An example of sensitivity analysis of a bioprocess using Bioprocess Library for Modelica

Jan Peter Axelsson, Vascaia AB, Sweden

Atiyah Elsheikh, independent scholar, Germany-Egypt

Presented at MODPROD in Linköping 2019-02-06

(slightly adjusted after the presentation)

Outline

- Problem formulation
- Experimental approach
- What can model-based technique contribute with?
- Difference in experimental data needed
- Wish-list
- Conclusion

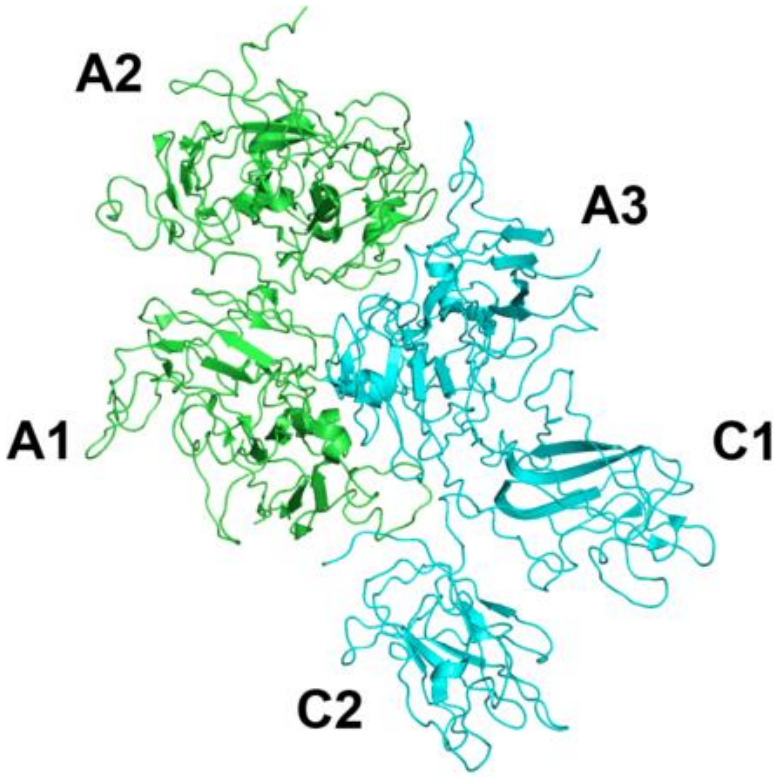
Work in progres…

Biopharma – the process defines the product

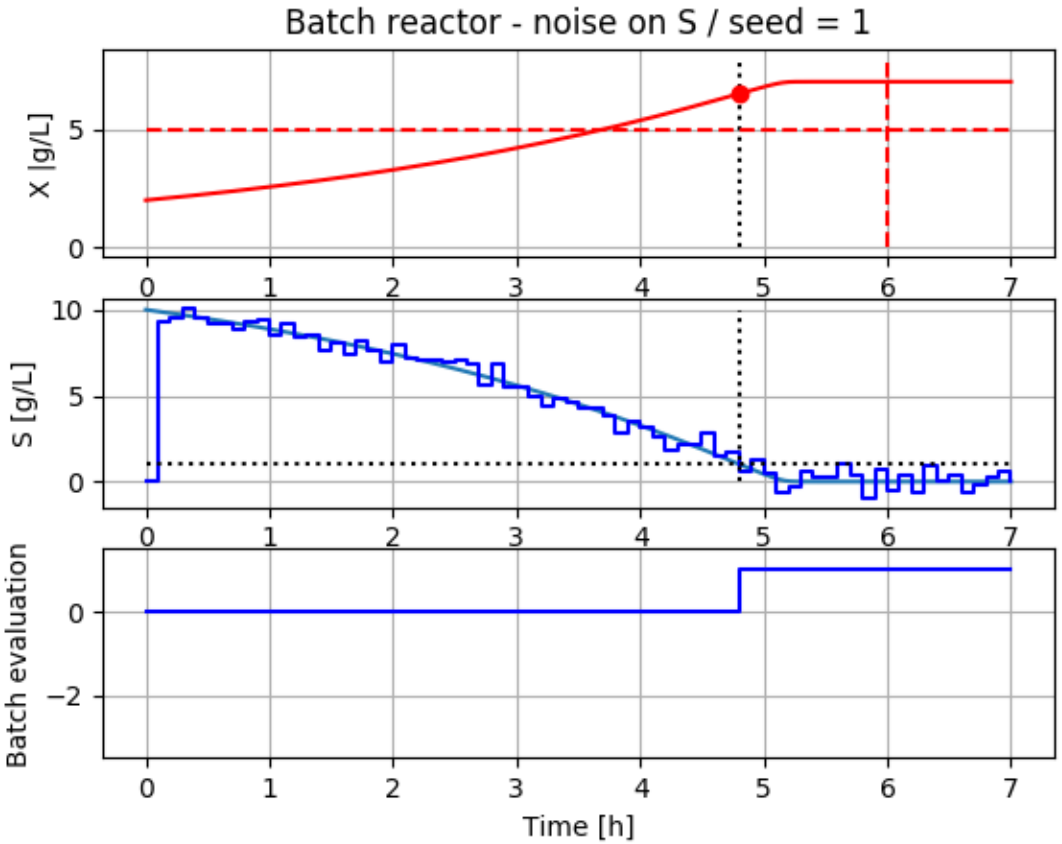
- Biomolecules very complex
- Patients immune system sensitive to small changes
- Still difficult to analyze the product well-enough
- Must ensure that production is run within limits
- Design space ≈ global sensitivity analysis

- Quality by Design (QbD) growing emphasis since year ≈ 2000 from FDA and other authorities

Example blood factor VIII
- treatment of Hemophilia A
(1438 amino acids)



Our example


Batch reactor - noise on S / seed = 1
X [g/L]
S [g/L]
Batch evaluation
Time [h]

Design space characterization

- 6 process parameters: temperature, pH, media preparation three aspects, batch-to-batch variation

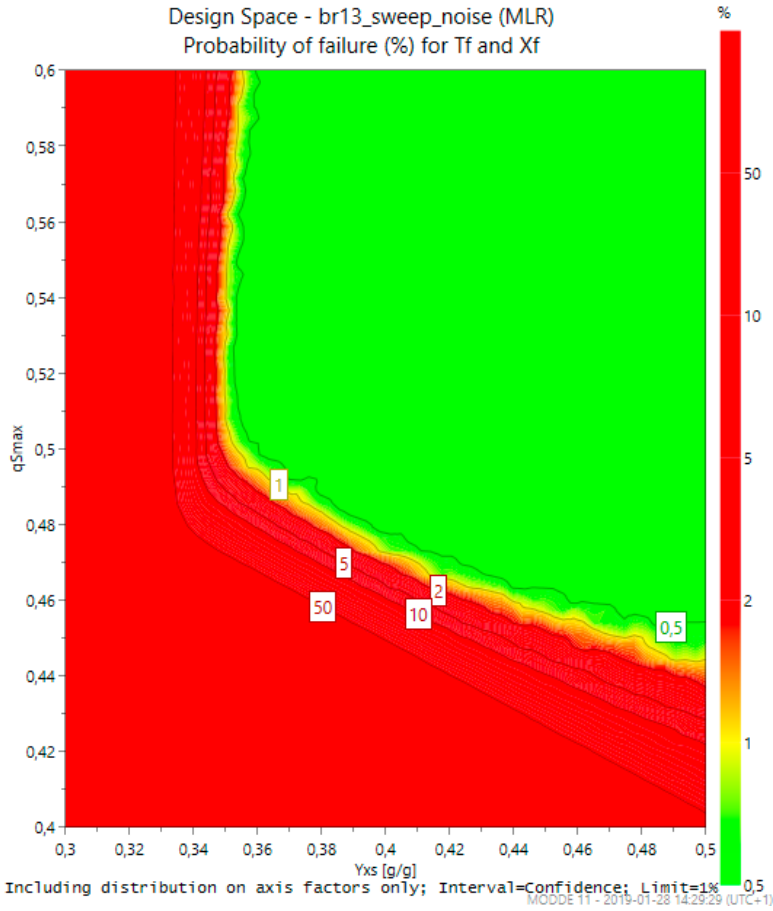
  -> 2 biological parameters: yield and growth rate

  -> 2 evaluation parameters: final cell conc and cultivation time

- Design-of-experiment
  - Evaluate the corners
  - Duplicate center-points
- Exploit assumptions of linearity to reduce number of experiments, i.e. do not evaluate all corners

Result from experimental series - an empical model with uncertainty

Growth rate max vs Yield



Monte Carlo simulation
10 000 runs

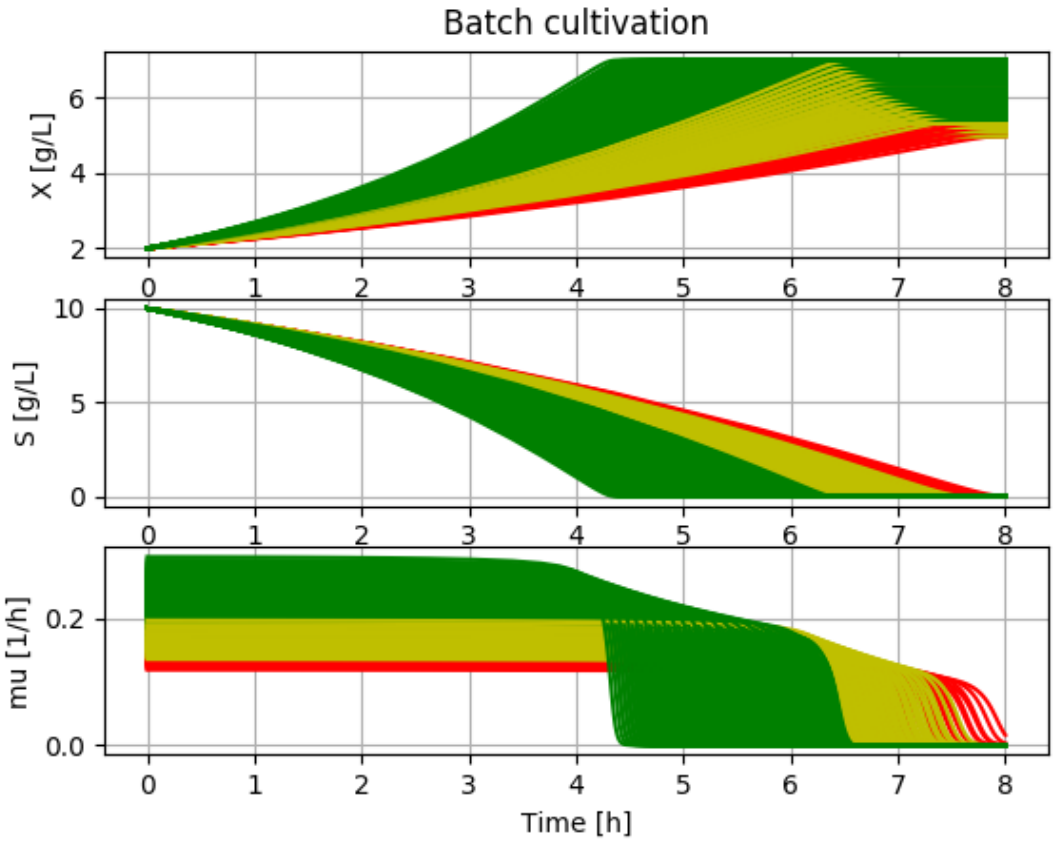
How can simulation contribute?

- Assume model is good and calibrated
- Non-linear model may give some new insight

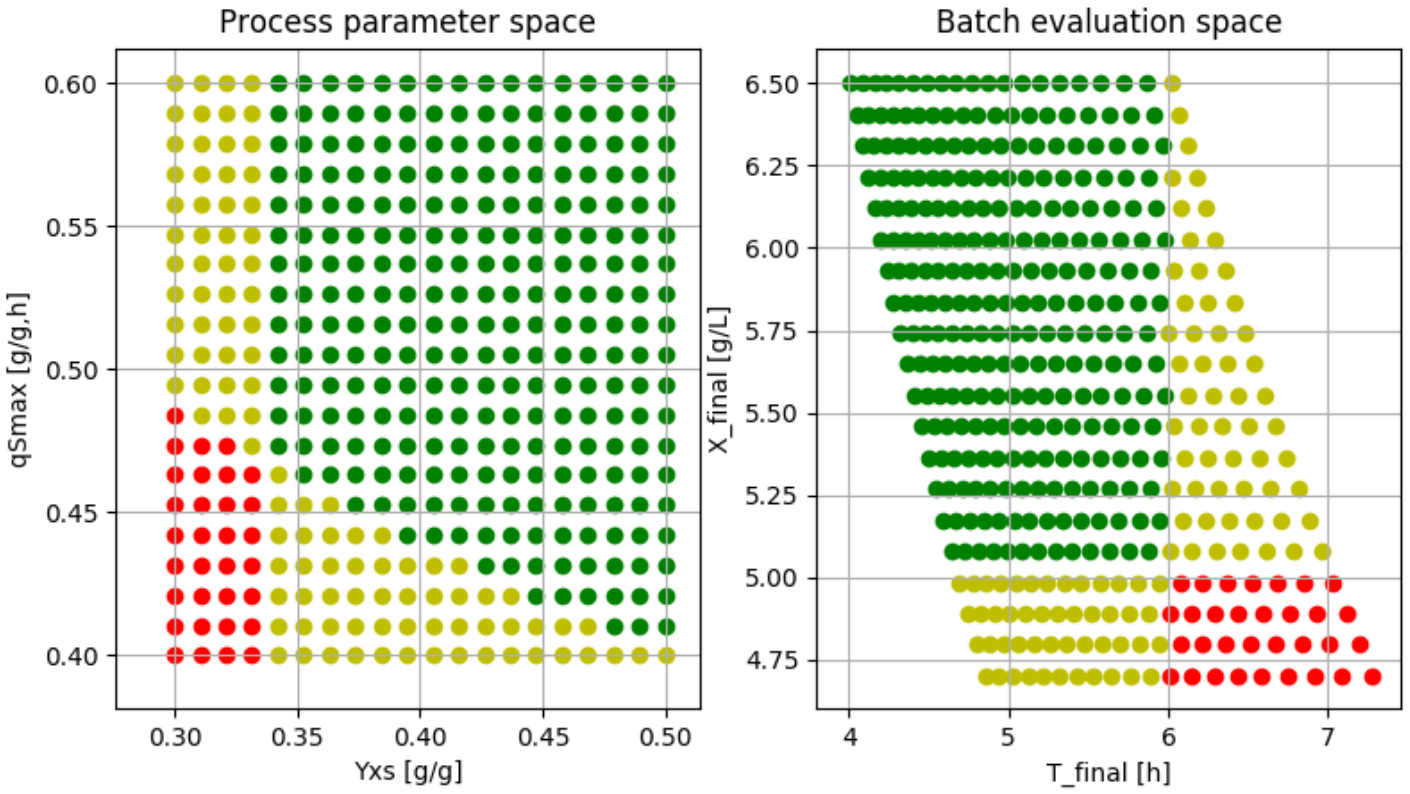
- Do brute-force full factorial parameter-sweep!

- Insight?

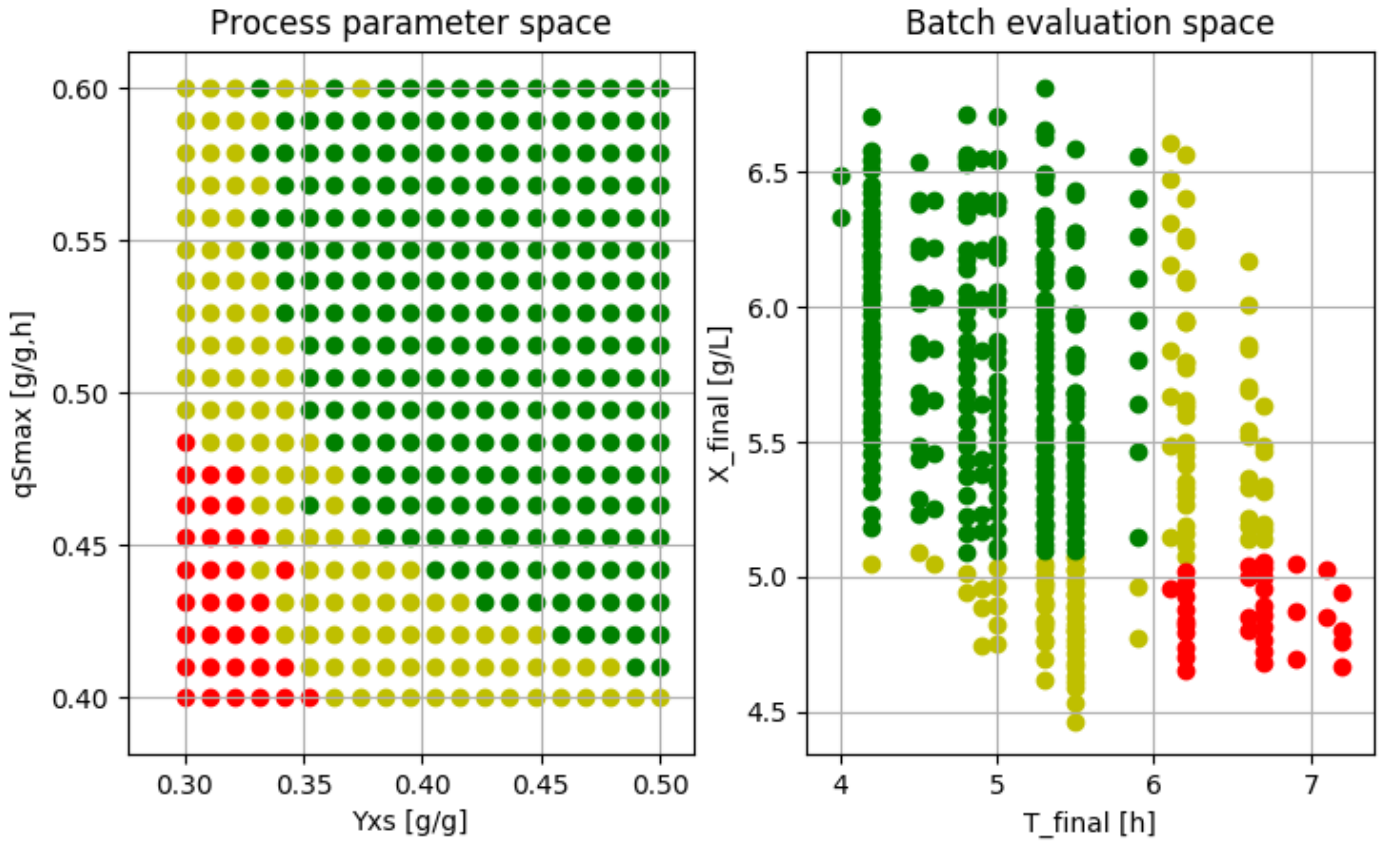
Result from simulation - without noise



Result from simulation - without noise



Result from simulation - with noise (S only)



Calculation of linear estimator

Idea: use a few well chosen data points (batches) and simply make a least square fit to a linear model

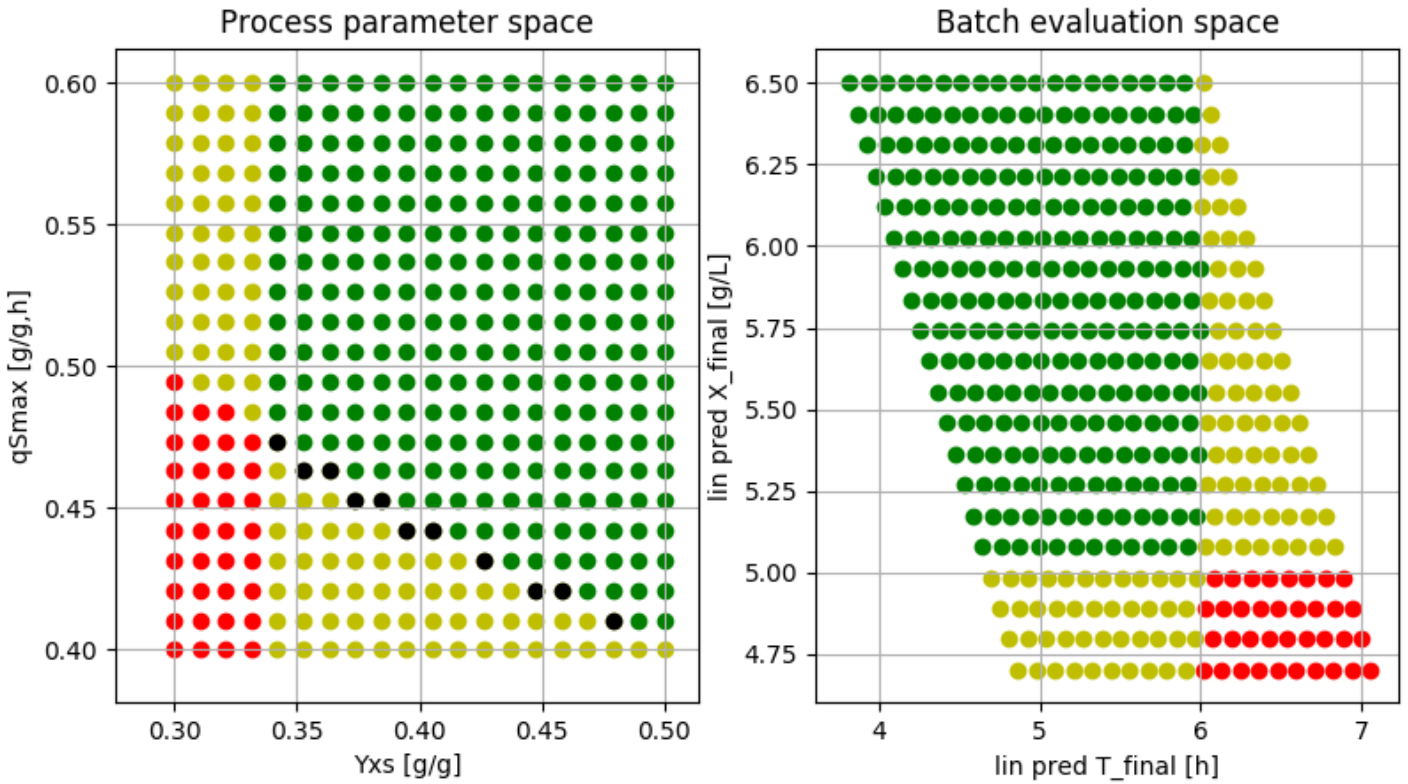
$$T_{final} = a_{11}\,\Delta Y_{sx} + a_{12}\,\Delta q_S^{max} + a_{13}$$

$$X_{final} = a_{21}\,\Delta Y_{sx} + a_{22}\,\Delta q_S^{max} + a_{23}$$

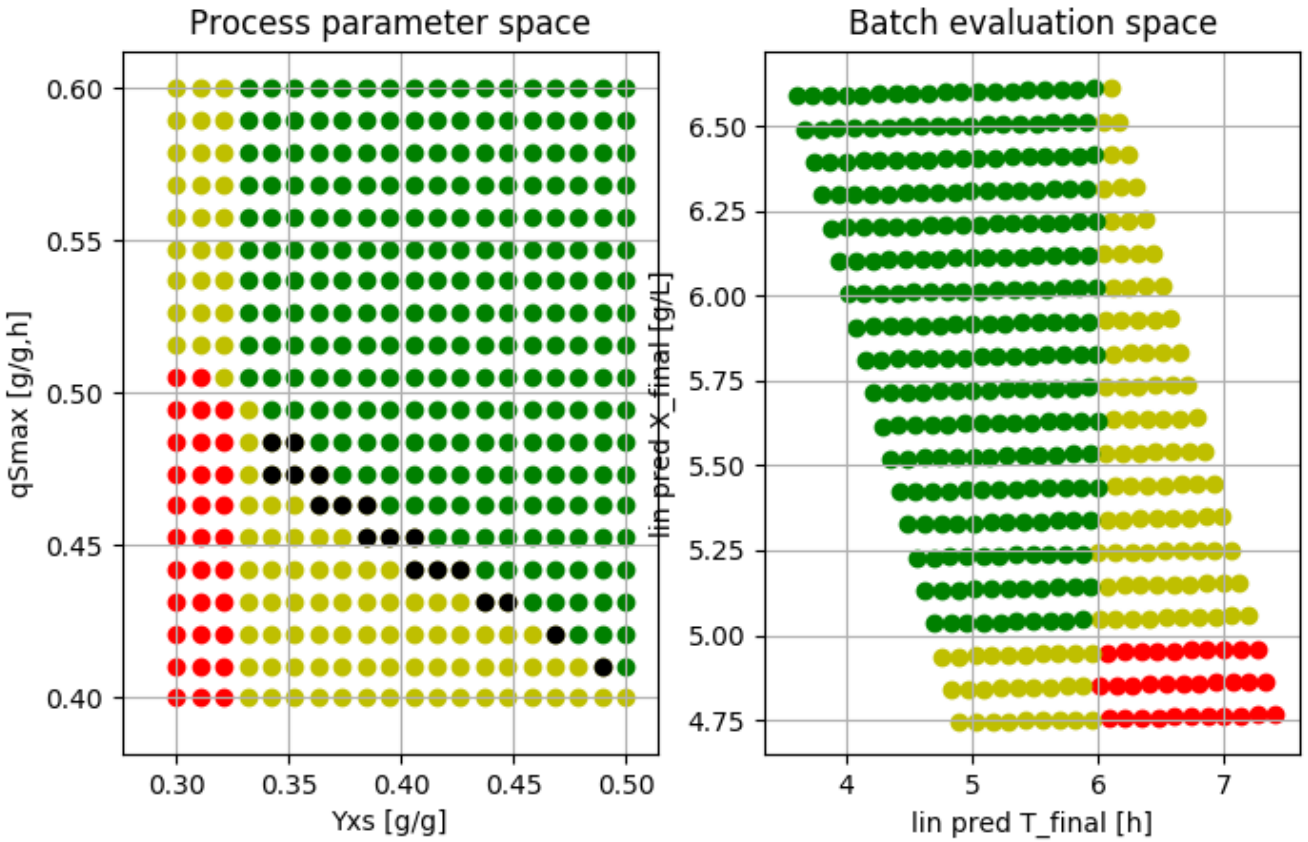
Choose 3-5 data points in a box and center point

- excitation

Comparison design space from linear estimator vs true design space



Comparison… with noise (S only)



Contribution from simulation so far

- Experimental data related reasonbly well to simulated model (not shown here)
- Interprete variation in 6 parameters in 2 biological model parameters interesting
- Design space based on linear approximation used in ”empirical model” is only slightly conservative

- Simulation gives comfort to the experimental approach – but can it be an alternative way?

How much data is needed?

Combinatorial explosion…. 2^4=16, 2^5=32, 2^6=64 etc

Assume linearity – brings down number of experiments

- $y = a_0 + a_1 x_1 + a_2 x_2 + \ldots. + a_6 x_6$
- 7 parameters, i.e. 7 experiments, not 64….
  (extend to model structures linear in parameters)

Reduced factorial design 25% of corners often enough

Ref Mongomery ”Design and analysis of experiments”
8th edition, 2012, John Wiley&Sons

How much data is needed?

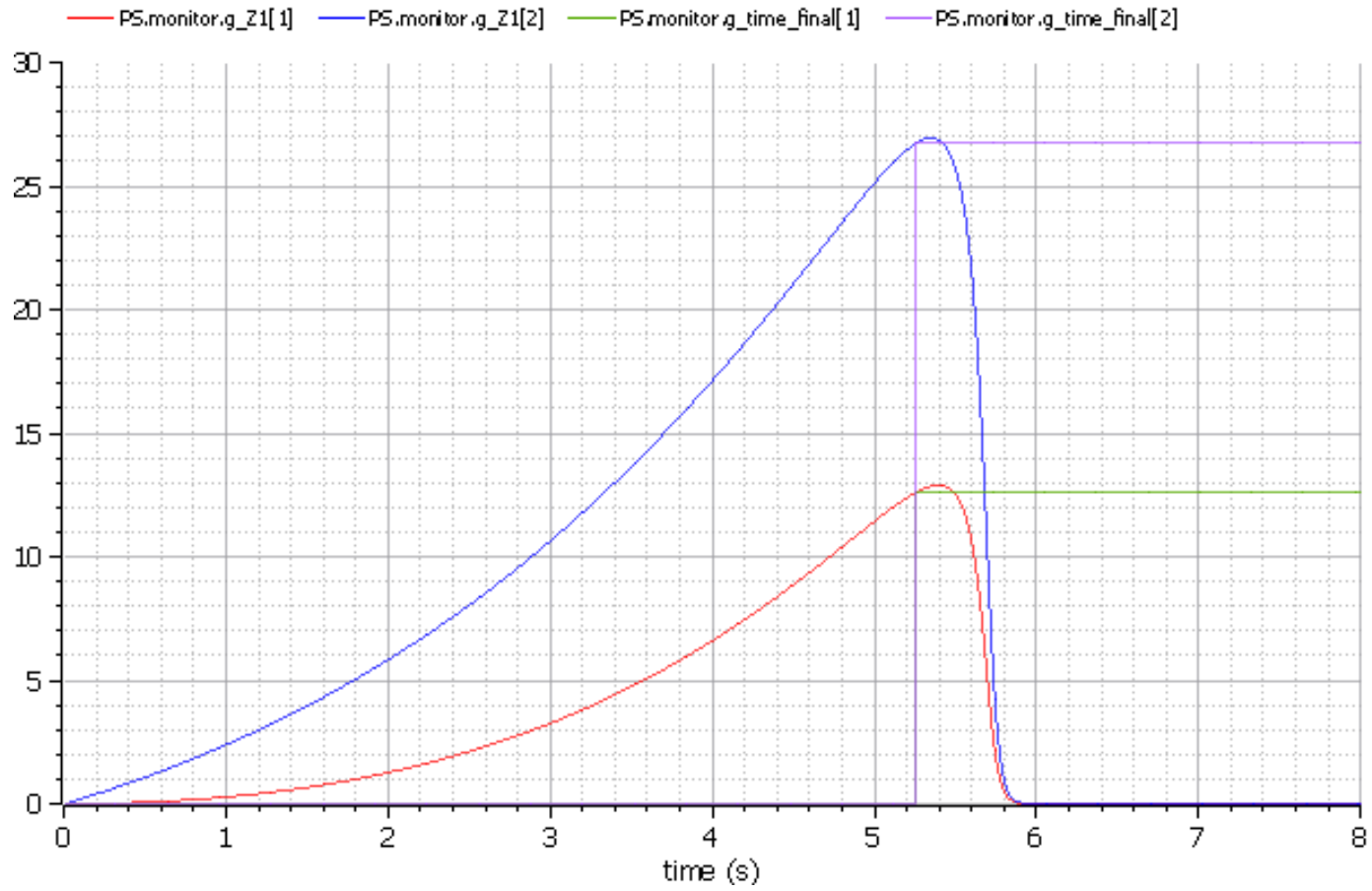
- Design-of-experiment?
  - 3 data points (batches) define a plane….
  - 2-3 more to get reproducibility ”noise level”
- Calibration of model, i.e. trust model structure?
  - 2-3 batches and monitor the trajectory
  - Thus less experiments needed
- Model validation for more uncertain structure
  - More batches…
  - Make use of qualitative aspects – tailor made analysis

Role of local analysis

- Local analysis provide sensitivity of the center point using only one (more complex) single simulation
- Taylor expansion around center points can provide an approximate design space
- Methodology should scale-up well with model complexity, linearly in parameters to investigate

- PSTools was straight forward to apply to the current problem, but not automated
- However, hybrid system nature of the end condition needs special further development of the tool

Time final sensitivity to Yield and Growth rate max



Wish-list

- Monte Carlo simulation
  - Takes time
  - Takes memory resources
  - Toolbox?
- Local analysis
  - Methodology to deal with hybrid systems
  - Der(x,p)?

Concluding remarks

- Pharma industry, QbD, global sensitivity analysis and experimental procedures dominate the field

- Here good model provide support for the experimental work – and make design space less conservative
- Simulation allows more precise modelling of where noise comes in – factors and/or measurement and may bring important insights. Work in progress.
- Calibrate model needs fewer experiments but of different nature, than routine DoE
- Monte Carlo simulation Modelica framework?
- Dynamic Parameter Sensitivity continue to evaluate

Software used

- Bioprocess Library *for* Modelica – J P Axelsson
- JModelica and Python scripting

- PSTools *for* Modelica – A Elsheikh
- OpenModelica – figure slide 19

- MODDE from Sartorius Stedim Data Analytics (former Umetrics AB) – figure slide 7

Contact information

Jan Peter Axelsson, Vascaia AB

E-mail: jan.peter.axelsson@vascaia.se