

# Mining higher-order triadic interactions

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Complex systems often present higher-order interactions which require us to go beyond their description in terms of pairwise networks. Triadic interactions are a fundamental type of higher-order interaction that occurs when one node regulates the interaction between two other nodes. Triadic interactions are a fundamental type of higher-order networks, found in a large variety of biological systems, from neuron-glia interactions to gene-regulation and ecosystems. However, triadic interactions have been so far mostly neglected. In this article, we propose a theoretical principle to model and mine triadic interactions from node metadata, and we apply this framework to gene expression data finding new candidates for triadic interactions relevant for Acute Myeloid Leukemia. Our work reveals important aspects of higher-order triadic interactions often ignored, which can transform our understanding of complex systems and be applied to a large variety of systems ranging from biology to the climate.

## I. INTRODUCTION

Higher-order networks [1–5] are key to capture many-body interactions present in complex systems. Inferring higher-order interactions from real, pairwise network datasets is recognised as one of the central challenges in the study of higher-order networks [2]. Despite the increasing attention given to the inference of higher-order interactions [6–14], the detection of triadic interactions, which are prevalent in a wide variety of complex systems, has been addressed only in few works [15–17] and remains an important scientific challenge.

Triadic interactions [18] are a fundamental type of signed higher-order interaction. A triadic interaction occurs when one or more nodes regulate the interaction between two other nodes. The regulator nodes may either enhance or inhibit the interaction between the other two nodes. Triadic interactions are known to be important in various systems such as ecosystems [19–21] where one species can regulate the interaction between two species, neuronal networks [22] where glial cells regulate synaptic transmission between neurons thereby regulating brain information processing, and gene regulation networks [16, 23] where a modulator can promote or silence the interaction between a transcription factor and a target gene. Despite evidence of triadic interactions in specific disciplines (neuroscience, ecology, molecular biology), the relevance of triadic interactions as a universal type of higher-order interactions with a well-defined mathematical definition has only recently been recognised [18, 24–27].

In this article, we explore the fundamental dynamical

properties of networks with triadic interactions between continuous variables. We formulate a general model of networks with triadic interactions, and propose an information theory framework and the Triaction algorithm that is able to mine triadic interactions from data. The Triaction algorithm leverages the induced variability of the mutual information between a pair of variables when conditioned on a third regulatory variable. Using our method, we show that triadic interactions are important in gene-expression data where genes can be involved in ‘trigenic’ processes [28]. We apply the Triaction algorithm to a gene-expression network data, and are able to detect known interactions as well as propose a set of new candidate interactions that can then be validated experimentally.

## II. TRIADIC INTERACTIONS

A triadic interaction occurs when one or more nodes modulate (or regulate) the interaction between two other nodes, either positively or negatively. A triadic interaction network is a heterogeneous network composed of a structural network and a regulatory network encoding triadic interactions (Figure 1). The structural network  $G_S = (V, E_S)$  is formed by a set  $V$  of  $N$  nodes and a set  $E_S$  of  $L$  edges. The regulatory network  $G_R = (V, E_S, E_R)$  is a signed bipartite network with one set nodes given by  $V$  (the nodes of the structural network), and another set of nodes given by  $E_S$  (edges of the structural network) connected by the regulatory interactions  $E_R$  of cardinality  $|E_R| = \hat{L}$ . The signed regulatory network can be encoded as an  $L \times N$  matrix  $K$  where  $K_{\ell i} = 1$  if node  $i$  activates the structural edge  $\ell$ ,  $K_{\ell i} = -1$  if node  $i$  inhibits the

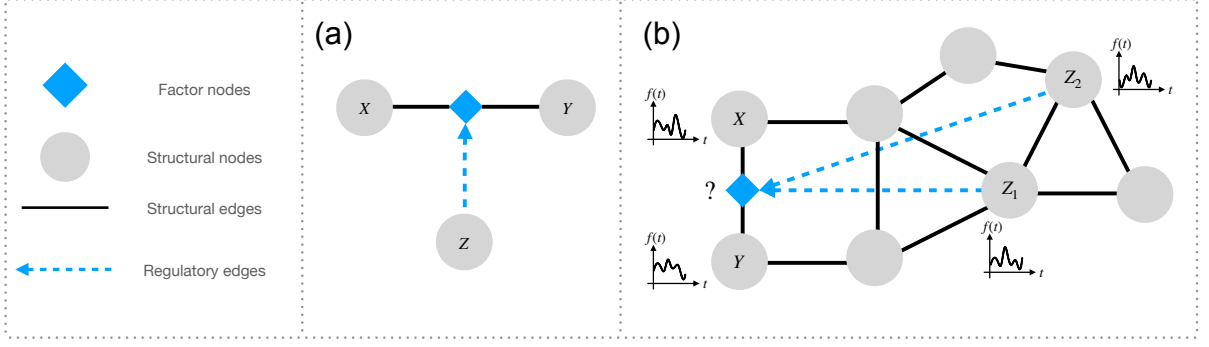


Figure 1. (Panel a) A triadic interaction occurs when a node, here shown as  $Z$ , regulates either positively or negatively the interaction between two other nodes  $X$  and  $Y$  connected in the structural network by an edge. The node  $Z$  is also called a *regulator node*. This edge can be conceptualised as a *factor node* (shown here as a cyan diamond). (Panel b) A network with triadic interactions can be seen as a network of networks formed by a simple structural network and by a bipartite regulatory network between regulator nodes and regulated edges (factor nodes).

structural edge  $\ell$  and  $K_{\ell i} = 0$  otherwise. If  $K_{\ell i} = 1$ , then the node  $i$  is called a positive regulator of the edge  $\ell$ , and if  $K_{\ell i} = -1$ , then the node  $i$  is called a negative regulator of the edge  $\ell$ . It's worth noting that node  $i \in V$  cannot serve as both a positive and negative regulator for the same edge  $\ell$  at the same time. However, node  $i$  can act as a positive regulator for edge  $\ell$  while simultaneously functioning as a negative regulator for a different edge, denoted as  $\ell'$ , where  $\ell' \neq \ell$ .

### III. THE CONTINUOUS TRIADIC INTERACTION MODEL

Here we formulate a general synthetic dynamical model for a network with triadic interactions between continuous variables. This model acts as a test benchmark to validate the Triaction algorithm that we propose to detect triadic interactions from continuous data. We assume that each node  $i$  of the network is associated with a dynamical variable  $X_i \in \mathbb{R}$ , and that the dynamical state of the entire network is encoded in the state vector  $\mathbf{X} = (X_1, X_2, \dots, X_N)^T$ . The topology of the structural network is encoded in the graph Laplacian matrix  $\mathbf{L}$  with elements

$$L_{ij} = \begin{cases} -a_{ij}J & \text{if } i \neq j, \\ \sum_j a_{ij}J & \text{if } i = j, \end{cases} \quad (1)$$

where  $\mathbf{A} = (a_{ij})$  is the adjacency matrix of the network, and  $J > 0$  is a coupling constant. In the absence of triadic interactions, we assume that the dynamics of the network is associated with a Gaussian process implemented as the Langevin equation

$$d\mathbf{X} = -\frac{\delta \mathcal{H}}{\delta \mathbf{X}} + \Gamma \boldsymbol{\eta}(t) \quad (2)$$

associated with the Hamiltonian

$$\mathcal{H} = \frac{1}{2} \mathbf{X}^\top (\mathbf{L} + \alpha \mathbf{I}) \mathbf{X}, \quad (3)$$

where  $\Gamma > 0$ ,  $\alpha > 0$ , and  $\boldsymbol{\eta}(t)$  indicates an uncorrelated Gaussian noise with

$$\langle \eta_i(t) \eta_j(t') \rangle = \delta_{ij} \delta(t - t'). \quad (4)$$

The resulting Langevin dynamics is given by

$$d\mathbf{X} = -(\mathbf{L} + \alpha \mathbf{I}) \mathbf{X} dt + \Gamma d\boldsymbol{\eta}(t). \quad (5)$$

We remark that the Hamiltonian  $\mathcal{H}$  has a minimum for  $\mathbf{X} = \mathbf{0}$ , and its depth increases as the value of  $\alpha$  increases. In a deterministic version of the model ( $\Gamma = 0$ ), the effect of the structural interactions will not be revealed at stationarity. However, the Langevin dynamics with  $\Gamma > 0$  encodes for the topology on the network. Indeed, at stationarity the correlation matrix  $C_{ij} = \mathbb{E}((X_i - \mathbb{E}(X_i))(X_j - \mathbb{E}(X_j)))$  is given by

$$C_{ij} = \frac{\Gamma^2}{2} [\mathbf{L} + \alpha \mathbf{I}]_{ij}^{-1}. \quad (6)$$

In other words from the correlation matrix between the dynamical variable it is possible to infer the Laplacian, and hence the connectivity of the network. We now introduce triadic interactions in the model. As explained earlier, triadic interactions occur when one or more nodes modulate the structural interactions between another two nodes. To incorporate triadic interactions into the network dynamics, we modify the definition of the Laplacian operator present in the Langevin equation. Namely, we consider the Langevin dynamics

$$d\mathbf{X} = -(\mathbf{L}^{(T)} + \alpha \mathbf{I}) \mathbf{X} dt + \Gamma d\boldsymbol{\eta}(t), \quad (7)$$

obtained from Eq.(2) by substituting the graph Laplacian  $\mathbf{L}$  with the *triadic Laplacian*  $\mathbf{L}^{(T)}$  whose elements are

given by

$$L_{ij}^{(T)} = \begin{cases} -a_{ij}J_{ij}(\mathbf{X}) & \text{if } i \neq j, \\ \sum_{k=1}^N a_{ik}J_{ik}(\mathbf{X}) & \text{if } i = j. \end{cases} \quad (8)$$

Moreover, we assume that the coupling constants  $J_{ij}(\mathbf{X})$  are determined by a perceptron-like model that considers all the regulatory nodes of the link  $\ell = [i, j]$  and the sign of the regulatory interactions. Specifically, if  $\sum_{k=1}^N K_{\ell k} X_k \geq \hat{T}$  then we set  $J_{ij} = w^+$ ; if instead  $\sum_{k=1}^N K_{\ell k} X_k < \hat{T}$  then we set  $J_{ij} = w^-$ , with  $w_+, w_- \in \mathbb{R}_+$  and  $w_+ > w_-$ . In other words, we set

$$J_{ij}(\mathbf{X}) = w_- + (w_+ - w_-)\theta\left(\sum_{k=1}^N K_{\ell k} X_k - \hat{T}\right), \quad (9)$$

where  $\theta(\cdot)$  is the Heaviside function ( $\theta(x) = 1$  if  $x \geq 0$  and  $\theta(x) = 0$  if  $x < 0$ ). Note that, in the presence of the triadic interactions, the stochastic differential equation (7) is not associated with any Hamiltonian, and a stationary state of the dynamics is not guaranteed, making this dynamical process significantly more complex than the original Langevin dynamics in Eq.(2). This generic model of triadic interactions is related to the recently proposed model [27] to capture information propagation in multilayer networks but does not make use of a multilayer representation of the data. Moreover the model is significantly different from models of higher-order interactions previously proposed in the context of consensus dynamics [29, 30] or contagion dynamics [31, 32]. Indeed, in our framework, triadic interactions between continuous variables are not reducible to standard higher-order interactions because they involve the modulation of the interaction between pair of nodes. Moreover, this modulation of the interaction is not dependent on the properties of the interacting nodes and their immediate neighbours such as in [29, 30] or in the machine learning attention mechanism [33]. On the contrary, the modulation of the interaction is determined by a third regulatory node or a larger set of regulatory nodes encoded in the regulatory network

Our model of triadic interactions, therefore, shows that triadic interactions are higher-order interactions that cannot be reduced to pairs of pairwise interactions. An important problem that then arises is whether such interactions can be mined (extracted) from real data. To address this issue, we will formulate a new algorithm – that we call the Triaction algorithm – to identify triadic interactions from data, and we will test its performance on the data generated from the model described above.

## IV. MINING TRIADIC INTERACTIONS

### A. The Triaction algorithm

We propose the Triaction algorithm (see Figure 2) to mine triadic interactions among triples of nodes. To simplify the notation we will use the letters  $X, Y, Z$  to indicate both nodes as well as their corresponding dynamical variables.

Given a structural edge between nodes  $X$  and  $Y$ , our goal is to determine a confidence level for the existence of a triadic interaction involving an edge between node  $X$  and node  $Y$  with respect to a potential regulator node  $Z$ . Specifically, we aim to determine whether the node  $Z$  regulates the edge between node  $X$  and node  $Y$ , given the dynamical variables  $X, Y$  and  $Z$  associated with these nodes. To do so, given a time series associated with node  $Z$ , we first sort the  $Z$ -values, and define  $P$  bins in terms of  $z$ -percentiles, chosen in such a way that each bin comprises the same number of data points (ranging in our analyses from 30 to 100). We indicate with  $z_m$  the quantile of  $Z$  corresponding to the percentile  $m/P$ . Therefore, each bin  $m$  indicates data in which  $Z$  ranges in the interval  $[z_m, z_{m+1})$ . We indicate with  $\mu(x|z_m), \mu(y|z_m)$  and  $\mu(x, y|z_m)$  the probability density of the variable  $X, Y$  and the joint probability density of the variables  $X$  and  $Y$  in each  $m$ -th bin.

A triadic interaction occurs when the node  $Z$  affects the strength of the interaction between the other two nodes  $X$  and  $Y$ . Consequently, our starting point is to consider the mutual information between the dynamical variables  $X$  and  $Y$  conditional to the specific value of the dynamical variable  $Z$ . We thus consider the quantity  $MIz(m) = MI(X, Y|Z = z_m)$  defined as

$$MIz(m) = \int dx \int dy \mu(x, y|z_m) \log \left( \frac{\mu(x, y|z_m)}{\mu(x|z_m)\mu(y|z_m)} \right).$$

In order to estimate this quantity, we rely on non-parametric methods based on entropy estimation from  $k$ -nearest neighbors [34–36]. For each triple of nodes, we visualize the mutual information  $MIz$  computed as a function of the  $z$ -th quantiles  $z_m$  and fit this function with a decision tree comprising  $r$  splits.

In the absence of triadic interactions, we expect  $MIz$  to be approximately constant as a function of the  $z$ -th quantiles  $z_m$ , while, in the presence of triadic interactions, we expect this quantity to vary significantly as a function of  $z_m$ . The discretized conditional mutual information CMI between  $X$  and  $Y$  conditioned on  $Z$  can be written as

$$CMI_{X,Y;Z} = \sum_{m=0}^{P-1} p(z_m) MIz(m) = \langle MIz \rangle, \quad (10)$$

where  $p(z_m) = 1/P$  indicates the probability that the  $Z$  value falls in the  $m$ -th bin. This quantity is known to indicate important information about the interaction

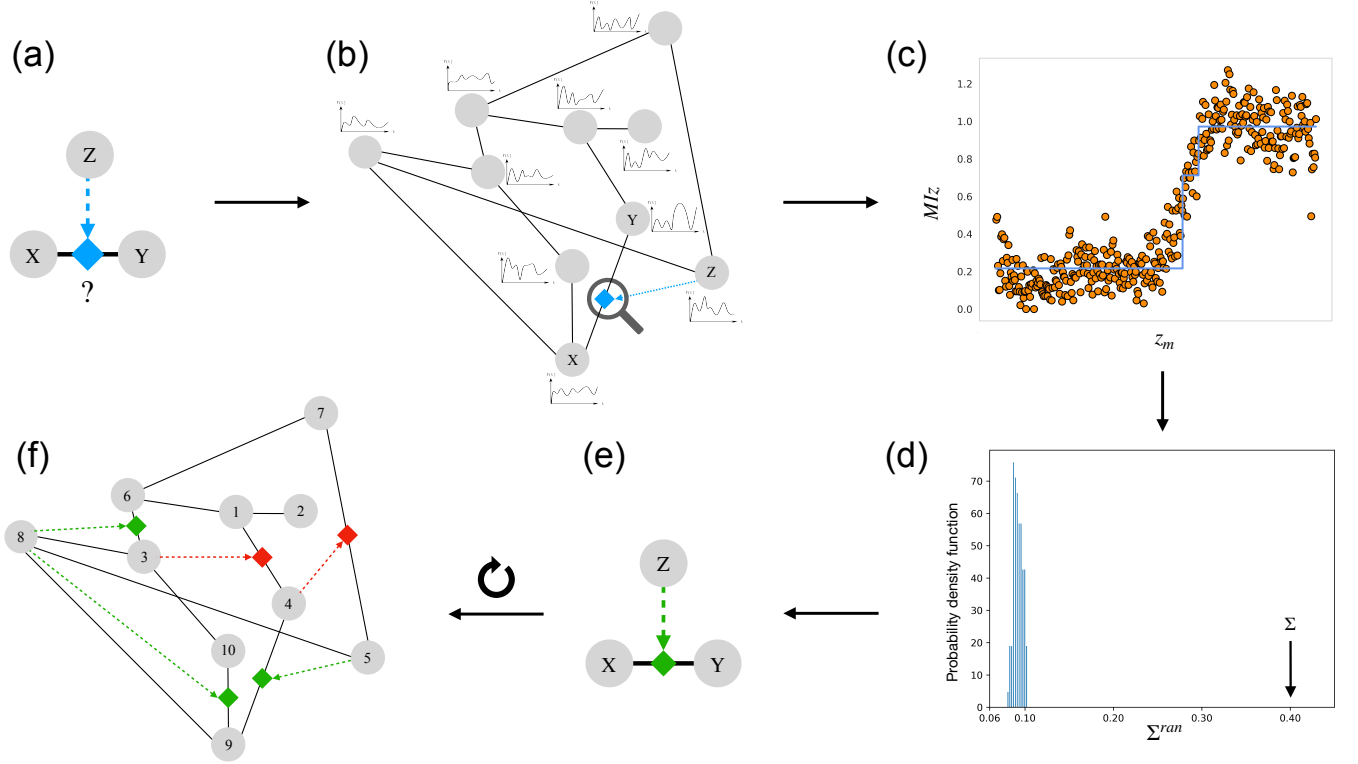


Figure 2. The Triaction algorithm identifies triples of nodes  $X$ ,  $Y$ , and  $Z$  involved in a putative triadic interaction, starting from the knowledge of the structural network and the dynamical variables associated with its nodes. For each putative triple of nodes involved in a triadic interaction (panel (a)) which belong to a network whose structure and dynamics is known (panel (b)), we study the functional behavior of the conditional mutual information  $MIz$  (panel (c)), and assess the significance of the observed modulations of  $MIz$  with respect to a null model (panel (d)). Given a predetermined confidence level, we can use these statistics to identify significant triadic interactions (panel (e)). This procedure can be extended to different triples of the network, thereby identifying the triadic interactions present in it (panel (f)).

between the nodes  $X$  and  $Y$  when combined with the information coming from the mutual information MI given by

$$MI_{X,Y} = \int dx \int dy \mu(x,y) \log \left( \frac{\mu(x,y)}{\mu(x)\mu(y)} \right),$$

where  $\mu(x)$ ,  $\mu(y)$  are the probability density functions for  $X$  and  $Y$  and  $\mu(x,y)$  is the joint probability density functions of the variables  $X$  and  $Y$ . In particular, true interactions between  $X$  and  $Y$  are typically associated with both high mutual information MI and high conditional mutual information CMI.

The conditional mutual information CMI, however, is not sensitive to variations in  $MIz$  and does not therefore provide the information needed to detect triadic interactions. In order to overcome this limitation, we define the following three quantities that measure how much the mutual information between  $X$  and  $Y$  conditioned on  $Z \in [z_m, z_{m+1})$  changes as  $z_m$  varies. Specifically we consider:

- (1) the standard deviation  $\Sigma$  of  $MIz$ , defined as

$$\Sigma = \sqrt{\sum_{m=0}^{P-1} p(z_m) [MIz(m) - \langle MIz \rangle]^2}; \quad (11)$$

- (2) the difference  $T$  between the maximum and minimum value of  $MIz$ , given by

$$T = \max_{m=0, \dots, P-1} |MIz(m) - \langle MIz \rangle|; \quad (12)$$

- (3) the largest absolute difference  $T_n$  of  $MIz$  between consecutive bins, i.e.

$$T_n = \max_{m=0, \dots, P-2} |\Delta_m(MIz)|, \quad (13)$$

where

$$\Delta_m(MIz) = MIz(m) - MIz(m+1).$$

The quantities  $\Sigma$ ,  $T$ , and  $T_n$  collectively measure the strength of the triadic interaction under question and can thus be used to mine triadic interactions in real

data. In order to assess the significance of the putative triadic interaction, we compare the observed values of these variables to a null model obtained by shuffling the  $Z$  values, to give  $\mathcal{N}$  randomization of the data, i.e. we use surrogate data for testing [37, 38]. In order to determine if the observed values are significant, we compute the scores  $\Theta_\Sigma$ ,  $\Theta_T$ ,  $\Theta_{T_n}$  given by

$$\begin{aligned}\Theta_\Sigma &= \frac{\Sigma - \mathbb{E}(\Sigma^{ran})}{\sqrt{\mathbb{E}((\Sigma^{ran})^2) - (\mathbb{E}(\Sigma^{ran}))^2}}, \\ \Theta_T &= \frac{T - \mathbb{E}(T^{ran})}{\sqrt{\mathbb{E}((T^{ran})^2) - (\mathbb{E}(T^{ran}))^2}}, \\ \Theta_{T_n} &= \frac{T_n - \mathbb{E}(T_n^{ran})}{\sqrt{\mathbb{E}((T_n^{ran})^2) - (\mathbb{E}(T_n^{ran}))^2}},\end{aligned}\quad (14)$$

and the  $p$ -values

$$\begin{aligned}p_\Sigma &= \mathbb{P}(\Sigma^{ran} > \Sigma), \\ p_T &= \mathbb{P}(T^{ran} > T), \\ p_{T_n} &= \mathbb{P}(T_n^{ran} > T_n).\end{aligned}\quad (15)$$

Note that since we consider  $\mathcal{N}$  realizations of the null model, we cannot estimate probabilities smaller than  $1/\mathcal{N}$ . Therefore, if in our null model we observe no value of  $\Sigma^{ran}$  larger than the true data  $\Sigma$ , we set the conservative estimate  $p_\Sigma = 1/\mathcal{P}$ . A similar procedure is applied also to  $p_T$  and  $p_{T_n}$ .

For each structural edge between node  $X$  and node  $Y$  we can, of course, mine for triadic interactions involving different regulators nodes  $Z$ . To compare predictions, we rank these interactions from most to least likely via lowest to the highest  $p$ -value, or alternatively from highest to lowest  $\Theta$  value and select the top  $k$  ranked triadic interactions, or those above a predetermined significance level.

As we will discuss below, the algorithm performs well on our synthetic model. However, this algorithm focuses exclusively on triples of nodes, and so neglects potentially important network effects. Thus, the algorithm is expected to give better results for triples of nodes in which  $Z$  is not significantly correlated with either  $X$  or  $Y$ .

### B. Validation of the Triaction algorithm on the triadic interaction model

To demonstrate the efficacy of the Triaction algorithm we consider a single network (see Figure 4(a)) of  $N = 10$  nodes,  $L = 12$  edges and  $\hat{L} = 5$  single triadic interactions (each formed by a single node regulating a single edge) on top of which we consider the triadic dynamical model proposed in Sec. III.

Simulations of Eq. (7) on this network show a strong dependence of  $MIz(m)$  on  $m$  for the triples of nodes involved in triadic interactions, with greater significance for smaller values of  $\alpha$ . Figure 3 shows evidence of this

interesting dynamical behavior in the case of a positive regulatory interaction. The function  $MIz(m)$  is fitted with a decision tree with two splits. In this way, three different intervals of values of  $Z$  are identified, each corresponding to a distinct functional behavior of the correlation functions between the variables  $X$  and  $Y$ . Note that our analysis of the function  $MIz(m)$  also allows us to distinguish between positive and negative regulatory interactions. These are associated respectively by an increase in  $MIz$  for larger values of  $z_m$  or decrease of  $MIz$  for larger values of  $z_m$ . In the Supplementary Figures S1-S2, we display further examples of the function  $MIz$  for triadic triples. We observe that as the parameter  $\Gamma$  is raised, the noise increases, which is reflected also in the increased variability of the  $MIz$  functional behavior.

In order to provide an overall assessment of the performance of Triaction in mining triadic interactions on this network, in Figure 4(b) we display the Receiver Operating Characteristic curve (ROC curve) based on the score  $\Theta_\Sigma$ , which we found to perform well for a wide range of parameters. Our numerical results show a very good performance for larger values of  $\alpha$ , and smaller  $\Gamma$  (see Figure 4(b)). As it is apparent from the ROC curve, the Triaction algorithm performs better for higher values of  $\alpha$  and smaller values of  $\Gamma$ . For any values of the parameters, we notice that the false positives are more likely involving short-range triples, i.e. triples in which the regulator node  $Z$  has short (small) structural network distance with the two nodes  $X$  and  $Y$ .

## V. DETECTING TRIADIC INTERACTIONS IN GENE-EXPRESSION DATA

Searching for trigenic interactions in gene-expression is a problem of major interest in biology. For instance, understanding the extent to which a modulator promotes or silences the interplay between a transcription factor and its target gene is crucial for deciphering gene regulation mechanisms. In order to address this question with our method, we considered gene-expression data from Acute Myeloid Leukemia (AML), extracted from the Grand Gene Regulatory Network Database [39, 40]. This dataset comprises  $N = 639$  genes and  $R = 151$  samples. Of course, this is for illustration and validation; the same analysis can be made on any gene expression data derived from human tissues, cancer, cell lines, or small molecule drugs as well as on any other dataset arising from different application domains such as climate data, where triadic interactions on networked data are relevant.

Exhaustive mining of all potential triadic interactions among each triple of nodes in the AML dataset is computationally very demanding (it would require testing of  $> 260M$  triplets). Instead, we focus on edges associated with known biophysical interactions, as identified in the human Protein-Protein Interaction network (PPI) [39]. To do so, we considered the subgraph of the human PPI network that contains all the genes/proteins included in

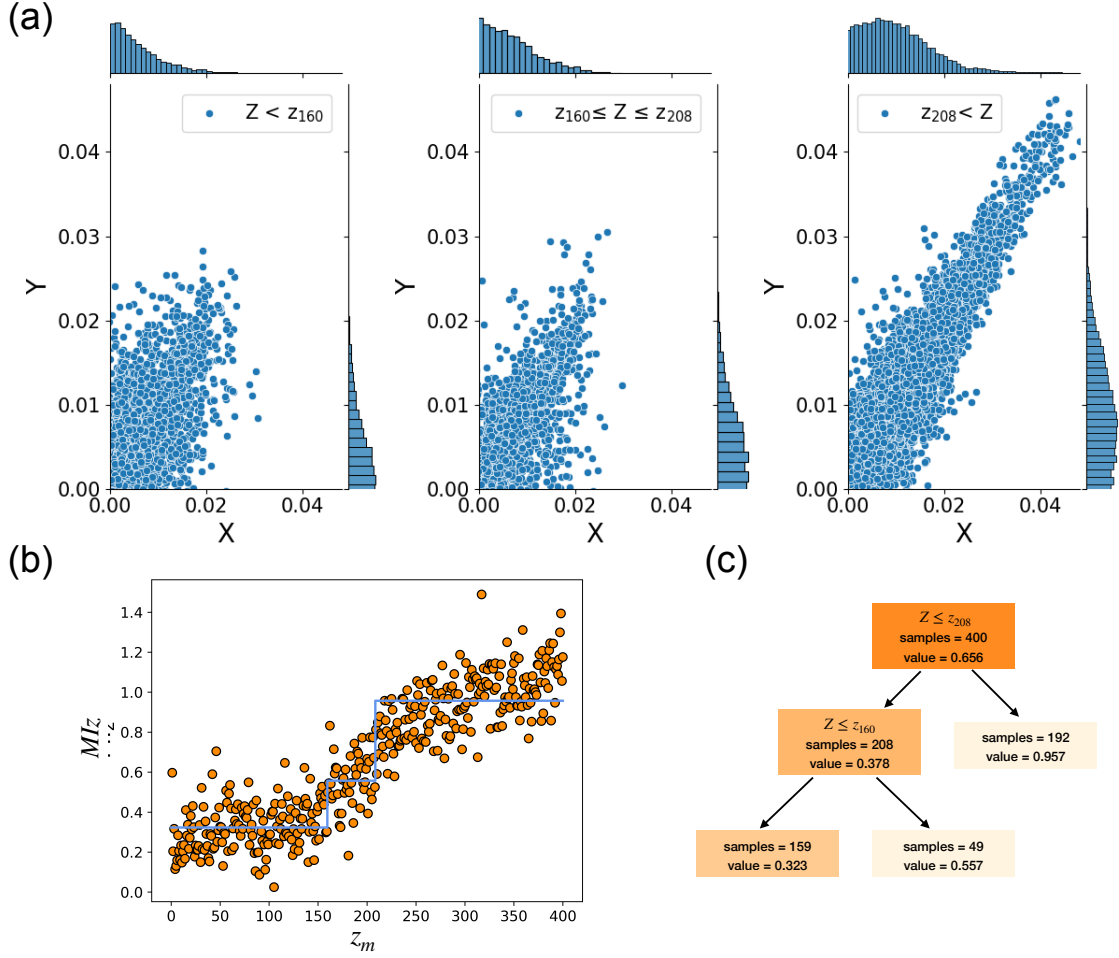


Figure 3. Representative results for a triples of nodes involved in triadic interactions in the continuous model with triadic interactions. The joint distributions of variables  $X$  and  $Y$  conditional on the values of  $Z$  are shown in panel (a). Panel (b) shows the behavior of  $MIz$  as a function of the values of  $z_m$ , which clearly departs from the constant behavior expected in absence of triadic interactions. Panel (c) presents the decision tree for fitting the  $MIz$  functional behavior and determining the range of values of  $Z$  for which the most significant differences among the joint distributions of the variables  $X$  and  $Y$  conditioned on  $Z$  are observed. For more details about the simulation result, we refer to the Supplementary Material.

the AML gene expression data. The number of edges in this subgraph is  $M = 42,511$ . We further refined our choice of candidate triples based on the pairwise information of the PPI network. We considered two random samples of short-range and longer-range triples formed by  $\mathcal{P} = 5000$  triples each (see the Supplementary Material for details). Here, range refers to the distance on the structural network between the regulator node  $Z$  and the nodes  $X$  or  $Y$ .

Here we present the results obtained by our mining algorithm using  $\Theta_\Sigma$  as the significance score,  $P = 5$  bins, and assessed by running  $\mathcal{N} = 5 \times 10^3$  realizations of the null model. These results have strong correlations with the results obtained with the other measures (see Supplementary Figures S3-S4 for comparison).

Figure 5(a) displays the results of our algorithm for both for short-range and longer-range triples, involving a structural edge associated the mutual information MI

and the conditional mutual information CMI between its two end-nodes. In the figure, each considered triple corresponds to a point, color coded according to the value of  $\Sigma$ . Low values of  $\Sigma$  correlate with low values of MI and low values of CMI, while the high values of  $\Sigma$  are typically found for data corresponding to higher values of MI and CMI. Figure 5(b) provides data from two exemplar triples: the top panels present evidence of a triadic interaction with high significance score ( $\Theta_\Sigma = 3.02$ ,  $p_\Sigma = 0.0024$ ), while the bottom panels present evidence of a triadic interaction with low significance score ( $\Theta_\Sigma = 0.97$ ,  $p_\Sigma = 0.84$ ). The modulation of the strength of the interactions in the top panels is demonstrated by the significantly different conditional distributions of gene-expression  $X$  and  $Y$  depending on the value of the gene-expression  $Z$ . On the other hand, in the bottom panels the conditional distributions do not change significantly depending on the value of the gene-

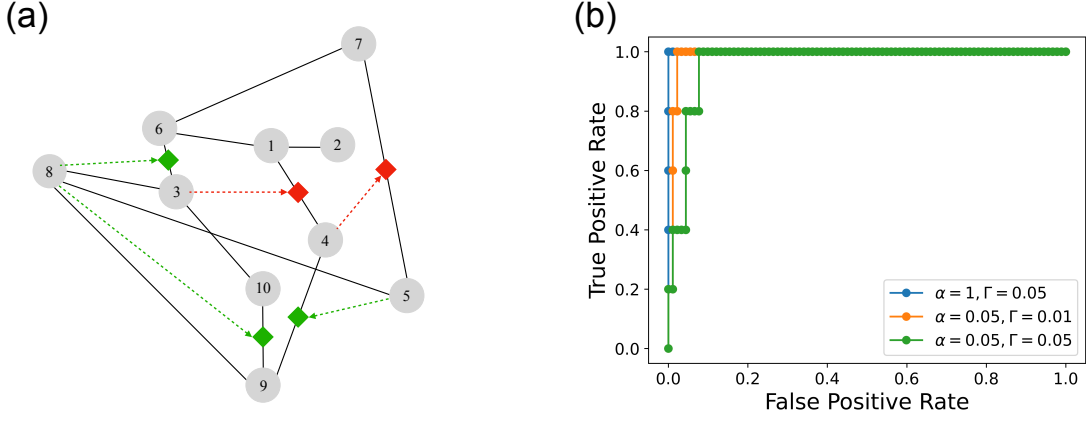


Figure 4. We consider a network with  $N = 10$ , nodes  $L = 12$  edges, and  $\hat{L} = 5$  regulatory interactions (panel (a)). The time series obtained by integrating the stochastic dynamics of the proposed dynamical model for triadic interactions (Eq.(7)) are analyzed with the Triaction algorithm. Panel (b) displays the Receiver Operating Characteristic curve (ROC curve) obtained by running Triaction with  $P = 400$  bins and  $\mathcal{N} = 10^3$  realizations of the null model on these synthetic time series, using  $\Theta_\Sigma$  to score for different parameters values indicated in the legend. The time series is simulated up to a maximum time  $t_{max} = 4000$  with a  $dt = 10^{-2}$ . For the analysis, we consider 40000 time steps (see the Supplementary Material for details). The parameters of the model are:  $\hat{T} = 10^{-3}$ ,  $w^+ = 8$ ,  $w^- = 0.5$ , and  $\alpha$  and  $\Gamma$  as indicated in the figure legend.

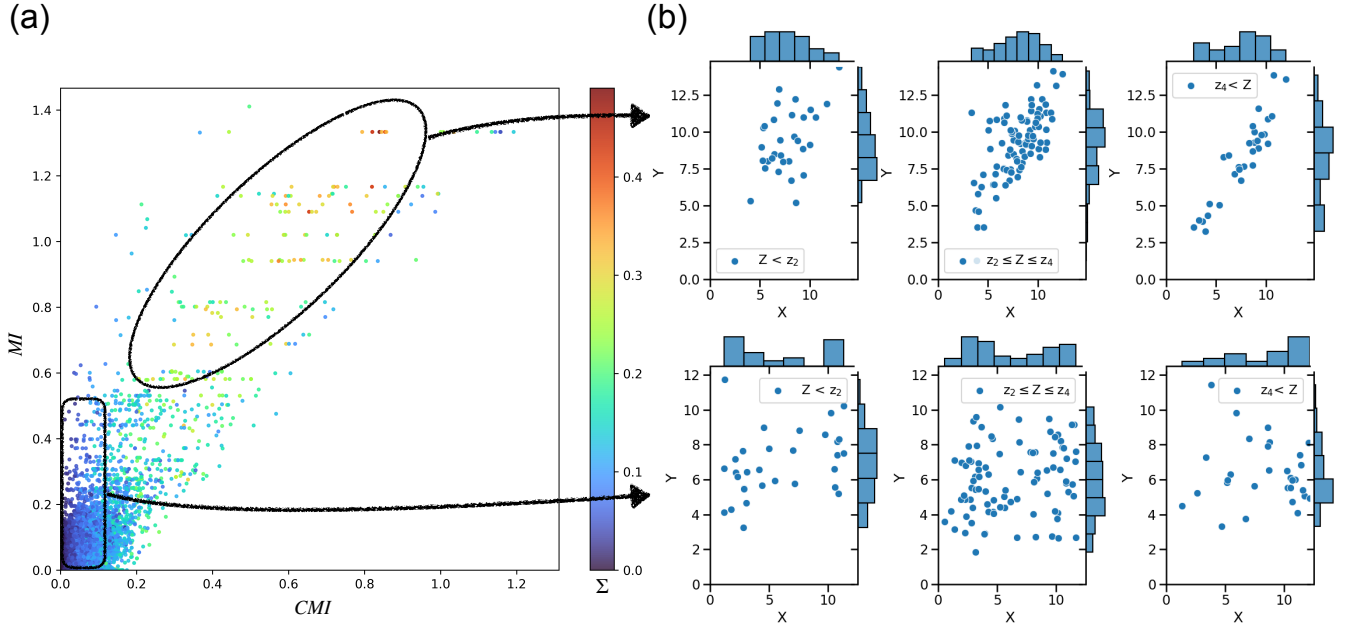


Figure 5. (a) Scatter plot of the results of the Triaction algorithm on AML gene expression data. Each data point shows the information-theoretic measures for a triple of nodes  $X$ ,  $Y$  and  $Z$ , namely MI and CMI, the mutual information and conditional mutual information between  $X$  and  $Y$ , respectively. The colour of each point corresponds to the value of  $\Sigma$ , which characterises the strength of the triadic interaction between gene  $Z$  and the edge between  $X$  and  $Y$ . (b) The results of the decision tree allow us to distinguish three intervals of the value of  $Z$  in which the conditional distribution of the gene expression of  $X$  and  $Y$  differs the most. Plots of these conditional distributions are provided for two exemplary triples: the top one displays a high significance score for the triadic interaction, indicating a meaningful biological association ( $X = \text{GATA1}$ ,  $Y = \text{TAL1}$ ,  $Z = \text{KLF5}$ ,  $\Theta_\Sigma = 3.07$ ,  $p_\Sigma = 0.0038$ ,  $\Sigma = 0.27$ ,  $z_2 = 5.3$ ,  $z_4 = 7.2$ ); the bottom one displays a low significance score ( $X = \text{AR}$ ,  $Y = \text{NR4A3}$ ,  $Z = \text{FLI1}$ ,  $\Theta_\Sigma = 0.99$ ,  $p_\Sigma = 0.838$ ,  $\Sigma = 0.024$ ,  $z_2 = 12.9$ ,  $z_4 = 13.3$ )

expression  $Z$ . For further examples of results obtained on gene-expression triples, see the Supplementary Material.

From this analysis, we can extract a subnetwork (Figure S5(a)) formed by node triplets with a high signifi-

cance score,  $p_{\Sigma} < 0.001$  in this case. Blue nodes and edges compose the structural network, that is, the PPI network. Structural edges are represented as black diamonds (factor nodes), while dashed lines illustrate triadic interactions between a regulatory node and a structural edge. We observe that the genes involved in the highest triadic interactions regulation are genes that play a critical role in AML (Figure S5 and Table I): the HOX family [41], PBX3 [42], and MEIS1 [43]. We also investigated the triadic interactions involving a particular edge, such as HOXB5-HOXB6 shown on Table I and Figure S5(b). In particular, most of the top regulatory nodes are consistent across all three measures ( $\Sigma, T, T_n$ ).

In the gene-expression literature, previous studies have proposed methods to detect modulation of interactions [16]. Our algorithm goes beyond this previous studies as it allows to detect not only strong monotonous positive and negative triadic interactions (see Supplementary Figure S6 and S7) but also strong triadic interactions with non monotonous  $MIz$  functional behavior (see Supplementary Figure S8). The detected interactions strongly depart from triples with low significance score for which the  $MIz$  does not vary significantly (see Supplementary Figure S9). Such results challenge the constraints of monotonic assumptions in existing measures within the gene expression literature. It is important to note that, while the monotonic assumption holds in the gene-expression context, non-monotonic behavior is a rare occurrence. However, in broader systems, the prevalence of mostly monotonic behavior, as observed in gene expression, cannot be assumed. Our measures can detect various functional behaviors, and are applicable to any context where triadic interactions may occur.

## VI. CONCLUSIONS

Our work proposes a comprehensive information theory approach to model and mine triadic interactions between continuous variables. The key observation is that

the mutual information between two variables can be significantly modulated by a third regulatory node. Hence, detecting triadic interactions requires going beyond pairwise measures such as the mutual information and the conditional mutual information. The proposed approach is here used to mine triadic interactions in gene expression data, and we are able to detect known triadic interactions together with new candidate triplets. Our approach outperforms classical methods in the gene expression community, which assume that the CMI function should exhibit monotonicity with the evolution of the conditioning node [16], and extends the method for broader applications. These results are encouraging and may inspire further research in the field of gene regulation, particularly within the context of tissue specificity. Investigating the extent to which triadic interactions are tissue-specific, as well as whether certain regulatory patterns are conserved across different tissues, could yield valuable insights. In the future, the method could be applied to other type of data including times series which can be relevant in other scientific applications, such as climate research.

## CODE AVAILABILITY

The Python package Triaction is available on GitHub at the following link: <https://github.com/anthbapt/triaction>

## ACKNOWLEDGMENTS

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| Regulator | node1 | node2 | rank $\Sigma$ | $\Theta_\Sigma$ | $P_\Sigma$ | rank $T$ | $\Theta_T$ | $P_T$  | rank $T_n$ | $\Theta_{T_n}$ | $P_{T_n}$ |
|-----------|-------|-------|---------------|-----------------|------------|----------|------------|--------|------------|----------------|-----------|
| MEIS1     | HOXB5 | HOXB6 | 1             | 6.94            | 0.0002     | 1        | 6.64       | 0.0002 | 1          | 6.66           | 0.0002    |
| ETS2      | HOXB5 | HOXB6 | 2             | 5.32            | 0.0002     | 2        | 5.93       | 0.0002 | 17         | 3.41           | 0.0028    |
| HOXA3     | HOXB5 | HOXB6 | 3             | 5.23            | 0.0002     | 3        | 5.81       | 0.0002 | 27         | 2.75           | 0.0096    |
| UNCX      | HOXB5 | HOXB6 | 4             | 5.01            | 0.0002     | 5        | 4.86       | 0.0002 | 7          | 4.46           | 0.0002    |
| THRA      | HOXB5 | HOXB6 | 5             | 4.92            | 0.0002     | 4        | 5.45       | 0.0002 | 2          | 6.02           | 0.0002    |
| HOXB7     | HOXB5 | HOXB6 | 11            | 4.14            | 0.0004     | 6        | 4.27       | 0.0006 | 4          | 4.86           | 0.0002    |
| FOSL1     | HOXB5 | HOXB6 | 12            | 4.06            | 0.0002     | 8        | 4.23       | 0.0002 | 3          | 4.90           | 0.0002    |
| HOXB8     | HOXB5 | HOXB6 | 14            | 3.93            | 0.0002     | 7        | 4.26       | 0.0002 | 5          | 4.82           | 0.0002    |

Table I. The list of the top 5 high-significant triples for the three measures  $\Sigma, T, T_n$  involving the structural network edge HOXB5-HOXB6. Across all three measures ( $\Sigma, T$ , and  $T_n$ ), the top triadic interaction involves MEIS1 as the regulatory node. The second highest regulatory node for the HOXB5-HOXB6 edge is ETS2 for the  $\Sigma$  and  $T$  measures, and THRA for the  $T_n$  measure. Notably, THRA also ranks highly for the  $\Sigma$  measure (ranked 5) and the  $T$  measure (ranked 4). The third highest regulatory node for the HOXB5-HOXB6 edge is HOXA3 for both the  $\Sigma$  and  $T$  measures, and FOSL1 for the  $T_n$  measure.

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## Supplemental Material on “Mining higher-order triadic interactions”

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### SUPPLEMENTAL INFORMATION ON THE TRIADIC MODEL WITHIN CONTINUOUS VARIABLES.

We use a network with  $N = 10$  nodes  $L = 12$  edges and  $\hat{L} = 5$  regulatory interactions (shown in Figure 3 of the main text). We consider the time series obtained by integrating the stochastic dynamics of the proposed dynamical model for triadic interactions within continuous variables. The time series is simulated up to a maximum time  $t_{max} = 4000$  with a  $dt = 10^{-2}$  leading to  $4 \times 10^5$  data points. For our analysis we consider the last 200,000 data points sampled every fifth point leading to 40,000 time steps. In Figure 2 of the main text we report the analysis done for the triplet  $[4,9,5]$ , which is triadic. For this figure the parameters of the model are:  $\alpha = 0.05$ ,  $\hat{T} = 10^{-3}$ ,  $\Gamma = 10^{-2}$ ,  $w^+ = 8$ ,  $w^- = 0.5$ , number of bins  $P = 400$ . In the Supplemental Figures S1 and S2 we report the analysis conducted on the same triadic triple of nodes for different parameter values: for Figure S1 we have  $\alpha = 0.01$ ,  $\Gamma = 10^{-2}$ , for Figure S2 we have  $\alpha = 0.05$ ,  $\Gamma = 5 \times 10^{-2}$ . The other parameter values are the same as in Figure 2 of the main text.

### SUPPLEMENTAL INFORMATION ON ANALYSIS OF GENE-EXPRESSION DATASET

#### Triplet selection

We choose two sub-samples of 5000 triples of triadic interactions from the gene-expression associated with Acute Myeloid Leukemia (AML) dataset for our Triaction analyses. The selection process for these sub-samples is motivated by studies indicating that for gene expression data, most of the genes involved in trigenic processes are also involved in digenic processes [1]. Hence, we utilize the Protein-Protein Interaction network (PPI) associated with AML, which captures digenic processes, to choose edges forming the triplets in our study. The selection of the regulatory node aims to encompass both short-range and longer-range interactions. To differentiate between these cases, we employ the shortest path distance in the PPI. The first sub-sample comprises short-range motifs, including the fully connected triangle and the partially connected triangle (see Figure S3(a)). We conduct a similar analysis for longer-range interactions. Figure S3(a) illustrates the distribution of the proportion of triplets categorized by the length of the shortest path between node Z and the edge composed of nodes X and Y. This path length can be expressed as  $\min(d_{XZ}, d_{YZ})$ , where  $d_{XZ}$  denotes the shortest path length between nodes X and Z, and  $d_{YZ}$  indicates the shortest path length between nodes Y and Z.

#### Comparison between short-range and longer range triples in AML dataset

Based on the structural network, specifically the Protein-Protein Interaction network (PPI), we distinguish interactions into short-range (depicted in blue) and longer-range (depicted in red). Longer-range interactions are characterised by a minimum shortest path between structural edges and the regulatory node candidate of at least 2. S3(b) display the probability density function estimated by Gaussian kernels on the histogram of the probability distribution of the score  $\Theta$  for the three measures:  $\Sigma$ ,  $T$ , and  $Tn$ . Curves in varying shades of blue represent short-range interactions, while those in shades of red represent longer-range interactions. Notably, significant  $\Theta$  scores are predominantly associated with short-range interactions. S3(e-f) showcase correlations between  $\Theta$  scores for the three measures. There is a strong correlation between  $\Theta_\Sigma$  and  $\Theta_T$  (S3(e)), these correlation is observed both for short- and long-range interactions. The correlation is also observed between  $\Theta_\Sigma$  and  $\Theta_{Tn}$  (S3(f)). S3(c-d) display mutual information between nodes ( $X$  and  $Y$ ) involved in structural edges, as well as mutual information between  $X$  and

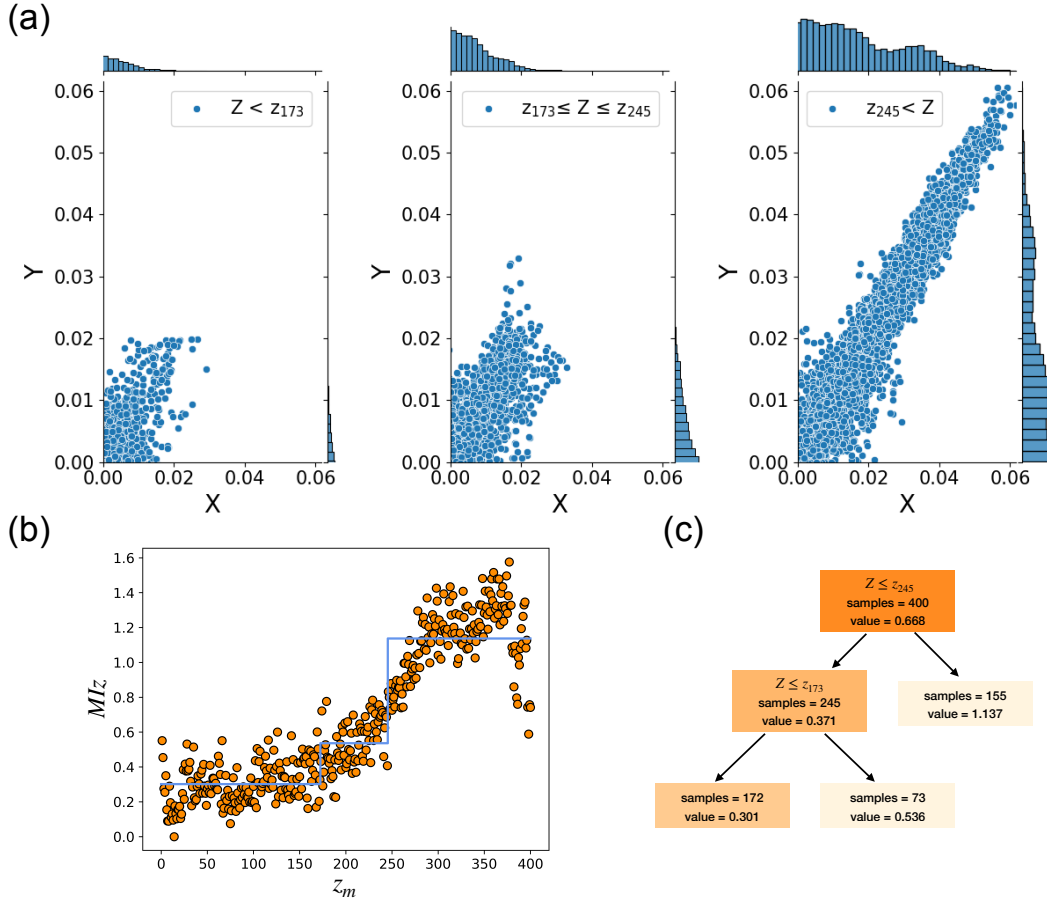


FIG. S1: Exemplary results obtained for a triple of nodes involved in a triadic interactions in the continuous model with triadic interactions. The joint distributions of variables  $X$  and  $Y$  conditional on the values of  $Z$  is shown in panel (a). Panel (b) displays the functional behavior of  $MIz$  as a function of the values of  $z_m$  which clearly departs from the constant behavior expected in absence of triadic interactions. Panel (c) presents the decision tree for fitting the  $MIz$  functional behavior and determining the range of values of  $Z$  for which the most significant differences among the joint distributions of the variables  $X$  and  $Y$  conditional to  $Z$  are observed. For more details about the simulation result we refer to the Supplemental Material. The time series is simulated up to a maximum time  $t_{max} = 4000$  with a  $dt = 10^{-2}$ . For the analysis we consider 40000 time steps. The parameters of the model are:  $\alpha = 0.01$ ,  $\hat{T} = 10^{-3}$ ,  $\Gamma = 10^{-2}$ ,  $w^+ = 8$ ,  $w^- = 0.5$ , number of bins  $P = 400$ . The analysis is done for the triplet  $[4,9,5]$ , of the network in Figure 2 of the main text, which is triadic.

$Y$  conditioned by the third node ( $Z$ ), which is designated as the regulatory node. Colour denotes the logarithm of the inverse of the P-value of the  $\Sigma$  measure ( $P_\Sigma$ ), emphasising significant P-values. Red dots represent short-range interactions (S3(c)), while blue dots represent longer-range interactions (S3(d)). Observations indicate that significant triplets, particularly for short-range interactions, necessitate high mutual information and conditional mutual information. However, for longer-range interactions, conditional mutual information must be higher than mutual information.

#### Comparison between the results obtained with different measures

In Figure S4 we display the results obtained on the gene-expression AML data by performing an analysis conducted using the  $T$  and the  $T_n$  measures. We observe that these results correlate with the results obtained using the  $\Sigma$  measure reported in Fig.4 of the main text.

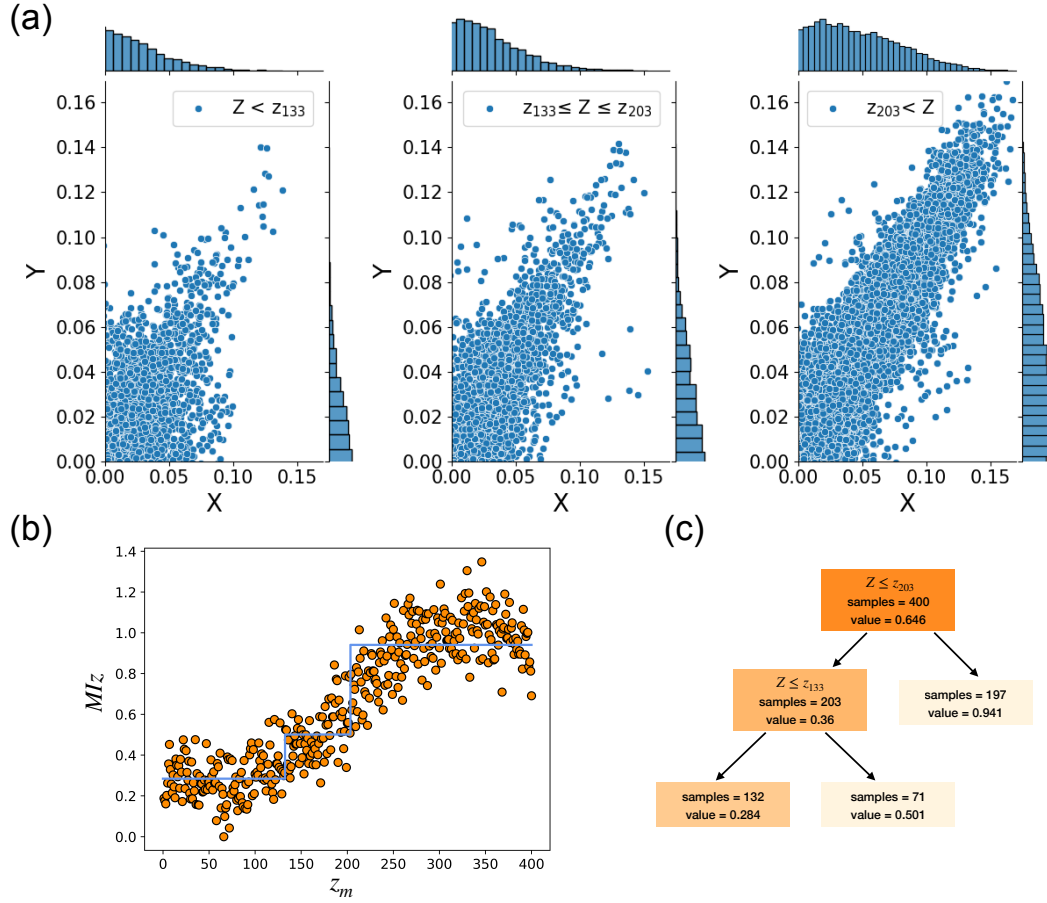


FIG. S2: Exemplary results obtained for a triple of nodes involved in a triadic interactions in the continuous model with triadic interactions. The joint distributions of variables  $X$  and  $Y$  conditional on the values of  $Z$  is shown in panel (a). Panel (b) displays the functional behavior of  $MIz$  as a function of the values of  $z_m$  which clearly departs from the constant behavior expected in absence of triadic interactions. Panel (c) presents the decision tree for fitting the  $MIz$  functional behavior and determining the range of values of  $Z$  for which the most significant differences among the joint distributions of the variables  $X$  and  $Y$  conditional to  $Z$  are observed. For more details about the simulation result we refer to the Supplemental Material. The time series is simulated up to a maximum time  $t_{max} = 4000$  with a  $dt = 10^{-2}$ . For the analysis we consider 40000 time steps (see SM for details). The parameters of the model are:  $\alpha = 0.05$ ,  $\hat{T} = 10^{-3}$ ,  $\Gamma = 5 \times 10^{-2}$ ,  $w^+ = 8$ ,  $w^- = 0.5$ , number of bins  $P = 400$ . The analysis is done for the triplet  $[4,9,5]$ , of the network in Figure 2 of the main text, which is triadic.

#### Supplemental figure and table of detected triadic interactions in AML dataset

We detected 32 triadic interactions with a  $p_\Sigma < 0.001$ , listed in Table S1. In the Table, we report  $\Sigma, T, T_n$ ,  $\Theta_\Sigma, \Theta_T, \Theta_{T_n}$  and the p-values  $p_\Sigma, p_T, p_{T_n}$  associated with each triadic interaction of the network displayed in Figure S5. We observe that the genes involved in the highest triadic interactions regulation are genes to play a critical role in AML (Figure 6), the HOX family [2], PBX3 [3], and MEIS1 [4]. Moreover, a recent study shows that HOXA5 is a regulation hub for AML patients [5] which can also be observed in Figure 6. Furthermore, known triple have been detected with a lower p-value threshold like (HOXA9, PBX3, MEIS1,  $p_\Sigma = 0.06$ ) which are known to cooperate all together in AML patients [6, 7].

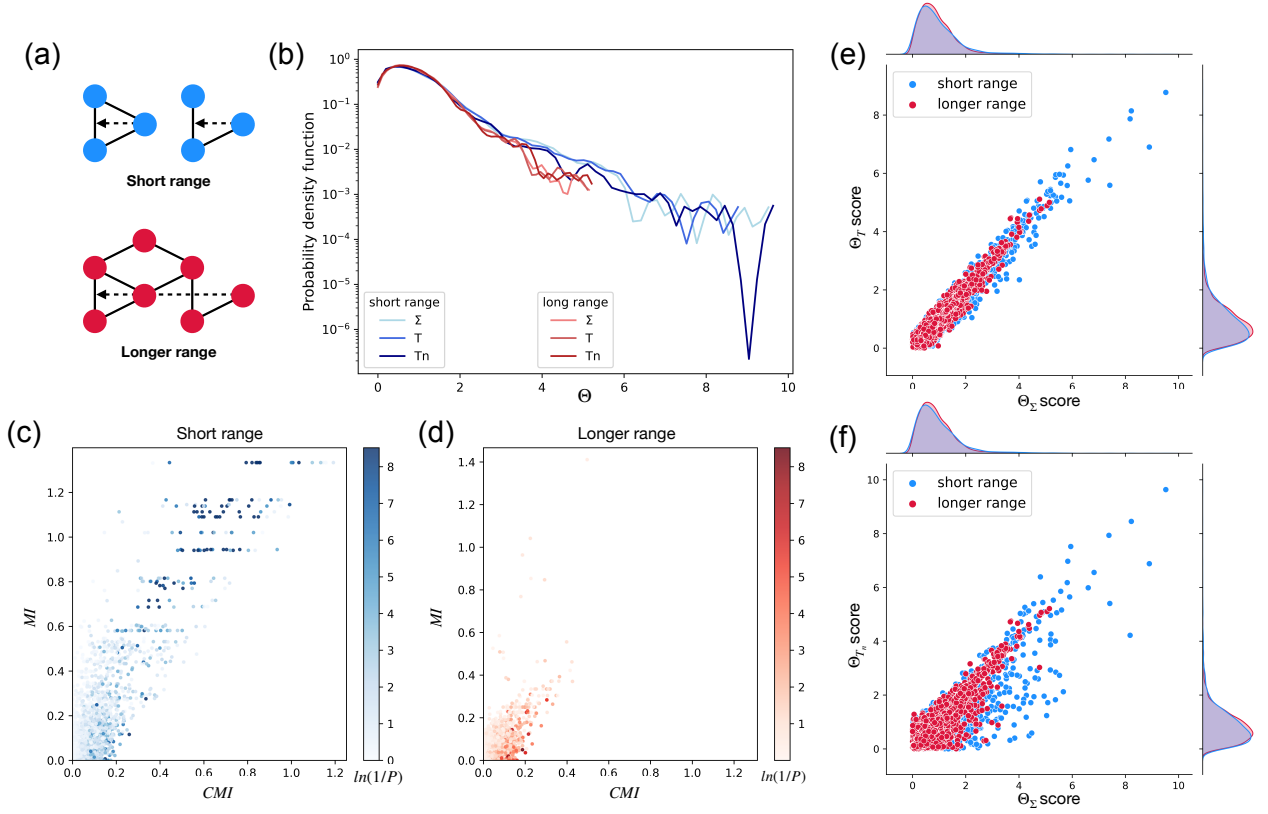


FIG. S3: (a) Candidate triadic interactions occur both at short-range (depicted in blue) and at longer-range (depicted in red). (b) Probability density function of  $\Theta$  for the three measures:  $\Sigma$ ,  $T$ , and  $T_n$ . Curves in varying shades of blue represent short-range interactions, while those in shades of red represent longer-range interactions. (c-d) Scatter plots of the mutual information between nodes ( $X$  and  $Y$ ) involved in structural edges and the mutual information between  $X$  and  $Y$  conditioned by the third node ( $Z$ ). Color denotes the logarithm of the inverse of the  $P$ -value of the  $\Sigma$  measure ( $P_\Sigma$ ). Red dots represent short-range interactions (c), and blue dots represent longer-range interactions (d). (e-f) Scatter plots between  $\Theta$  scores for the three measures: between  $\Theta_\Sigma$  and  $\Theta_T$  (e), and  $\Theta_\Sigma$  and  $\Theta_{T_n}$  (f).

### Supplemental Figures on gene-expression results

In Figure S6-S9 we display exemplary results obtained by applying the Triaction algorithm on the AML dataset. Figure S6 provides an example of high-significant positive triadic interaction. Figure S6 provides an example of high-significant negative triadic interactions. Figure S8 provides an example of triadic interactions displaying a non-monotonous  $MIz$  functional behavior. Figure S9 provides an example of triple with low significance score for triadic interactions with a almost flat  $MIz$  profile.

### TRIACTION PYTHON PACKAGE

The Triaction algorithm here proposed is implemented by a Python package, called Triaction, that we have developed for detecting triadic interactions within continuous and discrete variables. The Triaction package allows to work with both data-frames and data sets associated with a pairwise network. From this initial data, the package provides various ways to extract relevant features and detect triadic interactions. We have included several representations and visualisations in the package to aid in the interpretation of the results. The code is available on GitHub at the following link: <https://github.com/anthbapt/triaction>. Additionally, we offer documentation to guide users through the analysis process.

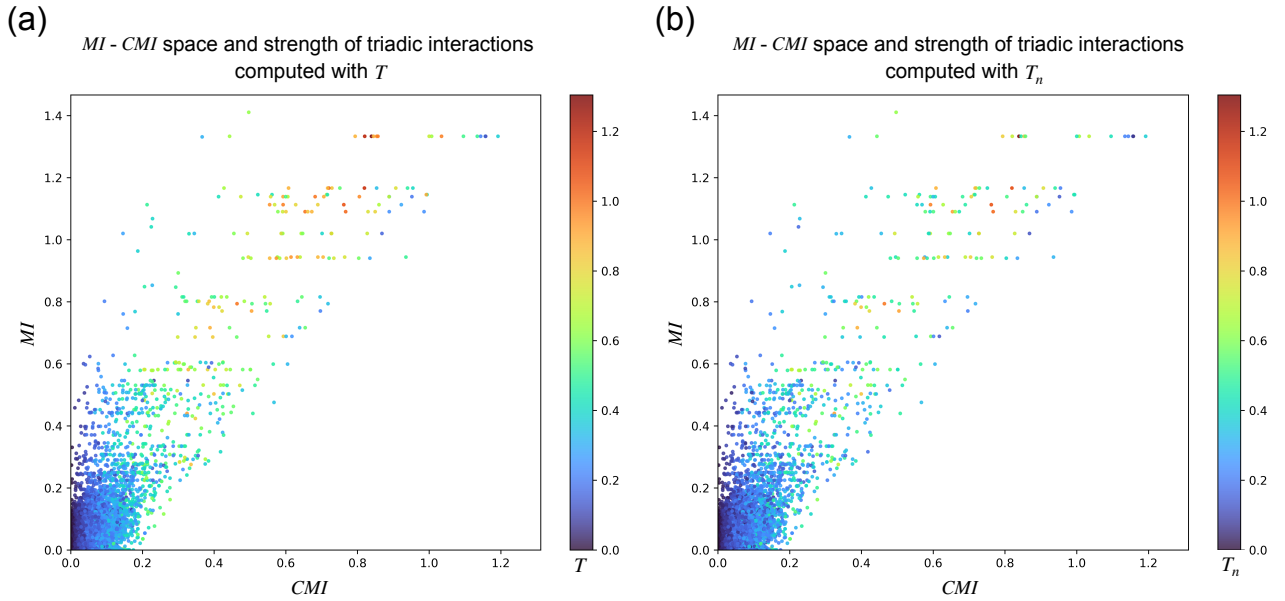


FIG. S4: (a) Scatter plot which displays the MI (Y-axis) value between two genes, denoted  $X$  and  $Y$ , and the CMI (X-axis) between the same genes  $X$  and  $Y$  conditioned by a third gene, denoted  $Z$ . The colour corresponds to the value of our measure  $T$  which characterises the strength of the triadic interaction between gene  $Z$  and edge involving  $X$  and  $Y$ . (b) Same figure for the measure  $T_n$ .

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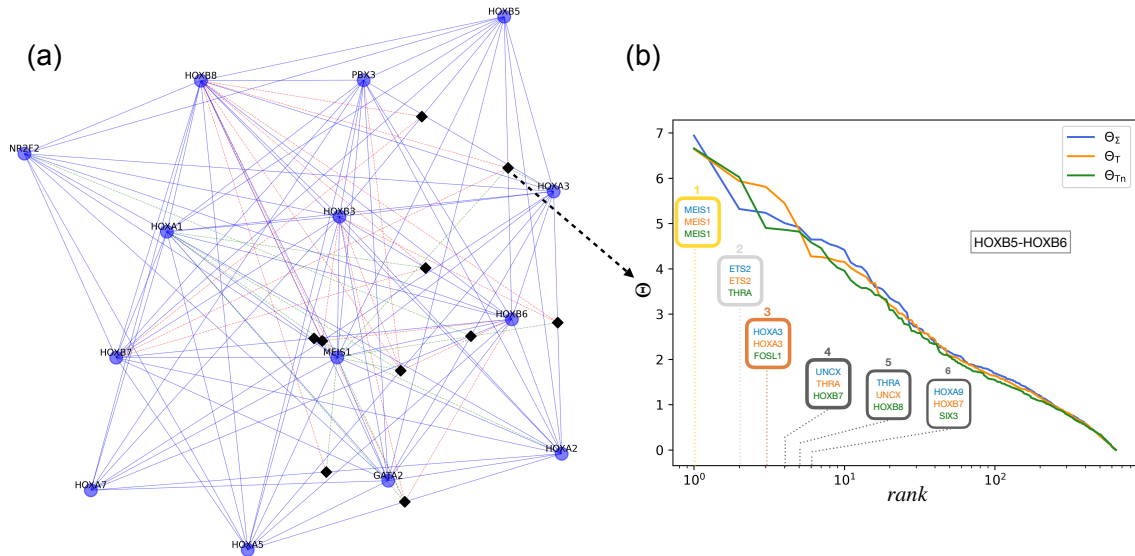


FIG. S5: (a) Visualization of the AML network with triadic interactions mined by the Triaction algorithm including the 32 detected triadic interactions with  $p_\Sigma < 10^{-3}$  (see Supplementary Table for the list of such interactions). Blue nodes and edges compose the structural network, which is a subgraph of the Protein-Protein Interaction network (PPI). Factor nodes are depicted as black diamonds, while dashed lines (green for positive and red for negative) illustrate regulatory triadic interactions. (b) We consider all the putative triadic interactions involving the structural network edge HOXB5-HOXB6 and any possible regulatory node. The obtained values of  $\Theta_\Sigma$ ,  $\Theta_T$ , and  $\Theta_{Tn}$ , are plotted against their rank. The nodes associated with the six highest ranked  $\Theta$  scores are indicated in the insets. Across all three measures ( $\Sigma$ ,  $T$ , and  $Tn$ ), the top triadic interaction involves MEIS1 as the regulatory node (depicted in a golden frame inset). The second highest regulatory node for the HOXB5-HOXB6 edge is ETS2 for the  $\Sigma$  and  $T$  measures, and THRA for the  $Tn$  measure (illustrated in a silver frame inset). Notably, THRA also ranks highly for the  $\Sigma$  measure (ranked 5) and the  $T$  measure (ranked 4). The third highest regulatory node for the HOXB5-HOXB6 edge is HOXA3 for both the  $\Sigma$  and  $T$  measures, and FOXL1 for the  $Tn$  measure (highlighted in a bronze frame-inset).

| Regulator | node1 | node2 | $\Sigma$ | $T$   | $T_n$ | $\Theta_\Sigma$ | $\Theta_T$ | $\Theta_{T_n}$ | $P_\Sigma$ | $P_T$  | $P_{T_n}$ |
|-----------|-------|-------|----------|-------|-------|-----------------|------------|----------------|------------|--------|-----------|
| HOXB3     | HOXA2 | HOXA5 | 0.280    | 0.870 | 0.518 | 4.310           | 5.070      | 2.437          | 0.0002     | 0.0002 | 0.0164    |
| MEIS1     | HOXA3 | HOXA5 | 0.490    | 1.304 | 1.304 | 9.521           | 8.777      | 9.634          | 0.0002     | 0.0002 | 0.0002    |
| MEIS1     | HOXB5 | HOXB6 | 0.427    | 1.163 | 1.082 | 6.824           | 6.466      | 6.555          | 0.0002     | 0.0002 | 0.0002    |
| HOXB6     | HOXA2 | HOXA5 | 0.292    | 0.835 | 0.530 | 4.727           | 4.861      | 2.598          | 0.0002     | 0.0002 | 0.0130    |
| HOXB8     | HOXA2 | HOXA5 | 0.256    | 0.744 | 0.571 | 3.782           | 4.019      | 3.005          | 0.0002     | 0.0002 | 0.0050    |
| HOXB3     | HOXA2 | HOXA3 | 0.325    | 0.942 | 0.715 | 5.186           | 5.446      | 4.059          | 0.0002     | 0.0002 | 0.0002    |
| PBX3      | HOXA3 | HOXA5 | 0.438    | 1.196 | 0.722 | 8.179           | 7.870      | 4.219          | 0.0002     | 0.0002 | 0.0002    |
| HOXB6     | HOXA3 | HOXA5 | 0.326    | 0.896 | 0.458 | 5.372           | 5.194      | 1.825          | 0.0002     | 0.0002 | 0.0460    |
| HOXB8     | HOXA3 | HOXA5 | 0.329    | 0.981 | 0.694 | 5.372           | 5.862      | 4.003          | 0.0002     | 0.0002 | 0.0004    |
| HOXB6     | HOXA3 | HOXA7 | 0.262    | 0.737 | 0.404 | 4.447           | 4.468      | 1.716          | 0.0002     | 0.0002 | 0.0570    |
| HOXB3     | HOXA3 | HOXA5 | 0.330    | 0.883 | 0.819 | 5.421           | 5.047      | 5.057          | 0.0002     | 0.0002 | 0.0002    |
| HOXB3     | HOXA3 | HOXA7 | 0.291    | 0.820 | 0.528 | 5.180           | 5.232      | 2.931          | 0.0002     | 0.0002 | 0.0074    |
| HOXB7     | HOXB5 | HOXB6 | 0.309    | 0.884 | 0.884 | 4.258           | 4.404      | 5.059          | 0.0002     | 0.0002 | 0.0002    |
| HOXB8     | HOXA3 | HOXA7 | 0.371    | 1.024 | 1.024 | 7.383           | 7.176      | 7.934          | 0.0002     | 0.0002 | 0.0002    |
| HOXA1     | HOXA3 | HOXA5 | 0.411    | 0.948 | 0.854 | 7.416           | 5.589      | 5.402          | 0.0002     | 0.0002 | 0.0002    |
| MEIS1     | HOXA3 | HOXA7 | 0.428    | 1.000 | 0.927 | 8.901           | 6.901      | 6.880          | 0.0002     | 0.0002 | 0.0002    |
| HOXA2     | HOXB6 | HOXB7 | 0.323    | 0.829 | 0.350 | 4.383           | 3.719      | 0.485          | 0.0002     | 0.0014 | 0.2832    |
| HOXA3     | HOXB5 | HOXB6 | 0.358    | 1.074 | 0.624 | 5.386           | 5.950      | 2.849          | 0.0002     | 0.0002 | 0.0062    |
| HOXB8     | HOXA2 | HOXA7 | 0.258    | 0.704 | 0.704 | 3.529           | 3.351      | 3.908          | 0.0006     | 0.0014 | 0.0006    |
| HOXB8     | HOXB3 | HOXB5 | 0.291    | 0.913 | 0.913 | 4.807           | 5.707      | 6.391          | 0.0002     | 0.0002 | 0.0002    |
| HOXA1     | HOXB3 | HOXB6 | 0.254    | 0.715 | 0.715 | 4.076           | 4.118      | 4.722          | 0.0006     | 0.0010 | 0.0002    |
| HOXB7     | HOXB3 | HOXB6 | 0.320    | 0.809 | 0.809 | 5.908           | 5.054      | 5.646          | 0.0002     | 0.0002 | 0.0002    |
| HOXB7     | HOXB3 | HOXB5 | 0.275    | 0.786 | 0.786 | 4.365           | 4.544      | 5.126          | 0.0002     | 0.0002 | 0.0002    |
| MEIS1     | HOXA2 | HOXA3 | 0.343    | 0.916 | 0.839 | 5.603           | 5.177      | 5.161          | 0.0002     | 0.0002 | 0.0002    |
| HOXB8     | HOXA2 | HOXA3 | 0.326    | 0.869 | 0.820 | 5.187           | 4.799      | 4.961          | 0.0002     | 0.0002 | 0.0002    |
| HOXA1     | HOXA3 | HOXA7 | 0.292    | 0.842 | 0.627 | 5.189           | 5.403      | 3.866          | 0.0002     | 0.0002 | 0.0004    |
| HOXB8     | HOXB5 | HOXB6 | 0.296    | 0.872 | 0.872 | 4.051           | 4.394      | 5.032          | 0.0002     | 0.0002 | 0.0002    |
| HOXB8     | HOXB3 | HOXB6 | 0.322    | 0.994 | 0.994 | 5.948           | 6.816      | 7.519          | 0.0002     | 0.0002 | 0.0002    |
| MEIS1     | HOXA2 | HOXA5 | 0.367    | 0.935 | 0.888 | 6.605           | 5.764      | 5.985          | 0.0002     | 0.0002 | 0.0002    |
| HOXA1     | HOXA2 | HOXA5 | 0.256    | 0.665 | 0.548 | 3.732           | 3.283      | 2.765          | 0.0002     | 0.0022 | 0.0102    |
| NR2F2     | GATA2 | HOXA3 | 0.271    | 0.690 | 0.690 | 8.225           | 8.144      | 8.451          | 0.0002     | 0.0002 | 0.0002    |
| MEIS1     | HOXA2 | HOXA7 | 0.266    | 0.664 | 0.632 | 3.780           | 3.049      | 3.276          | 0.0002     | 0.0040 | 0.0042    |

TABLE S1: The list of the 32 high-significant triples involving and new candidates for triadic interactions obtained by applying the Triaction algorithm to the AML gene-expression data.

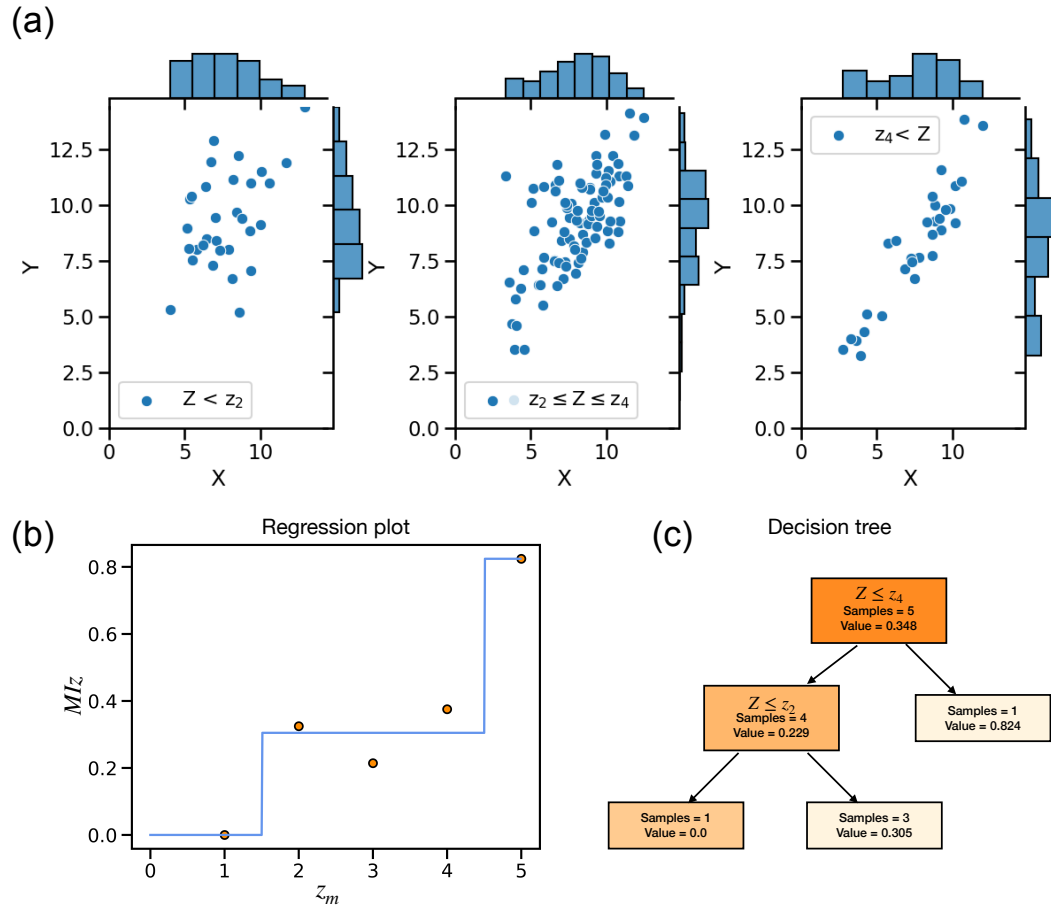


FIG. S6: **Strong triadic interaction:** We choose as thresholds the values defined by the tree to split the data (here  $z_2$  and  $z_4$ ).  $X = \text{GATA1}$ ,  $Y = \text{TAL1}$ ,  $Z = \text{KLF5}$ ,  $\Sigma = 0.27$ ,  $\Theta_\Sigma = 3.07$ ,  $P_\Sigma = 0.0038$ ,  $T = 0.82$ ,  $\Theta_T = 3.62$ ,  $P_T = 0.0014$ ,  $T_n = 0.45$ ,  $\Theta_{Tn} = 1.19$ ,  $P_{Tn} = 0.124$ ,  $z_2 = 5.3$ ,  $z_4 = 7.2$

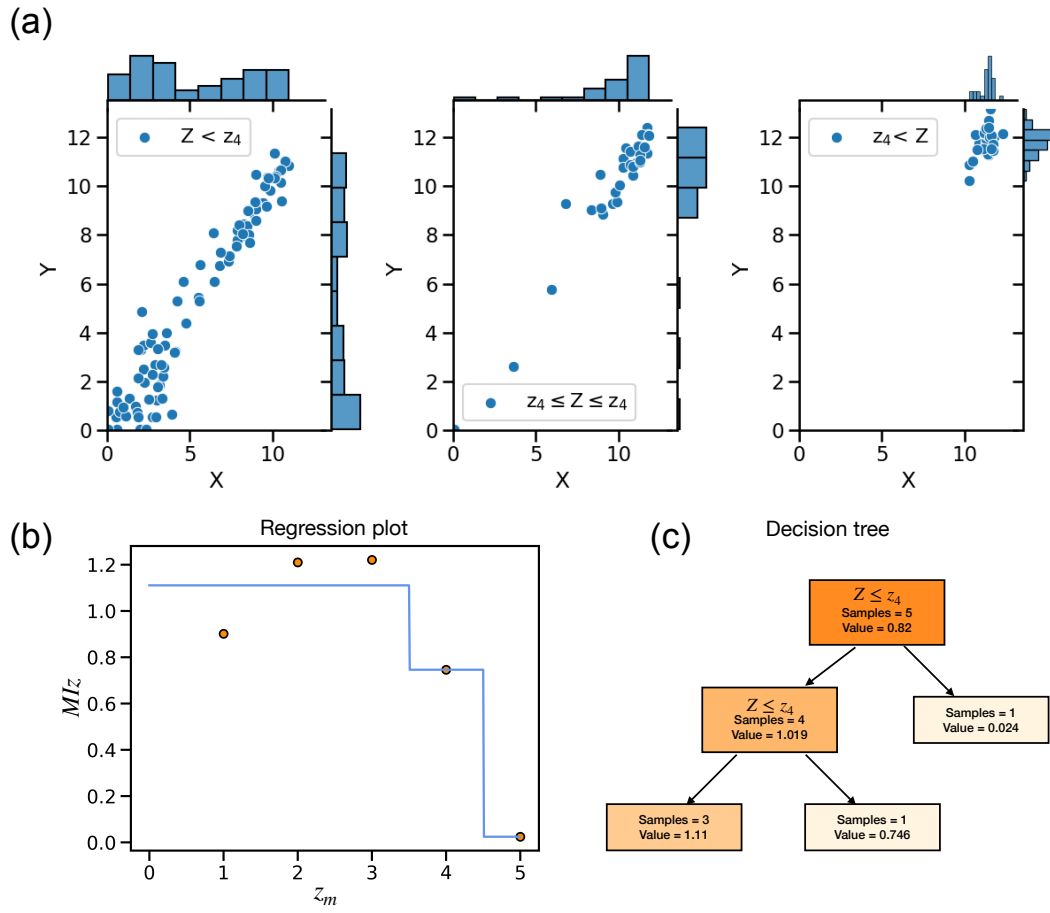


FIG. S7: **Strong triadic interaction:** We choose as threshold the value defined by the tree to split the data ( $z_4$ ).  $X = \text{HOXA3}$ ,  $Y = \text{HOXA5}$ ,  $Z = \text{PBX3}$ ,  $\Sigma = 0.44$ ,  $\Theta_\Sigma = 6.33$ ,  $P_\Sigma = 0.0002$ ,  $T = 1.20$ ,  $\Theta_T = 6.07$ ,  $P_T = 0.0002$ ,  $T_n = 0.72$ ,  $\Theta_{T_n} = 3.12$ ,  $P_{T_n} = 0.0048$ ,  $z_4 = 12.8$ .

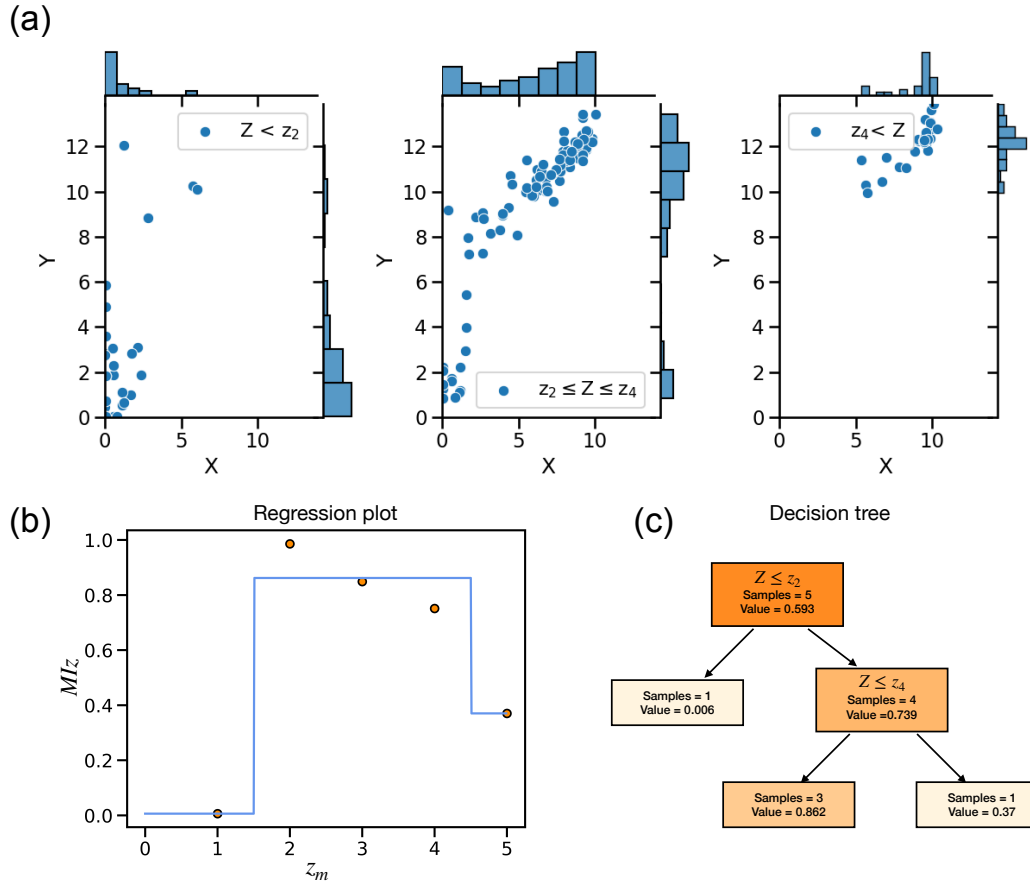


FIG. S8: **Strong triadic interaction:** We choose as thresholds the values defined by the tree to split the data (here  $z_2$  and  $z_4$ ).  $X = \text{HOXA7}$ ,  $Y = \text{HOXA9}$ ,  $Z = \text{HOXA1}$ ,  $\Sigma = 0.36$ ,  $\Theta_\Sigma = 4.09$ ,  $P_\Sigma = 0.0006$ ,  $T = 0.98$ ,  $\Theta_T = 3.93$ ,  $P_T = 0.0006$ ,  $T_n = 0.98$ ,  $\Theta_{Tn} = 4.52$ ,  $P_{Tn} = 0.0002$ ,  $z_2 = 4.6$ ,  $z_4 = 7.1$

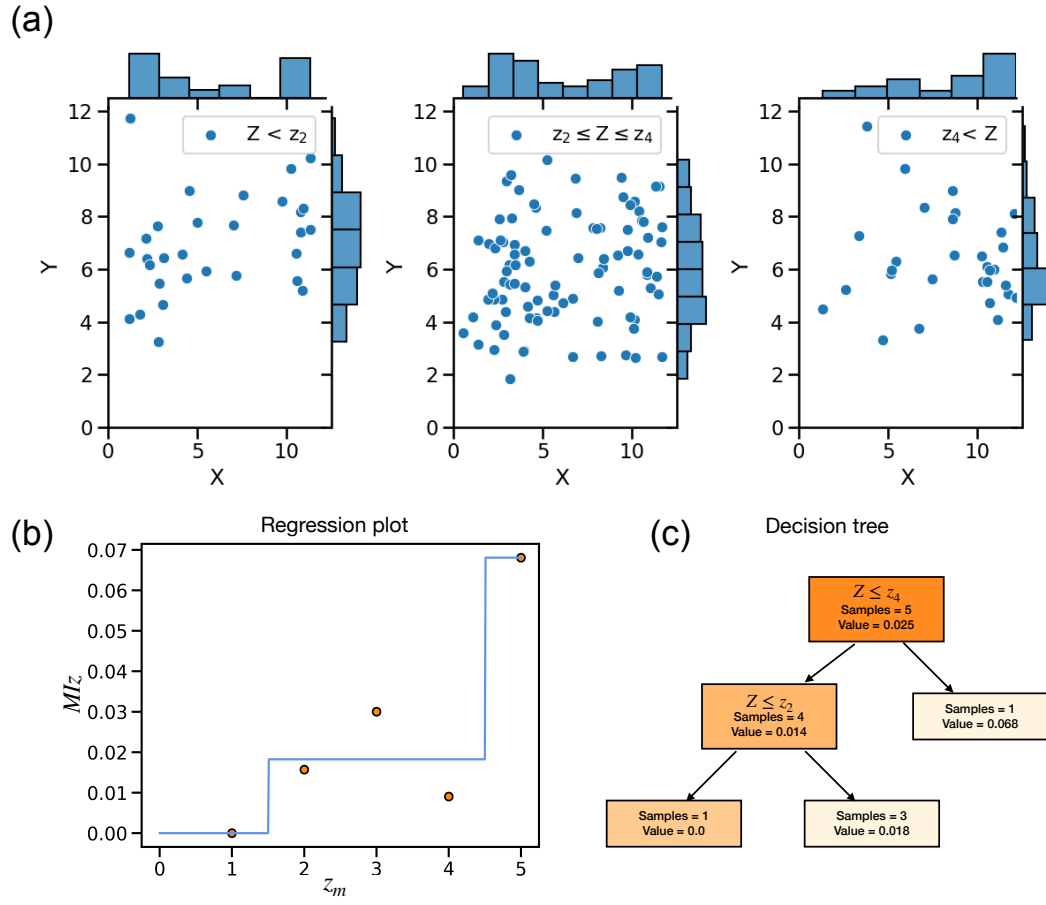


FIG. S9: **Non triadic interaction:** We choose as thresholds the values defined by the tree to split the data (here  $z_2$  and  $z_4$ ).  $X = \text{AR}$ ,  $Y = \text{NR4A3}$ ,  $Z = \text{FLI1}$ ,  $\Sigma = 0.024$ ,  $\Theta_\Sigma = 0.99$ ,  $p_\Sigma = 0.838$ ,  $T = 0.068$ ,  $\Theta_T = 0.88$ ,  $p_T = 0.81$ ,  $T_n = 0.059$ ,  $\Theta_{Tn} = 0.91$ ,  $P_{Tn} = 0.822$ ,  $z_2 = 12.9$ ,  $z_4 = 13.3$ .