University of Applied Sciences and Arts Northwestern Switzerland
School of Life Sciences

Workflow for modelling and scale-down of industrial solvent swap distillations

Mensing Dario
Master thesis, Major Chemical Engineering

FHNW Supervisor: Prof. Dr. Andreas Zogg
Expert: Dr. Marcello Bosco, F. Hoffmann-La Roche Ltd.
Company Supervisor: Kai Wegmann, F. Hoffmann-La Roche Ltd.

Introduction & Motivation

Solvent swap procedures are a common unit operation in API manufacturing. Their purpose is to exchange an original solvent with a chase solvent via distillation, typically to prepare the mixture for a subsequent reaction step or crystallization.

When transferring these processes from laboratory to production scale, they frequently show discrepancies from planned values in terms of solvent consumption and batch duration.

The physical regimes dominating at different scales differ (e.g., heat transfer limitations vs. evaporation kinetics). To address this, a structured, simulation-backed scale-down workflow is proposed to predict industrial plant behaviour and reduce operating costs.

Goal

The objective of this work is to develop and validate a structured scale-down workflow combining gPROMS process simulation with a 2L validation reactor.

This workflow models cycle time, solvent consumption, and composition profiles for a 6300L industrial stirred-tank reactor before the production campaign.

It is noted that product quality (e.g., thermal stability) must be evaluated through complementary experiments.

Model Overview

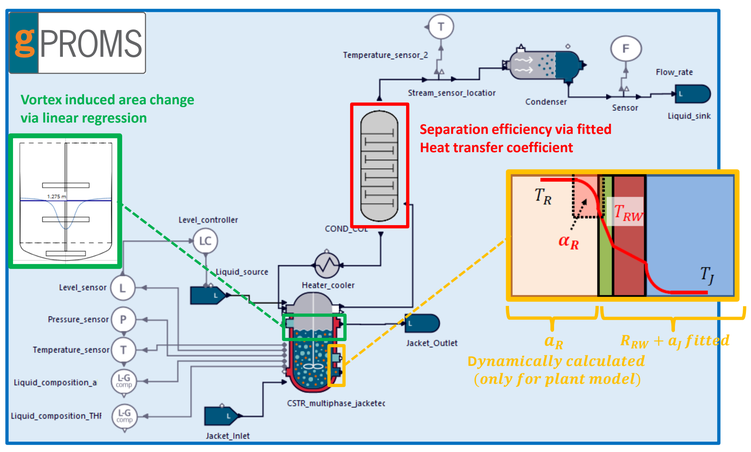


Figure 1: Model structure: composition-dependent heat transfer, volume-dependent wetted area, and theoretical separation stages.

Composition-dependent heat transfer — the reactor-side coefficient follows from a Nusselt correlation and is updated as the solvent composition shifts; wall and jacket resistances are fitted once per reactor and then kept fixed.

Volume-dependent wetted area — the heat transfer area follows the fill level during distillation, including the vortex-induced change described by a linear regression.

Separation efficiency from the condenser cascade — a fitted heat transfer coefficient in the condenser cascade sets the partial condensation; the effective theoretical stages follow from it rather than being fitted directly.

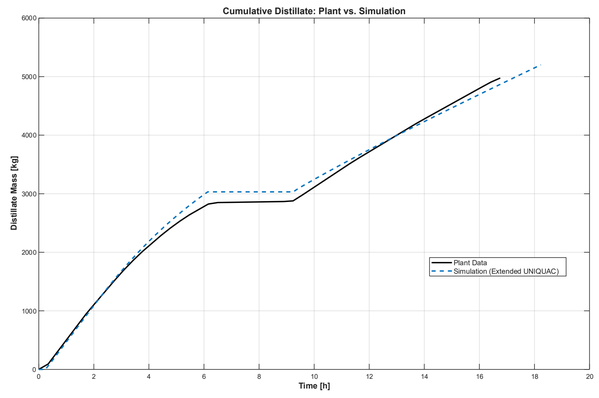


Figure 2: Simulated vs. measured cumulative distillate mass for a reference production batch. The calibrated plant model reproduces historical batches with deviations below 10 % in both cycle time and solvent consumption.

Proposed Workflow

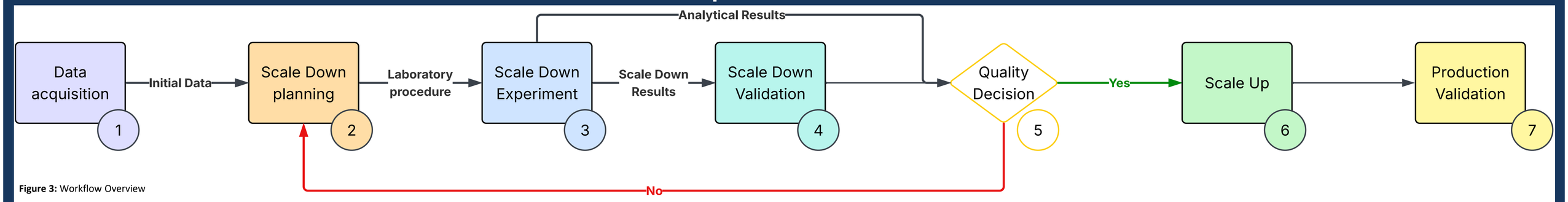


Figure 3: Workflow Overview

1. **Data Acquisition** — Collect all process information and boundary conditions for simulation design, in particular target reactor geometries and preliminary composition data.
2. **Scale-Down Planning** — Design the target process in-silico and derive a laboratory procedure that strictly matches geometric ratios, hydrodynamics (P/V) and energy input (Q/V).
3. **Scale-Down Experiment** — Execute the physical experiment section by section, with intermediate heat transfer calibrations, to generate a thermodynamically characterised validation dataset.

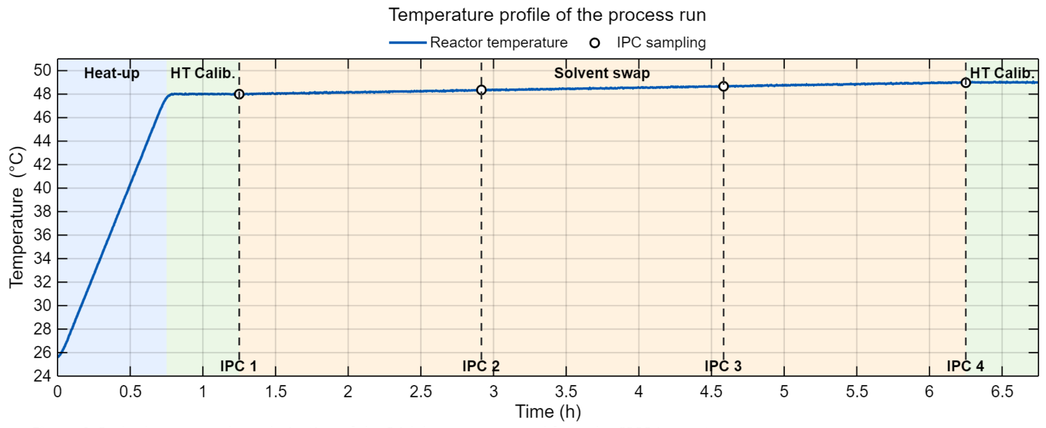


Figure 4: Scale-down procedure: derivation of the 2 L laboratory protocol from the 6300 L target process

4. **Scale-Down Validation** — Evaluate simulation accuracy and refine missing parameters, keeping control data (e.g. jacket temperature) strictly separate from validation data (e.g. in-process control profiles).

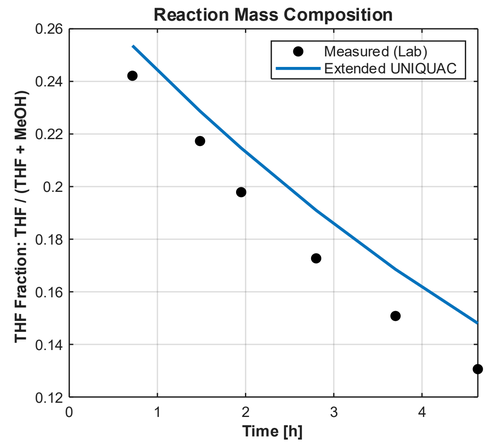


Figure 5: THF mass fraction during the continuous solvent exchange, 2 L scale-down experiment

5. **Quality Decision** — Assess model agreement and product quality, always complemented by empirical thermal stress and stability testing, to determine scale-up readiness.
6. **Scale-Up** — Predict industrial batch performance and define safe operating limits, using sensitivity analysis to identify process bottlenecks prior to the production campaign.
7. **Production Validation** — Confirm the calibrated plant model against production batch data in terms of cycle time and solvent consumption.

Conclusion & Outlook

The mechanistic model reproduces the industrial solvent swap within 10 % for cycle time and solvent consumption. At laboratory scale the Q/V-matched experiment confirms the predicted composition trend, with a residual deviation traced to the model substance rather than to the scale-down criteria. The next step is to apply the workflow to a new process ahead of its first campaign and to assess it against the resulting plant data. Once verified, it can be transferred across the Roche reactor portfolio to forecast solvent swap operations for a range of material systems.

References

Papadakis et al. (2016): Solvent Swap Methodology, *Chem. Eng. Res. Des.*
Li et al. (2008): Constant Volume Distillation, *Org. Process Res. Dev.*
Roche et al. (2022): Solvent Swap in Bubble Columns, *Org. Process Res. Dev.*
Elgue et al. (2006): Economic/Environmental Swap Optimisation, *Chem. Eng. J.*
VDI (2010): *VDI Heat Atlas* (2nd ed.), Springer.
EKATO (2000): *Handbuch der Rührtechnik*, EKATO.

Roche