

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

Presented by:

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in partial fulfillment of requirements for the degree of

Master in Bioinformatics

Advisors: **Janneth Gonzalez PhD.** and **Andrés Pinzon PhD.**
Bioinformatics and Computational Systems Biology Lab



Universidad Nacional de Colombia
Engineering Faculty - Department of Systems and Industrial Engineering
Bogotá, Colombia

Objectives:

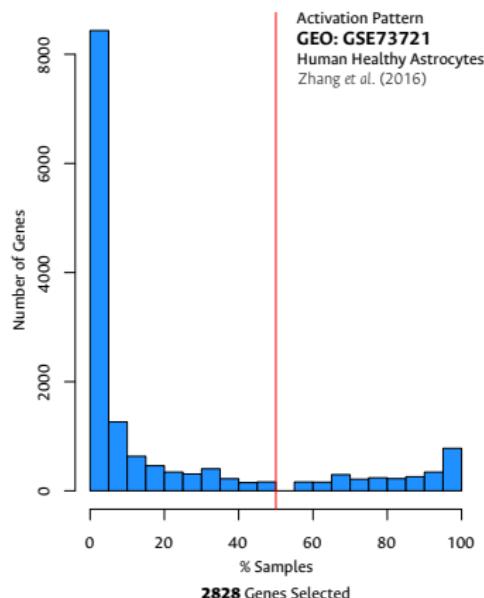
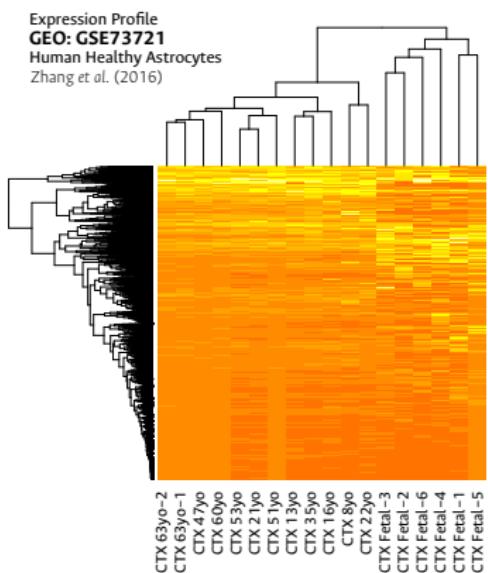
To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

- ▶ 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.

OBJECTIVE 1:

Build a tissue specific computational model of astrocytes metabolism using gene expression data integration.

Healthy Human Astrocytes Gene Expression Data



Mapping Reactions

RECON 2.04
Thiele et al. (2013)
Human Genome Scale
Metabolic Reconstruction

GENE ID CONVERSION
FROM GeneCards® HUMAN GENE DATABASE THROUGH UniProt TO

GEO: GSE73721
Zhang et al. (2016)
Human Healthy Astrocytes Transcriptomics

TISSUE
Specific Pathways
Literature Review



1191 Orphan Metabolites

368 • 333 • 490

Gap-Find and Gap-Fill Available Algorithms

ALGORITHM	ENVIRONMENT	HOW IT WORKS
SMILEY	Python - OpenSource	<ul style="list-style-type: none">Optimization based.Fills one metabolite per time.
gap-Find/Fill	GAMS - OpenSource	<ul style="list-style-type: none">Optimization based.Makes several intra model modifications.
growMatch	Python - OpenSource	<ul style="list-style-type: none">Optimization based.Fills one objective function per time.
fastGapFill	MATLAB - Privative	<ul style="list-style-type: none">Optimization based.Multiobjective.

Finding and Filling Gaps



'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

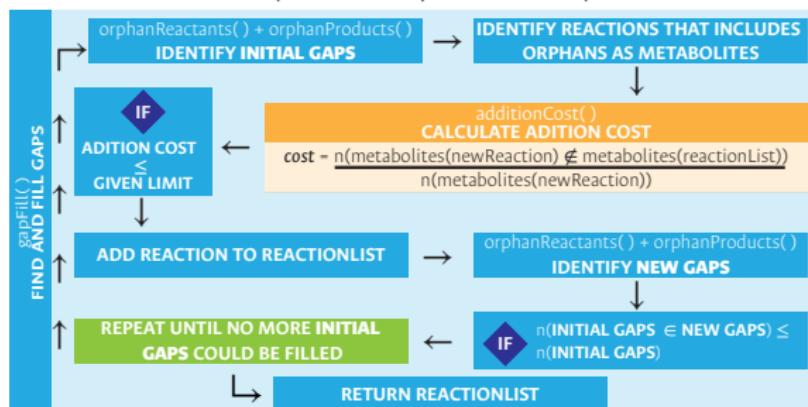
$\text{h2o[r]} + \text{dheas[r]} \Rightarrow \text{h[r]} + \text{dhea[r]} + \text{so4[r]}$
 $\text{uri[e]} \Leftrightarrow \text{uri[c]}$
 $\text{na1[e]} + \text{uri[e]} \Rightarrow \text{na1[c]} + \text{uri[c]}$
 $\text{atp[c]} + \text{pi[m]} \Rightarrow \text{pi[c]} + \text{atp[m]}$
 $\text{na1[e]} + \text{gchola[e]} \Rightarrow \text{na1[c]} + \text{gchola[c]}$
ASTROCYTE DRAFT GiBBS Lab (2016)

REACTI**L**IST

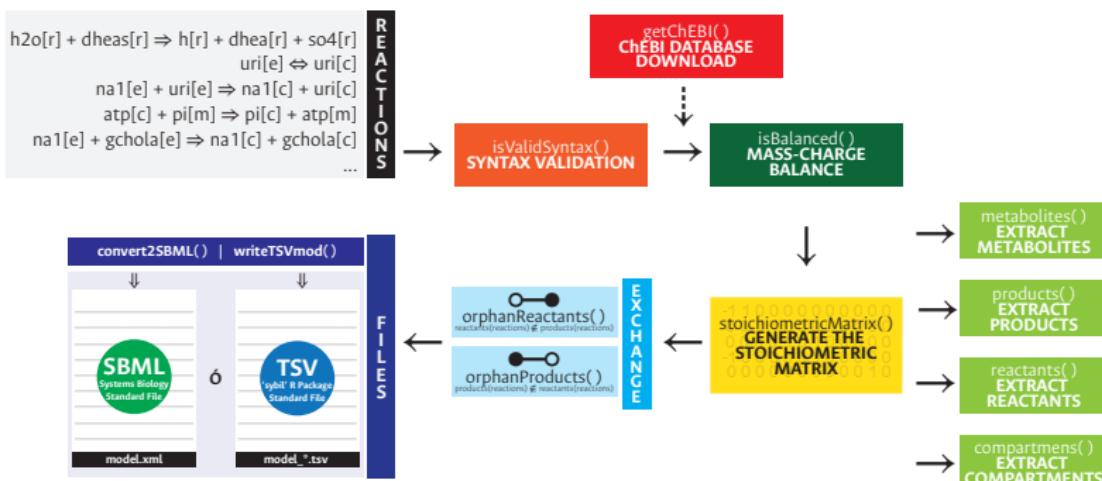


getReference()
 DOWNLOAD
 STOICHIOMETRIC REACTIONS
 FROM THE KEGG DATABASE

REFERENC**E**



Syntax, Mass-Charge Validation and SBML files



Metabolic Model Debugging



'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.

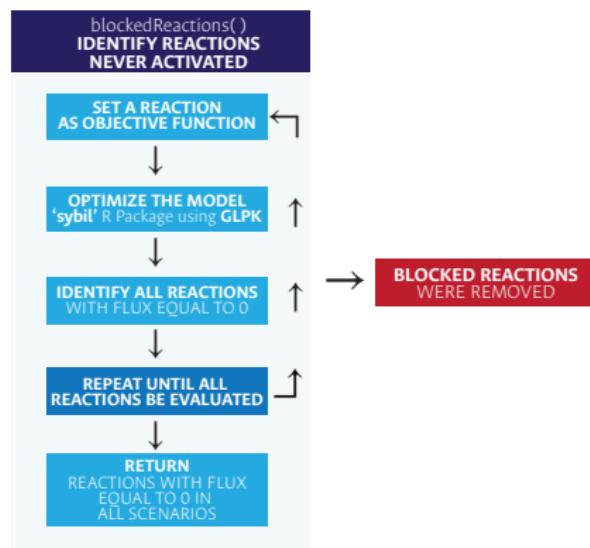
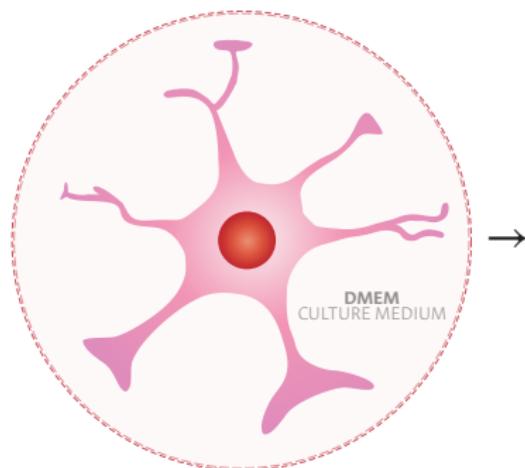
Language: R

Stable: CRAN

Development: [gibbslab/g2f](#)

License: [GPL-2](#)

Binaries: Windows - Linux - Mac



Gene Expression Integration Available Methods

METHOD	ENVIRONMENT	HOW IT WORKS
GIMME	MATLAB Privative	<ul style="list-style-type: none">· Binary Discretization· Ensures flux for a selected objective function
iMAT	MATLAB Privative	<ul style="list-style-type: none">· Integration proportional to gene-expression (H, M and L categorization)· Not objective function required
E-FLUX	Not implemented	<ul style="list-style-type: none">· Requires a user-given threshold· Continuous Integration
PROM	MATLAB Privative	<ul style="list-style-type: none">· Requires a user-given regulatory network· Constraints are setting according to the associated transcript. factor

Constraining the Metabolic Model



'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

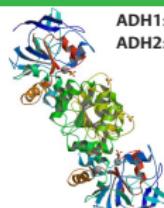
E.C: 1.1.1.1



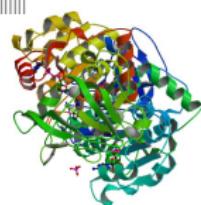
1.1.1.1

ADH2

ADH1



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



(ADH2 or ADH1)

sum (ExprADH2 + ExprADH1)

E.C: 3.4.21.5



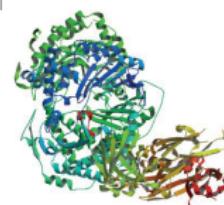
3.4.21.5

IDE.A

IDE.B

IDE.C

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



GPR

(IDE.A and IDE.B and IDE.C)

min (ExprIDE.A, ExprIDE.B, ExprIDE.C)

GENE EXPRESSION
DATA



exp2flux()
CONVERT GENE
EXPRESSION DATA
TO FBA FLUXES



CONSTRAINED
METABOLIC MODEL

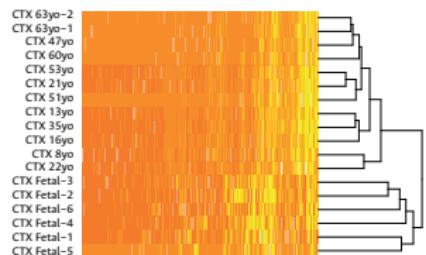


fluxDifferences()
COMPUTE FOLDCHANGE
OF FLUXES BETWEEN
METABOLIC SCENARIOS

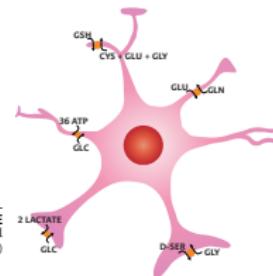
METABOLIC MODEL
WITH GPR



Human Healthy Mature Astrocyte Model



Expression Profile
GEO: GSE73721
Human Healthy Astrocytes
Zhang et al. (2016)



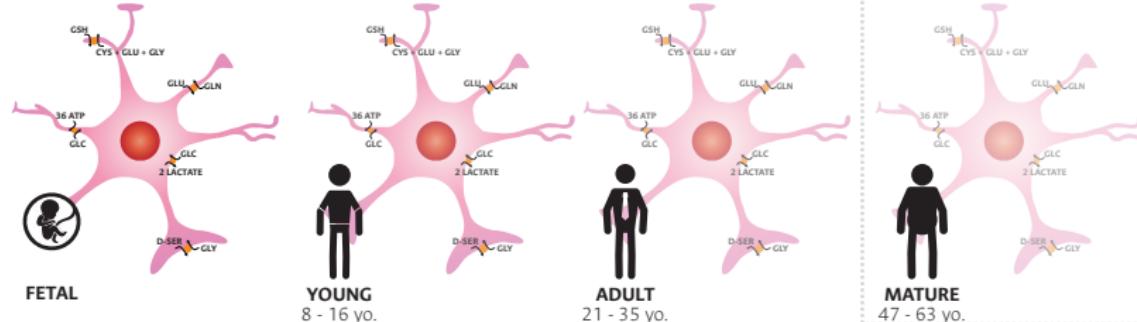
SBML
ASTROCYTE
Tissue Specific Model
GIBBSLab. (2016)



'exp2flux' Package

An R Package to convert expression data to FBA fluxes
Daniel Osorio, Kelly Botero, Janneth Gonzalez and Andres Pinzón-Velasco.

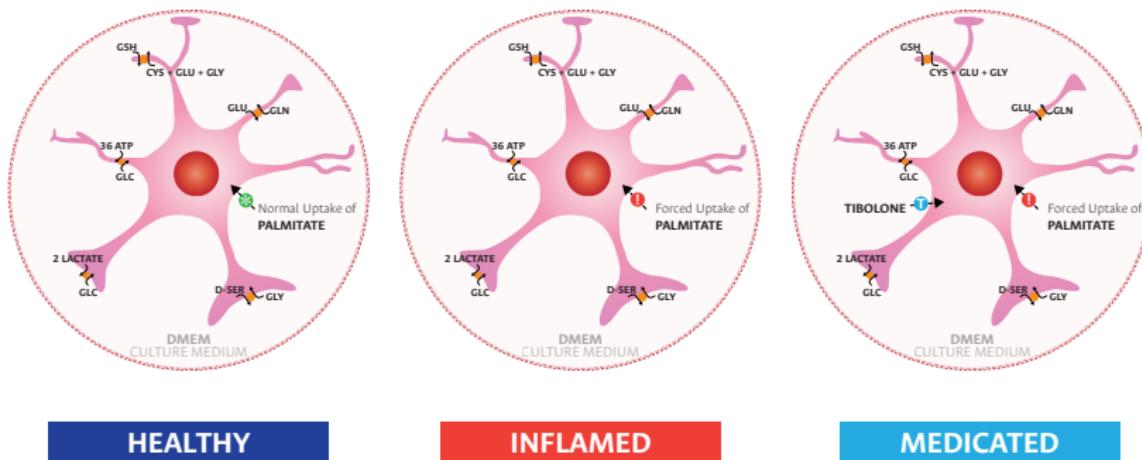
`exp2flux()`
CONVERT GENE
EXPRESSION DATA
TO FBA FLUXES



OBJECTIVE 2:

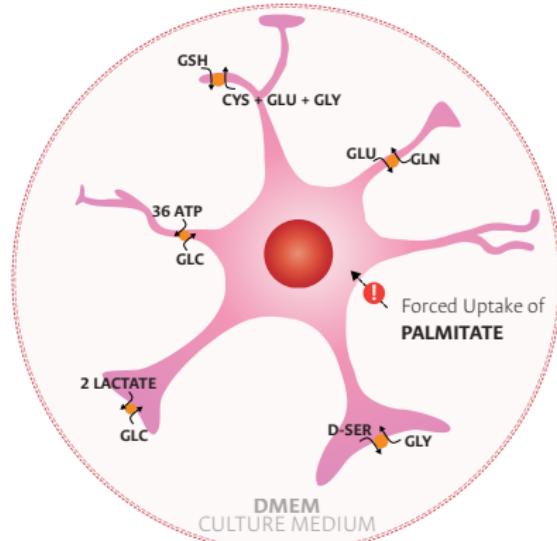
Evaluate the effects caused by the increase of free fatty acids and tibolone presence in astrocytes metabolism.

Metabolic Scenarios



MAIN OBJECTIVE FUNCTION:
Generic Human Biomass Reaction included in RECON 2.04
(Thiele *et al.*, 2013)

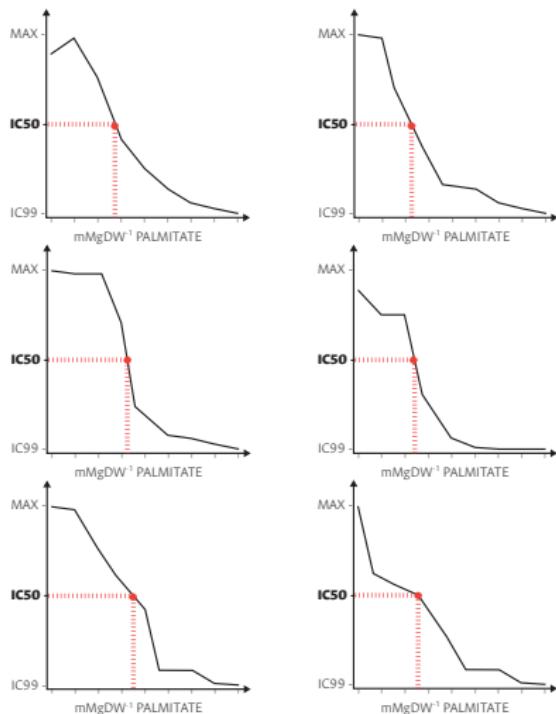
Inflamed Metabolic Scenario



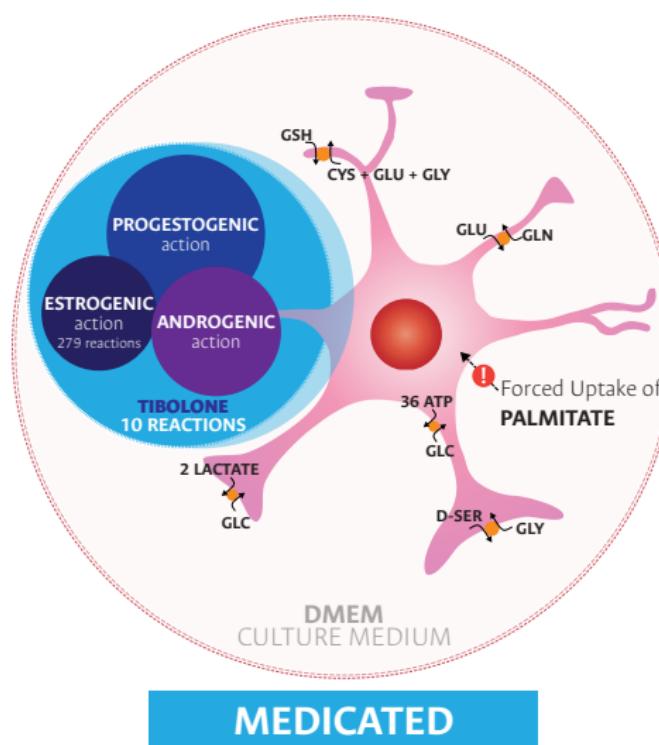
PALMITATE UPTAKE RATE: AVERAGED IC₅₀ VALUES

INFLAMED

ROBUSTNESS ANALYSIS



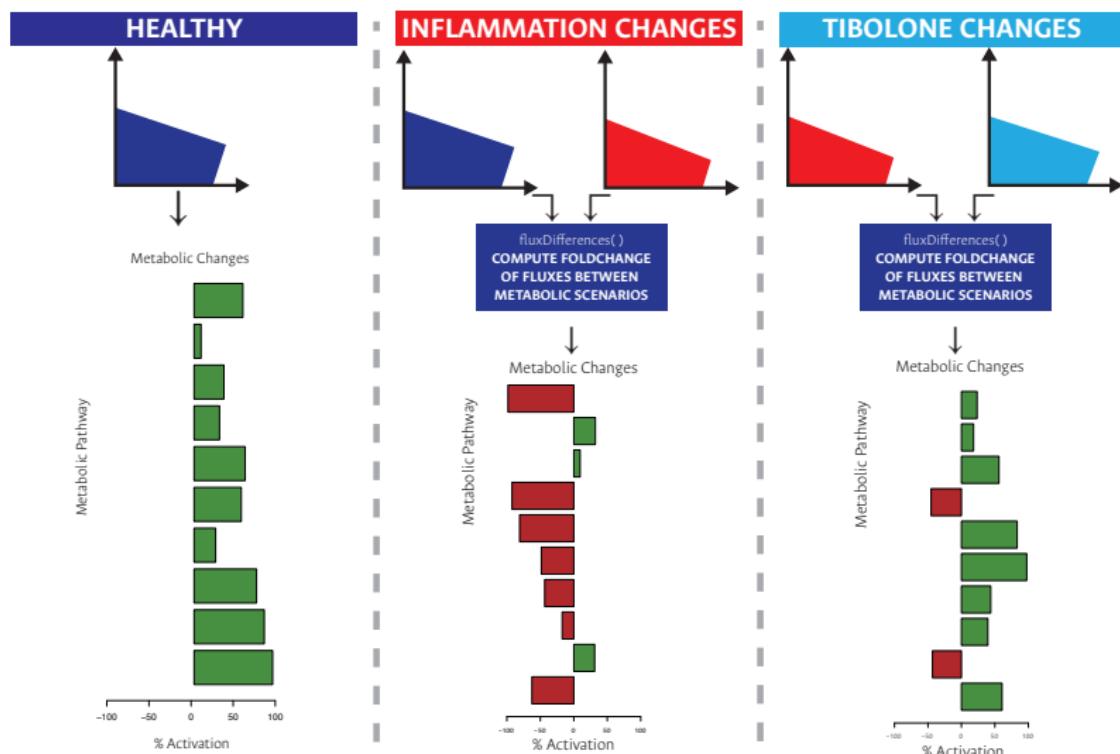
Medicated Metabolic Scenario



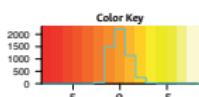
OBJECTIVE 3:

Determine metabolic pathways and relevant functional products in response to steroid tibolone through systems biology approximations.

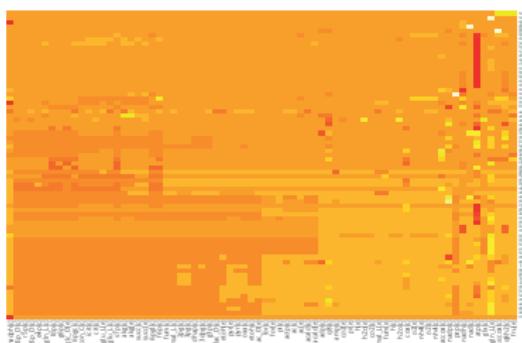
Metabolic Pathways Activation Pattern Changes



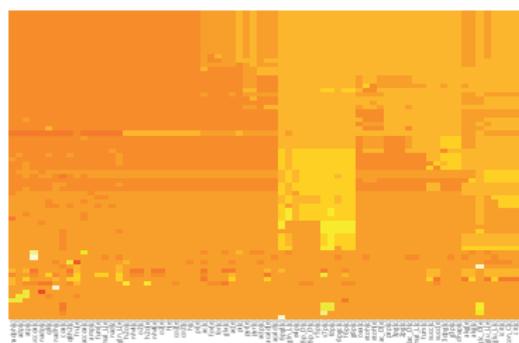
Changes in Metabolites Production



$$\text{foldChange} = \frac{\text{Scenario2} - \text{Scenario1}}{|\text{Scenario1}|}$$



Inflammation Related
Metabolic Changes



Tibolone Related
Metabolic Changes

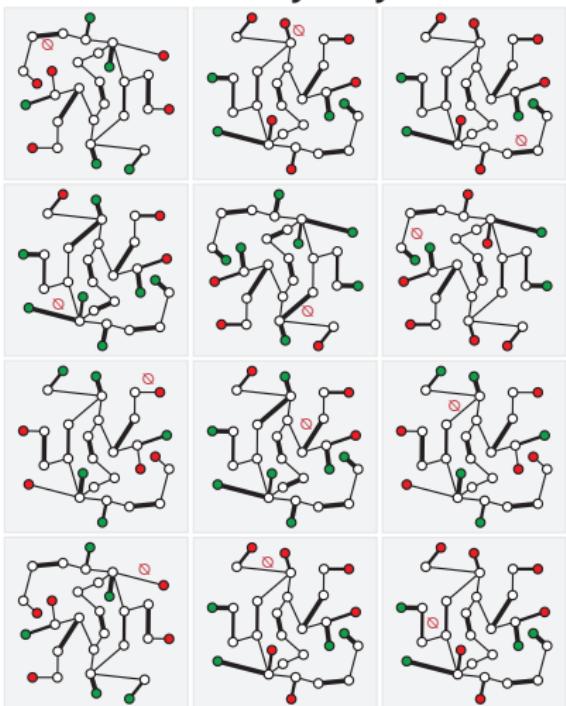
Now running at:



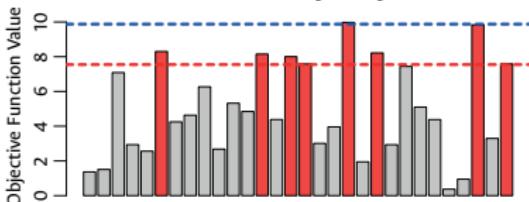
OBJECTIVE 4:

Evaluate the importance of proteins and metabolic pathways previously identified on the dynamics of the metabolic model.

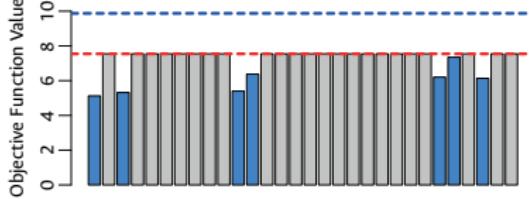
Essentiality Analysis



Pro-Inflammatory Enzymes



Anti-Inflammatory Enzymes



Software Packages



'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



'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



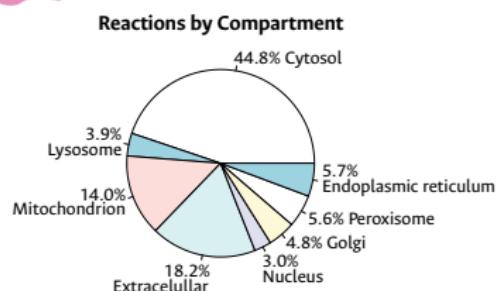
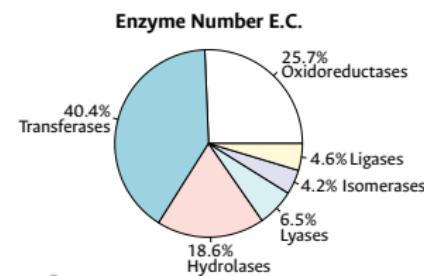
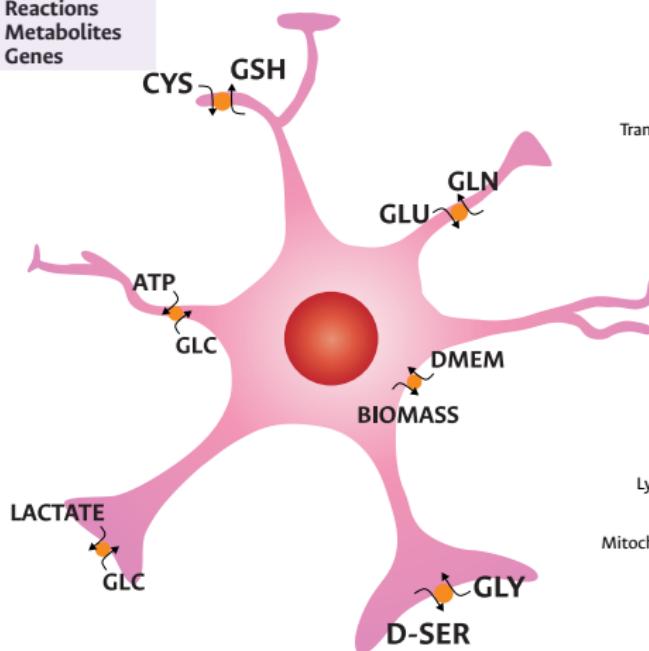
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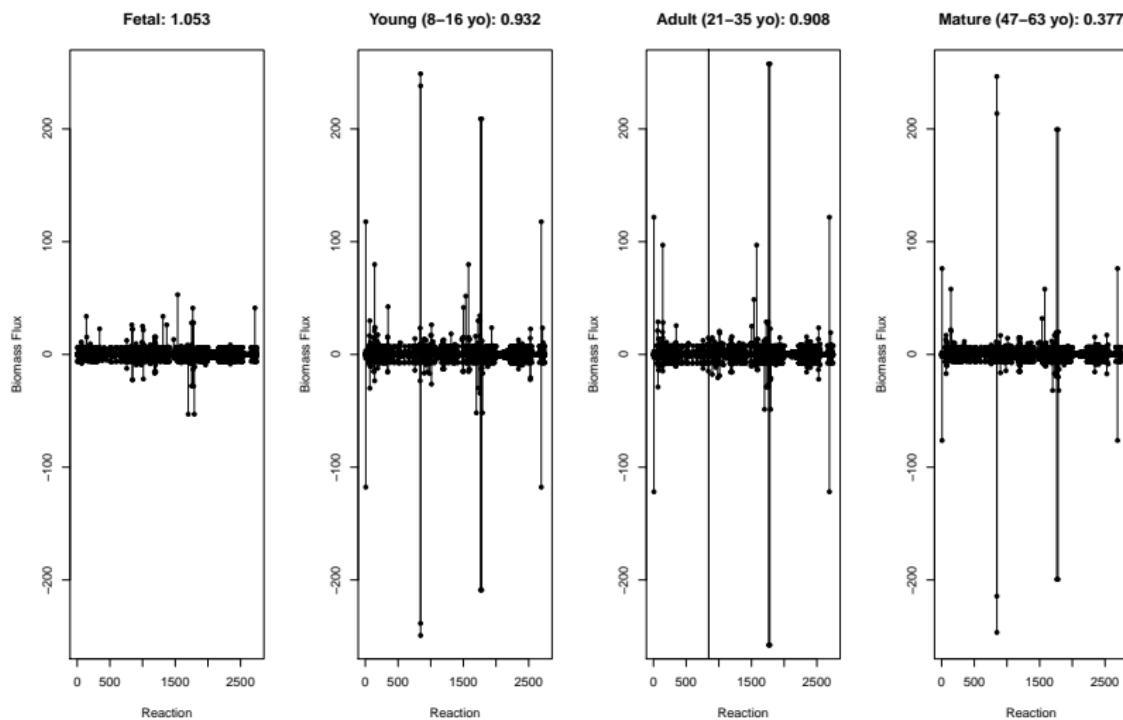
Language: R
Stable: CRAN
Development: gibbslab/exp2flux
License: GPL-2
Binaries: Windows - Linux - Mac

Astrocyte Model

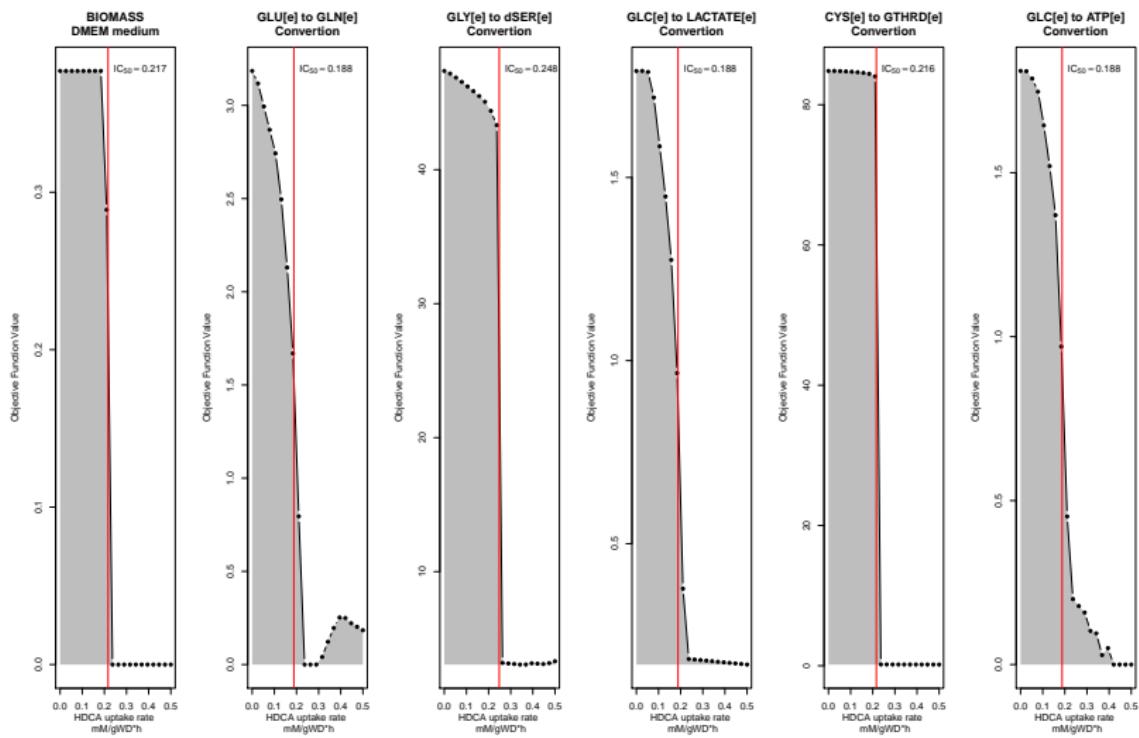
8 Compartments
2747 Reactions
1956 Metabolites
1262 Genes



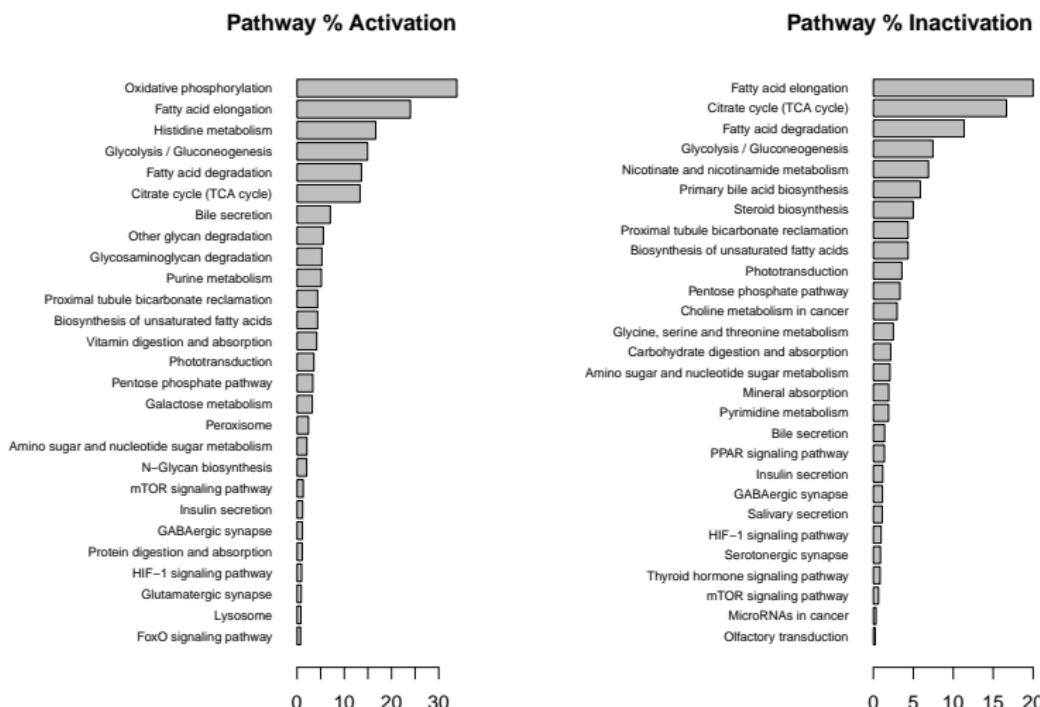
Age Related Metabolic Changes in Astrocytes



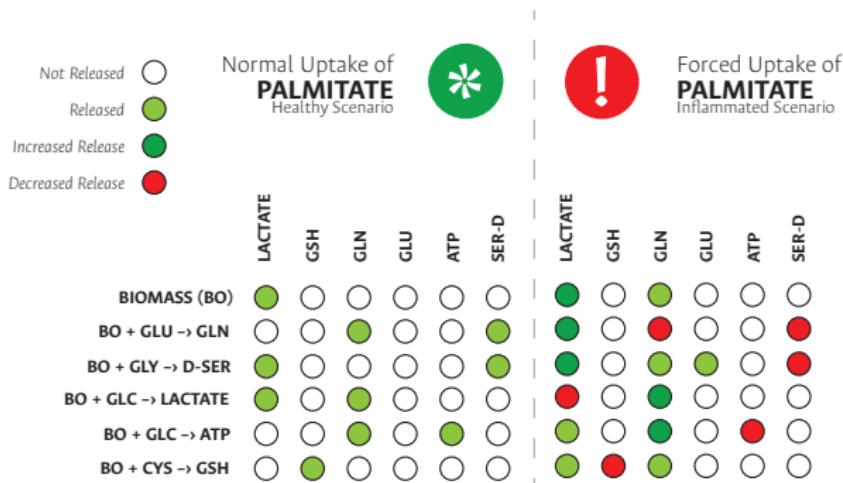
$$IC_{50} = 0.208 \pm 0.024 \text{ mMgDW}^{-1}\text{h}^{-1}$$



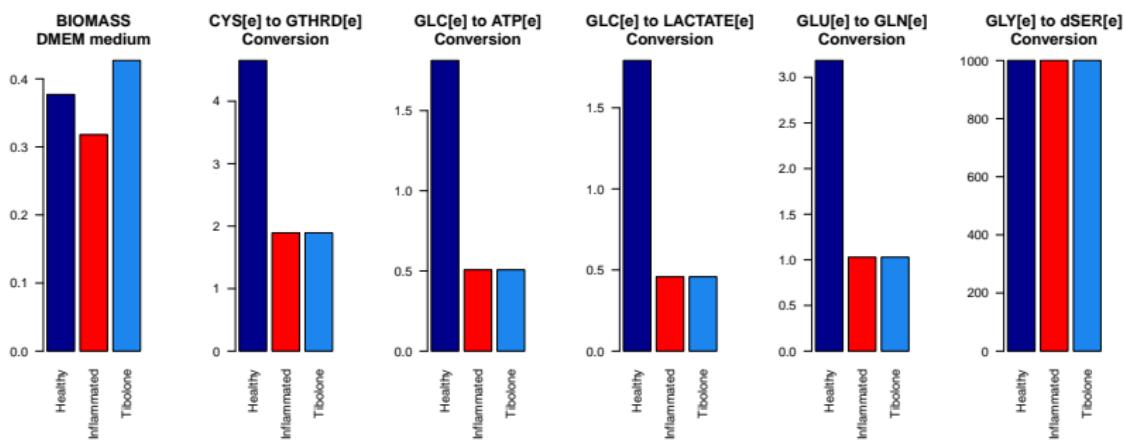
Inflammation Related Metabolic Changes in Astrocytes



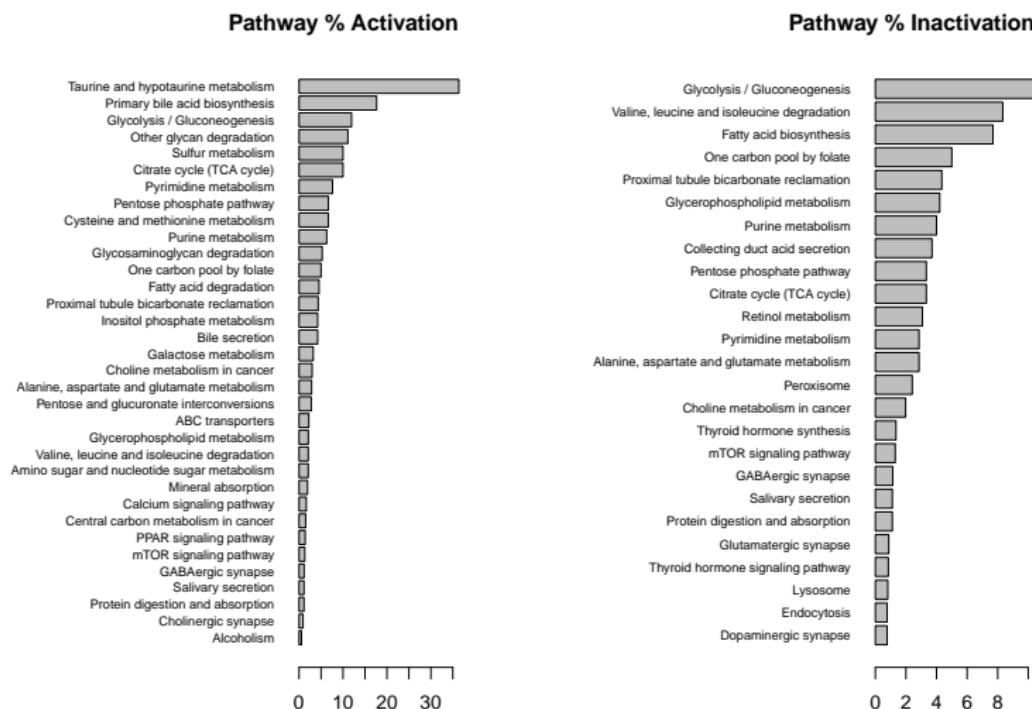
Gliotransmitters Release Rate



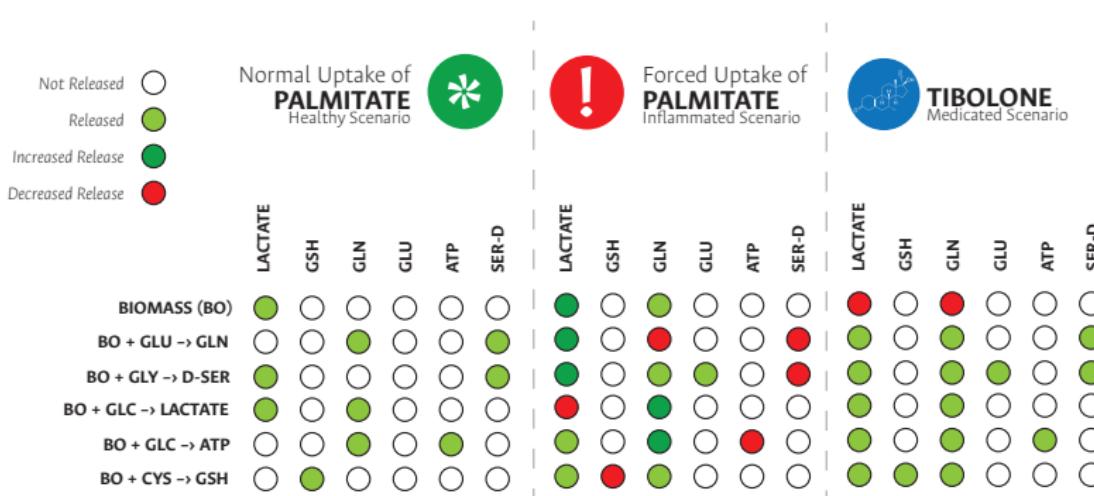
Tibolone Effects in Inflamed Astrocytes



Tibolone Metabolic Changes in Inflamed Astrocytes



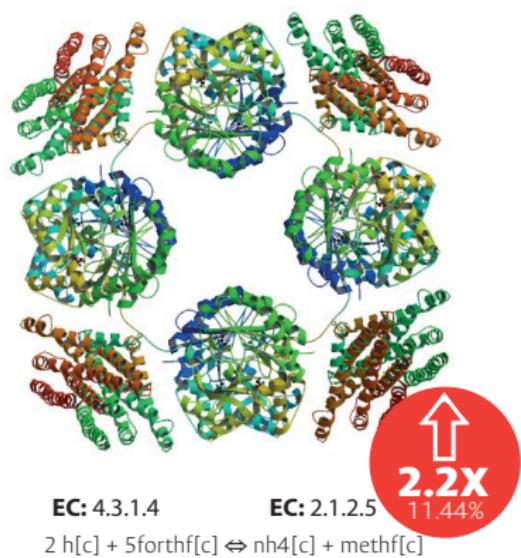
Gliotransmitters Release Rate



ProInflammatory Enzymes

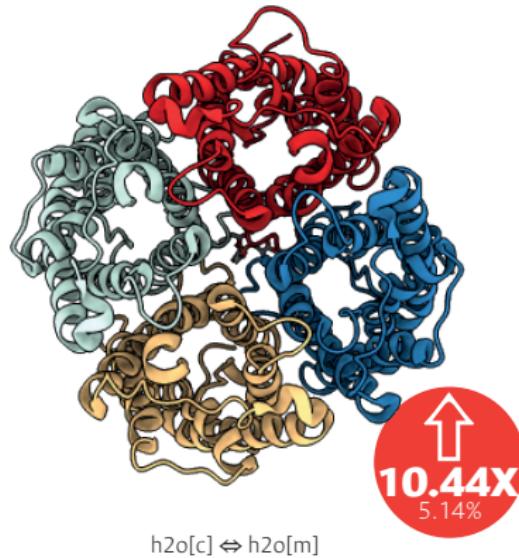
FTCD

FormimidoylTransferase CycloDeaminase



H2Otm

H2O Transport Mitochondrial



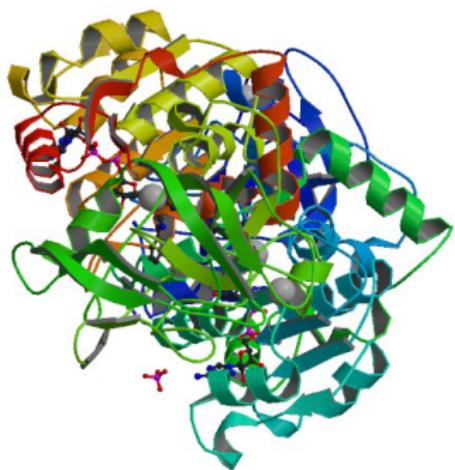
74 Anti inflammatory Enzymes



Tibolone Related Enzymes

r0739

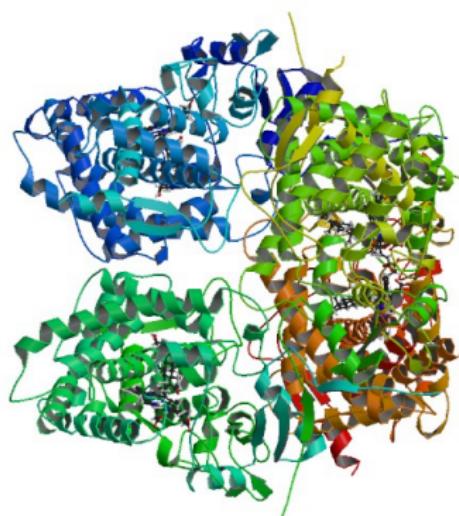
Alcohol Dehydrogenase 1 - 7



EC: 1.1.1.1

**REM1804m | REM1807m**

Cytochrome P450 Family 27 Subfamily A Member 1



EC: 1.14.15.15



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: _____



CDMX, México
Short Talk



Barcelona, España
Poster

ICGEB Course on Bioinformatics and Computational Neuroscience



Pontificia Universidad Javeriana
5 - 8 October - Bogotá, Colombia

Bogotá, Colombia
Short Talk

Acknowledgements

This study was developed at the:



Bioinformatics and Computational Systems Biology Lab

Institute for Genetics - Universidad Nacional de Colombia

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Andrés Pinzón PhD

ampinzonv@unal.edu.co