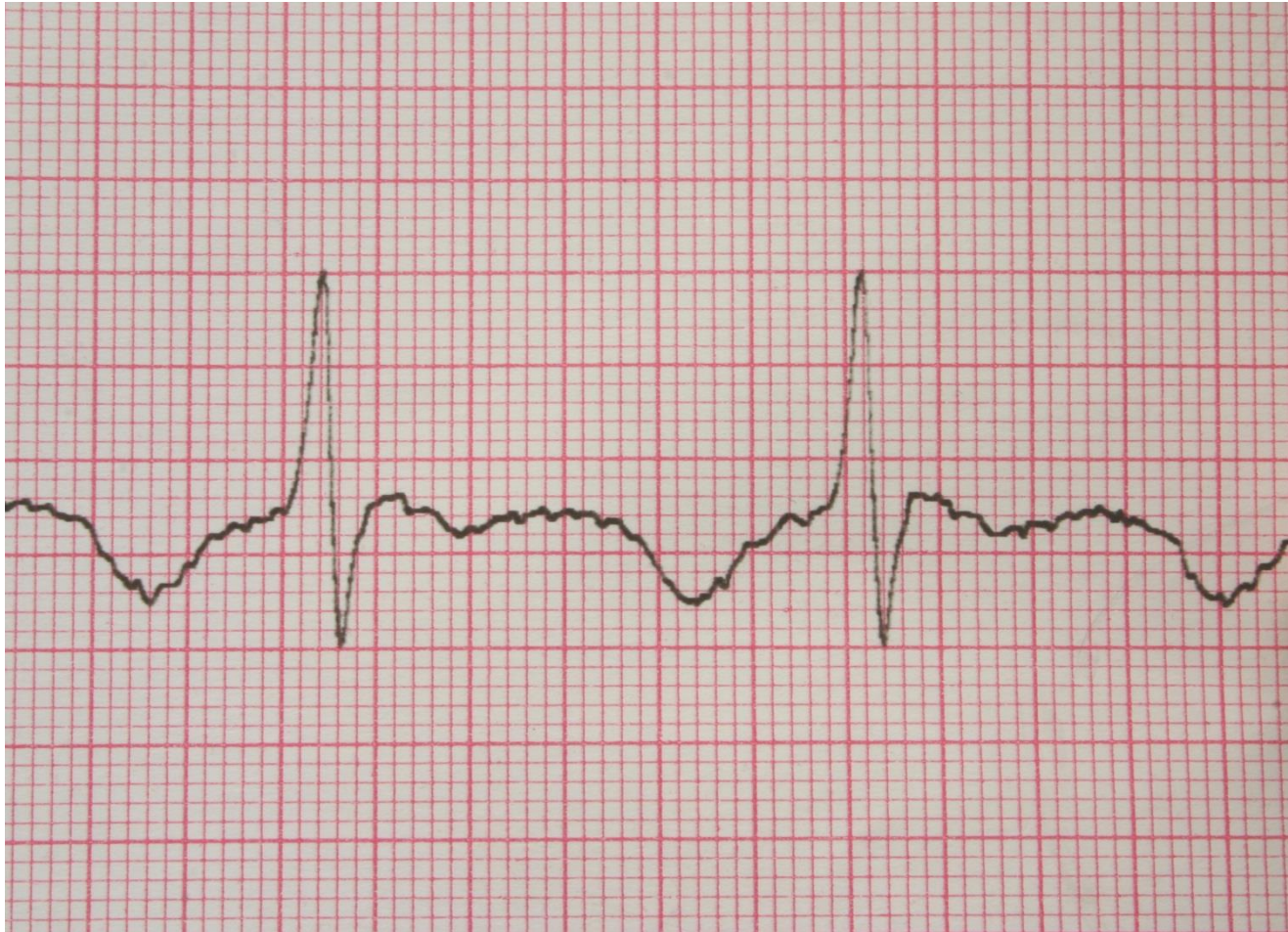


NISS Research Highlight
Thorough QT Studies of
Drug Safety

NISS aids collaborative precompetitive research

- a. drug safety, not efficacy
- b. NISS facilitated work by Merck, Lilly
- c. Industry gets cost-effective answers
- d. Academia gets
 - i. Real data on important problems
 - ii. Financial support for faculty and / or graduate students
 - iii. Publications

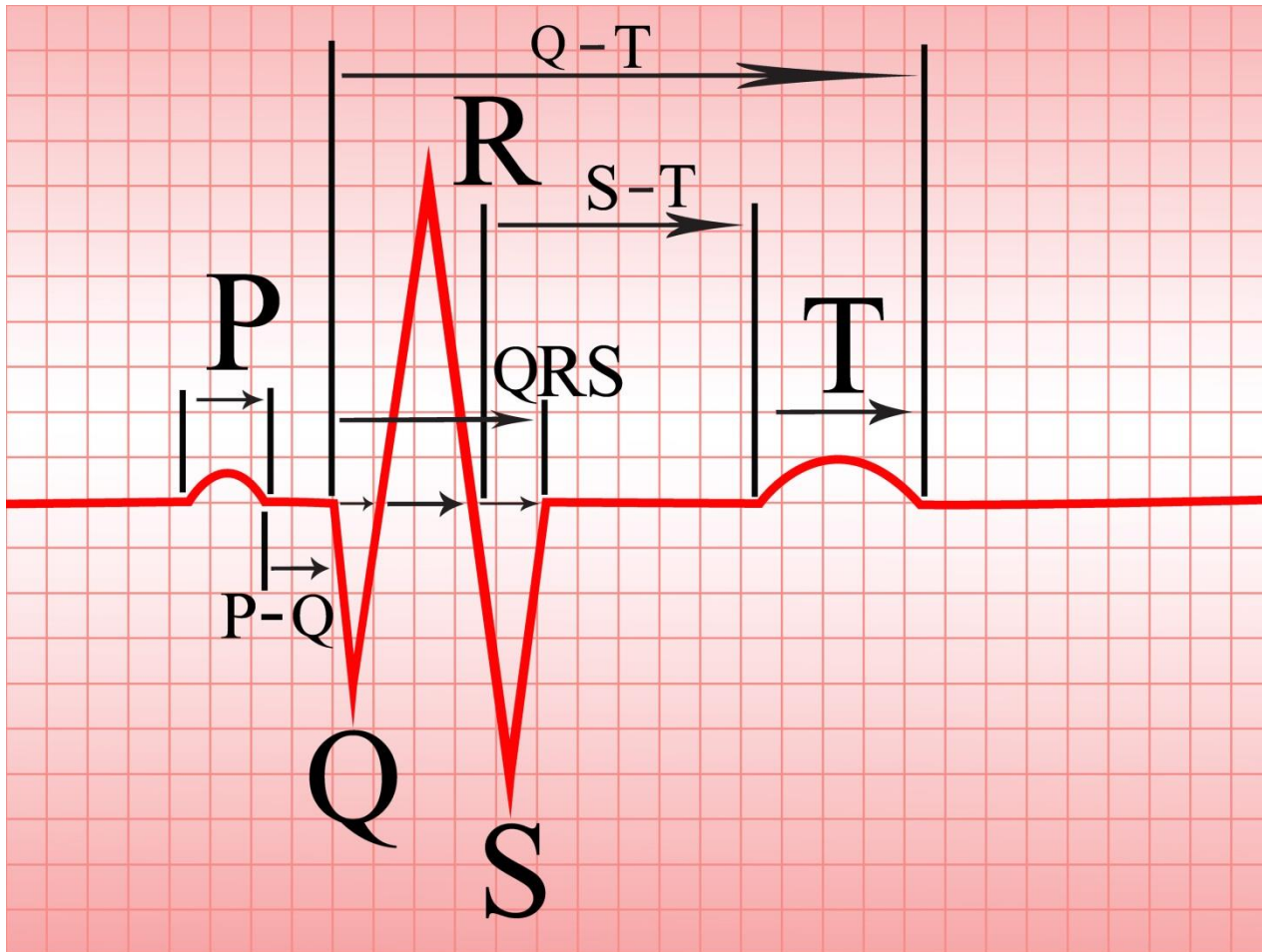
Example of Normal ECG



Some abnormal ECG are easier to detect than others



Quantification of ECG



Key features of the QT interval

- a. Not QT but QTc, corrected for heart rate.
- b. An increase in QTc is associated with
 - Mortality (all causes)
 - Sudden Death
- c. QT measurement is
 - Subjective
 - Imprecise
 - An extreme data reduction

Project 1: Improve Design & Analysis of Thorough QT Studies

- Lilly 2006 – 2007
- Postdoc, NISS staff, Lilly statisticians
- Correction for heart rate
- Adjustment for baseline(s)
- Mixed effects modeling of QTc

Closer Look at QT measurement

- a. $60 * 60 = 3,600$ observations / patient / hour.
- b. Conventional summary relies on a few selected heart beats.
- c. Automated QT measurement yields a time series for (QT, heart rate): all beats.

Project: 2: Description of ECG Changes

- Merck 2008
- Questions posed by Merck cardiologists
- Postdoc, NISS staff worked on research.
- Biologically interpretable summary of each beat
 - objective measure QT
- Show changes over time from 'reference beat' for each subject.
- Published Annals of Applied Statistics 2009

Publications and Invited Presentations (refereed)

- 1) Zhou, Y-C. and Sedransk, N. (2013). "A New Functional Data Based Biomarker for Modeling Cardiovascular Behavior." *Statistics in Medicine* 32: 1 153-164
- 2) Zhou, Y-C, and Sedransk, N. (2010) "Marking the Ends of T-waves: Algorithms and Experts." *Statistics in Biopharmaceutical Research* 2:3 359- 367.
- 3) Zhou, Y-C. and Sedransk, N. (2009). "Functional Data Analytic Approach of Modeling ECG T-wave shape to Measure Cardiovascular Behavior," *Annals of Applied Statistics* 3: 4 1382-1402.
- 4) Charles M. Beasley, Jr., Charles Benson, Jessie Q Xia, Stanley Young, *et al.* Systematic Decrements in QTc Between the First and Second Day of Contiguous Daily ECG Recordings Under Controlled Conditions. *Pacing and Clinical Electrophysiology*. doi: 10.1111/j.1540-8159.2011.03117.x
- 5) Charles M. Beasley, Jr., Charles Benson, Jessie Q Xia, Stanley Young, *et al.* Effect of Definition of Treatment Difference on QTc Evaluation. (to be submitted)
- 6) Jessie Q. Xia, Stanley S. Young, Nell Sedransk and Alex Dmitrienko, On the Design of Thorough QT Studies: A Simulation Study. *First International Symposium on Biopharmaceutical Statistics*, July 2008, Shanghai, China.