Additional file 1

Extended Legend to Figure 2

Figure 2 Petri nets as executable models of biochemical reactions. Petri nets are an intuitively understandable formal language to accurately describe biochemical reactions according to their molecular mechanism. Appropriate tools like Snoopy allow the direct execution of a Petri net to run simulations of the model. Having drawn the graphical representation of a Petri net in Snoopy, model equations required by the built-in simulators are automatically created in the background. Using the reversible phosphorylation of a protein as example, this figure briefly explains the Petri net formalism, gives an example of an executable model, and provides sufficient information for the non-expert to essentially follow the present work. (A) Biochemical reaction scheme of the phosphorylation of a transcription factor (TF) by a protein kinase and dephosphorylation of its phosphorylated form (TF-P) by a protein phosphatase. (B) Graphical elements of a Petri net and their use to model biochemical reactions. A Petri net is a bipartite graph composed of place(s), transition(s), arc(s), and token(s). Places represent biochemical components or states of a molecule. Transitions represent biochemical reactions. Arcs interconnect places and transitions and indicate the direction in which a reaction proceeds. The mere presence of a chemical compound is indicated by a token marking the respective place and its concentration may be represented by an integer number of tokens in the place. In so-called continuous Petri nets, the concentration of compounds is given by real numbers assigned to the places. Hybrid Petri nets may contain both types of places and may be used to simulate discrete events coupled by

continious changes of concentrations. (C) Petri net model of the reversible phosphorylation reaction shown in (A). Note that the model neglects formation and decay of enzyme-substrate complexes and hence will not show the effect of substrate saturation. Phosphorylated and dephosphorylated form of the transcription factor, the kinase and the phoshatase (PPTase) are represented as places. The token in place TF indicates that the transcription factor is in its dephosphorylated state. When transition t_1 fires, TF becomes phosphorylated by its kinase as indicated by the token moving from TF to TF-P. As the kinase is a catalyst which is not consumed by the reaction, the token is removed from and redelivered into the kinase place while the reaction occurs. The places TF and TF-P together form a so-called P-invariant. In the trivial case shown, the P-invariant means that the transcription factor will always be either in its phosphorylated or in its dephosphorylated form. In general, the weighted total number of tokens distributed among the places that form a P-invariant remains constant, no matter how often the transitions of the net will fire. The transitions t_1 and t_2 together form a so-called T-invariant. If all transitions of a T-invariant have fired, the marking of the net is back in its original state. (D) Coarse places and coarse transitions may be used to organize a Petri net into submodels. In the Petri net of panel (D), the kinase and the phosphatase reactions of (C) are lumped into a coarse transition. In Snoopy, coarse transitions represent submodels that are bordered by transitions whereas submodels represented by a coarse place are bordered by places. The Petri net of (C) for example could be represented in the form of one single coarse place. Coarse nodes, i.e. coarse places and coarse transitions, only serve to structure a Petri net into submodels, they do not enhance its expressiveness. Snoopy provides a command to bring submodels implemented as coarse nodes up to the top level, automatically displaying one coherent graph in which the interconnection of all nodes by arcs is displayed, no matter how deeply a

submodel has been nested. (E) The formation and decay and also the experimental addition or removal of biochemical components can be modeled by transitions [1, 2]. The kinetics in (F) was obtained by running (executing) the Petri net of (E) directly in Snoopy as a stochastic Petri net. It shows how the concentration of the phosphorylated transcription factor TF-P changes over time in response to the addition of kinase, the addition of phosphatase and the decay (or removal) of the kinase. At the beginning neither the kinase nor the phosphatase was present, only the unphosphorylated TF. At 25 time units a token was delivered to the kinase place by firing of t_3, after additional 25 time units a token was delivered to the phosphatase place by firing of t_5. After 75 time units the kinase was withdrawn by firing of t_4. The trace was obtained by averaging 1000 simulation runs.

References

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