A Multi-cellular Model of the Pancreatic Cancer Microenvironment

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Joint work with
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Pancreatic Cancer

- Pancreatic Cancer (PC): extremely aggressive, highly lethal, poor prognosis

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- **pancreatic stellate cells (PSC)**, endothelial cells, nerve cells, immune cells, lymphocytes, dendritic cells and the extracellular matrix.

Pancreatic Stellate Cells

- Location: periacinar, perivascular, and periductal regions

- Once activated, the quiescent state to a myofibroblast phenotype

- Main source, stromal reaction

- supporting role in tumor development

Graph model of PCCs and PSCs
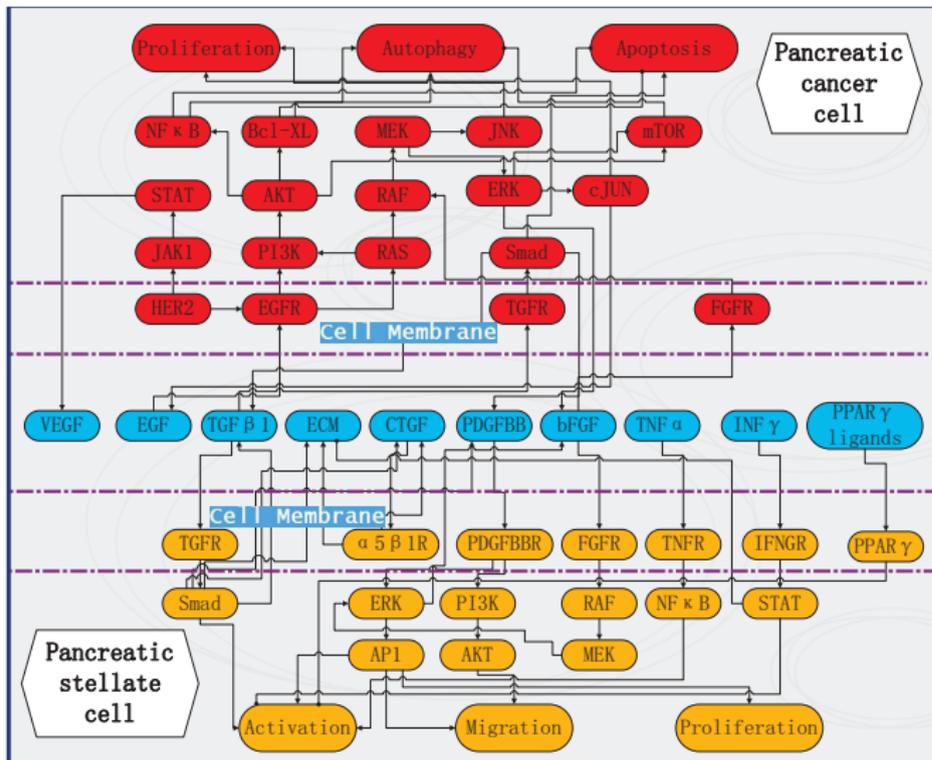
- PCCs
  - Mutations: K-Ras, Her2/neu
  - Proliferation
  - Apoptosis
  - Autophagy
- PSCs
  - Activation
  - Migration
  - Proliferation
- Interactions between PCCs and PSCs
  - TGFbeta1
  - PDGFBB
  - bFGF

Autophagy

- catabolic process, degradation of a cell's own components

- Another type of programmed cell death

- Apoptosis vs. Autophagy (In pancreatic cancer, mutual exclusion)

- Role in cancer development

BioNetGen Model

- specification and simulation of rule-based models

- molecular level of biochemical systems
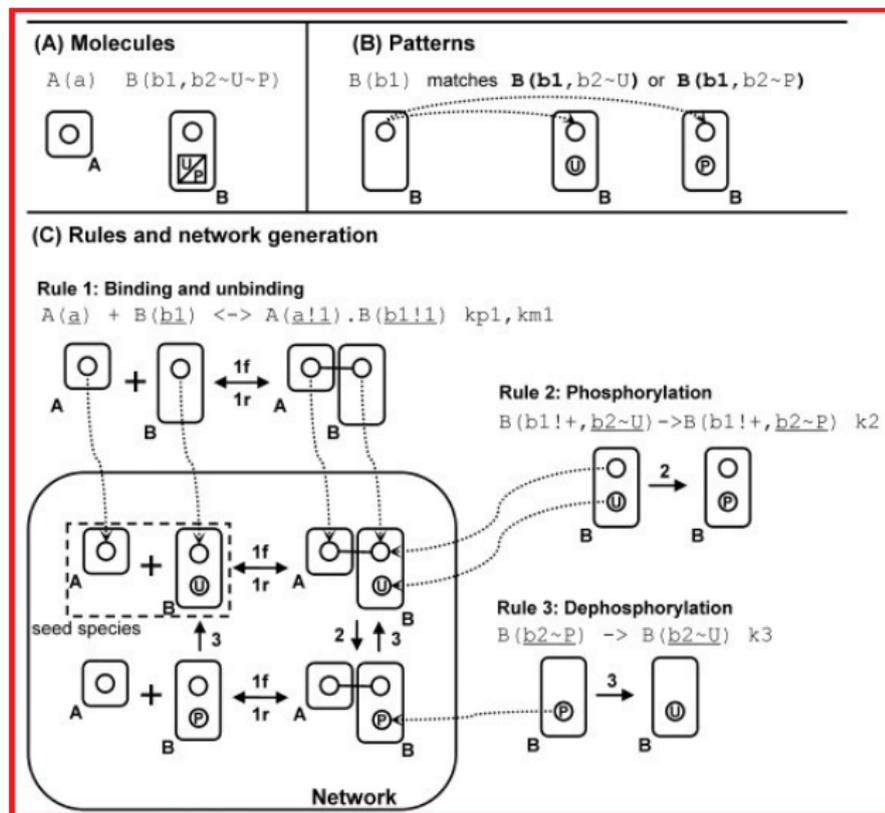
Redefine the component of BioNetGen language

We first enable BioNetGen language to specify cell level models through redefining the meaning of its basic components.

The basic building blocks: either extracellular molecules or cells

begin molecule types
EGF
PCC(Pro~T~F,
Apo~T~F,RAS~T~F)
end molecule types

begin seed species
EGF 0
PCC(Pro~F,Apo~F,
RAS~F) 2
end seed species
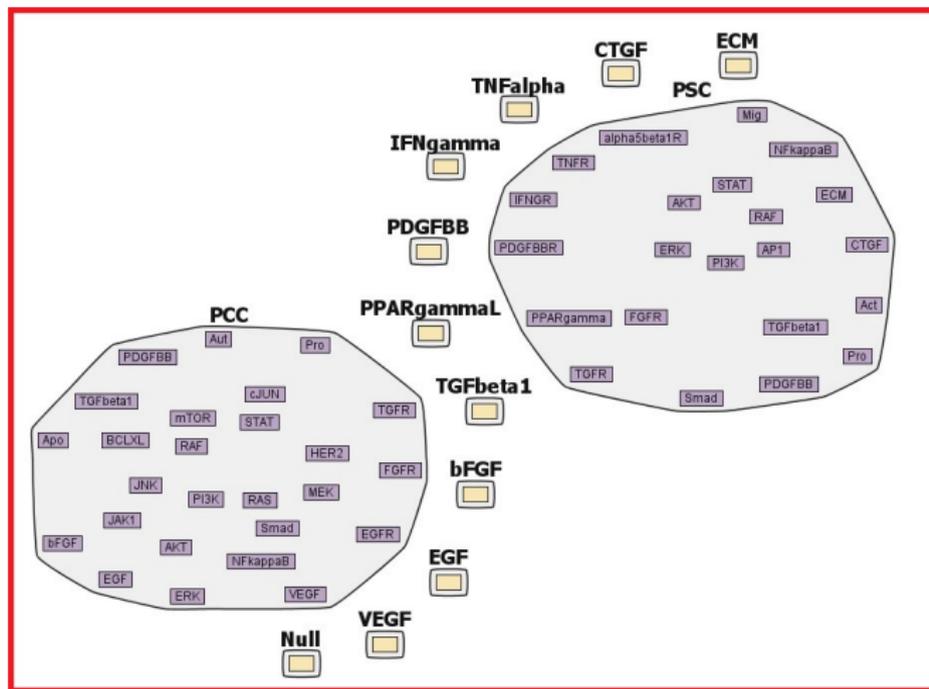
Patterns

Patterns are used to identify a set of cells that share a set of features, and their behavior.

Rules

Rule 1: Ligand-receptor binding

Example: EGF+PCC(EGFR~F)→PCC(EGFR~T) bindingrate

Explanation:

EGFR is free or unbound.

Bindingrate is decided according to affinity and whether the ligands are endogenous.

The multiple receptors on the surface:
PCC(EGFR~T,PI3K~T)→PCC(EGFR~F,PI3K~T) transrate (high)

Rules (cont.)

Rule 2: Mutated receptors form a heterodimer

Example: PCC(HER2∼F,EGFR∼F)→PCC(HER2∼T,EGFR∼T) bindingrate

Rule 3: Downstream regulation

Example:
PCC(MEK∼T,ERK∼T)→PCC(MEK∼F,ERK∼T) transrate
PCC(MEK∼T,ERK∼F)→PCC(MEK∼F,ERK∼T) transrate

Rules (cont.)

Rule 4: Cell functions

Examples:

Proliferation:
PCC(Pro~T) → PCC(Pro~F)+ PCC(Pro~F,Apo~F,RAS~F,PI3K~F) prorate

Apoptosis: PCC(Apo~T)→Null() apoprate

Autophagy: PCC(Aut~T)→EGF+TGFbeta1 autorate
(The molecules on the right side of this type of reactions depend on what
molecules are inside this cell.)

Migration: PSC(Mig~T)

Activation:PSC(Act~T)

Rules (cont.)

Rule 5: Secretion

Example:

PCC(TGFbeta1∼T)→PCC(TGFbeta1∼F)+ PCCTGFbeta1 secreterate1
PSC(TGFbeta1∼T)→PSC(TGFbeta1∼F)+ PSCTGFbeta1 secreterate2
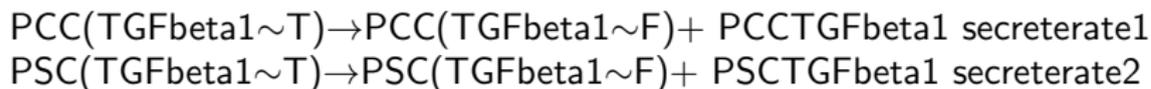
Explanation: The reason to label TGFbeta1 as either PCC- or PSC- is to differentiate the endogenous and exogenous molecules. The binding rates are different in these two cases.

Rules (cont.)

Rule 6: Mutation

Example: PCC(RAS$\sim$F)$\rightarrow$PCC(RAS$\sim$T) mutation

Explanation: The key idea of modelling mutations is to set a very high value to the mutation rate.

Rule 7: Degradation of extracellular molecules

Example: EGF$\rightarrow$Null() deg

Rules (cont.)

Rule 8: Human intervention

Example: PCC(EGFR∼T)→PCC(EGFR∼F) interv

Explanation:

The exemplified is to inhibit the expression of EGFR.

Predict whether a therapy targeting a certain protein could obtain effective outcome;

Well tuned intervention rate can, more or less, give indications when deciding the dose of medicine used in this therapy.

Tumor Development with or without PSCs

Firstly, the existing of stellate cells can promote the proliferation of tumor cells.
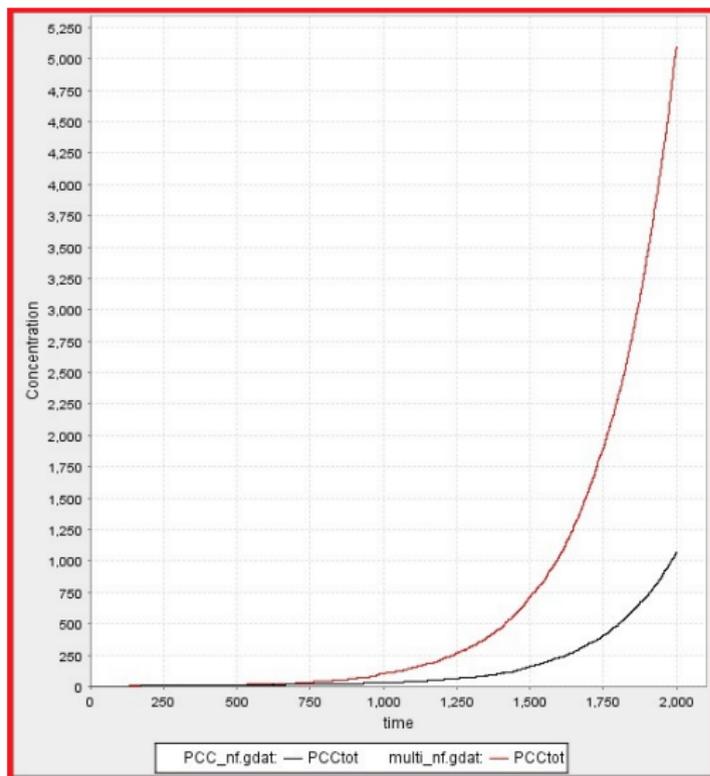
- PCCs: pancreatic cancer cells

- PSCs: pancreatic stellate cells

- Stochastic simulation

- Time unit: second

- Averaged plot of 20 trajectories

- We will use Statistical Model Checking in the near future.

Human interventions with or without PSCs

Then, the stellate cells protect tumor cells from the attack from therapies.
Now, we add the negative intervention on the binding of EGF and its receptor.

PCCs
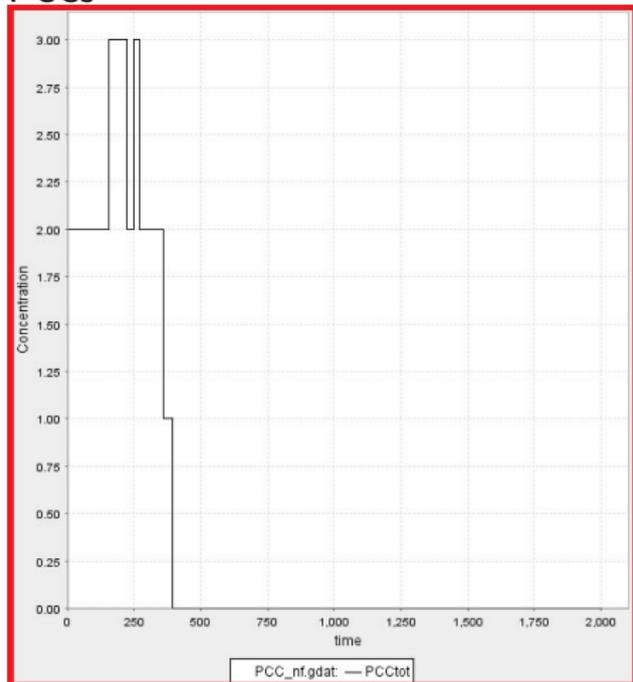
PCCs+PSCs
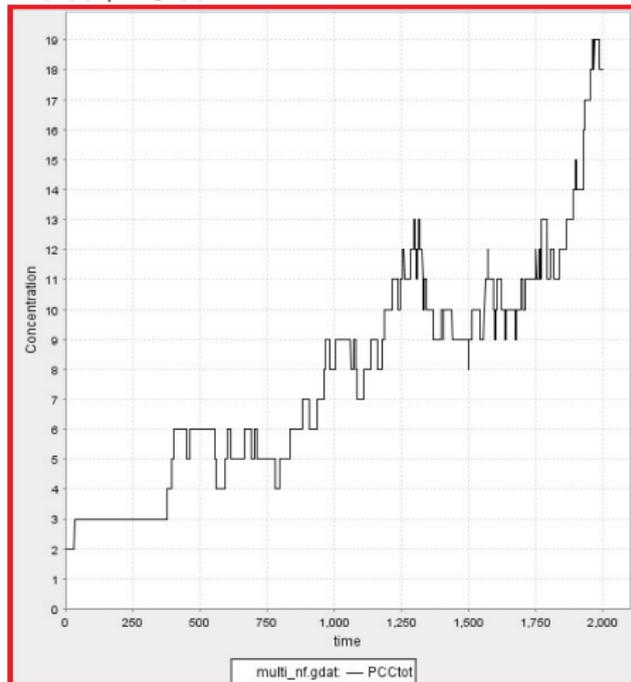
PSCs' activation and migration caused by PCCs

Finally, the Pancreatic Stellate Cells can be activated by tumor cells, and once activated, they will migrate to tumor cells. At the same time, they will actively proliferate.
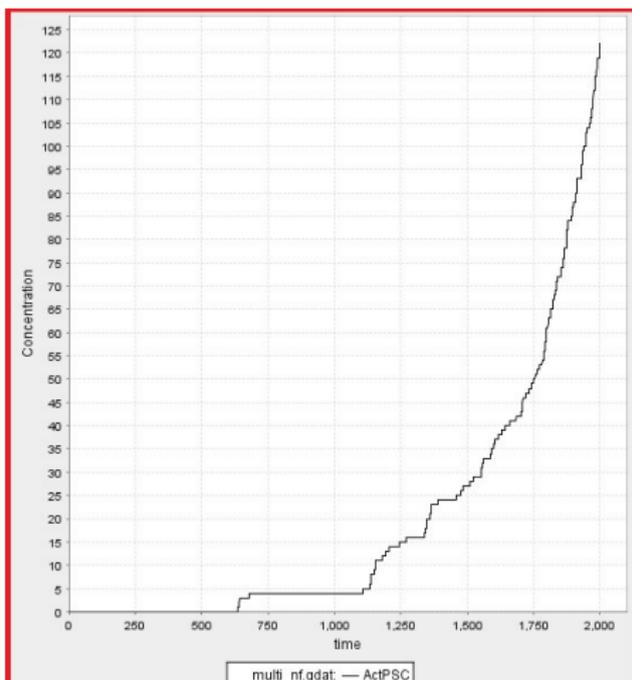
Activated PSC is counted when this stellate cell is both activated and migrated.

Boolean Network Model

- Each node: extracellular molecule or intracellular component; TRUE (high expression) or FALSE.
- Each edge: activation or inhibition.
- 51 variable nodes, 2^{51} possible states in state transition diagram
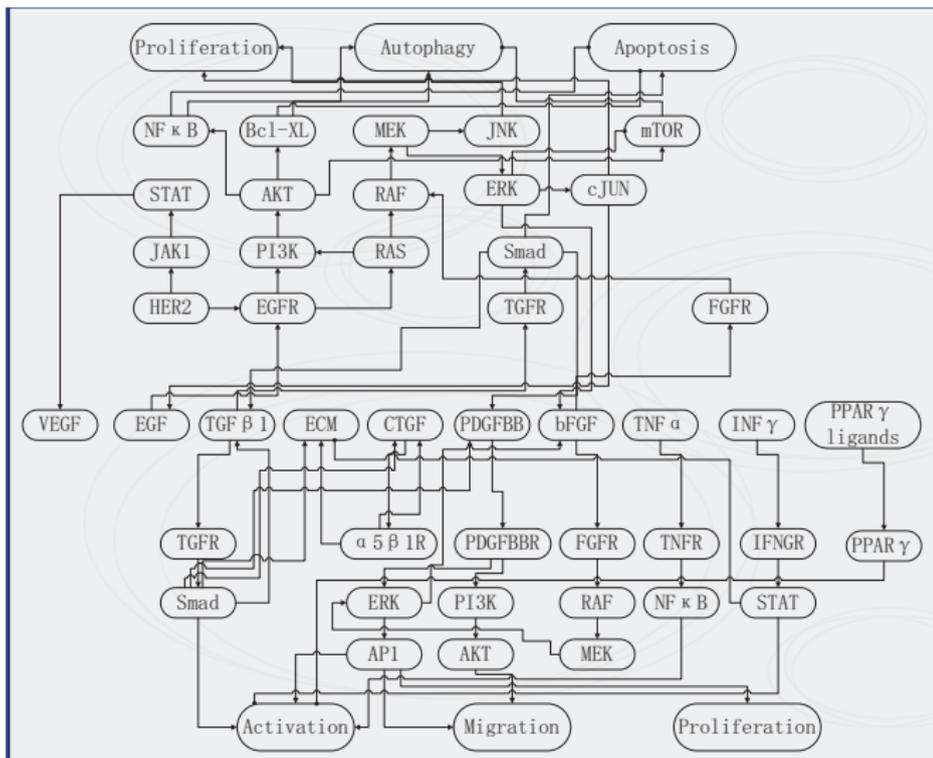
Properties and Model Checking results

Property 1: The mutation of K-Ras will promote proliferation, and inhibit apoptosis of pancreatic cancer cells.

LTL formula: G(PCCRAS → F(¬PCCApoptosis ∧ PCCProliferation))

Result: True.

Property 2: The mutation of HER2/neu will activate EGFR through forming a heterodimer, and then further promote proliferation, and inhibit apoptosis of pancreatic cancer cells.

LTL formula: G(PCCHER2 → F(PCCEGFR → F(¬PCCApoptosis ∧ PCCProliferation)))

Result: True.

Properties and Model Checking results (cont.)

Property 3: EGF can enhance PCC proliferation through autocrine.

LTL formula: $G(EGF \rightarrow F(EGF \rightarrow F(PCCProliferation)))$

Result: True.

Property 4: There is a mutually exclusive relationship between apoptosis and autophagy in pancreatic tumor cells.

LTL formula: $G((PCCApoptosis \rightarrow F(\neg PCCAutophagy)) \wedge (PCCAutophagy \rightarrow F(\neg PCCApoptosis)))$

Result: True.

Properties and Model Checking results (cont.)

Property 5: For pancreatic stellate cells, once activated, they will migrate towards tumor cells.

LTL formula: $G(PSCActivation \rightarrow F(PSCMigration))$

Result: True.

Property 6: PDGFBB secreted through the TGFbeta1 signalling pathway can further initiate autocrine.

LTL formula: $G(TGFbeta1 \rightarrow F(PDGFBB \rightarrow F(PDGFBB)))$

Result: True.

Conclusion

- Pancreatic Stellate Cells DO promote the development of Pancreatic Cancer!
- We also need to find out therapies which aim at PSCs to prevent it to be activated!
- BioNetGen is also an effective software to model cell-cell interactions!
- Model checking is a good way to verify your model!

Future work

- Extend this multi-cellular model through
  - Including more possibly involved signaling pathways;
  - Including more functional cell types, such as the macrophage, existing in the microenvironment of Pancreatic Cancer.
- Apply Statistic Model Checking to this model.

Acknowledgments

Thanks for your listening!

Questions and Suggestion?