ASSESSING INDIVIDUAL TREATMENT EFFECTIVENESS IN THE PRESENCE OF STRUCTURALLY MISSING MEASUREMENT OCCASIONS

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Abstract

In this paper, we propose an exploratory method for assessing individual treatment effectiveness over repeated measures, when the number of measurement occasions depends on whether subjects fulfil or not certain conditions. We address this situation with the concept of "structurally missing occasions". Our method involves three main steps. Firstly, we apply several strategies to overcome the problem of different numbers of occasions available for subjects. Secondly, given that data we consider are of "subjects-by-variables-by-occasions" type, we apply a specific multiway data analysis technique, using an iterative schema, for setting up indicators and assessing treatment effectiveness. In this context, we will focus on three-way multidimensional scaling, in that we adopt a subject-oriented approach to analyses. Finally, indicator trends can be studied over the different occasions by means of suitable graphical tools. To demonstrate the potential of our method, we consider a case study, based on data pertaining to personalized treatments for obesity and provided by the International Center for the Assessment of Nutritional Status (ICANS), University of Milan.

1. INTRODUCTION

Over the last years, many conceptual and practical efforts have led to the identification of the prominent dimensions in the evaluation of healthcare services. Thanks to the debate that has evolved and the many resultant scientific contributions, it is now widely recognized that quality assessment must necessarily proceed through the evaluation of three dimensions; efficiency, effectiveness and customer (patient) satisfaction. While efficiency is mostly concerned with economic, financial and resource-related aspects of healthcare services, effectiveness and patient satisfaction involve the final user more explicitly. In particular, effectiveness is defined as the ability to provide treatments to patients, improve health outcomes and modify patients' state of health (Donabedian, 1988). Strictly connected with this is the concept of "relative effectiveness", i.e. the effect of hospital care on patients, used to compare different healthcare institutions in terms of healthcare outcomes (Goldstein and Spiegelhalter, 1996). As widely argued, relative effectiveness needs to be adjusted for patient-specific and hospital-specific variables, in that numerous factors concerning patients, such as clinical, social-demographic and economic factors (patients' case mix), might be associated with a wide range of hospital characteristics (Vittadini, 2006).

The majority of statistical contributions made to effectiveness evaluation have tackled the problem by relying on modelling. Multilevel models have been undoubtedly the most popular approach for appraising the relative effectiveness of healthcare structures. The reasons are numerous: Hierarchical data structures are typical of healthcare systems; both patient and healthcare service characteristics can be taken into account; hospitals generally serve very different numbers of patients; and the distributional hypotheses regarding the random part of the model may need a more complex specification than usual. All these matters are extensively discussed in papers by Vittadini and colleagues (Vittadini, Sanarico and Rossi, 2003; Vittadini, Carabalona and Rossi, 2004), that thoroughly review the main aspects involved in the evaluation process (e.g., healthcare outcome definition, risk adjustment problem) along with recent methodological developments concerning the use of multilevel models in the evaluation of healthcare service effectiveness.

Nonetheless, there are fields of application in which the use of statistical models, including multilevel models, could be inappropriate, in that the type of study approach, the nature of the available data, and, last but not the least, the object of evaluation may not lend themselves to such a process. It may be necessary to undertake a study with exploratory rather than confirmative objectives. Initially there may be no clear, a priori conjectures; the study could serve rather to disclose particular, hidden patterns in the data. Furthermore, there are cases where data could present a range of specific features, often concomitant, such as small sets of subjects, the presence of non-normal data and of multivariate outliers, making it thus impractical to perform analyses with statistical-probabilistic models. Finally, the evaluation object may regard treatment effectiveness by expressly addressing attention to individuals, in which case the analyses should be more properly carried out in a subject-oriented perspective than in a modelling approach. For instance, the main concern could be assessing the effectiveness of personalized, not shareable, individual treatments in improving each subject's health state over a period of time. In that case, the main interest may be monitoring the evolution in the single subject's condition by also taking into account others' improvements or declines. All the above considerations suggest the importance of assessing the effectiveness of individual treatments by resorting to data analysis methods, which, as is well-known, allow for exploratory and subject-oriented analyses, and generally do not adopt restrictive, a priori assumptions.

Typical contexts where all of the above elements can arise are clinical settings, where personalized treatments concern cures for specific pathologies. With regard to this, here we will specifically focus on the problem of assessing treatments of obesity, in light of methodological purposes and the widespread, increasing attention to this issue. Indeed, although obesity has been widely recognized as a major predisposing factor for the development of type 2 diabetes mellitus, hypertension and cardiovascular disease (Sowers, 2003), the incidence of obesity continues to dramatically increase (e.g., see the web site of the Centers for Disease Control and Prevention in Atlanta, http://www.cdc.gov). Beyond describing the magnitude of this phenomenon, the primary objective of research should be to assess the impact of obesity treatment along with guidelines for its prevention, especially in purely clinical contexts where monitoring subjects' state changes over treatment periods turns out to be of essential importance.

Given that the assessment of certain specific individual pathological conditions is generally recognized over time, over repeated measurement occasions, it is crucial to adopt statistical approaches to analyses that allow for the role of time as well as the aforementioned elements, i.e. the type of study approach, nature of the data, and evaluation goal. From a statistical point of view, data containing a time dimension, in addition to subjects and variables, are defined as *three-way* and are organized accordingly in a data box. There are two main strategies for handling such a structure in a data analysis framework: 1) First, one of the three ways is collapsed by flattening the data box consistent with analysis purposes, e.g. monitoring changes in subjects' condition over time. Several optimal scaling techniques can then be applied to the flattened matrix (Bijleveld *et al.*, 1998, Sect. 2.3); 2) the data box can be directly analyzed by applying the so-called multiway data analysis techniques (Kroonenberg, 2008), of which three-way multidimensional scaling is a prominent example (Cox and Cox, 2001; Borg and Groenen, 2005).

In this paper we utilize the latter approach and propose an exploratory method to evaluate individual treatment effectiveness over repeated occasions, each viewed as a different source of information or, equivalently, a different point of data collection. Our primary concern will be the specific situation in which the number of information sources differs across subjects, in that it depends on whether individuals attain or not a previously fixed goal. We will refer to such situations as *structurally missing occasions*. To overcome the problem of different numbers of occasions over subjects, several strategies of analyses will be introduced. To our knowledge, this issue has not been yet systematically tackled in the literature, since most contributions in this area are devoted to imputation techniques (see, e.g., Kroonenberg, 2008, Chap. 7). Next, individual treatment effectiveness will be assessed through monitoring the trends of indicators set up with three-way multidimensional scaling, which is our approach here to subject-oriented type. Such an evaluation will be conducted in purely exploratory terms, by resorting primarily to graphs in which indicator trends are plotted by means of trajectories. A conceptually similar approach to evaluation, albeit based on a completely different statistical methodology and related to patient satisfaction, can be found in Solaro and Pagani (2007).

The paper is structured as follows. Section 2 briefly recalls the main methodological results about three-way multidimensional scaling methods. Section 3 contains the main core of our proposal, where the concept of "structurally missing occasions" will be introduced and several strategies will be presented for carrying out analyses in their presence. Section 4 is dedicated to a case study concerning the effectiveness assessment of personalized treatments for obesity, and is carried out with data from the International Center for the Assessment of Nutritional Status (ICANS), University of Milan. Finally, in Section 5 we report our conclusions.

2. SOME BRIEF NOTES ON THREE-WAY MULTIDIMENSIONAL SCALING TECHNIQUES

Multidimensional scaling (MDS) methods are a large family of multivariate analysis techniques that attempt to represent proximity data, typically dissimilarity or preference matrices, into a low-dimensional Euclidean space.

Depending on proximity measurement level, MDS models derived from the various methods are separated into metric MDS (e.g. Torgerson's MDS, least-squares MDS), which assumes at least interval-level proximities, and non-metric MDS (e.g. Kruskal's MDS), in which proximities are treated at ordinal level. The literature on MDS models is extremely rich: Complete references can be found in recent monographs by Cox and Cox (2001) and Borg and Groenen (2005).

One of the standard applications of MDS involves so-called two-way data, namely data that can be organized in a $n \times p$ "subjects-by-variables" matrix, here denoted with $\mathbf{Y}$. As known, in a subject-oriented analysis a specific dissimilarity measure, e.g. a distance from Minkowski's family, can be applied to obtain an $n \times n$ input dissimilarity matrix Δ, which is symmetric, non-negative and hollow (i.e. with zero diagonal elements). A suitable MDS model can be then applied according to the nature of dissimilarities in Δ.

In addition to the abovementioned well-known case, three-way data also can be handled in a MDS framework. These data typically arise when they are collected repeatedly on K occasions, for instance when p measurements are replicated K times on n subjects. In this case, data can be organized in a $n \times p \times K$ "subjects-by-variables-by-occasions" data box, which comprises the matrix $\mathbf{Y}_k$ as generic two-dimensional slice and where, in general, the index k stands for a different source of information, ($k = 1,\ldots,K$). Generalizing the above issue of two-way to three-way data, a number K of $n \times n$ dissimilarity matrices Δ_k can be computed for each $\mathbf{Y}_k$, thus giving rise to a sequence of K input matrices for the MDS analysis. These latter matrices are also called "three-way two-mode dissimilarities", given that they can be viewed as resulting from a three-dimensional Cartesian product $K \times n \times n$ of the two modes 'occasion' and 'subject' (Borg and Groenen, 2005, Sect. 3.7).

Three-way MDS models are then specific techniques developed for the analysis of three-way two-mode dissimilarities. Usually, they are classified into two main types. A first type falls within the context of Procrustes analysis and is known as Generalized Procrustean Analysis (GPA). The basic idea of GPA is to transform simultaneously a number K of $n \times q$ MDS configurations $\mathbf{X}_k$, each obtained independently from one of K dissimilarity matrices, in order to match them to each other as closely as possible (Borg and Groenen, 2005, Chap. 21).

A second approach, which we consider throughout this paper, is concerned with the simultaneous setting up of K occasion configurations of points along with a common space configuration by working directly on the set of K dissimilarity matrices[1]. Formally, let Δ_k be a dissimilarity matrix with generic element δ_{ijk}, ($i, j=1,\ldots,n$; $k=1,\ldots,K$). The problem of jointly determining K occasion configurations $\mathbf{X}_1,\ldots, \mathbf{X}_K$ and a common $n \times q$ configuration $\mathbf{G}$ can be solved within the framework of loss-function-minimization by employing the raw stress:

$$\sigma_r(\mathbf{X}_1,\ldots,\mathbf{X}_K) = \sum\nolimits_{k=1}^{K} \sum\nolimits_{i=1}^{n} \sum\nolimits_{j=i+1}^{n} w_{ijk} (\delta_{ijk} - d_{ij}(\mathbf{X}_k))^2 , \tag{1}$$

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[1] *Usually, in classical contributions on three-way MDS the terminology "individual configuration" is found instead of "occasion configuration". The reason lies in pioneering studies on three-way MDS, where subjects represented the different sources of information and dissimilarity matrices were related to sets of items or stimuli. Given that our sources of information are represented here by different data collection occasions, in this context we prefer using the expression "occasion configuration" to avoid possible misunderstandings.*

which represents the weighted sum of squared errors between the dissimilarities δ_{ijk} and the Euclidean distances $d_{ij}(\mathbf{X}_k)$ of subjects i and j computed with the coordinates in the rows of $\mathbf{X}_k$. In formula (1), w_{ijk} expresses the (non-negative) weight assigned to the couple i and j at the k-th occasion, $(i, j=1,\ldots,n; k=1,\ldots,K)$. Weights are usually used in formula (1) to comprise possible missing value patterns, thus for instance assigning $w_{ijk}= 0$ if the dissimilarity δ_{ijk} is missing and $w_{ijk}= 1$ otherwise.

Commandeur and Heiser (1993) explain in detail the algebra underlying the minimization of (1), which constitutes the theoretical framework of SMACOF (Scaling by MAjorizing a Complicated Function). This essence of this theory was introduced by de Leeuw and Heiser (1980) and has been recently extended by de Leeuw and Mair (2009) to a wider class of MDS models. Roughly speaking, the minimization of (1) being mathematically quite intractable, the problem is solved with the iterative majorization (IM) method, which proceeds through the minimization of a "surrogate" function that must be both majorizing for (1) and simpler to manage than (1). Then, assuming that the matrices $\mathbf{W}_k$ of weights w_{ijk} are irreducible (i.e., they cannot be reduced to block-diagonal matrices), the minimization of (1) consists of K independent minimization problems, each solved through the IM method. This procedure for MDS has been implemented in several popular statistical software packages, such as SPSS, with the PROXSCAL algorithm, and the R environment (R Development Core Team, 2009) with the 'smacof' package (de Leeuw and Mair, 2008).

In SMACOF theory, dimension extraction revolves around two main approaches, by which both the occasion and common configurations can be recovered. The first approach leads to *unconstrained* (or unrestricted) solutions for the occasion configurations $\mathbf{X}_k$, $(k=1,\ldots,K)$. They derive from a common configuration $\mathbf{G}$ after it has been set up appropriately over the K sources. For instance, in the 'smacof' package the default solution for $\mathbf{G}$ is derived as Torgerson's MDS of the dissimilarities Δ_k after they have been summed over the K sources. Next, the occasion configurations $\mathbf{X}_k$, initially set equal to $\mathbf{G}$, are iteratively determined through the IM method by means of the so-called 'update formula', represented, at the first iteration, by the Guttman transform of $\mathbf{G}$ and then, at the subsequent iterations, by the Guttman transform of the corresponding occasion configurations determined at the immediately previous iteration. The definition of the Guttman transform is not trivial, we therefore refer the interested reader to papers by de Leeuw and Heiser (1980), Commandeur and Heiser (1993) and the monograph by Borg and Groenen (2005, Chaps. 8, 10, 22).

The above procedure is repeated until either the difference between two consecutive values on raw stress (1) falls under a fixed, small threshold or the maximum number of iterations has been reached.

The second approach allows *constrained* solutions for the $\mathbf{X}_k$s to be derived by introducing several specific restrictions. Usually, these are linear of the type:

$$\mathbf{X}_k = \mathbf{G}\mathbf{C}_k\,, \tag{2}$$

where $\mathbf{C}_k$ is an order q square matrix of dimension weights. Depending on the form of $\mathbf{C}_k$, different MDS models can result: The identity model is obtained by constraining $\mathbf{C}_k$ to be an identity matrix, thus requiring each $\mathbf{X}_k$ to be equal to the common configuration $\mathbf{G}$. Again, if $\mathbf{C}_k$ is a diagonal matrix the INDSCAL model (INdividual Differences SCALing) is obtained, in the form introduced by Carroll and Chang (1970) as a dimension-weighting model. If $\mathbf{C}_k$ is a generic full rank matrix, the IDIOSCAL model (IDIOsyncratic SCALing) is derived, thus allowing each $\mathbf{X}_k$ to have a different orientation with respect to the common space. Once again, the constrained solutions are achieved by minimizing raw stress (1) with the IM method, but this time under the restriction (2). It has been proven that such a minimization can be carried out in two consecutive stages, the first producing the unconstrained solution and the second adjusting it to meet the constraints (2) (Commandeur and Heiser, 1993; Borg and Groenen, 2005; de Leeuw and Mair, 2008a).

The above constrained approach can be considered within the set of techniques developed for imposing external constrains on MDS configurations. Borg and Groenen (2005, Chap. 10) ascribe this approach to the confirmatory MDS, through which additional information can be comprised in MDS analyses by requiring that certain properties on point coordinates must be satisfied.

A further issue concerning three-way MDS is the normalization of observed dissimilarities, which can lead to, respectively, unconditional or matrix-conditional approaches (Commandeur and Heiser, 1993; Borg and Groenen, 2005, Sect. 22.5). Roughly, by the unconditional approach observed dissimilarities can be processed as they are, thus enabling comparisons of configurations over different occasions. In contrast, with the conditional approach, observed dissimilarities are opportunely normalized conditionally to the occasion, and consequently do not enable comparisons among different occasions. For a discussion of the advantages and limitations of the two approaches, see Borg and Groenen (2005). In the present version of ‘smacof’ package, both the observed dissimilarities and the reproduced Euclidean distances are suitably transformed, but the approach remains unconditional (see Commandeur and Heiser, 1993, Sect. 9).

Once MDS configurations have been determined, goodness-of-fit measures have to be provided in order to assess how well MDS solutions represent the input data. Given that three-way MDS, as treated to date, is based on the minimization of the raw stress (1), a natural fit-measure is the so-called normalized metric stress. In 'smacof' package, when unconstrained solutions are concerned, this is given by the ratio of raw stress (1), computed with transformed observed dissimilarities and distances, and the total number of non-redundant pairwise comparisons between subjects (de Leeuw and Mair, 2009). On the other hand, in the case of constrained solutions, in addition to the lack of fit due to the chosen MDS model, a lack of confirmation fit arises due to the presence of constraints. This part is appraised by means of the normalized constrained stress.

Finally, it is worth noting that de Leeuw and Mair (2009) call the unconstrained MDS model "INDSCAL with identity configuration weight matrix", thus leaving room for possible misunderstandings. We thus feel it advisable to emphasize that this "unconstrained INDSCAL" does not coincide with the identity model. It simply means the unconstrained solution, achieved without imposing explicit links between the occasion and common configurations.

3. STRUCTURALLY AND PSEUDO-STRUCTURALLY MISSING OCCASIONS: OUR STRATEGIES FOR ANALYSIS

In Sect. 2 we have seen that missing values, if present, can be naturally handled in the three-way stress MDS framework by opportunely specifying the subject weights w_{ijk} in formula (1). Alternatively, depending on the nature of the data, one of the numerous methods for imputing missing data can be applied in order to recover the non-observed values in data matrices $\mathbf{Y}_k$ and then compute missing dissimilarities. For a complete reference on missing data imputation in multivariate analysis see the monograph by Schafer (1997), while Kroonenberg (2008, Chap. 7) provides a review of the main contributions on this issue in cases of multiway data.

There are, however, situations in which handling missing data according to one of the above approaches may lead to impractical solutions or may not even be possible. This is particularly the case when, in a three-way pattern, where the K sources represent the total number of data collection occasions (e.g. as in repeated measurements), a number m_l of occasions, with $m_l > k$, $k = 1,\ldots,K-1$, is *structurally* missing for any subset S_{m_l} of subjects, $l = 1,\ldots,L$. By "structurally missing occasion", we mean the situation in which subjects cannot expose themselves to the same number of data collections due to the intrinsic nature of the phenomenon under study, in that going on to further collections could mean that one or more specific goals have not as yet been attained at that moment. In principle, this definition should not comprise subjects' "voluntary" drop-outs, since their leaving the study would not be connected with the nature of the phenomenon, but with their status towards it. Be that as it may, since this issue is not our primary concern here, we will not treat it thoroughly in the present paper, and hold more accurate reflections for future initiatives.

The above idea is essentially grounded in the concept of the "monotone missingness pattern" (Schafer, 1997; Schafer and Graham, 2002), which we rephrase for structurally missing occasions as follows. Whenever a value y_{irk} of subject i on variable Y_r at the k-th occasion is missing, the element y_{irm} is missing as well, for all $m > k$, due to the fulfilment of a set of conditions that subject i has realized at the previous $(k-1)$-th occasion.

The "structurally missing occasion" concept can also be extended to that of "pseudo-structurally missing occasion". In this respect, we refer to situations in which subjects are not exposed to the same number of data collections for two possibly concomitant reasons: 1) The nature of the phenomenon under study, in the abovementioned sense; 2) The instant in which (statistical) analyses are performed. As for the latter, if analyses are carried out before completing the study, at that time certain subjects might not yet have attained a formerly specified goal. Therefore, the lack of information for them cannot assume the form of a structural absence, but rather of a pseudo-structural absence.

Returning now to formula (1), monotone structurally (or pseudo-structurally) missing occasions could in principle be included therein by an opportune specification of weight matrices $\mathbf{W}_k$, that is, by assigning zero weight to subjects in subsets S_{m_l}, being those not going on to future occasions $m_l > k$, (k =1,…,K – 1, l = 1,…,L). However, this solution turns out to be mathematically intractable, in that the resulting rank reduction of the $\mathbf{W}_k$s also implies a rank reduction of the matrices involved in the computation of the Guttman transform, thus giving rise to singular equation systems.

These considerations demand the development of several convenient strategies for statistical analyses when data contain (pseudo-) structurally missing occasions. In particular, if the objective is setting up indicators over K occasions, it could help to consider the following proposals to overcome the problem of jointly analyzing data over occasions that differ in number for the subjects involved.

Hence, let $\mathbf{Y}_1,\dots,\mathbf{Y}_K$ be a sequence of K data matrices $\mathbf{Y}_k$ of dimensions $(n_k \times p)$, with $n_1 = n$ being the subject set size at the first occasion and $n_k \leq n_{k-1} \leq n$ the subject set sizes at subsequent occasions, where the strict inequality holds for at least one k, (k = 2,…,K). Then, we propose to augment each matrix $\mathbf{Y}_k$ by assigning suitable values to the $(n - n_k)$ subjects that are absent at the k-th occasion.

This row augmentation can be conducted by carrying forward the most recent observations available on these subjects. This strategy, which we call "LOCF-row augmentation" (LOCF, Last Observation Carried Forward), is drawn from the well-known idea of LOCF imputation of missing data, which is typical of most clinical settings, (Molenberghs and Kenward, 2007).

Formally, if at k-th occasion a number $(n-n_k)$ of subjects are not present, we have to "complete" the matrix $\mathbf{Y}_k$ so as to obtain the following augmented matrix $\mathbf{Y}_k^*$:

$$\mathbf{Y}_k^* = \begin{bmatrix} \mathbf{Y}_k \\ \cdots \\ \mathbf{Y}_{<k} \end{bmatrix}, \tag{3}$$

where $\mathbf{Y}_{<k}$ is a simplified notation to express the $(n-n_k)\times p$ sub-matrix containing values carried forward from each subject's last occasion available. Accordingly, the dissimilarity matrix computed with (3) takes the form:

$$\boldsymbol{\Delta}_k^{aug} = \begin{bmatrix} \boldsymbol{\Delta}_k & \boldsymbol{\Delta}_{k,<k} \\ \boldsymbol{\Delta}_{k,<k} & \boldsymbol{\Delta}_{<k} \end{bmatrix}, \tag{4}$$

where $\boldsymbol{\Delta}_{<k}$ is the square dissimilarity sub-matrix of subjects absent at the k-th occasion and $\boldsymbol{\Delta}_{k,<k}$ is the rectangular sub-matrix with the dissimilarities between absent subjects with LOCF values and subjects present at k-th occasion.

Given that in general observed variables have to be standardized before proceeding to joint analyses, the LOCF-row augmentation strategy can take two possible forms:

(a) FIrst Augment the Matrix, then Standardize (FIAMS strategy): After having augmented matrices $\mathbf{Y}_k$ as in (3), the resulting matrix $\mathbf{Y}_k^*$ is standardized to obtain matrix $\mathbf{Z}_k^*$:

$$\mathbf{Y}_k^* \quad \Rightarrow \quad \mathbf{Z}_k^* = \begin{bmatrix} \tilde{\mathbf{Z}}_k \\ \cdots \\ \tilde{\mathbf{Z}}_{<k} \end{bmatrix}, \tag{5}$$

which is column-centred, as usual. The symbol "~" over the two **Z**s denotes that standardization is carried out on them using the entire set of n values at the same time;

(b) FIrst Standardize, then Augment the Matrix (FISAM strategy): The matrix $\mathbf{Y}_k$ is firstly standardized on the n_k subjects to obtain the standardized matrix $\mathbf{Z}_k$. This latter is then completed by adding sub-matrix $\breve{\mathbf{Z}}_{<k}$ for the remaining $(n-n_k)$ subjects, which includes standardized scores carried forward from each subject's last available standardization. The resulting matrix $\mathbf{Z}_k^{**}$ is then given by:

$$\mathbf{Y}_k \quad \Rightarrow \quad \mathbf{Z}_k \quad \Rightarrow \quad \mathbf{Z}_k^{**} = \begin{bmatrix} \mathbf{Z}_k \\ \cdots \\ \breve{\mathbf{Z}}_{<k} \end{bmatrix}, \tag{6}$$

where in (6) $\mathbf{Z}_k$ is column-centred, while in general the sub-matrix $\breve{\mathbf{Z}}_{<k}$, being formed with scores coming from previous standardization, cannot share this property.

As stated, the two strategies FIAMS and FISAM are conceived to complete slices $\mathbf{Y}_k$ from a three-dimensional data box in the presence of (pseudo-) structurally missing occasions when the specific objective is to study the evolution of a phenomenon over occasions. In our view, these two strategies should help highlight underlying-data variation patterns differently. The FIAMS strategy (5) is a sort of *unconditional* analysis: At each k-th occasion, LOCF values for the $(n-n_k)$ subjects and observed values of the others n_k subjects are put on the same level, in that variables are transformed on all subjects to have zero-mean and unit-variance. In other words, LOCF subjects' history is conveyed to the k-th occasion and treated as if it were actually the "present history" for these subjects. Their situation renews "today", while the situation of the observed subjects is confounded with this renewal.

On the other hand, the FISAM strategy (6) is a sort of *conditional-to-past* analysis, in that LOCF subjects are bearers of information that are carried forward to the k-th occasion maintaining the same contextualization as received in the most recent available past. In other words, LOCF subjects' information always pertain their most recent history, and is conveyed in this form to the future. Their situation is bound to the past, while that of the observed subjects is entirely delineated within their present, exclusive sphere.

As regards the informative content, we argue that FIAMS strategy is more expressly adapted to capturing improvement or decline in the individual evolution of a phenomenon in a whole (or absolute) sense, while FISAM strategy is mostly involved with detecting variations in a conditional (or relative) sense, placing more emphasis on changes from one occasion to another.

From a practical point of view, exploiting the full potentiality of these strategies would require introducing several specific analysis tools for monitoring the evolution of some quantities or statistics of interest over the K sources. In this context, we propose to apply three-way stress MDS starting from the K augmented matrices, obtained as in (3), (5) or (6), according to the iterative hierarchical procedure outlined in Table 1. The main steps are the following. Three-way MDS is applied as many times as there are occasions. In other terms, the number of MDS procedure repetitions is equal to the number of occasions. Then, the first application is made using matrix $\mathbf{Y}_1$ (the first slice in data box), which requires no augmentation, as it comprises the information about all the n subjects. It is then straightforward to derive from $\mathbf{Y}_1$ the dissimilarity matrix Δ_1, on which a standard two-way MDS, also computed with SMACOF theory (Borg and Groenen, 2005; de Leeuw and Mair, 2008), is applied to give the occasion configuration matrix $\mathbf{X}_1^{[1]}$, where the superscript "[1]" stands for "1st repetition," and the subscript for "1st occasion". As for the second repetition, without loss of generality we can assume that all the n subjects get to the second occasion. Once again, as matrix $\mathbf{Y}_2$ requires no augmentation, the dissimilarity matrix Δ_2 can be computed as usual. This time, however, three-way MDS have to be applied on Δ_1 and Δ_2, thus producing two occasion configurations, $\mathbf{X}_1^{[2]}$ and $\mathbf{X}_2^{[2]}$, and a common configuration $\mathbf{G}^{[2]}$. At the third repetition, we assume that only a number $n_3 < n$ of subjects proceeds to the third occasion. Matrix $\mathbf{Y}_3$ thus needs to be augmented as in (3), and if standardization is involved, FIAMS (5) or FISAM (6) strategies have to be employed. On these bases, the dissimilarity matrix $\boldsymbol{\Delta}_3^{aug}$, which can be seen partitioned as in (4), is computed, and three-way MDS is applied on the sequence: Δ_1, Δ_2 and $\boldsymbol{\Delta}_3^{aug}$ to give three occasion configurations, $\mathbf{X}_1^{[3]}$, $\mathbf{X}_2^{[3]}$ and $\mathbf{X}_3^{[3]}$, and a common configuration $\mathbf{G}^{[3]}$. This same procedure is then iterated up to the K-th repetition, namely until the last K-th occasion is considered.

The iterative application of three-way MDS thus gives rise to sequences of occasion configuration $\mathbf{X}_m^{[k]}$, ($m=1,\ldots,k;\ k=1,\ldots,K$) which in a more convenient manner can be viewed as organized according to a triangular structure (Table 1, last column). In particular, there are: K solutions for the occasion configuration relative to the first occasion; $K-1$ solutions concerning the second occasion, and so on, till the one single solution relative to the last K-th occasion. K solutions for the common configuration $\mathbf{G}$ can also be counted, if the unique occasion configuration at first repetition is viewed also as a common configuration.

Tab. 1: Iterative application of three-way MDS with augmented data matrices.

Nr. rep.	*Subset size at k-th rep.*	*Data matrices*		*Dissimilarity matrices*	*Individual and common configurations*
[1]	$\xrightarrow{n=n_1}$	$\mathbf{Y}_1$	$\longrightarrow$	Δ_1	$\to \mathbf{X}_1^{[1]}\left(\equiv \mathbf{G}^{[1]}\right)$
[2]	$\xrightarrow{n=n_1=n_2}$	$\mathbf{Y}_1,\mathbf{Y}_2$	$\longrightarrow$	Δ_1,Δ_2	$\to \mathbf{X}_1^{[2]},\mathbf{X}_2^{[2]},\mathbf{G}^{[2]}$
[3]	$\xrightarrow{n<n_2=n}$	$\mathbf{Y}_1,\mathbf{Y}_2,\mathbf{Y}_3$	$\xrightarrow[\text{FIAMS, FISAM}]{\text{strategy}}$	$\Delta_1,\Delta_2,\Delta_3^{aug}$	$\to \mathbf{X}_1^{[3]},\mathbf{X}_2^{[3]},\mathbf{X}_3^{[3]},\mathbf{G}^{[3]}$
…	…	…	…	…	…
$[k]$	$\xrightarrow{n_k\le n_{k-1}<n}$	$\mathbf{Y}_1,\mathbf{Y}_2,\ldots,\mathbf{Y}_k$	$\xrightarrow[\text{FIAMS, FISAM}]{\text{strategy}}$	$\Delta_1,\Delta_2,\ldots,\Delta_k^{aug}$	$\to \mathbf{X}_1^{[k]},\mathbf{X}_2^{[k]},\mathbf{X}_k^{[k]},\mathbf{G}^{[k]}$
…	…	…	…	…	…
$[K]$	$\xrightarrow{n_K\le n_{K-1}<n}$	$\mathbf{Y}_1,\mathbf{Y}_2,\ldots,\mathbf{Y}_K$	$\xrightarrow[\text{FIAMS, FISAM}]{\text{strategy}}$	$\Delta_1,\Delta_2,\ldots,\Delta_K^{aug}$	$\to \mathbf{X}_1^{[K]},\mathbf{X}_2^{[K]},\mathbf{X}_K^{[K]},\mathbf{G}^{[K]}$

Now, consider the generic m-th occasion. Its occasion configurations, obtained over the K repetitions, are bearers of a different informative content, in that they are formed each time by jointly taking into account a different number of occasions. For instance, the configuration at the first occasion can be studied when it is formed alone or, alternatively, by taking into account more than one source of information, e.g. all the K sources.

In this respect, the last column of Table 1 suggests three possible readings of the results achieved for the occasion configurations:

(1) Horizontal reading: by keeping a specific repetition fixed, the occasion configurations can be studied as the occasions vary. While this would be the usual way to interpret three-way analysis results, the novelty of our method consists of generating a number K of configuration sequences which then become available for analyses;

(2) Vertical reading: by keeping a specific occasion fixed, the occasion configurations can be studied as the procedure repetitions vary. This is an original approach to analyses. What can be best verified in this way is the stability of dimensions over repetitions;

(3) Diagonal reading: a range of diagonals can be seen in the triangular structure. Perhaps the most interesting reading can be found on the principal diagonal, the one with elements $\mathbf{X}_k^{[k]}$, ($k=1,\ldots,K$). This reading should offer more thorough insight into the evolution of the extracted dimensions.

Finally, as they are actually very demanding, the three kinds of readings would require the creation of suitable tools for facilitating interpretations. We propose that it is advantageous to rely on graphic tools, with the main objectives of monitoring the dimensions of the various configurations over, respectively, the occasions (horizontal reading), the repetitions of the procedure (vertical reading), or both (diagonal reading). The graphic model proposed here entails the construction of trajectories, through which scores of a specific dimension can be represented for each subject as, respectively, the occasions, the procedure repetitions, or both, vary. Finally, the analyses of indicator trends can help determine both the quality and the magnitude of changes in the subject's state when considered relative to others.

4. A CASE STUDY: ICANS DATASET

Throughout this section, we apply the strategies of analyses outlined in Sect. 3 to data provided from the International Center for the Assessment of Nutritional Status (ICANS), Department of Food Science, Technology and Microbiology, Faculty of Agriculture, University of Milan. This Center is primarily engaged in assessing health and nutritional status of both healthy and chronic-degenerative-disease affected people. Among their various activities, expert physicians are concerned with diagnoses of various nutritional pathologies, such as alimentary behaviour disorders or obesity, which they treat with specific therapies, including pharmacological cures and personalized diets.

Hence, with the objective of assessing the effectiveness of treatments for obesity, 396 subjects among those cared for at the Center in the period 2003-2006 are considered. These subjects were included in our analyses because they shared the following features: a) they underwent more than one medical examination; b) they did not abandon treatments, so that no drop-out occurred. The variables we considered, fifteen in all, regard: age (years), weight (Kg.), height (m.), along with several metabolic and cardiovascular parameters. Metabolic aspects are represented by: Body Mass Index (BMI, i.e. body weight divided by squared height in meters), HDL (High Density Lipoprotein) and LDL (Low Density Lipoprotein) cholesterol (mg/dl), triglyceride (mg/dl), waist circumference (cm.). As regards cardiovascular parameters, we have systolic and diastolic arterial pressure (mmHg), and glycaemia (mg/dl). Moreover, certain obesity-related variables regarding the measurements of skin-folds are also considered, i.e., respectively, bicipital, tricipital, sub-scapular and supra-iliac skin-folds (mm.).

As a consequence of certain examinations, missing values have arisen on a subset of these variables, especially on glycaemia and skin-fold measurements. We have overcome this problem by applying a multiple imputation method developed expressly for data of time-series-cross-sectional type. In the R environment, such a method is implemented in the library 'Amelia' (Honaker *et al.*, 2009). Nevertheless, since the standard problem of imputing missing data is not our primary concern, we have omitted all the details pertaining to it. For a complete reference on missing data imputation in the specific context of clinical studies, see the monograph by Molenberghs and Kenward (2007), in addition to Schafer (1997), as already mentioned.

As we have stated, a different number of medical examinations characterizes these subjects (Figure 1). All of them underwent at least two medical visits, while the percentages of subjects that presented themselves at the successive visits are given, respectively, by: 81.1% for three visits, 65.4% for four, 49% for five, 31.8% for six, 25% for seven, and so on to the unique subject who underwent twenty-four visits.

According to clinical practice, one of the simplest ways to assess the effectiveness of individual treatments for obesity is based on the weight loss percentage computed on the initial weight. Physicians at ICANS considered a treatment effective whenever a subject loses more than 10% of his initial weight. Although this represents a simple-to-manage measure of the treatment outcome, it is better to discriminate among higher magnitude orders of weight loss. Accordingly, the following categories on the 'outcome' variable will be referred to: weight loss strictly inferior to 10% (the treatment has not yet succeeded, category 0); weight loss greater than 10% and strictly less than 15% (category 1); weight loss greater than 15% and strictly less than 20% (category 2); weight loss greater than 20% (category 3). Labels 1, 2 and 3 denote therefore positive outcome categories. In Figure 2 the distribution of the weight loss percentage is plotted within the four outcome categories, which are formed, respectively, by the 68.7% of subjects (category 0), the 16.9% (category 1), the 9.8% (category 2) and the 4.6% (category 3). Therefore, from a clinical point of view the effectiveness of supplied treatments could be summed up as follows: up to December 2006 personalized treatments for obesity have been effective in 31.3% of cases.

A more thorough insight is suggested by Figure 3, where subjects are classified according to outcome category and number of medical examinations. As clearly expected, most subjects who have not attained the goal have undergone a small number of visits. More interesting is the observation that certain subjects of categories 1-3 have attained the goal in just two to four visits, while a number of subjects in category 0 have not succeeded in losing weight even in ten to fourteen visits.

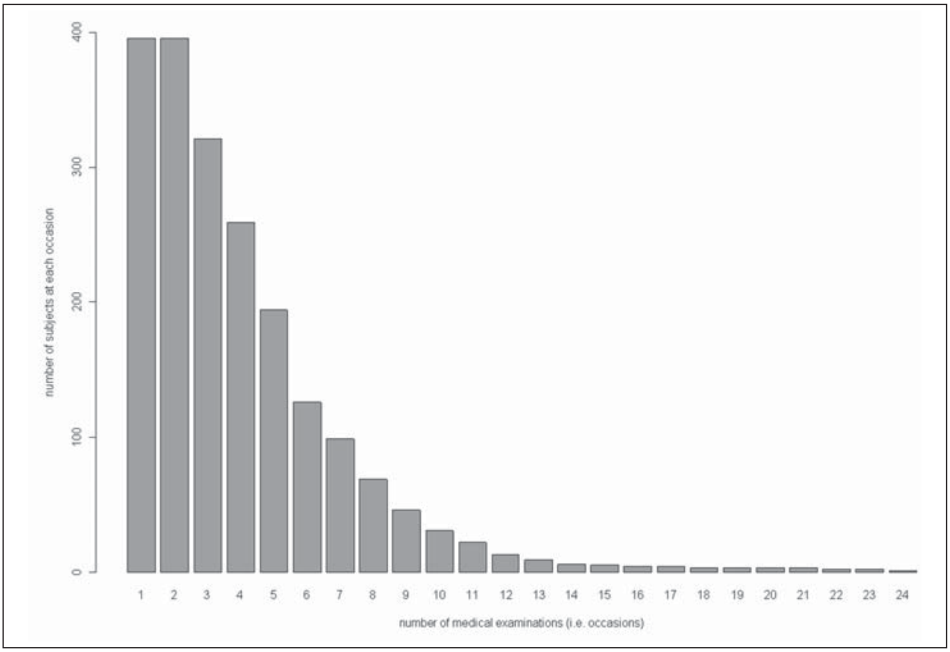

Fig. 1: Number of subjects for each occasion.

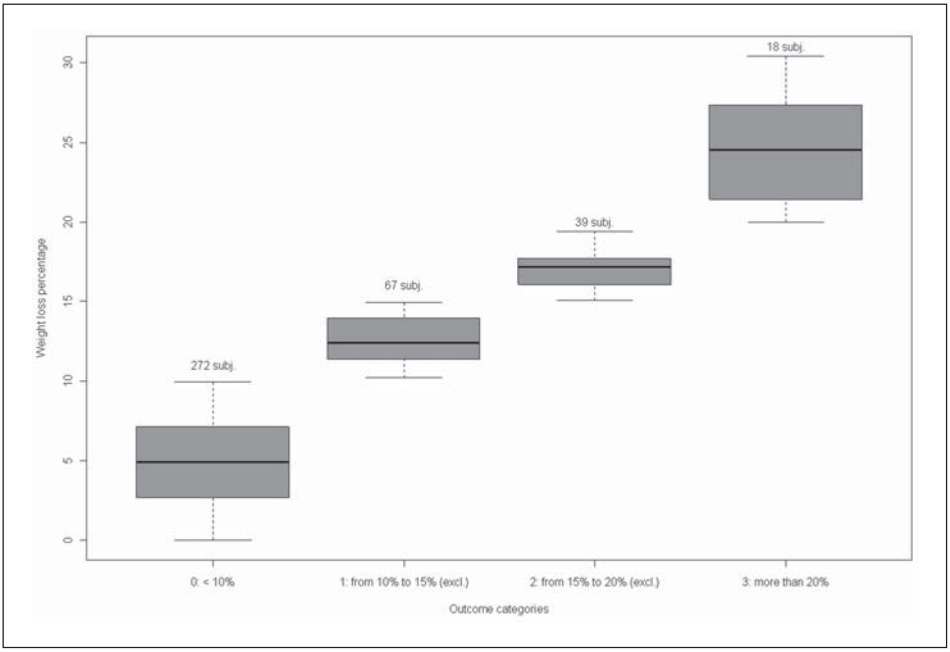

Fig. 2: Distribution of weight-loss-percentage within the four outcome categories.

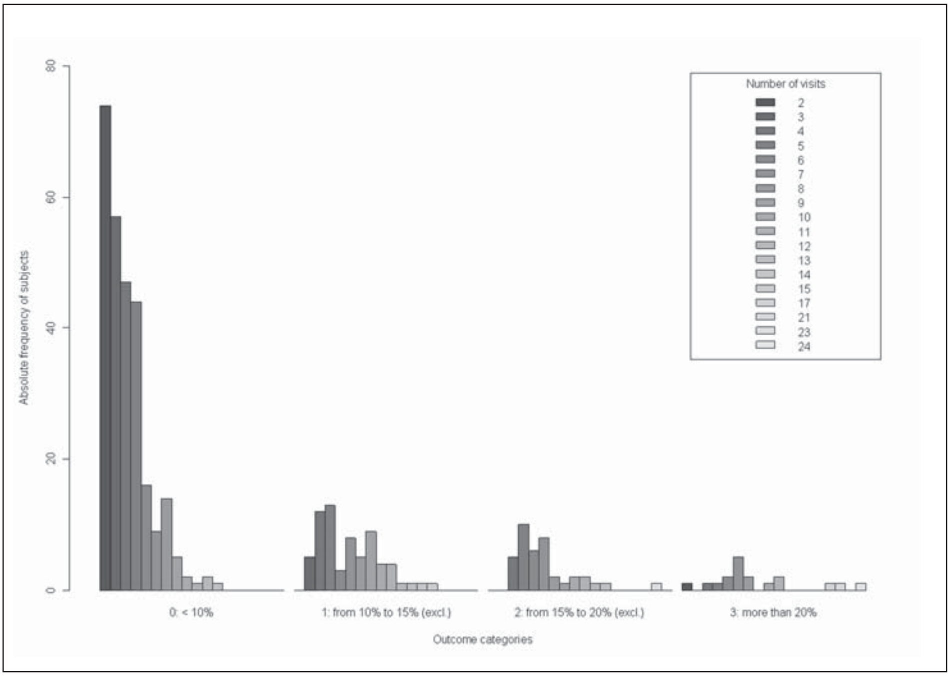

Fig. 3: Subjects classified into number of medical examinations within outcome categories.

While weight loss percentage is a measure that is easy to obtain and interpret, basing the whole evaluation of treatment effectiveness exclusively on it could lead to bias conclusions. Such a measure in fact suffers from the typical limitations that are intrinsic to all univariate measures, not taking into account possible relationships with other biological parameters, for instance the complex system of interrelations among individual metabolic aspects. The health condition of a subject should be more properly represented as a multidimensional continuum, in that it is the result of various forms of interaction among numerous biological parameters. In view of this, we have set up several obesity-related indicators on the ICANS data by jointly considering a subset of the main biological parameters. As previously mentioned, we have carried out the analyses with the MDS model that derives from the minimization of the raw stress (1). In what follows, we will then propose the main steps of our study: 1) setting-up of obesity-related indicators at the first medical examination through application of two-way stress MDS; 2) effectiveness assessment of obesity treatments over the total number of visits, twenty-four in all, by applying the strategies of analyses outlined in Sect. 3; 3) comparison between the two LOCF-row augmentation strategies for standardized variables.

All the analyses, including the implementation of the iterative procedure in Table 1, have been carried out in the R environment, vs. 2.9.0 (R Development Core Team, 2009).

(1) Setting-up of obesity-related indicators at the first visit. Two-way stress MDS has been applied to the fifteen variables above described. As they are not directly comparable, they have required standardization.

Next, two-way stress MDS has been applied to the Euclidean distance matrix computed for subjects at the first visit. We have retained a solution in three dimensions. As the normalized metric stress equals 0.0197, it guarantees a very good fit to data. Table 2 reports correlation coefficients between the original variables and the three dimensions extracted. We have based their interpretation on the coefficients that are highlighted in Table 2.

Tab. 2: Correlation matrix of original variables and extracted dimensions(*).

Variables	*Dimension 1*	*Dimension 2*	*Dimension 3*
age	0.122	-0.445	**0.615**
systolic arterial pressure	**0.625**	-0.365	0.387
diastolic arterial pressure	**0.606**	-0.313	0.331
weight	**0.817**	-0.176	-0.357
height	0.184	-0.525	**-0.558**
BMI	**0.897**	0.177	-0.035
waist circumference	**0.876**	-0.234	-0.111
glycaemia	0.373	**-0.397**	0.317
HDL	-0.314	0.185	**0.560**
LDL	-0.060	**-0.358**	0.263
triglyceride	0.306	**-0.364**	-0.219
bicipital skin-fold	0.539	**0.628**	0.160
tricipital skin-fold	0.449	**0.747**	0.110
sub-scapular skin-fold	**0.810**	0.359	-0.010
supra-iliac skin-fold	**0.765**	0.288	-0.124

(*) *In bold there are the highest correlation coefficients within the row; inside gray cells there are correlation coefficients larger than 0.35 in absolute value.*

Dimension 1 can be described as a real and proper obesity indicator, being highly positively correlated with arterial pressure, weight, BMI, waist circumference, sub-scapular and supra-iliac skin-folds, and, to a lesser extent, with bicipital and tricipital skin-folds. Dimensions 2 and 3 seem to identify specific typologies of subjects. In particular, the highest positive scores on Dimension 2 tend to detect younger subjects, who are less tall, do not have particular problems with cardiovascular and metabolic aspects, but nevertheless have the highest values on bicipital and tricipital skin-fold measures. The highest positive scores on Dimension 3 tend to identify older subjects, who are among the shortest, with a moderately high systolic arterial pressure and the highest levels of HDL cholesterol.

Figure 4 displays boxplots of scores for the three obesity-related indicators within the categories formed on BMI according to medical literature. In detail, subjects are generally classified into the following Body Mass Index classes: underweight (BMI ≤ 18.5); normal weight (BMI: 18.5 – 24.9); overweight (BMI: 25 – 29.9); Obesity Class I (BMI: 30 – 34.9); Obesity Class II (BMI: 35 – 39.9); Obesity Class III (or Severe Obesity) (BMI ≥ 40).

From the graph, it is immediately evident that obesity indicator scores (Dimension 1) are strictly connected with the five BMI classes (here the underweight class is not present), in that normal weight corresponds to the smallest scores, overweight to the next higher values, and so on, in ascending order, up to Obesity Class III, which corresponds to the highest scores. Moreover, the boxes do not overlap, thus denoting that this indicator succeeds in discriminating BMI classes fairly well. On the contrary, Dimensions 2 and 3 seem to exhibit no apparent trend with respect to BMI classes.

(2) Treatment effectiveness assessment through iterative application of three-way MDS with augmented data matrices. As outlined in Sect. 3, three-way MDS cannot be applied in situations where the K sources of information do not comprise the same number of subjects. In the present case study, the K sources are represented by the totality of medical examinations, in that a single visit can be considered as an occasion for data collection. As stated herein, since the subjects involved in the study underwent a different number of visits (Figure 1 and Figure 3), we shall necessarily proceed to the analyses by iteratively applying three-way MDS with augmented data matrices along with strategies FIAMS and FISAM (Table 1). By this approach, we intend to: (a) study the evolution of the obesity indicator (Dimension 1) over the occasions; (b) monitor the achievement of a positive outcome in a multidimensional framework; (c) study the “hypothetical” condition evolution of subjects that arrest at a first set of visits. They will be conveyed to future occasions by carrying their status forward up to that moment. In addition, they will be analyzed in the presence of subjects who have actually gone on to further occasions; and (d) study the “hypothetical” state evolution of subjects that actually go on till the last set of available visits, by referring their analysis to a “world” where the other subjects have stayed behind.

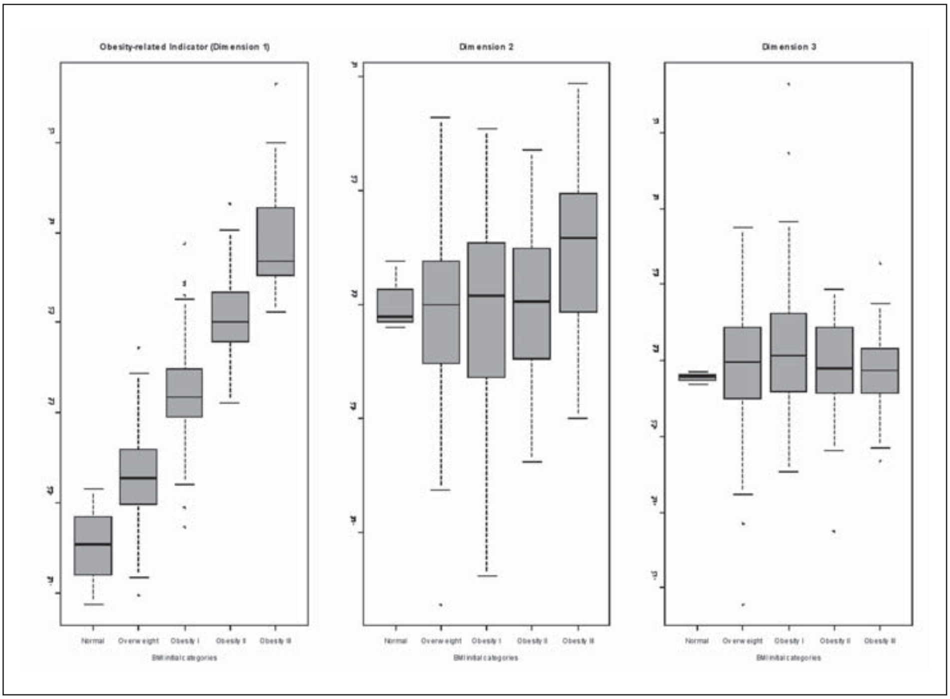

Fig. 4: Boxplots of scores for the three dimensions extracted within BMI classes at the first medical examination.

On the grounds of what we outlined in Sect. 3, in this present case we have carried out the analyses by applying the unconstrained three-way SMACOF MDS, with the identity, diagonal and IDIOSCAL models being beyond the scope of our study. Indeed, as aforementioned, such models can be ascribed more properly to the confirmatory MDS framework (Borg and Groenen, 2005, Sect. 10.3), while our study is more consistent with an exploratory approach. Before applying MDS, we have based matrices augmentation on both FIAMS and FISAM strategies, the original variables requiring standardization for joint analyses.

By proceeding in this way, we have obtained a considerable amount of analysis results, which obliged us to present only a small part of them here. In particular, we will restrict our attention to the obesity indicator (Dimension 1), as it was actually our primary concern.

As a first observation, although the FIAMS and FISAM strategies have led to two independent constructions for the obesity indicator, the magnitude of their scores is indeed very similar. Moreover, the FIAMS strategy tends to highlight subjects' condition changes over the various occasions in a milder fashion than does FISAM. For these reasons, we have opted to place greater emphasis here on FISAM results. We will however take the FIAMS strategy into account again at the end of this section, where we present an example comparing FIAMS and FISAM results.

Later on, we will show the main FISAM results gained when monitoring the evolution of both occasion and common space coordinates.

As regards occasion configurations, Figure 5 displays the monitoring of the obesity indicator scores at the first visit, according to the vertical reading of Table 1. In each panel, bold trajectories refer to subjects belonging to a specific BMI class. Two remarks are worth making: First, at the first visit scores of Dimension 1 appear to be extremely stable over the various procedure repetitions. In a certain sense, this could support the idea that Dimension 1 actually succeeds in capturing numerous, latent aspects intrinsic to the obesity condition. Second, bold trajectories in the four panels contribute to validate the interpretation of Dimension 1 as an "obesity indicator", since overweight and obesity classes on BMI continue to remain well separated during the procedure repetitions.

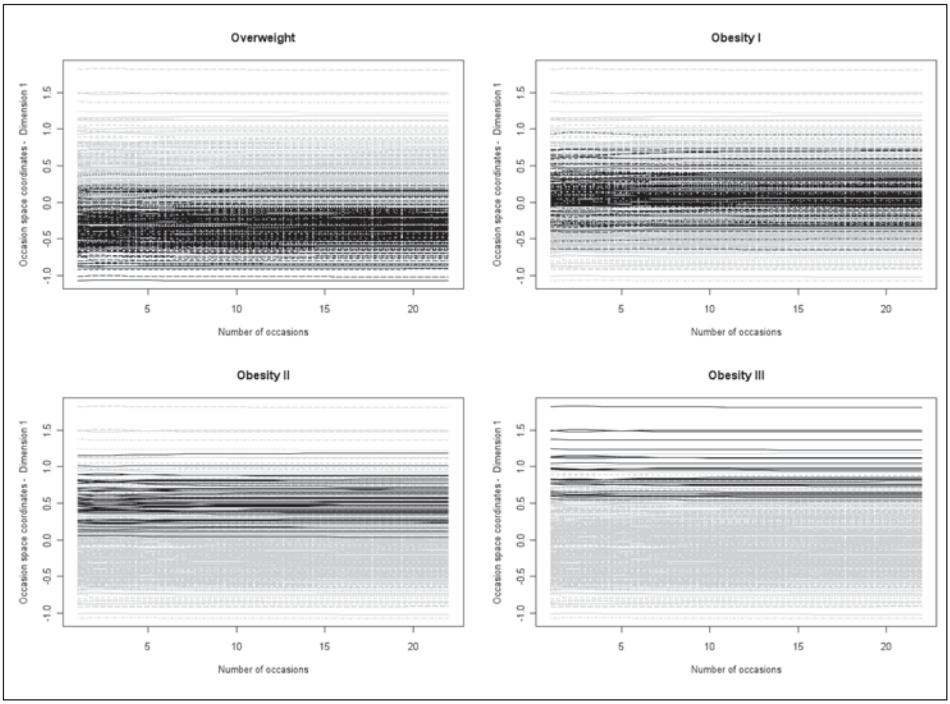

Fig. 5: Occasion space configuration, vertical reading (Table 1): monitoring of obesity indicator scores at first visit, within BMI classes.

As regards the horizontal reading of Table 1, we are going to show the monitoring of Dimension 1 scores obtained by holding the last procedure repetition fixed while varying occasions. Figures 6 and 7 display the trajectories thus obtained and distinguished according to outcome categories and BMI classes, respectively. Several aspects are worth noting. Firstly, several trajectories tend to flatten from a particular occasion onwards. Most of the time, this is a direct consequence of LOCF-row augmentation strategies. The flat part of trajectories simply represents the latest available history of left-behind subjects that is conveyed onwards and studied in connection with subjects who continue. As can be seen, their obesity condition tends not to change when it is investigated relative to subjects who continue.

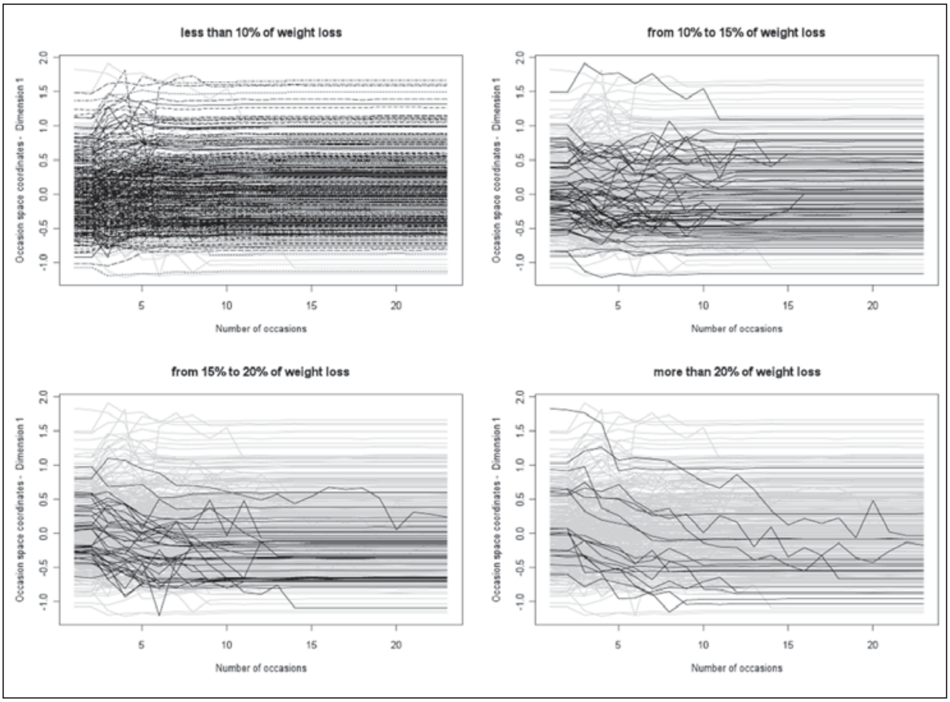

Fig. 6: Occasion space configuration, horizontal reading (Table 1): monitoring of obesity indicator scores at the last repetition, within outcome categories.

As a second observation, a range of trajectories exhibits a decreasing trend, though not monotonically. Given that subjects with a worse health status get the highest scores on the obesity indicator, decreasing trajectories represent subjects managing to improve their condition to a greater extent than do others. In other words, treatments they received seem to have been among the most effective. For instance, the four panels in Figure 6 can be read as follows. The first panel (on the top, left-hand), concerning subjects not having attained the goal yet, shows trajectories that are mostly parallel straight lines over the occasions, except the first ones. Their condition has therefore been left unchanged. The second panel (on the top, right-hand) shows trajectories of subjects having lost from 10% to 15% of their initial weight. In case of highest scores especially, trajectories tend to decrease. Nevertheless, when they later become straight lines, a number of them tend to rise again, settling down to slightly higher scores. This indeed well represents the core of our analysis strategy: when values for these subjects are carried forward by FISAM strategy, their health condition finds itself in "competition" with the other subjects who go on to subsequent occasions and possibly achieve greater weight loss. Finally, the third and fourth panels (on the bottom, left- and right-hand, respectively) show trajectories of subjects attaining the greatest weight loss. Their trend is fairly similar; they tend to decrease notably, though not monotonically, especially in the case of highest scores on the obesity indicator.

Again, as regards BMI classes, in the fourth panel of Figure 7 (Obesity Class III) three trajectories clearly decrease: Two take the form of line segments, falling from the first to the last occasions. The other trajectory, which lies below them, flattens at nearly the sixth occasion, remaining then a straight line parallel to the horizontal axis up to the last occasion. At first glance, and in line with our previous remarks, this might mean that the subject corresponding to this latest trajectory has attained his goal before the other two. But this is only conjecture. A more thorough analysis of trajectories such as these would be advisable, in that certain trends, especially those far from the main core, might actually hide anomalous situations.

In view of this, in the next part of this section we present a convenient way to proceed to a more thorough investigation. Specifically, we will focus our attention on trajectories for specific groups of subjects that are characterized by either apparently decreasing or markedly anomalous trends.

Figure 8 displays the enlargement of the fourth panel of Figure 6, related to subjects with a larger-than-20% weight loss. As an illustration, trajectories for subject with codes 686, 723, 745, 1155, 1210 and 1334 are depicted with bold lines, the first part being a straight continuous line, the second part a dotted line. The continuous mark over a first set of occasions denotes that a subject actually underwent those medical examinations. The dotted mark stands for his absence from the next set of visits, which have required applying a LOCF-row augmentation strategy. A first observation concerns subjects with codes 686 and 745. They underwent the greatest number of visits. In addition, from the raw, original data it can be ascertained that they lost more than 20% of their initial weight at a very

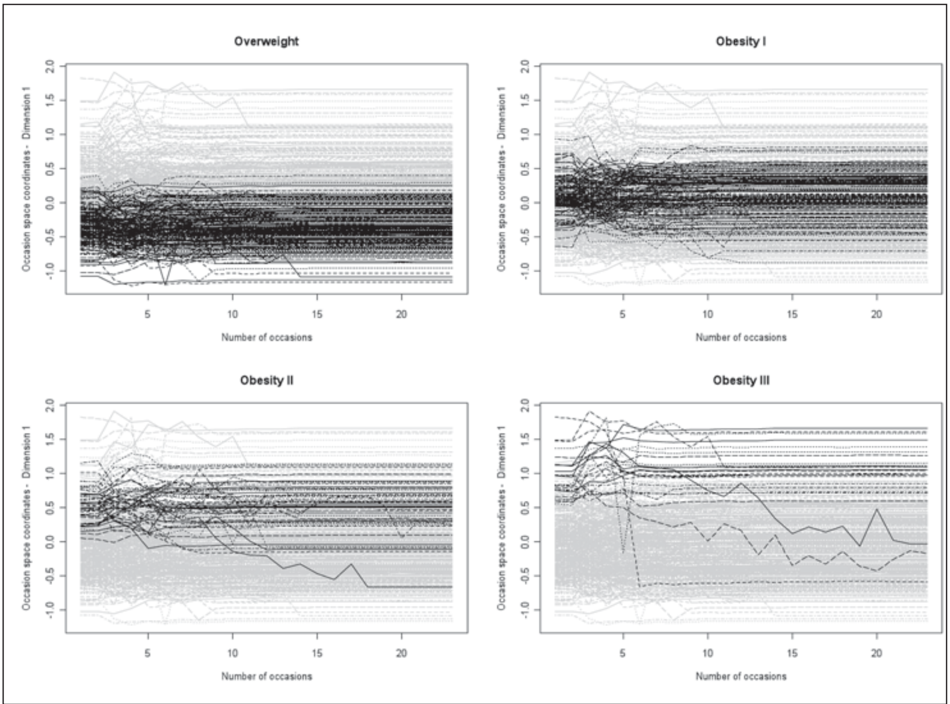

Fig. 7: Occasion space configuration, horizontal reading (Table 1): monitoring of obesity indicator scores at the last repetition, within obesity status on BMI.

similar rate. Examining their trajectories in greater depth, we observe that indeed their "whole" health condition, involving metabolic and cardiovascular parameters as well, has improved according to a similar pattern, especially as concerns the central part of the graph.

Subject with code 1334 manages to lose 20% of his initial weight by the fifth visit, while over the next two visits he regains weight. Consequently, the dotted line, referred to his reconstructed values, is drawn at a higher level than before. Finally, subject with code 1155, who is characterized by the worst initial health condition, loses nearly 28% of his weight in four visits. The first dotted segment descends accordingly very steeply, but soon thereafter it flattens in that subjects going on to further visits manage increasingly to improve their condition.

As a further illustration, Figure 9 shows trajectories of Obesity Class III subjects (4^{th} panel, Figure 7). Similar remarks as those made above could be made by looking at the highlighted trajectories. However, it is worth investigating trajectories for subjects 704 and 727 more in-depth, as they appear a bit anomalous with respect to the prevalent trends. In fact, if subject 704 is seen in prospect after

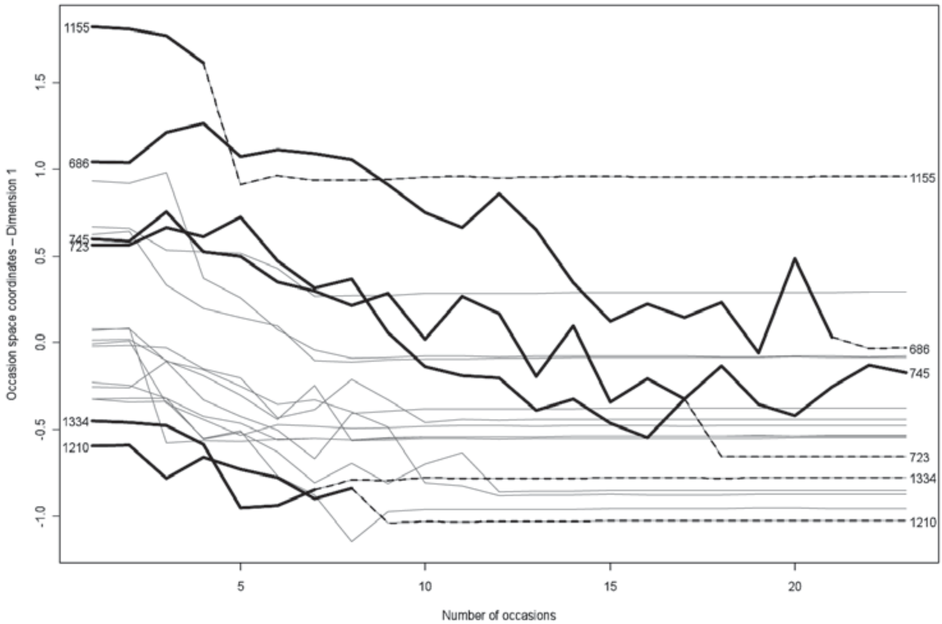

Fig. 8: Occasion space configuration, obesity indicator: Trajectories for subjects with a larger-than-20% weight loss, (4th panel, Figure 6).

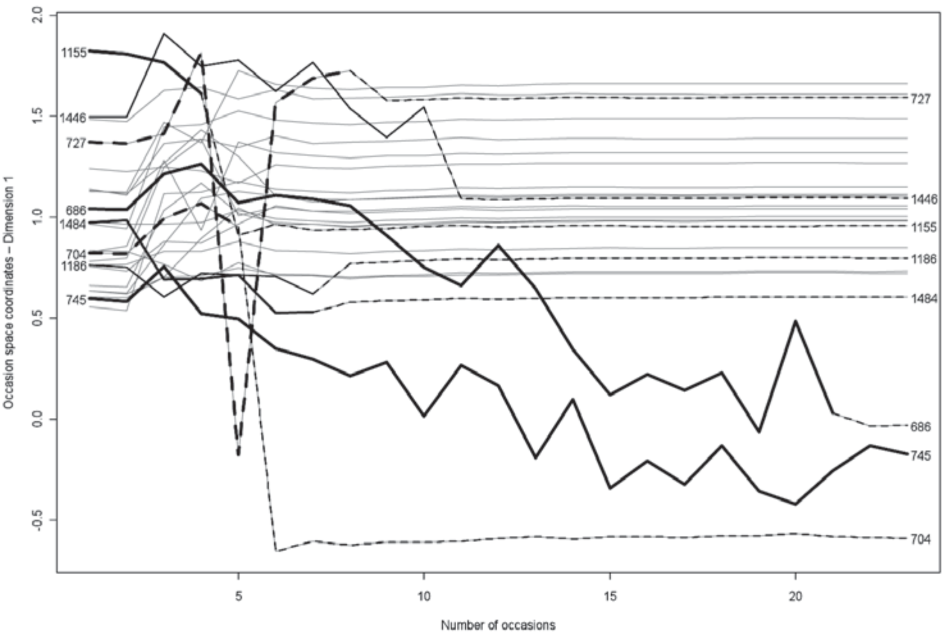

Fig. 9: Trajectories for subjects of Obesity Class III, (4th panel, Figure 7).

his last fifth visit, it could seem that he will be able to improve his health status to a greater extent than all the other subjects will. On the other hand, it appears that, after a fast improvement up to his fifth visit, subject 727 gets rapidly worse, thus maintaining a high score on the obesity indicator until the last occasion.

Unfortunately, these interpretations are not right. In the original ICANS database, at one single visit only, both these subjects were erroneously assigned a zero value on the variable "waist circumference", instead of inserting perhaps a missing value code. The anomalous trends of these two subjects' trajectories can be therefore explained in light of this, given that zero-values were assigned, respectively, to subject 704 at his last visit and to subject 727 at his fourth visit. In any case, we have decided to present here such cases in order to show that our method may help reveal also potential anomalies or errors in data. In spite of that, the results achieved for the other subjects have shown not to markedly suffer the effects of such errors. We ascertained this by performing the same analyses after having imputed proper values on waist circumference through the multiple imputation method concerning time-series-cross-sectional data, mentioned at the beginning of the section.

As a final observation, studying the occasion configurations according to the diagonal reading (Table 1) has not yielded added value as compared to the horizontal reading that pertains to the last procedure repetition. These results are thus omitted.

For the sake of completeness, we briefly describe the investigation in the common space. In Figure 10 the monitoring of the obesity indicator within the four outcome categories is displayed. The first aspect worth noting is that the highlighted trajectories appear smoother than in the previous analyses. Moreover, subjects losing weight to a great extent tend to have more rapidly decreasing trajectories than the others. Given that this graph can be interpreted with similar arguments as before, we do not further examine this case.

(3) Comparison between FIAMS and FISAM strategy results. As stated before, the obesity indicator scores obtained over the occasions through FIAMS and FISAM augmentation have turned out to be very similar in magnitude. A more thorough inspection prominently highlights two aspects. Firstly, the main differences between the two strategy results are concentrated in the last part of trajectories, that is, at the last occasions. This can be easily explained by considering that the last occasions contain the widest sets of LOCF values, which differ depending on which strategy is applied. As an illustration, Figure 11 displays the monitoring of the obesity indicator scores obtained with FIAMS strategy. By comparing this graph with Figure 8 (FISAM strategy), in this latter the last trajectories appear to be more peaked and marked. Secondly, tendency inversions may occur, especially in the last occasions.

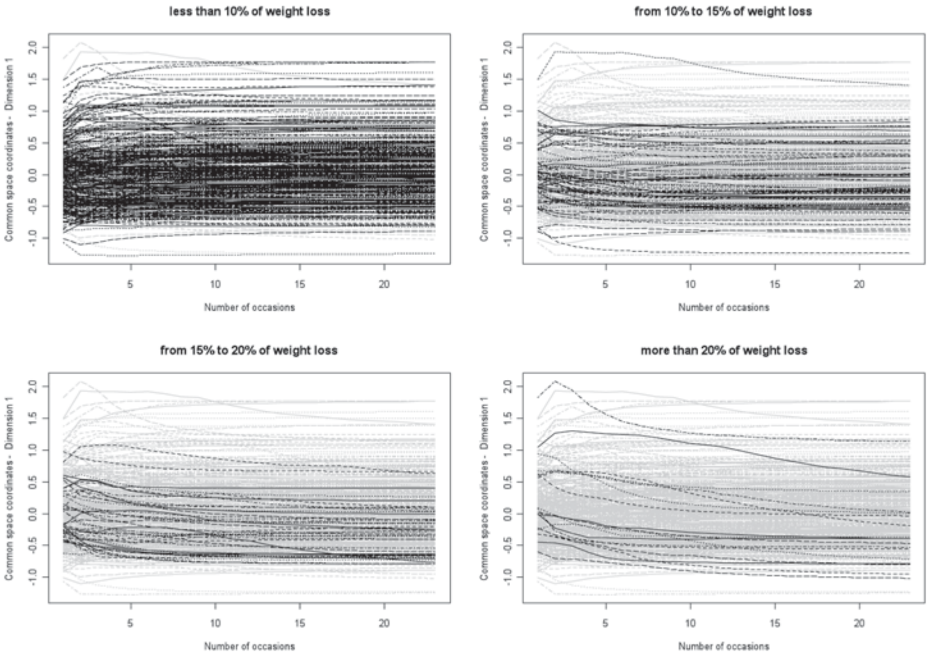

Fig. 10: Common space configuration: monitoring of obesity indicator scores within the four outcome categories.

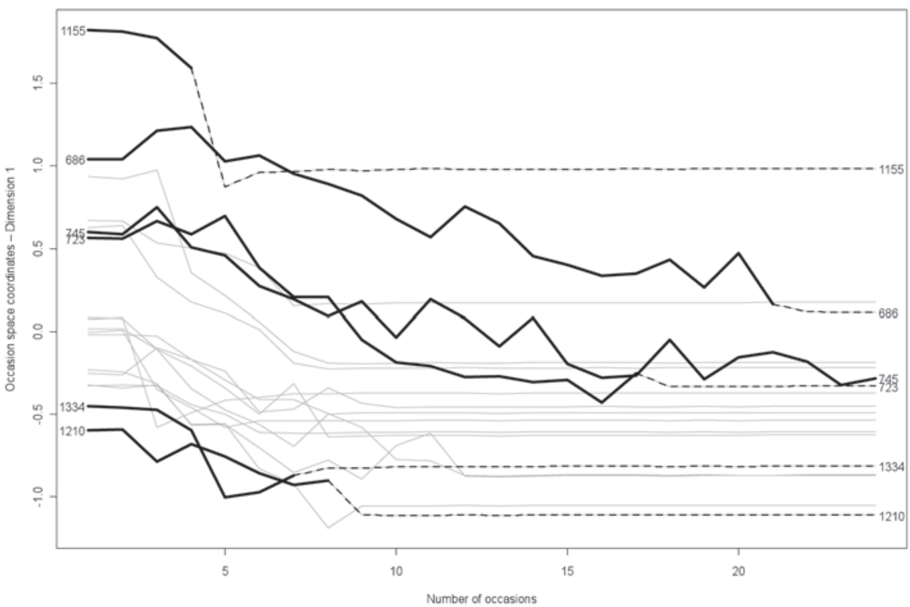

Fig. 11: FIAMS strategy: Trajectories for subjects with a larger than 20% weight loss.

For instance, examination of Figure 8 reveals that at nearly the 20th occasion subject with code 745 reached an improvement in his condition, given the local minimum on his trajectory. This would mean that this individual improved compared to subjects from a more recent past as well as subjects actually examined at that moment. Conversely, from Figure 11 it can be observed that at nearly the 20th occasion this same subject has declined on the whole, when compared with subjects that are examined at that moment as if they were actually all present at that moment. Similar interpretations can be advanced when looking at other subjects' states.

Clearly, conjointly reading these results is not effortless. Nevertheless, we maintain that it can contribute to more complete assessments of the effectiveness of specific treatments, or in general, the quality and the magnitude order of changes in individuals' conditions resulting from a range of specific actions towards them.

5. CONCLUSIONS

In this paper, we have focused on the problem of assessing individual treatment effectiveness in the presence of structurally missing occasions. We have introduced this concept to refer to situations in which subjects cannot expose themselves to the same number of data collections due to the attainment of a predetermined set of conditions. To overcome the problem of a different number of occasions over subjects, we have introduced several strategies to augment the matrices that enter the analysis process. Then, we have applied a specific multiway data analysis technique, i.e. three-way stress multidimensional scaling, to set up indicators over sequences of augmented dissimilarity matrices, formed according to an iterative procedure described in detail in the text. Our expectation is that this procedure should reproduce the dynamism in the process that leads to changes in subjects' state, or in other terms, it should simulate the effectiveness "path" that leads to the attainment of a (positive) outcome during a treatment period. To show the potentiality of our method we then considered a case study concerning obesity.

The approach we have adopted for analyses has been exploratory in nature. Our main concern, in fact, was to tackle the evaluation problem in situations where making a priori assumptions about data or proceeding with standard modelling are discouraged. In this sense, we feel that our approach can be fully considered within the effectiveness evaluation framework, though not typical of it.

In conclusion, in the present work we have applied our method in order to assess the effectiveness of treatments for obesity over different occasions. We argue that this method could be profitably applied in other situations that share similar conditions as those which we have started from. At any rate, what we have proposed here represents only a first contribution in this direction; more through examinations are necessary, especially on other sets of data. Moreover, the idea underlying the iterative application of three-way stress multidimensional scaling, outlined in Sect. 3, could in principle be extended to other multiway data analysis techniques, by introducing suitable adjustments depending on the method type. Finally, the augmentation strategies here proposed are not only possible approaches. At present, we are studying alternative, less intuitive ways to augment matrices in the presence of structurally missing occasions. It is our expectation that this could give rise to a more comprehensive methodology for exploratory effectiveness evaluation.

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VALUTAZIONE DELL’EFFICACIA DI TRATTAMENTI INDIVIDUALI IN PRESENZA DI RILEVAZIONI MANCANTI IN SENSO STRUTTURALE

Riassunto

In questo lavoro viene proposto un metodo esplorativo per la valutazione dell’efficacia dei trattamenti individuali quando i soggetti coinvolti nel processo di valutazione sono sottoposti ad un numero diverso di rilevazioni. Gli elementi fondamentali alla base del metodo consistono nell’applicazione di alcune strategie per la ricostruzione del dato quando è assente e l’impiego in termini iterativi del multidimensional scaling a tre vie.

INNOVAZIONE E COMPETITIVITÀ DELLE PMI IN ITALIA – Metodi e modelli di mercato

Amedeo De Luca, Franco Angeli, Milano, 2009, pp. 315.

Il tessuto produttivo italiano si caratterizza per la forte prevalenza numerica di piccole-medie e micro imprese, che costituiscono la spina dorsale del sistema economico nazionale.

Nonostante queste imprese rappresentino nel nostro Paese oltre il 90% del numero totale di unità produttive, gli accademici hanno normalmente trascurato questa realtà, rivolgendo la loro attenzione alle imprese di grandi dimensioni, per le quali hanno predisposto – nel tempo – efficaci strumenti di gestione dei processi aziendale e sofisticati modelli manageriali e di mercato.

Nel desiderio di contribuire a colmare questa lacuna Amedeo De Luca, autore prolifico e sensibile alle istanze provenienti sia dal mondo aziendale, ha elaborato un'opera che focalizza i metodi e i modelli quantitativi di mercato per le Pmi. Ciò in quanto, secondo l'Autore, nel nostro Paese il principale fattore di ostacolo all'innovazione e allo sviluppo delle Pmi e delle microimprese è la mancanza di una "cultura quantitativa d'impresa", che impedisce al management di percepire e recepire i vantaggi derivanti dall'utilizzazione di procedure statistiche rigorose, alla base di processi decisionali efficaci e di una corretta programmazione dell'attività aziendale.

D'altro canto, nell'attuale realtà di mercato globalizzato, data la complessità ambientale e la molteplicità delle variabili in gioco, non sono più sufficienti l'intuito e le capacità personali dell'imprenditore per l'assunzione di decisioni razionali in condizioni di incertezza e per pianificare l'attività aziendale. Le Pmi – così come le imprese di grandi dimensioni – non possano più, oggi, ignorare le metodologie quantitative e le piattaforme informatiche di business intelligence (BI), in grado di analizzare ed individuare le complesse relazioni causali che intercorrono tra l'impresa e l'ambiente esterno.

Stante l'anzidetta assenza nella letteratura aziendale di opere di carattere metodologico indirizzate specificamente alle Pmi, all'Autore è sembrato opportuno elaborare un manuale di metodologie quantitative di mercato (oltre che di alcuni modelli finanziari di ottimizzazione), quale guida alla gestione e alla pianificazione aziendale dell'impresa, per elevarne il livello di innovatività e di competitività. I metodi e le tecniche illustrati nel volume mirano a supportare le Pmi nel processo di trasformazione del "dato" in "informazione", prima, e in "conoscenza" poi, in una prospettiva di marketing intelligence, basata sul Data Mining (DM). Prospettiva, questa, volta ad analizzare, valutare e controllare le numerose variabili che interagiscono tra di loro e che caratterizzano i mercati ed i comportamenti dei consumatori, onde poter cogliere i rapporti intercorrenti tra le strategia dell'impresa e i suoi risultati economici e di mercato.

Quella di De Luca è un'opera trasversale, che analizza le principali aree funzionali dell'azienda (produzione, marketing, sistemi informativi, controllo di gestione, finanza) di piccola-media dimensione. Essa tratta, perciò, una vasta gamma di metodi quantitativi, di supporto alle attività strategiche e operative dell'azienda. Le aree tematiche analizzate sono di seguito riportate.

Marketing e segmentazione (modelli decisionali; targeting; marketing-mix, punto di pareggio; strumenti decisionali per il lancio di nuovi prodotti, quale la conjoint analysis; strumenti di Business Intelligence; valutazione della qualità oggettiva e della customer satisfaction).

Pianificazione operativa e strategica (*Activity Based Costing*; *Balanced Scorecard*; strumenti di pianificazione della comunicazione; ciclo di vita e valore del cliente; previsione delle vendite; pianificazione territoriale e strumenti di geomarketing; valutazione del potenziale territoriale di mercato; internazionalizzazione delle Pmi).

Sistemi informativi, **internet e web** (approcci di valutazione economica delle Pmi; *Information&Communication Technology*, rapporto delle Pmi con internet e con il web). **Valutazione delle Pmi nell'ottica di Basilea 2** (relazioni tra banche e Pmi, valutazione del rischio creditizio con il rating e con tecniche di segmentazione).

Modelli finanziari per le Pmi (ottimizzazione del portafoglio di attività finanziarie; *capital asset pricing model*; gestione del risparmio e misurazione della performance; scelta degli investimenti finanziari).

L'opera è di interessa per gli studenti dei corsi universitari e dei master in Statistica, in Marketing Management, in Informatica, oltre che per gli studiosi dei problemi di mercato riguardanti le Pmi.

Il volume è diretto agli imprenditori ed ai manager delle piccole-medie, micro imprese e imprese family; ai dirigenti della funzione marketing, Commerciale, Sistemi Informativi, Controllo di gestione, Amministrazione e Finanza.

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