Multi-study Factor Analysis

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Summary: We introduce a novel class of factor analysis methodologies for the joint analysis of multiple studies. The goal is to separately identify and estimate 1) common factors shared across multiple studies, and 2) study-specific factors. We develop a fast Expectation Conditional-Maximization algorithm for parameter estimates and we provide a procedure for choosing the common and specific factor. We present simulations evaluating the performance of the

method and we illustrate it by applying it to gene expression data in ovarian cancer. In both cases, we clarify the benefits of a joint analysis compared to the standard factor analysis. We have provided a valuable tool to accelerate

the pace at which we can combine unsupervised analysis across multiple studies, and understand the cross-study

reproducibility of signal in multivariate data. An R package, namely MSFA, is implemented and is available on

GitHub at https://github.com/rdevito/MSFA.

KEY WORDS: Cross-study analysis; Dimension reduction; ECM algorithm; Gene Expression; Meta-analysis; Reproducibility.

1. Introduction

Analyses that integrate multiple sources, studies, and data-collection technologies are common in current statistical research. When considering multiple studies, a fundamental challenge is learning common features shared among studies while isolating the variation specific to each study. Two important statistical questions remain largely unanswered in this context:

i) To what extent is the common signal shared across studies? ii) How can this shared signal be extracted? In this paper we develop a methodology to address these two questions for multi-study factor analysis.

Joint factor analysis of multiple studies is often used in several areas of science. For example Scaramella et al. (2002) researched adolescent delinquent behavior in two independent samples analyzing the same variables in order to identify the shared patterns across those two different samples. Andreasen et al. (2005) studied remission in schizophrenia, applying factor analysis (FA) for each individual samples. The work showed that replicable results are found across all these FA leading to similar components. In nutritional epidemiology Edefonti et al. (2012) analyzed the diet habits and the risk of head and neck cancer. In such work five different populations shared exactly the same variables (e.g. nutrients) to be then merged in one single "effective" population. Then they applied FA to this effective population to determine common dietary patterns and their relation with head and neck cancer. Wang et al. (2011) used FA to obtain a unified gene expression measurement from distinct types of measurements on the same sample.

These examples illustrate the urgent need for a model able to handle multiple studies and to derive in a single analysis (1) factors that capture common information, shared across studies, and (2) study-specific factors.

Our own motivating example derives from the analysis of gene expression data (Irizarry et al., 2003; Shi et al., 2006; Kerr, 2007). In gene expression analysis, as well as in much

of high-throughput biology analyses on human populations, variation can arise from the intrinsic biological heterogeneity of the populations being studied, or from technological differences in data acquisition. In turn both these types of variation can be shared across studies or not. As noted by Garrett-Mayer et al. (2008), the fact that the determinants of both natural and technological variation differ across studies implies that study-specific effects occur in most datasets. Both common and study-specific effects can be strong, and both need to be identified and studied. Our interest in this issue is a natural development of our previous work on unsupervised identification of integrative correlation (Parmigiani et al., 2004; Garrett-Mayer et al., 2008; Cope et al., 2014), and multi-study supervised analyses including cross-study differential expression (Scharpf et al., 2009), multi-study gene set analysis (Tyekucheva et al., 2011), comparative meta-analysis (Riester et al., 2014; Waldron et al., 2014), and cross study validation (Bernau et al., 2014).

In high-throughput biology, as well as in a number of other areas of application, the ability to separately estimate common and study-specific factors can contribute significantly to two important questions: the cross-study validation question of whether factors are found repeatedly across multiple studies; and the meta-analytic question of more efficiently estimating the factors that are indeed common. With regard to interpretation, the shared signal is more likely to capture genuine biological information, while the study-specific signal can point to either artifactual or biological sources of variation. Thus, modeling both shared and unshared factors may enable a more reliable identification of artifacts, facilitate more efficient experimental designs, and inform further technological advances.

In this article we propose a dimension-reduction approach that allows for joint analysis of multiple studies, achieving the goal of capturing common factors. Specifically, we define a generalized version of FA, able to handle multiple studies simultaneously. Our model, termed

Multi-study Factor Analysis (MSFA), learns the common features shared among studies, and identifies the unique variation present in each study.

While unsupervised multi-study analysis is not an adequately studied field, our work draws from existing foundations from related problems. In the social science literature, there is extensive methodology to identify factor structures shared among different groups, forming the body of multigroup factor analysis methods (see, among many others, Thurstone (1931); Jöreskog (1971); Meredith (1993)). Such methods are mainly focused on investigating measurement invariance among different groups, that typically results in testing whether the data support the hypothesis of a common loading matrix across groups. A notable special case is given by partial measurement invariance (see for example Byrne et al., 1989), which inspired our mathematical formulation. In our MSFA we have extended the scope to detection of both study-specific factors and factors that are identical across multiple studies. Our MSFA has also an exploratory nature, different from the confirmative approach under which measurement invariance is usually investigated in the social sciences.

The plan of the paper is as follows. Section 2 introduces the MSFA, and describes the estimation of model parameters based on maximum likelihood, implemented via an ECM algorithm. Section 3 presents simulation studies, providing numerical evidence on the performances of the proposed estimation methods. Next the determination of the dimension of the latent factor is investigated, tackled by casting it within the framework of model selection. Section 4 illustrates the application of the methodology to study of the Immune System pathway in ovarian cancer. Section 5 contains the final discussion.

2. Methods

2.1 The multi-study factor analysis (MSFA) model

The methodology proposed here has two main goals. First, we combine multiple studies to identify common factors that are consistently observed across the studies. Second, we explicitly model and identify additional components of variability specific to single studies, through study-specific factors. The latter aims to identify variation that lacks cross-study reproducibility, and separate it from variation that does.

We consider S studies, each with the same P variables. Generic study s has n_s subjects and, for each subject, P-dimensional centered data vector \mathbf{x}_{is} with $i=1,\ldots,n_s$. We begin by describing the case where a standard FA is carried out separately in each study. The observed variables in study s are decomposed into T_s factors. In particular, let \mathbf{l}_{is} , $i=1,\ldots,n_s$ be the values of the study-specific factors in individual i of study s and $\mathbf{\Lambda}_s$, $s=1,\ldots,S$ be the $P \times T_s$ corresponding factor loading matrix. FA assumes that \mathbf{x}_{is} is decomposed as

$$\mathbf{x}_{is} = \mathbf{\Lambda}_s \mathbf{l}_{is} + \mathbf{e}_{is} \quad i = 1, \dots, n_s \,, \tag{1}$$

where \mathbf{e}_{is} is a normal error term with covariance matrix $\mathbf{\Psi}_{s} = \operatorname{diag}(\psi_{1s}, \dots, \psi_{ps})$ (e.g. Jöreskog, 1967a,b; Jöreskog and Goldberger, 1972). FA aims at explaining the dependence structure among observations by decomposing the $P \times P$ covariance matrix $\mathbf{\Sigma}_{s}$ as $\mathbf{\Sigma}_{s} = \mathbf{\Lambda}_{s} \mathbf{\Lambda}_{s}^{\top} + \mathbf{\Psi}_{s}$.

Figure 1.a shows an overview of the studies analyzed in this work for which more information can be found in Supplementary Materials §A.

Figure 1.b suggests that some loading vectors may reveal common patterns across studies. This point is further explored in Figure 1.c where three of the loading vectors of the GSE9891 study are strongly correlated with four loading vectors in the GSE20565 study. Highly correlated pairs of loading vectors are more likely to represent common factors. On the other

hand, some loading vectors of GSE9891 (e.g. λ_{41}) exhibit low correlation with all loading vectors of GSE20565. These loadings are likely to result from feature unique to this study. Furthermore, in order to assess the multivariate correlation between the two loading matrices, we compute the RV coefficient (Robert and Escoufier, 1976). It is equal to 0.76 showing a very similar pattern between the two matrices, and equal to 0.86 taking in consideration the two matrices with the first four factor loadings only.

The MSFA model proposed here is designed to analyze multiple studies jointly, replacing the heuristic interpretation above with a principled statistical approach. It explicitly models common biological features shared among the studies, as well as unique variation present in each study. Specifically, the observed variables in study s are decomposed into K factors shared with the other studies, and J_s additional factors reflecting its unique sources of variation, for a total of $T_s = K + J_s$ factors. Let \mathbf{f}_{is} be the common factor vector in subject i of study s, and $\mathbf{\Phi}$ be the $P \times K$ common factors loading matrix. Moreover, let \mathbf{l}_{is} be the study-specific factor and $\mathbf{\Lambda}_s$ be the $P \times J_s$ specific factors loading matrix. MSFA assumes that the P-dimensional centered response vector \mathbf{x}_{is} can be written as

$$\mathbf{x}_{is} = \mathbf{\Phi} \mathbf{f}_{is} + \mathbf{\Lambda}_s \mathbf{l}_{is} + \mathbf{e}_{is}, \qquad i = 1, \dots, n_s \qquad s = 1, \dots, S.$$
 (2)

where the $P \times 1$ random error vector \mathbf{e}_{is} has a multivariate normal distribution with mean vector $\mathbf{0}$ and covariance matrix $\mathbf{\Psi}_s$, with $\mathbf{\Psi}_s = \operatorname{diag}(\psi_{s_1}^2, \dots, \psi_{s_p}^2)$. We also assume that the marginal distribution of \mathbf{l}_{is} is multivariate normal with mean vector $\mathbf{0}$ and covariance matrix \mathbf{I}_{J_s} , and the marginal distribution of \mathbf{f}_{is} is multivariate normal with mean vector $\mathbf{0}$ and covariance matrix \mathbf{I}_k , where \mathbf{I} denotes the identity matrix.

As a result of the model assumptions, the marginal distribution of \mathbf{x}_{is} is multivariate normal with mean vector $\mathbf{0}$ and covariance matrix $\mathbf{\Sigma}_s = \mathbf{\Phi}\mathbf{\Phi}^\top + \mathbf{\Lambda}_s\mathbf{\Lambda}_s^\top + \mathbf{\Psi}_s$, with the three terms reflecting the variance of the common factors, the variance of the study-specific factors, and the variance of the error, respectively.

This model can be applied to many settings when the aim is to isolate commonalities from differences across groups, population or studies. In the gene expression application of interest here the focus is on estimating the biological signal shared among the studies, while removing study-specific features less likely to be reproducible across populations, and potentially arising from technological issues. Elsewhere the goal may be to capture some study-specific features of interest while removing common factors shared among the studies. Finally, other applications may focus on both common and specific factors. Different examples focused in the study-specific pattern could be find in nutritional epidemiology (Carrera et al., 2007; Ryman et al., 2015) where population-specific diets have a lower or higher impact in specific disease, such as obesity and cancer.

2.2 Identifiability

To specify an identifiable model, the MSFA model must be further constrained to avoid orthogonal rotation indeterminacy, similarly to the classic FA. Let $\Omega_s = [\Phi, \Lambda_s]$ be the $P \times (K + J_s)$ loading matrix for the s^{th} study. If we define $\Omega_s^* = \Omega_s \mathbf{Q}_s$, where \mathbf{Q}_s is a square orthogonal matrix with $(K + J_s)$ rows, it readily follows that $\Omega_s^* (\Omega_s^*)^{\top} = \Omega_s \mathbf{Q}_s \mathbf{Q}_s^{\top} \Omega_s^{\top} = \Omega_s \Omega_s^{\top}$, so that $\Sigma_s = \Omega_s^* (\Omega_s^*)^{\top} + \Psi_s = \Omega_s \Omega_s^{\top} + \Psi_s$, and Σ_s is not uniquely identified.

FA (1) identifies the parameters by imposing constraints on the factor loadings matrix. One possibility often used in practice is to take Λ_s in (1) as a lower triangular matrix (Geweke and Zhou, 1996; Lopes and West, 2004; Carvalho et al., 2008). Here we adapt this approach to the MSFA, and specify $\Omega_s = [\Phi, \Lambda_s]$ to be lower triangular. Importantly, the matrices Φ and Λ_s are not interchangeable. As in FA, assuming a lower triangular form for Ω_s resolves the orthogonal rotation indeterminacy (Geweke and Zhou, 1996, pp. 565-566). There remain the issue that we can simultaneously change the sign to all the elements of the loading matrices and to all the latent factors without changing the model. This could be fixed by constraining

the sign of a subset of loadings, but for MLE of the model parameters this issue is largely inconsequential.

An important issue in maximum likelihood estimation of the MSFA model parameters concerns the complexity of the specifications that can be handled by the method, since there are some constraints that ought to be considered. In particular, for the s^{th} study, the number of elements in the sample covariance matrix, $\mathbf{C}_{x_s x_s}$, must be no greater than the number of parameters in $\mathbf{\Sigma}_s$, implying that $P(K+J_s)+P-\frac{(K+J_s)(K+J_s-1)}{2} \leqslant \frac{1}{2}P(P+1)$, $s=1,\ldots,S$. Another important constraint is that effective application of the method essentially requires more observations than variables. We will initially assume that $P<\min\{n_1,\ldots,n_s\}$. Some possible directions to consider to overcome the limitations will be highlighted in the Discussion.

2.3 Parameter estimation

The parameters to be estimated in the MSFA are $\boldsymbol{\theta} = (\boldsymbol{\Phi}, \boldsymbol{\Lambda}_s, \boldsymbol{\Psi}_s)$. For notational simplicity in both (1) and (2) we assume that the observed variables in each study have been centered. The log-likelihood function corresponding to the MSFA assumptions is

$$\ell(\boldsymbol{\theta}) = \log \prod_{s=1}^{S} \prod_{i=1}^{n_s} p(\mathbf{x}_{is} | \boldsymbol{\theta}) = \sum_{s=1}^{S} \left\{ -\frac{n_s}{2} \log |\boldsymbol{\Sigma}_s| - \frac{n_s}{2} \operatorname{tr}(\boldsymbol{\Sigma}_s^{-1} \mathbf{C}_{x_s x_s}) \right\}.$$

In the following, the MLE will be obtained by means of the Expectation Conditional Maximization (ECM) algorithm (Meng and Rubin, 1993), a class of generalized EM algorithms (Dempster et al., 1977; Rubin and Thayer, 1982). The details of the ECM algorithm for the MSFA model are reported in the Supplementary Materials.

2.3.1 Dimension Selection. Selecting the dimension of the model can be challenging. The following two-step procedure was found to be effective in the settings of interest. First the total latent dimension $T_s = K + J_s$ for each of the S studies is determined by using standard techniques for FA, such as Horn's parallel analysis (Horn, 1965), Cattell's scree test (Cattell,

1966) or the use of indexes, such as the RMSEA (Steiger and Lind, 1980). Next, model selection techniques are applied to the overall MSFA model to select the number K of latent factors sharing a common loading matrix Φ , as described in §3.2. The dimensions J_s are then obtained residually as $T_s - K$, with the restrictions that $T_s - K \ge 0$ for all s = 1, ..., S.

3. Simulation studies

We perform simulation experiments to evaluate the effectiveness of the ECM algorithm in estimating the MSFA model parameters, as well as the suggested strategy for selecting the dimensionality of the latent factors. The simulation studies are designed to closely mimic the data of Figure 1.a, therefore S=4 studies are considered, with dimension of the latent factors $T_s=\{6,7,10,9\}$, and \mathbf{x}_{is} generated from P-dimensional normal distributions, with sample size equal to $n_s=\{285,140,195,578\}$. The samples from the various studies are assumed to be drawn from the different population, each with zero mean and covariance matrix $\mathbf{\Sigma}_s=\mathbf{\Phi}\mathbf{\Phi}^\top+\mathbf{\Lambda}_s\mathbf{\Lambda}_s^\top+\mathbf{\Psi}_s$, with $S=1,\ldots,4$.

Three simulation scenarios are investigated. In Scenario 1 there are no common factors, i.e. K = 0, in Scenario 2 K = 1, and in Scenario 3 K = 3. To achieve more realistic results, in each scenario the data are generated by parameter values akin to those estimated with the data introduced in Section 2.

3.1 Parameter estimation via the ECM algorithm

We first analyze the performances of the ECM algorithm for a given selection of K and J_s , s = 1, ..., S.

Irrespective of the optimization method adopted, the choice of the starting point is crucial for achieving good performances. The following strategy is proposed, for given factor dimensions K and J_s , s = 1, ..., S.

- (1) A single data set is created by stacking the data of the four studies by row, obtaining a single data set with $n = n_1 + n_2 + n_3 + n_4 = 1198$ observations and P = 100 variables.
- (2) A Principal Components Analysis (PCA) is performed on the data obtained at step (1). The first K components are taken as the starting point of the common factor loadings.
- (3) We perform FA to the separated data. The loadings and uniquenesses obtained from the FA are used as the initial values for Λ_s and Ψ_s .

[Figure 2 about here.]

Figure 2 shows that the convergence of the ECM algorithm is obtained with fewer number of iterations compared to box-constrained Limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) method (e.g. Byrd et al., 1995). Moreover, severe convergence problems arise when the L-BFGS method is used for larger number P of variables.

Figure 3 shows that MSFA is able to recover the true common factor loadings. Moreover, MSFA performs better than FA in terms of estimating the true shared factor loadings. FA is computed after stacking the studies in a unique dataset. Different analysis for checking if the MSFA recovers the true factors, and results for the other scenarios are reported in Supplementary Materials.

[Figure 3 about here.]

3.2 Selection of the latent factor dimensions

The selection of the dimension of the latent space is studied, again by means of simulation experiments performed under the same three scenarios considered above. For each data set, we first choose T_s by means of standard FA techniques, and then choose K. We thus focus in particular on the problem of selecting K, tackled by applying existing model selection techniques, such as the AIC and BIC criteria, for which there is an extensive literature (Burnham and Anderson, 2002; Preacher and Merkle, 2012). The study of model selection

based on information criteria is still in progress in FA settings (Chen and Chen, 2008; Hirose and Yamamoto, 2014), so it seems useful to evaluate the behavior of both AIC and BIC for choosing K. Along the two information-based criteria, the likelihood ratio test (LRT) for choosing between nested models with different values of K is considered as well.

Table 1 shows the results obtained by our model fitting approach for 100 different data sets generated independently from the MSFA under the three different scenarios.

[Table 1 about here.]

AIC seems to be the best criterion, always leading to the selection of the true model. The contrast with the performance of the BIC is striking. Generally, BIC penalizes model complexity more strongly than AIC, so it is not surprising that BIC tends to prefer models with more common factor loadings and thus less parameters. In our application, subtracting a unit to K adds a large number of parameters to the model, as more factors are allowed to differ across studies.

The results of these three simulation studies point strongly towards the usage of AIC to select the value of K. This will therefore be the strategy employed in our applied example.

4. Gene expression example: Immune System pathway

To illustrate MSFA in an important biological example, we analyzed the four studies described in Figure 1.a where the sample size $n_s(s=1,\ldots,4)$ are listed, focusing on transcription of genes involved in immune system activity (P=63). Specifically, we considered genes included in the sub-pathways "Adaptive Immune System" (AI), "Innate Immune System" (II) and "Cytokine Signaling in Immune System" (CSI) from reactome.org. These sub-pathways belong to the larger Immune System pathway and do not have overlapping genes. In addition, we restricted attention to genes which are common across all studies.

Initially, we conducted preliminary analyses to asses the total latent factor dimensions, the

number of common factors across studies and the number of specific factors for each study.

Using the AIC, the number of common factors is set to one.

We then compare the cross-validation prediction errors computed by the MSFA to those computed by FA. Notice the latter method is applied in two different ways, namely the first is merging 4 studies into one single data set and the second is to separately compute FA in each study. We fit the MSFA and the standard FA on a random 80% of the data, and evaluate the prediction error on the remaining 20%. Predictions are obtained as

MSFA:
$$\hat{\mathbf{x}}_{is} = \hat{\mathbf{\Phi}}\hat{\mathbf{f}}_i + \hat{\mathbf{\Lambda}}_s^{MSFA}\hat{\mathbf{l}}_{is}$$
 FA: $\hat{\mathbf{x}}_{is} = \hat{\mathbf{\Lambda}}_s^{FA}\hat{\mathbf{l}}_{is}$.

where $\hat{\Lambda}_s^{MSFA}$ are the specific factor loadings estimated with MSFA and $\hat{\Lambda}_s^{FA}$ are the factor loadings estimated with FA. We evaluated the mean squared error of prediction MSE = $\frac{1}{n}\sum_{s=1}^{S}\sum_{i=1}^{n}(x_{is}-\hat{x}_{is})^2$, using the 20% of the samples in each study set aside for each cross-validation iteration. The MSE is 4% smaller for MSFA than for FA after merging the data and is 0.048% smaller for MSFA than for FA applied separately to each study.

This analysis illustrates how MSFA borrows strength across studies in the estimation of the factor loadings, in such a way that the predictive ability in independent observation is not only preserved but even improved. Moreover, the AIC obtained with FA after stacking all the study in a dataset is higher than the AIC computed by MSFA.

Next, we focus on the analysis of the factor themselves. The heatmap in Figure 4.a depicts the estimates of the factor loadings, both the common factor (highlighted in the black rectangle) that can be identified reproducibly across the studies, and the specific ones.

[Figure 4 about here.]

To help interpreting the biological meaning of the common factor, we apply Gene Set Enrichment Analysis (GSEA) for determining whether one of the three gene sets is significantly enriched among loadings that are high in absolute value (Mootha et al., 2003; Subramanian et al., 2005). We consider all the three sub-pathways in the Immune System pathway. We used

the package RTopper in R in Bioconductor, following the method illustrated in Tyekucheva et al. (2011). The resulting analysis shows that the common factor is significantly enriched by the II system sub-pathway, suggesting that genuine biological signal may have been identified.

Further, Figure 1.b shows that three of the specific factors of the GSE9891 study are strongly correlated with three corresponding factors in the GSE20565 study.

To further probe this possibility, at least within the Immune System pathway, we analyze studies GSE9891 and GSE20565 separately from the other two using MSFA (Figure reported in Supplementary materials). The AIC chooses a model with K=4. Studies GSE9891 and GSE20565 use the same microarray platform, Affy U133 Plus2.0, unlike the other two. This prompts the conjecture that the three stronger correlations observed may be related to technological rather than biological variation. Naturally it is also possible that there may be specific technical features of this platform that enable it to identify additional factors, although this is less likely in view of the fact that our analysis is restricted to a common set of genes.

We performed the GSEA on the estimated factor loadings for the two-study analysis. The results show that the first common factor is still related to the II system pathway, as was the case for the single common factor shared between the four studies in the earlier analysis. Also, the common factor of the four studies analysis is highly correlated with the first common factors of the two-study analysis, r = 0.60. The three remaining common factors are not related to any of the remaining pathways, further corroborating the hypothesis that they may represent the results of spurious variation unique to the specific platform used.

We also checked the impact of the choice of a gene order, because of the dependence induced by the block lower triangular structure assumed for Ω_s , to address identifiability. In particular, we repeated the same analysis after permuting the variables. Despite minor discrepancies, the final conclusion is not changed. Namely, the single common factor is significantly enriched only with the innate immune system sub-pathway.

Overall, this analysis illustrates important features of this method, including its ability to capture biological signal common to multiple studies and technological platforms, and at the same time to isolate the source of variation coming, for example, from the different platform by which gene expression is measured.

5. Discussion

In this article we introduced and studied a novel class of factor analysis methodologies for the joint analysis of multiple studies. We have provided a valuable tool to accelerate the pace at which we can combine unsupervised analysis across multiple studies, and understand the cross-study reproducibility of signal in multivariate data.

The main concept is to separately identify and estimate 1) common factors shared across multiple studies, and 2) study-specific factors. This is intended to help address one of the most critical steps in cross-study analysis, namely to identify factors that are reproducible across studies and to remove idiosyncratic variation that lacks cross-study reproducibility. The method is simple and it is based on a generalized version of FA able to handle multiple studies simultaneously and to capture the two types of information.

Several methods have been proposed to analyze diverse data sets and to capture the correlation between different studies. The CPCA was introduced by Flury (1984) to investigate the hypothesis that the covariance matrices for different populations are simultaneously diagonalizable. This method estimates a common principal axes across the different population and the deviation of the data from the model of common principal axes. The Co-inertia analysis (CIA) emerged in ecology to explore the common structure of two distinct sets of variables (such as species' abundances of flora and fauna) measured at the same sites (Dolédec and Chessel, 1994; Dray et al., 2003). It proceeds by separately performing dimension reduction

on each set of variables, to derive factor scores for the sites. In a second, independent, stage the correlation between these factors is investigated. The Multiple Co-inertia analysis (MCIA) (Dray et al., 2003) is a generalization of CIA to consider more than two data sets. MCIA finds a hyperspace, where variables showing similar trends are projected close to each other (Meng et al., 2014).

A related method is the Multiple Factor analysis (MFA) (Abdi et al., 2013), an extension of principal component analysis (PCA) which consists of three steps. The first is a PCA for each study. In the second step each data set is normalized by dividing by its first singular value. In the third step, a single data set is created by stacking the normalized data from different studies by row, and a final PCA is done.

Two differences can be emphasized between these approaches and Multi-study Factor Analysis. First they are focused on analyzing only the common structure after having excluded the noise. Instead our method gives an estimation of both common and study-specific components. Second they operate stage-wise, decomposing each matrix separately, while our study analyzed the data jointly. This is critical in a meta-analytic context because the presence of a recognizable factor in one study can assist with the identification of the same factor in other studies even when it is more difficult to recognize it.

We develop a fast ECM algorithm for parameter estimates and provide a procedure for choosing the common and specific factor. The MSFA needs to be constrained to be identifiable and so the constraints used here is the popular block lower triangular matrix. Although this condition is largely used in classical FA settings, it induces an order dependence among the variables (Frühwirth-Schnatter and Lopes, 2010). As noted in Carvalho et al. (2008), the choice of the first $K + J_s$ variables is an important modeling decision, to be made with some care. In our application, it is somewhat reassuring that the checking made on the impact of the chosen variable order on the final conclusion leads to the same conclusions, although

general conclusions cannot be drawn. Others constraints or rotation methods, such as the varimax criterion (Kaiser, 1958), could be considered, though their extension to the MSFA setting would require some further investigation.

In settings characterized by high-dimensional data, the n > P condition requires variations to the proposed computations. To this end, our ongoing research is focusing on the extension of the Bayesian infinite factor model proposed by Bhattacharya and Dunson (2011) to the MSFA setting.

The MSFA model can be applied to many settings when the aim is to isolate commonalities and differences across different groups, population or studies. There might be other applications where the goal is to capture study-specific features of interest and, instead, remove common factors shared among studies. Other applications may focus on capturing both common and specific factors, without removing any of them. MSFA may have broad applicability in a wide variety of genomic platforms (e.g. microarrays, RNA-seq, SNPs, proteomics, metabolomics, epigenomics), as well as datasets in other fields of biomedical research, such as those generated by exposome studies or Electronic Medical Record (EMR). However, the concept is straightforward, universal and of general interest across all applications of multivariate analysis.

An R package, namely *MSFA*, is implemented and available on GitHub at https://github.com/rdevito/MSFA.

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a.	Table 1 The four data sets considered in the illustration and their characteristics.											
	Study	Samples	Platform	Late Stage (%)		Reference	T_s					
	GSE9891	285	Affy U133Plus 2.0	85		Tothill et al. (2008)	6					
	GSE20565	140	Affy U133Plus 2.0	48		Meyniel et al. (2010)	7					
	GSE26712	195	Affy U133a	96		Bonome et al. (2008)	10					
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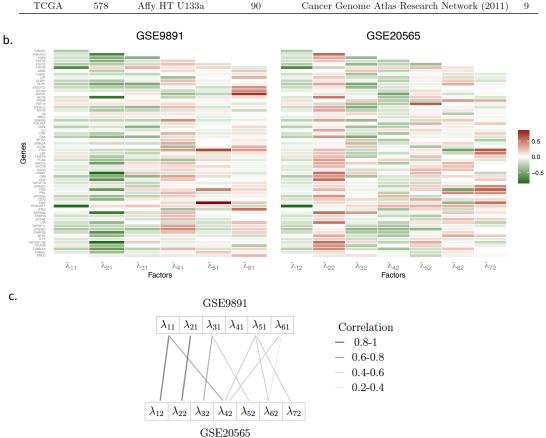


Figure 1: a: Table of the four data sets considered in the analysis. It provides an overview of the studies with corresponding samples, information about the specific microarray platform used, the proportion of patients diagnosed with Stage III or Stage IV OC, references, and finally the total latent dimension T_s obtained by nFactors package in R. b: Heatmap of the estimated factor loadings, $\Lambda_1 = \{\lambda_{11}, \lambda_{21}, \lambda_{31}, \lambda_{41}, \lambda_{51}, \lambda_{61}\}$ for the GSE9891 study and $\Lambda_2 = \{\lambda_{12}, \lambda_{22}, \lambda_{32}, \lambda_{42}, \lambda_{52}, \lambda_{62}, \lambda_{72}\}$, obtained by performing a separate factor analysis as in equation (1) in studies GSE9891 and GSE20565 from Figure 1.a. Each column λ_{is} is thus the i^{th} loading vector of the s^{th} study. We estimate parameters by maximum likelihood estimation (MLE), implemented via the Expectation-Maximization (EM) algorithm using the identifying constraint that the loading matrix is lower triangular, as will be detailed in §2.2-2.3. c: Graphical representation of the absolute value of correlations between pairs of study-specific factor loadings. Correlations smaller than .2 are not shown. Darker lines denote larger correlations in absolute value. In these correlations the same variables are considered in each study, and their order is preserved.

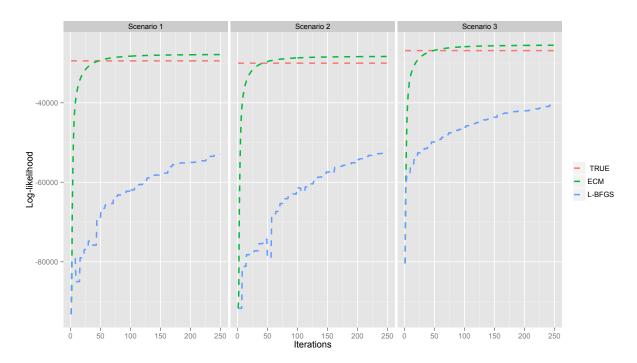


Figure 2: Log-likelihood by iteration. This graph compares the ascent of the log-likelihood function obtained with the ECM algorithm (green line) to those obtained by maximizing the log-likelihood $\ell(\theta)$ by a standard quasi-Newton optimizer, given by the box-constrained Limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) method (e.g. Byrd et al., 1995) (blue line), whereas the red line represents the log-likelihood calculated at the true parameter value. Each panel refers to a single representative data set, for each of the three scenarios. The two algorithms start from the same point. This method is used for benchmarking the ECM algorithm in its standard form, without any particular effort to tailor the optimization to the model at hand.

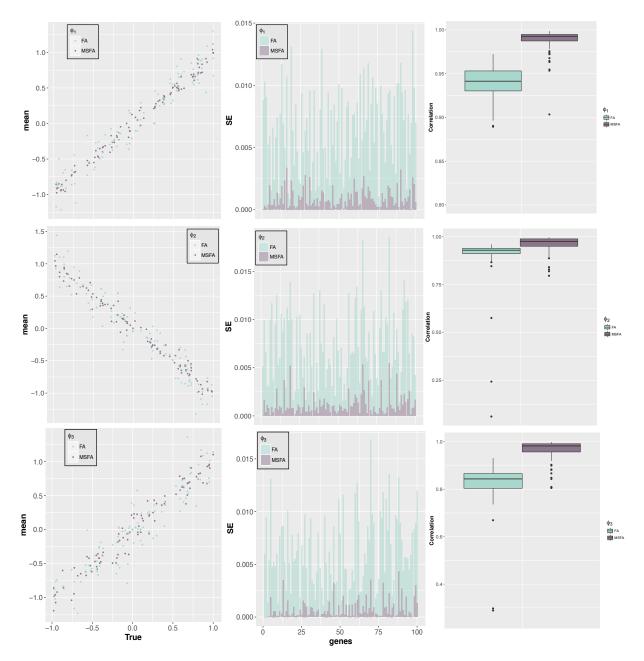


Figure 3: Distribution of the common factor loadings estimated by MSFA (in purple) and FA (in green) from 100 simulations under Scenario 3, i.e. K=3. The graph compares the distribution of the estimated three factor loadings identified by the MSFA (in purple) and FA (in green) after stacking the datasets in one. The left panel shows the mean of the estimated factor loadings after the 100 simulation and the distance from the true common factor loadings. Comparison with FA are also reported. In the center we report the standard errors of these distances. Standard errors of each variable or gene obtained by MSFA (in purple) are smaller than those obtained by FA (in green) for all the three common factor estimates. Finally, in the right panel we report the boxplot showing the correlation between the estimated factor loadings and the true common loadings for each simulation.



Figure 4: **a.**Heatmap of the estimated factor loadings obtained with MSFA, both common (black rectangle) and specific ones performed in the data sets in Figure 1.a. **b.** Graphical representation of the cross-study pairwise correlation of the specific factor loadings obtained with the MSFA. Darker grey lines correspond to higher correlations. Correlations smaller than .25 are not shown. Absolute correlations range from 0.66 to 0.81.

Table 1: Comparison of model assessment methods under Scenario 1, 2 and 3. Results are obtained by our model fitting approach on simulations for 100 different data sets generated independently from the MSFA with K=0, K=1 and K=3. In Scenario 1 the overall trend is that all the three methods favor choosing the model with K=0, but both AIC and LRT do so more consistently than BIC. In Scenario 2 and 3 AIC outperforms both BIC and LRT, though the latter is not far off.

	Method	K = 0	K = 1	K = 2	K = 3	K = 4	K = 5
	AIC	100	0	0	0	0	0
Scenario 1	BIC	91	1	2	6	0	0
	LRT	100	0	0	0	0	0
	Method	K = 0	K = 1	K = 2	K = 3	K = 4	K = 5
	AIC	0	100	0	0	0	0
Scenario 2	BIC	0	0	0	2	6	92
	LRT	3	97	0	0	0	0
	Method	K = 0	K = 1	K = 2	K = 3	K = 4	K = 5
	AIC	0	0	0	100	0	0
Scenario 3	BIC	0	0	0	1	23	76
	LRT	0	0	0	91	9	0