Implementation of a Reduced System Model to a Continuous Direct Compression Manufacturing Process

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Lilly

Continuous Manufacturing of Drug Product

- Shift in processing times
  - Days➔ Minutes
- Less material handling
- Lean manufacturing
- Small footprint
- Accelerated development

Model Based Design

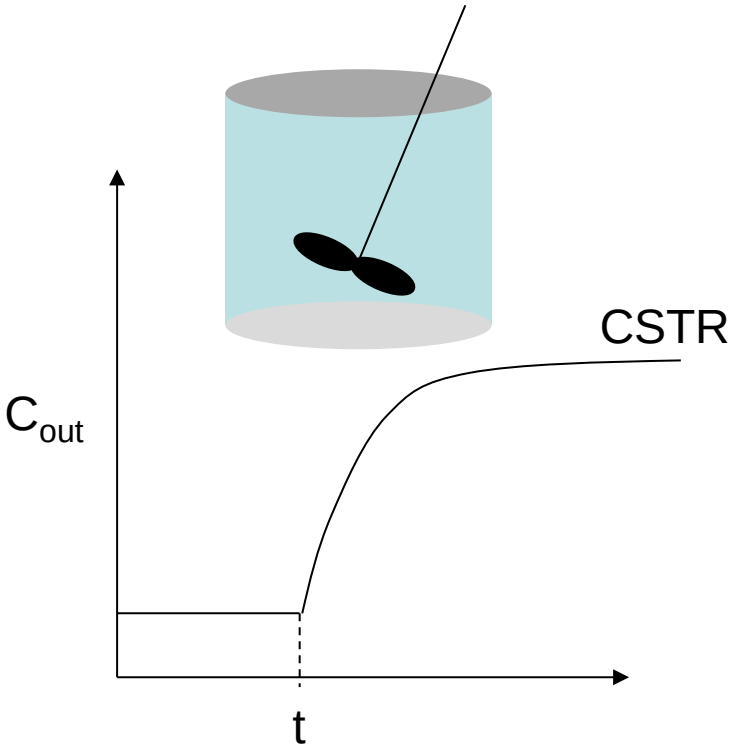
- Process Design:

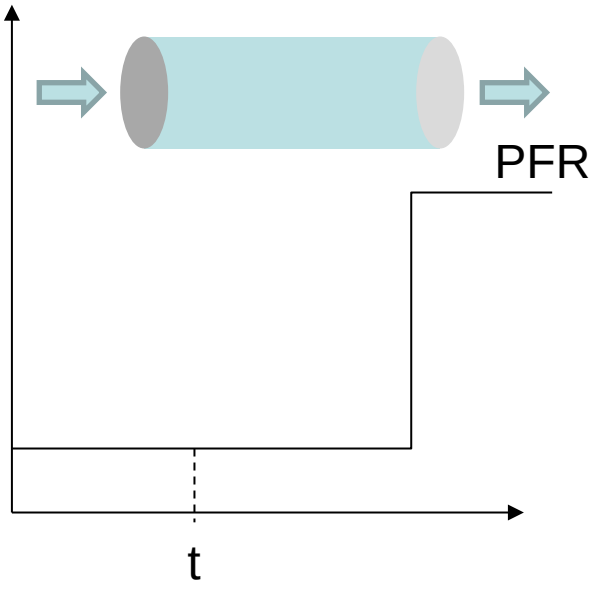
The study of continuous flow of material and it's mixing is a **very well** understood science

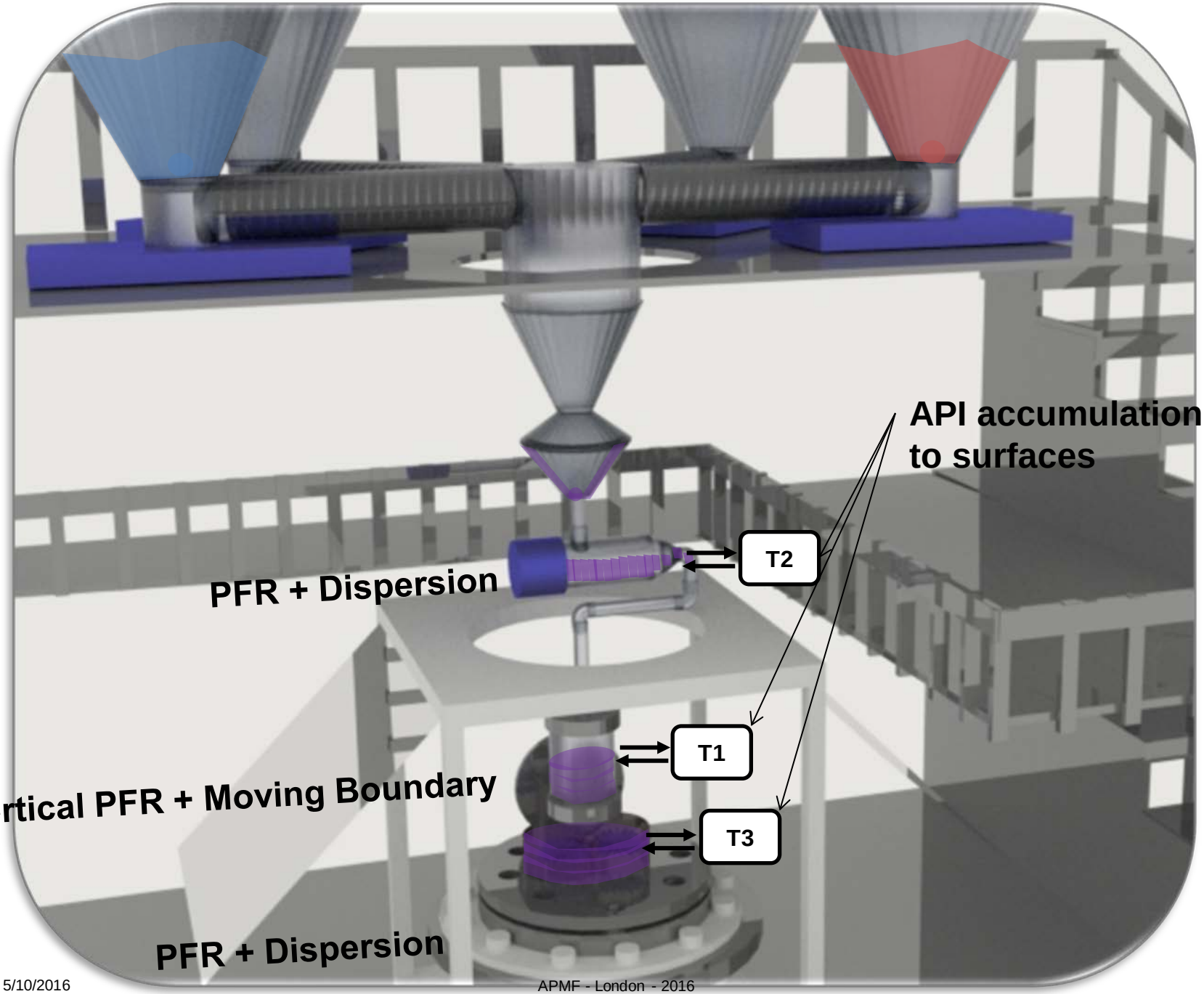
  - Some adjustments need to be done for powders, but the major points still apply.

Model Based Design

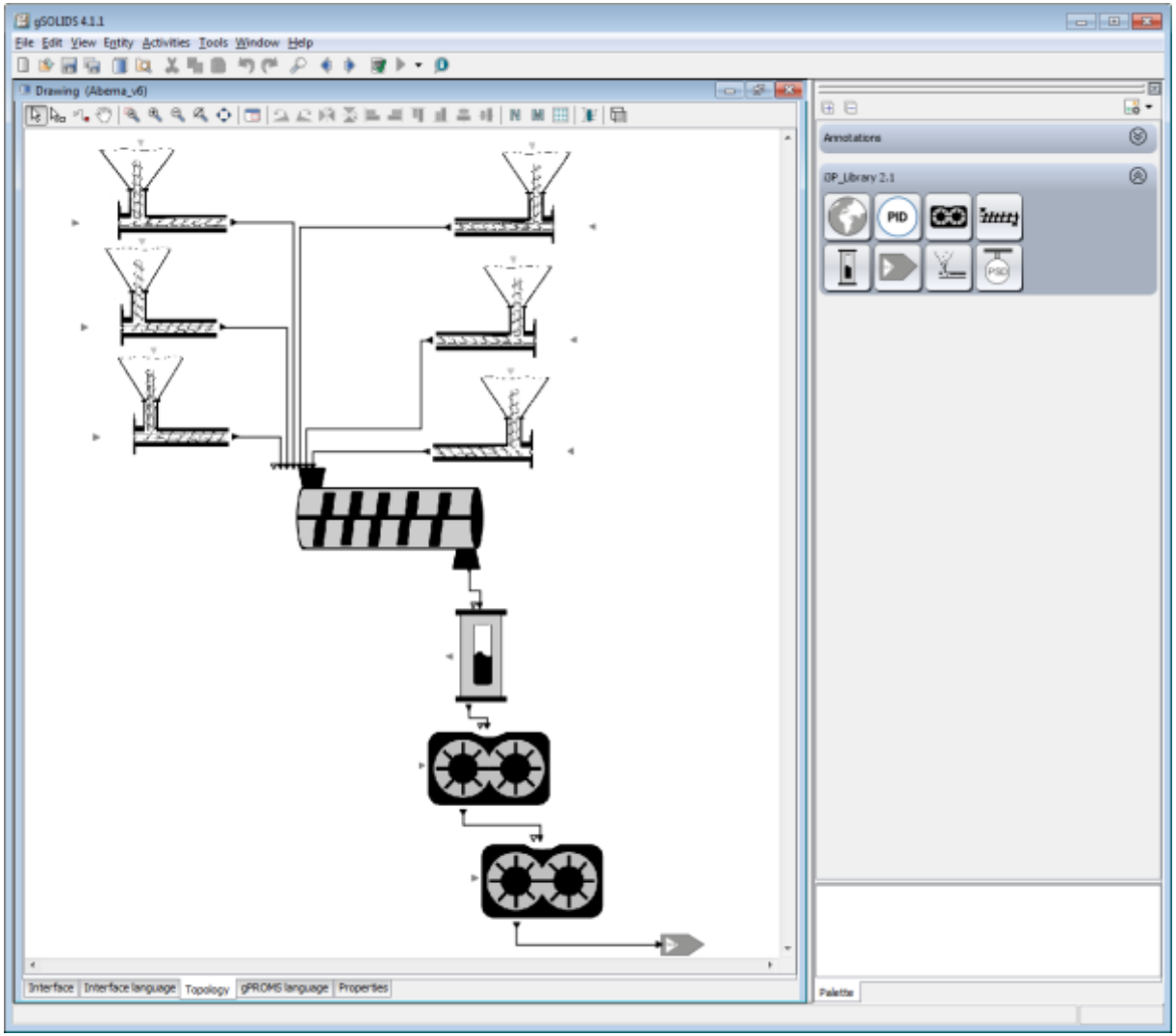
- Continuous mixing is a very well understood principle in chemical engineering






API accumulation
to surfaces
T2
PFR + Dispersion
T1
Vertical PFR + Moving Boundary
T3
PFR + Dispersion

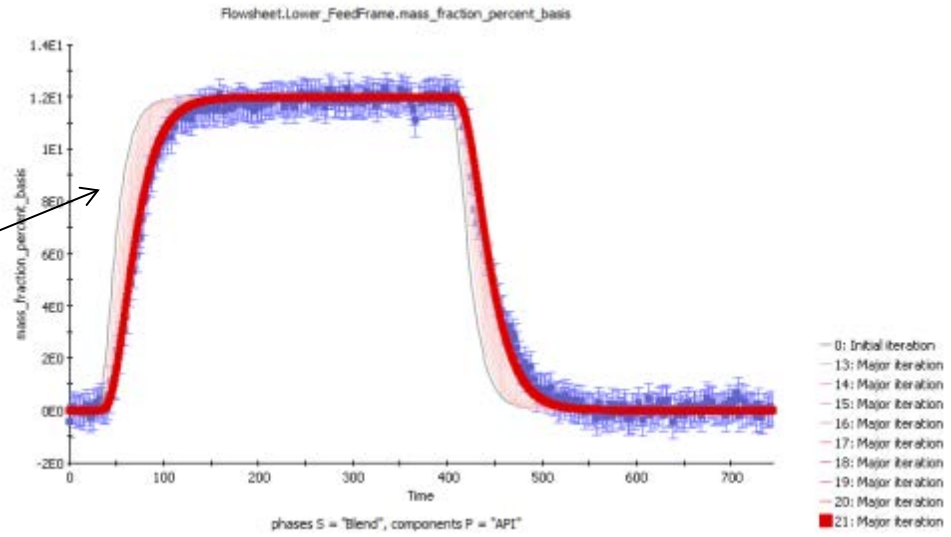
gPROMS implementation



Parameter Estimation

- System components are characterized by introducing step tests

Optimization sequence



Lack of Fit Test

Weighted Residual	χ^2-Value (95%)	Comment
528.663	580.463	Good fit: weighted residual less than χ^2-Value

TOP

Current Solution – Reduced System Model

- Knowing expected dispersion and noise sequence for a given new formula this model can be used (among other uses) to :

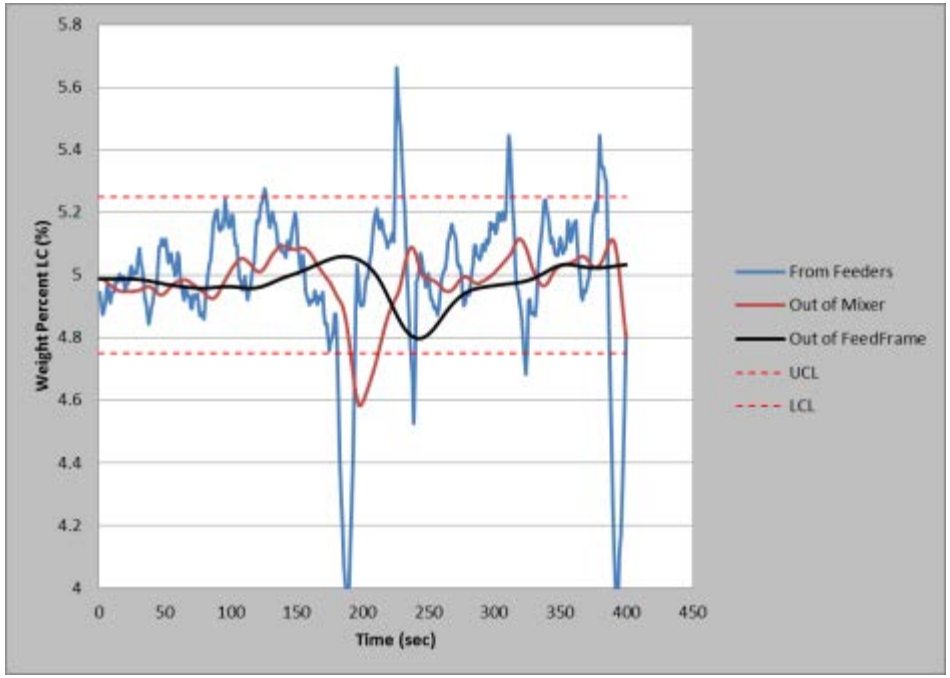
1. Aid Product Development

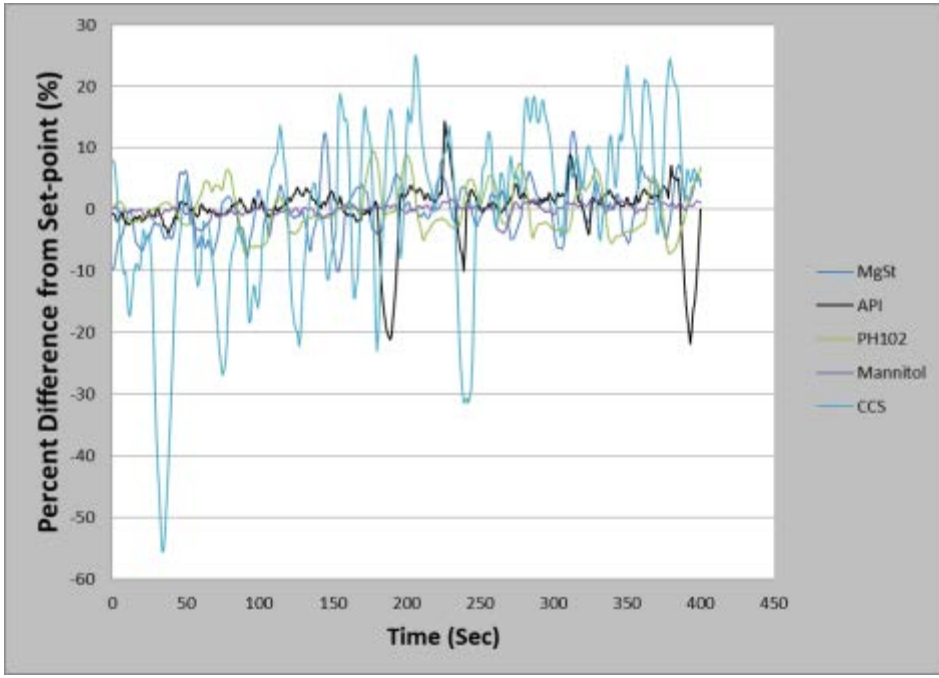
1. On-Line Model Based Application !
    - Moving Horizon Estimation

Disturbance rejection study

- Can system reject disturbances from feeders for a given compound/formulation?

  Yes, integration across system successfully rejects disturbances for this case.





Current Solution – Reduced System Model

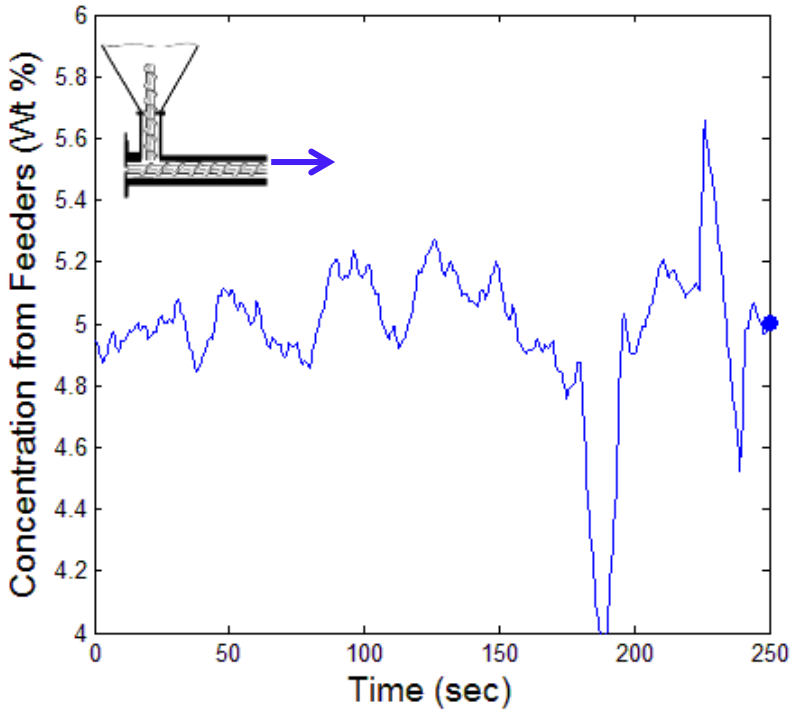
- Knowing expected dispersion and noise sequence for a given new formula this model can be used (among other uses) to :

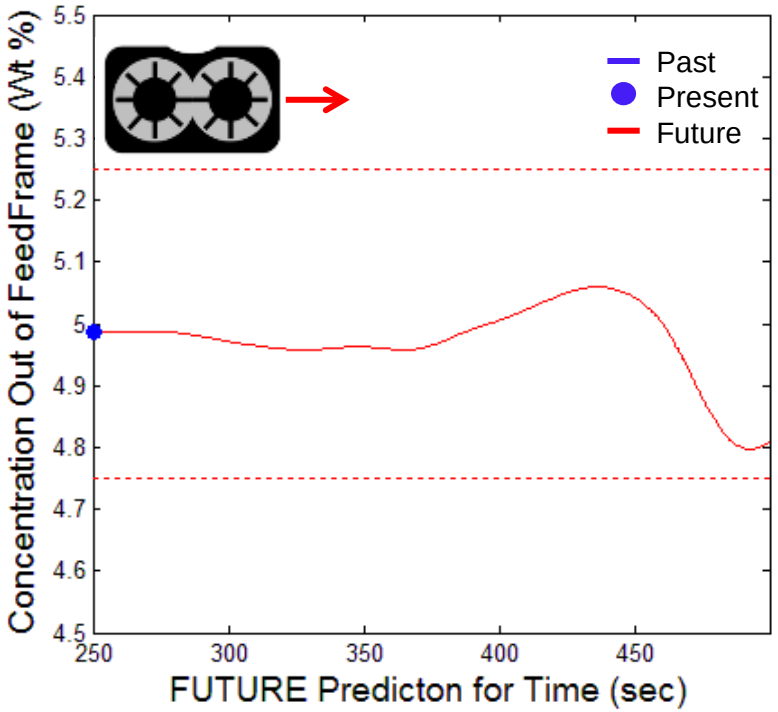
1. Aid Product Development

1. On-Line Model Based Application !
   - Moving Horizon Estimation

Desired solution – Non Linear State Estimation

- On-line, non-linear state estimation and prediction of downstream impact.





- Working towards this, **but not there today**
  - Computationally intense

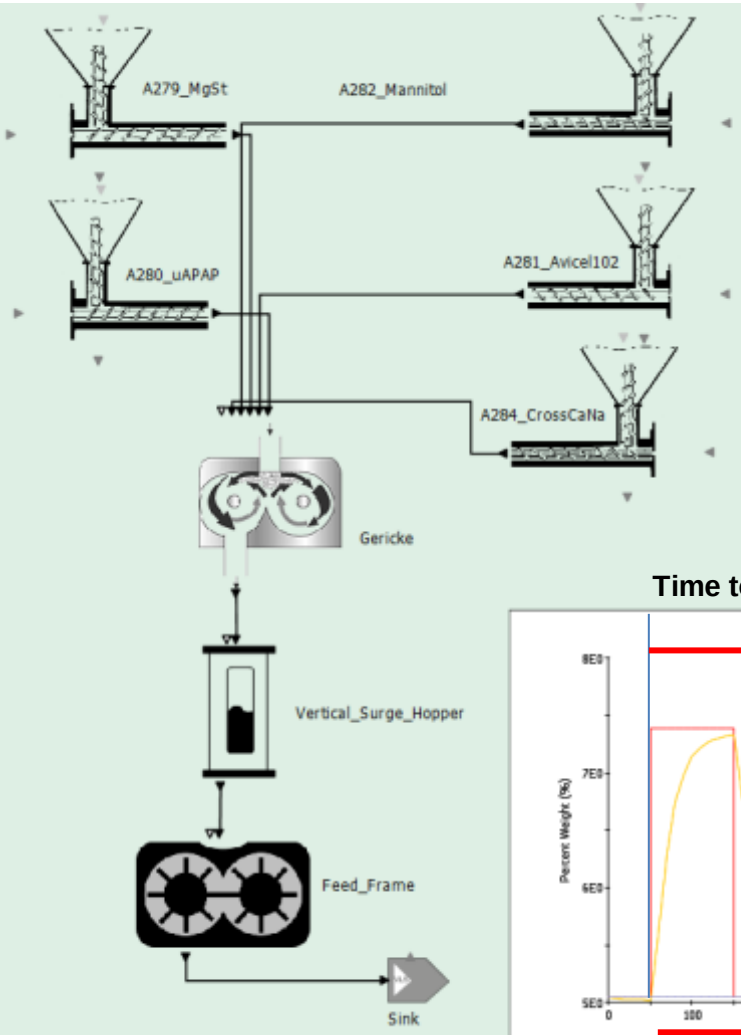
Current Solution – Reduced System Model

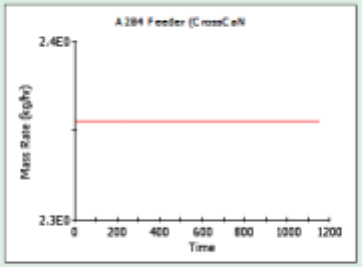
- Knowing expected dispersion and noise sequence for a given new formula this model can be used (among other uses) to :

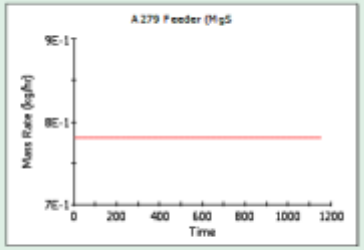
1. Aid product development

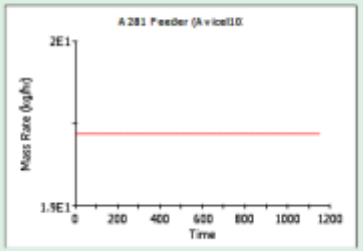
2. For the conditions chosen, what is the **Impact to Product**, **Time to Product** and **Time to Clear** for a disturbance in the feeders to enter/leave the system.

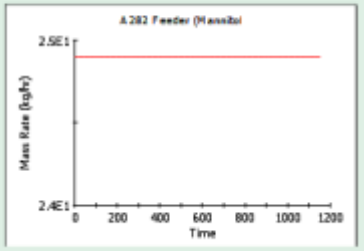
Product Impact, Time to Product and Time to Clear



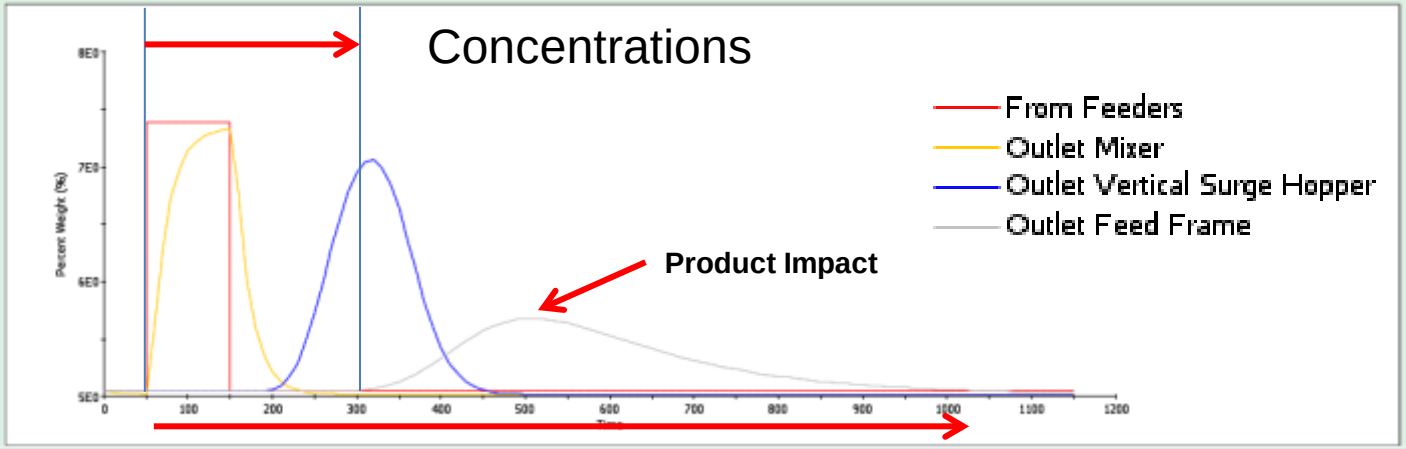








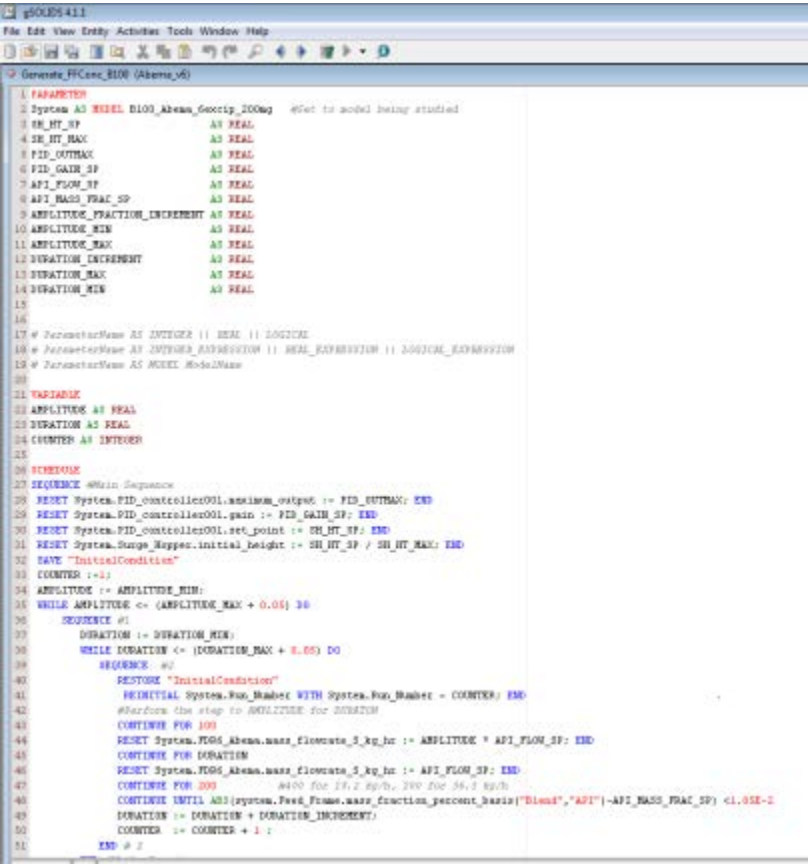
Time to Product



Time to Clear

TASKS and SCHEDULE

- Implementation is laborious and complex to transfer to a new owner



```
SCHEDULE
#continue for 5000
#    SEQUENCE
#        CONTINUE FOR 100
#        REASSIGN
#            Flowsheet.FDR6_Abema.mass_flowrate_S_kg_hr := 0;
#        END
#        CONTINUE FOR 2000
#    END


# Generate_T2P (System is Flowsheet,
#                                 PID_OUTMAX              is 1000,         #Typical value for 100mg is 10000 when not generating T2P
#                                 PID_GAIN                is 50,           #Typical value for 100mg is 50 when not generating T2P
#                                 VSH_HT_SP_INCREMENT     is 0.031,        #Steps of +10$ Level
#                                 VSH_HT_SP_MIN           is 0.031,        #Height a 10$ fill
#                                 VSH_HT_SP_MAX           is 0.31,         #Max. for angled hopper
#                                 FLOW_RT_MULT_INCREMENT  is 0.05,         #Based on 35.71$ / 6
#                                 FLOW_RT_MULT_MIN        is .90    ,       # 90$ of flow as min
#                                 FLOW_RT_MULT_MAX        is 1.1   ,       # 110$ of flow as max
#                                 FDR1_MASSFLOW_SP        is 0.5184 ,       #For 36.3 kg/h B100
#                                 FDR2_MASSFLOW_SP        is 2.0736 ,       #For 36.3 kg/h B100
#                                 FDR3_MASSFLOW_SP        is .9072 ,       #For 36.3 kg/h B100
#                                 FDR4_MASSFLOW_SP        is 6.3504 ,       #For 36.3 kg/h B100
#                                 FDR5_MASSFLOW_SP        is 1.8144 ,       #For 36.3 kg/h B100
#                                 FDR6_MASSFLOW_SP        is 6.48 ,        #For 36.3 kg/h B100
#                                 API_MASS_PCNT_SP        is 35.714058)


        Generate_FFConc (System is Flowsheet,
                         SH_HT_SP is 0.1319,        #Surge hopper height at 50$
                         SH_HT_MAX is 0.307986315,  #Surge hopper maximum height
                         PID_OUTMAX is 500,         #PID Controller maximum output
                         PID_GAIN_SP is 50,         #PID Controller gain setpoint
                         AMPLITUDE_FRACTION_INCREMENT is 0.1,
                         AMPLITUDE_MIN is 1,
                         AMPLITUDE_MAX is 2,
                         DURATION_INCREMENT is 20,
                         DURATION_MIN is 120,
                         DURATION_MAX is 180,
                         API_FLOW_SP is 6.48,      #For 18 kg/h
                         API_MASS_FRAC_SP is 35.714058)
```

Current implementation

PROCESS

DATA

MATLAB

Experiment Entity

Parameter Estimation

gPROMS

SCHEDULE

TASK

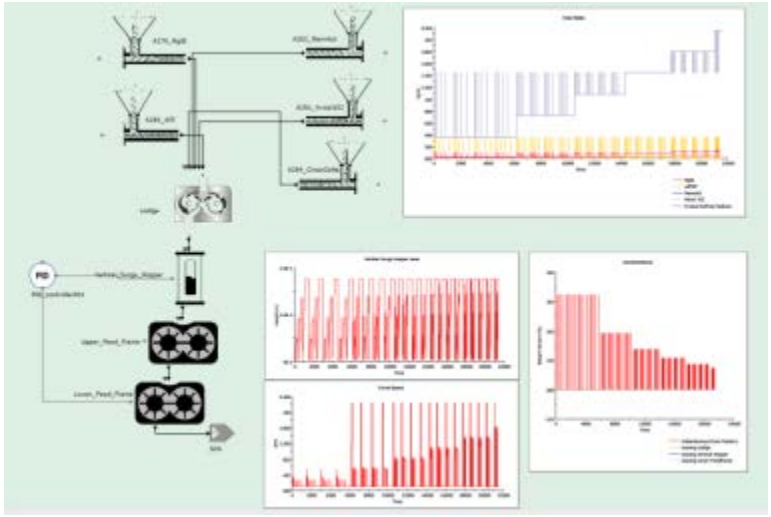
.xml exporter

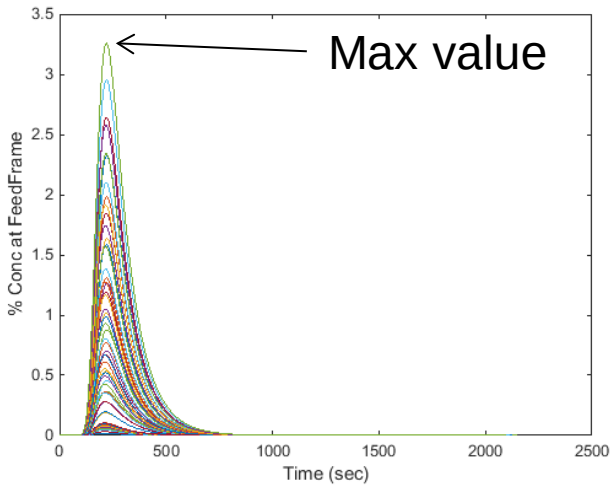
MATLAB

.dll's
For RT execution

Construction of a Reduced System Model - Impact to Product

- Simulated dispensed disturbances – THOUSANDS!
  - Spans from minute to large in both severity and duration
  - Example for Impact to Product:

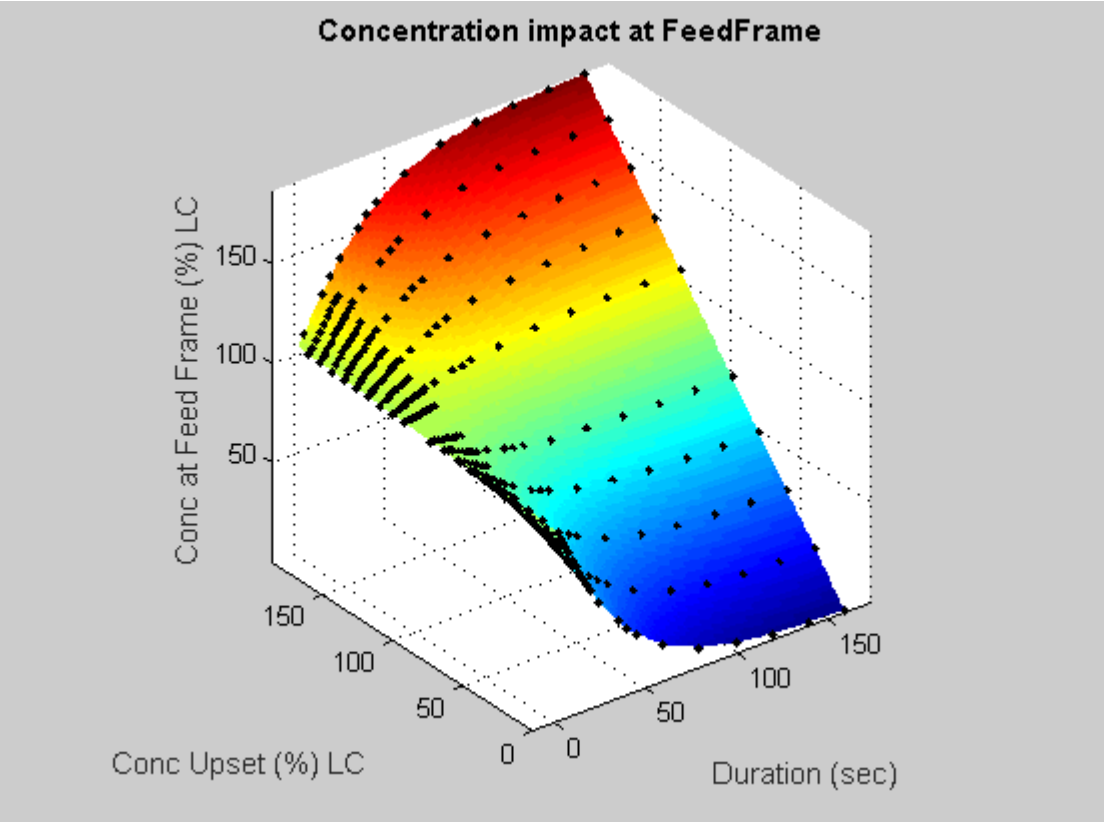




  - Peak of concentration upset is worst case

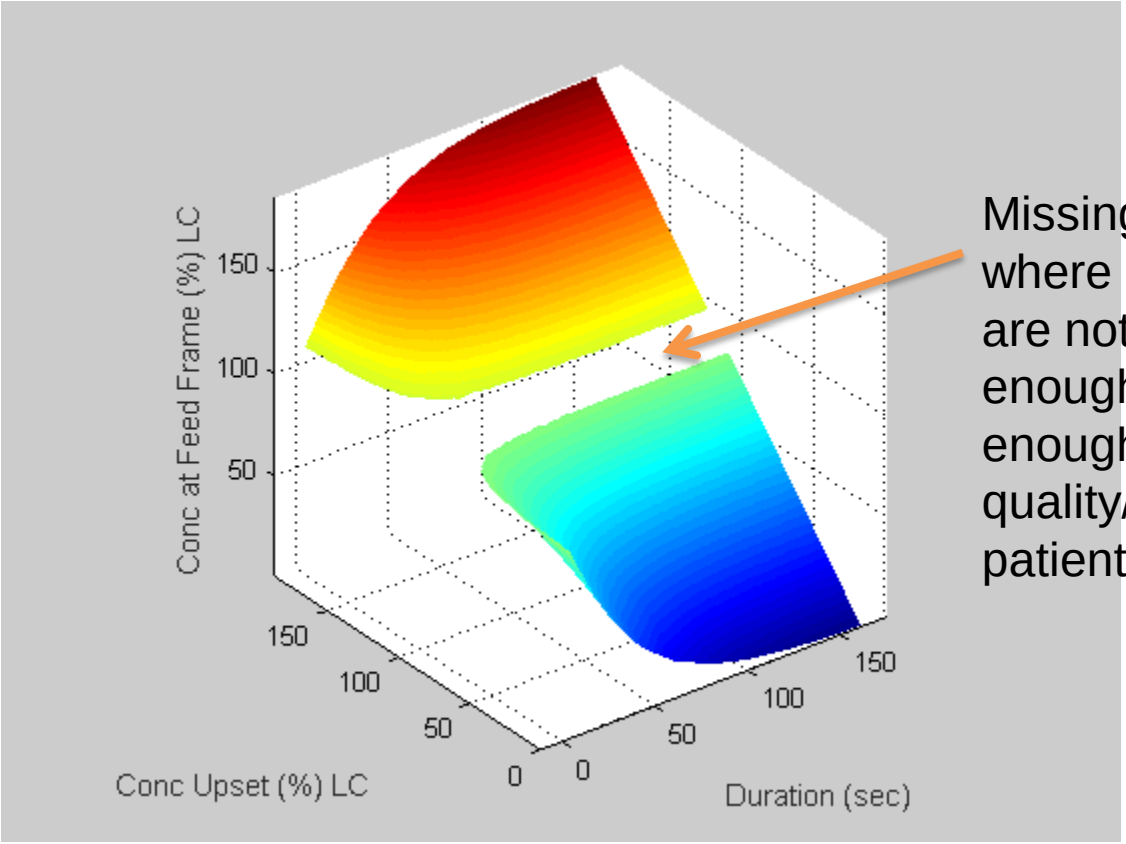
Construction of a Reduced System Model - Impact to Product

- Resulting surface encompasses output of digital experiments
- Practical execution would take days and consume large amounts of API



Construction of a Reduced System Model - Impact to Product

- Removing portion where disturbances do <u>not</u> impact product quality

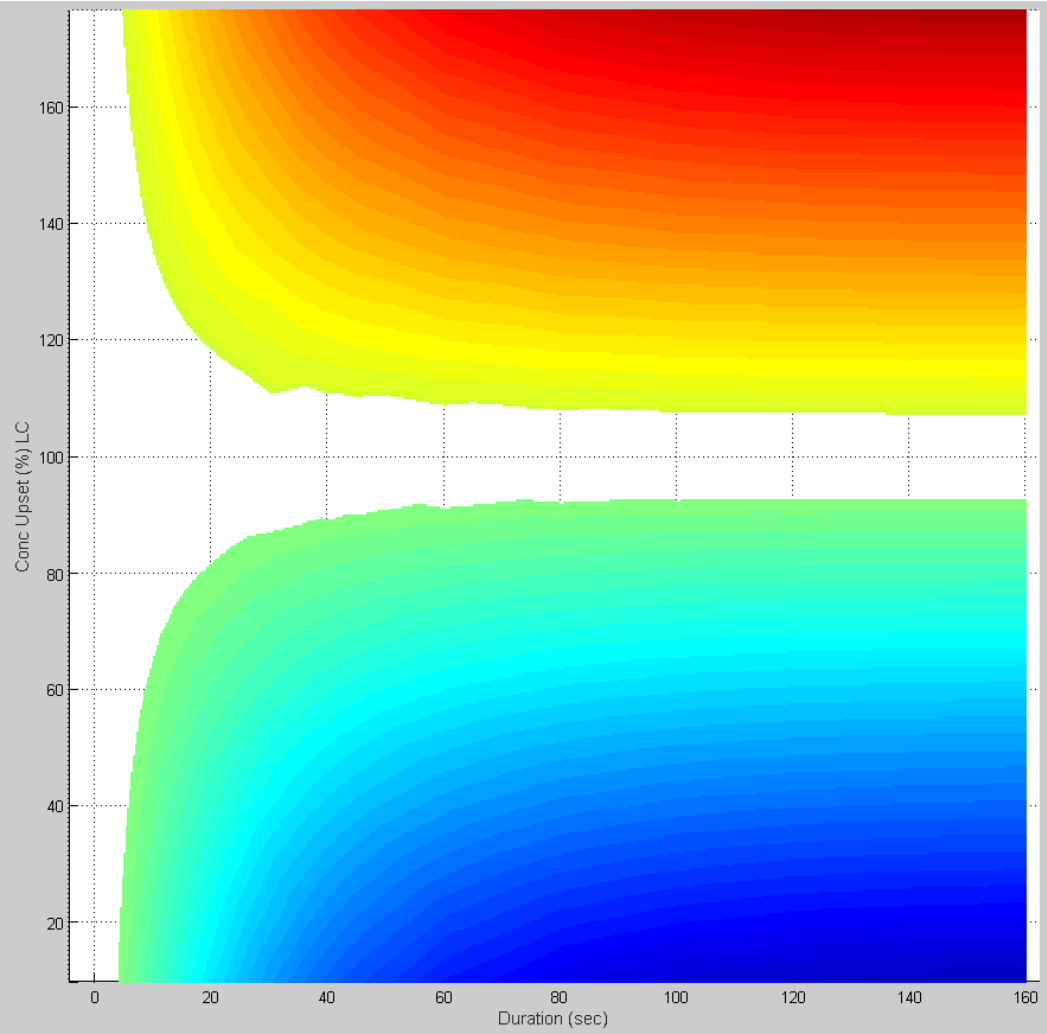


Missing surface is where disturbances are not severe enough or long enough to impact quality/safety for patient

Construction of a Reduced System Model - Impact to Product

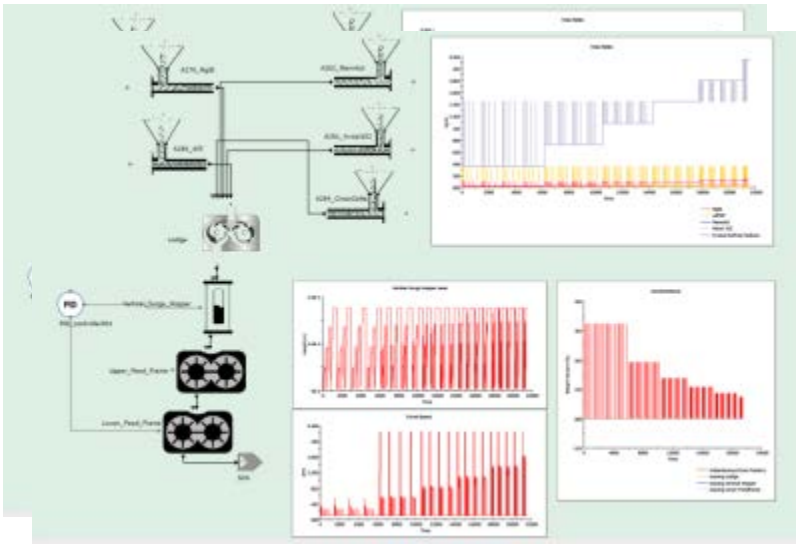
- X-Y projection (done for simplicity of upset testing)

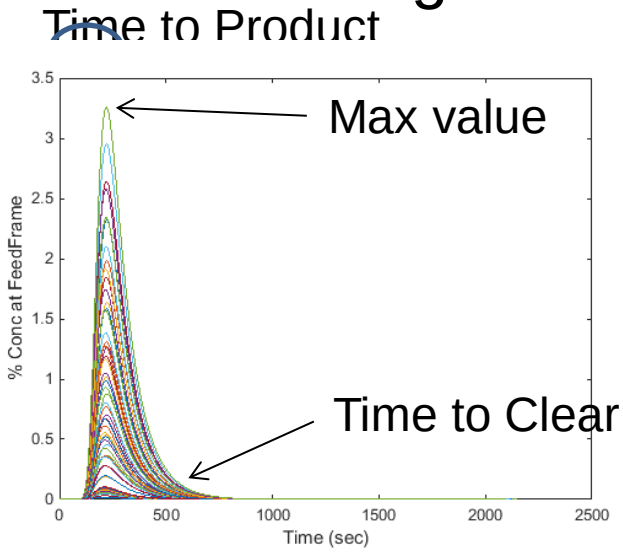
The "Funnel" Plot



Construction of a Reduced System Model – Time to Product/Clear

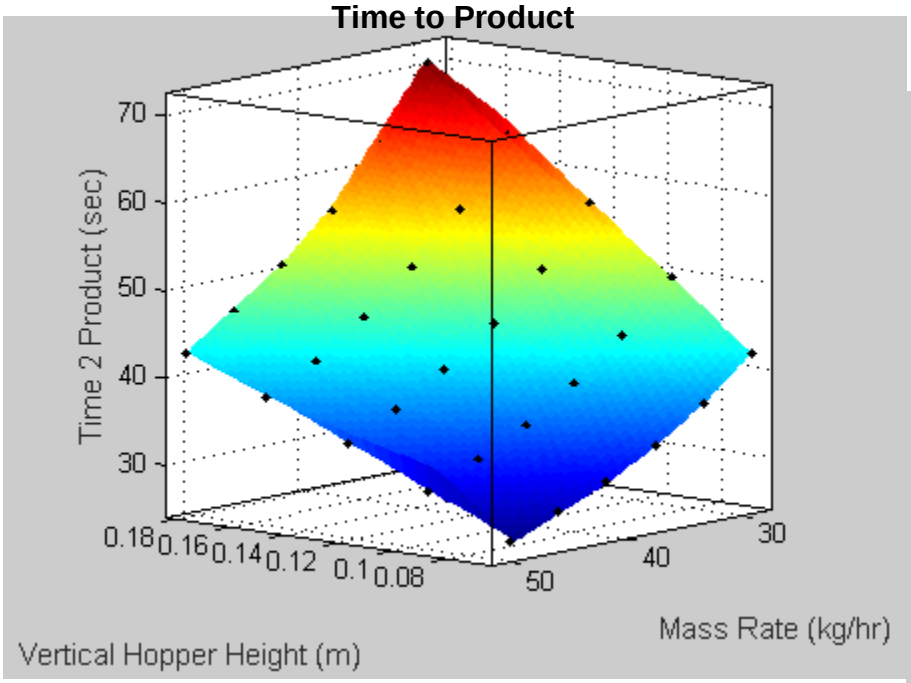
- Again, digital experiment in the Thousands
- Patient safety a core focus!
  - Looking for earliest sign of drift from target

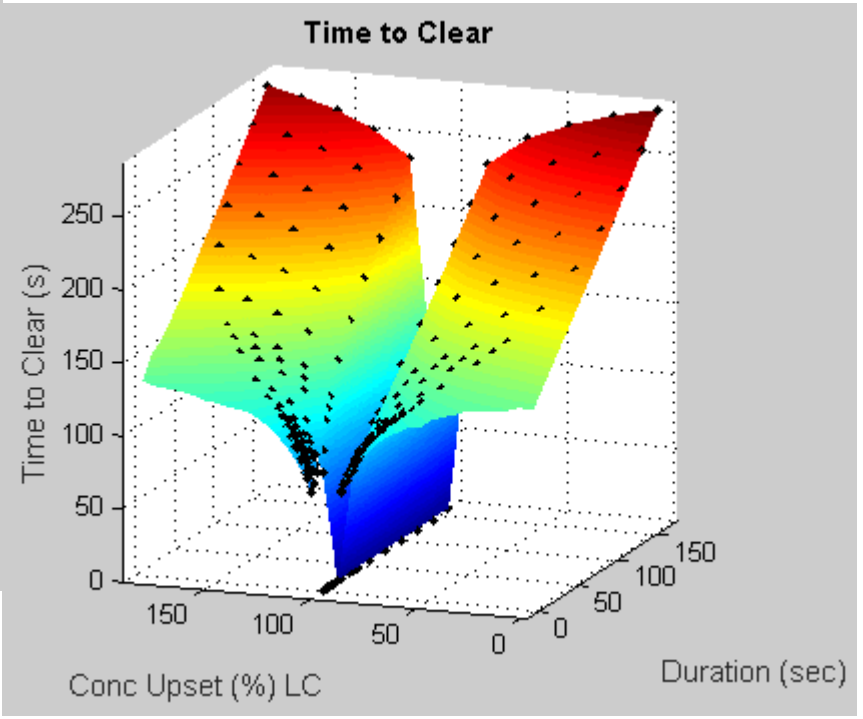




Time to Product Module

- Reduction of temporal element of deterministic model to simple surface

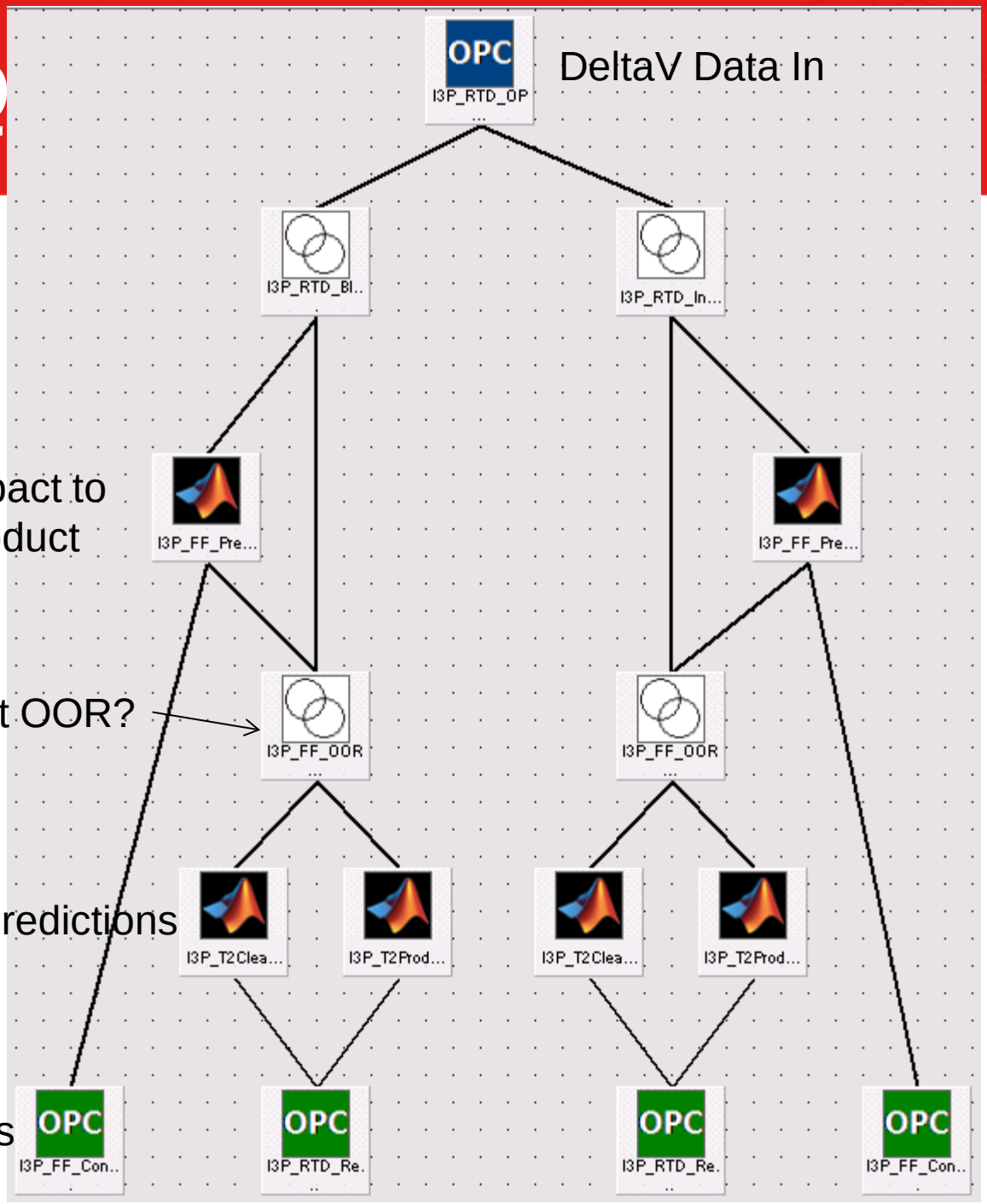




Matlab Interpolants

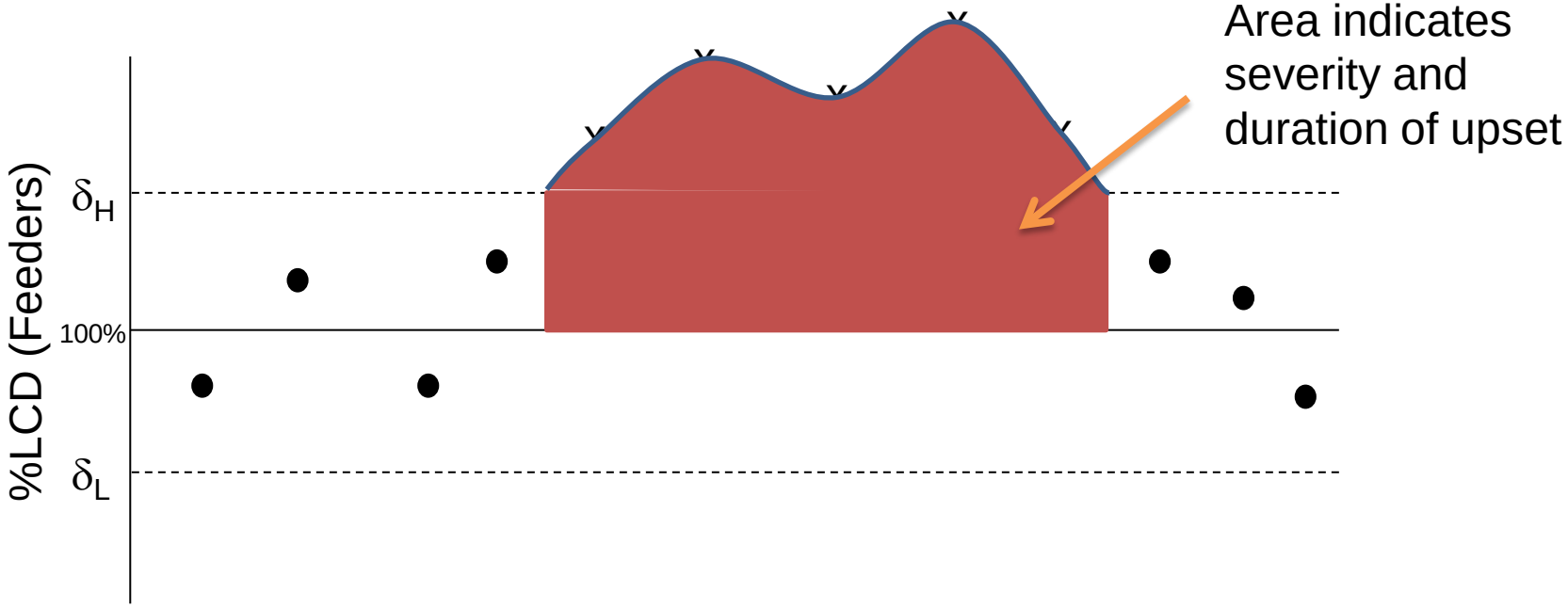
- Surfaces become interpolants in Matlab
  - Feed Frame Conc Prediction
  - Time to Product (Time to Reject)
  - Time to Clear (Time to Accept)
- Compiled in Matlab to DLLs and ran on the SynTQ server under a Matlab execution, as needed
  - Pass DV data to Matlab DLLs in SynTQ
  - Return predictions, calculate times within DV

SynTQ


DeltaV Data In
Impact to Product
Impact OOR?
Time Predictions
Return values
I3P_RTD_OP
I3P_RTD_Bl...
I3P_RTD_In...
I3P_FF_Pre...
I3P_FF_Pre...
I3P_FF_OOR
I3P_FF_OOR
I3P_T2Clea...
I3P_T2Prod...
I3P_T2Clea...
I3P_T2Prod...
I3P_FF_Con...
I3P_RTD_Re...
I3P_RTD_Re...
I3P_FF_Con...

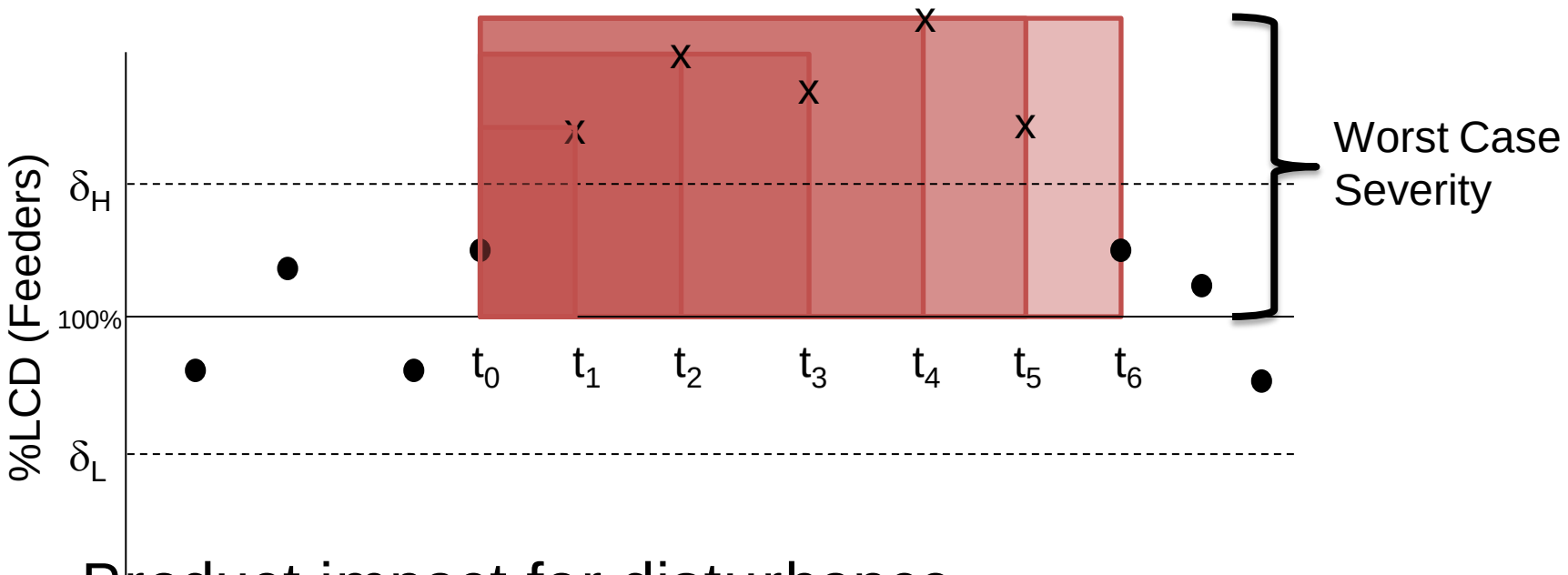
Characterizing Disturbance

- Easy in a retrospective, post-mortum analysis
  - Given the following disturbance:



Characterizing Disturbance

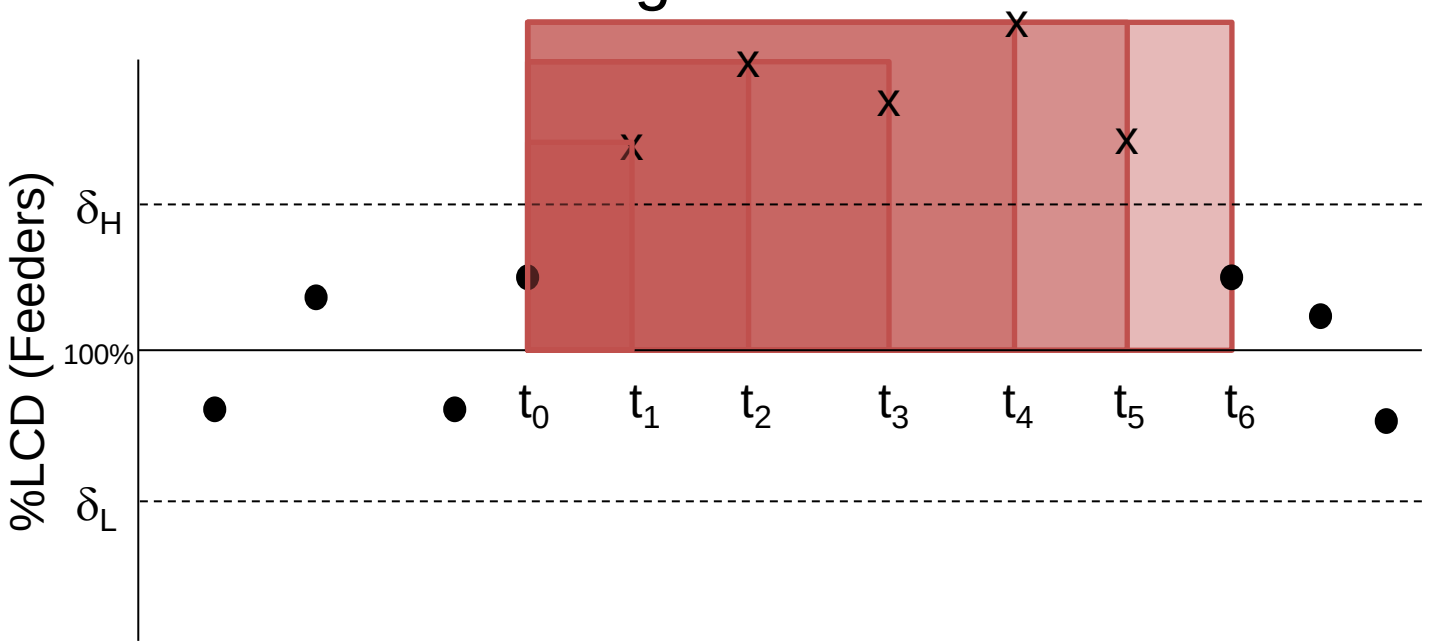
- Real time – future trending unknown
  - Given the following disturbance:



  - Product impact for disturbance
    $f(\max|\%LCD - 100\%|, \max t)$

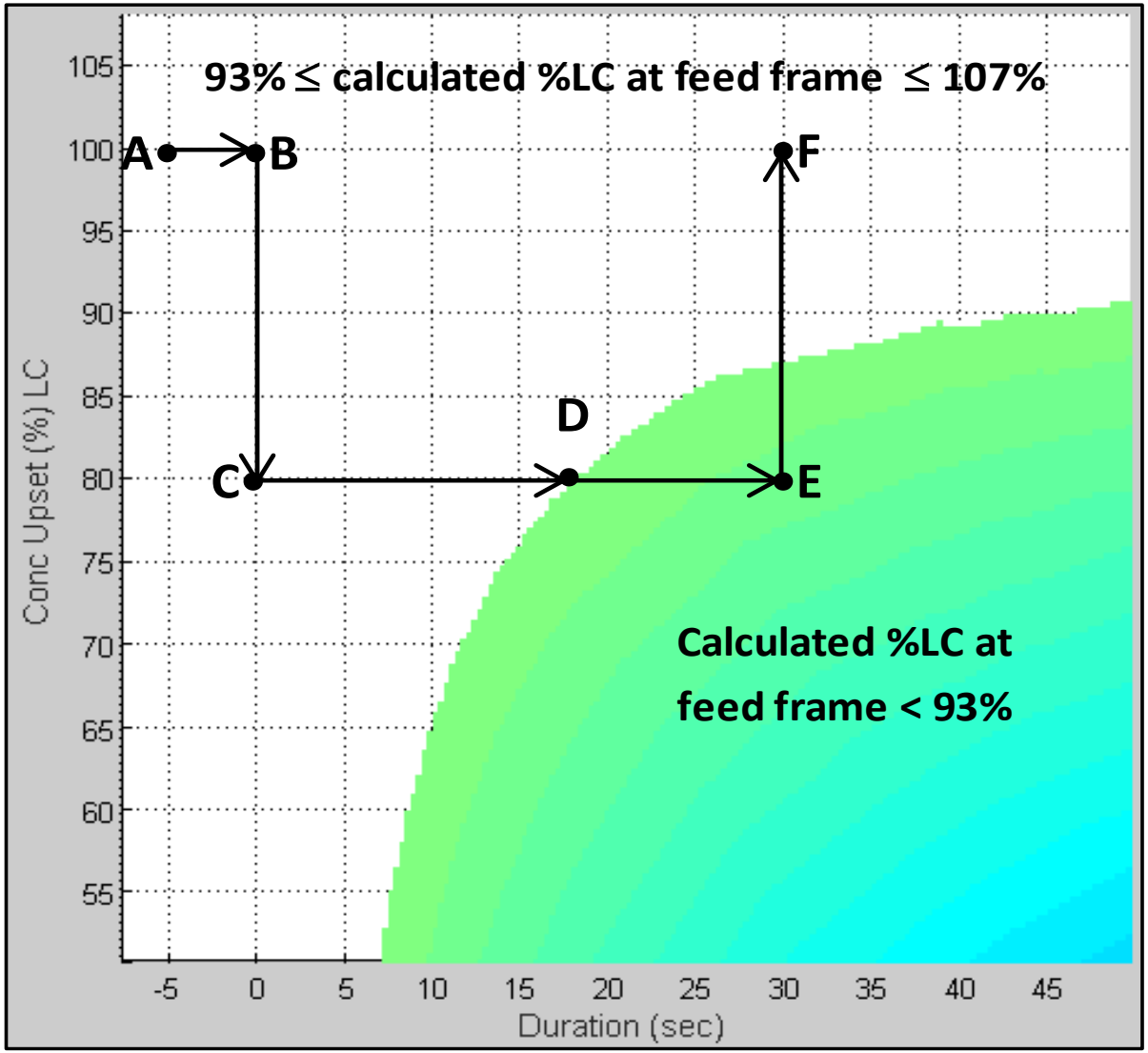
Characterizing Disturbance

- Time to Product/Clear
  - Given the following disturbance:

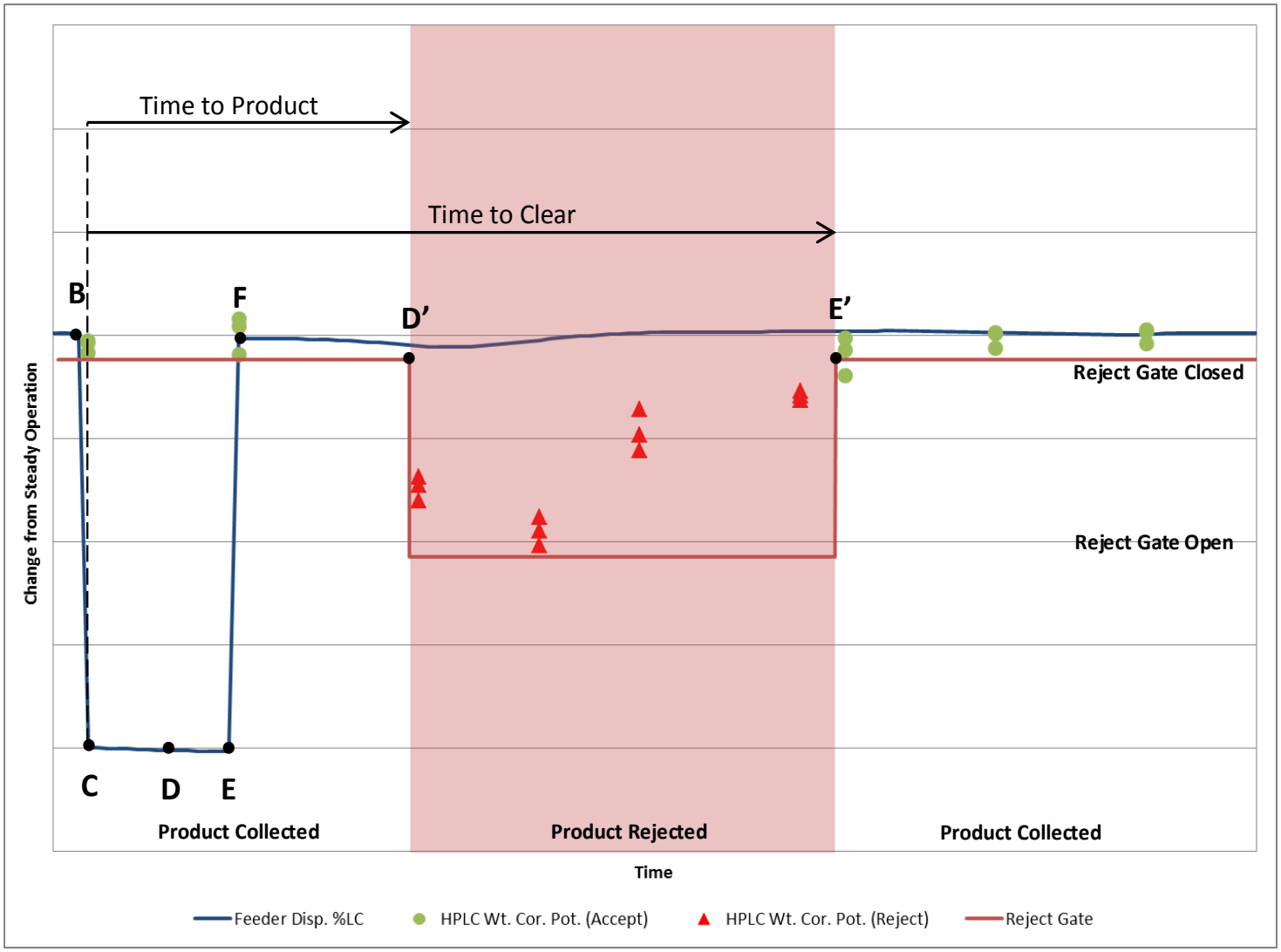


  - $T2P_i = \min(T2P_{i-1}, T2P(VSH,MF))$
  - $T2C_i = \max(T2C_{i-1}, T2C(\max|\%LCD - 100\%|, \max t))$
  - Again, erring on patient safety

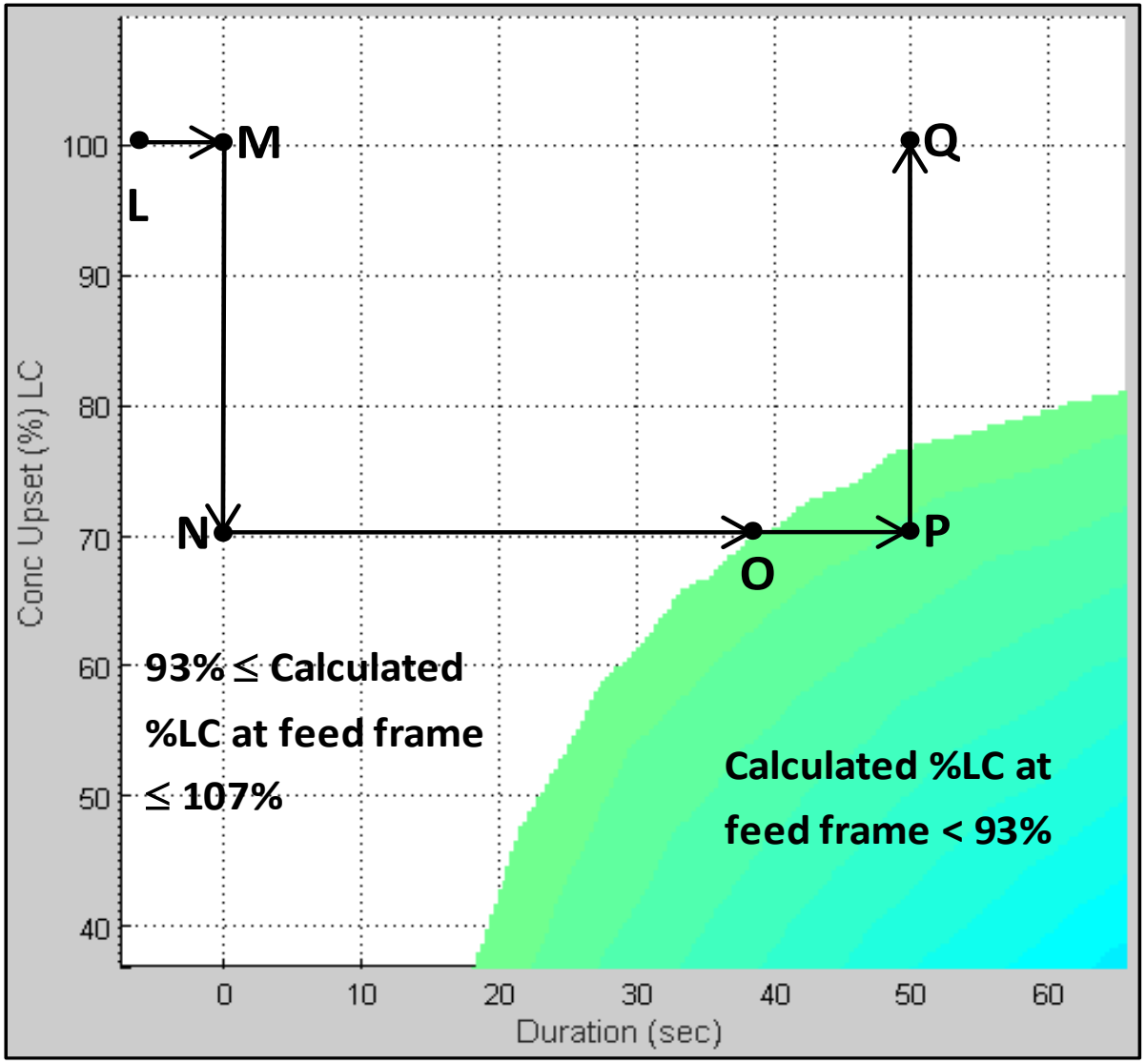
Funnel Plot for LY1 (20 mg) Challenge



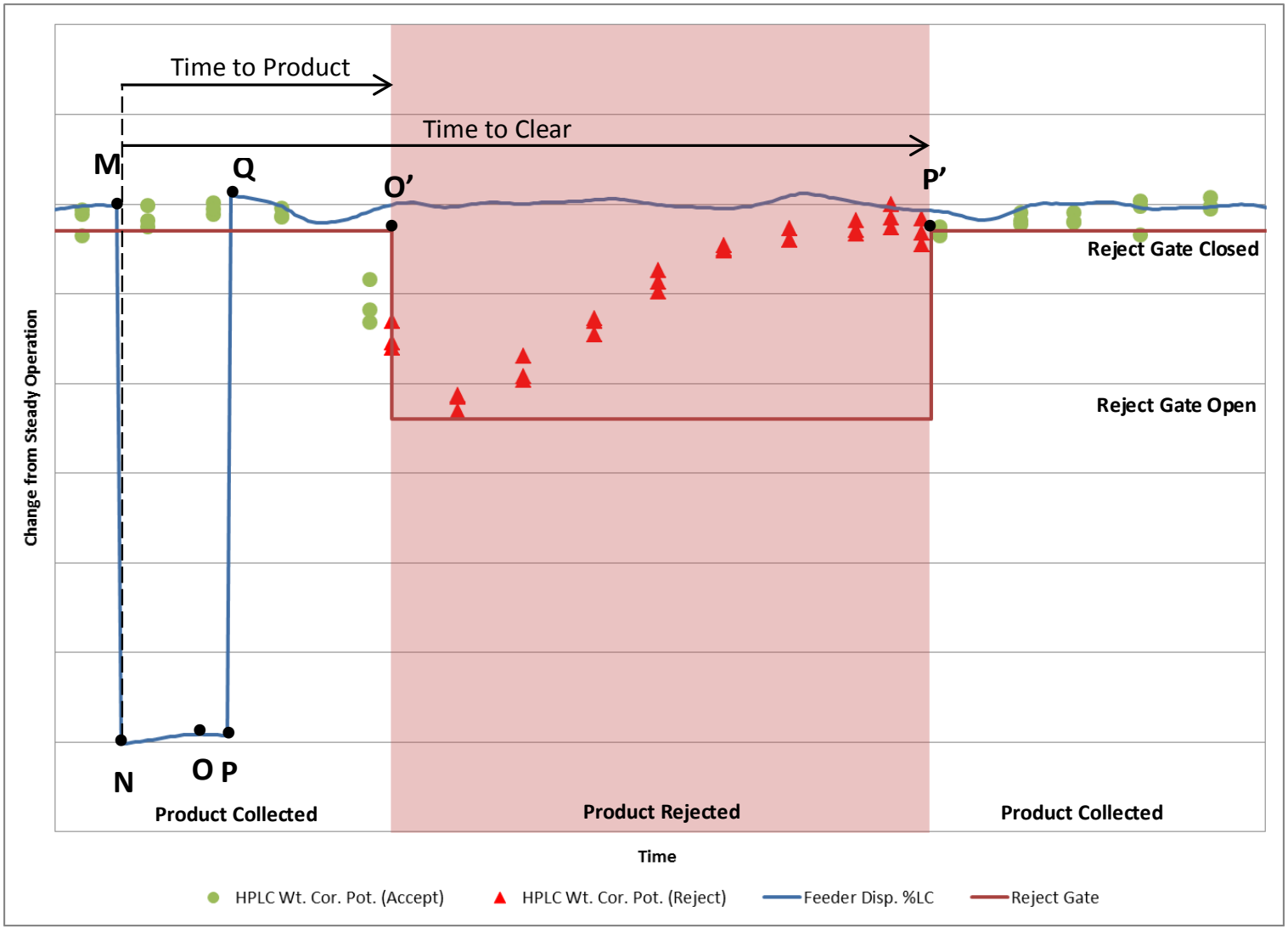
LY1 (20 mg) Challenge



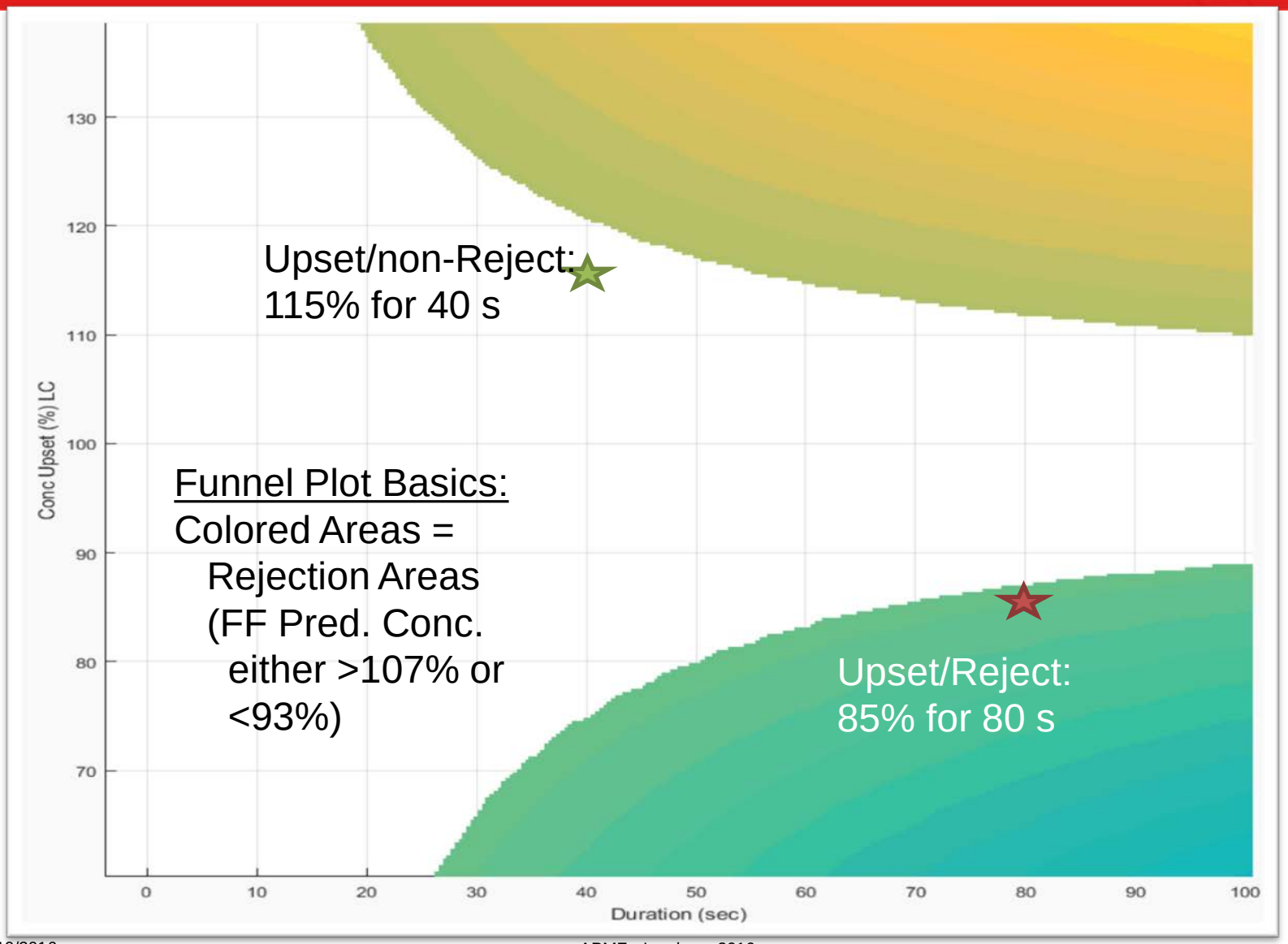
Funnel Plot for LY1 (10 mg) Challenge



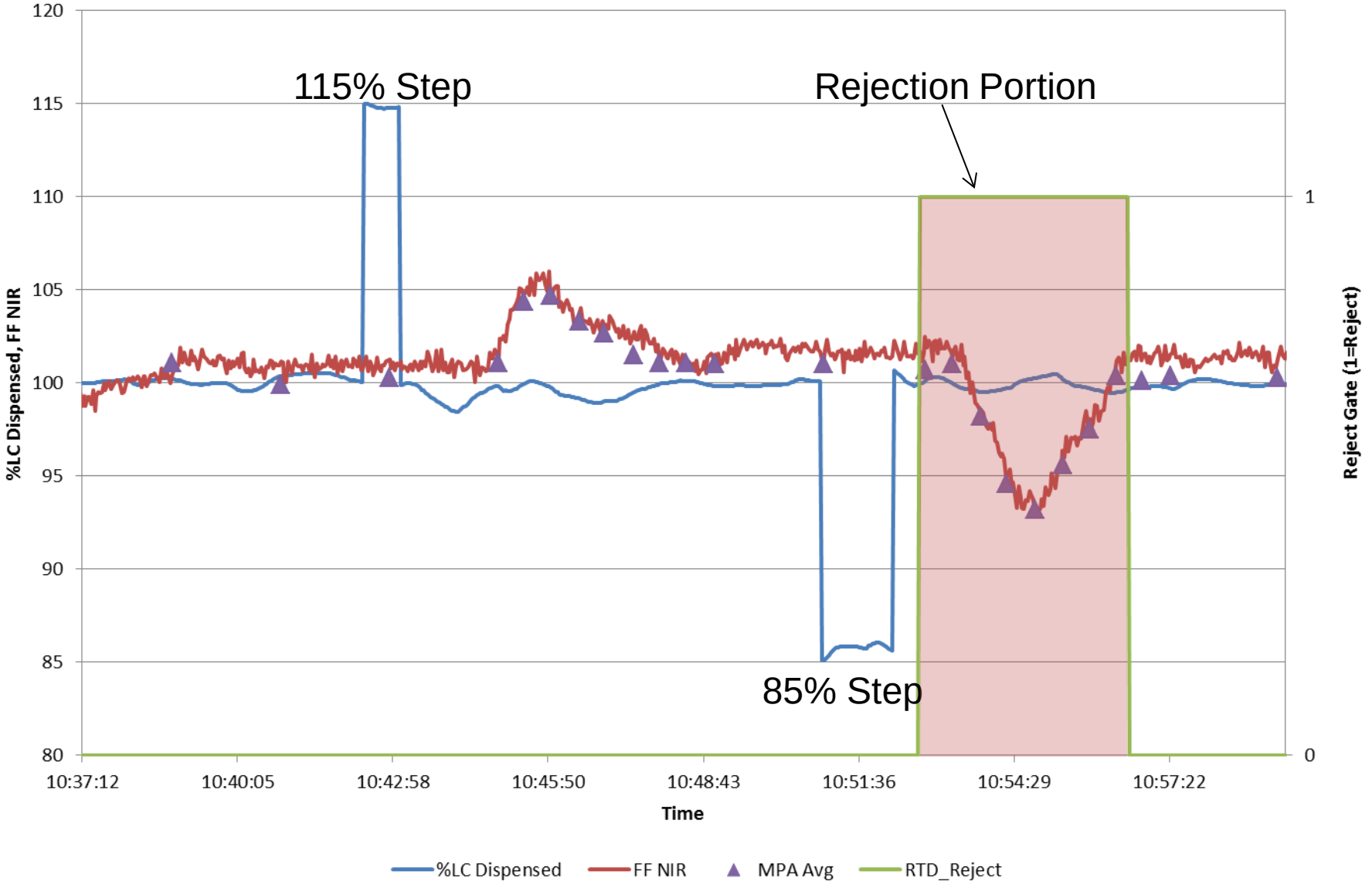
LY1 (10 mg) Challenge



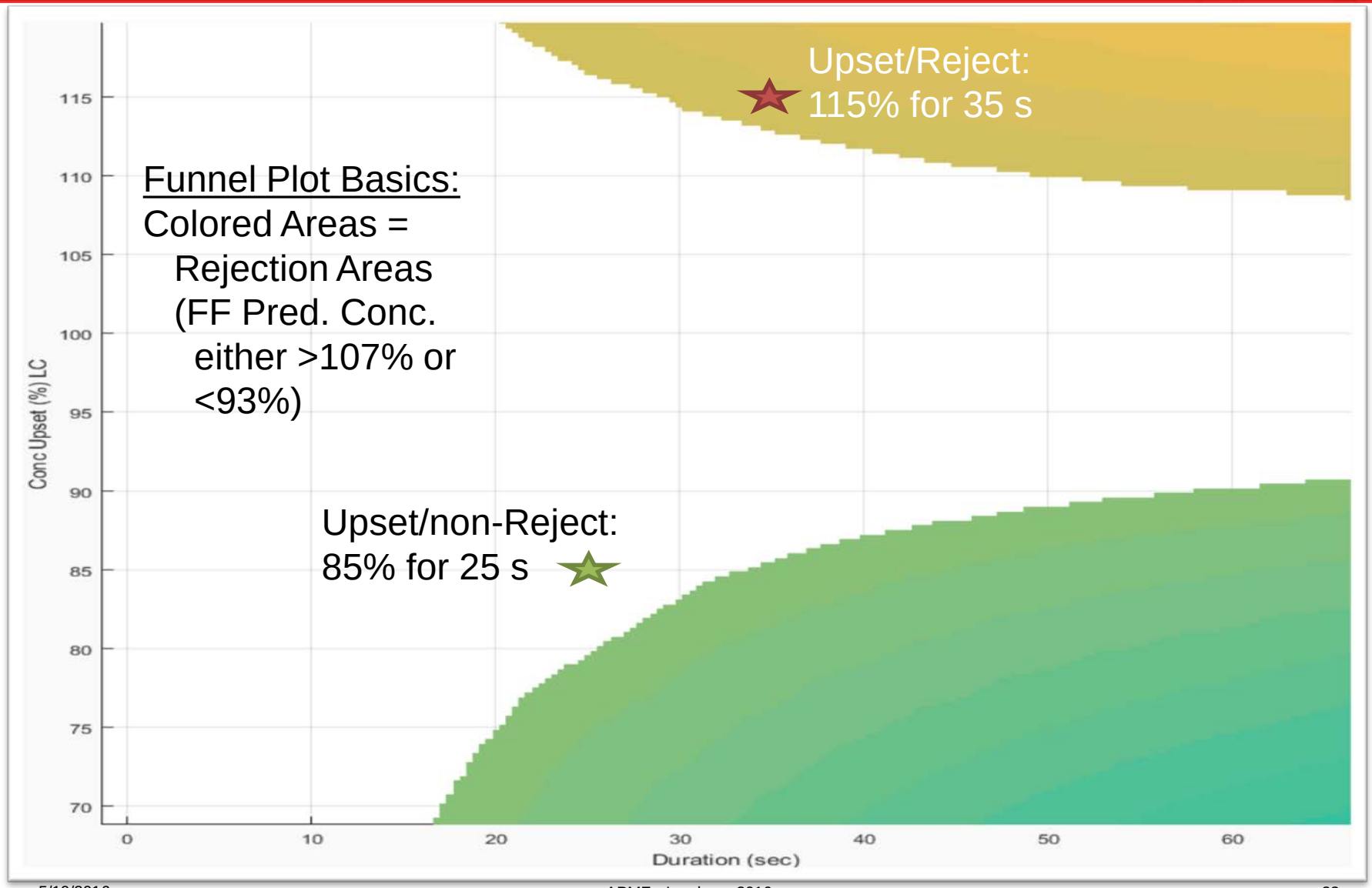
Funnel Plot for LY2 (150 mg) Challenge



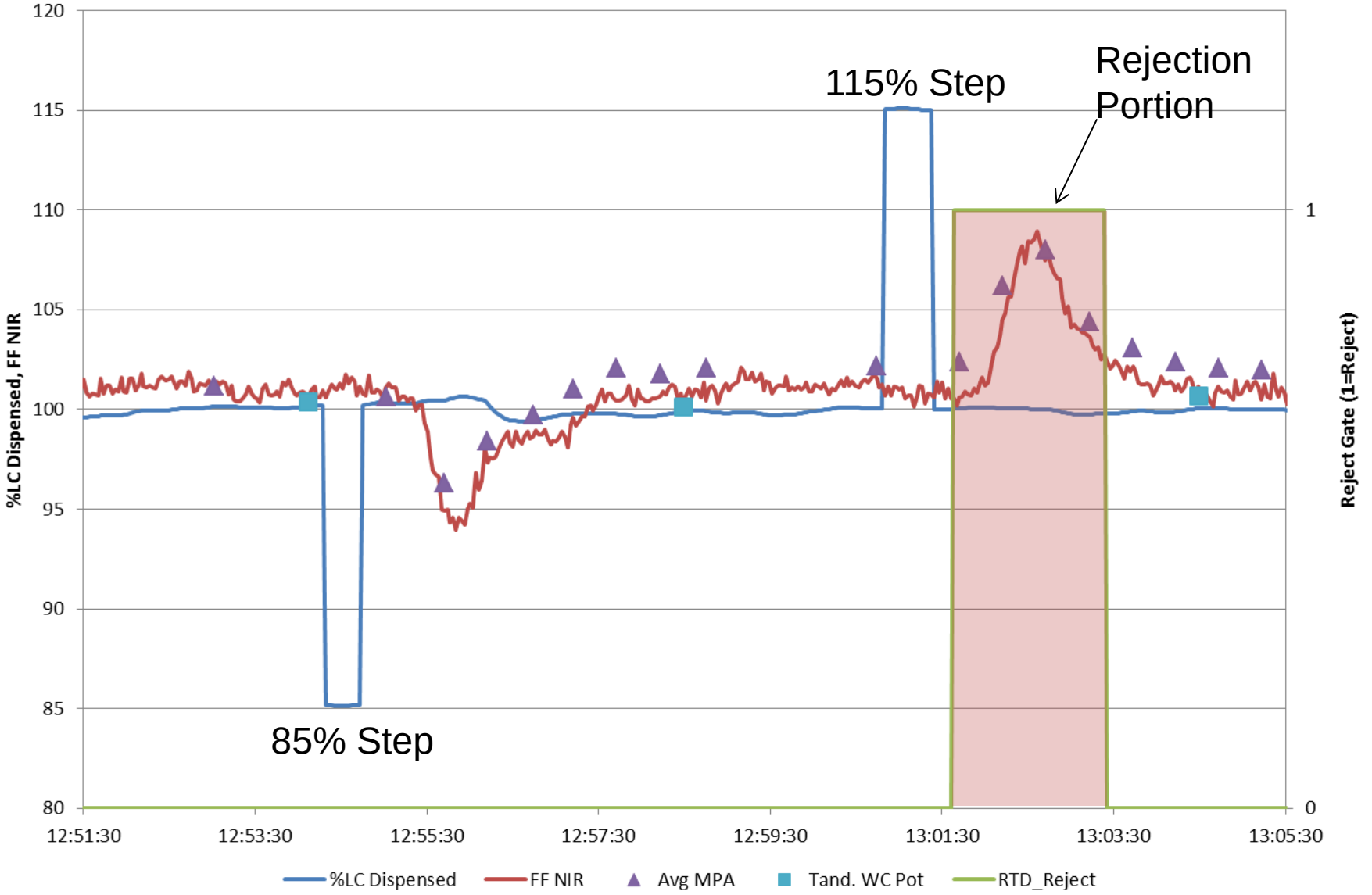
150 mg Challenge



Funnel Plot for LY2 (200 mg) Challenge



200 mg Challenge



Final Remarks

- An adequate model for the drug product continuous manufacturing process was built and implemented in gPROMS.
- Observability continues to be an issue in a powder manufacturing line.
- Real-time implementation of a reduced system model is done by pre-computing key actionable indexes from the full model.
- Such a scheme is part of the control strategy for the process.
- Real-time non-linear state estimation continues to be the goal.