

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:

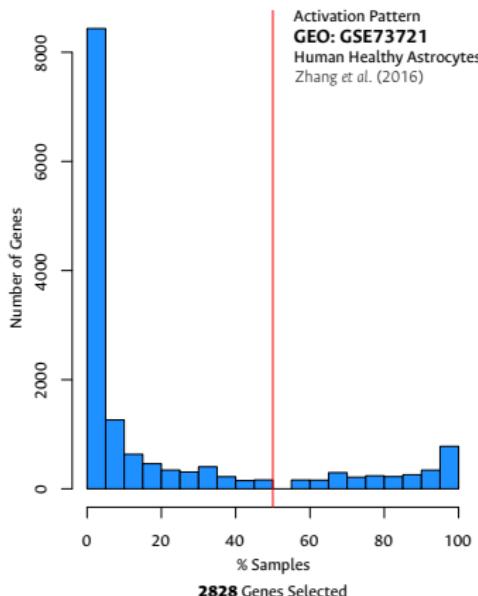
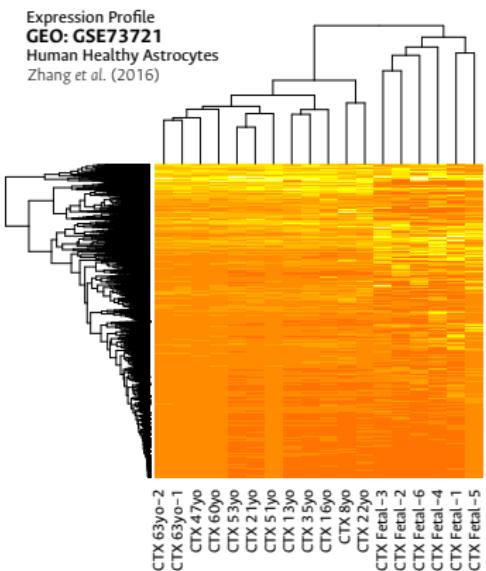
To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

- ▶ 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.

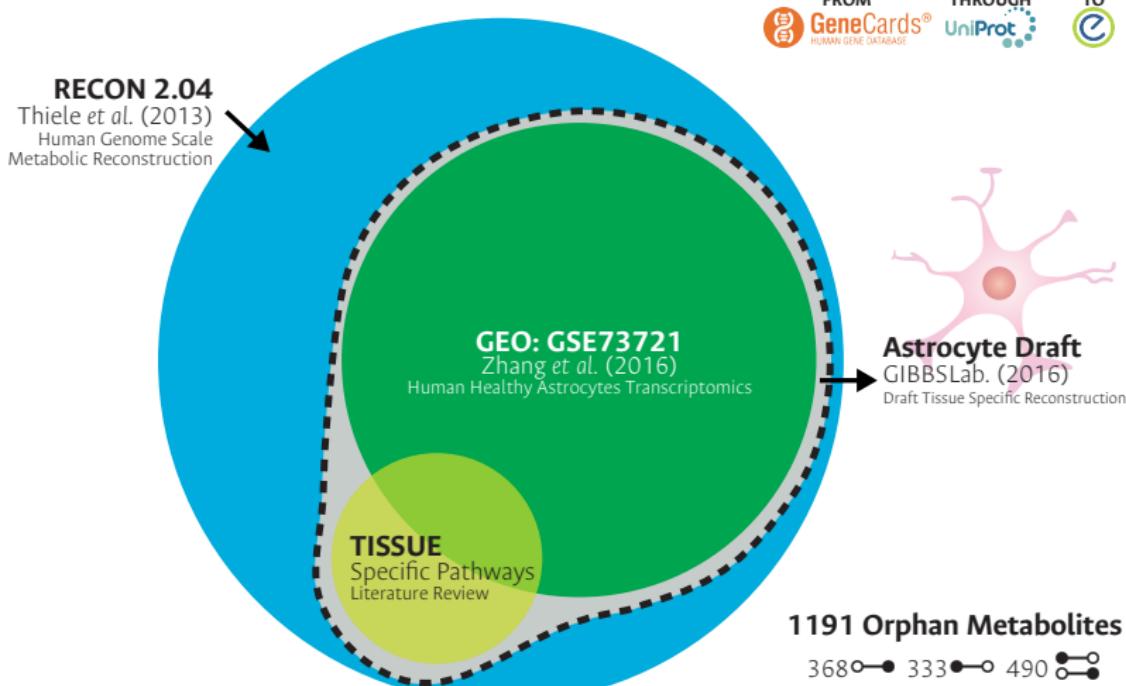
OBJECTIVE 1:

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

Healthy Human Astrocytes Gene Expression Data



Mapping Reactions



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.

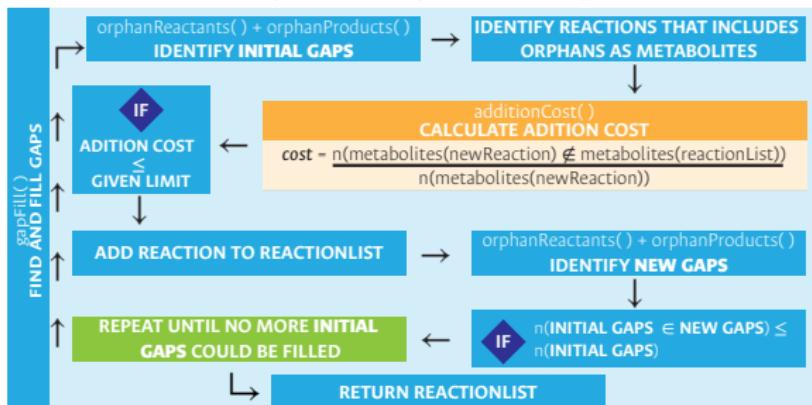
Language: R
 Stable: CRAN
 Development: gibbslab/g2f
 License: GPL-2
 Binaries: Windows - Linux - Mac

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

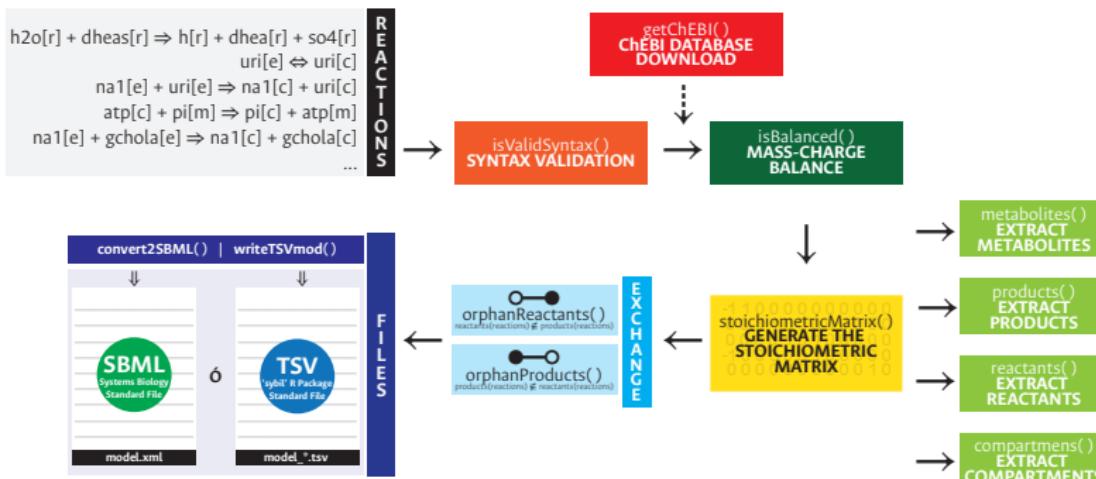
REACTI**L**IST



REFERENC**E**



Syntax, Mass-Charge Validation and SBML files



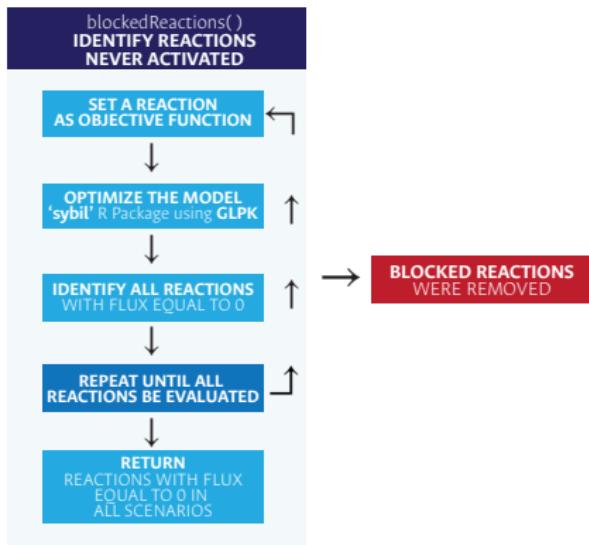
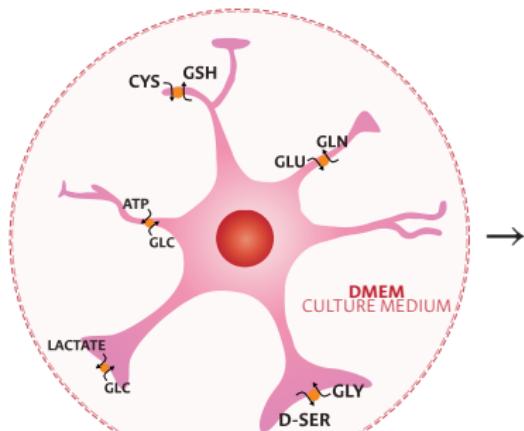
Metabolic Model Debugging



'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 Algorithms

ALGORITHM	ENVIRONMENT	HOW IT WORKS
GIMME	MatLab - Privative	<ul style="list-style-type: none">· Binary Discretization· Incorporation associated to a selected objective function
iMAT	MatLab - Privative	<ul style="list-style-type: none">··
E-FLUX	Not implemented	<ul style="list-style-type: none">··
PROM	MatLab - Privative	<ul style="list-style-type: none">··

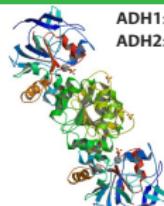
Constraining the Metabolic Model



'exp2flux' Package

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

E.C: 1.1.1.1



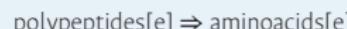
ADH1: |||||
 ADH2: |||||



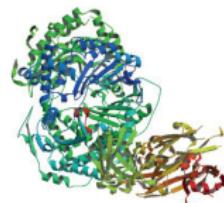
(ADH2 or ADH1)

sum (ExprADH2 + ExprADH1)

E.C: 3.4.21.5



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



3.4.21.5

IDE.A IDE.B IDE.C

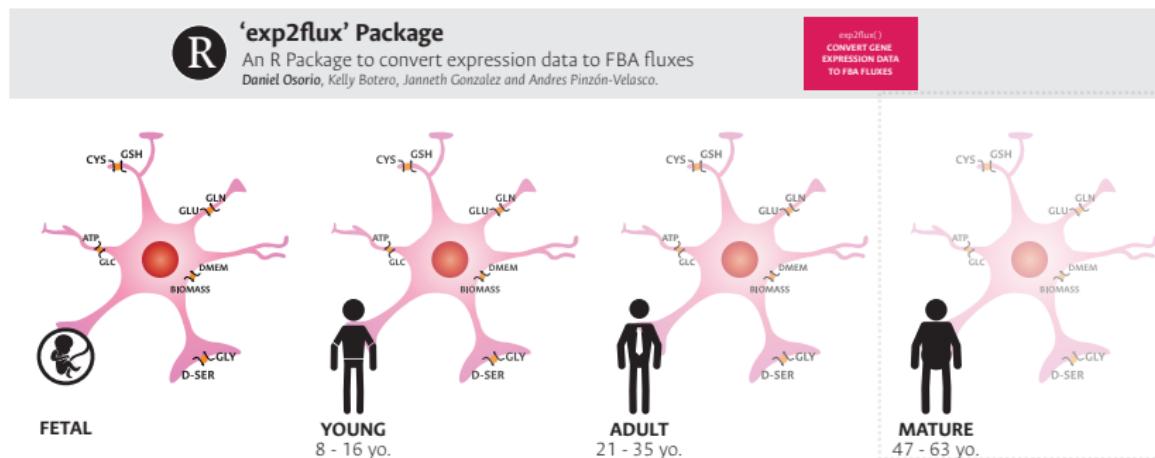
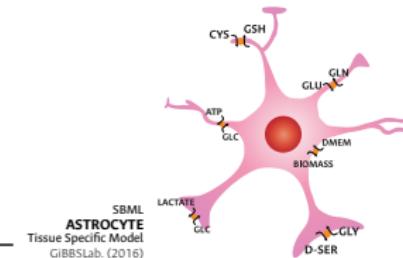
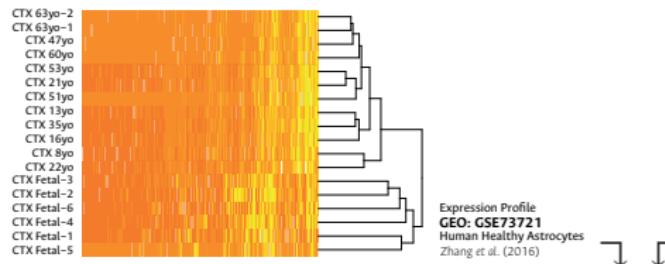
GPR

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

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



Human Healthy Mature Astrocyte Model

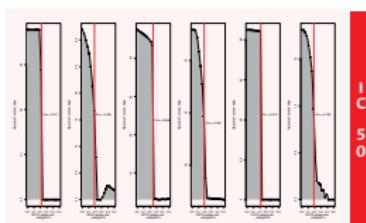


OBJECTIVE 2:

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

Metabolic Scenarios

Normal Uptake of PALMITATE



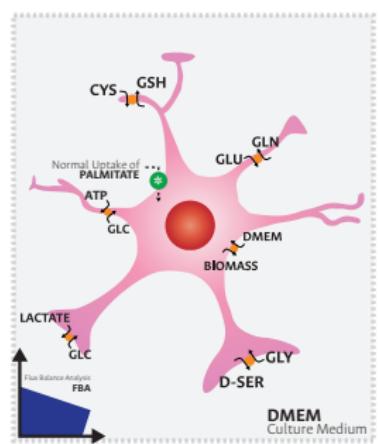
Force Uptake of PALMITATE



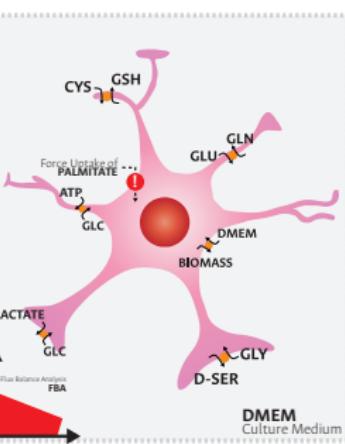
TIBOLONE



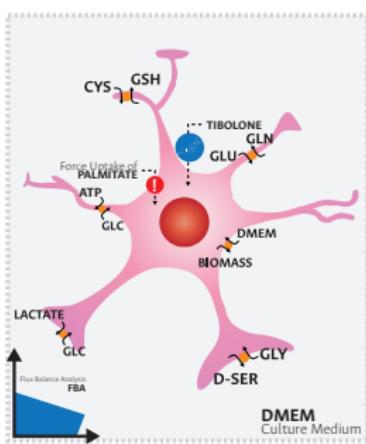
HEALTHY



INFLAMMATED



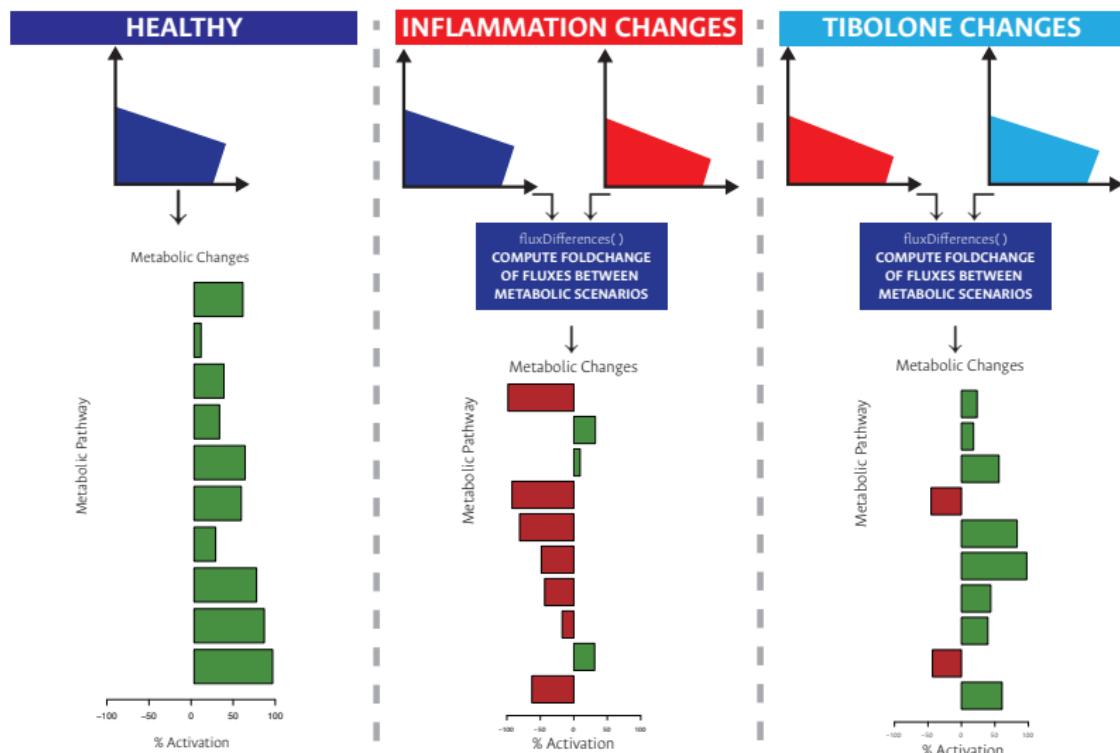
MEDICATED



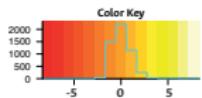
OBJECTIVE 3:

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

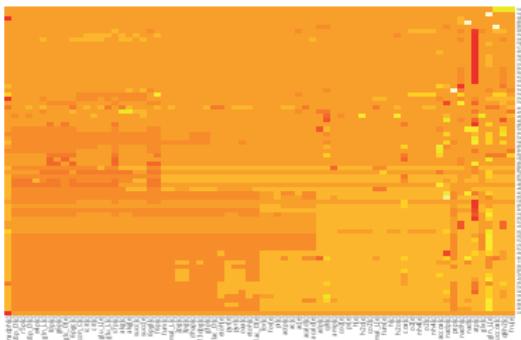
Metabolic Pathways Activation Pattern Changes



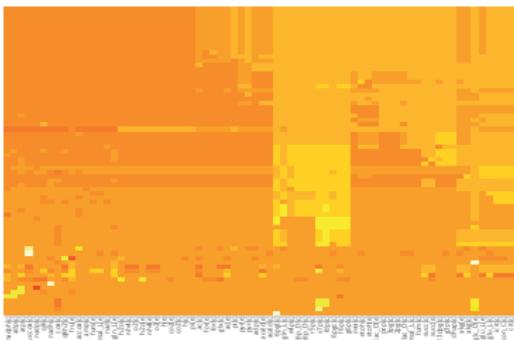
Changes in Metabolites Production



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



Inflammation Related
Metabolic Changes



Tibolone Related
Metabolic Changes

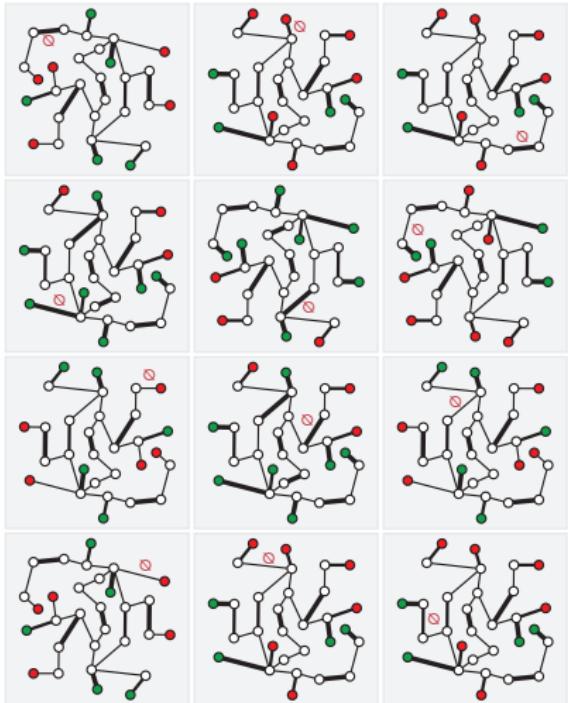
Now running at:



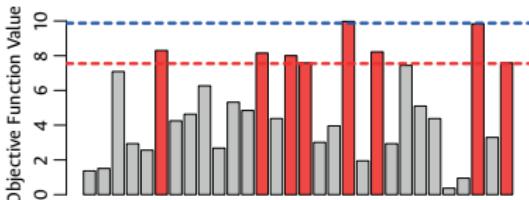
OBJECTIVE 4:

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

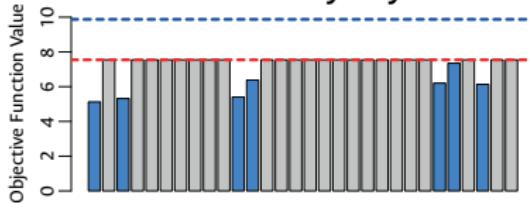
Essentiality Analysis



Pro-Inflammatory Enzymes



Anti-Inflammatory Enzymes



Software Packages



'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



'exp2flux' Package

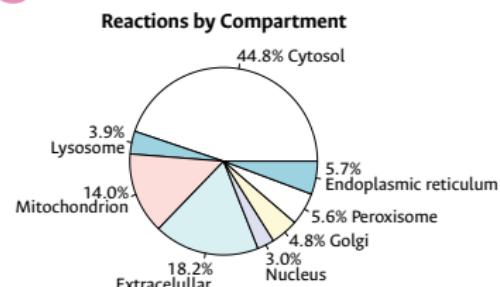
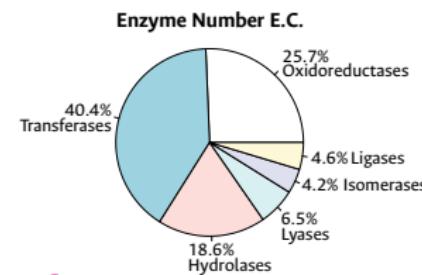
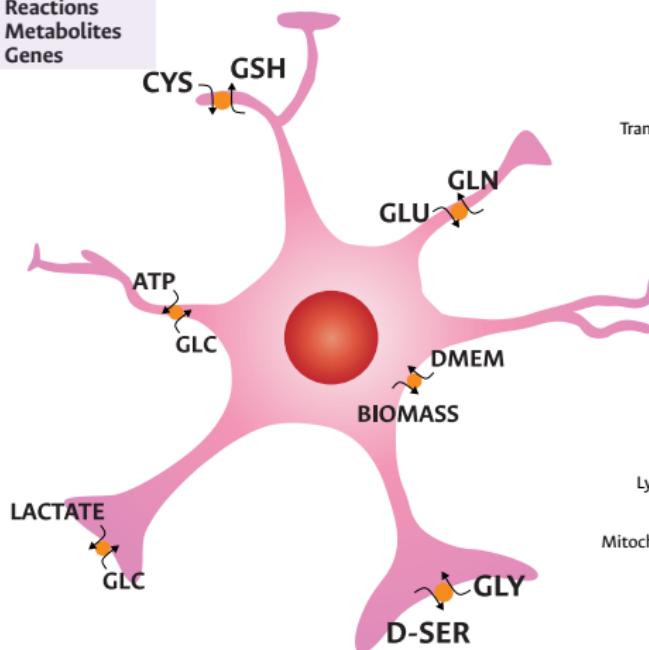
An R Package to convert expression data to FBA fluxes

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

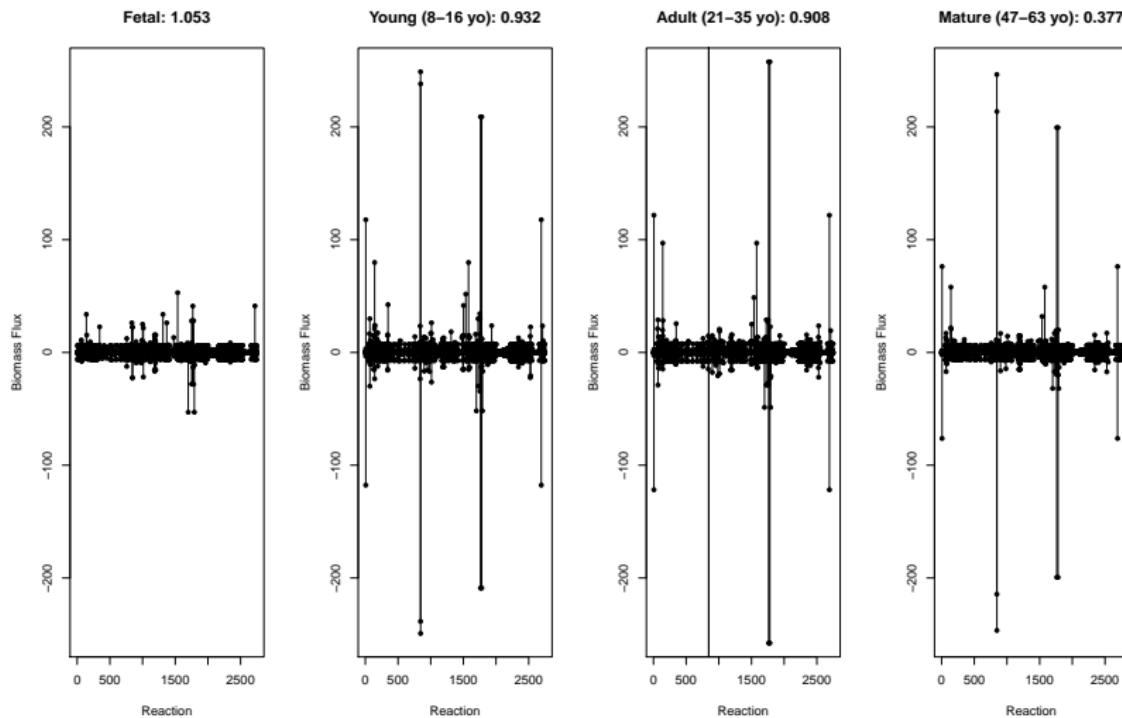
Language: R
Stable: CRAN
Development: gibbslab/exp2flux
License: GPL-2
Binaries: Windows - Linux - Mac

Astrocyte Model

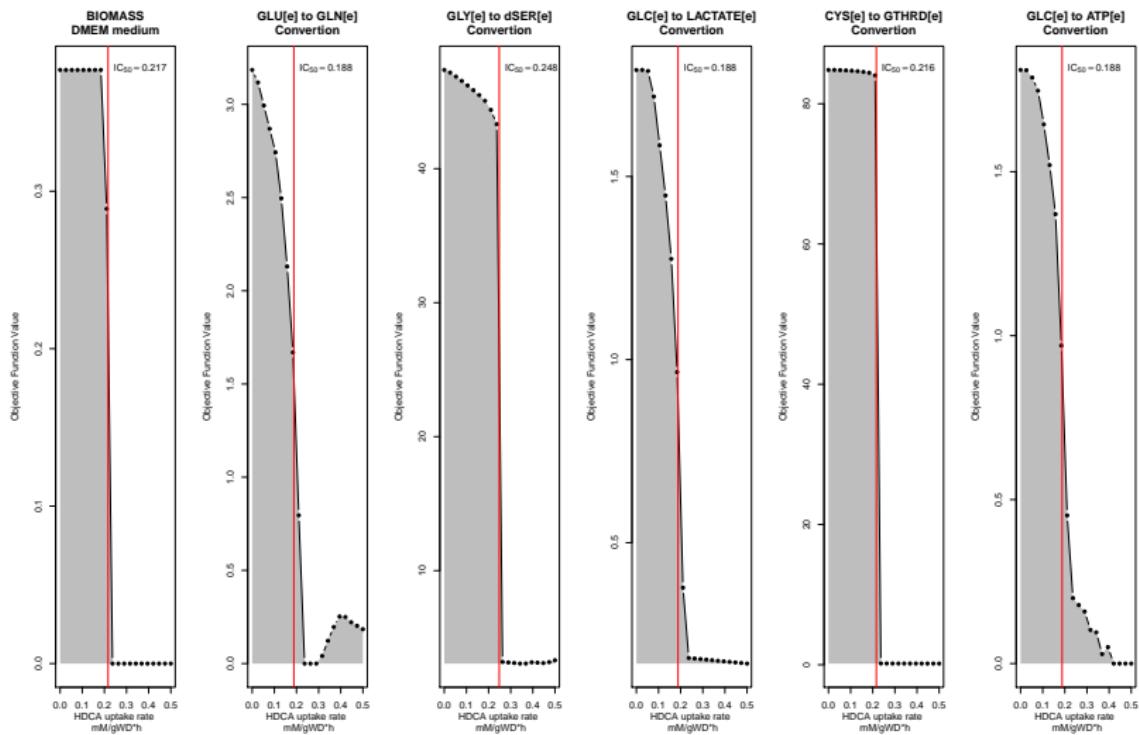
8 Compartments
2747 Reactions
1956 Metabolites
1262 Genes



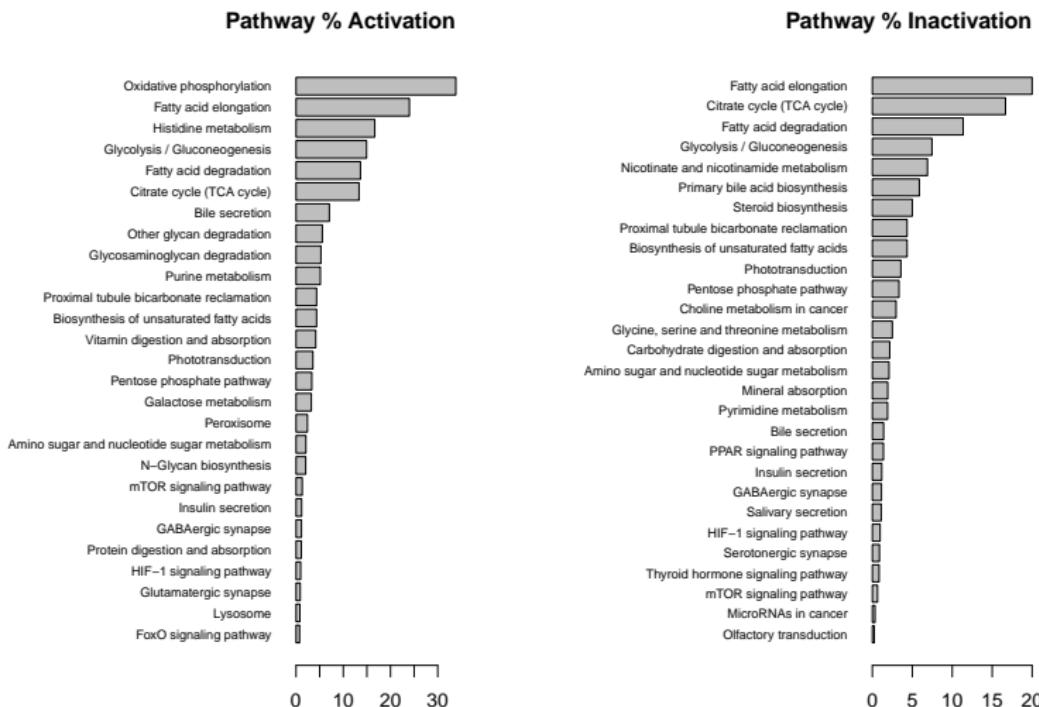
Age Related Metabolic Changes in Astrocytes



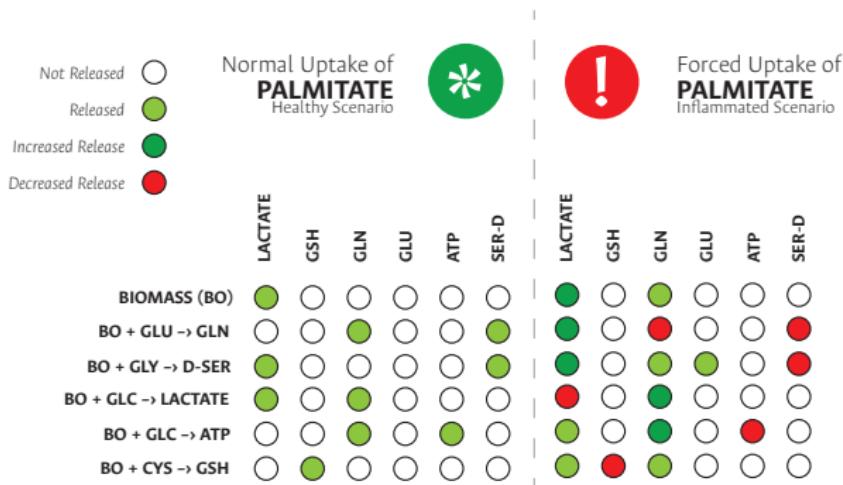
$$IC_{50} = 0.208 \pm 0.024 \text{ mMgDW}^{-1}\text{h}^{-1}$$



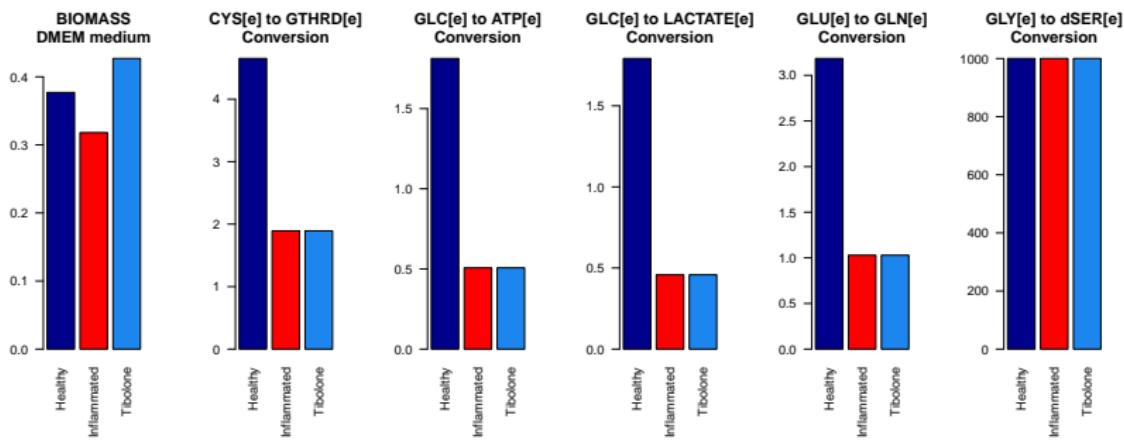
Inflammation Related Metabolic Changes in Astrocytes



Gliotransmitters Release Rate

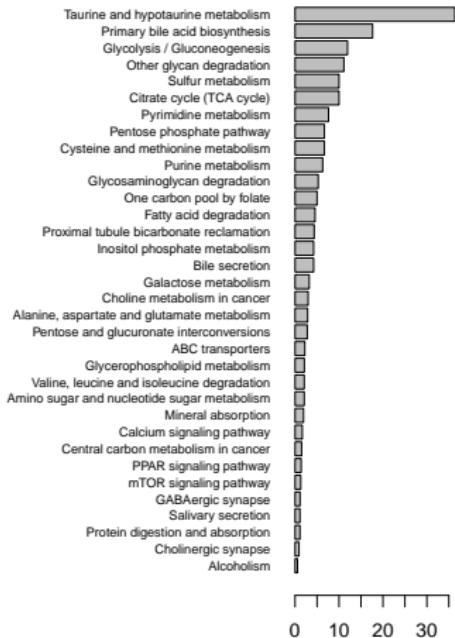


Tibolone Effects in Inflamed Astrocytes

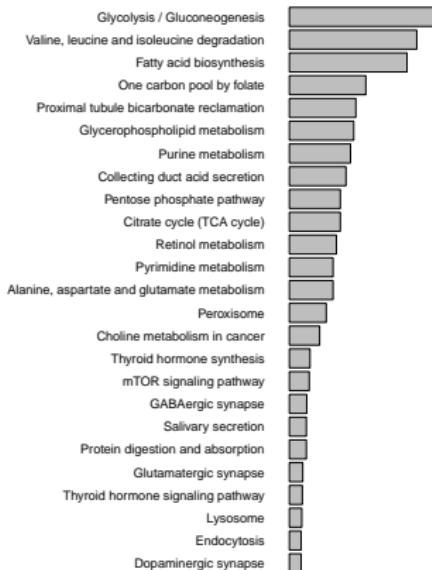


Tibolone Metabolic Changes in Inflamed Astrocytes

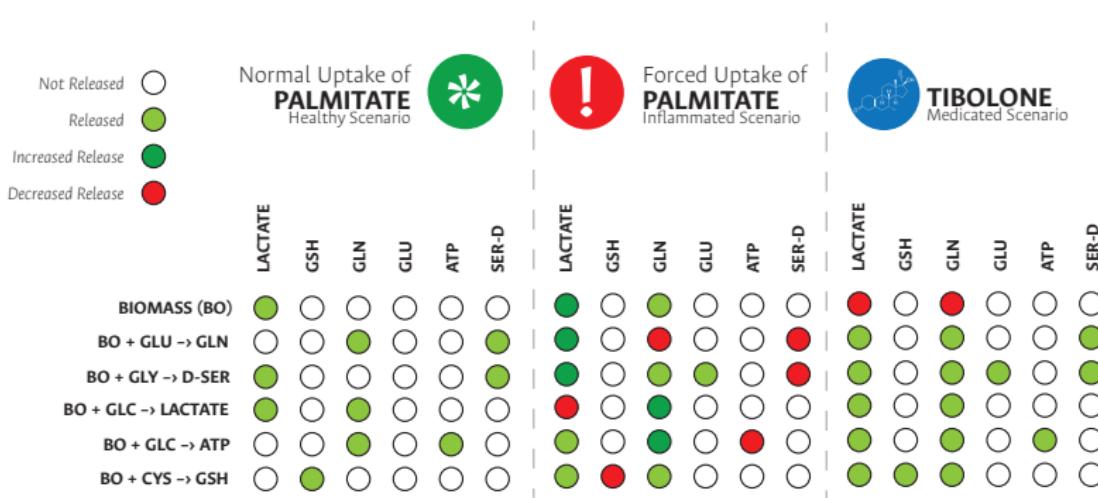
Pathway % Activation



Pathway % Inactivation



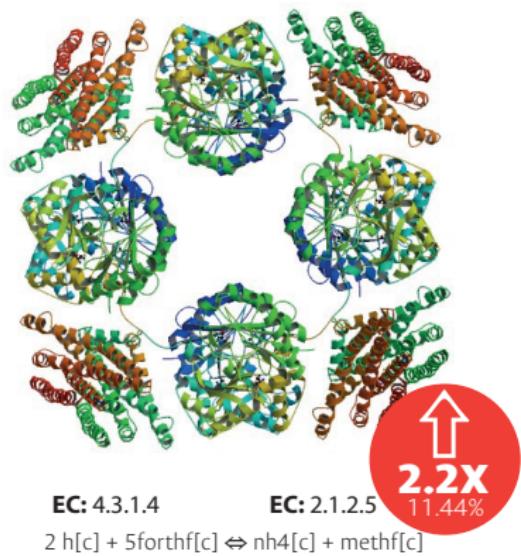
Gliotransmitters Release Rate



ProInflammatory Enzymes

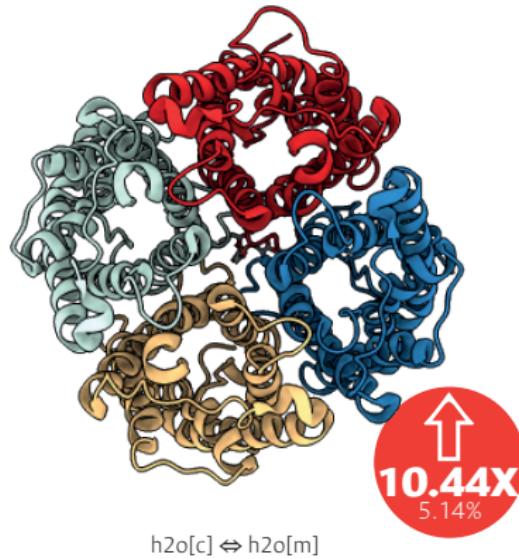
FTCD

FormimidoylTransferase CycloDeaminase



H2Otm

H2O Transport Mitochondrial



74 Anti inflammatory Enzymes



Tibolone Related Enzymes

r0739

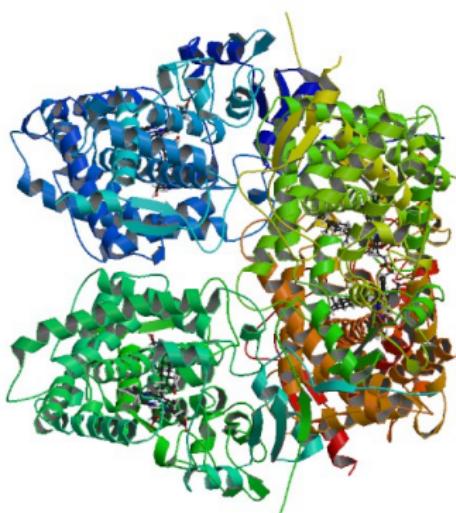
Alcohol Dehydrogenase 1 - 7



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



Pontificia Universidad Javeriana
5 - 8 October - Bogotá, Colombia

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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