Model Checking and Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), a 4th leading cause of cancer-related mortality in the United States, is characterized by a genetic history of altered cellular signaling pathways and dysfunctional growth factors. Model Checking is a formal verification technique widely used for the automated verification and analysis of hardware and software systems. Recent studies on pancreatic cancer have found that the overexpression of HMGB1, a DNA-binding protein, can decrease apoptosis and increase cancer cell survival time. To systematically understand the signaling components that link HMGB1 and cancer risk, we constructed a rule-based model [1, 2] of the HMGB1 network which was implemented using the BioNetGen language. In [1,2], we applied Statistical Model Checking methodology to verify some linear temporal logic (LTL) properties in the rule-based stochastic models of HMGB1. Accumulating evidence suggests that cancer-related pancreatic inflammation might be associated with diabetes mellitus, especially Type II diabetes which is characterized by hyperinsulinemia, hyperglycemia, obesity, and overexpression of multiple WNT pathway components. In [3], we constructed a single-cell Boolean network model, and applied Symbolic Model Checking methodology to verify some computation tree logic (CTL) properties related to insulin resistance, cancer cell proliferation and apoptosis.

Rule-based Model of HMGB1 [1,2]

We formulated a reaction model corresponding to the reactions illustrated in Fig.1 in the form of rules specified in the BioNetGen language. The ordinary differential equation (ODE) method and stochastic simulation algorithm (SSA) are used to simulate the model. Example ODE and BioNetGen rules:

1. Overexpression of HMGB1 will promote the expression of cell cycle regulatory protein CyclinE

2. p53 is expressed at low levels in normal human cells

3. Expression level of HMGB1 influences the 1st peak of p53's level

Verification of HMGB1 Stochastic Model [1,2]

Property 1: Overexpression of HMGB1 will induce the expression of the cell cycle regulatory protein CyclinE

Property 2: p53 is expressed at low levels in normal human cells

Property 3: Expression level of HMGB1 influences the 1st peak of p53's level

Diabetes-Cancer Boolean Network Model [1,2]

1. Graph G
2. Boolean transfer function
3. State of each node could be either ON (1) or OFF (0) at any time step.

The Boolean transfer function describes the transformation of the state of node from time t to t + 1 (A&kappa) = (t + 1)

References