

# Structural Analysis of FGFR1 Kinase Activation through Molecular Dynamics Simulation

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## Abstract

*Receptor tyrosine kinases are critical regulators of signal transduction pathways mediating cellular homeostasis. Enhanced kinase activities via mutation and other genetic alternations have been observed in many human cancers. We performed a 4 ns molecular dynamics (MD) simulation of the kinase domain of fibroblast growth factor receptor 1 (FGFR1) to study the mechanism that controls its activation. Our simulation revealed the key atomic events that allow substrate access and kinase activation. This dynamic information will facilitate the design of new inhibitors for use in the treatment of cancer.*

## 1. Introduction

Fibroblast growth factors (FGFs) play important roles in angiogenesis and tumor development. Genetic alterations that enhance FGF receptors activity have been observed in a number of cancers. The crystal structure of FGFR1 suggests a novel auto-inhibition mechanism in that FGFR1 exists in equilibrium of active and inhibitive conformations [1]. We have performed molecular dynamics simulation to study the structural dynamics of FGFR1 activation loop which hold key insights into FGFR1 regulation.

## 2. Materials and Methods

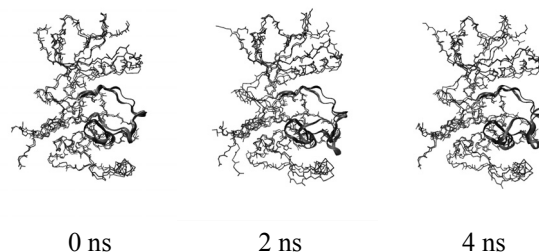
Simulation was performed with NAMD [2] using

CHARMM22 force field with explicit water model. The system was minimized by 10000 steps of conjugate gradient minimization. The system was then heated to 300K during which the protein backbone was fixed. The particle mesh Ewald (PME) method was used to treat long-range electrostatic interactions. The time step was 1 fs and trajectory was saved every 1 ps.

## 3. Results

### Activation loop adopted an open conformation

The c-terminus of activation loop moves away from initial conformation and adopts the open conformation at about 2 ns. It maintains the open conformation for the rest of simulation.

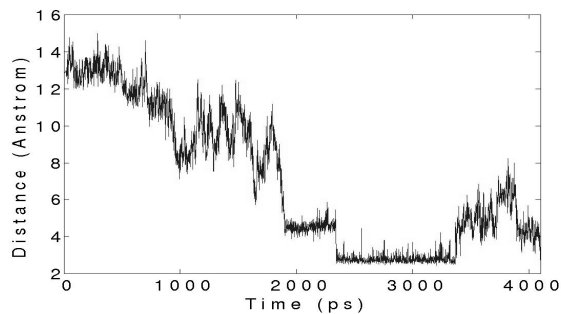


**Figure 1.**  $\alpha$  superposition of the starting structure (grey) and conformation adopted at various steps of simulation (black).

### Open conformation of activation loop was stabilized by hydrogen bond

Strong hydrogen bond was formed between

D652OD2 and T657OG1 which is the main force that attracts the c-terminus of the activation loop to the open conformation.

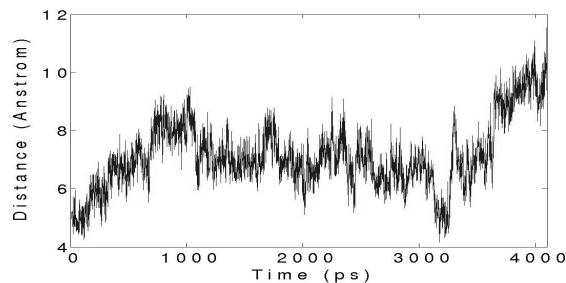


**Figure 2. Distance between D652OD2 and T657OG1.**

The two atoms become close enough to form hydrogen bond around 1800 ps. Particularly stable bond was formed between 2.4 ns and 3.4 ns.

### Open conformation of activation loop allows substrate access

With the rotation of the c-terminus end of activation loop towards open conformation, the proline 663 (P663) residue moves away from asparagine 623 (D623). The distance is far enough to allow the binding substrate peptide.



**Figure 3. Distance between D623 and P663.** The distance remains about 7 Å with notable increase after about 3700 ps. At such distance P663 is no longer capable of blocking Tyrosine substrate access to the catalytic residue: D623.

## 4. Summary

We have performed four ns MD simulation on FGFR1 kinase domain with explicit water solvation. We found the c-terminus of activation loop adopts an open conformation around 2 ns into the simulation. The rotation of the activation loop was triggered by the hydrogen bonding between D652OD2 and T657OG1. Residues involved in this interaction could serve as potential targets for therapeutic agents aimed to inhibit FGFR1 kinase activity. In the future, we will perform MD simulation on several mutations. These include hydrogen bond forming residues D652, T657 and mutations observed in cancer.

## Reference

- [1] M. Mohammadi, J. Schlessinger, S.R. Hubbard. Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism. *Cell*. 1996 86(4):577-87.
- [2] L. Kalé, R. Skeel, M. Bhandarkar, R. Brunner, A. Gursoy, N. Krawetz, J. Phillips, A. Shinozaki, K. Varadarajan, and K. Schulten. NAMD2: Greater scalability for parallel molecular dynamics. *Journal of Computational Physics*, 1999 151:283-312.

## Acknowledgement

**This work was supported by Georgia Cancer Coalition and Georgia Research Alliance**