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COMPUTATIONAL PROGRAMS FOR PHYSICS

FL-Online: An x-ray crystallographic web-server for atomic-scale structure analysis of biomolecule

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FL-Online (http://fanlab.ac.cn) is an out-of-box modern web service featuring a user-friendly interface and simplified parameters, providing academic users with access to a series of online programs for biomolecular crystallography, including SAPI-online, OASIS-online, C-IPCAS-online and a series of upcoming software releases. Meanwhile, it is a highly scalable and maintainable web application framework that provides a powerful and flexible solution for academic web development needs. All the codes are open-source under MIT licenses in GitHub.

Keywords: graphical web service, OASIS, IPCAS, direct methods, protein crystallography

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1. Introduction

Since Laue discovered x-ray crystal diffraction in 1912, x-ray crystallography has played a fundamental role in 20th-century science. With the advent of the fourth-generation synchrotron radiation sources,[1] x-ray crystallography continues to underpin science in the 21st century.

Crystallography programs stand as an indispensable tool in modern crystallographic research. Worldwide, numerous research teams and scientists have devoted themselves to the field of x-ray crystallography, developing a range of programs for structure determination such as XDS,[2] DIALS,[3] autoPROC,[4] iMOSFLM,[5] ACORN,[6] SnB,[7] SHELX,[8] Phenix,[9] Phaser,[10] SOLVE,[11] RESOLVE,[12] AutoBuild,[13] phenix.refine,[14] DM,[15] Baccnuer,[16] wARP,[17] AlphaFold2[18] and among others. CCP4 (collaborative computational project No. 4, United Kingdom) provides an integrated suite of programs for determining macromolecular structures through x-ray crystallography.[19]

Since 1965, a research group led by Hai-Fu Fan at the Institute of Physics, Chinese Academy of Sciences has been dedicated to solving the "phase problem" in x-ray crystallography (http://cryst.iphy.ac.cn). Two papers were published in 1965 both focusing on "direct methods" in crystallography.[20,21] The first paper[20] extended the Sayre equation[22] by considering the existence of heavy atoms with known positions. A subsequent systematic study on pseudo-symmetries and phase ambiguities[23] led to the development of the program SAPI (structure analysis programs with intelligent control),[24–26] which is the first direct-method computer program capable of detecting and solving superstructures. SAPI was adopted by the Rigaku Corporation (Japan) and the Molecular Structure Corporation (United States) from 1986 until the early 1990s, serving as the main structure-solving program for small crystal structures.

The second paper[21] proposed a method to resolve the phase ambiguity inherent in SAD (single-wavelength anomalous diffraction) or SIR (single isomorphous replacement) experiments, marking one of the earliest attempts to introduce direct methods to protein crystallography. The results of the research have been successfully applied in numerous disciplines, including materials and life sciences. Typical one is combining direct methods with protein crystallographic methods. The P_+ probability formula[27] was derived by combining the Cochran distribution in the direct methods, the bimodal distribution of SAD and SIR experiments in protein crystallography, and the Sim distribution in small-molecule crystallography. The program OASIS (one-wavelength anomalous scattering and single isomorphous substitution)[28] was written based on the P_+ formula, which has been adopted by CCP4 since 2000 as the only direct-method program capable of breaking the SAD/SIR phase ambiguity for diffraction data far below the 1.2 Å atomic resolution.[29] But only individual runs of direct-method SAD/SIR phasing could be performed with this version.

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In 2004, direct-method reciprocal-space fragment extension in the presence of SAD/SIR information was first introduced by Wang *et al.*,[30] which led to dual-space iterative SAD/SIR phasing and fragment extension. Yao *et al.*[31] showed that without SAD/SIR information, the fragment of MR (molecular replacement) model could also be extension in direct-method reciprocal space. In 2012, the pipeline IPCAS (iterative protein crystal structure automatic solution) was developed, in which the program OASIS performs direct-method single-wavelength anomalous diffraction/single isomorphous replacement phasing and direct-method-aided partial-structure extension. Moreover, IPCAS incorporates the widely used packages CCP4 and PHENIX for locating heavy atoms, density modification, molecular replacement, model building and refinement. In 2020, a new version (2.0) of the pipeline IPCAS[32] was released. Important extensions to the previous version of IPCAS include a resolution screening method for non-crystallographic symmetry searching, an alternate model-building protocol for avoiding premature convergence and direct-method image processing for electron microscopy maps, including single particle cryo-electron microscopy (cryo-EM) maps. Applications of the new IPCAS to difficult cases have yielded promising results, including 'direct-method phasing and fragment extension' from weak anomalous diffraction signal data, 'direct method-aided partial-structure extension' from low-homology/predicted models.

In addition, the group has also focused on exploring new applications of direct methods beyond their traditional fields. One is making the direct methods as a tool of image processing for electron diffraction and electron microscopy images. The program package VEC (visual computing in electron crystallography) was written for the automation of two-stage electron microscopy (EM) image processing.[33] A two-stage image processing procedure that combines information from an EM image and the corresponding electron diffraction (ED) pattern has been proposed.[34] Tests using the EM image of the high-critical-temperature (T_c) superconductor Bi-2212 showed that the resolution of the original EM image is enhanced by a factor of two.[35] Hopefully, this technique may also be useful in improving the resolution of cryo-EM images.

The other is the incommensurate modulated structures and composite structures solved by multidimensional direct methods. Multidimensional direct methods (MDDM) were proposed for the determination of incommensurate crystal structures without relying on a pre-assumed model.[36,37] The application of MDDM to the $0klm$ ED pattern of the high-T_c superconductor Bi-2223 revealed incommensurate modulation, which was reported by Zhong-Xian Zhao during the Nobel Jubilee Symposium of 1991.[38] The program DIMS (direct methods in multidimensional space) was written for the implementation of these methods,[39] and it was later incorporated into the VEC package.[40,41]

All previously introduced programs are offline software with numerous adjustable parameters, which can present challenges for both the local computing power and the user, particularly in the case of large or complex structures. In response to these challenges, FL-Online (Fan Lab Online) has been developed. It is a user-friendly web application with simplified parameters designed to provide free services for academic users, offering online access to programs developed by Prof. Hai-Fu Fan's group, including SAPI-online, OASIS-online, and C-IPCAS-online. Authorized users are free to log in to the website, submit jobs, and download results. For advanced users, other programs including DIMS[39] and VEC[40,41] can also be downloaded from the corresponding About page. It is worth mentioning that the core code for SAPI-online originated from SAPI 1.0;[42] for OASIS-online, it is derived from OASIS 4.0;[31] for C-IPCAS-online, it is a simplified version of IPCAS 2.0,[32] featuring two fundamental modules of SAD and MR.

2. Function

FL-Online is a multi-user single-page application which first includes signup, login, and authentication functions (Figs. 1(a) and 1(b)). The signup and login forms contain field verification. After successful login, the user will automatically enter the homepage (Fig. 1(c)). The homepage integrates information into cards for display. The card showing the map is the access statistics by RevolverMaps[43] (Fig. 1(d)). Click on the card to enter the About page of the corresponding program (Fig. 1(e)). On the homepage, there are two other subpages, Submit and History, in the sidebar navigation menu of the program. The Submit page provides the job submit form for the corresponding program (Fig. 1(f)). All form items have verification rules and are checked after losing focus. The website will remind users of form items that fail validation and prevent submission. For necessary parameters that depend on the MTZ file, the item will provide options corresponding to the MTZ file which was successfully uploaded. After the form is submitted successfully, it will jump to the History page, which displays the user's submission history in the form of a table (Fig. 1(g)). The table is sorted by the job ID and displays the submit time, title, job status and operation buttons which include terminating the job, downloading results, and viewing key result parameters (Fig. 1(h)).

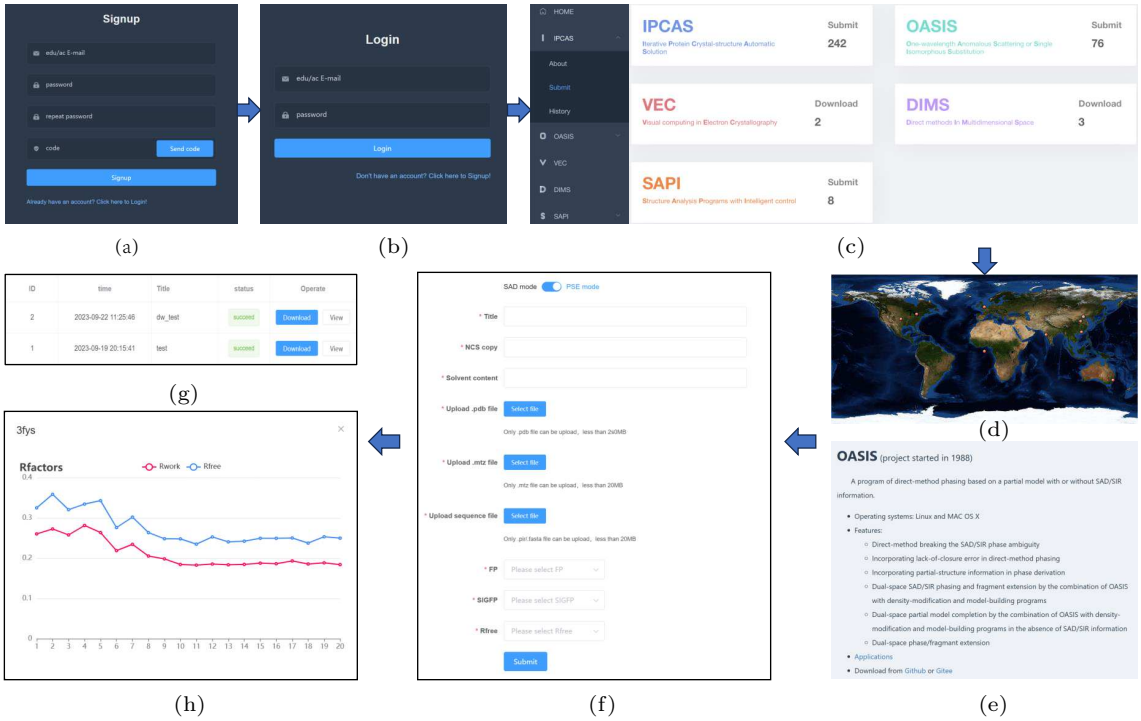


Fig. 1. The main interface of FL-Online. (a) Signup interface. (b) Login interface. (c) List of programs in the Home interface. (d) Access statistics in the Home interface. (e) IPCAS About interface. (f) IPCAS Submit interface. (g) IPCAS History interface. (h) IPCAS result display interface.

3. Development

FL-Online is a cutting-edge single-page application that follows a front-end and back-end separation architecture, utilizing the latest open-source development stack, as illustrated in Fig. 2. The front-end code repository, hosted on GitHub, is built upon the vue-element-admin project[44] and incorporates VUE.js,[45] a JavaScript framework, along with the Element-UI,[46] Desktop UI Library and other exceptional open-source development tools. These front-end files must be placed in the static resource folder of the HTTP service to ensure proper functionality. On the other hand, the back-end code repository, also hosted on GitHub, employs the powerful Koa2[47] web framework, MariaDB[48] as an open-source relational database, and Redis[49] as an in-memory database. These technologies work seamlessly together to ensure that the application's functionalities are robust and efficient. By adopting a front-end and back-end separation architecture, FL-Online offers a highly scalable and maintainable solution for various applications with command line interfaces (CLI). This approach allows developers to focus on specific aspects of the application, such as front-end design and user experience, while ensuring the back-end remains secure and reliable.

In addition, the back-end that interacts with the front-end through well-defined APIs integrates cross-domain resource access, database reading and writing, sending emails, identity authentication, information encryption, form verification and other functions, and combines Python[50] to parse MTZ file tags and atomic number statistics of sequence files. The calling and parameter passing of the crystallography program are implemented using bash[51] scripts.

The password set by the user is encrypted and stored in the database using SHA256 algorithm. The registration login system only allows the user to access the data of the logged-in user after authentication. Our server is enabled with SELinux, only the necessary ports are opened for port forwarding by Nginx,[52] and the database is only allowed for local access, which ensures the security of user data to the greatest extent.

In short, with its single-page application structure and front-end and back-end separation architecture, combined with the integration of cutting-edge open-source technologies, FL-Online provides developers with a powerful and flexible solution for their web development needs.

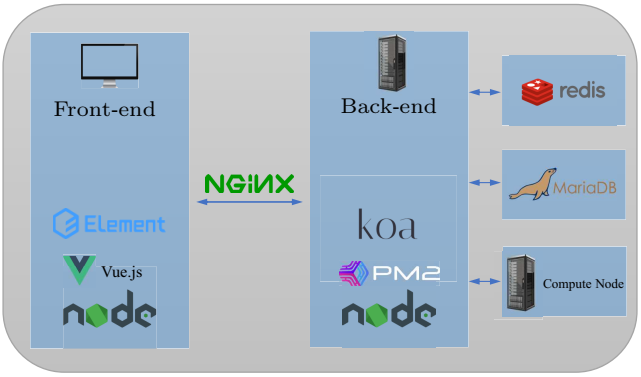


Fig. 2. The front-end and back-end separation architecture of FL-Online. The front-end is built using VUE.js framework along with the Element-UI. The back-end employs Koa2 web framework, MariaDB and Redis and hosted by pm2. The front-end and back-end communicate via NGINX.

4. Platform and workflow

The web application is deployed on a high-performance computing (HPC) environment using SLURM as the job scheduler (Fig. 3). The HPC system comprises a master node (Intel Core CPU i7-13700k, 3.4 GHz, 32 GB RAM.), 4 compute nodes (Intel Xeon CPU E5-2643 v4, 3.4 Ghz *2, 64 GB RAM), and a data server (4×18 T HDD). The master node serves as web server, login server, and task submission and scheduling server. All the necessary dependencies and software requirements for the web application are installed on the master node. The compute nodes have all the computational software or plugins that the web application needs to call installed on them. The compute nodes primarily provide computational functionality. After a computational task is submitted through the web, the actual calculations are performed on these compute nodes.

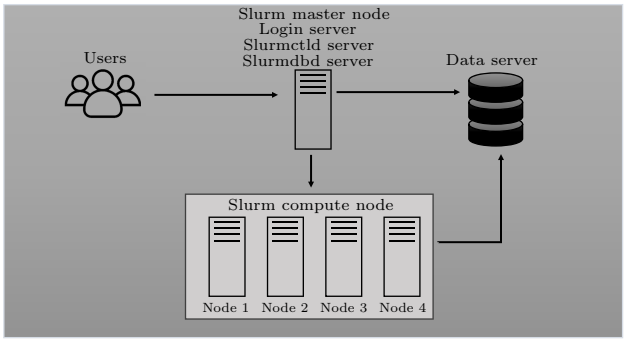


Fig. 3. Platform and workflow of FL-Online.

With the job script ready, the next step is to submit the job to SLURM for scheduling. This can be done using the 'sbatch' command, which submits the job script to the SLURM controller (master node) for processing. The master node then analyzes the job requirements and schedules the tasks on available compute nodes based on the specified parameters and the current state of the cluster.

All nodes in the HPC system share the storage server. The web application on the master node will monitor the generation of computation results in real-time. Once the computation is complete, the web application will read the results and push them to the web page for display.

5. Online services

FL-Online currently provides online services for SAPI-online, OASIS-online, C-IPCAS-online and provides downloads of all programs including DIMS and VEC that run on the Windows platform.

SAPI-online is originated from SAPI,[42] a direct-methods program for finding heavy-atom sites with SAD or SIR data. The program can automatically detect and handle diffraction data having pseudo-translational symmetry and lead directly to the superstructure without relying on an assumed structure model. In addition, it can recognize pseudo-centrosymmetric solutions when dealing with non-centrosymmetric structures. Moreover, the program can break the enantiomorphs ambiguity given the "atomic positions" of both enantiomorphs. In online version, job input is an MTZ file containing abnormal scattering data, DF, SIGDF column labels which represent abnormal scattering data, and of course a title. After calculation, SAPI-online will produce a file containing the coordinates of the heavy atom sites and a MTZ file with initial phases. Meanwhile, the coordinate of the heavy-atom site could be checked in history webpage shown as a three-dimensional scatter plot (Fig. 4(a)).

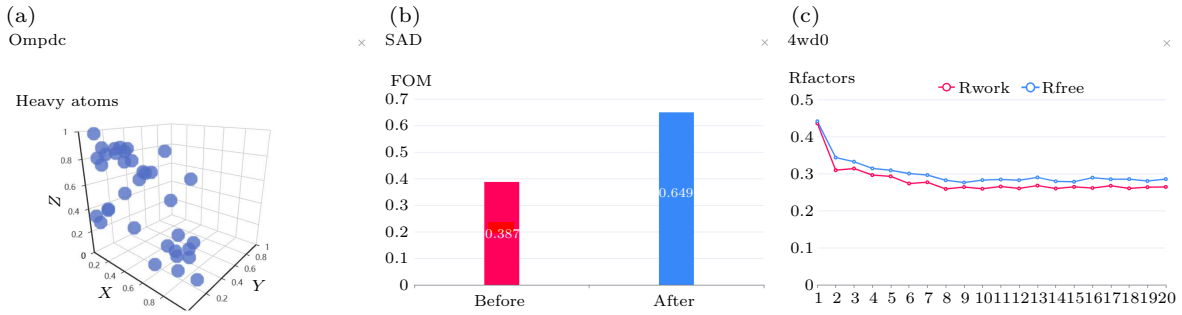


Fig. 4. Result display interface of online services. (a) SAPI-online displays the list of sites in the output SAPIPKS file. (b) OASIS-online displays the figure of merit (FOM) in MTZ files before and after OASIA runs. (c) C-IPCAS-online displays the Rwork and Rfree after every cycle.

OASIS-online is a direct method-based program for SAD phasing and MR phase extension. OASIS-online works entirely in reciprocal space, using the P+ formula for phasing or phases refinement iteratively until the results converge, and gives the MTZ file after calculation. In SAD module, OASIS-online resolves the phase ambiguity due to one-wavelength anomalous scattering or single isomorphous replacement.[53] In MR module, OASIS-online works in phase extension and phase refinement.[31] Job input for SAD module includes an MTZ file containing abnormal scattering data; column labels FP, SIGFP, FP(+), SIGFP(+), FP(−), SIGFP(−) which represent abnormal scattering data; the site type and the coordinate

of substructure. For MR module, input includes MTZ file, column labels and PDB file of current model. Final result (MTZ file) would be downloaded in history webpage, and the change of FOM value will be shown in a bar chart (Fig. 4(b)). FOM is defined as the expected value (probability-weighted average) of the cosine of the phase error. Blow & Crick shows that if this weight is applied to terms in an electron density calculation, the RMS error in the density is minimized.[54]

C-IPCAS-online is a simplified version of IPCAS 2.0,[32] featuring two fundamental modules: SAD and MR. In comparison to previous releases of IPCAS 2.0, C-IPCAS-online maintains the essential dual-space iterative framework for phasing and model building. In the SAD module, sites searching is performed using SHELXC/D. Subsequently, phasing, density modification, and model building are carried out through OASIS + DM + Phenix.AutoBuild (quick mode)/Buccaneer (alternate mode) within the dual-space framework. In the MR module, the user provides the initial model, and the entire workflow is iterative in phasing, density modification, and model building, which is the same as the SAD module. Previous tests have demonstrated that the majority of structures can be resolved within the current framework, as confirmed by the 60 blind tests conducted in this paper. When submitting a C-IPCAS-online job, users need to select the mode as SAD or MR. In addition to providing the job title and raw data (PDB, MTZ, sequence file), the SAD mode requires input of the x-ray wavelength, heavy atom type, and column labels representing anomalous scattering data for Friedel pairs in the MTZ file. Options are automatically generated only after the successful upload of the MTZ file. C-IPCAS-online will execute a specific number of dual-space iterations and will provide three sets of results: the smallest Rwork, the smallest Rfree, and the largest number of residues in the process. All the results with PDB and MTZ files could be downloaded in the history page and the View button allows users to review the Rwork and Rfree for completed iteration cycles at any time (Fig. 4(c)).

6. Performance testing

FL-Online is tested prior to each release. As for SAPI-online and OASIS-online, there have been no changes to the previously published version, and the test results are consistent with the data we have presented.[24–26,28,29] For C-IPCAS-online, we conducted a total of 60 blind tests, including 40 MR test cases and 20 SAD test cases. The MR search models were predicted by Alpha Fold2 and pre-processing by phaser. And the SAD test cases were downloaded from PDB with different resolutions, space groups, heavy atom sites and diffraction wave lengthes.

Figure 5(a) presents the Rfree analysis before and after using the C-IPCAS-online services in MR mode. The Rfree values of the C-IPCAS-online models consistently show improvement over the input predicted model for all cases, indicating the capability of our process to effectively correct biases in predicted models. In Fig. 5(b), the Rfree analysis of C-IPCAS-online services in SAD mode is listed. The majority of these cases exhibit Rfree values below 0.30, indicating a strong correlation between the observed diffraction data and the data calculated from the C-IPCAS-online models. This further confirms that C-IPCAS-online could also work well in SAD phasing and model completion.

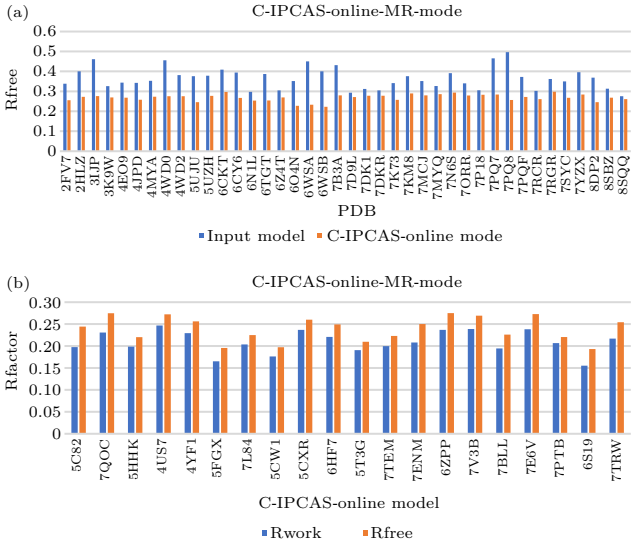


Fig. 5. (a) Plot of C-IPCAS-online results for the 40 MR data sets. Blue bar: Rfree value of input model, calculated by phenix.refine. Orange bar: Rfree value of the best C-IPCAS-online model. (b) Plot of C-IPCAS-online results for the 20 SAD data sets. Orange/blue bar: Rfree/Rwork value of the best C-IPCAS-online model.

7. Discussion

We present an out-of-box web application named FL-Online, with a user-friendly interface and simplified parameters for our programs. It enables users to easily use programs including SAPI-online, OASIS-online, and C-IPCAS-online on any device that can access the Internet, without having to compile and install them on the local Unix-like system. For advanced users, all programs including DIMS and VEC in addition can be downloaded from the corresponding About page.

FL-Online is developed in node.js mainly, based on the Vue-element-admin project, using Vue.js, Element-UI, Koa, MariaDB, Redis, Nginx[52] and more open-source projects. The web application framework is open source under MIT licenses in GitHub, allowing anyone to freely modify and redistribute it. Thanks to the front-end and back-end separation architecture, FL-Online is a highly scalable and maintainable solution for a wide range of programs. By modifying the necessary codes, developers can easily build their web application

servers. Combined with the integration of cutting-edge open-source technology stacks, FL-Online provides a powerful and flexible solution for academic web development needs.

In the future, more programs being developed by group members are coming soon, including IPCAS3.0, an updated version of IPCAS; AutoEMage,[55] an automated cryo-electron microscopy processing software, and PM-XFEL, an upcoming XFEL data processing software.

Program availability

The complete codebase for FL-Online is openly available on GitHub, facilitating transparency and reproducibility. Interested parties can review and download the code at https://github.com/FanLabIOP/FanLabOnline, providing a resource for both review and adaptation in related projects.

Data availability statement

For our data testing, the input data, comprising both diffraction data, model and sequence files, were sourced from the PDB, which are openly available in RCSB Protein Data Bank (RCSB PDB) at https://www.rcsb.org/.

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