MBROLE3 Use cases

Here we provide two use cases for MBROLE3 https://csbg.cnb.csic.es/mbrole3/

A tutorial on how to perform a whole analysis with MBROLE2 is provided on-line at:

https://csbg.cnb.csic.es/mbrole3/help.php#using

Use case 1: Metabolomics study of a diet intervention in a disease model

Study:
Fernandez-Millan et al.(https://doi.org/10.3390/nu14194127) measured the metabolic changes produced by cocoa ingest in Zucker fatty rats (an animal model to study Diabetes Type 2). A ^{1}H-NMR untargeted metabolomics approach was used to measure the metabolite changes in the urine of lean rats and diabetic rats fed with standard diet and a cocoa-rich diet.

Data:
In this use case we analyzed 30 metabolites identified in the urine of these animals that could be mapped to HMDB (as provided in Supplementary Table S2 of the manuscript).

1-Methylnicotinamide	HMDB0000699
Acetic acid	HMDB0000042
Acetoacetic acid	HMDB0000060
Azelaic acid	HMDB0000784
Choline	HMDB0000097
Creatine	HMDB0000064
Creatinine	HMDB0000562
D-Glucose	HMDB0000122
Dimethylamine	HMDB0000087
Formic acid	HMDB0000142
Hippuric acid	HMDB0000714
Hydroxyphenyllactic acid	HMDB0000755
Indoxyl sulfate	HMDB0000682
Ketoleucine	HMDB0000695
L-Alanine	HMDB0000161
L-Isoleucine	HMDB0000172
L-Lactic acid	HMDB0000190
L-Leucine	HMDB0000687
L-Threonine	HMDB0000167
L-Valine	HMDB0000883
Nicotinamide N-oxide	HMDB0002730
Oxoglutaric acid	HMDB0000208
Phenylacetylglycine	HMDB0000821
Phosphorylcholine	HMDB0001565
Pimelic acid	HMDB0000857
Pyruvic acid	HMDB0000243
Suberic acid	HMDB0000893
Sucrose	HMDB0000258
Tartaric acid	HMDB0000956
Urea	HMDB0000294

No annotations were found for 3 of the metabolites: HMDB0000893 HMDB0002730 HMDB0000682 (highlighted in red)

We analyze both direct annotations (KEGG pathways, selecting *Rattus norvegicus* as background) as well as indirect annotations (Uniprot Keywords from compound-protein interactions compiled in HMDB).

Results:

1.a Pathways:

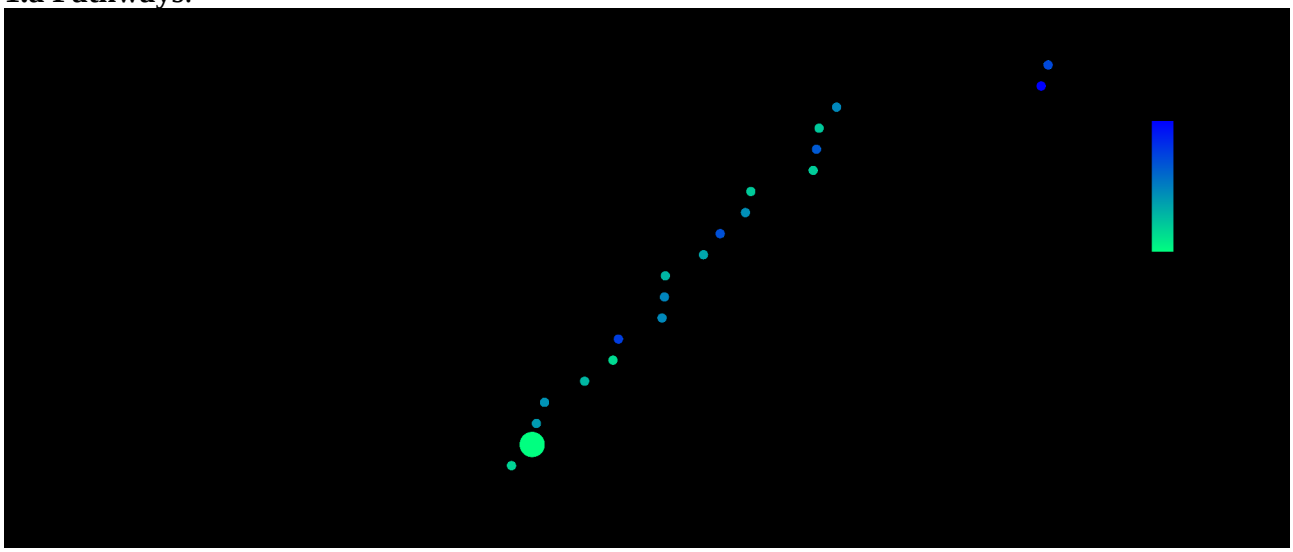

Figure 1: Pathways (from KEGG) enriched in use case 1.

We highlight the relevance of the top scoring pathways in relation to Diabetes mellitus type 2 by providing excerpts from the literature.

Annotation	Study	Excerpt
'Central carbon metabolism and cancer'	Diabetes and cancer: Epidemiological and biological links https://doi.org/10.4239%2Fwjd.v11.i6.227	*"A large body of epidemiological evidence has indicated that diabetes is considered as an independent risk factor for increased rates of heterogeneous types of cancer occurrence and death. […] Several studies have found that although T1DM and T2DM are associated with increased risks for cancer, T2DM has a stronger link with cancer both epidemiologically and biologically*".
'Valine, leucine and isoleucine biosynthesis', "Valine, leucine and isoleucine degradation"	Diabetes and branched-chain amino acids: What is the link? https://doi.org/10.1111/1753-0407.12645	"*Branched-chain amino acids (BCAA) have increasingly been studied as playing a role in diabetes*"
'Valine, leucine and isoleucine biosynthesis', 'Biosynthesis of amino acids', 'Protein digestion and absorption', 'Valine, leucine and isoleucine degradation'	Role of Branched-Chain Amino Acid Metabolism in Type 2 Diabetes, Obesity, Cardiovascular Disease and Non-Alcoholic Fatty Liver Disease https://doi.org/10.3390%2Fijms23084325	"*Branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine. Mammalians cannot synthesize these amino acids de novo and must acquire them through their diet. High levels of BCAAs are associated with insulin resistance; type 2 diabetes; obesity; and non-metabolic diseases, including several forms of cancer*"

‘Mineral absorption’	Role of minerals and trace elements in diabetes and insulin resistance https://doi.org/10.3390%2Fnu12061864	“*Minerals and trace elements are micronutrients that are essential to the human body but present only in traceable amounts [...] This review article is focused on some of these minerals and trace element deficiencies and their consequences in diabetes and insulin resistance. “*
‘ABC transporters’	Dyslipidemia in type 2 diabetes mellitus https://doi.org/10.1038/ncpendmet1066	“*The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance. […] Correct functioning of many gene products is involved in the lipid homeostasis, among these genes are the ATP-Binding Cassette (ABC) transporters. The ABC transporters are cell membrane proteins which use the energy from ATP hydrolysis to transport molecules from inside or outside of cell*”

1.b Uniprot Keywords (HMDB):

Uniprot Keywords are used in the UniProt protein sequence database to annotate protein functions. MBROLE3 analyzes Uniprot Keywords annotated to chemical compounds which have been established through compound-protein interactions. In this case we discuss the results obtained from those interactions described in the Human Metabolome Database (HMDB).

These annotations are ‘Indirect annotations’ and are reported in a separate table.

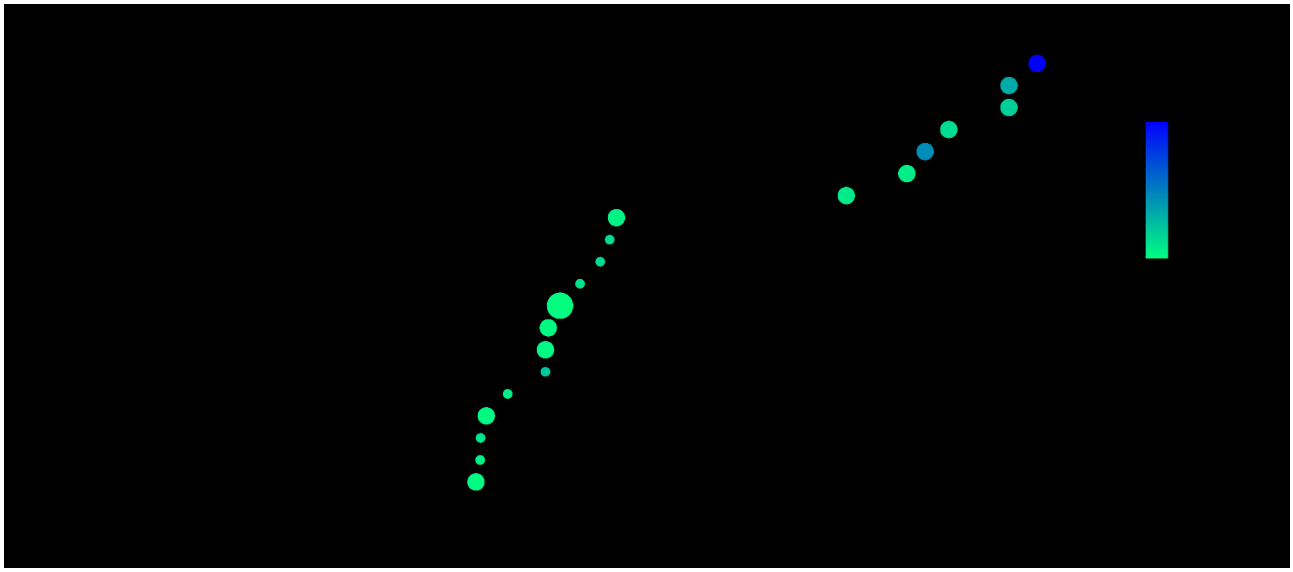

Figure 2: Uniprot keywords enriched in use case 1.

We highlight the relevance of the top scoring Uniprot Keywords in relation to Diabetes mellitus type 2 by providing excerpts from the literature.

Annotation	Study	Excerpt
‘branched-chain amino acid biosynthesis’	Diabetes and branched-chain amino acids: What is the link? https://doi.org/10.1111/1753-0407.12645	“*Branched-chain amino acids (BCAA) have increasingly been studied as playing a role in diabetes*“

‘protein biosynthesis’, ‘aminotransferase’, ‘amino-acid biosynthesis’, ‘aminoacyl-tRNA synthetase’	Insulin Regulation of Proteostasis and Clinical Implications https://doi.org/10.1016/j.cmet.2017.06.010	“*Insulin signaling regulates protein synthesis and degradation as well as posttranslational modifications at the tissue level and coordinates proteostasis at the organism level*”.
‘Pyridoxal phosphate’ (a coenzyme derived from vitamin B6)	Vitamin B6 and Diabetes: Relationship and Molecular Mechanisms https://doi.org/10.3390%2Fijms21103669	“*Epidemiological and experimental studies indicated an evident inverse association between vitamin B6 levels and diabetes, as well as a clear protective effect of vitamin B6 on diabetic complications*“
‘Neurotransmitter degradation’	Brain signaling systems in the Type 2 diabetes and metabolic syndrome: promising target to treat and prevent these diseases https://doi.org/10.4155%2Ffso.15.23	“*The main factors responsible for the development of Type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS) are insulin resistance, dysfunctions of pancreatic β-cells, hyperglycemia, the formation of advanced glycation end products, oxidative stress, mitochondrial dysfunctions, dyslipidemia, lipotoxicity and alterations in the hormonal signaling systems both in the CNS and the periphery*”

Use case 2: Metabolic biomarkers of Parkinson's disease

Study: Kori et al. (DOI: 10.1089/omi.2016.0106) compiled metabolite disease associations published in the literature for three neurodegenerative diseases: Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis. They analyzed disease-specific and common metabolic pathways for all diseases through enrichment analyses.

Data: Here, we analyzed with MBROLE3 the 52 metabolic biomarkers complied for Parkinson's disease (obtained from Table 1) that correspond to specific chemical compounds.

C00022
C00025
C00033
C00037
C00042
C00047
C00051
C00064
C00072
C00078
C00114
C00116
C00137
C00149
C00158
C00160
C00189
C00218
C00233
C00257
C00300
C00302
C00311
C00334
C00366
C00486
C00489
C00565
C00583
C00711
C00791
C00794
C01013
C01042
C01401
C01420
C01620
C01697
C01733
C01879
C02170
C02385
C03758
C05582
C08278
C13550
C16433
C16434
C16435
C16436
C16438
C19440

Results:
We analyze KEGG pathways (selecting *Homo sapiens* as background) and Gene Ontology terms (full database as background).

2.a. Pathways:

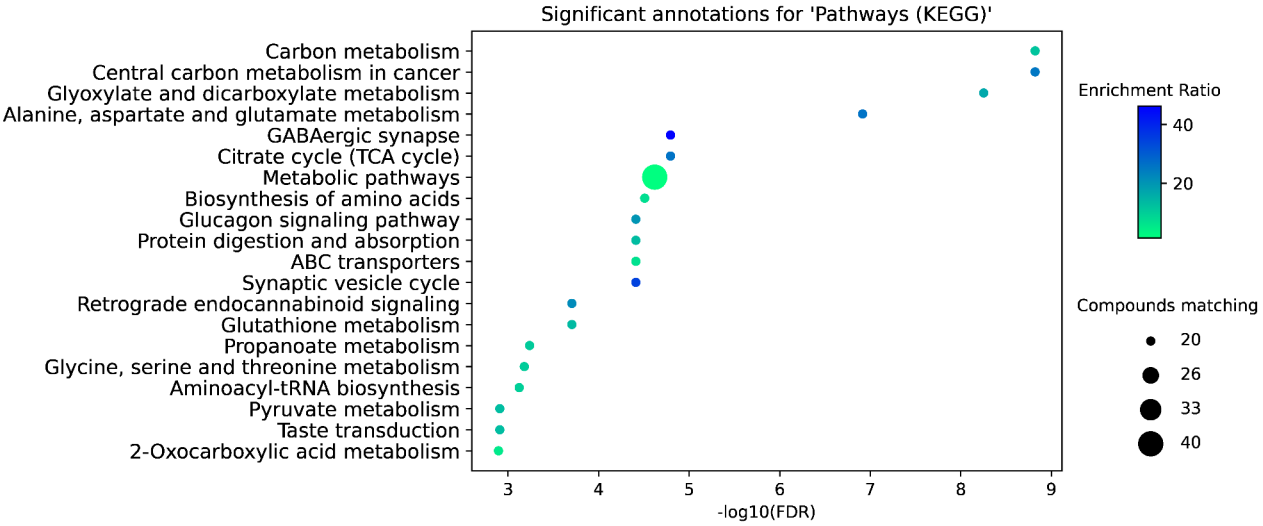

Figure 3: Pathways enriched in use case 2.

We highlight the relevance of the top scoring Pathways in relation to Parkinson's disease by providing excerpts from the literature.

Annotation	Study	Excerpt
'carbon metabolism' 'central carbon metabolism in cancer'	Metabolic Dysfunction in Parkinson's Disease: Bioenergetics, Redox Homeostasis and Central Carbon Metabolism https://doi.org/10.1016/j.brainresbull.2017.03.009	*"We and others have recently established a link between the alterations in central carbon metabolism induced by PD risk factors, redox homeostasis and bioenergetics and their contribution to the survival/death of dopaminergic cells. In this review, we focus on the link between metabolic dysfunction, energy failure and redox imbalance in PD, making an emphasis in the contribution of central carbon (glucose) metabolism"*
Alanine, aspartate and glutamate metabolism	Glutamate-induced excitotoxicity in Parkinson's disease: The role of glial cells https://doi.org/10.1016/j.jphs.2020.07.011	*"Glutamate-induced excitotoxicity is mainly linked to an impaired ability of glial cells to reuptake and respond to glutamate, then this is considered a common hallmark in many neurodegenerative diseases, including Parkinson's disease (PD)".*
GABAergic synapse	Contribution of the GABAergic System to Non-Motor Manifestations in Premotor and Early Stages of Parkinson's Disease https://doi.org/10.3389/fphar.2019.01294	*"This Mini Review aims to provide up-to-date information about the involvement of the GABAergic system for explaining non-motor manifestations in early stages of PD [Parkinson's disease]".*

2.b. Gene Ontology terms

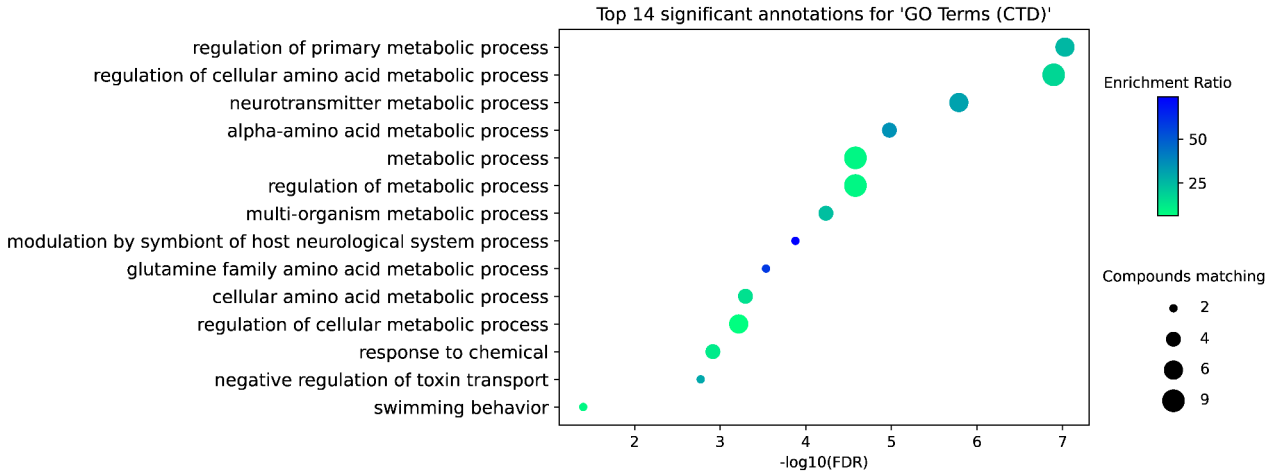

Figure 4: Gene Ontology terms enriched in use case 2.

We highlight the relevance of the top scoring Gene Ontology terms in relation to Parkinson's disease by providing excerpts from the literature.

Annotation	Study	Excerpt
'regulation of cellular amino acid metabolic process' 'alpha-amino acid metabolic process' 'regulation of metabolic process' 'metabolic process'	Dietary Amino Acids Impact LRRK2-Induced Neurodegeneration in Parkinson's Disease Models https://doi.org/10.1523/JNEUROSCI.2809-19.2020	*"The G2019S mutation in leucine-rich repeat kinase 2 (LRRK2) is a common cause of Parkinson's disease (PD) and results in age-related dopamine neuron loss and locomotor dysfunction in Drosophila melanogaster through an aberrant increase in bulk neuronal protein synthesis"*
'neurotransmitter metabolic process' 'regulation of metabolic process' 'metabolic process'	Brain-Region Specific Metabolic Abnormalities in Parkinson's Disease and Levodopa-Induced Dyskinesia https://doi.org/10.3389%2Ffnagi.2020.00075	*"Several lines of evidence point to alteration in brain metabolic homeostasis in Parkinson's disease (PD) and levodopa-induced dyskinesia (LID), yet the metabolic mechanism in different brain regions underlying PD and LID remains largely unknown. […] Compared with control rats, dopamine loss in PD rats produced a marked and persistent metabolic disturbance in neurotransmitter metabolism and energy pathway, resulting in a metabolic imbalance among different brain regions"*
'modulation by symbiot of host neurological system process'	Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation https://doi.org/10.1038/s41531-021-00156-z	*"The gut microbiota is emerging as an important modulator of neurodegenerative diseases, and accumulating evidence has linked gut microbes to Parkinson's disease (PD) symptomatology and pathophysiology. PD is often preceded by gastrointestinal symptoms and alterations of the enteric nervous system accompany the disease"*