Differential Network Learning Beyond Data Samples

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Abstract

Learning the change of statistical dependencies between random variables is an essential task for many real-life applications, mostly in the high dimensional low sample regime. In this paper, we propose a novel differential parameter estimator that, in comparison to current methods, simultaneously allows (a) the flexible integration of multiple sources of information (data samples, variable groupings, extra pairwise evidence, etc.), (b) being scalable to a large number of variables, and (c) achieving a sharp asymptotic convergence rate. Our experiments, on more than 100 simulated and two real-world datasets, validate the flexibility of our approach, and highlight the benefits of integrating spatial and anatomic information for brain connectome change discovery and epigenetic network identification.

1. Introduction

New technologies have enabled many scientific fields to measure variables at an unprecedented scale and via multiple dimensions. Learning the change of dependencies between random variables is an essential task in many scientific applications. For example, when analyzing functional magnetic resonance imaging (fMRI) samples, detecting the difference in brain connectivity networks across diseased and healthy human populations can shed light on understanding and designing treatments for psychiatric disorders (Di Martino et al., 2014). As another example, when analyzing genomics signals, interests may not be a particular graph representing interactions among genes, but instead on how interactions vary under an external stimulus such as a drug (Ideker & Krogan, 2012).

Differential Graphical Models: Undirected Graphical models (UGM) have been popular tools for estimating variable dependencies from observed multivariate samples. Two classes of UGM have gained significant attention in real-life tasks: (1) Gaussian Graphical Models (GGMs) on continuous variables, and (2) Ising models for categorical variables. Recent literature has made good advances in methods detecting changes in dependencies using samples from two different conditions. A naive approach to estimate structural change is a two-step procedure in which we estimate two separate dependency structures independently for each condition and calculate the difference by comparing the two derived structures. However, in a high-dimensional setting, researchers found the strategy tends to produce many spurious differences (de la Fuente, 2010). Multiple recent studies aimed to control the spurious differences, and the majority built upon Gaussian graphical models. We call these models differential GGMs, and learning the change structure between two dependency networks means to learn parameter of the corresponding differential GGM. Parameter learning of differential GGMs roughly fall into four categories: (1) Multitask MLE based. Multiple studies (Zhang & Wang, 2012; Danaher et al., 2013; Honorio & Samaras, 2010) used the fused norm or similar to learn the differential parameters via multi-tasking and followed the regularized maximum likelihood estimation (MLE) formulation. (2) Density ratio based: Recently, (Liu et al., 2017; 2014) used density ratio estimation (SDRE) to directly learn structural difference without having to identify the dependency structure of each. (3) Constrained $\ell_1$ minimization based. Diff-CLIME, another regularized convex program, was proposed to directly learn structural changes without going through the learning of each GGM (Zhao et al., 2014). (4) Elementary estimator based. The last category extends a so-called Elementary Estimator proposed by (Yang et al., 2014a;c;b) for direct learning of differential GGM. The resulting DIFFEE estimator (Wang et al., 2018b) is solved through a faster and closed-form solution, allowing it to scale to a large number of variables.

The estimators above provide excellent tools for practitioners to identify a differential dependency network. However, these methods only allow the inclusion of observed samples. Recent technological advances in data generation (like high-throughput sequencing and new sensors) have driven many fields in producing measurements of different kinds. For instance, over time, neuroscientists have gathered a large number of fMRI scans that measure and map human brains’ activity (Poldrack et al., 2013). Researchers have also gathered a considerable amount of other measurements like
those reflecting the physical wiring of brains using structural magnetic resonance imaging (structural MRI) (Damoiseaux & Greicius, 2009). Differential GGMs have been used to estimate the variability of functional connectivity among brain regions using fMRI scans as input samples. Integrating fMRI samples with additional data sources like structural MRI or anatomical priors of brain regions will provide an appealing way of making the estimation of functional connectivity more robust. Besides, including complementary sources of evidence can help the learned model better reflect domain experts’ beliefs (like short edges and certain anatomical regions are more likely to connect functionally (Watts & Strogatz, 1998)).

Unfortunately, all previous differential parameter estimators rely on observed samples alone; therefore, they can hardly capture the complexity of dependency structures relevant to complex phenomena like a disease. This paper fills the gap by proposing a novel method, namely KDiffNet, to add additional knowledge in identifying differential networks via an Elementary Estimator. By harnessing heterogeneous data across complementary sources of evidence, KDiffNet makes an essential step in enabling data integration for differential dependency estimation.

Another critical property of recent data generations is how the measured variables grow at an unprecedented scale. On $p$ variables, there are $O(p^2)$ possible pairwise interactions we aim to learn from samples. For even a moderate $p$, searching for pairwise relationships is computationally expensive. $p$ in popular applications ranges from hundreds (e.g., #brain regions) to tens of thousands (e.g., #human genes). This challenge motivates us to make the design of KDiffNet build upon a more scalable class of differential estimators like DIFFEE (Wang et al., 2018b).

Recent differential GGM estimators mostly work under the high dimensional regime, due to a large number of potential parameters ($p^2$). All previous estimators made the sparsity model assumption and used $\ell_1$ norm to enforce the learned differential graph as sparse. However, there exist many other assumptions real-life tasks may prefer on the differential structure. For instance, many real-world networks have hub nodes that are densely-connected to many other nodes. Hub nodes are more prone to get perturbed across conditions (e.g. p53 gene in human gene regulatory network (Mohan et al., 2014)) and become perturbed hub nodes in a differential network. A topology allowing perturbed hubs is, therefore, a desired assumption; however, $\ell_1$ based regularization can’t enforce such a prior. In another case, genes belonging to the same biological pathway tend to either interact with all others of the group (“co-activated” as a dense sub-network) or not at all (“co-deactivated”) (Da Wei Huang & Lempicki, 2008). Again, the $\ell_1$ norm could not model this type of group-sparsity pattern.

To tackle all the challenges explained above, we propose KDiffNet and make the following contributions:\footnote{We put details of theoretical proofs, details of how we generate simulation datasets, and detailed results when tuning hyper-parameters in the appendix. Notations with “S:” (as a prefix) are for contents in the appendix. We also wrap our code into an R toolkit and share via the zip appendix.}

- **Flexible**: KDiffNet is the first differential parameter estimator that can integrate multiple sources of evidence. KDiffNet designs a new hybrid norm and provides flexibility to enforce many different kinds of topology priors that an application may favor, including like group sparsity, hub structure, or combinations. The DIFFEE estimator is a special case of KDiffNet (Section 3.2).

- **Scalable**: We design KDiffNet via an elementary estimator based framework and solve it via parallel proximal based optimization. KDiffNet scales to large $p$ and doesn’t need to design knowledge-specific optimization (Section 3.4).

- **Theoretically Sound**: We theoretically prove the convergence rate of KDiffNet as $O\left(\sqrt{\frac{\log p}{\min(n_c, n_d)}}\right)$, achieving the same error bound as the state-of-the-art (Section 3.5).

- **Empirical Evaluation**: We evaluate KDiffNet on multiple synthetic and two real-world datasets. KDiffNet consistently outperforms the state-of-the-art baselines with better prediction accuracy while achieving less or same time cost. Our experiments showcase how KDiffNet can integrate knowledge like spatial distances, known edges, and anatomical grouping evidence when estimating differential graph from multivariate samples (Section 4).

## 2. Background and Formulation

The basic formulation of estimating differential GGMs includes two given sets of observed samples (as two matrices) $X_c \in \mathbb{R}^{n_c \times p}$ and $X_d \in \mathbb{R}^{n_d \times p}$. $X_c$ and $X_d$ were identically and independently drawn from two normal distributions $N_p(\mu_c, \Sigma_c)$ and $N_p(\mu_d, \Sigma_d)$ respectively. Here $\mu_c, \mu_d \in \mathbb{R}^p$ describe the mean vectors and $\Sigma_c, \Sigma_d \in \mathbb{R}^{p \times p}$ represent covariance matrices. The goal of differential GGMs is to estimate the structural change $\Delta$ defined by (Zhao et al., 2014)\footnote{For instance, on data samples from a controlled drug study, ‘c’ may represent the ‘control’ group and ‘d’ may represent the ‘drug-treating’ group. Using which of the two sample sets as ‘c’ set (or ‘d’ set) does not affect the computational cost and does not influence the statistical convergence rates.}

$$\Delta = \Omega_d - \Omega_c$$ (2.1)

Here the precision matrices $\Omega_c := (\Sigma_c)^{-1}$ and $\Omega_d := (\Sigma_d)^{-1}$. The conditional dependency structure of a GGM is encoded by the sparsity pattern of its precision matrix. Therefore, one entry of $\Delta$ describes if the magnitude of difference

$\Delta$ between $\Omega_d$ and $\Omega_c$ is not zero.
A naive approach to estimate $\Delta$ will learn $\Omega_d$ and $\Omega_c$ from $X_d$ and $X_c$ independently and calculate $\Delta$ using Eq. (2.1). However, in a high-dimensional setting, the strategy needs to assume both $\Omega_d$ and $\Omega_c$ are sparse (to achieve consistent estimation of each), although the assumption is not necessarily true even if the change $\Delta$ is sparse. Recent literature includes multiple differential parameter estimators to go beyond the naive strategy. They roughly fall into four categories (Section 1). We present one estimator from each group here.

**Multitask MLE based: JGLFused**: One study "Joint Graphical Lasso" (JGL) (Danaher et al., 2013) used multitask MLE formulation for joint learning of multiple sparse GGMs. JGL can estimate a differential network when using an additional sparsity penalty called the fused norm:

$$
\text{argmin}_{\Omega, \Omega_d \sim 0, \Delta} n_c (-\log \det(\Omega_c) + < \Omega_c, \hat{\Sigma}_c >) + n_d (-\log \det(\Omega_d) + < \Omega_d, \hat{\Sigma}_d >) + \lambda_2 (||\Omega_c||_1 + ||\Omega_d||_1) + \lambda_n ||\Delta||_1
$$

(2.2)

Another study (Honorio & Samaras, 2010) used $\ell_1/\ell_\infty$ regularization via a similar multi-task MLE formulation. Studies in this group jointly learn two GGMs and the difference. However, these multi-task methods do not work if each graph is dense but the change is sparse. For instance recent literature in neuroscience has suggested that each subject’s functional brain connection network may not be sparse, even though differences across subjects may be sparse (Belilovsky et al., 2016). When identifying how genetic networks vary between two conditions, an individual network may contain hub nodes, therefore not entirely sparse (Ideker & Krogan, 2012).

**Density ratio based: SDRE**: (Liu et al., 2014) proposed to directly estimate sparse differential networks for exponential family by Density Ratio Estimation:

$$
\text{argmax}_\Delta \mathcal{L}_{\text{KLEP}}(\Delta) - \lambda_n ||\Delta||_1 - \lambda_2 ||\Delta||_2
$$

(2.3)

$\mathcal{L}_{\text{KLEP}}$ minimizes the KL divergence between the true probability density $p_d(x)$ and the estimated without explicitly modeling the true $p_c(x)$ and $p_d(x)$. This estimator uses the elastic-net penalty for enforcing sparsity.

**Constrained $\ell_1$ minimization based: Diff-CLIME**: The study by (Zhao et al., 2014) directly learns $\Delta$ through a constrained optimization formulation.

$$
\text{argmin}_\Delta ||\Delta||_1
$$

Subject to: $||\hat{\Sigma}_c \Delta \hat{\Sigma}_d - (\hat{\Sigma}_c - \hat{\Sigma}_d)||_\infty \leq \lambda_n$

(2.4)

The optimization reduces to multiple linear programming problems with a computational complexity of $O(p^3)$. This method doesn’t scale to large $p$.

**Elementary estimator based: DIFFEE**: (Wang et al., 2018b) proposed a so-called DIFFEE for estimating sparse structure changes in high-dimensional GGMs directly:

$$
\begin{align*}
\text{argmin}_\Delta ||\Delta||_{1, \text{off}} \\
\text{Subject to: } ||\Delta - B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)||_{\infty, \text{off}} \leq \lambda_n
\end{align*}
$$

(2.5)

The design of (Wang et al., 2018b) follows a so-called family of elementary estimators. We explain details of $B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)$ in Section 3.1. DIFFEE’s solution is a closed-form entry-wise thresholding operation on $B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)$ to ensure the desired sparsity structure of its final estimate. Here $\lambda_n > 0$ is the tuning parameter. Empirically, DIFFEE scales to large $p$ and is faster than SDRE and Diff-CLIME.

## 3. Method: KDiffNet

Recent advances in data generation calls for the development of new learning methods tailored to the integration of multiple sources of information. KDiffNet aims to tackle challenges in this direction on the differential parameter learning task. Figure 1 shows an overview of our method.

### 3.1. $R(\cdot)$ Norm based Elementary Estimators (EE)

Multiple recent studies (Yang et al., 2014c; Yang et al., 2014a; Wang et al., 2018b) followed a framework “Elementary estimators”:

$$
\begin{align*}
\text{argmin}_{\theta} \mathcal{R}(\theta), \\
\text{Subject to: } R^*(\theta - \hat{\theta}_n) \leq \lambda_n
\end{align*}
$$

(3.1)

Where $\mathcal{R}(\cdot)$ represents a decomposable regularization function. $R^*(\cdot)$ is the dual norm of $\mathcal{R}(\cdot)$.

$$
R^*(v) := \sup_{u \neq 0} \frac{< u, v >}{\mathcal{R}(u)} = \sup_{\mathcal{R}(u) \leq 1} < u, v >
$$

(3.2)

Eq. (2.5) is a special case of Eq. (3.1), in which $\mathcal{R}(\cdot)$ is the $\ell_1$-norm for enforcing sparsity. The differential parameter $\Delta$ is the $\theta$ in Eq. (3.1) that we aim to estimate. $R^*(\cdot)$ in Eq. (2.5) is the dual norm of $\ell_1$, therefore Eq. (2.5) used $\ell_\infty$.

The design philosophy shared among elementary estimators is to construct $\hat{\theta}_n$ carefully from well-defined estimators that are easy to compute and come with strong statistical convergence guarantees. For example, (Yang et al., 2014a) conduct the high-dimensional estimation of linear regression models by using the classical ridge estimator as $\hat{\theta}_n$ in Eq. (3.1). When $\hat{\theta}_n$ itself is closed-form and $\mathcal{R}(\cdot)$ is the $\ell_1$-norm, the solution of Eq. (3.1) is naturally closed-form, therefore, easy and fast to compute, and scales to large $p$. 

The optimization reduces to multiple linear programming problems with a computational complexity of $O(p^3)$. This method doesn’t scale to large $p$. 

**Elementary estimator based: DIFFEE**: (Wang et al., 2018b) proposed a so-called DIFFEE for estimating sparse structure changes in high-dimensional GGMs directly:

$$
\begin{align*}
\text{argmin}_\Delta ||\Delta||_{1, \text{off}} \\
\text{Subject to: } ||\Delta - B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)||_{\infty, \text{off}} \leq \lambda_n
\end{align*}
$$

(2.5)

The design of (Wang et al., 2018b) follows a so-called family of elementary estimators. We explain details of $B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)$ in Section 3.1. DIFFEE’s solution is a closed-form entry-wise thresholding operation on $B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)$ to ensure the desired sparsity structure of its final estimate. Here $\lambda_n > 0$ is the tuning parameter. Empirically, DIFFEE scales to large $p$ and is faster than SDRE and Diff-CLIME.
Following the above design philosophy, (Wang et al., 2018b) proposed a closed and well-defined form for \( \hat{\theta}_n \):

\[
\hat{\theta}_n = B^*(\hat{\Sigma}_d, \hat{\Sigma}_c) = \left( [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1} \right) \tag{3.3}
\]

This was based on (Yang et al., 2014c) that proposed the following generic formulation to estimate canonical parameter for an exponential family distribution via EE framework:

\[
\operatorname{argmin}_\theta ||\theta||_1, \quad \text{Subject to:} \quad ||\theta - B^*(\hat{\varphi})||_\infty \leq \lambda_n \tag{3.4}
\]

For an exponential family distribution, \( \theta \) is its canonical parameter to learn. \( B^*(\hat{\varphi}) \) denotes a so-called proxy of backward mapping for the target exponential family.

Interestingly, the density ratio between two Gaussian distributions falls naturally in the exponential family (see details in Section 10.1). \( \Delta \) is one entry of the canonical parameter of this exponential family distribution. For an exponential family distribution, computing the canonical parameter through vanilla MLE can be expressed as a backward mapping from some given moments of the distribution (Wainwright & Jordan, 2008). In the case of differential GGM, the backward mapping (i.e., the vanilla MLE solution for \( \Delta \)) is a simple closed form: 

\[
B(\hat{\varphi}) = B(\hat{\Sigma}_d, \hat{\Sigma}_c) = (\hat{\Sigma}_d^{-1} - \hat{\Sigma}_c^{-1}),
\]

easily inferred from the two sample covariance matrices.

However, when in high-dimensional regimes, \( B(\hat{\Sigma}_d, \hat{\Sigma}_c) \) is not well-defined because \( \hat{\Sigma}_c \) and \( \hat{\Sigma}_d \) are rank-deficient (thus not invertible) when \( p > n \). Therefore DIFFEE designed a so-called proxy backward mapping \( B^*(\hat{\Sigma}_d, \hat{\Sigma}_c) \) in Eq. (3.3). Here \( [T_v(A)]_{ij} := \rho_v(A_{ij}) \) where \( \rho_v(\cdot) \) was chosen as a soft-thresholding function.

Importantly the formulation in Eq. (3.1) \(^3\) guarantees its solution to achieve a sharp convergence rate as long as \( \hat{\theta}_n \) is carefully chosen, well-defined, easy to compute and come with a strong statistical convergence guarantee (Negahban et al., 2009). In summary, Eq. (3.1) provides an intriguing formulation to build simpler and possibly fast estimators accompanied by statistical guarantees. We, therefore, use it to design KDiffNet in Section 3.3. To use Eq. (3.1) for estimating our target parameter \( \Delta \), we need to design \( R(\Delta) \).

### 3.2 Integrating Complementary Sources of Knowledge via kEV Norm: \( R(\Delta) \)

Our main goal is to enable differential parameter estimators to integrate extra evidence beyond data samples. We can group extra knowledge sources into two kinds: (1) edge-based, and (2) node-based.

1. **Knowledge as Weight Matrix:** We propose to describe edge-style knowledge sources via positive weight matrices

2. **Knowledge as Node Groups:** Many real-world applications include knowledge about how variables group into sets. For example, biologists have collected a rich set of group evidence about how genes belong to various biological pathways or exist in the same or different cellular locations (Da Wei Huang & Lempicki, 2008). Gene grouping information provides solid biological bias that genes belonging to the same pathway tend to co-activated (a dense sub-network) or co-deactivated (a block of sparse entries).

Figure 1. An overview of KDiffNet. KDiffNet integrates different types of extra knowledge for estimating differential GGMs using Elementary Estimators. As an example, the edge level knowledge can represent known edges (or non-edges) and group level knowledge represents information about multiple variables that function as groups.

The matrix form of \( W_E \) can represent many different kinds of prior knowledge. (1) For example, \( W_E \) can describe spatial distance among brain regions (publicly available in sites like openfMRI (Poldrack et al., 2013)). This can nicely encode the domain prior that neighboring brain regions may be more likely to connect functionally. (2) Another important example is when identifying gene-gene interactions from expression profiles. State-of-the-art bio-databases like HPRD (Prasad et al., 2009) have collected a significant amount of information about direct physical interactions between proteins. Here \( W_E \) can describe those known edges. (3) For known hub nodes, we can design \( W_E \) to assign all entries connecting to hubs with a smaller weight.

In summary, the positive matrix-based representation provides a powerful and flexible strategy that allows integration of many possible forms of knowledge to improve differential parameter estimation, as long as they can be formulated via edge-level weights.

\(^3\) DIFFEE: Eq. (2.5) is a special case of Eq. (3.4). Eq. (3.4) is a special case of Eq. (3.1).
However, this type of group evidence cannot be used via $W_E$ formulation. This is because even though it is safe to assume nodes in the same group share similar interaction patterns, but we do not know beforehand if a specific group’s pattern is "dense sub-network" or "group sparsity". To mitigate the issue, we propose integrating knowledge of feature groups into $\Delta$ by enforcing a group-structured regularization on corresponding edge groups in $\Delta$.

Mathematically, we use $G_p$ to denote a set of known vertex groups. We use each node group $g_k \in G_p$ to generate a corresponding edge-group $g'_k \in G_V$. This is done via defining $G_V := \{g'_k | (i, j) \in g'_k, \forall i \in g_k \}$. For vertex nodes in each node group $g_k$, all possible pairs between these nodes belong to an edge-group $g'_k$. We propose to use the group-wise norm $||\Delta||_{g'_V,2}$ to enforce group-wise sparse structure on $\Delta$. None of the previous differential GGM estimators have explored this knowledge-integration strategy.

**kEV norm:** Now we design $R(\Delta)$ as a hybrid norm that combines the two strategies above. First, we assume that the true parameter $\Delta^* = \Delta^*_c + \Delta^*_g$; a superposition of two "clean" structures, $\Delta^*_c$ and $\Delta^*_g$. Then we define $R(\Delta)$ as the "knowledge for Edges and Vertex norm (kEV-norm)":

$$ R(\Delta) = ||W_E \circ \Delta_c||_1 + \epsilon ||\Delta_g||_{g'_V,2} \tag{3.5} $$

Here the Hadamard product $\circ$ denotes element-wise product between two matrices (e.g. $[A \odot B]_{ij} = A_{ij} B_{ij}$). $||\cdot||_{g'_V,2} = \sum_k ||\Delta_{g'_k}||_2$ and $k$ denotes the $k$-th group. The positive matrix $W_E \in R^{p \times p}$ describes one aforementioned edge-level additional knowledge. $\epsilon > 0$ is a hyperparameter. $R(\Delta)$ is the superposition of edge-weighted $\ell_1$ norm and the group structured norm. Our target parameter $\Delta = \Delta_c + \Delta_g$.

### 3.3. kEV Norm based Elementary Estimator for identifying Differential Net (KDiffNet)

kEV-norm has three desired properties (see proofs in Section 9): (i) kEV-norm is a norm function if $\epsilon$ and entries of $W_E$ are positive. (ii) If the condition in (i) holds, kEV-norm is a decomposable norm. (iii) The dual norm of kEV-norm is $R^*(u)$.

$$ R^*(u) = \max(||(1 \odot W_E) \circ u||_\infty, \frac{1}{\epsilon} ||u||_{g'_V,2}) \tag{3.6} $$

Here, $(1 \odot W_E)$ indicates the element wise division.

Then we define the proxy backward mapping using the close-form formulation from DIFFEE: $\hat{\theta}_n = [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}$. Section 10.4 proves that the chosen $\hat{\theta}_n$ is theoretically well-behaved in high-dimensional settings. Now by plugging $R(\Delta)$, its dual $R^*(\cdot)$ and $\hat{\theta}_n$ into Eq. (3.1), we get the formulation of KDiffNet:

$$ \text{argmin}_{\Delta} ||W_E \circ \Delta_c||_1 + \epsilon ||\Delta_g||_{g'_V,2} \tag{3.7} $$

subject to:

$$ \begin{align*}
||((1 \odot W_E) \circ \Delta - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}) ||_\infty \leq \lambda_n \\
||\Delta - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}) ||_{g'_V,2} \leq \epsilon \lambda_n
\end{align*} $$

### 3.4. Solving KDiffNet

We then design a proximal parallel based optimization to solve Eq. (3.1), inspired by its distributed and parallel nature (Combettes & Pesquet, 2011). To simplify notations, we add a new notation $\Delta_{tot} : = [\Delta_c, \Delta_g]$ where $\epsilon$ denotes the row wise concatenation. We also add three operator notations including $L_c(\Delta_{tot}) = \Delta_c$, $L_g(\Delta_{tot}) = \Delta_g$ and $L_{tot}(\Delta_{tot}) = \Delta_c + \Delta_g$. Now we re-formulate KDiffNet as:

$$ \text{argmin}_{\Delta_{tot}} ||W_E \odot (L_c(\Delta_{tot}))||_1 + \epsilon ||L_g(\Delta_{tot})||_{g'_V,2} \tag{3.8} $$

subject to:

$$ \begin{align*}
||((1 \odot W_E) \odot (L_{tot}(\Delta_{tot})) - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}) ||_\infty \leq \lambda_n \\
||L_{tot}(\Delta_{tot}) - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}) ||_{g'_V,2} \leq \epsilon \lambda_n
\end{align*} $$

In fact the three added operators are affine mappings and can write as: $L_c = A_c \Delta_{tot}$, $L_g = A_g \Delta_{tot}$, and $L_{tot} = A_{tot} \Delta_{tot}$, where $A_c = [I_{p \times p} 0_{p \times p}]$, $A_g = [0_{p \times p} I_{p \times p}]$ and $A_{tot} = [I_{p \times p} I_{p \times p}]$.

Now we reformulate Eq. (7.1) to the following equivalent and distributed formulation:

$$ \text{argmin}_{\Delta_{tot}} F_1(\Delta_{tot}) + F_2(\Delta_{tot}) + G_1(\Delta_{tot}) + G_2(\Delta_{tot}) \tag{3.9} $$

subject to: $\Delta_{tot} = \Delta_{tot1} + \Delta_{tot2} + \Delta_{tot3} + \Delta_{tot4} = \Delta_{tot}$

Where $F_1(\cdot) = ||W_E \odot (L_c(\cdot))||_1$, $G_1(\cdot) = I ||(1 \odot W_E) \odot (L_{tot}(\cdot) - B^*(\hat{\Sigma}_d, \hat{\Sigma}_c))||_\infty \leq \lambda_n$, $F_2(\cdot) = \epsilon ||L_g(\cdot)||_{g'_V,2}$ and $G_2(\cdot) = I ||L_{tot}(\cdot) - B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)||_{g'_V,2} \leq \epsilon \lambda_n$.

Here $I_C(\cdot)$ represents the indicator function of a convex set $C$ denoting that $I_C(x) = 0$ when $x \in C$ and otherwise $I_C(x) = \infty$.

Algorithm 1 summarizes the Parallel Proximal algorithm (Combettes & Pesquet, 2011; Yang et al., 2014b) we propose for optimizing Eq. (3.9). Section 7.2 further proves its computational cost as $O(p^3)$. In Algorithm 1, we used the simplified notation for denoting proxy backward mapping.
3.5 Analysis of Error Bounds

B*(̂Sd, ̂Sc) := [T_u(̂Sd)]⁻¹ − [T_v(̂Sc)]⁻¹. Detailed solution for each proximal operator is summarized in Section 7.

There exist many other variations of KDiffNet. For instance, we can estimate the target ∆ through a closed form solution if we have only one kind of additional knowledge. Section 7.3 provides closed form solutions for edge-only or node-group-only cases. For the edge-only case, if we set W_E as a matrix with all 1, Eq. (8.1) becomes the DIFFEE formulation. We also generalize KDiffNet to multiple kinds of group knowledge plus multiple sources of weight knowledge in Section 8.

Algorithm 1 Parallel Proximal Algorithm for KDiffNet

input Two data matrices X_c and X_d, The weight matrix W_E and G_V.

Hyperparameters: α, ε, v, λ_n and γ. Learning rate: 0 < ρ < 2. Max iteration number iter.

output Δ

1: Compute B*(̂Sd, ̂Sc) from X_d and X_c
2: Initialize A_c = [I_p × p 0_p × p], A_g = [0_p × p I_p × p], A_tot = [I_p × p I_p × p],
3: Initialize Δ_{tot1}, Δ_{tot2}, Δ_{tot3}, Δ_{tot4} and Δ tot = Δ_{tot1} + Δ_{tot2} + Δ_{tot3} + Δ_{tot4} for i = 0 to iter do
5: p_i = \prox_{4γ_1p} Δ_i^i ; p_i = \prox_{4γ_2p} Δ_{tot1}_i ; p_i = \prox_{4γ_2p} Δ_{tot2}_i ; p_i = \prox_{4γ_2p} Δ_{tot3}_i ; p_i = \prox_{4γ_2p} Δ_{tot4}_i
6: p_i = \frac{1}{4}( \sum_{j=1}^{4} p_j^i )
7: for j = 1, 2, 3, 4 do
8: Δ_{tot1}_j = Δ_{tot1} + ρ(2p_i^j − Δ_{tot}^i − p_i^j)
9: for end
10: Δ_{tot1} = Δ_{tot1} + ρ(p_i^j − Δ_{tot}^i)
11: for end
12: ̂Δ = A_tot Δ iter

output ̂Δ

3.5 Analysis of Error Bounds

Borrowing analyses from (Yang et al., 2014c) and (Negahban et al., 2009), this section shows that KDiffNet achieves a sharp convergence rate, the same convergence rate O(√(log p)/n) as DIFFEE.

We reiterate the following conditions from (Yang et al., 2014c), regarding the decomposability of regularization function R with respect to the subspace pair (M, M⁺):

(C1) R(u + v) ≤ R(u) + R(v), ∀u ∈ M, ∀v ∈ M⁺.

(C2) \exists a subspace pair (M, M⁺) such that the true parameter satisfies proj M⁺(θ*) = 0

We further introduce the following condition on ‘true’ ∆:

(EV-Sparsity): The ‘true’ ∆* can be decomposed into two clear structures—{Δ_c* and Δ_g*}. Δ_c* is exactly sparse with s_c non-zero entries indexed by a support set S_c. Δ_g* is exactly sparse with √s_G non-zero groups (with at least one non-zero entry) indexed by a support set S_G, S_c ∩ S_G = ∅. All other elements equal to 0 (in (S_c ∪ S_G)c).

Section 11 proves that kEV Norm satisfies conditions (C1) and (C2). This leads us to the following theorem (see proof Section 11):

Theorem 3.1. Assuming ∆* satisfies the condition (EV-Sparsity) and λ_n ≥ R*(Δ* − Δ∗), then the optimal point ∆ has the following error bounds:

||̂Δ − Δ∗||F ≤ 4 max(√s_c, ε√s_G)λ_n (3.10)

Then to prove the convergence rate of KDiffNet, we state the following conditions on the true canonical parameter defining the class of differential GGMs: ∆* = Ω_c* − Ω_g*.

(C-MinInf−Σ): The true Ω_c* and Ω_g* of Eq. (2.1) have bounded induced operator norm i.e., \|||Ω_c*|||_∞ := sup \|||w_∗|||_∞ / |||w|||_∞ \leq W_{E_{min}} κ_1 and \|||Ω_g*|||_∞ := sup \|||w_∗|||_∞ / |||w|||_∞ \leq W_{E_{min}} κ_1. Here, intuitively, W_{E_{min}} corresponds to the largest ground truth weight index associated with non zero entries in Ω_c*. For set S_{nz} = {(i, j)|Ω_c_ij = 0}, W_{P_{S_{nz}}} > W_{E_{min}}.

(C-Sparse−Σ): The two true covariance matrices Σ_c* and Σ_g* are “approximately sparse” (following (Bickel & Levina, 2008)). For some constant 0 ≤ q < 1 and c_0(p), max_i \sum_j |||Σ_c*|||_q_j ≤ c_0(p) and max_i \sum_j |||Σ_g*|||_q_j ≤ c_0(p). We additionally require \inf \|||w_∗|||_∞ / |||w|||_∞ \geq κ_2 and \inf \|||w_∗|||_∞ / |||w|||_∞ \geq κ_2.

Using the above Theorem 11.3 and conditions, we have the following corollary about the convergence rate of KDiffNet (see its proof in Section 11.2).

Corollary 3.2. In the high-dimensional setting, i.e., p > max(n_c, n_d), let \nu := a √(log p)/min(n_c, n_d). Then for λ_n := \Gamma_{c_1} \nu \sqrt{\log p}/min(n_c, n_d), max(|C_1 - C_2| log(p)) for a probability of at least 1 − 2C_1 \exp(-C_2 p log(p)), the estimated optimal solution ̂Δ has the following error bound:

||̂Δ − Δ∗||F ≤ \Gamma_a max(√s_c, ε√s_G) \sqrt{log p}/min(n_c, n_d) (3.11)

Here \Gamma = 32κ_1 \max(W_{E_{min}} W_{E_{min}}), where a, c, C_1, C_2, κ_1 and κ_2 are constants. a depends on max_i Σ_c ii and c
depends on $p$, $\tau$, $\max_i \Sigma_{ii}^d$, $\tau$ is a constant from Lemma 1 of (Ravikumar et al., 2011).

We can prove that when under the same conditions above, DIFEE will achieve the same asymptotic convergence rate as Eq. (3.11). However its rate includes a different constant $\Gamma = 32k_1 \max(W_{\text{fin}}^e, W_{\text{fin}}^d)$. When $W_{\text{fin}} > 1$, KDiffNet gets a better constant in converging than DIFEE.

3.6. Connecting to Relevant Studies

To the authors’ best knowledge, only two loosely-related studies exist in the literature to incorporate edge-level knowledge for other types of graph models estimation. (1) One study with the name NAK (Bu & Lederer, 2017) (following ideas from (Shimamura et al., 2007)) proposed to integrate Additional Knowledge into the estimation of single-task graphical model via a weighted Neighbourhood selection formulation. (2) Another study with the name JEEK (Wang et al., 2018a) (following (Singh et al., 2017)) considered edge-level evidence via a weighted objective formulation to estimate multiple dependency graphs from heterogeneous samples. Both studies only added edge-level extra knowledge in structural learning and neither of the approaches was designed for the direct structure estimation of differential GGM. Besides, JEEK uses a multi-task formulation. (*

| Method          | Data-EG(F1-Score) | Data-G(F1-Score) |
|-----------------|------------------|------------------|
| KDiffNet-EG     | 0.926±0.001      | 0.934±0.002      |
| KDiffNet-G      | 0.656±0.000      | 0.576±0.000      |
| JEEK            | 0.582±0.001      | 0.582±0.001      |
| NAK             | 0.198±0.011      | 0.203±0.005      |
| SDRE            | 0.568±0.006      | 0.574±0.011      |
| DIFFEE          | 0.582±0.000      | 0.570±0.000      |
| JGLFused        | 0.489±0.001      | 0.504±0.001      |
| # Datasets      | 14               | 14               |

Table 1. Mean Performance(F1-Score) and Computation Time(seconds) with standard deviation for 10 random seeds given in parentheses of KDiffNet-EG, KDiffNet-E, KDiffNet-G and baselines for simulated data. We evaluate over 126 datasets: 14 variations in each of the three spatial matrices $W_E$: $p = 116(W1)$, $p = 246(W2)$, and $p = 160(W3)$ for the three data settings: Data-EG, Data-E and Data-G. * indicates that the method is not applicable for a data setting.

4. Experiments

In this section, empirically, we show that KDiffNet is flexible in incorporating different kinds of available evidence, leading to improved differential network estimation and without additional computational cost.

Data: We evaluate KDiffNet and baselines on three sets of datasets: (1) A total of 126 different synthetic datasets representing various combinations of additional knowledge (Section 4.1); (2) One real world fMRI dataset (ABIDE) for functional brain connectivity estimation (Section 4.2); and (3) One real biological dataset for differential epigenetic network estimation. (Section 4.3).

Baselines: We compare KDiffNet to (1) JEEK(Wang et al., 2018a), (2) NAK(Bu & Lederer, 2017), (3) SDRE (Liu et al., 2017), (4) DIFEE (Wang et al., 2018b) and (5) JGLFUSED(Danaher et al., 2013). We also check two variations of KDiffNet: KDiffNet-E using only edge knowledge and KDiffNet-G using only group knowledge. Both variations (KDiffNet-E and KDiffNet-G) can be solved via a closed form solution (Section 7.3). More details of setup and metric definitions are in Section 13.1.

Hyperparameters: We tune the key hyper-parameters:

- $v$: To compute the proxy backward mapping, we vary $v$ in $\{0.001, 0.01, 0.1, 1, 100\}$ to make $T_v(\Sigma_e)$ and $T_v(\Sigma_d)$ invertible.
- $\lambda_n$: According to our convergence rate analysis in Section 3.5, $\lambda_n \geq C \sqrt{\frac{\log p}{\min(n_e,n_d)}}$, we choose $\lambda_n$ from a range of $\{0.1 \times \sqrt{\frac{\log p}{\min(n_e,n_d)}} \times |i| \in \{1, 2, 3, \ldots, 100\}\}$ using cross-validation. For KDiffNet-G, we tune over $\lambda_n$ from a range of $\{0.1 \times \sqrt{\frac{\log p}{\min(n_e,n_d)}} \times |i| \in \{1, 2, 3, \ldots, 100\}\}$.
- $\epsilon$: For KDiffNet-EG, we tune $\epsilon$ in $\{0.0001, 0.01, 1, 100\}$.

4.1. Experiments on 126 different Simulated Datasets

First, we check the effectiveness of KDiffNet through a large set of simulation datasets. Our simulation settings mimic three possible types of additional knowledge in the real-world: (i) with both edge and known node group knowledge (Data-EG: 42 datasets), (ii) with only edge-level evidence (Data-E: 42 datasets) and (iii) with only known node groups (Data-G: 42 datasets). Due to space limit, we put details of the simulation settings in Section 14.1 and Figure 4.

Results: Table 4 provides a summary of our results (partial), using the columns to denote results on two sets of simulated data (Data-EG and Data-G). Table 4 compare methods (rows) via the mean F1-score and the computational time cost. Each column shows results averaged across 14 datasets with varying data properties ($p$, $n_e$, $n_d$, etc.) To get consistent results, we also repeat each experiment for 10 random seeds. Results on Data-E datasets are in Section 12.

Three main observations: (1) KDiffNet outperforms those

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3Different from JEEK, our method directly estimate differential parameters. Direct strategy has been proved more sample-efficient than the multi-tasking kind (Fazayeli & Banerjee, 2016).

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7We use the same range to tune $\lambda_1$ for SDRE and $\lambda_2$ for JGLFUSED. We use $\lambda_1 = 0.0001$ (a small value) for JGLFUSED to ensure only the differential network is sparse. Tuning NAK is done by the package itself.
baselines that do not consider knowledge. KDiffNet-EG achieves the highest F1-score across all the 42 Data-EG datasets. SDRE and DIFFEE perform worse indicating that integrating additional knowledge improves differential estimation. MLE-based JGLFused performs the worst in all cases. (2) KDiffNet outperforms those baselines that do consider knowledge, especially when group knowledge exists. While JEEK and NAK also consider the extra edge information, they cannot integrate group evidence. This results in lower F1-Score on Data-EG cases (for instance, in the column Data-EG:W2, 0.582 and 0.198, worse than KDiffNet-EG 0.926). As an ablation analysis, KDiffNet-EG also outperforms KDiffNet-E and KDiffNet-G across all the three Data-EG columns. (3) KDiffNet scales to large \( p \). Figure 2a compares methods’ average time cost per \( \lambda_n \) for a large \( p = 2000 \). KDiffNet-EG is faster than JEEK, JGLFUSED and SDRE. KDiffNet-E and KDiffNet-G are faster than KDiffNet-EG owing to closed form solutions.\(^6\)

4.2 Results on One Real-World fMRI Data

We evaluate KDiffNet on a publicly available resting-state fMRI dataset: ABIDE(Di Martino et al., 2014) (more in Section 12.1). This data aims to understand how functional dependency among brain regions vary between normal and autism conditions (Van Essen et al., 2013). ABIDE includes two groups of human subjects: autism and control. We utilize three types of additional knowledge: \( W_E \) built from the spatial distance between brain regions of interest (ROI) from (Dosenbach et al., 2010) and two types of groupings from Dosenbach Atlas(Dosenbach et al., 2010): one with 40 unique groups about macroscopic brain structures (G1) and the other with 6 higher level groups (G2) indicating functionally related regions.

![Figure 2a](attachment://figure2a.png)

(a) Computation Time (log milliseconds) per \( \lambda_n \) for large \( p = 2000 \): KDiffNet-EG has reasonable time cost with respect to baseline methods. KDiffNet-E and KDiffNet-G are fast due to closed form.

![Figure 2b](attachment://figure2b.png)

(b) ABIDE Dataset: KDiffNet-EG achieves highest Accuracy (averaged over 3 random seeds) without sacrificing computation speed (points towards top right are better).

![Figure 2c](attachment://figure2c.png)

(c) Epigenomic Dataset: KDiffNet-E achieves highest Accuracy (averaged over 3 splits) in comparison to the best performing baseline. (points above the diagonal \( x = y \) line mean KDiffNet-E better).

On ABIDE, we don’t have the ground truth of \( \Delta \). Therefore we evaluate the learned differential structure via a downstream classification task. We randomly partition the data into a train, validation and test set. We learn a differential graph using the train set. Then, its non-zero edges are used as generating pairwise interaction features. These features are fed to a logistic regressor with ridge penalty, which is trained via cross-validation on the validate set. Finally, we report the accuracy on the test set. We repeat the experiment for 3 random seeds and report the average test accuracy. Figure 2b compares KDiffNet-EG, KDiffNet-E, KDiffNet-G and baselines on ABIDE, using the \( y \) axis for classification test accuracy (the higher the better) and the \( x \) axis for the computation speed per \( \lambda_n \) (negative seconds, the more right the better). KDiffNet-EG1, incorporating both edge \( W_E \) and (G1) group knowledge, achieves the highest accuracy of 60.5% for distinguishing the autism versus the control subjects without sacrificing computation speed.

4.3 Results on One Epigenetic Data

Then we evaluate KDiffNet and baselines for estimating the differential epigenetic network across low and high gene expression states. Studies have shown that epigenetic factors (like histone modifications (HMs)) interact to regulate gene expression (Suganuma & Workman, 2008). Understanding how epigenetic network vary can help in developing ‘epigenetic drugs’ for diseases like cancer. Here the prior knowledge is that signals spatially closer to each other along the genome coordinate are more likely to interact in the gene regulation process.

Again, we don’t have ground truth and therefore use a downstream classification task to check the performance of differential estimation. Figure 2c reports the average test set performance across the three cell types we tried (i.e. three different datasets). \( y \)-axis shows the test accuracy by KDiffNet and \( x \)-axis shows the best performing baseline. KDiffNet outperforms both DIFFEE and JEEK. JEEK can incorporate extra weight evidence but estimates

\(^6\) Section 14.1 presents detailed results about F1-Score and time cost across 126 different data cases. Besides, we also analyze KDiffNet’s performance when varying hyper-parameter \( \lambda_n \) via the ROC curves. KDiffNet achieves the highest Area under Curve (AUC) in comparison to other baselines.
two networks separately. Figure 3 visualizes the epigenetic networks learnt by KDiffNet and DIFFEE. KDiffNet makes use of the spatial prior about genome, therefore its estimated network appears more consistent with biological validations. For instance we found the estimated interactions between promoter mark and distal promoter mark were reported by (Dong et al., 2012) before. 7

5. Conclusions

We believe the flexibility and scalability provided by KDiffNet can make differential structure learning of GGMs beneficial in many real-world tasks. We plan to generalize KDiffNet from Gaussian to semi-parametric distributions or to Ising Models.

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We consider five core HM marks across three major cell types from the REMC database (Kundaje et al., 2015). Each HM contributes 25 bins of features around a gene. Section 12.2 includes more details of HMs, cell types, priors and results.
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6. More about Relevant Studies

NAK (Bu & Lederer, 2017): For the single task sGGM, one recent study (Bu & Lederer, 2017) (following ideas from (Shimamura et al., 2007)) proposed to use a weighted Neighborhood selection formulation to integrate edge-level Additional Knowledge (NAK) as: $\beta^j = \text{argmin}_{\beta, \beta^j} \frac{1}{2} ||X^j - X\beta||^2 + ||\mathbf{r}_j \circ \beta||_1$. Here $\beta^j$ is the $j$-th column of a single sGGM $\hat{\Omega}$. Specifically, $\beta^j_i = 0$ if and only if $\Omega_{k,j} = 0$. $\mathbf{r}_j$ represents a weight vector designed using available extra knowledge for estimating a brain connectivity network from samples $X$ drawn from a single condition. The NAK formulation can be solved by a classic Lasso solver like glmnet.

JEEK (Wang et al., 2018a): Two related studies, JEEK (Wang et al., 2018a) and W-SIMULE (Singh et al., 2017) incorporate edge-level extra knowledge in the joint discovery of $K$ heterogeneous graphs. In both these studies, each sGGM corresponding to a condition is assumed to be composed of a task specific sGGM component $\Omega^{(t)}_i$ and a shared component $\Omega_S$ across all conditions, i.e., $\Omega^{(t)}_i = \Omega^{(t)}_i + \Omega_S$. The minimization objective of W-SIMULE is as follows: objective:

$$\text{argmin}_{\Omega^{(t)}_i, \Omega_S} \sum_i ||W \circ \Omega^{(t)}_i||_1 + \epsilon K ||W \circ \Omega_S||_1$$

subject to: $||\Sigma^{(t)}_i(\Omega^{(t)}_i + \Omega_S) - I||_\infty \leq \lambda_n, \ i = 1, \ldots, K$.

W-SIMULE is very slow when $p > 200$ due to the expensive computation cost $O(K^4 p^5)$. In comparison, JEEK is an EE-based optimization formulation:

$$\text{argmin}_{\Omega^{(t)}_i, \Omega_S} ||W^{(t)}_i \circ \Omega^{(t)}_i||_1 + ||W^{(t)}_S \circ \Omega_S||_1$$

subject to: $||\frac{1}{W^{(t)}_i} \circ (\Omega^{(t)}_i - B^* (\hat{\phi}))||_\infty \leq \lambda_n$

$$||\frac{1}{W^{(t)}_S} \circ (\Omega^{(t)}_S - B^* (\hat{\phi}))||_\infty \leq \lambda_n$$

$\Omega^{(t)} = \Omega^{(t)}_i + \Omega^{(t)}_S$

Here, $\Omega^{(t)}_i = (\Omega^{(t)}_{i1}, \Omega^{(t)}_{i2}, \ldots, \Omega^{(t)}_{iK})$ and $\Omega^{(t)}_S = (\Omega_S, \Omega_S, \ldots, \Omega_S)$. The edge knowledge of the task-specific graph is represented as weight matrix $\{W^{(t)}_i\}$ and $W_S$ for the shared network. JEEK differs from W-SIMULE in its constraint formulation, that in turn makes its optimization much faster and scalable than W-SIMULE. In our experiments, we use JEEK as our baseline.

Drawbacks: However, none of these studies are flexible to incorporate other types of additional knowledge like node groups or cases where overlapping group and edge knowledge are available for the same target parameter. Further, these studies are limited by the assumption of sparse single condition graphs. Estimating a sparse difference graph directly is more flexible as it does not rely on this assumption.

7. Optimization of KDiffNet and Its Variants

7.1. Optimization via Proximal Solution

In this section, we present the detailed optimization procedure for KDiffNet. We assume $\Delta_{tot} = [\Delta_e; \Delta_g]$, where $\Delta_e$ denotes row wise concatenation. Consider operator $L_d(\Delta_{tot}) = \Delta_e$ and $L_g(\Delta_{tot}) = \Delta_g$, $L_{tot}(\Delta_{tot}) = \Delta_e + \Delta_g$.

$$\text{argmin}_{\Delta} ||W_E \circ (L_e(\Delta_{tot}))||_1 + \epsilon ||L_g(\Delta_{tot})||_{\psi^2}$$

s.t.:

$$||1 \otimes W_E \circ (L_{tot}(\Delta_{tot}) - \left( [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_e)]^{-1} \right))||_\infty \leq \lambda_n$$

$$||L_{tot}(\Delta_{tot}) - \left( [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_e)]^{-1} \right)||_{\psi^2} \leq \epsilon \lambda_n$$

(7.1)

This can be rewritten as:

$$\text{argmin}_{\Delta} F_1(\Delta_{tot1}) + F_2(\Delta_{tot2}) + G_1(\Delta_{tot3}) + G_2(\Delta_{tot4})$$

$$\Delta_{tot} = \Delta_{tot1} = \Delta_{tot2} = \Delta_{tot3} = \Delta_{tot4}$$

(7.2)

Where:

$$F_1(\cdot) = ||W_E \circ (L_e(\cdot))||_1$$

$$G_1(\cdot) = \mathcal{I}_{||1 \otimes W_E \circ (L_{tot}(\cdot) - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_e)]^{-1})||_\infty \leq \lambda_n}$$

$$F_2(\cdot) = \epsilon ||L_g(\cdot)||_{\psi^2}$$

$$G_2(\cdot) = i_{||L_{tot}(\cdot) - ([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_e)]^{-1})||_{\psi^2} \leq \epsilon \lambda_n}$$

(7.3)

Here, $L_e, L_g$ and $L_{tot}$ can be written as Affine Mappings. By Lemma in (),

$$L_e = A_e \Delta_{tot}$$

$$A_e = [I_{p \times p} \ 0_{p \times p}]$$

$$L_g = A_g \Delta_{tot}$$

$$A_g = [0_{p \times p} \ I_{p \times p}]$$

$$L_{tot} = A_{tot} \Delta_{tot}$$

$$A_{tot} = [I_{p \times p} \ I_{p \times p}]$$

(7.4)

if $AA^T = \beta I$, and $h(x) = g(Ax)$,

$$\text{prox}_h(x) = x - \beta A^T(Ax - \text{prox}_{\beta^{-1} g}(Ax))$$

(7.5)

$\beta_g = 1$, $\beta_e = 1$ and $\beta_{tot} = 2$.

Solving for each proximal operator:
7.2 Computational Complexity

A. \( F_1(\Delta_{tot}) = \|W_E \circ (L_e(\Delta_{tot}))\|_1 \)
\( L_e(\Delta_{tot}) = A_e \Delta_{tot} = \Delta_e \).

\[
\text{prox}_{\gamma f_1}(y) = y - A_e^T (x - \text{prox}_{\gamma f}(x))
\]
\( x = A_e y \) \hspace{1cm} (7.6)

Here, \( x_{j,k} = \Delta_{e,j,k} \).

\[
\text{prox}_{\gamma f}(x) = \text{prox}_{\gamma ||W_v||}(x)
\]
\[
= \begin{cases} 
  x_{j,k} - \gamma w_{j,k}, & x_{j,k} > \gamma w_{j,k} \\
  0, & |x_{j,k}^{(i)}| \leq \gamma w_{j,k} \\
  x_{j,k} + \gamma w_{j,k}, & x_{j,k} < -\gamma w_{j,k}
\end{cases}
\]
\( \gamma = \gamma_{f_1} \) \hspace{1cm} (7.7)

Here \( j,k = 1, \ldots, p \). This is an entry-wise operator (i.e., the calculation of each entry is only related to itself). This can be written in closed form:

\[
\text{prox}_{\gamma f_1}(x) = \max((x_{j,k} - \gamma w_{j,k}, 0)) + \min(0, (x_{j,k} + \gamma w_{j,k}))
\]

We replace this in Eq. (7.6).

B. \( F_2(\Delta_{tot}) = \epsilon \|L_g(\Delta_{tot})\|_{G, v, 2} \)
Here, \( L_g(\Delta_{tot}) = A_g \Delta_{tot} = \Delta_g \).

\[
x = A_g y
\]
\[
\text{prox}_{\gamma f_2}(y) = y - A_g^T (x - \text{prox}_{\gamma f_2}(x))
\]
\( x = A_g y \) \hspace{1cm} (7.9)

Here, \( x_{j,k} = \Delta_{g,j,k} \).

\[
\text{prox}_{\gamma f_2}(x_g) = \text{prox}_{\gamma ||\|\cdot\|_{G, 2}}(x_g)
\]
\[
= \begin{cases} 
  x_g - \epsilon \gamma \frac{x_g}{\|x_g\|_2}, & \|x_g\|_2 > \epsilon \gamma \\
  0, & \|x_g\|_2 \leq \epsilon \gamma
\end{cases}
\]
\( \epsilon = \epsilon_{f_2} \) \hspace{1cm} (7.10)

Here \( g \in G_v \). This is a group entry-wise operator (computing a group of entries is not related to other groups). In closed form:

\[
\text{prox}_{\gamma f_2}(x_g) = \text{max}(1 - \frac{\epsilon \gamma}{\|x_g\|_2}, 0)
\]
\( \gamma = \gamma_{f_2} \) \hspace{1cm} (7.11)

We replace this Eq. (7.9).

C. \( G_1: \ G_1(\Delta_{tot}) = \mathcal{I}_{\{(1 \circ W_E) \circ (L_{tot}(\Delta_{tot}) - (T_v(\delta))^{-1} - (T_v(\delta_v))^{-1})\}} \|_\infty \leq \lambda_n \)
Here, \( L_{tot} = A_{tot} \Delta_{tot} \) and \( A_{tot} = [I_p \times p] \).

\[
x = A_{tot} \ y
\]
\[
\text{prox}_{\gamma G_1}(y) = y - 2A_{tot}^T (x - \text{prox}_{2-1, \gamma_{g_1}}(x))
\]
\( x = A_{tot} \ y \) \hspace{1cm} (7.12)

\[
\text{prox}_{\gamma_{g_1}}(x) = \text{proj}_{\{1 \circ (W_E) \circ (x - a)\}} \|_\infty \leq \lambda_n
\]
\[
= \begin{cases} 
  x_{j,k}, & x_{j,k} - a_{j,k} \leq w_{j,k} \lambda_n \\
  a_{j,k} + w_{j,k} \lambda_n, & x_{j,k} > a_{j,k} + w_{j,k} \lambda_n \\
  a_{j,k} - w_{j,k} \lambda_n, & x_{j,k} < a_{j,k} - w_{j,k} \lambda_n
\end{cases}
\]
\( \gamma = \gamma_{g_1} \) \hspace{1cm} (7.13)

In closed form:

\[
\text{prox}_{\gamma_{g_1}}(x) = \text{proj}_{\|x - a\|_\infty \leq \lambda_n}
\]
\[
= \min(\max(x_{j,k} - a_{j,k}, -w_{j,k} \lambda_n), w_{j,k} \lambda_n) + a_{j,k}
\]
\( \gamma = \gamma_{g_1} \) \hspace{1cm} (7.14)

We replace this in Eq. (7.12).

D. \( G_2(\Delta_{tot}) = \mathcal{I}_{\{(1 \circ L_{tot}(\Delta_{tot}) - B)^{\|\|_{G, 2} \leq \epsilon_{\lambda_n}}\}} \)
Here, \( L_{tot} = [I_p \times p] \).

\[
x = A_{tot} \ y
\]
\[
\text{prox}_{\gamma G_2}(y) = y - 2A_{tot}^T (x - \text{prox}_{2-1, \gamma_{g_2}}(x))
\]
\( x = A_{tot} \ y \) \hspace{1cm} (7.15)

\[
\text{prox}_{\gamma g_2}(x_g) = \text{proj}_{\|x - a\|_{G, 2} \leq \lambda_n}
\]
\[
= \begin{cases} 
  x_g, & \|x_g - a\|_2 \leq \epsilon \lambda_n \\
  \epsilon \lambda_n \frac{x_g - a}{\|x_g - a\|_2} + a, & \|x_g - a\|_2 > \epsilon \lambda_n
\end{cases}
\]
\( \gamma = \gamma_{g_2} \) \hspace{1cm} (7.16)

This operator is group entry-wise. In closed form:

\[
\text{prox}_{\gamma g_2}(x) = \text{proj}_{\|x - a\|_{G, 2} \leq \lambda_n}
\]
\[
= \min(\frac{\epsilon \lambda_n}{\|x_g - a\|_2}, 1)(x_g - a) + a
\]
\( \gamma = \gamma_{g_2} \) \hspace{1cm} (7.17)

We replace this in Eq. (7.15).

7.2. Computational Complexity

We optimize KDIfNet through a proximal algorithm, while KDIfNet-E and KDIfNet-G through closed-form solutions. The resulting computational cost for KDIfNet is \( O(p^3) \), broken down into the following steps:

- **Estimating two covariance matrices**: The computational complexity is \( O(\text{max}(n_c, n_d) p^2) \).
- **Backward Mapping**: The element-wise soft-thresholding operation \( T_v(\cdot) \) on the estimated covariance matrices, that costs \( O(p^2) \). This is followed by matrix inversions \( T_v(\cdot)^{-1} \) to get the proxy backward mapping, that cost \( O(p^3) \).
7.3 Closed-form solutions for Only Edge(KDiffNet-E) Or Only Node Group Knowledge (KDiffNet-G)

In cases, where we do not have superposition structures in the differential graph estimation, we can estimate the target $\Delta$ through a closed form solution, making the method scalable to larger $p$. In detail:

**KDiffNet-E Only Edge-level Knowledge $W_E$:** If additional knowledge is only available in the form of edge weights, the Eq. (7.1) reduces to:

$$\argmin_{\Delta} \|W_E \circ \Delta\|_1$$

subject to:

$$\|(1 \otimes W_E) \circ (\Delta - \left( [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1} \right))\|_{\infty} \leq \lambda_n$$

(7.18)

This has a closed form solution:

$$\hat{\Delta} = S_{\lambda_n \circ W_E} (B^*(\hat{\Sigma}_d, \hat{\Sigma}_c))$$

$$[S_{\lambda_n \circ W_{E,i}}(A)]_{ij} = \text{sign}(A_{ij}) \max(|A_{ij} - \lambda_n W_{E,i,j}, 0|)$$

(7.19)

**KDiffNet-G Only Node Groups Knowledge $G_V$:** If additional knowledge is only available in the form of groups of vertices $G_V$, the Eq. (7.1) reduces to:

$$\argmin_{\Delta} \|\Delta\|_{G_V,2}$$

subject to:

$$\|\Delta - B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)\|_{G_V,2} \leq \lambda_n$$

(7.20)

Here, we assume nodes not in any group as individual groups with cardinality= 1. The closed form solution is given by:

$$\hat{\Delta} = (S_{G_V \circ \lambda_n} (B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)))$$

(7.21)

Where $[S_{G_V \circ \lambda_n}(u)]_g = \max(|u_g|_2 - \lambda_n, 0) \frac{u_g}{||u_g||_2}$ and max is the element-wise max function.

| Table 2. The four proximal operators |
|-------------------------------------|
| $\text{prox}_{f_1}(x)_{j,k}$       | max((x_{j,k} - \gamma w_{j,k}), 0) + min(0, (x_{j,k} + \gamma w_{j,k})) |
| $\text{prox}_{f_2}(x)_{j,k}$       | x_g max((1 - \frac{\gamma}{||x_g||_2}), 0) |
| $\text{prox}_{f_3}(x)_{j,k}$       | min(max(x_{j,k} - a_{j,k} - w_{j,k} \lambda_n), w_{j,k} \lambda_n) + a_{j,k} |
| $\text{prox}_{f_4}(x)_{g}$         | min(\frac{\epsilon}{||x_g - a_g||_2}, 1)(x_g - a_g) + a_g |

Algorithm 2 shows the detailed steps of the KDiffNet estimator. Being non-iterative, the closed form solution helps KDiffNet achieve significant computational advantages.

**Algorithm 2 KDiffNet-E and KDiffNet-G**

**Input:** Two data matrices $X_e$ and $X_d$. The weight matrix $W_E$ or $G_V$.

**Hyper-parameter:** $\lambda_n$ and $\nu$

**Output:** $\Delta$

1: Compute $[T_v(\hat{\Sigma}_d)]^{-1}$ and $[T_v(\hat{\Sigma}_c)]^{-1}$ from $\hat{\Sigma}_c$ and $\hat{\Sigma}_d$.
2: Compute $B^*(\hat{\Sigma}_d, \hat{\Sigma}_c)$.
3: Compute $\hat{\Delta}$ from Eq. (7.19)($W_E$ only) or Eq. (7.21)($G_V$ only)

**8. Generalizing KDiffNet to multiple $W_E$ and multiple groups $G_V$**

We generalize KDiffNet to multiple weights and multiple groups. We consider the case of two weight matrices $W_{E1}$ and $W_{E2}$, as well as two groups $G_{V1}$ and $G_{V2}$. In detail, we optimize the following objective:

$$\argmin_{\Delta} \|W_{E1} \circ \Delta_{e1}\|_1 + \epsilon_e \|W_{E2} \circ \Delta_{e2}\|_1 + \epsilon_g \|\Delta_{g1}\|_{G_{V1},2} + \epsilon_g \|\Delta_{g2}\|_{G_{V2},2}$$

subject to:

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

$$\|\Delta - [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1}\|_{\infty} \leq \lambda_n$$

(8.1)

To simplify notations, we add a new notation $\Delta_{tot} := [\Delta_{e1}; \Delta_{e2}; \Delta_{g1}; \Delta_{g2}]$, where $\oplus$ denotes the row wise concatenation. We also add three operator notations including $L_{e1}(\Delta_{tot}) = \Delta_e, L_{e2}(\Delta_{tot}) = \Delta_e, L_{g1}(\Delta_{tot}) = \Delta_g, L_{g2}(\Delta_{tot}) = \Delta_g$ and $L_{tot}(\Delta_{tot}) = \Delta_{e1} + \Delta_{e2} + \Delta_{g1} + \Delta_{g2}$. The added operators are affine mappings: $L_{e1} = A_{e1} \Delta_{tot}, L_{g1} = A_{g1} \Delta_{tot}, L_{e2} = A_{e2} \Delta_{tot}, L_{g2} = A_{g2} \Delta_{tot}$ and $L_{tot} = A_{tot} \Delta_{tot}$.
where $A_{a1} = [I_{p \times p} \ 0_{p \times p} \ 0_{p \times p} \ 0_{p \times p}]$, 
$A_{a2} = [0_{p \times p} \ I_{p \times p} \ 0_{p \times p} \ 0_{p \times p}]$, 
$A_{a1} = [0_{p \times p} \ 0_{p \times p} \ I_{p \times p} \ 0_{p \times p}]$, and $A_{tot} = [I_{p \times p} \ I_{p \times p} \ I_{p \times p} \ I_{p \times p}]$.

Algorithm 3 summarizes the Parallel Proximal algorithm (Combettes & Pesquet, 2011; Yang et al., 2014b) we propose for optimizing Eq. (7.1). More concretely in Algorithm 3, we simplify the notations by denoting $B^*(\hat{\Sigma}_d, \hat{\Sigma}_e) := [T_1(\hat{\Sigma}_d)]^{-1} - [T_1(\hat{\Sigma}_e)]^{-1}$, and reformulate Eq. (7.1) to the following equivalent and distributed formulation:

\[
\begin{align*}
\text{argmin}_{\Delta_{tot}} & \quad F_1(\Delta_{tot}) + F_2(\Delta_{tot}) + G_1(\Delta_{tot}) + G_2(\Delta_{tot}) \\
& + F_3(\Delta_{tot}) + F_4(\Delta_{tot}) + G_3(\Delta_{tot}) + G_4(\Delta_{tot}) \quad \text{subject to:}
\end{align*}
\]

\[\Delta_{tot} = \Delta_{tot} = \Delta_{tot} = \Delta_{tot} \quad \text{(8.2)}\]

Where $F_3(\cdot) = ||W_{E1} \circ (L_{e1}(\cdot)||_1$, $G_1(\cdot) = \mathbb{I}_{\{1 \circ W_{E1} || (L_{e1}(\cdot)-B^*(\hat{\Sigma}_d, \hat{\Sigma}_e)) \leq \lambda_e\}$, $F_2(\cdot) = \epsilon_1 ||L_{e1}(\cdot)||_{\mathbb{G}^{1,2}}$, $G_2(\cdot) = \mathbb{I}_{\{1 \circ L_{e1}(\cdot)-B^*(\hat{\Sigma}_d, \hat{\Sigma}_e) \leq \epsilon_1 \lambda_e\}$, $F_3(\cdot) = \epsilon_2 ||W_{E1} \circ (L_{e2}(\cdot)||_1$, $G_3(\cdot) = \mathbb{I}_{\{1 \circ W_{E1} || (L_{e2}(\cdot)-B^*(\hat{\Sigma}_d, \hat{\Sigma}_e)) \leq \epsilon_2 \lambda_e\}$, $F_4(\cdot) = \epsilon_2 ||L_{e2}(\cdot)||_{\mathbb{G}^{1,2}}$, $G_4(\cdot) = \mathbb{I}_{\{1 \circ L_{e2}(\cdot)-B^*(\hat{\Sigma}_d, \hat{\Sigma}_e) \leq \epsilon_2 \lambda_e\}$.

Here $\mathbb{I}_{\cdot}$ represents the indicator function of a convex set $C$ denoting that $\mathbb{I}_{\cdot}(x) = 0$ when $x \in C$ and otherwise $\mathbb{I}_{\cdot}(x) = \infty$. The detailed solution of each proximal operator is summarized in Table 2 and Section 7.

9. Proofs about kEV Norm and Its Dual Norm

9.1. Proof for kEV Norm is a norm

We reformulate kEV norm as

\[\mathcal{R}(\Delta) = ||W_{E} \circ \Delta||_1 + \epsilon ||\Delta||_{\mathbb{G}^{1,2}} \quad \text{(9.1)}\]

to

\[\mathcal{R}(\Delta) = \mathcal{R}_1(\Delta) + \mathcal{R}_2(\Delta); \mathcal{R}_1(\cdot) = ||W_{E} \circ \cdot||_1; \mathcal{R}_2(\cdot) = \epsilon ||\cdot||_{\mathbb{G}^{1,2}} \quad \text{(9.2)}\]

Theorem 9.1. kEV Norm is a norm if and only if $\mathcal{R}_1(\cdot)$ and $\mathcal{R}_2(\cdot)$ are norms.

Proof. By the following Theorem 9.3, $R_1(\cdot)$ is a norm. If $\epsilon > 0$, $R_2(\cdot)$ is a norm. Sum of two norms is a norm, hence kEV Norm is a norm.

Lemma 9.2. For kEV-norm, $W_{E,j,k} \neq 0$ equals to $W_{E,j,k} > 0$.

Algorithm 3 A Parallel Proximal Algorithm to optimize KDiffNet

**input** Two data matrices $X_c$ and $X_d$. The weight matrix $W_{E1}, W_{E2}$ and $G_{V1,2}, G_{V2}$.

Hyperparameters: $\alpha, \epsilon_{c1, \epsilon_{2}}, \gamma, \lambda_e$ and $\gamma$. Learning rate: $0 < \eta < 2$. Max iteration number $iter$.

**output** $\Delta$

1: Compute $B^*(\hat{\Sigma}_d, \hat{\Sigma}_e)$ from $X_d$ and $X_c$

2: Initialize $A_{a1} = [I_{p \times p} \ 0_{p \times p} \ 0_{p \times p} \ 0_{p \times p}]$, 
$A_{a2} = [0_{p \times p} \ I_{p \times p} \ 0_{p \times p} \ 0_{p \times p}]$, 
$A_{a1} = [0_{p \times p} \ 0_{p \times p} \ I_{p \times p} \ 0_{p \times p}]$, and $A_{tot} = [I_{p \times p} \ I_{p \times p} \ I_{p \times p} \ I_{p \times p}]$.

3: Initialize $\Delta_{tot}, \forall k \in \{1, \ldots, 8\}$

4: Initialize $\Delta_{tot} = \sum_{k=1}^{8} \Delta_{tot}$

5: for $i = 0$ to $iter$ do

6: $p_i^1 = \text{prox}_{S_{\gamma F_1}} \Delta_{tot}^i; p_i^2 = \text{prox}_{S_{\gamma F_2}} \Delta_{tot}^i; p_i^3 = \text{prox}_{S_{\gamma G_1}} \Delta_{tot}^i; p_i^4 = \text{prox}_{S_{\gamma G_2}} \Delta_{tot}^i; p_i^5 = \text{prox}_{S_{\gamma F_1}} \Delta_{tot}^i; p_i^6 = \text{prox}_{S_{\gamma F_2}} \Delta_{tot}^i; p_i^7 = \text{prox}_{S_{\gamma G_1}} \Delta_{tot}^i; p_i^8 = \text{prox}_{S_{\gamma G_2}} \Delta_{tot}^i$

7: $p_i^1 = \frac{1}{8} \sum_{j=1}^{8} p_j^i$

8: for $j = 1, \ldots, 8$ do

9: $\Delta_{tot}^{i+1} = \Delta_{tot}^i + p_i^j - \Delta_{tot}^i - p_i^j$

10: end for

11: $\Delta_{tot}^{i+1} = \Delta_{tot}^{i+1} + \rho(p_i^j - \Delta_{tot}^{i+1})$

12: end for

13: $\Delta = \Delta_{tot} \Delta_{iter}$

**output** $\Delta$

Proof. If $W_{E,j,k} < 0$, then $\|W_{E,j,k} \Delta_{j,k}\| = \| - W_{E,j,k} \Delta_{j,k}\|$. Notice that $-W_{E,j,k} > 0$.

Theorem 9.3. $\mathcal{R}_1(\cdot) = ||W_{E} \circ \cdot||_1$ is a norm if and only if $\forall 1 \geq j, k \leq p, W_{E,j,k} \neq 0$.

Proof. To prove the $\mathcal{R}_1(\cdot) = ||W_{E} \circ \cdot||_1$ is a norm, we need to prove that $f(x) = ||W_{E} \circ x||_1$ is a norm function if $W_{i,j} > 0$. 1. $f(ax) = ||aW_{E} \circ x||_1 = |a||W_{E} \circ |x||_1 = |a|f(x)$. 2. $f(x + y) = ||W_{E} \circ (x + y)||_1 = ||W_{E} \circ x + W_{E} \circ y||_1 \leq ||W_{E} \circ x||_1 + ||W_{E} \circ y||_1 = f(x) + f(y)$. 3. $f(x) \geq 0$. 4. $f(x) = 0$, then $\sum_{i,j} W_{E,j,i,x} = 0$. Since $W_{i,j} \neq 0, x_{j,i} = 0$. Therefore, $x = 0$. Based on the above, $f(x)$ is a norm function. Since summation of norm is still a norm function, $\mathcal{R}_1(\cdot)$ is a norm function.

9.2. kEV Norm is a decomposable norm

We show that kEV Norm is a decomposable norm within a certain subspace, with the following structural assumptions of the true parameter $\Delta^*$.

(EV-Sparsity): The ‘true’ parameter of $\Delta^*$ can be...
decomposed into two clear structures—\{Δ∗, and Δ∗\}. 

**Definition 9.4. (EV-subspace)**

\[ M(S_E \cup S_V) = \{ \theta_j = 0 | \forall j \notin S_E \cup S_V \} \quad \text{(9.3)} \]

**Theorem 9.5. kEV Norm is a decomposable norm with respect to \( \mathcal{M} \) and \( \mathcal{M}^\perp \)**

Proof. Assume \( u \in \mathcal{M} \) and \( v \in \mathcal{M}^\perp \), \( R(u + v) = ||W_E \circ (u_c + v_c)||_1 + \epsilon||u_g + v_g||_{\mathbb{G}_V^2} = ||W_E \circ u_c||_1 + ||W_E \circ v_c||_1 + \epsilon||u_g||_{\mathbb{G}_V^2} + ||v_g||_{\mathbb{G}_V^2} = R(u) + R(v). \)

Therefore, kEV norm is a decomposable norm with respect to the subspace pair \((\mathcal{M}, \mathcal{M}^\perp)\). □

**9.3 Proofs of Dual Norms for kEV Norm**

**Theorem 9.6. Dual norm of kEV Norm is** \( R^*(u) = \max(||(1 \otimes W_E) \circ u||_\infty, \frac{1}{\epsilon}||u||_{\mathbb{G}_V^2}) \).

Proof. Suppose \( R(\theta) = \sum_{\alpha \in I} c_\alpha R_\alpha(\theta_\alpha) \), where \( \sum \theta_\alpha = \theta \).

Then the dual norm \( R^*(\cdot) \) can be derived by the following equation.

\[
R^*(u) = \sup_{\theta} \frac{\langle \theta, u \rangle}{R(\theta)} \\
= \sup_{\theta_\alpha} \frac{\sum_{\alpha} \langle u, \theta_\alpha \rangle}{\sum_{\alpha} c_\alpha R_\alpha(\theta_\alpha)} \\
= \sup_{\theta_\alpha} \frac{\sum_{\alpha} \langle u/c_\alpha, \theta_\alpha \rangle}{\sum_{\alpha} R_\alpha(\theta_\alpha)} \\
\leq \sup_{\theta_\alpha} \frac{\sum_{\alpha} R_\alpha^*(u/c_\alpha) R(\theta_\alpha)}{\sum_{\alpha} R_\alpha(\theta_\alpha)} \\
\leq \max_{\alpha \in I} R_\alpha^*(u/c_\alpha). \tag{9.4}
\]

Connecting \( R_1(\cdot) = ||W_E \cdot ||_1 \) and \( R_2(\cdot) = \epsilon||\cdot||_{\mathbb{G}_V} \). By the following Theorem 9.7, \( R_1^*(u) = ||(1 \otimes W_E) \circ u||_\infty \).

From (Negahban et al., 2009), for \( R_2(\theta) = ||\Delta||_{\mathbb{G}_V^2} \), the dual norm is given by

\[
||v||_{\mathbb{G}_V^2} = \max_{t=1,...,s_G} ||v||_{\alpha_t^*} \tag{9.5}
\]

where \( \frac{1}{\alpha_t} + \frac{1}{\alpha_t^*} = 1 \) are dual exponents. where \( s_G \) denotes the number of groups. As special cases of this general duality relation, this leads to a block \((\cdot, 2)\) norm as the dual.

Hence, \( R_2^*(u) = ||u||_{\mathbb{G}_V^2} \). Hence, the dual norm of kEV norm is \( R^*(u) = \max(||(1 \otimes W_E) \circ u||_\infty, \frac{1}{\epsilon}||u||_{\mathbb{G}_V^2}) \). □

**Theorem 9.7. The dual norm of ||W_E \circ ||_1 is:**

\[
R_1^*(\cdot) = ||(1 \otimes W_E) \circ u||_\infty \tag{9.6}
\]

For \( R_1(\cdot) = ||W_E \circ ||_1 \), the dual norm is given by:

\[
\sup_{||W_E \circ ||_1 \leq 1} u^T x \\
\leq \sup_{||W_E \circ ||_1 \leq 1} \sum_{k=1}^p |u_k| |x_k| \\
= \sup_{||W_E \circ ||_1 \leq 1} \frac{\sum_{k=1}^p |u_k||x_k| |w_k|}{|w_k|} \\
\leq \sup_{||W_E \circ ||_1 \leq 1} \left( \sum_{k=1}^p |w_k u_k| \right) \max_{k=1,...,p} \frac{|x_k|}{|w_k|} \\
= \frac{\max_{k=1,...,p} |x_k|}{\sum_{k=1}^p |w_k u_k|} \tag{9.7}
\]

**10. Background of Proxy Backward mapping and Theorems of \( T_v \) Being Invertible**

One key insight of differential GGM is that the density ratio of two Gaussian distributions is naturally an exponential-family distribution (see proofs in Section 10.2). The differential network \( \Delta \) is one entry of the canonical parameter for this distribution. The MLE solution of estimating vanilla (i.e., no sparsity and not high-dimensional) graphical model in an exponential family distribution can be expressed as a backward mapping that computes the target model parameters from certain given moments. When using vanilla MLE to learn the exponential distribution about differential GGM (i.e., estimating canonical parameter), the backward mapping of \( \Delta \) can be easily inferred from the two sample covariance matrices using \((\hat{\Sigma}_d^{-1} - \hat{\Sigma}_c^{-1})\) (Section 10.2). Even though this backward mapping has a simple closed form, it is not well-defined when high-dimensional because \( \hat{\Sigma}_c \) and \( \hat{\Sigma}_d \) are rank-deficient (thus not invertible) when \( p > n \). Using Eq. (3.4) to estimate \( \Delta \), Wang et. al. (Wang et al., 2018b) proposed the DIFFEE estimator for EE-based differential GGM estimation and used only the sparsity assumption on \( \Delta \). This study proposed a proxy backward mapping as \( \hat{\theta}_n = [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_c)]^{-1} \).
Here \( [T_v(A)]_{ij} := \rho_v(A_{ij}) \) and \( \rho_v(\cdot) \) is chosen as a soft-threshold function.

Essentially the MLE solution of estimating vanilla graphical model in an exponential family distribution can be expressed as a backward mapping that computes the target model parameters from certain given moments. For instance, when learning Gaussian GM with vanilla MLE, the backward mapping is \( \hat{\Sigma}^{-1} \) that estimates \( \Omega \) from the sample covariance matrix (moment) \( \hat{\Sigma} \). However, this backward mapping is normally not well-defined in high-dimensional settings. In the case of GGM, when given the sample covariance \( \hat{\Sigma} \), we cannot just compute the vanilla MLE solution as \( \hat{\Sigma}^{-1} \) when high-dimensional since \( \hat{\Sigma} \) is rank-deficient when \( p > n \). Therefore Yang et al. (Yang et al., 2014c) proposed to use carefully constructed proxy backward maps for Eq. (3.4) that are both available in closed-form, and well-defined in high-dimensional settings for exponential GM models. For instance, \( [T_v(\hat{\Sigma})]^{-1} \) is the proxy backward mapping (Yang et al., 2014c) used for GGM.

10.1 Backward mapping for an exponential-family distribution:

The solution of vanilla graphical model MLE can be expressed as a backward mapping (Wainwright & Jordan, 2008) for an exponential family distribution. It estimates the model parameters (canonical parameter \( \theta \)) from certain (sample) moments. We provide detailed explanations about backward mapping of exponential families, backward mapping for Gaussian special case and backward mapping for differential network in GGM in this section.

**Backward mapping:** Essentially the vanilla graphical model MLE can be expressed as a backward mapping that computes the model parameters corresponding to some given moments in an exponential family distribution. For instance, in the case of learning GGM with vanilla MLE, the backward mapping is \( \hat{\Sigma}^{-1} \) that estimates \( \Omega \) from the sample covariance (moment) \( \hat{\Sigma} \).

Suppose a random variable \( X \in \mathbb{R}^p \) follows the exponential family distribution:

\[
P(X; \theta) = h(X) \exp\{< \theta, \phi(X)> - A(\theta)\} \quad (10.1)
\]

Where \( \theta \in \Theta \subset \mathbb{R}^d \) is the canonical parameter to be estimated and \( \Theta \) denotes the parameter space. \( \phi(X) \) denotes the sufficient statistics as a feature mapping function \( \phi : \mathbb{R}^p \rightarrow \mathbb{R}^d \), and \( A(\theta) \) is the log-partition function. We then define mean parameters \( v \) as the expectation of \( \phi(X) \):

\[
v(\theta) := \mathbb{E}[\phi(X)] \quad (10.2)
\]

Mostly, the graphical model inference involves the task of computing moments \( v(\theta) \in M \) given the canonical parameters \( \theta \in (\Theta) \). We denote this computing as **forward mapping**:

\[
A : (\Theta) \rightarrow M \quad (10.3)
\]

The learning/estimation of graphical models involves the task of the reverse computing of the forward mapping, the so-called **backward mapping** (Wainwright & Jordan, 2008). We denote the interior of \( M \) as \( M^0 \). **Backward mapping** is defined as:

\[
A^* : M^0 \rightarrow \Theta \quad (10.4)
\]

which does not need to be unique. For the exponential family distribution,

\[
A^*(v(\theta)) = \sup_{\theta \in \Theta} \langle \theta, v(\theta) \rangle - A(\theta) \quad (10.5)
\]

Where \( A^*(v(\theta)) = \sup_{\theta \in \Theta} \langle \theta, v(\theta) \rangle - A(\theta) \).

10.2 Backward Mapping for Differential GGM

When the random variables \( X_c, X_d \in \mathbb{R}^p \) follows the Gaussian Distribution \( N(\mu_c, \Sigma_c) \) and \( N(\mu_d, \Sigma_c) \), their density ratio (defined by (Liu et al., 2014)) essentially is a distribution in exponential families:

\[
r(x, \Delta) = \frac{p_d(x)}{p_c(x)} = \frac{\sqrt{\det(\Sigma_c)}}{\sqrt{\det(\Sigma_d)}} \exp\left(-\frac{1}{2}(x - \mu_d)^T \Sigma_d^{-1} (x - \mu_d) \right)
\]

\[
= \exp\left(-\frac{1}{2}(x - \mu_c)^T \Sigma_c^{-1} (x - \mu_c) \right) + \frac{1}{2}(x - \mu_c)^T \Sigma_c^{-1} (x - \mu_c) - \frac{1}{2} \log(\det(\Sigma_d)) - \log(\det(\Sigma_c))
\]

\[
= \exp\left(-\frac{1}{2} \Delta x^2 + \mu_\Delta x - A(\mu_\Delta, \Delta) \right) \quad (10.6)
\]

Here \( \Delta = \Sigma_d^{-1} - \Sigma_c^{-1} \) and \( \mu_\Delta = \Sigma_d^{-1} \mu_d - \Sigma_c^{-1} \mu_c \).

The log-partition function

\[
A(\mu_\Delta, \Delta) = \frac{1}{2} \mu_\Delta^T \Sigma_d^{-1} \mu_\Delta - \frac{1}{2} \mu_c^T \Sigma_c^{-1} \mu_c + \frac{1}{2} \log(\det(\Sigma_d)) - \frac{1}{2} \log(\det(\Sigma_c)) \quad (10.7)
\]
The canonical parameter
\[
\theta = \left( \Sigma_d^{-1} \mu_d - \Sigma_c^{-1} \mu_c, -\frac{1}{2} (\Sigma_d^{-1} - \Sigma_c^{-1}) \right)
\]  \hspace{1cm} (10.8)

The sufficient statistics \( \phi([X_c, X_d]) \) and the log-partition function \( A(\theta) \):
\[
\phi([X_c, X_d]) = ([X_c, X_d], [X_c X_c^T, X_d X_d^T])
\]
\[
A(\theta) = \frac{1}{2} \mu_d^T \Sigma_d^{-1} \mu_d - \frac{1}{2} \mu_c^T \Sigma_c^{-1} \mu_c + \frac{1}{2} \log(\det(\Sigma_d)) - \frac{1}{2} \log(\det(\Sigma_c))
\]  \hspace{1cm} (10.9)

And \( h(x) = 1 \).

Now we can estimate this exponential distribution \( \theta \) through vanilla MLE. By plugging Eq. (10.9) into Eq. (10.5), we get the following backward mapping via the conjugate of the log-partition function:
\[
\hat{\theta} = \left( \Sigma_d^{-1} \mu_d - \Sigma_c^{-1} \mu_c, -\frac{1}{2} (\Sigma_d^{-1} - \Sigma_c^{-1}) \right) = A^*(v) = \nabla A^*(v)
\]  \hspace{1cm} (10.10)

The mean parameter vector \( v(\theta) \) includes the moments of the sufficient statistics \( \phi(\cdot) \) under the exponential distribution. It can be easily estimated through \( E([X_c, X_d], [X_c X_c^T, X_d X_d^T]) \).

Therefore the backward mapping of \( \theta \) becomes,
\[
\hat{\theta} = ((E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_d])^{-1}E_\theta[X_d] - (E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_c])^{-1}E_\theta[X_c]),
\]
\[
- \frac{1}{2} ((E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_c])^{-1} - (E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_c])^{-1})
\]
\hspace{1cm} (10.11)

Because the second entry of the canonical parameter \( \theta \) is \( (\Sigma_d^{-1} - \Sigma_c^{-1}) \), we get the backward mapping of \( \Delta \) as
\[
((E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_d])^{-1} - (E_\theta[X_c X_c^T] - E_\theta[X_c]E_\theta[X_c])^{-1}) = \hat{\Delta}
\]  \hspace{1cm} (10.12)

This can be easily inferred from two sample covariance matrices \( \hat{\Sigma}_d \) and \( \hat{\Sigma}_c \) (Att: when under low-dimensional settings).

10.3. Theorems of Proxy Backward Mapping \( T_v \) Being Invertible

Based on (Yang et al., 2014c) for any matrix \( A \), the element-wise operator \( T_v \) is defined as:
\[
[T_v(A)]_{ij} = \begin{cases} A_{ij} + v & \text{if } i = j \\ \text{sign}(A_{ij})(|A_{ij} - v|) & \text{otherwise, } i \neq j \end{cases}
\]

Suppose we apply this operator \( T_v \) to the sample covariance matrix \( \frac{X^T X}{n} \) to obtain \( T_v\left( \frac{X^T X}{n} \right) \). Then, \( T_v\left( \frac{X^T X}{n} \right) \) under high dimensional settings will be invertible with high probability, under the following conditions:

**Condition-1** (\( \Sigma \)-Gaussian ensemble) Each row of the design matrix \( X \in \mathbb{R}^{n \times p} \) is i.i.d sampled from \( N(0, \Sigma) \).

**Condition-2** The covariance \( \Sigma \) of the \( \Sigma \)-Gaussian ensemble is strictly diagonally dominant: for all row \( i \), \( \delta_i := \Sigma_{ii} - \Sigma_{i,j\neq i} \geq \delta_{min} > 0 \) where \( \delta_{min} \) is a large enough constant so that \( ||\Sigma||_\infty \leq \frac{1}{\delta_{min}} \).

This assumption guarantees that the matrix \( T_v\left( \frac{X^T X}{n} \right) \) is invertible, and its induced \( \ell_\infty \) norm is well bounded. Then the following theorem holds:

**Theorem 10.1.** Suppose Condition-1 and Condition-2 hold.
Then for any \( v \geq 8(max(\Sigma_{ii}) \sqrt{\frac{10 \log p'}{n}}) \), the matrix \( T_v\left( \frac{X^T X}{n} \right) \) is invertible with probability at least \( 1 - 4/p'^{\tau - 2} \) for \( p' := max\{n, p\} \) and any constant \( \tau > 2 \).

10.4. Useful lemma(s) of Error Bounds of Proxy Backward Mapping \( T_v \)

**Lemma 10.2.** (Theorem 1 of (Rothman et al., 2009)). Let \( \delta = max_{ij} \| [\frac{X^T X}{n}]_{ij} - \Sigma_{ij} \|_1 \). Suppose that \( v > 2 \delta \). Then, under the conditions (C-Sparse \( \Sigma \)) and as \( \rho_\nu(\cdot) \) is a soft-threshold function, we can deterministically guarantee that the spectral norm of error is bounded as follows:
\[
||T_v(\hat{\Sigma}) - \Sigma||_\infty \leq 5\nu^{-1}c_0(p) + 3\nu^{-q}c_0(p)\delta
\]  \hspace{1cm} (10.13)

**Lemma 10.3.** (Lemma 1 of (Ravikumar et al., 2011)). Let \( \mathcal{A} \) be the event that
\[
\frac{X^T X}{n} - \Sigma \|_\infty \leq 8(max_{i} \Sigma_{ii}) \sqrt{\frac{10 \log p'}{n}}
\]  \hspace{1cm} (10.14)

where \( p' := max\{n, p\} \) and \( \tau \) is any constant greater than 2. Suppose that the design matrix \( X \) is i.i.d. sampled from \( \Sigma \)-Gaussian ensemble with \( n \geq 40 max_i \Sigma_{ii} \). Then, the probability of event \( \mathcal{A} \) occurring is at least 1 - \( 4/p'^{\tau - 2} \).
11. Theoretical Analysis of Error Bounds

11.1. Background: Error bounds of Elementary Estimators

KDiffNet formulations are special cases of the following generic formulation for the elementary estimator.

\[
\arg\min_{\theta} \mathcal{R}(\theta) \quad \text{subject to:} \mathcal{R}^*(\theta - \hat{\theta}_n) \leq \lambda_n
\]  
(11.1)

Where \( \mathcal{R}^*(\cdot) \) is the dual norm of \( \mathcal{R}(\cdot) \).

\[
\mathcal{R}^*(v) := \sup_{u \neq 0} \frac{\langle u, v \rangle}{\mathcal{R}(u)} = \sup_{\mathcal{R}(u) \leq 1} < u, v >.
\]  
(11.2)

Following the unified framework (Negahban et al., 2009), we first decompose the parameter space into a subspace pair \((\mathcal{M}, \mathcal{M}^\perp)\), where \(\mathcal{M}\) is the closure of \(\mathcal{M}\). Here \(\mathcal{M}^\perp := \{v \in \mathbb{R}^p \mid \langle u, v \rangle = 0, \forall u \in \mathcal{M}\}\). \(\mathcal{M}\) is the model subspace that typically has a much lower dimension than the original high-dimensional space. \(\mathcal{M}^\perp\) is the perturbation subspace of parameters. For further proofs, we assume the regularization function in Eq. (11.1) is decomposable w.r.t the subspace pair \((\mathcal{M}, \mathcal{M}^\perp)\).

(C1) \(\mathcal{R}(u + v) = \mathcal{R}(u) + \mathcal{R}(v), \forall u \in \mathcal{M}, \forall v \in \mathcal{M}^\perp\).

(Negahban et al., 2009) showed that most regularization norms are decomposable corresponding to a certain subspace pair.

Definition 11.1. Subspace Compatibility Constant

Subspace compatibility constant is defined as \(\Psi(M, \cdot, \cdot) := \sup_{u \in \mathcal{M} \setminus \{0\}} \frac{\mathcal{R}(u)}{|\cdot|}\) which captures the relative value between the error norm \( |\cdot| \) and the regularization function \(\mathcal{R}(\cdot)\).

For simplicity, we assume there exists a true parameter \(\theta^*\) which has the exact structure w.r.t a certain subspace pair. Concretely:

(C2) \(\exists\) a subspace pair \((\mathcal{M}, \mathcal{M}^\perp)\) such that the true parameter satisfies \(\text{proj}_{\mathcal{M}^\perp}(\theta^*) = 0\)

Then we have the following theorem.

Theorem 11.2. Suppose the regularization function in Eq. (11.1) satisfies condition (C1), the true parameter of Eq. (11.1) satisfies condition (C2), and \(\lambda_n\) satisfies that \(\lambda_n \geq \mathcal{R}^*(\hat{\theta}_n - \theta^*)\). Then, the optimal solution \(\hat{\theta}\) of Eq. (11.1) satisfies:

\[
\mathcal{R}^*(\hat{\theta} - \theta^*) \leq 2\lambda_n
\]  
(11.3)

\[
|\hat{\theta} - \theta^*|_2 \leq 4\lambda_n \Psi(\tilde{\mathcal{M}})
\]  
(11.4)

\[
\mathcal{R}(\hat{\theta} - \theta^*) \leq 8\lambda_n \Psi(\tilde{\mathcal{M}})^2
\]  
(11.5)

Proof. Let \(\delta := \hat{\theta} - \theta^*\) be the error vector that we are interested in.

\[
\mathcal{R}^*(\hat{\theta} - \theta^*) = \mathcal{R}^*(\hat{\theta} - \hat{\theta}_n + \hat{\theta}_n - \theta^*)
\]  
(11.6)

By the fact that \(\theta^*_{\mathcal{M}^\perp} = 0\), and the decomposability of \(\mathcal{R}\) with respect to \((\mathcal{M}, \mathcal{M}^\perp)\)

\[
\mathcal{R}(\theta^*) = \mathcal{R}(\theta^*_{\mathcal{M}}) + \mathcal{R}(\theta^*_{\mathcal{M}^\perp})
\]  
(11.7)

Here, the inequality holds by the triangle inequality of norm. Since Eq. (11.1) minimizes \(\mathcal{R}(\hat{\theta})\), we have \(\mathcal{R}(\theta^* + \Delta) = \mathcal{R}(\hat{\theta}) \leq \mathcal{R}(\theta^*)\). Combining this inequality with Eq. (11.7), we have:

\[
\mathcal{R}(\mathcal{M}^\perp(\delta)) \leq \mathcal{R}(\mathcal{M}^\perp(\delta))
\]  
(11.8)

Moreover, by Hölder’s inequality and the decomposability of \(\mathcal{R}(\cdot)\), we have:

\[
||\Delta||_2^2 = \langle \delta, \delta \rangle \leq \mathcal{R}^*(\delta) \mathcal{R}(\delta) \leq 2\lambda_n \mathcal{R}(\delta)
\]  
(11.9)

where \(\Psi(\tilde{\mathcal{M}})\) is a simple notation for \(\Psi(\tilde{\mathcal{M}}, ||\cdot||_2)\).

Since the projection operator is defined in terms of \(||\cdot||_2\) norm, it is non-expansive: \(||\mathcal{M}^\perp(\Delta)||_2 \leq ||\Delta||_2\). Therefore, by Eq. (11.9), we have:

\[
||\mathcal{M}^\perp(\delta)||_2 \leq 4\lambda_n \Psi(\tilde{\mathcal{M}}),
\]  
(11.10)

and plugging it back to Eq. (11.9) yields the error bound Eq. (11.4).

Finally, Eq. (11.5) is straightforward from Eq. (11.8) and Eq. (11.10).

\[
\mathcal{R}(\delta) \leq 2\mathcal{R}(\mathcal{M}^\perp(\delta))
\]  
(11.11)
11.2 Error Bounds of KDiffNet

11.2.1 Error Bounds of KDiffNet through \( \lambda_n \) and \( \epsilon \)

**Theorem 11.3.** Assuming the true parameter \( \Delta^* \) satisfies the conditions (C1)-(C2) and \( \lambda_n \geq \mathcal{R}^*(\tilde{\Delta} - \Delta^*) \), then the optimal point \( \tilde{\Delta} \) has the following error bounds:

\[
\| \tilde{\Delta} - \Delta^* \|_F \leq \left( 4 \max\left( \frac{\sqrt{\theta}}{\epsilon}, \sqrt{\Theta} \right) \right) \lambda_n \tag{11.12}
\]

**Proof:**

KDiffNet uses \( \mathcal{R}(\cdot) = \|W_E \circ \cdot\|_1 + \epsilon \| \cdot \|_{\mathcal{G}_2} \) because it is a superposition of two norms: \( \mathcal{R}_1 = \|W_E \circ \cdot\|_1 \) and \( \mathcal{R}_2 = \epsilon \| \cdot \|_{\mathcal{G}_2} \). Based on the results in (Nehanban et al. 2009), \( \Psi(M_1) = \sqrt{\Theta}. \)

Assuming ground truth \( W_E^* \), we assume the model space \( \mathcal{M}(S) \), where for set of edges \( S = \{i,j, \Delta(S(i,j)) = 0\} \), and \( n(S) = s_E, \) then without loss of generality, setting \( W_S > 1 \), indicating \( \psi(M) = \sqrt{\Theta}. \)

Similarly, from (Nehanban et al. 2009), \( \Psi(M_2) = \sqrt{\Theta} \), where \( s \) is the number of non-zero entries in \( \Delta \) and \( s_E \) is the number of groups in which there exists at least one non-zero entry. Therefore, \( \Psi(M) = \max(\sqrt{\Theta}, \epsilon \sqrt{\Theta}). \)

Hence, using this in Equation (11.4), \( \| \tilde{\Delta} - \Delta^* \|_F \leq 4 \left( \max(\sqrt{\Theta}, \epsilon \sqrt{\Theta}) \right) \lambda_n. \)

**11.2.2. Proof of Corollary (3.2)-Derivation of KDiffNet error bounds**

To derive the convergence rate for KDiffNet, we introduce the following two sufficient conditions on the \( \Sigma_c \) and \( \Sigma_d \), to show that the proximal backward mapping \( \hat{\theta}_n = B^*(\hat{\psi}) = [T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\hat{\Sigma}_d)]^{-1} \) is well-defined (Wang et al., 2018b):

**C-MinInf**-\( \Sigma \): The true \( \Omega_c^* \) and \( \Omega_d^* \) on Eq. (2.1) have bounded induced operator norm i.e., \( \| \Omega^*_c \|_\infty, \| \Omega^*_d \|_\infty := \sup_{w \neq 0 \in \mathbb{R}^p} \frac{\| \Omega^*_c w \|_\infty}{\| w \|_\infty} \leq W_{c_{min}}^{\epsilon} \kappa_1 \) and \( \| \Omega^*_d \|_\infty := \sup_{w \neq 0 \in \mathbb{R}^p} \frac{\| \Omega^*_d w \|_\infty}{\| w \|_\infty} \leq W_{d_{min}}^{\epsilon} \kappa_1. \)

Here, intuitively, \( W_{c_{min}}^{\epsilon} \) corresponds to the largest ground truth weight index associated with non-zero entries in \( \Omega^*_c \). For set \( S_{nz} = \{i,j, \Omega^*_c(i,j) = 0\}, W_{S_{nz}} > W_{c_{min}}^{\epsilon}. \)

**C-Sparse**-\( \Sigma \): The two true covariance matrices \( \Sigma_c \) and \( \Sigma_d \) are “approximately sparse” (following (Bickel & Levina, 2008)). For some constant \( 0 \leq q < 1 \) and \( c_0(p), \)

\[
\max_{i,j} \| \Sigma^*_c(i,j) \|_q \leq c_0(p) \quad \text{and} \quad \max_{i,j} \| \Sigma^*_d(i,j) \|_q \leq c_0(p). \tag{11.13}
\]

We additionally require \( \inf_{w \neq 0 \in \mathbb{R}^p} \frac{\| \Omega^*_c w \|_{\infty}}{\| w \|_{\infty}} \geq \kappa_2 \) and \( \inf_{w \neq 0 \in \mathbb{R}^p} \frac{\| \Omega^*_d w \|_{\infty}}{\| w \|_{\infty}} \geq \kappa_2. \)

We assume the true parameters \( \Omega_c^* \) and \( \Omega_d^* \) satisfies C-MinInf and C-Sparse conditions.

Using the above theorem and conditions, we have the following corollary for convergence rate of KDiffNet (Att: the following corollary is the same as the Corollary 3.2 in the main draft. We repeat it here to help readers read the manuscript more easily):

**Corollary 11.4.** In the high-dimensional setting, i.e., \( p > \max(n_c, n_d) \), let \( v := \sqrt{\frac{\log p}{\min(n_c, n_d)}}. \) Then for \( \lambda_n := c \kappa_1 \sqrt{\frac{\log p}{\min(n_c, n_d)}}. \)

\[
\| \tilde{\Delta} - \Delta^* \|_F \leq \frac{c \kappa_1 \max(\sqrt{\Theta}, \epsilon \sqrt{\Theta})}{\kappa_2} \sqrt{\frac{\log p}{\min(n_c, n_d)}} \tag{11.14}
\]

where \( a, c, \kappa_1 \) and \( \kappa_2 \) are constants. Here \( \Gamma = \max(W_{c_{min}}^{\epsilon}, W_{d_{min}}^{\epsilon}) \).
11.2 Error Bounds of KDiffNet

and Lemma (10.3) hold with probability at least \(1 - 4/p^{\tau - 2}\). Armed with Eq. (10.13), we use the triangle inequality of norm and the condition (C-Sparse\(\Sigma\)): for any \(w\),

\[
||T_v(\Sigma_c)w||_{\infty} = ||T_v(\Sigma_c)w - \Sigma w + \Sigma w||_{\infty} \\
\geq ||\Sigma w||_{\infty} - ||(T_v(\Sigma_c) - \Sigma)w||_{\infty} \\
\geq \kappa_2 ||w||_{\infty} - ||(T_v(\Sigma_c) - \Sigma)w||_{\infty} \\
\geq (\kappa_2 - \|(T_v(\Sigma_c) - \Sigma)w||_{\infty})||w||_{\infty},
\]

(11.15)

Where the second inequality uses the condition (C-Sparse\(\Sigma\)).

Now, by Lemma (10.2) with the selection of \(v\), we have

\[
||T_v(\Sigma_c) - \Sigma||_{\infty} \leq c_1 \left(\frac{\log p'}{n_c}\right)^{(1-q)/2} c_0(p) \quad (11.16)
\]

where \(c_1\) is a constant related only on \(\tau\) and \(\max_i \Sigma_{ii}\).

Specifically, it is defined as \(6.5 \times 16(\max_i \Sigma_{ii}) \sqrt{10\tau}^{1-q}\).

Hence, as long as \(n_c > \left(\frac{2\kappa_1 \epsilon}{\kappa_2}\right)^{1/2} \log p'\) as stated, so that \(||(T_v(\Sigma_c) - \Sigma)||_{\infty} \leq \frac{\kappa_2}{2}\), we can conclude that \(||T_v(\Sigma_c)w||_{\infty} \geq \frac{\kappa_2}{2} ||w||_{\infty}\), which implies \(||(T_v(\Sigma_c))^{-1}||_{\infty} \leq \frac{2}{\kappa_2}||w||_{\infty}\).

The remaining term in Eq. (11.14) is \(||T_v(\Sigma_c) - \Sigma^*||_{\infty}\):

\[
||T_v(\Sigma_c) - \Sigma||_{\infty} \leq ||T_v(\Sigma_c) - \hat{\Sigma}_c||_{\infty} + ||\hat{\Sigma}_c - \Sigma^*||_{\infty}.
\]

By construction of \(T_v(\cdot)\) in (C-Thresh) and by Lemma (10.3), we can confirm that \(||T_v(\Sigma_c) - \hat{\Sigma}_c||_{\infty}\) as well as \(||\hat{\Sigma}_c - \Sigma^*||_{\infty}\) can be upper-bounded by \(v\).

Similarly, the \([T_v(\Sigma_d)]^{-1}\) has the same result.

Finally,

\[
||(1 \otimes W_E) \circ (\Delta^* - \left([T_v(\hat{\Sigma}_d)]^{-1} - [T_v(\Sigma_c))]^{-1}\right)) ||_{\infty}
\]

(11.17)

\[
\leq \|(1 \otimes W_E) \circ (\Omega_d - [T_v(\hat{\Sigma}_d)]^{-1}) ||_{\infty} \quad (11.18)
\]

\[
+ \|(1 \otimes W_E) \circ (\Omega_c - [T_v(\Sigma_c))]^{-1}) ||_{\infty} \quad (11.19)
\]

\[
\leq \frac{1}{W_{E_{\min}}} \left(\frac{4W_{E_{\min}}^{\epsilon}}{\kappa_2} \frac{\log p'}{n_c} + \frac{4W_{E_{\min}}^{d_s}}{\kappa_2} \frac{\log p'}{n_d}\right) \quad (11.20)
\]

\[
\leq \frac{1}{W_{E_{\min}}} \left(8 \max(W_{E_{\min}}^{\epsilon}, W_{E_{\min}}^{d_s})\kappa_1 a \sqrt{\frac{\log p'}{\min(n_c, n_d)}}\right) \quad (11.21)
\]

We assume \(W_{E_{\min}} > 1\). By Theorem 11.3, we know if \(\lambda_n \geq R^*(\hat{\Delta} - \Delta^*)\),

\[
||\hat{\Delta} - \Delta^*||_F \leq (4 \max(\sqrt{s_E}, \epsilon \sqrt{s_G}) \lambda_n)
\]

Suppose \(p > \max(n_c, n_d)\) we have that

\[
||\hat{\Delta} - \Delta^*||_F \leq \frac{\Gamma a \max((\sqrt{s_E}), \epsilon \sqrt{s_G})}{\kappa_2} \sqrt{\frac{\log p}{\min(n_c, n_d)}} \quad (11.22)
\]

Here, \(\Gamma = 32\kappa_1 \max(W_{E_{\min}}^{\epsilon}, W_{E_{\min}}^{d_s})\). Note that in the case of DIFFEE, \(\Gamma = 32\kappa_1 \max(W_{E_{\min}}^{\epsilon}, W_{E_{\min}}^{d_s})\).

By combining all together, we can confirm that the selection of \(\lambda_n\) satisfies the requirement of Theorem (11.3), which completes the proof.

\(\square\)
12 MORE DETAILS ON REAL DATA:

Supplementary Materials for Experimental Setup, Real Data, Simulated Data and More Results

12. More Details on Real Data:

12.1. Additional Details: ABIDE

In this experiment, we evaluate KDiffNet in a real-world downstream classification task on a publicly available resting-state fMRI dataset: ABIDE(Di Martino et al., 2014). The ABIDE data aims to understand human brain connectivity and how it reflects neural disorders (Van Essen et al., 2013). The data is retrieved from the Preprocessed Connectomes Project (Craddock, 2014), where preprocessing is performed using the Configurable Pipeline for the Analysis of Connectomes (CPAC) (Craddock et al., 2013) without global signal correction or band-pass filtering. ABIDE includes two groups of human subjects: autism and control. After preprocessing with this pipeline, 871 (number of features $p = 160$) regions of interest (ROIs) in the often-used Dosenbach Atlas (Dosenbach et al., 2010) are examined. We utilize three types of additional knowledge: $W_E$ based on the spatial distance between 160 brain regions of interest (ROIs) (Dosenbach et al., 2010) and two types of available node groups from Dosenbach Atlas (Dosenbach et al., 2010): one with 40 unique groups about macroscopic brain structures (G1) and the other with 6 higher level node groups having the same functional connectivity (G2).

To evaluate the learnt differential structure in the absence of a ground truth graph, we utilize the non-zero edges from the estimated graph in downstream classification. We tune over $\lambda_n$ and pick the best $\lambda_n$ using validation. The subjects are randomly partitioned into three equal sets: a training set, a validation set, and a test set. Each estimator produces $\hat{\Omega}_n - \hat{\Omega}_d$ using the training set. Then, the nonzero edges in the difference graph are used for feature selection. Namely, for every edge between ROI $x$ and ROI $y$, the mean value of $x$ over time was selected as a feature. These features are fed to a logistic regressor with ridge penalty, which is tuned via cross-validation on the validation set. Finally, accuracy is calculated on the test set. We repeat this process for 3 random seeds. For all methods, we choose $\lambda_n$ to vary the fraction of zero edges (non-edges) of the inferred graphs from $0.01 \times |i| \in \{50, 51, 52, \ldots, 70\}$. We repeat the experiment for 3 random seeds and report the average test accuracy. Figure 2b compares KDiffNet-EG, KDiffNet-E, KDiffNet-G and baselines on ABIDE, using the $y$ axis for classification test accuracy (the higher the better) and the $x$ axis for the computation speed per $\lambda_n$ (negative seconds, the more right the better). KDiffNet -EG1, incorporating both edge($W_E$) and (G1) group knowledge, achieves the highest accuracy of 60.5% for distinguishing the autism versus the control subjects without sacrificing computation speed.

12.2. Additional Details: Epigenetic Network Estimation

In this experiment, we evaluate KDiffNet and baselines for estimating the differential epigenetic network between low and high gene expression. Cellular diversity is attributed to cell type-specific patterns of gene expression, in turn associated with a complex regulation mechanism. Studies have shown that epigenetic factors (like histone modifications (HMs)), act combinatorially to regulate gene expression (Suganuma & Workman, 2008; Berger, 2007). The knowledge of changes in epigenetic network can help in developing ‘epigenetic drugs’ for diseases like cancer. We consider five core HM marks (H3K4me3, H3K4me1, H3K36me3, H3K9me3, H3K27me3) and three major cell types (K562 Leukemia Cells (E123), GM12878 Lymphoblastoid Cells (E116) and Psoas Muscle (E100)) with genome-level gene expression profiled in the REMC database (Kundaje et al., 2015). For each gene, we divide the 10,000 basepair (bp) DNA region ($\pm 5000$ bp) around the transcription start site (TSS) into bins of length 100 bp. Each bin includes 100 bp long adjacent positions flanking the TSS of a gene. We further pool each of the HM signals into 25 bins using the max value. We use the cell type specific median expression to threshold the expression into low and high expression. We partition the 19,795 genes into 6599 train, 6599 validation and 6597 test set genes. Gene expression measurements (RPKM) are available through the REMC database (Kundaje et al., 2015). We use the cell type specific median expression to threshold the values into up-regulated and downregulated genes. Further, to incorporate the prior knowledge that signals spatially closer to each other along the genome are more likely to interact in the gene regulation process, we use genomic distance (using relative difference of bin positions) as $W_E$. Similar to the previous case, we utilize the quadratic features from the estimated differential non-zero edges in downstream gene expression classification.

We repeat the experiments for 3 different data splits. Figure 2c reports the average test set performance across the three splits for the three cell types. We plot the test accuracy achieved by KDiffNet on the $y$-axis, with the best performing baseline on the $x$-axis. KDiffNet outperforms DIFFEE that does not use $W_E$ as well as JEEK, that can incorporate this information but estimates the two networks separately. Figure 3 shows a qualitative comparison of the epigenetic networks learnt by KDiffNet and DIFFEE. KDiffNet can both make use of the spatial prior as well as estimate biologically consistent networks. As expected, we observe a relationship among promoter and structural histone modi-
Table 3 shows the time cost of KDiffNet-E and baselines of estimating epigenetic network for cell type E123.

| Method     | Time Cost (seconds) |
|------------|---------------------|
| DIFFEE     | 0.001 (± 0.000)     |
| JEEK       | 3.004 (± 0.092)     |
| KDiffNet-E | 0.002 (± 0.000)     |

Table 3. Average time cost over three data splits for cell type E123

13. More Details on Setup:

13.1. Experimental Setup

The hyper-parameters in our experiments are \( v, \lambda_n, \epsilon \) and \( \lambda_2 \). In detail:

- To compute the proxy backward mapping in (7.1), DIFFEE, and JEEK we vary \( v \) for soft-thresholding \( v \) from the set \{0.001 \( i \) = 1, 2, \ldots, 1000\} (to make \( T_v(\Sigma_c) \) and \( T_v(\Sigma_d) \) invertible).
- \( \lambda_n \) is the hyper-parameter in our KDiffNet formulation. According to our convergence rate analysis in Section 3.5, \( \lambda_n \geq C \frac{\log p}{\min(n_c, n_d)} \), we choose \( \lambda_n \) from a range of \{0.01 \( i \) \( \sqrt{\frac{\log p}{\min(n_c, n_d)}} \) \( i \) \( \in \) \{1, 2, 3, \ldots, 1000\}\}. For KDiffNet-G case, we tune over \( \lambda_n \) from a range of \{0.1 \( i \) \( \sqrt{\frac{\log p}{\min(n_c, n_d)}} \) \( i \) \( \in \) \{1, 2, 3, \ldots, 100\}\}. We use the same range to tune \( \lambda_1 \) for SDRE. Tuning for NAK is done by the package itself.
- \( \epsilon \): For KDiffNet-EG experiments, we tune \( \epsilon \in \{0.0001, 0.01, 1, 100\} \).
- \( \lambda_2 \) controls individual graph’s sparsity in JGLFUSED. We choose \( \lambda_1 = 0.0001 \) (a very small value) for all experiments to ensure only the differential network is sparse.

Evaluation Metrics:

- F1-score: We use the edge-level F1-score as a measure of the performance of each method. \( F1 = \frac{2 \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \), where Precision = \( \frac{TP}{TP + FP} \) and Recall = \( \frac{TP}{TP + FN} \). The better method achieves a higher F1-score. We choose the best performing \( \lambda_n \) using validation and report the performance on a test dataset.
- Time Cost: We use the execution time (measured in seconds or log(seconds)) for a method as a measure of its scalability. The better method uses less time.

14. More Details on Simulated Data:

We use simulation to evaluate KDiffNet for improving differential structure estimation by making use of extra knowledge. In the following subsections, we present details about the data generation, followed by the results under multiple settings.

14.1. Simulation Dataset Generation

We generate simulated datasets with a clear underlying differential structure between two conditions, using the following method:

**Data Generation for Edge Knowledge (KE):** Given a known weight matrix \( W_E \) (e.g., spatial distance matrix between \( p \) brain regions), we set \( W_d = \logit(-W_E) \). We use the assumption that higher the value of \( W_{ij} \), lower the probability of that edge to occur in the true precision matrix. This is motivated by the role of spatial distance in brain connectivity networks: farther regions are less likely to be connected and vice-versa. We select different levels in the matrix \( W_d \), denoted by \( s \), where if \( W_{ij}^d > s_1 \), \( \Delta_{ij}^d = 0.5 \), else \( \Delta_{ij}^d = 0 \), where \( \Delta^d \in \mathbb{R}^{p \times p} \). We denote by \( s \) as the sparsity, i.e. the number of non-zero entries in \( \Delta^d \). \( B_I \) is a random graph with each edge \( B_{ij} = 0.5 \) with probability \( p \). \( \delta_c \) and \( \delta_d \) are selected large enough to guarantee positive definiteness.

\[
\Omega_d = \Delta_d + B_I + \delta_d I \quad \text{(14.1)}
\]

\[
\Omega_c = B_I + \delta_c I \quad \text{(14.2)}
\]

\[
\Delta = \Omega_d - \Omega_c \quad \text{(14.3)}
\]

There is a clear differential structure in \( \Delta = \Omega_d - \Omega_c \), controlled by \( \Delta_d \). To generate data from two conditions that follows the above differential structure, we generate two blocks of data samples following Gaussian distribution using \( N(0, \Omega_c^{-1}) \) and \( N(0, \Omega_d^{-1}) \). We only use these data samples to approximate the differential GGM to compare to the ground truth \( \Delta \).

**Data Generation for Vertex Knowledge (KG):** In this case, we simulate the case of extra knowledge of nodes in known groups. Let the node group size i.e., the number of nodes with a similar interaction pattern in the differential graph be \( m \). We select the block diagonals of size \( m \) as groups in \( \Delta^g \). If two variables \( i, j \) are in a group \( g^i \), in \( \Delta^g_{ij} = 0.5 \), else \( \Delta^g_{ij} = 0 \), where \( \Delta^g \in \mathbb{R}^{p \times p} \). We denote by

\[9\] The machine that we use for experiments is an Intel Core i7 CPU with a 16 GB memory.
We select different levels in the matrix $W$ with each edge $B_{I_{ij}} = 0.5$ with probability $p$.

$$\Omega_d = \Delta^g + B_I + \delta_d I$$  \hspace{1cm} (14.4)

$$\Omega_c = B_I + \delta_c I$$  \hspace{1cm} (14.5)

$$\Delta = \Omega_d - \Omega_c$$  \hspace{1cm} (14.6)

$\delta_c$ and $\delta_d$ are selected large enough to guarantee positive definiteness. We generate two blocks of data samples following Gaussian distribution using $N(0, \Omega_c^{-1})$ and $N(0, \Omega_d^{-1})$.

**Data Generation for both Edge and Vertex Knowledge (KEG):** In this case, we simulate the case of overlapping group and edge knowledge. Let the node group size, i.e., the number of nodes with a similar interaction pattern in the differential graph be $m$. We select the block diagonals of size $m$ as groups in $\Delta^g$. If two variables $i, j$ are in a group $g'$, in $\Delta^g_{ij} = 1/3$, else $\Delta^g_{ij} = 0$, where $\Delta^g \in \mathbb{R}^{p \times p}$.

For the edge-level knowledge component, given a known weight matrix $W_E$, we set $W^d = \text{inv.logit}(-W_E)$. Higher the value of $W_{E_{ij}}$, lower the value of $W^d_{ij}$, hence lower the probability of that edge to occur in the true precision matrix. We select different levels in the matrix $W^d$, denoted by $s$, where if $W^d_{ij} > s$, we set $\Delta^d_{ij} = 1/3$, else $\Delta^d_{ij} = 0$. We denote by $s$ as the number of non-zero entries in $\Delta^d$. $B_I$ is a random graph with each edge $B_{I_{ij}} = 1/3$ with probability $p$.

$$\Omega_d = \Delta^d + \Delta^g + B_I + \delta_d I$$  \hspace{1cm} (14.7)

$\delta_c$ and $\delta_d$ are selected large enough to guarantee positive definiteness. Similar to the previous case, we generate two blocks of data samples following Gaussian distribution using $N(0, \Omega_c^{-1})$ and $N(0, \Omega_d^{-1})$. We only use these data samples to approximate the differential GGM to compare to the ground truth $\Delta$.

We consider three different types of known edge knowledge $W_E$ generated from the spatial distance between different brain regions and simulate groups to represent related anatomical regions. These three are distinguished by different $p = \{116, 160, 246\}$ representing spatially related brain regions. We generate three types of datasets: Data-EG (having both edge and vertex knowledge), Data-G (with edge-level extra knowledge) and Data-V (with known node groups knowledge). We generate two blocks of data samples $X_c$ and $X_d$ following Gaussian distribution using $N(0, \Omega_c^{-1})$ and $N(0, \Omega_d^{-1})$. We use these data samples to estimate the differential GGM to compare to the ground truth $\Delta$. We vary the sparsity of the true differential graph $s$ and the number of control and case samples $(n_c$ and $n_d$ respectively) used to estimate the differential graph. For each case of $p$, we vary $n_c$ and $n_d$ in $\{p/2, p/4, p, 2p\}$ to account for both high dimensional and low dimensional cases. The sparsity of the underlying differential graph is controlled by $s = \{0.125, 0.25, 0.375, 0.5\}$ and $s_G$ as explained above. This results in 126 different datasets representing diverse settings: different number of dimensions $p$, number of samples $n_c$ and $n_d$, multiple levels of sparsity $s$ and number of
groups $s_G$ of the differential graph for both KE and KEG data settings. Figure 4 summarizes the different settings for simulation datasets.

15. Details of Results on Simulated:

15.1. Summary of Simulated Results:

Summary: We present a summary of our results (partial) in Table 4: the columns representing two cases of data generation settings (Data-EG and Data-G). Table 4 uses the mean F1-score (across different settings of $p, n_c, n_d, \ldots$) and the computational time cost to compare methods (rows). We repeat each experiment for 10 random seeds. We can make several conclusions:

1. **KDiffNet outperforms baselines that do not consider knowledge.** Clearly, KDiffNet and its variations achieve the highest F1-score across all the 126 datasets. SDRE and DIFFEE are differential network estimators but perform poorly indicating that adding additional knowledge improves differential GGM estimation. MLE-based JGLFUSED performs the worst in all cases.

2. **KDiffNet outperforms the baselines that consider knowledge, especially when group knowledge exists.** When under the Data-EG setting, while JEEK and NAK that take into account edge knowledge but cannot model node group evidence. On average the generated graph as prior edge knowledge $W_E$.

3. **KDiffNet achieves reasonable time cost versus the baselines and is scalable to large $p$.** Figure 2a shows each method’s time cost per $\lambda_n$ for large $p = 2000$. KDiffNet-EG is faster than JEEK, JGLFUSED and SDRE (Column 1 in Table 4). KDiffNet-E and KDiffNet-G are faster than KDiffNet-EG owing to closed form solutions. On Data-G dataset and Data-E datasets, our faster closed form solutions are able to achieve more computational speedup. For example, on datasets using $W_2$ $n = 246$, KDiffNet-E and KDiffNet-G are on an average $21000 \times$ and $7400 \times$ faster (Column 5 in Table 4) than the baselines, respectively.

Besides F1-Score, we also analyze KDiffNet’s performance when varying hyper-parameter $\lambda_n$ using ROC curves. KDiffNet achieves the highest Area under Curve (AUC) in comparison to all other baselines.

In the following, we use three different subsections to present detailed results for all the 126 datasets under the three different data simulation settings.

15.2. Simulated Results: when our knowledge is partial:

Varying proportion of known edges: We generate $W_E$ matrices with $p = 150$ using Erdos Renyi Graph (ERDdS & R&wi, 1959). We use the generated graph as prior edge knowledge $W_E$. Additionally, we simulate 15 groups of size 10 as explained in Section 14.1. We simulate $\Omega_c$ and $\Omega_d$ as explained in Section 14.1. Figure 5 presents the performance of KDiffNet-EG, KDiffNet-E and DIFFEE with varying proportion of known edges.

KDiffNet-EG has a higher F1-score than KDiffNet-E as it can additionally incorporate known group information. As expected, with increase in the proportion of known edges, F1-Score improves for both KDiffNet-EG and KDiffNet-E. In contrast DIFFEE cannot make use of additional information and the F1-Score remains the same.

15.3. Simulated Results: When Tuning Two hyperparameters:

Scalability in $p$: To evaluate the scalability of KDiffNet and baselines to large $p$, we also generate larger $W_E$ matrices with $p = 2000$ using Erdos Renyi Graph (ERDdS & R&wi, 1959), similar to the aforementioned design. Using the generated graph as prior edge knowledge $W_E$, we design $\Omega_c$ and $\Omega_d$ as explained in Section 14.1. For the case of both edge and vertex knowledge, we fix the number of groups to 100 of size 10. We evaluate the scalability of KDiffNet-EG and baselines measured in terms of computation cost per $\lambda_n$.

Figure 7 shows the computation time cost per $\lambda_n$ for all methods. Clearly, KDiffNet takes the least time, for large $p$ as well.

Choice of $\lambda_n$: For KDiffNet, we show the performance of all the methods as a function of choice of $\lambda_n$. Figure 6 shows the True Positive Rate (TPR) and False Positive Rate (FPR) measured by varying $\lambda_n$ for $p = 116$, $s = 0.5$ and $n_c = n_d = p/2$ under the Data-EG setting. Clearly, KDiffNet-EG achieves the highest Area under Curve (AUC) than all other baseline methods. KDiffNet-EG also outperforms JEEK and NAK that take edge knowledge but cannot model the known group knowledge.

15.4. Simulated Results: When we have both edge and group knowledge:

Edge and Vertex Knowledge (KEG): We use KDiffNet (Algorithm 1) to infer the differential structure in this case.
15.5 Simulated Results: When we have only edge knowledge:

**Simulation Experiments**

Figure 4. A schematic showing the different experimental settings for simulation experiments.

Figure 8(a) shows the performance in terms of F1 Score of KDifNet in comparison to the baselines for \( p = 116 \), corresponding to 116 regions of the brain. KDifNet outperforms the best baseline in each case by an average improvement of 414%. KDifNet-EG does better than JEEK and NAK that can model the edge information but cannot include group information. SDRE and DIFFEE are direct estimators but perform poorly indicating that adding additional knowledge aids differential network estimation. JGLFUSED performs the worst on all cases.

Figure 8(b) shows the average computation cost per \( \lambda_n \) of each method measured in seconds. In all settings, KDifNet has lower computation cost than JEEK, SDRE and JGLFUSED in different cases of varying \( n_e \) and \( n_g \), as well as with different sparsity of the differential network. KDifNet is on average 24× faster than the best performing baseline. It is slower than DIFFEE owing to DIFFEE’s non-iterative closed form solution, however, DIFFEE does not have good prediction performance. Note that \( B^*() \) in KDifNet, JEEK and DIFFEE and the kernel term in SDRE are precomputed only once prior to tuning across multiple \( \lambda_n \). In Figure 9(a), we plot the test F1-score for simulated datasets generated using \( W \) with \( p = 160 \), representing spatial distances between different 160 regions of the brain. This represents a larger and different set of spatial brain regions. In this case, KDifNet outperforms the best baseline in each case by an average improvement of 928%. Including available additional knowledge is clearly useful as JEEK does relatively better than the other baselines. JGLFUSED again performs the worst on all cases. Figure 9(b) shows the computation cost of each method measured in seconds for each case. KDifNet is on average 37× faster than the best performing baseline.

In Figure 10(a), we plot the test F1-score for simulated datasets generated using a larger \( W_E \) with \( p = 246 \), representing spatial distances between different 246 regions of the brain. This represents a larger and different set of spatial brain regions. In this case, KDifNet outperforms the best baseline in each case by an average improvement of 1400% relative to the best performing baseline. In this case as well, including available additional knowledge is clearly useful as JEEK does relatively better than the other baselines, which do not incorporate available additional knowledge. JGLFUSED again performs the worst on all cases. Figure 10(b) shows the computation cost of each method measured in seconds for each case. In all cases, KDifNet has the least computation cost in different settings of the data generation. KDifNet is on average 20× faster than the best performing baseline.

We cannot compare Diff-CLIME as it takes more than 2 days to finish \( p = 246 \) case.

15.5. Simulated Results: When we have only edge knowledge:

**Edge Knowledge (KE):** Given known \( W_E \), we use KDifNet-E to infer the differential structure in this case.
15.5 Simulated Results: When we have only edge knowledge:

Figure 5. F1-Score of KDiffNet-EG, KDiffNet-E and DIFFEE with varying proportion of known edges.

Figure 6. Area Under Curve (AUC) Curves for KDiffNet and baselines at different hyperparameter values $\lambda$. 
Table 4. Mean Performance (F1-Score) and Computation Time (seconds) with standard deviation for 10 random seeds given in parentheses of KDiffNet-EG, KDiffNet-E, KDiffNet-G and baselines for simulated data. We evaluate over 126 datasets: 14 variations in each of the three spatial matrices $W_p$: $p = 116$ (W1), $p = 246$ (W2), and $p = 160$ (W3) for the three data settings: Data-EG, Data-E and Data-G. * indicates that the method is not applicable for a data setting.

![Figure 7. Scalability of KDiffNet: Computation Cost (computation time per $\lambda$) as a function of $p$.](image_url)

Figure 11(a) shows the performance in terms of F1-Score of KDiffNet-E in comparison to the baselines for $p = 116$, corresponding to 116 spatial regions of the brain. In $p = 116$ case, KDiffNet-E outperforms the best baseline in each case by an average improvement of 23%. While JEEK, DIFFEE and SDRE perform similar to each other, JGLFUSED performs the worst on all cases.

Figure 11(b) shows the computation cost of each method measured in seconds for each case. In all cases, KDiffNet-E has the least computation cost in different cases of varying $n_c$ and $n_d$, as well as with different sparsity of the differential network. For $p = 116$, KDiffNet-E, owing to an entry wise parallelizable closed form solution, is on average $2356 \times$ faster than the best performing baseline. In Figure 12(a), we plot the test F1-score for simulated datasets generated using $W$ with $p = 160$, representing spatial distances between different 160 regions of the brain. This represents a larger and different set of spatial brain regions. In $p = 160$ case, KDiffNet-E outperforms the best baseline in each case by an average improvement of 67.5%. Including available additional knowledge is clearly useful as JEEK does relatively better than the other baselines, which do not incorporate available additional knowledge. JGLFUSED performs the worst on all cases. Figure 12(b) shows the computation cost of each method measured in seconds for each case. In all cases, KDiffNet-E has the least computation cost in different cases of varying $n_c$ and $n_d$, as well as with different sparsity of the differential network. KDiffNet-E is on average $3300 \times$ faster than the best performing baseline. In Figure 13(a), we plot the test F1-score for simulated datasets generated using a larger $W$ with $p = 246$, representing spatial distances between different 246 regions of the brain. This represents a larger and different set of spatial brain regions.
15.5 Simulated Results: When we have only edge knowledge:

Figure 8. KDdiffNet Edge and Vertex Knowledge Simulation Results for $p = 116$ for different settings of $n_c$, $n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_0$ for KDdiffNet and baseline methods.
Figure 9. KDiffNet Edge and Vertex Knowledge Simulation Results for $p = 160$ for different settings of $n_c, n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_i$ for KDiffNet and baseline methods.
15.5 Simulated Results: When we have only edge knowledge:

Figure 10. KDiffNet Edge and Vertex Knowledge Simulation Results for $p = 246$ for different settings of $n_c, n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_n$ for KDiffNet and baseline methods.
15.5 Simulated Results: When we have only edge knowledge:

Figure 11. KDiffNet-E Simulation Results for $p = 116$ for different settings of $n_c$, $n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_i$ for KDiffNet-E and baseline methods.
15.5 Simulated Results: When we have only edge knowledge:

![Figure 12. KDiffNet-E Simulation Results for \( p = 160 \) for different settings of \( n_c, n_d \), and \( s \): (a) The test F1-score and (b) The average computation time (measured in seconds) per \( \lambda_n \) for KDiffNet-E and baseline methods.](image-url)
15.5 *Simulated Results: When we have only edge knowledge:*

![Diagram showing performance and computation time](image)

**Figure 13.** KDiffNet-E Simulation Results for $p = 246$ for different settings of $n_c, n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_n$ for KDiffNet-E and baseline methods.
brain regions. In this case, KDiffNet-E outperforms the best baseline in each case by an average improvement of 66.4% relative to the best performing baseline. Including available additional knowledge is clearly useful as JEEK does relatively better than the other baselines, which do not incorporate available additional knowledge. JGLFUSED performs the worst on all cases. Figure 13(b) shows the computation cost of each method measured in seconds for each case. In all cases, KDiffNet-E has the least computation cost in different cases of varying $n_c$ and $n_d$, as well as with different sparsity of the differential network. KDiffNet-E is on average $3966 \times$ faster than the best performing baseline.

15.6. Simulated Results: When we have only group knowledge:

Node Group Knowledge : We use KDiffNet-G to estimate the differential network with the known groups as extra knowledge. We vary the number of groups $s_G$ and the number of samples $n_c$ and $n_d$ for each case of $p = \{116, 160, 246\}$. Figure 14 shows the F1-Score of KDiffNet-G and the baselines for $p = 116$. KDiffNet-G clearly has a large advantage when extra node group knowledge is available. The baselines cannot model such available knowledge.

15.7. Simulated Results: When we compare with Deep Neural Network based models (GNN)

We compare with Graph Attention Networks (Veličković et al., 2017). Although not designed for differential parameter learning, we explore the graphs learnt by the attention weights in relation to the true differential graph. We formulate it as a classification task, that is each distribution represents a labeled class. In detail, for each sample, we predict the corresponding data block $\in \{c, d\}$. We validate over number of layers $\in \{1, 2, 3, 4, 5\}$ and hidden size $\{5, 16, 32, 64\}$ for $W^2$, $p = 246$ and varying samples in $\{61, 123, 246, 492\}$ for train, validation and test sets in each setting. We use one attention head in this setting. We train the models using ADAM optimizer with learning rate 0.0005 and train each model for 300 epochs. We pick the model based on the epoch with best validation set classification performance. We use the training set samples to select a threshold for binarizing the aggregated difference of attention weights across the samples from the two data blocks(classes). We report the F1-Score on the aggregated difference from the classes using attention weights from the test data samples. Table 5 shows the GAT performance and corresponding KDiffNet-EG performance for the different settings.
15.7 Simulated Results: When we compare with Deep Neural Network based models (GNN)

![Graph showing Simulated Results](graph.png)

Figure 14. KDiffNet-G Simulation Results for $p = 246$ for different settings of $n_c, n_d$ and $s$: (a) The test F1-score and (b) The average computation time (measured in seconds) per $\lambda_n$ for KDiffNet-E and baseline methods.

| W2 | level | samples | hidden | layers | GAT F1 Score | KDiffNet-EG F1 Score |
|----|-------|---------|--------|--------|--------------|---------------------|
| 246 | 4     | 61      | 64     | 1      | 0.0054       | 0.9384              |
| 246 | 4     | 123     | 64     | 3      | 0.0102       | 0.9397              |
| 246 | 4     | 246     | 32     | 2      | 0.0095       | 0.9365              |
| 246 | 4     | 492     | 64     | 1      | 0.0205       | 0.9430              |
| 246 | 5     | 61      | 5      | 3      | 0.0114       | 0.9225              |
| 246 | 5     | 123     | 64     | 1      | 0.0136       | 0.9219              |
| 246 | 5     | 246     | 32     | 3      | 0.0231       | 0.9248              |
| 246 | 5     | 492     | 16     | 2      | 0.0740       | 0.9302              |

Table 5. Comparison of KDiffNet-EG and GAT (Veličković et al., 2017) for differential graph recovery.