Unsupervised EHR-based phenotyping via matrix and tensor decompositions

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Abstract
Computational phenotyping allows for unsupervised discovery of subgroups of patients as well as corresponding co-occurring medical conditions from electronic health records (EHR). Typically, EHR data contains demographic information, diagnoses and laboratory results. Discovering (novel) phenotypes has the potential to be of prognostic and therapeutic value. Providing medical practitioners with transparent and interpretable results is an important requirement and an essential part for advancing precision medicine. Low-rank data approximation methods such as matrix (e.g., nonnegative matrix factorization) and tensor decompositions (e.g., CANDECOMP/PARAFAC) have demonstrated that they can provide such transparent and interpretable insights. Recent developments have adapted low-rank data approximation methods by incorporating different constraints and regularizations that facilitate interpretability further. In addition, they offer solutions for common challenges within EHR data such as high dimensionality, data sparsity and incompleteness. Especially extracting temporal phenotypes from longitudinal EHR has received much attention in recent years. In this paper, we provide a comprehensive review of low-rank approximation-based approaches for computational phenotyping. The existing literature is categorized into temporal versus static phenotyping approaches based on matrix versus tensor decompositions. Furthermore, we outline different approaches for the validation of phenotypes, that is, the assessment of clinical significance.

This article is categorized under:
Algorithmic Development > Structure Discovery
Fundamental Concepts of Data and Knowledge > Explainable AI
Technologies > Machine Learning

KEYWORDS
electronic health records (EHR), low-rank approximations, matrix/tensor decompositions, phenotyping, temporal phenotyping

1 INTRODUCTION
The fast adoption of healthcare information systems and the resulting aggregation of electronic health records (EHR) has led to the development of different phenotyping methods with the goal of identifying co-occurring medical...
conditions and discovering subgroups of patients that, for instance, share certain disease (progression) characteristics. EHR are typically comprised of demographic data, diagnoses, laboratory test results and prescriptions. The discovery of patient subgroups was formerly based on medical expertise or by heuristics. Computational phenotyping accelerates and facilitates this process. As labeling EHR data is very labor-intensive (Hripcsak & Albers, 2013), and one of the main goals of computational phenotyping is to identify novel phenotypes, effective unsupervised methods are needed. These automated and unsupervised approaches are highly relevant for medical practitioners as well as researchers because of the potential of transforming idiosyncratic, raw and unlabeled health records into clinically relevant, explainable and interpretable concepts (Ho, Ghosh, & Sun, 2014; Shivade et al., 2014). Thus, the discovery and assessment of phenotypes might improve the understanding of a disease and can be of prognostic or therapeutic value thereby promoting personalized medicine (Abul-Husn & Kenny, 2019).

The trend from traditional rule-based phenotyping systems that require medical expertise towards data-driven methods is ongoing (Richesson et al., 2016; Shivade et al., 2014). Natural language processing (NLP) has been playing a crucial role to extract phenotypes and clinical relationships or features from unstructured EHR such as clinical notes (Banda et al., 2018; Friedman & Hripcsak, 1999). Phenotypes have been extracted from EHR using unsupervised methods such as various clustering approaches (Doshi-Velez et al., 2014; Pikoula et al., 2019; Schulam et al., 2015). Deep learning (DL) methods have become increasingly popular for the (mainly supervised) analysis of both static and temporal EHR data (Solares et al., 2020). However, the lack of interpretability and model transparency has been repeatedly raised as the main disadvantage of DL-based methods (Shickel et al., 2017; Xiao et al., 2018).

On the other hand, low-rank data approximations (matrix factorizations as well as tensor factorizations, that is, extensions of matrix factorizations to higher-order data sets) have shown promise in terms of providing medical practitioners and researchers with interpretable results (Banda et al., 2018; Luo, Wang, & Szolovits, 2017). Low-rank structures typically arise due to similar patient groups sharing a set of frequently co-occurring medical conditions. For instance, EHR data can be arranged as a patients by clinical features matrix (as in Figure 1), and a low-rank approximation of the matrix summarizes the data using only several factors (much smaller than the number of features) corresponding to various phenotypes. Since EHR data is quite rich and often multi-way, that is, has more than two modes of variation, the data can be represented as a multi-way array (also referred to as a higher-order tensor), for example, patients by diagnoses by medications tensor as in Figure 5 or patients by clinical features by time tensors as in Figure 7. Similar to matrix factorizations, tensor factorizations can provide interpretable summaries of such multi-way data revealing phenotypes. Matrix and tensor factorizations also allow for a variety of constraints, for instance, to enforce more distinct or sparse phenotypes; thereby, facilitating clinical analysis and interpretation.

As a result of their effectiveness in terms of revealing interpretable patterns from complex EHR data in an unsupervised way, matrix and tensor factorizations have been widely studied in recent years. Especially temporal phenotyping via tensor decompositions has received much attention (Afshar et al., 2018; Perros et al., 2017; Perros et al., 2019; Zhang et al., 2021; Zhao et al., 2019). Temporal phenotyping focuses on the discovery of phenotypes as well as their temporal changes through the analysis of longitudinal EHR data. Extracting temporal signatures of phenotypes can contribute to the general understanding of a disease and provide more accurate phenotypes (Perros et al., 2017;
| Reference | Model | SA | H | SL | L | M | Target (disease)/case study | T | Modes | Focus/main contribution |
|-----------|-------|----|---|----|---|---|----------------------------|---|-------|------------------------|
| **Matrix decomposition: static phenotyping** |       |    |   |    |   |   |                             |   |       |                        |
| Burgel et al. (2010) | PCA | × | × | C2 |   |   | COPD | m | p × cl | application |
| Georgiades et al. (2007) | PCA | × | × | C2 |   |   | autism spectrum disorder | m | p × cl | application |
| Aliberti et al. (2016) | PCA | × | × | C2 |   |   | bronchiectasis | m | p × cl | application |
| Vavougios et al. (2016) | PCA + opt. scaling | × |   | C2 |   |   | sleep apnea | m | p × cl | application |
| Rennard et al. (2015) | FA | × | × | C2 |   |   | COPD | m | p × cl | application |
| Joshi et al. (2016) | NMF₂ | × | × | C2 |   |   | ICU mortality | c | p × d | weak supervision |
| Wang et al. (2020) | NMF | × | × | C2 |   |   | lymphocytic leukemia | c | p × cl | application |
| Schuler et al. (2016) | GLRM |   |   |   |   |   | hospitalization | m | p × cl | application |
| **Matrix decomposition: temporal phenotyping** |       |    |   |    |   |   |                             |   |       |                        |
| Luo et al. (2016) | SANMF | × |   | C2 |   |   | ICU mortality | c | p × sg | SANMF |
| Ding and Luo (2021) | SANMF | × |   | C2 |   |   | sepsis | c | p × sg | application |
| Stroup et al. (2019) | SANMF | × |   | C2 |   |   | multiple organ dysfunction | c | p × sg | application |
| Hassaine et al. (2020) | NMFΚL | × |   | C2 |   |   | general multi-morbidity | r | age × disease per p | temporal concatenation |
| Schuler et al. (2016) | PCA_{Poisson} | × |   | C2 |   |   | autism spectrum disorder | c | p × t | application |
| **Tensor decomposition: static phenotyping** |       |    |   |    |   |   |                             |   |       |                        |
| Ho, Ghosh, and Sun (2014) | CP_{KL} | × |   | C2 |   |   | high cost beneficiaries | c | p × d × proc | sparse non-negative CP |
| Ho, Ghosh, Steinhubl, et al. (2014) | CP_{KL} | × | × | C2 |   |   | heart failure | c | p × d × med | sparse non-negative CP |
| Yang et al. (2017) | CP_{KL} | × |   | C2 |   |   | hospitalization/ expenses | c | p × d × med | supervision |
| Henderson et al. (2017) | CP_{KL} | × | × | C2 |   |   | hypertension | c | p × med × d | distinct phenotypes |
| He et al. (2019) | CP_{KL} | × | × | C2 |   |   | general multi-morbidity | c | p × d × med | distributed computation |
| Henderson et al. (2018) | CP_{KL} | × | × | C2 |   |   | hypertension/ diabetes | c | p × d × med | semi-supervision |
| Ferros et al. (2018) | CP | × |   | C2 |   |   | heart failure | c | p × d × med | integer-constrained factors |
| Kim, El-Kareh, et al. (2017) | CP | × |   | C2 |   |   | ICU mortality | c | p × d × med | supervision, distinct phenotypes |
| Kim, Sun, et al. (2017) | CP | × |   | C2 |   |   | general multi-morbidity | c | p × med × d | privacy-preserving |
| Ma et al. (2019) | CP | × |   | C2 |   |   | ICU mortality | c | p × d × proc | privacy-preserving |
| Wang et al. (2015) | CP | × |   | C2 |   |   | general multi-morbidity | b | p × d × med | guidance constraints |
| HITF | × | × | C2 |   |   | ICU mortality | c/r |          |                        |

(Continues)
Zhang et al., 2021). Here, we review matrix and tensor factorization-based approaches for electronic health records-based phenotyping, discuss their strengths and limitations, as well as possible future research directions.

While there are recent survey papers on computational phenotyping reviewing NLP methods (Zeng et al., 2018), deep learning-based approaches (Shickel et al., 2017; Solares et al., 2020), giving a more general overview over different data mining and machine learning techniques (Shivade et al., 2014), and discussing the general transition from rule-based systems towards machine learning models (Banda et al., 2018), to the best of our knowledge, tensor methods have only been briefly discussed for precision medicine (Luo, Wang, & Szolovits, 2017). In this paper, we provide a comprehensive review of low-rank approximation-based approaches for unsupervised phenotyping categorizing the existing literature as temporal versus static phenotyping approaches based on matrix versus tensor decompositions. Moreover, we review validation approaches crucial for unsupervised phenotyping. Within the context of this survey, we discuss the key challenges in phenotype discovery—identified and addressed in the literature: high dimensionality (Perros et al., 2019; Yang et al., 2017), data sparsity (Perros et al., 2017; Schuler et al., 2016; J. Zhou et al., 2014), incompleteness

| Reference                  | Model          | SA | H | SL | L | M | Target (disease)/case study | T | Modes                  | Focus/main contribution                      |
|----------------------------|----------------|----|----|----|----|----|-----------------------------|----|--------------------------|---------------------------------------------|
| Yin, Cheung, et al. (2020) | SANTF          | ×  | ×  |    |    |    | lymphoma                    | c  | p × sg × words            | SANTF                                       |
| Luo et al. (2015)          | SANTF          |    |    |    |    |    |                             |    |                         |                                             |
| J. Zhou et al. (2014)      | CMF            |    | ×  |    |    |    | congestive heart failure    | c  | feature × t               | densification of EHR                        |
| He et al. (2019)           | CP<sub>KL</sub> |    |    |    |    |    | flu patterns                | c  | r × w × y                 | distributed computation                     |
| Zhao et al. (2019)         | CP             | ×  | ×  | ×  |    |    | cardiovascular disease      | b  | p × disease × t            | application                                 |
| Zhang et al. (2021)        | CP             |    |    |    |    |    | sepsis/acute kidney injury  | r  | p × p × feature            | DTW-CP                                      |
| Yin, Afshar et al. (2020)  | PARAFAC<sub>2log</sub> | ×  |    |    |    |    | ICU mortality/heart failure | b  | p × cl × t                | logistic PARAFAC2                           |
| Perros et al. (2019)       | PARAFAC2       |    |    |    |    |    | medically complex children  | b  | p × cl × t                | application                                 |
| Perros et al. (2017)       | PARAFAC2       |    |    |    |    |    | medically complex children  | c  | p × (d med) × t            | scalable PARAFAC2                           |
| Ren et al. (2020)          | PARAFAC<sub>2prob+1,N</sub> | ×  |    |    |    |    | ICU mortality               | c  | p × d × t                 | robust PARAFAC2                             |
| Afshar et al. (2018)       | PARAFAC2       |    |    |    |    |    | general multi-morbidity     | b? | p × cl × t                | temporal smoothness                         |
| Yin et al. (2019)          | CNTF<sub>KL</sub> | ×  |    |    |    |    | ICU mortality               | b  | t × med × lab per p        | CNTF & RNN regularization                   |
| Afshar et al. (2020)       | PARAFAC2/MF    | ×  | ×  |    |    |    | heart failure               | b? | p × (d med) × t            | temporal & static information ×             |

Note: In the model column, subscripts such as I, informational, KL, Kullback–Leibler, or log, logistic; denote loss functions. If no subscript is used, the standard squared Frobenius norm (Frob) is used within the objective function.

Abbreviations: Modes column: cl, clinical features; d, diagnosis (codes); med, medication; p, patient; proc, procedure; r, regions; sg, subgraph; t, time; w, weeks; y, years. Validation approach columns: H, hypothesis testing; L, literature comparison; M, medical expertise; SA, survival analysis; SL, supervised learning. T column is for statistical data type: b, binary data; c, count data; m, mixed data; r, real data.
(Ren et al., 2020; Schuler et al., 2016; Yin, Afshar et al., 2020; J. Zhou et al., 2014), irregularity along the time mode (Afshar et al., 2018; Perros et al., 2019; Ren et al., 2020; Yin, Afshar et al., 2020; Yin et al., 2019), overlapping phenotypes (Henderson et al., 2017; Ho, Ghosh, & Sun, 2014; Kim, El-Kareh, Sun, Yu, & Jiang, 2017; Yin, Cheung, Fung, & Poon, 2020), different statistical data types (Perros et al., 2018; Schuler et al., 2016; Yang et al., 2017) and privacy-preserving computational phenotyping (Kim, Sun, Yu, & Jiang, 2017; Ma et al., 2019).

Using a hierarchical categorization, we first distinguish between matrix versus tensor factorizations-based approaches. Then, both categories are further subdivided into static versus temporal phenotyping. Sections 3 and 4 will follow this structure after a brief introduction of commonly used matrix and tensor factorizations in EHR-based phenotyping in Section 2. Table 1 shows different aspects under which a more fine-grained categorization of the existing literature is possible. For example, the approaches to validate phenotypes differ greatly (Section 5). This survey covers papers that have their emphasis on methodological development for phenotyping [e.g., (Ho, Ghosh, & Sun, 2014; Yin, Afshar et al., 2020; Yin, Cheung, et al., 2020)] as well as papers that focus on applications using well-established low-rank approximation-based methods [e.g., (Aliberti et al., 2016)].

2 | BACKGROUND: PHENOTYPING VIA LOW-RANK APPROXIMATIONS

2.1 | Data: From EHR to matrices and tensors

Extracting and categorizing information from unstructured EHR (e.g., clinical notes) is a research topic in itself. Both classical NLP models (Khalifa & Meystre, 2015) and DL-based methods (Shickel et al., 2017) have been used to transform raw EHR to concepts and relations, such as prescriptions, and diagnoses. Matrices and higher-order tensors can be naturally used to represent co-occurrences of patients, procedures, diagnoses, and/or prescriptions (over time).

For instance, EHR data can be arranged as a patients by clinical features matrix as in Figure 1 (Georgiades et al., 2007; Rennard et al., 2015), or given that different diagnoses and medications are the available data points for a cohort of patients, the data can be arranged as a patients by diagnoses by medications tensor (Figure 5) (Henderson et al., 2018; Ho, Ghosh, Steinhubl, et al., 2014; Kim, El-Kareh, et al., 2017). Consider, for instance, a patient \(i\) that is prescribed a medication \(k\) for a certain condition \(j\). This information can be encoded in a 3-way array by setting the corresponding entry \((i,j,k) = 1\). In this way, by linking medications and conditions, multi-modal interactions can be encoded. Tensors also prove useful in terms of representing temporal data, for example, multiple visits of patients can be recorded using an irregular tensor with modes: patients, clinical features, and time (Figure 7) (Perros et al., 2017; Ren et al., 2020; Yin, Afshar et al., 2020).

Table 1 shows matrix and higher-order tensor representations of various types of EHR data in the literature.

For an overview of commonly used data sets in the literature, see Table 2. The MIMIC-III (Medical Information Mart for Intensive Care) dataset, for instance, that contains health records of intensive care unit (ICU) patients, is used in several phenotyping studies based on matrix/tensor factorizations [e.g., (Joshi et al., 2016; Ma et al., 2019; Yin et al., 2019; Yin, Cheung, et al., 2020)]. Diagnosis codes are typically given according to the International Classification of Diseases (ICD). Resulting co-occurrences in the form of, for example, patient-diagnosis-prescription, are encoded using either binary values (Yin, Afshar et al., 2020) or counts (Ding & Luo, 2021; Ho, Ghosh, Steinhubl, et al., 2014; Ho, Ghosh, & Sun, 2014; Luo et al., 2016). Temporal scales (time between observations) vary a lot in different studies, that is, from weeks (Perros et al., 2017; J. Zhou et al., 2014) to months (Schuler et al., 2016) and years (Zhao et al., 2019).

2.2 | Preliminaries of low-rank approximations

Low-rank approximations are effective tools for revealing the underlying patterns from data in the form of matrices and higher-order tensors. In the following, we briefly review the basics of low-rank approximations using matrix and tensor factorizations, and link them to (temporal) EHR-based phenotyping.

2.2.1 | Matrix decompositions

Given a data matrix \(X \in \mathbb{R}^{I \times J}\) in the form of a samples by features matrix, it can be approximated using a matrix factorization as follows [Equation (1)]:

\[
X \approx U^T V
\]
TABLE 2  Commonly used datasets: Sutter (Choi et al., 2017), CMS, MIMIC-II (Saeed et al., 2011), MIMIC-III (Johnson et al., 2016).

| Dataset          | Data set description                                                                 | Used in                                                                 |
|------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Sutter           | Palo Alto Medical Foundation Clinics; medication and diagnosis information from 50 to 80-year old adults in a heart failure study | (Yin, Afshar et al., 2020); (Afshar et al., 2020); (Perros et al., 2018) |
| CMS              | 3 years of claim records synthesized from 5% of the 2008 Medicare population          | (Ren et al., 2020; Yin, Afshar et al., 2020; (Afshar et al., 2020; Perros et al., 2018) |
| MIMIC-II         | Physiologic data and vital signs time series collected from tens of thousands of ICU patient monitors | (Luo et al., 2016)                                                     |
| MIMIC-III        | Successor of MIMIC-II*                                                                | (Joshi et al., 2016; Ren et al., 2020; (Kim, El-Kareh et al., 2017); (Ding & Luo, 2021); (Yin, Cheung, et al., 2020); (Kim, Sun, et al., 2017); (Ma et al., 2019); (Yin et al., 2019); (He et al., 2019); (Yin, Afshar et al., 2020); (Zhang et al., 2021) |

*aSee https://mimic.mit.edu/docs/ for the documentation of MIMIC-II and MIMIC-III as well as for differences between the two databases. MIMIC-IV (Johnson et al., 2020), a successor of MIMIC-III, has been recently released but not yet widely used for phenotyping via low-rank approximations.

\[ X \approx AB^T, \quad (1) \]

where \( A = [a_1 \ldots a_R] \in \mathbb{R}^{I \times R} \) and \( B = [b_1 \ldots b_R] \in \mathbb{R}^{J \times R} \) are factor matrices corresponding to the samples and features modes summarizing the data matrix using \( R \) components, with \( R \ll \min\{I, J\} \). Alternatively, the formulation (1) can be expressed as the sum of \( R \) rank-one terms/components, that is, \( X \approx \sum_{r=1}^{R} a_r b_r^T \). Once the summarization of the data is obtained using such a low-rank approximation, factor matrices can be used for further analysis, for example, if \( X \) is a patients by clinical features matrix (as in Figure 1), the factor matrix \( A \) corresponding to the patients mode can be used to cluster the patients. In the literature, \( A \) is also referred to as the score matrix, and \( B \) as the loading matrix (Bro & Smilde, 2014), and in phenotyping literature, \( A \) is sometimes also called the membership matrix (Henderson et al., 2017, 2018; Ho, Ghosh, Steinhubl, et al., 2014) or patient mode, or patient factor matrix (Ma et al., 2019). We use these terms interchangeably.

Given a matrix \( X \), factor matrices \( A \) and \( B \) can be computed by solving the following optimization problem [Equation (2)]:

\[ \min_{A,B} \| X - AB^T \|_F^2, \quad (2) \]

where \( \| \cdot \|_F \) denotes the Frobenius norm, that is, \( \| X \|_F = \sqrt{\sum_{i=1}^{I} \sum_{j=1}^{J} x_{ij}^2} \).

In the presence of missing entries, for example, due to unavailable information or errors in the data collection process, matrix \( X \) with missing entries can be factorized by solving a weighted optimization problem (Buchanan & Fitzgibbon, 2005; H. A. L. Kiers, 1997; Srebro & Jaakkola, 2003) [Equation (3)]:

\[ \min_{A,B} \| W \ast (X - AB^T) \|_F^2, \quad (3) \]

where \( \ast \) is the Hadamard product (element-wise product), and matrix \( W \) of size \( I \times J \) encodes missing entries, that is [Equation (4)]:

\[ w_{ij} = \begin{cases} 0 & \text{if } x_{ij} \text{ is missing}, \\ 1 & \text{if } x_{ij} \text{ is observed}, \end{cases} \quad (4) \]

for all \( i = 1,...,I; j = 1,...,J \). Hospitalization records containing, for instance, admission events, diagnoses and demographics, might be incomplete for some patients and can be analyzed via weighted low-rank approximations (Schuler et al., 2016).
Imposing different constraints on the factor matrices $A, B$ leads to different matrix factorization approaches. For instance, in singular value decomposition (SVD), which can be used for principal component analysis (PCA) (Jolliffe & Cadima, 2016), factor matrices are constrained to have orthogonal columns. By imposing non-negativity constraints on the factor matrices, the problem can be formulated as a nonnegative matrix factorization (NMF) (Lee & Seung, 1999) problem. Note that the factorization of $X$ as $X \approx AB^T$ is not unique as factor matrices can be multiplied by a nonsingular matrix $M$ and its inverse, such that $AB^T = AMM^{-1}B^T = \tilde{A}\tilde{B}^T$, giving an equally good approximation of $X$, where $\tilde{A} = AM$ and $\tilde{B} = B(M^{-1})^T$. If the goal of data approximation using a matrix factorization is to reveal patterns, that is, columns of factor matrices, and interpret the individual patterns, for instance, as phenotypes, then the factorization must be unique. Therefore, often additional constraints on the factors such as orthogonality, non-negativity and sparsity or statistical independence are needed to obtain unique factorizations. Here, with uniqueness, we refer to essential uniqueness which means that the factorization is unique up to permutation of rank-one components, and scaling within each rank-one component.

The Frobenius norm-based loss function is common in data mining, and relies on the assumption that data is real-valued. On the other hand, for EHR data analysis and phenotyping applications, other types of loss functions may be more suitable, for example, when analyzing count data, a better suited loss function is based on Kullback–Leibler (KL) divergence relying on the Poisson distribution. The matrix factorization problem with different loss functions can be formulated as follows [Equation (5)]:

$$\min_{A,B} \quad d(X, \hat{X})$$

s.t. \hspace{1cm} \hat{X} = AB^T$$

where $d(X, \hat{X})$ indicates the loss function, for example, for KL-divergence, $d(X, \hat{X}) = \sum_i \sum_j d(x_{ij}, \hat{x}_{ij})$, with $d(x, y) = x \log \frac{x}{y} - (x - y)$, for $x, y > 0$. Recently, generalized low-rank models (GLRM) (Udell et al., 2016) have been introduced to model data matrices, where different columns may have different statistical data types (e.g., binary, count, real), and each column can be modeled using a suitable loss function.

Table 1 shows representative loss functions commonly used with matrix factorizations in the phenotyping literature.

### 2.2.2 Tensor decompositions

Higher-order tensors (or multi-way arrays) are higher-order extensions of data matrices. We use $\mathcal{X} \in \mathbb{R}^{I_1 \times \cdots \times I_N}$ to denote a tensor of order $N$. While vectors and matrices are special cases of tensors for $N = 1$ and $N = 2$, respectively, we use the term tensor to refer to the case $N \geq 3$. Tensor factorizations are extensions of matrix factorizations to such higher-order data sets, and have been successfully used to extract underlying patterns in multi-way data in many disciplines including neuroscience (Acar et al., 2007; Hunyadi et al., 2017; Williams et al., 2018), social network analysis (Dunlavy et al., 2011; Papalexakis et al., 2016) and chemometrics (Bro, 1997). Among various tensor factorization approaches, here, we briefly discuss the CANDECOMP/PARAFAC (CP) (Carroll & Chang, 1970; Harshman, 1970) and PARAFAC2 (Harshman, 1972; H. A. Kiers et al., 1999) models as they have been widely used in the phenotyping literature. Uniqueness properties of CP and PARAFAC2, that is, both being unique up to permutation and scaling ambiguities under certain conditions (H. A. Kiers et al., 1999; Kruskal, 1977), make them powerful tools in terms of discovering phenotypes compared to other tensor methods. See (Acar & Yener, 2009; Kolda & Bader, 2009; Papalexakis et al., 2016; Smilde et al., 2004) for thorough reviews on tensor methods and their applications in different fields.

**CANDECOMP/PARAFAC (CP)**

The CP model (Carroll & Chang, 1970; Harshman, 1970), also referred to as the canonical polyadic decomposition (Hitchcock, 1927), represents tensor $\mathcal{X}$ as the sum of minimum number of rank-one components. Given a tensor $\mathcal{X} \in \mathbb{R}^{I_1 \times \cdots \times I_K}$, its $R$-component CP model can be expressed as follows [Equation (6)]:

$$\mathcal{X} \approx \sum_{r=1}^{R} \mathbf{a}_r \circ \mathbf{b}_r \circ \mathbf{c}_r,$$
where \( \circ \) denotes the vector outer product, \( A = [a_1 \ldots a_R] \in \mathbb{R}^{I \times R} \), \( B = [b_1 \ldots b_R] \in \mathbb{R}^{J \times R} \), and \( C = [c_1 \ldots c_R] \in \mathbb{R}^{K \times R} \) are the factor matrices corresponding to each mode. The CP model is often denoted as \( \mathcal{X} \approx \langle A, B, C \rangle \). If \( \mathcal{X} \) is a "patients by diagnoses by medications" tensor, factor matrices \( A, B, C \) correspond to the patients, diagnoses and medications modes (see Figure 2). Here, \( A \) can be used as the phenotype membership matrix, and columns of \( B \) and \( C \) can be used to reveal phenotypes.

The CP model has been an effective tool in computational phenotyping as a result of its uniqueness properties, which enables interpreting columns of factor matrices as phenotypes or patient subgroups. The CP model is essentially unique, that is, factor matrices are unique up to scaling and permutation ambiguities, under mild conditions (Kruskal, 1977; Sidiropoulos & Bro, 2000) without the need to impose any additional constraints such as orthogonality or statistical independence on the columns of factor matrices. The scaling ambiguity indicates that individual vectors in each rank-one component can be scaled as in Equation (7):

\[
\mathcal{X} \approx \sum_{r=1}^{R} a_r \circ b_r \circ c_r = \sum_{r=1}^{R} \alpha a_r \circ \beta b_r \circ \gamma c_r,
\]

as long as \( \alpha \beta \gamma = 1 \). The permutation ambiguity refers to different ordering of rank-one components, for example, swapping the first rank-one tensor \( a_1 \circ b_1 \circ c_1 \) with the second \( a_2 \circ b_2 \circ c_2 \) in Figure 2. Neither scaling nor permutation ambiguity changes the interpretation of the factors.

An alternative way to represent the CP model, in matrix notation, is as follows [Equation (8)]:

\[
X_k \approx A \text{diag}(c_k) B^T,
\]

where \( X_k \) corresponds to \( k \)th frontal slice of tensor \( \mathcal{X} \), and \( \text{diag}(c_k) \) denotes an \( R \times R \) diagonal matrix with the \( k \)th row of \( C \) as diagonal entries. Given a tensor \( \mathcal{X} \), the CP model can be computed by solving the following optimization problem using alternating least squares (ALS) (Harshman, 1970) or all-at-once optimization based approaches (Acar, Dunlavy, & Kolda, 2011; Sorber et al., 2013) [Equation (9)]:

\[
\min_{A, B, C} \| \mathcal{X} - \langle A, B, C \rangle \|^2_F. \tag{9}
\]

Analog to the matrix decomposition case, the objective function can be adopted to account for missing data by introducing \( W \), a weight tensor of equal size as \( \mathcal{X} \), as follows (Acar et al., 2010; Tomasi & Bro, 2005) [Equation (10)]:

\[
\min_{A, B, C} \| W \ast (\mathcal{X} - \langle A, B, C \rangle) \|^2_F, \tag{10}
\]

where entries of \( W \) are given by [Equation (11)].

---

**Figure 2** Low-rank approximation of a third-order tensor (e.g., with modes "patients, diagnoses, and medications") via an \( R \)-component CP model.
\[ w_{ijk} = \begin{cases} 0 & \text{if } x_{ijk} \text{ is missing,} \\ 1 & \text{if } x_{ijk} \text{ is observed,} \end{cases} \quad (11) \]

for all \( i = 1, \ldots, I, j = 1, \ldots, J, k = 1, \ldots, K \), where \( x_{ijk} \) denotes the entry \((i,j,k)\) of \( \mathcal{X} \). This weighted low-rank approximation approach was extended to different tensor factorization approaches, for example, PARAFAC2, and was previously used to jointly analyze temporal health data for a cohort of patients in the presence of missing values (Ren et al., 2020).

Similar to matrix factorizations, loss functions other than the squared Frobenius norm, in particular, KL-divergence for count data, have been commonly used in the phenotyping literature (see Table 1). We mention here the corresponding optimization problem due to its prevalence in static phenotyping. Note that the following KL-formulation differs from the one given in [Equation (5)] as it omits the constants (i.e., terms that only include the data \( x_{ijk} \) and have no impact on the optimization). Let \( \hat{\mathcal{X}} \) be the approximation of \( \mathcal{X} \) by the factor matrices based on a CP model, and let \( x_{ijk} \) be the corresponding entry in tensor \( \mathcal{X} \), then [Equation (12)]:

\[
\min_{A, B, C} \sum_{i=1}^{I} \sum_{j=1}^{J} \sum_{k=1}^{K} \hat{x}_{ijk} - x_{ijk} \log \hat{x}_{ijk} \\
\text{s.t. } \hat{\mathcal{X}} = [A, B, C] 
\quad (12)
\]

PARAFAC2

While the CP model assumes that each frontal slice (or slab) is approximated by the same \( B \) matrix, the PARAFAC2 model (Harshman, 1972; H. A. Kiers et al., 1999) relaxes this assumption, and allows the \( B \) matrix to change across different slabs as follows [Equation (13)]:

\[
\mathcal{X}_k \approx A \text{diag}(c_k) B_k^T, \quad (13)
\]

subject to the so-called PARAFAC2 constraint, that is [Equation (14)],

\[
B_k^T B_{k_1} = B_{k_2}^T B_{k_2} = \Phi, \quad \forall k_1, k_2 \leq K. \quad (14)
\]

This constraint, which enforces invariance over the cross products, was introduced to preserve uniqueness (Harshman, 1972). Similar to CP, the factors matrices from a PARAFAC2 decomposition are essentially unique under mild conditions, for example, as long as there are enough slices \((K > 3)\) (H. A. Kiers et al., 1999). In addition to permutation and scaling ambiguities, we may encounter an additional sign ambiguity when fitting a PARAFAC2 model, where each entry in the \( k \)th row of \( C \) in Equation (13) may flip signs arbitrarily. One possible solution to handle the sign ambiguity is to impose non-negativity constraints on matrix \( C \) (Harshman, 1972; H. A. Kiers et al., 1999).

Allowing each slab to have its corresponding \( B_k \) also means that irregular \( \mathcal{X}_k \in \mathbb{R}^{I \times J \times K} \) can the modeled, that is, the dimension \((J_k)\) does not necessarily have to align across slabs (see Figure 3). This property of PARAFAC2 is particularly useful for the analysis of EHR data as it is often the case that clinical visits (or the time mode in general) do not align across different patients. For instance, if \( \mathbf{X}_k \), for \( k = 1, \ldots, K \), corresponds to a clinical features by time/visit matrix for patient \( k \), the factor matrix \( A \) reveals phenotypes together with their corresponding temporal profiles as the columns of factor matrix \( B_k \) for patient \( k \), while the factor matrix \( C \) corresponds to the patient mode potentially revealing patient groups (see Figure 7).

The PARAFAC2 model can be computed by solving the following optimization problem using an ALS-based algorithm (H. A. Kiers et al., 1999) [Equation (15)]:

\[
\text{minimize } \sum_{i=1}^{I} \sum_{j=1}^{J} \sum_{k=1}^{K} \left( \mathcal{X}_{ijk} - \sum_{l=1}^{L} A_{i,l} B_{j,l}^T (c_{k,l}) \right)^2 \\
\text{s.t. } (\text{for all } i, j, \text{ and } k) 
\]

\[
A_{i,l} \geq 0, \quad B_{j,l} \geq 0, \quad (\text{for all } l, i, \text{ and } j), \quad (15)
\]
where $B_k = P_k A$, and $P_k^T P_k = I$ so that the constant cross product constraint is implicitly satisfied. Here, $I \in \mathbb{R}^{R \times R}$ denotes the identity matrix, $\Delta \in \mathbb{R}^{R \times R}$ is common for all $B_k$, $k = 1, \ldots, K$. Other algorithmic approaches have also been studied when constraints are needed on the factor matrices (Cohen & Bro, 2018; Roald et al., 2022). Within the context of temporal phenotyping, PARAFAC2 has been extended to model binary data (Yin, Afshar et al., 2020). However, the standard formulation based on the Frobenius norm has so far been the most commonly used (see Table 1).

3 | MATRIX FACTORIZATION FOR PHENOTYPING

In this section, matrix factorization-based approaches are categorized into static versus temporal phenotyping. Different ways to represent temporal data in a two-way array have been proposed in the past. Thus, when discussing temporal phenotyping, the structure follows different data representation approaches to handle temporal information in a two-way context.

3.1 | Static phenotyping

Well-established matrix decomposition techniques, like PCA (Aliberti et al., 2016; Burgel et al., 2010; Georgiades et al., 2007; Vavougios et al., 2016) or NMF (Joshi et al., 2016), have been a standard tool for phenotyping. Phenotypes and patient-clustering for a plethora of different diseases and conditions have been studied in the past, ranging from chronic obstructive pulmonary disease (COPD) (Burgel et al., 2010; Rennard et al., 2015) to autism disorder (Georgiades et al., 2007) as well as sleep apnoe (Vavougios et al., 2016). Papers that fit into this categorization, typically begin with a patients $\times$ clinical attributes matrix (see Figure 1) and proceed to cluster patients using the factor matrices (Aliberti et al., 2016; Burgel et al., 2010; Vavougios et al., 2016). In the study by Wang et al., (2020), phenotypes related to chronic lymphocytic leukemia are extracted. Although longitudinal patient data is used in this study, the resulting phenotypes are not temporal, as the longitudinal information is collapsed by summing along the temporal axis. The resulting matrix is a patient $\times$ clinical features matrix that contains count data and is decomposed using NMF.
Various advances to PCA and NMF-based approaches have been introduced in the context of static phenotyping. For instance, in order to align phenotypes using NMF with target comorbidities, a supervision constraint that enforces phenotype definitions to have nonzero entries according to a known list of comorbidities has been introduced (Joshi et al., 2016). Besides, generalized low-rank models (GLRM) have been used to model mixed data, that is, tabular data where each column follows a different statistical data type (Schuler et al., 2016).

### 3.2 Temporal phenotyping

Given clinical features for a cohort over time, matrix decompositions cannot be applied readily as such temporal data cannot be represented as a two-way array. In the temporal phenotyping literature, this problem has been tackled using different approaches which can be categorized under: concatenation (Hassaine et al., 2020; Schuler et al., 2016) and augmentation (Ding & Luo, 2021; Luo et al., 2016; Stroup et al., 2019).

The most straightforward way to employ matrix factorizations for temporal phenotype extraction is to concatenate matrices along an axis. For instance, by Hassaine et al., (2020), age \( \times \) conditions matrices for all patients are concatenated along the time/age axis to form one “skinny” matrix for the whole cohort (see Figure 4). A different concatenation approach is used in the study by Schuler et al., (2016), where for each patient a vector is formed recording the counts of medical concepts in 6-month intervals, that is, the same set of medical features are recorded over time. The resulting matrices are then approximated by low-rank methods, that is, NMF in (Hassaine et al., 2020), and Poisson PCA (Collins et al., 2001), which is tailored to count data using a loss similar to the KL-divergence based loss in [Equation (5)] (Schuler et al., 2016).

The second approach to handle temporal data via matrix decompositions is subgraph augmented nonnegative matrix factorization (SANMF). Temporal information is encoded into a weighted graph. SANMF was introduced by Luo et al., (2016) with the specific use-case of analyzing physiologic time series data, and then also employed for unsupervised phenotyping of sepsis (Ding & Luo, 2021) and multiple organ dysfunction (Stroup et al., 2019). In the study by Luo et al., (2016), the time series of a physiological measurement is converted into a discretized representation that indicates whether the measurement is within the reference range or one or two standard deviations above or below it. The adjacent nodes in this time series graph are connected by three different kinds of edges, representing up, down, or no change. For each physiological measurement a corpus of time series graphs is formed that contains all different trends for all patients. Applying this to all physiological measurements leads to corpora of time series graphs. Frequent subgraph mining (Nijssen & Kok, 2005) is then used to find subgraphs that repeatedly occur for patients. The subgraphs...
are encoded in a patients $\times$ subgraphs matrix (see Figure 4). The first $n$ columns in this matrix could, for example, encode frequent subgraphs found for the first physiological variable. The resulting matrix is approximated using NMF to reveal patient groups and subgraph (trends) groups.

4 | TENSOR FACTORIZATIONS FOR PHENOTYPING

Data that has a multi-way structure, for example, the co-occurrence of patients, diagnoses and medications, can be naturally represented with a (data) tensor. The advantage of this approach is that multi-modal interactions can be modeled and revealed. Most studies in this category shape the data into regular-shaped tensors, where each slab has the same dimensions (Ho, Ghosh, & Sun, 2014; Kim, El-Kareh, et al., 2017; Perros et al., 2018; Wang et al., 2015). While in most cases co-occurrence counts are used (He et al., 2019; Henderson et al., 2017, 2018; Ho, Ghosh, & Sun, 2014), in some cases, tensors with binary values are constructed (Wang et al., 2015). Note that while most studies integrate count data over a certain time window, they are considered under static phenotyping because temporal information is not present in the resulting phenotypes (Ho, Ghosh, Steinhubl, et al., 2014; Ho, Ghosh, & Sun, 2014; Kim, El-Kareh, et al., 2017; Wang et al., 2015).

We categorize studies using tensor factorizations for EHR-based phenotyping under static phenotyping versus temporal phenotyping. On the highest categorization level within the subsections of static and temporal phenotyping, we first differentiate between CP based versus non-CP based models and PARAFAC2 based versus non-PARAFAC2 based models, respectively. We then follow a general structure that is based on different regularizations/constraints as this reflects the main advancements and contributions.

4.1 | Static phenotyping

For static phenotyping, the data is often arranged as third-order tensors recording diagnosis-prescription co-occurrences for a cohort as in Figure 5 (Ho, Ghosh, Steinhubl, et al., 2014; Ho, Ghosh, & Sun, 2014; Kim, El-Kareh, et al., 2017; Perros et al., 2018; Wang et al., 2015). While in most cases co-occurrence counts are used (He et al., 2019; Henderson et al., 2017, 2018; Ho, Ghosh, & Sun, 2014), in some cases, tensors with binary values are constructed (Wang et al., 2015). Note that while most studies integrate count data over a certain time window, they are considered under static phenotyping because temporal information is not present in the resulting phenotypes (Ho, Ghosh, Steinhubl, et al., 2014; Ho, Ghosh, & Sun, 2014; Kim, El-Kareh, et al., 2017; Wang et al., 2015).

The constructed tensors are then analyzed using a CP model, which has shown promising results in terms of uncovering clinically relevant phenotypes (Ho, Ghosh, & Sun, 2014; Wang et al., 2015). As tensors with co-occurrence counts are the most common way to represent static multi-way EHR data, KL-divergence is used when fitting the CP models in many instances (see Table 1).

In the first studies that analyzed such patient-diagnosis-medication tensors, nonnegative tensor factorizations based on a CP model were proposed, and coined Limestone and Marble (Ho, Ghosh, Steinhubl, et al., 2014; Ho, Ghosh, & Sun, 2014), respectively. Compared to Limestone, Marble introduces an offset tensor, and approximates the observed data using both an offset tensor and a so-called signal tensor. The offset part accounts for the common baseline characteristics in the population while the signal tensor models the phenotypes. Non-negativity has been used in many follow-up studies (Henderson et al., 2017, 2018; Wang et al., 2015) as it facilitates interpretability. Within this subsection, we categorize the papers on the basis of their constraints that enforce sparsity, distinctive phenotypes, incorporate prior knowledge or label information.

Sparsity of phenotypes is a desirable property as it makes interpretation easier by pushing less important values in the factor matrix towards zero. Generally, a typical way to enforce sparsity is to introduce an $\ell_1$ penalty term. Note, however, that introducing sparsity when using KL-divergence is challenging because the “inadmissible zeros” (Chi & Kolda, 2012), that can result from sparse factor matrices, make the objective ill-defined (due to the logarithm). In order to avoid this issue, an observed tensor can be factorized into a rank-one bias (or offset) tensor with strictly positive entries and a signal tensor that captures the phenotypes. Using this approach, the argument of the logarithm is always strictly positive. This way of modeling count data tensors is used, for instance, in Marble (Ho, Ghosh, & Sun, 2014) and Granite (Henderson et al., 2017). In Marble, sparsity in the phenotype factor matrices is enforced using simplex
constraints together with a threshold parameter constraining the feasible space for the values in the factor matrices to be either zero or above a certain threshold while in Granite an $\ell_2$ penalty term together with a simplex constraint is used.

More distinct phenotypes with less overlap is another way to make interpretation easier and allow for a more targeted care. Less overlap can be enforced by penalizing non-orthogonality as in Rubik (Wang et al., 2015) or by a more flexible angular regularization term (see Figure 6) that is enforced on the factor matrices as in the study by Henderson et al., (2018) or (S)Granite (He et al., 2019; Henderson et al., 2017). With the same goal of making phenotypes less overlapping, (Kim, El-Kareh, et al., 2017) introduce a similarity matrix that clusters similar phenotypes together. The similarity matrix is computed by Word2Vec, a neural network based method for word embeddings, using diagnoses and prescription sequences.

With unsupervised approaches, it is usually desirable that subgroups emerge without label information. Some studies, however, leverage a-priori medical knowledge (Henderson et al., 2018; Wang et al., 2015) or label information (Kim, El-Kareh, et al., 2017; Yang et al., 2017) to enforce separability of different classes of patients. In (Henderson et al., 2018), prior knowledge is integrated by using a cannot-link matrix so that patients with different disease status, for example, cases versus controls, are observed in different phenotypes. Rubik (Wang et al., 2015) also incorporates prior medical knowledge via guidance constraints such that factor matrices revealing phenotypes are constrained to be similar to a set of known features for certain diseases. Kim, El-Kareh, et al., (2017) propose to adapt the objective function to include a logistic regression term that enforces discriminative power by including label information, such that the phenotypes are separated according to mortality. In a similar way, Yang et al., (2017) propose a predictive task guided tensor decomposition model by incorporating label information and a discriminative model as a penalty term.

A further distinct line of research is more concerned with the privacy-preserving computation of phenotypes (Kim, Sun, et al., 2017; Ma et al., 2019). The scenario under consideration is to compute phenotypes coming from multiple hospitals without sharing patient data. Federated tensor factorization is proposed by Kim, Sun, et al., (2017) where patient-mode matrices are updated locally and feature-mode matrices are shared on a server, where a harmonized global feature-mode matrix is computed and then sent back. The research carried out by Ma et al., (2019) has the same privacy-preserving goal, but differs mainly in three points: (i) by the usage of a more communication-efficient algorithm to solve the global consensus problem between the server and local sites, (ii) by the flexibility to allow hospital-specific factors via $\ell_{2,1}$ norm, that is, by inducing sparsity in the patient-mode matrix, (iii) by giving differential privacy guarantees, that is, a formal and rigorous guarantee that individual-level patient data cannot be deduced from patient factor matrices.

4.1.1 | Non-CP based models for static phenotyping

All previously mentioned papers in this subsection use CP (together with different constraints) as a model to discover static phenotypes. There are two exceptions (Luo et al., 2015; Yin, Cheung, et al., 2020). In the study by Luo et al.,
subgraph augmented nonnegative tensor factorization (SANTF) is introduced for discovering lymphoma subtypes from clinical texts by using a Tucker decomposition (Tucker, 1966). Each entry in the tensor is the co-occurrence count of a patient, a subgraph that encodes a common relation between medical concepts and a word. A Tucker model, more precisely referred to as Tucker3, is more flexible than the CP model, and approximates a third-order tensor \( X \in \mathbb{R}^{I \times J \times K} \) as follows, using a \((P,Q,R)\)-component model [Equation (16)]:

\[
X \approx \sum_{p=1}^{P} \sum_{q=1}^{Q} \sum_{r=1}^{R} G_{pq,r} a_p \circ b_q \circ c_r = \mathbb{G} A B C,
\]

where \( \mathbb{G} \in \mathbb{R}^{P \times Q \times R} \) is the core tensor, \( A \in \mathbb{R}^{I \times P} \), \( B \in \mathbb{R}^{J \times Q} \), \( C \in \mathbb{R}^{K \times R} \) are the factor matrices corresponding to each mode. Tucker decompositions are not unique without further constraints. (Luo et al., 2015) use non-negativity constraints in all modes as well as for the core tensor. Uniqueness properties of such nonnegative Tucker decompositions are yet to be understood (G. Zhou et al., 2015). In the study by Yin, Cheung, et al. (2020), the co-occurrence assumption, which states that for example diagnoses and medications that occur at the same clinical examination correspond to each other, is critically examined. It is stated that while this assumption holds for certain data sets, it might not hold for all. Thus, the true interaction-tensor is assumed to be unknown, and only the marginal matrices (e.g., a patients—diagnoses—medications tensor, \( A, B, C \)) correspond to the factor matrices in patients, diagnoses and medications modes; \( \lambda \) is the penalty parameter, and \( \theta \) defines the threshold above which the angle between two components is penalized.

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where \( \mathbb{G} \in \mathbb{R}^{P \times Q \times R} \) is the core tensor, \( A \in \mathbb{R}^{I \times P} \), \( B \in \mathbb{R}^{J \times Q} \), \( C \in \mathbb{R}^{K \times R} \) are the factor matrices corresponding to each mode. Tucker decompositions are not unique without further constraints. (Luo et al., 2015) use non-negativity constraints in all modes as well as for the core tensor. Uniqueness properties of such nonnegative Tucker decompositions are yet to be understood (G. Zhou et al., 2015). In the study by Yin, Cheung, et al. (2020), the co-occurrence assumption, which states that for example diagnoses and medications that occur at the same clinical examination correspond to each other, is critically examined. It is stated that while this assumption holds for certain data sets, it might not hold for all. Thus, the true interaction-tensor is assumed to be unknown, and only the marginal matrices (e.g., a patients—diagnoses matrix, a patients by medications matrix) are given. Factor matrices are estimated by maximizing the likelihood of marginalizations of the underlying unknown interaction-tensor. This model was coined Hidden Interaction Tensor Factorization (HITF) and is distinct from a CP model. Experimental evidence indicates that HITF-based approaches produce meaningful phenotypes that are sparser and more diverse compared to Marble, Rubik, and Granite.

### 4.2 Temporal phenotyping

In recent years, temporal phenotyping using tensor decompositions has been studied. The first work that proposed to use PARAFAC2 to handle temporal irregularity was Spartan (Perros et al., 2017), to the best of our knowledge. Since then, it has been the most popular method to model temporal irregular EHR tensors. Applying PARAFAC2 to large-scale data sets has been a challenge due to computational issues (Bro, 1997). Scalable PARAFAC2 Spartan (Perros et al., 2017) was developed to render PARAFAC2 feasible for large-scale problems by exploiting the sparsity structure. This efficient approach has also been used in Copa (Constrained PARAFAC2) (Afshar et al., 2018) where the PARAFAC2 model is fitted with additional constraints. Moreover, efforts have been made to make the temporal phenotype discovery more robust (Ren et al., 2020), and more interpretable by enforcing a variety of different constraints such as

\[
R_{el}(B) = \lambda (||b_1||_1 + ||b_2||_1)
\]

where \( ||b_1||_1 = \sum_{i=1}^{I} |b_{1,i}| \)

\[
R(B; \theta) = \sum_{r=1}^{R} \sum_{p=1}^{P} (\max (0, \frac{b_{1,r}}{||b_{1,1}||_1} - \theta))^2
\]

where \( ||b_1||_1 = \sum_{i=1}^{I} b_{1,i}^2 \)
sparsity (Afshar et al., 2018), non-negativity (Afshar et al., 2018; Perros et al., 2019) and temporal smoothness (Afshar et al., 2018; Yin, Afshar et al., 2020). These advancements will be discussed in more detail in the following.

Non-negativity and sparsity are standard constraints that, as described in Section 4.1 for CP models, improve phenotype interpretability. It is, therefore, not surprising that one or both of these constraints are also incorporated when fitting PARAFAC2 models (Afshar et al., 2018; Yin, Afshar et al., 2020).

Better interpretability of temporal phenotypes is achieved by constraints that enforce temporal smoothness (Afshar et al., 2018; Yin, Afshar et al., 2020). Temporal smoothness of the time-mode is a desirable property as it means both less fitting to noise and improved interpretability. The interpretation of smooth trajectories is easier because it is assumed that clinical parameters or disease severity do not change abruptly. Smoothness in time was enabled by enforcing the temporal factors to be linear combinations of M-spline basis functions (Afshar et al., 2018), which form a nonnegative basis that is defined piecewise by polynomials, inspired by earlier work carried out by Helwig, (2017); Timmerman & Kiers, (2002), or by penalizing the difference between the entries for consecutive visits in the time-mode factors (Yin, Afshar et al., 2020).

For robustness to missing and erroneous entries, the Repair framework (Ren et al., 2020) proposes robust PARAFAC2 by modeling the observed entries in the tensor using a low-rank tensor and a sparse error tensor similar to the way robustness is introduced in matrix factorizations (Candès et al., 2011). The low-rank part relies on the PARAFAC2 model together with a new low-rank regularization function through nuclear norm constraints on the factor matrices. It has been demonstrated that Repair outperforms both Spartan (Perros et al., 2017) and Copa (Afshar et al., 2018) in terms of model fit in the presence of missing and erroneous entries.

### 4.2.1 | Non-PARAFAC2 based models for temporal phenotyping

While PARAFAC2 is the most widely used method to handle temporal irregularity in EHR, another line of research proposes what could be called patient-level decomposition (Yin et al., 2019; J. Zhou et al., 2014). Collective nonnegative tensor factorization (CNTF) (Yin et al., 2019) corresponding to a coupled CP model, and the *shared basis approach* through coupled matrix factorization (CMF) in J. Zhou et al., 2014 model the temporal dynamics of each patient separately while the phenotype definition is shared across the cohort.

Given two matrices $X \in \mathbb{R}^{I \times J_1}$ and $Y \in \mathbb{R}^{I \times J_2}$ coupled in the first mode, for example, *clinical features* by *visits* matrices are recorded for two patients for the same set of clinical features, CMF can be formulated as (Singh & Gordon, 2008) [Equation (17)]:
\[
\min_{A,B,C} \| X - AB^T \|_F^2 + \| Y - AC^T \|_F^2
\]

where \( A \in \mathbb{R}^{I \times R} \) corresponds to the factor matrix in the clinical features mode. This formulation can be extended to jointly analyze a higher-order tensor and a matrix or multiple tensors, referred to as coupled matrix and tensor factorizations (CMTF) (Acar, Kolda, & Dunlavy, 2011) or coupled tensor factorizations. In (Yin et al., 2019), for instance, \( time-labtest-medication \) tensors for a cohort of patients are jointly analyzed using a coupled CP model, where tensors are coupled via the \( labtest \) and \( medication \) modes. Temporal regularization is enforced via a recurrent neural network (RNN) for temporal dependency of consecutive disease states. This means that the RNN is part of the objective function, and is jointly learned (for each patient separately) together with the coupled CP model.

A different form of temporal irregularity is considered in the study by Zhang et al., (2021), where the varying sampling frequency between features, some of which are measured almost continuously (e.g., heart rate), while others only very sporadically (e.g., blood test results), is addressed. Dynamic time warping (DTW) is used for the computation of pairwise distances between all temporal features for the whole patient cohort. In this way, a regular \( pairwise \text{ distance tensor} \) where each slab encodes the pairwise DTW-distances between all patients for one feature, is formed and decomposed by a CP model.

In the study by Zhao et al., (2019) temporal irregularity does not arise and cardiovascular disease (CVD) is modeled via a CP model of a disease-patient-time tensor. The tensor is shaped in such a way that it records the time 10 years before a CVD event for each patient.

5 | VALIDATING PHENOTYPES

The approaches for phenotype validation, that is, the assessment of their clinical significance, can be grouped into internal and external categories. External validation means to bring in the expertise from a medical expert/practitioner or to collate the found phenotypes with the medical literature. Internal validation means to stay within data and assess the phenotypes using statistical testing (e.g., between cases and controls) or by using the extracted phenotypes in a subsequent supervised learning task.

Internal and external validation can complement each other. In conjunction, they can establish strong evidence for clinical relevance (Henderson et al., 2018; Ho, Ghosh, Steinhubl, et al., 2014; Joshi et al., 2016; Wang et al., 2020; Yin et al., 2019; Yin, Cheung, et al., 2020; Zhao et al., 2019), for example, when both a predictive task and medical expertise independently agree that a certain phenotype is important.

Many papers considered in this survey use both internal and external validation. Table 1 shows the validation approach for each paper. We observe that validation methods based on a prediction task and medical expertise are the most common ones. Moreover, the combination of a prediction task and the consultation of medical expertise is also quite common. In the following, we discuss internal and external validation approaches in more detail.

5.1 | Internal validation

5.1.1 | Survival analysis

In survival analysis (Bewick et al., 2004), the \textit{time until an event occurs} is studied. Typically, as the term \textit{survival} indicates, this event is death, but it can also be the onset of a disease. The term \textit{time-to-hazard} is used to refer to this notion. Compared to supervised learning, survival analysis is a less common way for phenotype validation (Perros et al., 2019; Rennard et al., 2015; Zhao et al., 2019). After the decomposition, the patient-mode can be understood as grouping of patients, for which \textit{survival functions} can be computed. The survival function is a non-increasing function that shows the cumulative survival times for the cohort. In this way, differences between phenotypes can be analyzed. In the study by Zhao et al. (2019), for example, where cardiovascular disease is studied, Kaplan–Meier models are presented that show the survival functions of six different patient subgroups, taking myocardial infarction as the event. Kaplan–Meier plots are a descriptive tool that can indicate differences between subgroups. Using a log-rank test, statistical significance
between different survival functions can be assessed. Thus, survival functions can directly link different subgroups of patients to survival statistics and thereby assess the clinical relevance of the uncovered phenotypes.

5.1.2 | Hypothesis testing

Given that the research questions and available data allow it, hypothesis tests can help to identify differences between subgroups (Ding & Luo, 2021; Schuler et al., 2016; Zhao et al., 2019). Hypothesis tests can, for instance, be performed in case–control studies, where the different uncovered phenotypes (score matrix) are compared between cases and controls. In the study by Ding & Luo, 2021, where the objective is to uncover sepsis phenotypes, two sample t-tests are used to assess differences between the three different phenotypes/subgroups. Demographic information and clinical features of the subgroups are compared against each other; for instance, age significantly differs between the subgroups, as well as the clinical feature fluid electrolyte imbalance. Performing statistical tests between all subgroups and features can show fine-grained differences between phenotypes.

5.1.3 | Supervised learning

A predictive task subsequent to the extraction of phenotypes makes quantitative evaluations and comparisons possible. The Pacifier framework (J. Zhou et al., 2014), for instance, decomposes incomplete features × time matrices to estimate missing entries and uncover phenotypes. They call this process densification. In order to validate the phenotypes and methodology, the completed matrix is used to predict heart failure via a sparse logistic regression, and compared with other baselines (e.g., interpolation). Applying a logistic regression to the phenotype membership matrix has been used for validating phenotypes for hypertension (Henderson et al., 2017; Henderson et al., 2018), high-cost beneficiaries (Ho, Ghosh, Steinhubl, et al., 2014), mortality prediction (Luo et al., 2016; Ma et al., 2019; Yin et al., 2019; Yin, Cheung, et al., 2020) and heart failure (Afshar et al., 2020; Ho, Ghosh, Steinhubl, et al., 2014). Supervised learning as a subsequent step to an unsupervised decomposition is a common way that can indicate clinical plausibility. However, it is important to note that a downstream predictive task does not measure interpretability which is why medical experts are often consulted in addition.

5.2 | External validation

In cases where neither a control group (or any other subdivision of the cohort) nor labeled data is present, the only option is external validation which will be discussed in the following.

5.2.1 | Comparison with existing literature

Existing research, even when performed using different cohorts or study designs, might supply evidence for the clinical relevance of phenotypes. Relating a phenotype to what is already known in the medical literature is used in some studies using matrix and tensor decomposition methods for phenotyping (Hassaine et al., 2020; He et al., 2019; Zhao et al., 2019). In the study by Zhao et al., 2019, for instance, where the disease under consideration is the cardiovascular disease, known comorbidities from the scientific literature are linked with the uncovered phenotypes.

5.2.2 | Medical expertise

Medical expertise is crucial for methodological and clinical validation. Using uncovered phenotypes for some supervised learning task, as described above, only quantifies the predictive power with respect to some target. However, it is a different question whether the phenotypes are clinically meaningful and easy to interpret. Including clinical experts to evaluate the phenotypes under these criteria is a common practice (see Table 1). Typically, clinicians are asked to assess the phenotypes on a certain scale, for example, (1) clinically meaningful, (2) possibly clinically meaningful, and
(3) not clinically meaningful (Henderson et al., 2017, 2018; Ho, Ghosh, Steinhubl, et al., 2014; Wang et al., 2015; Yin, Cheung, et al., 2020) or (1) poor, (2) fair, (3) good, (4) excellent (Joshi et al., 2016).

A further common practice is to let medical experts label the uncovered phenotypes (Afshar et al., 2018; Ho, Ghosh, Steinhubl, et al., 2014; Perros et al., 2017; Wang et al., 2020). This means that a medical expert examines the latent concepts (phenotype definitions) and finds succinct descriptions.

In one case, medical expertise was used for model selection (Wang et al., 2020), that is, NMF is run using different number of components, and then evaluated with respect to the clinical relevance of the uncovered latent concepts.

### 6 | DISCUSSION

Static and temporal phenotyping via low-rank approximation-based methods have been studied to gain a better understanding of raw EHR. The major advantages of these methods are their model transparency and the ability to uncover (temporal) phenotypes that are explainable and interpretable, as well as their potential to reveal novel phenotypes. In this section, we discuss some limitations that frequently arise within the phenotyping literature and lay out possible future directions.

#### 6.1 | Challenges and limitations

There are common challenges and limitations with matrix and tensor factorization-based approaches concerning model uniqueness, computational reproducibility, number of components, and the validation of components (or phenotypes).

##### 6.1.1 | Uniqueness

A general advantage of tensor factorizations such as CP and PARAFAC2 over matrix factorizations is their uniqueness guarantees (up to permutation and scaling ambiguities). A model that has no unique solution is arbitrary. The computed factor matrices (or phenotypes) could be meaningless as they change in different runs even when the same solution, that is, the same cost function value, is obtained. Thus, uniqueness is an essential requirement for a factorization model if the goal is to interpret the extracted components. Matrix factorizations such as NMF are not unique in general (Laurberg et al., 2008). However, enforcing additional sparsity can potentially make the factorization unique. Therefore, in order to provide certainty that the interpreted model and the extracted phenotypes are not arbitrary, it is crucial to discuss and investigate the uniqueness properties of matrix and tensor factorization-based approaches as in several phenotyping studies (Afshar et al., 2020; Perros et al., 2019, Perros et al., 2017; Yin, Afshar et al., 2020).

##### 6.1.2 | Computational reproducibility

While essential uniqueness is crucial for the interpretability of factors, that does not alone guarantee computational reproducibility. Here, with computational reproducibility, we refer to obtaining the same factors (e.g., phenotypes) using the same data and the same method (Adali et al., 2022). When fitting matrix/tensor factorization-based models, we often solve a non-convex optimization problem. Therefore, due to local minima, components from even essentially unique models, for example, CP and PARAFAC2, can be spurious when the methods are initialized using different initializations. To minimize the chance of ending up with spurious components from a local minimum, that is, different phenotypes in different runs, the optimization procedure needs to be run multiple times using different (random) initializations and the factors corresponding to the best run, for example, the one with the lowest cost function value (Perros et al., 2019), the most consistent run, should be interpreted (Adali et al., 2022). Despite being important for interpretability, computational reproducibility, best run selection and model stability have only been addressed in a few studies in matrix/tensor factorization-based computational phenotyping (Adali et al., 2022; Ho, Ghosh, Steinhubl, et al., 2014; Perros et al., 2019).
6.1.3 | Number of components

An appropriate low-rank model separates the systematic part of the data from the residuals that arise due to model and measurement errors. The number of components is commonly chosen based on whether an additional component significantly improves the model fit. However, determining the number of components is a challenging task, and various methods to determine the model order, that is, the number of components, have been studied such as imputation error or cross-validation-based approaches (Louwerse et al., 1999; Udell et al., 2016), core consistency diagnostic for CP and PARAFAC2 models (Bro & Kiers, 2003; Perros et al., 2019), automated methods based on core consistency (Papalexakis, 2016) as well as Bayesian approaches (Cheng et al., 2022; Mørup & Hansen, 2009). Choosing the appropriate number of components is discussed in some phenotyping studies (Perros et al., 2018, 2019; Zhao et al., 2019), and the sensitivity of the performance to the number of components has been discussed (Afshar et al., 2020; Yin, Afshar et al., 2020). Model order selection needs to be carried out carefully; otherwise, uncovered patterns might be spurious and non-reproducible. While not commonly used, choosing the number of components based on model stability, that is, by using the cross-correlation of factors from different runs (Wu et al., 2016), computational reproducibility (Adali et al., 2022), that is, reaching the same cost function value and/or the same factors consistently when the number of components is correctly estimated, replicability (Adali et al., 2022), that is, extracting the same factors through split-half analysis (Harshman & De Sarbo, 1984) or using different subsets of the data, can be sensible and supplementary approaches next to other common selection criteria. Within EHR-based phenotyping, model stability is used to determine the number of components in Sustain (Perros et al., 2018).

6.1.4 | Validation of components

It is crucial to assess the clinical relevance of a phenotype. Survival analysis has been successfully employed for internal validation. However, it has been used only in a few studies (Perros et al., 2019; Rennard et al., 2015; Zhao et al., 2019). In contrast to supervised learning, survival analysis has the potential to uncover fine-grained information about the progression of a disease, or different subgroups defined by a phenotype. Kaplan–Meier plots, although being purely descriptive, can indicate the severity of a phenotype definition, and thus, be of great therapeutic value.

6.2 | Possible future directions

There are several future directions that have the potential to advance computational phenotyping further.

First, jointly analyzing data from different modalities has the potential to reveal better phenotypes, and has shown promise in precision medicine (Price et al., 2017). While different data modalities can, in some cases, be represented as a single data tensor (Luo, Ahmad, & Shah, 2017a), often there is a need to jointly analyze data sets in the form of multiple matrices and higher-order tensors, for instance, to fuse temporal as well as static data sources (Afshar et al., 2020; Gujral et al., 2020) (as illustrated in Figure 8), to jointly analyze multiple modalities (Li et al., 2020) or for joint analysis

![Coupled matrix and tensor factorization (CMTF). Static and temporal information is, for instance, coupled via the patient mode. This approach reveals static and temporal phenotypes while it can potentially also uncover more meaningful patient groupings.](image-url)
of data from controls and patients (Yin et al., 2021). CMTF have been effective tools for joint analysis of such data sets in data mining (Acar et al., 2015; Acar, Kolda, & Dunlavy, 2011b; Papalexakis et al., 2016), in particular, in multi-modal neuroimaging data analysis (Acar et al., 2019; Chatzichristos et al., 2022) as well as recommender systems (Ermis et al., 2015; Zheng et al., 2010). In EHR-based phenotyping, CMTF-based approaches may allow for the incorporation of both temporal and nontemporal sources. The patient mode, for instance, can be enforced to be a low-rank representation of the temporal as well as the static information. Fusing these different data sources can lead to an improved clustering of patients while uncovering both temporal and static phenotype definitions. So far, CMTF-based phenotyping has been limited focusing only on EHR data (Afshar et al., 2020), where temporal diagnosis and medication data and static features have been jointly analyzed. Future work may extend EHR-based phenotyping by incorporating other modalities such as various omics data sets, and jointly analyze those data sets using CMTF-based approaches. Recent advances in CMTF methods (e.g., different loss functions for different data sets, various constraints (Schenker et al., 2021), PARAFAC2 models with flexible constraints in all modes (Roald et al., 2022)) may facilitate the progress in that direction.

Second, handling of different data types need further attention. Different statistical data types can be either ignored (Afshar et al., 2018; Luo et al., 2016) or modeled via adapting the loss functions (Henderson et al., 2018; Yin, Afshar et al., 2020). However, a question that does not seem to be conclusively answered is how the choice of loss functions influences the discovery of phenotypes. While there is some indication that “appropriate” loss functions outperform “non-appropriate” ones (Schuler et al., 2016), there is also evidence that applying the standard Frobenius norm to for example, count data results in meaningful phenotypes (Becker et al., 2022; Luo et al., 2016). For a more extreme case, consider a third-order tensor with mixed statistical data types across the feature-mode. That is, the tensor records, for instance, different laboratory parameters together with the disease severity over time. This means that there is one tensor structure that has multiple different statistical data types. For the matrix case, this has already been studied (Schuler et al., 2016; Udell et al., 2016). However, it has not yet been extended to the tensor case.

Finally, privacy-preserving phenotyping is still an under-researched field. While being studied for CP-models (Ma et al., 2019), it has not yet been applied to (irregular) temporal EHR data.

7 | CONCLUSION

In this paper, we provided a comprehensive review of low-rank approximation-based approaches for computational phenotyping and outlined how common challenges such as irregularity along the time mode or overlapping phenotypes are tackled. The appeal of low-rank methods lies in their well-understood theoretical foundations as well as in their model transparency. Our survey shows that CP and PARAFAC2 are common low-rank models for static and temporal phenotyping, respectively. Their uniqueness guarantees make them a suitable tool as the factors are non-arbitrary. Different constraints such as sparsity and non-negativity or regularizations such as an angular penalty to enforce more distinct phenotypes have been used with the ultimate goal to make phenotypes more interpretable and useful in clinical contexts. The validation of phenotypes is a major challenge that has been addressed in different ways. The most common being a subsequent supervised learning task or validation by medical expertise. We outlined that the literature would benefit from including a discussion about model uniqueness and computational reproducibility. Finally, we discussed CMTF, and the handling of different statistical data types as possible future directions.

AUTHOR CONTRIBUTIONS

Florian Becker: Conceptualization (supporting); investigation (lead); writing – original draft (lead). Age K. Smilde: Writing – review and editing (supporting). Evrim Acar: Conceptualization (lead); investigation (supporting); writing – original draft (supporting); writing – review and editing (lead).

FUNDING INFORMATION

This work was funded by the Research Council of Norway through project 300034 (DeCipher).

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.
RELATED WIREs ARTICLES

Applications of tensor (multiway array) factorizations and decompositions in data mining
Tensor decompositions and data fusion in epileptic electroencephalography and functional magnetic resonance imaging data
Tensor methods and recommender systems

FURTHER READING

Yin, K., Afshar, A., Ho, J. C., Cheung, W. K., Zhang, C., & Sun, J. (2020). LogPar: Logistic PARAFAC2 factorization for temporal binary data with missing values. In KDD'20: Proceedings of the 26th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining (pp. 1625–1635).

REFERENCES

Abul-Husn, N. S., & Kenny, E. E. (2019). Personalized medicine and the power of electronic health records. Cell, 177(1), 58–69.
Acar, E., Bingol, C. A., Bingol, H., Bro, R., & Yener, B. (2007). Multiway analysis of epilepsy tensors. Bioinformatics, 23(13), i10–i18.
Acar, E., Bro, R., & Smilde, A. K. (2015). Data fusion in metabolomics using coupled matrix and tensor factorizations. Proceedings of the IEEE, 103, 1602–1620.
Acar, E., Dunlavy, D. M., & Kolda, T. G. (2011). A scalable optimization approach for fitting canonical tensor decompositions. Journal of Chemometrics, 25, 67–86.
Acar, E., Dunlavy, D. M., Kolda, T. G., & Mørup, M. (2010). Scalable tensor factorizations with missing data. In SDM'10: Proceedings of the SIAM International Conference on Data Mining (pp. 701–712).
Acar, E., Kolda, T. G., & Dunlavy, D. M. (2011). All-at-once optimization for coupled matrix and tensor factorizations. In Proceedings KDD workshop mining learn. Graphs Available: https://arxiv.org/abs/1105.3422
Acar, E., Schenker, C., Levin-Schwartz, Y., Calhoun, V., & Adali, T. (2019). Unraveling diagnostic biomarkers of schizophrenia through structure-revealing fusion of multi-modal neuroimaging data. Frontiers in Neuroscience, 13(416), 1–16.
Acar, E., & Yener, B. (2009). Unsupervised multiway data analysis: A literature survey. IEEE Transactions on Knowledge and Data Engineering, 21(1), 6–20.
Adali, T., Kantar, F., Akhonda, M. A. B. S., Strother, S., Calhoun, V. D., & Acar, E. (2022). Reproducibility in matrix and tensor decompositions: Focus on model match, interpretability, and uniqueness. IEEE Signal Processing Magazine, 39(4), 8–24.
Afshar, A., Perros, I., Papalexakis, E. E., Searles, E., Ho, J., & Sun, J. (2018). COPA: Constrained PARAFAC2 for sparse & large datasets. In CIKM'18: Proceedings of the 27th ACM International Conference on Information and Knowledge Management (pp. 793–802).
Afshar, A., Perros, I., Park, H., Dellipippi, C., Yan, X., Stewart, W., Ho, J., & Sun, J. (2020). TASTE: Temporal and static tensor factorization for phenotyping electronic health records. In CHIL’20: Proceedings of the ACM Conference on Health, Inference, and Learning (pp. 193–203).
Aliberti, S., Lonni, S., Dore, S., McDonnell, M. J., Goeminne, P. C., Dimakou, K., Fardon, T. C., Rutherford, R., Pesci, A., Restrepo, M. A., Sotgiu, G., & Chalmers, J. D. (2016). Clinical phenotypes in adult patients with bronchiectasis. European Respiratory Journal, 47(4), 1113–1122.
Banda, J. M., Seneviratne, M., Hernandez-Boussard, T., & Shah, N. H. (2018). Advances in electronic phenotyping: From rule-based definitions to machine learning models. Annual Review of Biomedical Data Science, 1, 53–68.
Becker, F., Nygård, M., Nygård, J., Smilde, A. K., & Acar, E. (2022). Phenotyping of cervical cancer risk groups via generalized low-rank models using medical questionnaires. In NAIS’22: Norwegian AI symposium (pp. 94–110).
Bewick, V., Cheek, L., & Ball, J. (2004). Statistics review 12: Survival analysis. Critical Care, 8(5), 1–6.
Bro, R. (1997). PARAFAC: Tutorial and applications. Chemometrics and Intelligent Laboratory Systems, 38(2), 149–171.
Bro, R., & Kiers, H. A. L. (2003). A new efficient method for determining the number of components in PARAFAC models. Journal of Chemometrics, 17(5), 274–286.
Bro, R., & Smilde, A. K. (2014). Principal component analysis. Analytical Methods, 6, 2812–2831.
Buchanan, A. M., & Fitzgibbon, A. W. (2005). Damped Newton algorithms for matrix factorization with missing data. In CVPR’05: Proceedings of IEEE computer society conference on computer vision and pattern recognition (Vol. 2, pp. 316–322). IEEE.
Burgel, P. R., Paillasseur, J., Caillaud, D., Tillie-Leblond, I., Chanez, P., Escamilla, R., Court-Fortune, I., Perez, T., Carré, P., Roche, N., & Initiatives BPCO Scientific Committee. (2010). Clinical COPD phenotypes: A novel approach using principal component and cluster analyses. European Respiratory Journal, 36(3), 531–539.
Candès, E. J., Li, X., Ma, Y., & Wright, J. (2011). Robust principal component analysis? Journal of the ACM, 58(3), 1–37.
Carroll, J. D., & Chang, J.-J. (1970). Analysis of individual differences in multidimensional scaling via an N-way generalization of “Eckart-Young” decomposition. *Psychometrika, 35*(3), 283–319.

Chatzichristos, C., Kofidis, E., Paesschen, W. V., Lathauwer, L. D., Theodoridis, S., & Huffel, S. V. (2022). Early soft and flexible fusion of electroencephalography and functional magnetic resonance imaging via double coupled matrix tensor factorization for multisubject group analysis. *Human Brain Mapping, 43*(4), 1231–1255.

Cheng, L., Chen, Z., Shi, Q., Wu, Y., & Theodoridis, S. (2022). Towards flexible sparsity-aware modeling: Automatic tensor rank learning using the generalized hyperbolic prior. *IEEE Transactions on Signal Processing, 70*, 1834–1849.

Chi, E. C., & Kolda, T. G. (2012). On tensors, sparsity, and nonnegative factorizations. *SIAM Journal on Matrix Analysis and Applications, 33*(4), 1272–1299.

Choi, E., Schuetz, A., Stewart, W. F., & Sun, J. (2017). Using recurrent neural network models for early detection of heart failure onset. *Journal of the American Medical Informatics Association, 24*(2), 361–370.

Cohen, J. E., & Bro, R. (2018). Nonnegative PARAFAC2: A flexible coupling approach. In LVA/ICA’18: *Proceedings of the International Conference on Latent Variable Analysis and Signal Separation* (pp. 89–98).

Collins, M., Dasgupta, S., & Schapire, R. E. (2001). A generalization of principal components analysis to the exponential family. *Advances in Neural Information Processing Systems, 14*, 617–624.

Ding, M., & Lao, Y. (2021). Unsupervised phenotyping of sepsis using nonnegative matrix factorization of temporal trends from a multivariate panel of physiological measurements. *BMC Medical Informatics and Decision Making, 21*(5), 1–15.

Doshi-Velez, F., Ge, Y., & Kohane, I. (2014). Comorbidity clusters in autism spectrum disorders: An electronic health record time-series analysis. *Pediatrics, 133*(1), e54–e65.

Dunlavy, D. M., Kolda, T. G., & Acar, E. (2011). Temporal link prediction using matrix and tensor factorizations. *ACM Transactions on Knowledge Discovery from Data, 5*(2) Article no: 10, 1–27.

Ermiş, B., Acar, E., & Cemgil, A. T. (2015). Link prediction in heterogeneous data via generalized coupled tensor factorization. *Data Mining and Knowledge Discovery, 29*, 203–236.

Friedman, C., & Hripcsak, G. (1999). Natural language processing and its future in medicine. *Academic Medicine, 74*(8), 890–895.

Georgiades, S., Szatmari, P., Zwaigenbaum, L., Duku, E., Bryson, S., Roberts, W., Goldberg, J., & Mahoney, W. (2007). Structure of the autism symptom phenotype: A proposed multidimensional model. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(2), 188–196.

Gujral, E., Theocharous, G., & Papalexakis, E. E. (2020). C3APTION: Constrained coupled CP and PARAFAC2 tensor decomposition. In *ASONAM’2020*: IEEE/ACM International Conference on Advances in Social Networks Analysis and Mining (pp. 401–408).

Harshman, R. A. (1970). Foundations of the PARAFAC procedure: Models and conditions for an “explanatory” multi-modal factor analysis. *UCLA Working Papers in Phonetics, 16*, 1–84.

Harshman, R. A. (1972). PARAFAC2: Mathematical and technical notes. *UCLA Working Papers in Phonetics, 22*, 30–44.

Harshman, R. A., & De Sarbo, W. S. (1984). An application of PARAFAC to a small sample problem, demonstrating preprocessing, orthogonality constraints, and split-half diagnostic techniques. In *Research methods for multidime data analysis* (pp. 602–642). Praeger.

Hassaine, A., Canoy, D., Solares, J. R. A., Zhu, Y., Rao, S., Li, Y., Zottoli, M., Rahimi, K., & Salimi-Khorshidi, G. (2020). Learning multimorbidity patterns from electronic health records using non-negative matrix factorisation. *Journal of Biomedical Informatics, 112*, 103606.

He, H., Henderson, J., & Ho, J. C. (2019). Distributed tensor decomposition for large scale health analytics. In *WWW’19: Proceedings of the world wide web conference* (pp. 659–669).

Helwig, N. E. (2017). Estimating latent trends in multivariate longitudinal data via PARAFAC2 with functional and structural constraints. *Biometrical Journal, 59*(4), 783–803.

Henderson, J., He, H., Malin, B. A., Denny, J. C., Kho, A. N., Ghosh, J., & Ho, J. C. (2018). Phenotyping through semi-supervised tensor factorization (PSST). In *AMIA annual symposium proceedings* (p. 564).

Henderson, J., Ho, J. C., Kho, A. N., Denny, J. C., Malin, B. A., Sun, J., & Ghosh, J. (2017). Granite: Diversified, sparse tensor factorization for electronic health record-based phenotyping. In *ICHI’17: Proceedings of IEEE International Conference on Healthcare Informatics* (pp. 214–223).

Hitchcock, F. L. (1927). The expression of a tensor or a polyadic as a sum of products. *Journal of Mathematics and Physics, 6*(1–4), 164–189.

Ho, J. C., Ghosh, J., Steinhubl, S. R., Stewart, W. F., Denny, J. C., Malin, B. A., & Sun, J. (2014). Limestone: High-throughput candidate phenotype generation via tensor factorization. *Journal of Biomedical Informatics, 52*, 199–211.

Ho, J. C., Ghosh, J., & Sun, J. (2014). Marble: High-throughput phenotyping from electronic health records via sparse nonnegative tensor factorization. In *KDD’14: Proceedings of the 20th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (pp. 115–124).

Hripcsak, G., & Albers, D. J. (2013). Next-generation phenotyping of electronic health records. *Journal of the American Medical Informatics Association, 20*(1), 117–121.

Hunyadi, B., Dupont, P., Paesschen, W. V., & Huffel, S. V. (2017). Tensor decompositions and data fusion in epileptic electroencephalography and functional magnetic resonance imaging data. *WIREs Data Mining and Knowledge Discovery, 7*, e1197.

Johnson, A., Bulgarelli, L., Pollard, T., Horng, S., Celi, L. A., & Mark, R. (2020). MIMIC-IV (version 0.3). PhysioNet. https://doi.org/10.13026/a2mm-bn44
Ren, Y., Lou, J., Xiong, L., & Ho, J. C. (2020). Robust irregular tensor factorization and completion for temporal health data analysis. In *CIKM'20: Proceedings of the 29th ACM International Conference on Information and Knowledge Management* (pp. 1295–1304).

Rennard, S. I., Locantore, N., Delafont, B., Tal-Singer, R., Silverman, E. K., Vestbo, J., Miller, B. E., Bakke, P., Celli, B., Calverley, P. M. A., Coxson, H., Crim, C., Edwards, L. D., Lomas, D. A., MacNee, W., Wouters, E. F. M., Yates, J. C., Coca, I., & Agusti, A. (2015). Identification of five chronic obstructive pulmonary disease subgroups with different prognoses in the ECLIPSE cohort using cluster analysis. *Annals of the American Thoracic Society*, 12(3), 303–312.

Richesson, R. L., Sun, J., Pathak, J., Kho, A. N., & Denny, J. C. (2016). Clinical phenotyping in selected national networks: Demonstrating the need for high-throughput, portable, and computational methods. *Artificial Intelligence in Medicine*, 71, 57–61.

Roald, M., Schenker, C., Calhoun, V. D., Adali, T., Bro, R., Cohen, J. E., & Acar, E. (2022). An AO-ADMM approach to constraining PARAFAC2 on all modes. *SIAM Journal on Mathematics of Data Science*, 4(3), 1191–1222.

Saeed, M., Villarroel, M., Reisner, A. T., Clifford, G., Lehman, L.-W., Moody, G., Heldt, T., Kyaw, T. H., Moody, B., & Mark, R. G. (2011). Multiparameter intelligent monitoring in intensive care II (MIMIC-II): a public-access intensive care unit database. *Critical Care Medicine*, 39(5), 952–960.

Schenker, C., Cohen, J. E., & Acar, E. (2021). A flexible optimization framework for regularized matrix-tensor factorizations with linear couplings. *IEEE Journal of Selected Topics in Signal Processing*, 15(3), 506–521.

Schulam, P., Wigley, F., & Saria, S. (2015). Clustering longitudinal clinical marker trajectories from electronic health data: Applications to phenotyping and endotype discovery. In *AAAI’15: Proceedings of the 29th AAAI conference on artificial intelligence* (Vol. 29, pp. 2956–2964). AAAI Press.

Schuler, A., Liu, V., Wan, J., Callahan, A., Udell, M., Stark, D. E., & Shah, N. H. (2016). Discovering patient phenotypes using generalized low rank models. In *PSB16: Proceedings of the Pacific Symposium on Biocomputing* (pp. 144–155).

Shickel, B., Tighe, P. J., Bihorac, A., & Rashidi, P. (2017). Deep EHR: A survey of recent advances in deep learning techniques for electronic health record (EHR) analysis. *IEEE Journal of Biomedical and Health Informatics*, 22(5), 1589–1604.

Shivade, C., Raghavan, P., Fosler-Lussier, E., Embl, P. J., Elhadad, N., Johnson, S. B., & Lai, A. M. (2014). A review of approaches to identifying patient phenotype cohorts using electronic health records. *Journal of the American Medical Informatics Association*, 21(2), 221–230.

Sidiropoulos, N. D., & Bro, R. (2000). On the uniqueness of multilinear decomposition of N-way arrays. *Journal of Chemometrics*, 14(3), 229–239.

Singh, A. P., & Gordon, G. J. (2008). Relational learning via collective matrix factorization. In *KDD’08: Proceedings of the 14th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (pp. 650–658).

Smilde, A., Geladi, P., & Bro, R. (2004). *Multi-way analysis: Applications in the chemical sciences*. John Wiley & Sons.

Solares, J. R. A., Raimondi, F. E. D., Zhu, Y., Rahimian, F., Canoy, D., Tran, J., Gomes, A. C. P., Payberah, A. H., Zottoli, M., Nazarzadeh, M., Conrad, N., & Rahimi, K. (2020). Deep learning for electronic health records: A comparative review of multiple deep neural architectures. *Journal of Biomedical Informatics*, 101, 103337.

Sorber, L., Barel, M. V., & Lathauwer, L. D. (2013). Optimization-based algorithms for tensor decompositions: Canonical polyadic decomposition, decomposition in rank-(L,, L,), terms, and new generalization. *SIAM Journal on Optimization*, 23, 695–720.

Srebro, N., & Jaakkola, T. (2003). Weighted low-rank approximations. In *ICML’03: Proceedings of the 20th International Conference on Machine Learning* (pp. 720–727).

Stroup, E. K., Luo, Y., & Sanchez-Pinto, L. N. (2019). Phenotyping multiple organ dysfunction syndrome using temporal trends in critically ill children. In *BIBM’19: Proceedings of IEEE International Conference on Bioinformatics and Biomedicine* (pp. 968–972).

Timmerman, M. E., & Kiers, H. A. (2002). Three-way component analysis with smoothness constraints. *Computational Statistics & Data Analysis*, 40(3), 447–470.

Tomasi, G., & Bro, R. (2005). *PARAFAC and missing values*. *Chemometrics and Intelligent Laboratory Systems*, 75(2), 163–180.

Tucker, L. R. (1966). Some mathematical notes on three-mode factor analysis. *Journal of Psychometric*, 31, 279–311.

Udell, M., Horn, C., Zadeh, R., & Boyd, S. (2016). Generalized low rank models. *Foundations and trends®. Machine Learning*, 9(1), 1–118.

Vavougios, G. D., Natsios, G., Pastaka, C., Zarogiannis, S. G., & Gourgoulianis, K. I. (2016). Phenotypes of comorbidity in OSAS patients: Combining categorical principal component analysis with cluster analysis. *Journal of Sleep Research*, 25(1), 31–38.

Wang, Y., Chen, R., Ghosh, J., Denny, J. C., Kho, A., Chen, Y., Malin, B. A., & Sun, J. (2015). Rubik: Knowledge guided tensor factorization and completion for health data analytics. In *KDD’15: Proceedings of the 21th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (pp. 1265–1274).

Wang, Y., Wu, T., Wang, Y., & Wang, G. (2020). Enhancing model interpretability and accuracy for disease progression prediction via phenotype-based patient similarity learning. In *PSB20: Proceedings of the Pacific Symposium on Biocomputing* (pp. 511–522).

Williams, A. H., Kim, T. H., Wang, F., Vyas, S., Ryu, S. I., Shenoy, K. V., Schnitzer, M., Kolda, T. G., & Ganguli, S. (2018). Unsupervised discovery of demixed, low-dimensional neural dynamics across multiple timescales through tensor component analysis. *Neuron*, 98(6), 1099–1115.

Wu, S., Joseph, A., Hammonds, A. S., Celniker, S. E., Yu, B., & Frise, E. (2016). Stability-driven nonnegative matrix factorization to interpret spatial gene expression and build local gene networks. *Proceedings of the National Academy of Sciences*, 113(16), 4290–4295.

Xiao, C., Choi, E., & Sun, J. (2018). Opportunities and challenges in developing deep learning models using electronic health records data: A systematic review. *Journal of the American Medical Informatics Association*, 25(10), 1419–1428.
Yang, K., Li, X., Liu, H., Mei, J., Xie, G., Zhao, J., Xie, B., & Wang, F. (2017). TaGiTeD: Predictive task guided tensor decomposition for representation learning from electronic health records. In *AAAI*’17: Proceedings of the 31st AAAI conference on artificial intelligence (Vol. 31, pp. 2824–2830). AAAI Press.

Yin, K., Cheung, W., Fung, B. C., & Poon, J. (2020). Learning inter-modal correspondence and phenotypes from multi-modal electronic health records. *IEEE Transactions on Knowledge and Data Engineering, 34*, 4328–4341.

Yin, K., Cheung, W. K., Fung, B. C. M., & Poon, J. (2021). TedPar: Temporally dependent PARAFAC2 factorization for phenotype-based disease progression modeling. In *SDM’21: Proceedings of the SIAM International Conference on Data Mining* (pp. 594–602).

Yin, K., Qian, D., Cheung, W. K., Fung, B. C., & Poon, J. (2019). Learning phenotypes and dynamic patient representations via RNN regularized collective non-negative tensor factorization. In *AAAI’19: Proceedings of the 33rd AAAI conference on artificial intelligence* (Vol. 33, pp. 1246–1253). AAAI Press.

Zeng, Z., Deng, Y., Li, X., Naumann, T., & Luo, Y. (2018). Natural language processing for EHR-based computational phenotyping. *IEEE/ACM Transactions on Computational Biology and Bioinformatics, 16*(1), 139–153.

Zhang, C., Fanaee-T, H., & Thoresen, M. (2021). Feature extraction from unequal length heterogeneous EHR time series via dynamic time warping and tensor decomposition. *Data Mining and Knowledge Discovery, 35*(4), 1760–1784.

Zhao, J., Zhang, Y., Schlueter, D. J., Wu, P., Kerchberger, V. E., Rosenbloom, S. T., Wells, Q. S., Feng, Q., Denny, J. C., & Wei, W. Q. (2019). Detecting time-evolving phenotypic topics via tensor factorization on electronic health records: Cardiovascular disease case study. *Journal of Biomedical Informatics, 98*, 103270.

Zheng, V. W., Cao, B., Zheng, Y., Xie, X., & Yang, Q. (2010). Collaborative filtering meets mobile recommendation: A user-centered approach. In *AAAI’10: Proceedings of the 24th AAAI conference on artificial intelligence* (Vol. 24, pp. 236–241). AAAI Press.

Zhou, G., Cichocki, A., Zhao, Q., & Xie, S. (2015). Efficient nonnegative Tucker decompositions: Algorithms and uniqueness. *IEEE Transactions on Image Processing, 24*(12), 4990–5003.

Zhou, J., Wang, F., Hu, J., & Ye, J. (2014). From micro to macro: Data driven phenotyping by densification of longitudinal electronic medical records. In *KDD’14: Proceedings of the 20th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining* (pp 135–144).

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**How to cite this article:** Becker, F., Smilde, A. K., & Acar, E. (2023). Unsupervised EHR-based phenotyping via matrix and tensor decompositions. *WIREs Data Mining and Knowledge Discovery, 13*(4), e1494. [https://doi.org/10.1002/widm.1494](https://doi.org/10.1002/widm.1494)