Uncertainty analysis applied on drying model for pharmaceutical granules

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Introduction: Pharmaceutical processing

- **Shift** from batch to continuous processing ongoing
  $\longrightarrow$ Development of **mechanistic models** of multi-phase systems useful for
  - **Understand** the process (knowledge buildup)
  - Once understood, **control** the process
- Model = conceptualisation of reality $\longrightarrow$ Assumptions and simplifications of the system $\longrightarrow$ Model output uncertainty due to uncertainties in model structure, parameters and inputs
- **Objective**: quantify uncertainty through uncertainty analysis to investigate the prediction uncertainty induced by the main assumptions at the particle level and the most sensitive parameters using the **GLUE** methodology (see right)

Single particle drying model

A mechanistic model for single granules was calibrated and validated [1]
The drying process consisted of two distinct, sequential periods:

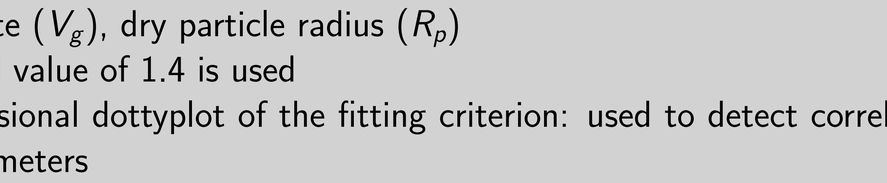
- First drying period: fast drop in moisture content:

$$\dot{m}_v = h_D(\rho_{v,s} - \rho_{v,\infty})A_d$$

- Second drying period: slow evaporation:

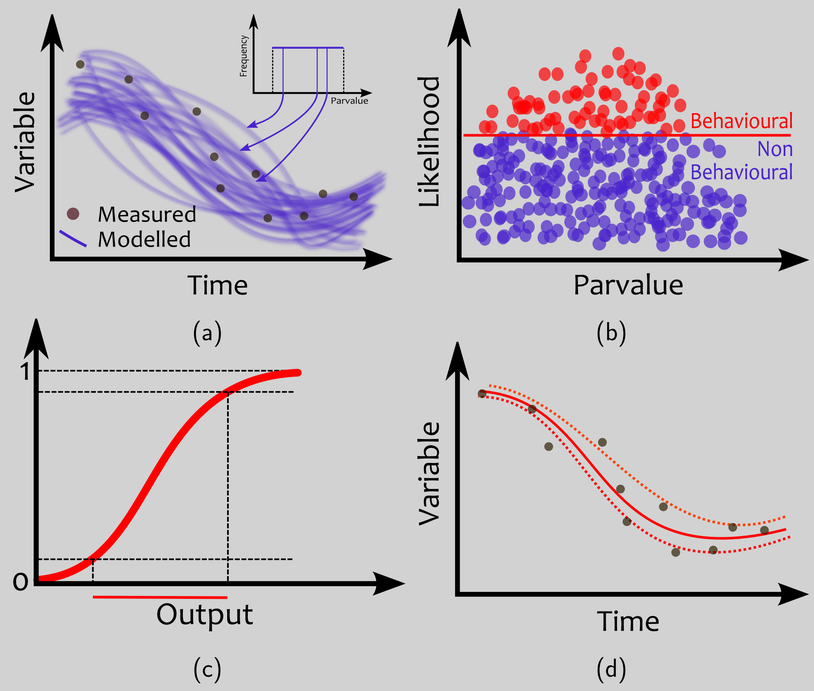
$$\dot{m}_v = -\frac{8\pi\epsilon^{\beta} D_{v,cr} M_w p_g}{\Re(T_{cr,s}+T_{wc,s})} ln\left[\frac{p_g - p_{v,i}}{p_g - (\frac{\Re}{4\pi M_w h_D R_p^2}\dot{m}_v + \frac{p_{v,\infty}}{T_g})T_{p,s}}\right]$$

$$\beta = \beta_1 * e^{-\beta_2 * T_g}$$



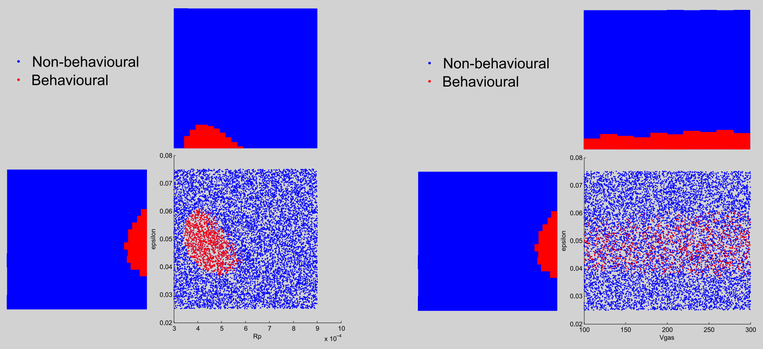
GLUE: Generalised Likelihood Uncertainty Estimation [2]

(a) Define uncertain parameter space (prior distribution of the individual parameters) and run a large number (10000) of simulations randomly sampled from the parameter space (uniform Latin Hypercube)
(b) Evaluate simulations based on a predefined evaluation criterion (**Likelihood**) ($wSSE = \sum_i((y_i - y_{m,i}) * W(i))^2$) and identify behavioural/non-behavioural simulations by selecting a limit of acceptance (threshold) (**Dottyplot**)
(c) Determine the Cumulative Distribution Function (**CDF**) of the model output by weighting the behavioural runs according to their likelihood value
(d) Model predictive uncertainty is defined by selected percentile (5%)



Results: Parameter set 1: ϵ, V_g, R_p

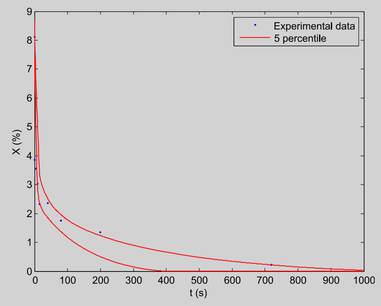
Influence of **'the particle assumptions'** on the model prediction: porosity (ϵ), gas flow rate (V_g), dry particle radius (R_p)
A threshold value of 1.4 is used
Two-dimensional dottyplot of the fitting criterion: used to detect correlations between parameters



Conclusions:

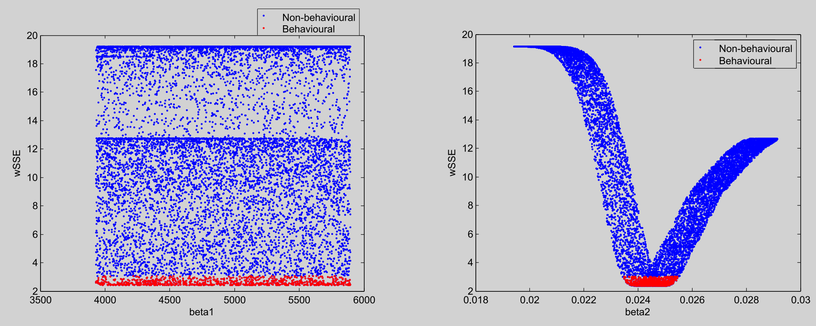
- ϵ and R_p: a distinct region within the prior distribution is obtained
- V_g: with available experimental data not able to identify parameter value

Predictive Uncertainty boundaries:



Results: Parameter set 2: β_1 and β_2

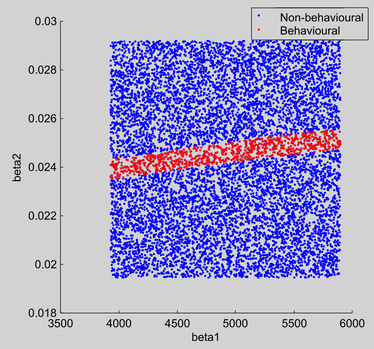
Influence of the most **sensitive parameters** on the model prediction
A threshold value of 3 is used (> 1.4: parameter set 1)



Conclusions:

- β_1: a low value for $wSSE$ is possible for any value
- β_2: shape is inherently connected to drying process itself

Two-dimensional dotty plot:



- If $\beta_1 \downarrow \Rightarrow \beta_2 \downarrow$
- Possible to detect identifiable and non-identifiable parameters

Take home message

- Parameter space is assessed by evaluating simulations according to the likelihood, which is based on experimental data
- Additional insight in the model structure can be obtained by performing a GLUE analysis (correlations between parameters)
- The extension of the model to a batch of granules can be used to investigate the distribution of the moisture content, which is important for the subsequent tabletting step

[1] S.T.F.C. Mortier, T. De Beer, K.V. Gernaey, J. Vercruysse, M. Fonteyne, J.P. Remon, C. Vervaet, and I. Nopens. Mechanistic modelling of the drying behaviour of single pharmaceutical granules. *Eur. J. Pharm. Biopharm.*, 80(3):682–689, 2012.
[2] K. Beven and A. Binley. The future of distributed models: model calibration and uncertainty prediction. *Hydrol. Process.*, 6(3):279–298, July 1992.

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