





Monday, 29 November 2010

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

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100,000 rpm





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):

 - {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 ~ 10²⁰ different configurations (that is the number of species one would need in a speciescentric 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~0)) < E(P(f~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~1,s!1),CheY(s~p!1))

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

Energy landscaping - iii

an <u>lsing 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

- we write rules in a way that the model is thermodynamically correct by construction

 we use perturbations to control the amount of CheY-P flipping the entire ring back and forth from all-0 to all-1





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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

10/1/2010 cs.ka sample=0.3000t.u



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: shines!
- esp. well suited for combinatorial molecular networks: 10²⁰!



a contact map CM - think of it as a type for our configurations
a set of patterns S (energy shapes) which defines H(x) for every state of type CM an occurrence vector in RS as H(x,s)=|[s;x]|
a vector of shape "price" ka(s) in RS which defines h(x)=(ka,H(x)) - think of it as a set of local preferences for our microstates

- pick rules such that:

1. every rule r has an <u>unambiguous energy balance</u> wrt s in S (independent of the match) – expressed as a column vector Er

2. reversibility: every rule r has an inverse rule r⁻¹ (supposing only simple bindings and mods – which implies atomic number is preserved)

3. simplicity: every jump is realised by a unique r with constant rate

Set k(r) st that $\log k(r^{-1})/k(r) = (ka, Er)$ (many solutions)

The obtained system converges to the invariant measure exp(-h (x)) on X(x0) the component of the initial state

example: simple allostery

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energy(x) = sum eps-R(f) + sum eps-RA(f)

Thermo correction forces relations between equilibrium constants
K(flip 0 to 1 busy) =
K(attach to A in state 1)*K(flip 0 to 1 free)*1/K(attach to A in 0) = 1/10

```
# flips
                                        -beta * Delta eps =
R(i \sim 0, x) < -> R(i \sim 1, x)  @1,1 # 0
R(i \sim 0, x!) < -> R(i \sim 1, x!) = -\ln(10) + 0 + 0
# binds
A(x), R(i \sim 0, x) < -> A(x!1), R(i \sim 0, x!1) @10,1 # ln(10)
A(x), R(i \sim 1, x) < -> A(x!1), R(i \sim 1, x!1) = 0
%init: 1000 * (B(), R(i~0,x))
# we observe the number of Rs in conformation 0
%obs: 'R0' R(i~0)
%obs: R(x!)
# we activate the A's at T=10 time units to observe the difference
'inj' B() -> A(x) @0
%mod: $T > 10 do 'inj':= $INF
```



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example 2: Ising ring again

a ring/3 shape classes









return to an Ising flip

'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)

for r <u>a flip</u> to have an unambiguous PP balance – we need r to include nearest neighbours (<u>with</u> their internal f state)

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ANC shapes: nearest neighbours w internal states

the ANC energy

 $\epsilon_1(x) = \sum_{A \in x} \phi(A, f) + \sum_{A, f, x, y, g, B \in x} \beta(A, f, x, y, g, B)$

 ANC rules are bindings, and flips with bound nn (with internal states in both cases)

- The Ising model is an ANC model

eR parameter hunger

of <u>independent</u> constraints on K(r)s is: rank (∂(r,s)) r in R, s in S

ANC system rank = #binds + #free flips whereas total#rules ~ 3<d>*rank