## Logical cooperativity of TFs with time delays

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## Application of Loregic to worm embryonic expression

- -- Expression profiles of ~20K protein-coding genes across 25 time points (30 min each)
- -- **520** (TF1, TF2, Target) triplets
- For each triplet consider all combinations of TF1\_delay = 0 .. max\_delay and TF2\_delay = 0 .. max\_delay, such as (for max\_delay = 3):

TF1\_delay = 0, TF2\_delay = 2

TF1 TF2 Target	X0 0 0 0	X0.5 0 0 0	X1 0 0 0	X1.5 0 0 0	X2 0 0 0	X2.5 1 0 0	X3 1 0 0	X3.5 1 0 0	X4 1 0 0	X4.5 1 0 0	X5 1 1 1	X5.5 1 1 1	X6 1 0 0	X6.5 1 1 0	X7 1 1 1	X7.5 1 1 1	X8 1 1 1	X8.5 1 1 1	X9 0 1 1	X9.5 0 1 1	X10 X 0 1 1	10.5 0 1 1	X11 > 0 1 1	(11.5 0 1 <b>1</b>	X12 0 0 0
																тг				~	<b>TC</b> 0			~	
																	1_0	lelay	/ =	3,	11-2	_de	elay	= 2	
	X0	X0.5	X1	X1.5	X2	X2.5	X3	X3.5	X4	X4.5	X5	X5.5	X6	X6.5	X7	<b>I⊢</b> X7.5	Т_С <sub>X8</sub>	x8.5	× = ×	З, х9.5	X10 X	<b>d€</b> 10.5	21 <b>ay</b> x11 >	= 2 (11.5	X12
TF1	X0 0	X0.5 0	X1 0	X1.5 0	X2 0	X2.5 1	X3 1	X3.5 <b>1</b>	X4 <b>1</b>	X4.5 <b>1</b>	X5 1	X5.5 <b>1</b>	X6 1	X6.5 <b>1</b>	X7 1	X7.5	T_C X8 1	X8.5 1	× = ×9 0	3, X9.5 0	1F2 X10 X 0	d€ 10.5 0	x11 > 0	= 2 (11.5 0	X12 0
TF1 TF2	X0 0 0	X0.5 0 0	X1 0 0	X1.5 0 0	X2 0 0	X2.5 1 0	X3 1 0	X3.5 1 0	X4 1 0	X4.5 1 0	X5 1 1	X5.5 1 1	X6 1 0	X6.5 1 1	X7 1 1	X7.5 1	T_C X8 1 1	X8.5 1 1	<pre>/ = X9 0 1</pre>	3, X9.5 0 1	1F2 X10 X 0 1	2_d€ 10.5 0 1	×11 > 0 1	= 2 (11.5 0 1	X12 0 0

TF1\_delay = 0, TF2\_delay = 0

	X0	X0.5	X1	X1.5	X2	X2.5	Х3	X3.5	X4	X4.5	X5	X5.5	X6	X6.5	X7	X7.5	X8	X8.5	X9	X9.5	X10 X	10.5	X11 >	(11.5	X12
TF1	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
TF2	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0
Target	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0

25 – max\_delay

Find maximum Loregic-scores for each triplet across all logic-gates and \_\_\_ all (TF1\_delay, TF2\_delay) combinations



all gates, score>=0.4; max\_delay=2



OR only, score>=0.4; max\_delay=2



all gates, score>=0.4; max\_delay=3

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most of the high-scored triplets have either

(TF1\_delay=0,TF2\_delay=max\_delay or (TF1\_delay=max\_delay,TF2\_delay=0

2,1

all gates, score>=0.4; max\_delay=4



2h delay ??





all gates, score>=0.4; max\_delay=5





2.5 h delay ??

## -- Delay vs no delay



What is the proper significance test for increase in scores with delays in TF activity?

Simulate many randomly shuffled (within rows) expression matrices and compare *P* values from t-test?

Highest (across all logic gates) scores for each triplet with (TF1\_delay=0,TF2\_delay=0) Highest (across all logic gates and all TF1\_delay>0,TF2\_delay>0) scores for each triplet

## Trying other methods

Information theory

METHODOLOGY ARTICLE

BMC Bioinformatics Open Access

TimeDelay-ARACNE: Reverse engineering of gene networks from time-course data by an information theoretic approach

Pietro Zoppoli<sup>1,2</sup>, Sandro Morganella<sup>1,2</sup> and Michele Ceccarelli\*<sup>1,2</sup>

• Cross-correlation, LASSO

Inferring Time-Delayed Gene Regulatory Networks Using Cross-Correlation and Sparse Regression

Piyushkumar A. Mundra<sup>1</sup>, Jie Zheng<sup>1,5</sup>, Niranjan Mahesan<sup>2</sup>, Roy E. Welsch<sup>3,4</sup>, and Jagath C. Rajapakse<sup>1,3,6</sup>

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