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

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Notation

Consider a dynamical system modelled by a set of ODEs

$$P_{\boldsymbol{\theta}_j} x_j = f_{\beta_j}(x_1, \ldots, x_m, u_j), \;\; j = 1, \ldots, m$$

that describes the time evolution of m interacting elements, *e. g.*,

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

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_{β_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.

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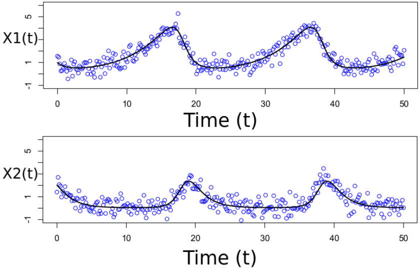
Problem statement

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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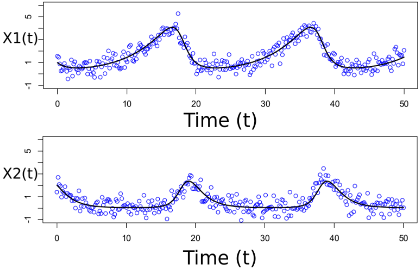

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Likelihood approach

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

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

Penalized Likelihood approach

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

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

How to define $\Omega(x_j)$?

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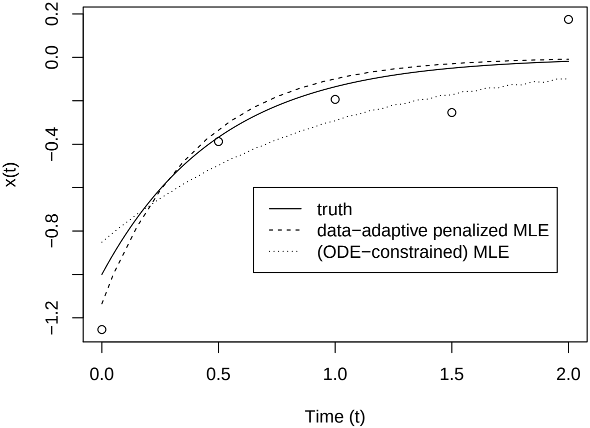
MLE vs PMLE: $dx/dt = \theta x$.



$$\theta_{true} = -2,\ \theta_{MLE} = -1{,}12,\ \theta_{PMLE} = -1{,}99$$

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 $\Omega(\hat{x}_j) = \|P_{\theta_j}\hat{x}_j - f_{\beta_j}(\hat{x}_1, \ldots, \hat{x}_m, u_j))\|_{L_2}$.

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].
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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_{θ_j} is a differential operator on some space of functions $\mathcal{H}$

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

- When $\|x_j\|^2_{\mathcal{H}} = 0$, x_j is a solution of $P_{\theta_j} x_j = 0$.
- Non homogeneous: Transform $\|P_{\theta_j} x_j - f_{\beta_j}\|^2_{\mathcal{H}}$ to $\|P_{\theta_j} \tilde{x}_j\|^2_{\mathcal{H}}$ where the $\tilde{x}_j$ depends on β_j. Transform the y_{ij} (details next talk).

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Properties of $\Omega_j(x_j) = \|x_j\|^2_{\mathcal{H}}$

RKHS in a nutshell

- Mercer kernel: continous, 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 $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_n)^T$.

$$\sum_{j=1}^{m} \left[-\frac{n}{2} \log(\sigma_j^2) - \frac{1}{2\sigma_j^2} \|\mathbf{y}_j - \mathbf{K}_{\theta_j} \boldsymbol{\alpha}_j\|^2 - \lambda \boldsymbol{\alpha}_j^T \mathbf{K}_{\theta_j} \boldsymbol{\alpha}_j \right]$$

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- $\mathcal{H}$ is a RKHS whose reproducing kernel is a Green's function of $P_\theta^* P_\theta$.
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where $(\mathbf{K}_{\theta_j})_{is} = K_{\theta_j}(t_i, t_s)$ and $\mathbf{y}_j = (y_{j1}, \ldots, y_{jn})^T$.

Properties of $\Omega_j(x_j) = \|x_j\|^2_{\mathcal{H}}$

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Computation of $\mathbf{K}_{\theta_j}$

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

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

  where $\Delta = diag(t_2 - t_1, t_4 - t_2, \ldots, t_n - t_{n-2}, t_n - t_{n-1})$.
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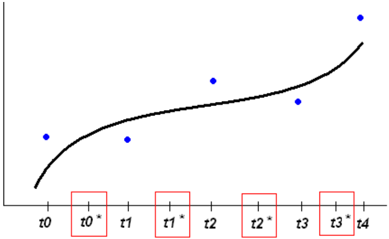
Finite dimensional approximation, EM algorithm

Idea

- To reduce the error of the finite dimensional approximation.
- To include a number of hidden data points $(\mathbf{t}_H^*, \mathbf{y}_H^*)$.
- K_{θ_j} only depends on the $t_i's$.
- More points -> better approximations of the derivatives.
- Iterate EM algorithm.
  1. **E-step** Expectation of the likelihood over $\mathbf{y}_H$.
  2. **M-step** Maximize the likelihood over the parameters using $(\mathbf{y}_O, \hat{\mathbf{y}}_H)$.



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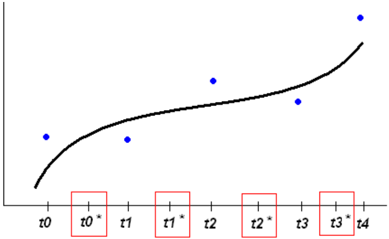

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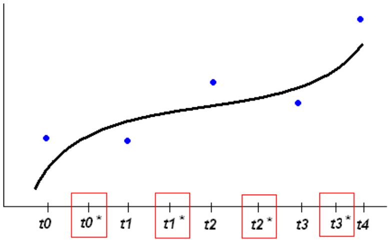

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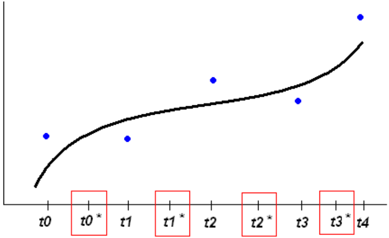

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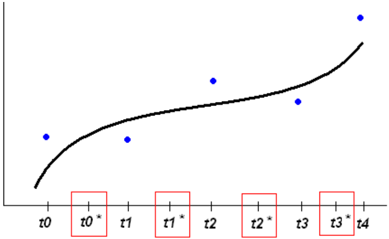

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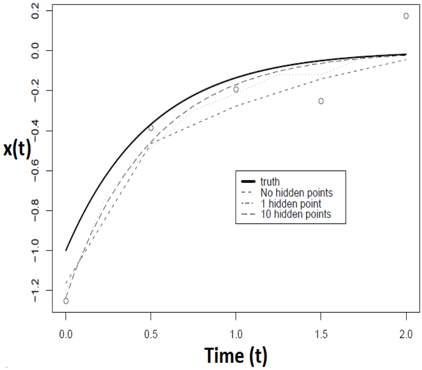
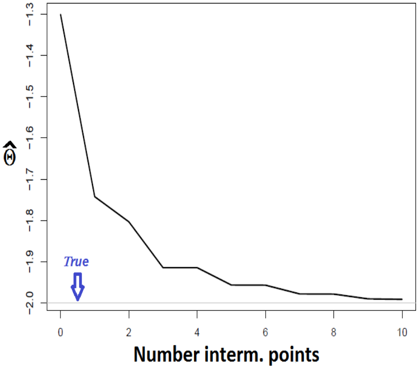


(a) ODE model, $dx/dt = \theta x$ with x(0)=-1 and $\theta = -2$. True function and obtained solution for 0, 1, and 10 intermediate points.



(b) Estimation of θ for different number of intermediate points.

Comparisons

- PMLE vs. TS-Ramsay approaches in small-sample-size cases.
- Model $dx/dt = \theta x$ 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 λ selected using the GCV criteria.
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TS-Ramsay	**Proposed method**
-1.6708 (0.2809)	-1.9448 (0.1594)

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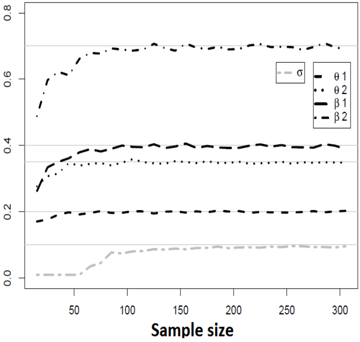
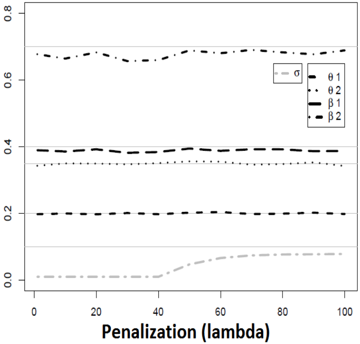
Simulated result, the Lotka-Volterra system

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

$\theta_1 = 0{,}2$, $\beta_1 = 0{,}35$ $\theta_2 = 0{,}7$ 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.
- Performance in real applications, next talk!

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The Green's function of a differential operator P

Definition

Let $T \in [a, b] \in \mathbb{R}$ and let $P : \mathcal{H} \longrightarrow L^2(T)$ 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.

Idea of the proof

Let H be a Hilbert space endowed with the inner product

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

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) $K_t = K(t, \cdot) \in \mathcal{H}$ because:

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

$$\langle K_t, f\rangle_{\mathcal{H}} = \langle PK_t, Pf\rangle_{L^2(T)} = \langle P^*PK_t, f\rangle_{L^2(T)} = \langle \delta(s-t), f\rangle_{L^2(T)} =$$

$$= f(t)$$

Non homogeneous equation I

- $\|P_{\boldsymbol{\theta}}x - f_{\beta}\|^2$ cannot be used as a norm in an RKHS.
- If $x = 0$ then $\|P_{\boldsymbol{\theta}}x - f_{\beta}\|^2$ is not necessarily zero.
- Let G be a Green's function of P_{θ} and take

$$\tilde{x}(t) = x(t) - x^*(t), \tag{1}$$

where $x^*(t) = \int_T G(z,t)f_{\beta}(z)dz$ 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_θ is a linear operator we have that for all $\tilde{x}$

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

  including for the trivial solution $\tilde{x} = 0$.
- Then $\|P_{\boldsymbol{\theta}}\tilde{x}\|^2 = \|P_{\boldsymbol{\theta}}x - f_\beta\|^2$ and we can use $\|P_{\boldsymbol{\theta}}\tilde{x}\|$ 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 $\mathbf{P}_\theta^{-1}$

Transformation, the Lotka-Volterra system

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

- $\tilde{\mathbf{y}}_1 = \mathbf{y}_1 - (\mathbf{D} - \theta_1 \mathbf{I})^{-1} \beta_1 (\hat{\mathbf{x}}_1 \hat{\mathbf{x}}_2)$
- $\tilde{\mathbf{y}}_2 = \mathbf{y}_2 - (\mathbf{D} - \theta_2 \mathbf{I})^{-1} \beta_2 (\hat{\mathbf{x}}_1 \hat{\mathbf{x}}_2)$

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