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# TVEM (Time-Varying Effect Modeling) SAS Macro Users' Guide

## Version 3.1.0

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**Runze Li**  
Penn State

**John J. Dziak**  
Penn State

**Xianming Tan**  
University of North Carolina

**Liyang Huang**  
Penn State

**Aaron T. Wagner**  
Penn State

**Jingyun Yang**  
Rush University Medical Center

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Please send questions and comments to [MChelpdesk@psu.edu](mailto:MChelpdesk@psu.edu).

The suggested citation for this users' guide is  
Li, R., Dziak, J. D., Tan, X., Huang, L. Wagner, A. T., & Yang, J. (2015). *TVEM (time-varying effect modeling) SAS macro users' guide* (Version 3.1.0). University Park: The Methodology Center, Penn State. Retrieved from <http://methodology.psu.edu>

The development of the SAS %TVEM macro was supported by National Institute on Drug Abuse Grant P50 DA039838. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIDA or the National Institutes of Health. The authors of this document would like to thank Deborah Kloska for her contributions and Stephanie Lanza, Sara Vasilenko, and Amanda Applegate for their helpful comments.

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# 1. Overview of the %TVEM Macro

## 1.1 Users' guide overview

This users' guide describes how to use the %TVEM macro. This SAS macro can be used to estimate time-varying coefficient functions in time-varying effect modeling for intensive longitudinal data when the outcome has a normal distribution, logistic distribution, or Poisson distribution. Intensive longitudinal data refers to longitudinal data with more frequent measurements than traditional longitudinal data, in which there are typically only a few widely spaced waves of data for each individual. Traditional analytic methods assume that covariates have constant (i.e., non-time-varying) effects on a time-varying outcome. These macros estimate the time-varying effects of the covariates.

This guide assumes you have a working knowledge of time-varying effect modeling (TVEM). Tan, Shiyko, Li, Li, & Dierker (2012) provide an introduction to TVEM for audiences in psychological science.

## 1.2 TVEM macro features

The previous version of the Methodology Center's TVEM software was a suite of multiple SAS files, one for each kind of distribution that could be modeled. The new version is a single self-contained SAS file that handles normal, logistic, or Poisson outcomes.

Key features of the previous and current macros:

- Option to include multiple non-time-varying covariates
- Option to include multiple time-varying covariates
- Accommodation of different distributions (normal, logistic, or Poisson) measured over time
- Option to employ a penalized truncated power spline basis instead of a B-spline basis function (Spline bases are discussed in Section 4.4 and Chapter 7)

The zero-inflated Poisson (ZIP) outcome distribution has not been implemented in version 3.0, but it is planned future development. To access version 2.1.1 of the %TVEM macro for ZIP outcomes, visit the %TVEM macro download page.

### Important changes from version 2.1.1

- Ability to model within-subject correlation using random effects or a robust sandwich variance estimator

- Consolidation into a single macro for usability
- Enhanced screen output for improved interpretability
- Option to generate new output datasets
- Improved plotting ability (Workaround for any SAS-Java-Windows compatibility issues)
- Enhanced code readability. (See Section 4.2.)

## 2. System Requirements

The %TVEM macro requires

- SAS version 9.2 or above
- SAS/IML (to generate B-spline or truncated power spline basis functions)
- SAS/STAT (to estimate linear mixed effects models using PROC GLIMMIX)

Note: SAS/IML and SAS/STAT are sold separately from the base SAS package, but most university licenses include them.

The macro has not been extensively tested on versions of SAS for operating systems other than Microsoft Windows, but may function there. One of the plotting options offered by the %TVEM macro requires Java and the SAS SGRENDER procedure, but a simpler plotting option that requires only the usual SAS GPLOT procedure is available.

### 3. Time-Varying Effect Models

TVEMs are a natural extension of linear regression models. The fundamental difference is this: in linear regression models, a single estimate of each covariate's effect is provided, but in TVEMs the coefficients can vary over time (Hastie & Tibshirani, 1993). Intensive longitudinal data are generally collected to capture temporal changes in a process, so it is natural to expect that both the outcome and the relationships between the covariates and the outcome might change over time. TVEMs are designed to evaluate whether and how the effects of covariates change over time.

Suppose we observe intensive longitudinal data  $\{(x_{ij}, y_{ij}, t_{ij}), i = 1, 2, \dots, n, j = 1, 2, \dots, n_{ij}\}$ , where  $y_{ij}$  is individual  $i$ 's response variable measured at time  $t_{ij}$ , and  $\mathbf{x}_{ij} = (x_{ij1}, x_{ij2}, \dots, x_{ijp})'$  is a corresponding  $p$ -dimensional **covariate vector**. Traditional linear models are

$$y_{ij} = \beta_1 x_{ij1} + \dots + \beta_p x_{ijp} + \varepsilon_{ij}, \tag{1}$$

where we can set  $x_{ij1} \equiv 1$  in order to include an intercept, and  $\varepsilon_{ij}$  is a random error term.

A TVEM is defined as

$$y_{ij} = \beta_1(t_{ij})x_{ij1} + \dots + \beta_p(t_{ij})x_{ijp} + \varepsilon_{ij}, \tag{2}$$

where  $\beta_1(t), \dots, \beta_p(t)$  are unknown coefficient functions that are assumed to be smooth over time  $t$ .

TVEM thus allows the effects to change over time, which may be particularly useful in the analysis of longitudinal data.

#### The generalized time-varying effect model

Traditional generalized linear model theory (McCullagh & Nelder, 1989) assumes that

$$E(y_{ij}) = \mu_{ij}, \quad g(\mu_{ij}) = \eta_{ij} = \beta_0 x_{0ij} + \beta_1 x_{1ij} + \dots + \beta_p x_{pij}, \tag{3}$$

where  $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_p)'$ ,  $\eta_{ij}$  is called a linear predictor, and the function  $g(\cdot)$  is called the link function, which may vary from case to case. For example, we can let  $g(a) = a$  for continuous responses, let  $g(a) = \log(a/(1 - a))$  if the outcome  $y_{ij}$  is binary, and let  $g(a) = \log(a)$  if we assume  $y_{ij}$  follows a Poisson distribution. In Equation 1, all coefficients in  $\boldsymbol{\beta}$  are assumed to be constant over time. This

generalized linear model can be extended similarly to allow its coefficients in the linear predictor to change over time :

$$E(y_{ij}) = \mu_{ij}, \quad g(\mu_{ij}) = \eta_{ij} = \beta_0(t_{ij})x_{0ij} + \beta_1(t_{ij})x_{1ij} + \cdots + \beta_p(t_{ij})x_{pij}, \quad (4)$$

where  $\boldsymbol{\beta}(\cdot) = (\beta_1(\cdot), \beta_2(\cdot), \dots, \beta_p(\cdot))'$  consists of  $p$  unknown coefficient functions of time that are assumed to be smooth over time  $t$ . If we let  $g(\mu_{ij}) = \ln(\mu_{ij} / (1 - \mu_{ij}))$ , the proposed model can handle binary responses, and setting  $g(\mu_{ij}) = \ln(\mu_{ij})$ , the model could handle count responses that follow a Poisson distribution. Choosing  $g(\mu_{ij}) = \mu_{ij}$ , we obtain the TVEM as in Equation 2, which could be considered a special case of the generalized TVEM.

The main purpose of the TVEM macro is to estimate the coefficients functions  $\beta_0(t_{ij})$  through  $\beta_p(t_{ij})$  in Equation 4 (including Equation 2, which is a special case of Equation 4).

Note that the %TVEM macros use all available data for every individual over time. Time-specific observations with missing values either for response  $y$  or for any covariates are automatically excluded. All %TVEM macros can also include non-time-varying covariates, such as gender, whose effects remain static over time. Details about the TVEM mathematical model can be found in Tan et al. (2012).

## 4. Using the %TVEM Macro

### 4.1 Preparation

A SAS macro is a special block of SAS commands. First the block is defined, and then it is called when needed.

Three steps need to be completed before running one of the %TVEM macros:

1. If you haven't already done so, download and save the macro to the designated path, (e.g., `S:\myfolder\`).
2. Direct SAS to read the macro code from the path, using a SAS %INCLUDE statement, such as

```
%INCLUDE 'S:\myfolder\TVEM_v310.sas';
```

Note: we suppose that the SAS macro file exists in the folder `S:\myfolder\`. This path represents any user-specified folder. This convention will be followed in the examples and the appendices.

3. Use a `libname` statement to direct SAS to the data file. The statement should give the `libname` command, name the library, and then identify the path to the data. For example,

```
libname sasf 'S:\myfolder\';
```

### 4.2 Syntax changes in version 3.x

Many arguments were renamed in version 3.1.0 of %TVEM.<sup>1</sup> Below is a basic example analysis in code from version 2.1.1 and version 3.1.0.

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<sup>1</sup> When updating software, we typically keep the code identical to previous versions to eliminate the learning curve for previous users. For %TVEM, however, there are enough changes that we decided to rename many arguments for the sake of comprehension.

**Table 1**  
**Syntax Changes for the %TVEM Macro v. 3.1.0**

v. 2.1.1 argument	v. 3.1.0 argument	Notes
%TVEM_normal (	%TVEM (	The distribution of the outcome variable was previously identified in the macro call, but now is the argument <i>dist</i> because the macros have been consolidated.
**N/A**	<i>dist</i> = normal ,	new argument
mydata = exampledata ,	data = exampledata ,	Changed
id = SubjectID ,	id = SubjectID ,	
time = Time ,	time = Time ,	
dep = Urge ,	dv = Urge ,	Changed
tcov = intercept ,	tvary_effect = intercept ,	Changed
method = P- spline ,	method = P- spline ,	Previously optional, now mandatory. See Section 4.4.
cov_knots = 10 ,	knots = 10 ,	Changed
cov = Loc1 Loc2 , ) ;	invar_effect = Loc1 Loc2 , ) ;	Changed

### 4.3 Running the %TVEM macro and syntax definitions

Call the macro using a percent sign, its name, and user-defined arguments in parentheses. The macro parameters, which we will refer to as “arguments,” are shown below. Arguments in bold text are mandatory.

```
%TVEM(data = dataset name ,
      id = variable ,
      time = variable ,
      dv = variable ,
      tvary_effect = variables ,
      knots = numbers ,
      dist = distribution name ,
      method = name ,
      degree = number ,
      evenly = number ,
      invar_effect = variables ,
      output_prefix = prefix ,
      outfile = file path and name ,
```

```

plot = option,
plot_scale = number,
random = option,
stderr = option );

```

The first seven arguments, shown in bold above, are required; they must be specified in order for the macro to work. The remaining arguments are optional; if any of them are not specified, the default value is used. See Tables 3 and 4 for default values.

<b>Table 2</b> <b>Required Arguments for the %TVEM Macro</b>	
<b>Name</b>	<b>Description</b>
data	The name of the input dataset. This dataset should have longitudinal data structure (one row for each assessment).
id	The variable in data containing the subject's identification. Statistically, it is assumed that observations having the same values of the id variable may be correlated with each other, but observations having different values on the id variable are independent. Values must be integers.
time	The measurement time variable. One and only one must be provided.
dv	The dependent variable. One and only one must be provided.
tvary_effect	The covariates which are assumed to have time-varying coefficients. At least one must be provided. To include a time-varying intercept, a variable should be created where all values equal 1, and this variable name should be included in this argument.
knots	A positive integer (such as 10) for each variable in tvary_effect. These numbers indicate the number of knots (a measure of flexibility) to be used in estimating the corresponding coefficient functions for the tvary_effect variables.
dist	A single word describing the kind of conditional distribution assumed for the dependent variable, and therefore the type of model to be fit. There are currently three choices: <ul style="list-style-type: none"> <li>normal assumes that the dependent variable is a continuous and normally distributed (i.e., Gaussian) numerical variable and that a linear regression link function should be used. The macro will accept the word Gaussian instead of normal.</li> <li>logistic assumes that the dependent variable is on a binary (0 or 1) scale and that a logistic regression link function should be used. The macro will accept the word binary or binomial instead of logistic. <b>Technical note:</b> The logistic regression model will be for predicting the probability of a 1 (like the descending option in PROC LOGISTIC).</li> <li>Poisson assumes that the dependent variable is a count variable (with possible values 0, 1, 2, ...) with a Poisson distribution, and that a log-linear regression link function should be used.</li> </ul>
method	The method to be used in estimating the coefficient functions. Specifying B-spline (or simply B) will fit an unpenalized B-spline, and specifying P-spline (or simply P) will fit a penalized truncated power spline.

<b>Table 3</b> <b>Important Optional Arguments for the %TVEM Macro</b>		
<b>Name</b>	<b>Description</b>	<b>Default</b>
<code>invar_effect</code>	The covariates, if any, which are assumed to have a non-time-varying effect. Variables listed here must not be listed in <code>tvary_effect</code> .	If omitted, there will be no non-time-varying-effects variables in the model.
<code>plot</code>	The technical mechanism used to plot the coefficient functions. Specify <code>full</code> to generate polished-looking plots; however, some users' SAS or Java installations may not work with this option. Specify <code>simple</code> to generate a less polished-looking plot that is likely to work in more systems. Specify <code>none</code> to suppress plotting; this would mainly be used in loops or simulations in which the macro is being called many times.	<code>full</code> -Try <code>simple</code> if this does not work.
<code>random</code>	The method to be used in estimating within-subject correlation. Specify <code>none</code> to estimate no within-subjects variability; this is not recommended unless there is only one observation per subject. Specify <code>intercept</code> to estimate a random intercept for each subject. Specify <code>slope</code> to estimate both a random intercept and a random slope for each subject. <sup>2</sup>	<code>slope</code> -Try <code>intercept</code> if this does not work.

Last, there are arguments that most users will not have to change. Only users who are very familiar with TVEM or who have specialized needs will wish to use them.

<sup>2</sup> The `random` option is currently relevant only if the B-spline method is being used; it is ignored if the P-spline method is being used, because within-subject correlation is accounted for differently in that case.

**Table 4**  
**Specialized Optional Arguments for the %TVEM Macro**

Name	Description	Default
degree	The degree of the spline used between each knot in the coefficient function. This is another measure of flexibility. The value specified must be 1 for linear, 2 for quadratic, or 3 for cubic.	3 (cubic) -Default recommended unless there is a reason to choose otherwise.
evenly	A number (0 or 1) telling how to choose the positions of knots within the time interval. Two methods are available. One (evenly=1) evenly spaces the inner knots over the range of measurement times of all observations. The other (evenly=0) positions the knots on evenly distributed quantiles of these observations. Default value = 0.	0 (quantiles) -Default recommended unless there is a reason to choose otherwise.
stderr	The method used to calculate standard errors. Specifying <i>model</i> means that standard error calculations will assume that the chosen model for random effects is correct. Specifying <i>robust</i> means that a “sandwich” (Taylor linearization) formula will be used to try to increase robustness against departure from the assumed model for random effects. <sup>3</sup>	robust -Default recommended unless there is a reason to choose otherwise.
plot_scale	The number of points to be plotted in the graphs of the estimated coefficient functions and their confidence bands.	100
output_prefix	Letters to be prefixed to the names of the output data sets generated by the macro, to indicate which analysis they came from. User can specify any name of 15 characters or less—may be useful in distinguishing one analysis from another if the macro is called multiple times. Advanced note: For output_prefix (but not outfile_name) you can include a SAS library name in the prefix. For example, you can use <i>mylib.tvem_</i> instead of <i>tvem_</i> if you want to save in a different SAS library. If you don't know what a SAS library is, ignore this note.	tvem_
outfile_name	The path and file name for an output file to be generated by the macro. The macro generates a .csv file with the path and name specified by this parameter. This file contains the data for plotting the coefficient curves and their confidence bands in another application such as R or Microsoft Excel.	If <i>outfile_name</i> is not specified, no such file is generated. However, SAS datasets will still be generated which can be exported from SAS in the usual way.

<sup>3</sup> The stderr option is currently only relevant for B-splines with random effects (intercept or slope). If B-splines with no random effects are used, then a model-based standard error is always used and the subject id variable is ignored. If P-splines are used, then a special form of the sandwich standard error is always used.

## 4.4 About spline basis: Should I use B-spline or P-spline?

**Summary recommendation.** Use P-spline for a quick understanding of your data. Then, select the proper number of knots using B-spline to see the proper level of detail in the association you are modeling.

**Details.** A spline is a shape composed of linear or quadratic segments. The so-called “knots” are the places where these segments join together. Splines are useful because they allow great flexibility when estimating the shape of a nonlinear function. There are various mathematical ways to represent a spline. In particular, when writing code to run the %TVEM macro, you will need to select either a P-spline or a B-spline. If you do not understand the difference, follow this procedure:

We recommend users start with a P-spline and a large number of knots (10 or more). The macro will use the P-spline penalty to automatically select a good amount of smoothness (read more in Section 4.5) and will use sandwich standard errors that do not require further adjusting. P-spline, then, gives you an immediate picture of the relationship you are modeling.

Once you have the big picture, you can optionally fine-tune the analysis using B-spline. When you use B-spline, you must run the model multiple times, incrementally increasing or decreasing the number of knots each time, in order to select the ideal model. This method is more sensitive than P-spline and can reveal more detail. B-spline also allows users to specify random effects using the `random` argument. For more details, see the examples in Sections 6.3 and 6.6.

## 4.5 Selecting the proper number of knots

When using P-spline, the correct number of knots will be selected by the macro if you select an adequate number of knots; we recommend 10. The number selected must be entered for each variable listed in the `tvary_effect` argument.

When using B-spline, select a low starting value and increment the number of knots. For example, change the value in the `knots` argument from `knots = 2` to `knots = 3`, to `knots = 4`, etc., running your model each time. Then, select the correct number of knots by comparing the fit statistics in the output. You can also choose the optional `deg` argument in this way, although it is also okay to leave `deg` at its default value. However, it may be easier try to change only one aspect of the code (such as the number of knots) at a time to avoid confusion when comparing many sets of output. Also, for reasons described below, the random effects structure cannot be chosen using fit statistics in the same way.

Specifically, when fitting a non-normal model with random effects, we use a pseudolikelihood method within PROC GLIMMIX. That means that GLIMMIX estimates the coefficients by repeatedly approximating the binary or Poisson model with better- and better-fitting weighted normal models, which makes the computation much easier. However, this means that the log-likelihood, AIC, and BIC fit statistics are based on a different distribution, known as the “pseudolikelihood” because it is the approximating distribution, rather than an actual binary distribution. This means that the likelihood, AIC, and BIC statistics cannot be compared between models with and without random effects in this macro. However, they can be used to select the number of knots in the usual way within a choice of random effects or no random effects.

## 4.6 Choosing how to model within-subject correlation

When multiple observations are taken from each individual in a sample, it is well known that observations within an individual are likely to be correlated with each other, and that some adjustment should be made to account for the lack of independence. There are several ways to do this. Two of the most commonly used are (a) “robust” or “sandwich” standard errors and (b) random effects (also known as mixed or multilevel modeling). The first method calculates the estimates as though the observations were independent and then adjusts the standard errors to account for the fact that they are not. The second method includes special terms in the model to account for the different characteristics of each individual. For reasons described in the technical details section, we use the first method with P-splines and the second method with B-splines. No action is required from the user for the first method; the adjustment is done automatically. However, the user does have to make choices in the second method.

Specifically, with B-splines you may use either (a) no random effect, (b) a random intercept only, or (c) a random intercept and random slope. In general, random quadratic or higher-level effects are not supported by the current version of the macro. Including no random effects treats all observations as independent. Including only random intercepts treats all observations within the same person as equally correlated. Including random intercept and random slope assumes that within the same person, observations closer in time are more highly correlated than those further away. Including both a random intercept and random slope is the richest and most realistic of these three choices. However, having additional random effects can make a model too complicated to fit easily on a given data set. The model might fail to converge if there is not sufficient information in the data set to estimate both the regression model and also the random effects. For this reason, it might be wise to try the random slope

and random intercept first, and then try a simpler model, with random intercept only, if the richer model fails.

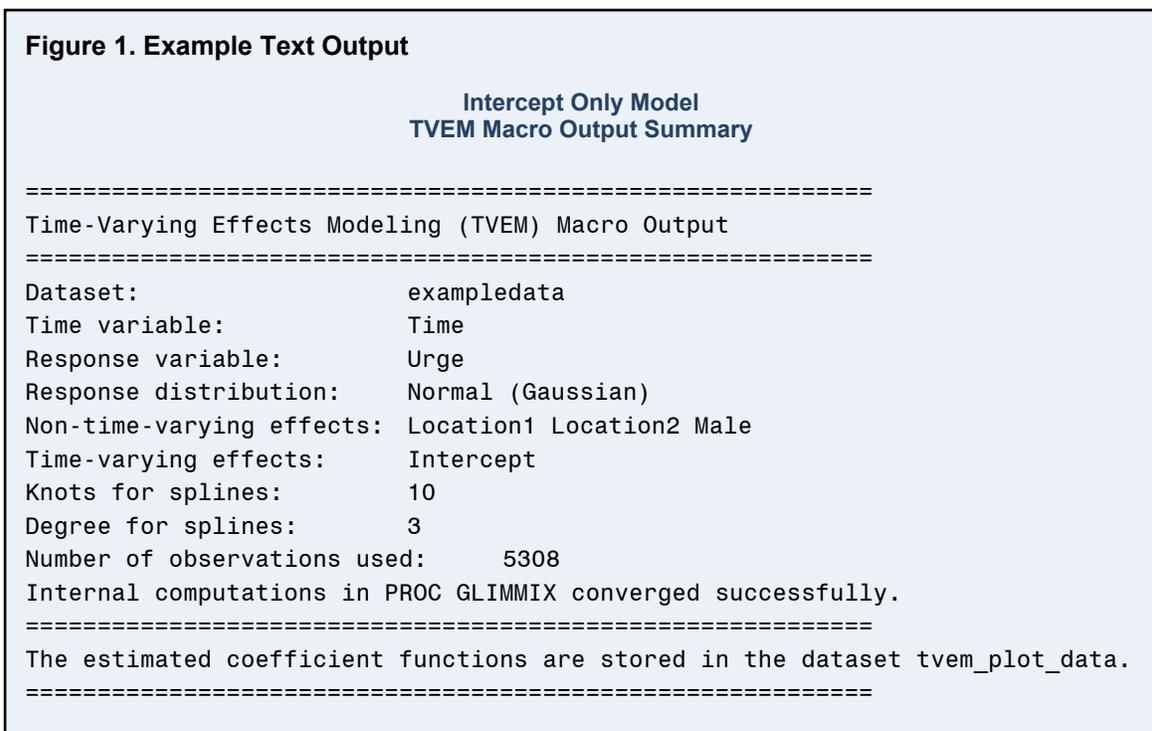
For reasons described above, in the context of this macro, it isn't valid to use AIC or BIC to choose the random effects structure. You could, however, get at least a rough idea of whether a particular kind of random effect (slope or intercept) is accounting for a statistically significant amount of variability by comparing the size of the estimated variance component to its standard error (both are shown in the output). The ratio of the estimated variance component to its standard error is not exactly a valid test statistic in the usual way (as though it were a z score), but it could be helpful as a heuristic. Another approach is to include both a random slope and intercept if this model converges, but try a simpler model if it does not.

## 5. Output

The TVEM macro produces three different kinds of output, and optionally a fourth. Each is described below.

### 5.1 Text output

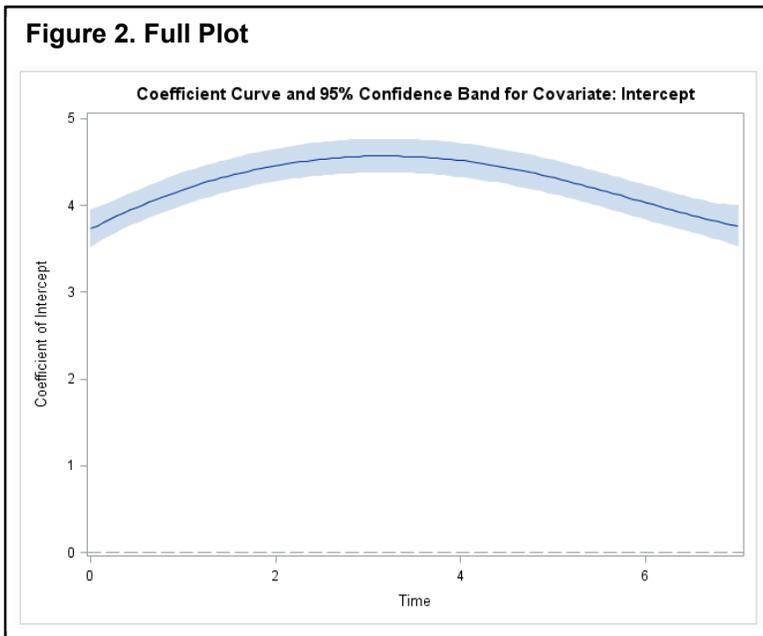
Some summary output is provided on the screen (Results window) or listing (if in batch mode). If the B-spline method is being used, this summary output includes the log-likelihood and information criteria which can be useful for model selection. If the P-spline method is being used, these criteria are



currently not shown, because a penalty function is being applied to select the degree of model complexity, and this indirectly creates certain complications for interpreting information criteria. If there are any non-time-varying-covariates, then their estimates, standard errors, and  $p$ -values are shown.

### 5.2 Plots

For each time-varying coefficient, a plot is drawn to show how its relationship with the dependent variable, as expressed by its estimated coefficient function  $\beta_j(t_{ij})$ , changes over time. Pointwise confidence bands created to have 95% confidence using standard techniques are also shown. These are pointwise confidence bands and do not imply joint confidence over all points together.



For logistic regression, in addition to the coefficient function, the odds ratio function (found by exponentiating  $\beta_j(t_{ij})$ ) is also plotted separately. In a previous version of the TVEM, this had to be specifically requested using an option; it is now provided automatically.

Plots are available in two formats, the full version, which is generated by default, and the simple version, which is generated when you argument specify `plot = simple` in your syntax. The

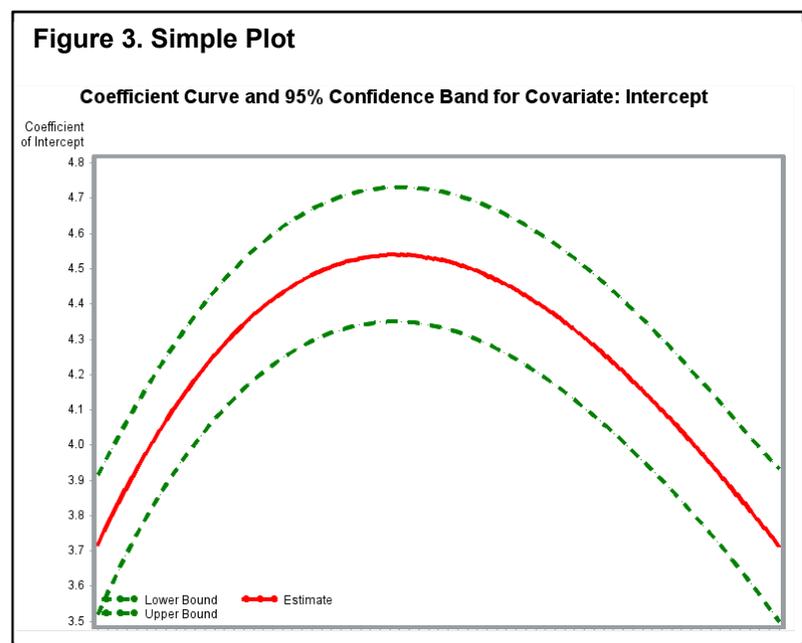
simple version is available for users whose machines fail to generate the full plots.

### 5.3 SAS datasets

Several SAS datasets are automatically produced by the macro. They have specific names describing their contents, but you can optionally add a common prefix to all of their names as a way of marking which analysis they came from, if you wish to run the TVEM macro more than once and compare the results. The default prefix is just “Tvem\_” if no other is specified.

**Note:** These datasets can be found in the SAS Work directory. That is, you can use them during the SAS session but they disappear when you close SAS. A LIBNAME and data step are needed to save the files to permanent SAS datasets on your hard drive or network.

Not all of these datasets are produced by all analyses (it depends on which options are chosen), and not all of these datasets will be meaningful for all



users. In fact, most users will not need the datasets, except perhaps for *plot\_data* and/or *plot\_data\_OR*. The other datasets are either duplicates of material shown in the screen output (e.g., fit statistics) or else are very technical and of interest only for specialized situations (e.g., estimates and covariance matrix of the coefficients for the individual basis functions, which would be interesting mainly to a methodological researcher studying the performance of different spline methods). These files and their contents are described in Table 4.

<b>Table 5 Datasets Produced by the %TVEM Macro</b>	
<b>Name</b>	<b>Description</b>
...converged	This dataset contains information about whether the estimation algorithm converged in PROC GLIMMIX, which does much of the behind-the-scenes work for the %TVEM macro. If it does not converge, the user will also be warned in the text output, and the interpretability of the results will be suspect. The main use of this dataset would be in a simulation or loop, for checking whether there were occasions in which TVEM estimation was not successful.
...covar_orig_coefs	This dataset contains the estimated covariance matrix for the underlying regression model containing all of the spline bases. It is not necessary for most users and would be of interest only to methodological researchers studying the properties of spline methods.
...covparms	This dataset, taken directly from PROC GLIMMIX output, contains the estimated variance components in a model with random effects. It is of main interest in a simulation setting
...fitstats	If the B-spline method is used then this dataset, taken directly from PROC GLIMMIX output, contains the fit statistics (log-likelihood and information criteria) for the fitted model. The most commonly used fit statistics are also shown in the text output, so most users will not need to read this dataset, but it could be very useful in a loop or simulation.
...glimmix_info	This is the MODELINFO output from the intermediate calculations in PROC GLIMMIX. Most users will not need to read this dataset.
...invariant_effects	This dataset will be produced if covariates with non-time-varying effects are requested via the <code>invar_effect</code> statement. It contains the coefficient estimates and standard errors for these covariates. This dataset is also printed in the text output, if it is generated.
...orig_coefs	This dataset contains the estimates for the underlying regression model containing all of the spline bases. It is not necessary for most users and would be of interest only to methodological researchers studying the properties of spline methods.
...plot_data	This dataset contains the estimated coefficients at a dense grid of time points. It is automatically used to create the coefficient plot, and can also be useful for other plots or reports.
...plot_data_OR	This dataset is similar to <code>plot_data</code> , but the coefficients are exponentiated to base $e$ . In the context of a logistic regression model, this transforms logistic regression coefficients to baseline odds (for the intercept) or odds ratios (for covariates). This is only produced for a logistic regression model, and it is also automatically plotted.
...predicted	This dataset, produced by PROC GLIMMIX, contains fitted values for each observation.

*Note.* The dataset names will be preceded by either `tvem_` or the user-specified prefix.

## 5.4 External file (optional)

If a valid Windows path and file name are provided for the *outfile* argument in the macro, then the contents of the *plot\_data* dataset will be automatically exported to a comma-separated (.csv) text file, which can be read in R or Microsoft Excel in order to create customized plots based on the estimated coefficient functions. You can also export the dataset by using the SAS top menu, right-clicking the dataset name, or calling PROC EXPORT.

## 6. Data Analysis Examples

Included with the macro is a simulated dataset based very loosely on intensive longitudinal studies of smoking cessation such as the one described in Shiffman et al. (2002).

In the very simplified scenario used in the dataset, 200 individuals who want to stop smoking are followed for 7 days after their quit attempt begins. At up to 30 random occasions during the week, they are randomly prompted by an electronic device to describe their feelings. Their levels of negative affect (distress, anxiety and sadness) and their levels of urge to smoke are recorded on a 0 to 10 scale. They are asked to answer yes or no to a question that asks whether they currently think their quit attempt will be successful. They also tell their location: whether they are at work, at home, or in a social or fun setting.

### 6.1 Data preparation: Adding an intercept, recoding, and adding a title

Before running the TVEM analysis, we have to use the INCLUDE function to get SAS to read the macro file.

```
%INCLUDE "C:\Users\MeMyself\Documents\Sims-Tvem\Tvem_v310.sas";
```

The data may need to be altered at this point using a data step. Below we create an intercept column and dummy code a three-level variable to create two separate two-level variables. The data preparation needed will be specific to each analysis.

```
/* Simulate data */
DATA exampladata;
  SET here.exempladata;
  * Create an intercept column;
  Intercept = 1;
  * Dummy-code the three-level location variable;;
  Location1 = 0; IF Location=1 THEN Location1 = 1;
  Location2 = 0; IF Location=2 THEN Location2 = 1;
RUN;
```

If you plan to run the macro several times (for example, if you select different numbers of knots), you can add a title to each macro run in the output. This can be done by preceding your macro syntax with a SAS command title like

```
Title "The first one";
```

The title will now appear as part of your macro output. To stop adding this title, just use the title command again either to specify a new title, or to specify no title at all. In the latter case you simply type

```
Title;
```

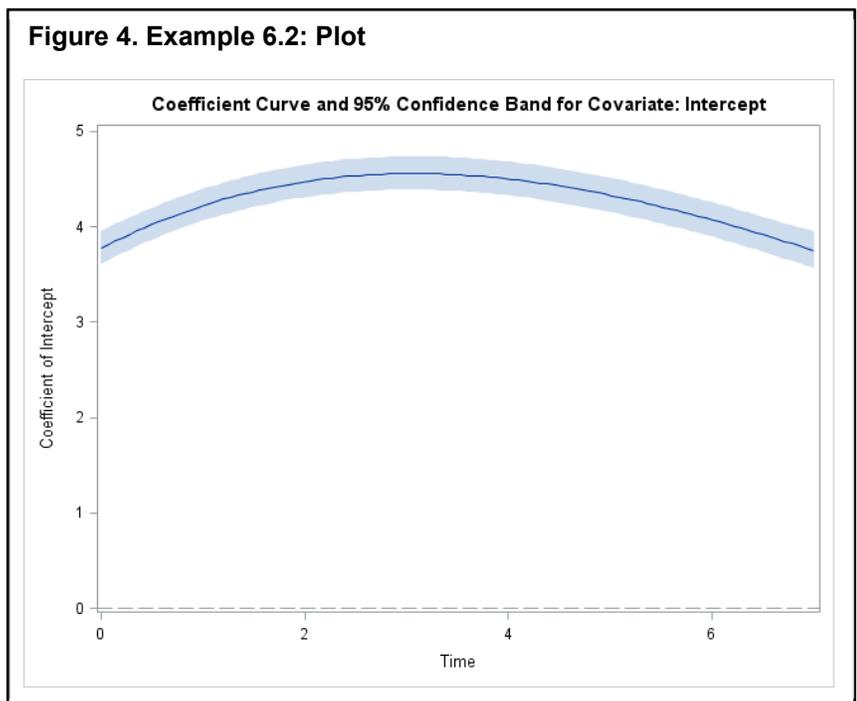
## 6.2 Example with a normal distribution

Now we can use TVEM. We could start by studying how urge to smoke changes, on average, over time, adjusting for subject's sex (coded as a dummy variable with 1=male, 0=female) and location (coded as above). We could start with an intercept-only TVEM, which reduces to simply a smoothed nonparametric regression of the dependent variable on time.

```
%TVEM(dist=normal,
      data = exampladata,
      id = SubjectID,
      time = Time,
      dv = Urge,
      tvary_effect = Intercept,
      method = P-spline,
      knots = 10,
      invar_effect = Location1 Location2 Male);
```

The output for fixed effects covariates suggests that participants had lower urge to smoke while at work. The effect of male gender seems significant using the model-based standard errors under the assumption of independent observations, but not significant using a robust standard error. However, the effect of location 1 remains very strongly significant.

The plot suggests that average urge to smoke increased and then decreased as the week went on. Note that this is the “full” version of the plot because the *plot* argument was not specified.



**Table 6**  
**Example 6.2: Fixed Effects Covariates Output**

Obs	Effect	Estimate	StdErr	RobustStdErr	ModelBasedZ	RobustZ	ModelBasedP	RobustP
1	Location1	-0.07503	0.03516	0.03165	-2.13415	-2.37090	0.032831	0.01774
2	Location2	0.06805	0.03747	0.03680	1.81587	1.84935	0.069390	0.06441
3	Male	0.09339	0.02988	0.11023	3.12498	0.84717	0.001778	0.39690

### 6.3 Example with normal distribution using B-spline

We can include random effects as follows.

```
%TVEM(
    dist=normal,
    data = exempladata,
    id = SubjectID,
    time = Time,
    dv = Urge,
    tvary_effect = Intercept,
    method = B-spline,
    knots = 2,
    random = slope,
    invar_effect = Location1 Location2 Male);
```

In practice we should try different values of `knots` to try to get a good AIC or BIC. To do this, we would use the same code, but use `knots = 3`, then `knots = 4`, etc. We would select the correct number of knots by the fit statistics in the output. (NOTE: Here we should keep the other aspects of our code the same while incrementing the number of knots, so that the comparison of fit statistics will apply directly to the question of the selection of knots.)

The resulting plot is rather similar (not shown), but we now see some new output (Tables 7 and 8).

It appears that there is both a random intercept and a random slope over time, although the random intercept seems to be more important.

**Table 7**  
**Example 6.3: Fixed Effects Covariates Output**

Obs	Effect	Estimate	StdErr	DF	tValue
1	Location1	-0.1098	0.02529	6644	-4.34
2	Location2	0.04233	0.03020	6644	1.40
3	Male	0.1091	0.1038	6644	1.05

**Table 8**  
**Example 6.3: Covariance Parameters**

Obs	CovParm	Subject	Estimate	StdErr
1	Intercept	SubjectID	0.4330	0.05062
2	Time	SubjectID	0.007879	0.001328
3	Residual		0.9196	0.01592

## 6.4 Example with a time-varying covariate

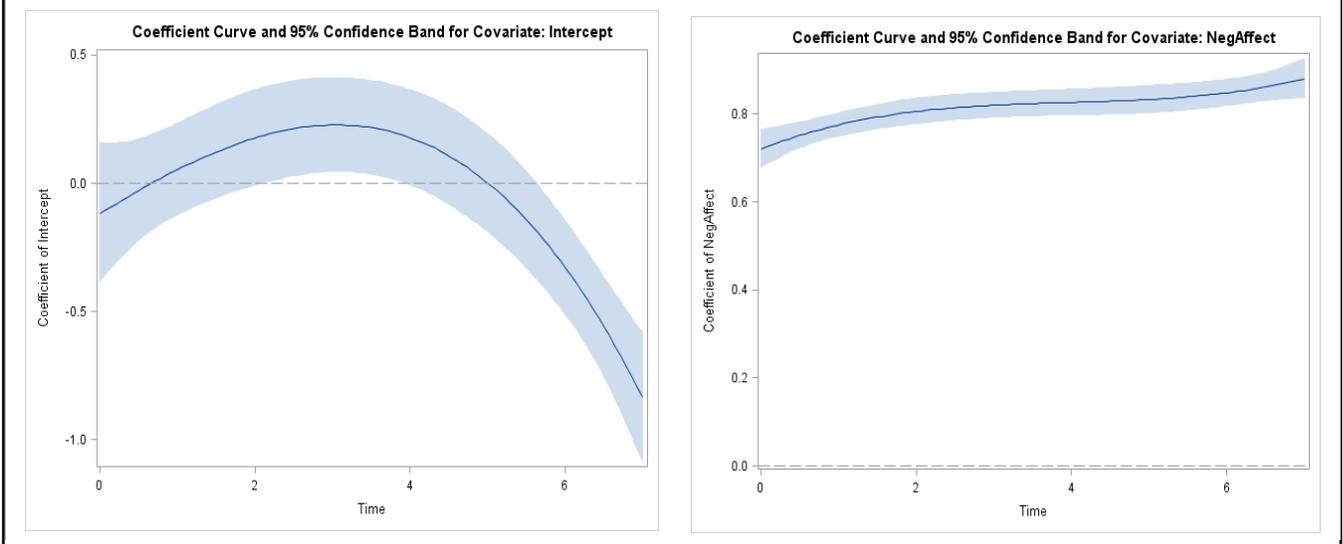
Now let us include a covariate, namely `NegAffect`, which may have a time-varying effect. We might run the following code:

```
%TVEM(dist=normal,
      data = exampladata,
      id = SubjectID,
      time = Time,
      dv = Urge,
      tvary_effect = Intercept NegAffect,
      method = P-spline,
      knots = 10 10,
      invar_effect = Location1 Location2 Male);
```

which will produce the plots in Figure 5.

It appears that the effect of negative affect on urge to smoke in this dataset is always significant and positive, and tends to increase over time.

Figure 5. Example 6.4: Plots

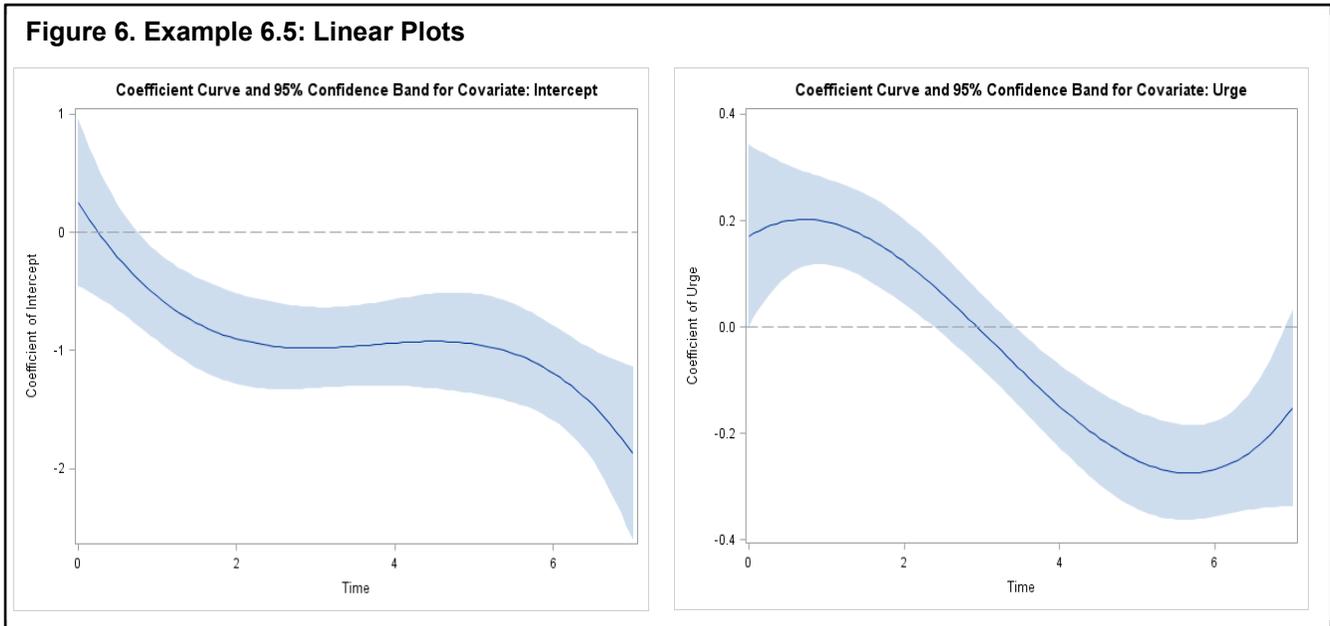


## 6.5 Example with a logistic distribution

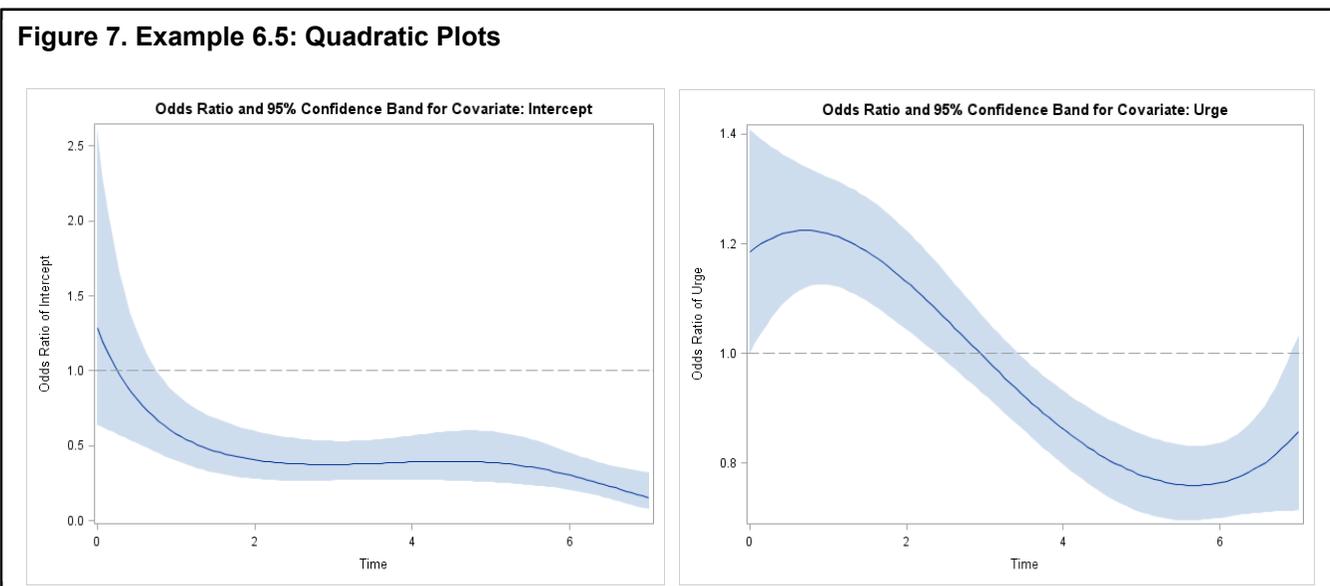
In the same dataset, we also have simulated binary data: the participant's prediction as to whether he or she will be able to quit in the long-term. Let's try fitting a TVEM to predict the success expectancy from urge.

```
%TVEM(dist = logistic,
       data = exempladata,
       id = SubjectID,
       time = Time,
       dv = ExpectedSuccess,
       tvary_effect = Intercept Urge,
       method = P-spline,
       knots = 10 10,
       invar_effect = Location1 Location2 Male);
```

In Figure 6, It appears from the plot on the left that confidence declines over time after adjusting for urge. It appears from the plot on the right that urge has a generally negative relationship with confidence, more so as time goes on.



Exponentiated versions of these curves are also generated, showing the time-specific odds of expecting success, and the odds ratio of expecting success between people differing by one unit of urge (See Figure 7).



We do not see any effect of location on confidence in one's quitting ability, unlike when we were predicting urge (Table 9).

**Table 9**  
**Example 6.5: Fixed Effects Covariates**

Obs	Effect	Estimate	StdErr	RobustStdErr	ModelBasedZ	RobustZ	ModelBasedP	RobustP
1	Location1	0.001619	0.07020	0.068221	0.02306	0.02373	0.98160	0.98107
2	Location2	0.01957	0.07495	0.073885	0.26105	0.26480	0.79406	0.79116
3	Male	0.1265	0.06000	0.089297	2.10898	1.41694	0.03495	0.15650

## 6.6 Example with logistic outcome using B-spline

We can also include random effects in this analysis. We try the following code:

```
%TVEM(dist=logistic,
      data = exempledata,
      id = SubjectID,
      time = Time,
      dv= ExpectedSuccess,
      tvary_effect = Intercept Urge,
      method = B-spline,
      knots = 2 2 ,
      random = slope,
      invar_effect= Location1 Location2 Male);
```

In the output (Table 10), we see a noticeable random intercept but not much of a random slope.

**Table 10**  
**Example 6.6: Covariance Parameters**

Obs	CovParm	Subject	Estimate	StdErr
1	Intercept	SubjectID	0.2150	0.04569
2	Time	SubjectID	0.003040	0.003052

## 7. Technical Details on Spline Bases

Without loss of generality, we consider the following generalized time-varying coefficient model (Equation 4), which we show here again for convenience:

$$E(y_{ij}) = \mu_{ij}, \quad g(\mu_{ij}) = \beta_0(t_{ij})x_{0ij} + \beta_1(t_{ij})x_{1ij} + \dots + \beta_p(t_{ij})x_{pij}.$$

### 7.1 B-spline basis

The process of estimating the unknown coefficient function  $\beta(\cdot)$  involves approximating this function with certain combinations of B-spline basis functions that are determined by knots and degree. Given  $m+1$  knots, say,  $t_0 \leq t_1 \leq t_2 \leq \dots \leq t_m$ , the  $m-d$  basis B-splines of degree  $d$  can be defined using the *Cox-de Boor recursion formula* (de Boor, 1972) with

$$b_{j,0}\{t\} = \begin{cases} 1, & t_j \leq t \leq t_{j+1} \\ 0, & t < t_j \text{ or } t \geq t_{j+1} \end{cases}$$

and

$$b_{j,d}(t) = \frac{t-t_j}{t_{j+d}-t_j} \times b_{j,d-1}(t) + \frac{t_{j+d+1}-t}{t_{j+d+1}-t_{j+1}} \times b_{j+1,d-1}(t), \text{ for } j = 0, 1, \dots, K-d-1$$

In addition, knots  $t_{d+1} \leq t_{d+2} \leq \dots \leq t_{m-d-1}$  are called internal knots (or inner knots). In the %TVEM macro, the knots  $t_0, \dots, t_d$  and  $t_{m-d}, \dots, t_m$  are determined by the minimal ( $t_{(min)}$ ) and the maximal ( $t_{(max)}$ ) observation time in the input data set as follows:

$$t_j = \begin{cases} t_{(min)} - (d+1-j) \times \varepsilon, & j = 0, 1, 2, \dots, d \\ t_{(min)} + (j-m+d) \times \varepsilon, & j > m-d, \end{cases}$$

where  $\varepsilon$  is a small positive number that is set at  $10^{-12}$  in this macro. In addition, we employ cubic splines ( $d = 3$ ) in this macro, as many applications do.

Given the number of inner knots, the inner knots are equally distributed over the range of the study period or uniformly distributed on quantiles of measurement times (depending on the designation in the `evenly` parameter). For example, suppose that the study period is from year 0 to year 1. If we use four knots and distribute them equally over the study period, the inner knots will be at year 0.2, 0.4, 0.6, and

0.8. Or, if we distribute the 4 inner knots uniformly on the quantiles of measurement times, they will be at the 20%, 40%, 60% and 80% quantiles of the pooled measurement times.

Hence, when we input the number of inner knots =  $k$  (using the `knots` parameter), and we define the method to posit these inner knots (using the `evenly` parameter), the %TVEM macro will calculate the  $k$  inner knots, and then all the  $k + 2 \times (d + 1)$  knots, and then  $k + d + 1$  B-spline basis functions by using the Cox-de Boor recursion formula. For example, if  $k = 4$ , then there are  $8(=4+3+1)$  cubic B-spline basis functions.

To estimate the coefficients in Equation 4, we approximate  $\beta(\cdot)$  by  $k + 3 + 1$  cubic B-spline basis functions:

$$\beta_0(t) \approx \sum_{k=0}^{K+3} a_j b_{j,3}(t) \tag{5}$$

where  $b_{j,3}(\cdot)$ ,  $j = 0, 1, \dots, k+3$ , are cubic B-spline basis as defined by the Cox-de Boor recursion formula, and  $a_j$ ,  $j = 0, 1, \dots, k+3$ , are unknown parameters. In this way, we transfer the problem of estimating the function  $\beta(\cdot)$  into a problem of estimating  $a_j$ ,  $j = 0, 1, \dots, k + 3$ . Combining Equations 4 and 5, we get the following regression model:

$$E(y_{ij}) = \mu_{ij}, g(\mu_{ij}) = \eta_{ij} = \sum_{j=0}^{k+3} a_j \times b_{j,3}(t_{ij}) \times x_{ij} + \varepsilon_{ij}.$$

The estimate of  $a_j$ ,  $j = 0, 1, \dots, k + 3$ , can be obtained using available software, such as the PROC GENMOD or the GLM package in R. The number of inner knots determines the number of basis functions used to approximate  $\beta(\cdot)$ . Intuitively, the larger the number of inner knots, the better the approximation. However, using too many basis functions could cause over-fitting, which can cause near interpolation of the data and undesirable “wiggly” curves. So, we need to select the ideal number of inner knots to ensure good approximation and avoid over-fitting. This can be done by using different numbers of inner knots and running the model repeatedly. Then, we select the optimal number based on the model fit statistics (AIC and/or BIC) provided in the output.

## 7.2 Truncated power basis

When a %TVEM macro employs a truncated power spline basis, it uses a penalized spline, also known as P-spline, to approximate an unknown coefficient function. Otherwise, it is similar in process to B-spline. Given  $k$  inner knots,  $t_1 \leq t_1 \leq t_2 \leq \dots \leq t_k$ , the  $k + 3 + 1$  basis P-splines of degree 3 are

$$1, t, t^2, t^3, (t - \tau_1)_+^3, (t - \tau_2)_+^3, \dots, (t - \tau_k)_+^3,$$

where  $(t - \tau)_+^3 = \begin{cases} (t - \tau)^3, & t > \tau \\ 0, & t \leq \tau \end{cases}$

is called the truncated power function. The specification of inner knots when using P-spline basis is the same as when using B-spline basis.

We assume that we can estimate  $\beta(\cdot)$  in Equation 4 by  $k+3+1$  cubic P-spline basis functions:

$$\beta(t) = b_0 + b_1t + b_2t^2 + b_3t^3 + \sum_{j=1}^k b_{3+j}(t - \tau_j)_+^3. \tag{6}$$

Then the estimation of  $\beta(\cdot)$  is transferred to the estimation of  $b_j(j = 0, 1, \dots, k + 3)$ .

Combining Equations 4 and 6, we get the following linear regression model:

$$E(y_{ij}) = \mu_{ij}, g(\mu_{ij}) = \eta_{ij} = \sum_{l=0}^3 b_l \times t_{ij}^l \times x_{ij} + \sum_{l=1}^k b_{3+l} \times (t_{ij} - \tau_l)_+^3 \times x_{ij}.$$

The estimation of  $b_j(j = 0, 1, \dots, k + 3)$  can be accomplished using SAS PROC GLIMMIX, which is a common software product for generalized linear mixed models.

Again, we need to balance between good approximation and over-fitting. This is much easier with P-spline than with B-spline. First, we can see that the coefficients,  $b_j(j = 4, \dots, k + 3)$ , of these truncated power functions represent “amounts of jump” in the estimated function of  $\beta(\cdot)$  and are relevant to the smoothness of the estimated function. Based on this observation, a strategy to reach smoothness is to appropriately shrink these coefficients toward zero. If we treat the coefficients  $b_j(j = 4, \dots, k + 3)$  as random effects and the remaining coefficients  $b_0, \dots, b_3$  as fixed effects, then the best linear unbiased predictor (BLUP) of these random coefficients optimally shrinks these coefficients (Wand, 2003; Tan, et al., 2012), and %TVEM macros obtain these BLUPs by calling SAS PROC GLIMMIX. This means that we need only choose a large enough number of inner knots (e.g., 10), and the macro will automatically output the optimal model with optimally shrunk coefficients for those truncated power functions.

### 7.3 Technical differences between using B-spline and P-spline

In summary, there are two main differences between using B-spline and using P-spline: (a) to approximate unknown coefficient functions, B-spline uses a B-spline basis, and P-spline uses a truncated power basis; and (b) to automatically counter over-fitting due to the large number of inner knots, P-spline uses a penalty (through the use of a mixed-effect model), but in B-spline this is done manually by comparing model fit statistics of different models using different numbers of knots. Note that the syntax `B-spline` refers to using a B-spline basis with a spline that is not penalized and the syntax `P-spline` refers to using penalized spline with a truncated power basis.

In general, P-spline will produce smoother estimates of coefficient functions than B-spline. Using P-spline frees the user from needing to try multiple models with different numbers of knots. However, truncated power basis functions can be highly correlated (i.e., multicollinear), which may cause numerical instability in computation. B-spline basis functions, on the contrary, are locally independent and hence are numerically stable in computation.

It would be reasonable to ask why random effects are not available for P-splines. The reason is that the usual method for determining the optimal penalty strength in P-splines is computationally nontrivial. It is not very difficult in itself, but when combined with also estimating random effects it could cause convergence difficulties in estimation. Therefore, we chose to limit P-splines to the simpler approach of robust standard errors without random effects.

### 7.4 Technical details about random effects

When random effects are used, Equation 4 for the expected value of observation  $j$  on subject  $i$  is replaced by

$$E(y_{ij}) = \mu_{ij}, \quad g(\mu_{ij}) = \beta_0(t_{ij})x_{0ij} + \beta_1(t_{ij})x_{1ij} + \dots + \beta_p(t_{ij})x_{pij} + a_i + b_it_{ij}, \quad (7)$$

where  $a_i$  and  $b_i$  are the random intercept and slope for the  $i$ th person. The  $a_i$  and  $b_i$  are assumed independent normal with mean zero and with variances  $\sigma_a^2$  and  $\sigma_b^2$ . If only a random intercept and not a random slope are used, then the term  $b_it_{ij}$  is omitted in Equation 7 (essentially assuming  $\sigma_b^2 = 0$  so that everyone has a  $b_i$  of zero).

Equation 7 has an unexpected but important consequence regarding the measurement of time. Usually, for TVEM, the scale on which time is measured does not matter very much; it simply changes the labeling of the x-axis of the coefficient plot. That is, for Equation 4 it doesn't matter much whether  $t_{ij}$  is

counted from 0 to 1, -1 to 1, 1 to 10, or 1950 to 2050. However, for Equation 7 the scaling of time matters much more, because the slope  $b_i$  is a contrast of the current time with time zero. In other words, the variance of the random effects at time  $t$ , from Equation 7, is

$$\text{Var}(a_i + b_it) = \sigma_a^2 + \sigma_b^2 t^2, \quad (8)$$

and time zero now has a special meaning as the point at which this function reaches its minimum. To see why this matters, consider a practical example.

Suppose that a researcher is studying the change in alcohol use in a sample of young people, starting in the calendar year 2005 (when they were all 13 years old) and ending in the calendar year 2015 (when they were all 23 years old). Should the first year of the study be coded as 0 (because it is the beginning of the study), as 13 (because the participants were thirteen years old), or 2005 (because that was the calendar year)? Ordinarily, the %TVEM macro can handle any of these three possibilities, and the researcher can use whatever metric is convenient. However, if a random slope is being used then the meaning of the coefficients in the model changes drastically. If the subject's age is used, then the random effects are estimated by extrapolating back to the subject's birth, years before the study began. This is unfortunate, but maybe not disastrous. However, if the calendar year is used, then the random effects are estimated by extrapolating back to the calendar year zero, many centuries before the participants were born. In this extreme case, the estimation algorithm probably would not converge, and even if it did converge the estimates would not have any interpretable meaning. Thus, in order to use a random slope the investigator will have to define the time variable as time from some event which is meaningful to the study (such as the start of the study, onset of adolescence, beginning of treatment, or whatever is deemed appropriate). This caveat is not specific to random effects TVEM, but arises in multilevel modeling in general, whenever a random slope is being used.

Even after deciding about the beginning point of measurement, the investigator might still have a question about the units or scale of measurement. Should the time variable be defined as weeks, months, years, or decades since the start of the study? Any of these could be meaningful, and none of them are wrong. However, they will lead to different estimates of the variance  $\sigma_b^2$ . This is because, if  $t$  is 12 times larger (a number of months instead of years), then  $\sigma_b^2$  must be 144 times smaller in order to provide the same  $\sigma_b^2 t^2$  in Equation 8. This is not inherently a problem. However, it does mean that a seemingly very small number for the random slope variance (maybe .001) might still represent an important variance component. That is because the absolute size of the number could be smaller or larger if the units of time were different. Fortunately, in the macro output, the estimated variance

components are provided side by side with standard errors for these estimates. The standard error is scaled appropriately for the variance component, and when thinking about the significance of the variance component it would be more reasonable in this case to compare it to its standard error than to look at its absolute size.

## References

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