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Identification of Kinetic Models by Incremental Refinement[1]

1 Introduction

Chemical (or process) engineering is an engineering science that focuses on the foundations of any kind of transformation of matter in order to change its molecular or morphological constitution. The primary subject of modeling is a (part of a) complete production process, which converts raw materials in desired chemical products. Any such (sub-)process comprises a set of connected pieces of equipment (or process units), which are typically linked by material, energy and information flows. The overall behaviour of the plant is governed by the behaviour of its constituents and their nontrivial interactions. The process can be considered as a system of systems (Marquardt, 1995): this process system forms a collection of subsystems, i.e., the pieces of equipment, which are connected by different types of flows forming a complex network. Every piece of equipment is structured itself; hence, its decomposition into interconnected subsystems is facilitated. Each of these subsystems is governed by typically different types of kinetic phenomena, such as (bio-)chemical reactions or intra- and interphase mass, energy and momentum transport. The resulting spatio-temporal behaviour is often very complex and yet not well-understood. This is particularly true if multiple, reactive phases (gas, liquid or solid) are involved.

Mathematical models are in the core "of methodologies for chemical engineering decisions (which) should be responsible for indicating how to plan, how to design, how to operate, and how to control any kind of unit operation (e.g., process unit), chemical and other production process and the chemical industries themselves" (Takamatsu, 1983). Given the multitude of model-based engineering tasks, any modeling effort has to fulfil specific needs asking for different levels of detail and predictive capabilities of the resulting mathematical model. While modeling in the sciences aims at an understanding and explanation of observed system behaviour in the first place, modeling in engineering is an integrated part of model-based problem solving strategies aiming at planning, designing, operating or controlling an artificial (process) system. There is not only a diversity of engineering tasks but also an enormous diversity of structures and phenomena

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[1] This paper is based on previous reviews on the subject (Marquardt, 2005; Bardow and Marquardt, 2009).

governing (process) system behaviour. Engineering problem solving is faced with such multiple dimensions of diversity. A kind of “model factory” has to be established in industrial modeling processes in order to reduce the cost of developing models of high quality, which can be maintained across the plant lifecycle (Marquardt et al., 2000).

Models of process systems are multi-scale in nature. They span from the molecular level with short length- and time-scales to the global supply chain involving many productions plants, warehouses and transportation systems. The major building block of a model representing some part of a process system (sometimes also called a balance envelope) is the differential balance equation, which is formulated for a selected set of extensive quantities (Bird et al., 2002). The balances constitute of hold-up, of transport and source terms which reflect the molecular behaviour of matter on the continuum scale. Averaging is often applied to coarse-grain the resolution of the model in time and space for complexity reduction (Slattery, J. C., 1999). The bridging from the molecular to the continuum scale by some kind of coarse-graining results unavoidably in so-called closure problems. Roughly speaking, a closure problem arises, because the application of linear averaging operators to a nonlinear expression in a balance equation cannot be evaluated analytically to relate the average of such an expression to the averaged state variables (such as velocity, temperature, concentrations). The closure condition refers to some constitutive (in some cases even differential equation) model which relates the average of a nonlinear expression to the averaged state variables. A well-known closure problem refers to the determination of the Reynolds stress tensor which results from averaging the Navier-Stokes equations with respect to time (Pope, 2000). Even if such closure conditions are derived from theoretical considerations using some kind of scale-bridging approach, they typically require the identification of empirical parameters in the sub-model structures or in extreme cases even the model structure (i.e., the mathematical expressions relating dependent and independent variables) itself. In particular, the so-called k-ε-model for the Reynolds stress tensor comprises a number of parameters which have to be determined from experiments (Bardow et al., 2008).

Since such model identification is a complex systems problem, a goal-oriented work process has to be established which systematically links high resolution measurement techniques, mathematical modeling, real (laboratory) or virtual (simulation) experiments (typically on a finer scale) with the formulation and solution of so-called inverse problems (Kirsch, 1996). These inverse problems come in different flavours: they may be used to design the most informative experiment by fixing the experimental conditions in a given experimental set-up appropriately (Walter, Pronzato, 1990; Pukelsheim, 2006), to estimate parameters (Bard, 1974; Schittkowski, 2002) in a given model structure or to discriminate among model structure candidates based on experimental evidence (Verheijen, 2003). Typically, the model identification task cannot be successfully tackled in one go. Rather, some kind of iterative refinement strategy is intuitively followed by the modeller to exploit the knowledge gained during the model development procedure. Probably the most important decision to be made is the level of detail to be included in the target model to result in a desired model resolution.

To this end, this contribution summarizes recent progress towards a systematic work process (Bardow and Marquardt, 2004; Marquardt, 2005) to derive valid mathematical models for kinetically controlled reaction and transport problems, which govern the behaviour of (bio-)chemical process systems. This work process is called *model-based experimental analysis* (or MEXA for short) and aims at *useful models at minimal engineering effort*. While mathematical models of kinetic phenomena can in principle be developed using standard statistical techniques including nonlinear regression (Bard, 1974) and multi-model inference (Burnham, Anderson, 2002), this direct approach typically results in strongly nonlinear and large-scale mathematical programming problems (Schittkowski, 2002; Biegler, 2010), which may not only be computationally prohibitive, but also result in models which are not capturing the underlying physico-chemical mechanisms appropriately. In contrast, *incremental model identification* (or IMI for short), which is an integral part of the MEXA methodology, constitutes a physically motivated divide-and-conquer strategy to kinetic model identification.

This paper is structured as follows: Section 2 presents a general overview on the MEXA methodology. Two identification strategies, simultaneous and incremental model identification are introduced in Section 3. Sections 4, 5 and 6 sketch the application of the MEXA and IMI methodologies exemplarily to three challenging and relevant process modeling problems including (bio-)chemical reaction kinetics in single- and multi-phase systems, multi-component diffusion in liquids and energy transport in wavy falling film flows. The final Section 6 provides a summarizing discussion.

2 Model-based experimental analysis

An overview on the MEXA methodology is presented in Fig. 1. The typical workflow involves the following steps:

1. An initial experiment (comprising the experimental apparatus and appropriate measurement devices) is built to observe a kinetic phenomenon of interest.

2. Experimental evidence and the available a-priori knowledge are used to build a first structured mathematical model of the experiment. Unknown parameters are initialized with plausible values.
3. Virtual experiments are carried out by means of simulation studies using this first model. Even if the simulation results were only qualitatively correct, they will provide insight into the behaviour of the experiment prior to actual laboratory work, which could result in a revision of the design of the initial experiment and its operation.
4. First experiments are performed. They should be guided by statistical design of experiments (Mason et al., 2003) to explore a telling set of experimental conditions. These experiments will provide some qualitative insight into the behaviour of the experiment and the governing kinetic phenomena.
5. The measurement data recorded in the initial experiments can be used to formulate a parameter estimation problem, which is a special kind of inverse problem, for the conjectured model structure. Not all parameters may be identifiable. Therefore, parameter estimation should be preceded by identifiability analysis (Vaida et al., 1989, Walter, Pronzato, 1997) to assess which (combinations of) parameters can be estimated uniquely from the available measurements.
6. The model of the experiment is now used to find experimental conditions by means of optimal design of experiments (Walter, Pronzato, 1990; Pukelsheim, 2006) resulting in most informative data for the intended purpose of the experimental investigation. Such a revision of the experiment targets, in the first place, the operating conditions of the experiment and the type and accuracy of the measurements taken. However, also the experimental set-up is subject to possible change.
7. The designed experiment is performed and the observations are recorded. One or more inverse problems are formulated and solved to calibrate sensors, to estimate unknown inputs, states or parameters of the model or to select and discriminate an appropriate model structure.
8. Most often, the resulting model does not reflect the kinetic phenomenon of interest with sufficient detail and accuracy. In particular, the selected model structure may not properly match reality sufficiently well, or, the model may be too detailed to allow for its identification. The accumulated understanding, however, allows for an iterative improvement of the model, either by model simplification to improve identifiability (Quaiser et al., 2011) or by model structure refinement to better capture reality (Verheijen, 2003).
9. The sequence of steps 6, 7 and 8 is repeated until a model is obtained, which is fully consistent with all the measurements available. The investigations

should ideally only be terminated if the model can not be falsified by any conceivable experiment (Popper, 1959).

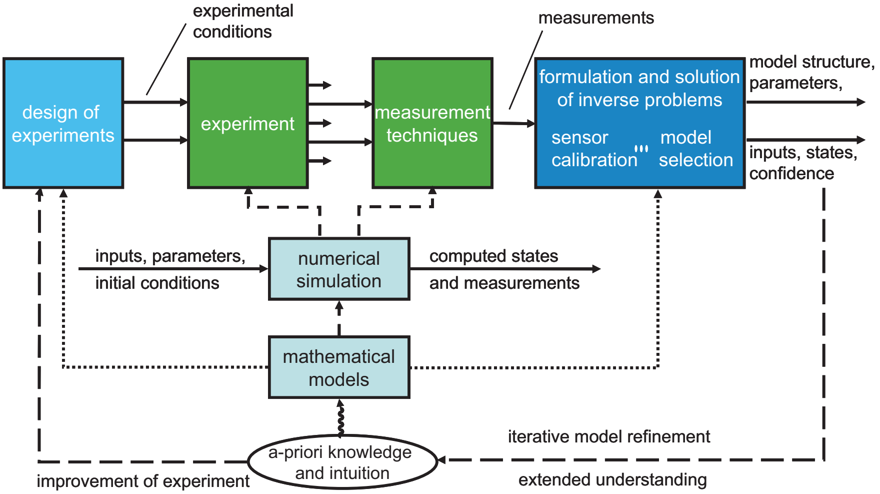

Figure 1: The MEXA methodology – an overview (Marquardt, 2005).

Research on systematic work processes for mathematical model development, which combine experiments, data analysis, modeling and model identification, dates back at least to the 1970s (Kittrell, 1970). However, the availability of current, more advanced experimental and theoretical techniques offers new opportunities to develop more comprehensive modeling strategies, which are widely applicable to a variety of modeling problems. For example, a modeling process with a focus on optimal design of experiments has been reported by Asprey and Macchietto (2000). The collaborative research centre CRC 540, "Model-based Experimental Analysis of Fluid Multi-Phase Reaction Systems" (cf. http://www.sfb540.rwth-aachen.de/), which was funded by the German Research Foundation (DFG), addressed the development of advanced modeling work processes comprehensively from 1999 to 2009. The research covered the development of novel high resolution measurement techniques, efficient numerical methods for the solution of direct and inverse reaction and transport problems and the development of a novel, experimentally driven modeling strategy which relies on iterative model identification.

3 Two alternative model identification strategies

This iterative model identification strategy is introduced in the following section and compared to the established simultaneous model identification (SMI) strategy.

3.1 Incremental model identification

Incremental model identification (IMI) relies on an incremental refinement of the model structure which is motivated by systematic model development (Fig. 2) as suggested by Marquardt (1995). The major model development steps and their relation to incremental model identification are outlined in the following.

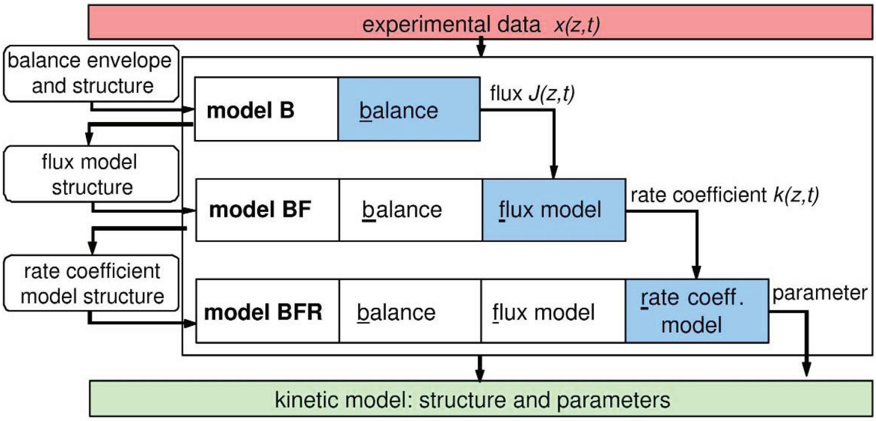

Figure 2: Incremental modeling and identification (Marquardt, 1995, 2005)

3.1.1 Model B

In model development, balance envelopes and their interactions are determined first to represent a certain part of the system of interest. The spatio-temporal resolution of the model is decided in each balance envelope, e.g., the model may or may not describe the evolution of the behaviour over time t and it may or may not resolve the spatial resolution in up to three space dimensions z. Those extensive quantities $y(z,t)$ are selected for which a balance equation is to be formulated. In case of spatio-temporally resolved models, the balance reads as

$$\begin{aligned} &\frac{\partial y}{\partial t} = -\nabla_z \cdot J_{f,y} + J_{s,y}, \quad y(z,t_0) = y_0(z), \quad z \in \Omega, \ t > t_0, \\ &\nabla_z y\big|_{\Gamma} = J_{b,y}, \quad z \in \Gamma, \end{aligned} \tag{1}$$

with y a selected extensive quantity (such as mass, mass of a certain chemical species, energy, etc.) propagated according to the transport term $J_{f,y}(z,t)$ and generated (or consumed) according to the source term $J_{s,y}(z,t)$ at any point in the interior of the balance envelope $\Omega \subset R^n, n = 1,2,3$. The symbol $J_{b,y}\ (z_b,t)$ refers to transport across the boundary G of the balance envelope. Any extensive quantity $y(\cdot)$ is related to a set of measured (typically intensive) quantities $x(\cdot)$ by some constitutive relation

$$y(\cdot) = h(x(\cdot),\cdot). \tag{2}$$

If no spatial resolution of the state variables is desired, the balance for some $y(t)$ is written as

$$\frac{dy}{dt} = j_{f,y} + j_{s,y} \quad , \qquad y(t_0) = y_0 \tag{3}$$

The symbols $j_{f,y}(t)$ and $j_{s,y}(t)$ refer to transport of $y(t)$ and its generation (or consumption) within the balance envelope, respectively.

Note that no constitutive equations are considered yet to specify either of the fluxes $J_{f,y}$, $J_{s,y}$, $J_{b,y}$, $j_{f,y}$ or $j_{s,y}$ as a function of the intensive thermodynamic state variables $x(\cdot)$. While these constitutive equations are selected on the following decision level, unknown fluxes $J_{\ldots}$ or $j_{\ldots}$ are estimated directly from the balance equation in incremental model identification. For this purpose, measurements of $x(\cdot)$ with sufficient resolution in time t and/or space z are assumed. An unknown flux, $J_{\ldots}$ or $j_{\ldots}$, can then be estimated from one of the balance equations as a function of time and/or space coordinates without specifying a constitutive equation.

3.1.2 Model BF

In model development, constitutive equations are specified for each flux term in the balances on the next decision level. In particular,

$$\begin{aligned} J_{f,y}(z,t) &= G_{f,y}(x, \nabla_z x, \ldots, k_{f,y}), \\ J_{s,y}(z,t) &= G_{s,y}(x, \ldots, k_{s,y}), \\ J_{b,y}(z,t) &= G_{b,y}(x, \nabla_z x, \ldots, k_{b,y}) \end{aligned} \tag{4}$$

for spatially distributed and

$$\begin{aligned} j_{f,y}(t) &= g_{f,y}(x, \ldots, k'_{f,y}), \\ j_{s,y}(z,t) &= g_{s,y}(x, \ldots, k'_{s,y}) \end{aligned} \tag{5}$$

for spatially lumped balance envelopes. The symbols $k_{\ldots}$ and $k'_{\ldots}$ refer to some rate coefficient functions which depend on time and space (in case of spatially distributed balance envelopes) or on time alone (in case of spatially lumped balance envelopes), respectively. These constitutive equations could, e.g., correlate interfacial fluxes or reaction rates with state variables.

Similarly, in incremental model identification, flux model candidates, as in Eqs. (4) or (5), are selected or generated on decision level *BF* to relate the flux to rate coefficients, to measured states, and possibly to their derivatives. The estimates of the fluxes $J_{\ldots}(z,t)$ or $j_{\ldots}(t)$ obtained on level *B* are now interpreted as *inferential* measurements. Together with the *real* measurements $x(z,t)$ or $x(t)$, one of these flux estimates can then be used to determine one of the rate coefficients $k_{\ldots}$ or $k'_{\ldots}$ as a function of time and space from the corresponding equation in (4) or (5), respectively. Often, the flux model can be analytically solved for the rate coefficient function $k_{\ldots}(z,t)$ or $k'_{\ldots}(t)$. These rate coefficient functions, for example, refer to heat or mass transfer or reaction rate coefficients.

3.1.3 Model BFR

In many cases, the rate coefficients $k_{\ldots}(z,t)$ or $k'_{\ldots}(t)$ introduced in the correlations on level *BF* depend on the states $x(\cdot)$ themselves. Therefore, a constitutive model

$$\begin{aligned} k_{\ldots} &= r_{\ldots}(x, \nabla_z x, \ldots, \theta), \\ k'_{\ldots} &= r_{\ldots}(x, \ldots, \theta), \end{aligned} \tag{6}$$

relating the rate coefficients to the states, has to be selected on yet another decision level named *BFR* (cf. Fig. 2).

Mirroring this last model development step in incremental model identification, a model for the rate coefficients has to be identified. The model candidates, cf. Eq. (6), are assumed to only depend on the measured states, their spatial gradients and on *constant* parameters $q \in R^p$. If only a single candidate structure is considered, the parameters q can be computed from the estimated functions $k_{...}(z,t)$ or $k'_{...}(t)$ and the measured states x by solving a (typically nonlinear) algebraic regression problem. In general, however, a model discrimination problem has to be solved, where the most suitable model structure is determined from a set of candidates.

The cascaded decision making process in model development and model identification has been discussed for three levels which commonly occur in practice. However, model refinement can continue as long as the sub-models of the last model refinement step not only involve constant q as in Eqs. (4)–(6), but rather coefficient functions, which depend on state variables. While this is the decision of the modeller, it should be backed by experimental data and information deduced during incremental identification such as the confidence in the selected model structure and its parameters (Verheijen, 2003).

This structured modeling approach renders all the individual decisions completely transparent, i.e., the modeller is in full control of the model refinement process. The most important decision relates to the choice of the model structures for the flux expressions and the rate coefficient functions in Eqs. (4)–(6). These continuum models do not necessarily have to be based on molecular principles. Rather, any mathematical correlation can be selected to fix the dependency of a flux or a rate coefficient as a function of intensive quantities. A formal, semi-empirical but physically founded kinetic model may be chosen which at least to some extent reflects the molecular level phenomena. Examples include mass action kinetics in reaction modeling (Higham, 2008), Maxwell-Stefan theory of multi-component diffusion (Taylor, Krishna, 1993) or established activity coefficient models like the Wilson, NRTL or Uniquac models (Prausnitz et al., 2000). Alternatively, a purely mathematically motivated modeling approach could be used to correlate states with fluxes or rate coefficients in the sense of black-box modeling. Commonly used model structures include multivariate linear or polynomial models, neural networks, or vector machines among others (Hastie et al., 2003). This way, a *certain type of hybrid (or grey-box) model* (Psichogios and Ungar, 1992; Agarwal, 1997; Olivera, 2004) arises in a natural way by combining first principles models fixed on previous decision levels with an empirical model on the current decision level (Kahrs, Marquardt, 2008; Romijn et al., 2008; Kahrs et al., 2009).

3.2 Simultaneous model identification

IMI exploits the natural hierarchy in kinetic models of process systems. All the established approaches to model identification, however, neglect this inherent structure. The so-called simultaneous model identification (SMI) approaches always assume that the model structure is correct and consider only the fully specified model. In particular, the decisions on the balance envelope and the desired spatio-temporal resolution, the selection of the models for the flux expression *(BF)* and the phenomenological coefficients *(BFR)* are specified prior to adjusting the model response to the measured data by some kind of identification method. Since the sub-models are typically not known, suitable model structures are selected by the modeller based on prior knowledge, experience and intuition. Obviously, the complexity of the decision making process is enormous. The number of alternative model structures grows exponentially with the number of decision levels and number of kinetic phenomena occurring simultaneously in the real system.

Any decision on a sub-model will influence the predictive quality of the identified kinetic model. The model predictions are typically biased if the parameter estimation is based on a model containing structural error (Walter, Pronzato, 1997). The theoretically optimal properties of the maximum likelihood approach to parameter estimation (Bard, 1974) are lost, if structural model mismatch is present. More importantly, in case of biased predictions, it is difficult to identify which of the decisions on a certain sub-model contributed most to the error observed.

One way to tackle these problems in simultaneous identification is the enumeration of all the combinations of the candidate sub-model structures for each kinetic phenomenon. Such combinatorial aggregation inevitably results in a large number of model structures. The computational effort for parameter estimation grows very quickly and calls for high performance computing, even in case of spatially lumped models, to tackle the exhaustive search for the best model indicated by the maximum likelihood objective (Wahl et al., 2006). Even if such a brute force approach were adopted, initialization and convergence of the typically strongly nonlinear parameter estimation problems may be difficult since the (typically large number of) parameters of the overall model have to be estimated in one step (Cheng, Yuan, 1997). The lack of robustness of the computational methods may become prohibitive, in particular, in case of spatially distributed process models if they are nonlinear in the parameters (Karalashvili et al., 2011). Appropriate initial values can often not be found to result in reasonable convergence of an iterative parameter estimation algorithm.

3.3 Implementation of the identification methods

After outlining the key ideas of the SMI and IMI methods, some discussion on the requirements for the implementation as a prerequisite for their roll-out in practical applications is presented next.

The implementation of SMI is straightforward and can be based on a wealth of existing theoretical and computational tools. Implicitly, SMI assumes a *suitable experiment* and the *correct model structure* to be available. Then, the following steps have to be enacted:

SMI procedure

1. Make sure that all the model parameters are identifiable from the measurements (Walter, Pronzato, 1997). If necessary, employ local identifiability methods (Vajda et al, 1987). Select initial parameter values based on a priori knowledge and intuition.
2. Do initial experiments for selected experimental conditions guided by statistical design of experiments (Mason et al., 2003).
3. Estimate the unknown parameters (Bard, 1974; Schittkowski, 2002; Biegler, 2010), most favourably by a maximum likelihood approach to get unbiased estimates, using the available experimental data.
4. Assess the confidence of the estimated parameters and the predictive quality of the model (Bard, 1974; Walter, Pronzato, 1997).
5. Design optimal experiments *for parameter precision* (Walter, Pronzato, 1990; Pukelsheim, 2006; Franceschini, Macchietto, 2008) and run the experiment.
6. Reiterate the sequence of steps 3 to 5 until no improvement in parameter precision can be obtained.

A number of commercial or open-source tools (Buzzi-Ferraris, Manenti, 2009; Balsa-Canto, Banga, 2010) are available, which can be readily applied to reasonably complex models, in particular to models consisting of algebraic and/or ordinary differential equations. Though this procedure is well established, a number of pitfalls may still occur (Buzzi-Ferraris, Manenti, 2009), which render the application of SMI a challenge even under the most favourable assumptions. An analysis of the literature on applications shows that the identification of (bio-) chemical reaction kinetics has been of most interest to date.

If a set S of candidate model structures M_i has to be considered because the correct model structure is unknown, the SMI approach as outlined above cannot be applied without modification. If the *correct model structure M_c were included in the set of candidate models*, the above SMI procedure has to be modified as follows: Steps 1, 3 and 4 have to be carried out for all the candidate models in the set S. A decision on the correct model in the set should not be based on the results of step 4, i.e., the model with highest parameter confidence and the best predictive quality should not be selected, because the experiments carried out so far may not allow to distinguish between competing model candidates. An informed decision requires replacing step 5 by step 5', the optimal design of experiments *for model discrimination* (Walter, Pronzato, 1990; Pukelsheim, 2006; Michalik et al., 2010), to determine experiments, which allow distinguishing between the models with highest confidence. The designed experiments are executed, the parameters in the (so far) most appropriate model structure are estimated. Since the optimal design of experiments relies on initial parameters, which may be incorrect, step 3 and 5' have to be reiterated until the confidence in the most appropriate model structure in the candidate set cannot be improved and hence model M_c has been found. Then, steps 5, 3 and 4 are reiterated to determine the best possible parameters in the correct model structure.

Only little software support is available to the user for an optimal design of experiments for parameter precision (e.g. VPLAN, Körkel et al., 2004) and even less for model discrimination, which is required for a roll-out of the extended SMI procedure. Only few experimental studies have been reported which tackle model identification in the spirit of the extended SMI procedure.

Obviously, if the correct model structure is not known, it cannot be safely assumed that the correct model structure is part of the candidate set S; rather, the correct model, often comprising of a combination of many sub-models, is not known. In this likely case, SMI should be replaced by IMI, the strength of which is to find an appropriate model structure composed of many sub-models. IMI comprises the following steps:

IMI procedure[2]

1. Decide on a balance envelope, on the desired spatio-temporal resolution and on the extensive quantities to be balanced. Develop *model B* (cf. Fig. 2).
2. Decide on the type of measurements necessary to estimate the unknown fluxes in *model B*.
3. Run informative experiments (following, e.g., a space-filling experiment design (Brendel, Marquardt, 2008) and estimate the unknown fluxes $J_{\dots}(z,t)$ or $j_{\dots}(t)$ as a function of time and space coordinates using the measurements $x(z,t)$ or $x(t)$ and Eqs. (1)–(3). Use appropriate regularization techniques to control error amplification in the solution of this inverse problem (Reinsch, 1967; Engl et al., 1996; Huang, 2001).

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[2] Note, this IMI procedure is not precise, because its details depend on the type of model considered. The presented procedure is abstracted to roughly cover all types of models.

4. Analyse the state/flux data and define a set of candidate flux models, Eqs. (4), (5), with rate coefficient functions $k_{...}(z,t)$ or $k'_{...}(t)$ parameterized in time and space. Fit the rate coefficient functions $k_{...}(z,t)$ or $k'_{...}(t)$ of all candidate models to the state-flux data. Error-in-variables estimation (Britt, Luecke, 1975) should be used for favourable statistical properties, because both, the dependent fluxes as well as the measured states are subject to error. A constant rate coefficient is obviously a reasonable special case of such a parameterization.
5. Form *candidate models* BF_i constituting balances and (all or only a few promising) candidate flux models. Re-estimate the parameters in the rate coefficient functions $k_{...}(z,t)$ or $k'_{...}(t)$ in all the *candidate models* BF_i to reduce the unavoidable bias due to error propagation (Bardow, Marquardt, 2004; Karalashvili et al., 2010). Some kind of regularization of the estimation problem is required to enforce uniqueness of the estimation problem and to control error amplification in the estimates (Kirsch, 1996; Engl et al., 1997). Rank order the updated *candidate models* BF_i with respect to quality of fit using an appropriate statistical measure such as Akaike's information criterion (Akaike, 1973; Burnham, Anderson, 2002) or posterior probabilities (Stewart et al., 1998). In case of constant rate coefficients, continue with step 8 replacing models *BFR* by *BF*.
6. Analyse the state/rate-coefficient data and define a set of candidate rate coefficient models $r_{i,j}$, Eqs. (6), for promising *candidate models* BF_i. Make sure that the parameters $q_{i,j}$ in the candidate rate coefficient models $r_{i,j}$ are identifiable from the state/rate-coefficient data using identifiability analysis (Walter, Pronzato, 1997). Estimate the parameters $q_{i,j}$ in the rate coefficient models $r_{i,j}$ by means of an error-in-variables method (Britt, Luecke, 1975).
7. Form the candidate models $BFR_{i,j}$ by introducing the rate coefficient models $r_{i,j}$ in the models BF_i. Re-estimate the parameters $q_{i,j}$ in the *candidate models* $BFR_{i,j}$ to remove the unavoidable bias due to error propagation.
8. Design *optimal experiments for model discrimination* using the set of *candidate models* $BFR_{i,j}$ to identify the most suitable model structure. Execute the design experiments and re-estimate the parameters $q_{i,j}$ in the *candidate models* $BFR_{i,j}$ using the available experimental data. Re-iterate this step until the confidence in the most suitable model structure BFR_c in the candidate set cannot be improved. If no satisfactory model structure can be identified in the set of candidate models, the set has to be revised by revisiting all previous steps.
9. Design *optimal experiments for parameter precision* using model BFR_c. Run the experiment and estimate the parameters q_c in model BFR_c. Re-iterate this step until the confidence in the parameters cannot be improved. If no sat-

isfactory parameter confidence and prediction quality can be achieved, all previous steps have to be revisited.

A successful implementation of the incremental identification approach requires tailored ingredients such as

- high resolution (in-situ and non-invasive) measurement techniques which provide field data of states like species concentrations, temperature or velocities as a function of time and/or space coordinates;
- algorithms for model-free flux estimation by an inversion of the balance equations; a problem, which is closely related to input estimation problems in systems and control engineering (Hirschhorn, 1979) and to inverse problems (in particular inverse source problems) in applied mathematics (Engl et al., 1997);
- algorithms for efficient function estimation comprising an (ideally error-controlled) adaptive discretization of the unknown flux or rate coefficient functions in time and space coordinates (Brendel, Marquardt, 2009) and robust numerical methods for ill-conditioned, large-scale parameter estimation (Hanke, 1995);
- methodologies for the generation, assessment and selection of the most suitable model structures; and
- model-based methods for the optimal design of experiments (Walter, Pronzato, 1990; Pukelsheim, 2006), which should be adapted to the requirements of IMI.

A detailed discussion of all these areas is definitely beyond the scope of this work. Some more detail in the context of IMI has been given by Marquardt (2005). Some aspects are highlighted in the applications of IMI approach described in the following sections, where recent progress is exemplarily reported for selected kinetic modeling problems of chemical process systems. In particular, reaction kinetics modeling, multi-component diffusion in liquids, and energy transport in falling liquid films will be addressed.

4 Reaction kinetics

Mechanistic modeling comprising both, the identification of the most likely mechanism and the quantification of the kinetics of a chemical reaction system, is one of the most relevant and still not yet fully satisfactorily solved tasks in process systems modeling (Berger, 2001). More recently, systems biology (Klipp et al., 2005) has revived this classical problem in chemical engineering to identify mechanisms, stoichiometry and kinetics of metabolic and signal transduction pathways in living systems (Engl et al., 2009). Though this is the very same problem as in process systems modeling, it is more difficult to solve it successfully, because of three complicating facts: (i) there are severe restrictions to in-vivo measurements of metabolite concentrations with sufficient (spatio-temporal) resolution, (ii) the number of metabolites and reaction steps is often very large, and (iii) the qualitative behaviour of living systems changes with time giving rise to variable-structure models.

IMI has been elaborated in theoretical studies for a variety of reaction systems. Bardow and Marquardt (2004) investigate the fundamental properties of IMI for a very simple reaction kinetic problem to elucidate error propagation and to suggest counteractions. Brendel et al. (2006) work out the IMI procedure for homogenous multi-reaction systems comprising any number of irreversible or reversible reactions. These authors investigate which measurements are required to achieve complete identifiability. They show that the method typically scales linearly with the number of reactions because of the decoupling of the identification of the reaction rate models. The method is validated with a realistic simulation study. The computational effort can be reduced by two orders of magnitude compared to an established SMI approach. Michalik et al. (2007) extend IMI to fluid multi-phase reaction systems. These authors show for the first time, how the intrinsic reaction kinetics can be accessed without the usual masking effects due to interfacial mass transfer limitations. The method is illustrated with a simulated two-phase liquid-liquid reaction system of moderate complexity.

More recently, Amrhein et al. (2010) and Bhatt et al. (2010) have suggested an alternative decoupling method for single- and multi-phase multi-reaction systems, which is based on a linear transformation of the reactor model. The transformed model could be used for model identification in the spirit of the SMI procedure. Pros and cons of the decomposition approach of Brendel et al. (2006) and Michalik et al. (2007) and the one of Amrhein et al. (2010) and Bhatt et al. (2010) have been rigorously analysed and illustrated by means of a simulated case study (Bhatt et al., 2012).

Selected features of IMI are elucidated for this important class of identification problems as follows. *IMI.i* refers to step *i* of the IMI procedure worked out in Section 3.3.

4.1 Single-phase reaction systems

Reaction kinetic studies of reaction systems are often carried out in continuously or discontinuously operated stirred tank reactors or in differential flow-through reactors where the spatial dependency of concentrations and temperature can be safely neglected. Typically, the evolution of concentrations, temperatures and flow rates is observed over time. The case of homogeneous reactions in a single phase is considered in this section.

IMI.1-IMI.3: Reaction flux estimation. The material balances for the mole number n_i of the n_c chemical species i specialize Eqs. (2) and (3) to result in *model B*, i.e.,

$$\frac{dn_i(t)}{dt} = q(t)c_i^{in}(t) - q(t)c_i(t) + f_i(t), \quad c_i(t)V(t) = n_i(t), \quad i = 1,\dots,n_c\,. \tag{7}$$

The first two terms on the right hand side refer to the molar flow rates into and out of the reactor with known (or measured) molar flow rate $q(t)$ and inlet concentrations $c_i^{in}(t)$.[3] The last term represents the unknown reaction flux of species i, i.e. the molar amount of species i produced or consumed by all chemical reactions present. The measured concentrations $c_i(t)$ are converted into the extensive mole numbers $n_i(t)$ by multiplication with the known (or measured) reactor volume $V(t)$. It should be noted that the fluxes enter the balance equations linearly and the equations are decoupled for each species. All reaction fluxes $f_i(t)$ can thus be estimated individually by numerical differentiation of measured concentration data for each measured species from the material balances. This ill-posed inverse problem can successfully be solved by Tikhonov-Arsenin filtering (Tikhonov, Arsenin, 1977; Mhamdi, Marquardt, 1999) or smoothing splines (Huang, 2001; Bardow, Marquardt, 2004). Regularization parameter choice based on the L-curve (Hansen, O'Leary, 1993) or generalized cross-validation (Golub et al., 1979) has been shown to give reliable estimates.

IMI.4: Reaction rate models. The reactions fluxes refer to the total amount of a certain species produced or consumed in a reaction system. Since any chemical species i participates in more than one reaction j in a multi-reaction system, the

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[3] Note that we tacitly assume measurements, which are continuous in time to simplify the presentation. Obviously, real measurements are taken on a grid of discrete times. Hence, the equations may have to be interpreted accordingly.

reaction rates $r_{i,j}$ have to be determined from the reaction fluxes f_i, $i=1,\ldots n_c$, by solving the (usually non-square) linear system

$$f(t) = V(t)N^T r(t) \tag{8}$$

for $r(t)$ using an appropriate numerical method. The symbol $f(t)$ refers to the vector of n_c reaction fluxes, $r(t)$ to the vector of reaction rates of the n_r reactions in the reaction system, $V(t)$ to the reactor volume and N to the stoichiometric matrix of appropriate dimension. Often the reaction stoichiometry is unknown; then, target factor analysis (Bonvin, Rippin, 1990) can be used to determine the number of relevant reactions and to test candidate stoichiometries suggested by chemical research. If more than one of the conjectured stoichiometric matrices is found to be consistent with the state/flux data, different estimates of $r(t)$ are obtained in different scenarios to be followed in parallel in subsequent steps. The concentration/reaction-rate data are analyzed next to suggest a set of candidate reaction rate laws (or purely mathematical relations) which relate each of the reaction rates $r_j(t)$ with the (possibly n_c) concentrations $c(t)$ according to

$$r_j = m_{j,l}(c,\theta_{j,l}), \quad j = 1,\ldots n_r, \quad l \in \Sigma_j . \tag{9}$$

This model assumes isothermal and isobaric experiments, where the quantities $q_{j,l}$ are constants. A model selection and discrimination problem has to be solved subsequently for each of the reaction rates r_j based on the sets of model candidate S_j because the correct or at least best model structures are not known. These problems are, however, independent of each other. At first, the parameters $q_{j,l}$ in Eq. (9) are estimated from $r_j(t) / c(t)$ data by means of nonlinear algebraic regression (Bard, 1974; Walter, Pronzato, 1997). The quality of fit is evaluated by some means to assess whether the conjectured model structures (9) fit the data sufficiently well.

IMI.5: Reducing the bias and ranking the reaction model candidates. Eqs. (8) and (9) are now inserted into Eqs. (7) to form a complete reactor model. The parameters in the rate laws (9) are now re-estimated by a suitable dynamic parameter estimation method such as multiple shooting (Lohmann et al., 1992) or successive single shooting (Michalik et al., 2009). Obviously, only the models in the subsets $S_{j,p}$ of the sets S_j in Eq. (9) are considered which have been identified to fit the data reasonably well. Very fast convergence is obtained, i.e., often a single iteration is sufficient, because of the very good initial parameter estimates obtained in step *IMI.4*. This dynamic parameter estimation reduces the bias in the parameter estimates computed in step *IMI.4*. The model candidates can now be rank ordered, for example, by Akaike's information criterion (Akaike, 1973) for a first assessment of their relative predictive qualities.

IMI.6 and IMI.7: Rate coefficient models. In case of non-isothermal experiments, the quantities $q_{j,l}$ in the rate models (9) are functions of temperature T. In this case, $q_{j,l}$ can be replaced by $k'_{j,l}$, which has to be estimated first without specifying a rate coefficient model as in step *IMI.6*. Then, Eq. (9) is modified and a parameterized rate coefficient model, such as the Arrhenius law,

$$k'_{j,l} = \theta_{j,1} e^{\frac{\theta_{j,2}}{T}}, \quad r_j = k'_{j,l} m_{j,l}(c,\theta_{j,l}), \quad j = 1,\ldots n_r, \quad l \in \Sigma_j. \tag{10}$$

is introduced and the constant parameters $q_{j,1}$ and $q_{j,2}$ are estimated from the $k'_{j,l}$ *(t) / T(t)* data for every reaction *j* (see Brendel (2006) for details).

IMI.8 and IMI.9: Selecting the best reaction model. The identification of the reaction rate models may not immediately result in reliable model structures and parameters because of a lack of information content in the experimental data. Iterative improvement with optimally chosen experimental conditions should therefore be employed. Optimal experiments are designed first for model structure discrimination and then, after convergence, for parameter precision to yield the best model $m_{j,b}(c,q_{j,b})$ contained in the candidate sets $S_{j,p}$ for all $j=1,\ldots n_r$.

Experimental validation. The development of the IMI approach solely relied on theoretical considerations which were supported by simulation case studies to validate the method and investigate its properties. An experimental validation of IMI has been carried out (Michalik et al., 2007; Schmidt et al., 2009) for an enzymatic reaction, i.e., the regeneration of NAD^+ to *NADH*, a cofactor used in many industrial enzymatic reactions where it is reduced to NAD^+. The reaction takes place in aqueous solution using formic acid as a proton donor. There are two reactions of interest, the reversible regeneration reaction which forms *NADH* and CO_2 as a by-product, and an undesired irreversible decomposition of the product *NADH*. The experiments were carried out in a micro-cuvette reactor of *300 ml*, where the NADH concentration was measured with high accuracy and high resolution using UV/Vis spectroscopy at an excitation wavelength of *340 nm*. The application of IMI to this industrially relevant problem (Michalik et al. 2007) resulted in a reaction kinetic model with much better predictive quality compared to existing and widely used literature models (Schmidt et al., 2009).

4.2 Multi-phase reaction systems

The application of IMI to multi-phase reactions is of great practical interest, because it is extremely difficult to access the intrinsic kinetics of a chemical reaction, which is completely independent of mass transfer effects. Current practice in kinetic modeling of two-phase systems aims at experimental conditions where the chemical reaction is clearly rate-limiting and the effect of the (very fast) mass transfer between the phases can be safely neglected. Obviously, this strategy is quite restrictive and inevitably results in systematic errors in reaction kinetics due to mass transfer contributions. IMI can remedy this long-standing problem in a straightforward manner.

Let us assume isothermal experiments in a stirred tank reactor, which is operated in batch mode (e.g. no material is exchanged with the environment) at isothermal conditions. A liquid-liquid (or liquid-gas) reaction is carried out, where the reaction occurs in one of the phases, say *(a)*, only. The experiment is set up such that two well mixed segregated phases *(a)* and *(b)* occur where spatial dependencies of the state variables are negligible. This assumption can easily be implemented by means of appropriate mixing and stabilization of the interface. Concentrations $c_i^{(\mathrm{a})}(t)$ and $c_i^{(\mathrm{b})}(t)$ of the relevant species are assumed to be measured (for example by some kind of optical spectroscopy) in both phases. The material balances, specializing Eqs. (2) and (3), read as

$$V^{(a)}\frac{dc_i^{(a)}(t)}{dt} = j_i(t) + f_i(t), \qquad V^{(b)}\frac{dc_i^{(b)}(t)}{dt} = -j_i(t), \quad i = 1,\ldots n_c. \tag{11}$$

The volumes $V^{(a)}$ and $V^{(b)}$ of both phases are assumed constant and known for the sake of simplicity. The symbols $j_i(t)$ and $f_i(t)$ refer to the mass transfer rate of species from phase *(b)* to phase *(a)* and the reaction flux in phase *(a)*, respectively.

Steps *IMI.1* to *IMI.3* have to be slightly modified compared to the case of homogenous reaction systems discussed in Section 3.1. In particular, the balance of phase *(b)* (on the right in Eq. (11)) and the measurements of the concentrations $c_i^{(b)}(t)$ are used to estimate the mass transfer rates $j_i(t)$ first without specifying a mass transfer model. These estimated functions can be inserted into the balances of phase *(a)* (on the left in Eq. (11)) to estimate the reaction fluxes $f_i(t)$ without specifying any reaction rate model. The intrinsic reaction kinetics can easily be identified in the subsequent steps *IMI.4* to *IMI.9* from the concentration measurements $c_i^{(a)}(t)$ and the estimated reaction fluxes $f_i(t)$. Obviously, mass transfer models can be identified in the same manner, if the mass transfer rates and the concentration measurements in both phases $c_i^{(a)}(t)$ and $c_i^{(b)}(t)$ are used accordingly.

This basic idea has been worked out in detail by Michalik et al. (2009) and has been evaluated in a simulated case study of a fluid two-phase system. These authors show that the intrinsic reaction kinetics can indeed be identified at high precision. Work on an experimental validation of IMI for reaction kinetic modeling of fluid two-phase systems is in progress.

5 Multi-component diffusion in liquids

Despite extensive and lasting research efforts on diffusive transport, there is still a surprising lack of experimentally validated diffusion models, in particular for complex multi-component liquid mixtures (Bird, 2004). This is in stark contrast to the relevance of the quantitative representation of diffusion to support the design of technical equipment. For example, the interplay of multi-component diffusion and chemical reaction determines the selectivity towards the desired product in industrial reactors. In particular, in micro-reactors, where mixing is only due to diffusion because of the laminar flow conditions, the complex mixing and diffusion patterns are decisive for reactor performance (Bothe et al., 2010).

The application of IMI to diffusive mass transport in liquid systems is featured in this section. It is based on a recently introduced Raman diffusion experiment (Bardow et al., 2003, 2006), where the inter-diffusion of two initially layered liquid mixtures is observed by Raman spectroscopy under isothermal conditions. Concentration profiles $c_i(z,t)$ of all species are measured on a line in the axis of a tailored cuvette at high resolution in time and space. The IMI procedure outlined in Section 3.3 is instantiated for this particular case as follows.

IMI.1-IMI.3: Diffusive flux estimation. The diffusion process is assumed to be well-described by a spatially one-dimensional model. The adaption of the general balance equation (1) results in *model B*, a system of mass balance equations for all species *i:*

$$\frac{\partial c_i(z,t)}{\partial t} = -\frac{\partial J_i(z,t)}{\partial z}, \quad \left.\frac{\partial c_i(z,t)}{\partial z}\right|_{z=0,z=l} = 0, \quad i = 1,\ldots,n_c - 1. \tag{12}$$

The molar concentrations $c_i(z,t)$ are determined from Raman spectra by means of indirect hard modeling (Alsmeyer et al., 2004, Kriesten et al., 2008) at high accuracy. The n_c-1 independent diffusive fluxes $J_i(z,t)$ are unknown and have to inferred from Eqs. (12) by an inversion of each of the evolution equations using the measured concentration profiles. In particular, the measurements have to be differentiated with respect to time t first using smooting splines (Reinsch, 1967) and appropriate regularization (Engl et al., 1997), and the result has to be integrated over the spatial coordinate z next to render the diffusive fluxes $J_i(z,t), i=1,\ldots n_c-1$, without specifying a diffusion model. Such a strategy has been followed for binary and ternary systems by Bardow et al. (2003, 2006). Again, there is only a linear increase in complexity due to the natural decoupling of the multi-component material balances (12).

IMI.4: Diffusion flux models. One or more flux models have to be introduced next. The generalized Fick model (or the Maxwell-Stefan model, which is not further considered here) is a suitable choice. In case of binary mixtures, the Fick diffusion coefficient $D_{1,2}(z,t)$ can be determined at any point in time and space by solving the flux equation

$$J_1(z,t) = -D_{1,2}(z,t)\frac{\partial c_1(z,t)}{\partial z} \tag{13}$$

for $D_{1,2}(z,t)$. This strategy does not carry over directly to multi-component mixtures because the diffusive flux is a linear combination of all concentration gradients:

$$J_i(z,t) = -\sum_{j=1}^{n_C-1} D_{i,j}(z,t)\frac{\partial c_j(z,t)}{\partial z}, \quad i = 1,\ldots n_c - 1. \tag{14}$$

Rather, the n_c-1 diffusion coefficients have to be parameterized somehow. For example, some approximating spatio-temporal function could be chosen to formulate a least-squares problem which determines the diffusion coefficients $D_{i,j}(z,t)$ as function of time and space coordinates. Alternatively, a physically based parameterization (e.g., a diffusion coefficient model) could be chosen to lump *IMI.4* and *IMI.6* and eliminate *IMI.5*.

IMI.5: Reducing the bias. The *model BF* can be formed by introducing Eqs. (14) into Eqs. (13). The diffusion coefficient functions can be re-estimated using the results of the last step *IMI.4* as initial values of the parameter estimation problem to reduce the bias due to error propagation.

IMI.6 and IMI.7: Diffusion coefficient models. Diffusion coefficient models can now be chosen to correlate the estimated diffusion coefficient data with the measured concentrations:

$$D_{i,j} = m_{i,j,l}(c,\theta_{j,l}), \quad i,j = 1,\dots n_c - 1, \quad l \in \Sigma_{i,j}. \tag{15}$$

Again, a model selection problem has to be solved. The parameters $q_{j,l}$ are identified by error-in-variables estimation (Britt, Luecke, 1975). The bias can be removed by inserting Eq. (15) into Eqs. (14) and the result into Eq. (12) and re-estimating the parameters. The models can be ranked with respect to model quality by some statistical measure (Burnham, Anderson, 2002; Stewart et al., 1998).

IMI.8 and IMI.9: Selecting the best diffusion model. To remedy the possible lack of information content in the experimental data an iterative improvement with optimally chosen experimental conditions should finally be employed to yield the best diffusion models $D_{i,j}$.

Experimental validation. The suggested strategy has been validated in a number of experimental studies including the determination of binary and ternary Fick diffusion coefficients with a very low number of Raman experiments (Bardow et al., 2003, 2006) and the identification of the full concentration dependency of the binary Fick diffusion coefficient by means of a single Raman inter-diffusion experiment (Bardow et al., 2005) and two additional NMR self-diffusion experiments at infinite dilution to improve accuracy (Kriesten et al., 2009).

6 Energy transport in falling liquid films

The applicability of IMI to relevant and challenging problems has been demonstrated in the two previous sections. Still, the complexity tackled has been moderate, since three-dimensional (3D), transient transport and reaction problems in complex spatial geometries have not yet been treated. Such problems are relevant not only in chemical process systems, but in many other areas of science and engineering. As a first step towards the application of IMI to general 3D transient transport and reaction problems the identification of a transport coefficient function in the energy equation of a model of a wavy falling film has been chosen (Karalashvili et al., 2008, 2011).

Falling liquid films are widely used in chemical engineering, e.g., to implement coolers, evaporators, absorbers or chemical reactors, where the wavy surface patterns are exploited to intensify heat and mass transfer between the liquid film and the surrounding gas. Even the dynamics of heated falling films of a single chemical species is complex and has been the subject of intensive research (e.g., Trevelyan et al., 2007; Meza, Balakotaiah, 2008). Direct numerical simulation of the free-surface, mixed initial-boundary problem involving the continuity, the momentum and the energy equations is very involved and has not yet been reported to the author's knowledge. Even if it were possible, the computational complexity would prevent its application for the design of technical equipment. As an alternative, Wilke (1962) suggested a long time ago to approximate the complex spatial domain of the wavy liquid film by a flat-film geometry and to introduce a so-called *effective transport coefficient* which has to account for the wave-induced backmixing present in the wavy film (Adomeit, Renz, 2000). Yet, there are no accepted and reasonably general models available, which correlate the effective transport coefficient with the velocity and temperature fields in the falling film. The IMI procedure seems to be a promising starting point to tackle this long-standing problem by the sequence of steps outlined in Section 3.3 as follows.

IMI.1-IMI.3: Diffusive energy flux estimation. The energy transport in a 3D, transient, flat falling film can be represented by the energy equation, which can be reformulated for incompressible fluids (with constant density ρ) to result in

$$\rho \frac{\partial u}{\partial t} = -\rho w \cdot \nabla u - \nabla \cdot J_u \tag{16}$$

with appropriate initial and boundary conditions. The velocity field *w(z,t)* is assumed to be known (either measured or computed from a possibly approximate solution of the Navier-Stokes equations), while the internal energy *u(z,t)* (or rather the temperature *T(z,t)*) is assumed to be measured at reasonable spatio-temporal resolution. This *model B* can be refined by decomposing the diffusive energy flux $J_u(z,t)$ into a known molecular and an unknown *wave-induced* term. This reformulation results finally in

$$\frac{\partial T(z,t)}{\partial t} + w(z,t) \cdot \nabla T(z,t) - \nabla \cdot \left[a_{mol}(z,t) \nabla T(z,t) \right] = F_{wavy}(z,t) \tag{17}$$

with the known molecular transport coefficient $a_{mol}(z,t)$ and the unknown wavy contribution to the energy flux $F_{wavy}(z,t)$. This flux contribution can be reconstructed from temperature field data by solving a source inverse problem, which is linear in the unkown $F_{wavy}(z,t)$ by an appropriate regularized numerical method (Karalashvili et al., 2008).

IMI.4: Wavy energy flux model. A reasonable model for the wavy contribution to the energy flux is motivated by Fourier's law. Hence, the flux $F_{wavy}(z,t)$ in Eq. (17) can be related to wavy transport coefficient $a_{wavy}(z,t)$ by the ansatz

$$F_{wavy}(z,t) = -\nabla \cdot J_{u,wavy}(z,t) = -\nabla \cdot (a_{wavy}(z,t)\nabla T(z,t)). \tag{18}$$

Note that the effective transport coefficient is defined as the sum of the molecular and the wavy transport coefficients, i.e., $a_{eff}=a_{mol}+a_{wavy}$. In order to estimate $a_{wavy}(z,t)$, a (nonlinear) coefficient inverse problem in the spatial domain has to be solved for any point in time t (Karalashvili et al., 2008).

IMI.5: Reducing the bias. The *model BF* is formed by introducing Eq. (18) into Eq. (17). The resulting equation is used to re-estimate the wavy coefficient $a_{wavy}(z,t)$, starting from the estimate in step *IMI.4* as initial values (Karalashvili et al., 2011).

IMI.6 and IMI.7: Models for the wavy energy transport coefficient. A set of algebraic models is introduced to parameterize the transport coefficients in time and space by an appropriate model structure:

$$a_{wavy} = m_{wavy,l}(z,t,\theta_{j,l}), \quad l \in \Sigma_j. \tag{19}$$

This set is the starting point for the identification of a suitable parametric model, which properly relates the transport coefficient with velocity and temperature and possibly their gradients. The bias can again be removed by first inserting Eq. (19) into Eqs. (18) and the result into Eq. (17) and next re-estimating the parameters prior to a ranking of the models with respect to model quality (Karalashvili et al., 2011).

IMI.8 and IMI.9: Selecting the best transport coefficient model. Optimal design of experiments should finally be employed to obtain most informative measurements to finally identify the best model for $a_{wavy}(z,t)$ (Karalashvili, Marquardt, 2010).

Experimental validation has not yet been possible. For one, the development of this variant of IMI has not yet been completed. Furthermore, high-resolution measurements of film thickness, temperature and velocity fields are mandatory. Optical techniques are under investigation in collaborating research groups (Schagen et al., 2006).

7 Concluding discussion

The exemplary applications of IMI as part of the MEXA work process section not only demonstrate its versatility but also its distinct advantages compared to established SMI methods (Bardow and Marquardt, 2004).

7.1 Comparing IMI to SMI

In contrast to SMI, the IMI approach explicitly accounts for the fact that often an appropriate structure of one or more sub-models in a complex process systems model is uncertain. The selection of the most suitable sub-model structure has to be considered an integral part of the model identification process. Since model identification cannot be reduced to estimating the parameters from most informative experiments in a given, identifiable model structure, the model (structure) identification process has to be fully transparent to the modeller. Partial prior knowledge regarding model structure can easily be incorporated. Missing sub-models are derived either from experimental or from inferred input-output data in the previous estimation step supported by theoretical investigations on a finer (often the molecular) scale. Any decision on the model structure relates to a single physico-chemical phenomenon and thus reduces ambiguity. Identifiability can be assessed more easily on the level of the sub-model. This way, the IMI strategy supports the discovery of novel model structures which are consistent with the available experimental data.

The decomposition strategy of IMI is also very favourable from a computational perspective. It drastically reduces computational load, because it breaks the curse of dimensionality due to the combinatorial nature of the decision making problem related to sub-model selection. IMI avoids this problem, because the decision making is integrated into the decomposition strategy and systematically exploits knowledge acquired during the previous identification steps. Furthermore, the computational effort is reduced, because the solution of a *strongly nonlinear inverse problem* involving (partial) differential-algebraic equations is replaced by a sequence of less complex, often *linear inverse problems* and a few *algebraic regression problems*. This divide-and-conquer approach also improves the robustness of the numerical algorithms and their sensitivity towards the choice of initial estimates. Last but not least, the decomposition strategy facilitates quasi-global parameter estimation in those cases, where all but the last nonlinear regression problem are convex. A general quasi-global deterministic solution strategy is worked out by Michalik et al. (2009) for identification problems involving differential-algebraic problems.

The computational advantages of IMI become decisive in case of the identification of complex 3D transport and reaction models on complex spatial domains. Our case studies indicate that SMI is computationally often intractable, while IMI renders the estimation problems feasible or at least reduces the load by orders of magnitude. Identifiability analysis and optimal design of experiments are key to success in case of 3D transport and reaction problems, because sufficient excitation in time and space can typically not be achieved intuitively.

Error propagation is unavoidable in IMI, because any estimation error will impair the estimation quality in the following steps. The resulting bias can, however, be easily removed by a final correction step, where a parameter estimation problem is solved for the best aggregated model(s) using very good initial parameter values. Convergence is typically achieved in one or very few iterations.

Both, IMI and SMI are not successful, if the information content of the measurements is insufficient. However, identifiability problems can be discovered and remedied more easily in IMI compared to SMI. Then, either the model has to be simplified (to result in less unknown model parameters) or additional sensors have to be installed in the experiment.

7.2 Previous work related to IMI

IMI is not the first multi-step approach to model identification. Similar ideas have been employed rather intuitively before in (bio-)chemical engineering. The sequence of flux estimation and parameter regression is, e.g., commonly employed in reaction kinetics as the so-called differential method (Kittrell, 1970; Hosten, 1979; Froment, Bischof, 1990). Markus et al. (1981) seem to be the first suggesting a simple version of IMI to the identification of enzyme kinetics models. Bastin and Dochain (1990) have introduced model-free reaction flux estimation as part of a state estimation strategy with applications to bioreactors. More recently, a two-step approach has been applied for the hybrid modeling of fermentation processes (Tholudur, Ramirez, 1999; van Lith et al., 2002), where reaction fluxes are estimated first from measured data and neural networks or fuzzy models are employed to correlate the fluxes with the measurements. The crystal growth rate in mixed-suspension crystallization has been estimated directly from the population balance equations (Mahoney et al., 2002).

The idea has not only been around in the chemical engineering community. For example, Timmer et al. (2000) and Voss et al. (2003) use the two-step approach of flux estimation and rate law fitting in the modeling of nonlinear electrical circuits. Ramsay and co-workers used a similar method, called functional data analysis, in quantitative psychology to model lip motion (Ramsay, 1996) and handwriting (Ramsay, 2000), and in production planning (Ramsay, Ramsay, 2002). These diverse applications and our own experience lead us to the expectation that IMI can be rolled out and tailored to many domains in engineering and the sciences.

7.3 Useful models at minimal effort

IMI is considered an integral part of the MEXA methodology. Our experience in a wide area of applications shows that a sensible integration of modeling and experimentation is indispensible if the mathematical model is supposed to extrapolate with adequate accuracy well beyond the region where model identification has been carried out. Such good extrapolation provides at least an indication that the physico-chemical mechanisms underlying the observed system behavior have been captured by the model to a certain extent.

A coordinated design of the model structure and the experiment as advocated in the MEXA work process is most appropriate for several reasons (cf. Bard, 1974; Iyengar and Rao, 1983; Kittrell, 1990; Beck, Woodbury, 1998). On the one hand, an overly detailed model is often not identifiable even if perfect measurements of all the state variables were available (cf. Quaiser and Mönnigmann (2009) for an example from systems biology). Hence, any model should only cover a level of detail, which facilitates an experimental investigation of model validity. On the other hand, an overly simplified model does often not reflect real behaviour satisfactorily. For example, equilibrium tray models in distillation assume phase equilibrium rather than accounting for the mass transfer resistance between the liquid and vapour phases. Though this model is still widely used in industrial practice, it has been shown to be inconsistent with basic physical principles, since it does not reflect the cross-effects of multi-component diffusion (Taylor, Krishna, 1993). Such a coordinated design of experiment and models is closely related to the requirement of refining a model only based on experimental evidence (Markus et al., 1981). In particular, if a model is able to predict the accessible observations on the associated real system sufficiently well, its further refinement cannot be justified because it reduces the level of confidence in the model.

The identification of *useful models at minimal effort* requires a multi-disciplinary team effort. Experts in high-resolution measurement techniques, in the application domain of interest, in numerical analysis and in modeling methodologies have to join forces to leverage the very high effort of model identification. Best-practices and suitable software environments, tailored to a certain application, such as reaction kinetics identification seem to be indispensible to roll out the MEXA framework into routine application.

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