		Hypothesis-driven methods	
Ref.	Pathway models		Features of the study
[36]	TGF-BETA		Pathway response with respect to parameters perturbation
			Effects of clathrin and non-clathrin dependent endocytosis
[37]			transient versus sustained response
			sensitivity to ligand doses at various timescales
[38]			Dynamics of nuclear SMAD2 accumulation
			SMAD2/4 concentration in function of changes in parameters
[39]	RTK		EGFR signaling response in function of ligand concentration
			signal efficacy in function of velocity of receptor activation
[40]			Comparison between FGFR and EGFR signaling response
[41]			Combining EGFR and IRT pathways
			Effects of feedback loops between EGFR and IR cascades
			Dose dependence of pathway responses
[42]			Role of ROCK in feedback loops involved in EGFR
[43]			EGFR: transient response versus sustained response
[44]			EGFR: contextual dependency of the parameter sensitivity
			to the experimental conditions
[45]			MAPK: identification of a negative feedback loop controlling
			the desensitization of signals
[46]			MAPK: Relationship between negative feedback and robustness
[47]			MAPK: Relationship between negative feedback and oscillations
[49]	NF-kB		Analysis of oscillatory behavior of nuclear NF-kB concentration
[50]			links between negative feedback and cellular heterogeneity
[52]			Identification of a delayed negative feedback loop
			responsible for oscillations in NF-kB translocation
[53]			Analysis of importance of IkB degradation using sensitivity analysis
[54, 55]	Apoptosis		Oscillation and negative feedback involving p53 and MDM2
[56]			Bistability and positive feedback loop between p53 and AKT
[57]			Analysis of topological structures controlling bistability switch
[58]	WNT		Positive feedback loop between WNT and ERK pathways
[59]			Sustained versus transient WNT stimulation
[60]			Oscillations controlled by negative feedback
[62]	mTOR		dynamical relationships between insulin regulation
			and gene transcription
[63]			amino-acid dependent regulation of mTORC1 activation
		Data-driven methods	
		Third generation methods	
	Name of the method		Features of the method
[76]	PLAGE		Computes pairwise comparisons of pathway activity levels
			Identify metagene using SVD
[77]	SPIA		Compute perturbation probabilities using DEGs of pathways
[79]	DART		Infer the activity of pathways using a set of DEGs
			Verify the coherence of the prior pathway information and topology
		Fourth generation methods	
	Name of the method	Topological decomposition	Features of the method
[80]	Clipper	Topological decomposition	Identify dynamic perturbation of pathways
[]		using cliques on DAG	
[82]	Pathiways	Use circuits in pathways (Dijkstra)	Compute the probability of signal transmission along the pathways
[21]	sub-SPIA	Use Minimal Spanning Tree (MST)	Mapping of DEGs on pathway maps
[83]	IPANDA	Use concept of gene modules	Pathway activation scores using clustering

Table 1: Summary of the mechanism-based model developed for hypothesis-driven studies and summary of the main data-driven methods available for pathway pertrubation analysis.