Toward a Mathematical Model for Wnt Signaling applicable to cancer

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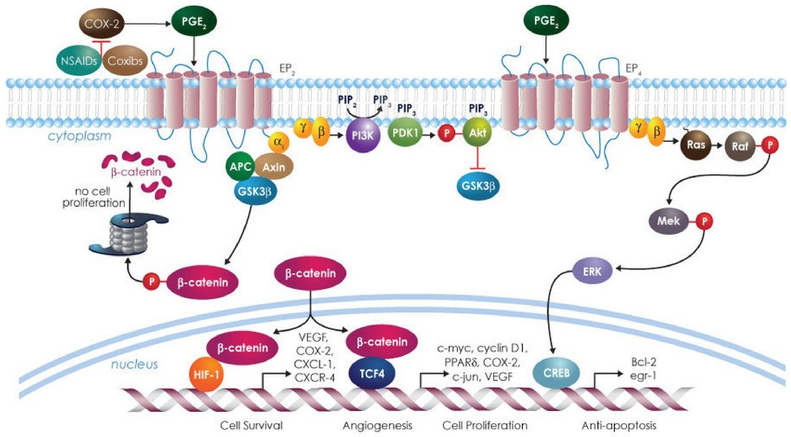
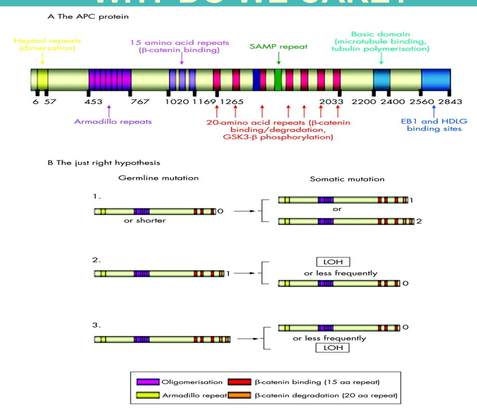


WHAT IS WNT SIGNALING?

Over the last two decades a lot of effort has been directed towards understanding the dynamics of the **Wnt signaling pathway**. The intracellular canonical Wnt pathway uses an intriguing mechanism that is still incompletely understood. Wnt genes encode for small secreted proteins that constitute the Wnt signal. In the absence of this signal, cells constantly synthesize and degrade beta catenin. The components of the so-called destruction complex are responsible for keeping beta catenin's levels low by targeting it for phosphorylation and ultimately for ubiquitination and proteasomal degradation. In response to Wnt stimulation the destruction complex is inhibited, leading to cytosolic beta catenin accumulation and to its nuclear translocation. Once in the nucleus, beta catenin regulates the expression of over a hundred genes (e.g., cMyc) involved, among other functions, in cell differentiation and proliferation.

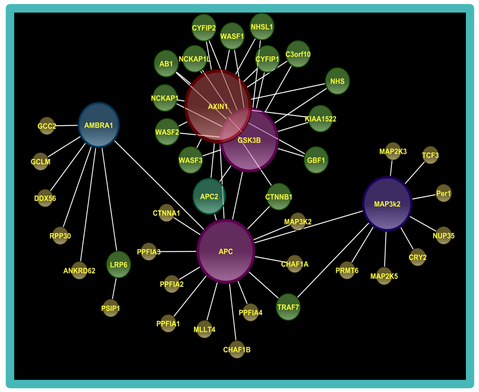
WHY DO WE CARE?



Wnt signaling is involved in cell proliferation, embryonic development and oncogenesis. One of its key – components, the tumor supressor Adenomatous Polyposis Coli (APC) is mutated in **80%** of the **colon cancers. These mutations are observed in regions that play major roles in the WNT pathway.** Therefore the understanding and modeling of the dynamical behavior of Wnt is crucial for helping design effective treatment.

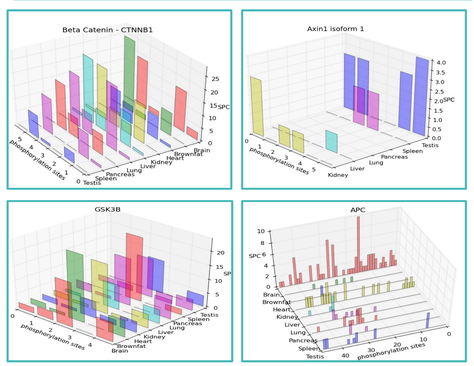
BUILDING THE WNT MODEL

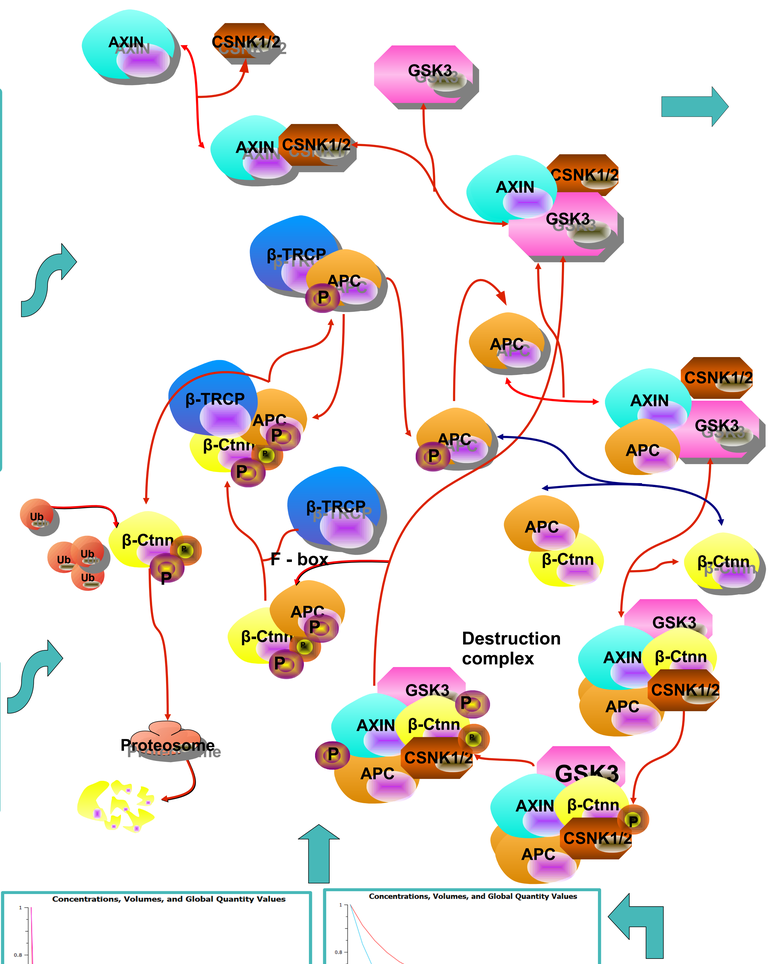
We rebuild and extend the model based on several previous models, through a careful analysis of available literature, experiments and data sets.

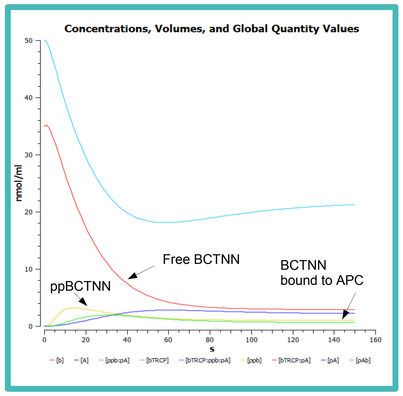


PPI Networks reveal information about new components worth considering, their interaction, function, and role in possible crosstalk with other pathways

Phosphorylation changes the affinity between proteins and is therefore important in the formation of the destruction complex as well as in the degradation of beta catenin.



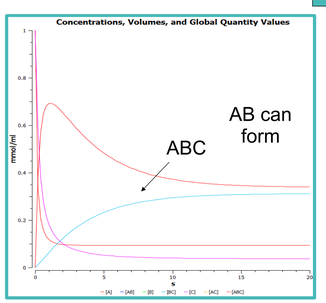


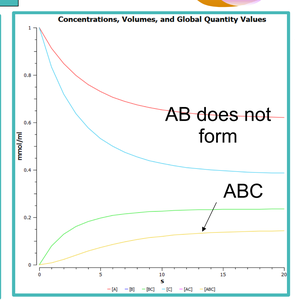


FUTURE WORK

Current model (cytosol) :
→ new framework
→ ODE model
→ formation of the destruction complex (catalytic model)
→ mechanism for protein synthesis and degradation
→ phosphorylation and dephosphorylation
→ beta catenin stabilization hypothesis

Ongoing work:
→ extend model (include membrane components)
→ include combinatorial analysis of complex assembly
→ incorporate experimental data to the theoretical model
→ apply control analysis





Destruction complex. What binds what? Toy Problem: Given three species A, B, C look at the possible ways in which the ABC complex can form. In the first case we allow all possible bindings $\mathbf{A_i + A_k = A_iA_k}$, $\mathbf{A_i + A_kA_j = ABC}$, where $A_i \in \{A, B, C\}$, in the second case we don't allow A to bind B. The dynamical behavior is qualitatively different

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