Artificial neural networks for solution scattering data analysis

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# Abstract

Small-angle X-ray scattering (SAXS) experiments are widely used for the characterization of biological macromolecules in solution. SAXS patterns contain information on the size and shape of dissolved particles in low-resolution. Here we propose a novel method for primary SAXS data analysis based on the application of perceptrons - interconnected artificial neural networks. Trained on synthetic SAXS data, the neural networks are able to predict molecular weight and maximum intraparticle distance (Dmax) of previously unseen experimental data. The application area of the method is of a wide range and includes SAXS data from nucleic acids (DNA/RNA), as well as from compact, partially unfolded, and extended proteins, including intrinsically disordered proteins. Potentially, this area is not limited by the described objects and can be easily extended towards e.g. data from heterocomplexes or inorganic nanoparticles by further extension of the training set. The method was rigorously tested against synthetic SAXS data and demonstrated higher accuracy and better robustness against simulated experimental noise compared to all available conventional methods. The code in python for NN model generation and applications is freely available at the git0hub for academic use (). REMOVE:implemented as a publicly available web service with a graphical interface (<https://dara.embl-hamburg.de/gnnom.php>).

# Introduction

Small-angle scattering (SAS) of X-rays and neutrons from biological macromolecules in solution is a powerful tool, providing information on supermolecular structures and dynamics under a wide range of conditions (Feigin et al., 1987; Gräwert and Svergun, 2020; Guinier and Fournet, 1955). Due to relatively soft requirements to sample preparation for SAS experiments and huge progress in the development of data analysis software (Hopkins et al., 2017; Liu et al., 2012; Manalastas-Cantos et al., 2021), the technique became high throughput and available to the non-specialists in the area. The molecular weight (MW) and maximum intraparticle distance (Dmax) are the crucial parameters derived from SAS experiment and used for the further analysis, e.g. for *ab initio* model reconstruction. However, their precise estimation still remains a non-trivial task with higher potential uncertainty linked to the lower quality of experimental data.

Recently, the application of neural networks (NN) has experienced a sudden leap virtually in all areas of modern life, due in no small part to the development of deep learning technologies (Schmidhuber, 2015). Huge progress has happened in many biological applications as well, including bioinformatics (Armenteros et al., 2019), a recent breakthrough in *in silico* protein folding (Senior et al.), and even in the SAXS area (He et al., 2020). Essentially, the application of deep NNs becomes clearly beneficial when the amount of data used for its training is so big, that other methods are not able to comprehend the common patterns in the data, so their learning curves reach saturation. On contrary, deep networks have a much deeper capacity and may be able to recognize the hidden from the human eye patterns in the data. Another major advantage of using the supervised NNs approach over the conventional methods is the possibility to augment the training set data, thus one can easily adjust the area of applicability of a given NN model and tailor it for the specific objects or instrumentation.

From the SAXS perspective, making a NN that is robust against experimental noise is as simple as generating a realistic experimental noise and augmenting the training set accordingly. Similarly one can overcome other common shortages of SAXS data collection, such as buffer sub/over subtraction, presence of a systematic beamline noise, buffer mismatch, etc. Along with that, the machine learning-driven approaches lack the limitations of a chosen approximation (e.g. the homogeneity of a model) and may bring more accurate predictions employing previously unrecognized patterns and connections between SAXS data and the derived parameters.

Inspired by the huge progress in AI field, we developed a NN for SAXS data analysis based on state-of-the-art machine learning principles. We employed a stack of interconnected artificial NNs trained on synthetic SAXS data generated from thousands of models from PDB databank (Berman et al., 2000) to perform principal data analysis. The training set was chosen using the supercube latin sampling method (McKay et al., 1979) to be as complete as possible to make the trained networks generally applicable.

To date, the presented method appears to be unique in the SAXS field for concentration-independent estimation of MW for intrinsically disordered proteins (IDP), and the second one for the nucleic acids (NA). Moreover, the application of NNs gear the only human independent way of Dmax estimation, based solely on the one-to-one correspondence (SAXS profile – Dmax), without the introduction of unnecessary regularization parameters.

In simplistic terms, the addition of experimental noise converts data at higher angles to the white noise, thus effectively shortening the available experimental s-range from the side of the higher angles. To address this problem, we further investigate the information content of the different angular ranges for the determination of MW and Dmax by training/testing the NNs on noiseless but truncated over smax data sets. Predictably, accurate Dmax prediction mostly requires only a low angle part of the curve, whereas MW prediction is more demanding in terms of the angular range. Finally, we demonstrate the higher accuracy and better robustness against simulated noise of our method over the conventional methods. We would like to stress, that this work aims to demonstrate the proof-of-principle capabilities of NNs in the field of SAXS, whereas further improvement in accuracy and stability is possible and limited only by the choice of the training set.

# On limitations of conventional methods.

The MW is a crucial parameter in SAXS that can be exploited for e.g. determination of predominant oligomeric state in solution. However, the currently available methods for MW estimation are not very accurate, a usual rule of thumb is 10% or more. To date, there are several well-established techniques for MW estimation, that nominally could be subdivided into two major categories: concentration-dependent and concentration-independent methods. Former ones account for the dependence of forwarding scattering I(0) on the total number of electrons in the irradiated molecule (and, thus, on MW) and rely on the scattering from calibrants, e.g. water or a protein with known MW (Mylonas and Svergun, 2007). The latter methods utilize a single background-subtracted curve and require no additional *a priori* information on sample concentration. In the scope of this work, we are interested in concentration-independent methods.

**Porod’s method.** The historically first concentration-independent method is the Porod’s method. It is based on the fundamental properties of the Fourier transform known as the Parseval theorem:

, (1)

where s is the scattering vector, I(s) – the intensity of the scattered beam, Δρ – excessive electron density, and Q is the Porod invariant. If we consider the scattering particle to be of homogeneous electron density, the right part of the equation simplifies to:

(2)

and given that intensity in the origin equals I(0) = (Δρ)2V2:

(3)

The MW is typically estimated as an empirical relation between the volume of the particle and its mass, which equals V/MW = 1.6 e.g. in the case of proteins (Petoukhov et al., 2012). Therefore the precise calculation is limited by the three governing factors: (i) integration in (1) can not be performed due to limitations in real experimental s-range (so I ~ s-4 power law is usually applied to extrapolate the intensities on higher angles); (ii) integration is affected by the experimental noise; and (iii) the equation (2) implies homogeneity of the scattering particle, which could be a quite crude approximation e.g. in case of protein-RNA heterocomplexes. This method can be very effective, however, it requires accurate knowledge of electron density and works only on proteins. Additionally, it is very sensitive to subtraction errors.

**Fisher’s method.** The further performance improvement is possible assuming the Guinier approximation at low s < smin and calculating the truncated integral up to smax (Fischer et al., 2010):

(4)

The authors introduce the so-called apparent volume as (similarly to (3)), and establish a linear dependence between V and V’:

V = A + BV’ , (5)

where the linear and angular coefficients A and B were determined empirically for different smax values. Given the look-up table with A and B values, one can find these coefficients corresponding to the experimental smax and obtain a more accurate prediction for the MW. The drawbacks of this method are essentially the same as those of Porod’s method.

**Volume of correlation.** Another approach was developed by Rambo&Tainer (Rambo and Tainer, 2013) and introduces the so-called volume of correlation:

(6)

The authors found an empirical dependence between Vcand the molecular weight:

(7)

Where c and k are empirically determined constants via fitting results from theoretical scattering profiles. The authors found different couples of c and k values for proteins and RNA, therefore, it is the only available to date method for estimating the MW of RNA. However, this approach is reported to be less accurate than the others for high signal-to-noise data, as well as for extended and small (<20 kDa) particles.

**Shape&Size.** The first machine learning based method for MW determination was developed by (Franke et al., 2018) and essentially represents a classical k-Nearest-Neighbor classifier. In this method, the Fisher’s truncated integral Q’ (eq.4) is calculated up to three values of sRg = 3,4,5 for a huge set of simulated SAXS patterns from geometrical bodies and proteins from PDB. The obtained three numbers can be treated as coordinates in some 3D space resulting in thousands of points, where each point corresponds to a model. The experimental data can also be mapped on this space and (since each model in this space has known MW and Dmax), these values can be estimated as the weighted average between the nearest k-neighbors. This approach has the advantage of taking into account the shape of particles alongside their size and can be used as a classifier for the molecule type (compact, extended, flat). The major drawback of the method is that it does not work for nucleic acids and flexible proteins.

**Bayesian statistics.** In the recent method (Hajizadeh et al., 2018) the authors calculate an MW using Bayesian inference with the MW calculations from all the above-mentioned methods as the evidence. The authors simulate a large test dataset of SAXS profiles, then calculate the MW for each curve using each method to build a probability distribution, that describes the original probability of obtaining a particular calculated MW given the true molecular weight. These probabilities are combined across all the methods, and the most likely molecular weight is thus estimated. The advantage of the method is that it employes all the other methods and provides the most probable MW alongside its credibility interval. The disadvantage is similar to the Shape&Size method: it works only for compact proteins.

**Maximum intraparticle distance Dmax.** To date, there are only two available methods for an estimate the Dmax: Shape&Size and the indirect Fourier transform (IFT). The principles of the former were described earlier, whereas the latter requires the introduction of the pair distance distribution function p(r). The p(r) function represents a histogram of distances between pairs of points in the particle, weighted by the product of their scattering contrasts (Guinier and Fournet, 1955). Mathematically, the p(r) function is closely related to the scattering intensity versus the momentum transfer I(s) via the spherically averaged Fourier transformation (Debye, 1915):

(8)

(9)

The limited angular range of discretely recorded experimental data, as well as the presence of experimental noise, makes the evaluation of p(r) an ill-posed problem. The method of solving this problem by the IFT has been originally proposed by Glatter (Glatter, 1977), and further enhanced by Svergun (Svergun, 1992) and Hansen (Vestergaard and Hansen, 2006). In the IFT approach, a guess on the Dmax must be given, then the p(r) function is expressed as a sum of some analytical functions (e.g. cubic splines). Finally, the classical regularization procedure (Bertero et al., 1980) is applied such that p(r) i) agrees to experimental data and ii) ensures satisfaction to the imposed constraints. Most commonly the constraint is the smoothness of p(r), so that termination effects are reduced or ideally completely removed. However, in all of these approaches, the choice of the final solution remains a subjective criterion left to the discretion of the user. Therefore, small deviations of Dmax are acceptable and do not change the final solution, thus precise estimation of Dmax is somewhat arbitrary and is usually left to the discretion of a user.

# Methods

Neural networks architecture. We exploited Keras and Tensorflow modules in the python framework to construct interconnected feedforward NNs (perceptrons) capable of predicting the MW and Dmax. The adequate choice of the NN architecture, together with the optimization of its hyperparameters, is the most crucial and typically the most time-consuming step while designing a NN for a particular purpose.

As we expect the NN models to predict either MW or Dmax, it seems natural to make the output layer containing a single unit with its value representing the value of the desired parameter. Since the expected output of the NNs is a numeric score and not a probability, we encounter a classical regression task of NN supervised learning. The used for training SAXS data first undergoes a normalization to I(0) = 1, then the data is rebinned to a particular common angular grid (0 ≤ s ≤ 10 nm-1, 256 points) and used as an input for the first layer of the NN. The fig.1 demonstrates an overlay of the training procedure for the determination of MW.



80 units

1 unit

256 units

Fig.1 On the architecture of neural networks used for primary SAXS data analysis.

It is a good practice to start a NN design with an estimation of the complexity of your problem to utilize an appropriate, not overloaded in terms of units and hidden layers, architecture. According to the universal approximation theorem (see e.g. (Cybenko, 1989)), a feed-forward artificial NN with a single hidden layer containing a finite number of units can approximate any continuous function, under mild assumption on the non-linearity of the activation function. In particular, it was recently shown (Lu et al.) that NNs utilizing the rectified Linear Unit (ReLU) activation function with a width (where the width is the number of units in one layer) of n+1 is capable to approximate any continuous convex function of n-dimensional input variables to any desired degree of precision (Hanin, 2019). In SAXS one typically analyzes a hugely oversampled curve, that in fact contains only up to 15-35 Shannon channels (Moore(crystallography and 1980). Therefore, in the context of SAXS with the typical angular range up to smax < 5 nm-1 it should be sufficient to use a NN with only one hidden layer and the width of ~ 35 neurons.

In practice, even though this model proved to work quite well on our data set, we have found that using a somewhat excessive architecture with 3 hidden layers and 80 units leads to faster convergence and more stable solutions, as well as to the slightly better prediction results. However, the further increase of the architecture complexity only worsens the predicted results, apparently because the backpropagation algorithm struggles to find an absolute minimum among too many optimization parameters.

During extensive testing, we have also found, that using hyperbolic tangent as an activation function instead of ReLU marginally improves the results. The possible explanation for that is connected to the output range of tanh values (-1, +1), which allows passing negative signals in between the layers and thus pushing more units to be activated. The hidden layers were initialized by the ‘he-uniform’ random function with zero biases, whereas the bias for the output layer was initialized as an averaged predicted parameter (MW or Dmax) over the whole training set.

Training set. Proteins.To train the neural networks, we used the models of solved proteins and nucleotides deposited in the worldwide protein databank PDB ([www.rcsb.org](http://www.rcsb.org)) (Berman et al.) for simulation. Theoretically, for the better performance of NNs it is recommended to prepare a complete and unbiased training set, ideally evenly distributed over the parameters for prediction. In other words, the “ideal” training set shall contain an equal number of proteins of all sizes (even distribution of a histogram over MW) and shapes (even distribution of a histogram over a radius of gyration Rg). However, as is seen from the fig.2, the distributions of deposited in PDB models are severely skewed towards small and globular proteins.



(a)

(b)

(a)

(b)

*numbers*

*numbers*



(c)



(d)

Fig.2. Distribution over the radius of gyration and MW of (a) all deposited in PDB proteins; (b) sampled for the training set by the Latin supercube sampling (c) MW vs Rg heat map for the 135 238 proteins (d) for the chosen training set.

It is intuitively clear, that small proteins are easier to solve and thus there are more of them in PDB, especially given the historical perspective of 1970-2000 years. Moreover, the vast majority of the structures in PDB were solved by crystallographic methods, which implies that the proteins must be able to form crystals, which is usually the case for the small and globular proteins as well.

On the contrary, since SAXS is a low-resolution technique and is typically used for the determination of supramolecular structures, it mostly deals with relatively big proteins or their complexes. Preliminary experiments confirmed, that NNs trained on the whole PDB data works good enough for the smaller compact proteins, but underperforms for bigger and elongated models (the right-hand part of fig.2 (c)). These results, however commendable, would fall short of the SAXS community aspirations, since one of the strongest sides of the method is its ability to analyze rather big, unfolded, and even intrinsically disordered proteins.

Thus, we decided to amend the training set to make it more diverse, complete, and evenly represented at the same time. Among other techniques we tried, the most successful turned out to be a Latin hypercube sampling (McKay et al., 1979) – a statistical method for generating a most representative near-random sample of parameter values from a multidimensional space. In this way, after filtering outliers we selected ~7000 models in two-dimensional space (MW, Rg) out of more than 135000 proteins available to date in PDB. As is demonstrated in fig.2, the chosen dataset has almost a step-like distribution across both parameters (MW, Rg) indicating drastically better subset of models for training a NN. As a preprocessing step, the heteroatoms were deleted from all models to remove binding ligands and other non-organic molecules. Then the data were randomly distributed as to 80% training, 10% validation, and 10% test sets.

For each model, a pair of (simulated SAXS curve – predicted parameter) was prepared using CRYSOL (Barberato et al., 1995), then the SAXS curves were augmented with the experimental noise and normalized on the I(0) = 1. It is worth noting, that additional normalization of the data such as using the other representations (e.g. Kratky plot or log I vs s), subtracting the average curve, and dividing by standard deviation did not bring improvements in the NNs performance. The experimental noise, simulated at 7 different protein concentrations c = 0.25, 05, 1, 2, 4, 8, 16 mg/ml, was generated based on experimental data from the p12 beamline (Blanchet et al.) that corresponds to the data acquired with the sample-to-detector distance of 1 meter, exposure time of 1 second, and X-ray energy of E = 10 keV. For MW and Dmax two separate NNs with similar architectures were trained.

Nucleic acids. The DNA and RNA are suitable objects to be study by SAXS as they have high electron contrast and they are typically less prone to radiation damage. The nucleic acid models (only nucleotides, not heterocomplexes with proteins) are not as massively populated in PDB as protein models and comprise only less than 2% of all entries. To collect only non-redundant models, we used the NDB server (<http://ndbserver.rutgers.edu/>) (Coimbatore Narayanan et al., 2014). After preliminary filtering, we fetched ~3000 models and distributed them in a similar way as 80%/10%/10% for training/validation/test sets. As is seen in fig.3, the models are also mostly small and compact with the vast majority of them populated in between MW of 10 and 20 kDa and Rg of 10 and 25 Ȧ. Given the limited number of models and the fact, that according to the SASBDB database (Kikhney et al., 2019) the majority of DNA/RNA models used in SAXS are within the same intervals, we decided to use those models as is without further shrinking.



6UES

(39 kDa)

2JYH

(28 kDa)

4KYY

(11 kDa)

3REC

(0.6 kDa)

1H1K 🡪

(605 kDa)

Fig.3. Training set from PDB for the nucleic acids

Intrinsically disordered proteins. In the context of thermodynamics, the IDPs are characterized by a low content of hydrophobic amino acids while having a high number of polar and charged amino acids. Thus IDPs cannot sufficiently bury a hydrophobic core to fold into stable globular proteins, i.e. they lack a stable tertiary structure in solution. Furthermore, high net charges promote disorder due to electrostatic repulsion in between charged residues (Oldfield and Dunker, 2014). Interestengly, many disordered proteins reveal regions without any regular secondary structure as well. These regions do not contain only one set of Ramachandran angles, and therefore are more flexible than the structured loops of globular proteins.

It has been predicted that more than 35% of human proteins have significant regions of disorder (Fukuchi et al., 2011) and about 25% are likely to be completely disordered (Uversky and Dunker, 2010). These proteins are functionally important for many cellular regulatory processes, and may also be involved in pathological processes associated with protein misfolding or aggregation (Chiti and Dobson, 2006), (Uversky et al., 2008). Under physiological conditions these proteins constantly fluctuate between different structural states, resulting in a dynamic mixture of conformations in a polydisperse solution. Quantitative characterization of such heterogeneous systems is a difficult task, and SAXS is among few methods capable of providing unique information on the structural properties of the flexible macromolecules (Kikhney and Svergun, 2015).

To prepare a training data set of the IDP models, we used currently the only available open database comprising IDP ensembles: the PED database (Lazar et al.). The snapshot of the database was made that included 192 ensembles and XXX models in total. The distribution of models, shown in fig.3, indicates…TODO

# Results and discussion

Benchmark. As was discussed in details in the previous section, different conventional methods have ads and procs and perform differently upon specific models and levels of noise. In order to produce some generic metric of the prediction accuracy, we applied these methods and the NNs to test sets, and average the relative error over all models:

(10)

Where N is the total number of models in the test set, P is predicted value and GT is the ground truth value. Since the test set was generated to comprise models of different sizes and shapes in mind, this value represents not only the accuracy of the given method, but also its robustness against models of various MW and degrees of compactness.

It is worth noting, that even though some of the methods are not applicable to unfolded proteins and nucleic acids, we decided to demonstrate their performance here as well just for the completeness of the picture. The comparison is presented in the fig.5, where it is seen than NNs not only outperform all conventional methods for all test object used, they are also more robust against simulated noise and mostly reach a plato at the concentrations as low as 1 or 2 mg/ml.

|  |  |  |
| --- | --- | --- |
| Type | MW | Dmax |
| Compact proteins |  |  |
| Nucleotides |  |  |
| IDP |  |  |

Fig.5 Comparison of performances of different methods (proteins, NAs, IDPs).

Information content. Upper bound. The usage of NNs offers the challenge to fundamentally estimate the accuracy of MW and Dmax predictions and to assess the information content in SAXS data independently from Shannon theorem. For doing that, we simulated the “ideal” training set of noiseless SAXS profiles, determined on a wide s-range up to smax=10 nm-1,and normalized it on I(0) = 1. Then we trained the NNs on these smooth curves and applied them on the similar smooth simulated data from the test set.

Surprisingly, as is seen from fig. 6, the obtained result is not drastically better than the ones we obtained for the noisy data, and equal to 2.7% for MW and 3% for Dmax. This simple experiment demonstrates two important facts: (1) we almost reached the theoretical limit of prediction accuracy of the NN method (and maybe the precision of SAXS as method); (2) the augmentation of the training set with experimental noise, as is seen from fig.5, helps to deal with noisy data and only marginally reduces the overall accuracy of predictions.



(b)

(a)

Fig.6. Predictions for “ideal” smooth datasets versus ground truth for all models from the test set: (a) MW, (b) Dmax

Interestingly, the highest deviations in MW have been observed for the biggest (> 360 kDa) proteins, potentially indicating the lack of such proteins in PDB, and consequently, in our training set.

Angular range. Another convenient opportunity that opens the usage of NNs is to get a deeper insight into the information content of the different angular ranges of SAXS curves and their impact on the prediction of MW and Dmax values. (Fig.7)

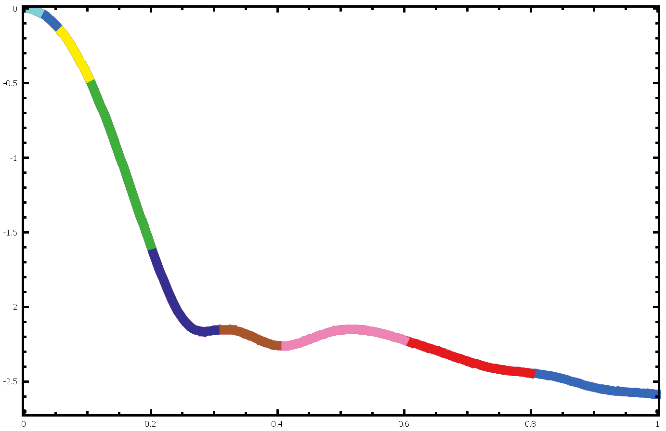


Fig.7 Error versus angular range for abs

As is shown in fig.7, the presence of higher angles does not drastically improve both estimates, while the plot for MW demonstrates more pronounced degradation upon the low smax values. That illustrates the well-known fact, that lower angles in reciprocal space contain information on the larger distances in real space, and estimation of maximal intraparticle distance essentially requires only the Guinier region, rapidly reaching a plato soon afterward. For MW prediction the situation is less pronounced, and the angles as high as smax = 6 nm-1 may be used to slightly improve the prediction. The angles on this scale mostly contain information on the molecule interface and its inner structure, which indeed may add a somewhat small correction to the overall estimation of the molecule mass.

**Web interface** (or we just say “to be included in the new release of ATSAS”??).

# Conclusions

Here we presented a novel independent method for the estimation of primary SAXS parameters using modern NN technologies. The comparison with existing well-established methods demonstrated higher accuracy and robustness of our method against simulated noise. Due to the fact, that the method is not confined within the frames of a homogeneous electron density particle, it also allows to anew assess the real capacities of SAXS data in terms of information content and to push further the accuracy of SAXS primary analysis results beyond the conventional 10%. Nevertheless, we believe that this work is merely a demonstration of the capacities of applying NNs to the SAXS field and can be easily extended and improved under specific needs and instrumentation. The presented methods along with the training sets and tools for preparing the figures are publicly available at the git-hub ().

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