

# Multi-Timescale Interactions of Glucose and Insulin in Type 1 Diabetes

## Reveal Benefits of Hybrid Closed Loop Systems



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### Introduction

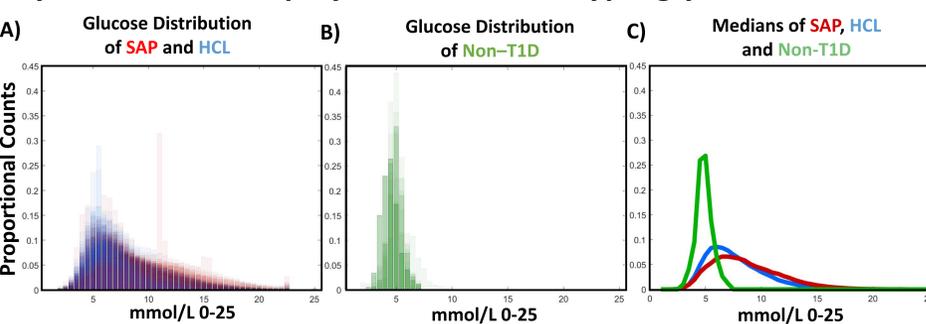
Blood glucose and insulin exhibit coupled biological rhythms at multiple timescales, including hours (ultradian, UR) and the day (circadian, CR) in individuals without diabetes. The presence and stability of these rhythms are associated with healthy glucose control in individuals without diabetes. (See right, adapted from Mejean et al., 1988).

However, biological rhythms in longitudinal (e.g., months to years) data sets of glucose and insulin outputs have not been mapped in a wide population of people with Type 1 Diabetes (PWT1D). It is not known how glucose and insulin rhythms compare between T1D and non-T1D individuals. It is also unknown if rhythms in T1D are affected by type of therapy, such as Sensor Augmented Pump (SAP) vs. Hybrid Closed Loop (HCL). As HCL systems permit feedback from a CGM to automatically adjust insulin delivery, we hypothesized that rhythmicity and glycemia would exhibit improvements in HCL users compared to SAP users. We describe longitudinal temporal structure in glucose and insulin delivery rate of individuals with T1D using SAP or HCL systems in comparison to glucose levels from a subset of individuals without diabetes.

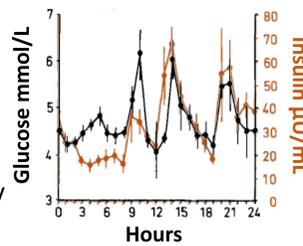
### Data Collection and Analysis

We assessed stability and amplitude of normalized continuous glucose and insulin rate oscillations using the continuous wavelet transformation and wavelet coherence. Data came from 16 non-T1D individuals (CGM only, >2 weeks per individual) from the Quantified Self CGM dataset and 200 (n = 100 HCL, n = 100 SAP; >3 months per individual) individuals from the Tidepool Big Data Donation Project. Morlet wavelets were used for all analyses. Data were analyzed and plotted using Matlab 2020a and Python 3 in conjunction with in-house code for wavelet decomposition modified from the "Jlab" toolbox, from code developed by Dr. Tanya Leise (Leise & Harrington, 2011), and from the Wavelet Coherence toolkit by Dr. Xu Cui. See middle panel for data pipeline schematic. Linear regression was used to generate correlations, and paired t-tests were used to compare AUC for wavelet and wavelet coherences by group (df=100). Stats used 1 point per individual per day.

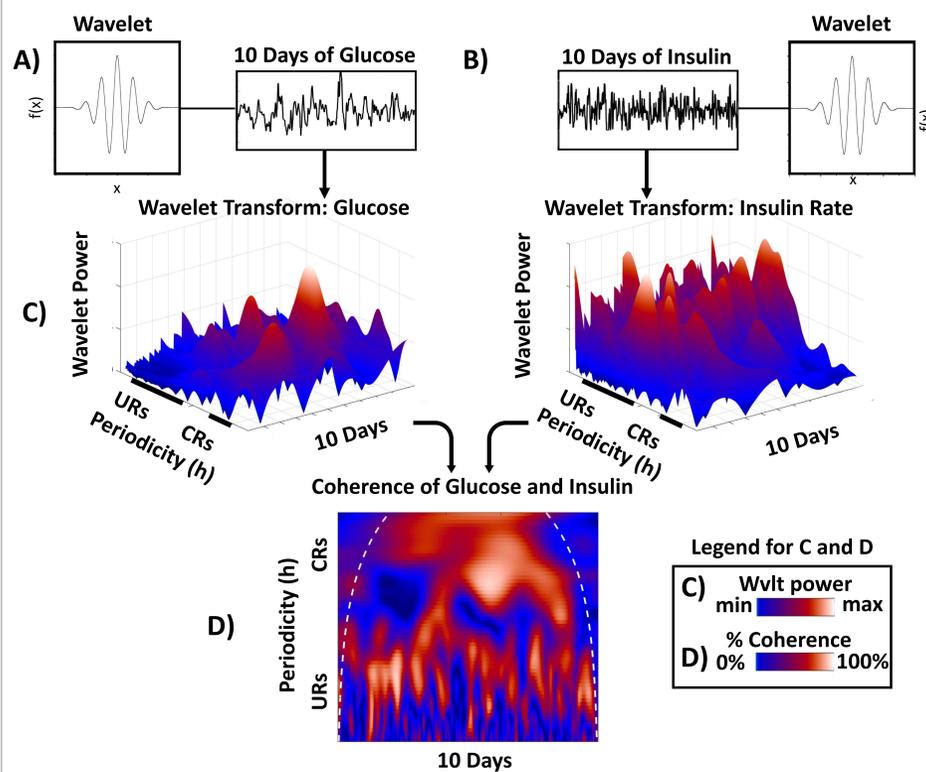
### Hybrid Closed Loop Systems Reduce Hyperglycemia



**A)** Proportional counts\* of glucose distributions of all individuals with T1D using **SAP** (n=100) and **HCL** (n=100) systems. SAP system users exhibit a broader, right shifted distribution in comparison to individuals using HCL systems, indicating greater hyperglycemia (>7.8 mmol/L). Hypoglycemic events (<4mmol/L) comprised <5% of all data points for either T1D dataset. **B)** Proportional counts\* of **non-T1D** glucose distributions. Although limited in number, our dataset from people without diabetes exhibits a tighter blood glucose distribution, with the vast majority of values falling in euglycemic range (n=16 non-T1D individuals). **C)** Median distributions for each dataset. \*Counts scaled such that each individual contributes the same proportion of total data per bin.

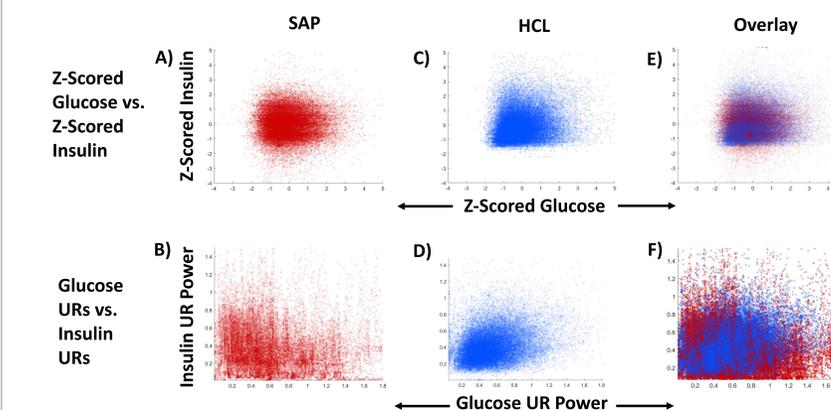


### Wavelets Assess Glucose and Insulin Rhythms and Interactions



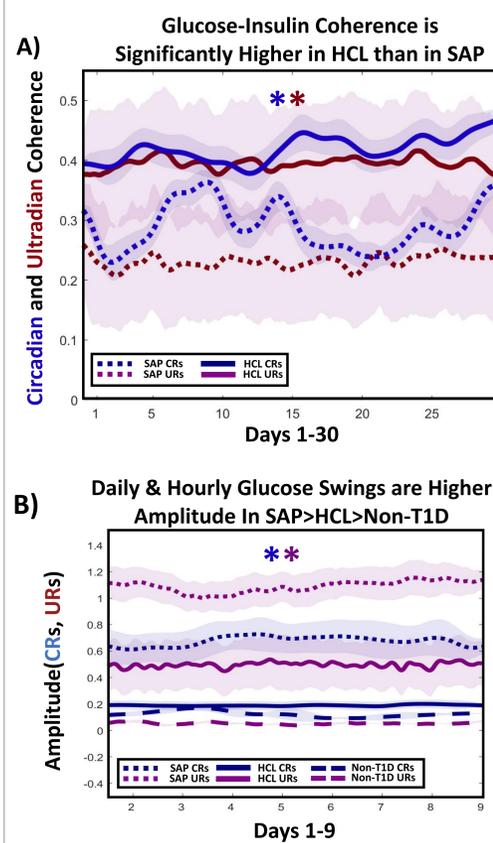
Morlet wavelets **(A)** estimate rhythmic strength in glucose or insulin data at each minute in time (a combination of signal amplitude and oscillation stability) by assessing the fit of a wavelet stretched in window and in the x and y dimensions to a signal **(B)**. The output **(C)** is a matrix of wavelet power, periodicity, and time (days). Transform of example HCL data illustrate predominantly circadian power in glucose, and predominantly 1-6 h ultradian power in insulin. Color map indicates wavelet power (synonymous with Y axis height). Wavelet coherence **(D)** enables assessment of rhythmic interactions between glucose and insulin; here, glucose and insulin rhythms are highly correlated at the 3-6 (ultradian) and 24 (circadian) hour timescales.

### HCL Improves Correlation of Glucose-Insulin Level & Rhythm



SAP users exhibit uncorrelated glucose and insulin levels **(A)** ( $r^2 = 3.3 \times 10^{-5}$ ;  $p=0.341$ ) and uncorrelated URs of glucose and insulin **(B)** ( $r^2 = 1.17 \times 10^{-3}$ ;  $p=0.165$ ). Glucose and its rhythms take a wide spectrum of values for each of the standard doses of insulin rates provided by the pump, leading to the striped appearance **(B)**. By contrast, Hybrid Closed Loop users exhibit correlated glucose and insulin levels **(C)** ( $r^2 = 0.02$ ;  $p=7.63 \times 10^{-16}$ ), and correlated ultradian rhythms of glucose and insulin **(D)** ( $r^2 = -0.13$ ;  $p=5.22 \times 10^{-38}$ ). Overlays **(E,F)**.

### Hybrid Closed Looping Results in Greater Coherence than SAP



Non-T1D individuals have highly coherent glucose and insulin at the circadian and ultradian timescales, but these relationships had not previously been assessed in T1D. **A)** Circadian (blue) and 3-6 hour ultradian (maroon) coherence of glucose and insulin in HCL (solid) and SAP (dotted) users. Transparent shading indicates standard deviation. Although both HCL and SAP individuals have lower coherence than would be expected in a non-T1D individual, HCL CR and UR coherence are significantly greater than SAP CR and UR coherence (paired t-test  $p=1.51 \times 10^{-7}$   $t=-5.77$  and  $p=5.01 \times 10^{-14}$   $t=-9.19$ , respectively). This brings HCL users' glucose and insulin closer to the canonical non-T1D phenotype than SAP users'. **B)** Additionally, the amplitude of HCL users' glucose CRs and URs (solid) is closer (smaller) to that of non-T1D (dashed) individuals than are SAP glucose rhythms (dotted). SAP CR and UR amplitude is significantly higher than that of HCL or non-T1D (T-test, 1,98,  $p=2.47 \times 10^{-17}$  and  $p=5.95 \times 10^{-20}$ , respectively), but HCL CR amplitude is not significantly different from non-T1D CR amplitude ( $p=0.61$ ). Together, HCL users are more similar than SAP users to the canonical Non-T1D phenotype in **A)** rhythmic interaction between glucose and insulin and **B)** glucose rhythmic amplitude.

### Conclusions and Future Directions

T1D and non-T1D individuals exhibit different relative stabilities of within-a-day rhythms and daily rhythms in blood glucose, and T1D glucose and insulin delivery rhythmic patterns differ by insulin delivery system.

#### Hybrid Closed Looping is Associated With:

- Lower incidence of hyperglycemia
- Greater correlation between glucose level and insulin delivery rate
- Greater correlation between ultradian glucose and ultradian insulin delivery rhythms
- Greater degree of circadian and ultradian coherence between glucose and insulin delivery rate than in SAP system use
- Lower amplitude swings at the circadian and ultradian timescale

These preliminary results suggest that HCL recapitulates non-diabetes glucose-insulin dynamics to a greater degree than SAP. However, pump model, bolusing data, looping algorithms and insulin type likely all affect rhythmic structure and will need to be further differentiated. Future work will determine if stability of rhythmic structure is associated with greater time in range, which will help determine if bolstering of within-a-day and daily rhythmic structure is truly beneficial to PWT1D.

### Acknowledgements

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