Tutorial Case Study – Analysis of MAPK Model

To demonstrate the tool's applicability, we consider a well-known model [1] of one of the most important signalling mechanisms in human cells – the MAPK pathway. The model investigates the influence of several extracellular stimuli on cancer cell fate decisions. It consists of 18 variables. Four of these variables have update functions characterized by function symbols with zero arity. For simplicity, we refer to such variables as *inputs*. They represent the extracellular stimuli (`TGFBR_stimulus`, `EGFR_stimulus`, `FGFR3_stimulus`, and `DNA_damage`). All possible settings of these inputs result in 16 different BN instances. Another three variables represent possible modes of the cell behaviour: `Apoptosis` (programmed cell death), `Growth_Arrest` (temporary stop of growth), and `Proliferation` (cell reproduction).

We are especially interested in the relationship among the individual settings of the inputs and the long-term behaviour of the model (attractors). Moreover, we investigate the possible presence of biologically unrealistic behaviour to assess the overall soundness of the model. With these goals in mind, we define the set of required properties $\Psi = \{\psi\}$ and the set of classification properties $\Phi = \{\varphi_1, \varphi_2, \varphi_3, \varphi_4\}$:

$\psi = \exists x. @_{\mathrm{x}}\ ((\mathbf{AG}\,\mathbf{EF}\,x) \wedge (\texttt{Apoptosis} \vee \texttt{Growth\_Arrest} \vee \texttt{Proliferation}))$
There exists an attractor state where some cell mode is active.

$\varphi_1 = \forall x. @_{\mathrm{x}}\ ((\mathbf{AG}\,\mathbf{EF}\,x) \Rightarrow (\texttt{Apoptosis} \wedge \mathbf{AX}\,x))$
Every attractor state is a fixed point with `Apoptosis` active (the system always converges to programmed cell death; *healthy* behaviour).

$\varphi_2 = \exists x. @_{\mathrm{x}}\ (\mathbf{AG}\,\texttt{Growth\_Arrest})$, $\varphi_3 = \exists x. @_{\mathrm{x}}\ (\mathbf{AG}\,\texttt{Proliferation})$
`Growth_Arrest` (φ_2) or `Proliferation` (φ_3) remain active in some attractor (programmed cell death may not be achieved; possibly *problematic* behaviour).

$\varphi_4 = \exists x. @_{\mathrm{x}}\ ((\mathbf{AG}\,\mathbf{EF}\,x) \wedge \texttt{Apoptosis} \wedge \texttt{Proliferation})$
Both `Proliferation` and `Apoptosis` are simultaneously active in an attractor state (biologically *unrealistic* behaviour).

We obtained classification results in less than two minutes, revealing several interesting model characteristics: (i) One instance (with all stimuli turned off) does not satisfy the required property ψ. In this case, the model does not manifest any known biological cell mode. (ii) Nine instances satisfy φ_1, i.e. the cell is guaranteed to undergo proper programmed death. Furthermore, all these instances also satisfy φ_2 (impeded cell growth). (iii) There is no instance where φ_3 holds (`Proliferation` cannot remain active indefinitely). However, (iv) three instances admit intermittent simultaneous activity of both `Apoptosis` and `Proliferation` (prop. φ_4).

Although we found that φ_4 holds for some instances, it does not necessarily make the model unsound. Biologically unrealistic conditions can be admissible, but it is important to *understand* when and how they occur to interpret the model correctly. To do that, we construct a decision tree (Fig. 1) where we explore the conditions leading to the validity of individual properties. In particular, we see that the biologically unrealistic property φ_4 occurs if and only if both `DNA_damage` and `TGFBR_stimulus` are inactive. The decision tree also guides us towards conditions that ensure proper programmed cell death. For example, we see that the presence of `TGFBR_stimulus` is a sufficient condition for φ_1.

References

1. Grieco, L., Calzone, L., Bernard-Pierrot, I., Radvanyi, F., Kahn-Perlès, B., Thieffry, D.: Integrative modelling of the influence of mapk network on cancer cell fate decision. PLOS Computational Biology **9**(10), 1–15 (10 2013). https://doi.org/10.1371/journal.pcbi.1003286

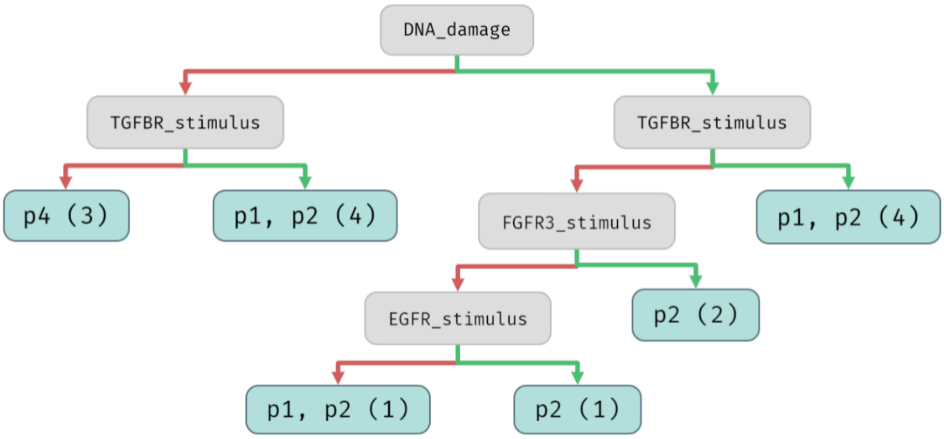

Fig. 1. Decision tree of the MAPK model produced by BNClassifier. It shows the effect of input variables on the classification properties. Each decision node contains the name of a variable used for the decision. Leaf node labels show the number of instances represented by the node (in brackets), plus the list of properties satisfied by these interpretations (with $\mathtt{p_i} = \varphi_i$).