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Use of HPC Computing for Accelerating Drug Discovery Targeting the SARS-CoV-2 S-RDB/ACE2 Interaction

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The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has led to a global health crisis, triggering an urgent need for effective therapeutic interventions to mitigate its impact. The virus primarily infects human cells by binding its spike protein (S-RDB) to the ACE2 receptor, making this interaction a key target for drug discovery. In response, this study aimed to identify novel compounds capable of blocking the S-RDB/ACE2 interaction to prevent viral entry into cells. This work utilized high-performance computing (HPC) to study the S/ACE2 complex and discover drugs that may target the S/ACE2 interface.

The interaction between spike and ACE2 was studied by performing molecular dynamics simulations with a length of 400 ns using the AMBER 21 software. The interfacial binding pocket was then defined using FPocket 2.0. Subsequently, a virtual screening protocol was employed. Using Autodock Vina and GOLD molecular docking software, 139,146 compounds were screened. These compounds belonged to different chemical libraries: the Chimiothèque Nationale, MuTaLig Virtual Chemotheca, and the Inhibitors of Protein-Protein Interactions Database.

From the results of the virtual screening experiment, 10 compounds were selected for experimental validation. Experimental validation, including binding assays such as AlphaLISA and Biolayer Interferometry, as well as cellular tests, confirmed the the effectiveness of two compounds in human lung cells. RT-qPCR and cytotoxicity assays demonstrated dose-dependent effects. Finally, the compounds also showed activity against SARS-CoV-2 variants.

This work underscores the importance of computational drug discovery, highlighting the critical role of HPC resources in accelerating the development of potential therapeutics for COVID-19.

Primary authors: MARTINS, Fábio G. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal); FERNANDES, Henrique S. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal); MAGALHÃES, Rita P. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal); SOUSA, Sérgio F. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal); VIEIRA, Tatiana F. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal)

Presenter: MARTINS, Fábio G. (LAQV/REQUIMTE,BioSIM Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal)

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