Technical Approaches to Ensuring High Ethical Standards in Science Publishing

科学出版における高い倫理基準を確保するための技術的アプローチ

Todd A. Carpenter
Executive Director, NISO
@TAC_NISO

JOSS Conference
June 8, 2022

NISO
How the information world CONNECTS

About NISO

NISO is a USA-based non-profit trade association that develops formal standards for publishers, libraries, and software providers.

NISO is a membership organization with about 300 members and about 600 volunteers, who do the work of developing the standards.

About 20% of NISO members are based outside of the United States.

NISO standards include MARC, Dublin Core Metadata, Digital Object Identifier (DOI), Journal Article Tag Suite (JATS), and DAISY Talking Books.

NISO also serves the international community as Secretariat for the ISO Committee responsible for ISO standard identifiers such as ISBN, ISSN, and DOI.

NISO について

NISOは、米国を拠点とする非営利の業界団体であり、出版社、図書館、ソフトウェアプロバイダー向けの正式な標準を開発しています。

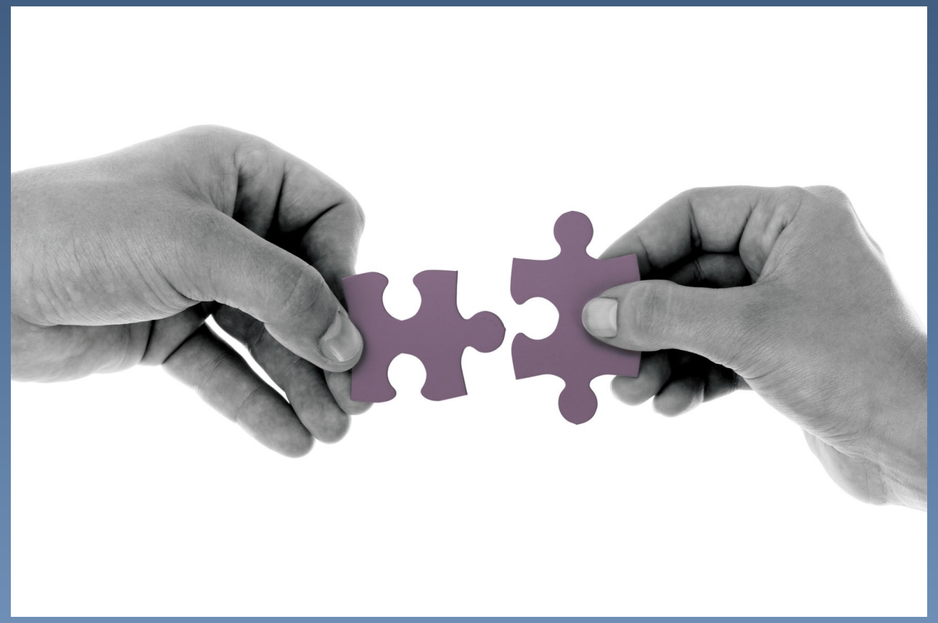
NISOは、約300人のメンバーと約600人のボランティアからなる会員組織であり、標準の開発作業を行っています。

NISOメンバーの約20%は米国外に拠点を置いています。

NISO標準には、MARC、ダブリンコアメタデータ、デジタルオブジェクト識別子（DOI）、ジャーナル記事タグスイート（JATS）、およびDAISYTalkingBooksが含まれます。

NISOは、ISBN、ISSN、DOIなどのISO標準識別子を担当するISO委員会の事務局として国際的コミュニティにも貢献しています。

Standards Connect the Pieces in Information Distribution So They Work Together



標準は、情報流通の各部分を接続して、
それらが連携するようにします

Standards Build Trust & Efficiency

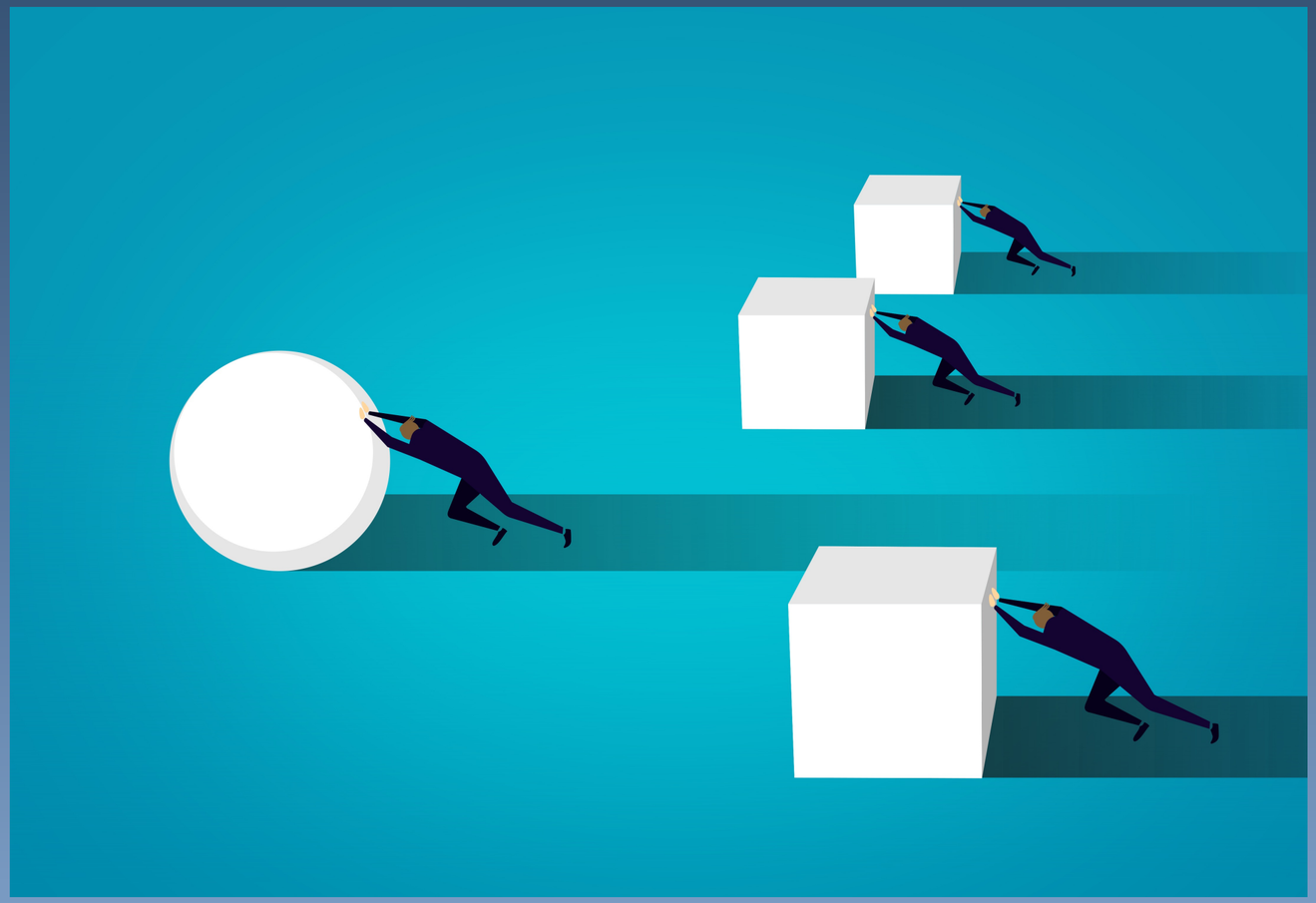
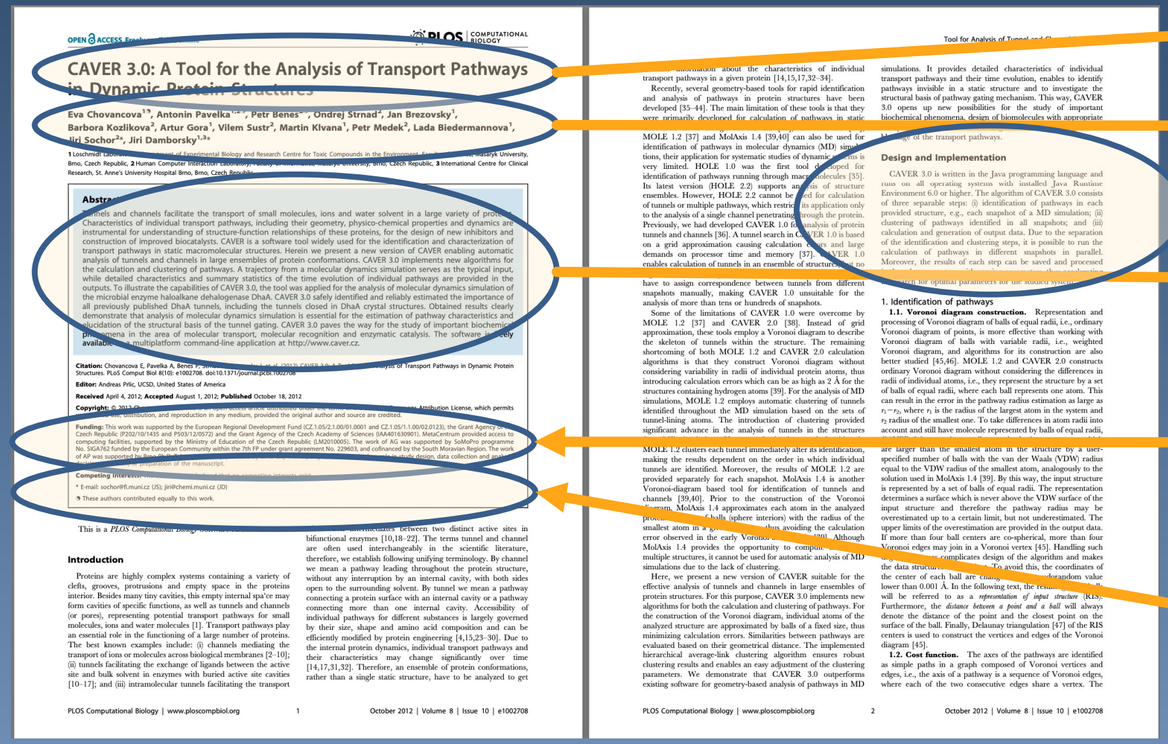


Photo by Jack Moreh from Freerange Stock

標準は信頼と効率を構築します

Standard Elements of Scholarship



CAVER 3.0: A Tool for the Analysis of Transport Pathways in Dynamic Protein Structures
Eva Chovancova, et.al. https://doi.org/10.1371/journal.pcbi.1002708

Title || 記事のタイトル

Authors || 著者

Abstracts || 要約

Funding Statement || 研究資金記述

Conflicts of Interests || 利益相反

Methods || メソッド

学術論文の標準要素

Standard Elements of Scholarship

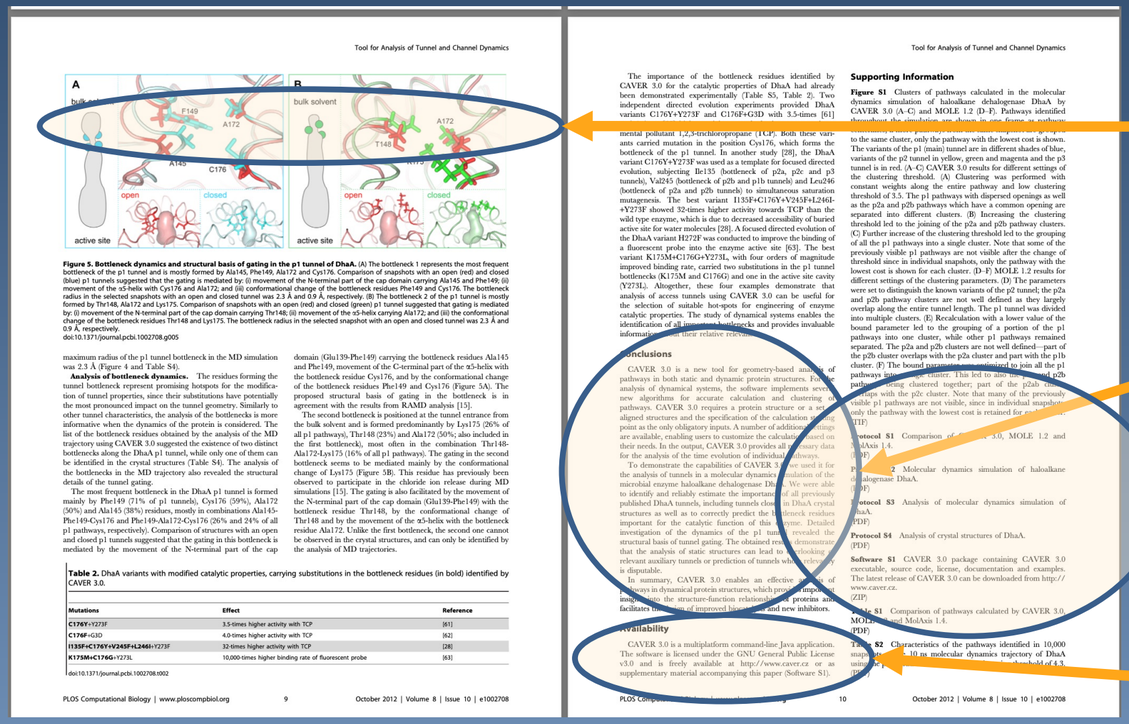


Figure 5. Bottleneck dynamics and structural basis of gating in the p1 tunnel of DhaA. (A) The bottleneck 1 represents the most frequent bottleneck of the p1 tunnel and is mostly formed by Ala145, Phe149, Ala172 and Cys176. Comparison of snapshots with an open (red) and closed (blue) p1 tunnels suggested that the gating is mediated by: (i) movement of the N-terminal part of the cap domain carrying Ala145 and Phe149; (ii) movement of the α5-helix with Cys176 and Ala172; and (iii) conformational change of the bottleneck residues Phe149 and Cys176. The bottleneck radius in the selected snapshots with an open and closed tunnel was 2.3 Å and 0.9 Å, respectively. (B) The bottleneck 2 of the p1 tunnel is mostly formed by Thr148, Ala172 and Lys175. Comparison of snapshots with an open (red) and closed (green) p1 tunnel suggested that gating is mediated by: (i) movement of the N-terminal part of the cap domain carrying Thr148; (ii) movement of the α5-helix carrying Ala172; and (iii) the conformational change of the bottleneck residues Thr148 and Lys175. The bottleneck radius in the selected snapshot with an open and closed tunnel was 2.3 Å and 0.9 Å, respectively.
doi:10.1371/journal.pcbi.1002708.g005

maximum radius of the p1 tunnel bottleneck in the MD simulation was 2.3 Å (Figure 4 and Table S4).

Analysis of bottleneck dynamics. The residues forming the tunnel bottleneck represent promising hotspots for the modification of tunnel properties, since their substitutions have potentially the most pronounced impact on the tunnel geometry. Similarly to other tunnel characteristics, the analysis of the bottlenecks is more informative when the dynamics of the protein is considered. The list of the bottleneck residues obtained by the analysis of the MD trajectory using CAVER 3.0 suggested the existence of two distinct bottlenecks along the DhaA p1 tunnel, while only one of them can be identified in the crystal structures (Table S4). The analysis of the bottlenecks in the MD trajectory also revealed the structural details of the tunnel gating.

The most frequent bottleneck in the DhaA p1 tunnel is formed mainly by Phe149 (71% of p1 tunnels), Cys176 (59%), Ala172 (50%) and Ala145 (38%) residues, mostly in combinations Ala145-Phe149-Cys176 and Phe149-Ala172-Cys176 (26% and 24% of all p1 pathways, respectively). Comparison of structures with an open and closed p1 tunnels suggested that the gating in this bottleneck is mediated by the movement of the N-terminal part of the cap domain (Glu139-Phe149) carrying the bottleneck residues Ala145 and Phe149, movement of the C-terminal part of the α5-helix with the bottleneck residue Cys176, and by the conformational change of the bottleneck residues Phe149 and Cys176 (Figure 5A). The proposed structural basis of gating in the bottleneck is in agreement with the results from RAMD analysis [15].

The second bottleneck is positioned at the tunnel entrance from the bulk solvent and is formed predominantly by Lys175 (26% of all p1 pathways), Thr148 (23%) and Ala172 (50%; also included in the first bottleneck), most often in the combination Thr148-Ala172-Lys175 (16% of all p1 pathways). The gating in the second bottleneck seems to be mediated mainly by the conformational change of Lys175 (Figure 5B). This residue has previously been observed to participate in the chloride ion release during MD simulations [15]. The gating is also facilitated by the movement of the N-terminal part of the cap domain (Glu139-Phe149) with the bottleneck residue Thr148, by the conformational change of Thr148 and by the movement of the α5-helix with the bottleneck residue Ala172. Unlike the first bottleneck, the second one cannot be observed in the crystal structures, and can only be identified by the analysis of MD trajectories.

Table 2. DhaA variants with modified catalytic properties, carrying substitutions in the bottleneck residues (in bold) identified by CAVER 3.0.

Mutations	Effect	Reference
C176Y+Y273F	3.5-times higher activity with TCP	[61]
C176F+G3D	4.0-times higher activity with TCP	[62]
I135F+C176Y+V245F+L246I+Y273F	32-times higher activity with TCP	[28]
K175M+C176G+Y273L	10,000-times higher binding rate of fluorescent probe	[63]

doi:10.1371/journal.pcbi.1002708.t002

The importance of the bottleneck residues identified by CAVER 3.0 for the catalytic properties of DhaA had already been demonstrated experimentally (Table S5, Table 2). Two independent directed evolution experiments provided DhaA variants C176Y+Y273F and C176F+G3D with 3.5-times [61] mental pollutant 1,2,3-trichloropropane (TCP). Both these variants carried mutation in the position Cys176, which forms the bottleneck of the p1 tunnel. In another study [28], the DhaA variant C176Y+Y273F was used as a template for focused directed evolution, subjecting Ile135 (bottleneck of p2a, p2c and p3 tunnels), Val245 (bottleneck of p2b and p1b tunnels) and Leu246 (bottleneck of p2a and p2b tunnels) to simultaneous saturation mutagenesis. The best variant I135F+C176Y+V245F+L246I-+Y273F showed 32-times higher activity towards TCP than the wild type enzyme, which is due to decreased accessibility of buried active site for water molecules [28]. A focused directed evolution of the DhaA variant H272F was conducted to improve the binding of a fluorescent probe into the enzyme active site [63]. The best variant K175M+C176G+Y273L, with four orders of magnitude improved binding rate, carried two substitutions in the p1 tunnel bottlenecks (K175M and C176G) and one in the active site cavity (Y273L). Altogether, these four examples demonstrate that analysis of access tunnels using CAVER 3.0 can be useful for the selection of suitable hot-spots for engineering of enzyme catalytic properties. The study of dynamical systems enables the identification of all [illegible] bottlenecks and provides invaluable information [illegible] their relative [illegible]

Conclusions

CAVER 3.0 is a new tool for geometry-based analysis of pathways in both static and dynamic protein structures. For the analysis of dynamical systems, the software implements several new algorithms for accurate calculation and clustering of pathways. CAVER 3.0 requires a protein structure or a set of aligned structures and the specification of the calculation starting point as the only obligatory inputs. A number of additional settings are available, enabling users to customize the calculation based on their needs. In the output, CAVER 3.0 provides all necessary data for the analysis of the time evolution of individual pathways.

To demonstrate the capabilities of CAVER 3.0, we used it for the analysis of tunnels in a molecular dynamics simulation of the microbial enzyme haloalkane dehalogenase DhaA. We were able to identify and reliably estimate the importance of all previously published DhaA tunnels, including tunnels closed in DhaA crystal structures as well as to correctly predict the bottleneck residues important for the catalytic function of this enzyme. Detailed investigation of the dynamics of the p1 tunnel revealed the structural basis of tunnel gating. The obtained results demonstrate that the analysis of static structures can lead to [illegible] relevant auxiliary tunnels or prediction of tunnels which [illegible] is disputable.

In summary, CAVER 3.0 enables an effective analysis of pathways in dynamical protein structures, which provides [illegible] insight into the structure-function relationship in proteins and facilitates the [illegible] of improved biocatalysts and new inhibitors.

Availability

CAVER 3.0 is a multiplatform command-line Java application. The software is licensed under the GNU General Public License v3.0 and is freely available at http://www.caver.cz or as supplementary material accompanying this paper (Software S1).

Supporting Information

Figure S1 Clusters of pathways calculated in the molecular dynamics simulation of haloalkane dehalogenase DhaA by CAVER 3.0 (A–C) and MOLE 1.2 (D–F). Pathways identified [illegible] are shown in one frame as surfaces. [illegible] to the same cluster, only the pathway with the lowest cost is shown. The variants of the p1 (main) tunnel are in different shades of blue, variants of the p2 tunnel in yellow, green and magenta and the p3 tunnel is in red. (A–C) CAVER 3.0 results for different settings of the clustering threshold. (A) Clustering was performed with constant weights along the entire pathway and low clustering threshold of 3.5. The p1 pathways with dispersed openings as well as the p2a and p2b pathways which have a common opening are separated into different clusters. (B) Increasing the clustering threshold led to the joining of the p2a and p2b pathway clusters. (C) Further increase of the clustering threshold led to the grouping of all the p1 pathways into a single cluster. Note that some of the previously visible p1 pathways are not visible after the change of threshold since in individual snapshots, only the pathway with the lowest cost is shown for each cluster. (D–F) MOLE 1.2 results for different settings of the clustering parameters. (D) The parameters were set to distinguish the known variants of the p2 tunnel; the p2a and p2b pathway clusters are not well defined as they largely overlap along the entire tunnel length. The p1 tunnel was divided into multiple clusters. (E) Recalculation with a lower value of the bound parameter led to the grouping of a portion of the p1 pathways into one cluster, while other p1 pathways remained separated. The p2a and p2b clusters are not well defined—part of the p2b cluster overlaps with the p2a cluster and part with the p1b cluster. (F) The bound parameter [illegible] to join all the p1 pathways [illegible] parameter. This led to also [illegible] and p2b pathways [illegible] clustered together; part of the p2ab cluster overlaps with the p2c cluster. Note that many of the previously visible p1 pathways are not visible, since in individual snapshots only the pathway with the lowest cost is retained for [illegible]
(TIF)

Protocol S1 Comparison of [illegible] 3.0, MOLE 1.2 and MolAxis 1.4.
(PDF)

Protocol S2 Molecular dynamics simulation of haloalkane dehalogenase DhaA.
(PDF)

Protocol S3 Analysis of molecular dynamics simulation of DhaA.
(PDF)

Protocol S4 Analysis of crystal structures of DhaA.
(PDF)

Software S1 CAVER 3.0 package containing CAVER 3.0 executable, source code, license, documentation and examples. The latest release of CAVER 3.0 can be downloaded from http://www.caver.cz.
(ZIP)

Table S1 Comparison of pathways calculated by CAVER 3.0, MOLE 1.2 and MolAxis 1.4.
(PDF)

Table S2 Characteristics of the pathways identified in 10,000 snapshots [illegible] 10 ns molecular dynamics trajectory of DhaA using [illegible] probe radius of 4.3 Å.
(PDF)

Figures || 図

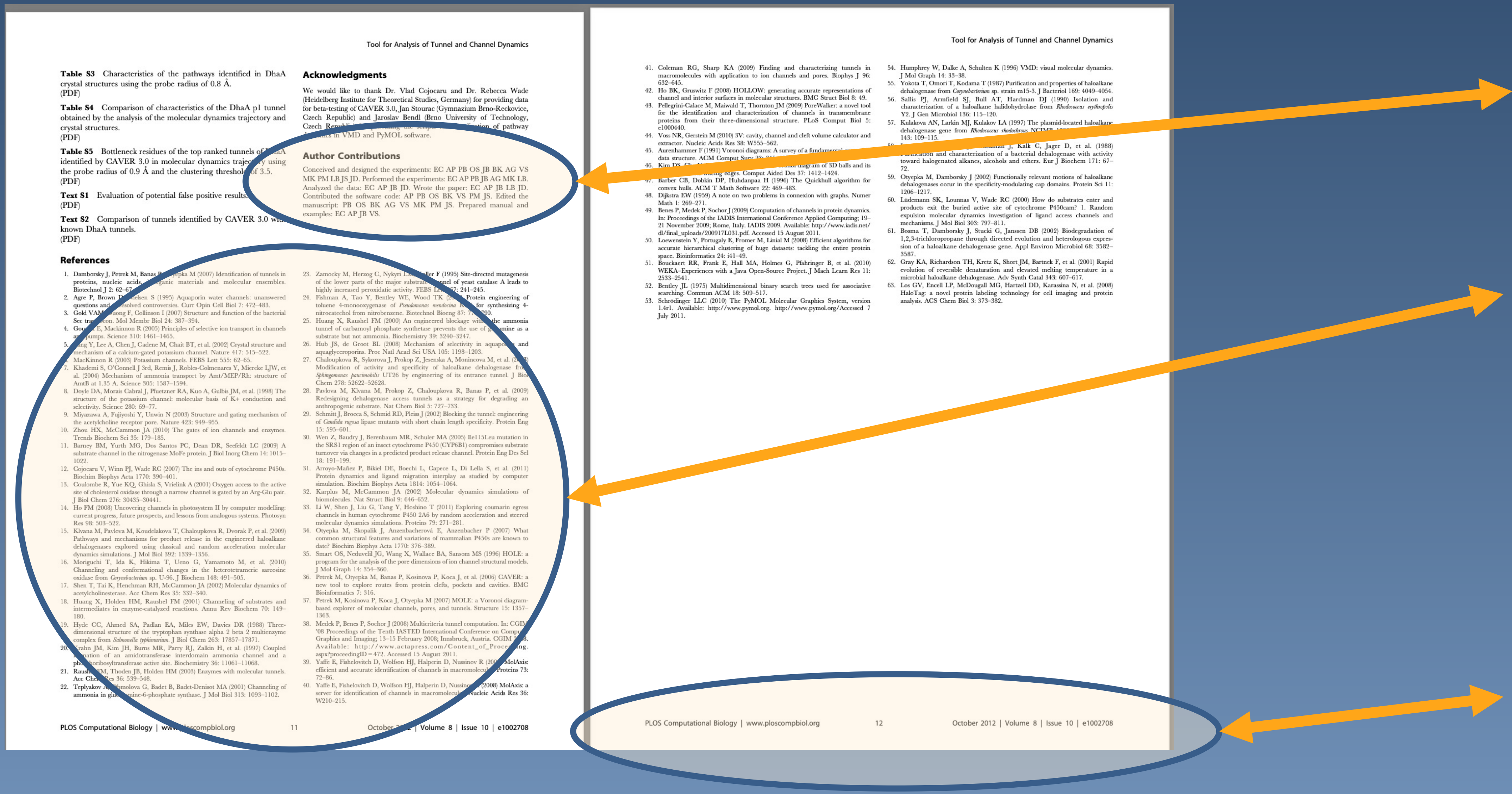
Conclusions || 結論

Methods/Protocols || メソッドとプロトコル

Data Availability || データの利用可能性

学術論文の標準要素

Standard Elements of Scholarship



CRediT Attribution || CRediT 属性

References || 参考文献

Publication Date, Title, Volume, Issue || 発行日, タイトル, 巻,号

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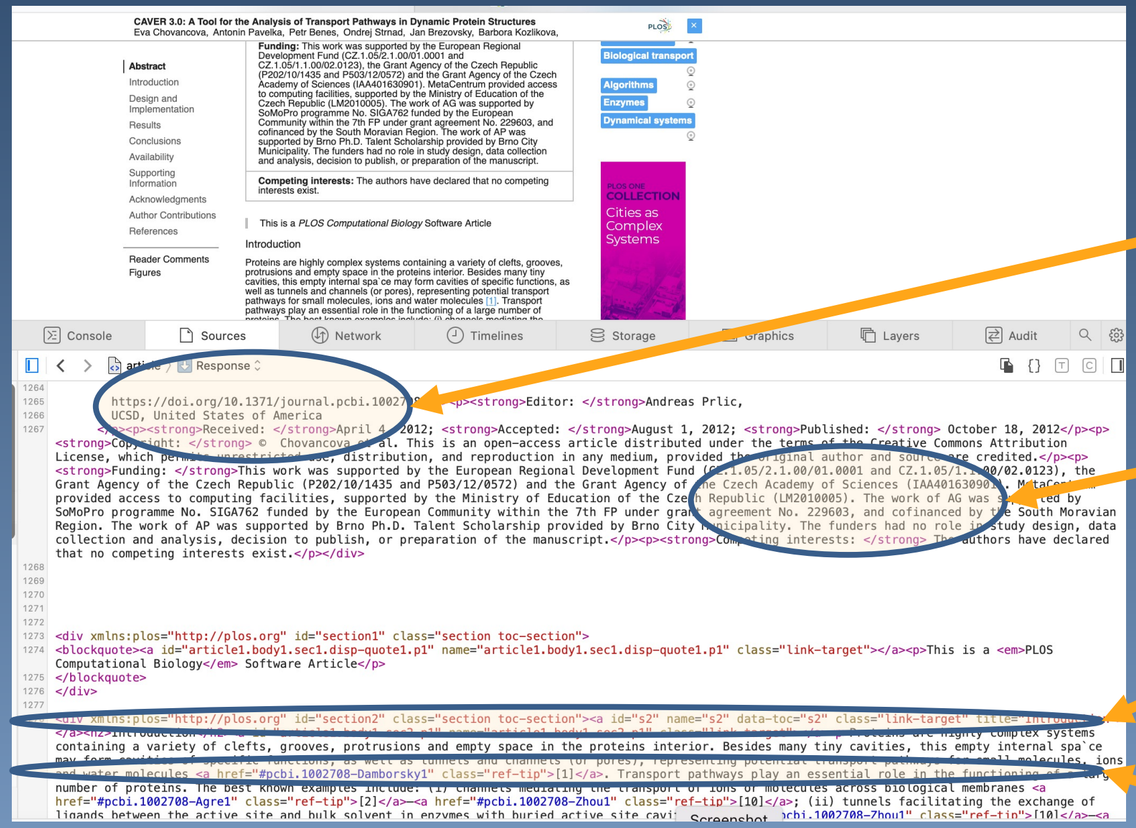
Behind the Scenes Standards



Funding information ||
研究資金情報

Funding identifiers ||
研究資金識別子

<h2>Introduction</h2>

<a href="#pcbi.1002708-Damborsky1"
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舞台裏の標準

Other standards, formal and informal

Standards for authorship, such as plagiarism and citation.

Standards for editorial processes, such as peer review.

Standards of behavior, such as confidentiality.

Standards of data sharing.

盗作や引用などの著者のための標準。

査読などの編集プロセスの標準。

機密保持などの行動標準。

データ共有の標準。

その他の標準（公式および非公式）

Technical Infrastructure for Integrity

Elements to Establish Trust in Validity

Definitions of Peer Review Process

CRediT Terminology for who is responsible for what in writing/research process

Established citation practices and methods

妥当性の信頼を確立するための要素

査読プロセスの定義

CRediT 執筆と研究プロセスで誰が何に関して責任を持つのかを示す用語

確立された引用慣行と方法

公正性のための技術インフラ

Technical Infrastructure for Reproducibility

Elements to Establish Trust in Reproducibility	再現性に対する信頼を確立するための要素
Identifiers for Methods/Protocols	メソッド/プロトコルの識別子
Preregistration	事前登録
NISO Reproducibility Badging	NISO再現性バッジ

再現性のための技術インフラ

Technical Infrastructure for Quality

Elements to Establish Trust in Quality	品質への信頼を確立するための要素
COPE Conflict of Interest	COPE 利益相反
COPE Misconduct	COPE 不正行為
NISO Communications of Retractions, Removals, and Expressions of Concern (CORREC)	NISO 撤回、削除、および懸念の表明の伝達 (CORREC)

品質のための技術インフラ

Future Areas of Work

Interoperability between preprint repositories and publisher’s systems

プレプリントリポジトリと出版社システムとの間の相互運用性

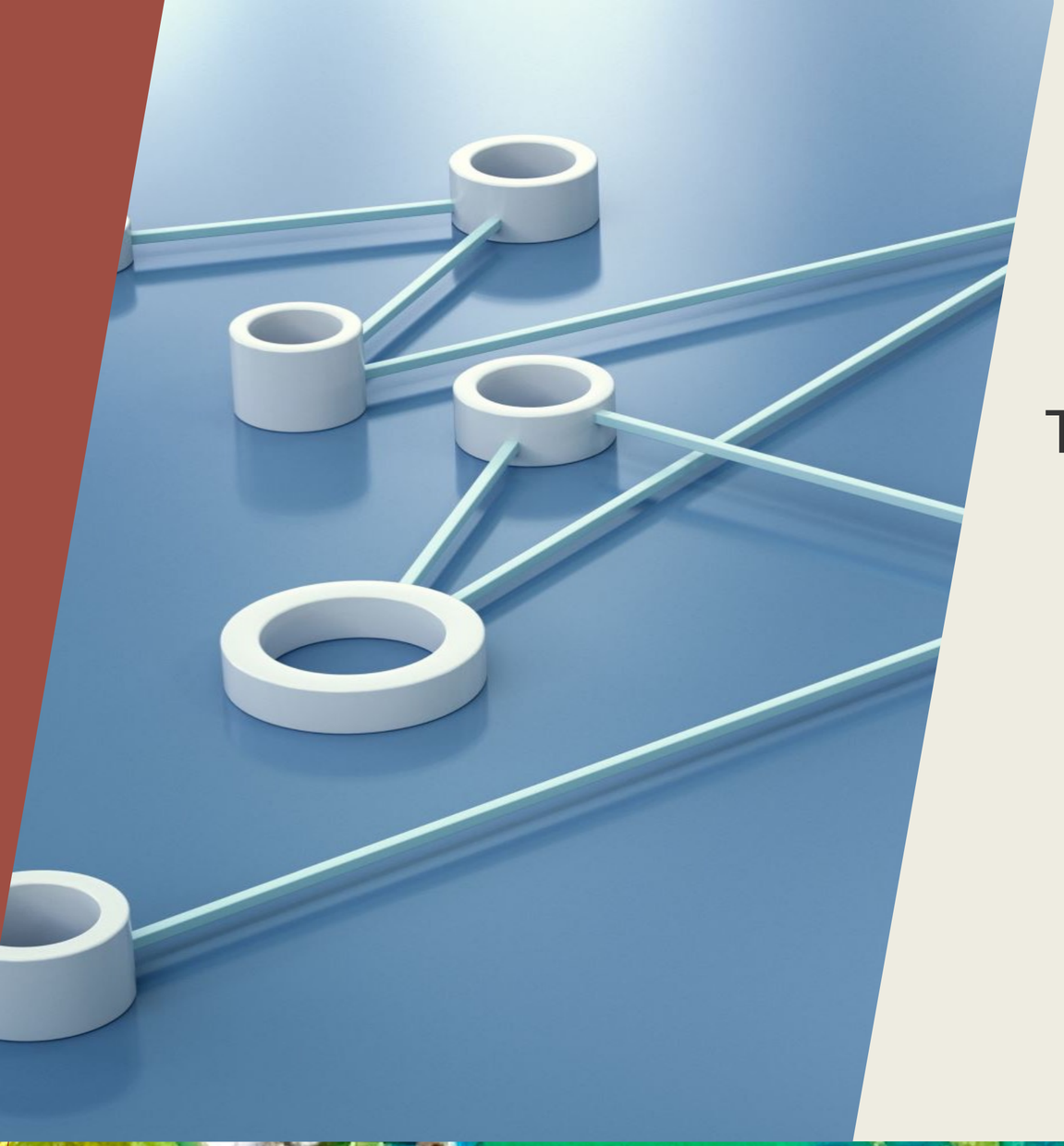
Versioning and content revision

バージョン管理とコンテンツの改訂

Linking together the ecosystems of various repositories

さまざまなリポジトリのエコシステムをつなぐ

今後の取り組み



THANK YOU

Todd Carpenter, Executive Director, NISO
@TAC_NISO
tcarpenter@niso.org
www.niso.org

ありがとうございました