Case Study - Hypothetical Immunological Response Model Graph Transformation Rules

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1 Introduction

This report accompanies current research on membrane-inspired graph transformation systems. Contained within are details of a hypothetical model of cellular viral infection and subsequent immunological response for some imagined multicellular organism. Section 2 describes the modelled scenario while Section 3 introduces the type graph and its elements (after the addition of *aggregating attributes*). Section 4 presents the graph transformation rules in a concrete model (after the addition of *aggregating attributes*) detailing the complete behaviour of the system. Section 5 shows the remaining rules after the concrete model has been abstracted. Rules that have become identity rules are removed from the abstract model and are not shown.

2 Scenario

We model two hierarchical levels: a tissue consisting of cells, which in turn contain organelles.

As a starting point, we model the situation in which viruses have already entered the body and reside in the region delimited by the tissue membrane. They invade cells and attack *maintainers* bonded to the inner surface of the cell, destroying them one by one. Once a cell's maintainers have been completely eliminated, it undergoes apoptosis, i.e., programmed cell death, where the cell membrane gradually dissolves. Between the time a cell enters the apoptosis stage and the dissolution of its membrane, viruses remaining within the cell can *tunnel* to any adjacent cell.

Immunos generated by the cell represent antibodies that can fight back against viruses. The reaction between an immuno and a virus eliminates them both. Viruses and immunos can be replicated within a cell with the aid of auxiliary species simply called A and X.

Upon cell dissolution, any species that can survive in the tissue membrane diffuse outwards. In our case, we only allow immunos and viruses to diffuses outwards. Species that cannot survive dissolve with the cell, i.e., any remaining A or X. Cells can be regenerated if there is a gap in the cell structure. An existing cell undergoes mitosis to create a copy which fills the space of a dead cell. The new cell is clean of infection even if the copied cell contains viruses. The tissue will die once all of its constituent cells have died.

3 Type Graph

Figure 1 shows the type graph for the immunological response model. The *par* edge encodes hierarchical containment in a flat manner, assuming that the source of the edge is contained within the target. There are therefore two containers in the model: *Cell* and *Tissue*. Each has an attribute *alive* indicating it's dissolution status. The node *Species* is a supertype, with *Immuno*, *Virus*, *A*, *X* and *Maintainer* as subtypes. A *Maintainer* is bonded to a *Cell* only via a *surface_bond* edge.

The *par* edge has a boolean attribute *mobile* indicating whether the source of the *par* edge can survive outside of the target, e.g., when the target dissolves.

There are two additional edge types representing topological relations: *adj* and *prox*. *adj* represents adjacency of cells in the cell structure. Note that the maximum cardinality of this edge is 7, which very crudely approximates a pentagonal layered geometry about a central cell, i.e., each cell is surrounded by 5 cells in the plane, with a plane above and below this one. The *prox* edge type encodes proximity of a *Species* node to a cell when it is in the *Tissue* region. For example, when a cell dissolves any viruses in the cell will diffuse into the region delimited by the parent *Tissue* container but will initially be closest to the cell from which it escaped.

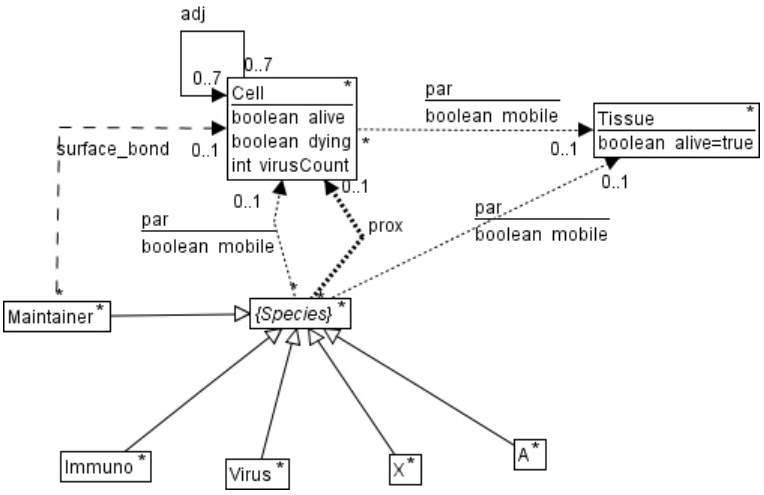

Fig. 1. Concrete type graph for immunological response model

4 Concrete Model Rules

Rule name abbreviations that have been used in some work are given after each rule name.

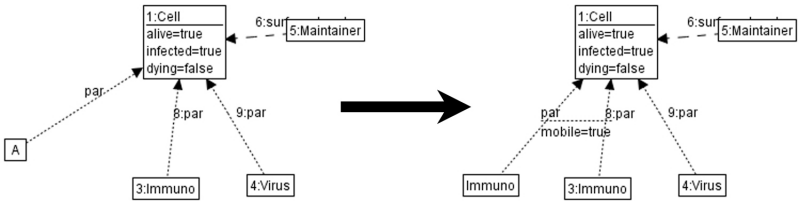

Fig. 2. Immuno creation (IC): The cell utilises auxiliary species A and replicates an existing *Immuno* when a *Virus* has invaded a living cell.

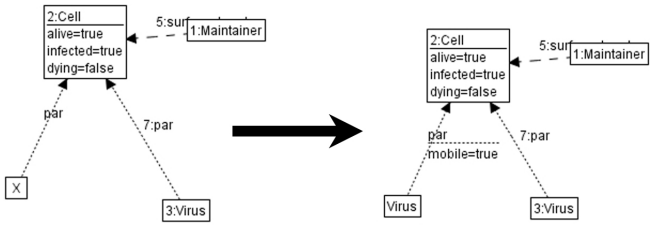

Fig. 3. Virus creation (VC): The *Virus* manipulates auxiliary species X to replicate itself within a living cell.

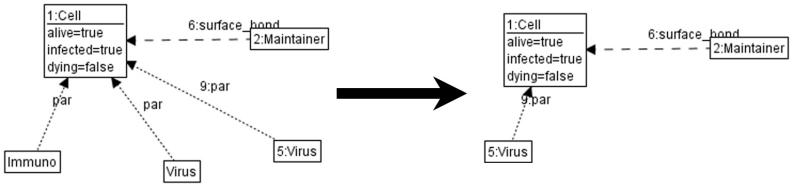

Fig. 4. Immunoresponse variation 1 ($IR1$): An *Immuno* eliminates a *Virus* within a cell.

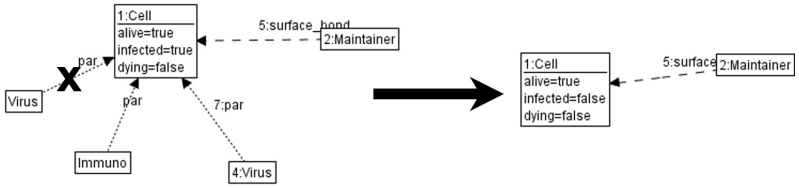

Fig. 5. Immunoresponse variation 2 (*IR2*): An *Immuno* eliminates the last *Virus* within a cell.

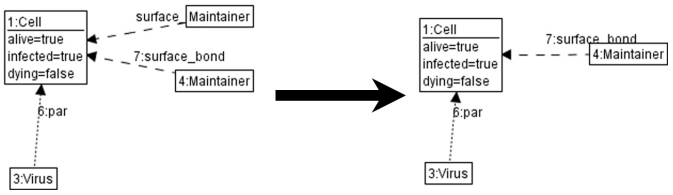

Fig. 6. Viral activity variation 1 (*VA1*): A *Virus* destroys a *Maintainer* bonded to the surface of a cell.

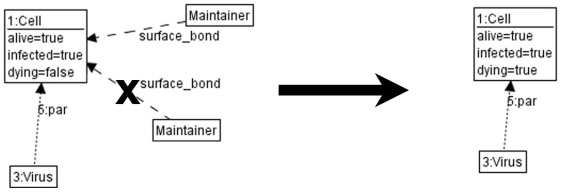

Fig. 7. Viral activity variation 2 (*VA2*): A *Virus* destroys the last *Maintainer* bonded to the surface of a cell, therefore initiating programmed cell death

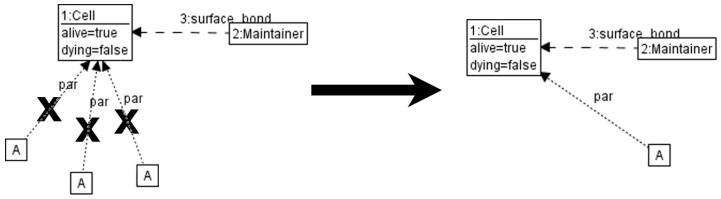

Fig. 8. *A* creation (*AC*): A living cell regenerates auxiliary species *A*, with an upper limit of 3 *A*'s per cell

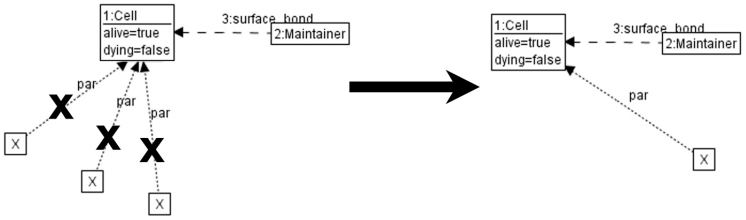

Fig. 9. X creation (XC): A living cell regenerates auxiliary species X, with an upper limit of 3 X's per cell

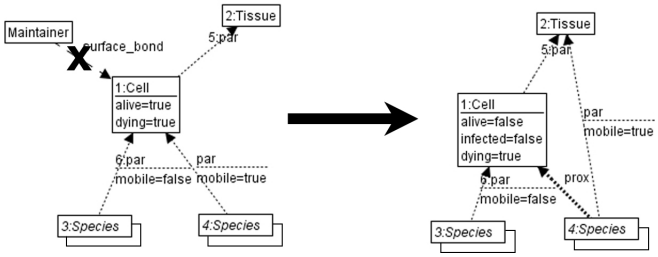

Fig. 10. Cell death (CD): A dying cell dissolves. Instead of deleting the cell, we keep its "ghost" for accounting purposes. The *Species* nodes in the cell are multiobjects [1]. Immobile species will dissolve, while mobile ones will be released into the area delimited by the tissue membrane.

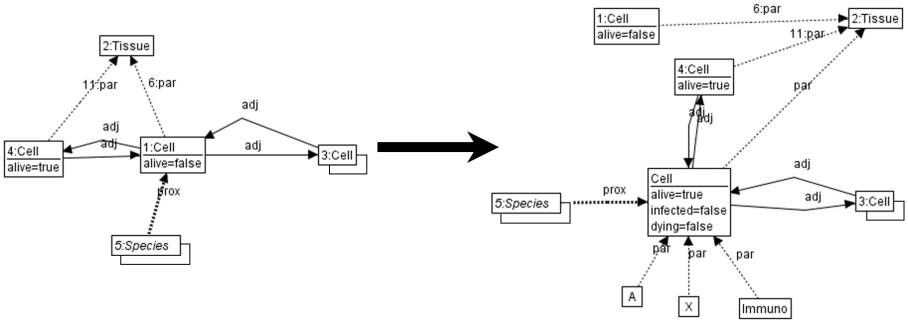

Fig. 11. Cell regeneration (CR): Given a gap in the cell structure, i.e., a dead cell, an adjacent living cell can replicate itself into the space. The new cell contains one X, one A and one *Immuno*, and inherits the old cell's *prox* and *adj* relations

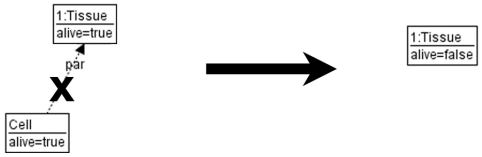

Fig. 12. Tissue death (*TD*): A tissue with containing no living cells dies.

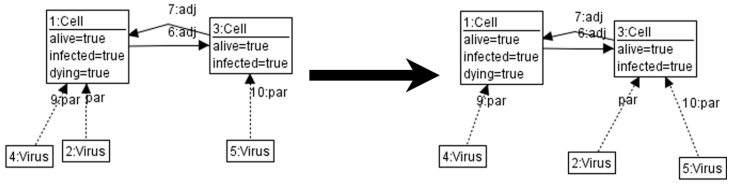

Fig. 13. Virus tunnelling variation 1 (*VT1*): A *Virus* tunnels from a dying cell to an adjacent cell. The infection state of both cells is unchanged.

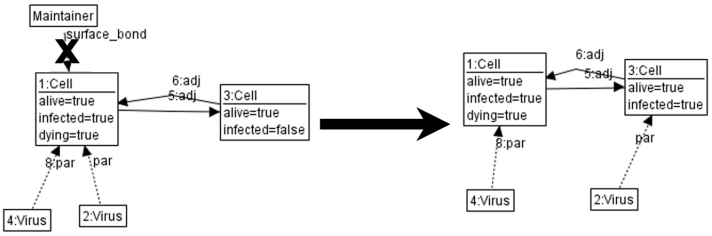

Fig. 14. Virus tunnelling variation 2 (*VT2*): A *Virus* tunnels from a dying cell to an adjacent cell. The infection state of the receiving cell is changed.

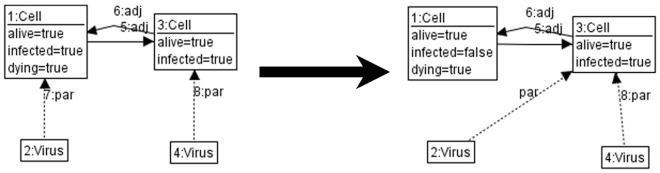

Fig. 15. Virus tunnelling variation 3 (*VT3*): A *Virus* tunnels from a dying cell to an adjacent cell. The infection state of the transmitting cell is changed.

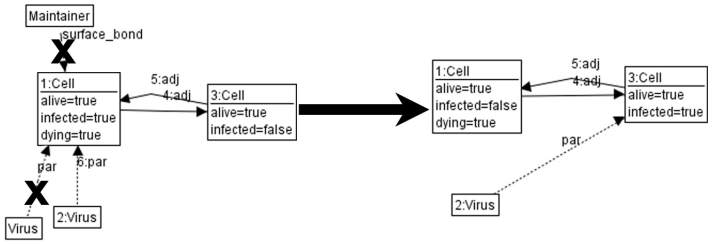

Fig. 16. Virus tunnelling variation 4 (*VT4*): A *Virus* tunnels from a dying cell to an adjacent cell. The infection state of both cells is changed.

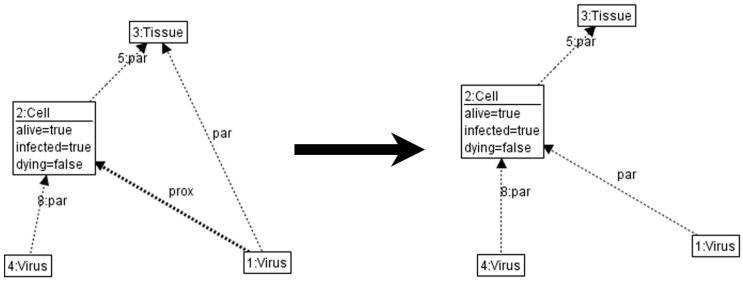

Fig. 17. Virus invasion variation 1 (*VM1*): A *Virus* enters a cell from the tissue membrane. The cell already contains virus(es) and its infection state is unchanged.

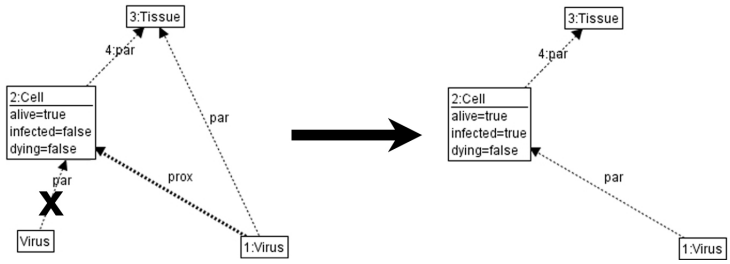

Fig. 18. Virus invasion variation 2 (*VM2*): A *Virus* enters a cell from the tissue membrane. The cell is previously clean and its infection state is changed.

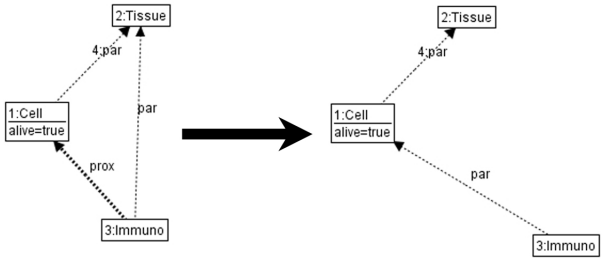

Fig. 19. Immuno migration (*IM*): An *Immuno* enters a cell from the tissue membrane.

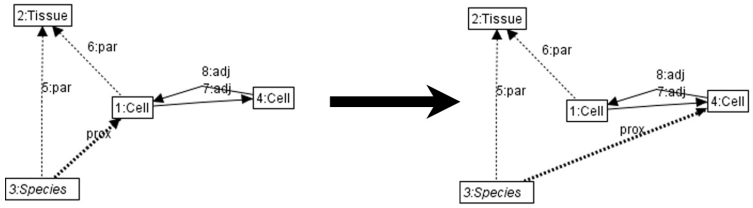

Fig. 20. Species movement (*SM*): A mobile *Species* can diffuse through the tissue when it is not within a cell. Movement is random over the cell structure and is tracked via its proximity to cell positions.

5 Abstract Model Rules

Fig. 21. Abstract immunoresponse variation 2 (*A_IR2*): An *Immuno* eliminates the last *Virus* within a cell, changing the cell's infection state

Fig. 22. Abstract viral activity variation 2 (*A_VA2*): A *Virus* destroys the last *Maintainer* bonded to the surface of a cell, therefore initiating programmed cell death

Fig. 23. Abstract cell death (*A_CD*): A dying cell dissolves. Instead of deleting the cell, we keep its "ghost" for accounting purposes. In the concrete model, viruses are returned to the tissue membrane when the cell dissolves. In the abstract model, since viruses are hidden within cells, we always return one virus to the tissue membrane. This number represents the modal number of viruses released and was determined by stochastic simulation experiments.

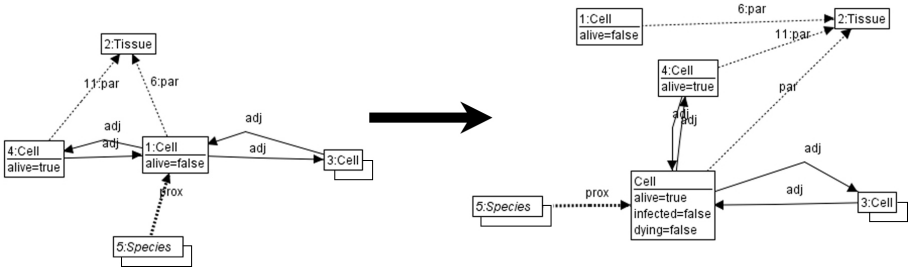

Fig. 24. Abstract cell regeneration (*A_CR*): Given a gap in the cell structure, i.e., a dead cell, an adjacent living cell can replicate itself into the space. The new cell contains one *X*, one *A* and one *Immuno*, and inherits the old cell's *prox* and *adj* relations

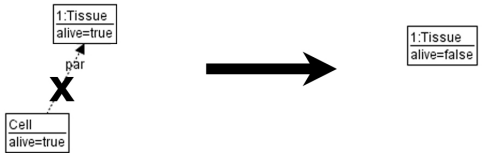

Fig. 25. Abstract tissue death (*A_TD*): A tissue with containing no living cells dies.

Fig. 26. Abstract virus tunnelling variation 2 (*A_VT2*): A *Virus* tunnels from a dying cell to an adjacent cell. The infection state of the receiving cell is changed. In the abstract model, we disregard the infection state of the transmitting cell. As such, only this variation of the rule remains.

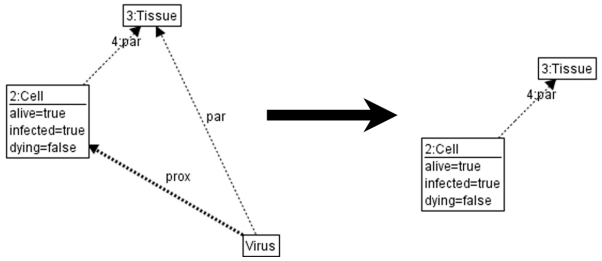

Fig. 27. Abstract virus invasion variation 1 (*A_VM1*): A *Virus* enters a cell from the tissue membrane. The cell is already infected and its infection state is unchanged.

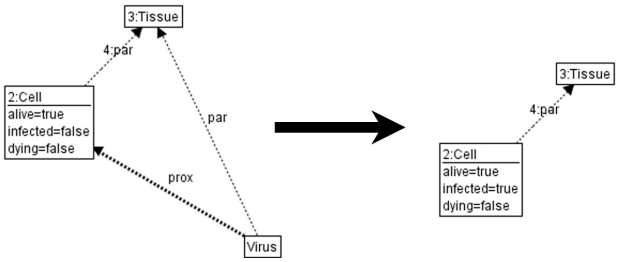

Fig. 28. Abstract virus invasion variation 2 (*A_VM2*): A *Virus* enters a cell from the tissue membrane. The cell is previously clean and its infection state is changed.

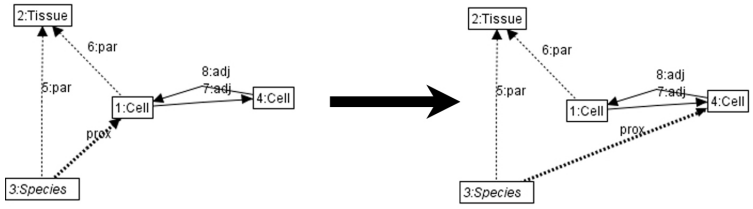

Fig. 29. Abstract Species movement (A_SM): A mobile *Species* can diffuse through the tissue when it is not within a cell. Movement is random over the cell structure and is tracked via its proximity to cell positions.

References

1. Heckel, R.: Graph transformation in a nutshell. Electronic Notes in Theoretical Computer Science 148(1), 187–198 (2006)