MetaboAnalyst 6.0

-- a unified platform for metabolomics data processing, analysis and interpretation

Dose Response Analysis

2024-03-10

Module Overview

The module offers dose response analysis to quantify relationships between the concentration of a chemical and its effects on metabolomics profiles

- ✓ Providing necessary processing, normalization and differential expression analysis to select promising features;
- ✓ Perform curve fitting on those selected features against a suite of linear and non-linear models (currently 10 methods);
- ✓ For each feature, computing its benchmark doses (BMD) based on the selected model

Content

1. Introduction

Background

- Dose-response analysis is commonly used in toxicology and pharmacology for understanding how varying concentrations of a chemical can impact a biological system.
- It plays a pivotal role in risk assessment of chemical exposures.
- A key output of dose-response analysis is the benchmark dose (BMD), the dose at which a chemical would cause a predetermined change in a physiological response.

Data Formats

- Both targeted and untargeted metabolomics data are accepted
- Dose-response experiment design includes a control group (dose = 0) and at least three different dose groups, typically with the same number of replicates in each group.
- The data required for processing should be a csv file, which has been correctly formatted.

Expected Results

This module provides user comprehensive results on feature level dose response analysis:

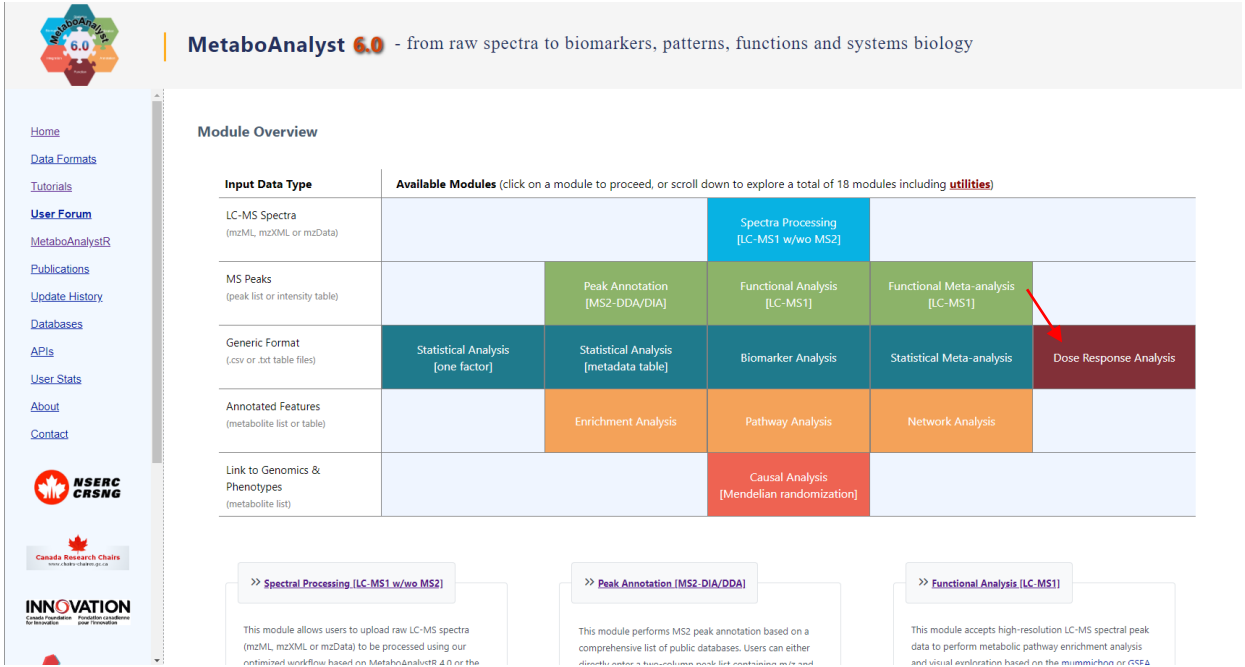
i. Dose response models and associated BMD summary table;

ii. Visualizing the fitted dose response curves of individual features;

iii. Estimated metabolomic-level point of departure (mPOD)

2. Choose the Module

Go to MetaboAnalyst (https://www.metaboanalyst.ca), and select the module



3. Data preparation

It is noted that this data table can be formatted as transposed with name and does values located in the 1st and 2nd column, respectively.

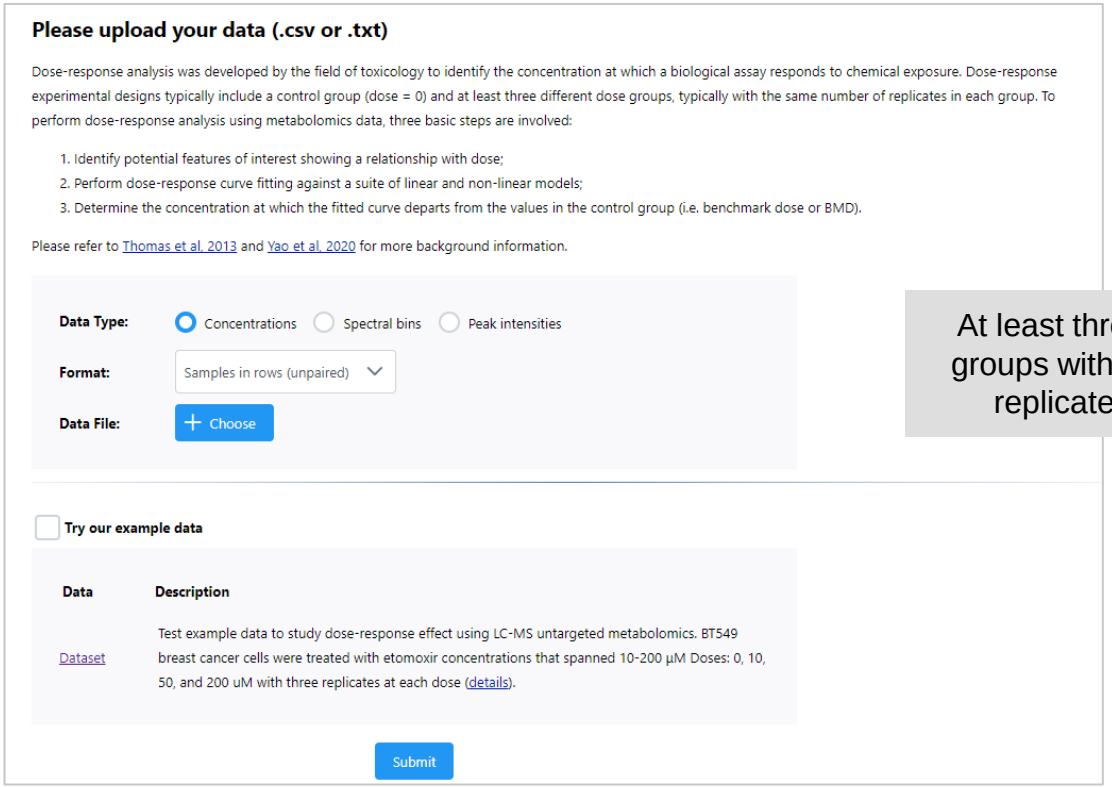
Sample Name (1st row)

Dose values of different sample (2nd row)

Feature intensities or responses. The features can be metabolic features or compounds from metabolomics.

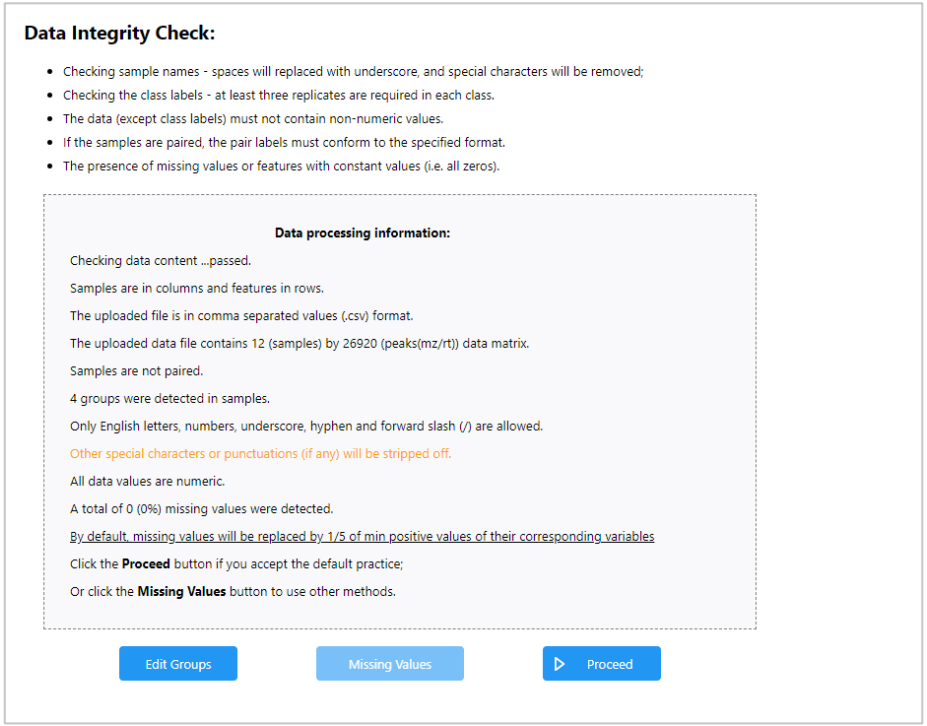
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	name	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_F	092816_RPLC_POS_50uM 3	
2	Dose	0	0	0	10	10	10	200	200	200	50	50	50	
3	M450T1918	203995.3683	217563.605	206360.6475	49882.62177	52102.0091	36055.98929	17470.06027	20520.12066	13559.56834	32409.96322	27836.25517	31369.52025	
4	M580T1785	204.9859732	202.8237309	205.9723909	0	0	0	5839.753433	6394.975863	449.602063	1220.134486	879.8721626	0	
5	M444T1420	29957.16125	29417.82161	30549.57536	5098.684784	2738.782886	3142.322513	3534.510789	2074.46172	1949.228619	3583.74107	2152.024487	3910.198024	
6	M800T1627	10575.86497	10706.35279	9986.178482	351.509363	549.2744133	324.2051702	525.5504516	0	1478.653961	252.9781982	0	517.8135026	
7	M308T1287	889.3524437	1091.860312	641.4121682	3232.341983	3565.742856	3215.614653	32194.58278	31819.46037	34294.52224	4691.3703	4713.492538	8338.712113	
8	M389T1183	117296.2056	133721.1368	113912.7402	22334.43181	3357.715012	18709.08761	13409.74373	2576.006445	11826.19853	7608.643396	4972.328562	5549.895598	
9	M387T1511	150364.5402	126302.0331	136395.3748	14270.10268	10222.55545	28123.90686	20607.16905	19444.7336	52866.21135	3671.167965	16204.65804	22909.92259	
10	M190T1223	9138.171288	9815.61261	9655.415637	5786.151917	6507.735962	5950.810303	11254.9024	8348.940084	8534.317535	8109.195221	8135.810486	11047.65009	
11	M232T388	19061465.42	16490090.83	17446301.05	7727540.716	5891152.241	5709789.886	5159685.13	5932085.813	4535381.245	6338732.865	6475621.299	4414371.818	
12	M565T1750	1003.198981	339.3318538	488.1213742	3697.674377	4239.20054	3512.164735	100336.4438	92970.48834	90220.45298	22806.02251	21969.01257	18739.81747	
13	M462T1193	5563.977581	5382.015211	5405.183925	3470.20892	3482.408521	3790.520871	4827.91632	3515.38382	4189.957398	5130.212695	2352.086731	4439.427197	
14	M452T1746	190686.929	215278.4454	178645.5976	62224.4245	30028.18797	53217.19754	18833.59055	18597.40397	11090.91621	26187.05963	25058.90052	17828.65056	
15	M260T698	331091.2717	366432.321	343185.6728	44331.19415	64350.08857	104085.9975	33037.93377	70971.49592	64702.78681	73346.69713	49456.81272	54889.41357	
16	M341T1626	424445.1727	365450.4113	353528.3321	122126.9206	95856.69608	58613.6839	102653.4532	96703.99084	92262.19953	98887.66677	96018.63663	95368.88071	
17	M343T1288	3019.144429	4356.646656	3618.879196	10690.64772	9238.541061	9312.61418	418700.2064	481260.0438	343238.2183	68340.67153	46418.23047	50616.38382	
18	M705T1892	2878.027802	377.1384973	303.8461908	17950.30013	19347.83247	15197.24066	27661.73861	32279.3809	13233.7861	47580.40577	45807.27924	32130.30244	
19	M387T51_2	8556.400767	9677.98932	9517.436563	3394.704202	3553.410391	3991.398228	4037.522973	4385.57024	3544.127228	12908.05068	2778.56977	4557.05195	
20	M444T1576	207302.1336	203098.1947	171184.3617	33104.63601	24336.61429	11907.24843	22771.87396	23089.3201	12191.42322	11642.10544	21079.44431	8056.315441	
21	M310T1288	4430.953105	5779.200848	4513.942339	11136.95004	9573.622561	10549.26244	87175.26532	94768.51664	86885.55002	29203.52311	22266.32695	22071.05407	
22	M400T1703	163351.8001	156146.3366	132747.0125	33587.57236	15716.20143	27522.42721	18993.13521	27731.49887	22402.65529	35711.44345	23292.04017	29170.81541	
23	M440T1810	243920.8999	254981.6229	258965.8579	47362.18168	4442.885803	35102.23311	26925.76894	26022.89148	15273.0098	26326.44813	30986.33317	23952.58071	
24	M158T951	17639.72294	17608.00915	14077.67288	5546.114102	3328.215983	2275.329763	22448.9819	18194.46	14341.4574	16671.26928	16004.73966	14896.10829	
25	M479T634	1402.726791	2488.595686	1775.597764	5132.739076	4880.473455	5838.991287	3752.600671	3447.639308	4051.065815	3508.146751	3848.700346	4298.524914	
26	M801T1627	4639.983871	5731.236819	5756.832029	515.7837901	0	329.4845928	0	250.4057955	271.8714018	581.4590297	204.1767565	0	
27	M847T617_1	5811.849485	6168.633802	6735.179887	3615.728367	3964.664256	3207.758753	7206.93015	5707.254481	6089.05068	9563.067588	3647.954126	12761.06029	
28	M451T1915	49492.57354	60622.94533	60461.73865	12810.68054	17047.88246	10582.75831	12387.35161	9179.382343	5714.845133	11295.06038	12626.55554	9186.650098	
29	M931T1065	23362.11643	26409.20213	25252.11723	17633.58758	16848.99484	14953.07643	23769.55259	19205.58039	18241.65102	14768.24595	20030.46819	13797.8082	
30	M198T745	201662.6442	204155.7142	207840.2078	167425.022	176840.0131	176084.2509	209636.0573	182760.9882	145357.7997	187671.9424	186492.6251	181294.1752	
31	M371T1301	197021.0325	233458.4916	257888.7775	69213.29601	43327.5088	34178.42046	43034.80947	46802.0047	28312.71441	17801.81957	39573.7525	45603.27148	
32	M435T1777	7203.383322	3580.267458	17407.228	68145.30004	60084.40634	49694.88459	94468.90044	16383.35597	61949.17847	13027.42092	64380.58974	62978.96722	
33	M170T745_2	22957.39003	21640.16169	23705.0306	17342.70086	17033.45302	15222.88931	23644.44526	21795.47393	14442.76924	21287.64035	19183.02961	18815.77927	
34	M233T388	2101305.007	2540890.938	2492390.743	979341.7046	746908.937	808830.5112	724367.661	802539.3374	447634.3992	677624.8805	773190.0094	685191.2547	
35	M170T1339	113349.7512	114809.4462	112140.7973	97161.76538	92845.90878	91395.24534	102067.2047	99602.10678	84654.17018	91176.01153	99770.0026	99742.56184	
36	M450T603	29236.31648	24759.12208	34031.77227	53971.75213	58768.22185	57202.07828	57158.03834	42529.97602	69418.27194	62659.08083	47793.7869	99995.55272	
37	M719T1420	3087.803497	3798.13979	3512.531245	1477.076739	1535.252312	1990.748262	2868.5357	7205.186493	21692.09023	4628.497288	25755.03495	1327.780263	
38	M658T1286	2069.366317	1785.620443	2080.050886	2997.087927	3363.669377	3482.552735	12022.18239	15446.76546	8174.165619	5691.812081	3339.97418	3112.458572	
39	M185T890	15137.43575	15845.64485	15456.91678	12639.04632	13586.54642	13126.86502	21491.97294	25222.73668	13269.18854	18692.71656	14547.91079	14875.89537	

4.1 Dose-response data upload

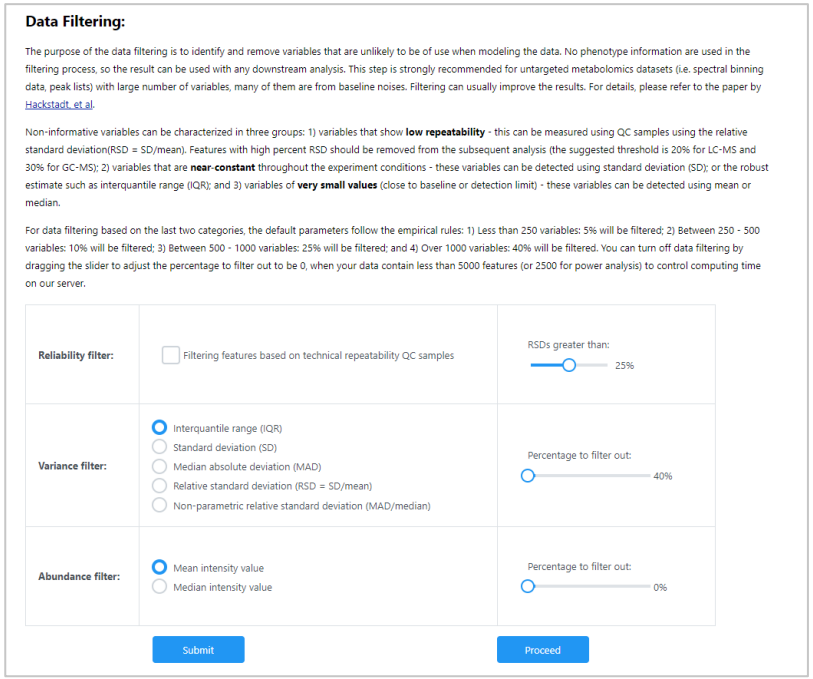


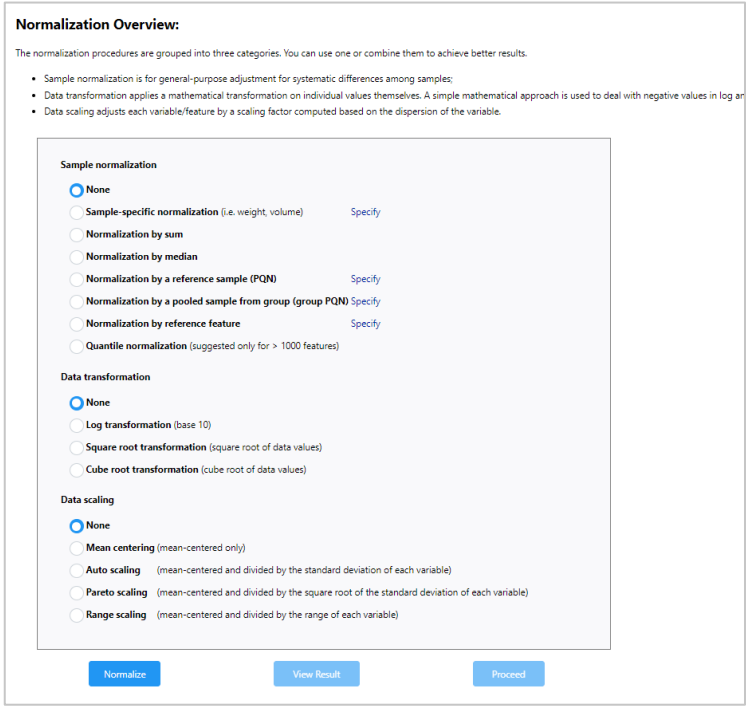
At least three different dose groups with same number of replicates are required

4.2 Data integrity check

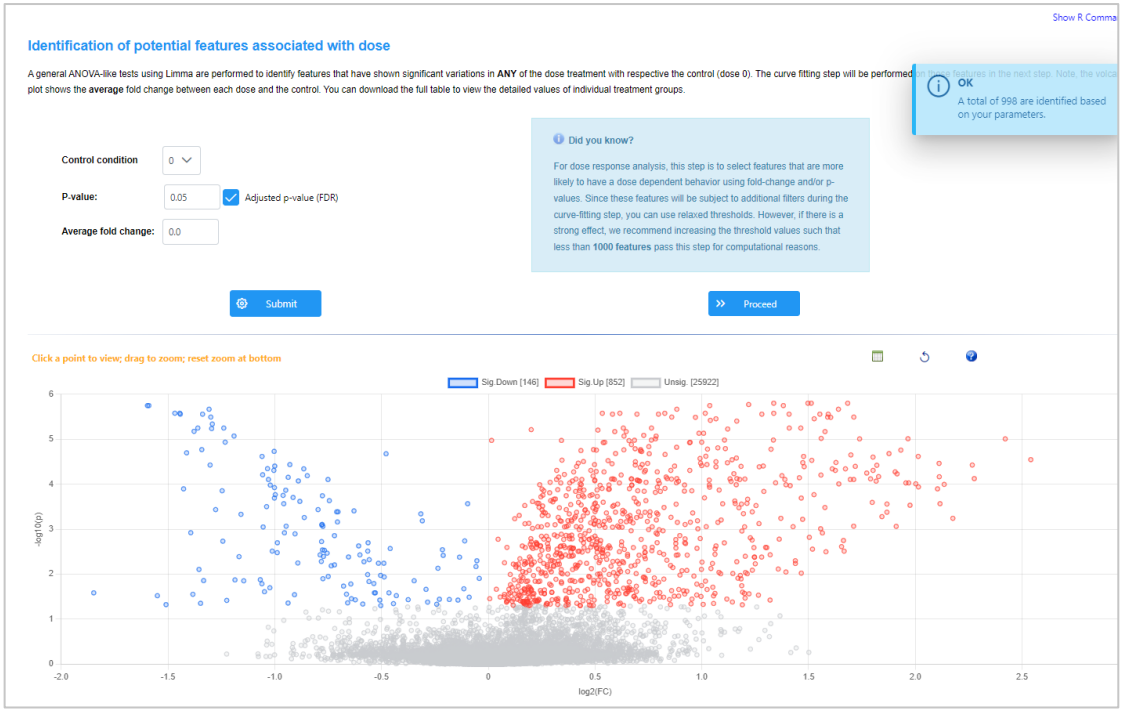


4.3 Data filtering and normalization



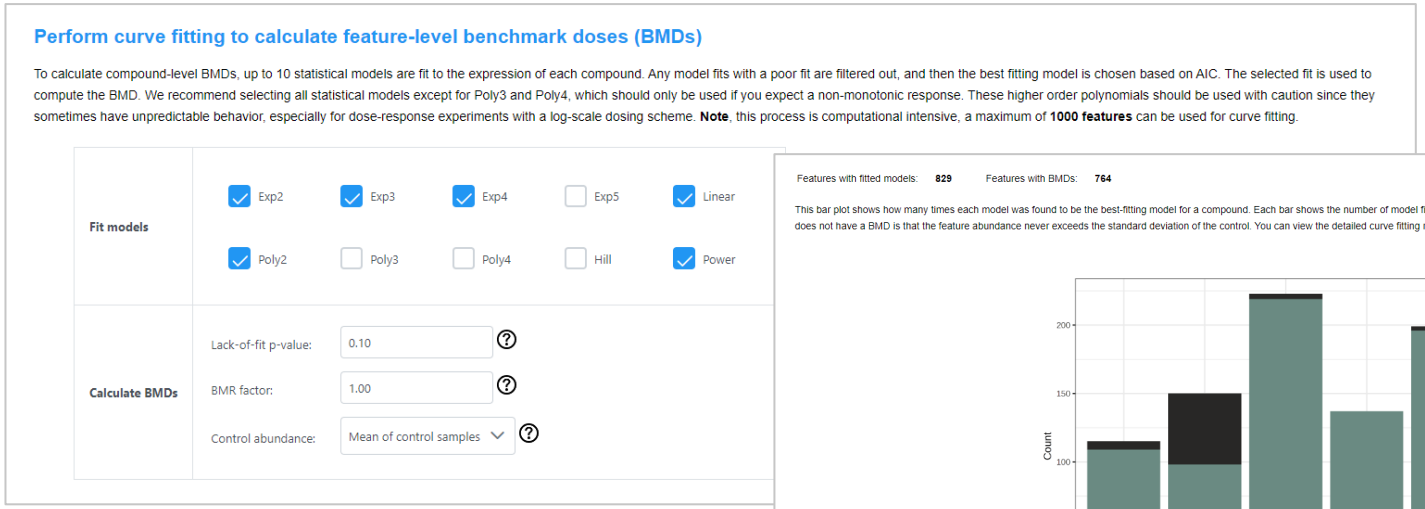


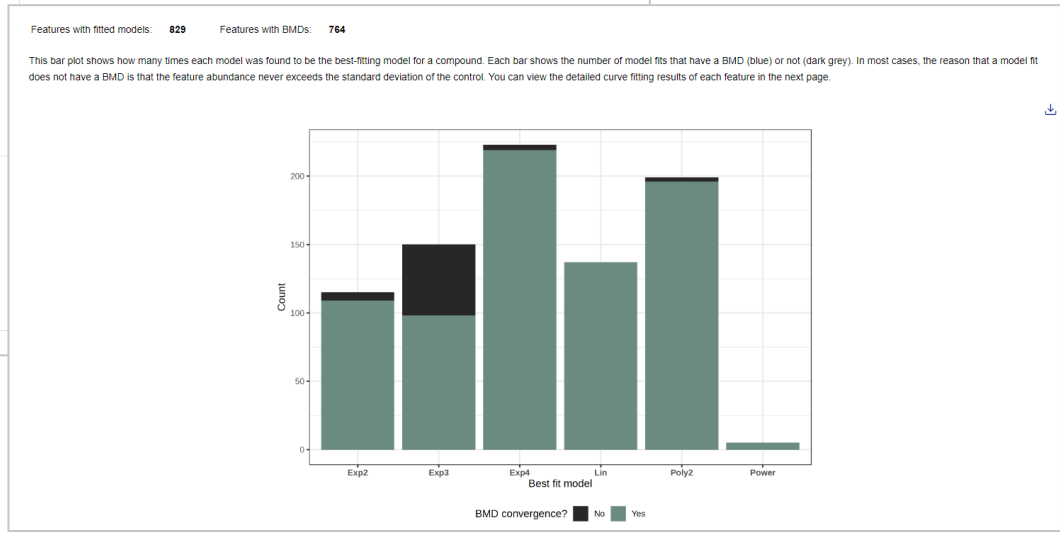
4.4 Identification of features associated with dose



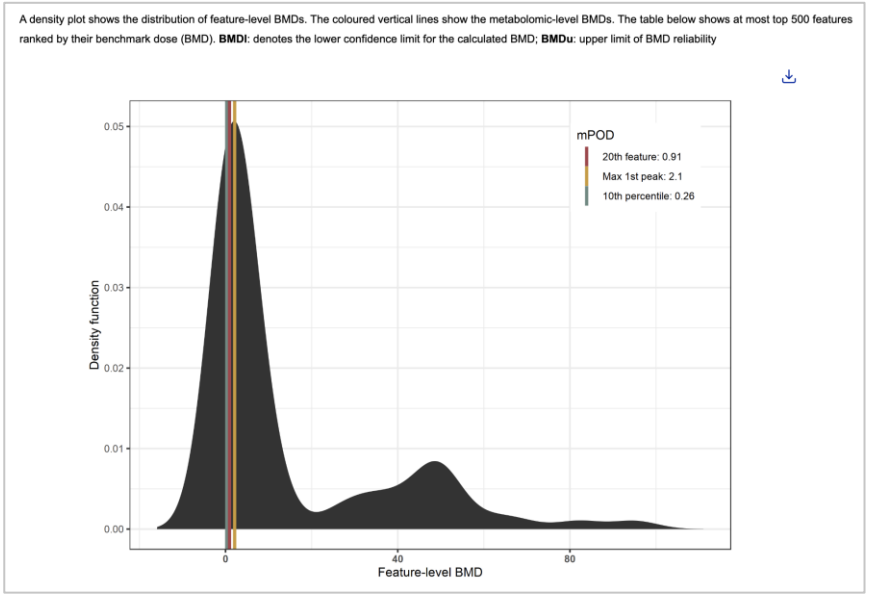
4.5 Curve fitting

Computing BMD requires a mathematical model describing the dose response curve – a process called curve fitting

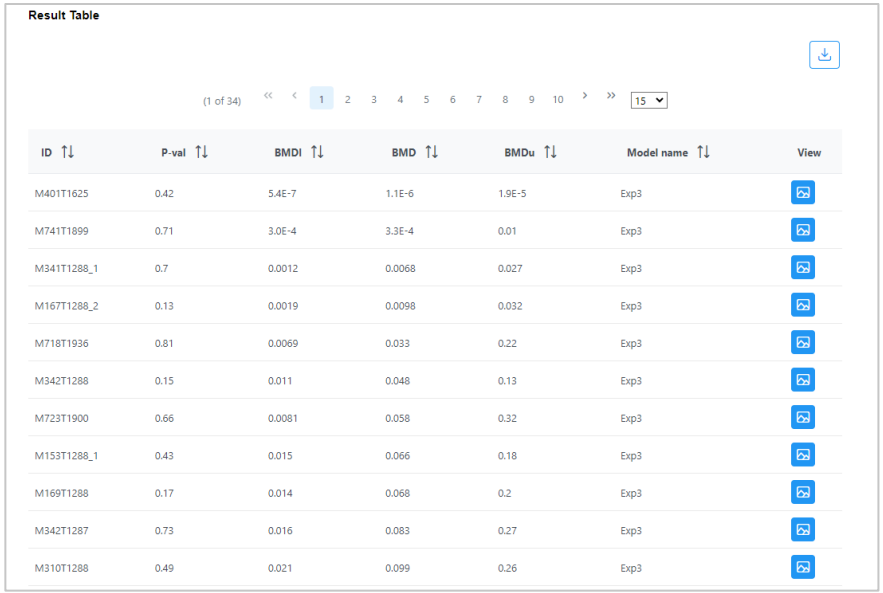




4.6 From feature-level BMDs to metabolomics-POD



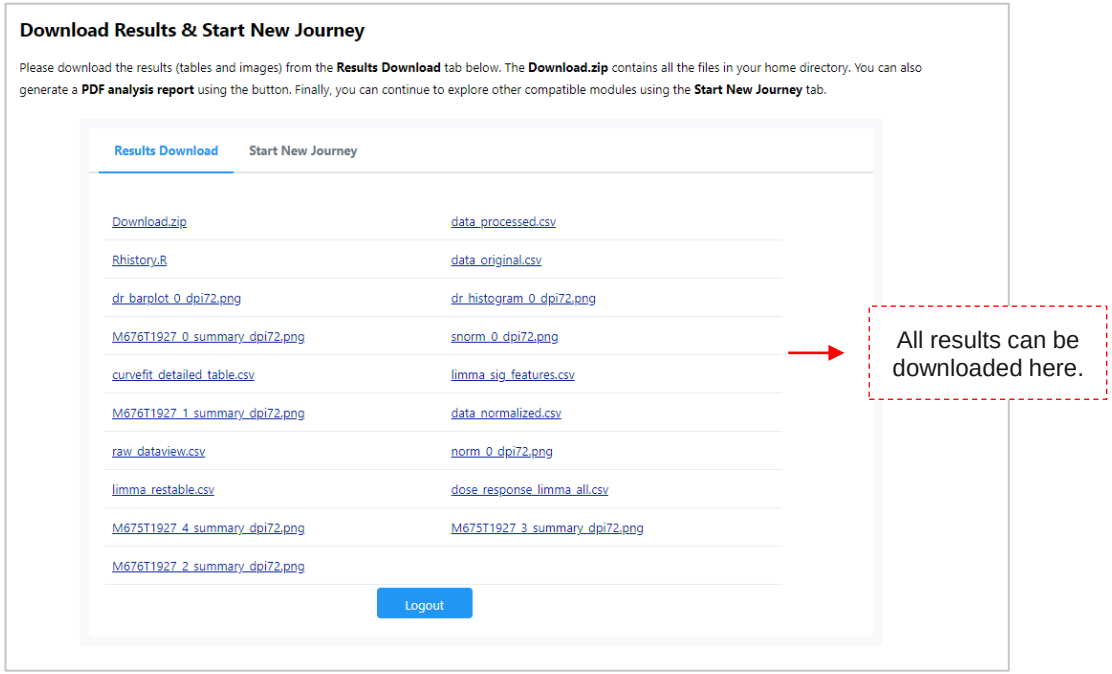
Using BMD distribution to estimate mPOD



ID	P-val	BMDl	BMD	BMDu	Model name	View
M401T1625	0.42	5.4E-7	1.1E-6	1.9E-5	Exp3	
M741T1899	0.71	3.0E-4	3.3E-4	0.01	Exp3	
M341T1288_1	0.7	0.0012	0.0068	0.027	Exp3	
M167T1288_2	0.13	0.0019	0.0098	0.032	Exp3	
M718T1936	0.81	0.0069	0.033	0.22	Exp3	
M342T1288	0.15	0.011	0.048	0.13	Exp3	
M723T1900	0.66	0.0081	0.058	0.32	Exp3	
M153T1288_1	0.43	0.015	0.066	0.18	Exp3	
M169T1288	0.17	0.014	0.068	0.2	Exp3	
M342T1287	0.73	0.016	0.083	0.27	Exp3	
M310T1288	0.49	0.021	0.099	0.26	Exp3	

Detailed BMD summary

5. Download results



In summary

If you have any questions, please read/post into OmicsForum (www.omicsforum.ca)

Or contact us:

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- Dose response data require special design – at least three doses and three replicates per dose are required
- Three basic steps are involved in dose response analysis require
  1. Identify potential features of interest showing a relationship with dose - this is achieved using regular differential expression analysis;
  2. Perform dose-response curve fitting against a suite of linear and non-linear models;
  3. Determine the concentration at which the fitted curve departs from the values in the control group (i.e. benchmark dose or BMD).
- The process can be computing intensive when there are a large number of features (i.e. LC-MS peaks from untargeted metabolomics)