Legend:

- Entity — (ellipse)
- Activity — (rectangle)
- Activity produces entity — (rectangle ← ellipse)
- Activity uses entity — (ellipse ← rectangle)
- Building sim. model — (grey rectangle)
- Calibrating sim. model — (yellow rectangle)
- Validating sim. model — (green rectangle)
- Analyzing sim. model — (red rectangle)
- Research question / aim of the study — (red)
- Assumption — (purple)
- Requirement — (green)
- Data — (yellow)
- Experiment — (orange)
- Qualitative model — (cyan)
- Simulation model — (blue)

Lee et al. 2003

Cho et al. 2006

Van Leeuwen et al. 2007

RQ1 Research question

Type	Label
Description	"Two main hypotheses have been proposed concerning the balance between β-catenin's adhesive and transcriptional functions: either β-catenin's fate is determined by competition between its binding partners, or Wnt induces folding of β-catenin into a conformation allocated preferentially to transcription" → "a series of in silico experiments and compare the behaviour of systems governed by each hypothesis"
Study	van Leeuwen et al. 2007

QM1 Qualitative model

Type	Label
Description	"As such it differs from the model proposed by Lee et al. (2003) and extended by Cho et al. (2006) in several ways. Firstly, we allow for competition between signalling and cell–cell adhesion. We also distinguish two conformations of β-catenin that differ in their binding affinities for E-cadherin. The emphasis of our analysis is also slightly different. Given that not all model parameters have been measured, we aim to reveal generic properties of the system."
Reference	Figure 2 and Figure 4
Species	APC (destruction) complex, axin, cell-cell adhesion molecules (e.g., α-catenin and/ or E-cadherin), transcription factors (e.g., BCL9/Legless and/or TCF), Wnt target protein, β-catenin
Compartments	Cytosol
Study	van Leeuwen et al. 2007

A1 Assumption

Type	Label
Description	"we assume that all kinetic reactions take place within a single cellular compartment (i.e. no distinction between cytoplasmic, nuclear and membrane-bound) and that the size of this compartment remains constant during the simulation period considered"
Category	Physical compartment (290)
Study	van Leeuwen et al. 2007

A2 Assumption

Type	Label
Description	"we assume that phosphorylation events (...) are irreversible"
Category	Phosphorylation (216)
Study	van Leeuwen et al. 2007

A3 Assumption

Type	Label
Description	"we assume that phosphorylation events (…) are irreversible"
Category	Irreversible process (651)
Study	van Leeuwen et al. 2007

A4 Assumption

Type	Label
Description	"assuming that, once in the nucleus, the two forms of β-catenin possess the same ability to induce gene expression."
Category	Transcription (183)
Study	van Leeuwen et al. 2007

A5 Assumption

Type	Label
Description	"C_c (closed-form β-catenin) and C_o (open-form β-catenin) do not differ in their binding affinities for the destruction complex"
Category	Kinetic constant (9)
Study	van Leeuwen et al. 2007

A6 Assumption

Type	Label
Description	"two β-catenin conformations, C_c and C_o, differ neither in their degradation rates nor in their binding affinities for the transcription molecules"
Category	Kinetic constant (9)
Study	van Leeuwen et al. 2007

A7 Assumption

Type	Label
Description	"constant Wnt signal S_∞, with $0 \leq S_\infty \leq 1$"
Category	Concentration of reactant (509)
Study	van Leeuwen et al. 2007

A8 Assumption

Type	Label
Description	"Under hypothesis H1 ('one molecular form of β-catenin'), the rate of Tyrphosphorylation is independent of Wnt"
Category	Kinetic constant (9)
Study	van Leeuwen et al. 2007

A9 Assumption

Type	Label
Description	"Under hypothesis H1 ('one molecular form of β-catenin'), the rate of Tyrphosphorylation is independent of Wnt"
Category	Phosphorylation (216)
Study	van Leeuwen et al. 2007

A10 Assumption

Type	Label
Description	"under hypothesis H2 ('two molecular forms of β-catenin'), the rate of Tyrphosphorylation is an increasing function of the Wnt signal"
Category	Kinetic constant (9)
Study	van Leeuwen et al. 2007

A11 Assumption

Type	Label
Description	"under hypothesis H2 ('two molecular forms of β-catenin'), the rate of Tyrphosphorylation is an increasing function of the Wnt signal"
Category	Phosphorylation (216)
Study	van Leeuwen et al. 2007

BSM1 Building simulation model

Type	Label
Description	Construction of simulation model
Study	van Leeuwen et al. 2007

SM1 Simulation model

Type	Label
Description	"The model consists of a system of ordinary differential equations (ODEs) that describes the changes in concentration of eleven compounds involved in Wnt signaling (Table 1)", eqs. (1)-(11), reaction rates in Table 2
Reference	https://www.ebi.ac.uk/biomodels/MODEL2001090001
Study	van Leeuwen et al. 2007

ASM1 Analyzing simulation model

Type	Label
Description	Tests of hypotheses
Study	van Leeuwen et al. 2007

SE1 Experiment

Type	Label
Description	"A sensitivity analysis of the equilibrium solution upon the parameter values is performed in Appendix"
Reference	Not available
Category	Sensitivity analysis
Study	van Leeuwen et al. 2007

SD1 Data

Type	Label
Description	Simulation results of SE1
Reference	Table A.2
Related to	SE1
Study	van Leeuwen et al. 2007

SE2 Experiment

Type	Label
Description	"Effects of continuous Wnt-exposure on gene expression" and "on cell-cell adhesion" (transcription complexes and target protein over time for H1 and H2)
Reference	Not available
Category	Parameter scan
Study	van Leeuwen et al. 2007

SD2 Data

Type	Label
Description	Simulation results of SE2
Reference	Summary Box 1 → Figure 5 and Figure 6
Related to	SE2
Study	van Leeuwen et al. 2007

SE3 Experiment

Type	Label
Description	"Response of wild-type (wt) and mutant cells to a Wnt gradient."
Reference	Not available
Category	Perturbation
Study	van Leeuwen et al. 2007

SD3 Data

Type	Label
Description	Simulation results of SE3
Reference	Summary Box 2 → Figure 7
Related to	SE3
Study	van Leeuwen et al. 2007

SE4 Experiment

Type	Label
Description	"Impact of changes in E-cadherin expression (occurring at time $\tau=0$) on cell–cell adhesion and Wnt signalling" and "impact of E-cadherin expression on Wnt target gene expression in wild-type cells (black bold lines) and APC mutants"
Reference	Not available
Category	Parameter scan
Study	van Leeuwen et al. 2007

SD4 Data

Type	Label
Description	Simulation results of SE4
Reference	Summary Box 3 → Figure 8 and Figure 9
Related to	SE4
Study	van Leeuwen et al. 2007

BSM2 Building simulation model

Type	Label
Description	Model extension
Study	van Leeuwen et al. 2007

SM2 Simulation model

Type	Label
Description	Extended SM1: "Wnt-mediated activation of AXIN2 expression, which gives rise to a negative feedback loop capable of downregulating β-catenin levels. This mechanism can easily be incorporated into our model"
Reference	Not available
Study	van Leeuwen et al. 2007

ASM2 Analyzing simulation model

Type	Label
Description	Analyzing feedback loop
Study	van Leeuwen et al. 2007

SE5 Experiment

Type	Label
Description	"Impact of the axin2 transcriptional feedback loop"
Reference	Not available
Category	Parameter scan
Study	van Leeuwen et al. 2007

SD5 Data

Type	Label
Description	Simulation results of SE5
Reference	Figure 10
Related to	SE5
Study	van Leeuwen et al. 2007