

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

Presented by:

Daniel Camilo Osorio Hurtado

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:

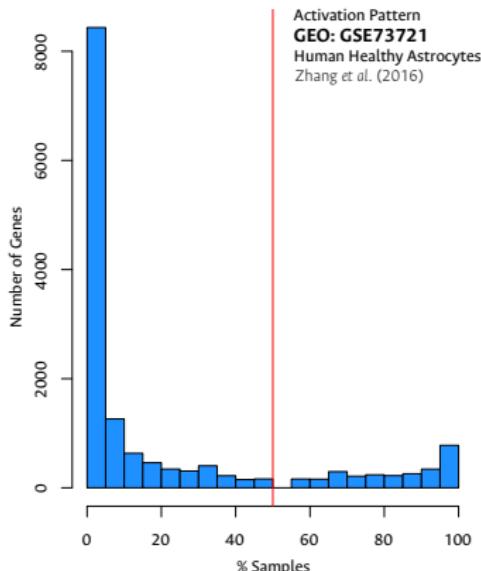
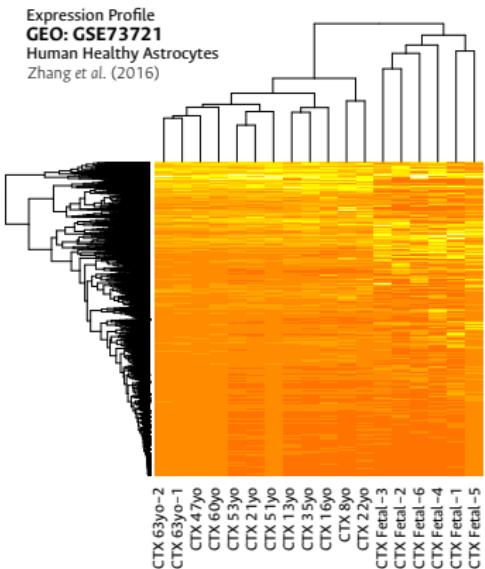
To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

- ▶ 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.

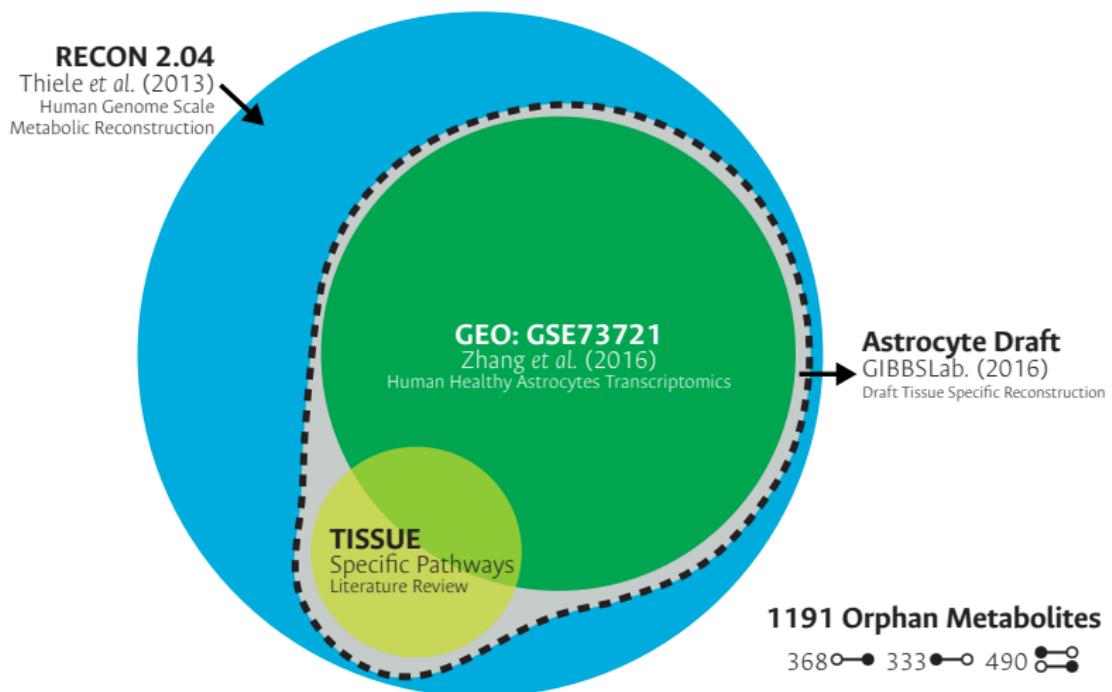
OBJECTIVE 1:

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

Human Astrocytes Gene Expression Data



Mapping Reactions



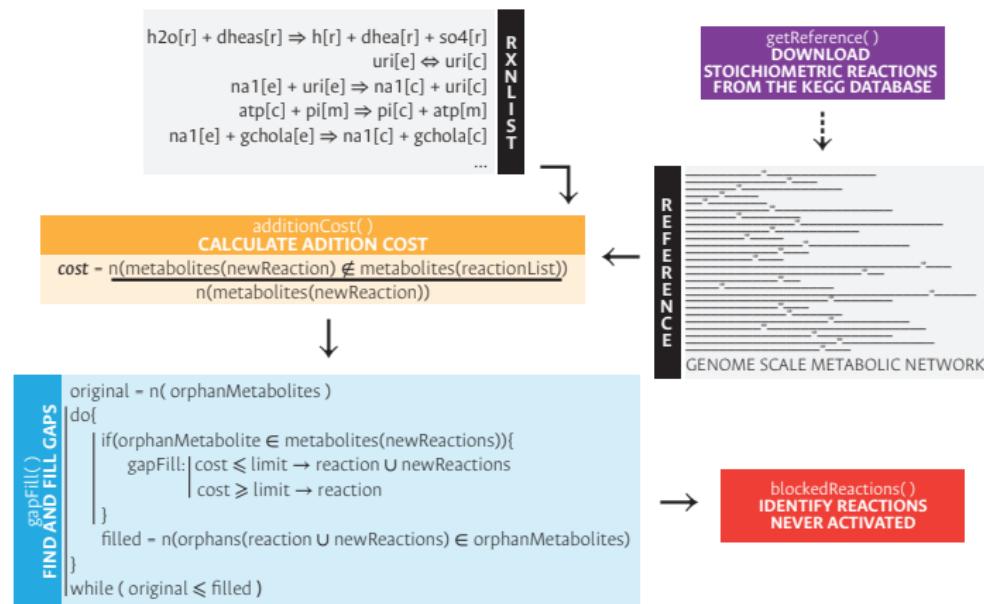
Software Development



'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



Software Development



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Language: R

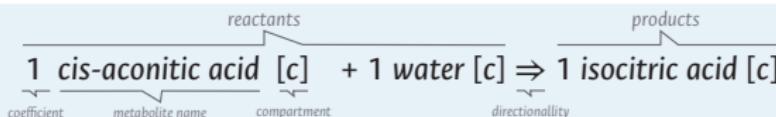
Stable: CRAN

Development: gibbslab/minval

License: GPL-2

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ENZYME



```

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]
...
  
```

REACTIONS

`getChEBI()`
CHEBI DATABASE
DOWNLOAD

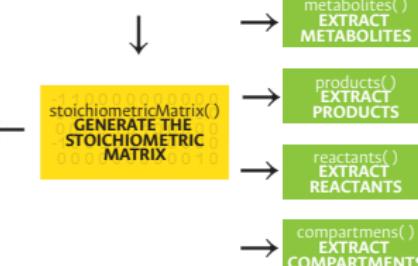
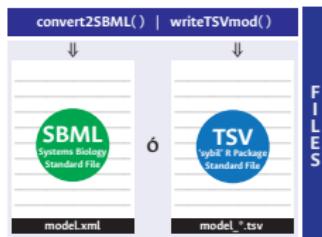


`isValidSyntax()`
SYNTAX VALIDATION



`isBalanced()`
MASS-CHARGE
BALANCE

products



Software Development



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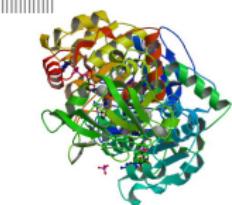
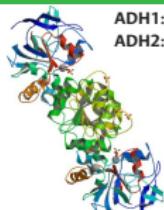
E.C: 1.1.1.1



1.1.1.1

ADH2

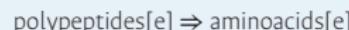
ADH1



(ADH2 or ADH1)

sum (ExprADH2 + ExprADH1)

E.C: 3.4.21.5



3.4.21.5

IDE.A

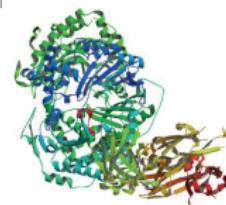
IDE.B

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



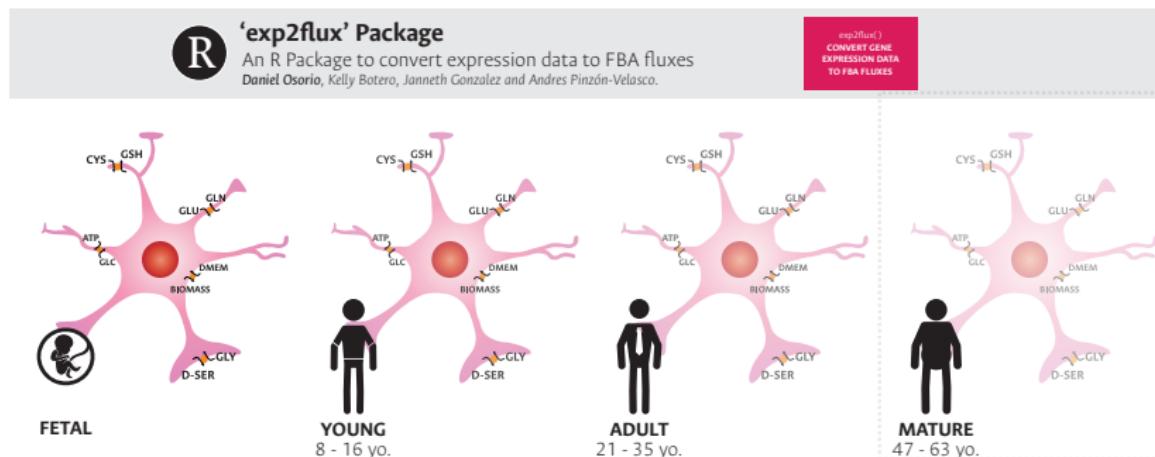
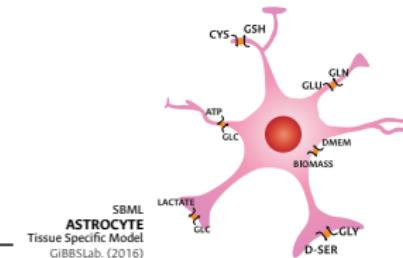
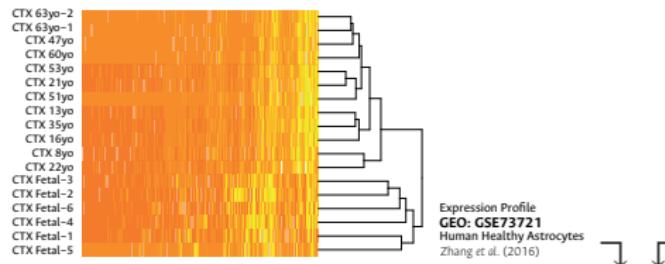
CONSTRAINED
METABOLIC MODEL



fluxDifferences()
COMPUTE FOLDCHANGE
OF FLUXES BETWEEN
METABOLIC SCENARIOS

METABOLIC MODEL
WITH GPR

Human Healthy Mature Astrocyte Model

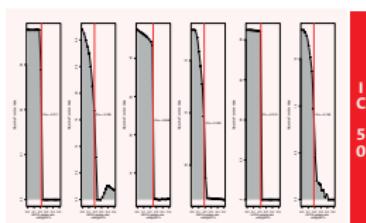


OBJECTIVE 2:

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

Metabolic Scenarios

Normal Uptake of PALMITATE



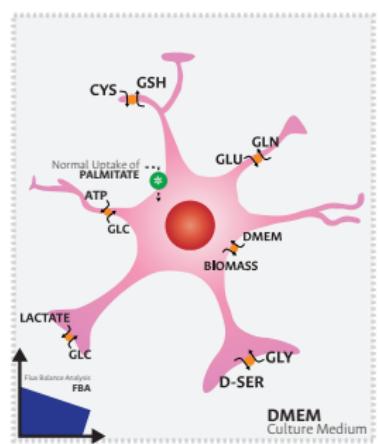
Force Uptake of PALMITATE



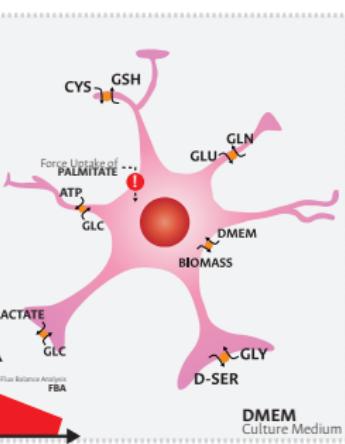
TIBOLONE



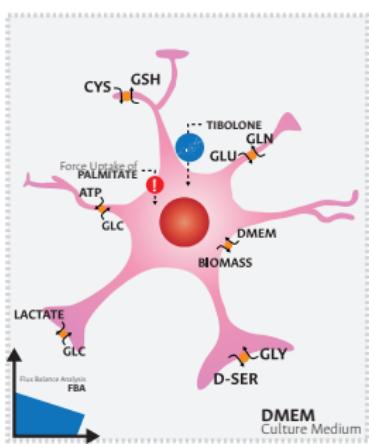
HEALTHY



INFLAMMATED



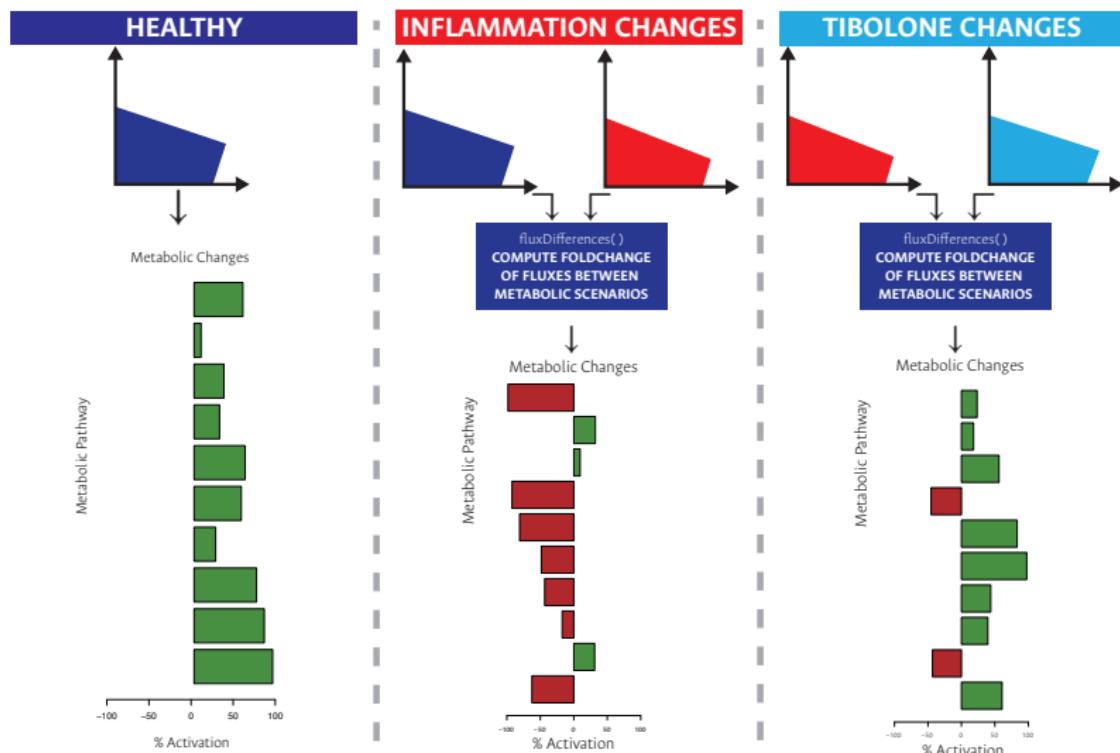
MEDICATED



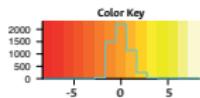
OBJECTIVE 3:

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

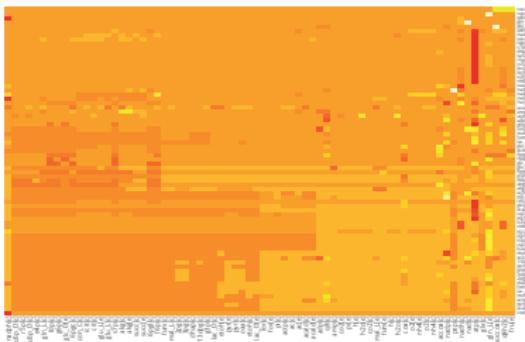
Metabolic Pathways Activation Pattern Changes



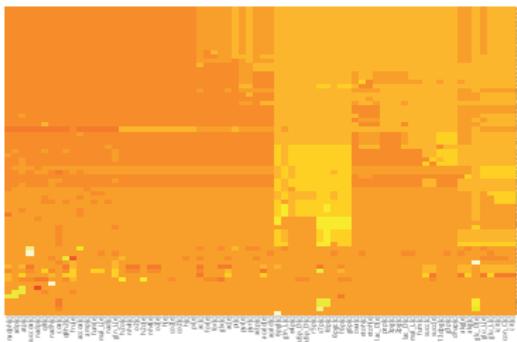
Changes in Metabolites Production



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



Inflammation Related
Metabolic Changes



Tibolone Related
Metabolic Changes

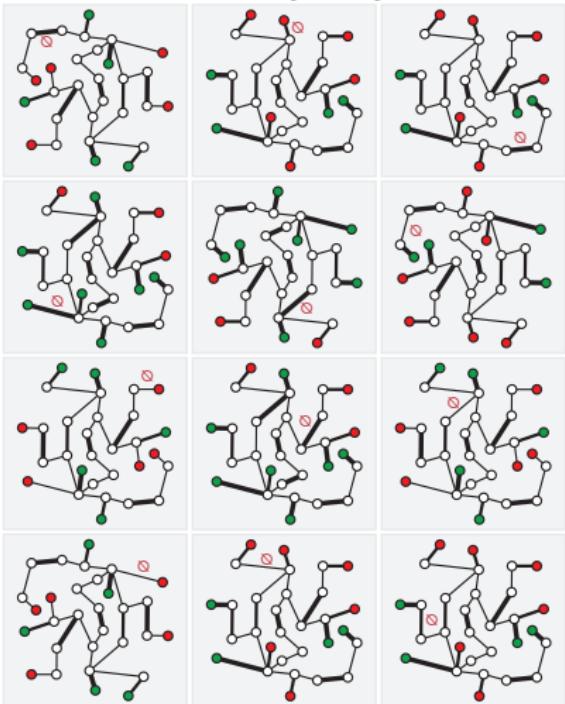
Now running at:



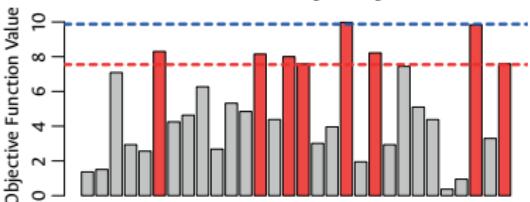
OBJECTIVE 4:

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

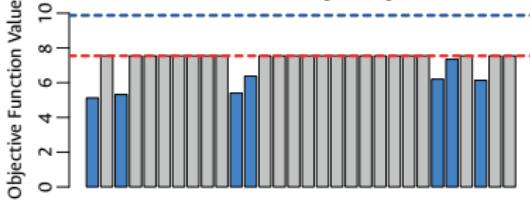
Essentiality Analysis



Pro-Inflammatory Enzymes



Anti-Inflammatory Enzymes



Software Packages



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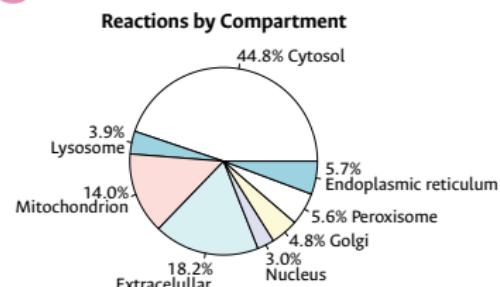
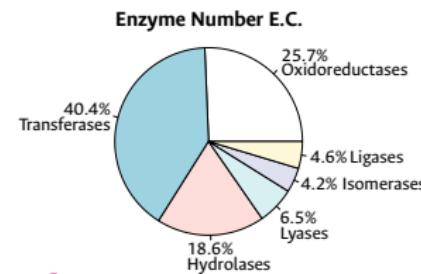
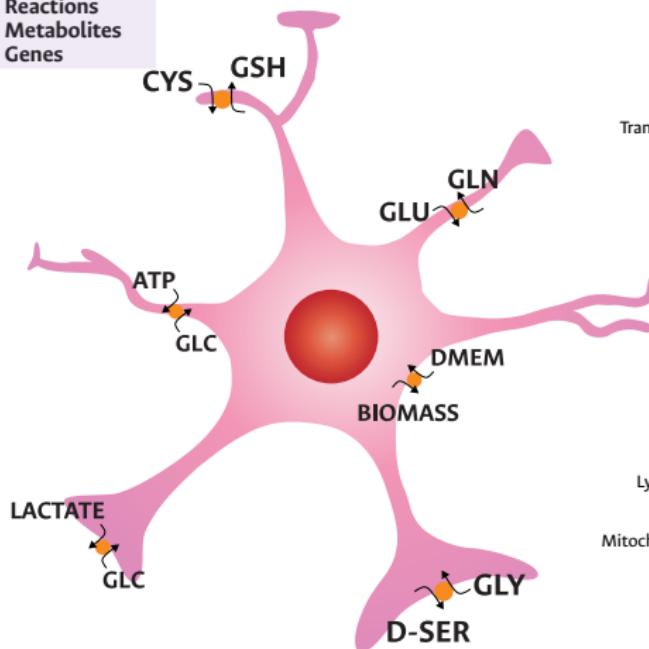
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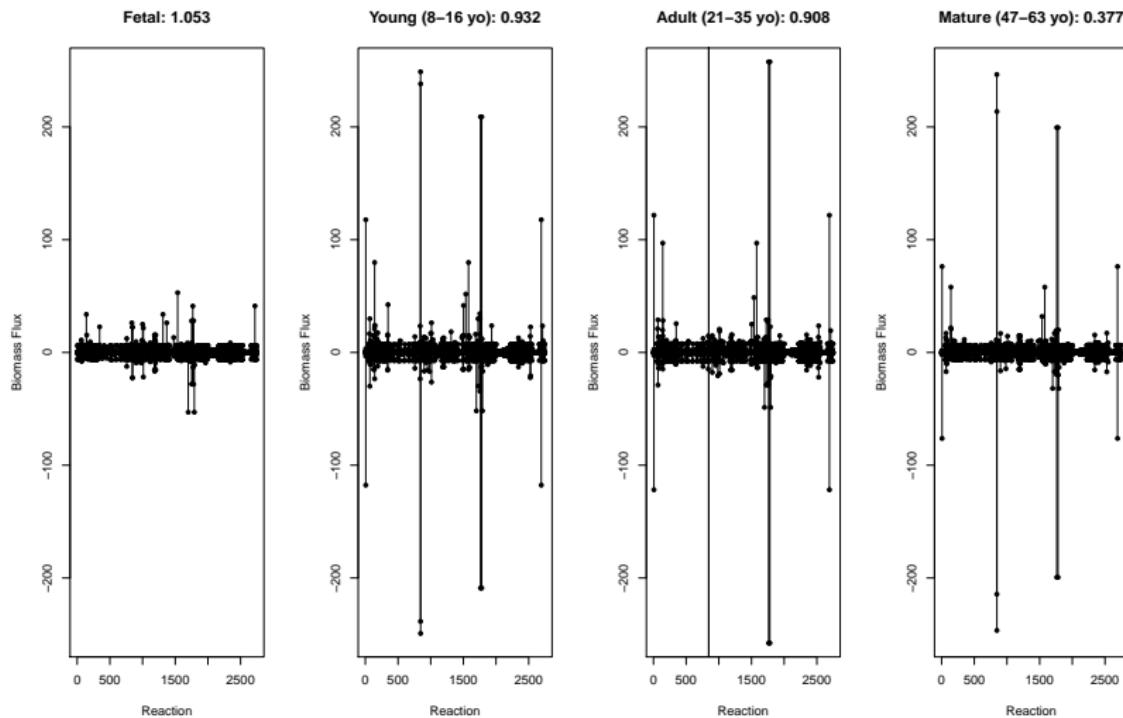
Language: R
Stable: CRAN
Development: gibbslab/exp2flux
License: GPL-2
Binaries: Windows - Linux - Mac

Astrocyte Model

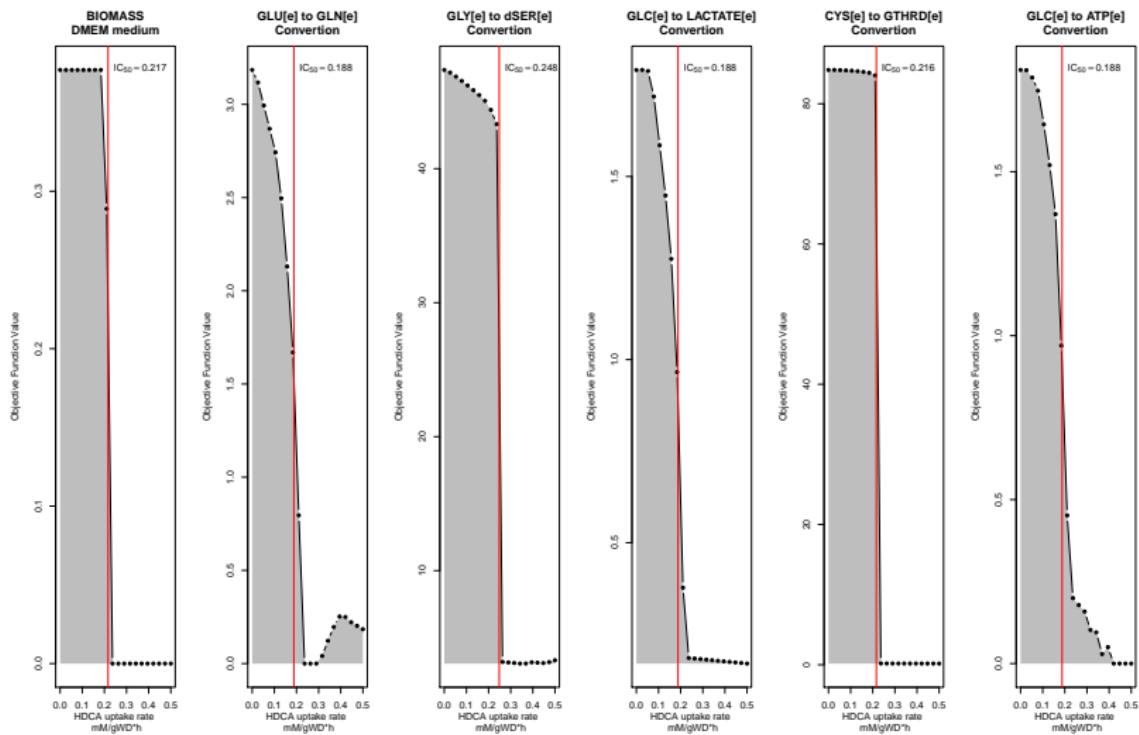
8 Compartments
2747 Reactions
1956 Metabolites
1262 Genes



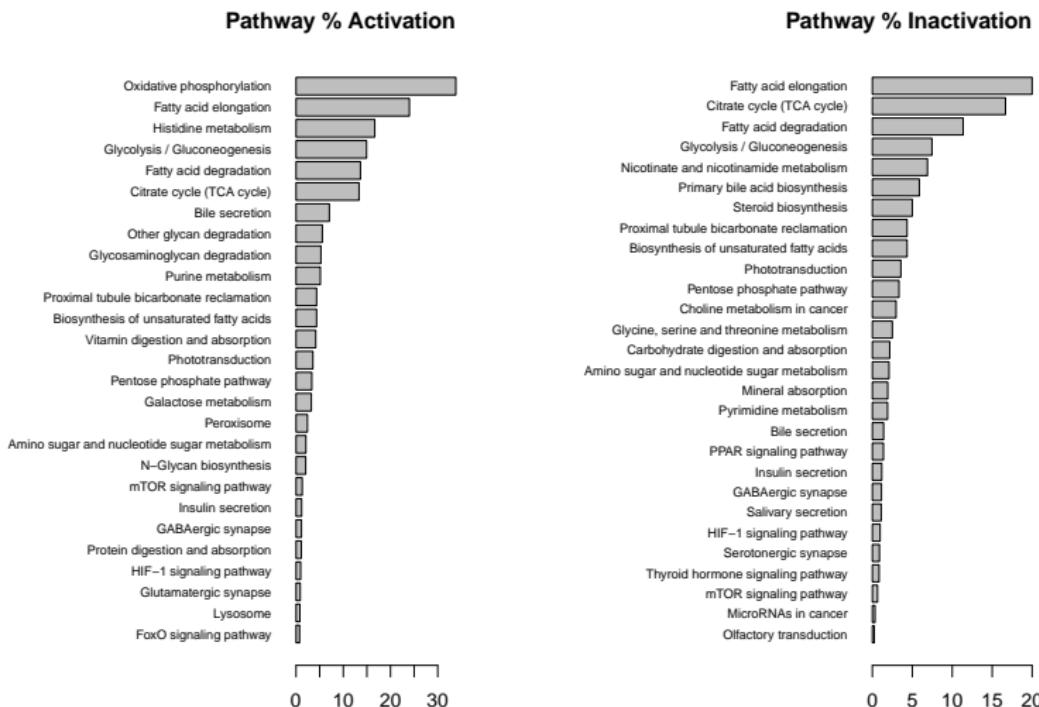
Age Related Metabolic Changes in Astrocytes



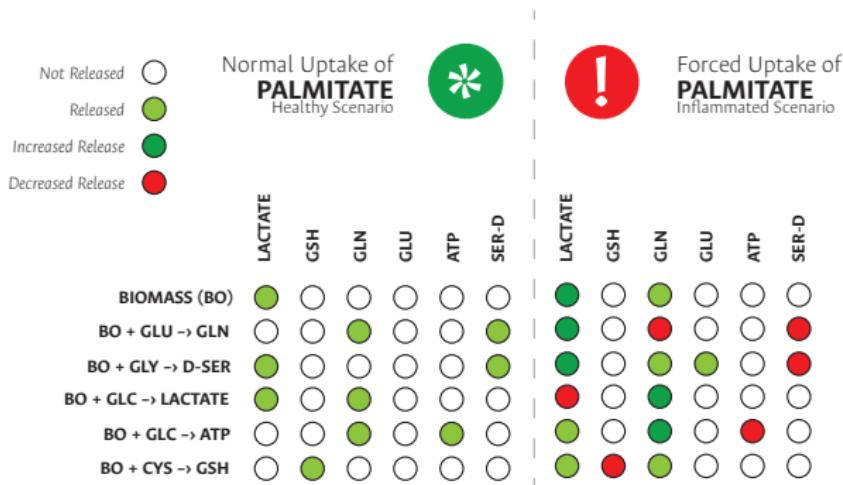
$$IC_{50} = 0.208 \pm 0.024 \text{ mMgDW}^{-1}\text{h}^{-1}$$



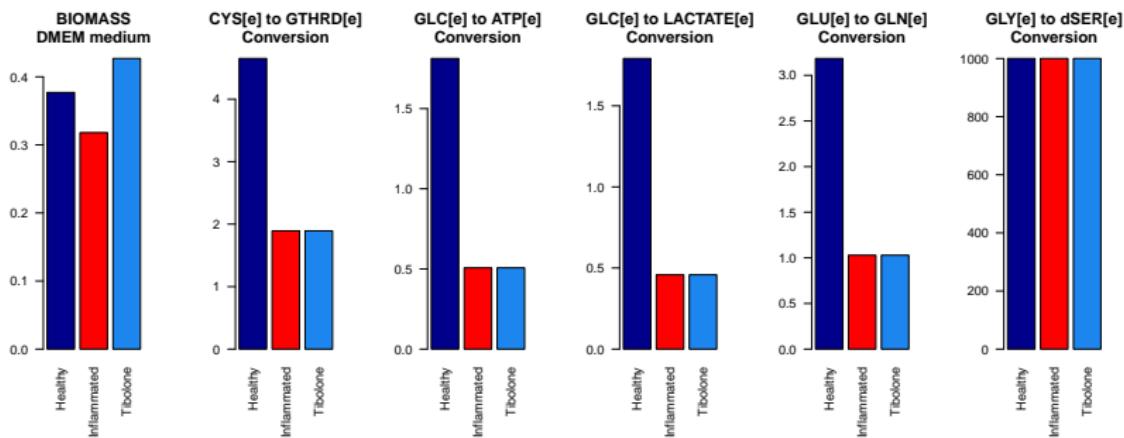
Inflammation Related Metabolic Changes in Astrocytes



Gliotransmitters Release Rate

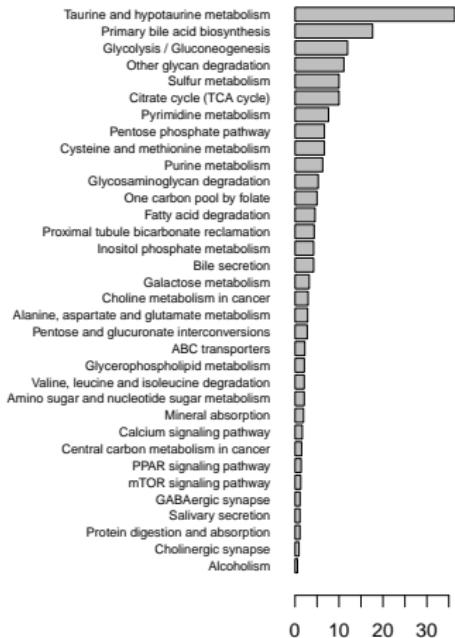


Tibolone Effects in Inflamed Astrocytes

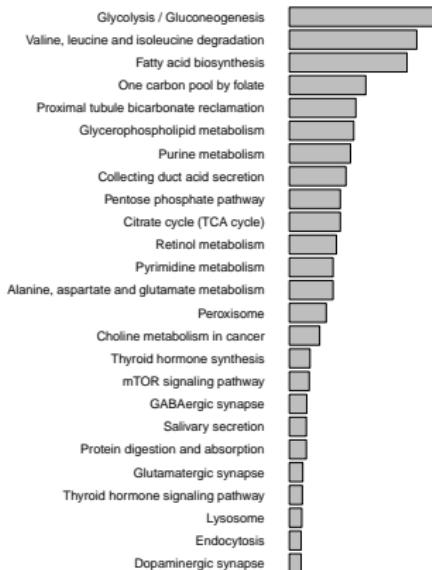


Tibolone Metabolic Changes in Inflamed Astrocytes

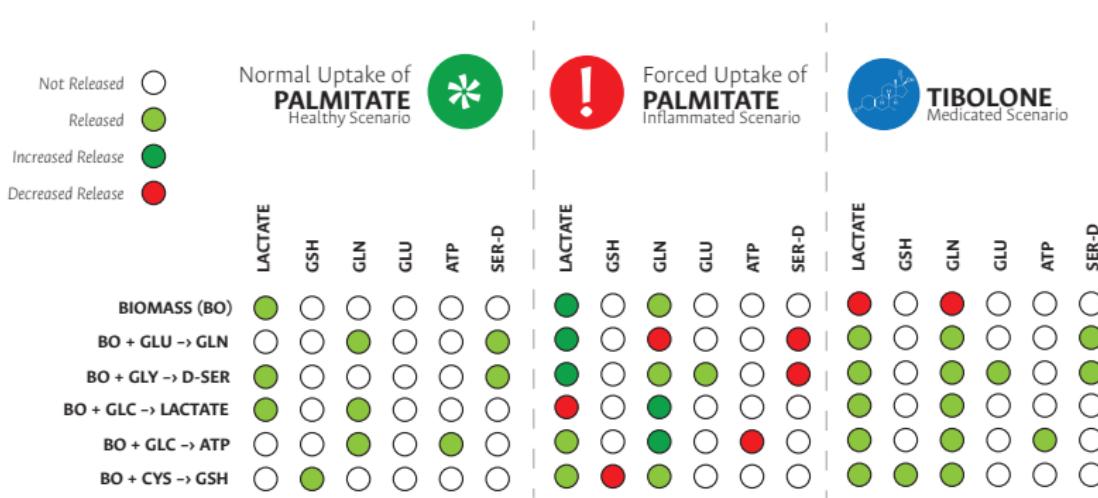
Pathway % Activation



Pathway % Inactivation



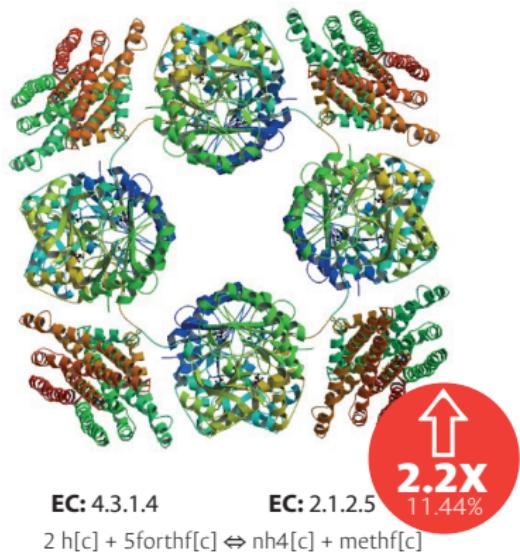
Gliotransmitters Release Rate



ProInflammatory Enzymes

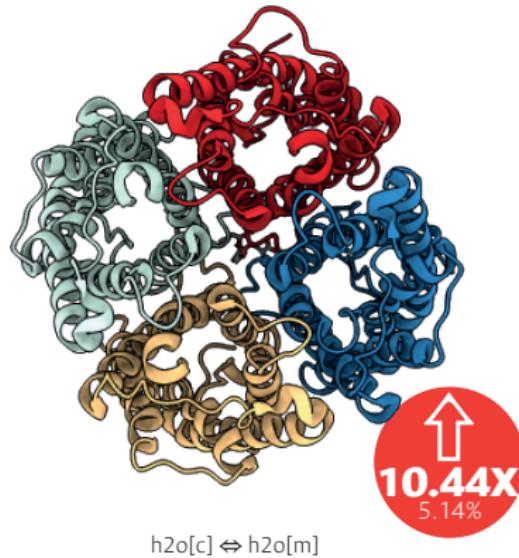
FTCD

FormimidoylTransferase CycloDeaminase



H2Otm

H2O Transport Mitochondrial



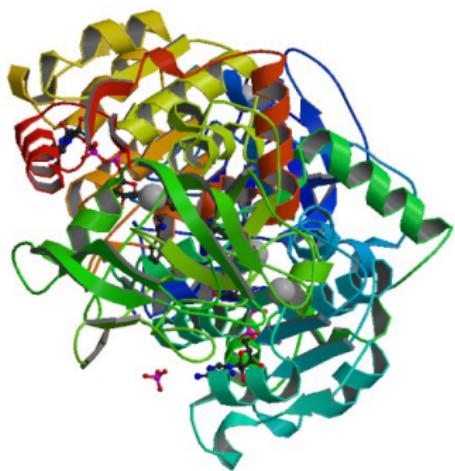
74 Anti inflammatory Enzymes



Tibolone Related Enzymes

r0739

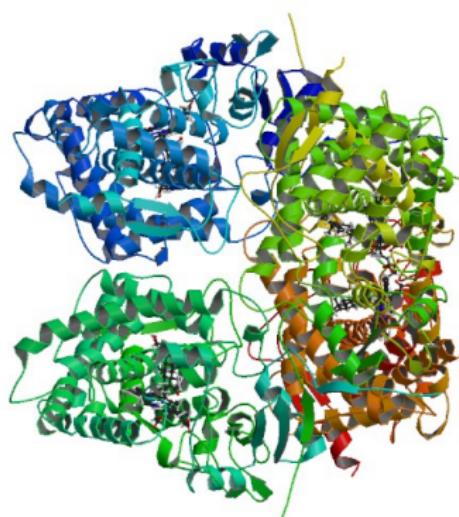
Alcohol Dehydrogenase 1 - 7



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



Bogotá, Colombia
Short Talk

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