Effect of Vitamin C Administration on Haematological Adaptation Produced by Intermittent Hypoxic Protocol Combined with Spring Interval Training

Daniel Martinez Bello

promotor :
De heer Auguste GADDAH, Maria del
CARMEN GOMEZ CABRERA

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Effect of vitamin C administration on haematological adaptations produced by intermittent hypoxic protocol combined with sprint interval training

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Daniel Adyro Martinez Bello

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Supervisors:
Dr. Maria del Carmen Gómez Cabrera
Mr. Auguste Gaddah

Master Science in Biostatistics
Hasselt University
Center for Statistics

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Author: Daniel Adyro Martinez Bello

Department: CenStat - Centrum voor Statistiek, Universiteit Hasselt, Belgium

Supervisor: dr. Maria del Carmen Gómez Cabrera

Co-supervisor: Mr.. Auguste Gaddah

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Abstract:

Intermittent periods of hypoxia (12-16 hours for 3 or 4 weeks) stimulates erythropoiesis with a resulting increase in red blood cells. Training in hypoxic conditions increase the production of reactive oxygen species, damaging the red blood cells by increasing the auto-oxidation of haemoglobyn, as a constant source of superoxide that affect the membrane proteins. Vitamin C is an important antioxidant in human plasma, and generates a protective effect on oxidative stress in animals submitted to intermittent hypoxic protocols, although little is known about the effects of vitamin C administration on hypoxic protocols combined with sprint interval training. The aim of the study was to determine whether the administration of vitamin C modulates the haematological adaptations (expressed in the variables total haemoglobyn, haematocrit, red blood cell, reticulocytes, count, mean corpuscular volume and mean corpuscular haemoglobyn induced by an hypoxic protocol combined with spring interval training in a 21 experimental period. Eigth treatments groups of randomly allocated male Wistar rats were compared: normoxia with resting and vitamin C (n=5), normoxia with spring interval training and vitamin C (n=5), normoxia with resting and water (n=5), normoxia with spring interval training and water (n=6), hypoxia with resting and vitamin C (n=5), hypoxia with spring interval training and vitamin C (n=5), hypoxia with resting and water (n=5), and hypoxia with spring interval training and water (n=5). We have found lower levels of haemoglobyn and haematocrit at the middle part of an experimental period of 21 days, without affecting the red blood cells count, reticulocytes, and mean corpuscular haemoglobyn in the protocol involving hypoxia with interval spring training plus vitamin C, and a slight change in the mean corpuscular volume. We postulate that the difference in haematocrit and haemoglobyn is mediated by a temporary change in the erithrocyte size, which motivate further investigations over the effect of the interaction between hypoxia, supplementation of vitamin C and spring interval training in rats.

Keywords:

vitamin C, hypoxia, spring interval training, rats, longitudinal analisis, haematological adaptations, hierarchical Bayesian modelling

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Chapter 1

Introduction

For the past few decades now, athletes have trained at high-altitudes to increase their performance (Wilber et al.; 2007). Among the various training regimens, that of living at high-altitudes while training at sea-level, the so-called "living high, training low" protocol, has become an important strategy for achieving this objective (Levine and Stray-Gundersen; 1992). One of the most desired adaptations that athletes and trainers expect from this type of regimen is an increased capacity for transporting oxygen to body tissue. As for the potential physiological effects of intermittent hypoxia, many studies have been carried out. Most of these have focused on the hematological responses related to the higher capacity of the blood to carry oxygen improving aerobic capacity (Powell and Garcia; 2000). The expression of the EPO gene is induced mainly under hypoxic conditions and is mediated by the stabilization of the hypoxia inducible factor 1 (Semenza and Wang; 1992). Currently, there is some confusion about the effects of intermittent hypoxia on the various hematological parameters that are modified through high-altitude training, specifically with the "living high, training low" method. Several studies in humans have found increases in EPO levels that were not accompanied by a concomitant increase in erythrocyte production in top-level athletes (Gore et al. (1998); Gore et al. (2006); Ashenden et al. (2000); Ashenden et al. (1999); Julian et al. (2004); Abellan et al. (2005)).

In contrast, other studies have shown that intermittent hypoxia stimulates erythropoiesis with a resulting increase in red blood cells (Levine and Stray-Gundersen (1992); Levine and Stray-Gundersen (1997); Berglund and Gennser (2002); Wehrlin and Marti (2006); Wehrlin et al. (2006)).The duration of the hypoxic stimulus is an important factor in augmenting the volume of red blood cells. A very short exposure (70 min) to high altitude conditions is not sufficient to achieve any significant increase (Julian et al.; 2004). In a highly trained athletes following a short-term intermittent hypoxia (3h/day, 5 day, for 4 weeks) increased serum erytrhropietin but reticulocyte and red cell parameters did not (Abellan et al.; 2005). A longer exposure of 8-10 hours at 2500-3000 m for between 10

and 21 days likewise has no effect on hemoglobin or haematocrit levels (Ashenden et al.; 1999), although in many cases an increase in erythropoietin levels occurs (Ashenden et al. (2000);Gore et al. (2006)). Still, a longer exposure to hypoxic conditions of 12-16 hours for 3 (Robach et al.; 2006) or 4 (Rusko et al.; 2004) weeks has been found to significantly increase the number of red blood cells.

In the other hand, it is generally agreed that the production of reactive oxygen species is increased in hypoxic conditions (Askew (2002); (Vij et al.; 2005)) and that high altitude training increase free radical generation resulting in oxidative stress (Radak et al.; 1994). It has shown an increase the level of oxidative protein damage, as measured by carbonyl derivatives in skeletal muscle of rats (Radak et al.; 1997) and blood cells membranes (Asha-Devi et al.; 2007); increased lipid peroxidation in skeletal muscle (Radak et al.; 1994), and increased MDA levels in plasma of rats exposed to altitude 6 h daily (7576 m) (Kumar et al.; 1999). The red blood cells are susceptible to oxidative damage under hypoxic conditions by increase the autooxidation of haemoglobyn as a constant source of superoxide that affect the membrane proteins (Rifkind et al. (1991); Gonzalez et al. (2002)). Vitamin C (ascorbic acid) is an important antioxidant in human plasma and it has been shown a protective effect on oxidative stress in animals submitted to intermittent hypoxic protocols (Asha-Devi et al. (2005); Asha-Devi et al. (2007)). In addition, the vitamin C supplementation is very popular among sport practitioners (Hathcock et al.; 2005) and in the same way it has been suggested that administration of antioxidants vitamins (specially vitamin C) could have positive effects reducing oxidative damage related with this type of protocols (Asha-Devi et al.; 2007). However, little is known about the effects of vitamin C administration on hypoxic protocols combined with sprint interval training.

Chapter 2

Objectives

The aim of the study was to determine whether the administration of vitamin C modulates the haematological adaptations, expressed in the variables total haemoglobyn (gr/dl), haematocrit (%), red blood cell count (U/ml), reticulocytes (%), mean corpuscular volume ($picograms/ml$), and mean corpuscular haemoglobyn ($femtograms/ml$), induced by normoxic or hypoxic protocols, combined with resting or spring interval training, plus Vitamin C or Water. Mainly, we are interested to determine if there are differences between the haematological adaptions (expressed in the outcome variables) in young rats between a hypoxic protocol plus vitamin C in spring interval training and a hypoxic protocol plus vitamin C in resting, compared with a hypoxic protocol plus water in spring interval training, a hypoxic protocol with water in resting, a normoxic protocol plus vitamin C with spring interval training, a normoxic protocol plus vitamin C with resting, a normoxic protocol plus vitamin C with spring interval training and a normoxic protocol plus water with resting, in an experimental period of 21 days. Additionally, we are interested in the comparison between the hypoxic protocols plus vitamin C with resting and spring interval training.

Chapter 3

Methods and Materials

3.1 Experimental settings

Two experiments involving different protocols were done. The first experiment consists in twenty male Wistar rats (3 1/2 months old) randomly divided into four experimental groups: the normoxic in resting plus water group (NRW) (n=5), the normoxic in resting treated with vitamin C (NRC) (n=5), the normoxic in spring interval training plus water group (NTW) (n=5), and the normoxic in spring interval training plus vitamin C group (NTC) (n=5). The second experiment consists in twenty one male Wistar rats (3 months old) randomly allocated in four experimental hypoxic groups, where the hypoxic protocol consisted in 12 hours in Oxygen at 12% and 12 hours in Oxygen at 21% (12h O_2 12% /12h O_2 21%) : the hypoxic in resting plus water group (HRW) (n=5), the hypoxic in resting plus vitamin C group (HRC) (n=5), the hypoxic with spring interval training group (HTW) (n=5) and the hypoxic with spring interval training plus vitamin C group (HTC) (n=6). The dose of vitamin C was 250 mg/kg of bodyweight in a daily basis, administered in the drinking water. Three blood samples were taken from the tails of the rats (0.4 mL each) and placed inside tubes containing Etilen diamino tetra acid (EDTA) : basal sample (initial), 12th day and a final sample (on the 21th day). The samples were collected in the morning at the same time to control for variations throughout the day. The animals were sacrificed the day after the final blood sample was drawn.
The direct measurements carried out included: haematocrit (%), reticulocytes (%), red blood cell count (U/ml), size (mean corpuscular volume $picograms/ml$), mean corpuscular haemoglobyn ($femtograms/ml$) and total hemoglobin (g/dl).
The Table 1 in the Appendix A provides with an overview of the dataset summary statistics. There are strong differences between and within treatments through the time mainly in the hypoxic treatments. For the haemoglobyn, haematocrit and haemoglobyn, the HRC treatment starts the experiment with lower values than the other groups.

3.2 Statistical Methodology

3.2.1 Estimation

Analytical methods for longitudinal data analysis have been developed within many estimation frameworks for the solution of complex problems and scientific questions (Fitzmaurice et al.; 2009). The linear mixed model for continuous data has been explored by authors like Verbeke and Molenberghs (2000) and Pinheiro and Bates (2000) within the maximum likelihood collection of methods for parameter estimation and inferences. Another estimation method is the Bayesian paradigm. In the Bayesian approach, the analyst estimates the model parameters given a prior probability which is combined with the data likelihood, and the inferences are obtained from the posterior probability distribution of the parameters, by means of central tendency measures like the mean or the median, and dispersion measures like the standard deviation or the quantiles. Therefore, the Bayesian parameters are considered random parameters that are sampled from the posterior distribution. When the models are not complex, a solution can be derived using analytical methods. But when the number of parameters increase as well as in the case of longitudinal models, a direct analytical solution is not possible to obtain and the analyst has to use simulation-based methods. Within the collection of Markov Chain Monte-Carlo (MCMC) Methods , the Gibbs sampling works estimating the conditional distribution of each parameter given all the other parameters, making a relatively simple estimation method for a complex joint posterior distribution. The WinBUGS software is a Bayesian estimation tool using Gibbs sampling algorithms that has been developed to fit models and estimate parameters under the full Bayesian framework and it is used currently for applied statisticians to solve inferential problems (Albert; 2009).

3.2.2 Modeling strategy

The modeling strategy consists of the following steps. First, in the normoxic and the hypoxic protocols, for every outcome variable (red blood cells, reticulocytes, haematocrit, haemoglobyn, mean corpuscular volumen and mean corpuscular haemoglobyn) a saturated hierarchical Bayesian linear mixed model is fitted. Then different submodels are tested searching for a final model. The selection procedure is based on the Deviance Information Criteria (DIC) (Spiegelhalter et al.; 2002). To understand DIC we start with the posterior distribution of the deviance statistic (Zhu et al.; 2006)

$$D(\Theta) = -2\log p(y|\theta) + 2\log f(y) \tag{3.1}$$

Where $p(y|\theta)$ is the likelihood function for the observed data vector y given the parameter vector θ, and $f(y)$ is a standardizing function of the data alone. The model fit is

summarized by the posterior expectation of the deviance, $\bar{D} = E_{\theta|y}(D)$, while model *complexity* is captured by the number of effective parameters p_D, which is defined as expected deviance minus deviance evaluated at the posterior expectations,

$$p_D = E_{\theta|y}(\theta) - D(E_{\theta|y}(\theta)) = \bar{D} - D(\bar{\theta}) \tag{3.2}$$

Then the deviance information criterion (DIC) is defined as the summation of *fit* and *complexity*

$$DIC = \bar{D} + p_D = 2\bar{D} - D(\bar{\theta}) \tag{3.3}$$

Smaller values of DIC indicate a better-fitting model (Zhu et al.; 2006).

The saturated initial model for the analysis of the normoxic and the hypoxic outcomes is presented in the equation 3.4.

$$\begin{aligned} Y_{ij} = {} & \alpha + \alpha_1 Day_{ij} + \alpha_2 Day_{ij}^2 \\ & + \beta_1 C_1 + \beta_2 C_2 + \beta_3 C_3 \\ & + (\beta_4 C_1 + \beta_5 C_2 + \beta_6 C_3) Day_{ij} \\ & + (\beta_7 C_1 + \beta_8 C_2 + \beta_9 C_3) Day_{ij}^2 \\ & + b_{0i} + b_{1i} Day_{ij} + \epsilon_{ij} \end{aligned} \tag{3.4}$$

Where:

- Y_{ij} corresponds to the outcome variables (haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular haemoglobyn or mean corpuscular volume), $i = 1, \cdots, n$, the number of subjects, and $j = 1, 12, 21$ the days when the outcome is recorded.
- The reference category corresponds to the treatment normoxia resting water (NRW) for the normoxic protocol or hypoxia resting water (HRW) for the hypoxic protocol.
- α corresponds to the intercept.
- α_1 and α_2 correspond to the effect of the experimental *day* and the day^2.
- C_1, C_2 and C_3 are dummy variables for the treatments normoxia training vitamin C (NTC), normoxia training water (NTW) and normoxia resting vitamin C (NRC), in the normoxic protocol, or the treatments hypoxia training vitamin C (HTC), Hypoxia training water (HTW) and hypoxia resting vitamin C (HRC), in the hypoxic protocol .

- β_1, β_2, β_3 are the effects of the treatments NTC, NTW and NRC, in the normoxic protocol, or the effects of the treatments HTC, HTW and HRC, in the hypoxic protocol .
- β_4, β_5 and β_6 are the effects of the interaction between *day* and the treatments NTC, NTW and NRC, in the normoxic protocol, or the treatments HTC, HTW and HRC, in the hypoxic protocol.
- β_7, β_8 and β_9 are the effects of the interaction between day^2 and the treatments NTC, NTW and NRC, in the normoxic protocol, or the treatments HTC, HTW and HRC, in the hypoxic protocol.
- b_{0i} are random intercepts, normally distributed with mean 0 and variance σ^2_{b0}.
- b_{1i} are random slopes for day, normally distributed with mean 0 and variance σ^2_{b1}.
- ϵ_{ij} are the error terms, normally distributed with mean 0 and variance σ^2.

Second, after the estimation and selection of the most parsimonious model for the normoxic and the hypoxic protocols for every outcome variable, a joint model considering the selected models for the normoxic and the hypoxic experiments for every outcome variable is fitted. The general model for the joint analysis of the hypoxic outcomes and the normoxic outcomes follows

$$\begin{aligned} Y_{ijt} = {} & \alpha + \alpha_1 Day_{ij} + \alpha_2 Day_{ij}^2 \\ & + \beta_1 C_1 + \beta_2 C_2 + \beta_3 C_3 + \beta_4 C_4 + \beta_5 C_5 + \beta_6 C_6 + \beta_7 C_7 \\ & + (\beta_8 C_1 + \beta_9 C_2 + \beta_{10} C_3 + \beta_{11} C_4 + \beta_{12} C_5 + \beta_{13} C_6 + \beta_{14} C_7) Day_{ij} \\ & + (\beta_{15} C_1 + \beta_{16} C_2 + \beta_{17} C_3 + \beta_{18} C_4 + \beta_{19} C_5 + \beta_{20} C_6 + \beta_{21} C_7) Day_{ij}^2 \\ & + \gamma Age_i + b_{0i} + b_{1i} Day_{ij} + \epsilon_{ijt} \end{aligned} \tag{3.5}$$

Where

- Y_{ijt} corresponds to the outcome variables (haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume or mean corpuscular haemoglobyn), $i = 1, \cdots, n$, the number of subjects, and $j = 1, 12, 21$ the days when the outcome is recorded, and $t = 1, \cdots, 8$ the number of treatments
- The reference category corresponds to the treatment normoxia resting water.
- α corresponds to the intercept.
- α_1 and α_2 correspond to the effect of the experimental *day* and the day^2.

- C_1, C_2, C_3, C_4, C_5,C_6 and C_7 are dummy variables for the treatments hypoxia training vitamin C (HTC), hypoxia training water (HTW), hypoxia resting vitamin C (HRC), hypoxia resting water (HRW), normoxia training vitamin C (NTC), normoxia training water (NTW) and normoxia resting vitamin C (NRC).
- β_1, β_2, β_3 , β_4, β_5, β_6, β_7 are the effects of the treatments HTC, HTW, HRC, HRW, NTC, NTW and NRC.
- β_8, β_9, β_{10},β_{11},β_{12},β_{13} and β_{14} are the effects of the interaction between *day* and the treatments HTC, HTW, HRC, HRW, NTC, NTW and NRC.
- β_{15}, β_{16}, β_{17}, β_{18}, β_{19}, β_{20} and β_{21} are the effects of the interaction between day^2 and the treatments HTC, HTW, HRC, HRW, NTC, NTW and NRC.
- b_{0i} are random intercepts, normally distributed with mean 0 and variance σ^2_{b0}.
- b_{1i} are random slopes for day, normally distributed mean 0 and variance σ^2_{b1}.
- ϵ_{ijt} are the error terms, normally distributed with mean 0 and variance σ^2_t allowing for unequal variances between treatments.

For the normoxic model, the hypoxic model and the model joining both protocols, the model parameters are estimated using Bayesian hierarchical estimation and MCMC. We have to consider distributional assumptions for the different parameters, and we need to define prior distributions to combine with the distributions assumed for the data. The general hierarchical Bayesian formulation for the different models follows,

$$\begin{aligned} Y_{ijt} &\sim N(b_{0i} + b_{1i} + \alpha + \alpha_1 + \alpha_2 + \beta_1 \cdots \beta_h + \gamma, \sigma_t^2) \\ \begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} &\sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{b_0}^2 & \rho\sigma_{b_0}\sigma_{b_1} \\ \rho\sigma_{b_0}\sigma_{b_1} & \sigma_{b_1}^2 \end{pmatrix} \right) \end{aligned} \tag{3.6}$$

Where the parameters are defined previously in the Models 3.4 and 3.5 for every outcome, the subindex h is from 1 to 9 for the normoxic or the hypoxic protocols, h is from 1 to 21 for the joint model combining the normoxic protocol and the hypoxic protocol, t is and indicator for treatment where $t = 1, \cdots, 8$ and γ parameter appears only in the models joining the normoxic and hypoxic protocols corresponding to a covariate adjusting for the differences in the age between the normoxic and the hypoxic groups. The Model (3.6) accounts for the fact that we have unequal variances between treatment groups. For the Model 3.4 we fit models assuming equal variances for every outcome, and for Model 3.5 we fit models with unequal and equal variances for every outcome.

The Bayesian estimation through MCMC requires definition of prior probability distributions for the parameters of interest. For the normoxic or hypoxic models the different parameters for the predictors receive non-informative normal priors , and the variance components receive non-informative uniform priors following Gelman (2006) who shows that is preferred to use uniform non-informative priors when we expect small variance components closed to zero. In the equation 3.7 the priors given for the different parameters in the general model (3.6) are presented.

$$
\begin{aligned}
Y_{ij} &\sim N(b_{0i} + b_{1i} + \alpha + \alpha_1 + \alpha_2 + \beta_1 \cdots \beta_h + \gamma, \tau_t) \\
\alpha &\sim N(0, 0.0001) \\
\alpha_1 &\sim N(0, 0.0001) \\
\alpha_2 &\sim N(0, 0.0001) \\
\beta_1 &\sim N(0, 0.0001) \\
\vdots &\quad \vdots \\
\beta_h &\sim N(0, 0.0001) \\
\gamma &\sim N(0, 0.0001) \\
\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} &\sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{b_0} & \rho\sqrt{\tau_{b_0}\tau_{b_1}} \\ \rho\sqrt{\tau_{b_0}\tau_{b_1}} & \tau_{b_1} \end{pmatrix} \right) \\
\tau_t &\sim \frac{1}{\sigma_t^2} \\
\tau_{b_0} &\sim \frac{1}{\sigma_{b_0}^2} \\
\tau_{b_1} &\sim \frac{1}{\sigma_{b_1}^2} \\
\sigma_t &\sim U(0, 100) \\
\sigma_{b_0} &\sim U(0, 100) \\
\sigma_{b_1} &\sim U(0, 100) \\
\rho &\sim U(-1, 1)
\end{aligned}
\tag{3.7}
$$

The Bayesian hierarchical models are fitted using WinBUGS (Gilks et al.; 1996) being interfaced by the R software (R Development Core Team; 2008), as it is shown by Albert (2009) and Gelman and Hill (2007) using the R2WinBUGS R package . The models are fitted using three parallel chains, random initial values are generated from normal distributions for the fixed effects or uniform distributions for the variance components, with an estimation period of 80000 iterations, a burning period of 40000 iterations, and chain thinning of 5 iterations. Convergence is assessed by checking the trace plots of the samples, autocorrelation plot functions, the Gelman-Rubin convergence statistic and density plots using the CODA R package (Albert; 2009) .

3.2.3 Inferences

The objective of the inferential task is to find if there are pairwise differences between the hypoxia in spring interval training plus vitamin C (HTC) and the hypoxia in resting plus vitamin C (HRC) compared with the other hypoxic and normoxic protocols on every outcome variable, and between HTC and HRC. The pairwise differences of interest are represented in the following hypothesis,

$$H_0 : \mu_{uk} = \mu_{vk} \tag{3.8}$$

$$H_A : \mu_{uk} \neq \mu_{vk} \tag{3.9}$$

Where u represents the treatment HTC or HRC, and v represents the treatment HTC, HTW, HRC, HRW, NRW, NRC, NTW or NTC, without considering differences between equal treatments, and k is a grid of time points from day 0 to day 21. The hypothesis will be tested using 95% Bayesian credible intervals and 95% Bayesian credible bands defined in the time period from day 0 to day 21. To estimate the Bayesian credible intervals we follow (Bolstad; 2007). A (1-α)% equal tail credible interval with unequal unknown variances is calculated as follows,

1. Define a grid of k values from 0 to 21, representing the total experimental period.

2. For every k point the difference between the estimate of the treatment mean u (denoted as $\hat{f}_u(x)$) and the estimate of the treatment mean v (denoted as $\hat{f}_v(x)$) is calculated using the fitted model for each k point for every outcome variable, and the difference is defined as $\hat{f}_d(x_k)$.

3. A pooled standard deviation σ_p is estimated using the standard deviation of $\hat{f}_{(u)}(x)$ and $\hat{f}_{(v)}(x)$, with the estimation of σ_p shown in the equation 3.10,

$$\hat{\sigma}_p = \sqrt{\frac{\hat{\sigma}_u^2}{n_u} + \frac{\hat{\sigma}_v^2}{n_v}} \tag{3.10}$$

4. We estimate the degrees of freedom ν using the Satterhwaite approximation

$$\nu = \frac{(\frac{\hat{\sigma}_u^2}{n_u} + \frac{\hat{\sigma}_v^2}{n_v})^2}{\frac{(\frac{\hat{\sigma}_u^2}{n_u})^2}{n_u - 1} + \frac{(\frac{\hat{\sigma}_v^2}{n_v})^2}{n_v - 1}} \tag{3.11}$$

5. Finally a (1-α) Bayesian credible interval for every time point k is equal to;

$$\left[\hat{f}_d(x_k) - t_{(\frac{\alpha}{2},\nu)}\hat{\sigma}_p, \hat{f}_d(x_k) + t_{(\frac{\alpha}{2},\nu)}\hat{\sigma}_p\right] \tag{3.12}$$

To estimate the (1-α)% Bayesian credible bands for every difference between means, in every outcome variable, for the 21 days experimental period, we have adapted the method of Crainiceanu et al. (2007) outlined in Krivobokova et al. (2009). The procedure is shown:

1. Define a grid of k values from 0 to 21, representing the total experimental period.

2. For every k point the difference between treatment mean u (denoted as $\hat{f}_u(x)$) and treatment mean v (denoted as $\hat{f}_v(x)$) is estimated using the fitted model for every outcome variable, and the difference is defined as $\hat{f}_d(x_k)$.

3. Following Bolstad (2007), a pooled standard deviation σ_p is estimated using the standard deviation of $\hat{f}_{(u)}(x)$ and $\hat{f}_{(v)}(x)$, with the estimation of σ_p shown in equation 3.10.

4. We generate l random samples from a t distribution with degrees of freedom ν estimated using the Satterhwaite approximation from equation 3.11, then adding the l random samples to every difference $\hat{f}_d(x_k)$ to produce $\hat{f}_d^{(l)}(x_k)$, and finally, estimating $z_{(1-\alpha)}$ using equation (3.13).

5. Then, the (1-α) sample quantile $z_{(1-\alpha)}$ of

$$\max_{k=1,\cdots,n} \left| \frac{(f_d^{(l)}(x_k) - \hat{f}_d(x_k))}{\sigma_p} \right| , l = 1, \cdots, L. \tag{3.13}$$

6. A (1-α)% credible band for the difference of means between $\hat{f}_{(i)}$ and $\hat{f}_{(j)}$ for every outcome variable, for the outlined method is given by

$$\left[\hat{f}_d(x_k) - z_{(1-\alpha)}\hat{\sigma}_p, \hat{f}_d(x_k) + z_{(1-\alpha)}\hat{\sigma}_p \right] \tag{3.14}$$

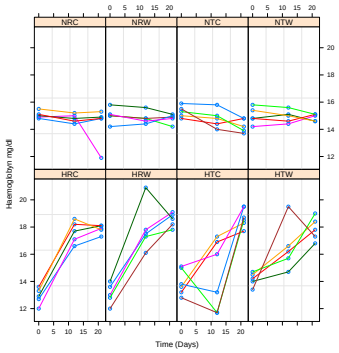
7. We conclude the null hypothesis of a pairwise difference between the treatment means equal to 0, at every time k in the interval 0 to 21 days, for every outcome variable, at α level of 0.05, if the credible band includes 0, and we conclude the alternative hypothesis otherwise.

Chapter 4

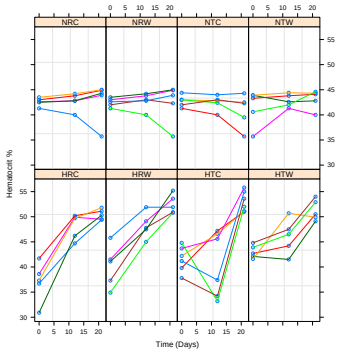
Results

4.1 Exploratory Data Analysis

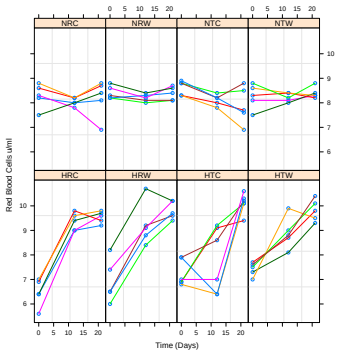
From Figure 4.1 we observe the individual profiles for every outcome variable. For the normoxic experiment, in reticulocytes, haemoglobyn and mean corpuscular volume the within and between subject variability is small compared with the mean corpuscular haemoglobyn, haematocrit and red blood cells. In general the hypoxic protocols expressed a great between and within subject variability, with the reticulocytes group presenting the greater between and within subject variability . Additionally, we observe that the hypoxic protocols produced more variable responses than the normoxic protocols.
In Figure 4.2, the mean profiles in every treatment and every protocol show that in the normoxic treatments the mean profile is almost horizontal, suggesting no differences between any of the normoxic treatments through the experimental period of 21 days. Additionally, in the hypoxic treatments we observe that in red blood cells, haematocrit and haemoglobyn the mean profiles increase through the time, for the mean corpuscular haemoglobyn the mean profile decreases, and for the reticulocytes and the mean corpuscular volume the mean profiles decrease at day 12, then reaching the initial values at day 21.
The variance profiles in every treatment are presented in Figure 4.3. The variances between treatments are unequal between and within the hypoxic and the normoxic treatments, anticipating a modeling development based on unequal variances, and, particularly, the HTC treatment produces higher variances at day 12, in the haemoglobyn, haematocrit and red blood cells, but decrease the variance of the reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn.



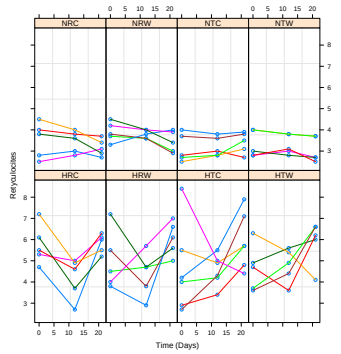
(a) Individual profiles for Haemoglobyn



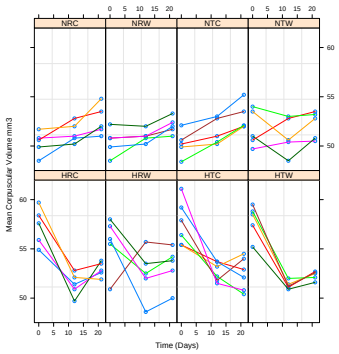
(b) Individual profiles for haematocrit



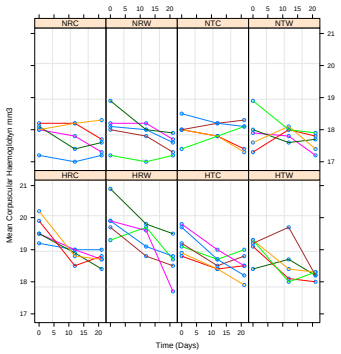
(c) Individual profiles for red blood cells



(d) Individual profiles for retyculocites

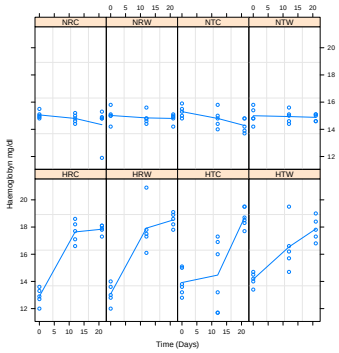


(e) Individual profiles for mean corpuscular volume

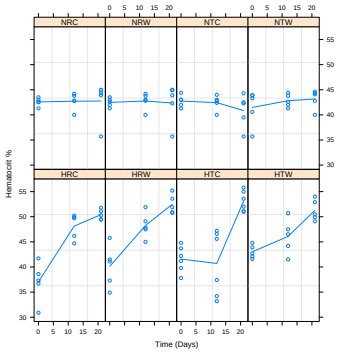


(f) Individual profiles for mean corpuscular haemoglobyn

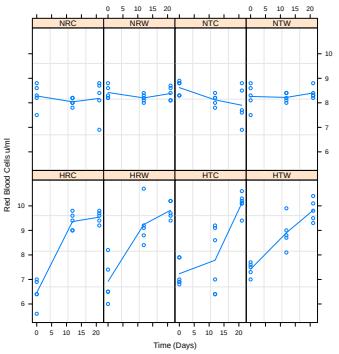
Figure 4.1: Individual profiles for haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn. NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C, HRC: Hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, HTC: Hypoxia training vitamin C.



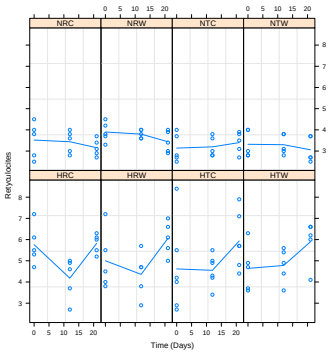
(a) Mean profiles for haemoglobyn



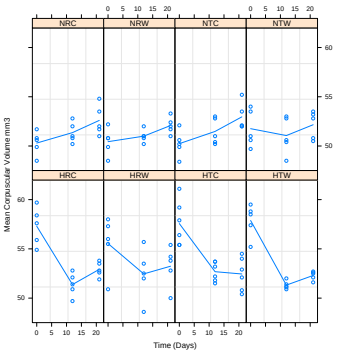
(b) Mean profiles for haematocrit



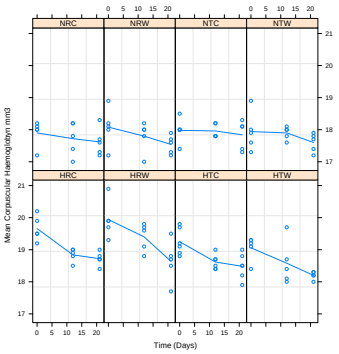
(c) Mean profiles for red blood cells



(d) Mean profiles for reticulocytes

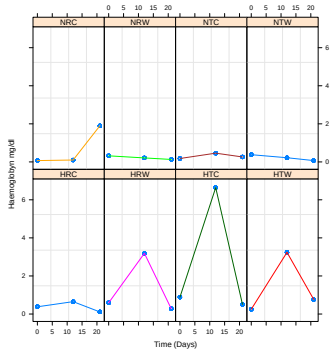


(e) Mean profiles for mean corpuscular volume

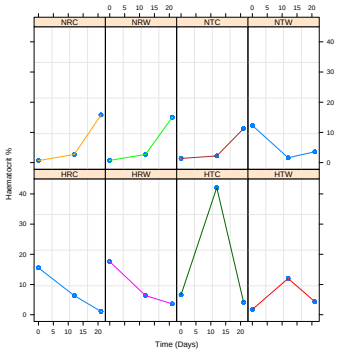


(f) Mean profiles for mean corpuscular haemoglobyn

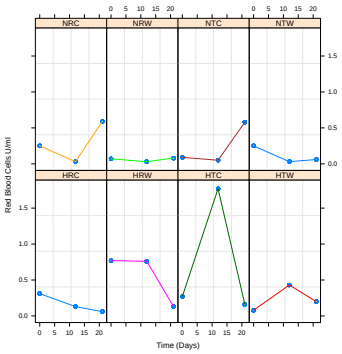
Figure 4.2: Mean profiles for haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn. NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C, HRC: Hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, HTC: Hypoxia training vitamin C.



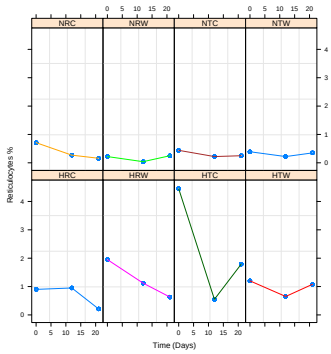
(a) Variance profiles for haemoglobyn



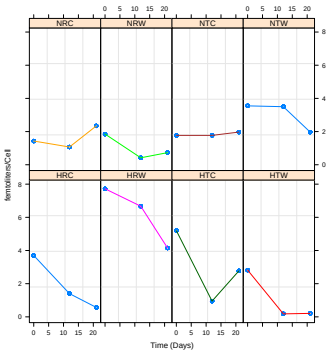
(b) Variance profiles for haematocrit



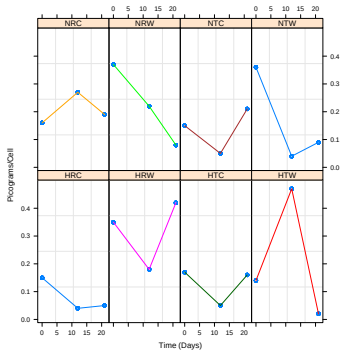
(c) Variance profiles for red blood cells



(d) Variance profiles for reticulocytes



(e) Variance profiles for mean corpuscular volume

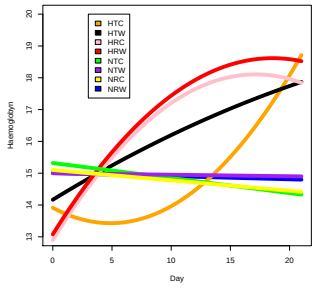


(f) Variance profiles for mean corpuscular haemoglobyn

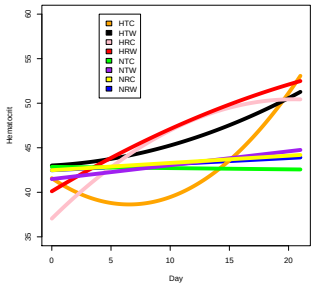
Figure 4.3: Variance profiles for haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn. NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C, HRC: Hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, HTC: Hypoxia training vitamin C.

4.2 Statistical Analysis

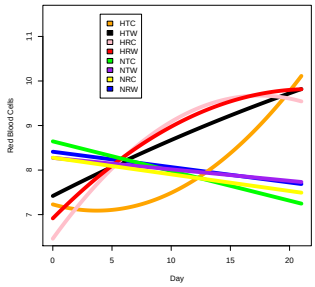
The most parsimonious model, for the normoxic protocol based, on the DIC selection for every outcome is shown in Table 2, in Appendix A. For all the outcomes, the selected model consists on a model with linear fixed effects, and variance components comprised by random intercepts and random slopes on time. For the hypoxic outcomes, using the DIC, we choose the model for every outcome from the Table 3, in the Appendix A. From Table 3, the selected models for the outcomes haemoglobyn, haematocrit, red blood cells, mean corpuscular haemoglobyn, reticulocytes and mean corpuscular volume correspond to fixed effects linear on time with variance components given by random intercepts and slopes on time. For the outcomes haemoglobyn, haematocrit, red blood cells and mean corpuscular haemoglobyn, the DIC is higher for the options with one variance component (random intercepts). Instead of using the one variance component model, we use two variance components (random intercepts and slopes), because the DIC are closer between the two options, and, we can provide estimates for the variance components which can fit the data in closer form.
Finally, joint models for the normoxic and hypoxic experiment are assembled, using the models chosen above. Four different models have been built, and the DIC are shown in Table 4 for every outcome variable. A first model consists in a linear and quadratic model, for fixed effects, in the hypoxic groups, and linear fixed effects, for the normoxic groups with random intercepts, random slopes on time and random residuals for the variance components, with unequal variances for every treatment group. The second model, is similar to the first model, but with equal variances. A third model, comprises linear and quadratic fixed effects, for the hypoxic groups, and linear fixed effects ,for the normoxic groups, and random intercepts and random residuals for the variance components, with unequal variances for every treatment group. A fourth model is established, similar to the third model, but considering equal variances for every treatment group. Following the selection process, based on a lower DIC, the best models for all the outcomes correspond to the option with unequal variances, and random intercepts and random slopes on time. In Tables 5 to 10, in the Appendix B, the parameter estimates, standard errors and 95% credible intervals of the final joint models are shown for haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume, and mean corpuscular haemoglobyn, respectively. The joint model for every outcome corresponds to the union of the selected final model for the normoxic, and the hypoxic protocols, adjusting for the difference in age (in days) between the rats, in both experiments. The reference treatment, for the joint models correspond to the normoxia in resting plus water group (NRW).
In the Figure 4.4, we observe how, the models fit the data, based on a marginal interpretation of every model. Here, it is possible to make comparisons, between the fitted marginal model, and the mean profiles in the Figure 4.2. We conclude that, the fit of ev-



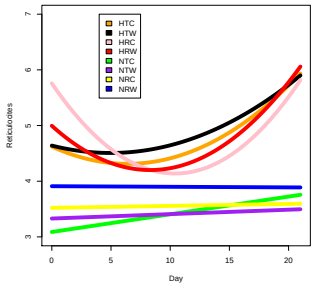
(a) Fitted Means for Haemoglobyn



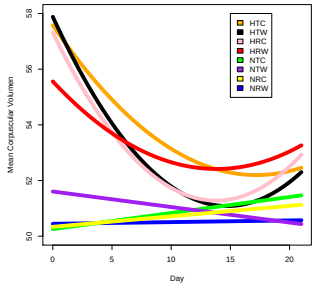
(b) Fitted Means for haematocrit



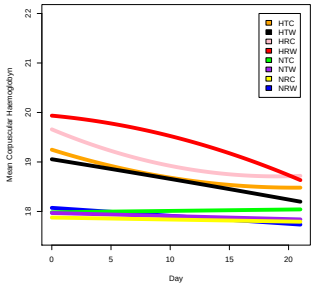
(c) Fitted Means for red blood cells



(d) Fitted Means for Reticulocites



(e) Fitted Means for Mean Corpuscular Volume



(f) Fitted Means for Mean Corpuscular Haemoglobyn

Figure 4.4: Fitted Mean profiles for red blood cells, reticulocytes,haematocrit, haemoglobyn, mean corpuscular volume and mean corpuscular haemoglobyn. NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C, HRC: Hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, HTC: Hypoxia training vitamin C.

ery model, for every treatment, in each outcome is pretty good. The selected joint models, for the normoxic treatments are random intercepts and random slopes, first order linear

models, with unequal variances, for haemoglobyn, haematocrit, red blood cells, mean corpuscular volume, reticulocytes and mean corpuscular haemoglobyn. In the hypoxic treatments, the selected models correspond to random intercepts and random slopes, with fixed effects quadratic on time (days), with unequal variances, for the haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn.
We have calculated Bayesian credible intervals, and Bayesian credible bands. The Bayesian credible intervals compare between the different treatments, through the time, without considering that many comparisons are made at the same time, and we are not correcting for the inflation of the α level. With the Bayesian credible bands, we are adjusting the comparisons, although the Bayesian credible bands are roughly 30 - 50 % wider than the pointwise credible intervals. The Figures 4.5 and 4.6 show the 95% credible bands and the 95% credible intervals, for selected differences between treatment means, for haemoglobyn, haematocrit, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn, for the comparison of the hypoxic treatments, using as reference, the HTC and the HRC treatments. In the Appendix C, the Figures 1, 2 and 3 show the 95% credible bands and the 95% credible intervals for the comparison of the HTC and HRC treatments, against the normoxic treatments (NTC, NRC, NTW, NTC) for the six outcome variables. Based on the 95% Bayesian Credible Bands, the results for the selected differences can be summarized:

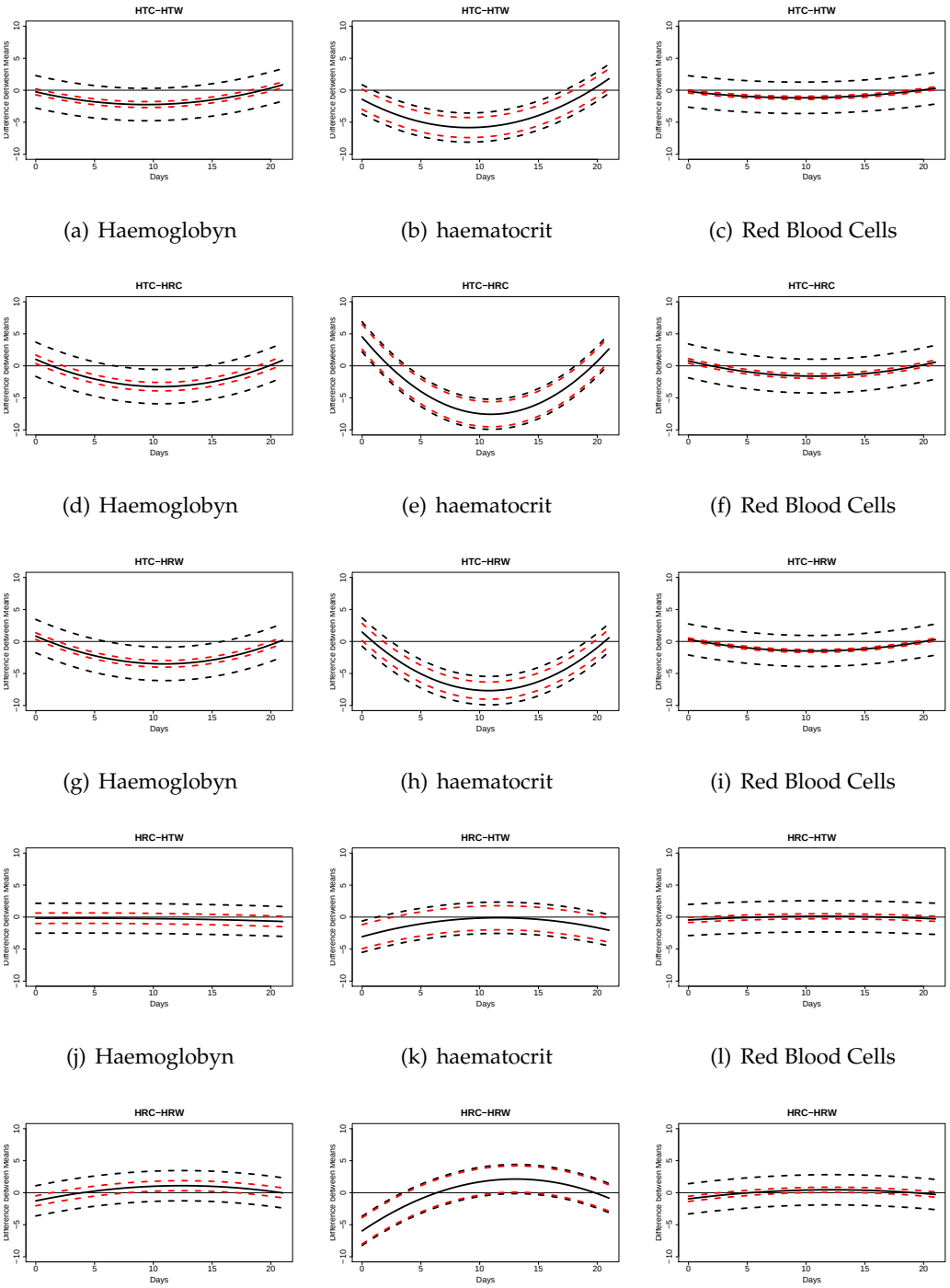
- In the haemoglobyn and haematocrit, there are differences between the treatment means at α level of 0.05, comparing HTC with HRC, HRW and HTW, at the middle part of the experimental period (from day 7 through day 13 approximately), with lower values for HTC than for the rest of the hypoxic treatments, and there are no differences between the treatment means at α level of 0.05, comparing HRC with HRW and HTW. Additionally, in the haematocrit there are significant differences at α level of 0.05 between HRC compared with HTC, HTW and HRW, with lower values of HRC from the day 0 to day 3 approximately.

- In the haemoglobyn, there are significant differences between the treatment means at α level of 0.05, comparing HTC and HRC with the normoxic treatments (NTC, NTW,NRC,NRW) in the last 2-3 days of the experimental period of 21 days, with higher values for HTC and HRC.

- In the haematocrit, we find significant differences between the treatment means at α level of 0.05, comparing HTC with the normoxic treatments (NTC, NTW,NRC,NRW), having lower values of HTC between the day 5 until the day 10, and with higher values of HTC from day 17 until day 21, and for the comparison of HRC with the normoxic treatments (NTC, NTW, NRC, NRW), presenting lower values of HRC

the first two experimental days, and with higher values of HRC from around the day 10 until the day 21.

- In the mean corpuscular volume we do not find significant differences between the treatment means at α level of 0.05, comparing HTC and HRC with the hypoxic outcomes (HTW and HRW), but, there are differences between HTC and HRC compared with the normoxic treatments (NTC, NTW, NRC, NRW) between day 0 until day 5, with higher values for the HTC and the HRC treatments.
- In the red blood cells, reticulocytes and mean corpuscular haemoglobyn, we do not find significant differences at α 0.05, between HTC and HRC compared with HTW, HRW, NTC, NTW, NRC and NRW.



(a) Haemoglobyn (b) haematocrit (c) Red Blood Cells

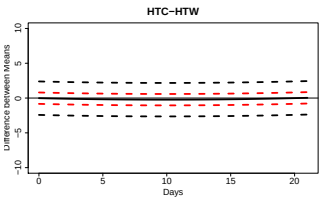
(d) Haemoglobyn (e) haematocrit (f) Red Blood Cells

(g) Haemoglobyn (h) haematocrit (i) Red Blood Cells

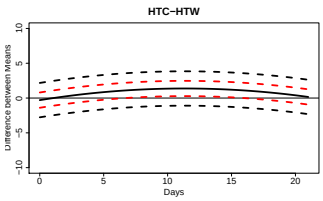
(j) Haemoglobyn (k) haematocrit (l) Red Blood Cells

(m) Haemoglobyn (n) haematocrit (o) Red Blood Cells

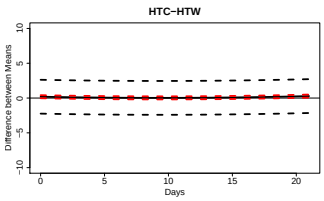
Figure 4.5: 95% Credible bands for selected differences between treatment means for haemaglobyn, haematocrit and red blood cells variables. Black dashed lines are upper and lower bounds, and bold line is the difference between treatment means. Red dashed lines are upper and lower bounds for 95 % credible intervals HTC: Hypoxia training vitamin C, HRC: hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water.



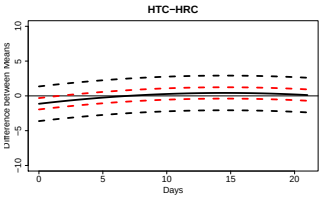
(a) Reticulocytes



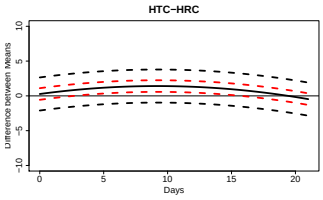
(b) Mean Corpuscular Volume



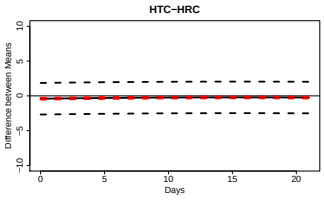
(c) Mean Corpuscular Haemoglobyn



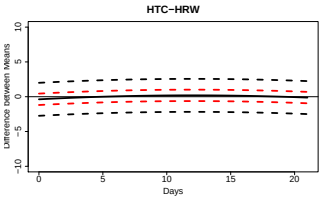
(d) Reticulocytes



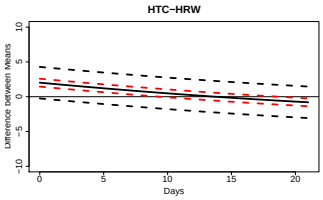
(e) Mean Corpuscular Volume



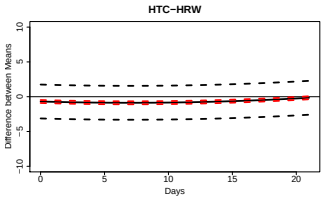
(f) Mean Corpuscular Haemoglobyn



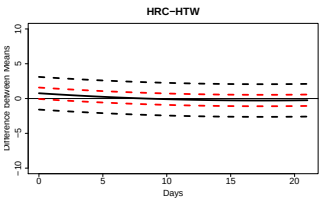
(g) Reticulocytes



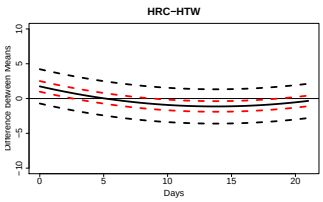
(h) Mean Corpuscular Volume



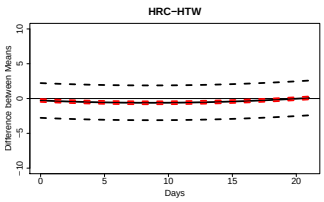
(i) Mean Corpuscular Haemoglobyn



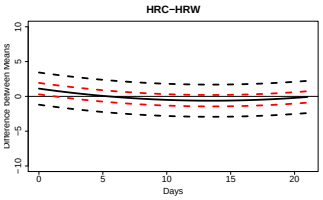
(j) Reticulocytes



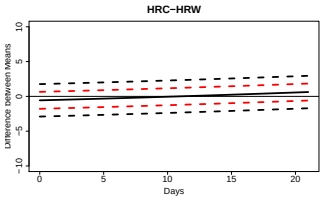
(k) Mean Corpuscular Volume



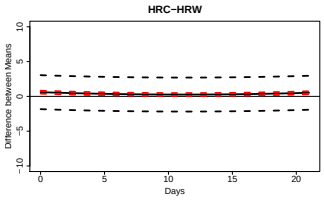
(l) Mean Corpuscular Haemoglobyn



(m) Reticulocytes



(n) Mean Corpuscular Volume



(o) Mean Corpuscular Haemoglobyn

Figure 4.6: 95% Credible bands for selected differences between treatment means for reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn variables. Black dashed lines are upper and lower bounds, and bold line is the difference between treatment means. Red dashed lines are upper and lower bounds for 95 % credible intervals. HTC: Hypoxia training vitamin C, HRC: hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water.

Chapter 5

Discussion

The kind of outcomes considered in this study have been modelled longitudinally, using linear and nonlinear mixed models, based on maximum likelihood estimation methods (Woo et al. (2006), Sanchis-Gomar et al. (2009)). In this study we have applied Bayesian hierarchical modeling to analyze outcome variables (haematocrit, haemoglobyn, red blood cells, reticulocytes, mean corpuscular volume and mean corpuscular haemoglobyn) from experiments, combining hypoxic and normoxic protocols, with resting or spring interval training, and with and without addition of vitamin C, in an experimental period of 21 days.

In the Bayesian hierarchical linear mixed model, the fixed effects are linear and quadratic on time, with interaction terms for time and treatment, a covariate adjusting for the age and the variance components including intercepts and slopes on time. We postulate that the evolution of the outcomes, during the experimental period can be explained by a linear function, based on three measures apart each one of the other in average 11 days. We can not support strongly the linear asumption for the physiological nature of the experiment, but instead of agreeing or not with that assumption, our interest is to make an initial modeling exercise for future studies. Based on this idea, we recommend for similar experiments, to include more measures in different days, apart for the days considered for this experiment, to have a more trustable picture of the evolution of the outcomes, through the experimental period.

The dataset initially was intended to be analyzed using maximum likelihood estimation methods, but, then due to problems in the estimation of the variance components, the need to make a longitudinal analysis, and to consider the effect of the variability between treatments, have guided the application of the Bayesian approach. Using the Bayesian hierarchical linear mixed model, we have chosen to do a population averaged interpretation, however, we are aware of the possibility to consider a subject specific approach, which could be applied for the researchers for future experimental designs.

Some additional findings have to be presented in this instance. First, the hypoxia in rest-

ing plus vitamin C (HRC) group started with lower values for haemoglobyn, haematocrit, and red blood cells than the other groups, although a random selection was undertaken for the experimental units to the treatments. A possible explanation is that it has occurred just by chance. Other possibility is that some rats, on that particular group were presenting a kind of association given by a parental effect. The consanguinity status of the experimental animals was unknown.

Second, the animals in the hypoxic group were younger than the animals in the normoxic experiment, and we have accounted this, using an age covariate as a fixed effect. However, we are mostly interested on the treatment effects in the hypoxic outcomes. Even so, our interest is also to provide a single model for every outcome.

Third, from the statistical point of view, we have many treatment groups, contrasted in different time points, with six different outcomes. We are confronted with the problem of multiple comparisons. We have accounted for the multiple time points, using Bayesian simultaneous credible bands for the difference between means. Still, it remains a correction for the comparison between outcome variables. Here, there are possibilities of using simulated p-values, in selected time points, and then, applying False Discovery Rate (FDR) methods exposed in the work of Lin (2008).

Finally, our findings show lower values of haemoglobyn and haematocrit, in the hypoxic treatment, with spring interval training plus vitamin C, around the middle part (day 8 to day 13) of an experimental period of 21 days, in young rats, with no alterations in the red blood cell count. The mean corpuscular volume (an indicator of erithrocytes size) is not different between the hypoxic treatments, but is significantly increased for the hypoxic protocols over the normoxic protocols, showing a temporary alteration of the erithrocyte size in the hypoxic protocols. These effects has not been reported previously. The results can be interpreted physiologically, at least in two forms. First, as a temporary smaller size of the red blood cells with lower values of haemoglobyn in the red blood cells. Or second, as a temporary alteration in the blood plasma conditions inducing shrinkage in the packed cell volume, together with lower values of haemoglobyn in the red blood cells. Whatever the mechanisms is behind the study results, it could be explained due to the effect of the interaction between hypoxia, spring interval training and vitamin C, inducing direct alterations of the erithocytic structure, or to blood plasma alterations, leading to erithrocytic changes. A recent *in vitro* study in red blood cells of rats, by Asha-Devi et al. (2009) shows that vitamin C was less effective in lowering the stress-induced acidosis in old red blood cell compared to the young. Additionally, the old cells were more spherical with lesser surface area. These results can support some of the findings from our study. To demonstrate if the changes in haematocrit and haemoglobyn are motivated by changes in erithrocyte size, produced by the interaction of hypoxia, spring interval training and vitamin C, and the physiological mechanism generating the changes, additional studies must be undertaken.

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Appendix A

Table 1: Summary statistics. NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C, HRC: Hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, HTC: Hypoxia training vitamin C.

	Day 0	Day 12	Day 21	Day 0	Day 12	Day 21
Treatment	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
	Haemoglobyn			Haematocrit		
NRW	15.02(0.57)	14.84(0.46)	14.8(0.35)	42.48(0.86)	42.76(1.65)	42.36(3.88)
NRC	15.06(0.27)	14.8(0.32)	14.34(1.38)	42.58(0.82)	42.72(1.64)	42.76(3.97)
NTW	15(0.62)	14.94(0.47)	14.88(0.26)	41.48(3.51)	42.82(1.27)	43.16(1.9)
NTC	15.3(0.43)	14.8(0.68)	14.28(0.51)	42.74(1.17)	42.44(1.49)	40.86(3.36)
HRW	13.08(0.77)	17.92(1.79)	18.52(0.53)	40.12(4.19)	48.26(2.52)	52.48(1.89)
HRC	12.9(0.61)	17.64(0.81)	17.84(0.33)	37.04(3.94)	48.14(2.52)	50.42(1.03)
HTW	14.16(0.5)	16.54(1.8)	17.86(0.87)	43.02(1.31)	46.08(3.47)	51.28(2.08)
HTC	13.92(0.94)	14.47(2.58)	18.7(0.7)	41.58(2.56)	40.7(6.49)	53.08(2.04)
	Red Blood Cells			Reticulocytes		
NRW	8.42(0.27)	8.2(0.16)	8.38(0.28)	3.9(0.46)	3.8(0.2)	3.44(0.5)
NRC	8.28(0.5)	8.04(0.17)	8.18(0.77)	3.52(0.84)	3.44(0.52)	3.16(0.4)
NTW	8.26(0.5)	8.22(0.18)	8.4(0.23)	3.32(0.63)	3.3(0.47)	3.06(0.59)
NTC	8.62(0.29)	8.12(0.23)	7.9(0.76)	3.14(0.67)	3.2(0.47)	3.4(0.5)
HRW	6.92(0.88)	9.24(0.87)	9.82(0.36)	5(1.39)	4.36(1.06)	6.06(0.79)
HRC	6.46(0.55)	9.36(0.36)	9.54(0.24)	5.76(0.95)	4.18(0.97)	5.82(0.45)
HTW	7.42(0.28)	8.9(0.65)	9.82(0.44)	4.64(1.09)	4.78(0.81)	5.9(1.04)
HTC	7.23(0.52)	7.78(1.33)	10.12(0.4)	4.62(2.11)	4.55(0.74)	5.93(1.34)
	Mean Corpuscular Volume			Mean Corpuscular Haemoglobyn		
NRW	50.44(1.36)	51(0.65)	52.08(0.85)	18.08(0.61)	17.8(0.47)	17.54(0.29)
NRC	50.3(1.19)	51.36(1.03)	52.6(1.53)	17.9(0.4)	17.72(0.52)	17.62(0.43)
NTW	51.76(1.88)	51.06(1.87)	52.16(1.4)	17.94(0.6)	17.9(0.2)	17.6(0.29)
NTC	50.24(1.33)	51.48(1.33)	52.96(1.4)	17.98(0.39)	17.96(0.22)	17.84(0.46)
HRW	55.54(2.78)	52.46(2.58)	53.24(2.04)	19.94(0.59)	19.4(0.43)	18.64(0.65)
HRC	57.3(1.92)	51.38(1.18)	52.92(0.75)	19.66(0.39)	18.84(0.21)	18.72(0.22)
HTW	57.88(1.68)	51.32(0.42)	52.3(0.45)	19.06(0.38)	18.58(0.68)	18.2(0.12)
HTC	57.57(2.28)	52.68(0.97)	52.45(1.66)	19.25(0.41)	18.62(0.23)	18.48(0.4)

Table 2: Deviance summaries for the models on the normoxic protocols. F.E.: fixed effects, R.E.: random effects. $\bar{D}$ = posterior mean of -2logLikelihood; $D(\bar{\theta})$ =-2LogLikelihood at posterior mean of stochastic nodes

Model	$\bar{D}$	$D(\bar{\theta})$	p_D	DIC
Haemoglobyn				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	88.853	63.888	24.965	113.818
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	2.488	-26.818	29.306	31.795
F.E. ($Time, Time^2$) R.E.($Intercept$)	31.104	6.519	24.585	55.689
F.E. ($Time$) R.E.($Intercept$)	25.562	4.467	21.095	46.657
Haematocrit				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	177.873	142.894	34.979	212.852
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	173.192	141.011	32.180	205.372
F.E. ($Time, Time^2$) R.E.($Intercept$)	227.015	201.459	25.556	252.571
F.E. ($Time$) R.E.($Intercept$)	221.485	199.516	21.969	243.454
Red Blood Cells				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	17.804	-14.139	31.943	49.748
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	18.982	-8.147	27.129	46.111
F.E. ($Time, Time^2$) R.E.($Intercept$)	41.624	18.873	22.751	64.375
F.E. ($Time$) R.E.($Intercept$)	38.753	19.537	19.215	57.968
Reticulocytes				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	-41.582	-80.516	38.934	-2.647
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	-29.397	-63.868	34.472	5.075
F.E. ($Time, Time^2$) R.E.($Intercept$)	23.936	-2.760	26.695	50.631
F.E. ($Time$) R.E.($Intercept$)	21.292	-1.684	22.976	44.267
Mean Corpuscular Volume				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	142.148	113.391	28.757	170.906
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	146.179	121.663	24.515	170.694
F.E. ($Time, Time^2$) R.E.($Intercept$)	143.969	117.528	26.442	170.411
F.E. ($Time$) R.E.($Intercept$)	147.250	124.827	22.423	169.673
Mean Corpuscular Haemoglobyn				
F.E. ($Time, Time^2$) R.E.($Intercept, Slope * Time$)	14.165	-16.473	30.638	44.803
F.E. ($Time$) R.E.($Intercept, Slope * Time$)	2.488	-26.818	29.306	31.795
F.E. ($Time, Time^2$) R.E.($Intercept$)	31.104	6.519	24.585	55.689
F.E. ($Time$) R.E.($Intercept$)	25.562	4.467	21.095	46.657

Table 3: Deviance summaries for the models on the hypoxic protocols. F.E.: fixed effects (linear and quadratic), R.E.: random effects. $\bar{D}$ = posterior mean of -2logLikelihood; $D(\bar{\theta})$ =-2LogLikelihood at posterior mean of stochastic nodes

Model	$\bar{D}$	$D(\bar{\theta})$	p_D	DIC
Haemoglobyn				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	202.959	184.471	18.488	221.446
F.E.($Time, Time^2$) R.E.($Intercept$)	201.999	184.709	17.290	219.289
F.E.($Time$) R.E.($Intercept, Slope * Time$)	228.32	215.703	12.617	240.936
F.E.($Time$) R.E.($Intercept$)	227.755	216.364	11.391	239.146
Haematocrit				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	316.853	295.385	21.468	338.321
F.E.($Time, Time^2$) R.E.($Intercept$)	317.368	297.687	19.681	337.049
F.E.($Time$) R.E.($Intercept, Slope * Time$)	347.58	333.836	13.744	361.324
F.E.($Time$) R.E.($Intercept$)	346.981	334.645	12.336	359.317
Red Blood Cells				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	118.669	97.958	20.711	139.380
F.E.($Time, Time^2$) R.E.($Intercept$)	118.274	98.895	19.379	137.653
F.E.($Time$) R.E.($Intercept, Slope * Time$)	145.924	132.211	13.713	159.637
F.E.($Time$) R.E.($Intercept$)	145.252	132.778	12.474	157.726
Reticulocytes				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	133.822	98.974	34.848	168.669
F.E.($Time, Time^2$) R.E.($Intercept$)	197.582	181.880	15.702	213.284
F.E.($Time$) R.E.($Intercept, Slope * Time$)	193.629	174.031	19.597	213.226
F.E.($Time$) R.E.($Intercept$)	207.785	196.916	10.869	218.654
Mean Corpuscular Volume				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	227.783	202.260	25.523	253.306
F.E.($Time, Time^2$) R.E.($Intercept$)	248.498	232.964	15.534	264.031
F.E.($Time$) R.E.($Intercept, Slope * Time$)	275.812	262.548	13.264	289.076
F.E.($Time$) R.E.($Intercept$)	277.080	266.434	10.645	287.725
Mean Corpuscular Haemoglobyn				
F.E.($Time, Time^2$) R.E.($Intercept, Slope * Time$)	60.487	38.397	22.090	82.577
F.E.($Time, Time^2$) R.E.($Intercept$)	62.741	43.671	19.071	81.812
F.E.($Time$) R.E.($Intercept, Slope * Time$)	60.394	42.563	17.832	78.226
F.E.($Time$) R.E.($Intercept$)	61.901	46.593	15.308	77.208

Table 4: Deviance summaries for the joint models on the normoxic and hypoxic protocols. U.V.: unequal variances, E.V.: equal variances, F.E.: fixed effects (linear for normoxic, and linear and quadratic for hypoxic), R.E.: random effects. $\bar{D}$ = posterior mean of -2logLikelihood; $D(\bar{\theta})$ =-2LogLikelihood at posterior mean of stochastic nodes

Model	$\bar{D}$	$(D\bar{\theta})$	p_D	DIC
Haemoglobyn				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	248.040	204.460	43.579	291.619
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	330.528	298.431	32.097	362.625
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	267.866	229.495	38.371	306.237
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	330.266	299.447	30.820	361.086
Haematocrit				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	490.399	439.933	50.467	540.866
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	558.158	513.855	44.304	602.462
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	535.652	490.998	44.654	580.306
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	558.799	516.954	41.845	600.644
Red Blood Cells				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	114.941	69.995	44.946	159.887
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	172.373	132.735	39.637	212.010
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	129.229	88.421	40.808	170.037
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	172.352	131.348	41.003	213.355
Reticulocytes				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	155.181	103.826	51.355	206.536
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	168.915	97.171	71.744	240.659
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	210.781	167.622	43.159	253.940
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	316.194	287.152	29.042	345.236
Mean Corpuscular Volume				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	365.769	318.015	47.754	413.523
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	389.194	334.219	54.975	444.170
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	373.742	329.231	44.511	418.253
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	433.745	398.220	35.525	469.270
Mean Corpuscular Haemoglobyn				
U. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	39.389	-13.284	52.673	92.061
E. V., F.E.($Time, Time^2$), R.E.($Intercept, Slope * Time$)	79.593	31.687	47.906	127.499
U. V., F.E.($Time, Time^2$), R.E.($Intercept$)	94.851	52.547	42.304	137.156
E. V., F.E.($Time, Time^2$), R.E.($Intercept$)	89.440	47.803	41.637	131.077

Appendix B

Table 5: Parameter estimates and standard deviation for the model of Haemoglobyn

Predictor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	11.17	44.74	-76.5	11.02	100
Day	α_1	-0.009828	0.02342	-0.05508	-0.01013	0.03725
Day^2	α_2	-4.61e-05	0.0009433	-0.001974	-2.612e-05	0.001788
HTC	β_1	2.743	44.74	-85.82	2.795	90.61
HTW	β_2	2.997	44.73	-85.76	3.097	90.67
HRC	β_3	1.727	44.74	-87.04	1.898	89.61
HRW	β_4	1.91	44.74	-86.89	1.955	89.86
NTC	β_5	0.3147	0.399	-0.4744	0.3172	1.106
NTW	β_6	-0.005662	0.3731	-0.7518	-0.002578	0.7265
NRC	β_7	0.09583	0.5041	-0.9031	0.09462	1.092
$HTC \times Day$	β_8	-0.1883	0.1818	-0.5512	-0.1869	0.1717
$HTW \times Day$	β_9	0.2372	0.1517	-0.06597	0.2368	0.5371
$HRC \times Day$	β_{10}	0.6179	0.06249	0.494	0.6175	0.7411
$HRW \times Day$	β_{11}	0.6061	0.1354	0.3379	0.6048	0.8805
$NTC \times Day$	β_{12}	-0.03741	0.02154	-0.08	-0.03741	0.005154
$NTW \times Day$	β_{13}	0.005078	0.01905	-0.03282	0.005093	0.04323
$NRC \times Day$	β_{14}	-0.02282	0.03065	-0.08276	-0.02275	0.03874
$HTC \times Day^2$	β_{15}	0.02036	0.008484	0.003651	0.0203	0.03721
$HTW \times Day^2$	β_{16}	-0.002389	0.007056	-0.01648	-0.002392	0.01161
$HRC \times Day^2$	β_{17}	-0.0177	0.00284	-0.02339	-0.01771	-0.01209
$HRW \times Day^2$	β_{18}	-0.01601	0.006302	-0.02875	-0.01601	-0.003624
Age	γ	0.2557	2.982	-5.662	0.2651	6.106
ρ	ρ	-0.6155	0.3659	-0.9778	-0.7306	0.5089
SD_{b0}	σ_{b0}	0.483	0.1314	0.2359	0.4782	0.7599
SD_{b1}	σ_{b1}	0.01818	0.00847	0.001942	0.01845	0.03498
SD_{HTC}	σ_{HTC}	0.5011	0.1597	0.2793	0.4729	0.896
SD_{HTW}	σ_{HTW}	1.183	0.3221	0.7172	1.131	1.966
SD_{HRC}	σ_{HRC}	1.772	0.3795	1.211	1.712	2.668
SD_{HRW}	σ_{HRW}	1.34	0.332	0.8667	1.282	2.153
SD_{NTC}	σ_{NTC}	0.8511	0.2185	0.5305	0.8158	1.376
SD_{NTW}	σ_{NTW}	0.3047	0.109	0.1512	0.2852	0.5635
SD_{NRC}	σ_{NRC}	0.4628	0.1353	0.2649	0.4404	0.7953
SD_{NRW}	σ_{NRW}	0.3272	0.1133	0.1694	0.3076	0.5995

Table 6: Parameter estimates and standard deviation for the model of Haematocrit

Predictor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	32.31	44.77	-56.14	32.38	119.8
Day	α_1	0.06845	0.0749	-0.08087	0.06901	0.2153
Day^2	α_2	-0.003584	0.002443	-0.008409	-0.0036	0.001227
HTC	β_1	9.273	44.79	-78.55	9.055	97.8
HTW	β_2	10.7	44.78	-76.67	10.77	99.03
HRC	β_3	4.738	44.81	-82.8	4.726	93.06
HRW	β_4	7.803	44.8	-79.85	7.69	96.46
NTC	β_5	0.3811	0.7589	-1.126	0.3819	1.891
NTW	β_6	-0.9879	1.185	-3.338	-0.9854	1.337
NRC	β_7	0.007154	0.7487	-1.486	0.01022	1.528
$HTC \times Day$	β_8	-0.97	0.471	-1.897	-0.9739	-0.03067
$HTW \times Day$	β_9	0.003215	0.2812	-0.5553	0.005281	0.5616
$HRC \times Day$	β_{10}	1.242	0.354	0.5332	1.242	1.947
$HRW \times Day$	β_{11}	0.7304	0.3775	-0.0185	0.7296	1.485
$NTC \times Day$	β_{12}	-0.08235	0.07919	-0.2395	-0.082	0.07497
$NTW \times Day$	β_{13}	0.08719	0.1027	-0.1155	0.08759	0.2905
$NRC \times Day$	β_{14}	0.013	0.07923	-0.1443	0.01291	0.1715
$HTC \times Day^2$	β_{15}	0.07257	0.02182	0.02899	0.07275	0.1157
$HTW \times Day^2$	β_{16}	0.01891	0.01272	-0.00631	0.01882	0.04418
$HRC \times Day^2$	β_{17}	-0.02847	0.01624	-0.06072	-0.02853	0.00418
$HRW \times Day^2$	β_{18}	-0.006393	0.01734	-0.04146	-0.006282	0.0283
Age	γ	0.6776	2.985	-5.15	0.6711	6.577
ρ	ρ	0.5618	0.3467	-0.3008	0.6469	0.9811
SD_{b0}	σ_{b0}	0.7431	0.3863	0.1346	0.6831	1.741
SD_{b1}	σ_{b1}	0.1076	0.02185	0.06991	0.1058	0.1552
SD_{HTC}	σ_{HTC}	3.029	0.8324	1.795	2.898	5.011
SD_{HTW}	σ_{HTW}	3.244	0.9011	1.914	3.105	5.38
SD_{HRC}	σ_{HRC}	4.559	1.006	3.072	4.404	6.92
SD_{HRW}	σ_{HRW}	2.38	0.6651	1.459	2.26	4.003
SD_{NTC}	σ_{NTC}	0.9075	0.3148	0.5092	0.8411	1.7
SD_{NTW}	σ_{NTW}	0.8146	0.2724	0.4635	0.757	1.501
SD_{NRC}	σ_{NRC}	0.8972	0.3014	0.4945	0.839	1.651
SD_{NRW}	σ_{NRW}	2.304	0.6494	1.3	2.211	3.836

Table 7: Parameter estimates and standard deviation for the model of Red Blood Cells

Predictor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	5.904	44.5	-81.23	5.925	92.87
Day	α_1	-0.03453	0.01462	-0.06286	-0.03475	-0.004436
Day^2	α_2	0.001551	0.0006165	0.0002927	0.001561	0.002745
HTC	β_1	1.326	44.51	-85.69	1.277	88.54
HTW	β_2	1.515	44.51	-85.5	1.476	88.6
HRC	β_3	0.5559	44.5	-86.44	0.5688	87.63
HRW	β_4	1.012	44.5	-86.04	0.9888	88.14
NTC	β_5	0.2329	0.2839	-0.3364	0.2329	0.7911
NTW	β_6	-0.1377	0.2563	-0.6517	-0.1363	0.3755
NRC	β_7	-0.1341	0.3101	-0.7459	-0.1316	0.4751
$HTC \times Day$	β_8	-0.04092	0.09622	-0.2328	-0.04164	0.1516
$HTW \times Day$	β_9	0.1702	0.06205	0.0466	0.1699	0.295
$HRC \times Day$	β_{10}	0.4024	0.03981	0.3217	0.4025	0.4823
$HRW \times Day$	β_{11}	0.302	0.07004	0.1612	0.3018	0.4433
$NTC \times Day$	β_{12}	-0.03203	0.01538	-0.06299	-0.0321	-0.001441
$NTW \times Day$	β_{13}	0.008735	0.01259	-0.01669	0.008807	0.03382
$NRC \times Day$	β_{14}	-0.002851	0.01759	-0.03755	-0.00289	0.03229
$HTC \times Day^2$	β_{15}	0.00858	0.004504	-0.0004395	0.008608	0.01753
$HTW \times Day^2$	β_{16}	-0.002569	0.002872	-0.008372	-0.002548	0.003102
$HRC \times Day^2$	β_{17}	-0.01208	0.001814	-0.01569	-0.01208	-0.008433
$HRW \times Day^2$	β_{18}	-0.007715	0.003259	-0.01434	-0.007697	-0.001168
Age	γ	0.1672	2.967	-5.631	0.1659	5.98
ρ	ρ	-0.4005	0.4785	-0.9675	-0.5387	0.7824
SD_{b0}	σ_{b0}	0.3267	0.1016	0.1499	0.3188	0.5476
SD_{b1}	σ_{b1}	0.01033	0.00637	0.0006928	0.009809	0.02392
SD_{HTC}	σ_{HTC}	0.3121	0.1174	0.1327	0.297	0.5842
SD_{HTW}	σ_{HTW}	0.5969	0.2121	0.2825	0.5669	1.095
SD_{HRC}	σ_{HRC}	0.935	0.2002	0.6356	0.9035	1.411
SD_{HRW}	σ_{HRW}	0.5335	0.142	0.3317	0.5096	0.8771
SD_{NTC}	σ_{NTC}	0.4761	0.1363	0.2636	0.4572	0.796
SD_{NTW}	σ_{NTW}	0.1579	0.05139	0.08876	0.1482	0.2862
SD_{NRC}	σ_{NRC}	0.3949	0.1211	0.2107	0.3764	0.6812
SD_{NRW}	σ_{NRW}	0.2794	0.08583	0.1529	0.2658	0.4866

Table 8: Parameter estimates and standard deviation for the model of Reticulocytes

Predictor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	4.558	44.7	-83.86	4.991	91.09
day	α_1	-0.001053	0.01805	-0.03723	-0.0007841	0.03391
day^2	α_2	-0.0009675	0.0005252	-0.001932	-0.0009968	0.0001756
HTC	β_1	0.06439	44.71	-86.39	-0.3987	88.65
HTW	β_2	0.08213	44.71	-86.46	-0.3846	88.56
HRC	β_3	1.199	44.7	-85.26	0.774	89.7
HRW	β_4	0.4379	44.71	-85.93	-0.001723	88.96
NTC	β_5	-0.8221	0.4564	-1.726	-0.822	0.09323
NTW	β_6	-0.5808	0.4421	-1.439	-0.5801	0.2966
NRC	β_7	-0.389	0.4495	-1.277	-0.3896	0.5046
$HTC \times Day$	β_8	-0.09601	0.1541	-0.4019	-0.09682	0.2112
$HTW \times Day$	β_9	-0.05255	0.1224	-0.2975	-0.05268	0.1937
$HRC \times Day$	β_{10}	-0.3101	0.08914	-0.4863	-0.3107	-0.129
$HRW \times Day$	β_{11}	-0.1905	0.1311	-0.4509	-0.1913	0.0706
$NTC \times Day$	β_{12}	0.03285	0.02106	-0.008884	0.03287	0.07492
$NTW \times Day$	β_{13}	0.008987	0.01988	-0.03092	0.008976	0.04827
$NRC \times Day$	β_{14}	0.004579	0.01996	-0.03439	0.004669	0.04474
$HTC \times Day^2$	β_{15}	0.008562	0.007173	-0.00577	0.008591	0.02292
$HTW \times Day^2$	β_{16}	0.006377	0.005666	-0.005199	0.00638	0.01763
$HRC \times Day^2$	β_{17}	0.01592	0.004092	0.007671	0.01594	0.02404
$HRW \times Day^2$	β_{18}	0.0125	0.006072	0.0003696	0.0125	0.02445
Age	γ	-0.04317	2.98	-5.816	-0.0682	5.862
ρ	ρ	-0.7364	0.165	-0.9363	-0.7708	-0.3416
SD_{b0}	σ_{b0}	0.6595	0.1332	0.4362	0.6451	0.9607
SD_{b1}	σ_{b1}	0.02615	0.009154	0.007642	0.02558	0.04607
SD_{HTC}	σ_{HTC}	0.758	0.2291	0.4282	0.7194	1.315
SD_{HTW}	σ_{HTW}	1.152	0.3126	0.6953	1.101	1.897
SD_{HRC}	σ_{HRC}	1.499	0.3558	0.9384	1.453	2.319
SD_{HRW}	σ_{HRW}	1.069	0.2908	0.6386	1.024	1.767
SD_{NTC}	σ_{NTC}	0.1845	0.08826	0.08345	0.1614	0.419
SD_{NTW}	σ_{NTW}	0.2072	0.1091	0.08017	0.1777	0.4817
SD_{NRC}	σ_{NRC}	0.2699	0.09787	0.1406	0.25	0.5161
SD_{NRW}	σ_{NRW}	0.208	0.07845	0.1104	0.1902	0.4064

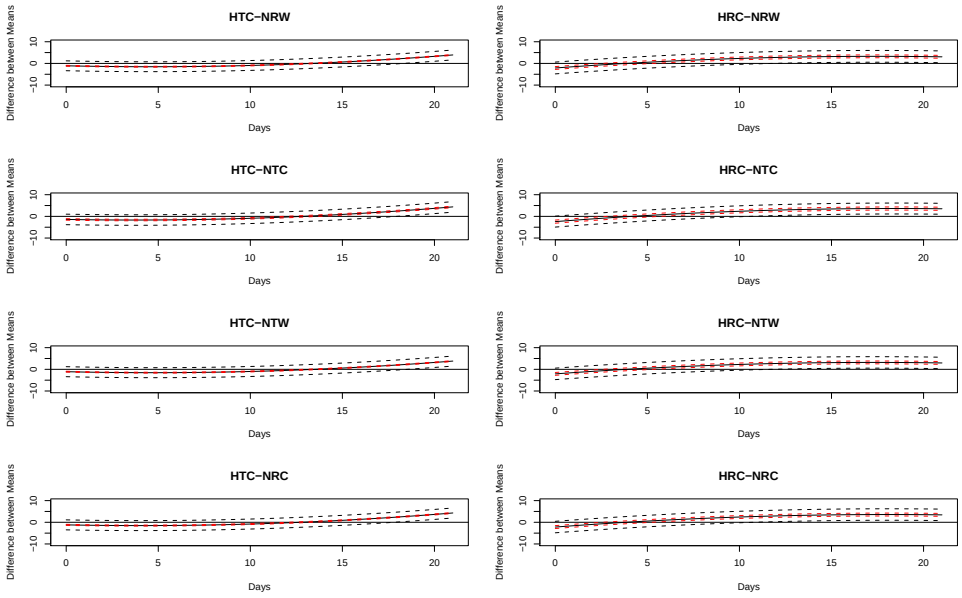
Table 9: Parameter estimates and standard deviation for the model of Mean Corpuscular Volume

Predictor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	44.8	44.75	-43.11	44.8	132.5
Day	α_1	0.006038	0.04271	-0.07862	0.006751	0.08945
Day^2	α_2	0.003433	0.001765	-5.957e-06	0.003407	0.006995
HTC	β_1	12.78	44.75	-74.85	12.87	100.8
HTW	β_2	13.08	44.74	-74.62	13.16	101
HRC	β_3	12.51	44.75	-75.26	12.63	100.4
HRW	β_4	10.76	44.75	-77.19	10.75	98.57
NTC	β_5	-0.1891	0.7973	-1.751	-0.1973	1.429
NTW	β_6	1.159	0.9545	-0.7185	1.165	3.015
NRC	β_7	-0.1092	0.8141	-1.703	-0.1113	1.509
$HTC \times Day$	β_8	-0.6321	0.1985	-1.026	-0.6321	-0.2361
$HTW \times Day$	β_9	-0.9275	0.1109	-1.146	-0.9281	-0.7049
$HRC \times Day$	β_{10}	-0.8803	0.1637	-1.205	-0.8799	-0.5547
$HRW \times Day$	β_{11}	-0.4609	0.3088	-1.078	-0.457	0.1495
$NTC \times Day$	β_{12}	0.05161	0.03261	-0.01348	0.05171	0.1164
$NTW \times Day$	β_{13}	-0.0617	0.05079	-0.1622	-0.0618	0.04049
$NRC \times Day$	β_{14}	0.03167	0.03688	-0.04176	0.03152	0.1042
$HTC \times Day^2$	β_{15}	0.01477	0.009209	-0.003642	0.0148	0.03291
$HTW \times Day^2$	β_{16}	0.0278	0.005068	0.01767	0.0278	0.03783
$HRC \times Day^2$	β_{17}	0.02826	0.007584	0.01332	0.02822	0.04341
$HRW \times Day^2$	β_{18}	0.01302	0.01448	-0.01536	0.01287	0.04171
Age	γ	0.3764	2.983	-5.474	0.3811	6.255
ρ	ρ	-0.4102	0.4579	-0.9676	-0.5363	0.7595
SD_{b0}	σ_{b0}	1.059	0.2229	0.6785	1.039	1.553
SD_{b1}	σ_{b1}	0.02323	0.01568	0.0009451	0.02119	0.05865
SD_{HTC}	σ_{HTC}	1.385	0.3893	0.814	1.322	2.323
SD_{HTW}	σ_{HTW}	2.729	0.6932	1.735	2.609	4.409
SD_{HRC}	σ_{HRC}	1.895	0.426	1.24	1.837	2.889
SD_{HRW}	σ_{HRW}	0.8855	0.2855	0.4718	0.8394	1.563
SD_{NTC}	σ_{NTC}	0.8382	0.2584	0.4856	0.7882	1.476
SD_{NTW}	σ_{NTW}	0.5969	0.1831	0.3482	0.5612	1.052
SD_{NRC}	σ_{NRC}	0.6186	0.2179	0.3284	0.5761	1.174
SD_{NRW}	σ_{NRW}	1.399	0.401	0.8334	1.328	2.368

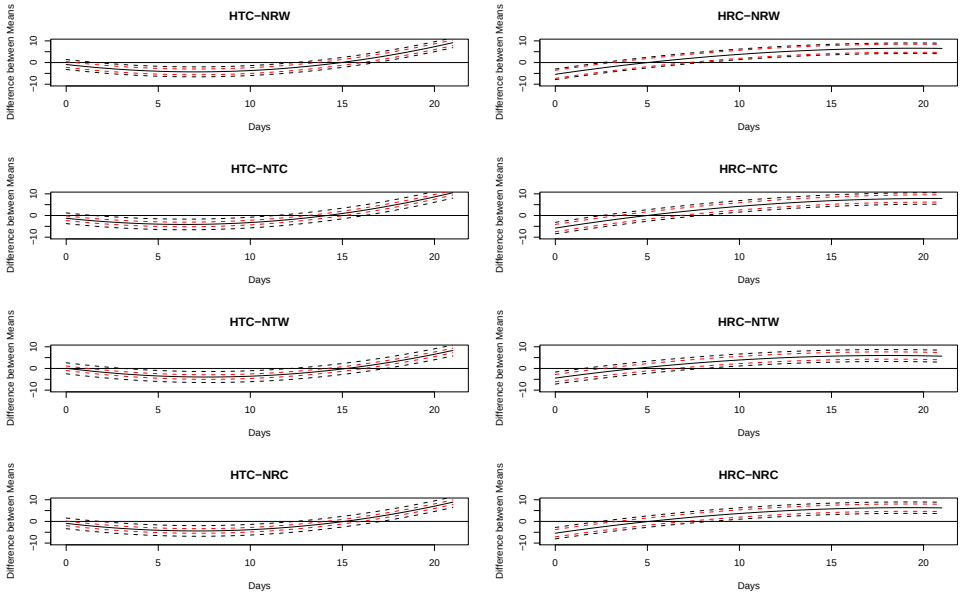
Table 10: Parameter estimates and standard deviation for the model of Mean Corpuscular Haemoglobyn

Predcitor	Parameter	Mean	Sd	2.5%	Median	97.5%
$Intercept$	α	14.71	44.65	-72.17	14.42	102.8
Day	α_1	-0.0161	0.01672	-0.0491	-0.01605	0.01719
Day^2	α_2	-0.0004627	0.0005723	-0.001603	-0.0004703	0.0007115
HTC	β_1	4.538	44.65	-83.47	4.792	91.42
HTW	β_2	4.345	44.65	-83.56	4.65	91.22
HRC	β_3	4.949	44.65	-83.12	5.234	91.77
HRW	β_4	5.226	44.65	-82.86	5.468	92.06
NTC	β_5	-0.0899	0.2836	-0.6474	-0.08979	0.4736
NTW	β_6	-0.1042	0.31	-0.7237	-0.1025	0.5033
NRC	β_7	-0.196	0.3003	-0.7901	-0.1947	0.3997
$HTC \times Day$	β_8	-0.05858	0.03083	-0.1196	-0.05846	0.003633
$HTW \times Day$	β_9	-0.02258	0.0597	-0.1411	-0.02254	0.09862
$HRC \times Day$	β_{10}	-0.08392	0.03993	-0.1644	-0.08382	-0.005299
$HRW \times Day$	β_{11}	-0.006049	0.06309	-0.1328	-0.005352	0.1191
$NTC \times Day$	β_{12}	0.01889	0.01585	-0.01282	0.01898	0.04981
$NTW \times Day$	β_{13}	0.009938	0.01842	-0.02639	0.009828	0.04657
$NRC \times Day$	β_{14}	0.01209	0.01743	-0.02305	0.01221	0.04665
$HTC \times Day^2$	β_{15}	0.00228	0.001291	-0.0003544	0.002281	0.004881
$HTW \times Day^2$	β_{16}	0.0003607	0.002727	-0.005111	0.0003547	0.005807
$HRC \times Day^2$	β_{17}	0.003096	0.001747	-0.0003099	0.00309	0.006593
$HRW \times Day^2$	β_{18}	-0.001437	0.002873	-0.007137	-0.001471	0.004334
Age	γ	0.2242	2.977	-5.652	0.242	6.011
ρ	ρ	-0.6369	0.2457	-0.9146	-0.6907	0.0297
SD_{b0}	σ_{b0}	0.3743	0.08042	0.2156	0.3727	0.537
SD_{b1}	σ_{b1}	0.01802	0.00629	0.001723	0.01876	0.02883
SD_{HTC}	σ_{HTC}	0.3085	0.09412	0.1753	0.2921	0.5395
SD_{HTW}	σ_{HTW}	0.5293	0.1555	0.3078	0.5033	0.9082
SD_{HRC}	σ_{HRC}	0.2338	0.08676	0.1136	0.2178	0.4404
SD_{HRW}	σ_{HRW}	0.5076	0.1375	0.3131	0.4833	0.8423
SD_{NTC}	σ_{NTC}	0.2919	0.1022	0.1513	0.2726	0.5408
SD_{NTW}	σ_{NTW}	0.2614	0.09841	0.1352	0.2405	0.5066
SD_{NRC}	σ_{NRC}	0.1785	0.1023	0.06241	0.1482	0.4293
SD_{NRW}	σ_{NRW}	0.3564	0.1047	0.2059	0.3389	0.6093

Appendix C

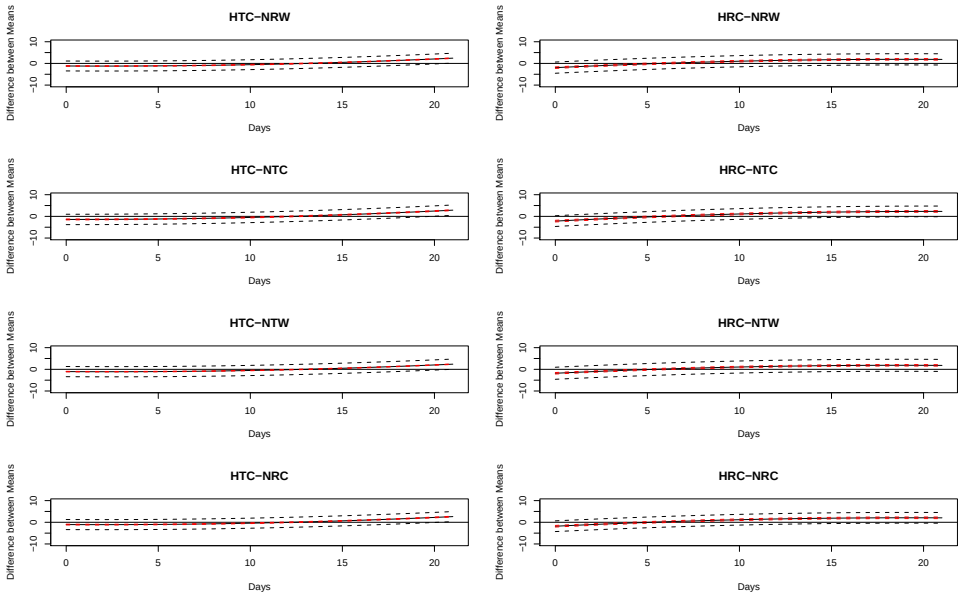


(a) Haemoglobyn

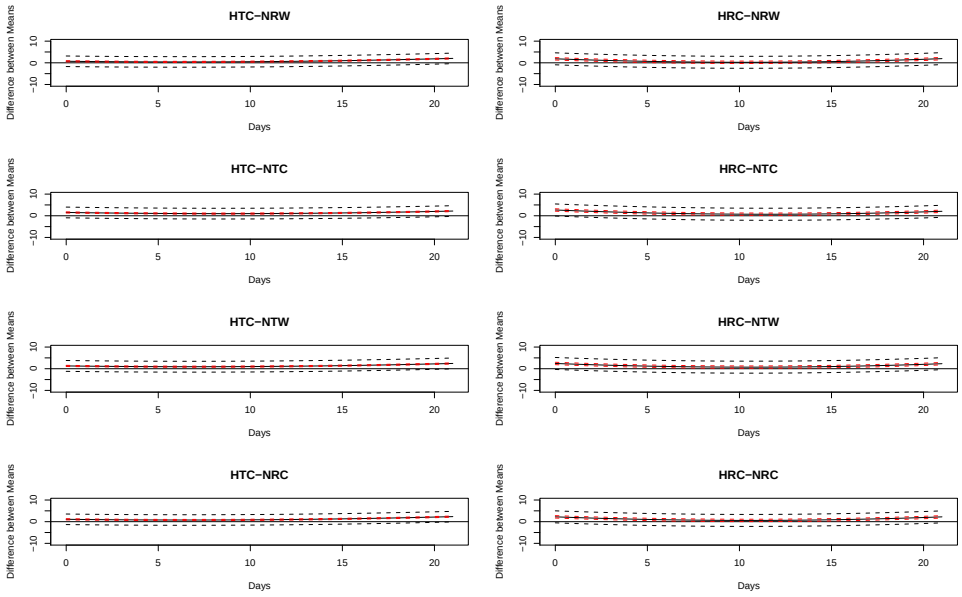


(b) haematocrit

Figure 1: 95% Credible bands for selected differences between treatment means for haemoglobyn and haematocrit. Black dashed lines are upper and lower bounds, and bold line is the difference between treatment means. Red dashed lines are upper and lower bounds for 95 % credible intervals. HTC: Hypoxia training vitamin C, HRC: hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C.

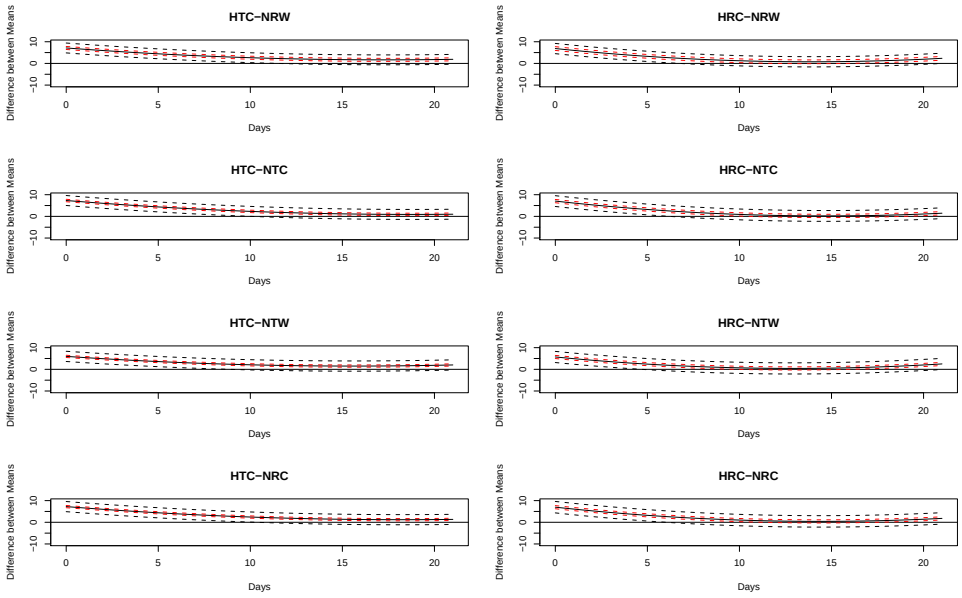


(a) Red Blood Cells

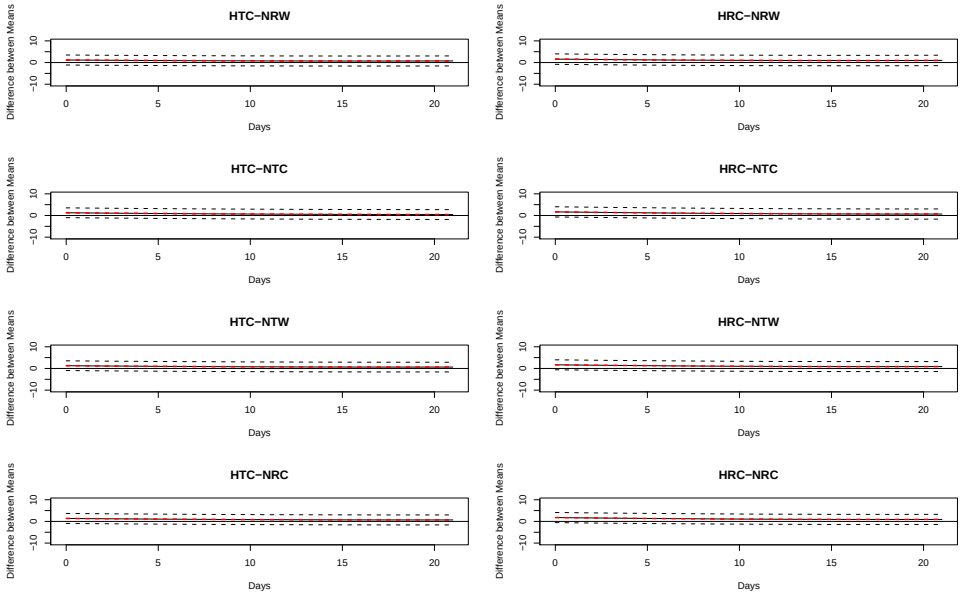


(b) Reticulocytes

Figure 2: 95% Credible bands for selected differences between treatment means for red blood cells and haematocrit. Black dashed lines are upper and lower bounds, and bold line is the difference between treatment means. Red dashed lines are upper and lower bounds for 95 % credible intervals. HTC: Hypoxia training vitamin C, HRC: hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C.



(a) Mean Corpuscular Volume



(b) Mean Corpuscular Haemoglobyn

Figure 3: 95% Credible bands for selected differences between treatment means for mean corpuscular volume and mean corpuscular haemoglobyn. Black dashed lines are upper and lower bounds, and bold line is the difference between treatment means. Red dashed lines are upper and lower bounds for 95 % credible intervals. HTC: Hypoxia training vitamin C, HRC: hypoxia resting vitamin C, HRW: Hypoxia resting water, HTW: Hypoxia training water, NRC: Normoxia resting vitamin C, NRW: Normoxia resting water, NTW: Normoxia training water, NTC: Normoxia training vitamin C.