world community grid

NEWSLETTER

Issue 1
February 2023

Our Vision: A healthier world.

Our Mission: Accelerating science by creating a supercomputer empowered by a global community of volunteers.

The Numbers:

- 18 years of WCG
- 2,450,152 years of computation
- 808,068 volunteers
- 7,627,753 devices
- 32 projects benefited

"WCG continues to support open-source and open-data research and helps reduce computational time to empower scientists to address the world's most pressing questions at no cost to the researchers".

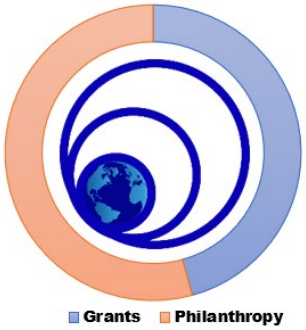
Dr. Igor Jurisica

Happy New Year. And what a year it was!

Welcome to our first newsletter. Sixteen months ago, management of the World Community Grid (WCG), which was originally launched by IBM in 2004 as a philanthropic project, was transferred to the Jurisica Lab at the Krembil Research Institute, University Health Network, in Toronto, Canada. This followed an incredibly successful contribution and commitment by IBM and its employees (and thousands of volunteers) to develop the largest free academic research network, globally. For over 17 years, IBM provided critical financial and operational support, and in doing so, allowed hundreds of researchers across diverse areas to access super-computer scale processing power. We want to extend a big THANK YOU to IBM!

While we are saying thank you, we can't forget the thousands of volunteers and partners who have donated their computing resources to WCG, enabling this large-scale research. WCG is incredibly fortunate to be able to capitalize on this support – including the passion and dedication of our volunteers, which shines through brightly.

With the transfer of WCG from IBM to the Krembil Research Institute, we needed to ensure the continuation of the WCG, as it was set to be discontinued by December 2021. Like most major transitions, it proved to be incredibly challenging. New hardware had to be sourced along with a data centre capable of hosting a system with sufficient capacity. As well, the entire software platform had to be changed to fit a new environment by a four-person team in the Jurisica Lab, funded by academic sources. It didn't help that this was all happening in the midst of a global pandemic and economic downturn.



Through all of the changes and challenges, the new WCG remains committed to the vision of providing the world's largest volunteer-driven supercomputer, enabling seemingly impossible scientific research to come to life, and doing so at no cost to researchers.

Since September 2021, funding for the WCG and its operation has come from a combination of Canadian research funds and philanthropy. With the loss of a major sponsor, a new sustainable model needs to be developed. Additionally, adding new projects will need more volunteers, which in turn will require more storage and processing capacity.

Early in WCG's transition from IBM to academia, we were fortunate to be introduced to Distributive (https://distributive.network), software company from Kingston, Ontario, Canada. Distributive specializes in building high throughput computing tools that streamline researchers' workflows for deploying large scientific projects to huge networks, of donated, or otherwise unused computing resources – networks like the World Community Grid! Distributive shares WCG's passion for advancing academic research and benefiting humanity. Early in 2022, Distributive provided WCG with a $200,000, no-strings-attached donation. We are very grateful for the funding, as well as the potential opportunities for collaboration in the coming year.

Distributive

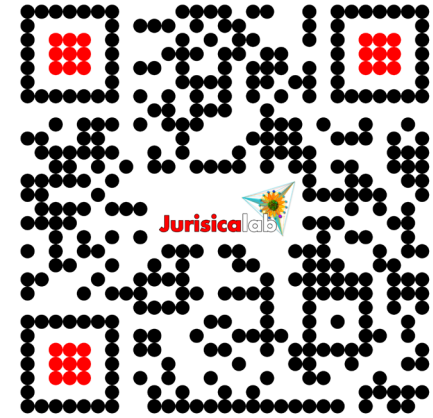
"By its very nature, World Community Grid is a collaborative effort involving individuals and institutions from around the world working towards innovative advancements in science that benefit humanity. Distributive is proud to be a part of this mission."

Dr. Dan Desjardins,

co-founder & CEO, Distributive Corp., Kingston, Ontario, Canada

Dr. Jurisica & the WCG Team

Transitioning from running two projects on the Grid to running and supporting them all.



PROJECTS CURRENT AND FUTURE

Africa Rainfall Project: The ARP team is finalizing storage issues, and plans to resume downloading results from the WCG servers, which will enable more work units to be sent to volunteers. Work units are being sent out at a slower rate due to the backlog of completed results. Further, errors in specific generations have caused some generations to lag behind. Together with the ARP team, we have investigated the cause of these errors, and we determined that re-sending them after adjusting the granularity/time-step should resolve the problem.

Help Stop TB: The team has been analyzing previous results and devising new strategies for the search. We are waiting for the Help Stop TB team to provide us with new work units.

Mapping Cancer Markers: We have increased the number of threads assigned to the creation of MCM work units by about 60% on each work unit management server. As a result, the seven-day average of completed batches sent back to MCM1 research servers (10,000 work units to a batch) has risen from 45 to 57, roughly a 25% increase. As we increased the number of threads in a two-step process and conducted maintenance on the storage server twice during the seven-day period over which the average is calculated, we do expect this number to increase further even without additional adjustment, and will continue to assess whether we can further optimize it.

Open Pandemics: OPNG work units are paused as the team is preparing a new set of protein targets. We will provide an update once the new work units are ready to be distributed.

Smash Childhood Cancer: Once the team finalizes new targets, they will be able to prepare work units for the next phase of the SCC project.

Open Zika Project: Dr. Carolina Horta Andrade (Faculdade de Farmácia Universidade Federal de Goiás, LabMol), together with Dr. Sean Ekins (Collaborations Pharmaceuticals, Inc.) and Dr. Alexander Perryman (Rutgers University–New Jersey Medical School) started the OpenZika project in May of 2016 in collaboration with IBM WCG to identify possible inhibitors of the Zika virus. Patients affected by this virus suffer paralysis of their nervous systems and children born to mothers affected by the virus have severe brain development defects. While it was already an enormous threat in Brazil, it had the potential to become a global threat unless a treatment was developed quickly. WCG's massive computational power enabled the team to rapidly test millions of compounds in search of possible inhibitors of various Zika virus targets.

Open Zika project, from IBM's World Community Grid

"This work has demonstrated the importance of the integration of computational and experimental approaches, as well as the potential of large-scale collaborative networks to advance drug discovery projects for neglected diseases and emerging viruses, despite the lack of available direct antiviral activity and cytoprotective effect data, that reflects on the assertiveness of the computational predictions."

Dr. Carolina Horta Andrade

By November, the list of 7,600 potential compounds was screened to test their efficacy against the NS3 helicase, a Zika virus protein that allows it to unwind its duplex RNA. The list of molecules was reduced to eight compounds, five of which were subsequently verified to be safe by a study conducted at the University of California, San Diego. In March of 2017, the team was ready to move onto the second stage of the project. The team used a server to create a large library of 30.2 million compounds to be tested against the NS2B-NS3 protease, NS3 helicase, and NS5-polymerase proteins. Running computational screening on this large library was only possible thanks to the combined efforts of the World Community Grid (WCG) volunteers.

The tests on these 30.2 million compounds continued through December of 2018, when the team analyzed an additional compound database supplied by ChemBridge. The list of one million compounds was tested in their effectiveness against NS5 polymerase, NS5 methyltransferase, and the NS3 helicase; ultimately reducing it to 55 compounds of interest. The results were sent to the University of California for evaluation in the virus, as well as to University of Sao Paulo for evaluation with the Zika virus proteins in July, 2019.

Powered by a community of 80,000 volunteers who donated on average almost 73 CPU years a day to the WCG project, the OpenZika team was able to finalize their modelling and the project was completed in December 2019. The next phase was focused on the experimental validation and prioritization of the selected molecules.

In October 2022, the team's four years of research culminated with a publication in the *Journal of Chemical Information and Modeling*[1].

The paper highlights the computational process and the validation steps performed during and after WCG analysis. The research team published the results for three important Zika virus proteins: NS3hel, NS2B-NS3pro, and NS5 RdRp. Using WCG, the researchers searched millions of commercially available compounds and identified 61 possible compounds of interest for further screening and optimization.

After the massive docking calculations, the compounds were filtered using machine learning models developed by LabMol group to identify those that were cytoprotective against Zika Virus infection. Then, compounds that were predicted to pass the blood brain barrier were retained, in order to select those that could counteract the effects the virus has on the central nervous system. Finally, a medicinal chemistry inspection identified and selected compounds with desirable features present in existing drugs.

From almost 404 million results generated by WCG, amounting to almost 93 thousand years of computation, 61 hits were prioritized for testing. Using enzymatic and phenotypic assays, five compounds were ultimately selected as they inhibited the

function of or destabilized the three viral proteins of interest, NS2B-NS3 protease, NS3 helicase and NS5-polymerase proteins. Further tests identified 8 compounds as being able to protect the cells from death caused by the virus, while showing low cellular toxicity in liver and kidney-derived cells. The two sets of 5 and 8 molecules overlap for two compounds, named by the authors LabMol-301 and LabMol-212.

The results of this research are exciting, and further optimization could lead to these molecules being tested as antiviral treatments for Zika virus. The researchers are now looking for partners for performing the hit-to-lead optimization with chemical synthesis and further experimental validations.

We thank the WCG volunteers who made these findings possible, and the OpenZika team for sharing this exciting update and their continued involvement with WCG.

[1] Melina Mottin, Bruna Katiele de Paula Sousa, Nathalya Cristina de Moraes Roso Mesquita, Ketllyn Irene Zagato de Oliveira, Gabriela Dias Noske, Geraldo Rodrigues Sartori, Aline de Oliveira Albuquerque, Fabio Urbina, Ana C. Puhl, José Teófilo Moreira-Filho, Guilherme E. Souza, Rafael V. C. Guido, Eugene Muratov, Bruno Junior Neves, João Hermínio Martins da Silva, Alex E. Clark, Jair L. Siqueira-Neto, Alexander L. Perryman, Glaucius Oliva, Sean Ekins, and Carolina Horta Andrade. Discovery of New Zika Protease and Polymerase Inhibitors through the Open Science Collaboration Project OpenZika. *Journal of Chemical Information and Modeling,* 62(24), 6825-6843, 2022. DOI: 10.1021/acs.jcim.2c00596. https://pubs.acs.org/doi/full/10.1021/acs.jcim.2c00596

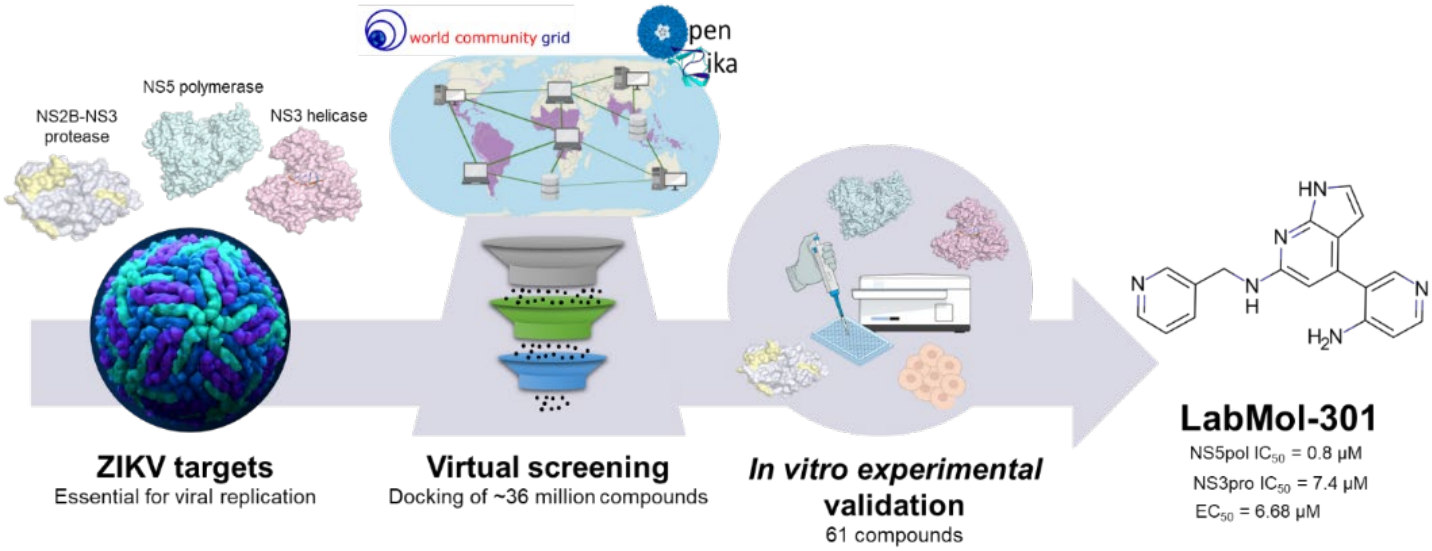
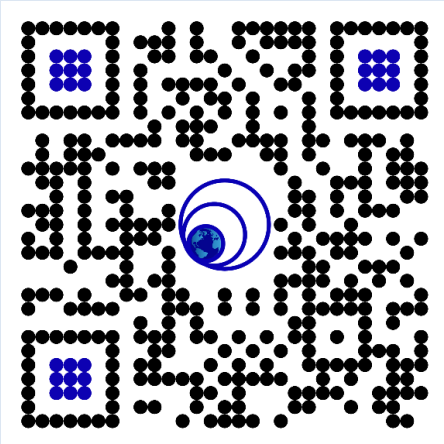


Figure 1Description of the discovery pipeline; created by Bruna K. P. Sousa from Dr. C. Horta Andrade lab.

World Community Grid

"With the help of volunteers, partners, and institutions, the WCG will continue to grow as the world's largest volunteer-driven supercomputer, enabling seemingly impossible scientific research to come to life".



General Updates:

To reduce time and resources needed to onboard new projects, we are working on generalizing the current software platform to enable a broader group of projects to use them. Working with Distributive, we will also have a platform for easier and faster onboarding of projects.

Work continues at the WCG data centre to refresh and expand the systems, providing more and faster processing, as well as storage. Efforts are ongoing to optimize the large data bandwidth requirements of WCG.

A CALL FOR HELP

The need for massive computational resources is growing exponentially with increased volume and improved data quality. Better algorithms and more specialized hardware have enabled seemingly impossible and world-changing breakthroughs in medical research and in the study of climate change. Never has the need for WCG been greater, and never has the potential to impact humanity been more profound.

As an academic resource, WCG faces significant financial and technical challenges in providing the necessary level of support to the global research community. WCG needs your help! If you are already contributing your computing resources, we thank you. If you haven't yet, you can sign up at https://www.worldcommunitygrid.org. Also, if you can, please consider donating to WCG – any amount of assistance is appreciated (https://www.worldcommunitygrid.org/donations).