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Local Alignment of Differential Causal Networks: A Methodological Framework for Detecting Recurrent Rewiring Motifs Across Multiple Systems

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Abstract

Differential Causal Networks (DCNs) were introduced to represent changes between two causal networks inferred under different conditions. In their original use, however, DCNs remain pairwise objects: each differential graph summarizes rewiring within a single system, while common differential structures shared across many systems remain implicit. We introduce a methodological framework for the *local alignment* of DCNs aimed at detecting *recurrent rewiring motifs*, that is, small directed differential subnetworks that reappear across multiple systems under the same contrast. The proposed framework transforms each system-specific comparison into a signed directed differential graph, preserves both edge direction and change type, and searches for approximate local correspondences rather than enforcing a full-network mapping. The method consists of four steps: construction of signed DCNs, extraction of differential seeds, pairwise local alignment by seed-and-extend, and progressive multiple alignment to build consensus motifs. We define a score that combines node compatibility, differential-edge conservation, directional consistency, and recurrence support, and we complement the alignment procedure with null-model testing and robustness analysis. The result is a collection of consensus local differential modules ranked by recurrence, confidence, and statistical significance. In this formulation, DCNs become comparable units in a higher-order analysis whose goal is not merely to describe pairwise causal change, but to identify the same local rewiring logic reused across multiple systems.

Keywords: local alignment; causal networks; biological networks

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1. Introduction

Causal networks provide a directed representation of dependency structure and are increasingly used to move from purely associative descriptions to mechanistic hypotheses about how changes propagate in complex systems. In this context, Differential Causal Networks (DCNs) offer a natural extension of differential network analysis by focusing on changes in *directed* edges rather than on changes in undirected association alone. A DCN is obtained by comparing two causal networks inferred under two conditions and retaining only the edges that differ between them [1–3].

This pairwise formulation is useful when the objective is to describe rewiring within a single system. However, when several systems are available, a more ambitious comparative question arises: *do different systems exhibit the same local pattern of causal change?* In other words, can one discover a small directed differential subnetwork that recurs across multiple system-specific DCNs under the same experimental or observational contrast? This question cannot be answered by inspecting each DCN independently, because recurrence is inherently a multi-network property.

The present manuscript addresses this methodological problem by proposing a framework for *local alignment of DCNs*. The term *local alignment* is used deliberately. Global network alignment

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attempts to match complete networks or very large fractions of them. In contrast, local alignment searches for compact, highly conserved subnetworks and is therefore better suited to identify recurring modules when whole-network similarity is neither expected nor required [**?**]. For differential causal analysis, this distinction is crucial: recurrent rewiring is likely to appear as a local motif rather than as full-system correspondence.

The central idea of the framework is to regard each DCN as a *rewiring map*. Similarity between two rewiring maps is then defined not by the preservation of ordinary interaction structure, but by the preservation of *differential* structure: a local region in one system is aligned to a local region in another if both exhibit compatible gains, losses, or reversals of directed causal edges. This makes the problem distinct from classical network alignment and motivates a dedicated formulation that explicitly preserves edge direction, differential sign, and recurrence across multiple systems.

To this end, we make four contributions. First, we define a unified signed representation of DCNs that encodes gained, lost, and reversed causal relations within a single directed labeled graph. Second, we formulate pairwise local alignment of DCNs as a score-driven search for matching differential subnetworks. Third, we extend the pairwise procedure to a progressive multiple-alignment setting that returns consensus rewiring motifs together with their support across systems. Fourth, we introduce a significance and robustness layer based on degree- and label-preserving null models as well as edge-stability estimates inherited from causal discovery.

The resulting manuscript is intentionally methodological. It does not include application-specific biological interpretation. Instead, it establishes the theoretical language, the graph representation, the optimization target, and the algorithmic pipeline needed to transform DCNs from isolated pairwise summaries into a comparative framework for identifying recurrent local rewiring motifs across many systems.

2. Preliminaries: Causal Networks and Differential Causal Networks

Let $\mathcal{S} = \{S_1, S_2, \ldots, S_m\}$ denote a collection of systems observed under the same contrast between two conditions, denoted by A and B. For each system S_ℓ, causal discovery produces two directed causal networks

$$C_\ell^{(A)} = (V_\ell, E_\ell^{(A)}), \qquad C_\ell^{(B)} = (V_\ell, E_\ell^{(B)}), \tag{1}$$

where V_ℓ is the node set and $E_\ell^{(A)}, E_\ell^{(B)} \subseteq V_\ell \times V_\ell$ are directed edge sets.

A causal edge $(u, v) \in E_\ell^{(A)}$ indicates that the state of node u is interpreted as a direct causal parent of node v under condition A. The same interpretation holds under condition B. The method used to infer each causal network is external to the alignment framework: any causal-discovery algorithm can be employed, provided that it returns a directed graph together with optional confidence information on edges.

Definition 1 (Differential Causal Network)**.** *Given two causal networks $C_\ell^{(A)}$ and $C_\ell^{(B)}$ on the same node set V_ℓ, a Differential Causal Network for system S_ℓ is a graph that represents the directed edges whose presence or direction differs between the two conditions.*

Existing DCN formulations can be described in three equivalent views:

(i) a one-sided difference $E_\ell^{(B)} \setminus E_\ell^{(A)}$ collecting edges gained under condition B;
(ii) the opposite one-sided difference $E_\ell^{(A)} \setminus E_\ell^{(B)}$ collecting edges lost under condition B;
(iii) a symmetric difference collecting all edges that belong to exactly one of the two networks.

These three views are useful descriptively, but the alignment task requires a unified graph object in which all types of rewiring can be handled jointly. This motivates the signed differential representation introduced in the next section.

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3. Signed Representation of DCNs

For each system S_ℓ, let $A_\ell^{(A)}$ and $A_\ell^{(B)}$ be the adjacency matrices of $C_\ell^{(A)}$ and $C_\ell^{(B)}$, respectively. We define the signed differential matrix

$$\Delta_\ell = A_\ell^{(B)} - A_\ell^{(A)}. \tag{2}$$

If the networks are unweighted, each entry satisfies $\Delta_\ell(i,j) \in \{-1,0,1\}$, with the interpretation

$$\Delta_\ell(i,j) = \begin{cases} 1 & \text{if } i \to j \text{ is present in } C_\ell^{(B)} \text{ but not in } C_\ell^{(A)}, \\ -1 & \text{if } i \to j \text{ is present in } C_\ell^{(A)} \text{ but not in } C_\ell^{(B)}, \\ 0 & \text{otherwise.} \end{cases} \tag{3}$$

Definition 2 (Signed Differential Causal Network). *The signed DCN associated with system S_ℓ is the directed labeled graph*

$$D_\ell = (V_\ell, E_\ell, \lambda_\ell, w_\ell), \tag{4}$$

where

$$E_\ell = \{(i,j) \in V_\ell \times V_\ell : \Delta_\ell(i,j) \neq 0\}, \tag{5}$$

$\lambda_\ell(i,j) = \Delta_\ell(i,j)$ is the differential label, and $w_\ell(i,j) \in [0,1]$ is an optional confidence score attached to the differential edge.

The label $\lambda_\ell(i,j) = 1$ denotes a gained edge, while $\lambda_\ell(i,j) = -1$ denotes a lost edge. Edge reversals are represented by a pair of opposite signed entries. For example, if $i \to j$ is present in $C_\ell^{(A)}$ and $j \to i$ is present in $C_\ell^{(B)}$, then the reversal is encoded by

$$\Delta_\ell(i,j) = -1, \qquad \Delta_\ell(j,i) = 1. \tag{6}$$

Thus gains, losses, and reversals are expressed in a single object without introducing separate graphs.

This representation is particularly convenient for local alignment because it turns each system-specific comparison into a directed graph whose edges carry the information that matters for recurrence: the existence of a change, its direction, and its type.

4. Local Alignment of two DCNs

We now consider two signed DCNs,

$$D_p = (V_p, E_p, \lambda_p, w_p), \qquad D_q = (V_q, E_q, \lambda_q, w_q). \tag{7}$$

The objective is to detect small connected differential subgraphs that can be regarded as instances of the same rewiring motif.

4.1. Motif Model

Definition 3 (Local rewiring motif). *A local rewiring motif is a connected directed labeled graph*

$$M = (U, F, \lambda_M), \tag{8}$$

where U is a finite motif node set, $F \subseteq U \times U$ is a directed edge set, and $\lambda_M : F \to \{-1,1\}$ assigns a differential sign to each motif edge.

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An occurrence of M in D_p is an injective mapping $\pi_p : U \to V_p$ such that each motif edge is mapped to a differential edge with matching sign:

$$(u,v) \in F \implies (\pi_p(u), \pi_p(v)) \in E_p \quad \text{and} \quad \lambda_M(u,v) = \lambda_p\big(\pi_p(u), \pi_p(v)\big). \tag{9}$$

The same definition applies to D_q through a mapping π_q.

In practice, exact matching is often too restrictive. We therefore consider approximate alignment, in which missing edges, incompatible labels, and unmatched nodes are allowed but penalized.

4.2. Node Correspondence

The pairwise alignment framework accommodates two scenarios.

Shared-node scenario.

All systems are defined on the same set of labeled nodes, so alignment is performed directly between identically named nodes. This is the simplest setting and often arises when all DCNs are inferred over the same measured variables.

Heterogeneous-node scenario.

Different systems can have different node sets. In this case, a node-compatibility function

$$\sigma_{pq} : V_p \times V_q \to [0,1] \tag{10}$$

is introduced to quantify whether two nodes are admissible matches. The value of σ_{pq} may combine prior correspondence information, node annotations, local topological descriptors, graph embeddings, or causal-role summaries.

4.3. Alignment Score

A local alignment consists of two connected induced differential subgraphs $H_p \subseteq D_p$ and $H_q \subseteq D_q$ together with a partial injective mapping

$$\phi : V(H_p) \to V(H_q). \tag{11}$$

We score an alignment by combining four ingredients:

$$\mathrm{Score}(H_p, H_q, \phi) = \alpha\, \mathrm{NC}(\phi) + \beta\, \mathrm{EC}(\phi) + \gamma\, \mathrm{LC}(\phi) + \delta\, \mathrm{WC}(\phi) - \eta\, \mathrm{Gap}(\phi), \tag{12}$$

where:

- $\mathrm{NC}(\phi)$ is the *node compatibility* term;
- $\mathrm{EC}(\phi)$ is the *edge conservation* term;
- $\mathrm{LC}(\phi)$ is the *label and direction consistency* term;
- $\mathrm{WC}(\phi)$ is an optional *edge-confidence consistency* term;
- $\mathrm{Gap}(\phi)$ penalizes unmatched nodes, missing edges, and conflicts.

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A concrete instantiation is

$$\mathrm{NC}(\phi) = \frac{1}{|\mathrm{Dom}(\phi)|} \sum_{u \in \mathrm{Dom}(\phi)} \sigma_{pq}(u, \phi(u)), \tag{13}$$

$$\mathrm{EC}(\phi) = \frac{1}{|\mathcal{P}_\phi|} \sum_{(u,v) \in \mathcal{P}_\phi} \mathbf{1}\Big[(u,v) \in E_p \wedge (\phi(u), \phi(v)) \in E_q\Big], \tag{14}$$

$$\mathrm{LC}(\phi) = \frac{1}{|\mathcal{P}_\phi|} \sum_{(u,v) \in \mathcal{P}_\phi} \mathbf{1}\Big[\lambda_p(u,v) = \lambda_q(\phi(u), \phi(v))\Big], \tag{15}$$

$$\mathrm{WC}(\phi) = \frac{1}{|\mathcal{P}_\phi|} \sum_{(u,v) \in \mathcal{P}_\phi} \min\Big\{w_p(u,v), w_q(\phi(u), \phi(v))\Big\}, \tag{16}$$

where $\mathcal{P}_\phi$ denotes the set of ordered node pairs whose endpoints are both matched by ϕ.

The separation between edge conservation and label consistency is essential. Two subnetworks may have the same topology but encode different rewiring logic if the corresponding edges carry different signs or incompatible directions. For DCN alignment, topological similarity alone is therefore insufficient.

4.4. Seed Generation and Local Extension

Exact optimization of Equation (12) is computationally prohibitive because the search is closely related to the maximum common subgraph and subgraph isomorphism problems. We therefore adopt a heuristic seed-and-extend strategy.

First, each DCN is filtered to remove low-confidence differential edges. Second, all connected signed directed graphlets up to a small size k_0 are enumerated. Each graphlet is converted into a canonical code that preserves edge direction and differential sign. Matching or near-matching graphlets in the two DCNs are used as seeds.

Each seed is then expanded iteratively by considering neighboring nodes and edges whose addition maximizes the marginal increase in the alignment score. To avoid early commitment to a single extension path, a beam of the top b partial alignments is maintained. Expansion stops when no candidate extension improves the score by at least a user-defined threshold τ.

5. Multiple Local Alignment Across Many Systems

Pairwise local alignment reveals whether two systems share a local rewiring pattern. Our main goal, however, is to identify motifs that recur across many systems. Let

$$\mathcal{D} = \{D_1, D_2, \ldots, D_m\} \tag{17}$$

denote the collection of signed DCNs.

5.1. Recurrent Motif Definition

Definition 4 (Recurrent rewiring motif). *A local rewiring motif M is recurrent in the collection $\mathcal{D}$ if there exists a subset of systems*

$$I_M \subseteq \{1, 2, \ldots, m\} \tag{18}$$

with $|I_M| \geq q$, for some minimum support threshold q, such that each D_ℓ with $\ell \in I_M$ contains an exact or approximate occurrence of M.

The set I_M is called the *support set* of the motif. Its cardinality,

$$\mathrm{supp}(M) = |I_M|, \tag{19}$$

measures recurrence across systems.

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5.2. Progressive Multiple Alignment

Direct simultaneous optimization over all DCNs is usually intractable. We therefore employ a progressive strategy inspired by multiple-alignment methods.

Step 1: pairwise similarity estimation.

For each pair (D_p, D_q), we compute a similarity score based on seed overlap, signed graphlet similarity, or the best pairwise local alignment score.

Step 2: guide tree construction.

The pairwise similarity matrix is converted into a guide tree over systems using hierarchical clustering.

Step 3: progressive alignment.

The two most similar DCNs are aligned first, producing an initial consensus motif or consensus alignment object. The remaining systems are then incorporated one by one according to the guide tree by aligning each new DCN against the current consensus.

Step 4: motif consolidation.

Consensus motifs that overlap substantially in node columns and signed directed edge structure are merged, and their support sets are updated.

5.3. Consensus Representation

A multiple local alignment is represented by a consensus object

$$\mathcal{C} = (\mathcal{U}, \mathcal{F}, \Lambda, \Pi), \tag{20}$$

where $\mathcal{U}$ is a set of alignment columns, $\mathcal{F}$ is a set of directed consensus edges, Λ stores the empirical label distribution for each consensus edge, and Π is the family of projection maps from the consensus object to each motif occurrence.

For each consensus edge $e \in \mathcal{F}$, we record its empirical support

$$\rho(e) = \frac{1}{r} \sum_{t=1}^{r} \mathbf{1}\{e \text{ is instantiated in occurrence } t\}, \tag{21}$$

where r is the number of aligned occurrences. Likewise, the consensus sign can be represented either by majority vote or by the full empirical distribution over $\{-1, 1\}$.

This representation yields a compact summary of a recurrent differential module together with its variability across systems. The output is therefore not a single rigid subgraph, but a consensus rewiring motif endowed with support statistics.

6. Scoring, Significance and Robustness

6.1. Recurrence-Aware Motif Ranking

To rank motifs after multiple alignment, we define a recurrence-aware score

$$\mathrm{RScore}(M) = \mu\, \overline{\mathrm{Score}}(M) + \nu\, \frac{\mathrm{supp}(M)}{m} + \xi\, \mathrm{Coh}(M) - \zeta\, \mathrm{Var}(M), \tag{22}$$

where:

- $\overline{\mathrm{Score}}(M)$ is the average pairwise or consensus alignment score across occurrences;
- $\mathrm{supp}(M)/m$ is the normalized support;
- $\mathrm{Coh}(M)$ measures within-motif coherence of signs, directions, and node correspondences;
- $\mathrm{Var}(M)$ penalizes motif instability across systems.

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This formulation ensures that a motif is favored not only because it appears often, but also because it appears in a coherent manner.

6.2. Null Models and Statistical Significance

Observed recurrence may arise by chance if the signed DCNs are sparse, highly structured, or degree-skewed. For this reason, each candidate motif is evaluated against a null model. For every system-specific DCN D_ℓ, we generate randomized signed differential graphs that preserve:

(a) the number of nodes,
(b) the in-degree and out-degree distributions,
(c) the total number of positive and negative differential edges,
(d) optionally, the distribution of edge-confidence values.

The complete alignment pipeline is then rerun on randomized collections

$$\mathcal{D}^{*(1)}, \mathcal{D}^{*(2)}, \ldots, \mathcal{D}^{*(B)}. \tag{23}$$

For an observed motif M, an empirical p-value is computed as

$$p(M) = \frac{1 + \#\{b : \mathrm{RScore}(M_b^*) \geq \mathrm{RScore}(M)\}}{1 + B}, \tag{24}$$

where M_b^* denotes the best null motif found in the b-th randomized replicate under the same motif-size regime. Multiple-testing correction can be applied across the final motif set using false-discovery-rate control.

6.3. Robustness to Upstream Causal Uncertainty

DCNs inherit uncertainty from the causal-discovery stage. Consequently, recurrence across systems should not be accepted unless the corresponding differential edges are themselves sufficiently stable within each system. Let

$$\pi_\ell(i, j) \in [0, 1] \tag{25}$$

denote the estimated stability of differential edge (i, j) in system S_ℓ, obtained for instance by bootstrap resampling, repeated causal discovery, or posterior edge probability.

These stability values can be used in two ways. First, unstable differential edges can be removed before alignment. Second, the confidence term $\mathrm{WC}(\phi)$ in Equation (12) can be replaced by a stability-aware term. In this way, motif recurrence is required to be compatible with both *between-system conservation* and *within-system reliability*.

7. Algorithmic Workflow and Complexity

7.1. Workflow

The full pipeline is summarized in Algorithm 1.

7.2. Complexity Analysis

Let $n_\ell = |V_\ell|$ and $e_\ell = |E_\ell|$ denote the number of nodes and differential edges of system S_ℓ. For simplicity, consider the average values $\bar{n}$ and $\bar{e}$ across systems.

Signed DCN construction.

If the two causal adjacency matrices are available explicitly, building D_ℓ requires $O(n_\ell^2)$ time in the dense case or $O(e_\ell^{(A)} + e_\ell^{(B)})$ time in sparse form.

Seed enumeration.

Enumerating all connected graphlets up to size k_0 is exponential in k_0 but practical when k_0 is small and fixed. With bounded k_0, the cost is polynomial in $\bar{e}$.

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Algorithm 1 Local multiple alignment of Differential Causal Networks

Require: Causal network pairs $\{(C_\ell^{(A)}, C_\ell^{(B)})\}_{\ell=1}^{m}$, edge-confidence information, parameters (k_0, b, τ, q)
Ensure: Ranked set of recurrent local rewiring motifs

```
for ℓ = 1 to m do
    Build signed DCN D_ℓ from C_ℓ^(A) and C_ℓ^(B)
    Filter low-confidence differential edges
    Enumerate connected signed directed seeds up to size k_0
end for
for all pairs (p, q) with p < q do
    Match compatible seeds between D_p and D_q
    Run seed-and-extend local alignment with beam width b
    Store best pairwise alignments and pairwise similarity score
end for
Build a guide tree from the pairwise similarity matrix
Initialize consensus motifs from the strongest pairwise alignments
for all systems according to the guide tree order do
    Align the current DCN to existing consensus motifs
    Update support, consensus labels, and confidence statistics
end for
Merge highly overlapping consensus motifs
Score and rank motifs by recurrence-aware score
Estimate empirical significance using randomized signed DCNs
Return statistically supported recurrent motifs
```

Pairwise local alignment.

Let s_{pq} be the number of compatible seeds for a pair (D_p, D_q). If beam width is b and each expansion explores at most Δ candidate extensions for at most h steps, then the heuristic extension stage costs approximately

$$O(s_{pq}\, b\, h\, \Delta). \tag{26}$$

Across all pairs, the total pairwise cost is

$$O\left(\sum_{p<q} s_{pq}\, b\, h\, \Delta\right). \tag{27}$$

Multiple alignment.

Given K candidate motifs after the pairwise stage, progressive incorporation of the remaining systems scales approximately with the cost of aligning one DCN to one consensus motif times the number of candidate motifs retained. In practice, this stage is manageable if aggressive seed filtering and motif pruning are applied.

Null-model assessment.

If B randomized collections are generated, significance estimation increases runtime by a factor of approximately $B + 1$. This step is embarrassingly parallel and can therefore be distributed efficiently.

Overall, the framework is heuristic rather than exact. Its computational feasibility depends on controlling the search space through confidence filtering, small seed size, beam-search truncation, and post hoc motif consolidation. This is appropriate because the target problem combines elements of graph matching, subgraph isomorphism, and multiple alignment, all of which are computationally demanding in their exact forms.

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8. Discussion

The methodology introduced here reinterprets Differential Causal Networks as objects that can themselves be compared, aligned, and summarized across many systems. This shift is conceptually important. Traditional DCN analysis answers the question "what changes between condition A and condition B in one system?" The proposed framework answers a different question: "which local causal changes recur across many systems under the same contrast?" The latter is the natural setting for discovering common rewiring logic.

The emphasis on local rather than global alignment is not merely algorithmic convenience. It reflects the expectation that complex systems rarely share full-network differential correspondence, whereas they may reuse compact causal modules or motifs. By preserving edge direction and differential sign, the proposed formulation ensures that recurrence is assessed at the level of *rewiring semantics*, not just graph topology. This is the main reason why a dedicated DCN-alignment framework is needed instead of a direct reuse of ordinary network-alignment tools.

The framework is intentionally modular. Different causal-discovery procedures can be used upstream; different node-similarity functions can be integrated in heterogeneous settings; and different significance models can be substituted downstream. The core contribution is therefore not a single hard-coded algorithm, but a coherent methodology for converting collections of pairwise causal differences into a dictionary of recurrent local differential motifs.

Several methodological extensions are possible. One may replace heuristic beam search with integer programming or constraint-based search for small motifs, incorporate temporal ordering when systems are sampled along trajectories, or define multiscale motifs that interpolate between graphlets and larger differential modules. Another direction is to embed the alignment problem in a probabilistic latent-variable model in which the recurrent motif is treated as an unobserved template generating noisy system-specific occurrences.

In summary, local alignment provides the missing comparative layer for Differential Causal Networks. Once DCNs are represented as signed directed rewiring maps, one can search not only for edges that differ within a system, but also for the same local differential pattern that reappears across systems. This is the methodological basis for a systematic study of recurrent causal rewiring.

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