Understanding Process Dynamics: the route to continuous improvement

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Understanding Process Dynamics: the route to continuous improvement

- Introduction: the languages we speak
- Chemistry
- Engineering
- Batch processing
- Continuous processing
- Steady state vs controlled state
- Perturbations vs Deviations
- Regulatory impact of continuous improvement





How to translate between related languages

Process dynamics for the chemist:

- Kinetic measurements precise, empirical,
- Equilibrium constants empirical
- Strict demarcation between kinetics and thermodynamics
- Scale of scrutiny generally small
- Chemists like reactions that proceed to completion
- Chemists almost always start with a round bottomed flask

Process dynamics for the engineer

- Mass transfer vs heat transfer
- Descriptors often not precise
 - Reynold's Number (or other dimensionless numbers) large or small
- Engineers generally look at whole systems
- Chemical engineers outside pharmaceutical industry like continuous processes
- Both approaches are needed
- Neither group traditionally strong in statistics, especially Bayesian
- Further translations for regulatory submissions and inspections needed!





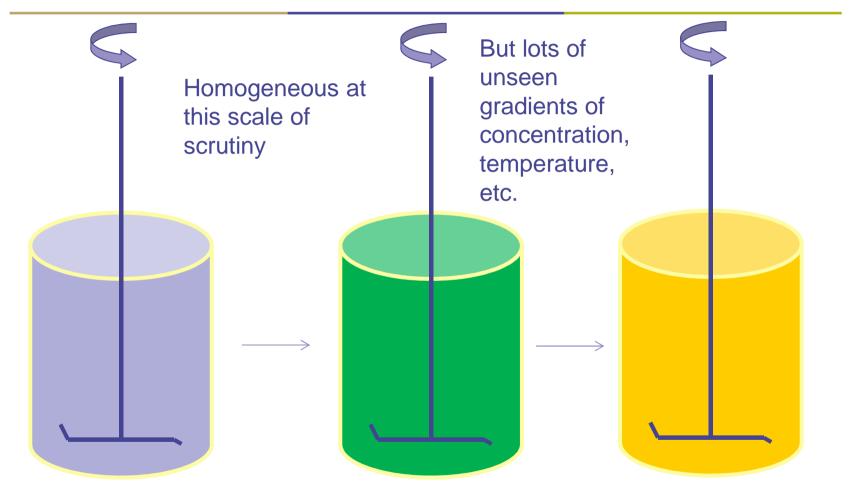
Batch processing

- Has been the preferred modus operandum for pharma industry for decades
- API
 - Use of glass lined or 316 SS/Hastelloy stirred tanks with 3 blade retreat curve impellors or anchor stirrers for reactions
 - Larger stirred tanks for extractions
 - Dedicated crystallisation vessels
 - Basket centrifuge or Nutsche filters for solid isolation
 - General purpose dryer (or filter dryer)
 - Milling
- DP (oral solid dose)
 - Blending
 - Wet granulation
 - Drying
 - Blending?
 - Tablet compression (or capsule filling)
 - Tablet coating
 - Printing
 - Packaging





Batch Reaction

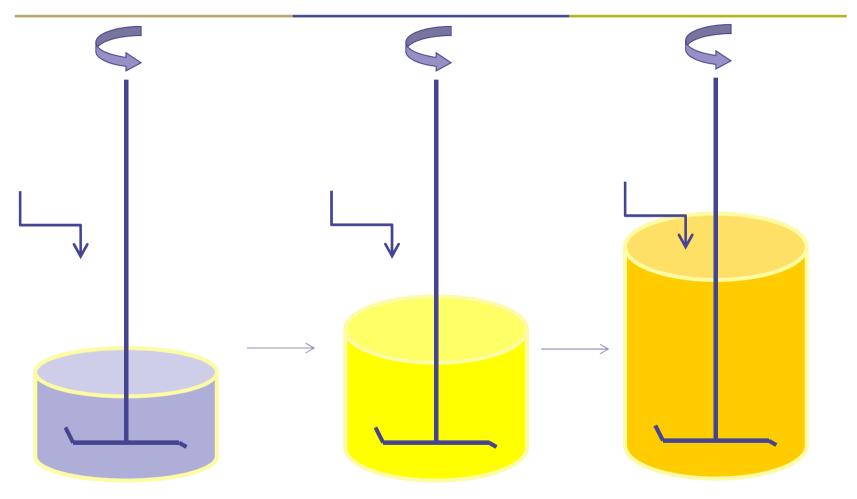


Does not operate at steady state





Semi-batch (fed batch for biotech) processing

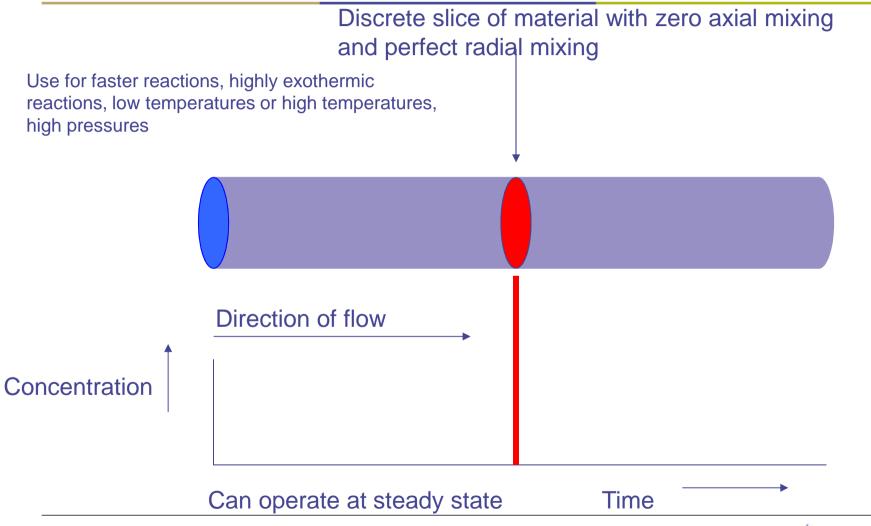


Does not operate at steady state





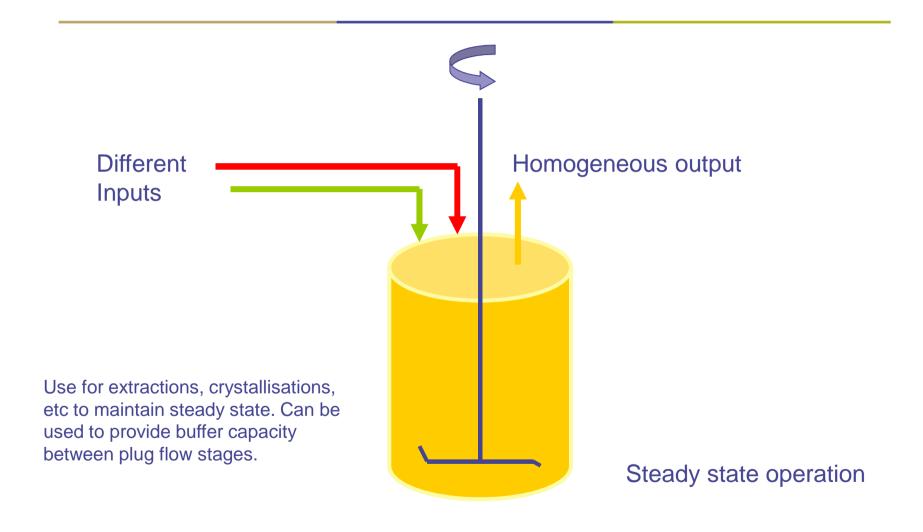
Idealised plug flow







Idealised CSTR (perfusion for biotech) regime







Flow regime characteristics

Plug flow

- Used for fast reactions, *etc.*Kinetic control predominates.
- Highly dynamic and responsive to change
- Susceptible to process "spikes"
- Needs PAT that is fast

CSTR behaviour

- Equilibrium (thermodynamic) control
- High buffering capacity and slow response time
- Insensitive to process "spikes"
- PAT needs to be stable





System dynamics and measurements

- Which regime requires rapid measurement and response?
 - Dynamic systems
 - Plug flow
 - Semi-batch
- Which regime needs accurate, but possibly imprecise measurement?
 - Less dynamic systems
 - CSTR
- Which regime can use less accurate, but precise measurement?
 - Systems which need batch to batch variation managed
 - Batch processes





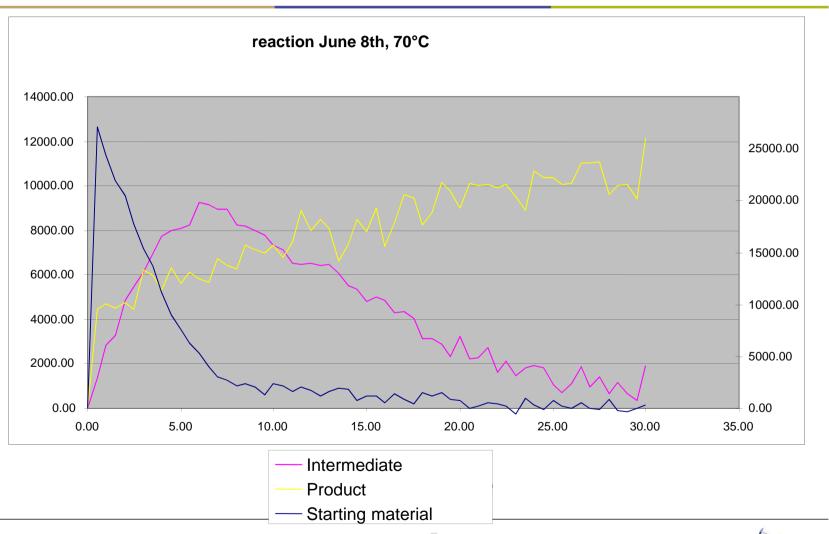
What do you do with process measurements?

- Do you make decisions based upon them?
- Do you make nice graphs?
- Are they made to tell you that everything is as it was before?
- Are they used for predictive maintenance?
- Do they add to process understanding?
- Are they used for continuous improvement?
- Are they made because you filed them?
- Do you believe them?
- How do they serve your business?





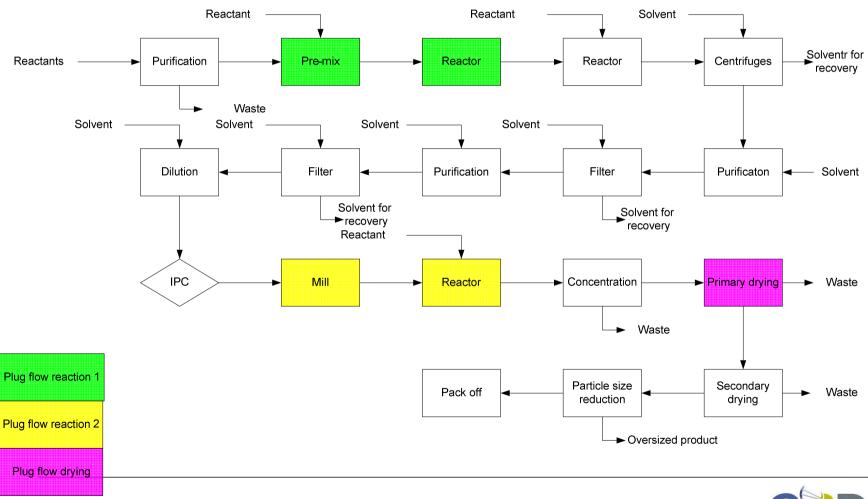
Process understanding is needed







Manufacturing Process Flow – real example operated at multi hundred TPA



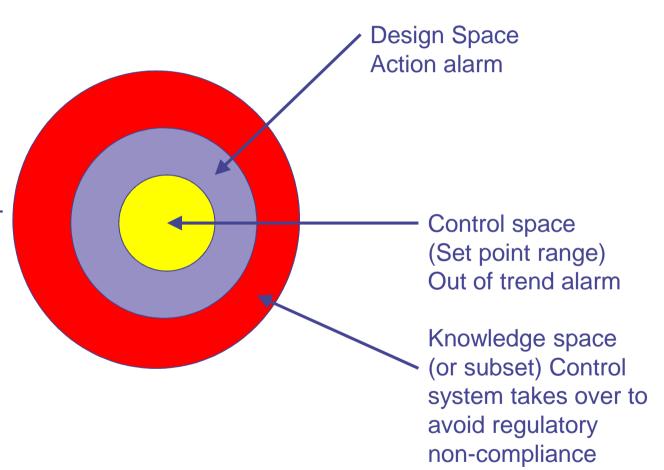




Design space and alerts/alarms

Current thinking has moved from maintaining steady state to maintaining control state.

You would like to be able to drive your car at different speeds wouldn't you?







Managing deviations

- Perform risk assessment on unit operations
 - Without necessarily considering the reason for a deviation consider what should happen to the product affected
 - Stop
 - Keep going
 - Divert affected product to waste
 - Do this during design phase!





Deviations

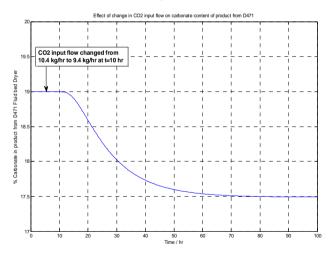
- Use risk assessment techniques prior to event if possible
- Write regulatory filings carefully to avoid regulatory non compliance which would have no adverse patient affect
 - Example:
 - A spray dryer indicates an outlet temperature of 123°C for 1 minute 17 seconds. The NDA/MAA filings state that the product is dried below 110°C. What do you do?
 - What temperature is the product?
 - Is primary drying over?
 - How long is the exposure?
 - What is the effect of the exposure?
 - Each particle is exposed for a very brief time however long the excursion lasts.
 - When does a dryer ever show the actual product temperature?

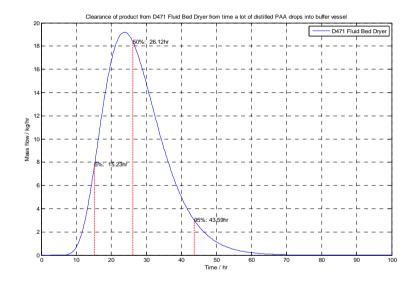




Coping with perturbations

- Almost impossible to detect change once product enters CSTR stage
- Need to wait for equilibrium to be attained before the process change is possibly identifiable
- Use development data to confirm that the new conditions have the effect that you anticipate

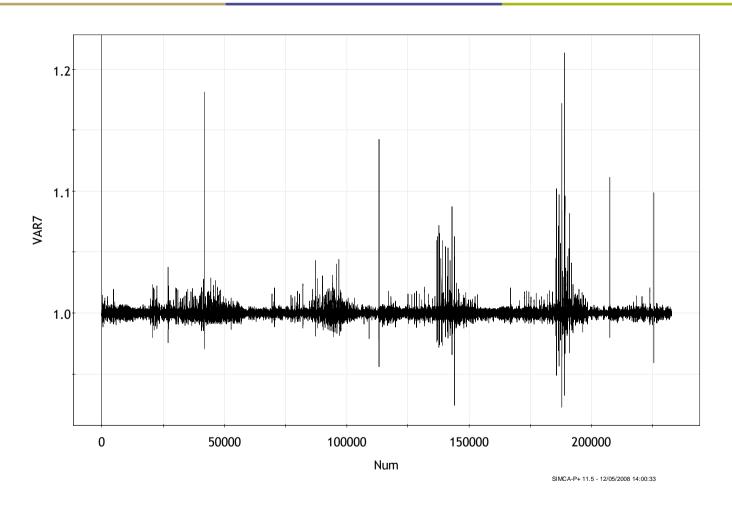








Example from commissioning (feed rate of a reactant with time) – raw data

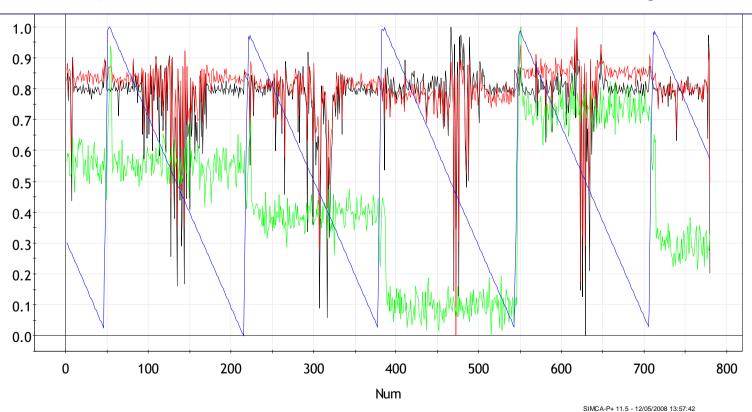






The explanation

Black = Feed rate reactant #1; Red = feed rate reactant #2; Green = Concentration (NIR) of reactant #1; Blue = fill level of vessel feeding reactant #1







Regulatory impacts of continuous improvment

- Write down your intention, not the way you have done it to date
 - A is added to B to give at least 80% C with no more than 2% D

VS

- Concentration X of A is added to concentration Y of B at Z litres/min maintaining the temperature between 5 and 10°C
- State criteria that you will use to implement improvement
 - Statistical methods, acceptance limits (not timelines) and how you will report them (Annual update, CBE0, etc.l)



