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Perspective

# PROTCROWN: A Manually Curated Resource of Protein Corona Data for Unlocking the Potential of Protein−Nanoparticle Interactions

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**ABSTRACT:** The emergence of the "Protein Corona" is a pivotal concept in bioinformatics and nanotechnology, crucial for understanding nanomedicine delivery and nanoparticle−biological entity interactions. After entering a biological fluid, such as blood, nanoparticles (NPs, such as nanomedical carriers) are quickly coated with proteins, forming a protein interface layer called the protein corona. An in-depth investigation into the protein corona is essential for elucidating the biological ramifications of NPs and their prospective applications within the medical field and beyond. To advance our understanding of the intricate interactions between NPs and biological systems, we have developed PROTCROWN, the inaugural protein corona database. This resource systematically curates and organizes data relevant to the protein corona, facilitating advanced analysis and research in the field. It provides a convenient data query platform for researchers and supports data visualization and analysis. Our database, PROTCROWN, is accessible at http://www.protcrown.cn.

**KEYWORDS:** *Protein corona, Nanoparticles, Relative protein abundance, Data visualization*



At the intersection of nanoscience and biomedical research, the protein corona, a complex interfacial layer formed by the interaction of nanoparticles (NPs) with biofluids, has become a key focus of research and a key driver of technological innovation.[1,2] The protein corona constitutes a dynamic network intricately woven by countless proteins, lipids, polysaccharides, and other biomolecules and serves as a bridge between the biological effects of NPs and the responses of organisms.[3] Its unique composition, structure, and dynamic evolution profoundly determine the fate of NPs in biological environments, including key biological behaviors such as biodistribution, cellular uptake, immunogenicity, and toxicity, all of which are directly related to the safety, efficacy, and clinical translation of nanomedicines, diagnostic probes, biosensors, and other nanomedical products.[4,5] The complexity of the protein corona lies in its compositional diversity and dynamics.[6,7] The specific or nonspecific interactions between different NPs, characterized by their unique physicochemical properties (e.g., size, shape, surface charge, chemical modification), and biomolecules (proteins, lipids) in biofluids generate personalized protein corona profiles.[8,9] In addition, changes in biological fluids (plasma, serum, cerebrospinal fluid, etc.), physiological conditions (temperature, pH, ionic strength), and time factors significantly regulate the composition and structure of the protein corona, increasing the complexity of research work.[1,10] This complexity has brought great challenges to the field of research on the protein corona,[11] such as comprehensive characterization, deciphering mechanisms, and precise manipulation of the protein corona.[12] The different physicochemical properties of nanomaterials, differences in the composition of biofluids, and dynamic changes in the biological environment all lead to substantial changes in the protein corona, thereby affecting the biological outcomes of the NPs.[13] Therefore, the establishment of a comprehensive, systematic, and accessible protein corona database is essential to deepen our understanding of the protein corona's formation mechanism, predict the behavior of NPs in vivo, optimize nanomaterials design, and accelerate the development of nanomedicines. The PROTCROPWN database aims to organize the latest research progress on the protein corona from around the world, including the features and composition of the protein corona formed by various NPs in different biofluids and visual analysis (Figure 1). We are committed to providing researchers with an efficient and user-friendly information retrieval and data analysis platform to promote in-depth cooperation and communication in the protein corona research community and ultimately promote the rapid development of nanomedicine and related fields. PROTCROWN can be accessed through the following link: http://www.protcrown.cn.

**Data Collection and Processing.** The protein corona is a key interface for the interaction between nanomaterials and the biological environment, and its composition data has become a research hotspot in the fields of nanomedicine and materials science.[14] The protein corona not only is composed of a variety of protein molecules but also has a high degree of dynamics and functionality, which profoundly affect the biological effects and the in vivo behaviors of nanomaterials.[15] The composition of the protein corona is mainly reflected in the diversity of its protein types.[16,17] These proteins are widely

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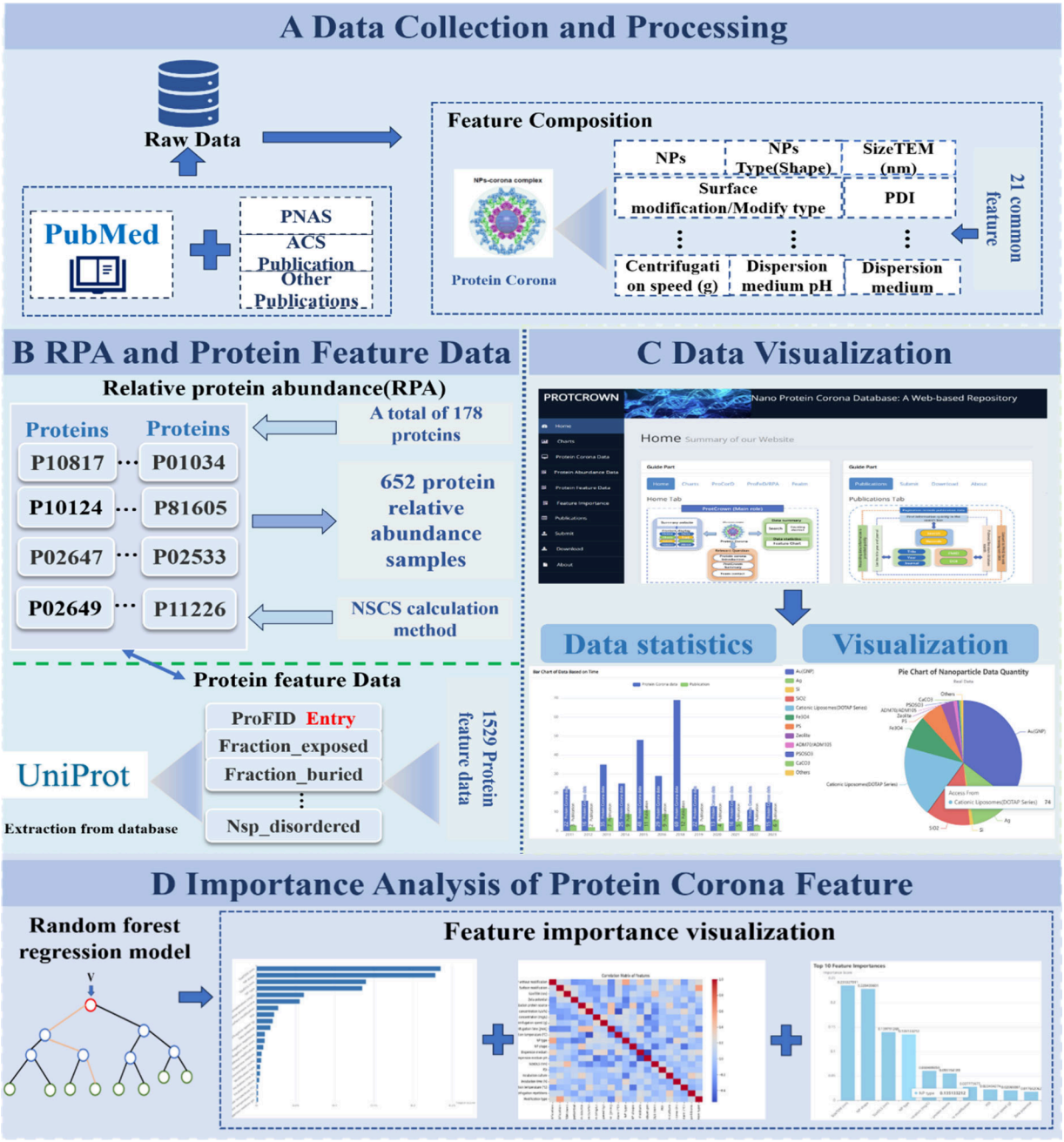


**Figure 1.** All data workflows of the PROTCROWN database. (A) Protein corona data are collected and processed. (B) Specific information on RPA and protein feature data is collated. (C) Data are statistically analyzed and visualized. (D) An importance analysis of protein corona features is conducted.

derived from plasma proteins,[18] immune proteins,[19] complement proteins,[20] apolipoproteins,[21] and other proteins in body fluids. Their types and proportions are regulated by factors such as the intrinsic properties of nanomaterials (e.g., size, shape, surface charge), the surrounding biological environment (e.g., pH, ionic strength, temperature), and the concentration of nanomaterials.[22−24] Therefore, the formation of the protein corona includes both qualitative and quantitative factors. In the process of constructing the PROTCROWN database, we used the powerful search capabilities of PubMed,[25] an excellent biomedical literature database, as well as chemical and materials science journals such as PNAS and ACS Publications, to start a comprehensive search for literature related to protein corona research. Based on these literature sources, we focused on 77 articles, from which we systematically extracted protein corona data built around key parameters, including NP types (e.g, Au, Ag, Si, $SiO_2$, cationic liposomes),[26] surface modifications and their features,[27] particle sizes determined by transmission electron microscopy (TEM)[28] and dynamic light scattering (DLS),[29] centrifugation repeat counts,[30] and polydispersity index (PDI),[31] among other qualitative and quantitative features of protein corona formation. A total of 21 common features covering the most collected data and the most comprehensive data for each item were retained (Figure 1A). For these 21 features, we focused on the features of nanomaterials and the environment in which protein coronas are formed, including the intrinsic properties of NPs (such as nano size, shape, type, etc.) and extrinsic properties (such as


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surface modification, dispersion medium, centrifugation speed, etc.), as shown in Supporting Information Figure S1 and Table S1. Through the careful collection and preprocessing of experimental process data and mass spectrometry data, the quality of the data is improved and the accuracy, completeness, and analyzability of the data are guaranteed. This process collects and processes the data; measurement experiments are not performed.

**Database Construction.** The PROTCROWN database is a comprehensive platform that combines advanced back-end technology with cutting-edge front-end design concepts, aiming to provide users with an efficient and intuitive data management and analysis experience. The back-end of the system is cleverly built using the Python Flask-RESTful API framework, ensuring robust and efficient services. The front-end combines the Bootstrap framework with the power of HTML, CSS, and JavaScript to achieve not only a beautiful interface but also a variety of functions. In addition, through deep integration with the Echarts chart library and the powerful data processing capabilities of Python scripts, the system is able to dynamically generate and display complex data charts, providing strong support for users' data analysis tasks. The structure of the PROTCROWN database has been carefully designed and consists of 10 main functional modules: Home, Charts, Protein Corona Data, Protein Abundance Data, Protein Feature Data, Feature Importance, Publications, Submit, Download, and About. Users can click TUTORIAL in the About section of the PROTCROWN Web site to get a detailed tutorial on the use of this database.

**Relative Protein Abundance (RPA) Data and Its Role in the Protein Corona.** The composition of the protein corona is not static but dynamically adjusts as nanomaterials move in the body and the biological environment changes.[32,33] This property enables the protein corona to quickly adapt to different biological environments and maintain the stability and biocompatibility of nanomaterials.[34] For example, when nanomaterials transition from the serum environment to the cytoplasm, the composition of the protein corona on its surface changes to adapt to the biological environment within the cell.[9] Relative protein abundance (RPA) plays a key role with regard to the composition of the protein corona and its interaction with NPs, determining its biological effects and potential applications in biomedicine.[35,36] The formation of the protein corona reflects the relative protein abundance (RPA), which is defined as the ratio of the content of a specific protein in the protein corona complex formed on the surface of the nanomaterial relative to other proteins or total proteins and will change with changes in the calculation method.[37] It is also an important parameter for describing the protein corona.[38] At present, most studies use mass spectrometry technology, with high sensitivity and high resolution, to conduct in-depth research on the protein corona formed on the surface of nanomaterials.[39] For example, based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS),[40] which is also a relative measure of specific conditions, researchers can accurately identify and quantify the protein components in the protein corona.[41] Essentially, the RPA is a key parameter for measuring protein adsorption on NPs. Changes in RPA may reflect the competitiveness and affinity of protein adsorption on the surface of nanomaterials and significantly affect the biodistribution, cellular uptake, toxicity, and immunogenicity of nanomaterials.[42] It has important research value and application prospects in the fields of nanomedicine, nanotoxicology, and nanobiotechnology. In future studies, we will further explore the specific mechanism of RPA changes, influencing factors, and how to optimize the biological properties and applications of nanomaterials by regulating the RPA.

RPA plays an important role in evaluating and optimizing biomedical applications of nanomaterials. Highly abundant proteins can guide nanomaterials into specific tissues or cells through specific receptor-mediated mechanisms.[43] In addition, changes in RPA can lead to the exposure of different recognition sites on the surface of nanomaterials, changing their interaction modes with cell membranes and their absorption efficiency.[44] Therefore, RPA is a core factor in regulating the biocompatibility, targeting, and therapeutic effects of nanomaterials and is crucial for a deep understanding and optimization of their behavior in biomedical applications.[45]

In the protein corona, RPA is affected by both the properties of nanomaterials and the properties of the biological environment.[46,47] The properties of nanomaterials, including size, shape, surface chemistry, and charge, significantly affect the adsorption behavior and pattern of proteins on their surfaces, thereby changing the distribution of the RPA.[37] At the same time, the properties of the biological environment, such as plasma and serum concentrations, pH, ionic strength, etc., also play important roles in the formation of protein coronas on the surfaces of nanomaterials and the influence of RPA.[48] Therefore, the RPA is estimated through mass spectrometry experiments and data analysis. In the relevant literature, we found that a method called normalized spectral counts (NSCs)[47,49] was used to estimate RPA and obtain RPA data (Figure 1B). At the same time, in this work, we extracted all the feature data of 178 proteins (including serum proteins, plasma proteins, etc.) used in the calculation of RPA data in the UniProt protein database[50] (Figure 1B) and provided them as independent data in our PROTCROWN database. We searched and identified 178 kinds of protein information in UniProt proteins, selected and viewed various characteristic data of proteins (such as amino acid sequence, protein name, gene name, etc.), and extracted all of these characteristics of proteins. These data entries are connected to the UniProt protein database and can be directly accessed.

**PROTCROWN Data Summary.** The PROTCROWN database consists of three main parts: protein corona feature data, relative protein abundance (RPA) evaluation data, and specific protein feature data. In the protein corona data we collated, we focused on 21 common features that were the most comprehensive in the data and obtained a total of 652 protein corona sample features. Specifically, we implemented interactive visualization of these sample sizes and selection functions in the PROTCROWN platform for the quantitative and qualitative factors affecting the protein corona, including 21 features of various properties such as proteins and NPs, as shown in Supporting Information Figure S2. The protein corona data can be accessed at http://www.protcrown.cn/templates/chart.html. For the RPA data, we obtained 652 RPA data samples estimated from 178 proteins on the protein corona data, as shown in Supporting Information Figure S3. These RPAs correspond to different protein corona features of the 178 proteins (Figure 1B). The RPA data can be accessed at http://www.protcrown.cn/templates/RPA.html. Regarding the protein feature data, we extracted all of the features of these 178 proteins in the UniProt protein library and obtained


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1529 data entries, which are connected to the UniProt protein database and can be directly accessed, as shown in Supporting Information Figure S3. The 1529 protein data entries can be accessed in PROTCROWN at http://www.protcrown.cn/templates/tab-panel.html. An overall data summary can be seen in the Supporting Information Figure S2. All our data can be downloaded from the "Download" section of the PROTCROWN database.

**Ranking of Protein Corona Data Features by Importance.** At present, we understand that the application of artificial intelligence algorithms is likely to enhance the scope and depth of protein corona research. In 2020, Ban et al. introduced a machine learning model for the first time to comprehensively predict the functional composition of protein coronas and the cell recognition of NPs.[51] In 2024, Fu et al. proposed that machine learning can comprehensively predict the relative protein abundance of multiple proteins on protein coronas.[35] At the same time, we also witnessed the introduction of artificial intelligence algorithms adding to the depth and value of protein corona research. In the PROTCROWN database, we clearly know that the protein corona features included in it are the main factors driving the formation of the protein corona. However, this is the result of experimental research. The introduction of artificial intelligence algorithms can not only stay at the level of these main factors but also more intuitively determine the feature importance score (the percentage of each feature in all features). For the analysis of protein corona data features, we proposed to use the random forest regression algorithm[52] in the machine learning algorithm to obtain the importance ranking of protein corona features. As part of the value of the PROTCROWN database, we used RPA as label data and protein corona data as the feature data. We divided 30% into a validation set and the remaining 70% as a training set and finally obtained the feature importance ranking and score. 10-fold cross validation was used to evaluate the model performance. In order to visualize these data more intuitively, we used dynamic bar charts on the PROTCROWN platform and paid special attention to the top 10 most important features (Figure 1D). The results showed that the four main physicochemical properties of NPs (SizeTEM (nm), Np Shape, SizeDLS (nm), and Np type) play key roles in determining the features of the protein corona,[53] which is consistent with the results of experimental studies in related literature, as shown in Supporting Information Table S2. This finding emphasizes the importance of NP selection in protein corona research. Specifically, these basic properties of NPs have an important impact on their mode of interaction with biomolecules, which may subsequently profoundly change their behavior and role in biological systems. This discovery may not only provide a new perspective for understanding the interactions between NPs and the biological environment but also provide new ideas and directions for research in fields such as nanomedicine, biosensing, and drug delivery. Due to the current limitations of the amount of data, we have not considered uploading other data and applying our artificial intelligence tools, but our database has been maintained, and we also believe that PROTCROWN will incorporate this work so that it can be provided to more people.

At this point in time, the development of protein coronas is an important research direction in the fields of nanomedicine and biotechnology. By adjusting the composition and thickness of the protein corona, the biocompatibility, targeting efficiency, and pharmacokinetic properties of nanomaterials can be optimized, providing new ideas and methods for the design and development of nanomedicines. With the continuous deepening of protein corona research, it is expected that it will promote further innovation and development in nanomedicine and biotechnology. In this paper, we propose the work of realizing a protein corona database, PROTCROWN. In the development of this database, we are committed to systematically collecting and organizing protein corona data, and through a series of dynamic chart visualization implementations, we aim to study more deeply the features of protein coronas.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.nanolett.4c05955.

Introduction to the feature and category distribution of protein corona data (PDF)

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### Notes

The authors declare no competing financial interest.

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