7th International Workshop on Biological Processes & Petri Nets (BioPPN 2016)

# The influence of IL-18 on the process of atherosclerosis modeled and analyzed by stochastic Petri net

Marcin Radom[1]
Dorota Formanowicz[2]
Piotr Formanowicz[1,3]

[1]Institute of Computing Science, Poznan University of Technology
[2]Department of Clinical Biochemistry and Laboratory Medicine, Poznan University of Medical Sciences
[3]Institute of Bioorganic Chemistry, Polish Academy of Sciences

Toruń, 20.06.2016

# Biological background

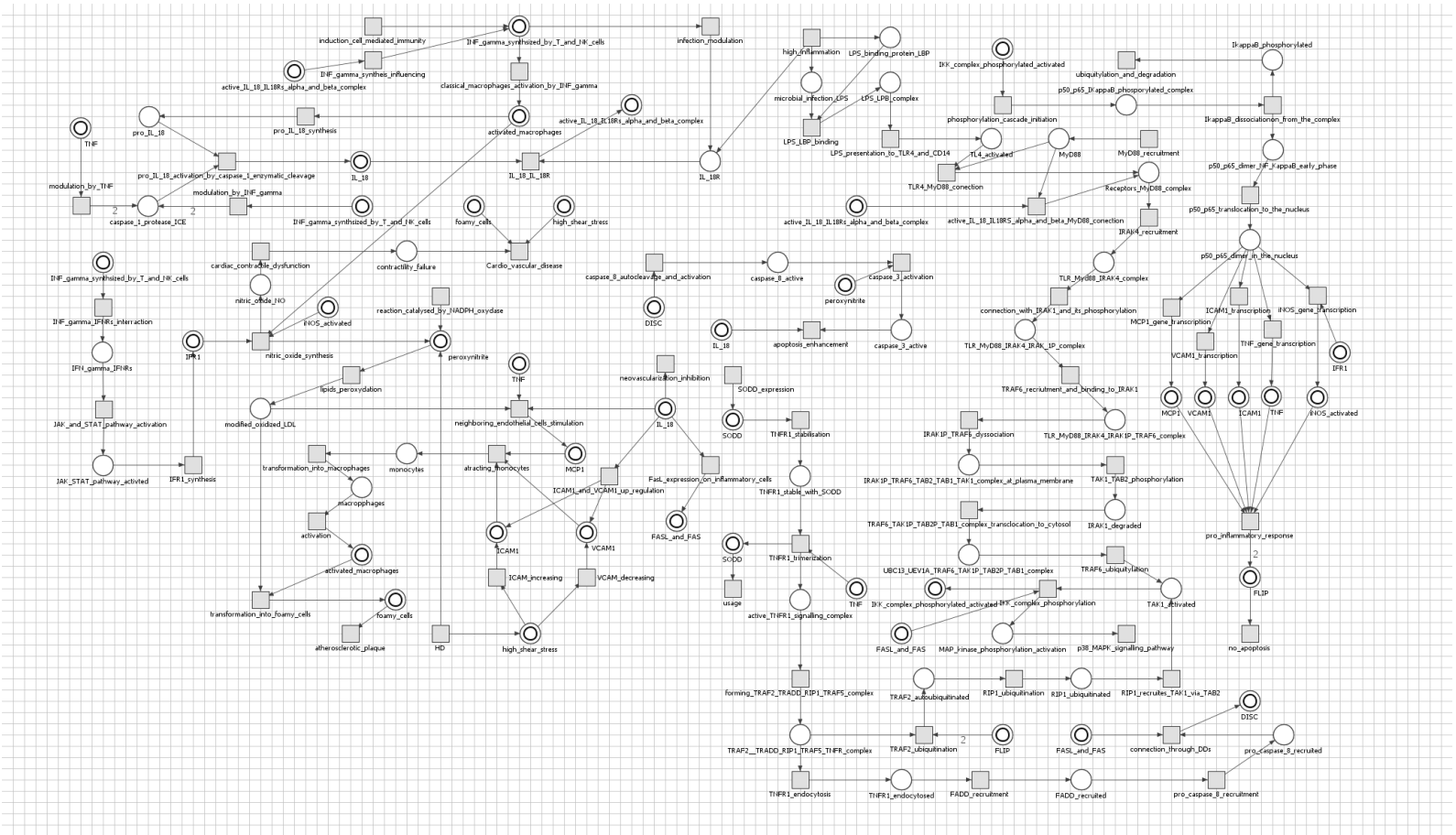
- The complexity of atherosclerosis makes it particularly difficult to manage; thereby it requires sophisticated methods and markers that would be involved in many signaling pathways.
- Interleukin-18 (IL-18) is a unique cytokine that has been analyzed in this study, it can initiate a cascade of pro-inflammatory cytokines and stimulate Th1 or Th2 response depending on cytokine surrounding.
- Both of these processes are crucial for formation of atherosclerosis lesions.

# Selected compounds used in the model

- **Caspase 1 protease ICE** (Interleukin-1 Converting Enzyme)
- **Caspase 3** and **8** proteins – cell apoptosis factors (model)
- **TNF** (Tumor Necrosis Factors) cytokins
- **FASL** transmembrame protein (member of TNF family)
- **MYD88** - Myeloid differentiation primary response gene 88
- **IFR1** – Interferon type I
- **VCAM-1** and **ICAM-1** - Vascular Cell Adhesion Molecule 1 and Intercellular Adhesion Molecule 1
- **Foam Cells** - fat-laden macrophages connected with the process of atherosclerosis formation

# Petri net

50 places, 76 transitions



# Structural analysis (former research)

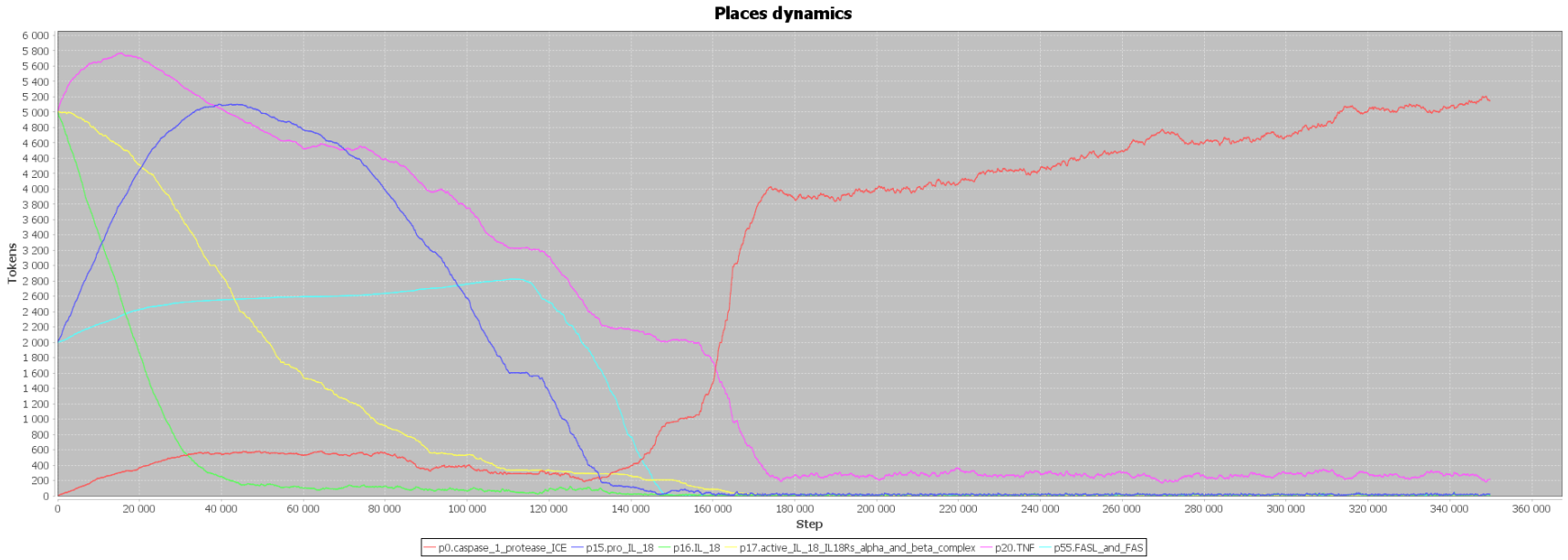
- 223 t-invariants (16 clusters)
- 11 MCT-sets

| MCT | No. of the contained transitions | Biological meaning |
|---|---|---|
| 1 | 15 | MyD88-dependent signaling pathway |
| 2 | 7 | induction of apoptosis influenced by caspases 3 and 8 that are situated at pivotal junctions in apoptosis pathways |
| 3 | 4 | activation of the innate immune system through TLR signaling pathways regulated by TIR domain-containing adaptors, such as MyD88 |
| 4 | 4 | JAK-STAT signaling pathway stimulated by INF-$\gamma$ and its impact on the regulation of iNOS expression |
| 5 | 3 | formation of an active TNFR1 signaling complex |
| 6 | 3 | influence of NO on cardiovascular system |
| 7 | 3 | transformation of monocytes into activated macrophages |
| 8 | 3 | activation of a silencer of TNFR1 signaling pathway |
| 9 | 2 | pro-IL-18 signaling pathway |
| 10 | 2 | activation of macrophages by the classical pathway |
| 11 | 2 | SODD signaling pathway |

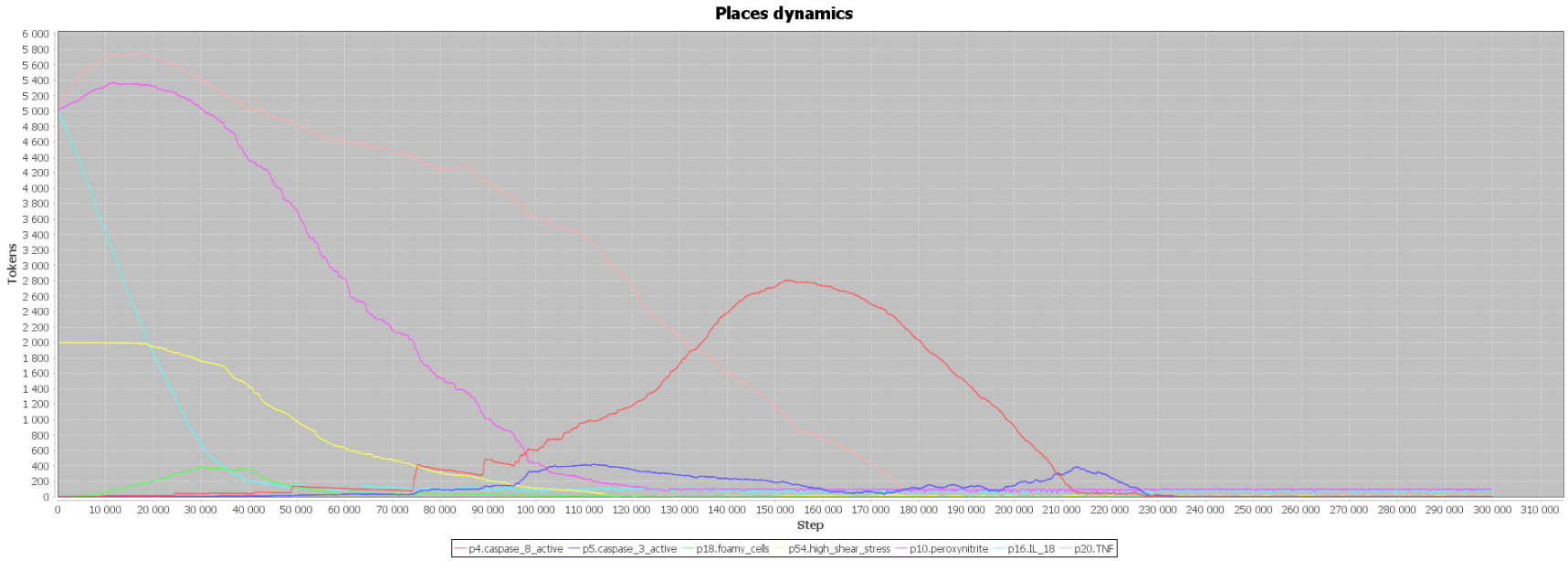
# Stochastic Petri net approach

- Firing rates for transitions:
  - Various sources from the literatury (vary, can be incomplete and inconsistent)
  - chosen and adjusted experimentally, depending on the scenario: high or low initial compounds contentrations, high or low external flow of significant compounds
- Different scenarios tested, i.e., allowing constant flow of significant model factors (IL-18, peroxinitrites) and its influence of the athrosclerosis factor behaviour
- Results are preliminary (a lot) and require further thorough studies

# Scenario example – higher initial concentrations of IL-18 production factors and their influence on TNF / FASL proteins



# High concentrations of IL-18 and TNF and their influence on factors related to atherosclerotic plaque enhacement & apoptosis within the model



# Plans for the ongoing analysis

- Extended stochastic Petri nets (especially with deterministic / scheduled transitions) for testing model behaviour in different scenarios.
- Further examination of transition firing rates / comparison with the literature data (if available).
- Knockout analysis connected with stochastic simulations.
- Simulations based on Gillespie SSA

# Thank you!