Funnel Gas Model for Protein Many-Body Systems under the Crowded Environment

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Goal of the talk

1. Introduce a simple lattice-gas type model to describe the system consisting of proteins and crowding molecules.
2. Apply the effective free-energy of the model to discuss the crowding effect on the folding of small globular proteins

Part 1

Construction of the Funnel Gas Model

Motivation

Background

- Foldable proteins have funnel-like energy landscape
  - Energy landscape theory or funnel picture (*e.g.* Wolyness)
- Interior of the living cells is crowded by biological molecules
  - Molecular crowding effect (*e.g.* Minton)

Purpose

To simulate the protein many-body system with crowding molecules, we need an appropriately coarse-grained model.

We develop a Lattice-gas based model

A prototype model has already been introduced in Shirai and Kikuchi, J.Chem.Phys. **144** (2016) 055101.

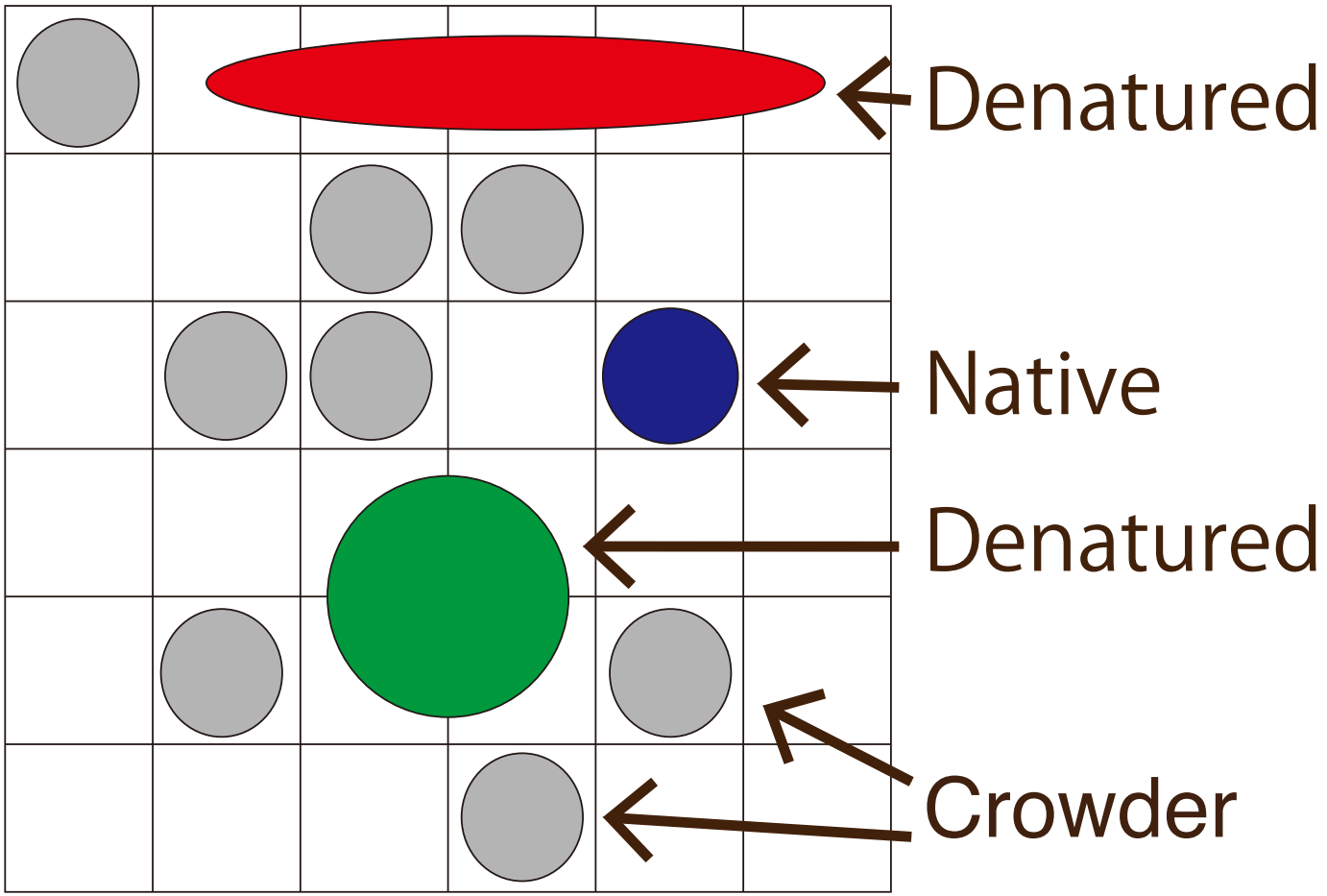
Setup

Proteins

- A protein has internal states, for which the funnel-like free-energy landscape is taken into account: FUNNEL GAS!
- The native state occupies a single site
- A few denatured states that occupy one or more sites (expanded)

Crowding molecules

- A crowding molecule occupy a single site
- Interact only through on-site excluded volume effect (no other interactions considered)



Concept of Funnel Gas Model

A Little bit of theory

Protein

- f_i : Free energy of i-th state
- v_i : Volume (number of the occupation sites) of i-th state
- n_i : Number of proteins at i-th state
  - $\sum_i n_i = N$: Total number of proteins

Protein-protein interactions can also be taken into account.

System

Fixed number of proteins
+ Grand-canonical ensemble of crowders

Partition Function

$$\Xi = \mathrm{Tr}\left[\sum_{m=0}^{M} \binom{M}{m} e^{\beta\mu m} e^{-\sum_i \beta f_i n_i}\right]$$

- β: Inverse temperature
- μ: Chemical potential of the crowders
- M: Number of the free sites on which the crowders can be placed

Using the binomial theorem, Ξ is rewritten as

$$\Xi = e^{\alpha V} \mathrm{Tr} \left[e^{-\sum_i (\beta f_i + \alpha v_i) n_i} \right],$$

where

$$\alpha = \log(1 + e^{\beta \mu})$$

The crowders are traced out.

Effective Free Energy for a Protein

$$\beta f_i^{\text{eff}} = \beta f_i + \alpha v_i$$

- Volume dependent modification
  - also depends on the density of crowders through α

Effective Partition Function

$$Z^{\text{eff}} = \text{Tr}\left[e^{-\beta \sum_i f_i^{\text{eff}} n_i}\right]$$

Equivalent to the canonical ensemble consisting only of proteins with the effective free-energy f_i^{eff}

- We can simulate the protein many-body systems under the crowding environment without explicitly considering the crowding molecules.
    - Computational effort is largely reduced.

Limitation of the model

- Crowding molecules should not be too small
  - The depletion force (Asakura and Osawa) is not taken into account.
- Crowding molecules should not be too large
  - The volume of denatured states does no effect

The model is suitable for the case that the size of the crowding molecules are comparable to that of the native state of the protein

Part 2

Molecular Crowding Effects on Protein Folding

Motivation

Effective free-energy derived for the funnel gas model

$$\beta f_i^{\text{eff}} = \beta f_i + \alpha v_i$$

By identifying v_i as the volume of i-th conformation, we can use f_i^{eff} to obtain an approximate free-energy landscape of the protein for any model

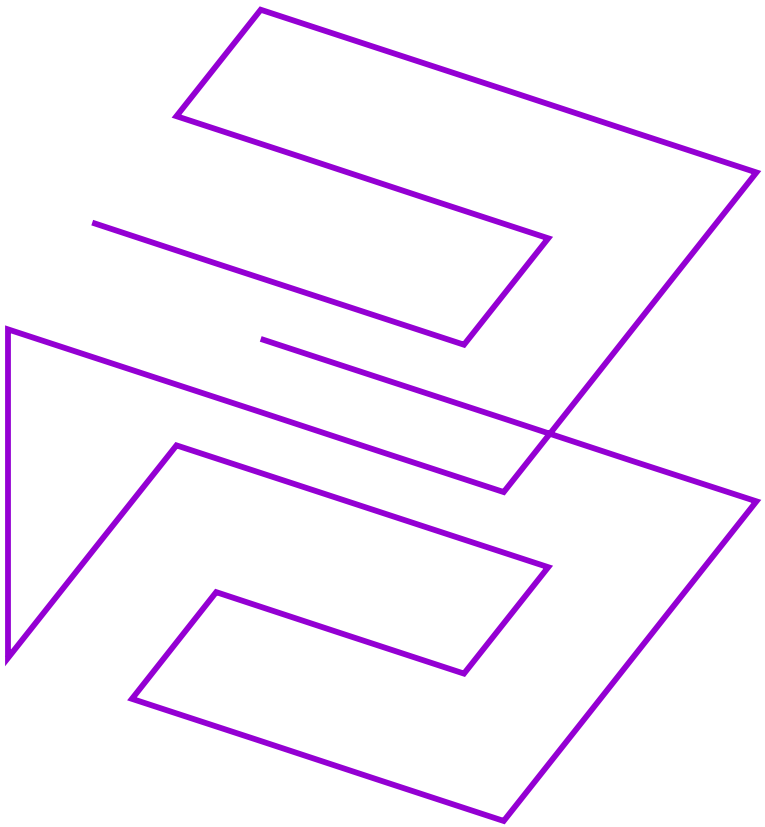
Application

Study the effect of molecular crowding on the folding of small globular proteins using f_i^{eff}.

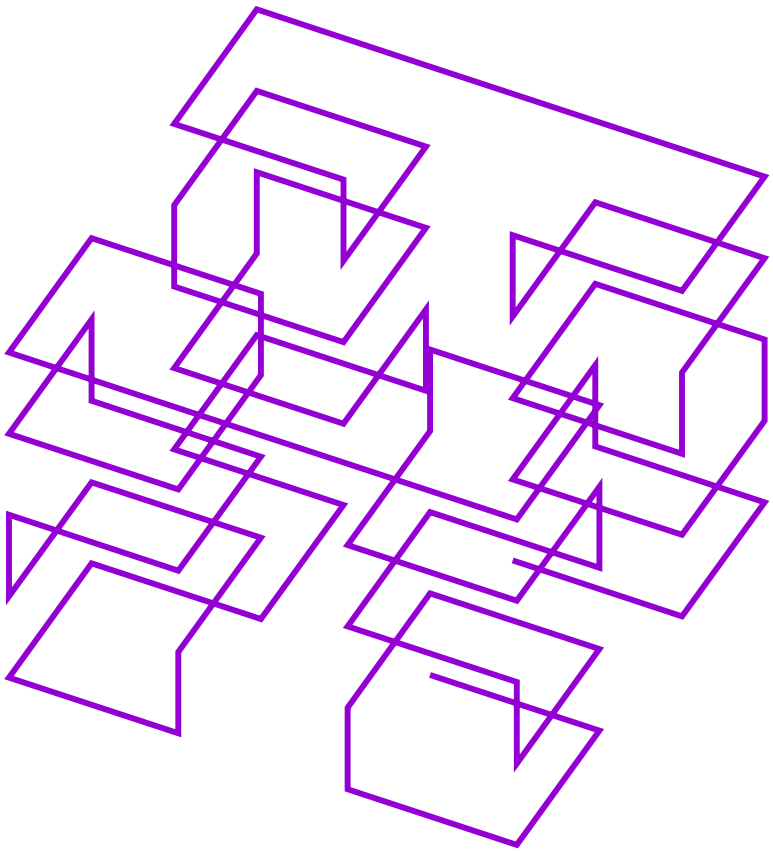
Model

- Go model on SC lattice for protein
  - This lattice is different from the one used in the funnel gas model
  - To calculate f_i^{eff}, the protein is considered as a sphere of the radius R_g (radius of gyration).
- Crowders are treated by the funnel gas model of closed-packed lattice.
  - Size of the crowders is taken as the same as that of the native state of the protein

Native conformations of toy proteins



Up-Down β Burrel

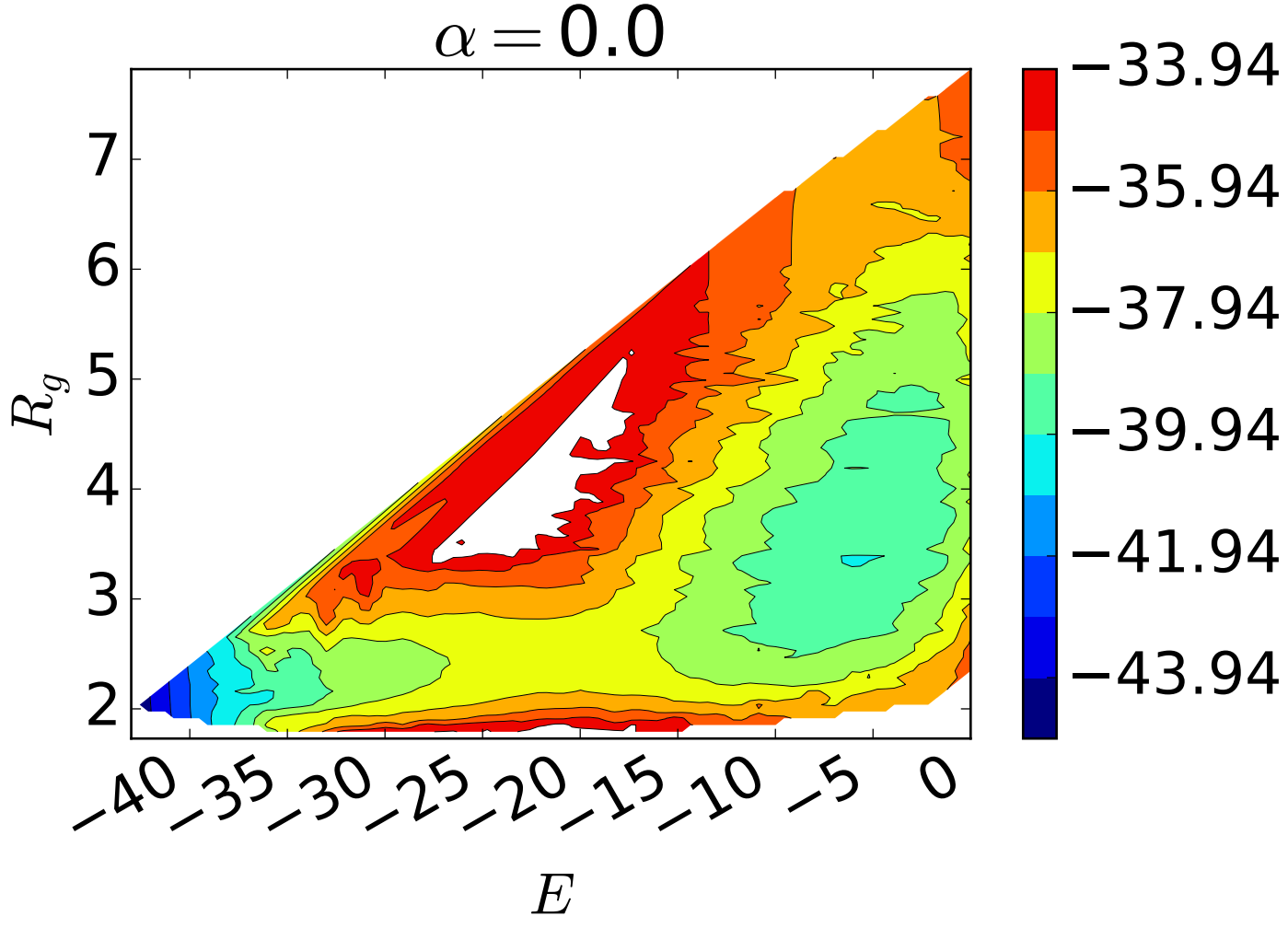


Four-Helix Bundle

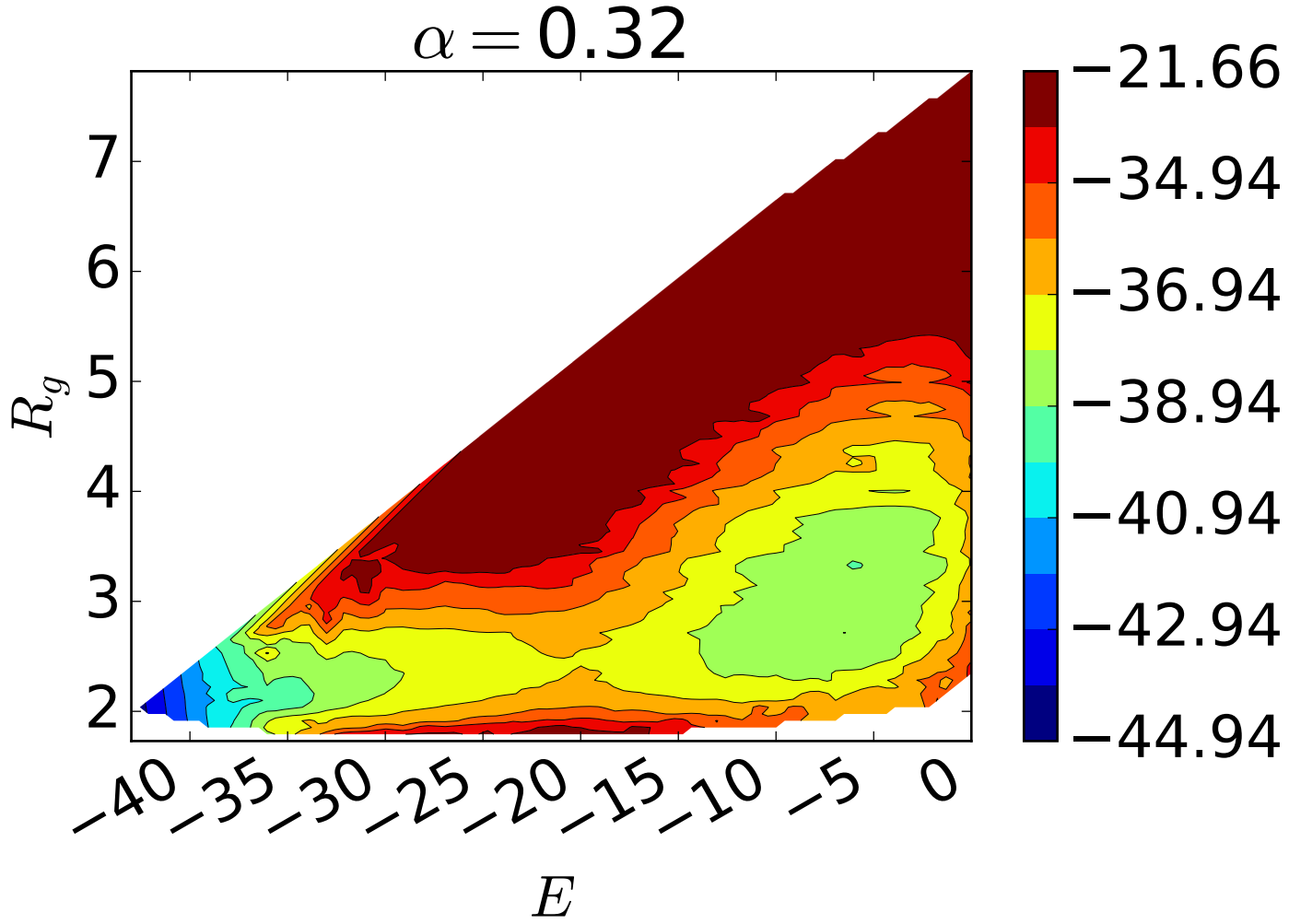
Free-energy landscapes for proteins without crowders are obtained using the Multi-Self-Overlap-Ensemble Monte Carlo method

Chikenji, Kikuchi and Iba, PRL **83** (1999) 1886.

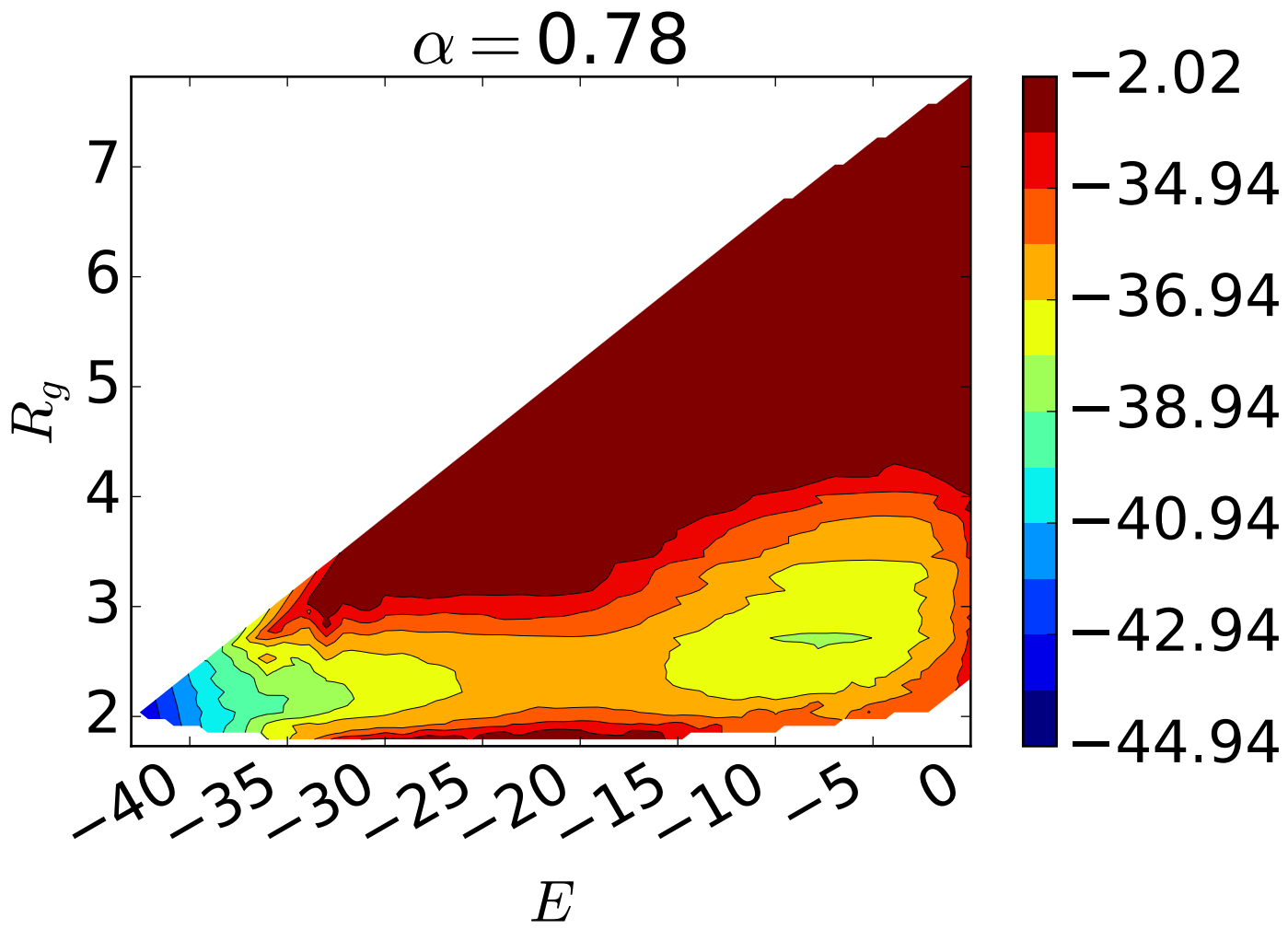
Result: Up-Down β burrel



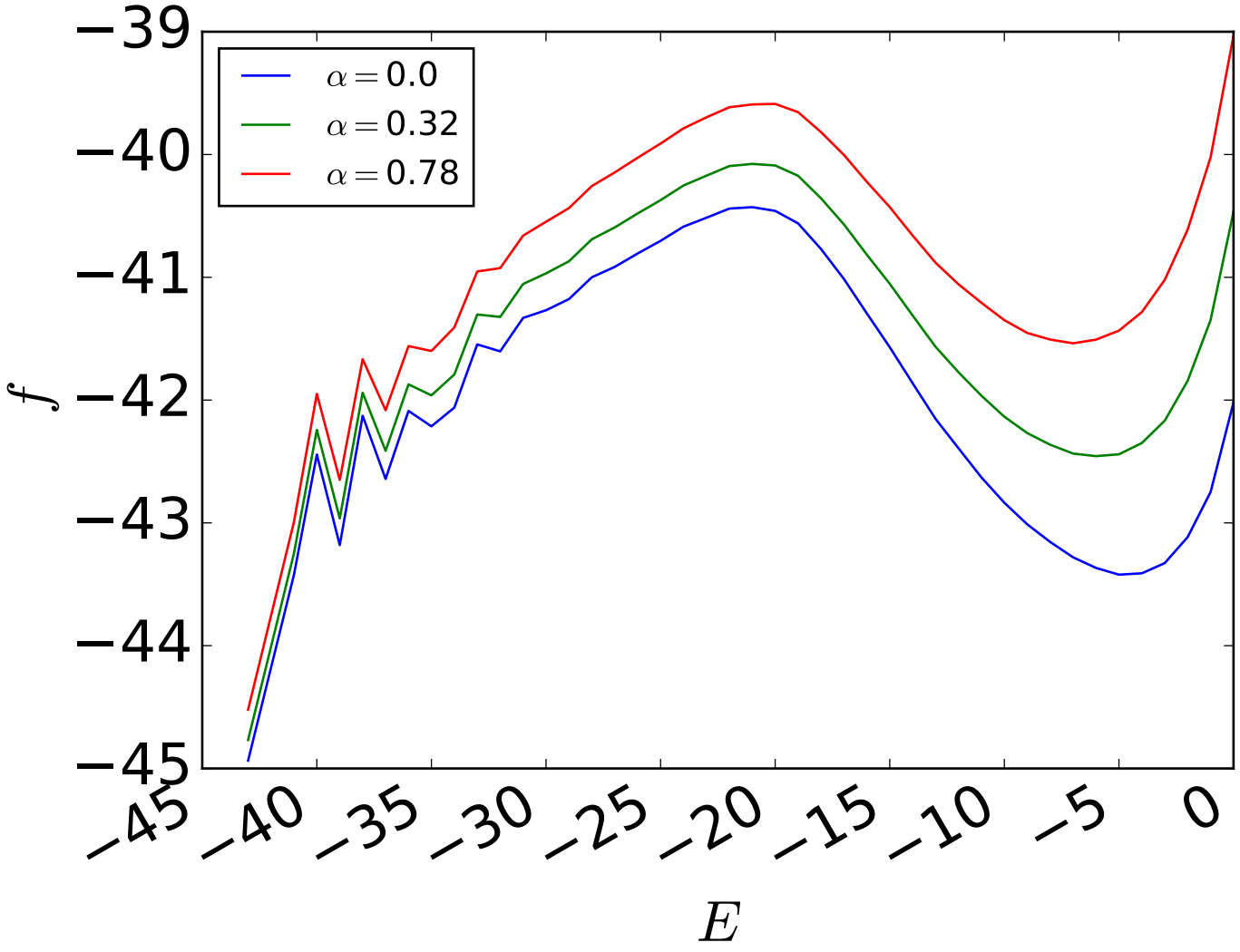
Free energy landscape at T_f (no crowder)



crowder volume fraction $\phi \simeq 0.2$

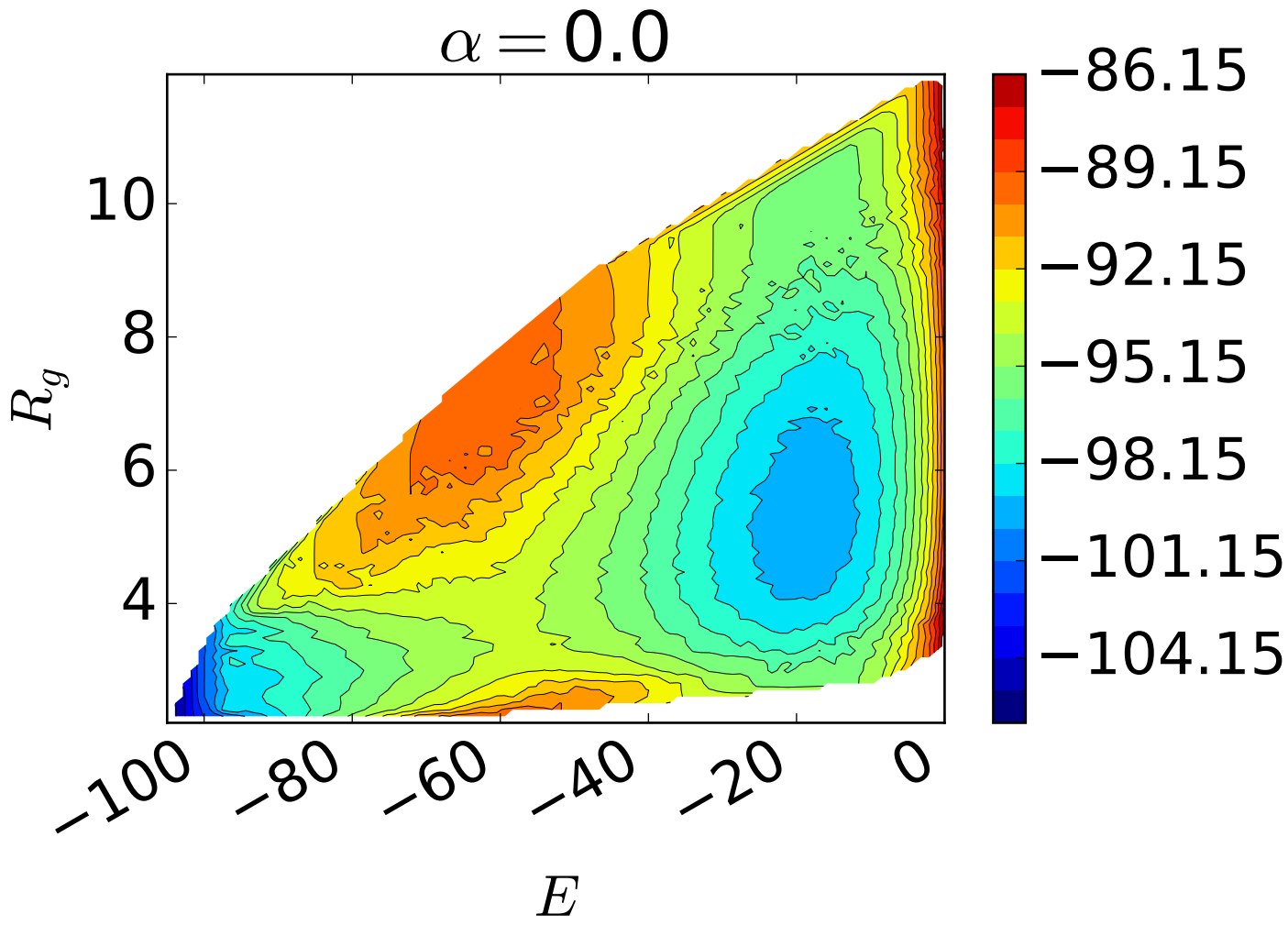


crowder volume fraction $\phi \simeq 0.4$

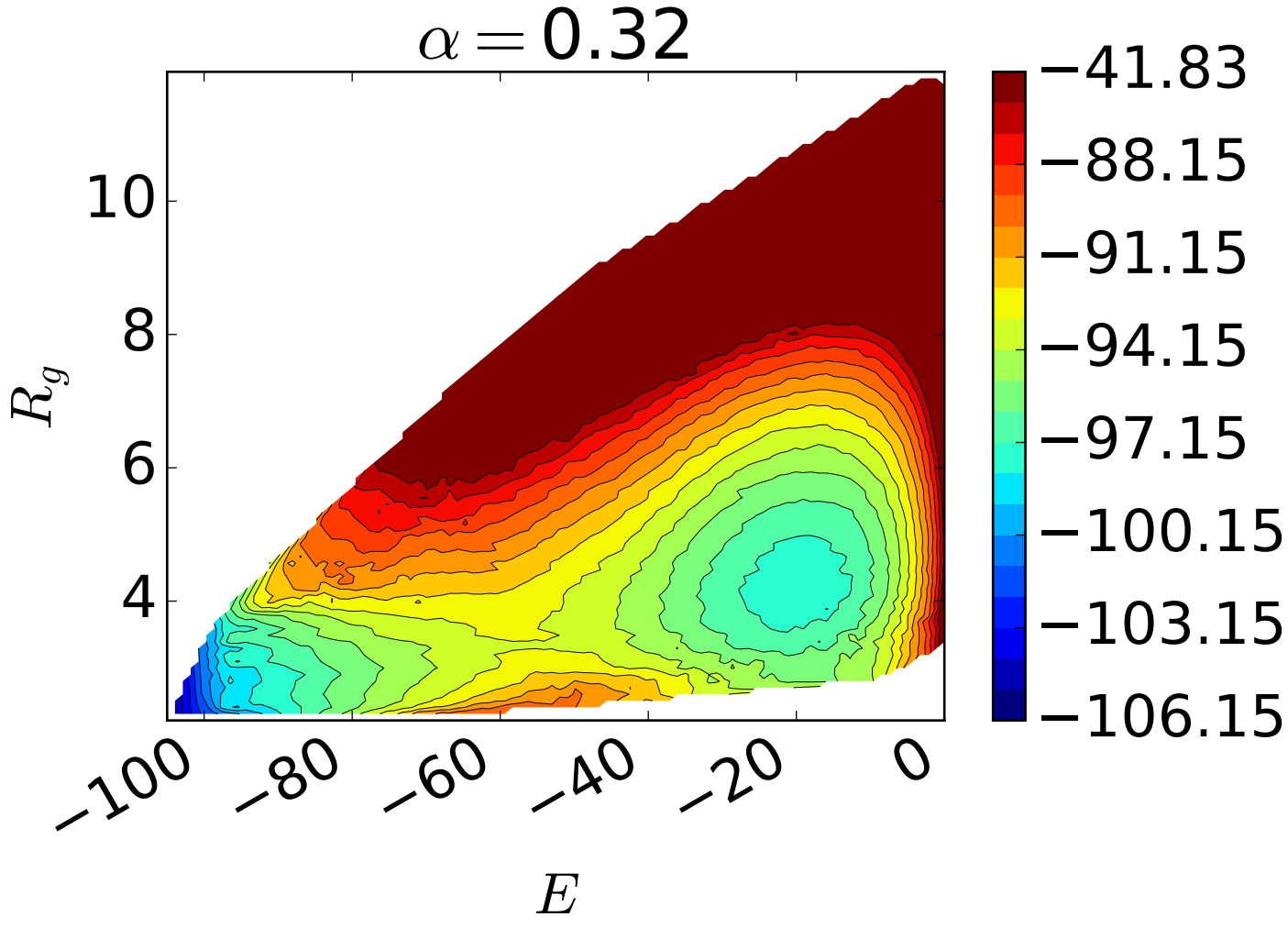


Energy vs. Free Energy at T_f

Result: Four-Helix Bundle



Free energy landscape at T_f (no crowder)



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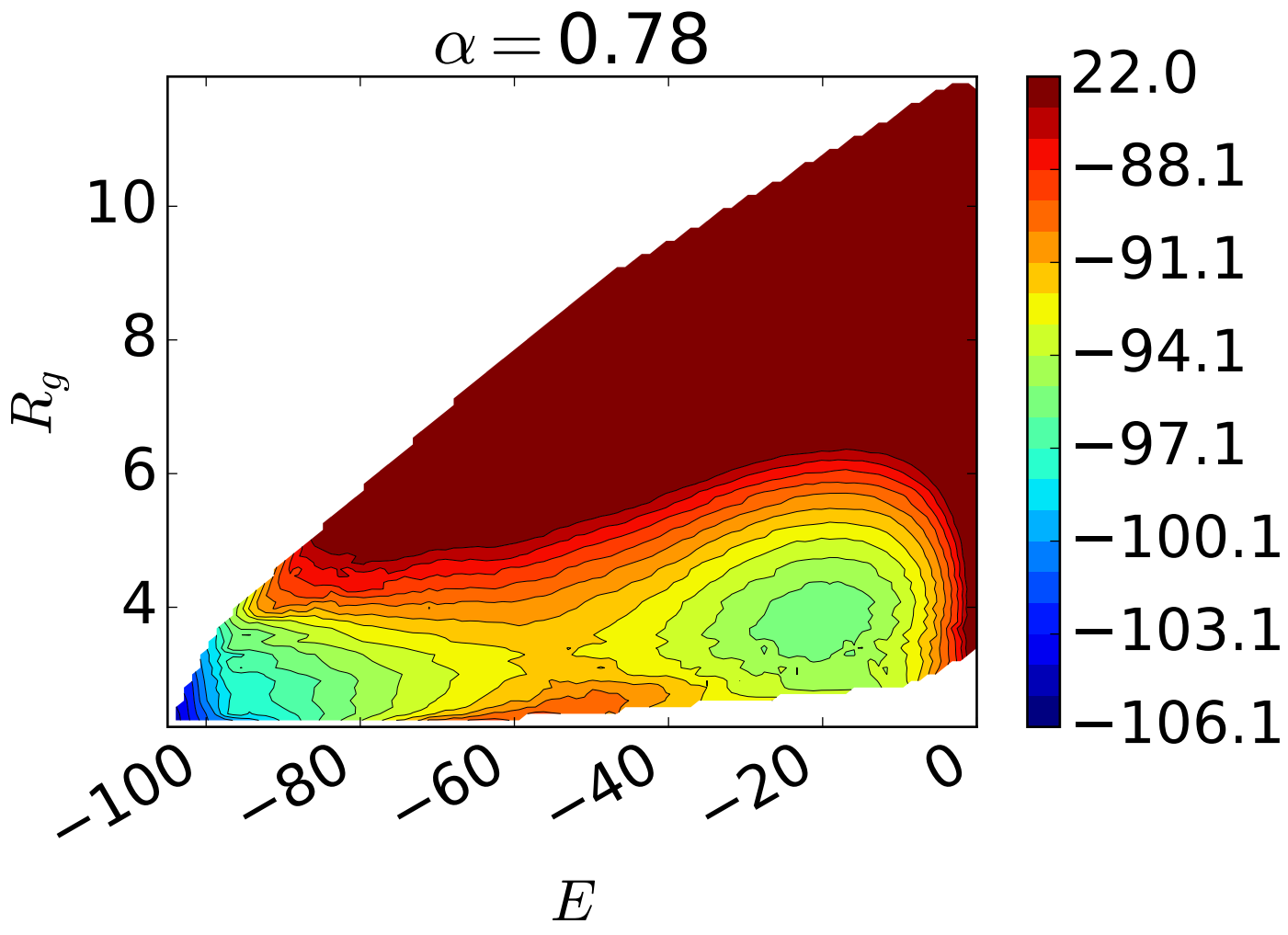

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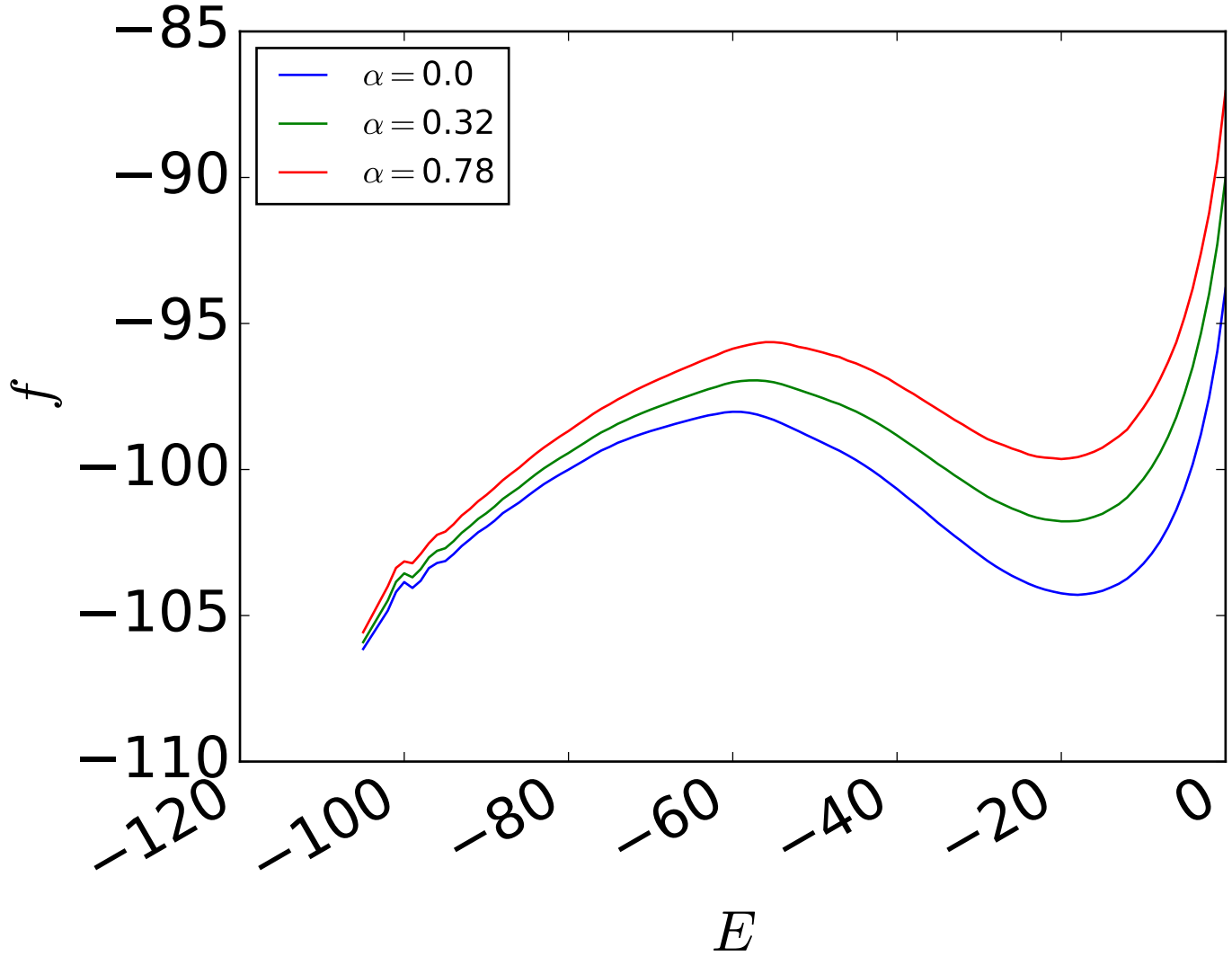

Energy vs. Free Energy at T_f

- The native state is stabilized by the crowding effect. $\leftarrow$ Expanded conformations of the denatured state becomes unstable
- Although this effect has long been expected intuitively or from some simulation results (*e.g.* Cheung *et al.* (2005)), the present formulation clearly explains the origin of the effect.

Summary

- We formulated the funnel gas model for simulating protein many-body systems under the crowded environment.
- The effect of the crowder is absorbed in the effective free energy of the protein as long as only the excluded volume interaction is taken into account.
- We applied the effective free energy to folding of small globular proteins and showed that the native states are stabilized by destabilization of the expanded denatured state due to the molecular crowding effect.