# Inchworm stepping of Myc-Max heterodimer protein diffusion along DNA

Liqiang Dai[1, 2], Jin Yu[3*]

[1] Shenzhen JL computational science and applied research institute, Shenzhen, China

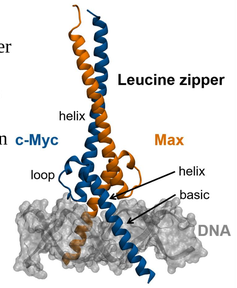
[2] Beijing Computational Science Research Center, Beijing, China

[3] Department of Physics and Astronomy, Department of Chemistry, NSF-Simons Center for Multiscale Cell Fate Research, University of California, Irvine

Email: dailiq@csrc.ac.cn, jin.yu@uci.edu

## Introduction

Oncogenic protein Myc serves as a transcription factor to control cell metabolisms. Myc dimerizes via leucine zipper with its associated partner protein Max to form a heterodimer structure, which then binds target DNA sequences to regulate gene transcription. The regulation depends on Myc-Max binding to DNA and searching for target sequences via diffusional motions along DNA. Here, we conduct structure-based molecular dynamics (MD) simulations to investigate the diffusion dynamics of the Myc-Max heterodimer along DNA. We found that the heterodimer protein slides on the DNA in a rotation-uncoupled manner in coarse-grained simulations, as its two helical DNA binding basic regions (BRs) alternate between open and closed conformations via inchworm stepping motions. In such motions, the two BRs of the heterodimer step across the DNA strand one by one, with step sizes reaching about half of a DNA helical pitch length. Atomic MD simulations of the Myc-Max heterodimer in complex with DNA have also been conducted. Hydrogen bond interactions are revealed between the two BRs and two complementary DNA strands, respectively. In the non-specific DNA binding, the BR from Myc shows an onset of stepping on one association DNA strand and starts detaching from the other strand. Overall, our simulation studies suggest that the inchworm stepping motions of the Myc-Max heterodimer can be achieved during the protein diffusion along DNA.

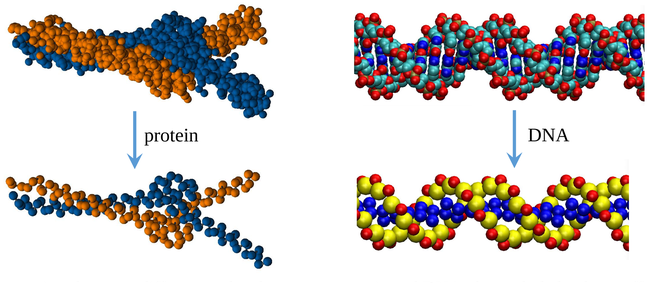



## Methods

### Coarse-grained simulations

Here we conduct coarse-grained simulations by CafeMol 3.0 software[1]. The initial structure of the Myc-Max heterodimer was taken from the crystal structure (pdb: 1NKP)[2].

The CG protein structure using the Go model in which the protein is represented by a chain of Cα atoms of every amino acids and with conformations biased towards the native structure, or crystal structure here. Meanwhile, the DNA is described by the 3SPN.2 model[3] .




the interactions between different molecules, e.g. as protein and DNA, the excluded volume effects and electrostatic interactions are considered as：

$$V_{\text{excluded}} = \sum_{\substack{ij\ s.t. \\ non-local}}^{non-native} \varepsilon_{ex} \left(\frac{d}{r_{ij}}\right)^{12}$$

$$V_{\text{ele}} = \sum_{i<j}^{N} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_k r_{ij}} e^{-r_{ij}/\lambda_D}$$

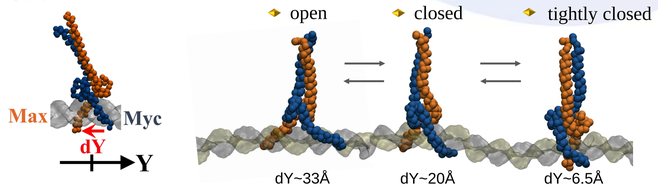
### Molecular Dynamics simulations

We also performed atomistic molecular dynamics simulations for MYC-MAX on different DNA sequence by Gromacs 5.1.2.

## Conformational changes

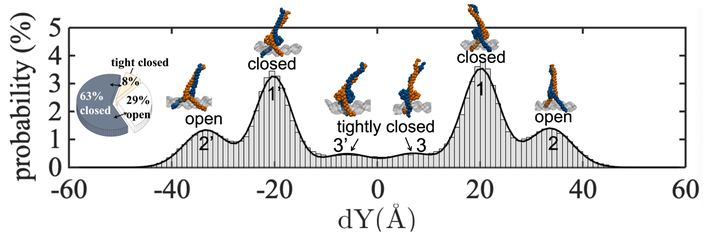
### Three main conformations of Myc-Max

The sliding of the Myc-Max heterodimer is coupled closely to significant conformational changes between the two BRs. Three main conformations of Myc-Max sliding on DNA are found.




- closed state: resembles the crystal structure, with the two BRs bound on the two sides of a same DNA groove
- open state: the leading BR moves across the DNA strand and binds to the next DNA groove, by starting from the closed state
- tightly closed state: the lagging BR moves further close to the leading BR, also starting from the closed state.

### Conformation proportions

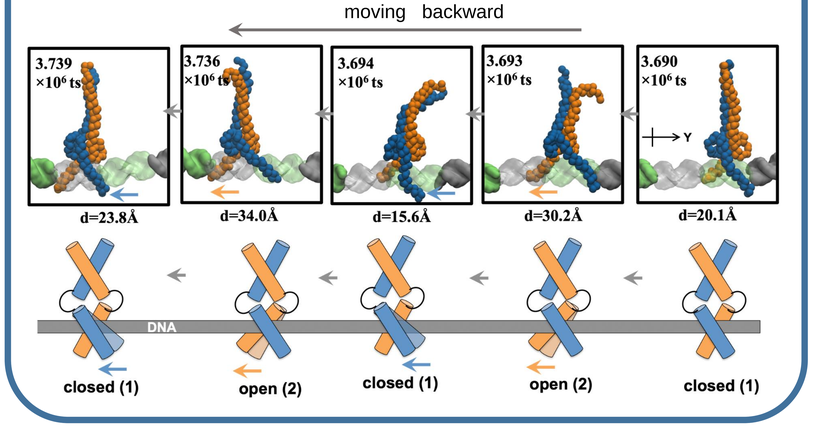



The closed state accounts dominantly for ~ 63% of the overall population.

## Sliding of Myc-Max on DNA

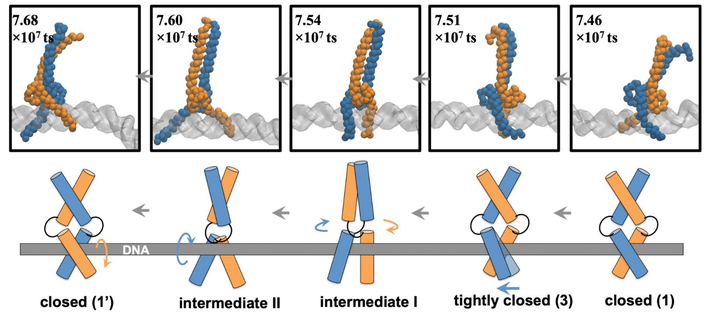
The coarse-grained simulations suggest that the Myc-Max heterodimer diffusion along DNA follows an inchworm model, moving either forward or backward.

### Inchworm stepping model



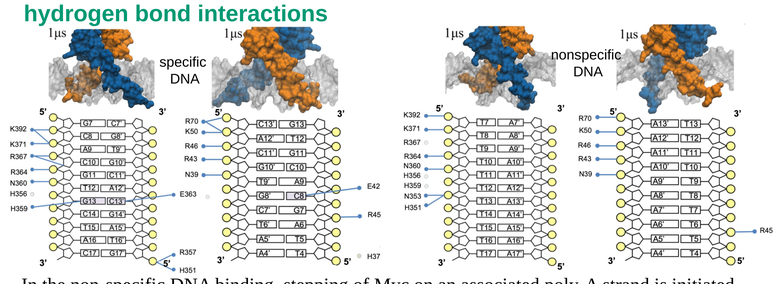

Starting from the highly populated closed conformation (state 1), the leading BR moves forward first across the DNA strand to the next DNA groove, at a step size of ~13 Å, so that Myc-Max transits to the open conformation (state 2); then the lagging BR follows to recover the protein back to the closed state.

### BR swapping




Occasionally, starting from the closed state, the lagging BR can also move forward first. In such a case, the heterodimer transits to the tightly closed state (state 3), which is of low population and shortly lived. Rather than transiting back to the stabilized closed state, the tightly closed state allows the BR 'swapping' so that the left-right positioning between the two BRs exchanges or reverses.

### hydrogen bond interactions




In the non-specific DNA binding, stepping of Myc on an associated poly-A strand is initiated (toward 5' direction).

## Conclusion

We conduct both coarse-grained simulations and atomistic molecular dynamics simulations to investigate the diffusion dynamics of Myc-Max along DNA.

I. Myc-Max can slide along DNA in a rotation uncoupled way (facilitated diffusion).
II. Three main conformations of Myc-Max while diffusion on DNA are found.
III. Myc-Max diffuses along DNA follows an inchworm model.
IV. Myc and Max can swap occasionally.

## References and Acknowledgements

[1] Kenzaki H, et al. (2011) CafeMol: A coarse-grained biomolecular simulator for simulating proteins at work. Journal of Chemical Theory and Computation 7(6):1979-1989.
[2] Nair SK & Burley SK (2003) X-ray structures of Myc-Max and Mad-Max recognizing DNA: molecular bases of regulation by proto-oncogenic transcription factors. Cell 112(2):193-205.
[3] Freeman GS, Hinckley DM, & de Pablo JJ (2011) A coarse-grain three-site-per-nucleotide model for DNA with explicit ions. The Journal of chemical physics 135(16):10B625.
We acknowledge the computational support from the Beijing Computational Science Research Center (CSRC).