Logical modelling and analysis of cell adhesion properties along Epithelial to Mesenchymal Transition

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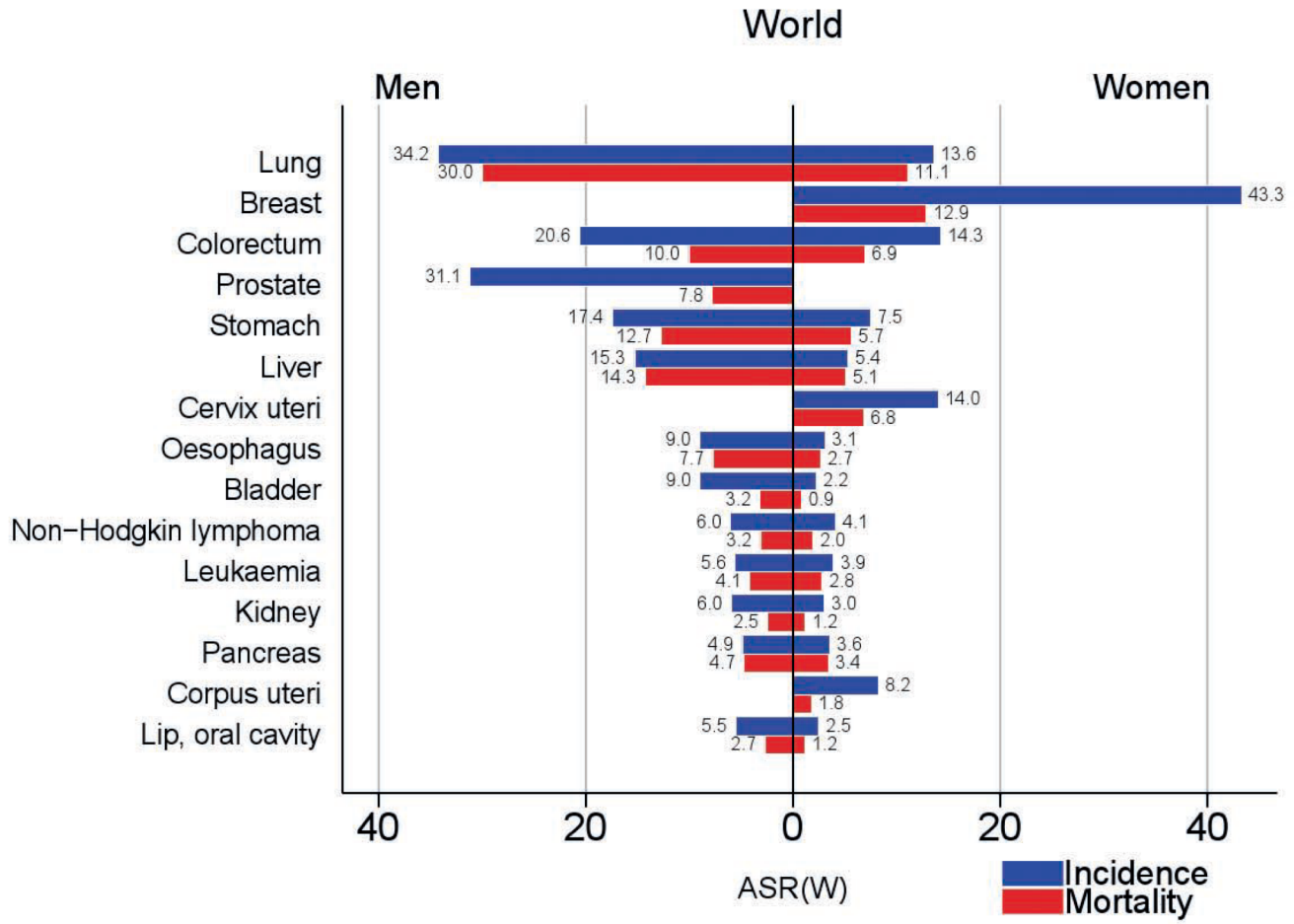
Workshop on Logical Modelling of Cellular Networks – ECCB18

Intro

Cancer is a leading cause of death worldwide with **8.8M** deaths in 2015.



ASR incidence and mortality per 100 000, by major sites, in men and women, 2012.
GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11
http://www.who.int/en/news-room/fact-sheets/detail/cancer

Intro

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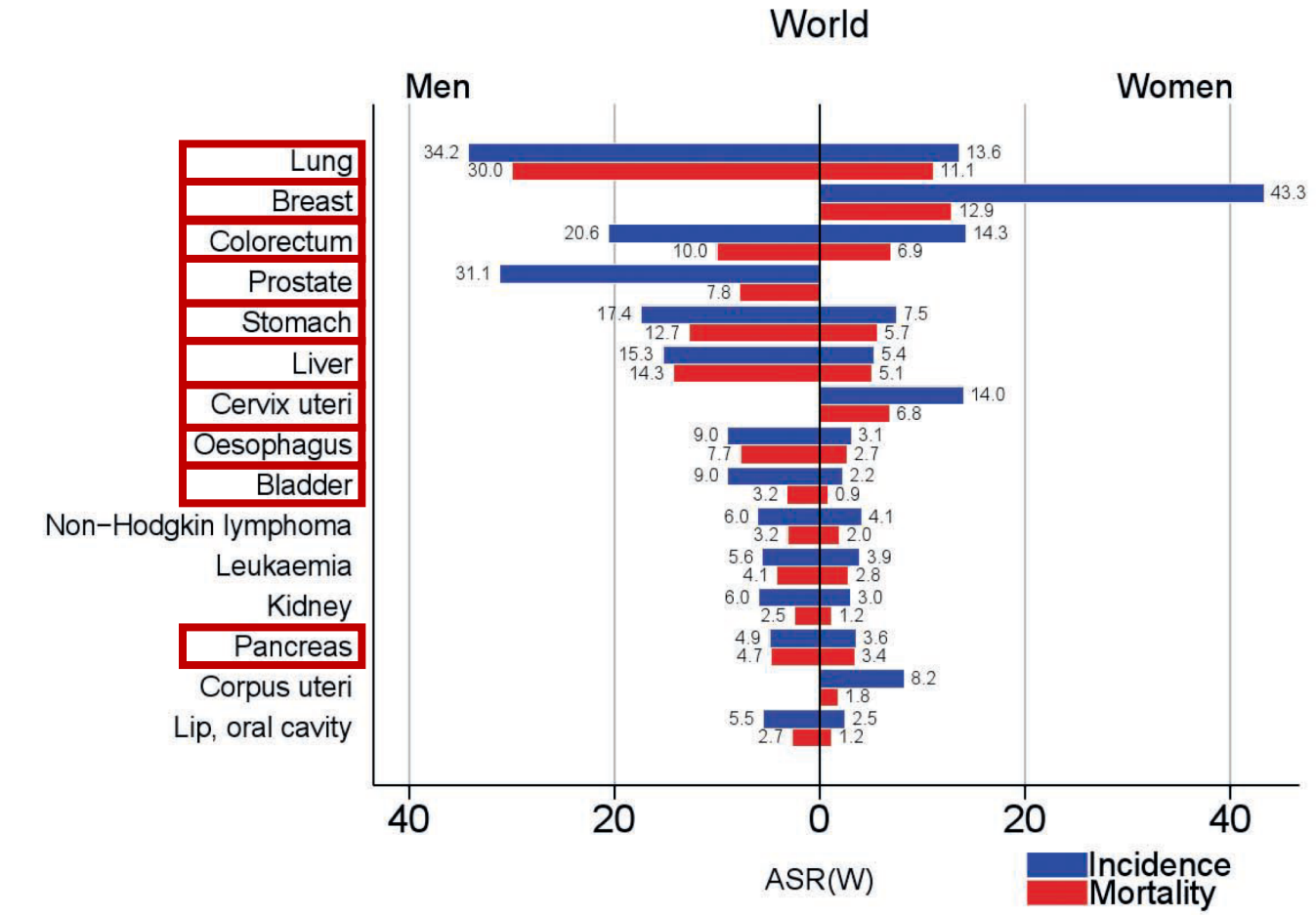
Carcinoma: cancers that arise from **epithelial** cells.



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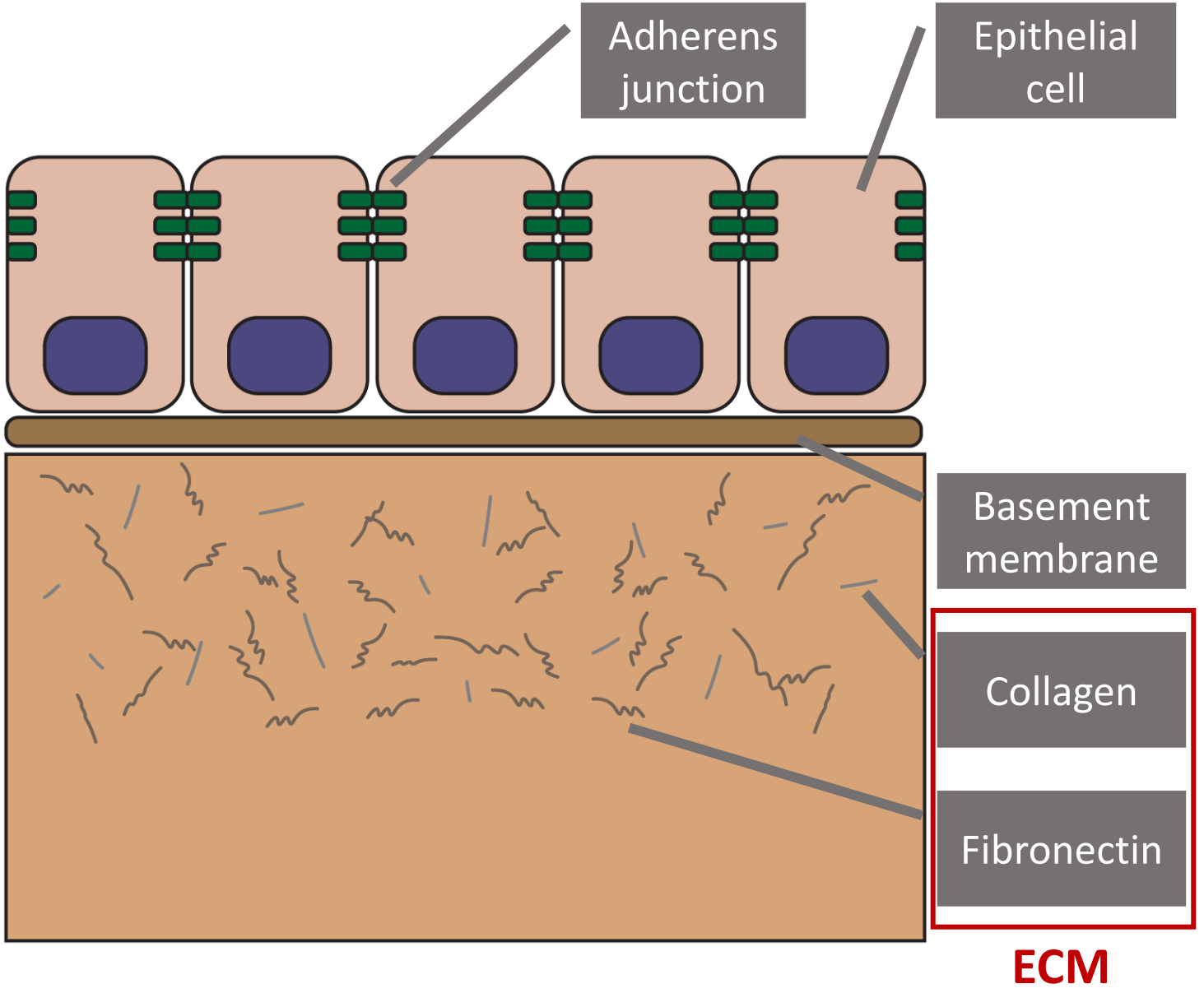
Epithelium

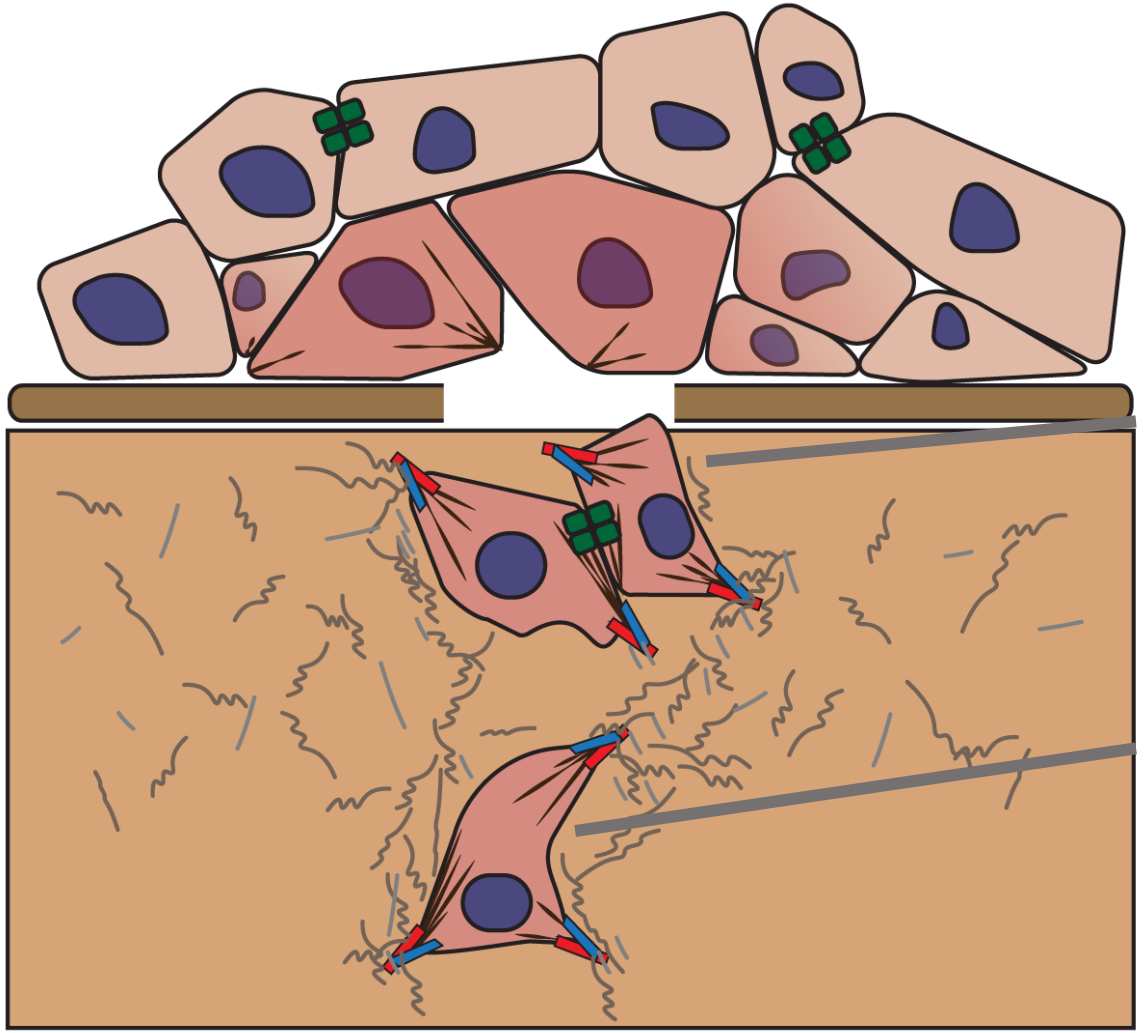
Thin layers of cells that cover internal/external surfaces of bodies and organs.



EMT: invasion and metastasis

Bidirectional signalling between cancer cells and the tumour microenvironment drives the progressive loss of **epithelial** properties combined with the cumulative acquisition of **mesenchymal** features (**EMT**).

Epi **Mes**



We propose a logical modelling approach to investigate and understand the mechanism at play during EMT, and the influence of the tumour environment on cell adhesion properties.

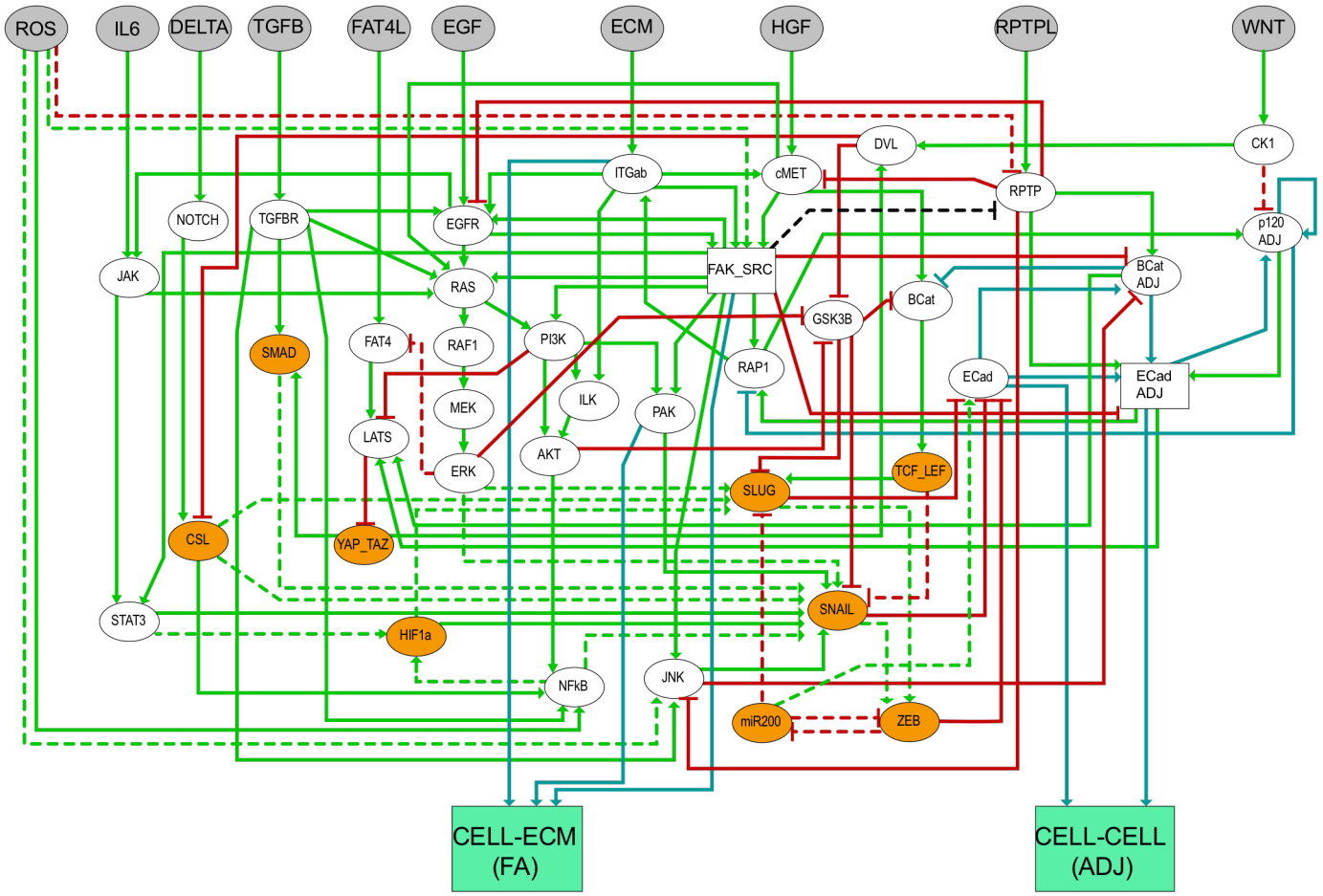
Logical formalism

The complexity and dimension (**components**) of the molecular network combined with a **lack** of **quantitative** information on **kinetic parameters**, **concentrations** and **mechanistic** insights on protein interactions motivate the use of logical modelling.

Boolean/Multivalued abstraction: each regulatory component is associated to a discrete variable representing its levels of activity, of concentration, etc. → **functional level.**

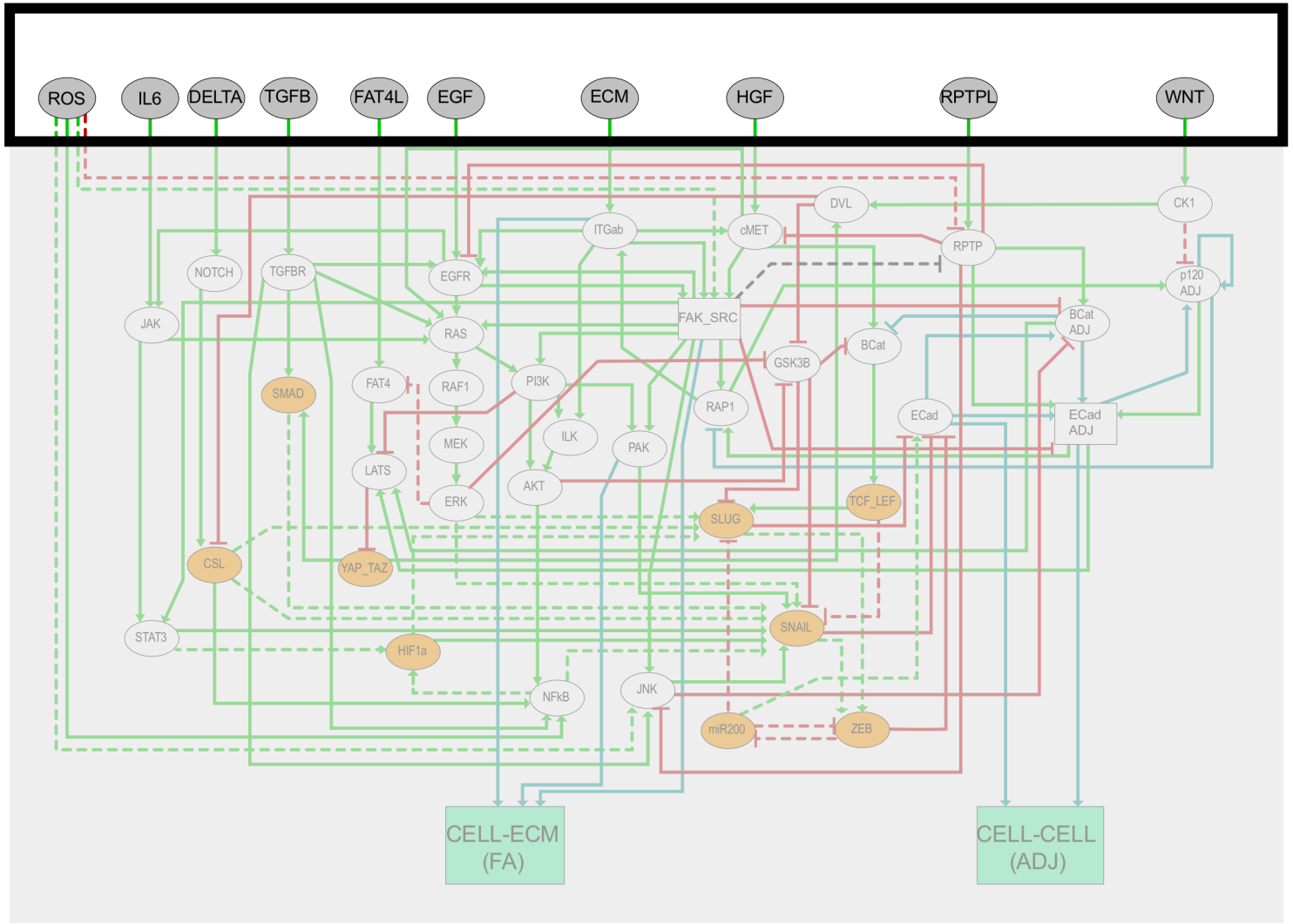
Each **regulatory component** is associated to a set of incoming interactions defining the evolution of the corresponding variable.

Model of cell adhesion properties



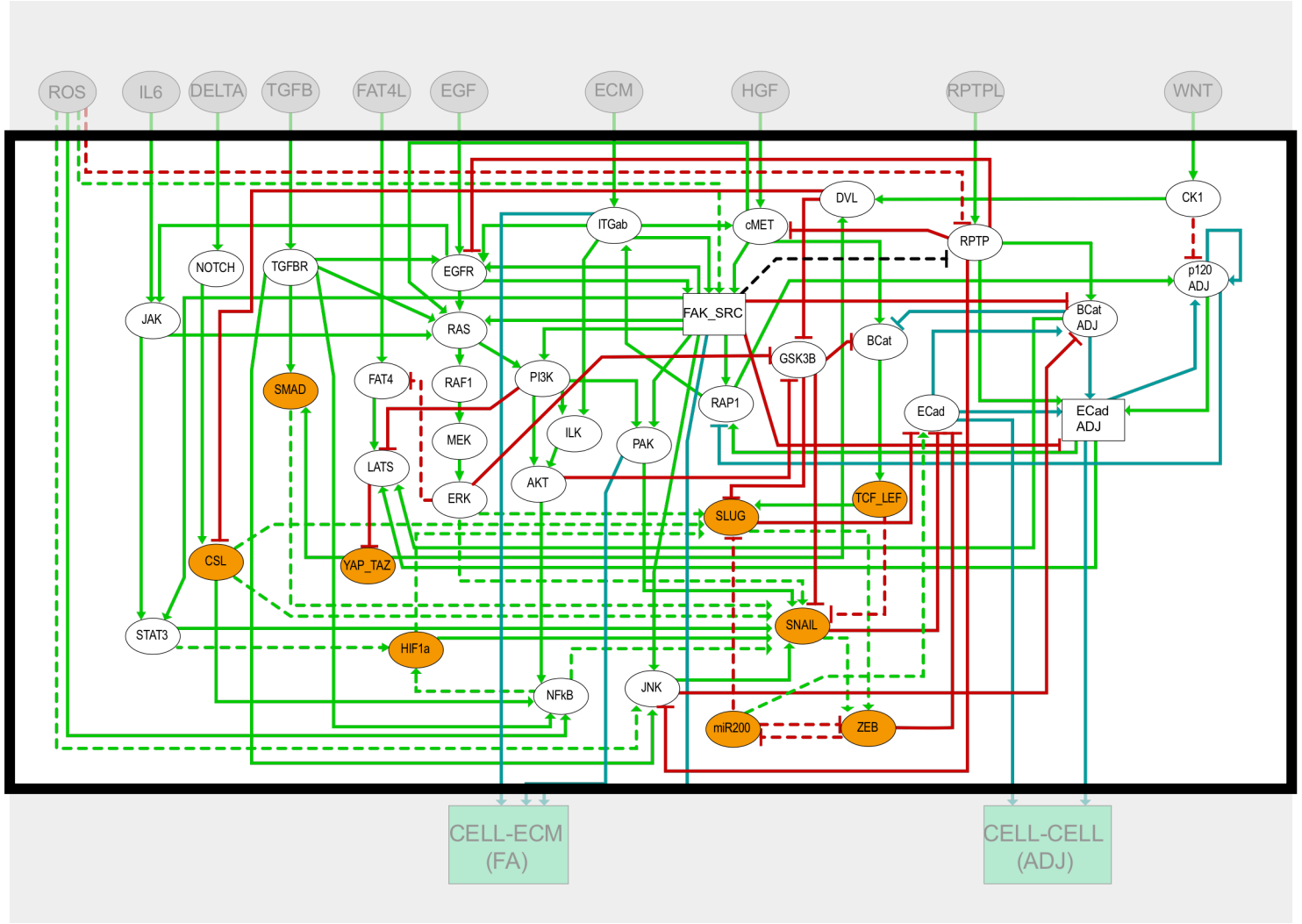
Model of cell adhesion properties

Input (*e.g.* growth factors, cell contacts, cytokines etc.)



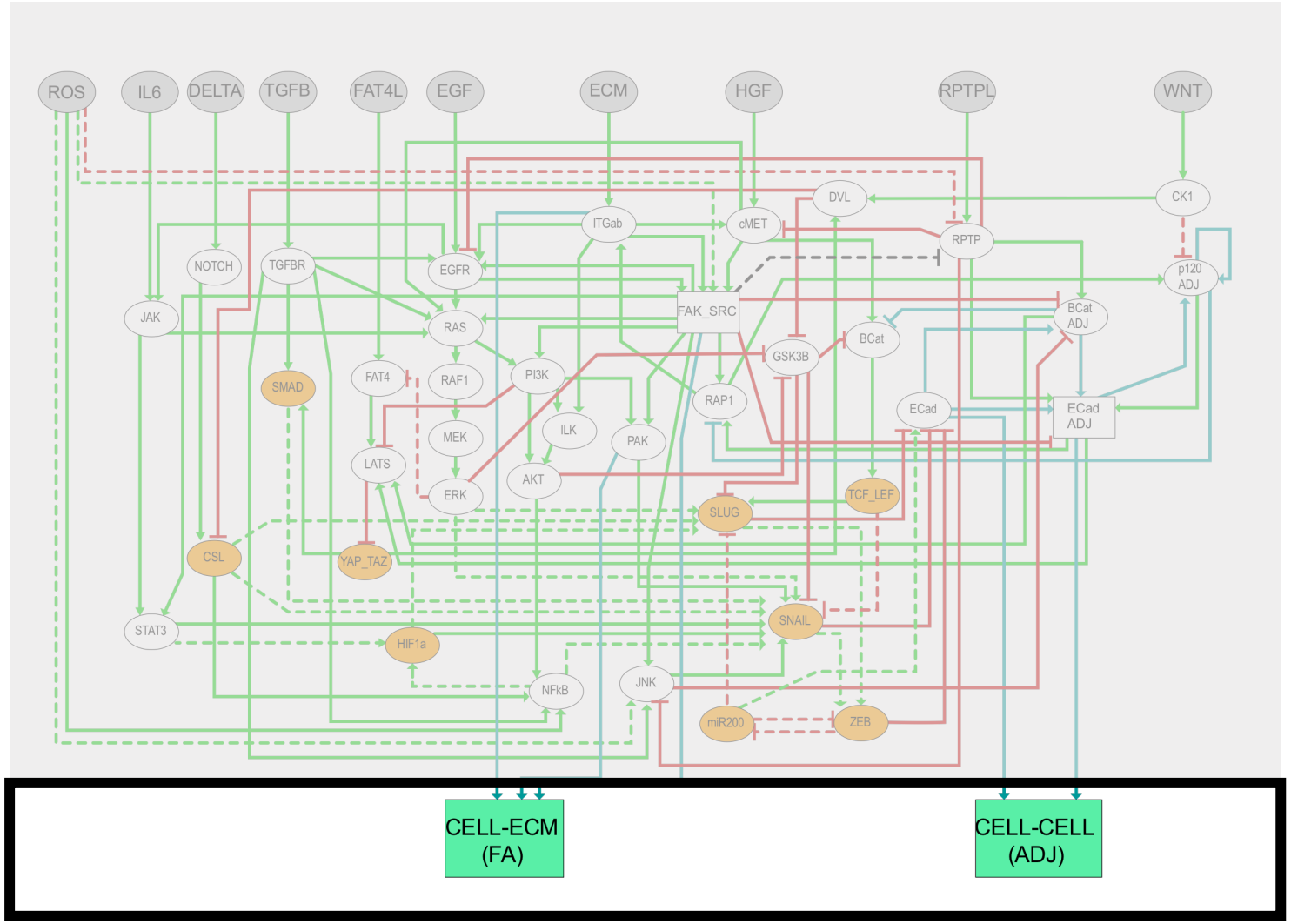
Model of cell adhesion properties

Internal components (*e.g.* kinases, transcription factors etc.)



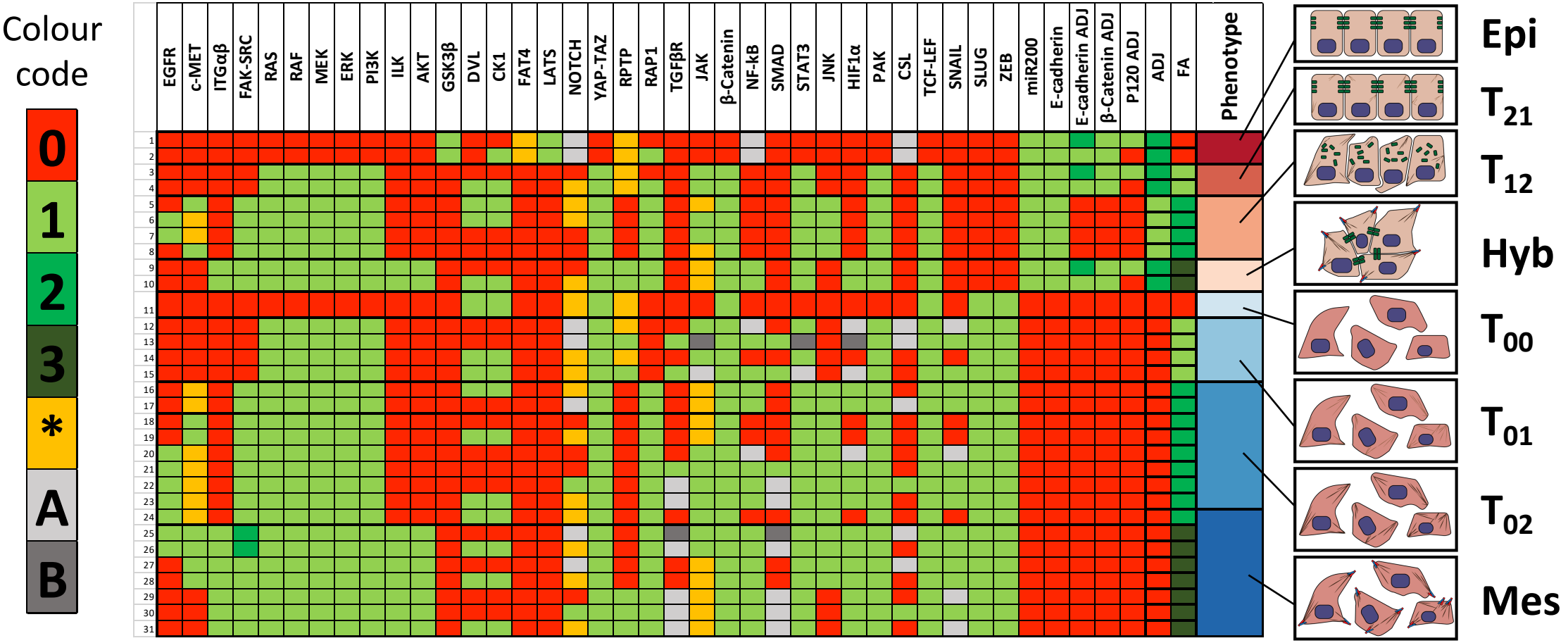
Model of cell adhesion properties

Outputs



Asymptotic behaviours

All model attractors are stable states (#**1452**, no cyclic attractor). Discarding inputs leads to unique stable patterns (#31), which are mapped to specific phenotypes.



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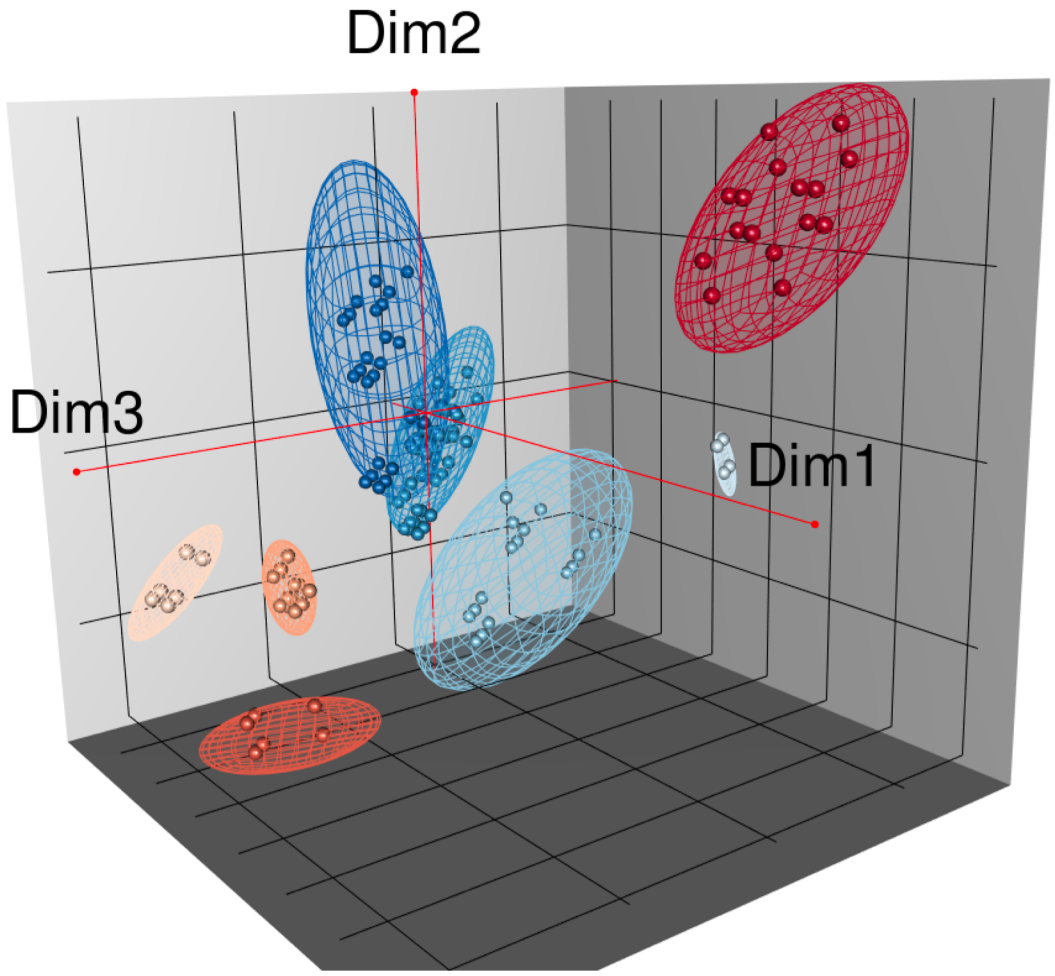
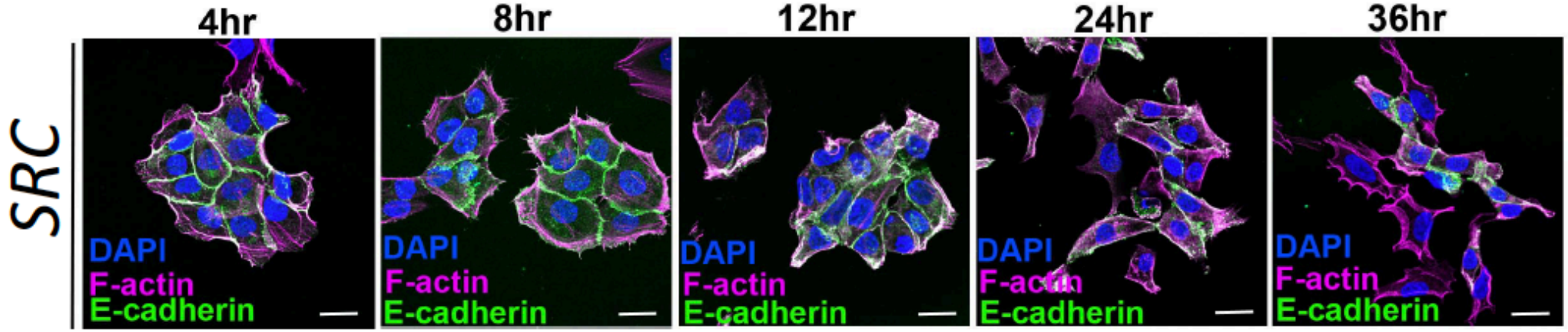


	Epi
	T_{21}
	T_{12}
	Hyb
	T_{00}
	T_{01}
	T_{02}
	Mes

Is there a clear difference between the hypothetical phenotypes?

Model Predictions

SRC is a proto-oncogene tyrosine kinase whose activation is capable of transforming **non-tumourigenic** epithelial breast cell line MCF10A.



With the first version of the model only **~49%** of the simulations starting from an **epithelial** state reached the **mesenchymal** phenotype

Model Predictions

μ-array data from literature (Hirsch, H.A. *et. al.* 2010) suggested **SRC inhibition of PTPR** (cell contact activated phosphatase).

Hirsch, H.A. et. al. – Cancer Cell. 17(4) - (2010)

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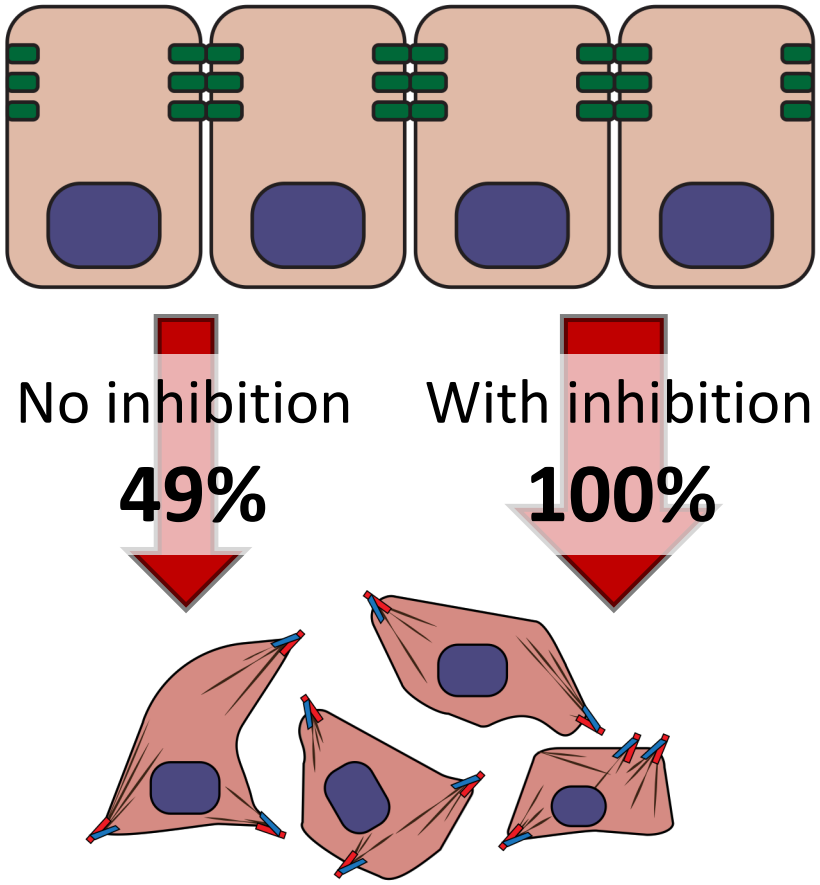

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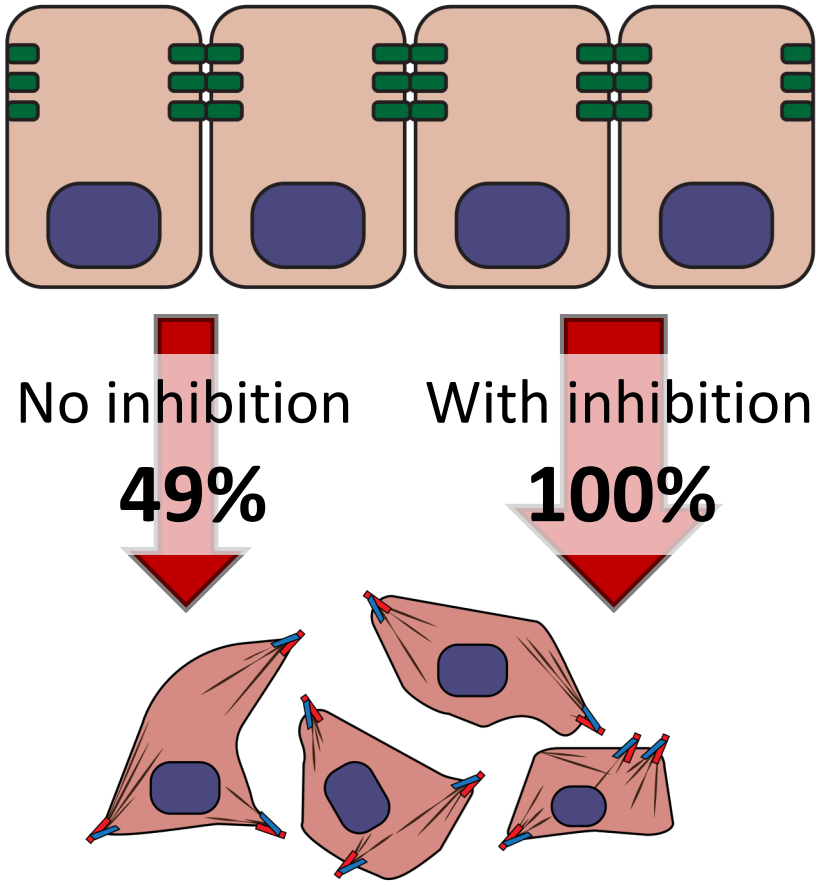

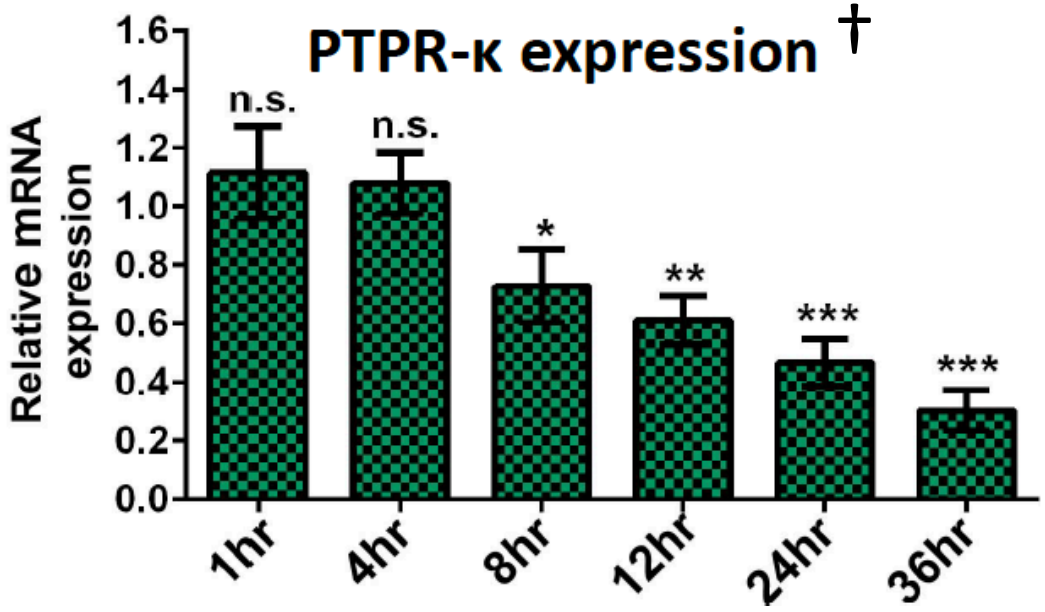

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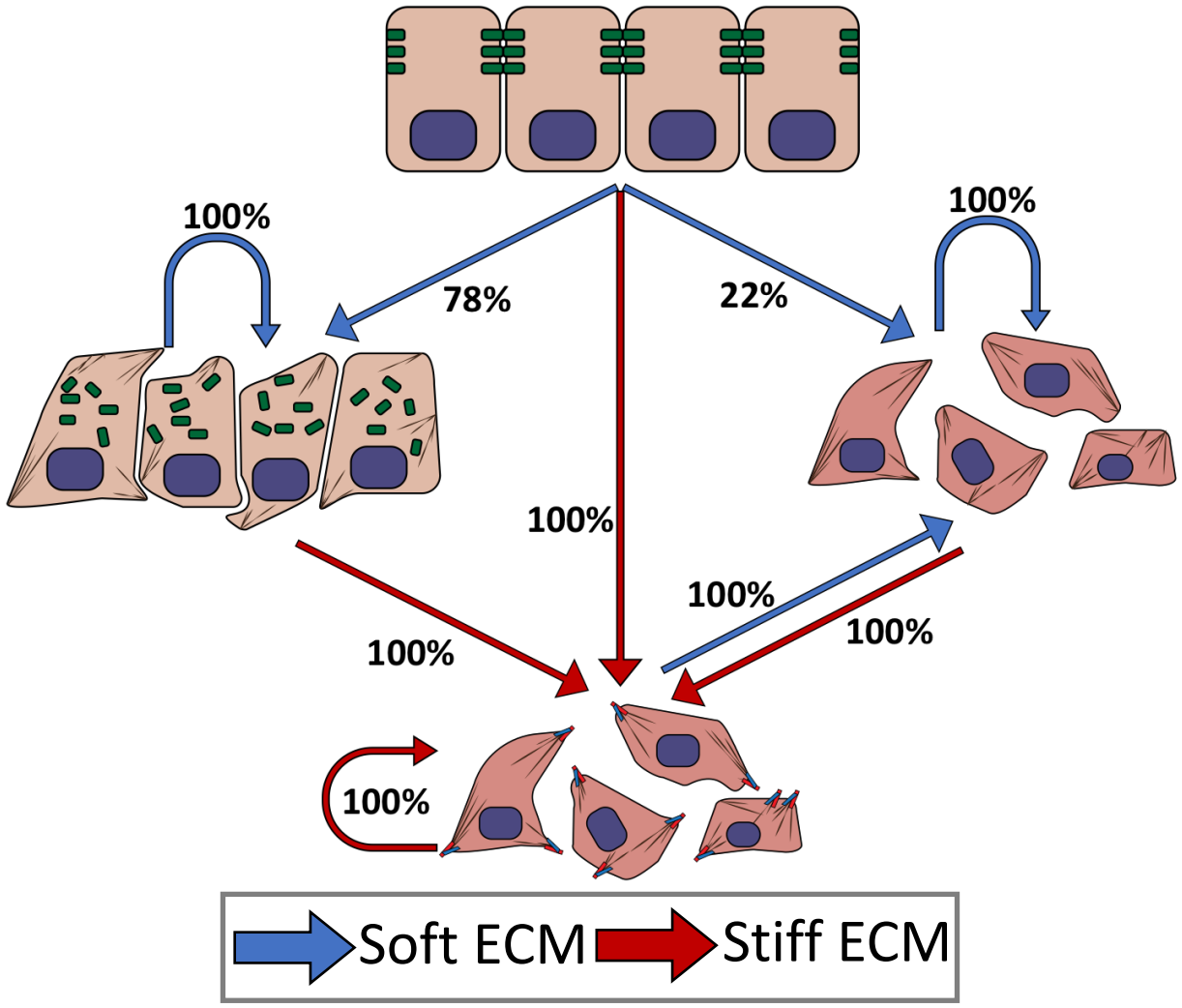
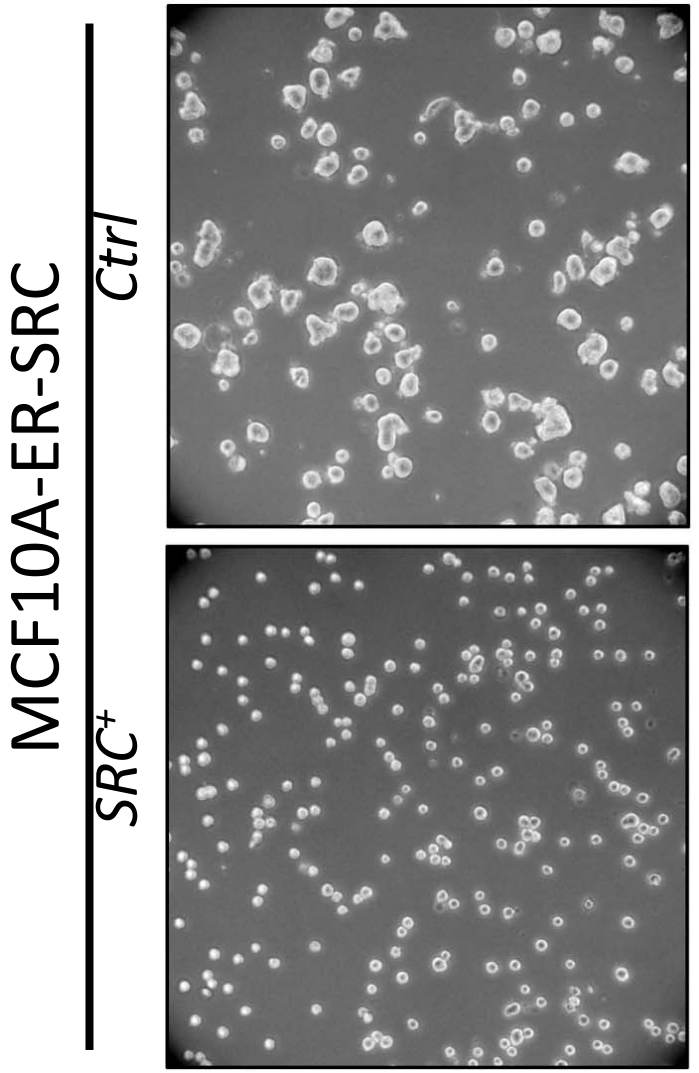
† In-house validation performed by A. Pawar

Model Predictions: *In silico* vs *in vitro*: *SRC*$^{+}$





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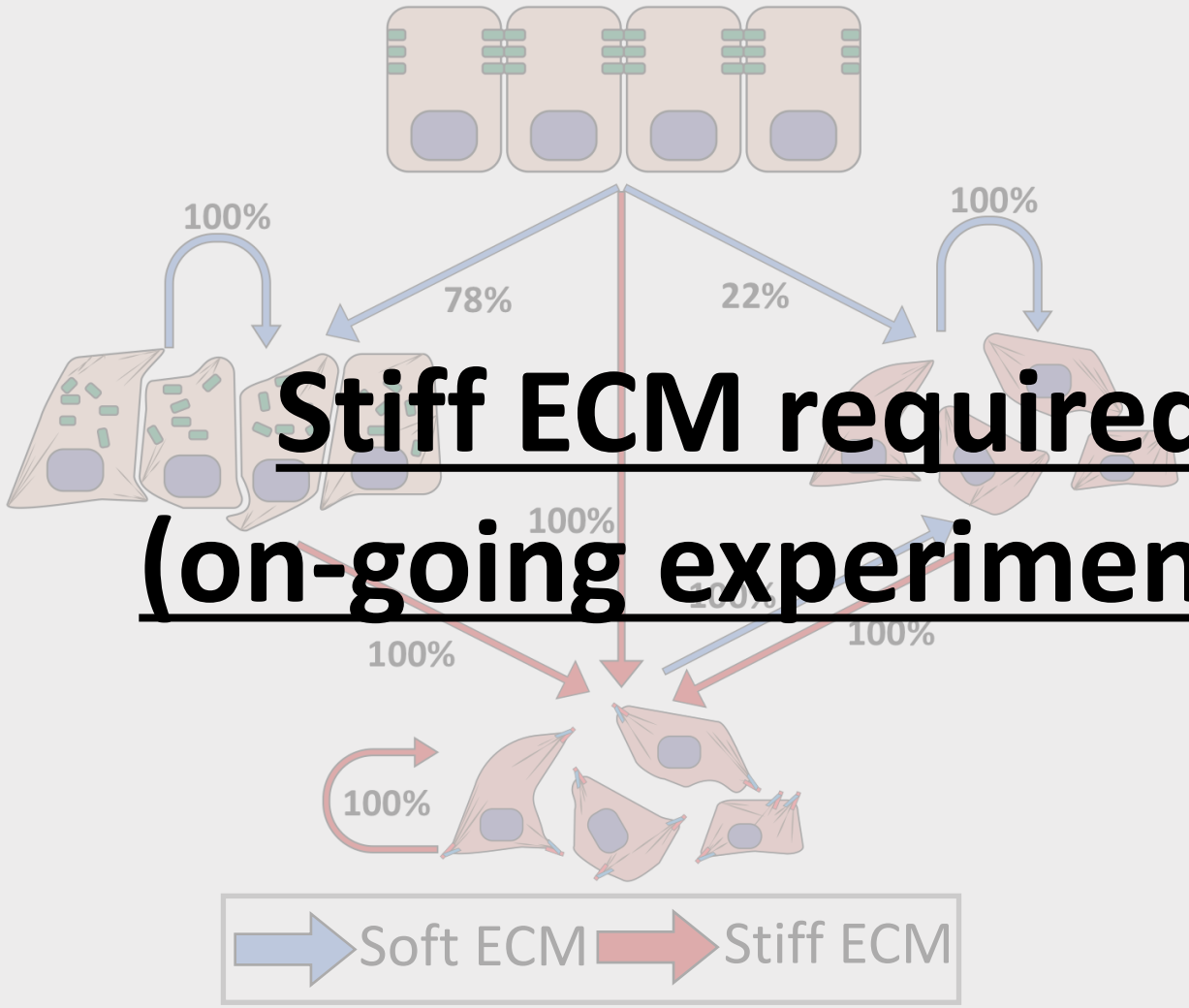
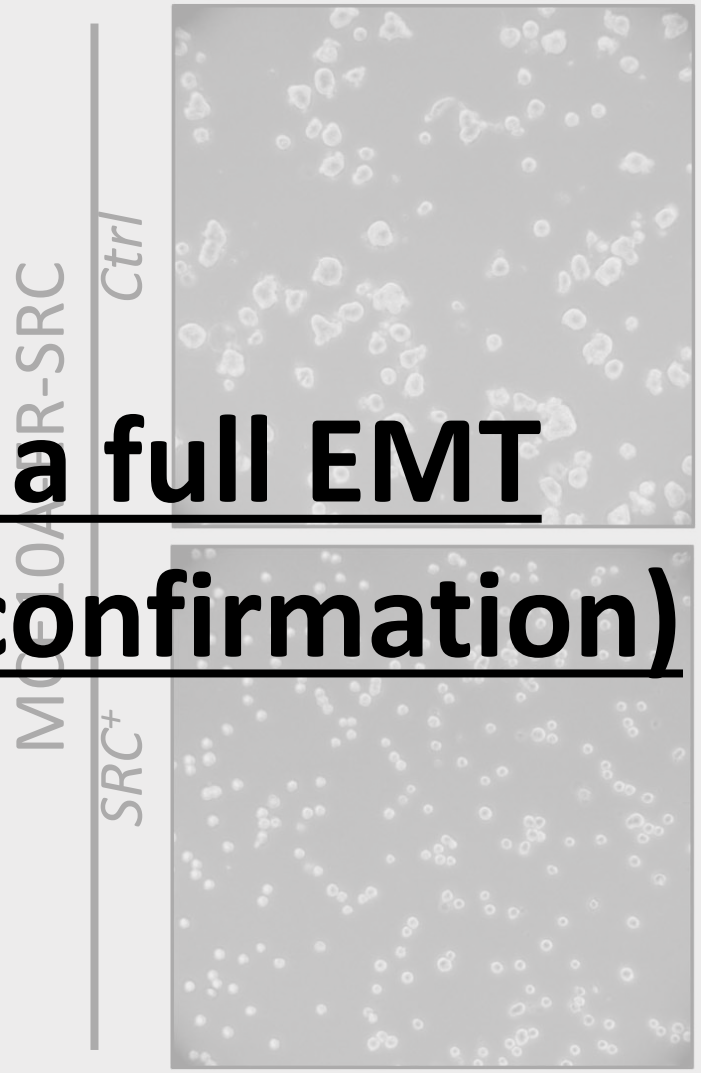
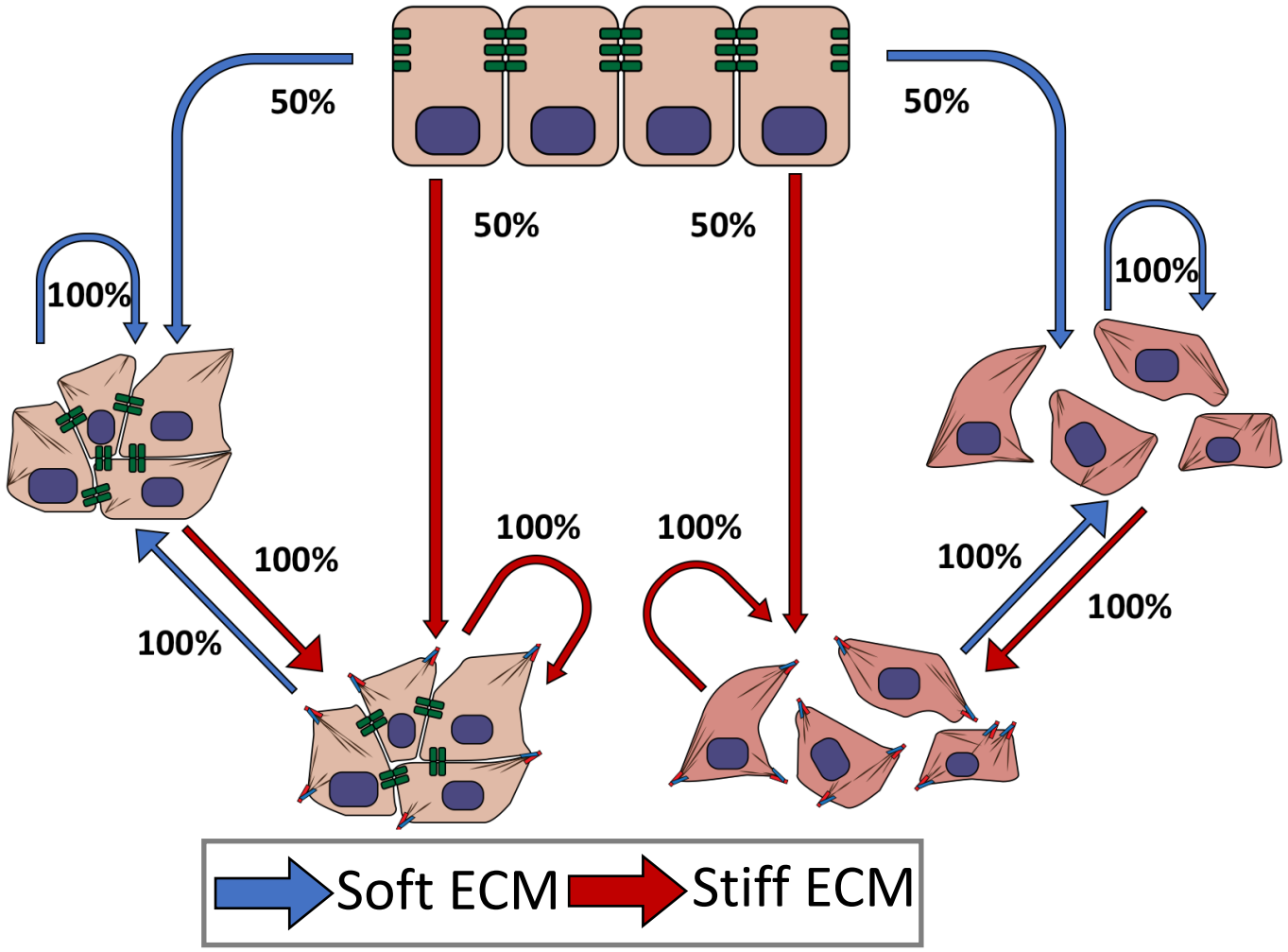
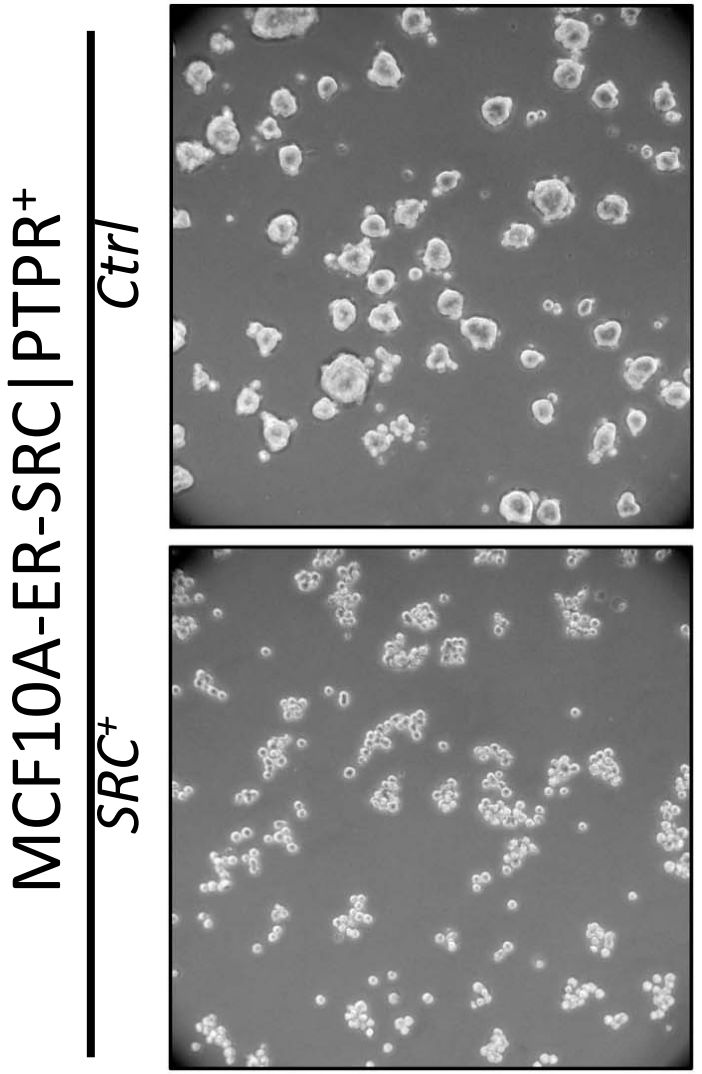


Stiff ECM required for a full EMT (on-going experimental confirmation)



Model Predictions: *In silico* vs *in vitro* $SRC^{+}|PTPR^{+}$





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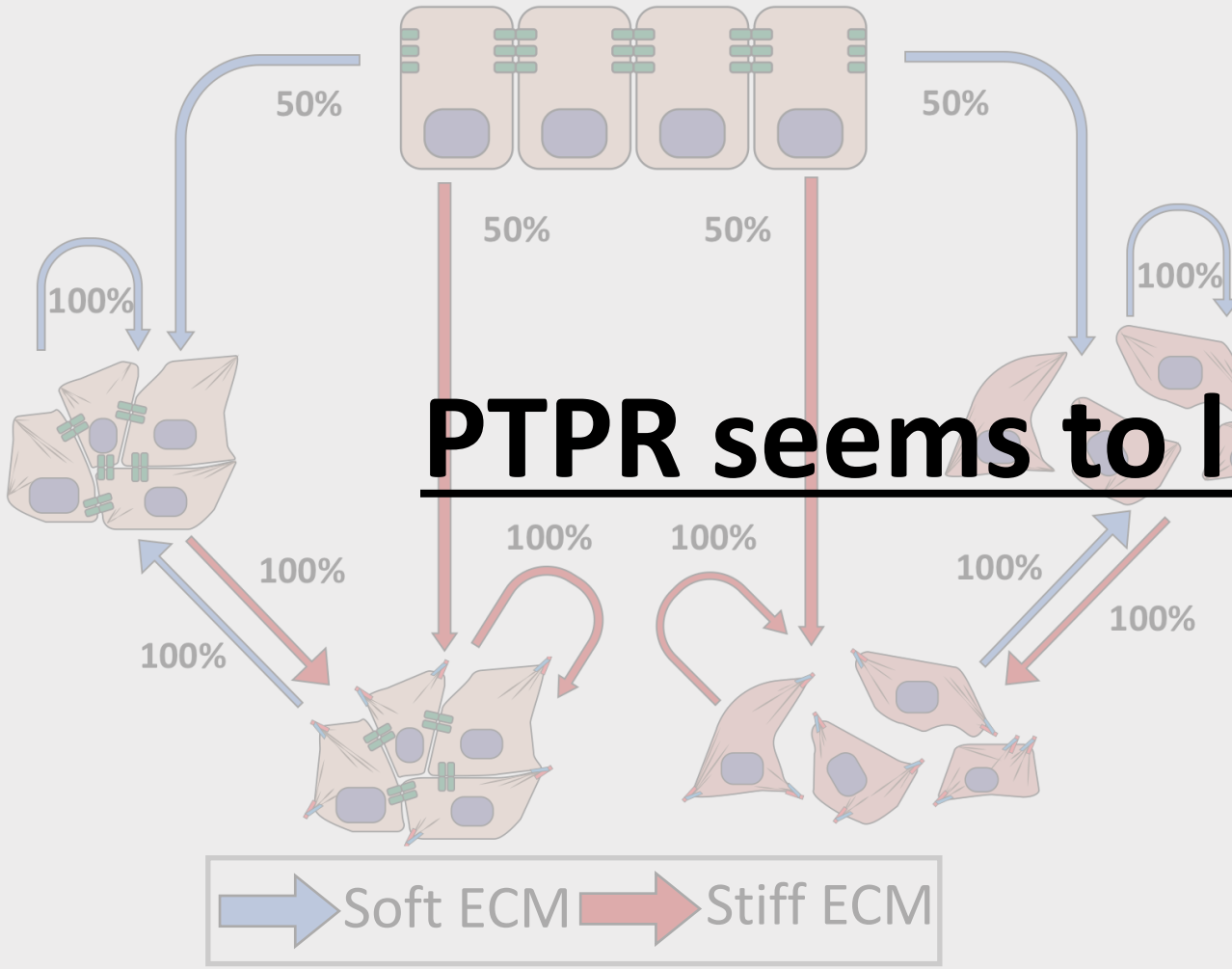
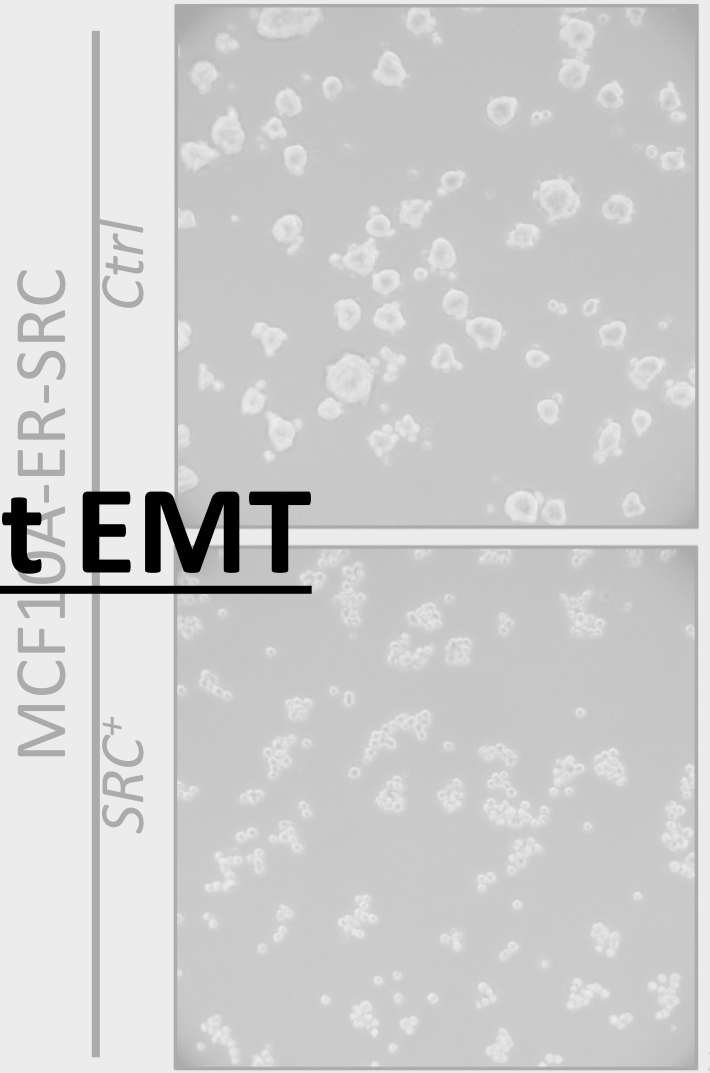
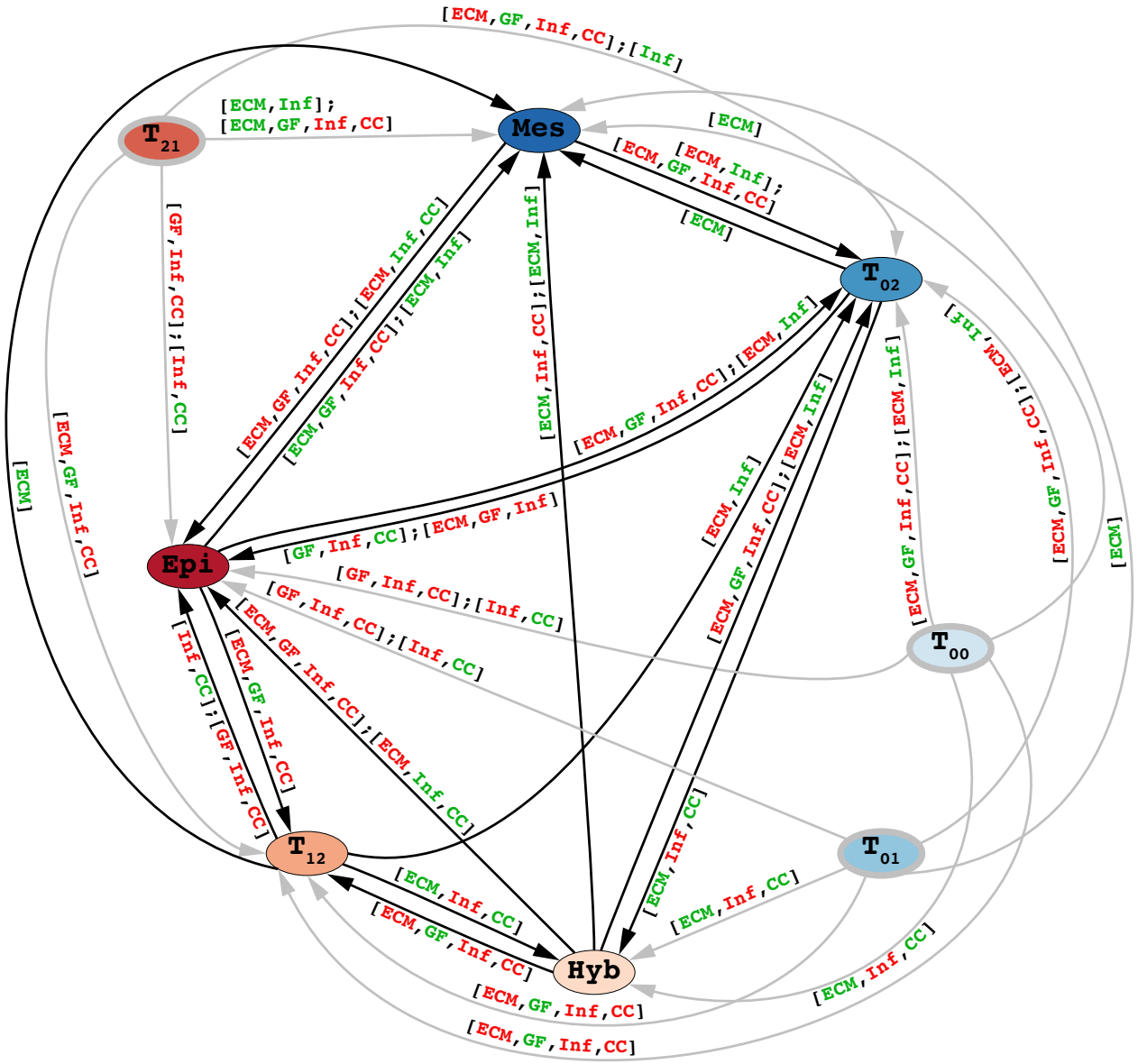


PTPR seems to limit EMT



We used model-checking techniques to assess environmental influence:



Model Predictions: Phenotype Plasticity

ECM	Growth Factors (GF)	Inflammation (Inf)	Cell-Cell contact (CC)
ECM	EGF, HGF	IL6, ROS, TGFβ	RPTPL, FAT4L

Conclusions

- We provide a **tool** for **probing** in silico **cellular responses** to internal and environmental perturbations
- **PTPR** might be a critical **EMT inhibitor** downstream of *SRC*, by limiting the mesenchymal phenotype and favouring the emergence of hybrid phenotype

Future prospects

- Model **extension** to investigate the link between **EMT** and acquisition of **stemness** features
- Embedding the model in a **multi-cellular** context to unravel interplay between **neighbouring cells**

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POSTER #P_Sy020 Monday @18:30

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