A Kappa model for hepatic stellate cells activation by TGFB1

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A Kappa model for hepatic stellate cells activation by TGBF1

GT Bioss 2021

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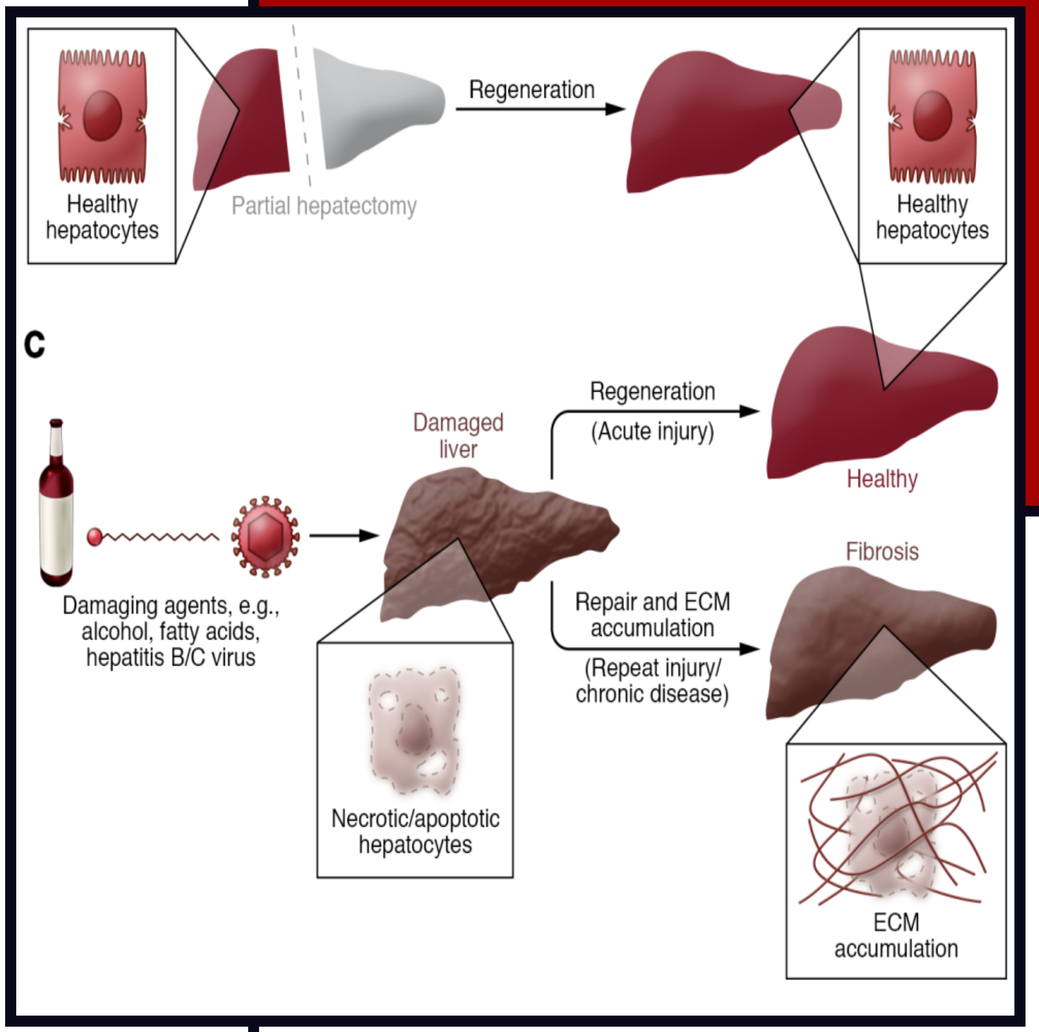
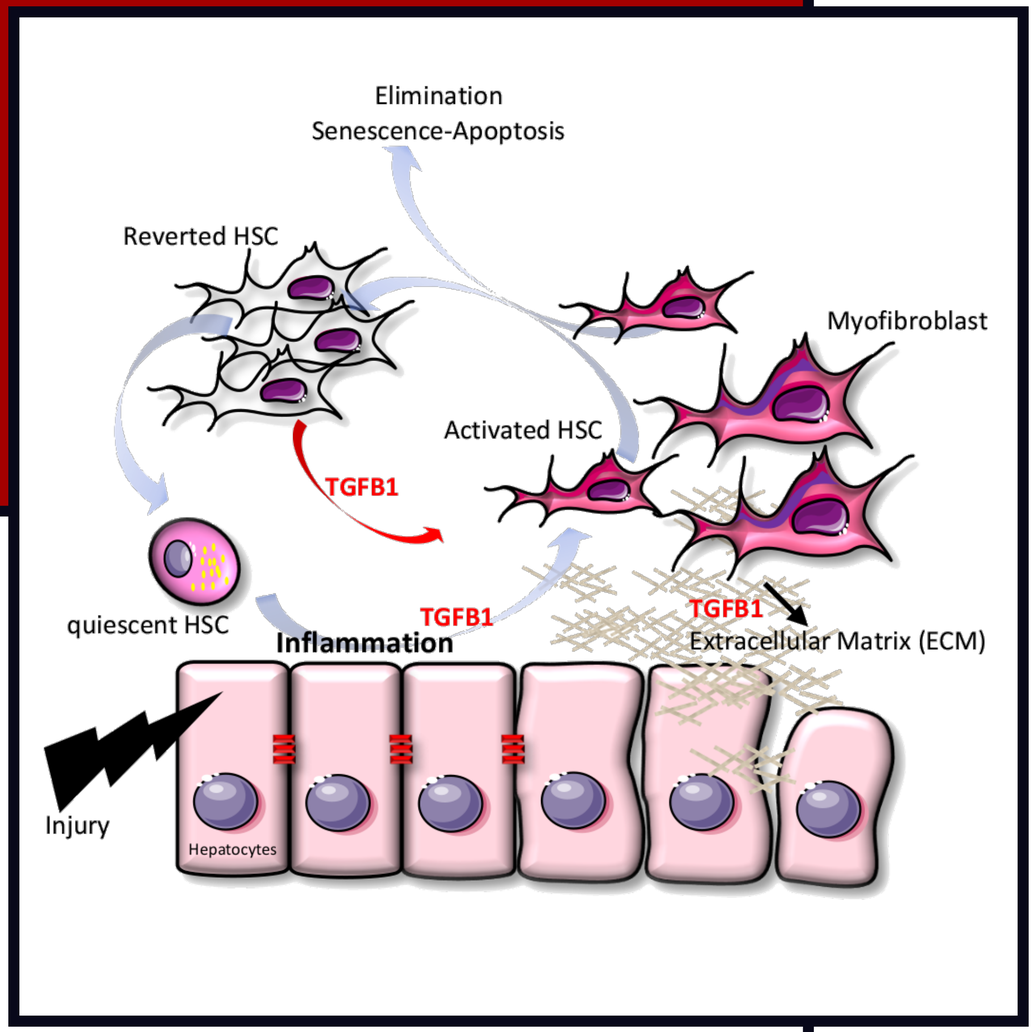
Liver Fibrosis

- Multiples causes
- Extracellular matrix (ECM) accumulation
- Reversible



Cordero-Espinoza The Journal of clinical investigation 128.1 (2018): 85-96

Hepatic Fibrosis



Liver injury induces inflammatory response leading to release of TGFB which activates quiescent qHSC towards a MFB phenotype promoting tissue repair

MFB are eliminated either by apoptosis/senescence pathways or by inactivation towards a inactivated HSC state.
The inactivated iHSC can be reactivated upon TGF-b stimulation in a faster manner

Upon chronic injuries, the dynamics of the system is modifief and MFB escaped to the elimination pathways leading to ECM accumulation

Objectives

A) Develop a Kappa-based model to analyze the dynamics of hepatic stellate cells upon TGF-beta stimulation

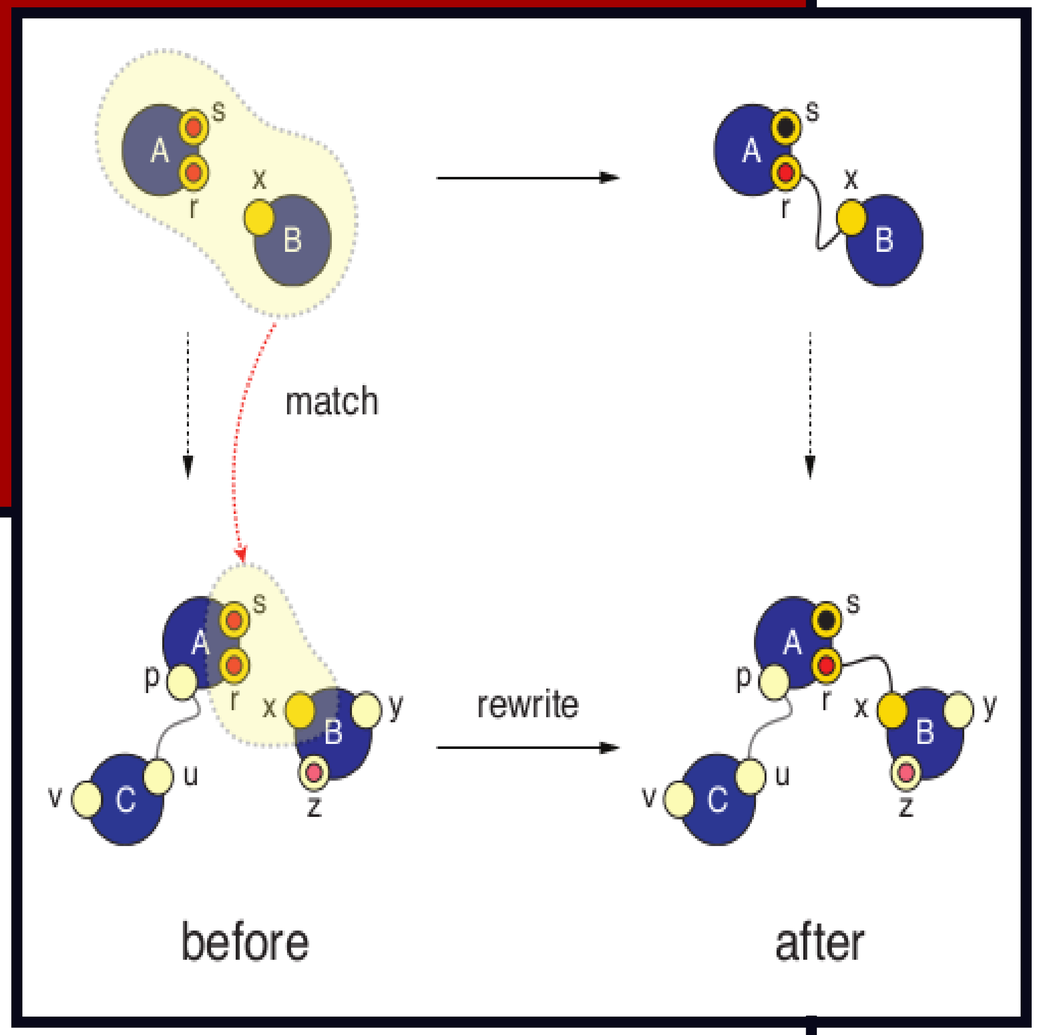
B) Identify the regulators of equilibrium between repair and fibrosis by integrating the matrix environment

C) While the equilibrium breaking is clearly the fibrosis threshold, founding target inhibiting TGF-β is the final aims of this project

Kappa

Walter Fontana
Pierre Boutillier
Jerome Feret
Jean Krivine

https://kappalanguage.org/



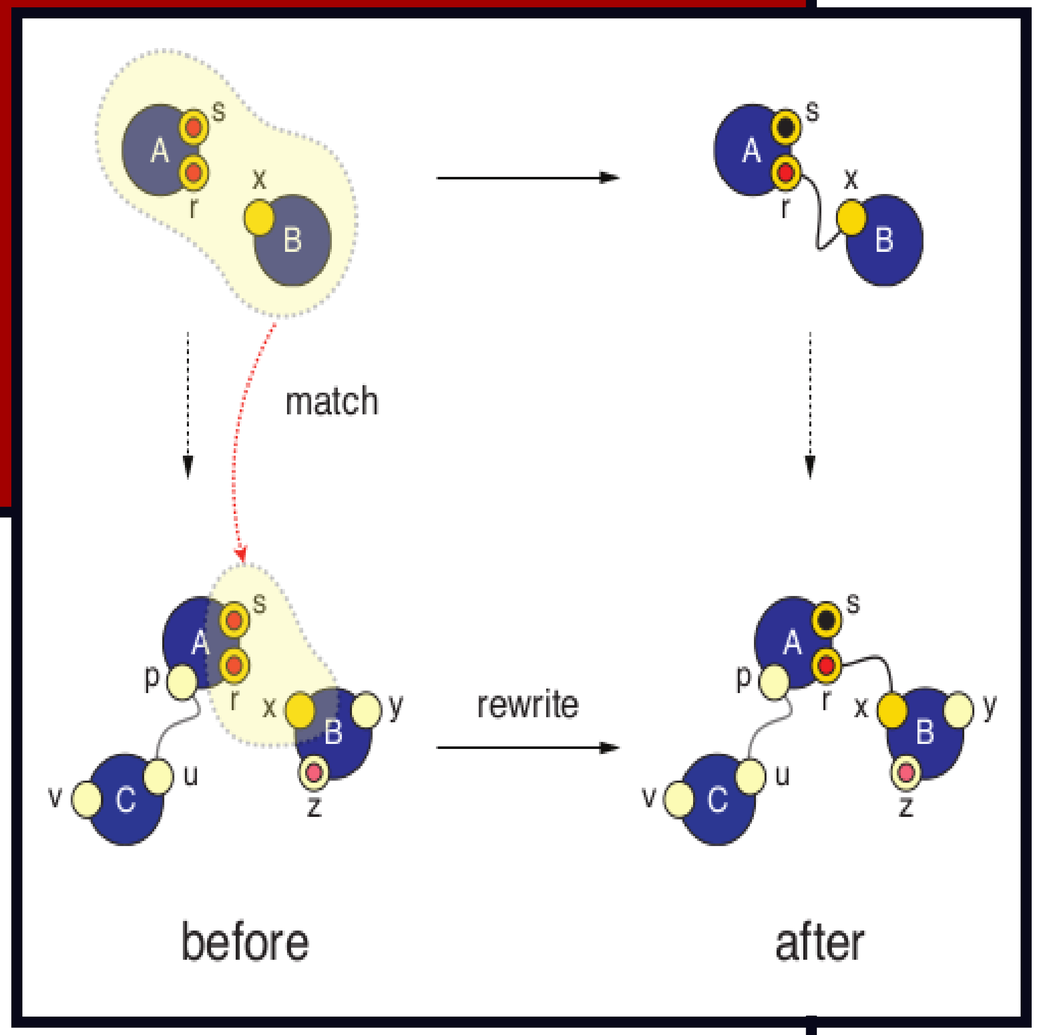
Kappa

Rules based language created in 2004 (V.Damos)

Rules describe *agent* behavior modifing *state* of *site* of this *agent*.

Exemple:

s site of the agent A will become red and the site r will be bound to the site x of B.



Kappa

Rules based language using agent

Rules based VS Agent Based

Rules based	Agent Based
only information on the modified part	all conformations of the agents or the processus must be describe

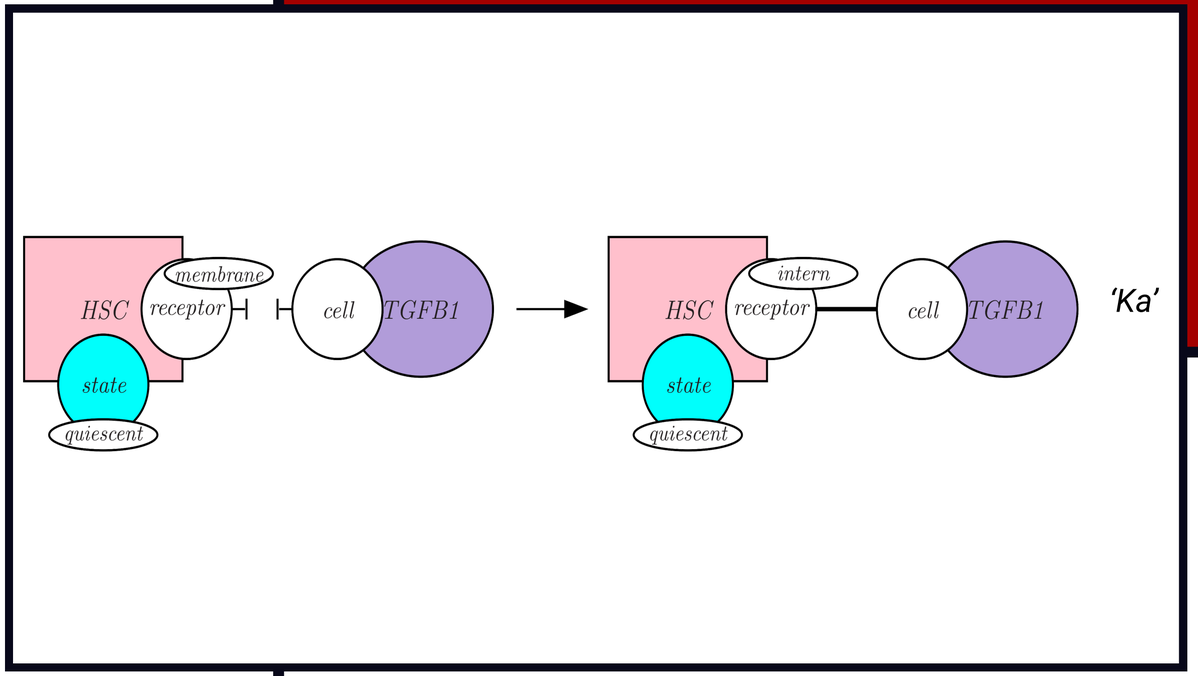
Kappa

Kappa is a graphs rewritting language, meaning a model is a graph where *Agent* are nodes and *interaction* are edges

A model is a graph composed of multiple graphs modified each time a rules is fired

Chemistry syntaxe:

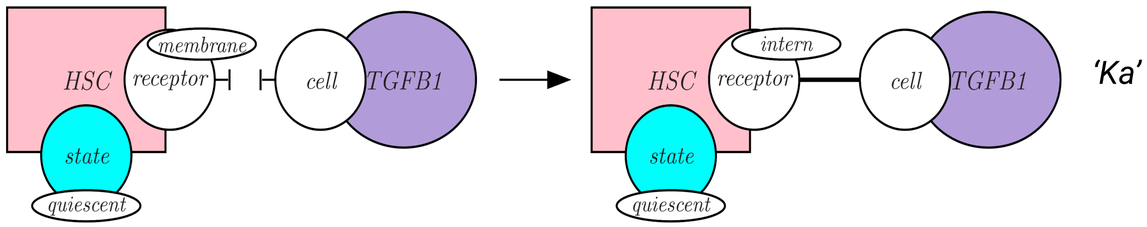
A + B -> C + D



Kappa rules

Rule describing TGFB binding to quiescent cell.

Interaction possible only if occurences of HSC have their receptors in a membrane state and free.




```
'HSC(state{quiescent} TGFBR1_2{membrane}[.]), TGFB1(cell[.] state{active})
-> HSC(state{quiescent} TGFBR1_2{intern}[1]), TGFB1(cell[1] state{active}) @ 'Ka'
```

Kappa Tools

KaSim

Stochastic Simulator using Gillespie algorithm.

KaSa

Static analyzer gives informations on:

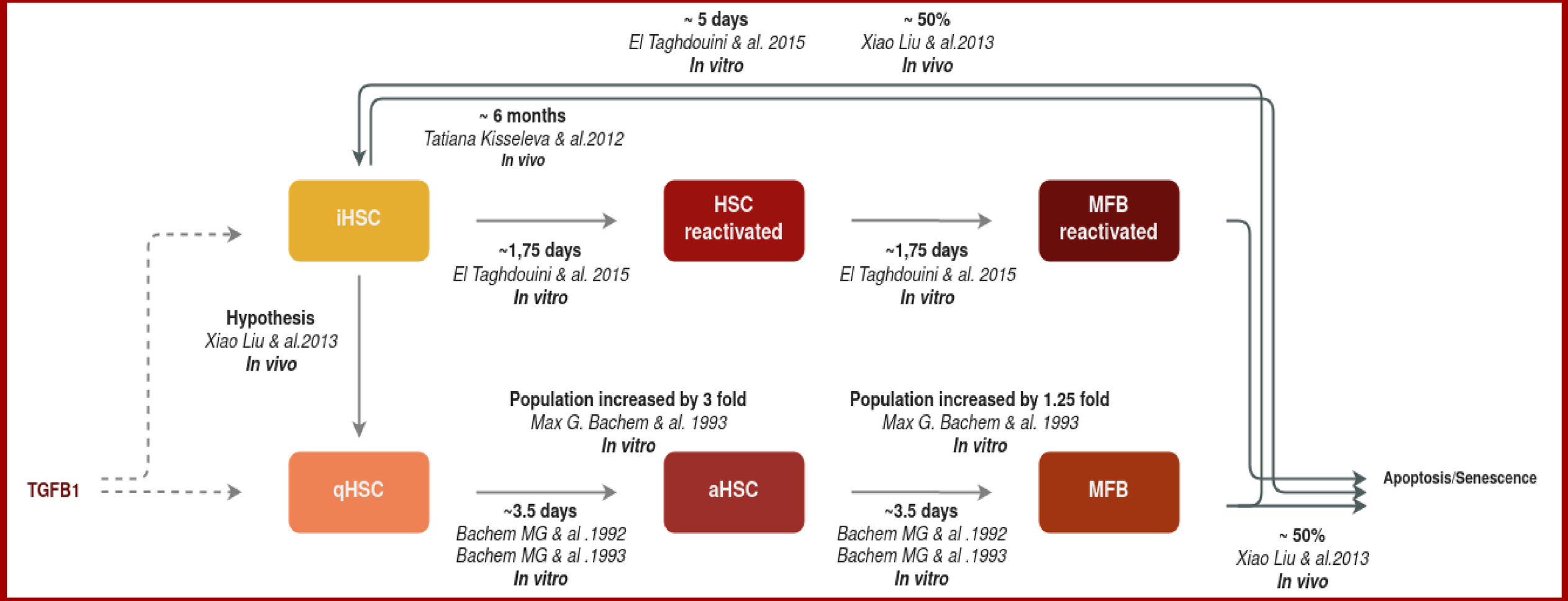
- link between *agents*,
- Impact of the state of site on link
- double link formation

Causality Analyzer

Understanding the impact between rules, what conditions must be met to allow another rule to be triggered.

Spatial Kappa

Extension introducing spatial information and compartmentalization in Kappa


~ 5 days
El Taghdouini & al. 2015
In vitro
~ 50%
Xiao Liu & al.2013
In vivo
~ 6 months
Tatiana Kisseleva & al.2012
In vivo
iHSC
HSC reactivated
MFB reactivated
~1,75 days
El Taghdouini & al. 2015
In vitro
~1,75 days
El Taghdouini & al. 2015
In vitro
Hypothesis
Xiao Liu & al.2013
In vivo
Population increased by 3 fold
Max G. Bachem & al. 1993
In vitro
Population increased by 1.25 fold
Max G. Bachem & al. 1993
In vitro
TGFB1
qHSC
aHSC
MFB
Apoptosis/Senescence
~3.5 days
Bachem MG & al .1992
Bachem MG & al .1993
In vitro
~3.5 days
Bachem MG & al .1992
Bachem MG & al .1993
In vitro
~ 50%
Xiao Liu & al.2013
In vivo

Model

- 1 Agent HSC with 7 state (quiescent, activated ...) and 1 site (TGFBR)
- 73 rules

Parameters:

Environnement
Number of HSC: 100
Number of receptor: 10000

qHSC
half life: 54.93d
activation speed: 1h

Proliferation
HSC proliferation half-time: 13.75h
MFB proliferation half-time: 886.9h

Activation
qHSC -> aHSC: 84h
aHSC -> MFB : 84h

MFB
half-life: 3.76d
Inactivation: 5d

iHSC
reactivation: 42h
iHSC half life: 54.93d

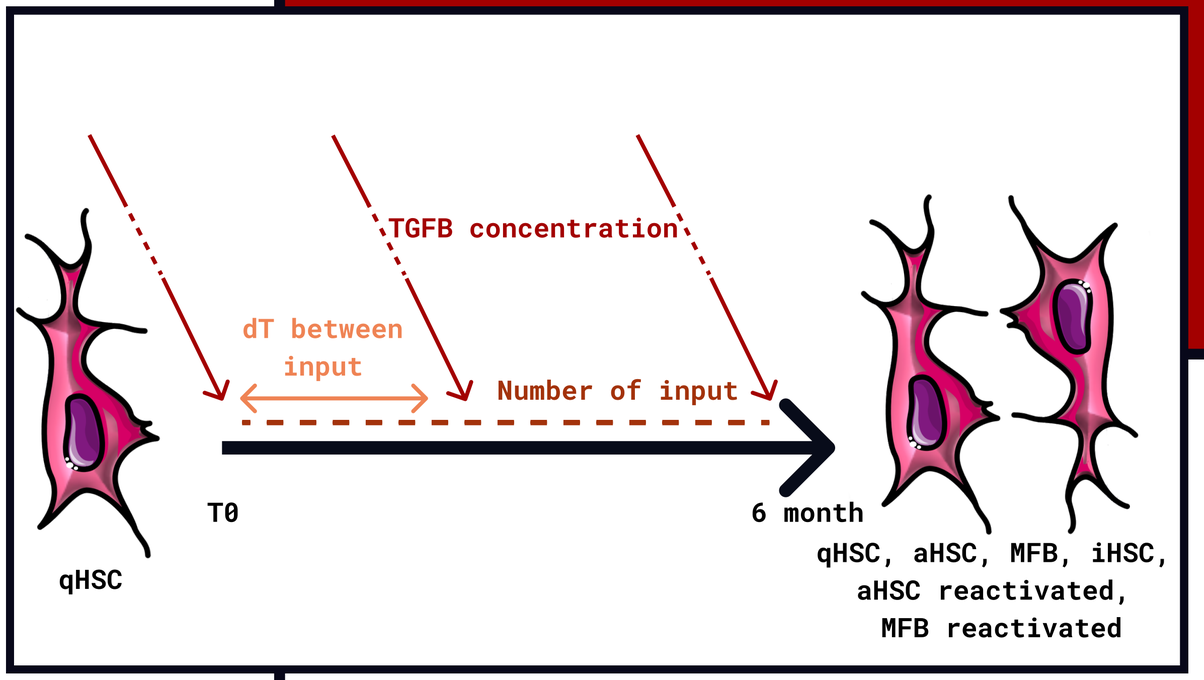
Receptor
Recycling rate: 30 min
Receptor production Rate: 4 min
Constitutive degradation rate: 36min
Ligand induced degradation rate :4 min

TGFB
TGFB1 half life 3min
TGBF wave: 5000 * number of HSC

Simulations protocol

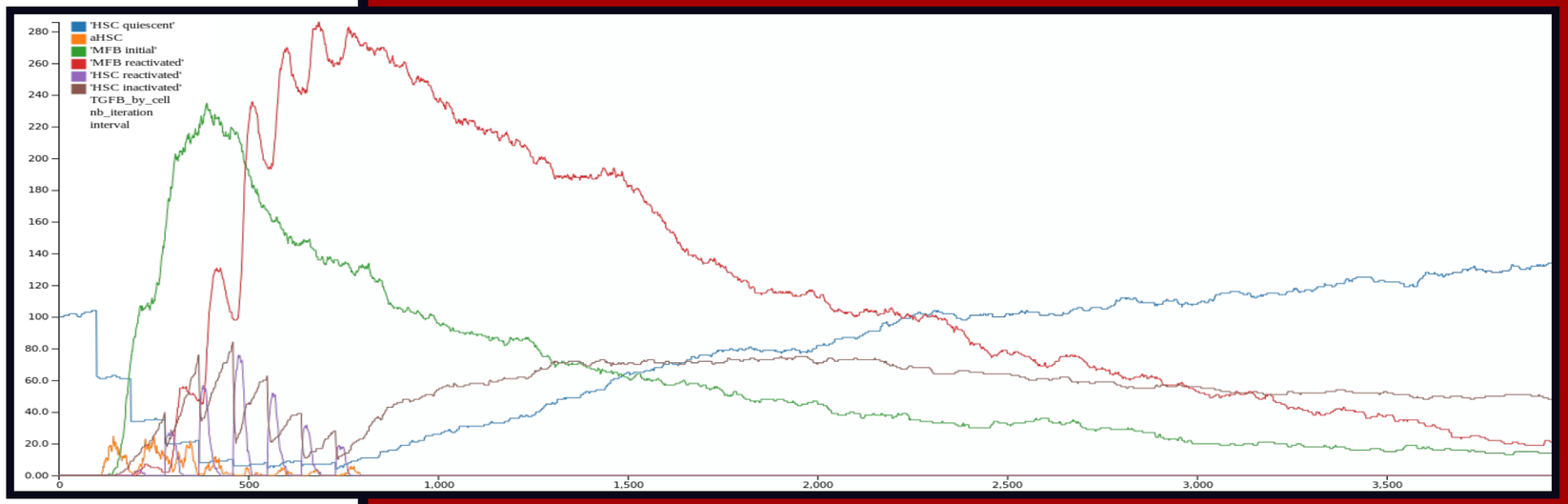
Perform multiple simulations to test the impact of the input

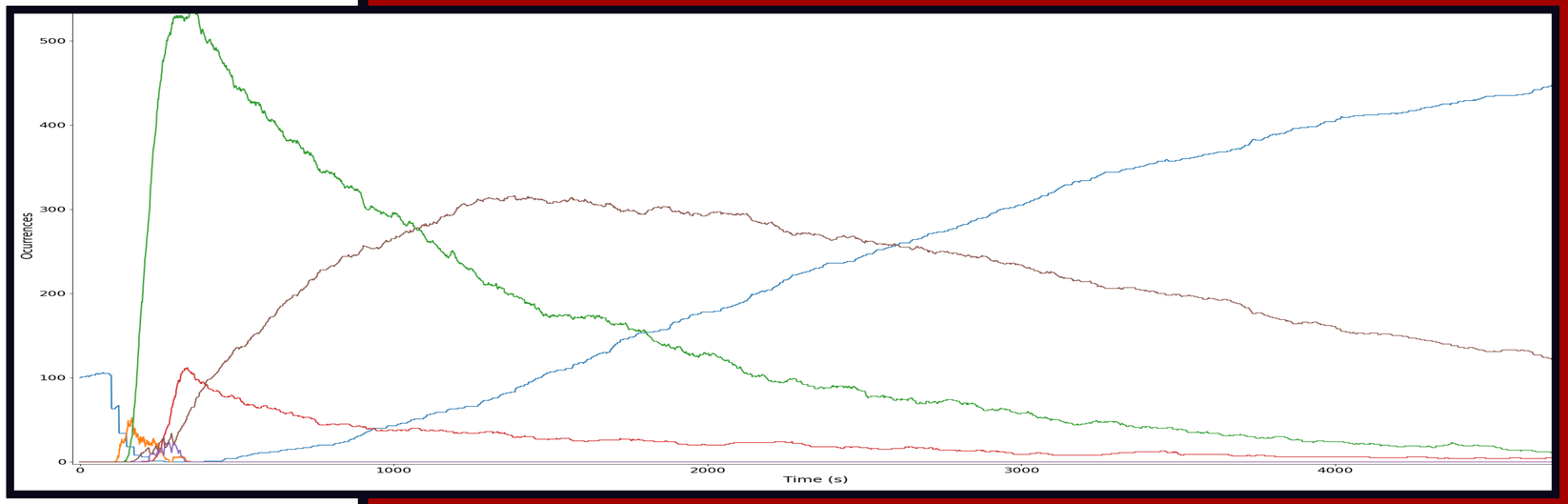
- TGFB concentration
- Frequence of TGFB input
- Number of TGFB input



Simulations

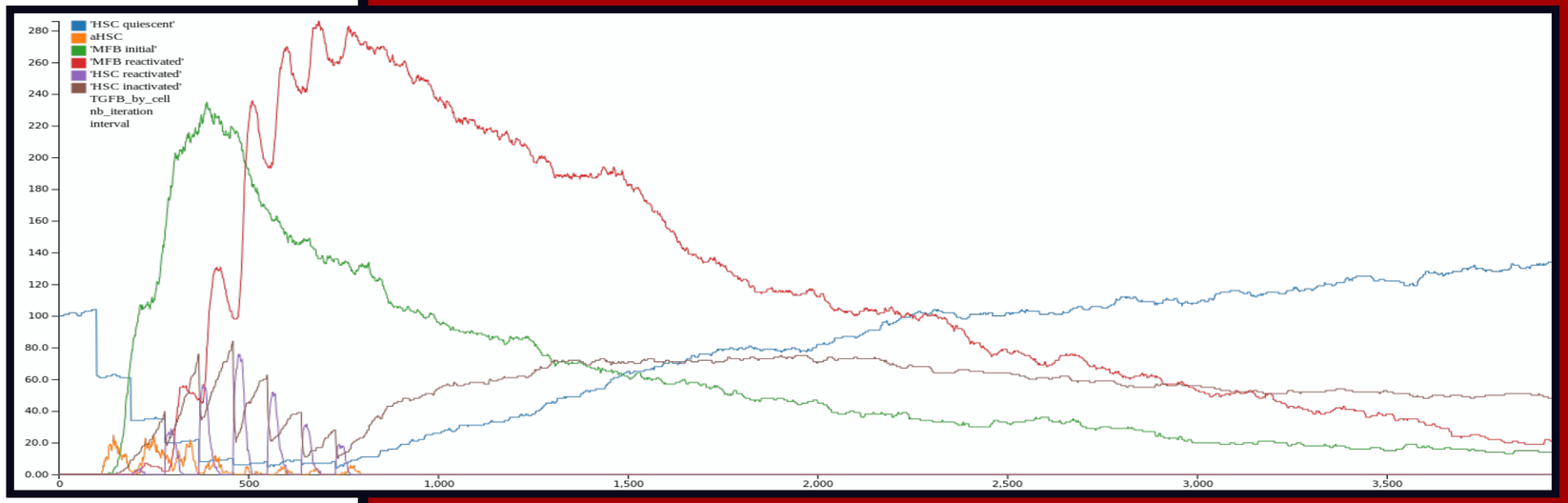
Parameters:
[TGFB]: 5000
number of input: 8
dT: 90h and 24h

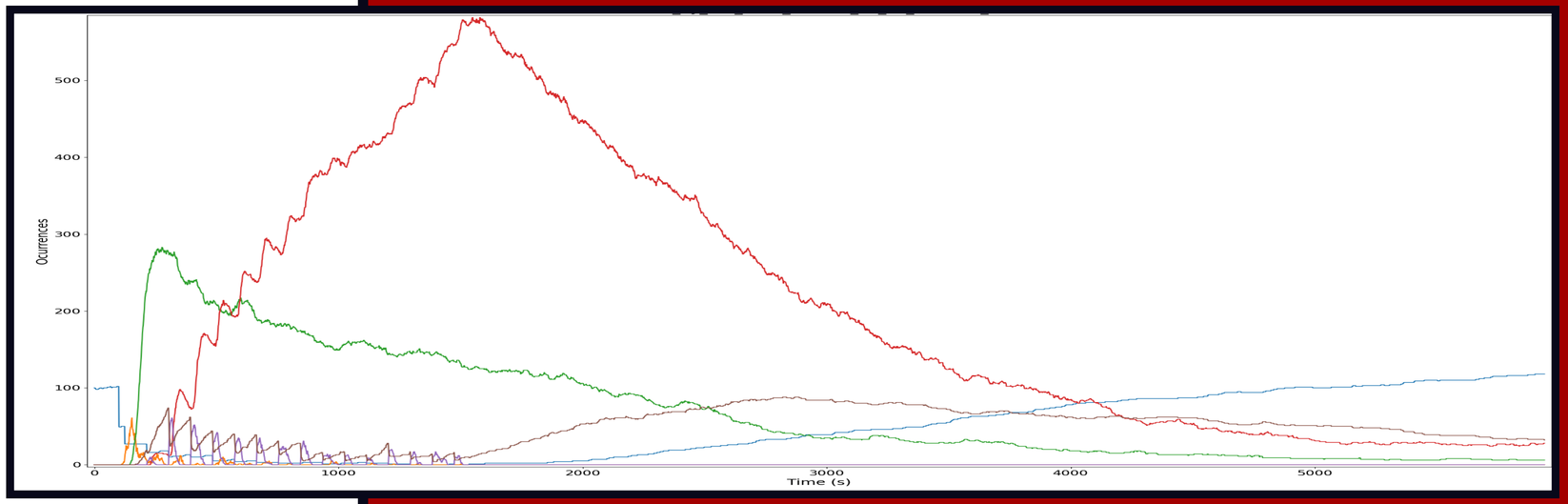




Simulations

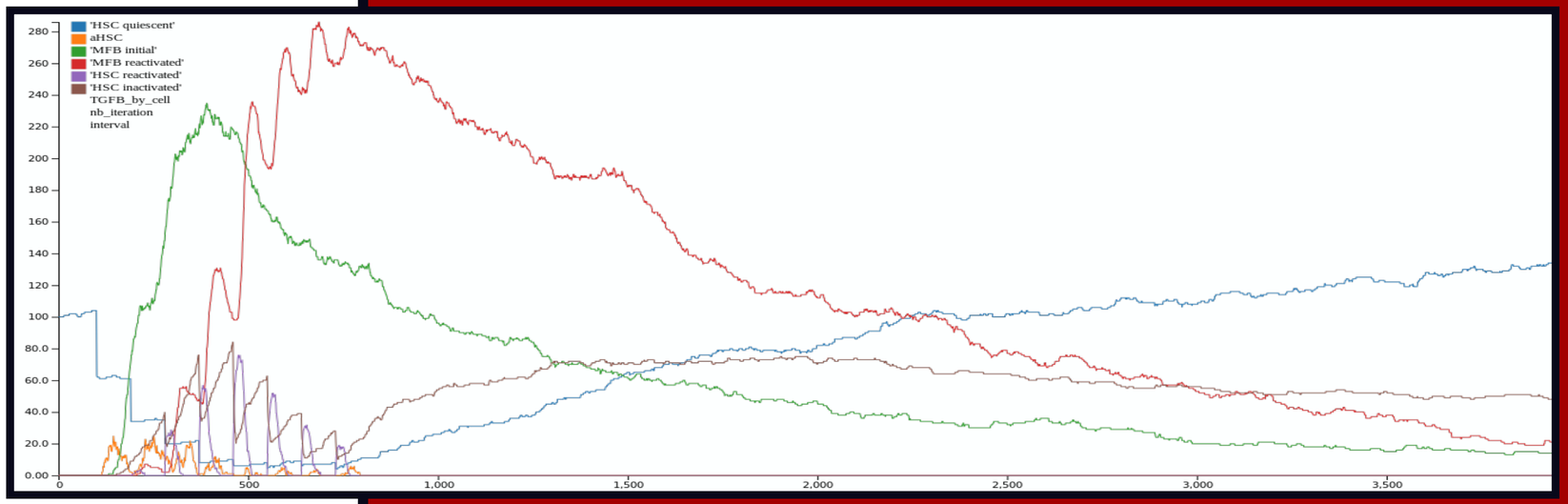
Parameters:
[TGFB]: 5000
number of input: 8 and 16
dT between input: 90h

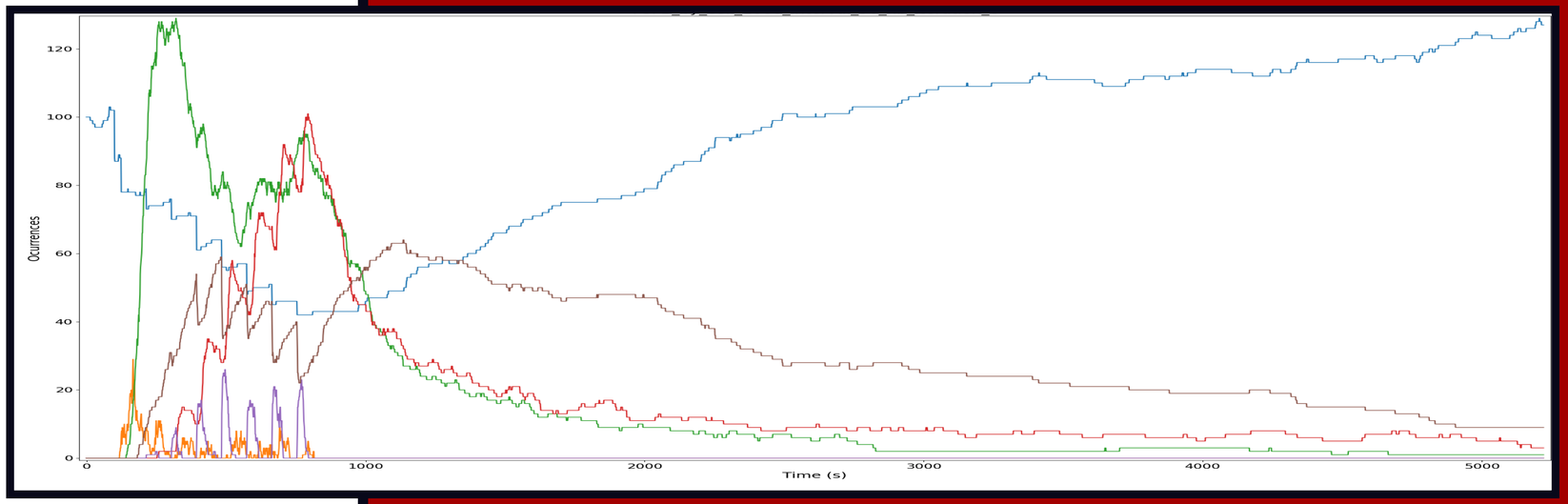




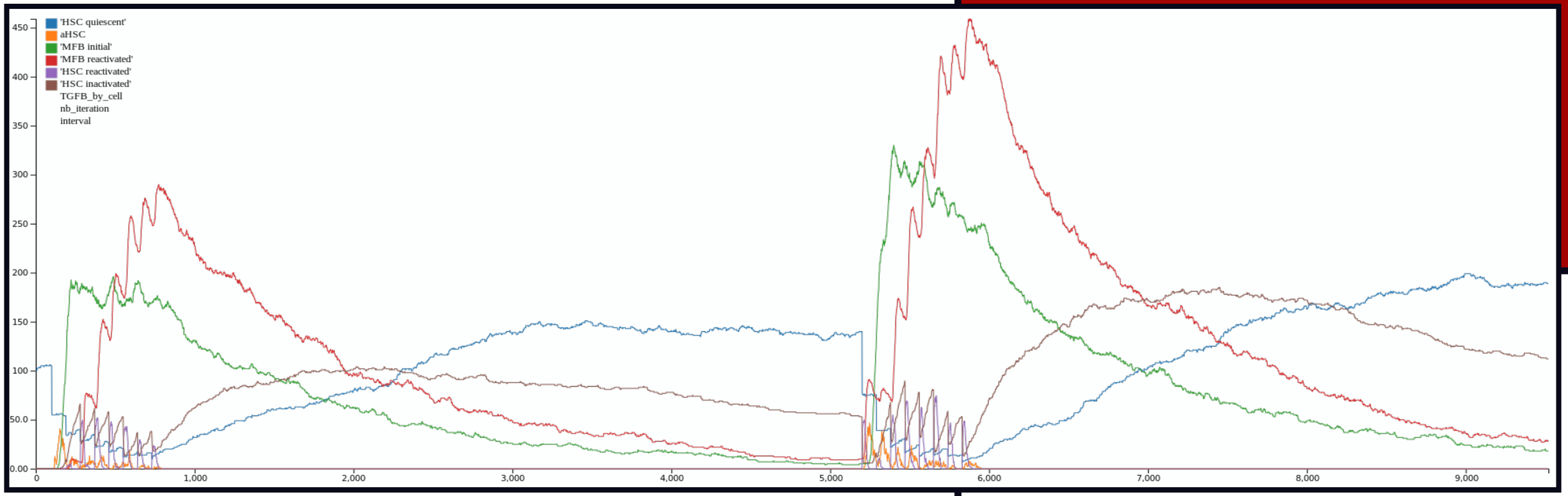
Simulations

Parameters:
[TGFB]: 5000 and 1000
number of input: 8
dT between input: 90h





Simulations



Parameters: [TGFB]: 5000, number of input: 8, dT between input: 90h

2 stimulations separate by 6 months

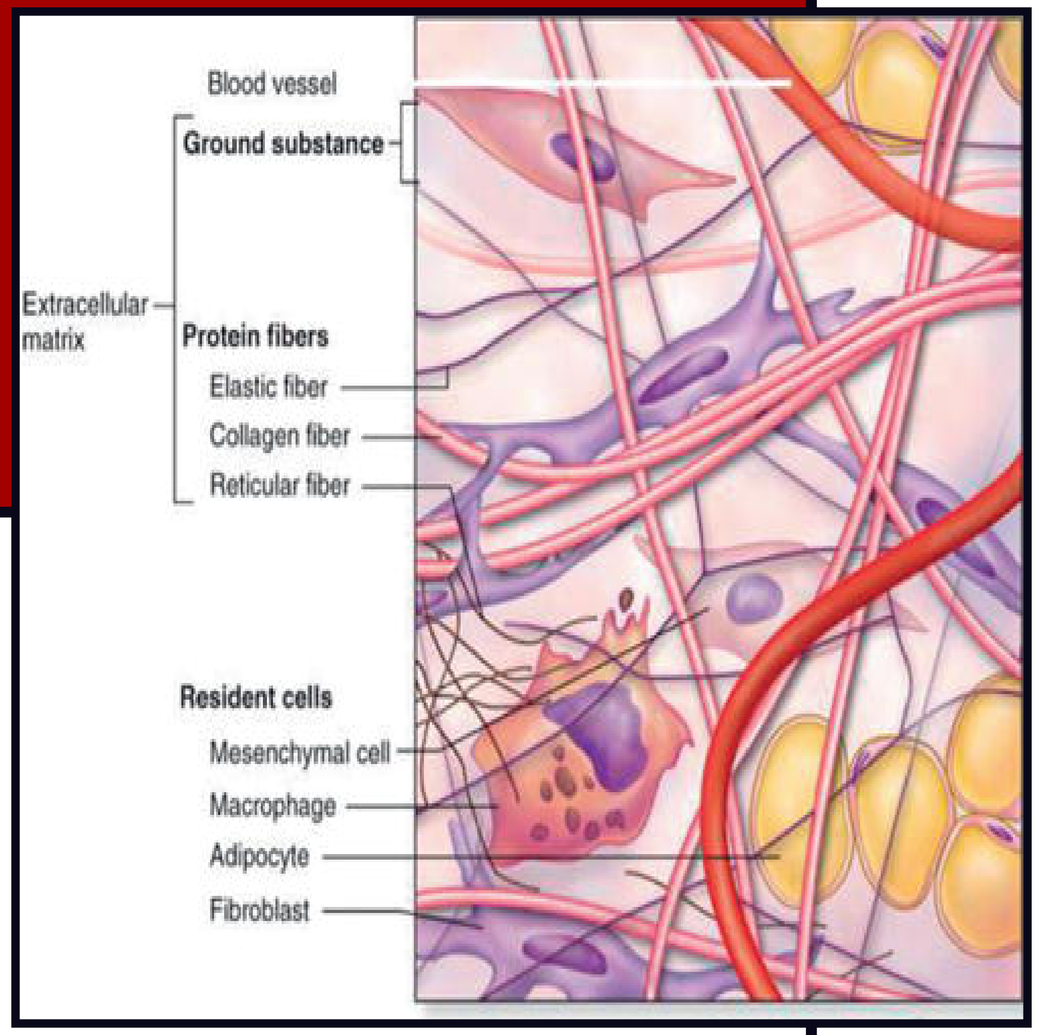
Analysis

- Despite the heterogeneity of the different source of data, we observed a recovery time consistent with the experimental data

- Chronic TGFb stimulation did not lead to accumulation of MFB that promote fibrosis

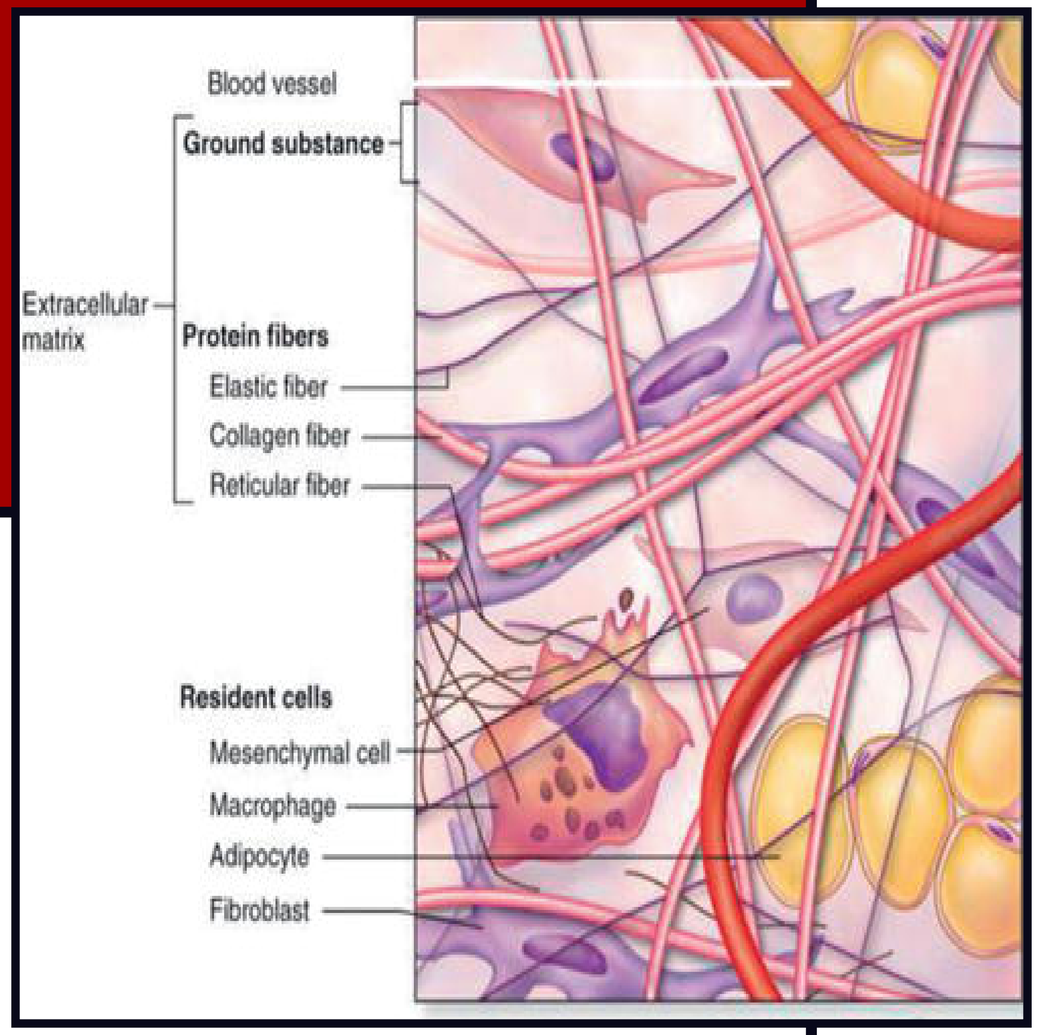
- Hypothesis; The extracellular matrix produced by activate hepatic stellate cells might contribute to the disequilibrium towards fibrosis

Extracellular Matrix



- provides physical support for cells
- establishes separation and maintenance of differentiated tissues
- regulates growth factors and receptor abundance
- maintains the level of hydration and the pH of the local environment

Extracellular Matrix



The components of ECM
- are mainly secreted by activated hepatic stellate cells
- the stiffness of ECM promotes activation of HSC
- the remodeling of ECM depends on protease activities also secreted by activated HSC
- increased stiffness of liver tissues is associated with the progression of fibrosis from stage 1 to stage 4

Perspectives

A) Integration of the mechanical effect of ECM on HSC activation by introducing the main driver of stiffness, the type I collagen that is produced by activated HSC and MFB

B) Comparative study of the use of molecules (TGFbeta receptor, collagen) as groups (token) or as individual agent. Computational challenge ?

Acknowledgements

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My supervisors

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Jérome Feret; Team Antique, Inria

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Octave Hazard; Team Antique, Inria

Thank you!

Any questions?

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