Working with CGM data in iglu

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Prerequisites

If you would like to follow along, make sure you install R package **iglu**. We would also use R package **dplyr**

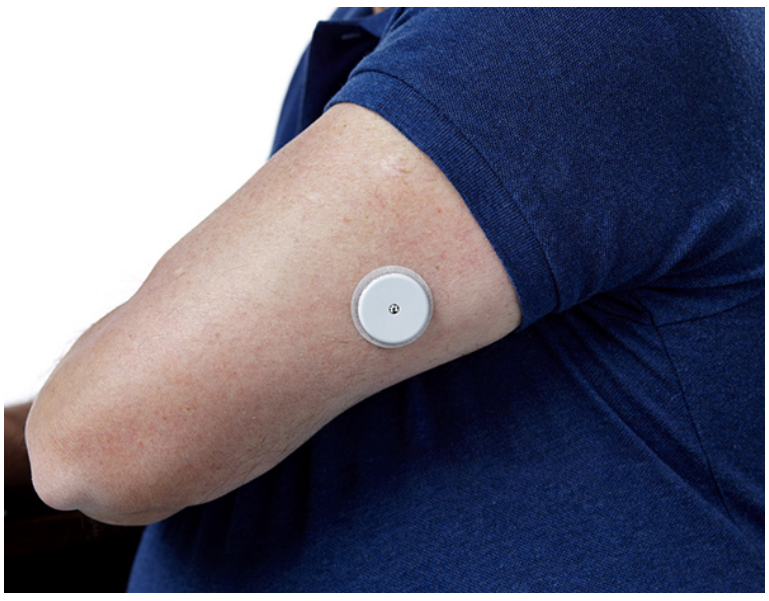
```
# From CRAN
install.packages("iglu")
install.packages("dplyr")

# Plain installation from GitHub
devtools::install_github("irinagain/iglu")

# For installation with vignette
devtools::install_github("irinagain/iglu",
                         build_vignettes = TRUE)
```

Alternatively, you can follow via Shiny App here

Objectives

- Familiarity with CGM data and context of use
- Visualization with iglu
- Consensus metrics of glycemic control and their computation
- Additional CGM metrics
- Broader CGM research perspectives

Introduction to CGM data

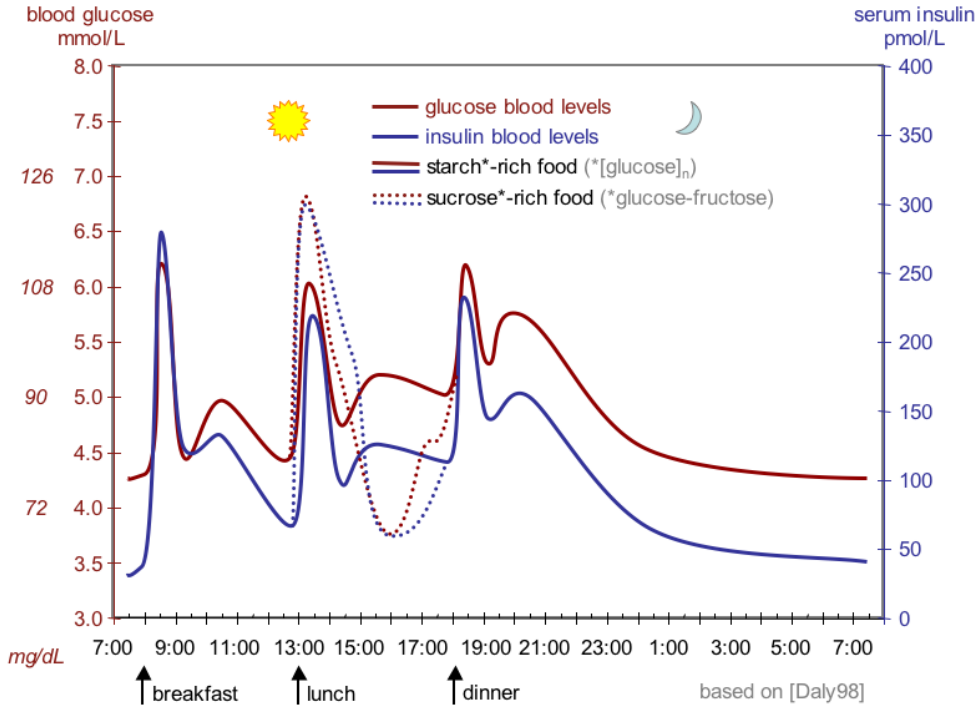


CGMs measure interstitial glucose levels continuously throughout the day, typical frequency is 5 min

One CGM lasts 10 days (most Dexcom models) or 14 days (most Libre models), after which it needs to be replaced

What does the normal insulin/glucose levels should look like?

- **Normal** blood glucose range - **70-120 mg/dL**
- Spikes as a result of the meal intake
- **Main challenge:** non-linear trend, highly dependent on the environment (time and content of meals, exercise, stress, etc)
- **HbA1c:** standard biomarker of glucose control, average glucose levels for preceeding 2-3

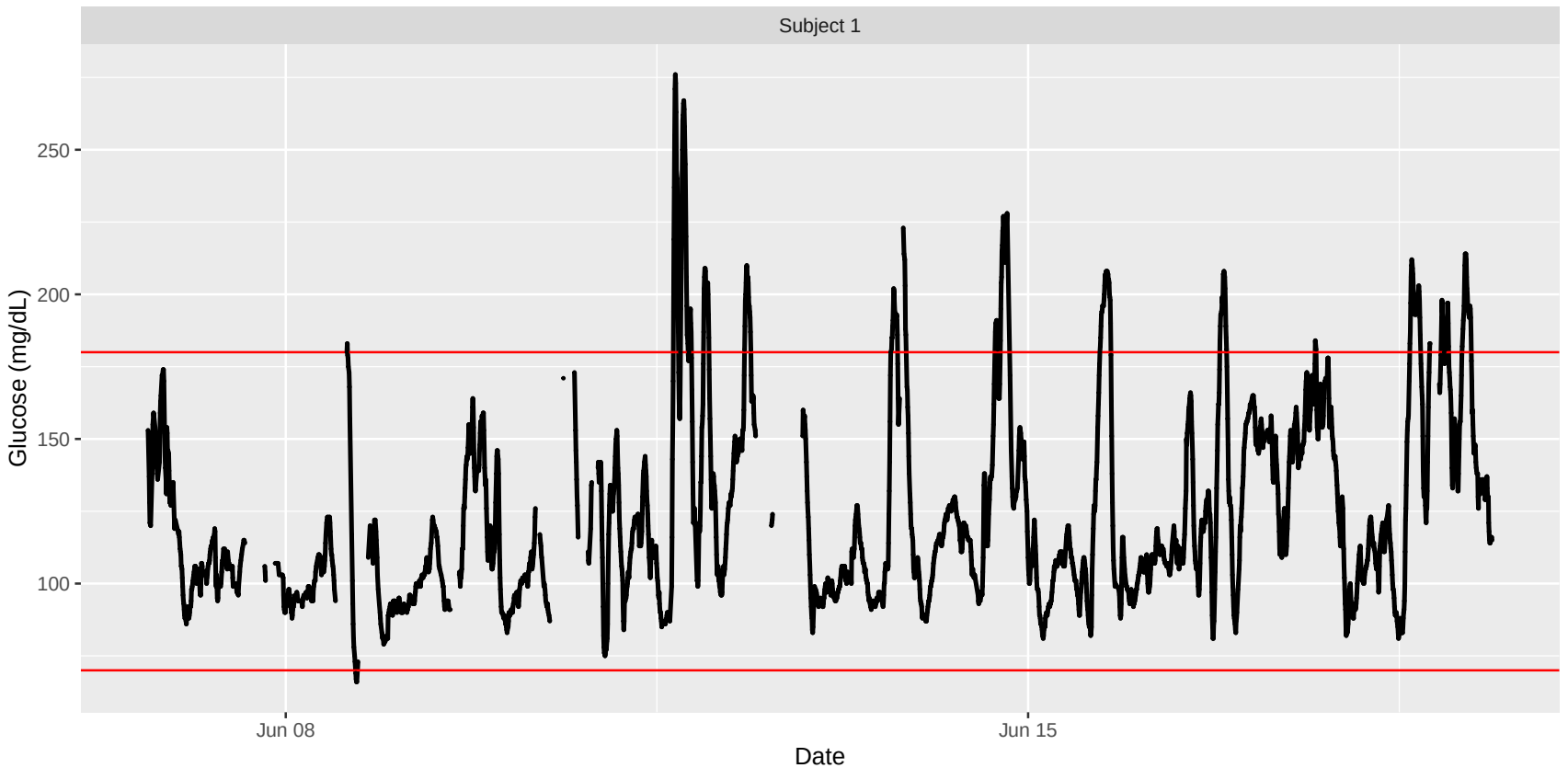


Credit: Wikipedia

Example CGM data from iglu

Dexcom G4 CGM measurements with 5 min frequency of a subject with type 2 diabetes. Horizontal lines are 70-180 mg/dL (typical target range).

```
library(iglu)
plot_glu(example_data_1_subject)
```



CGM context of use

Diabetes management

- Subjects with Type 1 diabetes use real time data to inform insulin usage
- Subjects with prediabetes, Type 2 and gestational diabetes use data to inform dietary choices and physical activity (if not on insulin)

Clinical practice: Endocrinologists use data to inform treatment decisions and make recommendations on insulin dosage adjustment

Clinical trials: CGM-based outcomes are used to evaluate treatment efficacy

Research at large

- Predictions of future glucose based on past CGM data (artificial pancreas)
- Retrospecticve associations between glycemic levels and characteristics
- Nutritionists use CGM data to study the effects of different diets on glycemic control

CGM-based metrics of glycemic control

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 11, Supplement 1, 2009

DOI: 10.1089/dia.2008.0132

Interpretation of Continuous Glucose Monitoring Data: Glycemic Variability and Quality of Glycemic Control

David Rodbard, M.D.

Summarizes *more than 40* different CGM-based glucose control and variability metrics. Many more developed and proposed in the literature since then.

Our **R package iglu** computes 60+ metrics corresponding to different aspects of glycemic control. Recently used in CGMap (Keshet et al., 2003) on over 7000 non-diabetic individuals to generate reference values for CGM-derived measured.

Metrics pros and cons

Pros:

- Capture different aspects of glycemic control
- Many software packages exist, and they generally agree with each other - recent review by Piersanti et al., 2023
- Community activities to build consensus on what should be used in clinical trials as endpoints

Continuous glucose monitoring and metrics for clinical trials: an international consensus statement

Tadej Battelino, Charles M Alexander, Stephanie A Amiel, Guillermo Arreaza-Rubin, Roy W Beck, Richard M Bergenstal, Bruce A Buckingham, James Carroll, Antonio Ceriello, Elaine Chow, Pratik Choudhary, Kelly Close, Thomas Danne, Sanjoy Dutta, Robert Gabbay, Satish Garg, Julie Heverly, Irl B Hirsch, Tina Kader, Julia Kenney, Boris Kovatchev, Lori Laffel, David Maahs, Chantal Mathieu, Dídac Mauricio, Revital Nimri, Rimei Nishimura, Mauro Scharf, Stefano Del Prato, Eric Renard, Julio Rosenstock, Banshi Saboo, Kohjiro Ueki, Guillermo E Umpierrez, Stuart A Weinzimer, Moshe Phillip

Lancet Diabetes Endocrinol 2023; 11: 42–57

Published Online December 6, 2022 https://doi.org/10.1016/S2213-8587(22)00319-9

Randomised controlled trials and other prospective clinical studies for novel medical interventions in people with diabetes have traditionally reported HbA_{1c} as the measure of average blood glucose levels for the 3 months preceding the HbA_{1c} test date. The use of this measure highlights the long-established correlation between HbA_{1c} and relative risk of diabetes complications; the change in the measure, before and after the therapeutic intervention, is used by regulators for the approval of medications for diabetes. However, with the increasing use of continuous glucose monitoring (CGM) in clinical practice, prospective clinical studies are also increasingly using CGM

Metrics pros and cons

Cons:

- Consensus is made primarily based on considerations for type 1 diabetes
- Metrics selection is based on interpretability
- Translation of more complex metrics into automatic algorithms can lead to disagreement across software

For more discussion:

- Gaynanova I (2022). Digital biomarkers of glucose control - reproducibility challenges and opportunities. ASA Biopharmaceutical Report, Vol. 29, No. 1, 21-26.

Example datasets

The iglu package comes with two example datasets

- `example_data_5_subject` are 5 min frequency Dexcom G4 CGM data from 5 subjects with type 2 diabetes not on insulin therapy. These data are part of a larger study analyzed in Gaynanova et al. (2020)
- `example_data_hall` are Dexcom G4 5 min frequency CGM data from 19 subjects with pre-diabetes and type 2 diabetes from Hall et all. (2018)

Awesome-CGM by Xu et al. (2024) has additional public CGM datasets assembled by our group

Additional resources on iglu

The website and paper references.

- Broll S, Urbanek J, Buchanan D, Chun E, Muschelli J, Punjabi N and Gaynanova I (2021). Interpreting blood glucose data with R package iglu. PLoS One, Vol. 16, No. 4, e0248560.
- Chun E, Fernandes JN and Gaynanova I (2024). An Update on the iglu Software for Interpreting Continuous Glucose Monitoring Data. Diabetes Technology and Therapeutics, Vol. 26, No. 12, 939-950.

The website has additional vignettes on MAGE, AGP and episode calculations and lasagna plots.

How much data do you need?

- 2 weeks of data with at least 70% non-missing is typical standard for *outpatient* CGM settings Battelino et al. (2023)
- Can check amoung of missingness in iglu with `active_percent`

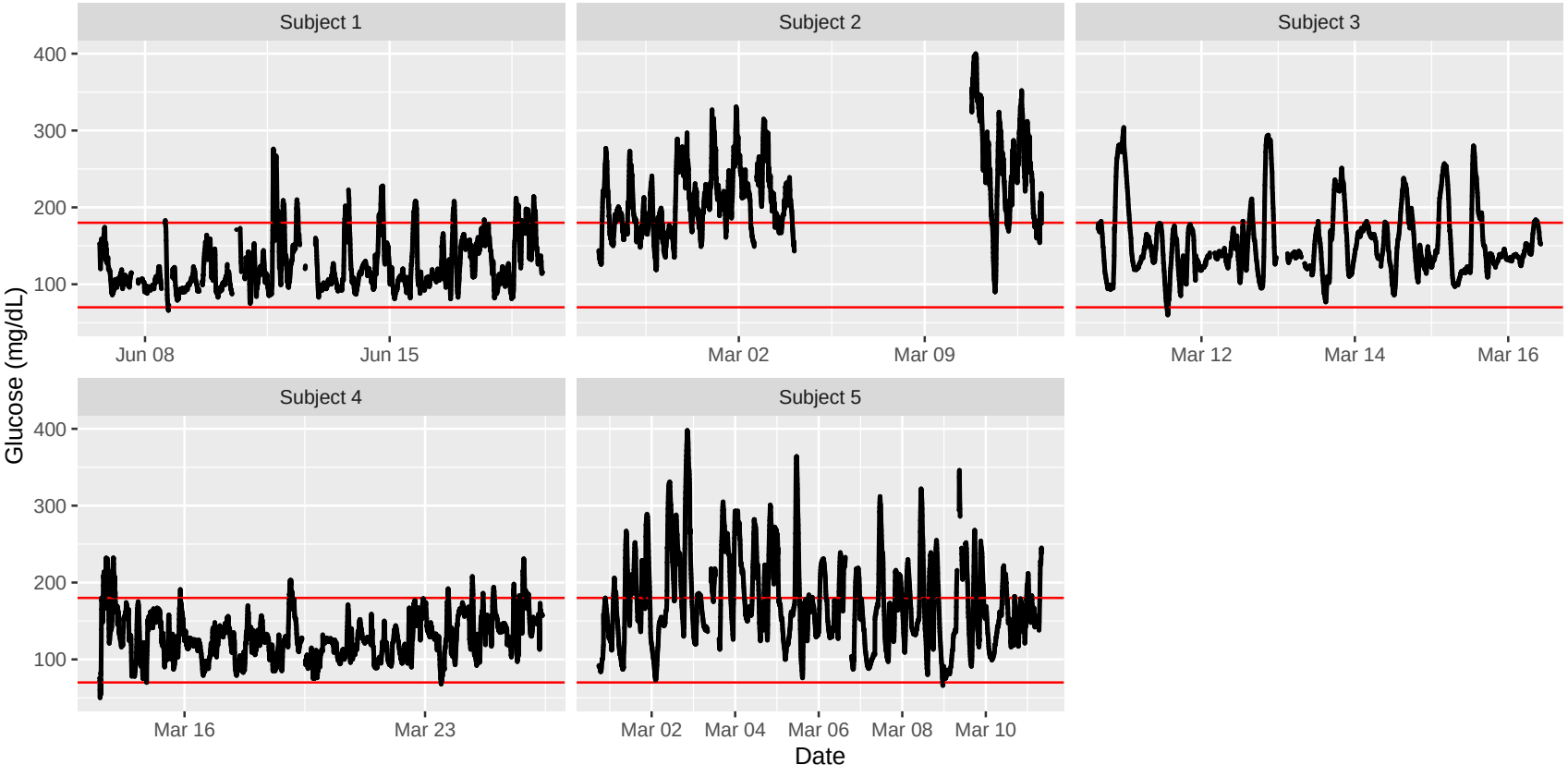
```
active_percent(example_data_5_subject)
```

```
## # A tibble: 5 x 5
##   id        active_percent ndays     start_date          end_date
##   <fct>              <dbl> <drtn>    <dttm>              <dttm>
## 1 Subject 1           79.8 12.7 days 2015-06-06 16:50:27 2015-06-19
## 2 Subject 2           58.9 16.7 days 2015-02-24 17:31:29 2015-03-13
## 3 Subject 3           92.1  5.8 days 2015-03-10 15:36:26 2015-03-16
## 4 Subject 4           98.7 12.9 days 2015-03-13 12:44:09 2015-03-26
## 5 Subject 5           95.8 10.6 days 2015-02-28 17:40:06 2015-03-11
```

Same data visually

Consider 5 subjects with type 2 diabetes and their CGM data

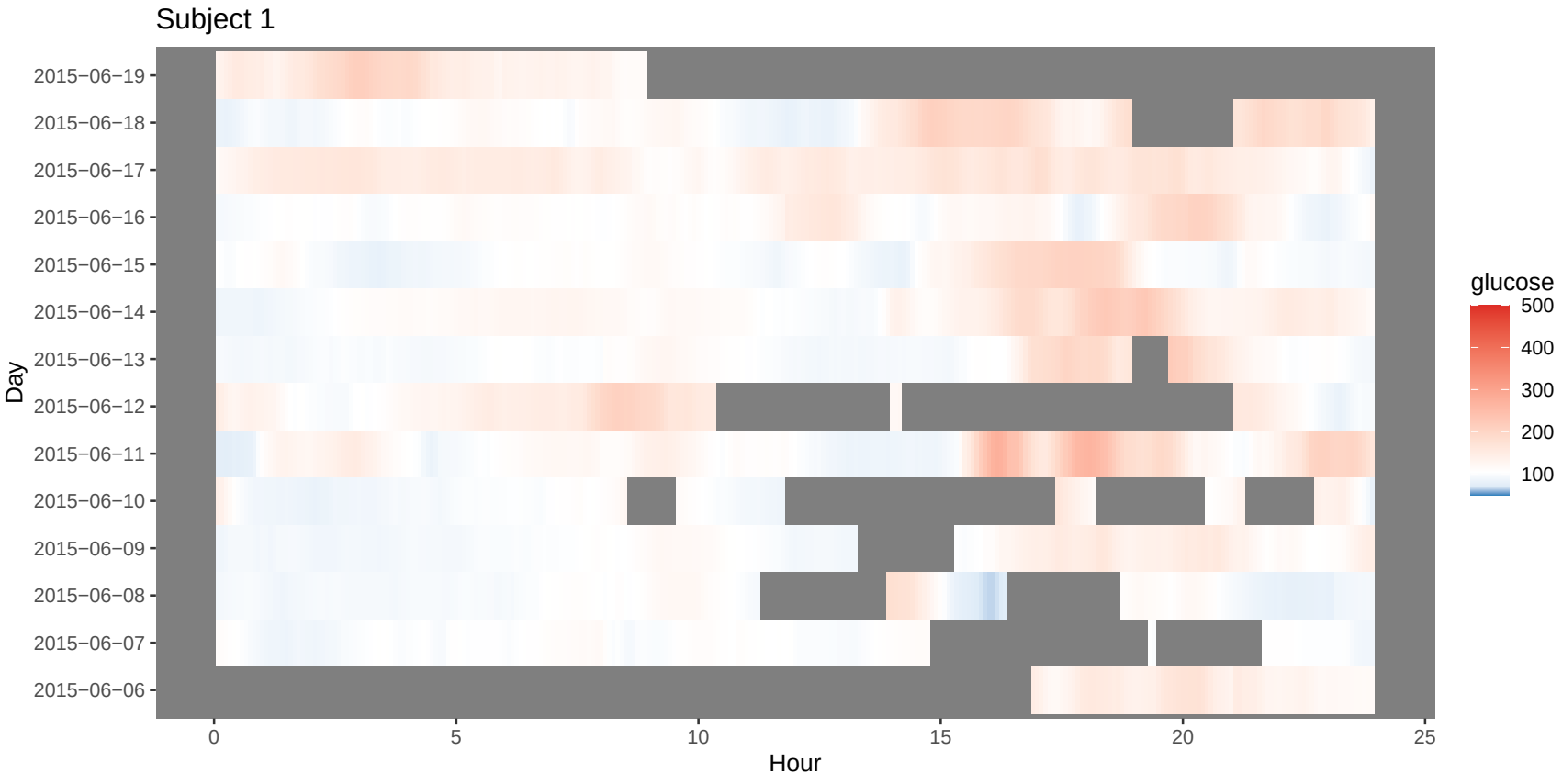
```
plot_glu(example_data_5_subject)
```



Other ways to visualize the data

Lasagna plots Swihart et al. (2010)

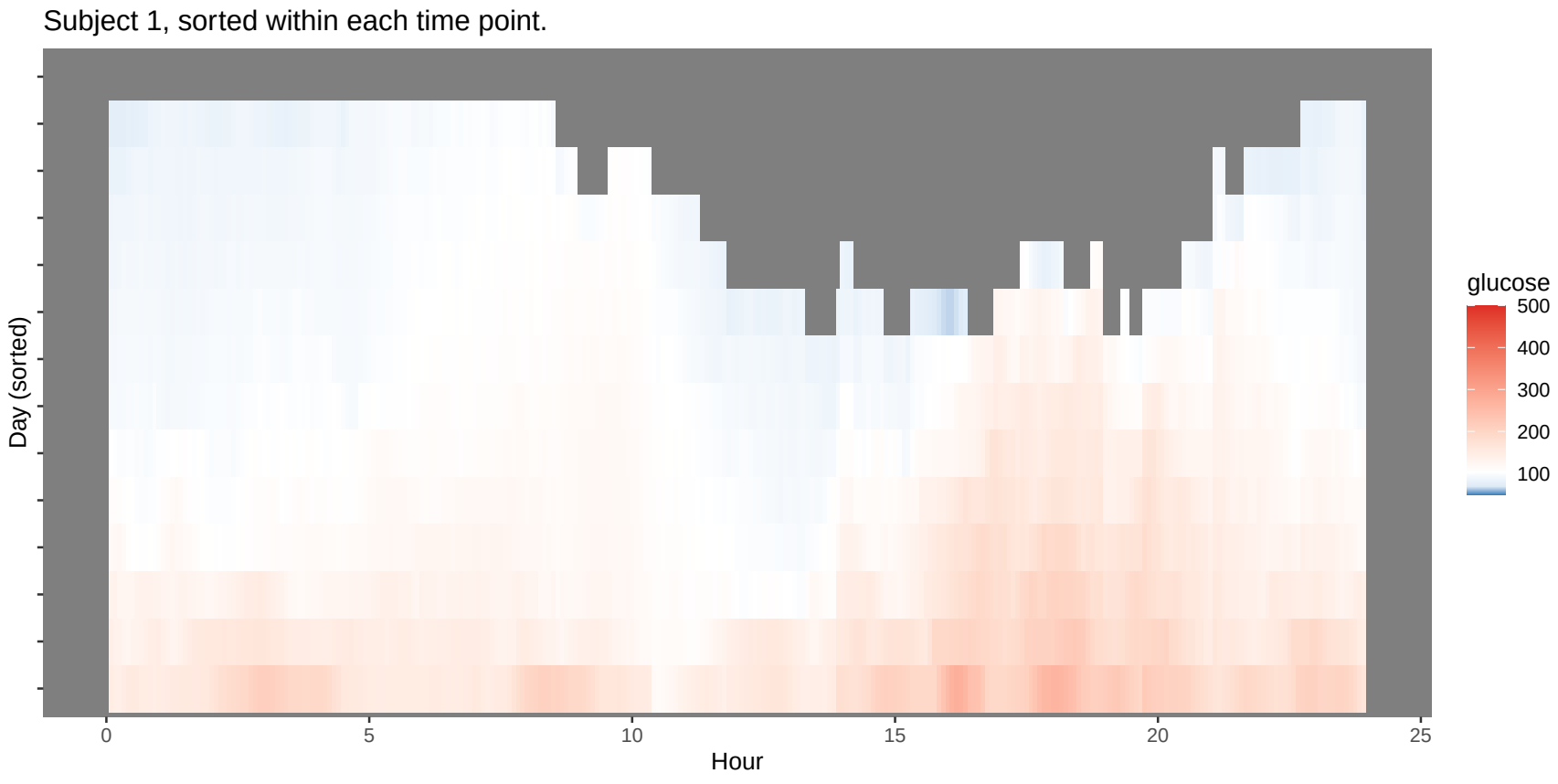
```
plot_lasagna_1subject(example_data_1_subject)
```



Other ways to visualize the data

Lasagna plots sorted by time - average 24 hours effects

```
plot_lasagna_1subject(example_data_1_subject,
                      lasagnatype = 'timesorted')
```



Common summaries of CGM data

Consensus CGM metrics described in Battelino et al. (2023)

- Mean glucose and GMI (Glucose Management Indicator)
- Time-in-Range (TIR, 70-180 mg/dL), Time in Hypoglycemia (Level 1 and Level 2), Time in Hyperglycemia (Level 1 and Level 2)
- CV (Coefficient of Variation)
- GRI (Glucose Risk Index)
- Glycemic Episodes

Mean and GMI

Check that our intuition is matched

```
mean_glu(example_data_5_subject)
```

```
## # A tibble: 5 x 2
##   id          mean
##   <fct>      <dbl>
## 1 Subject 1   124.
## 2 Subject 2   218.
## 3 Subject 3   154.
## 4 Subject 4   130.
## 5 Subject 5   175.
```

Mean and GMI

GMI is a deterministic transformation of mean on HbA1c scale

$$GMI = 3.31 + 0.02392 \times \text{mean glucose}$$

```
gmi(example_data_5_subject)
```

```
## # A tibble: 5 x 2
##   id           GMI
##   <fct>      <dbl>
## 1 Subject 1   6.27
## 2 Subject 2   8.54
## 3 Subject 3   6.99
## 4 Subject 4   6.41
## 5 Subject 5   7.49
```

HbA1c is a measure of average glucose over the past 3 months

Pre-diabetes - A1c of 5.7%-6.4%; **Diabetes** - A1c> 6.5%

Typical treatment goal: A1c $<$ 7%

Time in range (TIR)

Most common and accepted metric as treatment target

```
in_range_percent(example_data_5_subject,
                 target_ranges = list(c(70, 180)))
```

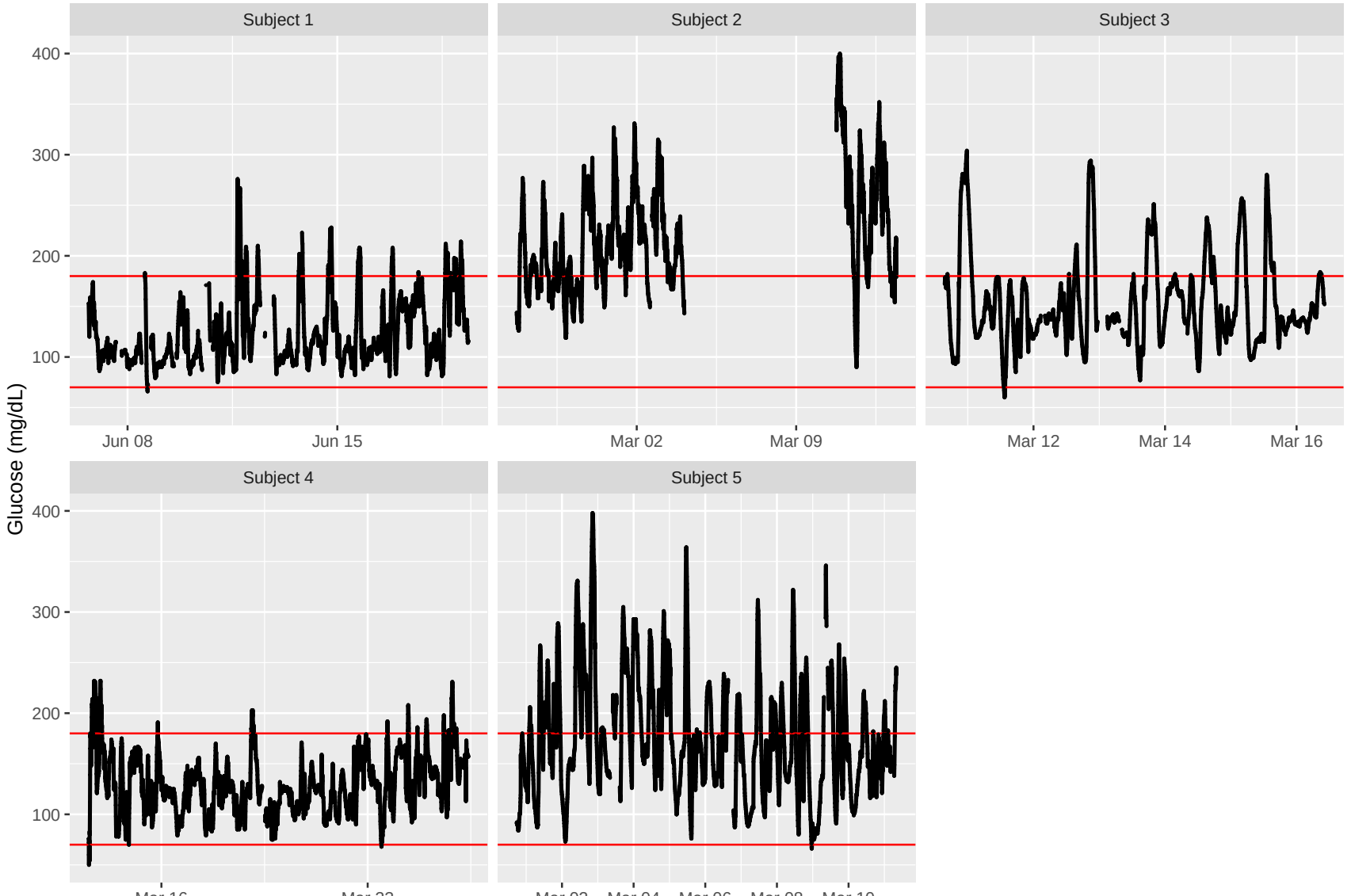
```
## # A tibble: 5 x 2
##   id        in_range_70_180
##   <fct>               <dbl>
## 1 Subject 1            91.7
## 2 Subject 2            26.4
## 3 Subject 3            81.3
## 4 Subject 4            95.1
## 5 Subject 5            62.1
```

A typical goal is over 70%. Subjects without diabetes typically have over 95% TIR

Time in range (TIR)

Can also be judged from the plots

```
plot_glu(example_data_5_subject, LLTR = 70, ULTR = 180)
```



Time in range and outside

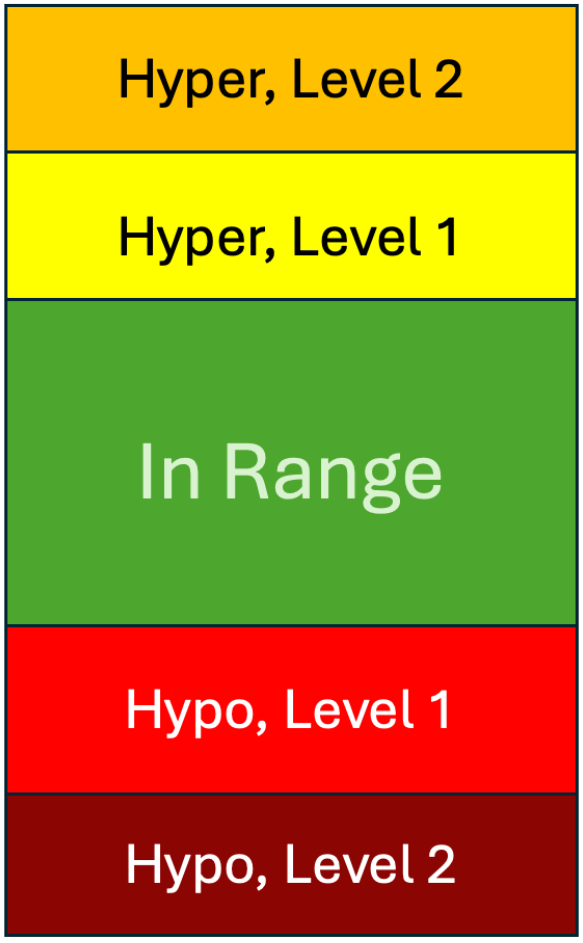
It is typical to divide the whole range of measurements into time spent within prespecified thresholds

- Level 2 Hypoglycemia [$<$ 54 mg/dL]
- Level 1 Hypoglycemia [54 - 70 mg/dL]
- In-range [70 - 180 mg/dL]
- Level 1 Hyperglycemia [180 - 250 mg/dL]
- Level 2 Hyperglycemia [$>$ 250 mg/dL]

The sum across ranges is 100%, giving rise to barplot

Sometimes, Levels 1 and 2 are combined, giving rise to just 3 areas.

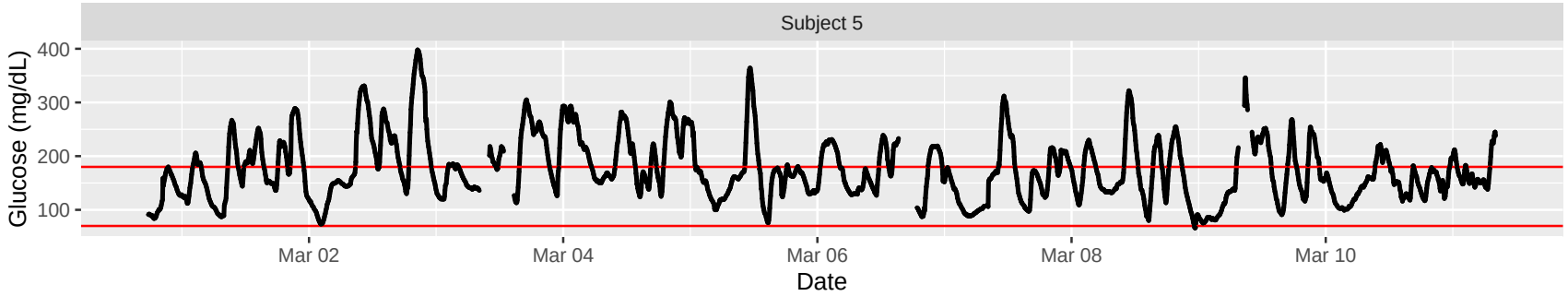
Glycemic thresholds



- Overall goal - spend as much time In Range as possible
- Recent analysis of over 7,000 subjects without diabetes (Keshet et al., 2023) finds that an average is about 94%
- One example subject with Type 2 diabetes from iglu has 26% TIR - clearly room for improvement

Time in range and outside

```
plot_glu(example_data_5_subject %>%
               dplyr::filter(id == "Subject 5"))
```




```
plot_ranges(example_data_5_subject %>%
               dplyr::filter(id == "Subject 5"))
```

For Subject 5, there is significant time in Hyperglycemia, and no time in Hypoglycemia. In general, Hypoglycemia is more prominent in subjects with Type 1 diabetes.

Time in range and outside

The ranges can be evaluated separately with any thresholds

```
below_percent(example_data_5_subject %>%
                dplyr::filter(id == "Subject 5"))
```

```
## # A tibble: 1 x 3
##   id        below_54 below_70
##   <fct>        <dbl>    <dbl>
## 1 Subject 5        0    0.103
```

```
above_percent(example_data_5_subject %>%
                dplyr::filter(id == "Subject 5"))
```

```
## # A tibble: 1 x 4
##   id        above_140 above_180 above_250
##   <fct>         <dbl>     <dbl>     <dbl>
## 1 Subject 5      69.8      37.8      11.3
```

Time in range and outside

- Fixed thresholds of 54, 70, 180, 250 mg/dL are common
- For data-driven unsupervised thresholds, see our recent work, not on iglu yet but is in python https://github.com/pjywang/OptiThresholds

Park et al. (2025) Beyond fixed thresholds: optimizing summaries of wearable device data via piecewise linearization of quantile functions

Coefficient of variation

CV is a global measure (100 $\times$ SD/mean). A typical treatment target is below 36%.

```
cv_glu(example_data_5_subject)
```

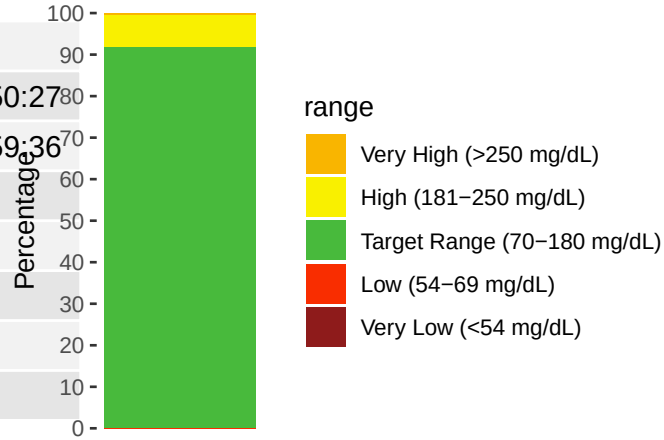
```
## # A tibble: 5 x 2
##   id            CV
##   <fct>      <dbl>
## 1 Subject 1   26.9
## 2 Subject 2   24.0
## 3 Subject 3   29.1
## 4 Subject 4   22.4
## 5 Subject 5   33.5
```

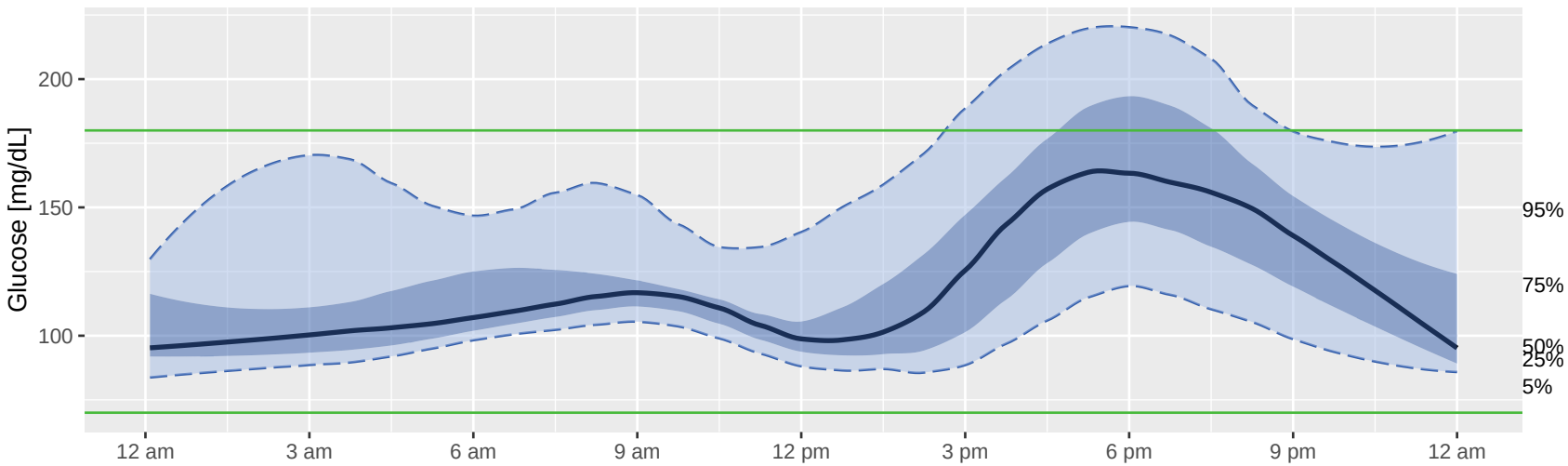
AGP (Ambulatory Glucose Profile)

Most consensus metrics are typically summarized in AGP.

```
agp(example_data_1_subject, daily = FALSE)
```

ID	Subject 1
Start Date	2015−06−06 16:50:27
End Date	2015−06−19 08:59:36
Duration	12.7 days
% Time CGM is Active	79.8%
Average Glucose	124 mg/dL
Glucose Management Indicator (GMI)	6.3%
Glucose Variability (CV)	26.9%





GRI (Glucose Risk Index)

More recent measure, based on PCA of clinicians' ratings [Klonoff et al. (2022). The final formula is based on percentages within each level - attempt to arrive at 1 summary.

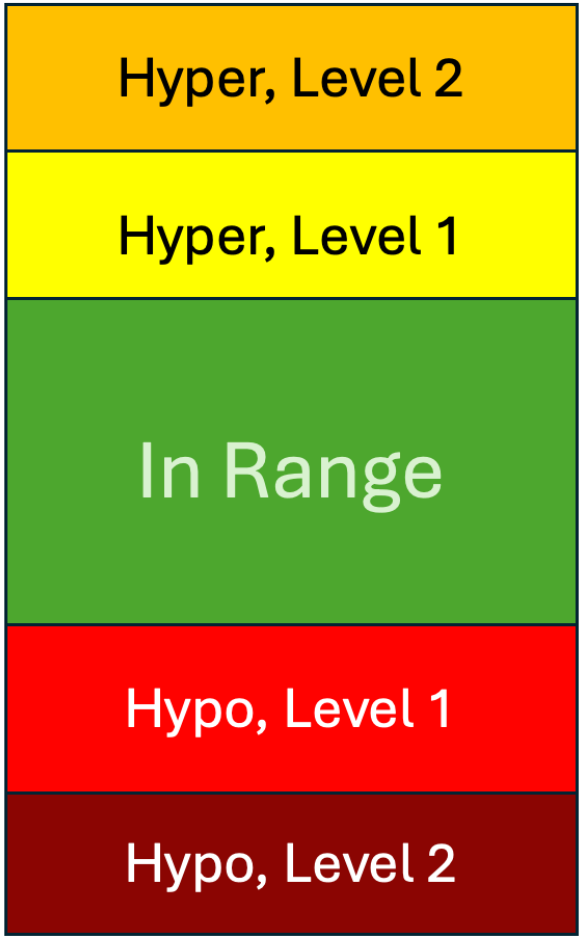
$$GRI = 3\times \text{ Lv2 Hypo} + 2.4\times \text{ Lv1 Hypo} + 0.8\times \text{ Lv1 Hyper} + 1.6\times \text{ Lv2 Hyper}$$

```
gri(example_data_5_subject)
```

```
## # A tibble: 5 x 2
##   id           GRI
##   <fct>      <dbl>
## 1 Subject 1  7.19
## 2 Subject 2 79.7
## 3 Subject 3 20.0
## 4 Subject 4  4.38
## 5 Subject 5 39.5
```

GRI $= 0$ indicates time-in-range of 100%. Maximum allowable GRI is 100%.

Glycemic Episodes



- High Glucose (Level 1) - >180, $\geq$15 consecutive min, ends when ≥ 15 consecutive min of values <180
- Very High Glucose (Level 2) - >250, $\geq$15 consecutive min, ends when ≥ 15 consecutive min of values <250
- Dexcom G6, G7- 5 measurement frequency, hence requires 3 consecutive readings; Free Style Libre 3 - 1 min (but typically agglomerated at 5 min)

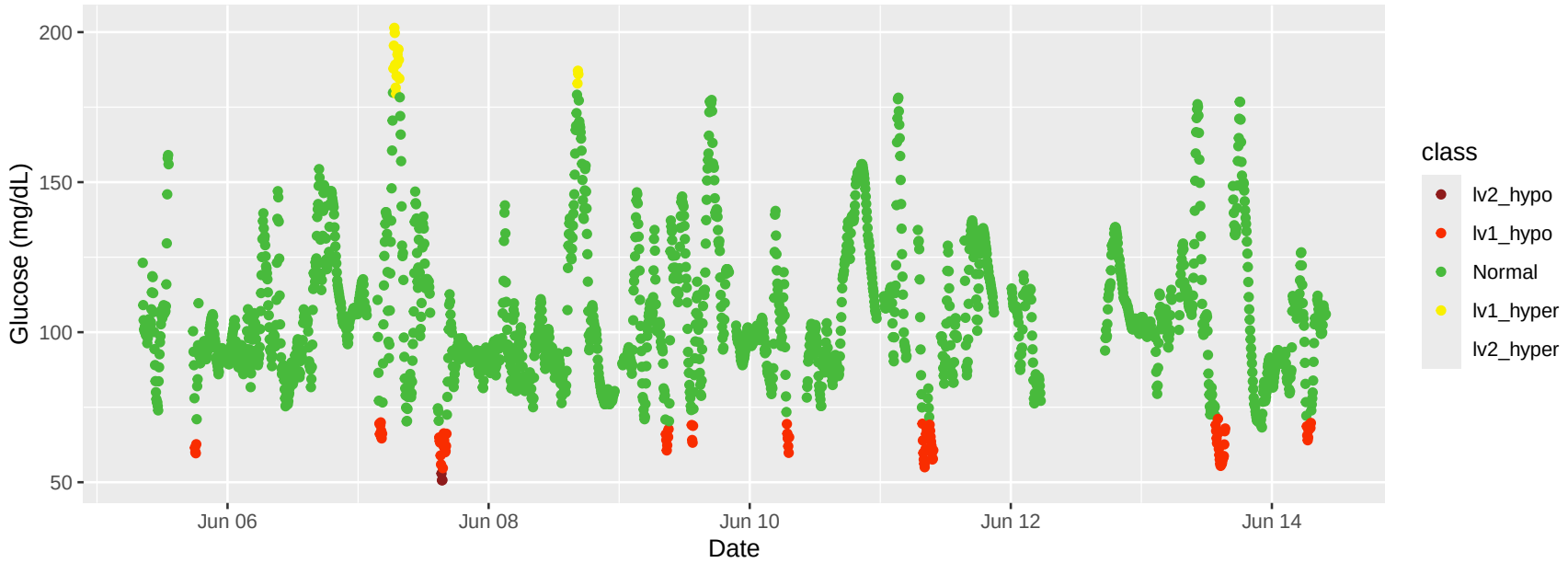
Episodes

```
epicalc_profile(example_data_hall %>%
                  dplyr::filter(id == "2133-039"))
```

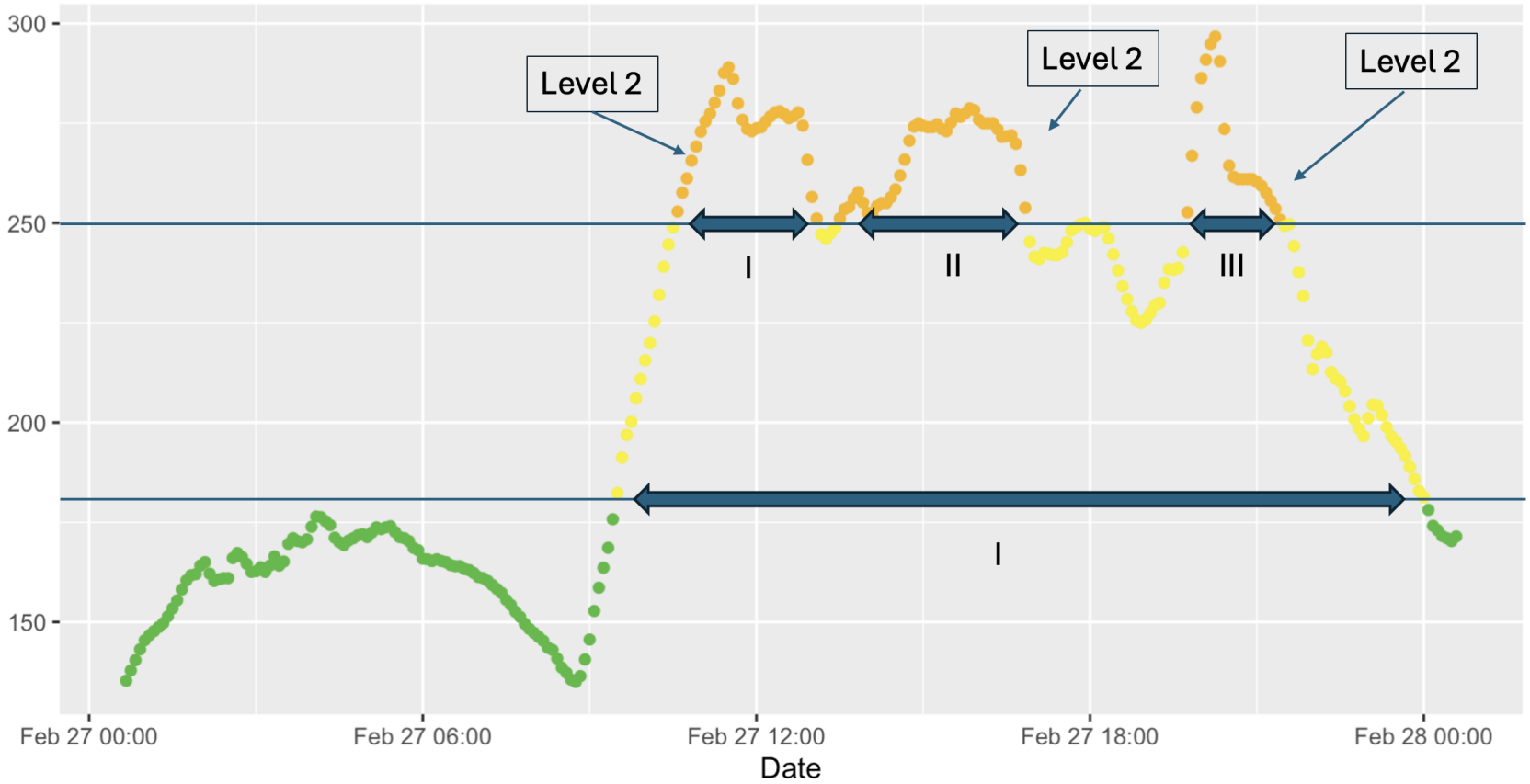
Episode Metrics – 2133–039

	Hypoglycemia Level 1	Hypoglycemia Level 2	Hypoglycemia Extended	Hyperglycemia Level 1	Hyperglycemia Level 2	Hypoglycemia Level 1 excl	Hyperglycemia Level 1 excl
Thresholds	<70 mg/dL	<54 mg/dL	<70 mg/dL	>180 mg/dL	>250 mg/dL	70–54 mg/dL	180–250 mg/dL
Avg Episodes/Day	1.33	0.13	0.00	0.27	0.00	1.20	0.27
Mean duration	49.00 min	15.00 min	0.00 min	42.50 min	0.00 min	45.00 min	42.50 min
Mean glucose	63.79 mg/dl	51.43 mg/dl	NA mg/dl	187.87 mg/dl	NA mg/dl	64.22 mg/dl	187.87 mg/dl
Total episodes	10.00	1.00	0.00	2.00	0.00	9.00	2.00

An episode is >= 15 continuous minutes



Count interpretation



- iglu counts 3 Level 2 episodes (> 250)
- iglu counts only 1 Level 1 episode (adjusted definition > 180)
- iglu counts 0 **Exclusive** Level 1 episodes

Episodes

Alternative numeric output directly

```
episode_calculation(example_data_hall %>%
                    dplyr::filter(id == "2133-039"))
```

```
## # A tibble: 7 x 7
##   id       type  level   avg_ep_per_day avg_ep_duration avg_ep_gl total_episodes
##   <chr>    <chr> <chr>            <dbl>           <dbl>     <dbl>          <dbl>
## 1 2133-039 hypo  lv1              1.33             49        63.8             10
## 2 2133-039 hypo  lv2              0.133            15        51.4              1
## 3 2133-039 hypo  extend~          0                 0        NA                0
## 4 2133-039 hyper lv1              0.266            42.5     188.               2
## 5 2133-039 hyper lv2              0                 0        NA                0
## 6 2133-039 hypo  lv1_ex~          1.20             45        64.2              9
## 7 2133-039 hyper lv1_ex~          0.266            42.5     188.               2
```

For more algorithmic discussion on episode calcultaion challenges, including missing data:

- Gaynanova and Lee (2025) When Algorithms Diverge: Quantification of Glycemic Episodes from Continuous Glucose Monitor Data Diabetes Technology & Theurapetics, ahead of print.

All consensus metrics at once

```
all_metrics(example_data_5_subject,
            metrics_to_include = "consensus_only")
```

```
## # A tibble: 5 x 18
##   id     below_54 below_70 in_range_70_180 above_180 above_250    SD  mean    CV
##   <fct>     <dbl>    <dbl>           <dbl>     <dbl>     <dbl> <dbl> <dbl> <dbl>
## 1 Subje~   0         0.137            91.7      8.20     0.377  33.3  124.  26.9
## 2 Subje~   0         0                26.4     73.6     26.1    52.4  218.  24.0
## 3 Subje~   0         0.326            81.3     18.3      5.68   44.8  154.  29.1
## 4 Subje~   0.0546    0.273            95.1      4.61     0      29.1  130.  22.4
## 5 Subje~   0         0.103            62.1     37.8     11.3    58.6  175.  33.5
## # i 9 more variables: active_percent <dbl>, ndays <drtn>, start_date <dttm>,
## #   end_date <dttm>, in_range_70_140 <dbl>, GMI <dbl>, GRI <dbl>,
## #   total_extended_hypo_episodes <dbl>, total_extended_hyper_episodes <dbl>
```

This includes missing via `active_percent`, mean, GMI, TIR measures, SD, CV, GRI, GRI and counts of extended hypo- and hyperglycemia episodes

Common summaries of CGM data

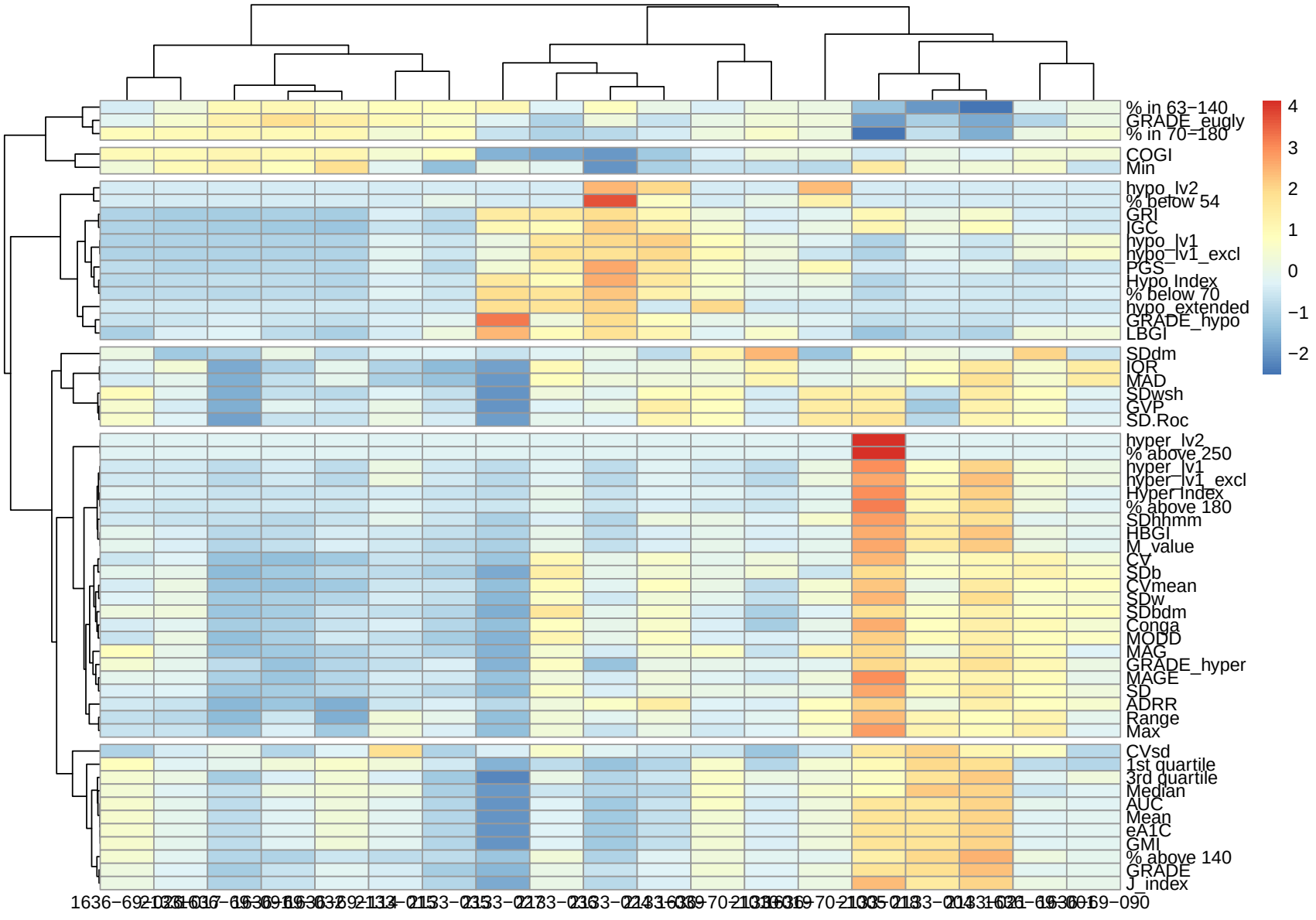
Consensus CGM metrics described in Battelino et al. (2023)

- Mean glucose and GMI (Glucose Management Indicator)
- Time-in-Range (TIR, 70-180 mg/dL), Time in Hypoglycemia (Level 1 and Level 2), Time in Hyperglycemia (Level 1 and Level 2)
- CV (Coefficient of Variation)
- GRI (Glucose Risk Index)
- Glycemic Episodes

TIR is the 1st default and most common standard.

More metrics

```
cluster_out = metrics_heatmap(data = example_data_hall)
```



More metrics - variability measures

- `sd_measures` - different types of standard deviation, betwen days, within time points, highly correlated

```
sd_measures(example_data_5_subject)
```

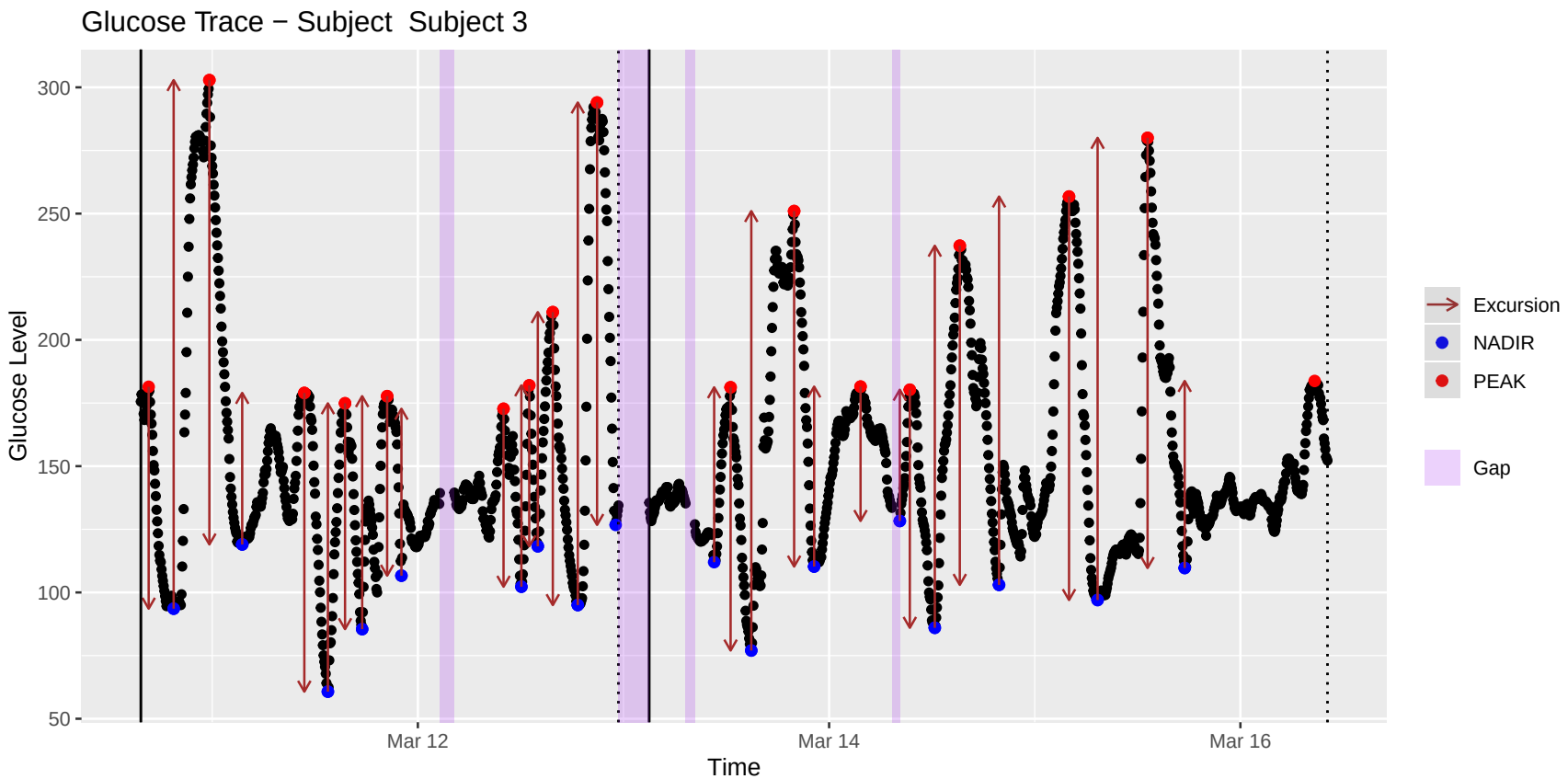
```
## # A tibble: 5 x 7
##   id            SDw SDhhmm SDwsh  SDdm   SDb SDbdm
##   <fct>       <dbl>  <dbl> <dbl> <dbl> <dbl> <dbl>
## 1 Subject 1  26.4    19.6  6.54  16.7  27.9  24.0
## 2 Subject 2  36.7    22.8  7.62  52.0  48.0  35.9
## 3 Subject 3  42.9    14.4  9.51  12.4  42.8  42.5
## 4 Subject 4  24.5    12.9  6.72  16.9  25.5  22.0
## 5 Subject 5  50.0    29.6 12.8   23.3  50.3  45.9
```

More metrics - variability measures

- `mage` - Mean Amplitude of Glycemic Excursions

Automatic peak identification algorithm, exclusion of smallest amplitudes, average amplitude returned

```
mage(example_data_5_subject %>%
       dplyr::filter(id == "Subject 3"), plot = TRUE)
```



More metrics - variability measures

- `mage` - Mean Amplitude of Glycemic Excursions

Automatic peak identification algorithm, exlusion of smallest amplitudes, average amplitude returned

```
mage(example_data_5_subject)
```

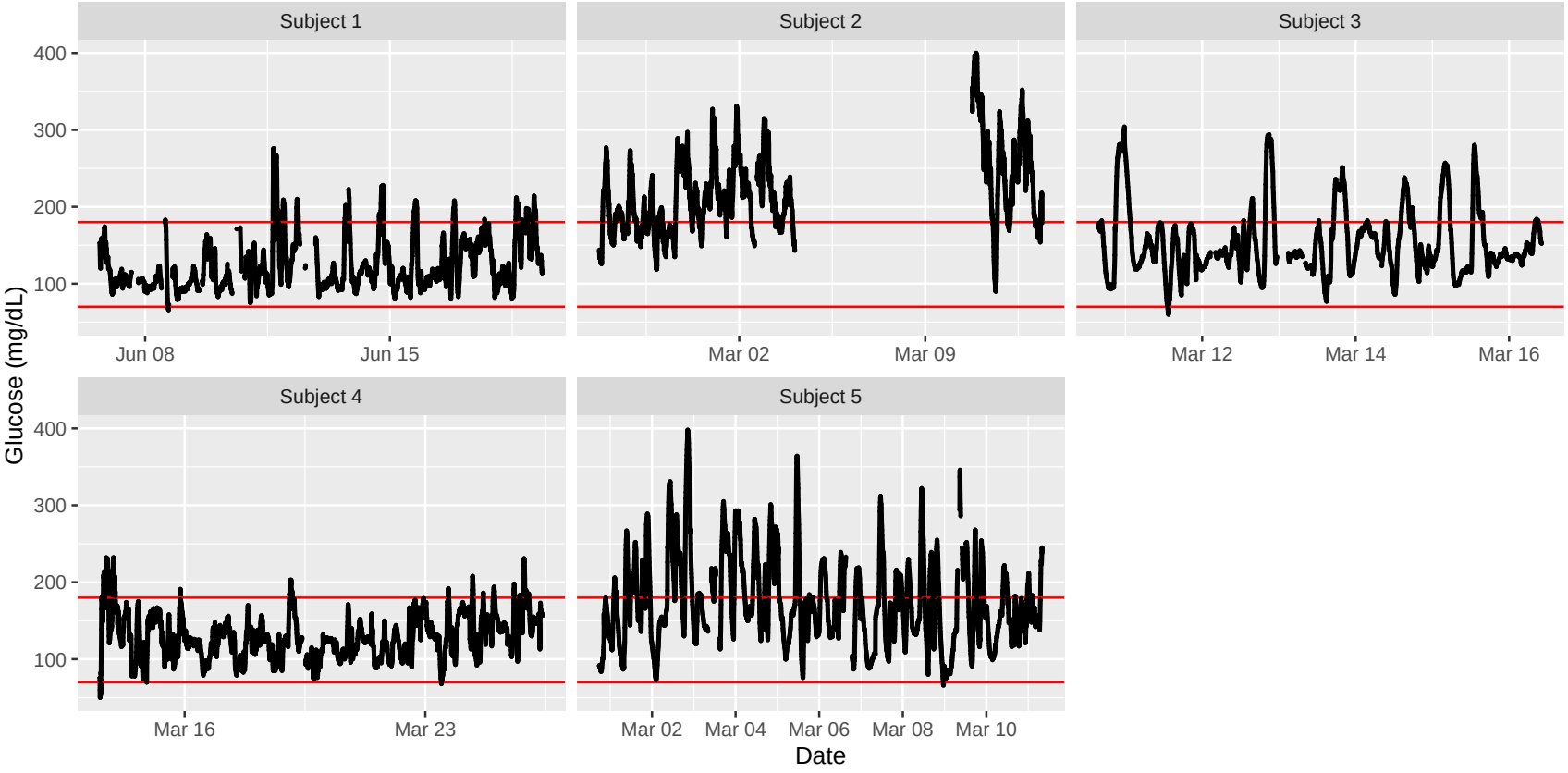
```
## Gap found in data for subject id: Subject 2, that exceed
```

```
## # A tibble: 5 x 2
## # Rowwise:
##   id          MAGE
##   <fct>      <dbl>
## 1 Subject 1  72.4
## 2 Subject 2 118.
## 3 Subject 3 116.
## 4 Subject 4  70.9
## 5 Subject 5 142.
```

More metrics - variability measures

- `mage` - Mean Amplitude of Glycemic Excursions

Automatic peak identification algorithm, exlusion of smallest amplitudes, average amplitude returned



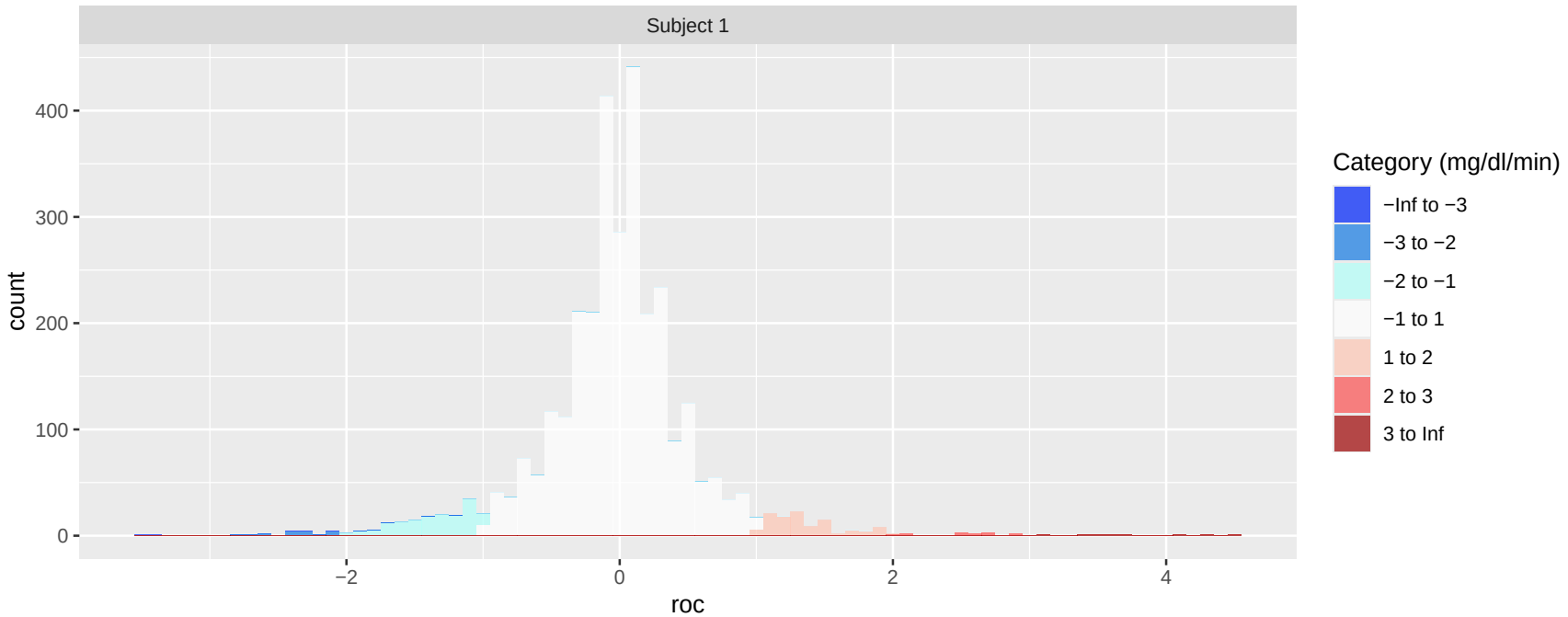
More metrics - variability measures

- `sd_roc` - standard deviation of rate of change (local variability)

Rate of Change, for CGM $\Delta t = 15$ min

$$\text{ROC}(t) = \frac{G(t + \Delta t) - G(\Delta t)}{\Delta t}$$

```
hist_roc(example_data_1_subject)
```



More metrics - variability measures

- `sd_roc` - standard deviation of rate of change (local variability)

```
sd_roc(example_data_5_subject)
```

```
## # A tibble: 5 x 2
##   id        sd_roc
##   <fct>      <dbl>
## 1 Subject 1  0.620
## 2 Subject 2  0.642
## 3 Subject 3  0.831
## 4 Subject 4  0.617
## 5 Subject 5  1.05
```

More metrics - iglu reference

- Website documentation reference for more metrics
- Heatmap implementation in `iglu` gives an idea on which metrics may provide complementary information on your data

Note on accuracy and processing

- all CGMs have measurement error
- CGM data from curated studies is usually used "as-is"
- CGM data from research data warehouses (RDW) may require additional processing due to multiple-device uploads (e.g., CGM and insulin pump), device switches, time zone changes, etc.

Williamson et al. (2025) A Processing Algorithm to Address Real-World Data Quality Issues With Continuous Glucose Monitoring Data, Journal of Diabetes Science and Technology, ahead of print.

Conclusions and opportunities

A personal take

- Integration
- Reproducibility and validation
- Involvement
- Novel methods
- Application and science-driven

Conclusions and opportunities

Integration of CGM data with other measurements

- Physical activity and sleep data from actigraphy
- For patients with type 1 diabetes, insulin administration from the pump - actively used in AI/ML for artificial pancreas
- Meal times (realistic) and meal composition (less so)

Conclusions and opportunities

Reproducibility and validation of consensus and other glycemic metrics

- Long-term prospective outcome studies
- Transfer and adjustment for patients outside of type 1 diabetes
- Deviations with respect to normative ranges (CGMap) rather than absolute
- Disentanglement of independent aspects of glycemic control

Conclusions and opportunities

Involvement of multiple stake-holders together

- Clinicians
- Regulatory agencies
- Statisticians
- Software developers
- Device manufacturers
- Patients

Conclusions and opportunities

Novel methods development to fully exploit CGM data complexity

- FDA with registration, multi-level structure, unequal trajectories length
- Distributional approaches on multiple-responses with local temporal information

Conclusions and opportunities

Application and science-driven development

- No new metrics for new metrics sake
- Methods informed by data problems

Conclusions and opportunities

A personal take

- Integration
- Reproducibility and validation
- Involvement
- Novel methods
- Application and science-driven

Thank you!

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