A Kappa model for hepatic stellate cells activation by TGFB1
Matthieu Bouguéon, Pierre Boutillier, Jerome Feret, Octave Hazard, Nathalie Theret

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A Kappa model for hepatic stellate cells activation by TGBF1
Liver Fibrosis

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

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

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 syntaxe:

\[ \text{A + B } \rightarrow \text{ C + D} \]
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.
<table>
<thead>
<tr>
<th>Kappa Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KaSim</strong></td>
</tr>
<tr>
<td>Stochastic Simulator using Gillespie algorithm.</td>
</tr>
<tr>
<td><strong>KaSa</strong></td>
</tr>
</tbody>
</table>
| 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 (TGFB
- 73 rules

Parameters:

<table>
<thead>
<tr>
<th>Environment</th>
<th>Activation</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HSC: 100</td>
<td>qHSC \rightarrow aHSC: 84h</td>
<td>Recycling rate: 30 min</td>
</tr>
<tr>
<td>Number of receptor: 10000</td>
<td>aHSC \rightarrow MFB: 84h</td>
<td>Receptor production rate: 4 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>qHSC</th>
<th>MFB</th>
<th>Constitutive degradation rate: 36 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>half life: 54.93d</td>
<td>half-life: 3.76d</td>
<td>Ligand induced degradation rate: 4 min</td>
</tr>
<tr>
<td>activation speed: 1h</td>
<td>Inactivation: 5d</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proliferation</th>
<th>iHSC</th>
<th>TGFB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSC proliferation half-time: 13.75h</td>
<td>reactivation: 42h</td>
<td>TGFB1 half life: 3 min</td>
</tr>
<tr>
<td>MFB proliferation half-time: 886.9h</td>
<td>iHSC half life: 54.93d</td>
<td>TGFBr wave: 5000 * number of HSC</td>
</tr>
</tbody>
</table>
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 TGFβ 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
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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Jérome Feret; Team Antique, Inria

Pierre Boutillier; Nomadic Lab
Octave Hazard; Team Antique, Inria
Thank you!

Any questions?

Matthieu Bougueon | matthieu.bougueon@irisa.fr