APPENDIX A: SUPPLEMENTARY MATERIAL

As we see in Fig. 2, the hub of the algorithm is the M matrix. Matrix element M_j^i represents the best way to fold the prefixes $s[1..i]$ and $t[1..j]$ given that i and j are paired.

$$M_j^i = \min\{ M_{j-1}^{i-1} + \texttt{NN}(i,j), \tag{A1a}$$

$$\texttt{tstack}(i-1, j-1) + \Delta G_{\text{init}} + \Delta G_{AU/GU}(i,j), \tag{A1b}$$

$$M_{j-1}^{i-2} + \texttt{NN}'(i,j,i-2,j-1) + \Delta G_{\text{bulge}}, \tag{A1c}$$

$$M_{j-2}^{i-1} + \texttt{NN}'(i,j,i-1,j-2) + \Delta G_{\text{bulge}}, \tag{A1d}$$

$$M_{j-2}^{i-2} + \texttt{il1x1}(i,j), \quad M_{j-3}^{i-2} + \texttt{il1x2}(i,j), \tag{A1e}$$

$$M_{j-2}^{i-3} + \texttt{il2x1}(i,j), \quad M_{j-3}^{i-3} + \texttt{il2x2}(i,j), \tag{A1f}$$

$$B_{j-1}^{i-1} + \Delta G_{AU/GU}(i,j), \quad b_{j-1}^{i-1} + \Delta G_{AU/GU}(i,j), \tag{A1g}$$

$$B2_{j-1}^{i-1} + \Delta G_{AU/GU}(i,j), \quad b2_{j-1}^{i-1} + \Delta G_{AU/GU}(i,j) \tag{A1h}$$

$$K_{j-1}^{i-1}.\mathbf{dG} + \Delta G_{AU/GU}(i,j), \quad k_{j-1}^{i-1}.\,\mathbf{dG} + \Delta G_{AU/GU}(i,j), \tag{A1i}$$

$$A_{j-1}^{i-1}.\,\mathbf{dG} + \texttt{ilstack}(i,j), \quad a_{j-1}^{i-1}.\,\mathbf{dG} + \texttt{ilstack}(i,j)\}. \tag{A1j}$$

The finishing matrix adds the terminal stacking energy and is given by

$$F_j^i = M_{j-1}^{i-1} + \texttt{tstack}(i,j) + \Delta G_{AU/GU}(i-1, j-1). \tag{A2}$$

The bulge loop recursions are

$$B_j^i = \min\{M_j^{i-2} + \Delta G_{2\text{ bulges}} + \Delta G_{AU/GU}(i-2, j), \tag{A3a}$$

$$B_j^{i-1} + \Delta\Delta G_{\text{bulge (short)}}\}, \tag{A3b}$$

$$b_j^i = \min\{M_{j-2}^i + \Delta G_{2\text{ bulges}} + \Delta G_{AU/GU}(i, j-2), \tag{A3c}$$

$$b_{j-1}^i + \Delta\Delta G_{\text{bulge (short)}}\}, \tag{A3d}$$

and

$$B2_j^i = \min\{M_j^{i-7} + \Delta G_{7\text{ bulges}} + \Delta G_{AU/GU}(i-7, j), \tag{A4a}$$

$$B2_j^{i-1} + \Delta\Delta G_{\text{bulge (long)}}\}, \tag{A4b}$$

$$b2_j^i = \min\{M_{j-7}^i + \Delta G_{7\text{ bulges}} + \Delta G_{AU/GU}(i, j-7), \tag{A4c}$$

$$b2_{j-1}^i + \Delta\Delta G_{\text{bulge (long)}}\}. \tag{A4d}$$

The recursion relations for $n \times 1$ loops are

$$K^i_j.\mathbf{dG} = \min\big\{M^{i-3}_{j-1} + \Delta G_{AU/GU}(i-3, j-1) + \texttt{iloop}(3,1), \tag{A5a}$$

$$K^{i-1}_j.\mathbf{dG} - \texttt{iloop}(K^{i-1}_j.\mathbf{size}, 1) + \texttt{iloop}(K^{i-1}_j.\mathbf{size}+1, 1)\big\}. \tag{A5b}$$

If Eq. (A5a) is better than Eq. (A5b), $K^i_j.\mathbf{n} = 3$. Otherwise, $K^i_j.\mathbf{n} = K^{i-1}_j.\mathbf{n} + 1$. Similarly, the recursion relations for the $1 \times n$ loops are

$$k^i_j.\mathbf{dG} = \min\big\{M^{i-1}_{j-3} + \Delta G_{AU/GU}(i-1, j-3) + \texttt{iloop}(1,3), \tag{A6a}$$

$$k^i_{j-1}.\mathbf{dG} - \texttt{iloop}(1, k^i_{j-1}.\mathbf{size}) + \texttt{iloop}(1, k^j_{i-1}.\mathbf{size}+1)\big\}. \tag{A6b}$$

As with K, if Eq. (A6a) is better than Eq. (A6b), $k^i_j.\mathbf{n} = 3$. Otherwise, $k^i_j.\mathbf{n} = k^i_{j-1}.\mathbf{n} + 1$.

The recursion relations for the general $n \times m$ asymmetric loops are

$$A^i_j.\mathbf{dG} = \min\big\{M^{i-3}_{j-2} + \texttt{istack}(i-2, j-1), \tag{A7a}$$

$$A^{i-1}_j.\mathbf{dG} - \texttt{iloop}(A^{i-1}_j.\mathbf{n}, A^{i-1}_j.\mathbf{m}) + \texttt{iloop}(A^{i-1}_j.\mathbf{n}+1, A^{i-1}_j.\mathbf{m}), \tag{A7b}$$

$$a^{i-1}_j.\mathbf{dG} - \texttt{iloop}(a^{i-1}_j.\mathbf{n}, a^{i-1}_j.\mathbf{m}) + \texttt{iloop}(a^i_{j-1}.\mathbf{n}+1, a^i_{j-1}.\mathbf{m})\big\}. \tag{A7c}$$

If Eq. (A7a) is the minimum, $A^i_j.\mathbf{n} = 3$ and $A^i_j.\mathbf{m} = 2$; if Eq. (A7b) is minimum, $A^i_j.\mathbf{n} = A^{i-1}_j.\mathbf{n}+1$ and $A^i_j.\mathbf{m} = A^{i-1}_j.\mathbf{m}$; otherwise, $A^i_j.\mathbf{n} = a^i_{j-1}.\mathbf{n}+1$ and $A^i_j.\mathbf{m} = a^i_{j-1}.\mathbf{m}$. Similarly, the a matrix is defined by the rules

$$a^i_j.\mathbf{dG} = \min\big\{M^{i-2}_{j-3} + \texttt{istack}(i-1, j-2), \tag{A8a}$$

$$A^i_{j-1}.\mathbf{dG} - \texttt{iloop}(A^i_{j-1}.\mathbf{n}, A^i_{j-1}.\mathbf{m}) + \texttt{iloop}(A^i_{j-1}.\mathbf{n}, A^i_{j-1}.\mathbf{m}+1), \tag{A8b}$$

$$a^{i-1}_j.\mathbf{dG} - \texttt{iloop}(a^i_{j-1}.\mathbf{n}, a^i_{j-1}.\mathbf{m}) + \texttt{iloop}(a^i_{j-1}.\mathbf{n}, a^i_{j-1}.\mathbf{m}+1), \big\}, \tag{A8c}$$

and if Eq. (A8a) is the minimum then $a^i_j.\mathbf{n} = 2$ and $a^i_j.\mathbf{m} = 3$; if Eq. (A8b), then $a^i_j.\mathbf{n} = A^i_{j-1}.\mathbf{n}$ and $a^i_j.\mathbf{m} = A^i_{j-1}.\mathbf{m} + 1$; else, $a^i_j.\mathbf{n} = a^{i-1}_j.\mathbf{n}$ and $a^i_j.\mathbf{m} = a^{i-1}_j.\mathbf{m} + 1$.

The term $\Delta G_{AU/GU}(i,j)$ accounts the free energy penalty of starting or closing a helix with an AU or GU pair [8]. $\Delta\Delta G_{\text{bulge}}$ is the free energy penalty for adding an additional base to a bulge loop. There are two versions, one for short bulge loops and one for long ones (see the section on bulge loops). $\texttt{NN}(i,j)$ represents the free energy of a nearest neighbor pair ending at s_i, t_j. $\texttt{NN}'(i,j,i-2,j-1)$ is the free energy of the nearest neighbors $\substack{s_{i-2}s_i \\ t_{j-1}t_j}$, corresponding to the stacking around bulging base s_{i-1}. The free energy of the special internal loops is given by $\texttt{il1x1}(i,j)$, $\texttt{il1x2}(i,j)$, and so on. $\texttt{ilstack}(i,j)$ gives the free energy for the dangling bases adjacent to the closing base-pairs. $\texttt{iloop}(n,m)$ gives the entropic energy for an $n \times m$ loop.