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Effect of Loop Entropy on the Helix–Coil Transition of α-Helical, Two-Chain, Coiled Coils. 2. Supermatrix Formulation of the Perfect-Matching Model

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ABSTRACT: The loops-excluded model of the α-helix to random coil transition of α-helical, two-chain, coiled coils (dimers) in which loop entropy acts to produce a single interacting helical stretch in the dimer has been reformulated in terms of the supermatrix method of Jernigan and Flory. It is demonstrated that the loops-excluded model is a member of the class of nearest-neighbor models. Serial matrix product expressions for the internal partition function of the dimer, Z_{sd}, the overall helix content, f_{hd}, the helix probability profiles, and the ratio, R_{d}, of the number of residues that are part of randomly coiled runs at the chain ends to the total number of random coils are derived. The supermatrix method is demonstrated to possess none of the numerical instabilities of our previously developed extension of the Poland recursion relation method to two-chain, coiled coils. Application of the supermatrix formalism to homopolymers demonstrates that all the conclusions of the loops-excluded model based on the recursion relation method remain unchanged. In the limit that R_{d} lies near unity, the neglect-loop-entropy theory (in which loop entropy is entirely ignored) and the loops-excluded model are identical. When R_{d} is significantly less than one, loop entropy makes the helix–coil transition more cooperative; thus values of the helix–helix interaction parameter w extracted from experiment and employing the neglect-loop-entropy theory may be significantly in error, overestimating the helix–helix interaction at high helix content and underestimating it at low helix content.

I. Introduction

In a previous work (hereafter designated paper I), using a modification of Poland's recursion relation method,[1] the theory of the α-helix to random coil transition in two-chain, coiled coils was extended to include the effect of loop entropy.[2] The important qualitative conclusion that emerges from the study is that in two-chain, coiled coils (dimers) of short to moderate length, the entropic cost of forming interior random coil loops between interacting helical stretches is so prohibitive as to eliminate them entirely. Thus, there is a single interacting helical stretch in the dimer, perhaps preceded or followed by noninteracting helical stretches punctuated by interior random coil sequences. The model that possesses these features is called the "loops-excluded model". While the qualitative conclusions are correct, certain numerical instabilities inherent in the recursion relation method as modified and applied to two-chain, coiled coils were found. In this paper we present an alternative matrix method that not only eliminates these numerical instabilities but is computationally faster, and we also, and much more importantly, demonstrate that the loops-excluded model is a nearest-neighbor interaction model, thus enabling us to employ matrix techniques developed previously.[2–4] The matrix method will be applied to homopolymeric, two-chain, coiled coils and compared with calculations made via the Poland recursion relation method and with the neglect-loop-entropy theory.

As a detailed discussion and justification of the underlying physical ideas that form the basis of the loops-excluded model has been given previously, we refer the reader to paper I, with particular emphasis on sections I and V. We content ourselves here with a brief review of the salient features of the helix–helix interaction.

The α-helical, two-chain, coiled coil tropomyosin is known to have a quasi-repeating heptet in the primary sequence that has been designated by the letters "a–g".[5–8] Positions "a" and "d" are almost always occupied by hydrophobic residues; position "e" is almost always anionic and position "g" cationic. The interaction of the hydrophobic residues "a" and "d" with their hydrophobic counterparts on the adjacent chain, "a′" and "d′", respectively, and the possible salt bridge formation of residues "e" and "g" with "g′" and "e′", respectively, on the adjacent chain are believed to be responsible for the greatly enhanced helix content of the dimer relative to the isolated single chains, i.e., monomers (the latter calculated from Zimm–Bragg helix–coil transition theory[9] using the σ and s values as determined by Scheraga et al.[10–23]). To incorporate the essential physics of the interaction into the theory, the two-chain, coiled coil is divided into alternating four- (a–d) and three-residue blocks (e–g) and treated by the coarse-graining method originally developed by Crothers and Kallenbach.[24] Thus we require that residues "a–d" (or "e–g") be in the all-helical state on both chains to effect the enhanced stability characterized by a parameter w. Thus, the coarse graining is not, as in the case of DNA, an approximation employed to simplify the calculations; rather it is a statement of the fundamental physics of the interaction.

Two problems are encountered when Poland's recursion relation method is applied to two-chain, coiled coils, and

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these arise whether or not loop entropy is included in the helix–coil transition theory. We should point out that neither has an effect on the qualitative conclusions of paper I but could lead to difficulties if quantitative results are desired. The first problem arises due to the magnitude of the values of the Zimm–Bragg helix initiation parameter σ.[9] The second problem, minor compared with the first, arises due to the requirement of coarse graining. We shall discuss the specific nature of each of the two problems in further detail below.

For single poly(amino acid) chains (or equivalently DNA-type helices) in the Zimm–Bragg approximation, Poland has pointed out that the original recursion relation method has instabilities when σ is very small and has given an alternative formulation to eliminate these numerical instabilities.[1] Unfortunately, in two-chain, coiled coils (in the neglect-loop-entropy model and in the loops-excluded model), the initiation parameter for two α-helices is of order σ^2, a number typically on the order of 10^{-7}, and we have encountered similar instabilities as seen in the single-chain poly(amino acid) case. Moreover, inclusion of loop entropy into the theory produces correlations of order N and Poland's alternative formulation cannot be directly employed. The instability is manifested as a minimum in the plot of the helix content of the dimer, f_{hd}, vs. w, the helix–helix interaction parameter, in the loops-excluded model (see Figure 2, curve B). This is a clearly nonphysical result; f_{hd} must be a monotonically increasing function of w. At sufficiently small values of σ, say 10^{-5}, this nonphysical minimum is also seen in calculations using the neglect-loop-entropy model employing our modification of Poland's recursion relation method for homopolymers containing identical blocks of size m equal to one and four, respectively. On the other hand, f_{hd} vs. w plots obtained from the original neglect-loop-entropy theory based on a matrix method are monotonically increasing functions of w. Thus, if quantitative results for f_{hd} vs. w are to be obtained, an alternative formulation for two-chain, coiled coils is required.

There is an additional problem that is inherent in the modified Poland recursion relation method as adapted by us to include coarse graining. This second problem arises at larger values of σ, say 10^{-3}, where the above effect is absent. The Poland technique relies on the calculation of the conditional probability that block $i + 1$ is helical given that block i is helical. However, imposition of coarse graining introduces random coil states in interfacial helical blocks. These random coil states are somewhat incorrectly handled by the modified Poland recursion relation method. In the case of the neglect-loop-entropy theory, differences in the helix content arise in the third significant figure as compared to the matrix calculation. Thus while the original recursion relation method as developed by Poland is very useful for DNA-type helices or single poly(amino acid) chains, an alternative technique is desirable for the case of two-chain, coiled coils of short to moderate length. We develop such a technique in the remainder of this paper.

In section II, we shall develop the matrix method of the loops-excluded model. Serial matrix products for the internal partition function of the dimer, Z_{sd} are presented, whereupon it will be immediately apparent that the loops-excluded model is really a nearest-neighbor model. Furthermore, expressions for the helix content of the dimer, f_{hd}, for the helix probability profiles, and for the fraction, R_{d}, of randomly coiled blocks that propagate from the ends are given. In section III we apply the matrix formulation to a hypothetical, homopolymeric, two-chain, coiled coil and calculate f_{hd} and R_{d} vs. w. We compare the results of the present method with the results of the neglect-loop-entropy theory as well as the loops-excluded model calculated with the modified Poland recursion relation method. Section IV summarizes the conclusions of the work and points out possible directions of future research.

II. Supermatrix Formulation of the Loops-Excluded Model

In the following we shall treat a parallel, in-register heteropolymeric, two-chain, coiled coil composed of identical chains. Each chain is made of N_{T} residues divided into N blocks, the ith block of which contains m_i residues. Hence, as previously, we are employing the perfect-matching model. Let H (C) represent a helical (random coil) block, i.e., a block whose m_i residues are in the helical (random coil) conformation, and let [C]H and [H]C represent helical and random coil blocks at the interface between a sequence of coil and helical blocks and between helical and random coil blocks, respectively. For an isolated single poly(amino acid) chain the statistical weights of the various conformations accessible to the ith block are

$$\begin{array}{ll} \text{conformation} & \text{statistical weight} \\ \text{[C]C} & 1 \\ \text{[C]H} & \tau_i = \sum_{j=1}^{m_i} \sigma_j \prod_{k=j}^{m_i} s_k \\ \text{[H]H} & \mathrm{SM}_i = \prod_{j=1}^{m_i} s_j \\ \text{[H]C} & \mathcal{S}_i = 1 + \sum_{j=1}^{m_i-1} \prod_{k=1}^{j} s_k \end{array} \tag{II-1}$$

wherein σ_j and s_j are the standard Zimm–Bragg helix initiation and propagation parameters for the jth amino acid.[9]

In the following we shall require w, the helix–helix interaction parameter. w is the ratio of the statistical weight of the interacting side-by-side pair of translationally localized helical blocks in the two-chain, coiled coil to the statistical weight of the translationally localized, noninteracting pair of helical blocks in the noninteracting (isolated) single chains. Thus w is the parameter that accounts for the interhelical interactions presumably responsible for the experimentally observed greatly enhanced stability of the helical conformation in α-helical, two-chain, coiled coils relative to the fairly low (<25%), theoretically calculated helix content of the isolated single chains.[25]

It should be pointed out that we have assumed the two chains in the dimer are identical for convenience only; extension to nonidentical chains is straightforward.

Calculation of the Internal Partition Function. The internal partition function of the dimer Z_{sd} in the loops-excluded model is given by

$$\begin{aligned} Z_{\mathrm{sd}} = {} & 2Z_{\mathrm{m}} - 1 + \\ & \sum_{l=1}^{N-1} \Big[\Big\{ \sum_{n=0}^{N-l-1} \mathcal{J}^* \prod_{i=1}^{n} \mathbf{U}_{\mathrm{d}i} \mathbf{U}_{\mathrm{CH}n+1} \prod_{i=2}^{l} \mathbf{U}_{\mathrm{HH}n+i} \mathbf{U}_{\mathrm{HC}n+l+1} \prod_{i=n+l+2}^{N} \mathbf{U}_{\mathrm{d}i} \mathcal{J} \Big\} + \\ & \quad \mathcal{J}^* \prod_{i=1}^{N-l} \mathbf{U}_{\mathrm{d}i} \mathbf{U}_{\mathrm{CH}N-l+1} \prod_{i=2}^{l} \mathbf{U}_{\mathrm{HH}N-l+i} \mathcal{J} \Big] + \tau_1^{\,2} \prod_{i=2}^{N} \mathrm{SM}_i^{\,2} w^N \end{aligned} \tag{II-2}$$

with Z_{m} the partition function of a noninteracting single chain, $\mathcal{J}^*$ = row (1,0,0,0), and $\mathcal{J}$ = col (1,1,1,1). The $2Z_{\mathrm{m}} - 1$ term accounts for the contribution to Z_{sd} of all those sequences in which one of the two chains is randomly coiled. It is included to ensure the correct normalization of the free energy consistent with the standard convention for s and thereby gives the correct behavior for the helix content in the limit of zero helix. Furthermore, the sum over l sums all possible lengths of the single interacting helical conformation in the molecule, except for the completely helical conformation accounted for by ${\tau_1}^2\prod_{i=2}^{N}\mathrm{SM}_i{}^2w^N$. The sum over n sums over the statistical weights of the l interacting helical block pairs. The n = 0 term places the l interacting block pairs at the end of the dimer, starting at block 1 and extending to block l (the "left end"). The subsequent terms move the l interacting block pairs to the right (increasing block number) until the l interacting block pairs are located at blocks $N - l$ to $N - 1$ (near the "right end"). The second set of matrix products sums the statistical weights of all sequences having the l interacting block pairs extending from residues $N - l + 1$ to N, i.e., at the right end of the dimer.

In eq II-2, $\mathbf{U}_{\mathrm{d}i}$ is the statistical weight matrix of noninteracting block pairs "i" in the dimer and is given by

$$\mathbf{U}_{\mathrm{d}i} = \mathbf{U}_{\mathrm{m}1} \otimes \mathbf{U}_{\mathrm{m}2} \tag{II-3a}$$

in which ⊗ denotes the direct product and

$$\mathrm{U}_{\mathrm{m}j} = \begin{bmatrix} 1 & \tau_i \\ \mathscr{S}_i & \mathrm{SM}_i \end{bmatrix}_j \tag{II-3b}$$

is the statistical weight matrix of noninteracting block "i" on chain j. Thus $\mathbf{U}_{\mathrm{d}i}$ is the statistical weight of the noninteracting ith block pair in the dimer.

$\mathbf{U}_{\mathrm{CH}i}$ in eq II-2 is the statistical weight matrix of the ith block pair that is helical and interacting and located at the interface between the noninteracting part of the molecule (blocks 1 to $i - 1$) and the parallel, in-register, helical part of the molecule (block pairs i to $i + l - 1$ in an l interacting helical block pair conformation).

$$\mathrm{U}_{\mathrm{CH}i} = \left[\begin{array}{c:cc} \bigcirc & 0 & \tau^2 w \\ & 0 & \tau\mathrm{SM}w \\ \hdashline \bigcirc & 0 & \tau\mathrm{SM}w \\ & 0 & 0 \end{array}\right]_i \tag{II-4}$$

$\bigcirc$ is a null 2 × 2 statistical weight matrix. $\mathbf{U}_{\mathrm{CH}i}$ may be thought of as the "initiation matrix" for an interacting helical block pair.

$\mathbf{U}_{\mathrm{HH}i}$ in eq II-2 is the statistical weight matrix of the jth interacting, helical block pair, with $i < j \le i + l - 1$, i.e., an interacting helical bock pair not on the "left" boundary of the l block pair interacting helical stretch. $\mathbf{U}_{\mathrm{HH}i}$ acts as a propagation matrix for interacting block pairs and is defined by

$$\mathrm{U}_{\mathrm{HH}i} = \left[\begin{array}{c:cc} \bigcirc & \multicolumn{2}{c}{\bigcirc} \\ \hdashline \bigcirc & 0 & 0 \\ & 0 & \mathrm{SM}^2 w \end{array}\right]_i \tag{II-5}$$

Finally, in eq II-4 and eq II-5 (see below) while we have written w as being site dependent, we shall in all calculations presented below employ a uniform site-independent w as was done previously. (In tropomyosin, Tm, based on fragment data,[26] w may in fact be region dependent.[27])

$\mathbf{U}_{\mathrm{HC}}$ in eq II-2 is the statistical weight matrix of the block following the l interacting helical blocks. Since loop entropy acts to exclude interior random coil sequences between interacting helical stretches of the dimer, block pair $i + l$ must contain at least one randomly coiled block. Hence

$$\mathrm{U}_{\mathrm{HC}i} = \left[\begin{array}{cc:cc} \multicolumn{2}{c}{\bigcirc} & \multicolumn{2}{c}{\bigcirc} \\ \hdashline 0 & 0 & 0 & 0 \\ \mathscr{S}_1\mathscr{S}_2 & \mathscr{S}_1\mathrm{SM}_2 & \mathscr{S}_2\mathrm{SM}_1 & 0 \end{array}\right]_i \tag{II-6}$$

where the subscripts label the statistical weight appropriate to the state of the block $i + l$ on chains one and two, respectively. It is convenient to view $\mathbf{U}_{\mathrm{HC}}$ as the "termination matrix" of the interacting helical stretch.

Several remarks are in order on the nature of the conformational states that are included in the loops-excluded model (eq II-2) as compared to the neglect-loop-entropy theory (see eq II-4 of paper I). In the original, neglect-loop-entropy theory, the internal partition function, ${Z_{\mathrm{sd}}}^0$, is constructed as the direct product of the two monomer statistical weight matrices, eq II-3b, times a statistical weight matrix that enhances the statistical weight of an H(1)H(2) pair by a factor w^0 (superscript zero is employed in the following to denote a quantity calculated in the neglect-loop-entropy theory). At low helix content and for very small values of σ, ${Z_{\mathrm{sd}}}^0$ contained an appreciable contribution from states in the dimer possessing no interacting helical block pairs whatsoever. Such states do not in fact belong in the dimer internal partition function. (These states are unimportant in the limit of high helix content.) Thus more correctly, in the loops-excluded model, apart from the all random coil state on each chain, we require that there be at least a single interacting helical block pair in the dimer. Thus, in the limit of low helix content, $Z_{\mathrm{sd}} < {Z_{\mathrm{sd}}}^0$. On the other hand, eq II-2 contains a larger number of states that are important at moderately low helix (and for w near one) that are absent in the neglect-loop-entropy theory. Hence, in the moderately low helix content regime at a given w near unity, the partition function and helix content in the loops-excluded model are larger than in the neglect-loop-entropy theory. (See also paper I, section IV.) A final effect occurs as w increases. Since the loops-excluded model excludes interior C(1)C(2)- and C(1)H(2)-type random coil states between interacting helical portions of the dimer, at high helix content, ${Z_{\mathrm{sd}}}^0 > Z_{\mathrm{sd}}$. Furthermore, the helix to random coil transition is more cooperative in the loops-excluded model than the neglect-loop-entropy model. Hence it is apparent that the relative magnitudes of Z_{sd} and ${Z_{\mathrm{sd}}}^0$ (and equivalently the dimer helix content) are the result of an interplay of various effects.

Equation II-2 contains $(N)(N + 1)/2$ terms, each of which requires on the order of $28N$ distinct multiplication and addition operations. As written, eq II-2 would consume sufficiently large amounts of computer time for reasonable values of N as to make interactive programing for all practical purposes impossible on computers such as the IBM 370/158. Thus in order to make the problem computationally tractable an alternative formulation of eq II-2 is required.

Consider, in fact, the five kinds of conformational states accessible to a given block pair on the two chains in a dimer. (1) It can be a noninteracting block pair to the left of the interacting helical state and having statistical weight matrix $\mathbf{U}_{\mathrm{d}i}$. (2) It can be an interacting helical block at a "left" interface between the interacting and noninteracting block pairs, i.e., an initiating block pair with statistical weight matrix $\mathbf{U}_{\mathrm{CH}}$. (3) It can be an interacting helical block pair not at the left interface, i.e., a propagating, interacting helical block pair with associated statistical weight matrix $\mathbf{U}_{\mathrm{HH}}$. (4) It can be a noninteracting block at a "right" interface, i.e., a terminating pair with statistical weight matrix $\mathbf{U}_{\mathrm{HC}}$. (5) It may be a noninteracting sequence to the right of the interacting helical sequence with statistical weight matrix $\mathbf{U}_{\mathrm{d}}$. In all five of the possible cases, the block pairs experience only nearest-neighbor interactions. Thus, in fact, we have a nearest-neighbor model,[28] and the statistical states accessible to the ith block must be expressible as a single statistical weight matrix.

In fact, the statistical weight matrix associated with the ith block pair is

$$\mathbf{U}_{\mathrm{s}i} = \left[\begin{array}{c|c|c} \mathbf{U}_{\mathrm{d}i} & \mathbf{U}_{\mathrm{CH}i} & \bigcirc \\ \hline \bigcirc & \mathbf{U}_{\mathrm{HH}i} & \mathbf{U}_{\mathrm{HC}i} \\ \hline \bigcirc & \bigcirc & \mathbf{U}_{\mathrm{d}i} \end{array}\right]_i \qquad \text{(II-7)}$$

$\mathbf{U}_{\mathrm{s}}$ is a partitioned 12 × 12 matrix in which $\bigcirc$ is a 4 × 4 null matrix. $\mathbf{U}_{\mathrm{d}}$ in the top left-hand corner is the statistical weight matrix associated with a noninteracting block pair to the left of the interacting helical stretch in the dimer, and $\mathbf{U}_{\mathrm{d}}$ in the bottom right-hand corner is the statistical weight matrix associated with the noninteracting block pair to the right of the interacting helical stretch in the dimer. Thus the loops-excluded model is expressible as a nearest-neighbor interaction model as is the original neglect-loop-entropy theory.

The internal partition function in the loops-excluded model is readily expressible as a serial matrix product as follows:

$$Z_{\mathrm{sd}} = 2Z_{\mathrm{m}} - 1 + \mathbf{J}^{*}\prod_{i=1}^{N}\mathbf{U}_{\mathrm{s}i}\mathbf{J} \qquad \text{(II-8)}$$

with $\mathbf{J}^{*}$ = row (1,0,0,0,0,0,0,0,0,0,0,0) and $\mathbf{J}$ = col (0,0,0,0,1,1,1,1,1,1,1,1). Hence the serial matrix product summation is identical with the terms to the right of $2Z_{\mathrm{m}} - 1$ in eq II-2. Z_{m} is conveniently obtained from the serial matrix product of eq II-8 by

$$Z_{\mathrm{m}}^{2} = \mathbf{J}^{*}\prod_{i=1}^{N}\mathbf{U}_{\mathrm{s}i}\mathbf{J}' \qquad \text{(II-9)}$$

where $\mathbf{J}'$ = col (1,1,1,1,0,0,0,0,0,0,0,0). This is true since the upper left-hand corner of the serial matrix product is merely the product of the $\mathbf{U}_{\mathrm{d}i}$.

In addition to being conceptually clearer, eq II-8 greatly enhances the computational speed at which the program is executed. In fact, the more realistic loops-excluded model is merely 9 times slower than the original neglect-loop-entropy calculation (eq II-4 of paper I). On the computer system available to us for N on the order of 71 and $m = 4$, the calculation is essentially instantaneous.

At this juncture it should be pointed out that there is also a serial matrix product expression that is equivalent to the sum over n in eq II-2 and reduces the evaluation of Z_{sd} from a double sum over matrix products to a single sum over l. While we have numerically verified the equivalence of this single-sum serial product expression to eq II-2 and to eq II-8, it is not particularly useful and we will not present it here.

Calculation of the Helix Content. With eq II-8 in hand we need merely follow the general technique of Flory[3] and Jernigan[4] to obtain the overall helix content of the dimer, f_{hd}. It immediately follows from eq II-8 that

$$f_{\mathrm{hd}} = \frac{f_{\mathrm{hm}}Z_{\mathrm{m}}}{Z_{\mathrm{sd}}} + \frac{\mathbf{J}_{\mathrm{s}}^{*}\prod_{i=1}^{N}\mathbf{A}_{\mathrm{s}i}\mathbf{J}_{\mathrm{s}}}{N_{\mathrm{T}}Z_{\mathrm{sd}}} \qquad \text{(II-10)}$$

where f_{hm} is the helix content of an isolated single chain. $\mathbf{J}_{\mathrm{s}}^{*}$ is a row vector consisting of one followed by 23 zeros, and $\mathbf{J}_{\mathrm{s}}$ is a column vector of 16 zeros followed by 8 ones. In addition, $\mathbf{A}_{\mathrm{s}i}$ is a partitioned 24 × 24 matrix defined by

$$\mathbf{A}_{\mathrm{s}i} = \left[\begin{array}{c|c} \mathbf{U}_{\mathrm{s}i} & \mathbf{U}'_{\mathrm{s}i} \\ \hline \bigcirc & \mathbf{U}_{\mathrm{s}i} \end{array}\right] \qquad \text{(II-11a)}$$

wherein $\mathbf{U}_{\mathrm{s}}$ has been defined in eq II-7 and $\mathbf{U}_{\mathrm{s}}'$ is a 12 × 12 matrix given by

$$\mathbf{U}'_{\mathrm{s}i} = \left[\begin{array}{c|c|c} \mathbf{U}'_{\mathrm{d}i} & \mathbf{U}'_{\mathrm{CH}i} & \bigcirc \\ \hline \bigcirc & \mathbf{U}'_{\mathrm{HH}i} & \mathbf{U}'_{\mathrm{HC}i} \\ \hline \bigcirc & \bigcirc & \mathbf{U}'_{\mathrm{d}i} \end{array}\right] \qquad \text{(II-11b)}$$

in which

$$\mathbf{U}'_{\mathrm{d}i} = \begin{bmatrix} 0 & \tau' \\ \mathscr{S}' & m\mathrm{SM} \end{bmatrix}_i \otimes \mathbf{U}_{\mathrm{m}_2} \qquad \text{(II-11c)}$$

where τ' and $\mathscr{S}'$ have been defined in eq 31a and eq 31c of ref 29. Moreover

$$\mathbf{U}'_{\mathrm{CH}i} = \left[\begin{array}{c|cc} \bigcirc & 0 & \tau'\tau w \\ & 0 & \tau'\mathrm{SM}w \\ \hline \bigcirc & 0 & m\mathrm{SM}\tau w \\ & 0 & 0 \end{array}\right]_i \qquad \text{(II-11d)}$$

and

$$\mathbf{U}'_{\mathrm{HH}i} = \left[\begin{array}{c|cc} \bigcirc & \multicolumn{2}{c}{\bigcirc} \\ \hline \bigcirc & 0 & 0 \\ & 0 & m\mathrm{SM}^{2}w \end{array}\right]_i \qquad \text{(II-11e)}$$

Finally

$$\mathbf{U}'_{\mathrm{HC}i} = \left[\begin{array}{cc|cc} \multicolumn{2}{c|}{\bigcirc} & \multicolumn{2}{c}{\bigcirc} \\ \hline 0 & 0 & 0 & 0 \\ \mathscr{S}'_{1}\mathscr{S}_{2} & \mathscr{S}'_{1}\mathrm{SM}_{2} & m\mathrm{SM}_{1}\mathscr{S}_{2} & 0 \end{array}\right]_i \qquad \text{(II-11f)}$$

The helix content of the monomer is also contained in the serial matrix product $\prod_{i=1}^{N}\mathbf{A}_{\mathrm{s}i}$ and may be calculated as follows:

$$f_{\mathrm{hm}} = \frac{\mathbf{J}_{\mathrm{s}}^{*}\prod_{i=1}^{N}\mathbf{A}_{\mathrm{s}i}\mathbf{J}_{\mathrm{s}m}}{N_{\mathrm{T}}Z_{\mathrm{m}}^{2}} \qquad \text{(II-12)}$$

where $\mathbf{J}_{\mathrm{sm}}$ is a column vector of 12 zeros, followed by 4 ones, followed by 8 zeros.

Calculation of the Helix Probability Profiles. The probability that the jth block is helical, $f_{\mathrm{hd}}(j)$, is simply obtained from

$$f_{\mathrm{hd}}(j) = \frac{Z_{\mathrm{m}}f_{\mathrm{hm}}(j)}{Z_{\mathrm{sd}}} + \frac{\mathbf{J}^{*}\prod_{i=1}^{j-1}\mathbf{U}_{\mathrm{s}i}\mathbf{U}'_{\mathrm{s}j}\prod_{i=j+1}^{N}\mathbf{U}_{\mathrm{s}i}\mathbf{J}}{m_{j}Z_{\mathrm{sd}}} \qquad \text{(II-13)}$$

$f_{\mathrm{hm}}(j)$ is the probability that the jth block is helical in the isolated single chain, with m_j the number of residues in the jth block. $\mathbf{U}_{\mathrm{s}i}$ is given by eq II-7 and $\mathbf{U}'_{\mathrm{s}i}$ is given by eq II-11b. Furthermore, $f_{\mathrm{hm}}(j)$ may be obtained from the serial matrix product of eq II-13 by

$$f_{\mathrm{hm}}(j) = \frac{\mathbf{J}^* \prod_{i=1}^{j-1} \mathbf{U}_{\mathrm{s}i} \mathbf{U}'_{\mathrm{s}j} \prod_{i=j+1}^{N} \mathbf{U}_{\mathrm{s}i} \mathbf{J}'}{m_j Z_{\mathrm{m}}^{\,2}} \qquad \text{(II-14)}$$

The factor $Z_{\mathrm{m}}^{\,2}$ appears in the denominator of eq II-14 because the numerator divided by Z_{m} is the average number of residues that are helical in block j on one of the two identical chains times the partition function of the isolated second chain. Thus the numerator of eq II-14 when divided by $m_j Z_{\mathrm{m}}^{\,2}$ gives $f_{\mathrm{hm}}(j)$, the quantity of interest.

Fraction of Random Coiled Blocks in the Terminal Sequences. Let N_{ERS} be the average number of random coil blocks located in random coil sequences. Then the fraction of blocks that are both randomly coiled and that propagate from an end in the two-chain coiled coil is given by

$$f_{\mathrm{dce}} = N_{\mathrm{ERS}}/N \qquad \text{(II-15)}$$

Following the analogous treatment as that given for the fraction of end coils, $f_{\mathrm{dce}}{}^0$, in the neglect-loop-entropy model (see section III of paper I), we have in the loops-excluded model

$$f_{\mathrm{dce}} = \frac{Z_{\mathrm{m}}(1 + f_{\mathrm{mce}}) - 1}{Z_{\mathrm{sd}}} + \frac{\mathbf{J}_{\mathrm{s}}{}^* \prod_{i=1}^{N} \mathbf{A}_{\mathrm{fs}i} \mathbf{J}_{\mathrm{s}} + \mathbf{J}_{\mathrm{s}}{}^* \prod_{i=1}^{N} \mathbf{A}_{\mathrm{bs}i} \mathbf{J}_{\mathrm{s}}}{N Z_{\mathrm{sd}}} \qquad \text{(II-16)}$$

where f_{mce} is the fraction of random coil blocks in terminal sequences in an isolated single chain and can be calculated from eq III-13 to III-16b of paper I. We present next a method more convenient for the present purpose. The matrix product of the $\mathbf{A}_{\mathrm{fs}i}$ ($\mathbf{A}_{\mathrm{bs}i}$) generates the contribution of f_{dce} of those random coil sequences that unwind from the left (right) end of the molecule. $\mathbf{A}_{\mathrm{fs}i}$ is a partitioned 24 × 24 matrix defined by

$$\mathrm{A}_{\mathrm{fs}i} = \left[\begin{array}{c|c} \mathrm{U}_{\mathrm{fs}i} & \mathrm{U}_{\mathrm{fs}i} \\ \hline \bigcirc & \mathrm{U}_{\mathrm{s}i} \end{array}\right] \qquad \text{(II-17a)}$$

with $\mathbf{U}_{\mathrm{s}i}$ given by eq II-7 and $\mathbf{U}_{\mathrm{fs}i}$ a 12 × 12 matrix of the form

$$\mathrm{U}_{\mathrm{fs}i} = \left[\begin{array}{c|c|c} \mathrm{U}_{\mathrm{fd}i} & \mathrm{U}_{\mathrm{fCH}i} & \bigcirc \\ \hline \bigcirc & \bigcirc & \bigcirc \\ \hline \bigcirc & \bigcirc & \bigcirc \end{array}\right] \qquad \text{(II-17b)}$$

$\bigcirc$ is a 4 × 4 null matrix, and with

$$\mathrm{U}_{\mathrm{fd}i} = \begin{bmatrix} 1 & \tau_p \\ 0 & 0 \end{bmatrix} \otimes \begin{bmatrix} 1 & \tau \\ \mathcal{S} & \mathrm{SM} \end{bmatrix}_i \qquad \text{(II-17c)}$$

and

$$\tau_p = \sum_{j=1}^{m_i} \frac{j-1}{m_i} \sigma_j \prod_{k=j}^{m_i} s_k \qquad \text{(II-17d)}$$

Finally

$$\mathrm{U}_{\mathrm{fCH}i} = \left[\begin{array}{c|cc} \bigcirc & 0 & \tau_p \tau w \\ & 0 & \tau_p \mathrm{SM} w \\ \hline \bigcirc & \multicolumn{2}{c}{\bigcirc} \end{array}\right]_i \qquad \text{(II-17e)}$$

In a similar fashion $\mathbf{A}_{\mathrm{bs}i}$ is a partitioned matrix of dimension 24 × 24 and is given by

$$\mathrm{A}_{\mathrm{bs}i} = \left[\begin{array}{c|c} \mathrm{U}_{\mathrm{s}i} & \mathrm{U}_{\mathrm{bs}i} \\ \hline \bigcirc & \mathrm{U}_{\mathrm{bs}i} \end{array}\right] \qquad \text{(II-18)}$$

where $\mathbf{U}_{\mathrm{s}i}$ is defined in eq II-7 and $\mathbf{U}_{\mathrm{bs}i}$ is a 12 × 12 matrix of the form

$$\mathrm{U}_{\mathrm{bs}i} = \left[\begin{array}{c|c|c} \bigcirc & \bigcirc & \bigcirc \\ \hline \bigcirc & \bigcirc & \mathrm{U}_{\mathrm{bHC}i} \\ \hline \bigcirc & \bigcirc & \mathrm{U}_{\mathrm{bd}i} \end{array}\right] \qquad \text{(II-19a)}$$

in which

$$\mathrm{U}_{\mathrm{bHC}i} = \left[\begin{array}{cc|c} \multicolumn{2}{c|}{\bigcirc} & \bigcirc \\ \hline 0 & 0 & \\ \mathcal{S}_p \mathcal{S}_2 & \mathcal{S}_p \mathrm{SM}_2 & \bigcirc \end{array}\right]_i \qquad \text{(II-19b)}$$

with

$$\mathcal{S}_p = 1 + \sum_{j=1}^{m_i - 1} \frac{m_i - j}{m_i} \prod_{k=1}^{j} s_k \qquad \text{(II-19c)}$$

and

$$\mathrm{U}_{\mathrm{bd}i} = \begin{bmatrix} 1 & 0 \\ \mathcal{S}_p & 0 \end{bmatrix} \otimes \begin{bmatrix} 1 & \tau \\ \mathcal{S} & \mathrm{SM} \end{bmatrix}_i \qquad \text{(II-19d)}$$

By extracting the appropriate terms from the serial matrix products in eq II-16, we can also obtain f_{mce}. Namely

$$f_{\mathrm{mce}} = \frac{\mathbf{J}_{\mathrm{s}}{}^* \prod_{i=1}^{N} \mathbf{A}_{\mathrm{fs}i} \mathbf{J}_{\mathrm{sm}} + \mathbf{J}_{\mathrm{bs}}{}^* \prod_{i=1}^{N} \mathbf{A}_{\mathrm{bs}i} \mathbf{J}_{\mathrm{bm}} - N Z_{\mathrm{m}}}{N Z_{\mathrm{m}}^{\,2}} \qquad \text{(II-20)}$$

$\mathbf{J}_{\mathrm{s}}{}^*$ and $\mathbf{J}_{\mathrm{sm}}$ are row and column vectors that have been defined following eq II-10 and II-12. $\mathbf{J}_{\mathrm{bs}}$ is a row vector, all of whose elements are zero, except for the ninth element, whose value is one. $\mathbf{J}_{\mathrm{bm}}$ is a column vector of 20 zeros followed by 4 ones. The reader will recognize that the expression in eq II-20 is identical with eq III-20 of paper I for $f_{\mathrm{dce}}{}^0$ when w^0 in the latter expression equals unity.

The quantity of interest in following the helix–coil transition in the dimer is not f_{dce} but R_{d}, the ratio of f_{dce} to the total fraction of blocks that are randomly coiled, f_{c}. $1 - f_{\mathrm{c}}$ may be obtained by replacing τ_i' and $\mathcal{S}_i'$ in eq II-11c, II-11d, and II-11f by τ_i'/m_i and $\mathcal{S}_i'/m_i$, respectively. Subsequent evaluation of the analogous expression to eq II-10 with N_{T} the number of residues replaced by N, the number of blocks, gives f_{bhd}, the fraction of blocks that are helical in the two-chain, coiled coil. Then

$$R_{\mathrm{d}} = f_{\mathrm{dce}}/(1 - f_{\mathrm{bhd}}) \qquad \text{(II-21))}$$

where f_{dce} is given by eq II-16. It should be pointed out that f_{bhd} is defined by

$$f_{\text{bhd}} = \sum_{j=1}^{N} f_{\text{hd}}(j)/N \qquad \text{(II-22a)}$$

with $f_{\text{hd}}(j)$ given in eq II-13. f_{hd}, the fraction of residues that are helical (eq II-10), is given by

$$f_{\text{hd}} = \sum_{j=1}^{N} m_j f_{\text{hd}}(j) \Big/ \sum_{j=1}^{N} m_j \qquad \text{(II-22b)}$$

In the case of a homopolymeric two-chain, coiled coil, eq II-22a and II-22b are identical, but for a heteropolymeric dimer they are not. The most significant differences between f_{hd} and f_{bhd} occur in fairly small chains and in which the number of residues in the blocks differs significantly. Such a situation occurs for some of the tropomyosin fragments prepared by Pato et al.[26] Calculations indicate that the differences between f_{hd} and f_{bhd} are rather small and are only important in the evaluation of R_{d}, where f_{bhd} should be used.

The results of this section may be summarized as follows: We have demonstrated that the loops-excluded model is in fact a nearest-neighbor interaction model. Using this insight, we have presented algorithms for the calculation of the internal partition function, the helix content, the helix probability profiles, and the fraction of the random coils that are in terminal random sequences of the two-chain, coiled coil, R_{d}. These algorithms are computationally compact and have the identical formal structure as algorithms presented in the original theory in which loop entropy was entirely ignored, i.e., the neglect-loop-entropy model.

III. Application of Loops-Excluded Model to Homopolymers

To verify the numerical equivalence of eq II-2 and II-8 for the internal partition function, we evaluated both expressions as a function of w for a homopolymeric, two-chain, coiled coil with $\sigma = 1 \times 10^{-3}$, $s = 0.94$, $N = 10$, and $m = 4$. Z_{sd} calculated via the two methods agreed to nine significant figures. Thus, we find satisfactory agreement between the two expressions for Z_{sd}.

We then proceeded to investigate the numerical stability of the matrix formulation of the loops-excluded model. We set $s = 0.94$, $N = 71$, and $m = 4$ (a homopolymer equivalent to tropomyosin in degree of polymerization and having the same geometric mean value of s)[2] and calculated Z_{sd} and f_{hd} for $\sigma = 10^{-7}$, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2}. Figure 1 shows plots of the f_{hd} values vs. w. For all values of σ chosen, Z_{sd} (not shown) and f_{hd} were found to be monotonically increasing functions of w, as they must be. No numerical instabilities, e.g., development of a minimum in either Z_{sd} or f_{hd}, were found. Since a value of $\sigma = 10^{-7}$ is about 2 orders of magnitude smaller than the smallest known σ (with the exception of proline) for all the poly(amino acids),[10-23] it is apparent that the matrix formulation of the loops-excluded model can be used with confidence.

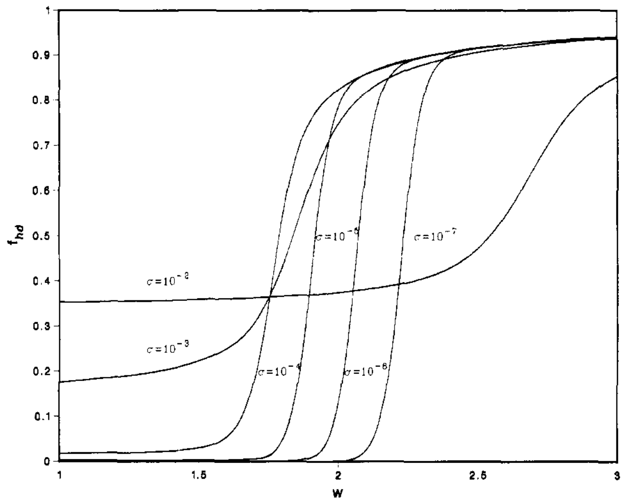

Figure 1. Plot of f_{hd} vs. w calculated with $\sigma = 10^{-7}$, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} for the loops-excluded model using the supermatrix formulation for a 284-residue, homopolymeric, α-helical, two-chain, coiled coil. In all cases $s = 0.94$, $N = 71$, and $m = 4$. The value of σ appropriate to the given curve is indicated in the figure.

The behavior of the various curves of Figure 1 can be rationalized as follows. Let us discuss the small-σ limit first, in which the transition is very cooperative. For $\sigma \leq 10^{-4}$ the fraction of random coils that are in terminal random coil sequences and calculated with the neglect of loop entropy, R_{d}^{0}, lies very near one. Thus when $\sigma = 10^{-4}$, helix content vs. w curves calculated in the loops-excluded model and the neglect-loop-entropy model are within a few percent of each other at moderate helix content and coalesce at higher helix content. Setting $\sigma = 10^{-6}$, the helix content vs. w curves calculated with and without the inclusion of loop entropy agree to three significant figures. This is in agreement with our previous observation that if R_{d}^{0} lies near unity the loops-excluded model and the neglect-loop-entropy model are equivalent. For $s = 0.94$ and σ very small, appreciable helix content can only arise due to the interhelical interaction. Thus the coil-to-helix transition reflects the growth of the single interacting helical stretch in the dimer. The large plateau region at small w reflects the entropic difficulties of aligning the two chains to produce the single interacting helical stretch (these sequences have a helix–helix initiation parameter σ^2). Increasing σ at a given w tends to increase the helix content at low helix and decrease the helix content at very high helix. Hence in the high-helix limit, the curves at larger values of σ must approach the curves at smaller values of σ from below. Although not visible on the scale of the figure, the f_{hd} curves at larger σ cross the smaller σ curves in the limit of high helix and do indeed approach the smaller σ, f_{hd} vs. w curves from below. The crossover point moves to smaller values of w with increasing values of σ. A similar qualitative effect is seen in isolated single homopolymeric chains.[3] Furthermore, note that the curves in the small-σ limit ($\sigma = 10^{-7}$–10^{-4}) tend to move in with increasing σ. This simply reflects the fact that in the short to moderate length limit and with a single interacting helical stretch per dimer the value of w necessary to induce helix formation decreases with increasing σ.

For a homopolypeptide chain, increasing σ from 10^{-4} to 10^{-3} produces a qualitatively different effect. Increasing σ has significantly changed the nature of the transition. (Even for a single isolated chain R_{m} has the value of 0.98 and 0.63 when $\sigma = 10^{-4}$ and 10^{-3}, respectively.) Below $\sigma \simeq 10^{-4}$, there are essentially no interior random coil sequences in the dimer, i.e., $R_{\text{d}} \simeq 1$, but above $\sigma \simeq 10^{-4}$, the number of interior random coil sequences (and the helix content) increases significantly. For example, while R_{d} increases to unity as w goes to infinity, it starts out as 0.17 and 0.57 at $w = 1$ when $\sigma = 10^{-2}$ and 10^{-3}, respectively. As usual, in the region of the high helix content f_{hd} must approach the helix content calculated at low σ from below. Hence the breadth of the entire transition increases with increasing σ and has become less cooperative.

In Figure 2 we have plotted f_{hd} vs. w for a homopolypeptide having $\sigma = 1.5 \times 10^{-3}$, $s = 0.94$, $N = 71$, and $m = 4$. Curve A (solid line) is for the neglect-loop-entropy model, curve B (dashed line) is for the loops-excluded

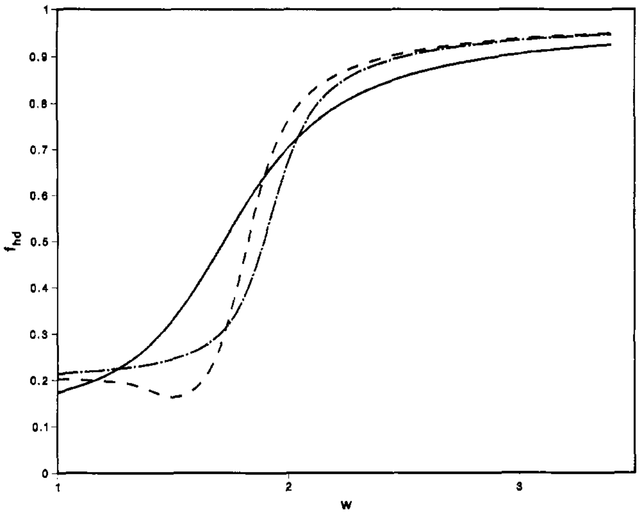

Figure 2. Curve A (solid line), $f_{\mathrm{hd}}{}^0$ vs. w for a homopolymeric, two-chain, coiled coil, in which loop entropy is ignored, the neglect-loop-entropy model. Curve B (dashed line), f_{hd} in the loops-excluded model, in which loop entropy produces a single interacting helical stretch, and calculated via the recursion relation method of paper I. Curve C (dot-dashed line), f_{hd} vs. w calculated using the supermatrix formulation of the loops-excluded model. In all cases $\sigma = 1.5 \times 10^{-3}$, $s = 0.94$, $N = 71$, and $m = 4$.

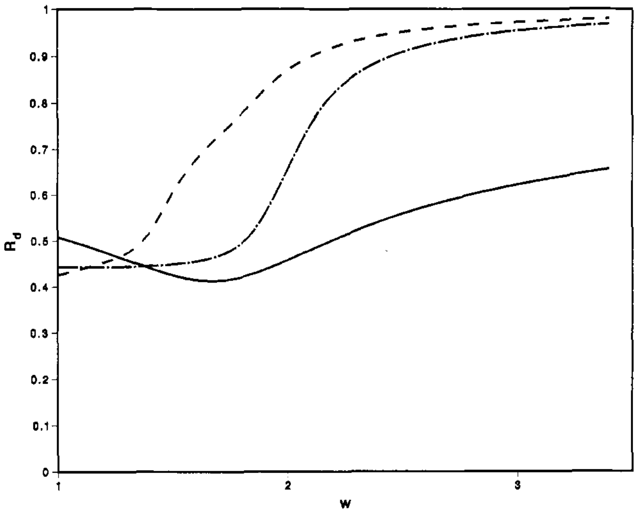

Figure 3. Curve A (solid line), $R_{\mathrm{d}}{}^0$ vs. w for a homopolymeric, two-chain, coiled coil, in which loop entropy is ignored, the neglect-loop-entropy model. Curve B (dashed line), R_{d} vs. w in the loops-excluded model, in which loop entropy produces a single interacting helical stretch, and calculated via the recursion relation method of paper I. Curve C (dot-dashed line), R_{d} vs. w calculated using the supermatrix formulation of the loops-excluded model. In all cases $\sigma = 1.5 \times 10^{-3}$, $s = 0.94$, $N = 71$, and $m = 4$.

model using the recursion relation method of paper I, and curve C (dot-dashed line) is for the loops-excluded model using eq II-10. As mentioned previously, the minimum in f_{hd} vs. w is entirely absent in the matrix calculation. Observe that the f_{hd} vs. w curves calculated in the neglect-loop-entropy model (curve A) and the loops-excluded model (curve C) are substantially different. The neglect-loop-entropy model curve crosses the loops-excluded model curve twice. The low and high helix content crossovers occur for the same reasons responsible for the behavior of Z_{sd} and $Z_{\mathrm{sd}}{}^0$ mentioned in the discussion following eq II-6.

While it is apparent from Figure 2 that the value of w required to produce a given helix content differs between curves B and C, the probability profiles calculated in the two methods (i.e., using eq IV-20 to IV-25 of paper I and eq II-13 of this work) at a given overall helix content are indistinguishable on the scale of Figure 7 of paper I. Thus no new plots of helix probability profiles are presented in this work.

In Figure 3, we have plotted R_{d} vs. w. Curve A (solid line) is for the neglect-loop-entropy model, curve B (dashed line) is for the loops-excluded model using the modified recursion relation method, and curve C (dot-dashed line) is for the loops-excluded model using the matrix method. Observe that $R_{\mathrm{d}}{}^0$ (curve A) is significantly diminished from unity. It is precisely that deviation of $R_{\mathrm{d}}{}^0$ from unity (with the concomitant growth of random coil stretches between interacting helical blocks) that produces the differences in helix content vs. w curves calculated in the neglect-loop-entropy model and the loops-excluded model seen in Figure 2. As expected, R_{d} in the loops-excluded model increases monotonically with increasing w; this is true because beyond the low-helix plateau regime, the growth of the single interacting helical stretch is responsible for the increase in helix content. Significant differences between curves B and C are apparent.

We again emphasize, however, that all the qualitative conclusions of paper I emerge unscathed from this study. That is, (1) in the case of α-helical, two-chain, coiled coils of short to moderate length, the effect of loop entropy is so severe as to entirely eliminate randomly coiled regions between two interacting helical regions. Thus, beyond the plateau regime at low helix that reflects the entropic difficulty in producing the single interacting helical stretch, R_{d} is a monotonically increasing function of w. Hence the random coil to helix transition in the dimer involves the growth of the single interacting helical stretch. Finally, the requirement that there be one and only one interacting helical stretch in the dimer serves to raise the maximum in the helix probability profile relative to the profile calculated in the neglect-loop-entropy theory. (2) The helix–helix interaction parameter required to produce a given helix content may differ significantly when calculated from the neglect-loop-entropy model (denoted by w^0) compared with that from the loops-excluded model (denoted by w). In the low to moderate helix content regime we find that $w_0 \leq w$. On the other hand, in the moderately high to high helix regime $w^0 \geq w$. In short, loop entropy can exert an important influence on the character of the helix to random coil transition in two-chain, coiled coils.

IV. Conclusion

The loops-excluded model of the α-helix to random coil transition has been recast in terms of the supermatrix formulation of Jernigan and Flory.[3,4] The current matrix formulation has several advantages over our previously developed extension of Poland's recursion relation method. We discuss each of these in turn.

First of all it is readily apparent in the supermatrix formulation that the loops-excluded model is a member of the class of nearest-neighbor interaction models (in fact, the loops-excluded model for homopolymers is isomorphic with a one-dimensional, two-component spin Ising model, as is the neglect-loop-entropy theory[28]) and thereby the expressions for the partition function, the overall helix content of the dimer, the helix probability profile, and the fraction of random coils that occur in terminal sequences follow immediately from previously established matrix methods.[2-4] For α-helical molecules of short to moderate length, loop entropy reduces the statistical weight of random coils located between interacting helical stretches in the dimer essentially to zero. In the loops-excluded model, such interior random coil sequences are a priori set equal to zero. Thus all interactions are characterized by the helix initiation and propagation parameters characteristic of the individual poly(amino acids) and the helix–helix interaction parameter w that accounts for the interaction between helical blocks on adjacent chains, i.e., a nearest-neighbor model.

A second advantage of the supermatrix method over our modified recursion relation approach is the inherent numerical stability of the former as compared to the latter. Whereas the recursion relation method as extended by us to two-chain, coiled coils exhibits minima in the plots of calculated helix content and internal partition function as functions of w, the supermatrix method displays no such artifacts; both quantities are always monotonically increasing functions of w. Moreover, the matrix method is found to be faster on an IBM 370/158 than is the recursion relation method. (The matrix method requires computer time of $\mathcal{O}(N)$; the recursion relation method computer time varies as the square of the number of blocks, $\mathcal{O}(N^2)$). Clearly then, we regard the supermatrix formulation of the loops-excluded model as superceding our previous extension in paper I of Poland's recursion relation method. Nevertheless, we again emphasize that all the qualitative conclusions of the effect of loop on the helix–coil transition in two-chain, coiled coils given in paper I remain unchanged.

As a referee has noted, the loops-excluded model bears a strong resemblance to the one-helical-sequence matrix formulation for isolated single-chain poly(amino acids).[28] There are, however, several differences. In the two-chain, coiled-coil there is a *single interacting* helical region in the two chains that may be preceded and/or followed by additional noninteracting, α-helical stretches. In the one-sequence approximation as applied to isolated single-chain poly(amino acids), there is just one α-helical stretch perhaps preceded and/or followed by completely randomly coiled stretches. Thus while some aspects of the character of the helix–coil transitions in the two cases are similar, they are not identical.

As pointed out in the original paper of this series,[29] Mattice has developed a modification of Zimm–Bragg theory of single poly(amino acid) chains that better accounts for end effects in heteropolymers.[25] The loops-excluded model presented so far lacks this refinement but when viewed in the context of a nearest-neighbor model, extension to include a somewhat more realistic treatment of end effects based on the 3 × 3 matrix method of Mattice et al.[25] is straightforward and will be the subject of a future publication.

In the current paper we have developed the loops-excluded model in the perfect-matching approximation. That is, we have a priori assumed that those parts of the chains in the dimer that are both helical and interacting remain parallel and in-register throughout the course of the entire helix to random coil transition. While this is almost certainly true in the high helix content regime, it may not in fact be true in the transition region. In a future paper, we shall extend the loops-excluded model to include the effects of mismatching of the chains, i.e, of out-of-register dimers on the helix–coil transition.[28] Then, we will be in a position to apply the loops-excluded theory with all the statistical effects accounted for (loop entropy with and without mismatch) to extract $w(T)$ for tropomyosin and its various fragments.

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