

微生物富集中*Reporter Score*的误用

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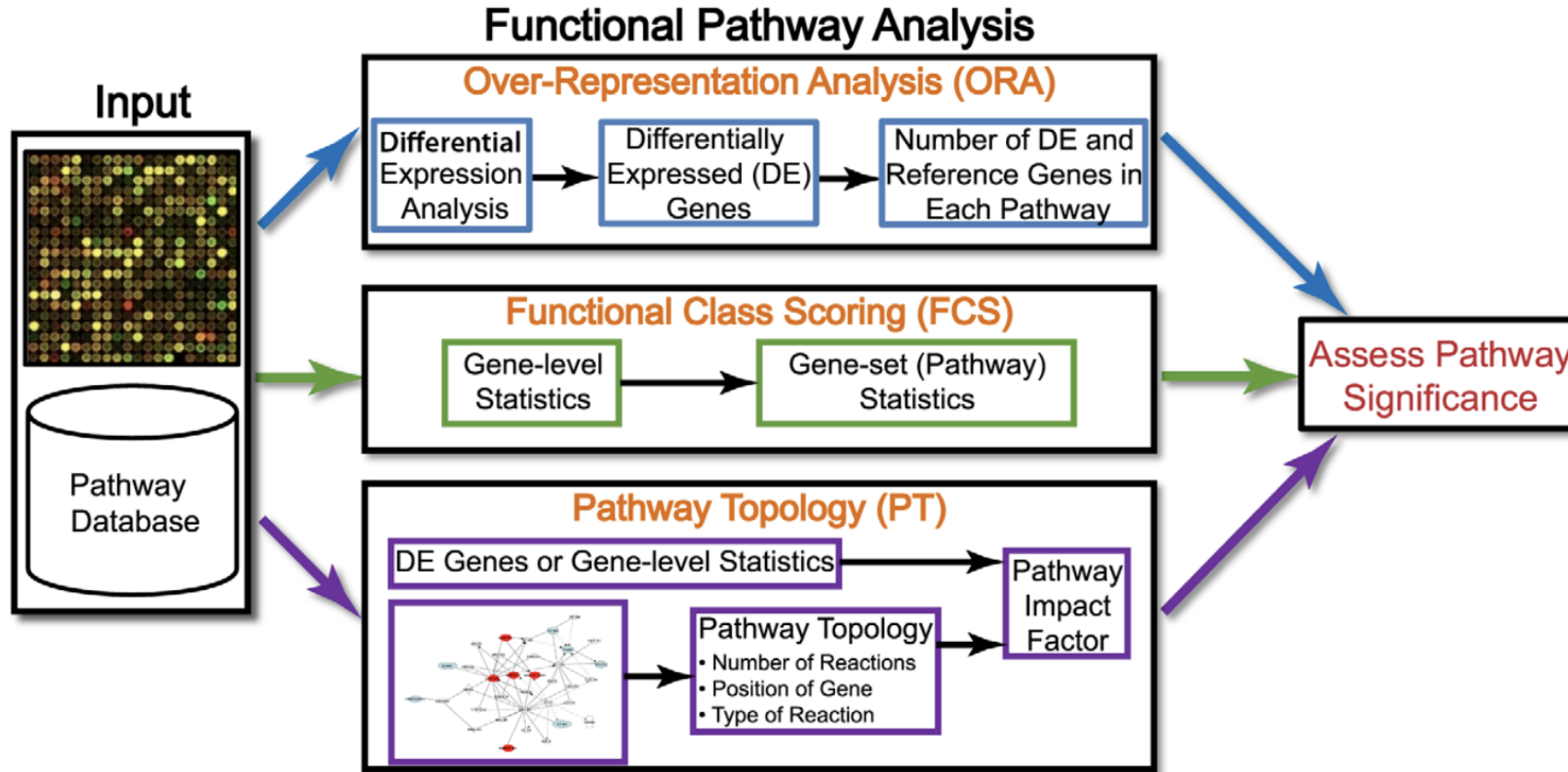


Liu, Lei, Ruixin Zhu, and Dingfeng Wu. 2023. "Misuse of reporter score in microbial enrichment analysis." *iMeta*. e95. <https://doi.org/10.1002/imt2.95>

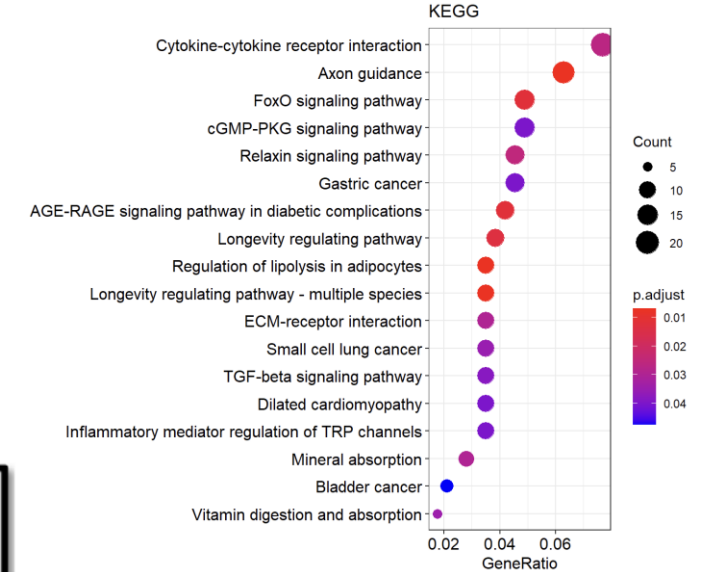


富集分析

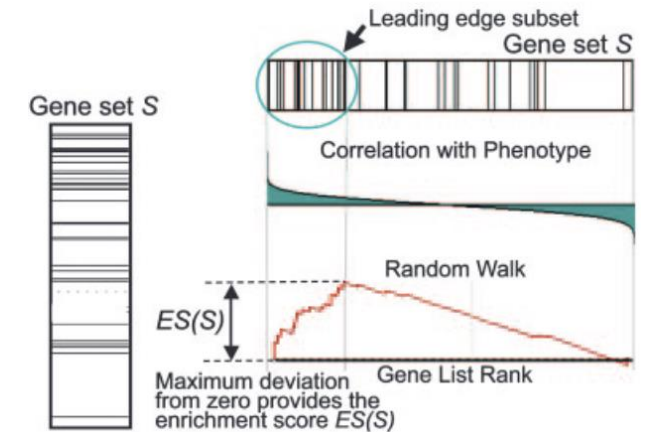
现有通路分析方法综述



富集分析

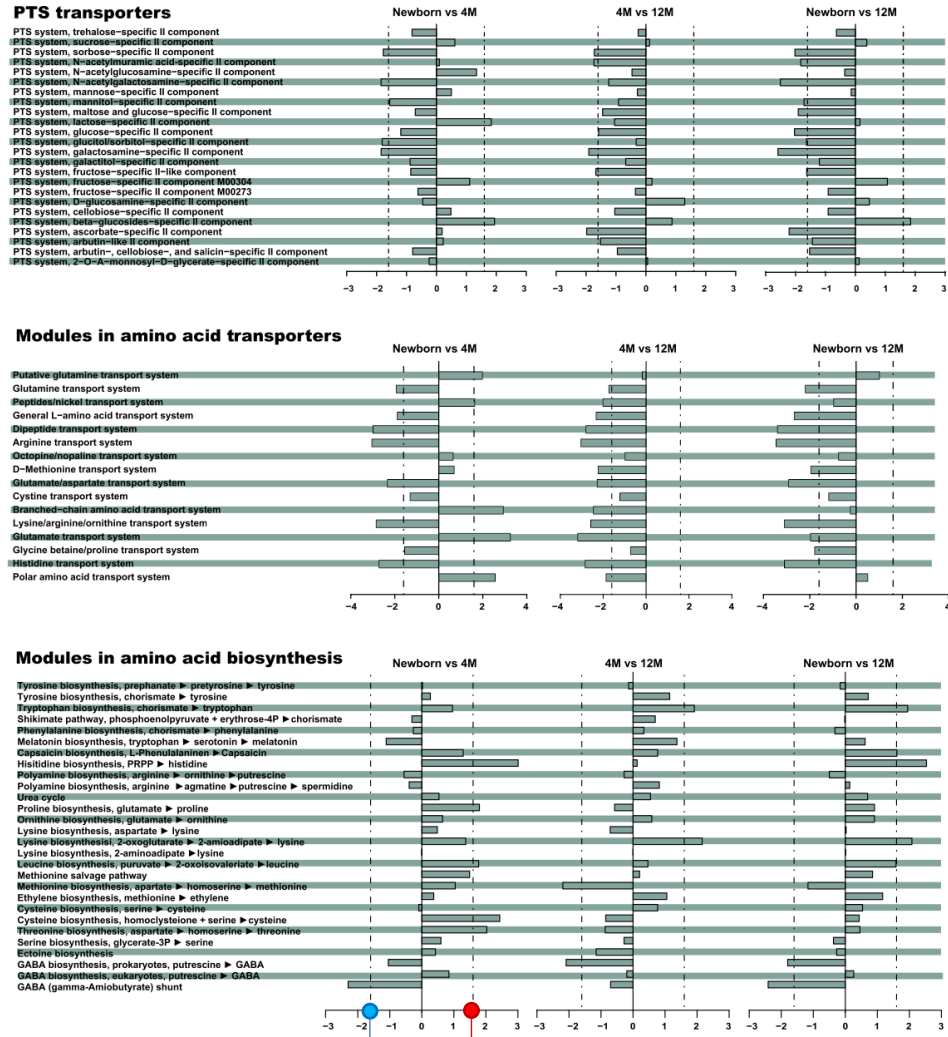


基因富集分析 (GSEA)



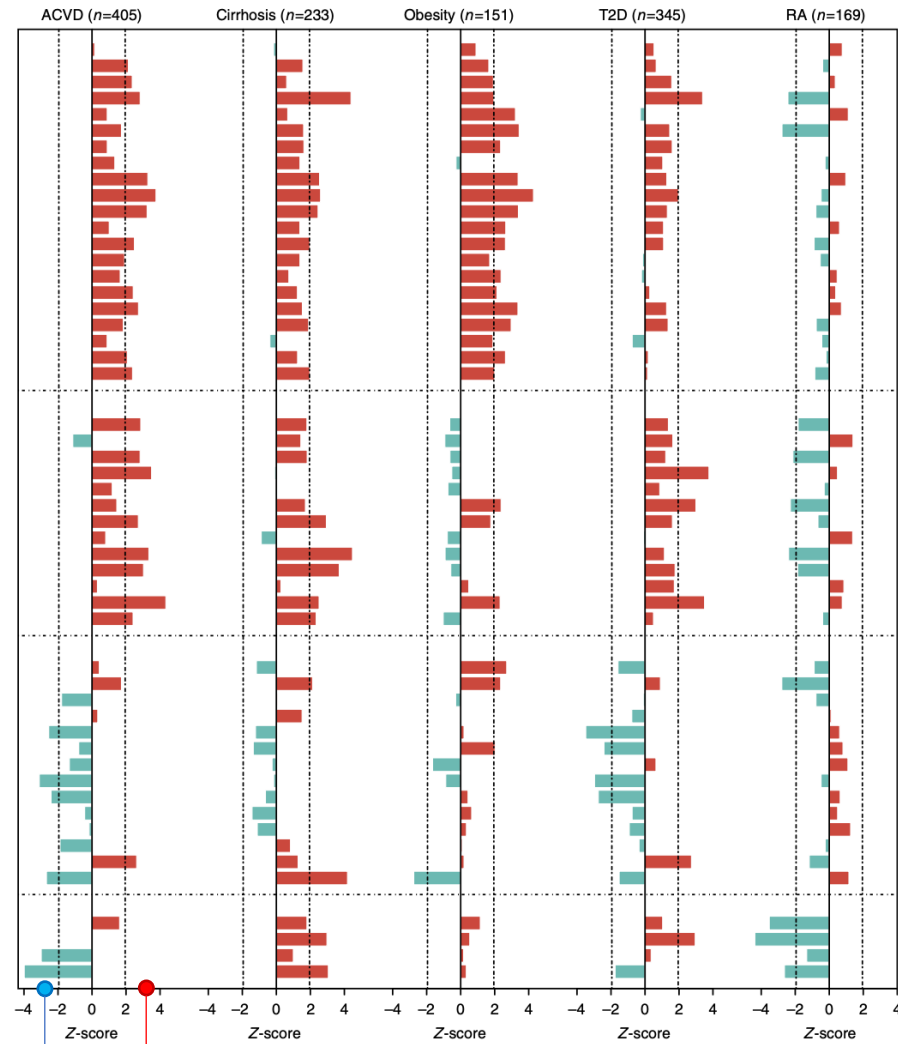
Reporter Score

Reporter score 在母婴肠道微生物组中的应用



下调 上调

Reporter score 在动脉粥样硬化性心血管疾病的肠道微生物组中的应用



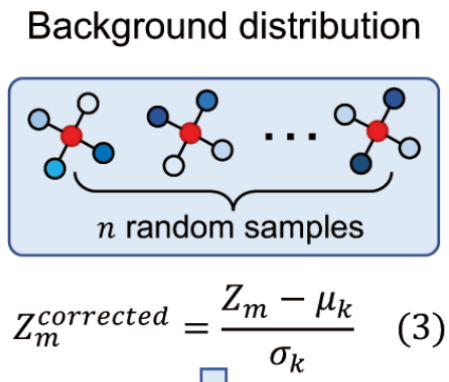
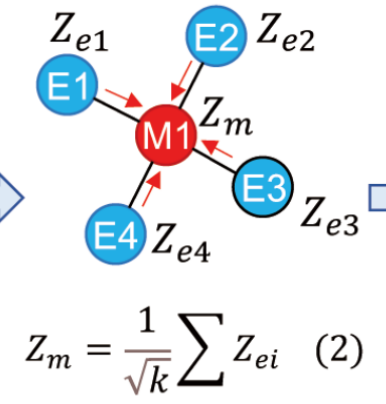
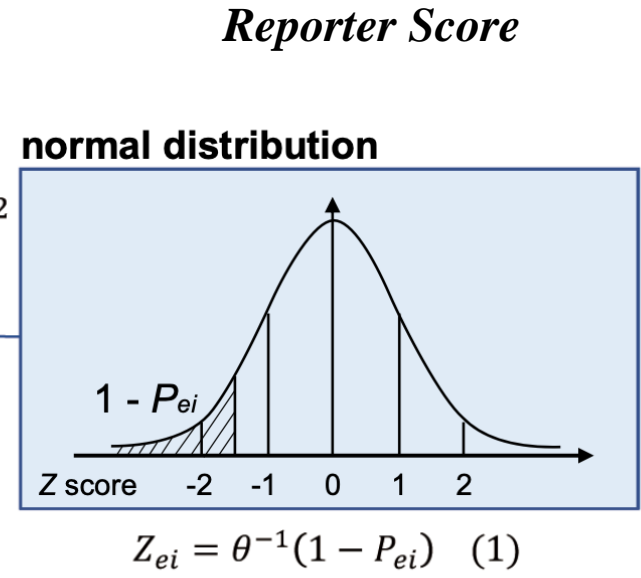
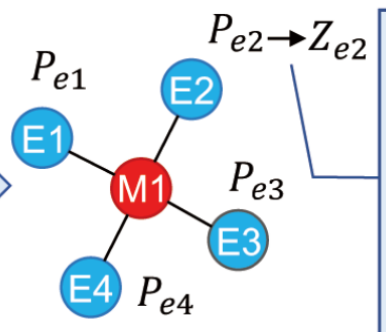
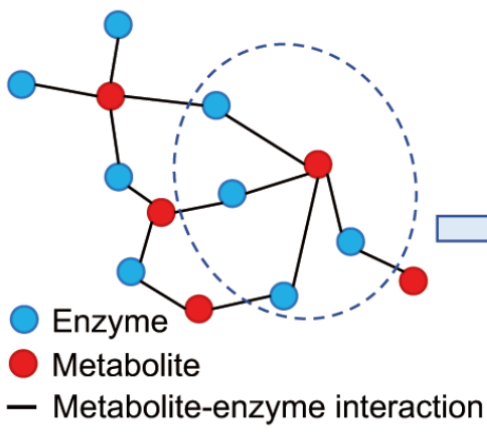
下调 上调

- Phosphotransferase system (PTS)**
- PTS system, fructose-specific II component.(M00304)
 - PTS system, N-acetylmuramic acid-specific II component.(M00303)
 - PTS system, galactosamine-specific II component.(M00287)
 - PTS system, ascorbate-specific II component.(M00283)
 - PTS system, lactose-specific II component.(M00281)
 - PTS system, glucitol/sorbitol-specific II component.(M00280)
 - PTS system, galactitol-specific II component.(M00279)
 - PTS system, sorbose-specific II component.(M00278)
 - PTS system, N-acetylgalactosamine-specific II component.(M00277)
 - PTS system, mannose-specific II component.(M00276)
 - PTS system, cellobiose-specific II component.(M00275)
 - PTS system, mannitol-specific II component.(M00274)
 - PTS system, fructose-specific II component.(M00273)
 - PTS system, arbutin-, cellobiose-, and salicin-specific II component.(M00272)
 - PTS system, beta-glucosides-specific II component.(M00271)
 - PTS system, trehalose-specific II component.(M00270)
 - PTS system, sucrose-specific II component.(M00269)
 - PTS system, arbutin-like II component.(M00268)
 - PTS system, N-acetylglucosamine-specific II component.(M00267)
 - PTS system, maltose and glucose-specific II component.(M00266)
 - PTS system, glucose-specific II component.(M00265)
- Amino acid transporters**
- Histidine transport system.(M00226)
 - Glycine betaine/proline transport system.(M00208)
 - Lysine/arginine/ornithine transport system.(M00225)
 - Branched-chain amino acid transport system.(M00237)
 - Cystine transport system.(M00234)
 - Glutamine transport system.(M00227)
 - D-Methionine transport system.(M00238)
 - Octopine/nopaline transport system.(M00231)
 - Arginine transport system.(M00229)
 - Dipeptide transport system.(M00324)
 - General L-amino acid transport system.(M00232)
 - Peptides/nickel transport system.(M00239)
 - Putative glutamine transport system.(M00228)
- Vitamins metabolism**
- Cobalamin biosynthesis, cobinamide => cobalamin.(M00122)
 - Heme biosynthesis, glutamate => protoheme/siroheme.(M00121)
 - Biotin biosynthesis, pimeloyl-CoA => biotin.(M00123)
 - Coenzyme A biosynthesis, pantothenate => CoA.(M00120)
 - Pantothenate biosynthesis, valine/L-aspartate => pantothenate.(M00119)
 - NAD biosynthesis, aspartate => NAD.(M00115)
 - Pyridoxal biosynthesis, erythrose-4P => pyridoxal-5P.(M00124)
 - Riboflavin biosynthesis, GTP => riboflavin/FMN/FAD.(M00125)
 - Thiamine biosynthesis, AIR => thiamine-P/thiamine-2P.(M00127)
 - C1-unit interconversion, prokaryotes.(M00141)
 - C1-unit interconversion, eukaryotes.(M00140)
 - Tetrahydrofolate biosynthesis, GTP => THF.(M00126)
 - Ubiquinone biosynthesis, prokaryotes, chorismate => ubiquinone.(M00117)
 - Menaquinone biosynthesis, chorismate => menaquinone.(M00116)
- Lipopolysaccharide biosynthesis**
- Lipopolysaccharide biosynthesis, inner core => outer core => O-antigen.(M00080)
 - ADP-L-glycero-D-manno-heptose biosynthesis.(M00064)
 - CMP-KDO biosynthesis.(M00063)
 - Lipopolysaccharide biosynthesis, KDO2-lipid A.(M00060)

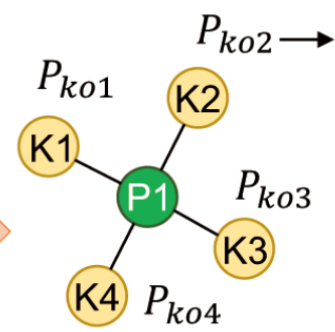
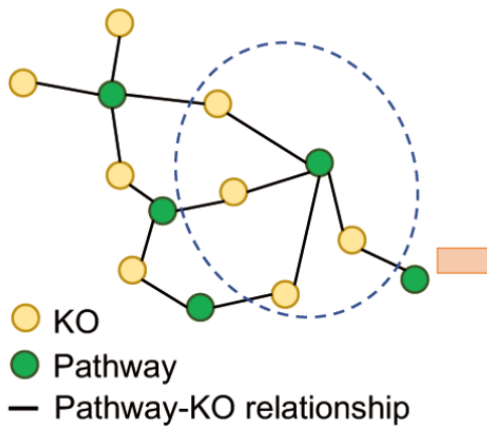
Jie Z, et. al. Nat Commun. 2017

误用 Reporter Score 导致微生物研究中产生错误结论

1) Patil et al., 2005

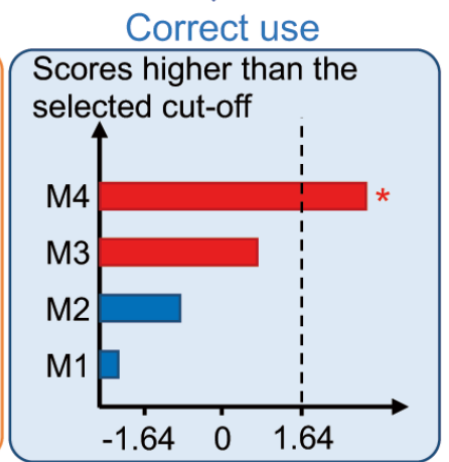
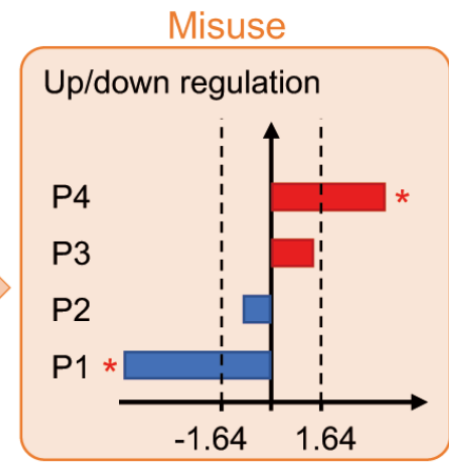


2) Surveyed articles



P value	0.01	0.05	0.5	0.95	0.99
Z score	2.33	1.64	0.0	-1.64	-2.33

... $Z_{corrected\ pathway}$



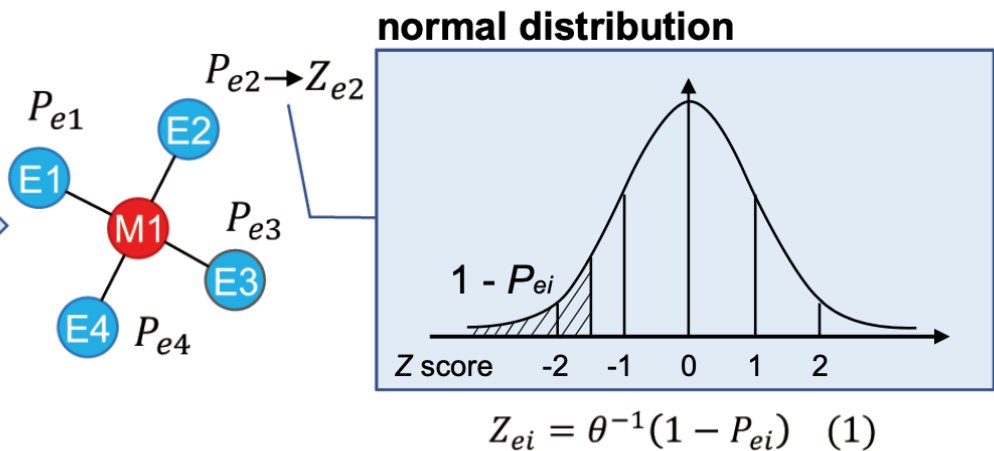
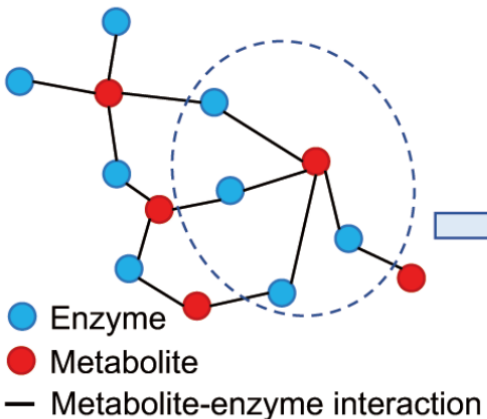
Patil and Nielsen. PNAS. 2005
Feng Q, et. al. Nat Commun. 2015



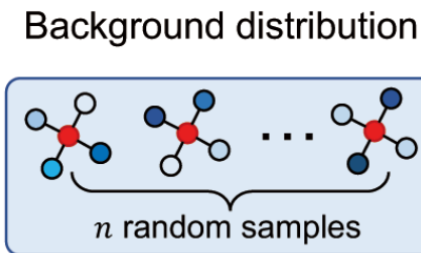
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Reporter Score的误用

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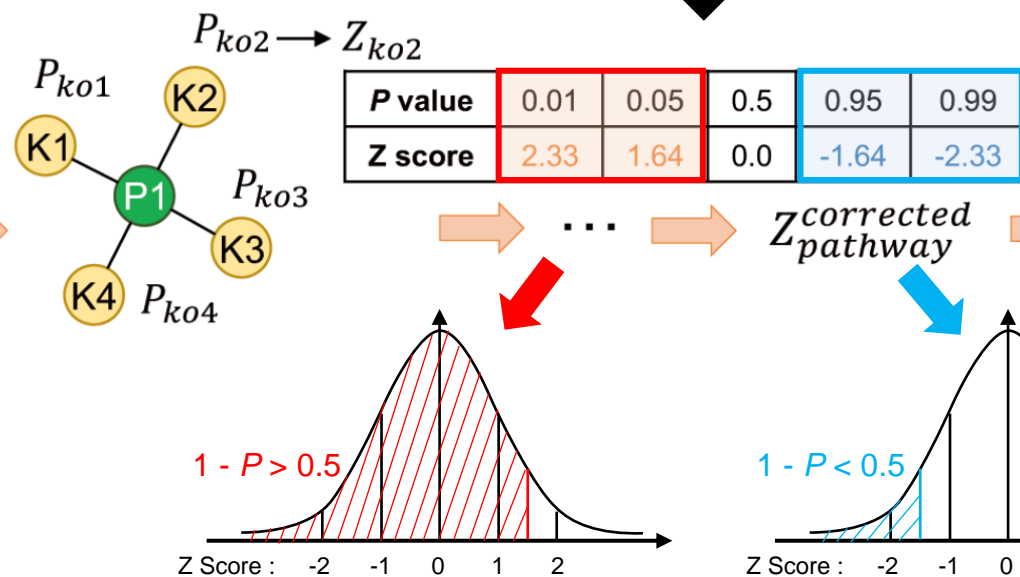
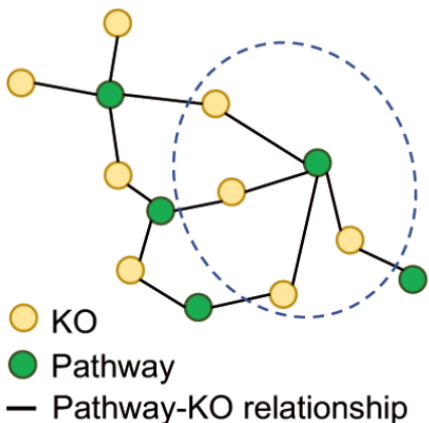


$$Z_m = \frac{1}{\sqrt{k}} \sum Z_{ei} \quad (2)$$

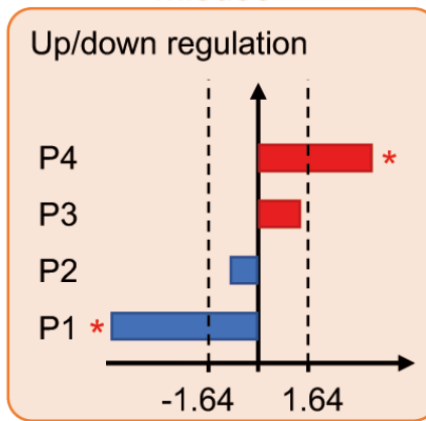


$$Z_m^{corrected} = \frac{Z_m - \mu_k}{\sigma_k} \quad (3)$$

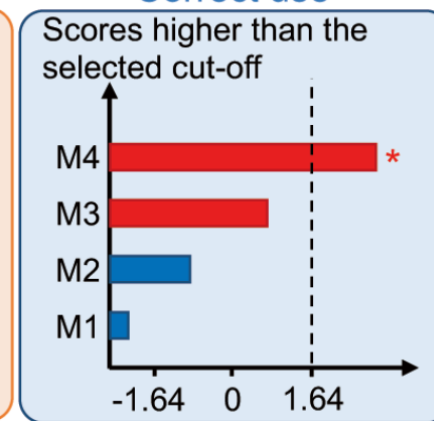
2) Surveyed articles



Misuse



Correct use

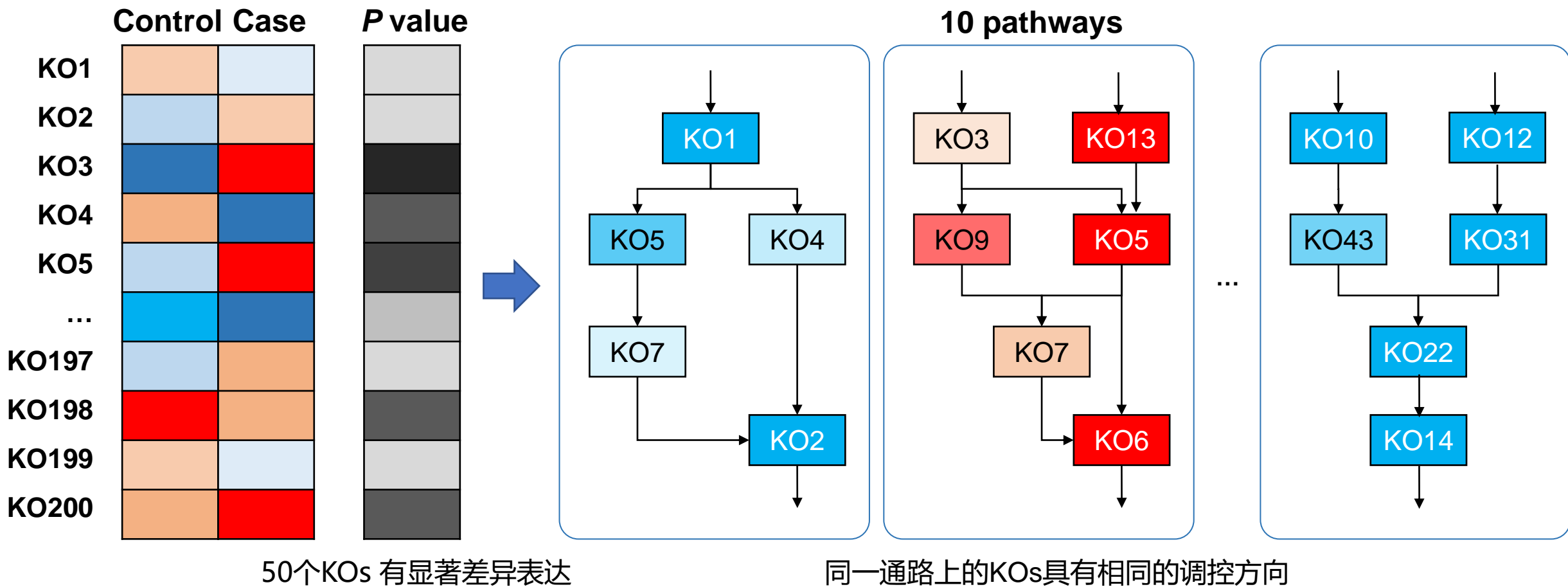


Patil and Nielsen. PNAS. 2005
Feng Q, et. al. Nat Commun. 2015



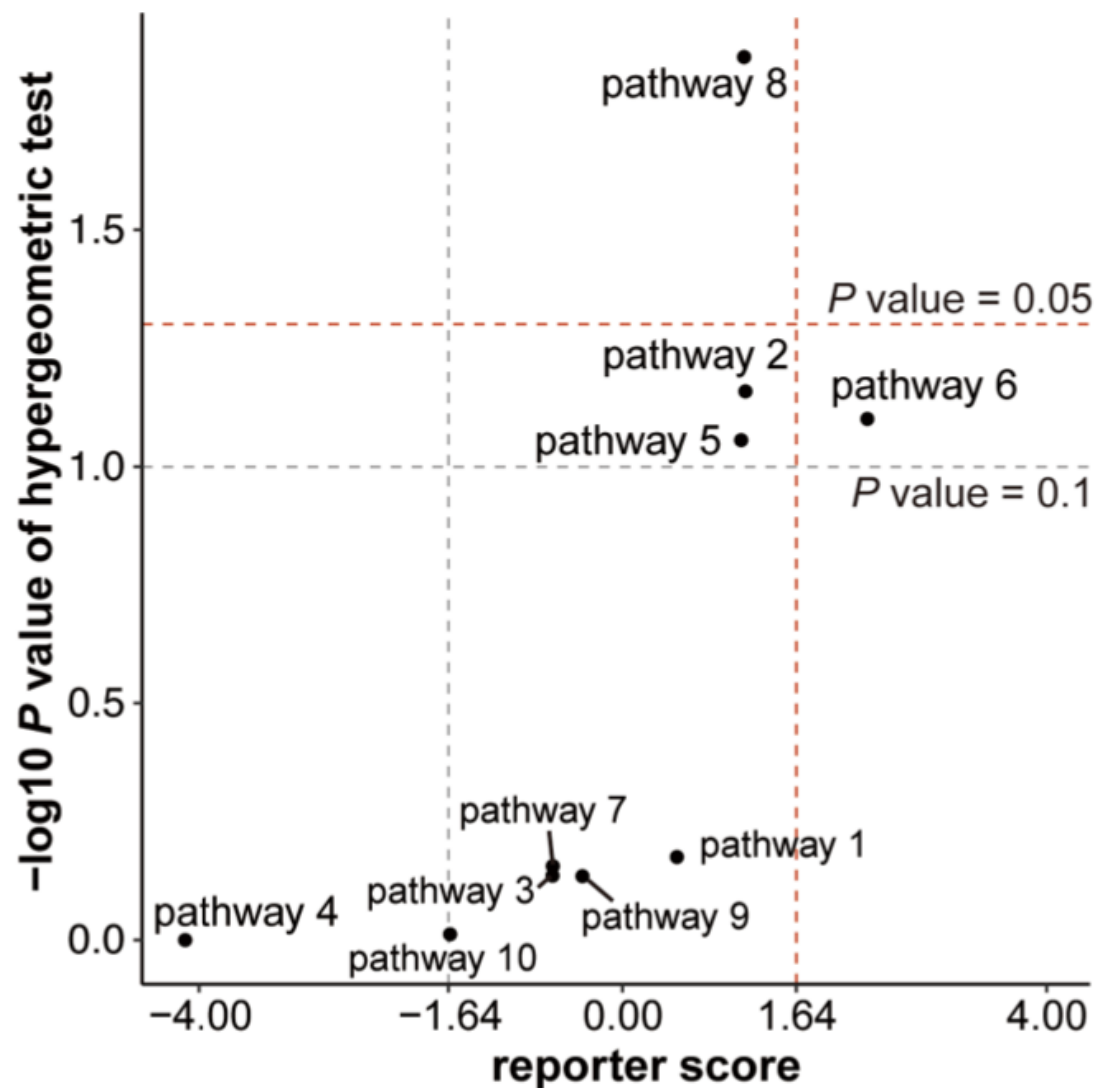
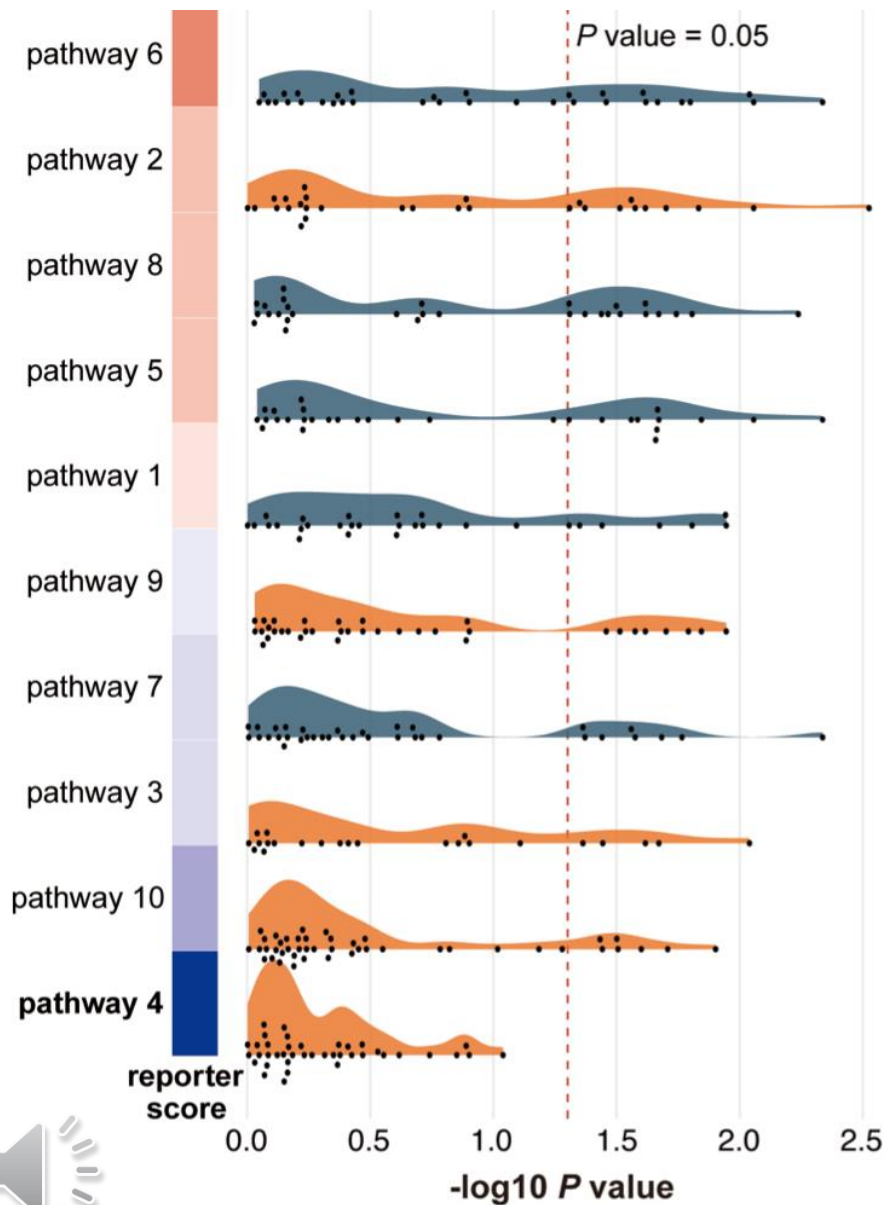
误用 Reporter Score导致微生物研究中产生错误结论

模拟数据集

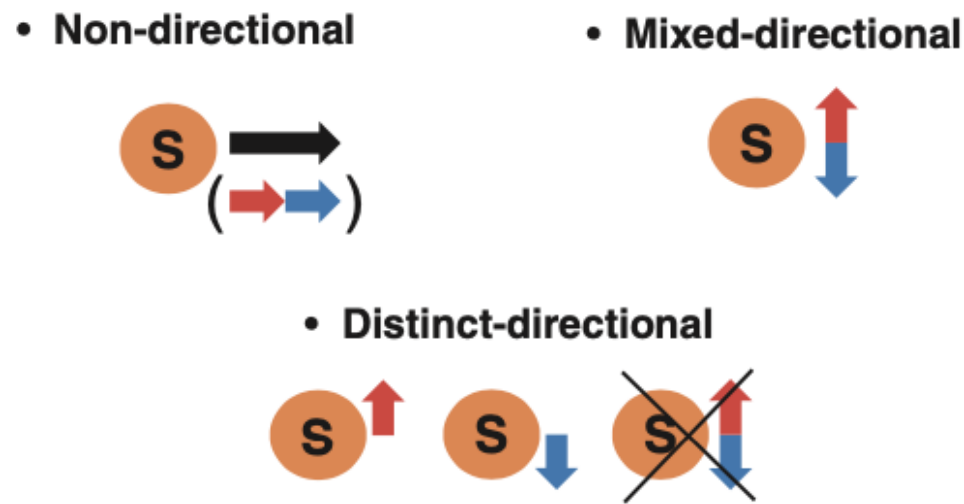
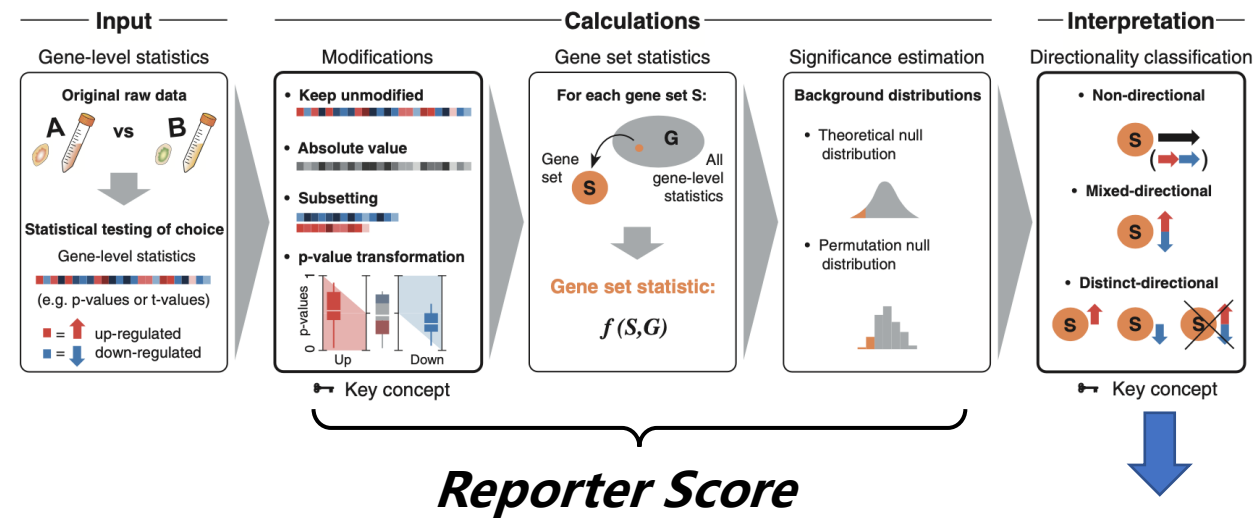
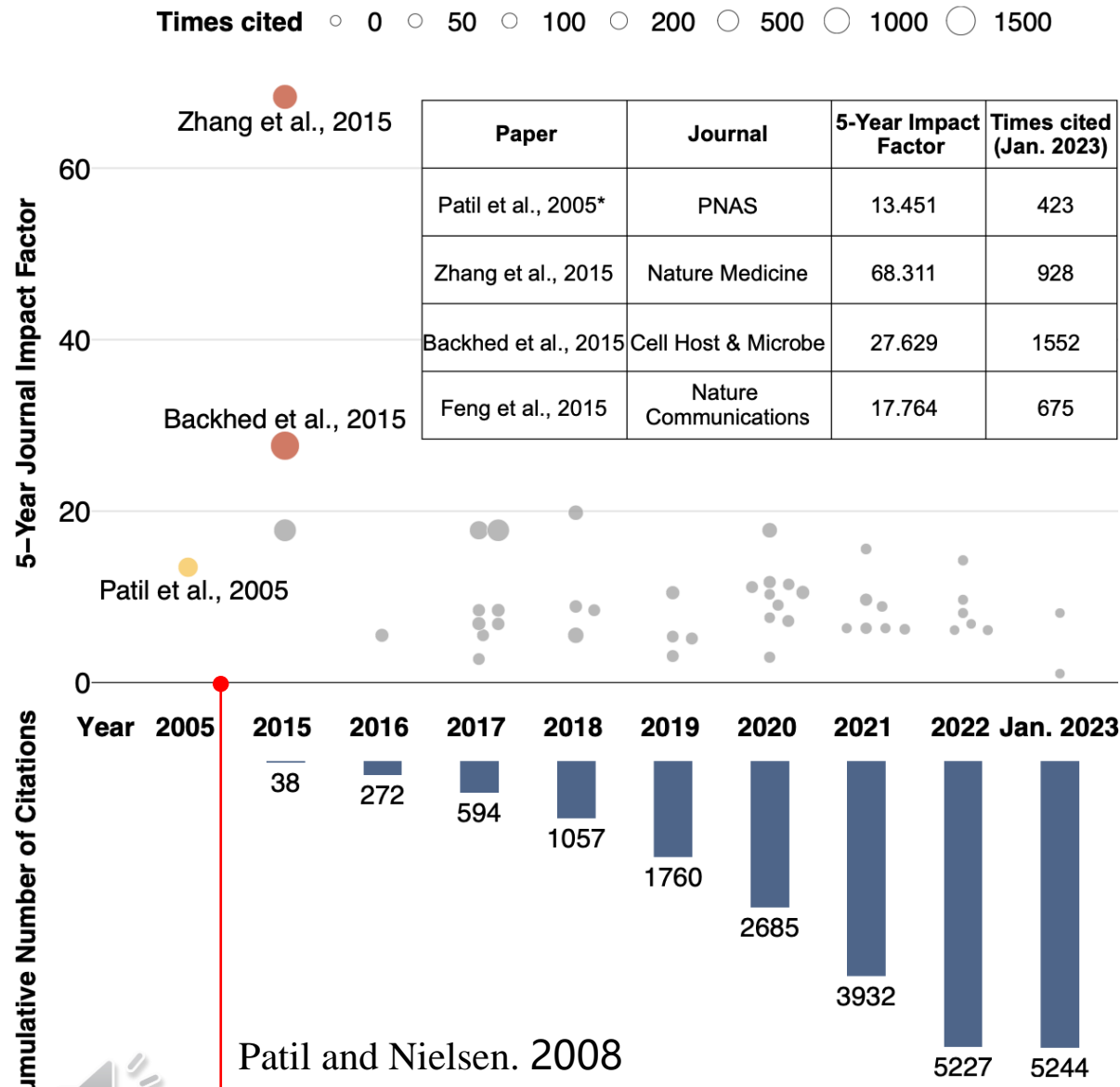


误用 Reporter Score 导致微生物研究中产生错误结论

模拟数据集



误用 Reporter Score 导致错误累积形成雪球效应



Reporter Feature analysis (Piano)

Leif Vařemo, et.al. NAR. 2013

Reporter Feature是Reporter Score的重要补充

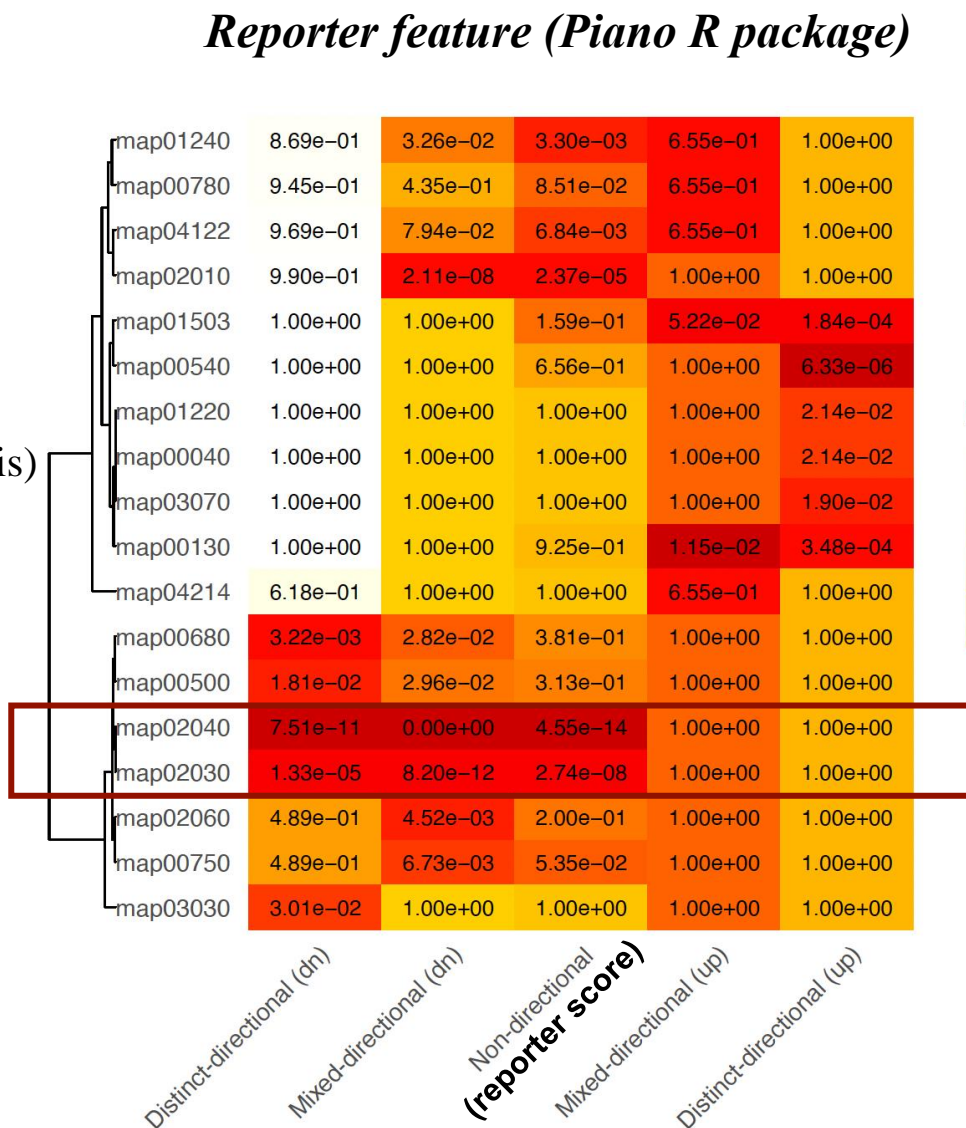
Demo dataset
(NAFLD with
Fibrosis vs. without Fibrosis)

Rohit Loomba, et. al. 2017

7246 KOs

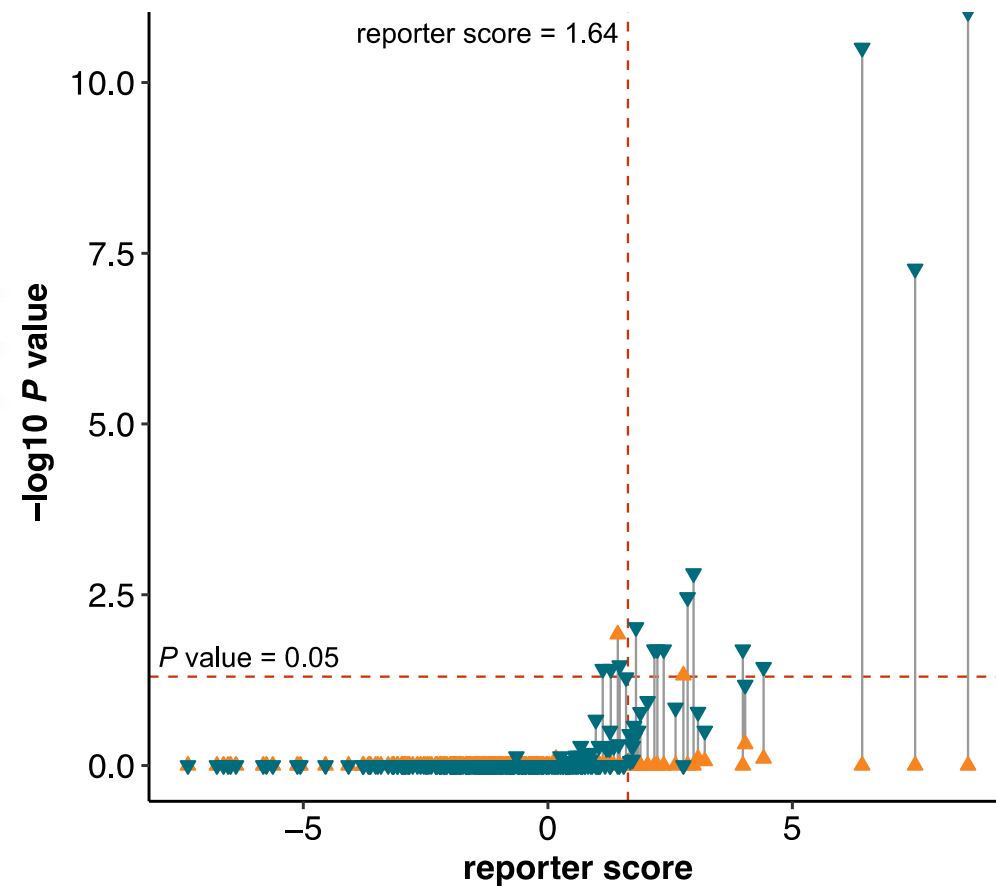


457 Pathways



Reporter score vs. Reporter feature

▲ mixed-directional (up) ▼ mixed-directional (down)



$$P \text{ value} = 1 - \theta(\text{reporter score})$$

map02040: non-directional reporter score = 8.596
map02030: non-directional reporter score = 6.429

<https://github.com/ddhmed/ReporterScore>

总结

- 在科学研究中，要特别注意统计技术的误用或误解，否则可能导致结果的不可靠和不可重复
- 在习惯性思维下解释 *reporter score*，并在不理解统计意义的情况下盲目地采用已有的方法，是导致这种低级错误不断发生的根本原因
- 在期刊审稿系统中，生物信息学研究纳入专门的检查表是必要的
- 应鼓励多学科合作，特别是与统计学家的合作，以促进更严谨的研究
- 加强对具有扎实的统计和数学基础知识的生物信息学家的培养尤为重要，这将保证生物信息学的快速、稳定发展，以促进各领域的科学研究



微生物富集中 *Reporter Score* 的误用

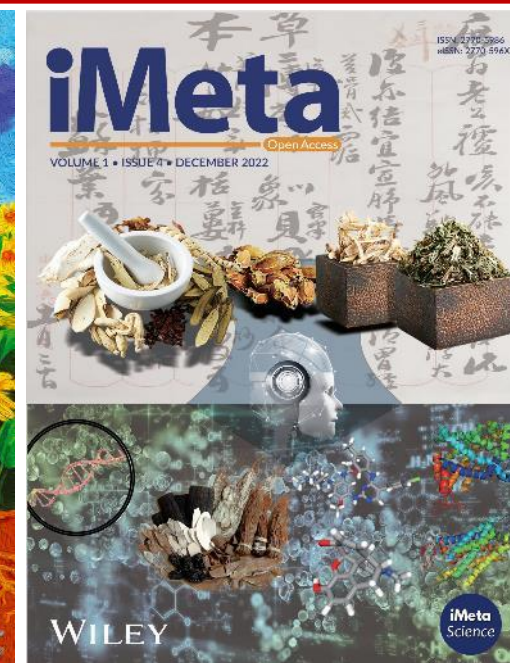
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Liu, Lei, Ruixin Zhu, and Dingfeng Wu. 2023. “Misuse of reporter score in microbial enrichment analysis.” *iMeta*. e95. <https://doi.org/10.1002/imt2.95>



“**iMeta**”由威立、肠菌分会和华人科学家出版的开放获取期刊，主编由中科院微生物所刘双江和荷兰格罗宁根大学傅静远教授共同担任。目的是发表原创研究、方法和综述以促进宏基因组学、微生物组和生物信息学发展。目标是发表前10%(IF > 15)的高影响力论文。期刊特色包括视频投稿、可重复分析、图片打磨、青年编委、前3年免出版费、50万用户的社交媒体宣传等。2022年的**三月**、**六月**、**九月**和**十二月**期已正式在线出版发行，相继被[Google Scholar](https://scholar.google.com/)、[PubMed\(部分\)](https://pubmed.ncbi.nlm.nih.gov/)、[DOAJ](https://doaj.org/)、[Scopus](https://scopus.com/)等数据库收录！



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