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How to model mechanisms

Mechanisms are usually viewed as inherently hierarchical, with lower levels of a mechanism "constituting" its higher-level behaviour, and the higher-level behaviour being "decomposable" into lower-level entities and activities. The distinction between different levels of organisation is common to complex biological systems, where macro-level features, such as traits and functions, are explained in terms of properties and relations of parts, such as genes and proteins. In biology textbooks, verbal and pictorial descriptions of mechanisms are typically qualitative. It is often desirable to associate to such qualitative descriptions also a quantitative description, in order to facilitate causal inferences that involve the complex relations between the levels. However, most available quantitative descriptions of biological mechanisms (e.g., differential equations, Petri nets, neural networks, Bayesian networks) fail to capture the hierarchical aspect of mechanisms.

To remedy this deficiency, the Recursive Bayesian Network (RBN) formalism was put forward by Casini, Illari, Russo and Williamson (2011) and its applicability was later extended to modelling cyclic mechanisms by Clarke, Leuridan and Williamson (2013). In a nutshell, an RBN represents hierarchical relations by decomposing certain higher-level variables into lower-level causal graphs. The associated probability distribution must satisfy not only the causal Markov condition (CMC), as in traditional causal BNs, but also an additional condition, viz. the recursive Markov condition (RMC). The conjunction of the two conditions is the so-called Recursive Causal Markov Condition (RCMC) – which says that for each variable in the RBN, that variable is probabilistically independent of non-inferiors-or-descendant variables, conditional on its direct superiors and its parents. When same-level causal relations involve cycles, one of the following two strategies is adopted: if the cycle is 'static', d-separation is used to determine the equilibrium BN; when the cycle is 'dynamic', the causal graph is unrolled by time-indexing the variables, so as to get a dynamic BN. In this paper, we illustrate a further advantage of RBNs, namely the representation of causal

relations that obtain in a particular kind of complex systems, namely non-modular mechanisms involving cycles. We illustrate our claim with the aid of an example from systems biology, namely a portion of the internal pathway for apoptosis, where two (dynamic) cycles cooperate to making apoptosis irreversible (Legewie et al., 2006).

Modularity is a property of systems (or of models of systems), such that, for all of the system's components, there exist interventions on each component that, by modifying the state of that component, influence the state of other components, which interact either directly or indirectly with said component, along one causal path and without interfering with properties of components that lie on other causal paths. When a system is modular, each causal path corresponds to an independently manipulable module, or submechanism. Failures of modularity are common in complex systems, where the existence of the relevant interventions is not always guaranteed. In complex biological systems, this is often due to the presence of nonlinearities and feedback loops. For instance, the mechanism for the irreversibility of apoptosis is non-modular, due to the presence of two overlapping cycles. Causal relations in non-modular systems are particularly resistant to modelling by means of traditional DAGs and to interpretations based on interventionist semantics (Woodward, 2003).

RBNs allow for the representation of such causal relations. More precisely, RBNs represent non-modularity in terms of decompositions of higher-level variables into overlapping lower-level causal graphs. Such complex constitutional relations are common of biological mechanisms, where lower-level entities are often involved in more than one higher-level function for the same behaviour. For instance, in the apoptosis mechanism, two lower-level entities are shared by the two cycles responsible for irreversibility. After unrolling the lower-level causal graph of the apoptosis mechanism into a dynamic BN, we show how interlevel causal inferences are drawn between higher-level variables on the one hand, and lower-level variables decomposing non-modular functions on the other. To this end, one needs knowledge of the relevant conditional probabilities in the flattening. If not directly inferrable from available datasets, these are calculated by selecting the probability distribution that, among those that satisfy the RBN constraints (conditional independences and conditional probabilities), maximises entropy (Williamson, 2010). Finally, we suggest that the applicability of the notions of mechanistic decomposition and of interlevel causation in complex systems

depends (among other things) on the degree of modularity: the larger the constitutional overlap, the less the distinction between entities and functions at different levels makes sense.

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