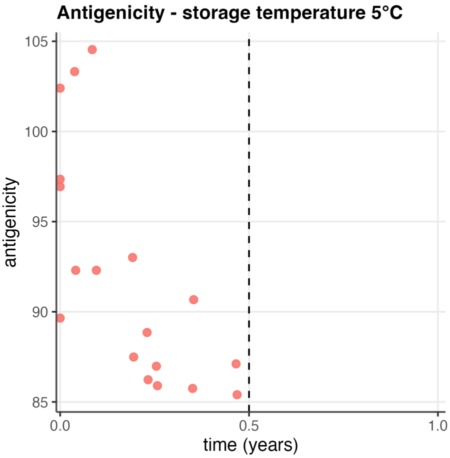
Kinetic Models by Physics-Informed Statistical Learning Methods

ENBIS-26 Conference - Florence, Italy, September 6-10, 2026

Marco Galliani[1] Bernard G. Francq[2] Laura M. Sangalli[1]

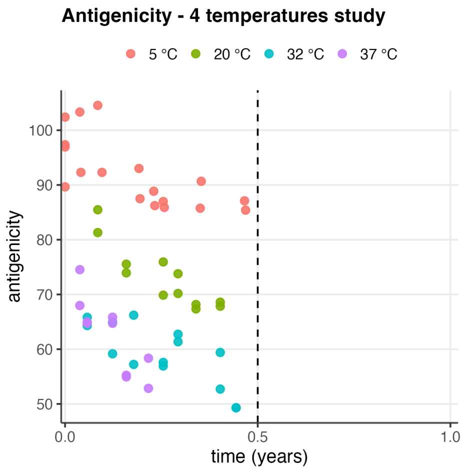
[1]MOX, Department of Mathematics, Politecnico di Milano, Milan, Italy.

[2]CMC Statistical Modeling, GSK, Rixensart, Belgium.



STABILITY STUDIES

- **Quantity of Interest:**
  Critical Quality Attribute (CQA), proxy of product effectiveness, e.g.,
  - concentration of Active Pharmaceutical Ingredient
  - vaccine potency
- **Goal:**
  - estimate CQA beyond the data time-window
  - determine product **shelf-life** with confidence



ACCELERATED STABILITY STUDIES

- **Stressed conditions:**
  Accelerate product degradation
  - higher storage temperatures
  - higher humidity
- **Goal:**
  - estimate CQA beyond the data time-window
  - determine product **shelf-life** with confidence
  - Reduce time window necessary for prediction

TIME

Šesták-Berggren model

$\alpha(t)$: reacted fraction of CQA at time t

$$\frac{d\alpha}{dt} = \alpha^m (1-\alpha)^n, \quad \alpha(0) = 0$$

m: autocatalytic term, n: reaction order

TEMPERATURE

Arrhenius equation

$k(T)$: reaction rate at temperature T

$$k(T; A, E_a) = A \exp\left\{-\frac{E_a}{RT}\right\}$$

E_a: activation energy, A: frequency of collisions

Final decay model

$Y(t)$: remaining qty of CQA at time t, $Y(t) = (C_0 - L_0)(1-\alpha(t)) + L_0 \in [L_0, C_0]$

$$\begin{cases} \frac{d\mathbf{Y}}{dt} = -\frac{\mathbf{k}(\mathbf{T}; A, E_a)}{(C_0 - L_0)^{m+n-1}} (C_0 - Y)^m (Y - L_0)^n \\ \mathbf{Y}(0) = \mathbf{y}_0 \end{cases}$$

Model parameters: $\boldsymbol{\theta} = \{E_a, A, m, n, C_0, L_0\}$

Methodology: statistical model

Nonlinear Least Squares:

- Difficult optimisation landscape
- Model misspecification

$$J(\boldsymbol{\theta}) = \sum_{j=1}^{k} (y_j - y(t_j))^2 \quad \text{s.t.} \quad \frac{dy}{dt} = f_{\boldsymbol{\theta}}(t, y)$$

Penalised Regression Framework

$$J(y, \boldsymbol{\theta}) = \sum_{j=1}^{k} (y_j - y(t_j))^2 + \lambda \int \left\| \frac{dy}{dt} - f_{\theta}(t, y) \right\|^2 dt$$

Kinetic model as a soft penalty, λ governs the trade-off:

- $\lambda \to 0$: completely data-driven estimate
- $\lambda \to \infty$: parameter estimation setup

FORWARD PROBLEM

Define $u = \frac{dy}{dt} - f_\theta(t, y)$, model misfit.
Optimal Control Problem (OCP) formulation:

$$\min_u J(u, \theta) = \sum_{j=1}^{k} (y_j - y(t_j))^2 + \lambda \int \|u\|^2 \, dt$$

$$\text{s.t.} \quad \frac{dy}{dt} = f_\theta(t, y) + u$$

Optimality system

$u \in L^2([0, T]), y \in H^1([0, T])$

$$\begin{cases} \frac{dy}{dt} = f(t, y) + u \\ -\frac{dp}{dt} = \frac{df}{dy}(t, y)^\top p + 2\sum_j (y(t_j) - y_j)\delta(t - t_j) \\ \nabla_u J = 2\lambda u - p = 0 \end{cases}$$

INVERSE PROBLEM

The problem reads as

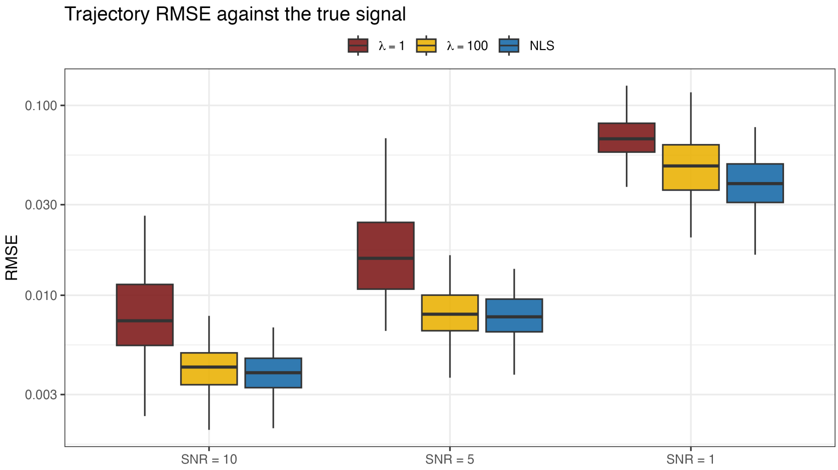
$$\min_{\boldsymbol{\theta}} \underbrace{\left\{ \sum_{j=1}^{k} (y_j - y^*_{\boldsymbol{\theta}}(t_j))^2 + \lambda \int \|u^*_{\boldsymbol{\theta}}\|^2 \, dt \right\}}_{H(\boldsymbol{\theta}) = \min_u J(u, \boldsymbol{\theta})}$$

where $u^*_{\boldsymbol{\theta}}, y^*_{\boldsymbol{\theta}}$ solves the forward problem for the corresponding $\boldsymbol{\theta}$. To compute the gradient

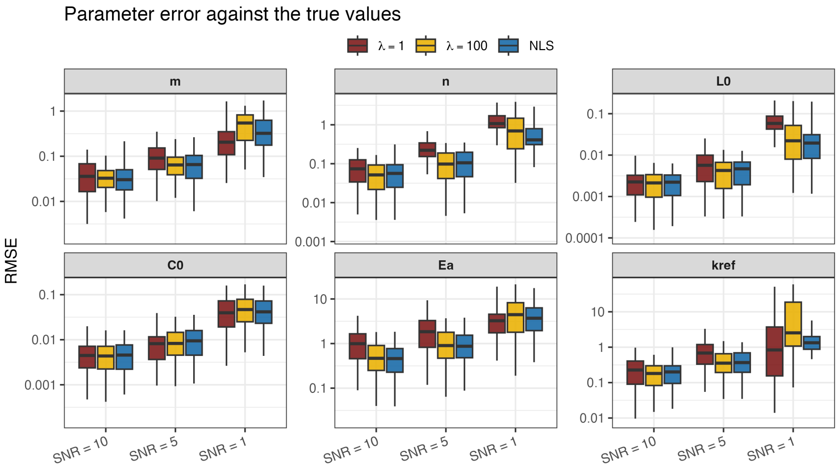
$$\frac{dH}{d\theta} = \frac{\partial J}{\partial y}\frac{dy}{d\theta} + \frac{\partial J}{\partial u}\frac{du}{d\theta}$$

where $\frac{dy}{d\theta}, \frac{du}{d\theta}$ obtained by differentiating forward problem's optimality system w.r.t. $\boldsymbol{\theta}$

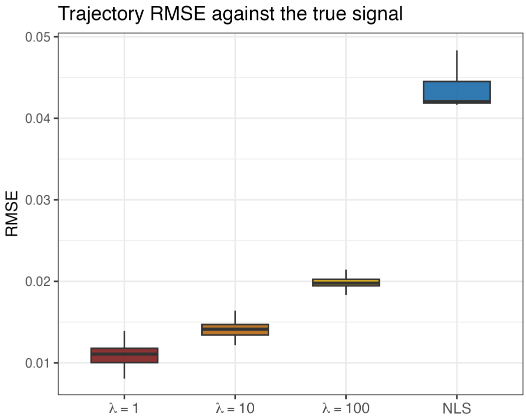
Šesták-Berggren model: $\frac{dY}{dt} = -\frac{k(T;A,E_a)}{(C_0-L_0)^{m+n-1}}(C_0 - Y)^m(Y - L_0)^n$, $\boldsymbol{\theta} = \{E_a, A, m, n, C_0, L_0\}$

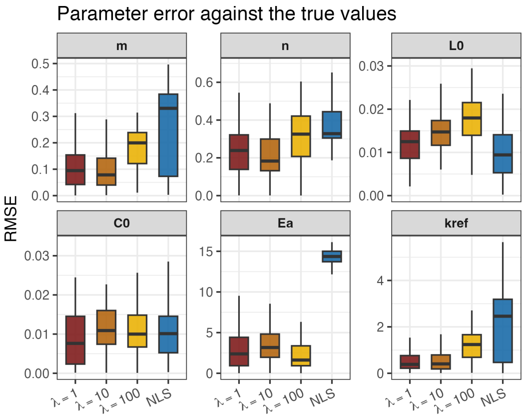


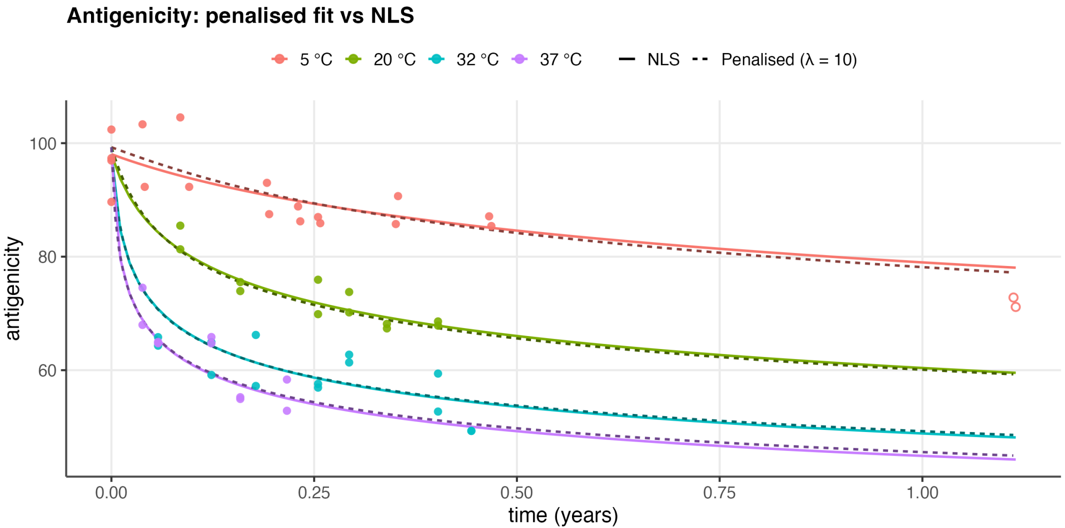
Šesták-Berggren model: $\frac{dY}{dt} = -\frac{k(T;A,E_a)}{(C_0-L_0)^{m+n-1}}(C_0 - Y)^m(Y - L_0)^n$, $\boldsymbol{\theta} = \{E_a, A, m, n, C_0, L_0\}$



Perturbed SB model: $\frac{dY}{dt} = -\frac{k(T;A,E_a)}{(C_0-L_0)^{m+n-1}}(C_0 - Y)^m(Y - L_0)^n + \sin(t)$ [to generate data], $\boldsymbol{\theta} = \{E_a, A, m, n, C_0, L_0\}$






Antigenicity: penalised fit vs NLS
5 °C
20 °C
32 °C
37 °C
NLS
Penalised (λ = 10)
antigenicity
100
80
60
0.00
0.25
0.50
0.75
1.00
time (years)

References

Quentin Clairon and Nicolas J.-B. Brunel.
Optimal control and additive perturbations help in estimating ill-posed and uncertain dynamical systems.
Journal of the American Statistical Association, 113(523):1195–1209, 2018.

Bernard G. Francq.
AccelStab: Accelerated Stability Kinetic Modelling, 2025.

James O. Ramsay and Giles Hooker.
Dynamic Data Analysis: Modeling Data with Differential Equations.
Springer New York, 2017.

James O. Ramsay, Giles Hooker, David Campbell, and Jiguo Cao.
Parameter estimation for differential equations: A generalized smoothing approach.
Journal of the Royal Statistical Society: Series B (Statistical Methodology), 69(5):741–796, 2007.

POLITECNICO MILANO 1863
DEPARTMENT OF MATHEMATICS

Software
fdaPDE
C++/R library
available from CRAN

Discretized optimality system:

$$\begin{cases} y_{t+1} = \Phi_t(y_t, u_t), \quad y(0) = y_0 \\ p_t = \dfrac{\partial \Phi_t}{\partial y}^{\top} p_{t+1} - 2\,\mathbb{I}_{\text{obs}}(y_t - y_{\text{obs},t}), \quad p_m := 0 \\ 2\lambda W_t u_t - \dfrac{\partial \Phi_t}{\partial u}^{\top} p_{t+1} = 0 \end{cases}$$

Integration scheme: an s-stage Runge–Kutta method with tableau (A, b, c),

$$\Phi_t(y, u) = y + h_t \sum_{i=1}^{s} b_i\, k_i,$$

$$k_i = f\Big(t_t + c_i h_t,\ y + h_t \sum_{j=1}^{s} a_{ij} k_j\Big) + u_i,$$

Collocation methods: on each interval the scheme carries a polynomial of degree s, determined by its stage derivatives $k_{t,i}$ and evaluable at any $\theta \in [0, 1]$,

$$y(t_t + \theta h_t) = y_t + h_t \sum_{i=1}^{s} \beta_i(\theta)\, k_{t,i}, \qquad u(t_t + \theta h_t) = \sum_{i=1}^{s} \ell_i(\theta)\, u_{t,i},$$

where $\{\ell_i\}$ is the **Lagrange basis** on the nodes $\{c_i\}$ and β_i its primitive,

$$\ell_i(\theta) = \prod_{j \neq i} \frac{\theta - c_j}{c_i - c_j}, \qquad \beta_i(\theta) = \int_0^{\theta} \ell_i(\tau)\, d\tau, \qquad \beta_i(c_j) = a_{ji}, \quad \beta_i(1) = b_i.$$

marco.galliani@polimi.it