Beyond pairwise network similarity: exploring Mediation and Suppression between networks

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Abstract

Network similarity measures quantify how and when two networks are symmetrically related, including measures of statistical association such as pairwise distance or other correlation measures between networks or between the layers of a multiplex network, but neither can directly unveil whether there are hidden confounding network factors nor can they estimate when such correlation is underpinned by a causal relation. In this work we extend this pairwise conceptual framework to triplets of networks and quantify how and when a network is related to a second network (of the same number of nodes) directly or via the indirect mediation or interaction with a third network. Accordingly, we develop a simple and intuitive set-theoretic approach to quantify mediation and suppression between networks. We validate our theory with synthetic models and further apply it to triplets (multiplex) of real-world networks, unveiling mediation and suppression effects which emerge when considering different modes of interaction in online social networks and different routes of information processing in the nervous system.

1 Introduction

Networks are usually seen as a parsimonious model to describe the backbone architecture of complex systems [1]. Accordingly, comparing different systems boils down to comparing their architecture, leading to the notion of network similarity measure [2, 3, 4, 5, 6, 7, 8]. In graph theory, two graphs are isomorphic if there exists a vertex permutation which maps one network into the other, naturally leading to a binary (and not very useful in real-world systems) notion of similarity. More useful approaches proceed by projecting networks into a suite of properties summarised in some vector $\mathbf{p}$ (e.g. degree distribution, centrality vectors, eigenspectra, etc.) and, subsequently constructing a similarity metric $\mathcal{D}$ by which two networks A and B are close in the space spanned by $\mathbf{p}$ if $\mathcal{D}(A, B) = ||\mathbf{p}_A - \mathbf{p}_B||$ is "small". Other ideas include the formalisation of graph kernels [2], comparing networks by comparing the statistics of random walks running over them [9, 10], or using statistical approaches such as estimating topological correlations between networks [11]. While in all these approaches we typically have $\mathcal{D}(A, B) = \mathcal{D}(B, A)$, i.e. a symmetrical relation, in many cases this undirected relation is hiding an actual direction (whether causal or not). As an example, consider social networks. The different layers in which the set of contacts of an individual (i.e., 'its social network') are typically correlated: my friends offline tend to be also friends on Facebook. However, such relation is directional: when a new link –i.e, a new social relationship– is created, then it is likely that such a link will be replicated within my online social network too (Facebook, Instagram), but it is less likely to observe a quantitatively similar effect when the direction of influence is inverted. So the offline and the online social network of a person are probably similar, but such similarity has a direction. Furthermore, in many cases such influence is not direct (not causal). Sometimes, there is a hidden network $\mathcal{C}$ that indeed confounds or mediates the relation between $\mathcal{A}$ and $\mathcal{B}$. For instance, the Facebook and Instagram networks of a certain individual are correlated not because there is a direct, causal relationship between them, but because both these networks are indeed related to the actual (offline) social network of the person.

In this work we are interested in understanding and disambiguating when the relation between two networks $\mathcal{A}$ and $\mathcal{B}$ (where for instance $\mathcal{A}\ r\ \mathcal{B}$ if $\mathcal{D}(\mathcal{A},\mathcal{B}) < \epsilon$) is a direct one, and when it is underpinned by the hidden interaction with a third network $\mathcal{C}$. We address these questions building on terminology from mediation analysis, a statistical framework centered on the notion of "causal paths", and mainly used in epidemiology and psychometrics [16, 15]. The aim of mediation analysis is to clarify the nature of the relationship between two variables $\mathcal{X}$ and $\mathcal{Y}$, by elucidating the role of a third hypothetical variable $\mathcal{Z}$. These roles can include *mediation*, when $\mathcal{Z}$ conveys the information from $\mathcal{X}$ to $\mathcal{Y}$ and/or vice versa [14], and *suppressor*, where $\mathcal{Z}$ increases the predictive validity of $\mathcal{X}$ in predicting $\mathcal{Y}$ or vice versa [17]. We introduce a set-theoretical approach where concepts such as network mediation or network suppression emerge naturally.

We benchmark our theory with simple generative models and then apply it to a range of empirical networks, where we unveil and discuss the concomitant roles of mediation and suppression.

2 Results

2.1 Theoretical setup

Let $\mathcal{A},\mathcal{B},\mathcal{C}$ be three unweighted networks with adjacency matrices $\mathbf{A},\mathbf{B},\mathbf{C}$, all with the same node set and respective edge sets a, b and c (i.e. they can also be identified with the layers of a multiplex network). Let us define the network-Jaccard index of two networks $\mathrm{NJ}(\mathcal{A}, B)$ as the Jaccard index over their edge sets

$$\mathrm{NJ}(\mathcal{A},\mathcal{B}) := J(a,b) = \frac{|a \cap b|}{|a \cup b|}. \tag{1}$$

$\mathrm{NJ}(\mathcal{A},\mathcal{B})$ is a similarity metric, and a distance can be easily defined as $d(\mathcal{A},\mathcal{B}) = 1 - \mathrm{NJ}(\mathcal{A},\mathcal{B})$. This quantity alone can be used to initially establish if two networks are related. Regardless of the fact that such a relation is effectively undirected or otherwise is causal (influence), in order to explore whether such relation is underpinned by a third network $\mathcal{C}$ we need to quantify the effect of conditioning such relation on $\mathcal{C}$ (in the sense of causal mediation analysis [14]). Let us then define the partial network-Jaccard index $\mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C})$ of two networks $\mathcal{A},\mathcal{B}$ conditioned on a third one $\mathcal{C}$ as the Jaccard index over the edge subsets of $\mathcal{A}$ and $\mathcal{B}$ formed by those edges which are absent in $\mathcal{C}$:

$$\mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C}) = \frac{|(a \cap b) \setminus c|}{|(a \cup b) \setminus c|}. \tag{2}$$

Let us see intuitively the effect of conditioning with respect to $\mathcal{C}$ in this way. Suppose initially that $\mathcal{C}$ is totally independent from $\mathcal{A}$ and $\mathcal{B}$. Then we may expect that the Jaccard index, on average, will be the same if evaluated just on the links which are absent in $\mathcal{C}$, so $\mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C}) \approx \mathrm{NJ}(\mathcal{A},\mathcal{B})$. Suppose on the other hand that $\mathcal{A}$ is influencing $\mathcal{B}$ indirectly, with the mediation of $\mathcal{C}$. Then, intuitively, removing the links of $\mathcal{C}$ would effectively push the partial Jaccard index to zero. A similar scenario takes place if $\mathcal{A}$ and $\mathcal{B}$ are indirectly related through direct relation to a confounding factor $\mathcal{C}$. Finally, $\mathcal{C}$ could be suppressing the influence of $\mathcal{A}$ in $\mathcal{B}$. For example, imagine that $\mathcal{B}$ somewhat depends on whether $\mathcal{A}$ and $\mathcal{C}$ interact synergistically, e.g. if links in $\mathcal{C}$ are more likely to occur if they are in one network but not on the other (probabilistic XOR gate); then removing the links of $\mathcal{C}$ will enhance the partial Jaccard index.
To distinguish these three scenarios, we define the Jaccard net difference

$$\Delta[\mathcal{A},\mathcal{B};\mathcal{C}] := \Delta = \mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C}) - \mathrm{NJ}(\mathcal{A},\mathcal{B}). \tag{3}$$

Intuitively, if $\mathcal{C}$ is independent of the relation between $\mathcal{A}$ and $\mathcal{B}$ then $\Delta \approx 0$, if it mediates or confounds such relation then $\Delta < 0$, and if it acts as a suppressor then $\Delta > 0$.
In what follows we construct simple generative models of independent, mediated and suppressor interactions, detailed as algorithms, we prove that these correctly generate these three types of trivariate relations, and depict numerical simulations of the outcome for finite networks.

2.2 Independency

A simple generative model of independency is given by three independent, Erdős-Rényi-type models, where in each of the networks each possible link independently occurs with probability p, see Algorithm 1. The following theorem can be proved.

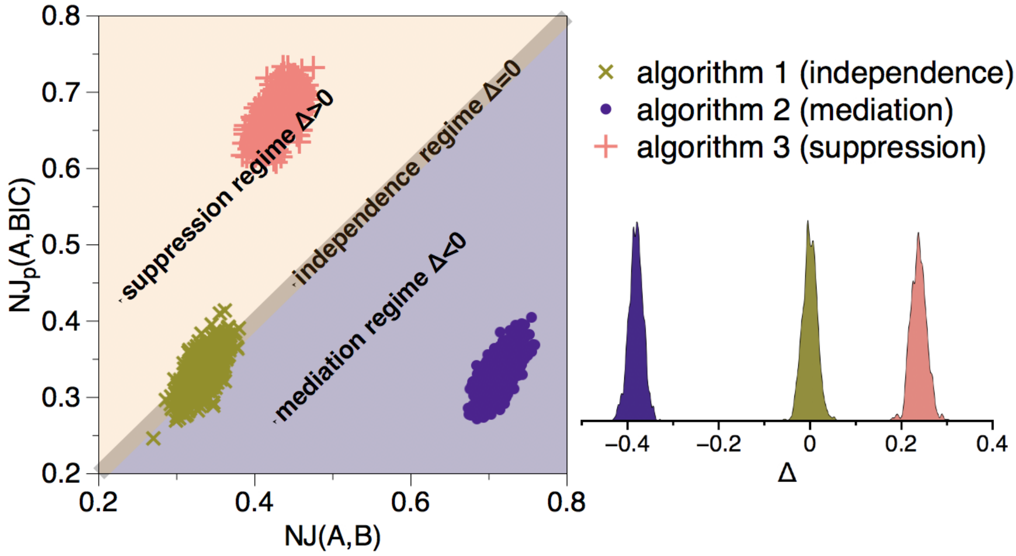

Figure 1: **Pure models of independency, mediation and suppression.** We plot the partial Network-Jaccard index $\mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C})$ vs the Network-Jaccard index $\mathrm{NJ}(\mathcal{A},\mathcal{B})$ of networks $\mathcal{A}$ and $\mathcal{B}$ conditioned on a third network $\mathcal{C}$, calculated on 1000 realizations of triplets of networks of $N = 50$ nodes wired such that $\mathcal{C}$ plays no effect (green crosses), plays a mediating effect (violet dots) or a suppression effect (red crosses) in the relation between $\mathcal{A}$ and $\mathcal{B}$. These interactions are constructed using the generative models described in Algorithms 1, 2 and 3 ($p = 0.5$ in every case, and $q = 1$). For completeness, we also depict the histograms $P(\Delta)$ of Jaccard net differences Δ, which certify that these algorithms generate networks where $\mathcal{C}$ play an independent role ($\Delta \approx 0$), a mediating role ($\Delta < 0$) or a suppressing role ($\Delta > 0$).

Algorithm 1 UNCORRELATED()

Input: p, N
Output: 3 Erdős-Rényi adjacency matrices $\mathbf{A}, \mathbf{B}, \mathbf{C}$ which are uncorrelated ($\Delta \approx 0$)

```
A ← 0
B ← 0
C ← 0
for i = 1 to N − 1 do
    for j = i + 1 to N do
        if RAND < p then A_ij, A_ji ← 1
        if RAND < p then B_ij, B_ji ← 1
        if RAND < p then C_ij, C_ji ← 1
return A,B,C
```

Theorem 2.1. *Let* $\mathbf{A}$, $\mathbf{B}$ *and* $\mathbf{C}$ *be as in Algorithm 1. Then for large networks* $\mathbb{E}(\Delta) = 0$ *and the expected values of* $NJ_p(\mathcal{A},\mathcal{B};\mathcal{C})$ *and* $NJ(\mathcal{A},\mathcal{B})$ *are equal to* $p/(2-p)$.

The proof of this theorem is given in the Supplementary Methods 1. We conclude that, on average, NJ_p and NJ are nearly equal for uncorrelated networks generated in this way, as partialization with respect to an independent network $\mathcal{C}$ does not have any effect. In Fig.1 we illustrate this case for finite networks with $N = 50$ nodes and $p = 0.5$, finding that indeed $\Delta \approx 0$ and that $\mathrm{NJ}_p(\mathcal{A},\mathcal{B};\mathcal{C}) \approx \mathrm{NJ}(\mathcal{A},\mathcal{B}) \approx 1/3$, in good agreement with the theorem.

2.3 Mediation

Suppose now that $\mathcal{A}$ and $\mathcal{B}$ are both dependent on $\mathcal{C}$, i.e. such that if there is a link in $\mathcal{C}$, then there is a link in $\mathcal{A}$ and $\mathcal{B}$ (see Fig.2 for an illustration of such case, and Algorithm 2 for a formal recipe of this generative model).
This describes a situation where $\mathcal{C}$ mediates the relation between $\mathcal{A}$ and $\mathcal{B}$ (or, alternatively, $\mathcal{C}$ is confounding that relation). Partializing with respect to $\mathcal{C}$ removes the dependence between $\mathcal{A}$ and $\mathcal{B}$ due to

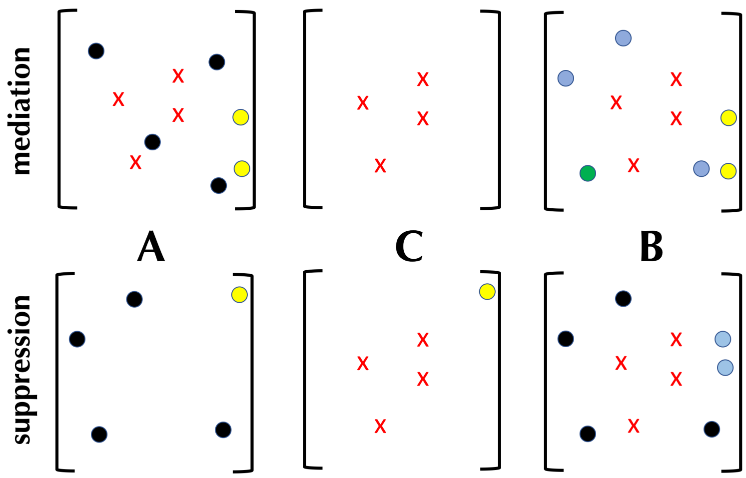

Figure 2: **Adjacency matrices cartoons displaying mediation and suppression.** Pictorical representations of triplets of adjacency matrices, where symbols (dots of different colours, crosses) represent the locations of 1s in the matrices. Symbols are chosen to schematically highlight how mediation and suppression operate. (Top) Network $\mathcal{C}$ is mediating the relation between networks $\mathcal{A}$ and $\mathcal{B}$ (Algorithm 2) and as such most of those edges which are common to $\mathcal{A}$ and $\mathcal{B}$ are due to the fact that both $\mathcal{A}$ and $\mathcal{B}$ share these edges with $\mathcal{C}$. (Bottom) Network $\mathcal{C}$ acts as a suppressor between $\mathcal{A}$ and $\mathcal{B}$ (Algorithm 3). Edges which are common to $\mathcal{A}$ and $\mathcal{C}$ are suppressed in $\mathcal{B}$, and otherwise $\mathcal{A}$ and $\mathcal{C}$ synergistically interact and $\mathcal{B}$ inherits edges which are present in one but not the other network.

Algorithm 2 MEDIATED()

Input: p, N
Output: 3 Erdős-Rényi adjacency matrices $\mathbf{A}, \mathbf{B}, \mathbf{C}$ where $\mathbf{C}$ mediates relation between $\mathbf{A}$ and $\mathbf{B}$ ($\Delta > 0$)

$\mathbf{A} \leftarrow \mathbf{0}$
$\mathbf{B} \leftarrow \mathbf{0}$
$\mathbf{C} \leftarrow \mathbf{0}$
for $i = 1$ **to** $N - 1$ **do**
  for $j = i + 1$ **to** N **do**
    if RAND $< p$ **then** $A_{ij}, A_{ji} \leftarrow 1$
    if RAND $< p$ **then** $B_{ij}, B_{ji} \leftarrow 1$
    if RAND $< p$ **then** $C_{ij}, C_{ji}, A_{ij}, A_{ji}, B_{ij}, B_{ji} \leftarrow 1$
return A,B,C

$\mathcal{C}$, which intuitively leads to $\Delta < 0$. The following theorem can be proved:

Theorem 2.2. *Let* $\mathbf{A}$, $\mathbf{B}$ *and* $\mathbf{C}$ *be as in Algorithm 2. If* $\mathbf{A}$ *and* $\mathbf{B}$ *share at least one edge besides the common edges shared with* $\mathbf{C}$*, then* $\Delta < 0$.

The proof of this theorem can also be found in the Supplementary Methods 2. In Fig.1 we show numerical results for finite networks with $N = 50$, with $p = 0.5$.

2.4 Suppression

Finally, let us consider the case where $\mathcal{B}$ depends on the interaction of $\mathcal{A}$ and $\mathcal{C}$ such that, an edge occurs in $\mathcal{B}$ with a certain probability if it appears in $\mathcal{A}$ but not in $\mathcal{C}$ or alternatively if it appears in $\mathcal{C}$ but not in $\mathcal{A}$ (see Fig. 2 for an illustration). This is akin to a probabilistic XOR gate. Then on average $\mathrm{NJ}_p(\mathcal{A}, \mathcal{B}; \mathcal{C}) > \mathrm{NJ}(\mathcal{A}, \mathcal{B})$, i.e. partializing with respect to $\mathcal{C}$ in this case evidences suppression effects.

Algorithm 3 encapsulates the generative model. The following theorem can be proved:

Theorem 2.3. *Let* $\mathbf{A}$, $\mathbf{B}$ *and* $\mathbf{C}$ *be as in Algorithm 3. Then* $\mathbb{E}(\Delta) > 0$.

Algorithm 3 SUPPRESSION()

Input: p, q, N

Output: 3 Erdős-Rényi adjacency matrices $\mathbf{A}, \mathbf{B}, \mathbf{C}$ where $\mathbf{C}$ acts as a suppressor between $\mathbf{A}$ and $\mathbf{B}$ $(\Delta > 0)$

$\mathbf{A} \leftarrow \mathbf{0}$
$\mathbf{B} \leftarrow \mathbf{0}$
$\mathbf{C} \leftarrow \mathbf{0}$
for $i = 1$ **to** N **do**
  for $j = i + 1$ **to** $N - 1$ **do**
    if RAND $< p$ **then** $A_{ij}, A_{ji} \leftarrow 1$
    if RAND $< p$ **then** $B_{ij}, B_{ji} \leftarrow 1$
    if RAND $< p$ **then** $C_{ij}, C_{ji} \leftarrow 1$
    if $A_{ij} * C_{ij} = 0$ & $A_{ij} + C_{ij} > 0$ & RAND $< q$ **then** $B_{ij}, B_{ji} \leftarrow 1$
return A,B,C

The proof for this theorem is contained in the Supplementary Methods 3. In Fig.1 we show numerical results for finite networks with $N = 50$, with $p = 0.5$ and $q = 1$, which are in full agreement with the theorem.

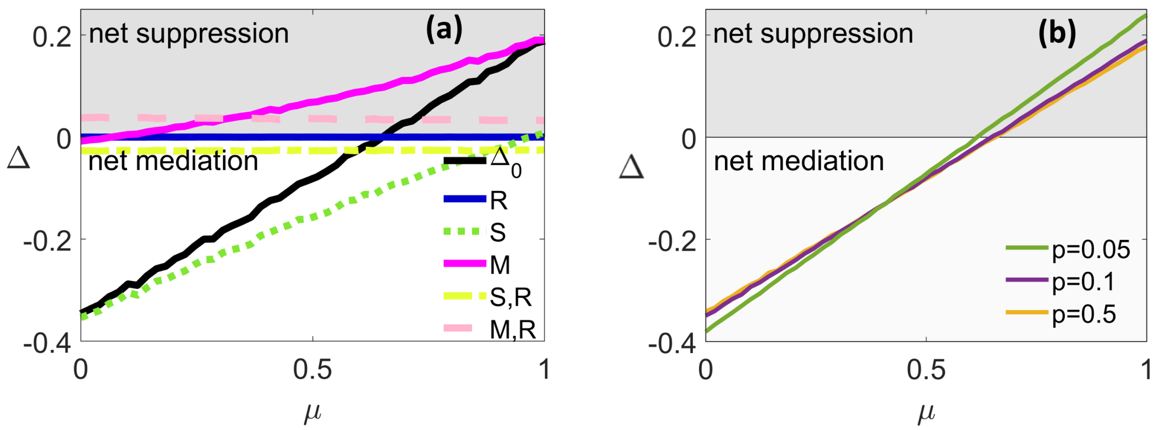

Figure 3: **Interpolating model.** (Panel a) Values of Jaccard net difference Δ (see the text), obtained averaging 50 realizations of an interpolating model giving a blend of mediation and suppression (see the text), where each network has $N = 300$ nodes and varying model parameter p, as a function of the interpolation parameter μ (in each of the N(N-1) steps we apply Algorithm 2 with probability $1 - \mu$ and Algorithm 3 with μ). (Panel b) Revised version of the left panel, this time selectively removing all suppression and mediation effects according to our theoretical framework. The original curve, for an interpolating model generating a blend of mediation and suppression, is depicted in black. The blue curve (R) is a pure randomisation, which generates $\Delta \approx 0$. The dotted green line (S) corresponds to a selective rewiring that removes all hidden suppression: in that case the curve is kept always below zero (increasing μ increases the amount of Algorithm 3, but then is selectively rewired, thus effectively randomising the networks and pushing Δ to zero). The pink curve (M) is the result of a selectively rewiring that removes all hidden mediation: in that case the curve is pushed to the regime $\Delta > 0$. As μ increases, the amount of Algorithm 3 (generating suppression) is increased, hence pushing Δ to larger values. The dashed yellow (S,R) and pink (M,R) lines are the result of selectively rewiring on the randomised networks, and only highlight the residual values of suppression or mediation which occur by chance (as a finite size effect) in randomised networks.

2.5 Coexistence of mediation and suppression effects

When we abandon ideal cases where only suppression or only mediation are present, and we go towards a mixture of the two, it becomes evident that both effects can be hidden and a single Δ cannot in principle tell us if the system evidences *only* one out of the two mechanisms. To investigate coexistence of both mechanisms, we run a simulation in which algorithms 2 and 3 above are combined: in each step with probability $1-\mu$ we take algorithm 2 and with probability μ we take algorithm 3. Since each algorithm is performed independently, the resulting model linearly interpolates between mediation and suppression, such that measurable $\Delta = (1-\mu)\Delta_{\text{med}} + \mu\Delta_{\text{syn}}$, where Δ_{med} and Δ_{syn} are hidden. The results are depicted in panel (a) of Fig.3, for different instances of parameter p and $q=1$. We can have negative, null or positive values of Δ underpinned by a balance of both mediation and suppression mechanisms, and actually for the concrete set of parameters, the effect of mediation in Δ is slightly stronger than the effect of suppression (this unbalance gets more pronounced for $q<1$). This simple interpolating model thus leads us to conclude that, in real cases, we might for instance be naively measuring $\Delta < 0$ and misleadingly concluding that there is only mediation where in fact both mediation and suppression could be at play. Accordingly, a measure describing the effects of suppression and mediation is not enough to describe and resolve the simultaneous presence of both.

Algorithm 4 NULL()

Input: 3 adjacency matrices **A, B, C** and mode X (mediation (M) or suppression (S))
Output: Null model net difference $\Delta_{W,X}$

$\mathbf{B2} \leftarrow \text{FULLREWIRE}(\mathbf{B})$
$\Delta_X \leftarrow \text{SELECTIVEREWIRE}(\mathbf{A},\mathbf{B},\mathbf{C},X)$
$\Delta_{RX} \leftarrow \text{SELECTIVEREWIRE}(\mathbf{A},\mathbf{B2},\mathbf{C},X)$
$\Delta_{W,X} \leftarrow [\Delta_X - \Delta_{RX}]/X_{\max}$
return $\Delta_{W,X}$

function FULLREWIRE(**G**)
  for $\ell_{ij} \in \mathbf{G}$ **do**
    if RAND $< p$ **then** $\ell_{ij} \leftarrow \ell_{kl}$, $\ell_{kl} \leftarrow \ell_{ij}$
  return G

function SELECTIVEREWIRE(**A, G, C**, X)
  if $X = S$ **then**
    for $\ell'_{ij} \in \mathbf{G}'$ **do**
      if $\ell'_{ij} = 1$ & $A_{ij} = 1$ & $C_{ij} \neq 1$ **then** $\ell'_{kl} \leftarrow \ell'_{ij};\ \ell'_{ij} \leftarrow 0$
  if $X = M$ **then**
    for $\ell'_{ij} \in \mathbf{G}'$ **do**
      if $\ell'_{ij} = 1$ & $A_{ij} = 1$ & $C_{ij} = 1$ **then** $\ell'_{kl} \leftarrow \ell'_{ij};\ \ell'_{ij} \leftarrow 0$
  SELECTIVE-REWIRE $\leftarrow \text{NJ}_p(\mathbf{A},\mathbf{G}';\mathbf{C}) - \text{NJ}(\mathbf{A},\mathbf{G}')$
  return SELECTIVEREWIRE

In order to disentangle both effects we now introduce Algorithm 4, which applies both for constructing null models for mediation (M) and suppression (S). To construct a surrogate where all suppression has been removed, starting from $\mathcal{A},\mathcal{B},\mathcal{C}$, we perform a selective rewiring in $\mathcal{B}$, where only those links in $\mathcal{B}$ which are also present in $\mathcal{A}$ but not in $\mathcal{C}$ (or that also appear in $\mathcal{C}$ but not in $\mathcal{A}$) are rewired randomly. Similarly, to construct a surrogate where all mediation has been removed, starting from $\mathcal{A},\mathcal{B},\mathcal{C}$, we perform a selective rewiring in $\mathcal{B}$, where only those links in $\mathcal{B}$ which are also present in $\mathcal{A}$ and in $\mathcal{C}$ are rewired randomly.
We then compute again the net Jaccard difference on the rewired versions, which are are labelled Δ_S (applied to the case where suppression is removed) and Δ_M (applied to the case where mediation is removed) respectively. The heuristic is then simple: if there is e.g. hidden suppression in the data (respectively mediation), then $\Delta_S < \Delta$ (respectively $\Delta_M > \Delta$), whereas if such mechanism is absent then $\Delta_S \approx \Delta$ ($\Delta_M \approx \Delta$).
Now, we also need to take into account finite-size effects which irremediably add spurious mediation and suppression effects (i.e. triplets of purely random, uncorrelated networks will show small but non-zero mediation and suppression due to chance). To counterbalance such effects, we also proceed to selectively remove suppression and mediation from a completely randomly rewired version of $\mathcal{B}$, which we call $\mathcal{B}\mathbf{2}$, leading to two new indices: Δ_{RS} and Δ_{RM}. We can finally combine these to produce normalised indices of mediation ($\bar{m}$) and suppression ($\bar{s}$) by normalising them dividing over the maximum possible value

of suppression (mediation) attainable by a generative model such as algorithm 3 (2) to the triplet of networks, i.e.

$$\bar{m} = \frac{\Delta_S - \Delta_{\mathrm{R,S}}}{M_{max}}, \quad \bar{s} = \frac{\Delta_M - \Delta_{\mathrm{R,M}}}{S_{max}}. \tag{4}$$

Accordingly, the role that $\mathcal{C}$ plays in the relation of $\mathcal{A}$ and $\mathcal{B}$ is described by the duple $(\bar{m}, \bar{s})$. Additionally, a significance value for these indices could be defined as:

$$\sigma_{\{\mathrm{S,M}\}} = \left| \frac{\Delta_{\{S,M\}} - \Delta_{\mathrm{R,\{S,M\}}}}{\mathrm{std}(\Delta_{\mathrm{R,\{S,M\}}})} \right|, \tag{5}$$

where $\cdot_{\{S,M\}}$ simply means that the expression equally applies for mediation and suppression, depending what label we take. It is worth to stress that for large networks the finite size effects become less common, and $\Delta_{\mathrm{R,\{S,M\}}}$ will tend to zero, for all the realizations, resulting in a small standard deviation, and in any value of suppression and mediation being highly significant.

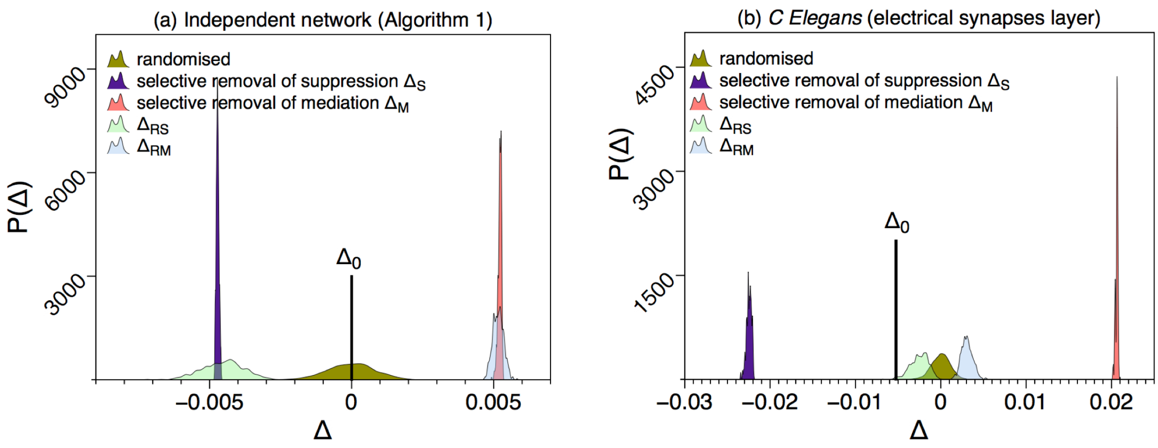

Figure 4: **Illustration of Algorithm 4.** We illustrate the procedure of how to disentangle mediation and suppression in two examples. (Panel a) Selective rewiring applied on a triplet of independent networks generated by Algorithm 1, with $N = 300$ nodes and $p = 0.3$ (these values are taken arbitrarily and chosen for illustration). The original value of the net Jaccard difference (close to zero) is denoted Δ_0, which is close to zero according in agreement with theorem 2.1. Each selective rewiring is repeated 500 times, and histograms representing the distributions of the outputs across all realizations are built. The selective removal of suppression and mediation yields only a marginal change in the Jaccard net difference Δ, similar to the one performed on a randomised version, which indicates that the amount of suppression and mediation in this configuration is residual and only due to finite size effects, as expected since $\mathcal{C}$ is independent of $\mathcal{A}, \mathcal{B}$ by construction. (Panel b) Similar to panel (a) but applied on the C Elegans triplet, where network $\mathcal{C}$ is assigned to the electrical layer. The actual value $\Delta_0 < 0$, initially suggesting mediation. The selective removal of suppression (mediation) significantly push the histograms towards more negative (positive) values of Δ –much more than such selective removal performed on a randomisation– suggesting that there exist a significant amount of mediation and suppression.

For illustration, in the left panel of Fig.4 we show the effects of the sequence of selective rewirings on Δ applied to a particular example of three independent, Erdős-Rényi networks with $N = 300$ nodes and wiring probability $p = 0.3$ (i.e., Algorithm 1). The original value of Δ is very close to zero, as well as the ones obtained from a full randomisation of $\mathcal{B}$. Since in this example the networks are independent, any mediation or suppression is only a spurious residual due to finite size effects, thus this residual is flagged out in similar terms by a selective rewiring on the actual network $\mathcal{B}$ (Δ_X) or on its full randomisation (Δ_{RX}), hence the violet and green histograms overlap, and similarly the pink and pale blue ones also overlap. As an additional illustration, we applied the sequence of selective rewirings on the results of the interpolating model. Results are shown in panel (b) of Fig.3.

2.6 Empirical networks

We now turn to real-world networks and consider four types of 3-layer multiplex networks, including (i) different modes of social interaction in Twitter during the 2014's New York City Climate March (NYC),

Summary of empirical networks					
Triplet	**Type**	N	**Network #1**	**Network #2**	**Network #3**
C. Elegans	neuronal; directed; unweighted	279	monadic (1639 edges)	polyadic (3193 edges)	electrical (1031 edges)
NYC	Twitter; directed; weighted	102439	retweet (213754 edges)	mentions (131679 edges)	replies (8062 edges)
Lazega law firm	social (offline); directed; unweighted	71	cowork (892 edges)	friendship (575 edges)	advice (1104 edges)
Copenhagen	social (offline/online); undirected; weighted	751	proximity (13020 edges)	facebook (12847 edges)	calls/sms (1760 edges)

Table 1: **Summary of network specificities.** The first three examples are multiplex networks collected from `comunelab.fbk.eu/data.php`, whereas the fourth one was found through `icon.colorado.edu`. The C Elegans multiplex describes the Caenorhabditis elegans connectome, where layers correspond to different synaptic junctions: chemical monadic ("MonoSyn"), polyadic ("PolySyn") and electrical ("ElectrJ") [20, 21]. The NYC multiplex describes Twitter activity during an exceptional event, the NYC Climate March in 2014, and layers correspond to retweet, mentions and replies [24]. The Lazega law firm depicts three kinds of social relationships (Co-work, Friendship and advice) between partners and associates of a corporate law partnership [22, 23]. Finally the Copenhagen multiplex describes social interaction in three layers corresponding to phone calls and text messages (merged), Facebook friendships, and proximity as measured with strength of Bluetooth signal [25].

(ii) different types of social interaction –proximity, phone call/text message, Facebook– as collected in Denmark (Copenhagen), (iii) different interpersonal relations inside a corporation (Lazega law firm) and (iv) different synaptic junctions in a neuronal network (C Elegans), see 1 for details.
To begin with, in Fig.5 we confirm that, with the exception of the pair NYC Retweets vs Replies, all other possible pairs of layers in the four examples are indeed genuinely related –i.e., showing substantially more similarity than a null model–. In each case we plot $\text{NJ}(\mathcal{A},\mathcal{B})$ (blue bars) and as a reference, as black lines we also plot the average result of $\text{NJ}(\mathcal{A},\mathcal{B})$ ($\pm$ one standard deviation) after $\mathcal{A},\mathcal{B}$ have been appropriately randomised. We confirm that the similarity between each pair of networks is not the result of a finite-size effect and thus exploring the role of a third network ($\mathcal{C}$) is justified.
We then turn to analyse the role of $\mathcal{C}$. For illustration, the whole selective rewiring process described in Algorithm 4 is depicted with detail for a specific example (the case of the C Elegans multiplex where we explore the role that the electrical synapses layer play in the relation between the monadic and the polyadic layers) in the right panel of figure 4. We provide the original value Δ_0, and the distributions of the Δ values obtained after each of the rewiring procedure, concluding that this network indeed shows non-negligible mediation and suppression effects.

The normalized indices of mediation and suppression for the rest of permutations in all the real-world multiplex networks are reported in figure 6. The first thing we can observe is that overall there is substantially more mediation than suppression, although we also observe the latter mechanism. All effects are statistically significant ($\sigma \gg 1$ in every case) except for the suppression in the Lazega advice layer and the NYC Retweet layer, where $\sigma \approx 2$ in both cases.
In the case of the Copenhagen multiplex, the only layer which evidences a significant role in the relation of the other two is the phone/sms layer, which we show displays both mediation and suppression effects, although the former is notably stronger. For the proximity network we considered averaged values over the whole four weeks, and used an adjacency matrix of a density comparable to the one of Facebook links, corresponding to the closest proximity range. Also the phone network was built irrespective of the timing of the interaction.

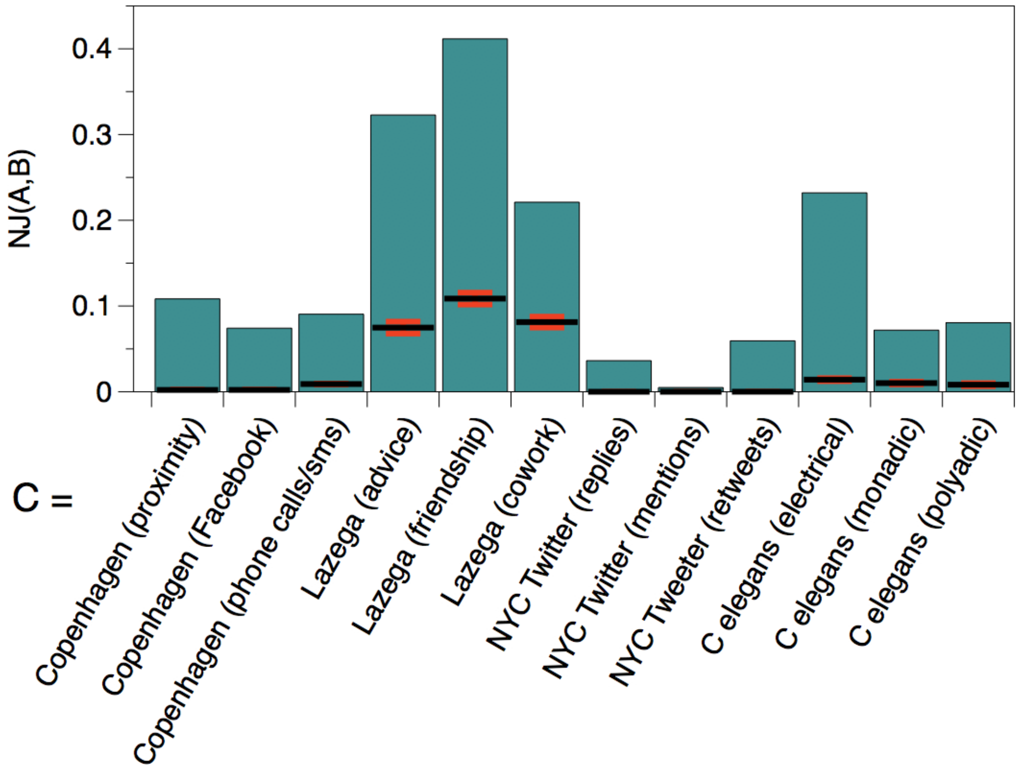

Figure 5: **Similarity between pairs of real-world networks.** Values of the Network-Jaccard index $\mathrm{NJ}(\mathcal{A},\mathcal{B})$ computed on the four empirical multiplex networks considered (for each multiplex, we consider the three pair permutations). As a reference, black horizontal lines display $\mathrm{NJ}_{\mathrm{null}}(\mathcal{A},\mathcal{B})$ which computes the average over several randomisations of layers $\mathcal{A},\mathcal{B}$ (red lines correspond to $\pm$ one standard deviation. We conclude that all pair of layers are genuinely related with the possible exception of the pair NYC Twitter replies vs NYC Twitter retweet.

In the case of the Lazega law firm, all three layers display very high mediation, but such effect is notably stronger for the co-working network, i.e. within this firm dyadic friendships are related to the dyadic advisory relations, and this is mediated by the fact that these are co-working. Only the friendship layer displays a suppressor effect (the one played by the advice layer is non-significant), i.e. pairs of individuals that are not co-working can have an advisory relationship (or otherwise) *because* they are friends, or pairs of co-working will also have an advisory relationship without the needs of them being friends.
In the case of the Twitter triplet (NYC), only the Replies network shows a mediating effect.
Finally, in the nervous system multiplex (C Elegans) we can see that all layers display some amount of mediation and suppression. The electrical synapses layer is the one displaying a stronger suppressing effect, whereas the monadic chemical layer is the one that displays a larger mediation role. The increased suppression role of the layer of electrical synapses reflects the evidence that chemical and electrical synapses closely interact and serve related functions [19], so that when the either of the chemical layers is taken as $\mathcal{C}$ the presence of the other chemical layer accounts for a reduced suppression/mediation.

As a final analysis, and in order to show how suppression and mediation can be functionally modulated within a particular real-world example, we examine the role played by the Proximity layer in the relation between the Facebook and phone calls/sms layers when such layer is systematically varied. In this multiplex, the proximity network is originally reconstructed using Bluethooth signal strength between participants, by assigning a link between each pair of nodes whose relative Bluetooth strength, averaged over the whole period of the recording (four weeks) belongs to a given range. In order to build different proximity networks (each of them accounting for a different spatial scale) and at the same time keeping the edge density constant, we build non-overlapping Bluetooth intensity ranges by taking into account the original Bluetooth intensity distribution (see the inset of Fig.7). In this way, ranges are non-uniform but the number of edges in each of this range is the same, hence the resulting proximity networks have all the same edge density while describing different scales of physical proximity. The intuition is that only the smaller scale is a meaningful proximity network, and for larger spatial scales the resulting proximity

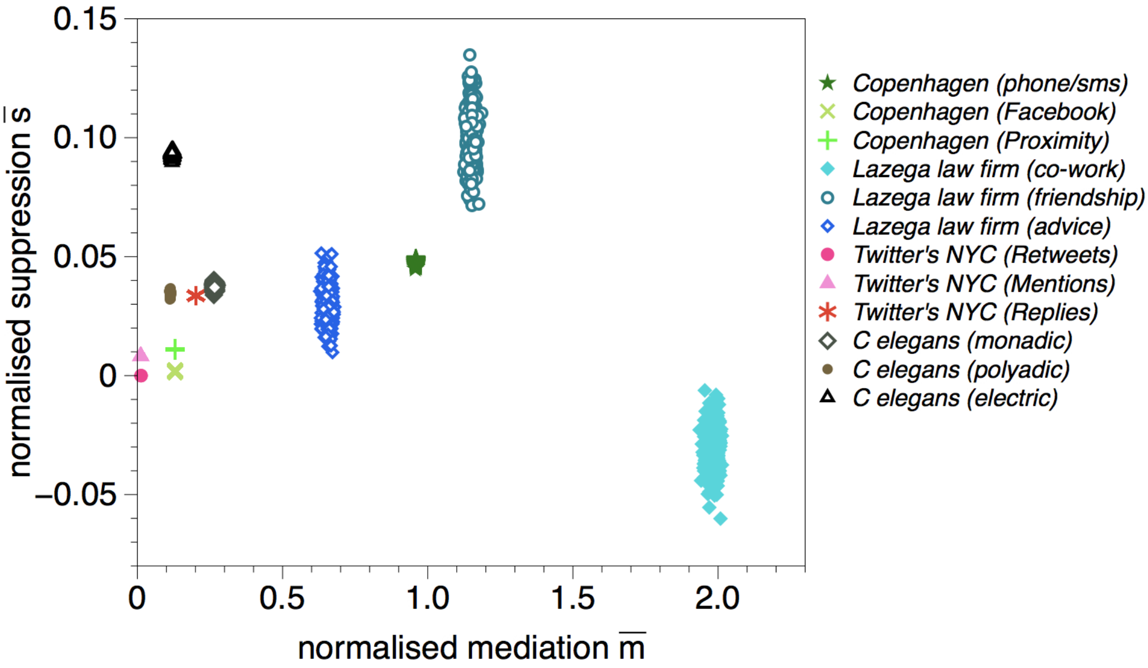

Figure 6: $(\bar{m}, \bar{s})$ **plane for real-world networks.** We display the normalised indices of mediation and suppression for four real-world multiplex networks. For each multiplex we permute the role of $\mathcal{C}$ across the three layers, and for each case the specific layer which plays the role of $\mathcal{C}$ is highlighted in parenthesis. Dot clouds are the result of repeating the rewiring procedures 500 times (for multiplexes with a large number of nodes, the figure displays very little dispersion, and the cloud is only perceptible for the Lazega triplet which is indeed the smallest multiplex).

networks do not really imply any real interaction between the nodes. Then, for each resulting proximity network, we estimate the role it plays in the relation between the other two networks and plot it in the $(\bar{m}, \bar{s})$-plane. Results are shown in the outer panel (a) of Fig.7. For proximity networks describing large spatial scales, the network is essentially independent of the other two, and it is only when the proximity network captures smaller spatial scale (i.e. when links describe real physical proximity) that an indirect effect (notably, mediation) gets amplified (see panel b of the same figure). This evidence would speak to the fact that taking Facebook links as a proxy of a wider and less compromising community-based relationship, one tends to communicate by phone/sms with people who are closer in daily life (same classroom/dorm/sports club).

3 Conclusion

In this paper we have proposed a simple strategy to assess the role that a given network might play in shaping the relation between two other networks, thus enlarging the paradigm of network similarity beyond the classical pairwise comparison. This approach is aligned to a recent endeavour that aims at going beyond dyadic interactions in the characterisation of complex systems [13], and takes inspiration from the causal mediation literature [14, 18]. We make use of a set-theoretic approach to define a similarity metric between a pair of networks and to further explore if such a relation is independent of, mediated by, or suppressed by a third network which might be hidden. We introduce simple generative models that, we prove, produce pure mediation and suppression. We then explore the coexistence between mediation and suppression and develop a procedure to disentangle both indirect effects. The whole methodology is subsequently applied to a range of real-world, 3-layer multiplex networks, and we unveil previously unnoticed mediation and suppression effects in social and neuronal networks which we also briefly interpreted.

Altogether, this works aims to set the scene for the development of concepts such as Network Causality. We hope that this work sparks further research in several areas. First, the simplicity and tractability of our selected approach makes it easily applicable across the disciplines (in that sense, note that user-friendly versions of all codes are freely available). Second, our approach can be readily generalised to consider not just isolated triplets of networks. Indeed, one can sequentially apply this protocol to a multiplex network of an arbitrary number of layers, or to a temporal network, and accordingly derive concepts of causality

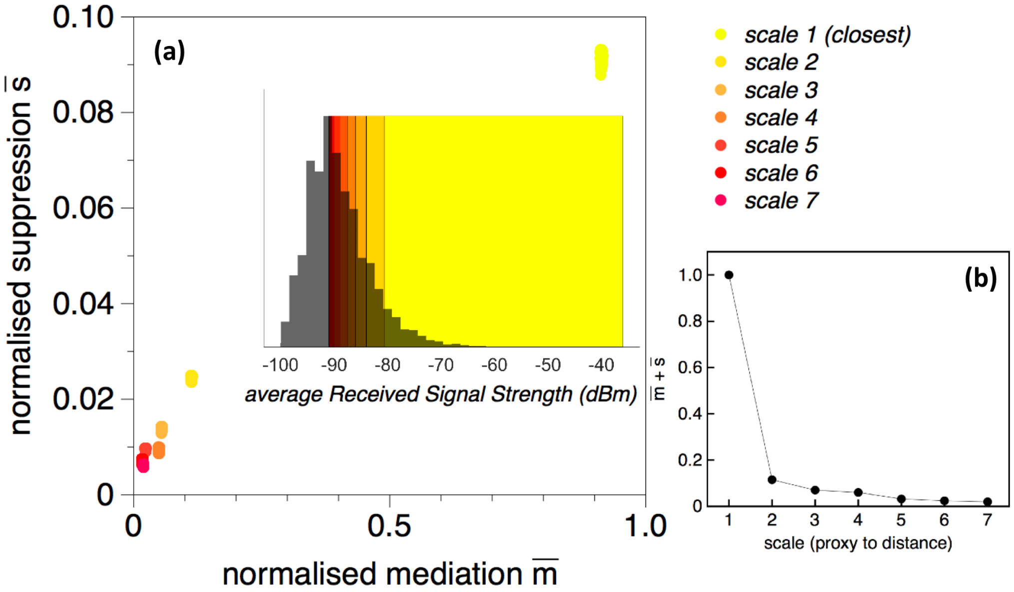

Figure 7: **Modulating mediation.** (Outer panel a) $(\bar{m}, \bar{s})$-plane for the role of the proximity network with respect to the relation of the Facebook and the phone/sms network (Copenhagen multiplex), for different proximity networks reconstructed by changing the spatial scale over which links are defined. The network displays a very clear mediating effect only when links represent close physical proximity (yellow), for other spatial scales such effect is lost. (Inset panel) Link average weight distribution (Received Signal Strength (RSSI)) is depicted in black. According to this distribution, we build seven non-overlapping RSSI windows. RSSI is inversely related to distance (the larger the signal strength, the closer two nodes are) so these windows represent different spatial scales. (Panel b) This panel describes $\bar{m} + \bar{s}$ for each spatial scale, further emphasising that only in the closer spatial scale the proximity network is playing a strong mediating role.

and directionality in those contexts.

As it currently stands, our method is applicable to both directed and undirected networks, but the current version does not take into account weights, something which could be taken into account in further generalisations. At the same time, observe that this work focuses on the special case where two networks are considered to be related if they are close according to a distance based on Jaccard's index. This is a concrete choice which was selected for simplicity, however the conceptual framework is much more general and flexible, and mediation and suppression between networks can be explored in a variety of ways. For instance, further work could explore (i) different distance functions –including those that do not require the networks to have the same number of nodes, thus extending the formalism to deal with multilayer networks–, and (ii) other types of relations beyond graph distances.

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Author Contributions

All authors participated in the conceptualization of the study, in the derivation of the theory and its numerical implementation, in the analyses, and in writing the paper. LL and DM prepared the figures.

Competing Interests

All authors declare no competing interest.

Data Availability

All relevant data are in the public domain and have been appropriately referenced.

Code Availability

All codes are available at `https://github.com/danielemarinazzo/partialjaccard`

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