Revealing Drug-Target Binding Pathway using Two-dimensional Replica-Exchange Molecular Dynamics Method

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Priority Issue 1 – Building innovative drug discovery infrastructure through functional control of biomolecular systems (Sub-issue A: MD advancement and algorithms for the post-K) by MEXT
Molecular Dynamics, MD Simulation
For analyzing biomolecular dynamics and functions

\[
\frac{d\mathbf{r}_i}{dt} = \frac{d\mathbf{p}_i}{m} \quad \frac{d\mathbf{p}_i}{dt} = \mathbf{F}_i
\]

\[
\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \frac{\mathbf{p}_i \Delta t}{m}
\]

\[
\mathbf{p}_i(t + \Delta t) = \mathbf{p}_i(t) + \mathbf{F}_i \Delta t
\]

Molecular Potential Energy

\[
U = \sum \frac{1}{2}K_b (b-b_o)^2 + \sum \frac{1}{2}K_\theta (\theta-\theta_o)^2
\]

All Bonds/All Angles

\[
+ \sum K_\phi [1-\cos(n\phi+\delta)]
\]

All Torsion Angles

\[
+ \sum \epsilon \left[ \frac{(r-r_c)^2}{2} - 2\left(\frac{r-r_c}{r_s}\right)^6 \right]
\]

All Nonbonded pairs

\[
+ \sum \frac{332q_i q_j}{|r|}
\]

All partial charges

\[
\text{Simple sum over many terms}
\]

Nobel Prize in Chemistry 2013
M. Karplus, M. Levitt, and A. Warshel
“Development of multiscale models for complex chemical systems”.

Levitt, M. Angew. Chemie Int. Ed. (2014)
Evolution of MD Simulation
Toward more realistic modeling, and longer timescale

1) McCammon et. al, Nature (1977)
2) Duan et al., Science (1998)
3) de Groot et al., Science (2001)
6) Zhao et al., Nature (2013)
GENESIS
Generalized-ensemble simulation system

Leader: Y. Sugita
Main developers:
C. Kobayashi, J. Jung, Y. Matsunaga, T. Mori, T. Ando, K. Tamura, M. Kamiya

This is free software under GPLv2 License.
https://www.r-ccs.riken.jp/labs/cbgt/
Current version: 1.3.0
Computational Drug Discovery
From “Docking” to “Binding”

“Key” Ligand
“Lock” Protein receptor

Static shape complementarity

Flexibility and molecular interaction
Replica-Exchange MD (REMD)
Overcome high energy barrier by parameter exchanges

Avoid trapping

2D-REMD for Ligand Binding

Enhanced sampling of ligand-binding events


Src Kinase – Inhibitor Binding

A key signaling kinase in cancer process

ATP competitive inhibitor design based on the X-ray structure is limited

Only a part of whole functional interactions is given.
Three Essential States
Bound, TS, Encounter, Unbound states

gREST/REUS simulations provide atomic-level details of these states, we will discuss them in the presentation.
Take-Home Message

MD simulations using enhanced sampling techniques as gREST/REUS can provide the information of multiple bound poses, multiple intermediates, and multiple pathways in protein-ligand bindings with high statistical accuracy.

The binding pathway information provides the functional interactions that cannot be seen in the X-ray structures, exploring new design principle.

GENESIS on K and post-K computers would be a promising tool for next-generation drug discovery.
Acknowledgement

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Priority Issue 1 – Building Innovative drug discovery infrastructure through functional control of biomolecular systems (Sub-issue A: MD advancement and algorithms for the post-K)

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Thank you for your attention!