Reproducing kernel Hilbert space based estimation of systems of ordinary differential equations

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Consider a dynamical system modelled by a set of ODEs

\[ P_{\theta_j} x_j = f_{\beta_j}(x_1, \ldots, x_m, u_j), \quad j = 1, \ldots, m \]

that describes the time evolution of \( m \) interacting elements, e.g.,

- gene regulatory networks in system biology,
- prey-predators systems in ecology or business.

**Elements**

- \( x_j, u_j \): state variables and external forces defined on a time interval \( T \).
- \( P_{\theta_j} = \sum_{k=0}^{d} \theta_{jk} D^k \) with \( D^k = d^k/dt \), \( k \in \mathbb{N} \) and \( \theta_j = \{\theta_{j1}, \ldots, \theta_{jd}\} \).
- \( f_{\beta_j} \) known parametric function where \( \beta_j = \{\beta_{j1}, \ldots, \beta_{jq}\} \).
- \( \Theta = \{\theta_1, \ldots, \theta_m\} \) and \( B = \{\beta_1, \ldots, \beta_1\} \), parameters.
Notation

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**Problem statement**

Noisy measurements \(y_{ij}\) of the state variables \(x_1, \ldots, x_m\) at \(n\) time points.

\[
y_{ji} \sim \mathcal{N}(x_j(t_i), \sigma_j^2)
\]

\[
\frac{d}{dt} x_1 = x_1(\theta_1 - \beta_1 x_2),
\]

\[
\frac{d}{dt} x_2 = -x_2(\theta_2 - \beta_2 x_1),
\]

**Problem to solve**

Use the sample \(S = \{(y_{ji}, t_i) \in \mathbb{R} \times T\}_{i,j=1}^{n,m}\) to provide estimators of \(\Theta = \{\theta_1, \theta_2\}, B = \{\beta_1, \beta_2\}, \Sigma = \{\sigma_1, \sigma_2\}\).
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Likelihood approach

\[ l_j(\theta_j, \beta_j, \sigma_j, x_j | S_j) = -\frac{n}{2} \log(\sigma_j^2) - \frac{1}{2\sigma_j^2} \sum_{i=1}^{n} (y_{ji} - x(t_i))^2 \]

for \( x_j \) satisfying that \( P_{\theta_j} x_j = f_{\beta_j} \).

\[ (\hat{\Theta}, \hat{B}, \hat{\Sigma}, \hat{x}_1, \ldots, \hat{x}_n | S) = \arg \max_{\Theta, B, \Sigma} \sum_{j=1}^{m} l_j(\theta_j, \beta_j, \sigma_j, x_j | S_j) \]

- To solve the ODE is needed.
- Parameter identification might be non-stable with noisy data.
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Regularization approach

- Regularization methods are appropriate in this context.
- Replace the original problem by a family of problems where the ODE is used to penalize the likelihood.

Penalized Likelihood approach

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for \( \lambda > 0 \) and \( \Omega(x_j) \) a convex functional.

How to define \( \Omega(x_j) \)?
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How to define \( \Omega(x_j) \)?
MLE vs PMLE: $dx/dt = \theta x$.

\[ \theta_{true} = -2, \quad \theta_{MLE} = -1.12, \quad \theta_{PMLE} = -1.99 \]
Regularization approaches in the literature

Likelihood based approaches [Ramsay et al., 2007, Bouchet, 2007]

- Estimation of the $x'_j$s by nonparametric regression (splines, SVR).
- Differentiation of $\hat{x}_j$ and minimization over the parameters using
  \[
  \Omega(\hat{x}_j) = \| P_{\theta_j} \hat{x}_j - f_{\beta_j}(\hat{x}_1, \ldots, \hat{x}_m, u_j) \|_{L_2}.
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Other approaches

- Bayesian method similar in spirit to Ramsay et al. (2007). Solution of the ODE given as a Gaussian process [Calderhead et al., 2008].
- Kernel Method for estimating 1-dimensional, periodic differential equations [Steinke et al. 2008].
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Idea and approach

Idea

1. Combine the frequentist set-up with the kernel approach.
2. Parameter estimation problem as the maximization of a likelihood with a Reproducing kernel Hilbert space (RKHS) based penalty.

- $P_{\theta_j}x_j = 0$, generalization to non-homogeneous is feasible.

- Penalty, $P_{\theta_j}$ is a differential operator on some space of functions $\mathcal{H}$

$$\Omega_j(x_j) = \|x_j\|_{\mathcal{H}}^2 = \int_T (P_{\theta_j}x_j(t))^2 dt.$$ 

- When $\|x_j\|_{\mathcal{H}}^2 = 0$, $x_j$ is a solution of $P_{\theta_j}x_j = 0$.

- Non homogeneous: Transform $\|P_{\theta_j}x_j - f_{\beta_j}\|_{\mathcal{H}}^2$ to $\|P_{\theta_j}\tilde{x}_j\|_{\mathcal{H}}^2$ where the $\tilde{x}_j$ depends on $\beta_j$. Transform the $y_{ij}$ (details next talk).
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Properties of $\Omega_j(x_j) = \|x_j\|_\mathcal{H}^2$

**RKHS in a nutshell**

- Mercer kernel: continuous, symmetric and positive definite function $K : T \times T \to \mathbb{R}$.
- RKHS: completed space spanned by $x(t) = \sum_{i=1}^{n} \alpha_i K(t_i, t)$, where $n \in \mathbb{N}$, $t_i \in T$ and $\alpha_i \in \mathbb{R}$ and $\langle f, g \rangle_\mathcal{H} = \sum_{i=1}^{n} \sum_{j=1}^{n} \alpha_i \beta_j K(t_i, t_j)$.

- $\mathcal{H}$ is a RKHS whose reproducing kernel is a Green’s function of $P_{\theta}^*P_{\theta}$.

- $P_{\theta}^*P_{\theta}K(t, z) = \delta(t - z)$.

- Functions in $\mathcal{H}$ are characterized by vectors $\alpha = (\alpha_1, \ldots, \alpha_n)^T$.

$$\sum_{j=1}^{m} \left[ -\frac{n}{2} \log(\sigma_j^2) - \frac{1}{2\sigma_j^2} \|y_j - K_{\theta_j} \alpha_j\|^2 - \lambda \alpha_j^T K_{\theta_j} \alpha_j \right]$$

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- $H$ is a RKHS whose reproducing kernel is a Green’s function of $P_\theta^* P_\theta$.
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- Functions in \( H \) are characterized by vectors \( \alpha = (\alpha_1, \ldots, \alpha_n)^T. \)

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\sum_{j=1}^{m} \left[ -\frac{n}{2} \log(\sigma_j^2) - \frac{1}{2\sigma_j^2} \|y_j - K_{\theta_j} \alpha_j\|^2 - \lambda \alpha_j^T K_{\theta_j} \alpha_j \right]
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where \( (K_{\theta_j})_{is} = K_{\theta_j}(t_i, t_s) \) and \( y_j = (y_{j1}, \ldots, y_{jn})^T. \)
Properties of $\Omega_j(x_j) = \|x_j\|_H^2$

**RKHS in a nutshell**

- Mercer kernel: continuous, symmetric and positive definite function $K : T \times T \rightarrow \mathbb{R}$.
- RKHS: completed space spanned by $x(t) = \sum_{i=1}^{n} \alpha_i K(t_i, t)$, where $n \in \mathbb{N}$, $t_i \in T$ and $\alpha_i \in \mathbb{R}$ and $\langle f, g \rangle_H = \sum_{i=1}^{n} \sum_{j=1}^{n} \alpha_i \beta_j K(t_i, t_j)$.

- $\mathcal{H}$ is a RKHS whose reproducing kernel is a Green’s function of $P_\theta^*P_\theta$.

- $P_\theta^*P_\theta K(t, z) = \delta(t - z)$.

- Functions in $\mathcal{H}$ are characterized by vectors $\alpha = (\alpha_1, \ldots, \alpha_n)^T$.

$$\sum_{j=1}^{m} \left[ -n \cdot \frac{1}{2} \log(\sigma_j^2) - \frac{1}{2\sigma_j^2} \|y_j - K_{\theta_j} \alpha_j\|^2 - \lambda \alpha_j^T K_{\theta_j} \alpha_j \right]$$

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Computation of $K_{\theta_j}$

- A Green’s function for $P_{\theta_j}^* P_{\theta_j}$ might be hard or impossible to compute.
- Replace $\alpha_j^T K_{\theta_j} \alpha_j$ by an approximation $\alpha_j^T \tilde{K}_{\theta_j} \alpha_j$.
- $P_{\theta_j} = \sum_{k=0}^{d} \theta_{jk} D^k$: difference operator defined on $t_1, \ldots, t_n$ and

$$D = \Delta^{-1} \cdot \begin{pmatrix} -1 & 1 \\ -1 & 0 & 1 \\ \vdots \\ -1 & 0 & 1 \\ -1 & 1 \end{pmatrix}$$

where $\Delta = \text{diag}(t_2 - t_1, t_4 - t_2, \ldots, t_n - t_{n-2}, t_n - t_{n-1})$.
- Focus on the difference equation $P_{\theta_j} x_j = 0$.
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Finite dimensional approximation, EM algorithm

Idea

- To reduce the error of the finite dimensional approximation.
- To include a number of hidden data points \((t^*_H, y^*_H)\).
- \(K_{\theta_j}\) only depends on the \(t'_i\)s.
- More points \(\rightarrow\) better approximations of the derivatives.
- Iterate EM algorithm.

  1. **E-step** Expectation of the likelihood over \(y_H\).
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(a) ODE model, $dx/dt = \theta x$ with $x(0) = -1$ and $\theta = -2$. True function and obtained solution for 0, 1, and 10 intermediate points.

(b) Estimation of $\theta$ for different number of intermediate points.
Comparisons

- PMLE vs. TS-Ramsay approaches in small-sample-size cases.

- Model \( \frac{dx}{dt} = \theta x \) with \( x(0) = -1 \) and \( \theta = -2 \).

- 100 independent data sets of size 5.

- PMLE method with 10 equally spaced points between each pair of observed data.

- Penalization \( \lambda \) selected using the GCV criteria.

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González, Vujacic and Wit (RUG)
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Simulated result, the Lotka-Volterra system

\[
\frac{dx_1}{dt} = x_1(\theta_1 - \beta_1 x_2), \quad \frac{dx_2}{dt} = -x_2(\theta_2 - \beta_2 x_2)
\]

\(\theta_1 = 0.2, \ \beta_1 = 0.35 \ \theta_2 = 0.7 \ \text{and} \ \beta_2 = 0.40, \ x_{1,0} = 1, \ x_{2,0} = 2.\)

(a) \(\lambda = 100\) and a level noise of \(\sigma = 0.1.\)

(b) \(n = 100\) and a level noise of \(\sigma = 0.1.\)
Conclusions and final remarks

- General methodology to estimate the parameters of system of ordinary differential equations in presence of noisy data.

- The system of equations is directly used as regularizer in the likelihood. A RKHS framework is used for this task. No need to solve the ODE to estimate the parameters.

- Method specially useful in problems with small samples. EM algorithm allows to incorporate into the system missing (or hidden) observations.

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The Green’s function of a differential operator \( P \)

**Definition**

Let \( T \in [a, b] \in \mathbb{R} \) and let \( P : \mathcal{H} \to L^2(T) \) be a differential operator on a class of functions \( \mathcal{H} \) then the Green’s function of \( P \) is a function such that

\[
PG(s, t) = \delta(s - t)
\]

where \( s, t \in T \)

**Remark**

Notice that this equality holds in the distributional sense. This means that for \( f \in L^2(T) \) then

\[
\langle PG(s, t), f \rangle = \langle \delta(s - t), f \rangle = f(t)
\]
Connection between Differential Operators, Green’s functions and Kernels

**Theorem**

Let $T = \mathbb{R}^d$ and $P$ a differential operator on a class of functions $\mathcal{H}$ such that, endowed with the inner product:

$$\langle f, g \rangle_{\mathcal{H}} = \langle Pf, Pg \rangle_{L^2(T)}$$

where $(f, g) \in \mathcal{H}^2$ it is a Hilbert space. Then $\mathcal{H}$ is a RKHS that admits as reproducing kernel the Green function of the operator $P^*P$, where $P^*$ denotes the adjoint operator of $P$. 

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Idea of the proof

Let $H$ be a Hilbert space endowed with the inner product

$$\langle f, g \rangle_H = \langle Pf, Pg \rangle_{L^2(T)}$$

and $K$ be the Green function of the operator $P^*P$, that is

$$P^*PK(s, t) = \delta(s - t)$$

Then, for all $s \in T$, (the evaluation functionals) $K_t = K(t, \cdot) \in H$ because:

- The evaluation functional $K_t$ are bounded.
- $K_t$ has the reproducing property: for all $f \in H$ and $x \in X$, we have that

$$\langle K_t, f \rangle_H = \langle PK_t, Pf \rangle_{L^2(T)} = \langle P^*PK_t, f \rangle_{L^2(T)} = \langle \delta(s - t), f \rangle_{L^2(T)} = f(t)$$
Non homogeneous equation I

- \( \| P_\theta x - f_\beta \|^2 \) cannot be used as a norm in an RKHS.

- If \( x = 0 \) then \( \| P_\theta x - f_\beta \|^2 \) is not necessarily zero.

- Let \( G \) be a Green’s function of \( P_\theta \) and take
  \[
  \tilde{x}(t) = x(t) - x^*(t),
  \]
  \( x^*(t) = \int_T G(z, t)f_\beta(z)dz \) is effectively a collection of solutions of the differential equation.
Non homogeneous equation II

- \( \tilde{x} \) can be calculated independent from the sample \( S \).
- Since \( P_\theta \) is a linear operator we have that for all \( \tilde{x} \)

\[
P_\theta \tilde{x}(t) = P_\theta x(t) - P_\theta x^*(t) = P_\theta x(t) - f_\beta(t),
\]

including for the trivial solution \( \tilde{x} = 0 \).
- Then \( \| P_\theta \tilde{x} \|^2 = \| P_\theta x - f_\beta \|^2 \) and we can use \( \| P_\theta \tilde{x} \| \) as a penalty
- This requires the transformation of the original observations,

\[
\tilde{y}_i = y_i - x^*(t_i)
\]

for \( j = 1, \ldots, n \).
- In the discrete case \( G \) is \( P_\theta^{-1} \)
Transformation, the Lotka-Volterra system

\[
\frac{dx_1}{dt} = x_1(\theta_1 - \beta_1 x_2), \quad \frac{dx_2}{dt} = -x_2(\theta_1 - \beta_2 x_2)
\]

\[\tilde{y}_1 = y_1 - (D - \theta_1 I)^{-1} \beta_1 (\hat{x}_1 \hat{x}_2)\]

\[\tilde{y}_2 = y_2 - (D - \theta_2 I)^{-1} \beta_2 (\hat{x}_1 \hat{x}_2)\]

where \( \hat{x}_1 \) and \( \hat{x}_2 \) are spline smoothers of the original data.