NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO

Moodeling for the Post-Genomic Age: Executable Knowledge in the Wnt Signaling Case Study

by

Héctor Francisco Medina Abarca

A thesis submitted in partial fulfillment for the
degree of Bachelor in Genomic Sciences

in the

Center for Genomic Sciences
Institute of Biotechnology

July 2012

Declaration of Authorship

I, HÉCTOR FRANCISCO MEDINA ABARCA, declare that this thesis titled, 'MODELING FOR THE POST-GENOMIC AGE: EXECUTABLE KNOWLEDGE IN THE WNT SIGNALING CASE STUDY' and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed: _____

Date: _____

“ A little Knowledge that Acts is worth infinitely more than much Knowledge that is Idle.”

Khalil Gibran

NATIONAL AUTONOMOUS UNIVERSITY OF MEXICO

Abstract

Center for Genomic Sciences
Institute of Biotechnology

Bachelor in Genomic Sciences

by Héctor Francisco Medina Abarca

The PostGenomic Age of Life Sciences is characterized by vast generators of data. However, there is a notable abscence of High Throughput techniques transforming said data into actual Knowledge. Addressing this problem requires establishment of a *Lingua Franca* enabling standardization of factoids. In this work, the usage of the $\varkappa$ language is presented as a viable alternative for Knowledge Representaion and Execution, within an extended modeling framework termed a "Moodel".

Acknowledgements

I would like to extend my sincere affection and recognition for the following people, who have contributed in one way or another to this Thesis as a culmination of my Undergraduate Degree:

- To my Teammates, Instructors, and Advisors for *iGEM 2010: UNAM_Genomics-Mexico & WiFi Coli: A CommunicoLight System*, for putting up with me and my crazy idea on the project that started my modeling path,
- To my Teammates, Instructors, and Advisors for *iGEM 2011: UNAM_Genomics-Mexico & Hydrobium etli*, for forcing me to mature as a modeler,
- To my Undergraduate Programme for not including Modeling as a required course, thus furthering independent trajectories,
- To my family, who have never limited my dreams and ambitions,
- To my friends, who keep encouraging the craziness that fuels Scientific Curiosity,
- To my lab mate, Mitchell G. Johnson, for long hours of insightful discussion as well as the programmatic support that is the Exploratorium,

and lastly, but definitively not leastly,

- To my Tutor, Walter Fontana, for the non-trivial efforts of incepting the idea, recruiting the talent, and catalyzing the Moodel.

Contents

List of Figures

List of Tables

List of Neologisms

Moodel	A Fat Model, Referenced, with Explicit Assumptions. Isomorphic to *bona fide* Executable Knowledge. Intended to be extensible.
Platoonic Agent	Agent representing the collective properties of its constituent Agents

Chapter 1

Introduction

As the title suggests, this Thesis presents a framework for "Executable Knowledge" in the Post-Genomic Life Sciences, using Wnt signaling as a case study. As such, the notions of *Knowledge* and *Executability* on this whole project are scoped to the relevancy as determined and allowed by the current state of Life Sciences. Moreover, *Wnt signaling* has proven to be a sufficiently rich set of phenomena as to allow theoretical exploration at multiple levels of mechanistic coarse-graining and scales [1–3]. To begin with, a small description will be given on these three key elements.

1.1 Knowledge

1.1.1 What Is Knowledge?

The subject of "Knowledge" has been explored and debated for several millenia, from the greek επιστημη (*episteme*) and τεχνη (*techne*) [4], to the current framework for Justified True Belief [5], touching on Cartesian Doubt [6], and even Kantian absolutisms [7]. As a formal definition of Knowledge lies outside the scope of this project, suffice it to pose that the Knowledge we deal with is the type that can best be described as a Scientific Hypothesis that must be, to the extend that reason and evidence allow, correct. A subtle point withing the Correctness of the hypothesis that must be rendered explicit is that the Hypothesis should be a true mechanistic statement. The reason for this is to ensure

compatibility with further statements. For example, propositions such as:

> Planar Cell Polarity patterning follows Dorso-Ventral Axis establishment. (1.1)

evidently gloss over information and variables when compared with statements such as:

> Wnt induction causes β-catenin upregulation. (1.2)

Yet the exact same applies when we compare the former with finer statements such as:

> Serine 33 on CTNB1_HUMAN can be phoshorylated by functional GSK3B_HUMAN only if Tyrosine 86 is already phosphorylated. (1.3)

It is clear that while 1.1 is written at a cheaply accessible level of information, it is too coarse to be integrative with other hypothesis [1]. As for 1.2, this was compatible to a degree with other statements of the sort, and to its credit goes the "Age of MicroArrays". But with the advent of High Throughput technologies, we are now accessing a vast level of information at the scale required by 1.3. And of particular intelecutal seduction is a possible lower bound for the mechanistic level our knowledge can achieve. Indeed, establishing a *Lingua Franca* of Knowledge in biochemical signaling will require integrating vast amounts of data from a myriad of sources, and the most effective way of ensuring integrability is to handle Knowledge as Factoids, that is an *atomized representation* of the empirical reality.

In other words, since the Knowledge that is of interest is by nature collaborative, said Knowledge must be expressed in a currency that is atomized to ensure on one hand consistency, and extensibility on the other. This *epistemic thing* still requires a formal way of being represented.

[1] The problem is the multi-referral of inner variables that simply make the set highly incompatible with other sets. For example, attempting to integrate new information such as "Patterning triggered by maternally inherited Wnt mRNA", introduces the notion of Wnt mRNA, which is partially implied in the phenomenology of "Dorso-Ventral Axis establishment".

1.1.2 Knowledge Representations

There are currently several frameworks that attempt to express Knowledge in regards to Life Sciences, all trying to ensure consistency and extensibility. Initiatives like the BioPAX [3], the Open Biological Expression Language [8], and the Microarray Gene Expression Markup Language [9], among many others attempt to offer a concise framework to express knowledge from various sources. These frameworks most often take the form of Resource Description Frameworks [10] specialized to a particular lexicon. Indeed, a key aspect of these resources is their particular Dictionary [3]. However, the same constraint that structures statements into machine-readable concatenations of classes, such as the typical *triple* of subject-predicate-object, has the side-effect of focusing expression to pre-defined Concepts. An evident caveat of these implementations is that Knowledge can only be *explicitly* expressible if the Dictionary *explicitly* expects it.

As should be evident from the previous section, the level of granularity for the Knowledge of interest is quite fine, and therefore a Knowledge Representation should allow for such fine expressions. This has the advantage of no longer requiring naming conventions for coarse phenomenology, such as "Creutzfeldt Jakob", but only dealing with finer dynamics, such as "Prion polymerization in Insoluble Conformation". It is thus clear that the *Lingua Franca* of interest must adequately express mechanistic knowledge as is relevant to biochemical signaling. In particular, support for protein-protein interactions, as well as protein modifications, should be quite robust.

1.1.3 Sources of Knowledge

Ideally, full integration of any and all sources of Knowledge into a cohesive corpus of truths would be the ultimate goal of Science. However, this is not yet a realized case. While there are databases of information on the web, freely accessible and curated, more often than not the bulk of their information is in raw English, which requires human intervention to be successfully integrated into a different context. For example, the Universal Protein Resource (UniProt) [11] offers excellent curated information in a programatically accessible way, however there's also much in the annotations and comments fields that is not truly standardized. The same applies to the Kyoto Encyclopedia of

Genes and Genomes (KEGG) [12], and even PhosphoSite [13]. In regards to Protein-Protein interactions, integrative databases such as the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) [14] holds information at an undefined physical location for the interaction, while some others such as DOMINE [15] utilize references that meld Domains, Families, and Motifs, within Pfam entries [16]. These levels of melding obscure a very important aspect of biochemical signaling, and that is the *time dimension*: what interactions exclude other interactions by nature of sequestering their binding site [17]?

In absence of digested and ready-to-use information, it is clear that the greatest resource for information regarding biochemical signaling is the Literature. As such, engines for text mining, such as Linguamatics [18] or the Information Hyperlinked Over Proteins (IHOP) effort [19] often yield promising results for small well-though queries. However, their poor integration with standardized knowledge representations yield results that although summarized, are still in traditional English, and thus still require a human to integrate these factoids into a cohesive set. Moreover, the often syntactical richness found in articles from different countries appears to prove too confusing for these algorithms, and thus renders them effectively illiterate at large scales.

These obstacles to knowledge integration unfortunately hinder a cataloging of information, with the expected result of a scientific community that is truly unaware of the bona fide "Current State of the Art" for a given topic. In other words, information that is unaccessible (by virtue of being hidden), is almost as good as information that is not there. Indeed, it is all too often that an ambitious representation of a particular signaling pathway is shot down because "We don't know enough". Yet how is the community supposed to know what it knows if that Knowledge is not represented in a *Lingua Franca*?

1.2 Execution

Execution is the effective fulfillment of a set of instructions. An ambitious extrapolation of this concept are the theoretical perspectives known as *Digital Physics* [20], where the entire Universe is a described as mathematically isomorphic to a vast Computation Machine carrying out a programme. As the scale of Plank-lengths, Qubits, and Quantum

Space-Time yields a frightengly heavy simulation for biologically relevant entities and times, let us avoid that extreme of reductionism and deal with a more comfortable idea: the execution of an Encoded Programme by a biological simulator entity, on biologically relevant "things" [2]. Indeed, given an Executable framework, Knowledge representation would gain the ability to be *Model checked*, that is to be verified for consistency given a specification. Evidently, having *verified*, *consistent*, and *specified* Knowledge would greatly reduce reduntant experimentation and would boost knowledge exchange.

1.2.1 What Constitutes Executability?

For an instruction set to be executable under current implementations of computation machines, it must basically be either a computer programme, or the input for one. In other words, it is a Model.

1.2.2 Current Modeling Limitations

The most simple of modeling frameworks would be a species-based Ordinary Differential Equation (ODE) set, however a problem quickly grows out of control when dealing with large systems: the Combinatorial Explosion. For a single protein, such as AXIN1_HUMAN, there are at least 9 known modified residues, and that effectively leads to $2^9 = 512$ flavors of that protein given full independence of each and all residues [3], this phenomenon is colorfully known as the *Curse of Dimensionality* [21]. A similar explosion occurs with polymerizations, as each length of the chain constitutes a different species. As such, what is the upper bound of the species number, and *why*? Evidently, a modeling approach that requires knowledge of the entire species space beforehand, or that requires the user to state the entire species space is evidently undesirable.

There have been several attempts at dealing with these situations in an executable framework, notable efforts include representing networks using π-calculus as an effort of pattern space computation [22], pattern-based shorthands for ODE generation using

[2] Though the notion of *Encoded Programme* may appear to reference the information encoded in the Genome, the recent rise of EpiGenetics has proven that we are not "Slaves to our Genes", and indeed the term is not meant to be interpreted in such a manner. Likewise, *biological simulator* does not exclusively mean cell, or even chemoton.

[3] If we acknowledge that some of those residues may have more than 2 states, the number grows to ridiculous heights. For H31_HUMAN, there are *at least* $2*2*6*2*3*5*2*2*2*3*3*3*5*2*5*2*2*4*2*2*5*2*2 = 9953280000$ flavors ...

the Bio Net Gen Language [23], and Rule Based modeling frameworks such as the $\varkappa$ Language [24].

1.3 Wnt Signaling

Of the mayor biochemical signaling cascades, those involving the family of Wnt proto-oncogenes have been extensively studied across species, from nematodes and amphibians, to humans and insects. In absence of the Wnt signal, the cytosolic level of the β-catenin protein is kept low by proteosomal degradation following ubiquitination by the SIFβ-TrCP complex, after phosphorylation by glycogen synthase kinase 3-β (GSK3-β) and casein kinase 1 (CK1). This phosphorylation involves two scaffold proteins, Axis Inhibitory Protein 1 (Axin), and tumor suppressor Adenomatous Polyposis Coli (APC). Interestingly, there exists a second pool of β-catenin located at the Adherens Junctions [25]. That β-catenin is an integral part of the α-cadherin assembly [26], and its depletion leads to cells loosing adhesion. Moreover, it has been shown that APC has ATP dependent movement along microtubules towards their plus terminus and concentrating there at ultrastructural aggregates [27], which may localize at adherens junctions [28]. The possible role of the unstructured APC sweeping the cytosol, collecting β-catenin, and increasing its local concentration at adherens junctions has not been explored.

In presence of a Wnt signal, β-catenin accumulates and enters the nucleus. Inside the nucleus, β-catenin displaces the family of Transducin-Like Enhancer proteins (TLE), homologues of the *Drosophila* Groucho protein, from the T Cell-specific transcription Factors (TCF) [4] their binding partners. While the TLE-TCF dimer usually acts as a repressor of transcription, the β-catenin / TCF dimer may act as an activator or a repressor, depending on where it binds with respect to the Transcription Start Site [29]. β-catenin then induces transcription of several different genes, among which there are several regulators of cell cycle progression, and others who act as feedbacks on the signaling cascade (discussed in Section 3.1.4).

One notable induced target of β-catenin is Cyclin D1 [30], which in turn activates the Transcription Factor E2F1, which posses a high affinity binding site on the β-catenin promoter [31], suggesting some level of autoinduction. Moreover, as will be discussed in

[4] TCFα is also known as the Lymphoid Enhancer-binding Factor 1, LEF1.

Protein	Family Members	Oligomerization
Wnt	12	None observed
Fzld	10	Observed homodimerization
LRP	8	Observed heterodimerization
Dsh	4	Observed heteropolymerization
Axin	2	Observed homopolymerization
APC	2	Observed homopolymerization

TABLE 1.1: Wnt Signaling related families of proteins

greater detail in section 3.1.3, Wnt signaling may activate part of the NFκB signaling pathway, and therefore the NFκB binding site on β-catenin promoter [31] would suggest a second route of auto-regulation. Finally, it would appear there is a direct LEF1 binding site on the β-catenin promoter, suggesting a third auto-regulation direct event [31].

In terms of the Wnt signal, upon Wnt stimulation the following cascade takes place:

- Recruitment of membrane co-receptor Frizzled (Fzld) by Wnt
- Recruitment of membrane co-receptor Low-density lipoprotein Receptor-related Protein (LRP) by Wnt
- Recruitment of the Segment polarity protein dishevelled homolog DVL (Dsh) by Fzld
- Recruitment of Axin by Dsh
- Recruitment of Axin by LRP
- Release of APC from Axin complex

Of particular note is the fact that there are several families for several of these components, often with overlapping functionalities. Moreover, these often form homopolymers, and even heteropolymers, sometimes with a marked phenotype upon polymerization abrogation [32]. Table 1.1 lists the number of known homologues listed in curated UniProt for the human species and their capacity to oligomerize.

Interest should be given to exploring the biological role of all these oligomerizations, as it should be evident that their maintenance throughout evolutionary history is no accident. However, as has been show in the Section 1.2.2, exploring a solution space where the total number of protein species is not known beforehand is no trivial task. Clearly a

different modeling framework is needed to even allow addressing these events. Moreover, given that the key step in β-catenin turnover is a post traductional modification (PTM), and considering the difference in binding affinities based on the tuning of the scaffolds by the kinases [33, 34], it is clear that PTMs should also be addressed in detail.

Chapter 2

Methods

2.1 Rule Based Modeling: The $\varkappa$ (Kappa) Language

At the heart of the $\varkappa$ modeling framework are two notions: Concurrency and Combinatorials [1]. The first is addressed by utilizing a Stochastic simulation, while the second is handled through Pattern-space encoding.

2.1.1 Stochastic Simulation

While traditional ODE systems treat time as a global variable, synchronized across species, and uniformly sampling the Instruction set, this grosses over the causal dependence some events have on others. As explained by Danos et al. [35]:

[1] Just as λ calculus represents Logic, and as π calculus captures Process, $\varkappa$ modeling addresses Combinatorials & Concurrency. As will be seen in Figures 4.1, 4.12, and the composite of 4.5, 4.6, and 4.7, the casual chains favor lateral concurrent events over linear cascades.

> In molecular systems, the temporal precedence among events cannot be defined (at first) on physical time, since cells or molecules do not bear watches, let alone synchronized ones. It is well known in concurrency that temporal precedence is a logical relation that gives rise to a partial order, as opposed to a total order. Some events must occur before others can happen, while other events may happen in any sequence, reflecting their mutual independence. Clearly, in any particular physical realization one will observe a particular sequence of events. The issue, however, is to uncover which aspects of that sequence are necessary and which contingent. The issue is to discover the invariant structure underlying all observable sequences. Differential equations are unable to resolve this causality, precisely because they treat time as global, as if everything proceeded in a synchronized fashion. (2.1)

Contrary to ODE systems, where reactions are modeled as occurring at infinite volumes with infinite molecules, with pre-determined concentrations and at synchronous times, $\varkappa$ uses a continuous time Markov chain as generated by a rule-based version of Gillespie's algorithm [36]. It therefore assumes a well mixed environment to simulate the stochastic interaction of a set of molecules. In particular, it is able to capture low-concentration effects while yielding an exact representation of the equation sampling distribution as predicted by the Master Equation for a random walk.

Having established the stochastic sampling of the rule set, the evolution of any particular trajectory is subject to the stochastic sampling of the rules. As such, there is an extremely large set of solutions the simulation may achieve. While some of these event-chains may be concurrent, some others will have causal dependencies on one another. Given the 2.2 set of conditions as described by Danos et al. [35], these *casual lineages* can be analogous to the idea of *pathways*.

- The sequence of events begins with the initial condition and ends with an event of a given type called the Observable,
- it consists only of events that are in the causal lineage to the Observable (which eliminates events that are concurrent to the observable),
- it contains no event subsequence with the same properties (which in particular eliminates cycles).

(2.2)

Indeed, encoding explicitly reactions in an ODE system leads to explicit *Pathway Reconstruction*, whereas representing reactions as Rules through a causal traceback enables *Pathway Discovery*.

2.1.2 Patterns instead of Species

A particular phenomenon was assailing the then current discipline of alchemy several decades ago, where every substance was a species of its own, and the *Curse of Dimensionality* was a formidable barrier to progress. However, the realization that the actual Laws that governed the field cared little for the *species*, but much more for the *pattern contained by the species* lead to the emergence of the current structure-less language of chemical reactions. Indeed, the very notion of a chemical group such as an *ester* conveys the notion of a pattern tethered to a molecule. Along those lines, full specification of the molecule is not required for an esterification reaction to be represented.

In $\varkappa$, proteins are represented as *Agents* who have *Sites*. These *Sites*, represent interaction potentials, and may have multiple *States*. An Agent's Sites and States are termed the Agent's Signature, and the syntax is explained in table 2.1. A particularly useful aspect of this representation is the fact that the Observables are specified by patterns, similarly to Degenerate Species, and as such the modeler is not required to explicitly state all the species to be grouped, nor is he presented with the full reaction mixture

signature_expression	::=	Id(*sig*)
sig	::=	Id *internal_state_list*, *sig* | ε
internal_state_list	::=	∼Id *internal_state_list* | ε

TABLE 2.1: Agent signature expression, as taken from the KaSim v3 manual. ε represents terminal symbols.

that is taking place [2]. In terms of the generation of Agents and their Signature, this is the area where the *Exploratorium* comes into play, further discussed in Section 2.2.

2.1.3 Rates, and the notion of Volume

It should come as no surprise that in a stochastic framework, a binding event is dependent on the volume. Indeed, reaction rate theory derives a rate constant in terms of a collision cross-section between its participants, their velocity, and internal quantum states. For a bimolecular reaction, given fixed concentrations, the collision probability is intuitively inversely proportional to the volume of the reaction. In general terms, given the *deterministic* rate constant k, the *stochastic* rate constant γ can be calculated by:

$$\gamma = \frac{k}{V^{a-1}}$$

Where V is the Volume and a is the arity of the reaction. Evidently, unimolecular reactions are unaffected by changing volumes. Moreover, given that three-body collisions are extremely rare, it is much more parsimonious these events can be represented as consecutive bimolecular reactions. As for changing the unit of measure from mol^{-1} to $molecule^{-1}$, it suffices to divide by Avogadro's number, $6.022 * 10^{23}$. This action only changes the unit of measure, but not the dimension of the rate. For more useful tricks on rate conversion, refer to Appendix B.

As stated above, reaction rates hold intrinsic properties of the conditions they are measured in: a species' state may be changed by a myriad of factors, from pH to different metal ion concentrations, while the molecule's diffusion is directly influenced by the viscosity of the fluid. Even though carefully defined experiments can successfully account

[2] As of the Kappa Simulator v3, the modeler may request the entire reaction mixture at a given time. This is intended to be an on-demand feature.

for these variations, traditional models usually indulge in fitting practices and machine-learning processes to square a model to the empirical observations, all while trying to avoid overfitting and overparametrizing.

2.2 The Exploratorium

The *Exploratorium* is the programatic support that is intended to house formalized factoids in a model-friendly environment. It may also be seen as a procedure that renders Knowldege model-ready.

2.2.1 Abstraction Scaffold: What is β-catenin?

When the word " β-catenin" is mentioned, it evokes different things to different people. A bioinformatitian could think of an amino-acid sequence, while a geneticist may contemplate a locus on a genome, and a protein crystallographer may even consider a three-dimensional physical entity [3]. Even more confusing, a specialist of *Caenorhabditis elegans* could think of *Wormadillo*, a specialist of *Drosophila melanogaster* may consider *Armadillo*, and a cancer clinician could think of *β-catenin*. It is therefore necessary to establish explicit criteria of meaning, as the term "β-catenin" is clearly an abstraction. For the Exploratorium, we decided to use a particular flavor of abstraction: phylogeny coupled with reasonable functional equivalence.

Based on the idea that the multiple proteins referred as β-catenin are bona fide homologues, this assumption is formalized by declaring the agents as phylogenetically related proteins. A special type of agents is created, one which will represent all its constituents. This agent will be referred to as a *Platoonic Agent*, where the term "platoonic" is expected to evoke the idea of a platoon of constituents, as well as of the cartoon that is an abstraction [4]. Thus, platoonic β-catenin refers to and incorporates *Wormadillo*, *Armadillo*, *β-catenin*, as well as many other proteins. For a justification for this procedure, as Jacques Monod said, "Anything found to be true of E. coli must also be true of

[3] Amino-acid sequences and gene loci are not necessarily isomorphic as a single locus may yield multiple mRNAs due to alternative slicing, whose proteins may be further edited to yield vastly different peptides. The same applies to protein crystals, as there are multiple conformations a given sequence may fall into.

[4] If the reader is generous, it may even evoke the ideal Platonic concept.

elephants.", particularly at the levels of the most basic aspects of proteins. Platoonism is therefore capable of enriching the notion of β-catenin with knowledge from different sources. For this Exploratorium, the KEGG phylogeny was used to obtain the initial set of constituents per orthology. This superset was further refined through removal of deprecated or un-curated UniProt entries. Table 2.2 lists the information as retrieved from the KEGG.

2.2.2 Agent Signature: What of β-catenin is Important?

It follows human intuition that two bodies must physically touch to interact, and while the concept of *Action at a Distance* has led to significant advances in Physics, it is clear that this phenomenon's contribution to biologically relevant scales is negligible. As such, the abstraction that represents β-catenin can be defined in terms of its interaction potentials *as physical interaction sites*. The notions of "Binding Domain" or "Binding Site" are natural and intuitive extensions of this idea, and they are anchored to a physical principle that governs said interaction. For example, the affinity a Transcription Factor to its target Promoter Region may be defined through the stability of the bound pair, which relies on the increase of free energy. Indeed, this precise physical mechanism of action can be regulated by processes that change the interacting partners: a hyper-phosphorylated protein is more negatively charged that its "normal" predecessor, and therefore may be better suited to bind positively charged entities. This is the basis for regulation by PTMs. As PTMs operate at the level of *residues*, we can therefore define β-catenin as a collection of *Binding Sites* and *Modification Sites*.

While the notion of a *Modification Site* is fairly straightforward [5], the notion of a *Binding Site* is less evident. The frequent use of the term "Binding Domain" introduces confusion by evoking the notion of a *Domain*, which was originally a concept regarding subsections of a protein who, by nature of "rapid self-assembly", were capable of being "structurally independent" [37]. Clearly, the structural notion of a *Domain* is different from the interaction potential that is a *Site*. This distinction notwithstanding, Sites are dependent on the structural information that is the Domain, but in no way are the two isomorphic.

[5] A Modification Site is a Residue at a particular location in a particular protein that undergoes a particular change from one defined state to another defined state.

UniProt Name	Status	Description or Name
A7SKL9_NEMVE	Unreviewed	Predicted protein
A8PUL8_BRUMA	Unreviewed	Armadillo/beta-catenin-like repeat family protein
A8Q356_BRUMA	Unreviewed	Armadillo/beta-catenin-like repeat family protein
WRM1_CAEBR	Reviewed	Armadillo repeat-containing protein wrm-1
BAR1_CAEBR	Reviewed	Beta-catenin/armadillo-related protein 1
A8XWE9_CAEBR	Unreviewed	Protein CBR-HMP-2
B0WHS4_CULQU	Unreviewed	Armadillo
B1MV73_HORSE	Unreviewed	Beta catenin 1
B3MXH2_DROAN	Unreviewed	GF19474
B3P8S9_DROER	Unreviewed	GG12670
B3RR98_TRIAD	Unreviewed	Putative uncharacterized protein
B4I9K6_DROSE	Unreviewed	GM18941
B4JWY3_DROGR	Unreviewed	GH17847
B4L5M8_DROMO	Unreviewed	GI21760
B4M333_DROVI	Unreviewed	GJ19138
B4N1V6_DROWI	Unreviewed	GK16376
B4Q1K8_DROYA	Unreviewed	GE16998
B4R322_DROSI	Unreviewed	GD16405
B6V8E6_CANFA	Unreviewed	Beta-catenin
B7QGW7_IXOSC	Unreviewed	Armadillo, putative
C3ZT37_BRAFL	Unreviewed	Putative uncharacterized protein
E0V8W8_PEDHC	Unreviewed	Armadillo segment polarity protein, putative
E5SLR3_TRISP	Unreviewed	Armadillo segment polarity protein
F6WBD5_ORNAN	Unreviewed	Uncharacterized protein
F7GNE4_MACMU	Unreviewed	Catenin beta-1
G1LYU0_AILME	Unreviewed	Uncharacterized protein
G4VFS7_SCHMA	Unreviewed	Putative beta-catenin
H2R2U1_PANTR	Unreviewed	Uncharacterized protein
H3I553_STRPU	Unreviewed	Uncharacterized protein
HMP2_CAEEL	Reviewed	Protein humpback-2
ARM_DROME	Reviewed	Armadillo segment polarity protein
CTNB1_HUMAN	Reviewed	Catenin beta-1
CTNB1_MOUSE	Reviewed	Catenin beta-1
CTNB1_BOVIN	Reviewed	Catenin beta-1
WRM1_CAEEL	Reviewed	Armadillo repeat-containing protein wrm-1
ARM_AEDAE	Reviewed	Armadillo segment polarity protein
BAR1_CAEEL	Reviewed	Beta-catenin/armadillo-related protein 1
ARM_DROPS	Reviewed	Armadillo segment polarity protein
Q4H3U7_CIOIN	Unreviewed	Beta-catenin
Q5R5L8_PONAB	Unreviewed	Putative uncharacterized protein DKFZp469E1714
ARM_ANOGA	Reviewed	Armadillo segment polarity protein
Q8WNW4_PIG	Unreviewed	Beta-catenin
CTNB1_RAT	Reviewed	Catenin beta-1

Table 2.2: β-catenin extended Platoon.

For the Exploratorium, the decision was made of generating a suggested Agent Signature based on the collected structural information for the platoon of proteins. Therefore, our platoonic Axin holds the superset of domain information from its constituent proteins. In other words, it holds the de-duplicated collection of PFAM entries, modifiable residues, and featurettes of interest, as cataloged by DOMINE and PhosphoSite, related to multiple Axins, as well as referencing the structural Protein Data Bank (PDB) information from them, all within a unified naming convention based on the position of the features on the multiple sequence alignment of the platoon. The Exploratorium is thus able to inform the modeler not only of the PDB entries 1dk8 (corresponding to the RGS domain) and 1wsp (corresponding to the DIX domain) from AXIN1_HUMAN, but also 1qz7 (corresponding to the Catenin Binding Domain) from AXIN1_XENLA. It is therefore up to the modeler to refine this predictions as needed by either explicitly refining the Domain-to-Site transition [6], or by accepting the suggested signature. Evidently, if the data were available at the mechanistic scope that is required to support the automatic generation of Agent Signatures, it could be fed directly into the Exploratorium. As such, this is not a technical limitation of the effort, but simply a lack of fine data.

2.2.3 Agent States: When & How can β-catenin act?

Given the platoonic agents with their respective signatures, we can suspect a particular level of causal information. For example, if a region known to participate as a binding interface between two proteins also contains sites know to be post-translationally modified, we can hint at the possible regulation at this level. This is clearly not actual confirmed knowledge that a particular site is required to be in a particular state for the binding to take place, however it is merely a hint. It is therefore up to the modeler to determine if that hint is relevant or not: a lysine within a binding pocket would surely break a binding event if that lysine is ubiquitinated. As such, even a coarse mapping of residues withing regions can prove to be a potent inference engine. When we consider also the platoonic nature of these agents, we can effectively map residues to regions across species. These hints can later be verified or disproved, which leads in effect to a refinement of the knowledge contained in the Exploratorium (i.e. it is now known that something matters, or not). This engine serves therefore a dual purpose, not only does

[6] For example, Axin's DIX domain can form polymers in a head-to-tail arrangement. The Domain therefore has two binding Sites. We refer to the splitting of such site DIX into DIX_a and DIX_b as a refinement of the suggested signature. Similar efforts must be done for Wnt, LRP, Fzld, and APC.

it organize and present the information contained within, it also serves as a guide for additional experimentation. Such are the benefits of model checking Knowledge.

2.2.4 Rule$\varkappa$raft: What does β-catenin do?

Regarding the dynamic aspect of an agent, the best source of information has proven to be the scientific literature. Indeed, as this data is fundamentally different from the static data that is a Protein, it deserves different treatment. Moreover, databases of protein-protein interactions are notoriously poor in terms of the actual physical interaction taking place. More often that not, they deal with phenomenologies that are too coarse to be of use. Therefore, an extensive literature dive is often required.

In terms of the actual information that can be acquired, it can be classified into two types of event, binding/unbinding events, and modification events. Table 2.3 lists some examples of $\varkappa$ification of knowledge. This factoids are the executable instructions that become $\varkappa$ rules. Careful translation of literature information eventually leads to a carefully assembled corpus of $\varkappa$ rules, which has the advantages of representing mechanistic knowledge, in a *Lingua Franca*, and being executable. Such a corpus of executable knowledge, with its agent definition support, will be referred to as a "Moodel". The differences between our "Moodel" and a traditional Model is that the assumptions that went into generating the Moodel are contained explicitly in the Moodel itself. Unlike a traditional Model, where only the author really understands its inception, its assumptions, its caveats, and that most likely dies when the person changes laboratory, a Moodel is expected to be self-sustaining. Not only are its rules human readable, they are the explicit statement of what they mean. But above all, a Moodel is capable of and expecting to, undergo continual expansion, revision, and growth. A discovery of a new state of a protein would yield to a re-write of a species-based model, but as a Moodel is pattern-based, it can effectively incorporate this new knowledge into an already existing rule pool by taking advantage of the *independence* of sites for the rules where this is the case. For the rules that would require refinement due to new causal restrictions, this clarification would effectively be independent from the rest of the rules, and as such the change is scoped to a sub-section of the Moodel. In other words, a Moodel is a kind of fat extended model that contains obsessively self-documented Executable Knowledge [7].

[7] Perhaps a useful distinction to make between Moodeling and Modeling is that the latter begins with a *construction* by the modeler of what the system represents. Notice that a model is not isomorphic

Empirical Observation	**κ-ification**
Axin binds APC's SAMP repeat through the RGS domain	`APC(SAMP), Axin(RGS) ->` `APC(SAMP!1), Axin(RGS!1)`
Axin's RGS unbinds APC's SAMP	`APC(SAMP!1), Axin(RGS!1) ->` `APC(SAMP), Axin(RGS)`
GSK3β phosphorylates Axin's T481 when bound through their interface	`GSK3(i_Axin!1), Axin(i_GSK3!1, T481~un) ->` `GSK3(i_Axin!1), Axin(i_GSK3!1, T481~ph)`
Phosphatase 2 dephosphorylates Axin's T481 when bound through their interface	`PP2(i_Axin!1), Axin(i_PP2!1, T481~ph) ->` `PP2(i_Axin!1), Axin(i_PP2!1, T481~un)`
Phospho-Axin binds β-catenin's ARM through the CBD	`Axin(T481~ph, CBD), Cat_b(ARM) ->` `Axin(T481~ph, CBD!1), Cat_b(ARM!1)`

Table 2.3: κ-ification of Empirical Observations.

to Reality, but is just a facet viewed from a particular angle. As such, there is no "One True Model". Moodels begin by integrating Knowledge from different sources, and then executing them. The moodeler is not required to wed a particular abstraction of what the system is. Perhaps a useful metaphore is the following: a Moodel is to a Model what a Primitive is to a Function.

Chapter 3

Results

The main Moodel serves as the initial corpus of rules to feed into the Exploratorium. This collection, termed *BigWnt*, is composed of around 180 rules of empirical facts observed in different cellular executions. The Contact Map for BigWnt is presented in Figure 3.1. Some factoids have been observed in the cytosol, some in the nucleus, some others at the membrane, and yet others beyond the same. Likewise, the rules do not refer exclusively to any one organism. The rules are constructed in a certain style to preserve the advantages of pattern-based models; refer to Appendix B for the Manual of Style for such ϰrafting. In terms of stories, or local miniature pathways, *BigWnt* can be divided into separate narratives [1]. For the full raw ruleset, please refer to Appendix A.

3.1 BigWnt

3.1.1 Membrane Signaling

The first set of events in Wnt signaling are the first interactions of the Wnt signaling peptide with the target cell. Wnt begins by recruiting a member of the Fzld family of receptors through their Frizzled domain, and also a member of the LRP proteins

[1] The rules are presented as a grouped entity for clarity. They are fully independent and therefore do not constitute a formal Pathway on their own. Indeed, some rules are members of multiple narratives, where they may have completely different consequences: Phosphatase 2 assembly of α and Catalytic subunits may lead to an active holoenzyme, or to an inactive compound depending on which β-subunit is loaded.

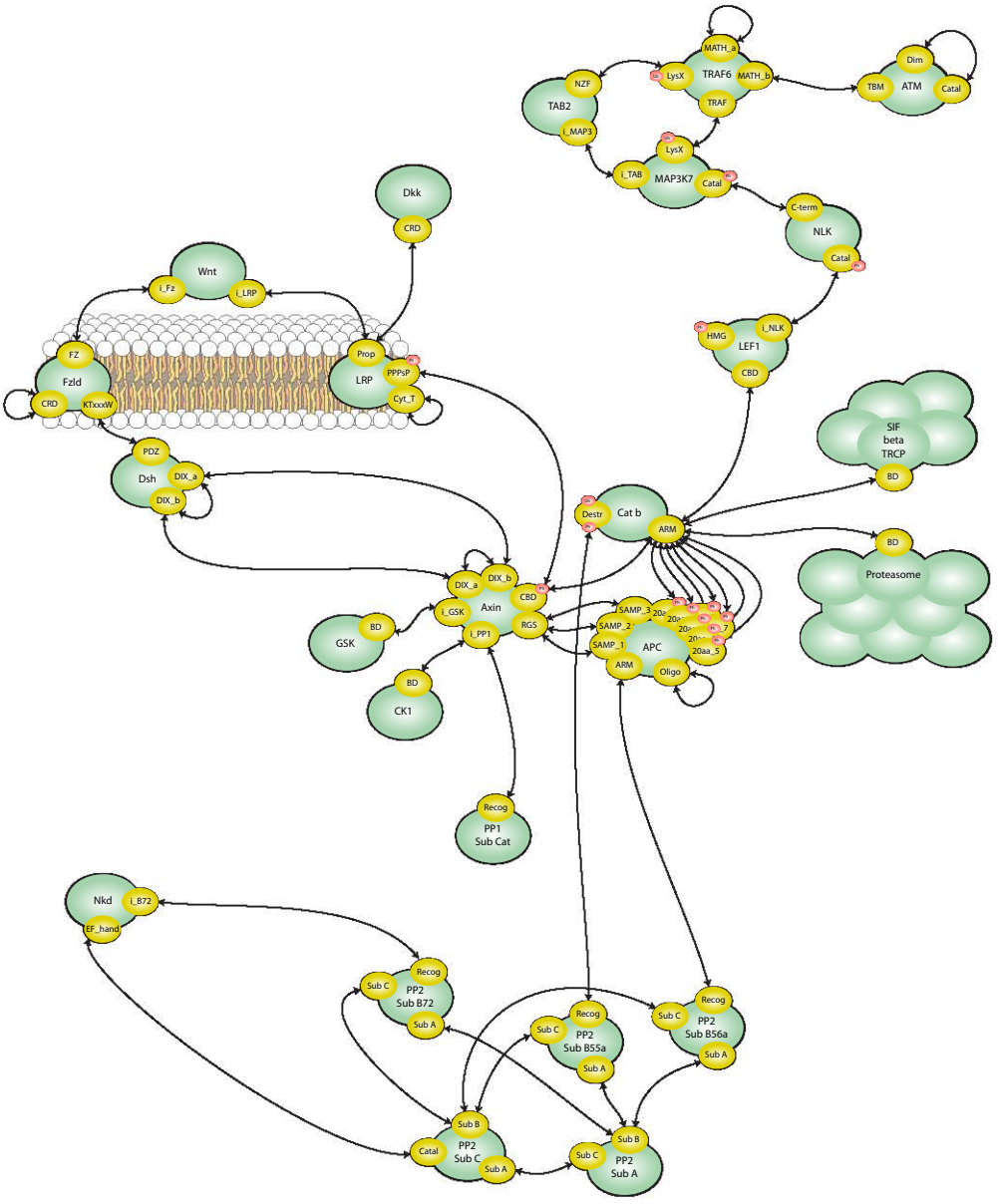

FIGURE 3.1: This is the Contact Map for BigWnt: the initial corpus of rules fed into the Exploratorium. The rampant oligomerization of agents is evident by the abundance of both by self-binding edges as well as cycles. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

[38] through one of the exposed β-propeler features. Regarding the binding interfaces on Wnt, they are not currently known. Of particular interest is that the same Wnt is able to bind simultaneously a Fzld and an LRP [39], yet the interaction between Fzld and LRP is extremely weak at best [40]. Though it may be tempting to speculate an interaction between Fzld and LRP within the context of a stabilization inside the hydrophobic mid-region of the cell membrane, this Moodel does not include such a rule.

Branching out, it has been found that LRP is able to form homodimers, probably through their C-terminus [41], as has been shown for Fzld through their Cystein Rich Domains [42]. Moreover, Fzld is able to recruit Dsh's PDZ domain through the conserved KTxxxW motif [40], while LRP's pppSpS motives can bind Axin's Catenin Binding Domain once they have been phosphorylated [40]. Considering that Dsh can oligomerize through it's DIX domain [43] in much the same way that Axin can with its own [32], and that these two can form *at least* heterodimers, it is tempting to ponder the lack of exploration of these phenomena: as can be seen in the Contact Map on Figure 3.2, why can *almost everyone* aggregate?

3.1.2 Destruction Complex

At the heart of Wnt signaling is the Destruction Complex. Traditional views group β-catenin, Axin, GXK3-β, CK1-α, and APC into a rigid, static, and defined structure with stoichiometric ratios of its components, the so called "Destroyer" [2]. However, even a simple exploration of the structures of these proteins reveals an interesting trend: multimerization. APC is able to dimerize through its Oligo domain [44], yet it is also endowed with three separate binding sites for Axin, the SAMP repeats [45]. APC also holds seven Cystein Rich regions, the primary binding sites of β-catenin also known as twenty amino-acid (20aa) repeats, and three secondary binding sites also for β-catenin, termed fifteen aminoacid (15aa) repeats. All these repeats are present in the unstructured [3] mid-section of the protein. In terms of the regulation of these events, most are subject to phosphoregulation by the same kinases that are loaded onto the complex, notably CK1α, CK1ε [46], and GSK3-β [47].

[2] This structure is akin to a network catalyst, and as such is able to generate interestingly unbelievable properties ...

[3] The usage of "unstructured" is meant to convey the idea that the protein has no fixed and defined three-dimensional configuration as an isolated peptide. It may however acquire such a conformation upon binding to another element.

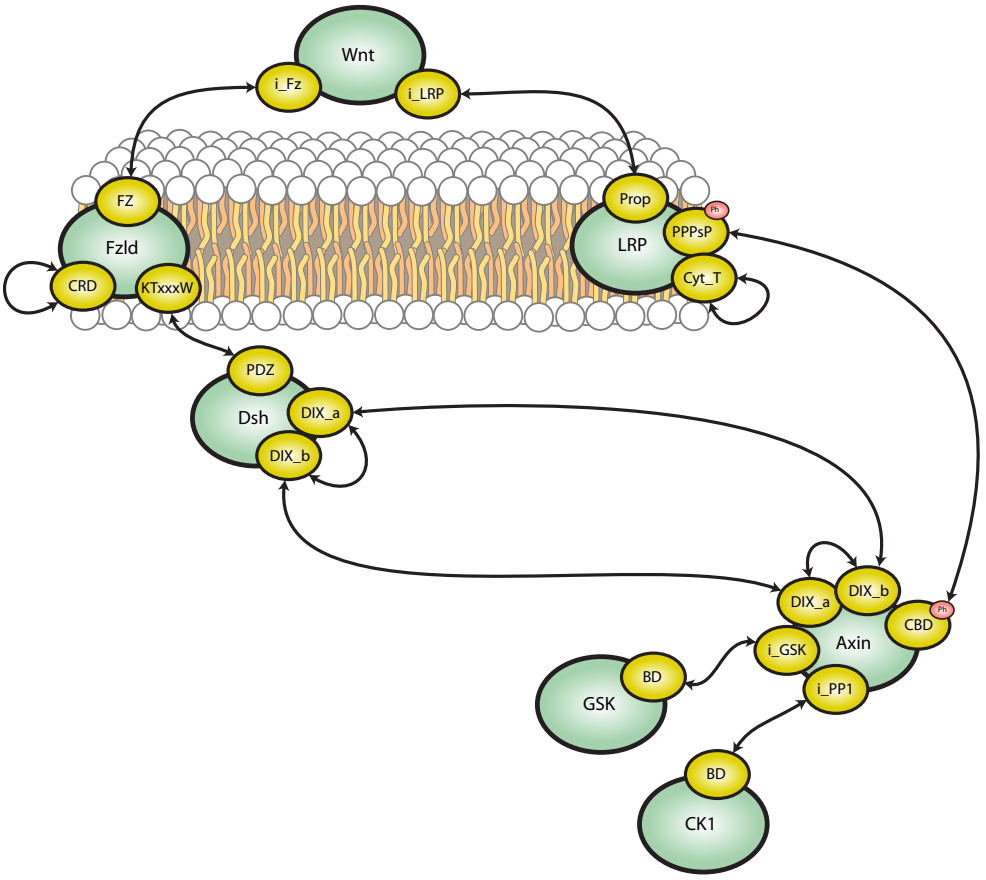

FIGURE 3.2: Wnt is able to find simultaneously a Fzld and an LRP. Fzld can dimerize through its CRD, as can LRP through its Cytosolic C-terminus Dsh and Axin can also oligomerize through their DIX domain. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

As for the actual phosphorylation of β-catenin, this is achieved by phosphopriming by CK1α at Threonine 41 and Serine 45 [47], subsequent hyperphosphorylation by GSK3-β at Serine 33 and Serine 37 [47], and protection of the Destruction Mark by APC [48]. Phospho-β-catenin is then fed to the SCF β-TrCP ubiquitination machinery [48]. Once ubiquitinated, it is targeted through unknown means to the 26s proteasome [4]. This associations are represented in the Contact Map on Figure 3.3.

In terms of the de-stabilization of the Destroyer, it has been observed that something related to the "sequence B" section on APC is related to its liberation from the complex if Dsh is also interacting with it [49].

[4]Evidently, moodeling the dynamic assembly of the SIF-β-TrCP complex or of the 26s proteasome requires some consideration, as it has been suggested APC may play an integral part in said targeting. However, this is not a formal part of the moodel. It is included through the use of fictitious agents for modeling purposes, yet it is not a formal part of the Exploratorium.

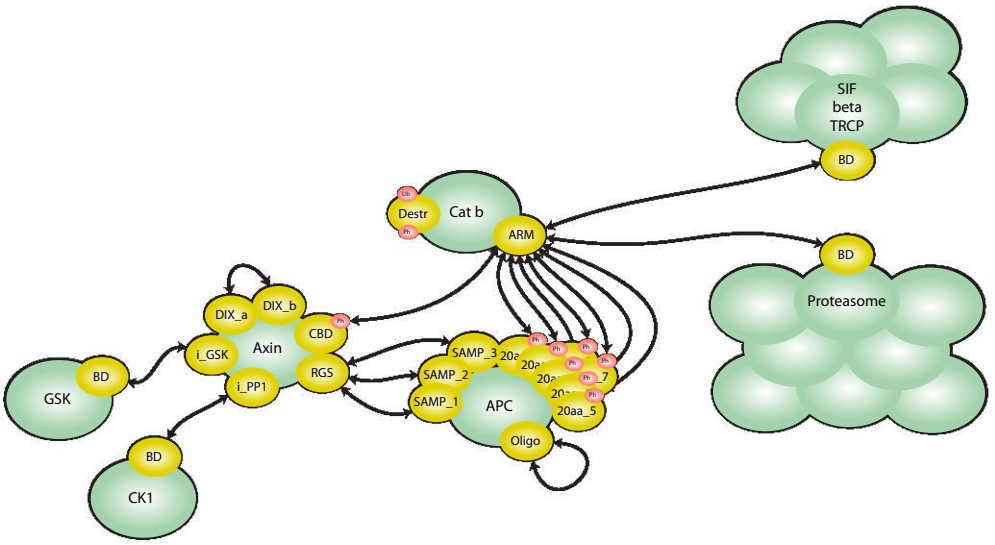

FIGURE 3.3: Binding of β-catenin to the Axin-APC-GSK3β-CK1α complex results in its hyperphosphorylation, subsequent ubiquitination by the SIFβTrCP, and consequent degradation by the 26S Proteasome. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

3.1.3 Calcium Signaling

Besides the canonical Wnt signaling cascade that involves directly interfering with the Destroyer, there appears to be a separate collection of events related to Ca^{2+} signaling [50]. These begin with the export of inactive *Ataxia Telangiectasia Mutated* (ATM) from the nucleus following the ion spike [51] [5]. Once in the cytoplasm, ATM can homo-oligomerize in a head-to-tail conformation through a region located at positions 1961-2046 targeting the Catalytic cleft [52]. Likewise, it also able to recruit *TNF Receptor-Associated Factor 6* (TRAF6) [51] through their respective *TRAF6 Binding Domain* (TBD) and *Meprin And TRAF Homology* (MATH) regions. Considering the TBD on ATM, at positions 2152-2157, is very close to the oligomerization interface, this could explain TRAF6's multimerization [53] through an increased local concentration.

Moreover, multimerized TRAF6 activates as an ubiquitination enzyme, and after auto-ubiquitination it gains full activity [53]. This triggers two synergistic events. On one hand TRAF6 is able to recruit through part of its MATH region an inactive *Mitogen-Activated Protein Kinase Kinase Kinase 7* (MAP3K7) [6] [54] and activate it through

[5] It is assumed Wnt induced Ca^{2+} spike is sufficiently similar to stress induced Ca^{2+} spike.
[6] MAP3K7 is also known as *Transforming growth factor-β-Activated Kinase 1* (TAK1).

ubiquitination. On the other hand, TRAF6's Lysine 63 polyubiquitination chain is recognized by the zinc finger of *TGF-β-Activated Kinase 1* (TAB1) [53], which happens to be a functional subunit of MAP3K7. Upon ubiquitination of MAP3K7 and recruitment of TAB1, MAP3K7 is able to auto-phosphorylate at Threonine 184, Threonine 187 and Serine 192, and consequently activate [55]. Considering these recruitments, it may be useful to think of multimerized TRAF6 as a scaffold for assembly and activation of MAP3K7. Active MAP3K7 is then able to phosphorylate *Serine/threonine-protein kinase Nemo Like Kinase* (NLK) at Serine 522, which activates and is translocated into the nucleus [56]. Within the nucleus, it is able to phosphorylate LEF1 at Threonine 155 and Serine 166. Phosphorylated LEF1 looses affinity for DNA, and gains recognition by a 14-3-3 export complex. Refer to the Contact Map on Figure 3.4 for a graphical representation of this narrative.

Evidently, this alternate cascade would appear to affect little the phosphorylation of β-catenin. Nonetheless, it would be able to significantly abrogate β-catenin transcriptional activity through co-activator depletion, as well as provide an export mechanism for nuclear β-catenin tethered to said co-activator. On a different note, TRAF6, MAP3K7, TAB1, and NLK are involved in NFϰB signaling. While massive crosstalk between signaling cascades is not unheard of, it is very uncommon to find a cohesive model of these regulations.

3.1.4 Nuclear-Related Events

Regarding the nuclear events, there are several phenomena that are puzzling. To begin with, APC shuttles into and out of the nucleus through unknown means [57]. On one hand it possesses several Nuclear Localization Signals, and several Nuclear Export Signals [58], some of them dormant, but most of them unnecessary [59]. On the other hand, it associates with β-catenin, which happens to compete with Importins for binding to the nuclear pore complex [57] [7]. Moreover, APC possesses an ARM domain that bears striking resemblance to β-catenin's, and indeed it may associate directly with the nuclear pore complex [59]. It has been postulated that APC may shuttle excess β-catenin from the nucleus, but exploring such a mechanism of action would require

[7] Importin Subunit α 6 contains 10 Armadillo repeats within its ARM domain, which is surprisingly similar to β-catenin's.

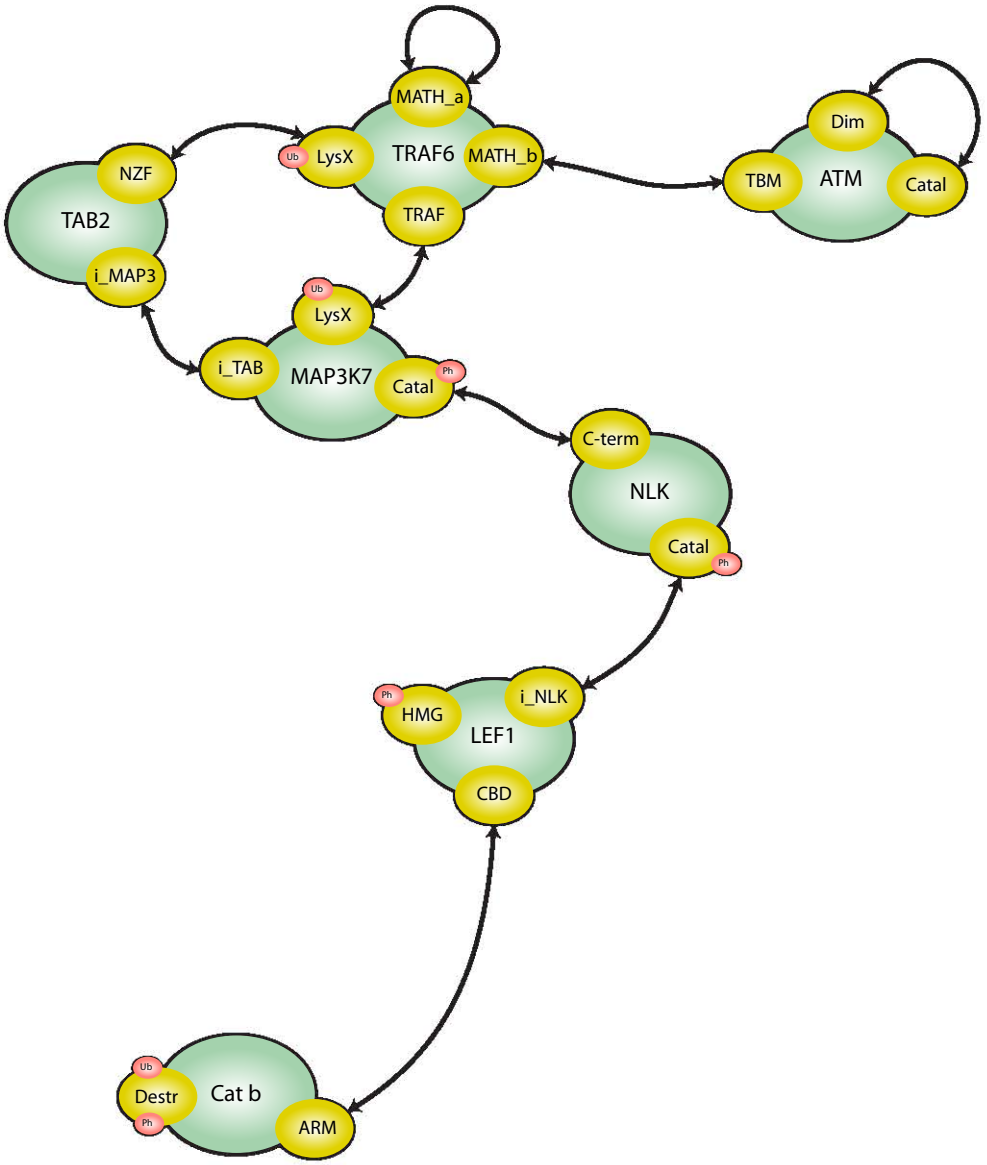

FIGURE 3.4: ATM induces polymerization of TRAF6, which activates MAP3K7 through recruitment of the TAB2 subunit. Active MAP3K7 activates NLK, which phosphorylates LEF1, reducing its affinity for DNA. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

profound understanding of said mechanism. Moodeling the nuclear pore complex lies outside the scope of this project for the time being.

Other events of interest withing the nucleus include the transcriptional feedbacks of the LEF1 / β-catenin activator. These include transcription of *Protein Naked Cuticle Homolog 1* (Nkd), which recruits Phosphatase 2 into an inactive complex along with Dsh [60] through several Calcium binding pockets in EF-hand domains; transcription of *Dickkopf-related protein 1* (Dkk), which after paracrine export sequesters the Wnt binding site on the Fzld domain [38]; transcription of Axin2 [61], which is functionally isomorphic to Axin1 [62], the concentration limiting protein in the Destruction Complex; and destabliziation of LRP mRNA [41]. While rigorous moodeling of transcription and translation mechanism in mammalian cells would be an interesting endeavor, it lies outside the present project's scope [8].

3.1.5 Additional Regulation: Phosphatases Everywhere!

Regarding the phosphatases, it is interesting to note that thermodynamically, they serve to balance the kinase activities of the Destroyer's members. Indeed, the phosphorylation marks on APC are erased by the holoenzyme *Protein Phosphatase two* (PP2), who binds APC's ARM through the B56 subunit, α isoform [59]. PP2 is also able to erase the Destruction Motif on β-catenin when bound through the B55 subunit, α isoform [63] [9]. As for Axin, it was surprising to find that Axin is also know as the PPP1R49: regulatory subunit 49 of *Protein Phosphatase one* (PP1). Indeed, the catalytic subunit of PP1 associates directly with Axin, and dephosphorylates it [64]. The Contact Map for the phosphatases is on Figure 3.5.

3.2 SmallWnt

SmallWnt is a subsection of *BigWnt*. It includes the 3.1.2 and 3.1.1 rules. This is the prototype formal cohesive model housed within the Exploratorium. The rules related to

[8] Note that Nkd is subject to alternative splicing, as is its binding parter PR72 on PP2. That would require assembly of the spliceosome and the regulation of such a complex, a process which is not fully understood at present.

[9] Notice these are two different subunits, the 55KDa and the 56KDa.

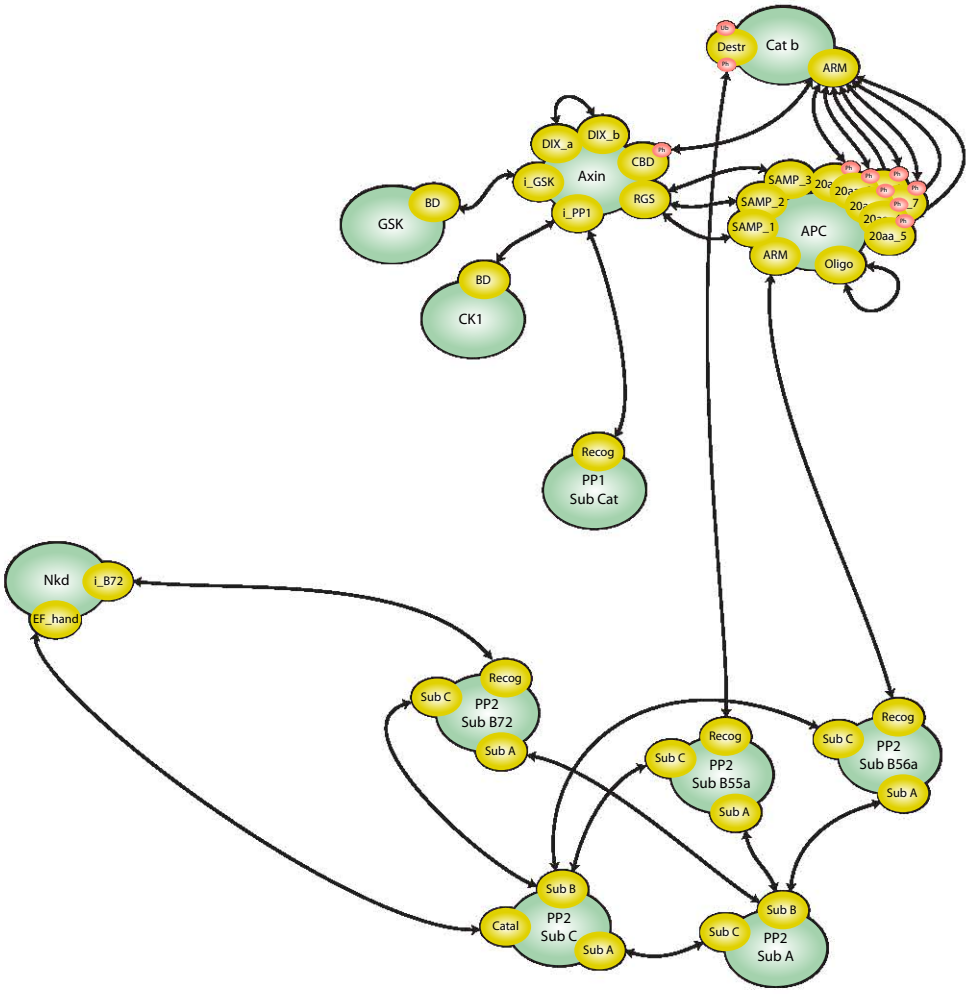

FIGURE 3.5: Contact Map for the Phosphatases, showing the multiple subunits of PP2 involved. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

the Ca^{2+} signaling are referred as *SideWnt* in Appendix A, where the transcriptional feedbacks are grouped under *FeedbackWnt*.

3.2.1 The Rule Set

While the link between the 3.1.2, 3.1.1 rulesets is fully compatible with the current state of the moodel, including the 3.1.4 in a formal sense would require additional endeavors that lie outside the current moodeling scope. Nonetheless, the Transcriptional Regulators can be included through their injection at given times. The Contact Map on Figure 3.6 is for SmallWnt, and it highlights the rampant polymerization potential of the elements in Wnt Signaling.

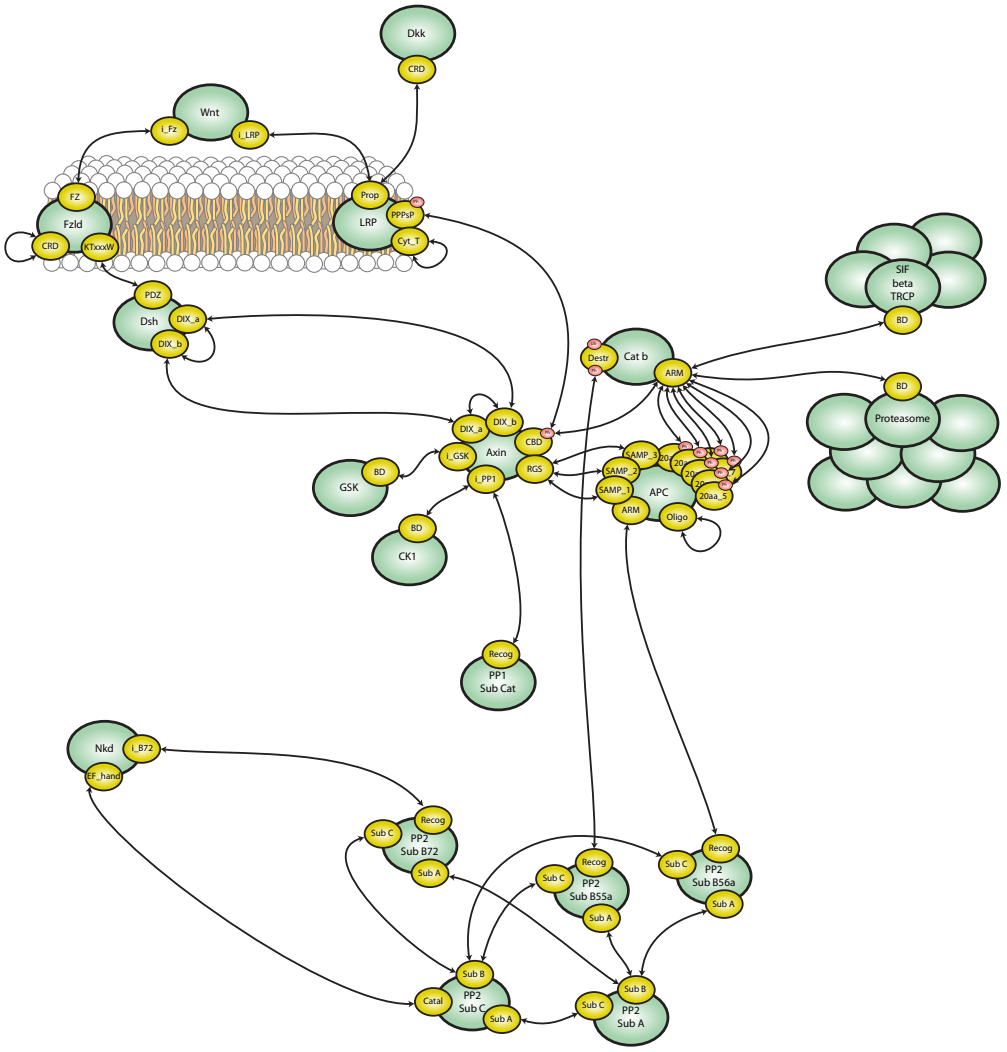

FIGURE 3.6: Map of the assembled pieces that constitute SmallWnt. Scaffolding proteins, such as Axin, can be seen in action by the their increased number of binding sites. Of note is the view that most agents can form homooligomers, or are at least part of a cycle group. Notice this contact map contains no causal information. The contact map has been simplified for clarity: residues and some sites have been omitted.

3.2.2 The Particulars of the Model

The initial conditions that make the executable part of *SmallWnt* are by nature not the type of Knowledge that would be desirable to include in the formal Exploratorium. Indeed, concentrations can vary vastly even within a particular cell line, more so during embryonic development. Moreover, the frequent use of referencing concentrations over quantities carries around an implicit volume definition, which hinders portability of models across conditions. In the case of Wnt signaling, some of these parameters were described previously [1], though others have contested their extrapolation and relevance

Molecule Count	Equivalent Concentration	Species
135000	100 nmol	Dsh †
5400	4 nmol	APC ‡
94500	70 nmol	GSK3 ‡
202500	150 nmol	Axin ‡
661500	490 nmol	Cat-b ‡
2700	2nmol	Fzld
2700	2nmol	LRP
67500	50nmol	CK1
6750	5nmol	PP2 A subunit
6750	5nmol	PP2 Catalytic subunit
6750	5nmol	PP2 B55a subunit
6750	5nmol	PP2 B56a subunit
6750	5nmol	PP2 B72 subunit
6750	5nmol	PP1 Catalytic subunit
135000	100nmol	SCFβ-TrCP
20250	15nmol	26s Proteasome

TABLE 3.1: Proposed Initial Concentrations in the SmallWnt model. Entries with a † were taken from [1] corresponding to *Xenopus laevis* egg extract; entries with a ‡ from [65], for HEK293T cells.

[65]. Nonetheless, these parameters must be chosen for a given execution, and therefore the molecule counts for the initial conditions are those presented in Table 3.1, assuming a typical volume for mammalian cell of around 2.25^{-12} liters.

The same applies to rates. Though ODE-based mathematical modeling is usually *obsessive* in regards to rates [10], anecdotal evidence suggests that pattern-based modeling is more concerned with having correct causal dependencies and ballpark rates. Indeed, as seen in Section 2.1.3, the deterministic rates are subject to all sorts of pitfalls that render them difficult to port across models. Therefore, the model states rates compatible with more general notions, such as a rate of $1.0 * 10^{-4} second^{-1}$ for a diffusion limited reaction, such as a binding event. Table 3.2 lists the different values used for general terms, with optional references indicated as BRENDA entries between chevrons. Though it could be argued the rates presented in [1] should be sufficient, most of those rates are not compatible with the level of granularity in this moodel; for example, their β-catenin production rate was constant, but as seen in Section 1.3, this is clearly not the case for variable β-catenin concentrations.

[10] The "fitting" step on most traditional models is often due to the inability of the model to actually model what it is supposed to model. Often, the modeler has to fall back on Machine Learning principles to fit the abstraction that is the model to desired observables that are supposed to be modeled. Moodeling is a very different approach because it is integrative instead of reconstructive.

Variable	Value Range	Unit
GeneralBinding	10.0^{-5} – 10.0^{-3}	$molecules^{-1}second^{-1}$
GeneralUnbinding	10.0^{-5} – 10.0^{-1}	$second^{-1}$
GeneralDephosphorylation	1.0	$second^{-1}$
GeneralPhosphorylation	10.0^{-1}	$second^{-1}$
ReceptorDimerization	$1.6 * 10^{-5}$	$molecules^{-1}second^{-1}$
ReceptorDissociation	$1.6 * 10^{-2}$	$second^{-1}$
GeneralUbiquitination	$3.0 * 10^{-2}$	$second^{-1}$ <6.3.2.19 >
GeneralDeubiquitination	1.0	$second^{-1}$ <3.4.19.12 >
GeneralProteolysis	$2.0 * 10^{1}$	$second^{-1}$ <3.4.21.4 >
RingClosureRate	$1.0 * 10^{4}$	Arbitrary Rate for ring closure

TABLE 3.2: General Rates used in the SmallWnt model. Values between chevrons indicate BRENDA entries as sources for the values.

Chapter 4

Discussion

Given such a big execution, here are presented some insights into Wnt Signaling. These simulations are not of the full moodel, but of notable slices of it. Moreover, as the molecular counts reported in the literature render the simulation extremely costly in terms of computing power, these simulations were run with a donwnscaling factor of 0.01 or 0.05, as described in Appendix B.

4.1 Dynamic Analysis

4.1.1 Causal Traceback

A particularly useful tool enabled by the standarized notation in $\varkappa$ rule-based modeling are the "stories", constrained in Table 2.2. These narratives are the sequential applications of rules that lead to a particular observable. They therefore constitute a systematic approach at pathway discovery: the input ruleset does not require an explicit declaration of the causal relationships *between* rules, and yet through Abstract Interpretation is able to extract the adequate narrative. Figure 4.1 shows one such in silico predicted pathway. The key events are clearly visible, notably recruitment of the kinases at level zero, phosphorylation of the CBD at level one, allowing recruitment of β-catenin at the subsequent level two, phosphopriming and hyperphosphorylation at levels three and four respectively, and finally ubiquitination and degradation. Notice these signaling events do not mention APC, which is indeed not *required* in the causal chain.

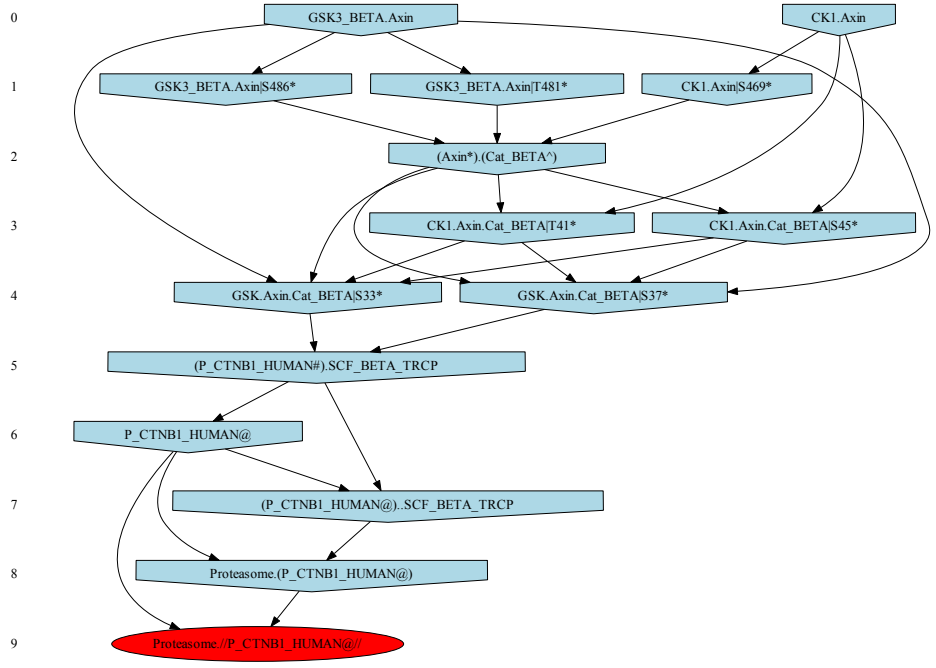

FIGURE 4.1: Weakly compressed story for the degradation of β-catenin. Blue boxes represent rules, red ovals the end observable. At level zero, the first rule is GSK3β recruitment by Axin, and CK1 recruitment by Axin. At level one, first rule is GSK3β mediated phosphorylation of Axin's S486, GSK3β mediated phosphorylation of Axin's T481, and CK1 mediated phosphorylation of Axin's S469. On level two, the rule is β-catenin recruitment by phosphoAxin. At level three, the rules are CK1 mediated phosphorylation of β-catenin's T41, and CK1 mediated phosphorylation of β-catenin's S45, these are the phosphopriming events. At level four, the rules are GSK3β mediated phosphorylation of β-catenin's S33, as well as GSK3β mediated phosphorylation of β-catenin's S37. At level five the rule is recruitment of hyperphosphorylated β-catenin by the SIF β-TrCP complex. At level six the rule is ubiquitination of β-catenin. AT level seven is release of ubiquitinated β-catenin from the SIF β-TrCP complex. At level eight the rule is recruitment of ubiquitinated β-catenin by the 26s Proteasome. Finally, at level nine, the tracked application is degradation of β-catenin. The labels on the boxes refer to the actual labels on the $\varkappa$ file. Refer to Appendix A for the rules.

The potential for such systematic approaches at pathway discovery at the mechanistic level that is being dealt with in this work is staggering. Far from requiring a curator to hold the entire idea of what a pathway is in mind, the usage of $\varkappa$ as a *Lingua Franca* allow the embedding of the pathway in the very rules that constitute it. Moreover, the interlocking dependiencies and allowances on the causal constraints on the rules yield a remakable feature: crosstalk ceases to be unwanted noise for traditional signaling *chains*, and is now an integral part of signaling *networks*.

4.1.2 Signalosome Assembly

LRP to Wnt, Wnt to Fzld, Fzld to Dsh, Dsh to Axin, Axin to LRP, these interactions form the kernel for assembly of a much larger structure termed the *Signalosome* [66]. These ribosome sized structures are a puzzle, as they appear to be extremely stable at the scaffold level even though the turnover rate for their constituents is fast [66–68]. It is tempting to consider such an assembly a dynamically unstable structure. This behavior is predicted by the moodel in the form of large aggregates of LRP, Wnt, Fzld, Dsh, and Axin, as seen in Figure 4.2 [1]. However, such aggregates are very sensitive to the composition of the reaction mixture, further highlighting the need to address and instanciate parameters per simulation, and therefore per intent. Figure 4.3 is a snapshot of the reaction mixture taken 100 time units after Wnt induction. The Patchwork rendering serves in comparing that mixture with the Pre-Wnt found in Figure 4.4. These highlight the extreme connectivity the reaction mixture aquires.

The appartition of this giant component is explained by the satisfaction of the causal restrictions that prevented an avenue of polymer growth: the LRP-Axin binding event. Wnt is equivalent to the Keystone in the LRP-Wnt-Fzld-Dsh-Axin arch. Without Wnt, LRP is completely disconnected. With Wnt, LRP is gained into the line, and following hyperphosphorylation by Axin-bound CK1 and GSK3-β, LRP is able to satisfy the causal dependiencies required for binding Axin, closing the cycle. Once the cylce has been assembled, and in absence of any dephosphorylation evidence, Wnt is dispensable: the causal dependiencies on LRP have been satisfied. In other words, the system was deadlocked. Indeed, as seen in the composite of Figures 4.5, 4.6, and 4.7, the system is unable to progress in the cycle closure in absence of Wnt. At level zero the components begin to recruit each other, however LRP remains a separate species. With the addition of Wnt, the system can progress to level one, where Wnt bridges LRP to Fzld. Once the proteins are assembled into a single species, then the GSK3β can phosphoprime LRP, as seen in level two. Consequently, hyperphosphorylation by CK1 follows at level three. Finally, LRP sequesters Axin's β-catenin binding site at level four. Notice however that in this conception, there is a single Dsh bridging Fzld to Axin. If Dsh can polymerize while tethered to the membrane, it may provide a much greater number of possible Axin

[1] Note however that ϰ is not spacially aware, and therefore these components are not subject to the physical constraints that would limit their growth. Once such a constraint may very well be the calveolin mediated endocytosis event.

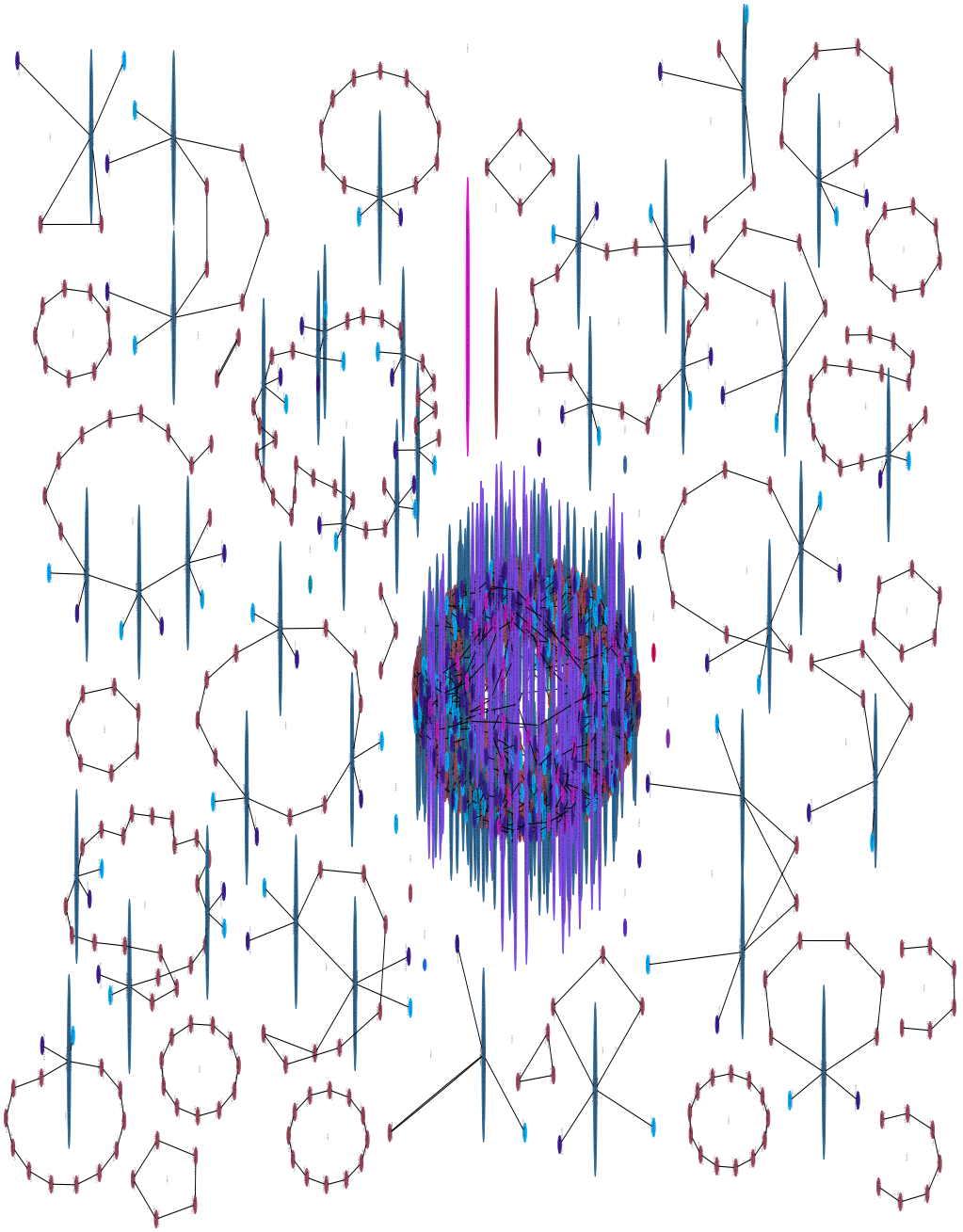

FIGURE 4.2: Snapshot of the Reaction Mixutre at 100 time units after Wnt induction, rendered using GraphViz SFDP algorithm. Each circular cluster represents a separate complex. Of note is the central giant agglomeration of hyperconnected components in a *single* complex.

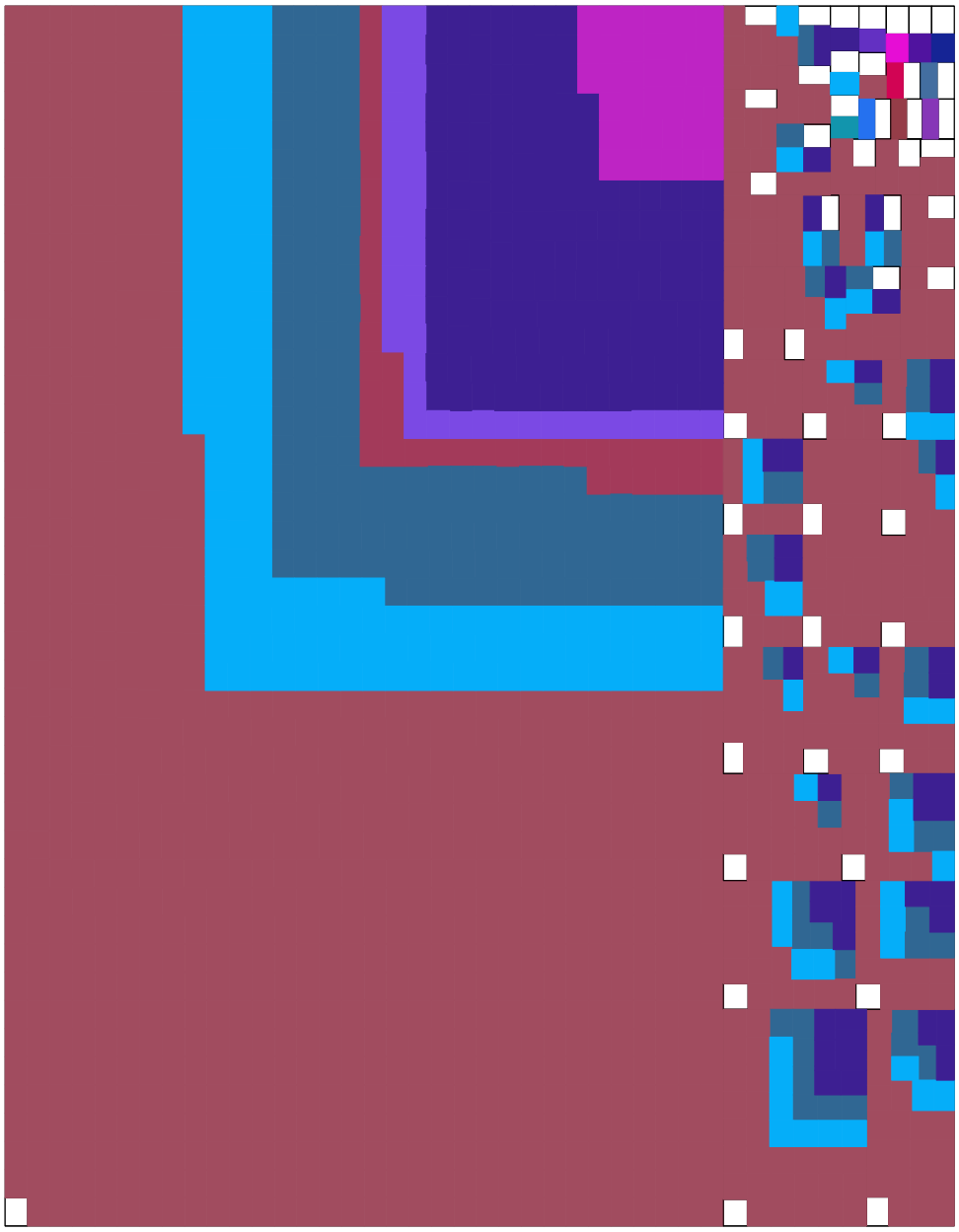

FIGURE 4.3: Snapshot of the Reaction Mixture at 100 time units after Wnt induction, rendered under GraphViz Patchwork algorithm. Clusters are sorted in descending complexity into patches. Cluster elements, the individual squares, are grouped radially with less frequent elements closer to the origin at the upper right corner of each patch. In color code and starting from the origin, light purple corresponds to Wnt, dark blue to CK1, mauve to LRP, dark red to Fzld, teal to Axn, cyan to GSK3, and brown to Dvl. Labels have been removed for clarity. Notice Wnt is found almost exclusively in a single species.

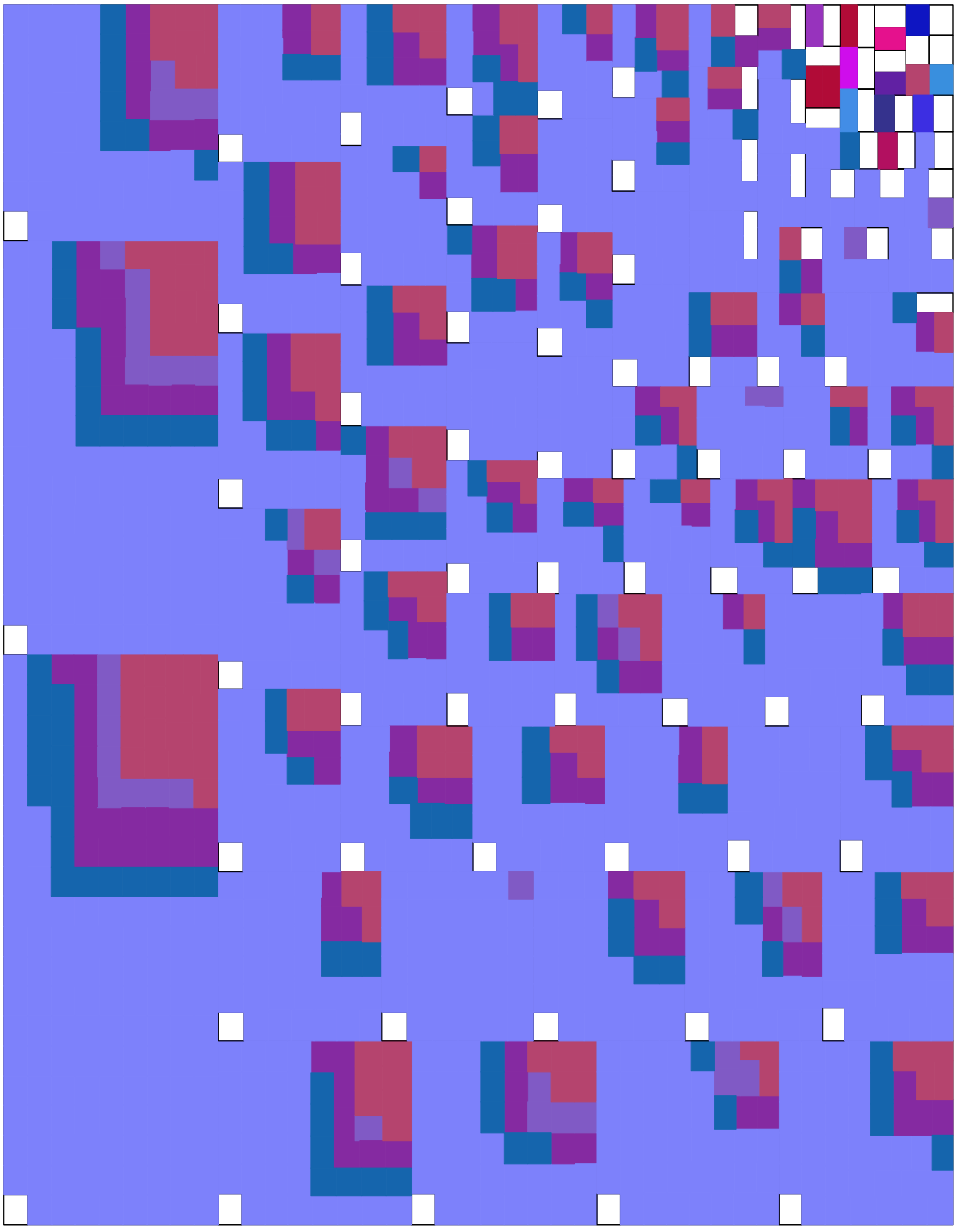

FIGURE 4.4: Snapshot of the Reaction Mixutre at 90 time units of simulation, rendered under GraphViz Patchwork algorithm. Clusters are sorted in descending complexity into patches. Cluster elements, the individual squares, are grouped radially with less frequent elements closer to the origin at the upper right corner of each patch. In color code and starting from the origin, red corresponds to CK1, mauve to Fzld, dark purple to Axin, teal to GSK3β, and blue to Dvl. Notice LRP, in dark red, is isolated.

binding sites on the chain in a unimolecular fashion, thereby increasing the expected local concentration of Axin. If such is the case, the association of Axin to the signalosome would be much more stable indeed. In $\varkappa$ modeling, this is handled painlessly through the use of dual rate notation: the simulator will determine if the Right Hand Side pattern contained in a rule is a conected graph and determine which rate to use.

However, these signalosomes pose an interesting problem for the "return to homeostasis" hypothesis: how is the Wnt signal abrogated? Indeed, the rampant oligomerization of its constituents renders the structure extremely stable, and evidence suggests such assemblies are internalized in a calveolin dependent manner [66, 69] into acidic multivesicular endosomes and / or lysosomes [70]. If the signalosome breaks apart, do endosomes somehow release Axin and GSK3β? If not, what is the fate of the endosome's contents? Is there a special transcriptional regulatory mechanism capable of rapidly restoring GSK3β concentrations [70]?

Considering that the Wnt induced Planar Cell Polarity pathway also involves assembly of a Signalosome, it is surprising such events also include receptor endocytosis, but through a clathrin dependent mechanism [71]. Moreover, recalling that the canonical Wnt pathway regulates dorso-ventral axis establishment in the developing embryo, it appears that the developmental aspect of Wnt signaling occurs at large timescales, further hinting at additional regulation mechanisms. Likewise, a developing embryo is subject to continuous morphological changes, ranging from differential concentrations of maternal mRNA, to massive synthesis of proteins, and even dramatic membrane reorganizations; all these events simply add complexity to the fate of the Signalosomes, and the consequent "return to homeostasis".

Recently, the assembly of large signaling protein complexes has been proposed as a *Phase Transition* [72] forming liquid-liquid demixing phase separations. Such assemblies require multivalent entities and some form or another of polymers. Considering the multi-valent binding events happening at the Signalosome, the puncta of Dsh proteins [67], and the extreme hydrophobicity of Wnt proteins [71, 73], it would be interesting to explore the fate of these Signalosomes: is their high stability due to a diffusion hindrance enforced by nature of being in a different phase? If so, has the cell evolved endocytosis mechanisms to sever the signaling cascade? Do Signalosomes un-assemble on their own, or is there a special mechanism to destroy them?

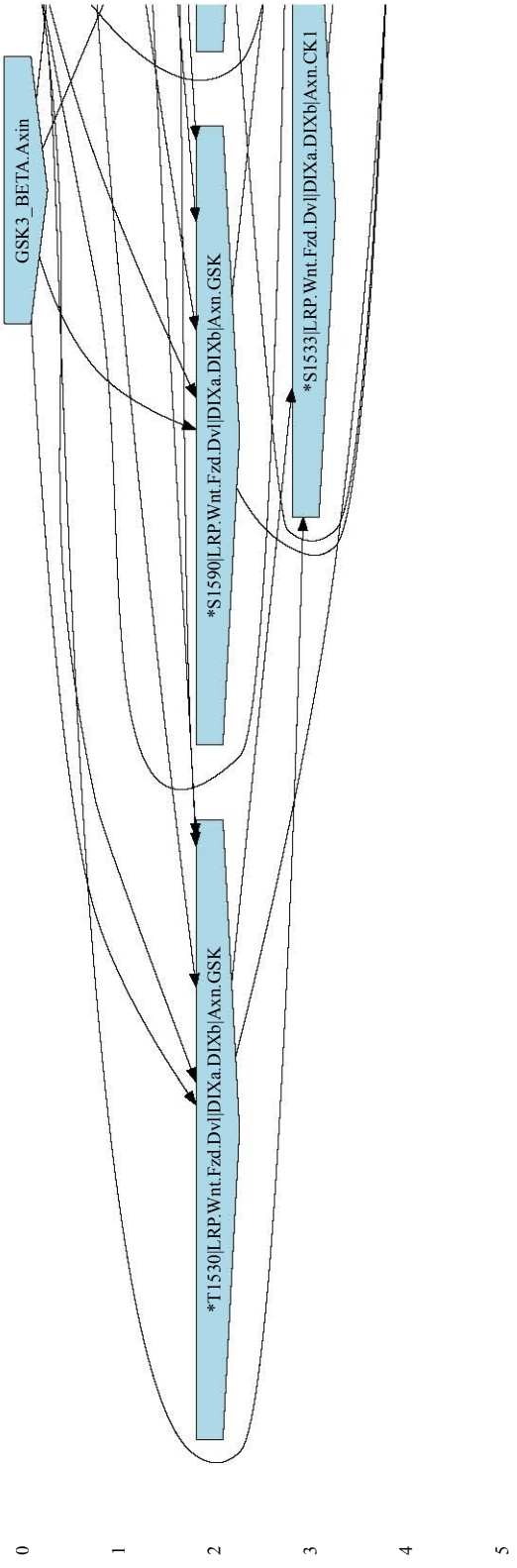

FIGURE 4.5: Left side of the Weakly compressed story for the sequestration of the β-catenin binding site on Axin by LRP. Refer to Figure 4.6 for the center, and Figure 4.7 for the Right side. Blue boxes represent rules, red ovals the end observable. The labels on the boxes refer to the actual labels on the ϰ file. Refer to the main text for a description.

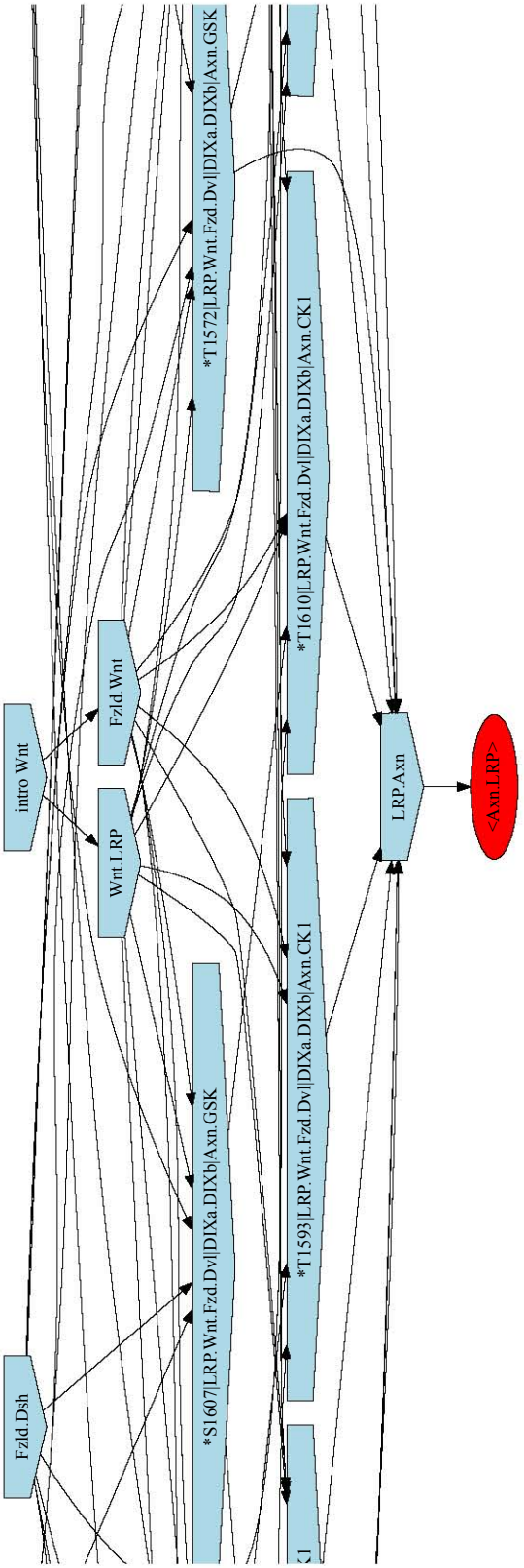

FIGURE 4.6: Center section of the Weakly compressed story for the sequestration of the β-catenin binding site on Axin by LRP. Refer to Figure 4.5 for the Left, and Figure 4.7 for the Right side. Blue boxes represent rules, red ovals the end observable. The labels on the boxes refer to the actual labels on the $\varkappa$ file. Refer to the main text for a description.

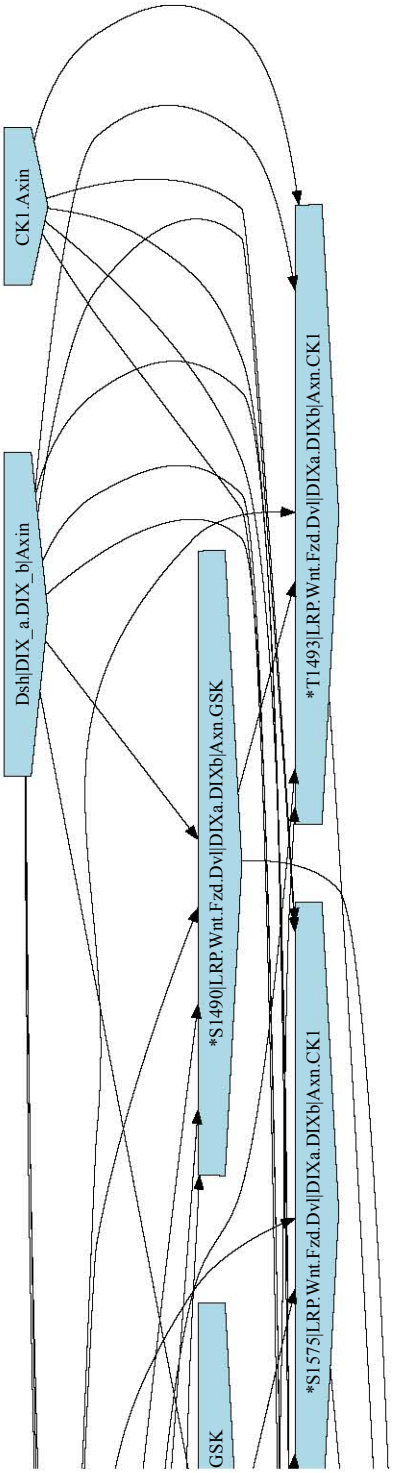

FIGURE 4.7: Right segment of the Weakly compressed story for the sequestration of the β-catenin binding site on Axin by LRP. Refer to Figure 4.5 for the Left side, and Figure 4.6 for the Center. Blue boxes represent rules, red ovals the end observable. The labels on the boxes refer to the actual labels on the $\varkappa$ file. Refer to the main text for a description.

4.1.3 Regulation of β-catenin

Traditional views involve a step of "Dsh Activation" that abrogates β-catenin phosphorylation by GSK3β [74]. To date, such an activation of Dsh by unknown means, or inactivation of GSK3β has not been observed, and apparently extracted post-Wnt GSK3β appears to be fully functional [70]. It was thus surprising to find in this moodel that the key event in the abrogation of β-catenin phosphorylation is sequestration of the Catenin Binding Site (CBD) on Axin by the C-terminus of LRP following hyperphosphorylation of ten Serine / Threonine residues by CK1 and GSK3β [34] [2]. Recruitment of these kinases to the membrane assembly is also found to dependent on Dsh [66]. Indeed, GSK3β is unable bind to or directly phosphorylate β-catenin, but requires Axin as an intermediary [75], and therefore the sequestration of the CBD would be sufficient to abrogate phosphorylation without modification of the enzyme. Moreover, as was seen in Section 4.1.2, the Signalosome also sequesters the enzyme itself into a separate compartment from the cytosol.

Previous modeling attempts invoked a Wnt induced inactivation of the Destoyer complex as a direct antagonistic component of the forward reaction rate for the network catalyst [1, 74]. It is therefore of no surprise that refinements of that same model with different initial parameters yield models of "questionable applicability" [65]. This moodel however, not only offers a mechanistic explanation of the events, but can elaborate on the effect of these initial concentrations.

While *Xenopus* embryos are undergoing their initial developpment stages, a system with limiting concentrations of Axin would indeed be particularly sensitive to Wnt signaling, with dynamics similar to those seen in Figure 4.9. However, in a normal mammalian kidney cell, such sensitivy could be expected to be abated to avoid erroneous signaling events. Such an abatement may be very well be due to much higher concentrations of Axin, beyond the capacity of the membrane receptors to sequester it, as seen in Figure 4.10. This tuning of the system at the concentration level leads to an interesting observation: Prozone effects [3] everywhere.

[2] These ten residues are organized into 5 motifs named the pppSpxS motifs. The second phosphorylated residue matches the recognition pattern of GSK3β, and after its phosphorylation, the first residue can be recognized by CK1α.

[3] Also known as the Hook Effect.

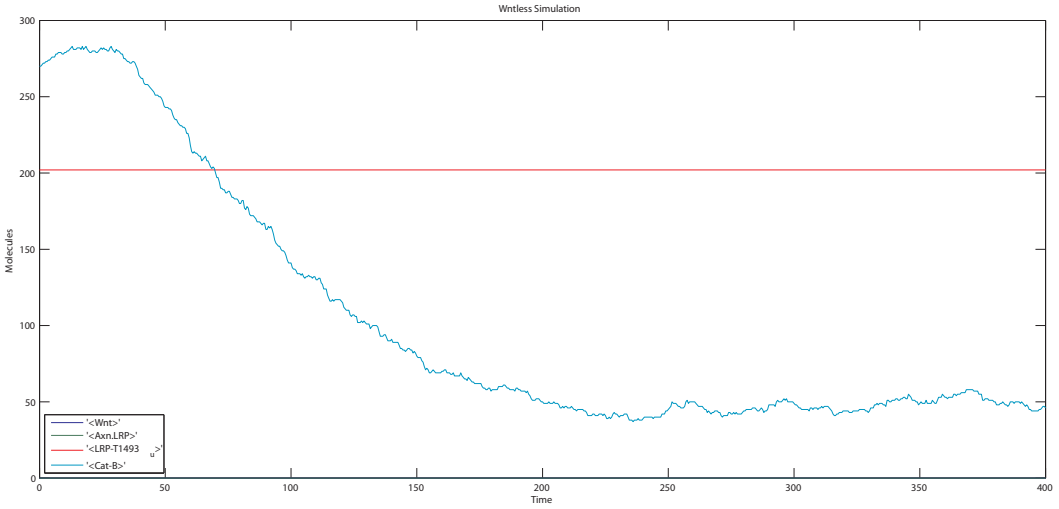

FIGURE 4.8: Simulation of the SmallWnt model without Wnt induction. Notice the different levels of β-catenin achieved by the systems when compared to Figure 4.9, where the concentration of β-catenin goes off the chart. The initial concentrations for this simulation are presented in Table 4.1. The observed variables, in order, are Wnt in dark blue, Axin bound LRP in dark green, unphosphorylated LRP in red, and β-catenin in light blue. As expected, both Wnt and Axin boudn LRP remain at zero, while LRP remains unphosphorylated.

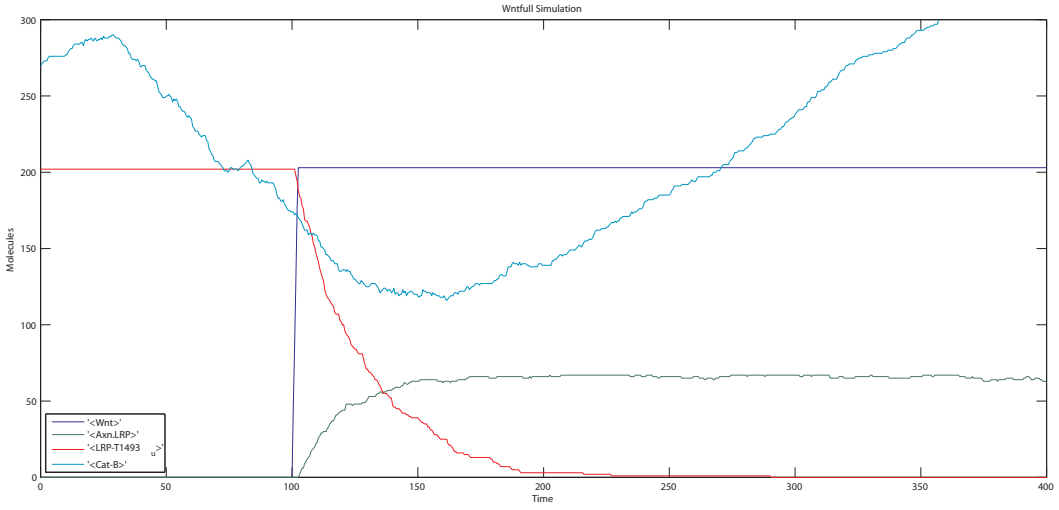

FIGURE 4.9: Simulation of the SmallWnt model with Wnt induction. Notice the different levels of β-catenin achieved by the systems when compared to Figure 4.8, where the steady state of β-catenin concentration appears to be at around 50 molecules. The initial concentrations for this simulation are presented in Table 4.1. The observed variables, in order, are Wnt in dark blue, Axin bound LRP in dark green, unphosphorylated LRP in red, and β-catenin in light blue.

Molecule Count	Equivalent Concentration	Species
135000	50 nmol	Dsh
5400	0 nmol	APC
94500	50 nmol	GSK3
202500	2 nmol	Axin
661500	20 nmol	Cat-b
2700	15 nmol	Fzld
2700	15 nmol	LRP
67500	50 nmol	CK1
67500	0 nmol	PP2 A subunit
67500	0 nmol	PP2 Catalytic subunit
67500	0 nmol	PP2 B55a subunit
67500	0 nmol	PP2 B56a subunit
67500	0 nmol	PP2 B72 subunit
67500	5 nmol	PP1 Catalytic subunit
135000	100 nmol	SCFβ-TrCP
20250	15 nmol	26s Proteasome

TABLE 4.1: Initial Concentrations in the SmallWnt model for the simulations yielding Figures 4.9 and 4.8.

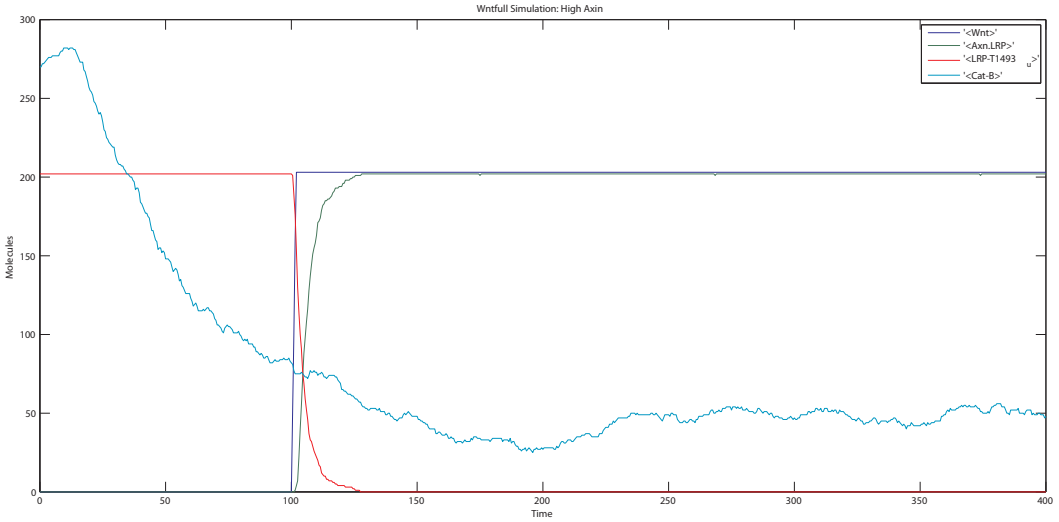

FIGURE 4.10: Simulation parameters identical to those presented for Figure 4.9, but with an initial Axin concentration of 50 nmol. Notice the steady state appears to be similar to the wntless simulation of Figure 4.8, even though there is a Wnt signal present with the consequent recruitment of Axin to LRP.

As seen in Figure 4.11 [4], the Prozone effect refers to the lower abundance of a composed entity when one of its constituents is at too high concentrations in regards to the other constituents. Indeed, dramatic variations in the composition of the membrane, notably the ratio of LRP to Fzld, may very well nullify any sensitivity to Wnt signaling. As for the CK1-Axin-GSK3β trio, particularly if Axin is not in dramaticly low concentrations, a prozone may reduce the overall turnover of β-catenin. These observations serve to exemplify the need for proper characterization of the system at the level of the concentrations of its components, as any of these effects can prove to be an avenue towards disease that does not direclty involve modification of the protein sequence.

In regards to the transcrptional feedbacks introduced in Section 3.1.4, it is tempting to speculate negative regulation tailored to different disturbances of the pathway. Mutations that lead to overexpression of Wnt, may desensitize the cell's LRP by action of Dkk after β-catenin induced transcription. Overexpression of LRP, which has been shown to trigger ectopic Wnt signaling [41], may also be countered by β-catenin mediated mRNA disruption. Likewise, disturbances that inactivate Axin1 may rescue a healthy phenotype through β-catenin mediated transcription of Axin2. Similarly, events that skew the phosphorylation state of the Destroyer's entities towards an unphosphorylated state may trigger β-catenin mediated transcription of Nkd and the subsequent recruitment of PP2 into an inactive complex. The pathway's auto-regulation appears to be diverse in nature, and this is likely just the tip of the iceberg. Nonetheless, there is one weak link in the auto-regulation cascade: tumor suppressor APC.

4.1.3.1 Prozone Code

```
%agent: A(s1,s2)
%agent: B(s1,s3)
%agent: C(s2,s3)
'/B/' -> B() @ 1.0
'A.B' A(s2),B(s1) <-> A(s2!1),B(s1!1) @ 1.0e-5,1.0e-3
'B.C' C(s2),B(s3) <-> C(s2!1),B(s3!1) @ 1.0e-5,1.0e-3
%init: 500 (A(),C())
%obs: '<B>' B()
%obs: '<A.B.C>' A(s2!1),B(s1!1,s3!3),C(s2!3)
```

[4] Refer to Section 4.1.3.1 for the code of such simulation.

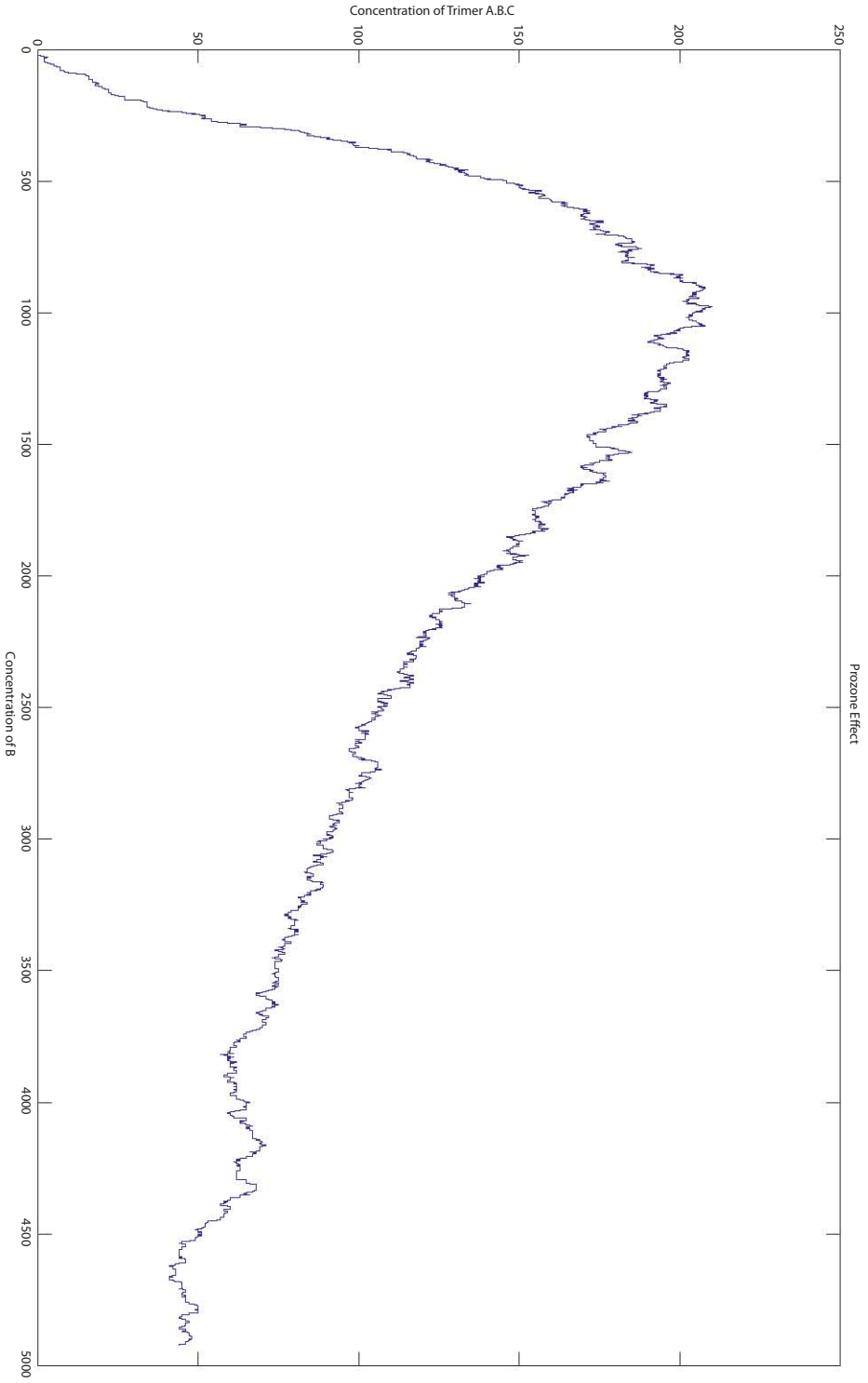

FIGURE 4.11: The Prozone effect refers to the lower concentration of a composed entitiy (Trimer A.B.C) when one of its constituents (B) is in much higher concentrations that the others (A & C). The code for such toy model is presented in subsection 4.1.3.1. In ELISA testing, high concentrations of the target antigen may overwhelm both the conjugate antibody and the coating antibody, reducing the likelyhood of *the same* antigen being bound at once to *both* antibodies.

4.1.4 APC and PP2

Why does the Destruction Complex require two Scaffold proteins? Indeed, APC does not appear to directly contribute to β-catenin phosphorylation [45], but it is a crucial part of the mechanism targeting β-catenin for ubiquitination [48]. Likewise, if both APC and Axin compete for the exact same binding domain in β-catenin [46], and as discussed in Section 4.1.3 Axin serves as a linker between the kinase GSK3β and its substrate β-catenin, how is APC contributing?

The answer emerges when we consider a bigger picture of the interacting agents. It would appear APC is responsible for *protecting* the phosphorylation mark of destruction on β-catenin from PP2 [48]. Indeed, the Causal Traceback seen in Figure 4.12 structures this idea. Moreover, as APC appears to be actively targeting phospho-β-catenin to the SIF β-TrCP complex, its role could be simply that of a *carrier*. If we additionally consider the following:

- APC having multiple binding sites for β-catenin, some of which are not even involved in the phosphorylation modification [44],
- APC shuttling into and out of the nucleus through unknown means [57], possibly shuttling β-catenin from the nucleus [76],
- Cancerous mutations on APC most often affect the 20aa and 15aa repeats [49], which are the binding sites of β-catenin,
- Phospho-APC has higher affinity for phospho-β-catenin than phospho-Axin [46].

It would appear the transitive association to the Destruction Complex is merely to clear Axin's CBD through recruitment of phospho-β-catenin after APC has been phosphorylated by CK1 and GSK3β, which are loaded on Axin [77]. It is perhaps reassuring that in models lacking phosphatases, APC has indeed no active role in Wnt signaling, sauf to satisfy stochiometric constrains for an "Active Destruction Complex" network catalyst. However, in this moodel, Tumor Suppressor APC is a key player in the signaling cascade, as it is effectively beyond control of the known transcriptional feedbacks, and as seen in Figure 4.13, it actively guards phosphorylated β-catenin, the "goal" of the Destruction Complex.

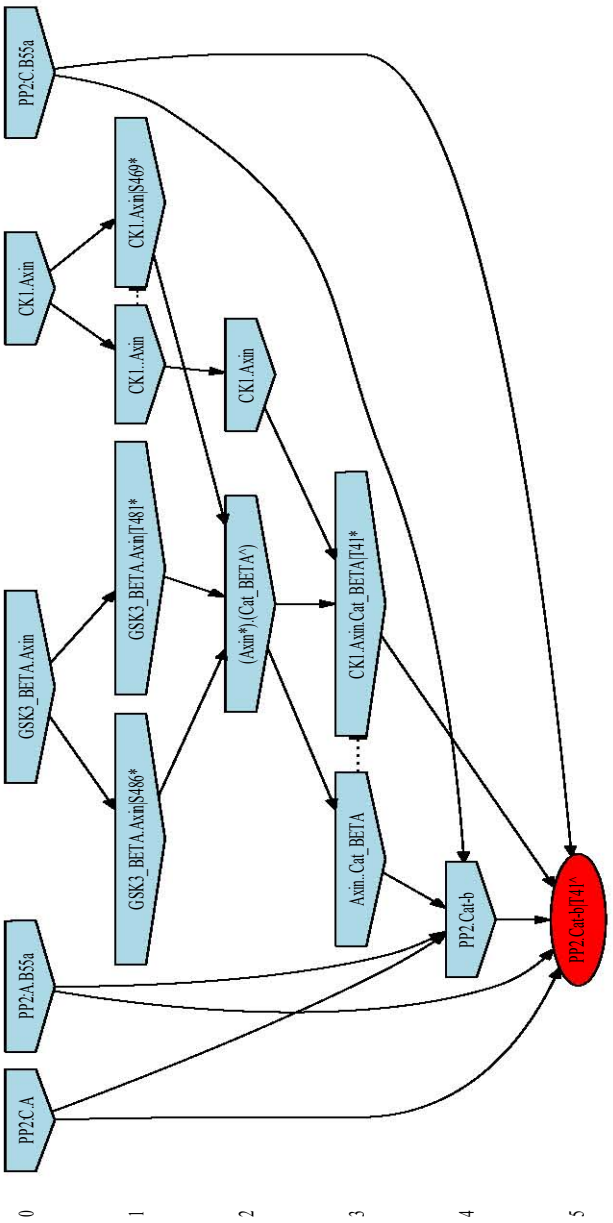

FIGURE 4.12: Weakly compressed story for the dephosphorylation of Tyrosine 41 of the Destruction Motif on β-catenin, by PP2. Blue boxes represent rules, red ovals the end observable. The labels on the boxes refer to the actual labels on the $\varkappa$ file. At level zero, assembly of the PP2 holoenzyme takes place, as well recruitment of the kinases to the Axin scaffold. Level one sees the phosphorylation of the Catenin Bindind Site of Axin by the kinases, thus enabling recruitment of β-catenin at level two. At level three, β-catenin is phosphorylated. This phenomenon is however reduced by premature release from Axin, symbolized by the dashed line. Once β-catenin is phosphorylated and released, it then is able to fall pray to PP2, as seen at level four. Finally, once recruited, PP2 dephosphorylates β-catenin at level five.

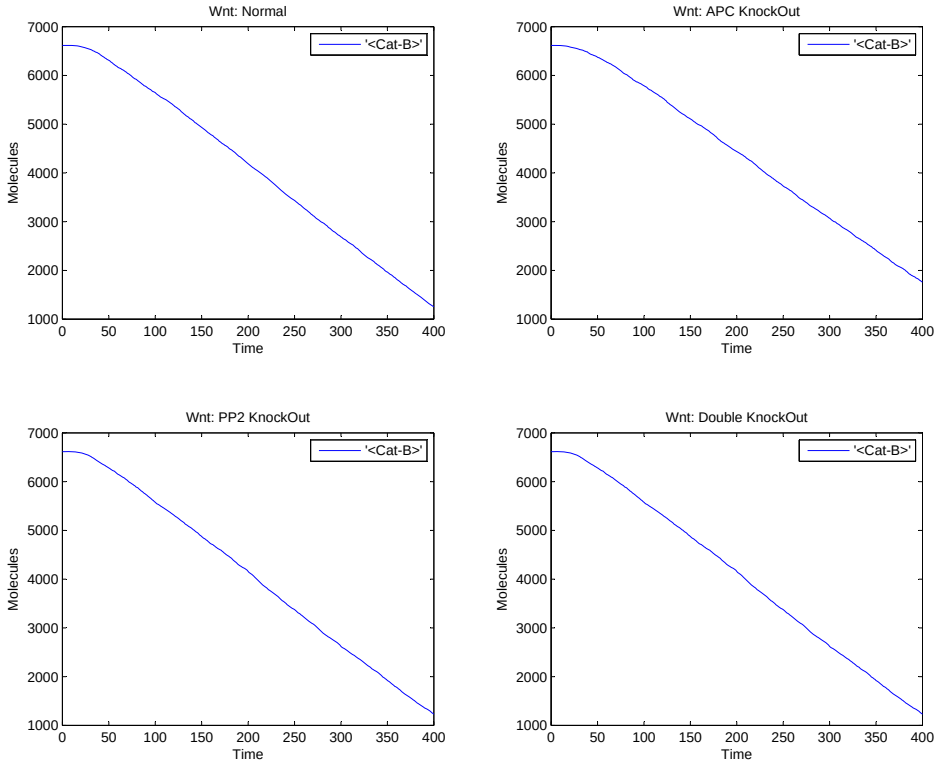

FIGURE 4.13: Stochastic Simulations of the system. Clockwise from topleft of the figure, Normal simulation with all agents, simulation with APC concentration of zero, simulation with PP2 concentration of zero, and simulation with concentrations of APC and PP2 both of zero. These simulations lack a basal expression level for β-catenin, as well as the transcriptional feedbacks on the system. Note that upon APC knockout, the overall turnover for β-catenin is lower, as is observed *in vivo*. However, upon additional PP2 knockout, the normal phenotype is restored. The single knockout of PP2 appears to contribue little to the destruction activity, suggesting APC is able to recruit all available phospho-β-catenins. This behaviour would be very sensitive to the concentrations of APC, which should be further explored. Note these simulations do not include the basal β-catenin expression in the interest of lower execution times for the simulation.

In all these reactions, there are some notable phosphorylations that are not balanced: LRP hyperphosphorylation by CK1α and GSK3β. Indeed, the biochemcial litterature is notoriously quiet in this regard. Though the fact that PP1 subunit 49 (a.k.a. Axin) is bound directly to it, there appears to be little, if any, evidence that LRP eventually get dephosphorylated by a phosphatase. It would therefore be tempting to consider the lack of requirement for dephosphorylation given that phospho-LRP gets recruited into a membrane enclosed endosome, thus limiting its capacity to recruit additional Axin. However, this simply highlights the need to address the fate of the Signalosomes after endocytosis.

4.2 Implications for "Modularity"

Throughout the text, several puzzling abuses of terminology may have been found. These are presented precisely to highlight the limitations of the current Protein-to-Function mental framework. For example:

- Why would a *phosphatase subunit* serve as a scaffold protein for *kinases*? (Axin)
- Why would an inactive kinase serve as a scaffold for assembly of a kinase-activating ubiquitination machinery? (ATM, TRAF6, & MAP3K7)
- Why can *multiple* proteins bind a *single* binding domain at the *same time*? (DIX domain)
- How does a conformational *change* induced by recruitment affect other binding *domains*? (APC's 20aa)
- How do protein-protein interactions change in *different contexts* within the *same cell*? (Acid Endosome)
- How can a *signaling* protein also be a *scaffolding* protein? (β-catenin in adherens junctions)
- Why are some promoter regions *auto*regulated at *different* scales? (β-catenin with LEF1, CycD-E2F1, NFκB-p65)
- Why are there phosphatases and kinases loaded at the *same* time on the same complex in an *unimolecular* do-undo loop? (CK1α and PP2 on Axin-APC)

Though it would seem counter-intuitive to think Nature would use a phosphatase subunit as a scaffolding protein for assembly of a hyperphosphorylation machinery, let us consider the words of François Jakob of "Evolution as a Tinkerer". Indeed, the notions of "scaffold", "subunit", "binding domain", "statically defined protein interactions", et cetera, are deprecated. They were once useful mental constructs, but now clinging to them will create mental barriers. We need to improve the current abstraction to accommodate new findings. Proteins are not *statically* defined, but may very well be a collection of *potentials*. As such, it may be more correct to think of protein *acting* as a kinase, instead of *being* a kinase.

4.3 Rate Obsession?

On a final note, as seen in Figures 4.9 and 4.8 the system behaves as expected while utilizing ballpark rates. This fact serves to illustrate an important aspect of rule based modeling: it's the causal architecture what matters, not so much the parameters. Indeed, biologically speaking across species, it would appear there is much more control on maintaining *activities* through *concentrations*, than through *turnover numbers*.

Chapter 5

Conclusion & Perspectives

5.1 Conclusion

A framework, philosophy, and manual of style have been provided to the Scientific Community in order to allow and encourage the effective exchange and collection of knowledge in biochemical signaling by the establishment of a *Lingua Franca*. Moreover, the examples provided here showcase the evident value of addressing knowledge as an executable set of Rules operating on a set of formally defined Agents in a mechanistic fashion. As a side bonus, the successful implementation of an Inventory of Knowledge is shown, shedding modeling insight into a myriad of interesting phenomena, and generating a tremendously valuable resource for the moodeling community that can reflect the State of the Art on Wnt Signaling given sufficient effort, and could potentially grow to accommodate the Biochemical Signaling, Transcriptional Regulation, and Metabolic Networks that are present within a Platoonic Cell.

Appendix A

BigWnt Ruleset

Presented here is the entire ruleset that is the corpus of dynamic knowledge in the Exploratorium, in addition to the elements that instantiate the moodel into an actual model. The code segments are listed as follows:

- SmallWnt Ruleset
- SmallWnt Agent Signatures, Perturbations, and NonFormal Rules
- SideWnt Ruleset
- SideWnt Agent Signatures, Perturbations, and NonFormal Rules
- FeedbackWnt Ruleset
- FeedbackWnt Agent Signatures, Perturbations, and NonFormal Rules

A.1 SmallWnt Ruleset

```
# ####################################
# Signal Initialization
# ####################################

# Wnt binds Fzld, then recruits the co-receptor LRP <10.1038/sj.onc.1208303>. Of
    interest, Wnt also binds LRP <10.1038/35035117>, generating a cycle: LRP-Axin
    -Dsh-Fzld-Wnt-LRP. Contrary to popular theory, LRP and Fzld do not bind
    <10.1242/dev.01318>. Though LRP dimerizes <10.1128/MCB.00773-07>, this model
    assumes all worthwhile instances are of the homodimer. On a different note,
    since Fzld dimerization is required for and induced by Wnt <10.1242/jcs
    .00451>, this may serve as a physical branch-point in the membrane cycle to
    further aggregate components of the signalosome.
'Fzld.Wnt' P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom), P_WNT1_HUMAN(P_WNT1_HUMAN
    -+-i_P_FZD8_HUMAN) -> P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!1),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'( 'RingClosureRate' * 'GeneralBinding' )
'Fzld..Wnt' P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!1), P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!1) -> P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom)
    , P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_FZD8_HUMAN) @ 'GeneralUnbinding'

'LRP.LRP' P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term), P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term
    ) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term!1), P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-
    term!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' * '
    GeneralBinding')
'LRP..LRP' P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term!1), P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-
    term!1) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term), P_LRP6_HUMAN(P_LRP6_HUMAN-+-C
    -term) @ 'GeneralUnbinding'

'Wnt.LRP' P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN), P_LRP6_HUMAN(P_LRP6_HUMAN
    -+-i_P_WNT1_HUMAN) -> P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!1),
    P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'( 'RingClosureRate' * 'GeneralBinding' )
'Wnt..LRP' P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!1), P_LRP6_HUMAN(
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!1) -> P_WNT1_HUMAN(P_WNT1_HUMAN-+-
    i_P_LRP6_HUMAN), P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_P_WNT1_HUMAN) @ '
    GeneralUnbinding'

'Fzld.Fzld' P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD), P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD) ->
     P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD!1), P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD!1) @ (1/
     'RescaleFactor' ) * 'ReceptorDimerization'( 'RingClosureRate' * '
    ReceptorDimerization' )
'Fzld..Fzld' P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD!1), P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD
    !1) -> P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD), P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD) @ '
    ReceptorDissociation'
```

```
# ####################################
# Dial D for Destroyer
# ####################################

# Axin can multimerize through the P_AXIN1_HUMAN-+-DIX_a to P_AXIN1_HUMAN-+-DIX_b
     domain <10.1074/jbc.274.6.3439>
'Axin.Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    DIX_b) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN
    -+-DIX_b!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' * '
    GeneralBinding' )
'Axin..Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN
    -+-DIX_b!1) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b) @ 'GeneralUnbinding'

# Dsh can multimerize through the P_DVL1_HUMAN-+-DIX_a to P_DVL1_HUMAN-+-DIX_b
    domain, and this process is enhanced by polyubiquitination of said domain.
    This polyubiquitination is antagonized by CYLD, though this fact is not in
    the model <10.1016/j.molcel.2010.01.035>
'Dsh.Dsh' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a), P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b)
    -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a!1), P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b!1)
     @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' * '
    GeneralBinding' )
'Dsh..Dsh' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a!1), P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_b!1) -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a), P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_b) @ 'GeneralUnbinding'

# APC can multimerize through the P_APC_HUMAN-+-Oligo domain <10.1093/hmg
    /10.7.721>
'APC.APC' P_APC_HUMAN(P_APC_HUMAN-+-Oligo), P_APC_HUMAN(P_APC_HUMAN-+-Oligo) ->
    P_APC_HUMAN(P_APC_HUMAN-+-Oligo!1), P_APC_HUMAN(P_APC_HUMAN-+-Oligo!1) @ (1/
    'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'APC..APC' P_APC_HUMAN(P_APC_HUMAN-+-Oligo!1), P_APC_HUMAN(P_APC_HUMAN-+-Oligo!1)
     -> P_APC_HUMAN(P_APC_HUMAN-+-Oligo), P_APC_HUMAN(P_APC_HUMAN-+-Oligo) @ '
    GeneralUnbinding'

# CK1 phosphorilates Axin on 4 residues, the first 3 are associated with Axin
    stability, the fourth is part of the Cat_BETA binding site. CK1 binds Axin on
     a region overlapping with the Phosphatase binding region <10.1016/j.pep
    .2007.02.020>, and therefore this model assumes exclusive binding of either
    enzyme
'CK1.Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Phosphatase_bind!1), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!1) @ (1/
     'RescaleFactor' ) * 'GeneralBinding'
'CK1..Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!1), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!1) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Phosphatase_bind), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom) @ '
    GeneralUnbinding'
```

```
'CK1.Axin|S75*' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN
    -+-S75~un), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) ->
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S75~ph),
    P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) @ 'GeneralPhosphorylation'
'CK1.Axin|S77*' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN
    -+-S77~un), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) ->
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S77~ph),
    P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) @ 'GeneralPhosphorylation'
'CK1.Axin|S217*' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN
    -+-S217~un), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) ->
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S217~ph),
    P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) @ 'GeneralPhosphorylation'
'CK1.Axin|S469*' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN
    -+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-S469~un), P_KC1A_HUMAN(P_KC1A_HUMAN-+-
    Prot_kinase_cat_dom!9) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9,
    P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-S469~ph), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!9) @ 'GeneralPhosphorylation' # Of the CK1
     mediated phosphorylated, S469 is directly within the CBD, therefore the
    latter must be free for the former to be modified

# GSK3_BETA finishes phosphorilating Axin at the last two residues of the
    Catenin_BETA binding domain
'GSK3_BETA.Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!1),
    P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'
'GSK3_BETA..Axin' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!1), P_GSK3B_HUMAN
    (P_GSK3B_HUMAN-+-i_Axin!1) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN),
     P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin) @ 'GeneralUnbinding'
'GSK3_BETA.Axin|T481*' P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!9), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!9, P_AXIN1_HUMAN-+-T481~un) -> P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!9,
    P_AXIN1_HUMAN-+-T481~ph) @ 'GeneralPhosphorylation'
'GSK3_BETA.Axin|S486*' P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!9), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!9, P_AXIN1_HUMAN-+-S486~un) -> P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!9,
    P_AXIN1_HUMAN-+-S486~ph) @ 'GeneralPhosphorylation'

# APC is recruited by Axin through the SAMP-to.Regulat_G_prot_signal binding
'APC|SAMP_1.Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1), P_AXIN1_HUMAN(P_AXIN1_HUMAN
    -+-Regulat_G_prot_signal) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!1),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) @ (1/ 'RescaleFactor'
    ) * 'GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'APC|SAMP_1..Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1)
    , P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal) @ 'GeneralUnbinding'
```

```
'APC|SAMP_2.Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2), P_AXIN1_HUMAN(P_AXIN1_HUMAN
    -+-Regulat_G_prot_signal) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!1),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) @ (1/ 'RescaleFactor'
    ) * 'GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'APC|SAMP_2..Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2)
    , P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal) @ 'GeneralUnbinding'
'APC|SAMP_3.Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3), P_AXIN1_HUMAN(P_AXIN1_HUMAN
    -+-Regulat_G_prot_signal) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!1),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) @ (1/ 'RescaleFactor'
    ) * 'GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'APC|SAMP_3..Axin' P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal!1) -> P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3)
    , P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal) @ 'GeneralUnbinding'

# The recruiting potential of APC for Cat_BETA is mediated by phosphorylation
    <10.1016/j.molcel.2004.08.010>, and this is mediated by Axin-bound CK1
    epsilon <10.1074/jbc.M105148200>
'CK1.Axin.SAMP_1|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_2|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_3|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_4|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
```

```
'CK1.Axin.SAMP_5|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_6|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_7|APC|APC_Cys-rich_rpt_1*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~un, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~ph, P_APC_HUMAN-+-SAMP_1!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_1|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_2|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_3|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
```

```
'CK1.Axin.SAMP_4|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_5|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_6|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_7|APC|APC_Cys-rich_rpt_2*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~un, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~ph, P_APC_HUMAN-+-SAMP_2!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_1|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_2|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
```

```
'CK1.Axin.SAMP_3|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_4|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_5|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_6|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.SAMP_7|APC|APC_Cys-rich_rpt_3*' P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~un, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) -> P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~ph, P_APC_HUMAN-+-SAMP_3!2), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2, P_AXIN1_HUMAN-+-Phosphatase_bind!3), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'

# PhosphoAxin recruits Catenin_BETA
'(Axin*).(Cat_BETA^)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-S469~ph, P_AXIN1_HUMAN-+-T481~ph, P_AXIN1_HUMAN-+-S486~ph,
    P_AXIN1_HUMAN-+-Axin_b-cat-bd) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-S469~ph, P_AXIN1_HUMAN-+-T481~ph, P_AXIN1_HUMAN
    -+-S486~ph, P_AXIN1_HUMAN-+-Axin_b-cat-bd!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'
'Axin..Cat_BETA' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd) @ 'GeneralUnbinding'

# Cat_BETA's T41 & S45 are phosphoprimed by CK1 <10.1016/S0092-8674(02)00685-2>
```

```
'CK1.Axin.Cat_BETA|T41*' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-T41~un, P_CTNB1_HUMAN-+-
    i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-
    Phosphatase_bind!3), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-T41~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Phosphatase_bind!3),
    P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'
'CK1.Axin.Cat_BETA|S45*' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S45~un, P_CTNB1_HUMAN-+-
    i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-
    Phosphatase_bind!3), P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S45~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Phosphatase_bind!3),
    P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!3) @ 'GeneralPhosphorylation'

# The S33 & S37 constitute the Destruction Motif that is recognized by the SCF-b/
    TRCP ubiquitination machinery <10.1016/j.molcel.2008.10.023>, this are
    phosphorylated by GSK3_BETA <10.1016/S0092-8674(02)00685-2,>
'GSK.Axin.Cat_BETA|S33*' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~un, P_CTNB1_HUMAN-+-
    T41~ph, P_CTNB1_HUMAN-+-S45~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!2),
    P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!2) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~
    ph, P_CTNB1_HUMAN-+-T41~ph, P_CTNB1_HUMAN-+-S45~ph, P_CTNB1_HUMAN-+-i_ARM!1),
     P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-
    i_P_GSK3B_HUMAN!2), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!2) @ '
    GeneralPhosphorylation'
'GSK.Axin.Cat_BETA|S37*' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S37~un, P_CTNB1_HUMAN-+-
    T41~ph, P_CTNB1_HUMAN-+-S45~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!2),
    P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!2) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S37~
    ph, P_CTNB1_HUMAN-+-T41~ph, P_CTNB1_HUMAN-+-S45~ph, P_CTNB1_HUMAN-+-i_ARM!1),
     P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-
    i_P_GSK3B_HUMAN!2), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!2) @ '
    GeneralPhosphorylation'

# Cat_BETA gets recruited by APC, more so after both are phosphorilated since the
     affinity of Axin for phosphCat_BETA is lower than APC's. Note however that
    the 15aa repeats have not made it into the model, as their mechanism of
    action is still murky. Once the model is running, this phenomenon may be
    included to "see what happens"... These rules do not use kappa's dual
    molecularity rates for a simple reason, APC bound Cat-b would also trigger
    such a rule and leads to hyperactive rules, deadlocking the simulation.
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_1*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_1~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_1~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
```

```
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_2*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_2~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_2~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_3*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_3~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_3~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_4*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_4~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_4~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_5*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_5~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_5~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_6*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_6~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_6~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_1|APC|APC_Cys-rich_rpt_7*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_7~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_7~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
```

```
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_1*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_1~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_1~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_2*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_2~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_2~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_3*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_3~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_3~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_4*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_4~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_4~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_5*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_5~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_5~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_6*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_6~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_6~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
```

```
'Cat_BETA.Axin.SAMP_2|APC|APC_Cys-rich_rpt_7*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_7~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_7~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_1*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_1~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_1~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_2*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_2~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_2~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_3*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_3~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_3~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_4*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_4~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_4~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_5*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_5~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_5~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
```

```
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_6*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_6~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_6~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.Axin.SAMP_3|APC|APC_Cys-rich_rpt_7*)' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33
    ~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1, P_AXIN1_HUMAN-+-Regulat_G_prot_signal!2),
    P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-APC_Cys-rich_rpt_7~ph) ->
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN
    -+-i_ARM!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!2), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!2, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_7~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'

'Cat_BETA.(APC_Cys-rich_rpt_1*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_1~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_1~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.(APC_Cys-rich_rpt_2*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_2~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_2~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.(APC_Cys-rich_rpt_3*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_3~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_3~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.(APC_Cys-rich_rpt_4*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_4~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_4~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.(APC_Cys-rich_rpt_5*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_5~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_5~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA.(APC_Cys-rich_rpt_6*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_6~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_6~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
```

```
'Cat_BETA.(APC_Cys-rich_rpt_7*)|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_ARM), P_APC_HUMAN(P_APC_HUMAN-+-
    APC_Cys-rich_rpt_7~ph) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph, P_CTNB1_HUMAN
    -+-S37~ph, P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~ph!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'

'Cat_BETA..20aa1|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_1!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_1!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa2|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_2!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_2!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa3|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_3!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_3!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa4|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_4!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_4!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa5|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_5!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_5!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa6|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_6!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_6!1) @ 'GeneralUnbinding'
'Cat_BETA..20aa7|APC' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_APC_HUMAN(
    P_APC_HUMAN-+-APC_Cys-rich_rpt_7!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1)
    , P_APC_HUMAN(P_APC_HUMAN-+-APC_Cys-rich_rpt_7!1) @ 'GeneralUnbinding'


# ######################################
# Wnt Induced Destroyer Inactivation
# ######################################

# Frizzled's KTxxxW motif recruits Dishevelled's P_DVL1_HUMAN-+-PDZ domain
    <10.1242/dev.01318>
'Fzld.Dsh' P_FZD8_HUMAN(P_FZD8_HUMAN-+-PDZ_bind), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    ) -> P_FZD8_HUMAN(P_FZD8_HUMAN-+-PDZ_bind!1), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' * '
    GeneralBinding')
'Fzld..Dsh' P_FZD8_HUMAN(P_FZD8_HUMAN-+-PDZ_bind!1), P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    PDZ!1) -> P_FZD8_HUMAN(P_FZD8_HUMAN-+-PDZ_bind), P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    PDZ) @ 'GeneralUnbinding'

# Dsh and Axin bind through their multi(poly?)merization interface P_DVL1_HUMAN
    -+-DIX_a to P_DVL1_HUMAN-+-DIX_b <10.1073/pnas.1017063108>
```

```
'Dsh|DIX_a.DIX_b|Axin' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b) -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a!1), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-DIX_b!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'Dsh|DIX_a..DIX_b|Axin' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!1) -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-DIX_b) @ 'GeneralUnbinding'

'Dsh|DIX_b.DIX_a|Axin' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a) -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b!1), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-DIX_a!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'Dsh|DIX_b..DIX_a|Axin' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!1) -> P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b), P_AXIN1_HUMAN
    (P_AXIN1_HUMAN-+-DIX_a) @ 'GeneralUnbinding'

# Upon Dsh binding to Axin, something in APC's "sequence B" breaks apart the
    complex and releases APC <10.1091/mbc.E10-11-0871>. Now if we only knew what
    interface is the important one......
'(Dsh|DIX_a.DIX_b|Axin)..P_APC_HUMAN-+-SAMP_1|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1) @
    100 * 'GeneralUnbinding'
'(Dsh|DIX_b.DIX_a|Axin)..P_APC_HUMAN-+-SAMP_1|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_1) @
    100 * 'GeneralUnbinding'

'(Dsh|DIX_a.DIX_b|Axin)..P_APC_HUMAN-+-SAMP_2|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2) @
    100 * 'GeneralUnbinding'
'(Dsh|DIX_b.DIX_a|Axin)..P_APC_HUMAN-+-SAMP_2|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_2) @
    100 * 'GeneralUnbinding'
```

```
'(Dsh|DIX_a.DIX_b|Axin)..P_APC_HUMAN-+-SAMP_3|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_a!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3) @
    100 * 'GeneralUnbinding'
'(Dsh|DIX_b.DIX_a|Axin)..P_APC_HUMAN-+-SAMP_3|APC' P_DVL1_HUMAN(P_DVL1_HUMAN-+-
    DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9, P_AXIN1_HUMAN-+-
    Regulat_G_prot_signal!1), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3!1) -> P_DVL1_HUMAN
    (P_DVL1_HUMAN-+-DIX_b!9), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!9,
    P_AXIN1_HUMAN-+-Regulat_G_prot_signal), P_APC_HUMAN(P_APC_HUMAN-+-SAMP_3) @
    100 * 'GeneralUnbinding'

# LRP is phosphoprimed by GSK3B <10.1038/nature04185>, then phosphorylated by
    Axin bound CK1. Considering that Axin can dimerize, that Dsh is also around,
    that APC may be re-recruited if Dsh is lost, and that LRP forms aggregates,
    this could explain the Ribosome-Sized-Signalosomes found. Moreover, this
    presents many cycle-forming possibilities, all dependent on Wnt exposure.
'*S1490|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*T1530|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1530~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
```

```
'*T1572|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1572~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*S1590|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1590~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*S1607|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1607~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_b!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*S1490|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
```

```
'*T1530|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1530~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*T1572|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1572~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*S1590|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1590~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
'*S1607|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.GSK' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1607~un,
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    !9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-
    Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7), P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ
    !7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-DIX_a!6,
    P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!5)
    -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),
    P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN
    !8), P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!5), P_GSK3B_HUMAN(
    P_GSK3B_HUMAN-+-i_Axin!5) @ 'GeneralPhosphorylation'
```

```
'*T1493|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1493~un,
    P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1493~ph
    , P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*S1533|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1533~un,
    P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1533~ph
    , P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*S1575|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1575~un,
    P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1575~ph
    , P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
```

```
'*T1593|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1593~un,
    P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1593~ph
    , P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*T1610|LRP.Wnt.Fzd.Dvl|DIXa.DIXb|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1610~un,
    P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1610~ph
    , P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_a!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*T1493|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1493~un,
    P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1493~ph
    , P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
```

```
'*S1533|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1533~un,
    P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1533~ph
    , P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*S1575|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1575~un,
    P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1575~ph
    , P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
'*T1593|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1593~un,
    P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1593~ph
    , P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'
```

```
'*T1610|LRP.Wnt.Fzd.Dvl|DIXb.DIXa|Axn.CK1' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1610~un,
    P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1610~ph
    , P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!9),P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!9, P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!8),
    P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!8, P_FZD8_HUMAN-+-PDZ_bind!7),
    P_DVL1_HUMAN(P_DVL1_HUMAN-+-PDZ!7, P_DVL1_HUMAN-+-DIX_b!6), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!6, P_AXIN1_HUMAN-+-Phosphatase_bind!5), P_KC1A_HUMAN(
    P_KC1A_HUMAN-+-Prot_kinase_cat_dom!5) @ 'GeneralPhosphorylation'

# Hyperphosphorylated LRP presents a docking site for Axin <10.1242/dev.013540>.
'LRP..Axn' P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_PPPSP!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Axin_b-cat-bd!1) -> P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_PPPSP), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd) @ 'GeneralUnbinding'
'LRP.Axn' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~ph, P_LRP6_HUMAN-+-T1530~ph,
    P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-S1590~ph, P_LRP6_HUMAN-+-S1607~ph,
    P_LRP6_HUMAN-+-T1493~ph, P_LRP6_HUMAN-+-S1533~ph, P_LRP6_HUMAN-+-S1575~ph,
    P_LRP6_HUMAN-+-T1593~ph, P_LRP6_HUMAN-+-T1610~ph, P_LRP6_HUMAN-+-i_PPPSP),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat-bd)-> P_LRP6_HUMAN(P_LRP6_HUMAN-+-
    S1490~ph, P_LRP6_HUMAN-+-T1530~ph, P_LRP6_HUMAN-+-T1572~ph, P_LRP6_HUMAN-+-
    S1590~ph, P_LRP6_HUMAN-+-S1607~ph, P_LRP6_HUMAN-+-T1493~ph, P_LRP6_HUMAN-+-
    S1533~ph, P_LRP6_HUMAN-+-S1575~ph, P_LRP6_HUMAN-+-T1593~ph, P_LRP6_HUMAN-+-
    T1610~ph, P_LRP6_HUMAN-+-i_PPPSP!1), P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Axin_b-cat
    -bd!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding' ( 'RingClosureRate' * '
    GeneralBinding')



# ######################################
# Phosphatases lurking everywhere!
# ######################################

# Phosphatase 2 holoenzyme assembly: recruitment of recognition subunit alpha, of
     catalytic subunit, and variable subunit beta. Notice the recoginition
    subunit undergoes a conformational change upong holoenzyme assembly,
    therefore the model assumes its binding potentials are for the holoenzyme
    conformation. Though specifying a fictitious site to reflect this change may
    be used, it would effectively duplicate the information as there is absolute
    correlation between the two conformations for the protein and the bound-ness
    with the holoenzyme.

# Recruitment of B55a Subunit B by Subunit A
```

```
'PP2:A.B55a' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_2ABA_HUMAN(P_2ABA_HUMAN-+-
    SubUnitA) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_2ABA_HUMAN(
    P_2ABA_HUMAN-+-SubUnitA!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:A..B55a' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_2ABA_HUMAN(P_2ABA_HUMAN
    -+-SubUnitA!1) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_2ABA_HUMAN(
    P_2ABA_HUMAN-+-SubUnitA) @ 'GeneralUnbinding'

# Recruitment of B56a Subunit B by Subunit A
'PP2:A.B56a' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_2A5A_HUMAN(P_2A5A_HUMAN-+-
    SubUnitA) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_2A5A_HUMAN(
    P_2A5A_HUMAN-+-SubUnitA!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:A..B56a' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_2A5A_HUMAN(P_2A5A_HUMAN
    -+-SubUnitA!1) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_2A5A_HUMAN(
    P_2A5A_HUMAN-+-SubUnitA) @ 'GeneralUnbinding'

# Recruitment of Catalytic alpha subunit by subunit B55a
'PP2:C.B55a' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_SubUnitC), P_PP2AA_HUMAN(P_PP2AA_HUMAN
    -+-SubUnitB) -> P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:C..B55a' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!1) -> P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_SubUnitC),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB) @ 'GeneralUnbinding'

# Recruitment of Catalytic alpha subunit by subunit B56a
'PP2:C.B56a' P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_SubUnitC), P_PP2AA_HUMAN(P_PP2AA_HUMAN
    -+-SubUnitB) -> P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:C..B56a' P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!1) -> P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_SubUnitC),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB) @ 'GeneralUnbinding'

# Recruitment of Catalytic alpha subunit by A Subunit PR65
'PP2:C.A' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitC), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    SubUnitA) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitA!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:C..A' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitC!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN
    -+-SubUnitA!1) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitC), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitA) @ 'GeneralUnbinding'

# Recruitment of B72 Subunit B by Subunit A
```

```
'PP2:A.B72' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-
    SubUnitA) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_P2R3A_HUMAN(
    P_P2R3A_HUMAN-+-SubUnitA!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'PP2:A..B72' P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1), P_P2R3A_HUMAN(P_P2R3A_HUMAN
    -+-SubUnitA!1) -> P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB), P_P2R3A_HUMAN(
    P_P2R3A_HUMAN-+-SubUnitA) @ 'GeneralUnbinding'

# Recruitment of Catalytic alpha subunit by subunit B72
'PP2:C.B72' P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_SubUnitC), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB) -> P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_SubUnitC!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'PP2:C..B72' P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_SubUnitC!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!1) -> P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_SubUnitC),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB) @ 'GeneralUnbinding'

# PP2-B56a is dephosphorylating APCs. Interestingly, it would appear APC's ARM
    may be sufficiently similar to B-cat's (and therefore to Importins), to allow
     it to migrate into the nucleous with help of B56a... <10.1074/jbc.M107149200
    >
'PP2.APC' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog,
    P_2A5A_HUMAN-+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) -> P_APC_HUMAN(
    P_APC_HUMAN-+-i_ARM!4), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!4, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB
    !1, P_2AAA_HUMAN-+-SubUnitC!3) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'PP2..APC' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!4), P_2A5A_HUMAN(P_2A5A_HUMAN-+-
    i_Recog!4, P_2A5A_HUMAN-+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog,
    P_2A5A_HUMAN-+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ 'GeneralUnbinding'
'PP2.APC|APC_Cys-rich_rpt_1^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_1~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_1~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
```

```
'PP2.APC|APC_Cys-rich_rpt_2^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_2~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_2~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
'PP2.APC|APC_Cys-rich_rpt_3^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_3~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_3~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
'PP2.APC|APC_Cys-rich_rpt_4^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_4~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_4~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
'PP2.APC|APC_Cys-rich_rpt_5^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_5~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_5~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
```

```
'PP2.APC|APC_Cys-rich_rpt_6^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_6~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_6~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'
'PP2.APC|APC_Cys-rich_rpt_7^' P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-
    APC_Cys-rich_rpt_7~ph), P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN
    -+-i_SubUnitC!2, P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3),
    P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) ->
    P_APC_HUMAN(P_APC_HUMAN-+-i_ARM!9, P_APC_HUMAN-+-APC_Cys-rich_rpt_7~un),
    P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog!9, P_2A5A_HUMAN-+-i_SubUnitC!2,
    P_2A5A_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3) @ '
    GeneralDephosphorylation'

# PP2-B55a is actively seeking branded Cat_BETA with active DestructionMotifs and
     removing the destruction mark <10.1016/j.molcel.2008.10.023> if accessible.
    APC protects the DestructionMotif. Subunit b55 alpha deals with beta-catenin
    <10.1074/jbc.M109.013698>
'PP2.Cat-b' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog, P_2ABA_HUMAN-+-i_SubUnitC!2,
    P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM) ->
    P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2,
    P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9) @ (1/ '
    RescaleFactor' ) * 'GeneralBinding'
'PP2..Cat-b' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2,
    P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9) ->
    P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog, P_2ABA_HUMAN-+-i_SubUnitC!2,
    P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM) @ '
    GeneralUnbinding'
```

```
'PP2.Cat-b|T41^' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC
    !2, P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9, P_CTNB1_HUMAN-+-T41~ph) -> P_2ABA_HUMAN(P_2ABA_HUMAN
    -+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2, P_2ABA_HUMAN-+-SubUnitA!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9,
    P_CTNB1_HUMAN-+-T41~un) @ 'GeneralDephosphorylation'
'PP2.Cat-b|S45^' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC
    !2, P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9, P_CTNB1_HUMAN-+-S45~ph) -> P_2ABA_HUMAN(P_2ABA_HUMAN
    -+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2, P_2ABA_HUMAN-+-SubUnitA!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9,
    P_CTNB1_HUMAN-+-S45~un) @ 'GeneralDephosphorylation'
'PP2.Cat-b|S33^' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC
    !2, P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9, P_CTNB1_HUMAN-+-S33~ph) -> P_2ABA_HUMAN(P_2ABA_HUMAN
    -+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2, P_2ABA_HUMAN-+-SubUnitA!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9,
    P_CTNB1_HUMAN-+-S33~un) @ 'GeneralDephosphorylation'
'PP2.Cat-b|S37^' P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC
    !2, P_2ABA_HUMAN-+-SubUnitA!1), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic,
    P_PP2AA_HUMAN-+-SubUnitB!2, P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(
    P_2AAA_HUMAN-+-SubUnitB!1, P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9, P_CTNB1_HUMAN-+-S37~ph) -> P_2ABA_HUMAN(P_2ABA_HUMAN
    -+-i_Recog!9, P_2ABA_HUMAN-+-i_SubUnitC!2, P_2ABA_HUMAN-+-SubUnitA!1),
    P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-i_Catalytic, P_PP2AA_HUMAN-+-SubUnitB!2,
    P_PP2AA_HUMAN-+-SubUnitA!3), P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB!1,
    P_2AAA_HUMAN-+-SubUnitC!3), P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9,
    P_CTNB1_HUMAN-+-S37~un) @ 'GeneralDephosphorylation'

# This <10.1038/sj.emboj.7601607> references PP1 as the enzyme responsible for
    dephosphorylating Axin. Since UniprotKB only mentions a binding site for Axin
     as PPP2CA, I'm assuming the similarities between PP1 and PP2 are sufficient
    for PP1 to bind here. If not, we require an additional PP1 binding site...
    somewhere.... somehow.....
```

```
'PP1.Axn' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind
    !1), P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'
'PP1..Axn' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!1), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!1) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-
    Phosphatase_bind), P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic) @ '
    GeneralUnbinding'

'Axn|S75^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S75~
    ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic!9) -> P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S75~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'
'Axn|S77^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S77~
    ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic!9) -> P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S77~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'
'Axn|S217^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-
    S217~ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic!9) -> P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-S217~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'

'Axn|S469^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-
    Axin_b-cat-bd, P_AXIN1_HUMAN-+-S469~ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-
    i_Catalytic!9) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9,
    P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-S469~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'
'Axn|T481^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-
    Axin_b-cat-bd, P_AXIN1_HUMAN-+-T481~ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-
    i_Catalytic!9) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9,
    P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-T481~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'
'Axn|S486^' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9, P_AXIN1_HUMAN-+-
    Axin_b-cat-bd, P_AXIN1_HUMAN-+-S486~ph), P_PP1A_HUMAN(P_PP1A_HUMAN-+-
    i_Catalytic!9) -> P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!9,
    P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-S486~un), P_PP1A_HUMAN(
    P_PP1A_HUMAN-+-i_Catalytic!9) @ 'GeneralDephosphorylation'
```

A.2 SmallWnt Agent Signatures, Perturbations, and Non-Formal Rules

```
# ######################################
# ######## AGENT SIGNATURES
# ######################################

# Membrane Signaling
%agent: P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_FZD8_HUMAN, P_WNT1_HUMAN-+-i_P_LRP6_HUMAN
    ) # P04628, P_WNT1_HUMAN
%agent: P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom, P_FZD8_HUMAN-+-CRD,
    P_FZD8_HUMAN-+-PDZ_bind) # Q9H461, P_FZD8_HUMAN
%agent: P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_P_WNT1_HUMAN, P_LRP6_HUMAN-+-C-term,
    P_LRP6_HUMAN-+-S1490~un~ph, P_LRP6_HUMAN-+-T1530~un~ph, P_LRP6_HUMAN-+-T1572~
    un~ph, P_LRP6_HUMAN-+-S1590~un~ph, P_LRP6_HUMAN-+-S1607~un~ph, P_LRP6_HUMAN
    -+-T1493~un~ph, P_LRP6_HUMAN-+-S1533~un~ph, P_LRP6_HUMAN-+-S1575~un~ph,
    P_LRP6_HUMAN-+-T1593~un~ph, P_LRP6_HUMAN-+-T1610~un~ph, P_LRP6_HUMAN-+-
    i_PPPSP) # O75581, P_LRP6_HUMAN

# Destruction Complex
%agent: P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a, P_DVL1_HUMAN-+-DIX_b, P_DVL1_HUMAN-+-
    PDZ, P_DVL1_HUMAN-+-i_Nkd) # O14640, P_DVL1_HUMAN
%agent: P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin) # P49841, P_GSK3B_HUMAN
%agent: P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Regulat_G_prot_signal, P_AXIN1_HUMAN-+-
    i_P_GSK3B_HUMAN, P_AXIN1_HUMAN-+-Axin_b-cat-bd, P_AXIN1_HUMAN-+-DIX_a,
    P_AXIN1_HUMAN-+-DIX_b, P_AXIN1_HUMAN-+-S75~un~ph, P_AXIN1_HUMAN-+-S77~un~ph,
    P_AXIN1_HUMAN-+-S217~un~ph, P_AXIN1_HUMAN-+-S469~un~ph, P_AXIN1_HUMAN-+-T481~
    un~ph, P_AXIN1_HUMAN-+-S486~un~ph, P_AXIN1_HUMAN-+-Phosphatase_bind) # O15169
    , P_AXIN1_HUMAN | Axin1 and Axin2 are FUNCTIONALLY EQUIVALENT <10.1128/MCB
    .25.11.4371-4376.2005 >
%agent: P_APC_HUMAN(P_APC_HUMAN-+-Oligo, P_APC_HUMAN-+-APC_Cys-rich_rpt_1~un~ph,
    P_APC_HUMAN-+-APC_Cys-rich_rpt_2~un~ph, P_APC_HUMAN-+-APC_Cys-rich_rpt_3~un~
    ph, P_APC_HUMAN-+-APC_Cys-rich_rpt_4~un~ph, P_APC_HUMAN-+-APC_Cys-rich_rpt_5~
    un~ph, P_APC_HUMAN-+-APC_Cys-rich_rpt_6~un~ph, P_APC_HUMAN-+-APC_Cys-
    rich_rpt_7~un~ph, P_APC_HUMAN-+-i_ARM, P_APC_HUMAN-+-SAMP_1, P_APC_HUMAN-+-
    SAMP_2, P_APC_HUMAN-+-SAMP_3) # APC_Human, P_APC_HUMAN
%agent: P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom) # P48729, P_KC1A_HUMAN

# Perifery Agents: Phosphatase 2
%agent: P_2AAA_HUMAN(P_2AAA_HUMAN-+-SubUnitB, P_2AAA_HUMAN-+-SubUnitC) # P30153,
    P_2AAA_HUMAN, holoenzyme regulatory subunit "a" PR65, isoform alpha
%agent: P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-SubUnitA, P_PP2AA_HUMAN-+-SubUnitB,
    P_PP2AA_HUMAN-+-i_Catalytic) # P67775, P_PP2AA_HUMAN, holoenzyme catalytic
    subunit, isoform alpha
%agent: P_2ABA_HUMAN(P_2ABA_HUMAN-+-i_Recog, P_2ABA_HUMAN-+-SubUnitA,
    P_2ABA_HUMAN-+-i_SubUnitC) # Q15173, P_2ABA_HUMAN, holoenzyme recognition
    subunit B55, isoform alpha
```

```
%agent: P_2A5A_HUMAN(P_2A5A_HUMAN-+-i_Recog, P_2A5A_HUMAN-+-SubUnitA,
    P_2A5A_HUMAN-+-i_SubUnitC) # Q15172, P_2A5A_HUMAN, honoenzyme recognition
    subunit B56, isoform alpha
%agent: P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_Recog, P_P2R3A_HUMAN-+-SubUnitA,
    P_P2R3A_HUMAN-+-i_SubUnitC) # Q06190 , P_P2R3A_HUMAN, holoenzyme recognition
    subunit B72

# Perifery Agents: Phosphatase 1
%agent: P_PP1A_HUMAN(P_PP1A_HUMAN-+-i_Catalytic) # P62136, P_PP1A_HUMAN,
    holoenzyme catalytic subunit alpha

# The Center of the Universe
%agent: P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~un~ph, P_CTNB1_HUMAN-+-S37~un~ph,
    P_CTNB1_HUMAN-+-T41~un~ph, P_CTNB1_HUMAN-+-S45~un~ph, P_CTNB1_HUMAN-+-i_LysX~
    un~ub, P_CTNB1_HUMAN-+-i_ARM) # CTNB1_Human, P35222

# Extra-Symbolic Agents
%agent: SCF_BETA_TRCP(SCF_BETA_TRCP-+-i_Catalytic)
%agent: Proteasome(Proteasome-+-i_Catalytic)


# ######################################
# ######## OTHER RULES
# ######################################
# The DestructionMotif is the mark carried by P_CTNB1_HUMAN that signals it to be
     ubiquitinated somewhere <10.1016/j.molcel.2008.10.023>, eventually leading
    to its Proteasome-regulated degradation
'(P_CTNB1_HUMAN#).SCF_BETA_TRCP' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_LysX~un), SCF_BETA_TRCP(
    SCF_BETA_TRCP-+-i_Catalytic) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S33~ph,
    P_CTNB1_HUMAN-+-S37~ph, P_CTNB1_HUMAN-+-i_LysX~un!1), SCF_BETA_TRCP(
    SCF_BETA_TRCP-+-i_Catalytic!1) @ 'GeneralBinding'
'(P_CTNB1_HUMAN@)..SCF_BETA_TRCP' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_LysX~ub!1),
    SCF_BETA_TRCP(SCF_BETA_TRCP-+-i_Catalytic!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN
    -+-i_LysX~ub), SCF_BETA_TRCP(SCF_BETA_TRCP-+-i_Catalytic) @ 'GeneralUnbinding
    '
'P_CTNB1_HUMAN@' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_LysX~un!9), SCF_BETA_TRCP(
    SCF_BETA_TRCP-+-i_Catalytic!9) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_LysX~ub!9),
     SCF_BETA_TRCP(SCF_BETA_TRCP-+-i_Catalytic!9) @ 'GeneralUbiquitination'
'Proteasome.(P_CTNB1_HUMAN@)' Proteasome(Proteasome-+-i_Catalytic), P_CTNB1_HUMAN
    (P_CTNB1_HUMAN-+-i_LysX~ub) -> Proteasome(Proteasome-+-i_Catalytic!1),
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_LysX~ub!1) @ 'GeneralBinding'
'Proteasome.//P_CTNB1_HUMAN@//' Proteasome(Proteasome-+-i_Catalytic!9),
    P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_LysX~ub!9) -> Proteasome(Proteasome-+-
    i_Catalytic) @ 'GeneralProteolysis'
```

```
# ######################################
# ######## PERTURBATIONS
# ######################################
%var: 'Init_P_DVL1_HUMAN' 100 * 'Nano_Avo_Vol' * 'RescaleFactor' # 100 nmol of
    Dsh <10.1371/journal.pbio.0000010.st002>
%var: 'Init_P_APC_HUMAN' 4 * 'Nano_Avo_Vol' * 'RescaleFactor' # 4 nmol of APC
    <10.1371/journal.pone.0031882>
%var: 'Init_P_GSK3B_HUMAN' 70 * 'Nano_Avo_Vol' * 'RescaleFactor' # 70 nmol of
    GSK3 <10.1371/journal.pone.0031882>
%var: 'Init_P_AXIN1_HUMAN' 150 * 'Nano_Avo_Vol' * 'RescaleFactor' # 150 nmol of
    Axin <10.1371/journal.pone.0031882>, or 0.02nmol <10.1371/journal.pbio
    .0000010.st002>
%var: 'Init_P_CTNB1_HUMAN' 490 * 'Nano_Avo_Vol' * 'RescaleFactor' # 490 nmol of
    Cat-b <10.1371/journal.pone.0031882>

%var: 'Init_P_FZD8_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of Fzld
    Arbitrary Concentration
%var: 'Init_P_LRP6_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of LRP
    Arbitrary Concentration
%var: 'Init_P_KC1A_HUMAN' 50 * 'Nano_Avo_Vol' * 'RescaleFactor' # 50nmol of CK1
    Arbitrary Concentration
%var: 'Init_P_2AAA_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of PP2 A
    subunit Arbitrary Concentration
%var: 'Init_P_PP2AA_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of PP2
    Catalytic subunit Arbitrary Concentration
%var: 'Init_P_2ABA_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of PP2
    B55a subunit Arbitrary Concentration
%var: 'Init_P_2A5A_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of PP2
    B56a subunit Arbitrary Concentration
%var: 'Init_P_P2R3A_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor' # 5nmol of PP2
    B72 subunit Arbitrary Concentration
%var: 'Init_P_PP1A_HUMAN' 5 * 'Nano_Avo_Vol' * 'RescaleFactor'  # 5 nmol of PP1
    Catalytic subunit Arbitrary Concentration

%var: 'Init_SCF_BETA_TRCP' 100 * 'Nano_Avo_Vol' * 'RescaleFactor'  # 100 nmol of
    the E2 ligase according to <10.1016/S1097-2765(00)80446-3>. We are assuming
    this is representative of the active E3 complex
%var: 'Init_Proteasome' 15 * 'Nano_Avo_Vol' * 'RescaleFactor'  # 15nmol of 26s
    Proteasome, arbitrary concentration

%init: 'Init_P_DVL1_HUMAN' P_DVL1_HUMAN()
%init: 'Init_P_APC_HUMAN' P_APC_HUMAN()
%init: 'Init_P_GSK3B_HUMAN' P_GSK3B_HUMAN()
%init: 'Init_P_AXIN1_HUMAN' P_AXIN1_HUMAN()
%init: 'Init_P_CTNB1_HUMAN' P_CTNB1_HUMAN()
%init: 'Init_P_FZD8_HUMAN' P_FZD8_HUMAN()
%init: 'Init_P_LRP6_HUMAN' P_LRP6_HUMAN()
%init: 'Init_P_KC1A_HUMAN' P_KC1A_HUMAN()
```

```
%init: 'Init_P_2AAA_HUMAN' P_2AAA_HUMAN()
%init: 'Init_P_PP2AA_HUMAN' P_PP2AA_HUMAN()
%init: 'Init_P_2ABA_HUMAN' P_2ABA_HUMAN()
%init: 'Init_P_2A5A_HUMAN' P_2A5A_HUMAN()
%init: 'Init_P_P2R3A_HUMAN' P_P2R3A_HUMAN()
%init: 'Init_P_PP1A_HUMAN' P_PP1A_HUMAN()

%init: 'Init_SCF_BETA_TRCP' SCF_BETA_TRCP()
%init: 'Init_Proteasome' Proteasome()

%obs: '<Wnt>' P_WNT1_HUMAN()
%obs: '<Wnt.LRP>' P_WNT1_HUMAN(P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!1), P_LRP6_HUMAN(
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!1)
%obs: '<Wnt.Fzd>' P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!1), P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!1)
%obs: '<Wnt.LRP.Fzd>' P_FZD8_HUMAN(P_FZD8_HUMAN-+-Frizzled_dom!1), P_WNT1_HUMAN(
    P_WNT1_HUMAN-+-i_P_FZD8_HUMAN!1, P_WNT1_HUMAN-+-i_P_LRP6_HUMAN!2),
    P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!2)
# %obs: '<Fzd.Fzd>' P_FZD8_HUMAN(P_FZD8_HUMAN-+-CRD!1), P_FZD8_HUMAN(P_FZD8_HUMAN
    -+-CRD!1)
# %obs: '<LRP.LRP>' P_LRP6_HUMAN(P_LRP6_HUMAN-+-C-term!1), P_LRP6_HUMAN(
    P_LRP6_HUMAN-+-C-term!1)
%obs: '<Fzd.Dvl>' P_FZD8_HUMAN(P_FZD8_HUMAN-+-PDZ_bind!1), P_DVL1_HUMAN(
    P_DVL1_HUMAN-+-PDZ!1)
# %obs: '<Dvl_b.Axn_a>' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_b!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_a!1)
# %obs: '<Dvl_a.Axn_b>' P_DVL1_HUMAN(P_DVL1_HUMAN-+-DIX_a!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-DIX_b!1)
%obs: '<Axn.LRP>' P_LRP6_HUMAN(P_LRP6_HUMAN-+-i_PPPSP!1), P_AXIN1_HUMAN(
    P_AXIN1_HUMAN-+-Axin_b-cat-bd!1)
%obs: '<LRP-S1490_u>' P_LRP6_HUMAN(P_LRP6_HUMAN-+-S1490~un)
%obs: '<LRP-T1493_u>' P_LRP6_HUMAN(P_LRP6_HUMAN-+-T1493~un)
%obs: '<Axn.CK1>' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!1), P_KC1A_HUMAN
    (P_KC1A_HUMAN-+-Prot_kinase_cat_dom!1)
%obs: '<Axn.GSK>' P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-i_P_GSK3B_HUMAN!1), P_GSK3B_HUMAN
    (P_GSK3B_HUMAN-+-i_Axin!1)
%obs: '<CK1.Axn.GSK>' P_KC1A_HUMAN(P_KC1A_HUMAN-+-Prot_kinase_cat_dom!1),
    P_AXIN1_HUMAN(P_AXIN1_HUMAN-+-Phosphatase_bind!1, P_AXIN1_HUMAN-+-
    i_P_GSK3B_HUMAN!2), P_GSK3B_HUMAN(P_GSK3B_HUMAN-+-i_Axin!2)
%obs: '<Cat|S37>' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-S37~ph)

%obs: '<Cat-B>' P_CTNB1_HUMAN()

'intro Wnt'  -> P_WNT1_HUMAN() @ 0.0
%var: 'Wnt' P_WNT1_HUMAN()
#%mod: [T] > 100 do $UPDATE 'intro Wnt' 100.0
#%mod: 'Wnt' > (2.7 * 'Nano_Avo_Vol' * 'RescaleFactor') do $UPDATE 'intro Wnt'
    0.0 # 2.7nM <10.1371/journal.pone.0030601>
```

```
#%def: "dotSnapshots" "true"
#%def: "colorDot" "true"
#%mod: [T] > 90 do $SNAPSHOT


#%def: "displayCompression" "weak"
#%mod: [T]>1250 do $TRACK '<Axn.LRP>' [true]
#%mod: [T]>1350 do $TRACK '<Axn.LRP>' [false]
#%mod: [true] do $TRACK 'Proteasome.//P_CTNB1_HUMAN@//' [true]
```

A.3 SideWnt Ruleset

```
# This block contains several elements common to the Ca2+ "non-cannonical" Wnt
    pathway. They are of relevance because they affect the transcriptional
    activity of the P_LEF1_HUMAN/Cat_BETA complex while taking as input Wnt1
    <10.1074/jbc.M307801200>. The mode of action of this pathway is complicated,
    but upon induced DNA-damage-related Ca2+ influx, P_ATM_HUMAN translocates to
    the cytosol <10.1016/j.molcel.2010.09.008>. We speculate that Wnt induced Ca2
    + influx also translocates P_ATM_HUMAN. Once in the cytosol, P_ATM_HUMAN can
    oligomerize, usually into 2mer o 4mer conformations. This oligomerizations
    bind the 1961-2046 region (Oligo) of one monomer, to a catalytic region of
    the next <10.1038/nature01368>. Of special interest is the fact that
    P_ATM_HUMAN con bind P_TRAF6_HUMAN through the 2152-2157 region <10.1016/j.
    molcel.2010.09.008>, which happens to be VERY close to Oligo. Considering
    that P_TRAF6_HUMAN can also multimerize <10.1002/jcp.21190>, it is logical to
     assume that P_ATM_HUMAN polymerization induces P_TRAF6_HUMAN aggregation.
    Another key step in this cascade is the activation of the P_TRAF6_HUMAN
    ubiquitination activity upon multimerization, and subsequent auto-
    ubiquitination <10.1002/jcp.21190>. This phenomenon leads to two events:
    firstly active P_TRAF6_HUMAN binds & ubiquitinates MAP3K7 <10.1038/35085597>.
     Secondly, ubiquitinated P_TRAF6_HUMAN is recognizable by P_TAB2_HUMAN'z zinc
     finger domain <10.1002/jcp.21190>. As this three components are found
    together <10.1038/35085597>, it is tempting to postulate that P_TRAF6_HUMAN
    acts as a scaffold to assemble MAP3K7 to TAB1. Once MAP3K7 and TAB1 are
    assembled, MAP3K7 autophosphorylates and activates <10.1128/MCB
    .22.20.7158-7167.2002>. Active MAP3K7 then phosphorylates P_NLK_HUMAN, which
    activates it and triggers its translocation to the nucleus <10.1074/jbc.
    M307801200>. Once in the nucleus, it phosphorylates P_LEF1_HUMAN/TCF. The
    ensuring complex formation and nuclear export of TCFs mediated by 14-3-3 lies
     beyond the scope of this model. This block makes one assumption to fill the
    gap between Wnt input and MAP3K activation, and that hole is filled in by
    P_ATM_HUMAN & P_TRAF6_HUMAN.
'P_ATM_HUMAN.P_ATM_HUMAN' P_ATM_HUMAN(P_ATM_HUMAN-+-Dim), P_ATM_HUMAN(P_ATM_HUMAN
    -+-Catalytic) -> P_ATM_HUMAN(P_ATM_HUMAN-+-Dim!1), P_ATM_HUMAN(P_ATM_HUMAN-+-
    Catalytic!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( 'RingClosureRate' *
    'GeneralBinding')
'P_ATM_HUMAN..P_ATM_HUMAN' P_ATM_HUMAN(P_ATM_HUMAN-+-Dim!1), P_ATM_HUMAN(
    P_ATM_HUMAN-+-Catalytic!1) -> P_ATM_HUMAN(P_ATM_HUMAN-+-Dim), P_ATM_HUMAN(
    P_ATM_HUMAN-+-Catalytic) @ 'GeneralUnbinding'
'P_ATM_HUMAN.P_TRAF6_HUMAN' P_ATM_HUMAN(P_ATM_HUMAN-+-TBM), P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_a) -> P_ATM_HUMAN(P_ATM_HUMAN-+-TBM!1), P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_a!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'P_ATM_HUMAN..P_TRAF6_HUMAN' P_ATM_HUMAN(P_ATM_HUMAN-+-TBM!1), P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_a!1) -> P_ATM_HUMAN(P_ATM_HUMAN-+-TBM), P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_a) @ 'GeneralUnbinding'
```

```
'P_TRAF6_HUMAN.P_TRAF6_HUMAN' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b),
    P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b
    !1), P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding' ('RingClosureRate' * 'GeneralBinding')
'P_TRAF6_HUMAN..P_TRAF6_HUMAN' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!1),
    P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!1) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-
    MATH_b), P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b) @ 'GeneralUnbinding'
'P_TRAF6_HUMAN.MAP3K7' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-
    TRAF), P_M3K7_HUMAN(P_M3K7_HUMAN-+-Lys63~un) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN
    -+-MATH_b!_, P_TRAF6_HUMAN-+-TRAF!1), P_M3K7_HUMAN(P_M3K7_HUMAN-+-Lys63~un!1)
     @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'P_TRAF6_HUMAN..MAP3K7' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-
    TRAF!1), P_M3K7_HUMAN(P_M3K7_HUMAN-+-Lys63~ub!1) -> P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-TRAF), P_M3K7_HUMAN(P_M3K7_HUMAN-+-
    Lys63~ub) @ 'GeneralUnbinding'
'P_TRAF6_HUMAN.MAP3K7@' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-
    TRAF!9), P_M3K7_HUMAN(P_M3K7_HUMAN-+-Lys63~un!9) -> P_TRAF6_HUMAN(
    P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-TRAF!9), P_M3K7_HUMAN(P_M3K7_HUMAN
    -+-Lys63~ub!9) @ 'GeneralUbiquitination'

'P_TRAF6_HUMAN@' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-Lys63~un
    ) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_b!_, P_TRAF6_HUMAN-+-Lys63~ub) @ '
    GeneralUbiquitination' # Oligomerized P_TRAF6_HUMAN has auto-ubiquitination
    activity

'(P_TRAF6_HUMAN@).P_TAB2_HUMAN' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-Lys63~ub),
    P_TAB2_HUMAN(P_TAB2_HUMAN-+-NZF) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-Lys63~ub!1)
    , P_TAB2_HUMAN(P_TAB2_HUMAN-+-NZF!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'
'(P_TRAF6_HUMAN@)..P_TAB2_HUMAN' P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-Lys63!1),
    P_TAB2_HUMAN(P_TAB2_HUMAN-+-NZF!1) -> P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-Lys63),
    P_TAB2_HUMAN(P_TAB2_HUMAN-+-NZF) @ 'GeneralUnbinding'
'P_TAB2_HUMAN.MAP3K7' P_TAB2_HUMAN(P_TAB2_HUMAN-+-i_MAP3K7), P_M3K7_HUMAN(
    P_M3K7_HUMAN-+-i_TAB2) -> P_TAB2_HUMAN(P_TAB2_HUMAN-+-i_MAP3K7!1),
    P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!1) @ (1/ 'RescaleFactor' ) * '
    GeneralBinding'( 'RingClosureRate' * 'GeneralBinding')
'P_TAB2_HUMAN..MAP3K7' P_TAB2_HUMAN(P_TAB2_HUMAN-+-i_MAP3K7!1), P_M3K7_HUMAN(
    P_M3K7_HUMAN-+-i_TAB2!1) -> P_TAB2_HUMAN(P_TAB2_HUMAN-+-i_MAP3K7),
    P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2) @ 'GeneralUnbinding'
'MAP3K7|P_M3K7_HUMAN-+-Thr184*' P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Thr184~un) -> P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Thr184~ph) @ 'GeneralPhosphorylation'
'MAP3K7|P_M3K7_HUMAN-+-Thr187*' P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Thr187~un) -> P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Thr187~ph) @ 'GeneralPhosphorylation'
'MAP3K7|P_M3K7_HUMAN-+-Ser192*' P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Ser192~un) -> P_M3K7_HUMAN(P_M3K7_HUMAN-+-i_TAB2!_,
    P_M3K7_HUMAN-+-Ser192~ph) @ 'GeneralPhosphorylation'
```

```
'MAP3K7.P_NLK_HUMAN' P_M3K7_HUMAN(P_M3K7_HUMAN-+-Thr184~ph, P_M3K7_HUMAN-+-Thr187
    ~ph, P_M3K7_HUMAN-+-Ser192~ph, P_M3K7_HUMAN-+-Prot_kinase_cat_dom),
    P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C) -> P_M3K7_HUMAN(P_M3K7_HUMAN-+-Thr184~ph,
    P_M3K7_HUMAN-+-Thr187~ph, P_M3K7_HUMAN-+-Ser192~ph, P_M3K7_HUMAN-+-
    Prot_kinase_cat_dom!1), P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C!1) @ (1/ '
    RescaleFactor' ) * 'GeneralBinding'
'MAP3K7..P_NLK_HUMAN' P_M3K7_HUMAN(P_M3K7_HUMAN-+-Prot_kinase_cat_dom!1),
    P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C!1) -> P_M3K7_HUMAN(P_M3K7_HUMAN-+-
    Prot_kinase_cat_dom), P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C) @ 'GeneralUnbinding'
'MAP3K7.P_NLK_HUMAN*' P_M3K7_HUMAN(P_M3K7_HUMAN-+-Prot_kinase_cat_dom!9),
    P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C!9, P_NLK_HUMAN-+-Ser522~un) -> P_M3K7_HUMAN(
    P_M3K7_HUMAN-+-Prot_kinase_cat_dom!9), P_NLK_HUMAN(P_NLK_HUMAN-+-Term_C!9,
    P_NLK_HUMAN-+-Ser522~ph) @ 'GeneralPhosphorylation'


# See the comment block on P_ATM_HUMAN, P_TRAF6_HUMAN, MAP3K7, TAB2, P_NLK_HUMAN,
     and P_LEF1_HUMAN.
'P_NLK_HUMAN.P_LEF1_HUMAN' P_NLK_HUMAN(P_NLK_HUMAN-+-Prot_kinase_cat_dom),
    P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK, P_LEF1_HUMAN-+-HMGbox) -> P_NLK_HUMAN(
    P_NLK_HUMAN-+-Prot_kinase_cat_dom!1), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!1,
    P_LEF1_HUMAN-+-HMGbox) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'P_NLK_HUMAN..P_LEF1_HUMAN' P_NLK_HUMAN(P_NLK_HUMAN-+-Prot_kinase_cat_dom!1),
    P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!1) -> P_NLK_HUMAN(P_NLK_HUMAN-+-
    Prot_kinase_cat_dom), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK) @ 'GeneralUnbinding'
'P_NLK_HUMAN.P_LEF1_HUMAN|P_LEF1_HUMAN-+-Thr155*' P_NLK_HUMAN(P_NLK_HUMAN-+-
    Prot_kinase_cat_dom!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!9, P_LEF1_HUMAN-+-
    HMGbox, P_LEF1_HUMAN-+-Thr155~un) -> P_NLK_HUMAN(P_NLK_HUMAN-+-
    Prot_kinase_cat_dom!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!9, P_LEF1_HUMAN-+-
    HMGbox, P_LEF1_HUMAN-+-Thr155~ph) @ 'GeneralPhosphorylation'
'P_NLK_HUMAN.P_LEF1_HUMAN|P_LEF1_HUMAN-+-Ser166*' P_NLK_HUMAN(P_NLK_HUMAN-+-
    Prot_kinase_cat_dom!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!9, P_LEF1_HUMAN-+-
    HMGbox, P_LEF1_HUMAN-+-Ser166~un) -> P_NLK_HUMAN(P_NLK_HUMAN-+-
    Prot_kinase_cat_dom!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-i_NLK!9, P_LEF1_HUMAN-+-
    HMGbox, P_LEF1_HUMAN-+-Ser166~ph) @ 'GeneralPhosphorylation'

'Cat_BETA.P_LEF1_HUMAN' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM), P_LEF1_HUMAN(
    P_LEF1_HUMAN-+-CBD) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_LEF1_HUMAN(
    P_LEF1_HUMAN-+-CBD!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Cat_BETA..P_LEF1_HUMAN' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!1), P_LEF1_HUMAN(
    P_LEF1_HUMAN-+-CBD!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM), P_LEF1_HUMAN(
    P_LEF1_HUMAN-+-CBD) @ 'GeneralUnbinding'
```

A.4 SideWnt Agent Signatures, Perturbations, and Non-Formal Rules

```
# ######################################
# ######## AGENT SIGNATURES
# ######################################
%agent: P_TAB2_HUMAN(P_TAB2_HUMAN-+-i_MAP3K7, P_TAB2_HUMAN-+-NZF) # TAB2_HUMAN,
    Q9NYJ8
%agent: P_M3K7_HUMAN(P_M3K7_HUMAN-+-Lys63~un~ub, P_M3K7_HUMAN-+-Thr184~un~ph,
    P_M3K7_HUMAN-+-Thr187~un~ph, P_M3K7_HUMAN-+-Ser192~un~ph, P_M3K7_HUMAN-+-
    Prot_kinase_cat_dom, P_M3K7_HUMAN-+-i_TAB2, P_M3K7_HUMAN-+-i_PP2) #
    M3K7_HUMAN, O43318
%agent: P_NLK_HUMAN(P_NLK_HUMAN-+-Ser522~un~ph, P_NLK_HUMAN-+-Prot_kinase_cat_dom
    , P_NLK_HUMAN-+-Term_C) # NLK_HUMAN, Q9UBE8
%agent: P_ATM_HUMAN(P_ATM_HUMAN-+-Dim, P_ATM_HUMAN-+-TBM, P_ATM_HUMAN-+-Catalytic
    ) # ATM_HUMAN, Q13315
%agent: P_TRAF6_HUMAN(P_TRAF6_HUMAN-+-MATH_a, P_TRAF6_HUMAN-+-MATH_b,
    P_TRAF6_HUMAN-+-TRAF, P_TRAF6_HUMAN-+-Lys63~un~ub) # TRAF6_HUMAN, Q9Y4K3
%agent: P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD, P_LEF1_HUMAN-+-i_NLK, P_LEF1_HUMAN-+-
    HMGbox, P_LEF1_HUMAN-+-Thr155~un~ph, P_LEF1_HUMAN-+-Ser166~un~ph) #
    LEF1_HUMAN, Q9UJU2

# Extra-Symbolic Agents
%agent: Genome(Genome-+-i_BS)


# ######################################
# ######## OTHER RULES
# ######################################
'(Cat_BETA.P_LEF1_HUMAN).Genome' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9),
    P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-Thr155~un, P_LEF1_HUMAN-+-
    Ser166~un, P_LEF1_HUMAN-+-HMGbox), Genome(Genome-+-i_BS) -> P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-
    Thr155~un, P_LEF1_HUMAN-+-Ser166~un, P_LEF1_HUMAN-+-HMGbox!1), Genome(Genome
    -+-i_BS!1) @ 'GeneralBinding'
'(Cat_BETA.P_LEF1_HUMAN)..Genome' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9),
    P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-HMGbox!1), Genome(Genome-+-
    i_BS!1) -> P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN
    -+-CBD!9, P_LEF1_HUMAN-+-HMGbox), Genome(Genome-+-i_BS) @ 'GeneralUnbinding'


# ######################################
# ######## PERTURBATIONS & INITIALS
# ######################################
%var: 'Init_P_TAB2_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'
%var: 'Init_P_M3K7_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'
%var: 'Init_P_NLK_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'
```

```
%var: 'Init_P_ATM_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'
%var: 'Init_P_TRAF6_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'
%var: 'Init_P_LEF1_HUMAN' 10 * 'Nano_Avo_Vol' * 'RescaleFactor'

%init: 'Init_P_TAB2_HUMAN' P_TAB2_HUMAN()
%init: 'Init_P_M3K7_HUMAN' P_M3K7_HUMAN()
%init: 'Init_P_NLK_HUMAN' P_NLK_HUMAN()
%init: 'Init_P_ATM_HUMAN' P_ATM_HUMAN()
%init: 'Init_P_TRAF6_HUMAN' P_TRAF6_HUMAN()
%init: 'Init_P_LEF1_HUMAN' P_LEF1_HUMAN()
%init: 1 Genome()
```

A.5 FeedbackWnt Ruleset

```
# Dkk is a secreted protein that binds LPR. Through the action of the Kremen
    receptor, Dkk induces the endocytosis of LPR <10.1038/sj.onc.1208303>. Since
    Kremen's presence appears to only play a role when LRP6 is over-expressed
    <10.1074/jbc.M802376200 >, this model will only consider the competitive
    binding of Dkk to LRP6. Likewise, since Kremen mediates internalization of
    LRP, and recently it was shown that sequestration of GSK3_BETA into multi-
    vesicular endosomes through the membrane-bound signalosome is required
    <10.1016/j.cell.2010.11.034>, this model deliberately ignores this.
'Dkk.LPR' P_DKK1_HUMAN(P_DKK1_HUMAN-+-CRD_2), P_LRP6_HUMAN(P_LRP6_HUMAN-+-
    i_P_WNT1_HUMAN) -> P_DKK1_HUMAN(P_DKK1_HUMAN-+-CRD_2!1), P_LRP6_HUMAN(
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'
'Dkk..LPR' P_DKK1_HUMAN(P_DKK1_HUMAN-+-CRD_2!1), P_LRP6_HUMAN(P_LRP6_HUMAN-+-
    i_P_WNT1_HUMAN!1) -> P_DKK1_HUMAN(P_DKK1_HUMAN-+-CRD_2), P_LRP6_HUMAN(
    P_LRP6_HUMAN-+-i_P_WNT1_HUMAN) @ 'GeneralUnbinding'

# Through PR72, a subunit of PP2, Nkd is able to bind and recruit Dsh into an
    phosphatase-inactive complex <10.1101/gad.328905>. It may also destabilize
    Dsh, possibly through CYLD mediated (de?)ubiquitination, though that is less
    clear...
'P72.Nkd' P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_Recog), P_NKD1_HUMAN(P_NKD1_HUMAN-+-
    i_PP2_a) -> P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_Recog!1), P_NKD1_HUMAN(
    P_NKD1_HUMAN-+-i_PP2_a!1) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'P72..Nkd' P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_Recog!1), P_NKD1_HUMAN(P_NKD1_HUMAN-+-
    i_PP2_a!1) -> P_P2R3A_HUMAN(P_P2R3A_HUMAN-+-i_Recog), P_NKD1_HUMAN(
    P_NKD1_HUMAN-+-i_PP2_a) @ 'GeneralUnbinding'

'Nkd.PP2c' P_NKD1_HUMAN(P_NKD1_HUMAN-+-i_PP2_b), P_PP2AA_HUMAN(P_PP2AA_HUMAN-+-
    i_Catalytic) -> P_NKD1_HUMAN(P_NKD1_HUMAN-+-i_PP2_b!4), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-i_Catalytic!4) @ (1/ 'RescaleFactor' ) * 'GeneralBinding'( '
    RingClosureRate' * 'GeneralBinding')
'Nkd..PP2c' P_NKD1_HUMAN(P_NKD1_HUMAN-+-i_PP2_b!4), P_PP2AA_HUMAN(P_PP2AA_HUMAN
    -+-i_Catalytic!4) -> P_NKD1_HUMAN(P_NKD1_HUMAN-+-i_PP2_b), P_PP2AA_HUMAN(
    P_PP2AA_HUMAN-+-i_Catalytic) @ 'GeneralUnbinding'
```

A.6 FeedbackWnt Agent Signatures, Perturbations, and NonFormal Rules

```
# ######################################
# ######## AGENT SIGNATURES
# ######################################
%agent: P_DKK1_HUMAN(P_DKK1_HUMAN-+-CRD_2) # DKK1_HUMAN, O94907
%agent: P_NKD1_HUMAN(P_NKD1_HUMAN-+-i_PP2_a, P_NKD1_HUMAN-+-i_PP2_b, P_NKD1_HUMAN
    -+-EF_hand) # NKD1_HUMAN, Q969G9


# ######################################
# ######## OTHER RULES
# ######################################
'/Nkd/' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD
    !9, P_LEF1_HUMAN-+-HMGbox!1), Genome(Genome-+-i_BS!1) -> P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-
    HMGbox!1), Genome(Genome-+-i_BS!1), P_NKD1_HUMAN() @ 0.1
'/Dkk/' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD
    !9, P_LEF1_HUMAN-+-HMGbox!1), Genome(Genome-+-i_BS!1) -> P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-
    HMGbox!1), Genome(Genome-+-i_BS!1), P_DKK1_HUMAN() @ 0.1
'/Axin2/' P_CTNB1_HUMAN(P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD
    !9, P_LEF1_HUMAN-+-HMGbox!1), Genome(Genome-+-i_BS!1) -> P_CTNB1_HUMAN(
    P_CTNB1_HUMAN-+-i_ARM!9), P_LEF1_HUMAN(P_LEF1_HUMAN-+-CBD!9, P_LEF1_HUMAN-+-
    HMGbox!1), Genome(Genome-+-i_BS!1), P_AXIN1_HUMAN() @ 0.1
```

Appendix B

$\varkappa$ Manual of Style

- Modifications are seldom "at a distance". It is generaly good practice to decipher the path from the modificator to the modified entity. For example, a phosphatase catalytic cleft would probably require a path that links the catalytic unit, to the recognition unit, to the substrate, in addition to other regulatory units that may be present. Though it may be tempting to simply collapse the holoenzyme into a single species, that would defeat the purpose of preserving the patterns entailed by the multi-agent representation. In other words, it's lazy modeling.

- Reactions are seldom irreversible. Inclusion of the reverse reaction, particularly for binding reactions, helps prevent locked terminal states. A good practice for model clarity is to group related rules together, such as binding and unbinding rules. The use of reversible rules in KaSim v3 is particularly useful in this regard. However, notice the causal dependencies: a binding may depend on being phosphorylated, but does the unbinding event mean the protein remains phosphorylated?

- Don't Care, Don't Write: Use the pattern philosophy to only specify what the reaction cares about.

- Fetch Agent Signature. The agent signature is your friend: it WILL help keep consistency across rules.

As for rule conversion, the following can be used as conversion methods from deterministic rates to stochastic rates.

For the dissociation constant K_d:

$$K_d = \frac{K_{unbind}}{K_{bind}} = \frac{\gamma_{unbind}}{\frac{\gamma_{bind}}{V}}$$

For the Michaelis-Menten constant K_m:

$$\gamma_m = K_m V$$

In terms of donwscaling a system by a given factor σ, in order to maintain the stochastic nature a coefficient is applied to the Volume term on elements. Thus, initial conditions are multiplied by the scaling factor, and rates are multiplied by the inverse factor. This means unimolecular reactions are unaffected. Given a concentration of x in moles:

$$Init_x = [x] * Volume * Avogadro * \sigma$$

Likewise, for a rate γ_1 in $molecules^{-1}second^{-1}$

$$\gamma_2 = \gamma_1 * \frac{1}{\sigma}$$

Bibliography

[1] Ethan Lee, Adrian Salic, Roland Krüger, Reinhart Heinrich, and Marc W Kirschner. The roles of APC and Axin derived from experimental and theoretical analysis of the Wnt pathway. *PLoS biology*, 1(1):E10, October 2003. ISSN 1545-7885. doi: 10.1371/journal.pbio.0000010. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=212691&tool=pmcentrez&rendertype=abstract.

[2] Sung-Young Shin, Oliver Rath, Armin Zebisch, Sang-Mok Choo, Walter Kolch, and Kwang-Hyun Cho. Functional roles of multiple feedback loops in extracellular signal-regulated kinase and wnt signaling pathways that regulate epithelial-mesenchymal transition. *Cancer Research*, 70(17):6715–6724, 2010. doi: 10.1158/0008-5472.CAN-10-1377. URL http://cancerres.aacrjournals.org/content/70/17/6715.abstract.

[3] Demir Emek, Cary Michael, Paley Suzanne, Fukuda Ken, Lemer Christian, and et al. The biopax community standard for pathway data sharing. *Nature Biotechnology*, 2010. doi: 10.1038/nbt.1666.

[4] Richard Parry. Episteme and techne. In Edward N. Zalta, editor, *The Stanford Encyclopedia of Philosophy*. The Metaphysics Research Lab
Center for the Study of Language and Information
Stanford University
Stanford, CA 94305-4115, fall 2008 edition, 2008.

[5] Matthias Steup. The analysis of knowledge. In Edward N. Zalta, editor, *The Stanford Encyclopedia of Philosophy*. The Metaphysics Research Lab
Center for the Study of Language and Information
Stanford University
Stanford, CA 94305-4115, summer 2012 edition, 2012.

[6] Richard Fumerton. Knowledge by acquaintance vs. description. In Edward N. Zalta, editor, *The Stanford Encyclopedia of Philosophy*. The Metaphysics Research Lab
Center for the Study of Language and Information
Stanford University
Stanford, CA 94305-4115, summer 2009 edition, 2009.

[7] Bruce Russell. A priori justification and knowledge. In Edward N. Zalta, editor, *The Stanford Encyclopedia of Philosophy*. The Metaphysics Research Lab
Center for the Study of Language and Information
Stanford University
Stanford, CA 94305-4115, summer 2012 edition, 2012.

[8] Selventa. Bel portal, 2012. URL http://belframework.org/.

[9] Paul Spellman, Michael Miller, Jason Stewart, Charles Troup, Ugis Sarkans, Steve Chervitz, Derek Bernhart, Gavin Sherlock, Catherine Ball, Marc Lepage, Marcin Swiatek, WL Marks, Jason Goncalves, Scott Markel, Daniel Iordan, Mohammadreza Shojatalab, Angel Pizarro, Joe White, Robert Hubley, Eric Deutsch, Martin Senger, Bruce Aronow, Alan Robinson, Doug Bassett, Christian Stoeckert, and Alvis Brazma. Design and implementation of microarray gene expression markup language (mage-ml). *Genome Biology*, 3(9):research0046.1–research0046.9, 2002. ISSN 1465-6906. doi: 10.1186/gb-2002-3-9-research0046. URL http://genomebiology.com/2002/3/9/research/0046.

[10] W3C. Rdf/xml syntax specification, 2004. URL http://www.w3.org/TR/rdf-syntax-grammar/.

[11] UniProt Consortium. Universal protein resource, 2012. URL http://www.uniprot.org/.

[12] Kanehisa Laboratories. Kyoto encyclopedia of genes and genomes, 2012. URL http://www.genome.jp/kegg/.

[13] Cell Signaling Technology. Phosphosite, 2012. URL http://www.phosphosite.org/.

[14] Damian Szklarczyk, Andrea Franceschini, Michael Kuhn, Milan Simonovic, Alexander Roth, Pablo Minguez, Tobias Doerks, Manuel Stark, Jean Muller, Peer Bork,

Lars J. Jensen, and Christian von Mering. The string database in 2011: functional interaction networks of proteins, globally integrated and scored. *Nucleic Acids Research*, 39(suppl 1):D561–D568, 2011. doi: 10.1093/nar/gkq973. URL http://nar.oxfordjournals.org/content/39/suppl_1/D561.abstract.

[15] Sailu Yellaboina, Asba Tasneem, Dmitri V. Zaykin, Balaji Raghavachari, and Raja Jothi. Domine: a comprehensive collection of known and predicted domain-domain interactions. *Nucleic Acids Research*, 39(suppl 1):D730–D735, 2011. doi: 10.1093/nar/gkq1229. URL http://nar.oxfordjournals.org/content/39/suppl_1/D730.abstract.

[16] Marco Punta, Penny C. Coggill, Ruth Y. Eberhardt, Jaina Mistry, John Tate, Chris Boursnell, Ningze Pang, Kristoffer Forslund, Goran Ceric, Jody Clements, Andreas Heger, Liisa Holm, Erik L. L. Sonnhammer, Sean R. Eddy, Alex Bateman, and Robert D. Finn. The pfam protein families database. *Nucleic Acids Research*, 40(D1):D290–D301, 2012. doi: 10.1093/nar/gkr1065. URL http://nar.oxfordjournals.org/content/40/D1/D290.abstract.

[17] Nurcan Tuncbag, Attila Gursoy, Ruth Nussinov, and Ozlem Keskin. Predicting protein-protein interactions on a proteome scale by matching evolutionary and structural similarities at interfaces using prism. *Nature Protocols*, 2011. doi: 10.1038/nprot.2011.367.

[18] Linguamatics Lmited. Linguamatics, 2012. URL http://www.linguamatics.com/.

[19] Robert Hoffmann and Alfonso Valencia. A gene network for navigating the literature. *Nature Genetics*, 2004. doi: 10.1038/ng0704-664.

[20] Konrad Zuse. *Rechnender Raum*. Friedrich Vieweg & Sohn, Braunshweig, 1969.

[21] Richard Bellman. *Dynamic Programming*. Princeton University Press, 1957. ISBN 978-0-691-07951-6.

[22] A Regev, W Silverman, and E Shapiro. Representation and simulation of biochemical processes using the pi-calculus process algebra. *Pacific Symposium On Biocomputing*, 6(42):459–470, 2001. URL http://www.ncbi.nlm.nih.gov/pubmed/11262964.

[23] James Faeder, Michael Blinov, and William Hlavacek. Rule-based modeling of biochemical systems with bionetgen. *Methods in Molecular Biology*, 2009. doi: 10.1007/978-1-59745-525-1_5.

[24] Vincent Danos, J Feret, and W Fontana. Scalable simulation of cellular signaling networks. *Programming Languages and Systems*, 4807(Lecture Notes in Computer Science):139–157, 2007. doi: 10.1007/978-3-540-76637-7_10. URL http://www.springerlink.com/index/k6202r6207358424.pdf.

[25] B M Gumbiner. Cell adhesion: the molecular basis of tissue architecture and morphogenesis. *Cell*, 84(3):345–57, February 1996. ISSN 0092-8674. URL http://www.ncbi.nlm.nih.gov/pubmed/8608588.

[26] J R Miller and R T Moon. Signal transduction through beta-catenin and specification of cell fate during embryogenesis. *Genes & Development*, 10(20):2527–2539, October 1996. ISSN 0890-9369. doi: 10.1101/gad.10.20.2527. URL http://www.genesdev.org/cgi/doi/10.1101/gad.10.20.2527.

[27] Y Mimori-Kiyosue, N Shiina, and S Tsukita. Adenomatous polyposis coli (APC) protein moves along microtubules and concentrates at their growing ends in epithelial cells. *The Journal of cell biology*, 148(3):505–18, February 2000. ISSN 0021-9525. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2174811&tool=pmcentrez&rendertype=abstract.

[28] Gemma Bellett, Jane M Carter, Jennifer Keynton, Deborah Goldspink, Colin James, David K Moss, and Mette M Mogensen. Microtubule plus-end and minus-end capture at adherens junctions is involved in the assembly of apicobasal arrays in polarised epithelial cells. *Cell motility and the cytoskeleton*, 66 (10):893–908, October 2009. ISSN 1097-0169. doi: 10.1002/cm.20393. URL http://www.ncbi.nlm.nih.gov/pubmed/19479825.

[29] Mark D Gustavson, Howard C Crawford, Barbara Fingleton, and Lynn M Matrisian. Tcf binding sequence and position determines beta-catenin and Lef-1 responsiveness of MMP-7 promoters. *Molecular carcinogenesis*, 41(3):125–39, November 2004. ISSN 0899-1987. doi: 10.1002/mc.20049. URL http://www.ncbi.nlm.nih.gov/pubmed/15457508.

[30] O Tetsu and F McCormick. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature*, 398(6726):422–6, April 1999. ISSN 0028-0836. doi: 10.1038/18884. URL http://www.ncbi.nlm.nih.gov/pubmed/10201372.

[31] Qingjie Li, Wan-Mohaiza Dashwood, Xiaoying Zhong, Mohamed Al-Fageeh, and Roderick H Dashwood. Cloning of the rat β-catenin gene (Ctnnb1) promoter and its functional analysis compared with the Catnb and CTNNB1 promoters. *Genomics*, 83(2):231–242, February 2004. ISSN 08887543. doi: 10.1016/j.ygeno.2003.08.004. URL http://linkinghub.elsevier.com/retrieve/pii/S088875430300243X.

[32] W Hsu, L Zeng, and F Costantini. Identification of a domain of Axin that binds to the serine/threonine protein phosphatase 2A and a self-binding domain. *The Journal of biological chemistry*, 274(6):3439–45, February 1999. ISSN 0021-9258. doi: 10.1074/jbc.274.6.3439. URL http://www.ncbi.nlm.nih.gov/pubmed/9920888.

[33] Karl Willert, Sayumi Shibamoto, and Roel Nusse. Wnt-induced dephosphorylation of axin releases beta-catenin from the axin complex. *Genes & development*, 13(14): 1768–73, July 1999. ISSN 0890-9369. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=316878&tool=pmcentrez&rendertype=abstract.

[34] Xin Zeng, Keiko Tamai, Brad Doble, Shitao Li, He Huang, Raymond Habas, Heidi Okamura, Jim Woodgett, and Xi He. A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature*, 438(7069):873–7, December 2005. ISSN 1476-4687. doi: 10.1038/nature04185. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2100418&tool=pmcentrez&rendertype=abstract.

[35] Vincent Danos, J Feret, W Fontana, and R Harmer. Rule-based modelling of cellular signalling. *Lecture Notes in Computer Science*, 4703:17–41, 2007. doi: 10.1007/978-3-540-74407-8_3. URL http://www.springerlink.com/index/N1020Q7126044X04.pdf.

[36] Daniel Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*, 1977.

[37] Donald Wetlaufer. Nucleation, rapid folding, and globular intrachain regions in proteins. *Proc. Nat. Acad. Sci.*, 1973. doi: 10.1073/pnas.70.3.697.

[38] José Manuel González-Sancho, Oscar Aguilera, José Miguel García, Natalia Pendás-Franco, Cristina Peña, Santiago Cal, Antonio García de Herreros, Félix Bonilla, and Alberto Muñoz. The Wnt antagonist DICKKOPF-1 gene is a downstream target of beta-catenin/TCF and is downregulated in human colon cancer. *Oncogene*, 24 (6):1098–103, February 2005. ISSN 0950-9232. doi: 10.1038/sj.onc.1208303. URL http://www.ncbi.nlm.nih.gov/pubmed/15592505.

[39] K Tamai, M Semenov, Y Kato, R Spokony, C Liu, Y Katsuyama, F Hess, J P Saint-Jeannet, and X He. LDL-receptor-related proteins in Wnt signal transduction. *Nature*, 407(6803):530–5, September 2000. ISSN 0028-0836. doi: 10.1038/35035117. URL http://www.ncbi.nlm.nih.gov/pubmed/11029007.

[40] Feng Cong, Liang Schweizer, and Harold Varmus. Wnt signals across the plasma membrane to activate the β-catenin pathway by forming oligomers containing its receptors , Frizzled and LRP. *Biomedical Research*, pages 5103–5115, 2004. doi: 10.1242/dev.01318.

[41] Zahid Khan, Sapna Vijayakumar, Teresa Villanueva de la Torre, Sabrina Rotolo, and Anna Bafico. Analysis of endogenous LRP6 function reveals a novel feedback mechanism by which Wnt negatively regulates its receptor. *Molecular and cellular biology*, 27(20):7291–301, October 2007. ISSN 0270-7306. doi: 10.1128/MCB.00773-07. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2168903&tool=pmcentrez&rendertype=abstract.

[42] Clémence Carron, Aude Pascal, Alexandre Djiane, Jean-Claude Boucaut, De-Li Shi, and Muriel Umbhauer. Frizzled receptor dimerization is sufficient to activate the Wnt/beta-catenin pathway. *Journal of cell science*, 116(Pt 12):2541–50, June 2003. ISSN 0021-9533. doi: 10.1242/jcs.00451. URL http://www.ncbi.nlm.nih.gov/pubmed/12734397.

[43] Marc Fiedler, Carolina Mendoza-Topaz, Trevor J Rutherford, Juliusz Mieszczanek, and Mariann Bienz. Dishevelled interacts with the DIX domain polymerization interface of Axin to interfere with its function in down-regulating β-catenin. *Proceedings of the National Academy of Sciences of the United States of America*, 108(5):1937–42, February 2011. ISSN 1091-6490. doi: 10.1073/pnas.1017063108. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3033301&tool=pmcentrez&rendertype=abstract.

[44] N. S. Fearnhead. The ABC of APC. *Human Molecular Genetics*, 10 (7):721–733, April 2001. ISSN 14602083. doi: 10.1093/hmg/10.7.721. URL http://hmg.oxfordjournals.org/content/10/7/721.shorthttp://www.hmg.oupjournals.org/cgi/doi/10.1093/hmg/10.7.721.

[45] Jun Yang, Wen Zhang, Paul M Evans, Xi Chen, Xi He, and Chunming Liu. Adenomatous polyposis coli (APC) differentially regulates beta-catenin phosphorylation and ubiquitination in colon cancer cells. *The Journal of biological chemistry*, 281 (26):17751–7, June 2006. ISSN 0021-9258. doi: 10.1074/jbc.M600831200. URL http://www.ncbi.nlm.nih.gov/pubmed/16798748.

[46] Nam-Chul Ha, Takashi Tonozuka, Jennifer L Stamos, Hee-Jung Choi, and William I Weis. Mechanism of phosphorylation-dependent binding of APC to beta-catenin and its role in beta-catenin degradation. *Molecular cell*, 15(4):511–21, August 2004. ISSN 1097-2765. doi: 10.1016/j.molcel.2004.08.010. URL http://www.ncbi.nlm.nih.gov/pubmed/15327768.

[47] Chunming Liu, Yiming Li, Mikhail Semenov, Chun Han, Gyeong Hun Baeg, Yi Tan, Zhuohua Zhang, Xinhua Lin, and Xi He. Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism. *Cell*, 108(6):837–47, March 2002. ISSN 0092-8674. doi: 10.1016/S0092-8674(02)00685-2. URL http://www.ncbi.nlm.nih.gov/pubmed/11955436.

[48] YunYun Su, Chunjiang Fu, Shinji Ishikawa, Alessandra Stella, Masayuki Kojima, Kazuhisa Shitoh, Emanuel M Schreiber, Billy W Day, and Bo Liu. APC is essential for targeting phosphorylated beta-catenin to the SCFbeta-TrCP ubiquitin ligase. *Molecular cell*, 32(5):652–61, December 2008. ISSN 1097-4164. doi: 10.1016/j.molcel.2008.10.023. URL http://www.ncbi.nlm.nih.gov/pubmed/19061640.

[49] David M Roberts, Mira I Pronobis, John S Poulton, Jon D Waldmann, Elise M Stephenson, Shahnaz Hanna, and Mark Peifer. Deconstructing the ßcatenin destruction complex: mechanistic roles for the tumor suppressor APC in regulating Wnt signaling. *Molecular biology of the cell*, 22(11):1845–63, June 2011. ISSN 1939-4586. doi: 10.1091/mbc.E10-11-0871. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3103401&tool=pmcentrez&rendertype=abstract.

[50] Tohru Ishitani, Jun Ninomiya-tsuji, and Kunihiro Matsumoto. Regulation of Lymphoid Enhancer Factor 1 / T-Cell Factor by Mitogen-Activated Protein Kinase-Related Nemo-Like Kinase-Dependent Phosphorylation in Wnt / beta - Catenin Signaling. *American Society for Microbiology*, 23(4):1379–1389, 2003. doi: 10.1128/MCB.23.4.1379.

[51] Michael Hinz, Michael Stilmann, Seda Çöl Arslan, Kum Kum Khanna, Gunnar Dittmar, and Claus Scheidereit. A cytoplasmic ATM-TRAF6-cIAP1 module links nuclear DNA damage signaling to ubiquitin-mediated NF-κB activation. *Molecular cell*, 40(1):63–74, October 2010. ISSN 1097-4164. doi: 10.1016/j.molcel.2010.09.008. URL http://www.ncbi.nlm.nih.gov/pubmed/20932475.

[52] Christopher J Bakkenist and Michael B Kastan. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. *Nature*, 421 (6922):499–506, January 2003. ISSN 0028-0836. doi: 10.1038/nature01368. URL http://www.ncbi.nlm.nih.gov/pubmed/12556884.

[53] Per-olof Hasselgren. Ubiquitination, Phosphorylation, and AcetylationTriple Threat in Muscle Wasting. *Journal of Cellular Physiology*, 213(May):679–689, 2007. doi: 10.1002/jcp.21190.

[54] C Wang, L Deng, M Hong, G R Akkaraju, J Inoue, and Z J Chen. TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature*, 412(6844):346–51, July 2001. ISSN 0028-0836. doi: 10.1038/35085597. URL http://www.ncbi.nlm.nih.gov/pubmed/11460167.

[55] Zhengfan Jiang, Jun Ninomiya-tsuji, Youcun Qian, and Kunihiro Matsumoto. Kinase-Dependent IL-1-Induced Signaling Complexes Phosphorylate TAK1 and TAB2 at the Plasma Membrane and Activate TAK1 in the Cytosol Interleukin-1 (IL-1) Receptor-Associated Kinase-Dependent IL-1-Induced Signaling Complexes Phosphorylate TAK1 and TAB2. *MOLECULAR AND CELLULAR BIOLOGY*, 22 (20):7158–7167, 2002. doi: 10.1128/MCB.22.20.7158.

[56] Linda Smit, Annette Baas, Jeroen Kuipers, Hendrik Korswagen, Marc van de Wetering, and Hans Clevers. Wnt activates the Tak1/Nemo-like kinase pathway.

The Journal of biological chemistry, 279(17):17232–40, April 2004. ISSN 0021-9258. doi: 10.1074/jbc.M307801200. URL http://www.jbc.org/cgi/content/abstract/279/17/17232http://www.ncbi.nlm.nih.gov/pubmed/14960582.

[57] Beric R Henderson and Francois Fagotto. The ins and outs of APC and beta-catenin nuclear transport. *EMBO reports*, 3(9):834–9, September 2002. ISSN 1469-221X. doi: 10.1093/embo-reports/kvf181. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1084234&tool=pmcentrez&rendertype=abstract.

[58] R Rosin-Arbesfeld, F Townsley, and M Bienz. The APC tumour suppressor has a nuclear export function. *Nature*, 406(6799):1009–12, August 2000. ISSN 0028-0836. doi: 10.1038/35023016. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=150338&tool=pmcentrez&rendertype=abstract.

[59] M a Galea, A Eleftheriou, and B R Henderson. ARM domain-dependent nuclear import of adenomatous polyposis coli protein is stimulated by the B56 alpha subunit of protein phosphatase 2A. *The Journal of biological chemistry*, 276(49):45833–9, December 2001. ISSN 0021-9258. doi: 10.1074/jbc.M107149200. URL http://www.ncbi.nlm.nih.gov/pubmed/11585828.

[60] Menno P Creyghton, Giulietta Roël, Pieter J a Eichhorn, E Marielle Hijmans, Irma Maurer, Olivier Destrée, and René Bernards. PR72, a novel regulator of Wnt signaling required for Naked cuticle function. *Genes & development*, 19(3):376–86, February 2005. ISSN 0890-9369. doi: 10.1101/gad.328905. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=546515&tool=pmcentrez&rendertype=abstract.

[61] E.-h. Jho, Tong Zhang, Claire Domon, C.-K. Joo, J.-N. Freund, and Frank Costantini. Wnt/ -Catenin/Tcf Signaling Induces the Transcription of Axin2, a Negative Regulator of the Signaling Pathway. *Molecular and Cellular Biology*, 22(4):1172–1183, February 2002. ISSN 0270-7306. doi: 10.1128/MCB.22.4.1172-1183.2002. URL http://mcb.asm.org/cgi/doi/10.1128/MCB.22.4.1172-1183.2002.

[62] Ian V Chia and Frank Costantini. Mouse Axin and Axin2 / Conductin Proteins Are Functionally Equivalent In Vivo Mouse Axin and Axin2 / Conductin Proteins Are Functionally Equivalent In Vivo. *Molecular and Cellular Biology*, 25(11), 2005. doi: 10.1128/MCB.25.11.43714376.2005.

[63] Wen Zhang, Jun Yang, Yajuan Liu, Xi Chen, Tianxin Yu, Jianhang Jia, and Chunming Liu. PR55 alpha, a regulatory subunit of PP2A, specifically regulates PP2A-mediated beta-catenin dephosphorylation. *The Journal of biological chemistry*, 284(34):22649–56, August 2009. ISSN 1083-351X. doi: 10.1074/jbc.M109.013698. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2755672&tool=pmcentrez&rendertype=abstract.

[64] Wen Luo, Annita Peterson, Benjamin a Garcia, Gary Coombs, Bente Kofahl, Reinhart Heinrich, Jeffrey Shabanowitz, Donald F Hunt, H Joseph Yost, and David M Virshup. Protein phosphatase 1 regulates assembly and function of the beta-catenin degradation complex. *The EMBO journal*, 26(6):1511–21, March 2007. ISSN 0261-4189. doi: 10.1038/sj.emboj.7601607. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1829374&tool=pmcentrez&rendertype=abstract.

[65] Chin Wee Tan, Bruce S Gardiner, Yumiko Hirokawa, Meredith J Layton, David W Smith, and Antony W Burgess. Wnt signalling pathway parameters for Mammalian cells. *PloS one*, 7(2):e31882, January 2012. ISSN 1932-6203. doi: 10.1371/journal.pone.0031882. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3283727&tool=pmcentrez&rendertype=abstract.

[66] Josipa Bilic, Ya-Lin Huang, Gary Davidson, Timo Zimmermann, Cristina-Maria Cruciat, Mariann Bienz, and Christof Niehrs. Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. *Science (New York, N.Y.)*, 316(5831):1619–22, June 2007. ISSN 1095-9203. doi: 10.1126/science.1137065. URL http://www.ncbi.nlm.nih.gov/pubmed/17569865.

[67] Keith a Wharton. Runnin' with the Dvl: Proteins That Associate with Dsh/Dvl and Their Significance to Wnt Signal Transduction. *Developmental Biology*, 253 (1):1–17, January 2003. ISSN 00121606. doi: 10.1006/dbio.2002.0869. URL http://linkinghub.elsevier.com/retrieve/pii/S0012160602908699.

[68] John B Wallingford and Raymond Habas. The developmental biology of Dishevelled: an enigmatic protein governing cell fate and cell polarity. *Development (Cambridge, England)*, 132(20):4421–36, October 2005. ISSN 0950-1991. doi: 10.1242/dev.02068. URL http://www.ncbi.nlm.nih.gov/pubmed/16192308.

[69] Xin Zeng, He Huang, Keiko Tamai, Xinjun Zhang, Yuko Harada, Chika Yokota, Karla Almeida, Jianbo Wang, Brad Doble, Jim Woodgett, Anthony Wynshaw-Boris, Jen-Chieh Hsieh, and Xi He. Initiation of Wnt signaling: control of Wnt coreceptor Lrp6 phosphorylation/activation via frizzled, dishevelled and axin functions. *Development (Cambridge, England)*, 135(2):367–75, January 2008. ISSN 0950-1991. doi: 10.1242/dev.013540. URL http://www.ncbi.nlm.nih.gov/pubmed/18077588.

[70] Vincent F Taelman, Radoslaw Dobrowolski, Jean-Louis Plouhinec, Luis C Fuentealba, Peggy P Vorwald, Iwona Gumper, David D Sabatini, and Edward M De Robertis. Wnt signaling requires sequestration of glycogen synthase kinase 3 inside multivesicular endosomes. *Cell*, 143(7):1136–48, December 2010. ISSN 1097-4172. doi: 10.1016/j.cell.2010.11.034. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3022472&tool=pmcentrez&rendertype=abstract.

[71] Akira Kikuchi and Hideki Yamamoto. Regulation of Wnt signalling by receptor-mediated endocytosis. *Journal of biochemistry*, 141(4):443–51, April 2007. ISSN 0021-924X. doi: 10.1093/jb/mvm061. URL http://www.ncbi.nlm.nih.gov/pubmed/17317692.

[72] Pilong Li, Sudeep Banjade, Hui-Chun Cheng, Soyeon Kim, Baoyu Chen, Liang Guo, Marc Llaguno, Javoris V Hollingsworth, David S King, Salman F Banani, Paul S Russo, Qiu-Xing Jiang, B Tracy Nixon, and Michael K Rosen. Phase transitions in the assembly of multivalent signalling proteins. *Nature*, 483(7389):336–340, March 2012. ISSN 1476-4687. doi: 10.1038/nature10879. URL http://www.ncbi.nlm.nih.gov/pubmed/22398450.

[73] J Susie Zoltewicz, Amir M Ashique, Youngshik Choe, Gena Lee, Stacy Taylor, Khanhky Phamluong, Mark Solloway, and Andrew S Peterson. Wnt Signaling Is Regulated by Endoplasmic Reticulum Retention. *PLoS ONE*, 4(7):e6191, 2009. ISSN 19326203. doi: 10.1371/journal.pone.0006191. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2703784&tool=pmcentrez&rendertype=abstract.

[74] A Salic, E Lee, L Mayer, and M W Kirschner. Control of beta-catenin stability: reconstitution of the cytoplasmic steps of the wnt pathway in Xenopus egg extracts.

Molecular cell, 5(3):523–32, March 2000. ISSN 1097-2765. URL http://www.ncbi.nlm.nih.gov/pubmed/10882137.

[75] Satoshi Ikeda, Shosei Kishida, Hideki Yamamoto, Hiroshi Murai, S Koyama, and A Kikuchi. Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK-3beta and beta-catenin and promotes GSK-3beta-dependent phosphorylation of beta-catenin. *The EMBO journal*, 17 (5):1371–84, March 1998. ISSN 0261-4189. doi: 10.1093/emboj/17.5.1371. URL http://www.nature.com/emboj/journal/v17/n5/abs/7590852a.htmlhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1170485&tool=pmcentrez&rendertype=abstract.

[76] B R Henderson. Nuclear-cytoplasmic shuttling of APC regulates beta-catenin subcellular localization and turnover. *Nature cell biology*, 2(9):653–60, September 2000. ISSN 1465-7392. doi: 10.1038/35023605. URL http://www.ncbi.nlm.nih.gov/pubmed/10980707.

[77] B Rubinfeld, D a Tice, and P Polakis. Axin-dependent phosphorylation of the adenomatous polyposis coli protein mediated by casein kinase 1epsilon. *The Journal of biological chemistry*, 276(42):39037–45, October 2001. ISSN 0021-9258. doi: 10.1074/jbc.M105148200. URL http://www.ncbi.nlm.nih.gov/pubmed/11487578.