**Electronic Supplementary Information (ESI)**

**Fluctuation Correlations as Major Determinants of Structure- and Dynamics-Driven Allosteric Effects**

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**Text S1  A simplified four-bead model with analytical solution**

Here we consider a simplified four-bead model where analytical solutions are available. The system is one-dimensional, and a periodic boundary condition (or a ring configuration) is assumed. To enable an analytical solution, we further assume a two-fold symmetry as demonstrated in the schematic below, i.e., \( k_{12} = k_{34} \equiv k_4 \).

![Schematic of the simplified four-bead system with two-fold symmetry. The force constant and the equilibrium length of springs are denoted by \( k \) and \( S \), respectively.](image_url)

**S1.1 Diagonalization of the Hessian matrix (eigenvalues and eigenvectors)**

The Hessian matrix of the system:

\[
H = \begin{bmatrix}
k_1 + k_2 & -k_1 & 0 & -k_2 \\
-k_1 & k_1 + k_3 & -k_3 & 0 \\
0 & -k_3 & k_3 + k_5 & -k_1 \\
-k_2 & 0 & -k_1 & k_1 + k_2
\end{bmatrix}
\]  

(S1)

The eigenvalues \( \{\lambda_n\} \) and eigenvectors \( \{u^{(n)}\} \) of the system are to be solved from the eigen equation:
\[
\begin{bmatrix}
(k_1 + k_2) - \lambda & -k_1 & 0 & -k_2 \\
-k_1 & (k_1 + k_3) - \lambda & -k_3 & 0 \\
0 & -k_3 & (k_1 + k_3) - \lambda & -k_1 \\
-k_2 & 0 & -k_1 & (k_1 + k_2) - \lambda
\end{bmatrix}
\begin{bmatrix}
u_1 \\
u_2 \\
u_3 \\
u_4
\end{bmatrix} = 0.
\]

(52)

Considering the two-fold symmetry of the system, the solutions have a definite parity. With an even parity, i.e.,
\[
\begin{cases}
u_4 = \nu_1 \\
u_3 = \nu_2
\end{cases}
\]

(53)

only one non-zero solution is found (while a trivial translational solution is \(\lambda = 0\)):
\[
\lambda_1 = 2k_1.
\]

(54)

The corresponding eigenvector is
\[
\mathbf{u}^{(1)} \equiv \begin{bmatrix}
u_1 \\
u_2 \\
u_3 \\
u_4
\end{bmatrix} = \frac{1}{2} \begin{bmatrix} 1 \\ -1 \\ -1 \\ 1 \end{bmatrix}.
\]

(55)

With an odd parity, i.e.,
\[
\begin{cases}
u_4 = -\nu_1 \\
u_3 = -\nu_2
\end{cases}
\]

(56)

two non-zero solutions are derived:
\[
\lambda_{2,3} = \lambda\pm = k_1 + k_2 + k_3 \pm \sqrt{(k_1 + k_2 + k_3)^2 - (2k_1 k_2 + 2k_1 k_3 + 4k_2 k_3)}
\]
\[
= k_1 + k_2 + k_3 \pm \sqrt{k_1^2 + (k_2 - k_3)^2}.
\]

(57)

The corresponding eigenvectors are
\[
\mathbf{u}^{(2,3)} \equiv \begin{bmatrix}
u_1 \\
u_2 \\
u_3 \\
u_4
\end{bmatrix}
= \frac{1}{2 \sqrt{k_1^2 + (k_2 - k_3)^2}} \begin{bmatrix}
-k_1 \\
-k_3 \pm \sqrt{k_1^2 + (k_2 - k_3)^2} \\
k_3 - k_2 \pm \sqrt{k_1^2 + (k_2 - k_3)^2} \\
-\nu_2 \\
-\nu_1
\end{bmatrix}
\]

(58)

**S1.2 Covariance of equilibrium fluctuations**

With the equation for the covariance of equilibrium fluctuations,
\[
\langle \Delta r_i \Delta r_j \rangle = k_B T \sum_n \frac{u_i^{(n)} u_j^{(n)}}{\lambda_n},
\]

(59)
and Eqs. (S4, S5, S7, S8) above, it yields:
\[
\frac{\langle \Delta d_{23} \Delta d_{41} \rangle}{k_B T} \equiv \frac{\langle (\Delta r_3 - \Delta r_2) \cdot (\Delta r_1 - \Delta r_4) \rangle}{k_B T} = -\frac{k_1}{k_1 k_2 + k_1 k_3 + 2k_2 k_3},
\]
(S10)

**S1.3 Dynamics-driven allosteric effect (perturbation on force constant)**

The free energy can be written as a function of all the non-zero eigenvalues:
\[
F = C_0 + \frac{k_B T}{2} \ln \prod_{n=1,2,3} \lambda_n,
\]
(S11)

where \( C_0 \) is a constant irrelevant to \( \lambda_n \). For arbitrary dynamics mutations on the springs 2-3 and 4-1, i.e.,
\[
\begin{align*}
(k_3 &\rightarrow k_3 + \Delta k_{23} \\
(k_2 &\rightarrow k_2 + \Delta k_{41}),
\end{align*}
\]
(S12)
a combination of Eqs. (S4, S7, S11, S12) gives
\[
F_{\text{mut}}(2-3,4-1)(\Delta k_{23}, \Delta k_{41}) = C_0 + \frac{k_B T}{2} \ln(2k_1) + \frac{k_B T}{2} \ln((k_1 + k_2 + k_3 + \Delta k_{23} + \Delta k_{41})^2 - [k_1^2 + (k_2 - k_3 + \Delta k_{23} - \Delta k_{41})^2]).
\]
(S13)

Therefore, the allosteric coupling free energy is
\[
\Delta F = F_{\text{mut}}(2-3,4-1)(\Delta k_{23}, \Delta k_{41}) - F_{\text{mut}}(2-3,4-1)(\Delta k_{23}, 0) - F_{\text{mut}}(2-3,4-1)(0, \Delta k_{41}) + F_{\text{mut}}(2-3,4-1)(0,0)
\]
\[
\equiv \frac{\partial^2 F_{\text{mut}}(2-3,4-1)(\Delta k_{23}, \Delta k_{41})}{\partial \Delta k_{23} \partial \Delta k_{41}} \Bigg|_{0} \Delta k_{23} \Delta k_{41}
\]
\[
= -\frac{k_B T}{2} \left( \frac{k_1^2}{(k_1 k_2 + k_1 k_3 + 2k_2 k_3)^2} \right) \Delta k_{23} \Delta k_{41}
\]
(S14)
up to the second-order expansion. Comparing Eq. (S10) and Eq. (S14), we finally obtain the dynamics-driven allosteric effect:
\[
\Delta F = -\frac{1}{2k_B T} \langle \Delta d_{23} \Delta d_{41} \rangle^2 \Delta k_{23} \Delta k_{41},
\]
(S15)
which is in fully agreement with Eq. (26) of the main text.

**S1.4 Structure-driven allosteric effect (perturbation on bead radius)**

Consider perturbation \( \Delta a_{23}, \Delta a_{41} \) on the equilibrium length of springs 2-3 and 4-1, the potential energy of the system becomes
\[
V = \frac{k_1}{2} (\Delta x_{12}^2 + \Delta x_{34}^2) + \frac{k_3}{2} (\Delta x_{23} - \Delta a_{23})^2 + \frac{k_2}{2} (\Delta x_{41} - \Delta a_{41})^2.
\]
(S16)
The period-boundary condition requires that
\[ \Delta x_{12} + \Delta x_{23} + \Delta x_{34} + \Delta x_{41} = 0. \] (S17)

Together with the two-fold symmetry of the system, we thus have
\[ \Delta x_{12} = \Delta x_{34} = -\frac{\Delta x_{23} + \Delta x_{41}}{2} \] (S18)

for the energy minimum state, so
\[ V = \frac{k_1}{4} (\Delta x_{23} + \Delta x_{41})^2 + \frac{k_3}{2} (\Delta x_{23} - \Delta a_{23})^2 + \frac{k_2}{2} (\Delta x_{41} - \Delta a_{41})^2. \] (S19)

The solution for the energy minimum state is
\[
\begin{align*}
\Delta x_{23} &= \frac{2k_3(k_1 + 2k_2)\Delta a_{23} - 2k_2k_1\Delta a_{41}}{(k_1 + 2k_3)(k_1 + k_2) - k_1^2} \\
\Delta x_{41} &= \frac{2k_2(k_1 + 2k_3)\Delta a_{41} - 2k_3k_1\Delta a_{23}}{(k_1 + 2k_3)(k_1 + 2k_2) - k_1^2}
\end{align*}
\] (S20)

and
\[ V_0(\Delta a_{23}, \Delta a_{41}) = \frac{k_1k_2k_3}{2(k_1k_2 + k_1k_3 + 2k_2k_3)}(\Delta a_{23} + \Delta a_{41})^2. \]

So the allosteric effect is
\[
\Delta \Delta V_0 = V_0(\Delta a_{23}, \Delta a_{41}) - V_0(\Delta a_{23}, 0) - V_0(0, \Delta a_{41}) + V_0(0, 0) \\
= \frac{k_1k_2k_3}{k_1k_2 + k_1k_3 + 2k_2k_3}\Delta a_{23}\Delta a_{41}.
\] (S21)

Considering Eq. (S10), we finally get
\[ \Delta \Delta V_0 = -\frac{k_2k_3}{k_BT} (\Delta d_{23}\Delta d_{41})\Delta a_{23}\Delta a_{41}. \] (S22)

It is consistent with Eq. (39) in the main text.
Table S1. A summary on the Pearson’s $R$ values between various quantities.

<table>
<thead>
<tr>
<th>$y$</th>
<th>$x$</th>
<th>R values</th>
<th>source</th>
</tr>
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<tr>
<td></td>
<td></td>
<td><strong>Dynamics-driven allostery</strong></td>
<td></td>
</tr>
<tr>
<td>$\Delta F$ (a single spring perturbed)</td>
<td>$C_{ij}^{(DP)}$</td>
<td>0.12</td>
<td>Fig. 4(a)</td>
</tr>
<tr>
<td></td>
<td>$\langle</td>
<td>\Delta r_i</td>
<td>^2 \rangle^{1/2} / \langle</td>
</tr>
<tr>
<td></td>
<td>$(\Delta d_{ij})^2$</td>
<td>1.000</td>
<td>Fig. 4(c)</td>
</tr>
<tr>
<td>$\Delta F_{\text{mut},i}$</td>
<td>$n_i$</td>
<td>0.88</td>
<td>Fig. 5(a)</td>
</tr>
<tr>
<td>$\Delta F_{\text{mut},i} / n_i$</td>
<td>$\langle</td>
<td>\Delta r_i</td>
<td>^2 \rangle^{1/2}$</td>
</tr>
<tr>
<td>$\Delta F_{\text{mut},i}$</td>
<td>$(\Delta d_{i,*})^2$</td>
<td>1.000</td>
<td>Fig. 5(c)</td>
</tr>
<tr>
<td></td>
<td>0.997</td>
<td>Fig. 5(d)</td>
<td></td>
</tr>
<tr>
<td>$\Delta \Delta F$</td>
<td>$\langle \Delta d_{i,<em>} \Delta d_{k,</em>} \rangle^2$</td>
<td>-1.000, -0.998, -0.994, -0.994</td>
<td>Fig. 6(d)</td>
</tr>
<tr>
<td></td>
<td>$C_{ik}^{(DP)}$</td>
<td>-0.50</td>
<td>Fig. 6(c)</td>
</tr>
<tr>
<td></td>
<td>$\langle \Delta r_i \cdot \Delta r_k \rangle$</td>
<td>0.38</td>
<td>Fig. 8(c)</td>
</tr>
<tr>
<td></td>
<td>$\langle \Delta d_{i,<em>} \Delta d_{k,</em>} \rangle$</td>
<td>-1.00, -0.97, -0.95, -0.98</td>
<td>Fig. 8(e)</td>
</tr>
</tbody>
</table>

|     |     | **Structure-driven allostery** |         |
| $\Delta V_{0,\text{mut},i}$ | $n_i$ | 0.86 | Fig. 7(a) |
| $\Delta V_{0,\text{mut},i} - n_i \gamma (\Delta a)^2 / 2$ | $\langle \Delta d_{i,*} \Delta d_{i,*} \rangle$ | 0.999 | Fig. 7(c) |
| $|\Delta \Delta V_0|$ | $C_{ik}^{(DP)}$ | 0.57 | Fig. 8(b) |
|     | $\langle \Delta r_i \cdot \Delta r_k \rangle$ | 0.38 | Fig. 8(c) |
| $\Delta \Delta V_0$ | $C_{ik}^{(DP)}$ | 0.19 | Fig. 8(b) |
|     | $\langle \Delta r_i \cdot \Delta r_k \rangle$ | 0.11 | Fig. 8(c) |
|     | $\langle \Delta d_{i,*} \Delta d_{k,*} \rangle$ | -1.00, -0.97, -0.95, -0.98 | Fig. 8(e) |
**FIGURE S1** The correlation between $C_{ij}^{(DP)}$ of Gō-like model (MD) and ANM for the protein CAP with different cutoff distance $r_c$ (in Å). Solid lines indicate the ideal curve of $y = x$. 
FIGURE S2 Root-mean-square-fluctuation (RMSF), i.e., $\langle |\Delta r_i|^2 \rangle^{1/2}$, as a function of the number of springs connected to the residue ($n_i$), calculated from ANM with parameters $m = 0.11$ kg/mol, $\gamma = 1.0$ kcal/(mol·Å$^2$) and various $r_c$ values as indicated in the graphs. Four systems were examined: chymotrypsin inhibitor 2 (CI2), pig plasma retinol binding protein (RBP), tyrosine-protein phosphatase nonreceptor type 1 (PTP1B) and the catabolite activator protein (CAP).
FIGURE S3  Distribution of vibration frequencies for four protein systems (from left to right) calculated from ANM with various $r_c$ values (from top to bottom). $m = 0.11$ kg/mol, $\gamma = 1.0$ kcal/(mol·Å$^2$). Solid lines indicate the prediction given by the Debye model of solids, i.e., $P(\omega) \propto \omega^2$, which can be used to well describe the distribution of lower frequencies. In addition, the frequencies satisfy $\hbar \omega < k_B T$, so the high temperature approximation is satisfied and the Boltzmann statistics can be applied reliably.
FIGURE S4 Calculated coupling free energy $\Delta\Delta F$ of dynamics-driven allostery in CAP with respect to (a) the scalar cross-correlation $\langle \Delta r_i \cdot \Delta r_k \rangle$ (in Å^2), (b) the product of the number of springs connected to the mutated residues $(n_i n_k)$, (c) $n_i n_k \langle \Delta r_i \cdot \Delta r_k \rangle$ and (d) $n_i n_k C_{ik}^{(DP)}$. $r_c = 9\text{Å}$, $m = 0.11 \text{ kg/mol}$, $\gamma = 1.0 \text{ kcal/(mol⋅Å^2)}$, and $\Delta\gamma = 0.1 \text{ kcal/(mol⋅Å^2)}$ were used in the calculations.
FIGURE S5 Allostery free energy ($\Delta\Delta F$) and coefficient ($\frac{k_B T \Delta F}{\Delta F_{mut, 1} \Delta F_{mut, k}}$) plotted against $r_{ik}^{(0)}$ for the four protein systems (from left to right) under different $\Delta \gamma$ values (from top to bottom). The average values as a function of $r_{ik}$ are plotted as black squares with the exponential fits ($y \propto e^{-x/x_0}$) given as solid lines. The fitted $x_0$ (in Å) are listed in the top two rows. $r_c = 9$ Å, $m = 0.11$ kg/mol, and $\gamma = 1.0$ kcal/(mol·Å²) were used in the calculations.
**FIGURE S6** Poor correlation between dynamics-driven and structure-driven allostery coefficients. (a) Correlation between $\langle \Delta d_i \Delta d_i \rangle$ [Eq. (43)] and $\langle (\Delta d_i)^2 \rangle$ [Eq. (40)] for the four systems, which describe single residue mutation effects. (b) Correlation between $\langle \Delta d_i \Delta d_k \rangle$ [Eq. (44)] and $\langle (\Delta d_i)^2 \Delta d_k \rangle$ [Eq. (41)], which describe the allosteric effects under a double residue mutation.

**FIGURE S7** Calculated coupling equilibrium potential ($\Delta V_0$) of structure-driven allostery in PTP1B plotted against to (a) the product of the number of springs connected to the mutated residues ($n_i n_k$), (b) $n_i n_k \langle \Delta r_i \cdot \Delta r_k \rangle$ and (c) $n_i n_k C_{ik}^{(DP)}$. $r_c = 9 \text{ Å}$, $m = 0.11 \text{ kg/mol}$, $\gamma = 1.0 \text{ kcal/(mol·Å²)}$, and $\Delta a = 0.1 \text{ Å}$ were used in the calculations.
FIGURE S8  Δ\(\Delta V_0\) and \(\frac{\Delta\Delta V_0}{(\Delta\Delta V_{0,\text{mut}})^{1/2}}\) with respect to \(r_{ik}^{(0)}\) for the four proteins in both linear and logarithmic scales. The average values as a function of \(r_{ik}^{(0)}\) are plotted as black squares with the exponential fits \((y \propto e^{-x/x_0})\) presented as solid lines. The fitted \(x_0\) (in Å) are listed in some panels. \(\tau_c = 9\) Å, \(m = 0.11\) kg/mol, \(\gamma = 1.0\) kcal/(mol·Å\(^2\)) and \(\Delta a = 0.1\) Å were used in the calculations.
FIGURE S9 Distribution of $\Delta \Delta V_0$, $\langle \Delta d_i \Delta d_k \rangle$ and $-\frac{k_B T \Delta F}{\Delta F_{\text{mut},i} \Delta F_{\text{mut},k}}$ data with $20 \text{Å} \leq r_{ik} \leq 25 \text{Å}$ for PTP1B. $r_c = 9 \text{ Å}$, $m = 0.11 \text{ kg/mol}$, $\gamma = 1.0 \text{ kcal/(mol·Å²)}$ and $\Delta a = 0.1 \text{ Å}$ were used in the ANM calculations.