Joint modeling of daily patterns of heart rate and physical activity data: Estimating individual heterogeneity in physiologic response to physical activity

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October 15, 2019

Motivation

- the “**big**" questions:
  1. What is the effect of physical activity (PA) on heart rate (HR)?
  2. Can we quantify individual heterogeneity in this effect adjusting for age, health status, and diurnal patterns of both PA and HR?
  3. Is this individual heterogeneity associated with outcomes of interest?
- Challenges:
  - Need (good) data (lots of it)
  - Normalize for differences in capacity (“maximum" and resting heart rate)
  - What is a sensible statistical model?

Data

- Baltimore Longitudinal Study on Aging (BLSA)
- Actiheart - chest worn uniaxial accelerometer and heart rate monitor
- Exclusion criteria
  - Ages 30-90
  - Peak respiratory exchange ratio ≥ 1.1
  - Estimated VO_2 max ≥ 10
  - No missing data for demographic variables, several comorbidities, and alcohol consumption
  - At least 3 days of "good" Actiheart data
  - No beta blockers
- Final sample: 446 subjects, 233 male and 213 female

Defining Activity Intensity Using Heart Rate Reserve

$$\text{Heart Rate Reserve} = \text{Maximum Heart Rate} - \text{Resting Heart Rate}$$

Vigorous:	60% or greater of HRR over resting
Moderate:	40-59%
Light:	20-39%
Sedentary:	<20%

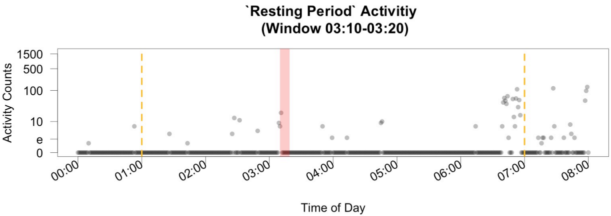
We can approximate maximum heart rate using observed maximum heart rate from the treadmill test, but we need to estimate resting heart rate.

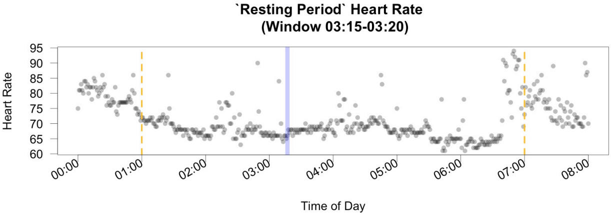
Estimating Resting Heart Rate

Resting heart rate estimation algorithm:

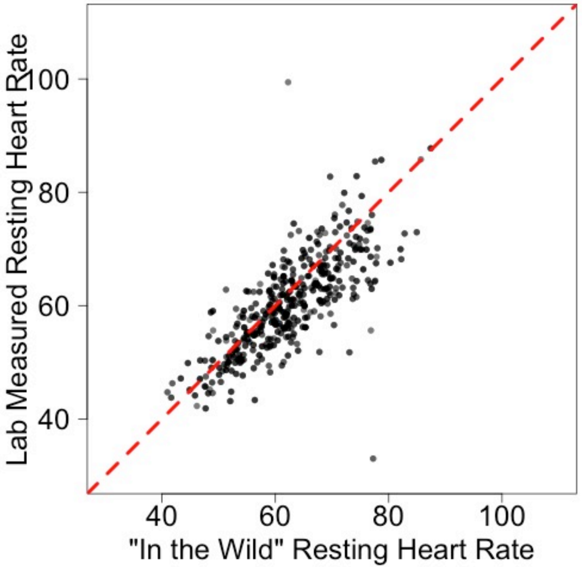
Step 1:	Examine 5 minute moving windows to find all 10-minute intervals between 01:00-07:00 with 0 total activity counts
Step 2:	Calculate average heart rate of the last 5 minutes of each interval found in (1)
Step 3:	Take the average of the heart rates found in (2)

Estimating Resting Heart Rate

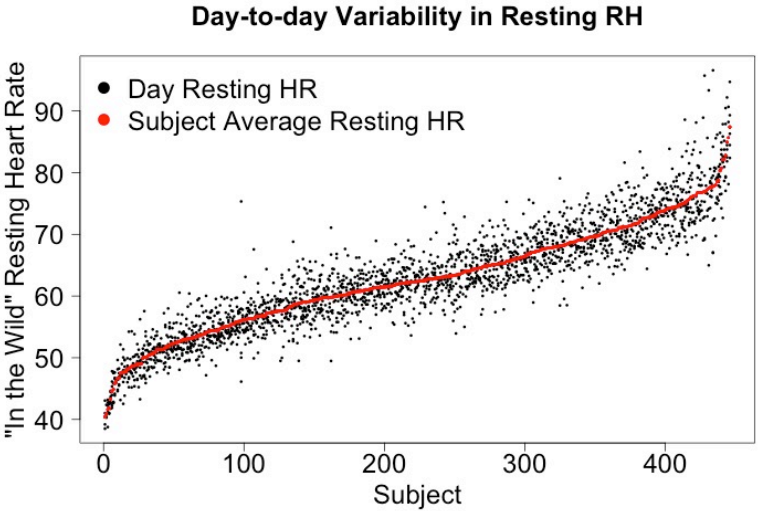




Estimating Resting Heart Rate

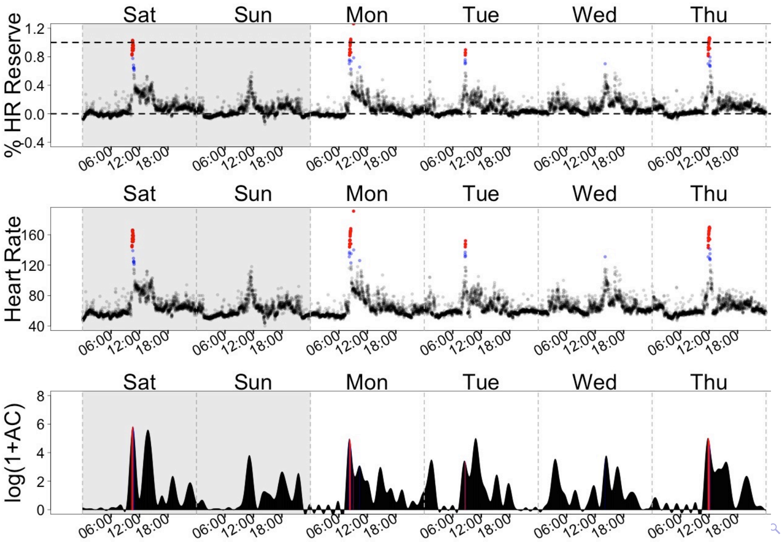


Estimating Resting Heart Rate



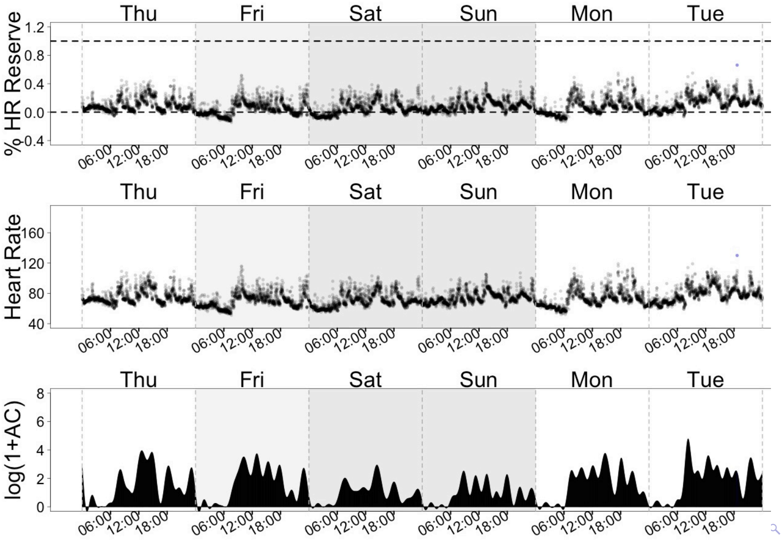
Estimated Heart Rate Reserve: $HRR(t)$

57M, healthy, 37 peak VO_2, 163 max HR



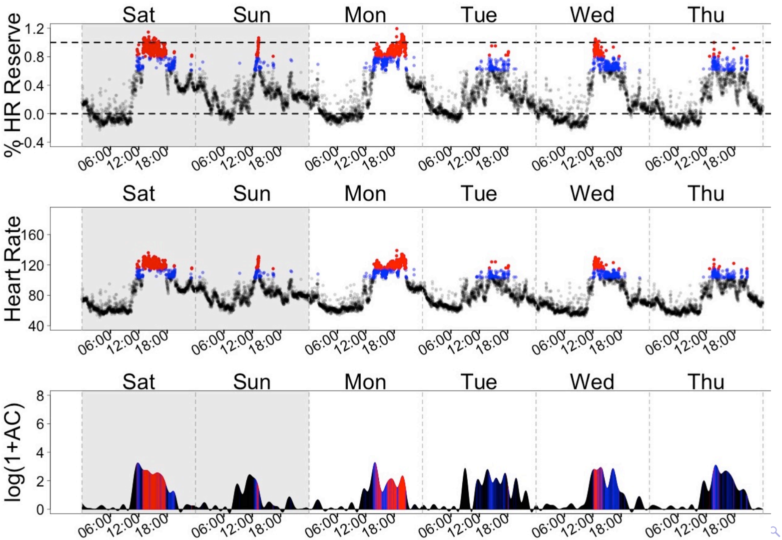
Estimated Heart Rate Reserve: $HRR(t)$

70F, healthy, 20 VO_2, 163 max HR



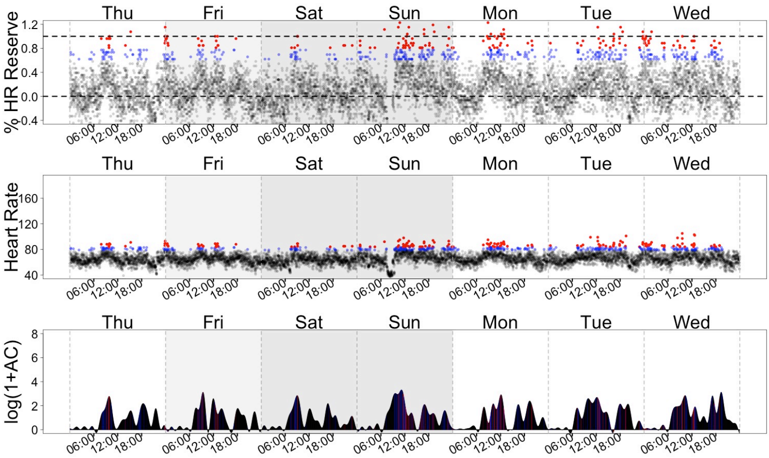
Estimated Heart Rate Reserve: $HRR(t)$

82M, cancer, 18 peak VO_2, 127 max HR, 9 borg scale



Estimated Heart Rate Reserve: $HRR(t)$

74F, hypertension, cancer, 16 VO_2, 89 max HR, 13 borg scale



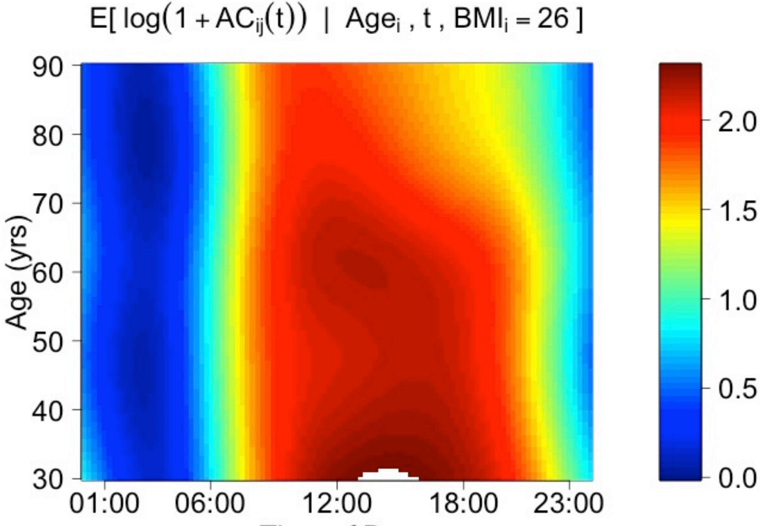
PA, HR, and HRR vs Age

- Model daily patterns of PA, HR, and HRR as a function of age
- Fit 3 separate models:

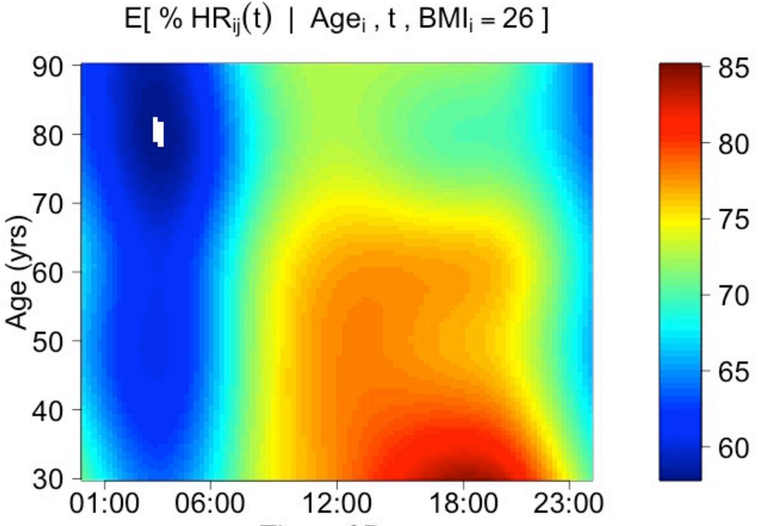
$$E[Y_{ij}(t)|\mathbf{X}_i, \text{Age}_i, t] = f_0(t) + \sum_{p=1}^{P} X_{ip} f_p(t) + \beta(\text{Age}_i, t)$$

- $i = 1, \ldots, N$ subject, $j = 1, \ldots, J_i$ day, $t = 1, \ldots, 1440$ minute of the day
- X_{ip} are scalar covariates (BMI, comorbidities, etc.)
- $\beta(\text{Age}_i, t)$ allows for outcome to vary smoothly in time and age

PA vs Age

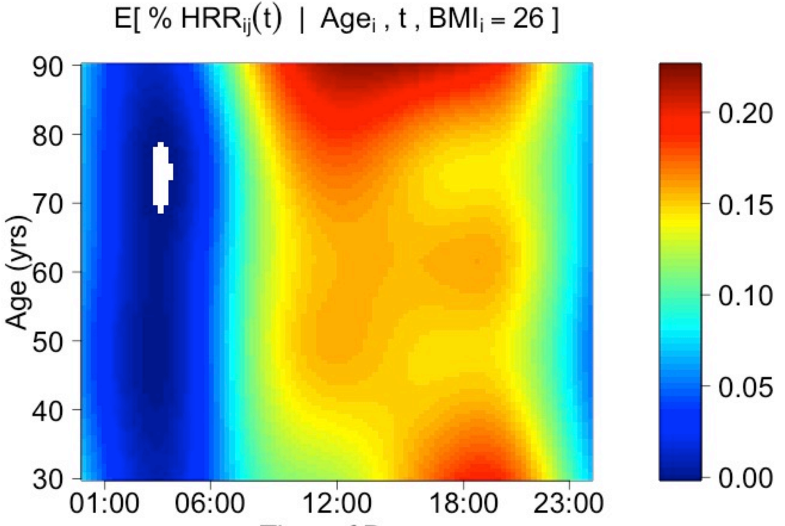

E[log(1 + AC_ij(t)) | Age_i , t , BMI_i = 26]
Age (yrs)
90
80
70
60
50
40
30
01:00
06:00
12:00
18:00
23:00
2.0
1.5
1.0
0.5
0.0

HR vs Age

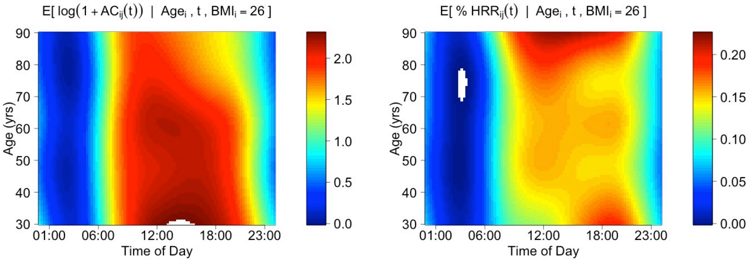


E[% HR_ij(t) | Age_i , t , BMI_i = 26]
90
80
70
60
50
40
30
Age (yrs)
01:00
06:00
12:00
18:00
23:00
85
80
75
70
65
60

HRR vs Age


E[% HRRij(t) | Agei , t , BMIi = 26]
Age (yrs)
90
80
70
60
50
40
30
01:00
06:00
12:00
18:00
23:00
0.20
0.15
0.10
0.05
0.00

PA, HR, and HRR vs Age



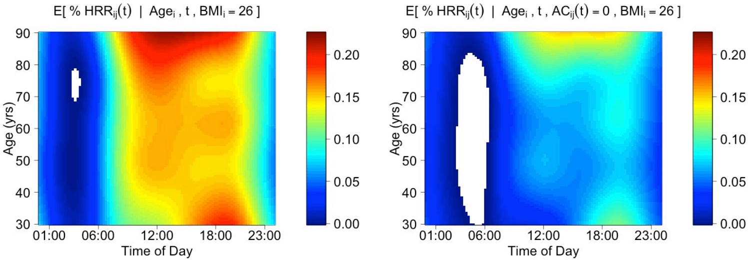
PA, HR, and HRR vs Age

- Attempt to adjust for PA at a given time

$$E[\mathrm{HRR}_{ij}(t)|\cdot] = f_0(t) + \sum_{p=1}^{P} X_{ip} f_p(t) + \beta(\mathrm{Age}_i, t) + \gamma_1(t)\mathrm{LAC}_{ij}(t)$$

- Concurrent effect of activity on heart rate
- Historical effect of PA?

HRR adjusting for PA



PA, HR, and HRR vs Age

- HRR at rest will vary from person-to-person (latent health status) and day-to-day (hydration, mental state, etc.)
- For now ignore day-to-day variability

PA, HR, and HRR vs Age

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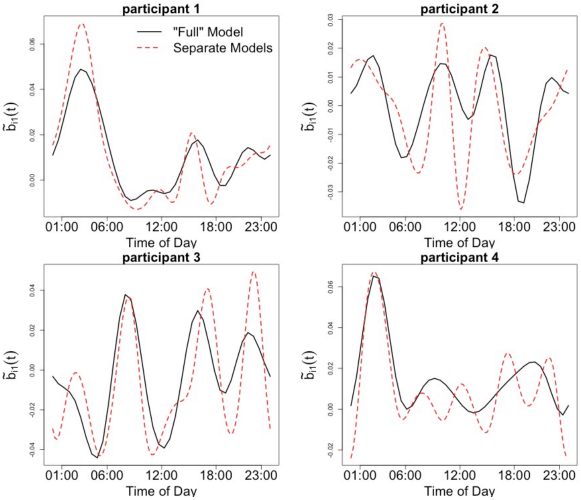
$$\text{HRR}_{ij}(t) = \eta_i(t) + \gamma(t)\text{LAC}_{ij}(t) + b_{0i}(t) + b_{1ij}(t)\text{LAC}_{ij}(t) + \epsilon_{ij}(t)$$

- $\eta_i(t) = f_0(t) + \sum_{p=1}^{P} X_{ip} f_p(t) + \beta(\text{Age}_i, t)$
- $b_{0i}(t)$ represents subject i's average HRR difference from the population at rest
- $b_{1i}(t)$ represents subject i's deviation from the population in response to PA

Estimating $b_{1i}(t)$

- How to estimate subject specific responses?
  1. Fit marginal model, obtain residuals, fit N separate regressions
  2. Fit marginal model, obtain residuals, GLS, fit N separate regressions
  3. Fit the “full" model (functional mixed effects model)
- Choice of estimation procedure depends on goals.

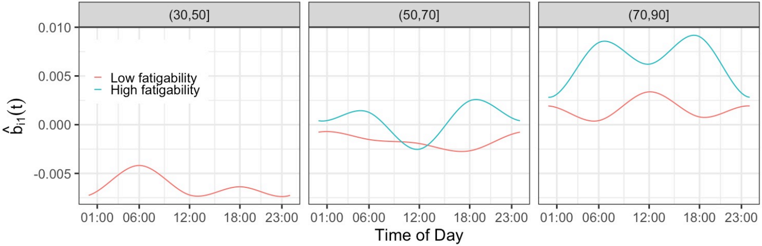
Estimating $b_{1i}(t)$



Using Estimated $\tilde{b}_{1i}(t)$

- $\tilde{b}_{1i}(t)$ as a functional predictor
- scalar summary (e.g. $\int_T \tilde{b}_{1i}(t)dt$, the average across the day)

Fatigability



Fatigability

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Residuals:
    Min      1Q  Median      3Q     Max
-2.8233 -1.2287 -0.3259  0.9551  5.5196

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  6.173061   0.885410   6.972 1.24e-11 ***
age          0.038331   0.007577   5.059 6.37e-07 ***
bmi          0.011762   0.019528   0.602 0.547284
sexMale     -0.728330   0.161772  -4.502 8.76e-06 ***
TAC_mu      -0.025157   0.007552  -3.331 0.000943 ***
b2i_mu      18.951565   6.392608   2.965 0.003206 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1.636 on 413 degrees of freedom
Multiple R-squared:  0.1978,    Adjusted R-squared:  0.1881
F-statistic: 20.37 on 5 and 413 DF,  p-value: < 2.2e-16
```

Next steps/Open questions

- What does it mean when $\gamma(t) + b_{i1}(t) \leq 0$? Individual thresholds? Bad data?
- Day-to-day variability?
- Building in a historical effect of activity (of heart rate?)

Scalar on Function Regression

- Scalar on function regression can take many forms
- **Functional Generalized Linear Model[1](FGLM):** Association varies with time of day, but scales linearly with (log) activity count

$$g(E[Y_i]) = X_i'\beta + \int_T f(t)Z_i(t)dt$$

- **Functional Generalized Additive Model[2](FGAM):** Association varies smoothly with both time of day and value of (log) activity count

$$g(E[Y_i]) = X_i'\beta + \int_T f[t, Z_i(t)]dt$$

[2] Müller HG, Stadtmüller U. Generalized functional linear models. Annals of Statistics. 2005;33(2):774-805.

[2] McLean MW, Hooker G, Staicu AM, Scheipl F, Ruppert D. Functional Generalized Additive Models. J Comput Graph Stat. 2014;23(1):249-269.

Scalar on Function Regression

- In both FGLR and FGAM estimation is done by applying a spline basis to the coefficient and then approximating the functional term numerically.

$$\begin{aligned}
\int_T f(t)Z_i(t)dt &= \int_t \sum_{k=1}^{K} \xi_k \phi_k(t) Z_i(t)dt \quad \text{Apply spline basis} \\
&\approx \sum_l \delta_l \sum_{k=1}^{K} \xi_k \phi_k(l) Z_i(l) \quad \text{Numeric Approximation} \\
&= \sum_{k=1}^{K} \xi_k \left[\sum_l \delta_l \phi_k(l) Z_i(l) \right] \\
&= \sum_{k=1}^{K} \xi_k \tilde{Z}_i(k)
\end{aligned}$$

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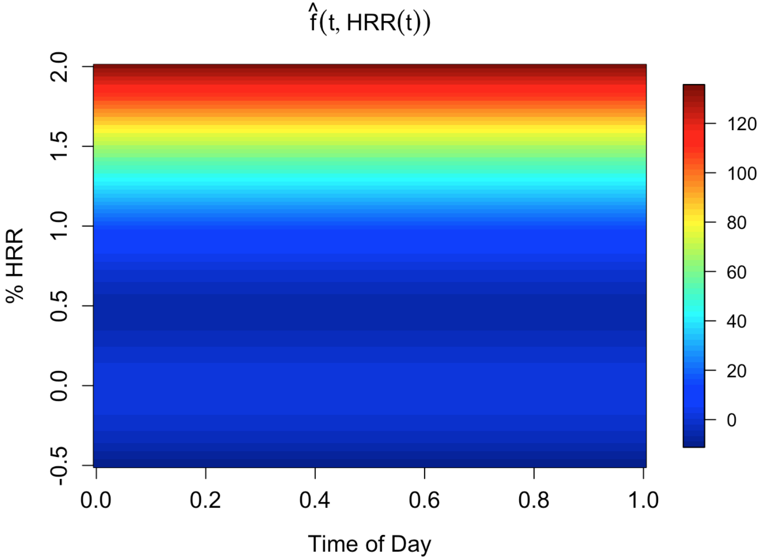
SoFR: Heavy Drinkers

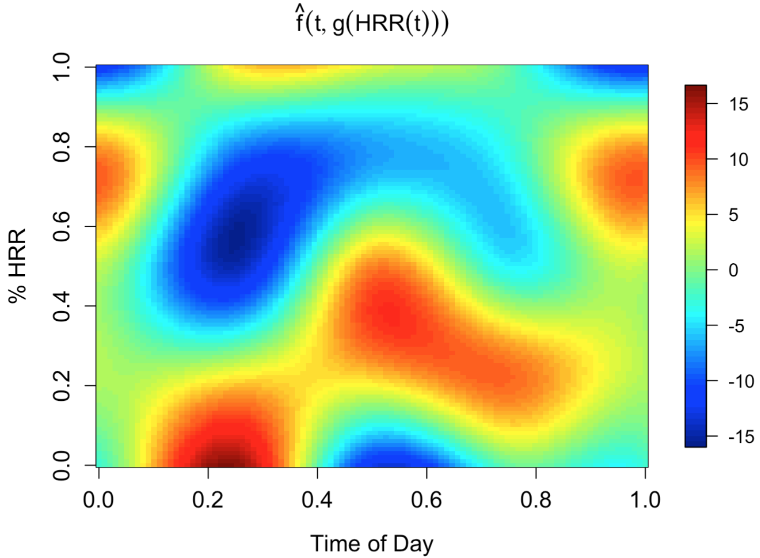
- Let Y_i be the binary indicator that subject i self reports heavy drinking
- Logistic regression
  - FGLR: $\text{logit}(p_i|X_i, \mathbf{Z}_i) = X_i'\beta + \int_T f(t)Z_i(t)dt$
  - FGAM: $\text{logit}(p_i|X_i, \mathbf{Z}_i) = X_i'\beta + \int_T f[t, Z_i(t)]dt$
- Estimation via using *refund::pfr()* function
- Adjust for linear effects of age, body mass index, and sex


$\hat{f}(t, HRR(t))$
% HRR
2.0
1.5
1.0
0.5
0.0
-0.5
0.0
0.2
0.4
0.6
0.8
1.0
Time of Day
120
100
80
60
40
20
0

FGAM

- Estimated coefficient surface seems to imply high heart rate at any time of the is associated with increased log odds of drinking heavily
- Very few "high" HRR during the early morning hours
- Consider a transformation to reduce data sparsity. Here we use the empirical CDF $\hat{g}_t(x) = \frac{1}{N}\sum_{i=1}^{N} I(Z_i(t) < x)$ for all t.

$$\text{logit}(p_i|X_i, \mathbf{Z}_i) = X_i'\beta + \int_T f[t, g_t(Z_i(t))]dt$$


$\hat{f}(t, g(HRR(t)))$
% HRR
Time of Day
0.0
0.2
0.4
0.6
0.8
1.0
15
10
5
0
-5
-10
-15