

## Databases and ontologies

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

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### 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](mailto:ihholmes+wtfgenes@gmail.com). **Supplementary Information.** None.

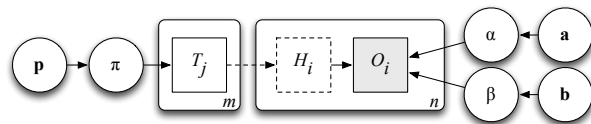


Fig. 1. The model

### 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  $\pi$  (term activation),  $\alpha$

(false positive observation) and  $\beta$  (false negative observation), 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

$$P(T_j = 1 | \pi) = \pi$$

$$P(O_i = 1 | H_i = 0, \alpha) = \alpha$$

$$P(O_i = 1 | H_i = 1, \beta) = 1 - \beta$$

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  $\pi$ ,  $\alpha$  and  $\beta$ .

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 future model variations where, for example, each gene has its own false positive parameter  $\beta_i$ . 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.

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)

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)

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