JAK-STAT Signalling as Example for a Database-Supported Modular Modelling Concept

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Abstract. We present a detailed model of the JAK-STAT pathway in IL-6 signaling as non-trivial case study demonstrating a new database-supported modular modeling method. A module is a self-contained and autonomous Petri net, centred around an individual protein. The modelling approach allows to easily generate and modify coherent, executable models composed from a collection of modules and provides numerous options for advanced biomodel engineering.

1 Background

The evolutionary conserved JAK-STAT pathway is one of the major signalling components in most of the eukaryotic cells [4]. JAK-STAT transmits stimuli from the cell membrane to the nucleus and is therefore mainly responsible for the gene regulation to control cell growth, differentiation and death. The dysfunctionality of the JAK-STAT pathway can lead to cancers or immune deficiency syndromes. An outstanding characteristic of the JAK-STAT pathway is the extensive crosstalk among its components (Fig. 1.A). The JAK protein as well as the STAT protein can appear in different isoforms that interact with several cytokine receptors and gene promoters, which leads to a combinatorial problem. It is a challenging task to explore the extensive cross-talk of the regulatory components, which we address by a new modular approach to biomodel engineering.

2 Results and Conclusions

Instead of creating a large monolithic mathematical model, we have developed a bottom-up modular description of the JAK-STAT pathway [1]. Each module as model component represents an individual protein and all its reactions with other interaction partners. In addition, each module contains metadata for documentation purposes; it, thus, corresponds to a wiki-like mini-review. Modules can be linked to each other in arbitrary combination accounting for the combinatorial complexity of regulation (Fig. 1.B). A coherent network is obtained via specific connection interfaces, these are identical shared subnets describing the interaction between to proteins. The characteristic advantage of the approach is that no further modifications are required in order to obtain an executable model. As modelling framework we chose Petri nets, which are intuitively understandable, allow

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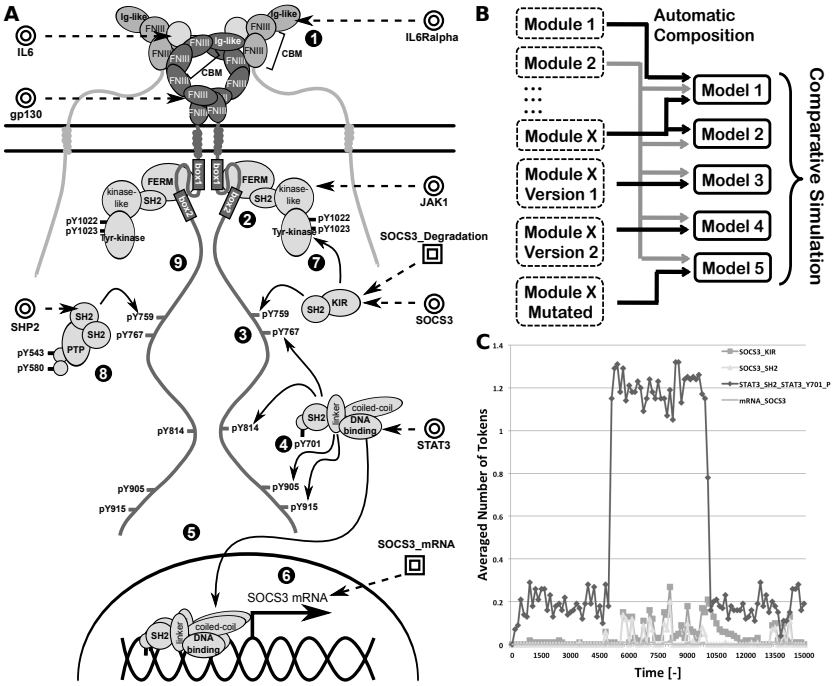

Fig. 1. JAK/STAT pathway in IL-6 signalling. (A) Mechanism of the JAK-STAT pathway in IL-6 signaling consists of the following steps: (1) Binding of interleukin-6 (IL-6) to IL6-receptor α (IL-6Rα) and glycoprotein gp130 and thereby formation of an active receptor complex, (2) activation of the JAK kinase by transphosphorylation, (3) phosphorylation tyrosine residues of gp130 by active JAK, (4) binding of STAT to phosphotyrosines of gp130 and phosphorylation by STAT, (5) dimerization of phosphorylated STATs and translocation to the nucleus, (6) activation of transcription of multiple genes, including SOCS, (7) binding of SOCS to gp130 and thereby inhibition of JAK (negative feedback), (8) dephosphorylation of gp130 by the SHP2 phosphatase, (9) phosphorylation of SHP2 by JAK and thereby inhibition of SHP2 (negative feedback); see [4] for a detailed review. The molecular mechanisms of each involved protein have been modelled in the form of separate Petri nets (modules) indicated by the corresponding coarse places (two nested circles) representing the underlying Petri net. The synthesis and degradation of SOCS3 are modelled within a biosynthesis/degradation module as indicated by the corresponding coarse transition (two nested squares) representing the underlying Petri net. The figure was redrawn from [4]. **(B)** Modules can be reused and recombined in various combinations. The obtained models can be used to test for the effect of alternative or modified reaction mechanisms. **(C)** Here, we employed stochastic simulations to demonstrate the response of the involved components dependent on IL-6 supply. IL-6 is injected only in the second third of the simulation time. The signalling activity increases during stimulation. The system shows basal activity before and after the stimulation.

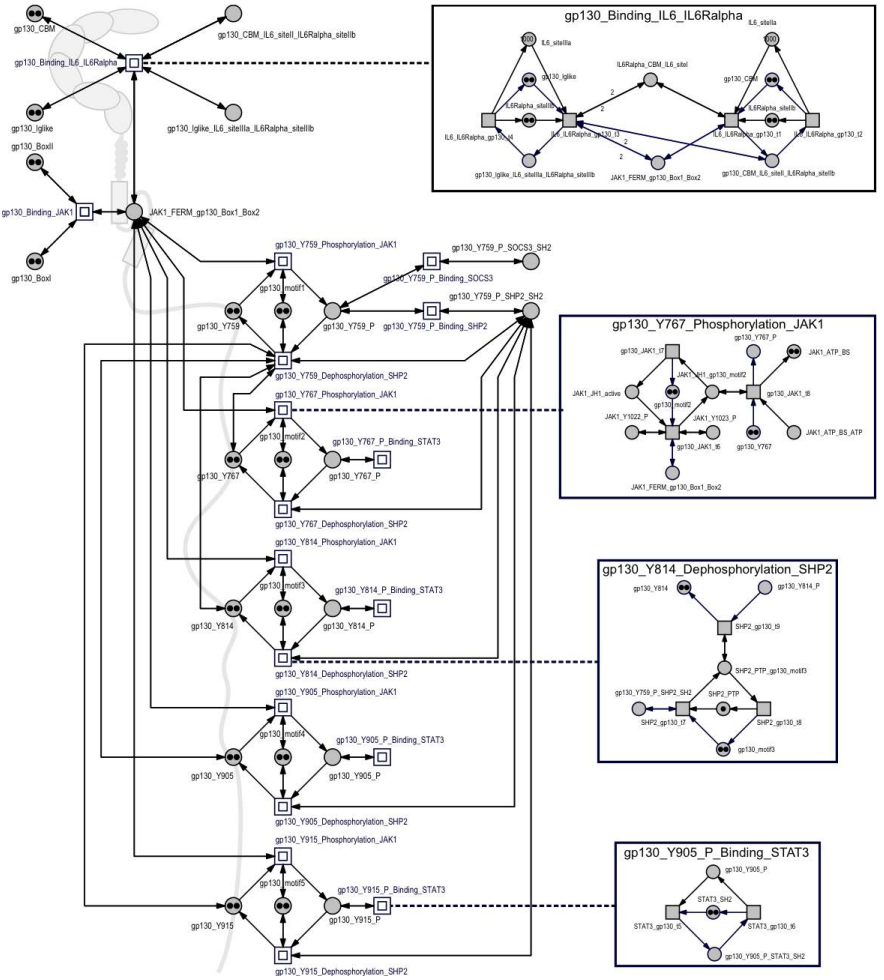

Fig. 2. The gp130 module. The extracellular part of the gp130 glycoprotein consists of the Ig-like domain and a cytokine-binding site, which are responsible for complex formation with IL-6 and IL6-Rα. The intracellular part of gp130 has an interbox 1-2 region, where JAKs are constitutively bound. Downstream of this binding site the gp130 receptor has several important tyrosine residues, which are phosphorylated by activated JAK. The phosphotyrosine pY759 is the specific binding site of SHP2 and SOCS isoforms via their SH2 domain, where STAT isoforms can interact via their SH2 domain with the other phosphotyrosines. In the corresponding Petri net model of gp130, the extracellular binding site of IL-6 and the intracellular binding site of JAK1 to the Box 1 and Box 2 sites are represented as coarse transitions. Three coarse transitions are assigned to each tyrosine residue downstream of Y759 describing the phosphorylation by JAK1, the dephosphorylation by SHP2, and the binding interaction with STAT3 (in the case of Y759 two coarse transitions are used to represent the interaction with SHP2 and SOCS3). The boxed panels on the right side of the Figure exemplify four subnets that are included in the corresponding coarse transitions in the gp130 module.

visual modelling and are executable. Petri nets have been shown to be perfectly suited to describe the inherently concurrent mechanisms in biological systems [3]. For providing a proof-of-principle for our modular modelling concept, we focus on JAK-STAT signalling induced by the IL-6 cytokine with only one isoform of each protein involved (JAK1, STAT3, SOCS3, SHP2, gp130, IL-6R, IL-6). Accordingly we constructed seven protein modules, one mRNA module for SOCS3 biosynthesis and one SOCS3 degradation module. Exemplarily, we show here the module of gp130 (Fig. 2). The networks which can be generated from this set of modules consist of up to 90 places and 100 transitions. The modules are hierarchically designed to obtain a clear graphical representation of the reaction mechanisms. The composed models comprise up to 58 pages with a nesting depth of 4. The modules were created and composed with *Snoopy* [5] and the built-in simulator was used to run stochastic simulations (Fig. 1.C). Structural analysis was performed with *Charlie* [2] to validate the structure of each module (not shown here, see [1]).

The model can be extended to include transcriptional regulation by employing gene modules, mRNA modules, degradation modules, and causal interaction modules. We have established a prototype database with a publically accessible web-interface [1]. The database can manage multiple versions of each module by strict version control. It supports the curation, documentation, and update of individual modules and the subsequent automatic composition of complex models, without requiring mathematical skills. The case study has demonstrated that modular modelling is ideally suited for exploring signalling networks with extensive cross-talk like in JAK-STAT. The supporting database essentially contributes to a powerful, comprehensive and unifying platform for modelling and analysis. The platform can be easily used by wet lab scientists to re-engineer individual modules in order to test the global consequences of alternative reaction mechanisms [2] (Fig. 1.B). The database associates meta-data to the individual modules, and thus is ideally suited for the documentation and validation of alternative reaction mechanisms. In the context of advanced biomodel engineering our modelling framework encourages the automated generation of biologically realistic synthetic and synthetically rewired network models.

References

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