Statistical Process Control for Assessing LC MS/MS Performance

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June 15, 2014

Skyline Users Group Meeting
2014 American Society for Mass Spectrometry Conference

Baltimore, Maryland

What is Statistical Process Control (SPC)?

A powerful collection of tools used in achieving process stability and improving capability through the identification and reduction of assignable causes of variation

Walter Shewhart

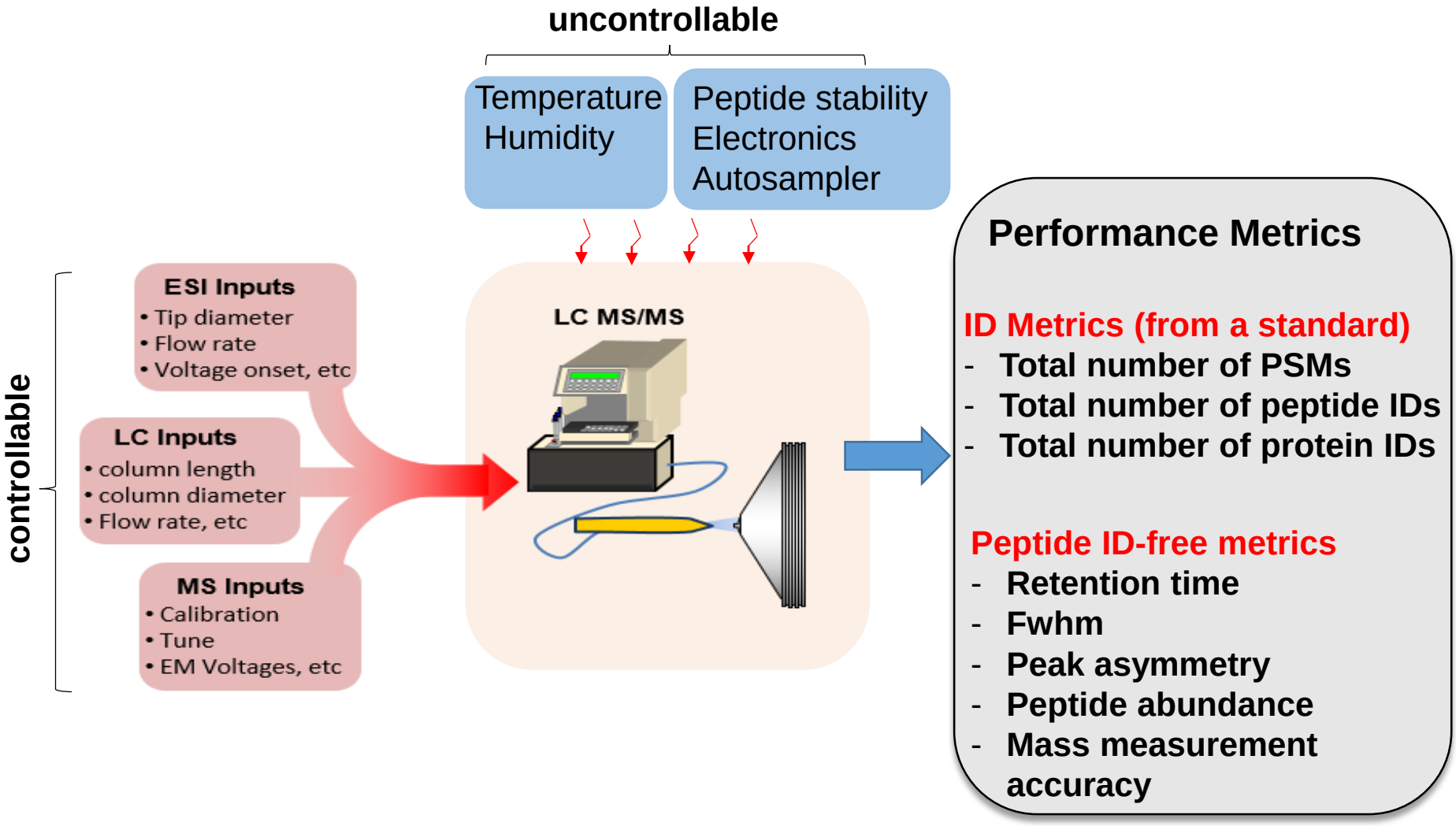
(1891-1967)

- **Special cause vs. chance cause variation**
- **1st implemented in Japan post WWII**
- **Revived in USA by the automotive industry in the 1980's**
- **Sales, marketing, finance, clinical diagnostics**

No definition of quality - SPC describes "quality" as inversely proportional to variance

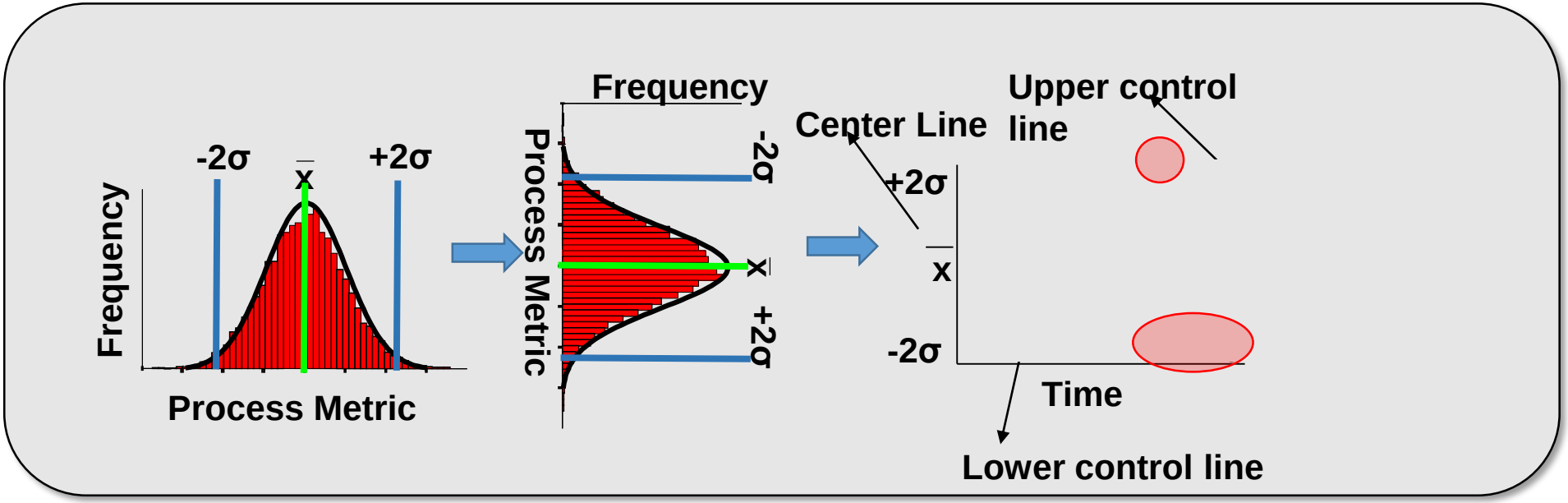
LC MS/MS is a Process

A process is everything required to turn an input(s) into the desired output



Shewhart Control Charts

Shewhart, W.A. J. Frankl. Inst. 226, 163, 1938

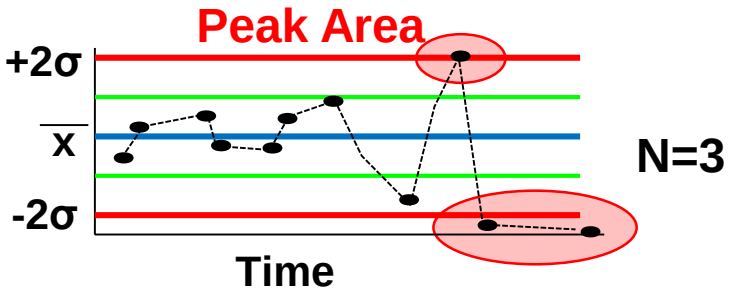


Primary tool in SPC – used for monitoring process output

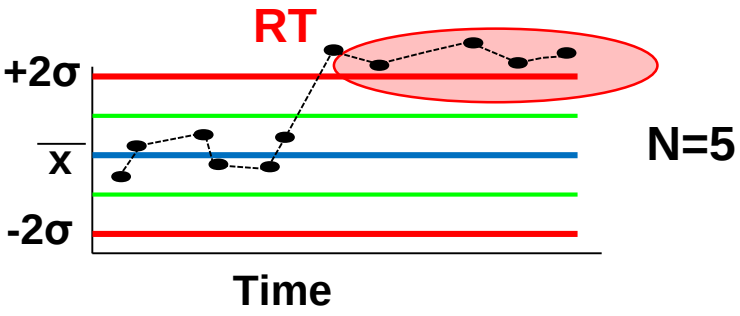
Pareto Analysis

80/20 Principle - Identifies the most significant problems – vital few

Juran, J.M., Quality Control Handbook 1974



N=3



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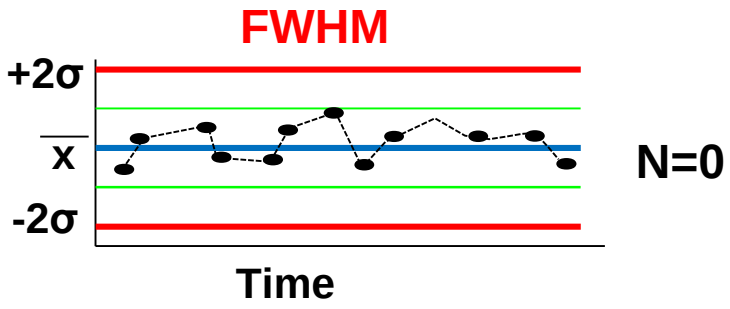

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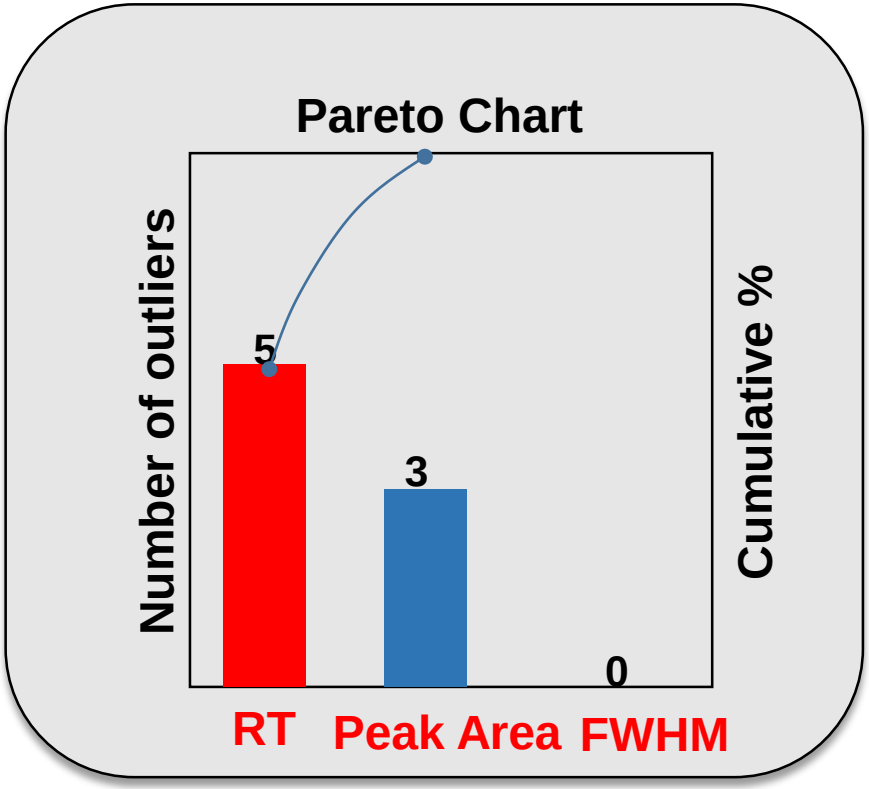
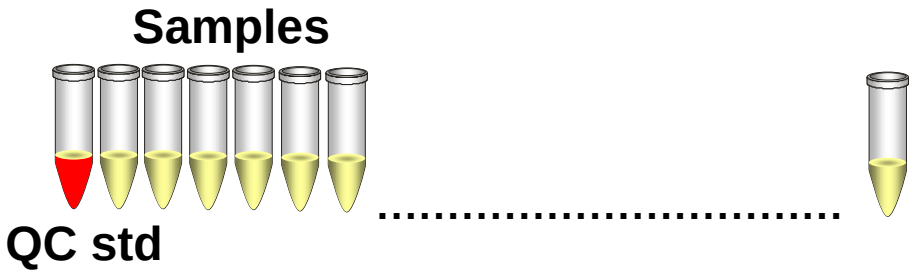
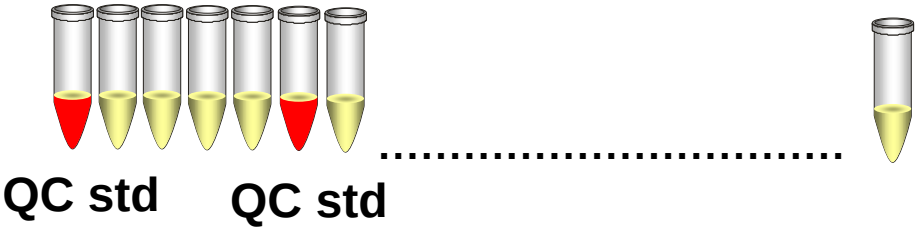


How Does One Monitor Performance in LC MS/MS

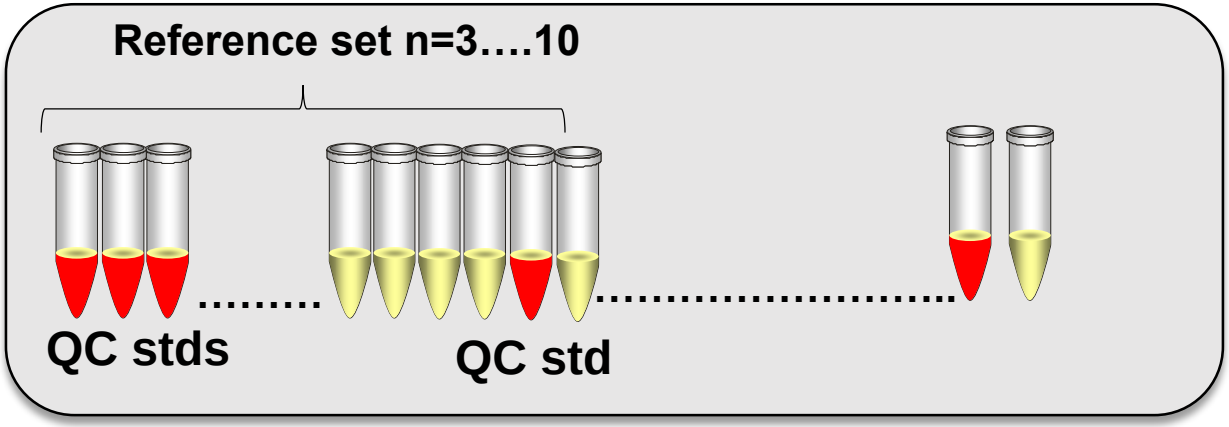
1. Run a standard before each analysis or at the beginning of each day



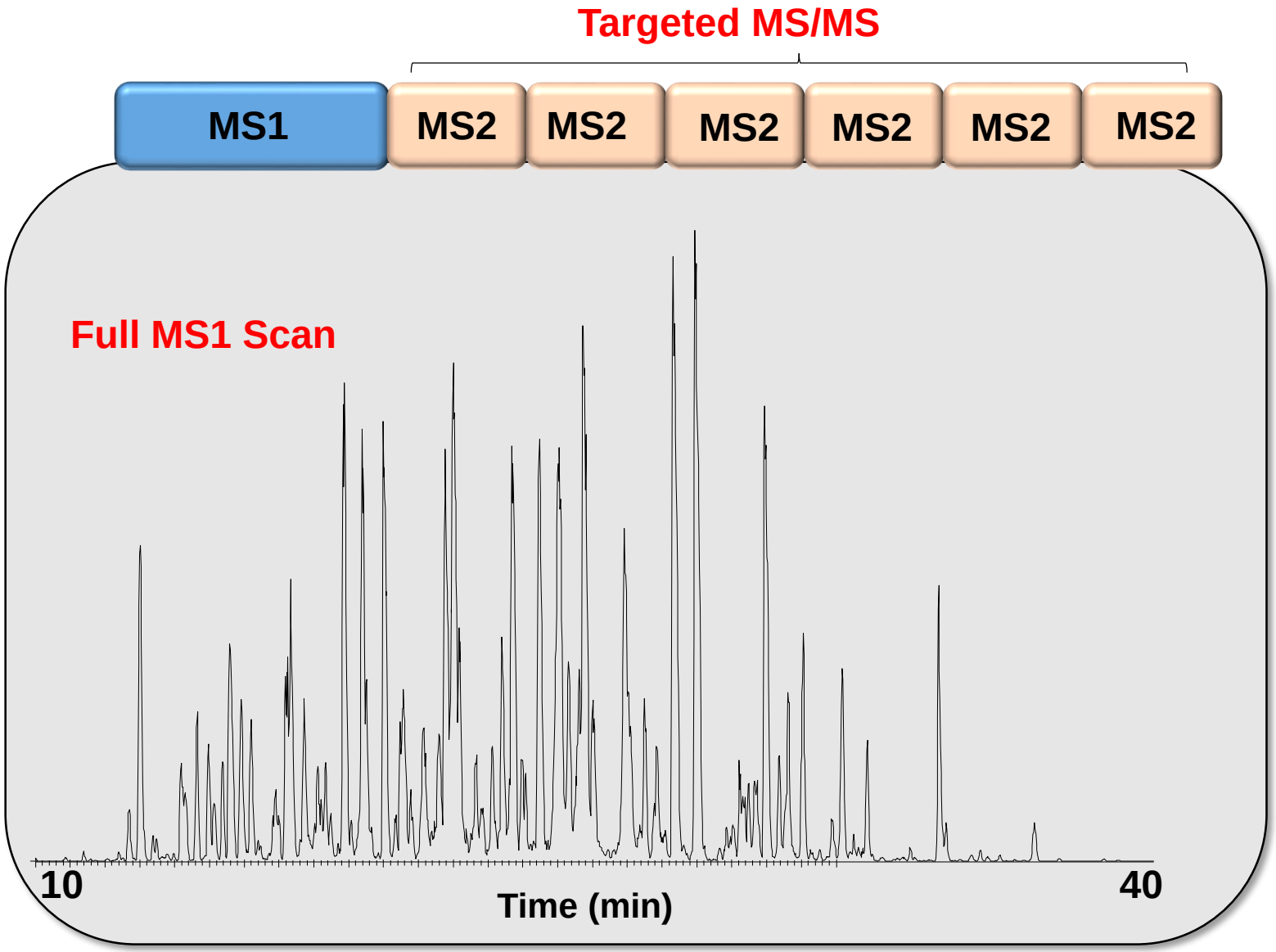
2. Run a standard systematically throughout a study



3. Run a reference set

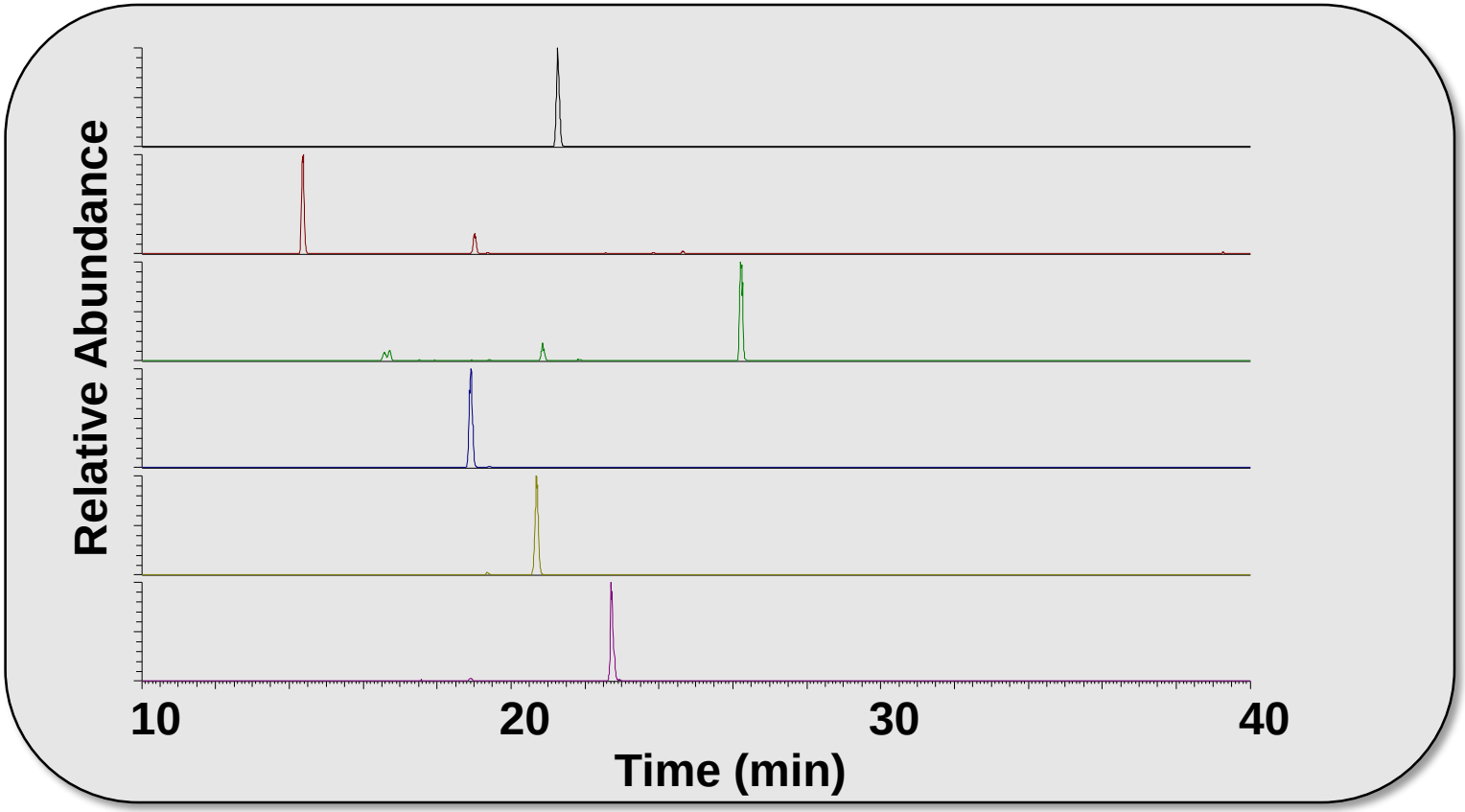


Scan Cycle for Quality Control Standards



Targeted MS/MS

Monitor several peptides across the gradient



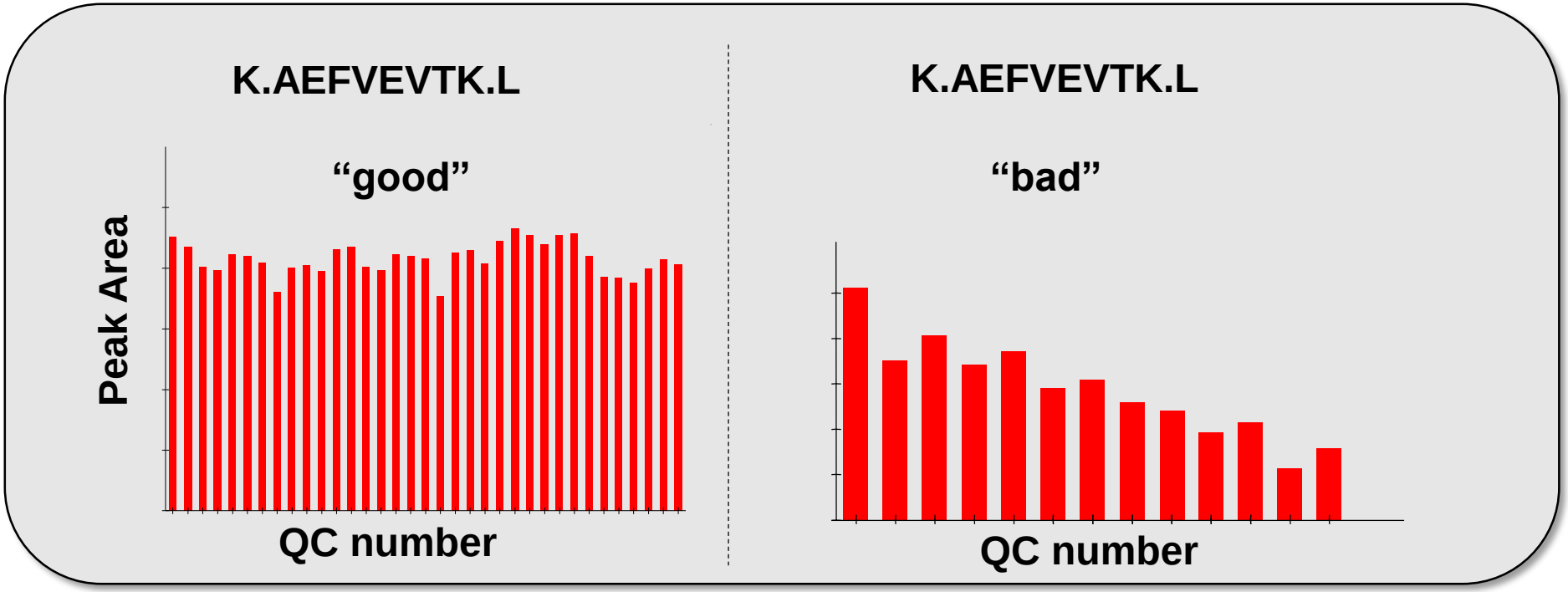
LC related

1. RT reproducibility
2. Peak asymmetry
3. FWHM

MS related

4. Peptide abundance
5. Mass measurement accuracy

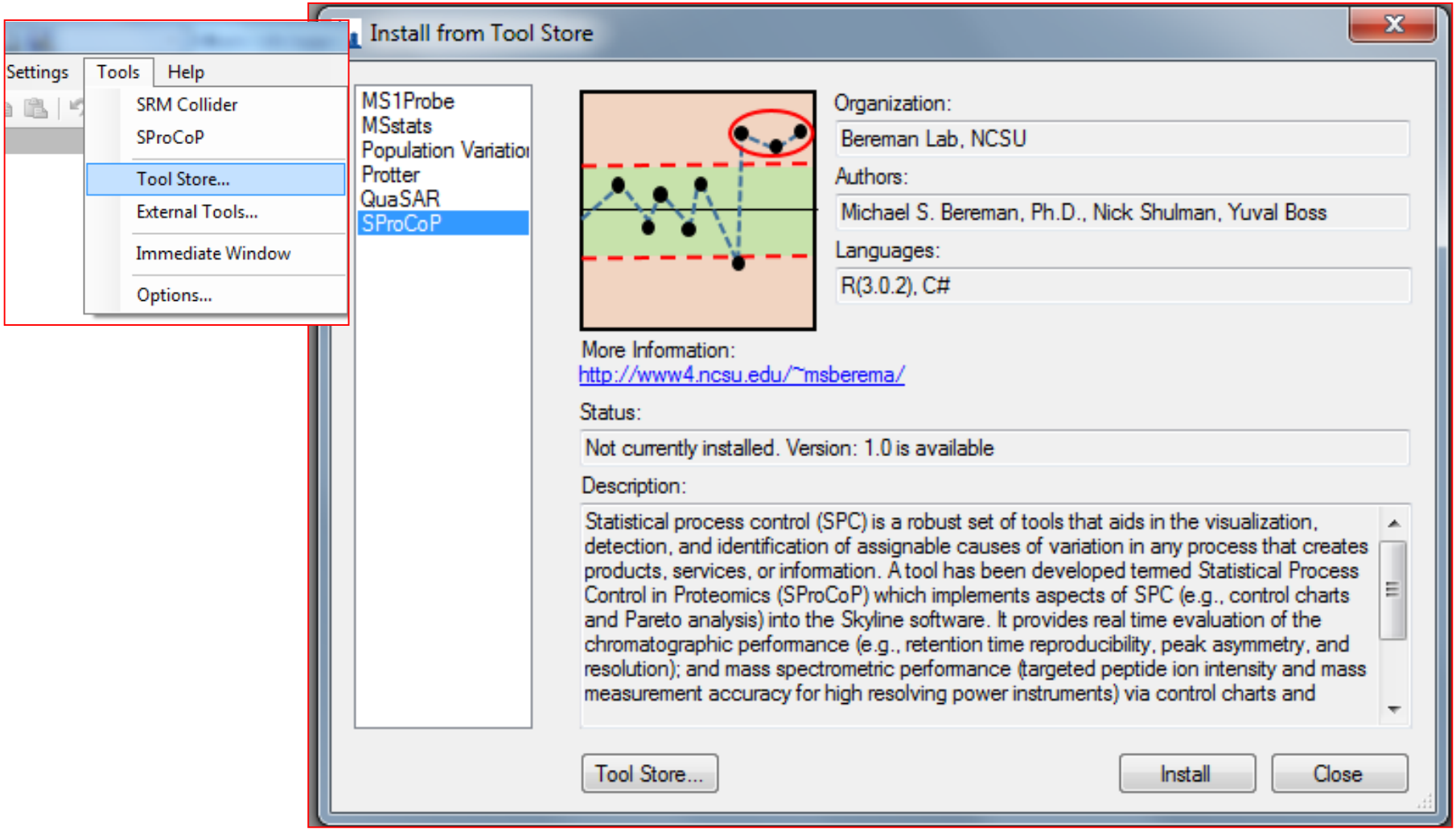
Motivation for Tool Development



1. Quantitative method to assess instrument performance
2. Visual tools
3. Methods for process monitoring
4. Versatile (SRM, MS1, Targeted MS/MS, high RP, low RP, and vendor neutral)
5. Easy and fast!

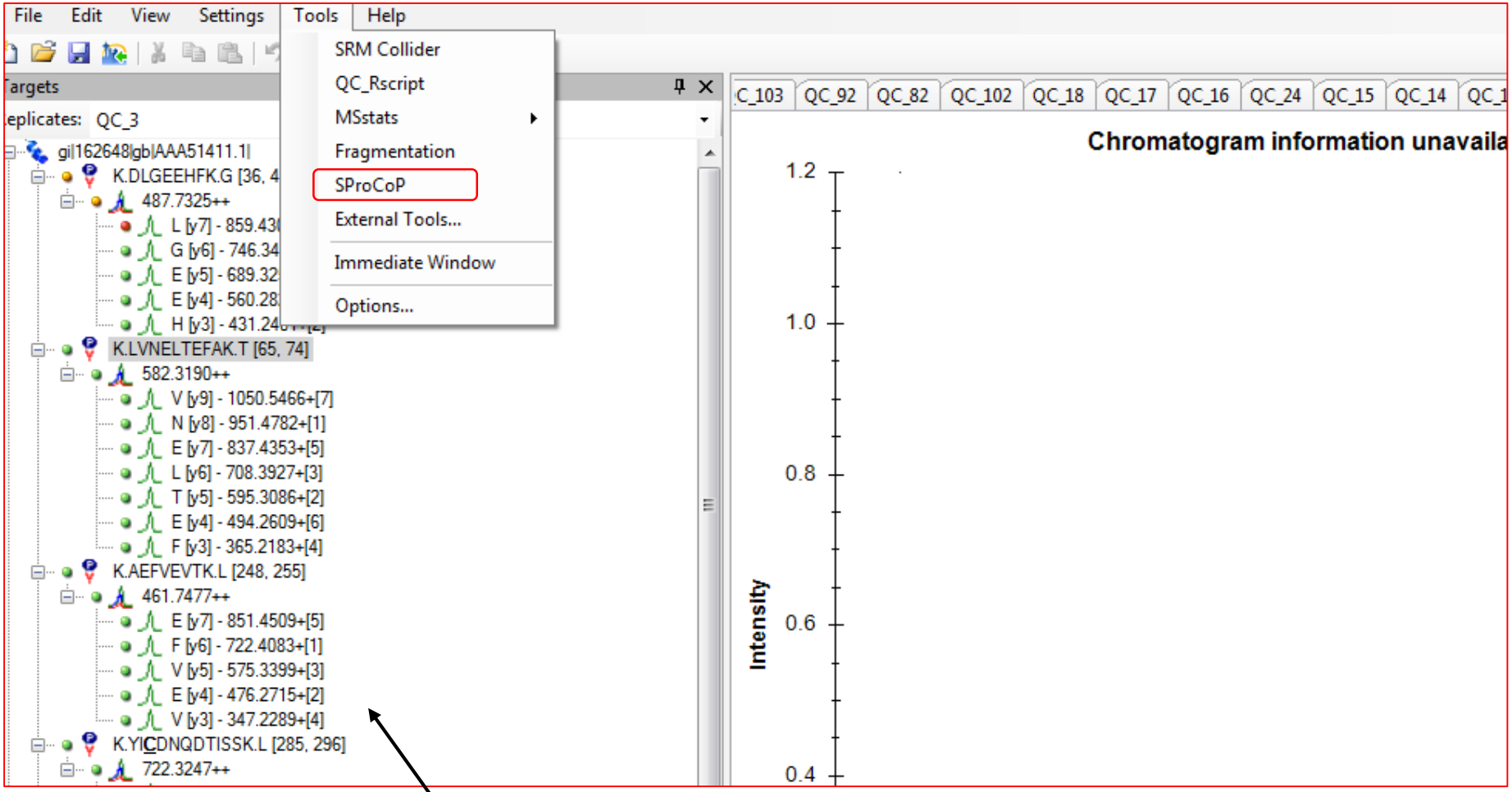
Statistical Process Control in Proteomics (SProCoP)

Bereman, MS *et. al*., JASMS 25(4) 581. 2014



Using SProCoP

Step 1 - Import QC standards



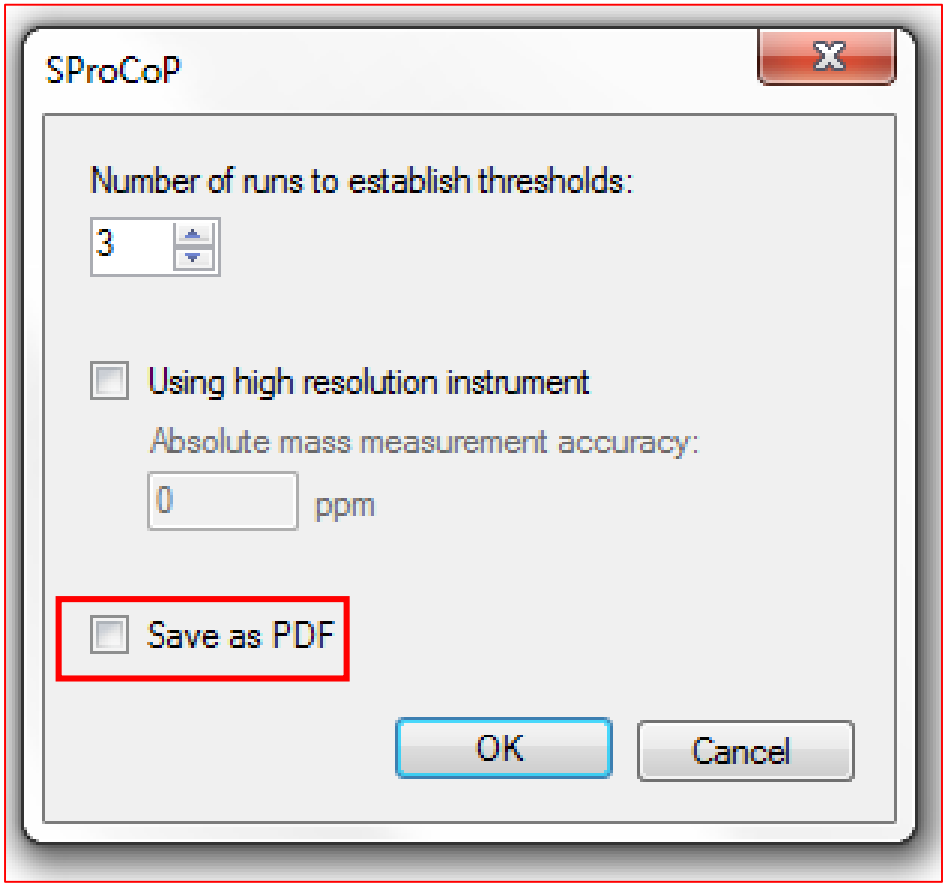
Targeted peptides

Step 2 – Defining Output

User can specify number of runs (i.e., Reference Set)
Default = 3

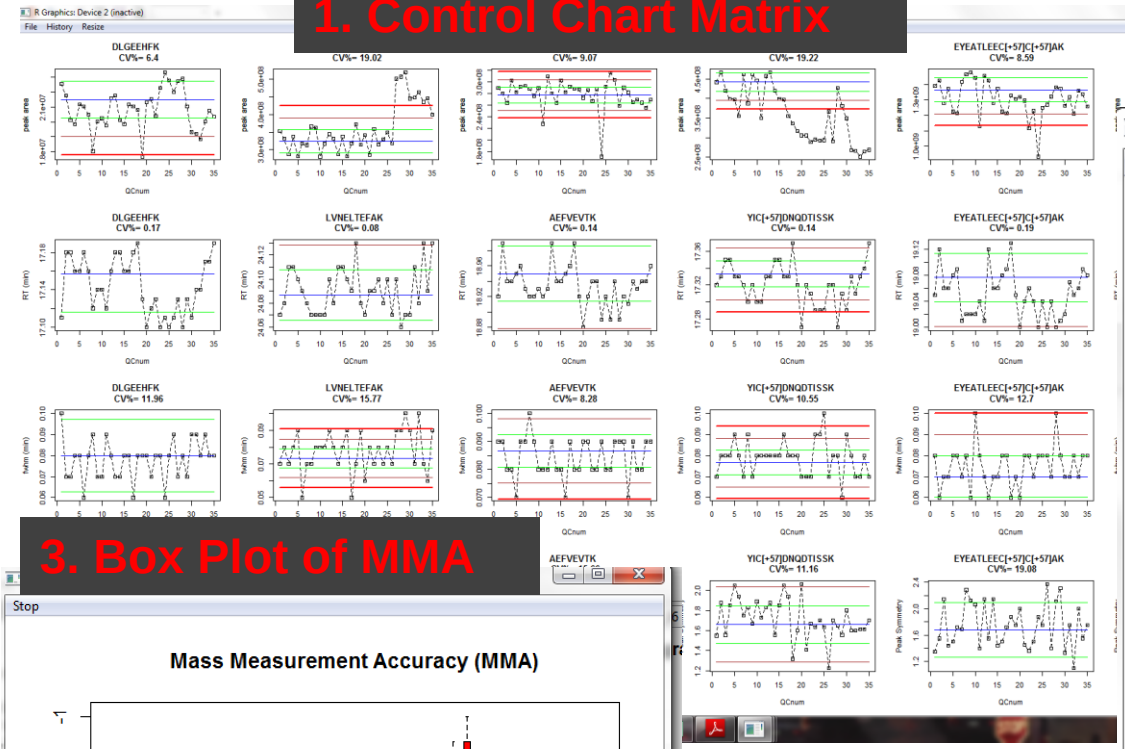
MMA in ppm
(only for high RP instruments)

Saves individual charts

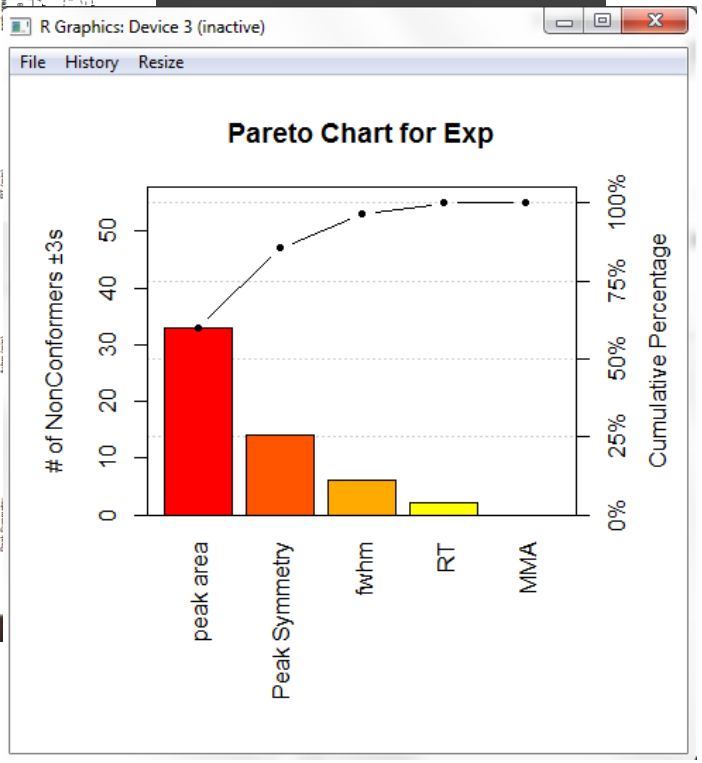


Simple – Yet Powerful Charts to Assess Performance

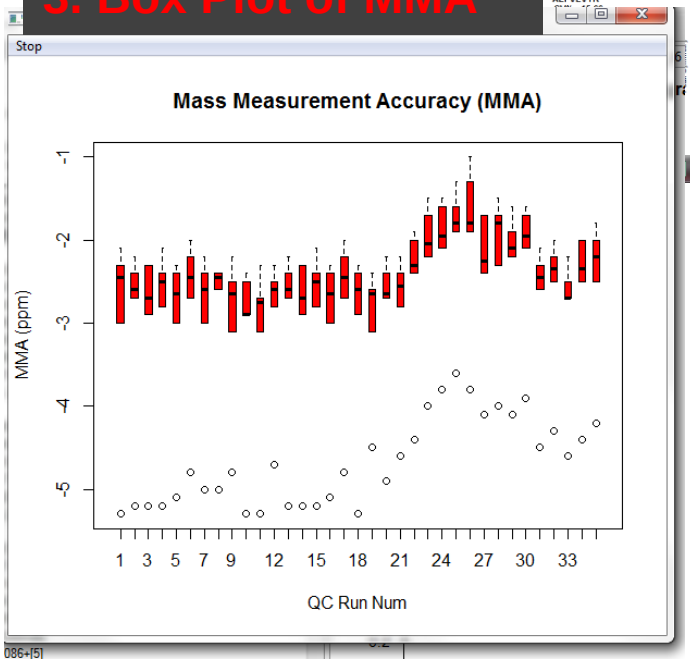
1. Control Chart Matrix



2. Pareto Chart



3. Box Plot of MMA

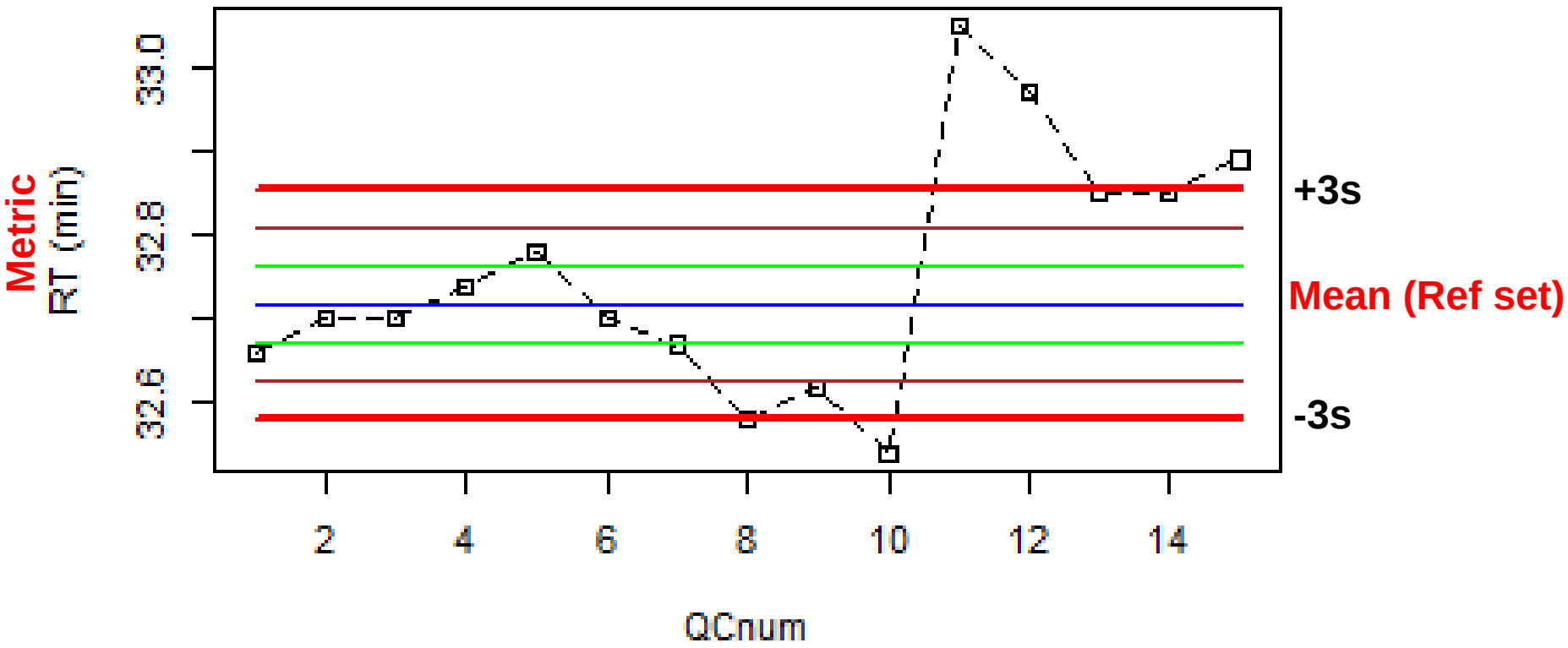


Shewhart Control Charts in SProCoP

3 - Sigma Quality Performance (~1 out of 370 to be a false positive)

Peptide sequence → VLVLDTDYK

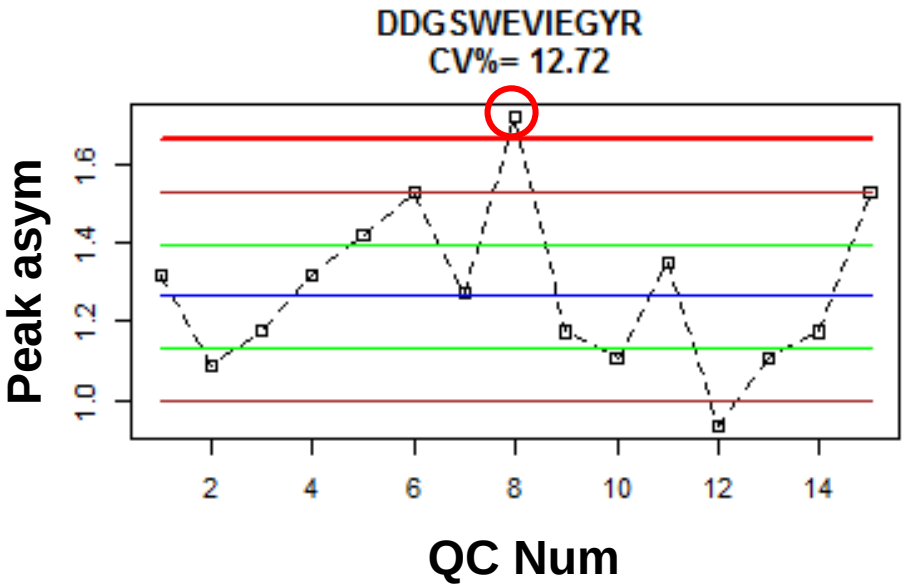
CV%= 0.44 ← CV across all runs

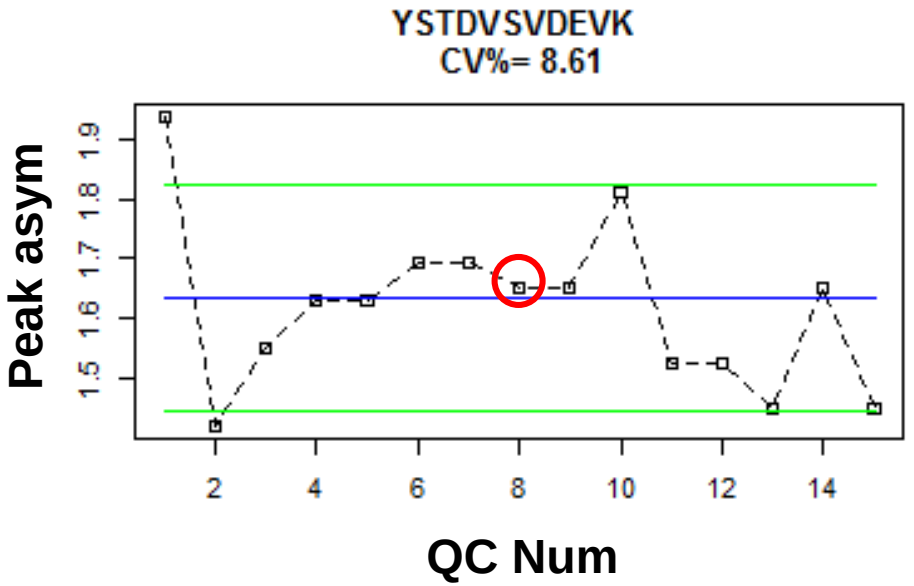


Interpretation of Control Charts

Detect systematic trends – instead of single semi random occurrences

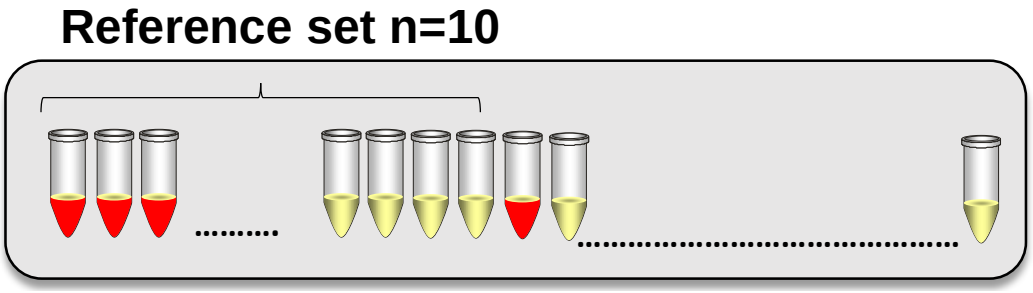
1. Do not rely on single peptide/metric measurements
2. How do the other peptides for that particular metric perform?
3. Is there an obvious systematic trend?
4. How does the next QC run perform?

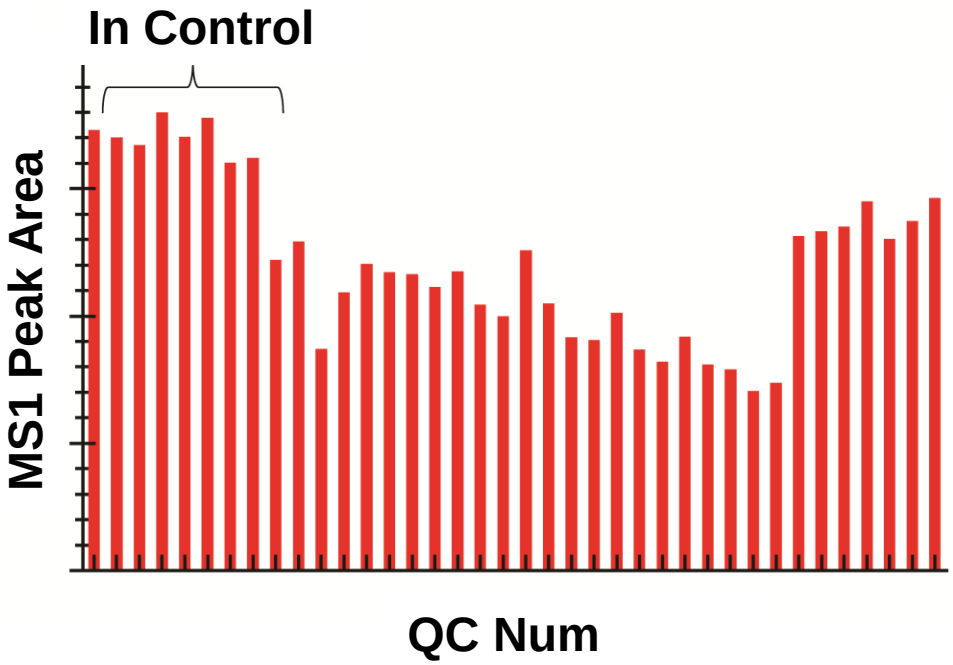


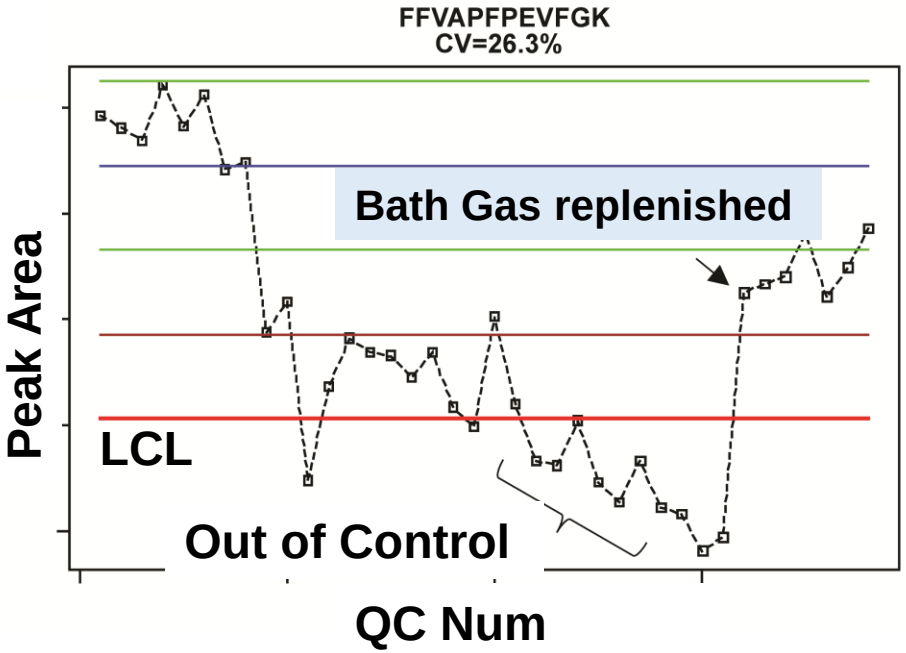


1. Utilizing SProCoP – Monitoring LC MS/MS – System Suitability

Bereman, MS *et. al*., JASMS 25(4) 581 2014







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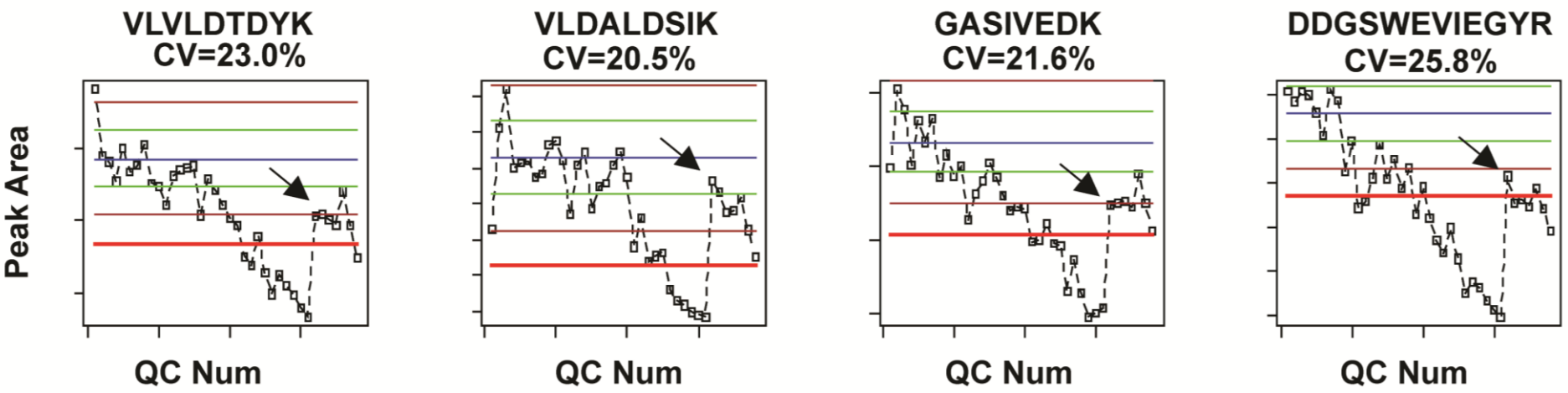


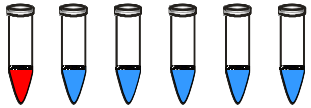
<u>Importance of Systematic Evaluation</u> – Problem may have not been diagnosed as quickly

2. Utilizing SProCoP – Identification of Sources of Variation

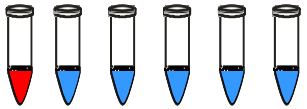
Do self packed traps affect the LC MS/MS process?

Bereman *et al.*, MCP 2013

1 lysate + 5 QC stds



Trap 1 (4.0 cm)



Trap 2 (3.9 cm)

Trap 3 (4.1 cm)

2. Utilizing SProCoP – Identification of Sources of Variation

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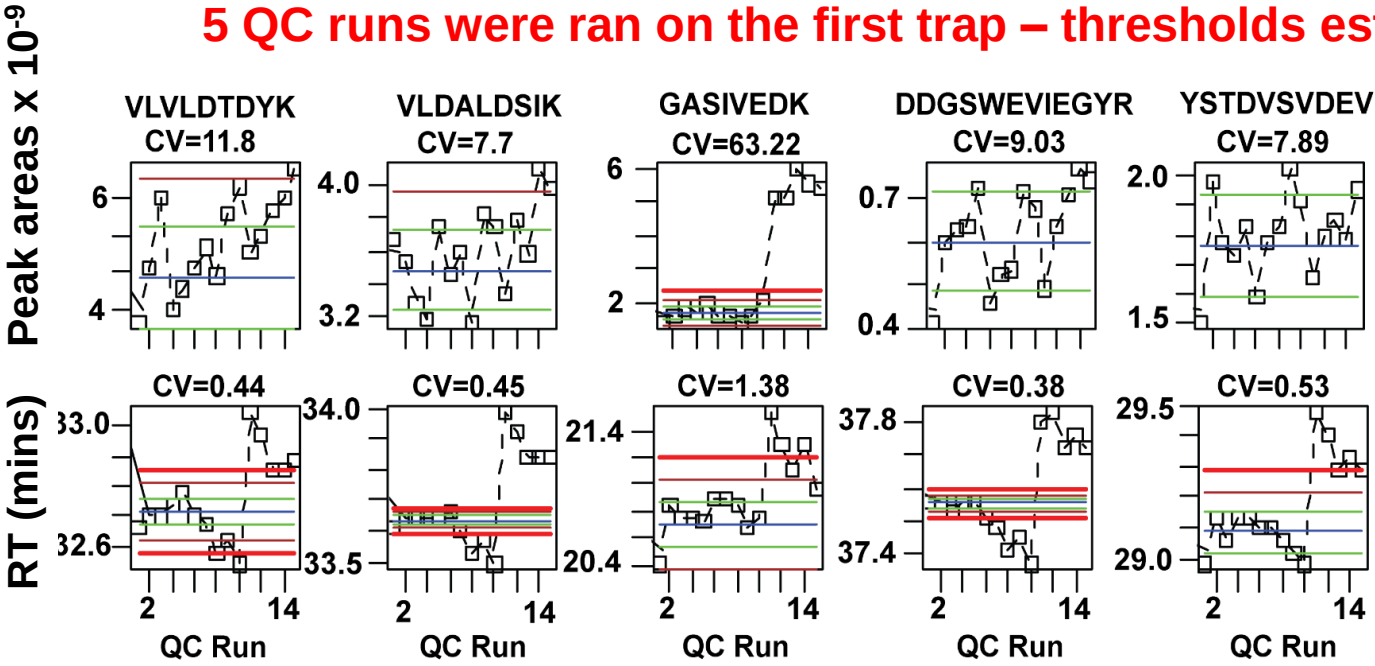
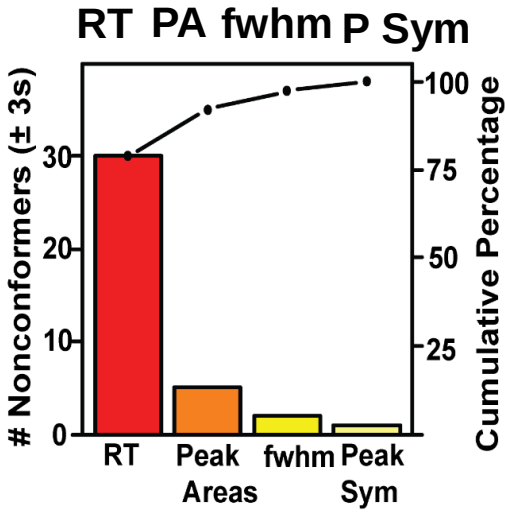
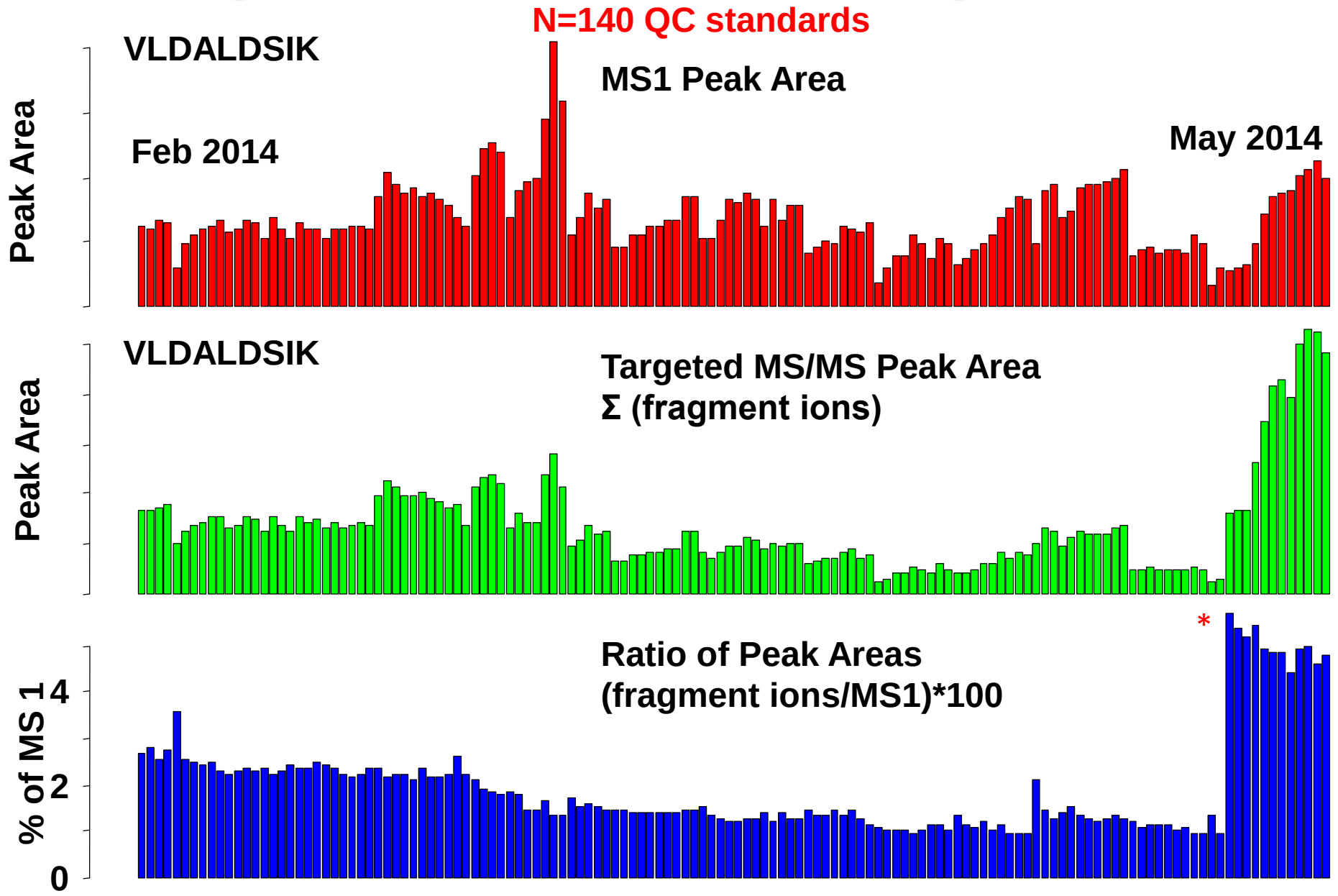
5 QC runs were ran on the first trap – thresholds established



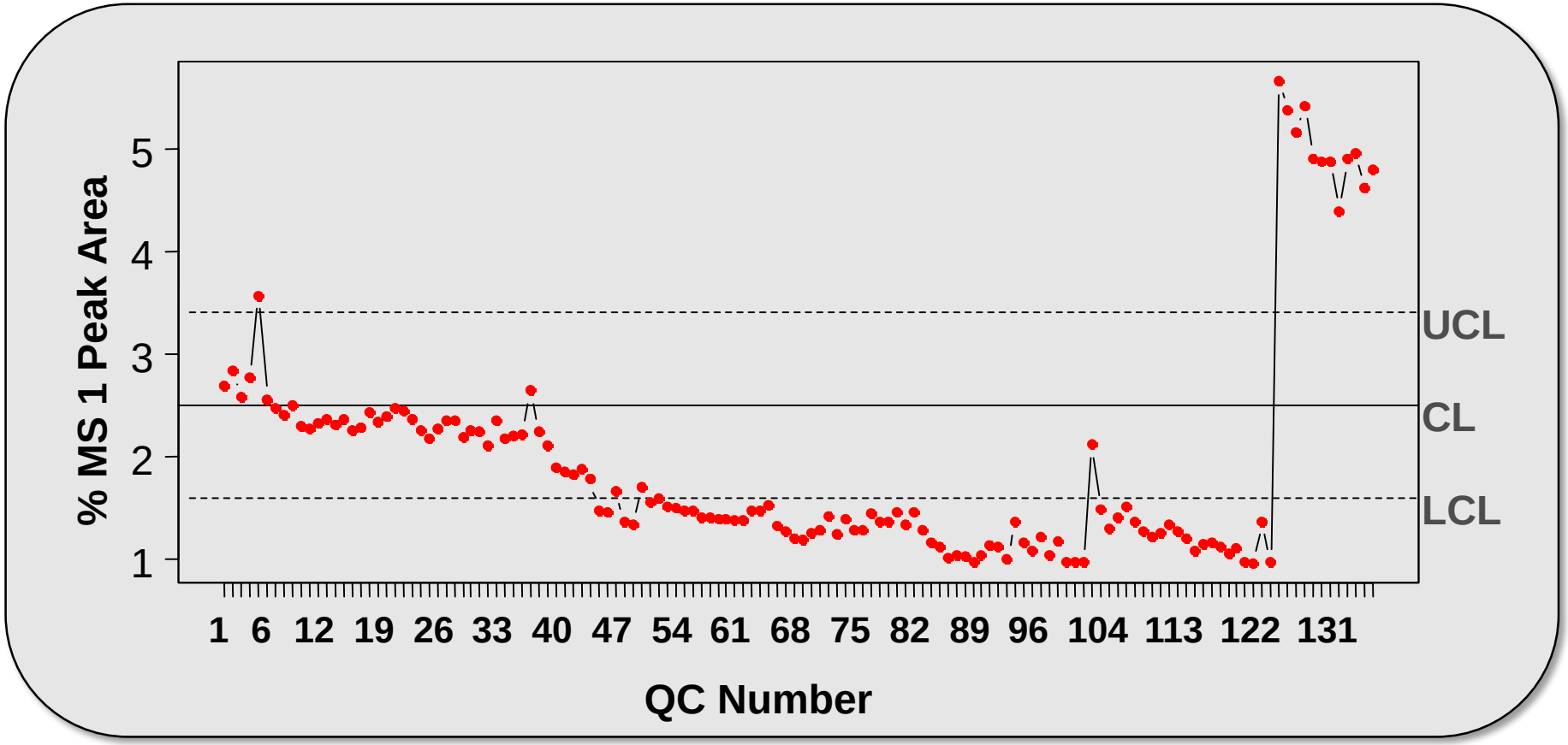


Pareto chart provides nice summary of data – and points to which metric is most variable

3. Longitudinal Instrument Tracking - SProCoP

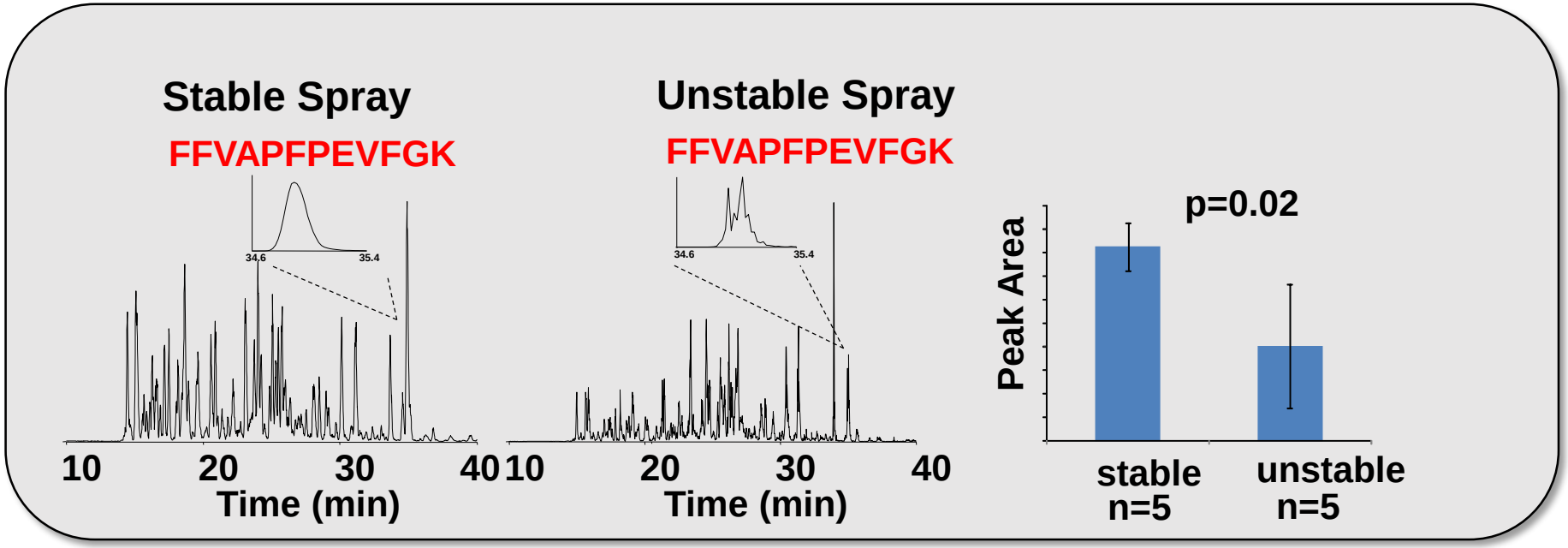


Longitudinal Instrument Tracking - SproCoP



Future Metric – Spray Stability

Difficult to quantify

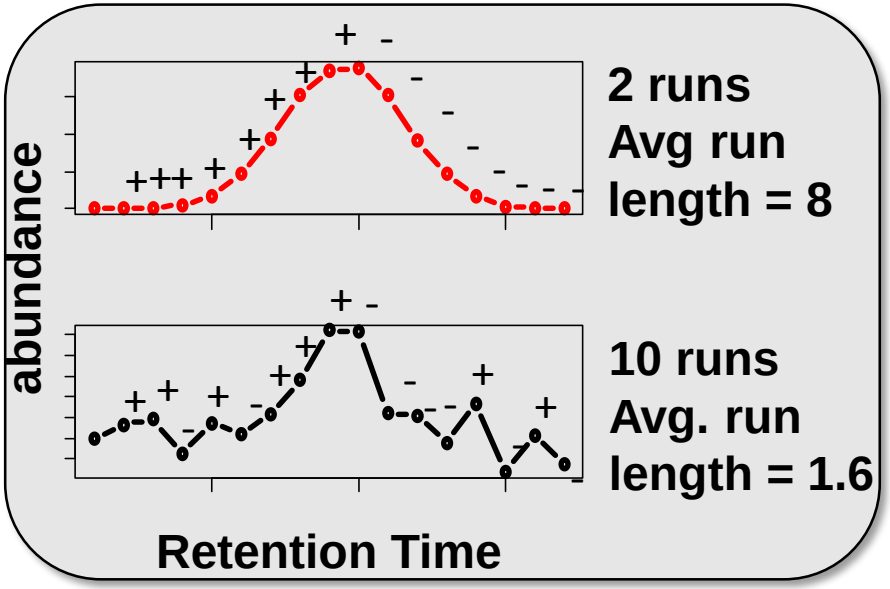


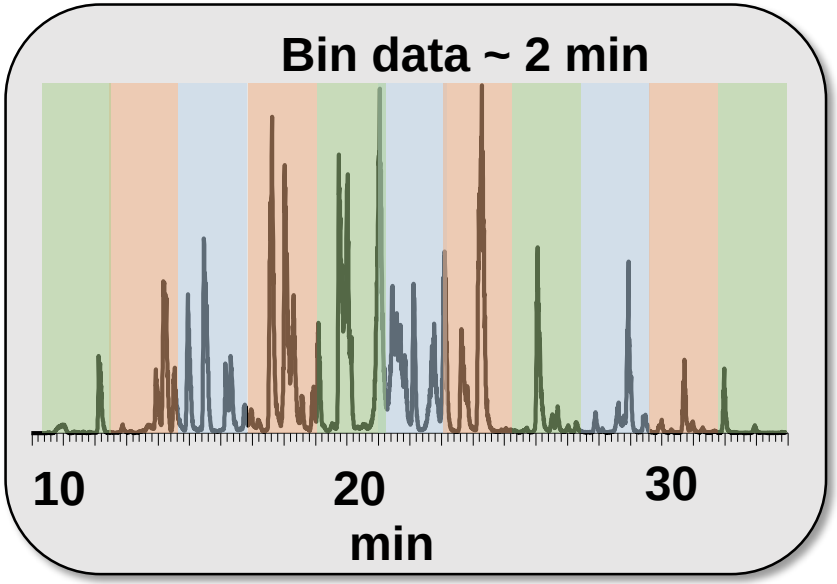
Increased variance in abundances – decreased power to identify differences and can lead to false positives

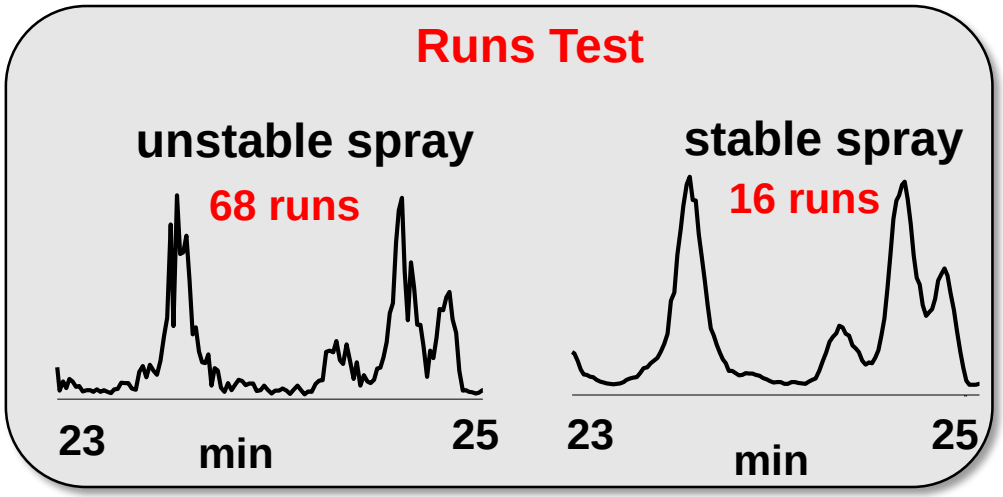
Qualitative detection is based on duty cycle

Runs Test to Determine When ESI Stability Changes

$$Sign = I_{N+1} - I_N$$

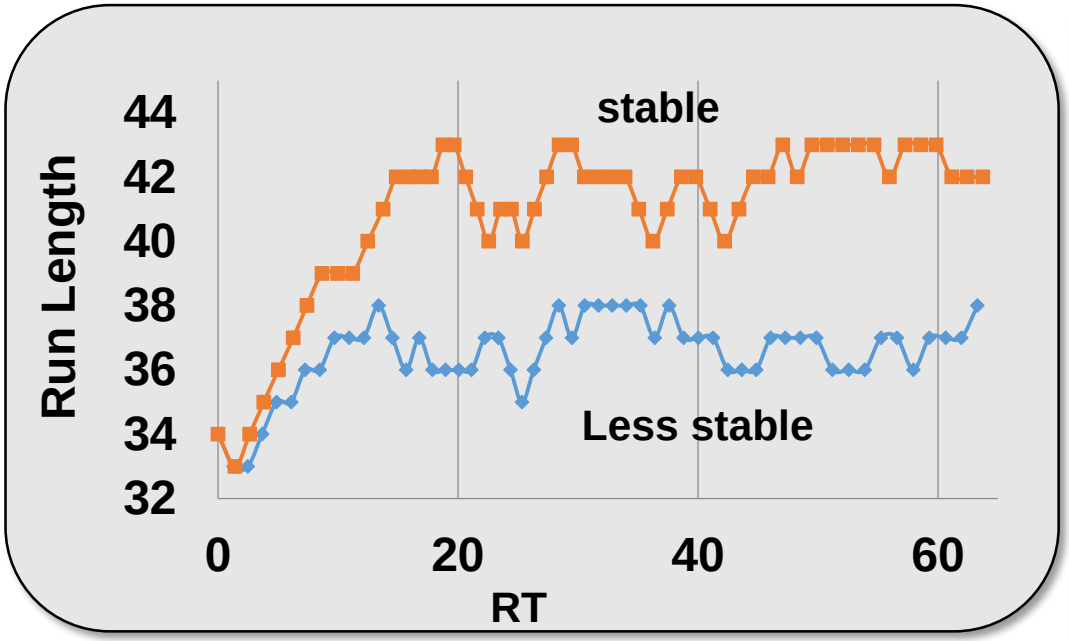


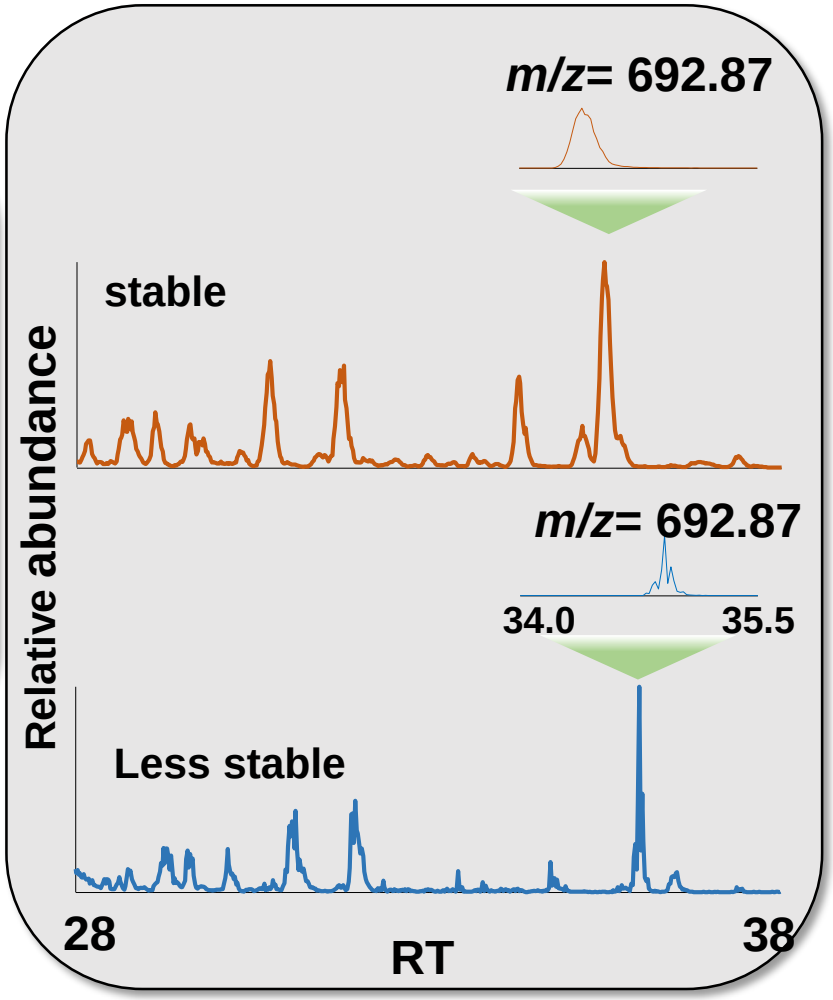




Unstable spray was smoothed (Boxcar n=3) to mimic stability

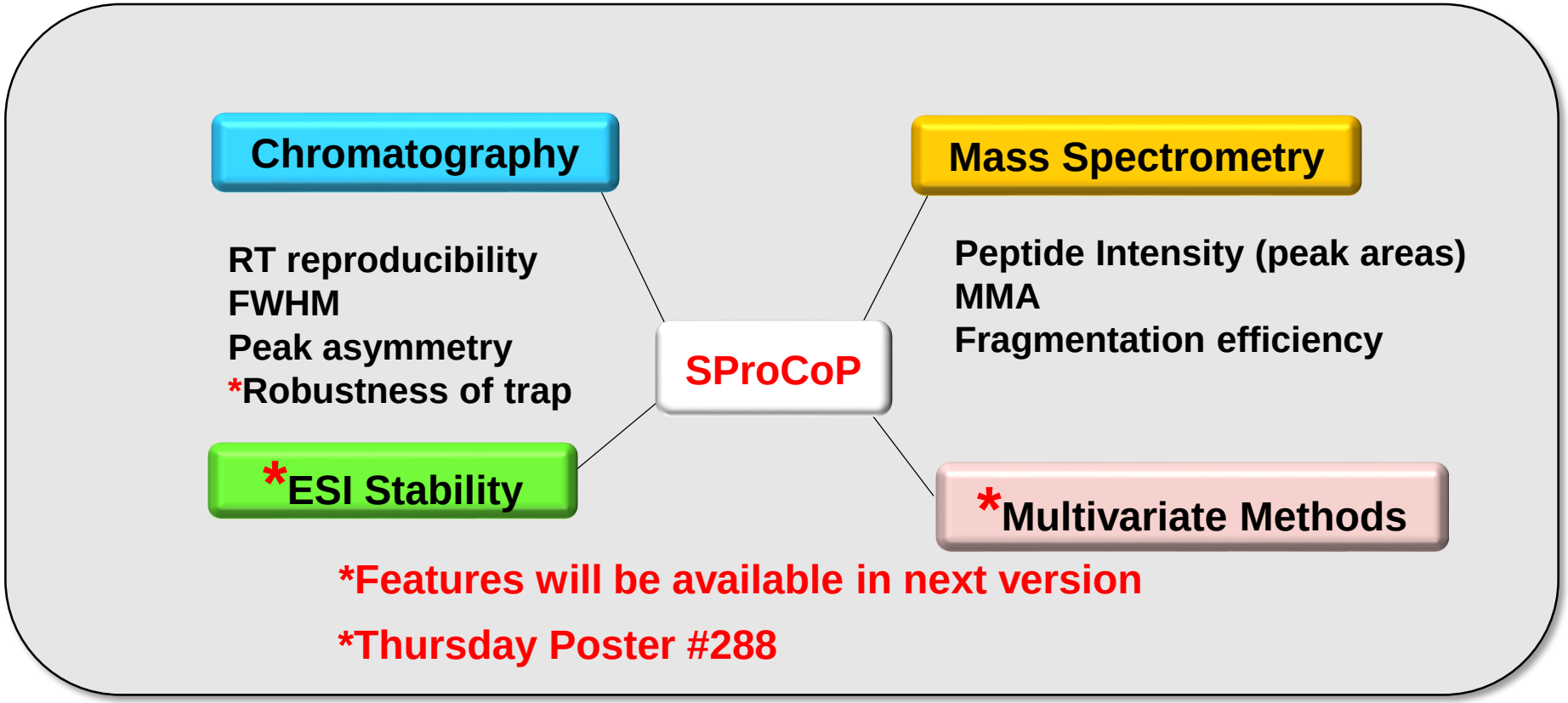
Average Run Length Differentiates ESI Stability





- Define spray stability based on reference set – track metric in control chart

Summary – What Can SProCoP do for YOU – ?



All from a couple of mouse clicks!

Acknowledgements

N.C. State University

Center for Human Health and the Environment
Dr. Emily Griffith - Department of Statistics

Skyline Team

Michael MacCoss
Brendan MacLean
Nick Shulman
Yuval Boss