ADVANCED PROCESS MODELLING FORUM
LONDON
20–21 APRIL 2016

# Global System Analysis

## From uncertainty quantification to risk management

Costas Pantelides – Managing Director

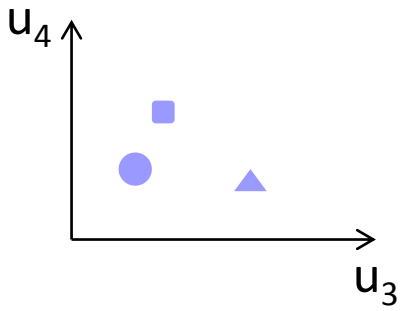
gPROMS

# Outline

- From point calculations to global system behaviour
- Global system analysis in gPROMS
- Examples
  - Air Separation unit
  - Tablet dissolution
- Concluding remarks

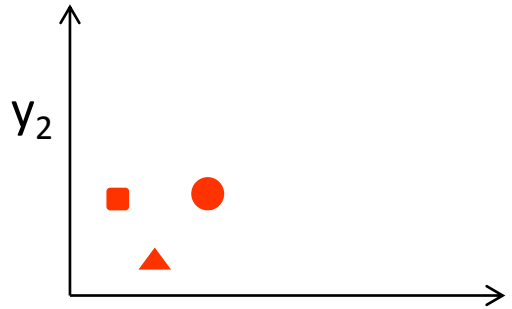
# From point calculations to global system behaviour

# System analysis




**Environmental inputs**

- External disturbances
- Commercial environment




**KPIs**

- Product quality / performance
- Operability
- Safety
- Environmental impact
- Economic performance

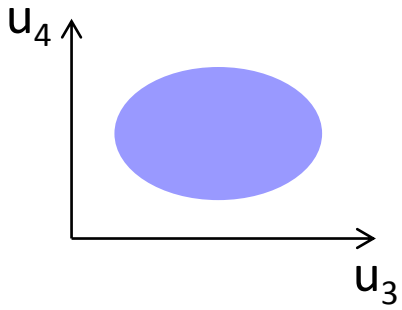
**Decisions**

- Design
- Operational

**System**


***System analysis***

# From point calculations to global system behaviour




**Environmental inputs**

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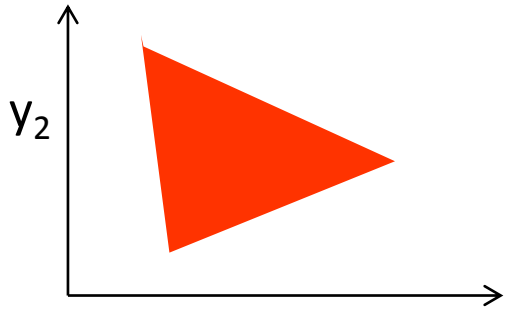
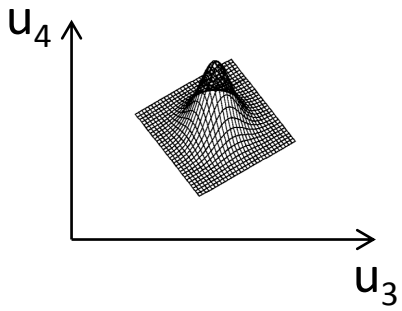



**KPIs**

- Product quality / performance
- Operability
- Safety
- Environmental impact
- Economic performance

***Global system behaviour***

# Global system behaviour in an uncertain world




**Environmental inputs**

- External disturbances
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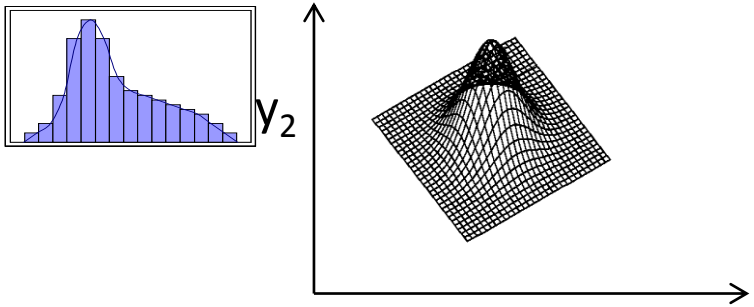



**KPIs**

- Product qu… performanc…
- Operability
- Safety
- Environmental impact
- Economic performance

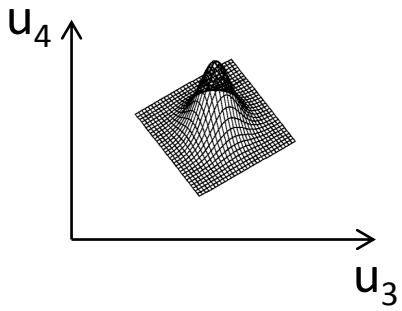
**Decisions**

- Design
- Operational

**System**


***Global system behaviour***

# Model-based analysis of global system behaviour




**Environmental inputs**

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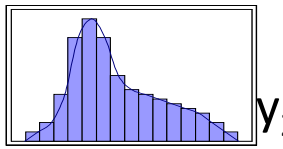
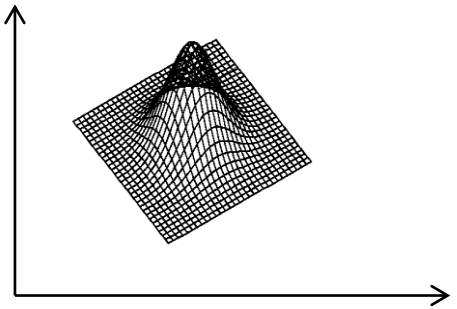




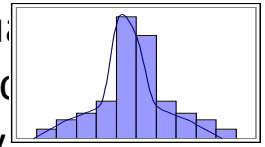

**Decisions**

- Design
- Operational

**System *Model***

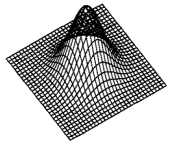
**KPIs**

- Product qu
  performanc
- Operability
- Safety
- Environmental impact
- Economic performance

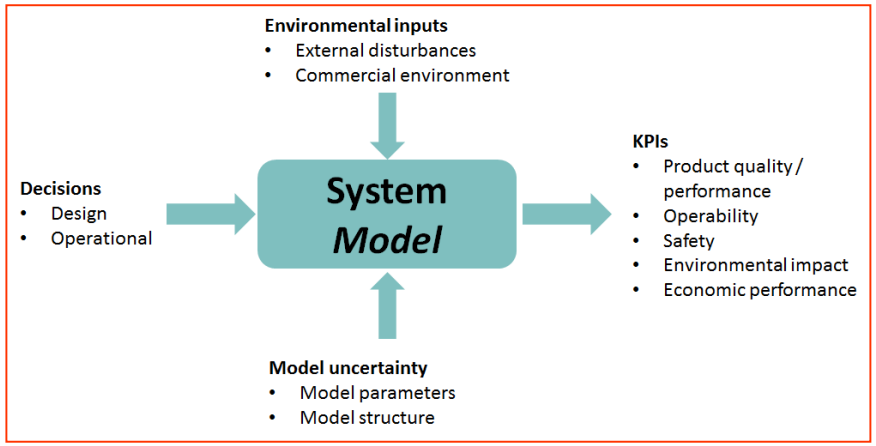



**Model uncertainty**

- Model parameters
- Model structure



# Model-based global system analysis in an uncertain world



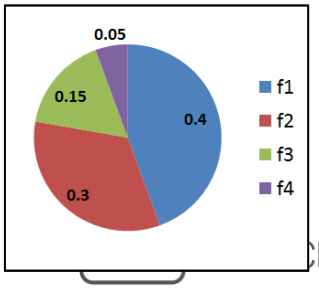

**INPUTS**
- Decisions
- Disturbances
- Model parameters

→ **OUTPUTS**
- KPIs

## Key objectives

- **Probability distribution of KPIs**
  - taking account of variability/ uncertainty in all system inputs
- **Global sensitivities of KPIs with respect to…**
  - decisions: process controllability
  - disturbances: process robustness
  - model parameters: model reliability

**over entire space of interest**




***Global sensitivity indices of an output response with respect to 4 input factors***

# Same slides as last year….

**So, what's new?**

System analysis

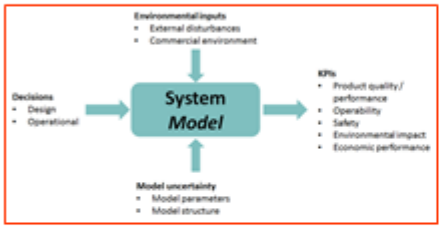
Decisions
- Design
- Operational

System analysis
From point calculations to global system behaviour

System analysis
Global system behaviour in an uncertain world

System analysis
Model-based analysis of global system behaviour

Model-based global system analysis in an uncertain world




**INPUTS**
- Decisions
- Disturbances
- Model parameters

→ **OUTPUTS**
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## Key objectives

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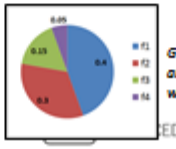


*Global sensitivity indices of an output response with respect to 4 input factors*

# Global System Analysis in gPROMS

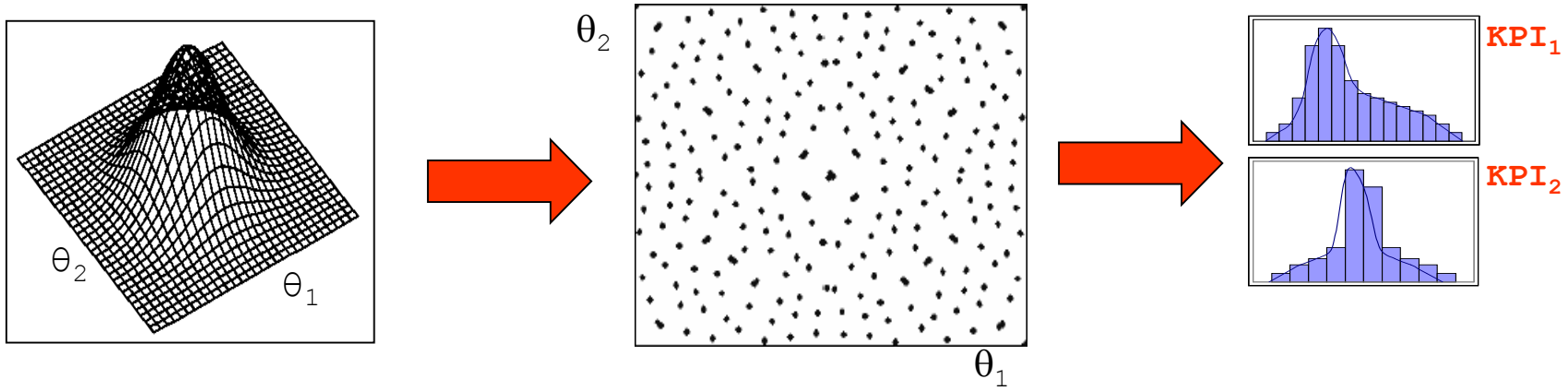
# Global System Analysis

## A general tool for the gPROMS platform

### I. Inputs ("Factors")

### II. Sampling

### III. Outputs ("Responses")




**A collaborative R&D project (June 2014-May 2016)**

- Project leader : PSE
- Consortium : AstraZeneca, GSK, Pfizer
- Funding (partial) : £988k (~$1.5m) by InnovateUK

**A fundamental capability within the gPROMS platform**

- Directly applicable to any gPROMS model in any gPRODUCT
  - (e.g. ModelBuilder, ProcessBuilder, ….)
- Initial version to be released as part of gPROMS v4.3

# Global System Analysis in gPROMS

## GSA development team

### GSA User Interface

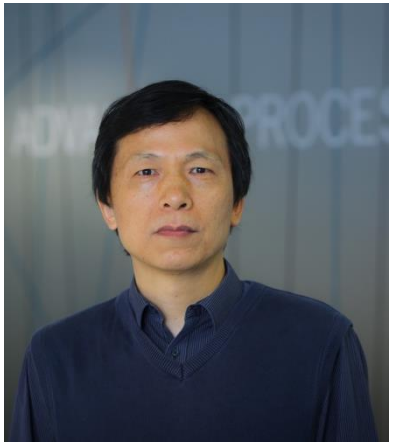
Kate Haddow

Elzbieta Abel

Cristi Marius-Pop

Daren Grant
GSA Team Leader

### GSA in gPROMS Kernel



Yuzhao Lu

### GSA Numerics

Xenia Kleniati

Ed Figura

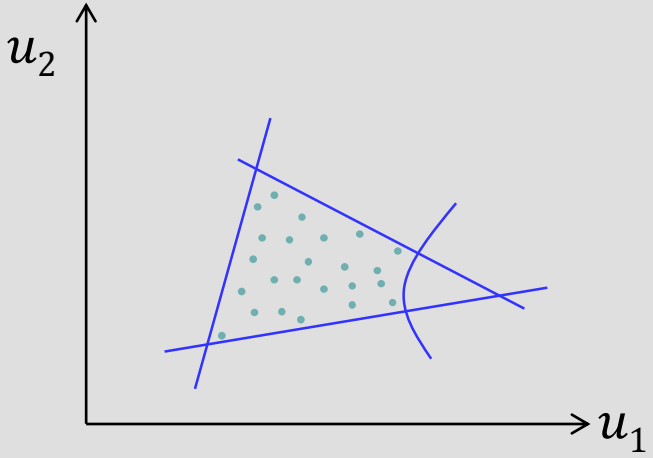
# I. Input factors

**Factors**: user-selected subset of the ASSIGNed variables in the PROCESS

## Deterministic Factors

- Multiple case study ("scenarios") capability

**Sampling restrictions**




## Probabilistic

- Discrete vs. continuous probability distributions
- Univariate distributions: uniform, normal, *lognormal**, ….
- Multivariate: normal
  - specified in terms of covariance matrix

**Feature not in v1.0*

# II. Output responses

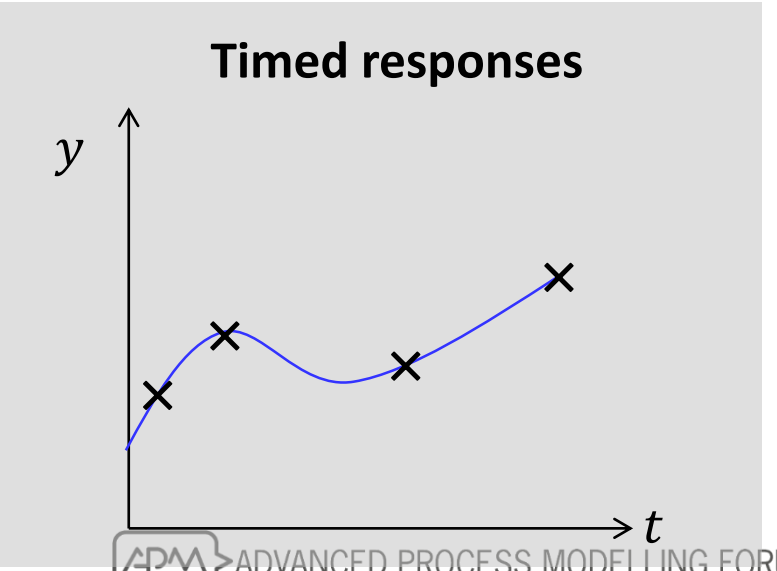
**Responses**: user-selected subset of the *un*ASSIGNed variables in the PROCESS

## Steady-state models

- Steady-state values of specified variables

## Dynamic models

- Values of specified variables
  - at final point
  - *on user-specified time grid(s)**




**Feature not in v1.0*

# III. Types of analysis

1. Elementary Effects analysis
   - Identify which of the input factors have a non-negligible effect on at least one of the output responses

   ➔ **eliminate unimportant factors from further consideration**

2. Uncertainty analysis
   - Determine probability distribution of output responses

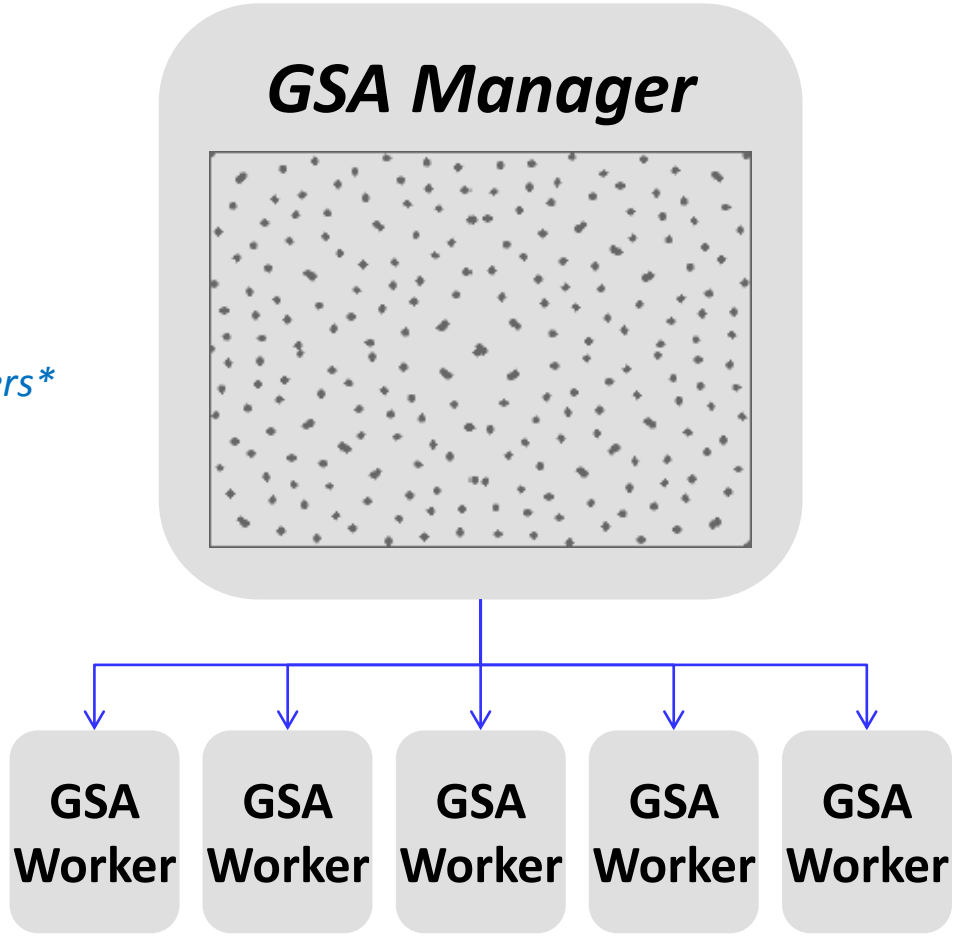
   ➔ **quantify uncertainty ➔ risk in model-based decisions**

3. Sensitivity analysis
   - Compute global sensitivity indices of each response with respect to each factor or combination of factors
     - first- & higher-order sensitivity indices
   - Apportion variability of outputs to variability of inputs

   ➔ **target risk management actions**

# IV. Execution

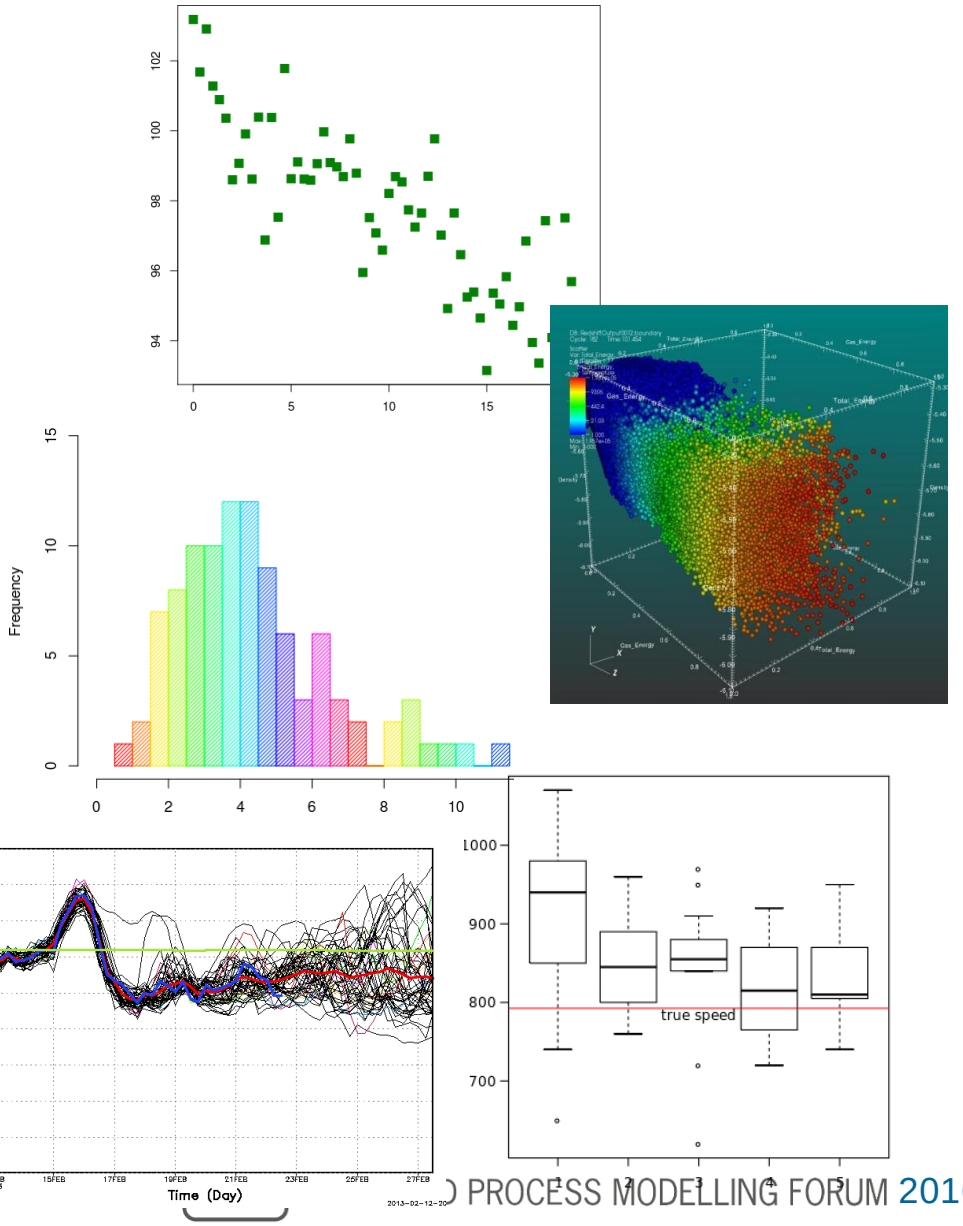
- **Sample generation**
  - Pseudo-random points
  - Quasi-random points
    - Low-discrepancy Sobol' sequences
- **Parallelized execution** of multiple samples
  - multicore processors and/or *multiprocessor clusters**
  - transparent to user
  - resilient, failure-tolerant execution
    - aim to complete number of sample points specified by user
- **Results**
  - Record values of factors & responses at each sampling point
    - failure points also recorded for subsequent analysis
  - HDF5 file format
    - scalable to huge data sets




*Feature not in v1.0

# V. Results analysis

- Extensive facilities for analysing and presenting large data sets
- Data filtering mechanisms
  - *System Constraints**
- Graphs & tables
  - created on the fly
  - organized in Reports
  - can be stored within original project file for future use

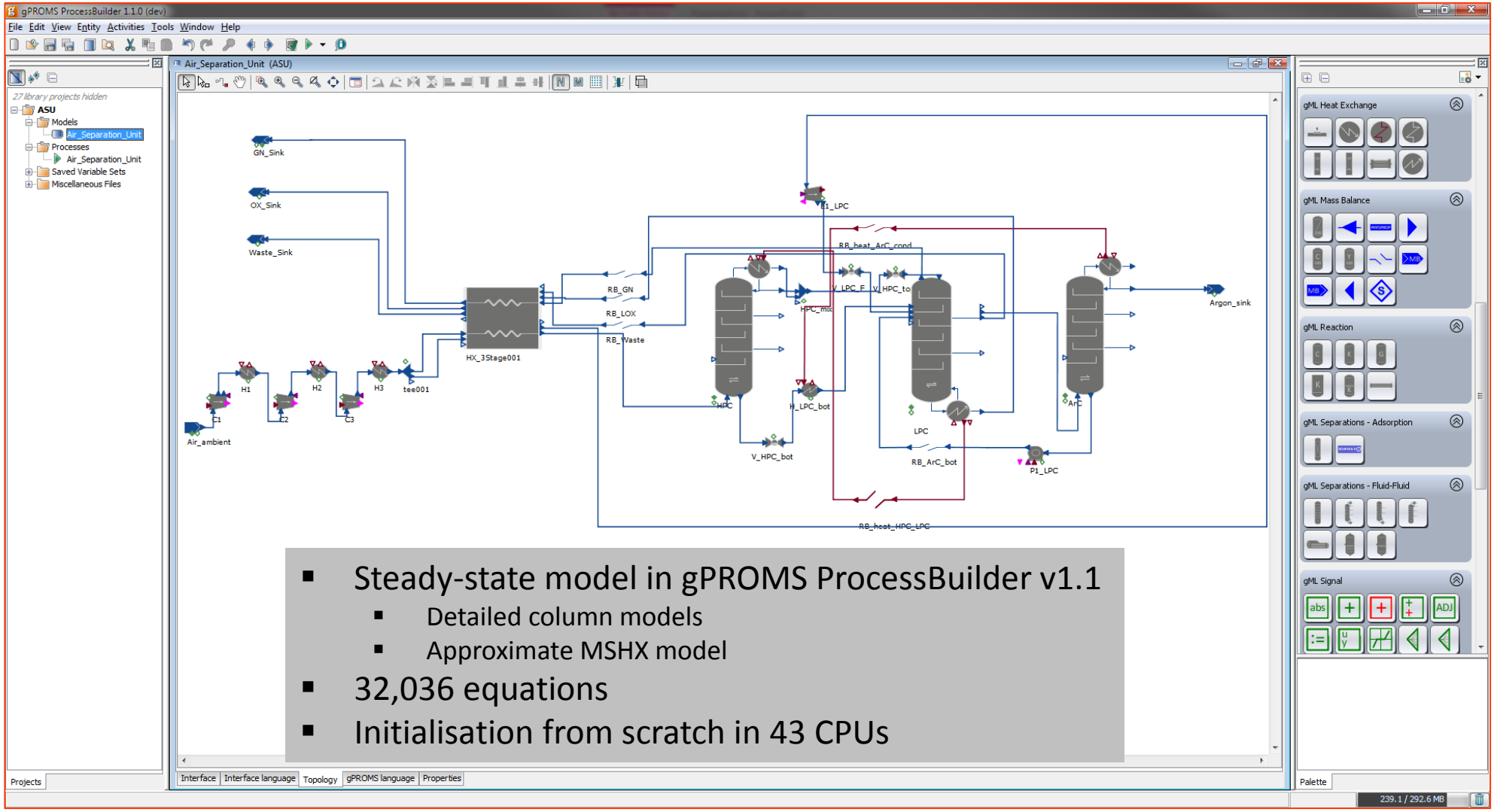



**Feature not in v1.0*

Global System Analysis

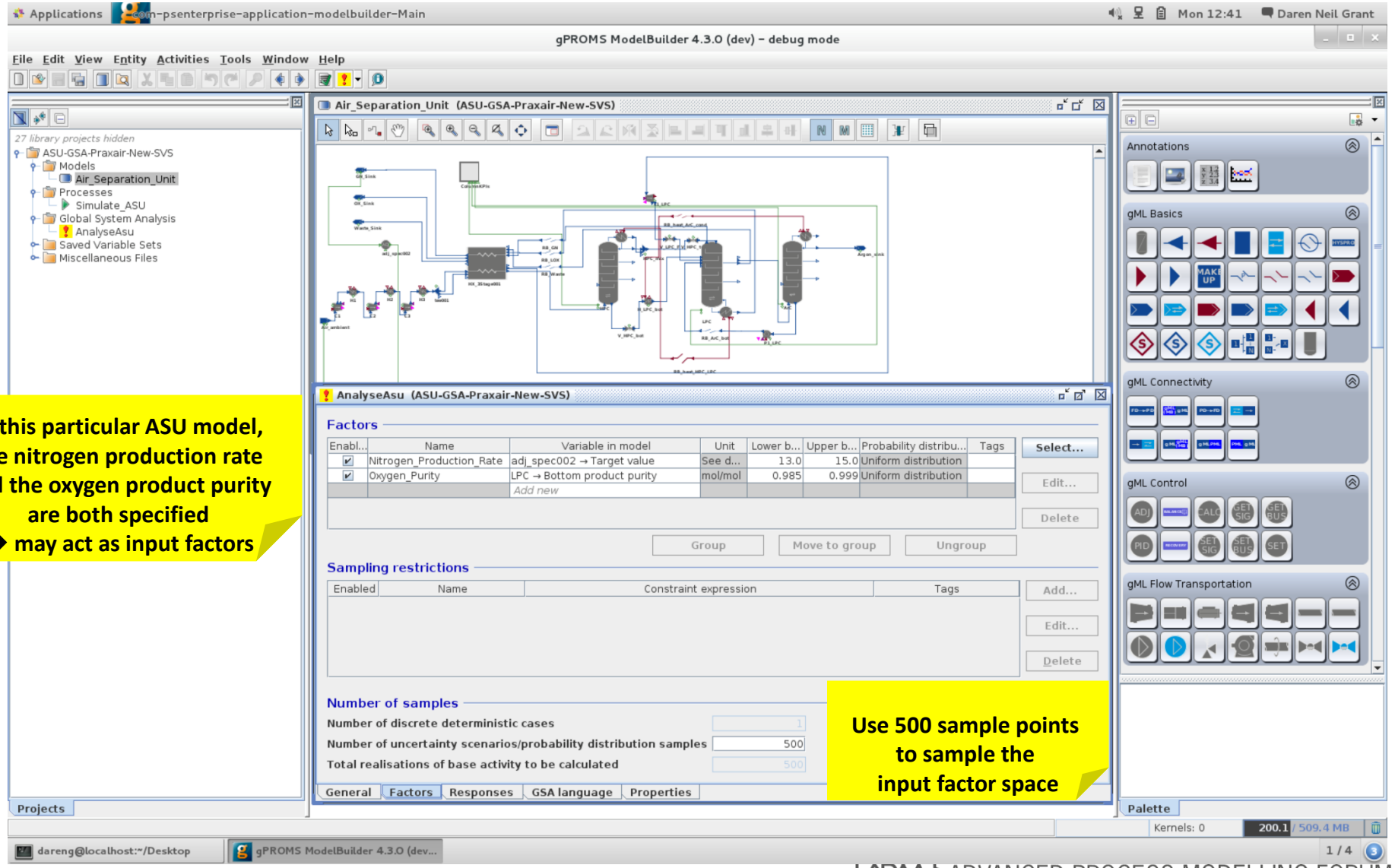
# Example #1: Air Separation Unit

# ASU model

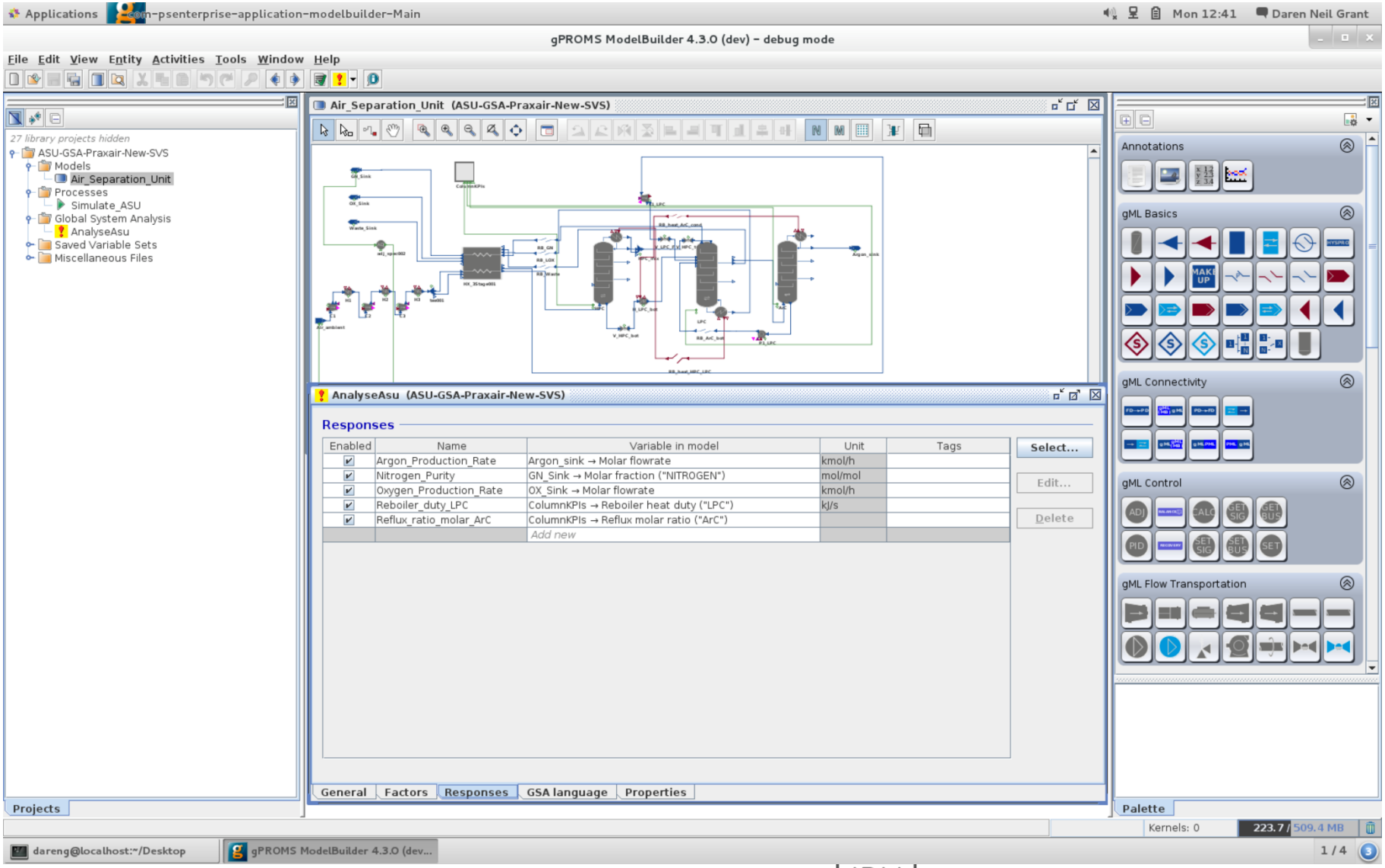



- Steady-state model in gPROMS ProcessBuilder v1.1
  - Detailed column models
  - Approximate MSHX model
- 32,036 equations
- Initialisation from scratch in 43 CPUs

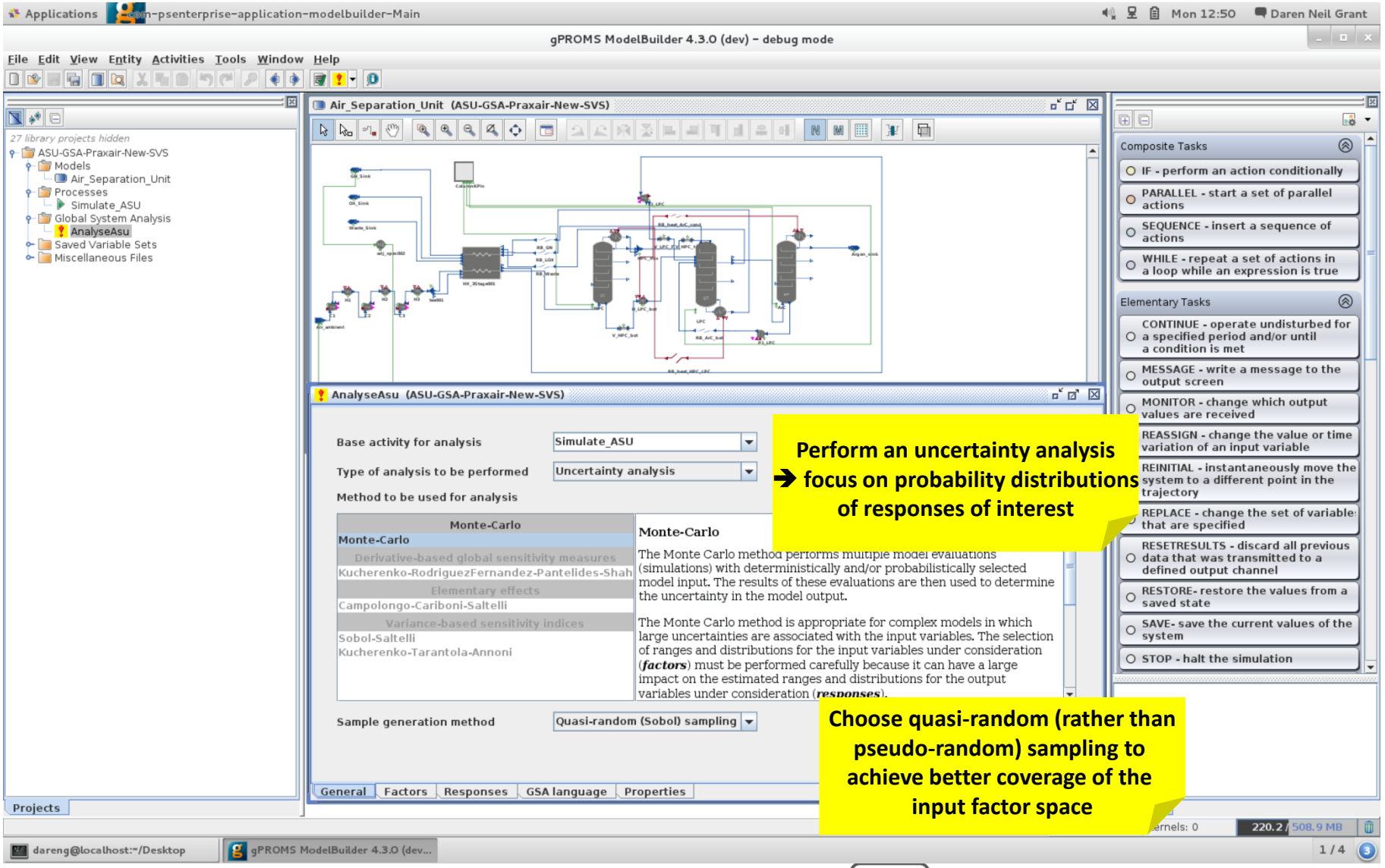
# Specifying the input factors for Global System Analysis



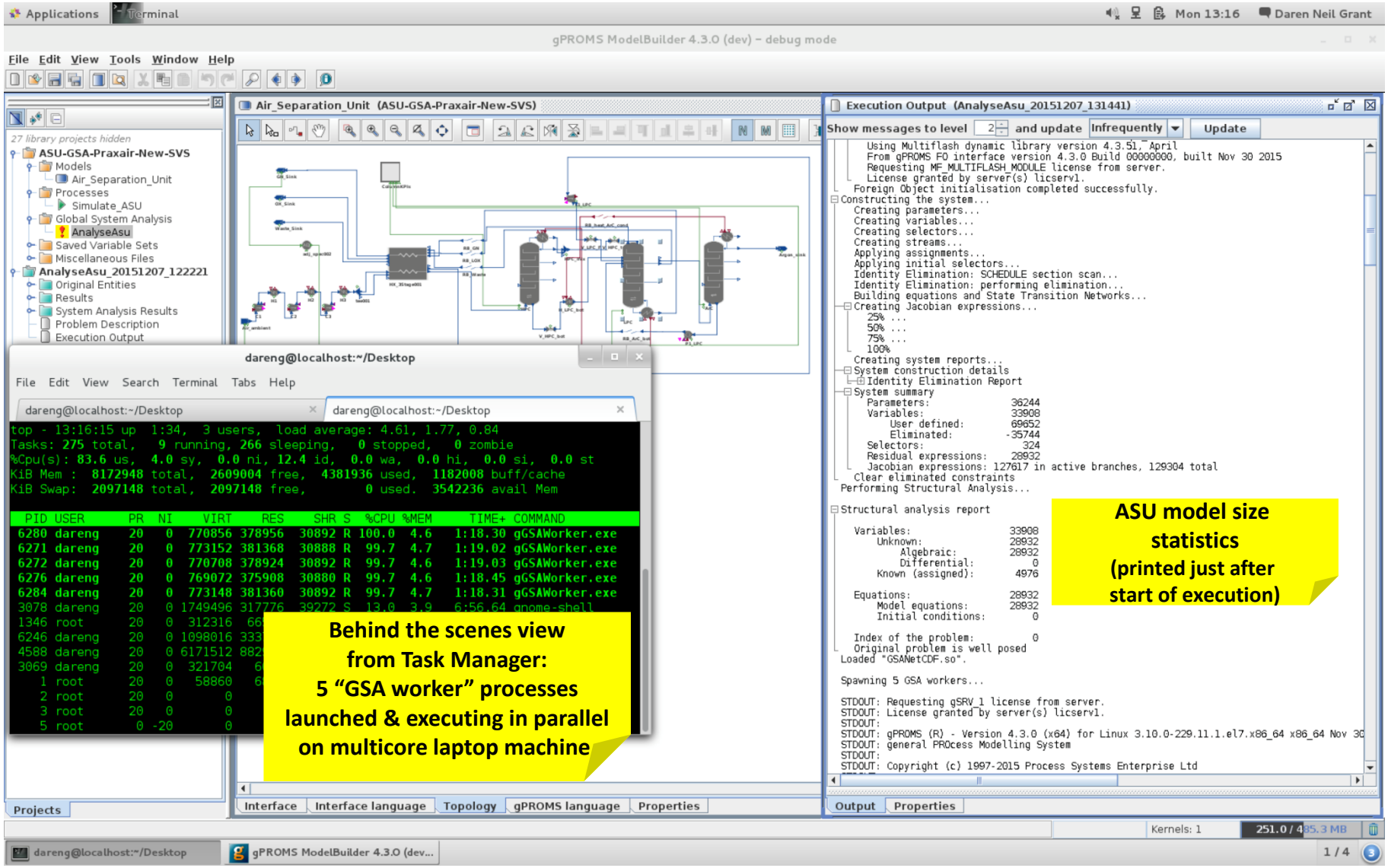
# Specifying the output responses of interest



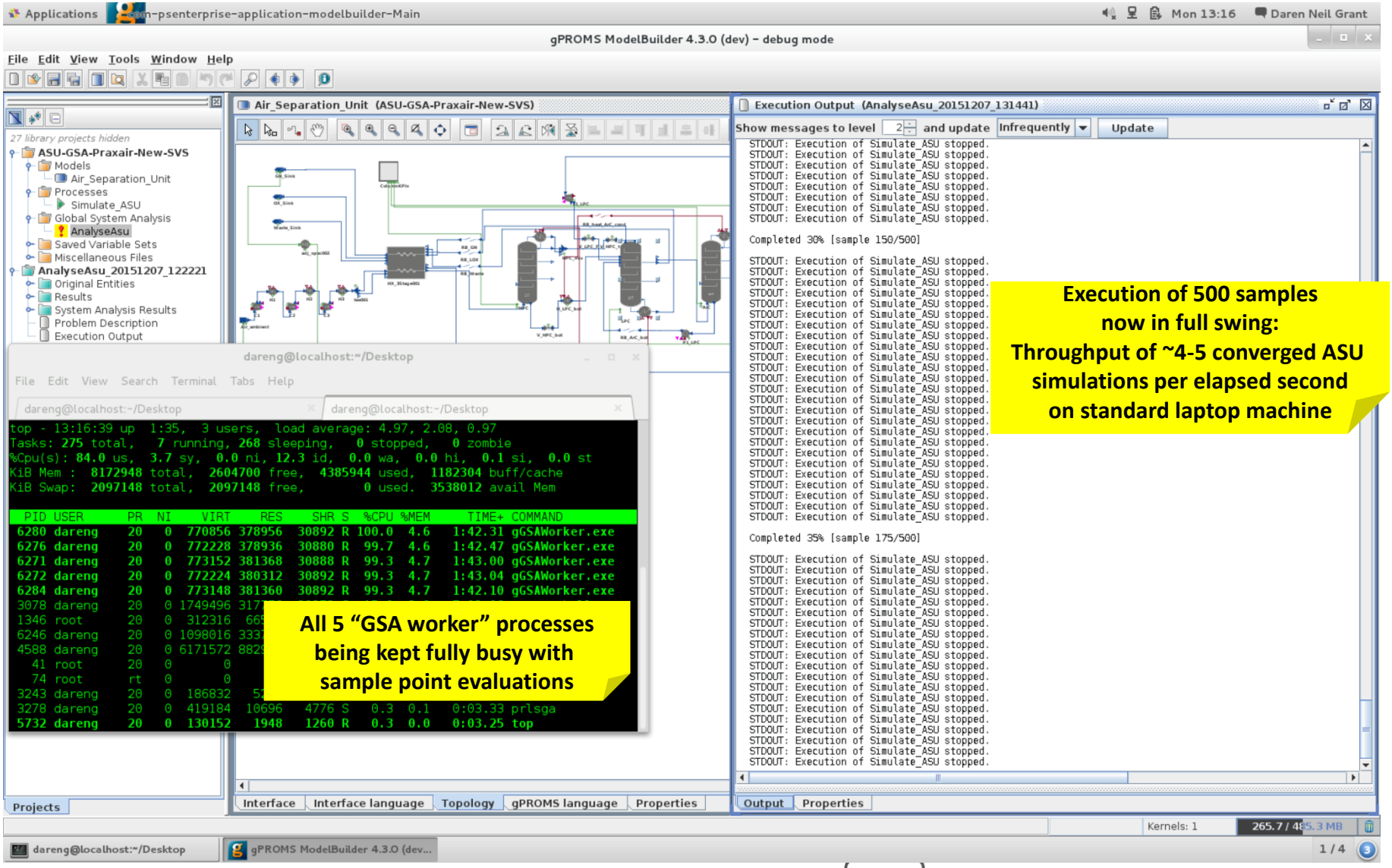
# Selecting the type of GSA to be performed



# Execution of GSA calculation – I

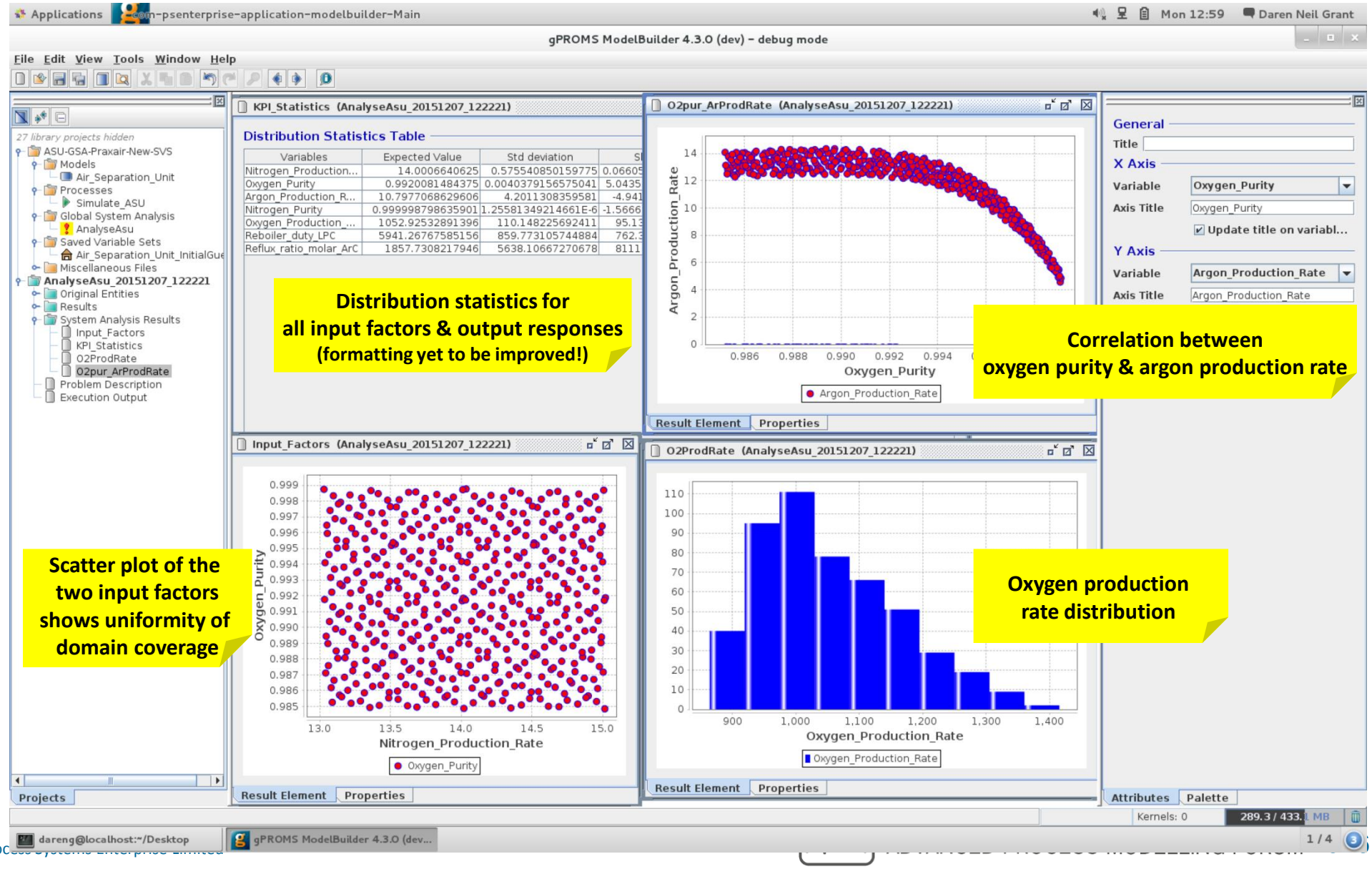


# Execution of GSA calculation – II



# Global System Analysis in gPROMS

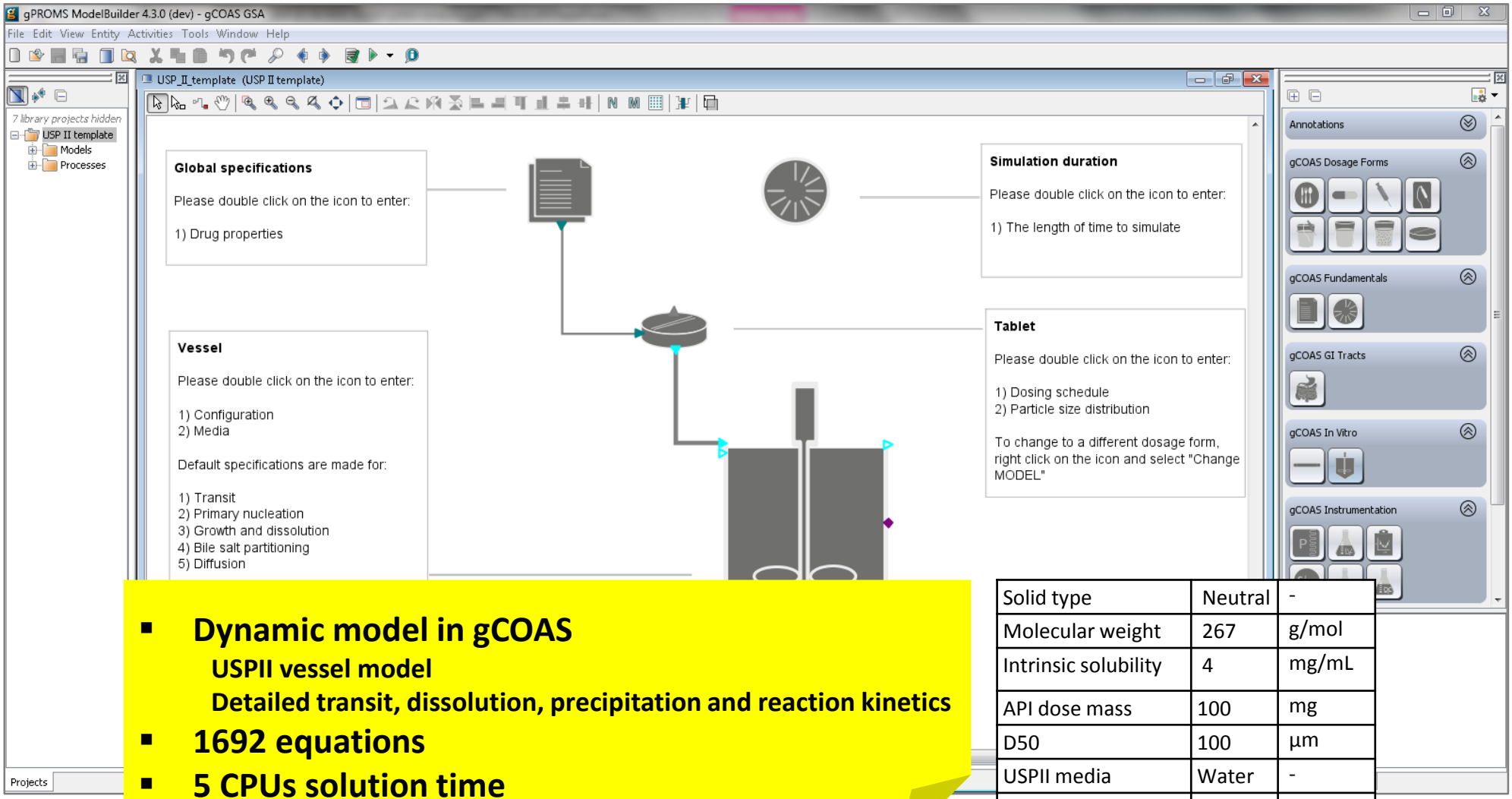
# Typical results



Global System Analysis

# Example #2: Tablet dissolution

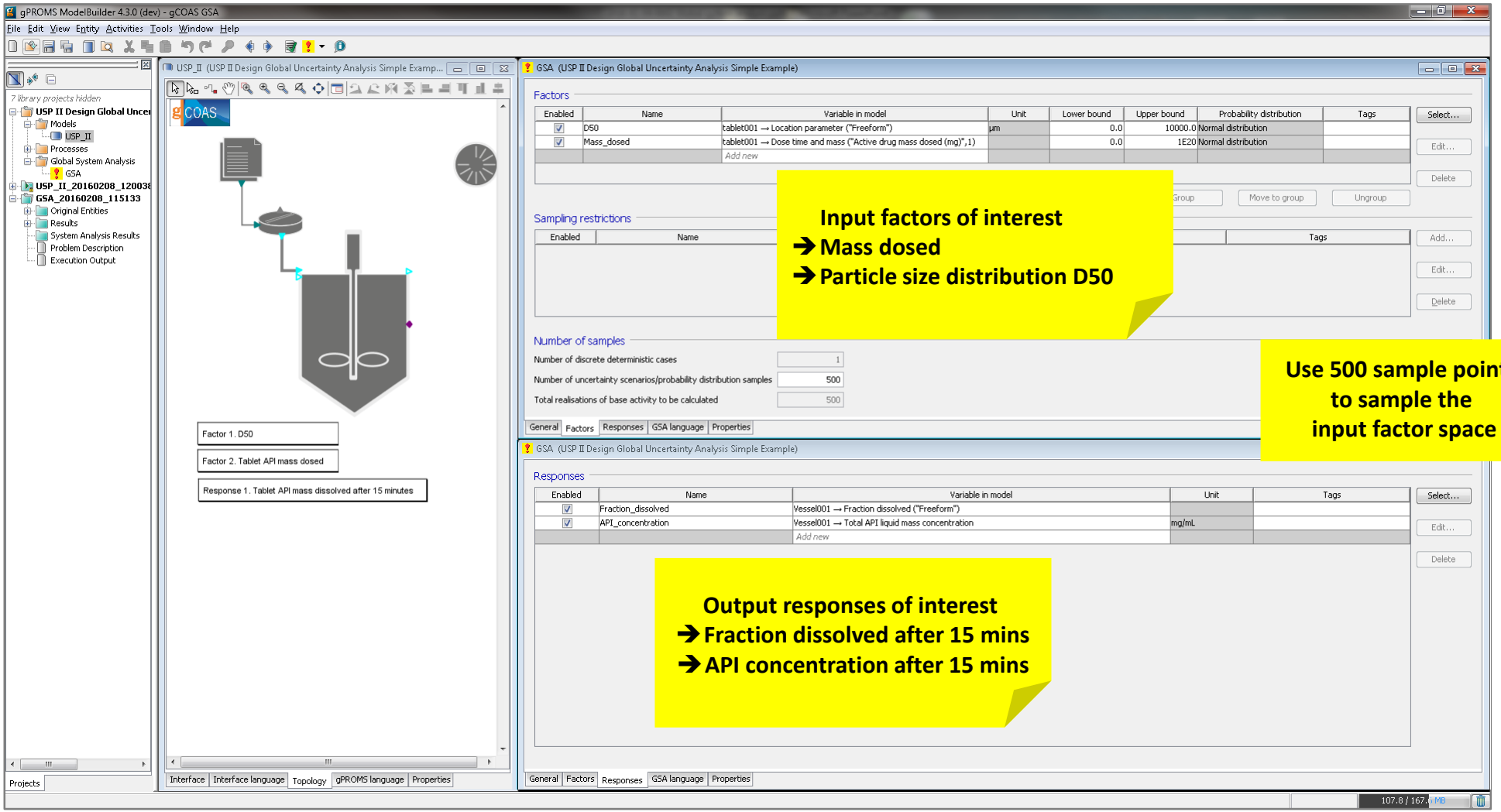
# USPII tablet dissolution model




- **Dynamic model in gCOAS**
  - **USPII vessel model**
  - **Detailed transit, dissolution, precipitation and reaction kinetics**
- **1692 equations**
- **5 CPUs solution time**

| | | |
|---|---|---|
| Solid type | Neutral | - |
| Molecular weight | 267 | g/mol |
| Intrinsic solubility | 4 | mg/mL |
| API dose mass | 100 | mg |
| D50 | 100 | µm |
| USPII media | Water | - |
| USPII media volume | 20 | ml |

# Specifying factors and responses



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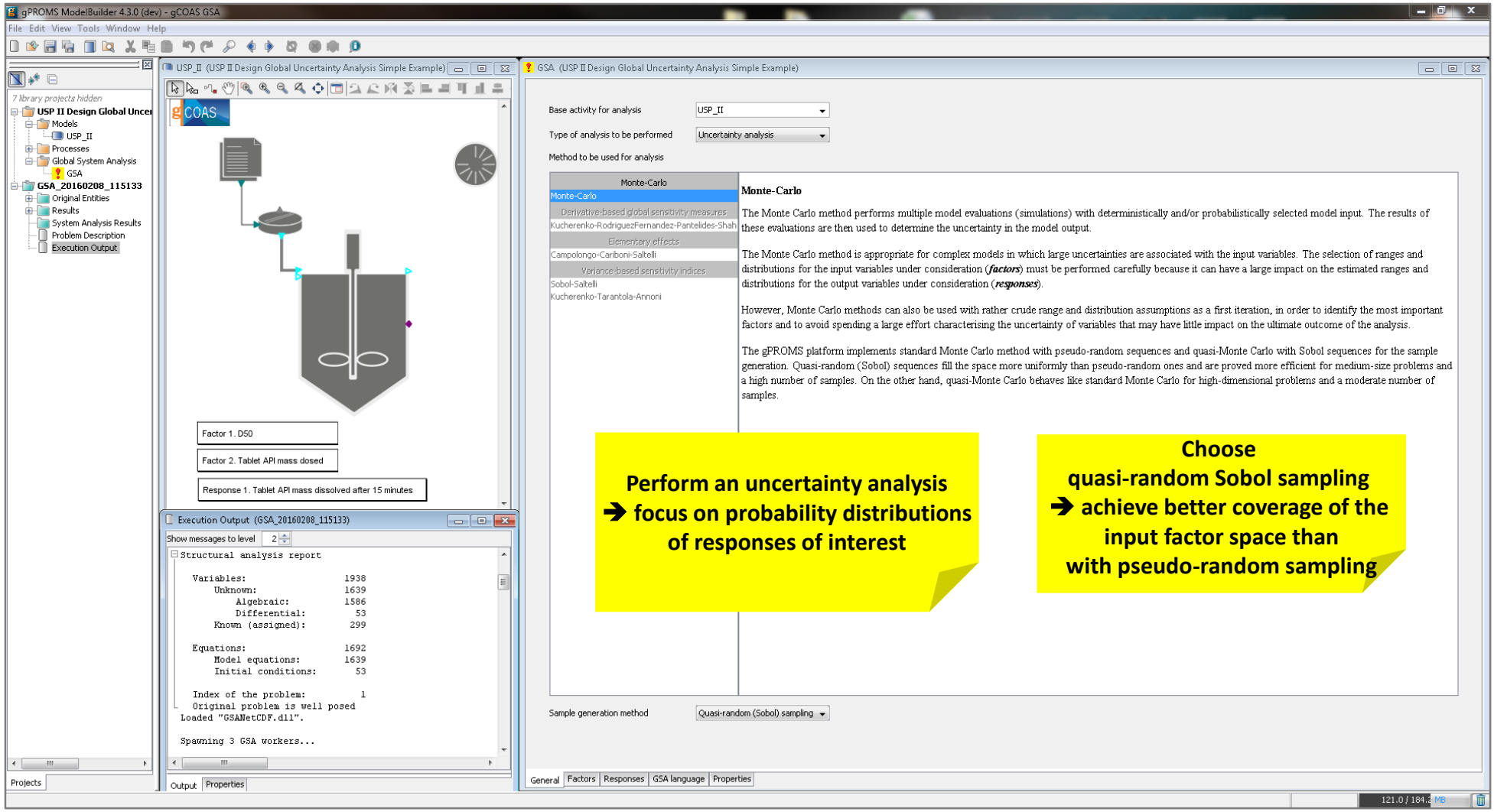
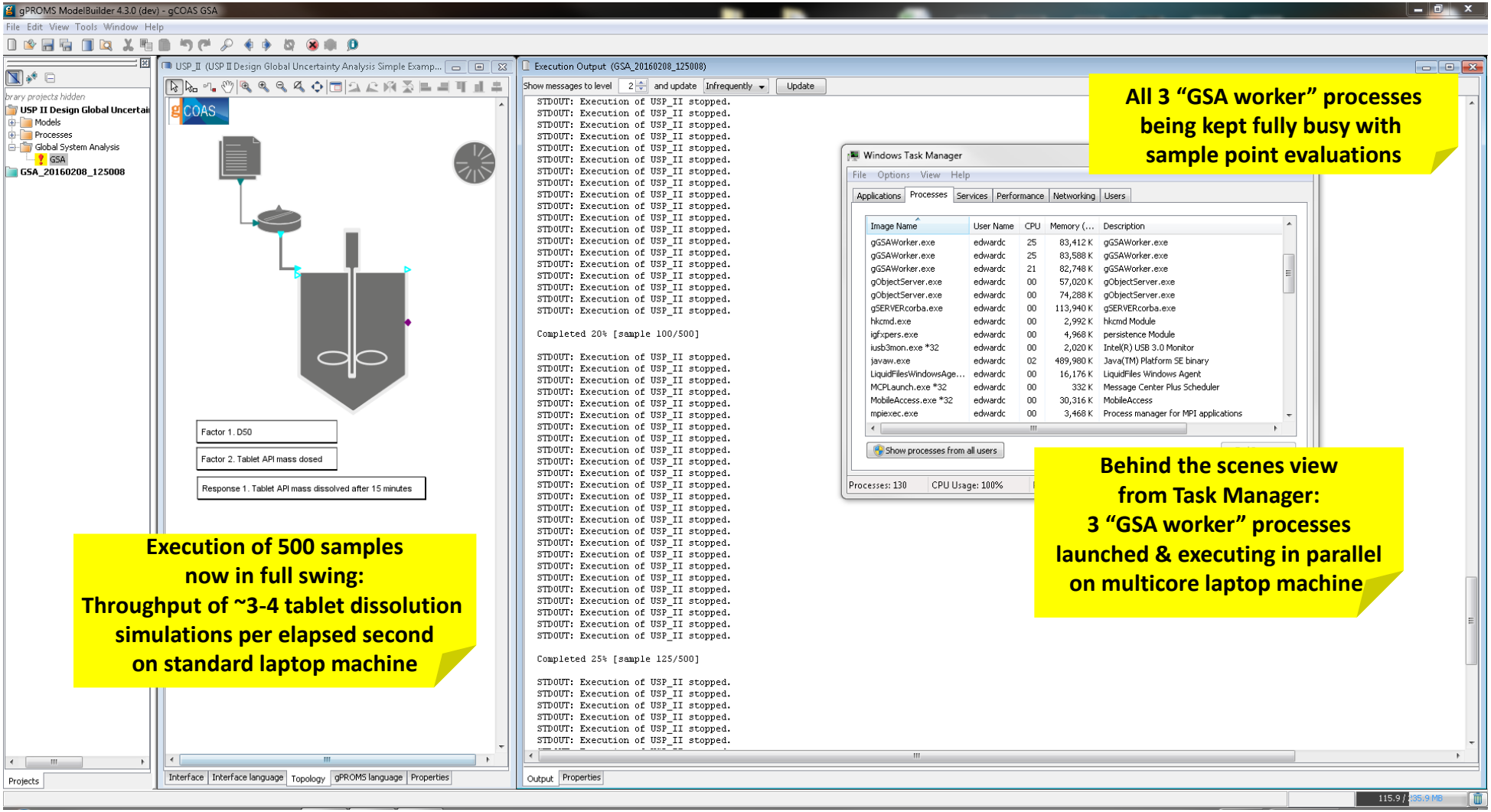


# Execution of GSA calculation

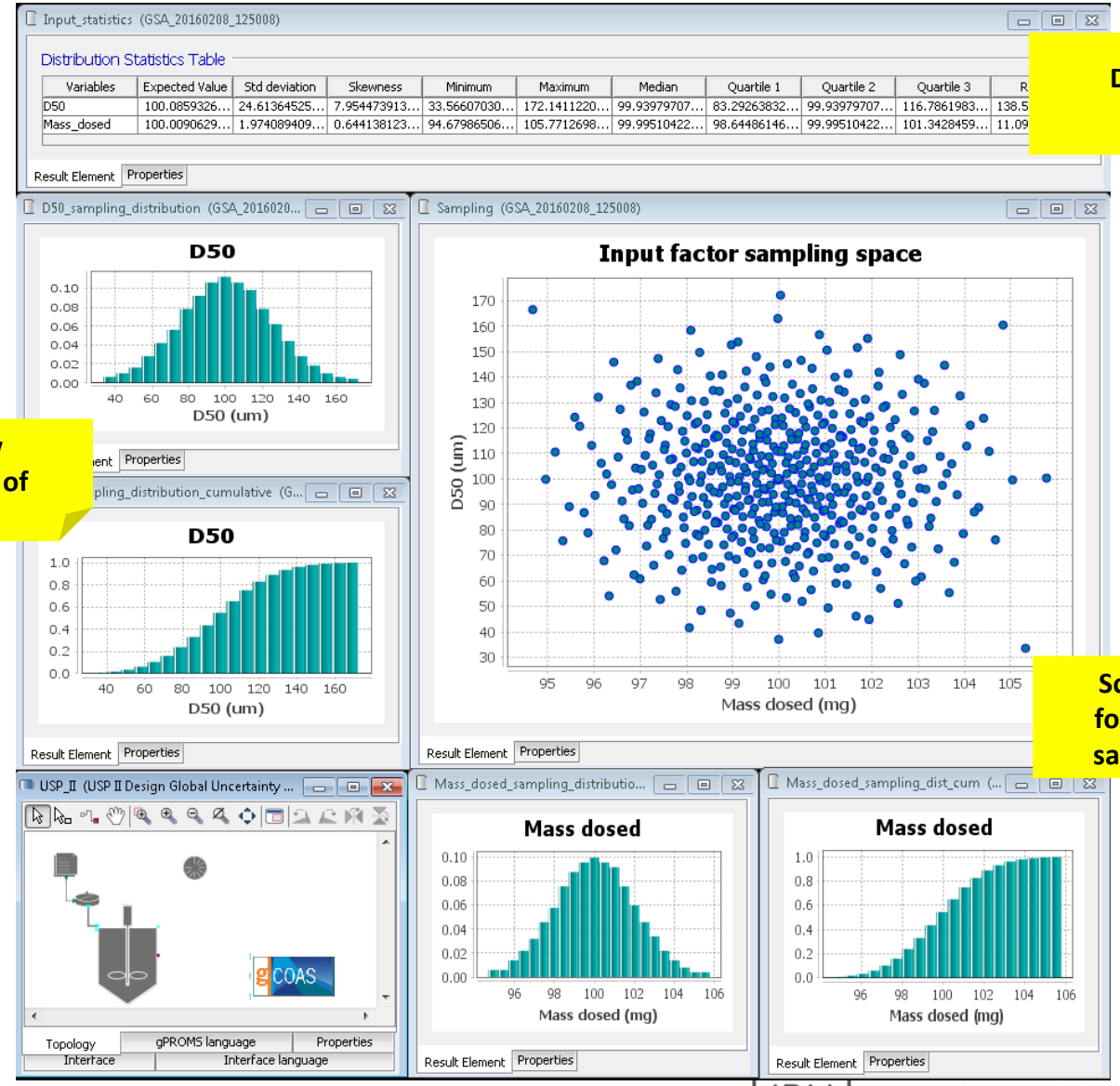


# Results analysis: input factor sampling space

**Distribution statistics for all input factors**

**Frequency plots show probability distribution of sampled factor space**

**Scatter plots for visualising sample space**



# Results analysis: output response design space


**Distribution statistics for all output responses**

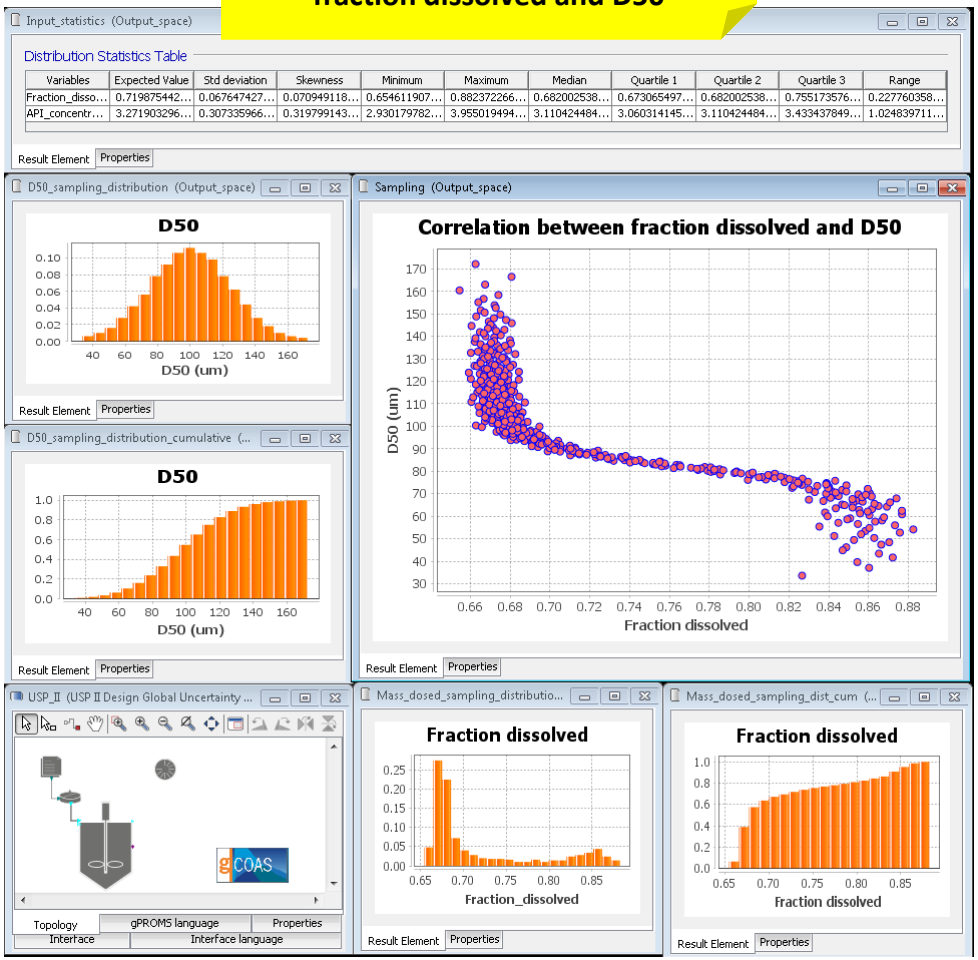
**Fraction dissolved distribution**

**Scatter plots for visualising response space**

**API concentration distribution**

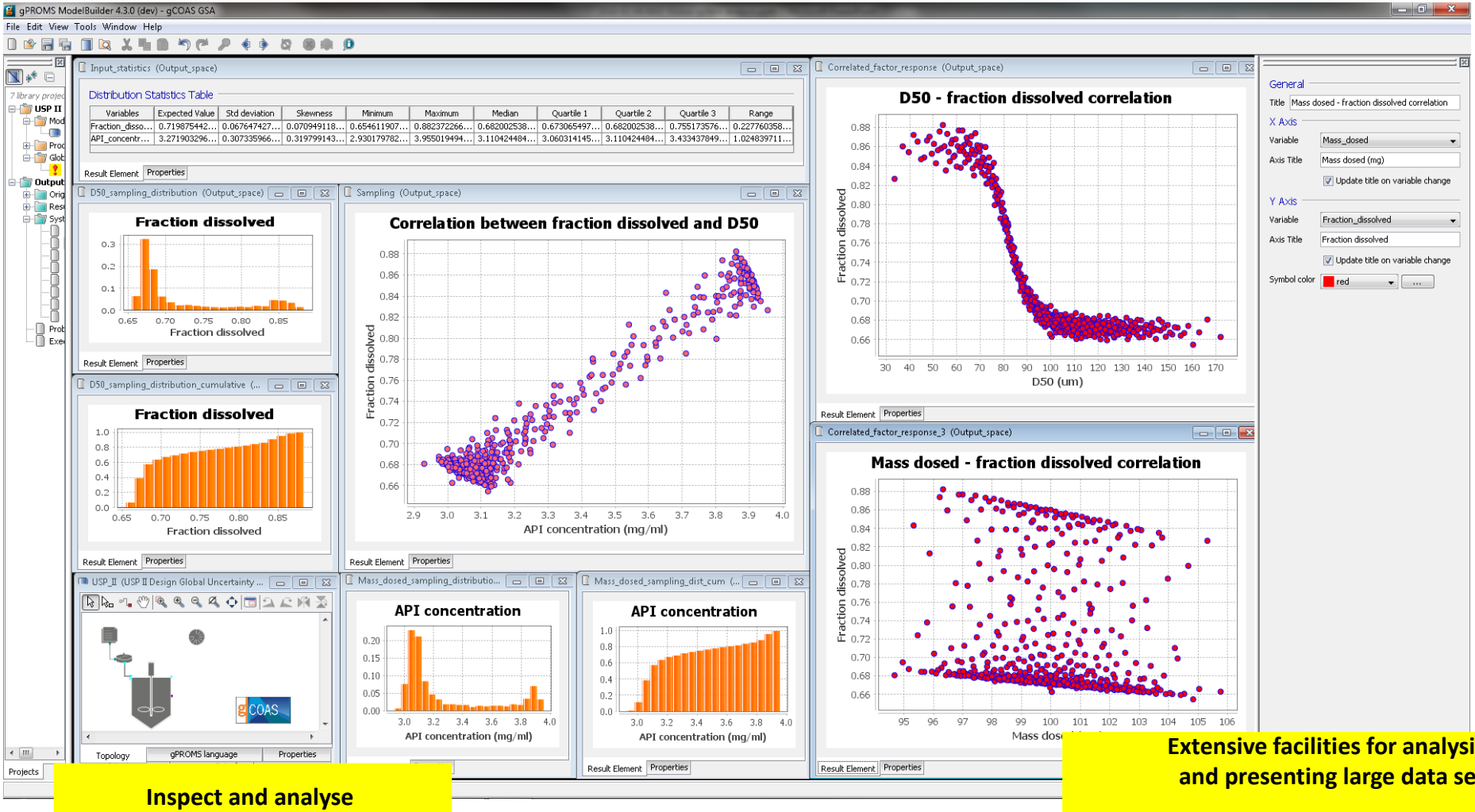
# Results analysis: factor-response correlations

**Correlation between fraction dissolved and D50**




**Correlation between fraction dissolved and mass dosed**

# GSA results management & analysis




**Inspect and analyse GSA results on the fly**

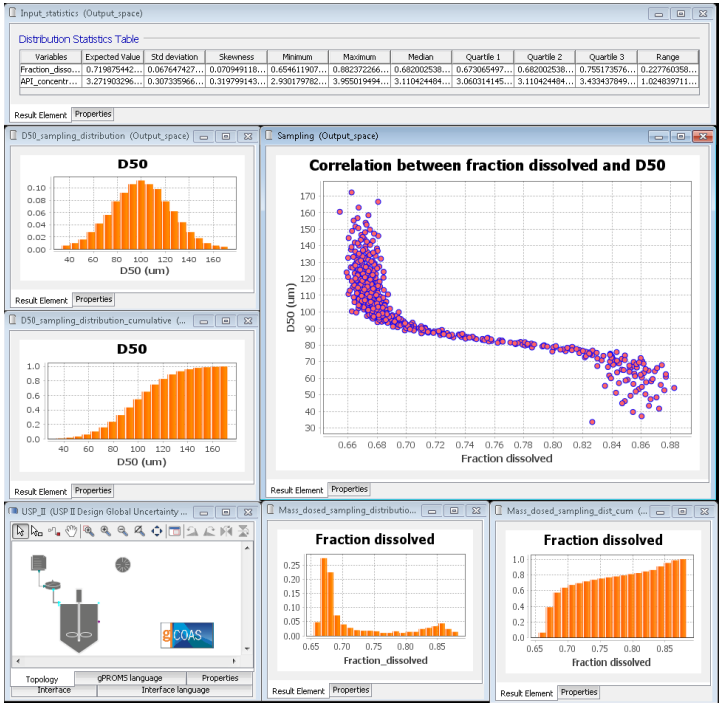
**Extensive facilities for analysing and presenting large data sets**

**➔ System constraints (data filtering),**
**➔ Result elements (graphs, tables, images, text etc.)**
**➔ Reports associated with such analysis**

# In conclusion…

# Concluding remarks

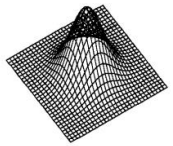
- **GSA: key to making the most from the modelling investment**
  - understanding global system behaviour
  - quantifying effects of uncertainty
  - identifying opportunities for optimisation
- **GSA: tool for investigating model robustness**
  - identify regions of input space which cause model failure and/or inaccurate predictions
- **GSA: major new capability in gPROMS**
  - …may become the *main* way in which users interact with models
  - …from a few distinct case studies to full uncertainty/sensitivity analysis
- **…immediately applicable to all gPROMS models**



# From uncertainty quantification to risk management

**2. Reduce variability in environmental inputs**
as indicated by Global Sensitivity Indices

**Environmental inputs**
- External disturbances
- Commercial environment

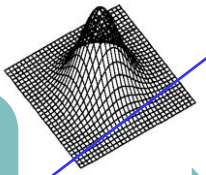


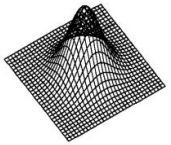
**4. Modify system**
e.g. allow operational decisions to be manipulated by control system

**KPIs**
- Product quality / performance
- Operability
- Safety
- Environmental impact
- Economic performance

**Decisions**
- Design
- Operational

**System *Model***





**3. Revise decisions to improve system robustness**
Robust Optimisation technology

**Model uncertainty**
- Model parameters
- Model structure

**1. Improve model, reduce parameter uncertainty**
R&D focus guided by Global Sensitivity Indices

# Thank you