STATISTICAL MATCHING AND SUBCLASSIFICATION WITH A CONTINUOUS DOSE: CHARACTERIZATION, ALGORITHM, AND APPLICATION TO A HEALTH OUTCOMES STUDY

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Subclassification and matching are often used in empirical studies to adjust for observed covariates; however, they are largely restricted to relatively simple study designs with a binary treatment and less developed for designs with a continuous exposure. Matching with exposure doses is particularly useful in instrumental variable designs and in understanding the dose-response relationships. In this article, we propose two criteria for optimal subclassification based on subclass homogeneity in the context of having a continuous exposure dose, and propose an efficient polynomial-time algorithm that is guaranteed to find an optimal subclassification with respect to one criterion and serves as a 2-approximation algorithm for the other criterion. We discuss how to incorporate dose and use appropriate penalties to control the number of subclasses in the design. Via extensive simulations, we systematically compare our proposed design to optimal non-bipartite pair matching, and demonstrate that combining our proposed subclassification scheme with regression adjustment helps reduce model dependence for parametric causal inference with a continuous dose. We apply the new design and associated randomization-based inferential procedure to study the effect of transesophageal echocardiography (TEE) monitoring during coronary artery bypass graft (CABG) surgery on patients’ post-surgery clinical outcomes using Medicare and Medicaid claims data, and find evidence that TEE monitoring lowers patients’ all-cause 30-day mortality rate.

1. Introduction.

1.1. Application: The effect of TEE monitoring during CABG surgery. Transesophageal echocardiography (henceforth TEE) is an ultrasound-based, cardiac imaging modality often used in cardiac surgeries to monitor patients’ hemodynamics. TEE may potentially improve post-surgery clinical outcomes by facilitating intraoperative surgery decision making and managing complications related to cardiopulmonary bypass (Hahn et al., 2013; Nishimura et al., 2017); indeed, MacKay et al. (2020a) found perioperative TEE use was associated with lower 30-day all-cause mortality among patients undergoing open cardiac valve repair or replacement surgery. Coronary artery bypass graft (henceforth CABG) surgery is the most widely performed surgery in the United States (The Society of Thoracic Surgeons, 2016). Compared to open valve surgery, evidence supporting the use of TEE during isolated CABG surgery is more equivocal: TEE monitoring is classified by American Heart Association/American College of Cardiology (AHA/ACC) guidelines as a Class IIb recommendation, meaning its “usefulness/efficacy is less well established by evidence/opinion”
MacKay et al. (2020b, 2021) proposed to study TEE’s effect on clinical outcomes using providers’ preference for TEE as an instrumental variable (IV).

One challenge in the study design is that the IV-defined exposure, providers’ preference in this case, is continuous. A straightforward strategy to deal with a continuous exposure is to dichotomize it according to some pre-specified dichotomization scheme. Despite its simplicity and popularity, this practice suffers from at least two major drawbacks. First, defining the potential outcome under a dichotomized exposure potentially violates the stable unit treatment value assumption (SUTVA) (Rubin, 1980, 1986). Let \( \tilde{Z} \) denote the continuous exposure and \( Z = 1 \{ \tilde{Z} > c^* \} \) the associated dichotomized version, e.g., \( c^* \) being the median. The potential outcome under \( Z = 1 \) is well-defined only when the potential outcome remains unchanged for all exposure doses \( \tilde{Z} \) exceeding the pre-specified threshold \( c^* \). This is at best an approximation to the complicated reality in most circumstances. Moreover, dichotomizing the continuous exposure inevitably censors the rich information contained in the original dose and prevents researchers from investigating a dose-response relationship. Therefore, we would prefer a study design that preserves the continuous exposure dose (Lopez et al. 2017).

In their original study protocol, MacKay et al. (2020b) embed observational data from Centers for Medicare and Medicaid Services (CMS) into a paired cluster-randomized encouragement experiment. MacKay et al. (2020b) matched hospitals with similar patient population and hospital-level characteristics but distinct preference for TEE using a design technique called optimal non-bipartite pair match (Lu et al., 2001, 2011; Baiocchi et al., 2010, 2012). A non-bipartite matching algorithm is distinct from bipartite matching algorithms suited only for statistical matching and subclassification with a binary treatment (Rosenbaum, 1989, 1991; Stuart, 2010) and matching algorithms based on generalized propensity score (Yang et al., 2016; Lopez et al., 2017; Wu et al., 2018); see Supplementary Material A for a detailed literature review. Figure 1 gives a graphical representation of pair matching in a bipartite and a non-bipartite setting. With a binary treatment, there are well-defined treated and control groups, and there is little ambiguity in the ultimate goal of statistical matching: the matching algorithm aims to “construct” or “design” a matched control group (or comparison group) that resembles the treated group in baseline covariates. On the other hand, with a continuous exposure, there are no pre-defined treated and control groups: in principle, any unit can be matched to any other unit similar in covariates. This structural difference between bipartite and non-bipartite settings makes it more challenging to characterize optimal subclassification and design efficient algorithms in the non-bipartite context.

Fig 1: Left panel: a pair match in a bipartite setting with a binary treatment. Right panel: a pair match in a non-bipartite setting with a many-level or continuous treatment dose.
1.2. Pair matching is not optimal. Full matching is a more flexible subclassification scheme that divides units into non-overlapping matched sets (or subclasses) of size at least, but not necessarily, equal to two. With a binary treatment, Rosenbaum (1991) found:

"[T]here may be no pair matching and no matching with multiple controls that is an optimal subclassification. ... [A] best pair match may be arbitrarily poor compared with the optimal full matching."

These statements remain true in the non-bipartite setting with a continuous dose. To see this, it suffices to consider the following simple example with 6 units \{a, b, c, d, e, f\} and the associated distance matrix

\[
M = \begin{pmatrix}
0 & \epsilon & \epsilon & \omega & \omega & \omega \\
\epsilon & 0 & \epsilon & \omega & \omega & \omega \\
\epsilon & \epsilon & 0 & \omega & \omega & \omega \\
\omega & \omega & \omega & 0 & \epsilon & \epsilon \\
\omega & \omega & \omega & \epsilon & 0 & \epsilon \\
\omega & \omega & \omega & \epsilon & \epsilon & 0 \\
\end{pmatrix}
\]

with \(\epsilon \ll \omega\). The \(ij\)th entry of \(M\) represents a measure of distance, e.g., the Mahalanobis distance of observed covariates, between unit \(i\) and \(j\). An optimal pair match produces the following three matched pairs:

\[\Pi_{\text{pair}} = \{\{a, c\}, \{b, d\}, \{e, f\}\} .\]

On the other hand, consider the following full match:

\[\Pi_{\text{full}} = \{\{a, b, c\}, \{d, e, f\}\} .\]

It is evident that \(\Pi_{\text{full}}\) achieves a better matched-sets homogeneity, which we will carefully define later, compared to \(\Pi_{\text{pair}}\) when \(\epsilon \ll \omega\); see Figure 2 for a transparent graphical representation. Moreover, since \(\omega\) can be arbitrarily larger than \(\epsilon\), \(\Pi_{\text{full}}\) can be arbitrarily better than \(\Pi_{\text{pair}}\) according to any reasonable homogeneity measure. In the most extreme case where \(\omega = \infty\), there exists no admissible pair match exhausting six units; however, there exists a feasible full match, and a good one when \(\epsilon\) is small.

Another concern with pair matching is that it is often not flexible enough to deliver a subclassification that is simultaneously homogeneous in units’ observed covariates and reasonably heterogeneous in units’ exposure doses; in fact, units are often removed in the design stage (Baiocchi et al., 2010, 2012) to achieve both goals. For instance, MacKay et al. (2020b) removed 20% of all hospitals in their matched-pair design using a design device known as “sinks” (Baiocchi et al., 2010). Ideally, we would prefer a design that utilizes all units while maintaining homogeneity in covariates and good separation in exposure doses. Lastly, one
minor issue with pair matching is that, when the number of units is odd, say \(N = 5\), the design necessarily discards one unit to produce two matched pairs.

These limitations of a non-bipartite pair match design and the abundance of observational studies with a continuous or many-level exposure motivate us to study optimal subclassification in the non-bipartite setting.

1.3. Outline: a characterization of optimal non-bipartite subclassification, an algorithm, two simulation studies, and an application. Two subclassification homogeneity measures and optimal subclassification with respect to each measure are defined in Section 2. Section 3 proves a useful relationship between the two homogeneity measures; this relationship suggests that any algorithm that finds a subclassification with respect to one homogeneity measure is automatically a 2-approximation algorithm for the other measure. An efficient, polynomial-time algorithm that finds an optimal subclassification with respect to one homogeneity measure and suitable weights is presented in Section 4. Section 5 discusses how to further incorporate the treatment dose in the design stage, and how to probe the middle ground between an optimal pair match and an optimal subclassification. Two simulation studies, one examining how combining the proposed subclassification scheme with regression adjustment helps reduce bias of the regression estimator, and the other systematically comparing the proposed subclassification method to optimal pair matching, are presented in Section 6 and 7, respectively. We leverage the proposed novel design and conduct randomized-based inference to study the effect of TEE monitoring during CABG surgery on patients’ 30-day all-cause mortality in Section 8. We conclude with a brief discussion in Section 9.

2. Two measures of subclassification homogeneity. Let \(\mathcal{N} = \{1, 2, \ldots, N\}\) denote a set of \(N\) units and \(2^\mathcal{N}\) its power set, i.e., the collection of all subsets of \(\mathcal{N}\). Let \(\Pi = \{\Pi_1, \Pi_2, \ldots, \Pi_K\}\) denote a subclassification (or partition) of these \(N\) units into \(K\) non-overlapping subclasses such that each subclass \(\Pi_k\) consists of \(|\Pi_k| \geq 2\) units, \(\sum_{1 \leq k \leq K} |\Pi_k| = N\), and their union \(\bigcup_{1 \leq k \leq K} \Pi_k\) recovers these \(N\) units. The number of subclasses \(K\) is not fixed a priori. Finally, let \(\mathcal{A}\) be the set of all possible subclassifications. We first develop two notions of subclass homogeneity.

**Definition 2.1 (Average pairwise homogeneity).** Let \(\delta(i, j)\) denote a distance between unit \(i\) and \(j\). Average pairwise homogeneity of subclass \(\Pi_k\), denoted as \(\nu(\Pi_k)\), refers to the following quantity:

\[
\nu(\Pi_k) = \frac{1}{|\Pi_k| \times (|\Pi_k| - 1)} \sum_{i,j \in \Pi_k, i \neq j} \delta(i, j).
\]

According to Definition 2.1, \(\nu(\Pi_k)\) is the average distance of all pairwise comparisons among units in the subclass \(\Pi_k\). For instance, in the TEE/CABG application with a hospital-preference-based instrumental variable exposure, \(\delta(i, j)\) could measure some distance between IV-outcome confounders (e.g., patient composition and hospital characteristics) of hospital \(i\) and \(j\), and \(\nu(\Pi_k)\) would then measure the homogeneity in these IV-outcome confounders of hospitals in the same subclass \(\Pi_k\).

Associated with a subclassification \(\Pi\) and \(\nu(\Pi_k)\) is the following homogeneity measure of \(\Pi\):

\[
\nu(\Pi; W) = \sum_{1 \leq k \leq K} w(\Pi_k) \times \nu(\Pi_k),
\]

where \(W\) is a shorthand for a pre-specified weighting scheme \(w(\cdot) : 2^\mathcal{N} \mapsto \mathbb{R}_{\geq 0}\) that maps each possible subclass \(\Pi_k \in 2^\mathcal{N}\) to a non-negative real number.
Definitions: Let $\nu$ be the homogeneity measure.

**Definition 2.2.** A subclassification $\Pi^\nu_{\text{opt}}$ is said to be optimal with respect to the homogeneity measure $\nu(\Pi; W)$ if

$$\Pi^\nu_{\text{opt}} = \arg\min_{\Pi \in A} \nu(\Pi; W).$$

In full matching with a binary exposure, each subclass consists of either one treated unit and multiple control units or one control unit and multiple treated units, and subclass homogeneity is measured by averaging over all pairwise comparisons between the treated unit and each control unit (or the control unit and each treated unit); see Rosenbaum (1991, Section 3). This structure motivates a second sensible homogeneity measure as follows.

**Definition 2.3 (Star homogeneity).** Let $i^*_k \in \Pi_k$ be a reference unit in subclass $\Pi_k$. Star homogeneity refers to the following quantity:

$$\nu_{\text{star}}(\Pi_k; i^*_k) = \frac{1}{|\Pi_k| - 1} \sum_{j \in \Pi_k, j \neq i^*_k} \delta(i^*_k, j).$$

Unlike $\nu(\Pi_k)$ which averages over all pairwise comparisons, $\nu_{\text{star}}(\Pi_k; i^*_k)$ first picks a reference unit (e.g., the unit with the highest or lowest dose in each subclass; see Section 5.1 for how to enforce this choice), compares all other units to this reference unit, and then averages over such comparisons. In the TEE/CABG application, if the hospital with the highest preference for TEE in the subclass $\Pi_k$ is chosen as the reference unit $i^*_k$, then $\nu_{\text{star}}(\Pi_k; i^*_k)$ measures how close in patient composition and hospital characteristics the other hospitals in the same subclass are compared to this highest-preference hospital.

Associated with a subclassification $\Pi$, the star homogeneity, a vector of reference units $i^* = (i^*_1, \ldots, i^*_K)$, and a weighting scheme $W$ is a second homogeneity measure of $\Pi$:

$$\nu_{\text{star}}(\Pi; i^*, W) = \sum_{1 \leq k \leq K} w(\Pi_k) \times \nu_{\text{star}}(\Pi_k; i^*_k).$$

**Definition 2.4.** A subclassification $\Pi_{\text{opt}}^{\nu_{\text{star}}} = \{\Pi_{\text{opt},1}^{\nu_{\text{star}}}, \ldots, \Pi_{\text{opt},K}^{\nu_{\text{star}}}\}$ with reference units $i_{\text{opt}}^* = (i_{\text{opt},1}^*, \ldots, i_{\text{opt},K}^*)$, $i_{\text{opt},k}^* \in \Pi_{\text{opt},k}^{\nu_{\text{star}}}$ is said to be optimal with respect to the homogeneity measure $\nu_{\text{star}}(\Pi; i^*, W)$ if

$$(\Pi_{\text{opt}}^{\nu_{\text{star}}}, i_{\text{opt}}^*) = \arg\min_{\Pi \in A} \arg\min_{i^*_k \in \Pi_k} \nu_{\text{star}}(\Pi; i^*, W),$$

where minimization is taken over all subclassifications and all possible reference units in each subclass.

**Remark.** In the special case of pair matching, it is easy to check that for all $\Pi_k \in \Pi$ and for all $i^*_k \in \Pi_k$, $\nu_{\text{star}}(\Pi_k; i^*_k) = \nu(\Pi_k)$, i.e., two measures of subclass homogeneity reduce to the same measure. Moreover, under a weighting scheme that assigns the same weight to all matched pairs, we have $\Pi_{\text{opt}}^{\nu_{\text{star}}} = \Pi_{\text{opt}}^{\nu}$ and this optimal solution is precisely returned by an optimal non-bipartite pair matching algorithm (Lu et al., 2001, 2011).

3. Relationship between two optimal solutions. A subclassification $\Pi_{\text{opt}}^{\nu_{\text{star}}}$ is optimal with respect to the homogeneity measure $\nu_{\text{star}}(\cdot)$ and a weighting scheme $W$. A natural question arises as to what can be said about its homogeneity under the other measure $\nu(\cdot)$, and how $\nu(\Pi_{\text{opt}}^{\nu_{\text{star}}}; W)$ compares to the optimal $\nu(\cdot)$ homogeneity under the same weights. This section establishes a revealing relationship between $\nu(\Pi_{\text{opt}}^{\nu_{\text{star}}}; W)$ and $\nu(\Pi_{\text{opt}}^{\nu}; W)$. 
**Lemma 3.1.** Let $\Pi_k$ be a subclass with size $|\Pi_k|$ and $\delta(i, j)$ a distance that satisfies the triangle inequality. We have

$$\min_{i^*_k \in \Pi_k} \nu_{\text{star}}(\Pi_k; i^*_k) \leq \nu(\Pi_k),$$

and

$$\nu(\Pi_k) \leq \frac{2(|\Pi_k| - 1)}{|\Pi_k|} \cdot \nu_{\text{star}}(\Pi_k; i^*_k), \quad \forall i^*_k \in \Pi_k.$$

In particular, when $|\Pi_k| = 2$, we have $\nu_{\text{star}}(\Pi_k; i^*_k) = \nu(\Pi_k), \quad \forall i^*_k \in \Pi_k$.

**Proof.** All proofs in this article are in Supplementary Material B. \qed

Let $\nu^*_{\text{star}}(\Pi_k) := \min_{i \in \Pi_k} \nu_{\text{star}}(\Pi_k; i)$ be the minimum $\nu_{\text{star}}(\cdot)$ homogeneity of a subclass $\Pi_k$ among all reference units $i_k \in \Pi_k$. Define

$$\nu^*_{\text{star}}(\Pi; \mathcal{W}) = \sum_{1 \leq k \leq K} \nu(\Pi_k) \cdot \nu^*_{\text{star}}(\Pi_k).$$

**Corollary 3.2.** For any subclass $\Pi_k$, we have

$$\nu^*_{\text{star}}(\Pi_k) \leq \nu(\Pi_k) \leq \frac{2(|\Pi_k| - 1)}{|\Pi_k|} \cdot \nu^*_{\text{star}}(\Pi_k).$$

Moreover, for any subclassification $\Pi$ and weighting scheme $\mathcal{W}$, we have

$$\nu^*_{\text{star}}(\Pi; \mathcal{W}) \leq \nu(\Pi; \mathcal{W}) < 2\nu^*_{\text{star}}(\Pi; \mathcal{W}).$$

Corollary 3.2 establishes a link between two homogeneity measures $\nu(\Pi; \mathcal{W})$ and $\nu_{\text{star}}(\Pi; \mathcal{W})$: any subclassification $\Pi$ has its $\nu(\Pi; \mathcal{W})$ sandwiched between $\nu^*_{\text{star}}(\Pi; \mathcal{W})$ and $2\nu^*_{\text{star}}(\Pi; \mathcal{W})$. Proposition 3.3 is an important consequence of Corollary 3.2.

**Proposition 3.3.** Let $\Pi^\nu_{\text{opt}}$ be an optimal partition with respect to the homogeneity measure $\nu_{\text{star}}(\cdot)$ and weighting scheme $\mathcal{W}$, and $\Pi^\nu_{\text{opt}}$ optimal with respect to $\nu(\cdot)$ and the same weighting scheme. We have

$$\nu(\Pi^\nu_{\text{opt}}; \mathcal{W}) \leq \nu(\Pi^\nu_{\text{opt}}; \mathcal{W}) < 2\nu(\Pi^\nu_{\text{opt}}; \mathcal{W}).$$

In words, $\Pi^\nu_{\text{opt}}$ is optimal under the homogeneity measure $\nu_{\text{star}}(\cdot)$, and its homogeneity under the other measure $\nu(\cdot)$ is no worse than the optimal homogeneity under $\nu(\cdot)$ by a factor of 2.

In the computer science and operations research literature, an approximation algorithm refers to an algorithm that finds an approximate solution to an optimization problem with a provable guarantee on the distance between the approximate solution and the optimal solution; see Vazirani (2013) and Williamson and Shmoys (2011) for general discussion. A $\rho$-approximation algorithm refers to an approximation algorithm that returns an approximate solution $x^\rho_{\text{approx}}$ whose objective function value $f^\rho_{\text{approx}}$ is no worse than that of the optimal solution $f_{\text{opt}}$ by a factor of $\rho$, i.e.,

$$f_{\text{opt}} \leq f^\rho_{\text{approx}} \leq \rho \times f_{\text{opt}}.$$

**Corollary 3.4.** Let $\Pi^\nu_{\text{opt}}$ and $\Pi^{\nu_{\text{star}}}_{\text{opt}}$ be defined as in Definition 2.2 and Definition 2.4 with respect to the same weighting scheme $\mathcal{W}$. If ALG is an algorithm for finding $\Pi^\nu_{\text{opt}}$, then ALG is also a 2-approximation algorithm for finding $\Pi^{\nu_{\text{star}}}_{\text{opt}}$.

Corollary 3.4 is important and useful because efficient, polynomial-time algorithms exist for finding $\Pi^{\nu_{\text{star}}}_{\text{opt}}$ with respect to suitable weights, as we demonstrate in the next section.
4. An efficient, polynomial-time algorithm.

4.1. Graph, edge cover, and suitable weights. We introduce some useful terminologies from the graph theory to carry forward the discussion. Let $G = (V, E)$ denote a graph with vertex set $V$ and edge set $E$. We use $e = (i, j)$, $i, j \in V$, to denote an edge connecting vertex $i$ and $j$, in which case we say vertex $i$ (and similarly $j$) is incident to edge $e = (i, j)$. A subset of edges $S \subseteq E$ is said to form a star if $S = \{ (i, j_1), (i, j_2), \ldots, (i, j_k) \}$; $i$ is often referred to as the internal node or center of the star, and $\{ j_1, j_2, \ldots, j_k \}$ leaves.

An edge cover of graph $G$ is a subset of edges $F \subseteq E$ such that all vertices in $G$ are incident to at least one edge in $F$. Let $F$ denote the class of all edge covers of graph $G$, and each edge $e = (i, j)$ be associated with a nonnegative cost $c(i, j)$. The cost of an edge cover $F$ is defined to be

\[ \text{COST}(F) = \sum_{(i, j) \in F} c(i, j). \]

Figure 3 gives two examples of an edge cover in the same graph. The cost of the edge cover in the left panel is $11.5$ and that in the right panel is $14$.

![Figure 3: Two edge covers (bold lines) of the same graph. The cost of the edge cover in the left panel is $1 + 2 + 1.5 + 3 + 4 = 11.5$, and that in the right panel is $1 + 3 + 2 + 3 + 1 + 4 = 14$.](image)

Lemma 4.1 states that for a suitable choice of weights, homogeneity measure $\nu_{\text{star}}(\Pi; i^*, \mathcal{W})$ corresponds to the cost of a particular edge cover.

**Lemma 4.1.** Let $\Pi = \{ \Pi_1, \ldots, \Pi_K \}$ be a partition, and $\mathcal{W}_{\text{suit}}$ a weighting scheme that assigns $w(\Pi_k) = |\Pi_k| - 1$ to subclass $\Pi_k$. Then

\[ \nu_{\text{star}}(\Pi; i^*, \mathcal{W}_{\text{suit}}) = \sum_{1 \leq k \leq K} \sum_{j \in \Pi_k, j \neq i_k^*} \delta(i_k^*, j), \]

and $\nu_{\text{star}}(\Pi; i^*, \mathcal{W}_{\text{suit}})$ is equal to the cost of an edge cover with connected components $\{ \Pi_1, \ldots, \Pi_K \}$, each connected component $\Pi_k$ being a star with internal vertex $i_k^*$ and leaves $\{ j \in \Pi_k, j \neq i_k^* \}$, and cost of any edge connecting two nodes $i$ and $j$ being $\delta(i, j)$. 
4.2. A minimum cost edge cover induces an optimal subclassification with respect to suitable weights. A minimum cost edge cover, i.e., the edge cover that attains the minimum cost among all edge covers of \( G \), can be efficiently found in polynomial time (Schrijver, 2003); in fact, the problem of finding a minimum cost edge cover can be reduced to the problem of finding a minimum cost matching in an expanded non-bipartite graph. Moreover, Proposition 4.2 states that a minimum cost edge cover induces an optimal subclassification with respect to the homogeneity measure \( \nu_{\text{star}}(\Pi; i^*, \mathcal{W}^{\text{suit}}) \) when the edge cost is nonnegative.

**Proposition 4.2.** Let \( G = (V, E) \) be a graph and \( c : E \rightarrow \mathbb{R} \geq 0 \) a nonnegative cost function. Then

1. There exists a minimum cost edge cover whose connected components are all stars; call this minimum cost star-tiled edge cover \( F_{\text{star}}^* \).
2. Let the cost function \( c(\cdot) \) of edge \( e = (i, j) \) be the distance \( \delta(i, j) \), then

\[
\text{COST}(F_{\text{star}}^*) = \min_{\Pi \in \mathcal{A}; i^*_k \in \Pi_k, 1 \leq k \leq K} \nu_{\text{star}}(\Pi; i^*, \mathcal{W}^{\text{suit}}).
\]

In other words, \( F_{\text{star}}^* \) induces an optimal subclassification with respect to the homogeneity measure \( \nu_{\text{star}}(\Pi; i^*, \mathcal{W}^{\text{suit}}) \).

4.3. An efficient algorithm that finds minimum cost edge cover. Algorithm 1 transforms the problem of finding a minimum cost edge cover into an optimal non-bipartite matching problem (Schrijver, 2003), the computation complexity of which is \( O(|V|^3) \) in a graph with \( |V| \) vertices. Algorithm 1 returns a minimum cost edge cover \( F^* \); we may further process \( F^* \) as described in the proof of Proposition 4.2 to obtain \( F_{\text{star}}^* \), a minimum cost edge cover consisting of all stars. The complexity of finding a minimum cost edge cover is the same as optimal non-bipartite matching. The algorithm is further illustrated in Supplementary Material D. We will refer to the subclassification scheme induced by \( F_{\text{star}}^* \) as a “non-bipartite full match design.”

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**Algorithm 1:** Finding a minimum cost edge cover for a graph \( G = (V, E) \)

**Input:** A graph \( G = (V, E) \)

1. Create a copy of \( G = (V, E) \) with the same topology and edge cost; denote it as \( G' = (V', E') \).
2. For each \( v \in V \) and its counterpart \( v' \in V' \), add an edge \( (v, v') \); a total of \( |V| \) edges are added.
3. Assign a cost equal to \( 2\mu(v) \) to each edge \( (v, v') \), where \( \mu(v) \) denotes the minimum cost among all edges incident to \( v \in V \).
4. Solve an optimal non-bipartite matching problem in the graph \( G \cup G' \); let \( M^* \) denote this optimal matching.
5. Delete from \( M^* \) any edge in \( E' \); replace any edge of the form \( (v, v') \) in \( M^* \) with an edge \( (v, u) \in E \) such that \( \delta(v, u) = \mu(v) \); denote by \( F^* \) the result.
6. Return the minimum cost edge cover \( F^* \).

5. Additional design considerations.

5.1. Dose caliper. With a binary treatment, there is a distance between each treated unit and each control unit, and this distance unequivocally measures the closeness of the treated and control units in their observed covariates. With a continuous or many-level treatment/encouragement dose, homogeneity in observed covariates is still an important aspect; however, distances in this case may further take into account the treatment/encouragement
dose in order to design matched sets that are homogeneous in observed covariates and well-separated in their exposure doses (Lu et al., 2001).

This is in particular relevant in our TEE/CABG application with an IV-defined continuous exposure. It is widely acknowledged that confidence intervals obtained from weak instruments are often excessively long and non-informative (Imbens and Rosenbaum, 2005). A large encouragement dose, on the other hand, would typically create stronger incentives for units to accept the treatment, increase the compliance rate, and eventually render the statistical inference substantially more powerful (Baiocchi et al., 2010; Heng et al., 2019; Zhang et al., 2021a). For instance, Heng et al. (2019) derived the asymptotic relative efficiency (ARE) of some commonly-used test statistics when testing the same proportional treatment effect model (Small and Rosenbaum, 2008) with two instrumental variables of different strengths. They found that for a weaker IV with compliance rate \( \epsilon_1 \) to achieve the same efficiency as a stronger IV with compliance rate \( \epsilon_2 \) (\( \epsilon_2 \geq \epsilon_1 \)), the weaker IV needs to have a sample size \( (\epsilon_2/\epsilon_1)^2 \) times larger than that of a stronger IV. Analytic results of this kind provide incentives to separate exposure doses in the design stage.

How to pursue this design aspect in a non-bipartite full match? We borrow the idea of a “caliper” from the literature on “caliper matching” (Cochran and Rubin, 1973) and “propensity score caliper” (Rosenbaum and Rubin, 1985). Let \( \delta(i, j) \) measure the distance between observed covariates, and \( Z_i \) and \( Z_j \) the encouragement doses of unit \( i \) and \( j \), respectively. One straightforward way to incorporate the encouragement dose is to define a new distance \( \delta'(i, j) = \delta(i, j) + C \times 1\{|Z_i - Z_j| \leq \tau_0\} \), where \( \tau_0 \) is called a dose caliper and \( C \) a large penalty applied when \( Z_i \) and \( Z_j \) differ by less than or equal to the caliper size. Hence, a large \( C \) would discourage an edge cover from connecting unit \( i \) and \( j \) whenever their doses are within the caliper size. Analogous to a propensity score caliper, a dose caliper may be implemented both as a hard constraint, by setting \( C = \infty \) or equivalently removing edges \( \{e = (i, j) \text{ such that } |Z_i - Z_j| \leq \tau_0\} \), or as a soft constraint by setting \( C \) to a large but finite number (Zhang et al., 2021b, Section 2.3). In Supplementary Material C.1, we illustrate the dose caliper using a simulation study.

A dose caliper facilitates interpreting the chosen reference unit in each subclass. Consider implementing a hard caliper with size \( \tau_0 \). Let \( Z_{i^*_k} \) be the dose of the internal node of a subclass \( \Pi_k \) and \( Z_{\text{leaves},k} = \{Z_j, j \in \Pi_k, j \neq i^*_k\} \) the collection of doses of leaves in \( \Pi_k \). By definition of a hard dose caliper, the dose of the internal node \( i^*_k \) necessarily satisfies

\[
Z_{i^*_k} > Z_j + \tau_0 \quad \text{or} \quad Z_{i^*_k} \leq Z_j - \tau_0,
\]

for all \( Z_j \in Z_{\text{leaves},k} \). In the former case, the internal node corresponds to the unit with the highest dose (and at least \( \tau_0 \) higher in dose than any other unit in the same subclass) and we may view it as a pseudo-treated unit in the subclass; in the latter case, it is one with the lowest dose and can be viewed as a pseudo-control unit. This particular structure, one pseudo-treated and a variable number of pseudo-control units (or one pseudo-control and a variable number of pseudo-treated units) is analogous to that of full matching with a binary exposure (Hansen, 2004; Hansen and Klopfer, 2006); see Figure 4 for an illustration. In the TEE/CABG application, matching with a dose caliper forces each matched set to have one high-preference hospital and a few low-preference hospitals, or one low-preference hospital and a few high-preference hospitals, and comparisons in the health outcomes will be made among high-preference and low-preference hospitals within each formed subclass.

5.2. Incorporating matched-sets-cardinality penalty. In a bipartite full matching, there are two parameters controlling for the maximum number of treated and control units in each matched set, respectively. Options max.controls and min.controls of function fullmatch in the R package optmatch (Hansen and Klopfer, 2006; Hansen, 2007) serve this purpose. For example, setting min.controls = 0.25 would restrict the matched set to have at most 4 treated
Exposure

Treated

Control

Fig 4: Left panel: full match with a binary treatment. Right panel: non-bipartite full match with a dose caliper \( \tau_0 = 2 \). From left to right are \( \Pi_1, \Pi_2, \Pi_3, \) and \( \Pi_4 \). The internal node in each subclass \( \Pi_k \) is either the unit with the highest dose as in \( \Pi_1, \Pi_2, \) and \( \Pi_4 \), or the unit with the lowest dose as in \( \Pi_3 \). The internal node has dose at least \( \tau_0 = 2 \) larger than leaves in the same subclass.

subjects for one control, and \( \text{max.controls} = 4 \) at most 4 controls for one treated; together, they restrict the cardinality of matched sets to be at most \( 4 + 1 = 5 \).

In the context of non-bipartite matching with a continuous dose, we may also want to have some control over the size of subclasses and hence how many subclasses in a subclassification. To this end, we consider adding to a homogeneity measure a proper penalty on the cardinality of subclasses. Let the homogeneity measure be \( \nu_{\text{star}} \), and consider the following modified homogeneity measure:

\[
\nu^{\lambda}_{\text{star}}(\Pi; i^*, W) = \nu_{\text{star}}(\Pi; i^*, W) + \lambda \times \left\{ \sum_{ \Pi_k \in \Pi } |\Pi_k| - 2 \right\}.
\]

**Definition 5.1.** A subclassification \( \Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda} = \{\Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda, 1}, \ldots, \Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda, K}\} \) with reference units \( i^{\text{opt}, \lambda} = (i^{\text{opt}, \lambda, 1}, \ldots, i^{\text{opt}, \lambda, K}) \), \( i^{\text{opt}, \lambda, k} \in \Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda, k} \), is said to be optimal with respect to the homogeneity measure \( \nu^{\lambda}_{\text{star}}(\Pi; i^*, W) \) if

\[
(\Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda}, i^{\text{opt}, \lambda}) = \arg\min_{\Pi \in A} \arg\min_{i^*_k \in \Pi_k, 1 \leq k \leq K} \nu^{\lambda}_{\text{star}}(\Pi; i^*, W)
\]

\[
= \arg\min_{\Pi \in A} \arg\min_{i^*_k \in \Pi_k, 1 \leq k \leq K} \left\{ \nu_{\text{star}}(\Pi; i^*, W) + \lambda \times \left\{ \sum_{ \Pi_k \in \Pi } |\Pi_k| - 2 \right\} \right\}.
\]

When \( \lambda = 0 \), this definition reduces to Definition 2.4; when \( \lambda = \infty \), \( \Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda = \infty} \) reduces to the solution to an optimal non-bipartite pair match because \( |\Pi_k| - 2 = 0 \) for matched pairs. As \( \lambda \) increases from 0 to \( \infty \), we explore the middle ground between a subclassification that is optimal with respect to \( \nu_{\text{star}}(\Pi; i^*, W) \) and an optimal non-bipartite pair matching.

With suitable weights \( W_{\text{suit}} \), we can find \( \Pi^{\nu_{\text{star}}}_{\text{opt}, \lambda} \) efficiently via a slightly modified version of Algorithm 1; in fact, it suffices to modify Step 3 in Algorithm 1 as follows:

3*. Assign a cost equal to \( 2\mu(v) + 2\lambda \) to each edge \( (v, v') \), where \( \mu(v) \) denotes the minimum cost among all edges incident to \( v \in V \).

Let \( F^{\lambda}_{\text{opt}} \) denote the output from the modified Algorithm 1. Following a similar argument in the proof of Proposition 4.2, we may further process \( F^{\lambda}_{\text{opt}} \) to obtain \( F^{\ast}_{\text{opt}, \lambda} \), an edge cover.
6. Simulation studies I: non-bipartite matching as a preprocessing step to remove bias in parametric causal inference with a continuous treatment dose.

6.1. Goal and structure. It is widely acknowledged that with a binary treatment, combining statistical matching with regression adjustment renders analysis more robust to model misspecification and helps remove bias in treatment effect estimation (Rubin, 1973, 1979); hence, many authors advocate using statistical matching as a nonparametric preprocessing step before parametric causal inference (Ho et al., 2007; Stuart, 2010). The primary goal of this section is to assess if combining the non-bipartite full matching developed in this article and regression adjustment helps reduce model dependence and remove bias in the continuous treatment setting.

Our simulation studies in this section can be compactly represented as a $2 \times 2 \times 2 \times 3 \times 2 \times 4$ factorial study with the following factors:

**Factor 1:** treatment effect estimator: $\hat{\beta}_{\text{reg}}$ and $\hat{\beta}_{\text{reg, match}}$.

**Factor 2:** dimension of covariates, $d$: 5 and 10.

**Factor 3:** sample size, $n$: 500 and 2000.

**Factor 4:** treatment dose model: a multi-level treatment $Z \sim \text{Uniform}\{-2, -1, 0, 1, 2\}$; two continuous treatments $Z \sim \text{Uniform}\{1 - \sqrt{3}, 1 + \sqrt{3}\}$ and $Z \sim \text{Exponential}(1)$ so that the continuous treatment $Z$ has mean 1 and variance 1.

**Factor 5:** observed covariates distribution: $X \sim \text{Multivariate Normal}(\mu, \Sigma)$, with $\mu = (cZ, 0, \ldots, 0)^T$ and $\Sigma = \left( \begin{array}{ccc} 4 & 0 & 0 \\ 0 & I_{d-1} & 0 \\ 0 & 0 & 1 \end{array} \right)$ with $c = -2$ and 2.

**Factor 6:** response model: $Y | X, Z \sim \text{Normal}(\{1 \{\exp\{aX_1 + bX_2\} \leq 100\} + \beta Z + 1, 1)$ with $(a, b) = (-0.5, 0.5), (0.5, -0.5), (0.5, 0.5)$, and $(0.5, -0.5)$, and $\beta = 1$.

Factor 1 defines the procedures, and Factor 2 through 6 define the data generating processes. In particular, we considered three different models for a non-binary treatment, and closely followed Rubin (1979) and Zhang et al. (2021b) in specifying the data generating processes for the observed covariates $X$ and the response surfaces $Y | X, Z$; see Rubin (1979, Section 3) and Zhang et al. (2021b, Section 5.1) for some rationals behind these data generating processes. While both Rubin (1979) and Zhang et al. (2021b) considered an additive effect for a binary treatment, we considered an effect proportional to the magnitude of the treatment dose. Two treatment effect estimators being considered here are $\hat{\beta}_{\text{reg}}$, the naive regression adjustment estimator, and $\hat{\beta}_{\text{reg, match}}$, the regression adjustment estimator with a fixed effect for each matched set after non-bipartite full matching. We calculate the bias, standard error, and mean squared error of both estimators under each of the 96 data generating processes defined by Factor 2 through 6.

6.2. Simulation results. Using non-bipartite matching as a preprocessing step followed by regression adjustment seems to help reduce bias and mean squared error in 92/96 circumstances. Supplementary Material C.3 summarizes the bias and mean squared error of $\hat{\beta}_{\text{reg}}$ and $\hat{\beta}_{\text{reg, match}}$ under each data generating process. Figure 5 visualizes the gain in bias reduction under a wide range of data-generating processes. We also observe that for a fixed $d$, the gain from using statistical matching as a nonparametric preprocessing step seems to increase as $n$ increases, which is as expected because with a larger $n/d$ ratio, matched sets formed by
non-bipartite matching tend to be more homogeneous; on the other hand, when the model is misspecified, a larger sample size does not seem to help remove bias of a naive regression estimator. For instance, when \( d = 5 \), \( Z \sim \text{Exponential}(1) \), \((c,a,b) = (-2, 0.5, 0.5)\), \((2, -0.5, -0.5)\), \((2, -0.5, 0.5)\), \((2, 0.5, -0.5)\), \((2, 0.5, 0.5)\).

Consistent with the binary treatment case studied in Rubin (1973, 1979) and discussed in Ho et al. (2007), our simulation results seem to suggest that using non-bipartite matching as a nonparametric preprocessing step before regression analysis with a continuous treatment dose helps reduce model dependence and remove some bias.

7. Simulation studies II: comparing non-bipartite full matching to pair matching.

7.1. Goal and structure. In this section, we systematically compare non-bipartite full matching with non-bipartite pair matching. We consider a continuous dose \( Z \sim \text{Uniform}[0, 1] \), \( d = 5 \), and the following factors that define a data generating process:

**Factor 1:** sample size, \( n: 500 \) and 2000.

**Factor 2:** observed covariates distribution: \( X \sim \text{Multivariate Normal}(\mu, \Sigma) \), with \( \mu = (cZ, 0, \ldots, 0)^T \) and \( \Sigma = \begin{pmatrix} 2^2 & 0 \\ 0 & I_{d-1} \end{pmatrix} \) with \( c = -2, -1, 1, \) and 2.

We compare the non-bipartite full matching procedure as in Algorithm 1 and the optimal non-bipartite pair matching procedure in Lu et al. (2001, 2011). This is the third factor:

**Factor 3:** matching procedure: non-bipartite full matching \( \mathcal{M}_{\text{nbp, full}} \) and optimal non-bipartite pair matching \( \mathcal{M}_{\text{nbp, pair}} \).
For both matching procedures, we consider the following distance:

$$\delta(i, j) = \text{Mahalanobis distance}(i, j) + C \times 1\{|Z_i - Z_j| \leq \tau_0\}.$$  

As discussed in Section 5.1, $$\delta(i, j)$$ may incorporate the treatment/encouragement dose $$Z$$ by adjusting the dose caliper $$\tau_0$$ and letting $$C$$ be a large penalty. Throughout the simulations, we let $$C = 100,000$$ and $$\tau_0$$ be the fourth factor:

**Factor 4:** dose caliper size, $$\tau_0$$: 0, 0.1, 0.2, 0.3, and 0.4.

To conclude, Factor 1 and 2 define the $$2 \times 4 = 8$$ data generating processes and Factor 3 and 4 define the $$2 \times 5 = 10$$ procedures to be studied.

7.2. Measurements of success. For a subclassification $$\Pi = \{\Pi_1, \ldots, \Pi_K\}$$, we compute $$\nu(\Pi_k)$$, the average Mahalanobis distance among all $$(1/2) \times |\Pi_k| \times (|\Pi_k| - 1)$$ pairwise comparisons in each subclass $$\Pi_k$$, and then report the 25th, 50th (median), 75th, and 90th empirical quantiles of $$\{\nu(\Pi_k), k = 1, \ldots, K\}$$. We also report two weighted averages of $$\{\nu(\Pi_k), k = 1, \ldots, K\}$$.

The weighting scheme $$\nu^{\text{const}}$$ assigns an equal weight to each matched set, regardless of its size, which corresponds to letting $$w(\Pi_k) \propto 1$$ in Definition 2.2; denote by HM1 this first measure. The second weighting scheme $$\nu^{\text{ad}}$$ assigns $$w(\Pi_k) \propto |\Pi_k| - 1$$ as described in Lemma 4.1. Denote by HM2 this second measure.

Next, for each subclass, we compute $$\nu^{*}_{\text{stat}}(\Pi_k)$$, the minimum $$\nu^{*}_{\text{stat}}(\Pi_k; i^*_k)$$ (based on the Mahalanobis distance) among all $$i^*_k \in \Pi_k$$ as defined in Definition 2.4. We also report two weighted averages of $$\{\nu^{*}_{\text{stat}}(\Pi_k), k = 1, \ldots, K\}$$: one with the weighting scheme $$\nu^{\text{const}}$$ and the other $$\nu^{\text{ad}}$$. Denote by HM3 and HM4 these two measures. Smaller values of HM1 through HM4 indicate better matched-sets homogeneity. Note that all four measures reduce to the same measure when the subclassification $$\Pi$$ consists of only matched pairs.

We also consider a measurement of overall balance. In each subclass $$\Pi_k$$, let $$\bar{X}_{i,k,\text{high}}$$ denote the average value of the $$i$$th observed covariate $$X_i$$ of units with treatment dose greater than or equal to the median treatment dose, and $$\bar{X}_{i,k,\text{low}}$$ that of units with treatment dose below the median. For instance, if the subclass consists of 5 units, each with the first observed covariate $$X_i \{1, 5, 2, 1, 1.5, 2\}$$ and treatment dose $$\{0.1, 0.2, 0.3, 0.4, 0.5\}$$, then $$\bar{X}_{i,k,\text{high}} = (1 + 1.5 + 2)/3 = 1.5$$ and $$\bar{X}_{i,k,\text{low}} = (1.5 + 2)/2 = 1.75$$ for this subclass. Let $$d_i = \sum_{\Pi_k \in \Pi} \bar{X}_{i,k,\text{high}} - \sum_{\Pi_k \in \Pi} \bar{X}_{i,k,\text{low}}$$ denote the difference in means of the $$i$$th covariate, and define $$SS = \sum_{i=1}^d d_i^2$$ to be the sum of the squared differences over all $$d = 5$$ or 10 observed covariates. In an ideal randomization experiment where treatment dose assignment is indeed randomized, distributions of observed covariates in the high and low dose groups are identical, and $$SS$$ is small. Hence, smaller $$SS$$ values signal better overall balance.

For each subclass $$\Pi_k$$, we further calculate $$\mu(\Pi_k)$$, the average absolute “internal-node-minus-leaf” difference in $$Z$$ as defined in Section 5.1. We report the minimum, 25th, 50th (median), and 75th empirical quantiles of $$\{\mu(\Pi_k), k = 1, \ldots, K\}$$. Finally, we report the number of matched set $$K$$, and the average pairwise Mahalanobis distance and balance measure $$SS$$ before matching.

7.3. Simulation results. Figure 6 summarizes the simulation results for 9 selected measures when $$d = 5$$, $$n = 2000$$, and $$c = -2$$. Simulation results for the other cases are qualitatively similar, and details can be found in Supplementary Material C.4.

We observe three consistent trends. First, when the dose caliper $$\tau_0 = 0$$ and the only goal of statistical matching is homogeneity in covariates $$X$$, non-bipartite full matching and non-bipartite pair matching produce similar matched sets and have very similar performance with respect to all measures. Second, we observe that the number of matched sets in non-bipartite full matching decreases as $$\tau_0$$ increases. Third, for both full matching and pair matching, all
Fig 6: Simulation results: Comparing the non-bipartite pair match and non-bipartite full match when $d = 5$, $n = 2000$, and $c = -2$. The average pairwise Mahalanobis distance before matching is 10 and SS before matching is 1.010. The number of matched pairs is each non-bipartite pair match is 1000, and the average number of matched sets in a non-bipartite full match is 969, 964, 951, 918, and 842 when the dose caliper size increases from 0 to 0.4.

Four homogeneity measures HM1 to HM4 deteriorate as the dose caliper $\tau_0$ increases; however, non-bipartite full matching is capable of striking a better balance between homogeneity in covariates and heterogeneity in doses compared to non-bipartite pair matching. In fact, when $d = 5$, $n = 2000$, $c = -2$, and $\tau_0 \geq 0.3$, non-bipartite full matching outperforms non-bipartite pair matching simultaneously in all 8 measurements of matched-sets homogeneity (4 quantiles of $\nu(\Pi_k)$ and HM1 through HM4), 4 measurements of heterogeneity in treatment/encouragement doses (4 quantiles of $\mu(\Pi_k)$), and the overall balance SS. For instance, when $\tau_0 = 0.4$, the median within-matched-sets Mahalanobis distance (i.e., 50th of $\nu(\Pi_k)$) is equal to 0.898 for pair matching and 0.756 for full matching, and the overall balance measurement SS is 0.389 for pair matching and as small as 0.105 for full matching.

Finally, Figure 7 helps visualize the difference between an optimal non-bipartite pair match structure and an optimal non-bipartite full match structure using a small simulated dataset with $d = 3$, $n = 50$, and $c = -2$. To facilitate data visualization, we do a principle component analysis (PCA) and plot each unit’s dose against its first principle component (PC1). Top left panel and top right panel depict the match structure of the optimal non-bipartite pair match and optimal non-bipartite full match, both with $\tau_0 = 0.3$. Two bottom panels eliminate matched pairs that are identical in two matches and focus on the match structure that are different in two matches. It is evident that the full match (corresponding to the bottom right panel) tends to connect units that are more different in the dose (i.e.,
larger difference in the y-axis) but similar in the first PC (i.e., small difference in the x-axis), compare to the pair match (corresponding to the bottom left panel).

Fig 7: Visualizing the difference between a non-bipartite pair match and a non-bipartite full match. We generated a small dataset with $d = 3$, $n = 50$, and $c = -2$. Top left panel: optimal non-bipartite pair match with $\tau_0 = 0.3$. Top right panel: optimal non-bipartite full match with $\tau_0 = 0.3$. Two bottom panels eliminate matched pairs that are identical in two matches and focus on the match structure that differ in two matches. In this simulated dataset, $HM_1 = 1.46$ for pair match and 1.19 for full match; average internal-node-minus-leaf difference in the dose is 0.48 for pair match and 0.51 for full match.

8. The effect of TEE monitoring during CABG surgery on 30-day mortality.

8.1. Data and study design. We obtained data on patients undergoing isolated CABG surgery from Centers for Medicare and Medicaid Services (CMS). We identified patients’ hospitals using the National Provider Identifier (NPI) numbers and obtained hospitals’ characteristics data from the American Hospital Association Survey. Patient-level data were merged to hospitals’ characteristics data using their unique NPI numbers. The study cohort consisted of all fee-for-service Medicare beneficiaries with a Part A (hospitalization) Medicare claim for isolated CABG surgery. Following MacKay et al. (2020b), we excluded (1) beneficiaries enrolled under managed care and not fee-for-service, (2) beneficiaries with less than six months of continuous enrollment in Medicare prior to the index admission for CABG surgery, (3) beneficiaries with age < 65 years, (4) beneficiaries without a cardiovascular or cardiac surgery-related Diagnosis Related Group (DRG) codes, (5) beneficiaries with a neurologic or stroke diagnosis as indicated by an ICD-9-cm code within the six months prior to the index admission or a stroke diagnosis with a “present on admission” (POA) indicator.

We follow MacKay et al. (2020b, 2021) and consider a cluster-level, instrumental variable analysis where each hospital defines a natural cluster and each hospital’s preference for TEE usage (defined as the fraction of CABG surgeries using TEE monitoring) is considered a valid instrumental variable after controlling for patients’ composition including
average age, percentage of male patients, percentage of white patients, percentage of elective
CABG surgeries, and percentage of patients having each of the following important comorbid
conditions: arrhythmia, diabetes, congestive heart failure (CHF), hypertension, obesity, pul-
monary diseases, and renal diseases, and hospital’s characteristics including total hospitals
beds, teaching status, presence of any cardiac intensive care unit, total number of full-time
registered nurses, and annual cardiac surgical volume. Our goal in the design stage is to di-
vide 1,217 hospitals into subclasses with good subclass homogeneity, overall balance, and
good separation in their encouragement doses.

8.2. Matched samples. The first 4 columns of Table 1 summarize the patient composi-
tion and hospital characteristics of hospitals whose preference for using TEE during CABG
surgery is above the median preference and those below the median preference. We observe a
systematic difference between the “above median” and “below median” groups before match-
ing: many standardized differences (defined as the difference in means divided by the stan-
ard deviation) are above 0.1 and two-sample Kolmogorov–Smirnov tests suggest that the
distribution of 6 covariates, including annual cardiac surgical volume, hospital beds, etc, are
statistically different at 0.01 level.

We then applied the developed non-bipartite full matching algorithm to the data using a
dose-incorporating distance \( \delta'(i,j) = \delta(i,j) + C \times 1\{\lvert Z_i - Z_j \rvert \leq \tau_0 \} \) with \( \delta(i,j) \) being the
Mahalanobis distance between 16 observed pretreatment covariates, \( C = 100,000 \) a large
penalty, \( \lambda = 0 \), and various choices of the dose caliper size \( \tau_0 \). We followed the advice in
Rubin (2007) and conducted the design without access to the outcome data in order to assure
the objectivity of the design.

In particular, non-bipartite full matching with \( \tau_0 = 0.15 \) divides these 1,217 hospitals into
543 matched pairs, 39 matched sets of size 3, 1 of size 4, and 2 of size 5. To get a sense of the
balance after matching, we collect hospitals with higher doses in each matched set (including
the one with median dose in a matched set with odd cardinality) and refer to them as the “high
dose” group. The “high dose” group thus consists of \( 1 \times 543 + 2 \times 39 + 2 \times 1 + 3 \times 1 = 629 \)
hospitals. Similarly, we define the other hospitals as “low dose” hospitals. In an ideal (yet
unattainable) randomized controlled trial where the dose assignment within each matched
set is indeed randomized, the “high dose” and “low dose” groups would have similar distri-
butions of patient composition and hospital characteristics. Non-bipartite full matching seems
to replicate this ideal experimental benchmark, as seen from the last 4 columns in Table 1:
the “high dose” and “low dose” groups have similar covariate distributions and in fact no
Kolmogorov-Smirnov test is significant at 0.1 level. Moreover, before matching, the median
Mahalanobis distance among all 1,217 hospitals is 14.14, while the median “average pair-
wise Mahalanobis distance” is as small as 1.54 after matching. Matched sets also have a good
separation in their encouragement doses: the average internal-node-minus-leaf difference in
the encouragement dose is 0.46 among all matched sets. In Supplementary Material E, we
further report the covariate balance of non-bipartite full matches under other choices of \( \tau_0 \).
We conduct inference with matched samples under \( \tau_0 = 0.15 \) because among all matches sat-
ifying the stringent balance requirements (all standardized differences less than 0.1 and no
Kolmogorov-Smirnov tests significant at 0.05 level), the match with \( \tau_0 = 0.15 \) produces the
best separation in the encouragement doses. Compared to the original matched-pair design
that discards approximately 20% of hospitals, the full match design achieves similar balance
while preserving all study units, and the outcome analysis based on the full match design is
likely to have better generalizability (Cole and Stuart, 2010).

8.3. Statistical inference: notation, potential outcomes, and a cluster-level sharp null hy-
pothesis. Does using TEE during CABG surgery reduce patients’ 30-day mortality? In this
section, we generalize the cluster-level, non-bipartite pair match set-up considered in Zhang et al. (2021a) to the current full match setting, and discuss how to test Fisher’s sharp null hypothesis of no treatment effect under the new design.

Suppose we have formed $K$ matched sets, indexed by $k = 1, \ldots, K$, each with $n_k$ hospitals, indexed by $j = 1, \ldots, n_k$, so that index $kj$ uniquely identifies one hospital and there are a total of $N = \sum_{k=1}^{K} n_k$ hospitals in total. Each hospital is associated with hospital-level covariates $x_{kj}$ and a hospital-level continuous instrumental variable (or encouragement dose) $Z_{kj}$. There are $N_{kj}$ patients in each hospital $kj$, indexed by $i = 1, \ldots, N_{kj}$, so that index $kji$ uniquely identifies one patient. Each patient is associated with a treatment indicator $D_{kji}^{obs}$, outcome of interest $Y_{kji}^{obs}$, and individual-level covariates $x_{kji}$. In our application, we have formed 585 matched sets so $K = 585$; $n_k$ is the number of hospitals in each matched set so $n_k = 2, 3, 4, 5$ in our design; hospital-level instrumental variable $Z_{kj} \in [0, 1]$ is hospital’s preference for TEE during CABG surgery; $N_{kj}$ is the number of patients undergoing CABG surgery in hospital $kj$; $D_{kj}^{0}$ is a binary indicator equal to 1 if patient $kji$ receives TEE monitoring and 0 otherwise; $R_{kji}$ is patient $kji$’s 30-day mortality status; finally, $x_{kj}$ describes hospital $kj$’s characteristics and $x_{kji}$ patient $kji$’s characteristics. Following Zhang et al. (2021a), we assume that after controlling for patient composition and hospital characteristics, preference for TEE usage is a valid cluster-level instrumental variable.

Let $D_{kj}(Z_{kj} = z_{kj})$ denote the potential treatment received of patient $kji$ when the hospital-level IV $Z_{kj}$ is set to $z_{kj}$, and $D_{kj}(Z_{kj})$ is a shorthand for $(D_{kj1}(Z_{kj}), \ldots, D_{kJ_{N_{kj}}}(Z_{kj}))$. Let $R_{kji}(Z_{kj} = z_{kj}, D_{kj}(Z_{kj}) = d_{kj})$ denote unit $kji$’s potential outcome under $Z_{kj} = z_{kj}$ and $D_{kj}(Z_{kj}) = d_{kj}$. Under exclusion restriction, we have $R_{kji}(Z_{kj}, D_{kj}(Z_{kj})) = R_{kji}(D_{kj}(Z_{kj})$). Finally, let $Z_k^{obs} = \{Z_{k1}^{obs}, \ldots, Z_{k_{n_k}}^{obs}\}$ denote the collection of IV doses in matched set $k$.

| Covariate | Before Matching | After Matching |
|-----------|-----------------|---------------|
|           | Below Median    | Above Median  | Diff. | K-S Test | Low Dose | High Dose |
|           | (n = 608)       | (n = 609)     |       | $P$-Value | (n = 588) | (n = 629) |
| Mean age, yrs | 75.10          | 75.29         | -0.11 | < 0.01   | 75.18    | 75.21     |
| Male, %    | 0.67           | 0.69          | -0.15 | 0.02     | 0.68     | 0.68      |
| White, %   | 0.85           | 0.85          | 0.01  | 0.05     | 0.85     | 0.85      |
| Male, %    | 0.46           | 0.47          | -0.05 | 0.32     | 0.47     | 0.47      |
| Diabetes, %| 0.17           | 0.17          | -0.02 | 0.42     | 0.17     | 0.17      |
| Renal diseases, % | 0.09 | 0.09 | -0.07 | 0.07 | 0.09 | 0.09 |
| Arrhythmia, % | 0.11 | 0.12 | -0.10 | < 0.01 | 0.11 | 0.11 |
| Crohn's disease, % | 0.29 | 0.30 | 0.05 | 0.32 | 0.30 | 0.29 |
| Obesity, % | 0.06           | 0.06          | -0.06 | 0.03     | 0.06     | 0.06      |
| Pulmonary diseases, % | 0.02 | 0.02 | -0.12 | < 0.01 | 0.02 | 0.02 |
| Cardiac ICU, yes/no | 0.70 | 0.72 | -0.04 | 0.99 | 0.71 | 0.71 |

Table 1: Covariate balance before and after non-bipartite full matching with a dose-incorporating Mahalanobis distance and $\tau_0 = 0.15$. 1, 217 hospitals are divided into 543 matched pairs, 39 matched sets of size 3, 1 of size 4, and 2 of size 5. After matching, no two-sample Kolmogorov-Smirnov test comparing the covariate distributions in the “high-dose” and “low-dose” groups is significant at 0.05 level.
A cluster-level Fisher’s sharp null hypothesis states that

\[
H_{0,\text{sharp}} : \ \sum_{i=1}^{N_{kj}} R_{kji} (D_{kj}(Z_{kj} = z)) - \sum_{i=1}^{N_{kj}} R_{kji} (D_{kj}(Z_{kj} = z')) = \beta \left( \sum_{i=1}^{N_{kj}} D_{kji}(Z_{kj} = z) - \sum_{i=1}^{N_{kj}} D_{kji}(Z_{kj} = z') \right)
\]

(6)

for all \( k, j \), and \( z, z' \in Z^\text{obs}_k \) such that \( z' < z \). The null hypothesis \( H_{0,\text{sharp}} \) generalizes the proportional treatment effect model in Small and Rosenbaum (2008) and Zhang et al. (2021a), and states that the mean difference of the hospital-aggregate potential outcomes when comparing any pair of two IV doses \( z, z' \in Z^\text{obs}_k \) is proportional to the mean difference of the potential treatment received under IV dose \( z \) and \( z' \) with structural parameter \( \beta \); see Baiocchi et al. (2010) and Zhang et al. (2021a) for other causal null hypotheses that may be of interest. We consider testing the causal null hypothesis \( \beta = 0 \), i.e., TEE received during CABG has no effect whatsoever on patients’ 30-day mortality, against \( \beta < 0 \), i.e., TEE received during CABG lowers patients’ 30-day mortality.

8.4. Randomization-based inference. There are three key ingredients to perform a Fisher-style randomization-based test: a sharp null hypothesis, a randomized treatment assignment scheme, and a test statistic (Rosenbaum, 2002, 2010; Ding, Feller and Miratrix, 2016).

1. Sharp null hypothesis: \( H_{0,\text{sharp}} \) is sharp null hypothesis that allows us to impute the potential aggregate-outcome of cluster \( kj \) under any IV doses \( z \in Z^\text{obs}_k \), see, e.g., Zhang et al. (2021a, Section 3.1).

2. Randomized treatment dose assignment: In a typical matched-pair design with \( I \) matched pairs, there are a total of \( 2^I \) possible randomization configurations. In a full match design, within each matched set of \( n_k \) hospitals, there are \( n_k! \) many IV dose assignments, each with equal probability; therefore, there are a total of \( \prod_{k=1}^{K} n_k! \) randomizations induced by a full match design. Let \( Z \) denote this collection of all randomizations and \( z \in Z \) one realization.

3. Test statistic: In principle, any test statistic \( t(Z, R(Z)) \) that depends on the treatment dose assignment \( Z \) and the potential outcomes only via potential outcomes’ dependence on \( Z \) can be combined with the randomization scheme to deliver a valid test for \( H_{0,\text{sharp}} \); see, e.g., Ding, Feller and Miratrix (2016). With a binary treatment, a commonly-used test statistic for a full match design is the rank-sum test; see Rosenbaum (2002, 2004); Heng et al. (2021). We modify the rank-sum test statistic to reflect the continuous dose. Let \( Z = \{Z_{11}^\text{obs}, \ldots, Z_{K_{ns}}^\text{obs}\} \), \( R_{kj} = N_{kj}^{-1} \left\{ \sum_{i=1}^{N_{kj}} R_{kji}^\text{obs} \right\} \), and \( R = \{R_{11}^\text{obs}, \ldots, R_{K_{ns}}^\text{obs}\} \). Consider the following double rank sum statistic:

\[
T_{\text{double rank}} = \frac{1}{N^2} \sum_{k=1}^{K} \sum_{j=1}^{n_k} q_1(Z_{kj}^\text{obs} \mid Z) \times q_2(R_{kj}^\text{obs} \mid R),
\]

(7)

where \( q_1(Z_{kj}^\text{obs} \mid Z) \) is the rank of \( Z_{kj}^\text{obs} \) among all doses \( Z \), and \( q_2(R_{kj}^\text{obs} \mid R) \) the rank of \( R_{kj}^\text{obs} \) among all the responses.

Researchers first impute all missing potential outcomes under \( H_{0,\text{sharp}} \) and then enumerate all \( |Z| = \prod_{k=1}^{K} n_k! \) possible dose assignments. For each enumerated \( Z' = z \in Z \), calculate the corresponding \( R' \) under \( Z' \) and the test statistic \( T'_{\text{double rank}} \). The distribution of \( T'_{\text{double rank}} \)
is then the exact null distribution of the test statistic $T_{\text{double rank}}$ under $H_{0,\text{sharp}}$ and conditional on the matched samples. By comparing $T_{\text{double rank}}$ to this exact null distribution, the exact $p$-value is obtained. In practice, researchers may sample with replacement from $Z$ and report a Monte Carlo $p$-value.

8.5. Results. For 585 matched sets we formed in the design stage, we generated the reference distribution using 1,000,000 samples from all possible $2^{543} \times 3^{39} \times 4^{11} \times 5^2$ randomizations; see Figure 8. We calculated $T_{\text{double rank}} = 294.27$; hence, one-sided $p$-value is 0.020 and the null hypothesis $H_{0,\text{sharp}}$ is rejected at 0.05 level in favor of the alternative hypothesis that $\beta < 0$, i.e., using TEE during CABG surgery lowers patients’ 30-day mortality rate.

Fig 8: Reference distribution and the test statistic evaluated at the observed data. Exact one-sided $p$-value is 0.020.

9. Discussion. In this paper we have systematically studied statistical matching and subclassification with a many-level or continuous exposure dose. We propose two optimality criteria for subclassification, each based on a natural subclass homogeneity measure. We characterize the relationship between these two criteria and leverage this relationship to develop an efficient polynomial-time algorithm that finds a subclassification that is guaranteed to be optimal with respect to one criterion and near-optimal with respect to the other criterion.

Our developed algorithm also allows empirical users to control separation in the exposure dose and cardinalities of formed subclasses. There are three tuning parameters involved in our flexible algorithm: dose caliper size $\tau_0$, dose caliper penalty $C$, and cardinality penalty $\lambda$. In many practical situations, we recommend setting $\tau_0$ to a minimum dose difference that would yield a meaningful difference in the potential outcomes, and $C = \infty$ (or a very large number) to enforce dose separation specified by $\tau_0$. This way to specify tuning parameters $(\tau_0, C)$ is similar to setting propensity score calipers in a bipartite match; see, e.g., Zhang et al. (2021b, Section 2.3). We recommend setting the cardinality penalty $\lambda = 0$ by default to deliver an optimal full match; in the case where some subclasses have too many study units, $\lambda$ should be gradually increased.
Our extensive simulations suggest that non-bipartite matching combined with regression adjustment helps remove bias in parametric causal inference; thus, we would recommend routinely using non-bipartite matching as a pre-processing step, as advocated by many researchers (Rubin, 1973, 1979; Ho et al., 2007; Stuart, 2010) in a binary treatment setting. Moreover, we found non-bipartite full match is advantageous over non-bipartite pair match in separating the treatment/encouragement doses and maintaining good subclass homogeneity and overall balance; therefore, the new design may be particularly useful in instrumental variable studies where separation of the IVs (or encouragement doses) would render outcome analysis much more efficient (Baiocchi et al., 2010).

SUPPLEMENTARY MATERIAL

Proofs, additional simulation studies, and more details on the application
Supplementary Material A contains a detailed literature review on bipartite and non-bipartite matching. Supplementary Material B.1-B.5 contain proofs of Lemma 3.1, Lemma 4.1, Corollary 3.2, Proposition 3.3 and 4.2. Supplementary Material B.6 proves that the output from the modified Algorithm 1 $F^*_{\text{star,} \lambda}$ induces a subclassification that is optimal with respect to $\nu_{\text{star}}^{\lambda}(\Pi; i^*, W_{\text{suit}})$. Supplementary Material C.1 and C.2 illustrate a dose caliper and choice of $\lambda$ using simulation studies. Supplementary Materials C.3 and C.4 provide additional simulation results. Supplementary Material D illustrates how to find a minimum-cost edge cover. Supplementary Material E provides further details on statistical matching in the application with different choices of the tuning parameter $\tau_0$.

nbpfull_0.1.0.zip

R code implementing the proposed non-bipartite full match algorithm.

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