**Motivation**

Kinesin switches its microtubule (MT) binding affinity between strong binding mode and weak binding mode depending on nucleotide states. For understanding this allosteric regulation mechanism, we studied the structural fluctuations of the motor head of the single-headed kinesin KIF1A in different nucleotide states using computer simulations of coarse-grained Go-like model.

\[
0 \to I \to II \to III \to IV \to V \to 0
\]

**Figure:** KIF1A-MT hydrolysis cycle

**Table:** Nucleotide states and the corresponding analog states. PDB IDs indicate X-ray structures used as the reference structures of Go-like models.

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>binding mode</td>
<td>strong</td>
<td>weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nucleotide state</td>
<td>ATP-1</td>
<td>ATP-Pi-1</td>
<td>ADP</td>
<td>ADP-Pi-2</td>
</tr>
<tr>
<td>analog</td>
<td>AMP-PCP</td>
<td>AMP-PNP</td>
<td>ADP-AIF</td>
<td>ADP-Vi</td>
</tr>
<tr>
<td>PDB ID</td>
<td>116l</td>
<td>1VFV</td>
<td>1VFX</td>
<td>1VFZ</td>
</tr>
</tbody>
</table>

**Method**

- A coarse-grained Go-like model for each nucleotide state.
- Nucleotides are also represented by a few beads.
- Langevin dynamics simulations for investigating the structural fluctuations when MT is absent.

**Model**

- **Total energy**
  \[ V_{\text{tot}} = V_e(\text{protein}) + V_e(\text{nucleotide}) + V_{\text{interaction}} + V_{\text{diss}}(\text{for ADP-Pi}) \]

- **Intra-molecule energy**
  \[
  V_{\text{diss}}(I, \eta(0)) = \sum_{\text{beads}} K_b (b_i - b_i(0))^2 + \sum_{\text{angles}} K_\theta (\theta_i - \theta_i(0))^2
  + \sum_{\text{dihedrals}} K_\phi \left(1 - \cos(\phi_i - \phi_i(0))\right)
  + \sum_{i,j} K_{\text{nnc}} \left[5 \left(\frac{r_{ij}}{r_{ij}^0}\right)^{12} - 6 \left(\frac{r_{ij}}{r_{ij}^0}\right)^{10}\right] + \sum_{i,j} K_{\text{nnc}} \left(\frac{C_{ij}}{r_{ij}^0}\right)^{12}
  \]

\[ \eta(0): \text{reference structure} r_{ij}; \text{distance between the } i\text{th and } j\text{th } C\alpha, \]

\[ b_i = \eta_i + 1 \]

**Interaction energy**

\[
V_{\text{interaction}}(I, \eta) = \sum_{i,k} \eta_{ik} \left[5 \left(\frac{r_{ik}}{r_{ik}^0}\right)^{12} - 6 \left(\frac{r_{ik}}{r_{ik}^0}\right)^{10}\right] + \sum_{i,k} K_{\text{nnc}} \left(\frac{C_{ik}}{r_{ik}^0}\right)^{12}
\]

**Results without nucleotide**

**Figure:** Superposition of the five reference structures. Highlighted are the switch II cluster regions.

**Effect of temperature and nucleotide**

**Conclusion**

We propose the following mechanism for the MT affinity regulation:

- The flexibility of the MT binding site (helix \(\alpha 4\) in particular) is allosterically controlled according to the nucleotide states during the ATP hydrolysis process.
- The affinity to MT is regulated through the flexibility of the MT binding site.
- The more flexible the MT binding site is, the stronger the binding affinity becomes.