The role of cyclin F in Motor Neurone Disease

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Motor Neurone Disease (MND) is characterised by the loss of motor neurons in the brain and spinal cord. Most patients with MND develop proteinaceous inclusions within affected neurons of the central nervous system, suggesting overall dysregulation of protein degradation systems. Our team identified mutations in *CCNF*, the gene encoding cyclin F. Cyclin F is a substrate binding component of a multi-protein ubiquitin ligase (denoted $\mathrm{SCF}^{\mathrm{cyclin\ F}}$), which mediates the ubiquitylation of substrates in order to influence the cell cycle.

Overarching aims of this thesis concern the impact of *CCNF* mutations on the ubiquitin ligase activity of $\mathrm{SCF}^{\mathrm{cyclin\ F}}$ and the downstream impact within cells. Addressing these aims involved using a series of biochemical assays (including *in vitro* ubiquitylation assays, immunoprecipitations, proximity-ligation assays and mass spectrometry). Results demonstrate that an MND-linked mutation in cyclin F leads to defective ubiquitylation activity, ultimately leading to the accumulation of proteins tagged for degradation.

Overall, the work provides insight into how the precise control of cyclin F ligase activity is dysregulated when cyclin F carries a disease-causing mutation. Furthermore, outcomes from this work provide novel links between cyclin F (a cell cycle regulator) and a devastating disease involving the degeneration of post-mitotic neurons.

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Belief change without compactness

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One of the main goals of Artificial Intelligence (AI) is to build rational agents that are capable of taking rational decisions autonomously. For this, it is essential to devise mechanisms to properly represent knowledge, and reason about the knowledge that an agent has about the world. However, an agent's knowledge is not static — it gets updated as the agent acquires new information. One of the big challenges involving knowledge representation is how an agent ought to change its own knowledge and beliefs in response to any new information it acquires. This, in short, is the problem of belief change.

Standard approaches of Belief Change come in two flavours: a set of rationality postulates that prescribes epistemic behaviours for an agent, and a collection of constructions, or functions, to perform such rational changes. The two foremost paradigms of Belief Change are the AGM paradigm (for belief change in a static environment) and the KM paradigm (for belief change in a dynamic environment). Both these paradigms make strong assumptions about the underlying logic used to express an agent beliefs, such as Supraclassicality and Compactness. Relying on these assumptions, however, is rather restrictive, since many logics that are important for both AI and Computer Science applications do not have them. This thesis focuses on extending Belief Change to the realm of non-compact logics.

One of the side effects of dispensing with compactness is that standard constructions of both the AGM and the KM paradigms no longer nicely connect with the respective rationality postulates. In this work, I identify the reasons behind this breakdown. This in turn helps us identify some minimal conditions under which the existence of rational AGM and KM belief change operations is guaranteed. Subsequently we provide constructive accounts of AGM- and KM-rational belief change operations without the compactness assumption, and we offer full accounts of belief change for both the paradigms. The main difference of our approach from the standard ones relies on the way epistemic preference of an agent is represented: instead of remainders and Grove's Systems of Spheres, we consider maximal complete theories and genuine partial relations over worlds.

Furthermore, we also consider the connection between AGM revision and non-monotonic reasoning (NMR) systems, often viewed to be two sides of the same coin. We demonstrate that the bridge between belief revision and NMR breaks down in the absence of compactness. We then identify the basis of this breakdown, and present a new non-monotonic system that appropriately connects with the AGM revision postulates even in absence of compactness. Significantly, this connection with the AGM paradigm is independent of any specific constructions (such as systems of spheres), and is directly established between the AGM postulates and the axioms of the proposed non-monotonic system.

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