# Structural and practical identifiability analysis of compartmental models for foliar uptake


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## ? Introduction and Motivation

**Problem**

Mathematical modelling of biological systems has several **challenges**:
- **Partial understanding** of the system
- **Limited observability**
- **High uncertainty** in the data (experimental error and intrinsic variability)
- Trade-off between model **complexity** and **interpretability**
- **Time consuming** and **resource hungry** experiments

**Solution**

Tackle these problems through a **systematic model building strategy**:
- Tests to ensure the **identifiability** of the model parameters
- **Statistically-sound comparison** of different models
- **Model-based design of experiments** for better exploitation of resources
- Quantification of the **errors**
- Quantification of **uncertainty** on parameter estimates and model predictions

## Methodology

The model building framework presented in the following diagram is based on well-established approaches[1].

**Key steps in the modelling procedure**

**Formulation of candidate models**
- Preliminary data
- Literature
- Knowledge on the system

→ **Preliminary tests on the models**
- A-priori identifiability
- A-posteriori identifiability
- Distinguishability of models

→ **Model discrimination**
- MBDoE for MD
- Model selection criteria (AIC, BIC)
- Statistical test (*F*-test, $\chi^2$-test )

→ **Precise parameter estimation**
- MBDoE for PP
- Statistical significance (*t*-test)

← **Model validation**
- Validate the model on new independent data

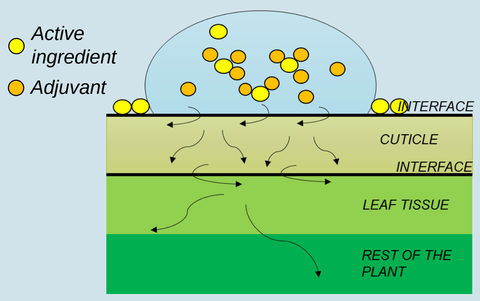
**Model identifiability analysis**

*Question*: can the model parameters be **uniquely determined** given the system inputs $\boldsymbol{u}(t)$ and the measurable outputs $\boldsymbol{y}(t)$ ?

The following tests are considered to check identifiability conditions on the model parameters**: *a-priori* structural identifiability and *a-posteriori* practical identifiability**. [2]
- Structural identifiability: **differential algebra** approach
- Practical identifiability: **correlation matrix** and **analysis of variances in the estimates**

## Case study

**Foliar uptake of pesticides**




Many phenomena involved in the foliar uptake of pesticides[3] :
- Absorption
- Diffusion
- Equilibrium at interfaces
- Metabolism
- Volatility
- Photostability

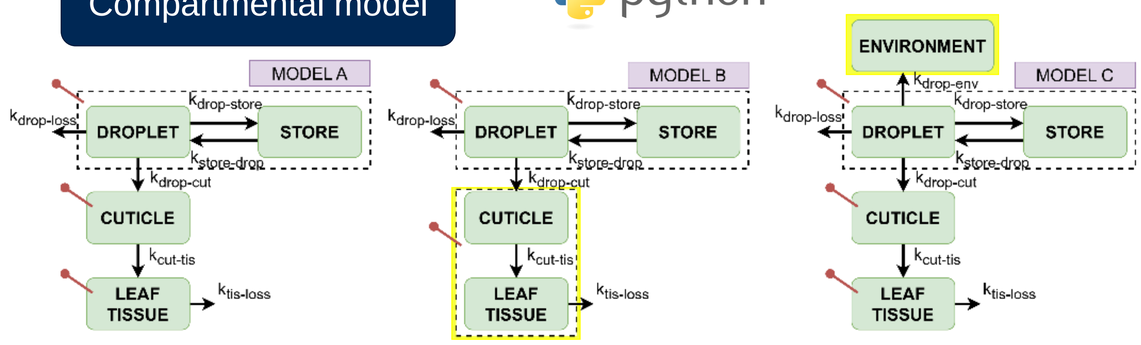
**Data understanding**

The experimental data are obtained by spraying the formulated product (AI + co-formulants) on whole plants. The variability observed in the data arises from both the measurement and the system (different plants/leaves for each data point).

In the dataset used for this study the collected measurements of are
**Leaf wash**: AI recovered on the surface of the leaf
**Wax extract**: the waxy cuticle in extracted with a solvent
**Tissue extract**: the samples are macerated with a solvent

Translocation in the rest of the plant was not observed.

**Compartmental model**




Material balance equations

$$\frac{dm_i}{dt} = \sum_j (k_{ji} m_j - k_{ij} m_i)$$

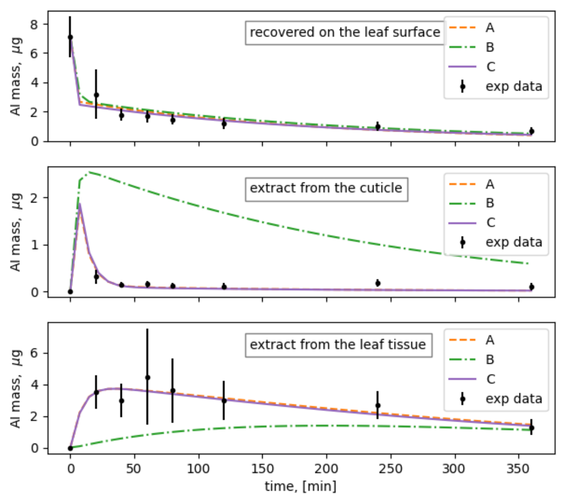
State variables
$\boldsymbol{x} \coloneqq \{m_i\}$ mass in the *i*-th compartment

Observed states
$\hat{\boldsymbol{y}}$ : dependent on the case A, B, C

Parameters
$\boldsymbol{\theta} \coloneqq \{k_{ji}\}$ mass transfer rates

Input
$\boldsymbol{u} \coloneqq \{M_0\}$ initial mass in the deposit

## Results and Learnings




***A-priori* structural identifiability test**

| A | B | C |
|---|---|---|
| Globally identifiable | Locally identifiable | Non-identifiable |

Globally identifiable: one solution $\boldsymbol{\theta} = \boldsymbol{\theta}^*$
Locally identifiable: finite number of solutions (more than one)
Non-identifiable: infinite solutions

Model C: $k_{drop-env} + k_{drop-loss} = k^*_{drop-env} + k^*_{drop-loss}$

***A-posteriori* practical identifiability tests**

**Parameters correlation matrix**

Requires a **preliminary estimation of the parameters** and considers practical limitations on the data available.
Results interpretation: **correlation > 0.99** for parameters is symptom **practical non-identifiability**.

**t-test on the estimates**

*t*-value: $t_{\theta_i} = \frac{\hat{\theta}_i}{\sqrt{V_{ii}}}$

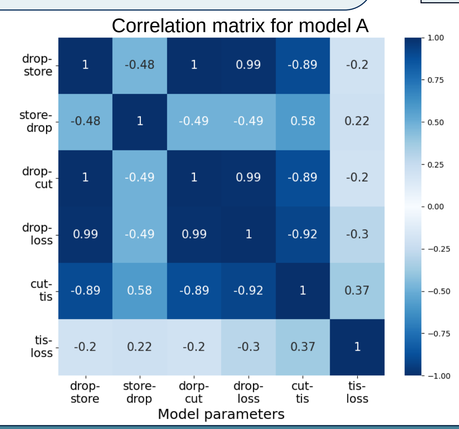
Tested with respect to a *t*-distribution with $(N_{data} - N_\theta)$ degrees of freedom.
Interpretation: a reliable estimate is identified by $t_{\theta_i} > t_{ref}$

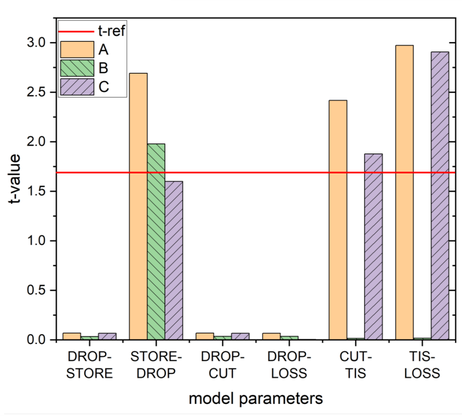
Fisher Information Matrix

$$\boldsymbol{H} = \sum_{j=1}^{N_y} \sum_{i=1}^{N_{sp}} \left(\frac{\partial \hat{y}_{ji}}{\partial \hat{\theta}}\right)^{\mathrm{T}} \boldsymbol{\Sigma}_{\mathbf{y_j}}^{-1} \left(\frac{\partial \hat{y}_{ji}}{\partial \hat{\theta}}\right)$$

→ Variance - Covariance matrix $\boldsymbol{V_\theta} = \{V_{ij}\} = \boldsymbol{H}^{-1}$

→ Correlation matrix $\boldsymbol{Corr} = \{r_{ij}\}$, $r_{ij} = \frac{V_{ij}}{\sqrt{V_{ii} V_{jj}}}$




## Future works

The analyses showed that the model complexity achievable is strongly limited by the system observability. Future works will include:
- Reformulation of non-identifiable models
- Conducting identifiability analysis on physics-based mechanistic model
- Testing the distinguishability of candidate models
- Proceeding with model discrimination and model-based design of experiments


## Acknowledgements

This project received funding from UCL Department of Chemical Engineering and Syngenta. The support is gratefully acknowledged.



References:
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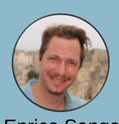
Personal Information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