Understanding Raynaud’s Phenomenon through a Hierarchical Model Based on Splines

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Abstract

Raynaud’s Phenomenon (RP) is a vasospastic disorder of some specific arteries, typically induced by cold exposure and emotional stress, causing discoloration of the fingers, toes, ears, and nipples. RP can be classified as primary (PRP), with no identifiable underlying pathological disorder, and secondary which is frequently associated with systemic sclerosis (SS). Patients who are classified as primary RP might evolve to secondary RP.

Thermal infrared (IR) imaging is a technique providing the map of the superficial temperature of a given body by measuring the infrared energy emitted, providing important indirect information on circulation, thermal properties and thermoregulatory functionality of the cutaneous tissue. PRP, SS and healthy controls (HC) groups show different thermal recoveries in consequence of the same standardized functional stimulation. In this study patients from HC, PRP and SS groups underwent a standard cold challenge, and temperatures of the 10 fingers of each patient, before and after the cold stress, were recorded. Temperatures of each finger of each person were measured every 30 seconds, 2.5 minutes before the cold stress and 20 minutes after it, resulting on \( T = 46 \) temperature measurements for each individual. We aim to estimate the mean temperature as a function of time for each finger of each patient. We also aim to obtain an overall mean function for each patient. This will provide us with tools to understand better the temperature behaviour of each patient from each group. For this, we propose a hierarchical model based on B-splines. Inference procedure is performed under the Bayesian paradigm, therefore we are able to clearly describe the uncertainty of our estimates.

1 Introduction

Raynaud’s Phenomenon (RP) is a vasospastic disorder of some specific arteries, typically induced by cold exposure and emotional stress, causing discoloration of the fingers, toes, ears, and nipples as described in Ippoliti et al. (2009). RP can be classified as primary (PRP), with no identifiable underlying pathological disorder, and secondary which is frequently associated with systemic sclerosis (SS). It has been estimated that 12.6% of patients suffering from PRP develops a secondary disease. On the other hand, between 5% and 20% of subjects suffering from secondary RP evolves to SS, all of the SS patients underwent or will experience RP. These epidemiological data makes clear the importance for early and proper diagnosis to identify the different forms of RP. Thermal infrared (IR) imaging is a technique providing the map of the superficial temperature of a given body by measuring the infrared energy emitted, providing important indirect information on circulation, thermal properties and thermoregulatory functionality of the cutaneous tissue. PRP, SS and healthy controls (HC) groups show different thermal recoveries in consequence of the same standardised functional stimulation. In this work, we have interest in classifying the functional response of the fingers to a standard cold challenge, recorded by means of functional infrared imaging in a set of HC, PRP and secondary to SS patients. The observed data consist of fingertip temperature vectors (one for each finger for each subject) documenting the thermal recovery from a standardised cold stress of both hands, acquired at time intervals equally spaced to monitor the response to a cold stress.
2 Proposed Model and Inference Procedure

In this work, we propose a normal hierarchical model based on splines to explain the mean temperature of a finger of a person at a given time. Under the Bayesian framework, to complete the specification of the model, we assign a prior distribution to the parameters. Besides that, we assign conjugated non-informative prior distributions, i.e., the posterior full conditional distribution of the parameter will be of the same class of their prior distribution. Thus, we guarantee closed form for the posterior full conditional distributions, facilitating the computational sampling.

More specifically, let \( Y_{ij}(t) \) be the mean temperature of finger \( j \) of person \( i \) at time \( t \). Denote by \( t^* \) the time of the cold stress. For \( j = 1, ..., J = 10 \) and \( i = 1, ..., n \), let

\[
Y_{ij}(t) = \left\{ \begin{array}{ll}
\mu_{0i} + \epsilon_{ij}(t), & t = 1, 2, ..., t^* - 1 \\
\mu_{0i} + \sum_{k=1}^{K} \beta_{ijk} f_k(t) + \epsilon_{ij}(t), & t = t^*, ..., T
\end{array} \right.
\]

(1)
such that \( \mu_{0i} \sim N(\mu_0, \sigma_0^2) \) is the personal overall mean; \( \epsilon_{ij}(t) \sim N(0, \sigma_j^2) \), where \( \sigma_j^2 \) is the variance of the temperature of the \( j^{th} \) finger of person \( i \); \( \sigma_j^2 \sim IG(a_0, b_0) \), is the overall variance of the baseline temperature from person to person, where \( a_0 \) and \( b_0 \) are known; \( \mu_0 \sim N(0, \sigma_0^2) \) is the overall mean baseline temperature, where \( \sigma_0^2 \) is large; \( \beta_{ijk} \sim N(\delta_{ik}, \sigma_{\beta_{ij}}^2) \) is the coefficient of the \( k^{th} \) basis of finger \( j \) of person \( i \) (with \( \sigma_{\beta_{ij}}^2 \) known) and where \( \delta_{ik} \sim N(\gamma_k, \sigma_{\gamma_k}^2) \) (with \( \sigma_{\gamma_k}^2 \) known) and \( \gamma_k \sim N(0, \sigma_{\gamma_k}^2) \) (with \( \sigma_{\gamma_k}^2 \) large); and \( f_k \), for \( k = 1, ..., K \) form the base of the spline, for each \( t \).

There are in the literature various types of spline basis. Among them the B-splines are widely used and we chose this class for our model. More details about splines in regression models can be found in Wahba (2000).

Hence, supposing a random sample \( y = \{y_{ijt}; i = 1, ..., n, j = 1, ..., J \text{ and } t = 1, ..., T \} \) of the mean temperature of \( n \) persons at \( T \) times, we define the likelihood function of the parameters by

\[
l(\Theta; y) \propto \prod_{i=1}^{n} \prod_{j=1}^{J} (\sigma_{ij}^2)^{-(T)/2} \exp \left\{ -\frac{1}{2\sigma_{ij}^2} \sum_{t=1}^{T} (y_{ijt} - \mu_{0i})^2 \right\} \exp \left\{ -\frac{1}{2\sigma_{ij}^2} \sum_{t=t^*}^{T} (y_{ijt} - \mu_{0i} - \sum_{k=1}^{K} \beta_{ijk} f_k(t))^2 \right\}.
\]

Following Bayes’ theorem, the posterior distribution is proportional to the likelihood function times the prior distribution of the parameter. Following the prior specification above the posterior distribution is given by

\[
p(\Theta|y) \propto \prod_{i=1}^{n} \prod_{j=1}^{J} (\sigma_{ij}^2)^{-(T)/2} \exp \left\{ -\frac{1}{2\sigma_{ij}^2} \sum_{t=1}^{T} (y_{ijt} - \mu_{0i})^2 \right\} \exp \left\{ -\frac{1}{2\sigma_{ij}^2} \sum_{t=t^*}^{T} (y_{ijt} - \mu_{0i} - \sum_{k=1}^{K} \beta_{ijk} f_k(t))^2 \right\} (\sigma_0^2)^{-n/2} \exp \left\{ -\frac{1}{2\sigma_0^2} \sum_{i=1}^{n} (\mu_{0i} - \mu_0)^2 \right\} (\sigma_j^2)^{-(a_0+1)} \exp \left\{ -\frac{b_0}{\sigma_j^2} \mu_0 \right\} \exp \left\{ -\frac{1}{2\sigma_j^2} \mu_0^2 \right\} \exp \left\{ -\frac{1}{2\sigma_j^2} \sum_{k=1}^{K} \gamma_k^2 \right\} \prod_{i=1}^{n} \prod_{j=1}^{J} (\sigma_{\beta_{ij}}^2)^{-K/2} \exp \left\{ -\frac{1}{2\sigma_{\beta_{ij}}^2} \sum_{k=1}^{K} (\beta_{ijk} - \delta_{ik})^2 \right\} \exp \left\{ -\frac{1}{2\sigma_{\gamma_k}^2} \sum_{k=1}^{K} (\delta_{ik} - \gamma_k)^2 \right\}.
\]

As the posterior joint distribution of the parameters does not have closed form, we use Markov chain Monte Carlo (MCMC) methods, specifically, the Gibbs sampler (Gamerman and Lopes, 2006), to obtain samples from the target posterior distribution. Below we present the posterior full conditional
distributions for each parameter of interest. For \( i = 1, \ldots, n \), \( j = 1, \ldots, J \) and \( k = 1, \ldots, K \), we have

\[
\begin{align*}
\mu_{0i} &\sim \text{Normal} \left( \sum_{j=1}^{J} \sum_{t=1}^{t_i-1} y_{ijt} + \sum_{j=1}^{J} \sum_{t=t_i}^{T} \left( y_{ijt} - \sum_{k=1}^{K} \beta_{ijk} f_{kt} \right) + \frac{\mu_0}{\sigma_0^2}, v_{\mu_0}, v_{\mu_0} \right), \\
\mu_0 &\sim \text{Normal} \left( \sum_{i=1}^{n} \frac{\mu_{0i}}{\sigma_0^2} \left( \frac{1}{\sigma_eta^2} + \frac{n}{\sigma_0^2} \right)^{-1}, \left( \frac{1}{\sigma_eta^2} + \frac{n}{\sigma_0^2} \right)^{-1} \right), \\
\sigma_{0i}^2 &\sim \text{IG} \left( a_0 + \frac{n}{2}, b_0 + \frac{1}{2} \sum_{i=1}^{n} (\mu_{0i} - \mu_0)^2 \right), \\
\gamma_k &\sim \text{Normal} \left( \sum_{i=1}^{n} \frac{\delta_{ik}}{\sigma_\delta^2} \left( \frac{1}{\sigma_\gamma^2} + \frac{n}{\sigma_\delta^2} \right)^{-1}, \left( \frac{1}{\sigma_\gamma^2} + \frac{n}{\sigma_\delta^2} \right)^{-1} \right), \\
\delta_{ik} &\sim \text{Normal} \left( \sum_{j=1}^{J} \frac{\beta_{ijk}}{\sigma_{\beta_i, j}^2} + \frac{\gamma_k}{\sigma_\delta^2} \sum_{j=1}^{J} \frac{1}{\sigma_{\beta_i, j}^2} + \frac{1}{\sigma_\delta^2} \right) \cdot \left( \sum_{j=1}^{J} \frac{1}{\sigma_{\beta_i, j}^2} + \frac{1}{\sigma_\delta^2} \right)^{-1} \\
\sigma_{\beta_i, j}^2 &\sim \text{IG} \left( a_1 + \frac{T}{2}, b_1 + \frac{1}{2} \left( \varepsilon_{ij} - \sum_{i=1}^{T} (y_{ijt} - \mu_0)^2 + \sum_{t=t_i}^{T} (y_{ijt} - \mu_0 - \sum_{k=1}^{K} \beta_{ijk} f_{kt})^2 \right) \right),
\end{align*}
\]

such that \( v_{\mu_0} = \left( \sum_{j=1}^{J} \sigma_{\beta_i, j}^2 + \sigma_{0i}^{-2} \right)^{-1} \) and \( \text{IG}(a, b) \) denotes the inverse-gamma distribution with shape parameter \( a \) and scale parameter \( b \).

3 Artificial Data generated by the Proposed Model

We start by simulating datasets from our model to check if it is able to provide temperature curves similar to what is observed in the patients. For this we have fixed the parameters of the model at reasonable values and simulated sets of artificial data. We assume there are \( n = 29 \) persons with \( J = 10 \) fingers. As is done in the experimental observations, we assume that the temperature (in degrees Celsius) of the fingers of each individual are measured every 30 seconds, 2.5 minutes before the cold stress and 20 minutes after this time resulting in \( T = 46 \). We have used B-splines basis with 13 knots. We have chosen the value of all of the variances of the temperature of each finger of each person \( \sigma_{\beta_i, j}^2 \) is equal to 0.0025 while the variance of the baseline temperature from person to person, \( \sigma_{0i}^2 \), is equal to 0.0001, and the overall mean baseline temperature is \( \mu_0 = 3.4 \). The knots were taken from 0.25 to 22.75. Figure 1 presents one of the resultant artificial data that we obtained, which provides a similar behaviour to the observed data.

4 Current Work

The previous section only shows data generated from the model by fixing the values of the parameters. We are currently writing a program in \( \text{C}++ \) to run the MCMC algorithm to estimate the parameters of the model. For this we follow the posterior full conditionals shown in Section 2. We will test this program using artificial data, and then fit our model to real data. We anticipate this analysis will be ready by July 2010. We also aim to investigate how sensitive the inference procedure is to the choice of the number of knots of the B-splines basis, and also their positions.

References

Figure 1: Artificial Data: Times series of re-warming curves for the different individuals
