

# National Academies Keck *Futures Initiative* Conference

## Mathematical Models in Signaling Systems - June 16-18, 2004

### ***Cellular Models and Spatial Complexity***

#### *Mathematical Modeling of Wnt Signaling* 🗣️

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#### ***Abstract:***

We have developed a mathematical model for the canonical Wnt pathway that describes the interactions among the core components: Wnt, Frizzled, Dishevelled, GSK3, axin,  $\beta$ -catenin, and TCF. Using a system of differential equations, the model incorporates the kinetics of protein-protein interactions, protein synthesis/degradation and phosphorylation/dephosphorylation. We initially defined a reference state of kinetic, thermodynamic, and flux data from experiments using *Xenopus* extracts. Predictions based on the analysis of the reference state were used iteratively to develop a more refined model from which we analyzed the effects of prolonged and transient Wnt stimulation on  $\beta$ -catenin and axin turnover. We predict several unusual features of the pathway, some of which we tested experimentally. An insight from our model, which we confirmed experimentally, is that the two scaffold proteins axin and APC promote the formation of degradation complexes in very different ways. We can also explain the importance of axin degradation in amplifying and sharpening the Wnt signal, and we show that the dependence of axin degradation on APC is an essential part of an unappreciated regulatory loop that prevents the accumulation of  $\beta$ -catenin at decreased APC concentrations. By applying control analysis to our mathematical model, we demonstrate the modular design, sensitivity, and robustness of the Wnt pathway and derive an explicit expression for tumor suppression and oncogenicity.

Source: Lee, E., Salic, A., Krüger, Heinrich, R., Kirschner, M.W. (2003) The Roles of APC and Axin Derived from Experimental and Theoretical Analysis of the Wnt Pathway. *Public Library of Science, Biology* 1: 116-132.