$$P(s) \sim s^{-\gamma}$$







Chain Organization
 of Biopolymers —











Lei Liu

• Chain Organization of RNA & proteins

Liu & Hyeon, Biophys. J. (2016) vol. 110, 2320-2327

• Chromatin organization inside cell nucleus

Kang, Yoon, Thirumalai, & Hyeon Phys. Rev. Lett. (2015) 115, 198102











Origin of exponent $\gamma = 1.5$?

polymer melt in equilibrium

$$P(\vec{r}_{1},\vec{r}_{2}) = \left(\frac{3}{2\pi\langle r_{12}^{2}\rangle}\right)^{3/2} \exp\left[-\frac{3(\vec{r}_{1}-\vec{r}_{2})^{2}}{2\langle r_{12}^{2}\rangle}\right] \rightarrow P(0) \sim s^{-1.5}$$

$$\langle r_{12}^{2}\rangle \sim s$$

$$\vec{r}_{1}$$

$$\vec{r}_{1}$$

$$\vec{r}_{2}$$

$$\vec{r}_{2}$$

$$\vec{r}_{3}$$

$$\vec{r}_{3$$

a subchain in a LONG collapsed polymer

Origin of exponent $\gamma = 1.5$?

Flory theorem :



A test chain in <u>a fully equilibrated homogeneous</u> semi-dilute or concentrated polymer melt, in spherical confinement, or even in globule is expected to obey the Gaussian statistics because of the screening of excluded volume interaction or counterbalance between attraction and repulsion; thus thus satisfying $R(s) \sim s^{1/2}$ or $P(s) \sim s^{-3/2}$.

P. J. Flory, J. Chem. Phys. 17, 303 (1949)

Grosberg and Khokhlov, Statistical Physics of Macromolecules (AIP Press, 1994).

Origin of exponent γ ?

V(t): a volume explored by a particle for time t

 $P_o(t)$: returning probability to the origin at time t

 $P_o(t) \sim [V(t)]^{-1}$

 $R(t) \sim t^{1/2}$: root mean square distance at time t (random walk)

$$\begin{array}{ccc} R(s) \sim s^{1/4} & V(t) \sim R(t)^3 \sim t^{3/2} \\ & & \downarrow \\ & \downarrow \\ P(s) \sim s^{-3/4} & P_o(t) \sim t^{-3/2} \end{array}$$

 $P_o(t) \sim t^{-3/2}$

Trajectory of random walk -

returning prob.

$$t^{3/2}$$
 $R(s) \sim s^{1/3}$
 \downarrow
 $space filling$
 $P(s) \sim s^{-1}$
 $crumpled$
 $globule$
Contour of an ideal polymer
 $P(s) \sim s^{-3/2}$

equilibrium

alobule

contact prob.

Contour of



 $P(s) \sim s^{-\gamma}$



RNA vs Proteins

Liu & Hyeon, Biophys. J. (2016) vol. 110, 2320-2327













$$P(s) \sim s^{-\gamma}$$



3

1.24

group-I intron ribozyme



$$P(s) \sim s^{-\gamma}$$





$$P(s) \sim s^{-\gamma}$$



Liu & Hyeon, Biophys. J. (2016) vol. 110, 2320-2327













$$P(s) \sim s^{-\gamma}$$





$$P(s) \sim s^{-\gamma}$$





$$P(s) \sim s^{-\gamma}$$













$$P(s) \sim s^{-\gamma}$$





Dependence of γ on size?





Proteins ...

After initial collapses, proteins undergo reptation-like process to fold, which may take place with ease because secondary structure elements of proteins (α -helix, β -sheet) are only marginally stable relative to the thermal energy.

If necessary, these motifs can be reassembled into thermodynamically more stable structures.

Therefore, thermodynamic hypothesis (e.g., identifying minimal

(free) energy configuration) can be

used for identifying the native state.



RNA ... Hierarchical folding

$$\sum_{i} \varepsilon_{i}^{\text{sec}} \gg \sum_{k} \varepsilon_{k}^{\text{ter}} \gg k_{B}T$$

* Hairpins and loops are basic building block of RNA



* RNA are similar to a collection of un-concatenated ring polymers (Knots are absent in RNA... *Micheletti..Orland PNAS (2015)*).

* Folding yield of *T. ribozyme* in vitro is very low (~< 10 %)... RNA chaperone







a-helical membrane proteins GPCRs





Two-stage membrane proteins folding:

- 1. insertion of TM alphahelices guided by translocon
- 2. post-insertion folding



Antiporter

Controlled Unfolding and Refolding of a Single Sodium-proton Antiporter using Atomic Force Microscopy

(N~380) Alexej Kedrov¹, Christine Ziegler², Harald Janovjak¹ Werner Kühlbrandt² and Daniel J. Müller^{1*}





J. Mol. Biol. (2004) 340, 1143-1152

γ=1.1

Spontaneous in vitro refolding (X)

elements were directional, while others were not. eractions appeared to occur between the secondary fter unfolding ten of the 12 helices, the extracted wed to refold back into the membrane. After five

seconds, the refolded polypeptide established all secondary structure elements of the native protein. One helical pair showed a characteristic spring like "snap in" into its folded conformation, while the refolding process of other helices was not detected in particular. Additionally, individual helices required characteristic periods of time to fold. Correlating these results with the primary structure of NhaA allowed us to obtain the first insights into how potential barriers establish and determine the folding kinetics of the secondary structure elements.



Tae-Young Yoon and coworkers Nat. Chem. Biol. (2015)



Concluding Remarks

- Time required for equilibrium sampling of conformation increases exponentially with the system size N as τ_{eq}~ exp(N). Signature of metastability in chain conformation (crumpled chain configuration, γ~1) could be ubiquitous in a macromolecular structure with large N (especially RNA).
- The present forms of crumpled chain organization with γ~1 of large RNAs and some classes of proteins are an ineluctable outcome of their folding mechanisms.
- Protein Folding Thermodynamic Control, (Large) RNA Folding Kinetic Control.
- Due to the hierarchical nature of folding mechanism of RNA, an inclusion of long non-coding RNA (Inc-RNA) would reinforce our finding.