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A Kappa model for hepatic stellate cells activation by TGF β 1

GT Bioss 2021

Matthieu Bougueon,^{1,2,3} Pierre Boutillier, Jérôme Feret, Octave Hazard and Nathalie Theret.



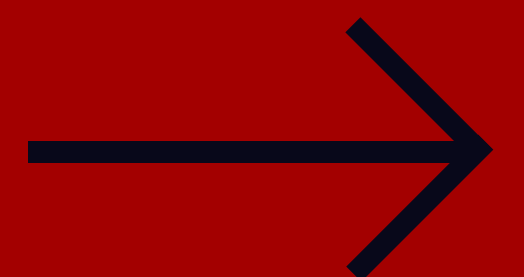
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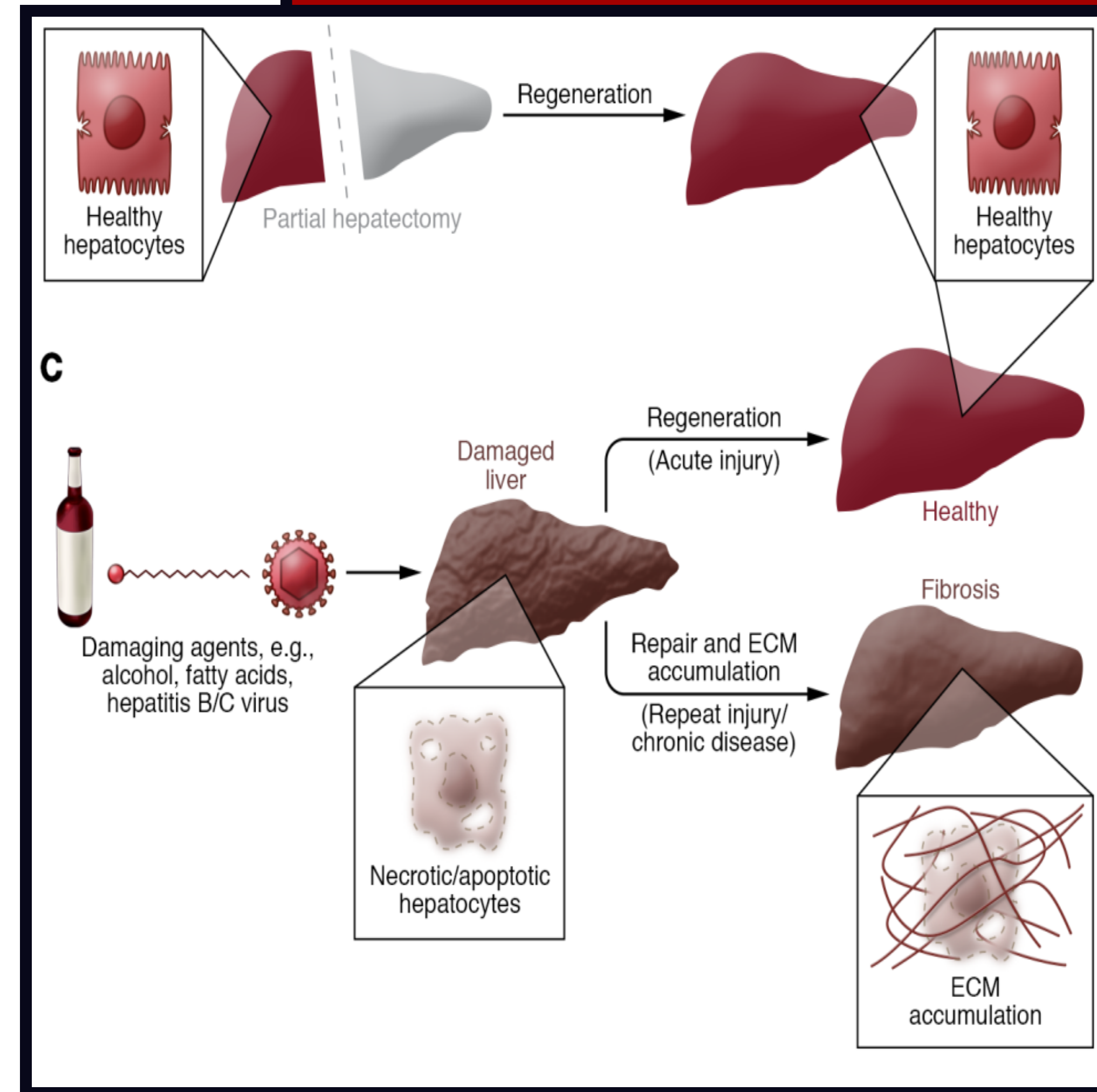


3



Liver Fibrosis

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



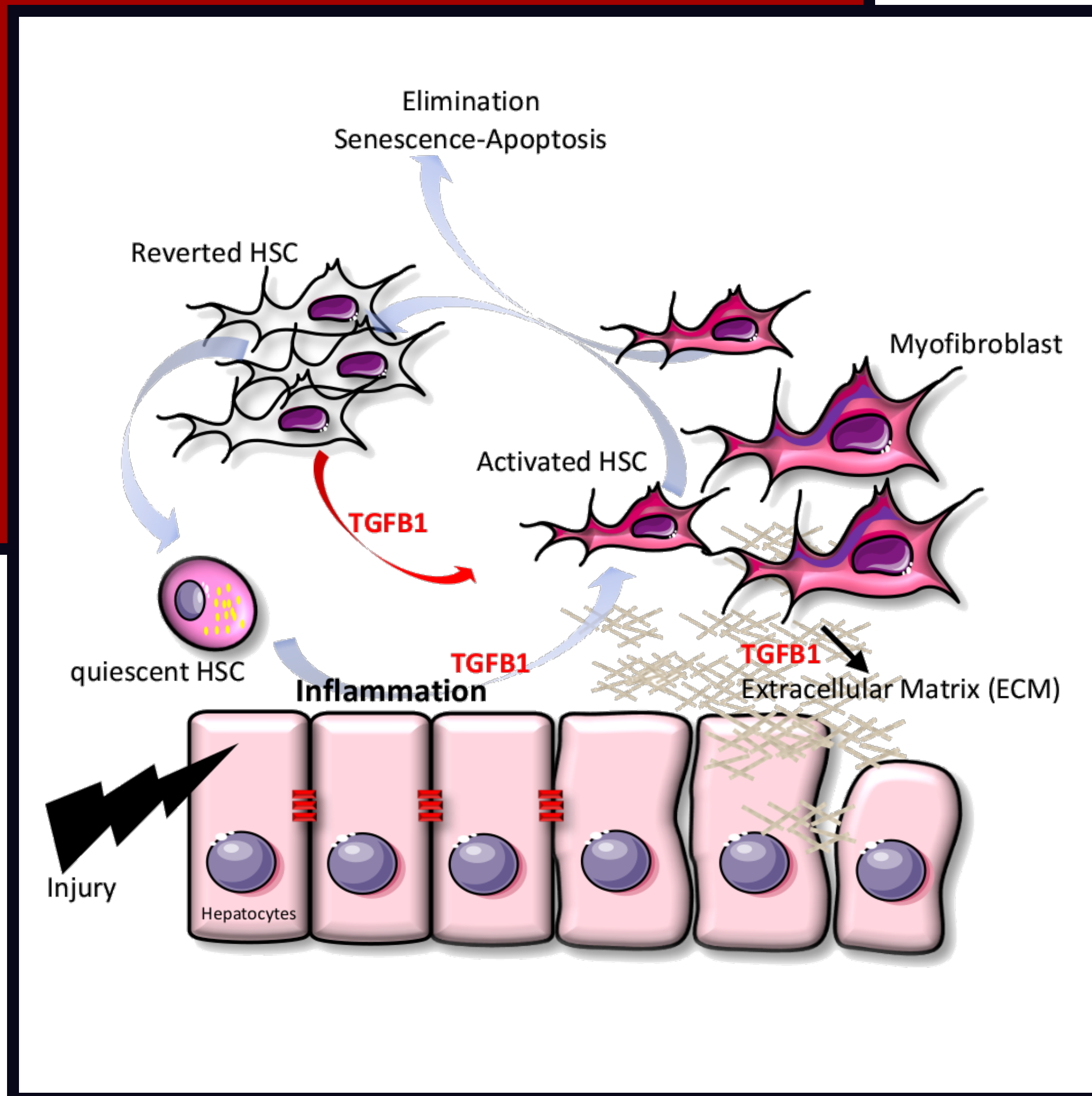
Hepatic Fibrosis

Liver injury induces inflammatory response leading to release of TGF β 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- β 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- β is the final aims of this project

Kappa

Walter Fontana
Pierre Boutillier
Jerome Feret
Jean Krivine



<https://kappalanguage.org/>

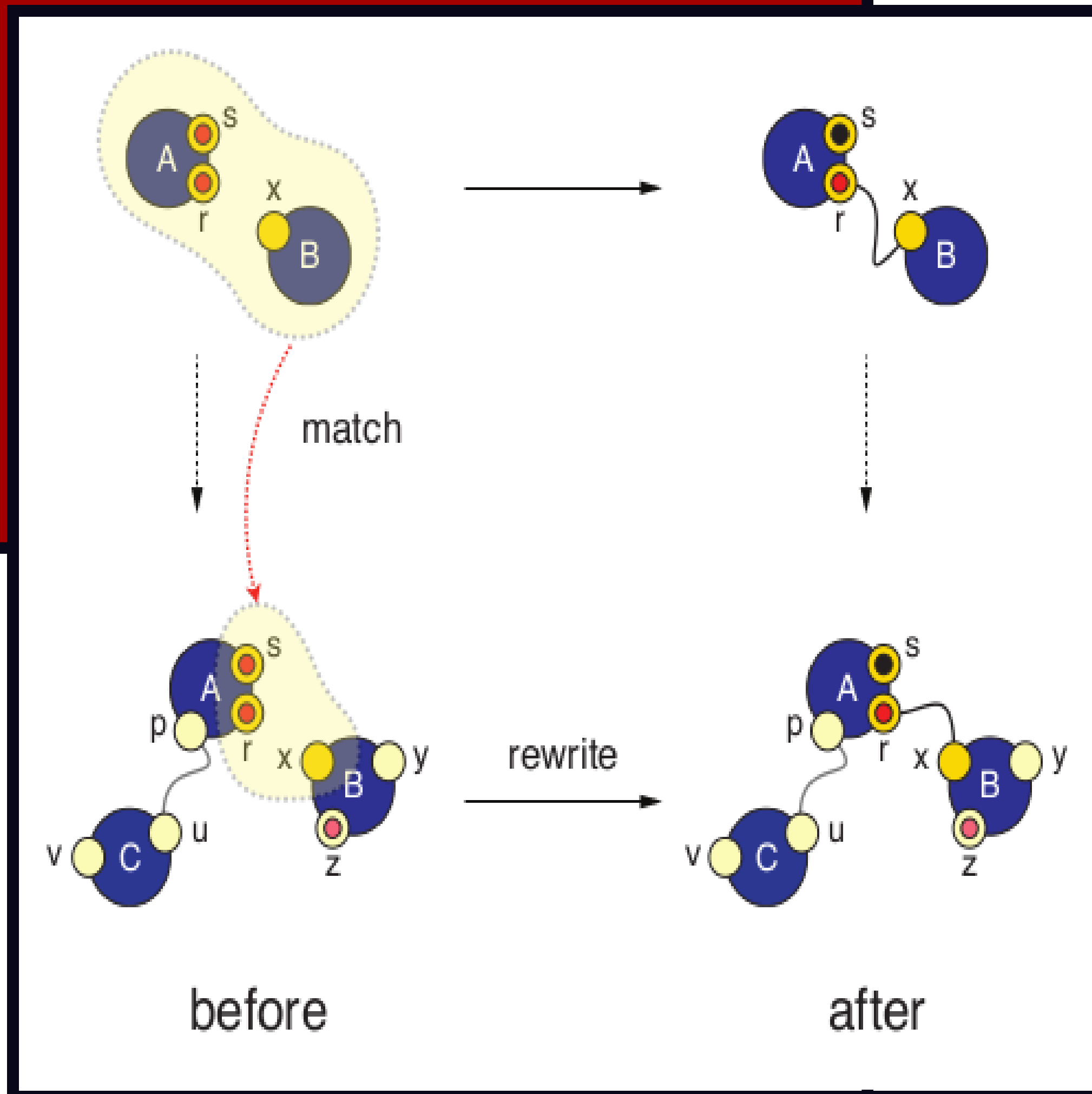
Kappa

Rules based language created in 2004
(V.Damos)

Rules describe *agent* behavior
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*.



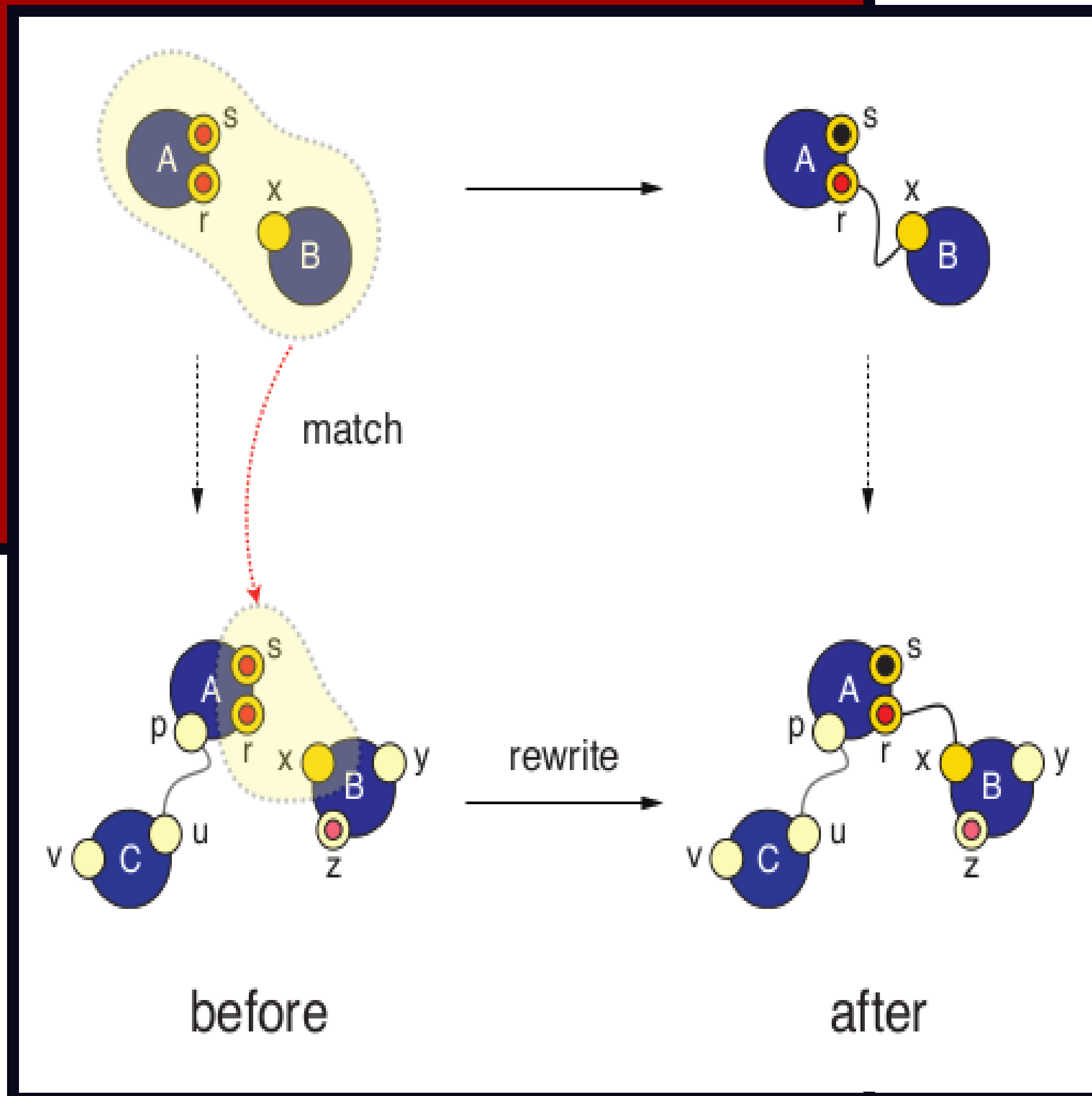
Kappa

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

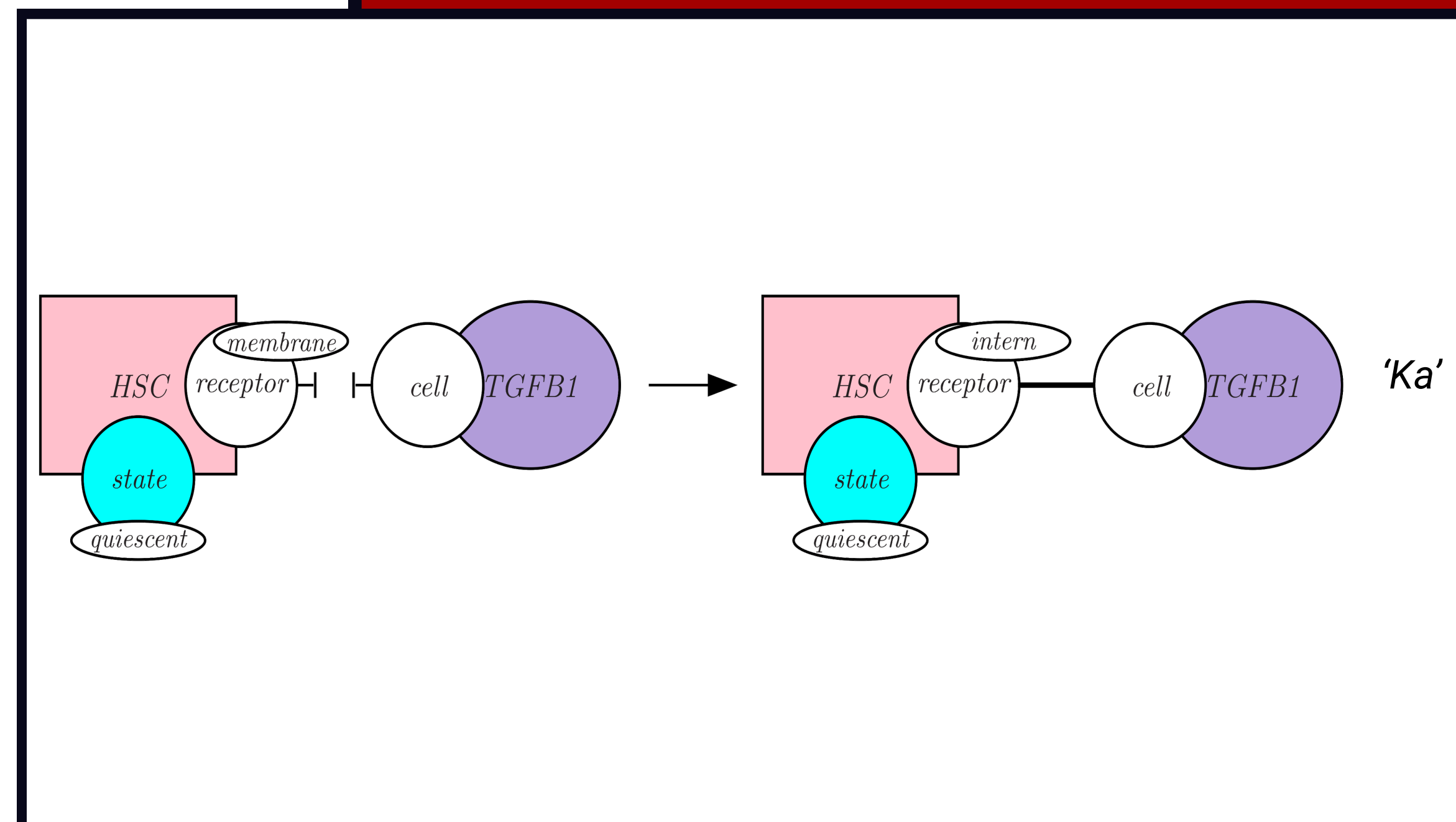


Kappa

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

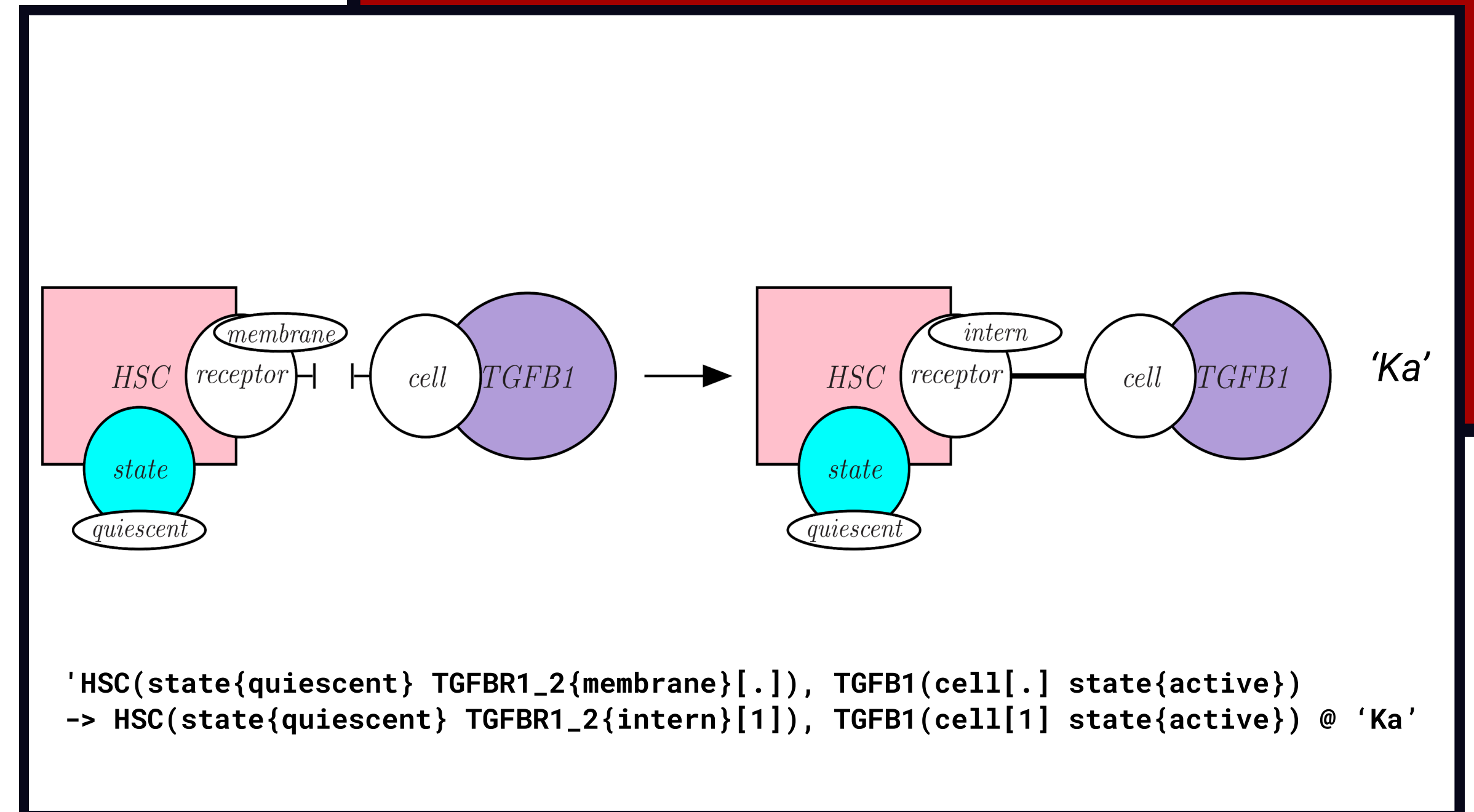
Chemistry syntax:



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:

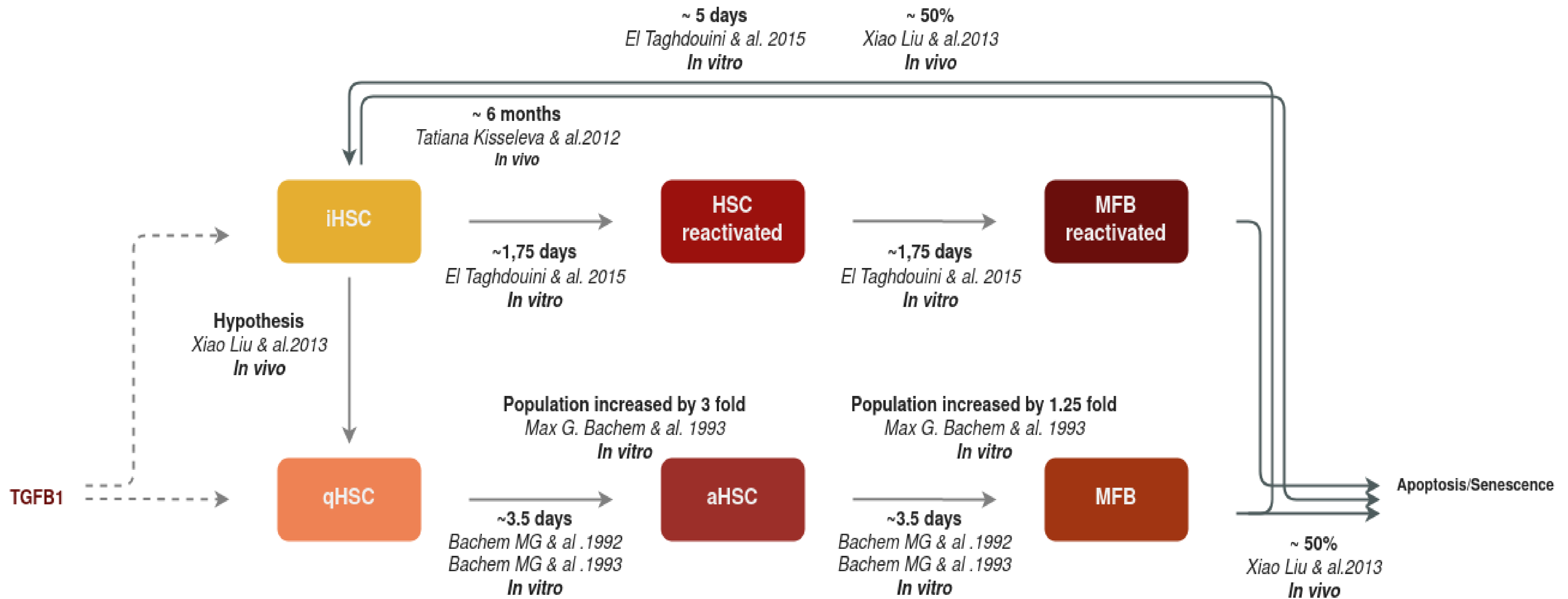
- link between *agents*,
- Impact of the state of
site on link
- double link formation

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

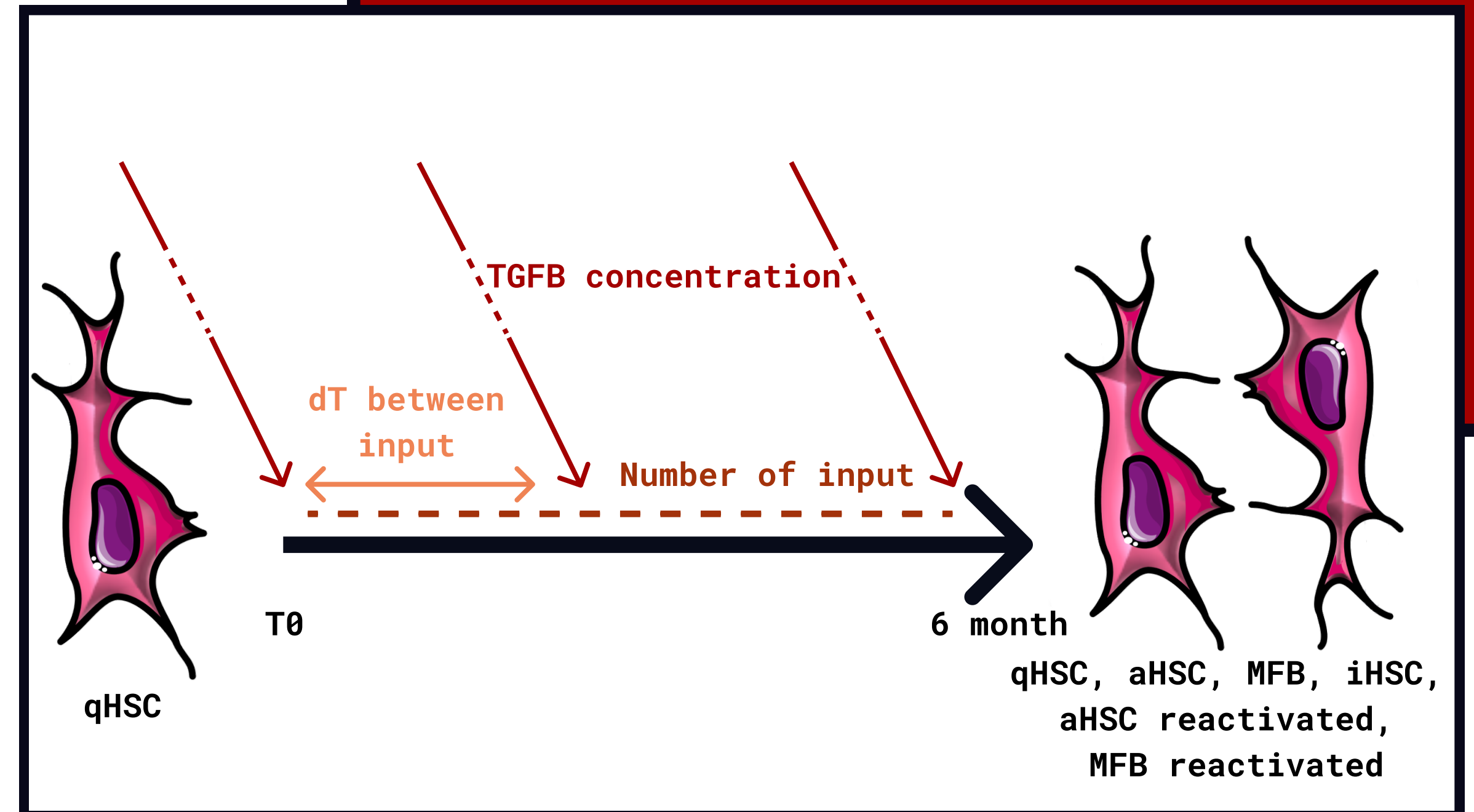
TGFB

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



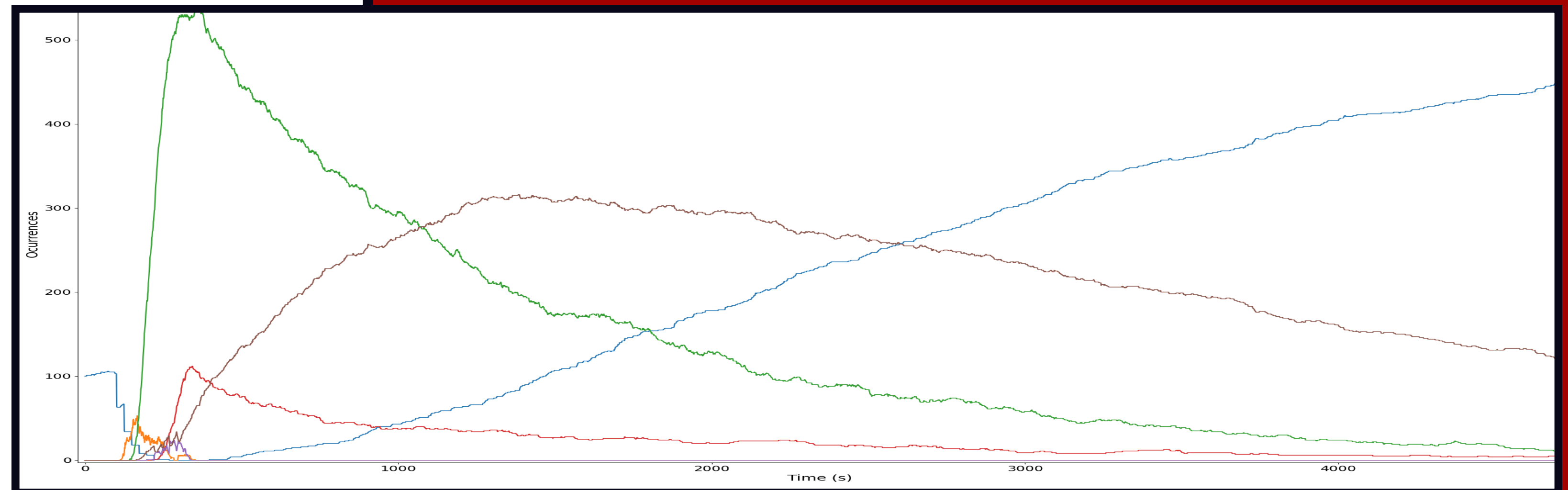
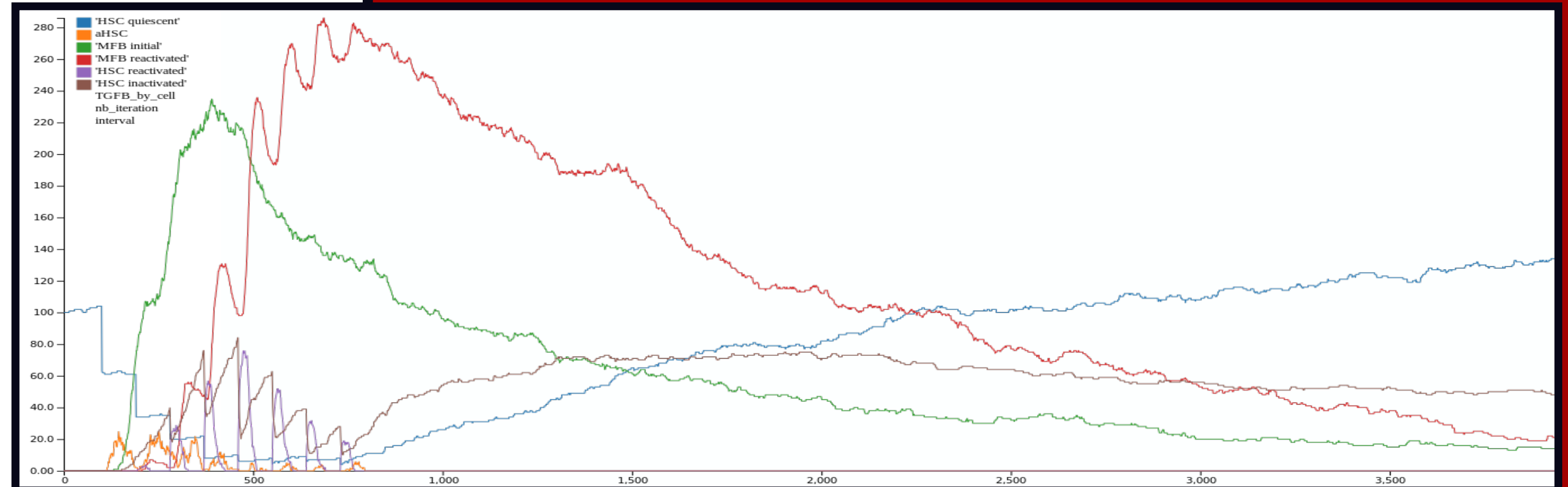
Simulations

Parameters:

[TGFB]: 5000

number of input: 8

dT: 90h and 24h



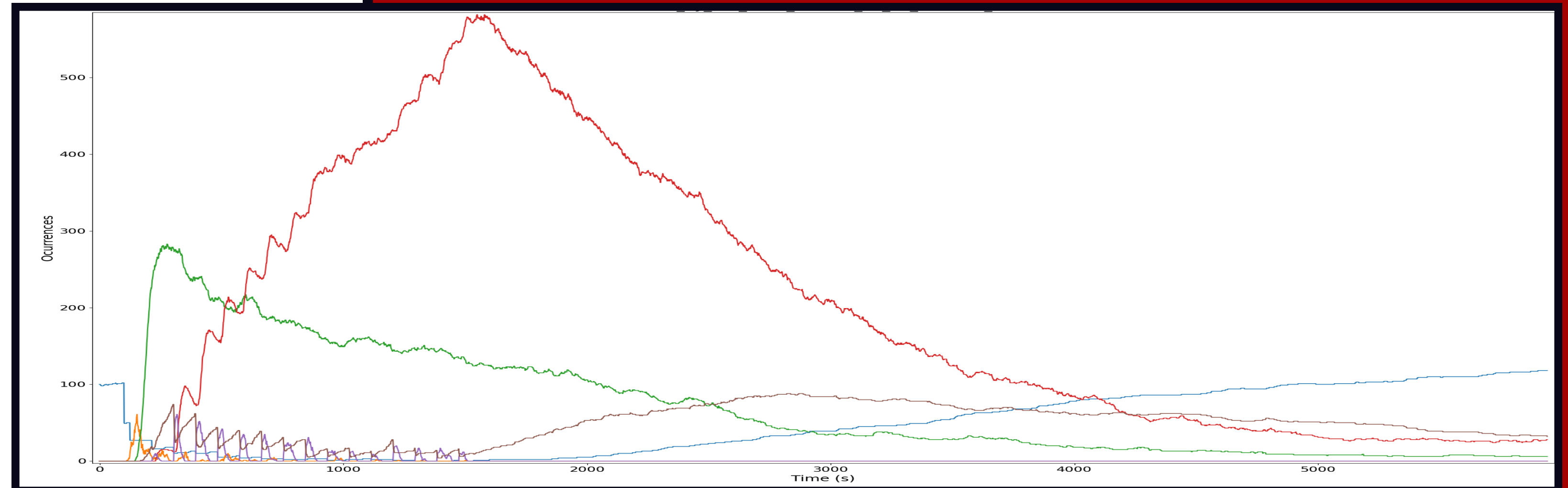
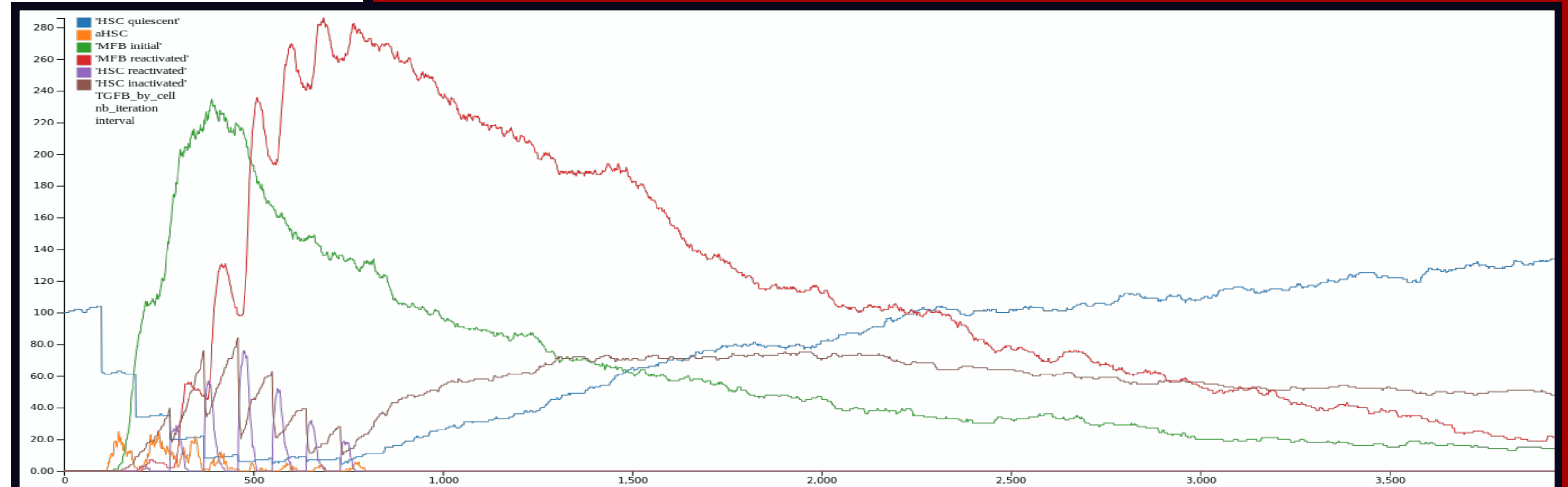
Simulations

Parameters:

[TGFB]: 5000

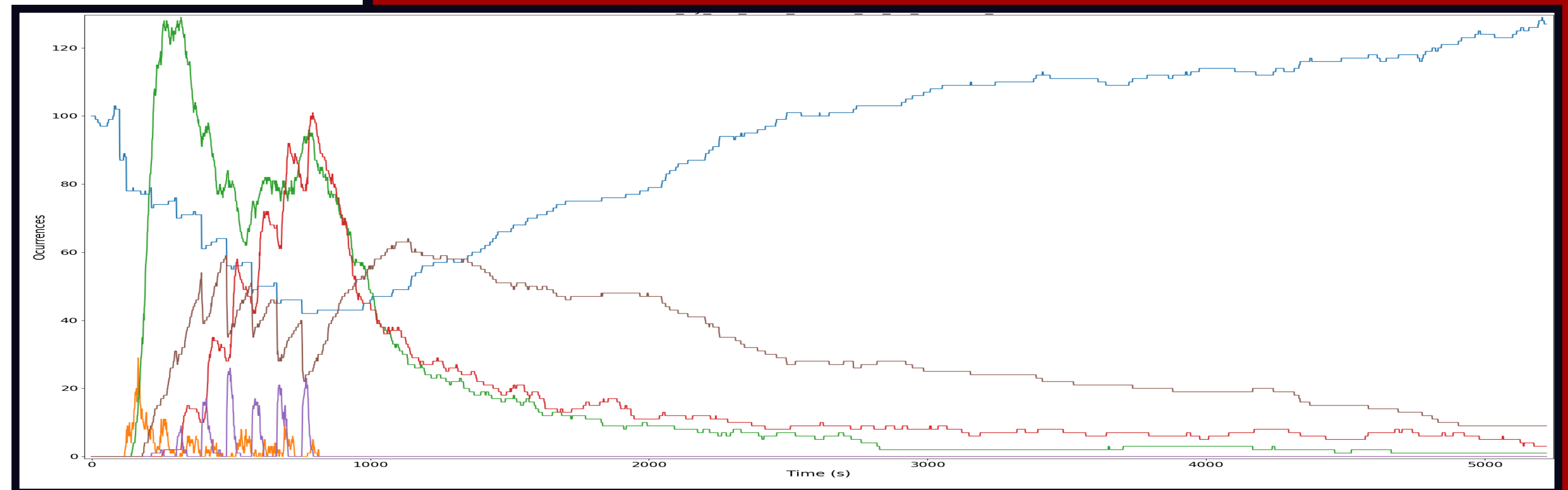
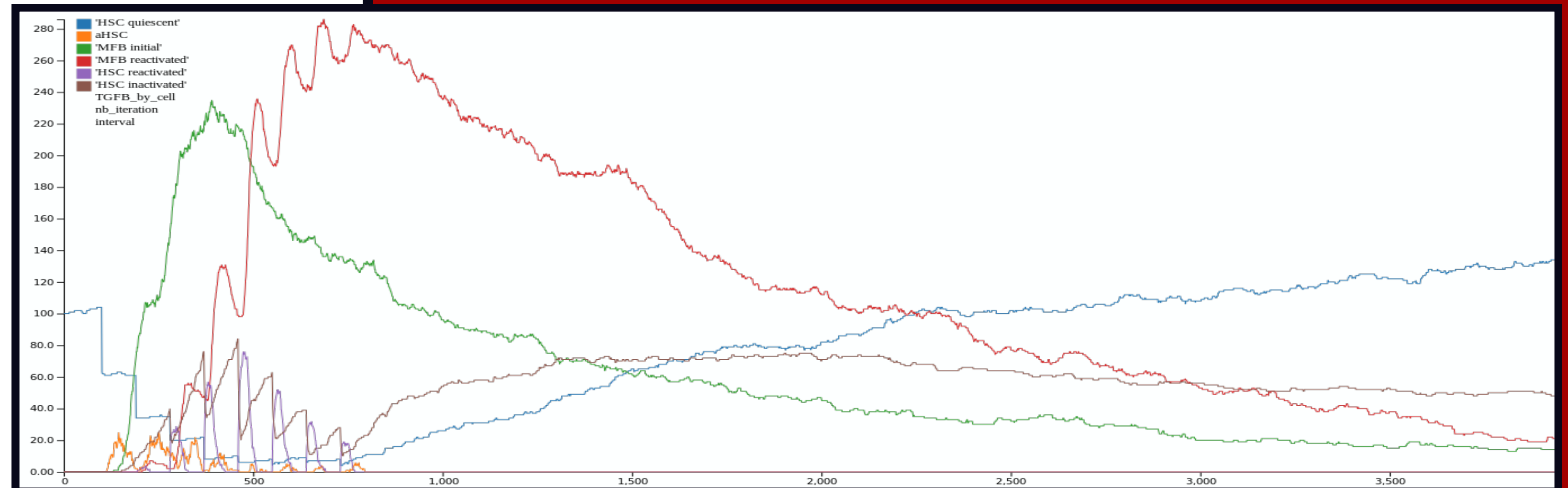
number of input: 8 and 16

dT between input: 90h

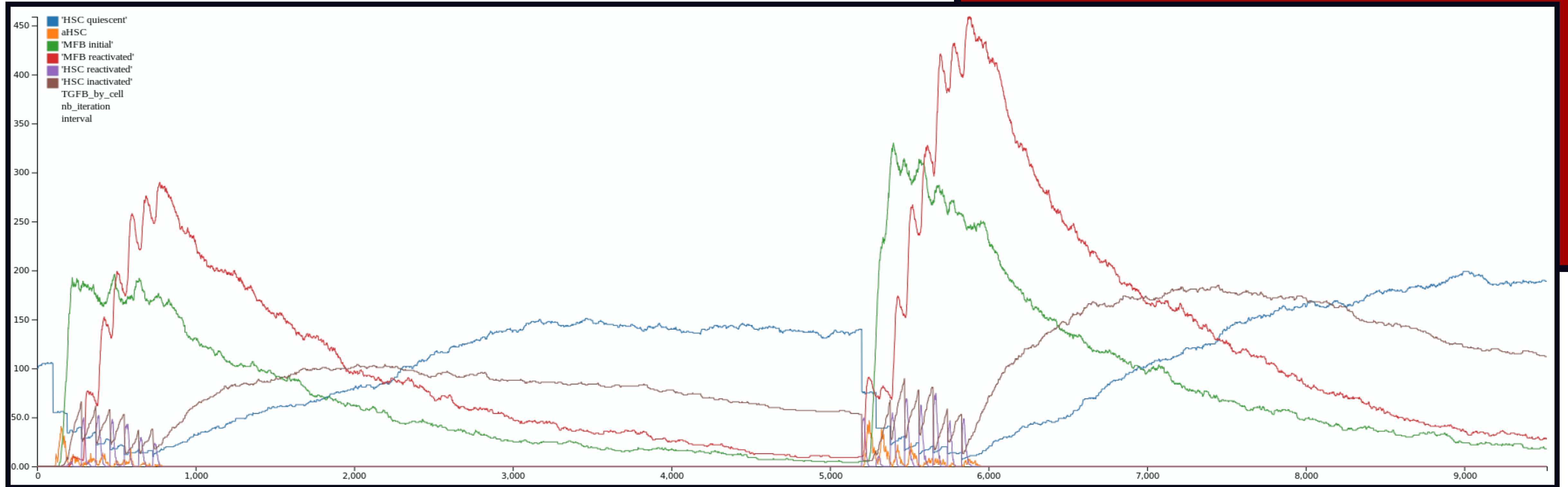


Simulations

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



Simulations



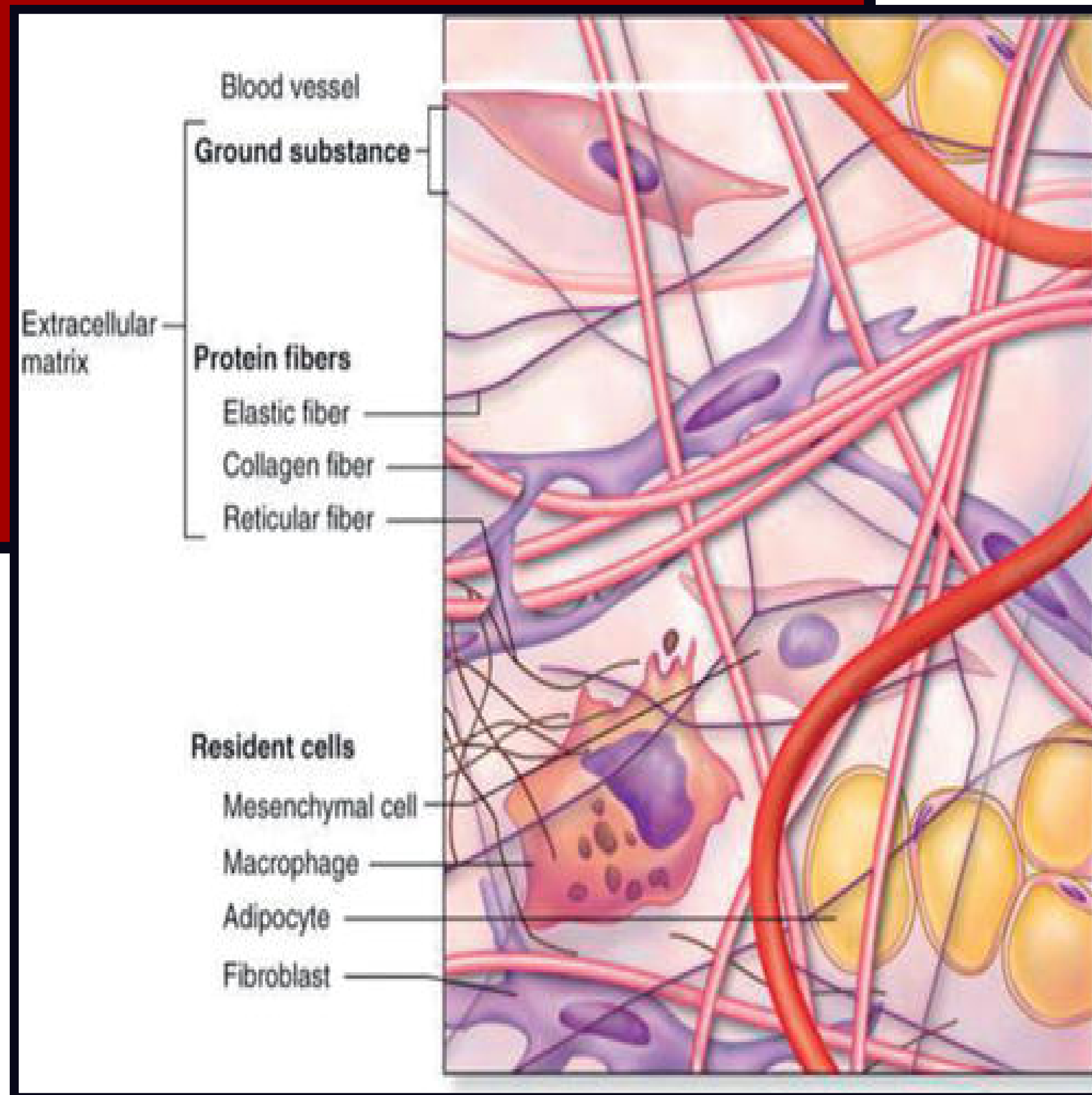
Parameters: [TGFB]: 5000, number of input: 8, dT between input: 90h

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

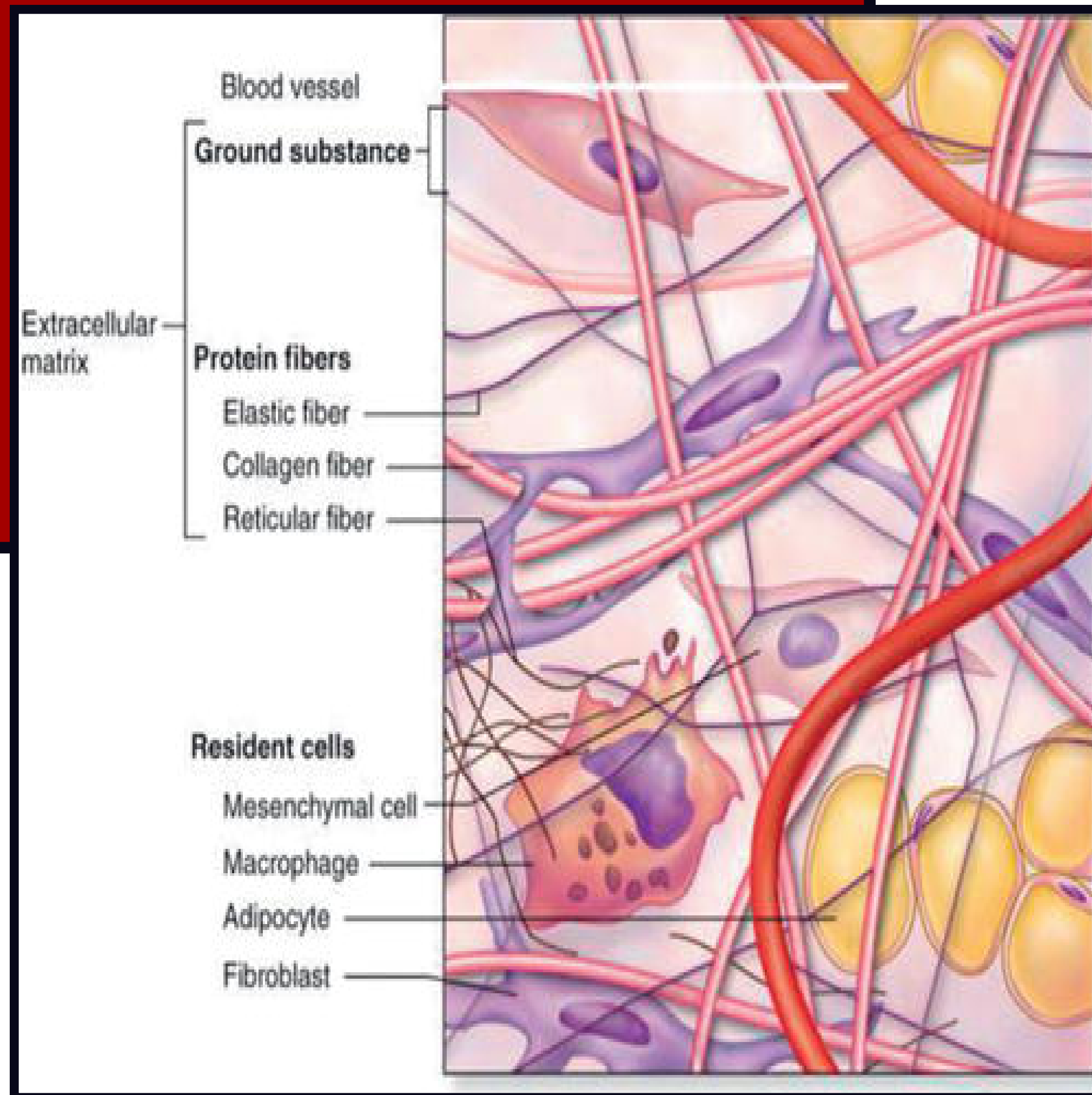
Extracellular Matrix



- 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 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 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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Jérôme Feret; Team Antique, Inria

Pierre Boutillier; Nomadic Lab

Octave Hazard; Team Antique, Inria

Thank you!

Any questions?



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