GAM: a computational pipeline for integrated transcriptional and metabolic network analysis

Alexey Sergushichev

Computer Technologies laboratory
ITMO University

biss2014

Integrated analysis

- Progress of omics profiling technologies
- Metabolic
  - What metabolite concentrations are in cells?
  - Corresponds to a network of biochemical reactions
- Transcriptional
  - How genes are expressed in cells?
  - Corresponds to reactions via enzymes

Numbers

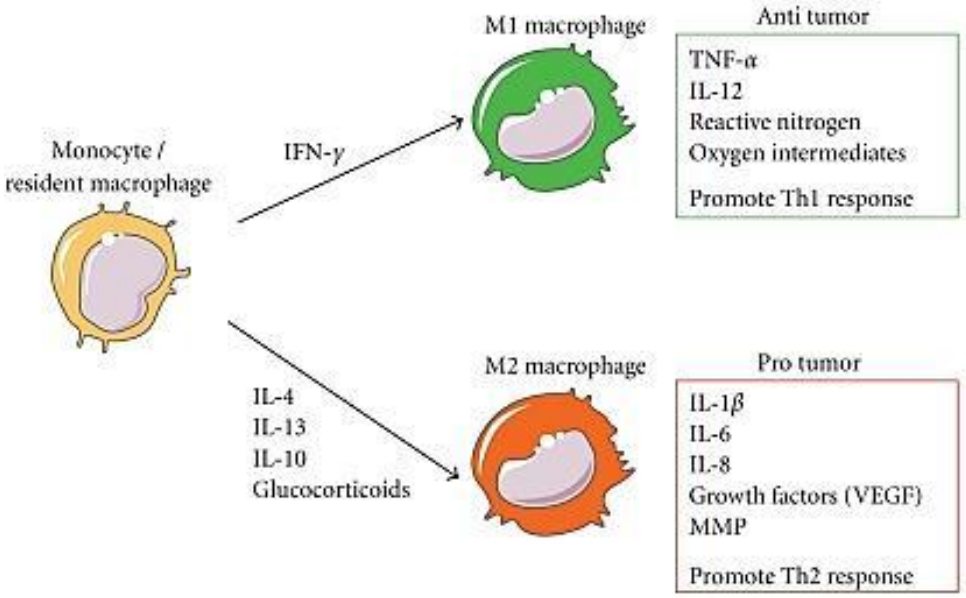
- ~2000 reactions for a species
- Metabolic profiling
  - ~500 metabolites
  - ~50-100 of them look regulated
- Transcriptional profiling
  - ~1000 expressed enzymes
  - ~300-500 of them look regulated

Integrated view

- Find a set of connected reactions that contains most regulated enzymes and metabolites
- Reducing to problem of finding maximum weight connected subgraph (MWCS)
  - It is NP-hard but there are solvers (or not)

Macrophages

- Type of immune cells:
  - Resting M0 macrophages
  - Proinflammatory M1 macrophages
  - Antiinflammatory M2 macrophages



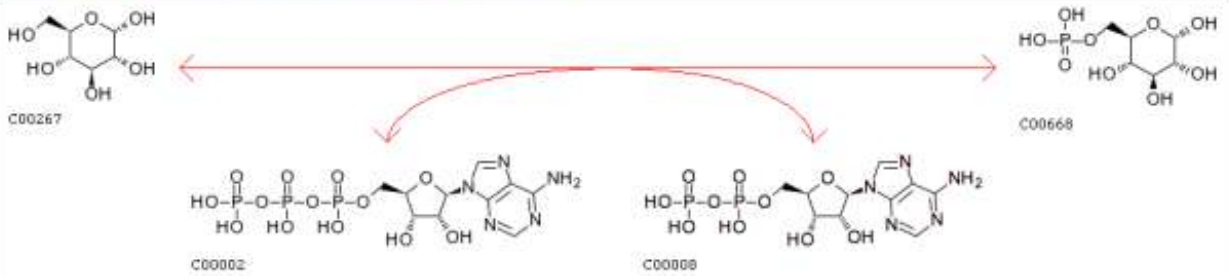
*http://islaslab.wikispaces.com/Cancer+and+the+Immune+System

KEGG REACTION database

KEGG

REACTION: R01786

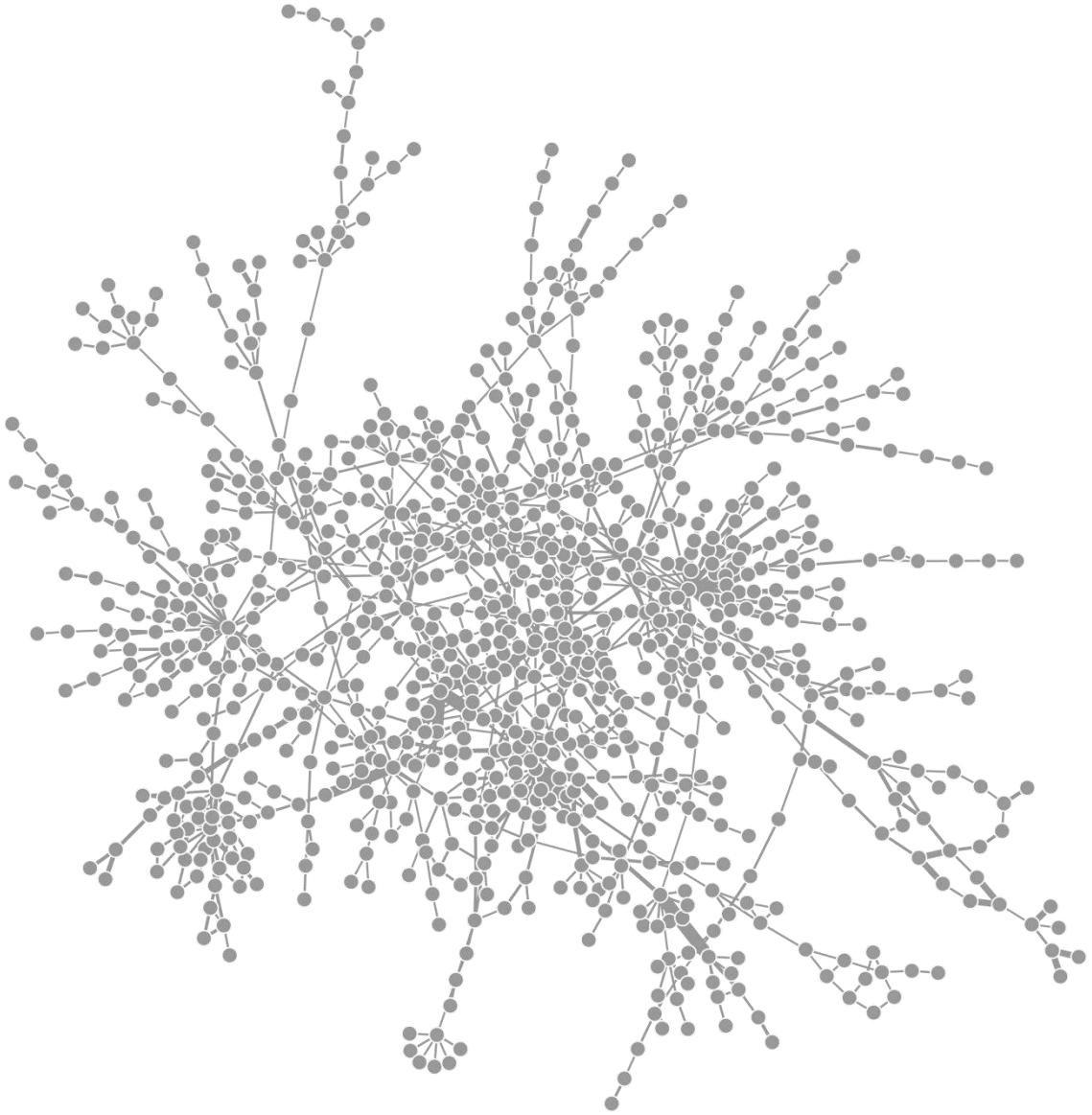
Help

Entry	R01786 Reaction
Name	ATP:alpha-D-glucose 6-phosphotransferase
Definition	ATP + alpha-D-Glucose <=> ADP + alpha-D-Glucose 6-phosphate
Equation	C00002 + C00267 <=> C00008 + C00668
	
RPair	RP00003 C00002_C00008 main RP00216 C00267_C00668 main RP06708 C00002_C00668 trans
Enzyme	2.7.1.1 2.7.1.2
Pathway	rn00010 Glycolysis / Gluconeogenesis rn00052 Galactose metabolism rn00500 Starch and sucrose metabolism rn00520 Amino sugar and nucleotide sugar metabolism rn01100 Metabolic pathways rn01110 Biosynthesis of secondary metabolites rn01120 Microbial metabolism in diverse environments rn01200 Carbon metabolism
Orthology	K00844 hexokinase [EC:2.7.1.1] K00845 glucokinase [EC:2.7.1.2] K12407 glucokinase [EC:2.7.1.2]

Mapping reaction network to a graph

- MWCS works with simple graphs (without hyperedges)
- Network of reactions is complex
- Bimolecular reactions:
  - Reactions as nodes (+ collapsing connected reactions sharing an enzyme)
  - Reactions as edges (+ RPAIRS)

Raw reaction graph



Scoring graph

- Assigning weights based on p-values from differential expresion:
  - Significantly changed metabolites/reactions get positive weight
  - Insignificantly changed metabolites/reactions get negative weight

Weighted graph

Here was a figure

Module

Here was a figure

Major regulatory subnetwork of M1 vs M2

Here was a figure

Major regulatory subnetwork of M1 vs M2

Here was a figure

New modules

Here was a figure

Conclusion

- A pipeline to systematically look at transcriptional and metabolic data together (**and separately**)
- It produces a nice picture of most regulated reactions
- It allows to discover new modules
  - Jha et al. “Network integration of parallel metabolomic-transcriptional data reveals novel metabolic modules regulating divergent macrophage polarization” (to be published)
- However,

Questions

- How to properly handle isomers in metabolic profiling?
- How to properly handle reactions with the same enzyme?
- How to get more (statistically) significant results?
- How to get more meaningful results?
  - Combine with flux balance analysis?

Availability

- A web-service at https://artyomovlab.wustl.edu/shiny/gam/
  - Feedback is welcome!
- An R-package to be released
  - Is available now upon a request

References

- Dittrich,M.T. et al. (2008). Identifying functional modules in protein–protein interaction networks: an integrated exact approach. Bioinformatics, 24(13), i223-i231.
- Beisser,D., et al. (2012). Integrated pathway modules using time-course metabolic profiles and EST data from Milnesium tardigradum. BMC systems biology, 6(1), 72.
- Xia, Jianguo, et al (2013). "INVEX—a web-based tool for integrative visualization of expression data." Bioinformatics 29(24), 3232-3234.

Acknowledgements

- Washington University in St. Louis
  - Maxim N. Artyomov
  - Edward J Pearce
- Agios Pharmaceuticals
  - Abhishek Jha
- ITMO University
  - Fedor Tsarev

Contacts

Алексей Сергушичев

alserg@rain.ifmo.ru