2022 44th Annual International Conference of
the IEEE Engineering in Medicine & Biology Society (EMBC)
Scottish Event Campus, Glasgow, UK, July 11-15, 2022

2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 978-1-7281-2782-8/22/$31.00 ©2022 IEEE | DOI: 10.1109/EMBC48229.2022.9871822

Modeling Individual Differences in Food Metabolism through Alternating Least Squares

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***Abstract*—Understanding how macronutrients (e.g., carbohydrates, protein, fat) affect blood glucose is of broad interest in health and dietary research. The general effects are well known, e.g., adding protein and fat to a carbohydrate-based meal tend to reduce blood glucose. However, there are large individual differences in food metabolism, to where the same meal can lead to different glucose responses across individuals. To address this problem, we present a technique that can be used to simultaneously (1) model macronutrients' effects on glucose levels over time and (2) capture inter-individual differences in macronutrient metabolism. The technique performs a linear decomposition of glucose responses, alternating between estimating the macronutrients' effect over time and capturing an individual's sensitivity to macronutrients. On an experimental dataset containing glucose responses to a variety of mixed meals, the technique is able to extract basis functions for the macronutrients that are consistent with their hypothesized effects on PPGRs, and also characterize how macronutrients affect individuals differently.**

I. Introduction

Consuming a meal generally leads to an increase in blood glucose, followed by a recovery to the original level. This characteristic response is known as the postprandial glucose response (PPGR). The main determinants of PPGRs are carbohydrates, but other macronutrients can also influence PPGRs. For example, adding protein, fat, or fiber to a meal generally yields smaller spikes and lengthier responses [1, 2]. Understanding the specific role that various macronutrients play in PPGRs is of great interest for health applications [3, 4]. As an example, metabolic models can be used to develop personalized nutrition programs [5], and may also be used to monitor diet automatically with the use of continuous glucose monitors (CGMs)[1] [6, 7]. However, developing these models is challenging since there exist large inter-individual differences in food metabolism: two individuals consuming the same meal can have very different PPGRs [5].

To address this issue, this article presents an approach that can be used to jointly (1) learn how each macronutrient contributes to the glucose response and (2) capture individual differences in sensitivity to macronutrients. The model assumes that each macronutrient adds a basis function to the PPGR, and that individual differences can be modeled as a scaling term for these basis functions. Then, the approach uses an optimization technique based on alternating least squares, where basis functions and individual differences are estimated iteratively until the model converges. We evaluate the approach on an experimental dataset where participants consumed a variety of predesigned meals with known amounts of carbohydrates, protein and fat, while their glucose responses to those meals was measured with a CGM.

*This work was supported by NSF PATHS-UP award #1648451 and NSF-IIS award #2014475.

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[1] A CGM is a wearable sensor consisting of a small electrode inserted in the skin that measures glucose in the interstitial fluid, and a transmitter that sends the measurements to an external device.

II. Related work

Given that adding protein and fat to a meal can alter the PPGR [1, 2], we recently conducted a study to test the hypothesis that the shape of the PPGR could be used to predict the meal macronutrients' amounts. In the study, 15 subjects consumed nine different mixed meals over the course of 2-3 weeks while wearing a CGM. Each meal had a known but varying amount of carbohydrates, protein and fat. Then, we built machine-learning models to predict the amount of macronutrients in a meal from features extracted from the shape of the corresponding PPGR [6, 7]. Using a leave-one-subject-out cross-validation procedure, e.g., using data from 14 subjects for training and the remaining subject for testing, we were able to predict the amount of macronutrients with a normalized root mean squared error of 22% for carbohydrates, 50% for protein and 40% for fat. This is a promising result given the large inter-individual differences in food metabolism and the fact that the models were not customized for each participant.

To this end, recent studies have examined how to model individual differences in food metabolism. In a seminal study, Zeevi et al. [5] tracked the glucose levels of 800 subjects for one week while they kept detailed records of their diet and wore a CGM. A main finding was that there exists high inter-individual variability in the glucose response to identical meals. To address this issue, the authors developed a machine-learning model that could predict the glucose response to a meal for individual subjects by using a variety of "phenotype" variables, such as anthropometric features, blood panels and gut microbiota. To validate the model, the investigators used an independent group of 100 subjects, for whom they developed personalized diet. On this new cohort, the model was able to predict which meals would led to lower postprandial glucose responses. More recently, Tily et al. [8] used CGMs to monitor over 500 adults for 2 weeks, while they consumed a variety of standardized meals with different proportions of carbohydrates, proteins, fats and fiber. Then, the authors built a multi-level mixed effects regression model that predicted postprandial glucose from the composition of

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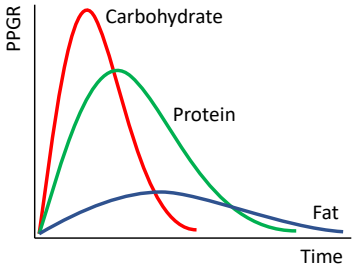

Figure 1. Effect of meal macronutrients on PPGRs

the meals and "phenotype" variables such as anthropometric features, gut microbiome and lifestyle variables.

III. Methods

Figure 1 depicts the characteristic PPGRs to a meal. Depending on the meal's contents, blood glucose rises 15-30 minutes after the meal, reaches a peak within the first 1-2 hours, and returns to baseline within 3-4 hours [9]. The figure also illustrates the effect of adding protein (P) and fat (F) to a meal with carbohydrates (C), which lead to lower peaks and delayed return to baseline.

Let us denote by $x_{ms}(t)$ the post-prandial glucose level of subject s at time $t = [1,2,\dots,T]$ after consuming meal m, and by $z_{ms,i}$ the amount of the i-th macronutrient in the meal, where $i \in \{C,P,F\}$. To model the PPGR, we assume that each macronutrient adds a characteristic basis function to the glucose response:

$$x_{ms}(t) = a_0(t) + z_{ms,C} \cdot a_C(t) + z_{ms,P} \cdot a_P(t) + z_{ms,F} \cdot a_F(t) \quad (1)$$

where $a_C(t)$, $a_P(t)$ and $a_F(t)$ are the basis function of each macronutrient, and $a_0(t)$ is an intercept term. More complex functions may be used (see discussion section), but for ease of interpretation we assume that the macronutrient effects are additive and linear. The hypothesized basis functions are illustrated in **Figure 2**. The marginal effect of carbohydrates is an immediate increase in blood glucose, followed by a slow decay. In contrast, the marginal effect of protein and fat is an immediate decrease in glucose, and a subsequent increase. When used in eq. (1), these basis functions would lead to the prototypical PPGRs depicted in **Figure 1**.

A. Least squares solution (average model)

Consider a dataset $\boldsymbol{X}$ containing the PPGRs of S subjects after consuming M different meals (for a total of $S \cdot M$ response curves), each meal with its corresponding macronutrient stored in $\boldsymbol{Z}$. Then, eq. (1) can be expressed in compact form as:

$$X = A\,Z \quad (2)$$

where $X \in \mathcal{R}^{T \times S \cdot M}$ (i.e., each column represents a PPGR), $Z \in \mathcal{R}^{4 \times S \cdot M}$ (i.e., each column represents the macronutrients in the meal, plus a constant term for the intercept), and $A \in \mathcal{R}^{T \times 4}$ (i.e., each column represents a basis function, plus the intercept.) Since $\boldsymbol{Z}$ is known and $\boldsymbol{X}$ is measured, the matrix of

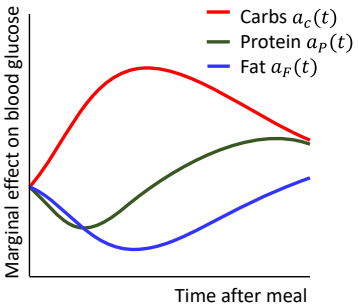

Figure 2. Hypothesized basis functions of the three macronutrients (adapted from Tily et al. [8])

basis function A can be obtained using the pseudo-inverse solution as:

$$A = XZ^T(ZZ^T)^{-1} \quad (3)$$

B. Accounting for individual differences

Unfortunately, the linear model in eq. (2) does not account for individual differences in food metabolism. For example, a given patient may be more sensitive to protein (or fat) being added to a carbohydrate-based meal than other participants. As a result, the "average" model in eq. (2) will not be able to model PPGRs accurately.

To address this issue, we define a set of sensitivity variables $\{\alpha_{sC}, \alpha_{sP}, \alpha_{sF}\}$ for each participant s, which capture the extent to which each macronutrient's basis function $a_i(t)$ contributes to the overall glucose response, leading to:

$$x_{ms}(t) = a_0(t) + z_{ms,C} \cdot \alpha_{sC} \cdot a_C(t) + z_{ms,P} \cdot \alpha_{sP} \cdot a_P(t) + z_{ms,F} \cdot \alpha_{sF} \cdot a_F(t) \quad (4)$$

or, in compact form,

$$X = A\boldsymbol{\alpha}Z \quad (5)$$

This equation now presents two sets of dependent variables, the basis function matrix A and the sensitivity matrix $\boldsymbol{\alpha}$. To solve for both, we use an algorithm based on alternating least squares (ALS) [10]. ALS is a matrix factorization technique commonly used in collaborative filtering [11] to decompose a user-item rating matrix R into the product of two lower dimensional matrices $R = UP$, one representing users (U) and the other representing items (P). ALS is a two-step iterative optimization process, in which it first fixes P and solves for U, then fixes U and solves for P. Alternating between these two steps is shown to reduce the reconstruction error until convergence to a (local) minimum.

In our case, we use a similar procedure to solve for A and $\boldsymbol{\alpha}$ iteratively. The algorithm starts with an initial value for $\boldsymbol{\alpha} = 1$, i.e., it assumes that all subjects have the same macronutrient sensitivity. Then, it solves for A through the least squares solution in eq. (3) using data from all the subjects in the dataset, i.e., the model assumes that the basis function of each macronutrient is common to all subjects. Given the new estimate for A, the algorithm computes the sensitivity variables $\boldsymbol{\alpha}$ for each subject s separately. This leads to a new set of estimates $\boldsymbol{\alpha}$, which the algorithm uses to recalculate A using eq. (3), and the process repeats until A and $\boldsymbol{\alpha}$ converge.

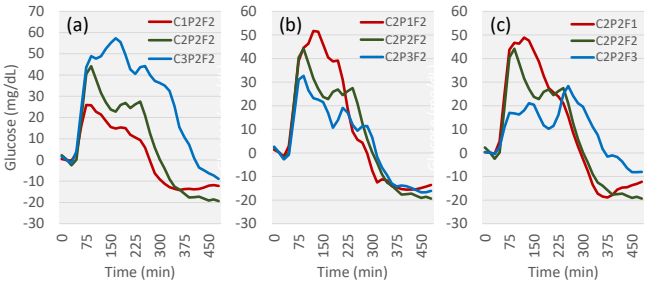

Figure 3. Average glucose response (across 15 subjects) at increasing levels of (a) carbs, (b) protein and (c) fat, while keeping the other two macronutrients at fixed levels

In our experience, convergence occurs rapidly, typically within the first 5 iterations.

C. *Experimental dataset*

To test the proposed model, we used a dataset in which 15 healthy subjects consumed 9 mixed meals on 9 different study days. The order of the meals was randomized for each participant. Subjects were asked to fast for at least 8 hours prior to the meal intake on each study day, so the first blood glucose reading was their fasting glucose level. After taking a baseline blood sample the morning of a study visit, each subject consumed a predefined meal. Subjects remained in a sedentary state and were not allowed to consume any other food for the next 8 hours. Each meal had a known but varying amount of carbohydrates (low: 52 g, medium: 95 g, high: 180 g), protein (low: 15 g, medium: 30 g, high: 60 g), and fat (low: 13 g, medium: 26 g, high: 52 g), which we denote as CxPxFx, where x represents the amount of each macronutrient (1: low; 2: medium; 3: high). To measure PPGRs, participants wore a CGM (Abbott Freestyle Libre Pro), which recorded glucose every 15 minutes. The study was approved by the Texas A&M Institutional Review Board (IRB #2017-0886).

We perform our analysis using the first 32 PPGR readings (8 hours) from the time the meal was consumed. To account for individual differences in fasting glucose, we subtracted the baseline glucose of each PPGR prior to performing the decomposition.

IV. Results

To illustrate the characteristic effect of carbohydrates, Figure **3**(a) shows the average PPGR across subjects for meals with low (C1), medium (C2) and high (C3) carbohydrates, when the other two macronutrients are at a medium level (P2, F2). As carbohydrates increase, the PPGR reaches a higher peak and becomes prolonged. In contrast, increasing protein and fat –see **Figure 3**(b-c) has a mixed effect: it makes PPGRs more sustained but at the same time reduces the PPGR peak. These results provide support to our overall strategy, as they show that meal macronutrients have a characteristic effect on postprandial glucose, as depicted in **Figure 1**.

In a second step, we analyze the convergence properties of the algorithm. **Figure 4** shows the evolution of the sensitivity parameter $\boldsymbol{\alpha}$ over iterations. The sensitivity parameter for carbohydrates converges rapidly, within 1-2 iterations, whereas those for protein and fat sometimes require 5 or more iterations. Of interest, the final values reflect a wide range of

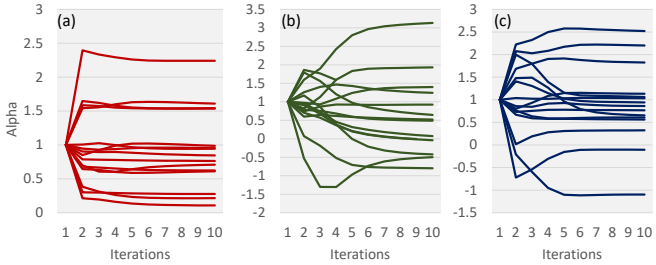

Figure 4. Convergence of the sensitivity variables $\boldsymbol{\alpha}$ as a function of the number of iterations. (a) carbohydrates (CHO), (b) protein, (c) fat.

sensitivities towards macronutrients. As an example, the sensitivity parameters for carbohydrates range from 0.1 to 2.24, indicating that for those two subjects there is a 20-fold difference in the impact that increasing carbohydrates has on postprandial glucose. The range of sensitivities is even larger for protein and fat, where for some subjects the sensitivity parameter becomes negative. This indicates that, for these subjects, the basis function of the corresponding macronutrient on PPGRs should be reversed. Altogether, these results reflect the large difference in carbohydrate, protein and fat metabolism that exist in our subject pool, which would make models based on averages rather limited.

How effective is the proposed model in capturing postprandial responses? **Figure 5** shows the raw PPGR for one of the meals in the study, the reconstruction from the least squares solution in eq. (3), which assumes $\alpha = 1$ for all subjects, and the reconstruction of the proposed model in eq. (5), which allows participants to have their own sensitivity parameters. As shown, the latter model provides a closer reconstruction of the raw PPGR, especially during the early part of the transient. In fact, across meals and participants, the proposed model reduces the reconstruction error by 27%, from 17.7 mg/dl (for the least squares solution) to 12.9 mg/dl.

Next, we analyze the shape of the basis function for the three macronutrients. Results are shown in **Figure 6** for the initial estimate and the one after the algorithm has converged. As shown, these basis functions reflect two distinct behaviors. First, the basis function for carbohydrates indicates that they induce high glucose right after consumption of the meal, as we observed earlier in **Figure 3**(a). Second, the basis functions for protein and fat indicate that both provide a compensatory effect for carbohydrates, reducing glucose levels during the first part of the postprandial period. This effect is then

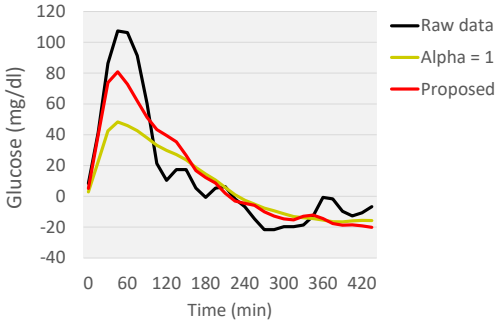

Figure 5. Original PPGR, as modeled with least squares ($\boldsymbol{\alpha} = \mathbf{1}$) and with the proposed algorithm.

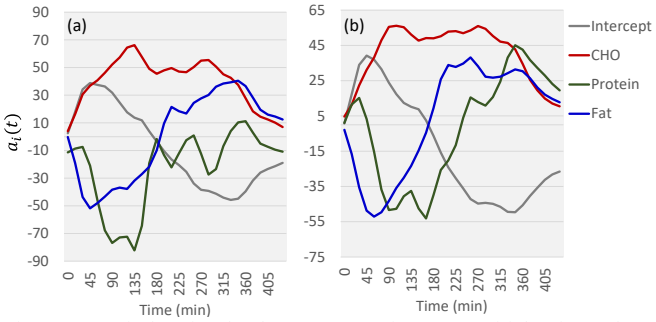

Figure 6. Basis function for the 3 macronutrients. (a) Initial estimate from least squares, i.e., assuming $\boldsymbol{\alpha} = \mathbf{1}$. (b) Final result after the algorithm has converged.

reversed during the latter part of the postprandial period. This combined effect reflects the fact that adding protein and fat to carbohydrate-based meals results in lower and more sustained postprandial glucose responses, as we saw in **Figure 3**(b-c). Notice also how the shape of the basis functions is consistent with the hypothesized marginal effect of macronutrients in **Figure 2**.

In a final analysis, we provide an interpretation for the sensitivity parameters. Assume a subject has high sensitivity to fat, α_F. This implies that the effect of adding fat to a meal will be very significant for that subject. Thus, we expect that the difference in PPGRs between a meal high in fat (e.g., C2P2F3) and one low in fat (e.g., C2P2F1), weighted by the basis function for fat:

$$\Delta x_F = (x_{C2P2F3} - x_{C2P2F1}) \times a_F(t) \qquad (6)$$

will be high for this subject. To verify this point, **Figure 7** shows the relationship between the sensitivity parameter and the measure Δx_i for each of the three macronutrients. We find a strong correlation between the two variables for carbohydrates and fat, and a modest correlation for protein[2]. Thus, the sensitivity parameters can be interpreted as being related to the expected change in PPGRs when the corresponding macronutrient is added to the meal or increased in quantity.

V. Discussion

We have presented an approach that can simultaneously extract the temporal effect on postprandial glucose of adding different macronutrient to a meal, and capture individual differences in macronutrient sensitivity. When tested on an experimental dataset of PPGRs from subjects consuming a variety of foods, we find that the basis functions of the macronutrients are consistent with their hypothesized marginal effect on glucose, and that the sensitivity parameters can be interpreted in terms of differences in PPGRs between meals high and low in the corresponding macronutrients.

In this work, we have assumed that the macronutrients' effects are linear and additive, but other relationships may be explored, such as product terms and other nonlinearities. Of

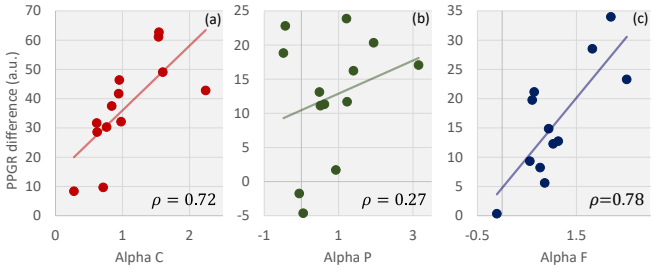

Figure 7. Sensitivity parameters $\boldsymbol{\alpha}$ vs. PPGR difference $\boldsymbol{\Delta x_i}$ between meals with high and low (a) carbs, (b) protein and (c) fat.

interest here, Rytz, et al. [12] have recently proposed a model to estimate the glycemic index of mixed meals, where the contributions of protein and fat appear in the denominator of an expression. Thus, an alternative to our additive model in eq. (7) would rearrange the terms as:

$$x_{ms}(t) = \frac{a_0(t) + z_{ms,C}\alpha_{sC}a_C(t)}{z_{ms,P}\alpha_{sP}a_P(t) + z_{ms,F}\alpha_{sF}a_F(t)} \qquad (7)$$

so that the effect of non-glycemic macronutrients (protein and fat) is divisive rather than subtractive, as in our model.

An additional direction for future work is to use the distribution of sensitivity parameters in the dataset to generate "synthetic patients" with different macronutrient sensitivities. This may be used a data-augmentation procedure to build models that predict macronutrients from PPGRs [6, 7]. Finally, the sensitivity parameters may also be used to develop personalized diet recommendations that reduce high glucose excursions after a meal [5].

VI. References

[1] T. M. Wolever and C. Bolognesi, "Prediction of glucose and insulin responses of normal subjects after consuming mixed meals varying in energy, protein, fat, carbohydrate and glycemic index," *The Journal of nutrition,* vol. 126, no. 11, pp. 2807-2812, 1996.

[2] A. Rytz, D. Adeline, K.-A. Lê, D. Tan, L. Lamothe, O. Roger, and K. Macé, "Predicting Glycemic Index and Glycemic Load from Macronutrients to Accelerate Development of Foods and Beverages with Lower Glucose Responses," (in eng), *Nutrients,* vol. 11, no. 5, p. 1172, 2019.

[3] B. J. Mortazavi and R. Gutierrez-Osuna, "A Review of Digital Innovations for Diet Monitoring and Precision Nutrition," *Journal of Diabetes Science and Technology,* p. 19322968211041356, 2021.

[4] M. Hagve, S. Y. Simbo, L. E. Ruebush, M. P. K. J. Engelen, R. Gutierrez-Osuna, B. J. Mortazavi, G. L. Cote, and N. E. P. Deutz, "Postprandial concentration of circulating branched chain amino acids are able to predict the carbohydrate content of

[2] This result is consistent with our earlier work [6, 7], which show that predicting the amount of protein in a meal from the PPGR is more challenging than predicting carbs or fat.

the ingested mixed meal," *Clinical Nutrition,* vol. 40, no. 8, pp. 5020-5029, 2021/08/01/ 2021.

[5] D. Zeevi, T. Korem, N. Zmora, D. Israeli, D. Rothschild, A. Weinberger, O. Ben-Yacov, D. Lador, T. Avnit-Sagi, M. Lotan-Pompan, J. Suez, J. A. Mahdi, E. Matot, G. Malka, N. Kosower, M. Rein, G. Zilberman-Schapira, L. Dohnalová, M. Pevsner-Fischer, R. Bikovsky, Z. Halpern, E. Elinav, and E. Segal, "Personalized Nutrition by Prediction of Glycemic Responses," *Cell,* vol. 163, no. 5, pp. 1079-1094, 2015/11/19/ 2015.

[6] A. Das, S. Sajjadi, B. Mortazavi, T. Chaspari, P. Paromita, L. Ruebush, N. Deutz, and R. Gutierrez-Osuna, "A Sparse Coding Approach to Automatic Diet Monitoring with Continuous Glucose Monitors," in *ICASSP 2021-2021 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 2021, pp. 2900-2904: IEEE.

[7] S. Sajjadi, A. Das, R. Gutierrez-Osuna, T. Chaspari, P. Paromita, L. E. Ruebush, N. E. Deutz, and B. J. Mortazavi, "Towards The Development of Subject-Independent Inverse Metabolic Models," in *2021 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 2021, pp. 3970-3974.

[8] H. Tily, A. Perlina, E. Patridge, S. Gline, M. Genkin, V. Gopu, H. Lindau, A. Sjue, N. Klitgord, and M. Vuyisich, "Gut microbiome activity contributes to individual variation in glycemic response in adults," *bioRxiv,* p. 641019, 2019.

[9] G. Freckmann, S. Hagenlocher, A. Baumstark, N. Jendrike, R. C. Gillen, K. Rössner, and C. Haug, "Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals," (in eng), *Journal of diabetes science and technology,* vol. 1, no. 5, pp. 695-703, 2007.

[10] P. Comon, X. Luciani, and A. L. De Almeida, "Tensor decompositions, alternating least squares and other tales," *Journal of Chemometrics: A Journal of the Chemometrics Society,* vol. 23, no. 7-8, pp. 393-405, 2009.

[11] X. Su and T. M. Khoshgoftaar, "A survey of collaborative filtering techniques," *Advances in artificial intelligence,* vol. 2009, 2009.

[12] A. Rytz, D. Adeline, K. A. Lê, D. Tan, L. Lamothe, O. Roger, and K. Macé, "Predicting Glycemic Index and Glycemic Load from Macronutrients to Accelerate Development of Foods and Beverages with Lower Glucose Responses," (in eng), *Nutrients,* vol. 11, no. 5, May 25 2019.