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# Comparison of the energy histograms and conformations between different lattice models of copolymers

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## Abstract

Based on large-scale Monte Carlo simulations the energy probability distribution functions are investigated for a large set of primary sequences in distinct lattice models of copolymers at low temperatures below transitions to compacted states. Amphiphilic copolymers with hydrophobic and hydrophilic units are found to produce single or double peak energy distributions corresponding to mono- or multi-meric micellar conformations. However, copolymers with short-ranged random ‘charge’ interactions in some cases are found to produce energy distribution functions with a well pronounced lowest energy state and a gap separating it from the rest of the spectrum. These, however have rather peculiar conformations corresponding to effectively immiscible domains comprised from monomers of likewise species. The relevance of these observations for coarse-grained models for protein folding is discussed.

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## 1. Introduction

Synthetic copolymers have numerous industrial applications due to their rich phase diagram and ability to tailor particular physical properties by a choice of the monomers used and the order in which they are polymerised. Generally, a synthesis would produce a quasi-random arrangement of

the monomers, which can be characterised by the probability distribution of the composition variables  $\{\sigma_i\}$ , where one agreed to assign  $\sigma_i = 1$  if the monomer  $i$  is of type  $a$  and  $\sigma_j = -1$  if the monomer  $i$  is of type  $b$ . The overall composition is then given by the ratio of the total number of  $a$  and  $b$  species, and it would typically be fixed and determined by the ratio of reactants concentrations during polymerisation, provided that further separation techniques have allowed one to ensure a good degree of monodispersity in the degree of polymerisation  $N$ . Likewise, by special procedures one can also prepare well controlled primary sequences  $\{\sigma_i\}$  corresponding to di-blocks, tri-blocks, and more generally shorter alternating blocks of  $a$

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URL: <http://darkstar.ucd.ie>.

and  $b$  units. Some of perhaps most well studied examples of synthetic water soluble polymers of these types would include PNIPAM, PEO–PPO systems and their various modifications [1].

Most important properties of monomers from the point of view of molecular modelling are their degree of hydrophobicity and effective charges, and these along with the primary sequence would determine the conformations of the copolymers in solution at given thermodynamic conditions. Both concepts, however, involve rather complex elementary inter-atomic interactions: degree of hydrophobicity results from a competition of the van der Waals, steric, hydrogen-bonding and solvent entropic effects, while the effective charges depend on the electronic properties of the polymer, solvent dielectric permittivity and degree of screening by the counter-ions present in solution.

While full-scale atomistic simulations are rather standard for concrete polymers in solutions nowadays, their ability to study thermodynamic universal properties of whole classes of macromolecules are rather limited due to unbearable computational expenses involved. For these purposes a number of simplified coarse-grained copolymer models, which phenomenologically capture the effects of hydrophobicity and charges, have been proposed and studied both analytically [2–5] and by Monte Carlo simulation (see e.g. [6] and references therein), often on a lattice, which further significantly reduces computational expenses.

A great deal of related research has also been undertaken in relation to the problem of protein folding in the context of random heteropolymer models of proteins [2,3]. Although natural proteins are composed of 20 types of amino acid residues with rather refined properties, in a simplified model one can roughly divide all amino acid residues into polar (hydrophilic) and apolar (hydrophobic), as well as into effectively charged and neutral. This broad division produces two-letter models of proteins, and as the primary sequence of each protein is unique, applied to a whole ensemble of sequences this leads to random heteropolymer models of proteins.

Depending on which particular feature one is trying to describe thus there are models of am-

phiphilic [7,8] and charged copolymers [2] after solvent molecules have been effectively excluded from the consideration by integration (see Refs. [9,10] for details).

The first model has a linear term in composition variables,  $(\sigma_i + \sigma_j)V(r_{ij})$ , in the Hamiltonian, so that hydrophobic units  $a$  effectively attract each other (and thus dislike solvent contacts), hydrophilic  $b$  units effectively repel each other (and thus like solvent contacts), whereas hydrophobic–hydrophilic  $ab$  direct pair-wise interactions are zero. Such model will be referred to as hydrophobic–hydrophilic or HH model. As a simple variation of this we can also introduce hydrophobic-ideal or HI model, in which  $b$  species have zero repulsion from each other and thus effectively behave as ideal.

The model with a quadratic term in composition variables,  $\sigma_i\sigma_jV(r_{ij})$ , in the Hamiltonian is often called the random ‘charge’ model. In this context one can introduce the true charge or briefly CA model, in which likewise charges repel and opposite charges attract each other, or the model in which the quadratic term appears in the Hamiltonian with the opposite sign, so that likewise charges attract and opposite ones repel each other, which is naturally to call the anti-charge or AC model. Although the latter model does not describe true atomistic charges, such terms nevertheless appear to reproduce complex non-local effective monomer-solvent interactions arising after coarse-graining of models with complex intra-molecular potentials. Namely, the AC model was most popular in literature in analytical and lattice Monte Carlo studies of random heteropolymer models of proteins [2,3]. As we shall see later it indeed has the most peculiar properties, and although its applicability to synthetic copolymers is least justified, no single model is good enough for describing the complex behaviour of proteins.

In this work we would be interested to extensively investigate the energy probability distribution functions  $P_T(E)$  in the HH, HI, CA and AC models for a large set of different heteropolymers sequences at low temperatures after transitions to compacted states, whether crystalline or glassy, as well as to try to relate the observed distributions to

copolymer conformations, by which we understand the arrangement of monomers in relation to each other in space.

The energy probability distribution is formally defined as

$$P_T(E) = \frac{1}{Z_T} \sum_m \exp\left(-\frac{H_m}{k_B T}\right) \delta(E - H_m), \quad (1)$$

$$Z_T \equiv \sum_m \exp\left(-\frac{H_m}{k_B T}\right),$$

where  $m$  refers to microstates of the system, and this is linearly related to the density of states times an explicit exponential factor and a constant  $Z_T$ ,

$$\mathcal{N}(E) \equiv \sum_m \delta(E - H_m)$$

$$= P_T(E) \exp\left(\frac{E}{k_B T}\right) Z_T. \quad (2)$$

We may remark that  $P_T(E)$  plays a role similar to, and just as fundamental as, the energy spectrum of a quantum-mechanical system. Basically,  $P_T(E)$  is precisely the finite-temperature generalisation of the energy spectrum applicable to any type of system. In so much as the energy eigenvalues have eigen wave functions associated with them, the peaks in  $P_T(E)$  correspond to statistical sets of representative polymer conformations in our case. Indeed, by definition a peak there signifies a large population of conformations with nearly identical energy within the statistical Gibbs ensemble. By capturing snapshots of these most common conformations one can see that they do possess similar global features in their 3-D shapes. Similarly, snapshots of typical second common types of conformations would correspond to the second tallest peak in  $P_T(E)$ . Therefore, the energy distribution function would be of particular interest for studying as it expresses in a concise form the accessibility of energy populations via the peak heights as well as their stability via the gaps in between. Hence one would like to examine  $P_T(E)$  distributions and, when obvious, try to relate the main peaks there to typical polymer conformations. In Ref. [11] Monte Carlo histogram technique, based on direct sampling of the energy

values during Monte Carlo steps, was successfully applied to a 27-mer on a cubic lattice without enumerating all compact  $3 \times 3 \times 3$  cube states. However, here we shall be able to investigate many copolymer sequences of a longer chain on a large lattice with a good statistical sampling able to distinguish universal patterns of behaviour in the four aforementioned copolymer models directly at low temperatures without using an extrapolation by means of Eq. (2). Previously, this was problematic as a much larger sampling is required at temperatures below the transitions to compacted states.

## 2. Model

We adopt the standard Metropolis technique in the lattice model of our Ref. [6], which attempts to move a randomly picked monomer in a random direction to a nearby non-occupied site and accepts only the moves satisfying the Metropolis check  $\Delta E \leq -k_B T \ln r$ , where  $r$  is the standard uniform deviate. In this model, apart from the connectivity and excluded volume constraints accounted for explicitly, there are short-ranged pairwise interactions between lattice sites depending on the separation and sites contents, described by the Hamiltonian

$$H = \frac{1}{2} \sum_{i \neq j} w(r_{ij}) \mathcal{J}_{s_i s_j}, \quad (3)$$

where  $i, j$  enumerate lattice sites;  $s_i$  labels the contents of site  $i$ ,  $\mathcal{J}_{s_i s_j}$  is a  $3 \times 3$  symmetric matrix of monomer and solvent interactions,  $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$  is the separation between the two sites, and  $w(r_{ij})$  is a function giving the shape of the potential. In practice, it would suffice to include only first nearest neighbours ( $w(r=1) = 1$ ), 2-D and 3-D diagonals ( $w(r=\sqrt{2}) = 1$  and  $w(r=\sqrt{3}) = 0.7$ ), as well as the second nearest neighbours ( $w(r=2) = 1/2$ ), so that no higher interaction ranges are present ( $w(r > 2) = 0$ ) as in Ref. [6].

In case of copolymers one has to distinguish two types of monomers  $a$  and  $b$  and ascribe to them three values of Flory interaction parameters as follows [6]:

$$\begin{aligned}\chi_{aa} &= \frac{2\mathcal{I}_{sa} - \mathcal{I}_{aa} - \mathcal{I}_{ss}}{k_{\text{B}}T}, \\ \chi_{bb} &= \frac{2\mathcal{I}_{sb} - \mathcal{I}_{bb} - \mathcal{I}_{ss}}{k_{\text{B}}T}, \\ \chi_{ab} &= \frac{\mathcal{I}_{sa} + \mathcal{I}_{sb} - \mathcal{I}_{ab} - \mathcal{I}_{ss}}{k_{\text{B}}T}.\end{aligned}\quad (4)$$

It is easy to show that for an incompressible solution the system is completely characterised by these combinations of the interaction parameters along with the polymer length  $N$  and linear size  $L$  of the lattice.

As in Ref. [10] we shall use the parametrisation such that  $\sigma_a = 1$ ,  $\sigma_b = -1$  and

$$\begin{aligned}\chi_{ij} &= \chi_0 + \Delta \frac{\sigma_i + \sigma_j}{2} \text{ (HH, HI)}, \\ \chi_{ij} &= \chi_0 + \Delta \sigma_i \sigma_j \text{ (CA, AC)}.\end{aligned}\quad (5)$$

Thus, all interaction parameters can be summarised as in Table 1. We may note that the hydrophobic–hydrophilic and hydrophobic–ideal models use the same formal expression, but different values of  $\chi_0$  and  $\Delta$ .

In our study we have considered copolymers of length  $N = 48$  units with equal number of  $a$  and  $b$  monomers in each sequence on a large enough cubic lattice of linear dimension  $L = 50$  in order to make the influence of boundary conditions negligible. For each of four models we have analysed a number of periodic and 1000 randomly generated sequences. Every initial random walk conformation was first subjected to a slow quasistatic equilibration corresponding to gradually decreasing temperatures until the values of  $\chi_{ij}$  presented in Table 1 have been reached. This procedure is similar to ‘simulated annealing’ and permits to overcome excessive trapping of the system in metastable states. Moreover, to be able to deal with the issue of ‘non-ergodicity’ this cooling was

Table 1  
Values of the Flory interaction constants for four different models of copolymers on lattice

| Model | $\chi_{aa}$ | $\chi_{ab}$ | $\chi_{bb}$ | $\chi_0$ | $\Delta$ |
|-------|-------------|-------------|-------------|----------|----------|
| HI    | 2           | 1           | 0           | 1        | 1        |
| HH    | 2           | 0.4         | −1.2        | 0.4      | 1.6      |
| CA    | 0           | 2           | 0           | 1        | −1       |
| AC    | 2           | 0           | 2           | 1        | 1        |

applied to a fairly large ensemble (typically over 200) of different initial conditions. To obtain probability distributions of various observables, such as e.g. energy, we then performed hundreds of measurements separated by large number of Monte Carlo sweeps (i.e. typically hundred of thousands of attempted Monte Carlo moves), resulting in the total number of independent statistical measurements equal to 20000 in each case. Finally, normalised energy histograms provide Monte Carlo approximations to the exact energy probability distribution functions  $P_T(E)$  defined by Eq. (1). Henceforth we shall omit the  $T$  subscript as the temperature will be fixed throughout.

Due to the very large amount of data obtained and obvious constraints of the paper size we shall only discuss here most interesting and representative results, while the whole data set is available online [12] for an interested reader.

### 3. Results

A typical energy distribution function of HI model shown in Fig. 1 has a bell shape. Note that low energy states contribute little to this function because the density of states  $\mathcal{N}(E)$  is rapidly decreasing with decreasing energy  $E$ . The general outlook of  $P(E)$  changes little for different sequences, with only mean value  $\langle E \rangle$  and width  $\langle (E - \langle E \rangle)^2 \rangle^{1/2}$  of the distribution being sensitive on the sequence.

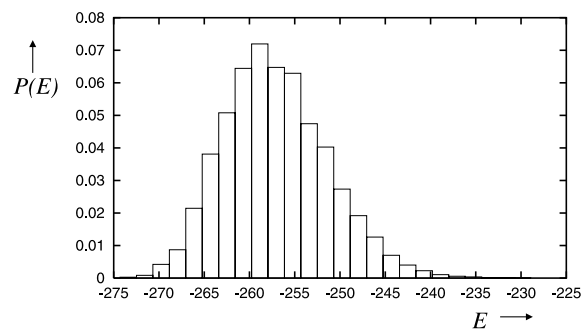


Fig. 1. Energy distribution function for the random sequence (s1) *abbbbabaabbaababababbbbaababbbabbbbaaaababaaaa* in the hydrophobic-ideal model. Here and below  $k_{\text{B}}T$  units of energy are used.

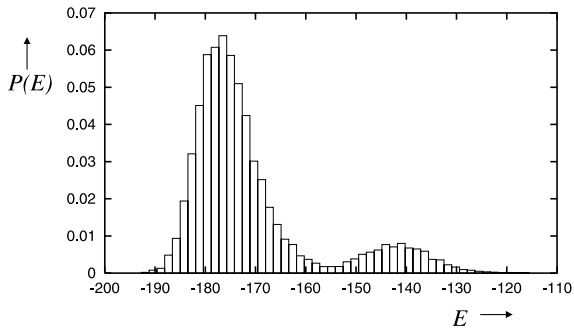


Fig. 2. Energy distribution function for the random sequence (s2)  $ababbaabababababababbbabbabababababababababababababab$  in the hydrophobic-hydrophilic model.

For most sequences the energy distribution function in the HH model is similar to that of the HI model. However, a few percents of sequences in the HH model also possess a second peak in  $P(E)$  as shown in Fig. 2. The secondary peak at higher

energies is considerably lower and could be simply understood by visualising typical copolymer conformations corresponding to a given energy distribution. First of all, a snapshot in Fig. 3(a) shows a typical 3-D polymer shape (conformation) for a single peak situation. A clear feature of both the HI and HH models is the micro-phase separation (MPS) of the globule onto a hydrophobic (black) core and a hydrophilic (gray) shell as in a micelle. As for the case of a sequence with a two-peak  $P(E)$  function, this would correspond to a dimer (or a multimer for longer chains) of subglobules connected by a predominantly hydrophilic bridge. Obviously, such a situation can be realised only for sequences which do have a fragment in their primary sequence with a predominantly hydrophilic units.

The energy distributions in the CA model also have a trivial single peak shape as in Fig. 1. However, the polymer conformations are rather different in this case. Thus, in Fig. 4 one can see

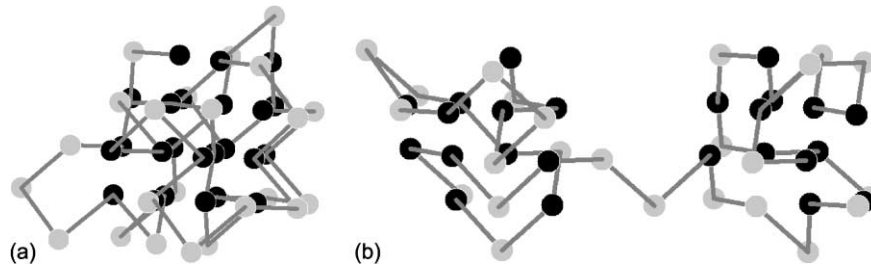


Fig. 3. Snapshots of typical copolymer conformations for sequence (s2) in the hydrophobic-hydrophilic model. (a) and (b) correspond to  $E = -172.2$  (left peak) and  $E = -135.8$  (right peak) in Fig. 2 respectively.

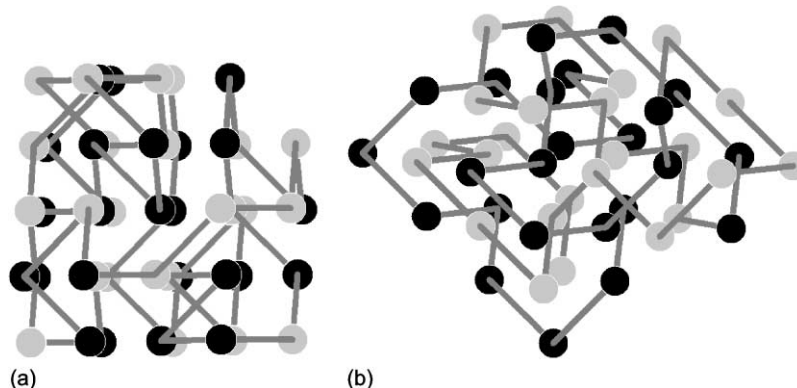


Fig. 4. Snapshots of typical low energy copolymer conformations in the charge model. (a) and (b) correspond to random sequence (s3)  $aababbbababababaaababababababaaabaaabbbabbabab$  and periodic sequence  $(a_{12}b_{12})_2$  respectively.

that although the globules are still compact, the internal arrangement of the monomers within are rather peculiar and have an alternating rather than a core-and-shell structure. This arrangement obviously tends to maximise the number of  $ab$  contacts favourable in this model. Fig. 4(a) and (b) corresponding to a random and a long blocks sequences respectively show, however, that there is no tendency of forming better structured conformations (in the sense of maximising the MPS between  $a$  and  $b$  units) for periodic sequences with increasing block length as was the case in the HH and HI models.

Most interesting energy distributions of the four considered models occur in the AC model. Although most sequences here would still have a single peak distribution as in the other models, there are a few percents of sequences in the AC model which have energy histogram as shown in Fig. 5. These sequences possess a highly populated

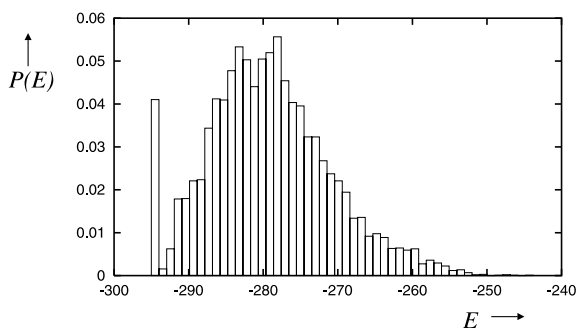


Fig. 5. Energy distribution function for the random sequence (s4)  $ababbabaababbbaaaababbabbbaaaabbbaabbbaabbbaab$  in the anti-charge model.

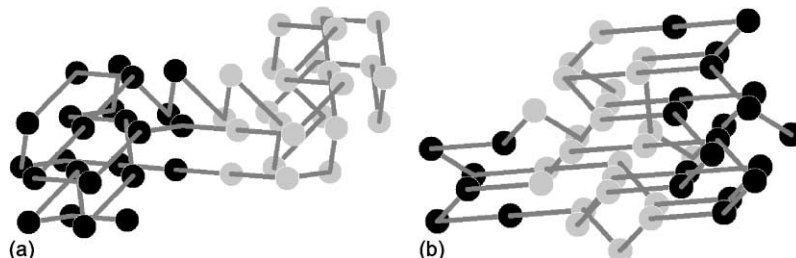


Fig. 6. Snapshots of typical low energy copolymer conformations in the anti-charge model. (a) and (b) correspond to sequences  $(a_{12}b_{12})_2$  (at  $E = -376$ ) and  $(a_3b_3)_8$  (at  $E = -324$ ) respectively.

visible lowest energy state, which is often separated by a gap from the rest of the spectrum. This may be rationalised as occurring due to a much higher density of states  $\mathcal{N}(E)$  at low energies.

This unusual behaviour of  $P(E)$  also corresponds to interesting conformations of the copolymer. In Fig. 6(a) and (b) these are shown for examples of periodic sequences of different block lengths. For long blocks sequence in Fig. 4(a) there is a clear dumbbell shape with  $a$  and  $b$  units in their separate homopolymer-like subglobules avoiding unfavourable contacts with each other. For shorter blocks sequences as in Fig. 4(b) this separation of  $a$  and  $b$  units cannot be as perfectly realised due to the chain connectivity constraints, thus producing merely a multi-domain globule of homopolymer-like clusters. Also, the increase of the block length shifts the  $P(E)$  function towards lower energies due to a better optimisation of competing pair-wise interactions.

#### 4. Discussion

As we have seen here the energy probability distributions are bell shaped and shifted towards low energies in most cases.

The second peak in the HH model occurring for some sequences, especially those having a long hydrophilic segments in the chain, corresponds to formation of dimers and multimers. Naturally, the HI model has similar features to HH model, although it has a lower tendency for forming multimers. Speaking of the conformations, only the HH and HI models produce good MPS with a

predominantly hydrophobic core and hydrophilic surface. The degree of MPS increases with increasing a characteristic repeating block in a sequence.

Conformations in CA model do not have a MPS structure and are rather complex amorphous (glassy) globules. The characteristic block length has little effect on the conformation and energy in this model.

The AC model has most interesting and most sequence-dependent energy distributions of all. It has a well populated lowest energy state separated by a gap from higher energy states for certain sequences, which perhaps can be viewed as *good folding sequences* [11]. This shape is generally believed to provide good accessibility and stability of the lowest energy state identified as an analog of the native state in proteins. We may note that this result agrees with Fig. 2 in Ref. [11], in which the AC model was in fact studied at somewhat different values of parameters as compared to Table 1.

However, the AC model exhibits phase separation of *a* and *b* species similar to two immiscible liquids under connectivity constraints, which is rather different from *a*-surface and *b*-core MPS in HH model. Increasing typical block length here leads to dumbbell structures rather than micelles, which also has an effect of lowering the energy considerably. Short block sequences produce multi-domain globules of identical species.

## 5. Conclusion

We have presented results for four distinct lattice models of copolymers obtained from Monte Carlo simulations of a large ensemble of 20 000 independent initial conditions for 1000 randomly generated and a number of regular sequences with equal ratio of *a* and *b* monomers. Features of energy distribution functions (histograms) and corresponding polymer 3-D shapes (conformations) are discussed in the hydrophobic–hydrophilic (HH), hydrophobic–ideal (HI), charge (CA) and anti-charge (AC) models of copolymers at a temperature much below transitions to compacted states. Most sequences in all of models have a single bell shaped energy probability distributions.

However, some sequences in the HH model have two peaks distributions. Moreover, a number of sequences in AC model have more than two peaks and often a gap between the lowest energy and higher energy states. Conformations and MPS of *a* and *b* species corresponding to distinct peaks in the distributions in these models are also analysed and these results may be of interest for a range of synthetic polymers in solution.

Finally, from our analysis it appears that while separate features expected from proteins can be represented by the HH and AC models of copolymers, neither model possesses all of these features together, at least at the level of two-letter models. Namely, while AC model has an energy histogram which bears resemblance to that of a protein in the native state, it has conformations which have little to do with typical protein 3-D shapes, especially in terms of MPS. The HH model, on the other hand, has conformations similar to those of globular proteins, but a trivial energy histogram with easily accessible low energy states and no barrier or special pathway to these states from the coil. Perhaps, a proper continuous space treatment with the account of Coulomb, van der Waals, bonded, or even specific interactions may be necessary to capture even in a minimal way the equilibrium folding behaviour of proteins.

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