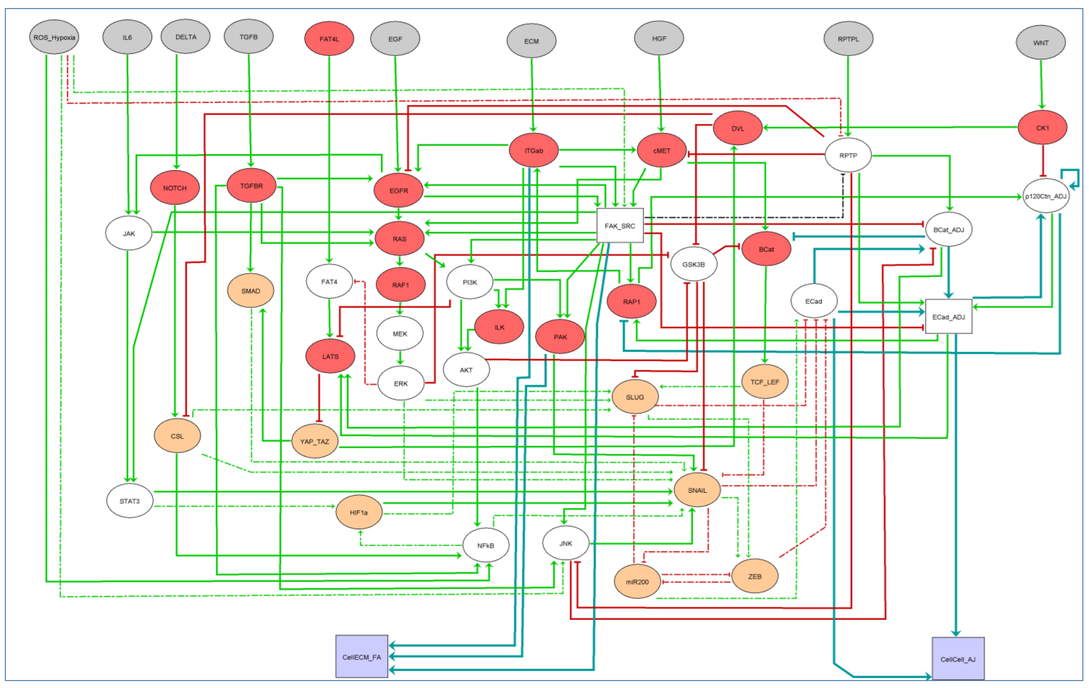
Cell Communication through Logical Modelling and Attractor Analysis

Introduction

- Cancer is a complex disease and a global burden. EMT is one of the main steps in cancer progression. Logical modelling is a powerful qualitative modelling approach to model large EMT gene regulatory and signalling networks.
- EpiLog is a software to do logical modelling in a multicellular environment. It accepts a cellular model in SBML format and apply this model on a grid of cells. So, in each cell there is a Signalling Network (SG). Each SG has inputs which come from The neighbouring cells. This is how cells affect one another. Inputs are defined based on the integration functions. An integration function is a logical function which explain how a cell could receive some inputs in a multicellular environment.



FAK_SRC	MEK	ERK	PI3K	AKT	GSK3B	FAT4	YAP_TAZ	RPTP	JAK	NFkB	SMAD	STAT3	JNK	HIF1a	CSL	TCF_LEF	SNAIL	SLUG	ZEB	miR200	Ecad	ECad_ADJ	Bcat_ADJ	p120Ctn_ADJ	CellCell_AJ	CellECM_FA
0	1	1	1	0	0	0	1	*	1	0	0	1	0	0	0	1	0	1	1	0	0	0	0	0	0	1
0	1	1	1	0	0	0	1	*	1	1	0	1	0	1	1	1	1	1	1	0	0	0	0	0	0	1
0	1	1	1	0	0	0	1	1	0	1	1	0	0	0	*	1	1	1	1	0	0	0	0	0	0	1
0	1	1	1	0	0	0	1	1	1	1	1	1	0	1	*	1	1	1	1	0	0	0	0	0	0	1
1	1	1	1	0	0	0	1	0	*	1	0	1	1	1	*	1	1	1	1	0	0	0	0	0	0	2
1	1	1	1	0	0	0	1	0	1	1	1	1	1	1	*	1	1	1	1	0	0	0	0	0	0	2
1	1	1	1	0	0	0	1	0	*	0	0	1	1	0	0	1	0	1	1	0	0	0	0	0	0	2
1	1	1	1	1	0	0	1	0	0	1	0	1	1	1	*	1	1	1	1	0	0	0	0	0	0	3
2	1	1	1	1	0	0	1	0	1	1	*	1	1	1	0	1	1	1	1	0	0	0	0	0	0	3
1	1	1	1	1	0	0	1	1	*	1	0	1	0	1	0	1	0	1	1	0	0	0	0	0	0	3
2	1	1	1	1	0	0	1	0	1	1	*	1	1	1	1	1	1	1	1	0	0	0	0	0	0	3
1	1	1	1	1	0	0	1	1	0	1	*	1	0	1	1	1	1	1	1	0	0	0	0	0	0	3
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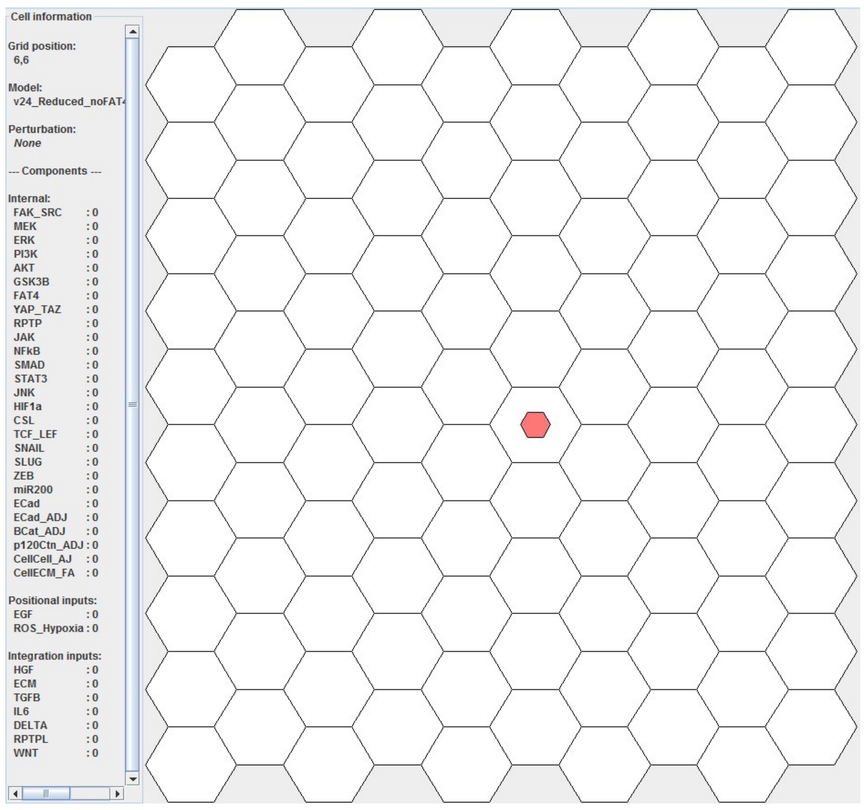
1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	*	1	1	1	1	0	0	0	0	0	0	3
1	1	1	1	1	0	0	1	0	*	1	0	0	1	1	0	0	1	0	0	0	1	1	0	0	0	2
0	0	0	0	0	1	1	0	*	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	1	1	0
0	0	0	0	0	1	1	0	*	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0
0	0	0	0	0	1	1	0	*	0	1	0	0	0	0	1	0	0	0	0	0	1	1	2	1	1	0
0	0	0	0	0	1	1	0	*	0	1	0	0	0	0	1	0	0	0	0	0	1	1	1	1	0	0
0	1	1	1	0	0	0	1	*	1	0	0	1	0	1	0	1	0	0	0	0	1	1	2	1	1	1
0	1	1	1	0	0	0	1	*	1	0	0	1	0	0	0	1	0	0	0	0	1	1	1	1	0	1
1	1	1	1	1	0	0	1	1	*	1	0	1	0	1	0	1	0	0	0	0	1	1	2	1	1	2
1	1	1	1	1	0	0	1	1	*	1	0	1	0	1	0	1	0	0	0	0	1	1	1	1	0	2

The figure is EMT gene regulatory network at cellular scale created in GINsim software. The model contains inputs (signals), internal components and outputs (phenotypes). This model is large, so it was reduced by ignoring the components in red. The table shows the stable states of the reduced model without inputs. The last two columns present Epithelial, Hybrid and Fully-Mesenchymal states. This reduced model is suitable to be implemented in EpiLog.

Inputs and integration functions	Definition of integration function	PMIDs
WNT = (!GSK3B and !SMAD) or (LEF or ERK or JAK)	The cell receive WNT signal if one neighboring cell does not have GSK3B and SMAD or have LEF or ERK or JAK	10523516
ECM= (SMAD or AKT) and (JNK or ERK)	The cell receive ECM signal if one neighboring cell has SMAD or AKT and JNK or ERK	15265520
DELTA = TCF_LEF	The cell receive DELTA signal if one neighboring cell has TCF_LEF complex	15545629
IL6 = NFkB and STAT3	The cell receive IL6 signal if one neighboring cell has NFkB and STAT3	22105366
TGFB = (ERK | JNK) & !GSK3B	The cell receive TGFB signal if one neighboring cell has NFkB or STAT3 and it must not have GSK3B	10208426
HGF = ((({STAT3} & {FAK_SRC}) | ({ERK} & {JNK})) & !{NFkB})	The cell receive HGF signal if one neighboring cell has STAT3 and Src or it has ERK and JNK and it must not have NFKB	11278729 , 17685427
RPTP = RPTPL	The cell receive RPTP signal if one neighboring cell has RPTPL	22682003

Epithelial grid in EpiLog

In this figure, a hundred-cell grid is depicted in EpiLog. All the components are zero (Wild condition) in the initial condition. By running the simulation, based on how integration functions and other parameters are defined, cells start to send signal to one another and the state inside each cell change.



Discussion and Conclusion

Multicellular modelling is controlled by a lot of aspects and parameters. For example, The size of the grid, the way integration functions are defined, location of perturbed cells in the grid, number of perturbed cells in the grid and geometry and distance between the perturbed cells.

In this experiment a lot of effort was done to simulate what would be happen in a slide of one layer epithelial tissue under going EMT. A thorough literature survey was done to define the integration functions and their specifications tried to be set based on biological evidence.

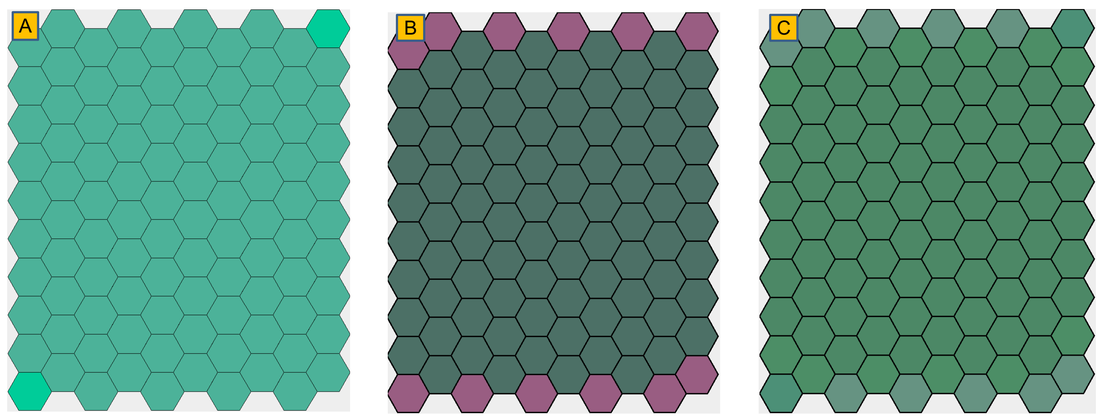
A few Src-perturbed cells do not have the power to impact the grid much, however cells themselves become fully-mesenchymal. If there is a short distance between the perturbed cells, the normal cells in the between receive more EMT signal from the perturbed cells and they will represent a fully-mesenchymal phenotype (H), while if the distance increases between the perturbed cells, normal cells would be affected less by perturbed cells (J). To sum up, there is a need for sufficient and observable biological evidence for multicellular logical modelling in EMT context and by controlling these parameters we can understand the mechanism of the EMT and cancer progression.

Running Simulation with different Initial state

Internal Components	A	B	C
FAK_SRC	0	2	2
MEK	0	1	1
ERK	0	1	1
PI3K	0	1	1
AKT	0	1	1
GSK3B	1	0	0
FAT4	1	0	0
YAP_TAZ	0	1	1
RPTP	1	0	1
JAK	0	1	1
NFkB	0	1	1
SMAD	0	1	0
STAT3	0	1	1
JNK	0	1	0
HIF1a	0	1	1
CSL	0	0	0
TCF_LEF	0	1	1
SNAIL	0	1	0
SLUG	0	1	0
ZEB	0	1	0
miR200	1	0	1
Ecad	1	0	1
ECad_ADJ	2	0	1
BCat_ADJ	1	0	1
p120Ctn_ADJ	1	0	0
CellCell_AJ	2	0	2
CellECM_FA	0	3	3
Positional inputs			
EGF	2	0	2
ROS_Hypoxia	0	3	3
Integration inputs			
HGF	0	0	0
ECM	0	1	1
TGFB	0	1	0
IL6	0	1	1
DELTA	0	1	1
RPTPL	1	0	1
WNT	0	1	1

The table shows the state of the components in simulations A, B and C. In EMT context, model checking is needed to see if the model or integration functions and other parameters works correctly. The whole grid should go from Wild type and Epithelial initial condition to the epithelial phenotype (A).

There is Src over-activation in whole the grid and after running the simulation whole the grid present fully-mesenchymal phenotype in B. There are Src over-activation and RPTP over-expression in whole the grid and after running the simulation all the cells become hybrid in C. different pattern of purterbed cells are presented in figures D to J. In these figures, the left panel represents the initial condition and the right panel represents the simulation result. The initial condition is epithelial in whole the grid and blue cells are Src over-activated cells.



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