Mathematical Modeling of the Wnt Pathway

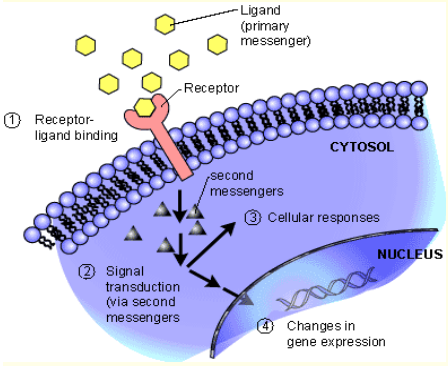
Monica Sullivan*, Christopher Cai, Namita Gupta, Robert Karp, Jeremy Gunawardena
Harvard Medical School

Abstract

The Wnt pathway is important in determining cell proliferation, cell polarity, and cell fate during embryonic development and adult tissue homeostasis. The destruction cycle of this pathway regulates the amount of Beta-catenin in the cytosol. Mutations in the Wnt pathway have been linked to colon cancer, coronary heart disease, osteoporosis and type II diabetes. We created a mathematical model based on differential equations for the Wnt pathway, to better understand how the signaling works. The more the Wnt pathway is understood the closer science comes to curing cancer and other related illnesses.

Summary

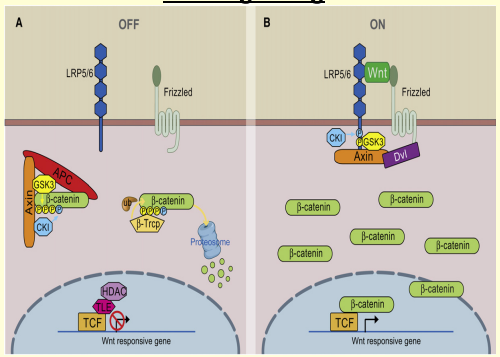
The Wnt pathway is a cell signaling pathway which regulates the level of Beta-catenin, which in turn controls controls the expression of over 100 genes. The pathway is studied in Drosophila (flies), Xenopus (frogs), mouse and humans, especially cancer cell lines. Each species in the Wnt pathway is carefully mapped out and labeled. Reversible binding steps are recognized by the equation $v_i = k_{+i}X_jY_i - k_i(X_j{*}Y_i)$, where X_j and Y_i denote the concentrations of binding partners and $(X_j{*}Y_i)$ the concentration of their complex. Irreversible reactions are described as $v_i = k_i{*}X_j$, where k_i is the first order rate constant and X_j is the concentration of the reactants. Our new model simulates the full Wnt pathway, as opposed to the original 2003 model.



Methods

A mathematica code is designed where each reaction and reversible binding steps is accounted for. The reactions included in this model are protein synthesis/degradation, protein phosphorylation and dephosphylation and the assembly/disassembly of protein complexes. We took binding, dissociation and catalytic rates from the literature, and did the same thing for initial concentrations.

Wnt Signaling



The above picture shows the before and after effects of the Wnt signal.

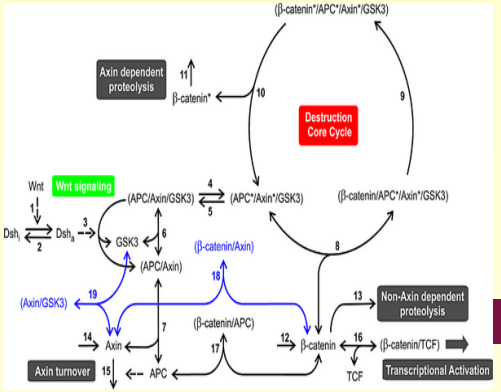
- **Figure A** shows the destruction complex before the Wnt signal attaches to the coreceptors LRP5/6 and Frizzled.
- **Figure B** shows Wnt binding to the coreceptors which activates Disheveled (Dsh). This causes Beta-catenin to accumulate and form a complex with TCF.

Differential Equations

$$dAAx/dt = GAAx\,k_{3->4} - AAxG\,k_{4->3} - AAx\,k_{12->13} + APCAx\,k_{13->12}$$
$$dAPC/dt = AAx\,k_{12->13} - APCAx\,k_{13->12} + A\beta\,k_{14->15} - APC\beta\,k_{15->14}$$
$$dAx/dt = AAx\,k_{12->13} - APCAx\,k_{13->12}$$
$$dA\beta/dt = -A\beta\,k_{14->15} + APC\beta\,k_{15->14}$$
$$dDsh_a/dt = Dsh_n\,k_{1->2} - Dsh_a\,k_{2->1}$$
$$dDsh_n/dt = -Dsh_n\,k_{1->2} + Dsh_a\,k_{2->1}$$
$$dG/dt = GAAx\,k_{3->4} - AAxG\,k_{4->3}$$
$$dGAAx/dt = -GAAx\,k_{3->4} - GAAx\,k_{3->5} + AAxG\,k_{4->3} + GAAxpp\,k_{5->3}$$
$$dGAAxpp/dt = GAAx\,k_{3->5} - GAAxpp\,k_{5->3} + \beta GAAxp\,k_{6->7} - GAAxpp\beta\,k_{7->6} + G\beta AAxPPP\,k_{8->9}$$
$$dG\beta AAxppp/dt = \beta GAAxpp\,k_{6->8} - G\beta AAxPPP\,k_{8->9}$$
$$dT/dt = T\beta\,k_{10->11} - \beta T\,k_{11->10}$$
$$d\beta/dt = \beta GAAxpp\,k_{6->7} - GAAxpp\,k_{7->6} + \beta T\,k_{10->11} - \beta T\,k_{11->10} + A\beta\,k_{14->15} - APC\beta\,k_{15->14}$$
$$d\beta GAAxpp/dt = -\beta GAAxpp\,k_{6->7} - \beta GAAxpp\,k_{6->8} + GAAxpp\,k_{7->6}$$
$$d\beta p/dt = G\beta AAxPPP\,k_{8->9}$$
$$d\beta T/dt = -T\beta\,k_{10->11} + \beta T\,k_{11->10}$$

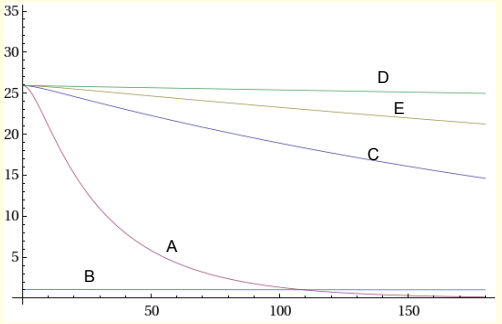
Results

The Wnt Pathway



Beta-Catenin Degradation Graph

B-catenin concentration(nM) vs. time(hours)



The following curves are listed from top to bottom:

- **Curve D** (inhibits GSK3β by setting k4=0 and k9=0)
- **Curve E** (added 1 μM of TCF)
- **Curve C** (has I additional μM activated Dsh)
- **Curve A** (reference curve)
- **Curve B** (has an addition of 0.2 nM axin)

Conclusion

Our main interests is to investigate cellular response under complex stimuli, which the cells would encounter under normal or pathological physiological conditions. Setting up a model is the first step in this direction. Our model recapitulates the known experimental facts of the Wnt pathway under traditional stimulation, and will serve as the basis for future experiments with complex stimuli; like pulses in a microfluidic torture chamber.

Acknowledgements

I would like to thank my mentors Dr. Jeremy Gunawardena and Dr. Robert Karp at the Harvard Medical School for allowing me the wonderful opportunity to work under their guidance. I would like to thank my collaborators Christopher Cai and Namita Gupta for the work contributed to the project. I would also like to thank the FAS Center for Systems Biology program for making this experience possible.

References

1. B Mariann and H Clevers: Linking Colorectal Cancer to Wnt Signaling. *Cell*. 103 (13 October 2000): 311-320
2. K Cho et al: Wnt pathway mutations selected by optimal β-catenin signaling tumorigenesis. *FEBS Letters*. 580 (26 June 2006): 3665-3670
3. H Clevers: Wnt/β-catenin Signaling in Development and Disease. *Cell*. 127 (3 November 2006) 469-480
4. R Kruger and R Heinrich: Model Reduction and Analysis of Robustness for the Wnt/β-Catenin Signal Transduction Pathway. *Genome Informatics*. 15 (2004):138-148
5. E Lee et al: Physiological regulation of β-catein stability by TCF and CK1ε. *Journal of Cell Biology*. 154 (27 August 2001):983-993
6. E Lee et al: The Roles of APC and Axin Derived from Experimental and Theoretical Analysis of the Wnt Pathway. *PLoS Biology*. 1 (13 October 2003):116-134