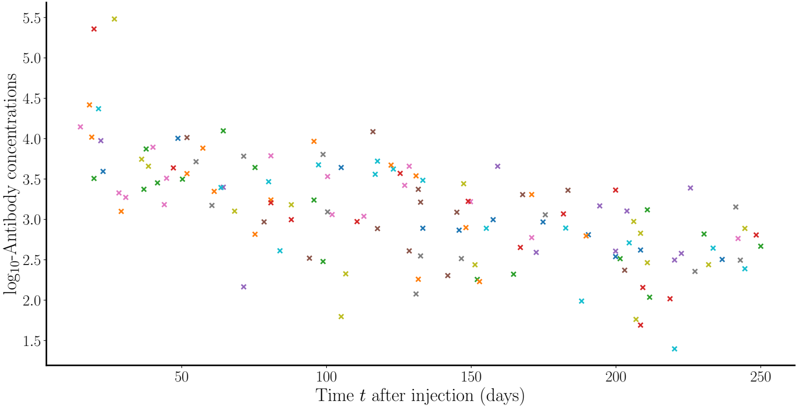
Gaussian Processes for the inference of partially known mechanistic models used for clinical trial data analysis

Julien Martinelli ¯_(ツ)_/¯

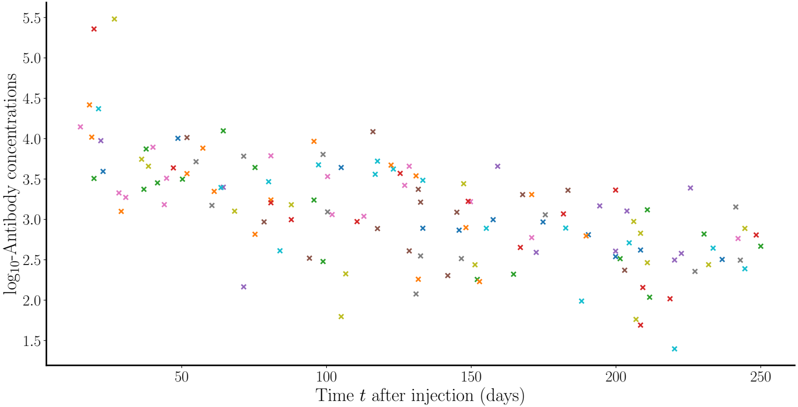
November 13rd, 2023

Motivation



5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
$\log_{10}$-Antibody concentrations
50
100
150
200
250
Time t after injection (days)

Motivation



Obs $y_i(t) = f(t;\theta_i) + \varepsilon$ for a **known mechanistic model** f and $1 \leq i \leq M$ patients.

$$f(t;\theta_i) = e^{-\delta_{Ab,i}(t-t_0)} Ab_{0,i} + \phi_{S,i} \frac{e^{-\delta_{S,i}(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_{S,i}} + \phi_L \frac{e^{-\delta_L(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_L}$$

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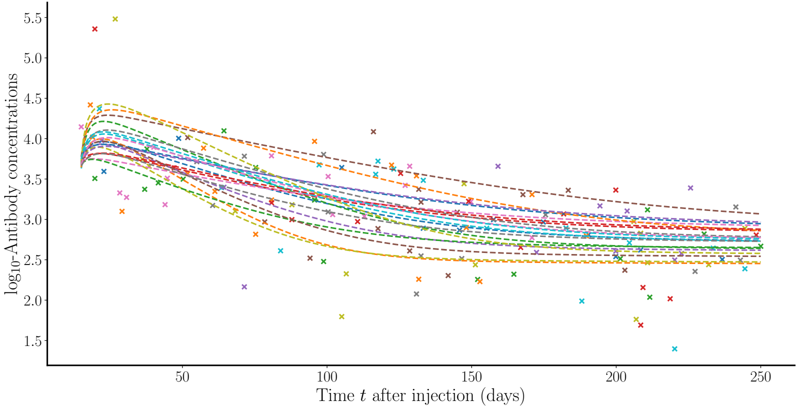

Latent trajectories $f(t;\theta_i)$ with **unkwown parameters** $\theta_i = \theta + b_i$ (mixed-effects)

$$f(t;\theta_i) = e^{-\delta_{Ab,i}(t-t_0)} Ab_{0,i} + \phi_{S,i} \frac{e^{-\delta_{S,i}(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_{S,i}} + \phi_L \frac{e^{-\delta_L(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_L}$$

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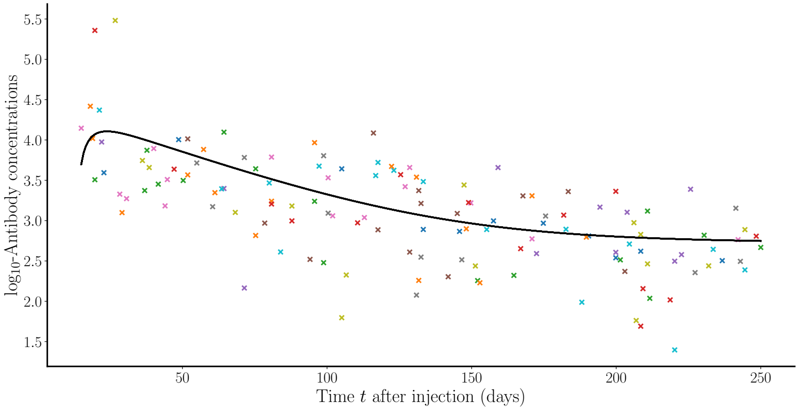

We want to say something about the population mean behavior characterized by θ.

$$f(t;\theta_i) = e^{-\delta_{Ab,i}(t-t_0)} Ab_{0,i} + \phi_{S,i} \frac{e^{-\delta_{S,i}(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_{S,i}} + \phi_L \frac{e^{-\delta_L(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_L}$$

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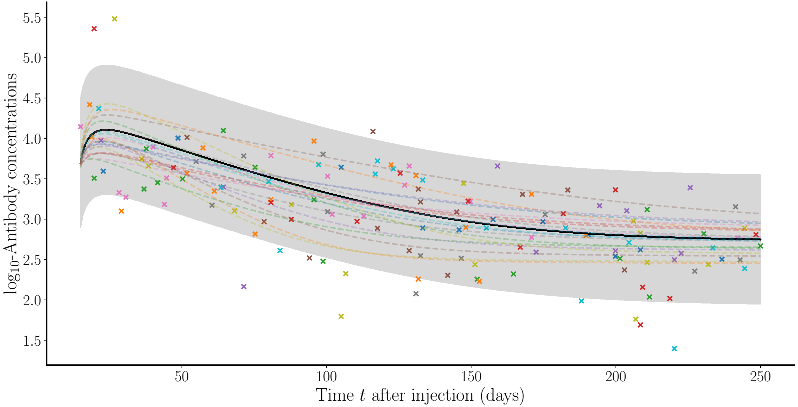
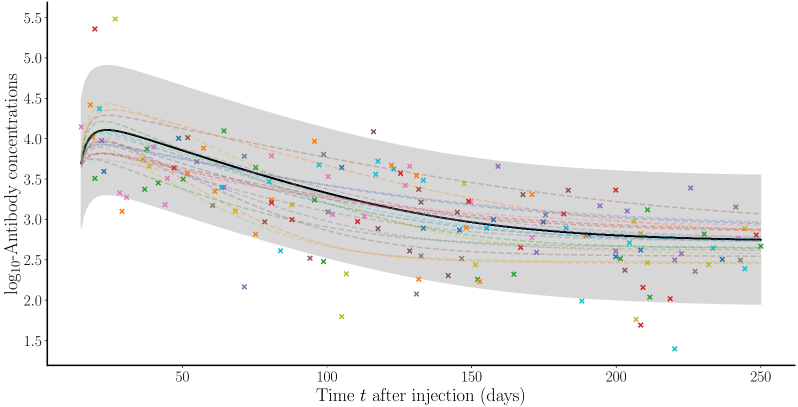


While being able to incorporate **prior information** about θ and $\{b_i\}_{i=1}^M$, leading to principled uncertainty quantification.

Motivation



Can we still do that when f is partially known, or even unknown?

$f_i(t) = \mu_0(t) + g_i(t) \iff$ learn **functions** not parameters

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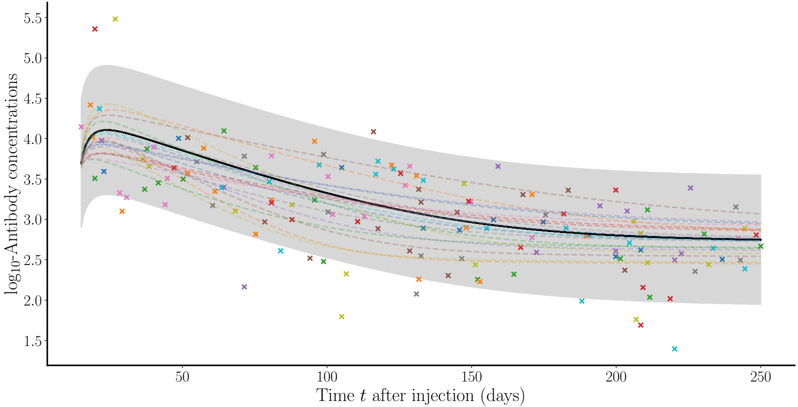

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Answer: yes (hopefully ¯_(ツ)_/¯), using **Gaussian Processes**

Outline

1. Gaussian Processes in a nutshell
2. Analogies, extensions
3. Application: learning partially known vector fields from heterogeneous data

Gaussian processes (GPs)

A GP is a stochastic process acting as a **prior distribution over function spaces**

$$f(x) \sim \mathcal{GP}(m_{\theta_m}(x), k_{\theta_k}(x, x'))$$

$m_{\theta_m}(x) = \mathbb{E}[f(x)]$ is the **mean function**, $k_{\theta_k}(x, x') = \mathrm{Cov}[f(x), f(x')]$ the **kernel**.
(Hyper-)Parameterized by (θ_m, θ_k).

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GPs generalize the multivariate normal distribution to infinite-dimensional spaces
For any collection of function values $\mathrm{f} = [f(x_1), \dots, f(x_n)]$

$$\mathrm{f} \sim \mathcal{N}(\mathrm{m}, \mathrm{K})$$

With $\mathrm{m} = [m_{\theta_m}(x_1), \dots, m_{\theta_m}(x_n)]$ and $\mathrm{K} = (k_{\theta_k}(x_i, x_j))_{1 \le i,j \le n}$

Example - Radial Basis Function Kernel

$$\mathrm{Cov}[f(x), f(x')] := k_{\theta_k}(x, x') = \sigma_{\mathrm{amp}} \exp\left(-\frac{(x - x')^2}{2\ell^2}\right) \qquad \theta_k = (\sigma_{\mathrm{amp}}, \ell)$$

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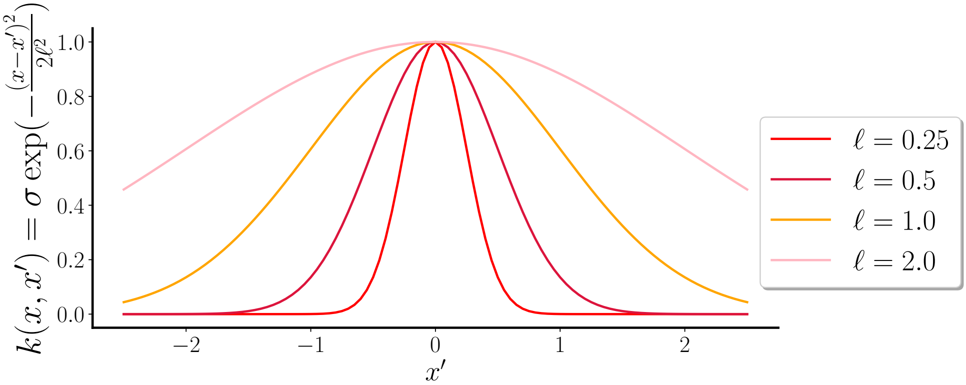

σ_{amp} handles the variance magnitude and ℓ how fast correlation decreases

Animations are always better to understand ¯_(ツ)_/¯

Nice thing about GPs: posterior predictive available in closed-form

Let $\mathscr{D} = (x_i, y_i)_{i=1}^n = (\mathrm{X}, \mathrm{y})$ with $y_i = f(x_i) + \varepsilon$. For a new function value f_* located at x_*,

$$f_*|\mathrm{y} \sim \mathcal{N}(m_{\theta_m}(x_*|\mathscr{D}), \sigma^2(x_*|\mathscr{D}))$$
$$m(x_*|\mathscr{D}) = m_{\theta_m}(x_*) + k_{\theta_k}(x_*, \mathrm{X})^T(\mathrm{K} + \sigma^2_{\text{noise}} I)^{-1}(\mathrm{y} - \mathrm{m})$$
$$\sigma^2(x_*|\mathscr{D}) = k_{\theta_k}(x_*, x_*) - k_{\theta_k}(x_*, \mathrm{X})^T(\mathrm{K} + \sigma^2_{\text{noise}} I)^{-1} k_{\theta_k}(\mathrm{X}, x_*)$$

Where $k_{\theta_k}(x_*, \mathrm{X})^T = [k_{\theta_k}(x_*, x_1), \dots, k_{\theta_k}(x_*, x_n)]$.

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Hyperparameters $(\theta_m, \theta_k, \sigma_{\text{noise}})$ learned through marginal likelihood maximization.

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Hyperparameters $(\theta_m, \theta_k, \sigma_{\text{noise}})$ learned through marginal likelihood maximization.

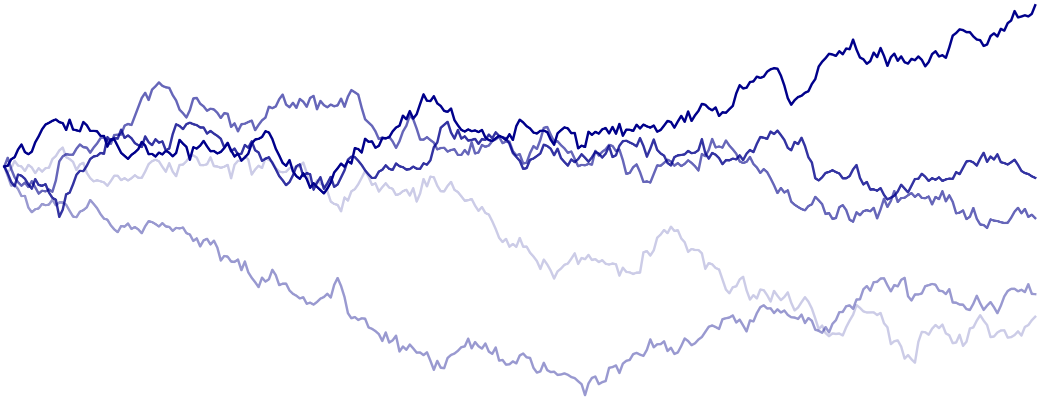
For a zero-mean prior m, the posterior mean can be written as

$$m(x_*|\mathscr{D}) = \sum_{i=1}^{n} \alpha_i k_{\theta_m}(x_*, x_i)$$

with $\alpha = (K + \sigma^2_{\text{noise}} I)^{-1}\mathrm{y}$. **GPs: probabilistic counterpart of kernel methods.**

Animations are always better to understand ¯_(ツ)_/¯

You probably used GPs at some point without even noticing



Brownian Motion is a GP where the kernel is $k(x, x') = \min(x, x')$

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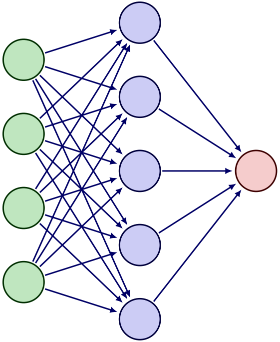
In the infinite number of neurons, 1-layer Neural Networks can be written as GPs

$$f(x) = b + \sum_{l=1}^{L} v_l s(w_l x + b_l)$$



Under the assumption of i.i.d Gaussian weights $\{v_l\}_l, \{w_l\}_l$ and biases $b, \{b_l\}_l$,

$$\mathbb{E}[f(x)] = 0 \text{ and } \mathrm{Cov}[f(x), f(x')] = \sigma_b^2 + \sigma_v^2 L \mathbb{E}_{w,b}[s(wx+b)s(wx'+b)]$$

Scale the output variance with $\sigma_v^2 = \frac{\omega}{L}$ and apply CLT to get the final kernel.

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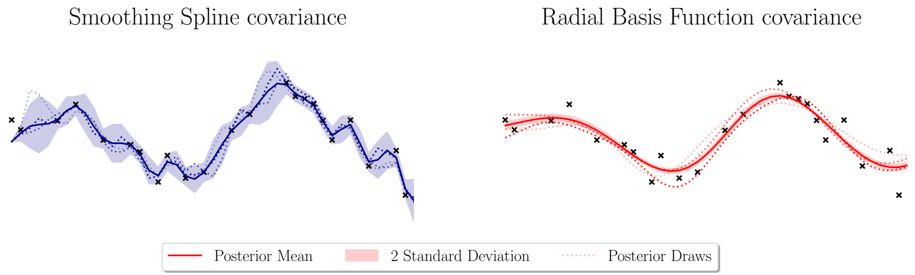
The cubic smoothing spline estimate $\hat{f}$ of the function f is also a GP

$$\underset{\hat{f}}{\operatorname{argmin}} \sum_{i=1}^{n} (\hat{f}(x_i) - y_i)^2 + \lambda \int_0^1 \hat{f}''(x)^2 \mathrm{d}x$$

$$\iff \hat{f} \sim \mathcal{GP}\left(0, \sigma_{\text{amp}} \left(\frac{|x - x'|}{2} \min(x, x')^2 + \frac{\min(x, x')^3}{3}\right) + \sigma_{\text{noise}} \delta_{xx'}\right)$$



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Kalman Filters are a particular type of GPs equipped with the Markov property

Classical GP regression problem **($\star$)**

$$U(t) \sim \mathscr{GP}(0, k(t, t'))$$
$$Y_t = U(t_k) + \xi_k$$

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Kalman Filters are a particular type of GPs equipped with the Markov property
Classical GP regression problem **(⋆)**

$$
\begin{aligned}
U(t) &\sim \mathscr{GP}(0, k(t, t')) \\
Y_t &= U(t_k) + \xi_k
\end{aligned}
$$

Will lead to the same solution as the smoothing problem **(⋆⋆)**

$$
\begin{aligned}
d\bar{U}(t) &= A\bar{U}(t) + BdW(t) \\
U(t_0) &= U_0 \sim \mathcal{N}(0, P_0) \\
U &= H\bar{U}
\end{aligned}
$$

(⋆): you provide the kernel k. **(⋆⋆)**: you provide the SDE matrices A, B.

Extensions

Nonstationary kernels

Classical kernels $k_{\theta_k}(x, x')$ can be written $k_{\theta_k}(h)$ with $h = (x - x')$:
$\implies$ output correlation only depends on the distance between inputs, not their location, **stationnarity**: $p(x_1, \ldots, x_n) = p(x_{1+\tau}, \ldots, x_{n+\tau})$.

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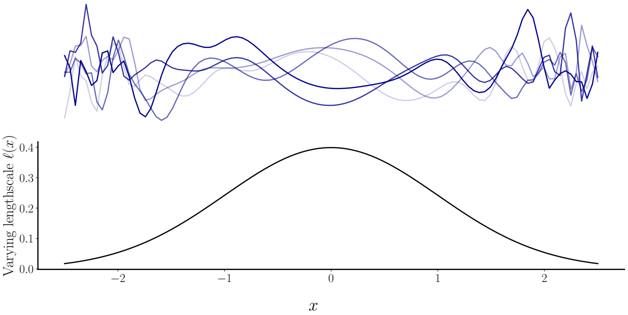
E.g. make hyperparameters a function of the input $k(x, x') = \sigma_{\text{amp}} \exp\left(-\frac{1}{2} \frac{(x - x')^2}{\ell(x)^2 + \ell(x')^2}\right)$



Extensions

Multitask GPs for multiple outputs

Extend the input space with a *patient dimension*: $x \leftarrow (x, i)$ and define

$$k((x, i), (x', i')) = k_\theta(x, x')k_{\mathsf{task}}(i, i').$$

Typically, k_{task} is the inter-patient covariance matrix, estimated from data.

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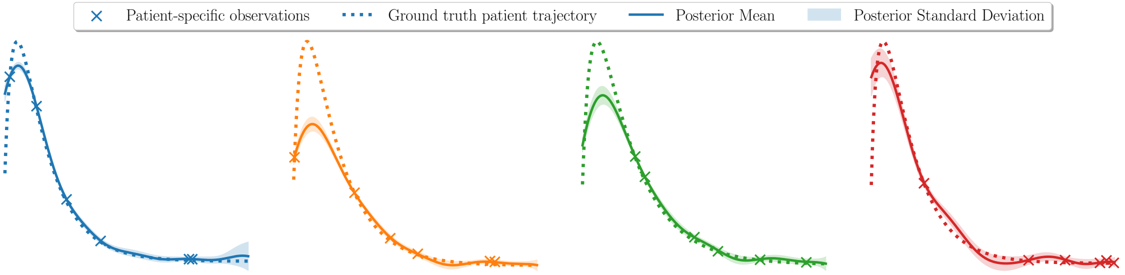
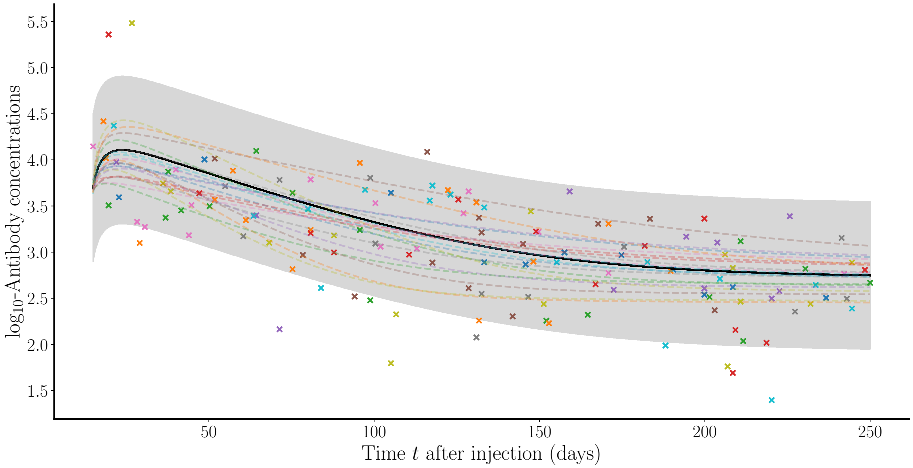


Back to the original problem



$$y_i(t) = \mu_0(t) + f_i(t) + \varepsilon_i(t), \qquad i = 1, \dots, M$$

MAGMA - Multi task Gaussian processes with common mean

Arthur Leroy, Pierre Latouche, Benjamin Guedj and Servane Gey, 2022

$$y_i(t) = \mu_0(t) + f_i(t) + \varepsilon_i(t)$$

$$\mu_0(\cdot) \sim \mathcal{GP}(m_0(\cdot), k_{\theta_0}(\cdot, \cdot))$$

$$f_i(\cdot) \sim \mathcal{GP}(0, c_{\theta_i}(\cdot, \cdot))$$

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Assumptions:

- f_i's independent, ε_i's independent
- $\forall i, \mu_0, f_i, \varepsilon_i$ are independent

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Assumptions:

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$\Longrightarrow$ $\{y_i|\mu_0\}_i$ **are independent**

$$\mathrm{y}_i(\mathrm{t}_i)|\mu_0(\mathrm{t}_i) \sim \mathcal{N}\left(\mathrm{y}_i; \mu_0(\mathrm{t}_i), \Psi^{\mathrm{t}}_{\theta_i,\sigma^2_{\text{noise},i}}\right)$$

m_0 is the (hyper)-prior mean, and encodes **mechanistic knowledge**.
It can be parametrized as well.

Population mean *a posteriori* distribution

Hyperparameters: $\Theta = (\theta_0, \{\theta_i\}_i, \{\sigma^2_{\text{noise,i}}\}_i)$. Assuming for simplicity $\mathrm{t}_i = \mathrm{t}_{i'} = \mathrm{t}$,

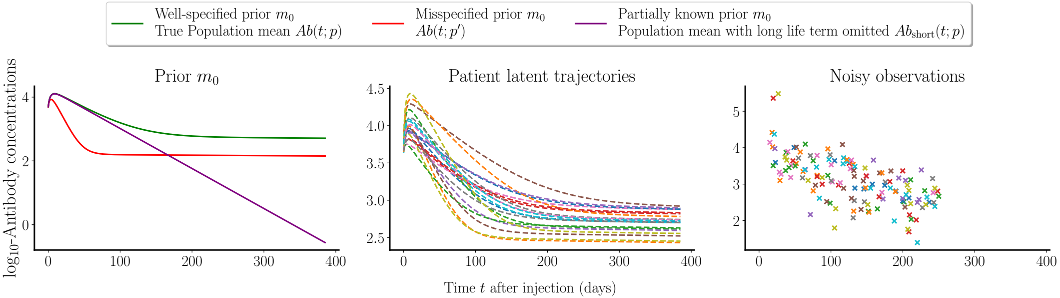
$$p(\mu_0(\mathrm{t}) | \{\mathrm{y}_i\}_i, \Theta) = \mathcal{N}(\hat{m}_0(\mathrm{t}), \hat{\mathrm{K}}^{\mathrm{t}})$$

$$\hat{\mathrm{K}} = \left({\mathrm{K}^{\mathrm{t}}_{\theta_0}}^{-1} + \sum_{i=1}^{M} {\Psi^{\mathrm{t}}_{\theta_i, \sigma^2_{\text{noise},i}}}^{-1} \right)^{-1}$$

$$\hat{m}_0(\mathrm{t}) = \hat{\mathrm{K}}^{\mathrm{t}} \left({\mathrm{K}^{\mathrm{t}}_{\theta_0}}^{-1} m_0(\mathrm{t}) + \sum_{i=1}^{M} {\Psi^{\mathrm{t}}_{\theta_i, \sigma^2_{\text{noise},i}}}^{-1} \mathrm{y}_i \right)$$

- $\hat{\theta}_0$ and $(\hat{\theta}_i, \hat{\sigma}^2_{\text{noise},i})$ obtained independently **like in usual mixed-effect models**
- We can investigate how m_0 and $\hat{m}_0$ differ, what happens if m_0 is misspecified...

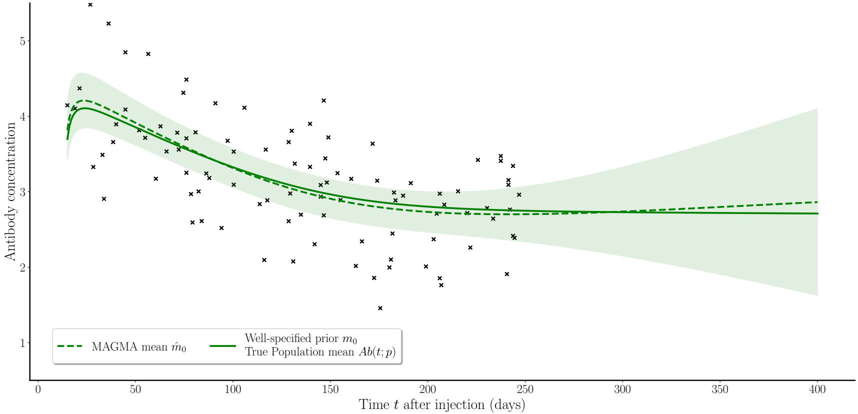
Case study



$$Ab(t;\theta_i) = e^{-\delta_{Ab,i}(t-t_0)} Ab_{0,i} + \phi_{S,i} \frac{e^{-\delta_{S,i}(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_{S,i}} + \phi_L \frac{e^{-\delta_L(t-t_0)} - e^{-\delta_{Ab,i}(t-t_0)}}{\delta_{Ab,i} - \delta_L}$$

- $M = 15$ patients
- $\approx 5 - 8$ observations per patient at different time points
- No mixed-effect for the long-life parameters δ_L and ϕ_L
- Noise is added to the observations

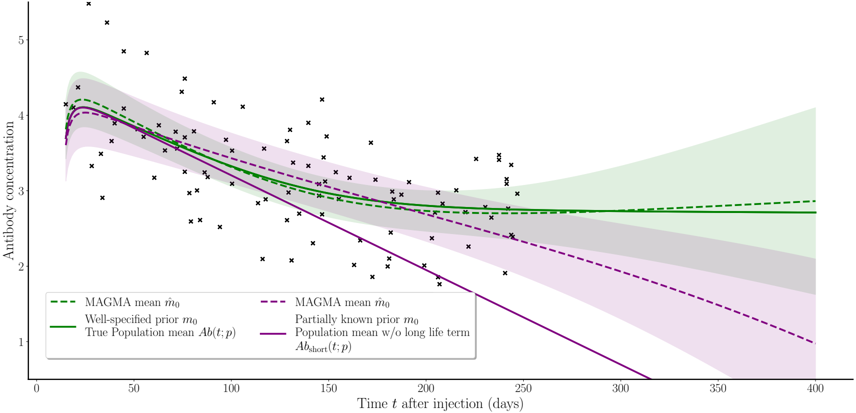
Comparing learned mean functions $\hat{m}_0$ for different priors m_0



$\hat{m}_0$ slightly deviates from the (well-specified) prior m_0 to better fit the data

Post hoc sanity check of the prior: m_0 included in the CIs computed from $\hat{m}_0$

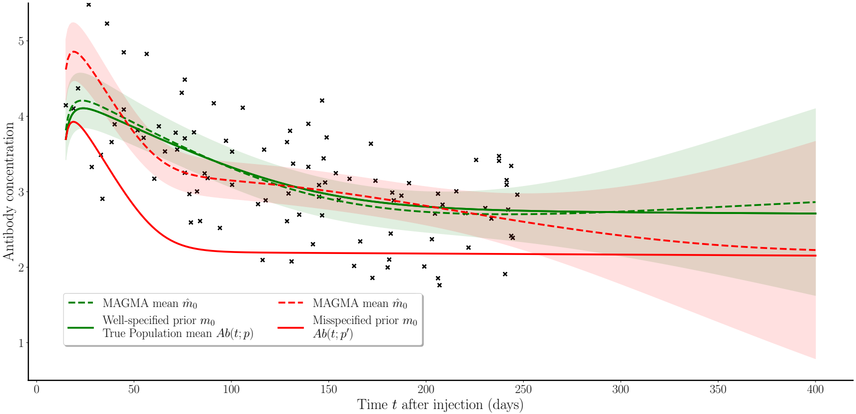
Comparing learned mean functions $\hat{m}_0$ for different priors m_0



$\hat{m}_0$ clearly deviates from the (misspecified) prior m_0 to better fit the data

Post hoc sanity check: over the long run, m_0 without long-life term is **not** included in $\hat{m}_0$'s confidence intervals!

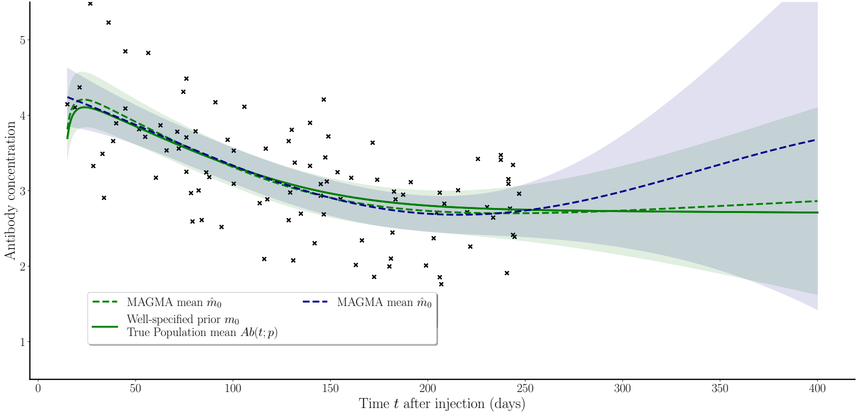
Comparing learned mean functions $\hat{m}_0$ for different priors m_0



For the misspecified case, $\hat{m}_0$ adapts its mean level

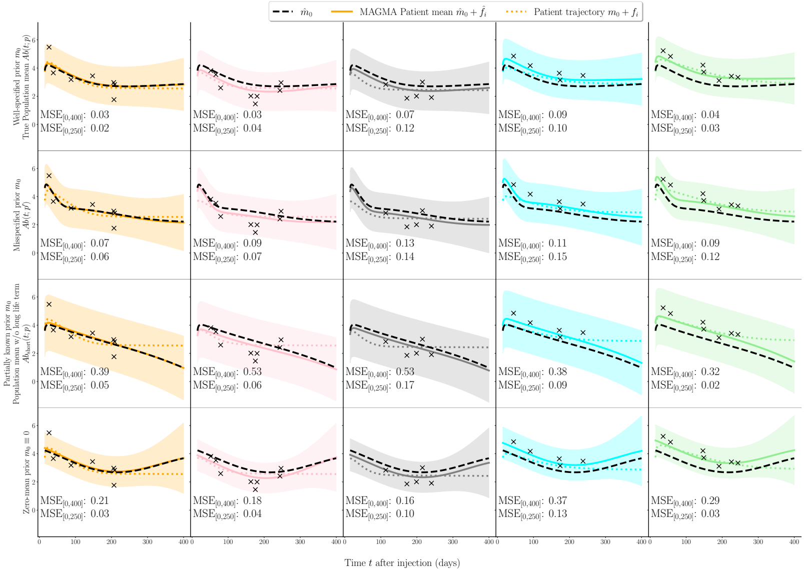
In the presence of data, confidence intervals clearly rule out the misspecified prior

Comparing learned mean functions $\hat{m}_0$ for different priors m_0



When data is abundant, even a zero-mean prior $m_0 \equiv 0$ yields a correct estimate of the population dynamics

Individual results for 5 out of 15 patients



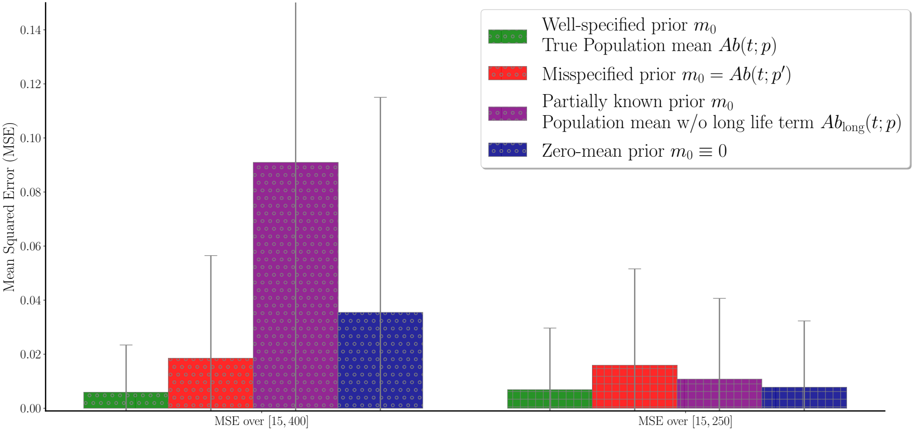
Metric:

$$\int \left(\hat{f}_i(t) - f_i(t)\right)^2 \mathrm{d}t$$

Using ground truth prior mean is best (top row)

Prior without long-life term worst performer (row 3) **over the long run**

Results averaged over 20 different datasets for $M = 15$ patients



- When considering the whole time horizon, the prior clearly matters
- Over $[15, 250]$, except for misspecified prior, performances are roughly similar

Roadmap

- Often, the dynamics are defined through ODEs with no closed-form solution

$$\begin{cases} y_i(t) = X_i(t) + \varepsilon_i(t) \\ \dot{X}_i(t) = \mu_0(X_i(t)) + f_i(X_i(t)) \\ X_i(0) = x_{0,i} \end{cases}$$

$p(\mu_0|\mathrm{y})$ **is not Gaussian anymore!** Requires MCMC, Variational Inference...

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- What if we do not know the full dynamics of **unobserved** variables

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- Handling D**-dimensional** ODE systems, $D > 1$
- What if we do not know the full dynamics of **unobserved** variables
- **Bayesian Experimental Design**
  - E.g., given the current model, when should patient i be called for the next measurement so that population predictive uncertainty is maximally reduced?

Conclusion

- GPs $\mathscr{GP}(m, k)$ are powerful tools for **nonparametric regression**
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Thank you for your attention ¯_(ツ)_/¯