

Predicting Sepsis using GLMs



Joe and the Joes

Problem Statement

Clinical standard is time consuming blood cultures, low resolution for diagnosis

Rapid increase of mortality rate in delayed diagnosis

Demographic risk comes down to the doctor to account for

Physiological Background

Sepsis

To be diagnosed with sepsis, you must exhibit at least two of the following symptoms:

- Body temperature above 101 F (38.3 C) or below 96.8 F (36 C)
- Heart rate higher than 90 beats a minute
- Respiratory rate higher than 20 breaths a minute
- Probable or confirmed infection

Sepsis induces autonomic nervous system change

“Circulating endotoxin impairs the sympathetic regulation of the cardiovascular system”

(<http://www.mayoclinic.org/diseases-conditions/sepsis/basics/symptoms/con-20031900>)

Approach

In order to accurately predict sepsis, we selected covariates that:

- fit real world modeling (Made physiological sense/can be supported through scientific research)
- Numerically rigorous (highest effect on improving linear model)
- Qualitatively resolvable histograms for septic / nonseptic patients

A stepwise glm (function: stepwiseglm) was implemented:

- Sequentially adds parameters, combinations and squares to see how metrics of model change

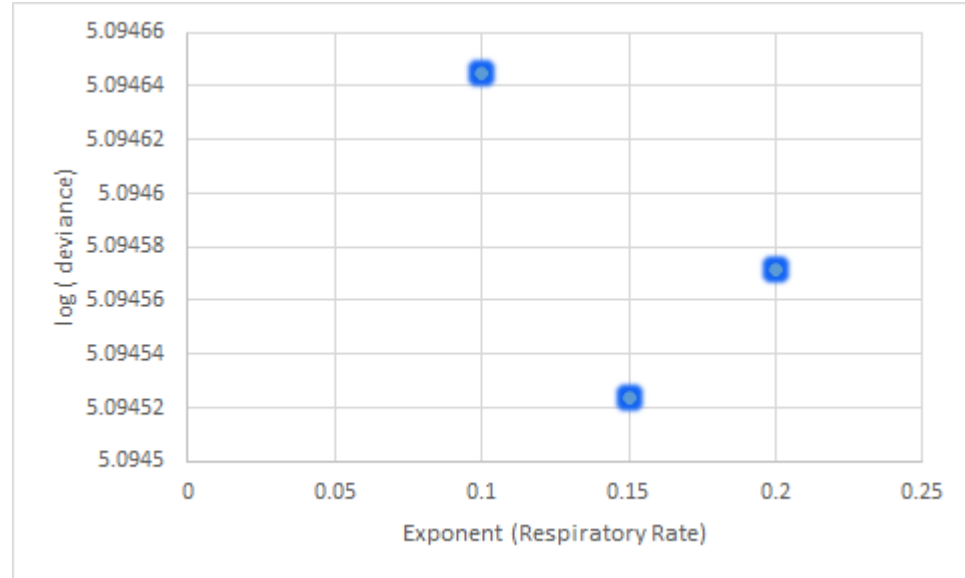
Choosing functional form of Data

General form: $(\text{waveform})^p$

- Only one parameter, can amplify either high or low data points

Powers for each waveform were determined experimentally (trial-and-error)

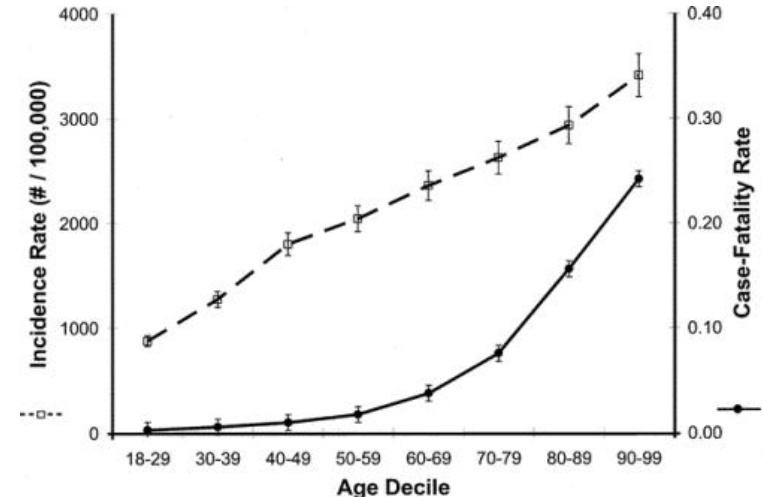
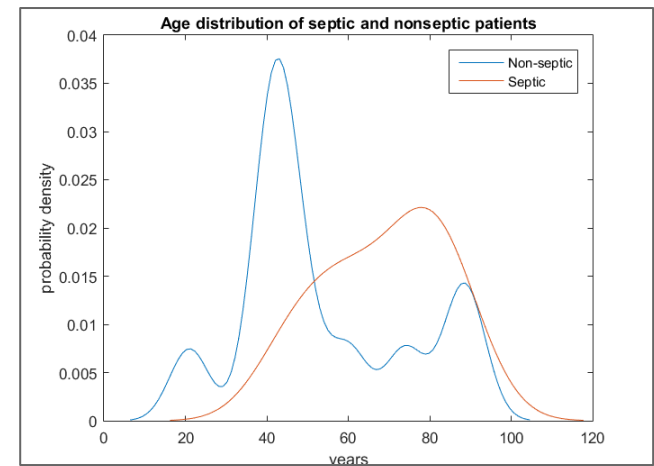
Minimizing deviance and sum-standard-error as a function of power



Age

Makes physiological sense

“The cumulative 24-yr age-specific incidence of sepsis increased exponentially across all age deciles, from 29.6 cases per 100,000 individuals in the 18–29 age decile to 2,422.3 cases per 100,000 in the 90–99 age decile.”



The effect of age on the development and outcome of adult sepsis *

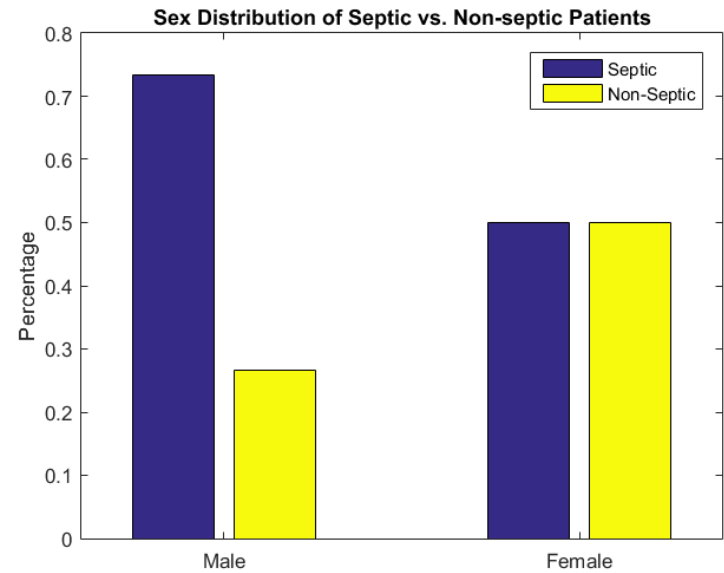
Martin, Greg S. MD, MSc; Mannino, David M. MD; Moss, Marc MD

Sex

Makes physiological sense

“There is increasing evidence that sex hormones not only modulate the immune and cardiovascular responses following trauma or sepsis”

“Metabolic modulators following trauma sepsis: Sex hormones” Hsieh, Ya-Ching PhD; Frink, Michael MD; Choudhry, Mashkoor A. PhD; Bland, Kirby I. MD; Chaudry, Irshad H. PhD)



Σ	Male	2426	1.4 %	186
			283 10.4 %	65.7 %
	Female	1395	114 7.6 % *	74 64.9 %

Incidence and mortality of severe sepsis in surgical intensive care patients: the influence of patient gender on disease process and outcome
Wichmann, M W; Inthorn, D; Andress, H -j; Schildberg, F
W. Intensive Care Medicine 26.2 (Mar 2000): 167-72.

Comorbidities

Comorbidities for heart/cardio/other problems:

Selective in a general population

HOWEVER

Not selective within the sample set of ICU patients

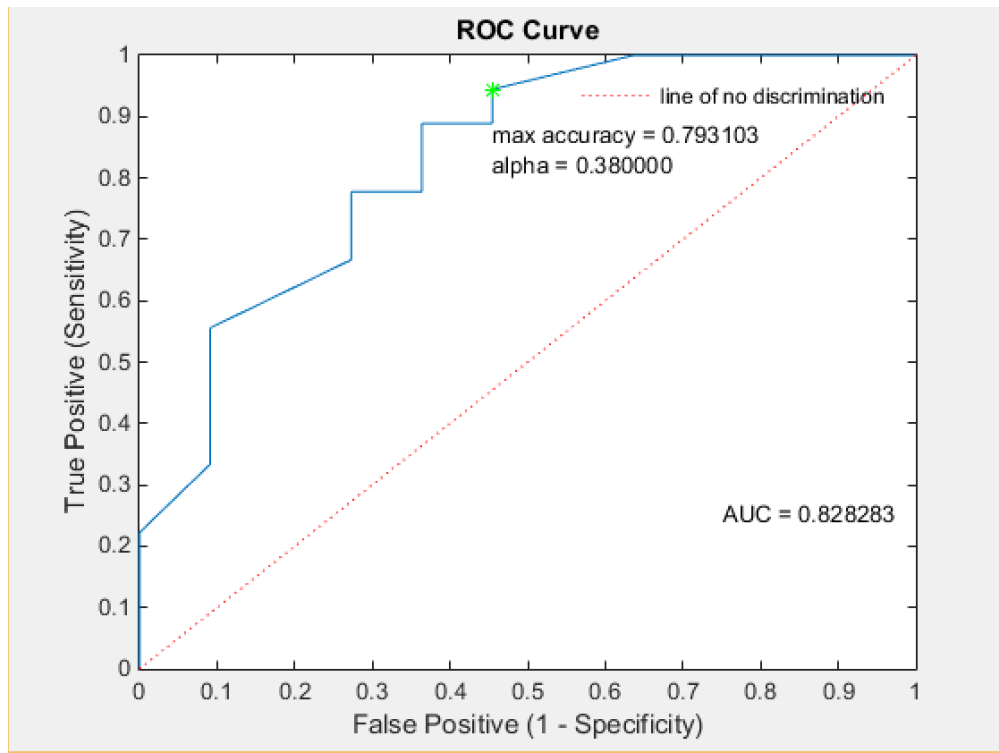
Therefore we omitted these parameters from the static model

Static Model

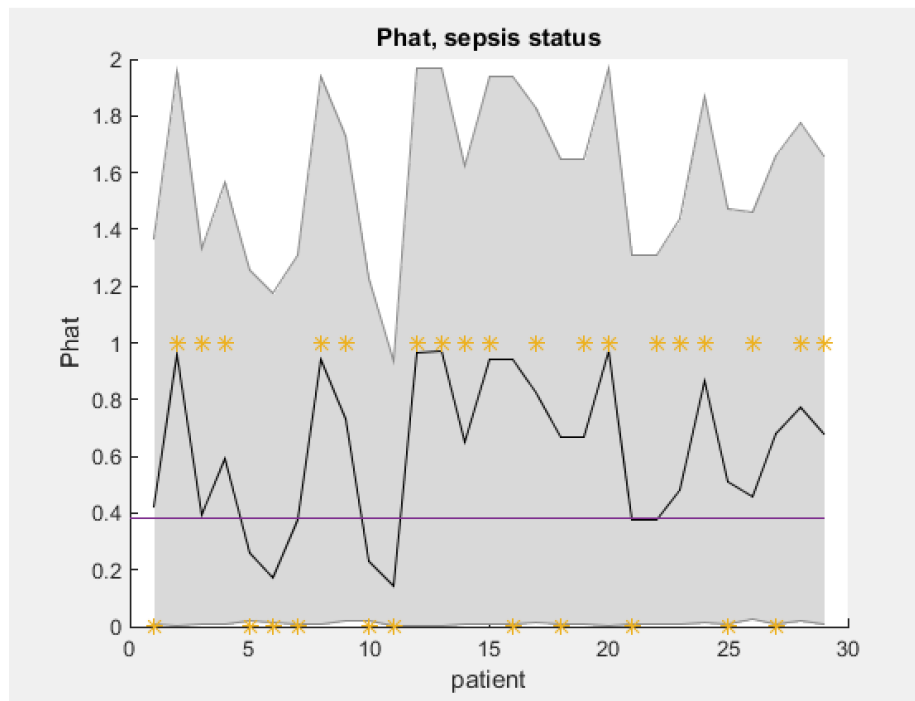
Covariates: $\text{Age}^{0.001}$, Sex, $\text{Age} * \text{Sex}$

Age, sex thought to be physiologically useful

Power law used, exponent determined empirically
-emphasizes younger ages, due to concavity of function



Static Model Performance

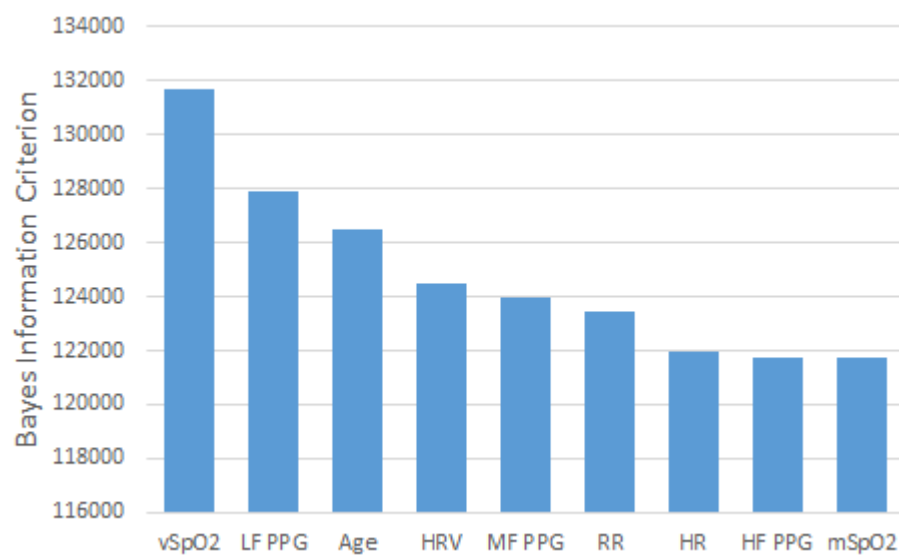
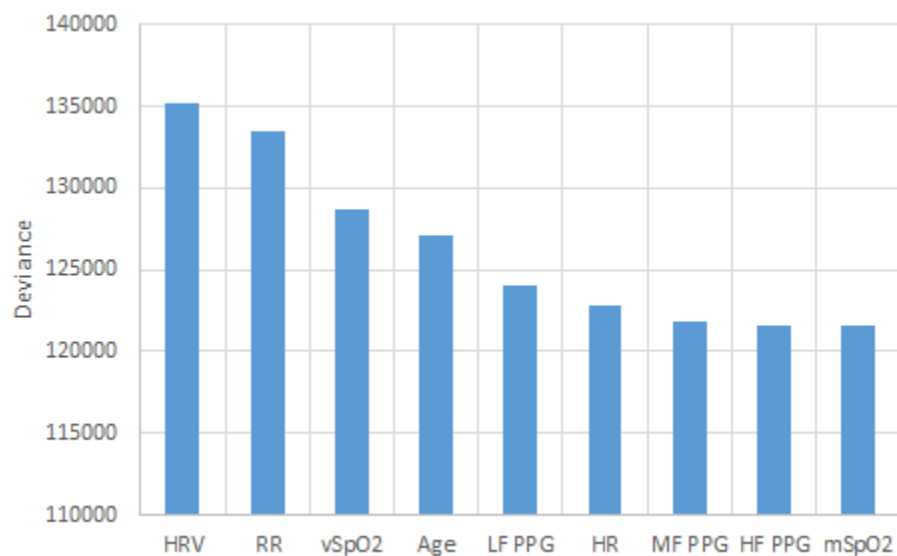


CI for P_{hat} very wide

P_{hat} follows septic status, but loosely

Maximizing AUC, minimizing deviance and goodness of model fit doesn't always lead to best model

Parameter Selection



$$D(y) = -2 \left(\log(p(y | \hat{\theta}_0)) - \log(p(y | \hat{\theta}_s)) \right).$$

$$\text{BIC} = -2 \cdot \ln \hat{L} + k \cdot \ln(n).$$

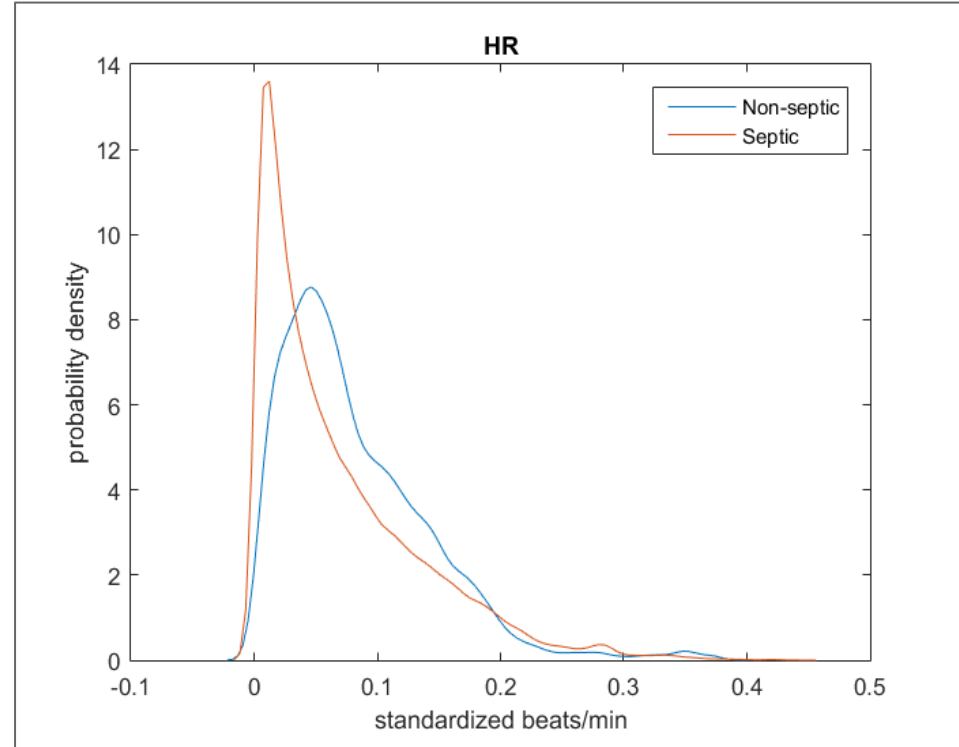
Heart Rate

Physiologically relevant; Part of the definition of sepsis diagnosis involves heart rate exceeding 90 bpm

Separation of Non-Sepsis and Sepsis

HOWEVER

Poor statistical fit (low effect on deviance, BIC) upon inclusion



Heart Rate Variability

Autonomic nervous system shutdown

Highly ranked in all of our fitglm
goodness of fit criteria

Studies done on ICU patients indicate
that low HRV is highly correlated with
presence of sepsis

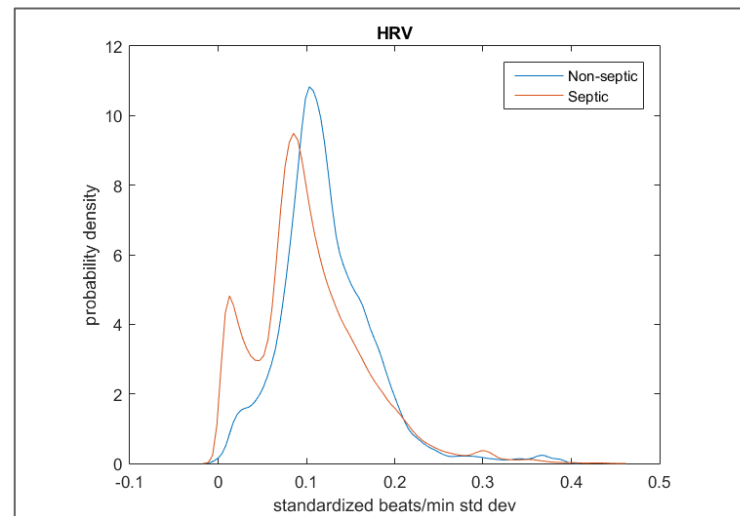
Low frequency from Fourier Analysis is
promising, but we lack resolution

Table 4. Diagnosing sepsis by using LF/HF

LF/HF Category	Presence of Sepsis	Absence of Sepsis	Likelihood Ratio
<1	9	3	6.47
1-1.9	3	9	0.72
>1.9	1	16	0.13
Total	13	28	

LF, low frequency; HF, high frequency.

Cardiac variability in critically ill adults: Influence of sepsis
Korarch et al

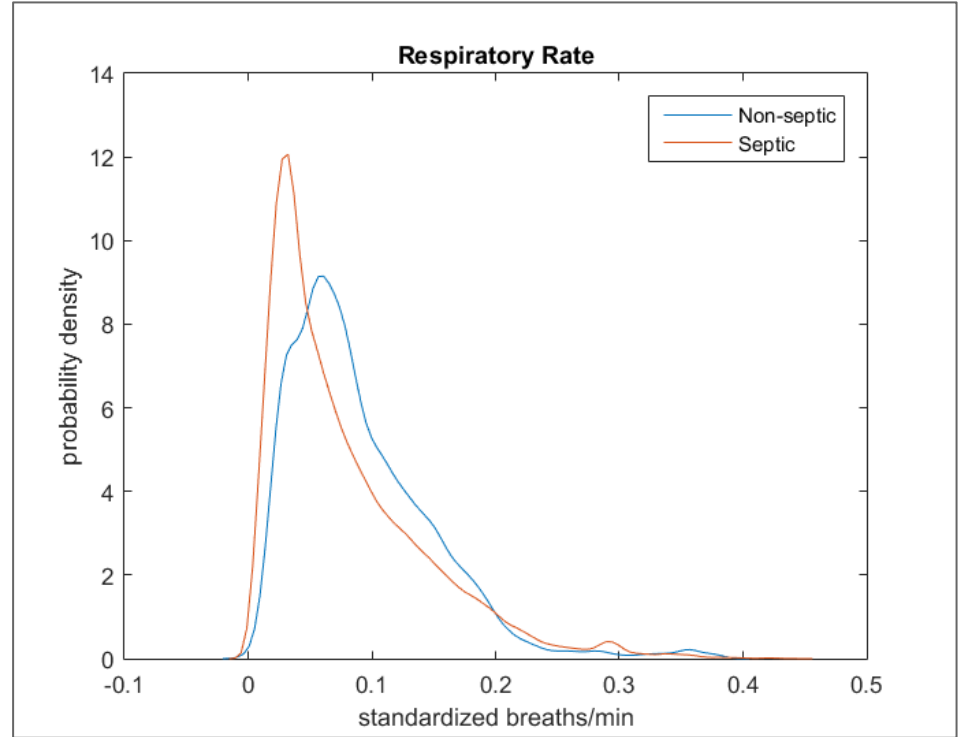


Respiratory Rate

Physiologically relevant; Part of the definition of sepsis diagnosis involves heart rate exceeding 20 breaths per minute

Highly ranked in all of our fitglm goodness of fit criteria (statistically relevant)

Separation among sepsis and non-sepsis waveforms



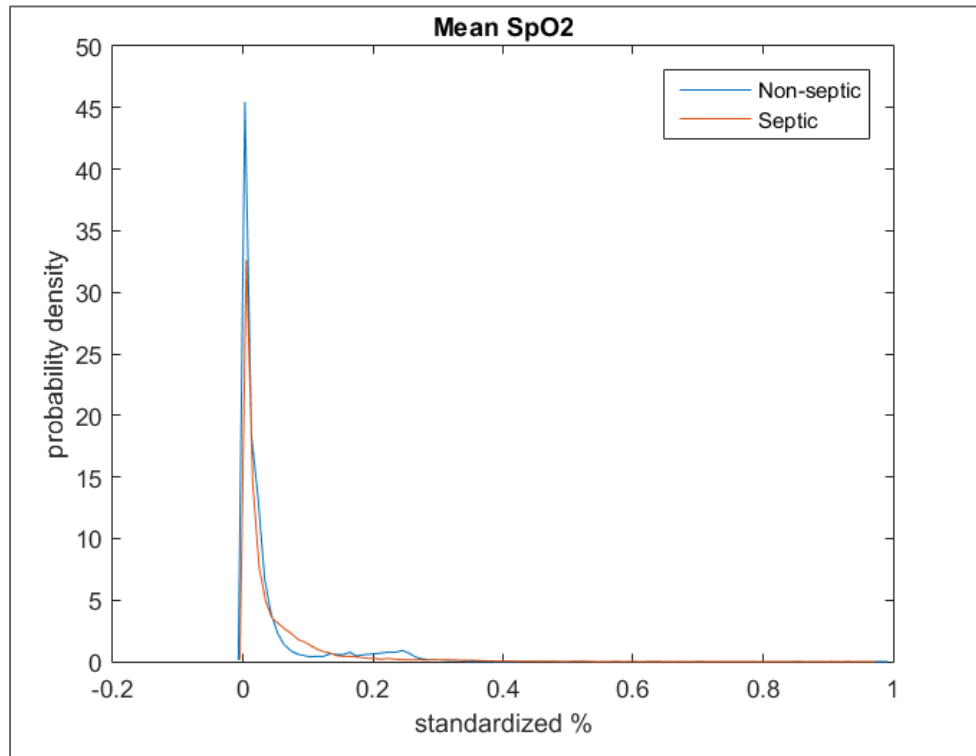
Mean of SpO2

Extremely poor separation in our patient waveforms

Poor statistical fit

Physiologically, SpO2 measurements can be confounded by hypoxemia, other symptoms from sepsis

Wilson, Ben J, Hamish J Cowan, Jason A Lord, Dan J Zuege, and David A Zygun. "The Accuracy of Pulse Oximetry in Emergency Department Patients with Severe Sepsis and Septic Shock: A Retrospective Cohort Study." BMC Emergency Medicine BMC Emerg Med: 9. Print.

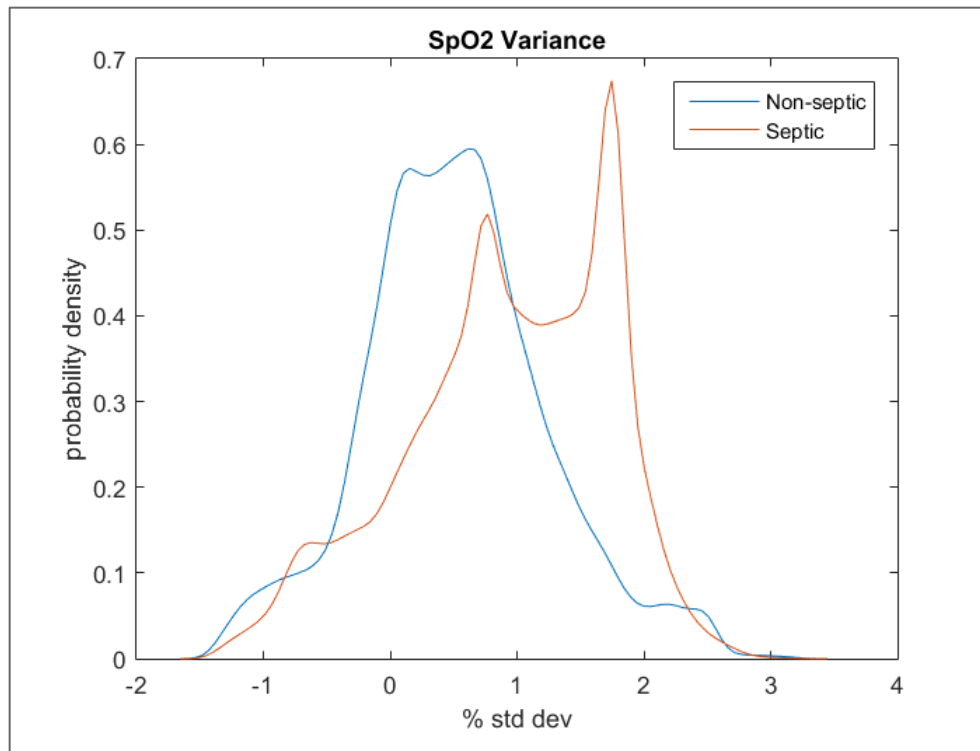


Variance of SpO2

Physiologically relevant; Variance of SpO2 is loosely correlated with heart rate variance (autonomic NS failure)

Highly ranked in all of our fitglm goodness of fit criteria (statistically relevant)

Excellent separation

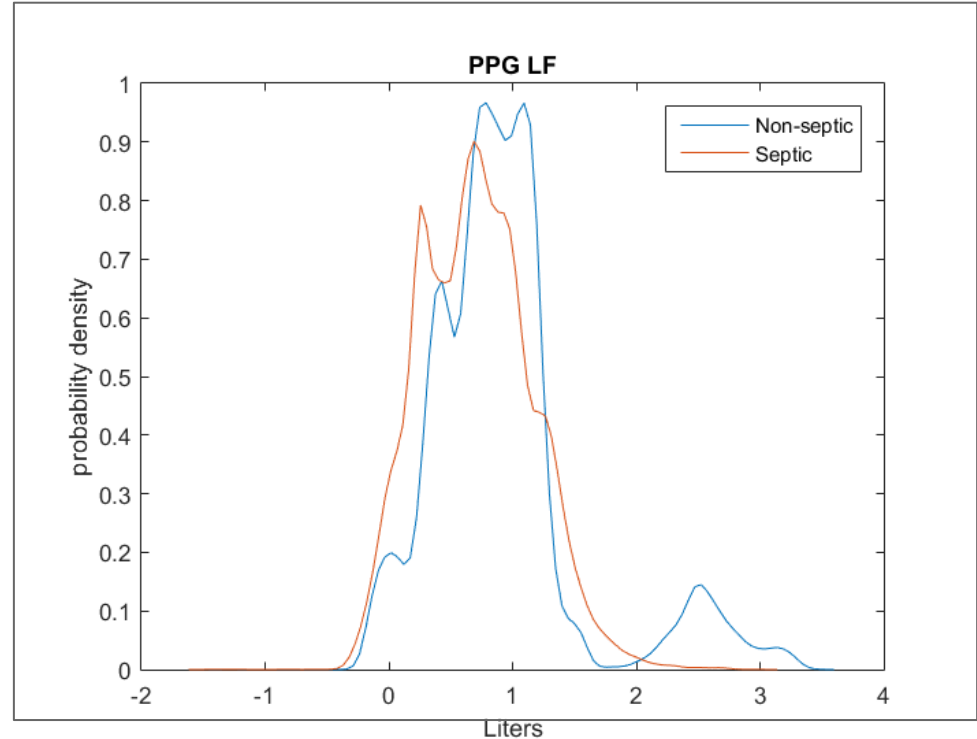


Low-frequency power of PPG

Measure of autonomic PPG control

Reduced LF components of the variability of cardiovascular signals are characteristic of septic shock, confirming the presence of abnormal autonomic control.

Resolution of high values



Mid-frequency power of PPG

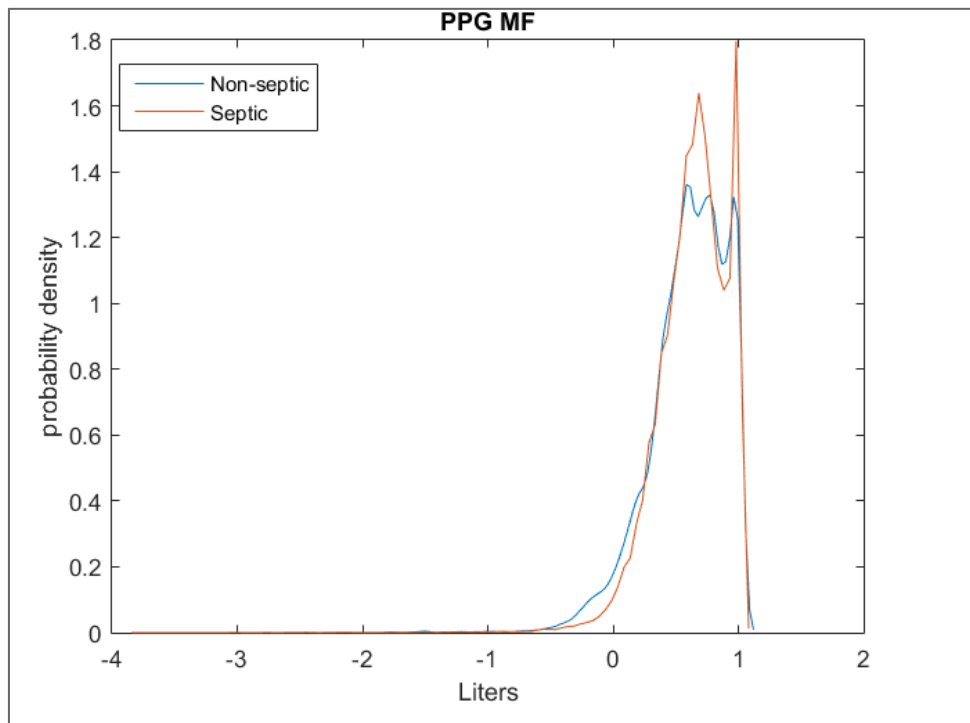
Measure of hemostatic pressure control

Previous results supported use of MF PPG, similar to LF PPG

“The normalised MF power in Ear-PPG was significantly reduced in severe sepsis patients with hyperlactataemia (lactate \geq 2 mmol/l), compared to SIRS patients ($P<0.05$).”

However, data was not resolvable, and this parameter was included late in our sequential model

Middleton et al (2010)



High-frequency power of PPG

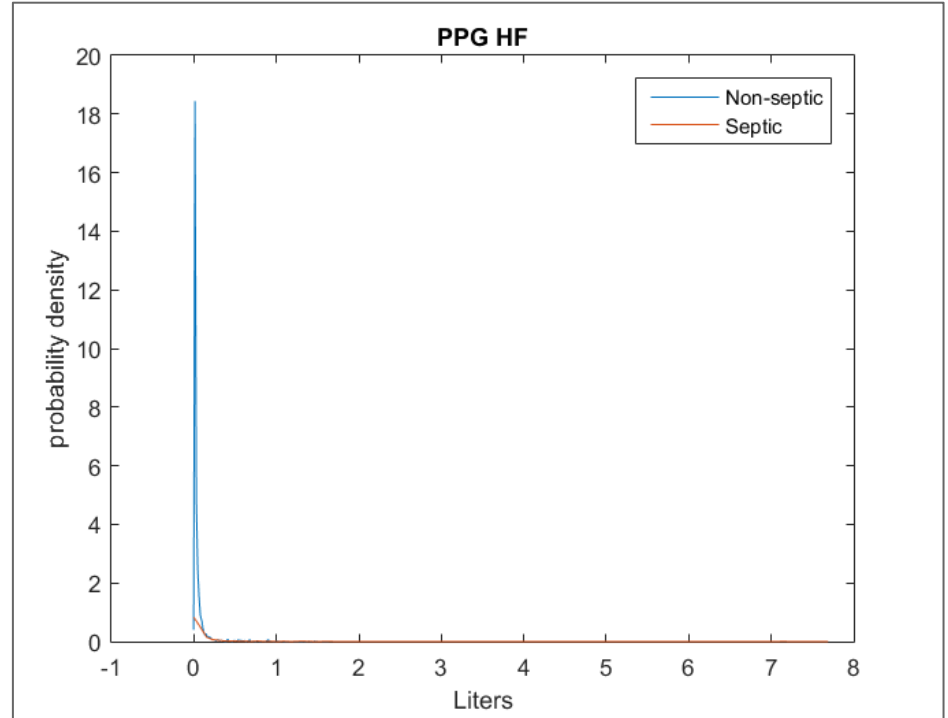
Measure of PPG fluctuation due to respiratory patterns

“High power PPG increased in septic patients, but without statistical significance”

Increase is to compensate for decrease in LF, MF PPGs due to loss of autonomic control

Some link to respiration (not correlated due changes occurring nonsimultaneously)

Middleton et al (2010)



Dynamic Model

Covariates: Age, HRV, RR, variance (SpO2),
LF PPG, and combination of Age:HRV, Age:
LF PPG

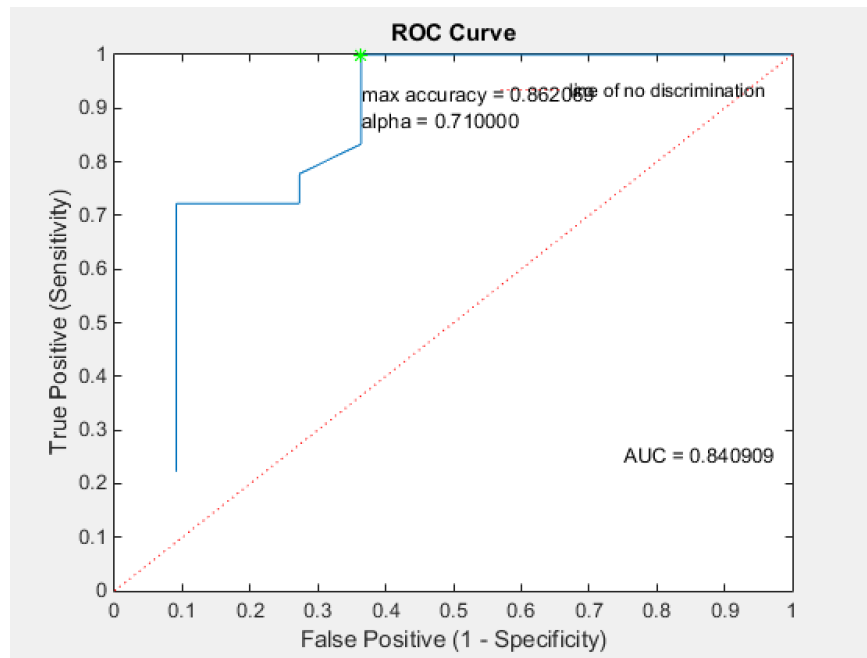
$$\text{logit}(p) = BX$$

X is waveforms and product of waveforms

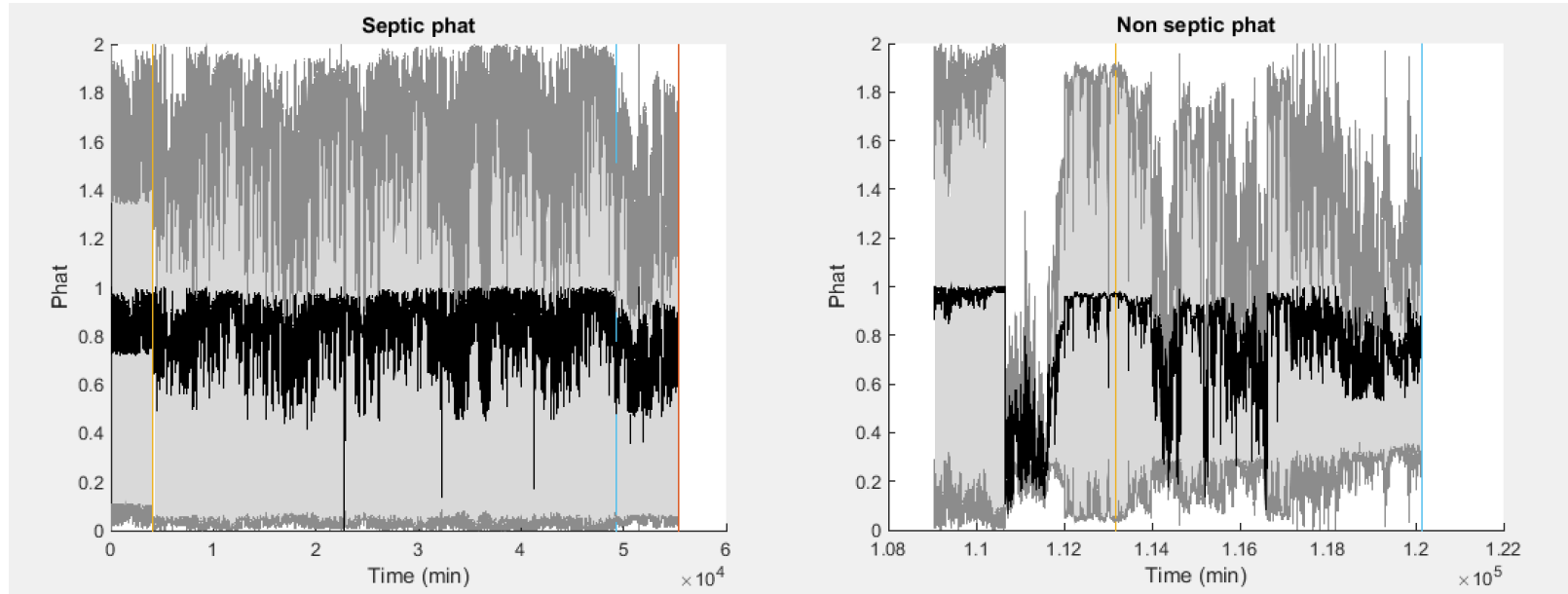
Interactions between sets of data: only two
most important were included

Sepsis classification kept in timepoints

Percent correct with training data: 86%



P_Hat for the Dynamic Model

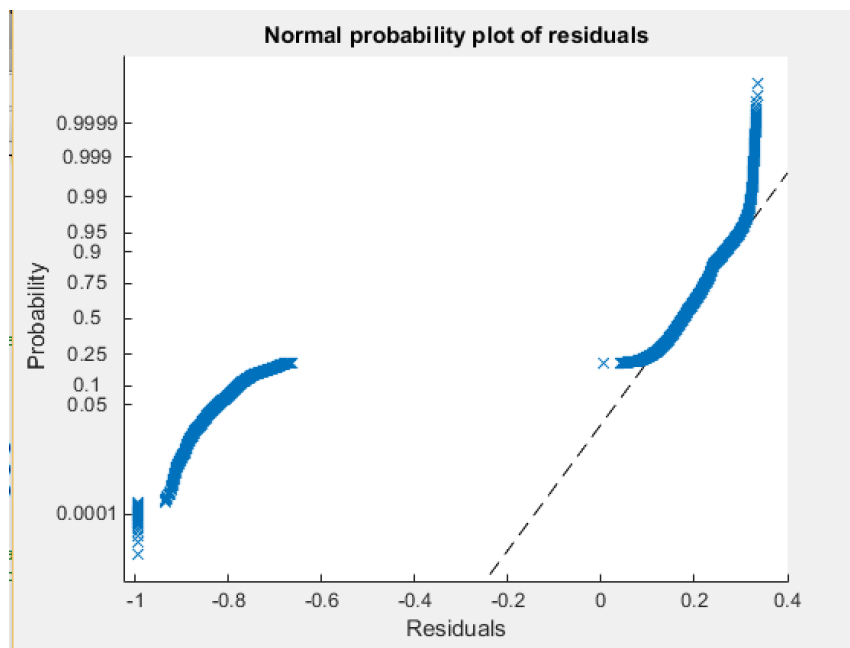


Non-septic vs septic is differentiable

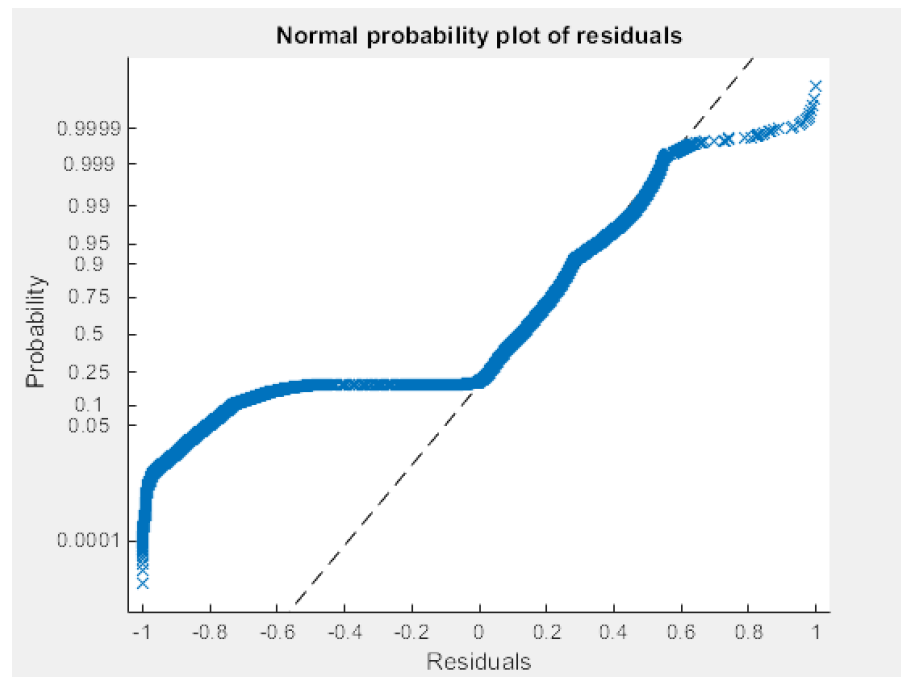
CI is very wide (threshold around 0.6)

Performance of Dynamic Model

Residual plot excluding interactions



Residual plot including interactions



Future Directions

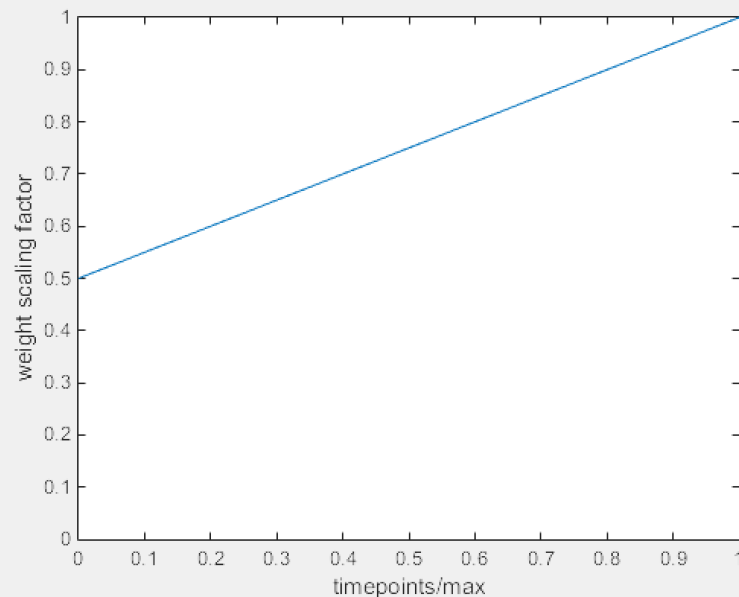
Very high sensitivity, low specificity:

Patients disproportionately weighted by data length

Extrapolate data for patients with less

Not implemented due to time constraints

Weight scaling curve



Citations

Piepoli, M., Garrard, C., Kontoyannis, D., & Bernardi, L. (1995). Autonomic control of the heart and peripheral vessels in human septic shock. *Intensive Care Med Intensive Care Medicine*, 112-119.

Middleton, P., Tang, C., Chan, G., Bishop, S., Savkin, A., & Lovell, N. (2010). Peripheral photoplethysmography variability analysis of sepsis patients. *Med Biol Eng Comput Medical & Biological Engineering & Computing*, 337-347.

Wilson, Ben J, Hamish J Cowan, Jason A Lord, Dan J Zuege, and David A Zygun. "The Accuracy of Pulse Oximetry in Emergency Department Patients with Severe Sepsis and Septic Shock: A Retrospective Cohort Study." *BMC Emergency Medicine BMC Emerg Med*: 9. Print.