

A Two-Level Approach for Plant-Wide Root Cause Analysis in API Manufacturing

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Introduction | Inter-Step Connectivity

Active pharmaceutical ingredients (APIs) are often produced through fermentation, followed by a **series of interconnected purification stages**



"Common-cause variance is the natural or expected variance in a process" As a consequence, **common cause process variance in one step can affect multiple other steps**

Introduction | Intra-Step Dynamics

Furthermore, each process step is influenced by a variety of **internal mechanisms and interactions**



Lead to a multitude of cause-and-effect relationships throughout the process line

*The industry often overlooks process-wide interactions and upstream effects on downstream processes in biopharmaceutical process development and production*¹

Develop a framework that integrates intra-step dynamics with inter-step connectivity

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¹Zahel T. et al. (2017) Integrated Process Modeling—A Process Validation Life Cycle Companion. Bioengineering. 4(4):86

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Develop a framework that integrates intra-step dynamics with inter-step connectivity

To support root cause analysis and identify optimization opportunities

> ¹Zahel T. et al. (2017) Integrated Process Modeling—A Process Validation Life Cycle Companion. Bioengineering. 4(4):86

Industrial pharmaceutical processes are usually batch-operated, and data come in various formats, frequencies, etc.



Inspired by Ventura Silva et al. (2023)

Digitalization Platform for Sustainable Battery Cell Production: Coupling of Process, Production, and Product Models. Energy Technol. 11:2200801











Solution | Hierarchical Approach



Input from process experts



Solution | Hierarchical Approach

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Input from process experts



INTRA-STEP LEVEL





apply process knowledge to identify abnormal batches and root causes



9 **Identify intra-step relations** *Fitting PLS to perform a multivariate analysis*



8 **Preprocess available intra-step data** *Mean centering, scaling, imputation and alignment*



7 Collect intra-step historical data

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Propose hypotheses and, if applicable, include data from small-scale systems













Conclusion | Summary and Next Steps

Inter-Step Level: Downstream concentration profile driven by fermentation concentration profile



Input from process experts: Fermentation concentration profile impacted by metabolite dynamics

Intra-Step Level: Metabolite dynamics correlating with high pH in fed-batch phase (work-in-progress)

In commercial production, measured process variables **may not reveal the root cause**, as **tightly controlled variables** show minimal variation, thus **hiding critical information**

Expand framework to include data from lower scales to improve extrapolation capabilities

