Modeling Clinical Time Series Using Gaussian Process Sequences

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Motivation

Development of accurate models of complex clinical time series data is critical for **understanding the disease**, its dynamics, and subsequently **patient management** and **clinical decision making**.


Disease understanding


Patient management


Making decision

Goal

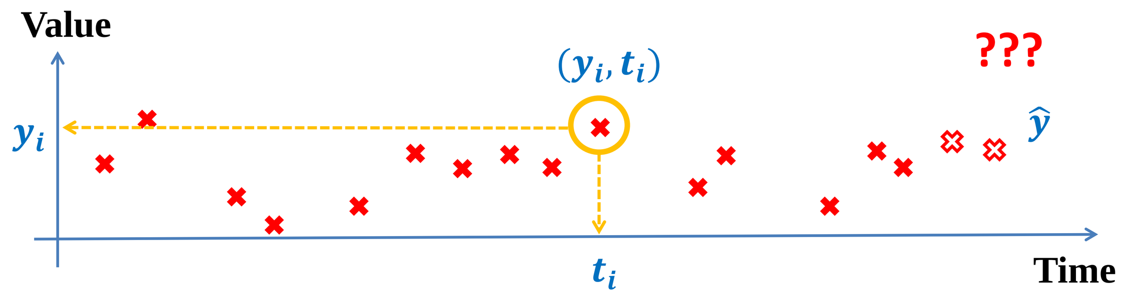
"Develop accurate models of complex clinical time series!"

Specifically, a prediction model that can:

1. Handle missing values
2. Deal with irregular time sampling intervals
3. Make accurate long term predictions

Problem Statement

We define the time series prediction/regression function for clinical time series as: $g : \mathbf{Y}_{\text{obs}} \times t \rightarrow \mathbf{y}$ where $\mathbf{Y}_{\text{obs}}$ is a sequence of past observation-time pairs $\mathbf{Y}_{\text{obs}} = (\mathbf{y}_i, t_i)_{i=1}^{n}$ such that, $0 < t_i < t_{i+1}$, $\mathbf{y}_i$ is a p-dimensional observation vector made at time (t_i), and n is the number of past observations; and $t > t_n$ is the time at which we would like to predict the observation $\mathbf{y}$. Irregularly sampled, $t_{i+1} - t_i \neq t_i - t_{i-1}$.



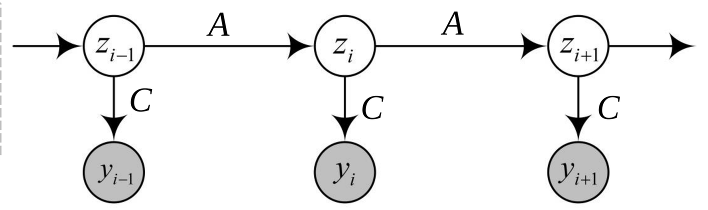
Background

- **Linear Dynamical System (LDS)**

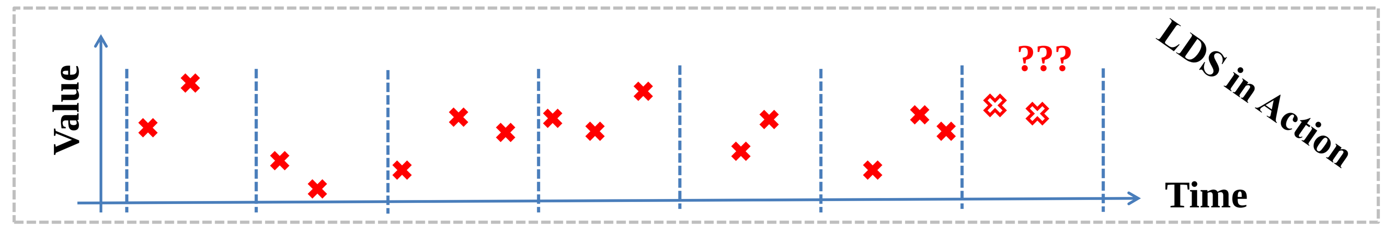
$$\mathbf{z}_{t+1} = A\mathbf{z}_t + \mathbf{w}_t \qquad \mathbf{y}_t = C\mathbf{z}_t + \mathbf{v}_t$$

$$\mathbf{z}_1 \sim \mathcal{N}(\pi_1, V_1),\ \mathbf{w}_t \sim \mathcal{N}(0, Q),\ \mathbf{v}_t \sim \mathcal{N}(0, R)$$

$$p(\mathbf{z}_{t+1} \mid \mathbf{z}_t) = \mathcal{N}(A\mathbf{z}_t, Q), \quad p(\mathbf{y}_t \mid \mathbf{z}_t) = \mathcal{N}(C\mathbf{z}_t, R)$$



Y – time series of observations;
Z – hidden states driving the dynamics.



Background (con't)

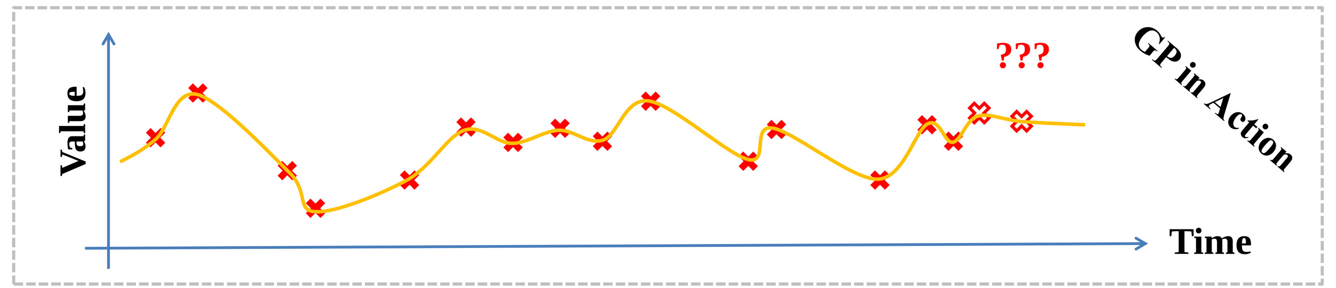
- **Gaussian Process (GP)**

GP is an extension of a multivariate Gaussian to **<u>distributions over functions</u>**. Defined by two components: $\mathcal{GP}(m(x), k(x, x'))$.

- Mean function: $m(\mathbf{x}) = \mathbb{E}[f(\mathbf{x})]$
- Covariance function: $K(\mathbf{x}, \mathbf{x}') = \mathbb{E}[(f(\mathbf{x}) - m(\mathbf{x}))(f(\mathbf{x}') - m(\mathbf{x}'))]$

GP regression equations:

- Estimated Mean ($\bar{f}_*$): $K(x_*, \mathbf{x})\left[K(\mathbf{x}, \mathbf{x}) + \sigma^2 I\right]^{-1} \mathbf{y}$
- Estimated Covariance ($Cov(f_*)$): $K(x_*, x_*) - K(x_*, \mathbf{x})\left[K(\mathbf{x}, \mathbf{x}) + \sigma^2 I\right]^{-1} K(x_*, \mathbf{x})$

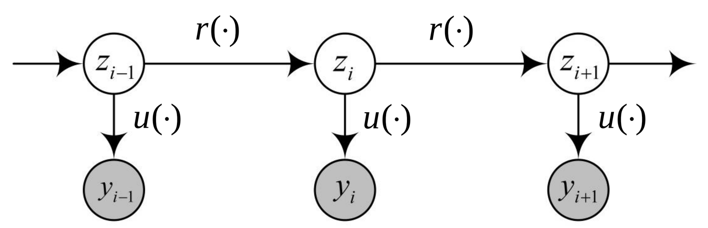


- **Discrete non-linear model (GPIL)**

$$\mathbf{z}_{t+1} = r(\mathbf{z}_t) + \mathbf{w}_t \qquad \mathbf{y}_t = u(\mathbf{z}_t) + \mathbf{v}_t$$

$$\mathbf{z}_1 \sim \mathcal{N}(\pi_1, V_1),\ \mathbf{w}_t \sim \mathcal{N}(0, Q),\ \mathbf{v}_t \sim \mathcal{N}(0, R)$$

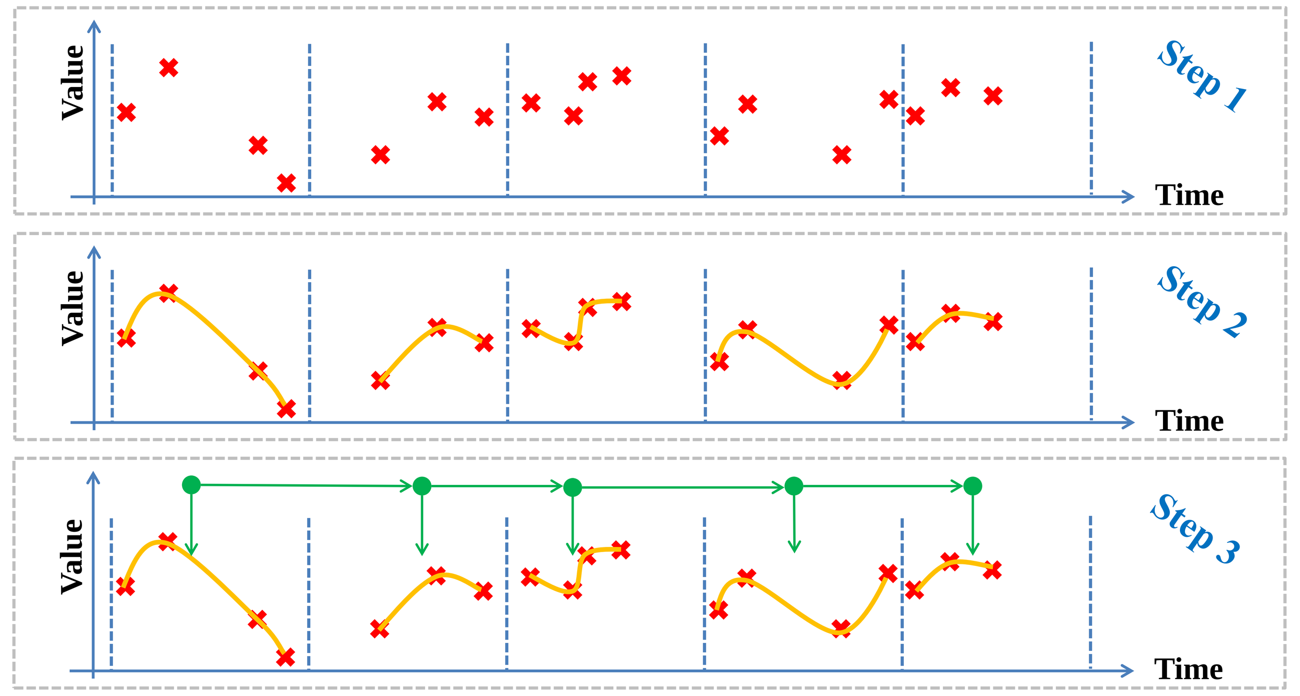
$r(\cdot)$ – unknown transition function;
$u(\cdot)$ – unknown measurement function.



Y – time series of observations;
Z – hidden states driving the dynamics.

State Space Gaussian Process

- **Idea Illustration**



State Space Gaussian Process (con't)

- **State Space Gaussian Process(SSGP) Model**

We consider the Gaussian process *q*(**t**) with the mean function formed by a combination of a fixed set of basis functions with coefficients, β:

$$q(\mathbf{t}) = f(\mathbf{t}) + \mathbf{h}(\mathbf{t})^T \boldsymbol{\beta}, \quad f(\mathbf{t}) \sim \mathcal{GP}_f(0, K(\mathbf{t}, \mathbf{t}'))$$

In this definition, *f*(**t**) is a zero mean GP , *h*(**t**) denotes a set of fixed basis functions, for example, $h(\mathbf{t}) = (1, t, t^2, \ldots)$, and β is a Gaussian prior, $\beta \sim \mathcal{N}(\mathbf{b}, I)$. Therefore, *q*(**t**) is another GP process, defined by:

$$q(\mathbf{t}) \sim \mathcal{GP}_q(\mathbf{h}(\mathbf{t})^{\mathrm{T}} \mathbf{b}, K(\mathbf{t}, \mathbf{t}') + \mathbf{h}(\mathbf{t})^T \mathbf{h}(\mathbf{t}'))$$

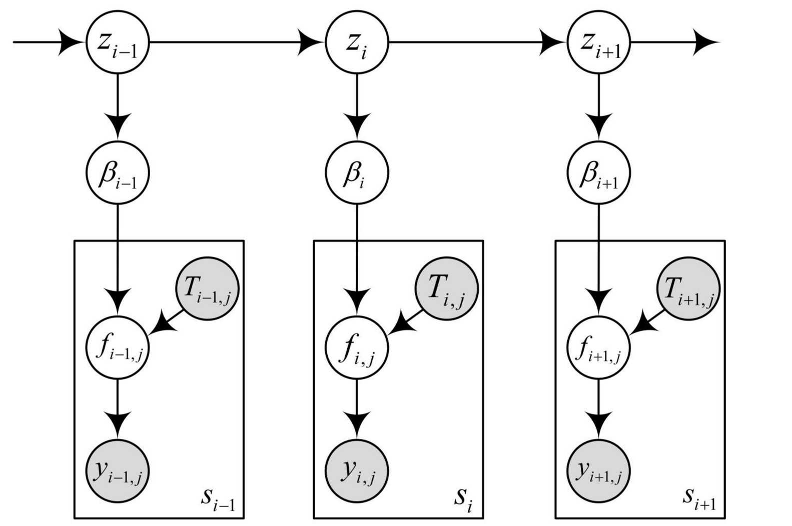


Figure 1. Graphical representation of the state-space Gaussian process model. Shaded nodes $y_{i,j}$ denote (irregular) observations and shaded nodes $T_{i,j}$ denote times associated with each observation. Each rectangle (plate) corresponds to a window, which is associated with its own local GP. S_i is the number of observations in each window. $f_{i,j}$ is Gaussian field.

Joint distribution: $p(D) = p(\mathbf{z}, \boldsymbol{\beta}, \mathbf{Y}) = p(\mathbf{z}_1) \prod_{i=2}^{m} p(\mathbf{z}_i \mid \mathbf{z}_{i-1}) \prod_{i=1}^{m} (\boldsymbol{\beta}_i \mid \mathbf{z}_i) \prod_{i=1}^{m} \prod_{j=1}^{s_i} p(\mathbf{y}_{i,j} \mid \boldsymbol{\beta}_i)$

- **Learning**

Parameter Set: $\Omega = \{\Theta, \{\boldsymbol{\beta}_i\}, A, C, R, Q, \pi_1, V_1\}$ (Θ denotes covariance function parameters)

- Learn Θ: gradient based methods($\frac{\partial \log p(\mathbf{Y} \mid \Theta)}{\partial \Theta} = -\frac{1}{2} \mathrm{Tr}\left[K^{-1} \frac{\partial K}{\partial \Theta}\right] + \frac{1}{2} \mathbf{Y}^T K^{-1} \frac{\partial K}{\partial \Theta} K^{-1} \mathbf{Y}$)
- Learn $\Omega \backslash \Theta$: EM algorithm with $\mathcal{Q} = \mathbb{E}_{\boldsymbol{\beta}, \mathbf{z}}[\log p(\boldsymbol{\beta}, \mathbf{z}, \mathbf{Y})]$

- **Prediction**

To support the prediction inference, we need the following steps:

1. Split $\mathbf{Y}_{\text{obs}}$ and *t* into windows.
2. For windows that do not contain *t*, extract the last values in those windows as **β**s and feed them into *Kalman Filter* algorithms to infer the most recent hidden state $\mathbf{z}_k$ where *k* is the index of the last window that does not contain *t*.
3. Get $\boldsymbol{\beta}_{k+1} = CA\mathbf{z}_k$ from $\mathbf{z}_{k+1} = A\mathbf{z}_k$ and $\boldsymbol{\beta}_{k+1} = C\mathbf{z}_{k+1}$.
4. If *t* is in window *k+1*, use observations $(\mathbf{y}_{k+1}, t_{k+1})$ in window *k+1* and $\boldsymbol{\beta}_{k+1}$ to make the prediction, where $\mathbf{y} = \boldsymbol{\beta}_{k+1} + K(t, t_{k+1}) K^{-1}(t_{k+1}, t_{k+1})(\mathbf{y}_{k+1} - \boldsymbol{\beta}_{k+1})$; otherwise find out the window index *i* where *t* belongs to. The prediction at *t* is $\mathbf{y} = CA^{i-k}\mathbf{z}_k$.

Experiments

- **Data**

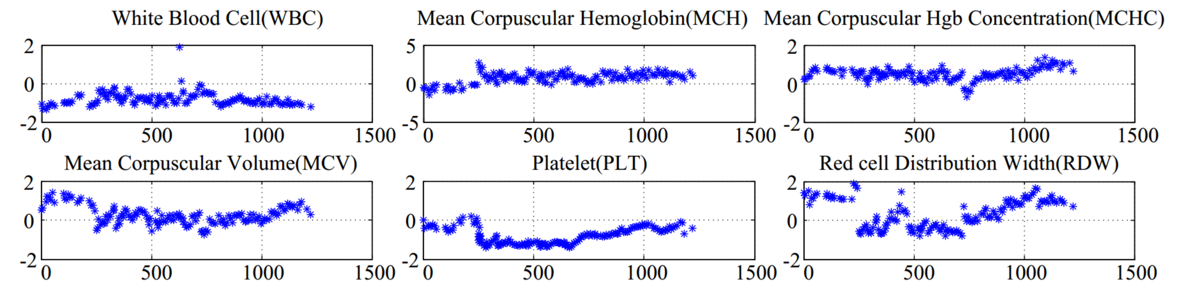


Figure 2. Time series for six tests from the Complete Blood Count(CBC) panel for one of the patients.

- **Choice of Covariance Functions**($K = K_1 + K_2$)
  - Mean Reverting Property: $K_1 = \sigma_1 \exp(\theta_1 |\mathbf{t} - \mathbf{t}'|)$
  - Periodicity: $K_2 = \sigma_2 \exp(\theta_2 \sin^2\left[\frac{\omega}{2\pi}(\mathbf{t} - \mathbf{t}')\right])$

- **Evaluation Metric**

Root Mean Square Error(RMSE):

$$RMSE = \left[n^{-1} \sum_{i=1}^{n} |y_i - y_i|^2\right]^{1/2}$$

- **Results**

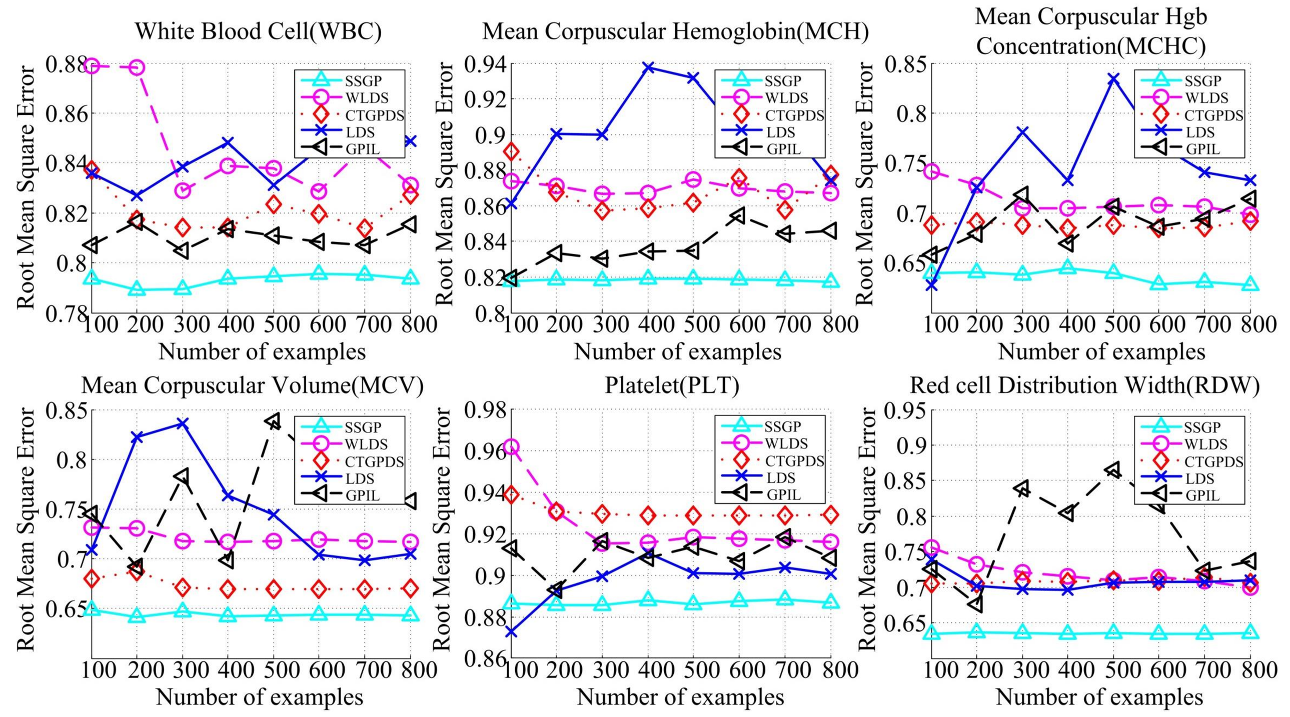


Figure 3. Root Mean Square Error(RMSE) on CBC test samples.

Future Work

- Study and model dependences among multiple time series
- Extend to switching-state and controlled dynamical systems

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Reference

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