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INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
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SMR.961 - 25

WORKSHOP ON:
PROTEINS, MEMBRANES and their INTERACTIONS

22 JULY - 2 AUGUST 1996

"Lessons from lattice models for folding kinetics"

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These are preliminary lecture notes, intended only for distribution to participants.

LESSONS FROM LATTICE MODELS OF PROTEIN FOLDING

CARLOS CAMACHO
(CHILE)

DIMA KLIMOV
(MARYLAND)

REFERENCES Camacho/DT PNAS 90, 1369 ('93)
" PRL 2 ('93)

Dill et. al. Prot. Sci. 4, 561 ('95) REVIEW

KLIMOV/DT PRL MAY 20 ('96)
" PROTEINS (in Press).

CAMACHO/DT EuroPhys Lett (in Press)

LATTICE MODELS - A BRIEF HISTORY

GO (Int. J. PEPTIDE RES.) (1975)

*DILL & GROUP (88 or 90)

SHAKHNOVICH & GUTIN ('90)

Jacci, Onuchic

LEVITT / HINDS

JERNIGAN / COVELL

MARYLAND GROUP

MOULT & UNGER

DENMARK Group

} mainly - now.

ADVANTAGES OF LATTICE MODELS

1) SMALL CHAINS - EXACT ENUMERATIONS OF ALL CONFORMATIONS POSSIBLE

2) USING CERTAIN KINETIC RULES - PATHWAYS; KINETIC SCHEMES, FOLDING TIMES ETC. COMPUTABLE (LANDSCAPES ?)

3) CREATE A "LAB" & A WORLD OF ONE'S OWN -

DISADVANTAGES

a) RESEMBLANCE TO REALITY ?

b) KINETIC MOVES ?

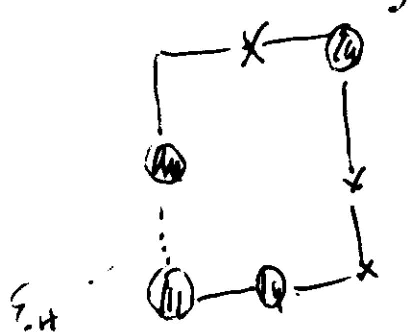
c)

MODELS / INTERACTIONS

LATTICE TYPES (Cubic / DIAMOND ---)

INTERACTIONS: a) 2 LETTER CODES (HP type ala Dill)

$$H = -\varepsilon_H \sum_{ij \in H} \delta_{r_{ij},a}$$



2/3 or many letter

MJ potential

b) Interaction matrix $H_{ig} = -\sum B_{ij} \delta_{r_{ij},a}$

$$P(B_{ij}) \sim \exp\left[-(B_{ij}-B_0)^2/2B^2\right]$$

B_0 ~ Average hydrophobic interaction ; B = dispersion

Random Bond Model (Contd.)

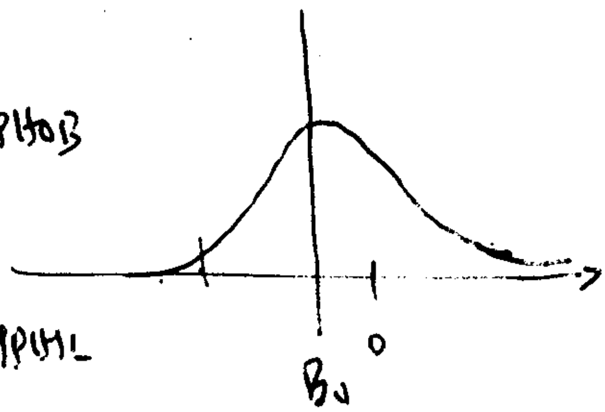
For a given B, B_0 what fraction is hydrophobic?

- LARGE B_0 ⇒ more hydrophobic.

$$B_{ij} = \begin{cases} -ve & \Rightarrow \text{hydrophobic} \\ +ve & \Rightarrow \text{HPhil} \end{cases}$$

B_{ij} $< B_H$ ⇒ HPHOB

$> B_P (= -B_H)$ HPHIL



$B_H < B_{ij} < B_P$ ⇒ mixed Interaction

$N = N_H + N_P$

λ_H (fraction of HPHOB) $\approx (N_H/N)^2$

$$\approx \int_{-\infty}^{B_H} P(B_{ij})\,dB_{ij}$$

$$\lambda_H \simeq (N_H/N)^2 = \int_{-\infty}^{B_H} P(B_{ij})\, dB_{ij}$$

$B_0 = 0 \Rightarrow N_H = N_P \Rightarrow$ $B_H = -0.675\,B$

NATURAL Chartering ~~[illegible]~~ $N_H/N \simeq 0.54$

$\Rightarrow$ A Good choice of $B_0 = -0.1B$

? $B_0 = -1.0\,B$ (a popular choice in CAMBRIDGE)

74% hydrophobic — a bit artificial

Advantage! Here one might think one can

get away thinking only about

Compact Structures!

— WRONG!

KLIMOV

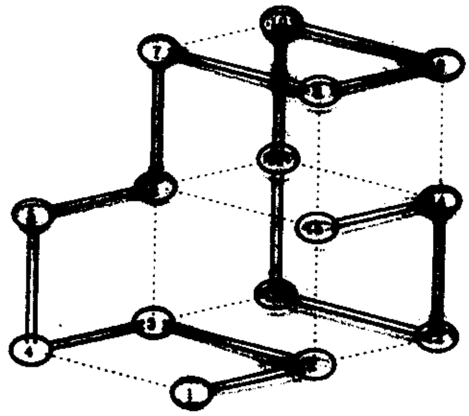
Unger & Moult

Socci & Onuchic

$N = 15$, $B_0 = -0.1$ $C^{15}_{FE} = 93,250,730.$

$|D| = 3|$

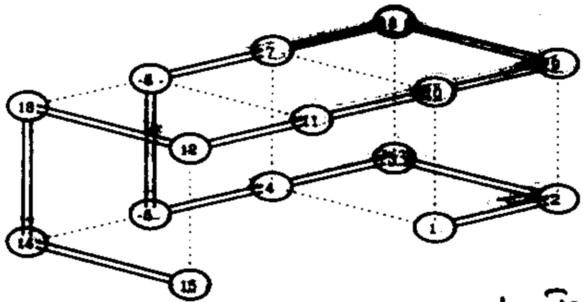
(a)



FULLY COMPACT

11 TOP. CONTACTS

(b)

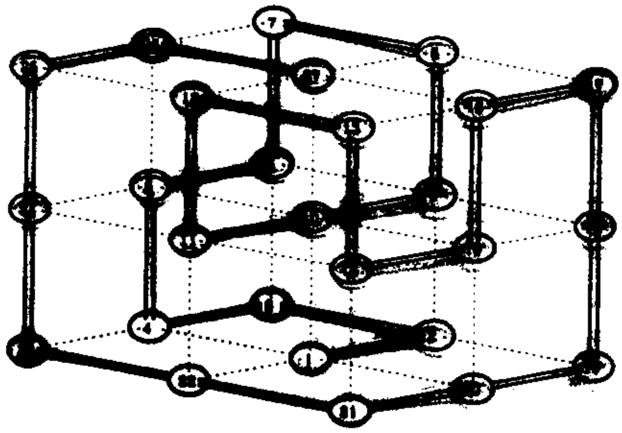


10 TOP. CONTACTS

Fig. 1(a,b)

"VENERABLE" CUBE – C_{compct} : 103,346 → (Chan/Dill Shakhnovich/ Gutin)

(a)

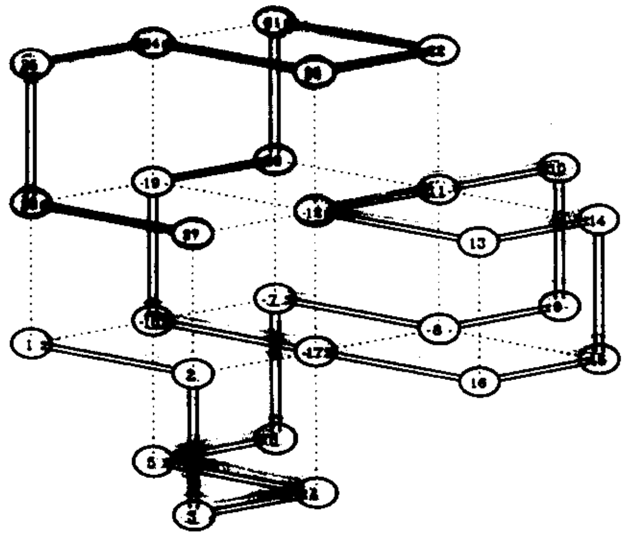


Fully Compact
C = 28

$B_0 = -0.1$

N = 3x3x3
= 27

(b)



22
Top. Contacts
Non-Compact
native state

less than 1/2 of all native conformations non-compact!

Fig. 2(a,b)

ENERGY SPECTRUM FOR N=27

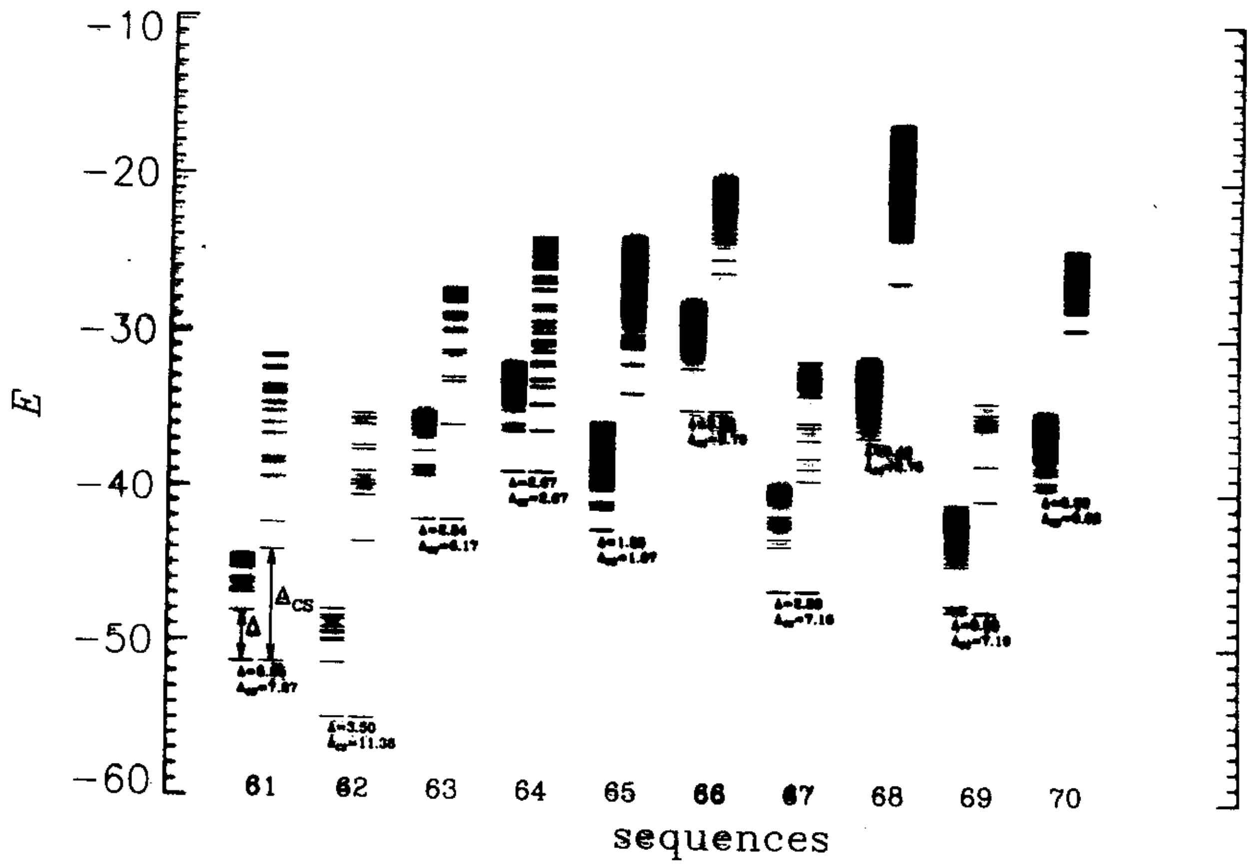


Fig. 4

$\Delta_{CS} \geq \Delta$ (generally true).

DETERMINING T_θ & T_F

(χ = 15)

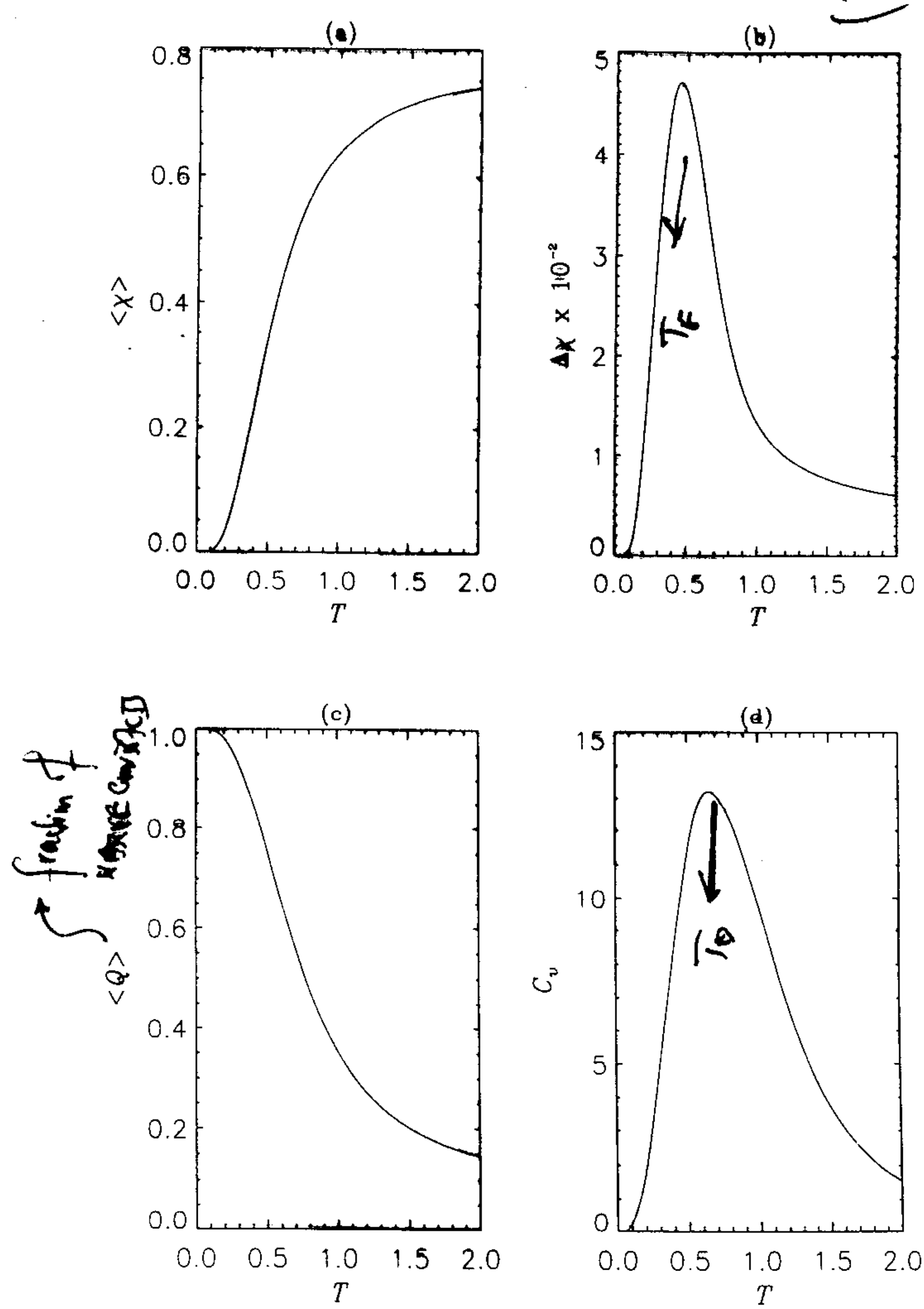


Fig. 6

[$\chi = 1 - \frac{1}{N^2 - 3N + 2} \sum \delta_{r_{ij}^{T}, r_{ij}^{N}}$ (overlap) Carlos '93]

N=15, β_0 = -0.1

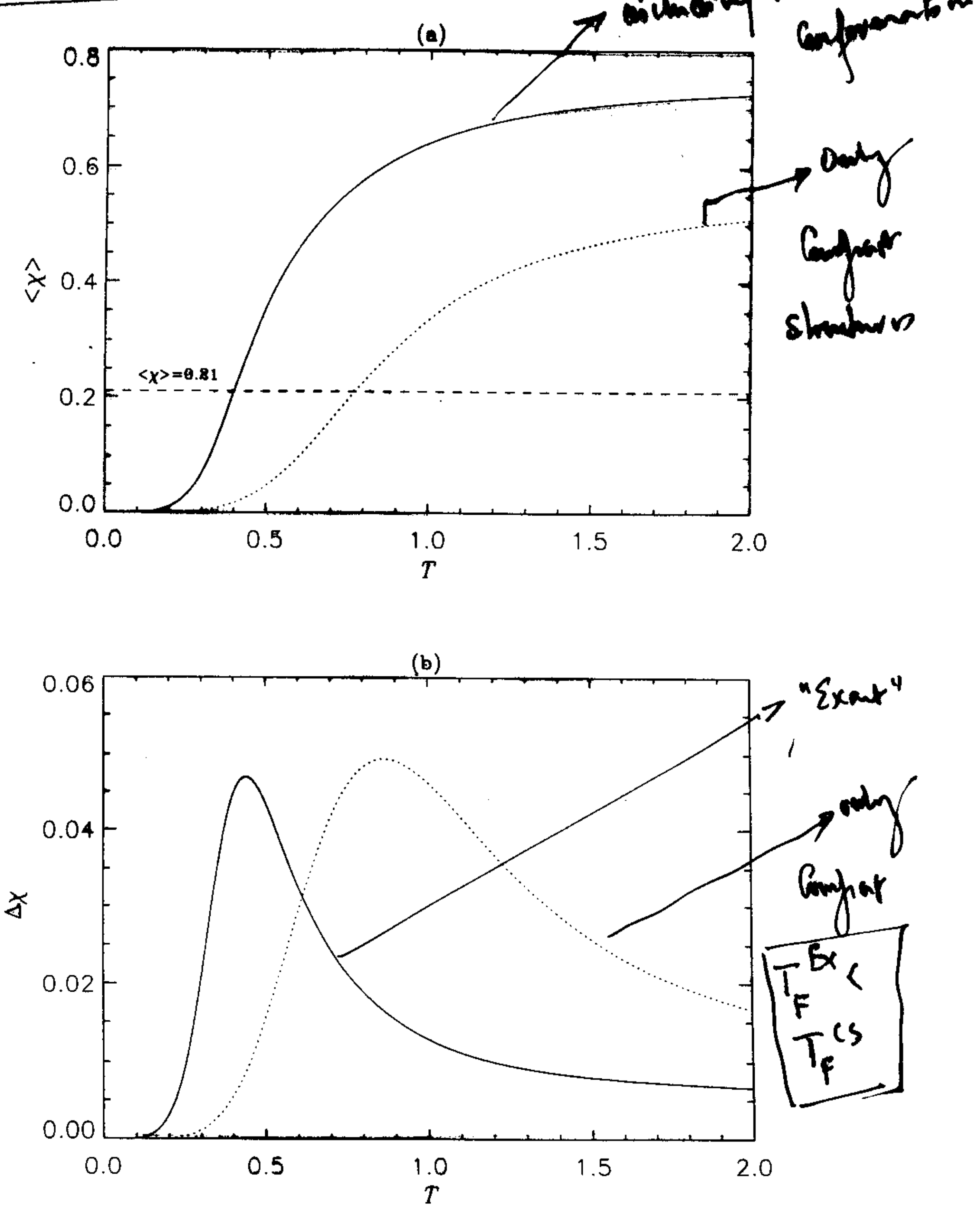
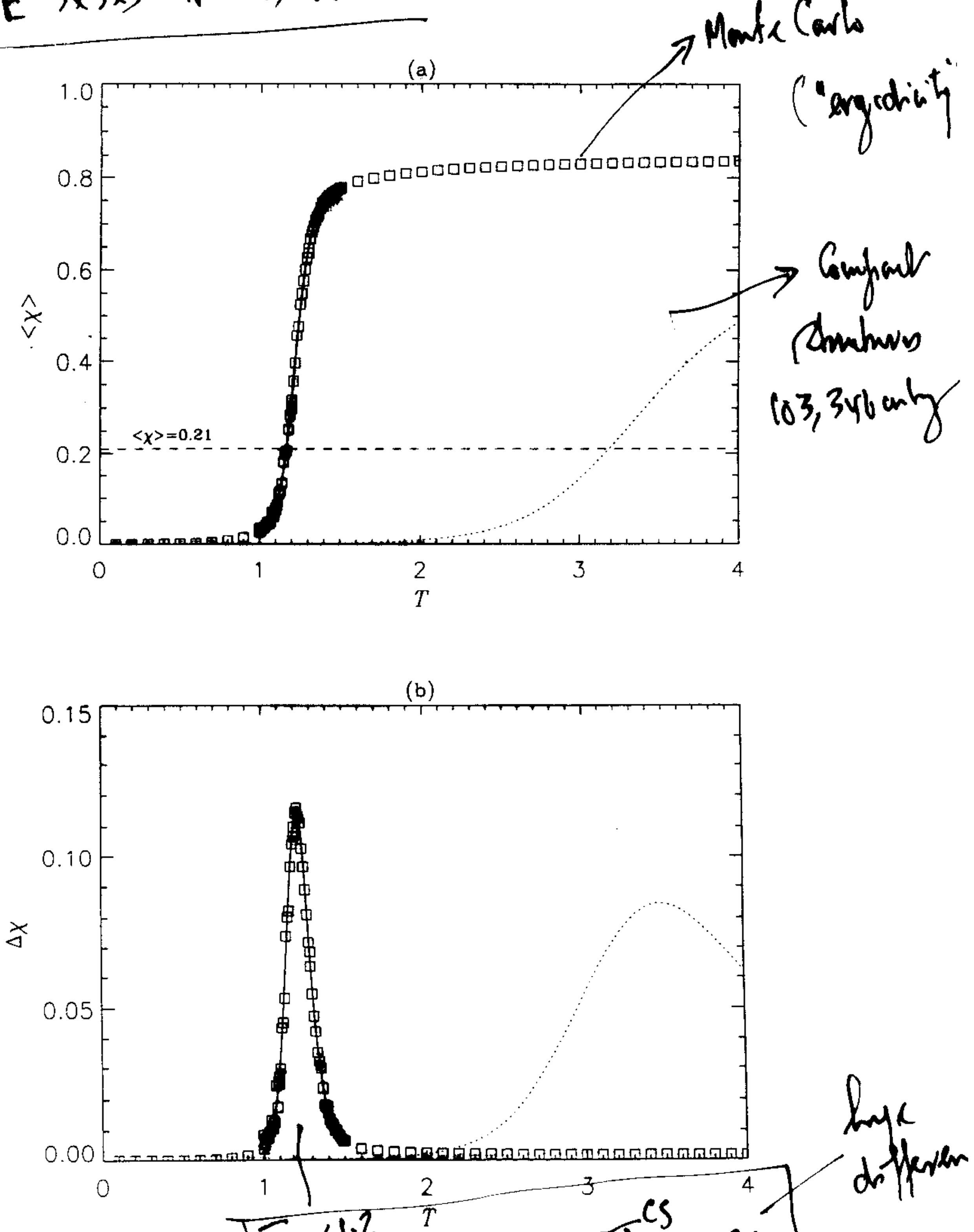


Fig. 9

CUBE 3x3x3 N=27; B_0 = -0.1



$T_F \approx 1.2$ Fig. 15 $T_F^{CS} \approx 3.4$

N = 27, β_0 = -2.0 | (SSK Case)

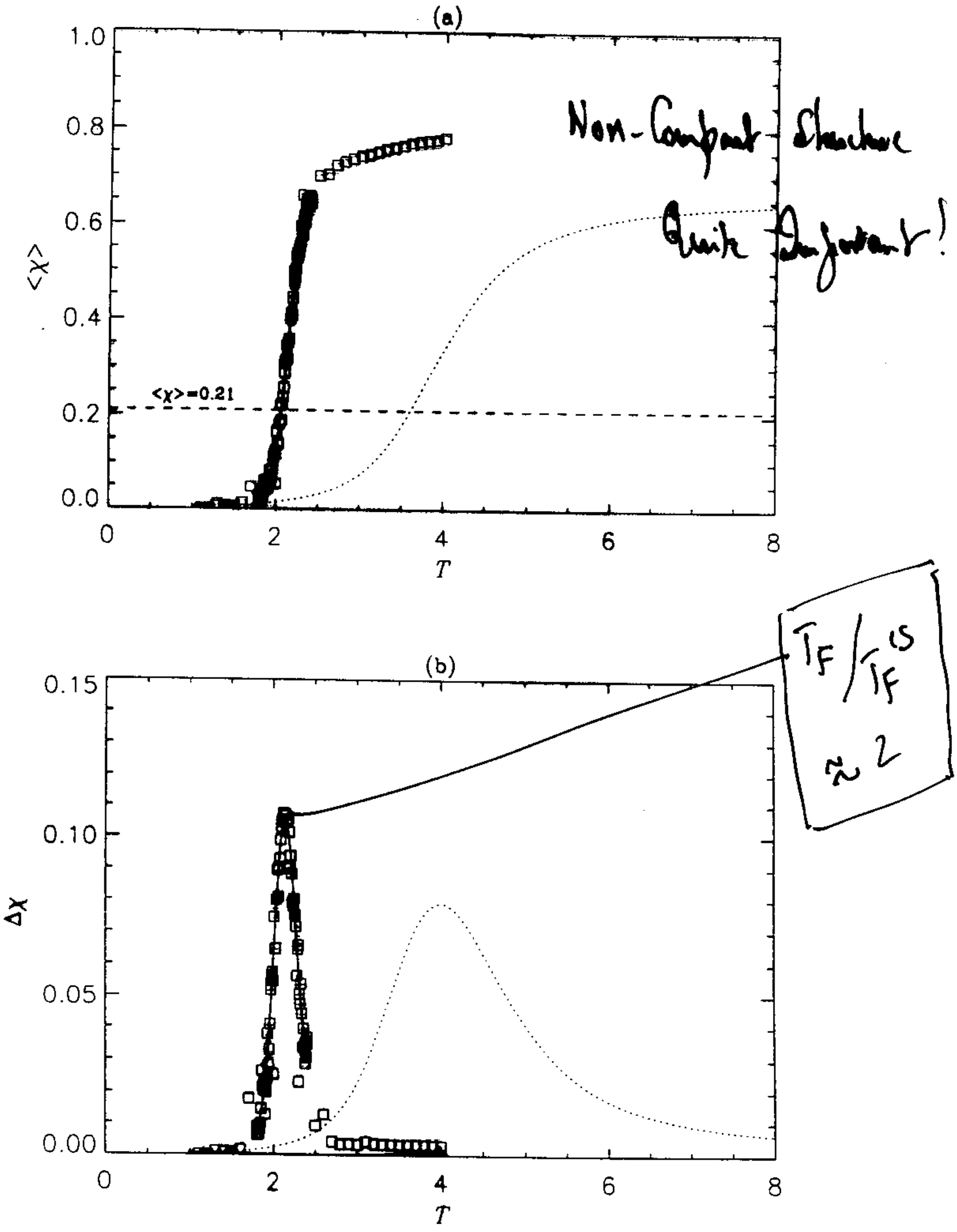


Fig. 16

TESTS OF FOLDING CRITERION

NECESSARY & SUFFICIENT CONDITION FOR FOLDING IN THESE MODELS

$\Delta = E_N - E_1$ (RESTRICTED TO ONLY CS)

BE LARGE COMPARED TO ——— (SSK) '94

FOLDING TIMES SHOULD CORRELATE (STATISTICALLY) WITH

$\sigma = (T_\theta - T_F)/T_\theta$

[CJC/DT '93]

→

FOLDABILITY & T_F/T_G (Goldstein, Schulten, Wolynes '92)

N = 15

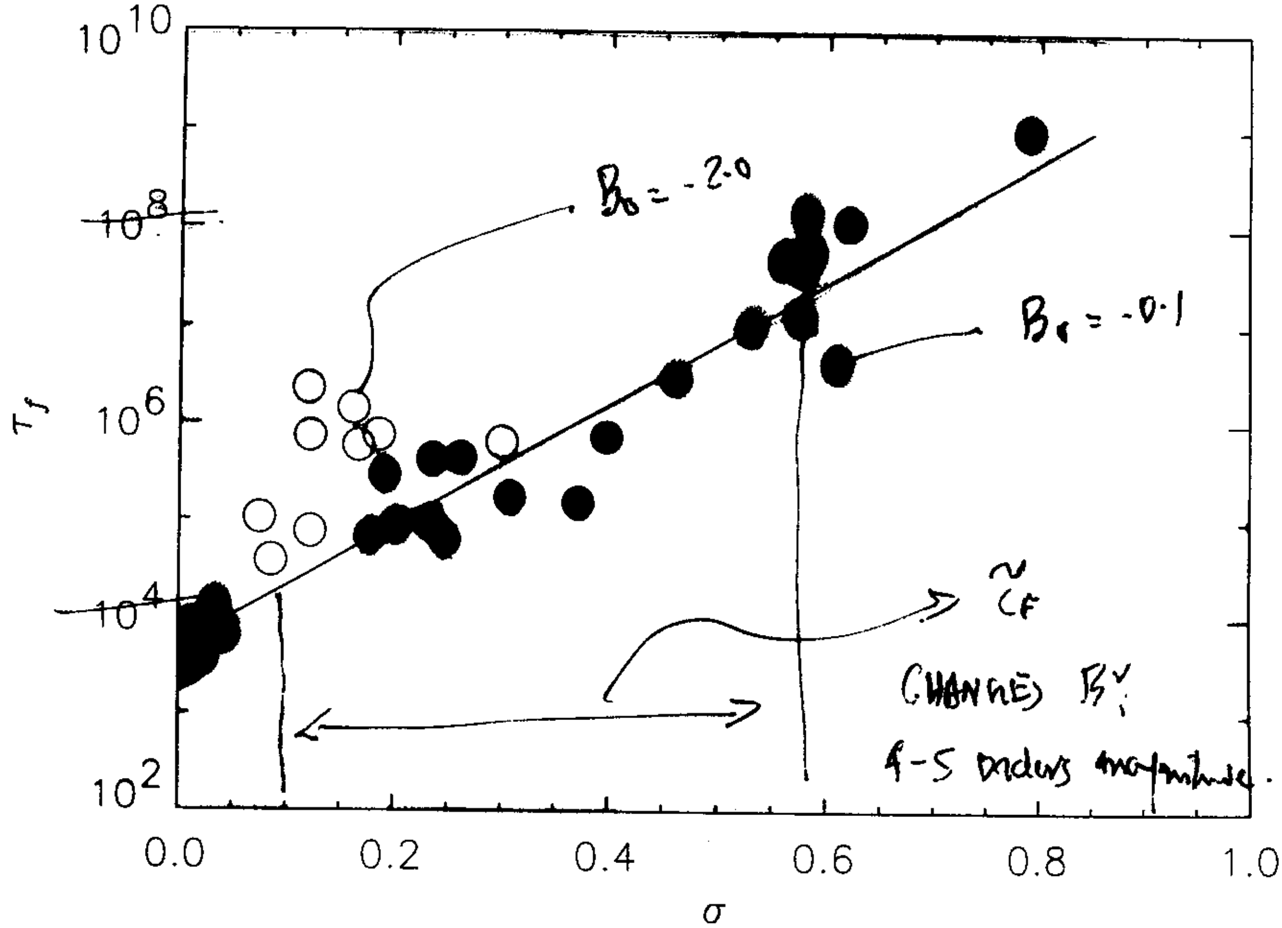


Fig. 11

$\tilde{\tau}_f \approx \exp(\sigma / \sigma_0)$ — fit

→ σ^m $m \approx 3$ (DT '95)

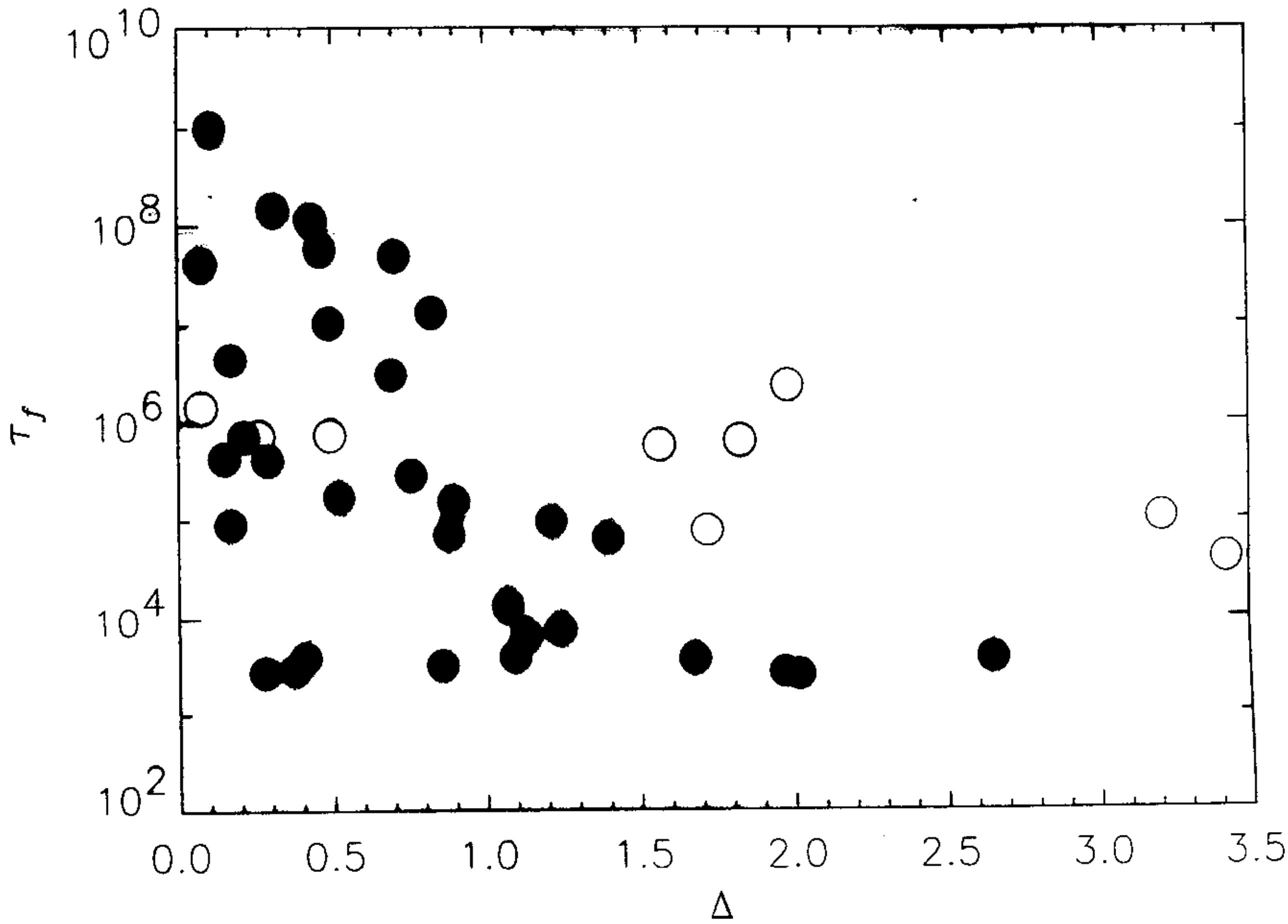


Fig. 12

THE [illegible] CRITERION τ_f Versus Δ

N=15 B_D = -2, -0.1

NO CORRELATION AT ALL.

NATIVE STATE OCC. PROBABILITY

N=15

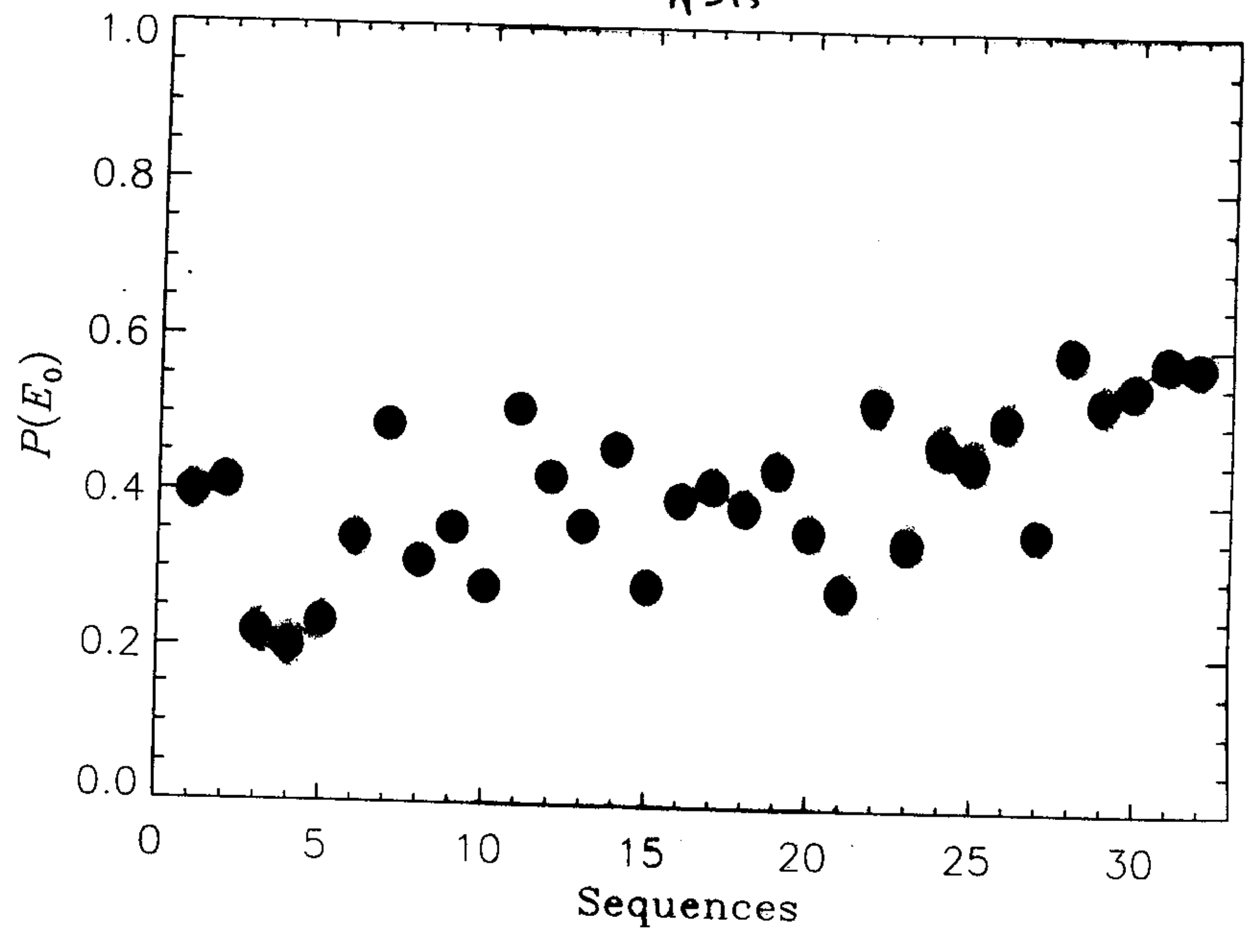


Fig. 25

$0.2 \leq P(E_0) \leq 0.6$

max $P(E_0)$ SSK ~ 0.4 → only one Reference

Most less than 0.1

84

N = 27 B_0 = -0.1

(15 [illegible])

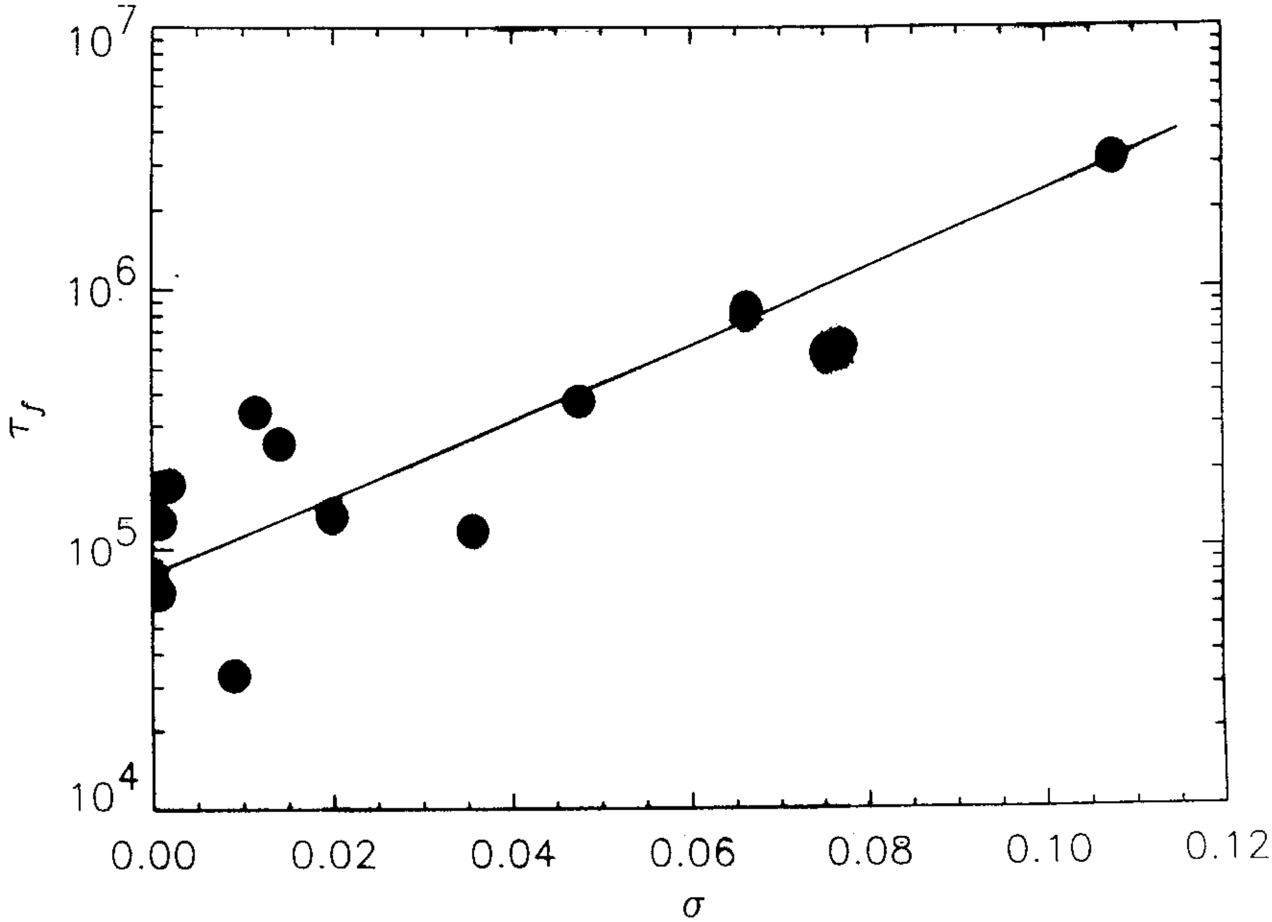


Fig. 19

SAME CONCLUSIONS AS
N = 15

$\tau_f \propto \exp(\sigma/\sigma_0)$

N = 27
$B_0 = -0.1$

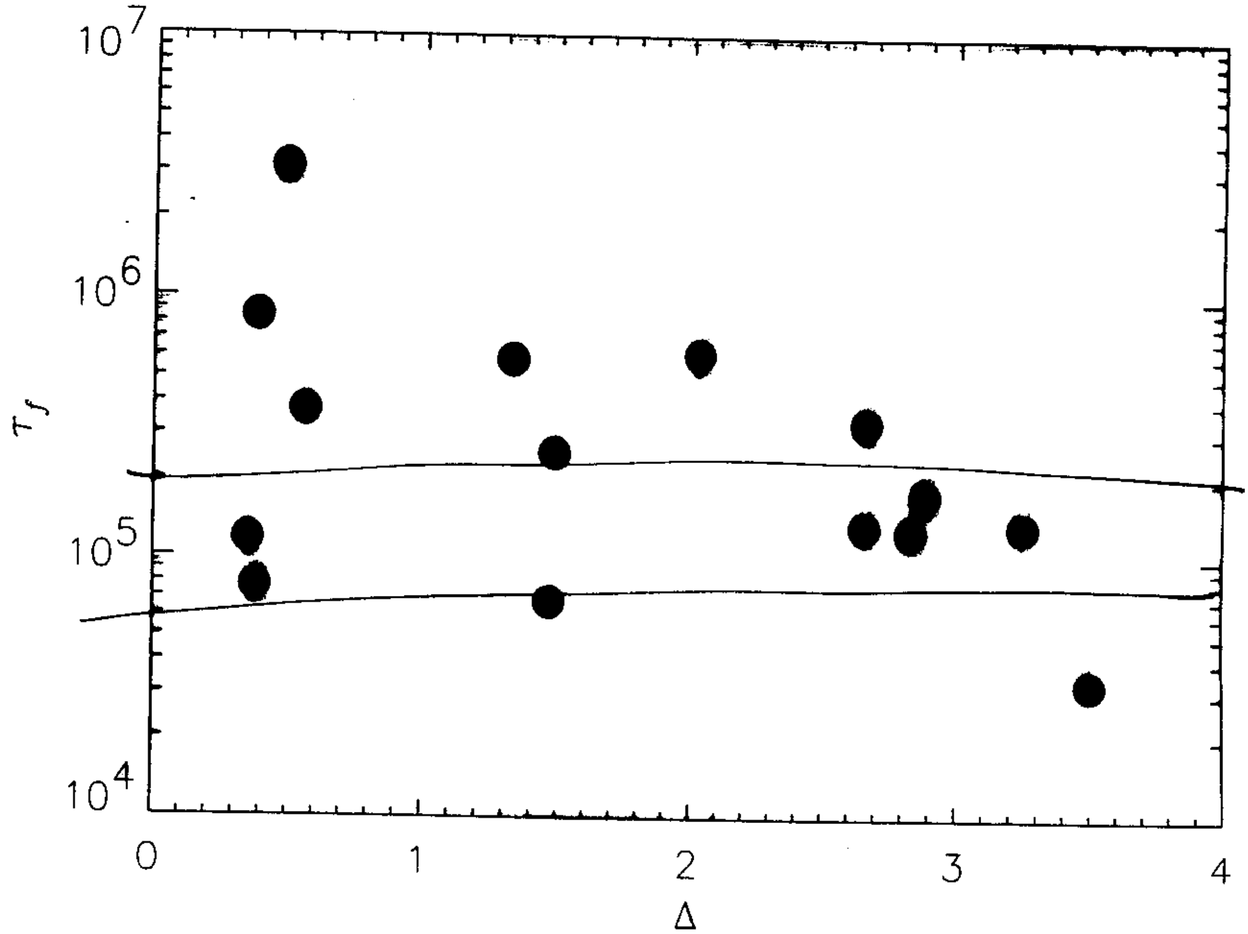


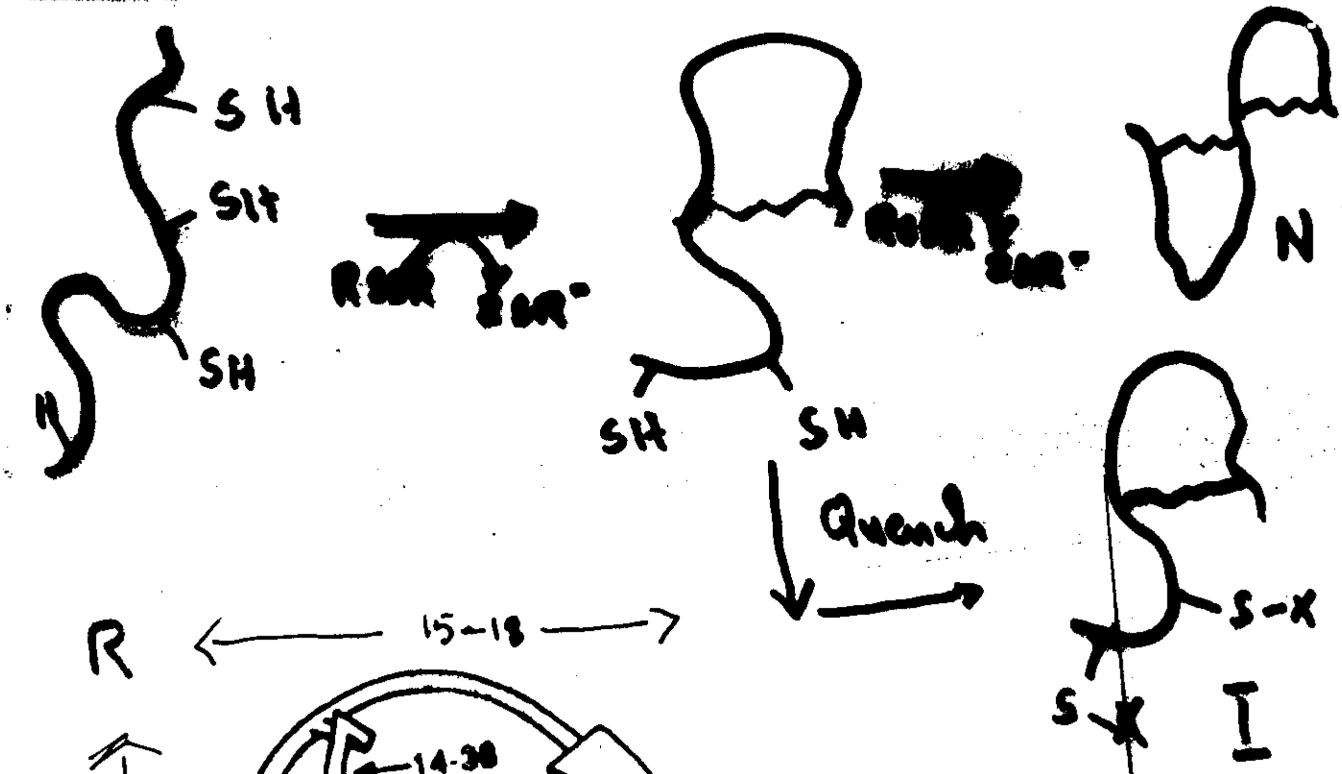
Fig. 20

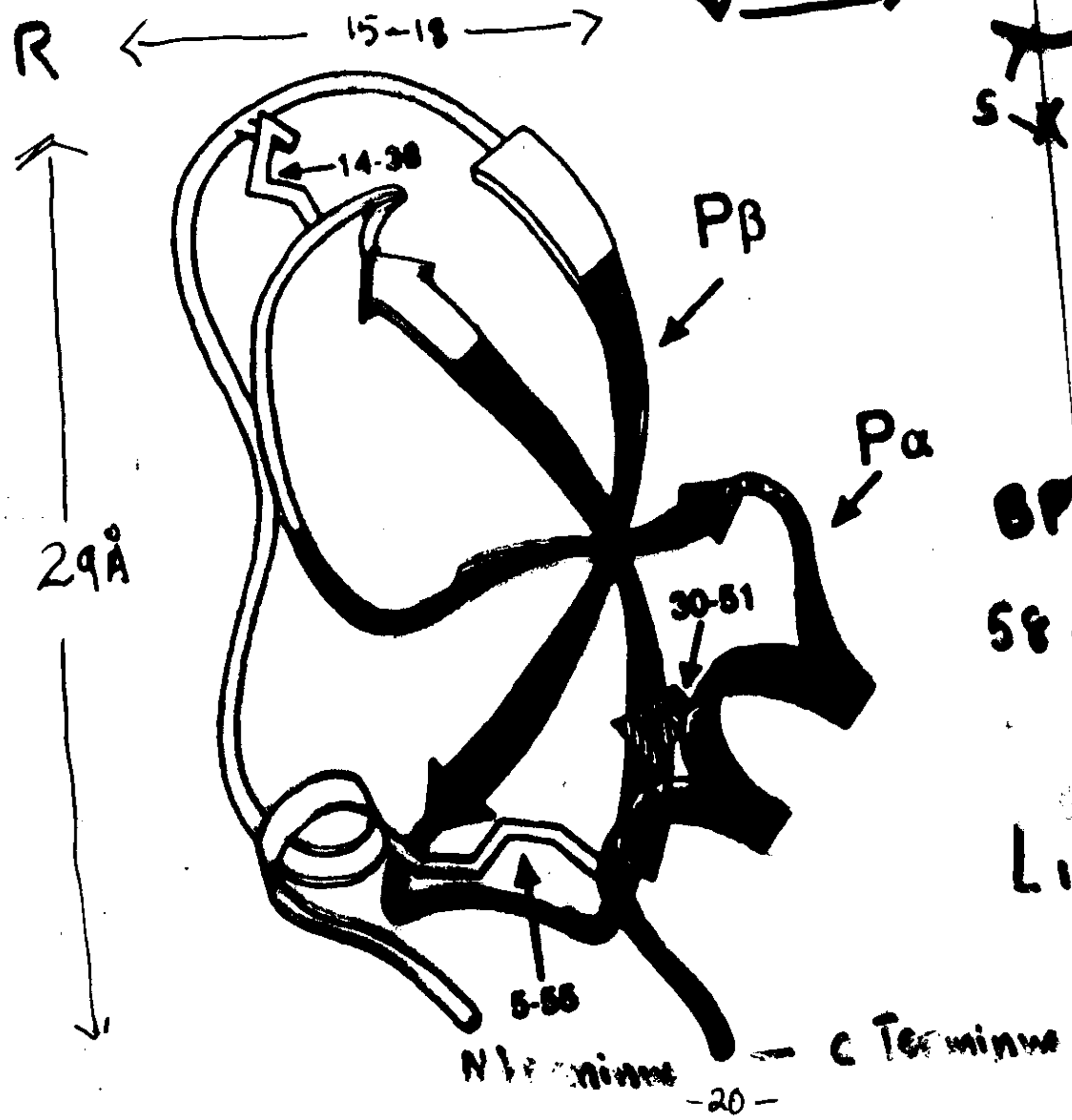
SSK Δ Criterion

• Fix $\tilde{\epsilon}_F$ — Can Engineer Several Sequences With Varying Δ!

• Exactly Same Conclusions in 2D HP Models (CJC/DT Europhys. Lett. '96)

Experimental Approach





BPTI

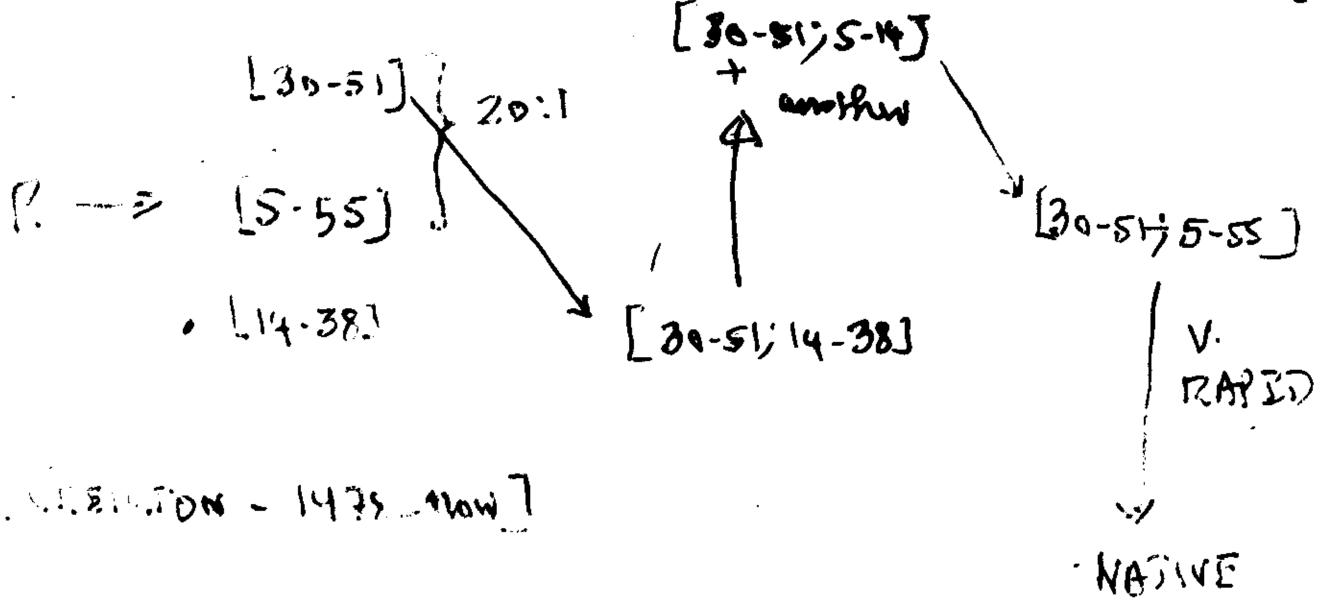
58 - Residues

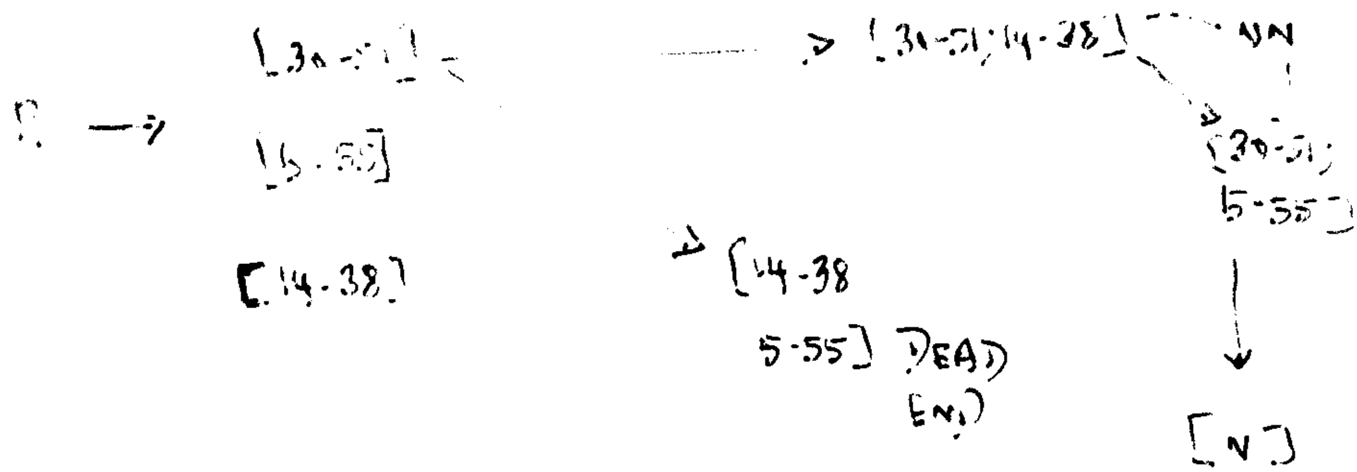
[51 - 5, 14-38]

(7)

ROLE OF DISULFIDE BONDS IN PROTEIN FOLDING

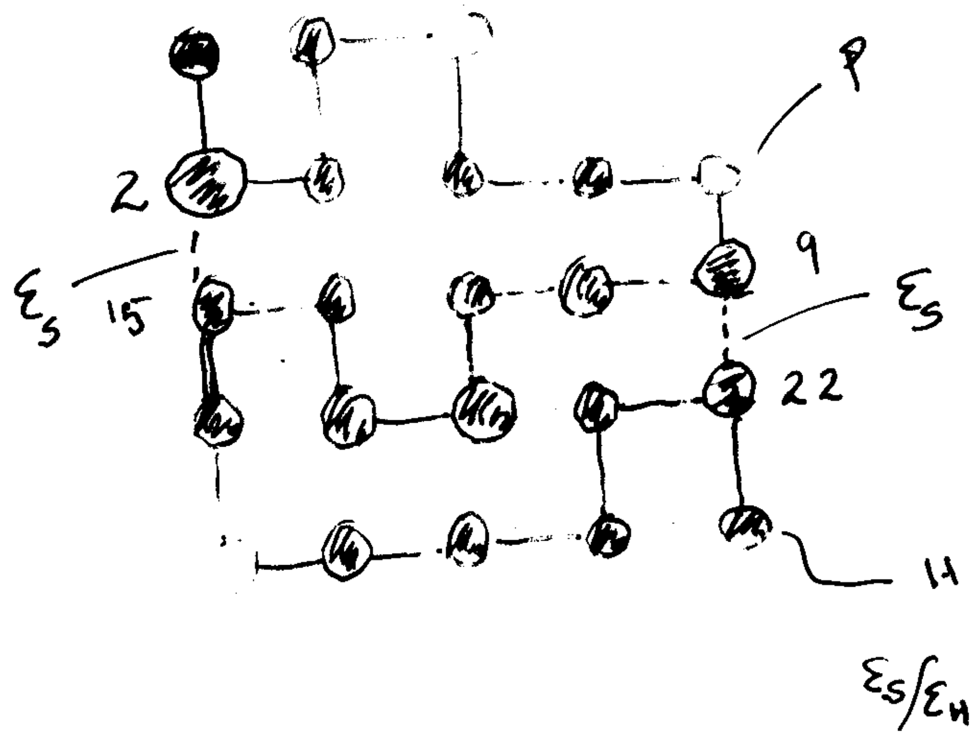
CJC/DJ PNAS '95
CJC/DJ Prot. Sci. ('96)





Weissman / Kim - Science 1990 -

A SIMPLE MODEL (3 COLORS)



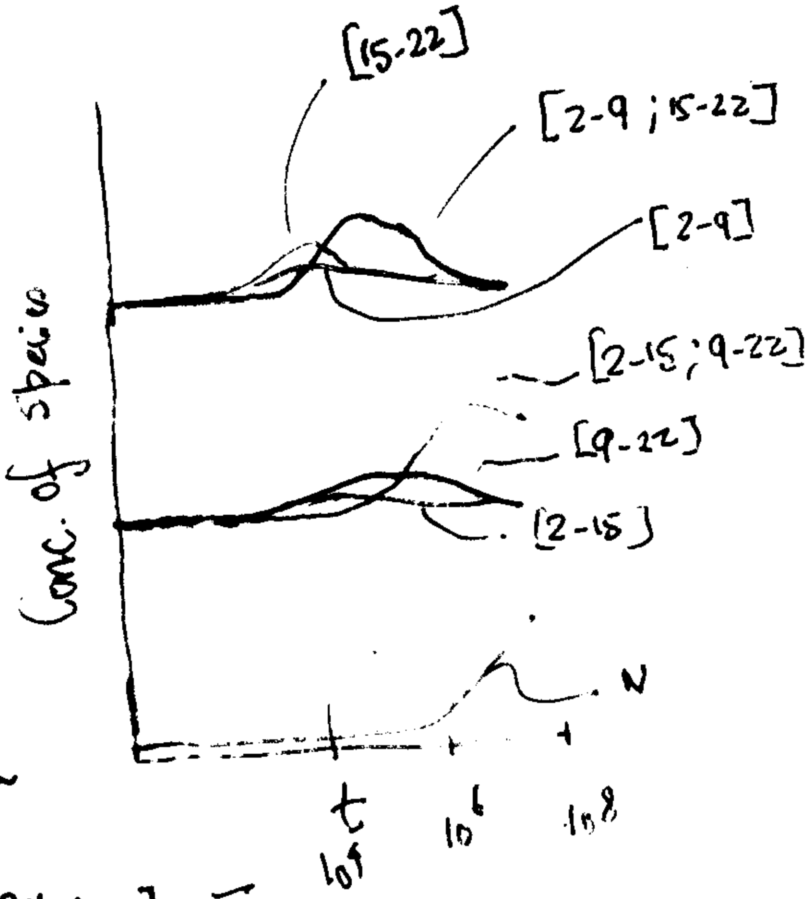
[illegible] = [2-15; 9-22]

MAX. INT. [illegible] ; [9-22]

MIN [illegible] ; [2-9]

[illegible] CONC. OF EACH SPECIE.

LESSONS



(a) Initial stages formation of disulfide species random & determined by loop formation probability [Random Collapse] I

(b) NATIVE INT. DOMINATE NN → native Intermediate (reordering regime) II

(c) All or none → Long time scale rearrangement from NATIVE LIKE SPECIES III.