








SOFTWARE TOOL ARTICLE

UPDATE BioPAN: a web-based tool to explore mammalian lipidome metabolic pathways on LIPID MAPS [version 2; peer review: 3 approved]

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Abstract


Lipidomics increasingly describes the quantification using mass spectrometry of all lipids present in a biological sample. As the power of lipidomics protocols increase, thousands of lipid molecular species from multiple categories can now be profiled in a single experiment.

Observed changes due to biological differences often encompass large numbers of structurally-related lipids, with these being regulated by enzymes from well-known metabolic pathways. As lipidomics datasets increase in complexity, the interpretation of their results becomes more challenging. BioPAN addresses this by enabling the researcher to visualise quantitative lipidomics data in the context of known biosynthetic pathways. BioPAN provides a list of genes, which could be involved in the activation or suppression of enzymes catalysing lipid metabolism in mammalian tissues.



Keywords

LIPID MAPS, Lipidomics, Biosynthetic pathway analysis, lipids, lipid profiling.

Open Peer Review

Reviewer Status 

Invited Reviewers

	1	2	3
version 2 (update) 09 Jun 2021			
version 1 06 Jan 2021	 report	 report	 report

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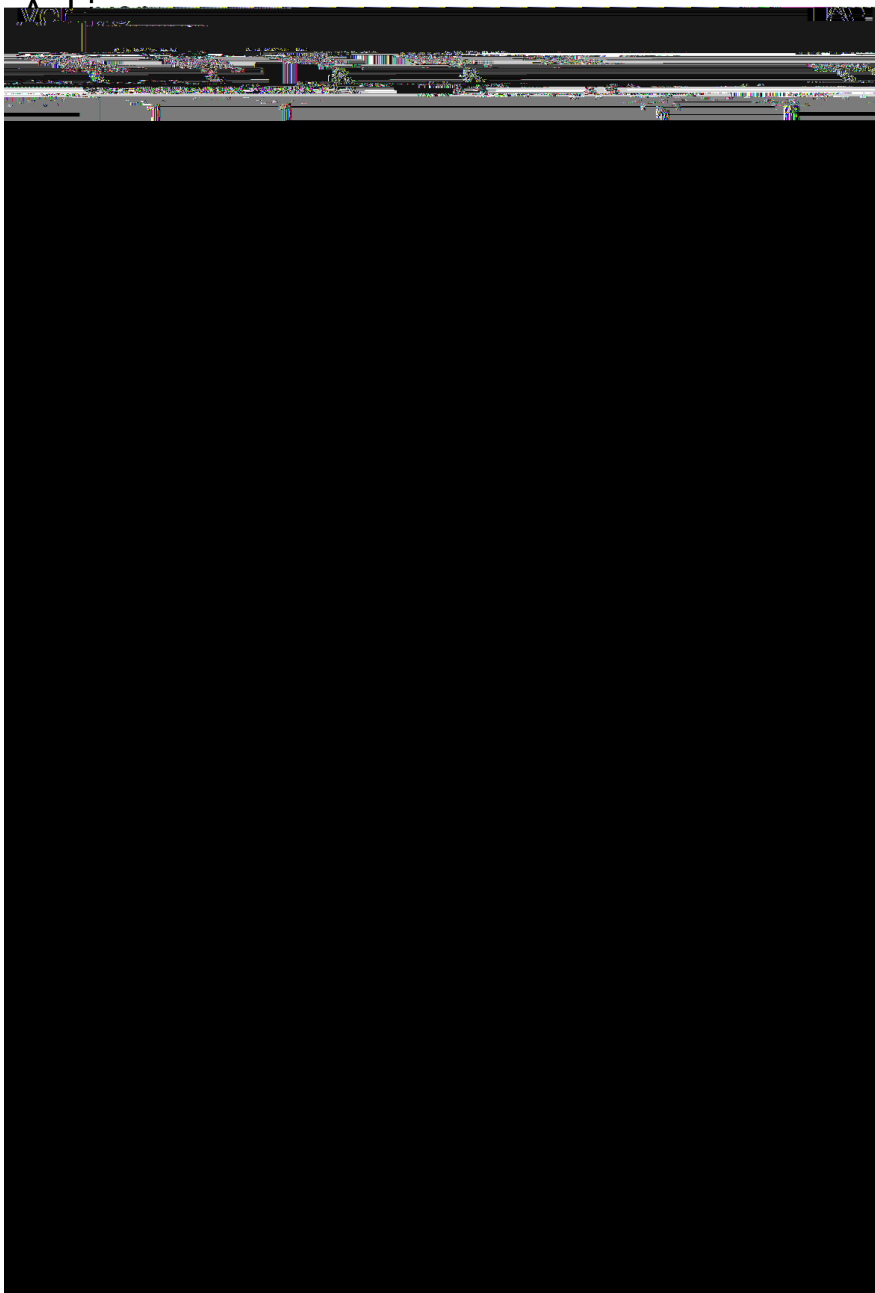
Lipids (fats) are essential and diverse families of molecules that play structural, energy storage and signalling roles. They are connected through complex metabolic pathways, which comprise linked series of enzymatic reactions (several are outside cells, *e.g.* PLA2 isoforms, autotaxin). Thus, lipids can be substrates, products or intermediates. It has been estimated that there are approximately 3–5000 different lipid species in mammalian cells although the true number is still unknown and extremely difficult to reliably measure^{1,2}. In recent years, great advances have been made in our ability to experimentally deter-

allowing users to focus on particular lipids of interest (see Extended Data, section S-2, Figure S-1). The search box allows the user to search for one or two queries using the logical operators AND / OR. Selecting the AND operator, the user can view lipid subclasses or molecular species for which the name implies both queries. For example, searching for “PC” and “34:0” on the lipid molecular species graph displays lipids “PC(34:0)” and “O-PC(34:0)”. Choosing the OR operator allow the user to visualise lipids whose names includes one of the two searches. For instance, searching “LPC” or “LPA” on the subclasses graph displays lipids “LPC”, “O-LPC” and “LPA”.

Calculation options. Under the Pathway Calculation section, the user can control details of the statistical calculation. They can change the threshold for significance from the default of $p < 0.05$. If replicates in the uploaded data were generated as matched pairs (*e.g.* control and treated sample coming from the same animal) then the calculation can also take this into account in the *t*-test step of the analysis.

Exporting results. Results of the statistical analysis of active/suppressed pathways are presented in four tables at the bottom of the page, where predicted gene changes can be visualised. Export options are also available on the top right corner in the BioPAN viewport, where the main graph can be exported in several formats (JPEG / PNG / JSON / TXT) and tables are exported as TSV files.

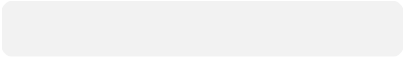
Lipidomics data from cerebral cortex and liver of young and aged mice¹⁷ were used here as an example to illustrate how to use BioPAN and interpret its results. Ando *et al.*¹⁷



FA graphs exported from BioPAN tool for the liver () and the cerebral cortex () of aged mice compared to young mice¹⁷. Green nodes correspond to active lipids and green shaded arrows to active pathways. Reactions with a positive Z score have green arrows while negative Z scores are coloured purple. Pathways options: aged condition of interest, young control condition, lipid type, active status, subclass level, reaction subset of lipid data, p value 0.05, and no paired-data.

1. Slatter DA, Aldrovandi M, O'Connor A, et al.: *Cell Metab.* 2016; (5): 930–944. *Anal Chem.* 2017; (17): 8800–8807.
2. Quehenberger O, Armando AM, Brown AH, et al.: *J Lipid Res.* 2010; (11): 3299–3305. 5.
3. Hartler J, Trötz Müller M, Chitraju C, et al.: *Bioinformatics.* 2011; (4): 572–577.
4. Ni Z, Angelidou G, Lange M, et al.: *Cell Metab.* 2016; (5): 930–944.

2003; (9): 481–482.



MYg

Bc Vta dYh]b[]bhYfYghg'k YfY'X]gWcgyX"

@d]Xca]Wjza Ugg'gdYVfca Yfna'cl]X]nYX''d]X'a YX]Uhcfgz''d]X'a YHUVc`]ga "

5i h\cfFYgdcbgY%- 'A Um&\$&%

ž6UVfU\ Ua 'bgh]hi hYž6UVfU\ Ua 'FYgyUfV\ '7Ua di gž7Ua Vf]X[YžI ?

K Y'h.Ub_ nci 'h\Y fYj]Yk Yf';]b[Yf'A]'bY'Zcf\Yf'Vta a Ybhtg"

FYVta a YbXU]cb.

H\Y]bhfcXi V]cb YbXg'UVfi dhm's-h'fYUXg'Ug.]Zh YfY]g'U'dUfU[fUd\ 'a]gg]b[]

Ya d\Ug]n]b['h\Y]a dcfHUbW 'UbX'Yi dYVWX'i gY'cZh]g'hcc"

!!2'5'gybhYbW'k Ug'UXXYX.' Gcž6]cD5B 'U]Xg'Zcf'Ui hca Uh]W]bhY[fUh]cb'cZ`d]X'a YHUVc`]ga

k]h`d]X'dfcZ]YgžZ]bX]b['ghfc]b['fY'Uh]cbg\]dgVYhk Yyb`d]X'gi VghfUhYg'UbX`d]X'dfcXi Vhg

W]H'ngYX'VmUW]j Y'cf'gi ddfYggYX'Ybnna Yg" "

BcbY

FYj]Yk YfFYdcfhs- 'Ubi Ufm&\$&%

\hhdg.##Xc]"cf[#/\$) &)* #Z/\$\$fYgYUfV "" \$--' "f+* +\$'

A Yhcxg :=

!!2'5'gybhYbW'k Ug'UXXYX.' : i fh\Yf'k cf_]bhc'h\Y'6]cD5B'XUHVUgY'k]''VY'Wff]YX'ci h'hc'
]bV'fdcfUH'Y'byk'V]cgnb'h\Yh]WdUH\k Umq'zgi'W'Ug.'Wc'YghYfc'zY]V'gUbc]Xg'z'UbX'ci]X]gYX''d]X'
gi'VWUggYg'z'Ua'cb['ch\Yfg''5XX]h]cb'cZ['i'V'gm'UbX'['U'U'V'gm'W'f'Ua']XYg'f' 'W' U'!7Yf'z'hc'
V'z'a'd'Ya'Ybh'hc'h\Y'Yi]gh]b['gd\]b['c'd]Xg'dUH\k Um]b'6]cD5B'k]''U'gc'VY'V'z'bg]XYfYX" ''

BcbY

FYj]Yk Yf FYdcfh&* \Ubi Ufm&\$&%

\hdg.##Xc]"cf[#/(\$") &) * #Z/\$\$\$\$fYgYUfW" \$--' "f+* +\$&

H\]g']g'Ub'cdYb'UWV'gd'YYf'fYj]Yk 'fYdcfhX]gh]Vi h'X'i bXYf'h\Y'h'fa'g'cZ'h\Y'7fYU'hj'Y'
7ca a cbg'5Hf]Vi h]cb'@]Wbg'z'k \]W' dYfa]hg'i bfYgh]W'X'i gY'z'X]gh]Vi h]cb'z'UbX'fYdfcXi W]cb']b'Ubma'YX]i a z'
dfcj]XYX'h\Y'cf][]bU'k cf_]g'dfcdYf'mV'W'X"



8YdUfha Ybh'cZ'6]cWYa]gh'f'n'z'M'c'b['@c'c'@]b'GW'cc''cZA'YX]W]b'Y'z'G]b[UdcfY'z'G]b[UdcfY'

H\Y'Ufh]W'Ybh]hYX' 6]cD5B.'U'k YV!VUgYX'h'cc'h'c'Yi d'cfY'a Ua a U']Ub''d]Xca Y'a YHUV'c']W
dUH\k Umq'cb'@=8'A 5DG'XYgW]VYX'Ub'cb']bY'h'cc'Zcf'j]gi U']gU]h]cb'cZV]c'c[]W' dUH\k Umq'z'f'ca'
ei Ubh]hU'hj'Y''d]Xca]W'XUH''H\Y'h'cc']g'Ub']a dcfh'Ubh'V'z'b'f]Vi h]cb'h'c''d]Xca]W'XUH'Ub'U'mq]g'
d]dY']bY'h\Uh'V'z'i 'X'\Y'd'a U_Y'gYbgY'cZYj Yf'a cfY'V'z'a d'Yi 'XUH'UgY'h'

; YbYfU'V'z'a a Yb'hg
K Y''!k f]h'Y'b'a Ubi gW]dh'UbX'Ub']bh'fY'gh]b['V'z'b'f]Vi h]cb'Z'cf'h'f

fYgc'i h]cb'cZk \]V\ 'gYYa g'hc XYdYbX'cb'hY'ncca 'ghUhi g]b'hY'X]gd'Umk]bXck "'K ci 'X'hVY'
 d'cg]V'Y'hc' UXX'Ub'cdh]cb'hc'YI dcfhUg] YW'fc'f[fUd\]Vgž"gi ['Zcf'YI Ua d'Y3
 A]bcf'Vt'a a Ybhg
 %"DU[Y'ž5VgfhUWtž"bY' . V\Ub[Y']bWfYUgY 'hc']bWfYUgYg "
 S
 &"DU[Y'ž5i h\cf'fc'Ygž"bY%' V\Ub[Y' j]gi U'nUh]cb 'hc' j]gi U'gUh]cb "
 S
 ' "DU[Y' žf][\hVt'i a bž' fX'dUfU[fUd\ž"bY' !(. V\Ub[Y' j]gi U'nYX 'hc' j]gi U'gYX "
 S
 ("DU[Y' -ž5W\bck 'YX[Ya Ybhg V\Ub[Y' 'b'a Ya cf]i a 'hc' 'b'a Ya cf]Ua "

Mg

Mg

Mg

Mg

Mg

'Bc'Vt'a dYh]b[]bhYfYgh'k YfY'X]gVt'cgYX"
 '@d]Xca]Vg"

5i h\cf'FYgdcbgY %- 'A Um&\$&%
 ž6UVfU\Ua 'bgh]h hYž6UVfU\Ua 'FYgYUfW '7Ua di gž7Ua Vf]X[YžI ?'
 K Y'h\Ub_'nci 'fYj]Yk Yf'5a Ui fm7UnYbUj Y; Ugg]ch'Zcf'\]gVt'a a Ybhg"
 .
Suggestions:
 With regards to the statistical model used by the software. Could the authors elaborate on whether correction for multiple testing is done for p-value calculations?
 !!2'6]cD5B 'XcYg'bchVt'ffYVh'Zcf'a i 'h]d'Y'hYgh]b['Ug]hVW'W'UhYg'U'N!gVt'fY'hc'Z]bX'gh'fcb[Yf'
 fY'Uh]cbg\]dg'k]h]b'hY'XUfUž\YbW'\][\Yf'N!gVt'fYg'fYdfYgYbhU'a cfY]bhYfYgh]b['fYgi 'h'

h\Ub'ch\Yfg"

In the "Pathway calculation" section, would it be possible to let the user input any value for the significance threshold, rather than choosing from a few drop-down options?

!!2'H\Y'Xfcd!Xck b'a Ybi \Ug'VYYb'fYd'UW'X'hc'U'h\I hVcl'UbX']h\Ug'VYYb']bV'f'cd'cf'U'h'X']b'hc'6]cD5B"s

The "Filter" field in the "Pathway options" section is very useful; however, it seems to take ~~only one~~ value at a time. Would it be possible to include logical operators? For instance, M one could filter for "PC 32:1 AND PE 32:1", or "38:5 OR 38:6".

!!2'5'dUFU[fUd\ 'k Ug'UXXYX']b'Y'CF'8]gd'f'U'ic'bl]c'bg'Y'W'W'X'k.U'W'W'g'Y'U'G'V'V'dh'U'W'ck'g'h'Y'i'g'Y'f'hc'g'Y'U'f'W'Z'cf'cb'Y'cf'k'c'ei'Y'f'Y'g'i'g]b['h'Y'c[]W'cd'Y'f'U'hc'fg'5B'8'#'C'F'"G'Y'W'W'j]b['h'Y'5B'8'cd'Y'f'U'hc'f'z'h'Y'i'g'Y'f'W'W'j]Y'k''d]X'g'i'V'W'U'gg'Y'g'cf'a'c'Y'W'U'f'gd'Y'W'Y'g'Z'cf'k'\]W'h'Y'b'U'a'Y'ja'd']Y'g'V'ch'ei'Y'f'Y'g":cf'Y'I'U'a'd'Y'z'g'Y'U'f'W'j]b['Z'cf' D7'UbX' (. '\$'cb'h'Y''d]X'a'c'Y'W'U'f'gd'Y'U'f'W'j]b['U'X'g'Y'U'd'X]gd'U'ng''d]X'g' D7'fl (. '\$'UbX' C!D7'fl (. '\$'U'ccg]b['h'Y'CF'cd'Y'f'U'hc'f'U'ck'h'Y'i'g'Y'f'hc'j]g'i'U'g'Y''d]X'g'k'cg'Y'b'U'a'Y'g]b'W'X'Y'g'cb'Y'c'Z'h'Y'h'k'c'g'Y'U'f'W'Y'g":cf']b'g'h'U'b'W'z'g'Y'U'f'W'j]b['@D7'cf'@D5'cb'h'Y'g'i'V'W'U'gg'Y'g'[f'U'd'\X]gd'U'ng''d]X'g'@D7'z'C!@D7'UbX'@D5'" "

Ultimately, the tool relies on information contained in the pathway database. While using an in-house data on conx " É M whytd ch onQ

S

("ssssssDU[Y' - ž5W\bck `YX[Ya Ybfg. `W\Ub[Y' ð'a Ya cf]i a `hc' ð'a Ya cf]Ua ""
8cbYžh\Ub_`nci ""

`BcbY

H\Y`VYbYZ]hg`cZdi V`]g\]b[`k]h : %\$\$\$FYgYUfW.

M:i f`Ufh]WY`]g`di V`]g\ YX`k]h]b`XUmžk]h `bc`YX]hc`f]U`V]Ug

M:i `W\b`di V`]g\ `fUX]h]cbU`Ufh]WYgžbi ``#bY[Uh]j Y`fYgi `hgž`WlgY`fYdc`fhgž`XUH`bchYg`UbX`a`cfY

H\Y`dYYf`fYj]Yk `dfc`Wgg`]g`f`Ubgd`UfYbh`UbX`W`U`V`c`f`Uh]j`Y

M:i f`Ufh]WY`]g`]bXYI YX`]b`Di`VA`YX`UZhYf`d`Ugg]b[`dYYf`fYj]Yk

8YX]WUhYX`W`ghca`Yf`gi`ddcfh`UhYj`Yfmg]h]j`Y

: cf`dfY!gi`Va`]gg]cb`Ybei`]f]Ygž`V`b`h`U`h`f`Y`g`Y`U`f`W`4`Z`A`B