Supplemental Figures
Captions

Figure S1: Example of a path. A path illustrates a series of reactions (instances of rules) that lead from a specified source observable to a specified target observable. A path is a non-repeating sequence that is reconstructed from a model simulation; only instances of rules that contributed to production of the target observable in a simulation are included in the illustration. Each instance of a rule in a path generates a chemical species that can be acted upon by the next rule instance until the target observable is reached. In this example, the source observable is an unphosphorylated monomeric receptor and the target observable is a phosphorlyated receptor dimer. This path represents the execution of Rules 1a, 1b, 2, and 3a. Note that the numbering of rules corresponds to the numbering of rules in Appendix S1 (ESI). Reaction rate constants are shown underneath reaction arrows. Reaction centers are highlighted using colors. Reaction centers that share the same color are modified by the same rule.

Figure S2: An influence map. An influence map reveals relationships among the rules of a model. An influence map indicates whether execution of one rule potentially increases (activates) or decreases (inhibits) the number of times another rule can be executed in a simulation. Incidences of activation and inhibition are represented with conventional activation (triangular) and inhibition (blunt) arrowheads. This figure shows the influence of the forward execution of Rule 2 on Rules 3a, 3b, and 5. Note that the numbering of rules corresponds to the numbering of rules in Appendix S1 (ESI). An influence map can be generated automatically from a rule set. This influence map was generated using RuleBase (http://www.rulebase.org) and redrawn for presentation.

Figure S3: SBGN-style diagram. The Systems Biology Graphical Notation (SBGN) provides a set of conventions for the representation of biochemical and cellular processes. Here, we have used features of SBGN to create an alternative drawing of the extended contact map shown in Fig. 4 in the main text. There are many minor stylistic differences between the extended contact map of Fig. 4 and the SBGN-style diagram shown here. More important differences arise because of the SBGN requirement for a machine-readable diagram. These differences include (a) a separate line for each interaction, avoiding forks and broken lines; and (b) annotation labels in boxes and linked to interaction lines to avoid ambiguity in assigning annotations to interactions. Note that the distinctions between solid and dotted lines discussed in the main text would not be compliant with SBGN. Nesting of physical entities has been proposed as an

extension of SBGN(http://sbgn.org/ER_development); however, this extension is not yet included in SBGN.

Figure S4: Representation of divisible proteins: a non-trivial example. A) Representation of the substructure of complement component C3. As indicated, C3 is composed of α and β chains linked by a disulfide bond, labeled SS. The α chain can be cleaved multiple times via proteolysis to yield various fragments, and a thioester bond is exposed after the initial cleavage event, which allows the C3b fragment to become conjugated to an acceptor via, for example, the formation of an ester bond between Q1013 in C3 and the hydroxyl group of a carbohydrate. Fragments that remain intact during the proteolytic cascade illustrated in panel B are depicted as white component boxes. These fragments include C3a, $\alpha'1$, C3g, C3d, C3f, and $\alpha'2$. Intermediate fragments, C3b, iC3b, and C3dg, are indicated by shaded areas attached to note boxes. The major proteolytic fragment, C3c, is also indicated by a shaded area attached to a note box. C3c is composed of the β chain and two fragments of the α chain, $\alpha'1$ and $\alpha'2$. Note that this panel is intended to illustrate how C3 might be represented in a map guide, where *ad hoc* illustrations can be used to supplement the representation of a molecule in a map. B) Extended contact map depicting proteolytic cleavage of C3 to C3d. The process begins when the N-terminal region of the α chain is cleaved by C3 convertase, liberating C3a and exposing a reactive thioester bond, which allows C3b to become covalently attached to an acceptor. The part of the α chain that is separated from C3a remains covalently bound to the β chain via the disulfide bond labeled SS. Next, iC3b is excised from the α chain by Factor I, which also cleaves iC3b to yield C3f and C3dg. Finally, C3dg is split to yield C3g and C3d. C3d contains the glutamine residue coupled to the acceptor via an ester or amide bond. The major proteolytic fragment, C3c, is generated by excision of iC3b, which produces two fragments of the α chain. These fragments, $\alpha'1$ and $\alpha'2$, are linked by a disulfide bond, labeled SS$'$. Residue numbers are based on UniProt entry P01024 (http://uniprot.org).

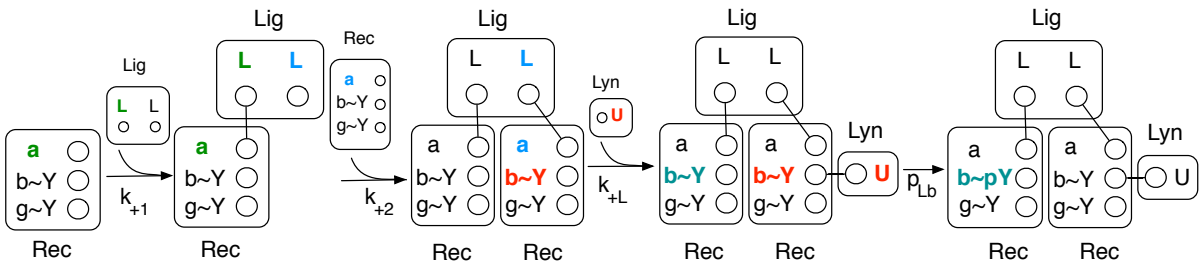


Figure S1: Example of a path.

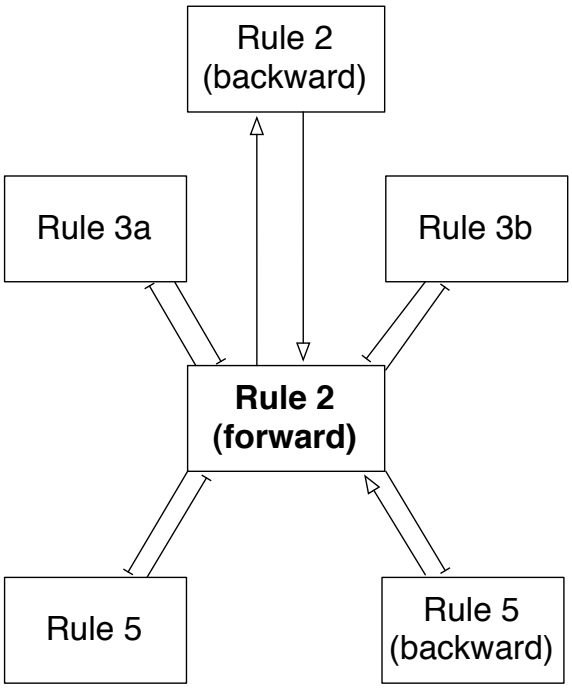


Figure S2: An influence map.

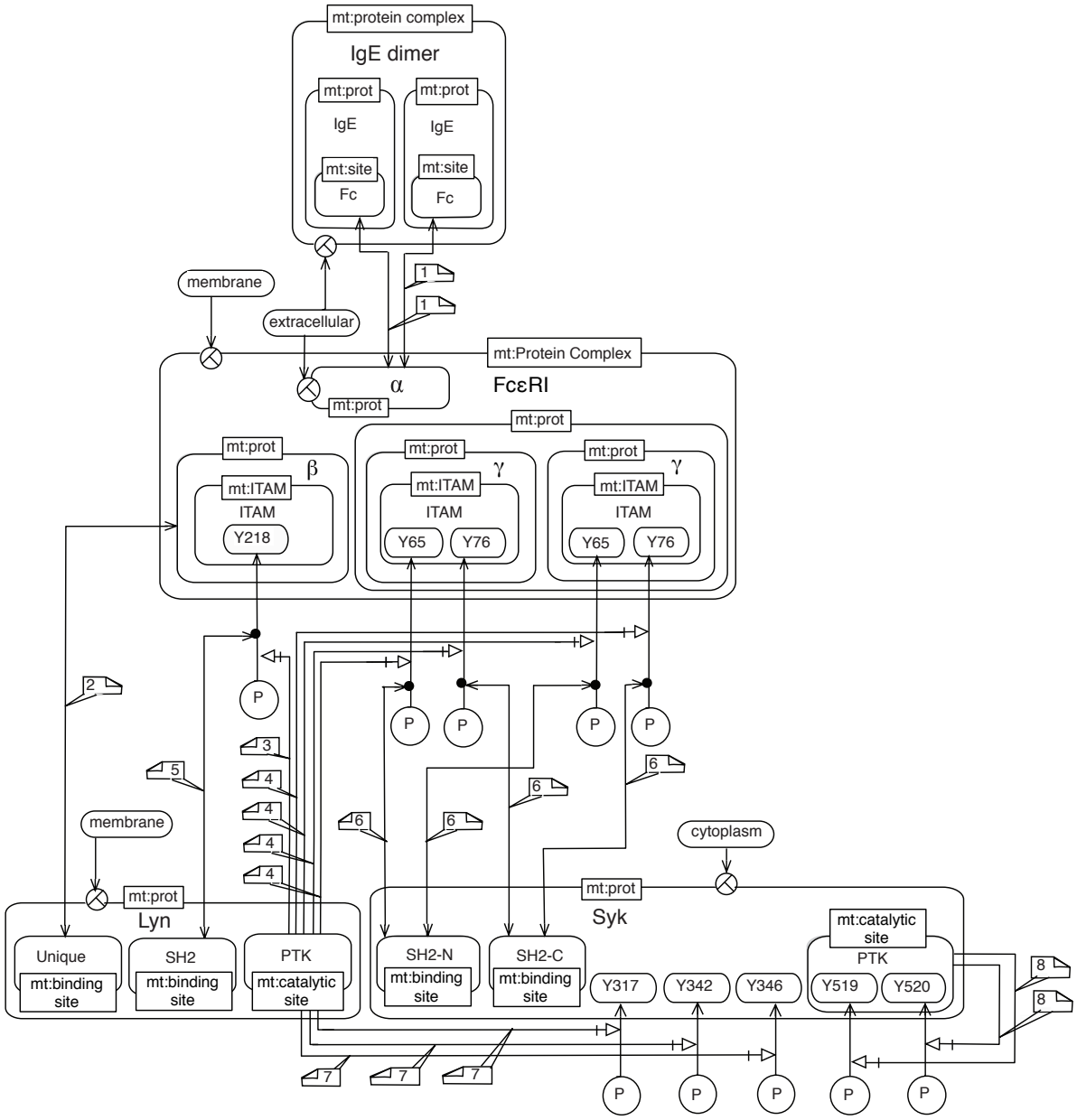
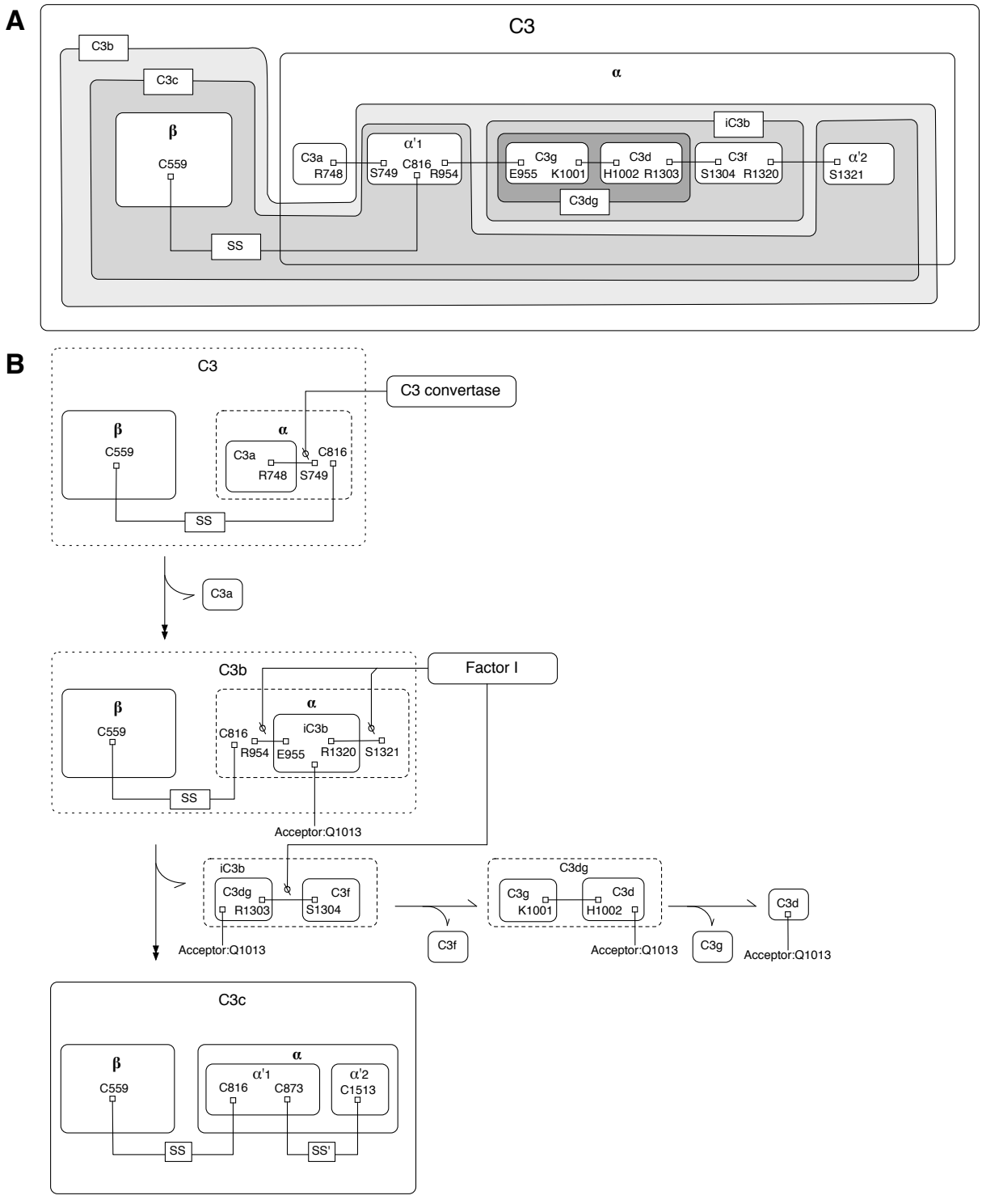


Figure S3: SBGN-style diagram.



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