Appendix

Derivation of the Linearly Forced Elastic Network Model (LFENM)

We indicate the position of the atom i by means of a vector $\mathbf{r}_i$ with respect to a properly chosen coordinate origin O. The distance between two atoms is given by $d_{ij} = \left|\mathbf{d}_{ij}\right|$, where $\mathbf{d}_{ij} = \mathbf{r}_i - \mathbf{r}_j$. The equilibrium position of atom i is $\bar{\mathbf{r}}_i$ so that $\bar{\mathbf{d}}_{ij} = \bar{\mathbf{r}}_i - \bar{\mathbf{r}}_j$ and $\bar{d}_{ij} = \left|\bar{\mathbf{d}}_{ij}\right|$. It is convenient to define the displacements $\mathbf{s}_i = \mathbf{r}_i - \bar{\mathbf{r}}_i$, $\mathbf{s}_{ij} = \mathbf{s}_i - \mathbf{s}_j = \mathbf{d}_{ij} - \bar{\mathbf{d}}_{ij}$ and $s_{ij} = \left|\mathbf{s}_{ij}\right|$.

In order to derive our model potential we expand the Elastic Network Model potential (ENM):

$$V = \frac{1}{2}\sum_i \sum_{j>i} k_{ij}\left(d_{ij} - \bar{d}_{ij}\right)^2 \tag{A.1}$$

in terms of the displacements s_{ij}. To this end, notice that

$$d_{ij} = \sqrt{\bar{d}_{ij} + 2\bar{\mathbf{d}}_{ij}.\mathbf{s}_{ij} + s_{ij}^2} \approx \bar{d}_{ij}\left[1 + \frac{\bar{\mathbf{d}}_{ij}.\mathbf{s}_{ij}}{\bar{d}_{ij}} + \frac{s_{ij}^2}{2\bar{d}_{ij}} - \frac{\left(\bar{\mathbf{d}}_{ij}.\mathbf{s}_{ij}\right)^2}{2\bar{d}_{ij}}\right] \tag{A.2}$$

from which it follows that $\left(d_{ij} - \bar{d}_{ij}\right)^2 \approx \left(\hat{\bar{\mathbf{d}}}_{ij}.\mathbf{s}_{ij}\right)^2$ where the cap denotes a vector of unit modulus: $\hat{\mathbf{e}} = \mathbf{e}/\left|\mathbf{e}\right|$. Neglecting terms of order greater than two we obtain the approximate potential

$$V_{wt} = \frac{1}{2}\sum_i \sum_j k_{ij}\left(\hat{\bar{\mathbf{d}}}_{ij}.\mathbf{s}_{ij}\right)^2 \tag{A.3}$$

In order to facilitate the discussion below, we treat the vectors also as 3×1 column matrices and define $\mathbf{G}_{ij} = k_{ij}\hat{\bar{\mathbf{d}}}_{ij}\hat{\bar{\mathbf{d}}}_{ij}^T$, where the superscript T stands for transpose. Notice that $\mathbf{G}_{ij} = \mathbf{G}_{ji}$ and $\mathbf{G}_{ij}{}^T = \mathbf{G}_{ij}$. If we rewrite equation (A.3) as

$$V_{wt} = \frac{1}{2}\left(\mathbf{s}_1^T\mathbf{K}_{11}\mathbf{s}_1 + \mathbf{s}_1^T\mathbf{K}_{12}\mathbf{s}_2 + \mathbf{s}_2^T\mathbf{K}_{21}\mathbf{s}_1 + \ldots\right) \tag{A.4}$$

we clearly appreciate that $\mathbf{K}_{ij} = -\mathbf{G}_{ij}, \quad i \neq j$ and

$$
\begin{aligned}
\mathbf{K}_{11} &= \mathbf{G}_{12} + \mathbf{G}_{13} + \ldots + \mathbf{G}_{1n} \\
\mathbf{K}_{22} &= \mathbf{G}_{12} + \mathbf{G}_{23} + \ldots + \mathbf{G}_{2n} \\
\mathbf{K}_{33} &= \mathbf{G}_{13} + \mathbf{G}_{23} + \mathbf{G}_{34} + \ldots + \mathbf{G}_{3n} \\
\mathbf{K}_{ii} &= \sum_{j=1}^{i-1} \mathbf{G}_{ji} + \sum_{j=i+1}^{n} \mathbf{G}_{ij} = \sum_{\substack{j=1 \\ j\neq i}}^{n} \mathbf{G}_{ij} = -\sum_{\substack{j=1 \\ j\neq i}}^{n} \mathbf{K}_{ij}
\end{aligned}
\tag{A.5}
$$

We can thus rewrite the potential (A.3) in a more compact matrix form

$$
V_{wt} = \frac{1}{2}\begin{pmatrix} \mathbf{s}_1^T & \mathbf{s}_2^T & \cdots \end{pmatrix} \begin{pmatrix} \mathbf{K}_{11} & \mathbf{K}_{12} & \cdots \\ \mathbf{K}_{21} & \mathbf{K}_{22} & \cdots \\ \vdots & \vdots & \ddots \end{pmatrix} \begin{pmatrix} \mathbf{s}_1^T \\ \mathbf{s}_2^T \\ \vdots \end{pmatrix} = \frac{1}{2}\mathbf{s}^T \mathbf{K}\mathbf{s} \tag{A.6}
$$

where $\mathbf{s}$ and $\mathbf{K}$ are $3N\times 1$ and $3N\times 3N$ matrices, respectively. If $\mathbf{r}$ and $\overline{\mathbf{r}}_{wt}$ are $3N\times 1$ column matrices with the elements of $\mathbf{r}_i$ and $\overline{\mathbf{r}}_i$, $i=1,2,\ldots,N$, respectively, then the potential (A.6) is exactly of the form introduced Eq. (1) of the main article because $\mathbf{s}=\mathbf{r}-\overline{\mathbf{r}}_{wt}$.

To model a mutation, we introduce in (A.1) a variation in the ENM parameters that represent the spring-lengths of the contacts of the mutated site: $\overline{d}_{ij} \to \overline{d}_{ij} + \delta\overline{d}_{ij}$. It is not difficult to verify that

$$
\delta V = -\sum_i \sum_{j>i} k_{ij}\delta\overline{d}_{ij} d_{ij} + C \tag{A.7}
$$

where C is a constant that does not have any effect on the molecule dynamics. An expansion of first order $d_{ij} \approx d_{ij}^0 + \hat{\overline{\mathbf{d}}}_{ij}.\mathbf{s}_{ij}$ leads to

$$
\delta V \approx -\sum_{m=1}^{n} \mathbf{f}_m.\mathbf{s}_m + C \tag{A.8}
$$

where

$$
\mathbf{f}_m = -\sum_{j\neq m} \mathbf{f}_{jm}, \quad \mathbf{f}_{jm} = k_{jm}\delta\overline{d}_{jm}\hat{\overline{\mathbf{d}}}_{jm} = -\mathbf{f}_{mj} \tag{A.9}
$$

The force components $\mathbf{f}_m$ satisfy

$$
\sum_m \mathbf{f}_m = \sum_m \left(\sum_{j<m} \mathbf{f}_{jm} + \sum_{j>m} \mathbf{f}_{jm} \right) = 0 \tag{A.10}
$$

We thus obtain the approximate deformed potential

$$V_{mut} = V_{wt} + \delta V = \frac{1}{2}\mathbf{s}^T\mathbf{K}\mathbf{s} - \mathbf{f}^T\mathbf{s} \tag{A.11}$$

where $\mathbf{f}$ is a $3N \times 1$ matrix constructed with the elements of all the $\mathbf{f}_m$. Since $\mathbf{s} = \mathbf{r} - \overline{\mathbf{r}}_{wt}$, Eq. (A.11) is Eq. (2) of the main article.

The stiffness matrix $\mathbf{K}$ has $3N$ eigenvectors $\mathbf{q}_n$ with eigenvalues λ_n. We choose the first $3N-6$, $n = 0,1,\ldots,3N-7$ to be the normal vibrational modes so that $\lambda_n = 0$ for all $n = 3N-7,\ldots,3N-1$ because the corresponding eigenvectors are related to the translations and rotations. It follows from

$$\mathbf{f} = -\left(\frac{\partial V_{mut}}{\partial \mathbf{r}}\right)_{\mathbf{r}=\overline{\mathbf{r}}_{wt}} \tag{A.12}$$

that

$$\delta\overline{\mathbf{r}} \equiv \overline{\mathbf{r}}_{mut} - \overline{\mathbf{r}}_{wt} = \mathbf{K}^{-1}\mathbf{f} \tag{A.13}$$

where $\mathbf{K}^{-1}$ is the pseudo inverse defined by

$$\mathbf{K}^{-1} = \sum_{n=0}^{3N-7} \lambda_n^{-1}\mathbf{q}_n\mathbf{q}_n^T \tag{A.14}$$

Clearly, $\delta\overline{\mathbf{r}}$ is orthogonal to the eigenvectors $\mathbf{q}_n$ associated to the translations and rotations ($3N-7 < n \le 3N-1$). Eq. (A.13) is Eq. (3) of the main article.