Examples of applications of MixNet

July 10, 2008

1 Buchnera metabolic network

Metabolic networks constitute a major instance of biological networks, whose comprehension appears crucial in the understanding of the functionning of the cell. In this example, we consider a particular example of metabolic network which is the metabolic network of Buchnera.

One particularity of metabolic networks is that they can be modeled by bi-partite graph, using one set of nodes for reactions, another set for compounds, the two sets being linked by edges indicating the use of compounds by reactions. When the aim is to study one set only (either reactions or compounds), the set of reactions is used to generate the reaction network, in which two reactions are connected if they share the same compound. In this example, the data is a directed network with reactions as nodes which are connected if oine reaction produces the substrate of the other.

This strategy requires an additional step that accounts for ubiquitary compounds which would create densily connected subgraphs if they were not removed from the data. Indeed, H_2O,ATP, ADP, NADP, are compounds which are used in numerous reactions and most reactions would be connected in the projection if they were not removed. Since Mixnet aims at finding structure, this kind of non informative structure hampers the discovery of smaller-scale structures (data not shown).

In order to avoid artefactual structures due to ubiquitary compounds, we used the filter proposed by [1], which means that substrat-products couples that correspond to co-factors are not considered. Subproducts such as Phosphate from the tandem ATP-ADP, and H_2O have also been removed. One reaction has been declared as being irreversible if it appears always in the same direction in MetaCyc, whatever the metabolic pathway. Overall the network is made of one connex component with 946 edges and 218 nodes.

The first result of MixNet is that 45% of the reactions are cluistered into the same class (Class 3) which is characterized by a low mean degree (see Table 1). This indicates that these reactions are not sufficiently structured from the connectivity point of view to be split into more subsets of reactions. The twelve remaining classes form 2 meta components whose links are very loose (they are not represented on the summary plot of Figure 1).

Structuration When studying the first component (classes 1-2-9-11-12), the MixNet summary reveals the flux of use of Phosphate. Indeed, class 1 produces di-Phosphate which is strictly used by reactions of class 1 that transform the di-phosphate into Phosphate. Then reactions of class 2 use the phosphate from two different sources : class 1 and class 11 with an obligate use of the phosphate produced by reactions of class 11. It can be seen from the summary table

that classes 1 and 2 are made of consumer reactions, with an important average mean in-degree. Neverthless, this structure may not be the most interesting since it is largely linked to the presence of the phosphate, which is an ubiquitary compound that is still in the data since it is used in other contexts that were not predicted by the filter. A similar pattern can be found in the second component where cluster 6 produces CO_2 that is used by reactions of class 13, whereas clusters 7 and 10 gather all reactions that produce and use protons (see table **??**). If we go to further details, a last interesting class of component 1 is class 9 which is made of reactions that involve sugars. Interestingly, these reactions are span among different metabolic pathways, as shown in Figure **??**. This indicates that they may play a similar role in terms of network structuration.

In component 2, we observe a very strong structure among classes 4-5-8, with a between classes connection probability of 1. From the functional point of view, it appears that glutamate is the compound that structures these subclasses. Reactions of class 8 are all irreversible, and produce glutamate. Then this product is a substrate for reactions of classes 5 and 4, which are split because of their different reversibility. Reactions of class 4 are all reversible and are involved in the metabolism of 3 Amino Acids (Ileu, Leu, Val) with a common EC number (2.6.1.42), whereas reactions of class 5 are strictly irreversible (83% of which being with EC numbers 2.6.1 and 6.3.2).

References

[1] Handorf T., Christian N., Ebenhoh O., and Kahn D. An environmental perspective on metabolism. *J. Theor Biol*, 252(3):530–537, 2008.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1	66.7	33.3	.	.	.	.	.	.	.	.	2.1	9.1	.
2	.	80.6	1.0	.	.	.	.	.	5.6	.	.	2.0	.
3	.	.	.	.	.	.	.	.	.	.	.	.	3.5
4	.	.	.	100.0	100.0	7.4	.	.	.	.	.	.	.
5	.	.	.	46.2	.	3.4	.	.	.	.	.	.	.
6	.	.	.	3.7	.	.	.	.	4.2	.	.	.	100.0
7	.	.	.	.	.	.	.	.	.	1.7	.	2.3	10.0
8	.	1.9	1.2	100.0	100.0	4.9	.	.	.	.	2.1	1.5	.
9	.	7.2	.	.	.	3.7	.	4.8	30.9	3.6	1.3	.	.
10	.	.	.	.	.	1.2	100.0	.	.	33.3	.	.	.
11	6.2	100.0	.	.	.	.	.	1.0	.	.	2.1	.	.
12	100.0	.	.	.	.	.	.	.	.	.	.	.	.
13	.	.	3.0	.	.	.	.	.	.	.	.	.	50.0
alpha	1.4	4.1	45.4	1.8	6.0	6.3	4.6	2.8	6.4	2.8	7.4	10.1	0.9
ave. in Deg.	24.33	24.88	1.52	16	10.33	2.78	6.80	1.16	5.14	2.66	1.81	1.54	18.50
ave. out Deg.	7	8.88	1.40	17.67	2.58	3.14	1.40	19.67	6.29	12.33	10.56	4	3.50

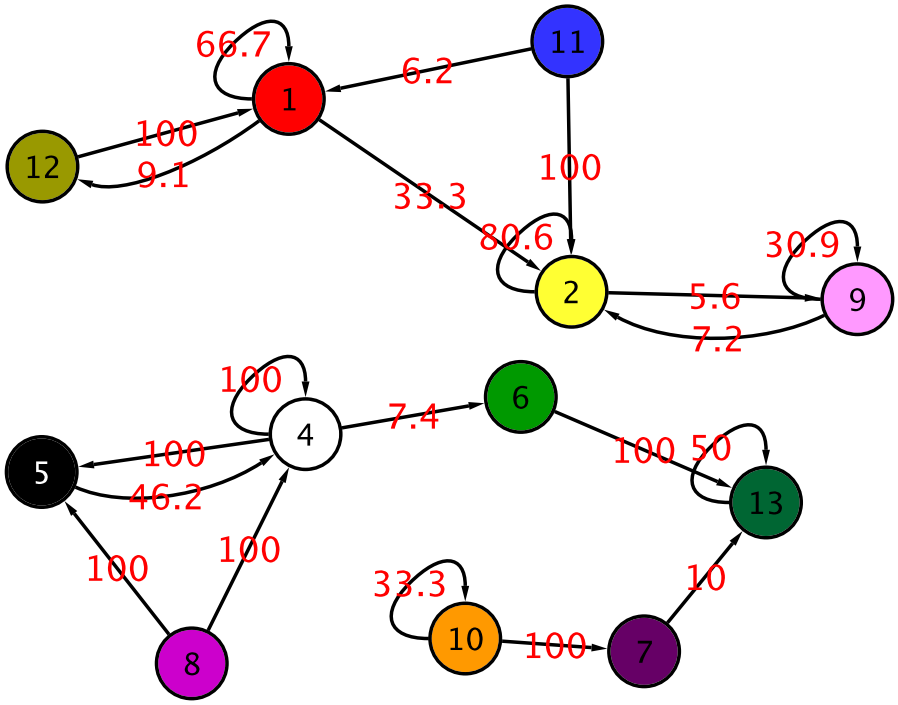

Table 1: MixNet parameters for the Buchnera metabolic network with a last filter and $Q = 13$ classes. Connections ($\times 100$) lower than 1% are not represented in the table, and connections lower than 5% are not displayed in the summary plot.

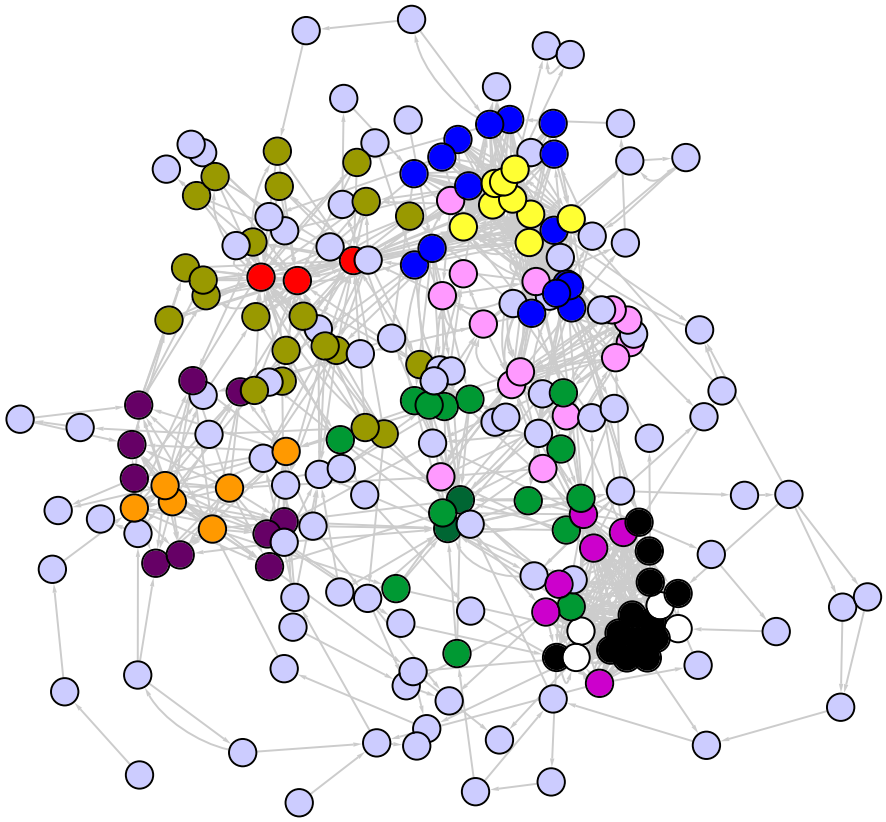

Figure 1: Reaction Network of buchnera revised displayed with colors for each MixNet class (13 groups).

MixNet Class	Reaction ID	substrate(s)		product(s)
10	ERYTH4PDEHYDROG-RXN	ERYTHROSE-4P	→	PROTON + ERYTHRONATE-4P
10	3-ISOPROPYLMALDEHYDROG-RXN	2-D-THREO-HYDROXY-3-CARBOXY-ISOCAPROATE	→	PROTON + CPD-7100
10	RXN0-1131	CPD-296	↔	PROTON + LIPOIC-ACID
10	RXN0-5268	PROTON + OXYGEN-MOLECULE	↔	PROTON
10	SIROHEME-FERROCHELAT-RXN	SIROHYDROCHLORIN + FE+2	→	PROTON + SIROHEME
10	GLU6PDEHYDROG-RXN	GLC-6-P	→	PROTON + D-6-P-GLUCONO-DELTA-LACTONE
7	RIBOFLAVINSYNREDUC-RXN	PROTON + CPD-602	→	CPD-1086
7	SUPEROX-DISMUT-RXN	PROTON + SUPER-OXIDE	→	HYDROGEN-PEROXIDE + OXYGEN-MOLECULE
7	ISPH2-RXN	PROTON + HYDROXY-METHYL-BUTENYL-DIP	→	—delta(3)-isopentenyl-pp—
7	RXN0-884	PROTON + HYDROXY-METHYL-BUTENYL-DIP	→	CPD-4211
7	RXN-7968	PROTON + 3-DEHYDRO-SHIKIMATE	→	SHIKIMATE
7	DIHYDROPICRED-RXN	PROTON + —2,3-dihydrodipicolinate—	→	DELTA1-PIPERIDEINE-2-6-DICARBOXYLATE
7	RXN-8447	PROTON + 2-AMINO-3-OXO-4-PHOSPHONOOXYBUTYRATE	→	1-AMINO-PROPAN-2-ONE-3-PHOSPHATE + CARBON-DIOXIDE
7	ACETOLACTREDUCTOISOM-RXN	PROTON + 2-ACETO-LACTATE	→	DIOH-ISOVALERATE
7	1.5.1.20-RXN	PROTON + METHYLENE-THF	→	5-METHYL-THF
7	HOMOSERDEHYDROG-RXN	PROTON + L-ASPARTATE-SEMIALDEHYDE	→	HOMO-SER

Table 2: Reactions of the Buchnera metabolic network that involve protons