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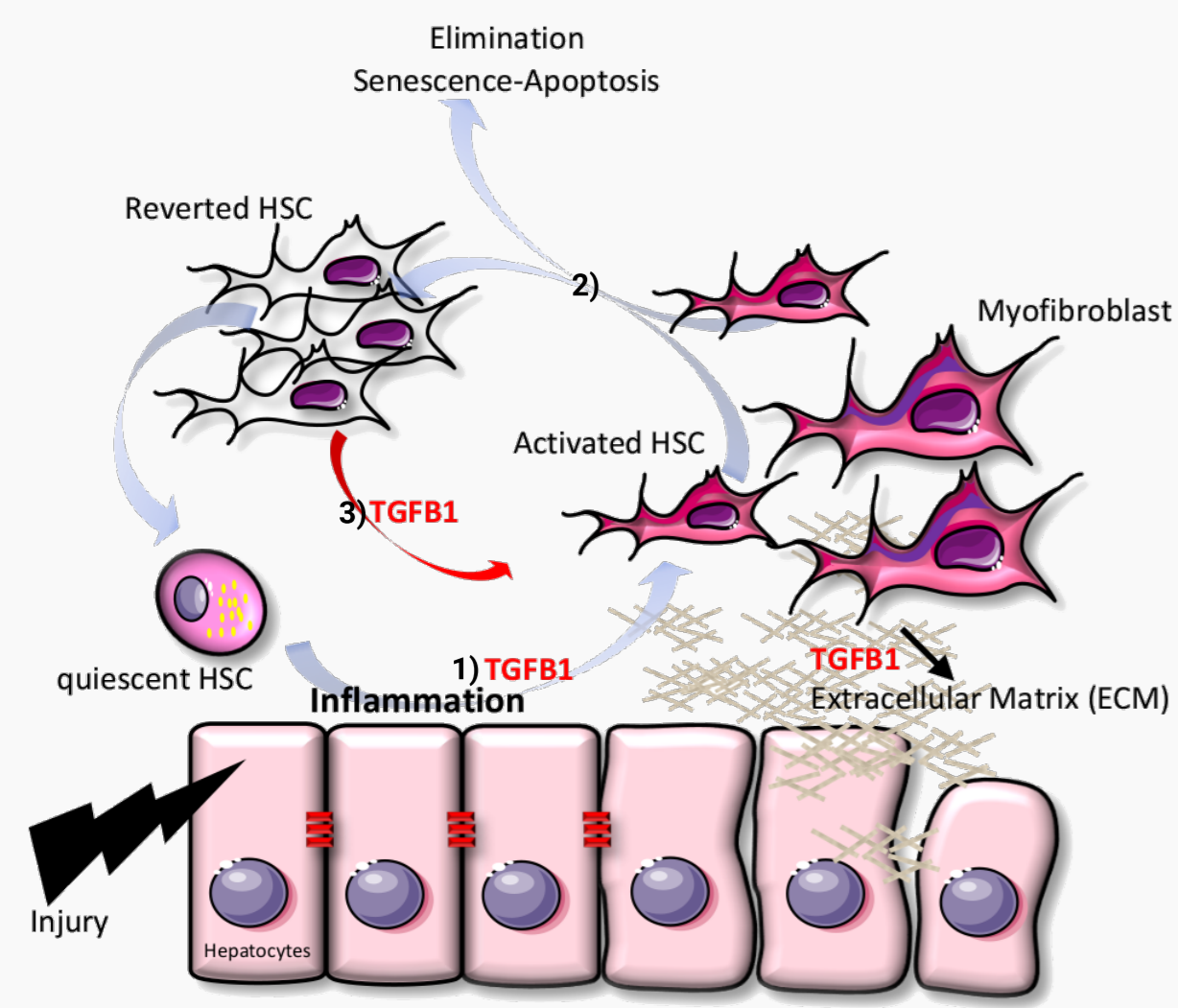
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A Kappa model for hepatic stellate cells activation by TGFB1

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Introduction

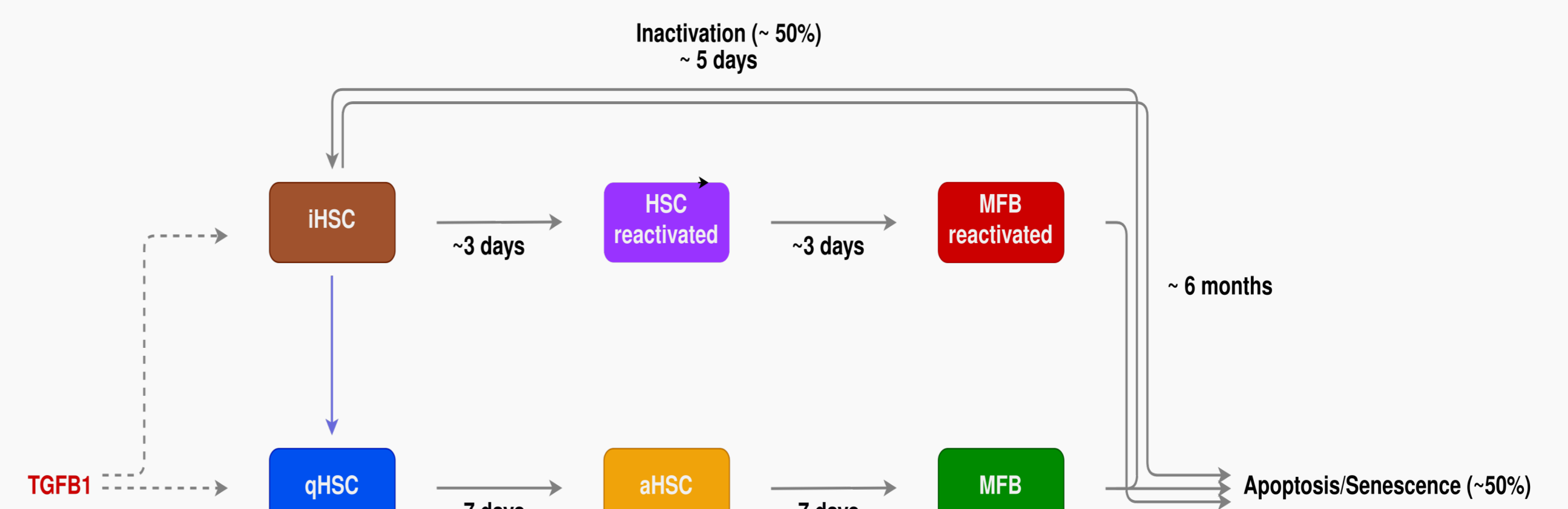


Chronic hepatitis is associated with the development of fibrosis, which results in the abnormal deposition of extracellular matrix (ECM) and a severe dysfunction of liver functions. The terminal stage of fibrosis is cirrhosis, which constitutes the major risk of occurrence of Hepatocellular Carcinoma (HCC). The matrix microenvironment is therefore the major regulator of events related to the fibrosis-cirrhosis-cancer progression and Hepatic Stellate Cells (HSC) are the main actors of the extracellular matrix remodelling.

- Upon liver injury, damaged hepatocytes produce signals inducing inflammation that in turn promotes **TGFB1**-dependent activation of **quiescent HSC (qHSC)**(1). **Activated HSC** orchestrate tissue repair and are either eliminated through Senescence and Apoptosis (2) or deactivated towards **reverted HSC (iHSC)**(2), that can be reactivated more rapidly(3).
- Upon chronic liver injuries, **activated HSC(aHSC)** progress toward a **Myofibroblast (MFB)** state that escape to control, leading to fibrosis.

The understanding of the dynamics of HSC activation and regulation by TGFB1 is essential to identify markers and therapeutic targets likely to promote the resolution of fibrosis at the expense of its progression. Here we develop a rule-based model to characterize the dynamics of HSC activation and identify the key regulators.

Model



Schematic representation of the model, built using biological data

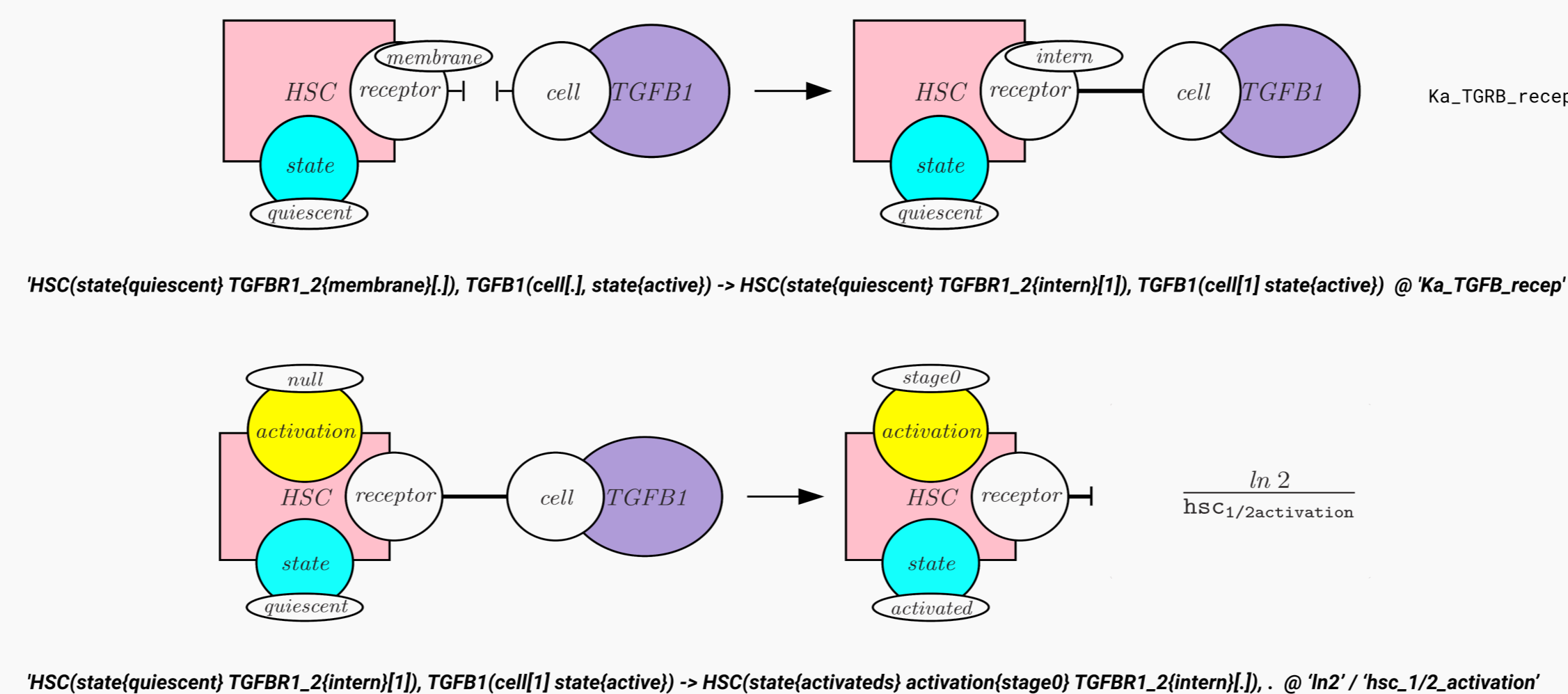
Kappa

Kappa:

- Rule-based language for modeling systems of interacting agents (<https://kappalanguage.org/>)
- Entities are graphical structures, rules are graph-rewrite directives.
- Rules locally modified the state of a system

Tools:

- Stochastic simulator **KaSim**
 - a. samples trajectory according to their probability density distribution
 - b. relies on a representation of the state of the system as a site graph
 - c. set of events that may be applied in the current state is computed dynamically
- Modeling platform
 - a. direct simulation
 - b. interactions during the execution of a model

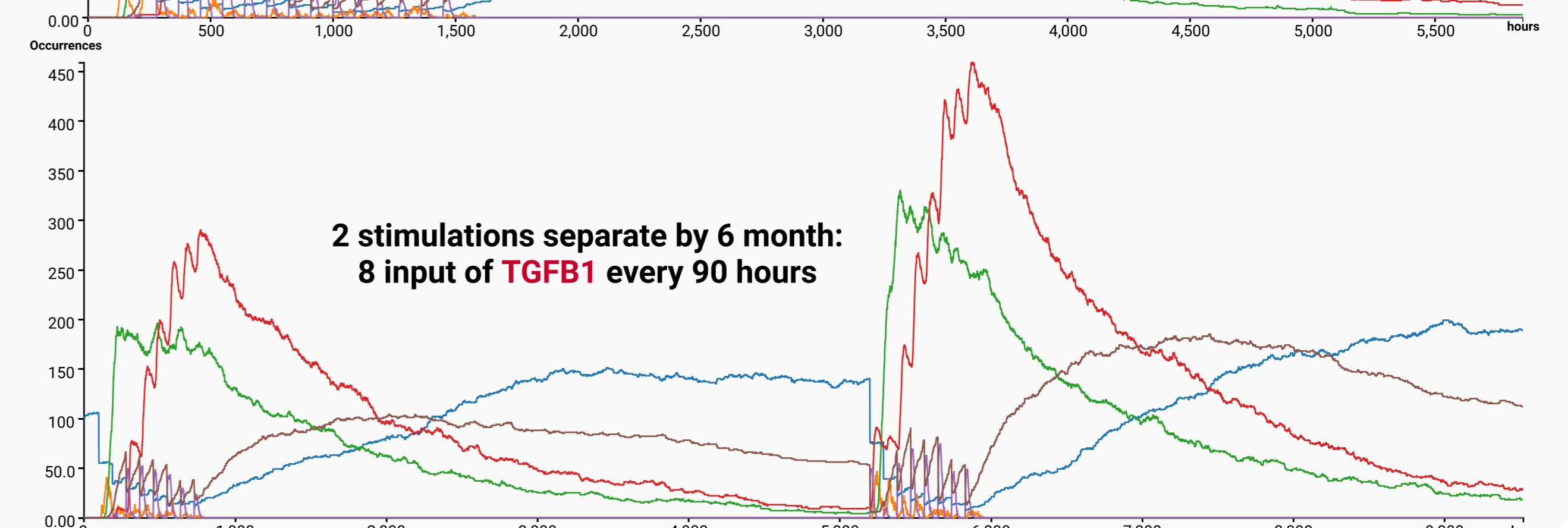
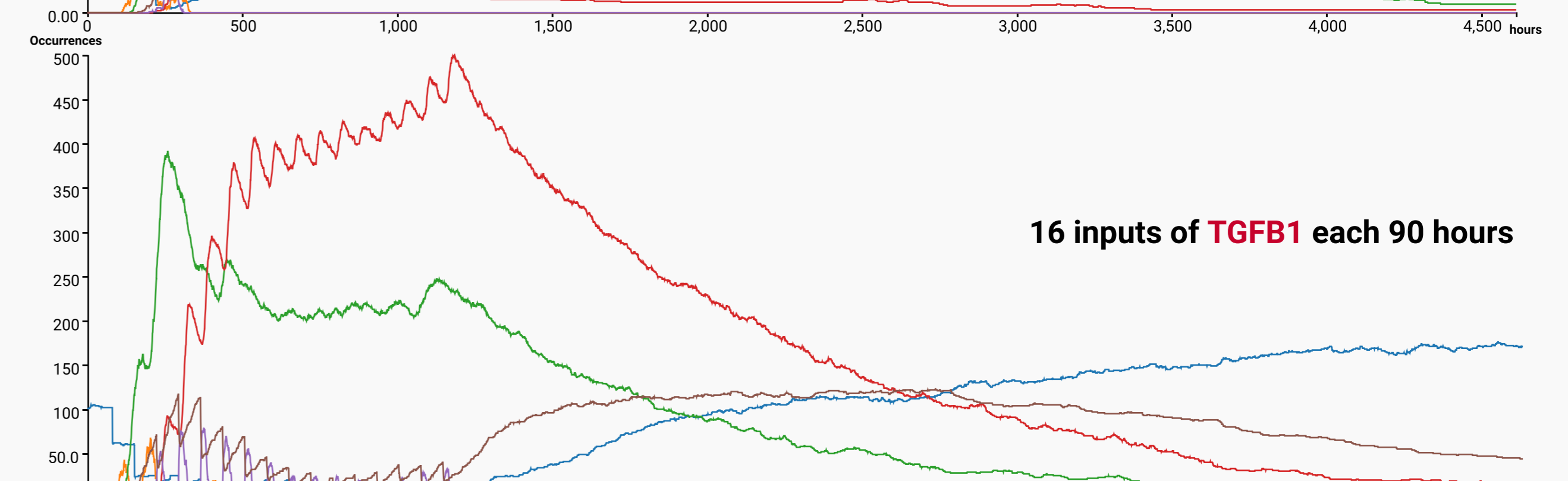
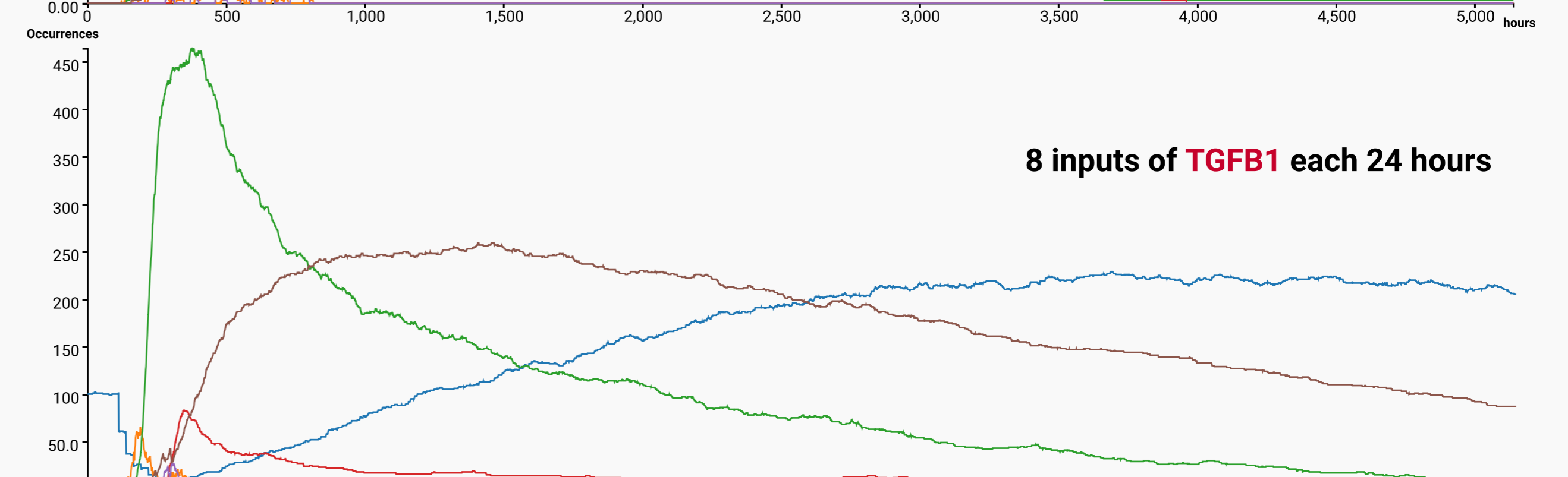
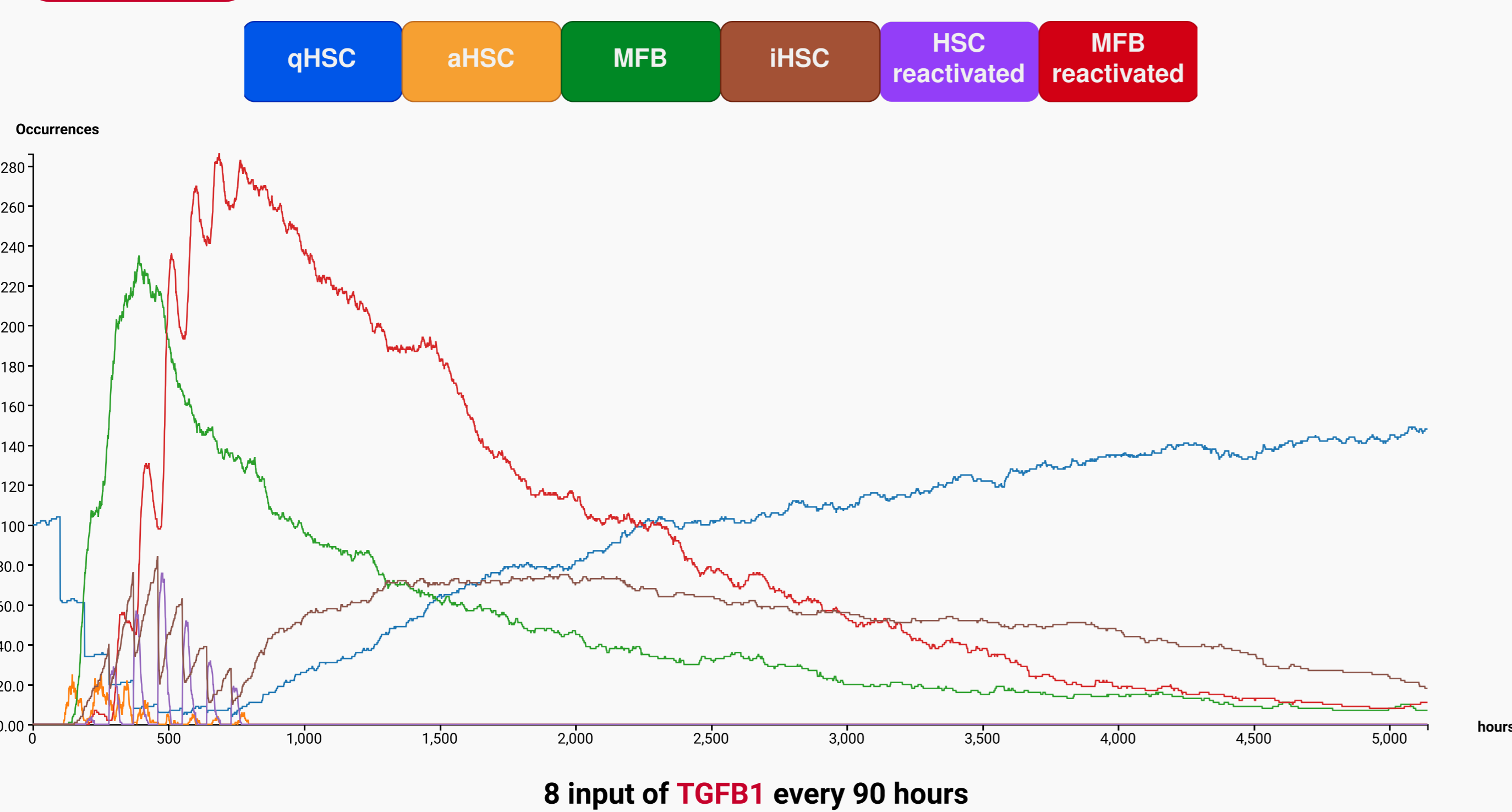


Agent (HSC and TGFB1) are defined by different sites:

- the site **receptor** which bind to the site **cell** of **TGFB1**
- the site **state** which have different values: **quiescent** or **activated**

M Bouguéon, P Boutillier, J Feret, O Hazard and N Theret. 2021 A Kappa model for hepatic stellate cells activation by TGFB, WILEY, Systems Biology Modelling and Analysis: Formal Bioinformatics Methods and Tools.

Results



Conclusion / Perspectives

Conclusion

- **Reverted HSC (iHSC)** are key regulators
- **TGFB1** is necessary to induce HSC activation but chronic stimulation by **TGFB1** doesn't allow to reach a fibrotic state characterised by persistent high level of **MFB**

Perspectives

Because **ECM** deposition induced by **activated HSC** and **MFB** lead to an increase of stiffness, which may also contribute to activation of **HSC** (4). The future challenges will be the integration of a new agent **ECM** to take into account this information.

