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MIFuzzy Clustering for Incomplete Longitudinal Data in Smart Health

Hua Fang

Department of Computer and Information Science, University of Massachusetts Dartmouth,
Department of Quantitative Health Sciences, University of Massachusetts Medical School,
Worcester, MA 01655

Abstract

Missing data are common in longitudinal observational and randomized controlled trials in smart health studies. Multiple-imputation based fuzzy clustering is an emerging non-parametric soft computing method, used for either semi-supervised or unsupervised learning. Multiple imputation (MI) has been widely-used in missing data analyses, but has not yet been scrutinized for unsupervised learning methods, although they are important for explaining the heterogeneity of treatment effects. Built upon our previous work on MIFuzzy clustering, this paper introduces the MIFuzzy concepts and performance, theoretically, empirically and numerically demonstrate how MI-based approach can reduce the uncertainty of clustering accuracy in comparison to non- and single-imputation based clustering approach. This paper advances our understanding of the utility and strength of MIFuzzy clustering approach to processing incomplete longitudinal behavioral intervention data.

Index Terms

longitudinal data; Missing values; Fuzzy clustering; Multiple imputation; MIFuzzy

I. Introduction

Missing data are common in longitudinal observational and randomized controlled trials in smart health studies. Behavioral interventions (e.g., physician advice; individual, group, or telephone counseling; self-help, including Internet use, and emerging use of wearable biosensors) [1]–[16] are commonly used to facilitate substance use treatments. Many such interventions have multiple components and are implemented over time, e.g., [17]–[32]. Over the course of an intervention, patients display complex and varying behaviors such as relapsing or dropping out for various psychological, social and environmental reasons, e.g., [33]–[41]. Their variations in engaging with or responding to interventions may contribute to different outcomes. Failure to appreciate these variations within, not only those between treatment and control groups, can ultimately lead to inappropriate and ineffective

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interventions, e.g., [38]–[42]. Thus, disentangling patients' behavioral variations, is a critical step for better understanding an intervention's effects on individual outcomes. However, capturing these variations poses significant computational and analytical challenges. Methods have been called for to address the variations in intervention effects for improving the design, conduct, and analyses of patient-oriented research [43]. Missing data also commonly exist in such complex longitudinal data, aggravating these methodological challenges. For these reasons, we propose an innovative trajectory pattern-recognition approach to tackle incomplete longitudinal behavioral intervention data, built upon our methods studied for observational studies and our previous work on fuzzy clustering and missing data in longitudinal studies [44]–[52].

Multiple imputation (MI) has been well studied for statistical analyses [53], [54] but has not yet been scrutinized for clustering [55], [56]. One of major reasons is that we do not know how much the uncertainty of imputed data will affect the clustering accuracy. To answer this question, we need to compare the MI approach with single- (SI) and non-imputation (NI) based clustering approaches, which are commonly adopted in current pattern recognition areas. Although no single clustering approach can handle every type of data problem, our proposed MI-based Fuzzy clustering [48] was especially designed for longitudinal behavior related data that are typically non-normal, high dimensional, contain missing values, and of different types (i.e., continuous, ordinal and nominal). MI-Fuzzy was developed primarily because no other clustering technique overcomes all eight disadvantages for processing such data: 1) Cannot handle missing data directly; relies on list-wise/pair-wise deletion or single imputation; 2) Lack (available, tractable, replicable, or easy-to-use) validation indices or integrated validating processes; 3) Require statistical or prior distribution assumptions; 4) Require (manually) complicated parameter settings and repeated adjustment of model constraints and starting values of parameters in the clustering process; 5) Computationally intensive or malfunction for high-dimensional and longitudinal data with relatively large portions of missing values or increased number of clusters; 6) Results are (sometimes) not replicable (even using the same data set); 7) No graphic visualization of clusters from high-dimensional data or longitudinal data trajectories; 8) Unclear utility in behavior-related data.

For example, probabilistic clustering, including Gaussian Mixture models [57] and Hidden Markov Model-based Bayesian clustering [58]–[61] are commonly used for clustering. For such models, we must specify underlying statistical distributions (Gaussian) or prior distributions (Bayesian approach). The expectation-maximum (EM) algorithm for the Gaussian model is iterative and requires specifying initial values of parameters and adjusting parameters during modeling. EM often converges to a local maximum or does not converge at all; also, it can be computationally very slow when there are multi-modal distributions or mixture of Gaussians (e.g., potential clusters) and large proportions, say greater than 20%, of missing values with high-dimensional data and many clusters. Gaussian Mixture Models used for clustering subjects with attributes (X) are different from growth mixture models or similar latent profile modeling under the latent variable modeling and structure equation modeling framework used for outcome tests (e.g., the relationship of attribute X and outcome Y). Growth Mixture models were first developed incorporating the idea of Gaussian Mixture Model that is used for clustering. With larger data, Growth mixture models could be robust when testing one outcome with repeated measures. Even if it is used for outcome tests, it has

similar disadvantages as commented as above in terms of jointly modeling multiple correlated components (or outcomes)..Bayesian clustering is also computationally intensive and requires parameter adjustment and setting model constraints. Bayesian clustering has been developed and tested for large datasets (e.g., gene data) but its utility beyond gene analyses is unclear. If the observed data are generated by the assumed distributions, these probabilistic clustering models should be robust. However, high-dimensional behavioral intervention data typically have multi-modal distributions and their exact (joint) distributions are a priori unknown.

Neural networks models [62], [63] are mostly used for supervised learning (e.g., classification where the group labels of each subject are previously known). The well-known neural networks model for unsupervised learning (clustering where the group labels of each subject are a priori unknown) is called Kohonen's Self Organizing Map (SOM). The SOM architecture consists of an input layer and a Kohonen layer. The number of neurons (nodes) in the input layer corresponds to the number of attributes. Each input to the Kohonen layer is modified by a weight, which multiplies with the input value. SOM initializes weights by assigning them random values. The Kohonen layer represents potential clusters. Hidden layers can also be added between the input and Kohonen layers to fit nonlinear data; however the number of neurons on this layer is arbitrary, and different settings lead to different results even for the same data. SOM has been applied in areas such as imaging, speech and voice recognition. Its validation indices or procedures are unclear. SOM itself cannot handle missing values. Its utility in behavioral intervention studies is unknown. Recently, neural network-based deep learning is becoming popular. As described above, it was mostly used for supervised learning and is SOM-based.

Hierarchical clustering [62], [64] has two major forms: Agglomerative (bottom-up) and Divisive (top-down). Agglomerative clustering starts with an every individual in his own cluster; at every step it merges the closest pair of clusters. Divisive clustering starts with all subjects in one cluster and split this cluster into smaller pieces. We will focus on agglomerative, as divisive clustering is much less used in applications [62], [64]. No matter what form, the disadvantages of hierarchical clustering are well-known: its inability to incorporate information about the shape and size of clusters, and its static nature (data are committed to a cluster once and cannot be moved to another cluster later [40]). It assumes the data have a hierarchical or nested structure which is implausible for, say, distinct components of behavioral interventions. Although it works in some areas, this model performed poorly in our preliminary prenatal tobacco exposure studies, yielding unreliable and trivial clusters (e.g., many small "clusters" with few individuals in each). With a pre-specified number of clusters, its clustering accuracy and inconsistency rates were the poorest in comparison to MI-Fuzzy and K-means. Partition-based clustering [62], [64] also comes in two flavors: hard (crisp) clustering that partitions the data set into mutually exclusive subsets, and fuzzy clustering that allows subjects to belong to several subsets but with different "degrees" of membership. The best-known hard clustering model is K-Means. It was designed to cluster numerical data into clusters in which each cluster has a center called mean. Although K-Means has been widely applied with appealing computational efficiency, it cannot handle missing values. Our preliminary analyses indicate that it has lower accuracy

and higher inconsistency rates than MI-based fuzzy-clustering for pregnant smoking behavioral data.

Another conceptual category of clustering, called subspace clustering [65], is emerging, which is an extension and/or combination of above specific techniques, therefore may inherit those disadvantages described below. This category is mostly used in image analyses and still has open areas to be investigated. Its utility in longitudinal smart health data of random controlled trial (RCT) and observational study is unclear.

Based on our prior research for longitudinal behavior intervention data, we will theoretically comparing MI- to SI- and NI-based fuzzy clustering approaches. In addition to our theoretical demonstration, we will use two real datasets. Table I are the notations of symbols used in this paper.

The rest of this paper is organized as follows: Section II introduces MI-based Fuzzy clustering. Section III theoretically compares and demonstrates MI-, SI- and NI-based fuzzy clustering approaches. Section IV presents numerical results under three missing data mechanisms. Section V concludes the paper.

II. Multiple Imputation Based Fuzzy Clustering

Figure 1 presents a simplified conceptual description of previous stepwise MI-Fuzzy approach. To identify smokers' differential engagement or response patterns in interventions, we will perform three major steps.

Step1: Identify attributes. The designs of longitudinal multiple-component behavioral intervention studies likely differ in the number and type of components. The three principles for attribute selection are: (a) use all intervention components, (b) include repeated measures of components, and (c) use smokers' actual engagement or response values including zeros and missing values, so as to quantify and reveal longitudinal behavioral changes. This strategy reflects another advantage of our MI-Fuzzy approach: researchers are not forced to use a single one-time measure, when time and money have been spent to collect multiple repeated measures. Rather, all measures available will be used to characterize the complexity of behavioral changes during the intervention.

For Quit-Primo, we will use all monthly repeated measures of the three components (*My Mail*, *Our Advice* and *Online Support Community*). For TDTA, we will use the four pre-defined repeated measures of Attitudes, Perceived Social Norms, and Self-Efficacy in Quitting.

Steps2 and 3: Clustering and iterative validation. We will use MI-Fuzzy clustering to search for engagement or response trajectory patterns for each intervention study through a comprehensive procedure that examines the following:

- Clustering rates: (a) the MI-Fuzzy Inconsistency Rate, the number of smokers with inconsistent labels across imputed data sets divided by the total sample size (smaller is better, as larger values indicate instability), and (b) the MI-Fuzzy Accuracy rate, the average fraction of correctly-classified cases across imputed

data sets where we know with certainty who is in the control or intervention group (larger is better).

- Validation indices: We will consider 3 indices, modified and computed as average scores across imputed data sets, (a) the Xie-Beni [66], widely used for fuzzy clustering, that is the ratio of total variation within to variation between latent classes (smaller is better), (b) the Partition Coefficient with decreasing monotonicity (smaller is better), and (c) Partition Entropy with increasing monotonicity (larger is better) [62].
- Graphs: Sammon mapping will be used to visualize clusters from multi-dimensional data in 2-dimensional space [63]. For each cluster, the trajectories will be generated based on repeated measures of each component and displayed to visually confirm the number of valid clusters (as in Figure 1).
- Statistical testing: Statistical tests for differences in included attributes among identified patterns.

Step4 Test attribute redundancy or overfitting. This test entails referencing the multiple-imputation based validation indices and our clustering accuracy rate in Step 3. It will be used to find the minimal number of attributes that characterize smokers' engagement with or responses to the intervention, so as to reduce model complexity. The criterion for this test is that if the accuracy rates decrease when using subsets of original attributes, we will retain the original attributes; if not, we will use the subsets.

Unlike previous step-wise procedure, current MIFuzzy has been integrated, employing a full theoretical integration of multiple imputation and fuzzy clustering and developed into integrated algorithms in Matlab. Importantly, it will cope with real-world situations where participants have membership in multiple clusters, handle non-normal, high-dimensional longitudinal data with missing values.

Two novel features differentiate MIFuzzy from other clustering approach: 1) Our pattern approach integrates MI techniques into the clustering to account for imputation uncertainty and thus the uncertainty of clustering accuracy. This paper demonstrates that MI-based clustering is robust to three missing data mechanisms when data are correlated and high dimensional (especially with repeated measures) 2) integrates the fuzzy-logic theories to handle real-world situations where participants can have membership in multiple clusters and data can be non-normal and high-dimensional. When clusters "touch" or "overlap", a single individual in a longitudinal study can have multiple memberships. Indeed, a participant can belong to different clusters with a different degree of membership in each cluster. For example, the participant may have a higher degree of membership in the cluster with overall "persistent" dietary response behavior during a treatment (as in "most often persistent") and a lower degree in a "nonpersistent" cluster (as in "but sometimes not persistent"). Unlike typical clustering models, MIFuzzy uses "fuzzy degrees" to handle this multiple membership situation: assigning each participant a fuzzy degree ("score") of membership in each cluster. This score "summarizes" the participants' response over time and determines his membership in the cluster with his highest degree score. MI-Fuzzy is analytically tractable and computationally efficient; it is especially useful when the data are complex. It

can handle non-normal and high-dimensional data with missing values and a mix of categorical and continuous variables, without prior assumptions of statistical distributions. MIFuzzy auto-implements the integrated algorithms.

To ensure the accuracy of our MI module, we compared our imputation results with those from SAS 9.3 MI procedure using the same publicized dataset “Fitness1” and parameter settings. The *Fitness1* data set contains 31 subjects with 3 variables: *Oxygen*, *RunTime*, and *RunPulse*, with missing rates of 10%–29%. This comparison step is essential to ensure the “base” of our MI module is correct before we study more complex. This step is also fundamental to integrate MI with fuzzing clustering. Our findings in Table 1 exhibit the exact consistency between the two MI procedures.

To compare the three missing data imputation approaches, two longitudinal behavioral intervention datasets will be used as examples to demonstrate our MI-based approach: TDTA [67], [68] and QuitPrimo (QP) [69]. TDTA data were collected from a culturally-adapted smoking cessation intervention for Korean Americans. Intervention attributes in MIFuzzy were based on data availability and/or selected to maximize information that depicts individual response variations resulting from their psychological factors and engagement with the intervention. All designed intervention components and time for cessation counseling were included at the beginning. The three components were (a) cognitive behavioral therapy, (b) cultural adaptation, and (c) nicotine replacement therapy. The first two components described smokers’ psychological reactions to the culturally adapted cognitive behavioral therapy, which were measured by scores on Perceived Risks and Benefits of Quitting Smoking, Perceived Family and Peer Norm for Quitting, and Self-efficacy in Quitting scales. Each scale has four repeated measures collected at four follow-ups: 1, 3, 6, and 12 months from the quit day, total 20 intervention attributes (5 subscales×4 times). The last component “Nicotine Replacement Therapy” was measured by the number of nicotine patches returned after use (1 attribute) and the counseling time was measured in the unit of minutes (1 attribute). In all, 22 intervention attributes were initially used for MIFuzzy clustering. The percentage of missingness of TDTA data ranges from 9% to 18% on each of tested intervention attribute; and 65% participants have all values, 34% have more than 5 values on intervention attributes.

QP is a two-arm longitudinal web trial used to assist in the smoking cessation of a general smoker population. The data were collected via an online referral portal with 1320 individuals. The intervention arm was engaged with three components which the control arm cannot see. The first intervention component describes how often smokers communicate with a tobacco treatment specialist in a secure form. The second one measures how often the smokers are engaged or encouraged by experts. The third main component describes how many times smokers view messages and dialogue from peers and ex-smokers through a resource website. Each smoker has six monthly measures for each component for six months (total 18 attributes). MIFuzzy is the first clustering model to date that employs a full theoretical integration of (a) multiple imputation (MI), (b) fuzzy clustering, and (c) comprehensive validation [48], [49]. It simultaneously copes with real-world situations where patients have membership in multiple clusters, handles high-dimensional longitudinal

intervention data with missing values (e.g. multiple repeatedly-measured correlated constructs), and validates response patterns.

Our MI process was described in detail elsewhere and implemented in Matlab [70]. Briefly, we assume intervention data follow an arbitrary missing pattern, where other missing patterns such as monotone patterns are special cases [71]. Imputed datasets were generated using the Markov Chain Monte Carlo (MCMC) method with multiple chains, non-informative Jeffreys prior of the Bayesian approach, and 500 burn-in iterations. Before the MCMC process, an expectation-maximization (EM) procedure is conducted to train the parameters of the data. At each MCMC iteration, an I-step is conducted to fill the data by random draws from the model according to the trained parameters, followed by a P-step to update the parameters in the new completed data. The I-step and P-step are conducted iteratively until the Markov Chains stabilized.

The fuzzy clustering aims to minimize an objective function

$$f_m(X, U, V) = \sum_{k=1}^c \sum_{i=1}^n (u_{ik})^w \|x_i - v_k\|^2 \quad (1)$$

$$\text{subject to } \sum_{k=1}^c u_{ik} = 1, \forall i,$$

where X is the dataset, V is the cluster centroids, k is the k -th cluster, w is parameter of U is a vector of u_{ik} where $0 \leq u_{ik} \leq 1, \forall i, k$ denotes the fuzzy degree of membership for subjects i , ($i = 1, 2, \dots, n$) in the respective cluster k . In MI-Fuzzy, we minimized this fuzzy objective function (e.g., we minimized the intra-cluster variance) for each imputed data set,

$$f_m(X, U, V) = \sum_{k=1}^c \sum_{i=1}^n (u_{ik})^w \|x_i - v_k\|^2 + \sum_{i=1}^n \lambda \left(\sum_{k=1}^c u_{ik} - 1 \right), \quad (2)$$

where λ is a weight and $\lambda \geq 0$.

Intervention data have a unique feature that can be used to evaluate clustering accuracy. For example, MI-Fuzzy can be evaluated based on the intervention clustering accuracy rate ($\mathfrak{I}$) for treatment data where we know the labels with certainty (for example, who is in the control vs. intervention group), but not whether there will be different clusters (subgroups) within the intervention group due to behavioral variations. This rate is calculated as the average clustering accuracy rates across M imputed datasets:

$$\mathfrak{I} = \frac{1}{M} \sum_{i=1}^M (N - n_{\text{control}} - n_{\text{intervention}}) / N, \quad (3)$$

where N is the total sample size, $n_{control}$ is the number of mislabeled control group members and $n_{intervention}$ is the number of mislabeled intervention group members. The larger the rate the more accurate the clustering.

Given a termination clustering number (CT), $CT = \sqrt{N/2}$, where N is the sample size, the MI-Fuzzy algorithm searched for the optimal number of clusters through a comprehensive validation procedure [48], [49], [51].

III. MI- VS. SI- AND NI- FUZZY CLUSTERING

For statistical analyses, MI-based parameter estimation were shown more reliable than single imputation approach (e.g., mean, regression, and hot deck) which can introduce bias or lose precision. However, for clustering, MI-based approach has not yet been theoretically demonstrated better than other imputations, although intuitively would improve the uncertainty of clustering accuracy. Below we showed our theoretical demonstration.

1) MI vs Non-imputation (NI) Clustering

Lemma 1—MI- achieves higher clustering accuracy rate than NI-based Fuzzy Clustering.

Proof: Let X denote the $N \times d$ data matrix, where n denotes the number of patients who belong to k clusters and d the number of attributes. Let X_{mis} denote the missing part of X , and X_{obs} denotes the observed part with N' patients, $N' < N$, who also belong to these k clusters. Assume the n patients are clustered into the k clusters with accuracy $\mathfrak{I}$. With NI-fuzzy clustering, $(N - N')$ patients are not clustered due to their missing values on d . Then the clustering accuracy for NI is

$$\mathfrak{I}_{NI} = \mathfrak{I} \times N'/N, \quad (4)$$

For MI, X_{mis} are multiply-imputed, therefore, N patients are clustered. Suppose N^{MI} ($0 < N^{MI} < N - N'$) patients with X_{mis} is correctly clustered, then the accuracy is,

$$\mathfrak{I}_{MI} = \mathfrak{I}(N' + N^{MI})/N. \quad (5)$$

Therefore, $\mathfrak{I}_{MI} > \mathfrak{I}_{NI}$. Thus, the MI-based achieves higher accuracy than NI-based fuzzy clustering.

2) MI vs Single Imputation (SI) Clustering

The most commonly used single imputation methods include mean, regression and hot-deck imputation [72], which are used for demonstration in comparison to MI based clustering hereafter.

Lemma 2—MI-based approach reduces the uncertainty of clustering accuracy for incomplete longitudinal data compared to SI-based fuzzy clustering.

Proof: 1) Mean based SI: The missing values are filled by the means of the observed values. The variance of data is underestimated after mean imputation. For clustering, the patients close to each other are more likely to be classified into the same cluster. Since the missing values are filled by the same value (the mean), the patients with these means become closer to each other, and likely to be classified into the same cluster.

For a completed d -dimensional data X with n patients, suppose X contains k clusters where each cluster has N/k patients. Let r be the percentage of missingness, then each cluster has rN/k patients with missing values. The missing values are imputed by the mean SI before clustering. Then patients with imputed values (μ) are likely to be clustered in the same cluster and the mean SI-based clustering accuracy is expressed as

$$\mathfrak{I}_{\text{SI-mean}} = 1 - rN(k-1)/k, \quad (6)$$

where $rN(k-1)/k$ is the number of mistakenly clustered patients.

Figure 1a demonstrates a scenario where the mean-imputation reduces the clustering accuracy $\mathfrak{I}$. The scatter plot shows a two-dimensional X represented by (x_{i1}, x_{i2}) , where $k = 2$. The missing values of x_{i1} are marked by green circles in the 1st cluster and by green squares in the 2nd cluster. The patient i with missing values are denoted by

$$X_{i-\text{mis}} = \{(x_{i1-\text{mis}}, x_{i2})\}. \quad (7)$$

By conducting one-time mean-imputation, all the missing values are filled by $x_{1\mu}$ (marked by red circles/squares), then the patients are represented by

$$X_{\text{SI-mean}} = \{(x_{i\mu}, x_{i2})\}, \quad (8)$$

where $x_{i\mu} = \frac{1}{n'} \sum_{i=1}^{n'} x_{i1}$ and n' is the number of observed x_{i1} from all patients.

This one-time imputed values are the same and treated as if they are observed values and then used for clustering. As demonstrated in Figure 1b, 50% of the patients with missing values can be mistakenly clustered into the 1st cluster marked by circles.

2) Regression based SI clustering: A regression model can be learned from X_{obs} and the learned model with estimated coefficient is used to impute missing values of a variable based on other variables. For illustrative purposes, the regression coefficient $\hat{\beta}$ can be learned based on observed two-dimensional data, e.g.,

$$x_{i2} = \hat{\beta}x_{i1} + \varepsilon, \quad (9)$$

then

$$x_{i2-mis} = \hat{\beta}x_{i1}. \quad (10)$$

Figure 2a demonstrates a scenario $\mathfrak{I}_{SI-reg}$ where the regression SI reduces the clustering accuracy. With the same notation, the patient i with missing values on the second variable are denoted by

$$X_{i-mis} = \{(x_{i1}, x_{i2-mis})\}. \quad (11)$$

The missing values are imputed only once by this regression SI (marked by red circles/squares), and more likely to fit perfectly along the regression line since the imputed data do not have an error term included in their estimation,

$$X_{SI-regression} = \{(x_{i1}, \hat{\beta}x_{i1})\}. \quad (12)$$

Again, this one-time imputed values with errors are treated as if they are actual observed values and used for clustering. In the worst case, all cases with missing values can be mistakenly clustered, as shown in Figure 2b.

3) Hot-deck SI clustering: This type of SI first sorts a dataset according to any variables, and fill the missing values by using the observed values immediately prior to them and repeat this process until all missing values are imputed. If the selected variable that used to order the data does not have a significant role in clustering patients, the imputed data could be fully messed up after sorting and the likelihood of clustering the patients with missing values to their corresponding clusters is small.

Figure 3a shows how hot-deck SI reduces the clustering accuracy. Similarly, for a two-dimensional data X , represented by (x_1, x_2) , where $k = 2$. The missing values of x_1 are marked by green or circles squares in these two clusters, respectively. By conducting the hot-deck SI, the data are sorted by x_1 , and the missing values are filled by the observed x_1 values just prior to them (marked by red circles/squares),

$$X_{SI-hotdeck} = \{(x_{i1}, x_{j2})\}, \quad (13)$$

where j is the index of the case just before the i -th cases ordered according to x_2 . As shown in Figure 3b, the cases with missing values could be completely misplaced in different clusters using this imputation.

Overall, the $\mathfrak{I}_{SI}$ can be computed as,

$$\mathfrak{I}_{SI} = (N - n_{\text{control}} - n_{\text{intervention}})/N. \quad (14)$$

Although SI-derived data have the appearance of completeness, it can mislead the clustering results because SI again does not account for the imputation uncertainty and clustering accuracy from such data is uncertain.

4) MI-clustering: Unlike SI methods, the uncertainty of clustering accuracy is accounted by computing the average of clustering accuracy from clustering each of multiply imputed datasets generated from the stochastic processes. The variance of $\mathfrak{I}_{MI}$ aforementioned above is computed as,

$$\text{var}(\mathfrak{I}_{MI}) = \frac{1}{M-1} \sum_{i=1}^M (\hat{\mathfrak{I}} - \bar{\mathfrak{I}})^2, \quad (15)$$

where M is the number of imputations which can be estimated given the expected relative efficiency and the missing information of parameter estimates of attributes [73]. As shown in Table II, given our expected relative efficiency of 0.98 and missing information for TDTA (20%) and QP (10%), we chose 10 imputations for each.

The confidence interval of $\mathfrak{I}_{MI}$ could be estimated as:

$$\mathfrak{I}_{MI} \pm 1.96 \times \sqrt{\text{var}(\mathfrak{I}_{MI})/N}. \quad (16)$$

For example, given two dimensions, x_1 and x_2 ,

$$\begin{array}{cc} x_1 & x_2 \\ \left| \begin{array}{cc} 3 & 6 \\ 5 & \cdot \\ 6 & 12 \end{array} \right| \end{array}$$

and assume the true value for the missing value is 4, the mean SI would fill the missing value as 9, regression SI will estimate 10 ($x_2 = 2 \times x_1$), and hotdeck sorts x_2 and gives 12. Then these values will be treated as “true”. Differently, MI can estimate the missing value 10 times to account for the imputation uncertainty and thus, for clustering, it can reduce the uncertainty of clustering accuracy. As shown in Figure 4a, two patients marked green in each cluster have missing values on x_1 or x_2 . Assuming missing values are imputed 10 times, based on the clustering results from the ten imputed datasets, the two patients would still stay in their own clusters, even if the ten impute values can differ widely, as shown in Figure 4(b). Thus, the imputation uncertainty is accounted in MI process and the consequent uncertainty of $\mathfrak{I}_{MI}$ is reduced.

Overall, our theoretical demonstration indicates MI-based clustering is superior to NI- and SI-clustering because it accounts for the uncertainty of imputation and clustering accuracy for incomplete data.

IV. NUMERICAL ANALYSES

Our previous model comparison results across real random controlled trials (RCT) and observational studies are summarized below.

This section evaluates the performance of MI-based fuzzy clustering in comparison to SI- and NI- clustering using TDTA and QP data. In addition, we simulated data using the parameters from these two behavioral intervention studies. Specifically, we evaluated these three imputation-based clustering approaches under three missing data mechanisms. We also varied the percentage of missingness to evaluate the clustering performance based on the same validation index, called overlap over septation validation (OOS [51]) and clustering accuracy.

A. The Missing Mechanisms

In statistical theories, the three missing data mechanisms are termed as missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) [74], [75]. Using incomplete TDTA and QP data as an example, let X be the complete data without missing values, $X = X_{obs} \cup X_{mis}$, X_{mis} are the missing values on observed attributes P in the incomplete data X ; and P' are unobserved attributes. For example, for QP web trial study, we have longitudinal zero-inflated count data, then zero-inflated Poisson (ZIP) models are considered for data simulation under the generalized linear mixed model (GLMM) framework while the typical GLMM were used to generate data using parameters from TDTA.

1. *Missing Complete At Random (MCAR)*: we simulated data assuming X_{mis} are missing independently of both observed attributes P and unobserved P' .
2. *Missing At Random (MAR)*: Data were simulated assuming X_{mis} are missing independently of unobserved P' .
3. *Missing Not At Random (MNAR)*: Data were simulated assuming X_{mis} relate to unobserved attributes P' . MNAR occurs when the condition of MAR is violated.

B. Performance Evaluation Using TDTA and QuitPrimo

As shown in Figure 5, for TDTA, MI-based fuzzy clustering identified the optimal number of clusters as three, because the validation index reaches the lowest value, with clustering accuracy of 100%. SI-based clustering identified 3 clusters with accuracy of 85% and NI-based identified 3 clusters with accuracy of 80%.

For QP, MI Fuzzy identified 4 clusters with clustering accuracy of 78%, as shown in Figure 6. SI-based clustering identified 5 clusters with accuracy of 70% and NI-based identified 4 clusters with accuracy of 68%.

As demonstrated in the theoretical section, SI- and NI-based approach do not account for the uncertainty of imputation and treated the imputed values as if they are observed for clustering. Therefore, their clustering results could be misleading, and the uncertainty of

clustering accuracy is also not counted. Even if they identified the same clusters as MI-, the results could be due to chance.

We also evaluated the three imputation clustering approaches using simulation, where we primarily focus on their performance with a medium percentage of missingness (10%–15%) for each missing mechanism. We set the sample size n at 1000 and the dimension d at 20.

C. Performance under MCAR

As shown in Figure 7, for MCAR, MI-based fuzzy clustering identified the correct number of clusters, 4, and achieves 95% and 94% accuracy for 10% and 15% missingness, respectively. SI-based fuzzy clustering identified 4 clusters, with accuracy of 89% and 87% for 10% and 15% missingness, respectively. NI-based fuzzy clustering identified 4 clusters, with accuracy of 85% and 84% for 10% and 15% missingness, respectively.

D. Performance under MAR

As shown in Figure 8, for MAR, MI-based fuzzy clustering identified the correct number of clusters, 4, and achieves the Fig. 8: MI- vs. SI- and NI-clustering under MCAR accuracy of 96% and 93% for 10% and 15% missingness, respectively. SI-based fuzzy clustering identified 4 clusters, with accuracy of 88% and 85% for 10% and 15% missingness, respectively. NI-based fuzzy clustering identified 4 clusters, with accuracy of 86% and 83% for 10% and 15% missingness, respectively.

E. Performance under MNAR

As shown in Figure 9, for MNAR, MI-based fuzzy clustering identified the correct number of clusters, 4, and achieves the accuracy of 90% and 89% for 10% and 15% missingness, respectively. SI-based fuzzy clustering identified 4 clusters, with accuracy of 81% and 82% for 10% and 15% missingness, respectively. NI-based fuzzy clustering identified 4 clusters, with accuracy of 80% and 79% for 10% and 15% missingness, respectively.

Overall, under three mechanisms, MI-based clustering performance are similar and seems invariant to different missing data mechanisms. This invariant property of MIFuzzy may attribute to the fact that the actual MIFuzzy algorithm does not learn the "concepts" of missing mechanisms but is somewhat sensitive to the real numbers such as the percentage of missingness. With the increase of the percentage of missingness, MI-based clustering accuracy decreased but still achieved at least 93% across the three mechanisms. Although SI and NI identified the same number of clusters, as discussed in the theoretical section, it is likely due to chance and their clustering accuracy is lower and misleading, as they cannot account for the imputation uncertainty and therefore the accuracy is uncertain.

V. Conclusion

Smart health systems are patient-centered. Longitudinal behavioral interventions generate complex data with missing values and high dimensionality. Reliable and more accurate trajectory pattern recognition approaches will help capture patients' variations in engaging with or responding to behavioral interventions. Explaining these observed variations within

and between treatment and control groups can ultimately lead to appropriate and effective interventions adaptive to patients with at-risk patterns. This paper advances our understanding of the utility and strength of multiple-imputation (MI) based fuzzy clustering approach to processing incomplete longitudinal behavioral intervention data. Specifically, this paper theoretically, empirically and numerically demonstrated how MI-based approach can reduce the uncertainty of clustering accuracy in comparison to non- and single-imputation based clustering approach. Our future research will further evaluate MI-based approach under a large percentage of missingness and focus on visualization-aided validation to further expand the MI-based clustering approaches.

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Fig. 1.
Conceptual diagram of MI-Fuzzy procedure

(a) A 2-dimensional 2-cluster dataset with simulated missingness

(b) Mean-imputation Results

Fig. 2.
An illustration of mean-imputation

(a) The true two-dimensional incomplete data with two clusters

(b) Mistakenly clustered data after regression SI

Fig. 3.
Clustering accuracy of single regression imputation

(a) The true two-dimensional incomplete data with two clusters

(b) Mistakenly clustered data after hotdeck SI clustering

Fig. 4.
Clustering accuracy of single hotdeck imputation

(a) The true two-dimensional incomplete data with two clusters

(b) Imputed data for the missing values

Fig. 5.
Clustering accuracy of multiple imputation

Fig. 6.
Performance of MI-, SI- and NI-clustering on TDTA data

Fig. 7.
Performance of MI-, SI- and NI-clustering on QP data

(a) Simulated MCAR data with 10% missingness

(b) Simulated MCAR data with 15% missingness

Fig. 8.
MI- vs. SI- and NI-clustering under MCAR

(a) Simulated MAR data with 10% missingness

(b) Simulated MAR data with 15% missingness

Fig. 9.
MI- vs. SI- and NI-clustering under MAR

(a) Simulated MNAR data with 10% missingness

(b) Simulated MNAR data with 15% missingness

Fig. 10.
MI- vs. SI- and NI-clustering under MNAR

TABLE I

Notations

Symbols	Notations
X_{obs}, X_{mis}	Observed data and missing values
X	Dataset consists of X_{obs} and X_{mis}
M	Number of imputations
N	Number of cases in data X
N'	Number of cases in data X with missingness
$n_{control}$	Number of mislabeled control group members
$n_{intervention}$	Number of mislabeled intervention group members
$\mathfrak{I}$	Clustering accuracy
$\mathfrak{I}_{NI}$	Non-imputation clustering accuracy
$\mathfrak{I}_{SI-mean}$	Mean-imputation clustering accuracy
$\mathfrak{I}_{SI-regression}$	Regression-imputation clustering accuracy
$\mathfrak{I}_{SI-hotdeck}$	Hot deck-imputation clustering accuracy
$\mathfrak{I}_{MI}$	Multiple-imputation clustering accuracy
P, P'	Observed and unobserved attributes of X
CT	Termination clustering number
U	Fuzzy degree of cluster membership
V	Cluster centroids
n'	Number of patients with observed first attribute
r	Percentage of missing values
μ	Mean value
d	dimension of data X
k	Number of clusters

TABLE II

Output of SAS and MIFuzzy

Parameters	SAS_MI		MIFuzzy_MI	
	Oxygen	RunTim	Oxygen	RunTim
Mean	47.164819	10.549936	47.16481889	10.54993604
Std Erro	.994145	.273312	.99414456	.27331186
95CI_lower	45.1212	.98	45.12116282	.988031
95CI_upper	49.2085	11.1118	49.20847497	11.11184037
DF	25.95	25.90	25.95754831	25.90172223
Minimu	46.8580	10.476886	46.85801981	10.47688622
Maxmum	47.3635	10.659412	47.36354022	10.65941173
Mu	50	10	50	10
t for H0: Mean=Mu0	-2.85	.01	-2.85188012	.01211918
Pr bigger than t	.0084	.0547	.00841364	.05471599

Note: a we keep parameter names in SAS output.

TABLE IIIRE vs. r and M

M	r=10%	r=20%	r=30%	r=50%
3	0.968	0.938	0.910	0.857
5	0.980	0.962	0.934	0.910
10	0.990	0.980	0.971	0.952
20	0.995	0.990	0.985	0.976

	MIFuzzy	Kmeans	GMM	Bayesian based HMM	Neural Network based SOM	Hierarchical Clustering
Clustering Accuracy (%) ^a	97	78	77	79	66	48
Clustering inconsistency (%)	3	19	17	20	21	52

Note:

^a Averaged across two observational studies MIDS, MISSEB, and three RCT TDTA, QUITPRMO and P-DIET. GMM, Bayesian, Neural network were summarized across the last three RCTs as other two observational studies. However, even with these two OS, we do not think these models could outperform MIFuzzy based on our simulation studies.