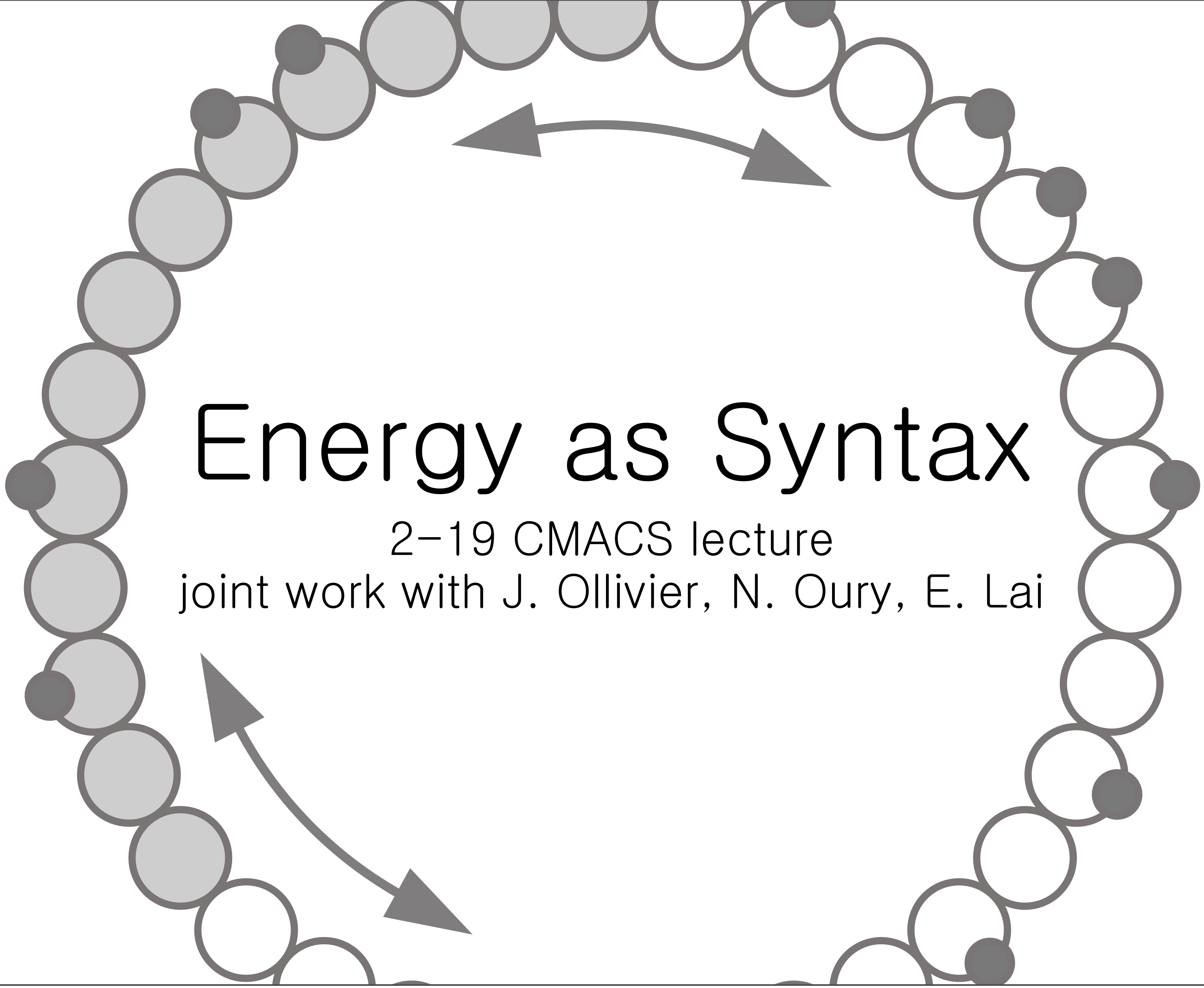


Energy as Syntax

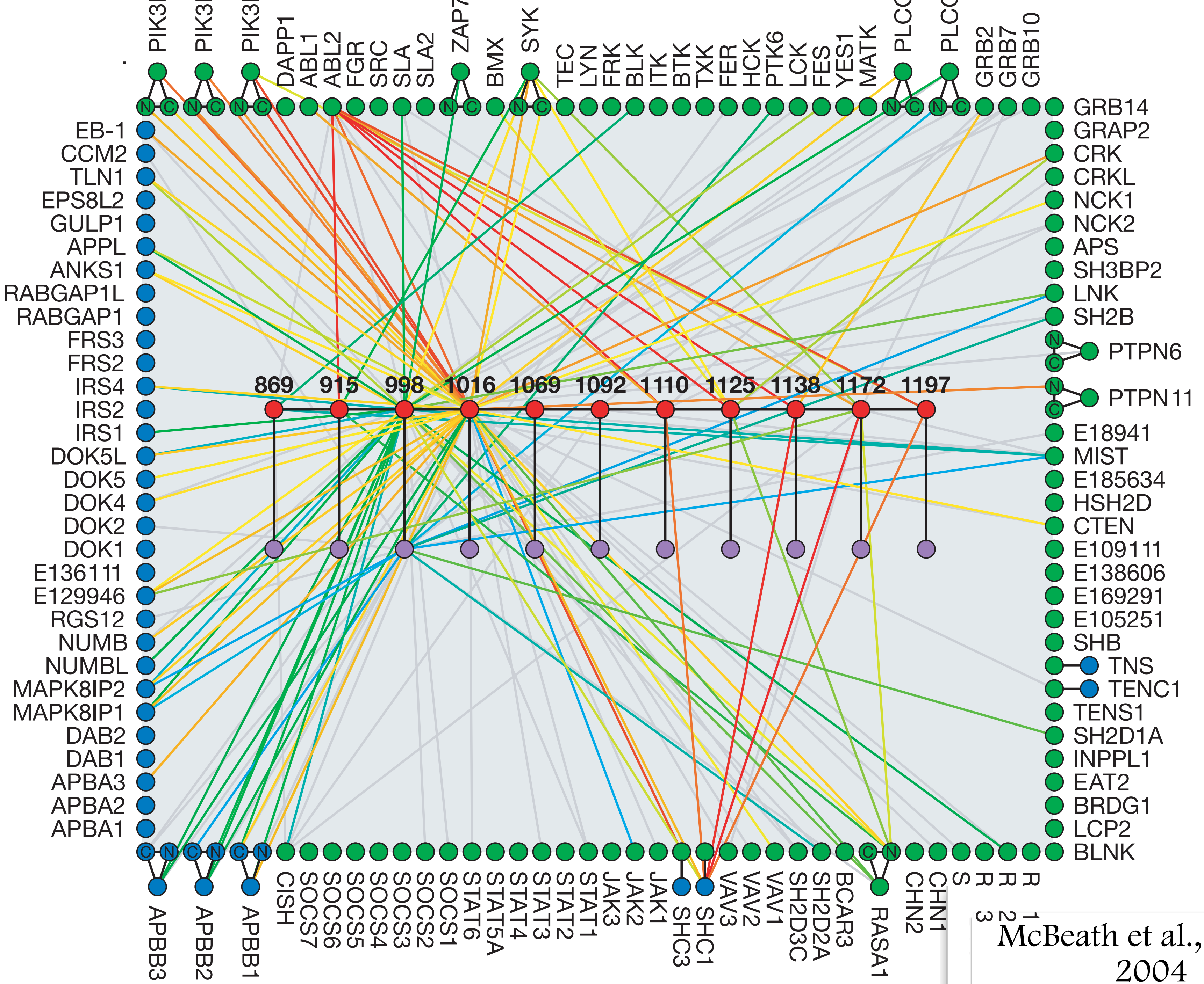
2-19 CMACS lecture

joint work with J. Ollivier, N. Oury, E. Lai

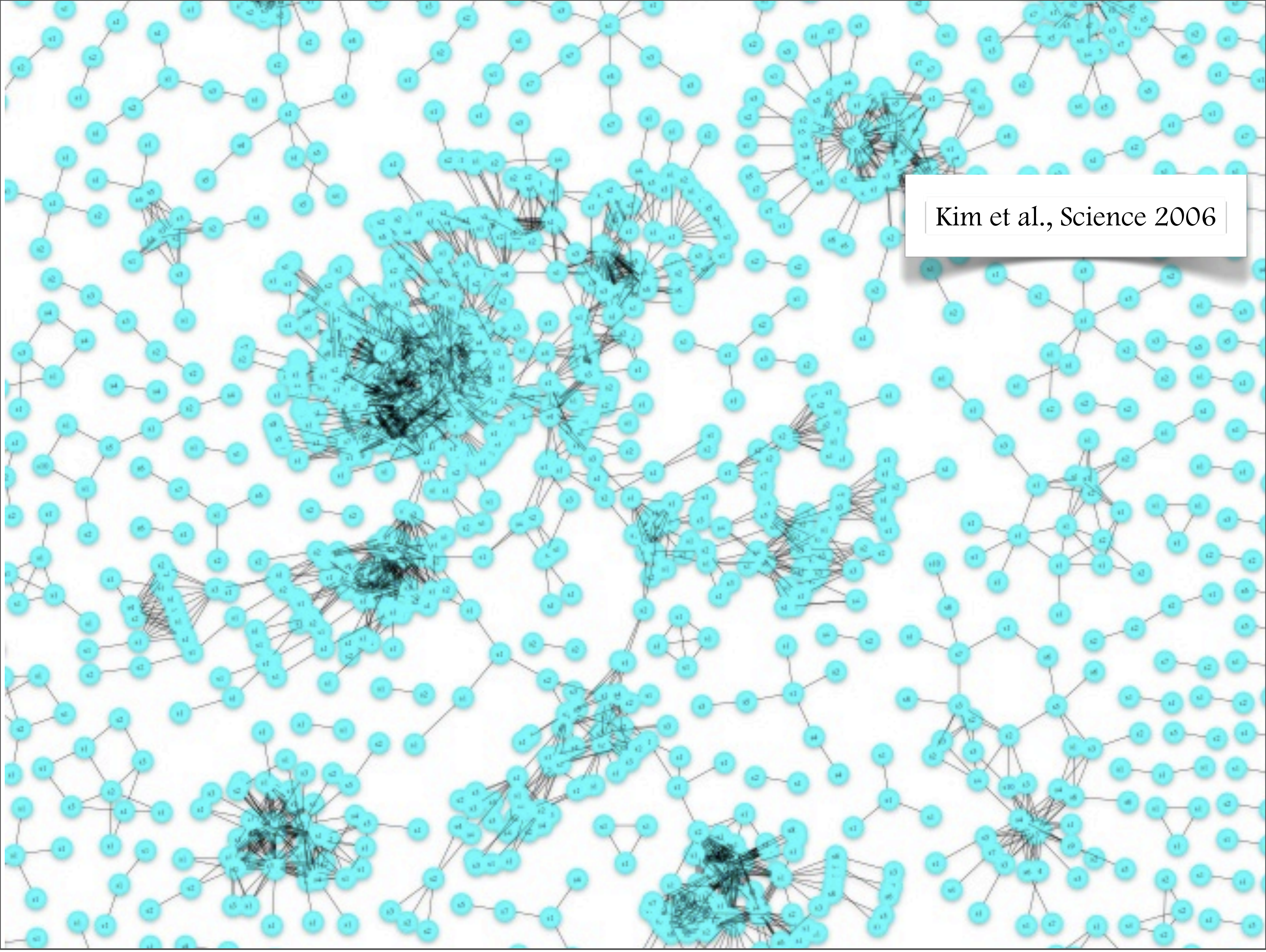
turbo introduction to Kappa/BNGL

why rules are great

EGFR



McBeath et al., Nature 2004

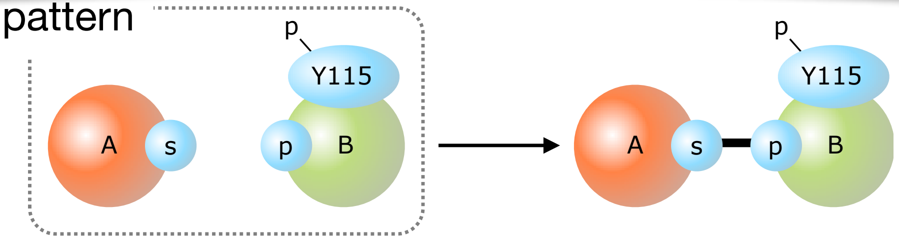


Kim et al., Science 2006

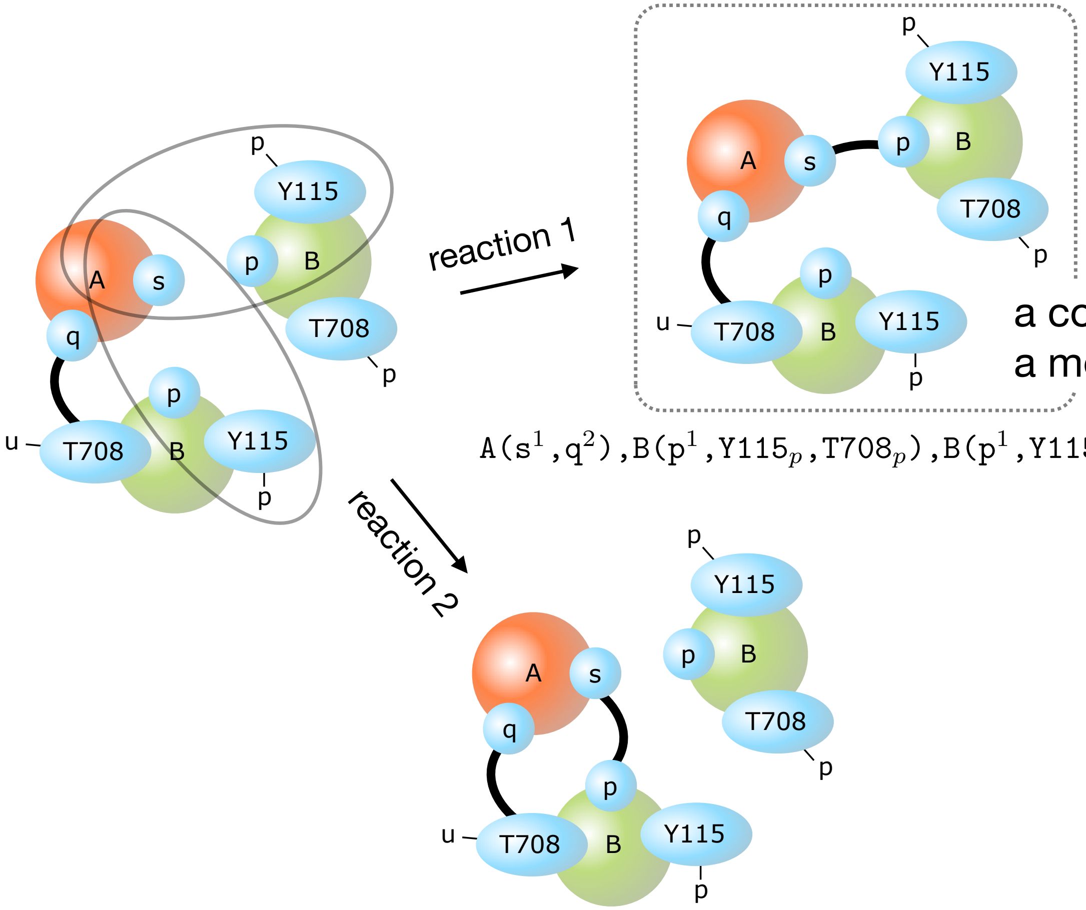
probabilistic (site) graph rewriting

a rule

a pattern



$$A(s),B(p,Y115_p) \rightarrow A(s^1),B(p^1,Y115_p)$$



a complex,
a molecular species

$$A(s^1,q^2),B(p^1,Y115_p,T708_p),B(p^1,Y115_p,T708^2_u)$$

try Kappa!

http://www.pps.jussieu.fr/~jkrivine/binaires/Telechargements/Outils_danalyses_et_de_simulation.html forget about rules!

energy as syntax

energy-oriented modelling/programming

- more <u>structured</u> approach

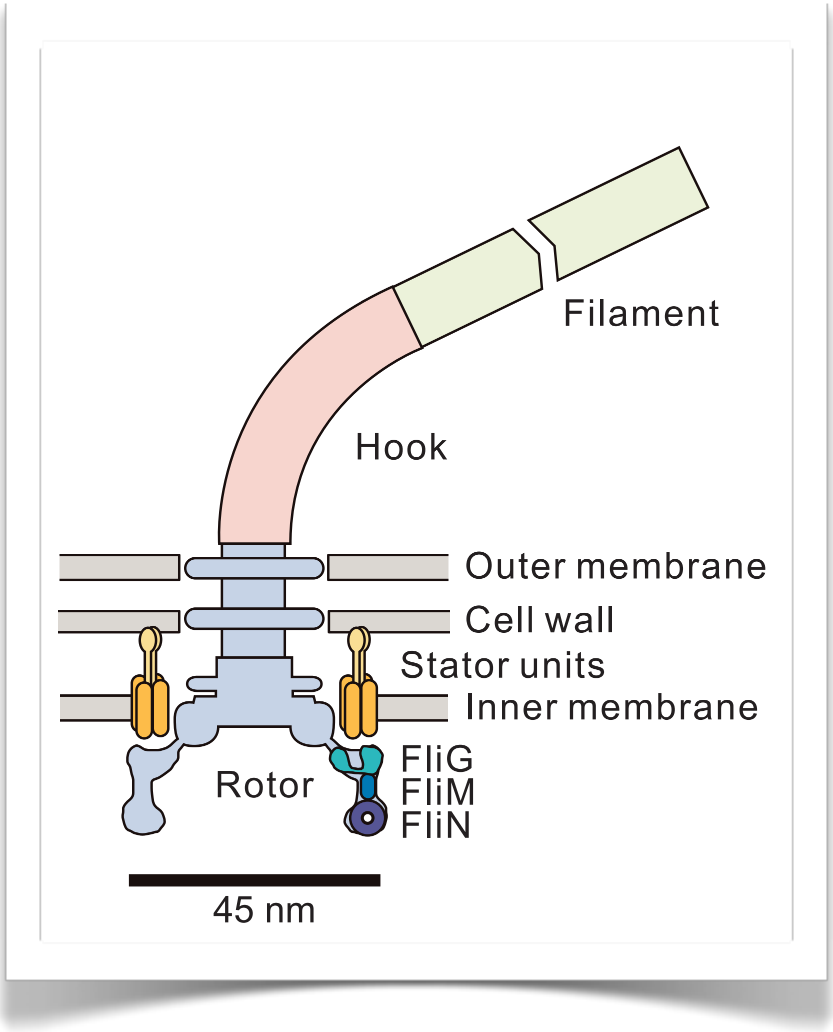
  - as in structured programming
  - esp. well suited for combinatorial molecular network for which:
  - no structure means no analysis possible ...

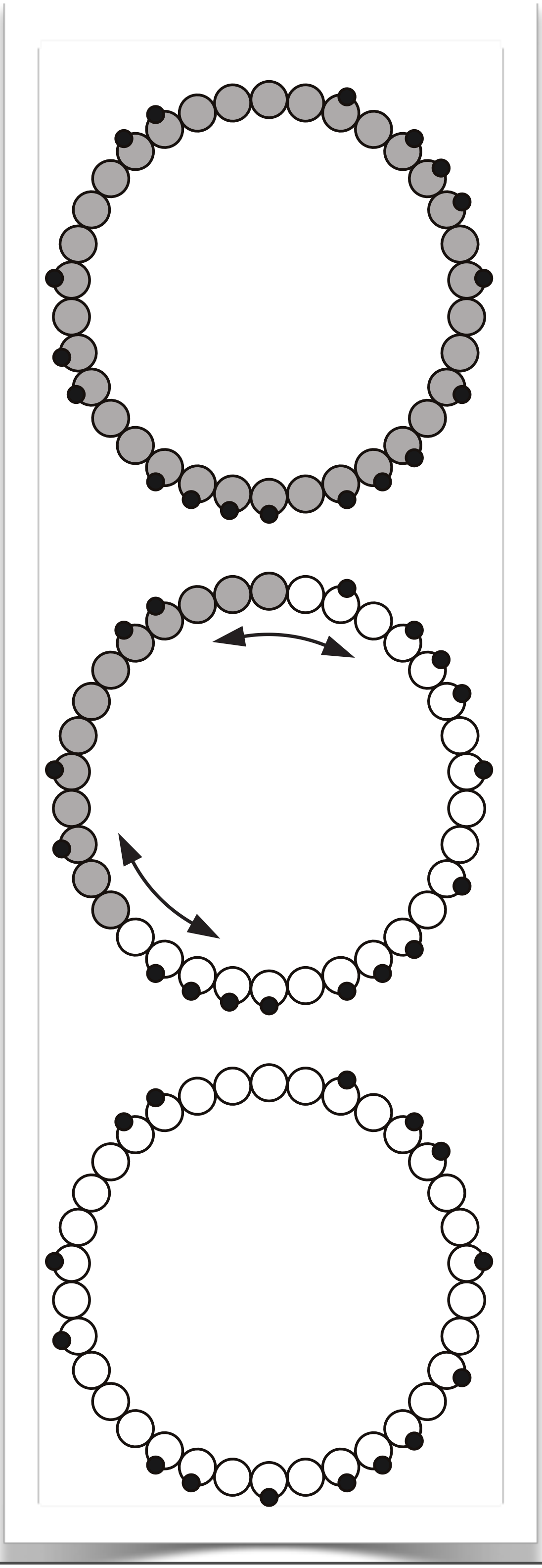
- more physically realistic

- less parameter-hungry

example: an allosteric Ising model

[Science – Feb 5 2010]


Filament
Hook
Outer membrane
Cell wall
Stator units
Inner membrane
Rotor
FliG
FliM
FliN
45 nm



an allosteric Ising model

an allosteric model of the E. Coli flagellar switch (with ANC-style energy)

- a ring of 2-state protomers P(f):
  - [favoured] f=0=inactive (counter clockwise)
  - [disfavoured] f=1=active (clockwise)
- potential bindees CheY that favour f=1

combinatorics & nn

CheY(s~p) might bind any P, which means an astonishing ~ 10^{20} different configurations (that is the number of species one would need in a species-centric approach)

we are going to write the Hamiltonian/ energy of the system - a sum of 3 different contributions

all terms are nn=<u>nearest neighbour</u>

Energy landscaping - i

a <u>P conformational term</u> whereby it is said that P prefers conformation 0

$$E(P(f{\sim}0)) < E(P(f{\sim}1))$$

convention: lower energy = more favoured

Energy landscaping - ii

a <u>CheY-P binding term</u> whereby we say that if bound to pho'ed CheY, P prefers conformation 1

E(P(f~0,s!1),CheY(s~p!1)) >
E(P(f~0,s!1),CheY(s~p!1))

nb: this term overlaps with the first one E(P((f~0/1)))

Energy landscaping - iii

an <u>Ising penalty term</u> for n.-neighbours not being in the same conformation which will "spread conformation"

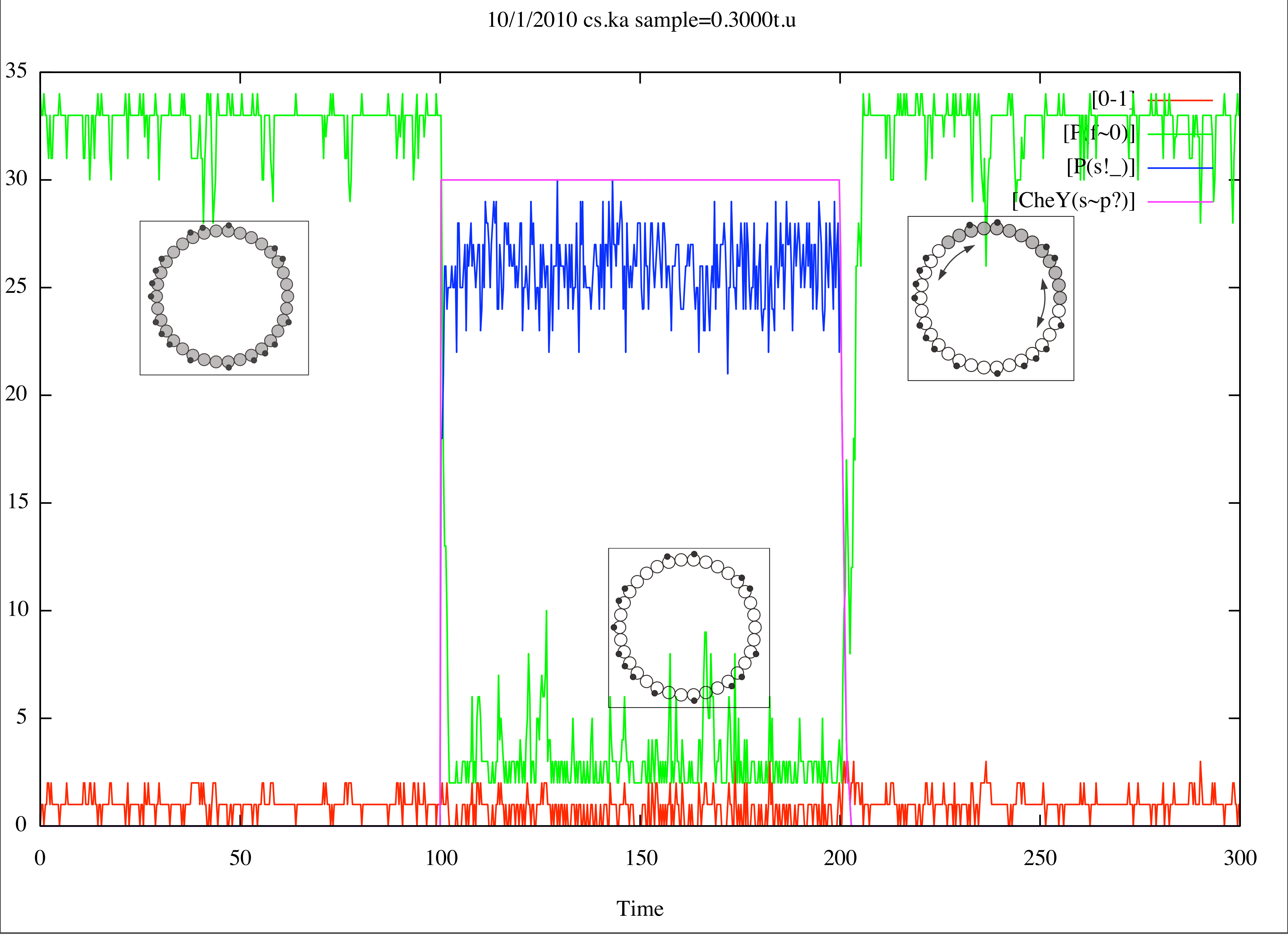
E(P(f~1,x!1),P(y!1,f~0)) =
E(P(f~0,x!1),P(y!1,f~1)) >
E(P(f~0,x!1),P(y!1,f~0)) =
E(P(f~1,x!1),P(y!1,f~1))

dynamics ii – rules

```
# 10 reversible rules
## 2 binds
### P-CheY binding: CheY needs to be pho'ed & prefers conformation P(f~1) by a factor of 10
'bind 0' P(f~0,s), CheY(s~p) <-> P(f~0,s!1), CheY(s~p!1)@1,10
'bind 1' P(f~1,s), CheY(s~p) <-> P(f~1,s!1), CheY(s~p!1)@1,1

## 8 flips (aka conformational change)
### 4 P flips without CheY - note that P(f~0) is favoured 2/1
'flip 000' P(f~0,y!1),P(x!1,f~0,y!2,s),P(x!2,f~0) <-> P(f~0,y!1),P(x!1,f~1,y!2,s),P(x!2,f~0)@1,200
'flip 100' P(f~1,y!1),P(x!1,f~0,y!2,s),P(x!2,f~0) <-> P(f~1,y!1),P(x!1,f~1,y!2,s),P(x!2,f~0)@1,2
'flip 001' P(f~0,y!1),P(x!1,f~0,y!2,s),P(x!2,f~1) <-> P(f~0,y!1),P(x!1,f~1,y!2,s),P(x!2,f~1)@1,2
'flip 101' P(f~1,y!1),P(x!1,f~0,y!2,s),P(x!2,f~1) <-> P(f~1,y!1),P(x!1,f~1,y!2,s),P(x!2,f~1)@100,2

### 4 P flips with CheY - note that all forwards are multiplied by 10 (one simple way to satisfy the ANC
### thermodynamic constraint, aka the Wegscheider condition)
'flip 000b' P(f~0,y!1),P(x!1,f~0,y!2,s!_),P(x!2,f~0) <-> P(f~0,y!1),P(x!1,f~1,y!2,s!_),P(x!2,f~0)@10,200
'flip 100b' P(f~1,y!1),P(x!1,f~0,y!2,s!_),P(x!2,f~0) <-> P(f~1,y!1),P(x!1,f~1,y!2,s!_),P(x!2,f~0)@10,2
'flip 001b' P(f~0,y!1),P(x!1,f~0,y!2,s!_),P(x!2,f~1) <-> P(f~0,y!1),P(x!1,f~1,y!2,s!_),P(x!2,f~1)@10,2
'flip 101b' P(f~1,y!1),P(x!1,f~0,y!2,s!_),P(x!2,f~1) <-> P(f~1,y!1),P(x!1,f~1,y!2,s!_),P(x!2,f~1)@1000,2
```



Sunday, February 21, 2010

conformation spread

The lower curve - tracking the Ising energy of the ring stays low at all time

- despite fraction of inactive P's ranging in [0,1] depending on nb of CheY-Ps

NB: a Duke, Bray, Le Novere model; does not need a regular and/or permanent lattice

home run!

- more physically realistic: seems to fit really well in this case (see Ref)

- less parameter-frenzy:

  - 10 reversible rules
  - 8 energy terms = 2 flips + (2+4) binds
  - 16 independent choices of kinetic rates “time scales”

- more structured approach: it really shines!

- esp. well suited for combinatorial molecular networks: 10^{20}!