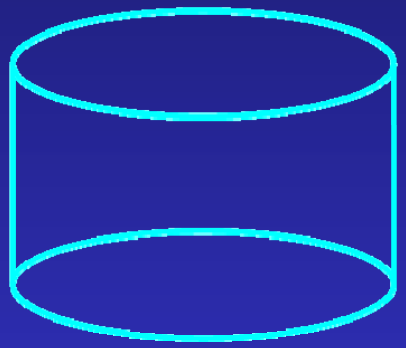
The Holter bin approach and beyond

Fabio Badilini, PhD
AMPS LLC, New York, USA
Pierre Maison-Blanche, MD
Hopital Lariboisiere, Paris, France

Outlines

- Background of quantitative digital ECG
- The rate RR bin approach in depth
- Results of RR bin from different trials
- Rate-bin versus Time-bin
- Coping with Hysteresis phenomenon

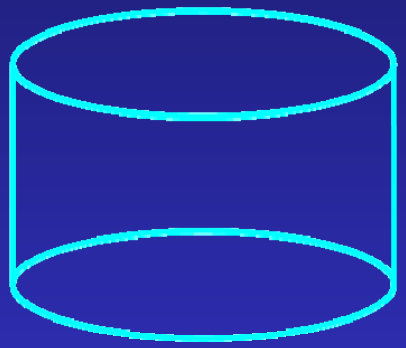
« Binning » a Gold Standard in Digital Electrocardiography



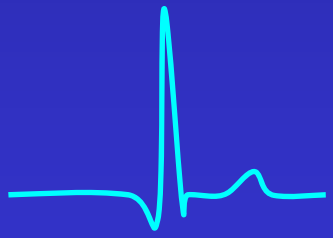
« bin » : a box used for storage

Digital cardiac waveform stored in « bin »

« Binning » a Gold Standard in Digital Electrocardiography



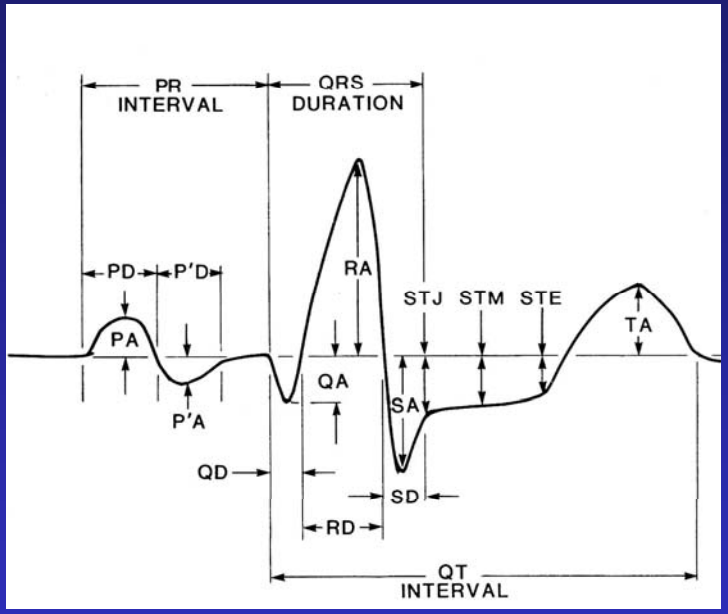
« bin » : a box used for storage



Digital cardiac waveform stored in « bin »

- What is an ECG Bin ?
- It is a digital box in which one does stires ECG waveforms

Quantitative Digital Electrocardiography Objectives



Wave measurement, all leads

Matrix of measurements

Diagnosis

	PA	PPA	QA	QD	RA	RD	SA	SD	RPA	RPD	SPA	STJ	STM	STE	TA	TPA
V1	53	−73	0	0	234	29	839	59	0	0	0	−49	43	58	63	0
V2	53	−29	0	0	332	37	1035	51	0	0	0	−54	58	112	263	0
V3	68	0	0	0	341	41	605	47	0	0	0	−25	39	78	219	0
V4	68	0	0	0	410	46	253	42	0	0	0	0	24	48	190	0
V5	73	0	0	0	668	88	0	0	0	0	0	39	24	34	170	0
V6	63	0	53	20	708	68	0	0	0	0	0	58	19	24	131	0
I	68	0	87	22	766	66	0	0	0	0	0	19	4	9	112	0
aVL	−14	48	78	22	522	37	136	29	0	0	0	−20	−10	−5	43	0
II	102	0	14	19	517	69	0	0	0	0	0	83	29	29	146	0
aVF	73	0	0	0	29	24	34	9	356	55	0	73	29	24	92	0
III	53	−29	0	0	73	23	278	30	312	35	0	63	24	19	0	0
aVR	−83	0	0	0	48	21	629	67	0	0	0	−54	−20	−20	−131	0

On an average waveform ECG algorithms are making some measurements, then providing a matrix, from which automated diagnoses are extracted

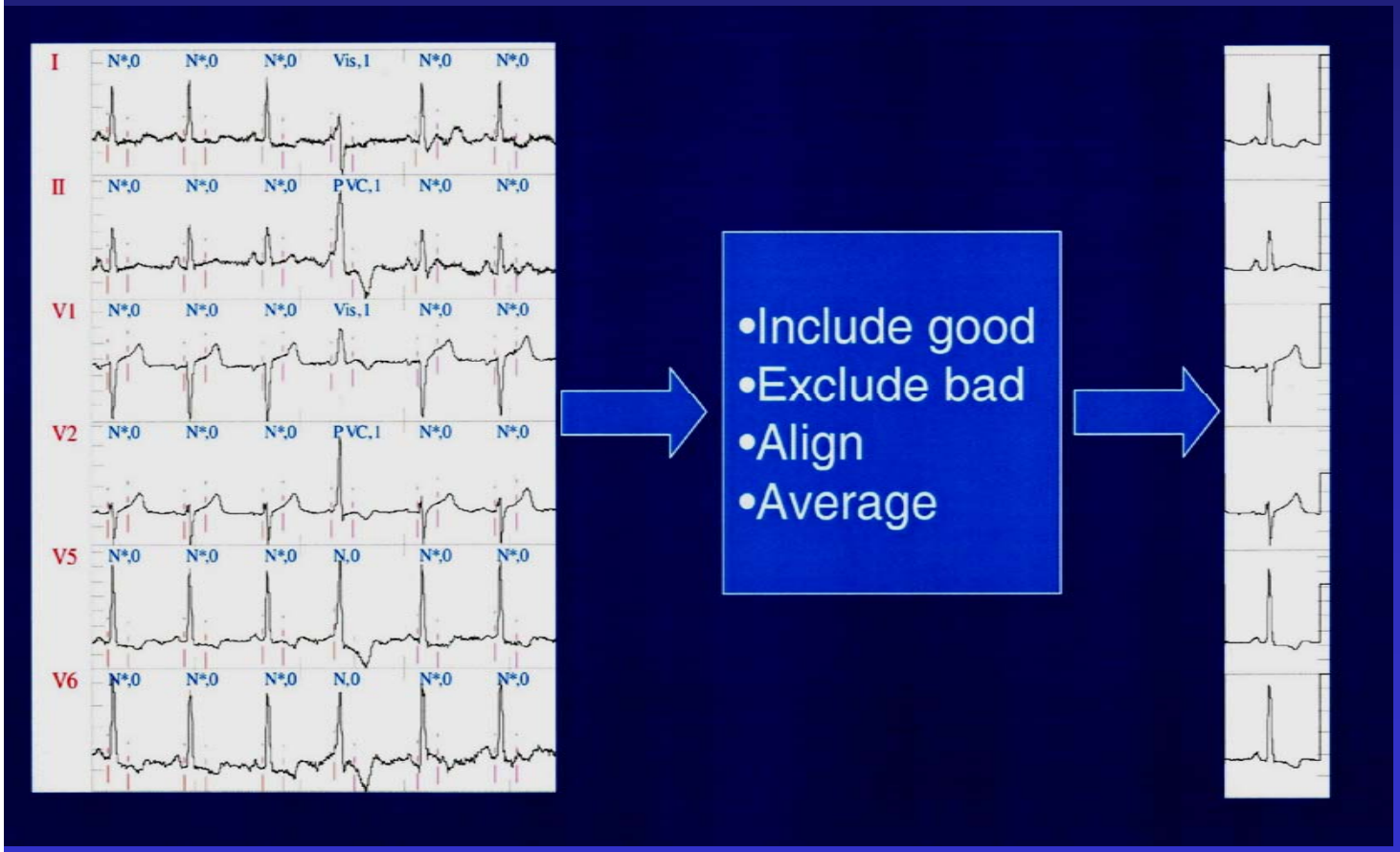
Quantitative Digital Electrocardiography
3 strategies for analysis

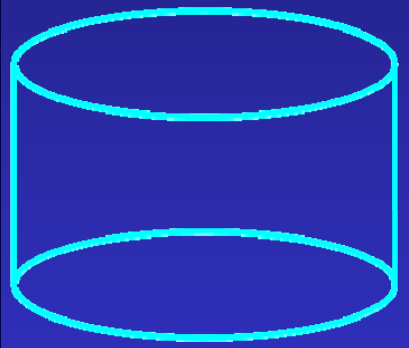
- « best complex » for analysis, the one with the least noise and baseline wander
- Analysis of every complex and subsequently averaging of measurements
- Averaging of *all complexes morphologically of the same type*, « binning » or « representative beat formation »

Inside a bin, there are 3 strategies as shown in previous slide, dealing with the cardiac beats stored in the bin

Our approach is the third one, ECG averaging of all complexes morphologically of the same type

Representative Beat Formation



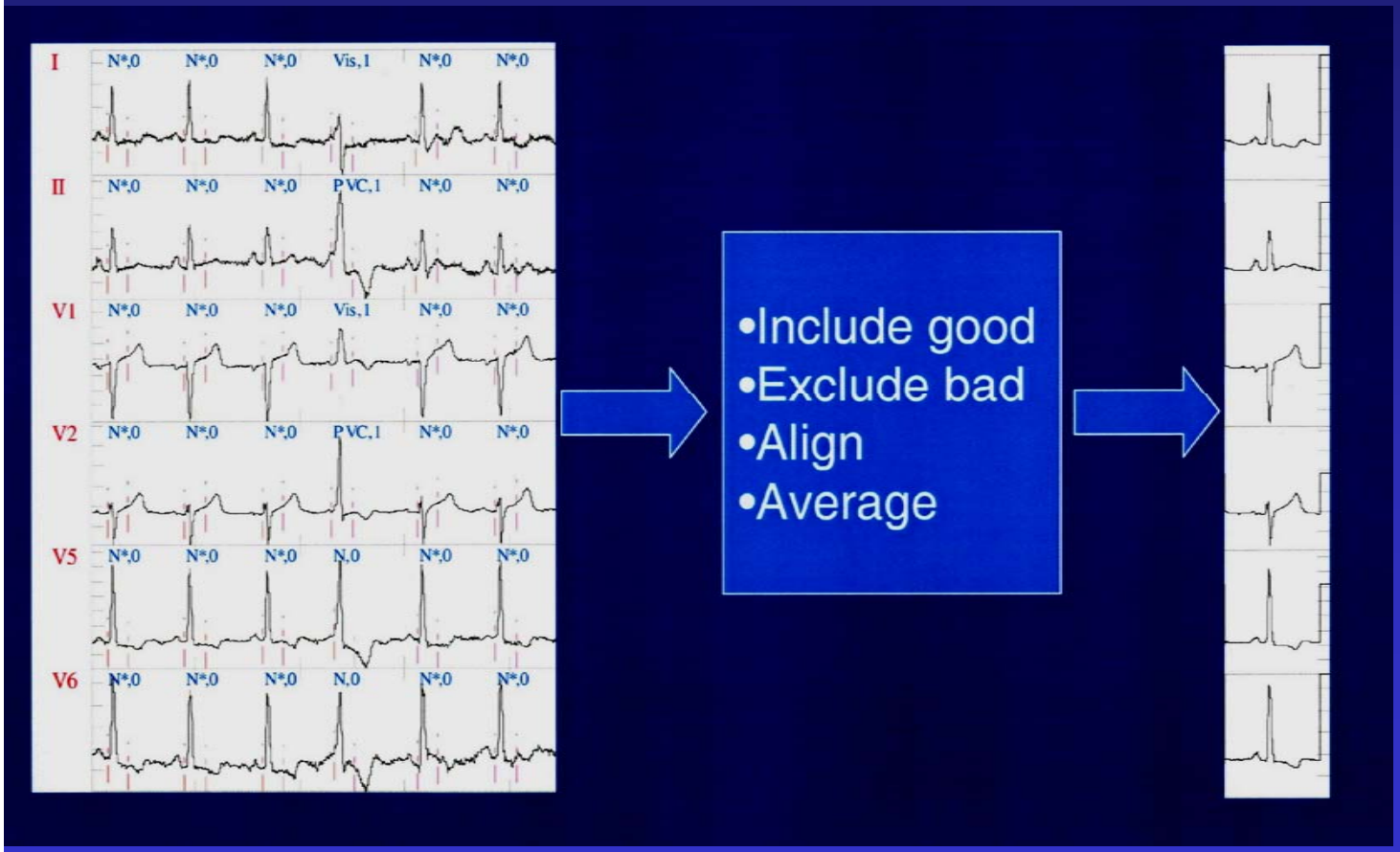


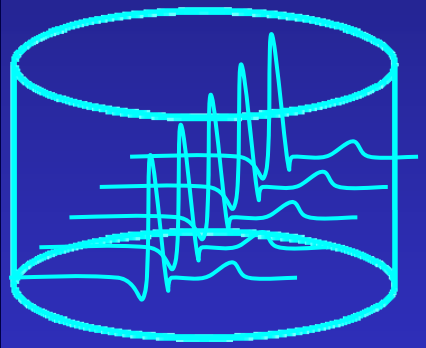
10 second « bin »

08:00 AM

10-second digital ECG recording

Representative Beat Formation





10 second « bin »

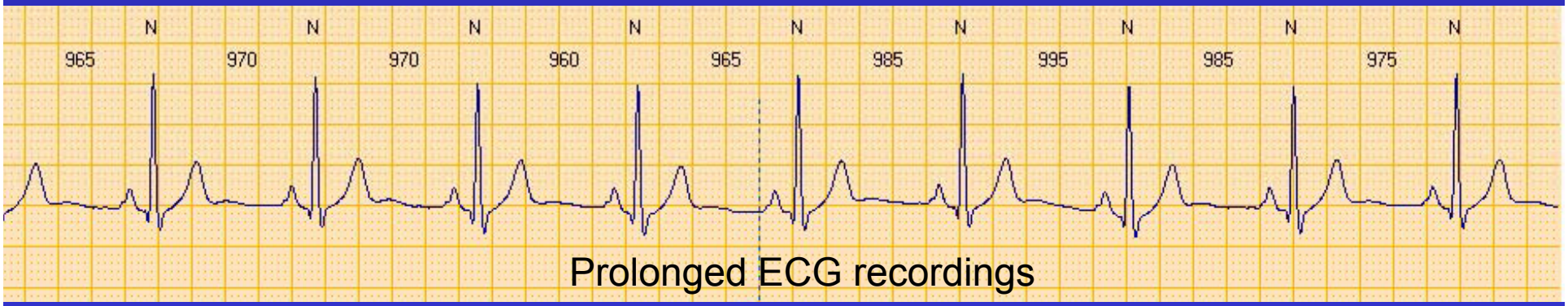
08:00 AM

10-second digital ECG recording

- You can see in the previous slide another illustration of the averaging process inside a bin
- Include good (sinus) complexes
- Reject others (VPBs, artifacts, noisy complexes …)

Representative Beat Formation
Other rules

- By rate
- By autonomics (circadian periods)
- By physical activity (exercise, recovery)
- By rate x autonomics
- By rate x physical activity



Prolonged ECG recordings

- How to store cardiac beats in a bin from long term Holter recordings ?

- 1 - as said in the previous slide, because they are all the same morphologically
- 2 - by rate in another rule
- 3 - by autonomics, for instance diurnal bins against nocturnal bins
- 4 - and combination of diiferent rules

Representative Beat Formation, by rate

900 msec

900 msec

900 msec

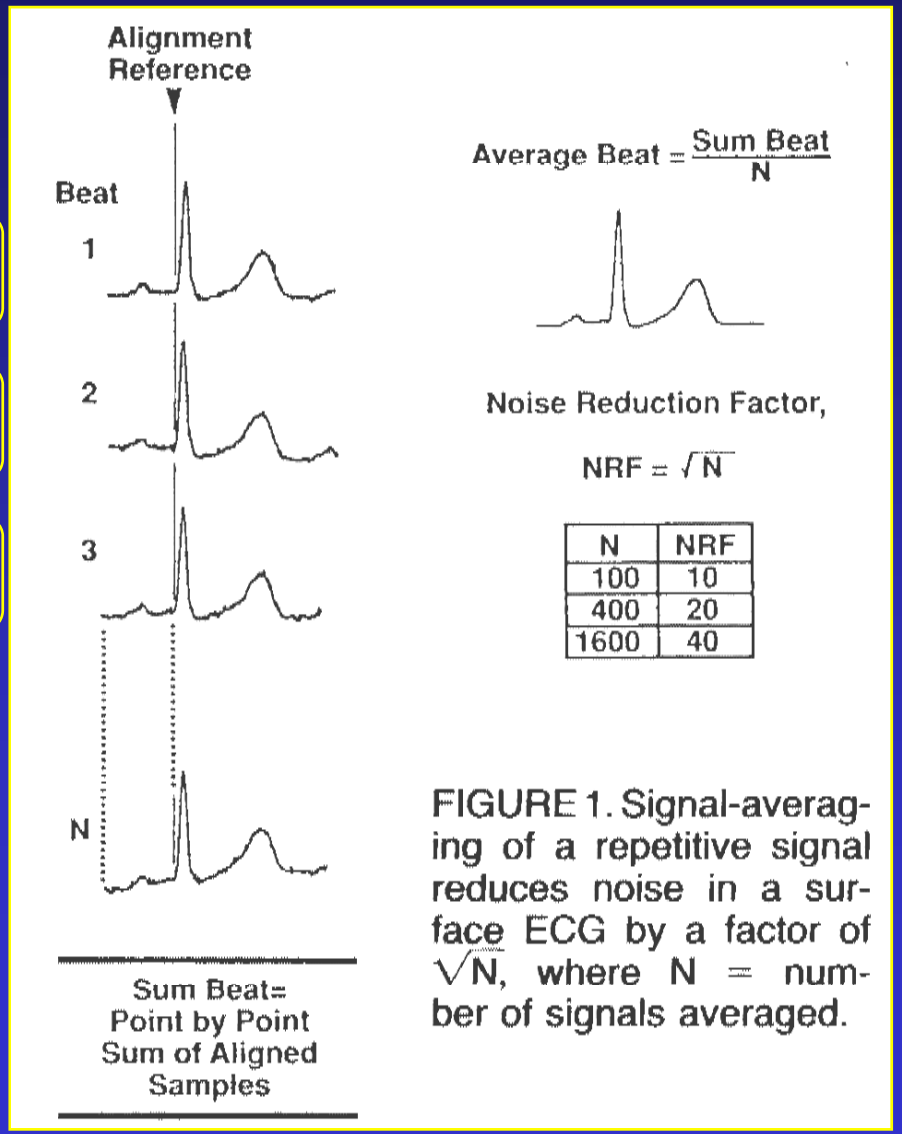
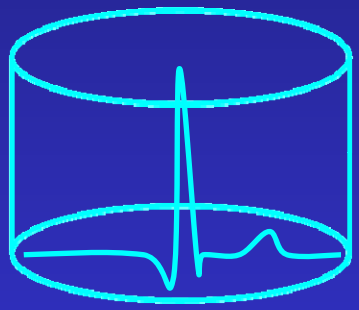


FIGURE 1. Signal-averaging of a repetitive signal reduces noise in a surface ECG by a factor of $\sqrt{N}$, where N = number of signals averaged.

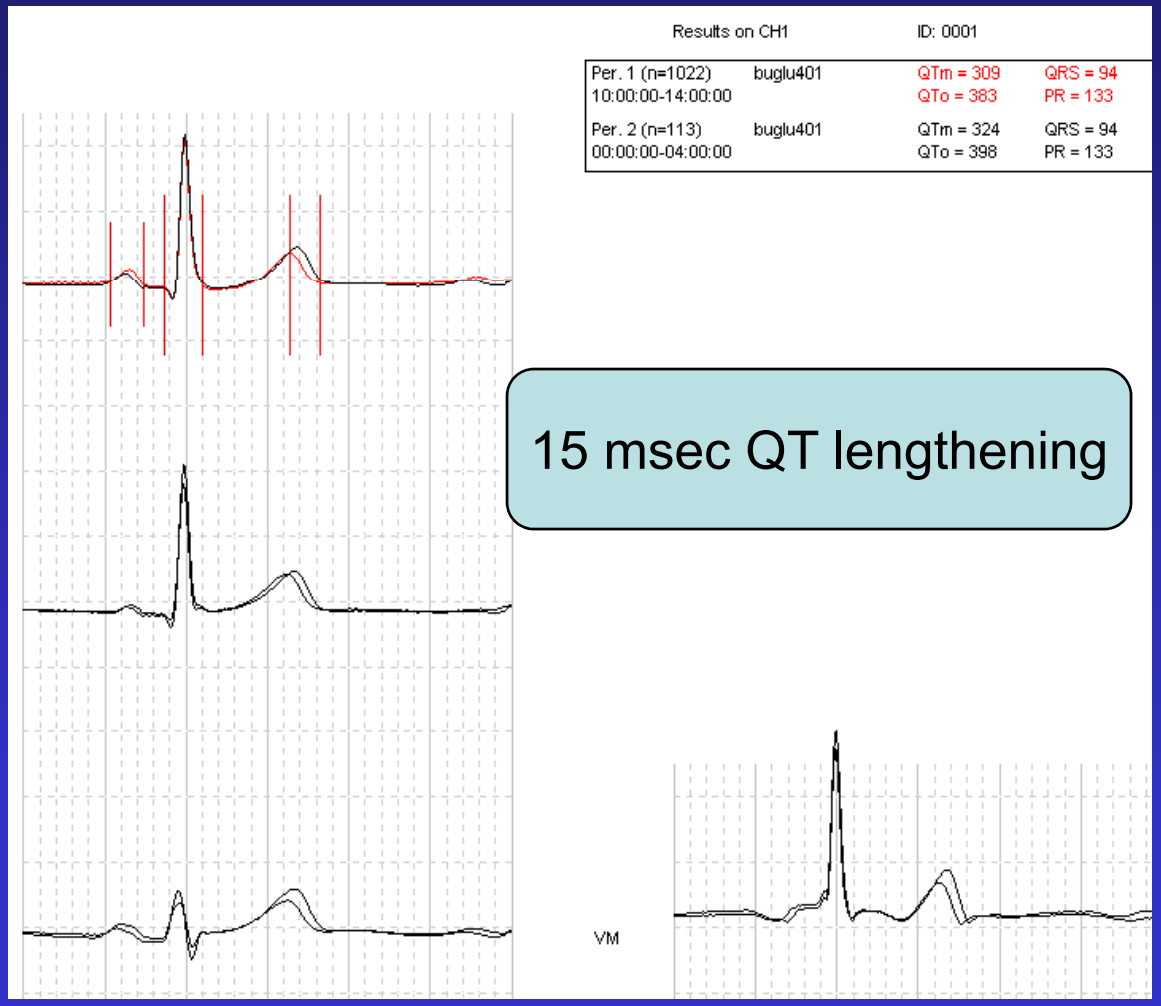


RR 900 bin

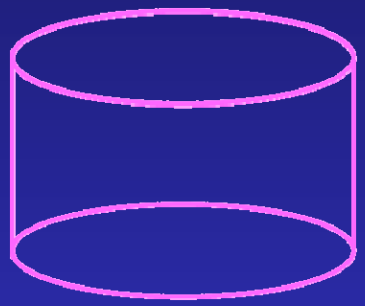
After S Reddy et al

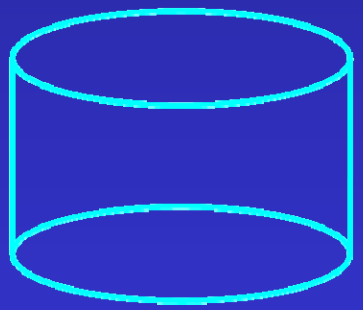
- 3 beats, all preceded by an RR interval of 900 msec
- Binning creates a « 900 msec » bin
- Averaging improves the signal to noise ratio

Circadian Periods x Rate



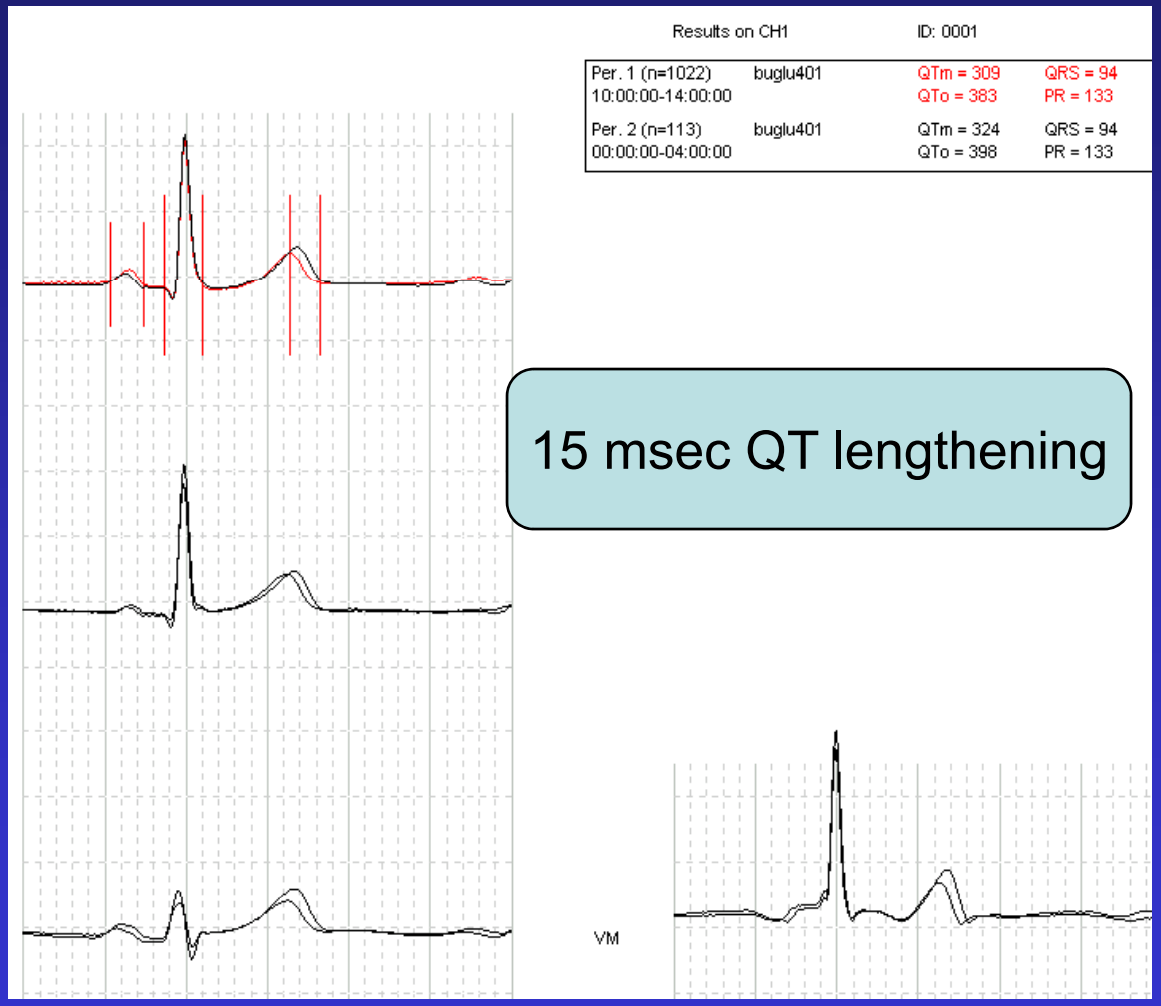
Day bin, RR 800



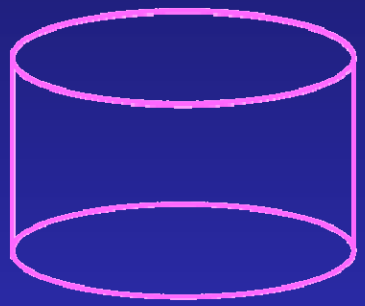


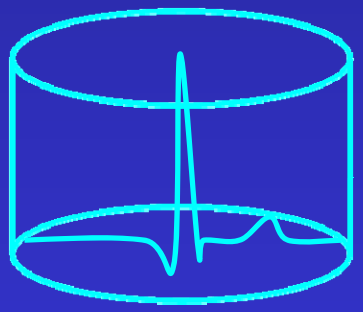
Night bin, RR 800

Circadian Periods x Rate



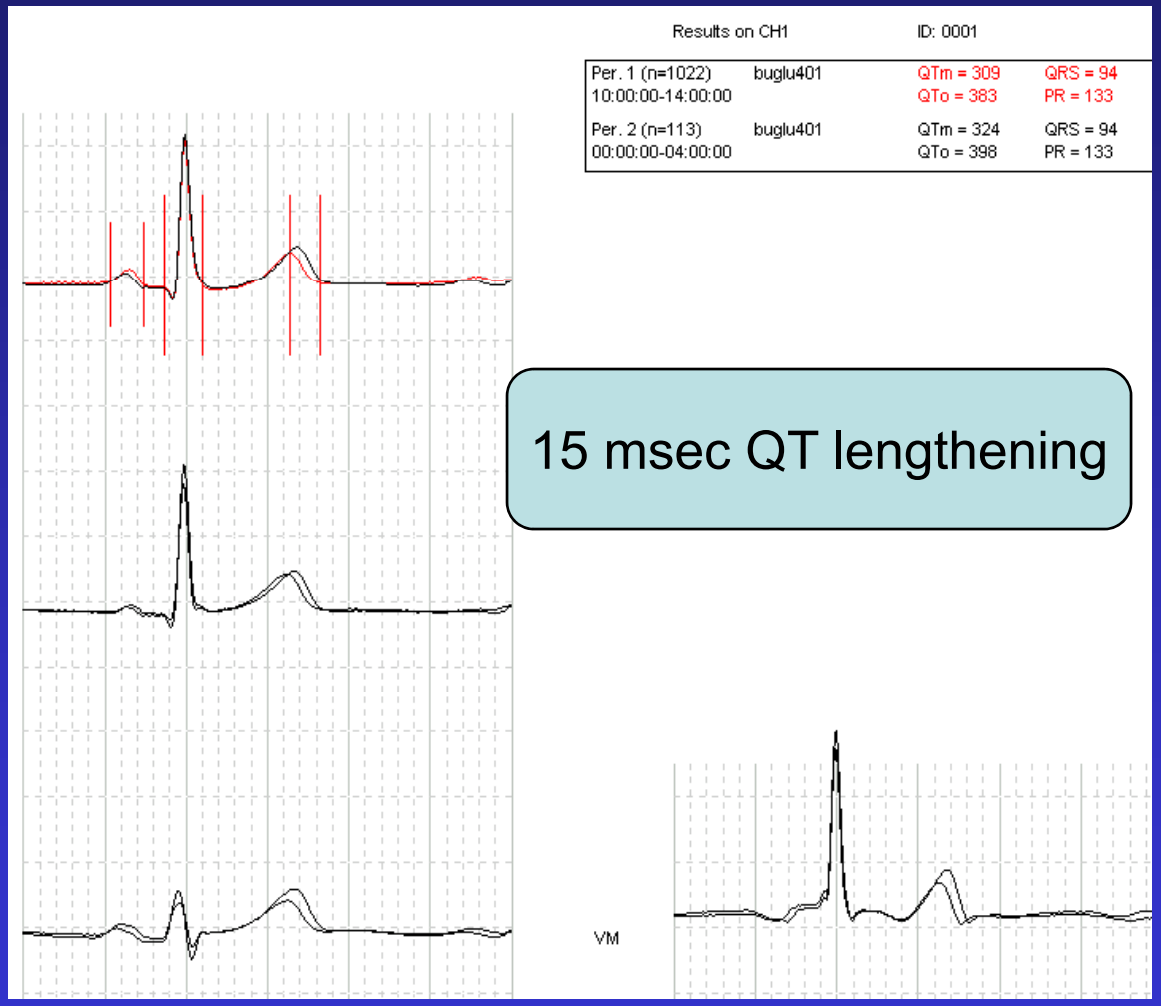
Day bin, RR 800



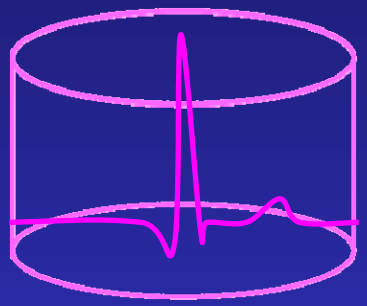


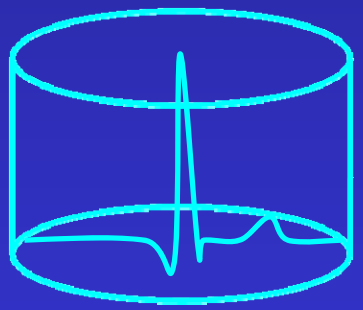
Night bin, RR 800

Circadian Periods x Rate



Day bin, RR 800

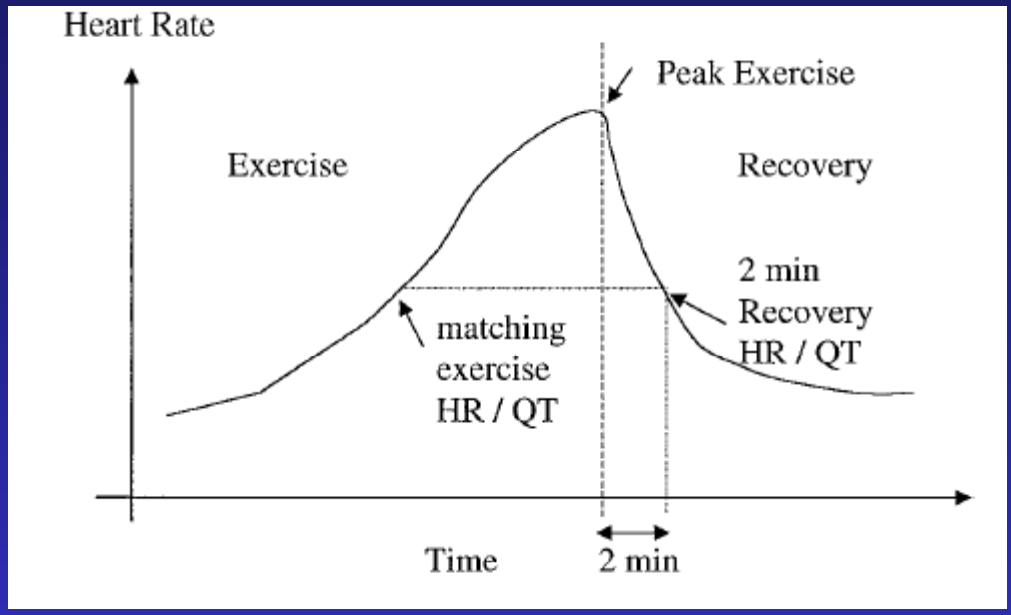


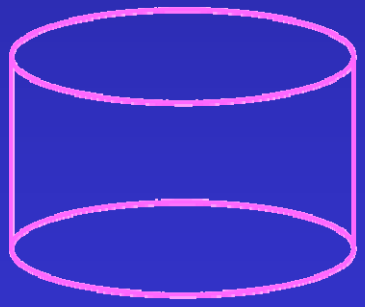


Night bin, RR 800

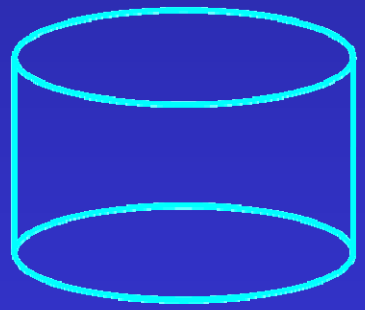
- Same concept, twice from Holter
- Binning at 800 msec, separately during the day and during the night

Physical Activity x Rate





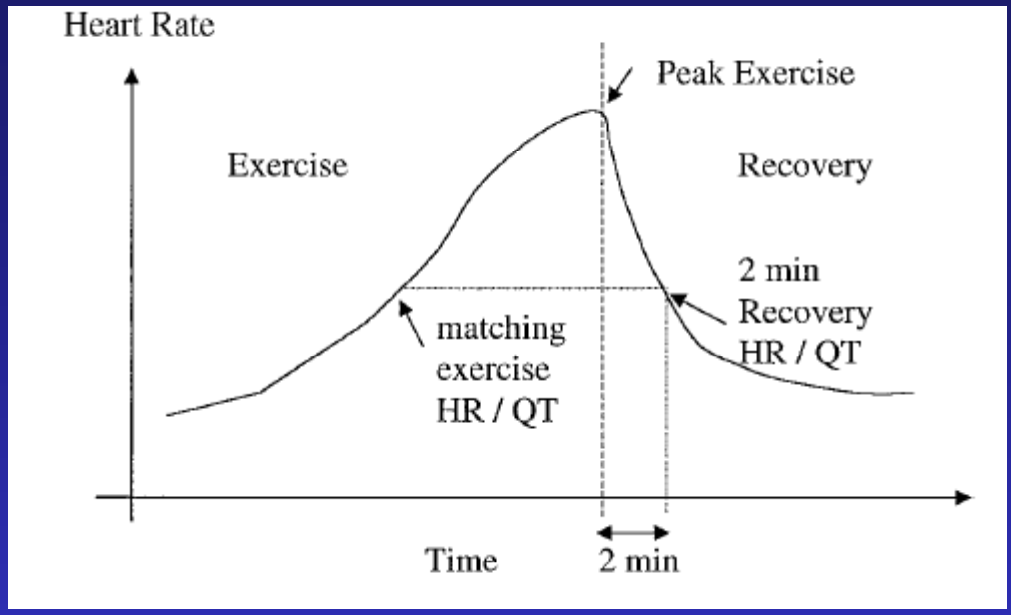
Exercise bin 80 bpm

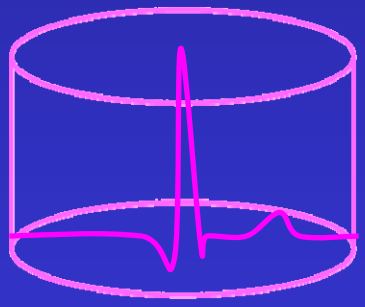


Recovery bin 80 bpm

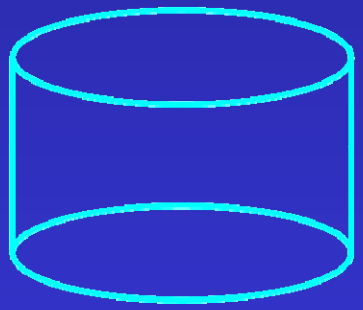
After Krahn *Am Heart J 2002*

Physical Activity x Rate





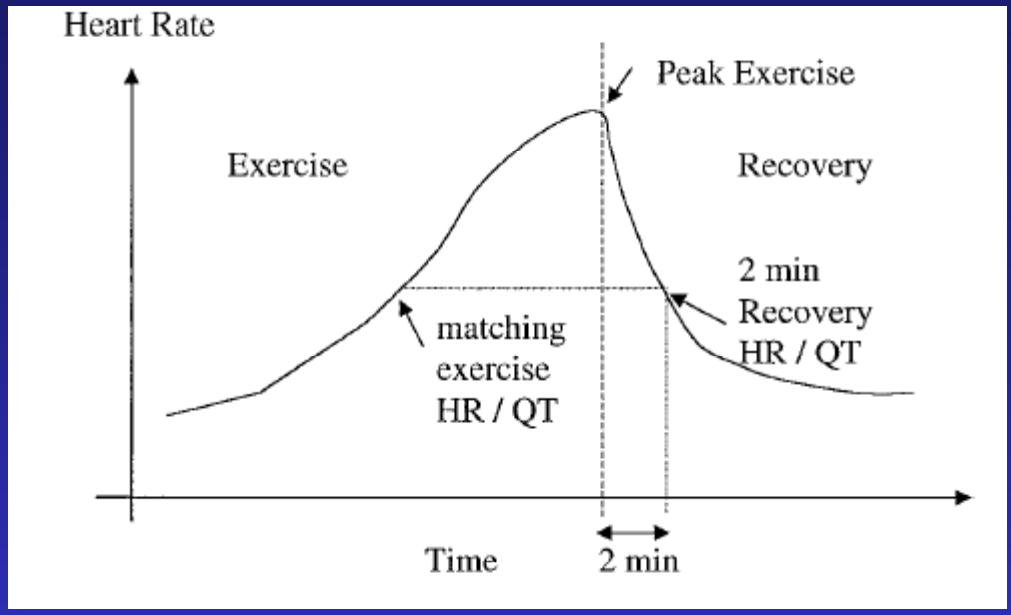
Exercise bin 80 bpm

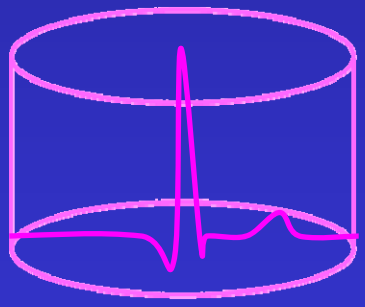


Recovery bin 80 bpm

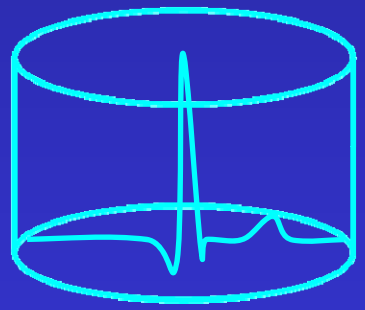
After Krahn *Am Heart J 2002*

Physical Activity x Rate





Exercise bin 80 bpm



Recovery bin 80 bpm

After Krahn *Am Heart J 2002*

Another example frequently used in the litterature, to explore the so called « hysteresis » phenomenon during exercise testng

Say we are looking at an heart rate of 80 bpm

Which is obtained twice, the first one during exercise AND during recovery

Two ECG bins

Overview of the Holter Bin Method

- Patient specific, rate-independent approach of time matched ECGs
- Wide range of RR interval explored for each subject allowing: direct comparison of QT at the same HR between placebo and drug, development of QT/RR regression model
- Control rather than correct for HR

A Key feature of the Holter bin method is that it allows to control, rather than correct for heart rate variations.

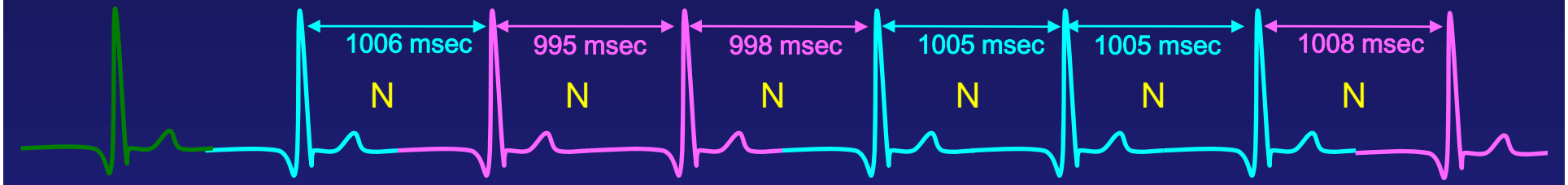
Furthermore, by allowing the exploration of a wide range of RR interval for each subject, it is possible either to directly compare QT at the same heart rate between placebo and drug, without any model assumption, and/or to develop QT / RR regression model, as shown in the next slide.

Holter Bin Method: a 3-step process

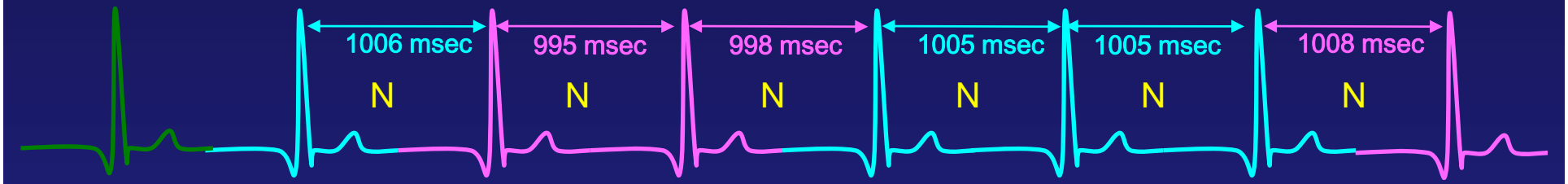
1. Sinus complexes detected and edited from Holter data of each subject are:
   - 1-Sorted by calculated RR intervals
   - 2-Arranged in successive RR categories (bins) of 10 msec
   - With or without control for hysteresis
2. For each RR bin, signal averaged waveforms are derived
3. QT interval (or other parameters) measured for each bin

1. RR interval measurement

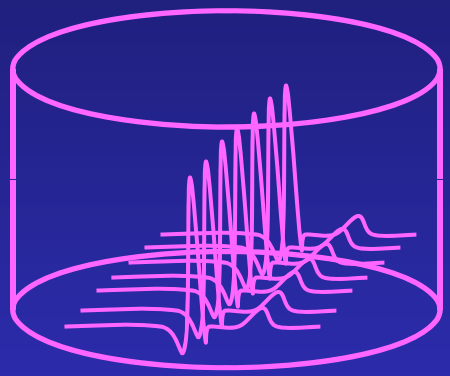
1. RR interval measurement



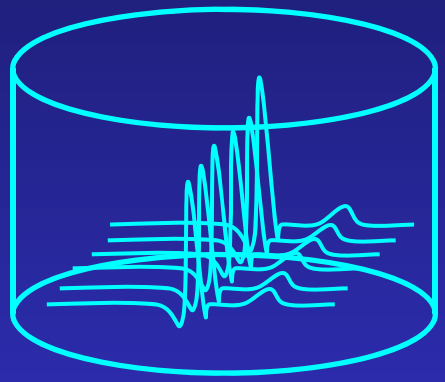
1. RR interval measurement



2. Classification of ECG complexes into 10ms groups (« Bins »)

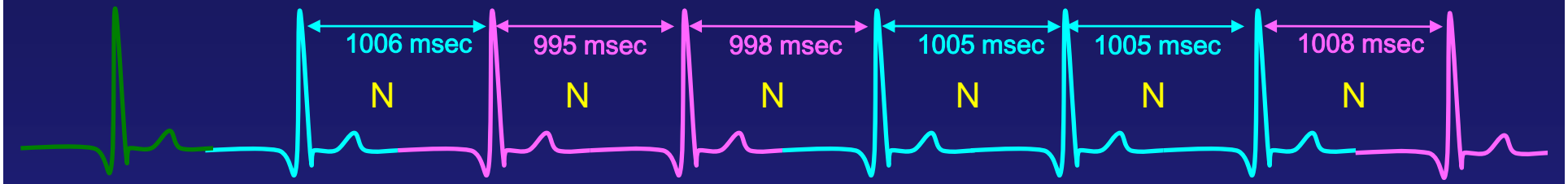


1000msec RR Bin



1010msec RR Bin

1. RR interval measurement



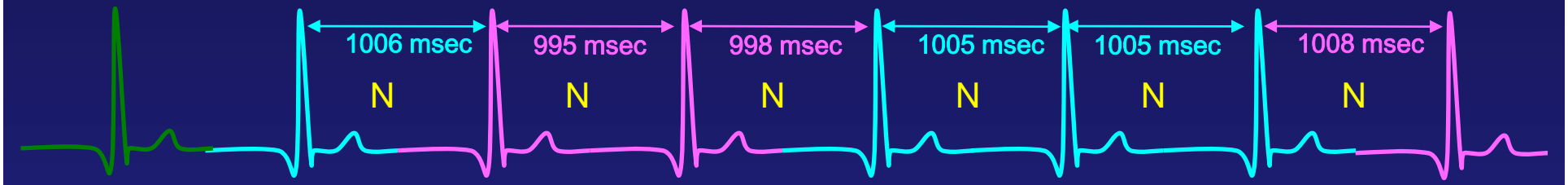
2. Classification of ECG complexes into 10ms groups (« Bins »)

1000msec RR Bin

1010msec RR Bin

3. Averaging of complexes and measurement of QT intervals

1. RR interval measurement



2. Classification of ECG complexes into 10ms groups (« Bins »)

1000msec RR Bin

1010msec RR Bin

3. Averaging of complexes and measurement of QT intervals

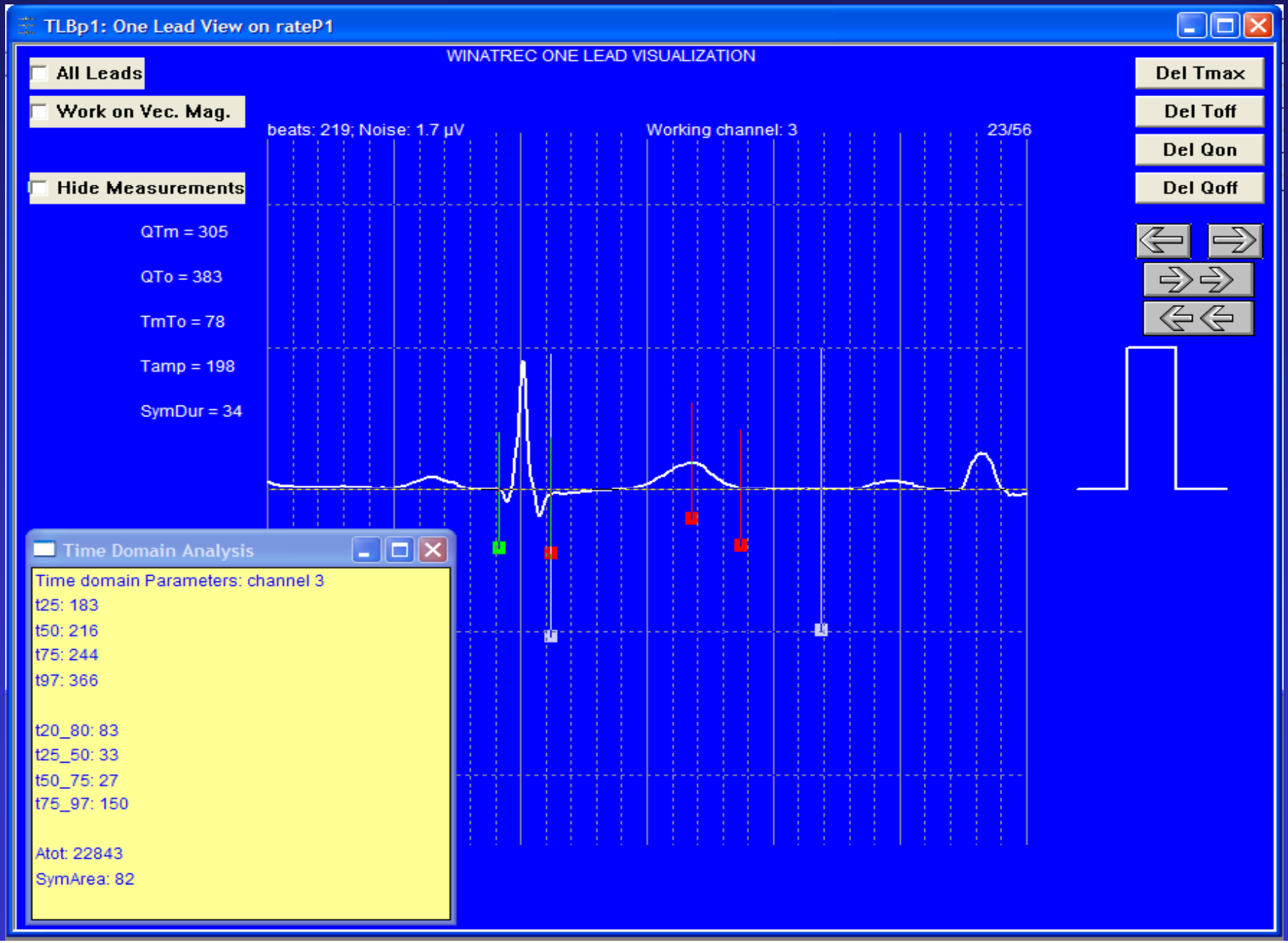
QT_{1000}

QT_{1010}

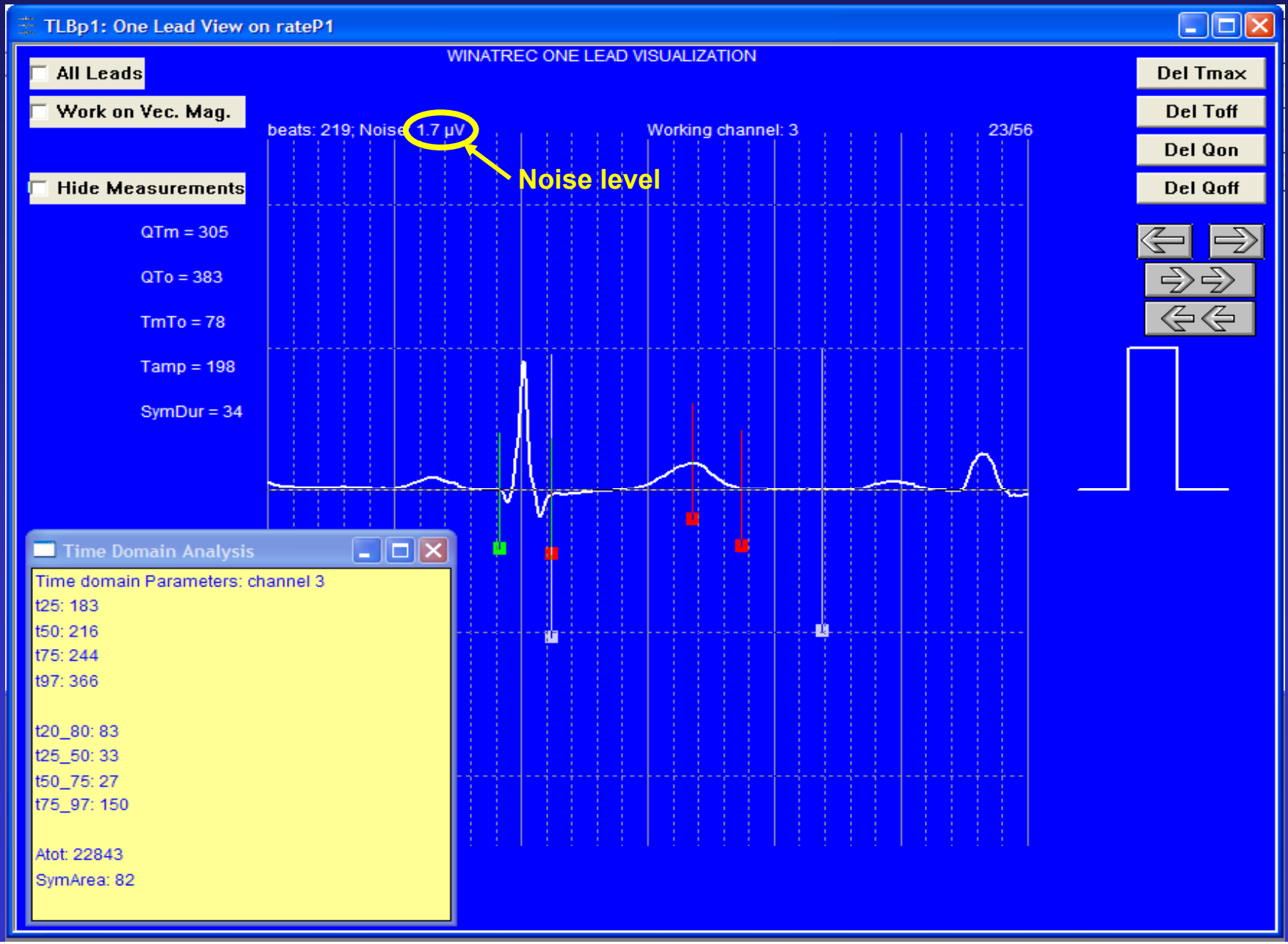
- Holter bin approach consists of three steps, illustrated here (see previous slides):
  1. Sinus complexes are isolated and sorted by RR intervals, then grouped into 10 msec categories (« bins »)
  2. For each RR bin, signal averaged waveforms are derived
  3. QT interval is measured for each RR bin

- Measurement is performed manually and annotated waveforms with fiduciary marks are stored in a digital database. Reader is blinded to treatment assignment and study period.

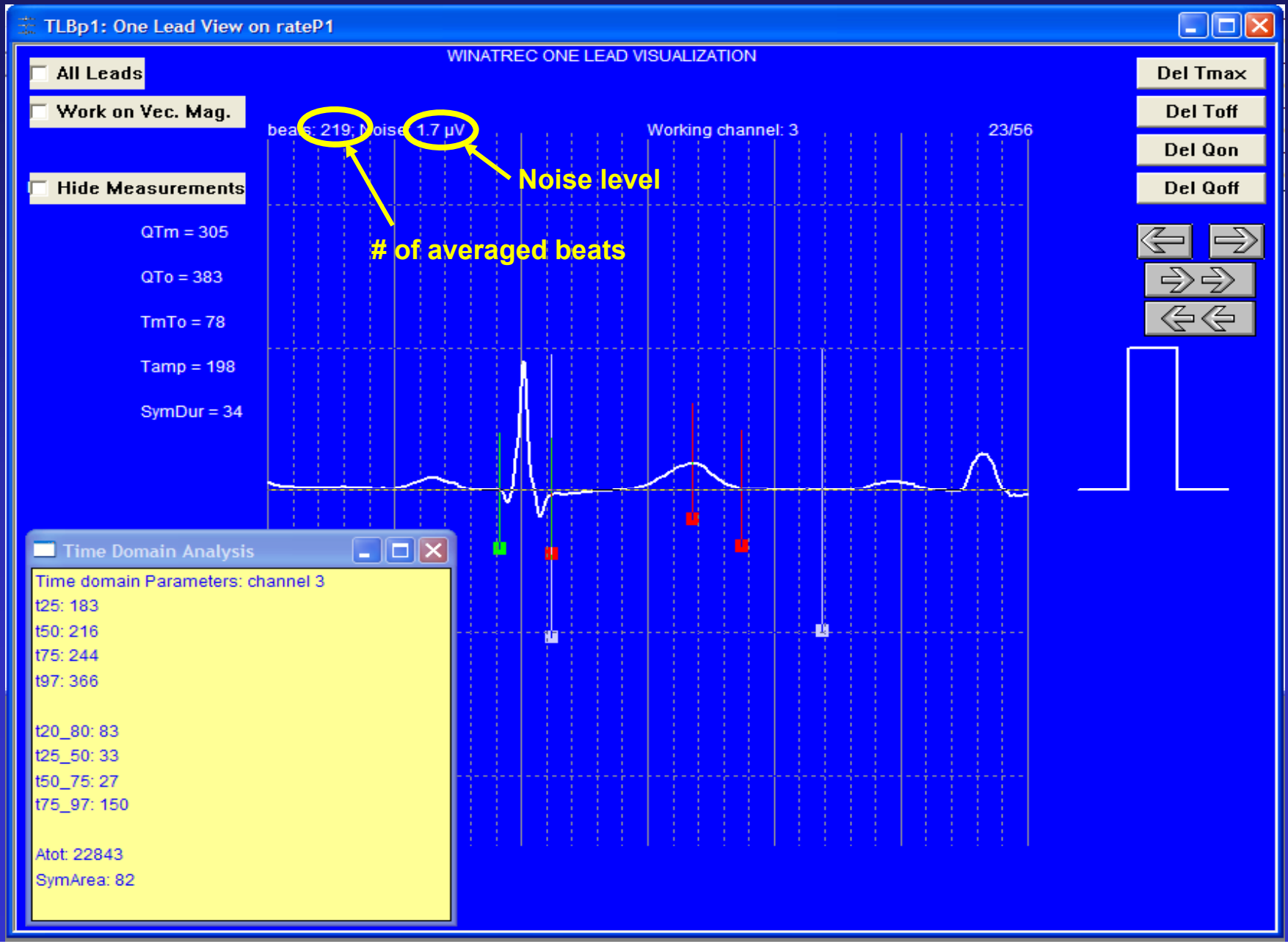
On-screen calipers analysis



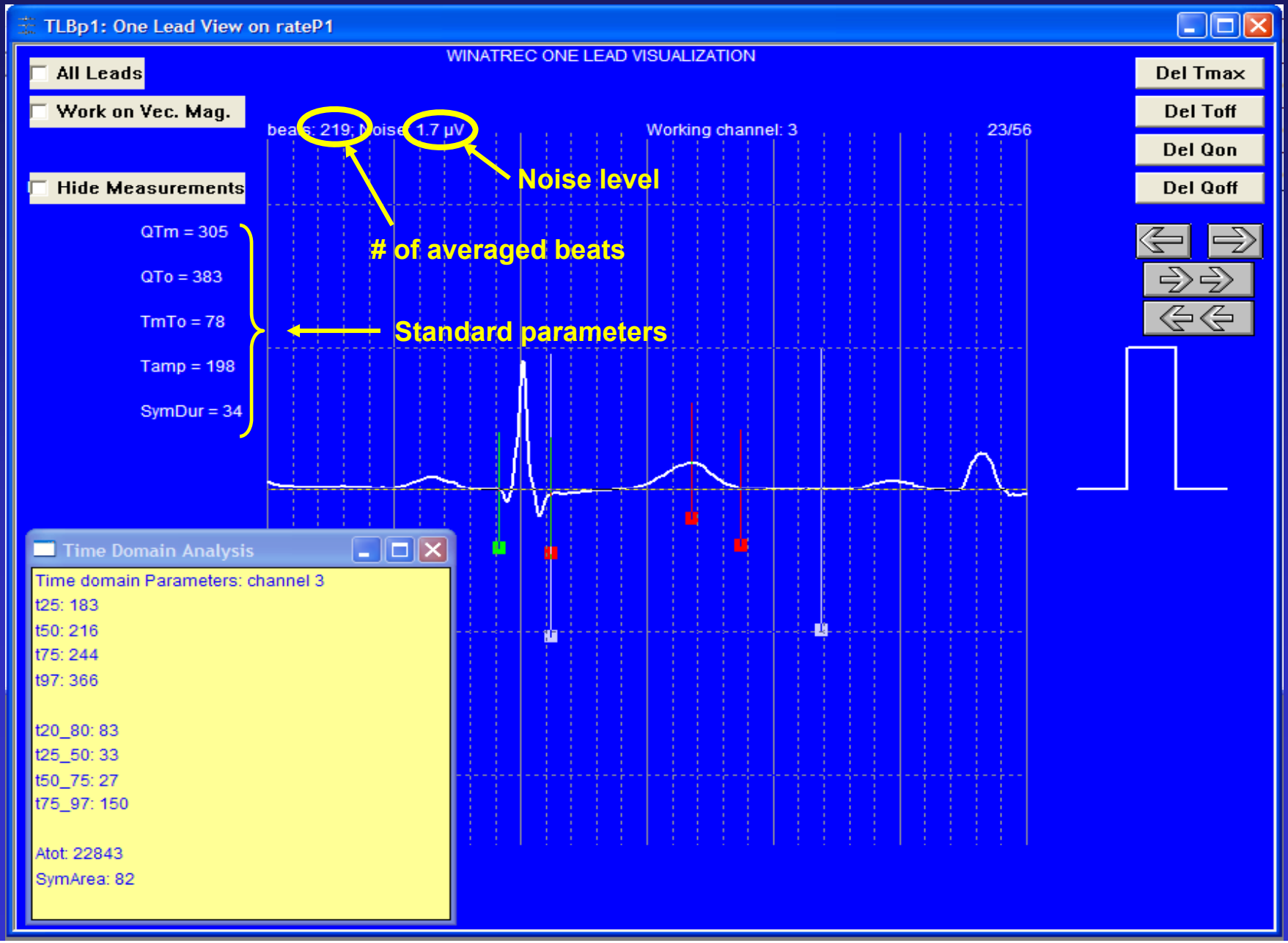
On-screen calipers analysis



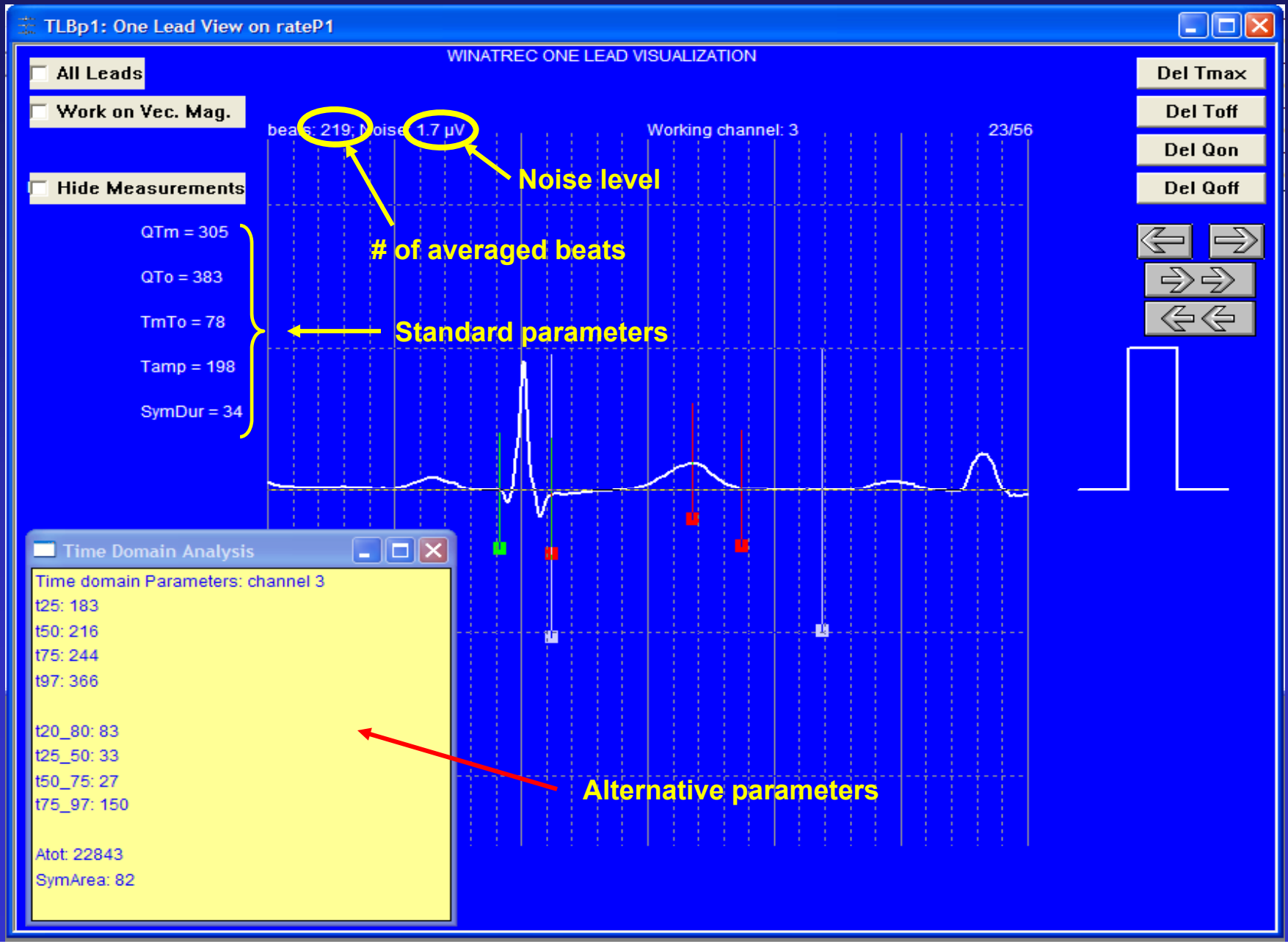
On-screen calipers analysis



On-screen calipers analysis



On-screen calipers analysis



Of note from high quality ECG bins many digital parameters can be extracted

Different bin techniques

Average the waveforms
WinAtrec

- Only 1 PQRST per RR bin.
- Audit trail of individual beats statistics (e.g. noise, QT, …).
- Reasonable editing.

Average the intervals
Compass

- n PQRST per RR bin
- Beat-to-beat QT variability is a direct output.
- Beat-to-beat editing.

The University of Rochester introduced recently a variant of the binning process

Instead of averaging the waveform, « Compass » algorithm averages indidual measurement outputs from the algorithm

Heart Rate Changes with Alfuzosin

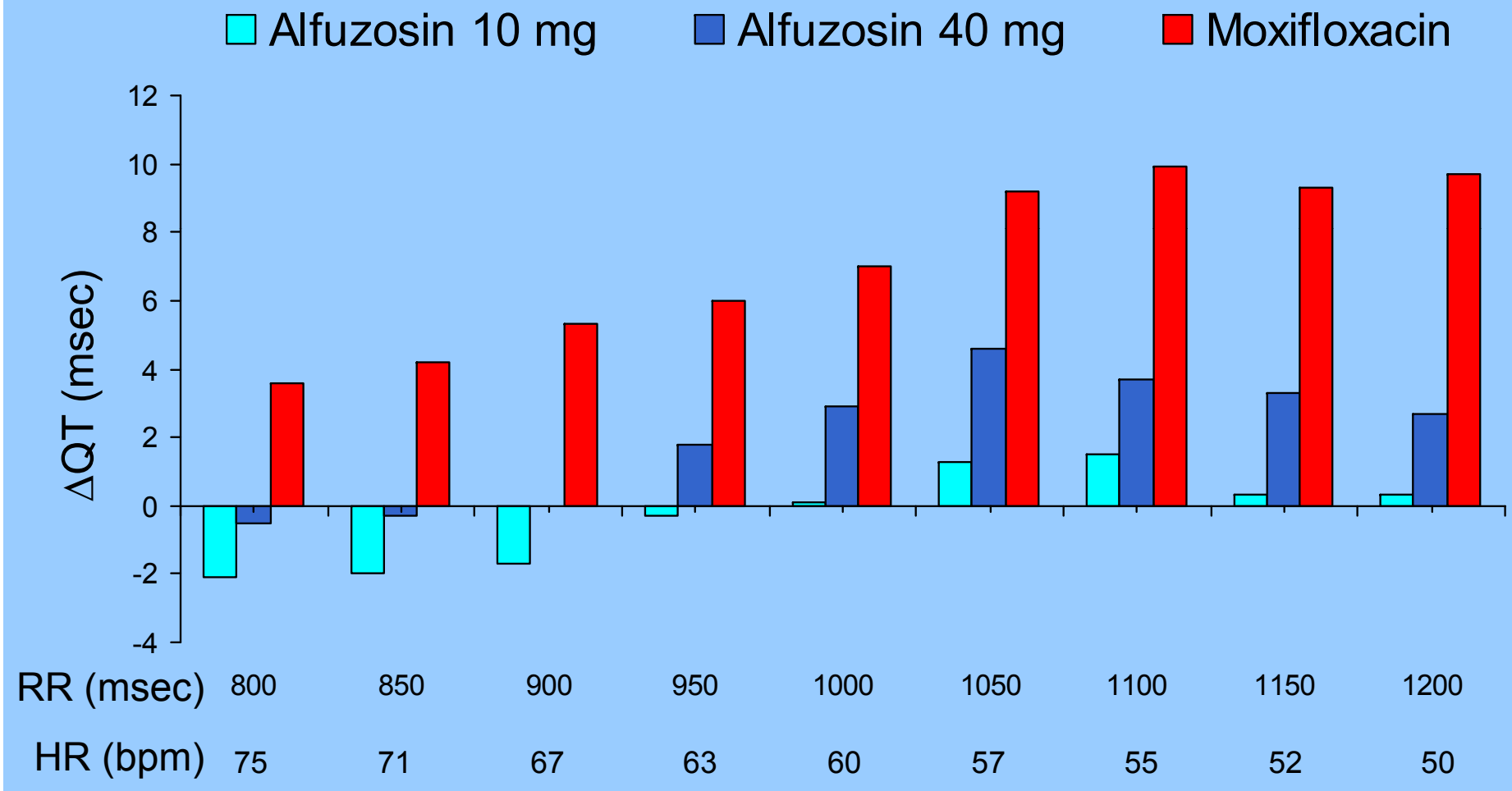
	Alfuzosin 10 mg	Alfuzosin 40 mg	Moxifloxacin 400 mg
ΔHR (bpm) Mean*	1.5	3.7	1.5
Subjects with ΔHR >15 bpm	7%	33%	9%

*HR differences vs. placebo – Study 5105

- Alfuzosin is an alpha-1 blocker,and as such increases the heart rate.
- This previous slide presents the effect on heart rate observed in study a Thoriugh QT trial
- As you can see, average HR increase observed with Alfuzosin 10 mg is small – around 2 bpm - , about the same as Moxifloxacin. There is a somewhat larger HR effect of alfuzosin 40 mg, a 4 bpm increase.
- It is important to notice, however, that despite this modest average effect, there is about 1/3 of the subjects in the alfuzosin 40mg group who exhibit a substantial increase in HR of more than 15 bpm.
- QT interval is correlated with heart rate (as HR increase, QT interval shortens), and therefore, when comparing QT interval either for a same individual at different timepoints, or between groups of individuals, it is important to properly account for this confounding effect.

- See in the next slide 9 RR ECG bins
- The effects of alfuzosin and the effects of Moxifloxacin as a positive control

QT Changes at Various RR Intervals



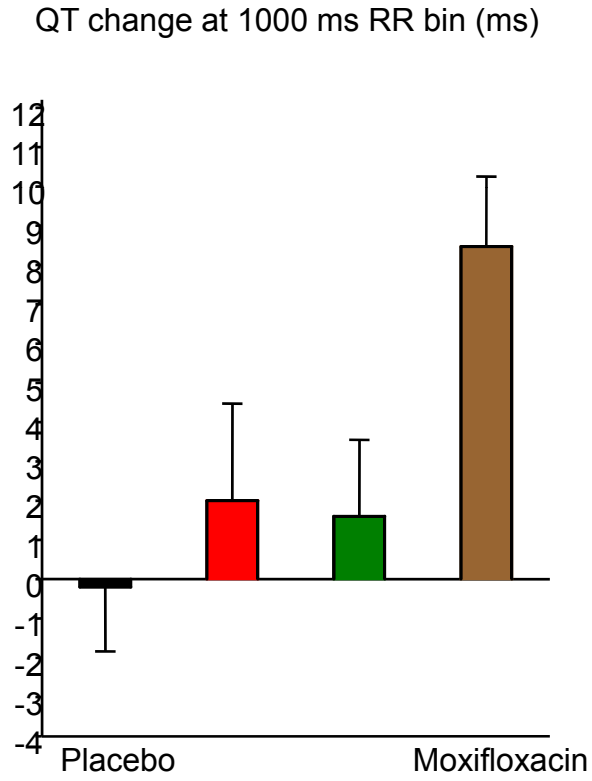
sanofi~synthelabo

Binning vs regular ECG samples

	Endpoint Change from baseline	Mean difference vs placebo (ms)	95% CI		P-value
			Lower bound	Upper bound	
Holter bin method	QT_{1000} (ms)	+ 10.26	+ 3.38	+ 17.14	0.0039
	QT at largest sample size RR bin (ms)	+ 9.33	+ 3.93	+ 14.73	0.0009
	Average QT change of all RR bin (ms)	+ 8.75	+ 3.30	+ 14.19	0.0019
12-lead ECGs	QTcNi (ms)	+ 8.91	+ 3.33	+ 14.32	0.0019
	QTcF (ms)	+ 10.10	+ 4.63	+ 15.56	0.0004
	QT (ms)	+ 6.12	- 2.20	+ 14.44	0.1476
	HR (bpm)	+ 2.14	- 1.28	+ 5.55	0.2169

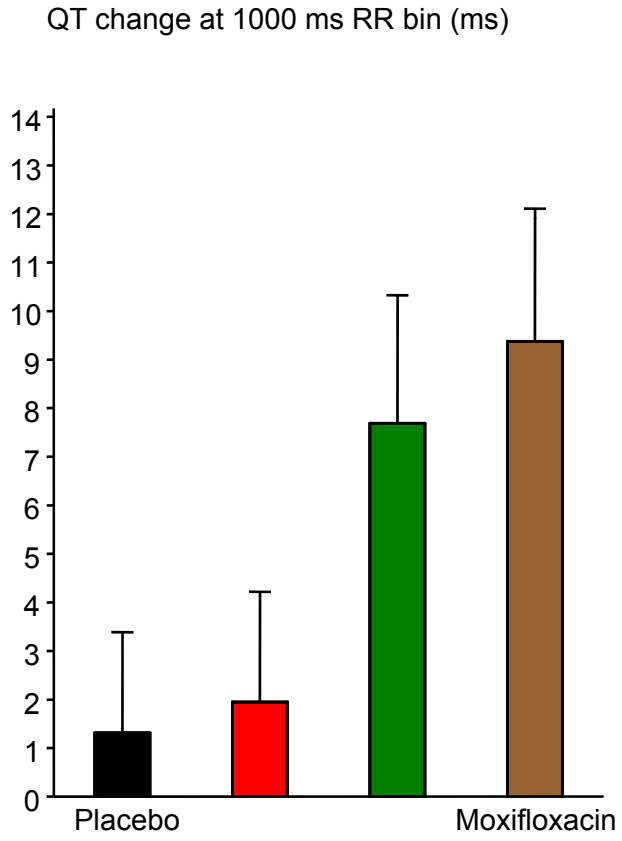
- This method has been compared to current standard approach, in this previous slide from another thorough QT trial
- The effects of Moxifloxacin are pretty much the same

Holter Bin Method
Negative Thorough QT Study



Another TQTn « negative » trial (see ICHE14 document which provides definition formositive and negative TQT trials)

Holter Bin Method
Positive Thorough QT Study



And a positive trial

Clinical Trials with RR bin

- *Flecainide*

  Coumel P, Maison-Blanche P, Tarral E, Perier A, Milliez P, Leenhardt A. Pharmacodynamic equivalence of two flecainide acetate formulations in patients with paroxysmal atrial fibrillation by QRS analysis of ambulatory electrocardiogram. ***J Cardiovasc Pharmacol. 2003 May;41(5):771-9****.*

- *Amiodarone*

  Milliez P, Leenhardt A, MaisonBlanche, P, Vicaut E, Badilini F, Siliste C, Benchetrit C, Coumel P. Usefulness of Ventricular Repolarization Dynamicity in Predicting Arrhythmic Deaths in Patients with Ischemic Cardiomyopathy (From the European Myocardial Infarct Amiodarone Trial), ***Am J Cardiol, 2005; 95:821-826****.*

- *Alfusozin (moxi-validated)*

  Extramiana F, Maison-Blanche P, Cabanis MJ, Ortemann-Renon C, Beaufils P, Leenhardt A. Clinical assessment of drug-induced QT prolongation when associated with heart rate changes. ***Clin Pharmacol Ther. 2005;77:247-58.***

- *Three other compounds (all moxi-validated)*

  using both conventional 3 leads and 12 leads Holter recordings, using both rate and time bins

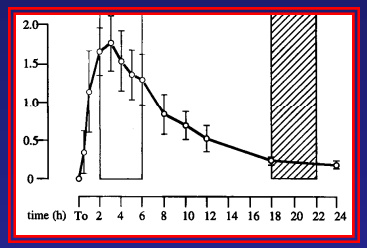
A list of references, out of TQT studies

- In the next slide you can see advantages and pitfalls of the bin methods
- Some criticims are true, others are not

Criticisms to the Holter bin

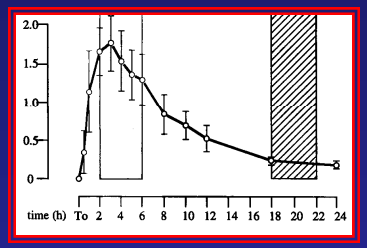
- Within the Period, the time reference is lost.
- Averaging waveforms in Holter can be a problem.
- Does not account for hysteresis

Criticisms to the Holter bin



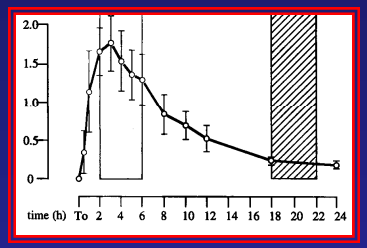
- Within the Period, the time reference is lost. → True!
- Averaging waveforms in Holter can be a problem.
- Does not account for hysteresis

Criticisms to the Holter bin



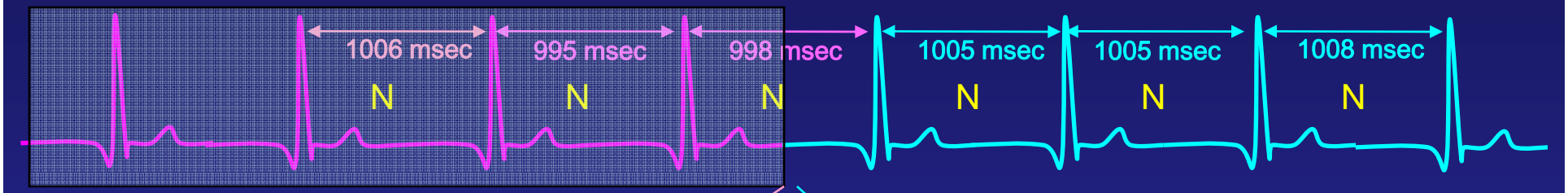
- Within the Period, the time reference is lost. → True!
- Averaging waveforms in Holter can be a problem. → Maybe…..
- Does not account for hysteresis

Criticisms to the Holter bin



- Within the Period, the time reference is lost. → True!
- Averaging waveforms in Holter can be a problem. → Maybe…..
- Does not account for hysteresis → Not True!

From rate-bins to time-bins



2. Classification of ECG complexes into N seconds (« Time-Bins »)

Tx Bin

Tx+1 Bin

3. Averaging of complexes and measurement of QT intervals

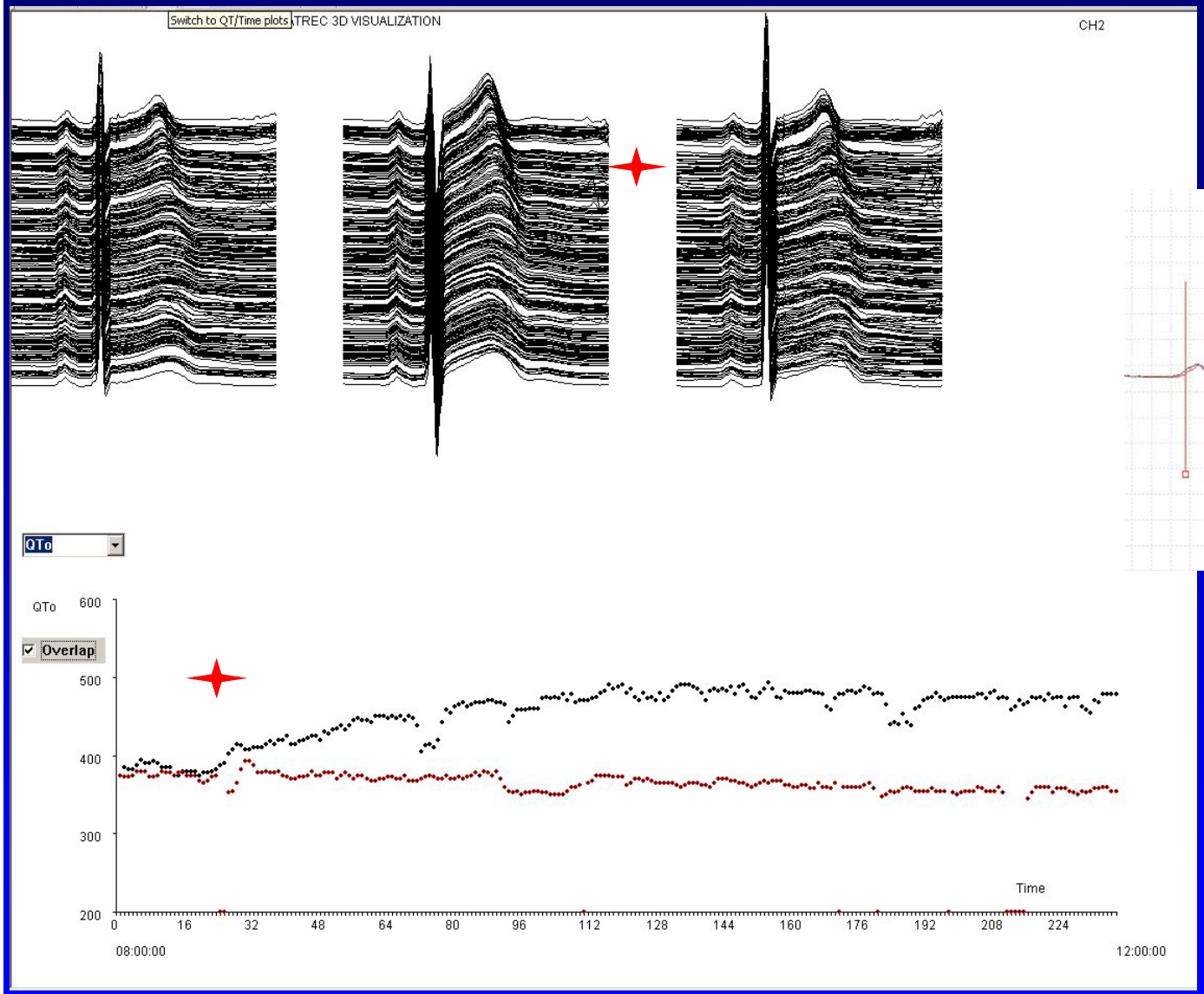
RR/QT_x

Tmax / Emax / triplicate

RR/QT_{x+1}

- Holter bin approach consists of three steps, illustrated in the previous slide:
  1. Sinus complexes are isolated and sorted by RR intervals, then grouped into 10 msec categories (« bins »)
  2. For each RR bin, signal averaged waveforms are derived
  3. QT interval is measured for each RR bin

- Measurement is performed manually and annotated waveforms with fiduciary marks are stored in a digital database. Reader is blinded to treatment assignment and study period.



Time bins, 1 minute

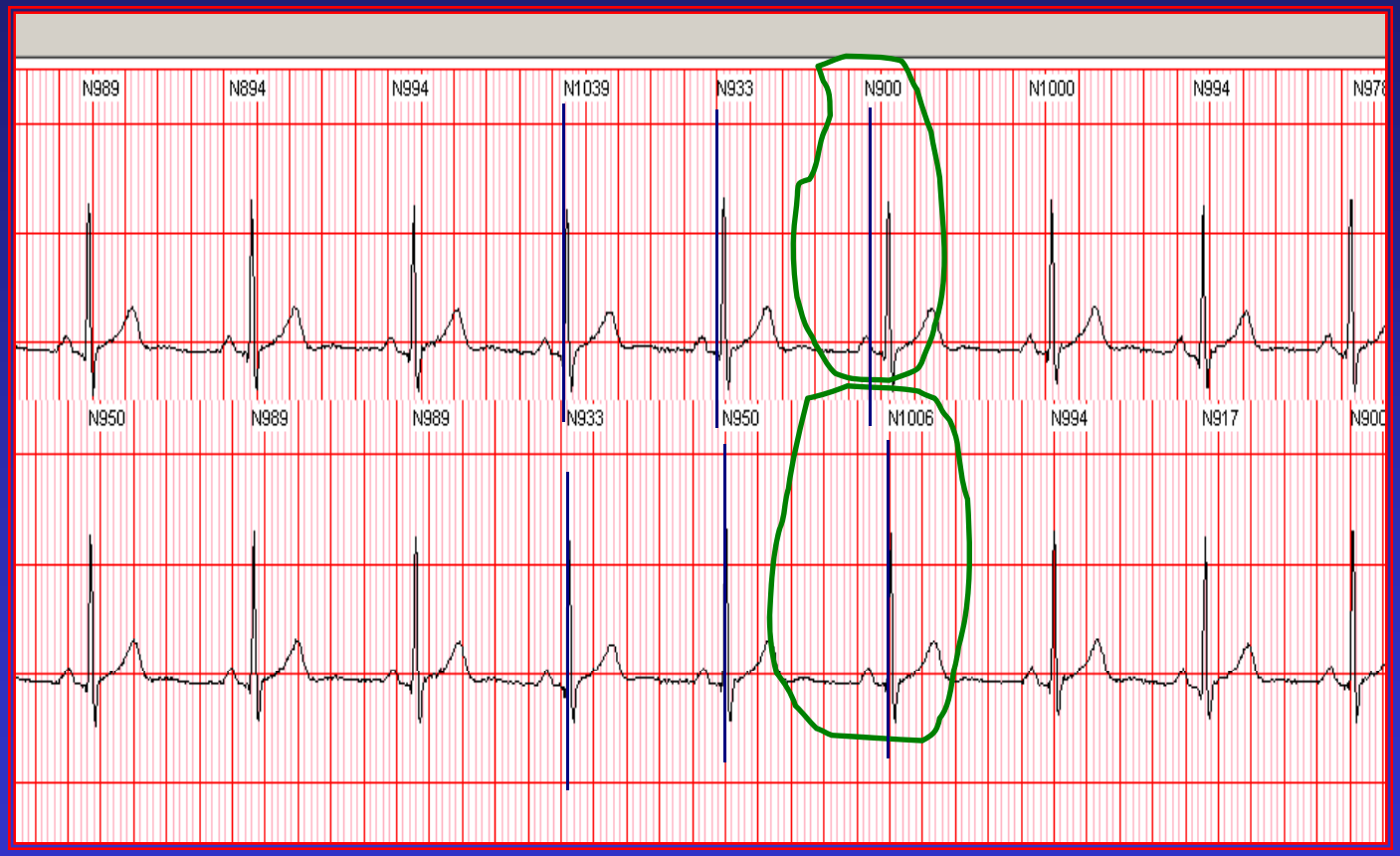
OFF drug Bins ON drug Bins

Proper Beat Averaging

Trigger jitter correction

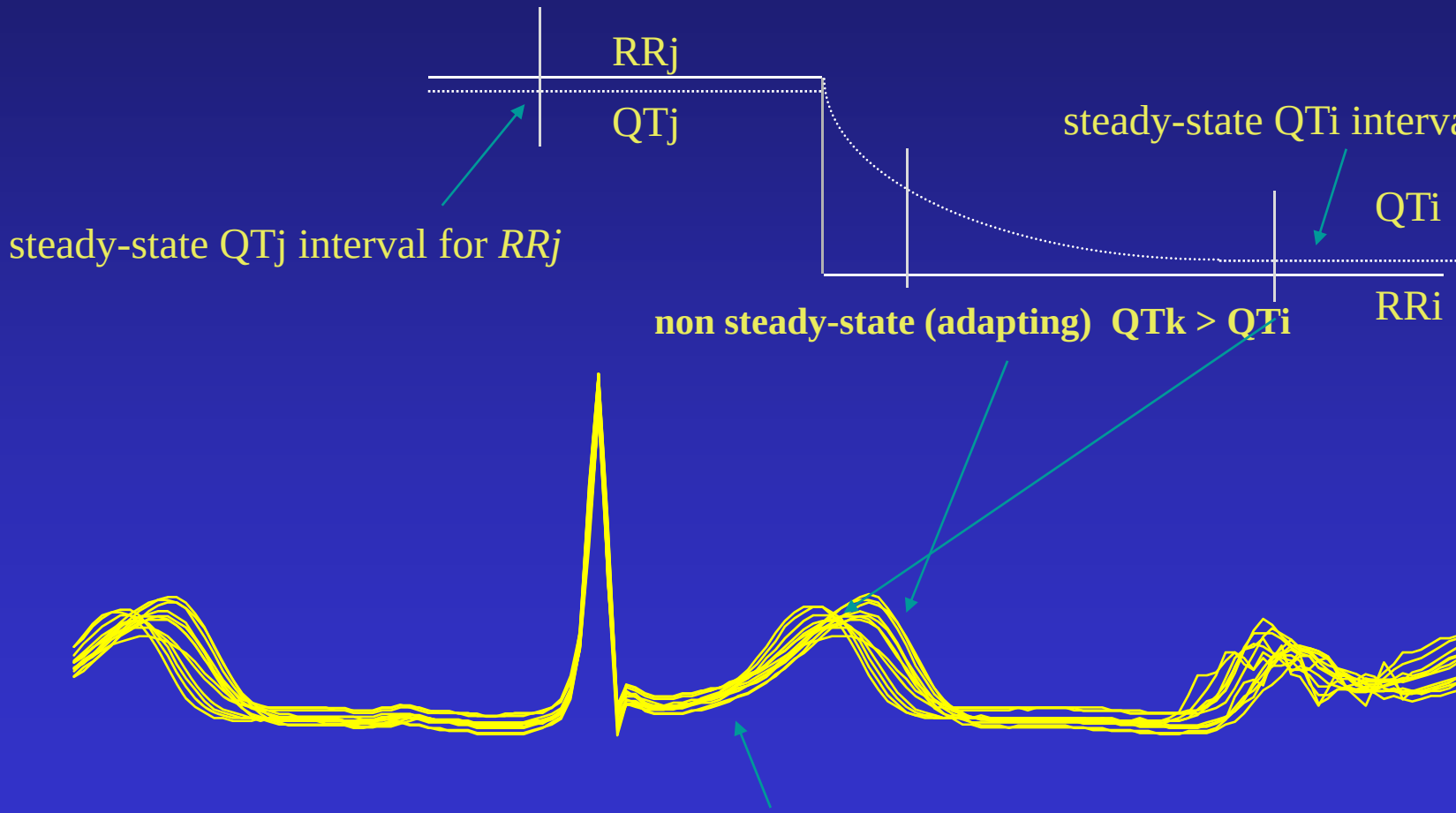
Before correction

After correction



With 20 msec bin resolution, the same QRS could have been assigned 4 bins to the left!!!!

Hysteresis during Holter



Hysteresis

two simple examples

$RR\text{-}1 = RR\text{-}2 = RR_{MIN\text{-}1} \pm th$

Where *th* is a threshold set by user

Determines the RR bin

Subperiods of $RR_{MIN\text{-}1}$

$RR_{P1} = RR_{P2} = RR_{P3} \pm th$

Where P1 = P2 = P3

F. Badilini, Med Biol Eng Comput 1999; 37: 71

Moxifloxacin effects on QT interval Control for heart rate stability

	RR-1	R30	R60
ΔQT700	4.3±3.9	7.0±4.7	4.3±5.1
ΔQT800	2.7±3.9	4.4±3.2	3.7±3.2
ΔQT900	4.2±7.2	7.3±6.7	7.5±6.4*
ΔQT1000	**8.2±11.2**	**10.7±9.4***	**11.1±10.6***
ΔQT1100	10.5±13.0	12.6±13.0	13.8±9.5
ΔQT1200	15.0±21.2	15.0±11.3	13.0±14.1

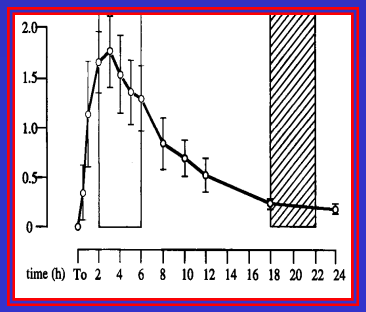
2D binning: Rate and Time

RATE BINS

- Few templates to edit
- Loose time track
- No need HR correction
- Good for slow response drugs

TIME BINS

- Many templates to edit
- Track time
- Need QTci
- Good for fast response drugs



Thank You !