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On Parameter Interpretability of Phenomenological-Based Semiphysical Models

Laura Lema-Perez^{a,*}, Rafael Muñoz-Tamayo^b, Jose Garcia-Tirado^c, Hernan Alvarez^a

^a*Universidad Nacional de Colombia, Facultad de Minas, Escuela de Procesos y Energía. Kalman research group, Cra 80 No 65-223, 050041, Medellín - Colombia*

^b*UMR Modélisation Systémique Appliquée aux Ruminants, INRA, AgroParisTech, Université Paris-Saclay, 75005, Paris, France*

^c*Center for Diabetes Technology, University of Virginia, Charlottesville, VA.*

Abstract

Empirical and phenomenological based models are used to represent biological and physiological processes. Phenomenological models are derived from the knowledge of the mechanisms that underlie the behaviour of the system under study, while empirical models are derived from analysis of data to quantify relationships between variables of interest. For studying biological systems, the phenomenological modeling approach offers the great advantage of having a structure with variables and parameters with physical meaning that enhance the interpretability of the model and its further used for decision making. The interpretability property of models, however, remains a vague concept. In this study, we tackled the interpretability property for parameters of phenomenological-based models. To our knowledge, this property has not been deeply discussed, perhaps by the implicit assumption that interpretability is inherent to the phenomenological-based models. We propose a conceptual framework to address the parameter interpretability and its implications for parameter identifiability. We use as battle horse a simple but relevant model representing the enzymatic degradation of β -casein by a *Lactococcus lactis* bacterium.

*Corresponding author
URL: llemap@unal.edu.co (Laura Lema-Perez)

Keywords: Biological systems, identifiability, mechanistic models, parameter interpretability, phenomenological based semi-physical model (PBSM)

1 1. Introduction

2 How can we assess the capability of a mathematical model to provide mech-
3 anistic insight on the system under study? That is, how the mathematical
4 structure of the model translates and captures the knowledge of the phenomena
5 taking place in the system? To what extent can we interpret mechanistically our
6 model? In biotechnology, biology, and biomedical fields two main approaches ex-
7 ist to model processes of interest, namely empirical and phenomenological based
8 modeling. Empirical based models are derived from data, while phenomenolog-
9 ical based models are derived from knowledge about the process. In biomedical
10 fields, phenomenological based models are more relevant than empirical based
11 models since, in addition to prediction, their parameters and variables provide
12 information that can be used to perform diagnosis, discriminate clinical risk
13 groups and guide treatment for stratifying patients by disease severity [1, 2]. In
14 spite of this, in the fields mentioned before many models have been developed
15 from an empirical point of view by using black box modeling approaches like
16 machine learning and fuzzy models. Machine learning models, for example, are
17 increasingly used in the field of medicine and healthcare but there is still an
18 inability by humans to understand how those models work and what meaning
19 their parameters have. Some approaches have been proposed to improving the
20 level of explanation and interpretability of such empirical models, that is to
21 open the black box [3]. The deployment of the above mentioned approaches en-
22 counters its first hurdle by the difficulty of formalising the definition of central
23 concepts such as transparency, explanation, and interpretability. In the present
24 work, we focus on the interpretability concept but applied to phenomenological-
25 based models. Many studies propose interpretability as a means to engender
26 trust in empirical-based models and to reach features as close as possible to
27 humans [1, 4, 5, 6, 7] regarding decision making. In this context, Caruana, R.

28 et al. [1] evaluated a method for rule-based learning [8] and applied general-
29 ized additive models [2, 9, 10] to real healthcare problems to get *intelligible*
30 and accurate models, in order to predict risk prior to hospitalizations, to have
31 a more informed decision about hospitalization, and to reduce healthcare cost
32 by reducing hospital admissions [1]. In the same line, Lou et al. [9, 10] call
33 *intelligible* models to those models that can be easily interpreted by users. For
34 decision models, the interpretability concept has been ascribed to (i) the ability
35 of making decisions as close as a human being will do [11, 12], and (ii) the ability
36 of being understood [11, 13]. Since, decision making is favored by the under-
37 standing of how the model works, optimal decision-based models are those that
38 provide a trade-off between the predictive accuracy and interpretability [14].

39 Model interpretability is a term used in various works but without an explicit
40 definition [11, 15]. The meaning of that term is not direct because the model
41 as a whole is a complex piece of knowledge. Therefore, the model interpretabil-
42 ity, scarcely will be an on-off property, i.e, a model is or is not interpretable.
43 To grade the model interpretability will be equivalent to establish a scale of
44 interpretability. Obviously, that scale requires a metric to generate the value
45 of interpretability for a given model. That metric is the major problem to
46 establishing an interpretability scale. For example, two models, one with 30
47 parameters and the other with only 3 parameters, but both has only one of
48 their parameters without interpretability. If an on-off approach is maintained,
49 both models are not interpretable. If an interpretability index (*II*) is staed as:
50 $II = 1 - \frac{NP_{NoI}}{N_{TotP}}$, with NP_{NoI} number of non-interpretable parameter and N_{TotP}
51 the total number of parameters, the *II* for first model will be $1 - \frac{1}{30} = 0.9666$
52 and for the second one will be $1 - \frac{1}{3} = 0.6666$. Does this proposed *II* give useful
53 information about model size or complexity? Due to this unsolved item, in the
54 current work the interpretability will be only evaluated in terms of individual
55 parameters. Interpretability of model parameters is the result of multiple fac-
56 tors including the level of detail or specification [16], that is its granularity [17].
57 Due to the lacking of formalism about interpretability like a property of the
58 parameters in a model, there is no consensus about quantifying or measuring

59 such a property. The approach we want to elaborate in this article consists in
60 referring the interpretability of a model to its parameters and the degree by
61 which those parameters have physical meaning. We focus on Phenomenological
62 Based Semi-physical Models (PBSMs) [18], of which, to the best of our knowl-
63 edge, the concept of interpretability has not been deeply discussed, perhaps by
64 the implicit assumption that interpretability is inherent to the PBSM since they
65 are derived from a phenomenological representation of the system under study.
66 In this work, we propose a conceptual framework that can facilitate the incor-
67 poration of interpretability for model construction. We use as battle horse a
68 simple model to elaborate our developments. The paper is organized as follows.
69 In Section 2, we present a summary of the steps of a modeling methodology
70 proposed by [19] to build PBSMs. In Section 3, a conceptual framework for
71 interpretability analysis is set using a simple mathematical model of the dy-
72 namics of enzymatic hydrolysis of β -casein by a *Lactococcus lactis* bacterium.
73 Finally, we discuss in Section 4 the potential links between interpretability and
74 identifiability. Some concluding remarks are provided in Section 5.

75 **2. The process of PBSM construction**

76 The construction of a model may be linked to a form of art. This subjec-
77 tive character explain the existence of several methodologies for building PB-
78 SMs [20, 21, 22, 23, 24, 25]. In our group (KALMAN, Universidad Nacional de
79 Colombia), several studies have been developed [19, 26] to propose the following
80 methodology, described by 10 steps, which are summarized here in the interest
81 of completeness.

82
83 **1. Process description and model aim:** a verbal description of the pro-
84 cess taking place is performed including a process flow diagram as graph-
85 ical representation. Also, the model aim is set by the question that is
86 expected to be answered by the model.

- 87 **2. Model hypothesis and level of detail:** a hypothesis or analogy about
88 the behavior of the real process is proposed. Although the present method-
89 ology was originally intended for process engineering systems, it can be
90 extended to any type of process by mean of a model hypothesis. A model
91 hypothesis is a feasible analogy of the unknown phenomena in terms of
92 known and well studied phenomena. If the modeled process is located in a
93 specific area of the engineering in which the phenomena of the process are
94 known, the hypothesis is the description of those phenomena and an anal-
95 ogy is not necessary. Otherwise, the process must be related to a known
96 process, an analogy is required, and a set of assumptions is fixed. The
97 level of detail is determined by the model objective, that is, the question
98 that will be solved by the model.
- 99 **3. Definition of the process systems:** a process system is an abstraction
100 of a part of the process under study [22]. Each process system (PS) is
101 a partition of the real process, and this partition should be as real as
102 possible, that is, physical distinctions, changes in phases or characteristics
103 showing spatial variations in the process of interest.
- 104 **4. Application of the conservation law:** the conservation law is applied
105 to every PS defined in step 3. Typically, mass, energy, and momentum are
106 mainly accounted for. The equations obtained are described by either a
107 set of ordinary differential equations in lumped models or a set of partial
108 differential equations in distributed models; they form the basic structure
109 of the model.
- 110 **5. Determination of the basic structure of the model:** after applying
111 the conservation principle, select the set of equations needed to describe
112 the model objective. Discard those equations with trivial information.
- 113 **6. Definition of the variables, structural parameters and constants:**
114 make a list of variables, structural parameters, and constants. Variables
115 are quantities whose values result from the solution of the model equations
116 forming the basic structure. Parameters are values that need to be defined
117 beforehand to solve the model. They can be known values or must be

118 identified. Finally, the constants are fixed values either because of its
119 universality (*e.g.*, the gravity constant) or because of the modeler choice
120 (*e.g.*, setting a parameter with a known value from literature).

121 **7. Definition of constitutive and assessment equations and func-**
122 **tional parameters:** constitutive and assessment equations are proposed

123 to calculate the largest number of unknown parameters of each process
124 system. The set of constitutive and assessment equations are selected
125 according to the modeler knowledge and criteria.

126 **8. Verification of the degrees of freedom (DoF):** the DoF are the dif-
127 ference between the number of unknowns and the number of equations.

128 **9. Construction of the computational model:** the solution of the math-
129 ematical model is carried out by a computational program able to solve
130 the set of differential and algebraic equations forming the model.

131 **10. Model validation:** verification of the model's domain of validity with
132 respect to available experimental data or other validated models.

133 **3. Setting a conceptual framework for interpretability analysis**

134 In this section, we propose a conceptual framework for parameter inter-
135 pretability analysis. The concepts that constitute the proposed framework to
136 analyse parameter interpretability are defined and summarized in Table 1. For
137 the sake of clarity, the conceptual framework is studied using a simple mathe-
138 matical model that describes the dynamics of enzymatic hydrolysis of β -casein
139 by a *Lactococcus lactis* bacterium in a batch system [27]. The **basic structure**
140 of the model is obtained from applying a component mass balance, which results
141 in the following unique differential equation:

$$\frac{dx}{dt} = -r(\cdot) \quad (1)$$

142 where x (in μM) is the concentration of the substrate and $r(\cdot)$ ($\mu\text{M}/\text{min}$)
143 is the reaction rate, using the symbol (\cdot) to indicate the dependency of this
144 structural parameter with respect to time and any other variable or parameter

145 of the model. It is worth to point out that global mass balance is worthless
146 in this type of processes since no continuous inflow or outflow occurs. From
147 Table 1, x is the **variable** whose dynamic trajectory is obtained by solving the
148 model and $r(\cdot)$ is the unique **structural parameter**. Note that at this level of
149 detail, the mathematical equation that represent $r(\cdot)$ is not yet defined. This
150 fact suggests that for this example, Equation (1) is a unique representation of
151 the phenomena of interest (*i.e.*, the hydrolysis of β -casein).

152

153 The mathematical definition of the structural parameter $r(\cdot)$ is the key el-
154 ement for the construction of the complete **model structure**, that is, for the
155 set of equations that define the model in its basic and extended form. Multiple
156 mathematical functions exist to define $r(\cdot)$ and describe the hydrolysis rate of
157 the intact β -casein. In the study here analyzed [27], the authors evaluate four
158 kinetic candidate functions to determine the best function for $r(\cdot)$ parameter in
159 terms of the goodness of fit:

- 160 • First-order kinetics:

$$r(\cdot) = k_1 E x \quad (2)$$

- 161 • n th-order kinetics:

$$r(\cdot) = k_n E x^n \quad (3)$$

- 162 • Michaelis-Menten kinetics:

$$r(\cdot) = k_c E \frac{x}{K_m + x} \quad (4)$$

- 163 • Competitive inhibition kinetics:

$$r(\cdot) = k_c E \frac{x}{K_m(1 + \frac{I}{K_i}) + x} \quad (5)$$

164 with $I = x_0 - x$. This expression can be further manipulated to reduce
165 the number of its parameters as:

$$r(\cdot) = b_1 E \frac{x}{b_2 - x} \quad (6)$$

166 with

$$b_1 = \frac{k_c K_i}{K_m - K_i} \quad (7)$$

167

$$b_2 = \frac{K_m(K_i + x_0)}{K_m - K_i} \quad (8)$$

168 where E is the enzyme concentration, measured in optical density units
169 (OD_{600}). The parameter k_1 ($1/OD_{600} \text{ min}$) is the hydrolysis rate constant for
170 the first-order kinetics, and k_n ($1/\mu M^{n-1} OD_{600} \text{ min}$) is the rate constant for
171 the kinetics of order n . For the Michaelis-Menten equation, k_c ($\mu M/OD_{600} \text{ min}$)
172 denotes the catalytic rate constant and K_m (μM) the substrate affinity con-
173 stant. For the inhibition kinetics, K_i (μM) is the inhibition constant. The
174 concentration of the inhibitor I (μM) is considered to be equal to the concen-
175 tration of β -casein that has been hydrolyzed ($x_0 - x$), with x_0 the initial protein
176 concentration.

177

178 It is up to the modeler to decide which kinetic function to use for represent-
179 ing the hydrolysis rate of β -casein. Once, the kinetic function is defined by a
180 new equation in addition to the basic structure, we obtain the **extended struc-**
181 **ture** of the model. The selected kinetic function is a **constitutive equation**
182 of the model that allows to determine $r(\cdot)$. For example, if we select the first-
183 order kinetic function $r(\cdot) = k_1 E x$, we say that $r(\cdot)$ is a **structural coupled**
184 **parameter** that depends on the **variable** x and two **functional parameters**:
185 k_1 and E . In this case, both functional parameters have physical meaning and
186 are thus considered to be **interpretable**. While, the enzyme concentration E
187 is a known numerical value imposed by the experimental protocol, k_1 is a rate
188 constant that needs to be determined *via* parameter estimation.

189

190 Following the case when $r(\cdot)$ is specified by the first-order kinetic rate as in
191 in (2)), let's analyze the parameter interpretability (the analysis also applies to
192 other candidate kinetic functions, bearing in mind that the Michaelis-Menten

193 equation is derived from a biological hypothesis on the enzyme action and thus
194 its parameters have a stronger level of interpretability than for instance those of
195 the kinetic of order n). By analyzing different experimental conditions, it was
196 found that the hydrolysis rate of β -casein was dependent of the initial protein
197 concentration x_0 [27]. That is, the kinetic rate was slower at higher initial pro-
198 tein concentrations. To account for the dependency of the kinetic rate on the
199 initial β -casein concentration, the authors performed a regression analysis with
200 the estimated parameter values obtained for each experimental condition. After
201 regression, the parameter k_1 was further expressed as a power function of the
202 initial β -casein concentration

203

$$k_1 = \frac{c_1}{x_0^{m_1}} \quad (9)$$

204 Equation (9) is referred to as a **constitutive equation**, defined by two new
205 **functional parameters**: c_1 and m_1 . These **scalar parameters** are numeri-
206 cal values identified by regression analysis. Table 2 shows a classification of the
207 components of the β -casein model according to the conceptual framework pre-
208 sented in Table 1 and considering that $r(\cdot)$ is defined by the first-order kinetic
209 rate in Equation (2). It is important to note that for the other kinetics options
210 (Equations (3) - (5)) this classification is also applicable. That is, the basic
211 structure or zero specification level is preserved, but the extended structure
212 changes according to the chosen kinetic constitutive equation. The extended
213 structure begins with the first specification level while the basic structure is the
214 zero specification level and it is the only one with inherent interpretability in a
215 PBSM.

216

217 With respect to the **parameter interpretability** of this simple model, it
218 can be said that the **structural parameter** $r(\cdot)$ has **general interpretability**
219 because in the the specific scientific domain of chemical and process engineering,
220 the symbol $r(\cdot)$ denotes a reaction rate. The reaction rate determines the dy-

221 namics at which reactants are converted into products, *i.e.*, it is the number of
222 moles of substance reacting by time unit within the reaction. The **functional**
223 **parameter** k_1 has **contextualized interpretability** and refers to the kinetic
224 rate constant derived from the assumption that the hydrolysis rate follows a
225 first-order kinetics. The **functional parameter** E has also **contextualized**
226 **interpretability** representing the concentration of the enzyme. Contextualized
227 means that these symbols, k_1 and E , in other context can be used for repre-
228 senting another physical properties of the process.

229
230 When k_1 is further defined by the constitutive equation (9) with the scalar
231 functional parameters c_1 and m_1 , they are **not interpretable**, since c_1 and m_1
232 are empirical parameters without physical meaning. However, the parameter k_1
233 is still interpretable in spite of being expressed as function of non interpretable
234 parameters. The interpretability of a parameter is not dependent on the con-
235 stitutive equation that defines it in a lower specification level.

236
237 In this example, we can appreciate the peculiarity of the basic structure
238 of a model and the dependency on the modeler choices to define the extended
239 structure. One basic structure can lead to multiple extended structures. This
240 extended structure results from the mathematical specification of the structural
241 parameters. Additionally, it is highlighted how the parameters interpretabil-
242 ity of the model can be affected when the specification levels appear, that is
243 when the structural and functional parameters must be defined through further
244 parametrization. A graphical explanation of the concepts applied in the exam-
245 ple is shown in Figure 1.

246

247 **4. Links between parameter interpretability and identifiability**

248 In this section, we discuss about possible relations between the concepts of
249 interpretability and identifiability.

250 *4.1. Brief recall on parameter identifiability*

251 Identifiability is a structural property of the model referred to the ability to
252 find a unique best value of the model parameters from available measurements
253 [28, 29]. Under the assumption that the model represents perfectly the system,
254 model identifiability is tested in the hypothetical scenario set by continuous
255 noise-free data and experimental conditions that provide a sufficient excitation
256 on the model response. The structural identifiability is independent of real
257 experimental data. Identifiability is a necessary condition for the parameter
258 identification problem to be well posed. Identifiability testing is of great rele-
259 vance for models where the parameters are biologically meaningful (as it is the
260 case for PBSMs) and we may wish to identify them uniquely [30]. Identifiability
261 testing can be helpful to provide guidelines to deal with non-identifiability, ei-
262 ther providing hints on how to simplify the model structure or indicating when
263 more information (measured data) are needed for the specific experiment [31].

264 Let us consider $\mathbf{M}(\mathbf{p})$ a fixed model structure with a set of parameters \mathbf{p}
265 describing the input-output behavior of the system under study. The structural
266 identifiability of the parameter p_i is determined from the following equality

$$\mathbf{M}(\mathbf{p}) = \mathbf{M}(\mathbf{p}^*) \Rightarrow p_i = p_i^* \quad (10)$$

267 If the equality (10) holds for a unique value of the parameter p_i , the param-
268 eter is structurally globally identifiable. If there are a finite number of values
269 for p_i that hold the equality (10), the parameter is structurally locally iden-
270 tifiable. If infinite solutions exist for p_i , the parameter is nonidentifiable. A
271 model is structurally globally (or locally) identifiable if all its parameters are
272 structurally globally (or locally) identifiable. A model is non-identifiable if at
273 least one of its parameters is non-identifiable. Different methods have been
274 proposed to test identifiability of linear and nonlinear models. The interested
275 reader is referred to dedicated literature [32, 28, 33]. To facilitate identifiability
276 testing, software tools such as DAISY (Differential Algebra for Identifiability of
277 SYstems) [31] and GenSSI have been developed [34]. DAISY is implemented in

278 the symbolic language REDUCE and GenSSI is implemented in Matlab. Both
279 of them are freely available. We made use of both toolboxes for our analysis.

280 *4.2. Interpretability vs. identifiability*

281 In our conceptual framework, interpretability is defined as the ability to find
282 a physical meaning of a parameter when the model structure (basic plus ex-
283 tended) and some knowledge of the real process are given. Interpretability is
284 the property of the model parameters, inherited from the model structure, as-
285 signing a physical meaning to a parameter within the context where the model
286 is constructed. When the parameter has a physical meaning, it is possible to
287 find from available knowledge a span of numerical values to make easier its iden-
288 tification.

289

290 The main role of parameter interpretability for parameter identification is
291 to narrow the search space/domain of the cost function where the identification
292 procedure operates, constraining the values of feasible parameters to match with
293 the existing body of knowledge. On the other hand, structural identifiability is
294 considered a theoretical property. In practice, however, model structure mis-
295 specification and noise data can affect the identifiability of the parameters of
296 the model [31] and therefore an accurate identification of the model parameters
297 is not guaranteed. Practical identifiability is then subjected to the quality of
298 available data. Interpretability can be of help in parameter identification [35]
299 by adding prior knowledge that can be used to constraint the parameter esti-
300 mation. For instance, if a parameter is interpretable, it is possible to know the
301 threshold in which it should be placed. Also, the threshold could be restricted
302 to improve the practical identification. A parameter can be non-identifiable,
303 but if it is interpretable, then the prior information can be used to facilitate its
304 practical identifiability.

305 Identifiability and interpretability are relevant properties of PBSMs con-
306 structed to gain mechanistic insight of the system under study. A PBSM has
307 a basic structure that is universal and interpretable, that is, all its structural

308 parameters are interpretable. However, it is often required to specify the struc-
309 tural parameters in the extended structure, yet maintaining the interpretability
310 of a model become more challenging.

311 Identifiability analysis applies only to scalar parameters (see definition of
312 scalar parameters in Table 1). In the β -casein model, the structural parameter
313 $r(\cdot)$ is a time variant quantity and thus identifiability testing is not relevant. The
314 quantity $r(\cdot)$ is interpretable and we might wonder if it is possible to estimate
315 it from the available measurements (x). The reconstruction of $r(\cdot)$ belongs to
316 another subject namely observability, which is not detailed here.

317 A structural identifiability analysis was performed for the β -casein model by
318 using both DAISY software tool [31] and GenSSI-Matlab [34], to evaluate how
319 the identifiability properties of the model change with respect to the level of
320 specification or granularity and the candidate constitutive equations. Table 3
321 summarizes the identifiability and interpretability analysis. It can be noted that
322 the basic structure of the model is interpretable but its identifiability cannot be
323 tested because $r(\cdot)$ is not a scalar. However, its identifiability analysis is latter
324 applied and is affected when the structural parameter $r(\cdot)$ is defined by the
325 different kinetics. When $r(\cdot)$ is replaced by the first-order kinetic, the model is
326 still identifiable. But, when k_1 is further defined by a mathematical expression
327 dependent on the initial concentration of the protein (located in the second
328 specification level), its identifiability is modified. In the same way, for the second
329 form of competitive inhibition kinetics, where functional parameters b_1 and b_2
330 are not replaced, the model is globally identifiable, but once b_1 and b_2 are defined
331 and replaced at the next level of specification, the identifiability of the model is
332 affected. Parameters k_1 , k_n , k_c , K_m , and K_i are interpretable from Michaelis-
333 Menten kinetics, but parameters b_1 and b_2 are not interpretable. When the
334 mathematical expression of Michaelis-Menten is changed for the expression with
335 parameters b_1 and b_2 to make easier its identification, the interpretability is
336 affected.

337 We deduce that a PBSM can have an extended structure to identify its
338 parameters and an extended structure to interpret the model parameters. In

339 the case of the β -casein model, two extended structures of the model can be
340 considered depending on the interest: if the interest is to perform parameters
341 identification, the mathematical expression containing parameters b_1 and b_2 is
342 more convenient. Contrary, if the interest is to exploit the descriptive ability of
343 the model, the mathematical expression with interpretable parameters is then
344 selected. Note that to perform an identifiability analysis of the whole model,
345 all parameters must be replaced by the mathematical expression defining them,
346 whilst interpretability analysis does not require to replace the constitutive equa-
347 tions in the upper specification levels.

348

349 5. Conclusion

350 Due to the lack of a formal definition of the interpretability concept in the
351 literature and that this topic is just emerging, we propose a conceptual frame-
352 work for parameters interpretability. We discussed the links between parameter
353 interpretability and identifiability.

354 The concepts here described provide a useful framework to undertaking
355 the construction of models of biological/biomedical systems where the physi-
356 cal meaning of the model structure is a desired property. These concepts are of
357 particular usefulness for modeling systems that are poorly studied and thus
358 facilitate further exploitation of *in silico* simulation. PBSMs offer great ad-
359 vantages for representing biological systems as they allow to enhance model
360 capabilities in sequential way, integrate multiscale information into the same
361 model, and guarantee direct interpretability of model basic structure. In addi-
362 tion, to endow with interpretability a parameter of a PBSM is an easier task
363 when compared with the same effort over empirical models.

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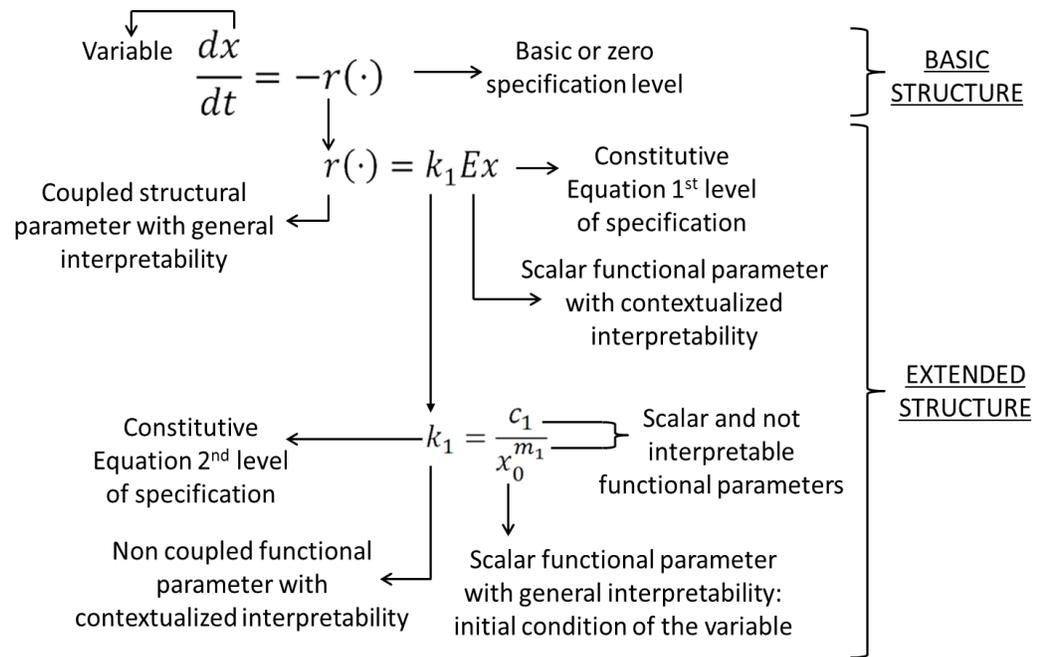


Figure 1: Concepts applied in a simple model of β -casein hydrolysis by a *Lactococcus lactis* bacterium.

Table 1: Definition of concepts used in this study

| Term | Definition |
|---------------------------------------|---|
| Variable | Quantity to be solved by the model. |
| Basic structure | Set of equations obtained after applying the conservation law. At this level, the functions that represent the phenomena that take place in the study object are not detailed mathematically. |
| Extended structure | Set of equations allowing to specify the parameters represented by mathematical functions. The extended structure results from defining the mathematical equations of the parameters contained in the model basic structure. Some of these equations, called assessment equations, are trivial, i.e., they imply only the assignment of a numerical value to a parameter. |
| Model structure | Set of equations consisting in the union of the basic and extended structures. |
| Constitutive and assessment equations | Equations inside the extended structure of the model acting as a mathematical specification of a parameter. |
| Structural parameter | Parameter inside the basic structure of the model. The structural parameter represents either a quantity that varies in time or a scalar. |
| Functional parameter | Parameter inside any constitutive or assessment equation. It is categorized in coupled parameter, no coupled parameter or scalar parameter. These parameters result from the extended structure, once the mathematical equations of the structural parameters are specified. |
| Scalar functional parameter | Parameter with numerical value (datum) time independent. This type of parameter can be known <i>a priori</i> or determined by parameter estimation. |
| Non coupled functional parameter | Parameter associated to a mathematical function that does not depend on any variable of the model. |
| Coupled functional parameter | Parameter that depends on at least one variable of the model. |

| Term | Definition |
|---------------------------------|--|
| Parameter interpretability | Given a model structure for a system, a parameter p_i is interpretable if it has physical meaning into the real object. In a specific knowledge context, the symbol of the interpretable parameter provides additional information or knowledge about the phenomena under consideration compared to a simple numerical value. The interpretability of a parameter as a property depends on the model structure. Also, the parameter position into the model structure helps to provide interpretability to that parameter being defined. |
| Contextualized interpretability | Physical meaning of a parameter valid only into a specific mathematical model. The meaning is dependent on the considerations and hypothesis used to deduce the mathematical model within a given context. |
| General inter-pretability | Inherent physical meaning of the parameter within a model in a specific scientific domain, i.e., its interpretation is independent on assumptions used to deduce the basic model structure. |
| Non inter-pretability | The parameter has not physical meaning within the model. Non interpretable parameters must be then represented by a symbol without an interpretable property in the knowledge domain of the process. |

Table 2: Classification of the β -casein model components when using the first-order kinetic rate to represent β -casein hydrolysis

| Symbol | Type | Equation | Interpretability |
|---|----------------------------------|-----------------------------|---------------------------|
| Basic structure and basic specification or zero specification level | | | |
| x | Variable | $\frac{dx}{dt} = -r(\cdot)$ | Non required ^a |
| r | Structural parameter | $r(\cdot) = k_1 E x$ | General |
| 1st specification level | | | |
| k_1 | Non coupled functional parameter | $k_1 = \frac{c_1}{x_0 m_1}$ | Contextualized |
| E | Scalar functional parameter | $E = known$ | Contextualized |
| 2nd specification level | | | |
| c_1 | Scalar functional parameter | $c_1 = known$ | Non interpretable |
| m_1 | Scalar functional parameter | $m_1 = known$ | Non interpretable |
| x_0 | Scalar functional parameter | $x_0 = known$ | General |

^aAny model variable has inherent interpretability

Table 3: A comparison between identifiability and interpretability analysis in β -casein model

| Mathematical expression | Unknown parameters | Identifiability | Interpretability |
|---|--------------------|--|------------------|
| Basic structure and basic specification or zero specification level | | | |
| $\frac{dx}{dt} = -r$ | r | Identifiability does not apply at this level | General |
| Extended structure - 1st specification level | | | |
| $r = k_1 E x$ | k_1 | Globally identifiable ^a | Contextualized |
| $r = k_n E x^n$ | k_n, n | Locally identifiable ^b | Contextualized |
| $r = k_c E \frac{x}{K_m + x}$ | k_c, K_m | Globally identifiable | Contextualized |
| $r = k_c E \frac{x}{K_m(1 + \frac{x}{K_i}) + x}$ | k_c, K_m, K_i | Non identifiable | Contextualized |
| $r = b_1 E \frac{x}{b_2 - x}$ | b_1, b_2 | Globally identifiable | No interpretable |
| 2nd specification level | | | |
| $k_1 = \frac{c_1}{x_0^{m_1}}$ | c_1, m_1 | Locally identifiable | No interpretable |

^aGlobal analysis is performed by using DAISY [31].

^bLocal analysis is performed by using GenSSI [34]

