Retrospective Power

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1. I enjoy statistics policy things.

2. People trust me to be honest.

3. I don't like inefficiencies in design.

4. People expect others to act in good faith.

Through QT and Positive Control

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Points to make

0. Absolute vs Relative Comparisons

1. Statistical Sensitivity – retrospective power.

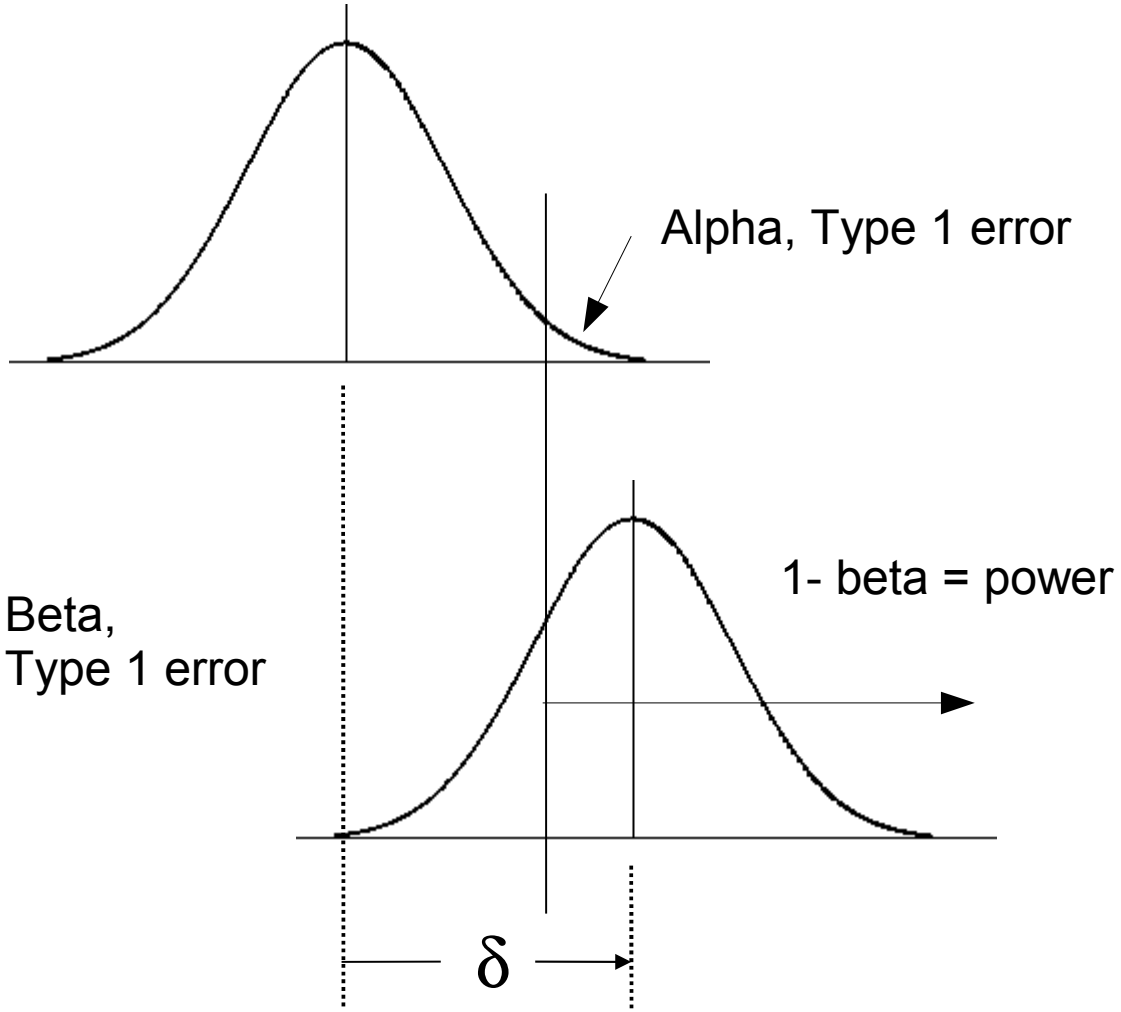
2. We are the target species.

3. Very few precedents for use of positive control.

4. hERG effects have been designed/selected out.
   (A hERG positive, positive control, is not likely to
   demonstrate sensitivity to a Non-hERG positive.

5. Ethincs. Why subject subjects to known + hERG?

Retrospective Power



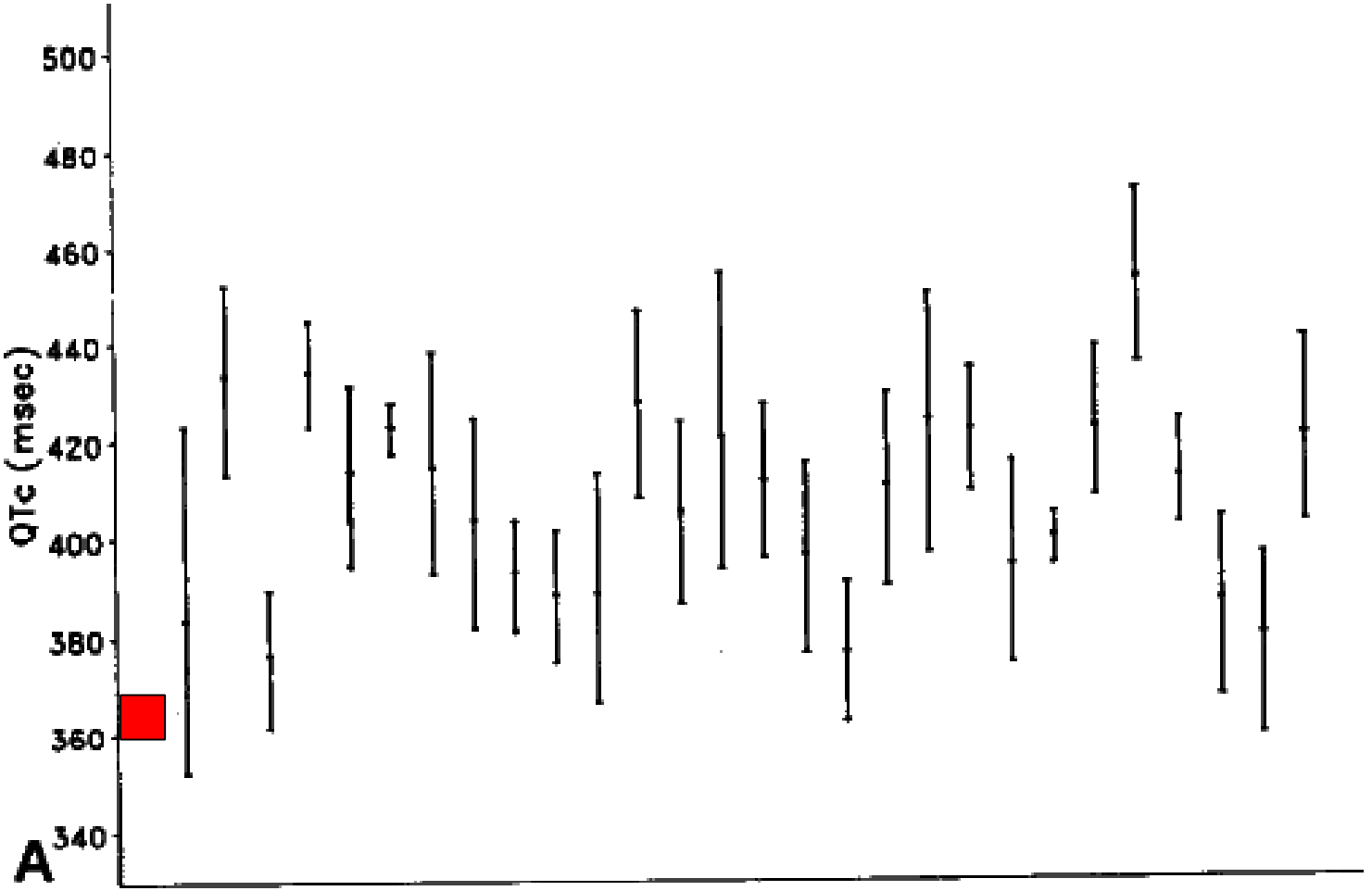
Comments

1. SDs known
2. n1, n2 known
3. Vary δ and compute
   1-beta = Power.

Design

1. Minimize SD
2. Determine n's
   to detect δ
3. Covariate adjust

Real QT variation, normals



Variability within and between humans for QT is large.

Anti-psychotic examples
FDA dictated Pfizer study

Drug[a]	Baseline Mean	Change at Steady State Mean	Change at Steady State 95% CI
Ziprasidone (N=31)	402.1	20.3	14.2 to 26.4
Risperidone (N=20)	396.3	11.6	7.4 to 15.8
Olanzapine (N=24)	397.9	6.8	0.8 to 12.7
Quetiapine (N=27)	398.0	14.5	9.5 to 19.5
Thioridazine (N=30)	395.9	35.6	30.5 to 40.7
Haloperidol (N=20)	394.7	4.7	–2.0 to 11.3

(Some deaths with Thiordiazine.)

Therefore set δ at 15-20 msec.

~5 msec Bias

Systematic Decrements in QTc between the First and Second Day of Contiguous Daily ECG Recordings under Controlled Conditions

CHARLES M. BEASLEY, JR., M.D.,* CHARLES BENSON, M.D., PH.D.,* JESSIE Q. XIA, PH.D.,† S. STANLEY YOUNG, PH.D.,† HARRY HABER, M.P.H.,*,‡ MALCOLM I. MITCHELL, M.B.B.S., M.F.P.M.,* and CORINA LOGHIN, M.D.*

In two well-conducted studies unexpected bias occurred of the same magnitude as size target effect size, 4.2 vs 5.0 msec.

Comment from chemist

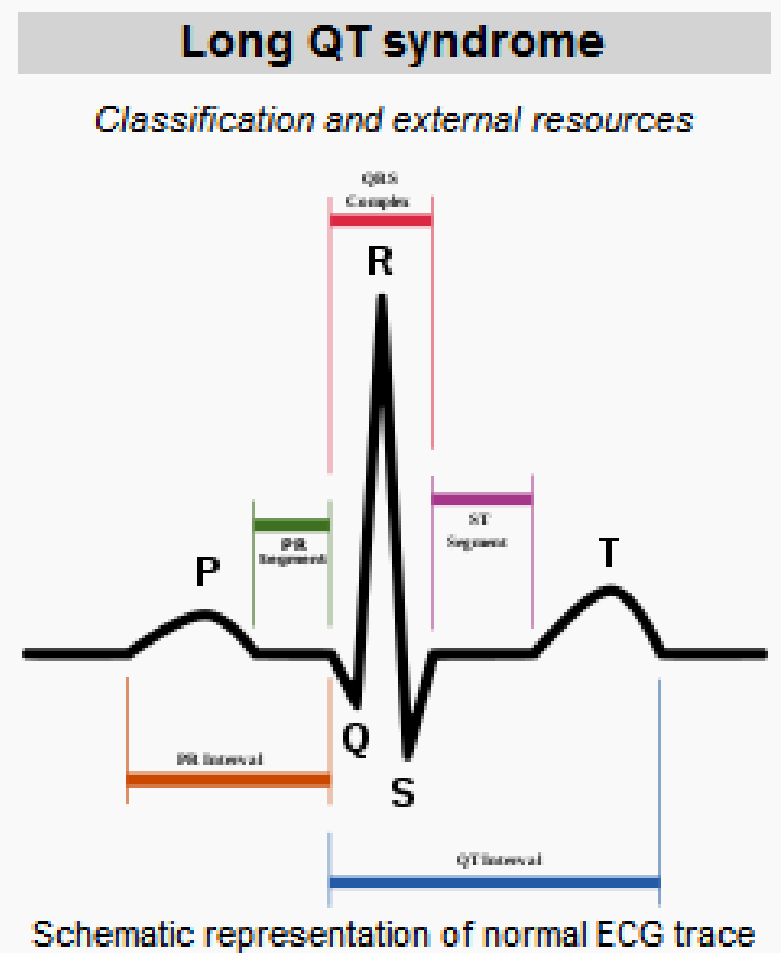
HERG is well studied.

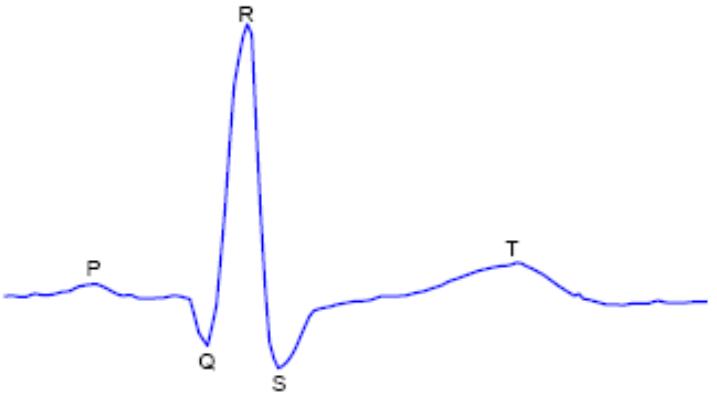
Med chemists have pretty good strategies that are tried routinely.

Strategies include removing the often present basic nitrogen, increasing polarity (e.g add an acid), or making key nitrogens less basic with electron withdrawing groups.

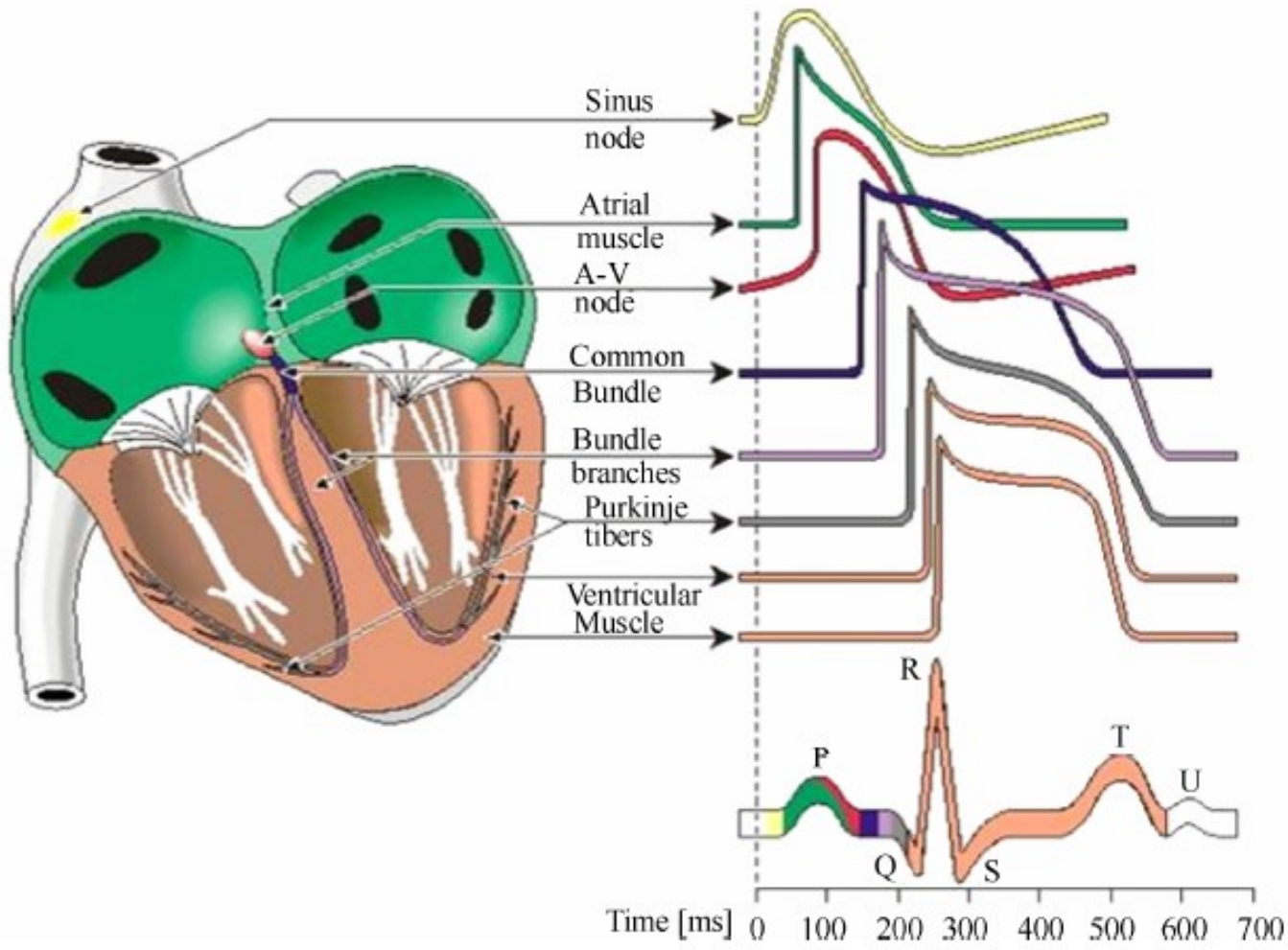
SSY: hERG is designed out. Any QT effect it is unlikely due to hERG.

Textbook versus Reality

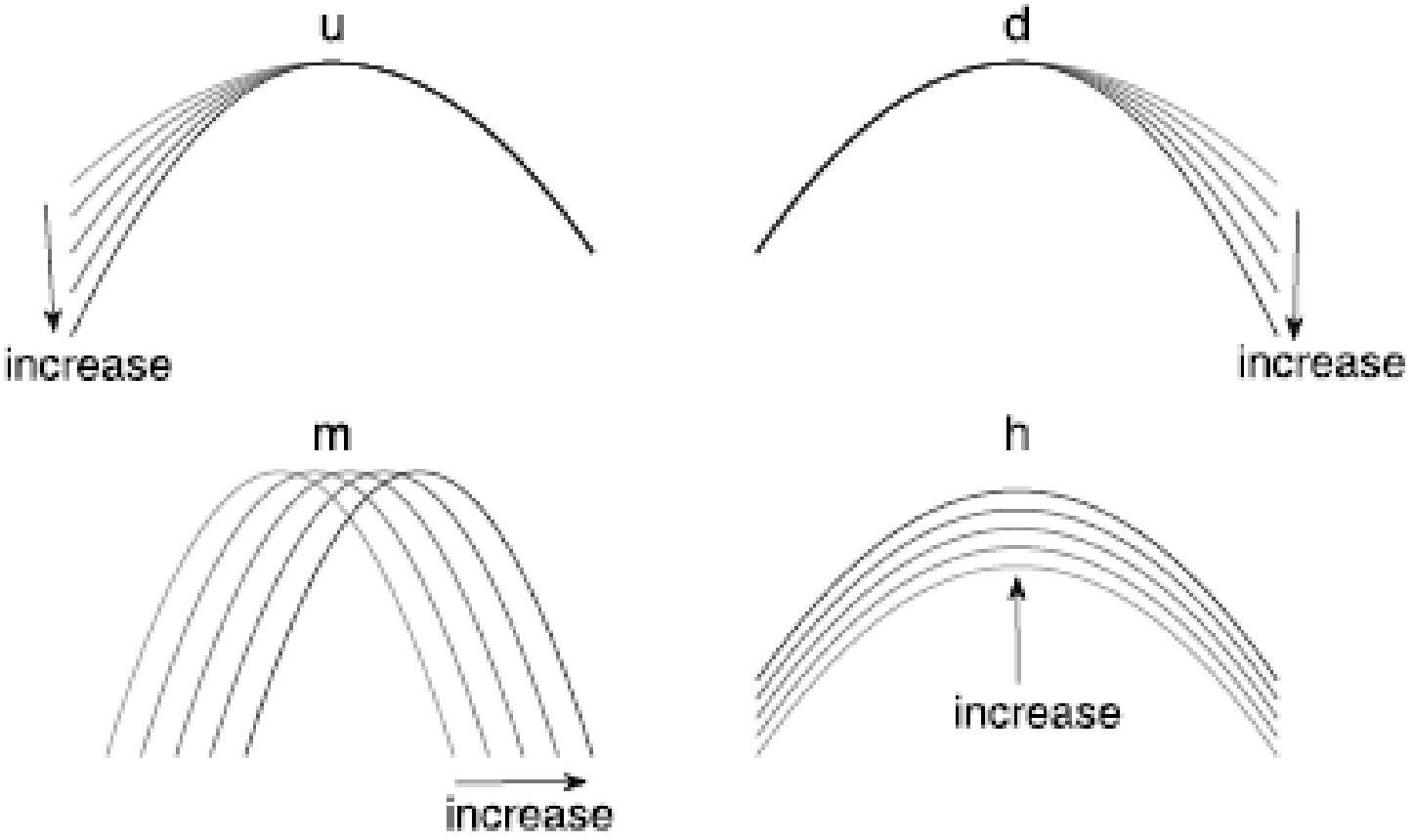




The heart is complex

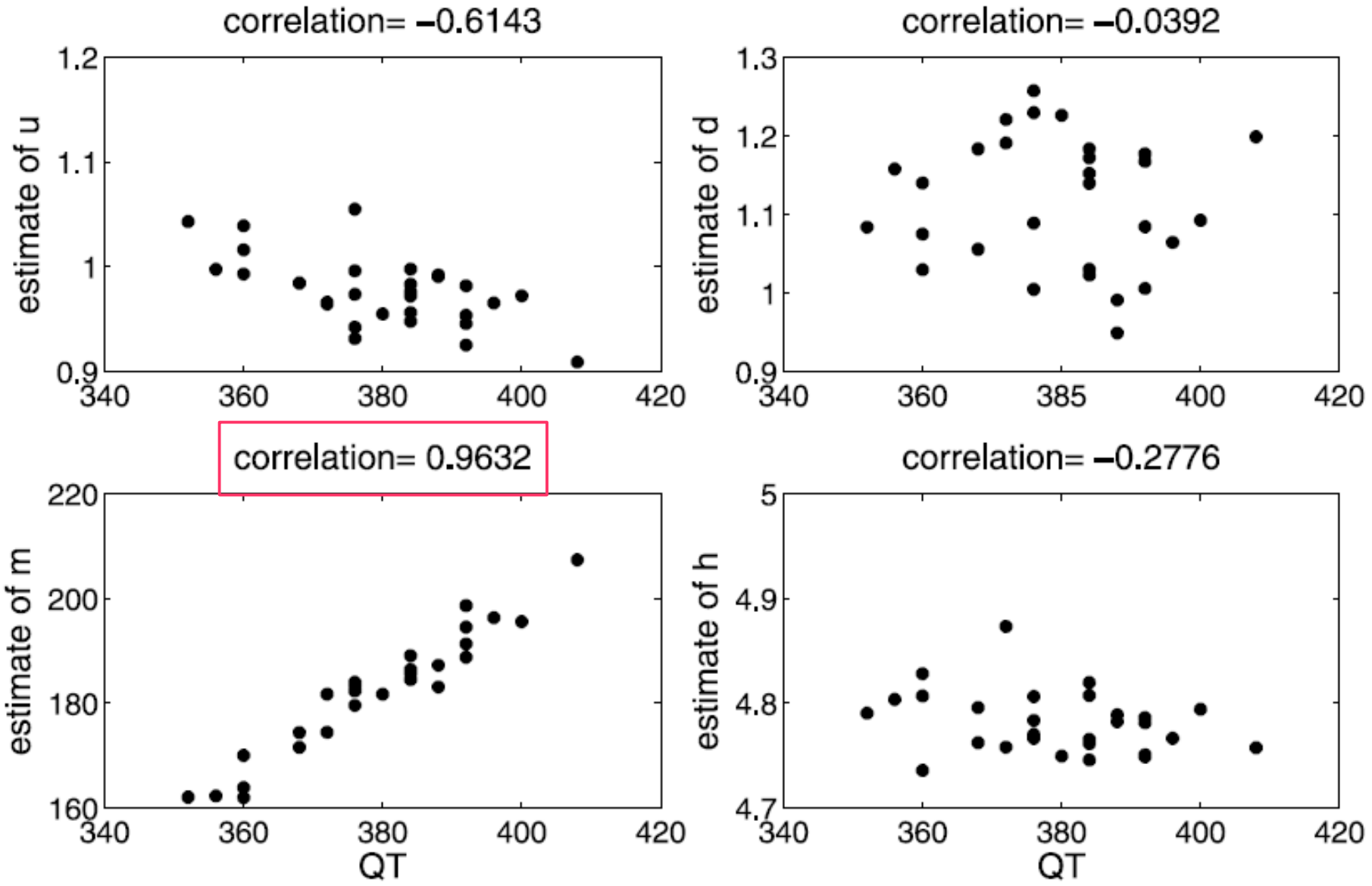


Four parameters for “t”
up, down, max location, height



Zhou, Sedransk 2009 NISS

u, d, h, m relation to QT



What matters?

- Absolute magnitude
- Outside personal range
- Some feature of wave form
- Interaction with nutrition
- Interaction with genetics
- Interaction with other drugs
- Etc.

We really don't know.

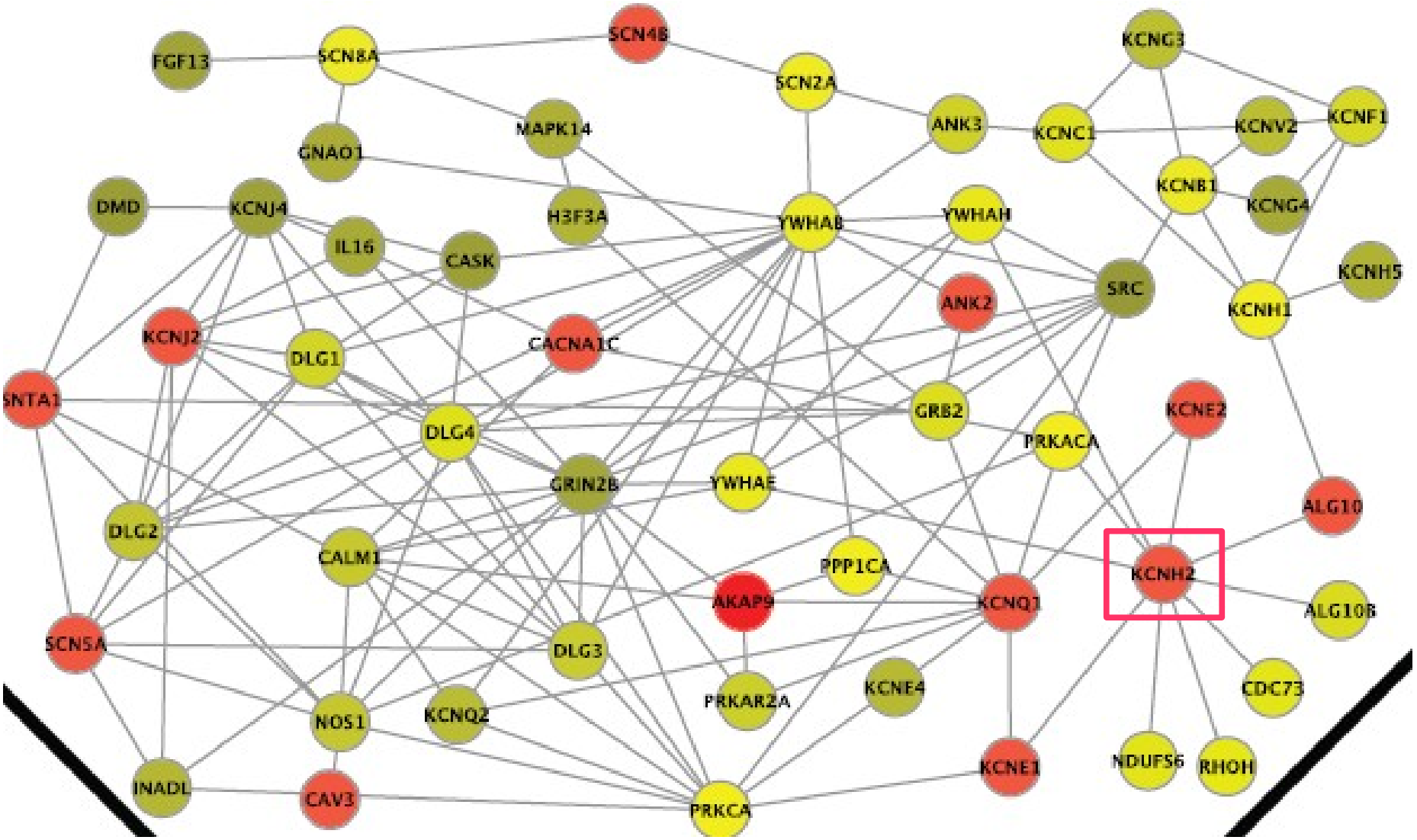
Need good faith on both sides

- Multiple testing
- Continued use of positive control
- Setting Mean at 5msec and UB at 10 msec (any small bias will mess things up/too conservative)
- Correction formula
- Select single time point based on blood levels
- Selection of two points, QT, likely stifled innovation

Contact info : young @ niss.org

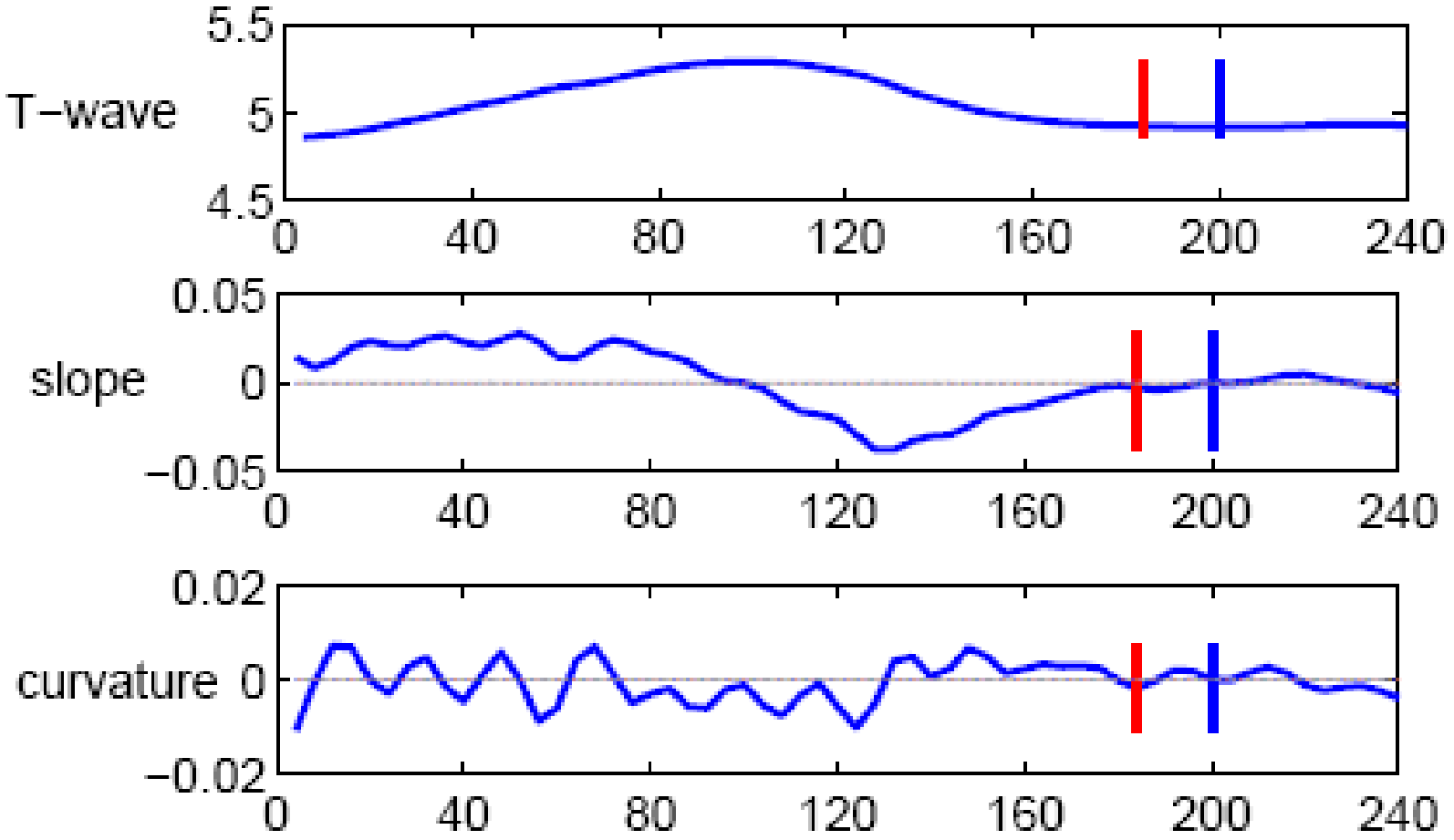
Ask for short written summary.

Gene Network



Only 2 of the 81 QT-prolonging drugs with targets in the neighborhood had KCNH2 as their only target in the neighborhood.

Expert Variability for End of T



Zhou and Sedransk