Towards a Platform Model of the IL-1 Stimulated NF-κB Signalling Pathway using UML and Communicating Stream X-Machines

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Extended Abstract

The Nuclear Factor-kappa B (NF-κB) signalling pathway is one of the key signalling pathways involved in the control and regulation of the immune system [3]. Activation of the NF-κB transcription factor is a tightly regulated event, with NF-κB normally sequestered in the cytosol of non-stimulated cells. Following activation of a cell membrane receptor and propagation of the signal via intracellular signalling to the IκB Kinase (IKK), phosphorylation-induced degradation of IκB inhibitors occurs to facilitate the release of NF-κB and its translocation to the nucleus. Dysregulation of the pathway is known to be involved in a large number of inflammatory diseases.

Although considerable research has been performed since its discovery in 1986, we are still not in a position to control the signalling pathway, and thus limit the effects of NF-κB within promotion of inflammatory diseases. Through adherence to the CoSMoS framework, we are developing a computational model of the IL-1 stimulated NF-κB intracellular signalling pathway, to assist in promoting our understanding of the mechanistic behaviours within the signalling network, and therefore identify potential targets for therapeutic interventions. We have previously developed a separate *domain model* [4, 5] as advocated by the CoSMoS framework, which captures the essential processes and entities of the system under study using; in particular, the emergent behaviour, at an appropriate level of abstraction using a mixture of cartoon and UML diagrams, along with statistical techniques to define the temporal-spatial dynamics.

The next step in the CoSMoS framework is the development of a *platform model*, which details how the simulation is designed and provides an intermediate model that links the domain model to the forthcoming agent-based computational model (the *simulation platform*). We have developed our platform model, through the use of UML diagrammatic notations for modelling the high-level interactions between agents and the activities that they may perform; along with X-Machine mathematical notation, X-Machine diagrams and stategraph diagrams for modelling the low-level detailed specification of (programming language and architecture specific) interactions between agents, and the internal processing logic of individual agents.

As per our previous domain model, UML class diagrams were used in our platform model to represent the containment, inheritance and association characteristics of agents. The order of interactions within the system has again been documented through UML sequence, communication and activity diagrams. UML state machine diagrams were also used to express the detailed biological state changes of individual system components, however these were also complemented with X-Machine diagrams to express the detailed internal state changes of individual system components.

As found when developing the domain model, we believe that the activity diagram with swim-lanes has been the most useful notation for conveying the technical specifications of the system regarding the consequences of interactions between components, and that state machine diagrams are the most useful notation for defining the technical specification of individual system components. Unlike the domain model, the platform model also includes implementation specific details and as per [1] we have found it useful to document the various assumptions and constraints (regarding the technical scope of the computational model) as bullet points.

One of the key strengths of the CoSMoS process is the advocation of separating the abstracted view of biology (documented within the domain model) from the technical specification of the computational model (documented within the platform model). This separation ensures the abstracted view of biology and the technical specifications of the system remain discrete models, and thus aims to minimise confusion during the development of the computational model around what aspects of the programming code relate to biology requirements, and what aspects are necessary as technical workarounds due to constraints of the specific programming frameworks being used (e.g. communicating X-Machines and FLAME). As such, we believe the process of platform modelling to be an integral part of the development lifecycle for computational models of biological systems, and believe that our platform model will provide an unambiguous specification for the *simulation platform*, which will be developed using the FLAME simulation framework [2].

References

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