Lifelong health and wellbeing : the Neurological disease burden

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World disease, Royal Society 2013

✤ Growing population which is ageing in the developed world

✤ Global cost of mental illness estimated at $2.5 trillion in 2010 (~5% of global GDP)

✤ Set to rise to $6 trillion by 2030

✤ Currently affecting 500 million people (~ twice the population of USA)

✤ Huge impact on quality of life and society

✤ **Challenge** : Chronic lack of new drugs, soaring R&D costs and lack of validation of novel targets

Research : A systems Neuroscience approach to brain disease

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**Rationale** : use of statistical, ML and CS methods can :-

✤ cut R&D costs

✤ reveal novel targets and relationships

✤ increase quality of targets taken forward

✤ based on "mechanistic" and "systemic" understanding

**Suite of methods** : Data Science for the brain

✤ formal integration of bio-molecular data types

 (e.g. hierarchical Bayesian networks, coDA, 'graph' biology)

✤ digitisation of biology

 (e.g. ontological, graph-based mapping, NLP methods)

✤ dynamical modeling of biological systems across scales

 (e.g. rule-based-languages, Kappa, BioPepa)

Exemplar projects in Informatics

✤ pharmaceutical companies

 Joint PhD. studentship (2013) UCB Celltech.

  "Towards a semi-automated framework of rule-based modelling for neurological disease"

✤ inter-disciplinary funding (Biology and Informatics)

 Synprot (EU-FP7) *"Translational regulation of synaptic plasticity"*

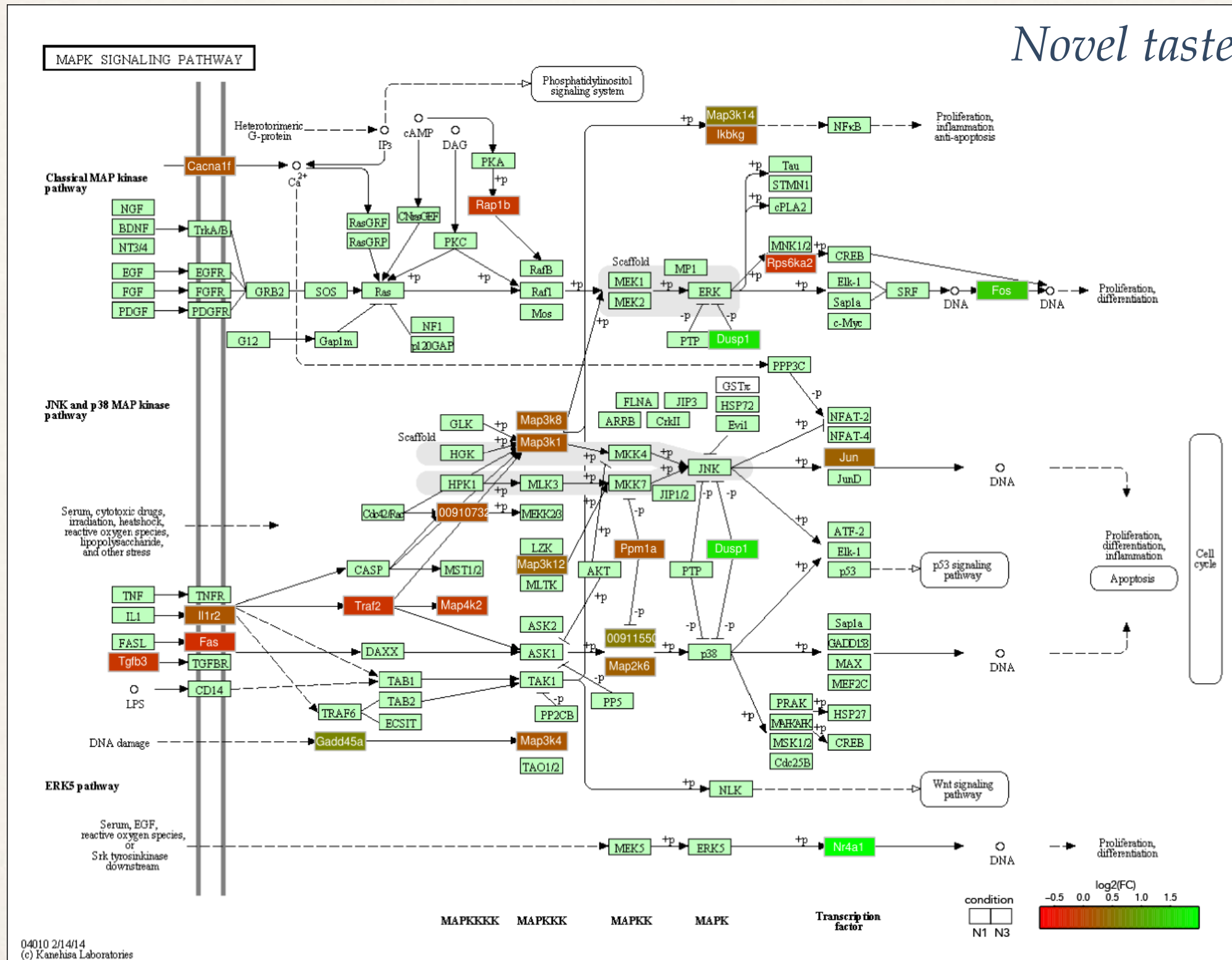 (synaptic proteins are associated with >1000 diseases)
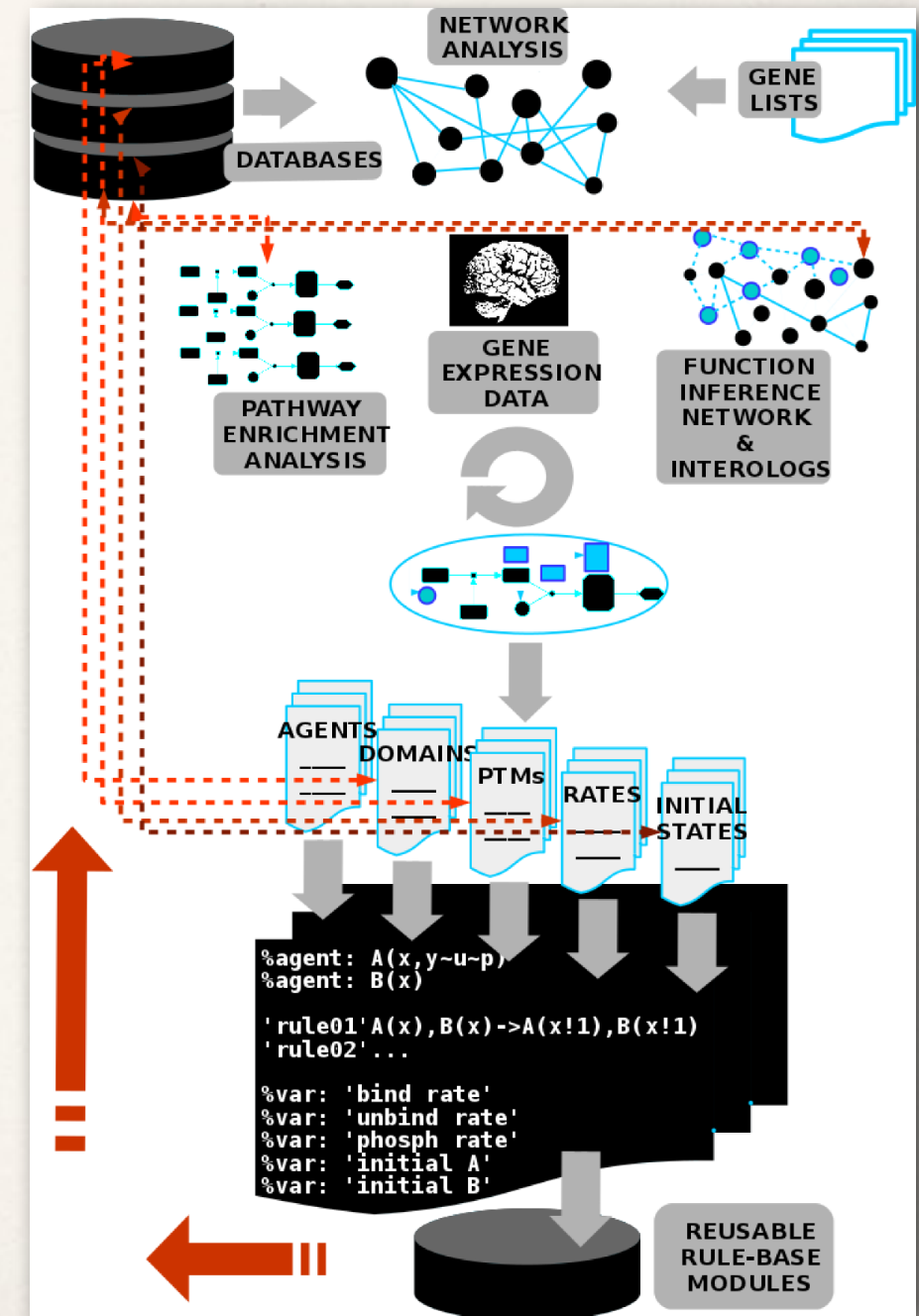
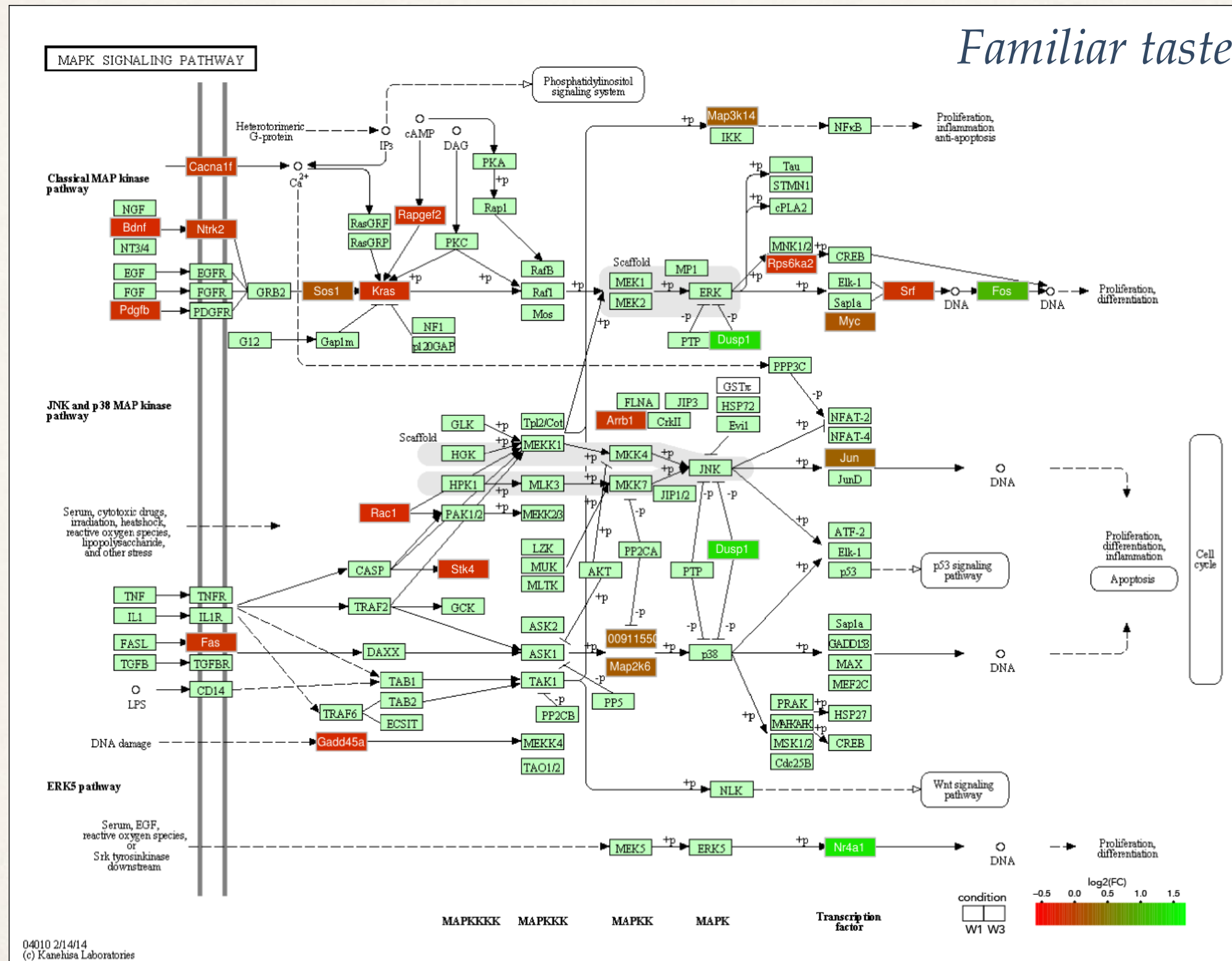# Schizophrenia disease gene association network
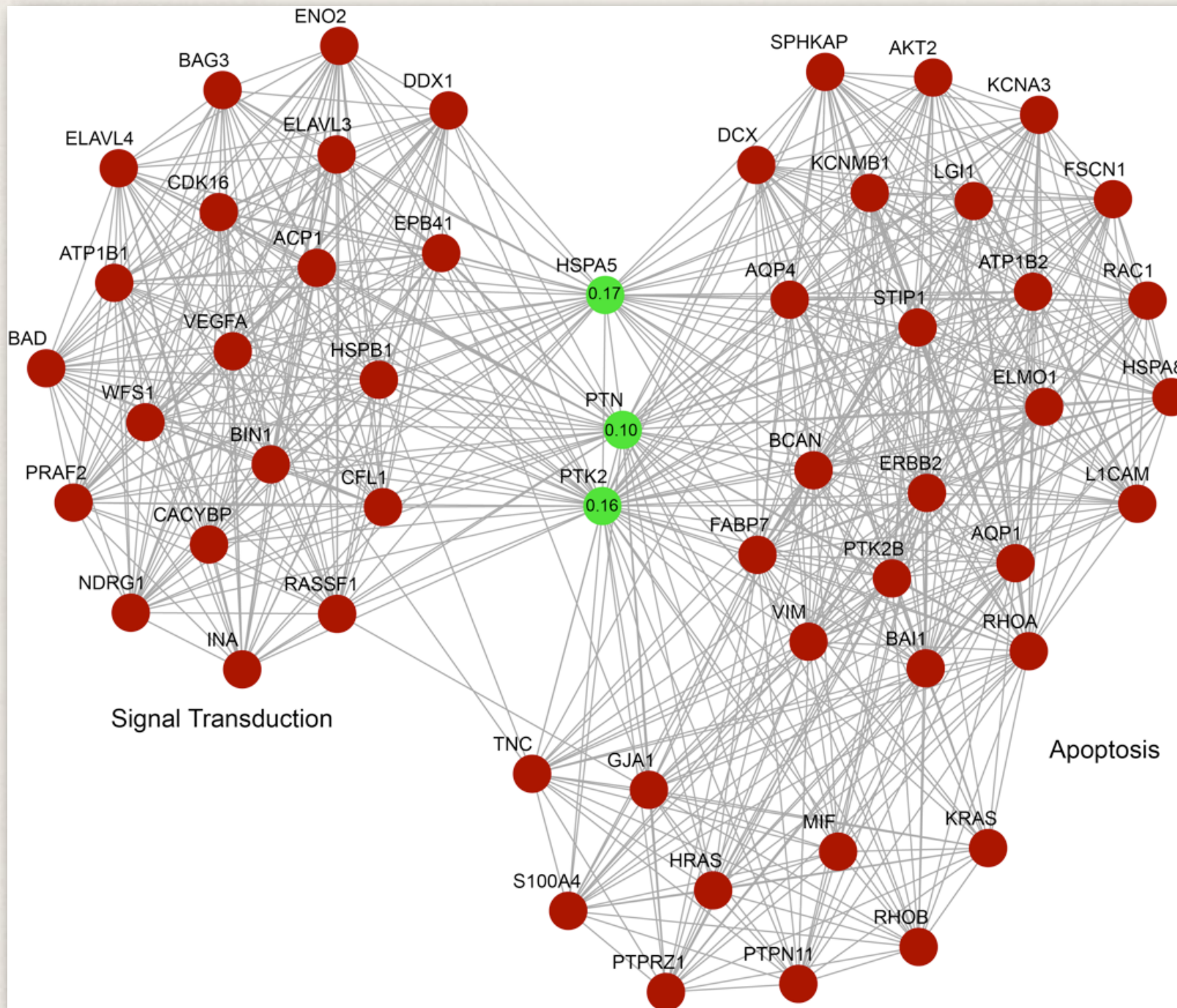
disease gene network
1. Mine gene disease associations
    ✦ OMIM / HDO / GeneRIF
2. Calculate pair-wise common disease counts between all gene pairs
3. Set genes as nodes, disease counts as edges
4. Cluster network by community (Newman and Girvan 2002)
5. Functional annotation
    ✦ semantic similarity
    ✦ BINGO / GO
    ✦ InterPro domain
    ✦ KEGG, COG
6. Network analyses
    ✦ betweenness centrality
    ✦ modularity
    ✦ clustering coefficients
    ✦ power-law
7. Stress testing
    ✦ critical genes (targets)
    ✦ information flow
    ✦ destruction

Project : Graph methods for disease biology

Biological pathway activation in memory and learning

Novel taste

Project : Graph methods for disease biology

Biological pathway activation in memory and learning

Familiar taste
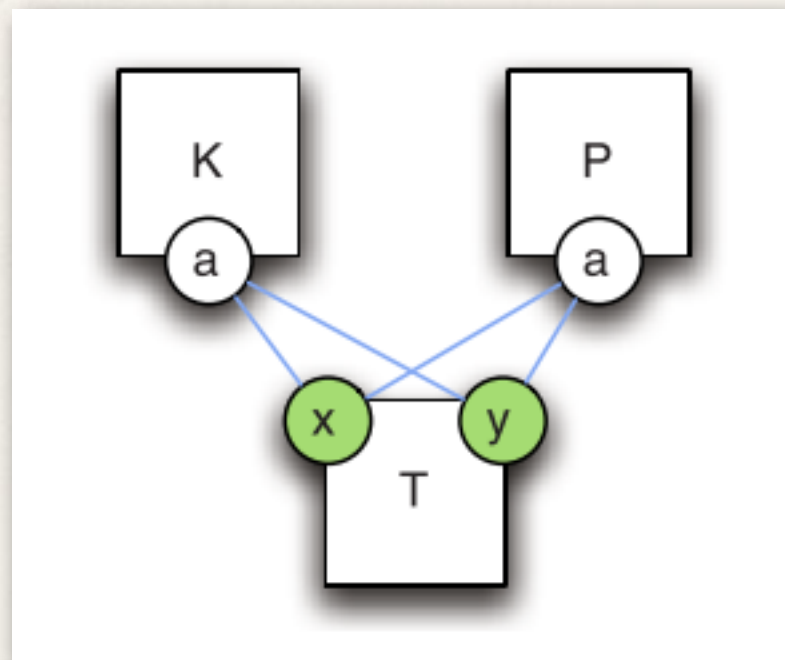
Project : Graph methods for disease biology

Kappa language

Rule-based language based on ∏-calculus (computer science concurrent process theory)

Kinase Rules

```
'KT@x' K(a),T(x) <-> K(a!1),T(x!1)
'Tp@x' K(a!1),T(x~u!1) -> K(a!1),T(x~p!1)
'KT@y' K(a),T(y) <-> K(a!1),T(y!1)
'Tp@y' K(a!1),T(y~u!1) -> K(a!1),T(y~p!1)
```

Phosphatase Rules

```
'PT@x' P(a),T(x) <-> P(a!1),T(x!1)
'Tu@x' P(a!1),T(x~p!1) -> P(a!1),T(x~u!1)
'PT@y' P(a),T(y) <-> P(a!1),T(y!1)
'Tu@y' P(a!1),T(y~p!1) -> P(a!1),T(y~u!1)
```

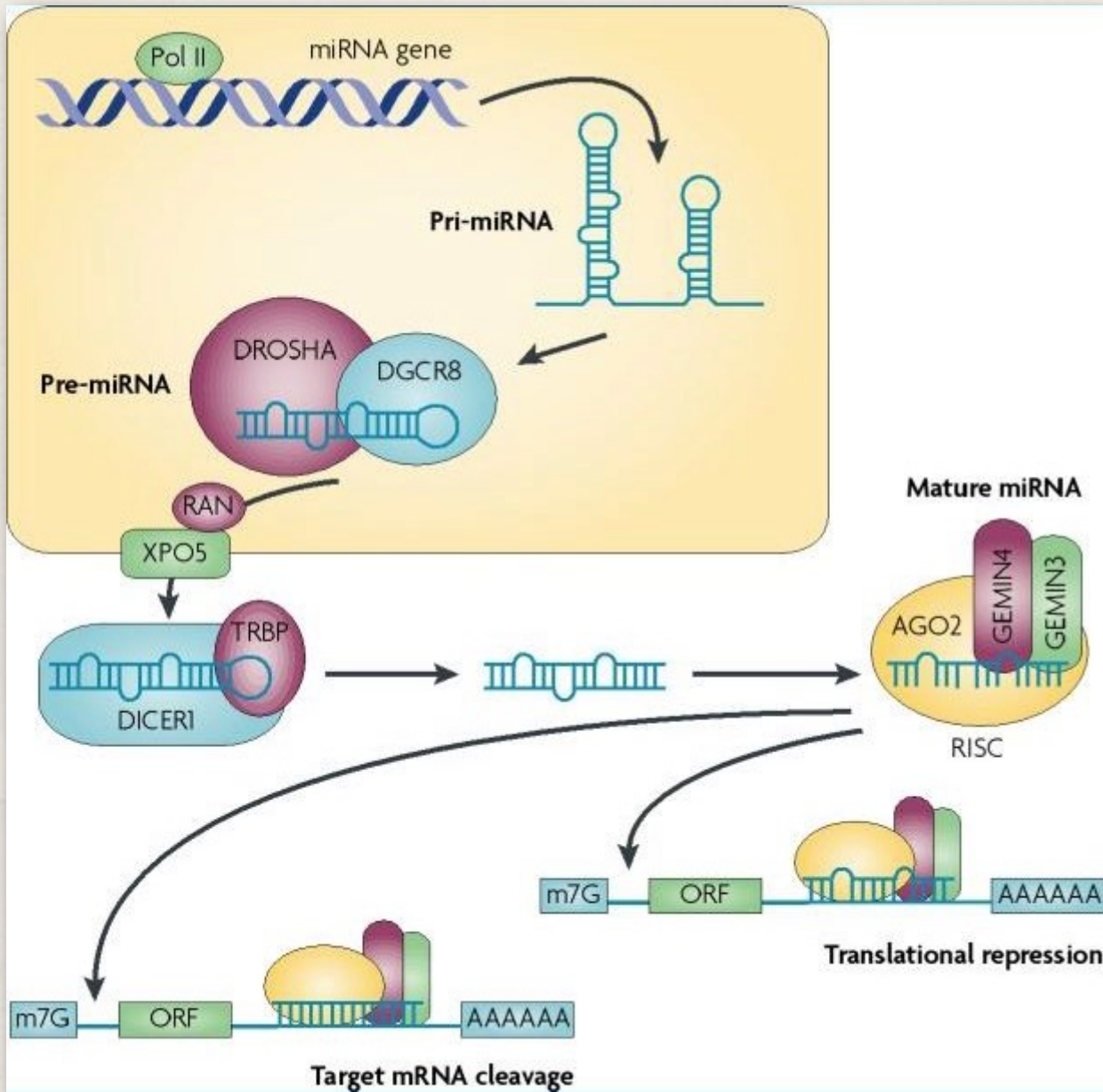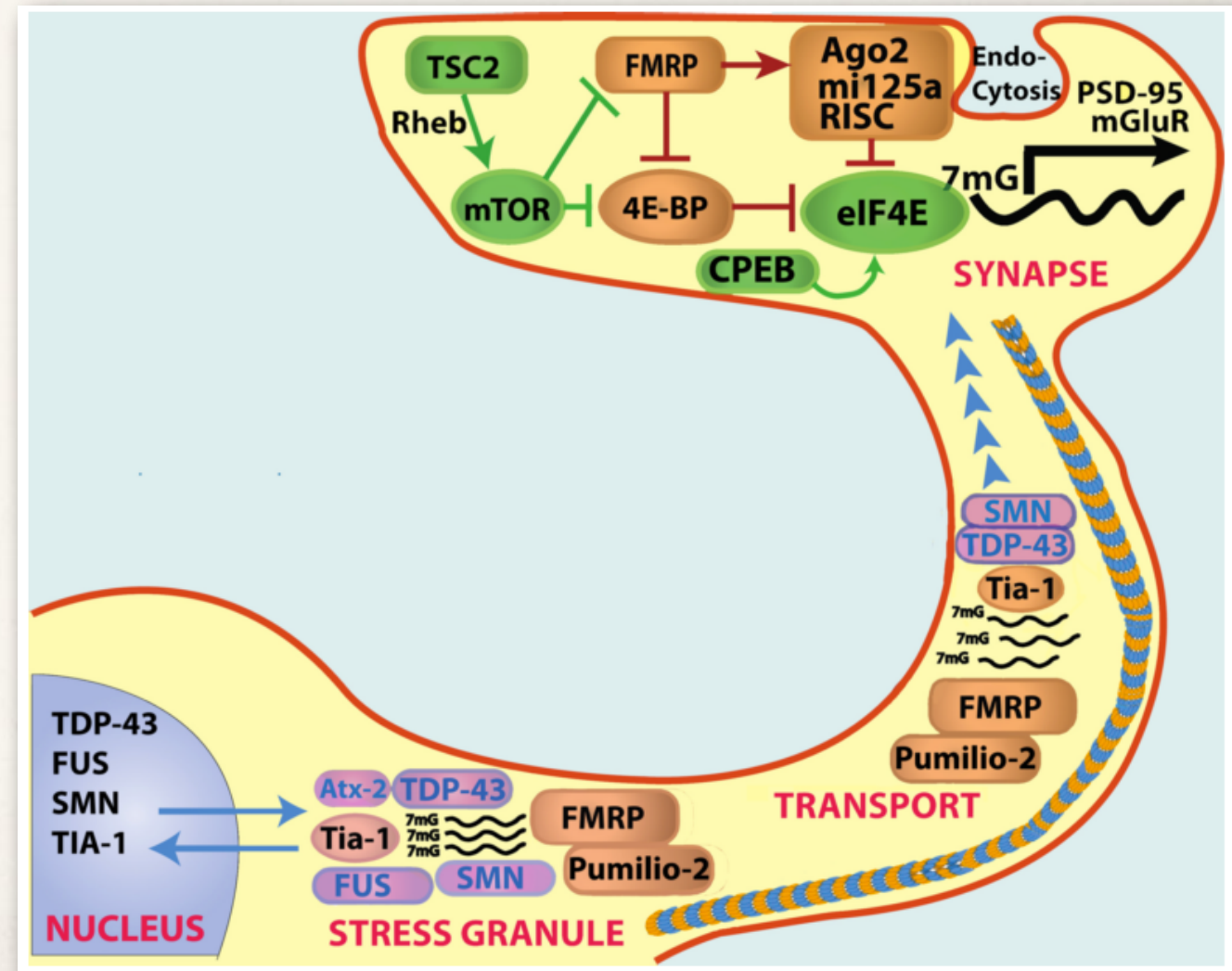Rule-sets are used to build a Continuous Time Markov chain (CTMC)
Simulated with a stochastic version of the "mass action" law (Gillespie algorithm)

Dynamical modeling of translation regulation by miRNA
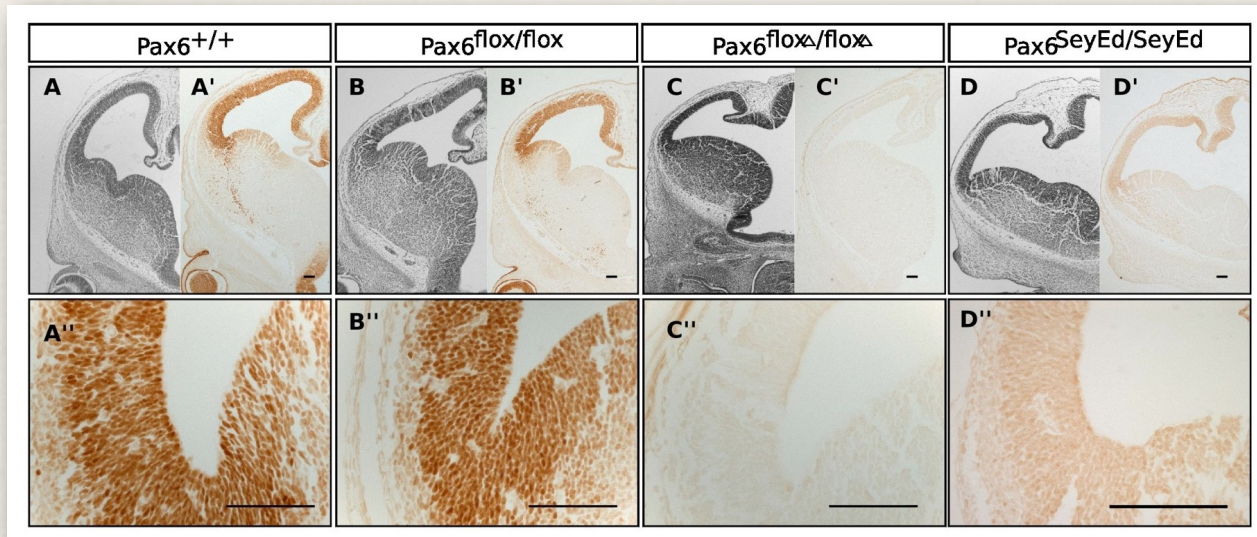
miRNA processing

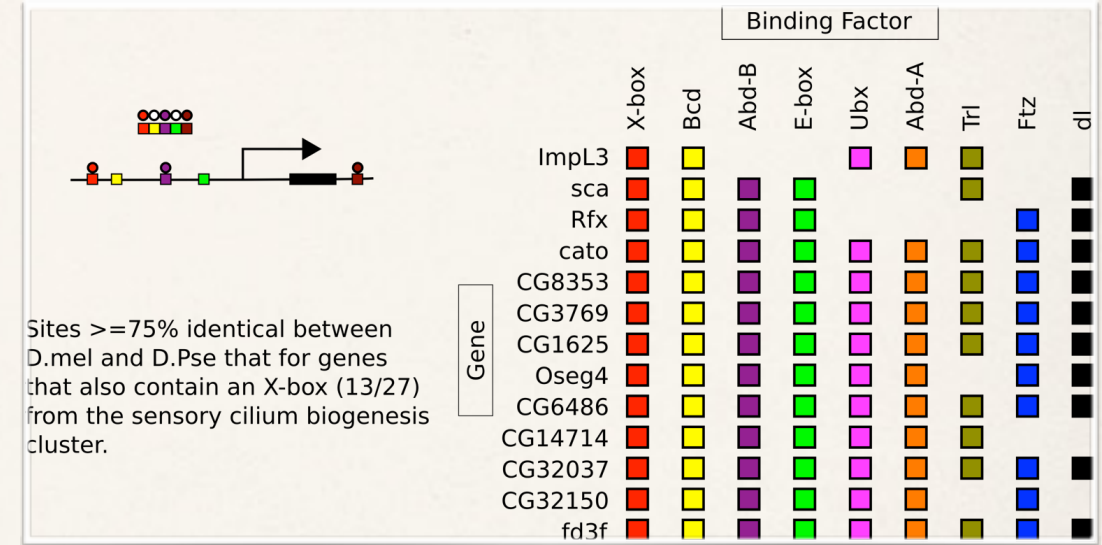spatial Kappa, local protein translation

Project : Modeling miRNA biology

Genetic control of gene expression in the brain

Pax6

Gli3
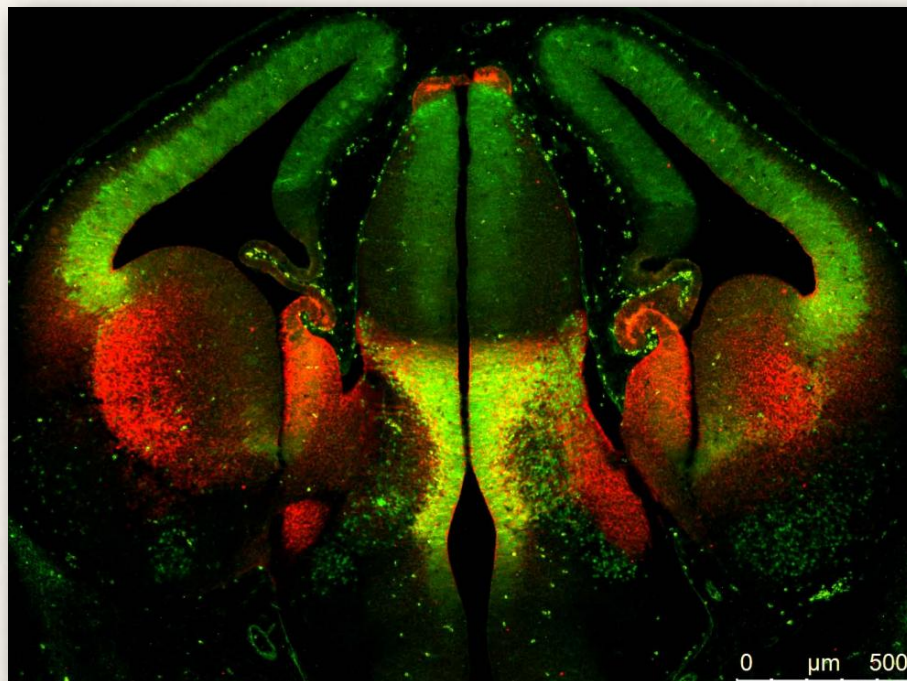
Atonal

Atonal E-box

Scute E-box

Project : Transcriptional regulatory control networks in the brain

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