Estimating Stabilization Time in Continuous Manufacturing

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Overview

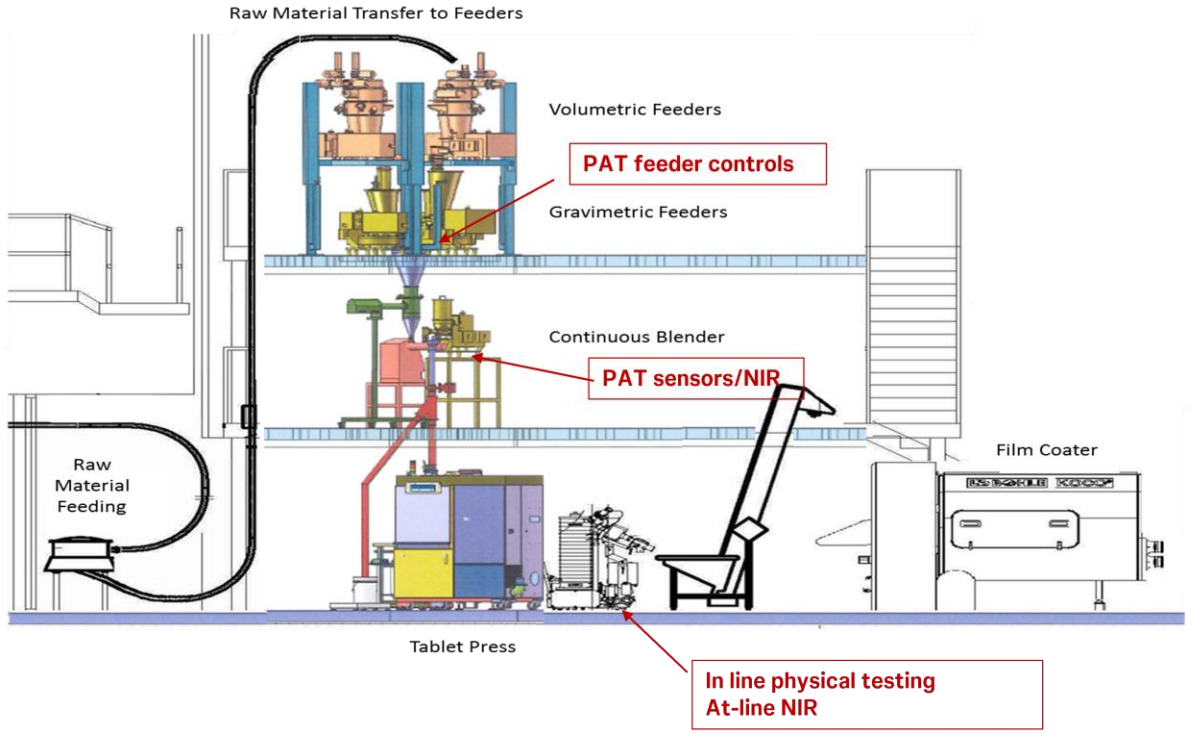
- Background
- Data
- Methodology
- Results
- Conclusion

In-process control in Continuous manufacturing

Understanding of process, Quality by design, feedback loops, real time release

Sampling options:

- Batch process: off-line and at-line
  - Traditional analytical methods “in lab”
- Continuous process: on-line and in-line monitoring needed
- **Process analytical technology**:
  - various types of sensors that allow continuous evaluation of material in the line
  - Spectroscopy very commonly used (**NIR**)
  - Broader use: some PAT leveraged in batch process as well



IPC average values range

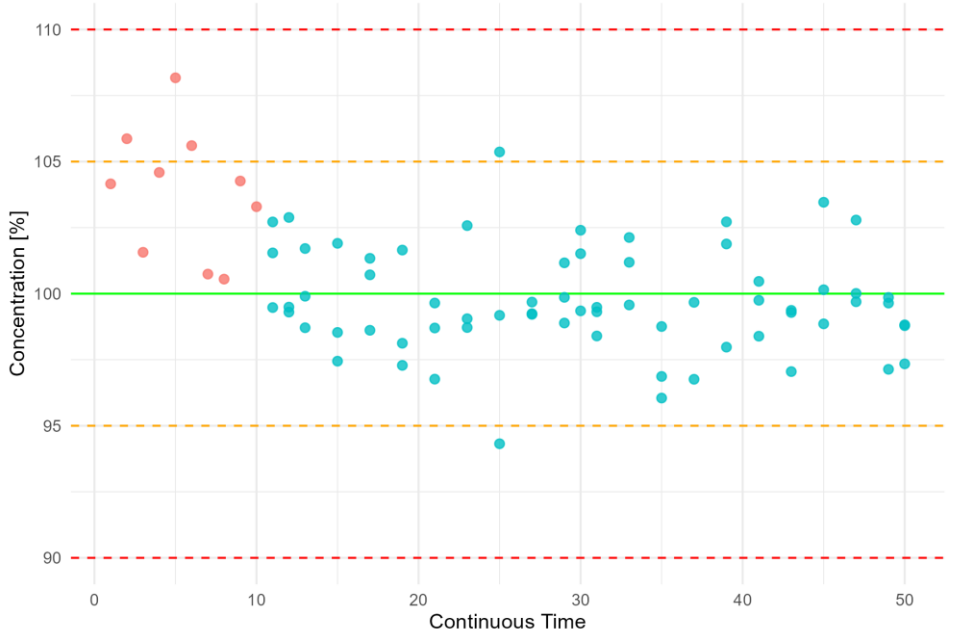
Eric Sánchez Rolón, Mauricio Futran, & William Randolph. (2022). Chapter 15 - Continuous manufacturing process development case study. In F. J. Muzzio & S. Oka (Eds.), *How to Design and Implement Powder-To-Tablet Continuous Manufacturing Systems* (pp. 319-381). Academic Press. https://doi.org/10.1016/B978-0-12-813479-5.00016-1

CM process

Start-up → State-of-control → Shutdown

- Feeders, blenders, tablet press being filled and started
- "stable" process performance and product quality

Concentration measurement for a simulated CM run



State-of-Control

Mean/Slope-based

- The process is considered slope-stable at the earliest stabilization time such that the chosen slope criterion (slope ≈ 0) holds for the entire trailing window.

Target-concentration-based

- Stability defined by reaching and staying near a target concentration level, i.e. 100%, or within a concentration band (95%-105%)
- Stabilization time is the time to threshold-crossing and staying there for a defined window.

Variability-based

- Start-up ends when process variability becomes stable.

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State-of-Control: slope-based

Smooth broken-stick model with logistic transition

- Assumes the profile changes from an initial trend to a plateau
- Fits a linear part before a smooth/rough transition to a flat part after

$$Y_t = a + b \cdot [(1 - s(t)) \cdot t + s(t) \cdot t_{\text{break}}] + \epsilon_t$$

The logistic transition function $s(t)$ operates as follows:

$$s(t) = \frac{1}{1 + e^{-\gamma \cdot (t - t_{\text{break}})}}$$

The parameters in this formulation have the following interpretations:

- a: Intercept value of the start-up phase (initial concentration level).
- b: Slope value of the start-up phase (rate of change before stabilization).
- t_{break}: Estimated stabilization time (breakpoint).
- γ (gamma): Smoothness parameter; increasing this value leads to a sharper transition between the two components.
- ϵ_t: Error term at time t .

State-of-Control: slope-based

Broken-stick model (Segmented Regression)

- Fits two connected linear trends with an unknown breakpoint
- Estimates both slopes: before and after the breakpoint

$$Y_i = \beta_0 + \beta_1 t_i + \beta_2 (t_i - \psi)_+ + \varepsilon_i,$$

where Y_i is the concentration measurement at time t_i, ψ is the unknown breakpoint, and ε_i is the residual error term.

$$(t_i - \psi)_+ = \max(0, t_i - \psi).$$

In this parameterization, β_1 is the slope before the breakpoint and $\beta_1 + \beta_2$ is the slope after the breakpoint. The breakpoint ψ is therefore the estimated time at which the concentration trend changes [8].

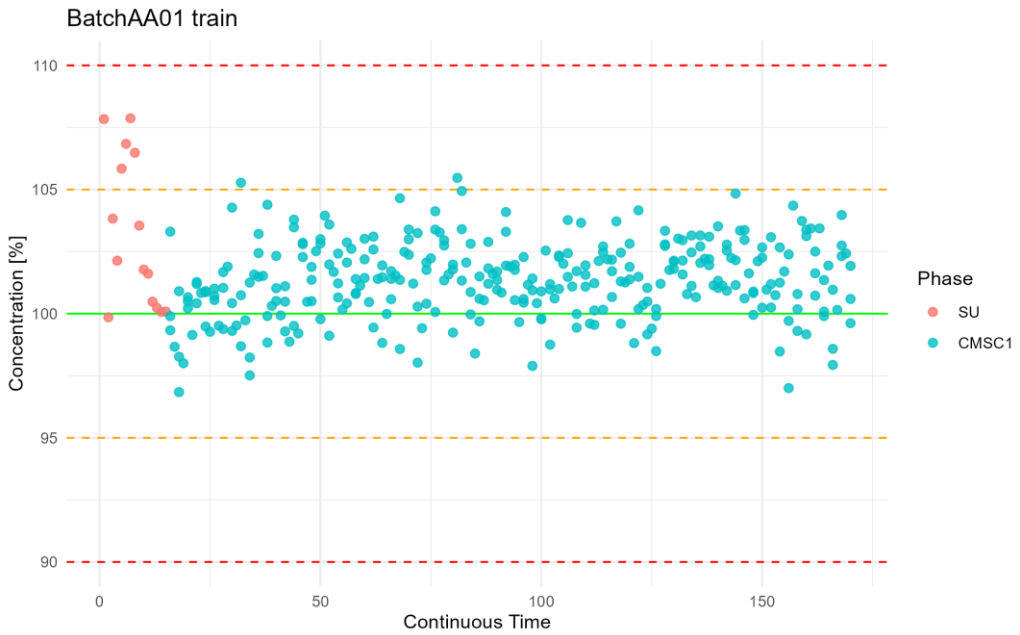
State-of-Control: variance-based

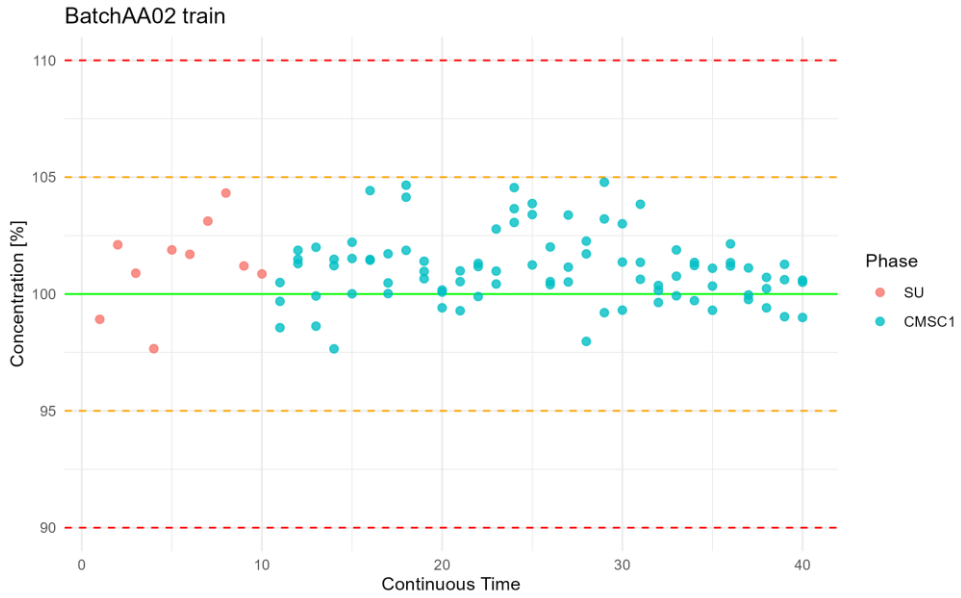
Variance change-point detection

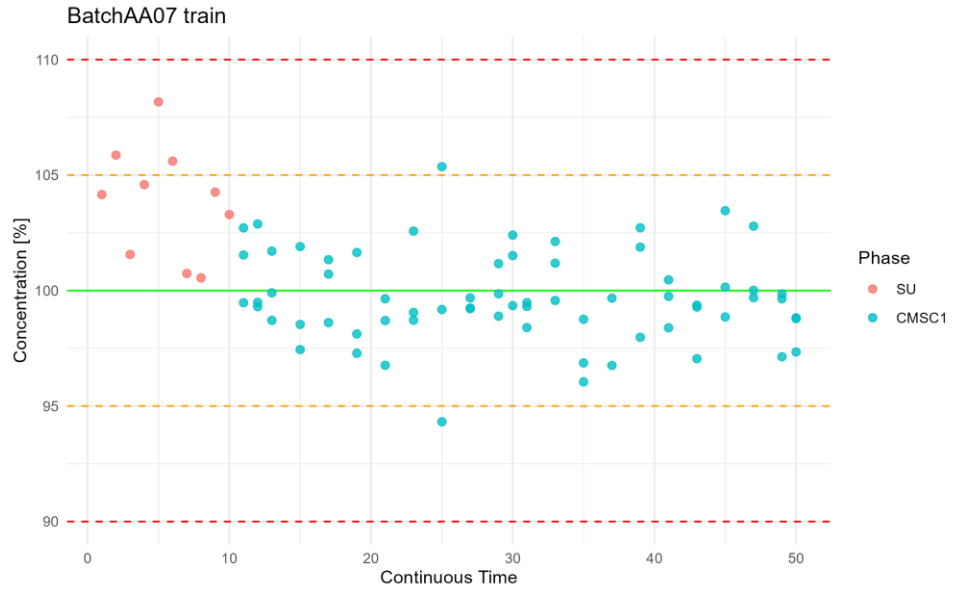
- Detect changes in variability across time
- Searches for time points where variability changes between segments

Data: Simulated CM run

- Concentration data of 10 simulated CM runs of varying sizes.
- Start-up length of 10 or 15 sampling time was initially set.







Results

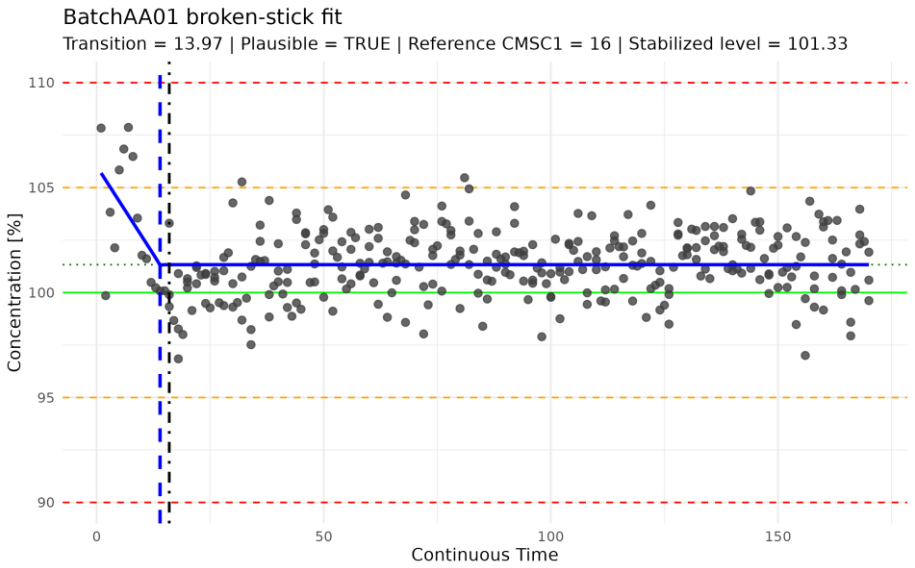
	Smooth broken-stick		Segmented regression		Variance-based	Set start-up
Batch	$\hat{\psi}$	95% CI for $\hat{\psi}$	$\hat{\psi}$	95% CI for $\hat{\psi}$	First CP	
BatchAA01	13.97	(8.71, 19.24)	16.00	(11.96, 20.04)	8	16
BatchAA02	40.25	(-11951.00, 12031.50)	25.00	(18.26, 31.74)	8	11
BatchAA03	32.16	(19.01, 45.32)	38.00	(28.18, 47.82)	14	16
BatchAA04	135.72	Undefined	22.70	(12.06, 33.35)	16	16
BatchAA05	31.28	(20.27, 42.28)	17.56	(9.89, 25.23)	11	16
BatchAA06	10.04	(5.58, 14.50)	10.76	(6.65, 14.87)	6	11
BatchAA07	15.00	(10.97, 19.03)	15.00	(10.22, 19.78)	6	11
BatchAA08	7.63	(4.17, 11.10)	15.00	(7.68, 22.32)	8	11
BatchAA09	203.02	Undefined	85.00	(70.11, 99.89)	7	16
BatchAA10	63.17	(18.42, 107.92)	78.90	(62.44, 95.36)	18	16

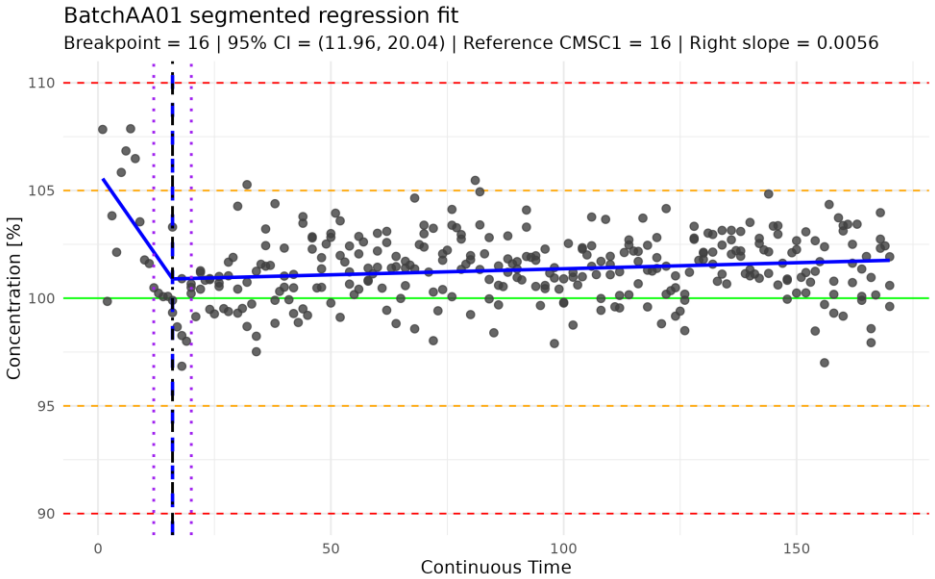
Early window (0-50):

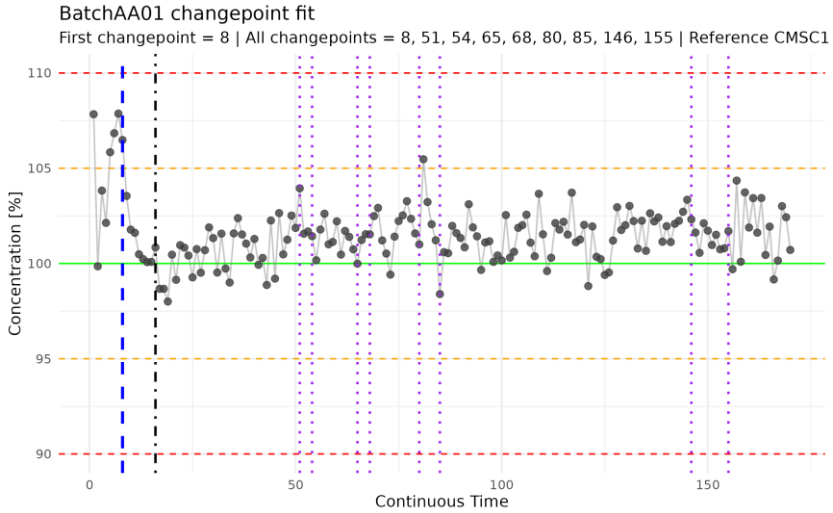
- AA09: 85.00 -> 28.00
- AA10: 78.90 -> 11.53

Results

Long-run: BatchAA01

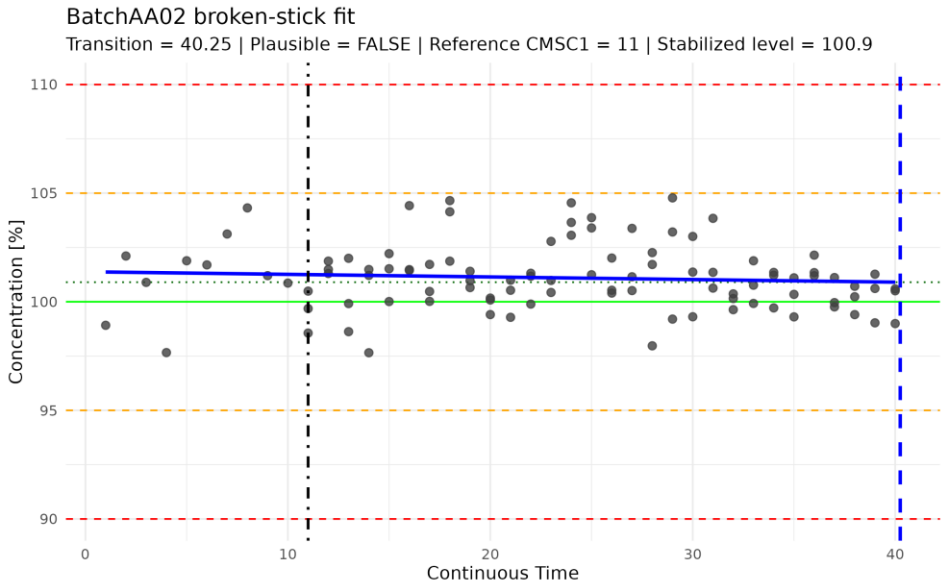


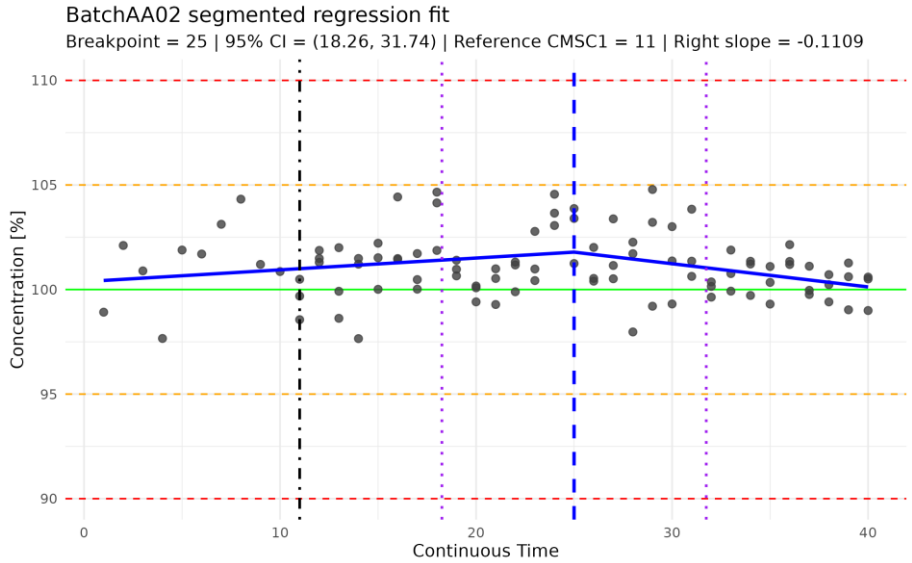


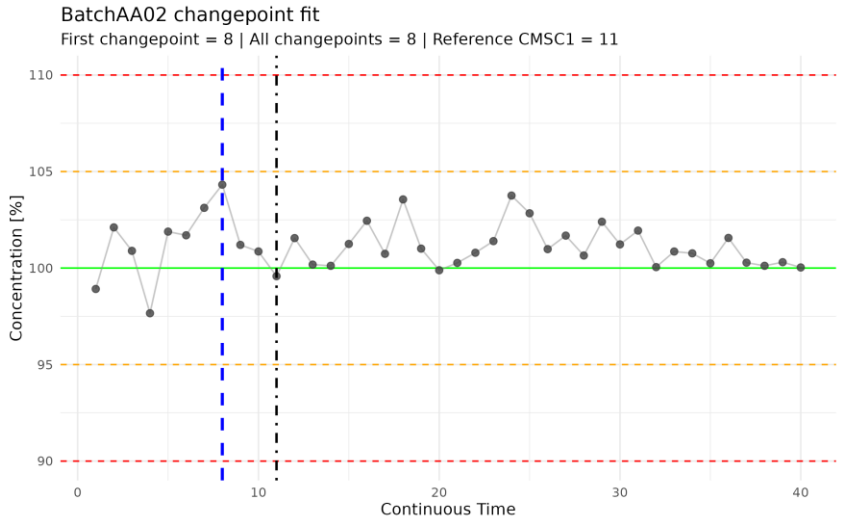


Results

“Already stable” short-run: BatchAA02

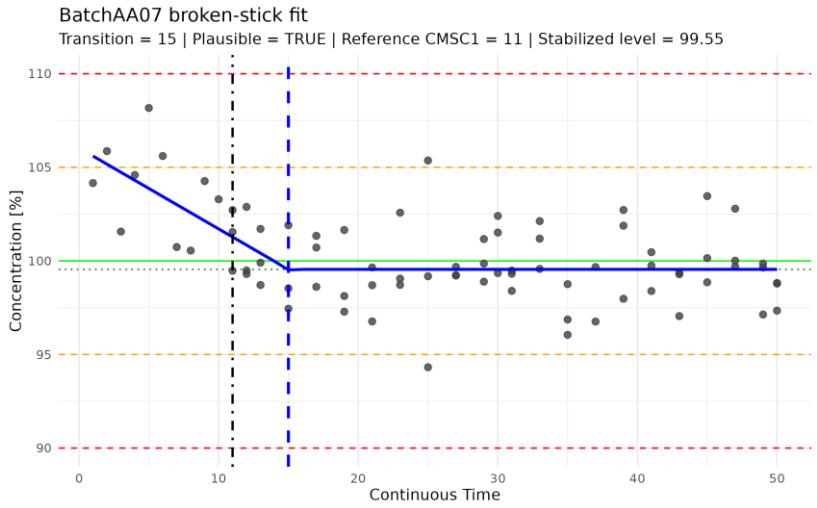


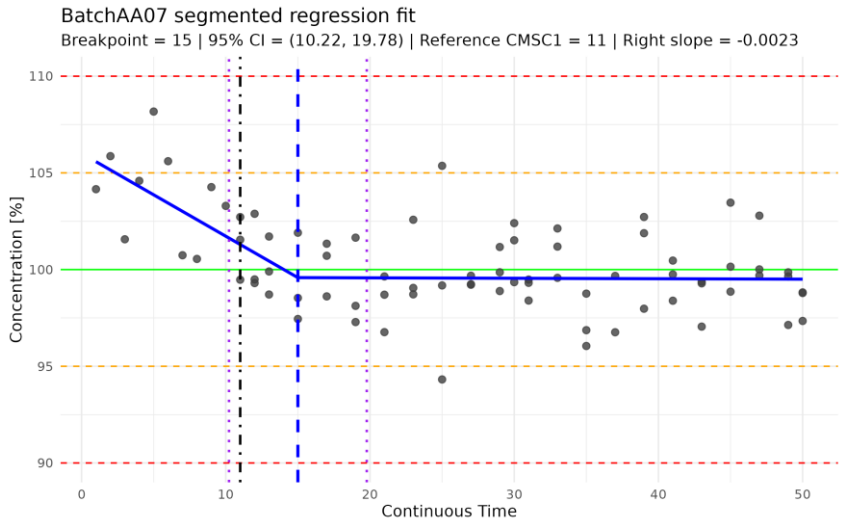


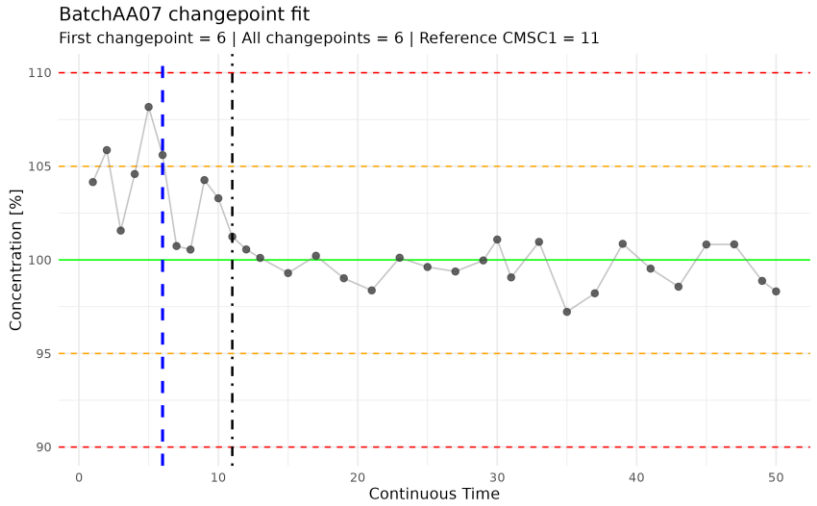


Results

Short-run: BatchAA07







Conclusion

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Key Considerations

- Define process stability using clear operational criteria.
- Exclude batches that are already stable at start-up.
- Use historical runs from a comparable process window, as stabilization behavior may differ between short and long runs.
- Clean-up of raw run data: handling of line pauses and different sampling time.

Interpretation of Results

- Stabilization time and maintenance of stability are distinct concepts.
- Different methods detect different types of process changes and may yield different stabilization time estimates.

Recommendation

- Select one primary method for estimating stabilization time.
- Use alternative methods as sensitivity analyses.
- The start-up phase duration can be defined using the upper tolerance limit of stabilization times observed across historical runs.

Acknowledgement

The content presented today originates from the master's thesis research carried out by

Samuel Nadrchal (Hasselt University, BE).

If you have more questions, please contact:
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