Diet and PPGR

Slide source: Nomi Hadar
Personalized Nutrition by Prediction of Glycemic Responses

• The **glycemic response** to a food is the effect that food has on blood sugar (glucose) levels after consumption.
• Some foods cause higher and faster blood glucose levels after meals than others
Def: *pran·di·al* `prandēəl/ : during or relating to dinner or lunch.
• **PPGR** = postprandial glycemic response
• High PPGR is a major risk for prediabetes and Type II diabetes.
86 million American adults—more than 1 out of 3—have prediabetes.

9 out of 10 people with prediabetes do not know they have it.
The dynamic picture is even more alarming:

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• Dietary intake is a central determinant of blood glucose levels.

• To achieve normal glucose levels, it is imperative to make food choices that take into account PPGR.

• Despite their importance, no method exists for predicting PPGRs to food.
• The current practice is to use the meal carbohydrate content, even though it is a poor predictor of the PPGR.

• Other methods: glycemic index, glycemic load.

• Ascribing a single PPGR to each food assumes that the response is solely an intrinsic property of the consumed food.
• However, few small-scale studies found **high variability in PPGRs of different persons to the same food.**

• **Factors that may affect interpersonal differences in PPGRs:**
  - Genetics.
  - Lifestyle.
  - Insulin sensitivity.
  - Propensity for obesity
  - Gut microbiota (little known).
  - And more.
Goals of study

• To quantitatively measure individualized PPGRs, characterize their variability across people and identify factors associated with this variability.

• Devised a machine learning algorithm that predicts personalized PPGRs.
The researchers continuously monitored glucose levels during an entire week in a cohort of 800 healthy and prediabetic individuals.

**Continuous glucose monitoring (CGM)**

**iAUC**: The incremental area under the glucose curve in the 2 hr after the meal
Main cohort: 800 healthy and prediabetic individuals

Gut microbiome: a single stool sample, used for microbiota profiling by both 16S rRNA and metagenomic sequencing.
16S rRNA sequencing

rRNA: Ribosomal RNA: the RNA component of the ribosome.
16S rRNA: subunit that appears in virtually all species.
Differences in the sequence can tell us about different species present
By sequencing the RNA we can obtain the relative abundance of each species

Jo et al. J. Investigative Dermatology 136, 3 2016
16S rRNA SEQUENCING

- Gold standard for bacterial identification
- 16S rRNA gene
  - ~1500 bp
  - Small subunit of ribosome
  - Common to all bacteria
  - Present in 1 or more copies
  - Critical to cell function

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Metagenome sequencing

Much more informative than 16S but requires 100x more data
During the connection week, participants were asked to follow their normal daily routine and dietary habits, except for the first meal of every day, which we provided as one of four different types of standardized meals, each consisting of 50 g of available carbohydrates.
Main cohort: 800 healthy and prediabetic individuals

Per person profiling

- **Gut microbiome**
  - 16S rRNA
  - Metagenomics
- **Blood tests**
- **Questionnaires**
  - Food frequency
  - Lifestyle
  - Medical
- **Anthropometrics**

**Diary** (food, sleep, physical activity)
Using smartphone-adjusted website
5,435 days, 46,896 meals, 9.8M Calories, 2,532 exercises

**Continuous glucose monitoring**
Using a subcutaneous sensor (iPro2)
130K hours, 1.56M glucose measurements

**Standardized meals** (50g available carbohydrates)

<table>
<thead>
<tr>
<th>Day</th>
<th>Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bread</td>
</tr>
<tr>
<td>2</td>
<td>Bread</td>
</tr>
<tr>
<td>3</td>
<td>Bread &amp; butter</td>
</tr>
<tr>
<td>4</td>
<td>Bread &amp; butter</td>
</tr>
<tr>
<td>5</td>
<td>Glucose</td>
</tr>
<tr>
<td>6</td>
<td>Glucose</td>
</tr>
<tr>
<td>7</td>
<td>Fructose</td>
</tr>
</tbody>
</table>

Computational analysis

- **Main cohort**
  - 800 Participants
- **Validation cohort**
  - 100 Participants
- **PPGR prediction**
  - 26 Participants
- **Dietary intervention**
Basic summary statistics

PPGRs associate with risk factors. Shown are PPGRs, BMI, HbA1c%, age, and wakeup glucose of all participants, sorted by median standardized meal PPGR (top, red dots).

Correlation of factors with the median PPGRs to standardized meals is shown along with a moving average line.
PPGR is food type specific

Smoothed histogram of the PPGR for four types of standardized meals provided to participants. Dashed lines represent histogram modes.
PPGR is individual

Example of **high interpersonal** variability and **low intra**-personal variability in the PPGR to bread across four participants (two replicates per participant consumed on two different mornings).
PPGR: High interpersonal variability

Example of two replicates of the PPGR to two standardized meals (left) / real-life meals (right) for two participants exhibiting reproducible yet opposite PPGRs.
Participants response to the standardized meals

Heatmap of PPGR of participants (rows) to three types of standardized meals (columns) consumed in replicates. Clustering is by each participant’s relative rankings of the three meal types.
Carbs vs. PPGR in real-life meals
Clinical and microbiome data vs. PPGR

statistically significant associations (p < 0.05, FDR corrected) between participants’ standardized meals PPGRs and participants’ clinical and microbiome data
So how can we know which food is best for us in terms of glycemic response?
Design

• Discovery phase: develop alg on the main cohort (800 participants)
• Evaluate the alg using leave-one-out CV
• Validation: apply to a indep cohort (100 participants) and compare predicted and measured PPGR
Background

Meal response predictor

Results

General scheme
Regression trees
Gradient boosting regression
Partial dependence plots

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**Constructed 137 features representing**

- meal content (e.g., energy, macronutrients, micronutrients)
- daily activity (e.g., meals, exercises, sleep times)
- blood parameters (e.g., HbA1c%, HDL cholesterol)
- CGM-derived features
- questionnaires
- microbiome features (16S rRNA and metagenomic RAs, KEGG pathway and module RAs and bacterial growth dynamics – developed in prev study).
Prediction of Personalized Postprandial Glycemic Responses

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Prediction of Personalized Postprandial Glycemic Responses

![Diagram showing the prediction of personalized postprandial glycemic responses using a meal response predictor.](image_url)
Decision trees - reminder

• Decision tree is a predictive model that maps observations about an item (the branches) to conclusions about the item's target value (the leaves).

• **Classification trees**: target variable is *categorical*.

• **Regression trees**: target variable is *continuous*. 
Background
Meal response predictor
Results

Prediction based on a single explanatory variable

Model prediction based on person-specific factors

Approaches the presumed upper bound limit set by the 0.71–0.77 correlation observed between the PPGR of the same person to two replicates of the same standardized meal.
Partial dependence plots

- Dataset D: N observations y_k of a response variable y, for k=1,2,...,N, along with p covariates denoted x_{i,k} for i=1,2,...,p and k=1,2,...,N.

- Consider an arbitrary model fitted to D. The model generates predictions of the form:

\[ \hat{y}_k = F(x_{1,k}, x_{2,k}, \ldots, x_{p,k}), \]

- In the case of a single covariate x_j DPDs are obtained by computing the following average:

\[ \phi_j(x) = \frac{1}{N} \sum_{k=1}^{N} F(x_{1,k}, \ldots, x_{j-1,k}, x, x_{j+1,k}, \ldots, x_{p,k}). \]

and plotting it over a useful range of x values.

- \( \phi_j(x) \) tells us how the value of the variable x_j influences the model predictions \( \{\hat{y}_k\} \) after we have “averaged out” the influence of all other variables.
Partial Dependence Plots

• Give insight into the contribution of the different features to the algorithm’s predictions.

• Graphically present the marginal effect of a feature on prediction outcome after accounting for the average effect of all other features.

• Indicative of feature importance – but can be misleading due to higher-order interactions.
Beneficial feature: lower predicted PPGR with predicted feature value.
PDPs of other features

**C**

Meal fat / carbohydrates (4)

Partial dependence (a.u.)

\[ \log_2(\text{fat/carbs}) \]

-2 -1 0 1 2

8303

7611

**E**

Meal sodium (5) Time from last sleep (12) Meal dietary fiber (14) Meal water (21) 24-hour dietary fiber (25)

Partial dependence (a.u.)

0 1 2

-1

8623 7290 10947 8697 5588 7575

4971 6968 10330 8342

0 1000 2000 3000 4000 5000

0 1 2 3 4 5 6 7 8 9 10

0 3 6 9 12 15 18 21

0 300 600 900 1200

0 20 40
PDP microbiome features
Personally Tailored Dietary Interventions

• Recruited 26 new participants
• Dietician gave each 4-6 dietary isocaloric meal options
• Monitored them while eating the meals for a week
• Devised a predictor of which foods will decrease their PPGR and which will increase it
• Let them eat the bad diet for a week, and the good diet for a week, in random order
• Same with expert advice based on the data
Good / bad diets make a difference – and are indeed personal
Choose the foods that are right for you!

The Goal: Our food choices directly affect our health. We want to choose foods that are healthy for us.

The Problem: We are all different. Every person responds differently to the same food.

The Solution: Choose the foods that are right for you, by measuring your own personal response.

TAKE A TOUR  READ MORE  SIGN UP

Watch our lectures
Recap

• Data: Continuous monitoring of glucose levels and food consumption + other parameters
• Devised a meal response predictor of PPGR based on these data
• Method: gradient boosting regression
• Good results – better than previous approaches
• Can affect PPGR in individuals (if they adhere to the prescribed diet..)