Quality-Assurance for the NMR Data Consumer

Integrating NMR into Modern Laboratory Workflow

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EAS 2008

NMR's Assimilation into Analytical Chemistry

- Samples in plates and vials
- Robotic injection
- Walkup instruments
- Quantitative analysis
- Data interpretation software interface
- **Quality Assurance** with system suitability samples

One-Minute NMR™ and CapNMR™

Background Information

Automated Capillary Flow NMR

High Pressure PUMP

10-15µL LOOP

SOLV. A

SYRINGE

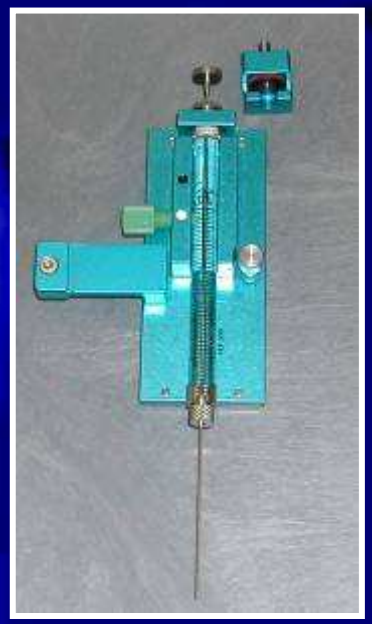
NEEDLE

INJECT

WASTE

Details

CapNMR PROBE



Sample Return Option

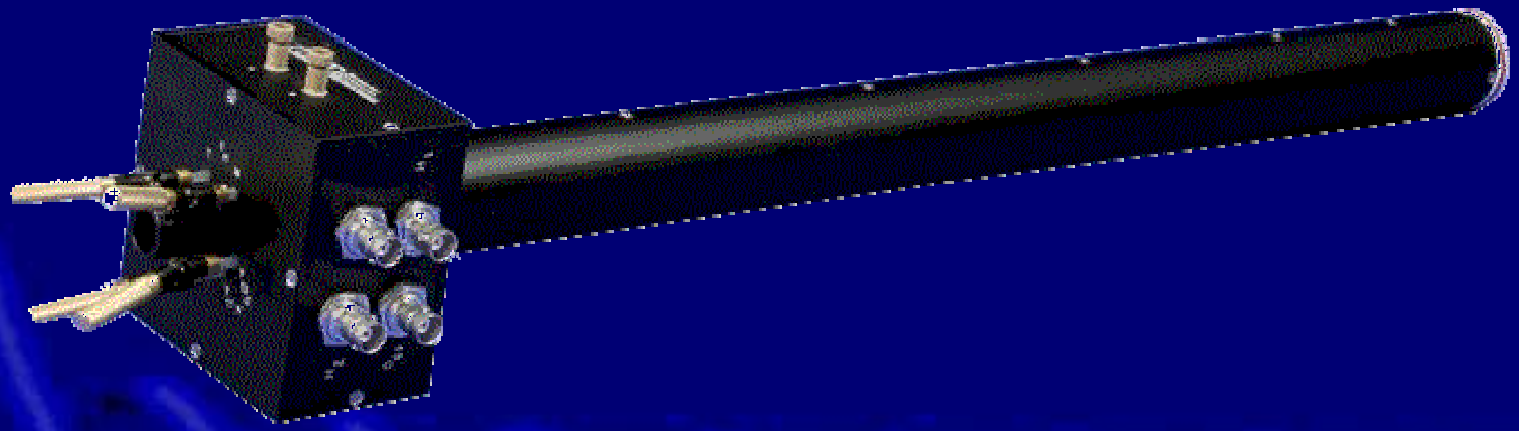
SAMPLES

Tubeless

For incredible Time Savings

- **Directly Use LC or MS samples**
- **No shimming between samples**
- No washing tubes
- No buying tubes ($2 - $25)
- Efficient storage
- Disposable

CapNMR™ Flow Probe



- 10 - 200µg Samples
- Best mass sensitivity
- 5 or 10µL flow cell
- Proton, Carbon, Nitrogen, Deuterium Lock
- Dual flow cell available

Use CapNMR

CapNMR™
A Great Scale-Match or HPLC Purified Fractions

- **UPLC™ Scale** (2.1x150mm 1.7μ)
  - < ~2 mg sample, plenty for MS (.1μg) + CapNMR (50μg)
  - Amazing chromatographic resolution
  - highest purity fractions
  - CapNMR on **2.5%** of total fraction mass
- **Analytical Scale** – (4.6x150mm 3-5μ)
  - < ~7mg sample
  - Good chromatographic resolution
  - CapNMR on **0.7%** of total fraction mass
- **Semi-Prep Scale**
  - 50mg to grams of sample
  - Longer runs
  - Less resolution, more impure fractions
  - Typical for compound libraries
  - CapNMR on < **0.1%** of total fraction mass

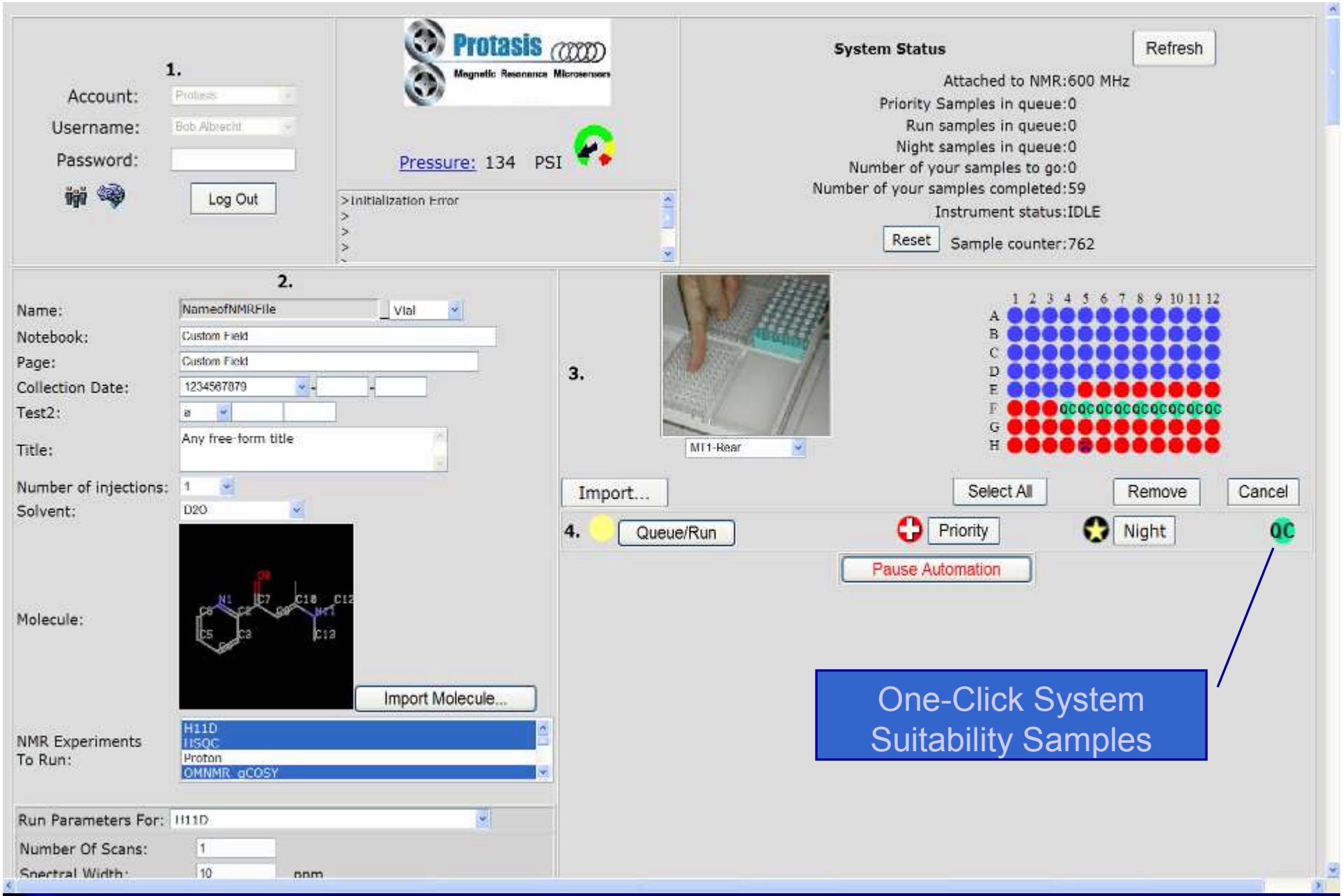
Leap / CTC Liquid Handler

- Fast
- Low Volume Pickup
- Low Dead Volume
- Syringe-Only Technology
- Flexible Sample Storage
- Dilute / Reconstitute
- Sample Return

One-Minute NMR Software

- Customizable multi-user open-access
- Web based with e-mail reporting
- Sample and user list importing

- Accepts any plate or vial in multiple solvents
- Interface to processing software (ACD/Labs, DataChord)
- Closed-loop NMR Instrument control enables **system suitability samples**


1.
Account:
Username:
Password:
Log Out
Protasis
Magnetic Resonance Microsensors
Pressure: 134 PSI
>Initialization Error
System Status
Refresh
Attached to NMR:600 MHz
Priority Samples in queue:0
Run samples in queue:0
Night samples in queue:0
Number of your samples to go:0
Number of your samples completed:59
Instrument status:IDLE
Reset
Sample counter:762
2.
Name:
NameofNMRFile
Vial
Notebook:
Custom Field
Page:
Custom Field
Collection Date:
1234567879
Test2:
Title:
Any free-form title
Number of injections:
Solvent:
D2O
Molecule:
Import Molecule...
NMR Experiments To Run:
H11D
HSQC
Proton
OMNMR gCOSY
Run Parameters For:
H11D
Number Of Scans:
Spectral Width:
ppm
3.
MT1-Rear
1 2 3 4 5 6 7 8 9 10 11 12
A
B
C
D
E
F
G
H
Import...
Select All
Remove
Cancel
4.
Queue/Run
Priority
Night
OC
Pause Automation
One-Click System Suitability Samples

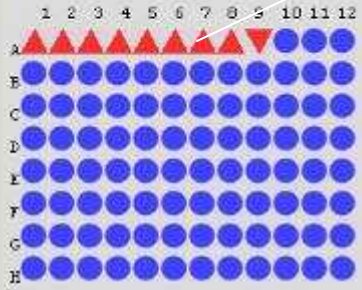
Interface to NMR Processing Software

- Full control of basic NMR System Processing
- ACD/Labs automated structure confirmation with HTML reporting and Web Librarian
- ADC/Labs Enterprise Database archival
- One-Moon Scientifics' DataChord connection

In your ***Inbox***

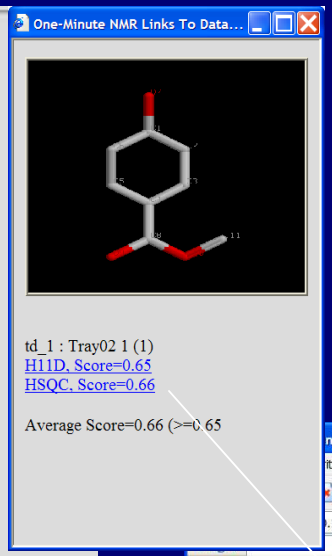
Tray02

Click…

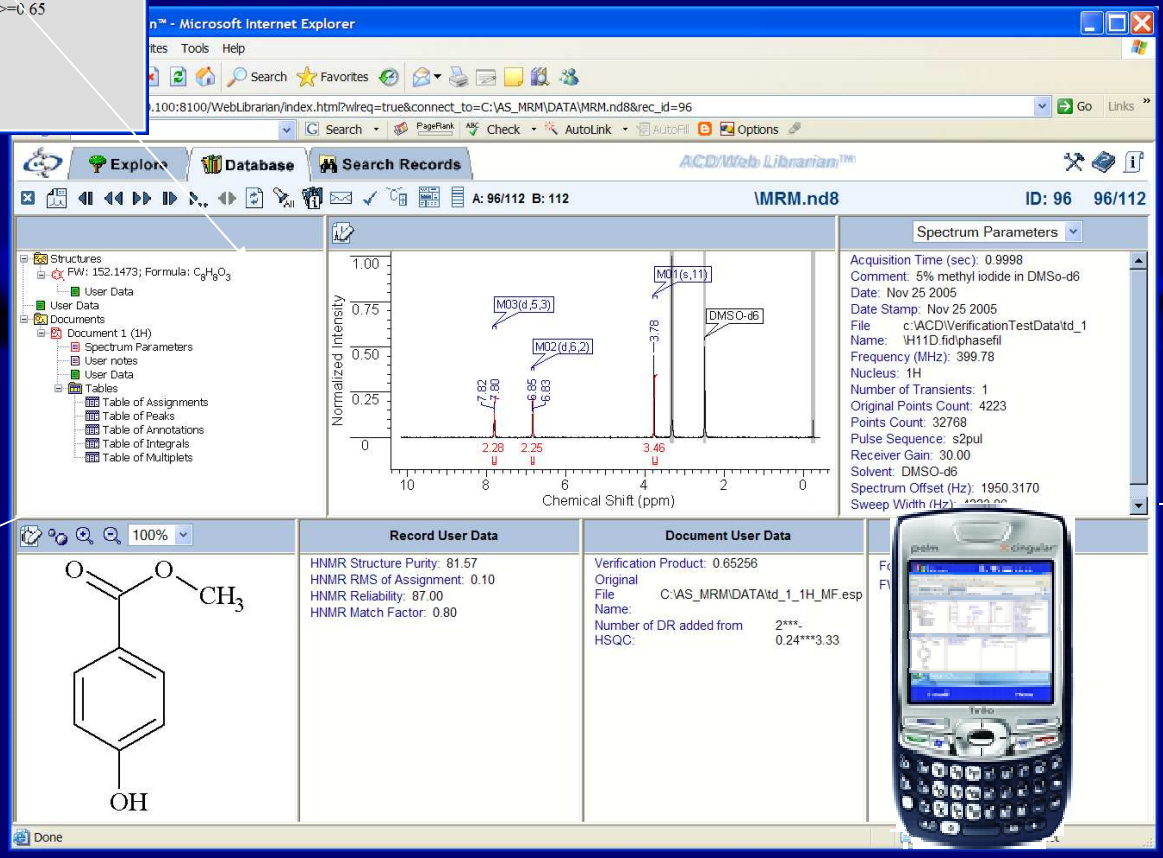


Structure Confirmation Results

Sample ID	Code	H11D	HSQC
td_1	CONF	0.65	0.66
td_2	CONF	0.65	0.66
td_3	CONF	0.65	0.66
td_4	CONF	0.65	0.66
td_5	CONF	0.65	0.66
td_6	CONF	0.65	0.66
td_7	CONF	0.65	0.66
td_8	CONF	0.65	0.66
td_9	REJ	0.06	0.66



Integrated ACD/Labs Web Librarian



Hot-linked E-mail report

NMR Quantitation

- Perfect for novel compounds
- Linear proton counter
- **Flow NMR works best**: No re-tuning with fixed flow-cell for constant signal response
- Use ERETIC for artificial internal standard
- Good results with external standards
- Reproducible robotic injection

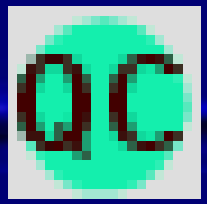
Why System Suitability?

- Does the average walkup chemist know good system performance?
- Trust is important with precious samples, especially with flow NMR

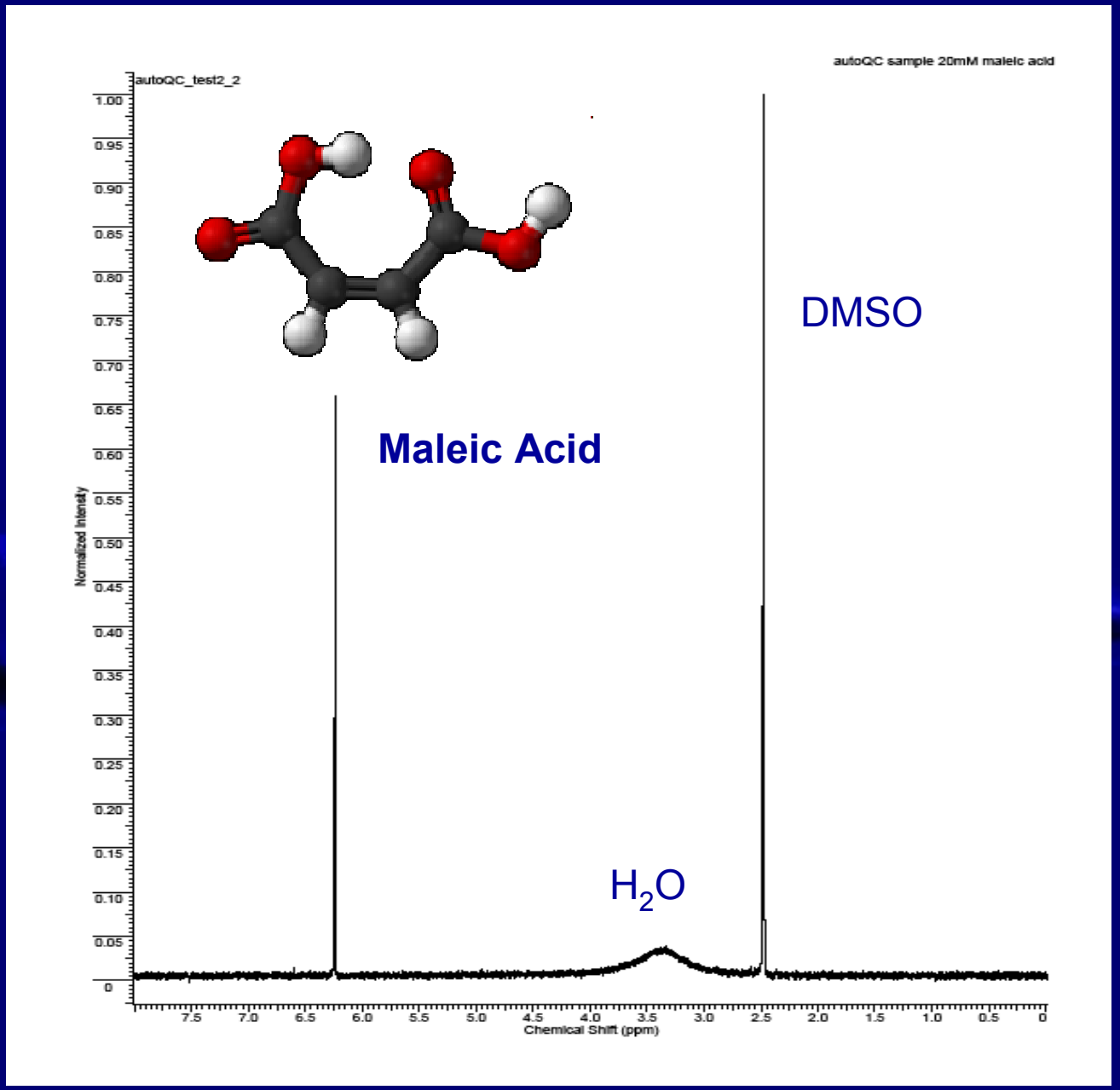
- Optimized automated structure verification, elucidation, and quantitation
- Automation makes system suitability painless

Automated System Suitability

- The only way to test the entire system: **Run a Sample, Analyze Results**
- Flow has many benefits, but more complexity



- Tests all sub-systems: auto-sampler, fluidics, probe, magnet, shims, tuning, spectrometer, and software
- Confidence for precious samples


autoQC sample 20mM maleic acid
autoQC_test2_2
DMSO
Maleic Acid
H_2O
Normalized Intensity
Chemical Shift (ppm)

Maleic Acid

- Boring NMR Spectrum (1 peak)
- Great for system suitability standard
- Easy signal/noise calculation

- Clean spectrum for residual peak detection
- Sharp line for asymmetry and width calculation
- Dissolves in aqueous and organic solvents
- Non-toxic

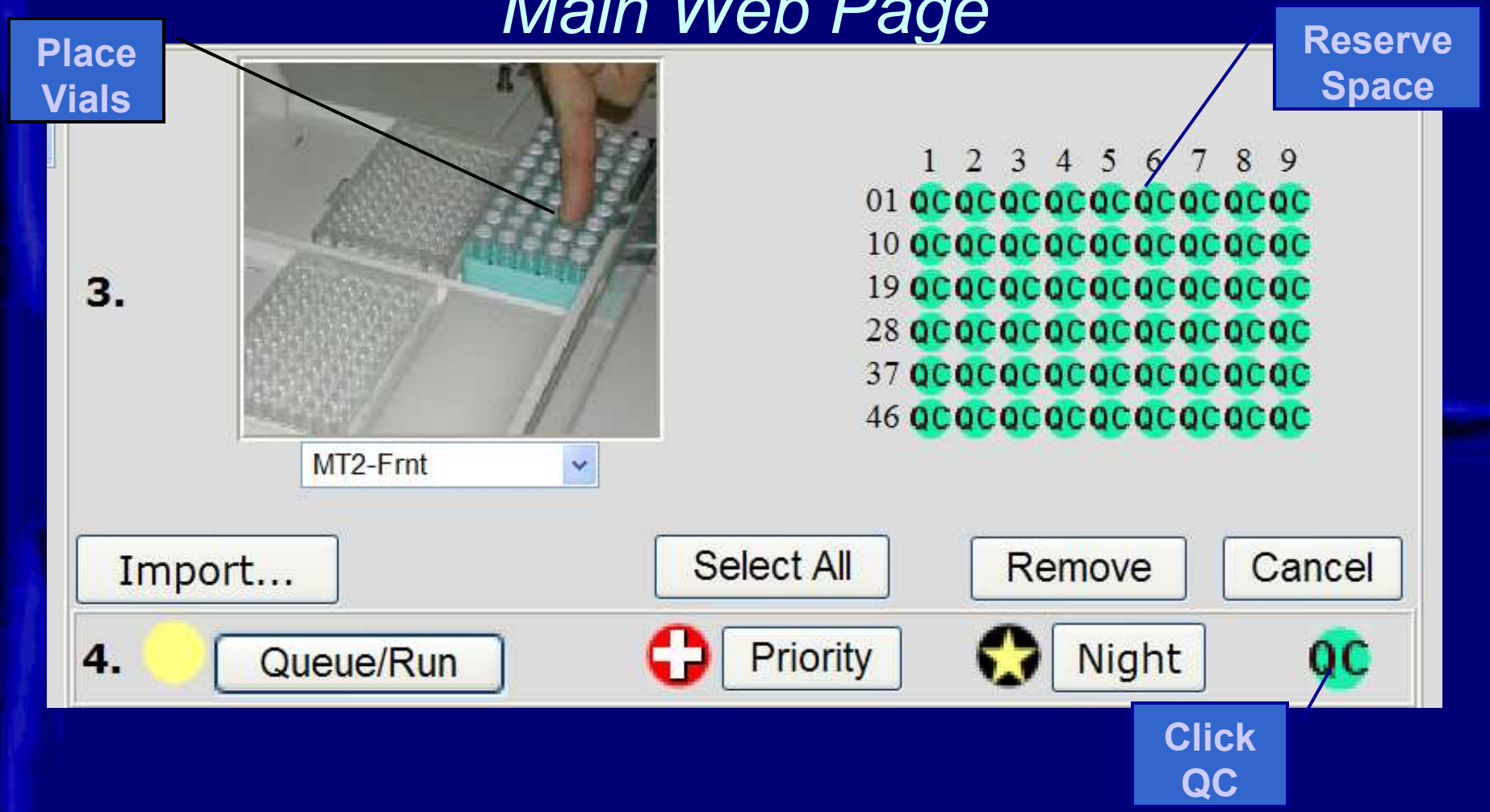
We Sell Certified QC Standards
or Make Your Own

- Pre-tested known concentration (20mM)
- Sealed vials
- Dry solvents of known purity

- High-purity maleic acid
- Inexpensive
- Convenient
- Use to verify make-your-own standards

Loading QC Samples

Main Web Page



Software Configuration

- Solvent specific S/N limit
- Solvent specific line-shape limit
- Maximum number of bands
- Checking frequency (every Nth sample, startup)

Settings Category: General Settings Settings Filter: QC

	Setting	Value	Description
Edit	QC.BrukerWindows.omnmr_qc	c:\protasis\omnmr_qc.bat	Program to run for Bruker.Windows to get QC results.
Edit	QC.Countdown	1	Counter for QC samples.
Edit	QC.Enabled	true	True enables QC samples.
Edit	QC.ExperimentName	autoqc	The name of the experiment to run for QC samples.
Edit	QC.Frequency	4	How often to run a check sample.
Edit	QC.LineShapeLimit	1.5	The maximum line shape deformation.
Edit	QC.LineShapeLimit.D2O	1.5	The maximum line shape deformation.
Edit	QC.LineShapeLimit.DMSO	1.5	The maximum line shape deformation.
Edit	QC.MaximumNumberOfSignals	3	The maximum number of signals in the region tested for S/N.
Edit	QC.SignalToNoiseLimit	10	The minimum signal to noise value.
Edit	QC.SignalToNoiseLimit.D2O	10	The minimum signal to noise value.
Edit	QC.SignalToNoiseLimit.DMSO	10	The minimum signal to noise value.
Edit	QC.SignalToNoiseLowerPPM	2	Lower ppm limit for signal to noise calculation.
Edit	QC.SignalToNoiseUpperPPM	12	Upper ppm limit for signal to noise calculation.

QC Sample Automation Details

- QC Samples can be run *at will*, or..
- Run after every Nth sample
- A QC Sample is loaded and positioned in the CapNMR probe
- The 1D proton experiment *autoQC_setup* is automatically started by One-Minute NMR

QC Sample
Automation Details

- Post processing experiment *autoQC_proc* calculates signal / noise, asymmetry, and the number of peaks in a ppm window
- Results are stored in *qc.log* and retrieved by One-Minute NMR using the *omnmr_qc* macro
- Results are compared to acceptable limits,
- Out of range, automation is stopped and an e-mail alert explaining why is sent

QC Documentation

- QC Sample results are stored as NMR FIDs and can be reviewed later
- Path to most recent QC FID, and the calculated results for *S/N*, *Asymmetry*, and *Peak Count* are stored in a tabular file
- NMR data file parameters can be created and stored with QC information

Future NMR QC Directions

- Injection volume detector
- Automated system pressure profile monitor
- Sample identity verification with barcodes
- Automated sample scan count measurements
- Automated sample return efficiency measurements

Conclusions

- NMR data consumers need quality data
- Chemists sometimes don’t recognize poor instrument performance

- Automation makes QC easy and routine
- One-Minute NMR provides a comprehensive and flexible solution

Thank You

Craig Milling, PhD for developing Varian macros and system testing

Dean Olson, PhD for developing chemistry and selecting / testing containers for certified samples

Contacting Protasis

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