Multivariate Conditional Transformation Models. Application to Thyroid-Related Hormones

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Abstract. Multivariate Conditional Transformation Models (MCTMs) were recently proposed as a new multivariate regression technique. These models characterize jointly the covariates effects on the marginal distributions of the responses and their correlations without requiring parametric assumptions. Flexibility, in both the responses and covariates effects are achieved using Bernstein basis polynomials. In this paper we compare MCTMs estimations with the well established Copula Generalized Additive Models (CGAMLSS). MCTMs conditional correlation estimations outperform the CGAMLSS ones, showing lower estimation error, and variability. Finally, MCTMs were applied to the joint modelling of three thyroid hormones concentrations – Thyroid Stimulating Hormone (TSH), triiodothyronine (T3), and thyroxine (T4) – conditionally on age. Our results show how the marginal distribution and correlations of the hormones concentrations are influenced by the age of the patients.

Keywords: Multivariate regression · Bernstein basis · Most likely transformations · Thyroid hormones

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1 Introduction

The thyroid gland is a small gland located in front of the neck, that performs a vitally important function: the control of the metabolism. This is fulfilled by taking the iodine found in many foods and converting it into two thyroid hormones: triiodothyronine (T3), and thyroxine (T4). The normal thyroid gland produces about 20% T3, and about 80% T4 and every cell in the body depends upon thyroid hormones for regulation of their metabolism. Only a small fraction of the thyroid hormones is free to enter tissues and has a biologic effect.

The thyroid gland is under the control of the pituitary gland. This small gland located at the base of the brain, produces Thyroid Stimulating Hormone (TSH) when the T3 and T4 levels drop too low, in order to stimulate the thyroid to produce more hormones (see Fig. 1).

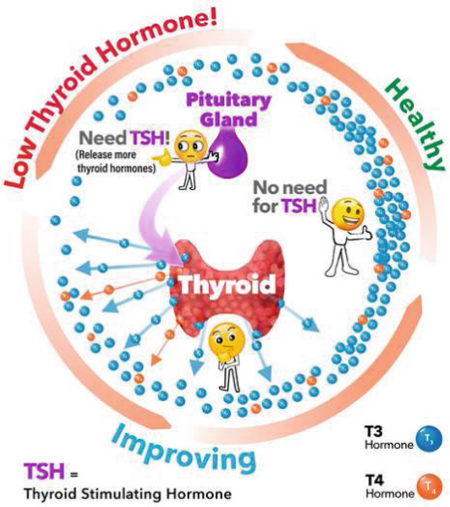


Fig. 1. Diagram of the functioning of thyroid hormones (Source: [13]).

But this mechanism does not always work well, and when that happens, it can lead to profound adverse effects if undiagnosed or untreated. Thyroid dysfunction is a common disease. For instance, the estimated prevalence of hyperthyroidism ranges from 0.2% to 1.3% in parts of the world with enough iodine [12], being larger in those places with a lack of iodine.

Primary thyroid failure brings with it a number of different symptoms, raging from fatigue, sensitivity to cold or poor memory and concentration, to dyspnea, weight gain or even depression. As this gland is in charge of the regularization of the metabolism, its malfunction is harmful to the whole body.

The relationship between TSH and T4 was broadly studied since it seems that this tandem has the greatest diagnostic value for primary thyroid failure [9].

Many studies suggested an inverse, linear relationship between log-TSH and T4, being this taken as a generally accepted principle of thyroid physiology thanks to Spencer et al. (1990) [11]. It was not until 2010 that studies began to emerge refuting the linearity of the relationship [4,5].

It is obvious that the simultaneous study of the thyroid-related hormone may improve the diagnosis of primary thyroid failure. In addition, it is also possible that the relationship between these hormones varies with age and should be included as a covariate. To this aim, Multivariate Conditional Transformation Models (`MCTM`, [8]) were considered in this paper. These models characterize the covariates effects not only on the correlations (relationship) between the outcomes, but also on the Cumulative Distribution Functions (CDF) of each response. It is also possible to obtain percentile curves from these models for each biomarker, facilitating interpretability.

The remainder of the paper is structured as follows: in Sect. 2, the structure of `MCTM` is briefly explained; a simulation study is described in Sect. 3, comparing `MCTM` performance in the bivariate case with conditional Copula Generalized Additive Models, for Location, Scale, and Shape (`CGAMLSS`, [10]); Sect. 4 presents the results of the clinical study; and, finally, the paper ends with some conclusions (Sect. 5).

2 Multivariate Conditional Transformation Models

Multivariate Transformation Models were developed for a J-dimensional, absolutely continuous response vector $\mathbf{Y} = (Y_1, \ldots, Y_J)^\top \in \mathbb{R}^J$. In these models, an unknown, bijective, strictly monotonically increasing transformation function $h : \mathbb{R}^J \to \mathbb{R}^J$ maps the outcome $\mathbf{Y}$ to a set of J independent and identically distributed, absolutely continuous random variables $Z_j \sim \mathbb{P}_Z, j \in \{1, \ldots, J\}$, where $\mathbb{P}_Z$ is a pre-defined distribution (usually, $Z_j \sim \mathrm{N}(0, 1)$). That is:

$$h(\mathbf{Y}) = (h_1(\mathbf{Y}), \ldots, h_J(\mathbf{Y}))^\top = (Z_1, \ldots, Z_J)^\top = \mathbf{Z} \in \mathbb{R}^J. \tag{1}$$

`MCTM` are obtained by extending the transformation function (1) to include a vector of potential covariates $\mathbf{X}$, resulting in:

$$h(\boldsymbol{y}|\boldsymbol{x}) = (h_1(\boldsymbol{y}|\boldsymbol{x}), \ldots, h_J(\boldsymbol{y}|\boldsymbol{x}))^\top. \tag{2}$$

A triangular structure is imposed on the transformation function h in order to simplify calculations, without imposing any limitation on the estimation of the responses. This means that the jth component of the transformation function depends only on the first j elements of $\boldsymbol{y}$. Therefore, for each $j \in \{1, \ldots, J\}$, the components of (2) can be written as:

$$h_j(\boldsymbol{y}|\boldsymbol{x}) = h_j((y_1, \ldots, y_J)|\boldsymbol{x}) = h_j((y_1, \ldots, y_j)|\boldsymbol{x}). \tag{3}$$

Finally, the h_j transformation functions in (3) are set to be linear combinations of marginal transformation functions $\tilde{h}_j : \mathbb{R} \to \mathbb{R}$:

$$h_j(\boldsymbol{y}|\boldsymbol{x}) = \sum_{j=1}^{j-1} \lambda_{jj}(\boldsymbol{x}) \tilde{h}_j(y_j|\boldsymbol{x}) + \tilde{h}_j(y_j|\boldsymbol{x}), \tag{4}$$

where $\lambda_{jj}(\boldsymbol{x})$ and $\tilde{h}_j(y_j|\boldsymbol{x})$ are expressed in terms of basis function expansions. Thus:

$$\tilde{h}_j(y_j|\boldsymbol{x}) = \boldsymbol{a}_j(y_j)^\top \boldsymbol{\vartheta}_{j,1} - \boldsymbol{b}(\boldsymbol{x})^\top \boldsymbol{\vartheta}_{j,2}, \tag{5}$$

and:

$$\lambda_{jj}(\boldsymbol{x}) = \boldsymbol{x}^\top \boldsymbol{\gamma}_{jj}, \quad 1 \leq \jmath < j \leq J. \tag{6}$$

Here, $\boldsymbol{a}_j$ and $\boldsymbol{b}$ are polynomial Bernstein basis functions for the response and the covariates respectively, and $(\boldsymbol{\vartheta}_{j,1}, \boldsymbol{\vartheta}_{j,2}, \boldsymbol{\gamma}_{jj})$ are the parametric coefficients of the model. Their estimation and inference are based on the model log-likelihood. In Fig. 2, a representation of the Bernstein basis of four different orders is shown.

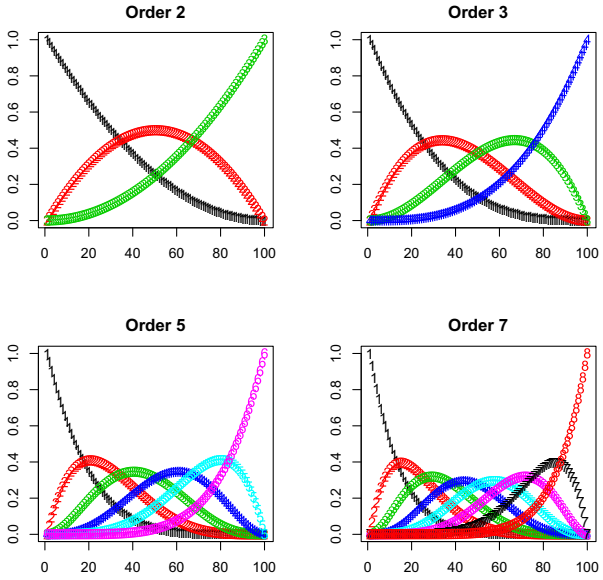


Fig. 2. Representation of Bernstein basis of order 2, 3, 5, and 7.

Summing up the model's specifications, the `MCTM` are characterised by a set of marginal conditional transformations $\tilde{h}_j(y_j|\boldsymbol{x})$, $j \in \{1, \ldots, J\}$ (computed as in (5)), each of which applying to only one component of $\mathbf{Y}$ and the covariates $(\boldsymbol{X})$, and by a lower triangular $(J \times J)$ matrix of transformation coefficients $\boldsymbol{\Lambda}(\boldsymbol{x})$:

$$\boldsymbol{\Lambda}(\boldsymbol{x}) = \begin{pmatrix} 1 & & & 0 \\ \lambda_{21}(\boldsymbol{x}) & 1 & & \\ \lambda_{31}(\boldsymbol{x}) & \lambda_{32}(\boldsymbol{x}) & 1 & \\ \vdots & \vdots & & \ddots \\ \lambda_{J1}(\boldsymbol{x}) & \lambda_{J2}(\boldsymbol{x}) & \ldots & \lambda_{J,J-1}(\boldsymbol{x}) \; 1 \end{pmatrix},$$

with $\lambda_{jj}(\boldsymbol{x})$, $1 \leq \jmath < j \leq J$, defined as in (6). Under the standard normal reference distribution $\mathbb{P}_Z = \mathrm{N}(0,1)$, the coefficients of $\boldsymbol{\Lambda}(\boldsymbol{x})$ characterise the dependence structure of the responses. This is so because $\tilde{\boldsymbol{Z}}(\boldsymbol{x}) = (\tilde{Z}_1(\boldsymbol{x}), \ldots, \tilde{Z}_J(\boldsymbol{x}))^\top$, defined by the random variables $\tilde{Z}_j(\boldsymbol{x}) = \tilde{h}_j(\mathrm{Y}_j \,|\boldsymbol{x})$, follows a multivariate Gaussian distribution $\tilde{\boldsymbol{Z}}(\boldsymbol{x}) \sim \mathrm{N}(\mathbf{0}_J, \boldsymbol{\Sigma}(\boldsymbol{x}))$, with $\boldsymbol{\Sigma}(\boldsymbol{x}) = \boldsymbol{\Lambda}(\boldsymbol{x})^{-1}(\boldsymbol{\Lambda}(\boldsymbol{x})^{-1})^\top$. Inference on the responses correlations is done by using parametric bootstrap (see [8] for more details).

In `MCTM`, the conditional Cumulative Distribution Function (CDF) for each outcome, $\mathrm{F}_\mathrm{Y}(\mathrm{Y}_j \,|\boldsymbol{x})$, is given by:

$$\mathbb{P}(\mathrm{Y}_j \leq y_j | \mathbf{X} = \boldsymbol{x}) = \Phi_{0,\sigma_j^2}\left(\tilde{h}_j(y_j|\boldsymbol{x})\right) = \mathrm{F}_Z\left(\boldsymbol{a}_j(y_j)^\top \boldsymbol{\vartheta}_{j,1} - \boldsymbol{b}_j(\boldsymbol{x})^\top \boldsymbol{\vartheta}_{j,2}\right).$$

3 Simulation Study for the Bivariate Case

In Sect. 5 of their paper, Klein et al. (2019) [8] evaluated the performance of `MCTM` with a simulation of a bivariate response depending on one covariate, comparing the results of `MCTM` models with two other approaches: Bayesian structured additive distributional regression models, and vector generalised additive models (`VGAM`). In this Section, we are going to replicate that simulation study, considering now as a competitor the conditional Copula Generalized Additive Models, for Location, Scale, and Shape (`CGAMLSS`, [10]).

`CGAMLSS` are bivariate copula models with parametric marginal distributions, one-parameter copulas, and semi-parametric specification for the predictors of all parameters of both the marginal and the copula jointly, using a penalised likelihood framework. Unlike `MCTM`, this approach is only limited to the bivariate case for continuous responses. Even so, we do not see that this is a good enough reason not to compare them when we have two possibly related responses.

3.1 Simulation Design

In the simulation set-up, $\mathrm{R} = 100$ data sets of size $\mathrm{n} = 1000$ were simulated and one single covariate $x \sim \mathrm{U}[-0.9, 0.9]$ was considered. The two continuous outcomes were considered following a Dagum distribution. The bivariate response dependence structure depends on x, being $\lambda(x) = x^2$ (to see all of the details, go to [8], Subsect. 5.1). With this construction, the first margin is independent of the covariate x, but the scale parameter of the second margin is not (not so the shape parameters a and p, which remain constant).

For the `MCTM`, we applied Bernstein polynomials of order 8 and 3 in the responses and the covariate respectively.

For the `CGAMLSS`, we used the true specification of the model, i.e. a Gaussian Copula and Dagum marginals, with the correlation parameter and the b_2 parameter of the Dagum distribution for y_2 dependent on x, while all of the parameters of the first marginal, as well as the shape parameters a_2 and p_2 of the second one did not depend on any covariate. For this purpose, both the predictor for b_2 and the correlation parameter ρ of the copula were specified using cubic B-splines

with 20 inner knots, as it was done for the other approaches compared in the original paper. Likewise, the other parameters of the model were estimated as constants.

3.2 Evaluation of the Performance

The performance of the methods was evaluated by estimating the lower element of $\boldsymbol{\Lambda}^{(r)}$, $\hat{\lambda}^{(r)}(x)$, from every data replicate $r \in \{1, \ldots, R\}$, on a grid of length G = 100 within the range of x, and comparing it to the real one, $\lambda(x)$. On the one hand, we considered the estimated curves as they were; on the other hand, we computed the root mean squared error $\mathrm{RMSE}\left(\lambda, \hat{\lambda}^{(r)}\right) = \sqrt{\frac{1}{G}\sum_{g=1}^{G}\left(\lambda(x_g) - \hat{\lambda}(x_g)\right)^2}$ and the standard deviation $\mathrm{SD}\left(\hat{\lambda}^{(r)}\right)$ of each sample as a numeric measure of discordance.

3.3 Results of the Simulation Study

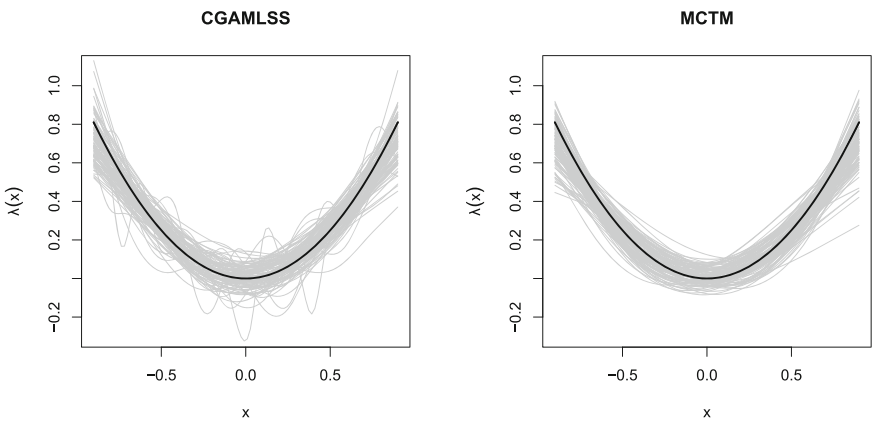


Fig. 3. Function estimates $\hat{\lambda}(x)$ for the effect $\lambda(x) = x^2$ on the correlation parameter for `CGAMLSS` (left) and `MCTM` (right). The black line represents the true function and the grey lines are the estimations of the R = 100 simulation samples.

Figure 3 shows the estimations for $\lambda(x) = x^2$ of the 100 simulated data sets for `CGAMLSS` (left panel) and `MCTM` (right panel). Even though both models seemed to capture the general form properly, `MCTM` led to better smoothed curves. Although `CGAMLSS` was fitted using the actual model specification, in terms of RMSE and SD both approaches were very similar (Fig. 4). This is highly remarkable because `MCTM` was fitted without specifying parametric marginal distributions, a requirement that is restrictive, and an obstacle in practice. Besides this, we have found a big difference in the execution times, since, on average, the adjustment of `MCTM`

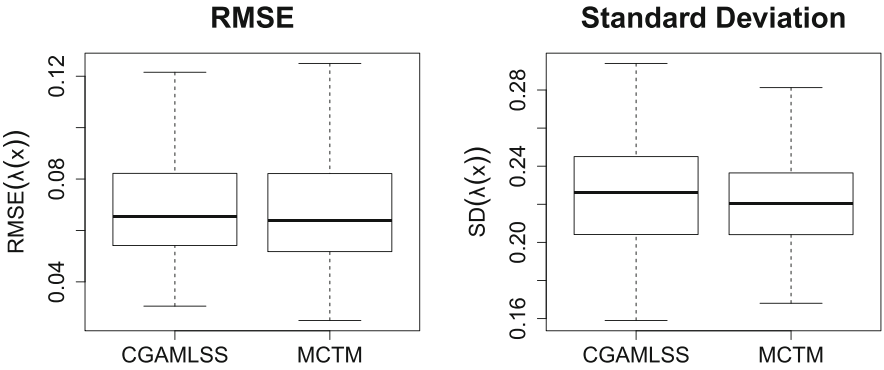


Fig. 4. Left: RMSE $\left(\lambda, \hat{\lambda}^{(r)}\right)$ for `CGAMLSS` and `MCTM`. Right: SD $\left(\lambda, \hat{\lambda}^{(r)}\right)$ for `CGAMLSS` and `MCTM`.

was less than a second (0.480 s), while a `CGAMLSS` model took almost 5 s (4.807 s). Therefore, a `MCTM` approach seemed to be more advisable than a `CGAMLSS` approach.

4 Joint Modelling for Thyroid-Related Hormones

As we stated in Sect. 1, a good control of the activity of the thyroid gland is vital for the overall functioning of our bodies. In order to do so in the best way, it is really important to know the relationship between the hormones involved (TSH, T3 and T4)as thoroughly as possible, adjusting for age. In this Section, we used the statistical methodology of `MCTM` for that purpose.

The data we have available comes from A-Estrada Glycation and Inflammation Study (AEGIS), which is a cross-sectional population-based study being performed in the municipality of A Estrada (NW, Spain). Its aim is to investigate the association between glycation, inflammation, lifestyles, and their association with common diseases and to study discordances between markers for glycaemia. In this database, we have a total of 1516 subjects who agreed to participate in the study, and the data collection and recruiting phase were completed in March 2015. After excluding extreme values and the treated ones due to high variability of the values, a total of 1282 healthy subjects remains.

We studied the relationship between TSH (mIU/L), free T3 (pmol/L), and free T4 (ng/dL). We considered the logarithm of the TSH (log-TSH) because of previous studies [4,5,11]. In Fig. 5, the two-by-two scatter plots of the variables are shown.

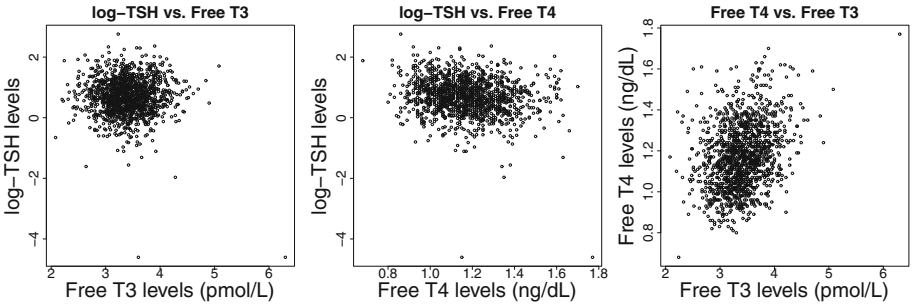


Fig. 5. Two-by-two scatter plot of the thyroid-related hormones. Left: log-TSH vs. Free T3. Centre: log-TSH vs. Free T4. Right: Free T4 vs. Free T3.

4.1 Trivariate Conditional Transformation Models for Log-TSH, Free T3, and Free T4 Hormones

We applied `MCTM` to study the relationship between log-TSH, free T3, and free T4, adjusting for the age of the patient to take into account a possible variation of these hormones and their relationship with age.

Model Specification. Based on a $\mathbb{P}_Z = \mathrm{N}(0, 1)$ distribution, our marginal conditional distribution is parametrised as:

$$\tilde{h}_j(y_j|\text{Age}) = \boldsymbol{a}_j(y_j)^\top \boldsymbol{\vartheta}_{j,1} - \boldsymbol{b}(\text{Age})\boldsymbol{\vartheta}_{j,2},\ j \in \{\text{log-TSH, Free T3, Free T4}\}, \quad (7)$$

where basis functions $\boldsymbol{a}$ are Bernstein polynomials of order eight and $\boldsymbol{b}$ is a Bernstein polynomial of order three. The coefficients of $\boldsymbol{\Lambda}$ were parametrised as:

$$\lambda_{jj}(\text{Age}) = \boldsymbol{b}(\text{Age})\boldsymbol{\gamma}_{jj}, \quad \jmath < j \in \{\text{log-TSH, Free T3, Free T4}\}, \quad (8)$$

Results for Marginal Distributions. The estimated marginal conditional CDFs $F_j(y_j|\text{age})$, and densities $f_j(y_j|\text{age})$, are shown in Fig. 6. The different colours represent the ages of the individuals. We can see that the shapes differ for the three hormones, and that hormone levels decrease as age increases for log-TSH and Free T3, specially for the latter. For Free T4, we can see that higher values are obtained in middle-aged individuals. Another way of seeing this is as depicted in Fig. 7, with the scatter plot of the hormones as a function of age, and the percentile lines shown in red. Here it can be clearly seen that, although log-TSH levels appear to decrease with age, this change is very small, and the log-TSH level be considered invariant with respect to age.

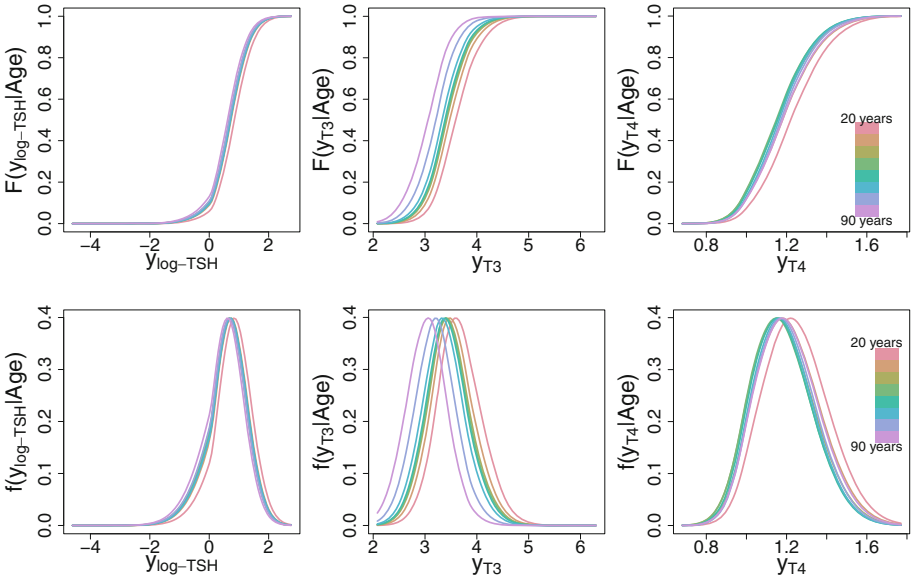


Fig. 6. Estimated marginal conditional CDFs $F_j(y_j|\text{age})$, and conditional densitiy functions $f_j(y_j|\text{age})$, for $j =$ log-TSH (left), $j =$ Free T3 (centre), and $j =$ Free T4 (right), from age = 20 (brown) to age = 90 (purple). (Color figure online)

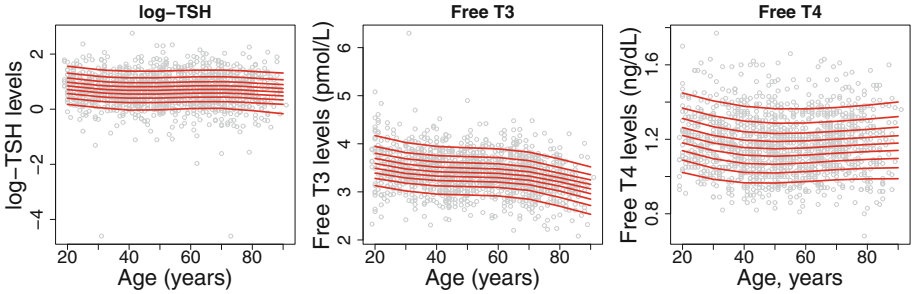


Fig. 7. Scatter plot of thyroid-related hormones vs. age. In red, percentile curves are shown. Left: log-TSH levels. Centre: Free T3 levels. Right: Free T4 levels. (Color figure online)

Results for Dependence Structure. In Fig. 8 it is shown that the two-by-two conditional Spearman's rho $\rho^S(\text{Age})$ for the three hormones, is statistically significant in all three cases. The grey area represents the confidence interval estimates at 95% from 1000 parametrically drawn bootstrap as explained in Subsect. 3.4 in [8]. We can see that the relationship between log-TSH and Free T3 is negative, and statistically significant for individuals between 30 and 50 years old. Correlation between log-TSH and Free T4 is negative (as expected). Finally, correlation between Free T3 and Free T4 is positive and decreases with age.

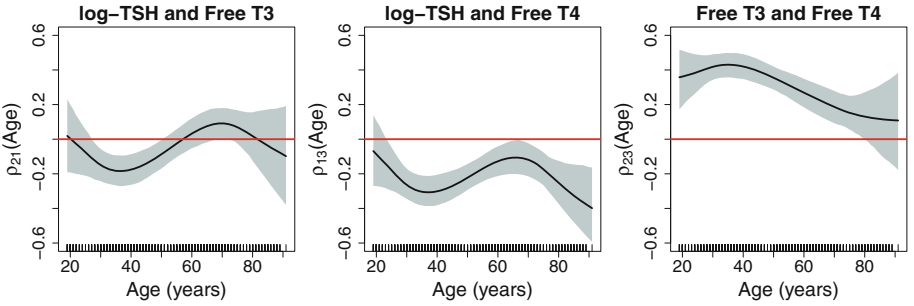


Fig. 8. Two-by-two conditional Spearman's rho $\rho^S(\text{age})$ for the thyroid-related hormones (left: log-TSH and Free T3; centre: log-TSH and Free T4; right: Free T3 and Free T4). Grey area represents the 95% bootstrap confidence interval, while black line represents the bootstrapped point estimate. Red line indicates the 0. (Color figure online)

5 Conclusions

In this work we demonstrate the usefulness of MCTMs in the biomedical setting. MCTMs allow for a joint estimation of the covariates effects on the distribution of each response, and on their correlations. MCTMs performance was evaluated in comparison with the frequentist conditional copula regression models. Finally, MCTMs allowed us to model jointly, for the first time, the age effect on the concentrations of the three thyroid hormones, offering a better understanding of these endocrinological measurements.

Thyroid dysfunction diagnosis have been the object of research in several works. However, given the state of art of regression analysis, these studies have been conducted considering thyroid hormone concentrations as mutually independent variables. For instance, Jonklaas et al. (2019) [7] focused on the clinical variables effect over the thyroid hormones distribution, with independence of any pathological status. Hoermann et al. (2016) [6] discussed the convenience of estimating a trivariate reference region for TSH, T3, and T4. Indeed, they proved that univariate reference curves for each hormone cause thyroid dysfunction overdiagnosis. Therefore, trivariate regression modelling might be advantageous for thyroid dysfunction diagnosis. In this context, the proposal of trivariate reference regions – i.e., regions characterizing the 95% of healthy patients' results - are desirable in the clinical setting. In future work, we will investigate the MCTMs extension for conditional trivariate reference region estimation.

MCTMs represent a leap forward in the multivariate regression analysis application to real clinical problems. To date, multivariate regression usage in the clinical setting is anecdotal [1–3]. Indeed, currently, when several correlated measurements are available for the same patient, they are treated as mutually independent variables, or a pre-specified transformation is applied to them resulting in a univariate problem. This common strategy may depreciate useful information arising from the continuous measurements joint distribution. Hence,

MCTMs may enhance the application of multivariate regression for diseases whose diagnosis is based on several continuous biomarkers, or clinical assessments that are based on correlated measurements.

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