Large-scale benchmark of Endeavour using MetaCore maps

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ABSTRACT

Summary: Endeavour is a tool that detects the most promising genes within large lists of candidates with respect to a biological process of interest and by combining several genomic data sources. We have benchmarked Endeavour using 450 pathway maps and 826 disease marker sets from MetaCore™ of GeneGo, Inc. containing a total of 9911 and 12 432 genes, respectively. We obtained an area under the receiver operating characteristic curves of 0.97 for pathway and of 0.91 for disease gene sets. These results indicate that Endeavour can be used to efficiently prioritize candidate genes for pathways and diseases.

Availability: Endeavour is available at http://www.esat.kuleuven.be/endevour

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Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION

Identifying disease causing genes is a key challenge in human genetics. In the process of identifying such disease genes, researchers are often confronted with large lists of candidate genes among which only one or a few are actually causal. The validation of each candidate is often too costly and time consuming, so that only a few candidates are further experimentally validated. A related problem arises when trying to identify new members of a biological pathway. The selection of a small subset of optimal candidates for validation is called gene prioritization. Since going manually through all possible sources of information is a slow and tedious process, several bioinformatics methods have been developed to tackle this problem (Oti and Brunner, 2007; Zhu and Zhao, 2007). We previously developed Endeavour (Aerts et al., 2006; Tranchevent et al., 2008) whose key feature is that it uses multiple genomic data sources (e.g. sequence, expression, literature and annotation) to estimate how promising a candidate gene is by measuring its similarity with a set of training genes. The training genes are genes which are already known to play a role in the biological process under study. The underlying assumption is that the most promising candidate genes are the ones that exhibit many similarities with the training genes. A schematic view of the algorithm is shown in Figure 1. Originally, Endeavour was benchmarked by leave-one-out cross-validations on 32 gene sets corresponding to

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of Endeavour to capture the information of known pathway and disease-related gene sets, we used the pathways maps and disease marker sets of MetaCore™ from GeneGo, Inc. Since the gene sets in MetaCore are manually curated, we consider them as a reliable representation of the current knowledge of the functional contexts in which the genes are active. We have benchmarked Endeavour using 450 pathway maps and 826 disease marker sets containing a total of 9911 pathway members and 12 432 disease genes, respectively. In addition, we have also benchmarked 29 OMIM diseases and 37 Gene Ontology pathways that contain 620 and 1216 genes, respectively. For each prioritization run, the position of the left-out gene among 99 randomly chosen candidates is recorded (see also Supplementary Material). We use the area under the receiver operating characteristic (ROC) curves (AUC) as a measure of the performance. We obtained an AUC of 0.97 for the MetaCore pathways. Moreover, 64% of the prioritizations have the left-out gene being ranked in the first position. The AUC value obtained for the MetaCore disease marker sets is 0.91 and 33% of the prioritizations have the left-out gene being ranked in the first position (Fig. 2). The AUC values obtained for the Gene Ontology pathways and OMIM diseases are 0.93 and 0.94, respectively. Altogether, the results indicate that Endeavour efficiently prioritizes candidate genes for both pathways and diseases. As observed and discussed in our previous work (Aerts et al., 2006), the performance of gene prioritization is higher for pathways than for disease marker sets because data sources such as Gene Ontology contain pathway specific information and because diseases often implicate a complex set of cascades making their profiling more challenging. Furthermore, the performance is higher for OMIM diseases than for MetaCore diseases because the MetaCore sets include markers derived from gene expression studies whereas the OMIM sets only rely on known causative genes. Such markers are indirectly associated to the disease and it is therefore harder to prioritize them. Assessing the performance of a novel type of bioinformatics tool, such as gene prioritization methods, is of crucial importance. Our large-scale benchmark demonstrates the effectiveness of Endeavour. It should be noted that the evaluation was carried out at Novartis by S. Schuierer and U. Dengler independently of the core Endeavour team. In particular, the Endeavour platform was used as is and no parameter fine tuning was performed (i.e. all available data sources were used, see also Supplementary Material). We are aware of the many pitfalls of benchmarking gene prioritization and function prediction methods (Myers et al., 2006), so that the performance observed in cross-validation studies is likely to be higher than that observed in prospective studies. We have recently conducted such a prospective validation in Drosophila (Aerts et al., 2009), which also confirmed further the effectiveness of our strategy.

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**REFERENCES**


