Structural and Computational Biology Unit Review

The review of the Structural and Computational Biology Unit took place on 2 – 4 May 2022. The review panel consisted of 20 international experts, including six members of EMBL's Scientific Advisory Committee (SAC). The panel chair was Adrian Bird, from the University of Edinburgh, UK. Several observers were present, including the Chair of Council Eiríkur Steingrímsson, the Chair of SAC James Briscoe and the EMBL Director General Edith Heard. The review was convened in a hybrid format.

Evaluation Summary

The panel considered that the research done within the Structural and Computational Biology Unit in the past four years has been at the very highest international level. The science is rigorous, imaginative, collaborative, transdisciplinary and often at the cutting-edge technologically.

The unit is one of the largest on the EMBL Heidelberg site, comprising 14 groups and teams. It was jointly headed by Christoph Müller and Peer Bork, but in 2021 Christoph became the sole head of the unit, following Peer's installation as Director of the EMBL Heidelberg site. Since the merging of a structural biology unit and a computational biology unit respectively, the unit's themes have broadened to include structural cell biology, systems biology, microbiome research, spatial metabolomics, single-cell genomics, multi-omics, data integration, and structural bioinformatics. In spite of this diversity in areas, the interactions between groups appears to be excellent, as reflected in collaborations and joint publications. The continued success of the unit is highlighted by the fact that all the group and team leaders who have left the unit have secured senior posts in renowned academic institutions and the new recruits who presented at this review all showed exceptional promise.

Structural biology output remains extremely strong in the unit and will grow in importance as macromolecules are increasingly to be investigated in their cellular context. The panel was, for example, particularly struck by the demonstration of ribosome structures *in situ* at 3.5 Å atomic resolution. In-cell cryo-electron tomography (cryo-ET) technology unlocks a new level of interoperability and information depth. Computational biology is the other huge strength in the unit. The panel were concerned that specialised computational expertise within the unit would be lost in the next few years due to continued group and team leader turnover. Depending on the evolution of computational biology at EMBL Heidelberg, it will be important to consider how the unit can continue to develop in this area and replenishment of this aspect of the unit should be a priority. Ideally, computational biologists working at the intersection of genome-wide protein structure prediction and structural cell biology might help to unify the unit's various themes, also bridging to data science and theory.

Given the rather diverse research interests within the unit, bringing the members of the unit together is particularly important and pre- and post doc fellows expressed the desire for more cohesion within the unit. A unit-wide annual retreat and pairs of weekly shorter talks by scientists from different fields could be considered. Overall however, the fellows reported being generally very happy with their training, mentorship, scientific independence, transferable skills, and experience within the Structural and Computational Biology Unit.

Implementation of the new EMBL Programme has had a considerable impact on the Structural and Computational Biology Unit's portfolio. Notably, the Transversal Themes of Planetary Biology and Microbial Ecosystems cut across several aspects of the unit's existing research. Of these, Microbial Ecosystems has become a natural feature of the unit's activity. This Transversal Theme will further generate many new scientific questions that can be addressed by detailed mechanistic studies and the unit is in a prime position to exploit this. Expansion of this effort may well be justified in the future, subject to the availability of high quality group leader applicants.

EMBL is expanding its molecular focus to include biological systems at larger scales. This should be accompanied by method development to ensure future capacity to cope with the larger scale specimens. Hardware development could benefit from further integration of efforts between the Hamburg, Grenoble, and Heidelberg sites. As a specific example, plasma-focused ion beam-scanning electron microscopy (plasma-FIB-SEM) promises to allow rapid and efficient preparation of large numbers of lamellae from frozen, complex, large-scale specimens. EMBL could consider investing in this technology although this would need to be matched with recruitment in these areas.

The future of NMR in Heidelberg is uncertain due to the imminent departure of the specialist group leader within the Structural and Computational Biology Unit. Given the number of groups at EMBL interested in metabolites and unstructured regions, combined with the unique ability of NMR to investigate these areas, it is expected that there will be a stable future demand for NMR at EMBL Heidelberg, and beyond. NMR is absent at EMBL's other structural biology sites and nearby institutions, therefore the panel considered it strategically important to maintain NMR access and support at EMBL Heidelberg.

Overall, the panel would like to congratulate the Structural and Computational Biology Unit and its leadership on their outstanding achievements over the review period. With their imaginative and transdisciplinary research and their impressive capacity to nurture top scientists, the members of the unit are not merely pursuing biological themes but are instrumental in propelling them forwards.

Response to the Panel's Recommendations

I would like to extend my thanks to the chair, Adrian Bird, and the whole panel for their time and effort in reviewing the Structural and Computational Biology Unit. I join them in congratulating everybody within the unit, particularly the leadership, Christoph Müller and Peer Bork as the respective current and former heads of the unit, who have both consistently done an outstanding job. This unit has driven some of the most transdisciplinary and innovative research in the fields of structural biology and computational biology at EMBL and the research of every group and team in this unit can be considered a success story. The unit was also one of the driving forces behind the creation of EMBL's new Imaging Centre, of which Christoph Müller is deputy head and the Structural and Computational Biology Unit hosts the high throughput cryo-electron microscopy (cryo-EM) team leader. It is also remarkable how quickly the unit embraced the new EMBL programme, particularly in the areas of Planetary Biology and Microbial Ecosystems Transversal Themes. The unit's traditional structural and computational biology approaches fully align with EMBL's new Programme. Furthermore, several of the group and team leaders within the unit were directly involved in initiating and developing these Transversal Themes which emerged from an EMBL-wide brainstorming retreat in 2019.

I agree with the panel that the quality of the research undertaken by groups and teams within the Structural and Computational Biology Unit is outstanding. The unit's technology development and research focused on cryo-EM and cellular cryo-ET is accelerating highly novel research and providing unprecedented insights into the functional organisation of cells in the context of organisms. Likewise, global microbiome initiatives and advanced computational approaches that lead to important discoveries with these large and complex data sets, are propelling ambitious research both within and outside of the unit.

During the review, there was a perceived separation due to the unusual diversity of areas within the unit. Nevertheless, the unit collaborates and functions extremely well, with many collaborations. This success is a testimony to the way that the unit has evolved. To further strengthen the unit's cohesion, the format of the unit seminars will be amended to ensure that there are speakers representing computational biology and structural biology at each seminar. Furthermore, prior to the COVID-19 pandemic, the unit held retreats for all faculty members. These will be enlarged in 2023 to enable all unit members to participate.

Looking to the future, I support Christoph Müller's vision to continue focusing on structural and computational biology, hiring the best talent, whilst also nurturing the increasing importance of Transversal Themes stemming from the new EMBL Programme. By prioritising the hiring of excellent scientists and giving them the freedom to explore their scientific interests the unit can continue to evolve.

In terms of future recruitments, the unit will carefully consider bioinformatics and computational areas, given the numerous departures planned. It should be emphasised that the computational

scientists within the Structural and Computational Biology Unit have done a phenomenal job in propelling computational training and network building for scientists from diverse disciplines and with different computational abilities. The importance of computational approaches within the unit, and across all of EMBL is clear. This is one of the reasons for the establishment of the EMBL Data Sciences Centre that was supported by Peer Bork as he took on his role as Director of EMBL Heidelberg. The Centre, which is a pan-EMBL initiative, will strengthen existing data science activities in the Structural and Computational Biology Unit, while also adding new actions to make data sciences at EMBL more effective. Balancing this EMBL-wide need to strengthen computational activities with the Structural and Computational Biology Unit's computational focus will need to be discussed carefully.

In the area of structural biology and imaging, I agree with the suggestion by the panel to invest in the development of technologies for large-scale samples, such as plasma-FIB-SEM. This activity is well aligned with EMBL's mission to innovate and make new technologies accessible to other scientists. EMBL already has key personnel that are well-positioned to facilitate this activity. Integral to this, is the panel's suggestion for experts within the Structural and Computational Biology Unit to join forces with engineering and technology development experts at the EMBL Grenoble and EMBL Hamburg sites. I agree that this potential synergy should be nurtured. There is capacity and significant expertise available at EMBL's synchrotron sites that could be utilised to considerably larger effect. This has already been demonstrated with the development of the cryo-EM sample preparation technology, EasyGrid.

Regarding the continuation of NMR as a methodology at EMBL, I agree with the panel about the importance of sustained access to NMR for groups across EMBL sites as well as external users. In the context of the departure of Janosch Hennig, EMBL management will look closely at all possibilities to ensure that NMR can be maintained, considering the constraints of the current indicative scheme funding.

I would like to conclude by thanking the panel once again and extending my congratulations to Christoph Müller and Peer Bork, for their outstanding leadership, and to the entire Structural and Computational Biology Unit for their stellar research and contributions to EMBL. I look forward to seeing the evolution of this exceptional unit.

Professor Edith Heard, FRS
Director General
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