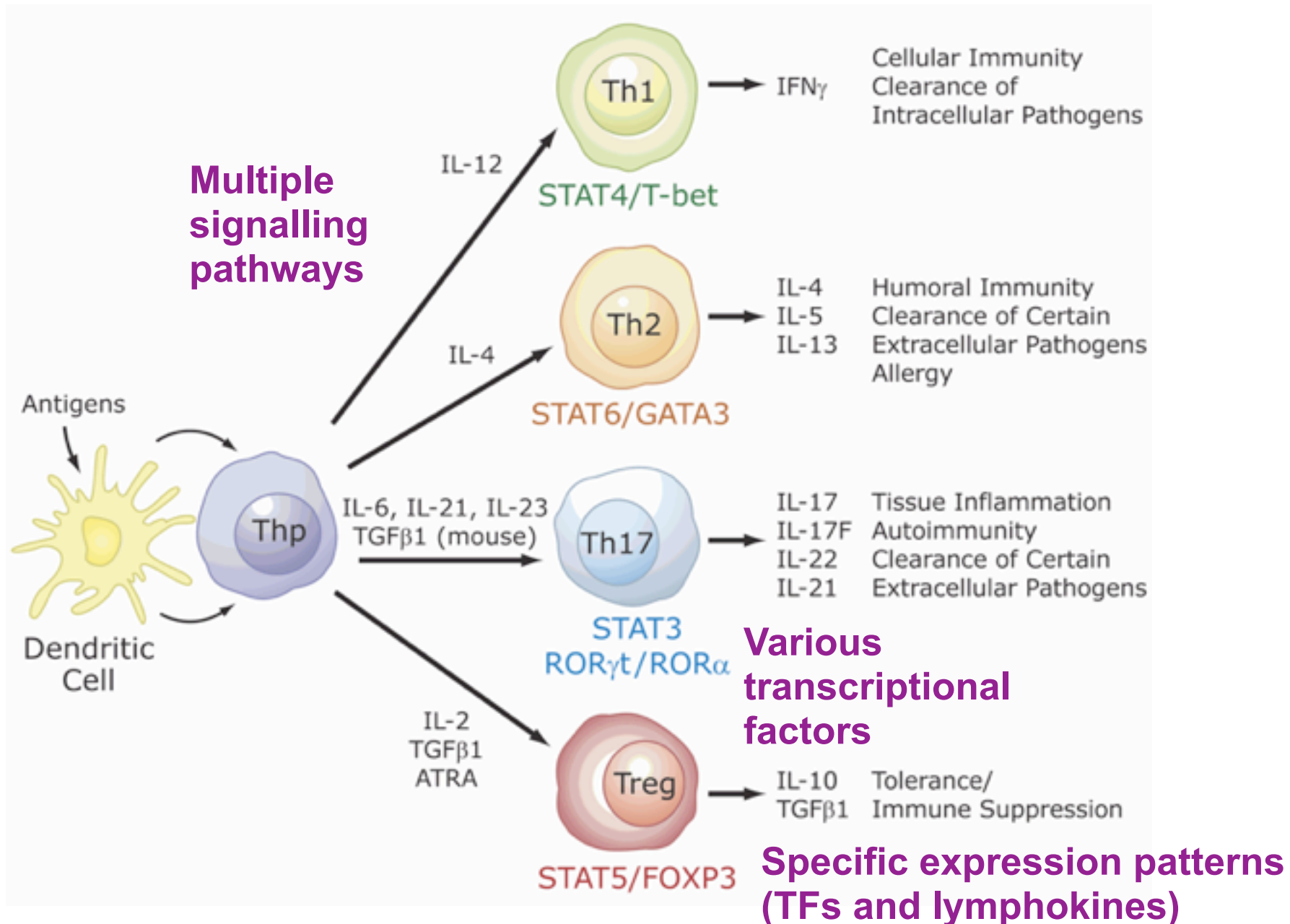




# Logical modelling of T-helper cell differentiation

**Denis Thieffry** ([thieffry@ens.fr](mailto:thieffry@ens.fr))

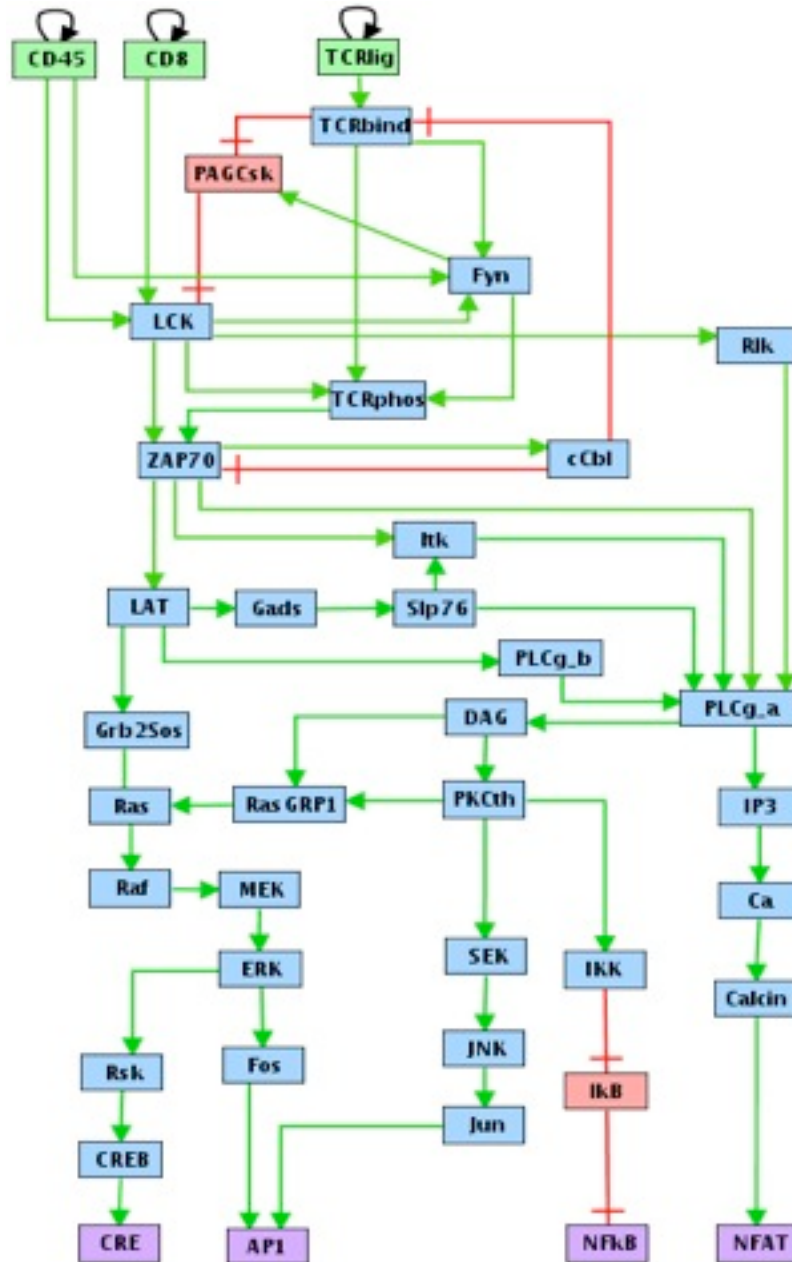
# CD4+ T-helper cell differentiation



# Biological questions

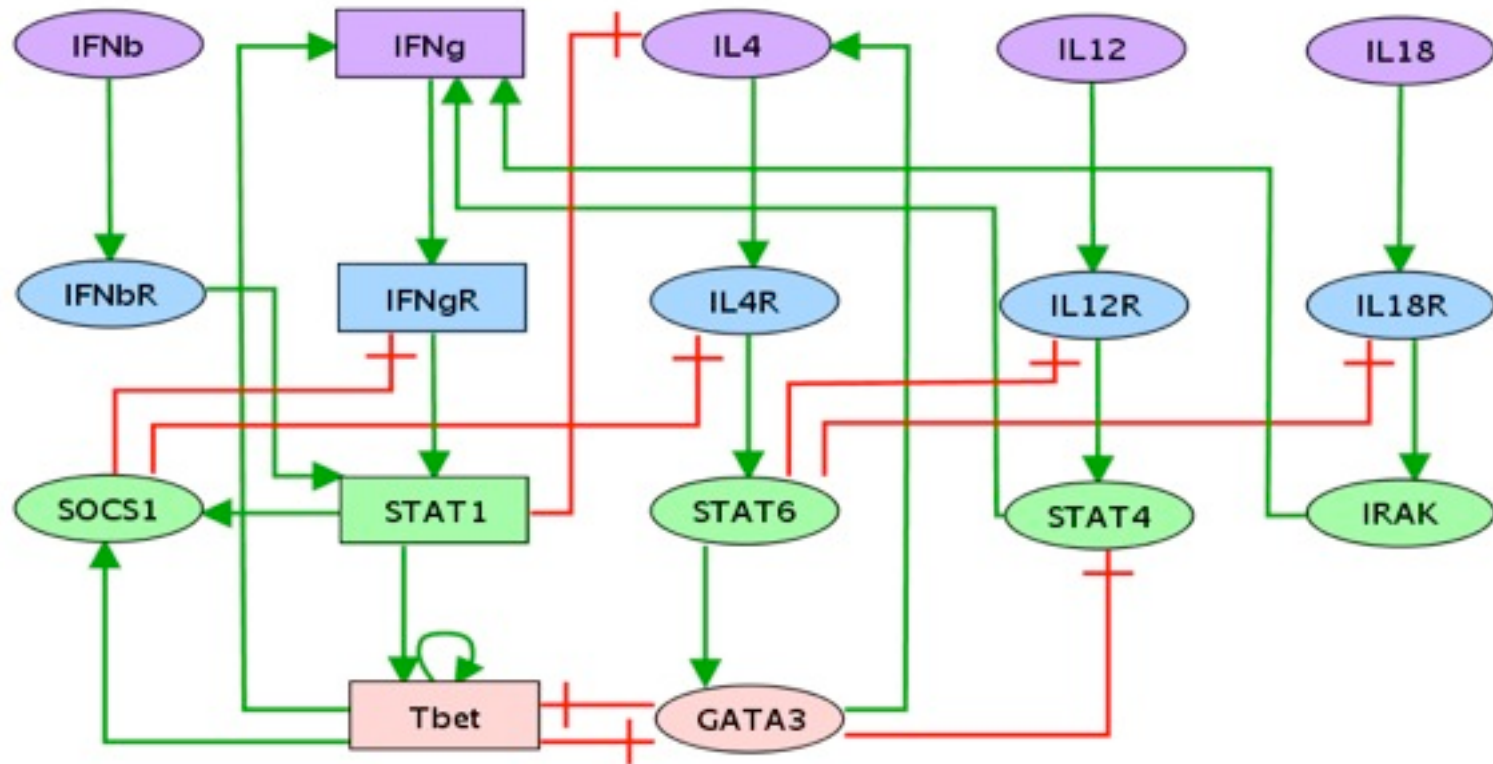
- How does a cell decide which differentiation pathway to follow?
- When and to what extent cells become committed?
- To what extent and how is it possible to force cell to change their differentiation states?

# Modelling of Th activation and differentiation

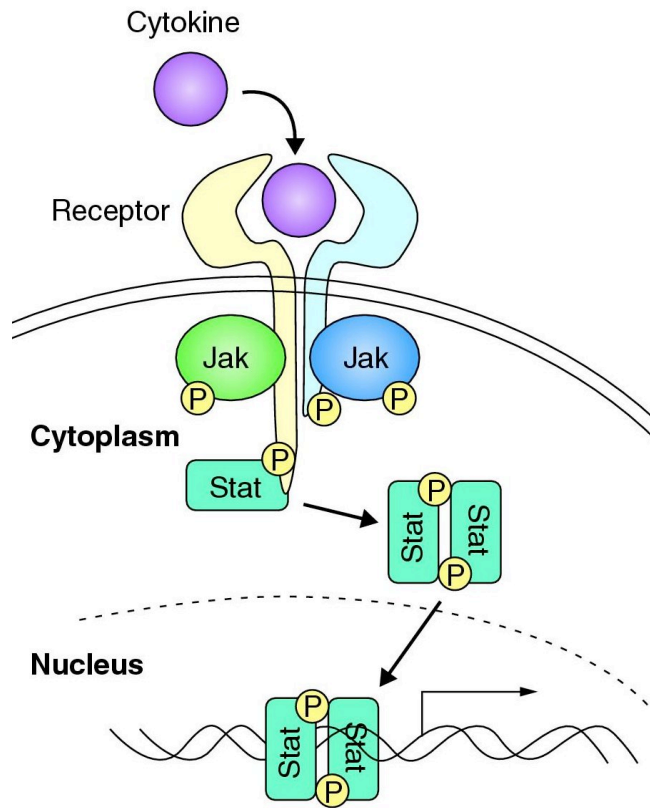


Klamt S et al (2006).  
*BMC Bioinformatics* 7: 56.

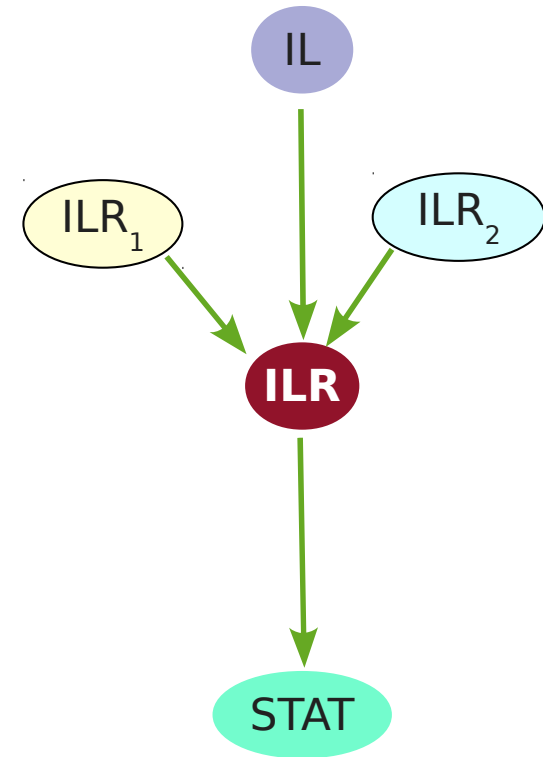
# Modelling of peripheral Th1/Th2 cell differentiation



# Towards a comprehensive, modular logical model of the Th differentiation network

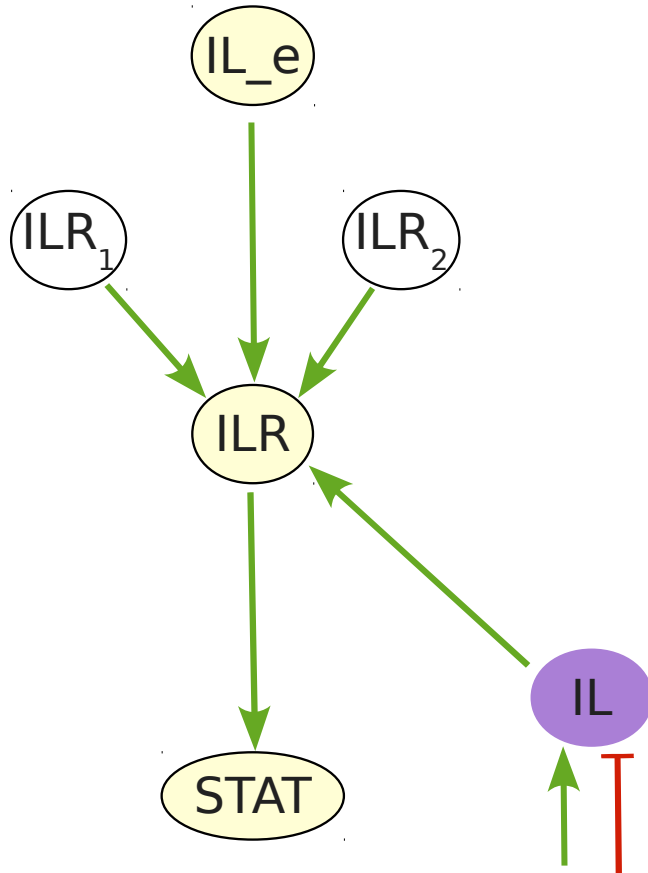


Yamoka *et al* (2004)



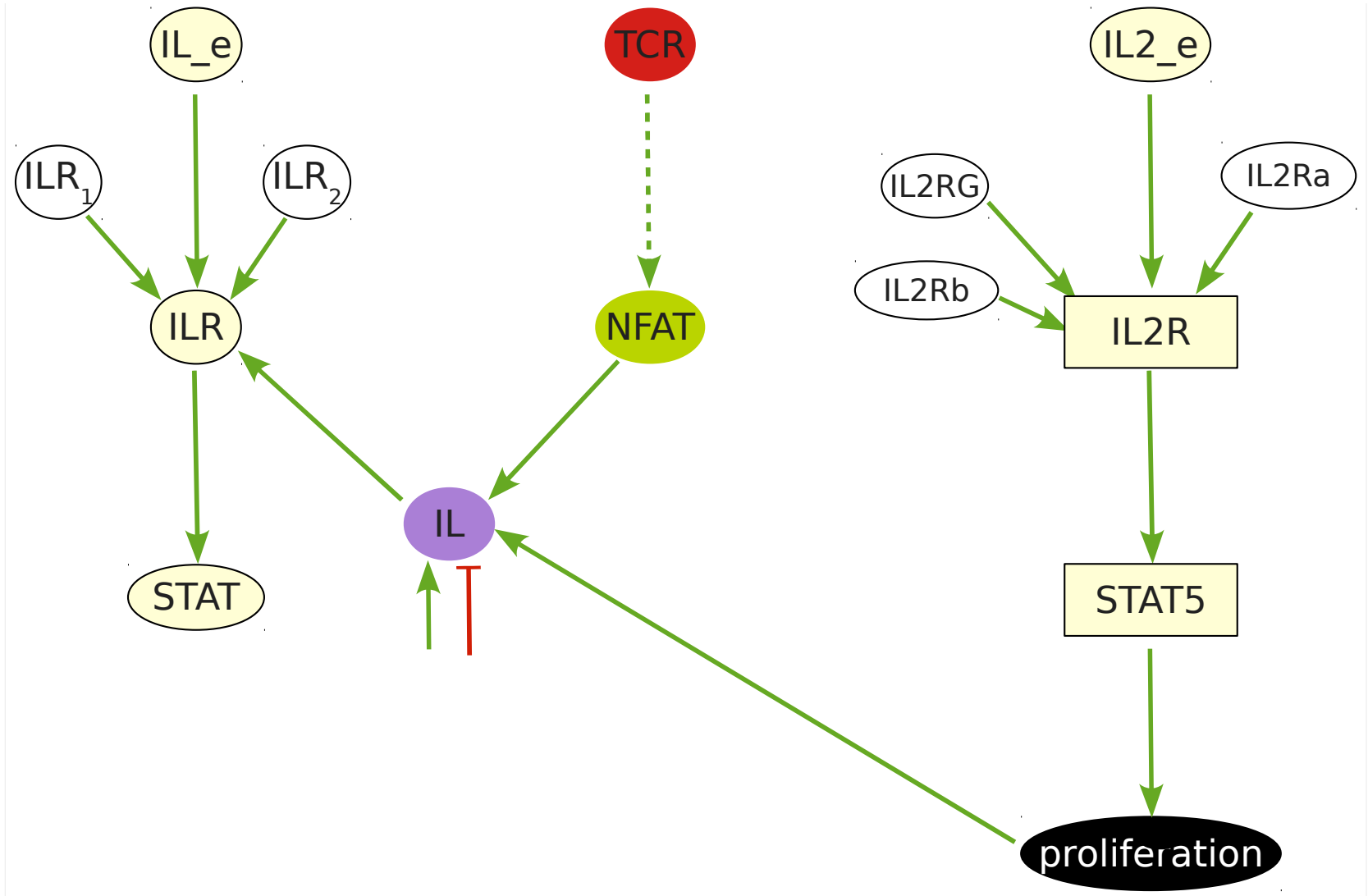
$ILR = 1$  IFF  $IL$  AND  $ILR1$  AND  $ILR2$

# Logical modelling of the Th network

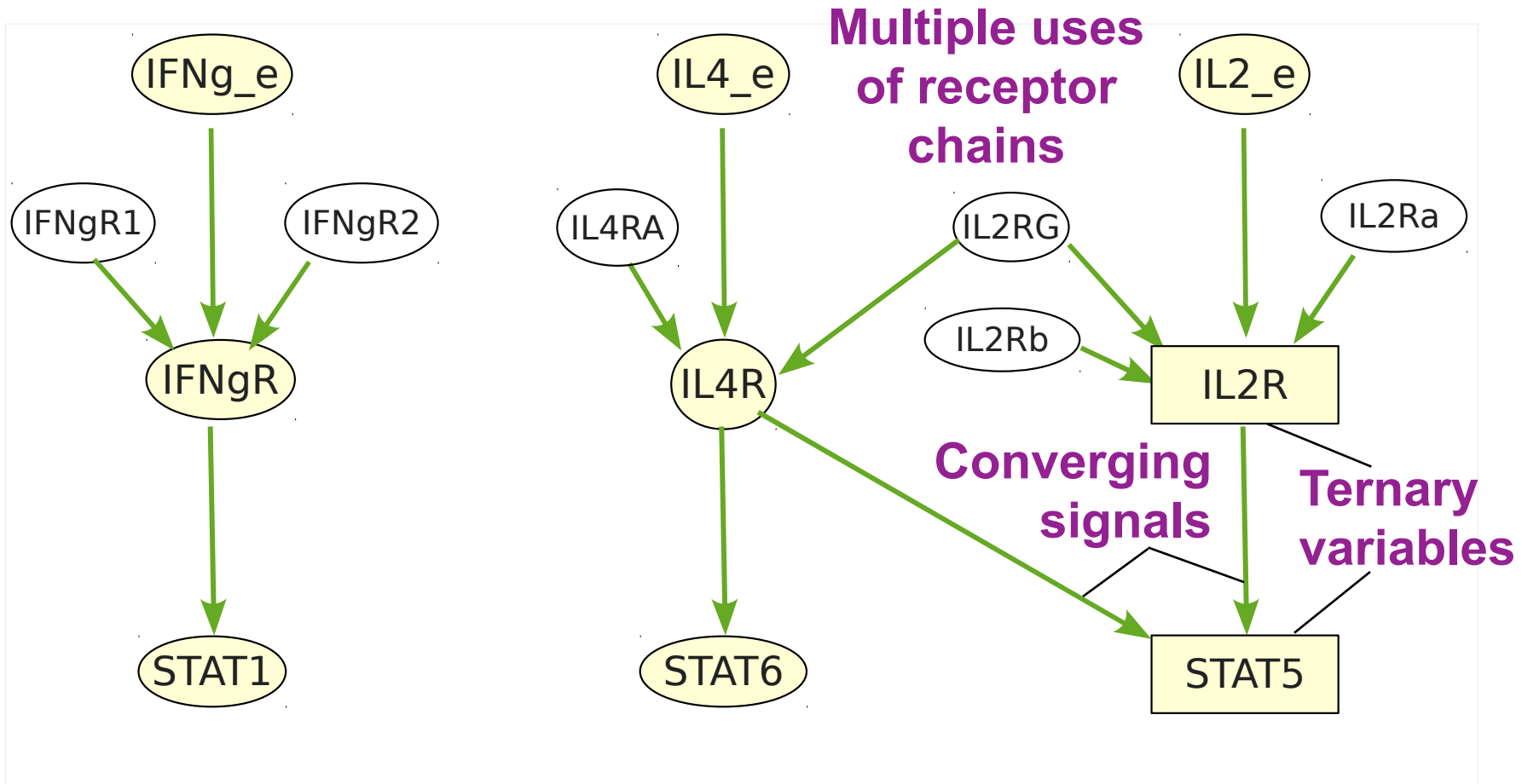


$$ILR = 1 \text{ IFF } (IL \text{ OR } IL_e) \text{ AND } ILR1 \text{ AND } ILR2$$

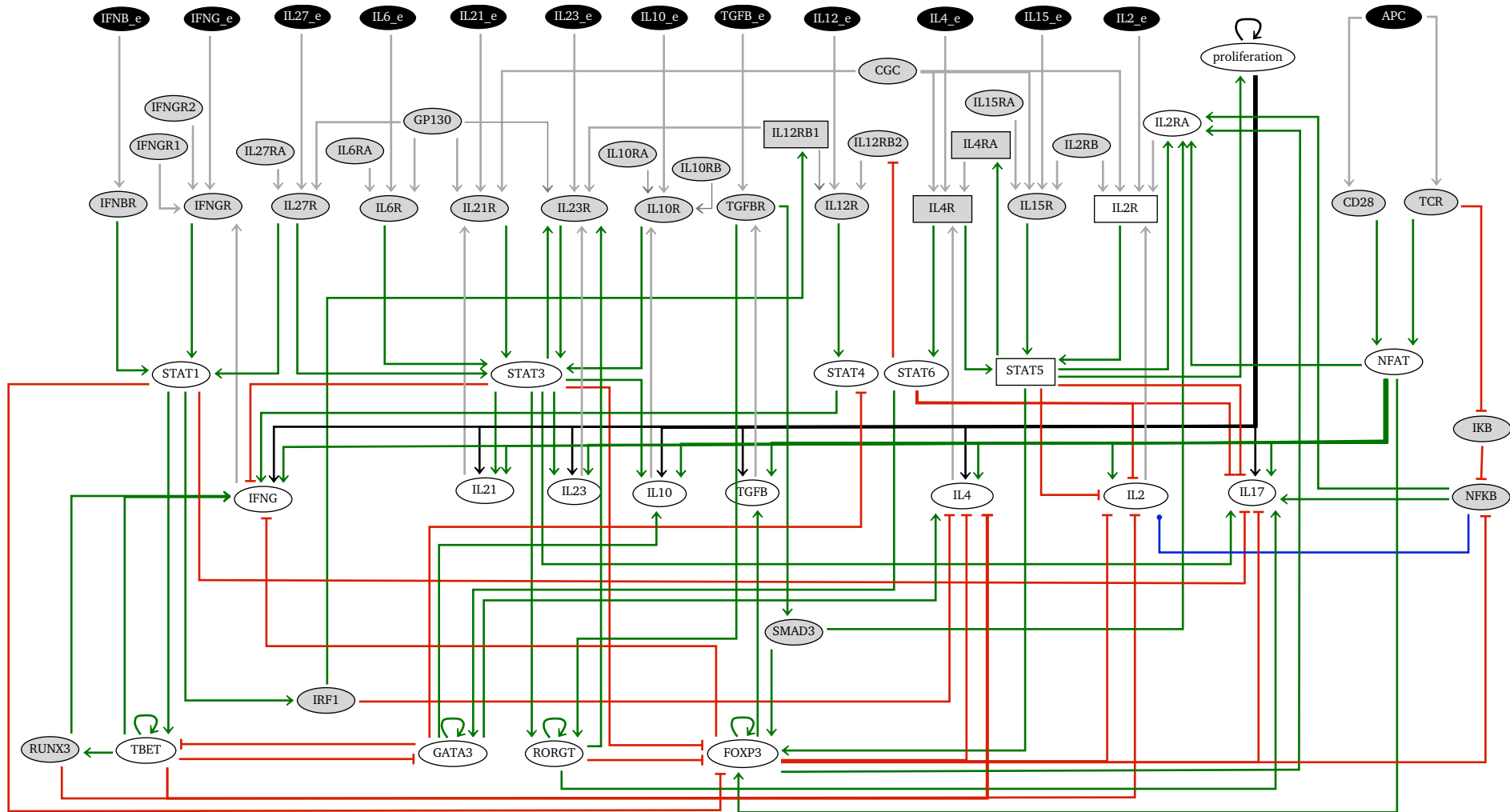
# Logical modelling of the Th network



# Logical modelling of the Th network

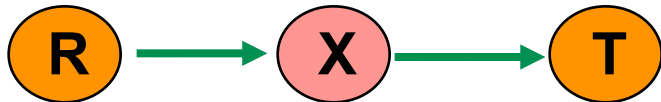


# Current logical model of the Th network



**13 input components, 52 internal components, 339 circuits**  
**=> too large to perform simulations**

# Model Reduction



## Detailed model

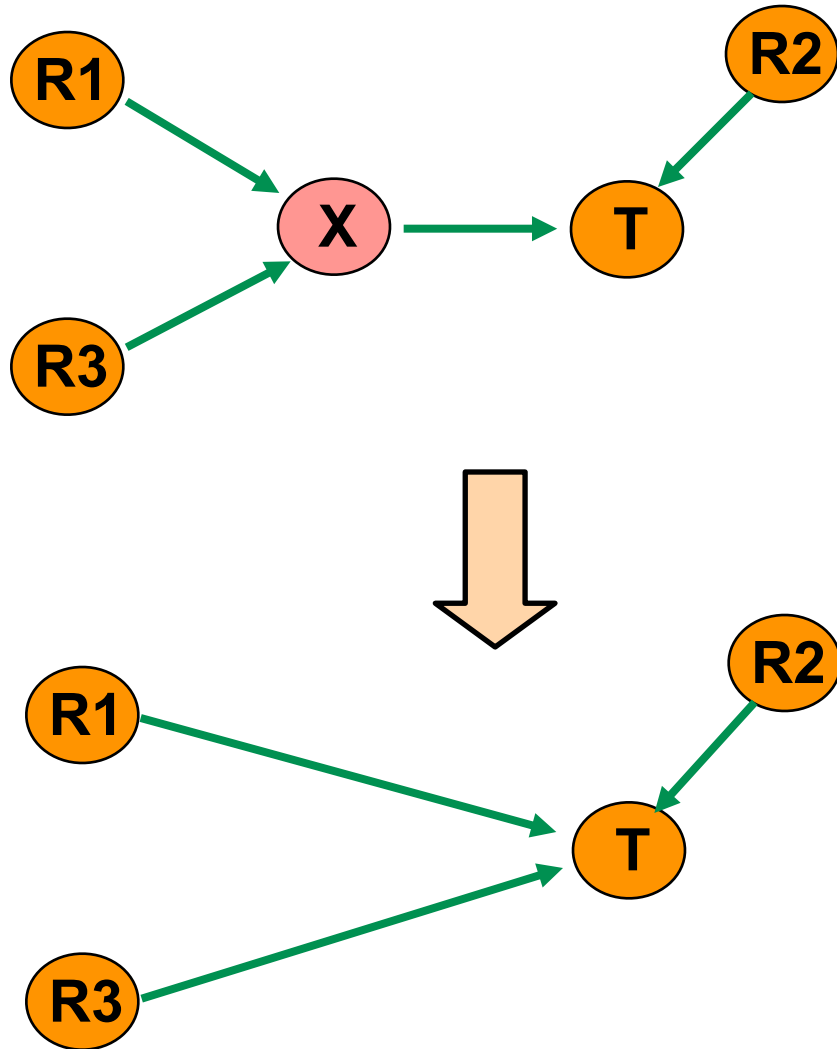
- Comprehensive
- Difficult to analyse

## Reduced model



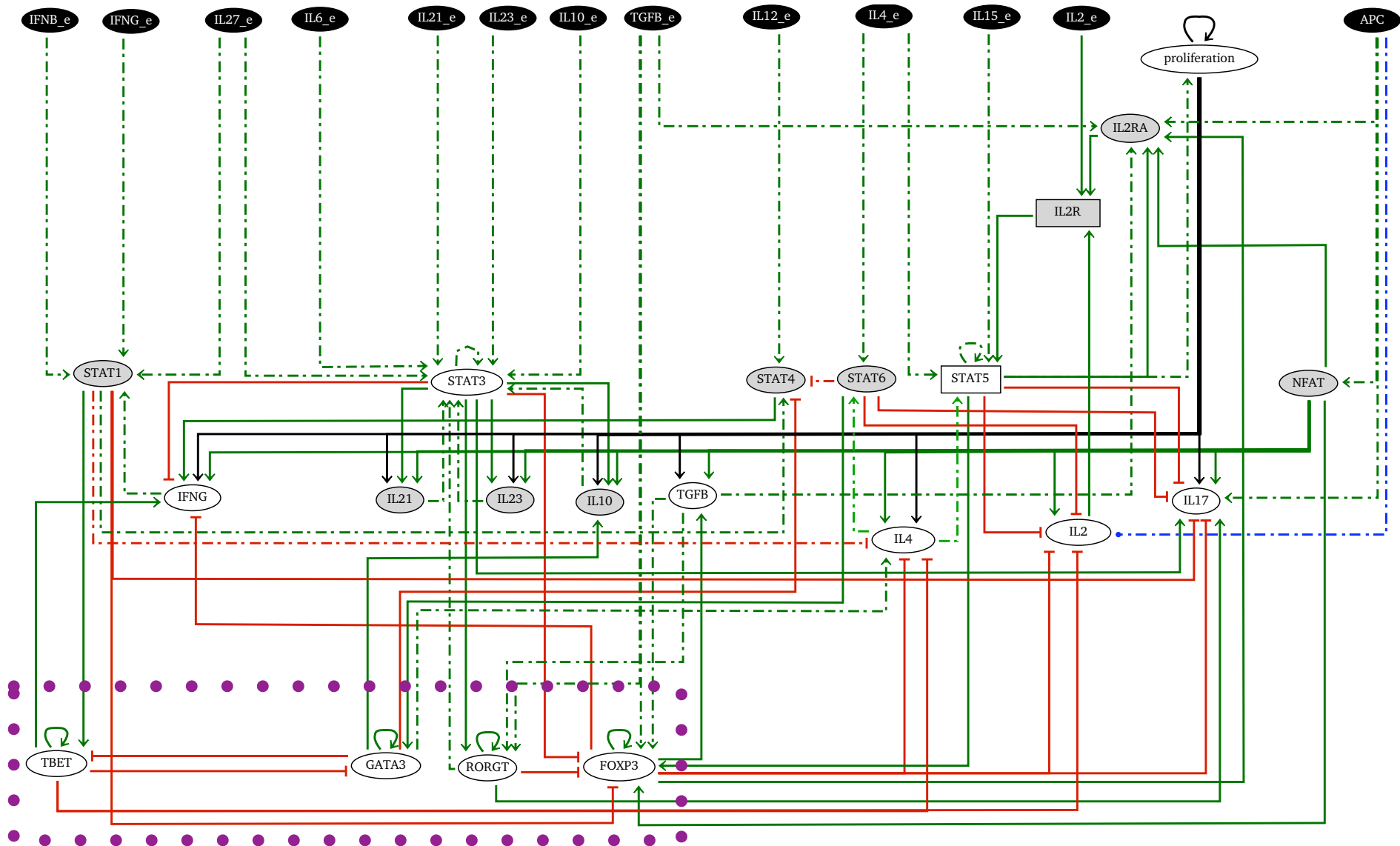
- Easier to analyse
- Loss of information
  - Biological (indirect effect)
  - Dynamical (delays)

# Model Reduction



- **Keep the detailed model**
- **Reduction before analysis**  
=> New rules for targets of hidden nodes
- **Choice of reduction**
- **Dynamical consistency**
  - **No** circuit deletion
  - Same stable states
  - Reachability may change

# Reduced logical model



13 input components, 21 internal components

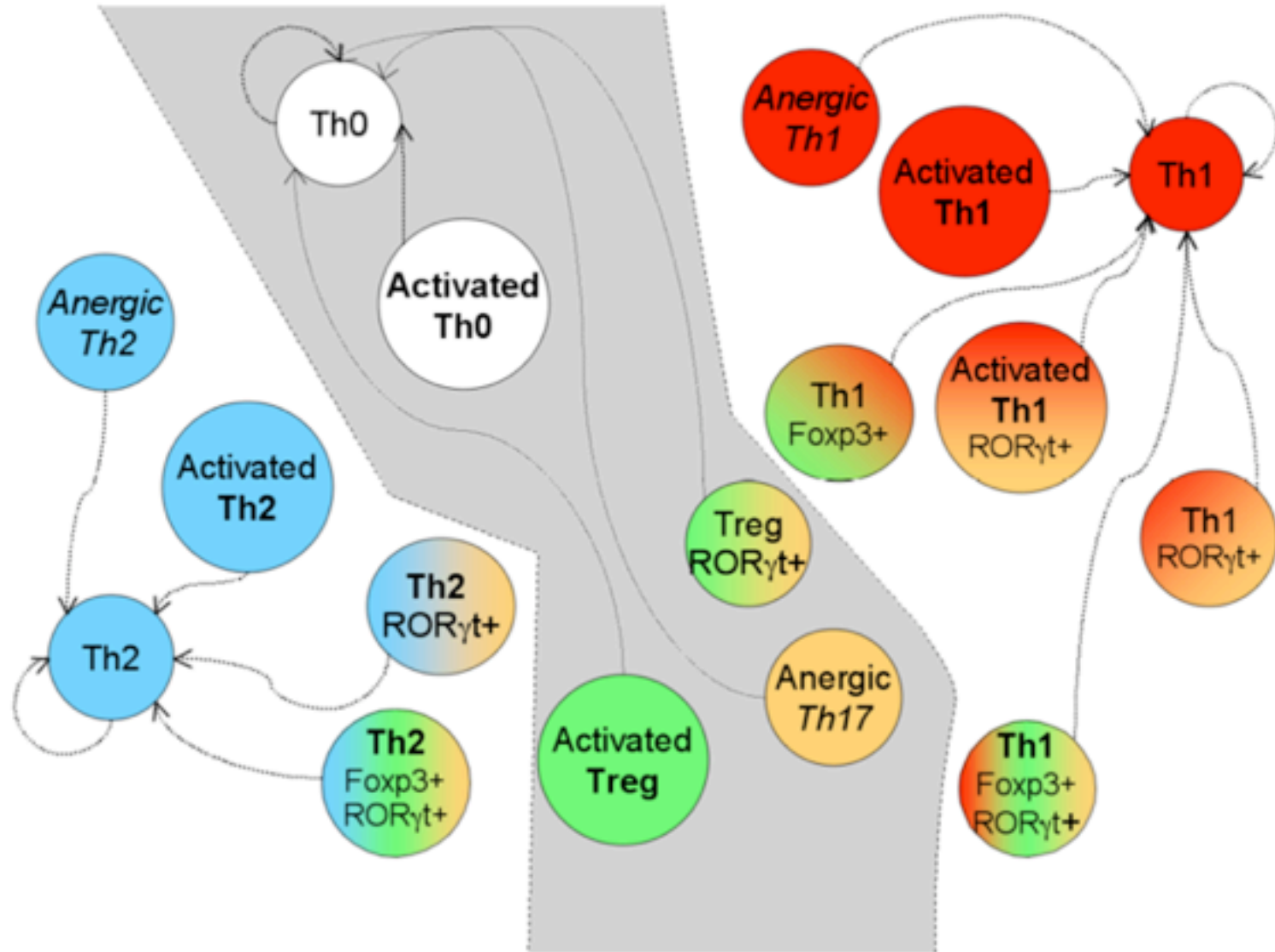
# Selected environments for simulations

	<b>APC</b>	<b>IL2</b>	<b>IL4</b>	<b>IL6</b>	<b>IL10</b>	<b>IL12</b>	<b>IFNG</b>	<b>TGFB</b>
<b>No input</b>								
<b>APC</b>								
<b>Pro-Th1</b>								
<b>Pro-Th1'</b>								
<b>Pro-Th2</b>								
<b>Pro-Th17</b>								
<b>Pro-Treg</b>								
<b>Pro-Treg'</b>								

# Stable signatures

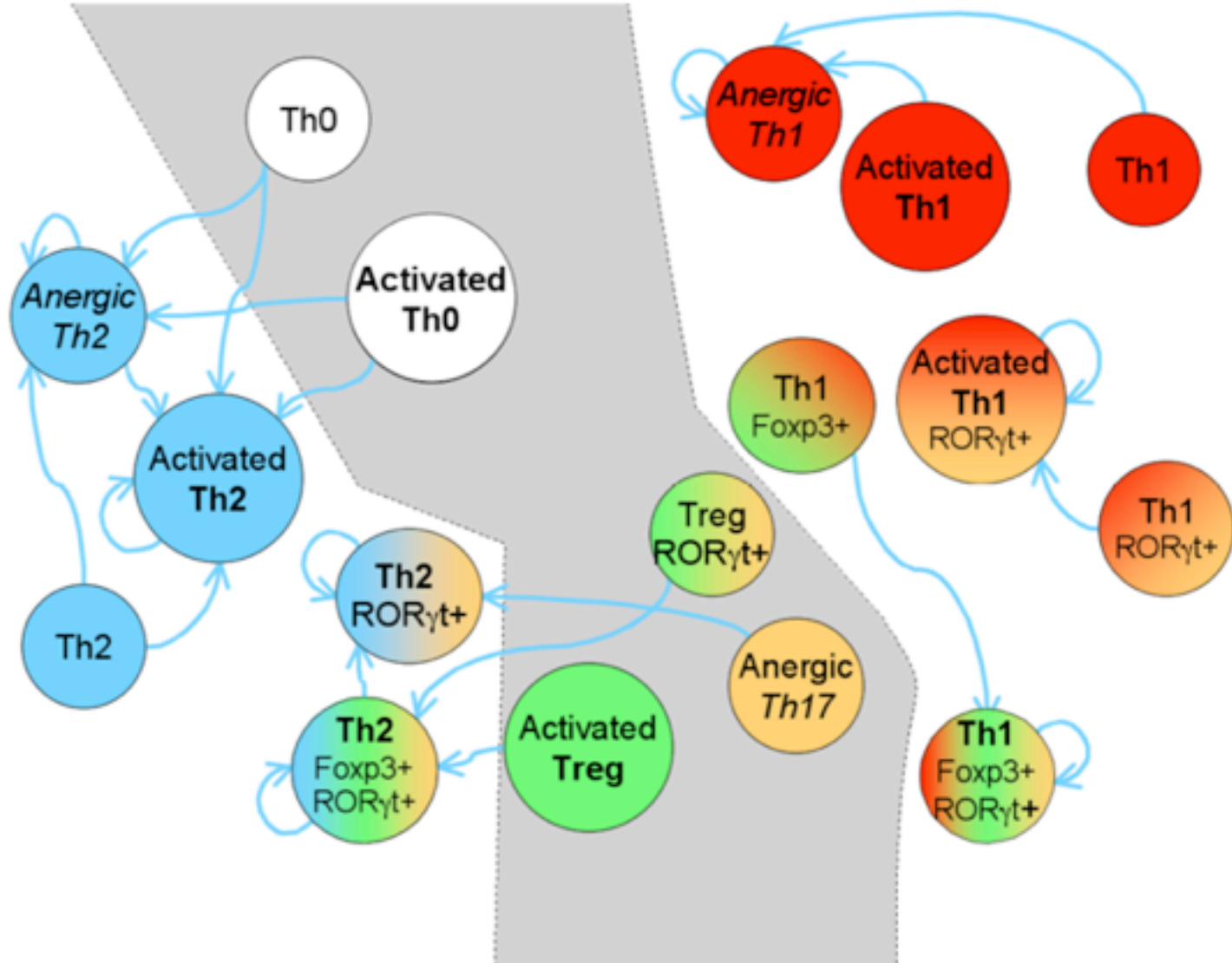
	IL2R	IL2RA	IFNG	IL2	IL4	IL10	IL21	IL23	TGFB	TBET	GATA3	FOXP3	NFAT	STAT1	STAT3	STAT4	STAT5	STAT6	proliferation	RORGT	IL17	Support		
Th0																							[7]	
Activated Th0	█			█		█	█	█					█		█					█				[7]
Th1										█										█				[7]
Activated Th1	█	█	█							█			█	█		█				█				[7]
Anergic Th1	█	█	█			█	█	█		█			█	█	█					█				[78]
Anergic Th1 ROR $\gamma$ t+	█	█	█			█	█	█		█			█	█	█					█				predicted
Th1 ROR $\gamma$ t+						█	█	█		█			█	█	█					█		█		[44, 45, 70]
Th1 Foxp3+	█											█		█						█				[12]
Anergic Th17	█	█		█		█	█	█		█			█	█	█					█		█		
Th2																								[7]
Activated Th2		█				█	█	█					█	█	█					█				[7]
Anergic Th2	█	█		█		█	█	█		█			█	█	█					█		█		[78]
Th2 ROR $\gamma$ t+	█	█		█		█	█	█		█			█	█	█					█		█		[49]
Activated Treg	█																			█				[79]
Treg ROR $\gamma$ t+	█																			█		█		[46-48]
Th1 Foxp3+ ROR $\gamma$ t+	█	█												█						█		█		predicted
Th2 Foxp3+ ROR $\gamma$ t+	█	█												█						█		█		predicted

# Simulations in the absence of stimulation



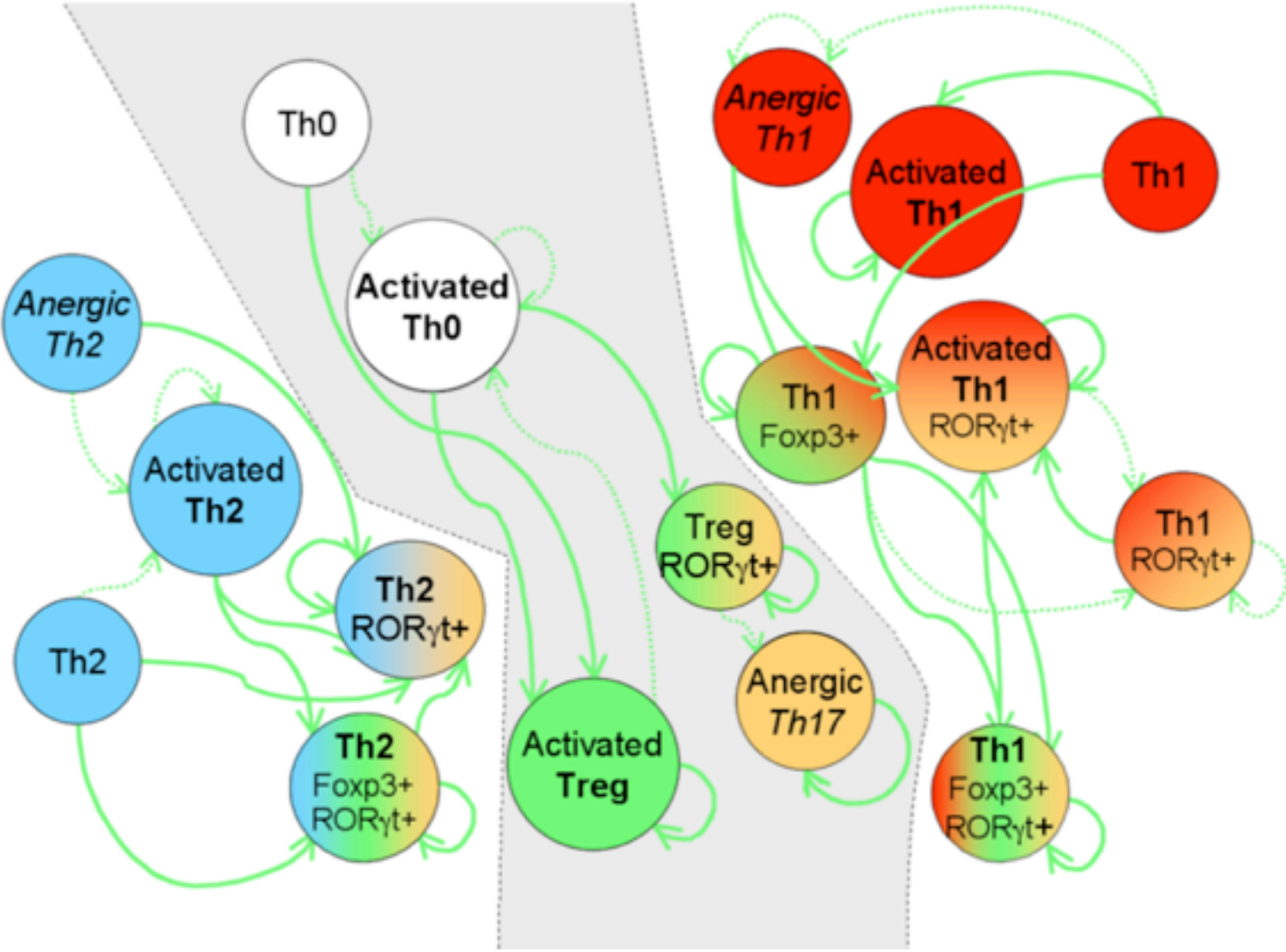
**GATA3**, **Tbet**, **Foxp3** and **ROR $\gamma$ t**

# Pro Th2 environment (IL4 & IL6)



**GATA3, Tbet, Foxp3 and ROR $\gamma$ t**

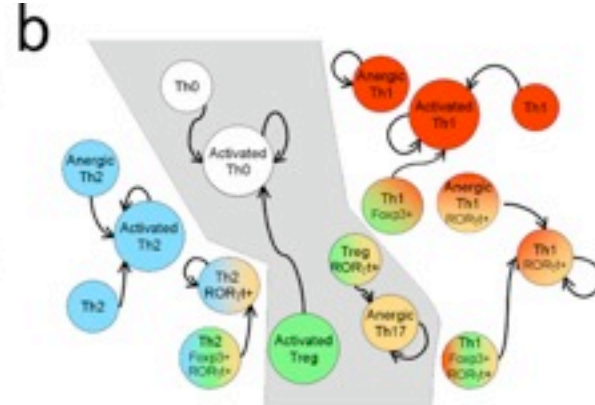
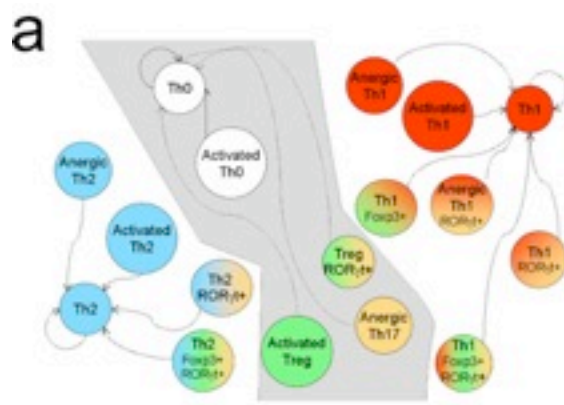
# Pro Treg environment (IL2 & TGFb | IL10)



**GATA3, Tbet, Foxp3 and RORyt**

# Overview of the simulation results for ≠ micro-environments

Absence of stimulation



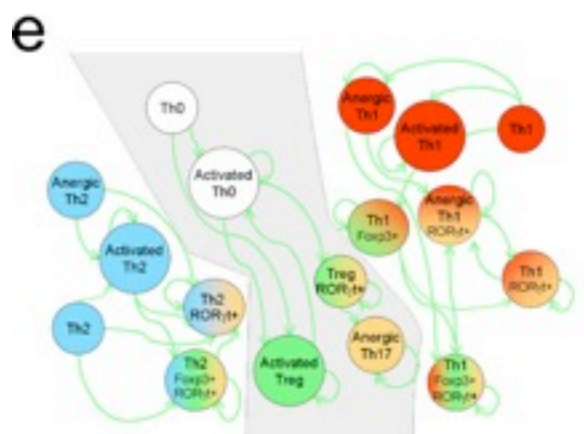
APC only

Pro-Th1  
IL2 & IFNg  
or IL12



Pro-Th2  
IL4 & IL6

Pro-Treg  
IL2 & TGFb  
or IL10



Pro-Th17  
IL6 & TGFb

GATA3 Tbet  
Foxp3 RORγt

# Conclusions

- **Model** reproducing the main reported **Th subtypes** (Th0, Th1, Th2, Treg, Th17) in terms of stable states
- Many more stable states depending on signalling environment, including **hybrid subtypes**
- **Plasticity** of Th subtypes depending on signalling environment
- **Differentiation network** rather than **lineage tree** ?

# Prospects

- Simulations of **mutants** and other perturbations
- **Extension** of this cellular model (additional pathways, transcription factors, interactions)
- Consideration of **novel subtypes**
- Coupling with **cell cycle** and **apoptosis** modules
- **Quantification** of alternative outcomes
- **Multi-cellular** (hierarchical?) **model**

# Contributors & supports

## ★ TAGC (Marseille)

- Aurélien Naldi
- Claudine Chaouiya



## ★ IML (Marseille)

- Elisabeth Rémy



## ★ IGC (Lisboa)

- Claudine Chaouiya
- Jorge Carneiro



**Belgian Inter-university  
Attraction Pole**  
*Bioinformatics and  
Modelling :*  
*from Genomes to Networks*