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
graphical representation of pY-mediated recruitment (Fig. 2). These diagrams provide a system-level view of the ErbB receptors, showing biophysical interactions between signalling proteins and known sites of tyrosine phosphorylation. Which proteins are actually recruited in a given cell will depend on many factors, including the effective concentrations of both the activated receptors and the signalling proteins. These diagrams should therefore be viewed as quantitative maps of the receptors, rather than a depiction of protein recruitment in any specific cell type or state.

To evaluate how well our microarray experiments recapitulate known interactions, we compiled a list of previously reported interactions between SH2/PTB-containing proteins and the ErbB receptors (Supplementary Table 5). For interactions with EGFR and ErbB2, we relied on hand-curated databases (ref. 10 and http://proteome.incyte.com/); for ErbB3 and ErbB4, we surveyed the literature ourselves. Overall, our arrays detected 43 of the 65 previously reported interactions. For example, we observed that peptides derived from EGFR were able to bind strongly \( (K_D, 2 \text{mM}) \) to the SH2/PTB domains of Crk, Grb2, Nck1, PI3K \( \alpha \) (also known as PIK3R1), PI3K \( \beta \) (also known as PIK3R2), PLC-\( \gamma \)1 (also known as PLCG1), PLC-\( \gamma \)2 (also known as PLCG2), Shp2 (also known as PTPN11), RasGAP (also known as RASA1), Shc1, Shc3, Syk and Vav1, and weakly to the SH2 domains of Grb10, Grb7, Nck2, Shp1 (also known as PTPN6), Nsp1 (also known as SH2D3A), Socs1, Stat1, Stat3, Vav2 and Vav3. Many of the known interactions that were not detected were members of the STAT and SOCS families of...
probabilistic (site) graph rewriting

A rule:

A(s), B(p, Y115_p) → 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_p)
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 structured 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

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Recent technical advances have allowed us to observe these signatures of conformational spread.

Changes in the flagellar (FliG) track, which interfaces with the torque-generating units to determine rotation direction (absolute coupling between subunit conformations). Structural studies indicate that conformational changes in FliG (~10 copies, orange) and the torque-generating stator units MotA complex proteins FliG (~26 copies), FliM (~34 copies), and FliN (~136 copies) are coupled indirectly to conformational switches varying in speed monotonically through one revolution for completion, and not all switches are evident. (Right) The same data as the inset in (B), center, right panels. Switches were observed with a broad range of durations across the population (Fig. 2, B to D) and switches were evident. (Right) The same switch of duration 78.4 ms, taking almost one revolution to complete and demonstrating nonmonotonic speeds (Fig. 2A, right panel). A typical switch event is displayed in detail in Fig. 2B. Filtering, median filtered speed trace correspond to smooth rotation; the sign of the phase shift between CW and CCW is required to show the CW and CCW states and incomplete switching to speed levels shown as unfiltered bead angle versus time. Scale bars show 0.5 revolutions and 10 ms. The median filtered motor speed records show the peak shape is asymmetrically broad, corresponding to CW rotation). (Center) The same switch (amplitude x 2) or not bound (absolute coupling between binding sites and radii of the bead trajectory were obtained by focal-plane interferometry of polystyrene beads attached to truncated flagella of E. coli J53). (Left) Schematic of the bacterial flagellar motor. Indicated are the likely positions of switch crossings analyses of motor switching. Crossings of single motors with a steady bead trajectory were counted and radii of the bead trajectory were obtained by Gaussian curves were fitted to the peak shape. Complete and incomplete switches were set at two-thirds of the mean CW and CCW speeds (Fig. 2A, left panel). The multistate sequential model in the limit of large random walk until it either encompasses the entire ring or collapses back to the initial position. Median filtered speeds clearly, extends the apparent duration of switching, set at two-thirds of the mean CW and CCW speeds (Fig. 2A, right panel). A typical switch of duration 20.8 ms, in red was calculated as the interval during which the switch was observed. (Left) Interactions between adjacent protomers in the Antenna domain of FliG (black circle) bound. (Image 57x144 to 373x531). Structural studies indicate that conformational changes independent of CheY-P binding. These interactions add 0, +2, -2, set at two-thirds of the mean CW and CCW speeds (Image 18), CCW). (Fig. 2, B, center and right panels). Switches were observed with a broad range of durations across the population (Fig. 2, B to D) and switches were evident. (Right) The same data as the inset in (B), center, right panels. Switches were observed with a broad range of durations across the population (Fig. 2, B to D) and switches were evident.
an allosteric Ising model

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

- a ring of 2-state protomers $P(f)$:
  - $f=0$ = inactive (counter clockwise)
  - $f=1$ = active (clockwise)

- potential bindees CheY that favour $f=1$
combinatorics & nn

CheY(s~p) might bind any P, which means an astonishing $\sim 10^{20}$ 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 $nn=nearest\ neighbour$
Energy landscaping – i

a P conformational term whereby it is said that P prefers conformation 0

\[ E(P(f\sim0)) < E(P(f\sim1)) \]

convention: lower energy = more favoured
Energy landscaping – ii

a CheY–P binding term whereby we say that if bound to pho’ed CheY, P prefers conformation 1

\[ E(P(\sim 0, s^1), CheY(s^p 1)) > E(P(\sim 0, s^1), CheY(s^p 1)) \]

nb: this term overlaps with the first one \[ E(P((f \sim 0/1))) \]
Energy landscaping – iii

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

\[ E(P(f\sim1,x\!1),P(y\!1,f\sim0)) = \]
\[ E(P(f\sim0,x\!1),P(y\!1,f\sim1)) > \]
\[ E(P(f\sim0,x\!1),P(y\!1,f\sim0)) = \]
\[ E(P(f\sim1,x\!1),P(y\!1,f\sim1)) \]
# 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' $P(f\sim0,s), \text{CheY}(s\sim p) \leftrightarrow P(f\sim0,s!1), \text{CheY}(s\sim p!1)@1,10$

'bind 1' $P(f\sim1,s), \text{CheY}(s\sim p) \leftrightarrow P(f\sim1,s!1), \text{CheY}(s\sim p!1)@1,1$

### 8 flips (aka conformational change)

#### 4 P flips without CheY – note that P(f~0) is favoured 2/1

'flip 000' $P(f\sim0,y!1),P(x!1,f\sim0,y!2,s),P(x!2,f\sim0) \leftrightarrow P(f\sim0,y!1),P(x!1,f\sim1,y!2,s),P(x!2,f\sim0)@1,200$

'flip 100' $P(f\sim1,y!1),P(x!1,f\sim0,y!2,s),P(x!2,f\sim0) \leftrightarrow P(f\sim1,y!1),P(x!1,f\sim1,y!2,s),P(x!2,f\sim0)@1,2$

'flip 001' $P(f\sim0,y!1),P(x!1,f\sim0,y!2,s),P(x!2,f\sim1) \leftrightarrow P(f\sim0,y!1),P(x!1,f\sim1,y!2,s),P(x!2,f\sim1)@1,2$

'flip 101' $P(f\sim1,y!1),P(x!1,f\sim0,y!2,s),P(x!2,f\sim1) \leftrightarrow P(f\sim1,y!1),P(x!1,f\sim1,y!2,s),P(x!2,f\sim1)@100,2$

#### 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' $P(f\sim0,y!1),P(x!1,f\sim0,y!2,s!\_),P(x!2,f\sim0) \leftrightarrow P(f\sim0,y!1),P(x!1,f\sim1,y!2,s!\_),P(x!2,f\sim0)@10,200$

'flip 100b' $P(f\sim1,y!1),P(x!1,f\sim0,y!2,s!\_),P(x!2,f\sim0) \leftrightarrow P(f\sim1,y!1),P(x!1,f\sim1,y!2,s!\_),P(x!2,f\sim0)@10,2$

'flip 001b' $P(f\sim0,y!1),P(x!1,f\sim0,y!2,s!\_),P(x!2,f\sim1) \leftrightarrow P(f\sim0,y!1),P(x!1,f\sim1,y!2,s!\_),P(x!2,f\sim1)@10,2$

'flip 101b' $P(f\sim1,y!1),P(x!1,f\sim0,y!2,s!\_),P(x!2,f\sim1) \leftrightarrow P(f\sim1,y!1),P(x!1,f\sim1,y!2,s!\_),P(x!2,f\sim1)@1000,2$
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: $10^{20}$!