A Multi-scale Extensive Petri Net Model of Bacterial-macrophage Interaction

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Leiden University. The university to discover.

Introduction

- Mycobacterial infection
  - Dynamics interactions between host and bacteria forms a complex system
    - Activations, inhibitory and control structures
- System approach
  - Multiple and simultaneously events
    - Molecular and cellular components of the host-pathogen
- Bacterial-macrophage signaling pathways
  - Extended Petri Net formalism
    - Snoopy tool
  - Multi-scale qualitative approach exploring the interaction
    - from the cellular, intracellular and molecular level scale
- Visualization
  - Dynamics of the interactions
  - Animation of different scenarios

Infection Process Model

- Cell dynamics level
  - Early stage of *mycobacterium* infection process and granuloma formation
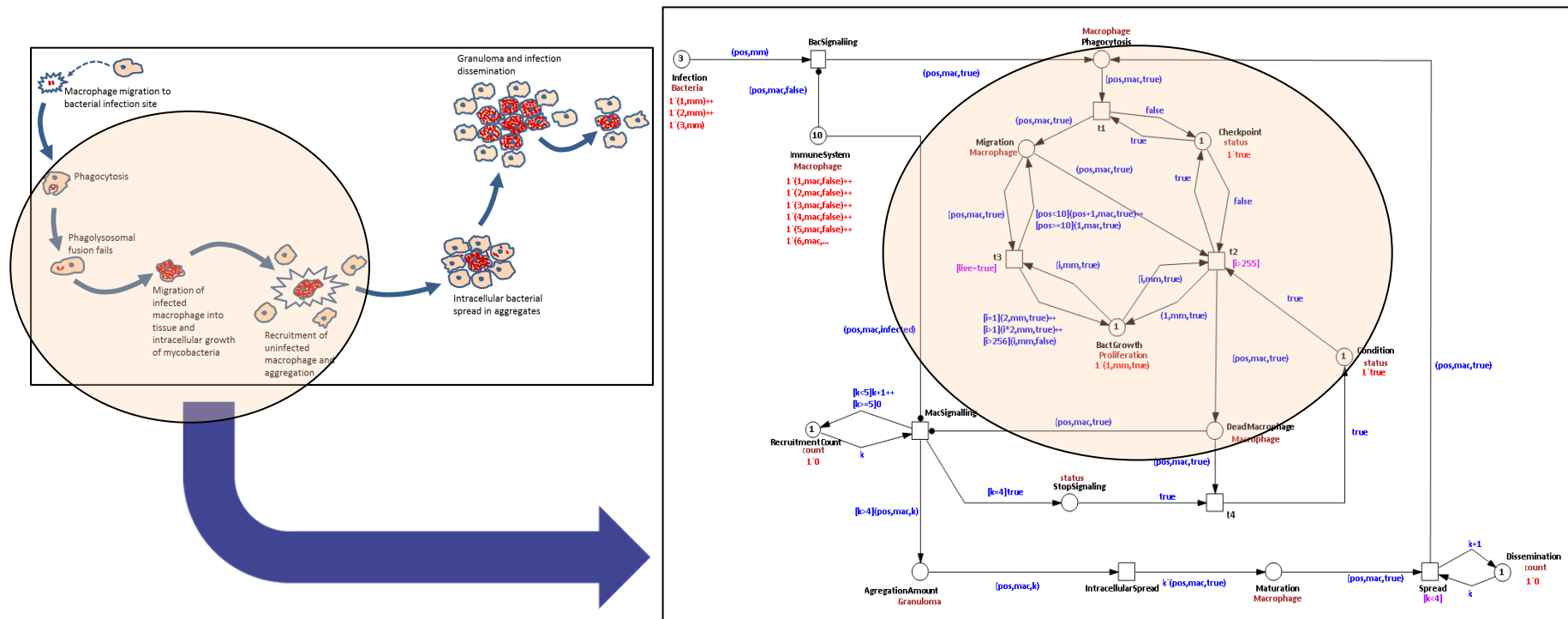
Carvalho, Rafael V.; Kleijn, Jetty; Meijer, Annemarie H.; Verbeek, Fons J. **Modeling Innate Immune Response to Early Mycobacterium Infection**. *Comp. Math. Methods in Medicine 2012.*

Bacterial-Macrophage interaction

- Identify and connect important pathways in the host-pathogenic interaction
  - Functional process of the macrophage exposure to mycobacteria
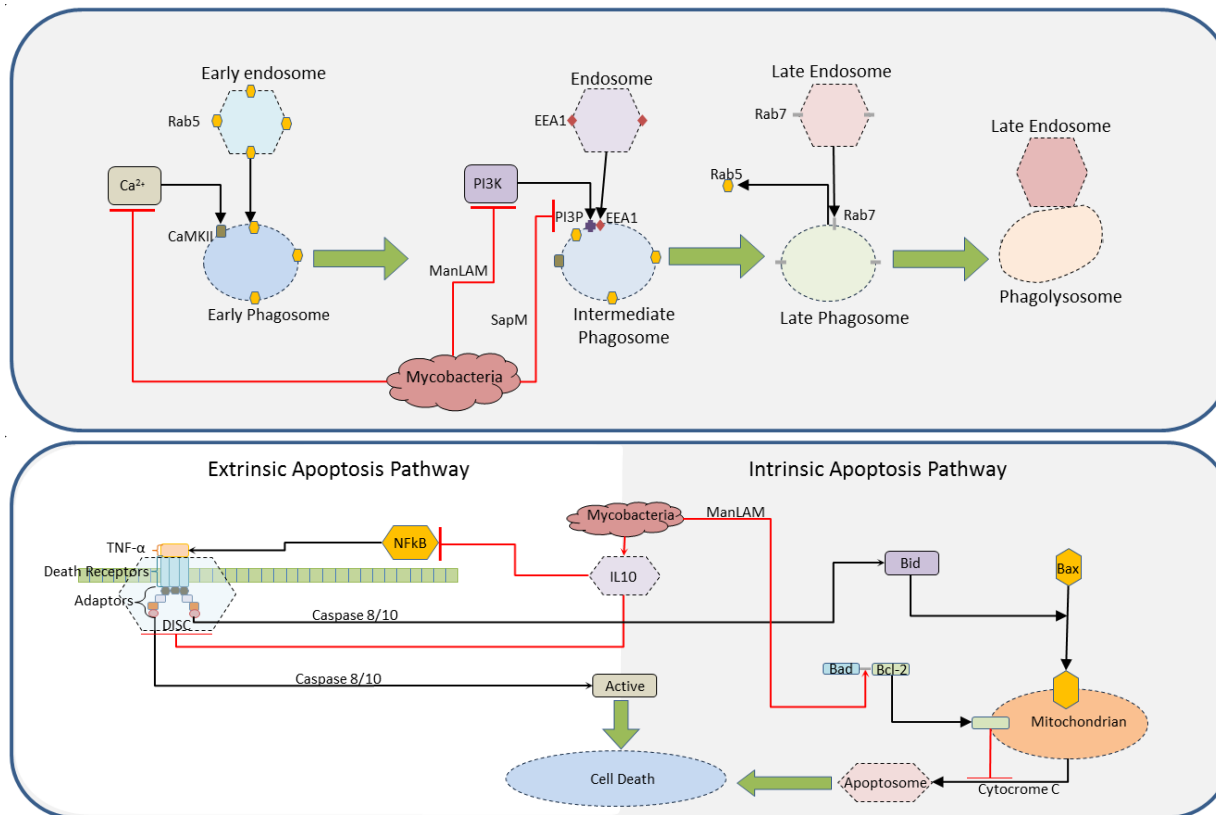
Extended model

- Multi-scale qualitative model
    - Cellular => bacterial-macrophage interaction through protein
    - Intracellular => Signaling process
    - Molecular => Reactions

    • Visualization and interaction of signaling pathways
        - How the macrophage reacts to the bacteria
        - How the bacteria exploits those pathways to survive

    • Animation
        - Bacterial proliferation in the macrophage
        - Phagosome maturation and Bacterial death
        - Phagolysosome failure and Apoptosis process

    • Pre-analysis using Charlie tool
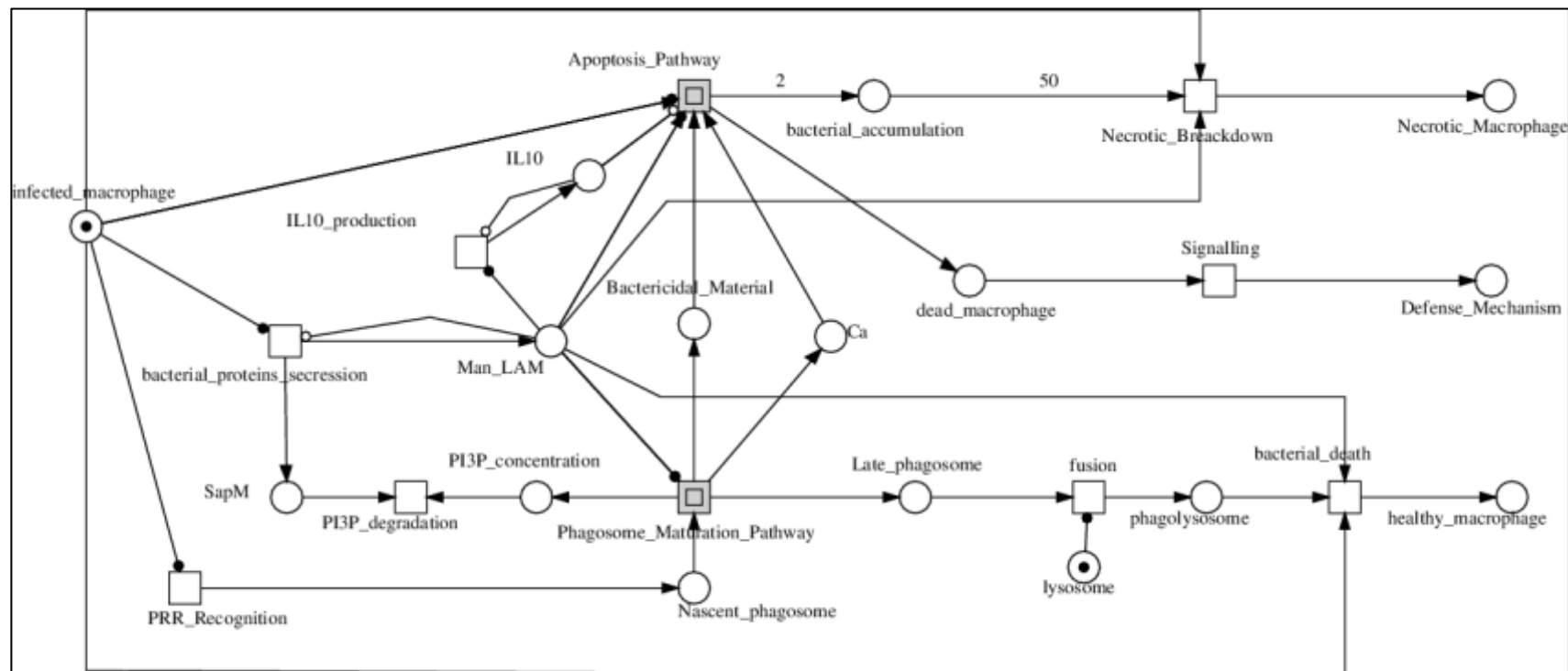   - Net not structurally bounded and not reversible
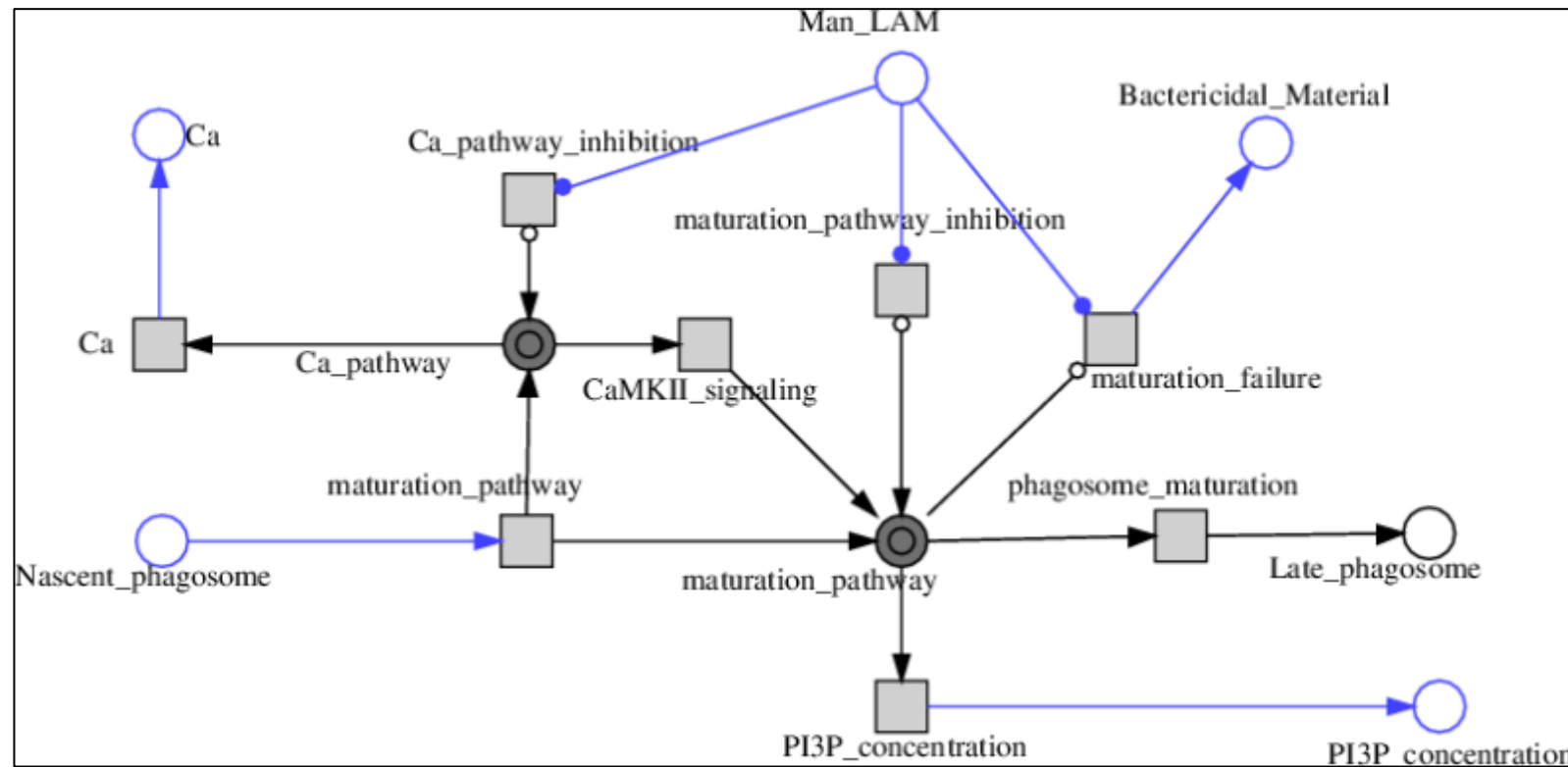
Hierarchical Representation
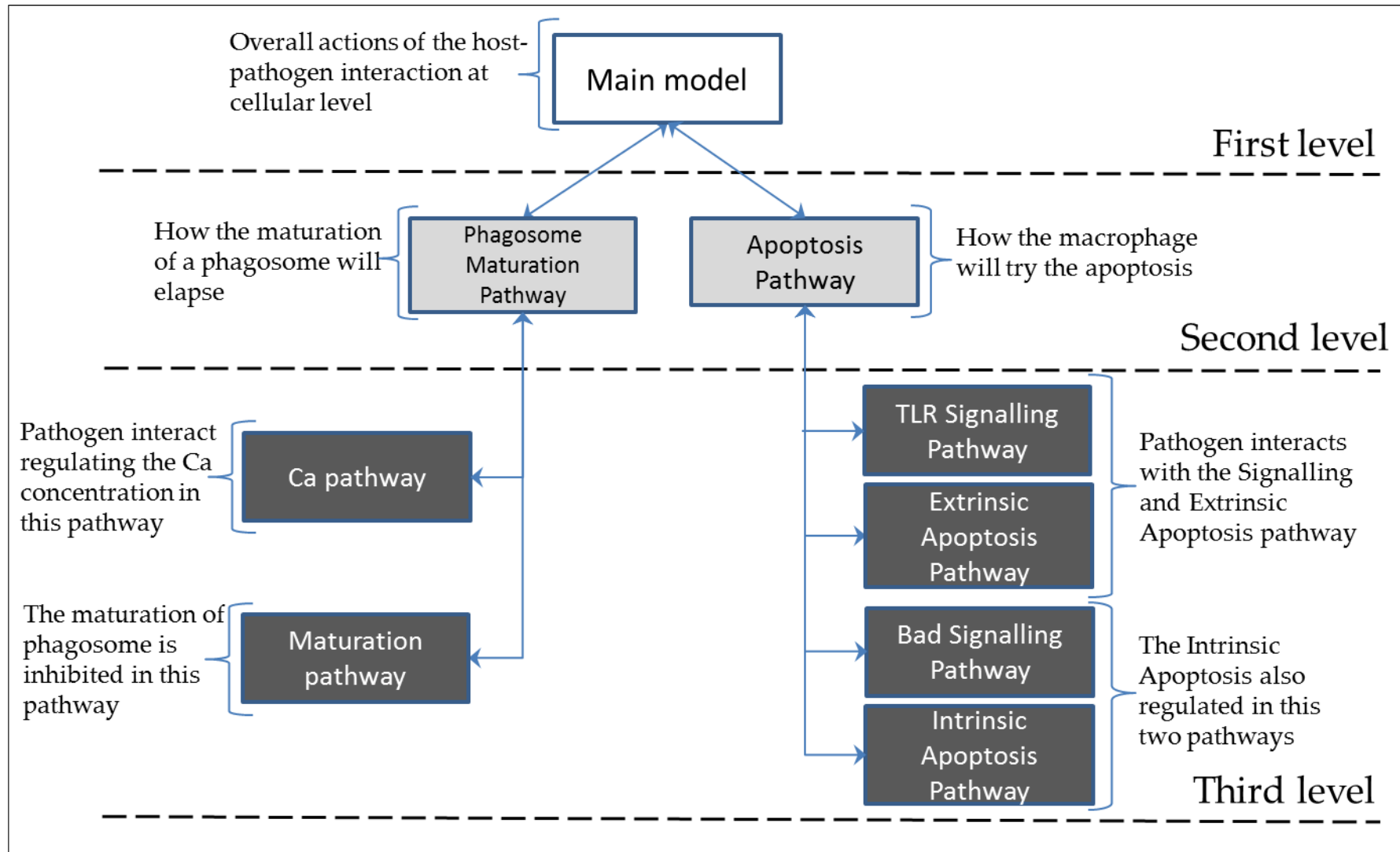
Multi-scale model

- First level: Bacteria-Macrophage interaction
  - intercellular signalling network
    - Proteins that trigger/inhibit bacterial elimination
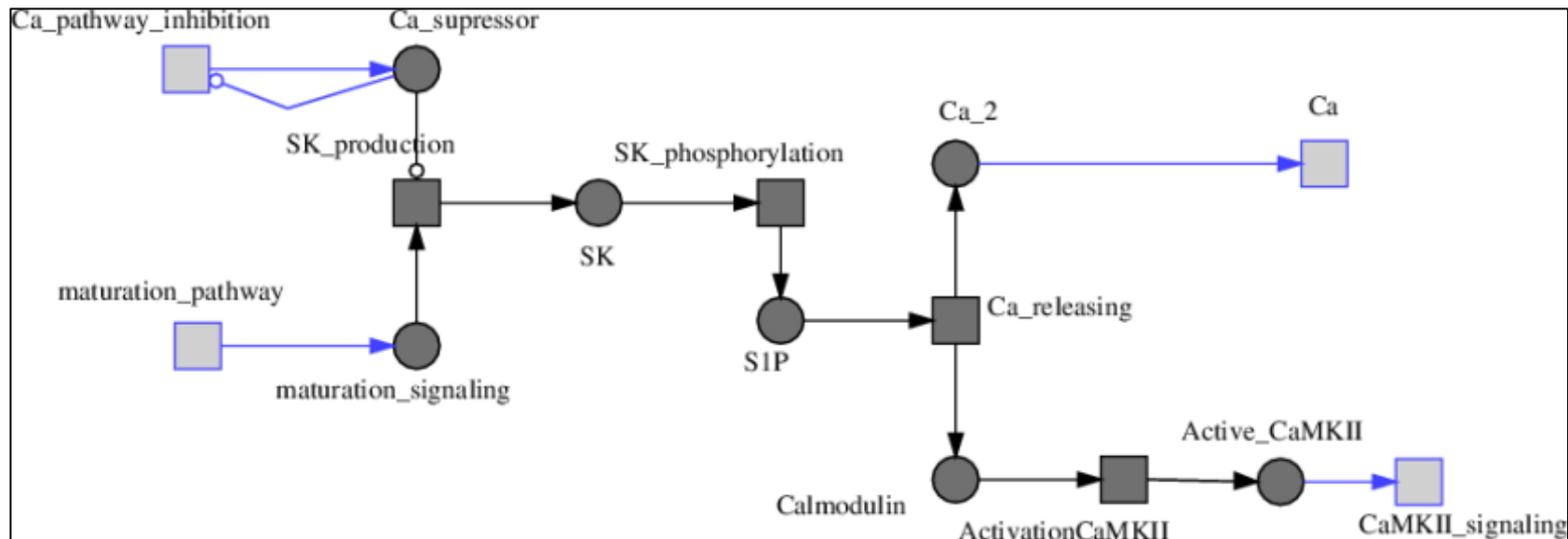
Multi-scale model

- Second level: Phagosome Maturation Pathway
  - Intracellular signalling network
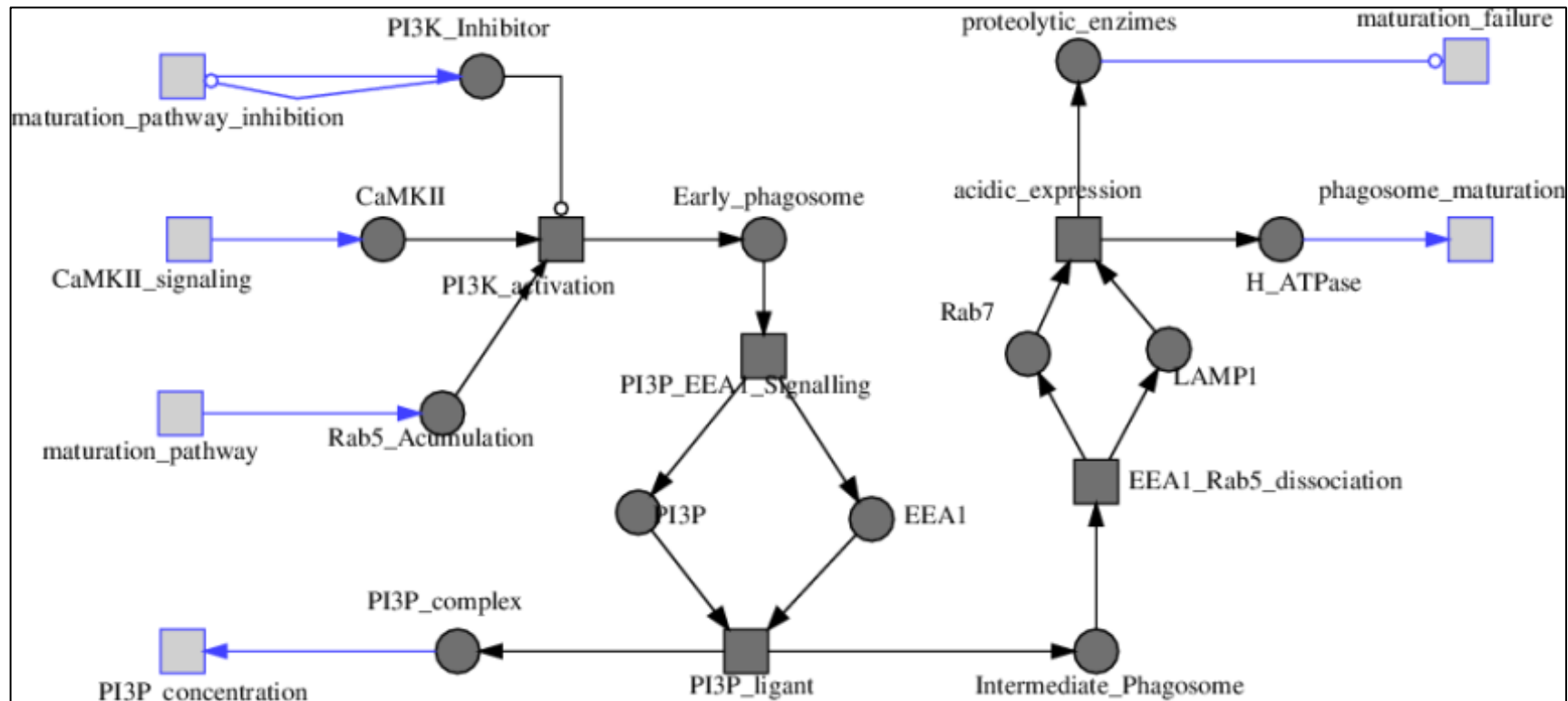   - Proteins signalling that trigger/inhibit the phagosome maturation and Ca+ production

Multi-scale model

- Third level: Ca Pathway
  - Molecular network process
    - Ca^+ Protein regulation in the macrophage
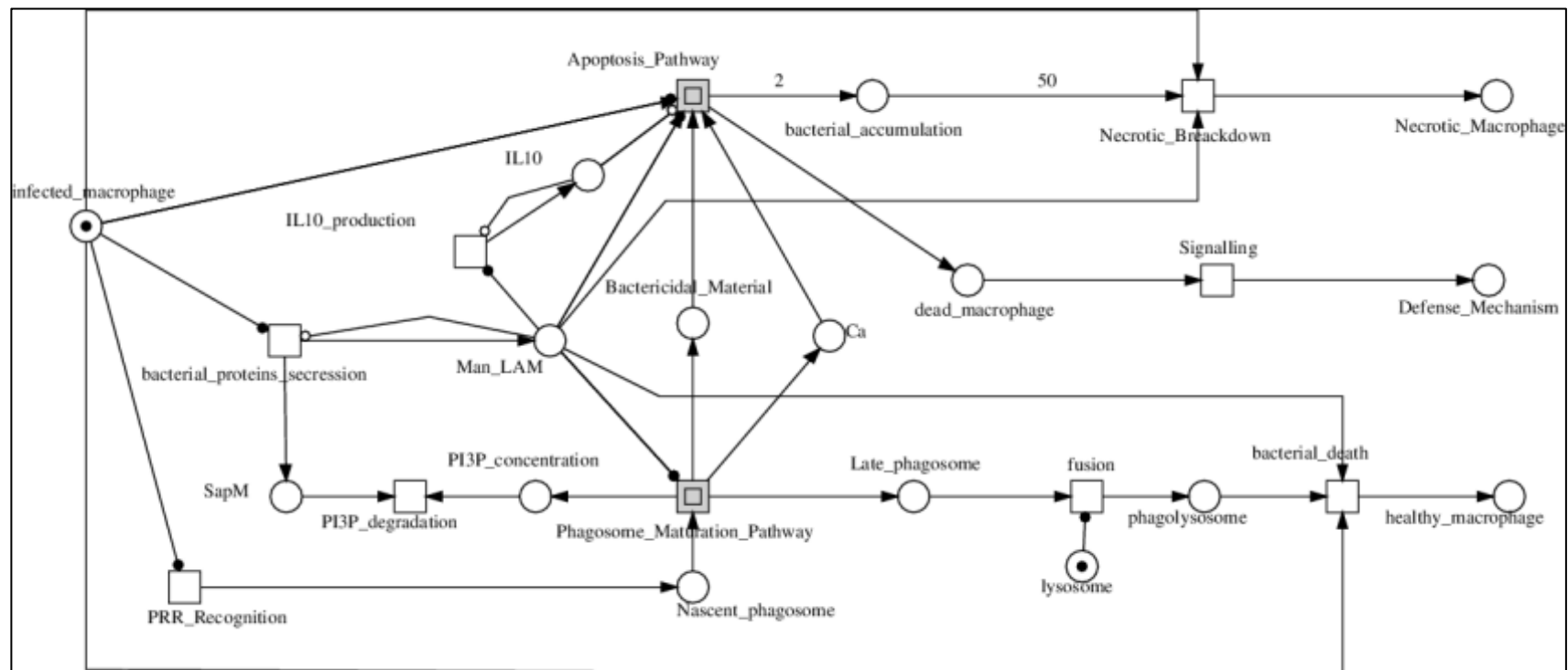
Multi-scale model

- Third level: Maturation Pathway
  - Molecular network process
    - Formation/maturation of the phagosome
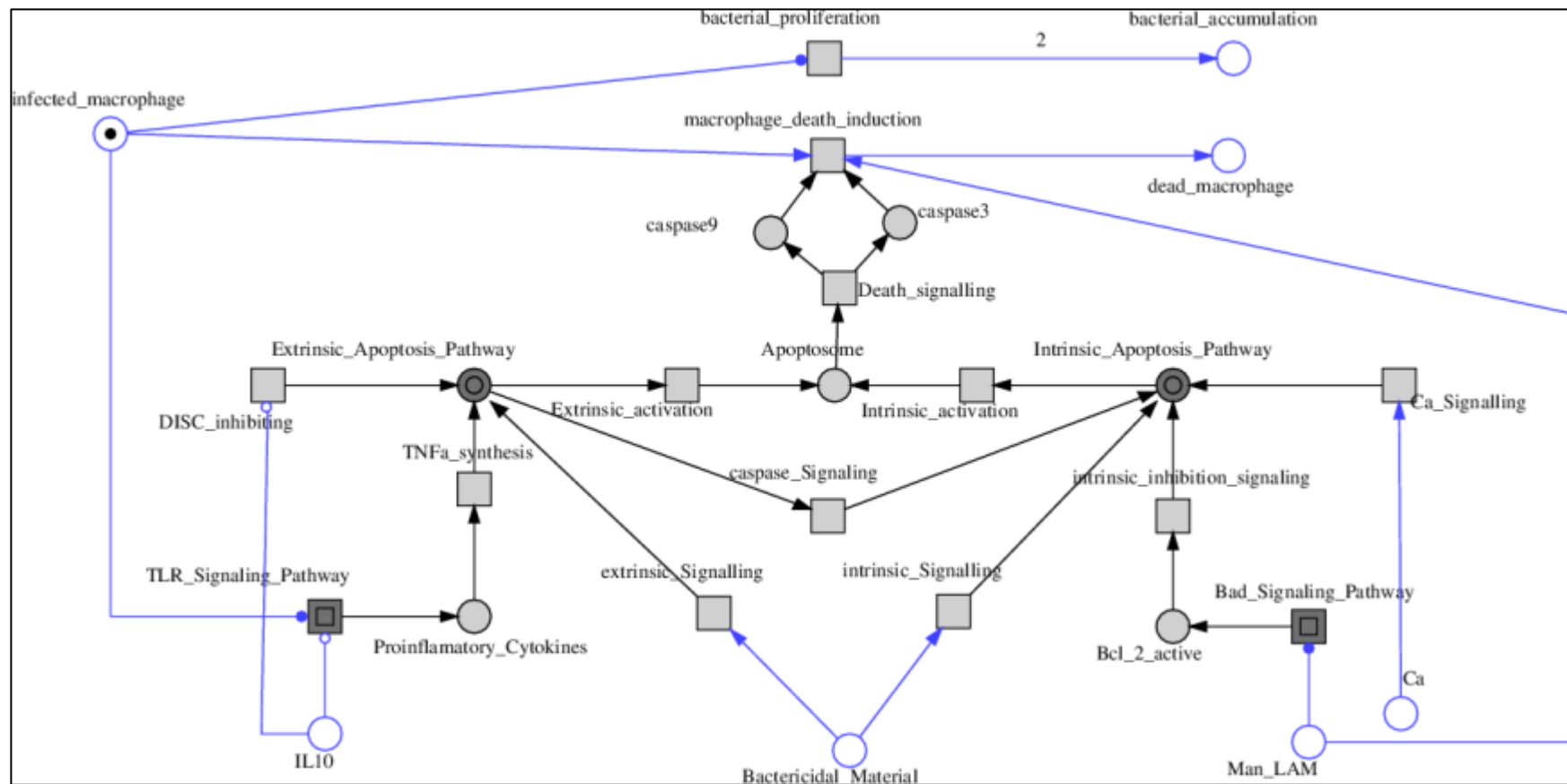
Multi-scale model

- First level
  - Cellular signalling network
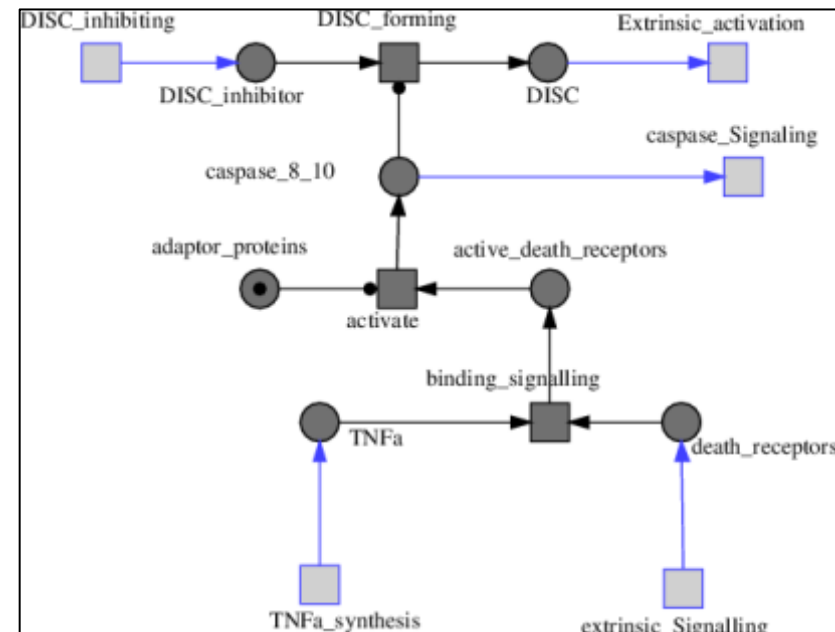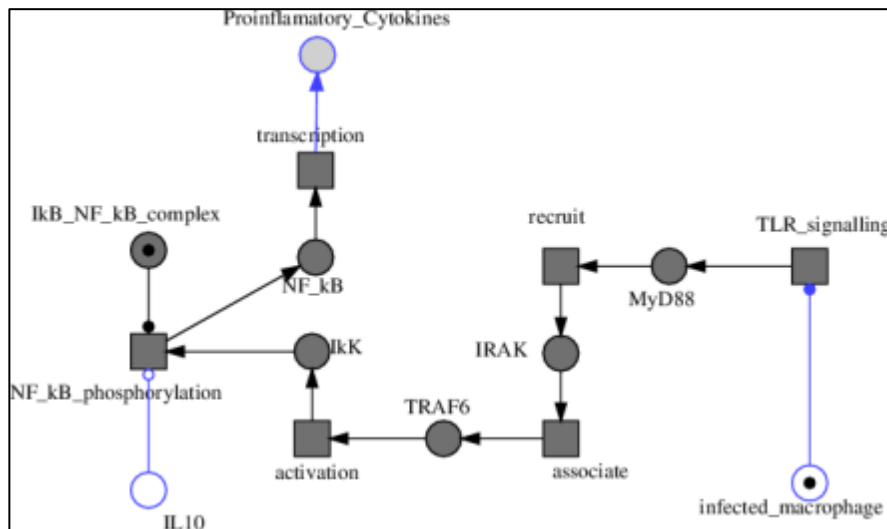   - Proteins that trigger/inhibit bacterial elimination

Multi-scale model

- Second level: Apoptosis Pathway
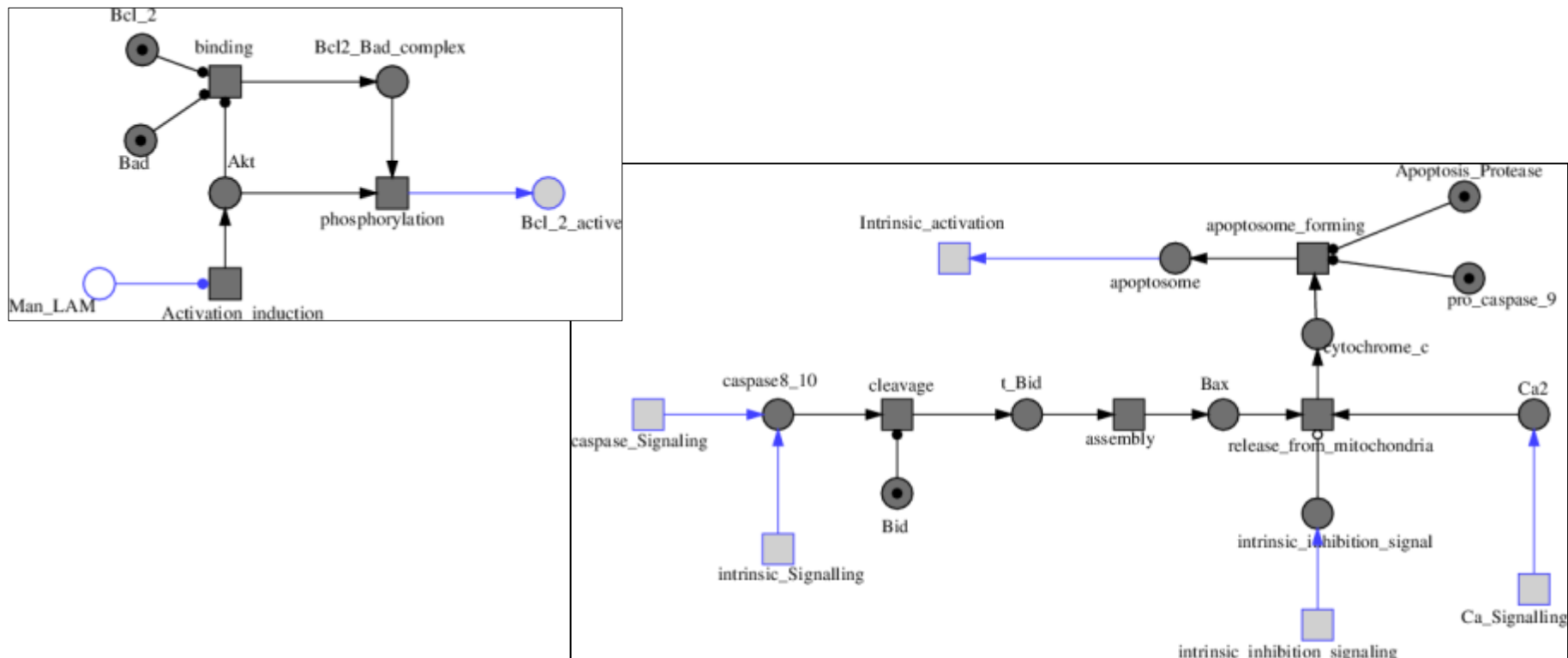 - Intracellular signalling network

Multi-scale model

- Third level: Pro-inflamatory cytokines and Extrinsic Apoptosis Pathway
 - Activation/inhibition TNFa, Disc formation and Caspase signaling

Multi-scale model

- Third level: Bad/BLC2 and Intrinsic Apoptosis
  Pathway

  • Bad/BCL2 phosphorylation and activation/inhibition of the
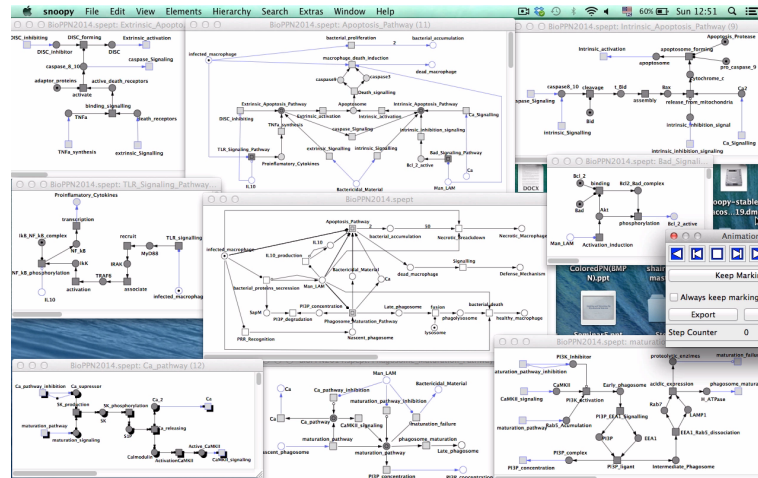   apoptosome

Animation Mode

- First Scenario: Infection Persistence

  - Phagosome maturation inhibition
    - Ca$^+$/CaMKII and PI3K
    - PI3P degradation

  - Extrinsic/Intrinsic Apoptosis inhibition
    - Synthesis of TNF-a
    - Disc formation
    - Bad/BCL-2 Phosphorylation (Cytochrome C inhibition)
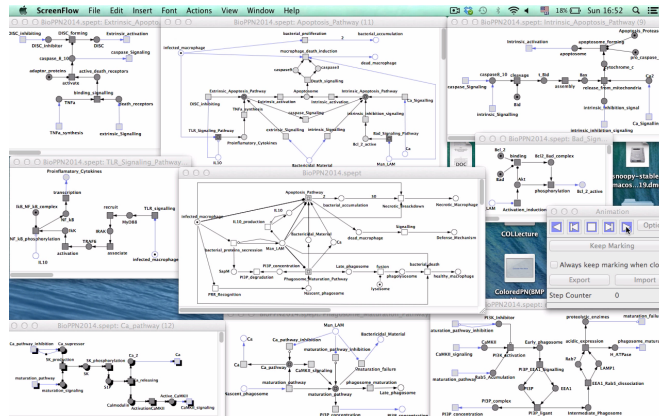
Animation mode available in: http://bio-imaging.liacs.nl/galleries/epn-infection/
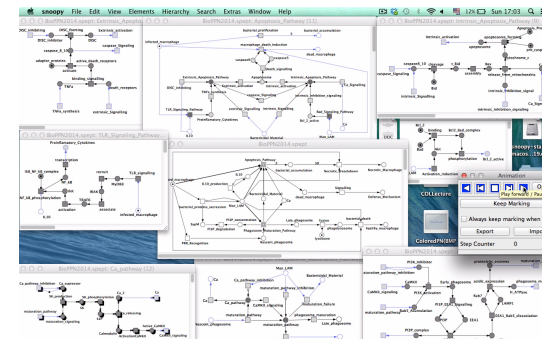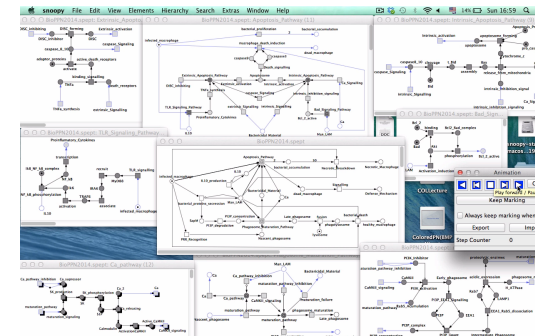
Animation Mode

- Second Scenario: Phagosome Maturation
  - Production of Ca$^+$/CaMKII
  - Activation of PI3K
  - Fusion with lysosome
  - Bacterial death

Animation mode available in: http://bio-imaging.liacs.nl/galleries/epn-infection/

Animation Mode

- Third Scenario: Apoptosis

    - Extrinsic apoptosis pathway
        - Synthesis of TNFa (activation of Nf-kB)
        - Caspase release
        - Disc Formation
        - Apoptosome
        - Death Macrophage
        - Defense mechanism

    - Intrinsic Apoptosis pathway
        - Ca$^+$ Signaling
        - Release of Cytochrome-C
        - Apoptosme
        - Death Macrophage
        - Defense Mechanism

Animation mode available in: http://bio-imaging.liacs.nl/galleries/epn-infection/

Challenges

- Qualitative model hierarchically connected
  - Add/develop structures as extension
    - Bacteria pathways
- Quantitative model
  - Continuous/Probabilistic model based on the statistical analysis and quantitative data
- Validation
  - Verify and validate the model using Model checking tools and biological experiments
- Simulation
  - Perform "what-if" situations addressing new hypothesis

Thank You!!!

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