



Figure 1 – figure supplement 1: **Schematic representation of the various models considered in the manuscript.** Models M0-M1 represent the basic unit of (de)modification, the covalent modification cycle and its simple extension with the substrate forming an additional complex with the enzyme. Models M2-M5 represent different systems of ordered distributive double site modification of a substrate (by different or common enzymes acting on each modification site). Models M6-M7 represent other architectures of modification systems in chemical reaction networks, such as cascaded system (with different and common enzymes affecting (de)modification) and coupled covalent modification networks (coupled through enzyme sharing in (de)modification). Models N0-N5, represent different networks and network motifs with biphasic dose-response subsumed in an interaction.