Bayesian hierarchical nonlinear modelling of intra-abdominal volume during pneumoperitoneum for laparoscopic surgery

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Abstract

Laparoscopy is an operation carried out in the abdomen or pelvis through small incisions with external visual control by a camera. This technique needs the abdomen to be insufflated with carbon dioxide to obtain a working space for surgical instruments’ manipulation. Identifying the critical point at which insufflation should be limited is crucial to maximizing surgical working space and minimizing injurious effects. Bayesian nonlinear growth mixed-effects models are applied to data coming from a repeated measures design. This study allows to assess the relationship between the insufflation pressure and the intra–abdominal volume.

MSC: 62P10, 62F25.

Keywords: Intra-abdominal pressure, logistic growth function, Markov chain Monte Carlo methods, random effects.

1. Introduction

Laparoscopy is an operation carried out in the abdomen or pelvis through small incisions with the help of a camera. It is performed by insufflating CO\textsubscript{2} into the

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abdomen that yields a working space, i.e., pneumoperitoneum, and passing surgical instruments through small incisions using a camera to have external visual control of the procedure (Neugebauer et al., 2010). Laparoscopy has been gaining ground since its inception because it is associated with less morbidity than the traditional method performed through a single, larger skin incision (Pache et al., 2017).

The introduction of CO₂ into the abdomen is performed by medical devices, i.e., laparoscopic insufflators, through small plastic tubes, i.e. trocars, inserted in the patient’s abdominal wall. Laparoscopy technological development has been limited to improvements in camera image quality, whereas little innovation has been made in insufflation devices (Colon Cancer Laparoscopic or Open Resection Study Group, 2009).

The CO₂ insufflation pressure, i.e., intra–abdominal pressure (IAP), is set manually on the insufflator by the surgical team. IAP is measured in millimeters of mercury (mmHg), and the usual figures during laparoscopic surgery range between 12 and 15 mmHg. Although international guidelines recommend working with the lowest IAP value that ensures an adequate working space, the standard practice is still to initially set the IAP value without further adjustments regardless of the amount of generated intra–abdominal volume (IAV) (Neudecker et al., 2002), measured in litres (L). Operating at such high IAP increases perioperative morbidity since it leads to decrease abdominal blood perfusion, greater postoperative pain, peritoneal injury, and increased risk of pulmonary complications.

The abdominal compartment shows an anisotropic behavior during pneumoperitoneum which is explained by its combination of rigid borders, e.g., spine, rib cage, and pelvis, and semirigid borders, e.g., abdominal wall muscles and the diaphragm (Becker et al., 2017). Initially, marginal gains in volume in response to pressure increments are proportional. In other words, the abdominal compliance (C_{abd}) which defines the change in volume determined by a change in pressure, follows an approximately linear relationship (Mulier et al., 2009). According to biomechanics laws, the yield stress point is eventually reached, after which applying additional pressure leads to diminishing gains in volume (Forstemann et al., 2011). Identifying this critical point at which insufflation should be limited is crucial to maximizing surgical working space while minimizing injurious IAP effects.

The abdomen pressure–volume dynamics during pneumoperitoneum has been discussed in previous papers (Diaz-Cambronero et al., 2019, 2020; Mazzinari et al., 2020, 2021). These studies suggest the adequacy of an increasing sigmoidal model for describing the relationship between both variables. The aim of this paper is to estimate such a model to gain knowledge about the relationship between IAP and IAV, especially about the parameters that determine the different
growth stages of the process in accordance with the specific characteristics of the individuals in the target population. The hypothesis is that, in a personalised medicine environment, patient responses to insufflation can be estimated and predicted so that an ideal IAP value could be determined to optimise IAV with the lowest risks of potential negative effects.

The statistical framework of this study are nonlinear growth mixed-effects models, also known as hierarchical nonlinear growth models. They have a long and important scientific tradition for describing biological, medical, and environmental growth phenomena such as pharmacokinetics (Giltinan, 2006), epidemiology (Lindsey, 2001), physiological-response processes (Peek et al., 2002), or forestry (Fang and Bailey, 2001) among others. One of the major appeals of these models is that their parameters contain direct and intuitive information on the process under study. This fact generates a multifaceted knowledge about the phenomena in question of great scientific value (Davidian, 2008).

Data for the study come from a repeated measures design (Lindstrom and Bates, 1990). In our case, the variable of interest IAV is measured for each individual with regard to different IAP values. This design generates two types of data: data from the same individual and data from several individuals. Random effects in these models are essential elements to glue together the different observations of the same individual as they could be considered as a within-individual variation (Laird and Ware, 1982).

The statistical analysis of the problem has been carried out using Bayesian inference. This statistical methodology accounts for uncertainty in terms of probability distributions (Loredo, 1989, 1992) and uses Bayes’ theorem to update all relevant information. Bayesian statistics allows to draw individual’s inferences and population outcomes. This feature of Bayesian models is of utmost importance in the case of growth models because it expresses in a natural probabilistic way all information about the parameters and other relevant features of the growth process through the respective posterior distribution.

The paper is organised as follows. Section 2 presents the data and contains a brief description of them that emphasises the particular features of the repeated-means design through the number of observations per individual and their IAV trajectories according to AIP values. Section 3 introduces and formulates the statistical modelling. Subsection 3.1 discusses the posterior distribution of the inferential process. Subsections 3.2 and 3.3 contain, respectively, some relevant results of clinical interest at specific individual levels and in general terms for different population groups. The paper ends with an overview of the results and some conclusions.
2. Intra-abdominal volume and intra-abdominal pressure data

The data for the current modelling come from a previously published individual patient meta-analysis (Mazzinari et al., 2021) that included experimental information from three previous clinical studies (Mazzinari et al., 2020; Diaz-Cambronero et al., 2019, 2020). All patients in these studies underwent a standardized pneumoperitoneum insufflation at a constant low flow, i.e., 3 L min$^{-1}$, under deep neuromuscular block with a posttetanic count (PTC) between one and five assessed by quantitative monitoring. The insufflation was carried out through a leakproof trocar up to an IAP of 15 mmHg for abdominal wall pre-stretching and then stepwise changes in IAP in the 8 to 15 mmHg pressure range were recorded. In all studies, patients’ legs were placed in padded leg-holder supports with hips flexed before the initial insufflation.

The original databank had information on 204 patients, but 6 patients presented missing information on IAP, IAV, and/or age values. There are very few individuals whose missing observations do not appear to have been generated by non-ignorable mechanisms. For this reason, we decided to eliminate them directly and not engage in a very unhelpful imputation process. The final databank has 198 patients, 118 men and 80 women, and a total of 6985 observations. We have a repeated measures design with a very different number of observations per individual: from individuals with only one observation to individuals with 75. Figure 1 shows the number of repeated measures for the group of men and of women in order of age. It is interesting to note that women have less measurements than men in all ages, but especially when they are young.

The data have a very wide age range. The youngest patient is 23 years old and the oldest is 92, with a mean age of 64.65 years. In the men’s group, the minimum and maximum also are 23 and 92, respectively, and their average is 64.49 years. Women have a minimum age of 34.77 and a maximum of 85.92, and their mean is 64.87 years.

IAP values range between 0 and 16 mmHg, and IAV values between 0.5 and 13 L. Figure 2 shows a spaghetti plot of IAV, in L, for men and women. Men and women show a fairly similar pattern of the IAV with IAP, although a greater range of values is observed in men, especially in large values of IAP. In both groups there are individuals with different behaviour but men behave more homogeneously than women.
3. Logistic growth mixed-effects modelling

Let the nonlinear mixed-effects model for the random variable $Y_{ij}$ that records the IAV value for individual $i$, $i = 1, \ldots, n$ with standardized IAP value $x_{ij}$, $j = 1, \ldots, J_i$, defined in terms of a conditional normal distribution as follows

$$ (Y_{ij} \mid \mu_{ij}, \sigma^2) \sim N(\mu_{ij}, \sigma^2), $$

where the mean $\mu_{ij}$ is the true IAV value of a patient with IAP value $x_{ij}$ and can be expressed in terms of the conditional logistic growth function

$$ (\mu_{ij} \mid a_i, b_i, c_i, x_{ij}) = \frac{a_i}{1 + \exp\{- (b_i + c_i x_{ij})\}}, $$

with parameters $a_i$, $b_i$, and $c_i$ determining the growth of the function, and $\sigma^2$ the
unknown variance associated to the random measurement error of the normal (1).

The logistic growth model for $\mu_{ij}$ has important features which are very valuable to better understand the relationship between IAP and IAV (Davidian, 2008):

- It is an increasing sigmoid function (see Figure 3), or S-curve, whose name comes from its shape and was introduced by the mathematician Pierre-François Verhulst in the 19th century to study the growth of populations in autocatalytic chemical reactions (Cramer, 2004).

- The asymptotic value of $\mu_{ij}$ when IAP goes to infinity is $a_i$.

- The inflection point (IP), where the curve changes from being concave downward to concave upward and therefore it is the point at which the acceleration of the process switches from positive to negative, is $-b_i/c_i$. The value of $\mu_{ij}$ at this point is $a_i/2$.

- The asymptotic deceleration point (ADP), which determines the point from which the deceleration of the function is very slow and it is expected,
therefore, that the increase of the function is not of much practical practical interest, is \( -(\ln(5 - 2\sqrt{6}) + b_i)/c_i \). The value of \( \mu_{ij} \) at this point is \( a_i(3 + \sqrt{6})/6 \).

- The maximum acceleration and deceleration point, \( MAP \) and \( MDP \) respectively, and the subsequent true \( IAV \) value is \((-(\ln(2 + \sqrt{3}) + b_i)/c_i, a_i/(3 - \sqrt{3})) \) and \( (-(\ln(2 - \sqrt{3}) + b_i)/c_i, a_i/(3 + \sqrt{3})) \).

By way of illustration, Figure (3) shows the graph of the logistic growth model \( y = 5/[1 + \exp\{-(10 + x)\}]^{-1} \) and the location on the graph of the special points described above.

![Figure 3. Graphics of the logistic growth function 5/[1 + \exp\{-(10 + x)\}]^{-1}, the subsequent asymptotic value, and its MAP, IP, ADP, and MDP points.](image)

Hierarchical modelling for parameters \( a_i, b_i \) was based on expert information and connected them with covariates age and gender. Parameter \( c_i \) was associated to covariate gender. We discarded its connection to covariate age as a consequence of a previous analysis of variable selection that we will discuss later. Furthermore, \( a_i \) and \( b_i \) also included a random effect specifically associated to each individual that allow to connect all their repeated observations. We have not included any random effect in the modelling of the parameter \( c_i \) because it would generate a random interaction term with the \( IAP \) values that would be difficult to understand and justify. Following this reasoning, our model would be
\[ a_i = \beta_0^{(a)} + u_i^{(a)} + \beta_W^{(a)} I_W(i) + \beta_A^{(a)} \text{Age}_i, \]
\[ b_i = \beta_0^{(b)} + u_i^{(b)} + \beta_W^{(b)} I_W(i) + \beta_A^{(b)} \text{Age}_i, \]
\[ c_i = \beta_0^{(c)} + \beta_W^{(c)} I_W(i), \]

where \( \beta_0 = (\beta_0^{(a)}, \beta_0^{(b)}, \beta_0^{(c)})' \) stands for the common intercept with the men group being the reference group, \( I_W(i) \) is the indicator variable with value 1 if individual \( i \) is a woman and 0 otherwise, \( \beta_W = (\beta_W^{(a)}, \beta_W^{(b)}, \beta_W^{(c)})' \) and \( \beta_A = (\beta_A^{(a)}, \beta_A^{(b)})' \) are the vector of regression coefficients associated with individual \( i \) being a woman and their standardized age, respectively. Random effects \( u_i^{(a)} \) and \( u_i^{(b)}, u_i^{(c)} \), \( i = 1, \ldots, n \), are assumed conditional independent given \( \sigma_a^2 \) and \( \sigma_b^2 \) and normally distributed according to \( f(u_i^{(a)} | \sigma_a^2) = N(0, \sigma_a^2) \) and \( f(u_i^{(b)} | \sigma_b^2) = N(0, \sigma_b^2) \).

The Bayesian model is completed with the elicitation of a prior distribution for the parameters and hyperparameters \( \theta = (\beta_0, \beta_W, \beta_A, \sigma, \sigma_a, \sigma_b)' \) of the model. We assume prior independence between them and select the uniform distribution \( U(0, 10) \) for all standard deviation terms. The elicited marginal prior distribution for \( \beta_0^{(a)} \) and \( \beta_0^{(c)} \) is \( U(0, 20) \) and \( U(0, 10) \), respectively. These uniform distributions are sufficiently large to cover generously the whole range of possible values of both parameters. A normal distribution \( N(0, 10^2) \) is selected for \( \beta_0^{(b)} \) to allow the parameter to move freely between a wide range of positive and negative values.

### 3.1. Posterior distribution

The relevant quantities in the inferential process are the parametric vector \( \theta \) and the set of random effects associated to the individuals in the sample \( u = (u_1, \ldots, u_n)' \), where \( u_i = (u_i^{(a)}, u_i^{(b)}) \). The posterior distribution \( \pi(\theta, u | D) \), where \( D \) represents the observed data, contains all the relevant information of the problem and it is usually the starting point of all relevant inferences. It was approximated by means of Markov Chain Monte Carlo (MCMC) simulation methods through the JAGS software (Plummer, 2003). For each estimated model, we ran three parallel chains with 1,000,000 iterations and a burn-in of 1,000,000. Chains were also thinned by storing every 1,000th iteration to reduce autocorrelation in the sample. Convergence to the joint posterior distribution was guaranteed by visualising every autocorrelation function plot by means of \texttt{mcmcplot} package for the R software and assuring an effective number of independent simulation draws greater than 100. For the sake of reproducibil-
ity we have generated a fictitious databank, which together with the R code for the analyses is available as supplementary material here https://github.com/gcalvobayarri/intra_abdominal_volume_model.git.

Table 1 summarizes $\pi(\theta, u | D)$. The posterior mean of $\beta_0^{(a)}$ and $\beta_0^{(b)}$ provides an approximate overall assessment of the baseline values of $a_i$ and $b_i$ for male patients. In the case of the asymptotic value $a_i$, it decreases by about 0.344 in the female group (although this estimation has a lot of uncertainty), and shows a slight positive trend with age. Differences between individuals are relevant as it can be seen from the estimation of the standard deviation of the random effect in $a_i$, 1.743. The parameter $b_i$ has an approximate basal value of 0.922 in the men group, which decreases by -0.24 units in the women group. Age also has a positive estimation and the random effect associated to individuals are also important for $b_i$, especially because this term appears on an exponential scale and negative sign in the quotient of the growth curve. Finally, the posterior mean for the $c_i$ term is about 2.184 in the men group and decreases in 0.245 units in the group of women. The posterior mean of the standard deviation associated to the measurement error is not very large but it does have a very high accuracy. The fact that the IP, ADP, MAP and MDP of individual $i$ depends on $b_i$ and $c_i$ proportionally to $-b_i/c_i$ and that the estimated coefficients associated to gender are negative for both $b_i$ and $c_i$ implies that IP’s, ADP’s, MAP’s and MDP’s for women will be slightly higher than the subsequent for men. The relationship of the IP, ADP, MAP and MDP with age is negative but barely important.

The posterior distribution is the starting point for the analysis of the different outcomes of interest in the study. In the following, we will present different results that may be useful to better understand the relationship between IAV and IAP at both the individual and population level and thus be able to answer the scientific questions raised by the study. But first we would like to make a brief comment on the variable selection process discussed above for parameter $c_i$ of the growth model. In this context, we considered different modelling approaches for $c_i$ with regard to covariate gender. The Deviance Information Criterion (Spiegelhalter et al., 2002) was used for model comparison and according to this criterion the best model was the one with only the gender covariate and a common population term in parameter $c_i$ as stated before.

3.2. Posterior individual outcomes

The basic inferential process allows the Bayesian methodology to obtain information both individually and in terms of the target population.

In the following we focus on ADP. The true ADP value for individual $i$, ADP$_i$, depends on $b_i$ and $c_i$, which in turn depend on $(\theta, u_i)$. Consequently, we
Table 1. Posterior summaries (mean, standard deviation and 95% credible interval) for the parameters and hyperparameters of the logistic growth model with covariates gender and standardized age.

| Parameters | Logistic growth model |            |            |
|------------|-----------------------|------------|------------|
|            | mean      | sd         | IC         |
| $\beta_0^{(a)}$ | 5.597    | 0.392     | (4.861, 6.376) |
| $\beta_W^{(a)}$ | -0.344   | 0.264     | (-0.875, 0.153) |
| $\beta_{Age}^{(a)}$ | 0.110    | 0.122     | (-0.123, 0.347) |
| $\sigma_a$ | 1.743     | 0.095     | (1.571, 1.938) |
| $\beta_0^{(b)}$ | 0.922    | 0.166     | (0.601, 1.238) |
| $\beta_W^{(b)}$ | -0.246   | 0.112     | (-0.464, -0.028) |
| $\beta_{Age}^{(b)}$ | 0.120    | 0.054     | (0.017, 0.224) |
| $\sigma_b$ | 0.733     | 0.041     | (0.658, 0.818) |
| $\beta_0^{(c)}$ | 2.184    | 0.040     | (2.108, 2.262) |
| $\beta_W^{(c)}$ | -0.245   | 0.029     | (-0.300, -0.188) |
| $\sigma$ | 0.361     | 0.003     | (0.355, 0.367) |

can compute the posterior distribution of the true $ADP_i$ of each individual $i$ in the sample from the subsequent posterior distribution $\pi(\theta, u_i | \mathcal{D})$. Figure 4 shows the posterior mean and a 95% credible interval for that quantity of the individuals in the sample ranked by age. The first thing that is striking in both graphs is the great difference in both the men and women groups in the range of credibility intervals, which is mainly explained by the differences in the number of repeated observations for each of them. This situation is more evident in the women’s group due to the low number of repeated measures per individual with regard the subsequent number in the men’s group.

The prediction of observations for new individuals in the target population is an important issue that Bayesian statistics approaches in a natural way. The posterior predictive distribution of the random variable $Y_{n+1,j}$ that records the $IAV$ value for a new individual, $n + 1$, of the population with regard to their $x_{n+1,j}$ values depends on the conditional model in (1) and the posterior distribution $\pi(\theta, u_{n+1} | \mathcal{D})$, where $u_{n+1}$ are the random effects associated to that individual $n + 1$, and is computed as follows.
Figure 4. Posterior mean and 95% credible interval of the ADP value of the men (top panel) and the women (bottom panel) in the sample. Patients are ordered in the x-axis according to their age from youngest to oldest.

\[(Y_{n+1,j} \mid x_{n+1,j}, \mathcal{D}) \sim \int (Y_{n+1,j} \mid \theta, u_{n+1}) \pi(\theta, u_{n+1} \mid \mathcal{D}) \, d(\theta, u_{n+1}), \tag{6}\]

where the posterior \(\pi(\theta, u_{n+1} \mid \mathcal{D})\) factorizes in terms of the marginal posterior distribution \(\pi(\theta \mid \mathcal{D})\) and the conditional distributions for the random effects \(f(u_{n+1}^a \mid \sigma_a^2) = N(0, \sigma_a^2)\) and \(f(u_{n+1}^b \mid \sigma_b^2) = N(0, \sigma_b^2)\). Figure 5 shows the posterior predictive mean and a 95% predictive interval for the \(IAV\) value of a new individual of the target population with respect to their \(IAP\) and in relation to their gender. Both groups behave very similarly. The stabilisation of the values of \(IAV\) in both groups can be clearly seen, as well as the variability associated with the predictive processes, which is always greater in comparison with the estimation processes themselves.
3.3. Posterior population outcomes

Random effects connect the different repeated measures of the same individual in the statistical model and allow for the computation of individual-specific outcomes. We would also like to be able to have not only that individual information, but also outcomes that can provide general information about the target population. This aim implies to work with the marginal formulation of the model in (1) and (2) which we would obtain by integrating out the random effects as follows

\[
(Y_{ij} \mid \theta, x_{ij}) \sim \int N(\mu_{ij}, \sigma^2) f(u \mid \theta) \, du.
\]

This marginal formulation only depends on the parameter and hyperparameters of the model \( \theta \) and is the basis for the computation of any feature of this marginal model. For simplicity, we only focus in the paper on the true asymptotic
IAV value and the true asymptotic deceleration point ADP and its subsequent value for IAV.

Figure 6. Posterior distribution of the asymptotic IAV for men (on the left) and women (on the right).

Figure 6 shows the posterior distribution of the asymptotic IAV for men and women aged 64.56 years (the mean of the sample). There is not much difference between the two distributions. An estimation of the asymptotic IAV in the group of men is 5.60 L, while in the group of women it is 5.25 L. Figure 7 shows the joint posterior distribution, in terms of contour lines, of the ADP pressure point and the subsequent volume value for men and women aged 64.56 years (the sample mean) as well as the marginal distributions of both quantities. Posterior mean for the ADP’s pressure and volume is 10.06 mmHg and 5.05 L in men aged 64.56, and 8.86 mmHg and 4.12 L in the group of women with the same age, respectively.
Conclusions

Precision medicine tenets are that different interventions have distinct effects in different people and that this variability can, at least in part, be characterized and predicted (Senn, 2016). In this study we have tried to lay the foundation for
the mathematical modeling of the abdomen behavior during pneumoperitoneum insufflation. We have also parameterized such model to achieve predictive capability based on a few simple baseline characteristics. This is the first step in a precision medicine approach to pneumoperitoneum insufflation for laparoscopic surgery. This process can be potentially scaled up and recursively performed throughout the duration of the surgical intervention to ensure that even if conditions change, we could be able to provide an optimal surgical field to the surgeon while exposing the patient the lowest possible pressure.

With this procedure, we would like to achieve an optimal surgical workspace while minimizing the pressure administered to the patient. In other words, each subject would receive a titrated pressure according to his characteristics. Also, the ability to predict where the marginal gain in volume diminishes by deriving critical points on the parameterized curve have an especially interesting clinical potential.

Bayesian inference can provide a suitable inferential framework in this context. First of all, Bayesian hierarchical models are useful to elicit and formulate the different sources of variation and uncertainty of the problem and incorporate suitable terms into the model to account for them. In this particular case, the model includes non-linear effects through a logistic growth function. As model fitting relies on MCMC methods, inference about particular elements of interest in the model becomes feasible. For example, the logistic growth model has a known parametric form from which some crucial critical points can be derived analytically but inference on these points is far from straightforward. However, the output produced by MCMC during model fitting can be exploited to compute the posterior marginals of these particular points as well as those of the other model parameters. This provides extra information that can be used during the laparoscopic surgery. Inference about these critical points under other inferential frameworks would not be so straightforward.

The most important critical point in our study is $ADP$, as this controls how much air is insufflated during surgery. From a clinical point of view, when operating on new patients, $ADP$’s predictive distribution can help physicians provide adequate insufflation during laparoscopic surgery. The study presented in this paper illustrates a preliminary analysis in which 198 patients have been enrolled. In the future, we aim to conduct a larger trial so that a wider range of patients is represented. Furthermore, other covariates will be recorded and included into the model to reduce the uncertainty about the estimates and predictions, and increase the accuracy of insufflation.
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