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IFAC PapersOnLine 58-23 (2024) 73–78

Foliar Uptake Models for Biocides: Testing Practical Identifiability of Diffusion-Based Models

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Abstract: With the expanding global population and diminishing resources, the imperative of ensuring sufficient food production becomes increasingly urgent. It is pivotal to develop safer biocides to enhance crop yields and address the escalating demands for food. Mathematical models are essential for understanding and characterizing the dynamic behaviour of complex biological systems. This work focuses on the development and statistical validation of a model for the description of biocide uptake through the leaves of plants. The systematic modelling strategy applied follows the steps: 1) formulation of candidate models; 2) conduction of identifiability tests to verify that model parameters can be estimated from observations; 3) selection of the best model based on its statistical performance in representing the experimental observations; 4) design of experiments for improving the precision of parameter estimates from data; 5) statistical validation of the final model. This paper presents a diffusion-based model for foliar uptake and a study on the practical identifiability of the model parameters (steps 1 and 2 of the procedure outlined). These results will guide further model-driven experimentation in the context of foliar uptake of pesticides.

Keywords: model identification, foliar uptake, systems biology, diffusion model, practical identifiability

1. INTRODUCTION

Mathematical models are effective tools for understanding and characterizing the dynamic behaviour of complex biological systems. The development of mathematical models to characterize complex systems subject to high uncertainty in experimental data and in the model structure, i.e. which phenomena should be included in the mathematical formulation, is a typical challenge when studying biological systems. This project aims at developing and validating systematic modelling methods that can deal with this complexity, in order to build reliable predictive models. In this context, the study of the foliar uptake of crop protection products is a perfect case study for the project, since it involves a system with high variability in the experimental data and several physicochemical processes still not completely understood.

The applications of mathematical models for foliar uptake can impact in addressing several global issues. With the expanding global population and diminishing resources, the imperative of ensuring sufficient food production becomes increasingly urgent. It is pivotal to develop safer biocides to enhance crop yields and address the escalating demands for food, while aligning with sustainable agricultural practices (Umetsu and Shirai, 2020).

Despite being essential for crop protection and beneficial for tackling food demand needs, the use of pesticides raises concerns about environmental impact, particularly in terms of soil and water contamination (Aktar et al., 2009), as well as the impact on global ecosystems (Sharma et al., 2019). This underscores the heightened importance of developing tools and technologies that can contribute to the production of safer pesticides.

Crop protection products such as herbicides and pesticides can be delivered to the plants via different methods, with the spraying on the foliage being one of the most relevant ones for field applications.

When the formulated product is delivered to the plants many processes take place both on the leaf surface and within the leaf. In the field application, the spray drift effect and bouncing of droplets must also be considered, which reduce the percentage of product that reaches the target (i.e. the leaf surface) from the tank. However, when the product is deposited on the leaf surface in a controlled environment, such as in lab experiments, these loss processes can be avoided and neglected from the description of the system.

The droplets interact with the leaf surface, and surfactants in the formulation help to spread the solution on the leaf. The increased contact interface between droplet and leaf favours the mass transfer processes, leading to higher active ingredient (AI) penetration rates. The droplet evaporation, mainly related to the environmental conditions of relative humidity (RH) and temperature, impact the concentration of AI which is the driving force for AI uptake from the droplet to the leaf interior. Loss processes that reduce the amount of available AI may

10.1016/j.ifacol.2024.10.013

occur on the surface, such as crystallization of the AI, loss due to AI volatilization, photo-instabilities and chemical instabilities (Bronzato et al., 2023), e.g. dissociation of the AI from its acid form. If crystallized AI is present on the leaf surface, it can undergo solubilization in the droplet especially when the RH is high.

To reach the target sites at the cellular level, the AI in solution on the surface has to penetrate through the cuticle (i.e. the external barrier). The literature agrees that lipophilic and hydrophilic AI follow different paths to penetrate the leaf (Fernández et al., 2017). These mechanisms are complex and still to be completely understood. Common simplified descriptions for the uptake of lipophilic molecules assume that at the interface between the aqueous solution and the waxy cuticle equilibrium is established. The AI then penetrates the cuticle by diffusion to reach the cellular tissue (Schreiber, 2006). The environment in the inter-cellular spaces is aqueous, therefore the assumption is that equilibrium is established with the waxy cuticle. Loss processes such as chemical instabilities can occur also at this stage, reducing the amount of effective AI. The xenobiotic then needs to pass through the wall of leaf cells to reach the active sites, which depend on the mode of action of the AI. The molecule is then metabolized by the leaf and reaches its target (Zhang and Yang, 2021). Another process that may take place, depending on the combination of AI/formulation/plant species, is the translocation of the AI via the phloem to other locations of the same leaf (short-distance transport) or of the plant (long-distance transport) (Neumann, 1988).

As described, several processes are involved in the system, and the uptake of agrochemicals through the leaves is influenced by environmental conditions (Zhang et al., 2022), as well as by physicochemical characteristics of both the leaves and the product formulation (Baker et al., 1992), i.e. the active ingredient and other components in the formulation such as adjuvants and safeners (Wang and Liu, 2007).

Several studies have been conducted on the foliar uptake of xenobiotics to develop mathematical models for characterizing the system behaviour. The models describing the phenomena involved in foliar uptake that can be found in the literature are mainly of three types: empirical correlations (Forster et al., 2004), compartmental models (Bridges and Farrington, 1974), and diffusion-based models (Tredenick et al., 2019).

However previous studies did not assess systematically if the model parameters can be accurately and precisely estimated from data (i.e. parameters identifiability), a crucial aspect to consider when applying the model for making predictions. This research aims at applying a systematic model building framework to develop a mathematical model that can be effectively applied to describe the system and predict the dynamic uptake profile on different combinations of plant and product, while ensuring identifiability of the parameters.

2. METHODOLOGY

In this project it is proposed to approach the modelling of foliar uptake of biocides in a systematic and statistically-sound fashion. The general modelling framework (Franceschini and Macchietto, 2008), is reported in Figure 1.

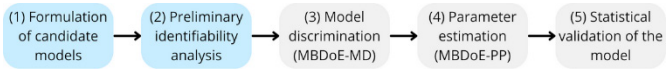

Figure 1. Systematic model building procedure, adapted from Franceschini and Macchietto (2008). This paper focuses on the steps highlighted in blue.

The procedure is divided in 5 key steps:

i. The formulation of candidate models for describing the system.

ii. Preliminary tests to assess the identifiability of model parameters are performed. If identifiability issues arise, they must be addressed before proceeding with the following steps.

iii. Model-based design of experiments (MBDoE) for discriminating among the candidate models.

iv. MBDoE for reaching a precise estimation of the model parameters.

v. The model is validated from experimental data based on statistics on the quality of fitting and on the quality of the parameter estimates.

The focus of this paper is on the first two steps of the procedure in Figure 1. Compartmental models formulated for the description of foliar uptake have been analysed by the authors in previous works (Sangoi et al., 2024), while this paper considers a diffusion-based model (step 1) and a study on the identifiability of its parameters is presented (step 2).

The general form considered for a dynamic model formulated as a set of partial differential and algebraic equations (PDE-AEs) is:

$$\begin{aligned} \boldsymbol{f}(\dot{\boldsymbol{x}}(z,t),\boldsymbol{x}(z,t),\boldsymbol{u},\boldsymbol{\theta},t) &= 0 \\ \hat{\boldsymbol{y}} &= \boldsymbol{g}(\boldsymbol{x}(z,t),\boldsymbol{u},\boldsymbol{\theta},t) \end{aligned} \tag{1}$$

In (1), $\boldsymbol{x} \in \mathbb{R}^{N_x}$ is a vector of state variables, $\boldsymbol{y} \in \mathbb{R}^{N_y}$ the vector of predicted model outputs, $\boldsymbol{u} \in \mathbb{R}^{N_u}$ the vector of known system inputs, $\boldsymbol{\theta} \in \mathbb{R}^{N_\theta}$ the model parameters vector. The symbol $\dot{\boldsymbol{x}}(z,t) \in \mathbb{R}^{N_x}$ indicates the partial derivatives of the states with respect to time t and space z (for 1D models). The foliar uptake model that will be presented in this work is formulated as system of PDEs and AEs expressed as in (1).

The tests for the identifiability of model parameters assess whether it is possible uniquely determined and precisely estimate the full set of parameters $\boldsymbol{\theta}$ from the given system inputs $\boldsymbol{u}(t)$ and the measurable system outputs $\boldsymbol{y}(t)$ (Miao et al., 2011). The parameter identifiability tests are categorized as: i) *a-priori* structural identifiability not requiring preliminary experimental data (Chis et al., 2011), and ii) *a-posteriori* practical identifiability tests (Miao et al., 2011). In this paper, the identifiability of parameters in a diffusion-based model for foliar uptake formulated as a set of PDE-AEs is tested by means of a-posteriori practical tests, aiming to understand if the experimental data are sufficient for uniquely

determine and precisely estimate the full set of model parameters. Since the objective is to validate a reliable predictive model for the description of foliar uptake, structural identifiability studies are not presented in this manuscript, while a-posteriori practical identifiability tests are chosen because they take into consideration constraints on the quantity and quality of data that can be practically obtained from the system, on which the model parameters are then calibrated.

2.1 A-posteriori practical identifiability

The practical identifiability tests in this work are based on the study of parameters correlation through the correlation matrix method (Rodriguez-Fernandez et al., 2006). Given two parameters θ_i and θ_j in the model to be estimated from data, their correlation is evaluated with the correlation coefficient R_{ij}. The correlation coefficient is calculated for every pair of parameters (θ_i, θ_j), which will be the ij-th entry in the correlation matrix $\mathbf{R}$ $[N_\theta \text{ X } N_\theta]$. The value of R_{ij} is calculated starting from the variance-covariance matrix of the model parameters $\mathbf{V_\theta} := \{V_{\theta_{ij}}\}$ $[N_\theta \text{ X } N_\theta]$ as in (2).

$$R_{ij} = \frac{V_{\theta_{ij}}}{\sqrt{V_{\theta_{ii}} V_{\theta_{jj}}}}, \quad i,j = 1, \dots N_\theta \tag{2}$$

From the definition in (2), it can be seen that high values of R_{ij} are associated to parameter pairs having a covariance comparable with their variances.

Typically in the literature a critical (absolute) value of 0.99 is assumed for the correlation in the context of parameter identifiability (Rodriguez-Fernandez et al., 2006). Correlations between parameters greater than 0.99 lead to singular Fisher Information Matrix (5), which indicates the presence of non-identifiable parameters.

This practical identifiability technique is applied a-posteriori since it needs prior experimental data, i.e. N_{sp} sampling points for the N_y observed states. In fact, the covariance matrix $\mathbf{V_\theta}$ is calculated from two contributions: i) the dynamic sensitivity matrix $\mathbf{S}$ $[N_y N_{sp} \times N_\theta]$, which carries information about the mathematical structure of the model and the location of the sampling points, and ii) the variance-covariance matrix of the measurement errors $\mathbf{\Sigma_y}$ $[N_y N_{sp} \times N_y N_{sp}]$, which characterizes the variability in the experimental observations. This analysis is *local*, being conducted around a nominal parameter vector $\widehat{\boldsymbol{\theta}}^*$, which can be estimated from preliminary data. The dynamic sensitivity matrix $\mathbf{S}$ is defined as

$$\mathbf{S}_{N_y N_{sp} \times N_\theta} = \begin{bmatrix} s_{11}(t_1) & \cdots & s_{1N_\theta}(t_1) \\ \vdots & \ddots & \vdots \\ s_{N_y 1}(t_1) & \cdots & s_{N_y N_\theta}(t_1) \\ \vdots & \vdots & \vdots \\ s_{11}\left(t_{N_{sp}}\right) & \cdots & s_{1N_\theta}\left(t_{N_{sp}}\right) \\ \vdots & \ddots & \vdots \\ s_{N_y 1}\left(t_{N_{sp}}\right) & \cdots & s_{N_y N_\theta}\left(t_{N_{sp}}\right) \end{bmatrix} \tag{3}$$

The entries in the matrix are sensitivity coefficients. The sensitivity $s_{ij}(t_k)$ of the i-th response y_i to the j-th parameter θ_j at the k-th sampling time t_k is calculated as in (4).

$$s_{ij}(t_k) = \frac{\partial y_i(t_k)}{\partial \theta_j} \tag{4}$$

The matrix $\mathbf{\Sigma_y}$ is obtained by modelling the variance observed in the replicates. So, the definition of this matrix requires information on the experimental setup and the measurement system, to understand the reproducibility of the measurements. The elements of this matrix can be characterized by using a variance model, e.g. homoscedastic and heteroscedastic models.

The two matrices $\mathbf{S}$ and $\mathbf{\Sigma_y}$ are combined together to calculate the Fisher Information Matrix ($\mathbf{H}$) as in (5).

$$\mathbf{H} = \mathbf{S}^T \cdot \mathbf{\Sigma_y^{-1}} \cdot \mathbf{S} \tag{5}$$

The matrix $\mathbf{V_\theta}$ is finally calculated as the inverse of $\mathbf{H}$.

$$\mathbf{V_\theta} = \mathbf{H^{-1}} \tag{6}$$

Once $\mathbf{V_\theta}$ is obtained, the correlation coefficients R_{ij} can be calculated as in (2). The value of R_{ij}, ranging from -1 to 1, indicates how closely linked the parameters θ_i and θ_j are. Parameters pair having $R_{ij} = 1$ are said totally correlated, if $R_{ij} = -1$ the parameters are totally anti-correlated, while if the value of R_{ij} is 0 the parameters are non-correlated. Values of correlation between these limit conditions are interpreted as an indicator of proximity to a condition of (anti-)correlation or non-correlation.

3. MODEL DESCRIPTION

As introduced in Section 1, models can be found in the literature to describe the foliar uptake, among which there are compartmental models and diffusion-based models. Compartmental models formulated as a set of ODEs have been analysed by the authors in previous works (Sangoi et al., 2024), to study the practical identifiability of the model parameters (i.e. the mass transfer rates between the compartments in the model). Conversely, the model presented in this paper includes the mathematical description of the diffusion process by means of a PDE, along with AEs and ODEs to describe the other phenomena in the systems, such as the equilibrium at the interface droplet-leaf and the AI consumption due to metabolism (Figure 2).

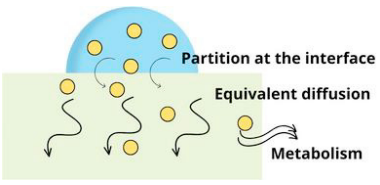

Figure 2. Graphical representation of the system under investigation (deposit – leaf). The processes included in the mathematical description of the system dynamics are indicated.

Studies in the literature (Schreiber, 2006) indicate that diffusion may be assumed to describe the process of AI uptake

through the cuticle, i.e. the outermost layer of leaves, which is a combination of epicuticular waxes and cutin (a polymeric matrix). However, the AI uptake in the cuticle is not commonly measured in routine experiments but rather the total AI mass in the leaf at the sampling points is observed. Therefore in this model the leaf geometry is not divided into sub-spaces (i.e. cuticle, cellular tissue, etc.), but an *equivalent leaf internal* is considered instead, as depicted in Figure 2, where also the processes influencing uptake included in the mathematical model are indicated. The diffusion is then defined as *equivalent diffusion* in the equivalent leaf internal in the following discussion. The system is divided into two regions: the *deposit* on the surface and the *equivalent leaf internal*.

3.1 Deposit dynamics

It is assumed that the droplet is well mixed, i.e. no spatial gradients of concentration are present inside the deposit. The volume of the deposit V_{dep}, AI mass m_{dep}, and AI concentration C_{dep} are related by

$$m_{dep}(t) = C_{dep}(t) \cdot V_{dep}(t) \tag{7}$$

The evaporation process determines the change of volume in the deposit. Evaporation is modelled as a linear process characterized by a constant evaporation rate K_{evap}, up until a limit volume V_{min} is reached, so that

$$\frac{dV_{dep}(t)}{dt} = -K_{evap} \cdot f\big(V_{dep}\big) \tag{8}$$

subject to

$$\begin{cases} f\big(V_{dep}\big) = 1 & \text{if } V_{dep} > V_{min} \\ f\big(V_{dep}\big) = 0 & \text{if } V_{dep} \le V_{min} \end{cases} \tag{9}$$

Potential losses in the deposit due to photo- and chemical-instability of the AI are described with a first order term characterized by the parameter K_{loss}. Therefore, the dynamics of the concentration of AI in the deposit $C_{dep}(t)$ is given by

$$\frac{dC_{dep}}{dt} = -\frac{f\big(V_{dep}\big)}{V_{dep}}\frac{dV_{dep}}{dt}C_{dep} - K_{loss}C_{dep} \tag{10}$$

Mass transfer takes place between the droplet and the leaf. It is assumed that equilibrium is established within a boundary layer at the interface between the two regions. The equilibrium condition is described mathematically by means of a constant parameter, i.e. the partition coefficient between droplet and leaf K_{DL}.

$$K_{DL} = \frac{C_{leaf}(0,t)}{C_{dep}(t)} \tag{11}$$

In (11), $C_{leaf}(0,t)$ indicates the concentration of AI at the interface on the leaf side.

3.2 Equivalent leaf internal dynamics

Given the heterogenous nature of the leaf structure in the direction normal to the surface, it is assumed that diffusion is mono-directional, so the concentration of AI in the equivalent leaf internal is spatially discretized in one spatial dimension z, i.e. $C_{leaf} = C_{leaf}(z,t)$. The AI can be consumed in the leaf tissue due to metabolism (K_{met}) and translocation (K_{trans}) to other parts of the plant. It is assumed that metabolism takes place with the same rate K_{met} in the whole leaf domain, which in reality is not the case given the heterogeneous structure of the leaf. In conclusion, the dynamics in the equivalent leaf internal is formulated as in (12).

$$\frac{\partial C_{leaf}(z,t)}{\partial t} = D_{eq}\frac{\partial^2 C_{leaf}(z,t)}{\partial z^2} + \\ -K_{met}C_{leaf}(z,t) - K_{trans} \tag{12}$$

The total concentration in the leaf $C_{leaf,tot}(t)$is calculated by averaging $C_{leaf}(z,t)$ over the spatial domain $[0, L_{leaf}]$, where L_{leaf} indicates the thickness of the equivalent leaf internal, i.e. a fixed parameter in the model.

$$C_{leaf,tot}(t) = \frac{1}{L_{leaf}}\int_{z=0}^{L_{leaf}} C_{leaf}(z,t)dz \tag{13}$$

From $C_{leaf,tot}(t)$, the total mass in the leaf $m_{leaf}(t)$ is obtained as in (14), where V_{leaf} is the volume of the equivalent leaf internal.

$$m_{leaf}(t) = C_{leaf,tot}(t) \cdot V_{leaf} \tag{14}$$

The boundary condition at $z = 0$ is given by (11), while at the boundary $z = L_{leaf}$ it is imposed that there is no transport as in (15).

$$\frac{\partial C_{leaf}\big(L_{leaf},t\big)}{\partial t} = 0 \tag{15}$$

To solve the set of equations presented above, which includes coupled AEs, ODEs and PDEs, the model is implemented in Python 3.10. For solving the diffusion equation in the equivalent leaf internal Crank-Nicolson method is used.

4. RESULTS

The diffusion-based model here presented is fitted to experimental measurements of foliar uptake provided by Syngenta. The fitting of the model parameters is performed with a maximum likelihood estimation approach (Bard, 1974). The Nelder-Mead method is used to solve the optimization problem, among the methods available in the python library *scipy.optimize*., the results presented here are at convergence.

Figure 3 shows the model predictions of the uptake profiles compared to the experimental data. Data are normalized with respect to the mass of AI deposited on the leaf surface, i.e. the mass in the deposit at time *t* = 0, therefore the normalized mass values range between 0 and 1. The experimental values reported are the average measurements over 8 replicates of the same experiments, and the error bars refer to 95% confidence intervals based on the observed variance in the replicates.

In Figure 3 the dynamics in the system is observed: after the first 2 hours 80% of the AI initially in the deposit is no longer there due to the uptake and loss processes. The equivalent leaf internal reaches a maximum concentration of AI in relatively short time and then it shows a decreasing trend due to the metabolic processes. The model predictions in Figure 3 are

obtained assuming that evaporation and other loss processes do not occur in the deposit (i.e. $K_{evap} = 0$ and $K_{loss} = 0$), and also that translocation is not taking place (i.e. $K_{trans} = 0$) therefore the only parameters to estimate are $\boldsymbol{\theta} = [D_{eq}, K_{DL}, K_{met}]$: equivalent diffusion, partition coefficient, and metabolism rate constant.

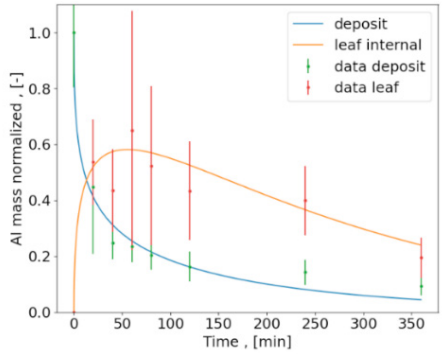

Figure 3. Time profiles of the normalized mass of AI in the surface deposit (blue line) and in the *equivalent* leaf internal (orange line) after the calibration of the model parameters on the experimental data provided by Syngenta.

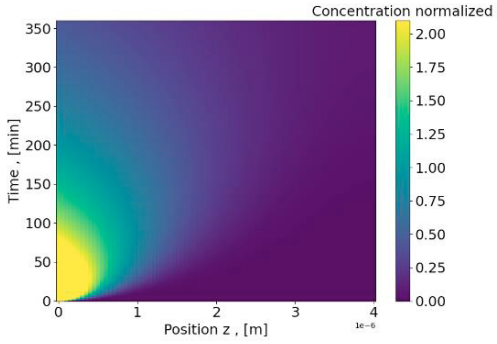

Figure 4. Contour plot representing the dynamic evolution in space (x-axis) and time (y-axis) of AI concentration inside the *equivalent leaf internal*.

The combined effect of equivalent diffusion and metabolism inside the leaf is shown in Figure 4, where the evolution in the time and space domain of the normalized concentration of AI in the *equivalent leaf internal* is represented through a contour plot. The data are normalized to the initial mass of AI in the deposit, so the normalized concentration in the equivalent leaf internal can be higher than 1 due to the different volumes of droplet and leaf interior. It is observed that the transfer from the deposit to the leaf at the interface (i.e. position z=0) dominates for the first 2 hours, and the AI starts to diffuse inside the leaf. However, the concentration decreases slowly in time due to metabolism.

Figure 3 shows that the diffusion-based model captures well the dynamics in the leaf tissue, however it must be underlined that the experimental data are subject to high variability. The estimated values of the model parameters with the 95% confidence intervals are reported in Table 1. Based on the confidence intervals the metabolism rate is precisely estimated, while the estimates of D_{eq} and K_{DL} are affected by a large uncertainty.

Table 1. Values of the model parameters estimates with 95% confidence intervals.

Parameter	Estimate ± 95% C.I.	Units
$\boldsymbol{D_{eq}}$	$3.751\times10^{-14} \pm 1.394\times10^{-13}$	m^2/s
$\boldsymbol{K_{DL}}$	$4.928\times10^{+01} \pm 9.024\times10^{+01}$	-
$\boldsymbol{K_{met}}$	$4.610\times10^{-02} \pm 5.029\times10^{-03}$	1/s

Table 2. Results of the one-tailed *t*-test with significance α=0.95 to assess the quality of parameter estimates. The symbol * indicates parameters failing the test (*t*-value < *t*-reference).

Parameter	*t*-value	*t*-reference	Test result
$\boldsymbol{D_{eq}}$	0.125*	1.771	Failed
$\boldsymbol{K_{DL}}$	0.253*	1.771	Failed
$\boldsymbol{K_{met}}$	4.243	1.771	Passed

Statistical studies on the quality of the parameter estimates and their practical identifiability are essential to ensure the applicability of the model for predictions. To establish the statistical significance of the parameter estimates a *t*-test has been adopted. The results of the test with significance 95% are reported in Table 2.

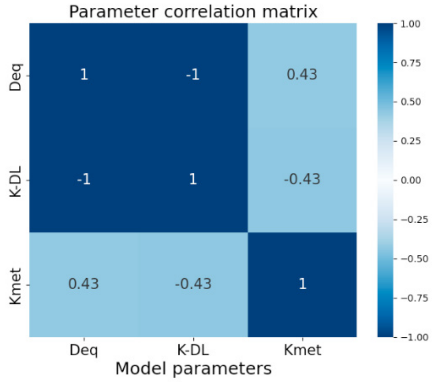

Figure 5. Heatmap showing the correlation matrix for the diffusion-based model of foliar uptake.

Since the *t*-value obtained for parameters D_{eq} and K_{DL} is lower than the *t*-reference, the estimates of these two parameters have failed the test, i.e. they are not statistically significant. On the other hand, the estimate of K_{met} has successfully passed the *t*-test. To test the practical identifiability of the parameters (D_{eq}, K_{DL}, K_{met}), the correlation coefficients are calculated starting from the variance-covariance matrix of the parameters using (2). The parameters identifiability issues emerged from the analysis hindering the possibility of applying MBDoE techniques for precise parameter estimation at this stage. The identifiability issues must be addressed before proceeding with steps 3-5 in the proposed modelling framework (Figure 1). To overcome the non-identifiability of D_{eq} and K_{DL}, model re-parametrization techniques could be applied to avoid singularity of the variance-covariance matrix of model

parameters (6), a key issue arising in model-based experimental design (Quaglio et al., 2020). The identifiability issues can also be tackled by independently evaluate specific parameters, e.g. by correlating K_{DL} to physio-chemical properties of the formulation and of the leaf.

5. CONCLUSIONS

In this paper a diffusion-based model to describe foliar uptake of pesticides has been presented, where the concept of equivalent leaf internal has been introduced to take into account the limited system observability in routine experimental procedures. A systematic approach based on statistical tests is proposed to validate the model and to guarantee its applicability. To assess the possibility of precisely estimating the model parameters, a practical identifiability test based on the analysis of parameter correlation matrix has been applied. The identifiability issues can be overcome by re-parameterizing the model or by independently evaluate specific parameters, to reduce the set of parameters that has to be estimated from the bio-kinetic data of uptake. Further studies will be conducted using experimental data from systems where AI translocation was observed, in order to verify the practical identifiability when additional parameters are included in the diffusion-based model. A statistics-based comparison between compartmental models (Sangoi et al., 2024) and diffusion-based models for the description of foliar uptake of pesticides will then be conducted, paving the way to the application of Model-Based Design of Experiments (MBDoE) techniques to this system subject to high uncertainties in its mathematical description.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of the Department of Chemical Engineering, University College London, UK and Syngenta.

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