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Integrative Analysis and Imputation of Multiple Data Streams via Deep Gaussian Process

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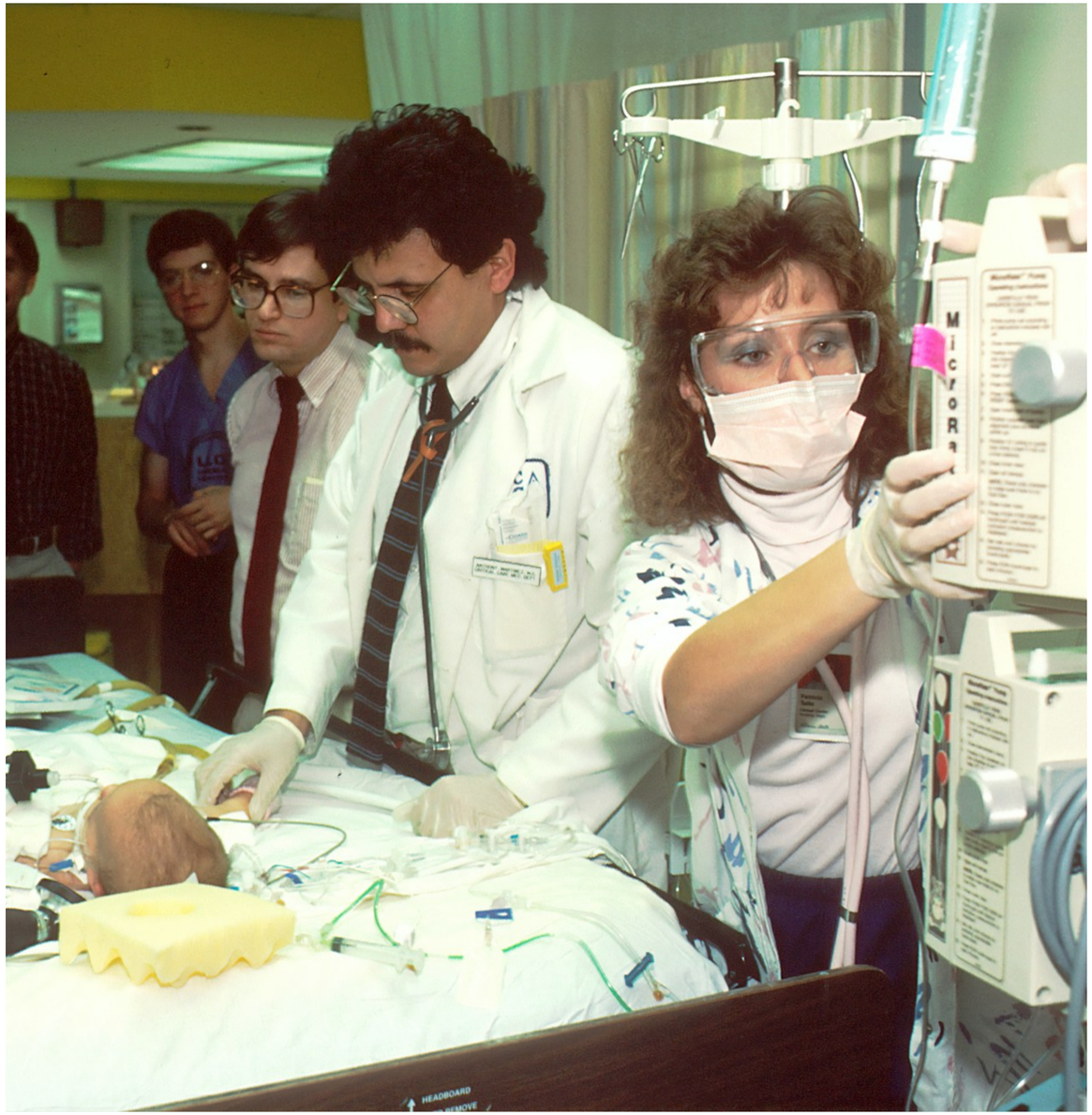
Background

- In ICU settings, data come from multiple sources and are inherently related
- Measurements collected at irregular intervals (informative sampling)—aligning them will result in missing values
- Cannot always get more samples! Some measurements are invasive (Siegal et al., 2023)



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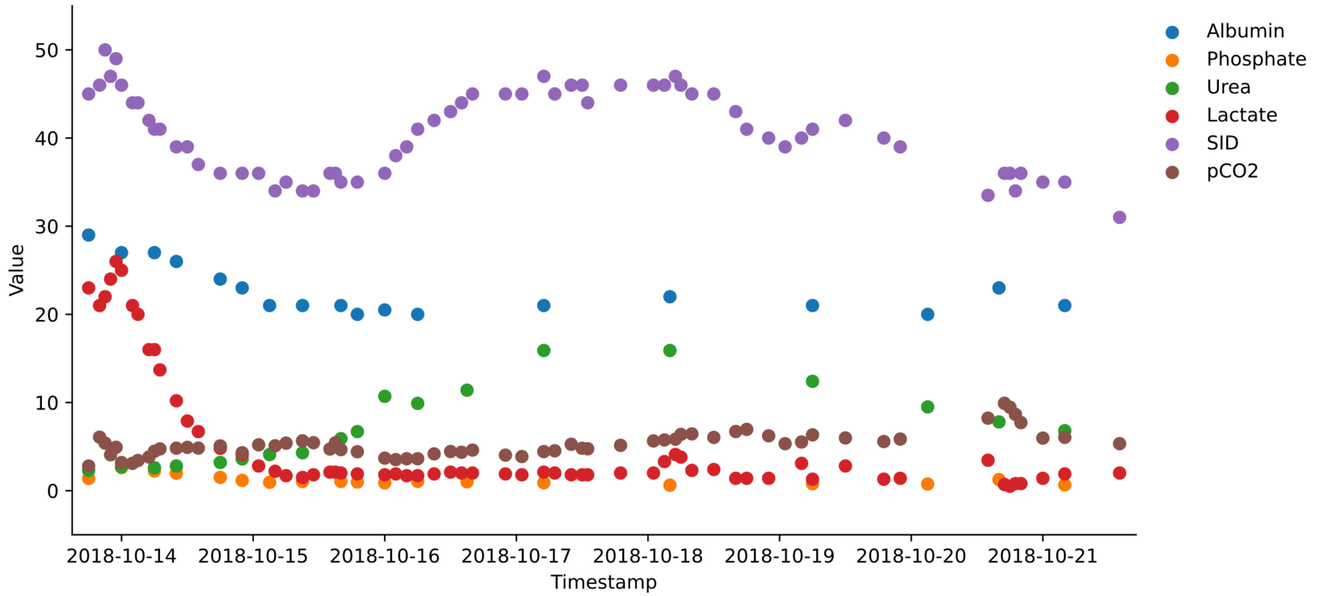
Challenges

- We want to impute missing values…
- but traditional imputation often ignores temporal structure (e.g. MICE) & uncertainty (e.g. deep learning)
- Need for robust, uncertainty-aware imputation in critical care datasets



On uncertainty quantification

- Medical observations are inherently uncertain, coming from measurement errors or the use of surrogate markers → leading to unreliable model predictions (Cabitza et al., 2017)

- Alerts triggered by prediction tools are often not accompanied by a clinically actionable change → *alarm fatigue* (Embi & Leonard, 2012; Umscheid et al., 2015)

Physicochemical model

- In critical care medicine, clinicians monitor pH levels to inform them about the conditions of a patient
- While pH is the primary variable to monitor, other covariates provide information on metabolic status (Gattioni et al., 2017)
- pH can be modelled from strong ion difference (SID), total weak acid, and pCO2 by the Stewart-Fencl approach

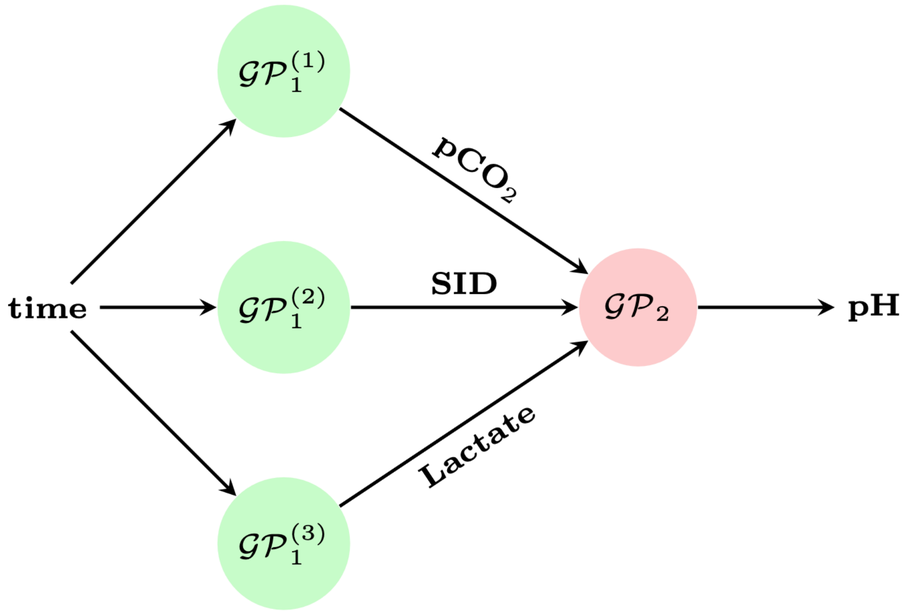
$$[SID] + [H^+] - K_C\frac{pCO_2}{[H^+]} - \frac{K_A A_{TOT}}{K_A + [H^+]} - K_3\frac{K_C pCO_2}{[H^+]^2} - \frac{K_W}{[H^+]} = 0$$

where SID, A_{TOT}, and pCO_2 are independent variables and K_X are constants.

Proposed solution

Deep Gaussian Process with Stochastic Imputation (Ming et al., 2023)

- GPs and Deep GPs are typically used for emulating computationally expensive numerical models
- Integrates longitudinal & cross-sectional information
- Joint modelling for all data streams
- Provides uncertainty quantification for imputed values



Gaussian Processes

$$\mathbf{Y} \sim \mathcal{N}(\boldsymbol{\mu}, \sigma^2 \mathbf{R}(\mathbf{X}))$$

where $\boldsymbol{\mu} \in \mathbb{R}^N$ is the mean vector, σ^2 is the scale parameter, and $\mathbf{R}(\mathbf{X}) \in \mathbb{R}^{N \times N}$ is the correlation matrix

Cell ij in the matrix $\mathbf{R}(\mathbf{X})$ is specified by $k(\mathbf{X}_{i*}, \mathbf{X}_{j*}) + \eta 1_{\{\mathbf{X}_{i*} = \mathbf{X}_{j*}\}}$, where $k(\cdot, \cdot)$ is a given kernel function with η being the nugget term and $1_{\{\cdot\}}$ being the indicator function

Gaussian Processes

Given a new input position $\mathbf{x_0} \in \mathbb{R}^{1\times D}$, then

$$\mu_0 = \mathbf{r}(\mathbf{x}_0)^T \mathbf{R}(\mathbf{x})^{-1}\mathbf{y}$$

$$\sigma_0^2 = \sigma^2(1 + \eta - \mathbf{r}(\mathbf{x}_0)^T \mathbf{R}(\mathbf{x})^{-1}\mathbf{r}(\mathbf{x}_0))$$

where $\mathbf{r}(\mathbf{x}_0) = [k(\mathbf{x}_0, \mathbf{x}_{1*}), \ldots, k(\mathbf{x}_0, \mathbf{x}_{N*})]^T$

Deep GPs

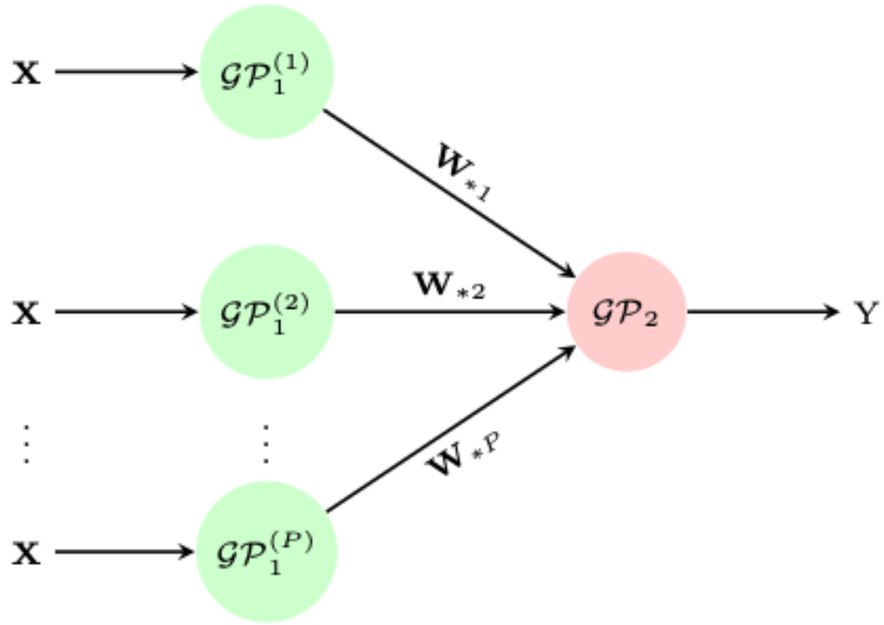
- Consider a GP model with N sets of D-dimensional input ($\mathbf{X} \in \mathbb{R}^{N \times D}$) and produces N sets of P-dimensional output ($\mathbf{W} \in \mathbb{R}^{N \times P}$)
- In the Stewart–Fencl approach, this multi-output GP model can be interpreted as using time as a shared input variable and predicting covariates as outputs
- We can assume that the output $\mathbf{W}$ of this model, i.e. the column vectors $\mathbf{W}_{*p}$, is conditionally independent with respect to $\mathbf{X}$
- We then link the output $\mathbf{W}$ to a second GP model that produces N one-dimensional outputs ($\mathbf{Y} \in \mathbb{R}^{N}$), e.g. to predict pH

Deep GPs

We can see it as a linked GP where, for a new input position $\mathbf{x}_0$, the posterior predictive distribution of the output can be written as

$$p(y_0 \mid \mathbf{x}_0; \mathbf{y}, \mathbf{w}, \mathbf{x}) = \int p(y_0 \mid \mathbf{w}_0; \mathbf{y}, \mathbf{w}, \mathbf{x}) p(\mathbf{w}_0 \mid \mathbf{x}_0; \mathbf{y}, \mathbf{w}, \mathbf{x}) d\mathbf{w}_0$$

$$= \int p(y_0 \mid \mathbf{w}_0; \mathbf{y}, \mathbf{w}) \prod_{p=1}^{P} p(w_{0p} \mid \mathbf{x}_0; \mathbf{w}_p^*, \mathbf{x}) d\mathbf{w}_0$$



Deep GPs

Then the mean and variance become

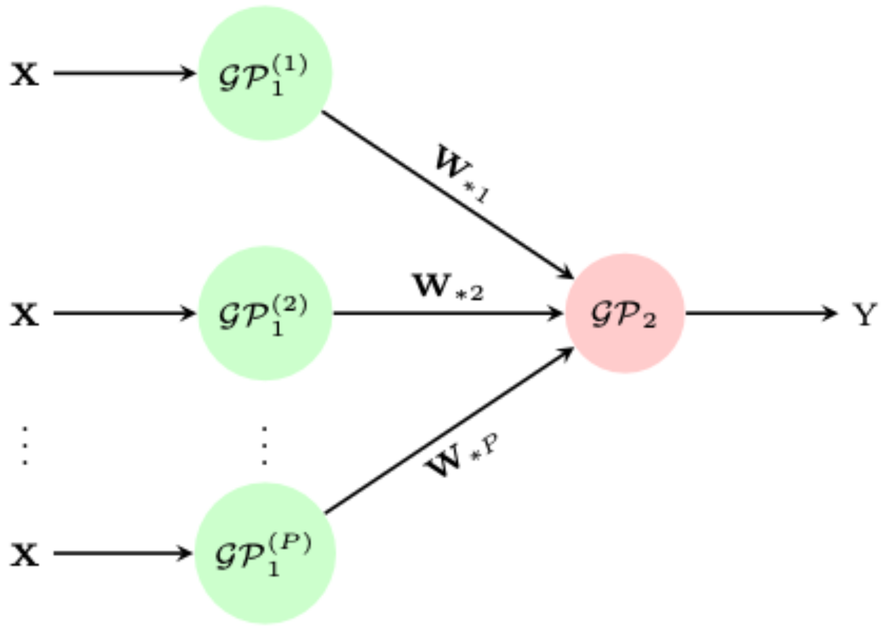
$$\tilde{\mu}_0 = \mathbf{I}(\mathbf{x}_0)^T \mathbf{R}(\mathbf{w})^{-1} \mathbf{y}$$

$$\tilde{\sigma}_0^2 = \mathbf{y}^T \mathbf{R}(\mathbf{w})^{-1} \mathbf{J}(\mathbf{x}_0) \mathbf{R}(\mathbf{w})^{-1} \mathbf{y} - \left[\mathbf{I}(\mathbf{x}_0)^T \mathbf{R}(\mathbf{w})^{-1} \mathbf{y}\right]^2 + \sigma^2 \left(1 + \eta - \text{tr}\left[\mathbf{R}(\mathbf{w})^{-1} \mathbf{J}(\mathbf{x}_0)\right]\right)$$

where $\mathbf{I}(\mathbf{x}_0) \in \mathbb{R}^{N \times 1}$ with its i-th element $I_i = \prod_{p=1}^{P} \mathbb{E}[k_p(W_{0p}(\mathbf{x}_0), w_{ip})]$

and $\mathbf{J}(\mathbf{x}_0) \in \mathbb{R}^{N \times N}$ with its ij-th element $J_{ij} = \prod_{p=1}^{P} \mathbb{E}[k_p(W_{0p}(\mathbf{x}_0), w_{ip}) k_p(W_{0p}(\mathbf{x}_0), w_{jp})]$

Deep GP algorithm



Algorithm 1 Construction of a DGP emulator with the hierarchy in Figure 2

Input: i) Realisations $\mathbf{x}$ and $\mathbf{y}$; ii) A new input position $\mathbf{x}_0$; iii) The number of imputations N.

Output: Mean and variance of $y_0(\mathbf{x}_0)$.

1: **for** $i = 1, \ldots, N$ **do**

2: Given $\mathbf{x}$ and $\mathbf{y}$, draw an imputation $\{\mathbf{w}_{*p,i}\}_{p=1,\ldots,P}$ of the latent output $\{\mathbf{W}_{*p}\}_{p=1,\ldots,P}$ via an Elliptical Slice Sampling [40] update.

3: Construct the LGP emulator $\mathcal{LGP}_i$ with the mean $\tilde{\mu}_{0,i}(\mathbf{x}_0)$ and variance $\tilde{\sigma}^2_{0,i}(\mathbf{x}_0)$, given $\mathbf{x}$, $\mathbf{y}$, and $\{\mathbf{w}_{*p,i}\}$.

4: **end for**

5: Compute the mean $\mu(\mathbf{x}_0)$ and variance $\sigma^2(\mathbf{x}_0)$ of $y_0(\mathbf{x}_0)$ by

$$\mu(\mathbf{x}_0) = \frac{1}{N}\sum_{i=1}^{N} \tilde{\mu}_{0,i}(\mathbf{x}_0),$$

$$\sigma^2(\mathbf{x}_0) = \frac{1}{N}\sum_{i=1}^{N} \left([\tilde{\mu}_{0,i}(\mathbf{x}_0)]^2 + \tilde{\sigma}^2_{0,i}(\mathbf{x}_0) \right) - \mu(\mathbf{x}_0)^2.$$

Numerical experiment

- Data used: Paediatric ICU admissions (n=14)
- Variables: pCO2, SID (Na^+, Cl^-), lactate (weak acid), pH
- Preprocessing: Hourly discretisation, z-score normalisation, masking to simulate missingness
- Benchmarks:
  - Last observation carried forward (LOCF)
  - MICE
  - GP interpolation

Model evaluation

- Four levels of missingness: 10%, 20%, 30%, 40%
- Two evaluation metrics
  - Mean absolute error – imputation accuracy

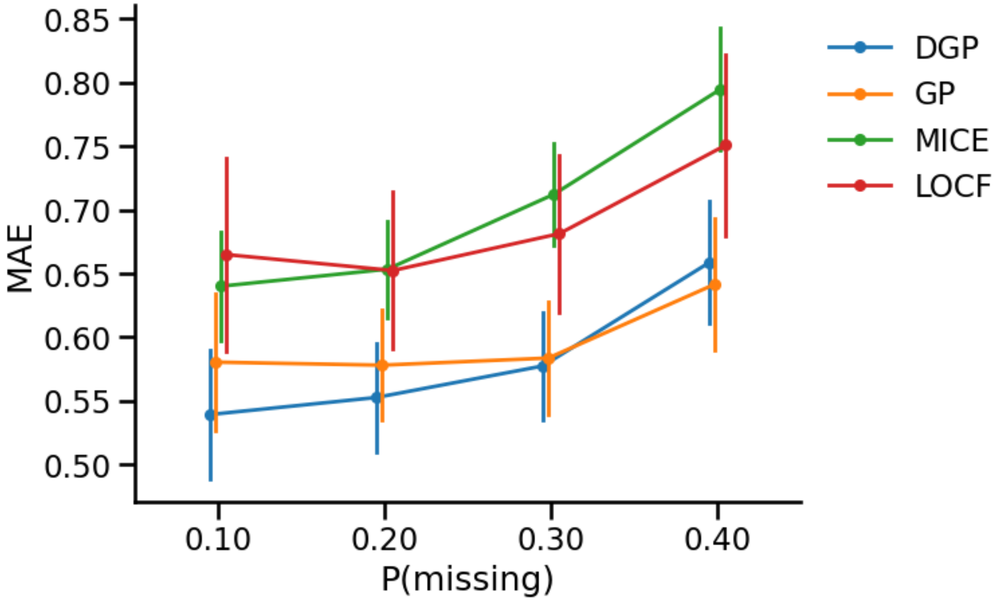
$$\text{MAE} = \frac{1}{N \times D} \sum_{i=1}^{N} \sum_{d \in D} |Y_{id} - \hat{Y}_{id}|$$

  - Negative log likelihood – uncertainty quantification

$$\text{NLL} = -\sum_{i=1}^{N} \log p(Y_i | X_i; \theta)$$

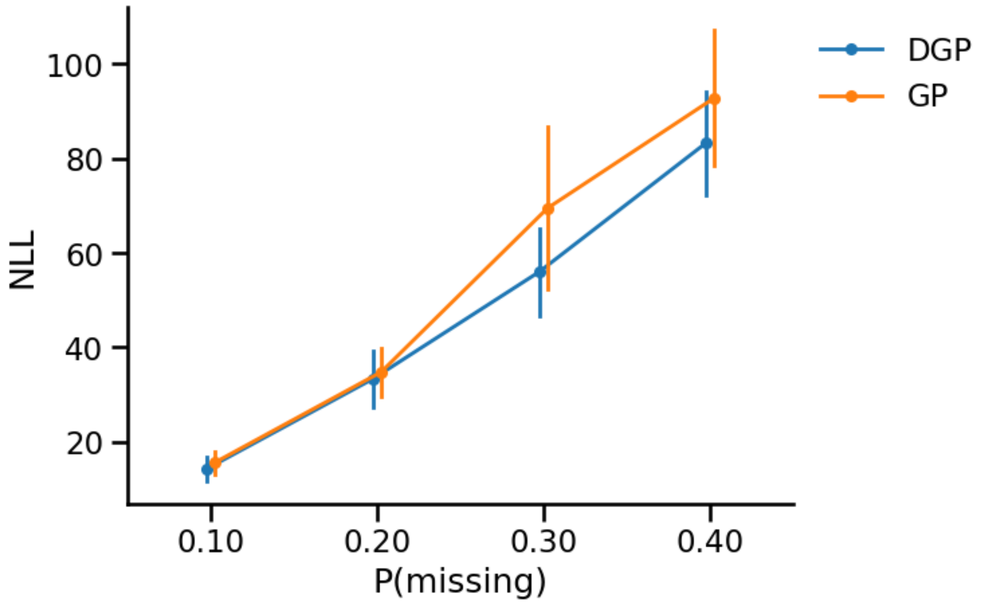
Imputing missing values

- DGP achieved the lowest error rates at 10% to 30% missing values—covering the typical 15–30% missingness in critical care data (Luo et al., 2017)
- As missingness rate increases, longitudinal information is more valuable than cross-sectional information
- DGP combines both → optimal results in lower missingness



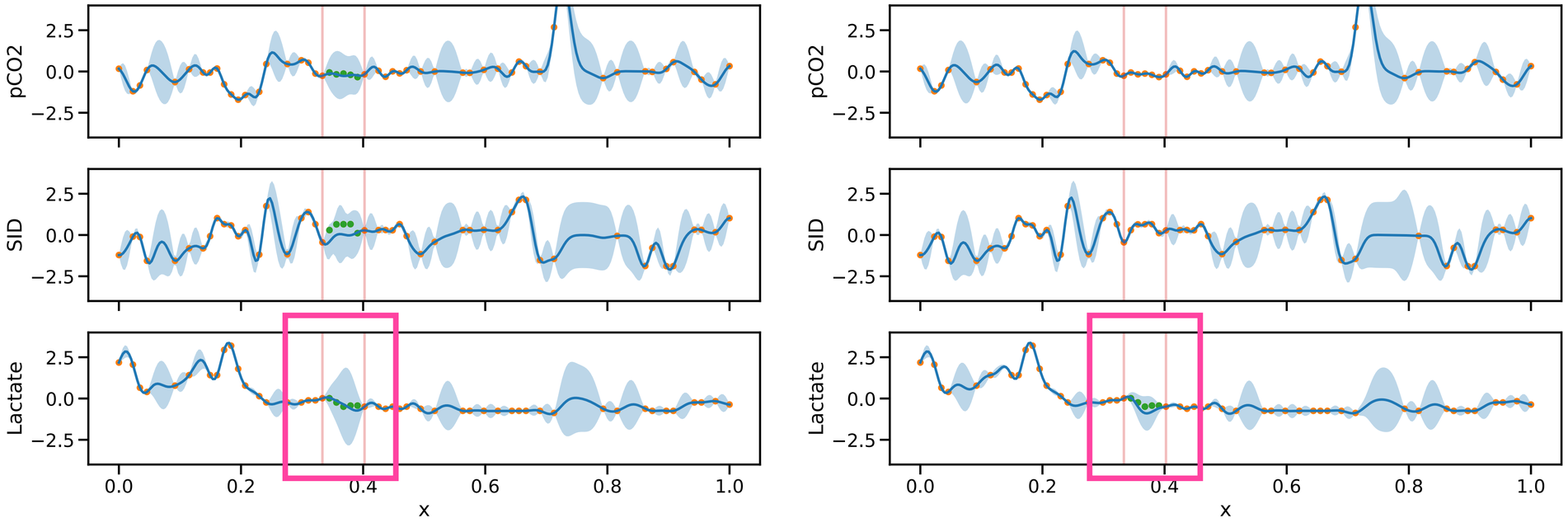
Uncertainty quantification

- DGP performs best when taking into account the uncertainty quantification
- As missingness rate increases, DGP maintains tighter uncertainty bounds than GP
- LOCF was excluded as it does not provide uncertainty quantification



Uncertainty quantification

As the covariates were connected through pH in the output layer using DGP-SI, an observation from one covariate could affect the uncertainty of another covariate where an observation was unavailable.



Implications

- DGP-SI provides reliable, uncertainty-aware imputations to aid clinical decision-making
- Insight into patient status between lab measurements
- Similar problems can be found in human activity recognition from multiple sensors, sleep disorder diagnosis using EEG, and hepatocellular carcinoma (Han et al., 2021)

Limitations & future work

- Computational expense with large datasets → sparse GP (Snelson & Ghahramani, 2007) or GPU parallelisation (Wang et al., 2019)
- Propagated uncertainty which may result in worse performance for predicting pH
- Comparison to deep learning models
- Analysis in higher missingness

Thank you

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