The 1st R-CCS International Symposium, Feb 18-19, 2019, Kobe, Japan

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

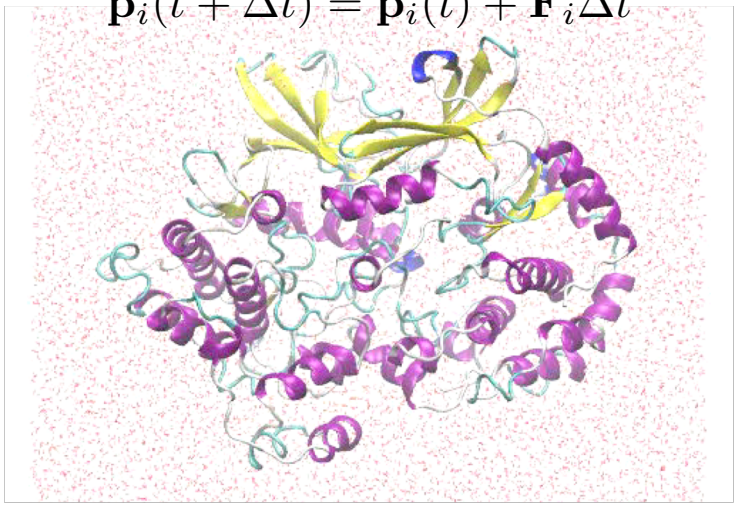
Molecular Dynamics, MD Simulation

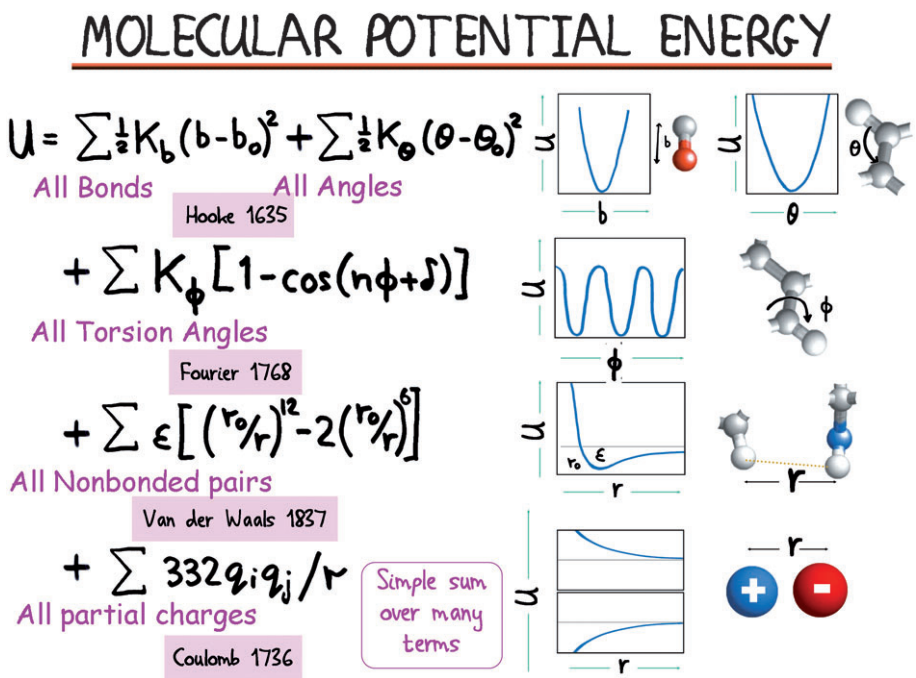
For analyzing biomolecular dynamics and functions

$$\frac{d\mathbf{r}_i}{dt} = \frac{d\mathbf{p}_i}{m} \qquad \frac{d\mathbf{p}_i}{dt} = \mathbf{F}_i$$

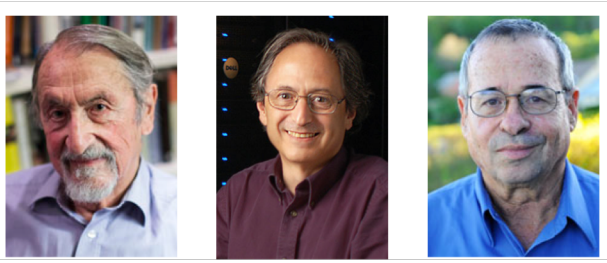
$$\mathbf{r}_i(t+\Delta t) = \mathbf{r}_i(t) + \frac{\mathbf{p}_i}{m}\Delta t$$

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





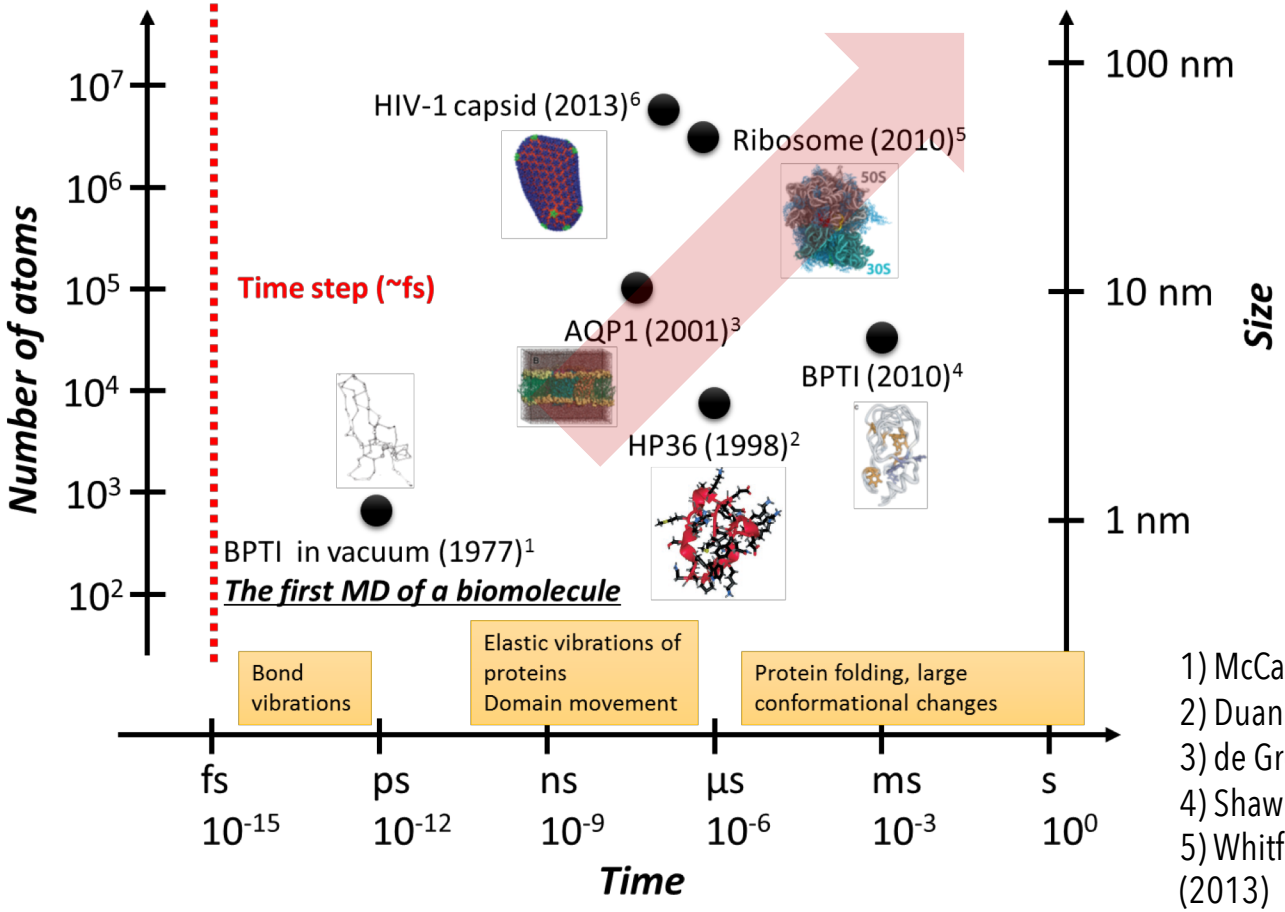
Levitt, M. Angew. Chemie Int. Ed. (2014)



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

Evolution of MD Simulation

Toward more realistic modeling, and longer timescale



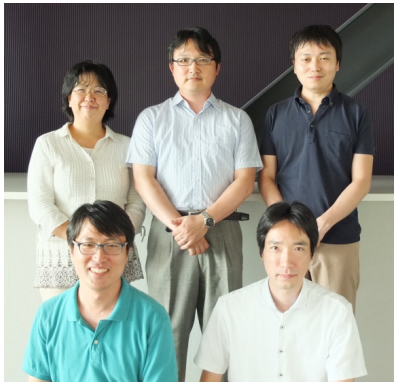
1) McCammon et.al, Nature (1977)
2) Duan et al., Science (1998)
3) de Groot et al., Science (2001)
4) Shaw et al., Science (2010)
5) Whitford et al., PLOS Comput. Biol (2013)
6) Zhao et al., Nature (2013)

(Slide from Dr. C. Kobayashi)

GENESIS

Generalized-ensemble simulation system

Highly scalable
Enhanced sampling
General purpose



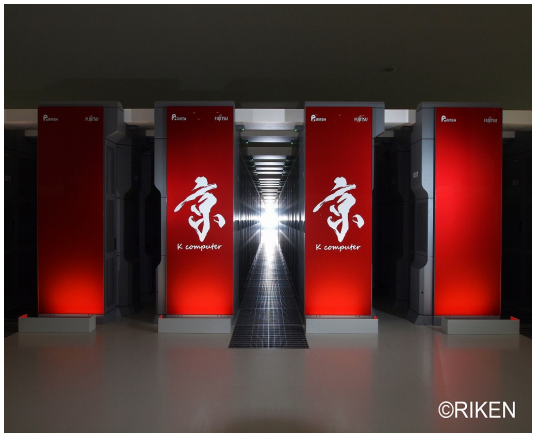
Leader: Y. Sugita

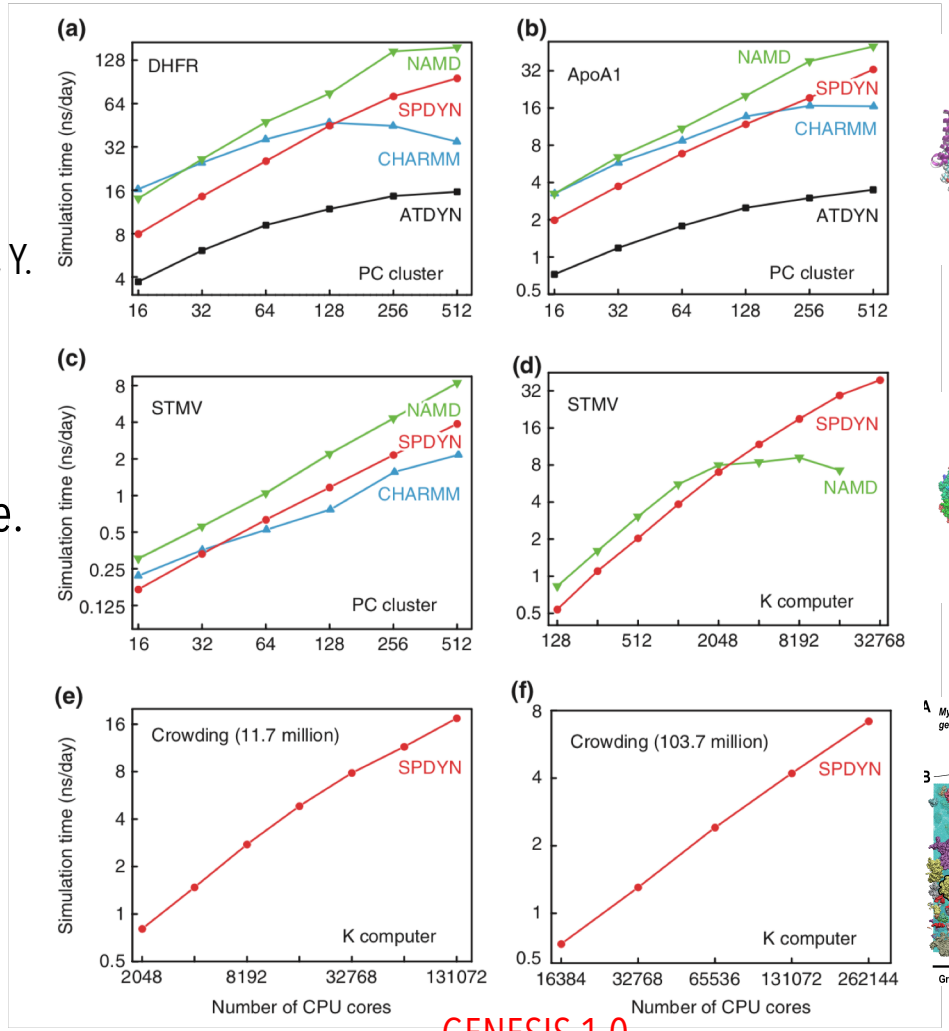
Main developers:
C. Kobayashi, J. Jung, Y. Matsunaga, T. Mori, T. Ando, K. Tamura, M. Kamiya

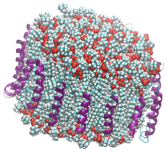
This is free software under GPLv2 License.

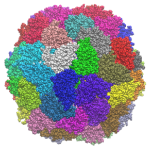
https://www.r-ccs.riken.jp/labs/cbrt/

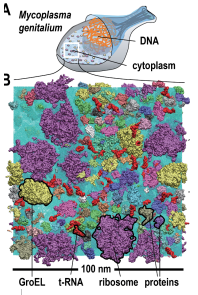
Current version: 1.3.0









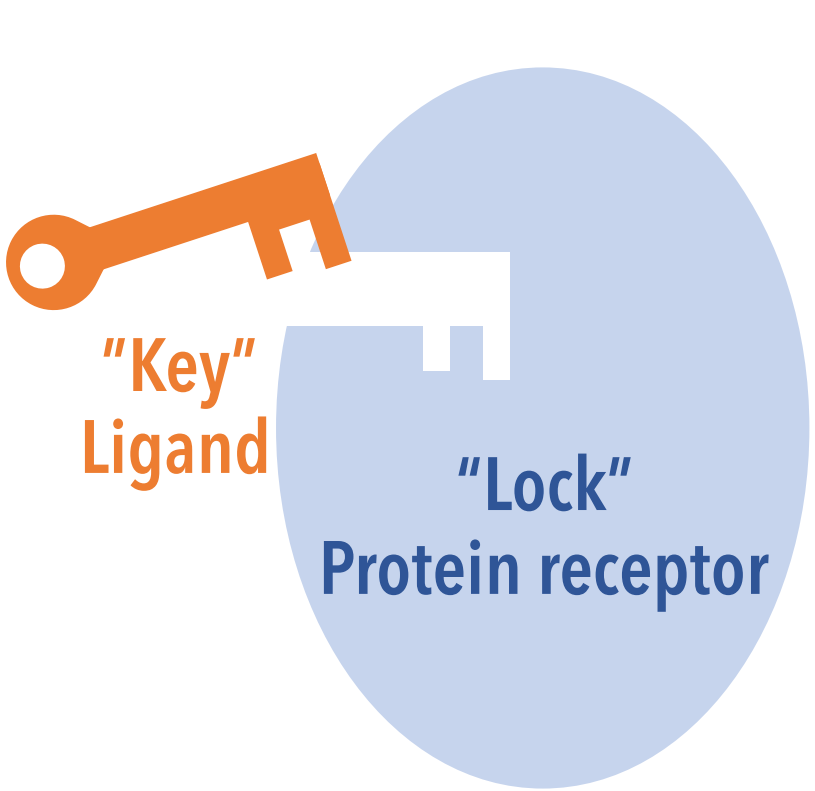


GENESIS 1.0

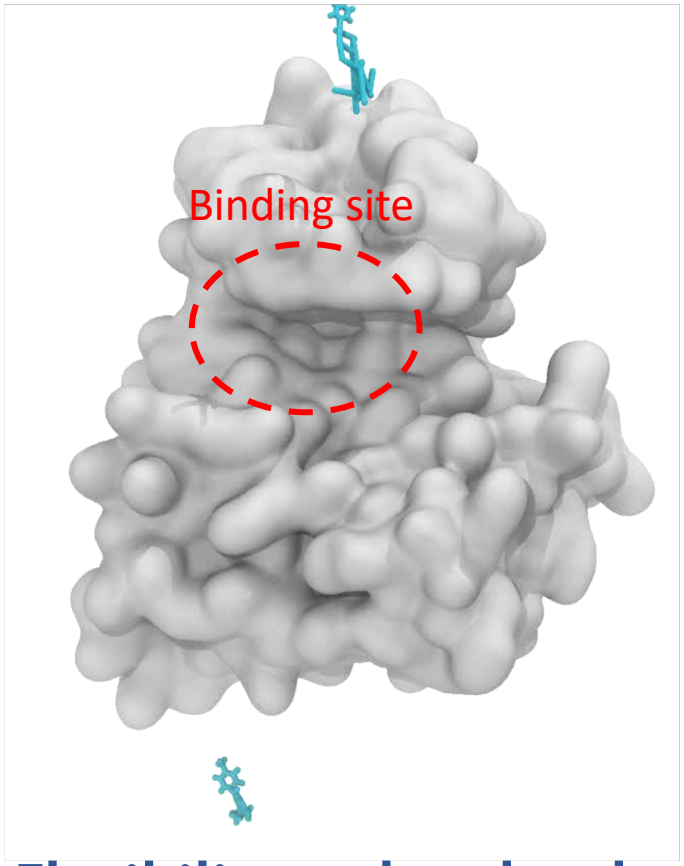
J. Jung, T. Mori et al. WIREs Comput. Mol. Sci. 5, 310-323 (2015)

Computational Drug Discovery

From "Docking" to "Binding"



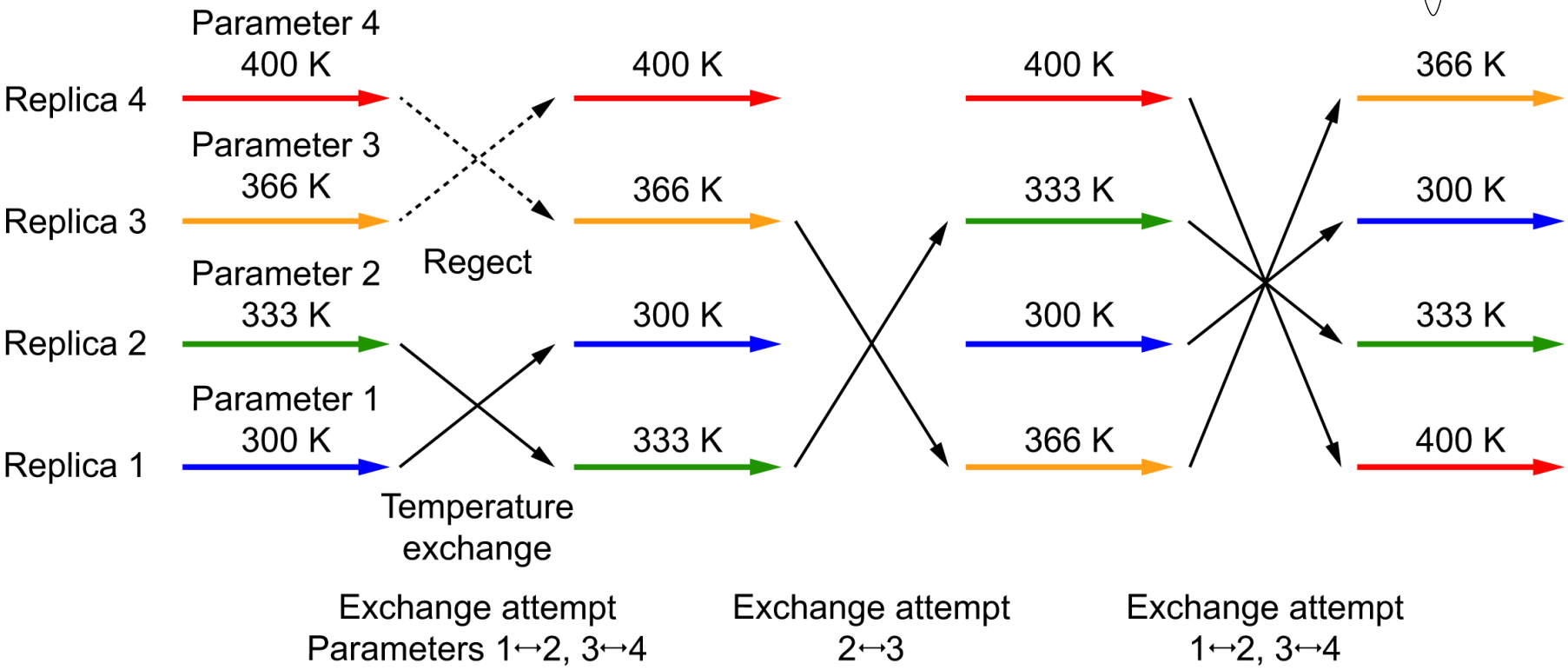
Static shape complementarity



Flexibility and molecular interaction

Replica-Exchange MD (REMD)

Overcome high energy barrier by parameter exchanges



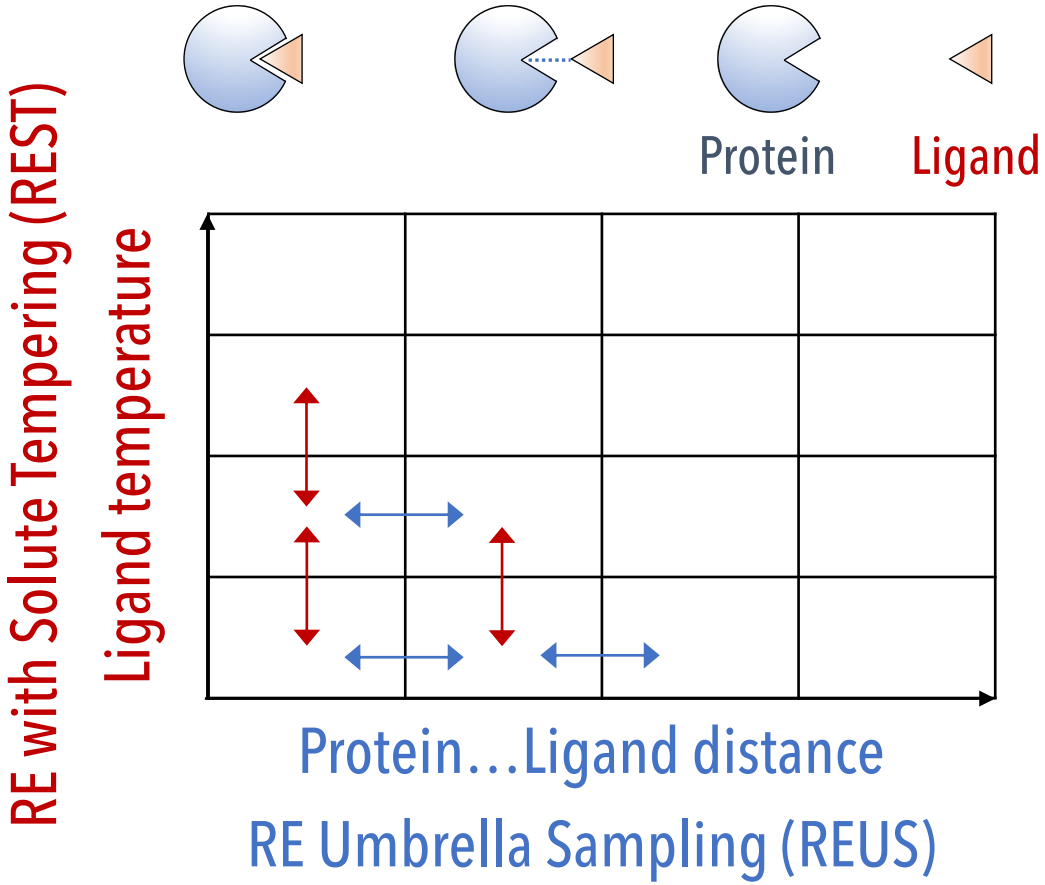
Y. Sugita and Y. Okamoto, Chem. Phys. Lett. 314:141-151 (1999)

2D-REMD for Ligand Binding

Enhanced sampling of ligand-binding events

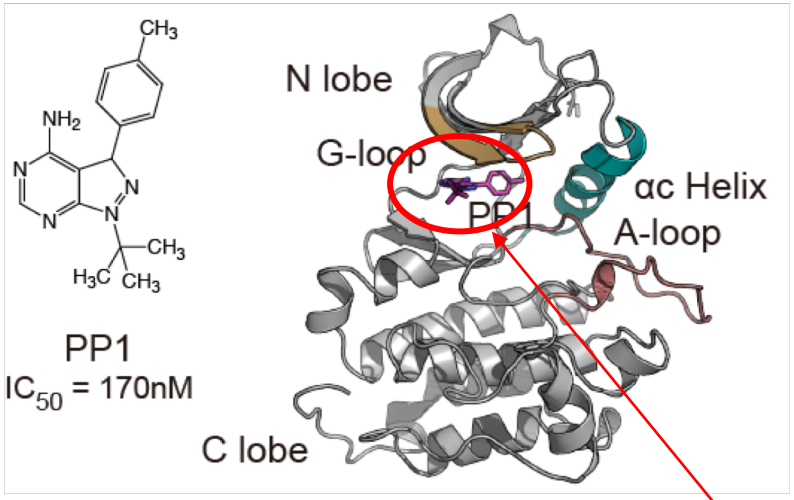
Multidimensional REMD: Y. Sugita, A. Kitao, and Y. Okamoto, J. Chem. Phys. 113: 6042-6051 (2000), MREM, REUS, H. Fukunishi, O. Watanabe, and S. Takada, J. Chem. Phys. 2002, 116 (20), 9058–9067, H-REMD

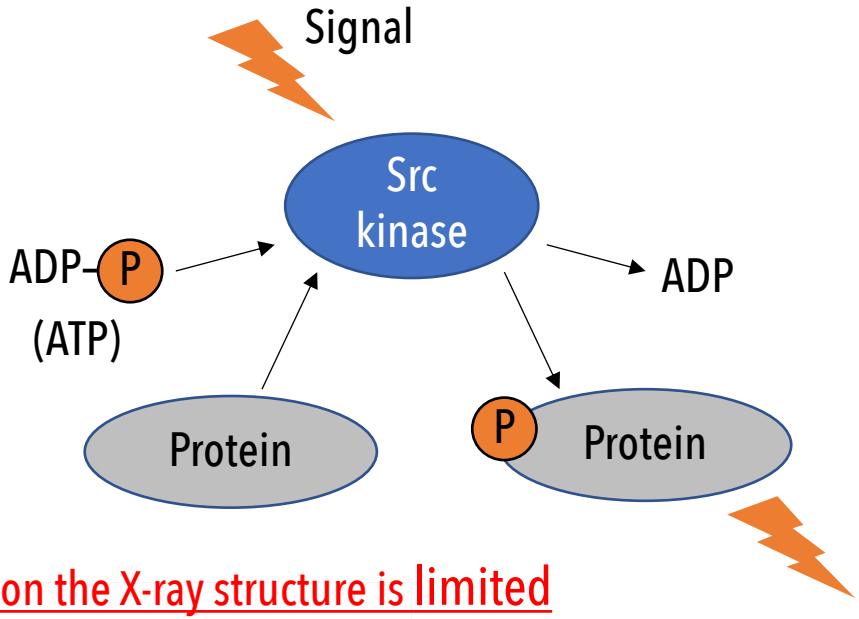
First application: H. Kokubo et al. J. Comput. Chem. 34:2601-2614 (2013)



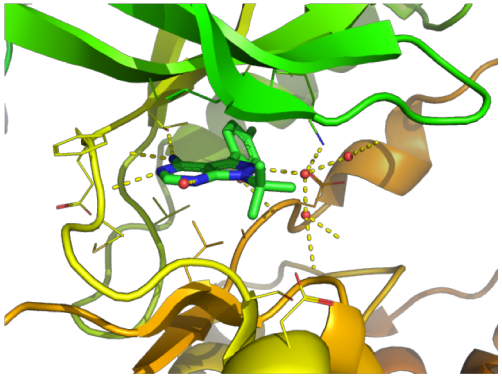
Src Kinase – Inhibitor Binding

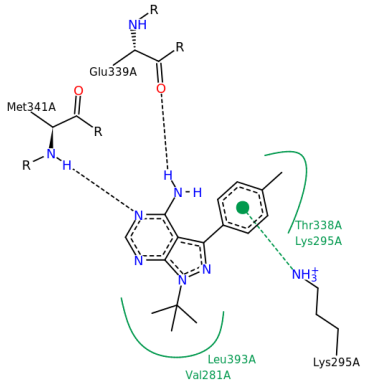
A key signaling kinase in cancer process





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

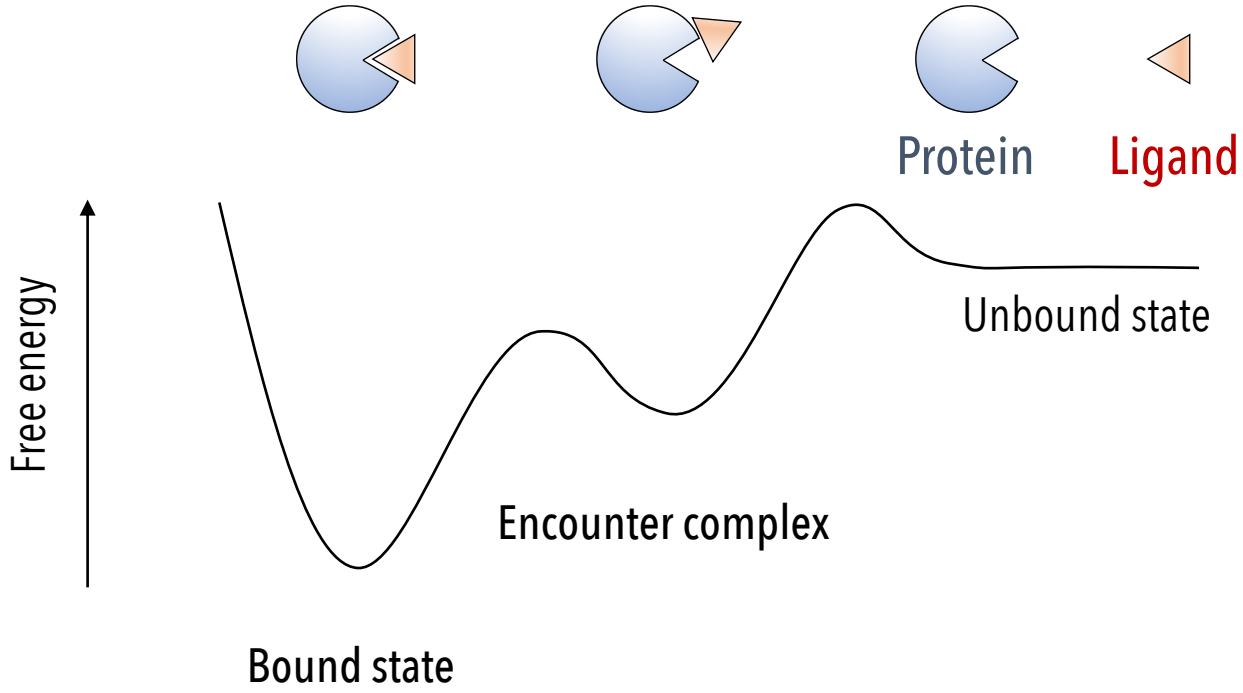




Only a part of whole functional interactions is given.

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 deign principle.

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

Acknowledgement

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Laboratory for Biomolecular Function Simulation
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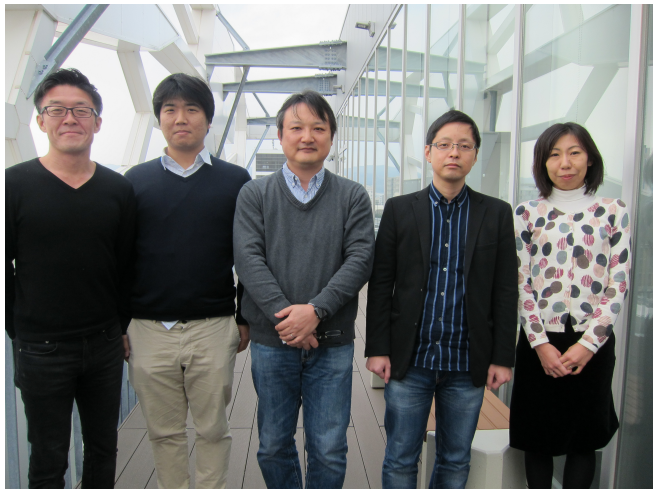
Dr. Ai Niitsu (RIKEN Wako)
Prof. Michael Feig (MSU, USA)

About GENESIS usage
Dr. Jung Jaewoon
Dr. Chigusa Kobayashi



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)

Computational resources: K computer (Project ID: hp170254), FX10 in University of Tokyo (Project ID: hp170115) by HPCI system, and HOKUSAI (Project ID: G17016) by RIKEN Advanced Center for Computing and Communication.

Thank you for your attention!