Identifying proteins and metabolic pathways associated with the neuroprotective response mediated by tibolone in astrocytes under an induced inflammatory model

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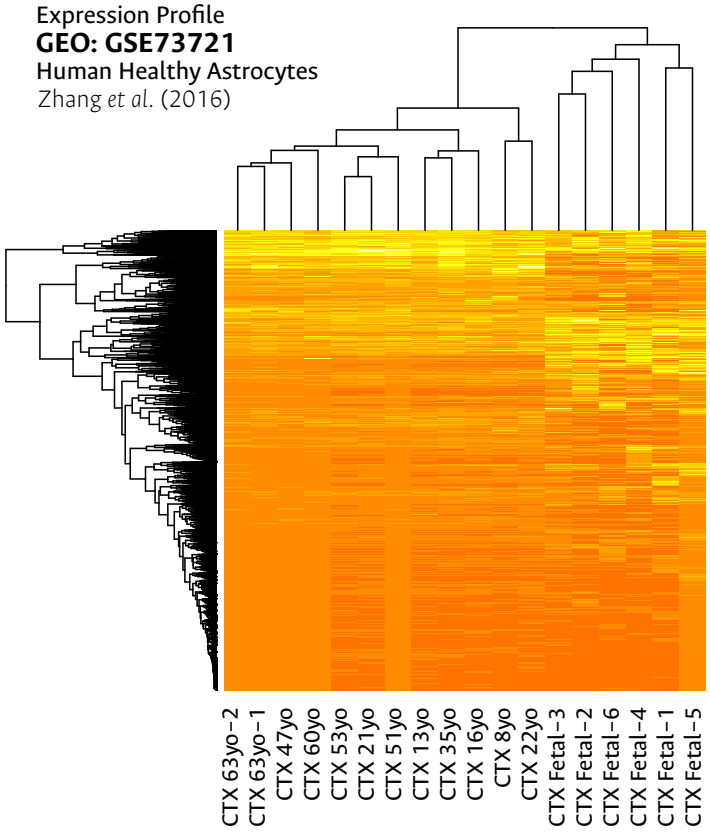
Universidad Nacional de Colombia, November 2016

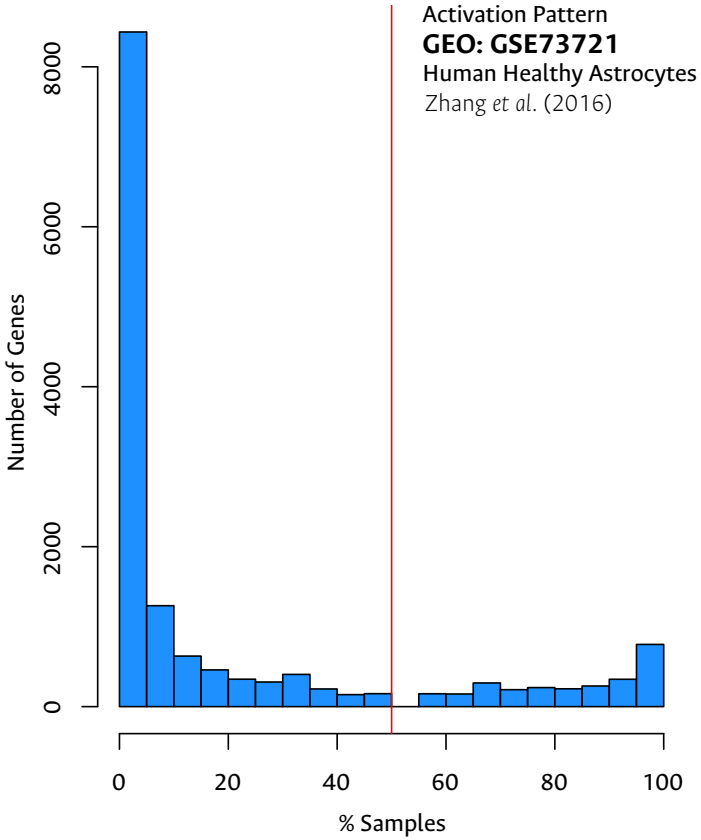
Objectives:

To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

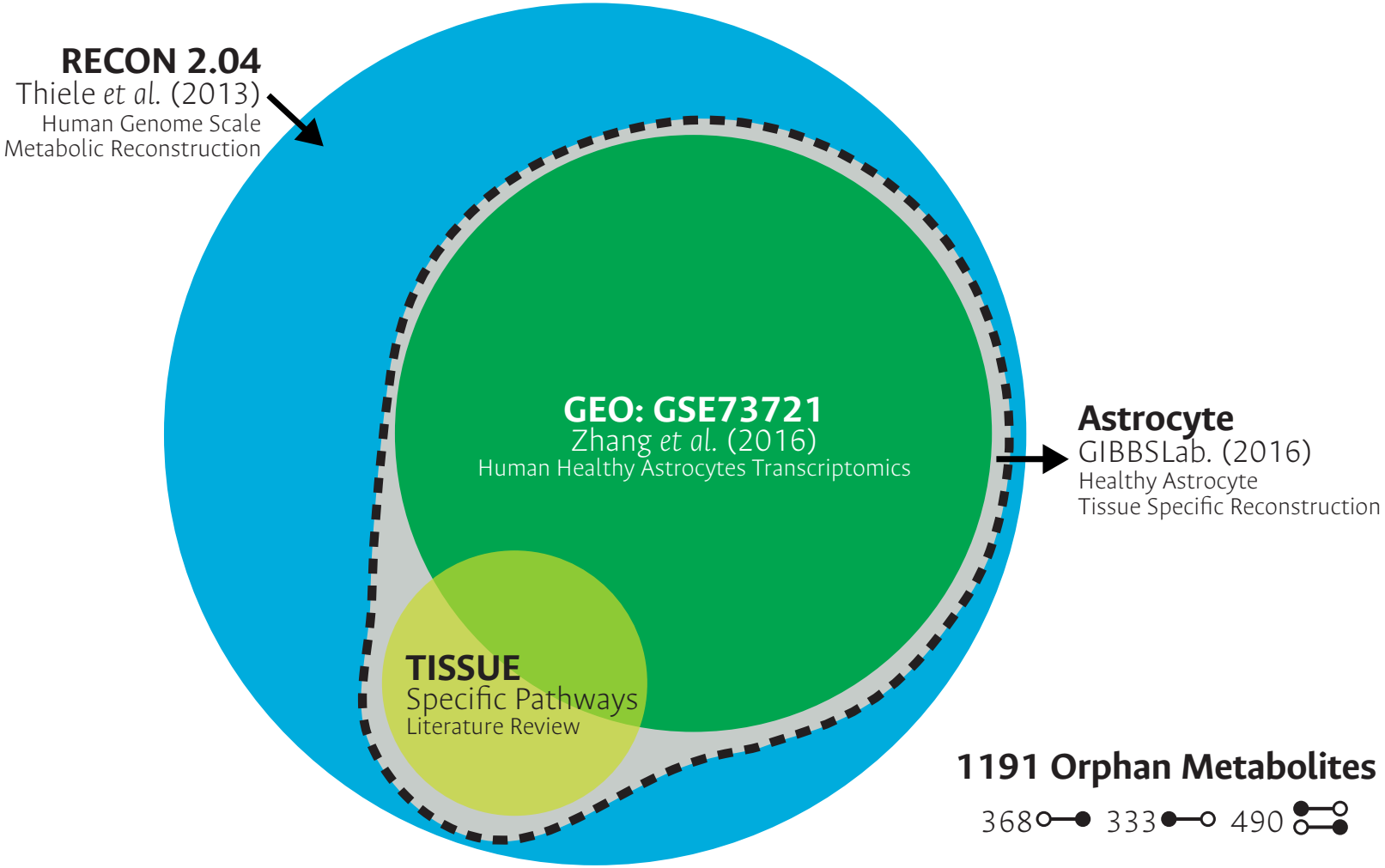
- Build a tissue specific computational model of astrocytes metabolism using gene expression data integration.
- Evaluate the effects caused by the increase of free fatty acids and tibolone presence in astrocytes metabolism.
- Determine metabolic pathways and relevant functional products in response to steroid tibolone through systems biology approximations.
- Evaluate the importance of proteins and metabolic pathways previously identified on the dynamics of the metabolic model.

Human Astrocytes Gene Expression Data





Mapping Reactions



Software Development

'g2f' Package

An R Package to Find and Fill Gaps for genome-scale metabolic networks

*Kelly Botero, **Daniel Osorio**, Janneth Gonzalez and Andres Pinzón-Velasco.*

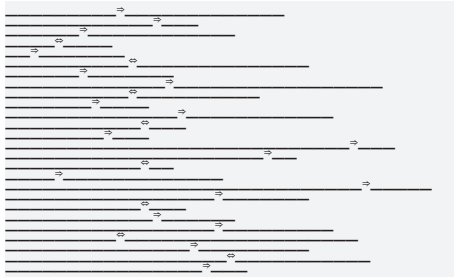
Language: R
Stable: CRAN
Development: gibbslab/g2f
License: GPL-2
Binaries: Windows - Linux - Mac

RXNLIST

h2o[r] + dheas[r] ⇒ h[r] + dhea[r] + so4[r]
uri[e] ⇔ uri[c]
na1[e] + uri[e] ⇒ na1[c] + uri[c]
atp[c] + pi[m] ⇒ pi[c] + atp[m]
na1[e] + gchola[e] ⇒ na1[c] + gchola[c]
...

getReference( )
DOWNLOAD STOICHIOMETRIC REACTIONS FROM THE KEGG DATABASE

REFERENCE



GENOME SCALE METABOLIC NETWORK

additionCost( )
CALCULATE ADITION COST

$$cost = \frac{n(metabolites(newReaction) \notin metabolites(reactionList))}{n(metabolites(newReaction))}$$

gapFill( )
FIND AND FILL GAPS

```
original = n( orphanMetabolites )
do{
    if(orphanMetabolite ∈ metabolites(newReactions)){
        gapFill: cost ⩽ limit → reaction ∪ newReactions
                 cost ⩾ limit → reaction
    }
    filled = n(orphans(reaction ∪ newReactions) ∈ orphanMetabolites)
}
while ( original ⩽ filled )
```

blockedReactions( )
IDENTIFY REACTIONS NEVER ACTIVATED

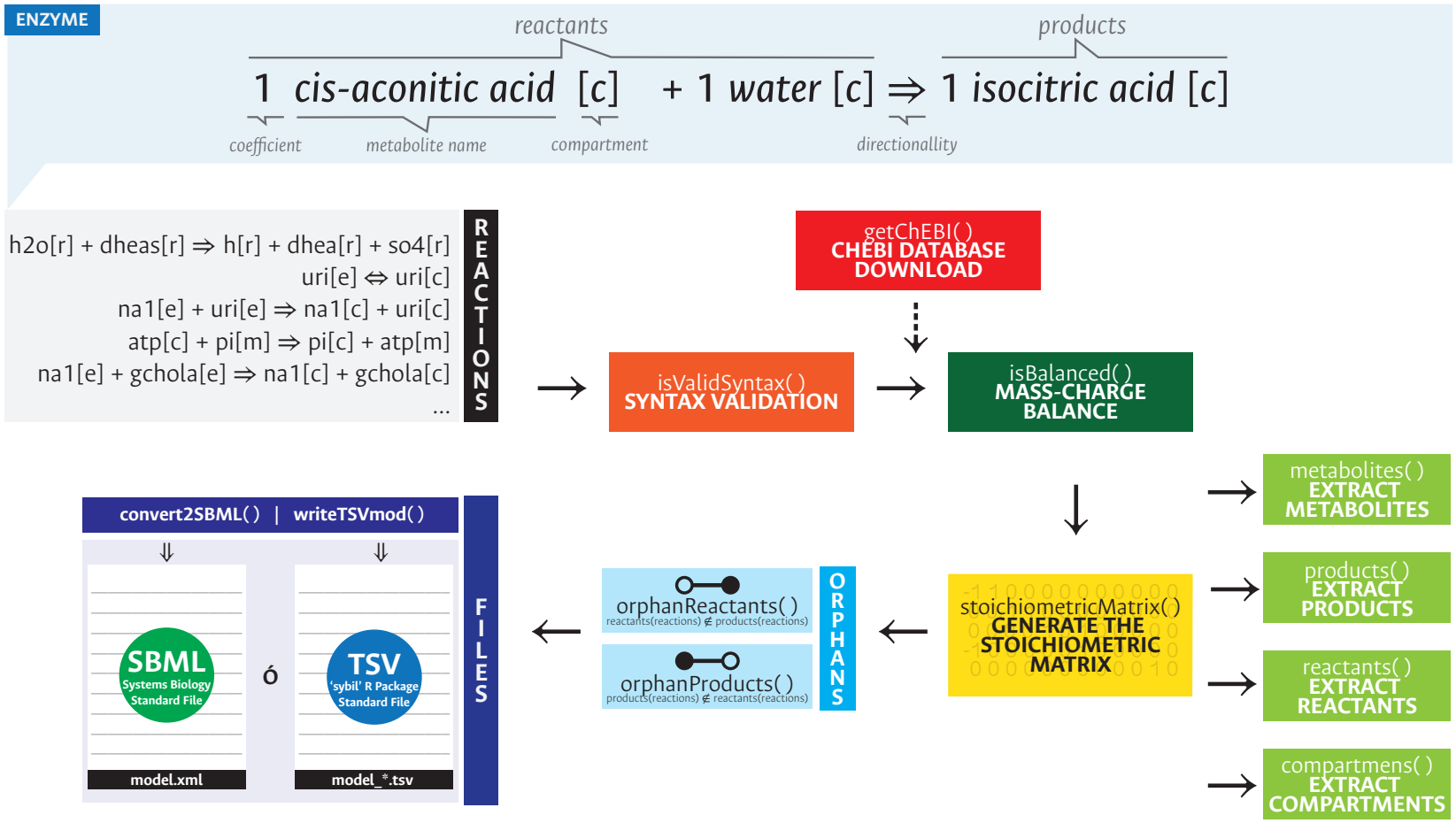
Software Development

'minval' Package

An R Package for MINimal VALidation of stoichiometric reactions

Daniel Osorio, Janneth Gonzalez and Andres Pinzón-Velasco.

Language: R
Stable: CRAN
Development: gibbslab/minval
License: GPL-2
Binaries: Windows - Linux - Mac



Software Development

'exp2flux' Package

An R Package to convert expression data to FBA fluxes

Daniel Osorio, Kelly Botero, Janneth Gonzalez and Andres Pinzón-Velasco.

Language: R
Stable: CRAN
Development: gibbslab/exp2flux
License: GPL-2
Binaries: Windows - Linux - Mac

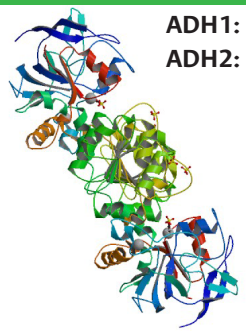
E.C: 1.1.1.1

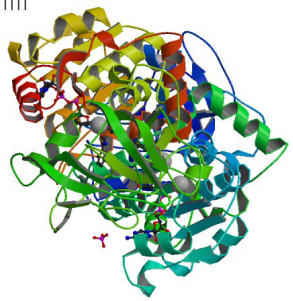
alcohol[c] + NAD(+)[c] ⇔ aldehyde[c] + NADH[c]

1.1.1.1

ADH2 | **ADH1**

ADH1: ||||||||||||||||||||||||||
ADH2: ||||||||||||





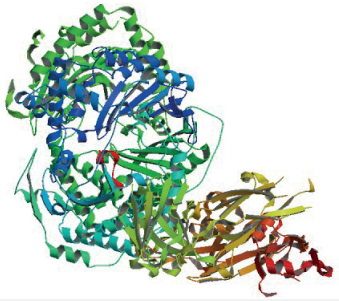
E.C: 3.4.21.5

polypeptides[e] ⇒ aminoacids[e]

3.4.21.5

IDE.A | **IDE.B** | **IDE.C**

IDE.A: ||||||||||||||||||||||||||
IDE.B: ||||||||||||
IDE.C: ||||||||||||||||||||



(ADH2 or ADH1) GPR **(IDE.A and IDE.B and IDE.C)**

sum (ExprADH2 + ExprADH1) | min (ExprIDE.A, ExprIDE.B, ExprIDE.C)

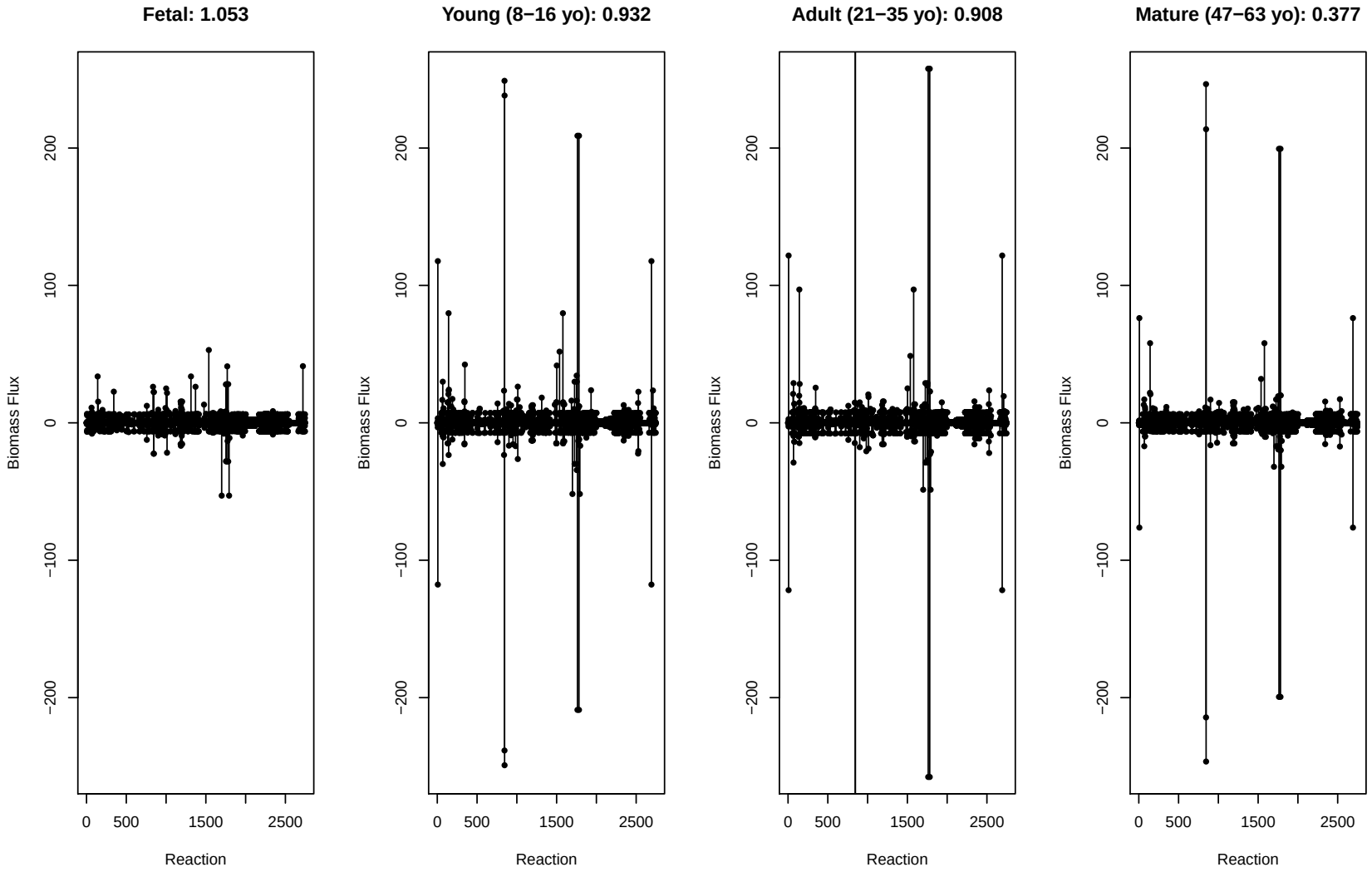
GENE EXPRESSION DATA →
METABOLIC MODEL WITH GPR →

exp2flux( )
CONVERT GENE EXPRESSION DATA TO FBA FLUXES →

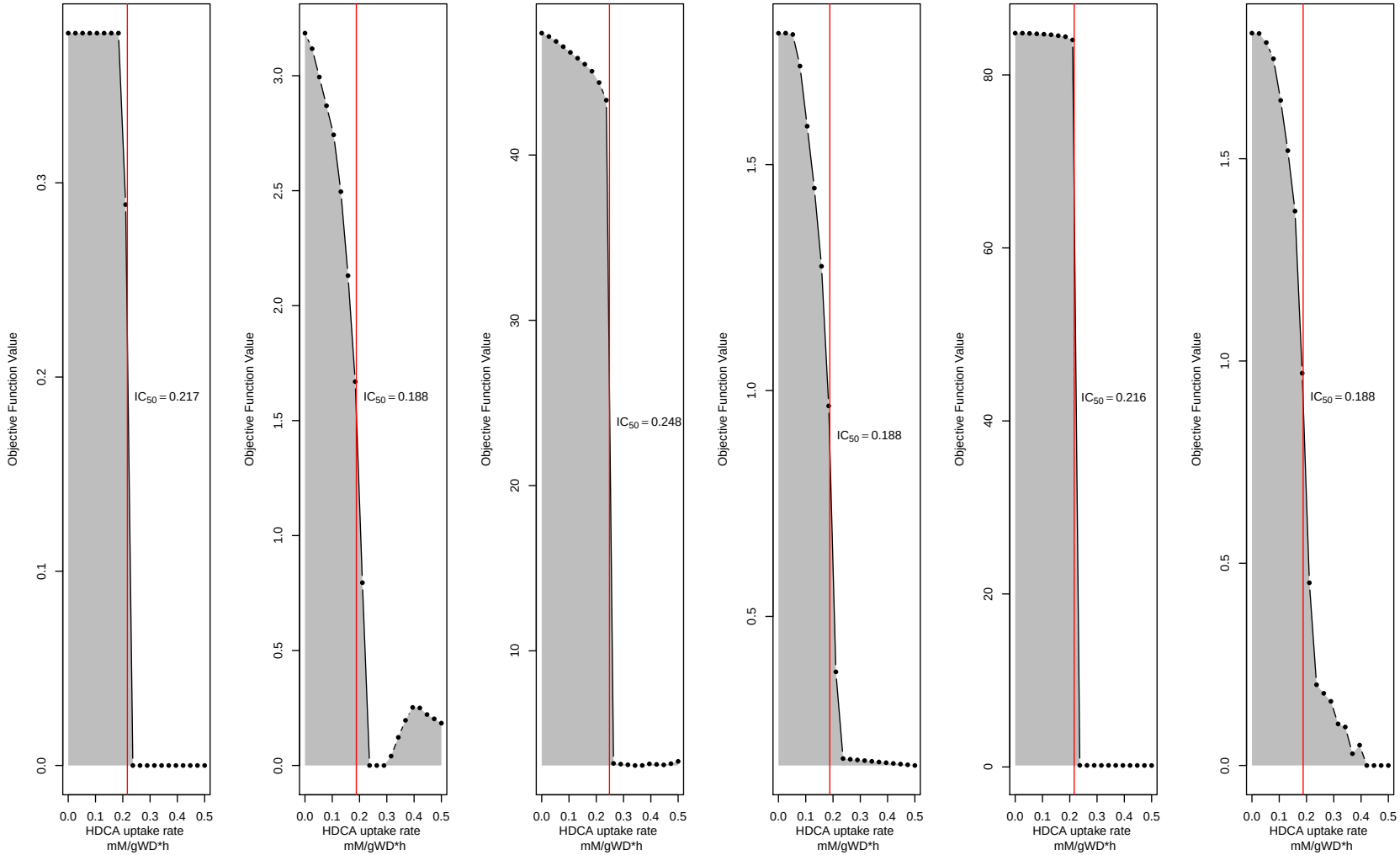
CONSTRAINED METABOLIC MODEL →

fluxDifferences( )
COMPUTE FOLDCHANGE OF FLUXES BETWEEN METABOLIC SCENARIOS

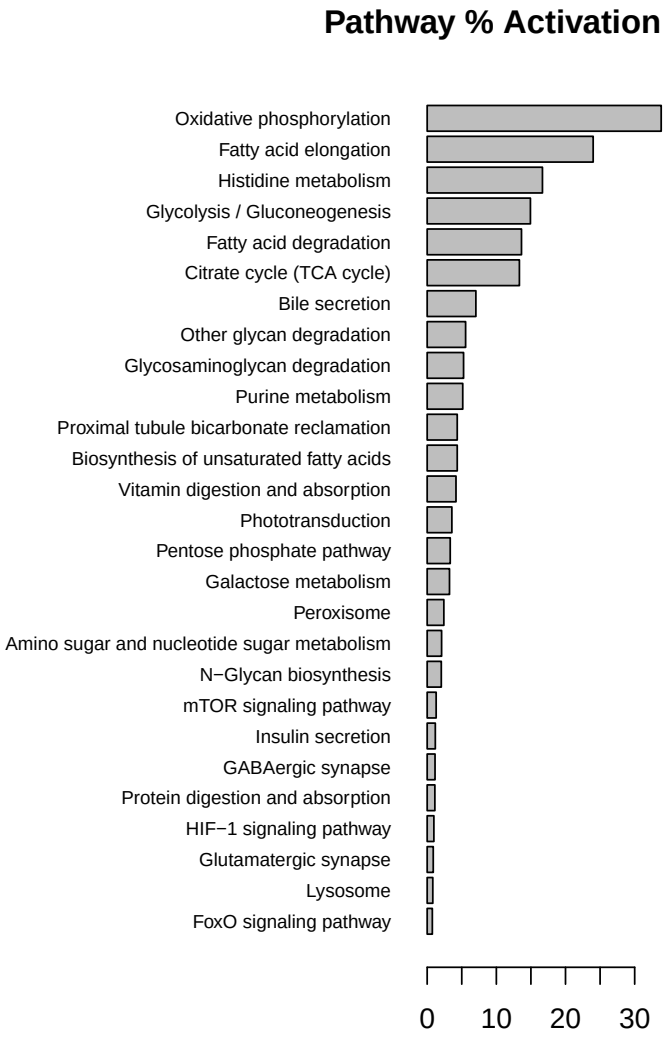
Age Related Metabolic Changes in Astrocytes

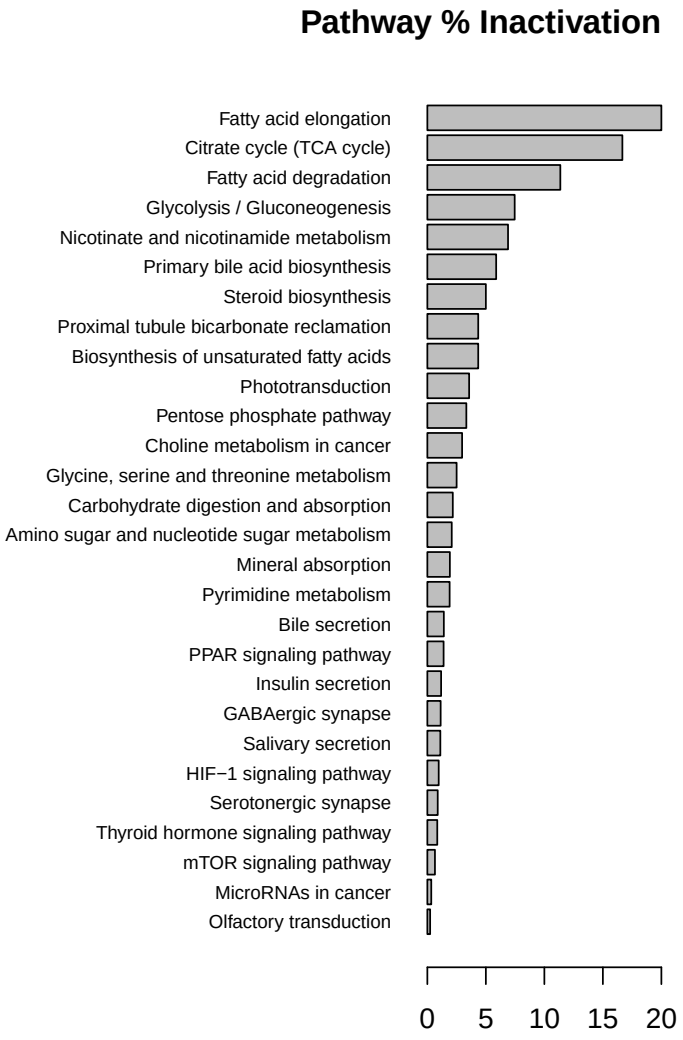


$IC_{50} = 0.208 \pm 0.024$ mMgDW^{-1}h^{-1}

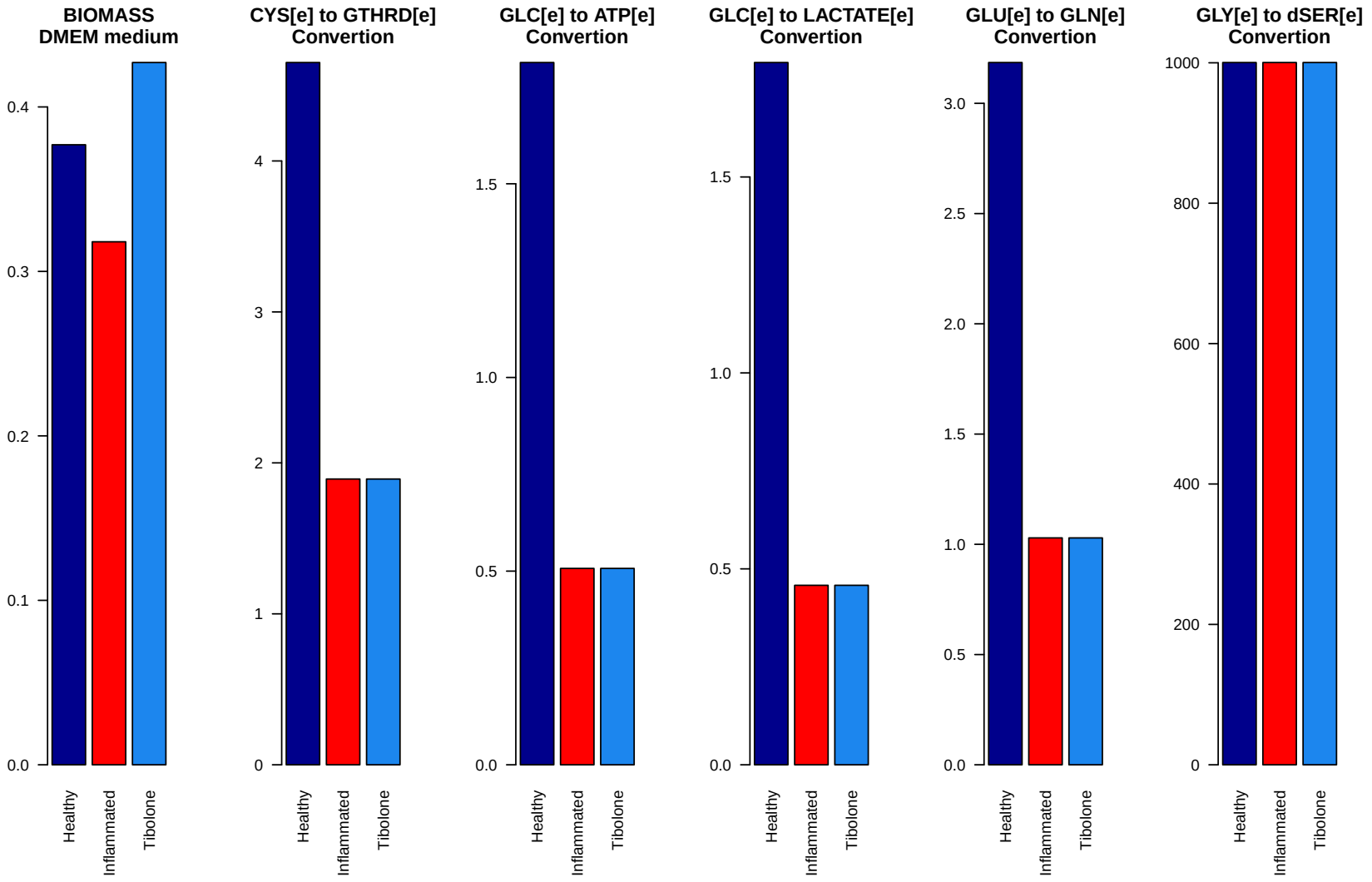


Inflammation Related Metabolic Changes in Astrocytes

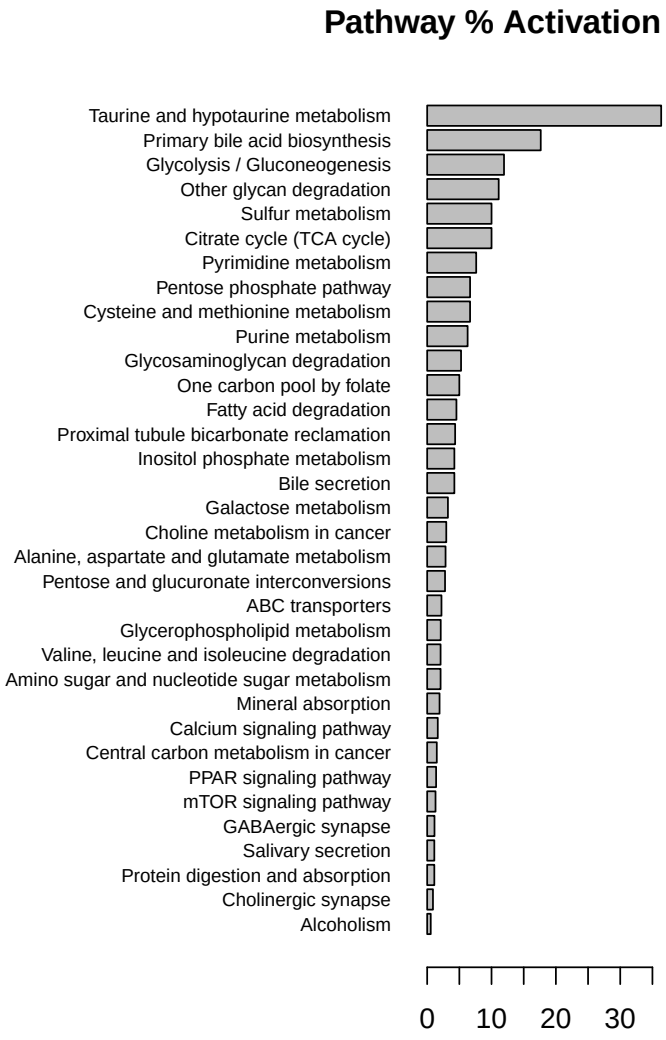


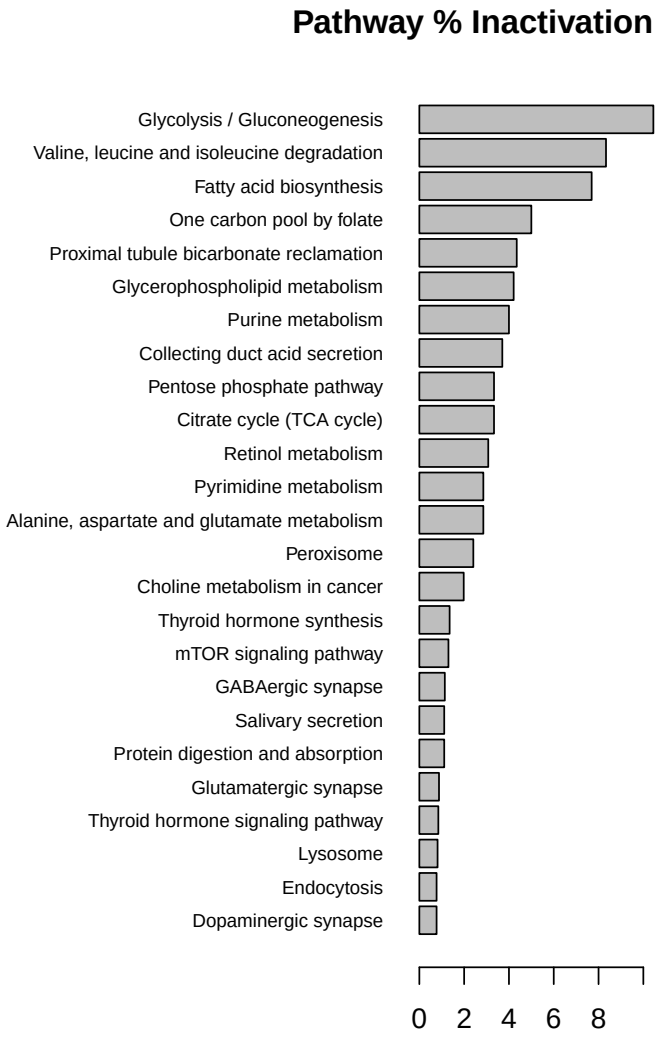


Tibolone Effects in Inflammated Astrocytes



Tibolone Metabolic Changes in Inflammated Astrocytes





Advances of this work were presented as:

Metabolic inflammation effects over the gliotransmitters release in mature astrocytes: a network-based approach.

Daniel Osorio MSc., Janneth Gonzalez PhD., Andrés Pinzón-Velasco PhD.

Bioinformatics and Computational Systems Biology Lab, Universidad Nacional de Colombia.

at:

2nd International Summer Symposium on Systems Biology
August 2-4, 2016
INMEGEN

CDMX, México
Short Talk

ICSB 2016
International Conference on Systems Biology

Barcelona, España
Poster

ICGEB Course on Bioinformatics and Computational Neuroscience
Pontificia Universidad Javeriana
5 - 8 October - Bogotá, Colombia

Bogotá, Colombia
Short Talk

This study is under development at the:

Bioinformatics and Computational Systems Biology Lab

Institute for Genetics - Universidad Nacional de Colombia

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