Technical R&D/CHAD/
CM Unit

Continuous Manufacturing

We change the way medicines are made

Needs and Opportunities for Continuous Manufacturing (industrial perspective)

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Every morning, I have a dream:

- Of a world, where we pharmaceutical scientists focus on making the best possible medicines for our patients that the current medicinal or pharmaceutical chemistry allows
- ...where the potential of our molecules is unfolded to the maximum benefits they can provide; business, IP, Health Care policies are made to unfold the state of the science for our patients.
- ...where the effort that is needed to develop new medications is focused on unfolding the value of the molecules applying highest ethical standards.
- ...where the manufacturing of our drugs is intrinsically of high quality, safe, environmentally friendly, and provides no economic driving force to counterfeiting
- ...where, once we have developed a medicine, the manufacturing is reliable, practical for the supply and intrinsically of high quality. Right the first time, cost-efficient, and flexible to help develop new medications at the pace the medicinal knowledge develops
- ...where the regulations that are in place are globally harmonized, simple and effective and allow for easy compliant adoption of innovative approaches.
- However, I am not only a dreamer and without a sense for realities, but I do believe that CM has huge potential to help us get there, if we do it right.

Regulatory Objective

How to do it right

- 1) To discuss pragmatic ways and show options to demonstrate acceptability of quality when using CM technologies
- 2) To show a comprehensive overview over the current state of quality management in CM implementations in the industry
- 3) To find the optimal approach to define regulatory expectations for CM that allow to unfold the inherent benefits of CM for both supply of medications and quality assurance
  - ➢ Goal: optimal usage of the technology and assure adequate quality with maximum flexibility and effective oversight

Why CM offers a paradigm-shifting opportunity

- Continuous Manufacturing excels by allowing a new process management paradigm with consequences like:
  - All material passing through the system is detectable and can be monitored (no hidden pockets of material attributes)
  - Process control is much better on a micro scale
  - Process control enables optimal control of process trajectory dynamically
  - Process allows much more data acquisition from the process per amount of material (data density= information per kg material)
  - Process data acquisition can be adapted to process dynamics hence it becomes physically impossible to miss critical information
  - In specific cases 100% of the products can be inspected in a serial mode online

And the good news…

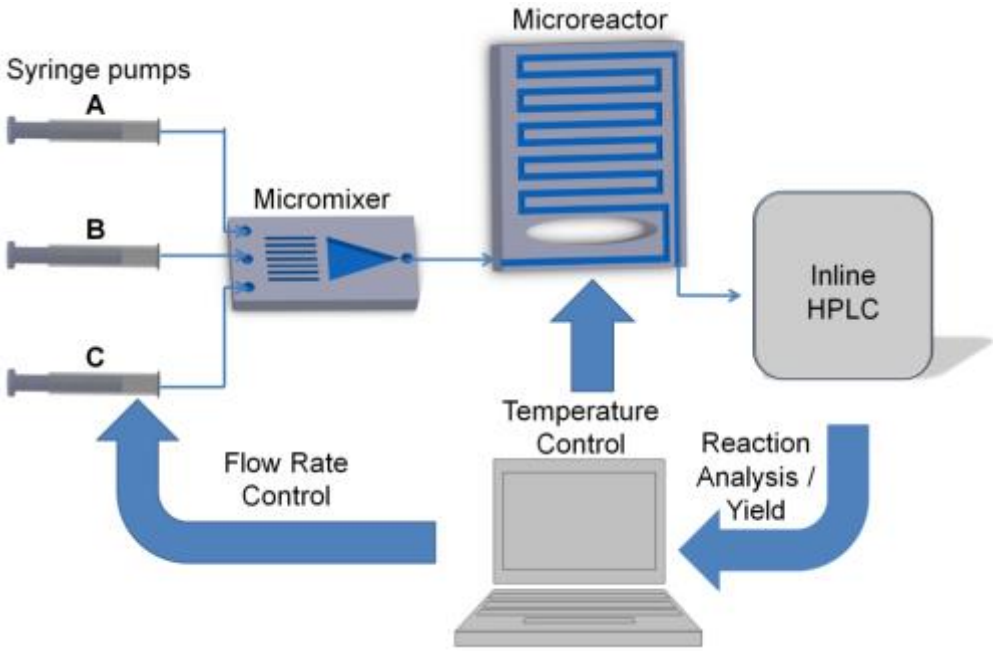
- Continuous Manufacturing can be implemented like many other manufacturing technologies and **does not require new regulations**!

BUT:

- To explore its full potential, it can benefit from a shift in focus to performance based process management, so a **new perspective does help!**

Example 1: Rapid reaction optimization using inline analysis and feedback

- Automated system with feedback capabilities for optimization
  - Plug-and-play
  - Different in-line analysis methods, e.g., HPLC, FTIR
  - Self calibrating
  - Customizable, experimental optimization algorithms
    - ‘Black-box’ approaches
    - Model based methods



Parameters: temperature, residence time, catalyst/ligand loading, solvent composition, ionic strength, pH

J.P. McMullen and K.F. Jensen, *Annu. Rev. Anal. Chem.* 3, 19–42 (2010).
Org. Proc. Res. Dev. 14, 1169–1176 (2010)

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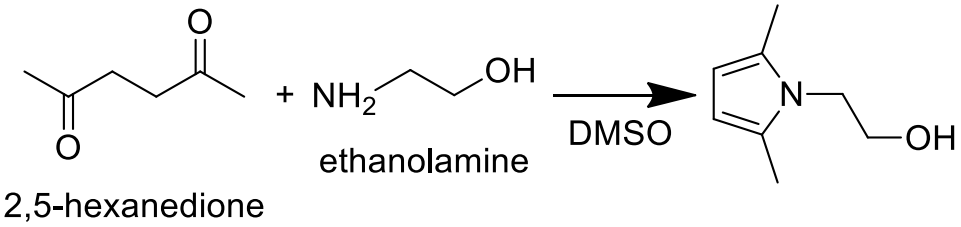
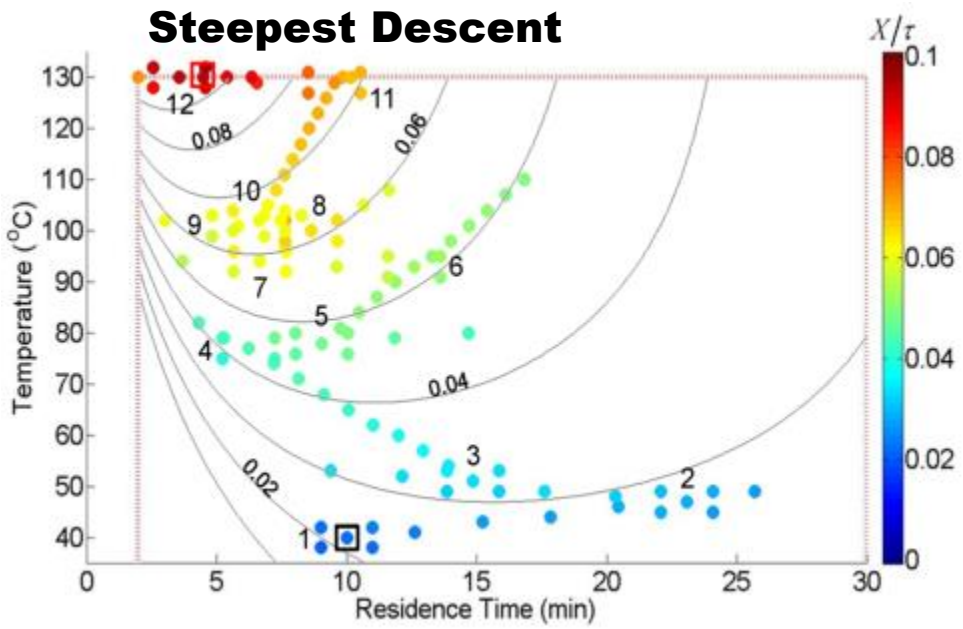
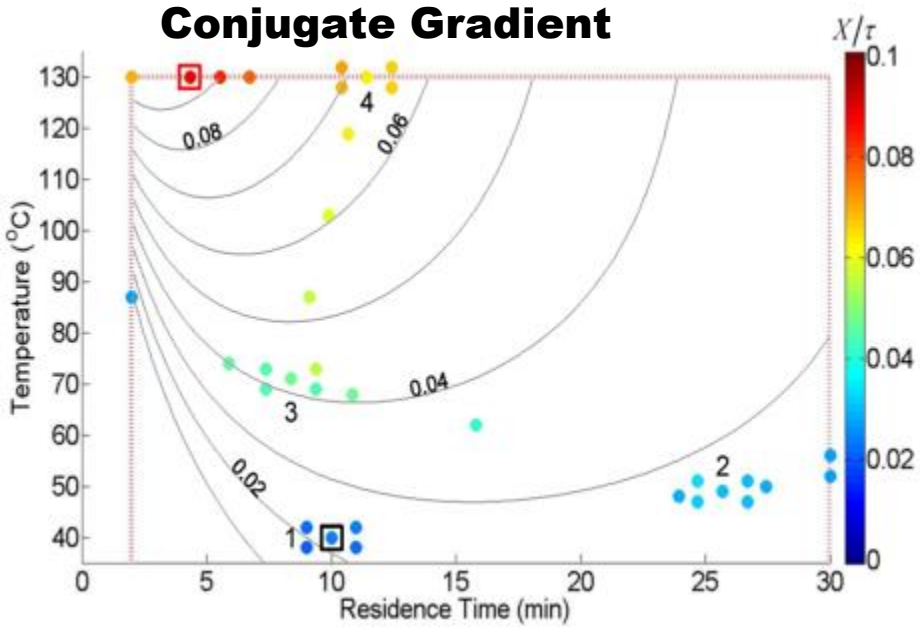
Online optimization with ReactIR flow cell



2,5-hexanedione





- Black box optimization is feasible with a variety of optimization techniques.
- The choice of methods significantly influences the number of experiments

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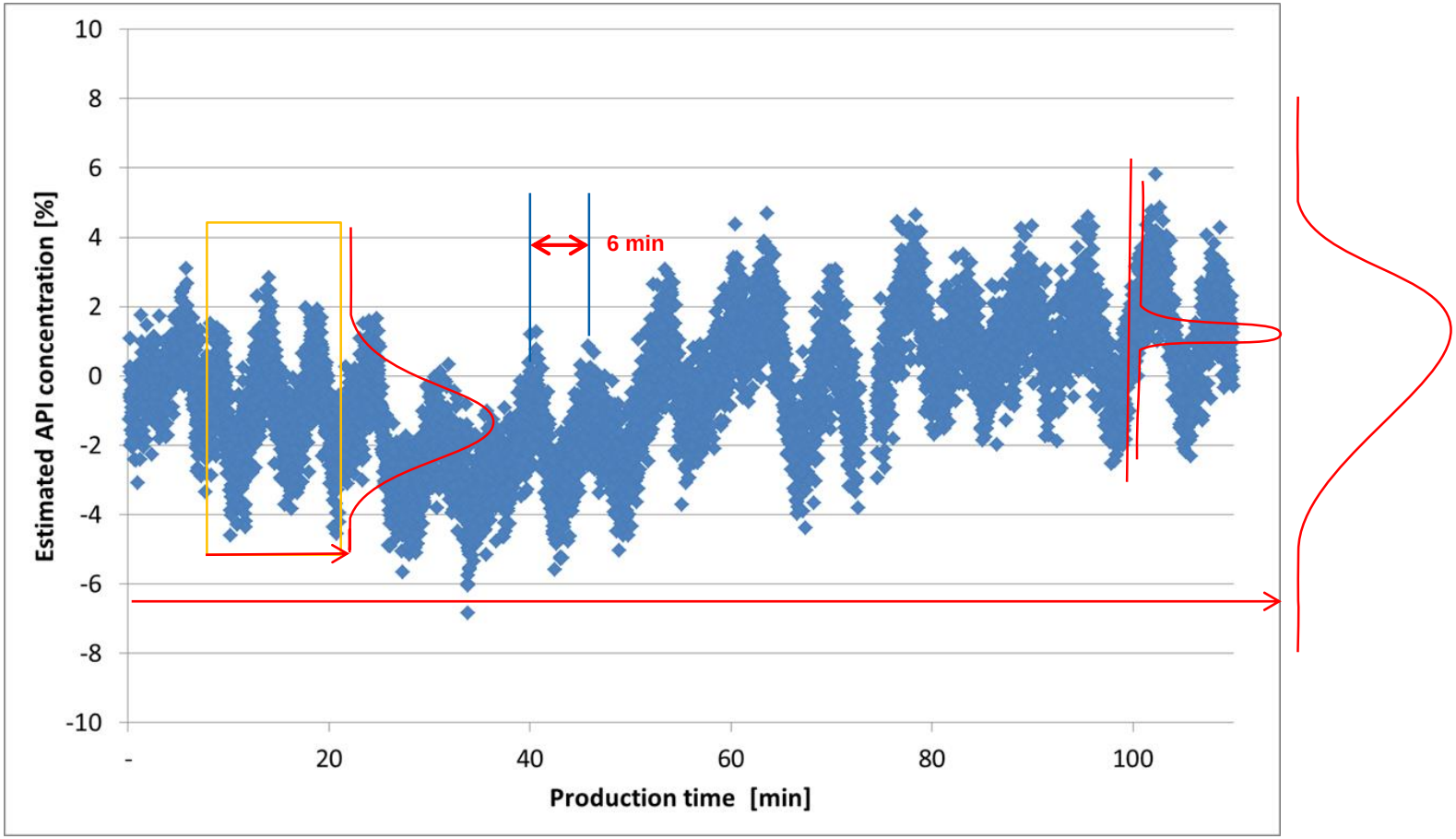
What are we doing here?

- Take an actuator (the reactor periphery), a sensor (the HPLC) and a self-optimizing algorithm to explore the system response and optimize the outcome

- Automated development!
- But also: self optimizing operations performance conceivable
- What if the system changes its behavior? Let the algorithm self-optimize within an acceptable range.
- What matters: the system performance

Example 2: Dryer in “steady state” or state of control



- Perfect agreement with step data
- Razor-sharp process appears poor
- Apparent dispersion of CQAs is in reality instable process
- Affects observed process capability

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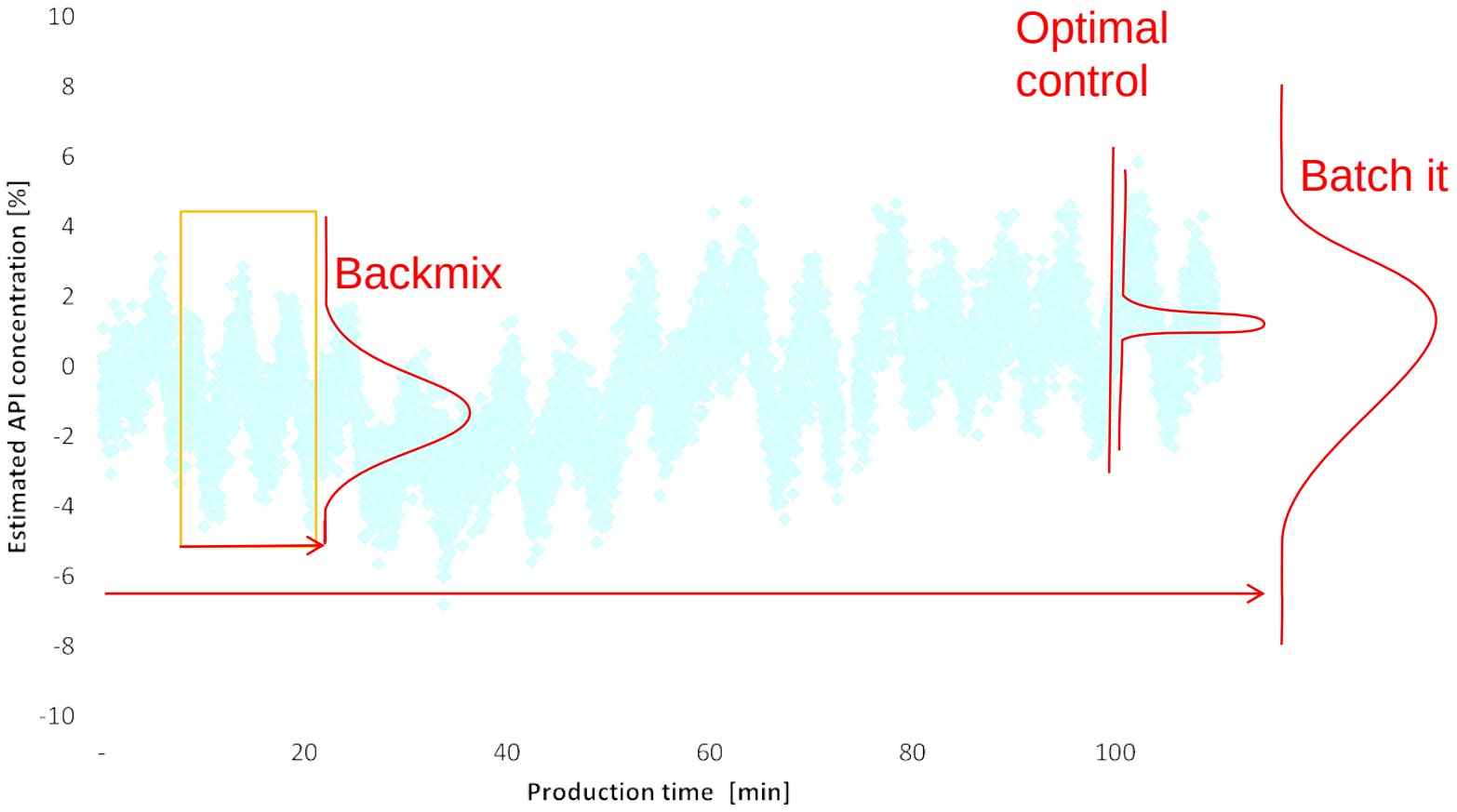
Example 2: quality implications of approach



- Choice of solution drives apparent performance
- Optimal control may give better performance
- Equipment improvements may even be better
- Performance is what matters in the end

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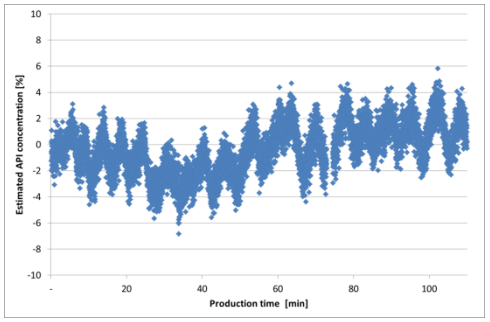
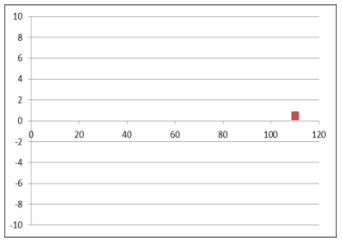
What can we do with such a process?



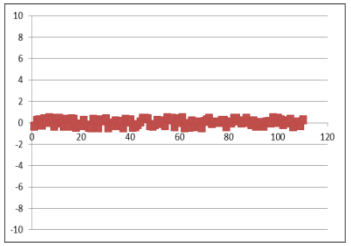
Batch it



good

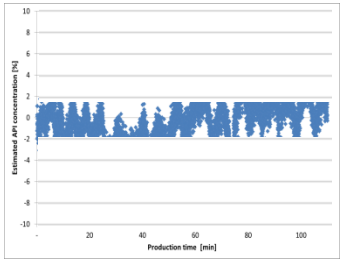
Add Backmixing

Creates apparent homogeneity
potentially bad product is still in



Truncate, divert

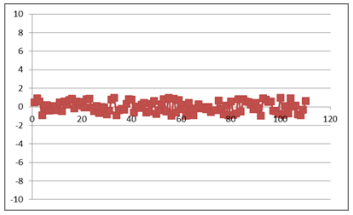
Creates real homogeneity, yield lower



better

Apply active control

Creates real homogeneity, yield high



best

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Approaches to demonstrate Quality 1/3

Classical approach (bin to bin)

- Define finite quantities of corresponding raw materials and products the as the entity of interest
- Use a stochastic approach, sample, test and demonstrate the correlation process to quality (QbD Philosophy)
- The same can be done for CM, however the material propagation needs to be considered when establishing the correlations (finite, discrete amounts = product keys/plugs/sublots)
- Optionally this enables to make occasional adjustments to the process in a predictive way (feed forward control) or lock everything down with ranges

Approaches to demonstrate Quality 2/3

Performance based

- Determine key quality attribute control points in the process considering process risks such that the relevant specifications can be verified
- Determine the inherent process dynamics at these points and derive the necessary measuring frequency and field of view for these points (network dynamics)
- Verify performance of the process based on the node points for the desired runtime or:
- Optionally disturb the process occasionally with small spikes to demonstrate that the process robustness or effectiveness of control is given (process control is alive)

Approaches to demonstrate Quality 3/3

Model based

- Determine relevant Quality attribute control points in the process considering process risks such that the relevant specifications can be verified
- Determine a complete model (empirical or first principles) for both amplitudes and dynamics
- Verify model validity regularly, e.g. during startup.
- Control the process based on predictions of the model in a feed-forward manner.
- Model validity is critical...

Which means….Summary

And variants of that are conceivable as well

- Three options to manage processes and quality in CM
  - 1) Classical (as in batch), based on QbD or QbD elements, optionally considering final blending (e.g. collection tank, coating), sampling and testing (bin to bin, discretized plugs)
  - 2) Performance based. Requires PAT testing rates linked to process dynamics and verifies relevant CQAs directly, no need for model other than dynamic characterization (RTD). Universally applicable.
  - 3) with predictive quantitative characterization (full dynamic model). Allows justification of quality over time and limits. Deepest process understanding, however most costly, both in development and OPs. Model validation is critical. May not be possible for all unit ops. Minimal to no secondary FB control loops needed.

The last slide…

- If we focus on scientifically adequate (in time, space and amplitude) process knowledge, we know all we need to know. There are three options to do so.
- CM offers denser process data and usage of performance based data to adapt the process going forward
- Performance based regulatory expectations give effective oversight and allow the industry more effective process management
- **The goal:**
- **Giving the industry flexibility and ground for innovation and the regulators effective oversight**