D4.1 – CINECA Transnational Access success story

Deliverable No.:	D4.1
Deliverable Name:	CINECA Transnational Access success story
Contractual Submission Date:	30/04/2022
Actual Submission Date:	23/09/2021
Version:	v1.0

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 730897.

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	**HPC-Europa3**
Project Full Name:	Transnational Access Programme for a Pan-European Network of HPC Research Infrastructures and Laboratories for scientific computing
Deliverable No.:	D4.1
Document name:	CINECA transnational access success story
Nature (R, P, D, O):	R
Dissemination Level (PU, PP, RE, CO):	PU
Version:	V1.0
Actual Submission Date:	23/09/2021
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ABSTRACT:
This document provides an overview of two visits to CINECA. The visits were not only scientifically successful with very interesting scientific outputs produced but they also led to a career change for both visitors who are now both hired as CINECA team members.

KEYWORD LIST:
HPC-Europa3, Transnational Access, research, collaboration, CINECA, HPC

MODIFICATION CONTROL			
Version	**Date**	**Status**	**Author**
0.1	07/09/2021	Draft	D. Testi (CINECA)
0.2	17/09/2021	Draft	C. Inglis (UEDIN-EPCC)
1.0	23/09/2021	Final	D. Testi (CINECA)

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Executive summary

This document will present two among the numerous success stories of visitors who have decided to make use of CINECA resources and establish a collaboration with a scientific research group in Italy.

The two visitors were selected for the interesting results achieved but also because, after their visits ended and they returned to their home institutions, they both have applied to open positions at CINECA, and they are now enrolled within the CINECA team.

This provides strong evidence of how the experience gained during the HPC-Europa3 visit can open new career opportunities.

1 Introduction

At the time of her visit, Maria Montagna was a Post Doc researcher at the Institute of Materials Science of the Technological University Dresden (Germany) and her project was successfully selected at the tenth HPC-Europa3 call in November 2019. Maria carried out her 13-week visit between January and April 2020 and was hosted by Prof. Marco D'Abramo of University La Sapienza in Rome. The project titled "Modelling Src conformational transitions by means of classical molecular dynamics and essential dynamic sampling" was carried out using resources provided on the CINECA Galileo HPC system. The visit lasted a bit longer than originally planned due to the start of the COVID-19 lockdown in Italy, but the pandemic did not prevent Maria from achieving very nice results. The host reported very interesting scientific outcomes after the visit and he was very happy with the overall visit.

Nitin Shukla's application was successfully approved at the sixth HPC-Europa3 call in November 2018. At the time, Nitin was a postgraduate student at the Department of Physics at the Instituto Superior Tecnico in Lisbon (Portugal). Nitin carried out his 4-week visit between January and February 2019, hosted directly at CINECA under the scientific supervision of Dr. Elisabetta Boella. His project, "Relativistic collisionless shocks: microphysics and long-term dynamics", was supported with resources on the CINECA HPC system Marconi A2.

Both projects really resulted in interesting outcomes and are described in the following sections. Now both Nitin and Maria are, since March 2020 and January 2021 respectively, colleagues in the HPC department at CINECA, contributing to the Specialistic support and to the HPC User Support groups.

2 Maria Montagna – Modeling Src conformational transitions by means of classical molecular dynamics and essential dynamic sampling

2.1 Project Overview

The Src-family protein kinases are a class of enzymes with implications in many crucial processes regulating cell functions such as growth, differentiation, and proliferation. Src is formed by a myristoylated SH4 domain which anchors the kinase to the cell membrane the structural SH3 and SH2 domains and the kinase domain (KD), which contains the active site, see Fig.1 [1].

They play a crucial role catalysing the transfer of a phosphate group from a triphosphate donor to a protein tyrosine residue (phosphorylation) [2]. In this way, they can activate T cell and B cell receptors, which are involved in pathologies like cancer and autoimmune diseases [3]. The Src enzymatic activity is regulated by the switch between two conformations, called open and closed state, see Fig.1 [1], with a three-dimensional rearrangement modulated by phosphorylation and interaction with other proteins.

Detailed picture of the structural molecular changes involved in Src kinases activation/deactivation mechanism could represent an important achievement in drug design for the therapeutic treatment of diseases. Furthermore, a new mutation (E527K) has been recently identified in Src protein, as a possible cause of an immunological disease. In this work, the open and closed state have been characterized in wild type (WT) and E527K mutants to identify possible structural significance differences between them.

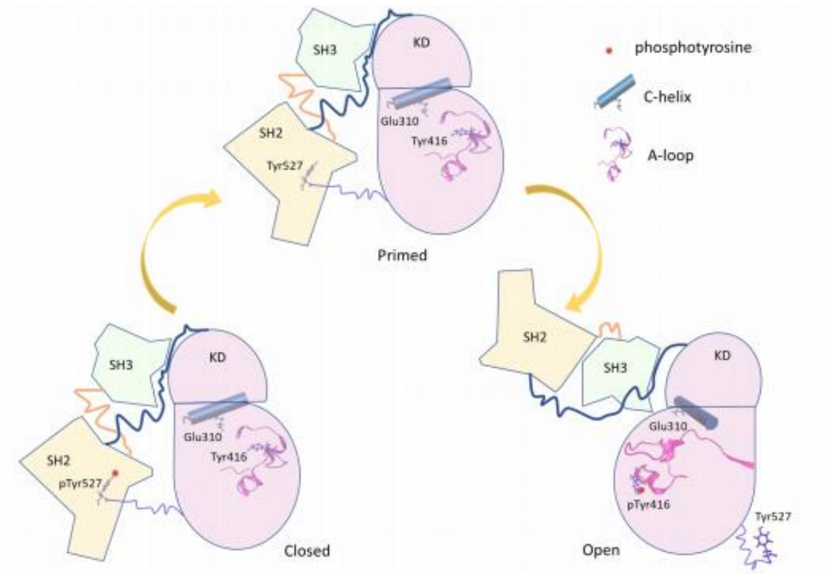

Figure 1. Scheme of the principal conformational states of the full-length Src. The three Src domains are represented in different colours: SH2 in yellow, SH3 in light green, and kinase domain (KD) in pink. [1]

2.2 Project results

Molecular dynamic (MD) simulations using Gromacs Software and Amber99sb force field were performed. The two proteins, namely Src WT and E527K, were solvated separately in a cubic box. The systems have been initially equilibrated in the NPT ensemble and then evolved in the NVT ensemble, keeping the temperature constant at 300 K. Water molecules were described using the TIP3P model. The long-range coulomb interactions were treated using Particle Mesh Ewald approach. All the simulations were performed with an integration time step of 2 ps, saving the trajectory each 1000 steps.

Once the trajectories were collected, the root mean square deviation (RMSD) and the root mean square fluctuation (RMSF), of Src and E527K, were calculated and compared in order to identify possible structural differences. Concerning the RMSD, the same behaviour was observed in the open/closed conformations, in case of WT and its mutant. With respect to the RMSF, a slight reduction of the Kd and SH2 domain residue fluctuations was identified in the case of E527K.

The principal component analysis (PCA) was performed using the covariance matrix of C-*alpha* fluctuations as obtained by the simulations, in both the conformational states. By the MD trajectory projections in the essential 2D subspace of the two main eigenvectors, it is possible to discriminate between the open and the closed forms for both the proteins. As expected, the open form is characterized by a greater structural variability, due to the higher mobility of Kd, able to explore a wider region of the essential subspaces (see Fig.2 [1]). This behaviour is verified for both the proteins, WT and E527K mutant.

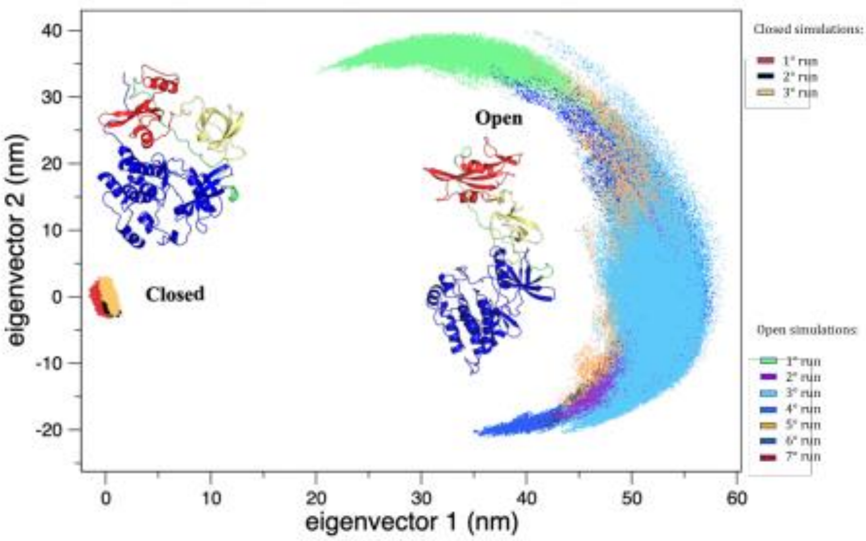

Figure 2. The 2D trajectory projections on the common conformational space. On the left is the region explored by the closed states, and on the right is the region explored by the open states. [1]

Essential dynamic sampling (EDS) has been performed and analysed in the case of WT Src on the two different mechanisms related to the activation (close-to-open) and to the deactivation (open-to-close) pathways. The results suggest that the activation pathway is mainly driven by the conformational change of the A-loop chain while the deactivation process (open-to-close) is governed by the C-helix rearrangement.

To summarize, the closed and open state of the WT and E527K mutant have been investigated and characterized. No significant changes were observed in structural features except a slight reduction of the Kd and SH2 mutant flexibility that will be better investigated. The results concerning the investigation of WT protein are reported in detailed in Ref [1].

2.3 Personal and Professional Experience.

Maria says of her research background: "I received my master degree in Physics in 2009 at La Sapienza-University of Rome, under the supervision of Prof. Leonardo Guidoni. In October 2013, I completed my PhD, which was part of a project between the University of L'Aquila (Italy) and a private industrial partner, Eni spa. During the doctorate, I carried on a computational study of some catalysts, based on transition-metal complexes, involved in polymerization processes.

After my PhD, I worked in two different departments in La Sapienza, specifically, in the Pharmacy and Chemistry Departments. During this time, I had the opportunity to interact closely with theoretical and experimental researchers, focusing my activity on molecular modelling, and in particular on classical and first principles MD simulations and theoretical chemistry calculations.

In 2016 I moved to Dresden, in Germany, joining the group of Dr. Olga Guskova, at Leibniz Institute of Polymer Research. Here, I worked on the multi-scale modelling of light-sensitive polymeric materials. Then, I have joined to the group for Materials Science and Nanotechnology Group of Prof. Cuniberti, at Dresden University of Technology. I was involved in an interdisciplinary project devoted to characterising organic/inorganic interactions in biosilica mineralization processes, using a multi-scale approach combining MD and quantum chemistry methods.

The main interests of my scientific career are devoted to biophysics, nanotechnology and material science using computational modelling approaches. Specifically, I worked on organic/un-organic interactions in bioinspired systems; Thermodynamic and structural properties of hybrid and complex materials; Hydration processes and vibrational biospectroscopy.

At the end of the HPC-Europa3 project, I applied for a position at Cineca; currently, I am a member of the User Support Group, assisting the HPC users in their research activities."

2.4 Role of HPC-Europa3

Maria explains why the HPC-Europa3 was a valuable step in her research career:

"During the time I was working as postdoc in Dresden, I have obtained the HPC-Europa3 fellowship that gave me the opportunity to spend 3 months in the group of Prof. Marco D'Abramo, at the Chemistry Department of La Sapienza University in Rome. This group focuses its research on computational methods and advanced molecular theories, investigating thermodynamic and structural properties of biological systems, in particular, proteins.

I would say that the HPC-Europa3 project was extremely helpful to lay the foundations for stimulating and fruitful collaborations. I was incorporated into the host group, sharing my own technical expertise in classical and quantum MD simulations with the group, and, on the other hand, I was enriched by the host's experience in Protein modelling and EDS procedure. This complementary cooperation helped me to consolidate and to expand my knowledge on molecular modelling in the biological field. Furthermore, this research has been highly extended and recently published in Biophysica [1].

Once my postdoc in Dresden was completed, thanks to the network established during the HPC-Europa3 project, I obtained a new research position at the Department of Information Engineering, (La Sapienza University), to work in the group of Prof. G. D'Inzeo. The main topic of this project was devoted to investigating the effect of interaction between some protein targets and electromagnetic fields. All these collaborations led to the production of an additional paper, currently under revision in Bioelectrochemistry [4], and another two works that are now in preparation.

To conclude, I should spend some words about the excellent support provided by CINECA Center, first of all for the HPC facilities, that were crucial for the success of the project, but also for the logistical assistance provided during this critical pandemic period. I have really appreciated their availability and efforts."

3 Nitin Shukla - Magnetization of plasmas: microphysics and long-term dynamics

3.1 Project overview

Magnetic fields are ubiquitous in the universe. The quest of identifying mechanisms, which are capable of generating magnetic fields from unmagnetized systems, has been puzzling the scientific community for decades. We live in an exciting era where technology could unleash the possibility of unfolding the mystery of our universe. In particular, the progress in laser technology nowadays allows us to explore processes relevant for astrophysics on earth under controlled conditions. However, experiments need to be carefully planned and appropriate laboratory conditions must be properly identified. Numerical simulations modelling the laboratory conditions play a vital role here. In this project, by performing accurate numerical simulations, experimental parameters were identified that allow for the investigation of mechanisms for magnetic field generation in unmagnetized plasmas through laser-solid interaction. The results were summarised in the following publication: N. Shukla, K. Schoeffler, E. Boella, J. Vieira, R. Fonseca and L.O. Silva, "Interplay between the Weibel instability and the Biermann battery in realistic laser-solid interactions", Physical Review Research, vol. 2, p. 023129, 2020.

3.2 Project results

Two and three-dimensional simulations were performed, modelling the interaction of an intense laser pulse with a pre-formed plasma target at the solid density. A pre-plasma in front of the main target was considered. This pre-plasma could be generated by the laser pre-pulse or by the laser amplified spontaneous emission. When the intense pulse illuminates the target, plasma electrons are strongly heated and thus expand away from the interaction region. The expansion creates a density gradient while the heating causes a temperature gradient. The latter is perpendicular to the former and so, as a result, a toroidal magnetic field is generated via the mechanism known as Biermann battery. The simulations showed that if the pre-plasma scale-length is too long, then the Biermann battery is not efficient. However, an intense magnetic field is generated through a plasma micro-instability: the Weibel instability. The Weibel instability is triggered by electrons being heated much more in the laser propagation direction with respect to the transverse directions. Summarising, work demonstrated that, by shining an intense laser on a solid, two different mechanisms to generate magnetic field in unmagnetized plasmas could be explored. This opens the door to mimic processes relevant for astrophysics in the laboratory and collect a new series of data and details which will shed light on phenomena, such as gamma ray burst, supernovae explosions etc, of which we only have remote information through the emitted radiation.

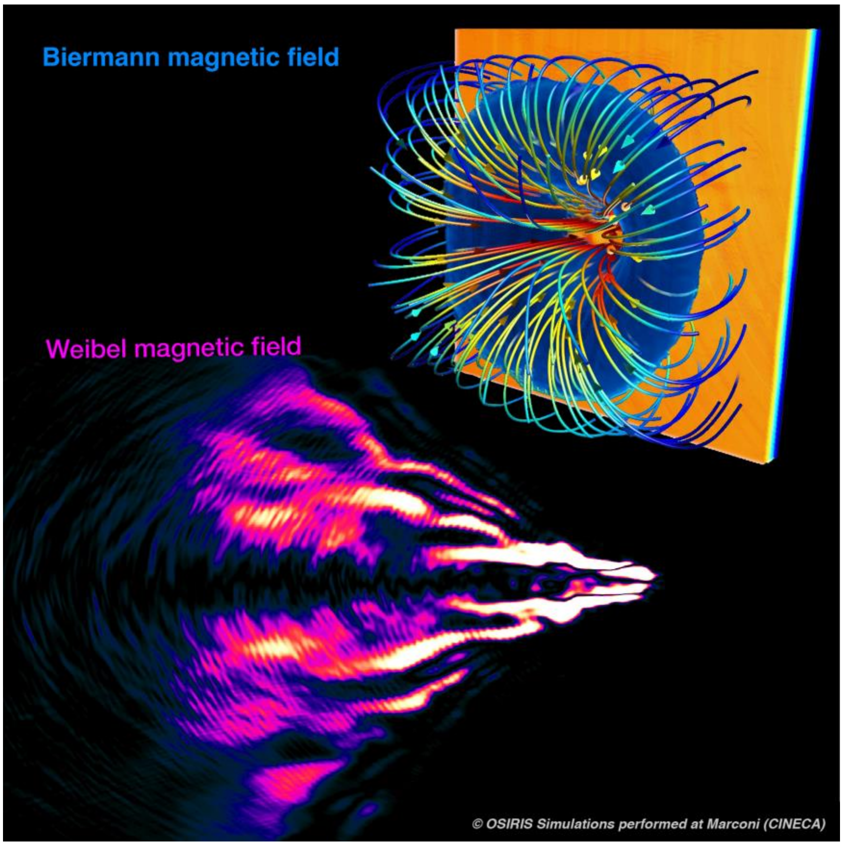

Figure 3: Magnetic field generated via the Biermann battery mechanism and the Weibel instability in intense laser-solid interaction. By varying the scale length of the pre-plasma one mechanism can dominate over the other.

3.3 Personal and professional experience

Nitin says: "HPC-Europa3 provided me with the amazing opportunity of collaborating with Dr. Boella and performing my simulations on Marconi (CINECA). The visit to CINECA was extremely fruitful. Interacting with CINECA staff, besides Dr. Boella, helped me in developing new High-Performance-Computing and scientific visualisation knowledge.

During my visit to CINECA, I got the chance to interact with CINECA High-Performance-Computing (HPC) specialists and discuss their work. I was inspired to hear their passion for HPC. I had the opportunity to see a supercomputer for the first time with my own eyes. I was very excited. That day, I thought how cool it would be to work at CINECA with such amazing colleagues. At that time, I was at the end of my Ph.D. and was looking for my next career steps. This visit inspired my interest in HPC. So, when a position opened at CINECA, I immediately sent my candidature. I passed the selection, and now here I am working in my dream place."

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