augmentation techniques could be used to generate synthetic data to train the macronutrient prediction models. As an example, a recent study [37] used Generative Adversarial Networks (GANs) to synthesize realistic CGM daily patterns conditioned on HbA1c levels. A similar GAN approach could be used to synthesize postprandial responses conditioned on the amount of macronutrients, and other information such as participants' gender, age, body mass index or gut microbiota.

VI. Conclusion

In this paper, we evaluated a number of dietary biomarkers (amino acids, triglycerides, insulin) by their ability to improve the prediction of meal macronutrients, when compared to using glucose measurements from CGMs. Our results show that adding measurements of amino acid and triglyceride concentrations lead to significant improvements in the prediction of protein and fat, respectively. This support the idea of augmenting current CGM systems to measure these additional dietary biomarkers, as a step towards the development of automated methods for monitoring food intake.

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