

Databases and ontologies

WTFgenes: What's The Function of these genes? Static sites for model-based gene set analysis

Ian H. Holmes¹

¹Department of Bioengineering, University of California, Berkeley, CA 94720, USA

Abstract

Motivation. A common technique for interpreting experimentally-identified lists of genes is to look for enrichment of genes associated to particular Gene Ontology terms. The most common technique uses the hypergeometric distribution; more recently, a model-based approach was proposed. These approaches must typically be run using downloaded software, or on a server. **Results.** We develop a collapsed likelihood for model-based gene set analysis and present WTFgenes, an implementation of both hypergeometric and model-based approaches, that can be published as a static site with computation run in JavaScript on the user's web browser client. Apart from hosting, zero server resources are required: the site can (for example) be served directly from an S3 bucket. A faster C++ implementation yielding identical results is also provided. Our implementation of model-based Gene Ontology enrichment uses some optimizations which permit probability parameters to be integrated out directly. **Availability and Implementation.** WTFgenes is available from <https://github.com/evoldoers/wtfgenes>. **Contact.** Ian Holmes ihholmes+wtfgenes@gmail.com. **Supplementary Information.** None.

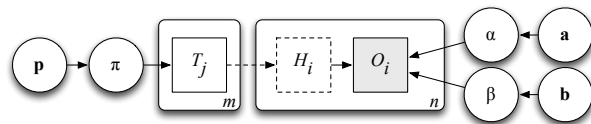


Fig. 1. The model

(false positive) and β (false negative), and the respective hyperparameters are $\mathbf{p} = (p_0, p_1)$, $\mathbf{a} = (a_0, a_1)$ and $\mathbf{b} = (b_0, b_1)$. The model is

$$\begin{aligned} P(T_j = 1 | \pi) &= \pi \\ P(O_i = 1 | H_i = 0, \alpha) &= \alpha \\ P(O_i = 1 | H_i = 1, \beta) &= 1 - \beta \end{aligned}$$

Introduction

Gene Set Enrichment Analysis (GSEA) Subramanian *et al.* (2005) Numerous implementations e.g. GO::TermFinder Boyle *et al.* (2004)

Model-based Gene Set Analysis (MGSA) Bauer *et al.* (2010) Bioconductor Bauer *et al.* (2011)

builds on earlier generative model by Lu *et al.* (2008)

The MGSA model is sketched in Figure 1. For each of the m terms there is a boolean random variable T_j ("term j is activated"). For each of the n genes there is a directly-observed boolean random variable O_i ("gene i is observed in the gene set"), and one deterministic boolean variable H_i ("gene i is activated") defined by $H_i = 1 - \prod_{j \in G_i} T_j$ where G_i is the set of terms associated with gene i (including directly annotated terms, as well as ancestral terms implied by transitive closure of the directly annotated terms). The probability parameters are π (term activation), α

with $\pi \sim \text{Beta}(\mathbf{p})$, $\alpha \sim \text{Beta}(\mathbf{a})$ and $\beta \sim \text{Beta}(\mathbf{b})$. The model of Bauer *et al.* (2010) is similar but used an *ad hoc* discretized prior for π , α and β .

Most MGSA and GSEA implementations are designed for desktop use.

Several GSEA implementations are designed for web use, notably Enrichr Chen *et al.* (2013); Gundersen *et al.* (2015); Kuleshov *et al.* (2016) which has a rich dynamic web front-end. However these web-facing GSEA implementations generally require a server-hosted back end. Further, there are no web-based MGSA implementations.

Results

We sample from a collapsed version of the model by integrating out the probability parameters. Let $c_p = \sum_j T_j$ count the number of activated terms, $c_g = \sum_i H_i$ the activated genes, $c_a = \sum_i O_i(1 - H_i)$ the false positives and $c_b = \sum_i O_i H_i$ the false negatives. Then

$$P(\mathbf{T}, \mathbf{O} | \mathbf{a}, \mathbf{b}, \mathbf{p}) = Z(c_p; m, \mathbf{p}) Z(c_a; n - c_g, \mathbf{a}) Z(c_b; c_g, \mathbf{b})$$

where

$$Z(k; N, \mathbf{A}) = \binom{N}{k} \frac{B(k + A_0, N - k + A_1)}{B(A_0, A_1)}$$

is the beta-binomial distribution for k successes in N trials with pseudocounts (A_0, A_1) , using the beta function

$$B(x, y) = \int_0^1 t^{x-1} (1-t)^{y-1} dt = \frac{\Gamma(x)\Gamma(y)}{\Gamma(x+y)}$$

Integrating out probability parameters improves sampling efficiency and allows for higher-dimensional models where, for example, we observe multiple gene sets and give each term its own probability π_j or each gene its own error rates (α_i, β_i) . Our implementation by default uses uninformative priors with hyperparameters $\mathbf{a} = \mathbf{b} = \mathbf{p} = (1, 1)$ but this can be overridden by the user.

For MCMC we use a Metropolis-Hastings sampler where each proposed move perturbs some subset of the term variables. These moves include *flip*, where a single term is toggled; *step*, where any activated term and any one of its unactivated ancestors or descendants are toggled; *jump*, where any activated term and any unactivated term are toggled; and *randomize*, where all term variables are uniformly randomized. The relative rates of these moves can be set by the user; after some empirical investigation of mixing efficiency, we set the defaults such that *flip*, *step*, and *jump* are equiprobable, while *randomize* is disabled.

The non-model based GSEA implementation uses a standard one-tailed Fisher’s Exact Test with a Bonferroni correction for multiple hypothesis testing.

We present JavaScript implementation of MGSA and GSEA, allowing easy comparison. Static site: can be hosted as static files, inexpensively and with considerable security benefits

For reference we also provide C++ implementation that should yield numerically identical results (MCMC uses same random number generator)

Autocorrelation plots

Speed comparison: C++ vs JavaScript

Discussion

Not a direct competitor to Enrichr, which has much richer visualizations and allows user submission of gene sets

GREAT McLean *et al.* (2010)

Funding

IHH was partially supported by NHGRI grant R01-HG004483.

References

- Bauer, S., Gagneur, J., and Robinson, P. N. (2010). GOing Bayesian: model-based gene set analysis of genome-scale data. *Nucleic Acids Res.*, **38**(11), 3523–3532.
- Bauer, S., Robinson, P. N., and Gagneur, J. (2011). Model-based gene set analysis for Bioconductor. *Bioinformatics*, **27**(13), 1882–1883.
- Boyle, E. I., Weng, S., Gollub, J., Jin, H., Botstein, D., Cherry, J. M., and Sherlock, G. (2004). GO::TermFinder—open source software for accessing Gene Ontology information and finding significantly enriched Gene Ontology terms associated with a list of genes. *Bioinformatics*, **20**(18), 3710–3715.
- Chen, E. Y., Tan, C. M., Kou, Y., Duan, Q., Wang, Z., Meirelles, G. V., Clark, N. R., and Ma’ayan, A. (2013). Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. *BMC Bioinformatics*, **14**, 128.
- Gundersen, G. W., Jones, M. R., Rouillard, A. D., Kou, Y., Monteiro, C. D., Feldmann, A. S., Hu, K. S., and Ma’ayan, A. (2015). GEO2Enrichr: browser extension and server app to extract gene sets from GEO and analyze them for biological functions. *Bioinformatics*, **31**(18), 3060–3062.
- Kuleshov, M. V., Jones, M. R., Rouillard, A. D., Fernandez, N. F., Duan, Q., Wang, Z., Koplev, S., Jenkins, S. L., Jagodnik, K. M., Lachmann, A., McDermott, M. G., Monteiro, C. D., Gundersen, G. W., and Ma’ayan, A. (2016). Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. *Nucleic Acids Res.*, **44**(W1), W90–97.
- Lu, Y., Rosenfeld, R., Simon, I., Nau, G. J., and Bar-Joseph, Z. (2008). A probabilistic generative model for GO enrichment analysis. *Nucleic Acids Res.*, **36**(17), e109.
- McLean, C. Y., Bristor, D., Hiller, M., Clarke, S. L., Schaar, B. T., Lowe, C. B., Wenger, A. M., and Bejerano, G. (2010). GREAT improves functional interpretation of cis-regulatory regions. *Nat. Biotechnol.*, **28**(5), 495–501.
- Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., Paulovich, A., Pomeroy, S. L., Golub, T. R., Lander, E. S., and Mesirov, J. P. (2005). Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. U.S.A.*, **102**(43), 15545–15550.