2nd INTERNATIONAL WORKSHOP NSFDE&A'22

SOZOPOL, BULGARIA

NUMERICAL SOLUTION OF FRACTIONAL DIFFERENTIAL EQUATIONS AND APPLICATIONS

S. HARIZANOV, R. LAZAROV, I. LIRKOV, S. MARGENOV (EDS.)

INTERNATIONAL WORKSHOP

NSFDE&A'22

SOZOPOL, BULGARIA

NUMERICAL SOLUTION OF FRACTIONAL DIFFERENTIAL EQUATIONS AND APPLICATIONS

PROCEEDINGS OF SHORT COMMUNICATIONS

S. HARIZANOV, R. LARAROV, I. Lirkov, S. MARGENOV (EDS.)

Editors

Stanislav Harizanov
Bulgarian Academy of Sciences
Sofia, Bulgaria

Raytcho Lazarov
Texas A&M University
College Station, Texas, US

Ivan Lirkov
Bulgarian Academy of Sciences
Sofia, Bulgaria

Svetozar Margenov
Bulgarian Academy of Sciences
Sofia, Bulgaria

ISBN 978-619-7320-10-7 (eBook)

Institute of Information and Communication Technologies, Bulgarian Academy of Sciences,
Acad. G. Bonchev Str., Bl. 25A, 1113 Sofia, Bulgaria, 2020

Computational modeling of the replicase-transcriptase complex of SARS-CoV-2

N. Todorova[1], M. Rangelov[2], P. Petkov[3], N. Ilieva[4], E. Lilkova[4], and L. Litov[3]

[1] Institute of Biodiversity and Ecosystem Research, Bulgarian Academy of Sciences
[2] Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences
[3] Faculty of Physics, Sofia University "St. Kl. Ohridski"
[4] Institute of Information and Communication Technologies, Bulgarian Academy of Sciences

COVID-19 pandemic poses unprecedented societal challenges on a global scale with enormous medical, economic, political and ethical impact. To devise therapeutic strategies to counteract SARS-CoV-2 infection it is crucial to develop a comprehensive understanding of how the virus hijacks the host and inactivates its immune response during the course of the infection. This knowledge is indispensable for developing new drugs, alongside with repurposing existing ones.

To ensure its replication, the SARS-CoV-2 virus blocks the innate immune response of the host cell by interrupting mRNA transportation from nuclei to the cytoplasm and influences the IFN signalling pathway by preventing the transportation of STAT1 trough the nuclear pores thus blocking the expression of type I IFN induced genes. It was hypothesised that the SARS-CoV-2 Nsp13 protein influences the IFN type I production by interacting with two key players of IFN signalling pathway – TANK-binding kinase 1 (TBK1) and TANK-binding kinase 1-binding protein 1 (TBKBP1/SINTBAD [1]. We aim at ellucadating the mechanism of this interaction in order to unblock the inhibited interferon pathways. For this, we focused on the viral replicase-transcriptase complex (RTC), part of which is the helicase Nsp13.

We developed a precise model of the replicase-transcriptase complex of SARS-CoV-2 from the crystallographic structure deposited in Protein Data Bank (PDB ID 6XEZ [2]), adding the missing amino acids and nucleotides. Bigger missing parts were modeled *de novo* and the final structure of the complex was protonated by simulated physiological conditions of pH=7, T=300K, and salt content 0.15 M/l. A topology was created for the resultant structure with the software package GROMACS [3], accounting for Zn^{2+}

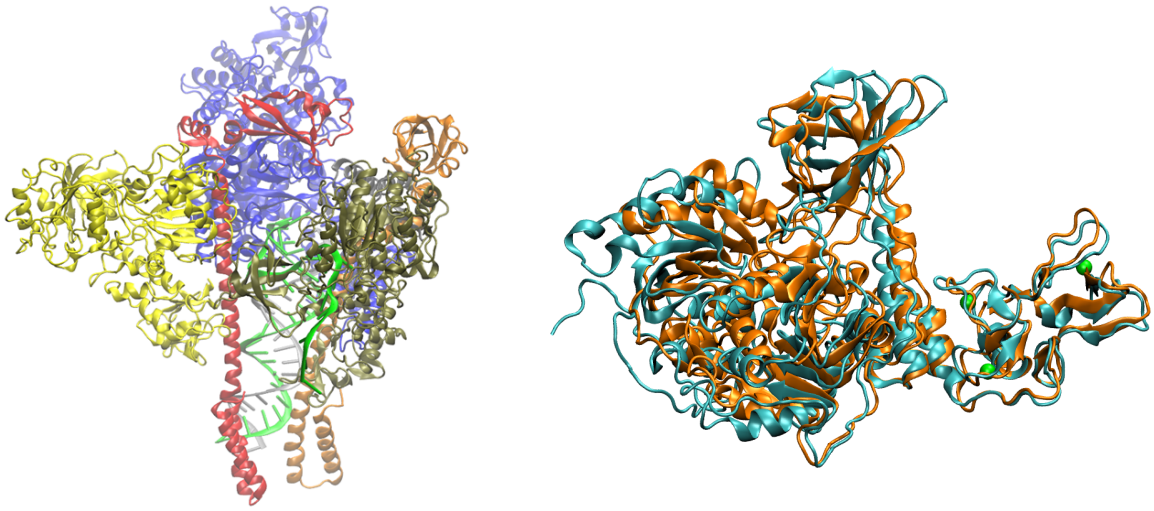

Figure 1: The replicase-transcriptase complex of SARS-CoV-2; PDB ID 6XEZ, Nsp8 in red, Nsp13 in yellow (left panel; Nsp13: PDB apo form in yellow, the structure after 330 ns of MD simulation, with parameterized Zn^{2+} ions in blue (right panel).

containing fragments of protein structure (Fig. 1). The contact sites between Nsp8 [4] and Nsp13 were identified and ranked based on their importance.

Further, similarities between Nsp8 and TBK1 were explored on the sequence level and with the secondary structure taken into account. To this end, all possible fragments derived from the Nsp8 sequence and longer than 10 amino acids were examined for similarities with all possible positions with respect to the TBK1 sequence [5] means of similarity matrices BLOSUM45, BLOSUM62, BLOSUM80 and BLOSUM90 [6, 7, 8]. The identified fragments with the highest degree of similarity were used for the assessment of the possibility of stable complexes formation between Nsp13 and TBK1.

Acknowledgements This work was supported in part by the Bulgarian National Science Fund under Grant KP-06-DK1/5/2021. Computational resources were provided at the HPC cluster BIOSIM at the Faculty of Physics of Sofia University "St. Kl. Ohridski".

References

[1] Gordon, D. et al. (2020) A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. Nature **583** (2020) 459–468 doi

[2] Chen, J., Malone, B., Llewellyn, E., Grasso, M., Shelton, P.M.M., Olinares, P.D.B., Maruthi, K., Eng, E.T., Vatandaslar, H., Chait, B.T., Kapoor, T.M., Darst, S.A.,

Campbell, E.A. Structural Basis for Helicase-Polymerase Coupling in the SARS-CoV-2 Replication-Transcription Complex. Cell **182**(6) (2020) 1560–1573.e13 doi

[3] Abraham, M.J., Murtola, T., Schulz, R., Pll, S., Smith, J., Hess, B., Lindahl, E. GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX **1-2** (2015) 19–25.

[4] Wilamowski, M., Hammel, M., Leite, W., Zhang, Q., Kim, Y., Weiss, K.L., Jedrzejczak, R., Rosenberg, D.J., Fan, Y., Wower, J., Bierma, J.C., Sarker, A.H., Tsutakawa, S.E., Pingali, S.V., O'Neill, H.M., Joachimiak, A., Hura, G.L. Transient and stabilized complexes of Nsp7, Nsp8, and Nsp12 in SARS-CoV-2 replication. Biophys J. **120**(15) (2021) 3152–3165 doi

[5] Larabi, A., Devos, J.M., Ng, S.L., Nanao, M.H., Round, A., Maniatis, T., Panne, D. Crystal structure and mechanism of activation of TANK-binding kinase 1. Cell Rep. **3**(3) (2013) 734–746 doi

[6] Styczynski, M.P., Jensen, K.L., Rigoutsos, I., Stephanopoulos, G. BLOSUM62 miscalculations improve search performance. Nature Biotechnol. **26**(3) (2008) 274–275 doi

[7] Jianzhu Ma, Sheng Wan. Algorithms, Applications, and Challenges of Protein Structure Alignment. In: Rossen Donev (Ed). Advances in Protein Chemistry and Structural Biology, Vol. 94 (Academic Press, 2014), pp 121–175; ISSN 1876-1623, ISBN 9780128001684.

[8] Gauthier, J., Vincent, A.T., Charette, S.J., Derome, N. A brief history of bioinformatics, Briefings in Bioinformatics **20**(6) (2019) 1981–1996 URL