Modelling of T cell co-inhibitory pathways to predict anti-tumour responses to checkpoint inhibitors

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Biological context : immunotherapies

Immunotherapies using **checkpoint inhibitors**

Cancer can be cured

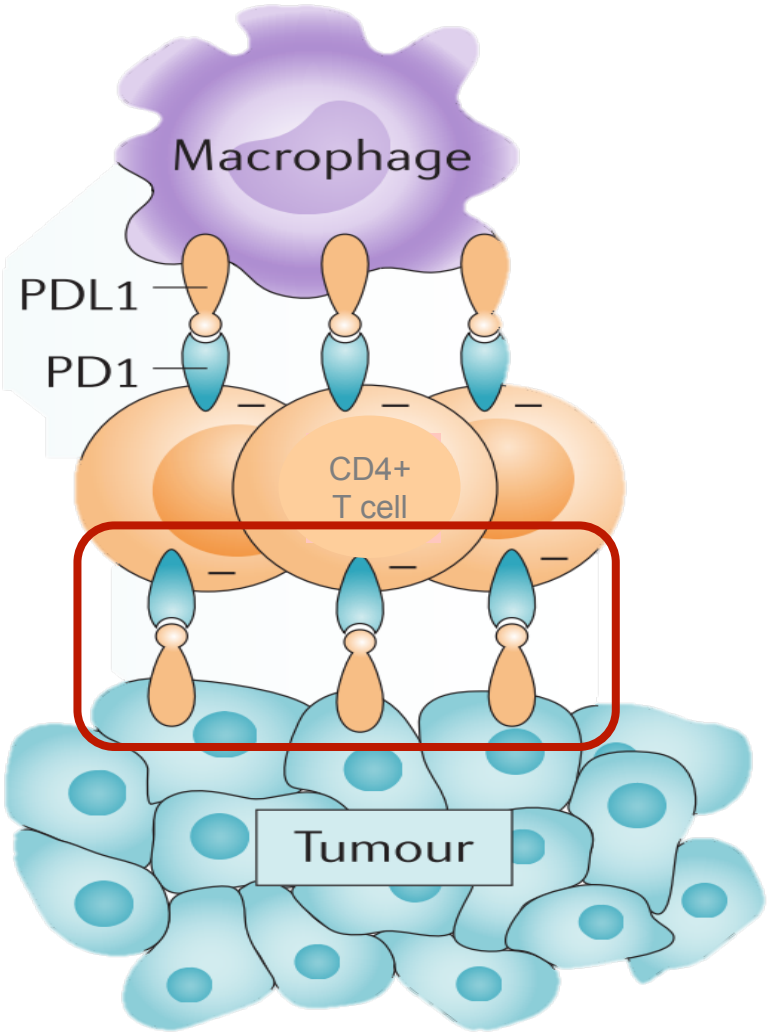
by our own immune system

Biological context : immunotherapies

Tumour cells

- Are detected by the immune system (e.g. T cells)
- But present ligands to inhibitory receptors, i.e. **checkpoints** (CTLA4, PD1)
- Thus evade the immune system recognition, preventing the response

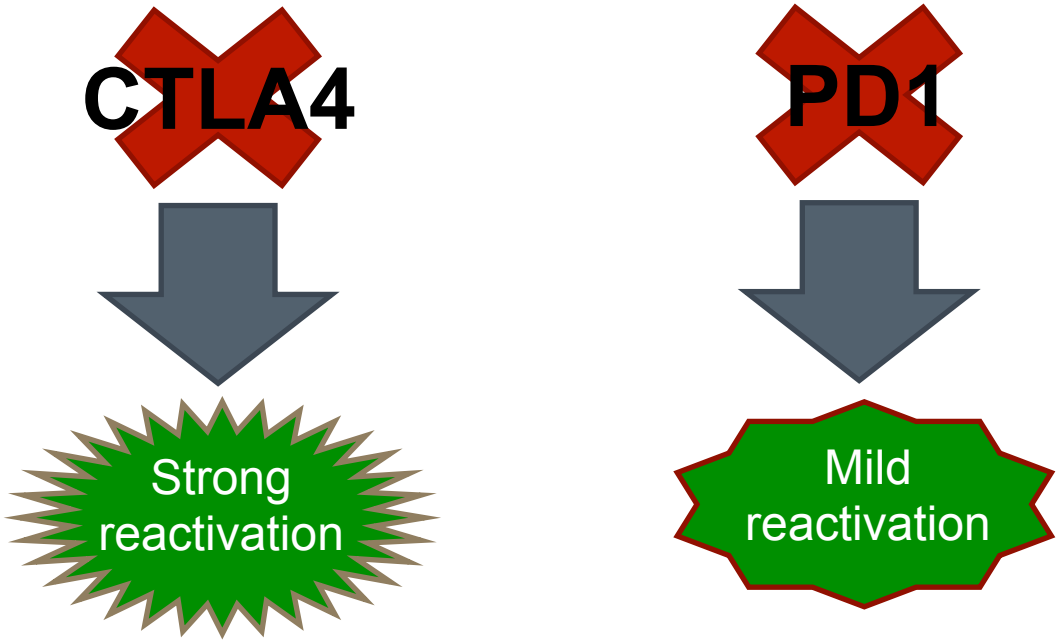
FDA-approved anti-CTLA4 and anti-PD1 immunotherapies



Topalian *et al.* 2016

Biological context : immunotherapies

- Checkpoint inhibitors target specific ligand/receptor communication to re-activate T cells
- Downside: serious adverse effects, different in intensities



Biological context : immunotherapies

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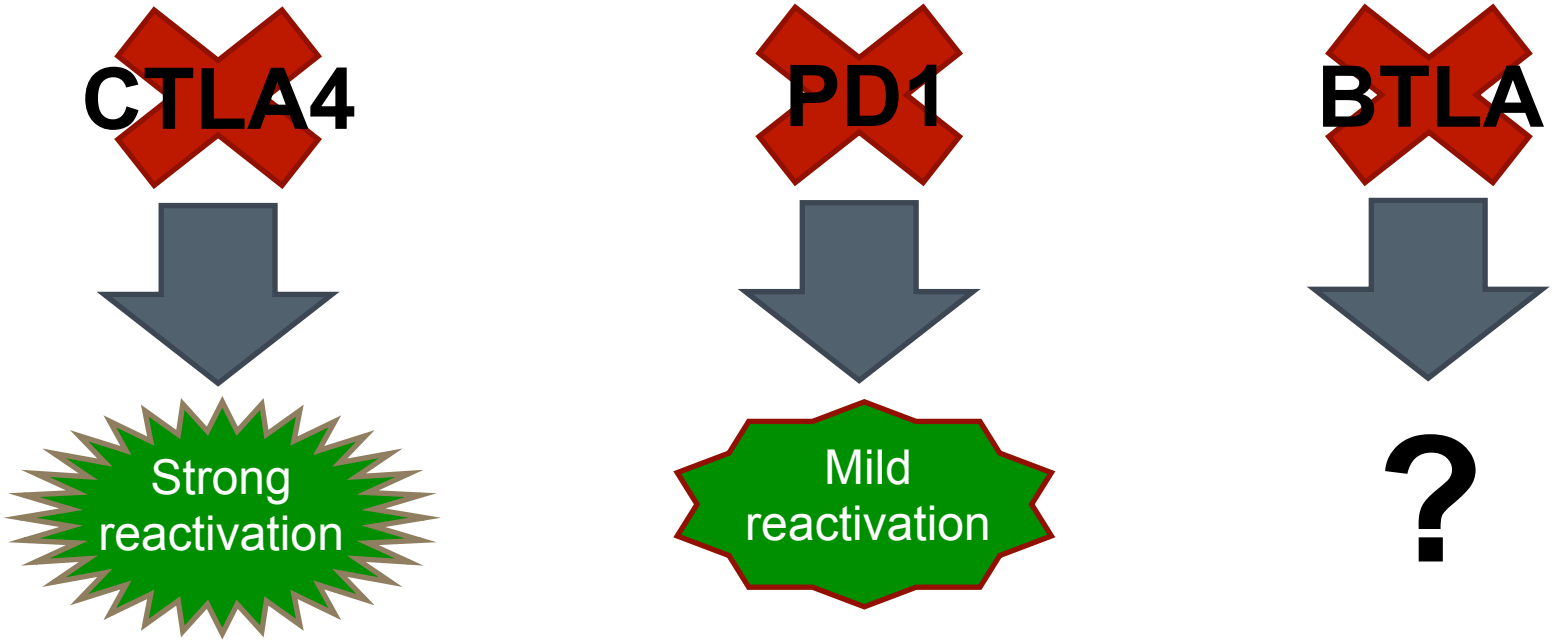
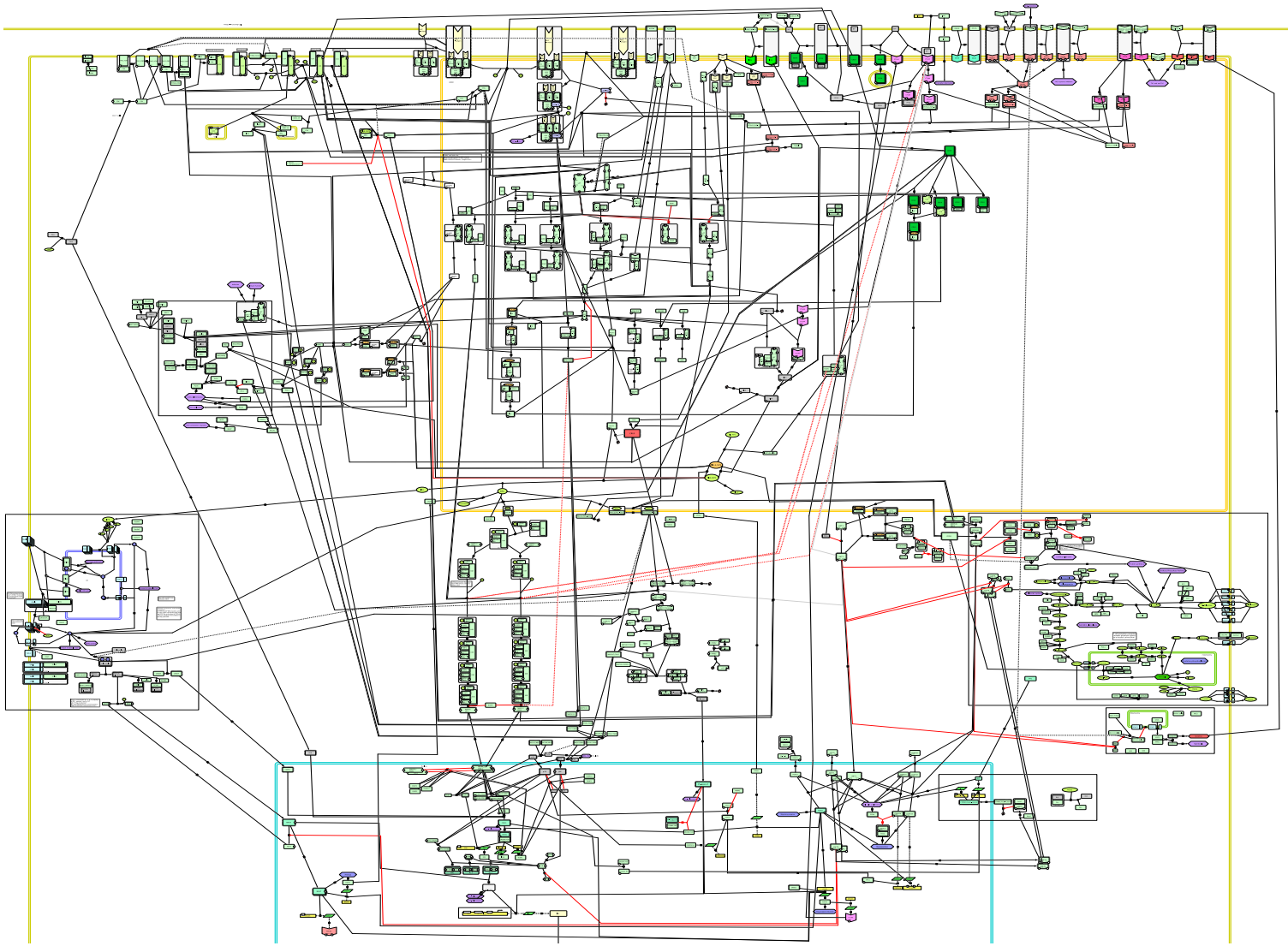


Why?
What's the difference?

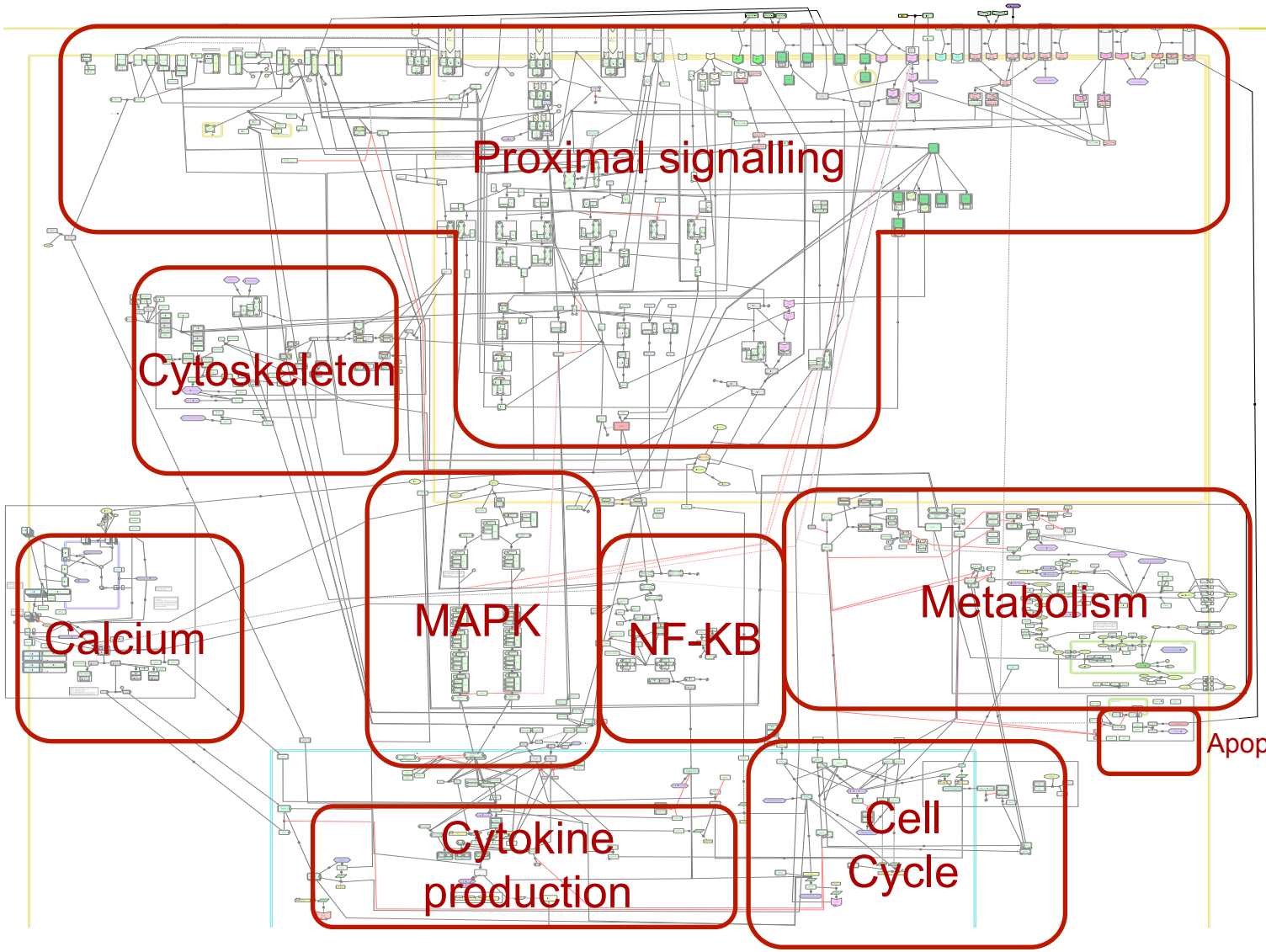
Molecular mapping of CD4+ T cell activation



CellDesigner

726 species
516 reactions
123 articles

Molecular mapping of CD4+ T cell activation



SBML

CellDesigner

726 species
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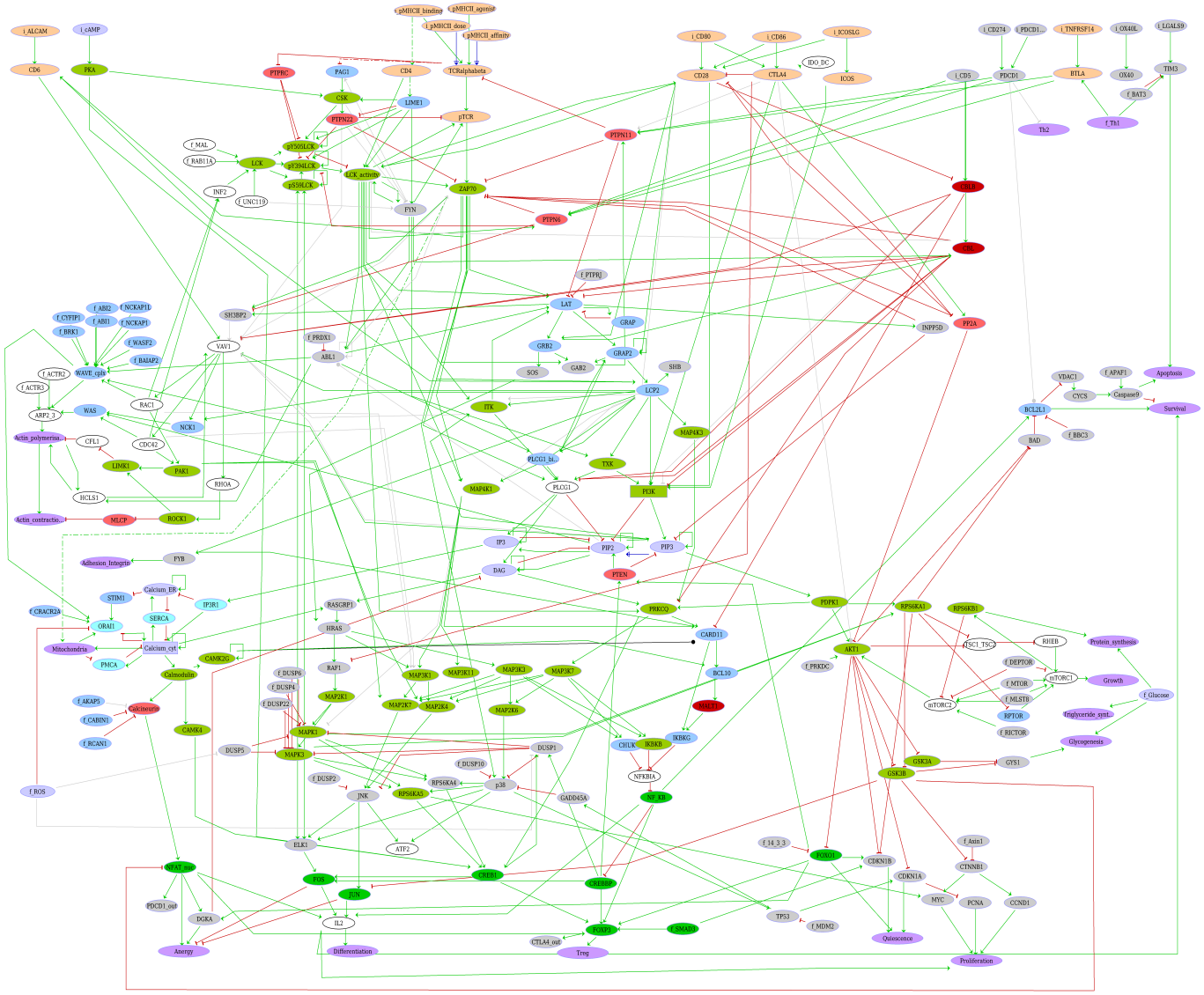
Dynamical modelling: regulatory graph

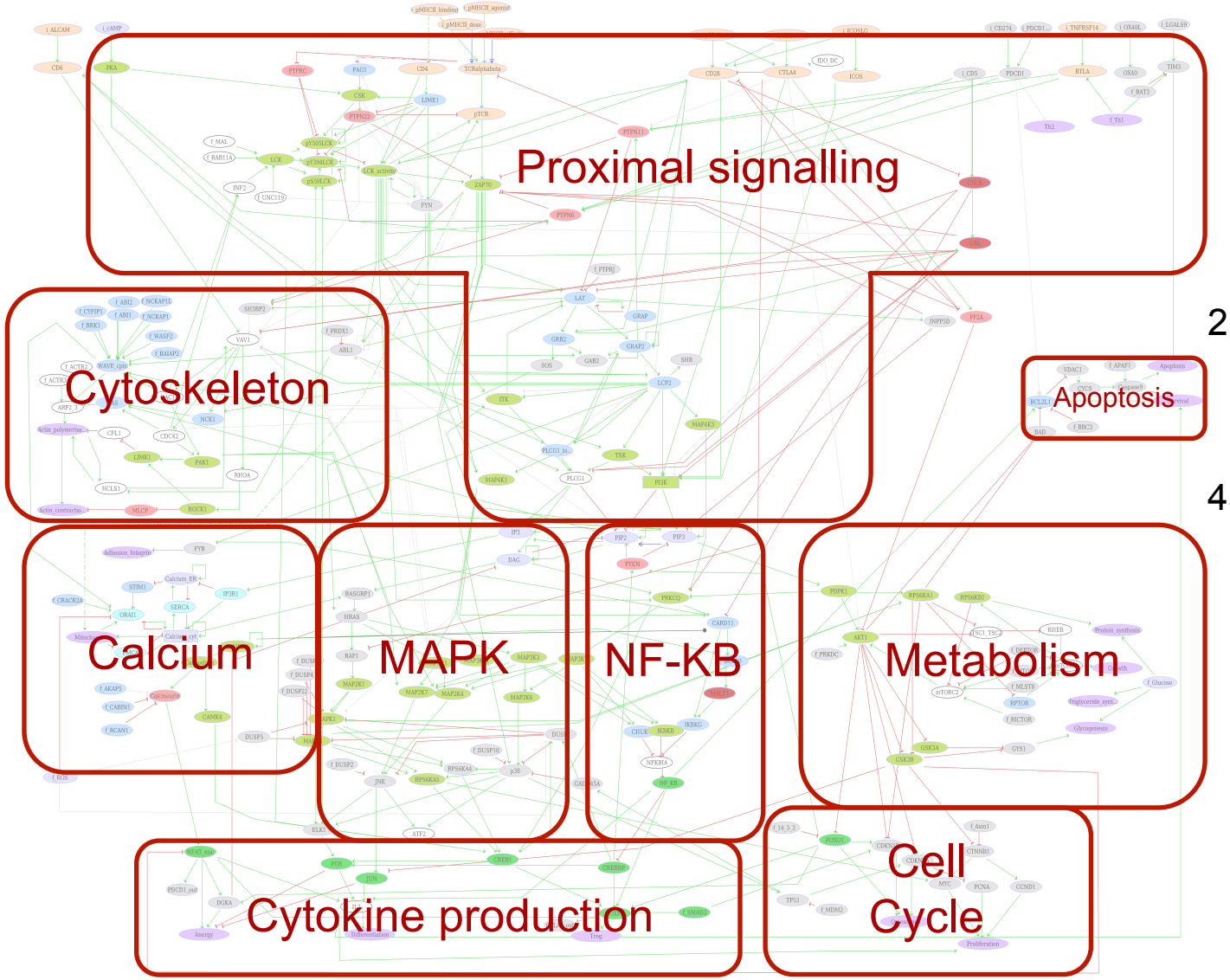


GINsim

216 nodes
- 15 inputs
- 40 fixed values

450 edges
- 322 activations
- 120 inhibitions

Dynamical modelling: regulatory graph



GINsim

216 nodes
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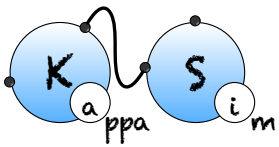
Dynamical modelling: coping with complexity

- Dynamical modelling using a Rule-based approach

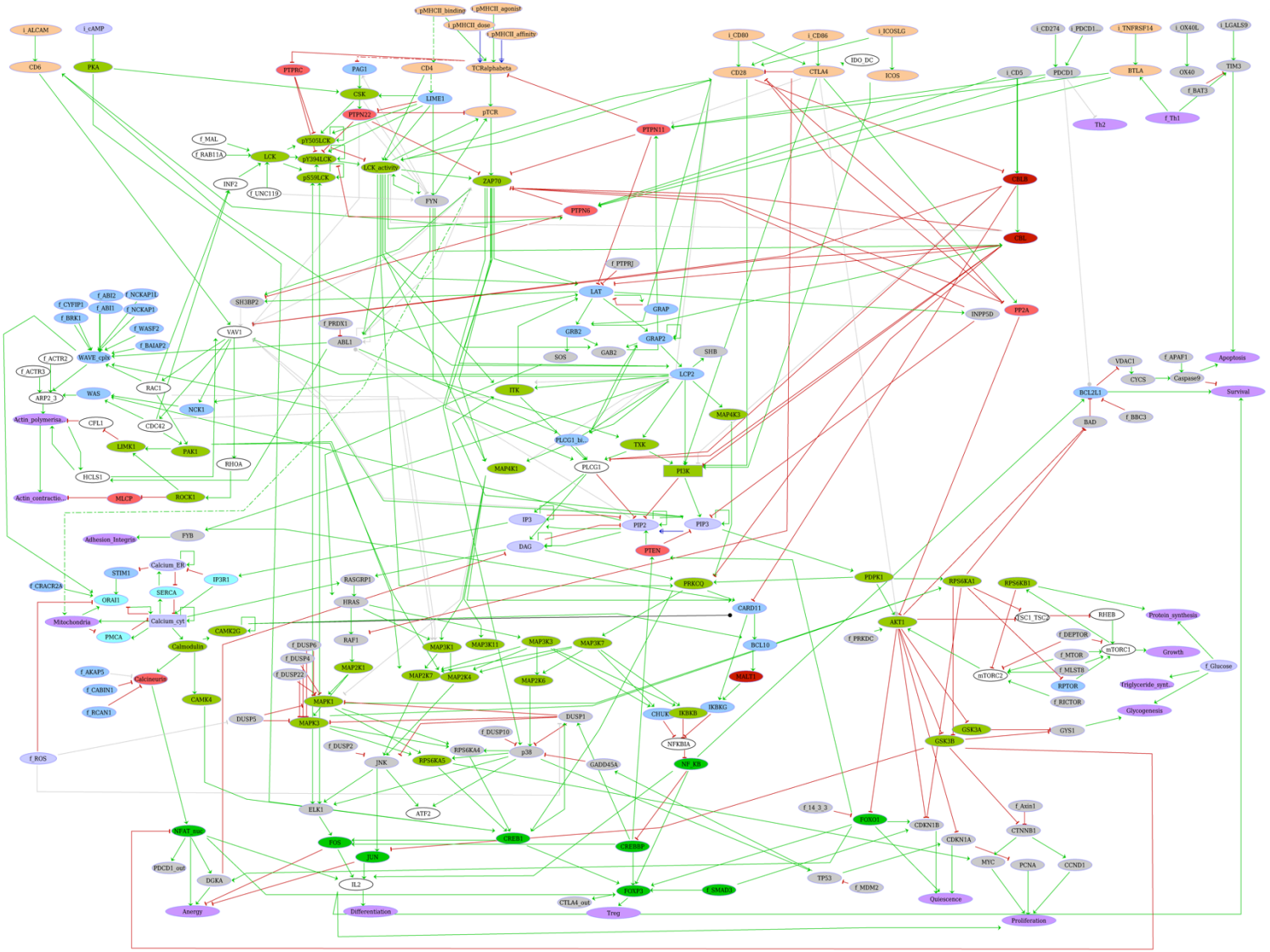
  Collaboration with J. Ferret (ENS Paris)



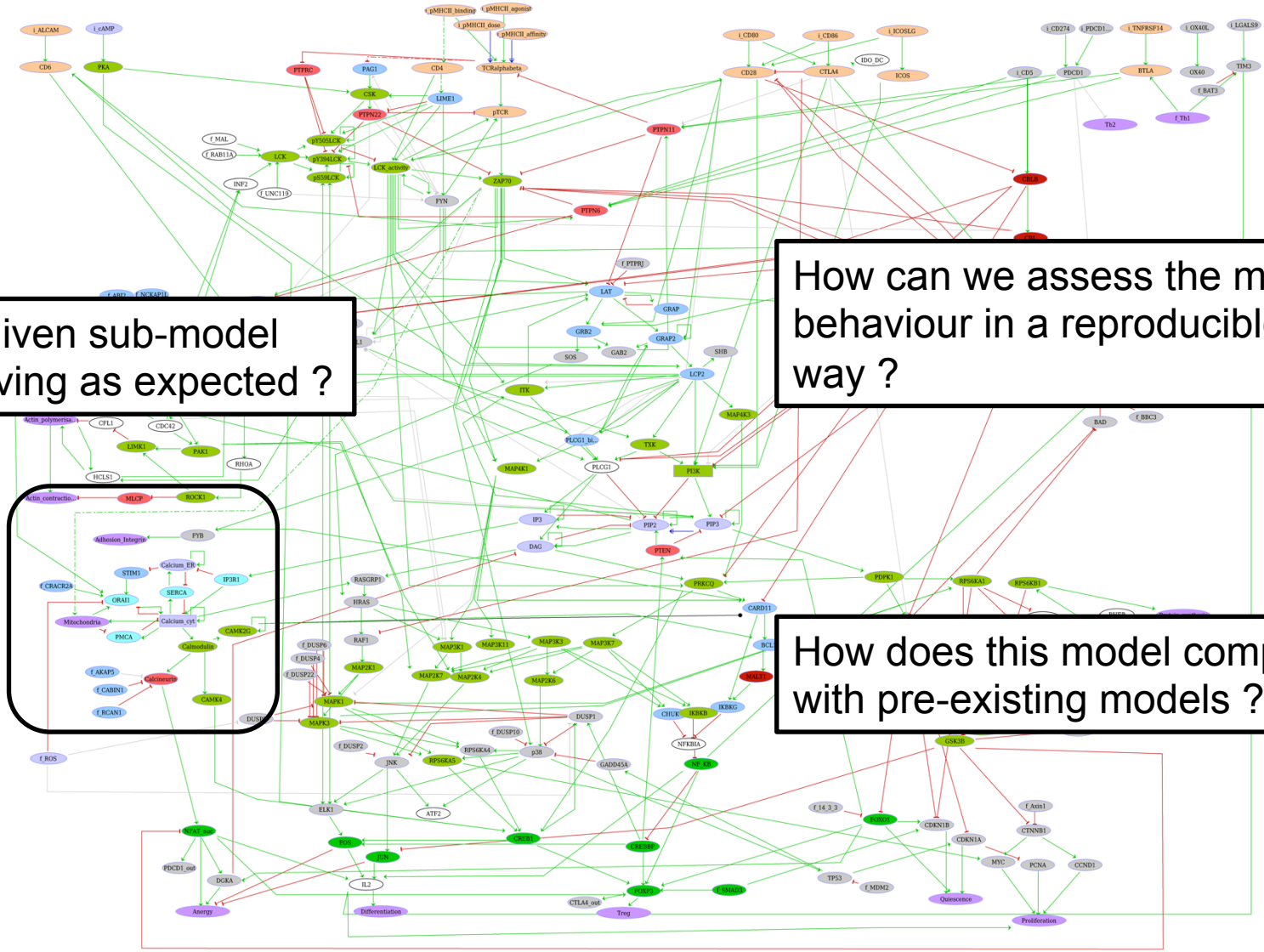
- Logical modelling with a combination of **unit testing** and **sub-model extraction**

  CoLoMoTo Docker image

Logical modelling : questions and challenges



Logical modelling : questions and challenges



Is a given sub-model behaving as expected ?

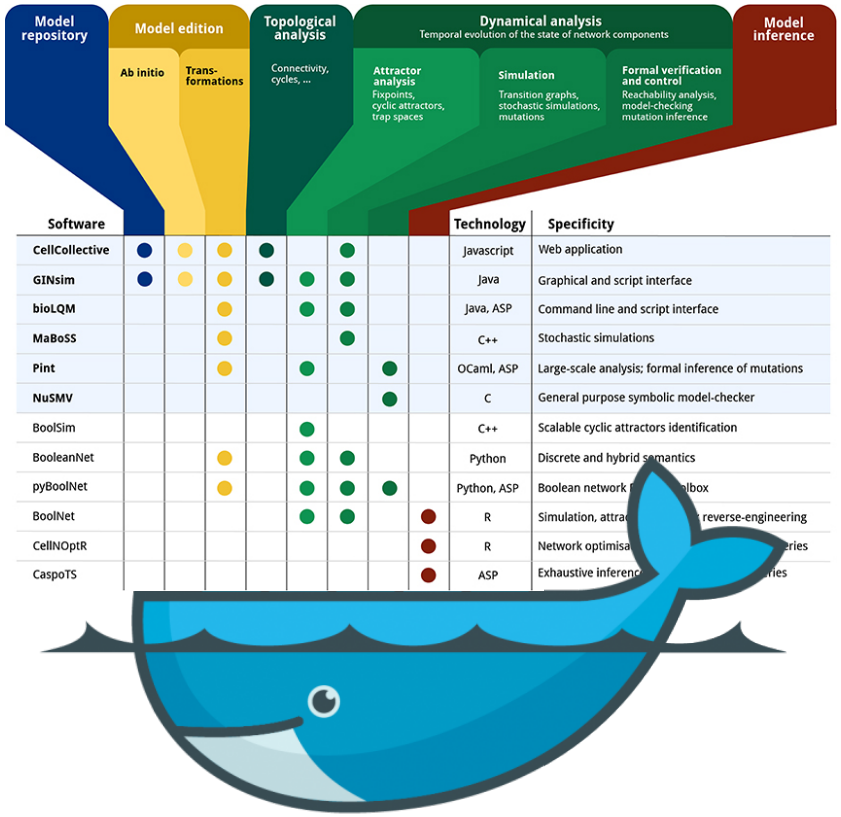
How can we assess the model behaviour in a reproducible way ?

How does this model compare with pre-existing models ?

Logical modelling with the CoLoMoTo Docker image

How can we assess the model behaviour in a reproducible way ?

CoLoMoTo Docker image + Unit testing (Python)



Adapted from Naldi et al. (2018) Front. Physiol.

```
In [1]:
1  import unittest
2  import biolqm
3
4  class ExampleTest(unittest.TestCase):
5      def test_fixedpoints(self):
6          # Load model to be tested
7          lqm = biolqm.load("http://ginsim.org/sites/default/f
8          # Compute fixed points using bioLQM
9          fixpoints = biolqm.fixpoints(lqm)
10         # Test case: there should be only one fixed point
11         self.assertEqual(len(fixpoints), 1)
12
13 runner = unittest.TextTestRunner(verbosity=2)
14 runner.run(unittest.makeSuite(ExampleTest))
```

This notebook has been executed using the docker image `colomoto/colomoto-dc`

```
test_fixedpoints (__main__.ExampleTest) ...
```

Downloading 'http://ginsim.org/sites/default/files/phageLambda4.zginml'

```
ok

----------------------------------------------------------------------
Ran 1 test in 0.314s

OK
```

```
Out[1]: <unittest.runner.TextTestResult run=1 errors=0 failures=0>
```

jupyter

Logical modelling with the CoLoMoTo Docker image

How does a model compare with pre-existing models ?

Create dedicated notebooks for already published models

GINsim repository

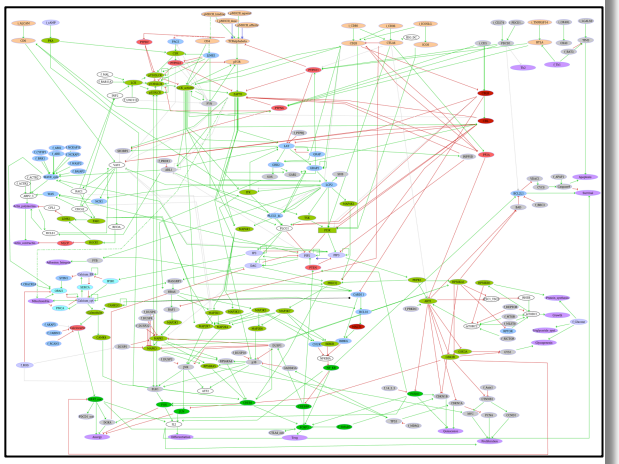
cellcollective

BioModels

Unit testing

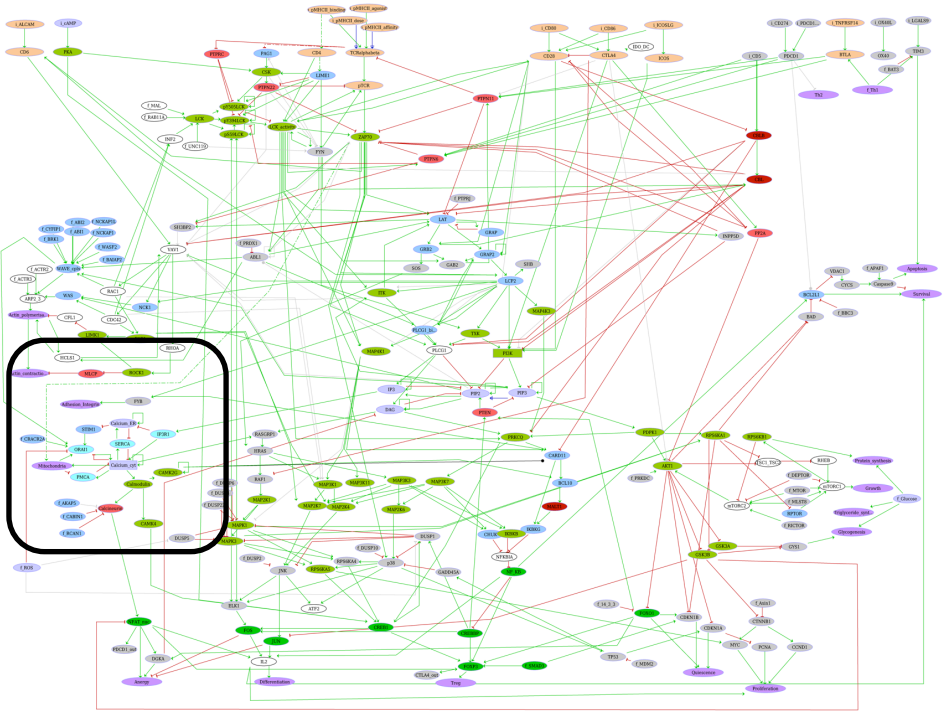
jupyter

Transposable test cases



Logical modelling with the CoLoMoTo Docker image

Is a given sub-model working as expected ?

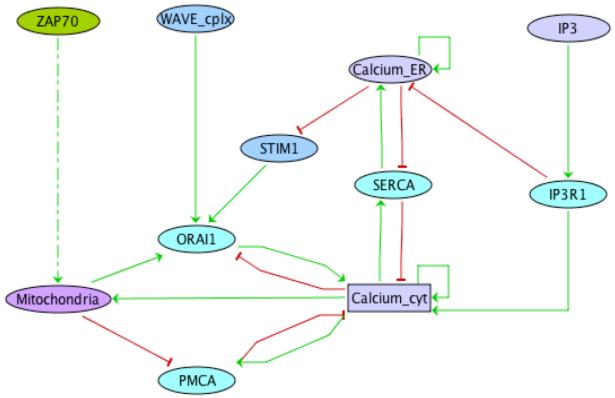


on-the-fly extraction of a sub-model

bioLQM

new "`submodel`" modifier

http://www.colomoto.org/biolqm

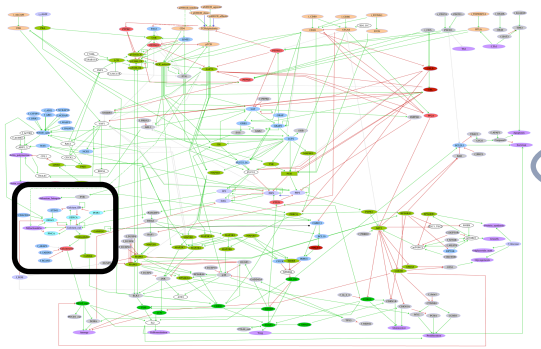


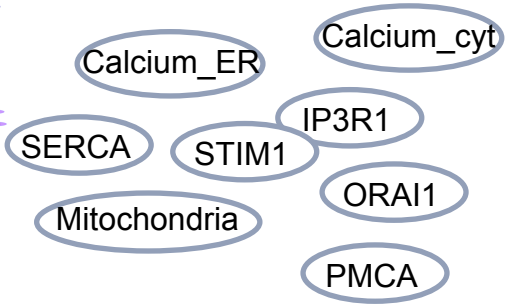
- Extract a core set of components
- Additional regulatory components considered as inputs

Logical modelling with the CoLoMoTo Docker image

”IP3 diffuses through the cytosol and binds to IP3 receptors located on the endoplasmic reticulum (ER) membrane, which results in a rapid release of intracellular calcium stores. This moderate and transient rise in the intracellular calcium concentration activates store-operated calciumentry (SOCE) channels in the plasma membrane to induce sustained elevations of intracellular calcium required for optimal TCR-induced signal transduction.” Baine et al. 2009 Immun. Rev.

?





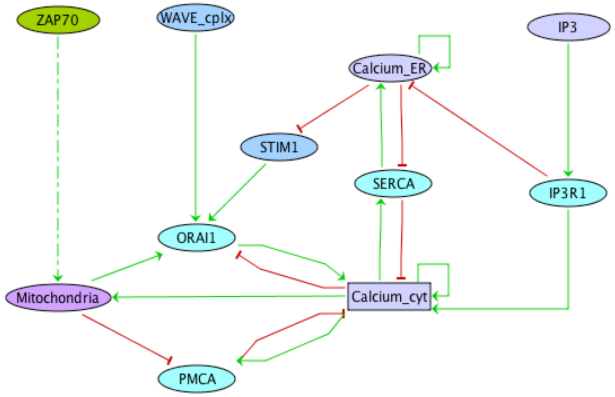
Test case

IP3	ZAP70	WAVE_cplx	IP3R1	Calcium_cyt	Calcium_ER	SERCA	STIM1	ORAI1	PMCA	Mitochondria
1	1	1	*	*	1	*	*	*	*	*
Expected :										
1	1	1	?	2	?	?	?	?	?	?

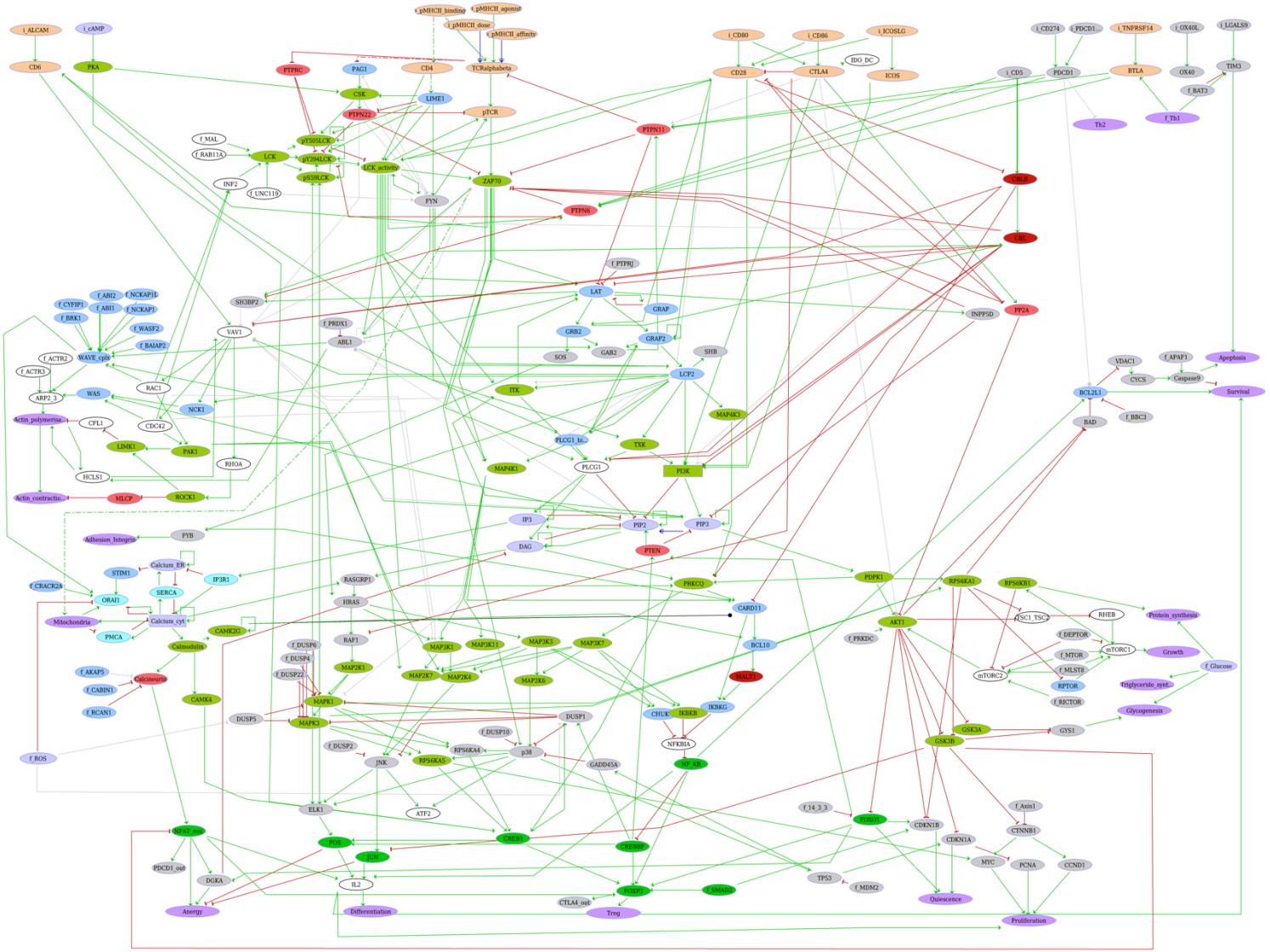
```
Ran 1 test in 0.051s

OK
```

`biolqm.fixpoints()`

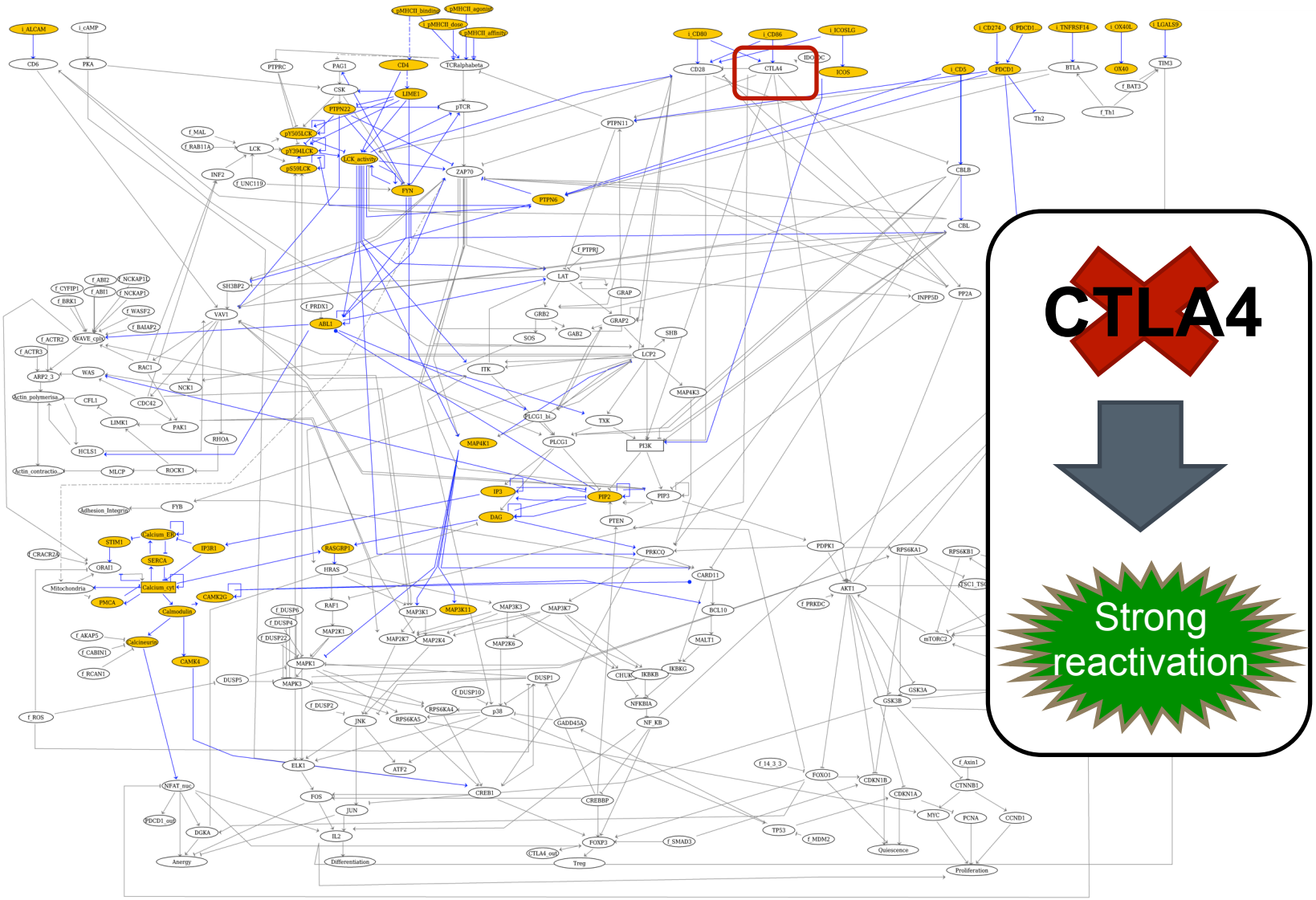
`biolqm.submodel()`



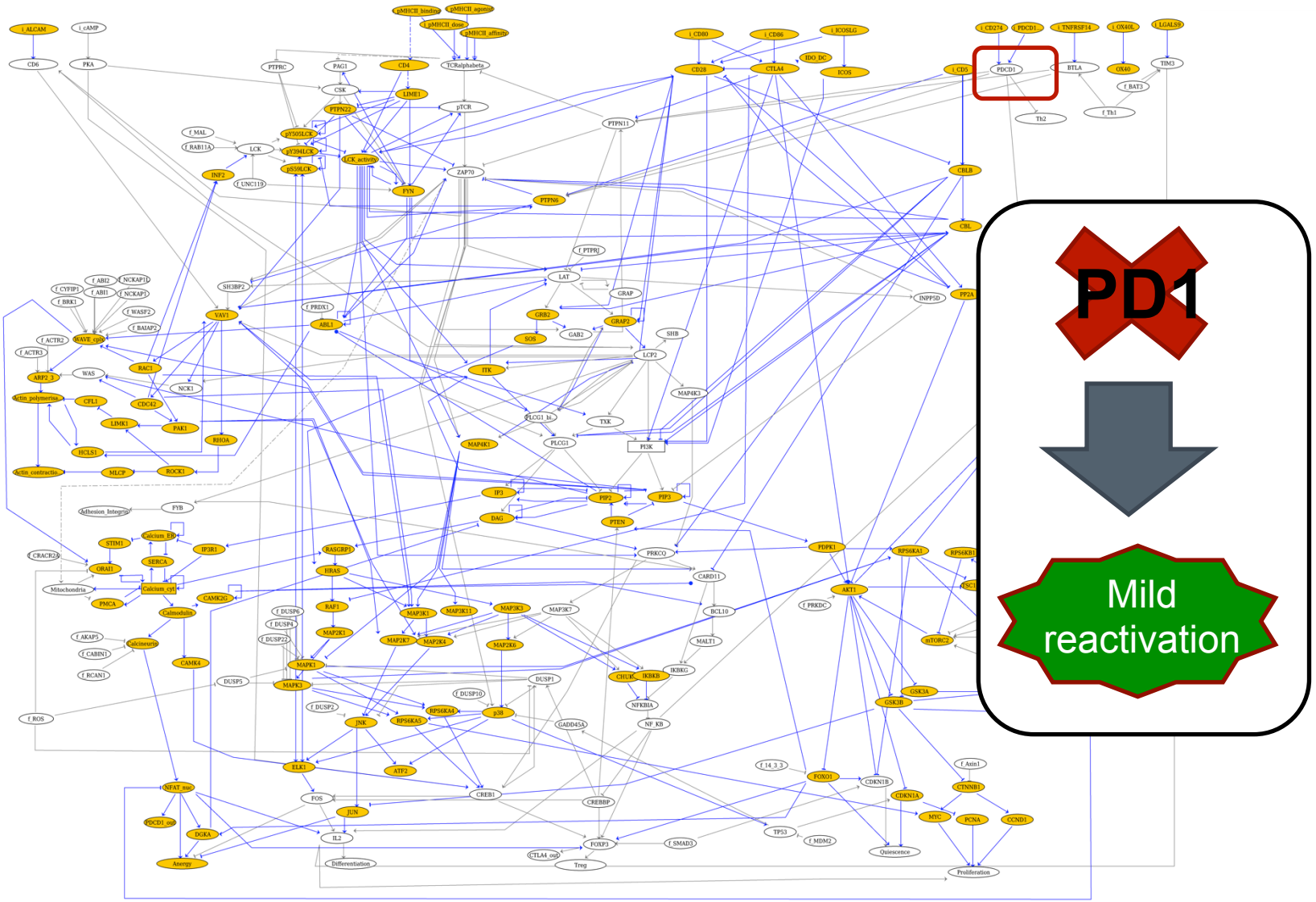
Logical modelling T cell co-inhibitory pathways



Percolation of CTLA4 activation



Percolation of PD-1 activation



Take home messages

- An automated framework based on unit testing
  - Reproducible (CoLoMoTo Docker image)
  - Allows comparison with previous models
- Iterative and modular method of model refinement
  - On-the-fly extraction of sub-models
  - Implemented in bioLQM (http://colomoto.org/biolqm/)
- Percolation analysis to understand the impact of checkpoint inhibitors
- Perspectives
  - Validation of other sub-models
  - Global simulation

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