## S.1 Supplementary material

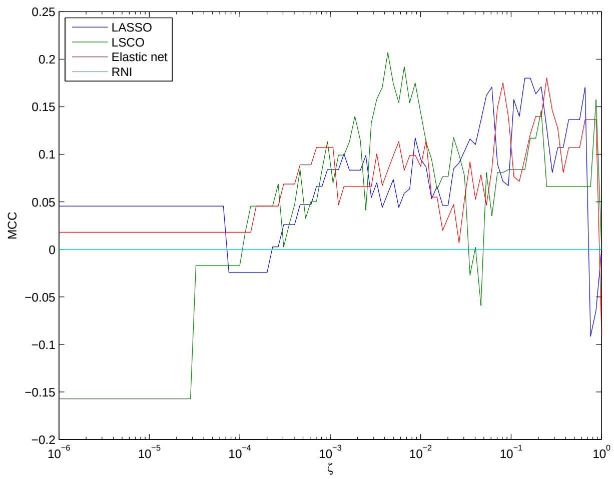
### S.1.1 Analysis of biological data

Lorenz *et al.*[2] presents the result of running the inference method NIR on their data set in terms of sensitivity = TP/(TP+FN) and precision = TP/(TP+FP), and reports the values 62% and 69%, respectively. The corresponding values that we calculate without considering the sign of the interactions for the given matrices in their supplemental data is 0.7% and 0.76%, respectively.

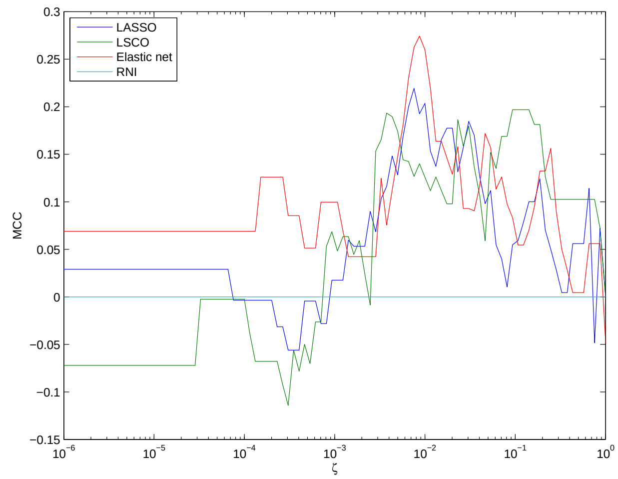
To calculate the variance, $\lambda$ of the data matrices in Lorenz *et al.*[2], we extracted the propagated standard error (SE)[1] for each data point as reported in their supplementary table S2 and S3. We then calculated the weighted average variance,

$$\lambda = \frac{R}{NM}\sum_{i=1}^{N}\sum_{j=1}^{M}\mathrm{SE}_{ij}^{2}, \tag{S12}$$

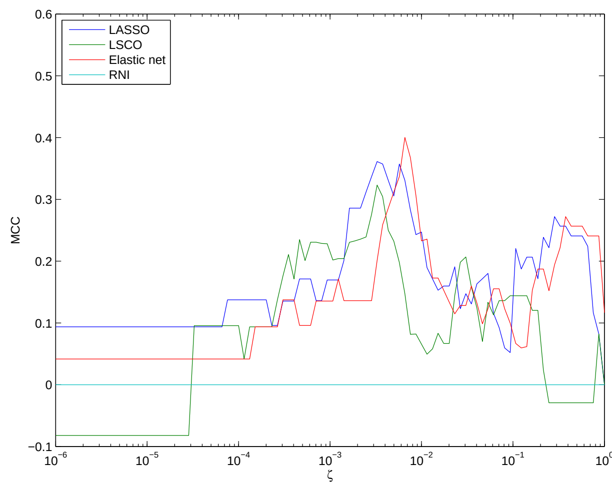
where $R$ is the number of biological replicates, $N$ is the number of genes, $M$ the number of experiments and $\mathrm{SE}_{ij}$ is the propagated standard error for data point $ij$.




(a) Lorenz *et al.*[2] S10 network




(b) Lorenz *et al.*[2] S19 network




(c) Lorenz *et al.*[2] S9 network

**Fig. S.1** Performance over the full regularisation path for Lorenz *et al.*[2] networks

**Table S.1** Properties of data sets with SBED perturbations used in simulations. $\kappa(\boldsymbol{A})$ is the interampatteness degree of the network and $\kappa(\boldsymbol{Y})$ is the condition number of the response matrix. $\#(\ p_{ij} \neq 0)$ is the total number of perturbations in the matrix $\boldsymbol{P}$. The $\overline{\boldsymbol{p}_{1,0}} = \max_j ||\boldsymbol{p}_i \neq 0||_1$, that is, the maximum number of perturbations/experiment over all experiments and $\underline{\boldsymbol{p}_{1,0}} = \min_j ||\boldsymbol{p}_i \neq 0||_1$ is the corresponding minimum. $\lambda(\text{SNR} = 1)$ is the variance of the noise for SNR = 1.

| ID | $\kappa(\boldsymbol{A})$ | $\kappa(\boldsymbol{Y})$ | $\#(\ p_{ij} \neq 0)$ | $\underline{\boldsymbol{p}_{1,0}}$ | $\overline{\boldsymbol{p}_{1,0}}$ | $\lambda(\text{SNR} = 1)$ |
|---|---|---|---|---|---|---|
| 1 | 100.56 | 1.54 | 56 | 2 | 5 | 0.00237 |
| 2 | 107.95 | 1.45 | 45 | 1 | 4 | 0.0025 |
| 3 | 6.90 | 1.76 | 29 | 1 | 3 | 0.00198 |
| 4 | 7.55 | 1.93 | 28 | 1 | 2 | 0.00175 |
| 5 | 7.82 | 1.87 | 28 | 1 | 2 | 0.00169 |
| 6 | 7.89 | 1.98 | 34 | 1 | 3 | 0.00172 |
| 7 | 8.76 | 1.48 | 31 | 1 | 4 | 0.00242 |
| 8 | 9.07 | 1.43 | 38 | 1 | 4 | 0.00264 |
| 9 | 91.61 | 1.49 | 68 | 1 | 5 | 0.00248 |
| 10 | 92.75 | 1.57 | 90 | 3 | 5 | 0.00225 |
| 11 | 92.75 | 1.40 | 50 | 1 | 4 | 0.00265 |
| 12 | 92.87 | 1.33 | 56 | 1 | 6 | 0.00288 |
| 13 | 9.44 | 1.34 | 36 | 1 | 4 | 0.00263 |
| 14 | 94.95 | 1.47 | 33 | 1 | 4 | 0.00257 |
| 15 | 9.54 | 1.80 | 42 | 1 | 6 | 0.00181 |
| 16 | 96.49 | 1.47 | 35 | 1 | 4 | 0.00253 |
| 17 | 96.97 | 1.57 | 56 | 1 | 6 | 0.00221 |
| 18 | 99.00 | 1.81 | 35 | 1 | 3 | 0.00188 |
| 19 | 9.95 | 1.70 | 29 | 1 | 3 | 0.00196 |
| 20 | 9.99 | 1.78 | 39 | 1 | 5 | 0.00178 |

**Table S.2** Properties of data sets with NRDP experimental design used in simulations. $\kappa(\boldsymbol{A})$ is the interampatteness degree of the network and $\kappa(\boldsymbol{Y})$ is the condition number of the response matrix. $\#(\ p_{ij} \neq 0)$ is the total number of perturbations in the matrix $\boldsymbol{P}$. The $\overline{\boldsymbol{p}_{1,0}} = \max_j |\boldsymbol{p}_i \neq 0|_1$, that is, the maximum number of perturbations/experiment over all experiments and $\underline{\boldsymbol{p}_{1,0}} = \min_j ||\boldsymbol{p}_i \neq 0||_1$ is the corresponding minimum. $\lambda(\text{SNR} = 1)$ is the variance of the noise for SNR = 1.

| ID | $\kappa(\boldsymbol{A})$ | $\kappa(\boldsymbol{Y})$ | $\#(\ p_{ij} \neq 0)$ | $\underline{\boldsymbol{p}_{1,0}}$ | $\overline{\boldsymbol{p}_{1,0}}$ | $\lambda(\text{SNR} = 1)$ |
|---|---|---|---|---|---|---|
| 1 | 100.56 | 93.69 | 40 | 2 | 2 | 0.000108 |
| 2 | 107.95 | 175.47 | 40 | 2 | 2 | 7.72e-05 |
| 3 | 6.90 | 9.52 | 40 | 2 | 2 | 0.0187 |
| 4 | 7.55 | 10.56 | 40 | 2 | 2 | 0.0143 |
| 5 | 7.82 | 10.92 | 40 | 2 | 2 | 0.0167 |
| 6 | 7.89 | 11.52 | 40 | 2 | 2 | 0.0129 |
| 7 | 8.76 | 14.22 | 40 | 2 | 2 | 0.0103 |
| 8 | 9.07 | 15.71 | 40 | 2 | 2 | 0.00855 |
| 9 | 91.61 | 131.57 | 40 | 2 | 2 | 5.57e-05 |
| 10 | 92.75 | 124.70 | 40 | 2 | 2 | 7.97e-05 |
| 11 | 92.75 | 153.94 | 40 | 2 | 2 | 8.4e-05 |
| 12 | 92.87 | 135.91 | 40 | 2 | 2 | 0.000104 |
| 13 | 9.44 | 13.52 | 40 | 2 | 2 | 0.00936 |
| 14 | 94.95 | 95.24 | 40 | 2 | 2 | 0.000126 |
| 15 | 9.54 | 16.48 | 40 | 2 | 2 | 0.00659 |
| 16 | 96.49 | 99.79 | 40 | 2 | 2 | 0.000111 |
| 17 | 96.97 | 181.29 | 40 | 2 | 2 | 5.07e-05 |
| 18 | 99.00 | 150.37 | 40 | 2 | 2 | 0.000103 |
| 19 | 9.95 | 23.03 | 40 | 2 | 2 | 0.00306 |
| 20 | 9.99 | 11.92 | 40 | 2 | 2 | 0.00771 |

**Table S.3** Properties of network models of size N=10. $\kappa(\boldsymbol{A})$ is the interampatteness degree of the network, # SC is the number of strongly connected components in the network as reported by `graphconncomp` in MATLAB. $\tau(\boldsymbol{G})$ is the time constant for the system $\boldsymbol{G} = -\boldsymbol{A}^{-1}$.

| ID | Type | $\kappa(\boldsymbol{A})$ | # links | # SC | $\tau(\boldsymbol{G})$ |
|---|---|---|---|---|---|
| 1 | random | 100.56 | 25 | 8 | 0.11 |
| 2 | random | 107.95 | 25 | 5 | 0.115 |
| 3 | random | 6.90 | 25 | 4 | 0.186 |
| 4 | random | 7.55 | 25 | 6 | 0.193 |
| 5 | random | 7.82 | 25 | 5 | 0.146 |
| 6 | random | 7.89 | 25 | 3 | 0.163 |
| 7 | random | 8.76 | 25 | 8 | 0.176 |
| 8 | random | 9.07 | 25 | 6 | 0.183 |
| 9 | random | 91.61 | 25 | 4 | 0.204 |
| 10 | random | 92.75 | 25 | 10 | 0.107 |
| 11 | random | 92.75 | 25 | 6 | 0.108 |
| 12 | random | 92.87 | 25 | 9 | 0.114 |
| 13 | random | 9.44 | 25 | 3 | 0.188 |
| 14 | random | 94.95 | 25 | 7 | 0.163 |
| 15 | random | 9.54 | 25 | 10 | 0.179 |
| 16 | random | 96.49 | 25 | 6 | 0.127 |
| 17 | random | 96.97 | 25 | 5 | 0.21 |
| 18 | random | 99.00 | 25 | 5 | 0.101 |
| 19 | random | 9.95 | 25 | 4 | 0.203 |
| 20 | random | 9.99 | 25 | 10 | 0.289 |


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**Table S.4** Properties of network models of size N=45. $\kappa(\boldsymbol{A})$ is the interampatteness degree of the network, # SC is the number of strongly connected components in the network as reported by `graphconncomp` in MATLAB. $\tau(\boldsymbol{G})$ is the time constant for the system $\boldsymbol{G} = -\boldsymbol{A}^{-1}$.

| ID | Type | $\kappa(\boldsymbol{A})$ | # links | # SC | $\tau(\boldsymbol{G})$ |
|---|---|---|---|---|---|
| 1 | random | 25.42 | 145.00 | 10 | 0.144 |
| 2 | random | 27.16 | 144.00 | 25 | 0.104 |
| 3 | random | 28.15 | 141.00 | 11 | 0.103 |
| 4 | random | 28.72 | 146.00 | 10 | 0.139 |
| 5 | random | 30.52 | 141.00 | 16 | 0.121 |
| 6 | random | 31.82 | 142.00 | 13 | 0.12 |
| 7 | random | 33.82 | 144.00 | 11 | 0.123 |
| 8 | random | 34.40 | 143.00 | 13 | 0.149 |
| 9 | random | 40.47 | 144.00 | 14 | 0.114 |
| 10 | random | 411.53 | 146.00 | 12 | 0.159 |
| 11 | random | 41.31 | 141.00 | 11 | 0.105 |
| 12 | random | 428.70 | 144.00 | 8 | 0.132 |
| 13 | random | 434.30 | 145.00 | 7 | 0.1 |
| 14 | random | 452.73 | 140.00 | 15 | 0.118 |
| 15 | random | 458.01 | 142.00 | 16 | 0.1 |
| 16 | random | 460.35 | 142.00 | 10 | 0.102 |
| 17 | random | 482.32 | 144.00 | 12 | 0.11 |
| 18 | random | 484.46 | 143.00 | 14 | 0.123 |
| 19 | random | 489.59 | 142.00 | 13 | 0.101 |
| 20 | random | 492.81 | 145.00 | 7 | 0.1 |

**Table S.5** Properties of SSSD data sets used in simulations. $\kappa(\boldsymbol{A})$ is the interampatteness degree of the network and $\kappa(\boldsymbol{Y})$ is the condition number of the response matrix. $\#(\,p_{ij} \neq 0)$ is the total number of perturbations in the matrix $\boldsymbol{P}$. The $\overline{\boldsymbol{p}_{1,0}} = \max_j |\boldsymbol{p}_i \neq 0|_1$, that is, the maximum number of perturbations/experiment over all experiments and $\underline{\boldsymbol{p}_{1,0}} = \min_j ||\boldsymbol{p}_i \neq 0||_1$ is the corresponding minimum. $\lambda(\text{SNR} = 1)$ is the variance of the noise for SNR = 1.

| ID | $\kappa(\boldsymbol{A})$ | $\kappa(\boldsymbol{Y})$ | $\#p_{ij}$ | $\min_i \sum_j p_{ij}$ | $\max_i \sum_j p_{ij}$ | $\lambda(SNR = 1)$ |
|---|---|---|---|---|---|---|
| 1 | 25.42 | 25.67 | 225 | 1 | 2 | 6.37e-05 |
| 2 | 27.16 | 27.26 | 225 | 1 | 2 | 5.61e-05 |
| 3 | 28.15 | 28.38 | 225 | 1 | 2 | 5.17e-05 |
| 4 | 28.72 | 28.76 | 225 | 1 | 2 | 5.06e-05 |
| 5 | 30.52 | 30.59 | 225 | 1 | 2 | 4.42e-05 |
| 6 | 31.82 | 32.50 | 225 | 1 | 2 | 4.06e-05 |
| 7 | 33.82 | 34.16 | 225 | 1 | 2 | 3.62e-05 |
| 8 | 34.40 | 33.79 | 225 | 1 | 2 | 3.45e-05 |
| 9 | 40.47 | 41.55 | 225 | 1 | 2 | 2.43e-05 |
| 10 | 411.53 | 412.78 | 225 | 1 | 2 | 2.44e-07 |
| 11 | 41.31 | 41.86 | 225 | 1 | 2 | 2.38e-05 |
| 12 | 428.70 | 447.17 | 225 | 1 | 2 | 2.15e-07 |
| 13 | 434.30 | 439.99 | 225 | 1 | 2 | 2.15e-07 |
| 14 | 452.73 | 453.91 | 225 | 1 | 2 | 2.02e-07 |
| 15 | 458.01 | 459.05 | 225 | 1 | 2 | 1.97e-07 |
| 16 | 460.35 | 469.02 | 225 | 1 | 2 | 1.89e-07 |
| 17 | 482.32 | 488.93 | 225 | 1 | 2 | 1.74e-07 |
| 18 | 484.46 | 495.41 | 225 | 1 | 2 | 1.7e-07 |
| 19 | 489.59 | 495.54 | 225 | 1 | 2 | 1.71e-07 |
| 20 | 492.81 | 504.51 | 225 | 1 | 2 | 1.64e-07 |

### S.1.2 Signed MCC

We also wanted to take into account the sign of each link and therefore we extended the MCC to the Signed MCC (SMCC) with the conditions in Table S.6. Similar extensions to performance measures have been used before to account for a signed structure of the inferred model, see *e.g.* Hache *et al.*[40]. Here we define a false negative (FN) as a link that is wrongly assumed to not exist or has the wrong sign, *i.e.* our hypothesis is wrong when we should have a link with a specific sign. The optimal estimate is then obtained for the regularisation parameter $\zeta$ that maximises SMCC.

**Table S.6** Signed Matthew Correlation Coefficient (SMCC) extension to MCC

| | | Inferred | | |
|---|---|---|---|---|
| | | 1 | 0 | -1 |
| True | 1 | TP | FN | FN |
| | 0 | FP | TN | FP |
| | -1 | FN | FN | TP |


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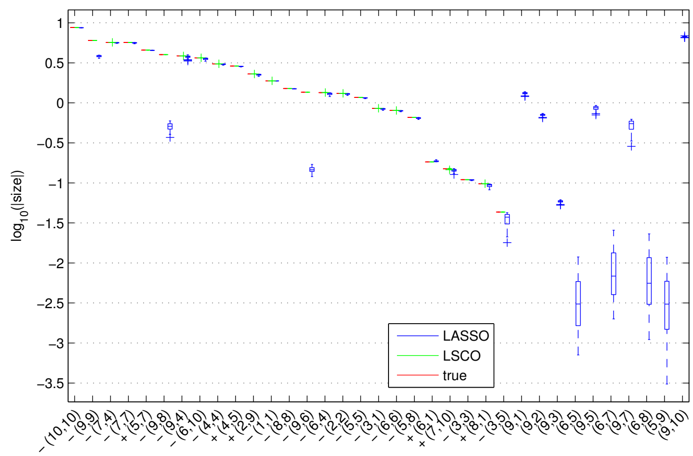
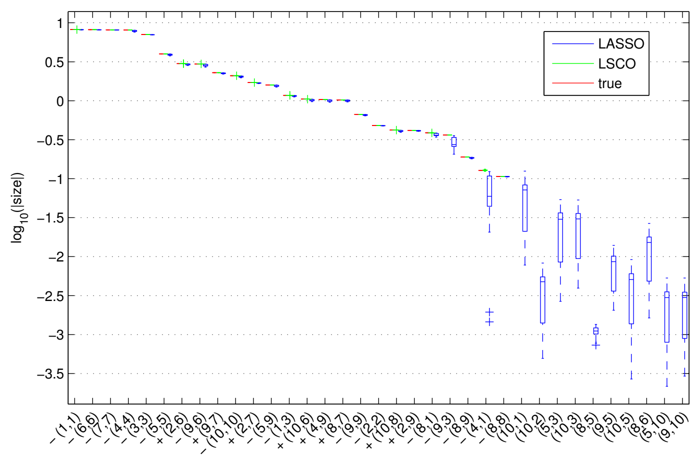
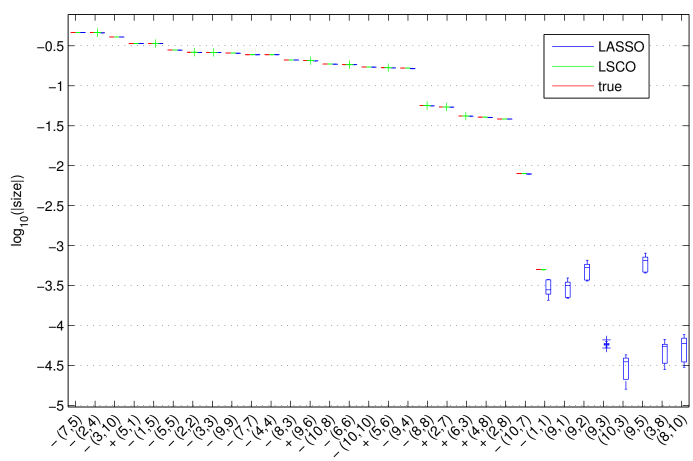



(a) Data set with $\kappa(A) = 100.56$ and $\kappa(Y) = 93.69$ corresponding to ID= 1 in Table S.2




(b) Data set with $\kappa(A) = 92.75$ and $\kappa(Y) = 124.70$ corresponding to ID= 10 in Table S.2




(c) Data set with $\kappa(A) = 6.90$ and $\kappa(Y) = 9.52$ corresponding to ID= 3 in Table S.2

**Fig. S.2** Optimal network inference with corresponding link estimates for LASSO (blue) and LSCO (green) compared to true network (red), evaluated at a variance, $\lambda = 10^{-9}$. True Links are marked with sign and denoted with $(i,j)$ where $j$ influences $i$. False links are only marked by the influence of the link *i.e.* the sign marks the true network influence, $\{+,-,0\}$.

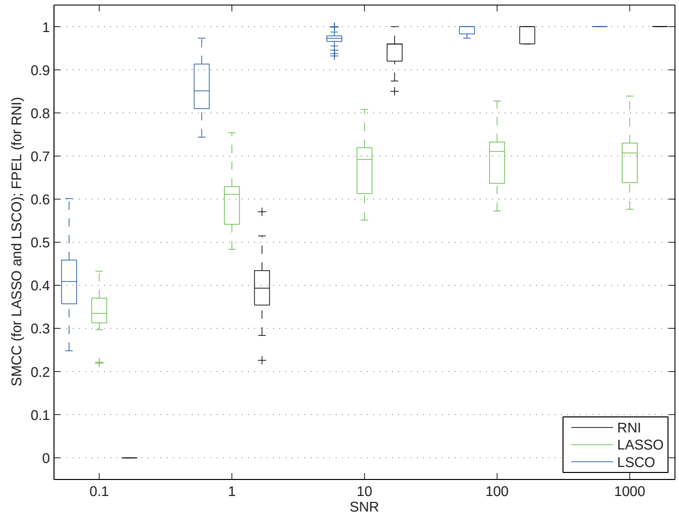



**Fig. S.3** GRN inference accuracy versus signal to noise ratio using LASSO, LSCO, and RNI on NRDP data sets with high condition number $\kappa(\boldsymbol{Y})$. LASSO fails even when all existing links can be proven to exist, *i.e.* when RNI reaches FPEL$=1$. Boxes are grouped according to five SNR values. Box edges signifies $q_1 = 25$th and $q_3 = 75$th percentile, whiskers encapsulate the most extreme data points not considered outliers. Outliers are considered points which are $> q_3 + w(q_3 - q_1)$ or $< q_1 - w(q_3 - q_1)$ where $w = 1.5$ and marked with $+$.

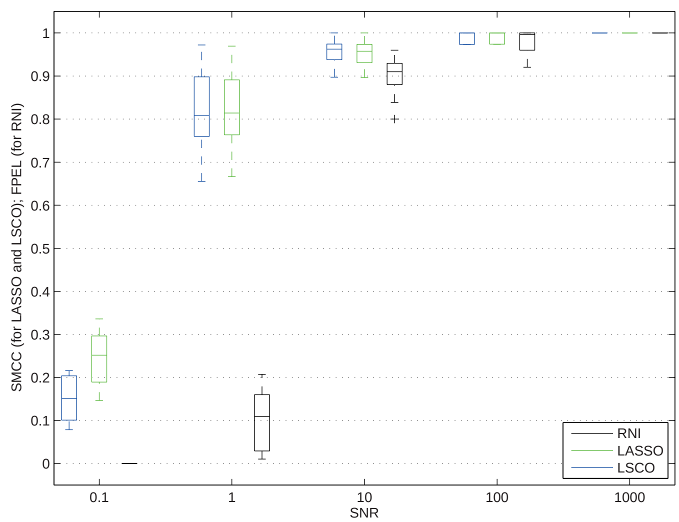



**Fig. S.4** GRN inference accuracy versus signal to noise ratio using LASSO, LSCO, and RNI on SBED data sets with low condition number $\kappa(\boldsymbol{Y})$. For an SNR of 10 both LASSO and LSCO can infer the true network structure for some of the data sets even though all existing links cannot be proven to exist (RNI has a FPEL $< 1$). For an SNR $> 10$ the median of all methods inference accuracy is approaching 1 and is above 90% for all data sets. For a description of the plot see Figure 1.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