Heart rate characteristics monitoring to detect neonatal sepsis

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METHOD

- **Pick the right problem.**

Little babies are dying.

Neonatal Sepsis: A Major Public Health Problem

- **Of 4 million births each year, 56,000 are very low birth weight infants (VLBW, <1500 grams; about 3.5 lbs)**
- **Risk of sepsis is high**
  - 21 - 40% of VLBW infants develop sepsis while in the neonatal intensive care unit (NICU)
- **Significant mortality and morbidity (NICHD 2002)**
  - In VLBW infants, sepsis more than doubles the risk of dying
  - Length of stay is increased by 3 weeks
  - Health care costs are increased

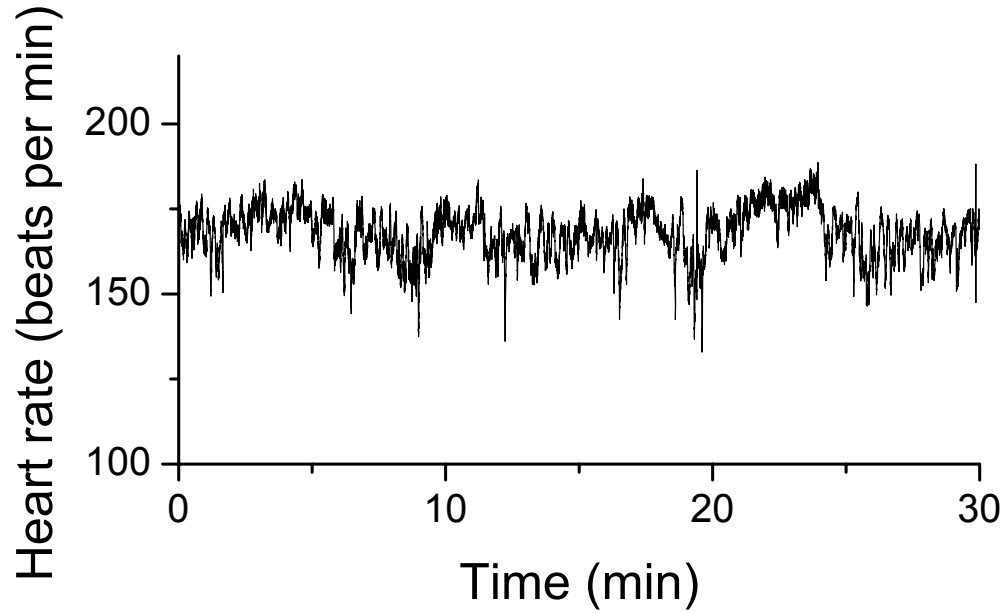
Is this baby septic?

- **The diagnosis of neonatal sepsis is difficult**
- **The outcome of sepsis is potentially catastrophic**
- **Leading physicians to:**
  - obtain lab tests
  - administer antibiotics early and often

METHOD

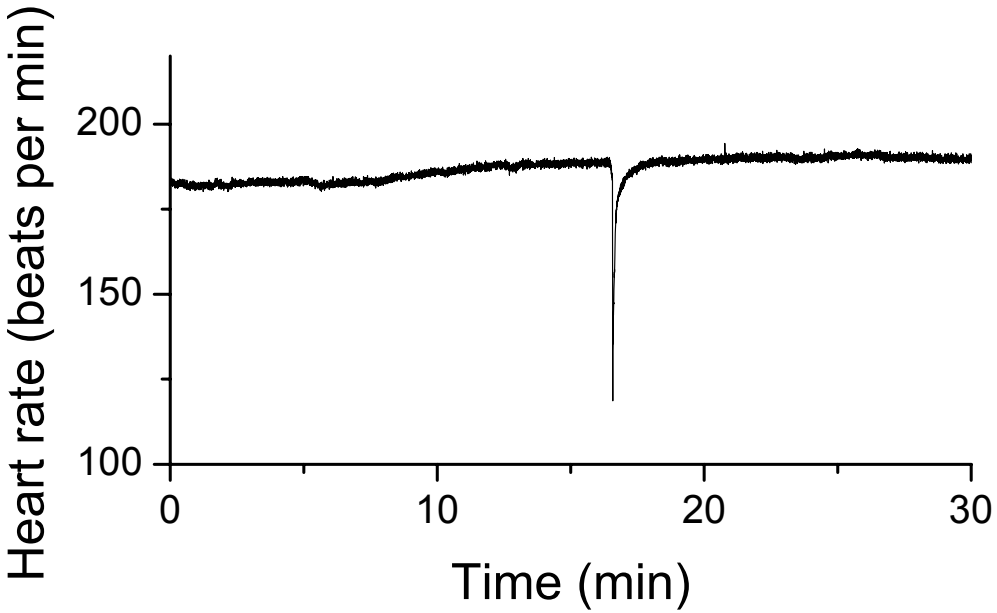
- **Pick the right problem.**
- **Look at the data.**

We observed *reduced variability and transient decelerations* prior to clinical illness and death.



Hours prior to death

>150



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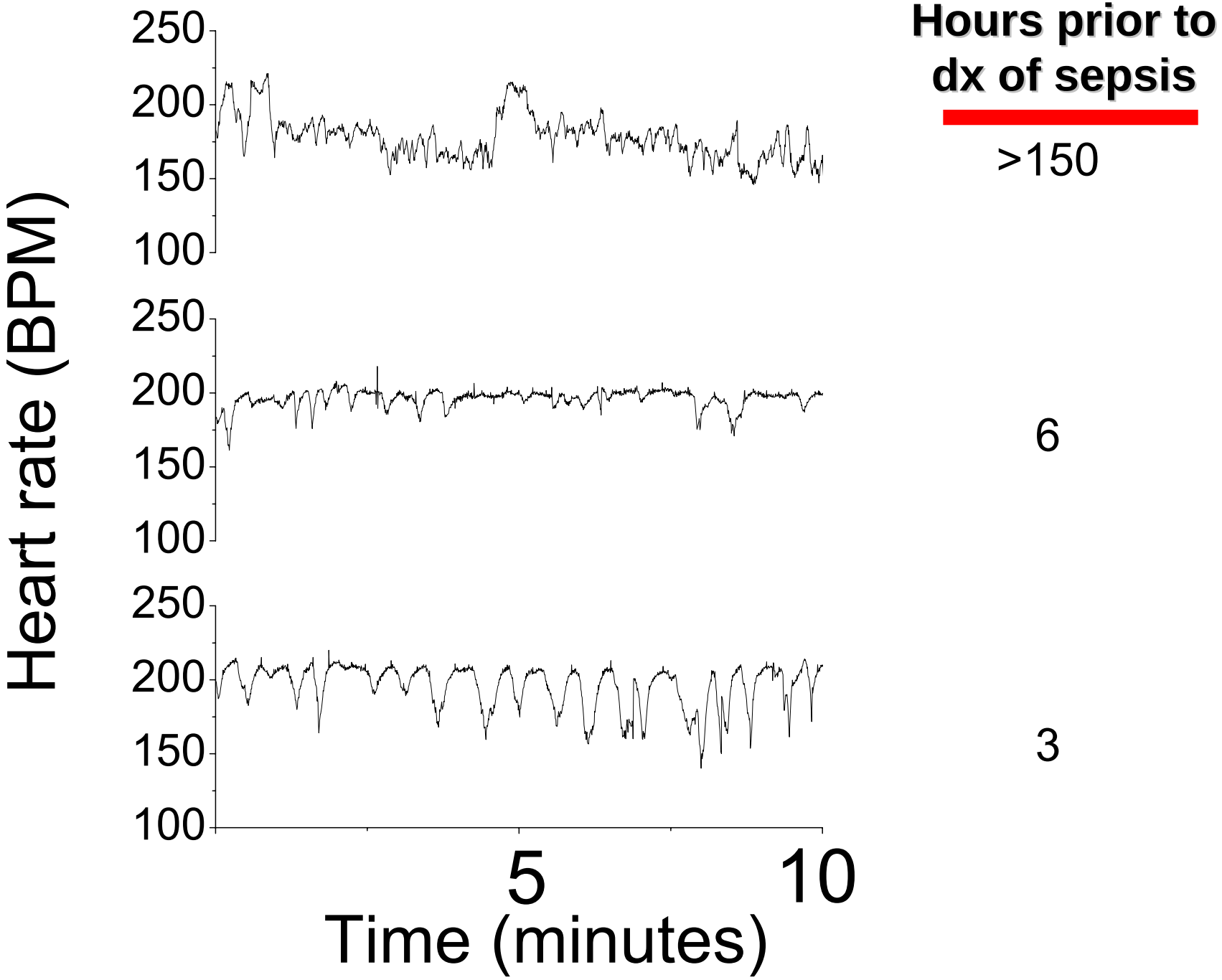
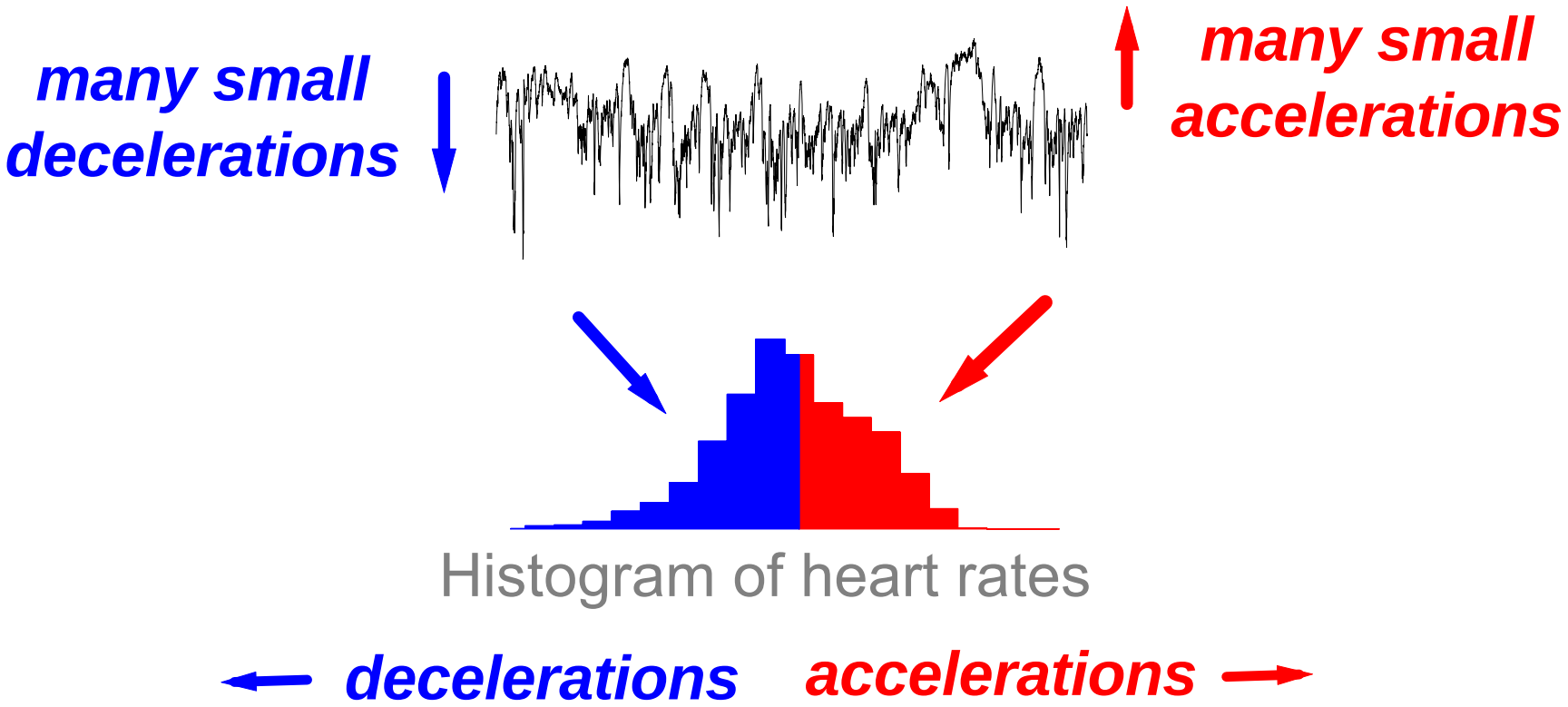
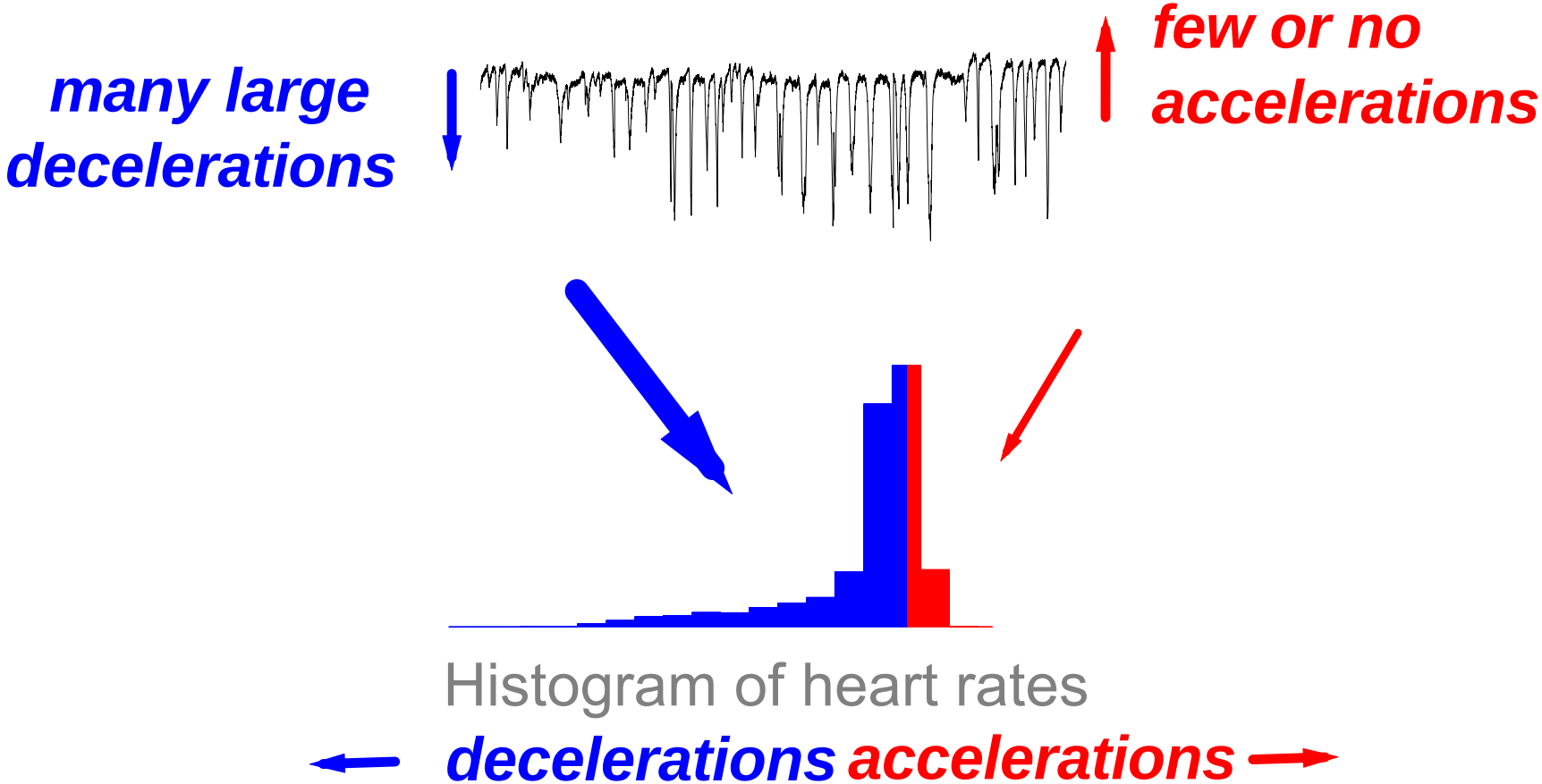

Heart rate (BPM)
250
200
150
100
250
200
150
100
250
200
150
100
5
10
Time (minutes)
Hours prior to dx of sepsis
>150
6
3

Normal heart rate characteristics



Abnormal heart rate characteristics



METHOD

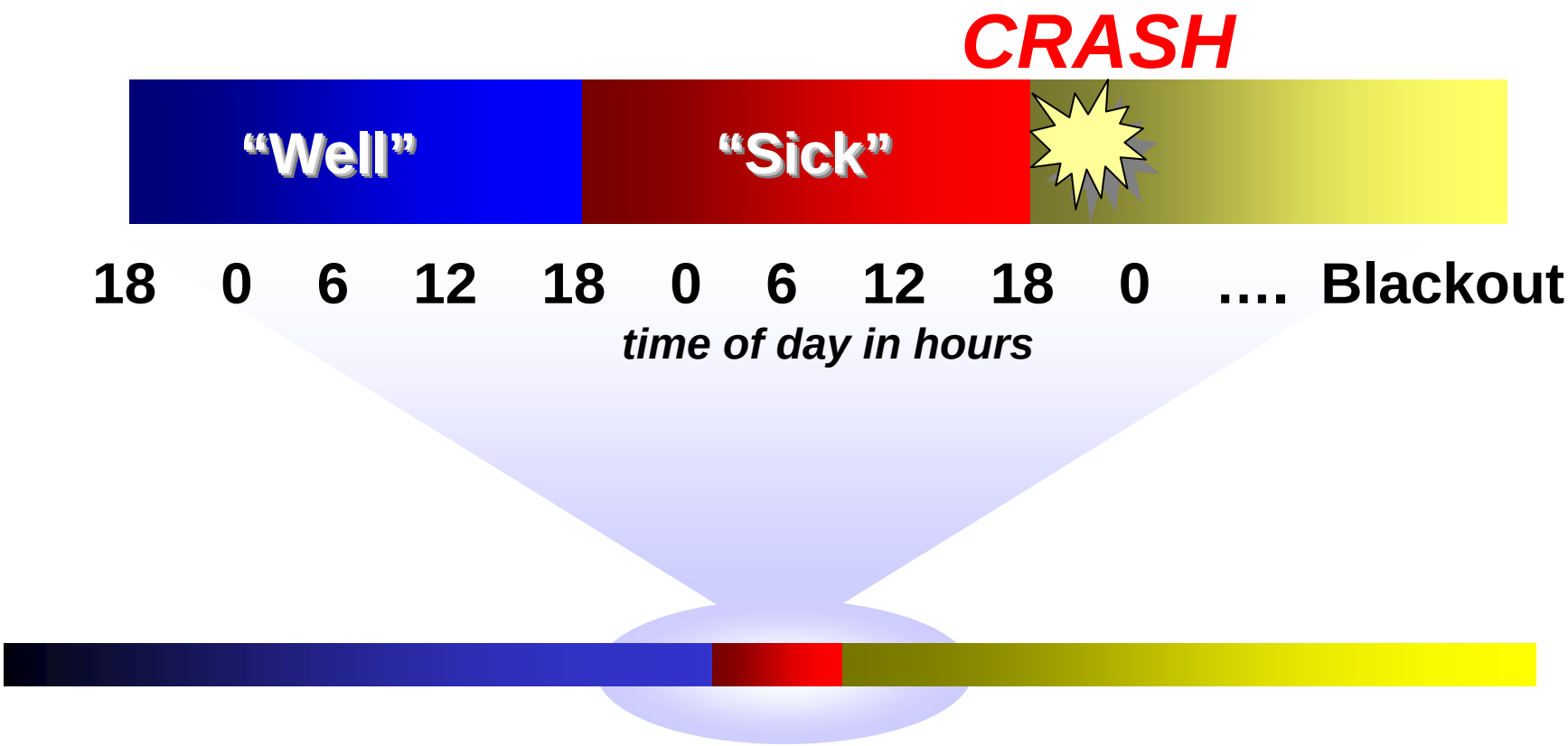
- **Pick the right problem.**
- **Look at the data.**
- **Assume nothing.**

Conventional HRV measures do not detect reduced variability and transient decelerations, so we made some up.

HRC algorithm development

- **Mathematical analysis of reduced variability and transient decelerations**
  - standard deviation
  - sample asymmetry
  - sample entropy
- **Biostatistical analysis of HRC prior to clinical diagnosis of neonatal sepsis**
  - multivariable logistic regression
- **Result: an on-line continuous estimate of the risk of sepsis in the next 24 hours, based on the degree of reduced variability and transient decelerations**

Predictive model – study design



CRASH **= *C*ultures, *R*esuscitation, & *A*ntibiotics *S*tarted *H*ere**

Epochs were defined as "well"(more than 24 hours prior to *CRASH* event), "sick", or a 14-day "blackout" period that was not analyzed.

Predictive model - HRC index

The **HRC index** is derived from regression modeling and uses HRC measures of *standard deviation* (S.D.), *Sample Asymmetry* (R1 and R2), and *SampEn* to estimate the risk of upcoming sepsis and sepsis-like illness.

The formula for the HRC index is:

$$\textbf{HRC index} = [\exp(A) / 1+\exp(A)]$$

where:

$$A = \text{intercept} + \beta_1(\text{S.D.}) + \beta_2(\text{R1}) + \beta_3(\text{R2}) + \beta_4(\text{SampEn})$$

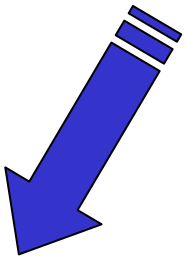
We derived the intercept and coefficients β using UVa data, and then calculated the **HRC index** for WFU data.

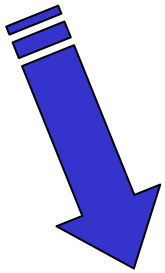
HRC INDEX PREDICTS SEPSIS AT 2 NICUs

TRAIN AT UVa:
316 infants;
155 events in
101 infants

TEST AT WFU:
317 infants;
118 events in 93
infants

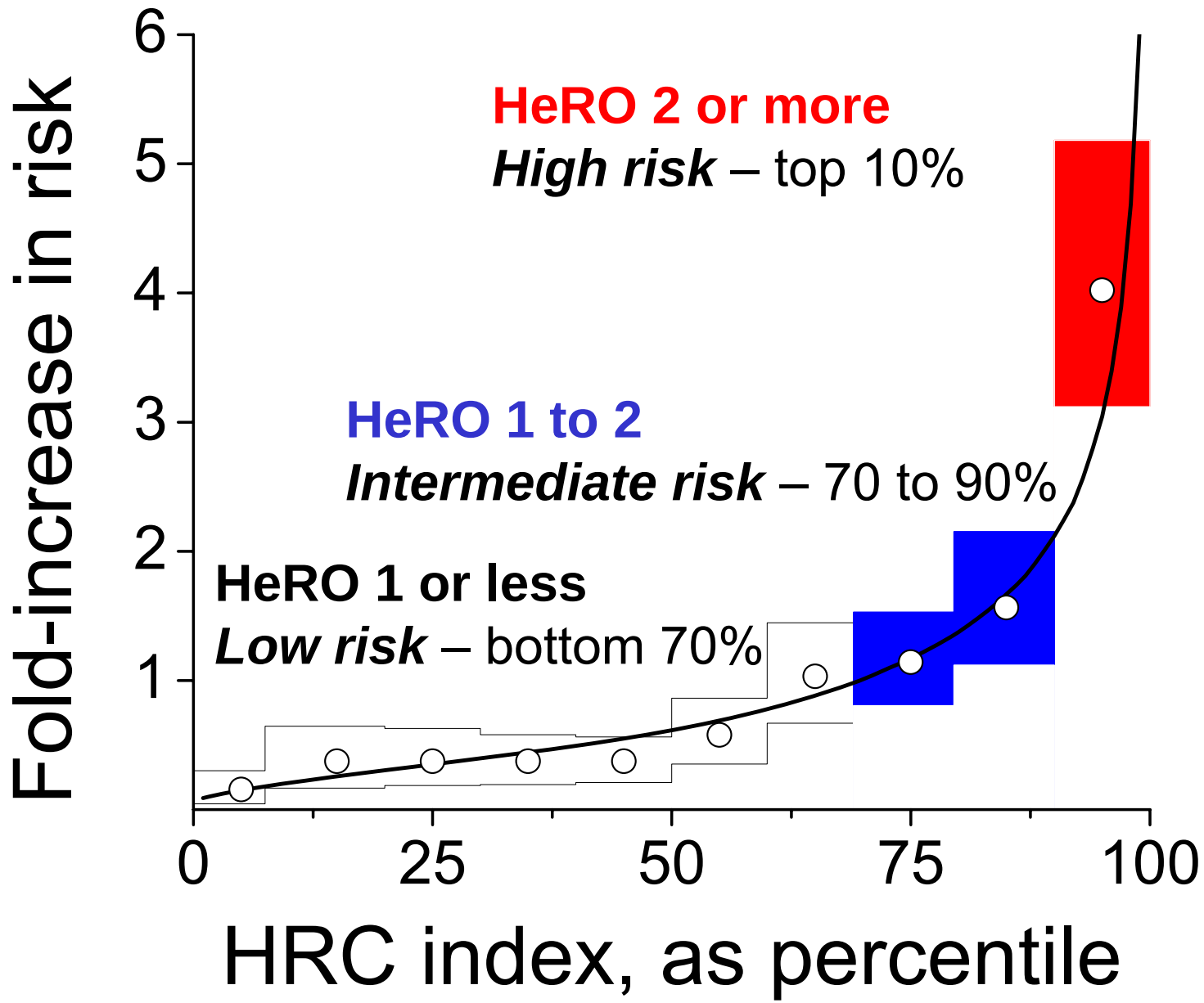
result: formula for
HRC index





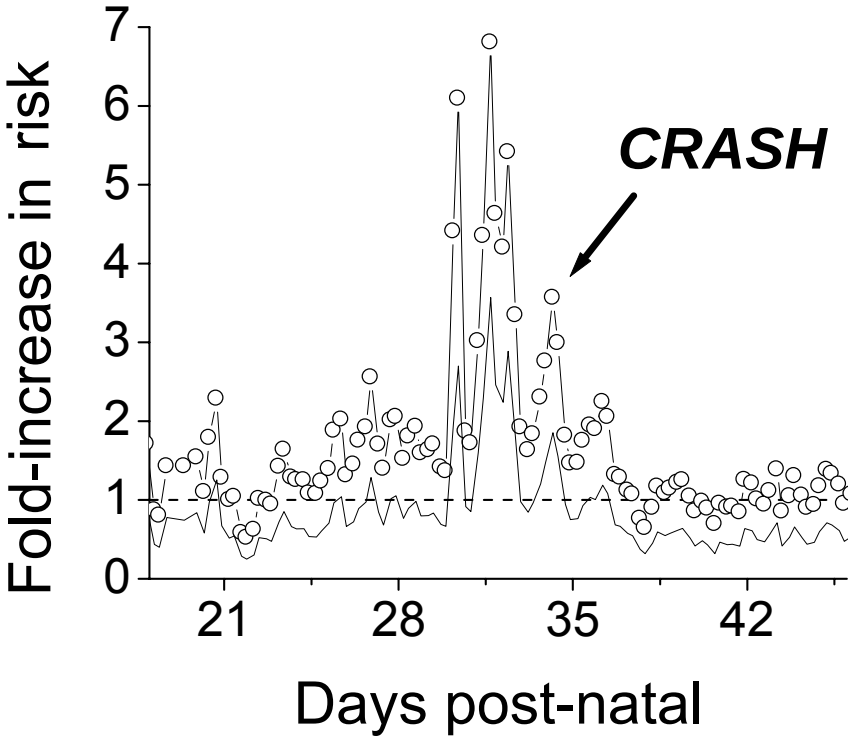
HRC index is associated with sepsis and sepsis-like illness p<0.0001

HRC index adds significantly to BW, GA and days of age p<0.0001

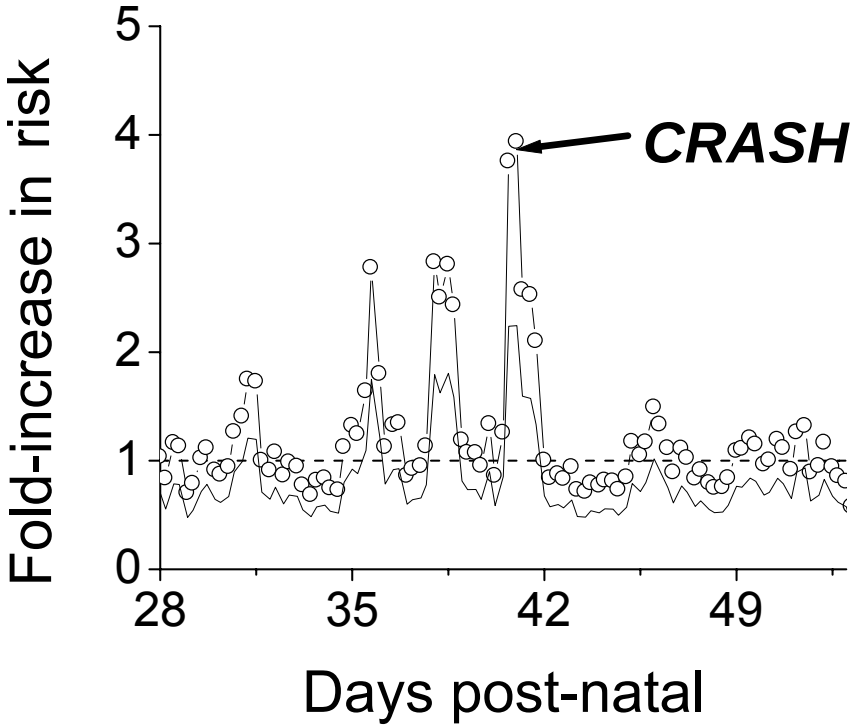

Fold-increase in risk
6
5
4
3
2
1
0
25
50
75
100
HRC index, as percentile
HeRO 2 or more
High risk – top 10%
HeRO 1 to 2
Intermediate risk – 70 to 90%
HeRO 1 or less
Low risk – bottom 70%

HRC index rises prior to sepsis

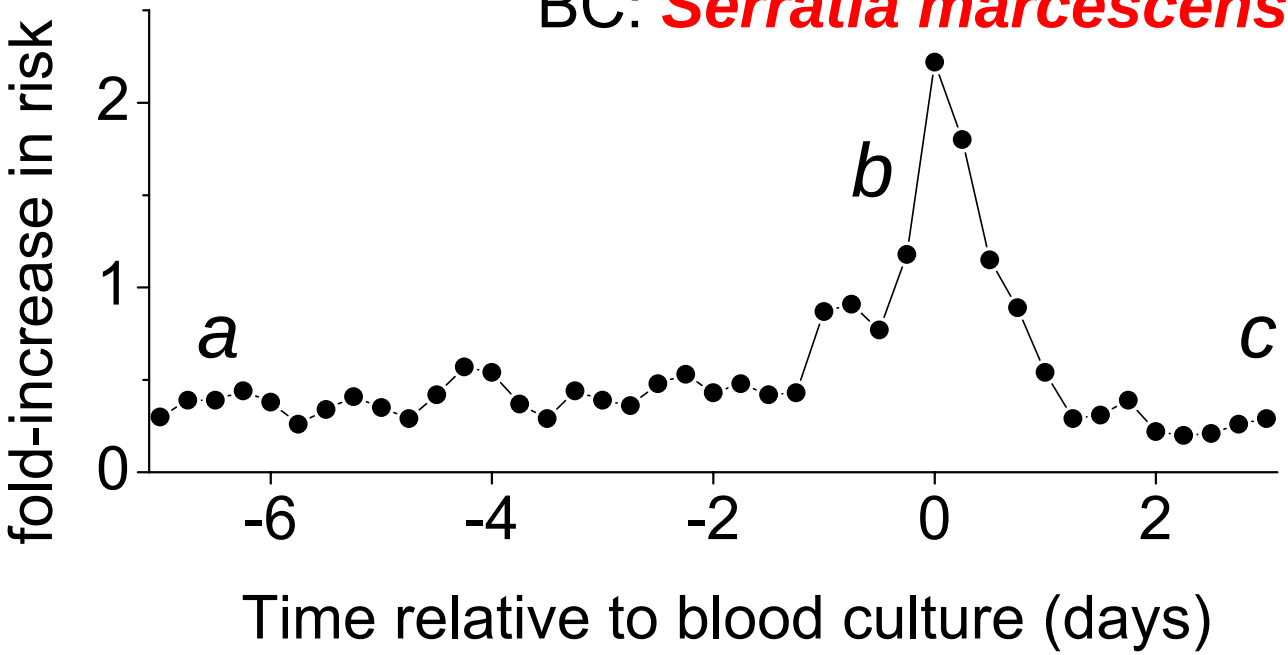
Term infant

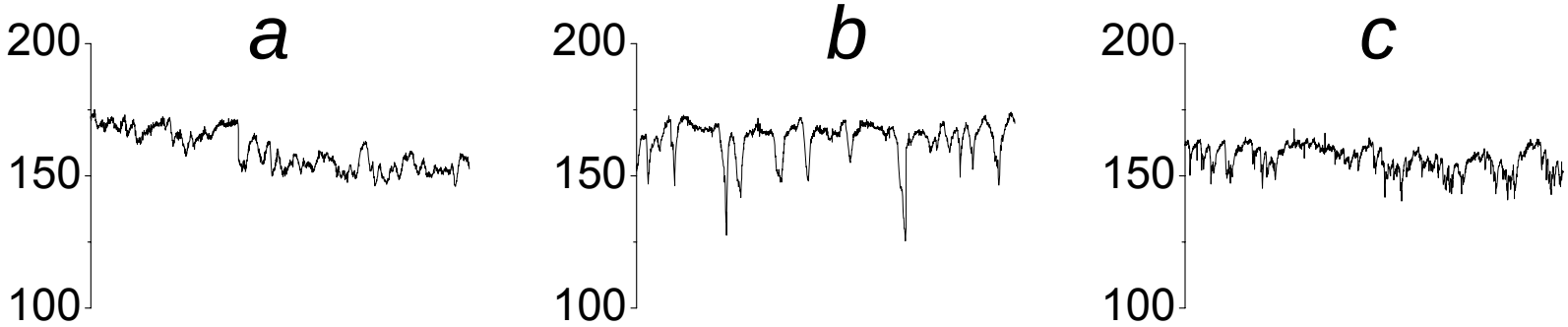


Premature infant

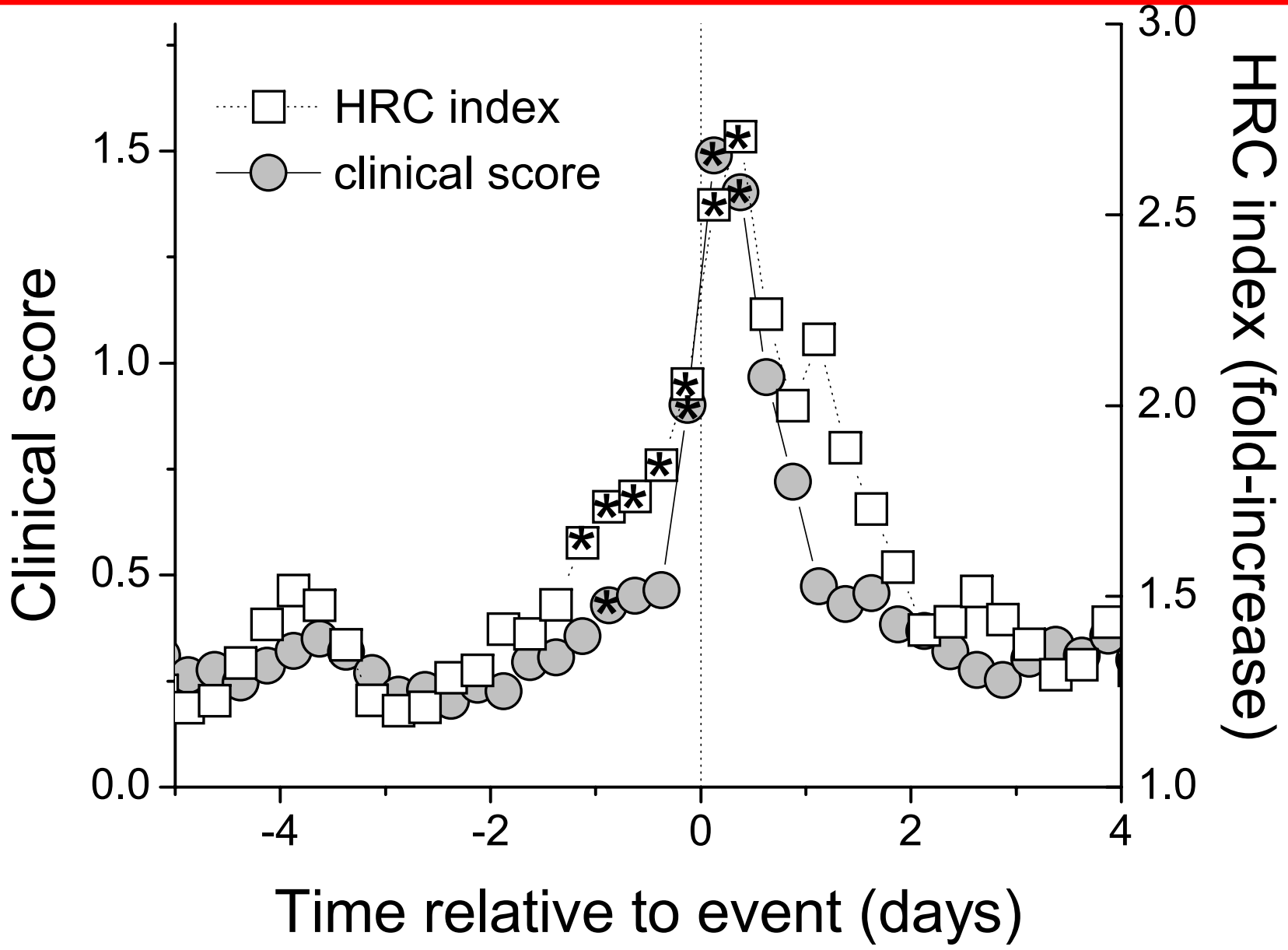


Symptoms: none
Labs: normal
BC: ***Serratia marcescens***

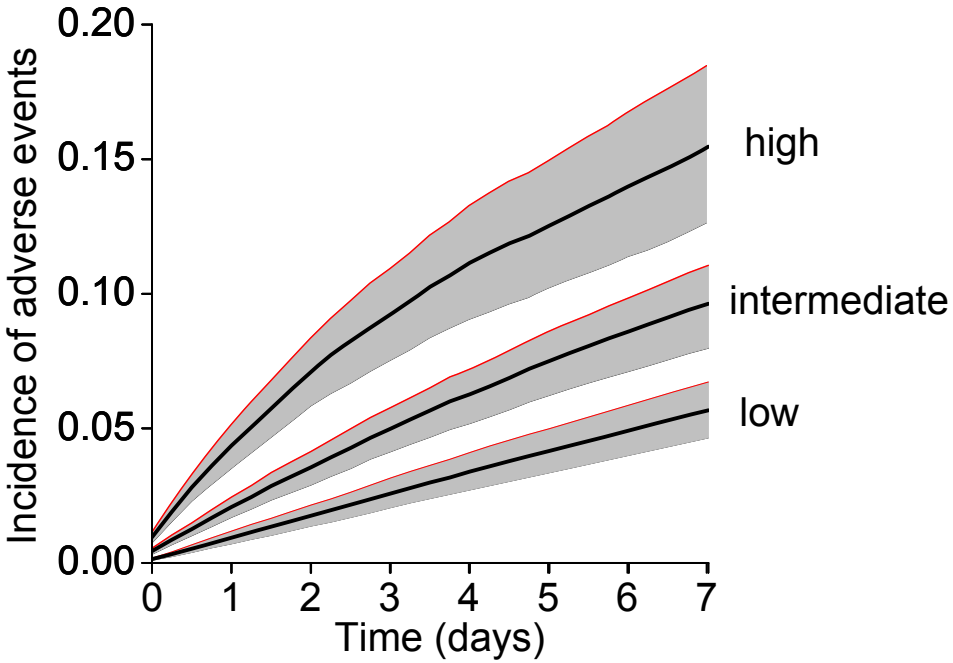


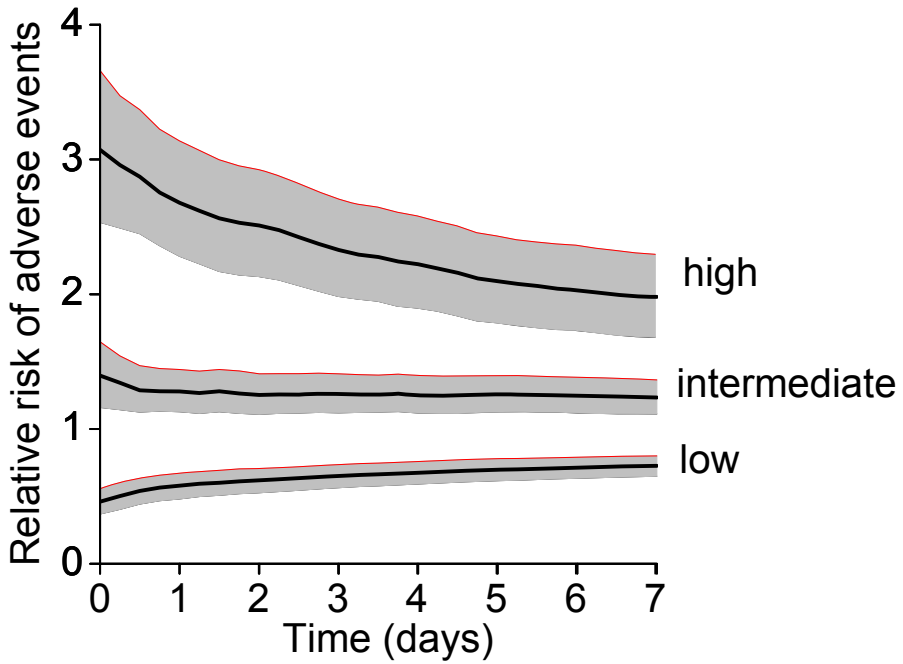


HRC rises before illness score



Fate of HRC (VLBW infants)





A neonatal sepsis risk scorecard

HRC index

Clinical score

	Not measured	Low	Inter-mediate	High
Not measured	1.0	0.5	1	3
0	0.7	0.5	1	2.5
1	2	1	2	4
≥2	3	3	3	4

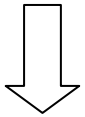
METHOD

- **Pick the right problem.**
- **Look at the data.**
- **Assume nothing.**
- **Do a randomized trial.**

1 R01-HD 048562-01
“Impact of neonatal heart rate characteristics”
ClinicalTrials.gov identifier NCT 00307333

Does HRC display improve outcomes in the NICU?

admission to NICU



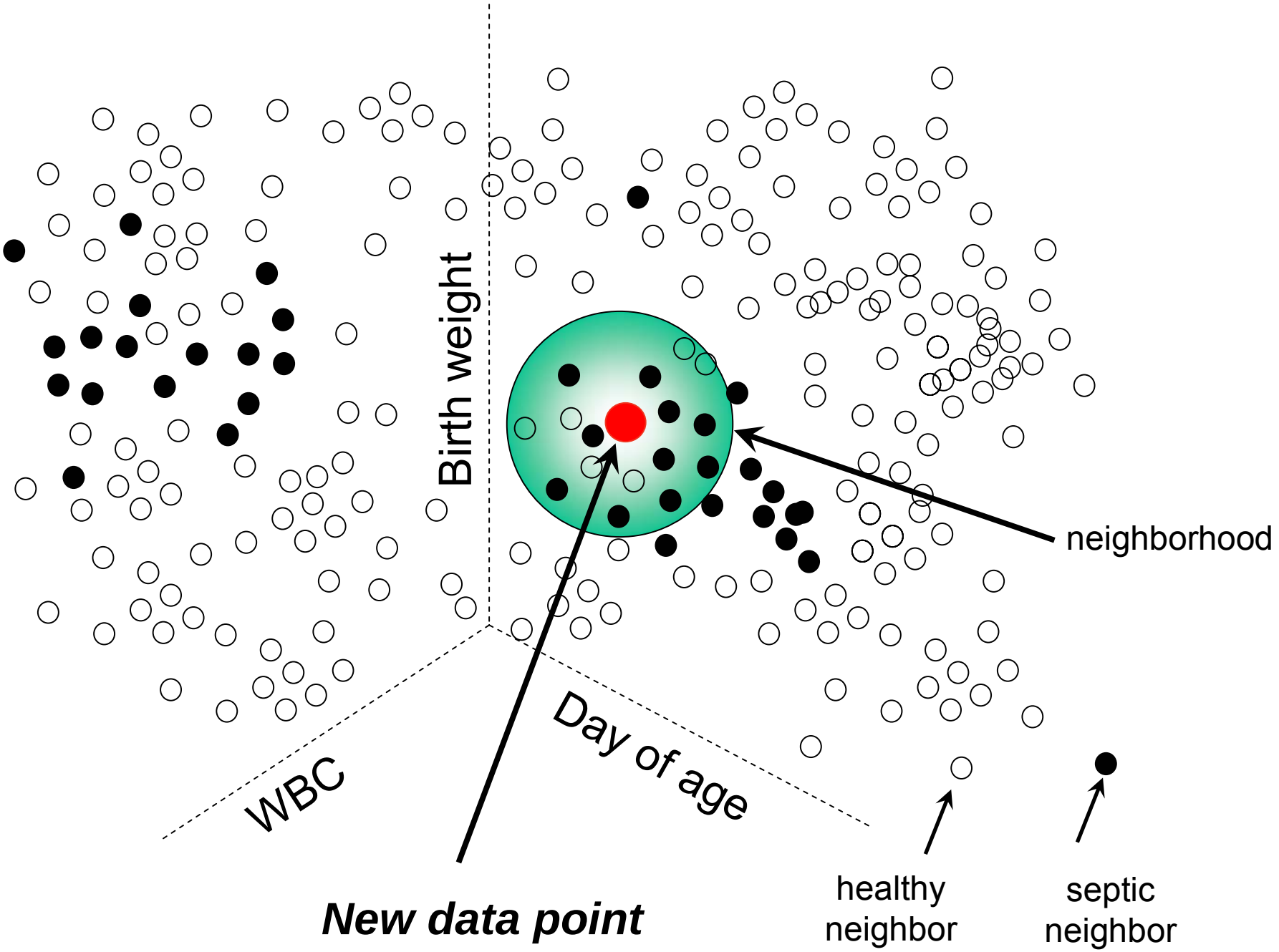
randomize

HRC display **no** *HRC display*

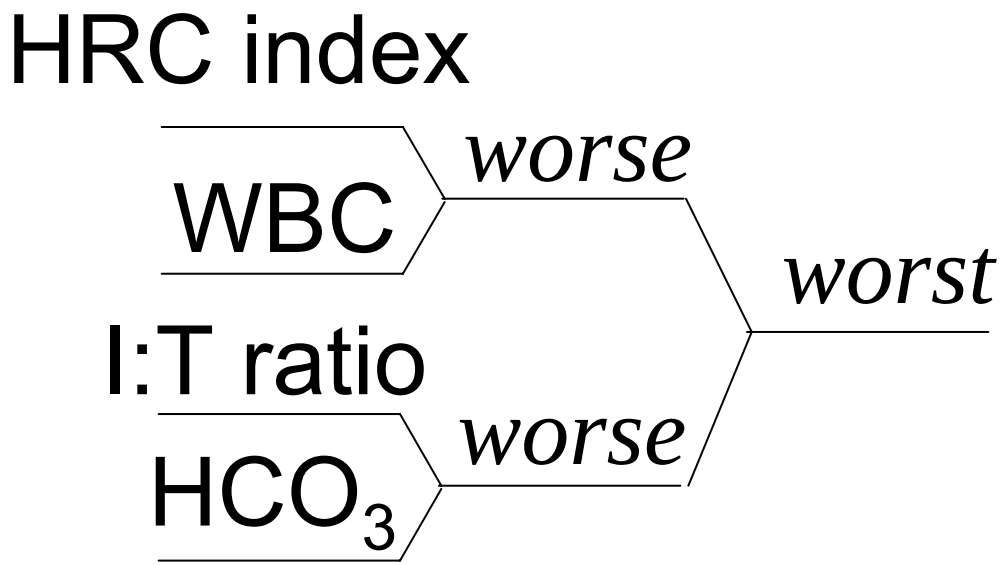
outcome measures:
- ventilator-free days during first 120 days of life (primary)
- days in hospital
- days on antibiotics
- in-hospital mortality

Mathematical analyses of neonatal heart rate

- **Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test (Cao)**
  - Neonatal HR is non-stationary, and even less so prior to sepsis.
- **Nearest-neighbor analysis and tournaments of models (Xiao)**


Birth weight
WBC
Day of age
neighborhood
New data point
healthy neighbor
septic neighbor

Invitational tournament

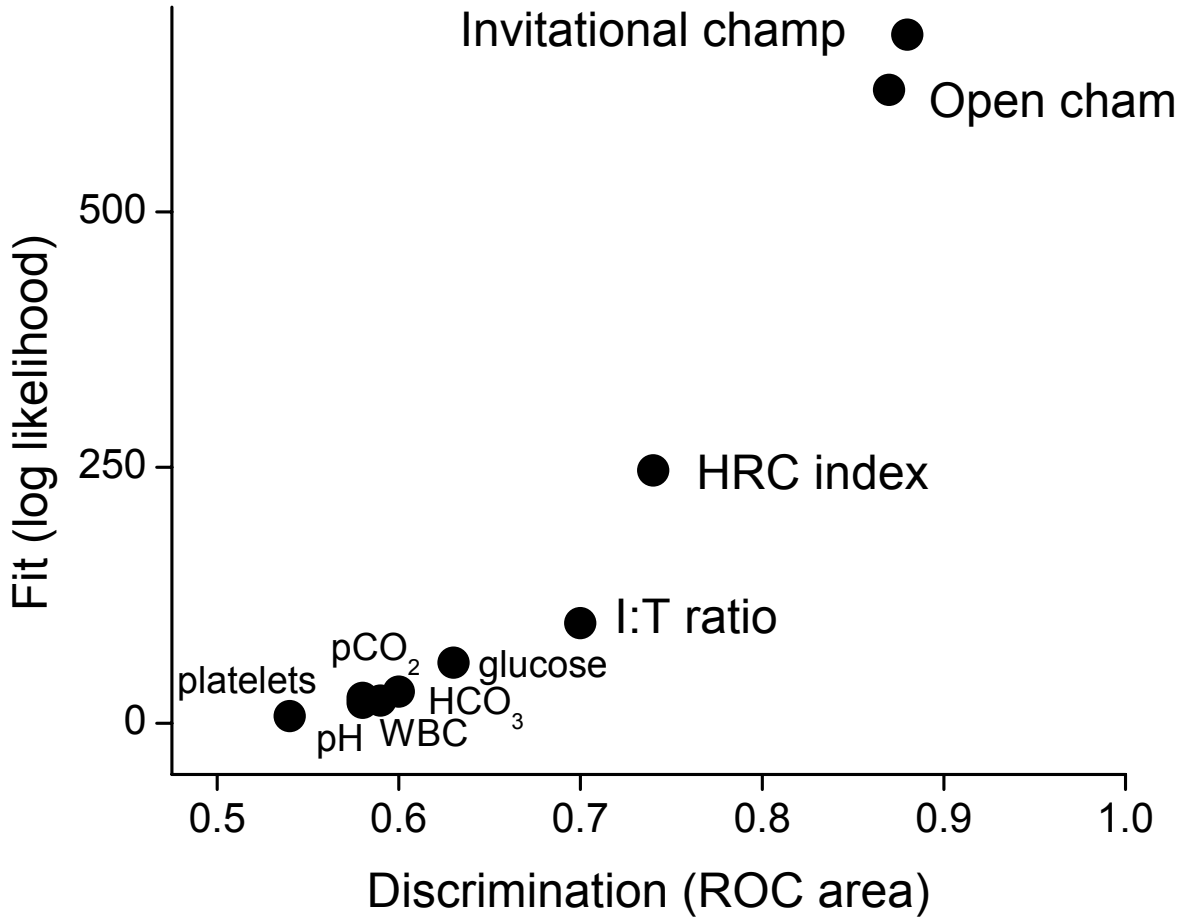


Are the biggest pessimists the best predictors of sepsis?

Results

•Nearest-neighbor analysis added independent information to logistic regression (*p*<0.05).

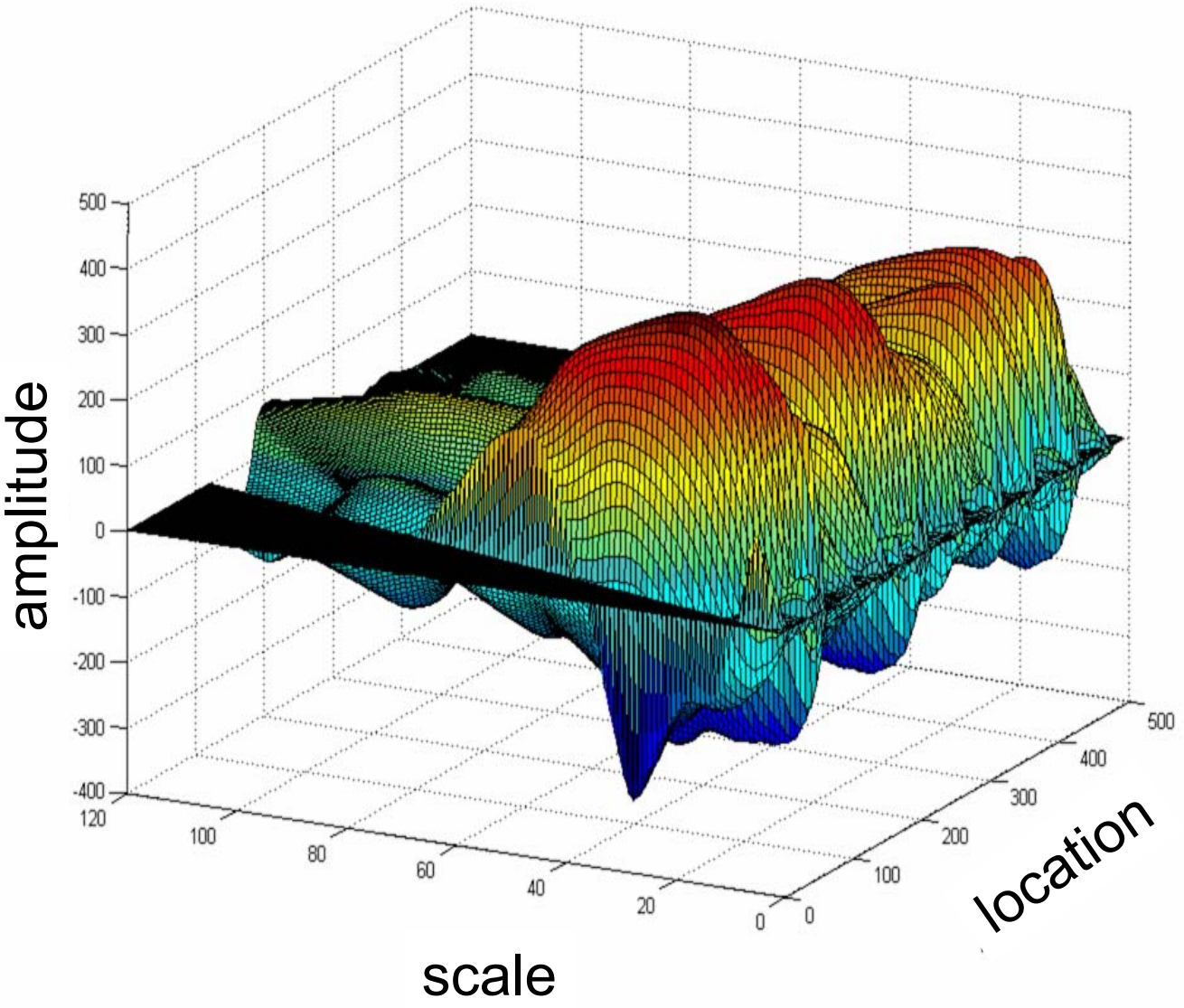
• HRC index was the most predictive individual finding, but tournaments of models led to the best predictions.



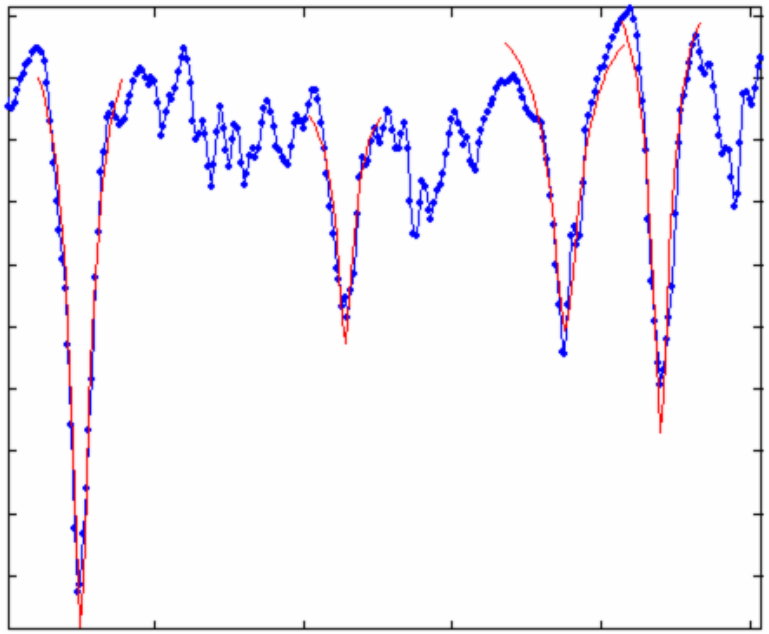
Mathematical analyses of neonatal heart rate

- Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test (Cao)
- Nearest-neighbor analysis and tournaments of models (Xiao)
- Deceleration detection using wavelet transform analysis (Flower)

Wavelet transform analysis of decelerations



Wavelet transform analysis of decelerations



Raw data with fitted wavelet templates superimposed

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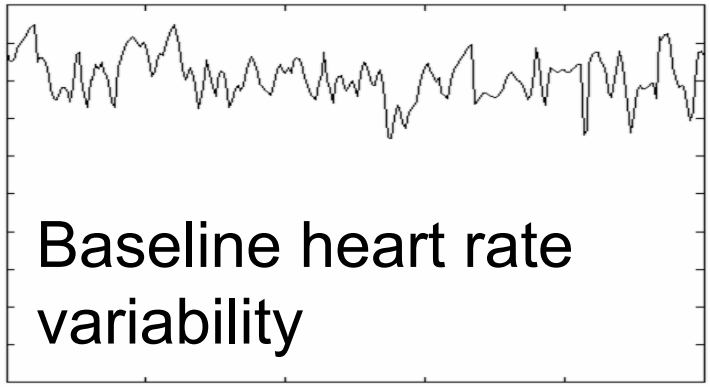
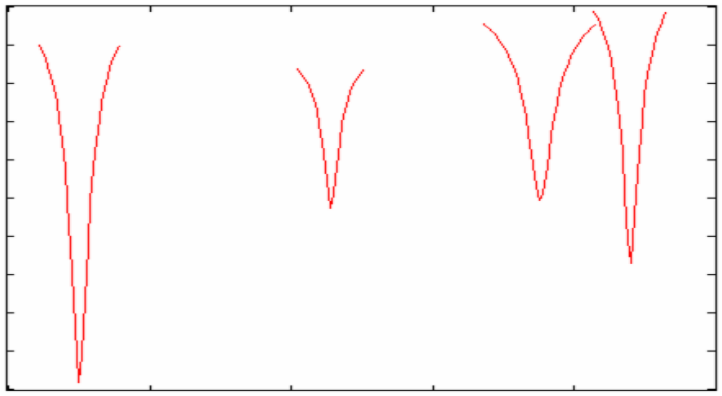


Baseline heart rate variability

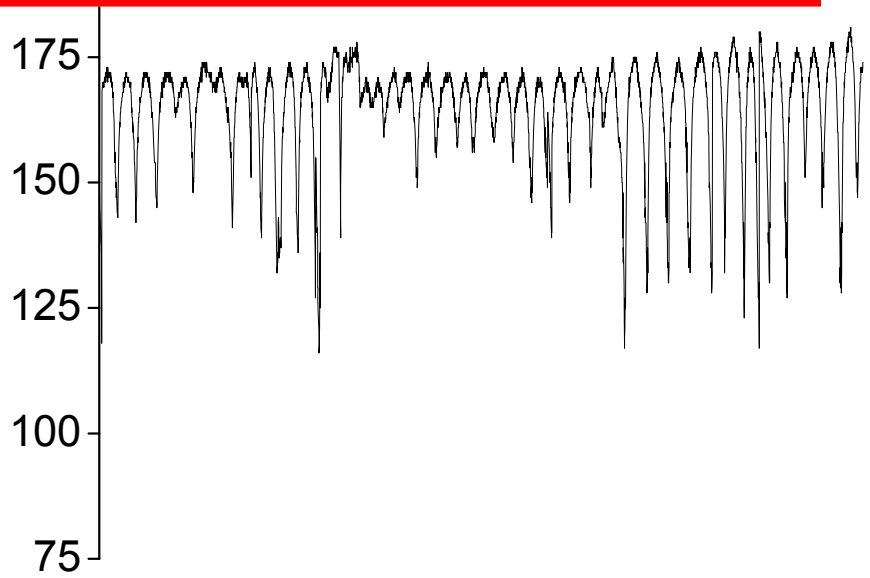
+

Detected decelerations

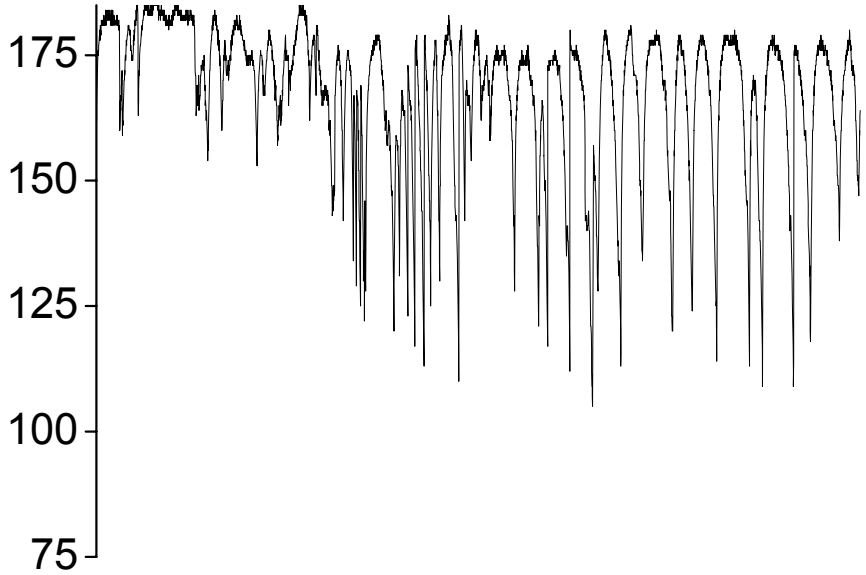


Some infants had storms of decelerations

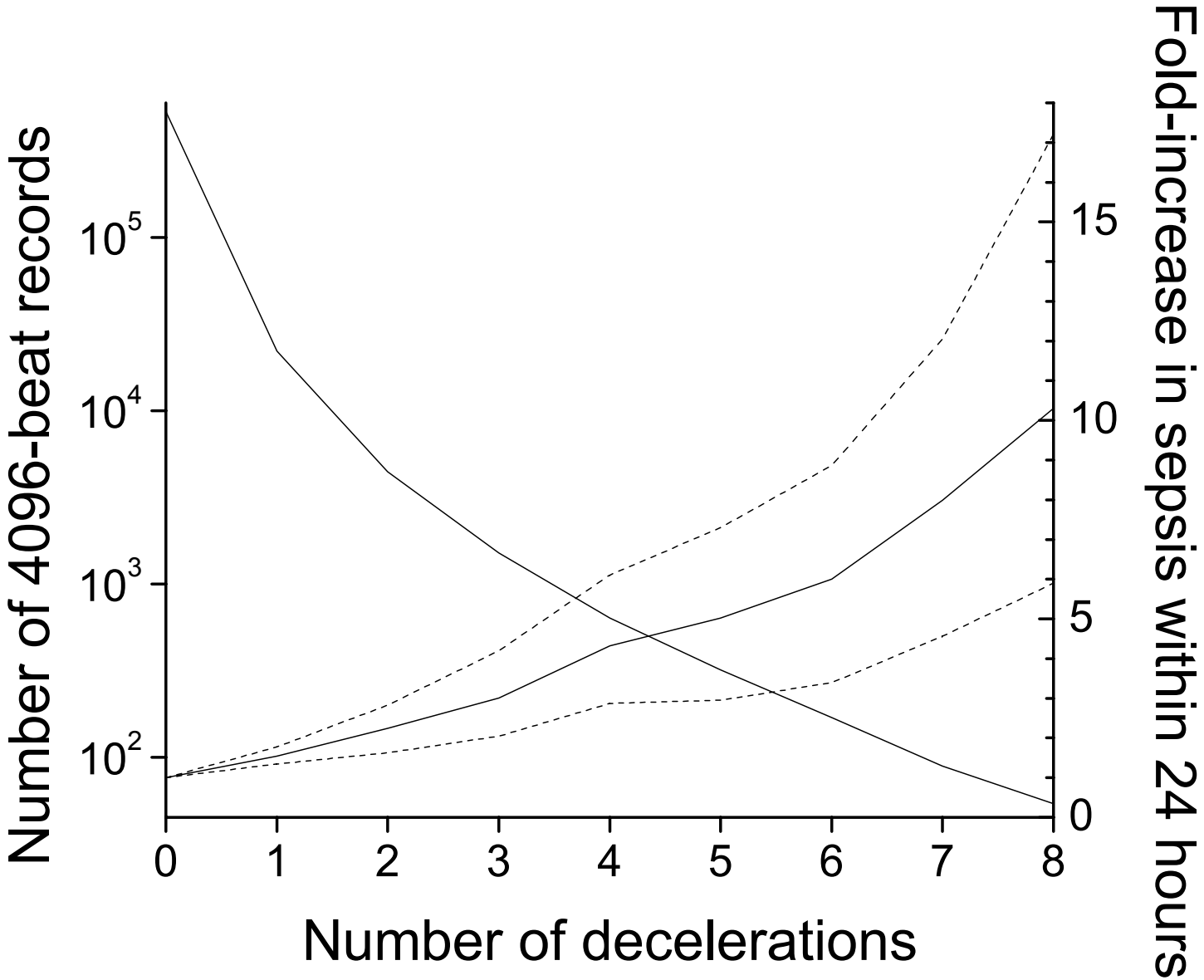
BW 1285 g, GA 29 weeks
Day 18 of life
2 hours before
Klebsiella sepsis



BW 1005 g, GA 27 weeks
Day 21 of life
7 hours before
Pseudomonas sepsis



These storms were highly predictive of sepsis



Decelerations add information to the HRC index

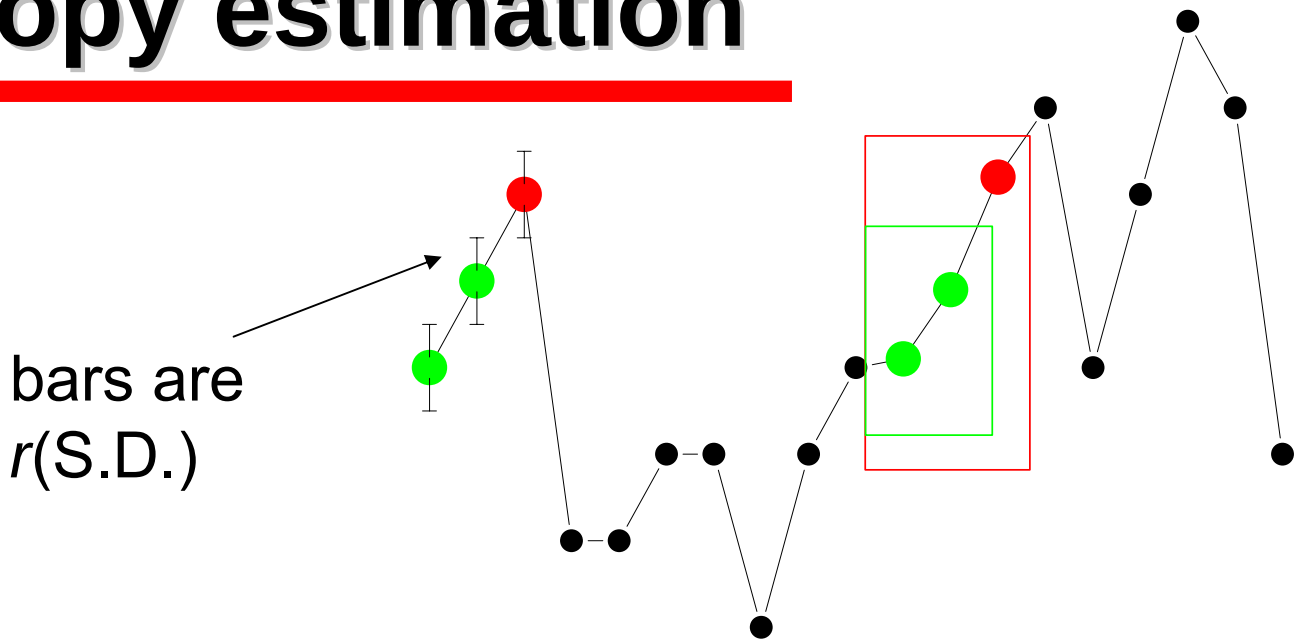
predictor 1	predictor 2	ROC	*p*1	*p2*
S.D. of RR intervals		**0.70**	*	
S.D. of RR intervals	**number of decelerations**	**0.75**	*	*
HRC index		**0.75**	*	
HRC index	**number of decelerations**	**0.77**	*	*

S.D. = standard deviation; *p*1 is for significance of predictor 1; *p2* is for added information of predictor 2; * = <0.05.

Mathematical analyses of neonatal heart rate

- **Empirical cumulative distribution functions and the Kolmogorov-Smirnov two-sample test**
- **Nearest-neighbor analysis and tournaments of models**
- **Deceleration detection using wavelet transform analysis**
- **Entropy estimation:**
  - ApEn is biased, but Sample Entropy (SampEn) is less so (Richman).
  - Low values of entropy can arise from spikes in the data (Lake).
  - Atrial fibrillation detection based on entropy requires only short records (Lake, Xiao).
  - Closed form estimates of the variance of SampEn (Richman, Lake)…
  - …allow optimization of *m* and *r* (Lake, Rushton, Xiao).

Entropy estimation



A = match of length *m+1*
B = match of length *m*

Sample Entropy = -ln ΣA / ΣB
Approximate Entropy ≈ Σ -ln (1+ΣA) / (1+ΣB)

For regular, repeating data, ΣA / ΣB nears 1 and entropy nears 0.

Toward improved entropy estimates

- Signal $x_1, x_2, \ldots, x_n$
- $X_i(m) = (x_{i-m+1}, \ldots, x_i)$ template i of length m
- B_i=number of matches with $X_i(m)$
- A_i=number of matches with $X_i(m+1)$
- $B = \Sigma B_i$ =number of matches of length m
- $A = \Sigma A_i$ =number of matches of length m+1
- Conditional probability: p=A/B
- SampEn=-log(p)

Conditional probability variance

$$\sigma_p^2 = \frac{1}{4B^2}(\sigma_A^2 - 2p\sigma_{AB}^2 + p^2\sigma_B^2)$$

$$\sigma_A^2 = n\sum_{i=1}^{n}(A_i - A/n)^2 + 2n\sum_{h=1}^{K}\sum_{i=1}^{n-h}(A_i - A/n)(A_{i+h} - A/n)$$

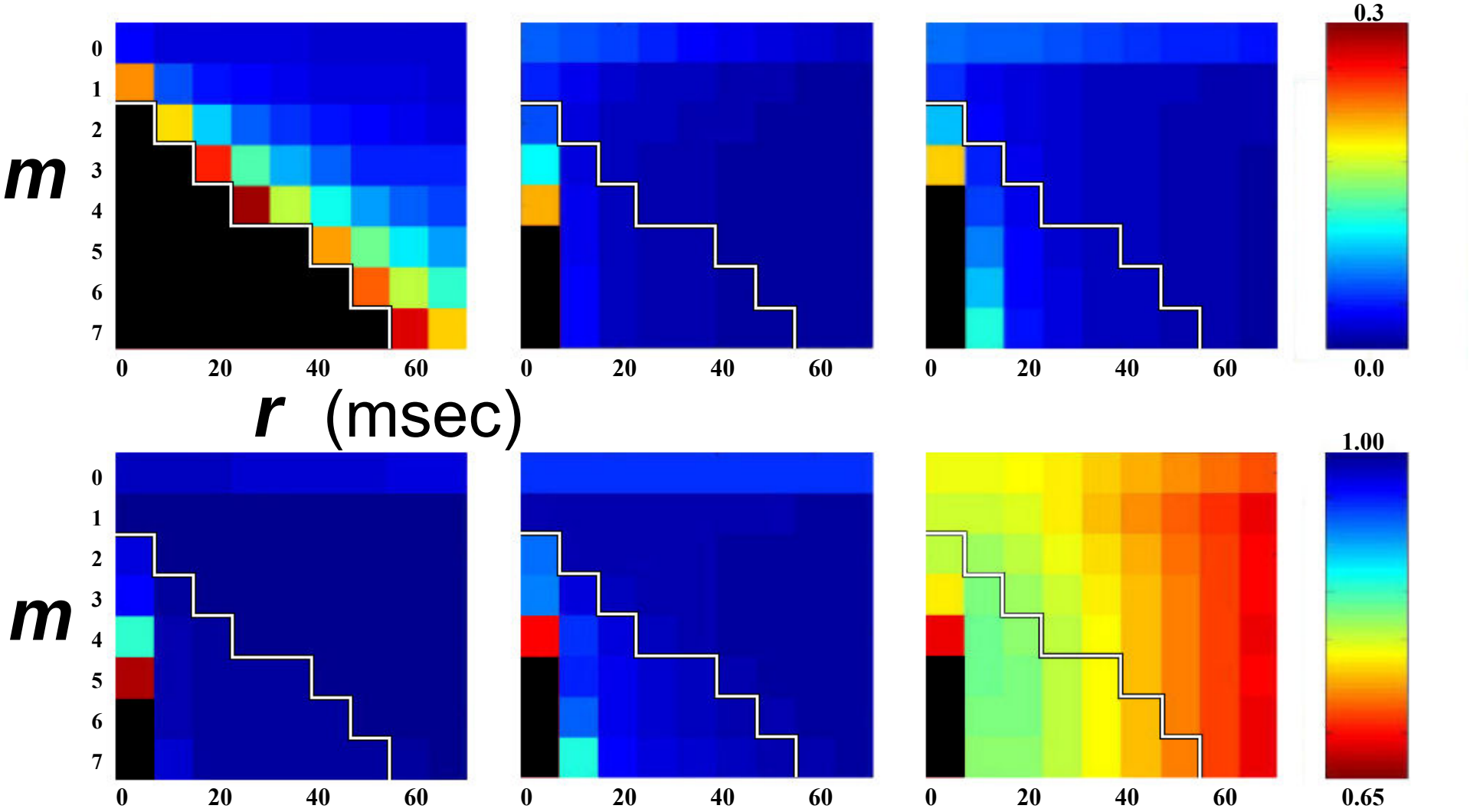
$$\sigma_{AB}^2 = \mathrm{Cov[A,B]} = n\sum_{h=-K}^{K}\sum_{|i-j|=h}(A_i - A/n)(B_j - B/n)$$

- Factor of 4 needed to account for counting each match twice
- *K* selected based on correlation length of signal and *m*
- Conservative estimate is maximum value among all *K*

Estimated SampEn Standard Error

- Above estimate more accurate and generally smaller than that previously reported (Lake et al, 2002) and available on Physionet
- Estimate motivated by more accurate U-statistic approach of Richman (Ph.D. dissertation 2005)
- New estimate requires less computation and agrees favorably on MIT-BIH NSR data base
- Standard error of SampEn is approximately standard error of *p* divided by *p*

Relative error of the SampEn estimate



ROC areas

AF vs NSR AF vs CHF NSR vs CHF

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