Mapping Cancer Markers, December 2019 update

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The MCM project was designed to process multiple cancer datasets. The first three datasets in MCM plan are Lung, Ovarian, and Sarcoma, representing the past, present and future of MCM. Lung processing is complete. Ovarian is underway, but nearing completion. We are now preparing for a switch to Sarcoma.

Processing a dataset on World Community Grid over months and years produces a huge amount of data, and this data is not directly usable, but must then be collated, filtered, and analyzed in different ways. We have been focusing on this post-processing step in our lab.

In this update, we will mainly discuss some of the work done with the processed Lung dataset, but first, we will take a quick glance at the future.

Final preparations for Sarcoma dataset

The upcoming Sarcoma dataset will be MCM's most complex dataset to-date. It contains potential biomarkers drawn from multiple sources: measurements of RNA, DNA, and protein activity, mutations, and other biological modalities.

With such detailed information about each sample in the dataset, it took some effort to reduce the dataset and result sizes to practical levels. We are currently testing work units of our draft dataset and are planning the work.

A future update will announce the launch of Sarcoma and provide more details.

Results from the Lung dataset

The biomarkers in the MCM Lung dataset measure the activity of thousands of genes. Collectively, these biomarkers cover most of the human genome. The majority of MCM Lung work processed on World Comunity Grid surveyed signatures randomly drawn from the entire set of biomarkers. A shorter, second phase of MCM Lung drew signatures from optimized subsets of those biomarkers.

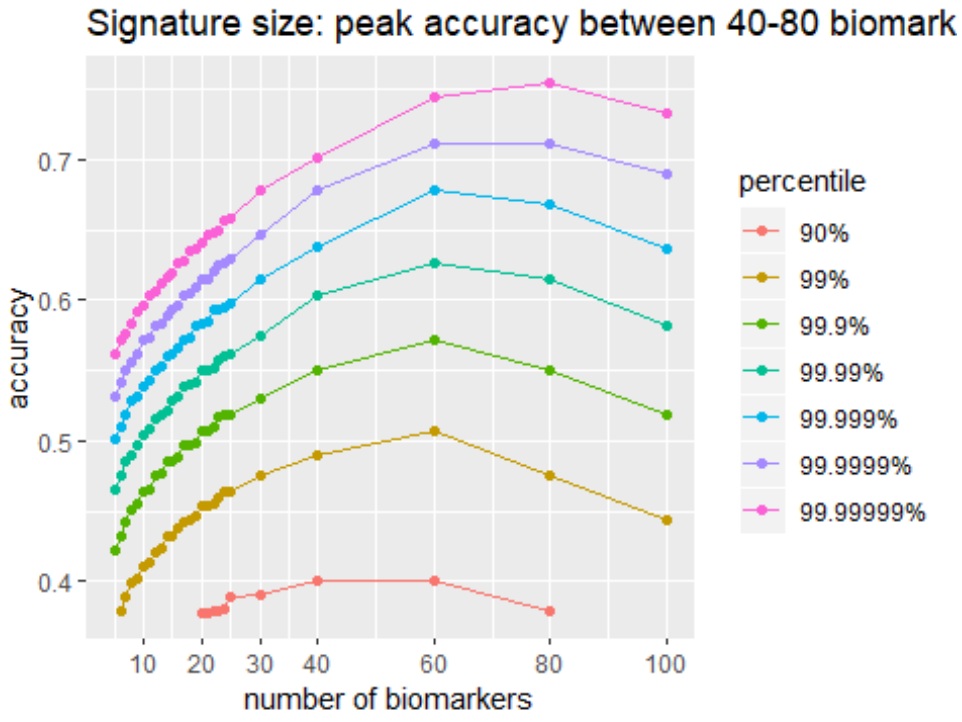
The contribution of compute cycles to the project was extraordinary. World Community Grid members processed 4.5 *trillion* (4.5×10^{12}) candidate lung cancer signatures in the main phase of MCM Lung, 220 billion in an initial experimental phase, and 1.6 trillion signatures in the optimizing phase.

We will discuss some findings from the main phase of MCM Lung in this update.

The question of signature size

MCM Lung surveyed signatures of multiple sizes. Sizes varied from 5 biomarkers to 100, with the greatest focus on signatures in the range of 10-20 biomarkers. For a cancer signature to succeed in clinical use, signature size is a compromise between diagnostic power, complexity, and cost. Every biomarker can potentially add diagnostic information to a signature, increasing accuracy, but too many biomarkers can also add noise and unnecessarily increase cost and complexity for practical use in the clinic.

The figure below shows the effect of signature size on peak accuracy. For almost any size, a signature built from randomly-chosen biomarkers will have poor accuracy, but by testing enough such signatures, and then looking at the accuracy of the top fraction (say, the top 0.01%), we see the effect made by signature size. Carefully-engineered signatures should achieve the same accuracy using fewer biomarkers.



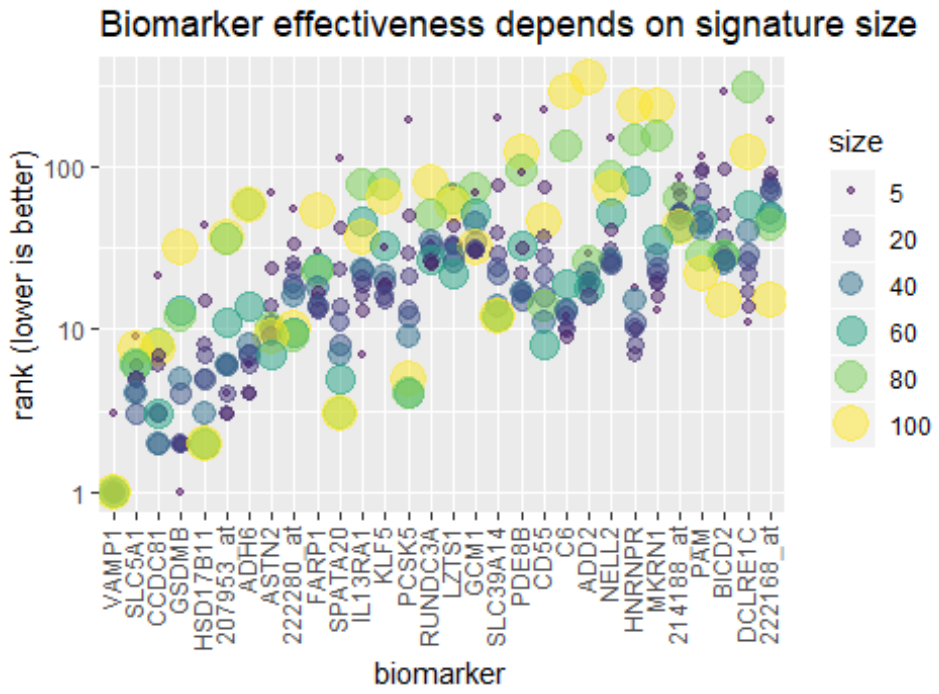
accuracy of signatures built from randomly-chosen biomarkers.

Which biomarkers are most successful?

In the main phase of MCM Lung, signatures were built from biomarkers chosen randomly from the dataset. As such, every biomarker had an equal chance of appearing in each new signature. This does not mean, though, that all biomarkers are equally useful – as we said above, a random signature will most likely have low accuracy. If, however, we take only the most accurate fraction of signatures, and see which biomarkers they contain, we see that a few biomarkers appear frequently, and that the rest are relatively rare. (We may even notice patterns in ways that certain groups of biomarkers appear together, as we discussed in a previous update.) We can determine

then how effective or useful each biomarker is from how often it appears in these top signatures.

After analyzing the full set of MCM Lung results, we can confirm an effect that we had noticed in earlier, preliminary studies: the effectiveness of each biomarker depends on the signature size, affecting each biomarker differently. The figure below illustrates the effect for some of the top-ranked biomarkers.



f the Lung cancer signature determines how useful a biomarker may be.
size of signature grows, biomarkers may become more or less effective.

Pathway enrichment among the top biomarkers

To get a higher-level view of the biomarkers discovered in the Lung dataset, we examined them from the pathway perspective. A *pathway* is a group of genes that cooperate to perform the same biological function. We fed lists of top-1% biomarkers into our lab's pathDIP database [1,2]. *pathDIP* is a comprehensive, integrated database of

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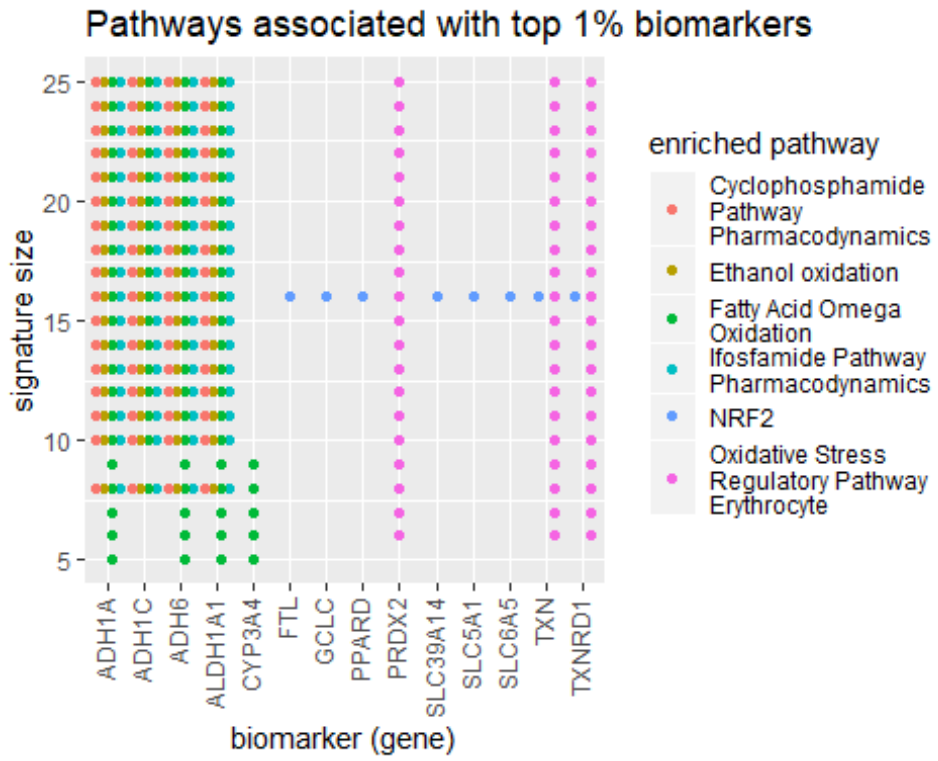
[1] Rahmati, S., Abovsky, M., Pastrello, C., Jurisica, I. pathDIP: An annotated resource for known and predicted human gene-pathway associations and pathway enrichment analysis. *Nucl Acids Res* **45(D1)**: D419-D426, 2017.

[2] Rahmati, S., Abovsky, M., Pastrello, C., Kotlyar, M., Lu, R., Cumbaa, C.A., Rahman, P., Chandran, V. and Jurisica, I. pathDIP 4: An extended pathway annotations and enrichment analysis resource for human, model organisms and domesticated species, *Nucl Acids Res*, In press. 2019. https://doi.org/10.1093/nar/gkz989

known pathways (signaling cascades), and given a list of genes, it will find all pathways associated with any gene in the list. Most usefully, it will measure the *enrichment* of each pathway in your gene list – the degree to which pathway has an above-average connection to your list. Using such analysis, we aim to find biologically meaningful interpretation of our identified biomarkers.

The figure below shows the results from *pathDIP*.



Across a large number of signature sizes, *pathDIP* consistently found five pathways enriched in our gene lists:

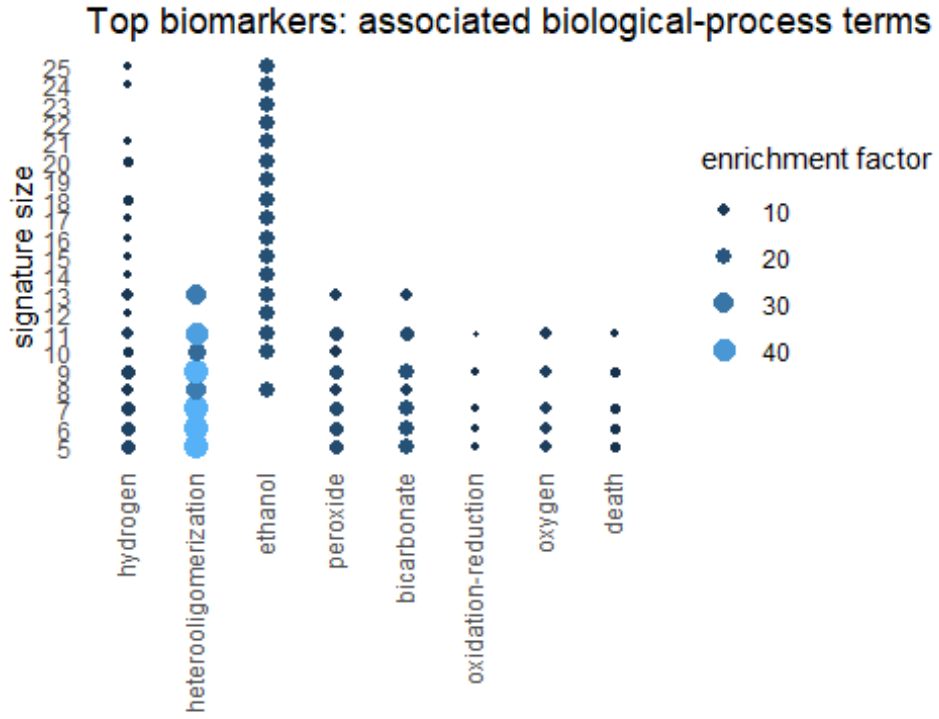
- Cyclophosphamide Pathway, Pharmacodynamics
- Ifosfamide Pathway, Pharmacodynamics
- Ethanol oxidation
- Fatty Acid Omega oxidation
- Oxidative Stress Regulatory Pathway (Erythrocyte)

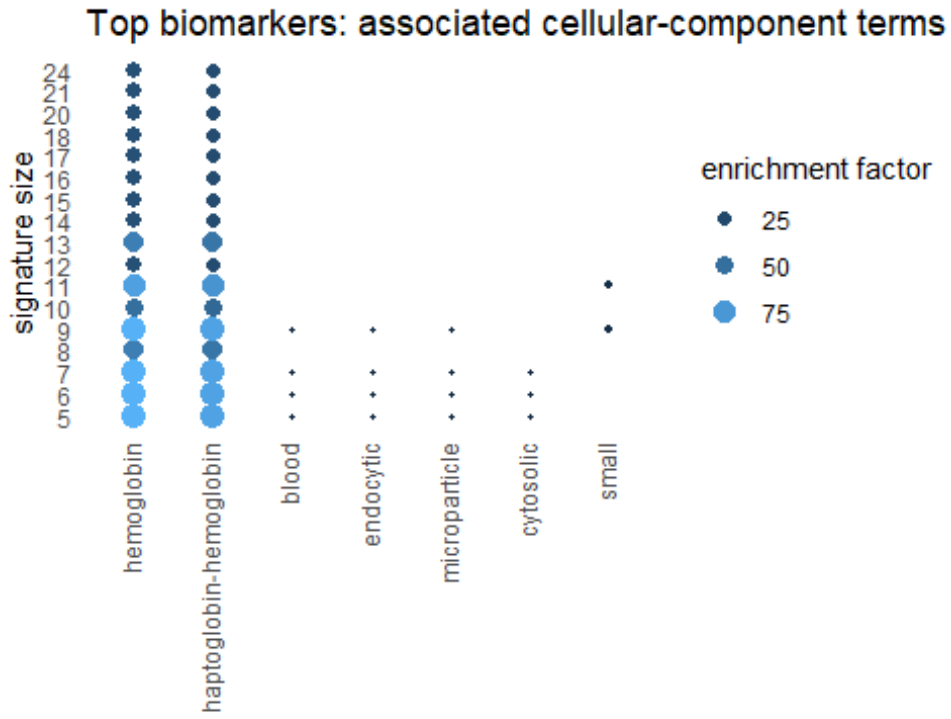
All five enriched pathways relate to metabolism, meaning the breakdown of chemicals in the body. Curiously, the first two pathways relate specifically to metabolism of chemotherapy drugs, Cyclophosphamide and Ifosfamide. The last three relate to either oxidation or the prevention of oxidative stress (free radicals) in red blood cells.

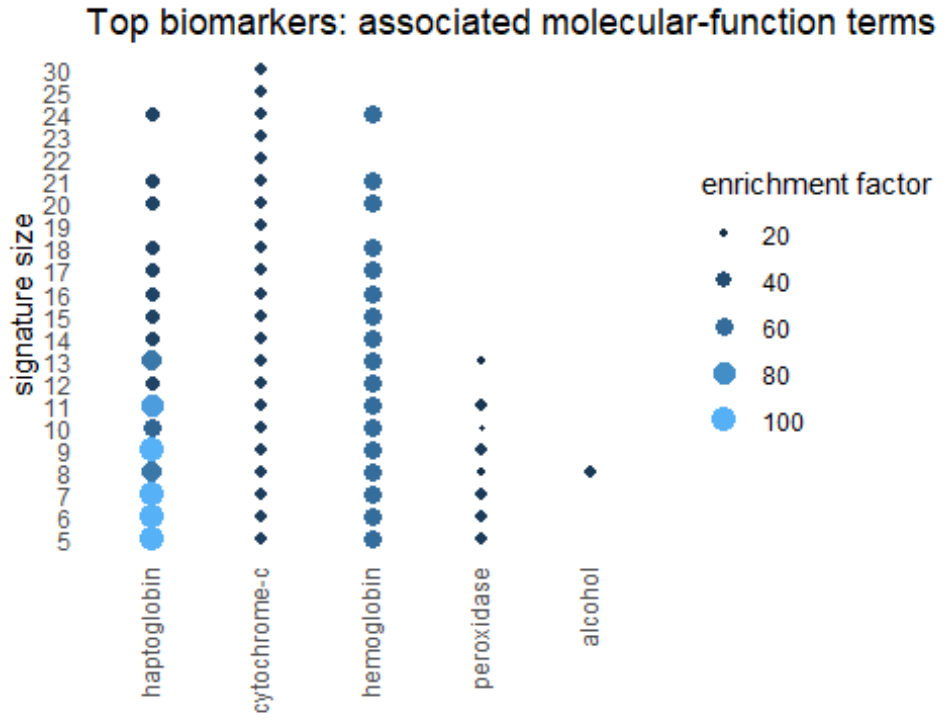
Using the Gene Ontology Resource to describe top biomarkers

We can get a related view from the (Gene Ontology Resource) [http://geneontology.org/]. *GO* categorizes each gene from three different perspectives:

biological process, molecular function, and cellular component. The figures below show terms in *GO* categories that appear frequently in top 1% biomarkers.







Many of the terms reflect the themes found in pathways: oxidation, alcohol, and red-blood-cell chemistry.

Looking ahead

We are in the process of expanding and combining multiple additional analyses of the main-phase Lung data, and substantial analyses of the second phase Lung results. After that, the Ovarian data awaits. For Ovarian, some of the same techniques will apply, but some will need to be adapted, and some we'll need to develop. In short, the MCM project will keep us busy for a long time. In the meantime, we would like to thank you for your interest and for your generous donation of computing power to this and other World Community Grid projects. We will provide updates more frequently now.

Additional Results

Over the last two years, we have published several original manuscripts and multiple applications using our tools and programs, many of which we have been using to increase value of MCM analyses:

- PMID: 31583635Kennedy, S., Jarboui, M-A, Srihari, S, Raso, C, Bryan, K, Dernayka, L, Charitou. T, Bernal-Llinares, M, Herrera-Montavez, C, Krstic, A, Matallanas, D, **Kotlyar, M, Jurisica, I**, Curak, J, Wong, V, Stagljar, I, LeBihan, T, Imrie, L, Pillai, P, Lynn, M, Fasterius, E, Szigyarto, C. A-K, Breen, J, Kiel, C, Serrano, L, Rauch, N, Rukhlenko, O, Kholodenko, B, Iglesias-Martinez, L, Ryan, C, Pilkington, R, Cammareri, P, Sansom, O, Shave, S, Auer, M, Horn, N, Klose, F, Ueffing, M, Boldt, K, Lynn, D, Kolch, W, Extensive Rewiring of the EGFR Network in Colorectal Cancer Cells Expressing Transforming Levels of KRASG13D, *Nat Commun*, 2019. In press.
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On other news, we have been able to secure several grants to enable funding for the project, including, Novel methods for integrative computational biology from Natural Sciences and Engineering Council of Canada, Interactome mapping of disease-related proteins using split intein-mediated protein ligation (SIMPL) from Genome Canada, The Next Generation Signalling Biology Platform from Ontario Research Funds, and most recently from Canadian Institutes of Health in collaboration with European fundi agencies.

Importantly, we also had a chance to host one of the WCG and MCM supporters at our institute[3]. Dylan Bucci, Sisler High School student and network and cybersecurity

teacher Robert Esposito were the first volunteers ever visited a research institution to meet with scientists who use the program. It was interesting for us to learn about their motivation and for them to experience direct and indirect research links to MCM.

Thank you for all the contributed computing power that makes this research possible.

MCM Team

CTV News Interview on IBM World Community Grid, Mapping Cancer Markers, May 3 (https://toronto.ctvnews.ca/mobile/more/health; https://toronto.ctvnews.ca/video?clipId=1675312&jwsource=em)