Formalisation, visualisation and analysis of signal transduction networks with rxncon

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The metabolic modelling community has established the gold standard for bottom-up systems biology with formalisation and analysis of genome-scale models. However, it is difficult to apply these methods to large-scale signalling networks. Signal transduction networks have a key feature that distinguishes them from metabolic networks: Their components can encode information in internal states (e.g. phosphorylation of specific residues) and through complexation. This causes the combinatorial complexity, which leads to severe scalability issues with explicit modelling formalisms. Hence, different tools are needed to formalise, visualise and analyse large-scale signalling networks. We present rxncon, the reaction-contingency language, as a tool to formalise, visualise and analyse large-scale models of signal transduction. The language uses a bipartite definition with reactions and contingencies, where reactions are possible events and contingencies define constraints on these events. By defining elemental reactions and contingencies in terms of elemental states, i.e. states at specific residues and domains, the model definition can be made as complex and precise as the empirical data requires, but not more. Hence, scalability is limited by knowledge rather than by methodological issues. We support the language with a compiler which automates export of a rxncon model to different graphical and executable formats, which enables visualisation and simulation of even large-scale models. In particular, the rxncon regulatory graph makes it possible to visualise large-scale models of signal transduction networks in full mechanistic detail. Most recently, we used rxncon to compile, visualise and analyse a comprehensive model of the cell cycle in budding yeast, encompassing 229 proteins, at full mechanistic detail. Taken together, the rxncon language and toolbox enables the formalisation, visualisation and analysis of large-scale mechanistic models of signal transduction networks.