Statistical Tools for Continued Process Verification Changepoint Control Charts

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Overview

- Introduction
- Statistical methods used for CPV
  - Changepoint analysis combined with Ppk and control limits
- Summary

Note: All data and plots shown on the following slides are based on simulations and are not real production data.

Introduction

Introduction

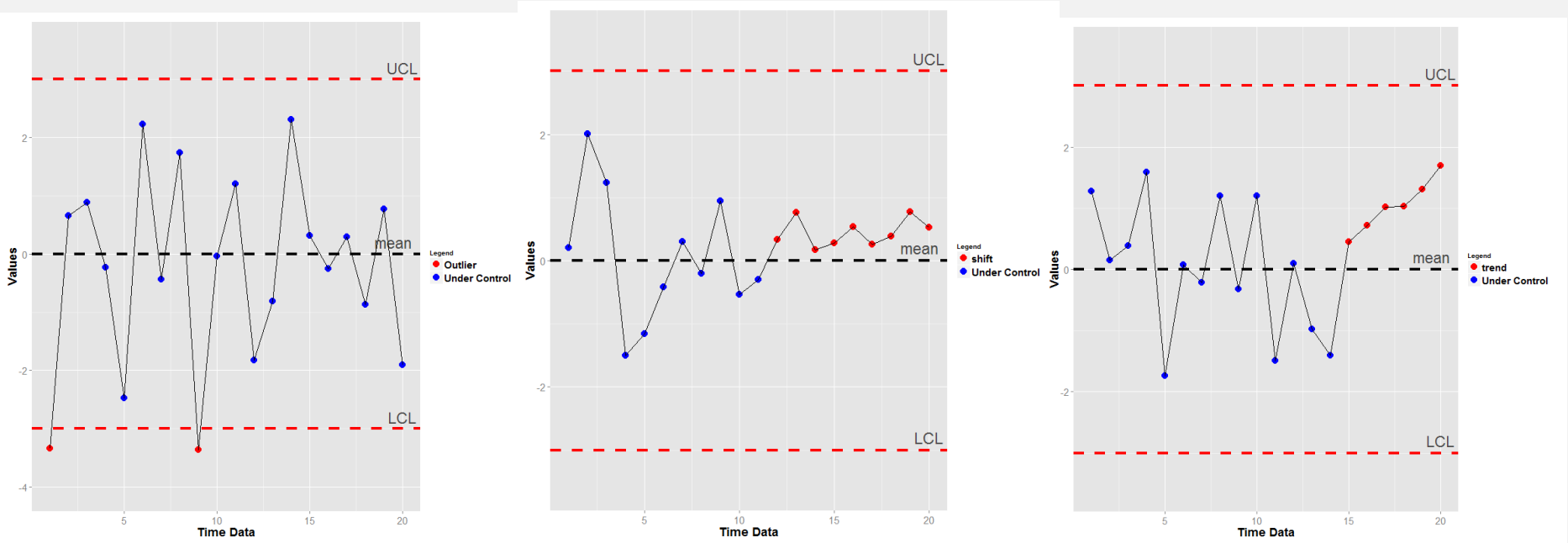
- FDA Guideline on Process Validation (2011): "**Production data should be collected to evaluate process stability and capability**"
- Classical statistical tools for CPV are control charts, Cpk (short-term), Ppk (longterm)
- GSK applies a combined approach of (a posteriori) **changepoint analysis, control limits, short term + long term Ppk**

Statistical Methods in CPV

Changepoint Control Charts

Control Chart

Classical tool to detect shifts and trends / pattern



Outlier

Nelson Rule 1:
One Point out of +/- 3*SD

Shift / Changepoint

Nelson Rule 2:
Nine (or more) points in a row
all above the average or
all below the average

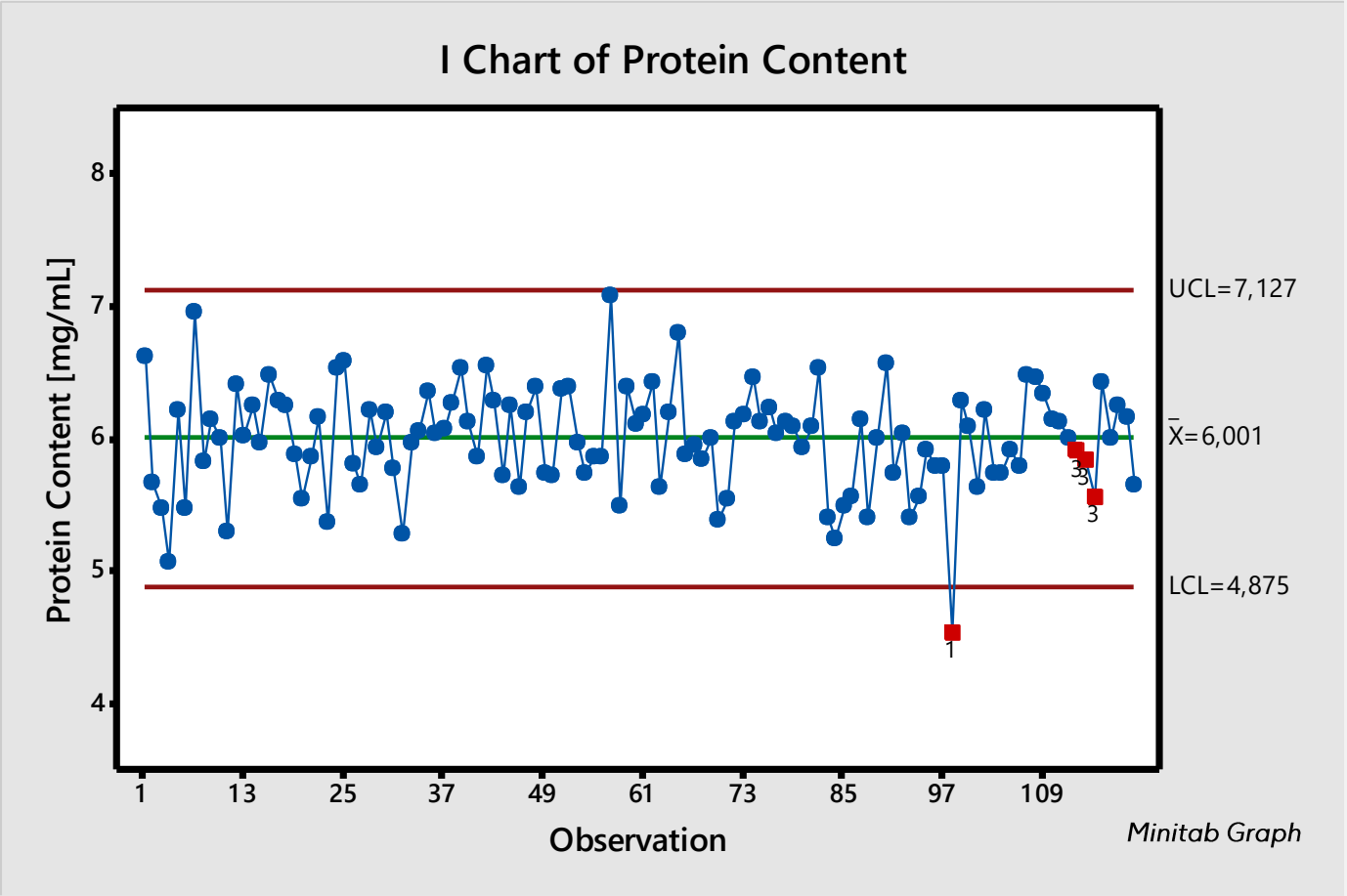
Pattern

Nelson Rule 3:
6 or more points in a row
all increasing or
all decreasing

LCL = Lower Control Limit, typically defined as average - 3*standard deviation
UCL = Upper Control Limit, typically defined as average + 3*standard deviation

Control Chart

Classical tool to detect shifts, outliers, trends / pattern

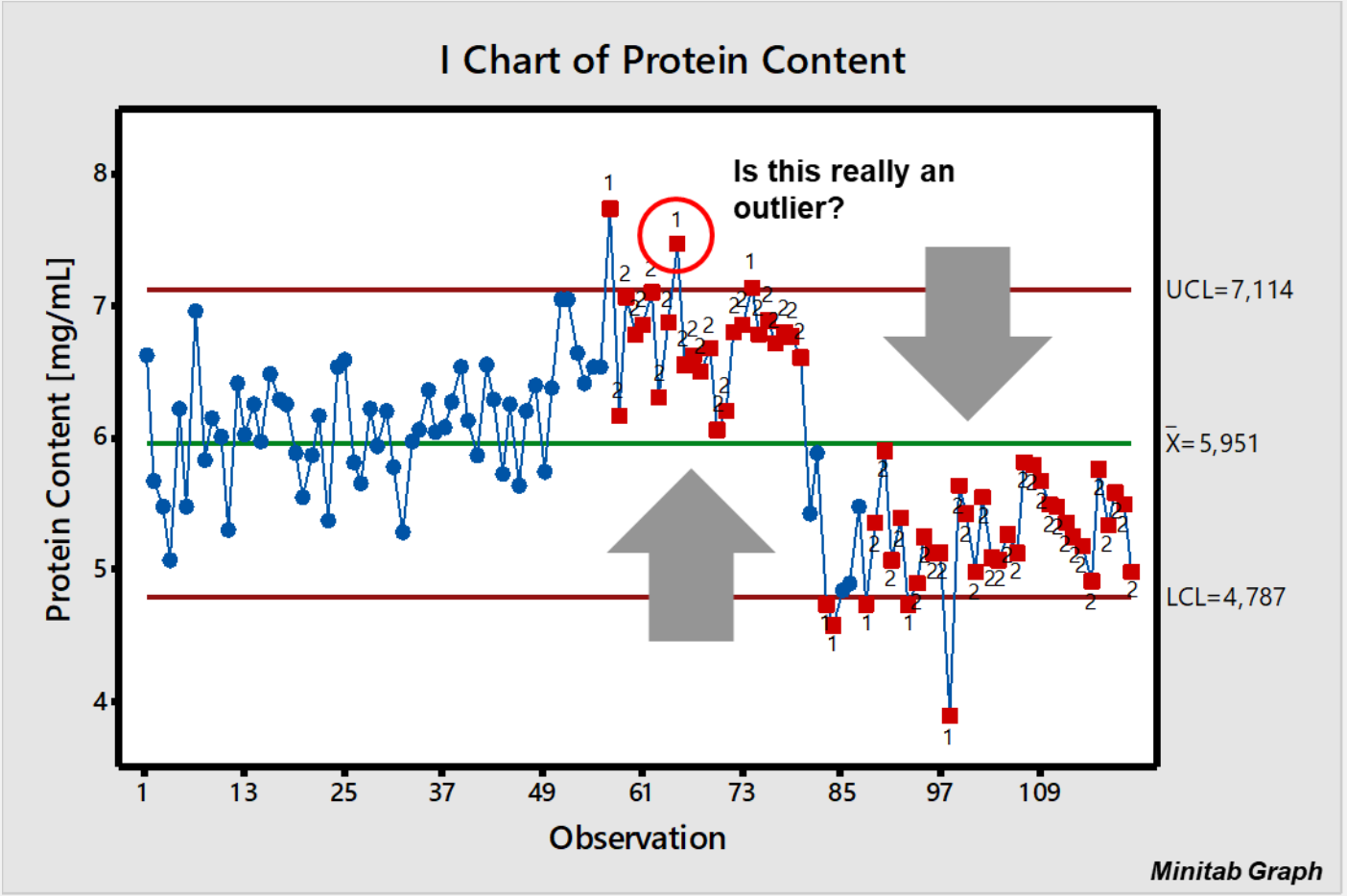


no change-point within the data

1: outlier
2: shift
3: trend/pattern

Control Chart

No tool for (automated) analysis for not stable long-term data



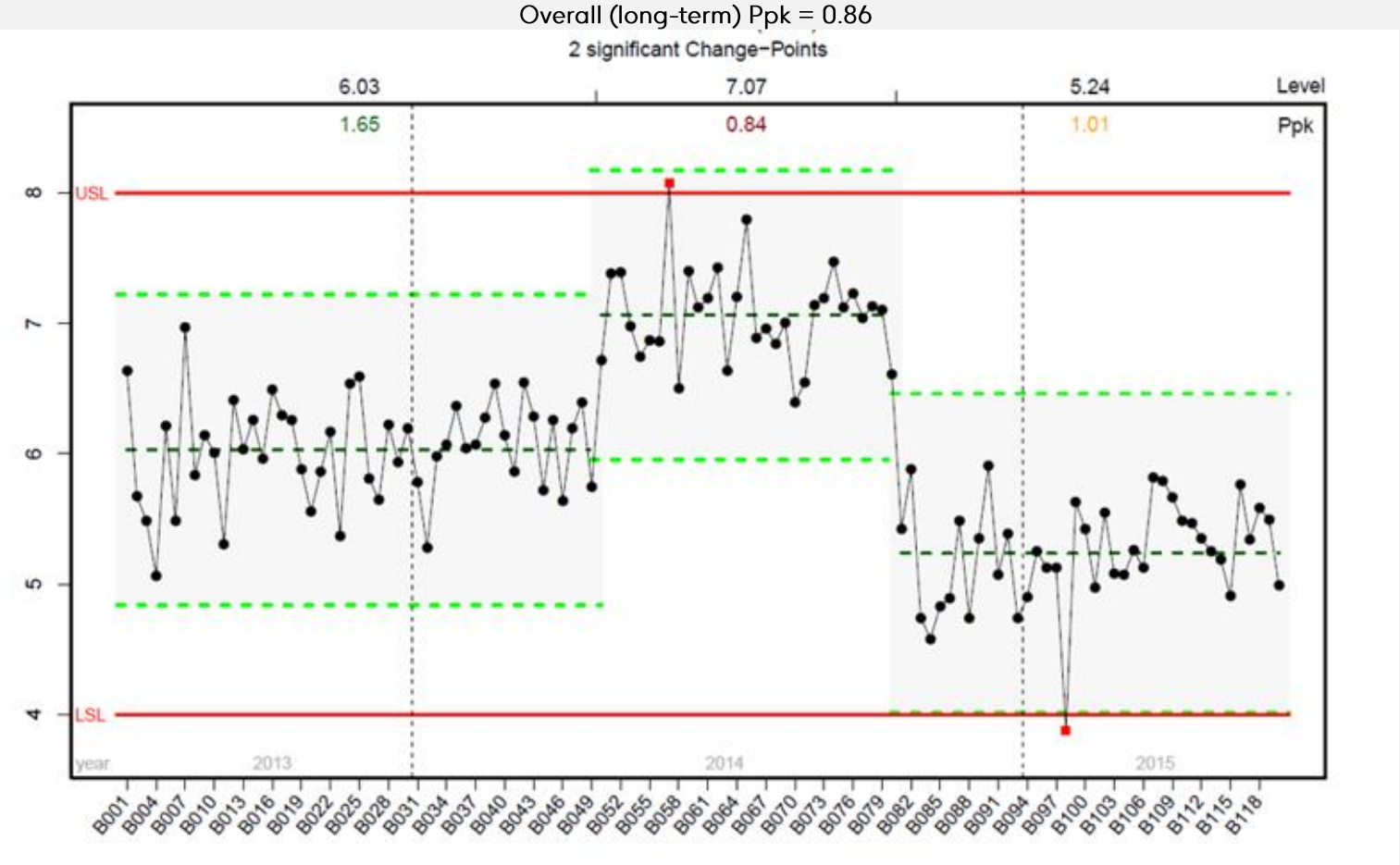
changepoint 1
+ 2 standard deviations

changepoint 2
- 2 standard deviations

1: outlier
2: shift
3: trend/pattern

Changepoint Control Chart

Combined approach using changepoint analysis, statistical control limits and Ppk

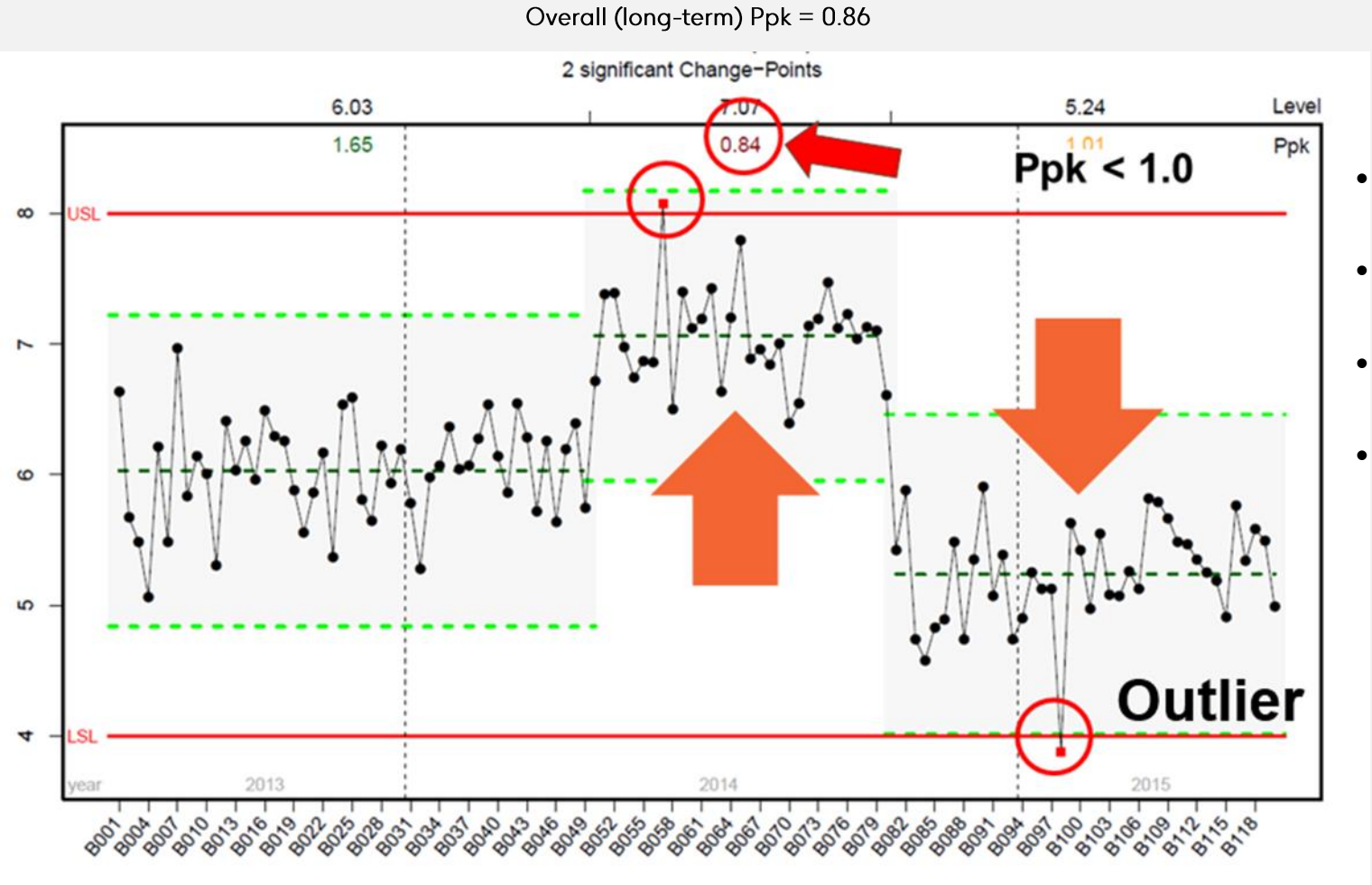


- Red lines: specification limits
- Dotted green lines:
  +/- 3*standard deviation around the mean per changepoint segment

Note: In addition to the short-term (flexible) control limits per changepoint segment fixed longterm control limits could be used.

Changepoint Control Chart

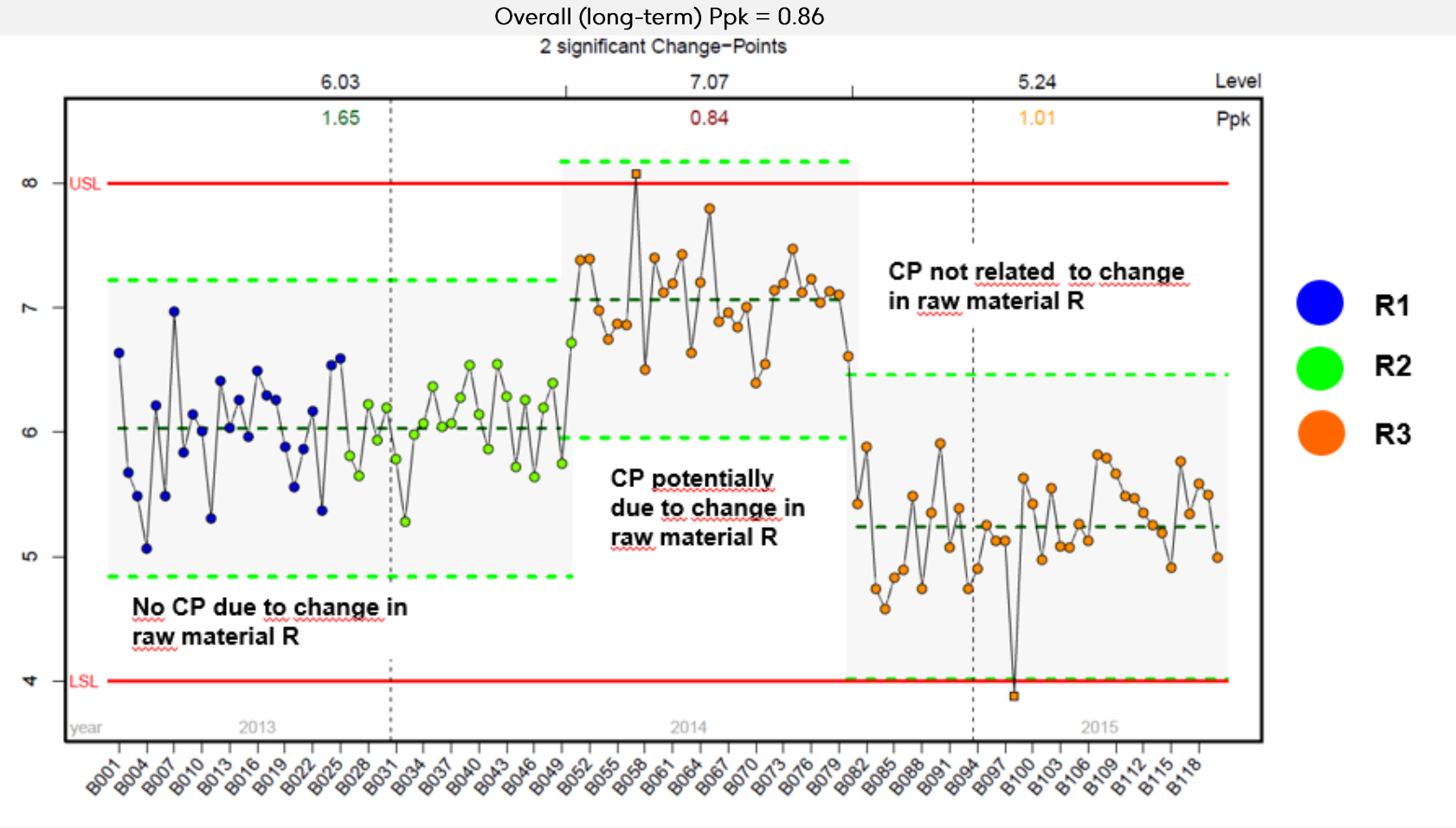
Combined approach using changepoint analysis, statistical control limits and Ppk



- **Sequential (batch by batch)** analysis by control limits
- **Retrospective** analysis by changepoint analysis
- **Short-term** process performance evaluation by short-term Ppk
- **Long-term** process performance evaluation by long-term Ppk.

Colored Changepoint Analysis for Root Cause Analysis

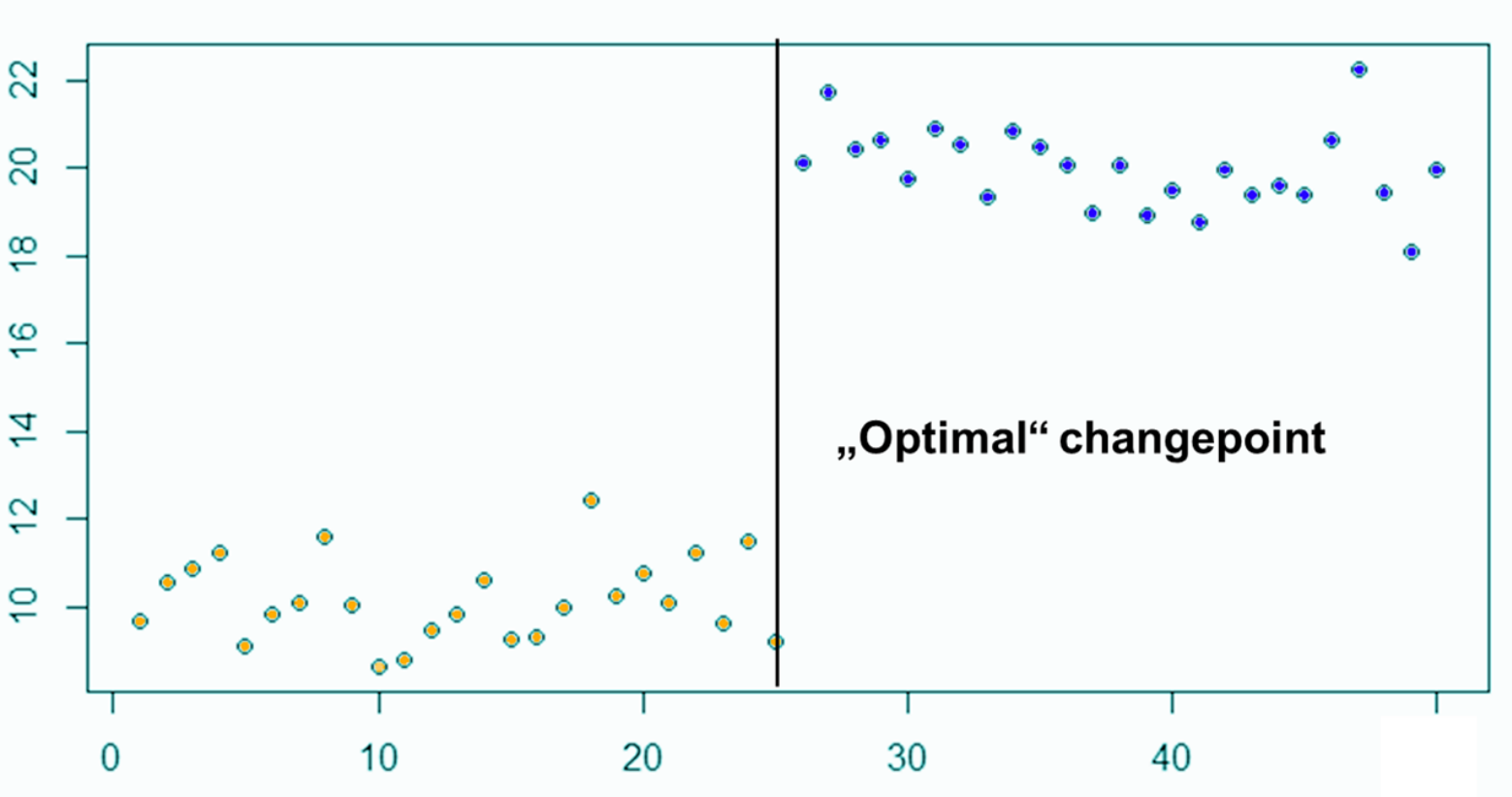
Change of raw material root cause for changepoint?



Changepoint Analysis (a posteriori)

How does it work – search for most probable changepoint candidate

Step1: Search for „optimal“/most probable changepoint in mean

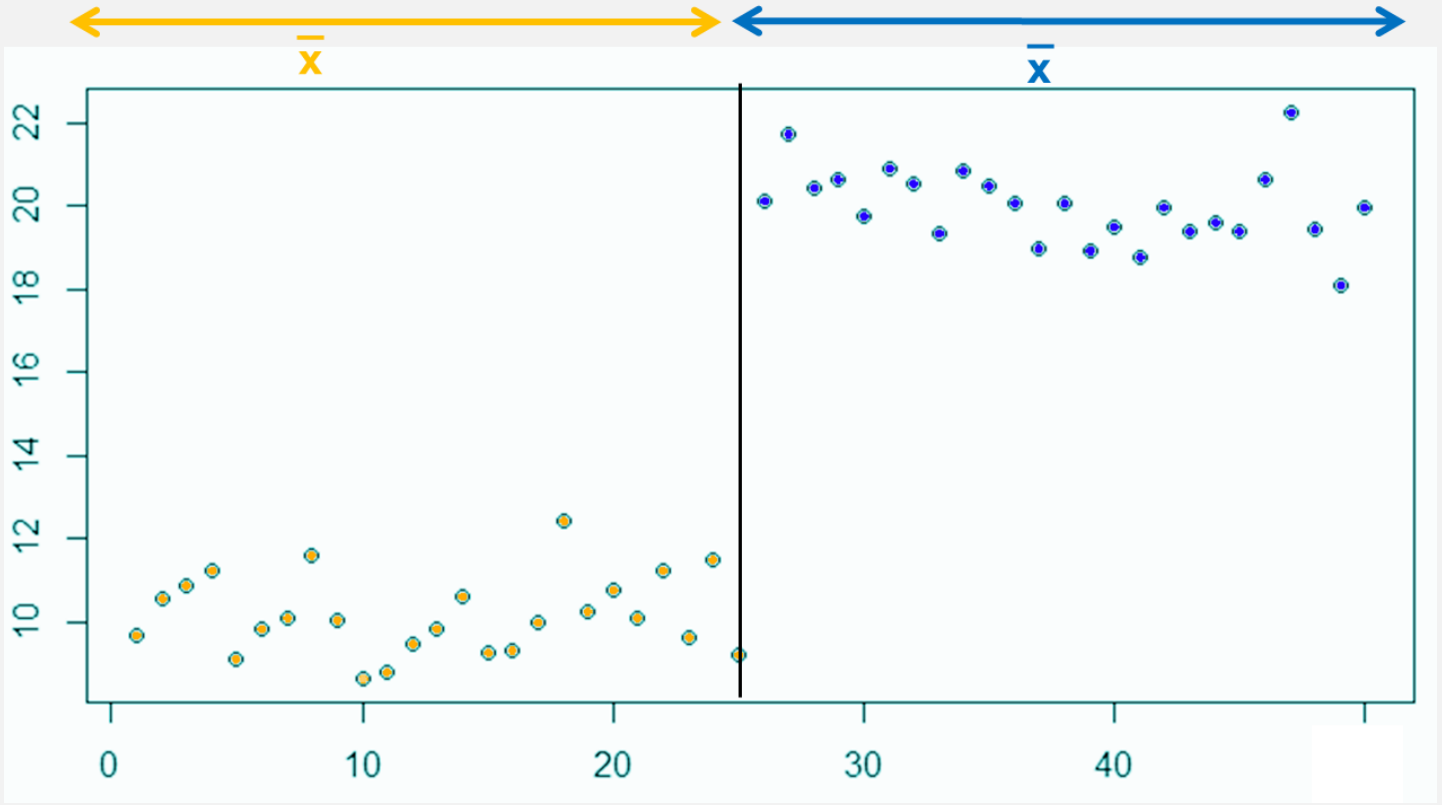


Changepoint Analysis (a posteriori)

How does it work - Test for significance

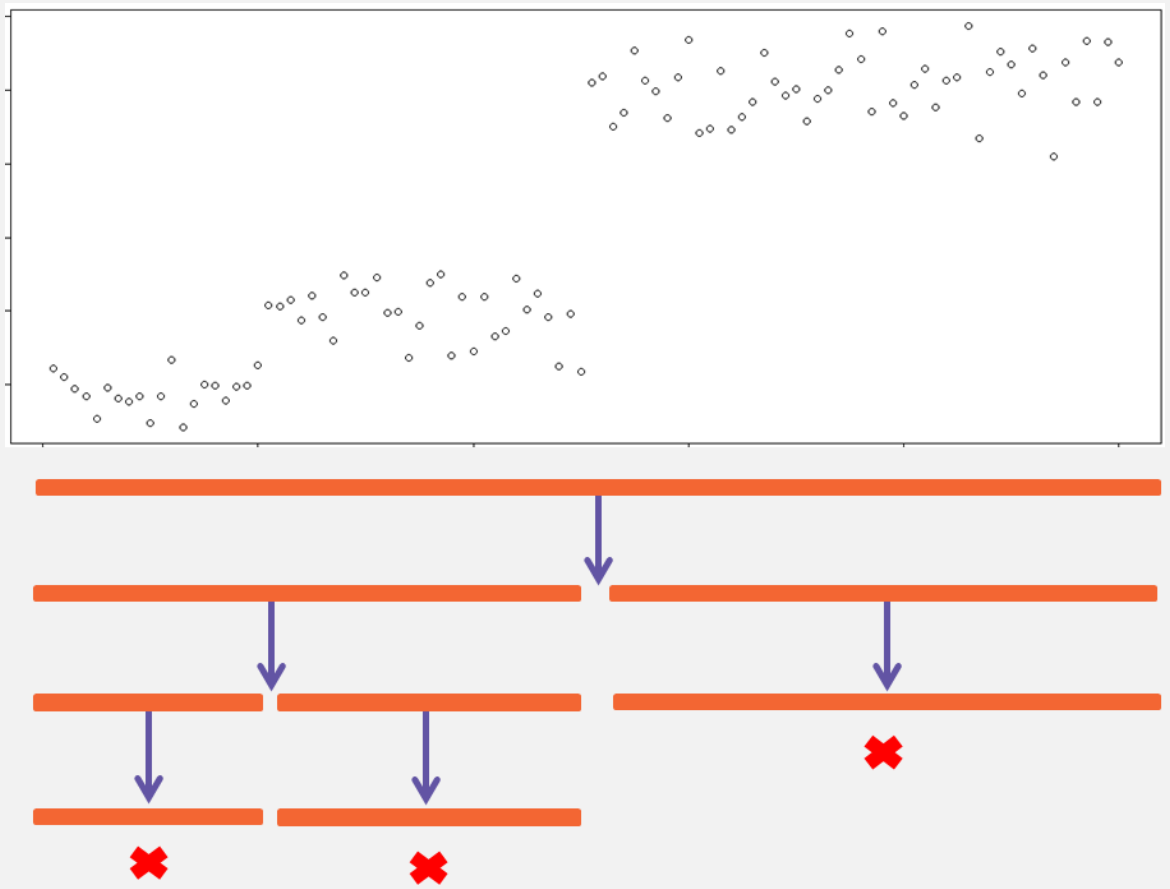
Step 2: Check if the „most probable“ changepoint is significant

Teststatistic: (Weighted) difference in mean compared to results for random permutations of given data set.



Changepoint Analysis (a posteriori)

How does it work – Iterative approach to detect more than one changepoint



The algorithm applies the test iteratively until no more significant changepoints are detected.

Summary

- Changepoint Analysis is able to detect (multiple) systematic shifts in mean.
- A combined „Changepoint Control Chart“ enables to perform:
  - Sequential (batch by batch) analysis by control limits
  - Retrospective analysis by changepoint analysis
  - Short-term process performance evaluation by short-term Ppk
  - Long-term process performance evaluation by long-term Ppk.
- Combined approach enables to distinguish between systematic shifts and „isolated“ outliers
- Use of „Short-term“ Ppk (Ppk per change-point segment) instead of Cpk avoids the impact of autocorrelation

References

Changepoint Analysis

Biostatistics (2004), **5**, 4, *pp.* 557–572
doi: 10.1093/biostatistics/kxh008

Circular binary segmentation for the analysis of array-based DNA copy number data

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Segments DNA copy number data using circular binary segmentation to detect regions with abnormal copy number

Author: Venkatraman E. Seshan, Adam Olshen

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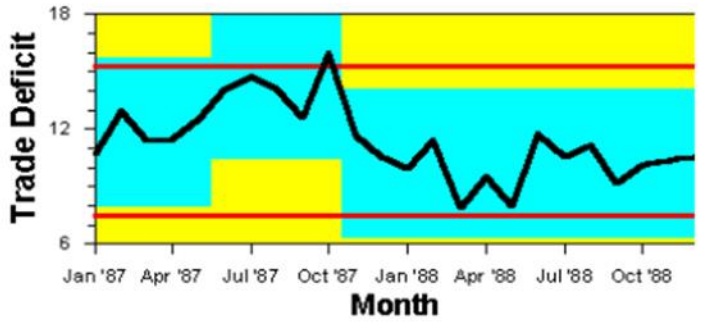
Change-Point Analyzer Software



http://www.variation.com/cpa/index.html

http://cran.r-project.org/index.html

Disclaimer

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Jochen Giese is employee of the GSK group of companies.