

Receptor activation mechanism selection in the JAK–STAT signalling pathway model

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1 Introduction

- JAK–STAT pathway
- Receptor activation models

2 Models comparison

- Bayesian ranking
- (Global) Sensitivity Analysis

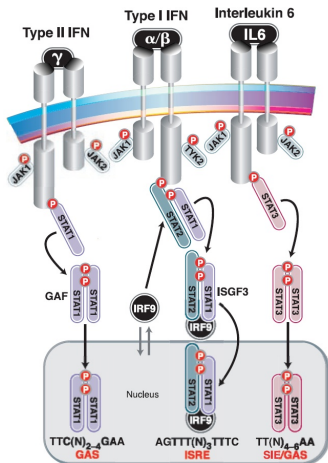
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Family of the JAK–STAT pathways



Responsibilities

- Antiviral, innate and adaptive immunity control.
- Anti-tumor immune responses.

(STAT1/2 pathways)

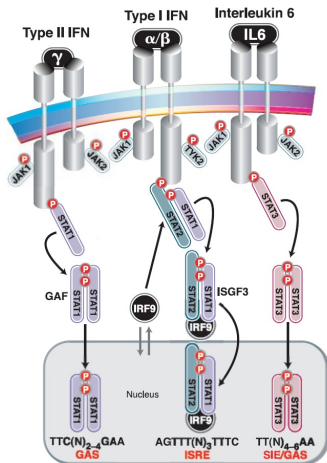
- Cell growth and apoptosis processes regulation.

- Embryonic stem cell self-renewal control.

(STAT3/5 pathways)

Aaronson and Horvath (2002)

JAK-STAT pathway signal transduction

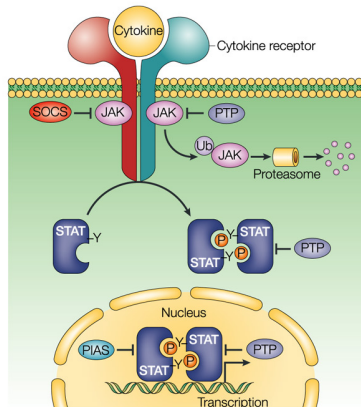


Aaronson and Horvath (2002)

Signal flow

- 1 Ligand binding induces receptor activation.
- 2 Activated receptor phosphorylates STATs which dimerize and are translocated to nucleus.
- 3 STAT dimer induces transcription and translation of dozens of target genes.

JAK-STAT pathway signal transduction



Nature Reviews | Immunology

Shuai and Liu (2005)

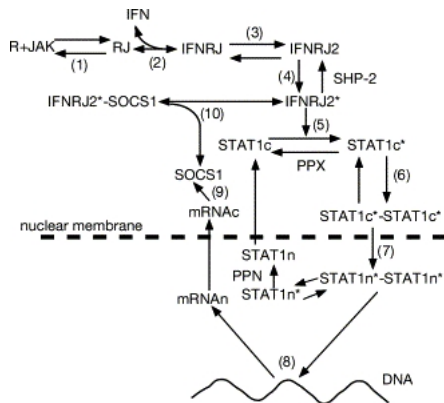
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Negative regulation

- 1 Protein Tyrosine Phosphatases (PTPs)
- 2 Inhibitors (SOCS, PIAS).
- 3 Proteolysis (via ubiquitination).

JAK-STAT pathway model



Yamada et al. (2003)

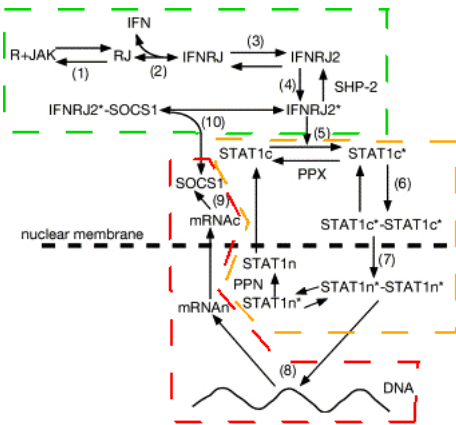
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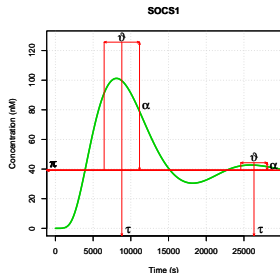
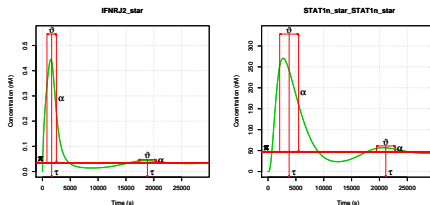
Negative regulation

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JAK-STAT pathway model numerical simulations



Yamada et al. (2003)



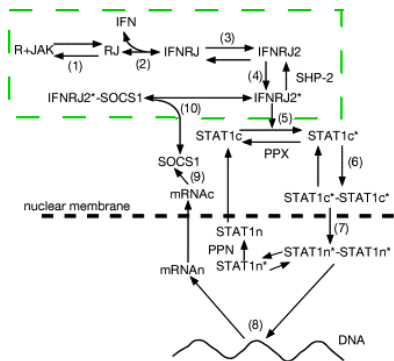
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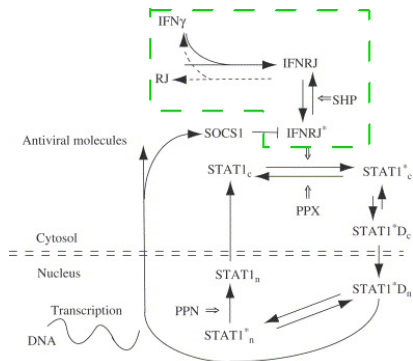
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Cytokine receptor activation inconsistencies



Yamada et al. (2003)

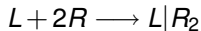
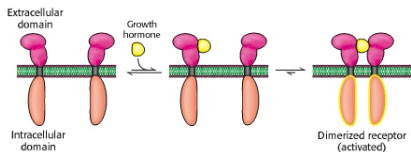


Shudo et al. (2007)

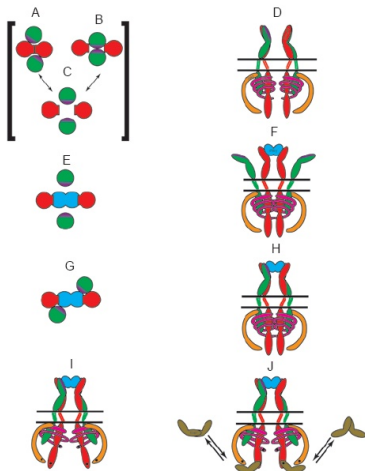
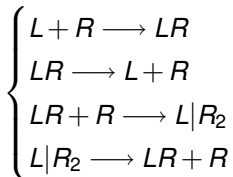
Shudo et al. (2007): "However, evidence has shown that the receptor dimers exist constitutively on cell membrane in the absence of IFN γ . Therefore, in this paper, we remove the receptor dimerization step and also assume that JAK is constitutively associated with the receptor."

Views on the receptor activation mechanism

Berg et al. (2006)

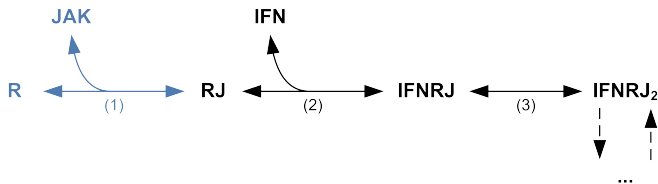


decomposes to

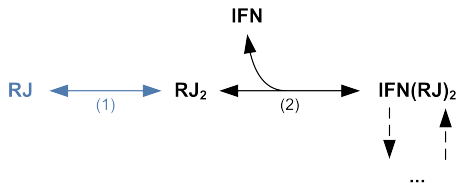


Krause et al. (2006)

Receptor activation models

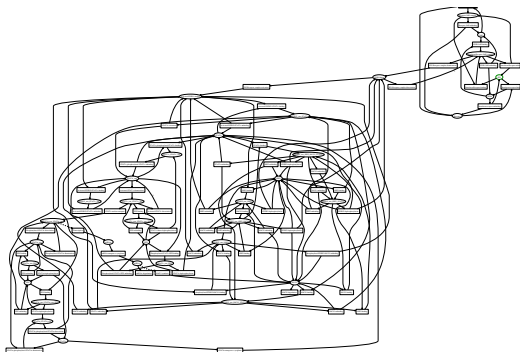


(d) Original model and No JAK variant.



(e) IFN to dimer binding case and its variant without receptor dimerization step.

Receptor activation models



Model	#Species	(rec)	#Params	(rec)
Original	34	(7)	72	(10)
No JAK	32	(4)	66	(4)
IFN to dimer	32	(4)	66	(4)
No dimerization	31	(2)	64	(2)

Dilemma

- Can you say that one model is better than the other?
- How does the small changes in the “ODEs network” influence the dynamics?

Headaches

- All JAK–STAT pathway models perfectly fit the Original model simulations results.
- Arguably (artificial) data goodness of fit criteria is not the best to assess models in context of biological systems inherent uncertainty/stochasticity.

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Biochemical models bayesian inference

Marginal likelihood

$$\Pr(D|M, \theta) = \prod_{i=1}^T f_{x_i}^{M, \theta}(D_i),$$

where $f_{x_i}^{M, \theta}$ is a pdf of $Norm(\phi(M, \theta, x_i), \sigma)$.

Likelihood of reproducing data D of T iid data points with model M .

Bayes Factor (BF)

$$B_{12} = \frac{\Pr(D|M_1)}{\Pr(D|M_2)} = \frac{\int \Pr(D|M_1, \theta_1) \cdot \Pr(\theta_1|M_1) d\theta_1}{\int \Pr(D|M_2, \theta_2) \cdot \Pr(\theta_2|M_2) d\theta_2}$$

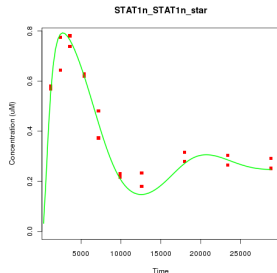
Summary of the evidence provided by the data D in favor of one hypothesis M_1 as opposed to another M_2 .

- Unbiased estimates of marginal likelihood can be obtained e.g. by **Annealed Importance Sampling (AIS)**.
- Software tool: BioBayes (Vyshemirsky and Girolami (2008)).

JAK-STAT receptor activation models bayesian inference

Setting

- 2 manually selected 10 timepoints series of species STAT1n_STAT1n_star with random noise ($Norm(x_i, 0.05)$)
- Receptor module parameters k_j priors set to $Gamma(1, k_j^0)$.



AIS estimate of $\ln(\Pr(D|M_i))$

Model	Mean	SD
Original	25.2573064	0.0497029
No JAK	25.7705084	0.0185170
IFN to dimer	25.7278839	0.0049351
No dimerization	26.0244009	0.0553714

JAK-STAT receptor activation models bayesian inference

$\log_{10}(\text{BF})$

	Original	No JAK	IFN to dimer	No dimerization
Original				
No JAK	0.2228808		0.0185116	
IFN to dimer	0.2043692			
No dimerization	0.3331449	0.1102641	0.1287757	

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BF evidence support
(Jeffreys'61)

	$\log_{10}(\text{BF})$
None	$[0, 0.5]$
Substantial	$(0.5, 1]$
Strong	$(1, 2]$
Decisive	$(2, \infty]$

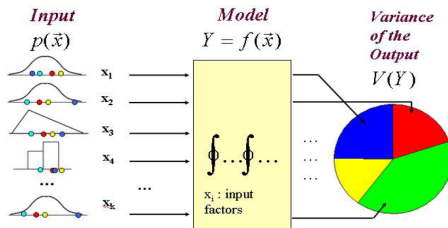
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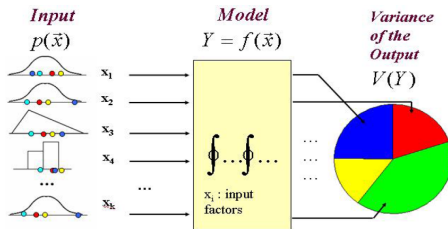
Sensitivity analysis (SA) outline



SA possible goals

- Finding essential parameters (research prioritization).
- Identifying insignificant parameters (model reduction; parameters estimation).
- Parameters clustering.
- Finding functionally critical regions.
- Models comparison.
- ...

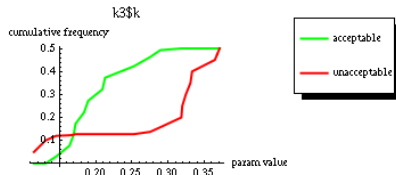
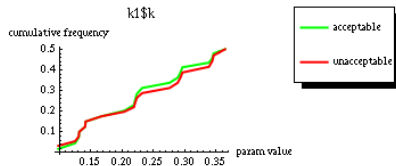
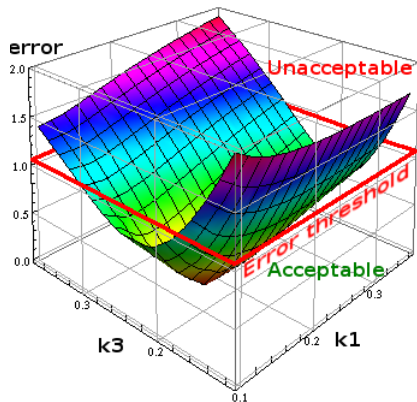
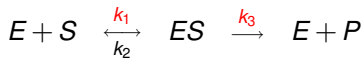
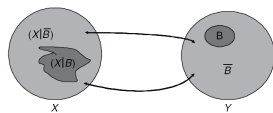
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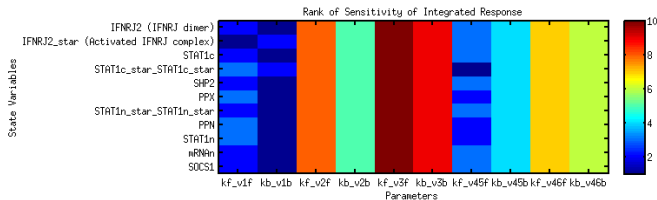
Why Global SA?

- Local coefficients can be misleading for nonlinear models.
- Biochemical reactions models are usually highly non-linear.
- We want to use coefficients independent of the model (e.g. it's linearity).

Multi-Parametric Sensitivity Analysis (MPSA; by example)



JAK-STAT models receptor module MPSA



Benchmark quantity: inactive receptor complex formation sensitivity.

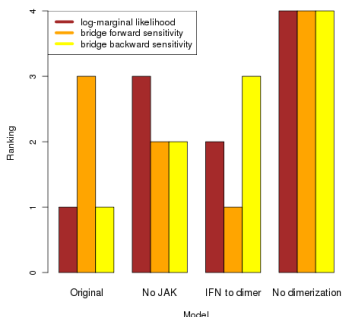
Model	Fwd	Bckwd
Original	0.52910	0.48788
No JAK	0.47249	0.49156
IFN to dimer	0.45781	0.50588
No dimerization	0.58701	0.56271

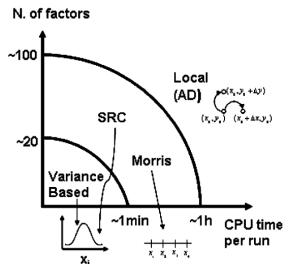
JAK-STAT models receptor module GSA vs. BF

- No dimerization model is the most ductile (in terms of noised data fit) and the least robust (in terms of original behaviour).
- In context of the range of responsibilities of JAK-STAT pathways and parsimony No dimerization receptor activation variant is recommended.
- With SA we can do more than just small receptor module. . .

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Saltelli et al. (2005)

- Choose your method.
- Confucius says: to perform MPSA (or SOBOL) you have to do screening for important parameters.

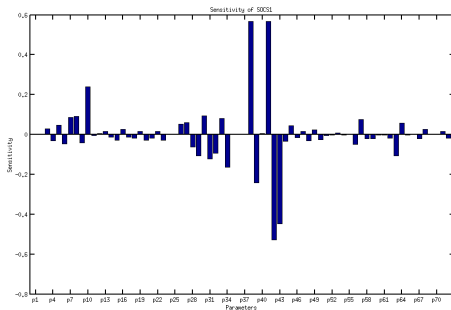
normalized Local Sensitivity Coefficient (nLSC)

$$S_{X_i}^{\log}(\mathbf{x}) = \frac{x_i}{y} \frac{\partial Y}{\partial X_i} \Big|_{\mathbf{x}=\mathbf{x}}, \quad \mathbf{x} = \bar{\mathbf{X}} (x_i = \bar{X}_i), y = \bar{Y}$$

Parameters' screening (WALS)

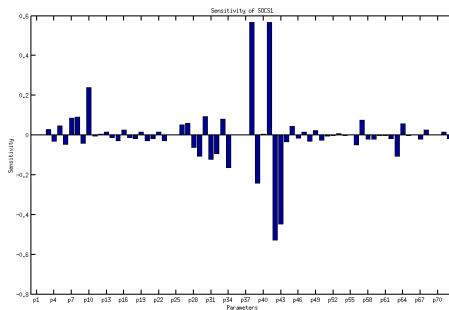
Weighted Average of Local Sensitivites (WALS)

- Calculate nLSC approximates at multiple (10k) random points.
- Take weighted average of them to approximate the global sensitivity. (Boltzmann–distribution weighting function.)
- An alternative: elementary–effects Morris' method.
- Tool: SBML-SAT (Zi et al. (2008)).



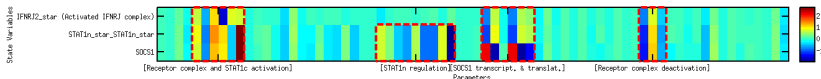
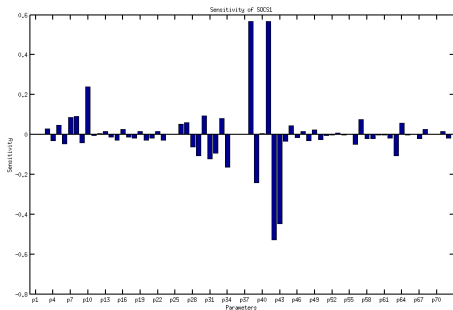
Parameters' screening (WALS)

Parameter	Reaction
kf_v4	IFN-Receptor complex activation
kf_v5f	Activated IFNRJ2-STAT1c binding
kf_v6	STAT1c activation
kf_v16	STAT1c-nuclear transport
kf_v17f	Phosphorylated STAT1n dimerization
kb_v17b	Phosphorylated STAT1n dissociation
kf_v18f	PPN binding
kb_v18b	PPN unbinding
kf_v19	STAT1n dephosphorylation
kf_v20f	PPN binding
kb_v20b	PPN unbinding
kf_v21	STAT1n dephosphorylation
ka_v24	Transcription
kb_v24	Transcription
kf_v26	SOCS1 synthesis
kf_v27	mRNAC degradation
kf_v28	SOCS1 degradation
kb_v36b	SHP2 unbinding
kf_v42f	SOCS1 binding
kb_v42b	SOCS1 unbinding

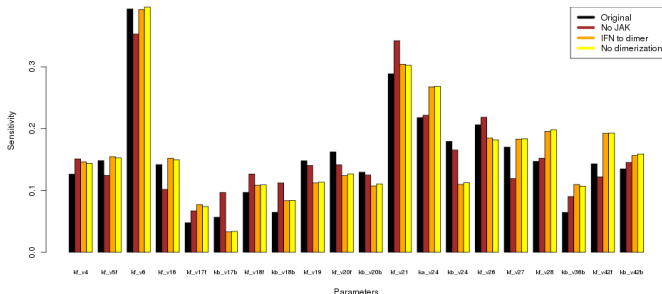


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kf_v5f	Activated IFNRJ2-STAT1c binding
kf_v6	STAT1c activation
kf_v16	STAT1c-nuclear transport
kf_v17f	Phosphorylated STAT1n dimerization
kb_v17b	Phosphorylated STAT1n dissociation
kf_v18f	PPN binding
kb_v18b	PPN unbinding
kf_v19	STAT1n dephosphorylation
kf_v20f	PPN binding
kb_v20b	PPN unbinding
kf_v21	STAT1n dephosphorylation
ka_v24	Transcription
kb_v24	Transcription
kf_v26	SOCS1 synthesis
kf_v27	mRNAC degradation
kf_v28	SOCS1 degradation
kb_v36b	SHP2 unbinding
kf_v42f	SOCS1 binding
kb_v42b	SOCS1 unbinding

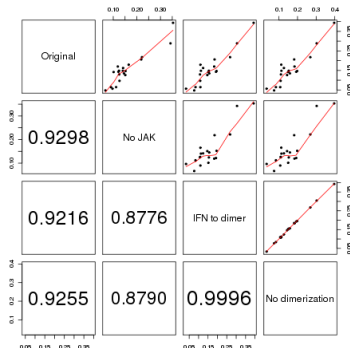


JAK-STAT models MPSA



- Most significant differences in SOCS parameters.
- Dimerized models more sensitive in negative autoregulation.
- No JAK model robustness is slightly more scattered.

JAK-STAT models MPSA

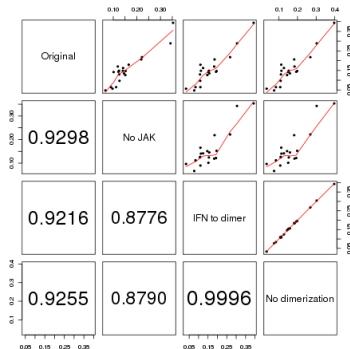


Shannon entropy:

Original	2.872931
No JAK	2.900137
IFN to dimer	2.875043
No dimerization	2.874591

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mean	Original	No JAK	IFN to dimer	No dimerization
MPSA SC	0.137397730	0.139193220	0.139540105	0.139734990
SOBOL TE	0.097850699	0.090896033	0.097909986	0.106474585
nMSSE	0.008711590	0.008684724	0.009369146	0.011586549

Summary

- Yamada et al. (2003) and Shudo et al. (2007) models of the JAK–STAT pathway receptor activation are **indistinguishable** by data fit criteria, and do not display major differences in assessments based on reaction rates parameters variation.
 - The good: small modelling inadequacies or simplifications are not crucial for the dynamics.
 - The bad: no easy way to select between biochemical reaction models details.
 - (The ugly: prevailing sense of vanity.)
- Outlook
 - Used methods results certainty assessment (including increasing data noise parameter etc).
 - JAK–STAT SA wrt initial conditions and TPV–based robustness analysis.
 - Delayed differential equation simplification (cut everything below the receptor).

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