

Protein Kinase Inhibitor Studies – an *ab initio* Quantum Mechanical Computational Approach Linearly-Scalable to Thousands of Atoms

Scientists from a number of leading research institutions combined a classical dynamics simulations method with a new *ab initio* approach, ONETEP, to study the interactions of five distinct inhibitors with the cyclin-dependent kinase protein CDK2.

ONETEP¹ is a new density functional method designed to achieve linear-scaling of computational time and memory with the number of atoms, while retaining the high accuracy² of the conventional cubic-scaling plane-wave methods .

“This unique development allows us to extend the applicability of *ab initio* calculations to molecules with thousands of atoms,” said Dr Chris-Kriton Skylaris, University of Southampton.

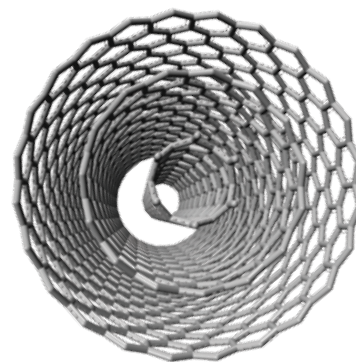
The inhibition of the human protein kinase CDK2, one of 500 kinases encoded in the human genome and involved in DNA replication, is a potential target for cancer therapies. However, both the potency and selectivity of candidate inhibitors, crucial in inhibitor design, are hard to predict, despite rational development based on crystallographic studies.

To address this challenge, the researchers, reporting in *Journal of Medicinal Chemistry*,³ used this novel computational approach to study the action of five CDK2 inhibitors. The ONETEP large-scale density functional calculations were able to accurately predict the binding energies of the inhibitors to the pocket of the CDK2 protein while the classical dynamical simulations provided access to large regions of the potential energy surface and long time scales. The computations revealed that peptides of about 1000 atoms are required to describe the binding accurately. Polarization, charge transfer and hydrogen bonding effects over such large clusters were found to play significantly role.

“These effects can only be described accurately by an *ab initio* quantum approach, so the use of ONETEP here enabled us to explain in detail all the protein-ligand interactions involved and obtain the correct relative potencies of the inhibitors,” concluded Dr Skylaris.

References

1. Chris-Kriton Skylaris, Peter D. Haynes, Arash A. Mostofi, and Mike C. Payne, *J. Chem. Phys.*, **2005**, *122*, 084119; See also <http://www.onetep.soton.ac.uk/>
2. Chris-Kriton Skylaris, Peter D. Haynes, Arash A. Mostofi, and Mike C. Payne, *J. Phys.: Condens. Matter*, **2005**, *17*, 5757.
3. Lucy Heady, Marivi Fernandez-Serra, Ricardo L. Mancera, Sian Joyce, Ashok R. Venkitaraman, Emilio Artacho, Chris-Kriton Skylaris, Lucio Colombi Ciacchi, and Mike C. Payne, *J. Med. Chem.* **2006**, *49*,(17) 5141.



Module used

ONETEP – Exclusive to the Nanotechnology Consortium

Industry sectors

Pharmaceuticals

Organizations

- University of Cambridge, UK
- Université Claude Bernard Lyon, France
- Curtin University of Technology, Australia
- Tyndall National Institute, Ireland
- Hutchison/MRC Research Centre, Cambridge, UK
- University of Southampton, UK
- Fraunhofer Institut für Werkstoffmechanik, Germany