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Context-specific co-expression networks to explore the impact of anti-sense transcription

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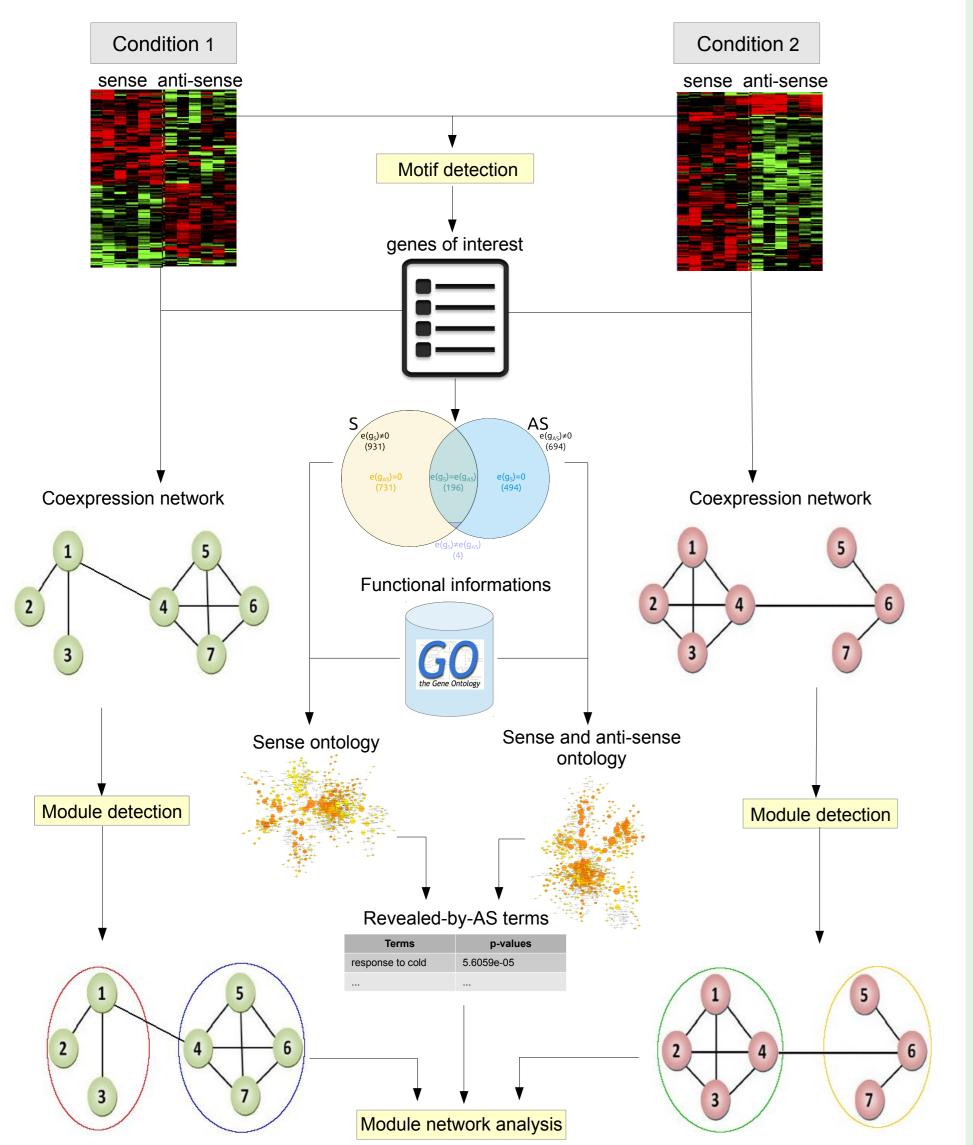
Motivations

Understanding the regulation mechanisms in a cell is a key issue in bioinformatics. Anti-sense RNAs are endogenous RNA molecules whose partial or entire sequences exhibit complementarity to other transcripts. Their different functional roles are not completely known but some studies suggest that they play an important role in stress response mechanisms. A recent study with a full genome microarray for the apple has detected anti-sense transcription for 65% of expressed genes, which suggests a high potential of anti-sense regulation. Our work integrates anti-sense transcripts into context-specific gene networks and proposes a differential analysis of those networks.

Biological materials

We use microarray data of RNA extracted from the apple fruit (*Malus* \times *domestica*) thanks to the chip AryANE v1.0 containing 63011 predicted sense genes and 63011 complementary anti-sense sequences. We study the fruit ripening process described by two conditions: harvest (H) and 60 days after harvest (60DAH), and for each condition, 22 samples of apple fruit have been analyzed.

Methods



We start with expression data of sense and anti-sense genes in two stress-response conditions. From there, we propose five steps to analyse the role of anti-sense transcripts:

- Identification of genes of interest: genes (sense and anti-sense) differentially expressed.
- Functional analysis of genes of interest to compute the revealed-by-AS terms.
- Ontextual construction of gene network for the genes of interest. We construct a co-expression gene network for each condition from the expression of the genes of interest.
- Module detection. In each network, we look for

Genes of interest

With a threshold of 1 log change between the two conditions, we found 931 sense (S) and 694 anti-sense probes (AS) differentially expressed, with among them, 200 genes $(S \cup AS)$ for which both sense and anti-sense fulfill the condition.

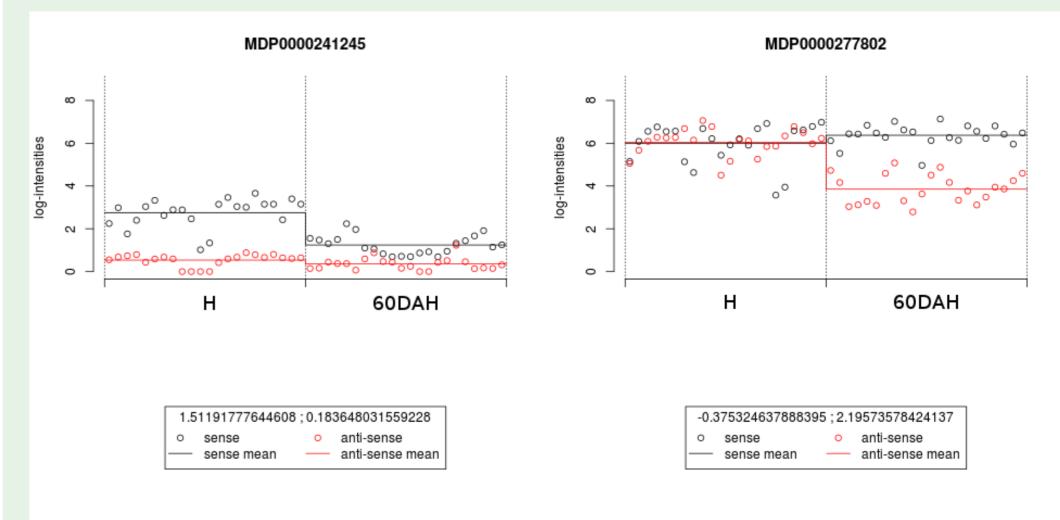


Figure 2: Expression profile of two genes of interest.

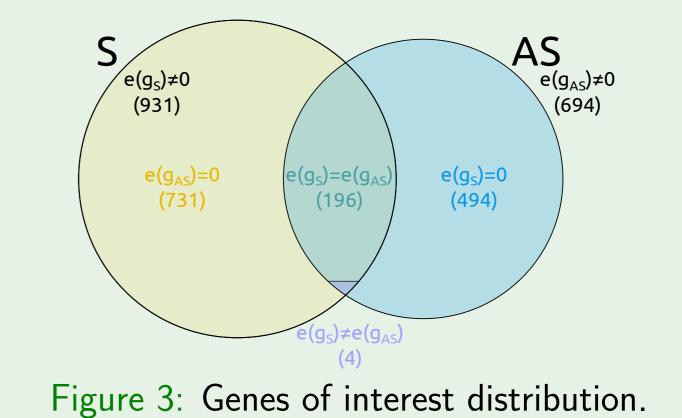
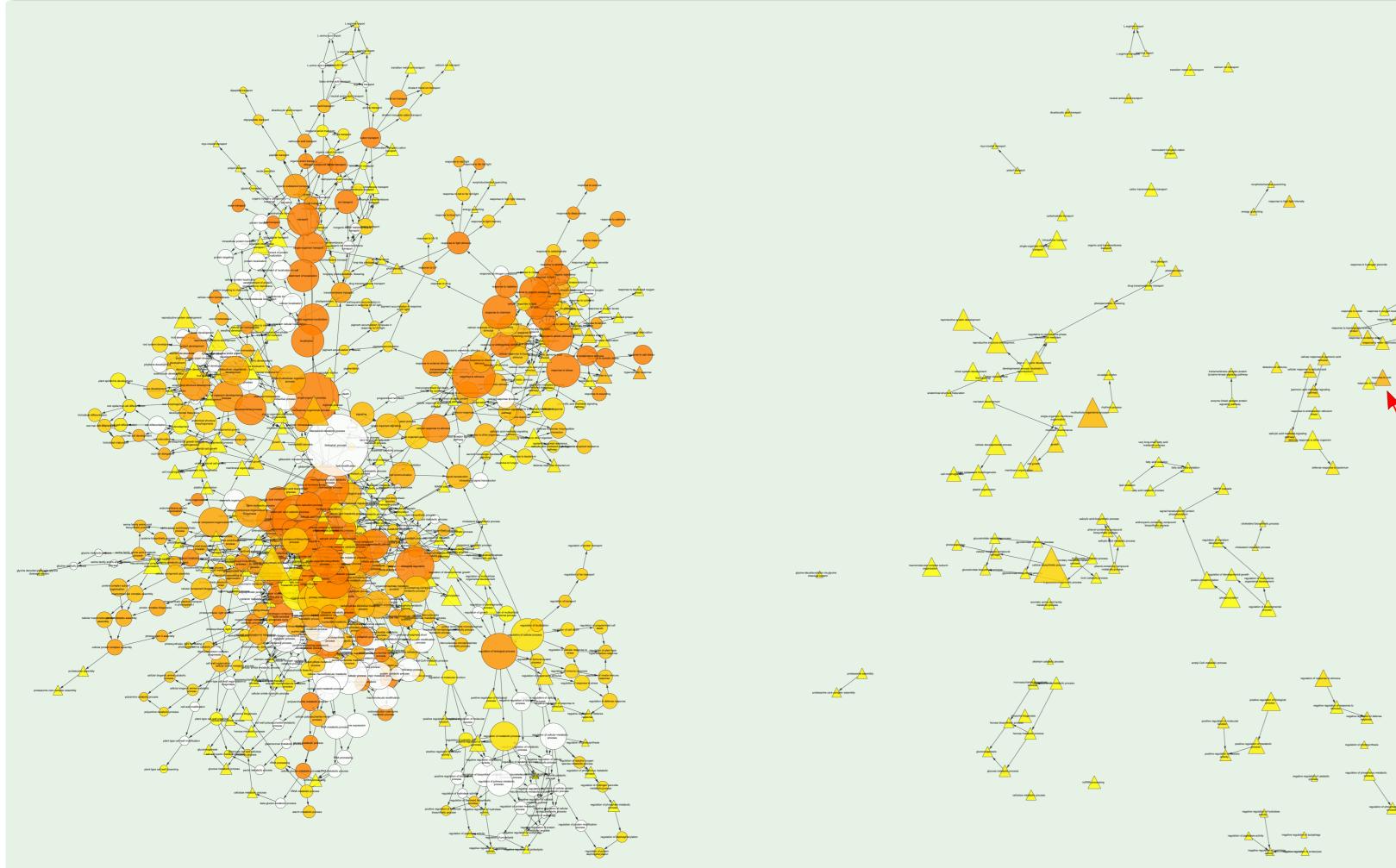


Figure 1: Diagram of the methods.

highly correlated genes by grouping them in modules thanks to a hierarchical clustering .

Solution Network analysis, this work is in progress.

Functional analysis



Revealed-by-AS terms allow us to identify biological functions which could not have been noticed by enrichment analysis without anti-sense data.

For the dataset described before, one of the most significant revealed-by-AS terms is the term "response to cold" (red arrow in Figure 5). Ripening clearly involves cold reaction since between the conditions H and 60DAH, the apples are stored cold; yet this term is not observed if we only consider the differentially expressed sense

ANTISENS	EVOL	UTION	SENS	AT
MDP0000151721	-1	-1	MDP0000151721 r	AT5G67590
MDP0000223905	-1	-1	MDP0000223905 r	AT2G39730
MDP0000272802	-1	-1	MDP0000272802 r	AT5G67590
MDP0000561026	-1	-1	MDP0000561026 r	AT2G36830
MDP0000944409	-1	-1	MDP0000944409 r	AT2G39730
MDP0000132480	-1	0	MDP0000132480 r	AT2G35730
MDP0000134273		Ŏ	MDP0000134273 r	AT2G26250
MDP0000134685	1	Ŏ	MDP0000134685 r	AT4G37930
MDP0000146698	1	0	MDP0000146698 r	AT5G38480
				AT3G2412
MDP0000151190		0	MDP0000151190_r	
MDP0000169619	-1	0	MDP0000169619_r	AT1G56070
MDP0000206093	-1	0	MDP0000206093_r	AT4G04330
MDP0000206314	-1	0	MDP0000206314_r	AT3G05890
MDP0000215630	-1	0	MDP0000215630_r	AT3G51780
MDP0000224974	-1	0	MDP0000224974_r	AT3G61580
MDP0000231051	-1	0	MDP0000231051_r	AT2G46210
MDP0000234570	-1	0	MDP0000234570_r	AT4G37930
MDP0000237499	-1	0	MDP0000237499_r	AT3G23050
MDP0000268045	-1	0	MDP0000268045_r	AT1G15950
MDP0000297425	-1	0	MDP0000297425 r	AT4G03280
MDP0000324254	-1	0	MDP0000324254 r	AT4G24960
MDP0000325574	-1	Ō	MDP0000325574 r	AT3G62410
MDP0000325582	-1	Õ	MDP0000325582 r	AT3G62410
MDP0000564897	-1	Ō	MDP0000564897 r	AT2G22430
MDP0000642609	-1	ŏ	MDP0000642609 r	AT3G53990
MDP0000760376	-1	ŏ	MDP0000760376 r	AT2G46210
MDP0000777793	-1	ŏ	MDP0000777793 r	AT1G56070
MDP0000797759	1	Ö	MDP0000797759 r	AT2G21660
MDP0000920069	1	0	MDP0000920069 r	AT1G64060
MDP0000920089	-1	1	MDP0000310152 r	AT1004000
MDP0000126738	0	-1	MDP0000126738_r	AT3G18990
MDP0000132477	0	-1	MDP0000132477_r	AT4G37930
MDP0000148186	0	-1	MDP0000148186_r	AT1G32060
MDP0000241245	0	-1	MDP0000241245_r	AT1G49480
MDP0000244771	0	-1	MDP0000244771_r	AT3G55800
MDP0000287992	0	-1	MDP0000287992_r	AT1G01060
MDP0000300321	0	-1	MDP0000300321_r	AT3G45140
MDP0000317816	0	-1	MDP0000317816_r	AT5G01600
MDP0000321244	0	-1	MDP0000321244_r	AT2G39730
MDP0000429215	0	-1	MDP0000429215_r	AT2G46590
MDP0000647652	0	-1	MDP0000647652_r	AT4G17090
MDP0000835914	0	-1	MDP0000835914 r	AT1G42970
MDP0000122458	0	1	MDP0000122458 r	AT4G25140
MDP0000205588	Ō	1	MDP0000205588 r	AT3G11170
MDP0000210504	0	- i -	MDP0000210504 r	AT3G01570
MDP0000253300	0	1	MDP0000253300 r	AT2G38560

Figure 4: Ontology of all the genes of interest. Figure 5: Revealed-by-AS terms. In order to study the impact of anti-sense transcription, we compare the ontological terms significantly represented in the set $S \cup AS$ of sense and anti-sense genes (Figure 4) with the ontological terms significantly represented in the set S of sense genes. The difference enables to define the *revealed-by-AS terms* (Figure 5).

genes.

MDP0000671114	0	1	MDP0000671114_r	AT5G54770	
MDP0000813339	0	1	MDP0000813339_r	AT4G34710	
MDP0000151030	1	0	MDP0000151030_r	AT4G25140	
MDP0000191203	1	0	MDP0000191203 r	AT3G16785	
MDP0000253809	1	0	MDP0000253809 r	AT5G65020	
MDP0000281110	1	0	MDP0000281110 r	AT1G22770	
MDP0000728753	1	0	MDP0000728753 r	AT5G06860	
MDP0000766240	1	0	MDP0000766240 r	AT4G01370	
MDP0000836165	1	1	MDP0000836165 r	AT4G02330	
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			с I		
6. Evolution of prohes as					

Figure 6: Evolution of probes associated with the term "response to cold".

We define the evolution of a probe as the

expression difference between the two conditions with respect to a threshold of 1 log change. We observe that almost half of the probes associated with the term "response to cold" have the same evolution pattern: the sense expression level is nearly constant between the two conditions whereas the anti-sense expression level decreases (highlighted in Figure 6). This confirms that anti-sense data provide valuable information to study this process.







