Multiplicity-Corrected Nonparametric Tolerance Regions for Cardiac ECG Features

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NISS
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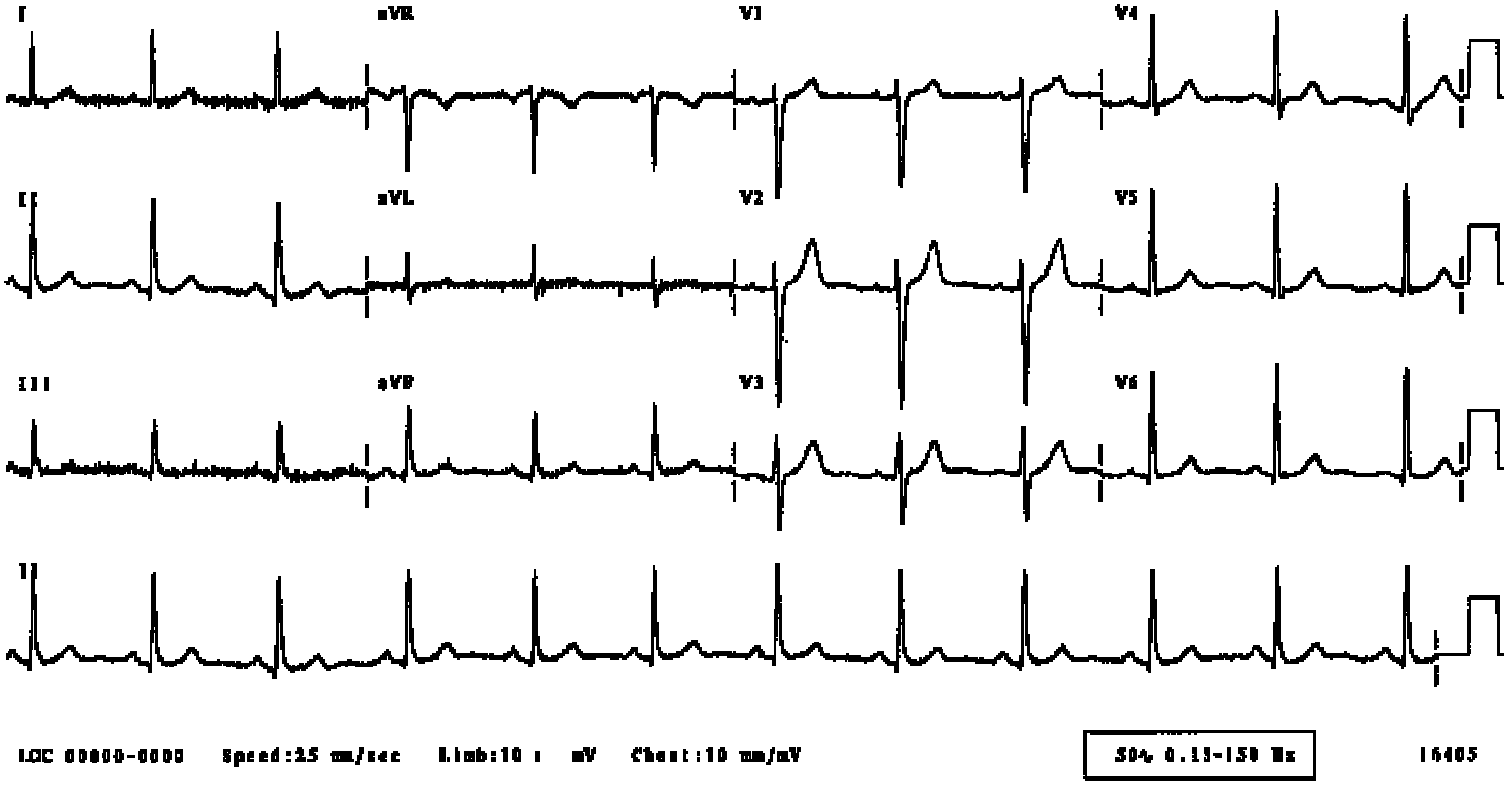
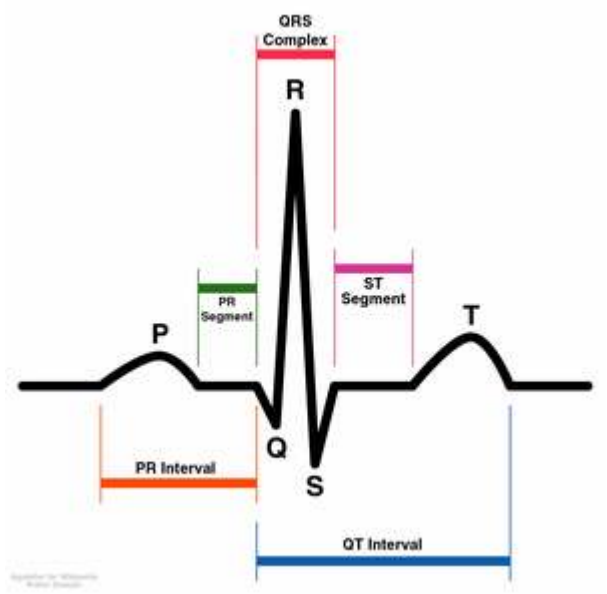
ECG

Normal adult 12-lead ECG



ECG

QT Interval



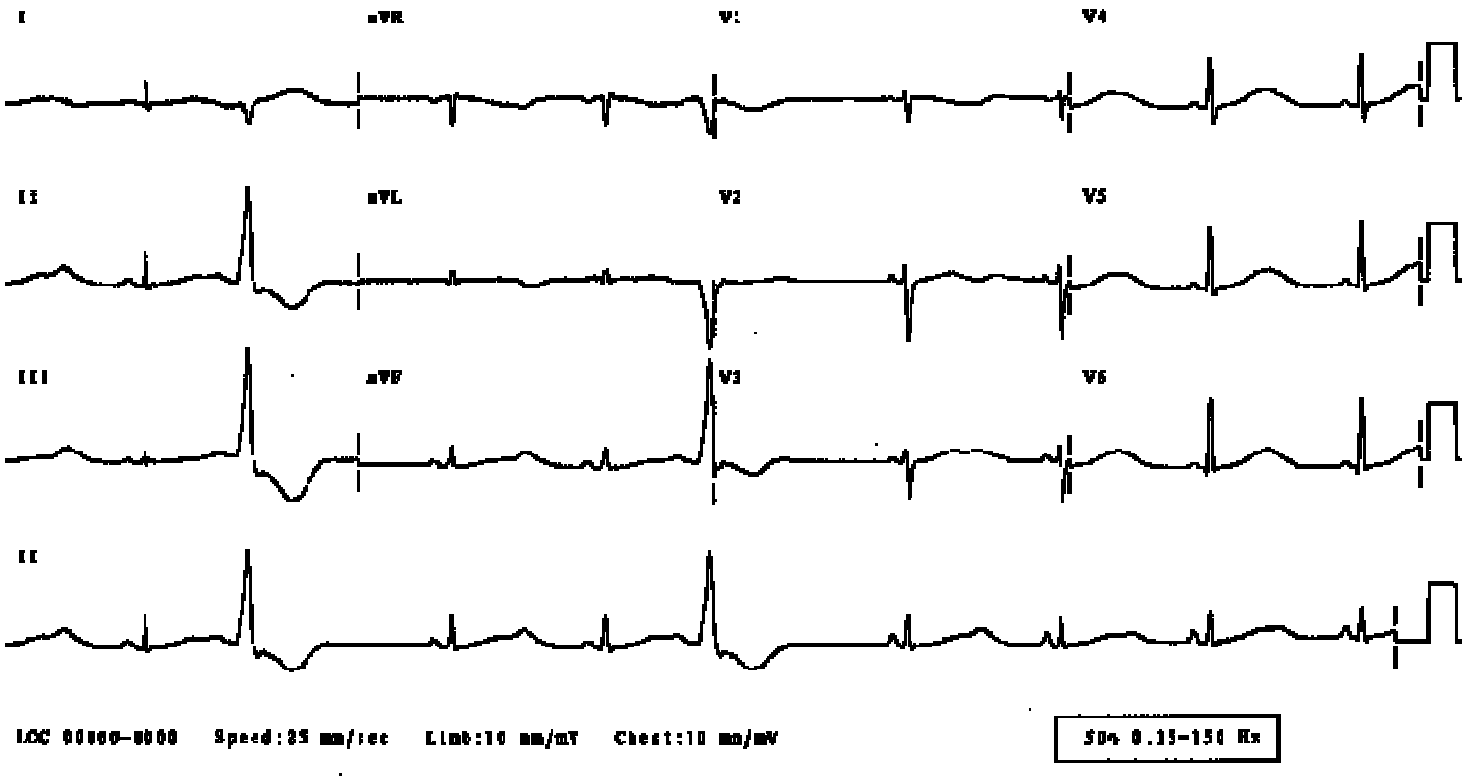
1. Ventricular Depolarization and **Repolarization**
2. Correction for the heart rate (RR interval)

http://en.wikipedia.org/wiki/QT_interval

ECG

Long QT Interval

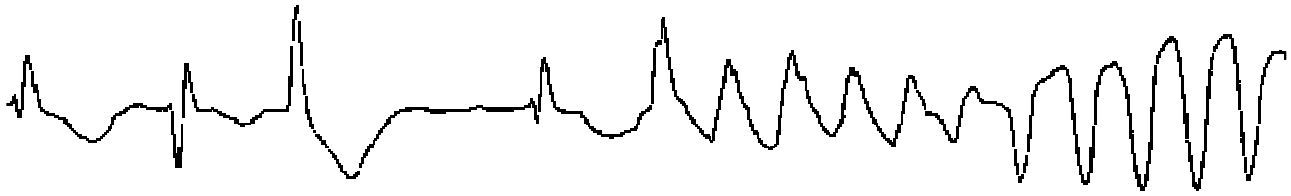
Romano-Ward Syndrome



ECG

Torsade de Pointes

Polymorphous ventricular tachycardia



ECG

The PTB Diagnostic ECG Database

PhysioNet/Computers in Cardiology Challenge 2006:

QT Interval Measurement

Nonparametric Tolerance Intervals

Introduction

Cover (at least) P of the population
with confidence level (at least) γ

$$\Pr\left(\int_L^U f(x)dx \geq P\right) \geq \gamma$$

$$L = X_{(r)}$$

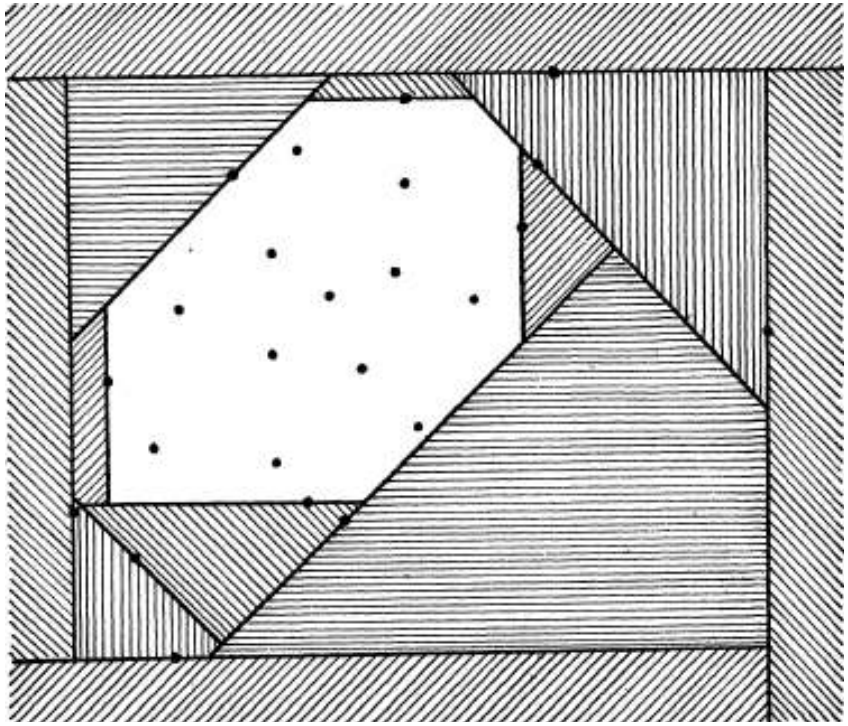
$$U = X_{(n-r+1)}$$

$$B_{n-2r+1,\,2r}(P) \leq 1-\gamma$$

Wilks (1941)

Nonparametric Tolerance Regions

Statistically Equivalent Blocks



Tukey (1947)

Calibration for Simultaneity

Introduction

Buja and Rolke (2003):

Re(sampling) Methods for Simultaneous Inference

1. Limit the search for **coverage regions** to a family of nested regions indexed by the **pointwise** coverage probability
2. Select from the family the coverage region for which the estimated **simultaneous** coverage probability equals the desired level

Calibration for Simultaneity

Applications

Simultaneous inference based on a single distribution

- Null regions for testing null hypotheses
- Bootstrap standard error regions
- Diagnostic curves for distributional assessment and two-sample comparisons
- Smooths and non-parametric transformation of data
- Curves that arise as functional data

Calibration for Simultaneity

Steps

1. Construct the **family** of nested regions indexed by the pointwise coverage probability, say γ
2. **Simulate** from the distribution of interest and determine the **minimal** γ for which **simultaneous** coverage is achieved
3. **Repeat** step 2
4. Determine the upper $1-\alpha$ **quantile** for the collection of γ values

Calibration for Simultaneity

Connection

- Special case of a single null hypothesis is equivalent to **p-value adjustment** (Westfall and Young 1993)

- **Pointwise** p-values
- **Simultaneous** p-values
- **Adjusted** p-values

- The notion of p-value can be extended to simultaneous coverage problems

Multiplicity-Corrected Nonparametric Tolerance Regions

Introduction

Combine two statistical methodologies:

1. Nonparametric tolerance regions
2. Calibration for simultaneity

To obtain nonparametric tolerance regions that:

1. Adapt to the shape of the observed distributions
2. **Control** over the family-wise error rate

Multiplicity-Corrected Nonparametric Tolerance Regions

Steps

1. Construct the **family** of nested tolerance regions of fixed coverage P indexed by the pointwise confidence level γ
2. **Bootstrap** and determine the **minimal** γ for which coverage of at least P is achieved **simultaneously**
3. **Repeat** step 2
4. Determine the upper $1-\alpha$ **quantile** for the collection of γ values

Application

PTB Diagnostic ECG Database

5 nonparametric tolerance intervals with (at least) 90% coverage and (at least) 95% **simultaneous** confidence level

5 different manual QT measurements of a representative beat from each of the 548 records from the database

Correlations ranging from 0.88 to 0.96

Application

PTB Diagnostic ECG Database

Pointwise 95% confidence	Simultaneous 95% confidence Pointwise 97.5% confidence
1. 310, 457	1. 310, 458
2. 311, 454	2. 311, 455
3. 312, 464	3. 312, 466
4. 303, 542	4. 303, 452
5. 315, 463	5. 315, 463

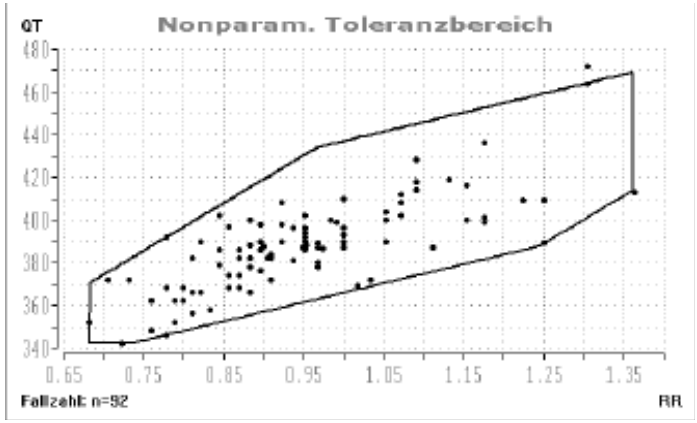
Application
Lilly Data

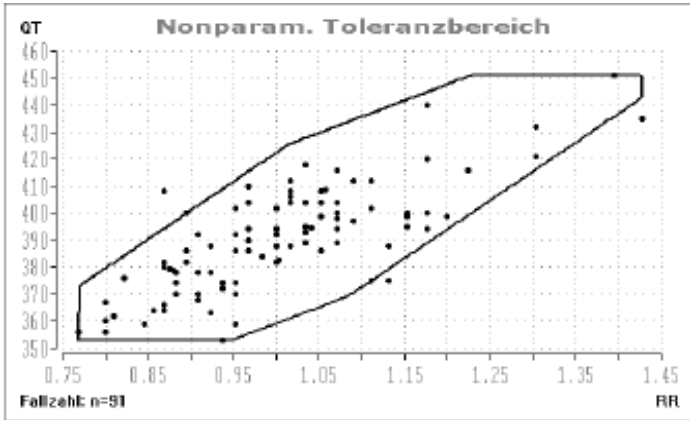
Multiple (at different time points) bivariate nonparametric tolerance regions for the QT interval and the RR interval

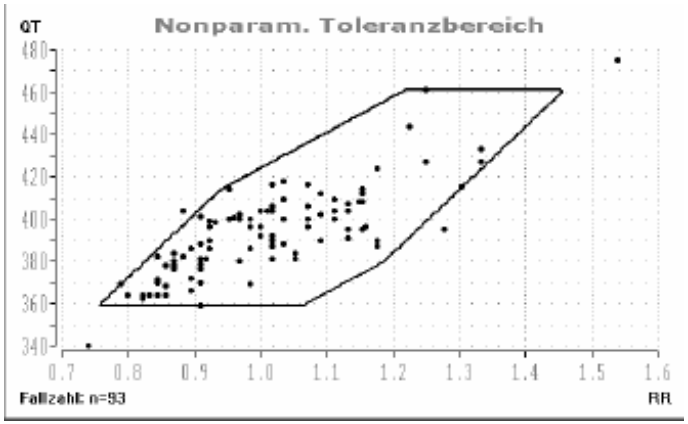
- 6 time points: 0, 3, 4, 6, 9, and 12 (hours)
- Placebo data from a Lilly TQT study
- About 92 measurements at each time point

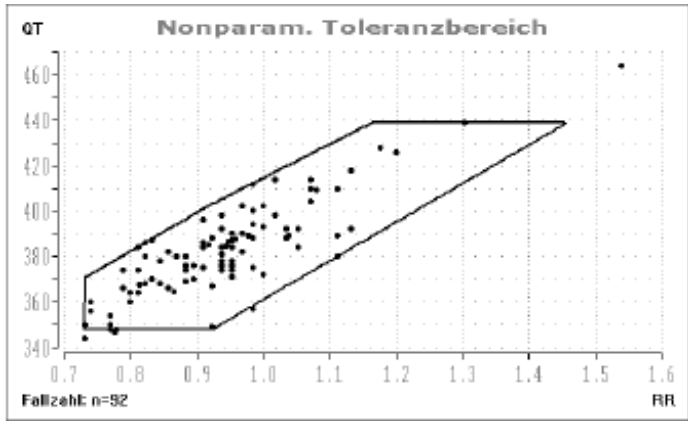
Application

Lilly Data



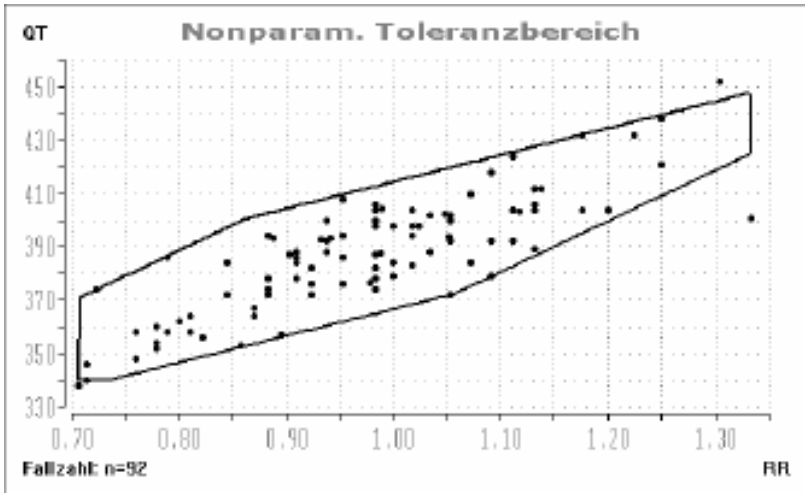


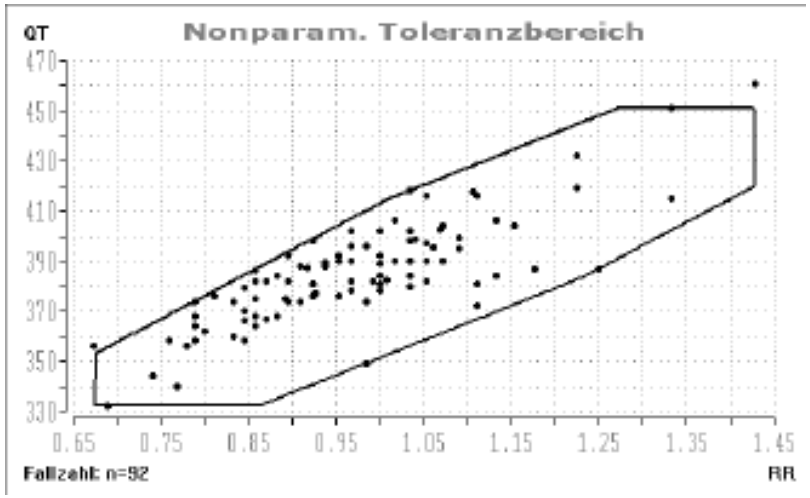




Application

Lilly Data





BiAS Software:

At least 90% coverage

Modulo 4 adjustment to get complete structures

8 SEB eliminated in all six cases

Acknowledgements

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