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## Modelling hepatic stellate cells activation by TGFB1 using Kappa language

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# A Kappa model for hepatic stellate cells activation by TGF $\beta$ 1

GT Bioss 2021

Matthieu Bougueon,<sup>1,2,3</sup> Pierre Boutillier, Jérôme Feret, Octave Hazard and Nathalie Theret.



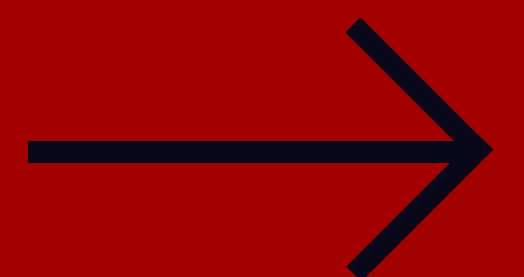
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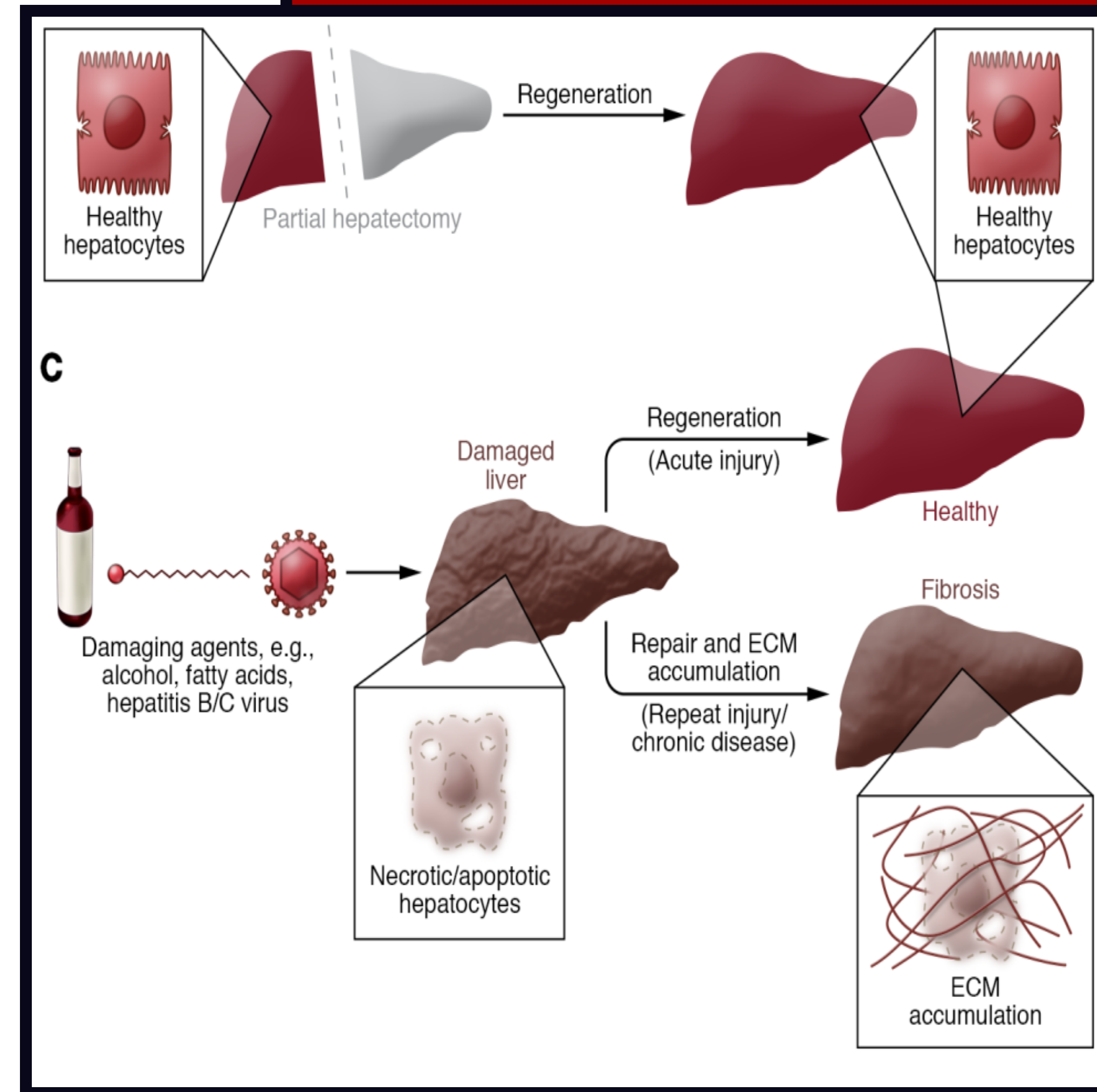


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# Liver Fibrosis

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



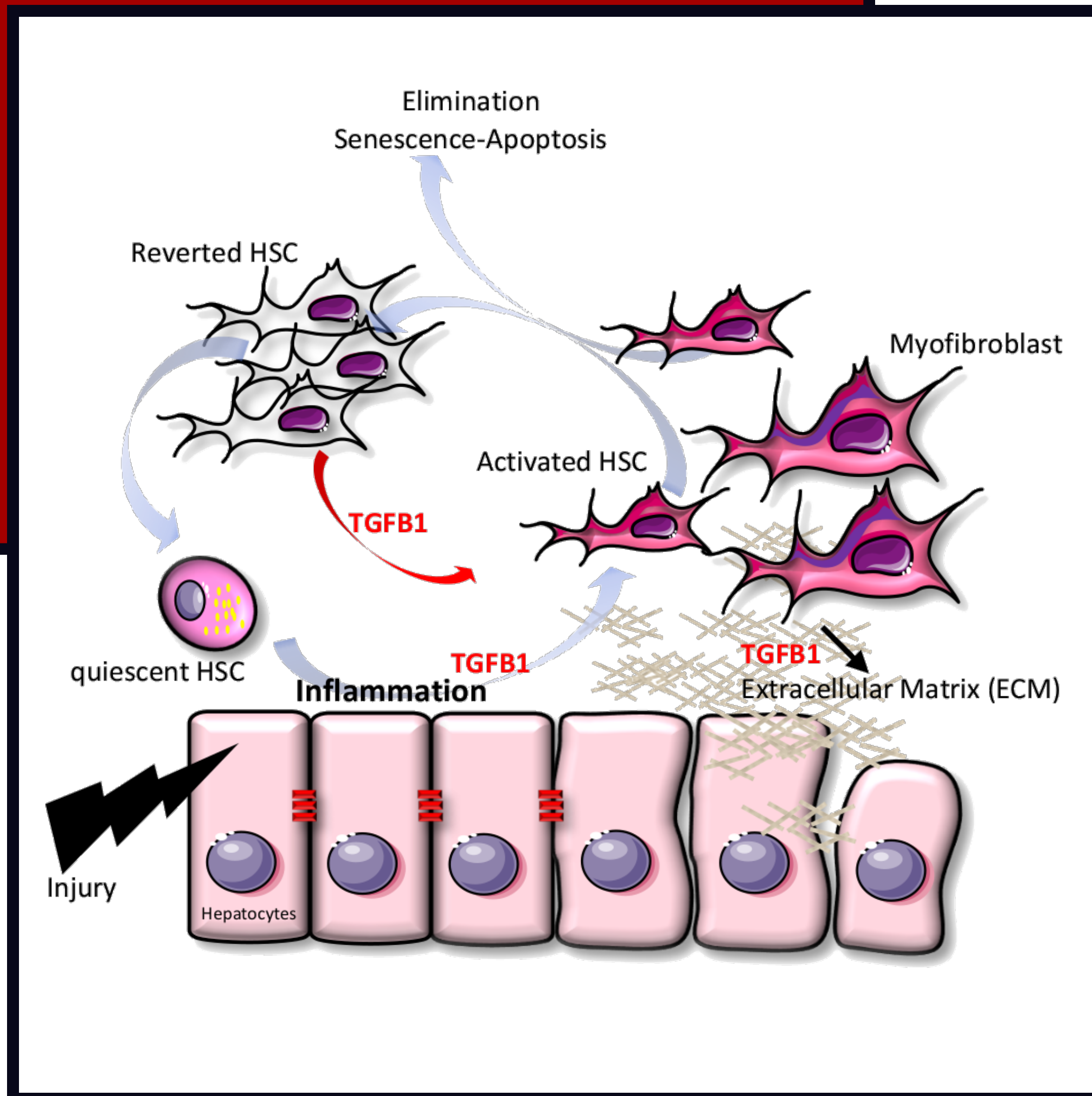
# Hepatic Fibrosis

Liver injury induces inflammatory response leading to release of TGF $\beta$  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- $\beta$  stimulation in a faster manner

Upon chronic injuries, the dynamics of the system is modified 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- $\beta$  is the final aims of this project

# Kappa

Walter Fontana  
Pierre Boutillier  
Jerome Feret  
Jean Krivine



<https://kappalanguage.org/>

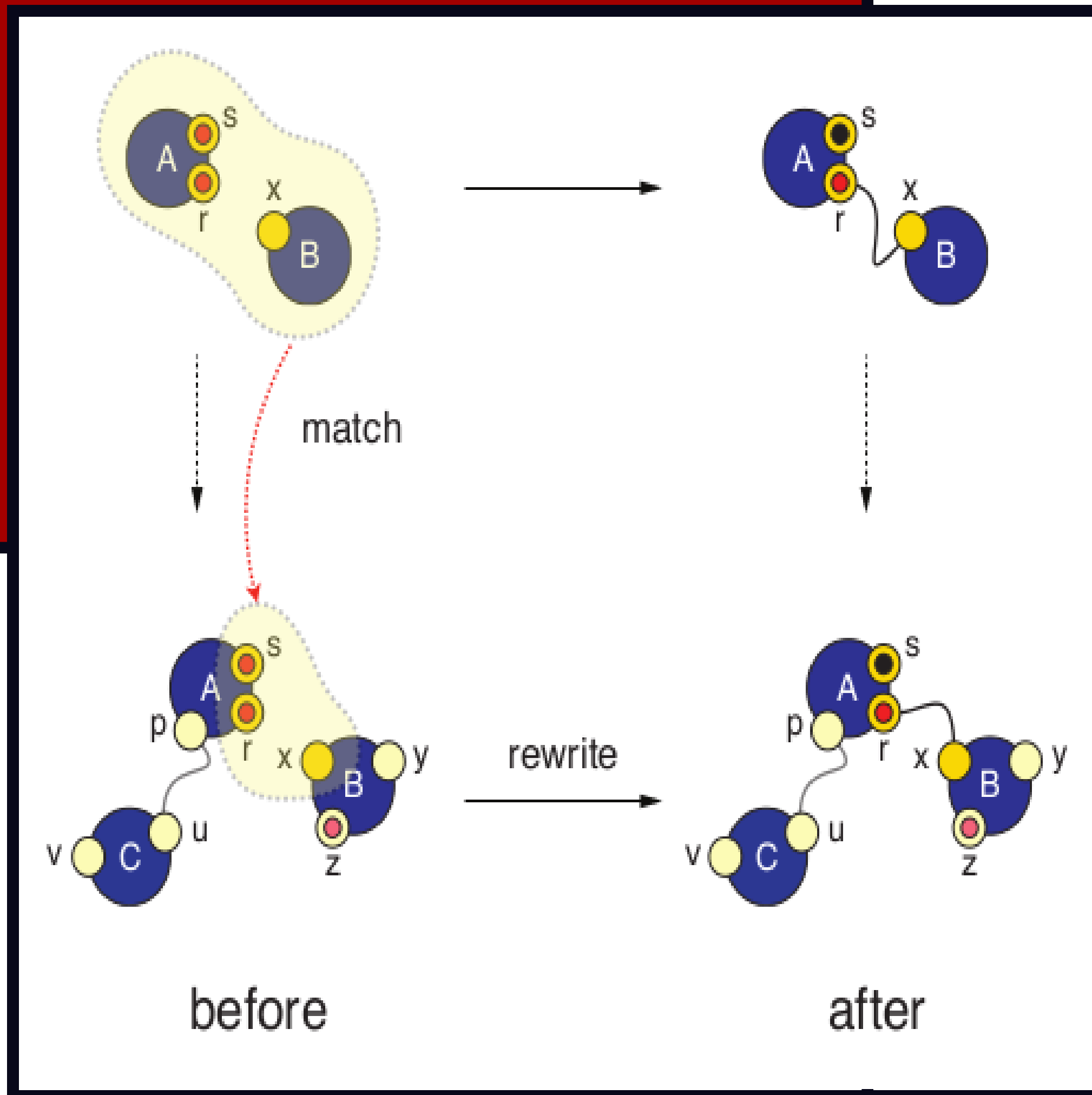
# Kappa

Rules based language created in 2004  
(V.Damos)

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

## **Example:**

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



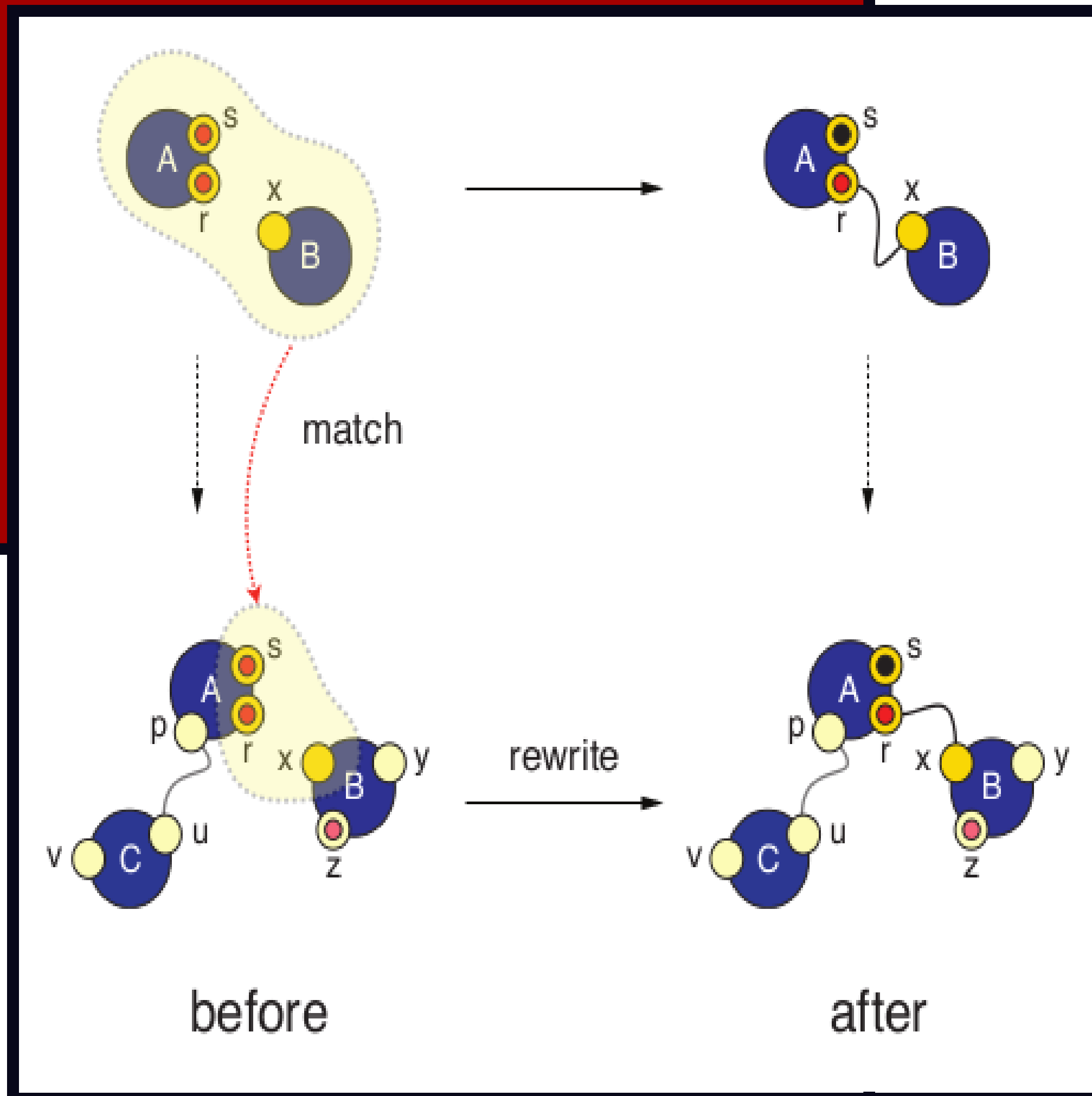
# Kappa

Rules based language using agent

Rules based VS Agent Based

only information  
on the modified  
part

all conformations  
of the agents or  
the processus  
must be describe



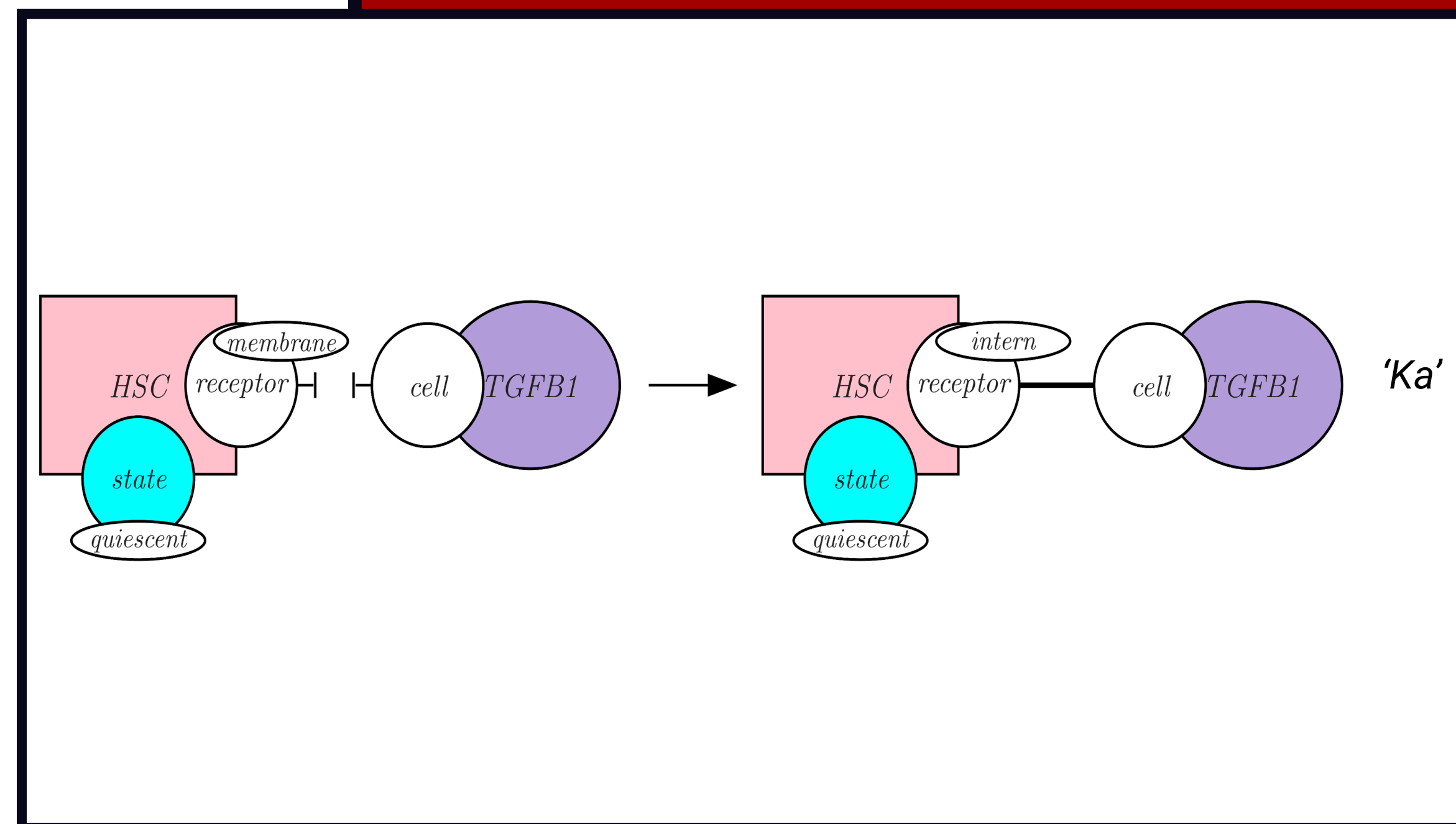


# Kappa

Kappa is a graphs rewriting 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

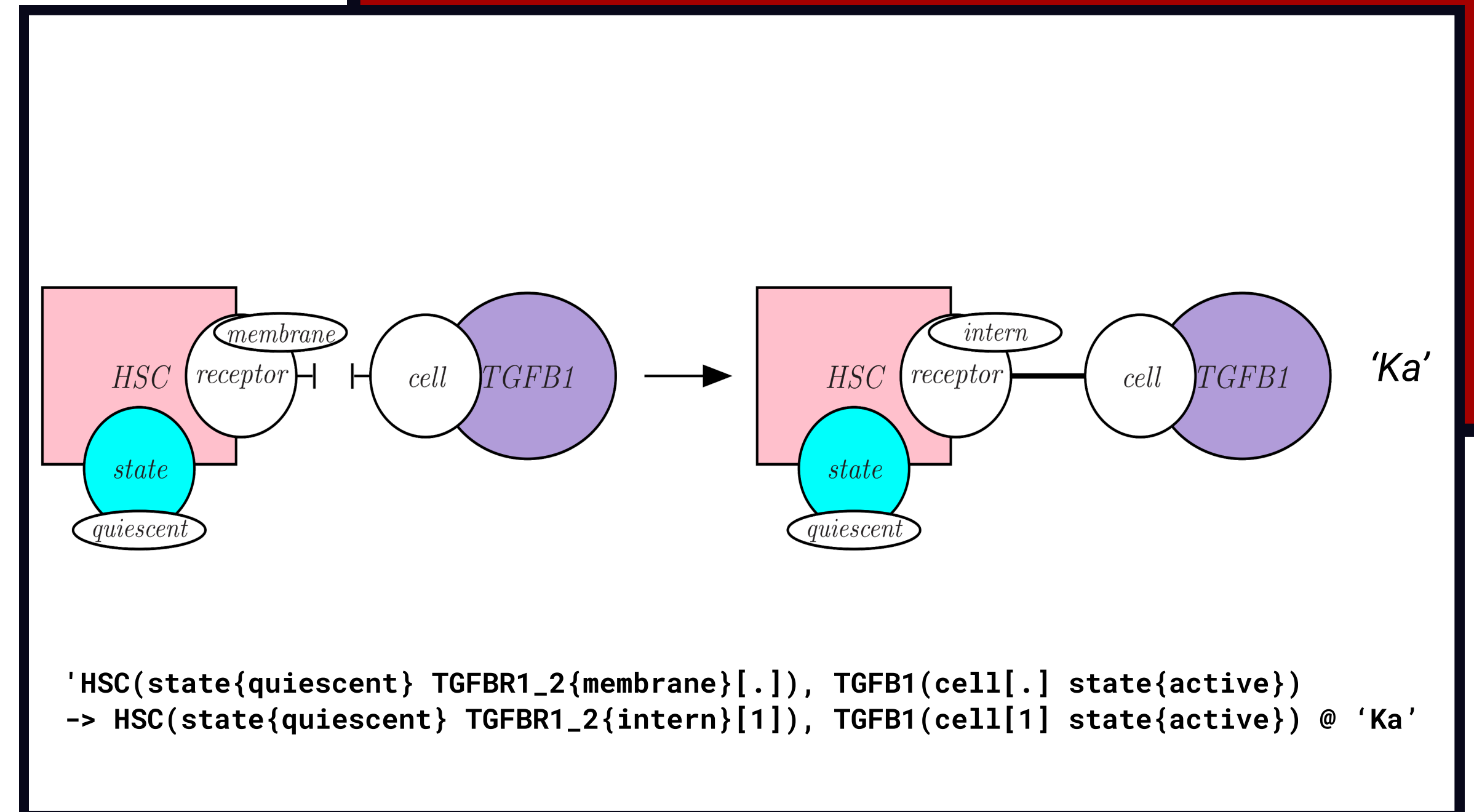
***Chemistry syntax:***



# Kappa rules

Rule describing TGFB binding to quiescent cell.

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



# Kappa Tools

## KaSim

Stochastic Simulator  
using Gillespie  
algorithm.

## KaSa

Static analyzer gives  
informations on:

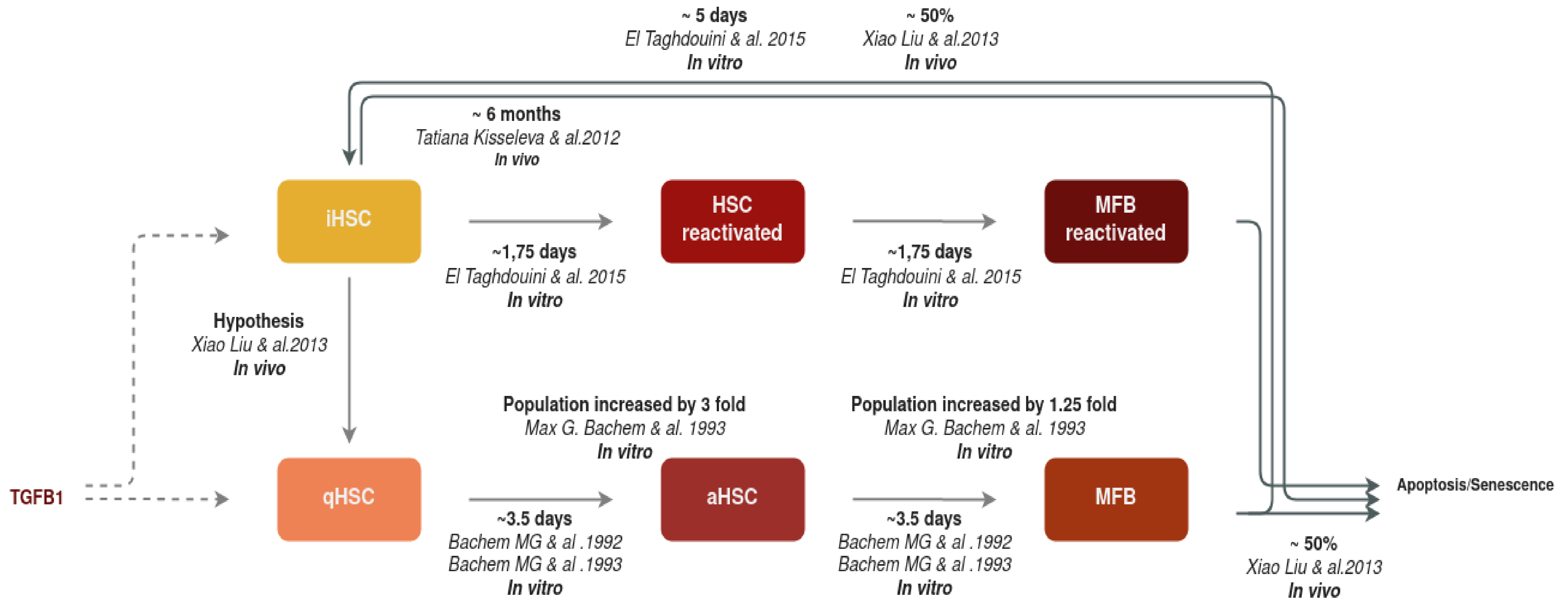
- link between *agents*,
- Impact of the state of  
site on link
- double link formation

## 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



# 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

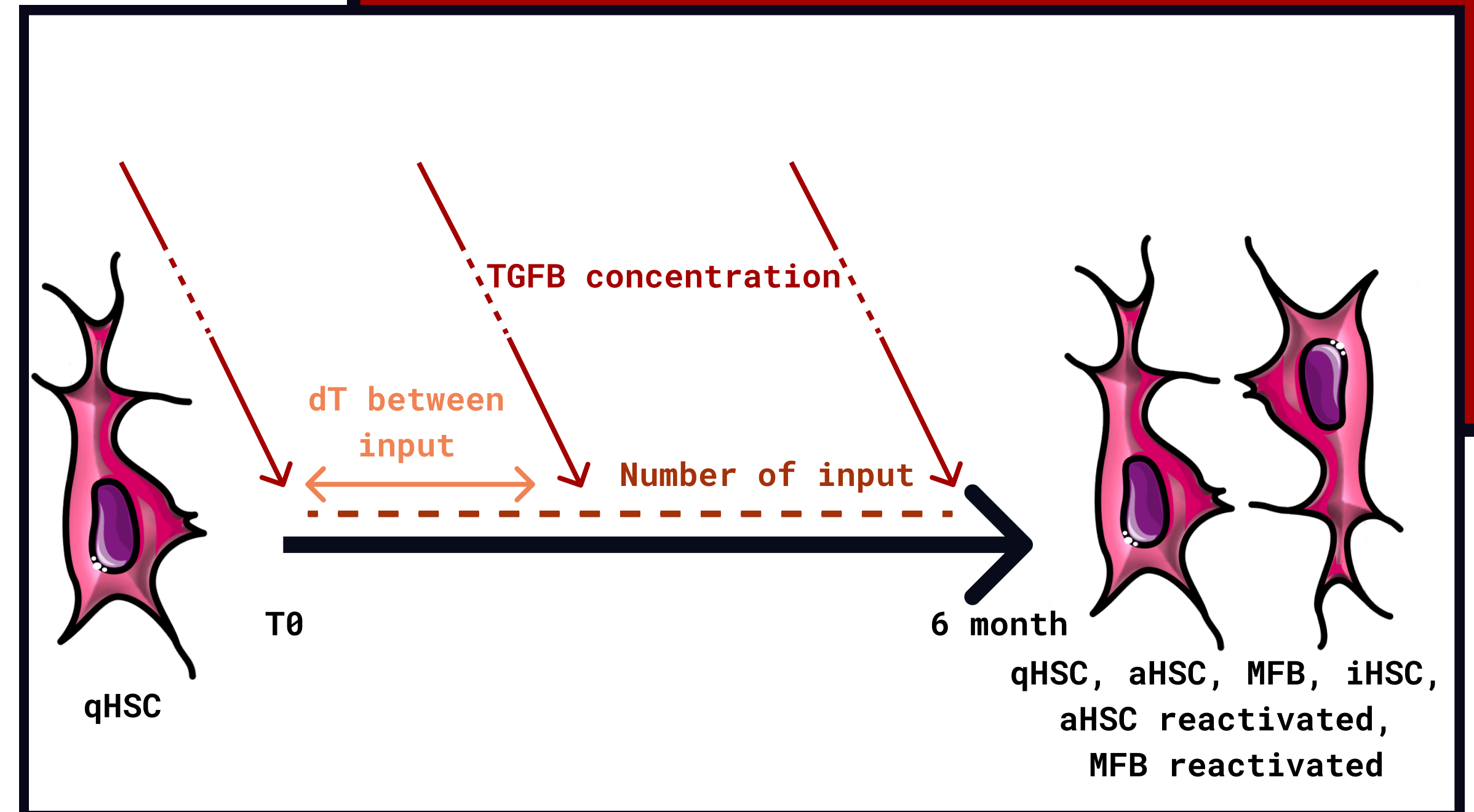
### TGFB

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

# Simulations protocol

Perform multiple simulations to test the impact of the input

- TGFB concentration
- Frequency of TGFB input
- Number of TGFB input



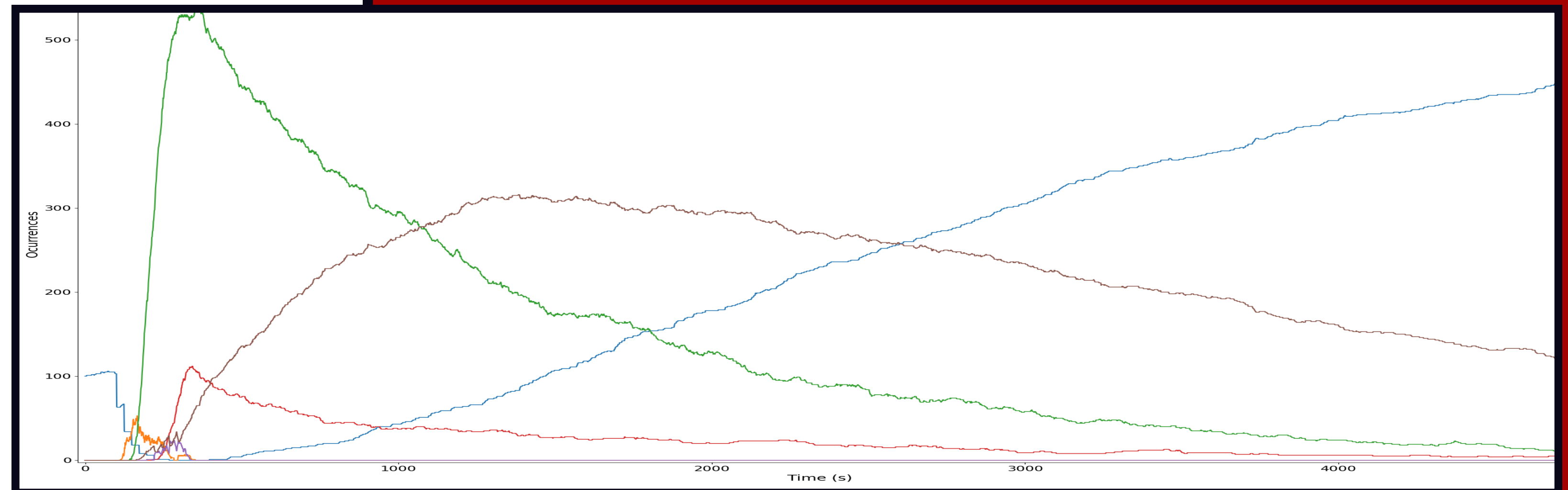
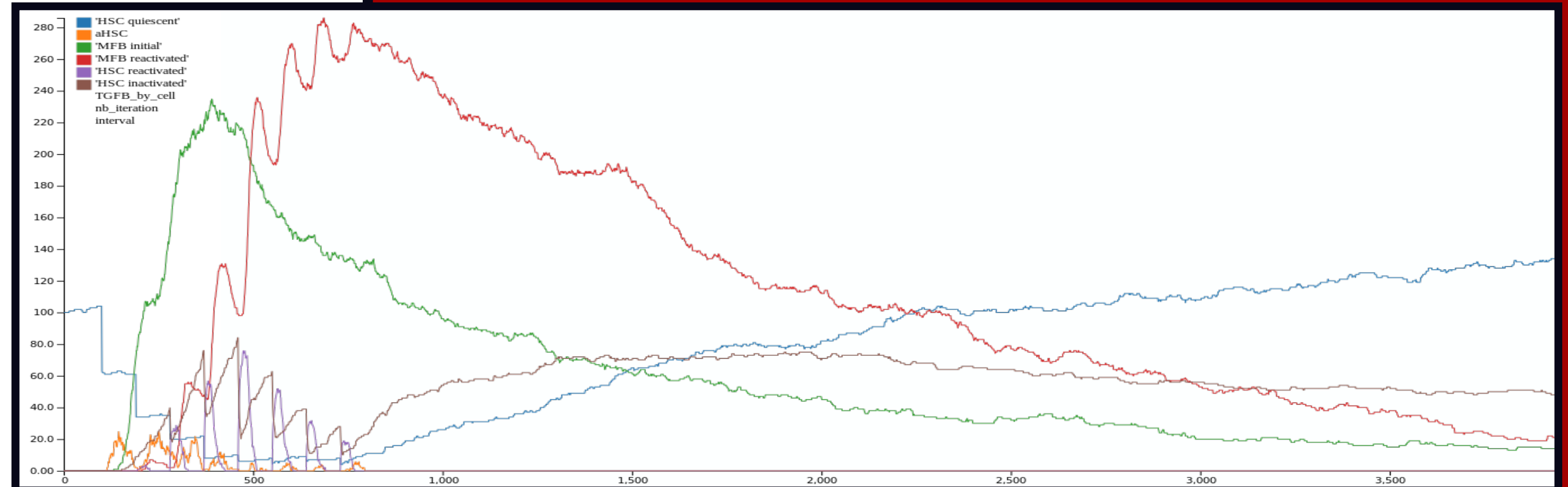
# Simulations

Parameters:

[TGFB]: 5000

number of input: 8

dT: 90h and 24h



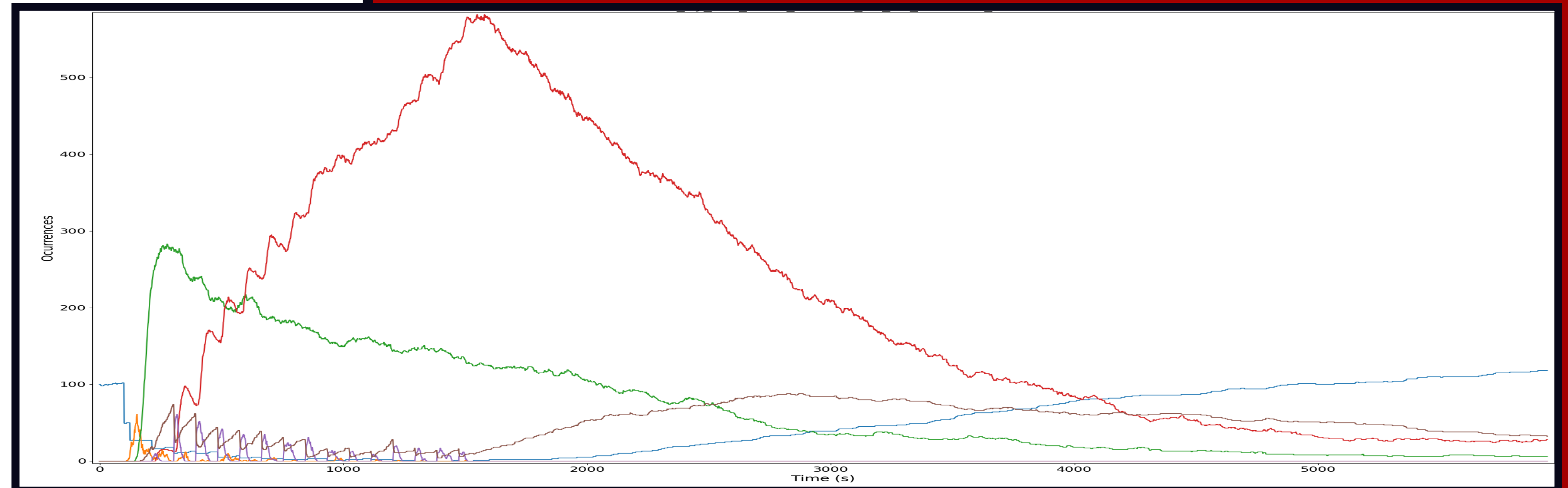
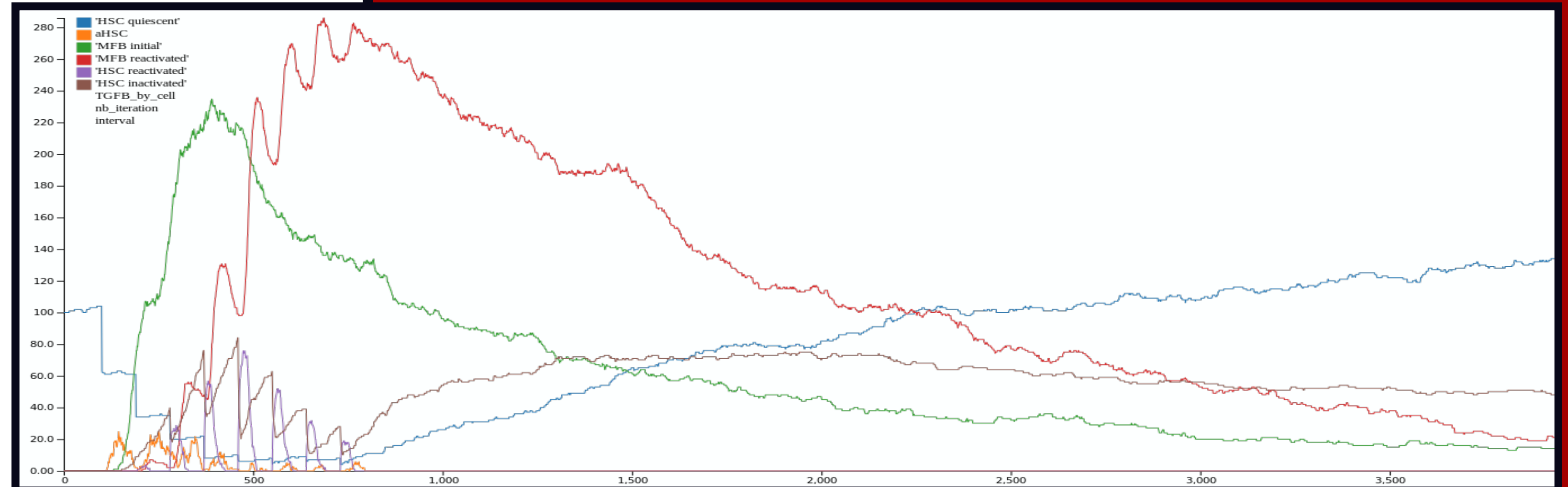
# Simulations

Parameters:

[TGFB]: 5000

number of input: 8 and 16

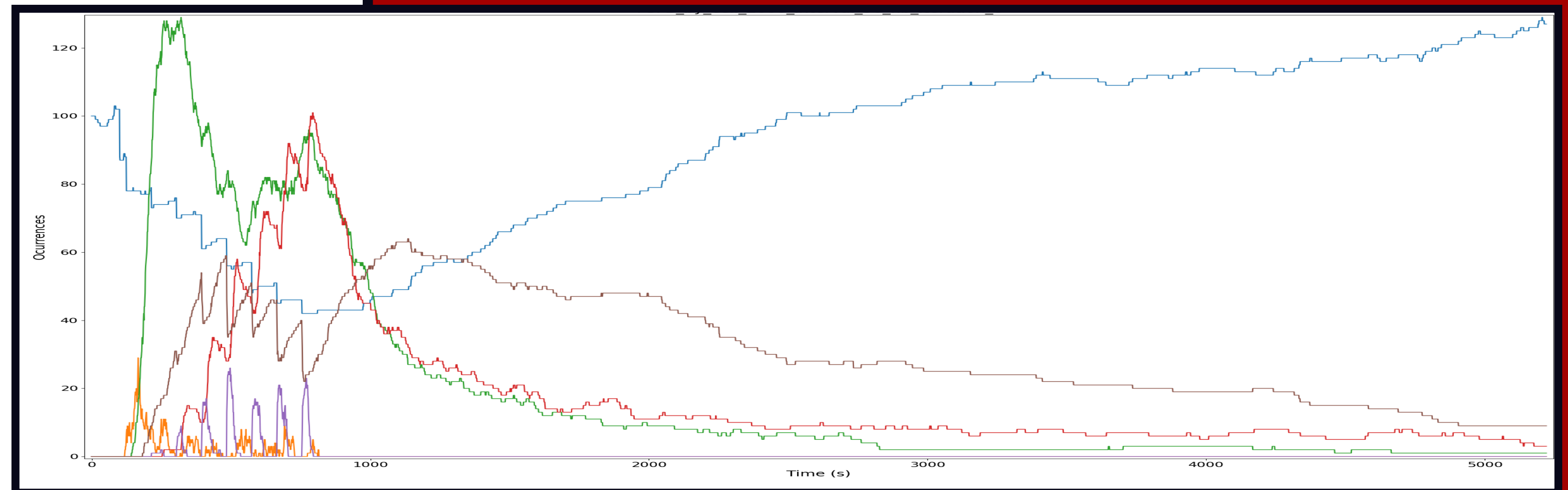
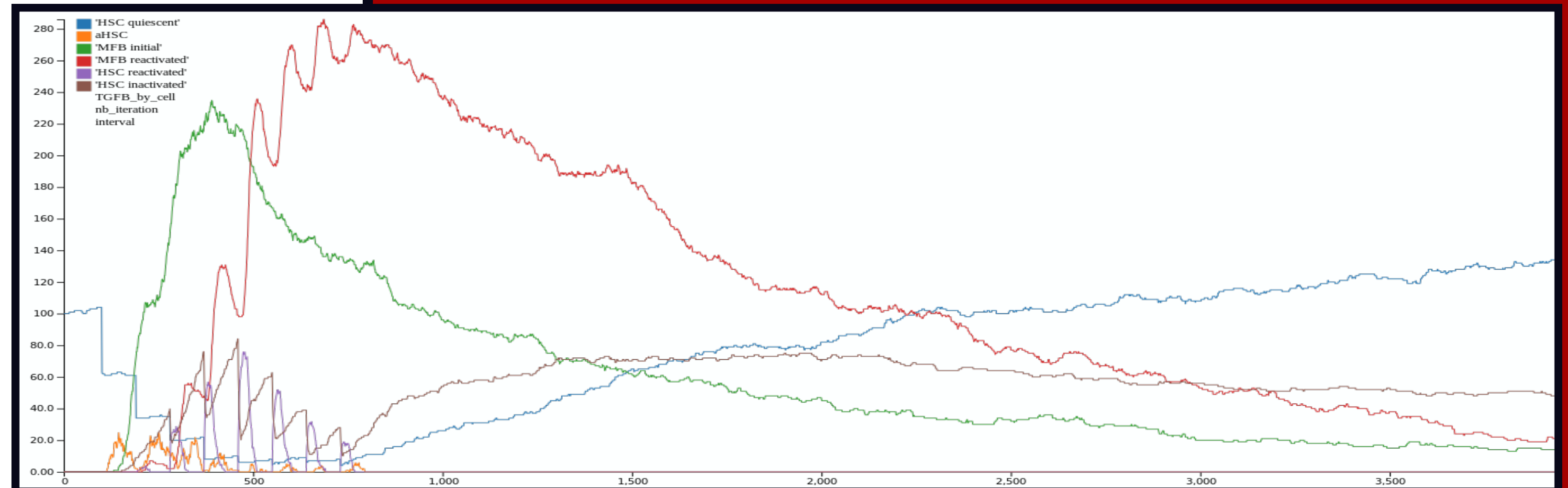
dT between input: 90h



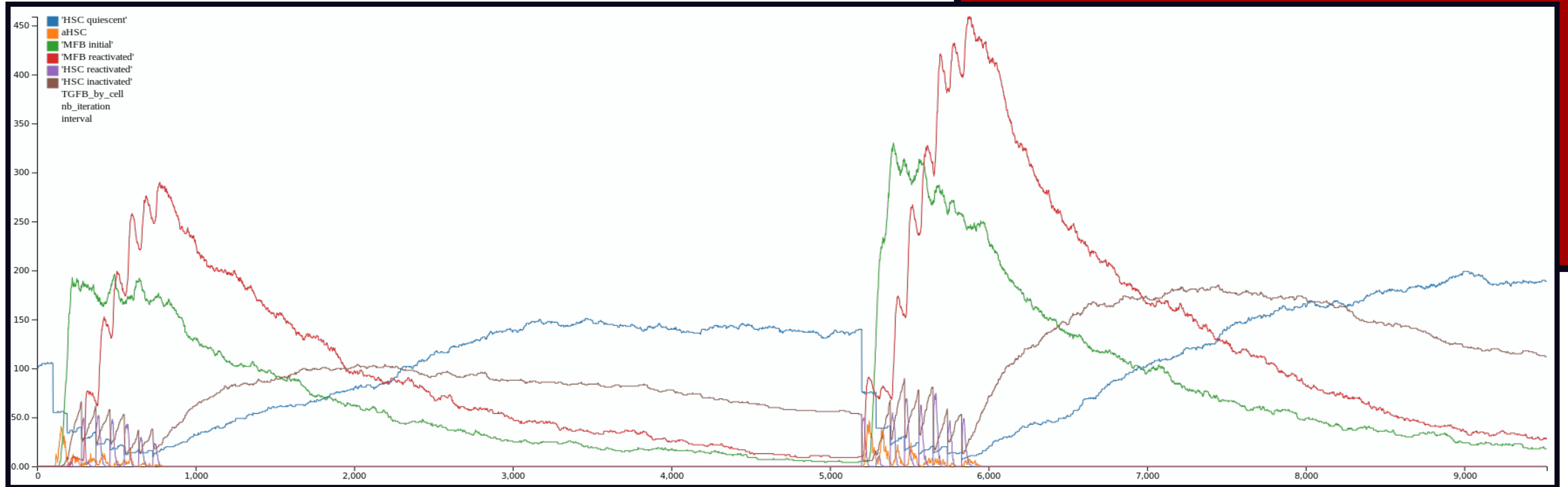


# Simulations

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



# Simulations



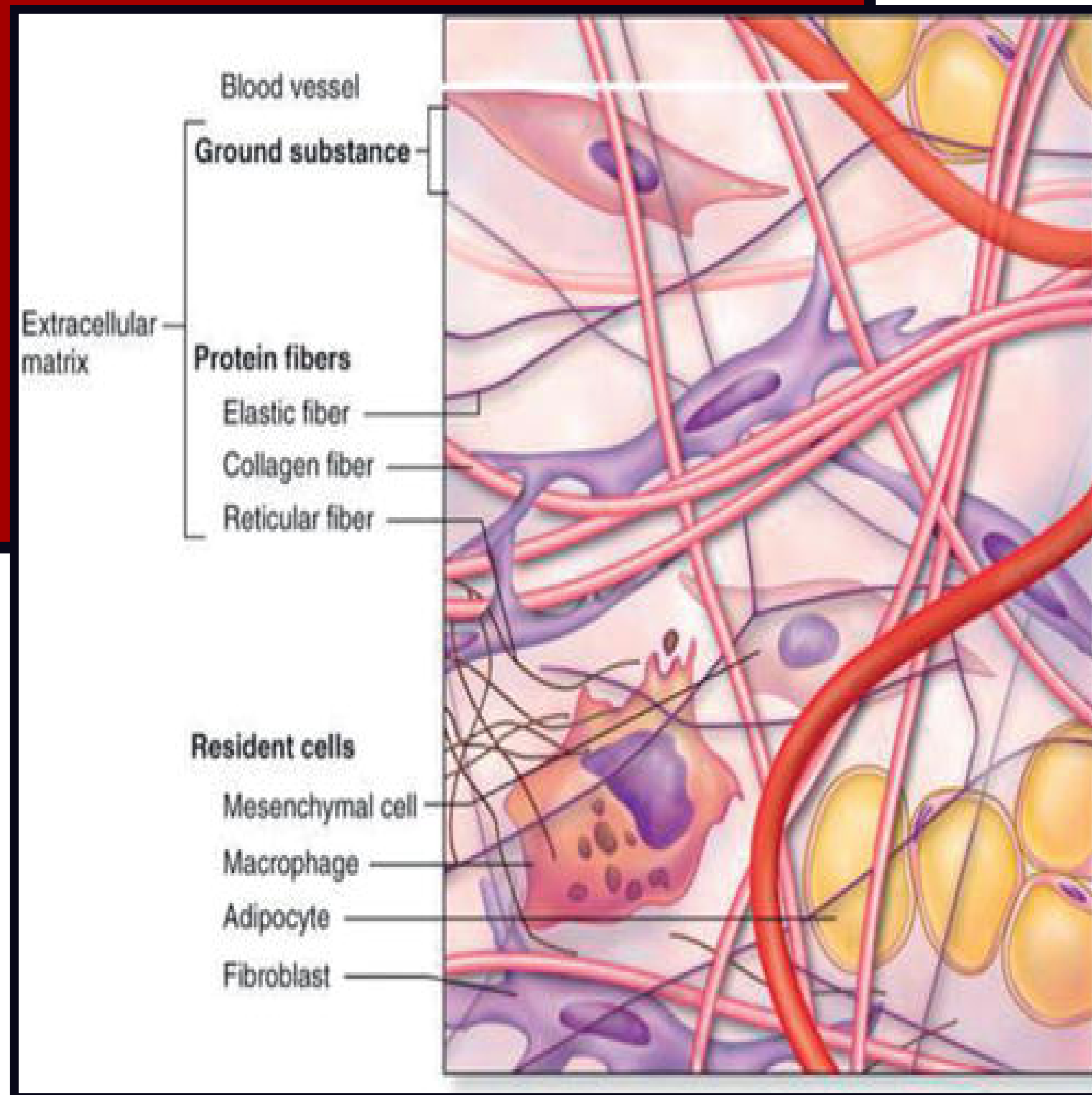
Parameters: [TGFB]: 5000, number of input: 8, dT between input: 90h

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

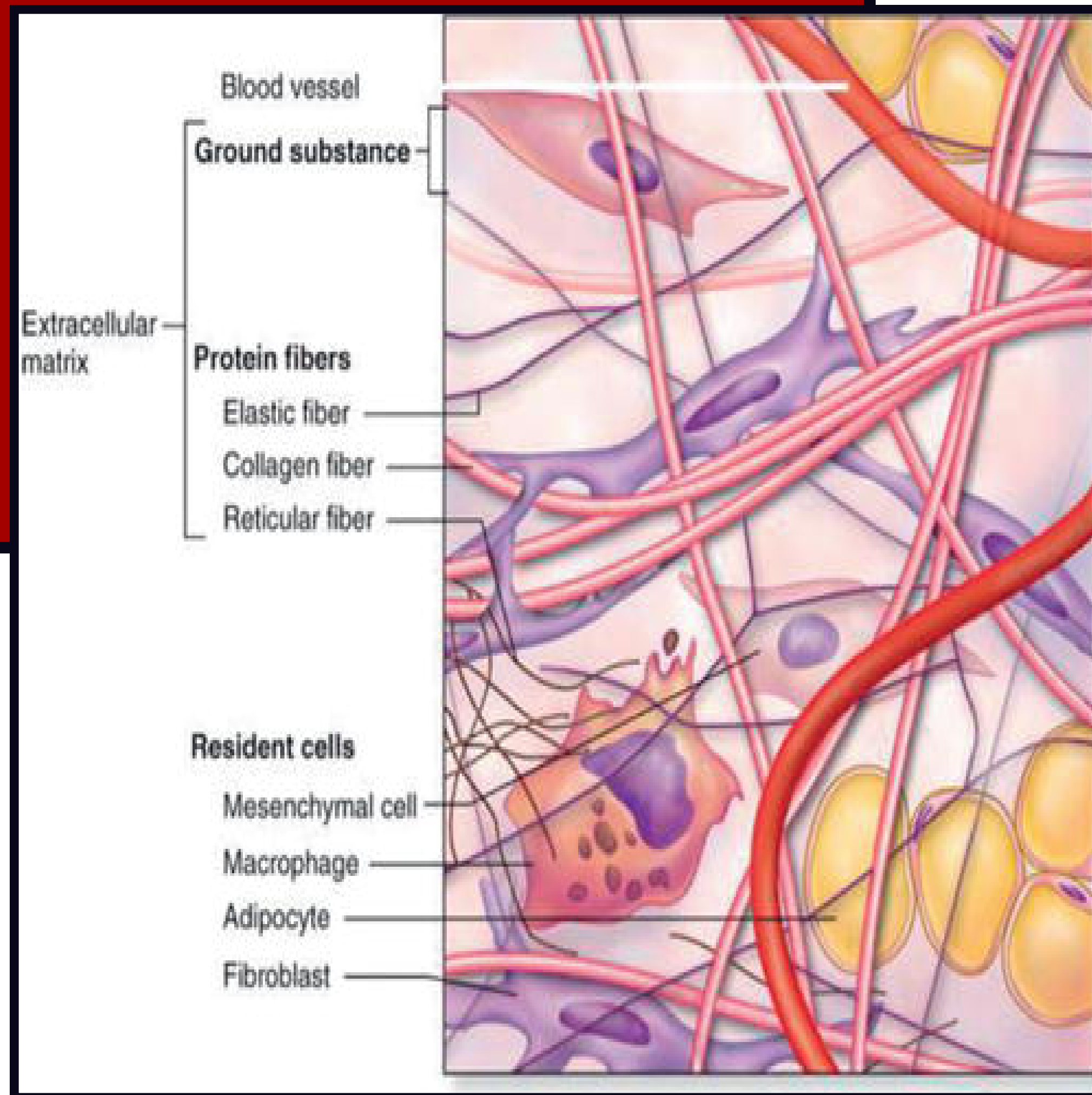
# Extracellular Matrix



- 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

Source: Michael W. King: Integrative Medical Biochemistry Examination and Board Review, [www.accesspharmacy.com](http://www.accesspharmacy.com) Copyright © McGraw-Hill Education. All rights reserved

# 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

Source: Michael W. King: Integrative Medical Biochemistry Examination and Board Review, [www.accesspharmacy.com](http://www.accesspharmacy.com) Copyright © McGraw-Hill Education. All rights reserved

# 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

Nathalie Theret; Irset, Inserm

Anne Siegel; Irisa, Inria

Jérôme Feret; Team Antique, Inria

Pierre Boutillier; Nomadic Lab

Octave Hazard; Team Antique, Inria

# Thank you!

Any questions?



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