Understanding Oncogenic Transformation in Colon Cancer

Annika Jacobsen[1, 2], Folkert Verkaar[2, 3], Jaap Heringa[1, 2, 4], Martine J. Smit[2, 3], K. Anton Feenstra[1, 2, 4]

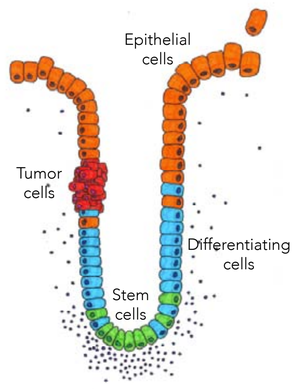
[1]Centre for Integrative Bioinformatics (IBIVU), Department of Computer Science, VU University Amsterdam; [2]Amsterdam Institute for Molecules, Medicines and Systems (AIMMS); [3]Division of Medicinal Chemistry, VU University Amsterdam; [4]Netherlands Bioinformatics Centre (NBIC)

Dysregulation of the Wnt/ β-catenin Signaling Pathway Can Lead to Tumor Formation

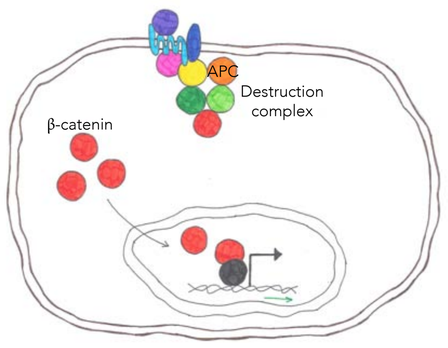
The Wnt/ β-catenin signaling pathway is important for stem cell maintenance and development. Dysregulation of Wnt signaling can lead to tumor formation and cancer.

A petri net model of the Wnt/ β-catenin signaling pathway was constructed in order to better understand the mechanism of oncogenic signals. The goal of this study is to:

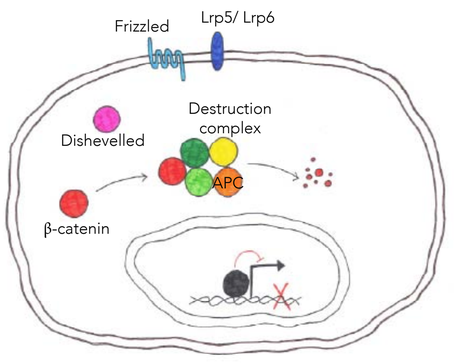
Recapitulate pathway responses from different perturbation of the Wnt/ β-catenin signaling pathway



COLON CRYPT



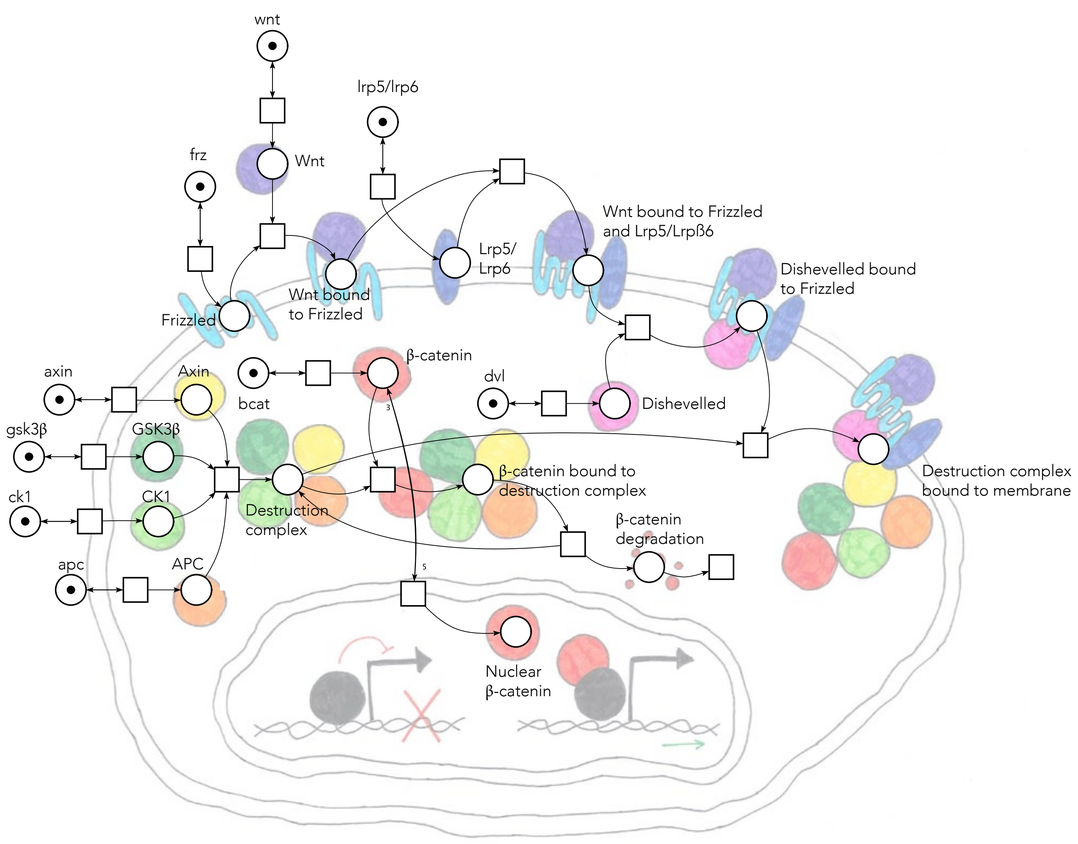
Wnt ON



Wnt OFF

Stem cells are located in the base of the colon crypt, with active Wnt signaling. As the cells proliferate and differentiate they migrate towards the top where there is no Wnt signal. Progression into tumor cells can be caused by oncogenic signaling. The signaling pathway is active in stem cells (Wnt ON) and β-catenin translocates to the nucleus and activates transcription of β-catenin target genes. In epithelial cells (Wnt OFF) β-catenin is degraded in the cytoplasm by the destruction complex. Mutations in adenomatous polyposis coli (APC) and β-catenin are found in ~80 and ~15% of colon cancer patients, respectively, and are among the most common oncogenes. Abberant Wnt signaling leads to both onset and progression of colon cancer.

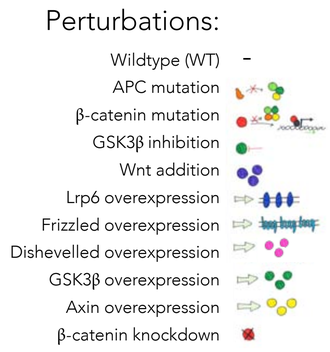
PETRI NET MODELING

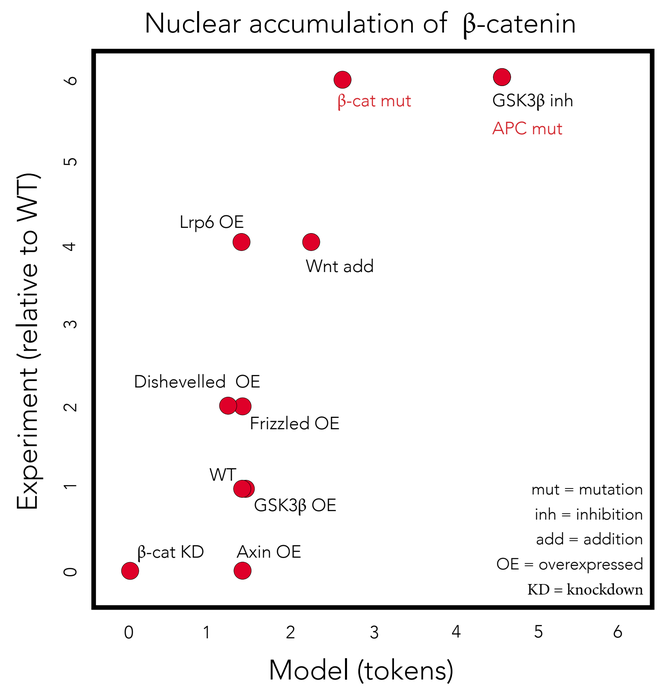


A non-deterministic petri net model was constructed for the Wnt/ β-catenin signaling pathway based on current knowledge of the system from litterature and work performed experimentally. The places (round nodes) represent biological entitites such as genes, proteins and complexes. The transitions (squared nodes) represent gene expression, protein interactions, protein degradation and protein translocation. The level of the tokens range from 0 to 6 and represents the availability of the entity in the place (gene places are only 0 or 1). The arcs (edges) show the direction of flow and the weights indicate requirements for the transitions from the input place and the effect it has on the output place.

REPRODUCING PATHWAY RESPONSES

Perturbations:





Simulations of the model with different perturbations showed different levels of nuclear accumulation β-catenin, as seen by experiments. Next, recapitulation of more perturbation experiments will be done to adapt the model further. Further, double experiments will be done for validating prediction by the model. The model will then be used to explain how β-catenin reaches steady state in the different experiments.

It is also of interest to gain more insight into the regulation mechanism of the β-catenin target genes (e.g. Axin2 and Lgr5) and the mechanism in which the Human cytomegalovirus (HCMV) disrupts the Wnt/ β-catenin signaling pathway.

The extended model will hopefully lead to greater understanding of how oncogenic signals propagate through the network from dysrupting the Wnt/ β-catenin signaling pathway to transcription of target genes and regulation of gene transcription.

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Centre for Integrative Bioinformatics VU

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