

GINsim: overview and hands-on

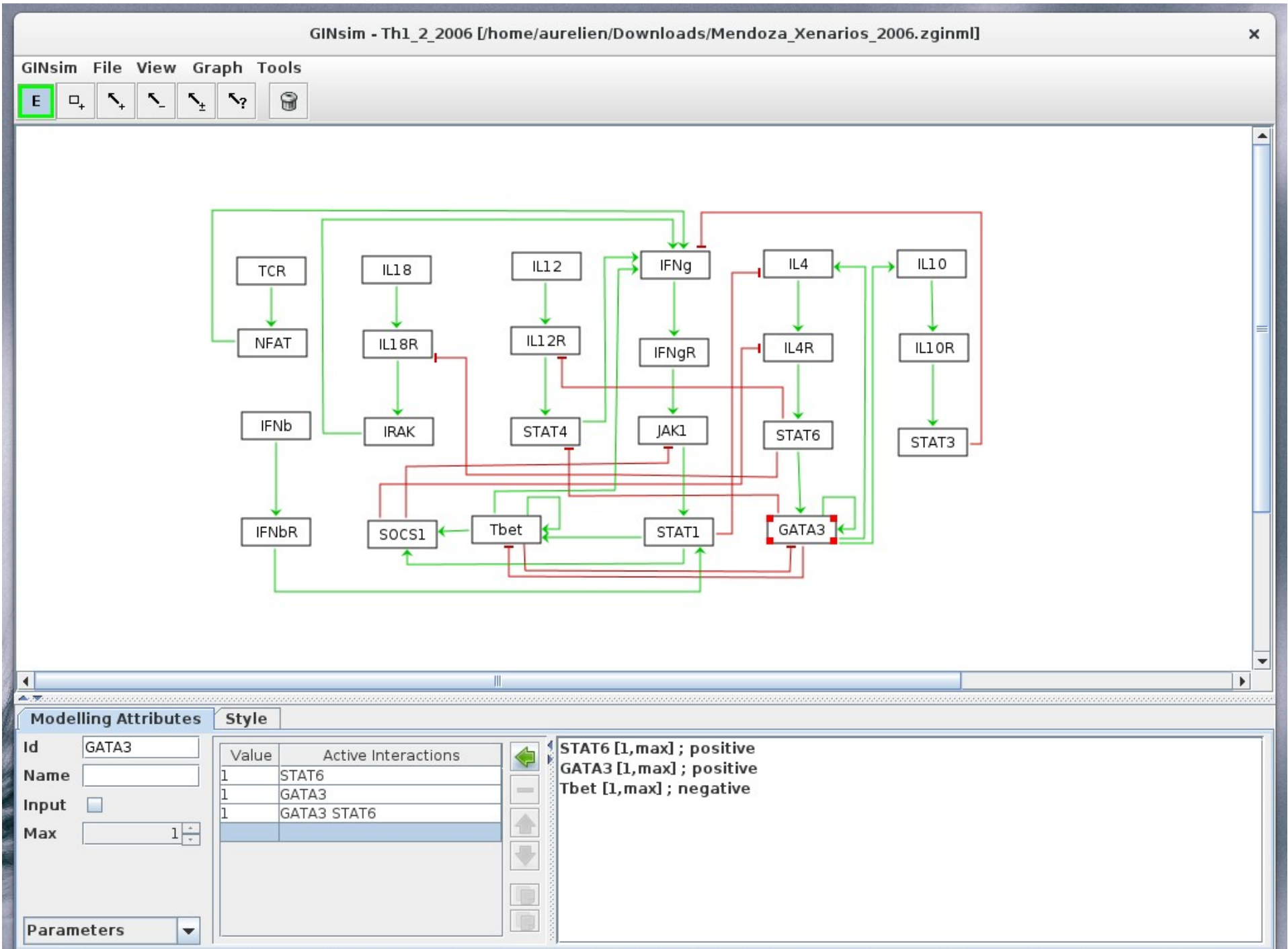
<http://www.ginsim.org>



Open the model



Th1-Th2 model



Selecting tools

GINsim - Th1_2_2006 [/home/aurelien/Downloads/Mendoza_Xenarios_2006.zginml]

GINsim File View Graph Tools

E [Icons: Copy, Paste, Undo, Redo, Zoom In, Zoom Out]

Tools menu:

- Run simulation
- Compute stable states
- Construct SCC Graph
- Reduce model
- Compose model instances
- Analyse circuits
- Compute interaction functionality

Diagram showing a signaling pathway with components: TCR, IL18, IL12, IFNg, IL4, IL10, NFAT, IL18R, IL12R, IFNgR, IL4R, IL10R, IFNb, IRAK, STAT4, JAK1, STAT6, IFNbR, SOCS1, Tbet, STAT1, and GATA3. Interactions are shown with green (positive) and red (negative) arrows.

Modelling Attributes Style

Id: GATA3

Name:

Input: ☐

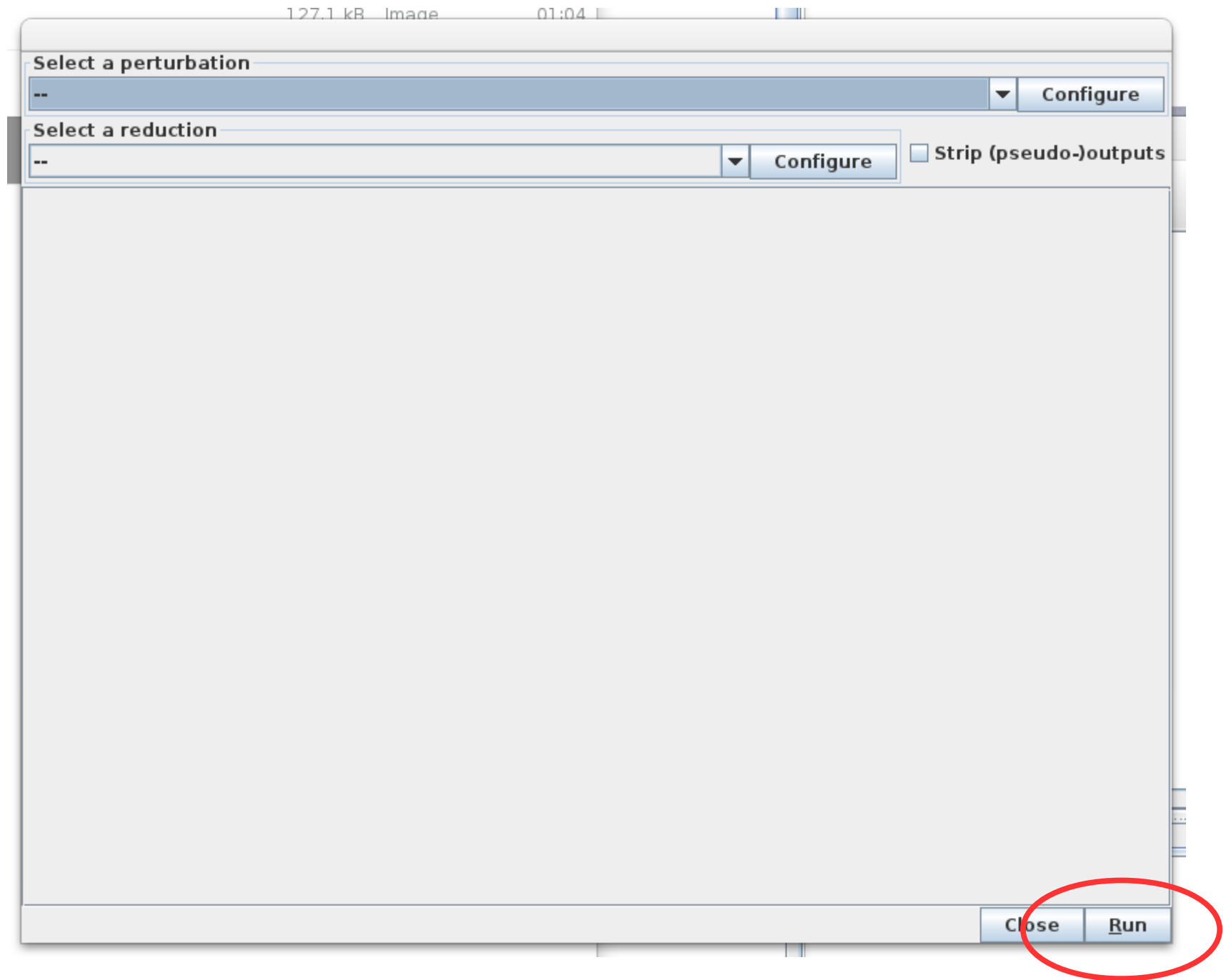
Max: 1

Parameters:

Value	Active Interactions
1	STAT6
1	GATA3
1	GATA3 STAT6

STAT6 [1,max] ; positive
GATA3 [1,max] ; positive
Tbet [1,max] ; negative

Stable states



Stable states

127.1 kB Image 01:04

Select a perturbation

--

Configure

Select a reduction

--

Configure

☐ Strip (pseudo-)outputs

Name	GATA3	IFN γ R	IFN γ	IFN γ R	IL10	IL10R	IL12R	IL18R	IL4	IL4R	IRAK	JAK1	NFAT	SOCS1	STAT1	STAT3	STAT4	STAT6	Tbet	IFN β	IL12	IL18	TCR
Th0																							
Th1			1											1					1				
			1										1	1					1				1
			1					1			1		1	1				1			1		
			1					1			1		1	1				1			1	1	
			1				1						1	1			1		1				1
			1				1						1	1			1		1		1	1	
			1				1	1			1		1	1			1		1		1	1	1
			1				1	1			1		1	1			1		1		1	1	1
			1				1						1	1	1			1					1
			1				1				1		1	1	1			1			1	1	
			1				1				1		1	1	1			1			1	1	1
			1				1				1		1	1	1			1			1	1	1
			1				1	1			1		1	1	1			1			1	1	1
			1				1	1			1		1	1	1			1			1	1	1
			1				1	1			1		1	1	1			1			1	1	1
			1				1	1			1		1	1	1			1			1	1	1
Th2	1				1	1			1							1		1		*	*		
	1				1	1			1				1			1		1		*	*		1
	1				1	1							1	1	1	1						1	
	1				1	1		1			1		1	1	1	1					1		
	1				1	1		1			1		1	1	1	1					1	1	
	1				1	1	1						1	1	1	1				1			
	1				1	1	1						1	1	1	1				1	1		
	1				1	1	1	1			1		1	1	1	1				1	1		
	1				1	1	1	1			1		1	1	1	1				1	1	1	

Close

Run

Simulation

Construction of the Dynamics

Select a perturbation
-- Configure

Select a reduction
-- Configure ☒ Strip (pseudo-)outputs

parameter + - ↑ ↓

Construction Strategy
State Transition Graph ▼

☐ Breadth First ☒ Depth First
Depth Number of States

Priority Class Selection
asynchronous Configure

Initial States
+ - ↑ ↓ ⌂

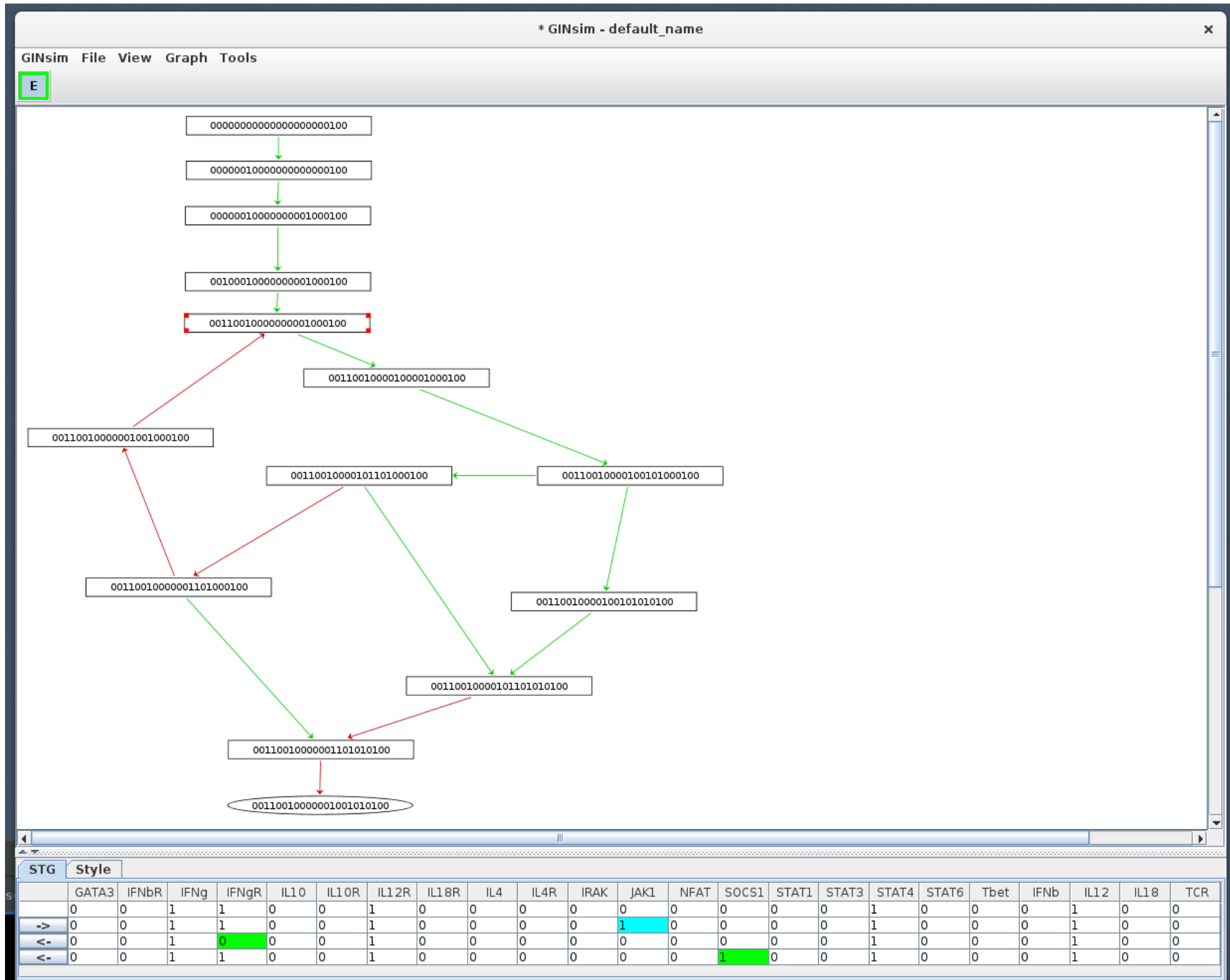
name	use	GATA3	IFNbR	IFNg	IFNgR	IL10	IL10R	IL12R	IL18R	IL4	IL4R	IRAK	JAK1	NF
Th0	<input checked="" type="checkbox"/>	0	0	0	0	0	0	0	0	0	0	0	0	0
Th1	<input type="checkbox"/>	0	0	M1	M1	0	0	0	0	0	0	0	0	0
Th2	<input type="checkbox"/>	M1	0	0	0	M1	M1	0	0	M1	M1	0	0	0
	<input type="checkbox"/>													

Fixed inputs
+ - ↑ ↓ ⌂

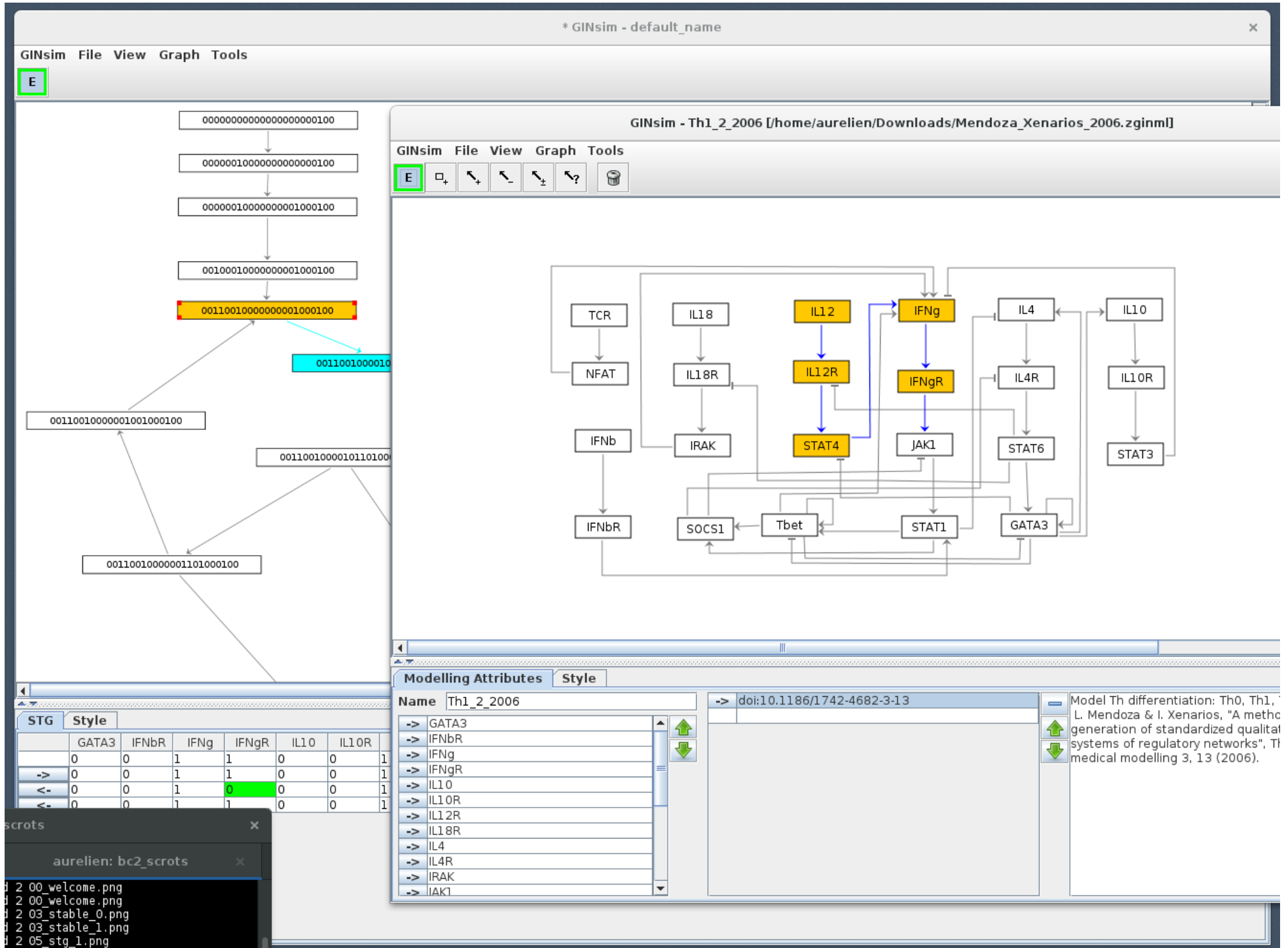
name	use	IFNb	IL12	IL18	TCR
no_stimul	<input type="checkbox"/>	0	0	0	0
pro_Th1	<input checked="" type="checkbox"/>	0	M1	0	0
input	<input type="checkbox"/>	M1	0	0	0
input_1	<input type="checkbox"/>	0	0	0	M1
	<input type="checkbox"/>				

Close Run

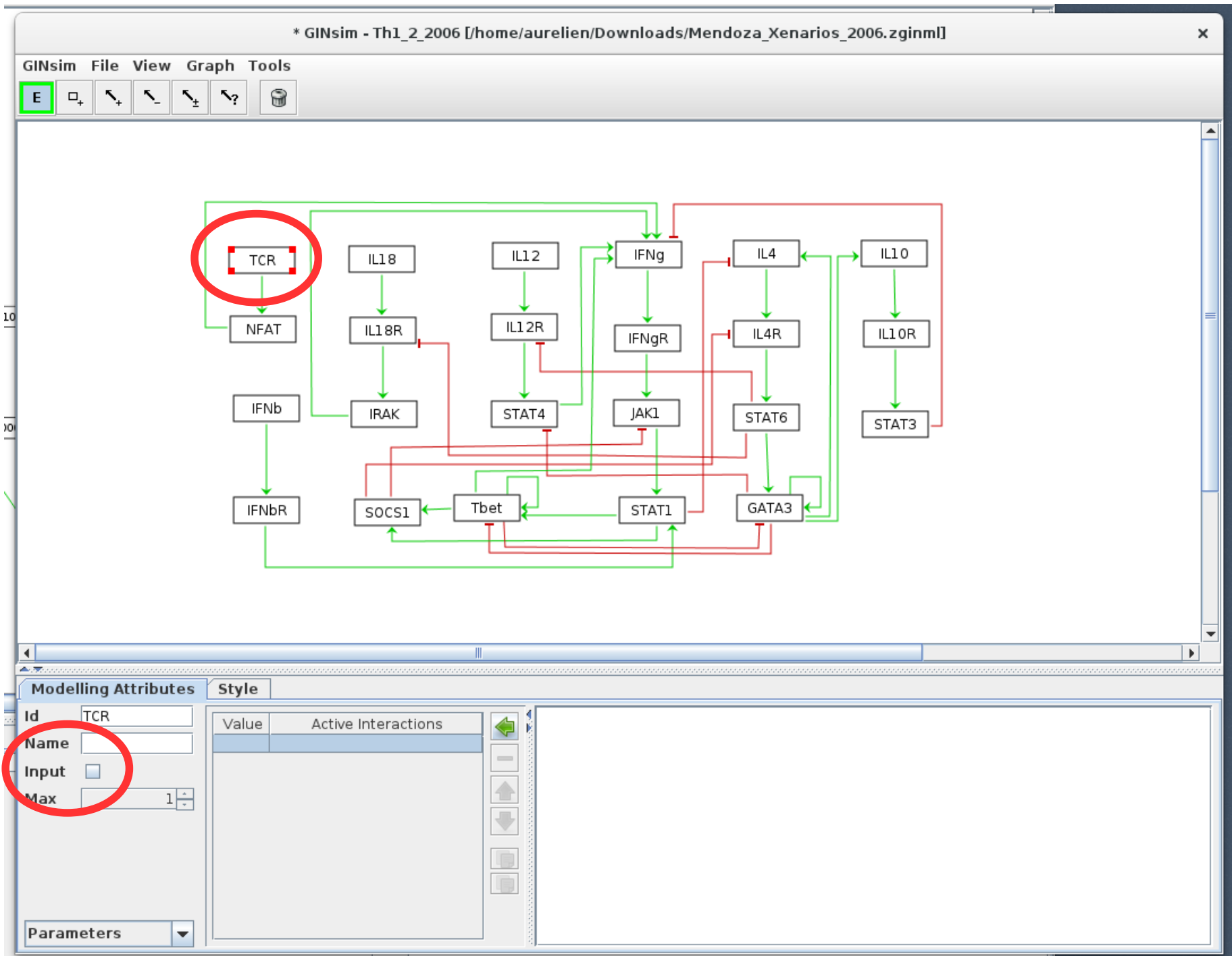
State Transition Graph (STG)



Colorize LRG based on states



Unlock the TCR input



Adapt initial states

Construction of the Dynamics

Select a perturbation
-- Configure

Select a reduction
-- Configure ☒ Strip (pseudo-)outputs

parameter + - ↑ ↓

Construction Strategy
State Transition Graph
☐ Breadth First ☒ Depth First
Depth Number of States

Priority Class Selection
asynchronous Configure

Initial States
+ - ↑ ↓ ⌂

OR	IL12R	IL18R	IL4	IL4R	IRAK	JAK1	NFAT	SOCS1	STAT1	STAT3	STAT4	STAT6	Tbet	TCR
	0	0	0	0	0	0	0	0	0	0	0	0	0	M1
	0	0	0	0	0	0	0	M1	0	0	0	0	M1	0
	0	0	M1	M1	0	0	0	0	0	M1	0	M1	0	0

Fixed inputs
+ - ↑ ↓ ⌂

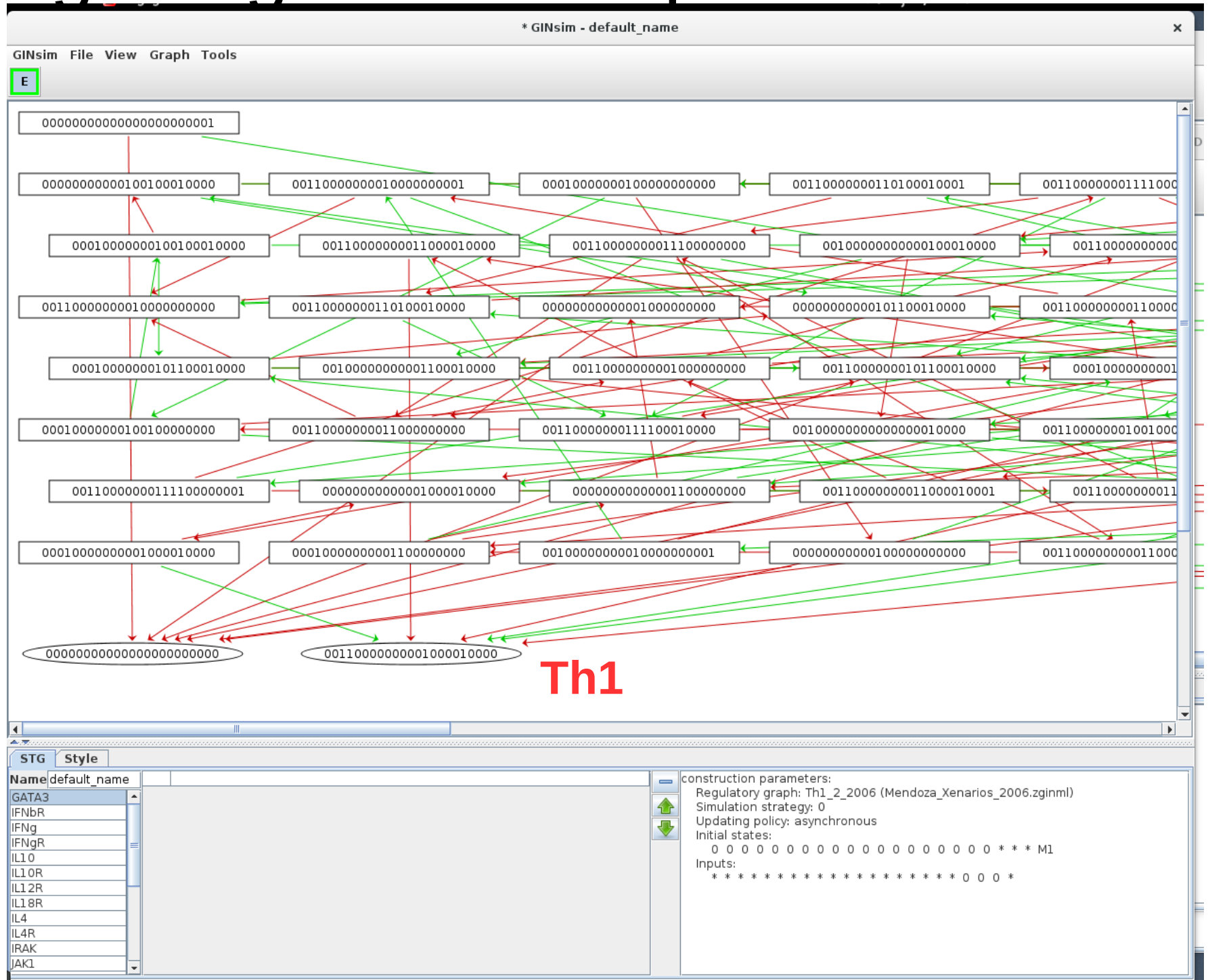
name	use	IFNb	IL12	IL18
no_stimul	<input checked="" type="checkbox"/>	0	0	0
pro_Th1	<input type="checkbox"/>	0	M1	0
input_	<input type="checkbox"/>	M1	0	0
input_1	<input type="checkbox"/>	0	0	0

Close Run

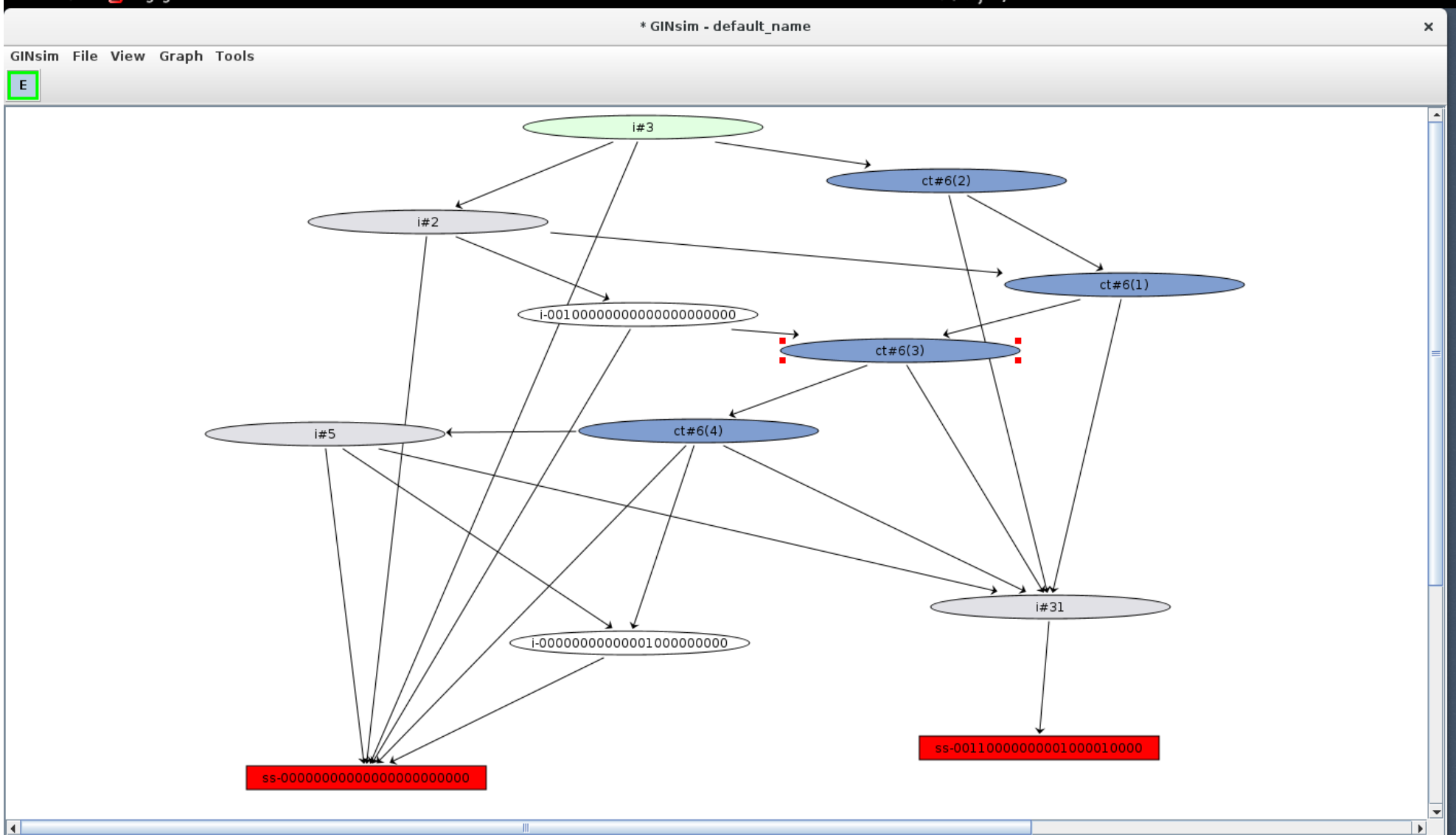
STG getting more complex...

Th0

Th1



Hierarchical compression: HTG

[illegible]

Perturbations

Construction of the Dynamics

Select a perturbation
--

Select a reduction
--

parameter

Construction Strategy

State Transition Graph

☐ Breadth First ☒ Depth First

Depth Number of States

Priority Class Selection

asynchronous

Initial States

name	use	GATA3	IFNbR	IFNg	IFNgR	IL10	IL10R	IL12R	IL18R	IL4	IL4R	IRAK	JAK1	NF
Th0	<input checked="" type="checkbox"/>	0	0	0	0	0	0	0	0	0	0	0	0	0
Th1	<input type="checkbox"/>	0	0	M1	M1	0	0	0	0	0	0	0	0	0
Th2	<input type="checkbox"/>	M1	0	0	0	M1	M1	0	0	M1	M1	0	0	0
	<input type="checkbox"/>													

Fixed inputs

name	use	IFNb	IL12	IL18	TCR
no_stimul	<input type="checkbox"/>	0	0	0	0
pro_Th1	<input checked="" type="checkbox"/>	0	M1	0	0
input	<input type="checkbox"/>	M1	0	0	0
input_1	<input type="checkbox"/>	0	0	0	M1
	<input type="checkbox"/>				

Close Run

medical modelling 3.13 (2006)

Perturbations: fixing a component

Construction of the Dynamics

Type of perturbation	Component
RANGE Fix component value	STAT1

☒ 0 - Knockout
☐ 1 - Ectopic activity

Create

You can also select multiple perturbations to combine them

Back

Perturbations: changing an interaction

Construction of the Dynamics

	Type of perturbation	Component
STAT1 KO	REGULATOR	Tbet
Tbet [STAT1@0]	Fix a regulator for this component	

STAT1

☒ 0 - Knockout
☐ 1 - Ectopic activity

Create

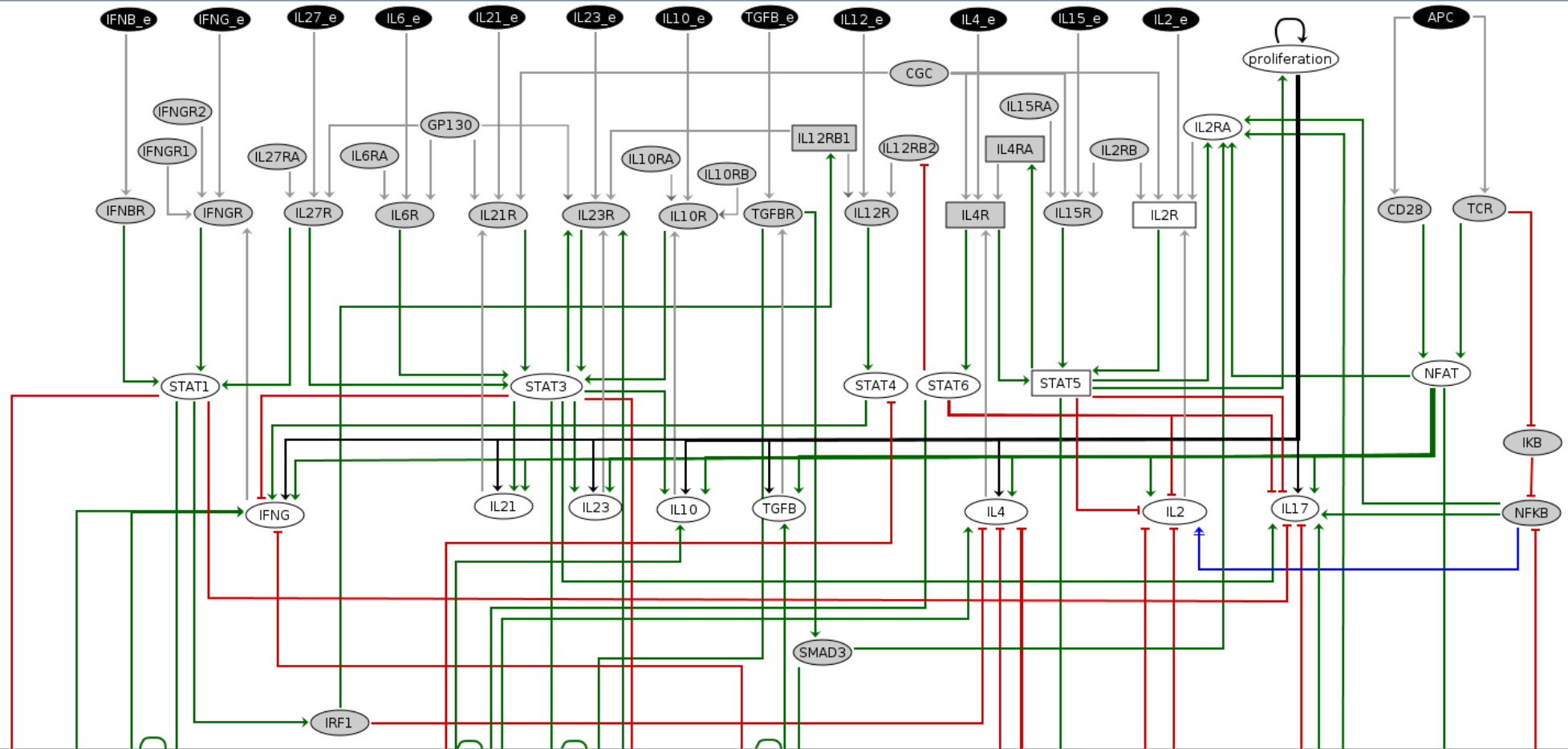
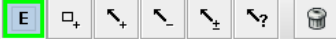
You can also select multiple perturbations to combine them

Back

Opening a larger model

GINsim - Th_differentiation [/home/aurelien/Downloads/Naldi_etal_2010.zginml]

GINsim File View Graph Tools



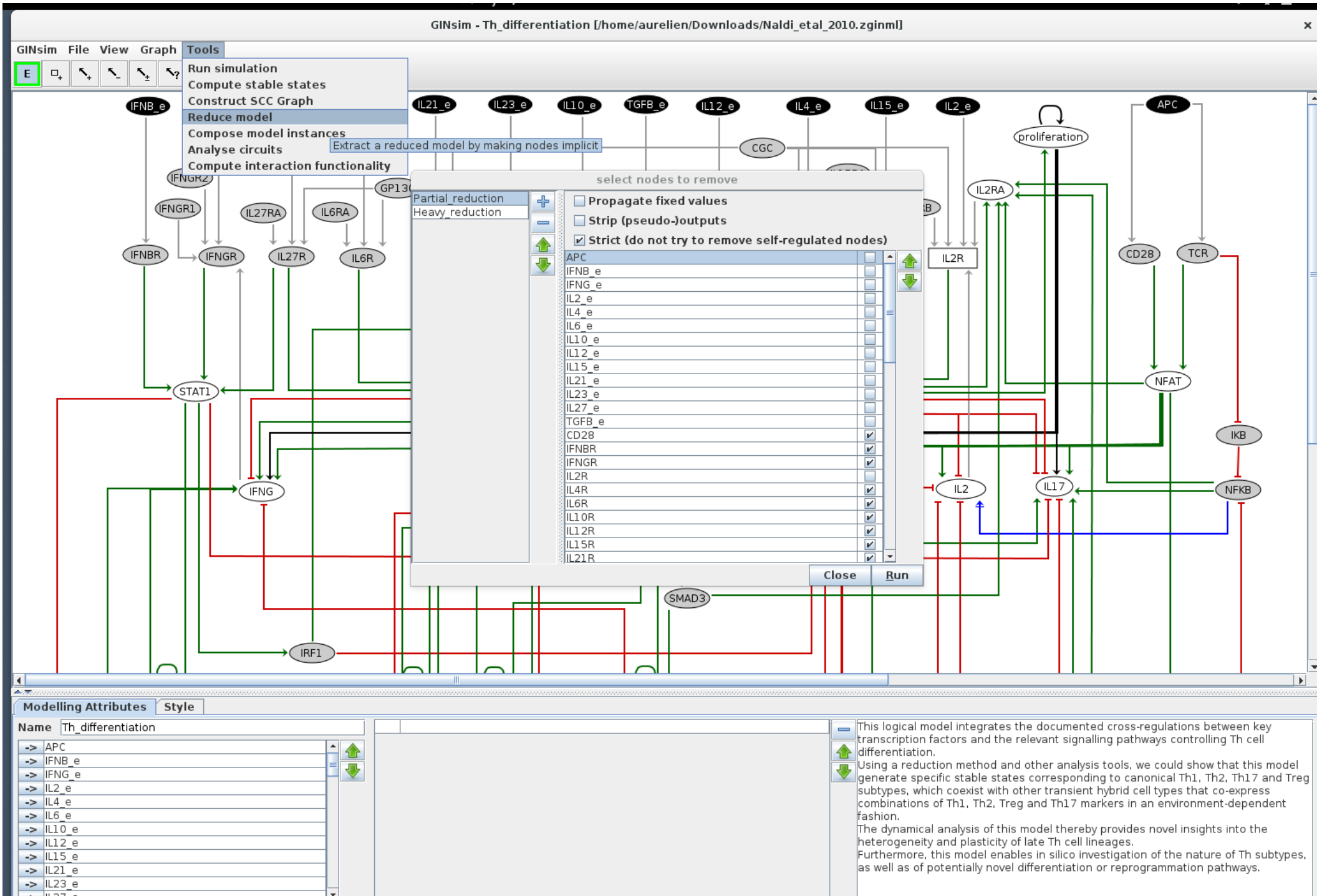
Modelling Attributes Style

Name Th_differentiation

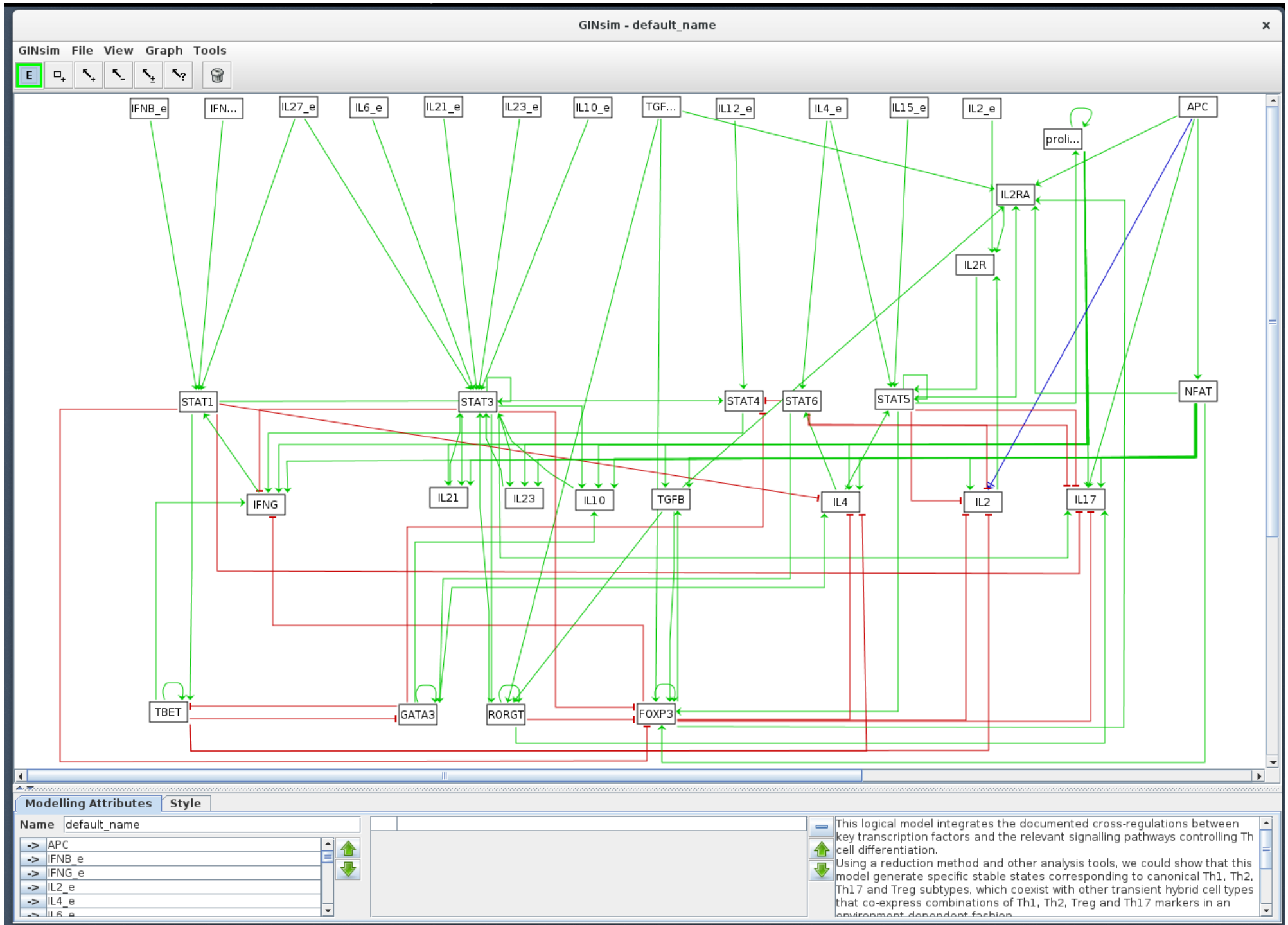
- > APC
- > IFNB_e
- > IFNG_e
- > IL2_e
- > IL4_e
- > IL6_e
- > IL10_e
- > IL12_e
- > IL15_e
- > IL21_e
- > IL23_e

This logical model integrates the documented cross-regulations between key transcription factors and the relevant signalling pathways controlling Th cell differentiation. Using a reduction method and other analysis tools, we could show that this model generate specific stable states corresponding to canonical Th1, Th2, Th17 and Treg subtypes, which coexist with other transient hybrid cell types that co-express combinations of Th1, Th2, Treg and Th17 markers in an environment-dependent fashion. The dynamical analysis of this model thereby provides novel insights into the heterogeneity and plasticity of late Th cell lineages. Furthermore, this model enables in silico investigation of the nature of Th subtypes, as well as of potentially novel differentiation or reprogramming pathways.

Model reduction



Reduced model



Exporting models

