Biome Distributions

Linas Vepstas

revised 24 May 2020

Abstract

An exploration of the statistical distribution of interactions between genes, proteins and pathways, extracted from public genome, proteome and reactome datasets. This is an exploratory diary that attempts to understand the large-scale statistical properties of the network structure of bio-molecular interactions.

It was naively hypothesized that genome/proteome reaction pathways form a scale-free network, and thus would have a Zipfian distribution. Much to our surprise, this is not the case! It seems like *everything* follows a square-root Zipfian distribution! I do not know of any network theory or biology theory that would explain this, so it is a surprise.

An exploration of the mutual information of interaction pathways is also performed. It appears that these are easily fit with a bimodal Gaussian distribution.

Introduction

Publicly available genomics and proteomics databases describe a large number of interactions between genes and pathways. Taken together, these data-sets describe a large graph, and the one may reasonably wonder about the properties and general structure of that graph. For example, one might ask if the graph is scale-free, or if it has a hub-and-spoke structure, or make other graph-theoretic inquiries into it.

In this short monograph, a study is made of “triangles”: three genes that mutually interact, and “pentagons”: a pair of genes that express a pair of proteins that lie on a common pathway. If the genome (proteome, reactome) network were scale-free, then one might expect Zipfian distributions of triangles and pentagons.[1] This appears not to be the case. A further study is made of the mutual information (“lexical attraction”) of interacting pairs. It appears to be easy to describe this as a pair of Gaussians. A theoretical grounding for these results is unknown to the author. Clarifications are solicited.

[1] These questions originally arose during the characterization of a bioinformatics data-mining benchmark, found in `https://github.com/opencog/benchmark/query-loop`, and was elaborated in the “Genome distribution!?” email discussion.

Datasets

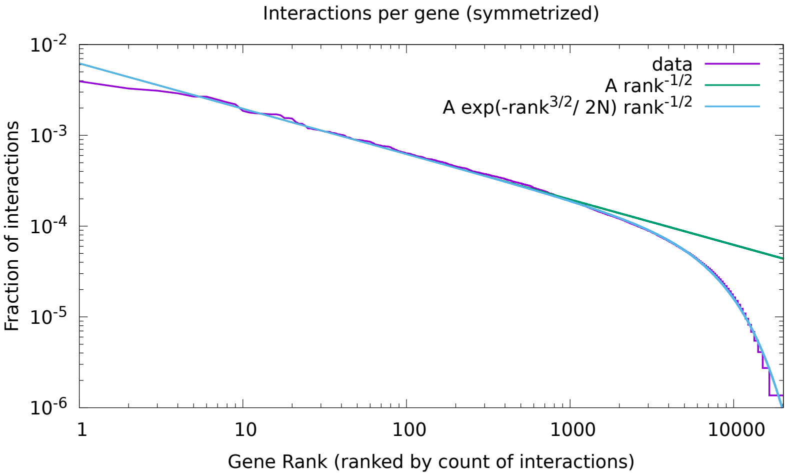
The graph networks explored here were constructed from public data-sets from MCBI, ChEBI, PubMed, UniProt, SMPDB, Entrez and BioGrid. These datasets include information about genes that regulate one-another, genes that express proteins, and proteins that appear on a common reaction pathway.

All gene-gene interactions were taken as symmetric, so that if one gene up- or down-regulates another, the interaction was represented by a symmetric (undirected) edge: namely, that two genes interact, without any specific direction information noted. The datasets contained a total of 20123 genes participating in 365745+2939 pair-wise interactions. Of these, there were 2939 self-interacting genes; these self-interactions were removed, so as to avoid confusion during counting.

Pathways are from https://reactome.org and from http://smpdb.ca/

Pair-wise interactions

At the most basic level, one can ask about the distribution of gene interactions. This is straight-forward: one simply crawls over the dataset, and simply counts how many interactions a gene particiates in. Ranking the genes by count produces the distribution shown below.



There are 20123 interacting genes participiating in a total of $N_{tot} = 365745$ interactions. The vertical axis shows the fraction of all interactions that a given gene participates in. That is, if the k'th gene in the ranking participates in $N(k)$ interactions, then the fraction of interactions is given by

$$p(k) = \frac{N(k)}{N_{tot}}$$

so that the integral under the curve is $N = N_{tot}$.

The first unexpected surprise is that this graph is not Zipfian. That is, the distribution is not of the form $k^{-\alpha}$ with exponent $\alpha \approx 1$. The leading slope is instead given by $\alpha = 0.5$. There is also a pronouned tail that seems too large to ignore or ascribe to statistical rounding. The overlayed fitting curves are "eyeballed", in that they look visually reasonable during plotting. The best eyeballed fitt is surprisingly good, and has a fairly simple expression:

$$p(k) = A\frac{\exp\left(-k^{3/2}/2N\right)}{\sqrt{k}}$$

The normalization A can be solved for exactly in the limit of large N:

$$\int_0^\infty \frac{\exp -\beta x^{-3/2}}{\sqrt{x}} dx = \frac{2}{\beta^{1/3}} \int_0^\infty e^{-u^3} du = \frac{2}{3\beta^{1/3}} \int_0^\infty y^{-2/3} e^{-y} dy$$

The last integral is the gamma function $\Gamma(1/3) \approx 2.67893853\cdots$ and so, bassed on the eyeballed fit, one has

$$A = \frac{3}{2\Gamma\left(\frac{1}{3}\right)(2N)^{1/3}}$$

The author does not know of any reason why the initial fall-off should follow a square-root slope, or why there should be a simple exponential correction: that is, the theoretical underpinnings and implications for this form is unknown.

Triangles

A triangle is defined as a three-way interaction, of gene A regulating gene B, gene B regulating gene C and C regulating A. Such triangles are one of the most basic components of the topological structure of regulatory networks. It is worth understanding their structure.

Any given gene may appear in multiple triangles; clearly, some genes might participate in many, and some in only a few. So, the first statistical question becomes: what is the distribution of these genes? This is answered via a Zipf-style graph: one makes a list of all of genes, ranking them according to the number of triangles they participated in, and then graphing, on a log-log graph, the number of triangles vs. the rank. Similarly, one can pose the same question, but for edges: how many triangles does a given gene-gene interaction participate in?

By counting the number of times an edge participates in some triangle, one obtains a count $N(g_a, g_b)$ that relates gene g_a to g_b. Given the counts of such pairs, this opens the door to a stable of standard statistical questions: what are the marginal distributions, the entropies, and the mutual information of such pairs? This is explored in a subsequent section.

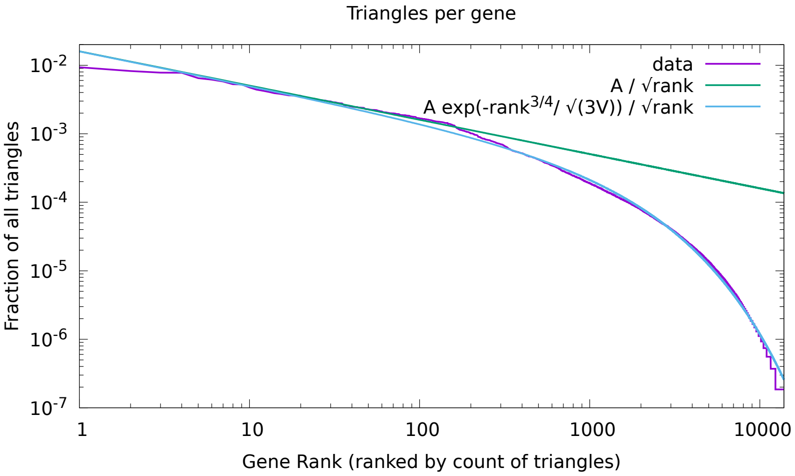
Because these explorations are perfomed on curated data-sets carried out by research labs, one has an open question of whether one is measuring "true biology", or whether one is measuring the social network of the scientists, and their intellectual interests. There does not appear to be any obvious way of answering this question.

Characterization

Not all of the interacting genes participate in triangular relations; only 13846 of the initial 20123 appear in such relations. In total, there were 308765 distinct pairs participating in triangles (out of 365745 pair-wise interactions in the dataset). A total of 1797281 triangles were observed.

Zipf graphs

The following figure shows the fraction of triangles in which a gene participates in.



The general slope, of a square-root-of-rank, is as before. The eyeballed fit is given by

$$p(k) = Ak^{-1/2} \exp\left(-k^{3/4}/\sqrt{3V}\right)$$

where $V = 13846$ is the number of vertexes (number of genes participating in triangles). Notice that the leading slope is one-half, as before, but the exponential fall-off is not as sharp. It still appears to have a very simple numerological value that is easily guessed. As before, the integral is again in the form of a gamma:

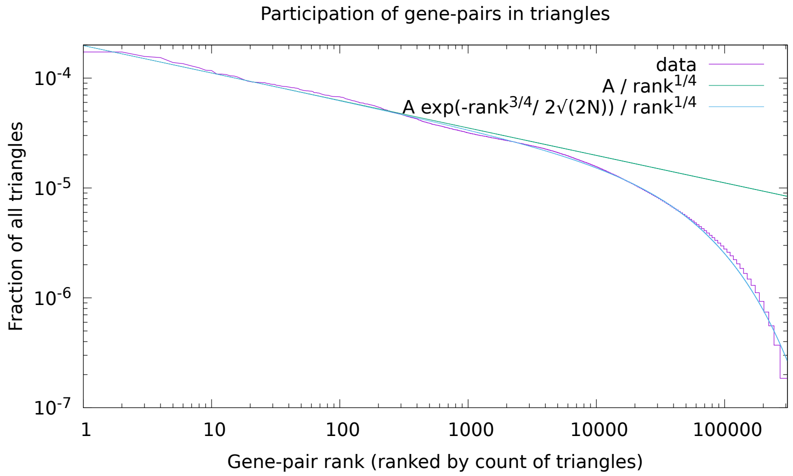
$$\int_0^\infty \frac{\exp -\beta x^{-3/4}}{x^{1/2}} dx = \frac{2}{\beta^{2/3}} \int_0^\infty \exp\left(-u^{3/2}\right) du = \frac{4}{3\beta^{2/3}} \Gamma\left(\frac{2}{3}\right)$$

so that the normalization is

$$A = \frac{3}{4(3V)^{1/3}\Gamma(2/3)}$$

with $\Gamma(2/3) \approx 1.354117939\cdots$. As before, the fit seems very good, despite effectively being numerological guess-work.

Similarly, one may ask how many triangles a given edge (a given gene-pair) participates in. This is shown below.



The rank exponent is now 1/4, instead of 1/2. The eyeballed fit is given by

$$p(k) = Ak^{-1/4} \exp\left(-k^{3/4}/2\sqrt{2N}\right)$$

where $N = 1797281$ is the total number of triangles. The integral is again in the form of a gamma, but much simpler:

$$\int_0^\infty \frac{\exp -\beta x^{-3/4}}{x^{1/4}} dx = \frac{4}{3\beta} \int_0^\infty e^{-u} du = \frac{4}{3\beta}$$

Thus, the normalization is

$$A = \frac{3}{8\sqrt{2N}}$$

The preciseness of the numerology is remarkable, but the underlying theory is unknown.

Tetrahedra

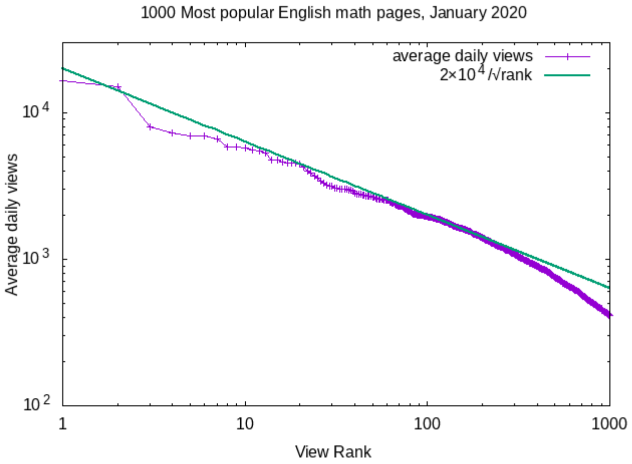
One may search for graph cliques of higher order than 3: a clique of 4 is a tetrahedron, a clique of order 5 is a 5-simplex, and so on. Data mining tetrahedra is considerably more CPU-intensive. The results are presented below.

Prior Results

Hmm. Apparently, I've seen square-root Zipfian distributions before, in language data.
I'd forgotten about that. See page 43 of this PDF: https://github.com/opencog/learn/raw/072f0a46d143d94fc27cb5a04dd8
lang-diary/connector-sets-revised.pdf

Related Results

Page views of the most popular pages on Wikipedia show the same square-root scaling. See https://en.wikipedia.org/wiki/Wikipedia:Does_Wikipedia_traffic_obey_Zipf%27s_law%3F for a demonstration. Here's a graph from this:



This shows the distribution of the 1000 most commonly viewed English-language Wikipedia Mathematics articles, as of Janurary 2020. A square-root distribution appears to hold up to at least a rank of 200 or 300; after that, the behavior is unclear.

TODO

What is the degree distribution? Viz, for scale-free networks, one usually examines the degree distribution, and not the triangle distribution. What about deg(u).deg(v) for edges connecting u,v?

Mutual Information

Mutual information (MI) is an entropic concept that characterizes the degree to which a pair of objects associate with one-another. For any given pair, one may examine how often the members of that pair occur together, versus how often each member associates with other, third parties. It's "entropic", in the sense that specific sum and difference of marginal entropies, and thus fits naturally into theoretical frameworks founded on entropic concepts.

The raw genome databases do not provide any particular gene-pairing information, beyond a yes/no assertion that a pair has been observed to interact in some laboratory setting. By pattern-mining triangles, one gets far more detailed interaction information. So, again, each triangle has three corners, the genes, and three edges, the gene pairs. By counting all possible triangles, one obtains a count of how often each edge is seen -- that is, how often an edge appears in some triangle. That is, one has a count $N(g_a, g_b)$

of the number of triangles that the pair (g_a, g_b) participated in. The rest is downhill. MI is defined as usual as Yuret's lexical attraction.

Given counts $N(x,y)$, one can readily compute the lexical attraction between the elements (x,y) as

$$MI(x,y) = \log_2 \frac{N(x,y)N(*,*)}{N(x,*)N(*,y)}$$

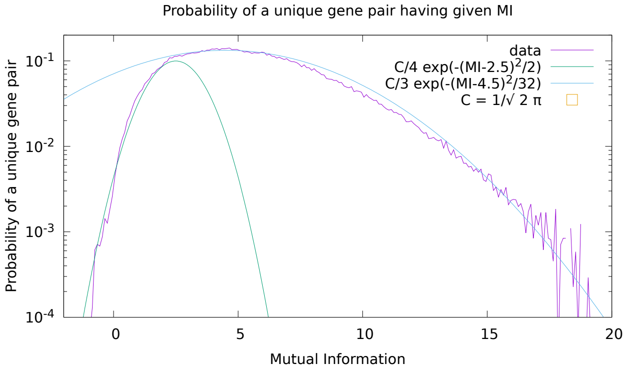
The total MI for a data-set is defined as

$$MI = \sum_{x,y} p(x,y) MI(x,y)$$

where $p(x,y) = N(x,y)/N(*,*)$ is the (frequentist) probability of observing the pair (x,y). For the symmetric data-set, it is 3.49. The total entropy for the data-set is 18.21. The sparsity is 9.36, where the sparsity is defined as $\log_2$ of the number of non-zero entries in the matrix. In this case, there are 20123 genes that participated in triangles, and 617530 non-zero entries (out of 404935129 possible; the $\log_2$ of this ratio provides the sparsity).

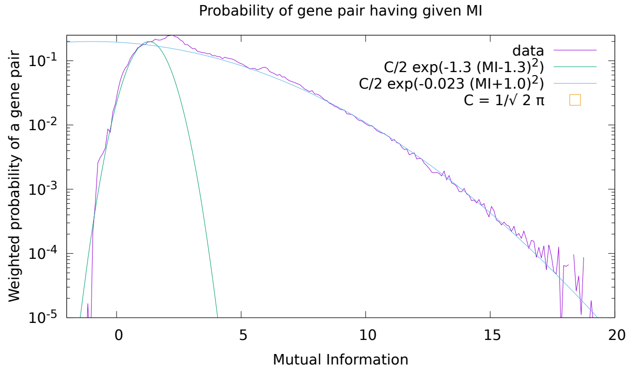
The distribution of the MI as a function of pair frequency is an interesting distribution to explore. There are two variants of this distribution that one can examine. One may consider only unique gene-pairs, or one may consider pairs weighted by their counts. So, in the first case, if two gene-pairs were found to have the same MI, then they are treated as equiprobable; when binned into a histogram, they are placed in the same bin with equal weighting. In the second case, their contribution to a bin is relative to the number of times each was observed. Equivalently, one may also say that one is counting "without and with degeneracy", or is examining "unweighted and weighted distributions".

The figure below shows the first case: the distribution of MI, counted without degeneracy (all gene pairs are treated as equi-probable).



The normalization is such that the area under the data curve will integrate to 1.0. The data is fit with two gaussian distributions. Recall that gaussians appear to be parabolas on a semi-log plot. The parameters of each fit are as marked in the legend. The fits are hand-built, or "eyeballed", chosen to look good, and are *not* the result of some automated curve-fit. The fit parameters are “numerology”: rounded to integers that look pleasing. Whether or not the integers are meaningful or are incidental is unclear.

The second case, where the bin-counts are weighted by frequency, results in a graph that is similar. Again, it is easily fit with two gaussians, but this time, the centers of the gaussians are quite different, as are the widths.



As before, the fit is eyeballed, with a preference of finding numerological simple-fraction fits, so as to expose simple laws, if these exist.

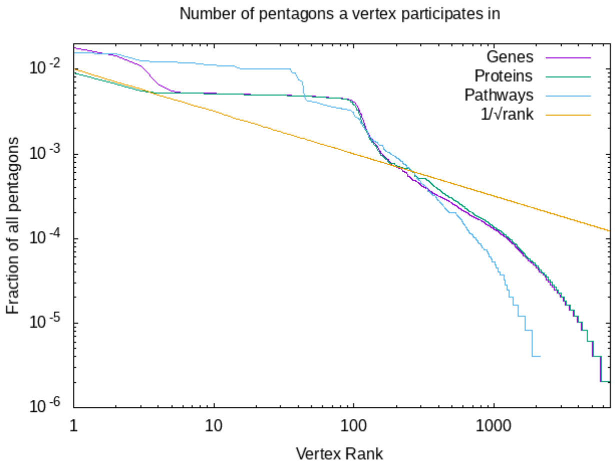
Pentagons

The pentagon has five vertexes: a pathway (as a single, named vertex), two proteins on that pathway, two genes, each of which express the corresponding protein, and finally, the two genes interacting with each other. Here, there are five edges, and three edge types: (protein in pathway), (gene expresses protein) and (gene-pair interaction). Thus, characterizing this statistically requires six Zipfian graphs: three for the different vertex types, and three for the different edge types. Each edge type will also have an MI distribution, and so six MI graphs: one for each type, weighted and unweighted. So, twelve graphs in total. Not all prove to be that interesting.

There are 50566 pathways in which some protein in the data-set is a member of. These are both SMP and R-HSA-tagged pathways (from the smpdb.ca and reactome.org, respectively). Each of these is observed in at least one pentagon. There is a total of 1082860 pathway-protein pairs in the data-set, but only 38843 appear in a pentagon. There are a total of 148734 gene-protein expression pairs, of which only a paltry 6794 appear in a pentagonal relationship. As before, there is a total of 365745 pairs of interacting genes; of these only 77304 appear in pentagons. Thus, the data-set, although quite large, appears to be quite disconnected: there are many interactions that have been mapped out, but these remain sparse enough that there are relatively few of these pentagonal interactions. This is presumably an artifact of the scientific exploration done to date, rather than an innate feature of actual biology. That is, there are presumably far more interactions, but these remain unknown and uncharted in the data-set.

Distributions of Vertexes

Pattern mining the above-described pentagon resulted in the observation of 491558 distinct pentagons (taking into account mirror symmetry: there are twice as many, if the mirror image is counted separately.) There are 6694 unique genes, 6735 unique proteins and 2129 distinct pathways that appeared in pentagonal relationships. All have an unexpected distribution; they are graphed below, on the same graph.[2]



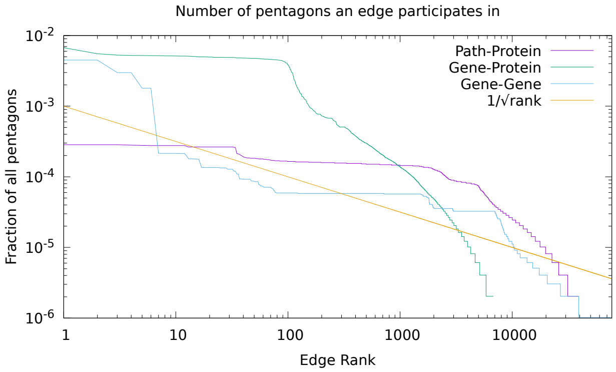
The normalization is with respect to the total number of pentagons that a given vertex appears in. Thus, for example, the highest-ranked gene, and the highest-ranked pathway appears in approximately 1 out of 50 pentagons; the highest-ranked protein appears in approximately 1 out of 100, which can be read directly off the y-intercept in the above graph.

I cannot come up with any plausible hypothesis for the plateaus, nor for the tails. These may be data-set artifacts: interactions that have been studied sufficiently to have been captured in the data-set. That is, a sociological artifact, rather than a statement about biology.

Distribution of Edges

There were 38843 distinct edges connecting pathways to proteins. There were 6794 distinct gene-protein expression edges. There were 77304 gene-gene interaction edges. The distribution of these edges, *viz.* the number of pentagons a given edge participates in, is shown below.

[2] Per contents of the `graphs/pentagon-paths` directory.



The overall lumpiness of these graphs provides no particular insight. It seems plausible that the lumpiness is an artifact of the data-set, rather than any indication that nature is structured in this way.

Gene-protein expression

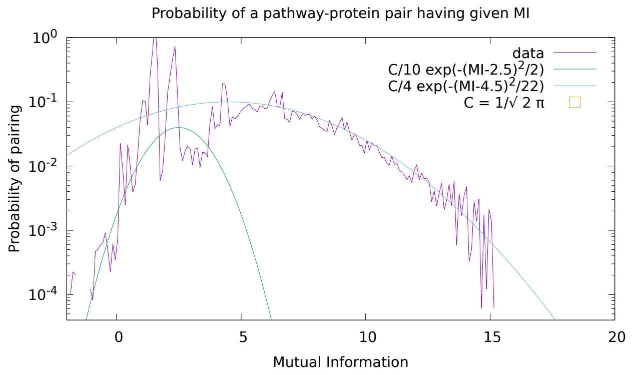
Lets look at gene-protein expression pairs that appear in pentagons. The matrix reports 6694 genes and 6735 proteins. The matrix appears to have 6794 non-zero matrix entries. On average, each gene-expression pair appeared in 144.7 pentagons. For those gene-expression pairs that appear in pentagons, very nearly all genes express just one protein, with only a few exceptions. Of the 6694 genes, there were 20 genes that expressed two proteins, and four that expressed more than two: HLA-B, HLA-A, HLA-C and HLA-DRB1. All remaining genes express just one protein. However, these same genes also participate in a (comparatively) huge fraction of all pentagons.

There is no point in computing MI for gene-protein interactions; they occur in tightly-bound and exclusive pairs; there is no free association.

Pathways

There are a large number of pathway-protein pairs available in the data-set, of which only a small fraction, 38843 pairs, appeared in pentagons. As proteins can appear in multiple pathways, it is meaningful to explore correlations and affinities between these.

Below is the pathway-protein MI graph. It is fit with two Gaussians, as suggested by the previous observations. Note that the parameters are very similar.



It's clearly much noisier, as the set of edges is much smaller. The proteome/reactome data-set although large, seems not as well-developed as the genome data-set.

TODO

weighted in-degree of vertexes?

Better Algos:

Explore more efficient algos:

- A fast algorithm plus source code here: Sampo Niskanen and Patric R.J. Östergård, "CLIQUER USER'S GUIDE Version 1.0" Helsinki University of Technology Communications Laboratory Technical Report T48 Espoo 2003 https://users.aalto.fi/~pat/cliquer/
- Description of above algorithm: P. R. J. Östergård, "A fast algorithm for the maximum clique problem", Disrete Appl. Math. 120 (2002), 195–205.
- Review of clique algos and related problems: I. M. Bomze, M. Budinih, P. M. Pardalos, and M. Pelillo, The maximum clique problem, in: D.-Z. Du and P. M. Pardalos (Eds.), Handbook of Combinatorial Optimization, Supplement Volume A, Kluwer, Dordreht, 1999, pp. 174

The End

That's all.