On the development and application of a general model identification framework to biological systems

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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

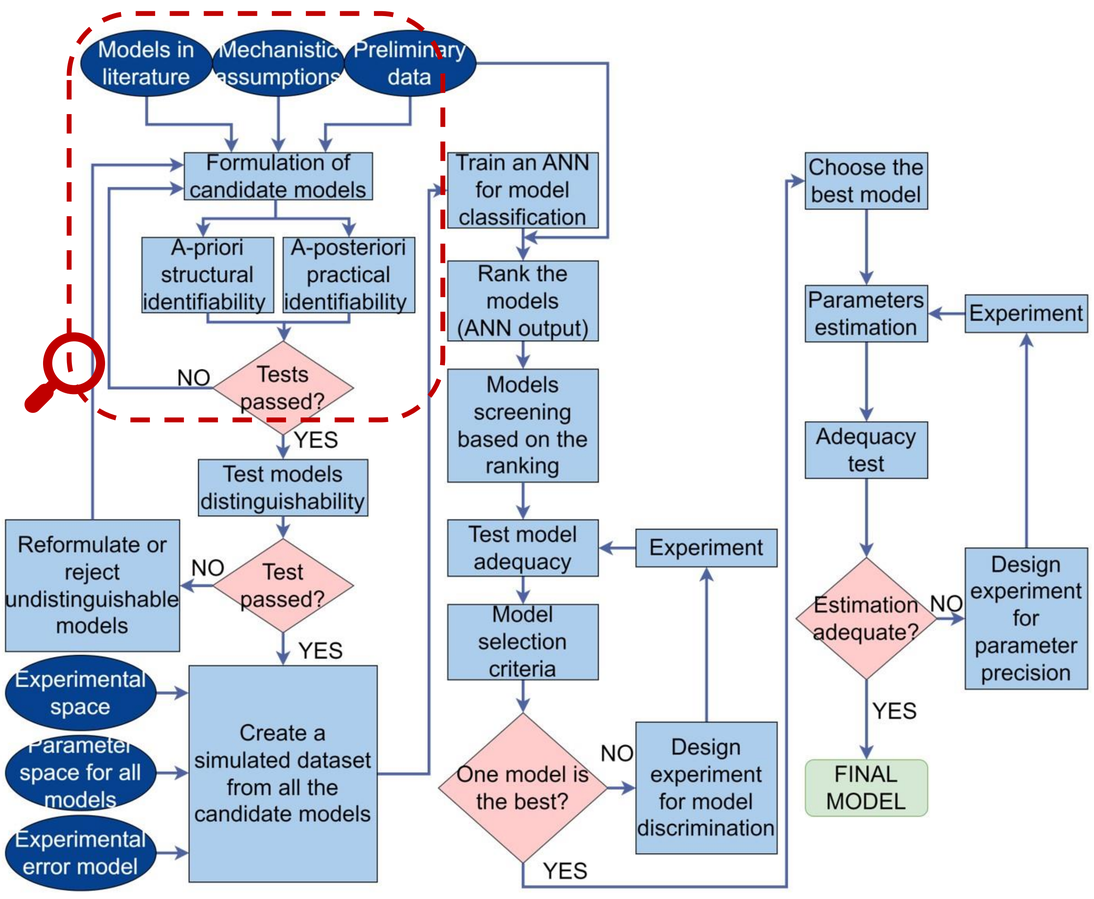
Solution

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], but also employs a novel ANN-based model selection method[2] for model screening.



Key steps in the modelling procedure

1. Models formulation
2. Preliminary analysis of the models
3. ANN-based first screening of the models
4. Model discrimination + MD-MBDoE loop
5. Parameter estimation + PP-MBDoE loop

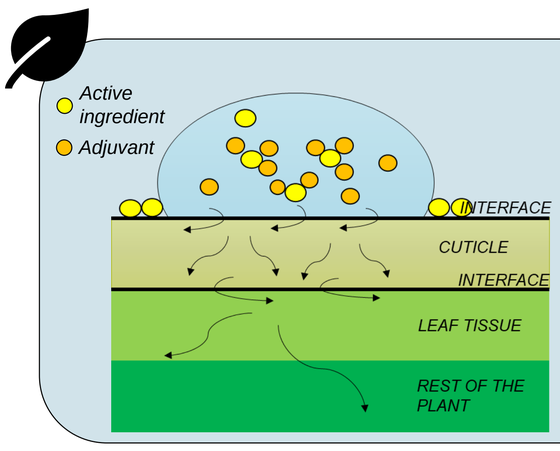
Preliminary analysis

The following tests are considered to check identifiability conditions on the model parameters: ***a-priori* structural identifiability** and ***a-posteriori* practical identifiability.** [3]

- Structural identifiability: **differential algebra** approach
- Practical identifiability: **correlation matrix** and **local sensitivity profiles**

Case study

Foliar uptake of pesticides



Many phenomena involved in the foliar uptake of pesticides[4]:

- Absorption
- Diffusion
- Equilibrium at interfaces
- Metabolism
- Volatility
- Photostability

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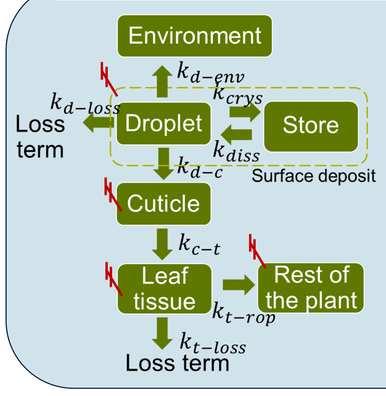
Compartmental model



Material balance equations

$$\frac{dC_i}{dt} = \sum_j (k_{ji}C_j - k_{ij}C_i)$$

$$m_i = C_i V_i$$

State variables

$$\boldsymbol{x} := \{C_i, m_i\}$$

Observed states

$$\hat{\boldsymbol{y}} : \{m_{deposit}, m_{cuticle}, m_{tissue}, m_{rop}\}$$

Parameters

$$\boldsymbol{\theta} := \{k_{ji}, V_i\}$$

Results

a-posteriori practical identifiability tests

Parameters correlation matrix

Requires a **preliminary estimation of the parameters** (maximum likelihood estimate), it considers practical limitations on the data available.
Results interpretation: **highly correlated** parameters are **not practically identifiable**, their effect cannot be decoupled with the I/O specified.

Fisher Information Matrix

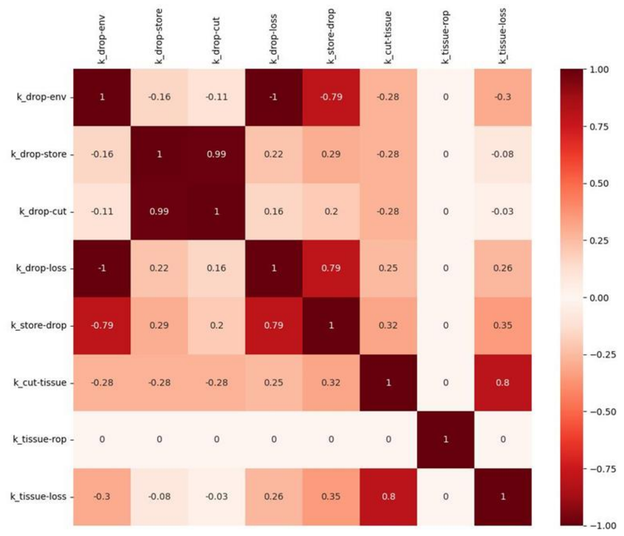
$$\boldsymbol{FIM} = \sum_{i=1}^{N} \left(\frac{\partial \hat{y}_i}{\partial \hat{\theta}}\right) \boldsymbol{V}^{-1} \left(\frac{\partial \hat{y}_i}{\partial \hat{\theta}}\right)$$

Variance-Covariance matrix

$$\boldsymbol{VarCov} = \{C_{ij}\} = \boldsymbol{FIM}^{-1}$$

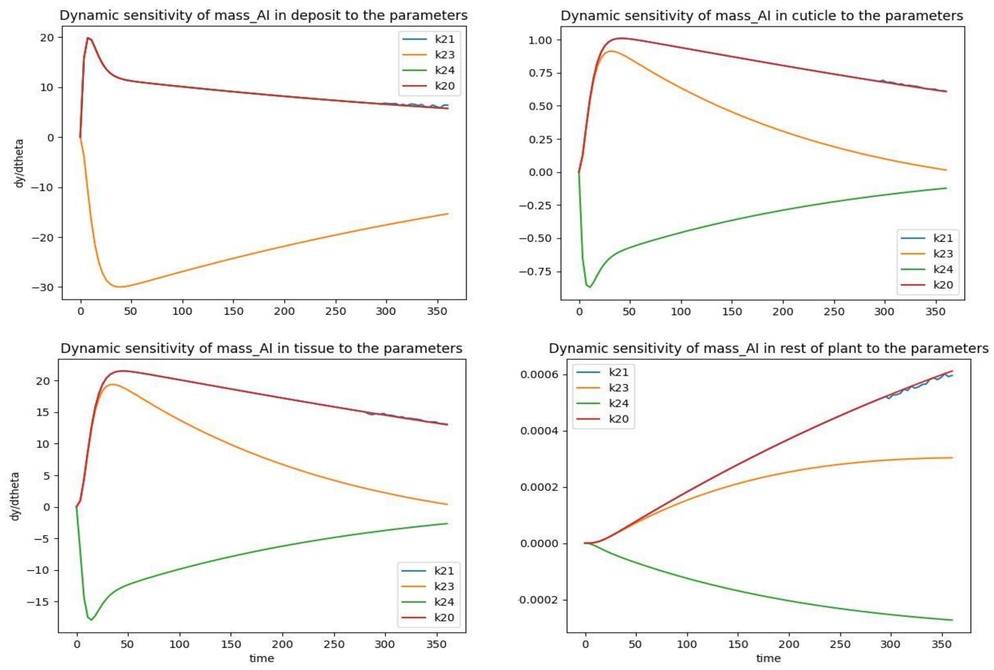
Correlation matrix

$$\boldsymbol{Corr} = \{r_{ij}\}; r_{ij} = \frac{C_{ij}}{\sqrt{C_{ii}C_{jj}}}$$



Local sensitivity profiles

The profiles are obtained by manipulating **one parameter at a time**.
Results interpretation: **overlapping profiles** lead to unidentifiable parameters. From the analysis it **emerges which parts of the model should be modified** to obtain an identifiable model.



Future work

The analyses conducted on the compartmental model showed that some parameters are unidentifiable, therefore it must be reformulated. Future works will include:

- Reformulate non-identifiable models
- Conduct identifiability analysis on physics-based mechanistic model
- Test for distinguishability of the models
- Proceed with model discrimination and model-based design of experiments

Acknowledgement

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References:

1. Franceschini, G., Macchietto, S., (2008). Model-based design of experiments for parameter precision: State of the art. Chemical Engineering Science, Model-Based Experimental Analysis 63, 4846–4872.
2. Quaglio, M., Roberts, L., Bin Jaapar, M.S., Fraga, E.S., Dua, V., Galvanin, F., (2020). An artificial neural network approach to recognise kinetic models from experimental data. Computers & Chemical Engineering 135
3. Miao, H., Xia, X., Perelson, A.S., Wu, H., 2011. On identifiability of nonlinear ODE models and applications in viral dynamics. SIAM Rev Soc Ind Appl Math 53, 3–39.
4. Wang, C.J., Liu, Z.Q., (2007). Foliar uptake of pesticides—Present status and future challenge. Pesticide

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