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Phase diagram of an imprinted copolymer in a random external field

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Abstract. Recently, a procedure to create renaturable heteropolymers, 'imprinting', has been proposed and examined theoretically. The significance of imprinting is that certain aspects of a heteropolymer's native conformation may be controlled during the synthesis stage. We examine this possibility theoretically by introducing an external field during the synthesis and renaturation stages of the model. We find that imprinting in an external field leads to protein-like heteropolymers which can renature to native conformations which are affected by the field, even in the absence of the field during renaturation. We conclude by commenting on the relevance of these results to the biological and prebiological creation of biopolymers, such as proteins, *influenced by the analogues to our external field, such as antigens or ligands.*

1. *Introduction*

Disordered polymers are one of the most important objects in the physics of disordered systems, mainly because of the potential biological applications. Among other disordered polymeric systems, such as branched polymers and knots, two have acquired most attention in recent years: heteropolymers, linear chains with an uneven sequence of different links, and homopolymers situated in a disordered environment, such as a white-noise external field.

The main physical peculiarity of heteropolymers is the frustration imposed by the conflicting requirements of the segregation of different monomers in space due to monomer–monomer volume interactions and the connection of monomers due to the polymeric bonds. When interactions are strong enough, freezing behaviour similar to the one observed in spin glasses is found. The frozen phase of heteropolymers is dominated by one or very few conformations, or chain folds, that are minimally frustrated [1].

For a homopolymer in a disordered medium, there are also several models to be mentioned. The simplest one views an ideal chain (without excluded volume or other volume interaction between monomers) looking for the deepest potential well. This is described in [2, 3]. Not surprisingly, the polymer in this model collapses to microscopic size independently of the chain length. In a more realistic model, this pathological indefinite collapse is prevented by the monomer excluded volume, and the corresponding conformations are described in [4, 5]. In this case, frustration is also imposed by the linear connections between chain monomers, the conflicting tendencies being the placement of monomers in the deepest possible wells of the potential (to keep polymer density below the densely packed maximum) and the maintenance of prescribed distances between monomers.

Our aim in the present paper is to consider a generalized model, where both types of disorder are presented simultaneously: a heteropolymer with frozen sequence of links in the

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disordered external field. The appealing property of this model is that heterogeneity enters the system twice, first because volume interactions of monomers are of a heteropolymeric fashion and second because different monomers also feel the external field in different ways.

For the sake of simplicity, we restrict ourselves to the simplest assumption of a dense-packed system. This means that our polymer is closely packed into the box which is supported by some external pressure, so that density of the system remains spatially uniform, no matter what the corresponding energy of the external field. For this system, the behaviour in one extreme is known: if the external field is negligibly small (as compared with volume interactions), very few conformations will be frozen out at low temperatures because of the normal heteropolymer freezing transition [8, 10]. On the other hand, a strong external field imposed on the system with weak volume interactions can also be expected to cause freezing of some distinct conformations—those that best fit the field configuration. What is important, however, is that these two small sets of conformations are generally completely different. This means that sufficiently strong external field destroys the freezing of heteropolymer to the conformation dictated by its sequence.

Another important aspect of the problem is which sequences of monomers we are speaking about. This is to be taken seriously, because sequences are responsible for coding functions in biopolymers and therefore the adequacy of random sequences to model real ones is at least questionable. To this end, two ways to model real sequences were recently suggested [6–8]. Even though there are important differences between the two, they both employ the idea to form sequences thermodynamically. Speaking now of an external field, we can consider this field affecting sequence formation, or polymer folding with an already formed sequence, or both. All these possibilities are of great interest, as an external field can represent (to a schematic approximation) some target molecules or ligands, which are either used to control some desirable properties of the sequence, such as presence of an appropriate active site in the 'native' conformation, or influence renaturation processes, etc.

We believe that the above-mentioned models of sequence design are of great interest for the understanding of biopolymers. In this context, the incorporation of the external field in the model allows us to approach various questions related to the design procedure: suppose we form the sequence under the action of the field; will it be able to renature without the field? Or vice versa—if the sequence is formed without any field, will the field help or destroy the renaturation? Or what happens to renaturation if the acting field is opposite to the one presented in the polymerization process? We will address these questions below.

In the present paper, we examine systematically the model where

(i) heteropolymer has two types of monomers ('black-and-white model') with Ising-type interactions;
(ii) overall polymer density is maintained such that polymer volume fraction is always one;
(iii) external field is modelled as a quenched random δ-correlated potential;
(iv) interactions are considered unchanged at the stages of sequence formation and of chain folding.

2. The model

We model heteropolymeric monomer–monomer and monomer–field interactions with the Hamiltonian

$$\mathcal{H} = -B \sum_{I,J}^{N} s_I s_J \delta(r_I - r_J) - h \sum_{I}^{N} s_I \sigma(r_I) \tag{1}$$

where $\sigma(x)$ is the external field. All homopolymeric contributions, such as excluded volume virial coefficients, are omitted for brevity, as they do not couple to heteropolymeric contributions. We repeat, however, that polymer density is kept constant.

Because of self-averaging, and since both the sequence and external field are quenched in each existing chain, the relevant free energy is to be averaged over an ensemble of sequences and external fields σ:

$$F = -\int \mathcal{D}\sigma \sum_{\text{seq}} \mathcal{P}[\text{seq}, \sigma] \ln Z[\text{seq}, \sigma] \tag{2}$$

where $Z[\text{seq}, \sigma]$ is the corresponding partition function. Ignoring for the moment the technical question of how to perform this average, we note that the two elements of frozen disorder presented here, the sequence and the field, play a considerably different role. Indeed, we are considering the model in which the sequence is formed by a special design procedure and therefore may or may not be dependent on the external field. Moreover, the external field which acts during the chain polymerization may generally be different from the field acting on the already prepared chain. To take care of this fact, we write

$$\mathcal{P}[\sigma, \text{seq}] = \int \mathcal{D}\sigma_p \mathcal{P}[\sigma, \sigma_p] \times \mathcal{P}_{\{\sigma_p\}}[\text{seq}] \tag{3}$$

where $\mathcal{P}_{\mathcal{B}}[\mathcal{A}]$ stands for *conditional* probability of $\mathcal{A}$ under the condition $\mathcal{B}$. $\mathcal{P}_{\{\sigma_p\}}[\text{seq}]$ is really the distribution of sequences, and it is dictated by the design procedure. As both of the known procedures to design sequences are based on the equilibration of either the monomer soup in real space [7, 8] or the polymer in sequence space [6], the distribution of sequences is given as corresponding Boltzmann distribution, and it is therefore proportional to

$$\mathcal{P}_{\{\sigma_p\}}[\text{seq}] = Z_p[\text{seq}, \sigma_p] \tag{4}$$

where $Z_p[\text{seq}, \sigma_p]$ is the partition function of the polymerization system. Hereafter, we omit all irrelevant normalization constants.

We now employ the replica trick

$$\langle \ln Z \rangle = \lim_{n \to 0} \frac{\langle Z^n \rangle - 1}{n} \tag{5}$$

to perform the average in (2). Collecting equations (2) through (5) together, we get

$$F = \lim_{n \to 0} \frac{1}{n} \left(\int \mathcal{D}\sigma \mathcal{D}\sigma_p \mathcal{P}[\sigma, \sigma_p] \sum_{\text{seq}} Z^n[\text{seq}, \sigma] Z_p[\text{seq}, \sigma_p] - 1 \right). \tag{6}$$

The structure of this expression allows us to consider the preparation state as an additional $n+1$ replica, albeit with its own temperature and some Hamiltonian parameters. To see it, we write

$$Z_r[\text{seq}, \sigma_r] = \sum_{\text{conformations}} \exp\left\{ -\frac{1}{T_r} \mathcal{H}_r[\text{seq}, \sigma_r, \text{conformation}] \right\} \tag{7}$$

where index r may be absent for replicas $1, \ldots, n$ and stands for p ('polymerization') for additional replica 0.

For simplicity, we do not consider various cases of statistical interdependencies of the fields σ and σ_p. Furthermore, we consider both to be δ-correlated white noise, such that

$$\langle \sigma_r(R) \rangle = 0 \qquad \langle \sigma_r(R) \sigma_r(R') \rangle = w^2 \delta(R - R'). \tag{8}$$

As we assume that the value of the field at one position is uncorrelated with its value at a different position, the probability distribution of σ is Gaussian:

$$\mathcal{P}[\sigma, \sigma_p] = \delta[\sigma(R) - \sigma_p(R)] \exp\left\{-\int \mathrm{d}R w^{-2}\sigma(R)^2\right\} \tag{9}$$

where w controls the width of the probability distribution of the external field. Even though we consider σ and σ_p to be strongly correlated, we can examine several physical situations by choosing various combinations of h and h_p in the Hamiltonians $\mathcal{H}$ and $\mathcal{H}_p$ in equation (7):

(i) If the field effects chain design and folding in the same way, we take $h = h_p$;
(ii) If the field is presented during design only, we take $h = 0$, $h_p \neq 0$;
(iii) By contrast, if the field is presented for the existing prepared chain only, when the chain folds, then $h \neq 0$, $h_p = 0$;
(iv) The field can affect the system during the folding stage in the *opposite direction* compared to the design stage; in this case $h = -h_p \neq 0$.

Thus, to gain physical insight into the system, it should be enough to consider the simplest probability distribution for the external field (9), but taking into account the general situation with respect to different h and h_p.

Since the interactions in the monomer soup are the same as those found in the polymer, the parts of the Hamiltonians $\mathcal{H}$ and $\mathcal{H}_p$ describing interactions should be identical; namely, there should be the same B.

Thus, the $(n+1)$-replica partition function has the following form:

$$Z^{n+1} = \sum_{\text{conf}} \exp\left\{\int \mathrm{d}R_1\, \mathrm{d}R_2 \sum_{\alpha=0}^{n}\sum_{I,J}^{N} \frac{B}{T_\alpha} s_I s_J\, \delta(r_I^\alpha - R_1)\delta(r_J^\alpha - R_2)\delta(R_1 - R_2)\right.$$
$$\left. + \int \mathrm{d}R \sum_{\alpha=0}^{n}\sum_{I}^{N} \frac{h_\alpha}{T_\alpha} s_I\, \sigma(R)\delta(r_I^\alpha - R) - \int \mathrm{d}R w^{-2}\sigma(R)^2\right\} \tag{10}$$

where h_α and T_α is defined according to

$$h_\alpha = \begin{cases} h_p & \text{for } \alpha = 0 \\ h & \text{for } \alpha > 0 \end{cases} \quad \text{and} \quad T_\alpha = \begin{cases} T_p & \text{for } \alpha = 0 \\ T & \text{for } \alpha > 0. \end{cases} \tag{11}$$

As elsewhere in the paper, we drop all the normalization constants.

We go from spins to fields by performing the Hubbard–Stratonovich transformation on the quantity $\sum_I^N s_I\, \delta(r_I^\alpha - R)$ and average over the sequences and external field to get

$$\langle Z^{n+1}\rangle = \sum_{\text{conf}} \int \mathcal{D}\{\phi\}\mathcal{D}\{\sigma\} \exp\left\{-\int \mathrm{d}R \left[w^{-2}\sigma(R)^2 + \sum_{\alpha=0}^{n} \frac{T_\alpha}{4B}\phi_\alpha(R)^2\right]\right.$$
$$\left. + \sum_I \ln\cosh\left[\sum_{\alpha=0}^{n} \int \mathrm{d}R\, \delta(r_I^\alpha - R)\left(\phi_\alpha(R) + \frac{h_\alpha}{T_\alpha}\sigma(R)\right)\right]\right\}. \tag{12}$$

We can expand the $\ln\cosh$ to $\mathcal{O}(\phi^2, h^2)$ to get

$$\langle Z^{n+1}\rangle = \sum_{\text{conf}} \int \mathcal{D}\{\phi\}\mathcal{D}\{\sigma\} \exp\left\{-\int \mathrm{d}R_1\, \mathrm{d}R_2 \sigma(R_1)\sigma(R_2)\right.$$
$$\left. \times\left[w^{-2}\delta(R_1 - R_2) - \frac{1}{2}\sum_{\alpha,\beta=0}^{n} \frac{h_\alpha}{T_\alpha} Q_{\alpha\beta}(R_1, R_2)\frac{h_\beta}{T_\beta}\right]\right.$$

$$-\int \mathrm{d}R_1\,\mathrm{d}R_2 \sum_{\alpha,\beta=0}^{n} \phi_\alpha(R_1)\phi_\beta(R_2)\left[\frac{T_\alpha}{4B}\delta_{\alpha\beta}\delta(R_1-R_2)-\frac{1}{2}Q_{\alpha\beta}(R_1,R_2)\right]$$

$$+\int \mathrm{d}R_1\,\mathrm{d}R_2 \sum_{\alpha,\beta=0}^{n} Q_{\alpha\beta}(R_1,R_2)\phi_\alpha(R_1)\frac{h_\beta}{T_\beta}\sigma(R_2)\Bigg\} \tag{13}$$

where $Q_{\alpha\beta}(R_1,R_2)\equiv\sum_I \delta(r_I^\alpha-R_1)\delta(r_I^\beta-R_2)$ is the conformation correlator between replicas [9, 8]. This expression (13) is rather cumbersome, but it can be substantially simplified by noting that for a polymer in 3D the one-step replica-symmetry breaking scheme is valid, as was first noted in [9]. This result holds true for the case in hand, where an external field is presented, as can be easily shown by reproducing arguments of [9] in the form of [8]. In the one-step replica-symmetry breaking, the free energy is minimized for the correlator Q such that two replicas either have complete overlap or do not overlap at all [9, 8]. Thus, this corresponds to the form

$$Q_{\alpha\beta}(R_1,R_2)=\rho\; q_{\alpha\beta}\;\delta(R_1-R_2) \tag{14}$$

where ρ is the density of the system and $q_{\alpha\beta}$ is a $(n+1)\times(n+1)$ matrix of the single-step replica-symmetry breaking form (figure 1)

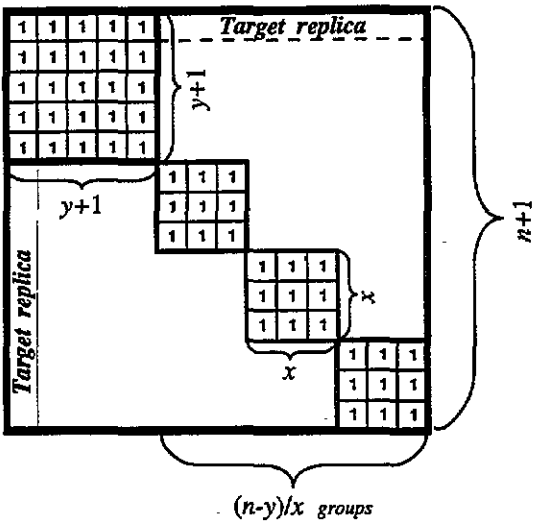

Figure 1.

There are two ways in which replica symmetry is broken: (i) spontaneously, in which frustrations lead to certain conformations which have differing energies and (ii) due to the the selection procedure which explicitly breaks replica symmetry. We parameterize $q_{\alpha\beta}$ in terms of the number of replicas y which overlap with replica 0 (and therefore have the polymerization conformation), and the $(n-y)/x$ groups of replicas which each overlap with x replicas due to spontaneous replica-symmetry breaking.

For further simplification, it is useful to substitute $\phi_\alpha\to\phi_\alpha 2\sqrt{\rho B/T_\alpha}$ (still omitting the irrelevant factors in front of the integral) and to use bra ket vector and matrix notations [8] (where the dimensionality of the vector space is $n+1$):

$$\langle Z^{n+1}\rangle=\sum_{\text{conf}}\Bigg[\int \mathrm{d}^{(n+1)}\vec{\phi}\,\mathrm{d}\sigma\,\exp\Bigg\{-\sigma^2\left[\frac{1}{\rho w^2}-\frac{1}{2}\langle\vec{h}\,|\hat{q}|\,\vec{h}\rangle\right]$$

$$-\langle\vec{\phi}\,\Big|\hat{I}-2\rho B\hat{T}^{-1}\hat{q}\Big|\,\vec{\phi}\rangle+2\sqrt{\rho B}\langle\vec{\phi}\,\Big|\hat{T}^{-1/2}\hat{q}\Big|\,\sigma\vec{h}\rangle\Bigg\}\Bigg]^N. \tag{15}$$

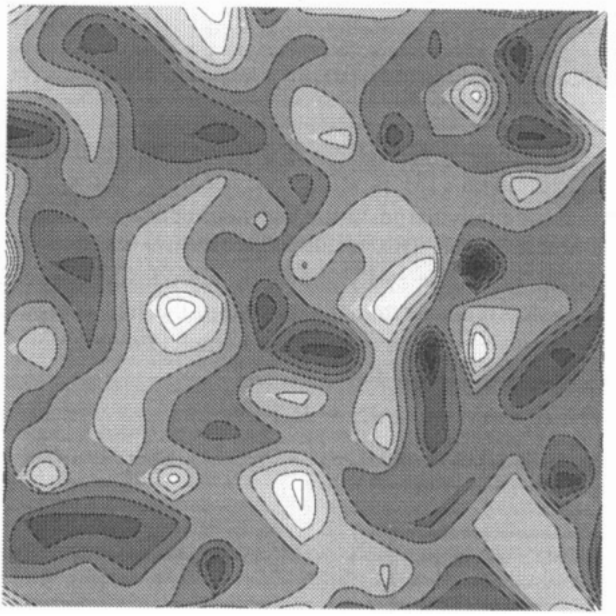

Figure 2. Cartoon contour plot of a random field. For a polymer which consists of only two types of monomers ('black' and 'white'), we examine Ising interactions for monomer–monomer and monomer–field interactions. Even without monomer–monomer interactions, the polymeric bonds cause frustration since they prevent the monomers from matching 'colours' with the field.

We evaluate this Gaussian integral, which yields $\langle Z^{n+1}\rangle = \exp(-E+S)$, where

$$E = \tfrac{1}{2}\ln\det\left[\hat{I} - 2\rho B\hat{q}\hat{T}^{-1}\right] + \tfrac{1}{2}\ln\left[\frac{1}{\rho w^2} - \langle\vec{h}|\hat{q}B\rho\hat{T}^{-1}\left(\hat{I} - 2\rho B\hat{q}\hat{T}^{-1}\right)^{-1}\hat{q} + \tfrac{1}{2}\hat{q}|\vec{h}\rangle\right] \tag{16}$$

where we have taken into account that $\hat{T}$ and $\hat{q}$ do commute to each other. S is the entropy due to the transformation between the sum over conformations and functional integration over $Q_{\alpha\beta}(R_1, R_2)$.

To simplify further, we need the eigenvalues and eigenvectors of the $\hat{M} = \hat{I} - 2\rho B\hat{q}\hat{T}^{-1}$ matrix. These have been previously calculated [8]. These calculations are facilitated by the fact that all of the matrices are block matrices and the associated scalar products can be calculated for each block, then summed. In terms of x and y, we find

$$\langle\vec{h}|\hat{q}B\rho\hat{T}^{-1}\left(\hat{I} - 2\rho B\hat{q}\hat{T}^{-1}\right)^{-1}\hat{q}|\vec{h}\rangle = B\rho\left(\frac{y}{T} + \frac{1}{T_p}\right)\left(\frac{yh}{T} + \frac{h_p}{T_p}\right)^2\left[1 - 2B\rho\left(\frac{y}{T} + \frac{1}{T_p}\right)\right]^{-1} + \frac{n-y}{x}\left[\frac{(B\rho x/T)(hx/T)^2}{1 - 2B\rho x/T}\right]. \tag{17}$$

One can easily show that

$$\langle\vec{h}|\hat{q}|\vec{h}\rangle = \left[\left(\frac{h_p}{T_p}\right)^2 + 2y\left(\frac{hh_p}{TT_p}\right) + \left(\frac{yh}{T}\right)^2 + \frac{n-y}{x}\left(\frac{xh}{T}\right)^2\right] \tag{18}$$

and it has been previously shown that [8]

$$\ln\det\left[\hat{I}-2\rho B\hat{q}\hat{T}^{-1}\right]=\frac{n-y}{x}\ln\left[1-\frac{2B\rho}{T}x\right]+\ln\left[1-2B\rho\left(\frac{y}{T}+\frac{1}{T_p}\right)\right]. \tag{19}$$

We have now written the energy entirely in terms of the new scalar order parameters x and y. We can do the same for the entropy [10, 8]:

$$S=Ns\left[\frac{n-y}{x}(x-1)+y\right] \tag{20}$$

where $s=\ln(a^3/v)$. Thus, we can now write the free energy entirely in terms of x and y:

$$\begin{aligned}\frac{F}{N}=&\tfrac{1}{2}\ln\left[\frac{1}{\rho w^2}-\zeta\right]+\tfrac{1}{2}\frac{n-y}{x}\ln\left[1-\frac{2B\rho}{T}x\right]\\&+\tfrac{1}{2}\ln\left[1-2B\rho\left(\frac{y}{T}+\frac{1}{T_p}\right)\right]+s\left[n-\frac{n-y}{x}\right]\end{aligned} \tag{21}$$

where

$$\begin{aligned}\zeta=&B\rho\left(\frac{y}{T}+\frac{1}{T_p}\right)\left(\frac{yh\rho}{T}+\frac{h_p\rho}{T_p}\right)^2\left[1-2B\rho\left(\frac{y}{T}+\frac{1}{T_p}\right)\right]^{-1}\\&+\frac{n-y}{x}\left[\frac{(B\rho x/T)(h\rho x/T)^2}{1-2B\rho x/T}\right]+\tfrac{1}{2}\left[\left(y\frac{h\rho}{T}+\frac{h_p\rho}{T_p}\right)^2+\frac{n-y}{x}\left(x\frac{h\rho}{T}\right)^2\right].\end{aligned} \tag{22}$$

To find the temperature at which the system freezes into random conformations, we optimize F with respect to x. Note that the $n\to 0$ limit must be kept in mind during these calculations, i.e. the free energy should be linearized in terms that are of $\mathcal{O}(n)$ (i.e. n and y). We find a solution similar to the zero-field case [10, 8]

$$x=\begin{cases}\xi_f T/\rho & \text{for}\quad \xi_f T/\rho\leqslant 1\\ 1 & \text{for}\quad \xi_f T/\rho\geqslant 1\end{cases} \tag{23}$$

where ξ_f is the solution to the equation

$$2s=\ln\left(1-2B\xi_f\right)+\frac{2B\xi_f}{1-2B\xi_f}+\frac{(h\xi_f)^2}{\Gamma\left(1-2B\xi_f\right)^2}\qquad \Gamma=\frac{2}{\rho w^2}-\left(h_p\xi_p\right)^2-\frac{2Bh_p\xi_p^2}{1-2B\xi_p} \tag{24}$$

and $\xi_p=\rho/T_p$. If we expand for small ξ and ξ_p, we get $T_f=\rho\sqrt{(B^2+h^2\rho w^2/4)/s}$.

Thus, there are two sources for freezing: the external field and the polymer interaction. Thus, even in the case where the chain is a homopolymer with respect to volume interactions ($B=0$), but has heteropolymeric interactions with the external field ($h\neq 0$), freezing occurs due to the desire to place monomers in low-energy positions with respect to the field and the polymeric bonds which frustrate this goal. Moreover, in the limit in which there is no field during imprinting ($h_p=0$) and polymer–polymer interactions are negligible compared to the external field ($h\gg B$), we can exactly find the freezing temperature $T_f=h\rho^{3/2}w(4s)^{-1/2}$; it is clear that the external field contributes to frustrations and therefore leads to freezing.

We now examine the transition to the target group. As there are no extrema within the region $y=0\ldots n$, the free energy is maximized at the boundary, i.e. either at $y=0$ (no replicas overlap with the target replica) or $y=n$ (all replicas overlap with the target replica and therefore the polymer renatures to the designed conformation). To find which value of

y maximizes the free energy, we linearize the free energy in y and examine the condition where the slope of the free energy with respect to y changes sign:

$$2s = \ln(1-2B\xi) + \frac{2B\xi}{1-2B\xi_p} - \frac{1}{\Gamma}\left[h^2\xi^2 - 2hh_p\xi\xi_p + \frac{2Bh^2\xi^3}{1-2B\xi} + \frac{2B\xi\xi_p(2Bh_p\xi_p - h - h_p)}{1-2B\xi_p}\right]. \tag{25}$$

If we expand for small ξ's, which corresponds to the small s (flexible chain) limit, we get the relation

$$\xi^2 + \xi_f^2 = 2g\xi\xi_p \qquad \text{where} \quad g = \frac{4B^2 + 2B(h+h_p) + hh_p}{4B^2 + h^2}. \tag{26}$$

Thus, we have

$$T_p^c = \begin{cases} 2gT/(1 + T^2/T_f^2) & \text{for} \quad T \geqslant T_f \\ gT_f & \text{for} \quad T \leqslant T_f. \end{cases} \tag{27}$$

To this order, we find that T_p^c is simply the zero-field ($h = h_p = 0$) case multiplied by g and with a modified T_f (since T_f is a function of h to this order). Note that in the limit $B \to 0$, (26) and (27) are exact.

3. Discussion

We have found that in the flexible chain limit, the external field case is a simple generalization of the zero-field case, simply with a newly defined freezing temperature T_f and a factor $g(h, h_p)$ in the definition of the threshold polymerization temperature T_p^c. To examine these modifications, we must first look at the behaviour of $g(h, h_p)$, shown in figure 3.

We examine the following cases:

(i) *Imprinting and renaturation in the presence of the field ($h = h_p$).*
We see that for the same field strength during imprinting and renaturation, freezing to the target conformation is enhanced, as $g(h, h) > 1$, and therefore the threshold

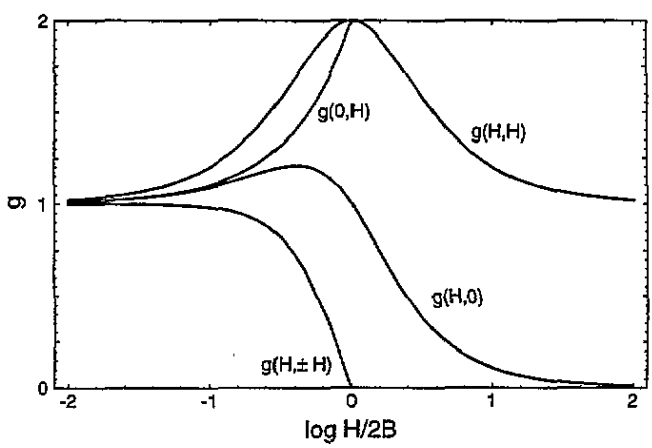

Figure 3. In the flexible chain limit, the effect of the external field during design (h_p) and/or during renaturation (h) enters into the theory as a rescaling of the polymerization temperature T_p. The effective polymerization temperature is given by $T_p \to T_p/g(h, h_p)$. We plot g for the four cases addressed in the discussion.

polymerization temperature T_p^c is greater than the $h = h_p = 0$ case. In fact, for $h = h_p = 2B$, we find that the frustration is maximized, as both the polymer–polymer and polymer–field interactions contribute equally. At very high fields ($h \gg B$), the contribution from the polymer–polymer interactions are negligible and there is freezing solely due to the external field; thus, in this limit $g \to 1$.

(ii) *Imprinting with the field, but renaturation without the field ($h = 0$, $h_p \neq 0$).* We see trivially from (26) that in the limit, $g = 1 + h_p/2B$. Thus even without the external field during renaturation, the polymer renatures to the polymerization conformation. This is crucial to the molecular recognition ability of imprinted polymers, as we would require the polymer to fold to its native state in order to recognize the external field. As one would expect, we can see directly from the plot of g in figure 2 that T_p^c for this case must be lower than the case where the polymer is designed *and* renatured with the field ($h = h_p$): the polymer must be better optimized in order to renature without the field originally present during imprinting. For the high-field limit ($h \gg B$), then g (and therefore T_p^c) grows linearly with h_p. Of course, in this extreme, the effect of B is unimportant and what must be examined is h_p/T_p: there is no distinction between lowering the temperature at a fixed field strength and raising the field strength with a fixed temperature.

(iii) *Imprinting without the field, but renaturation with the field ($h \neq 0$, $h_p = 0$).* In this case, the field acts to destroy the process of renaturation. If the field is sufficiently strong ($h \gg B$), g approaches zero. For the intermediate field case ($h \simeq B$), there is a maximum in $g(h, 0)$, with $g(h_{\max}, 0) > 1$; this is due to the added frustrations due to the competition between the polymer–polymer and polymer–field interactions.

(iv) *Imprinting without the field, but renaturation with the opposite field ($h = -h_p$).* Here, we apply exactly the opposite field which the system wishes to recognize. When the field strength is equal to the strength of the polymer–polymer interactions ($h = B$), the field destroys any possibility of renaturation to the target conformation. For higher field strengths ($h > 2B$), g becomes negative; this implies that for imprinting to work, we need a negative polymerization temperature, which simply switches back the sign of h_p (the switching of the sign of B is irrelevant in this limit).

In conclusion, imprinted polymers in an external field display protein-like behaviour. For example, they can renature to an imprinted conformation which has been affected by a given external field without the field present during renaturation. This property is analogous to an antibody renaturing without the antigen present. Also, we have shown that the field can disrupt folding to the polymerization conformation in the cases where either the field was absent or of the opposite sign during imprinting.

Furthermore, these results are not only applicable to the *in vitro* imprinting procedure. Indeed, one can consider the optimization of proteins by biological evolution to be a selection of sequences which minimizes the energy of the heteropolymer in a particular conformation [6], which on the level of mean-field calculations, is formally identical to imprinting [7, 8]. Therefore, these results can be interpreted in terms of possible biological or prebiological evolutionary mechanisms. Indeed, in terms of biological evolution, one can consider many forms of external fields whose effects nature would like to incorporate in the native conformation of a given enzyme or antibody. Furthermore, due to its minimal requirements and simple design scheme, imprinting has been proposed as a mechanism for prebiotic evolution [7, 8]; one may speculate that the monomer soup of the primordial earth was an *in vivo* imprinting-like experiment, in which primitive ligands acted as external

fields, allowing the creation of heteropolymers capable of biological-like functions, such as molecular recognition.

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