QR and Mathematical Modeling

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Outline

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3. Problems in SI
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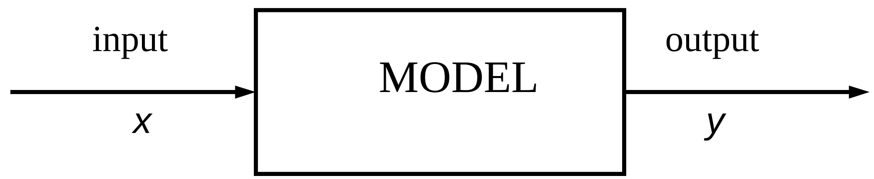
7. *Part 2* - QR for *black-box (non-parametric)* SI
   - Case Study: Kinetics of Thiamine (vitamin B_1) in the cells of the intestine tissue

Introduction

Quantitative mathematical model

A mathematical description of the relations between the inputs x (causes) and the outputs y (effects) of a system

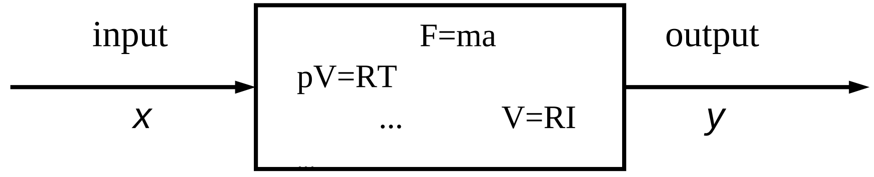


Model: a mapping $y = f(x)$

Three modeling approaches:

- white box
- grey box
- black box

White box modeling

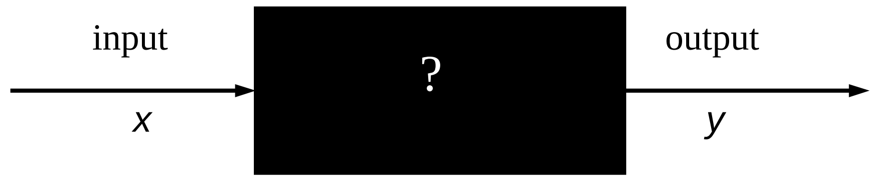


- Physical laws are available
- Typical examples: mechanical and electrical systems
- The box is “transparent”

Grey box modeling

- Physical laws are available but the values of some parameters are unknown
- the internal structure of the box is only partially known
- **Idea**: tune the unknown parameters until the outputs predicted by the model match the observed data

Black box modeling



- physical knowledge is not available
- physical knowledge is very incomplete
- parameter estimation is not possible due to the lack of adequate observed data sets
- useful for very complex systems
- **Idea**: collect data and use them to find the links between inputs and outputs

Problems in SI

- Choice of the structural model or identifier scheme
- appropriate set-up of numerical procedures
  (e.g. initial conditions, start guess ...)
- Choice of adequate numerical methods
  (e.g. curve fitting, ODE solvers,...)

What can QR do for SI ?

QR helps to:

- find model classes consistent with prior knowledge
- find an initial guess of parameter values
- choose proper numerical methods

Related work

- Kay [1996], Kay, Rinner, Kuipers [2000];
  semi-quantitative SI
- Bradley [1994], Bradley, O’Gallagher, J. Rogers [1997];
  M. Easley, E. Bradley [1999]
  quantitative structural SI
- Capelo, Ironi, Tentoni [1996, 1998];
  quantitative structural SI
- Bellazzi, Guglielmann, Ironi [1997,1998,2000];
  quantitative “black-box” SI

Part 1

QR for structural SI

Case study: Automated modeling of
visco-elastic material

Structural modeling from data

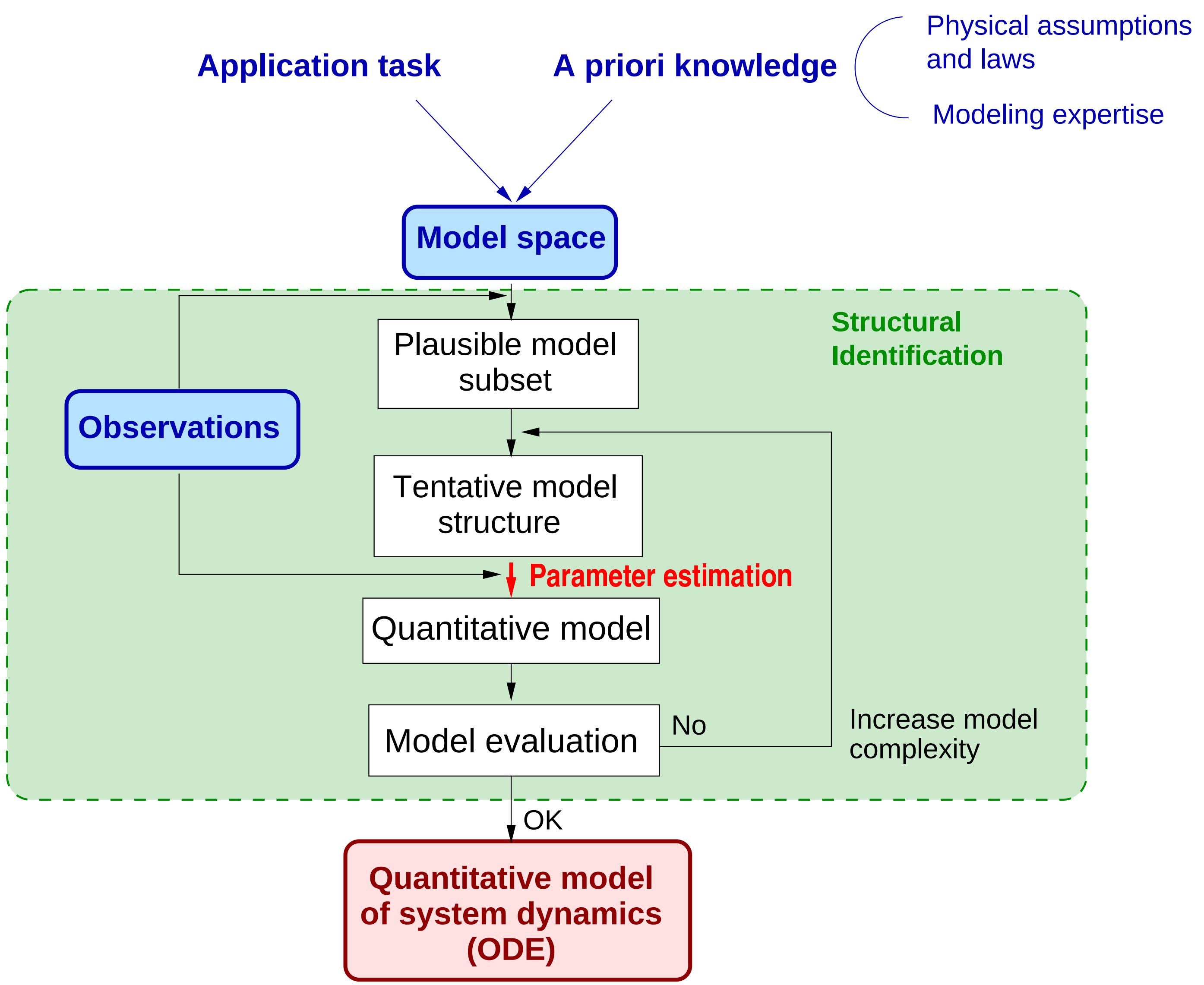
- Physical insight helps defining the model space (grey vs. black-box models)
- The model space definition requires modeling expertise

$\longrightarrow$ difficult task, not easily made automatic

System Identification: given the model space, the process of deriving a *good model* for the system dynamics from the observations

- SI grey modeling must not reduce to a mere numerical fit process
  - *adherence to the observations*
  - *minimal complexity*

System Identification



Use of QR in SI

- Intelligent data analysis
- Structural identification
- Parameter estimation

Automated modeling of visco-elastic materials

Motivations: assessment of visco-elastic materials from data

data from standard rheological experiments → quantitative accurate model of mechanical behavior of tested material

- deriving models by hand is a hard task
- models can be used for simulations, and provide a deeper insight w.r. to a mere experimental study

Goal: to formulate the constitutive equation $\mathcal{R}(s, e) = 0$ (linear ODE) describing the mechanical behavior of a material under suitable assumptions

Modeling issues

- **Modeling approach:** compositional strategy (rheology)

  The model space was automatically generated, and partitioned into QB-homogeneous classes (see Capelo, Ironi, Tentoni 1998)

- **Experimental data**: Standard static tests - step input signal
  - Creep experiments: $s(t) \longrightarrow e(t)$
  - Relaxation experiments: $e(t) \longrightarrow s(t)$

Model space characterization (1)

The **mathematical model** describes the relation between $s(t)$ and $e(t)$:

$$\sum_i \theta_i^{(e)} D^i e = \sum_j \theta_j^{(s)} D^j s \qquad \theta_i^{(e)}, \theta_j^{(s)} \in \ R$$

Formal model(FM):
symbolic ODE with the same ODE structure and $\theta_i \neq 0 \ \rightarrow \ 1$

The model space $\mathcal{FM}$ can be partitioned as $\mathcal{FM} = \cup_{i=1}^{4} \mathcal{FM}_i$,
and each class is associated with its own QB

Model space characterization (2)

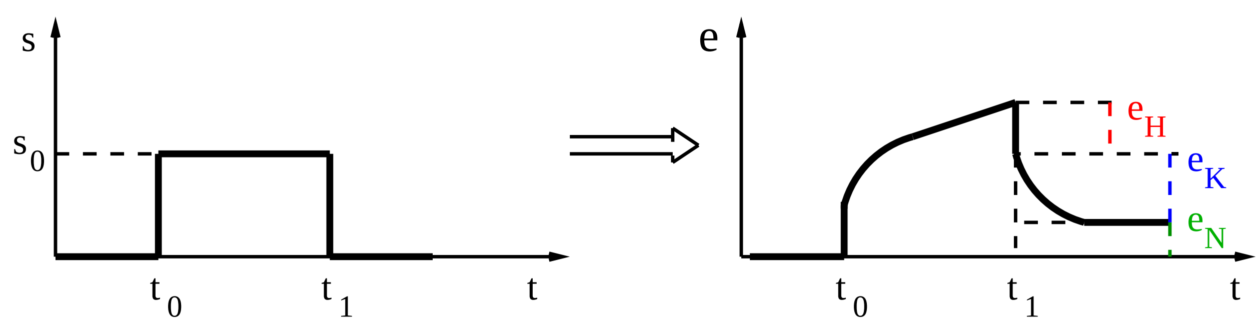
$$\mathcal{FM}_1 = \{FM_{1,k} : \sum_{i=0}^{k} D^i s = \sum_{i=0}^{k} D^i e,\ k \geq 0\} \leftrightarrow QB_1 = \text{(T,T,F); (T,F,F)= QB(H)}$$

$$\mathcal{FM}_2 = \{FM_{2,k} : \sum_{i=0}^{k} D^i s = \sum_{i=1}^{k+1} D^i e,\ k \geq 0\} \leftrightarrow QB_2 = \text{(F,T,T); (F,F,T)= QB(N)}$$

$$\mathcal{FM}_3 = \{FM_{3,k} : \sum_{i=0}^{k} D^i s = \sum_{i=0}^{k+1} D^i e,\ k \geq 0\} \leftrightarrow QB_3 = \text{(F,T,F);}$$

$$\mathcal{FM}_4 = \{FM_{4,k} : \sum_{i=0}^{k+1} D^i s = \sum_{i=1}^{k+1} D^i e,\ k \geq 0\} \leftrightarrow QB_4 = \text{(T,T,T); (T,F,T)= QB(H–N)}$$

Creep test

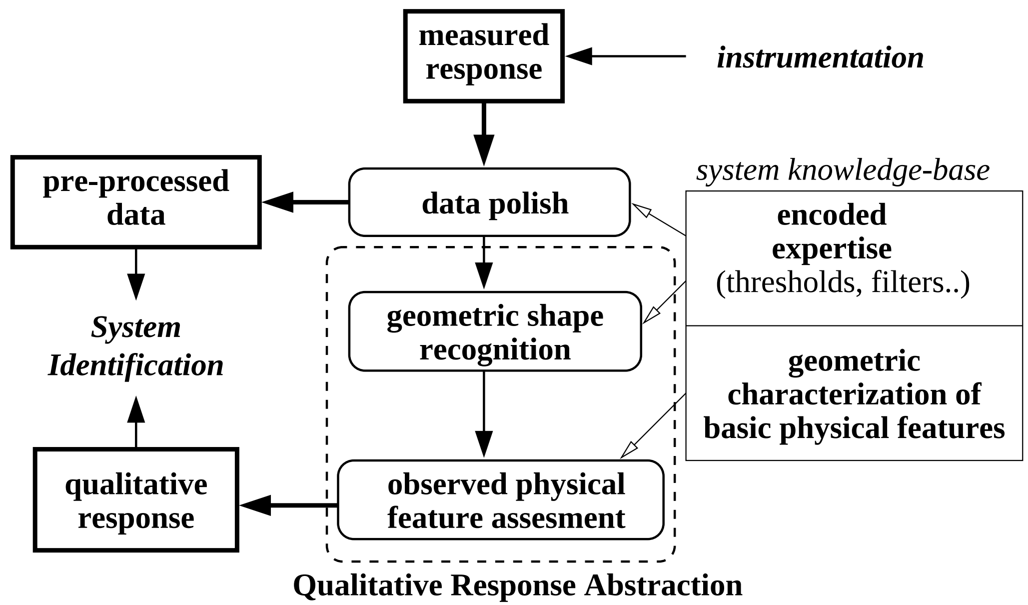


Qualitative strain response: $e = e_H + e_K + e_N$

QB= $(\alpha_H, \alpha_K, \alpha_N)$, where $\alpha_* =$ True $\Leftrightarrow$ $e_* \neq 0$

Intelligent Data Analysis

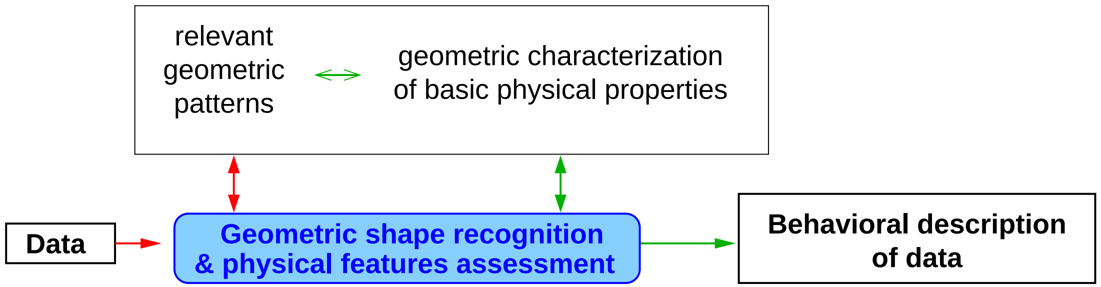
- Observations drive the whole modeling process



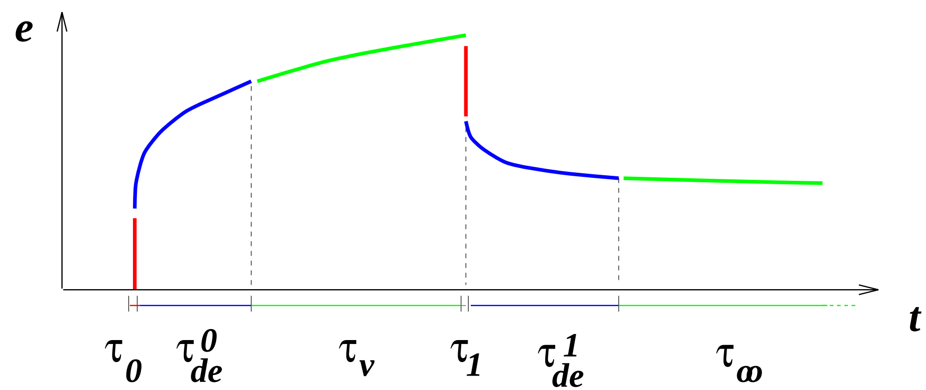
Data pre-processing

- removal of outliers
- filtering
- evaluation of measure uncertainty

Qualitative Response Abstraction



- **Geometric reasoning: shape recognition and data segmentation**



- **Inference of observed behavior from the extracted geometric features**

Structural Identification

Issue: select, within the model space, the subset of plausible models

$\longrightarrow$ more efficient computation
(reduced SI search space)

$\longrightarrow$ ensured physical accuracy

How:

$$DATA \xrightarrow{\qquad\qquad} \mathrm{QB}_O \longrightarrow \overline{\mathcal{FM}} \mid \mathrm{QB}_I = \mathrm{QB}_O$$

$$\overline{\mathcal{FM}} \xrightarrow{\mathrm{FM}^{-1}} \overline{\mathcal{M}} = \{M_k(\underline{\theta}),\ \underline{\theta} \in R^{N(k)} \backslash \{\underline{0}\},\ k = 0,..,\overline{n}\}$$

$$M_k(\underline{\theta}) \ :\ \sum_i \theta_i^{(e)} D^i e = \sum_j \theta_j^{(s)} D^j s$$

Quantitative Identification

The plausible model set $\overline{\mathcal{M}} = \{M_k(\underline{\theta})\}$ is hierarchical
(k: model complexity index, $\underline{\theta}$: model parameters)

Problem: Find $k^*, \underline{\theta}^*$ such that:

- $\underline{\theta}^* =$ arg min$_\theta \sum_i^{N_D} \left(\frac{e(t_i;\underline{\theta}) - \overline{e}_i}{\sigma_i} \right)^2$
- and rcond$(\mathcal{F}) > 1.e-5$, $\mathcal{F}$: information matrix
- $k^* =$ arg min$_k AIC(k)$, AIC: Akaike Information Criterion

Properties of $M_{k^*}(\theta^*)$:

- numerical and statistical reliability
- minimal complexity
- reasonably good data fitting

Problems

$(\mathcal{P}1)$ ∘ A *good* starting guess $\underline{\theta}^0$ must be provided

$(\mathcal{P}2)$ ∘ Initial conditions $\mathbf{De}(\mathbf{t_0}) = \mathbf{e^0}$ must be given

($\mathbf{De}$ vector of the time derivatives of e)

∘ ODEs $M_k(\underline{\theta})$ may be stiff

Problem $(\mathcal{P}1)$

A good guess θ^0 is needed to ensure convergence to the true (rather than to a local) minimum.
But θ^0 has no explicit physical meaning, and extracting information from data is not a straightforward task.

$$\Downarrow$$

QR-driven curve fitting:

$$y(t; \text{QB}_O, \underline{c}, \underline{\lambda}) = \chi(\alpha_K) \cdot \sum_{i=1}^{r} c_i (1 - \exp(-\lambda_i t)) + \chi(\alpha_N) \cdot c_{r+1} t + \chi(\alpha_H) \cdot c_{r+2}$$

(exploits a priori knowledge and qualitative data interpretation)

+ *least-squares ODE collocation*: $\underline{\theta}^0$ l.s. solution of

$$\sum_i \theta_i^{(e)} D^i y(t_k) = \sum_j \theta_j^{(s)} D^j s(t_k) \quad , \quad (k = 1, .., N_D).$$

Problem $(\mathcal{P}2)$

- **Initial conditions $\mathbf{e^0}$ must be given .**
  e_i^0 could be treated as further parameters to be identified as well, but this would entail a higher computational effort.

$$\Downarrow$$

$\mathbf{e^0}$ is defined by: $\mathbf{e^0} := \mathbf{D}\mathbf{y}(t_0)$

- $M_k(\underline{\theta})$ **may be stiff, according to the elastic components of the response**
  Explicit Adams or Runge-Kutta methods may be unstable

$$\Downarrow$$

Implicit, backward difference schemes (BDF, NDF) are preferred (less accurate but stable)

Remark: Stiff systems are frequent in many application domains: chemical kinetics, chemistry of polymers, mechanics...
A “stiff” system is characterized by time constants widely varying in magnitude.

Remarks

Traditional structural SI does benefit from the integration with QR

Integrated frameworks:

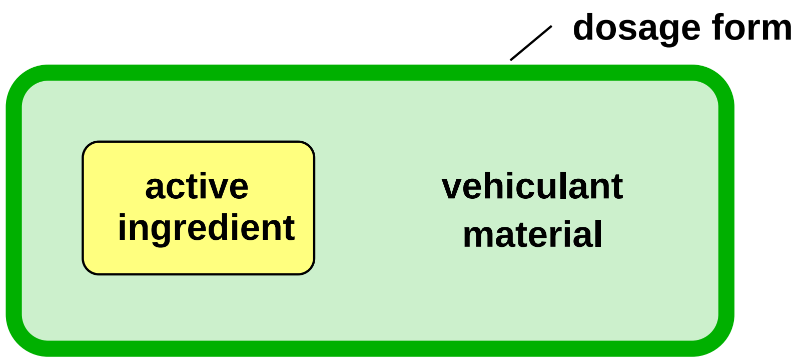
- allow us to deal automatically with modeling problems difficult to be handled by hand
- provide methodologies and tools for a deeper, more robust and economic investigation of physical domains traditionally studied at a mere experimental level

Application to Pharmacology

Motivations

Polymeric drug delivery research within the design of Drug Delivery Systems (DDS's)

DDS



Aim: ensuring optimal drug bioavailability (fast targeting + most effective delivery mode)

The development of a new DDS requires assessment of those physicochemical properties of carrier materials which affect bioavailability

Mucoadhesion

Mechanism whereby a polymeric carrier adheres to a mucosal tissue

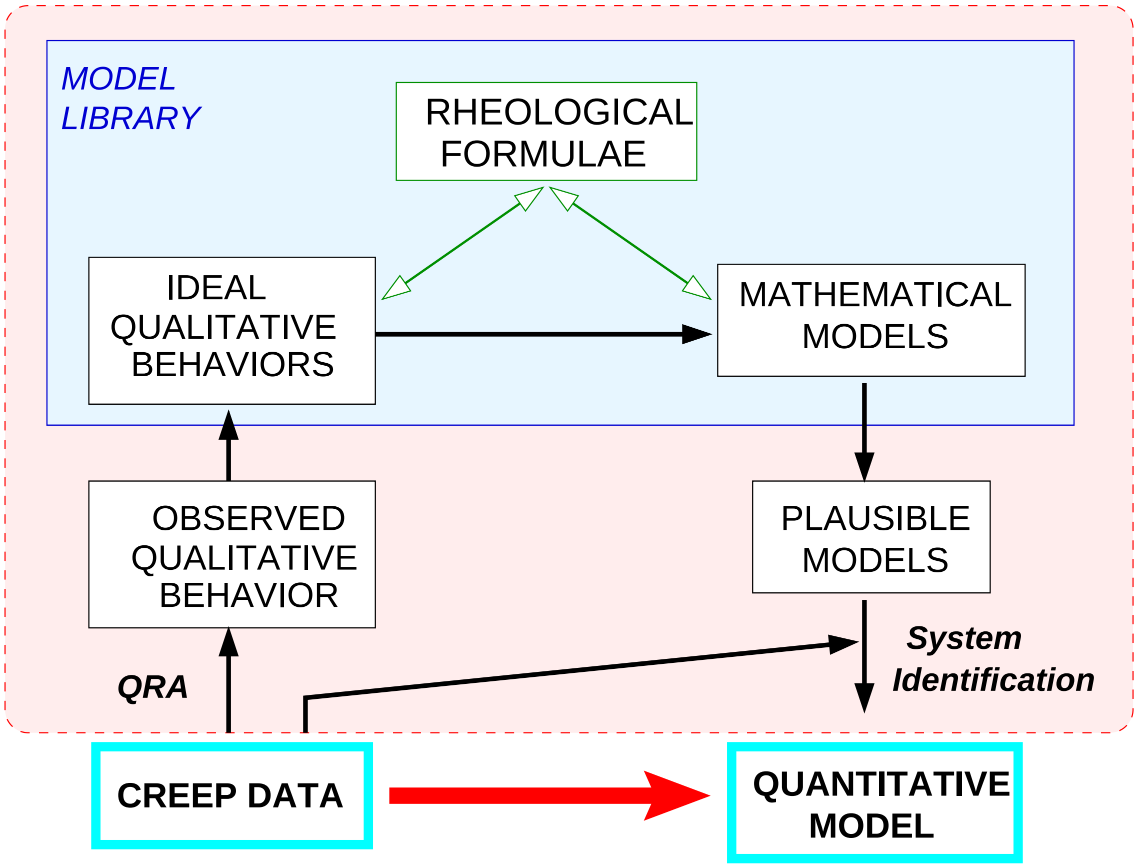
→ A better mucoadhesive performance would improve drug bioavailability

Traditional approach is entirely experimental:

- time consuming and costly
- it hardly provides info on the structural requirements for adhesion

A model based approach would provide a deeper comprehension of the polymer-mucus interaction

RHEOLO's architecture



Output: ODE model
compliance model

Résumé

Variables:

- $s(t)$ perturbation on the system (input)
- $e(t)$ elicited system response (output)

Data:

- Standard creep test: $s(t) = s_0 H(t - t_0)$

Models:

- ODE model
- Compliance model

Structural identification $\rightarrow$) class and order of the model
Parameter estimation $\rightarrow$ values of the parameters

Compliance model

Explicitly related to the rheological structure of the material:

$$J(t) = J_0 + \sum_{i=1}^{k} J_i \left(1 - \exp\left(-\frac{t}{\tau_i}\right)\right) + \frac{t}{\eta_N}$$

$J_H(t) \leftrightarrow$ (instantaneous elasticity) J_0

Prompt elastic stretching of bonds between the primary structural units

$J_K(t) \leftrightarrow$ (retarded elasticity) $\{J_i, \tau_i\}_{i=1..k}$

Bonds break and reform, producing a slower, still recoverable, deformation.

$k \leftrightarrow$ number of bond types

$J_i \leftrightarrow$ intensity of each bond type

$\tau_i \leftrightarrow$ times at which the greater part of each bond type establishes

$J_N(t) \leftrightarrow$ (viscous flow) η_N

Irreversible rupture of bonds.In particular:

1. the # retardation times (model order),related to the establishment of new types of bonds, characterizes the material complexity
2. the compliance values express the strength of the structural units

The application problem

- Materials

  NaCMC: solutions of polymer at three viscosity grades (LV, MV, HV), each one at three concentration levels (low, medium, high).

  Polymer+mucin: mixtures of each polymer with mucin at three different concentrations

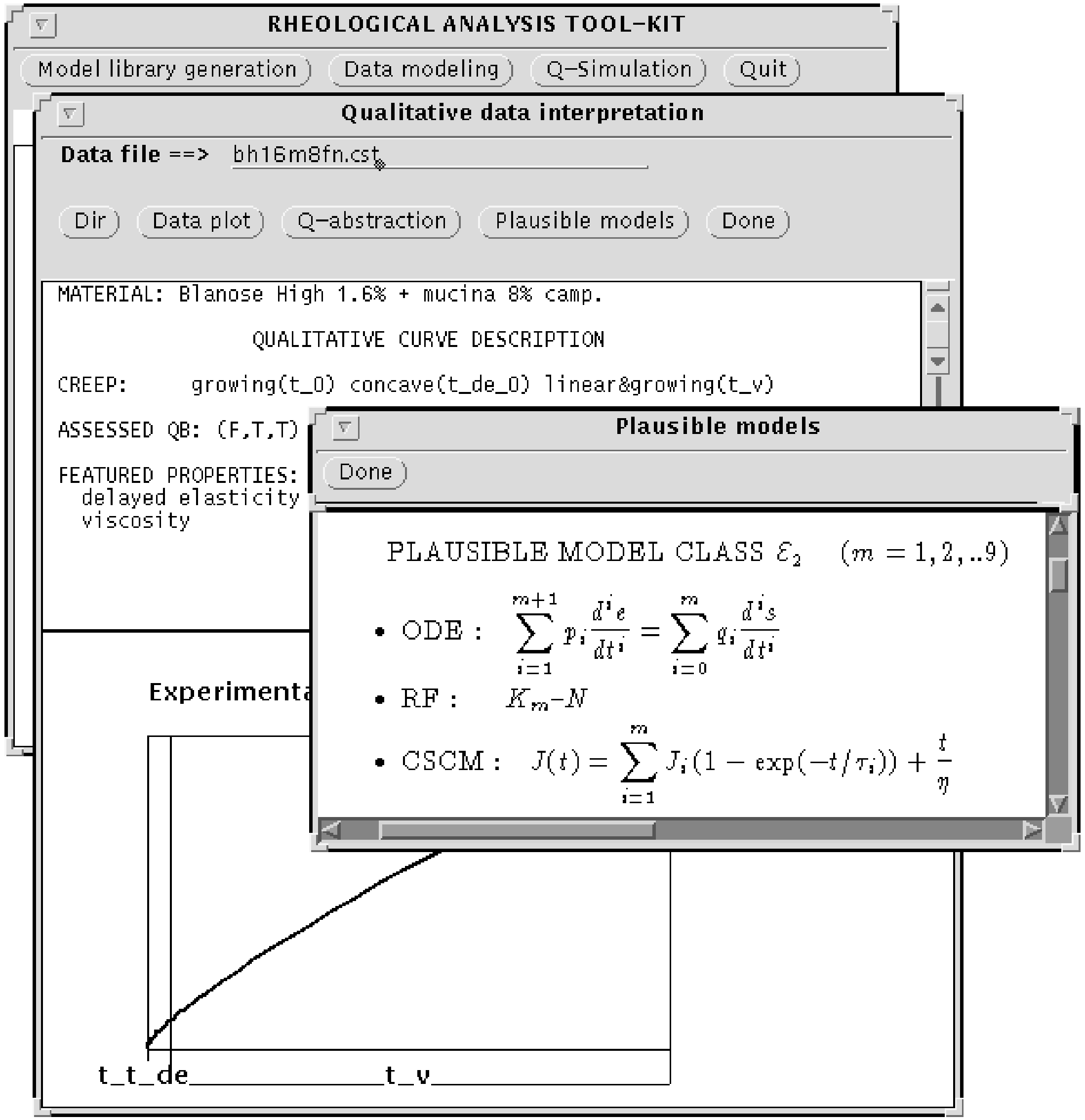
- Aim

  Model-based investigation of polymer mucoadhesive performance, to get a deeper knowledge on the polymer-mucin interaction

Method

1. Quantitative characterization of rheological properties of each material by means of model order and parameters
2. Highlight structural conditions at which polymer-mucin synergy is higher (best mucoadhesive performance)

1 - Results



RHEOLOGICAL ANALYSIS TOOL-KIT
Model library generation
Data modeling
Q-Simulation
Quit
Qualitative data interpretation
Data file ==> bh16m8fn.cst
Dir
Data plot
Q-abstraction
Plausible models
Done
MATERIAL: Blanose High 1.6% + mucina 8% camp.
QUALITATIVE CURVE DESCRIPTION
CREEP: growing(t_0) concave(t_de_0) linear&growing(t_v)
ASSESSED QB: (F,T,T)
FEATURED PROPERTIES:
delayed elasticity
viscosity
Experimenta
t_t_de
t_v
Plausible models
Done
PLAUSIBLE MODEL CLASS $\mathcal{E}_2$ $(m = 1,2,..9)$
• ODE : $\sum_{i=1}^{m+1} p_i \frac{d^i e}{dt^i} = \sum_{i=0}^{m} q_i \frac{d^i s}{dt^i}$
• RF : K_m–N
• CSCM : $J(t) = \sum_{i=1}^{m} J_i(1 - \exp(-t/\tau_i)) + \frac{t}{\eta}$

1 - Results

Model evaluation: Akaike indexes and condition numbers

Polymer (H.V. NaCMC 1.6%) + 8%mucin

	k	rcond	$\mathcal{A}(k)$
	0	1.00 e+00	1005.5
	1	4.00 e-04	780.4
$k^* =$	2	9.33 e-03	591.4
	3	2.19 e-08	423.6

Optimal model order and parameter estimates (95% confidence intervals)

Polymer (H.V. NaCMC 1.6%) + 8%mucin

k^*	2		
θ_1^*	1.568 e+2	[1.562 e+2, 1.574 e+2]	Pa· s
θ_2^*	2.880 e+3	[2.879 e+3, 2.882 e+3]	Pa·s^2
θ_3^*	8.128 e+2	[8.123 e+2, 8.132 e+2]	Pa·s^3

2 - Results

		k^*
L.V. NaCMC low		**0**
Mixture with mucin		**3**
L.V. NaCMC medium		0
Mixture with mucin		2
H.V. NaCMC low		1
Mixture with mucin		2
H.V. NaCMC medium		2
Mixture with mucin		2

LV-NaCMC and HV-NaCMC at different concentrations, and their mixture with mucin at 8% concentration : optimal model order (k^*)

2 - Results

The addition of mucin causes an increase in the elastic properties, by the establishments of new bonds:

- increase in model order $\leftrightarrow$ better interaction between polymer and mucin chains
- increase in the compliance values $\leftrightarrow$ furher strengthening of the mucoadhesive interface

The polymer-mucin interaction is highest when LV-NaCMC is used at the lowest concentration (deeper interpenetration)

Conclusive remarks

- RHEOLO has favoured a model based approach to the investigation of physicochemical properties relevant in DDS's design (e.g. mucoadhesion)
- The proposed approach can be used to investigate phenomena involving variations in the material structure revealed by changes in the rheological behavior
- The model based approach has provided
  - deep insight into the polymer-mucin interactions
  - cheaper and more effective evaluation of polymer mucoadhesive performances through model parameters and complexity (rheological properties)

New application: Hemodynamics: study of blood rheological properties for diagnostic and therapeutic purposes

References

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1. C. Bonferoni, C. Caramella, L. Ironi, S. Rossi, S. Tentoni, Model-Based Interpretation of Creep Profiles for the Assessment of Polymer-Mucin Interaction, Pharmaceutical Research, 16, 9, 1999.
2. A. C. Capelo, L. Ironi, S. Tentoni, The need for qualitative reasoning in automated modeling: a case study, Proc. 10th International Workshop on Qualitative Reasoning, Stanford Sierra Camp, 32-39, 1996.
3. A.C. Capelo, L. Ironi, S. Tentoni, Automated mathematical modeling from experimental data: an application to material science, IEEE Transactions on Systems Man and Cybernetics, 28, 3, 356-370, 1998.
4. G. De Nicolao, System Identification: Problems and perspectives, 11th International Workshop on Qualitative Reasoning", Cortona, Istituto di Analisi Numerica - C.N.R., Pavia, 379-386, 1997.
5. L. Ljung, System Identification - Theory for the User, Prentice-Hall, Englewood Cliffs, 1987.