Structural bioinformatics

KScons: a Bayesian approach for protein residue contact prediction using the knob-socket model of protein tertiary structure

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Abstract

Motivation: By simplifying the many-bodied complexity of residue packing into patterns of simple pairwise secondary structure interactions between a single knob residue with a three-residue socket, the knob-socket construct allows a more direct incorporation of structural information into the prediction of residue contacts. By modeling the preferences between the amino acid composition of a socket and knob, we undertake an investigation of the knob-socket construct’s ability to improve the prediction of residue contacts. The statistical model considers three priors and two posterior estimations to better understand how the input data affects predictions. This produces six implementations of KScons that are tested on three sets: PSICOV, CASP10 and CASP11. We compare against the current leading contact prediction methods.

Results: The results demonstrate the usefulness as well as the limits of knob-socket based structural modeling of protein contacts. The construct is able to extract good predictions from known structural homologs, while its performance degrades when no homologs exist. Among our six implementations, KScons MST-MP (which uses the multiple structure alignment prior and marginal posterior incorporating structural homolog information) performs the best in all three prediction sets. An analysis of recall and precision finds that KScons MST-MP improves accuracy not only by improving identification of true positives, but also by decreasing the number of false positives. Over the CASP10 and CASP11 sets, KScons MST-MP performs better than the leading methods using only evolutionary coupling data, but not quite as well as the supervised learning methods of MetaPSICOV and CoinDCA-NN that incorporate a large set of structural features.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Due to the resource intensive nature of experimental protein structure determination, the amount of information about protein structure lags far behind the amount of known protein sequence data. Yet, a protein structure yields a deeper understanding of how a protein functions as well as how it is controlled in a biological system. Since Anfinesen’s insightful experiments on protein folding (Anfinesen, 1973), it is generally accepted that all the information on a protein’s structure is coded in its amino acid sequence. Therefore, automatic methods that predict protein structure from its sequence are a particular focus of computational biochemistry. As a step towards developing a protein structure prediction method, this
work describes the statistical model for the prediction of protein residue contacts using the novel knob-socket model of protein residue packing structure.

There are four distinct levels of protein structure. The sequential chemical bonded nature of a polypeptide chain of amino acids allows the primary (1st) structure of a protein to be simply represented as the linear sequence of the amino acids. At the secondary (2nd) level of protein structure, the patterns of chemical interactions called hydrogen bonds determine the state assigned at that position in the sequence. The set of interactions that bring these 2nd structure elements together within a polypeptide chain is called the tertiary (3rd) level of protein structure. The last quaternary (4th) level of protein structure occurs between two separate polypeptide chains. In prediction of protein structure, the goal is to predict a protein’s 3rd structure from the amino acid 1st sequence. An important part of predicting protein 3rd structure is to correctly identify the residues close in three-dimensional space that defines the topology of the folded backbone. As a result, residue contact prediction has become its own category in computational structural biology.

As discussed in the most recent Critical Assessment of Structure Prediction (CASP) review of contact prediction methods (Monastyrsky et al., 2015), accurate predictions of residue contacts have been successfully used to model soluble (Kamisetty et al., 2013; Marks et al., 2011) as well as transmembrane (Hopf et al., 2012; Nugent and Jones, 2012) protein structures. Recently, it has been estimated that 1 long range contact is needed per every 12 residues for an accurate prediction of protein 3rd structure (Kim et al., 2014). A thorough review comparison of the major contact prediction methods has been performed and serves as a good benchmark (Ma et al., 2015). Generally, these approaches to contact prediction are based on the concept of evolutionary coupling (EC), where residues packing near in space will most likely mutate with each other (Gobel et al., 1994; Shindyalov et al., 1994). This approach is most successful when there are many sequence homologs to provide a deep enough multiple sequence alignment to identify covariation between positions. To address cases with low sequence information, characteristics from protein structure usually on the order of hundreds have been added to EC. To properly integrate these large number of multiple inputs, machine learning methods like support vector machines (Cheng and Baldi, 2007; Wu and Zhang, 2008) or neural nets (Ma et al., 2015; Tegev et al., 2009) have been used. At the most recent 1st CASP meeting, the CONSIP2 server of the MetaPSICOV method (Kosiełek and Jones, 2015) demonstrated quantifiable progress even on targets with little to no sequence homologs (Monastyrsky et al., 2015) by implementing a supervised machine learning approach that combined several EC protocols with over 600 protein features to address the lack of sequence information.

By identifying exact residue contacts from 3rd structure packing, the knob-socket model provides a simpler and more direct approach to incorporate structural data that is complementary to the aforementioned methods for predicting protein contacts. In a series of papers (Fraga et al., 2015; Joo and Tsai, 2014; Joo et al., 2012, 2015), a novel description of protein 3rd packing has been developed that uses a new construct to predict protein contacts. The knob-socket model represents a paradigm shift in the characterization of protein structure by directly relating protein sequence and the arrangement of residues in 3rd structure. As shown in Figure 1, the model decomposes the complexity of the multi-body residue interactions into discrete patterns of a four-residue packing unit called the knob-socket. Essentially, the entire 2nd structure simply maps into 3-residue sockets (which include irregular coil structure) that exist in either a filled or free state to define 3rd structure. A filled socket packs with a knob residue to form 3rd structure and reduces the many-bodied residue packing interactions into a simple two-body mapping of knob-socket patterns. A free socket indicates those regions of the structure that are not involved in 3rd structure. It has been shown that the types of amino acids that make up the socket determine whether a socket is filled or free. As a result, filled sockets provide a scoped definition for predicting residue contacts in 3rd. In other words, protein contacts can be modeled based on the propensity of the filled knob-socket interactions.

In this work, we investigate the usefulness of a knob-socket based approach to protein contact prediction. One challenge in identifying the residue contacts is projecting the 1st and 2nd one dimensional structures into a three dimensional arrangements of amino acids. The characterization of packing as a knob residue contacting three residues in a socket allows the direct mapping of three dimensional residue arrangements to one dimensional contact pairs. Unlike the supervised learning approaches that use hundreds of inputs to include structural information, our approach uses only the knob-socket construct. We incorporate this protein structural information defined by the knob-socket construct into a principled statistical approach. The 3rd packing information provided by the knob-socket model is captured by our likelihood and the evolutionary data from structural homologs provides prior information in our Bayesian approach. We name our proposed residue contact prediction program KScons. To properly assess predictions, KScons is run against three structure sets. The first is the set of 150 structural families used to comprehensively compare a number of current contact prediction routines (Ma et al., 2015) that was originally used to characterize PSICOV (Jones et al., 2012). The last two are the more challenging sets of structures from CASP10 (Monastyrsky et al., 2014) and CASP11 (Kryshtafovych et al., 2015). From the standard scores used in these comparisons, KScons produces an improvement...
in the prediction of protein contacts and therefore demonstrates the usefulness of a structure-based modeling of protein contacts in prediction.

2 Approach

2.1 Datasets

The SCOPe: Structural Classification of Proteins—extended family Astral 2.05 dataset (Fox et al., 2014) with sequence identity cutoff of 70% was used to calculate the knob-socket frequencies. After cleaning up the fragmented structures, 20 158 domains were used to collect knob-socket frequencies as described in previous work (Fraga et al., 2015; Joo and Tsai, 2014; Joo et al., 2012, 2015). The training data (ALN) set was created from the same Astral 2.05 dataset by including only sequences with sequence identities between 70% and 90%, and families with more than three domains were used, which left 212 families including 2008 domains. For each family, all the sequences were aligned using MUSCLE multiple sequence alignment (Edgar, 2004a,b) and the structures were aligned using MUSTANG multiple structure alignment (Konagurthu et al., 2006). The knob-socket data and residue contact matrices were calculated using aligned structures following the methods used in previous studies (Fraga et al., 2015; Joo and Tsai, 2014; Joo et al., 2012, 2015).

As test sets, 150 PSICOV (Jones et al., 2012), 124 CASP10 (Moult et al., 2014) and 110 CASP11 (Kinch et al., 2016) targets were used. As it is common, 21 of 131 of the CASP11 target domains have not yet been released to the public. Among 110 CASP11 target domains, no good templates were found for 22 domains and we used templates for only 88 domains. For each target sequence, homologous sequences were searched in non-redundant sequence database using Position-Specific Iterative Basic Local Alignment Search Tool (PSI-BLAST) (Altschul et al., 1997). Templates were selected from the list of RCSB protein data bank (Bernstein et al., 2000) structures released before December 2012, excluding target proteins. Multiple sequence alignments and multiple structural alignments were performed for each target/template as for the training dataset. The knob-socket analyses were carried out and the residue contact matrices were calculated on the aligned structures.

3 Model

3.1 Socket triplets and filled knob-socket quartets

The amino acid sequence or 1'st structure of a protein consisting of L amino acids is represented by a linear string as \( a = (a_1, \ldots, a_L) \), where \( a_i \) is one of the 20 naturally occurring amino acids. Each position in the 1'st sequence can be assigned a 2'st structure state \( \rho = (\rho_1, \ldots, \rho_L) \). Kabsch and Sander (1983) proposed the Dictionary of Protein Secondary Structure (DSSP) for protein 2'st structure with single letter codes. The original eight structure types (in parentheses) are commonly collapsed into the following four types (in italics):

- Helix ‘H’: 310 helices (G), \( \alpha \)-helices (H), or \( \pi \)-helices (I);
- Strand ‘E’: extended strands in parallel or anti-parallel \( \beta \)-sheets (E);
- Turn ‘T’: hydrogen bonded turns of length 3 or more amino acids (T);
- Coil ‘C’: \( \beta \)-bridge residues (B), bends (S), or random coils (C).

These four types of 2'st structure appear in contiguous stretches of the same type giving the general form of local segments and referred to as ‘block types.’

The 3’st structure of a protein is its geometric shape and is defined by the multi-body packing of residues distant in sequence but close in three-dimensional space. As introduced in Figure 1, the knob-socket model of protein packing structure provides a simple construct to characterize protein 3’st structure and decomposes the complexity of many-body residue interactions into a simpler two-body problem between elements of 2’st structure. For a knob-socket pair, the socket made up of 3 residues on one element of 2’st structure presents a surface that favors packing a knob residue from another 2’st structure. Therefore, the socket represents short range protein contacts, while the knob-socket interactions are a representation of long-range protein contacts. Contact prediction then reduces down to identifying which amino acids form these 3-residue sockets. In this paper, the 3-residue sockets are modeled based the propensity to be filled with a knob or free, given the 2’st structure type and the amino acid sequence (Joo and Tsai, 2014; Joo et al., 2012, 2015). Notationally, we write a three-residue socket as \( (u, v, w) \) \((\rho_u, \rho_v, \rho_w)\), where \( u, v, w \) are positions such that \( 1 \leq u < v < w \leq L \) and \( \rho_u, \rho_v, \rho_w \) are the secondary structure types of the corresponding positions. Each socket may be filled with a knob (i.e. a residue whose position is in sequence from those forming the socket) or ‘free’ of the ‘knob’ (i.e. when the socket is not involved in 3’st structure). If all of the free sockets and filled knob-sockets are known, these can be used as simple constraints to rebuild the entire protein fold or 3’st structure (i.e. its geometric shape).

The inferential goal of the statistical model presented in this paper is as follows. Given the 1’st structure \( a \) and the 2’st structure \( \rho \) of the target protein with length \( L \), we seek to provide a list of all the three-residue free sockets and \((1 + 3)\)-filled knob-sockets of the protein. Because of sampling variability, our list of predicted sockets may exclude some true sockets and include sockets that are not actually present in the protein.

All of the sockets in the 2’st and 3’st structure of a protein are a small fraction of all possible combinations of \( (u, v, w) | (\rho_u, \rho_v, \rho_w) \) that could be formed from the integers \( 1, \ldots, L \) and the associated 2’st structure types. We let a \textit{triplet} be one possible combination of \( (u, v, w) | (\rho_u, \rho_v, \rho_w) \) that may or may not form a socket in the 3’st structure. For a target protein which has \( L \) residues in total, the total number of such triplets, denoted by \( K \), is \( C(L, 3) = \frac{L(L - 1)(L - 2)}{6} \). Only a small fraction of those \( K \) triplets actually form sockets. We postulate the existence of a latent binary vector \( \gamma = (\gamma_1, \ldots, \gamma_K) \), with \( \gamma_k = 1 \) if combination \( k \), denoted \((u_k, v_k, w_k) | (\rho_{u_k}, \rho_{v_k}, \rho_{w_k})\), is actually a socket and \( \gamma_k = 0 \) otherwise.

Searching through all possible \( K \) combinations is computationally prohibitive. As such, we reduce the space to those triplets of amino acids that could possibly form sockets based on known propensities calculated in the characterization of the knob-socket model (Joo and Tsai, 2014; Joo et al., 2012, 2015). As discussed in those analyses, the entire 2’st structure forms sockets, and the composition of sockets from different 2’st structure exhibits preferences for certain amino acids. Furthermore, the amino acid preferences also identify if the socket tends to be free or filled with a knob residue. First, we divide all the triplets into two groups according to their ranges, i.e. \( w_k - u_k \). If \( w_k - u_k > 5 \), those triplets are non-local and only the triplets with secondary structure \((\rho_u, \rho_v, \rho_w) = (E, E, E) \) and the following four structures could form sockets: \((u_k, v_k, w_k) = (u_k + 1, w_k)\), \((u_k, v_k, w_k) = (u_k + 2, w_k)\), \((u_k, v_k, w_k) = (w_k - 1, u_k)\) and \((u_k, v_k, w_k) = (u_k, w_k - 2, w_k)\). We can also denote the above four structures by their gaps \( 1x, 2x, x1, x, x, 2 \), respectively, where the first number indicates the gap between position \( u_k \) and \( v_k \), the second number indicates the gap between position \( v_k \) and \( w_k \), and \( x \) means any other possible value. On the other hand, if \( w_k - u_k \leq 5 \),
those triplets are local and there are 10 possible structures:

\((u_k, v_k = u_k + 1, w_k = v_k + 1), (u_k, v_k = u_k + 1, w_k = v_k + 2), (u_k, v_k = u_k + 1, w_k = v_k + 3), (u_k, v_k = u_k + 1, w_k = v_k + 4), (u_k, v_k = u_k + 2, w_k = v_k + 1), (u_k, v_k = u_k + 2, w_k = v_k + 2), (u_k, v_k = u_k + 2, w_k = v_k + 3), (u_k, v_k = u_k + 3, w_k = v_k + 1), (u_k, v_k = u_k + 3, w_k = v_k + 2),\) and \((u_k, v_k = u_k + 4, w_k = v_k + 1),\) denoted by their gap

notations 1, 2, 3, 4, 1, 2, 2, 3, 3.1, 3.2 and 4.1, respectively. Finally, some triplets must be form sockets and we therefore do not need to predict them. For example, it is well known that the triplets \((u_k, v_k = u_k + 1, w_k = v_k + 4))\) and \((u_k, v_k = u_k + 3, w_k = v_k + 4)\,(H, H, H)\) and \((u_k, v_k = u_k + 3, w_k = v_k + 4))\,(H, H, H)\) always form sockets. Table 1

summarizes those triplets that must be, might be, and must not be.

Table 1. Summary of triplets that must be (‘✓’) or might be (‘?’) sockets by secondary structure and gap patterns. We reduce the sample space for \(γ\) by only considering those triplets that might be sockets

<table>
<thead>
<tr>
<th>Structure</th>
<th>Local gap patterns</th>
<th>non-local gap patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1_1</td>
<td>1_2</td>
</tr>
<tr>
<td>HHH</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>EEE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Set’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* Set = \{CCC, TTT, HHC, HCC, CCH, CHH, HHT, HTT, TTH, THH, EEC, ECC, CEE, EET, ET, TIE, TEE, CCT, CTT, TTC, TCC, ECT\).
\( \sim \) Binomial \((N, \psi_{ij})\) and \( \psi_{ij} \sim \text{Beta}(x, \beta) \), where \( x \) and \( \beta \) can be set to 1 for convenience. Therefore we have conjugate posterior \( \psi_{ij} | X \sim \text{Beta} \left( \sum_{i} X_{ij} + x, N - \sum_{i} X_{ij} + \beta \right) \). Then we assume that the contact matrix follows a product of \( L \cdot (L - 1)/2 \) p.m.f.'s, i.e. \( p(\gamma, \delta, \epsilon) = \prod_{i=1}^{L} \prod_{j=1}^{i-1} \psi_{ij} (1 - \psi_{ij})^{i-j-1} \). The more similar \( C \) is to the average of \( C^{\text{MST}(1)}, \ldots, C^{\text{MST}(N)} \), the higher the prior probability will be.

Analogously, using the multiple sequence alignment (MSQ) information \( C^{\text{MSQ}(1)}, \ldots, C^{\text{MSQ}(N)} \), we can estimate another set of hyperparameters \( \psi_{ij} \) to reshape the prior distribution.

### 4 Model fitting

#### 4.1 MCMC algorithm

We use Markov chain Monte Carlo (MCMC) methods to sample from the posterior distribution \( p(\gamma, \delta, \epsilon | a, \rho) \). We update the three parameters using a Metropolis algorithm. We note that this algorithm is sufficient to guarantee ergodicity for our model. See the details in the supplement.

#### 4.2 Posterior estimation

The goal is to infer the socket list \((\gamma, \delta, \epsilon)\). However, for a proper assessment of performance, we map predicted sockets and knobs into the corresponding contact matrix \( C \). We considered two ways to summarize the posterior distribution to yield point estimators: (1) Choosing a particular \( C \) that maximizes the posterior probability \( p(\gamma, \delta, \epsilon | a, \rho) \), i.e. \( C^{\text{MAP}} = (\gamma^{\text{MAP}}, \delta^{\text{MAP}}, \epsilon^{\text{MAP}}) = \arg \max_{c} p(\gamma, \delta, \epsilon | a, \rho) \) and (2) Selecting the most likely \( C_{ij} \) as the maximum \( a \text{ posteriori} \) method (MAP) and the marginal probability method (MP), respectively.

### 5 Results and discussion

#### 5.1 Results

We first trained the KScons sampling model, i.e. Equation (2), with the ALN dataset. The training set does not contain any target from any test sets, and so is properly jack-knifed with respect to the test datasets. The statistics of these four datasets are summarized in the supplement. Then, we evaluated the performance of our method with different prior distributions and posterior estimates against the 150 targets in the PSICOV test set, the 124 targets in the CASP10 test set, and the 110 available targets in the CASP11 test set. Using common accuracy metrics, KScon’s pairwise contact prediction was compared consistently based on test set with leading methods of CoinDCA (Ma et al., 2015) and PSICOV (Jones et al., 2012), including the new implementations MetaPSICOV (Jones et al., 2015) and CONSPI2 (Koscielak and Jones, 2015).

For KScons with an independent Bernoulli prior, we set the hyperparameter \( \omega = 0.5 \). When using the MST or MSQ priors, we set the hyperparameters \( x = \beta = 1 \), which leads to a non-informative hyperprior. Comparisons of different variants and marginal probability, which can be calculated by \( \sum_{b=1}^{B} (C_{ij}^{(b)} | a, \rho)/B \), where \( B \) is the number of iterations after burn-in. A point estimate of \( C \) is then obtained by identifying those marginal probabilities that exceed a given threshold \( t \), i.e. \( C_{ij}^{\text{MAP}} = 1 \left( \sum_{b=1}^{B} C_{ij}^{(b)} | a, \rho \geq t \right) \). We recommend \( t = 0.5 \), resulting in the median model. We name these two posterior estimators as the maximum \( a \text{ posteriori} \) method (MAP) and the marginal probability method (MP), respectively.

### Table 2. Means and standard deviations (in parentheses) of contact prediction accuracy achieved by PSICOV, CoinDCA and our method (KScons) under different prior distributions and posterior estimates in the PSICOV set

<table>
<thead>
<tr>
<th></th>
<th>Short range</th>
<th>Medium range</th>
<th>Long range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/10</td>
<td>L/5</td>
<td>L/2</td>
</tr>
<tr>
<td>PSICOV</td>
<td>0.369</td>
<td>0.299</td>
<td>0.205</td>
</tr>
<tr>
<td>CoinDCA</td>
<td>0.528</td>
<td>0.446</td>
<td>0.316</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.195</td>
<td>0.136</td>
<td>0.090</td>
</tr>
<tr>
<td>Bern-MAP</td>
<td>0.191</td>
<td>0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.335</td>
<td>0.281</td>
<td>0.198</td>
</tr>
<tr>
<td>Bern-MP</td>
<td>0.24</td>
<td>0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.533</td>
<td>0.485</td>
<td>0.326</td>
</tr>
<tr>
<td>MSQ-MAP</td>
<td>0.26</td>
<td>0.23</td>
<td>0.19</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.792</td>
<td>0.701</td>
<td>0.478</td>
</tr>
<tr>
<td>MSQ-MP</td>
<td>0.18</td>
<td>0.2</td>
<td>0.16</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.581</td>
<td>0.516</td>
<td>0.336</td>
</tr>
<tr>
<td>MST-MAP</td>
<td>0.24</td>
<td>0.22</td>
<td>0.19</td>
</tr>
<tr>
<td>KScons w/</td>
<td>0.823</td>
<td>0.717</td>
<td>0.493</td>
</tr>
<tr>
<td>MST-MP</td>
<td>0.17</td>
<td>0.18</td>
<td>0.16</td>
</tr>
</tbody>
</table>

The numbers which achieve the highest value are shown in boldface.

### Table 3. Means of contact prediction accuracy achieved by our method with MST prior and MP posterior estimation, PSICOV, CoinDCA, MetaPSICOV and CoinDCA-NN in the CASP10 set

<table>
<thead>
<tr>
<th></th>
<th>Short range</th>
<th>Medium range</th>
<th>Long range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/10</td>
<td>L/5</td>
<td>L/2</td>
</tr>
<tr>
<td>KScons</td>
<td>0.536</td>
<td>0.481</td>
<td>0.341</td>
</tr>
<tr>
<td>PSICOV</td>
<td>0.234</td>
<td>0.191</td>
<td>0.14</td>
</tr>
<tr>
<td>CoinDCA</td>
<td>0.517</td>
<td>0.435</td>
<td>0.311</td>
</tr>
<tr>
<td>MetaPSICOV</td>
<td>0.7</td>
<td>0.615</td>
<td>0.458</td>
</tr>
<tr>
<td>CoinDCA-NN</td>
<td>0.725</td>
<td>0.64</td>
<td>0.471</td>
</tr>
</tbody>
</table>
estimation methods are summarized in Tables 2–4 with complete
tables in the supplement. The prediction accuracy is defined as the
percentage of native contacts among the top predicted L/10, L/5 and
L/2 predicted contacts, where L is the sequence length. Contacts are short-, medium- and long-range when the sequence dis-
tance between the two residues in a contact falls into three intervals
(6, 12), (12, 24) and (24, L), respectively.

In Table 2, only the performance of all 6 different combinations of
the 3 prior distributions and 2 posterior estimates on the PSICOV test
set is compared to identify the best implementation of KScons. Because the Bernoulli prior was limited to only modeling sockets, no
information about long range knob residue contacts are modeled. As
a result, this prior performed the poorest at predicting contacts for
long range, but also was not much more accurate for medium and
short range contacts. The multiple structure/sequence alignment
(MST/MSQ) priors that incorporate evolutionary information im-
proved the prediction accuracy. However, these priors need to be
paired with an appropriate posterior estimate to take advantage of
the evolutionary relationships and produce significantly improved ac-
curacy. Of the 2 posterior estimates, the maximum a posteriori
method (MAP) estimates did the worst with both priors. This ap-
proach favored the socket triplets and knob/socket quartets with the
highest probabilities in the ALN dataset at the cost of identifying
the unique and correct contacts for each protein. In contrast, using
the marginal probability (MP) that selected pairs based on homology
over a threshold included more correct contacts. Of the 3 priors, the
Bernoulli exhibited the worst improvement with the MP posterior es-
timate. Between the MSQ and MST priors, the MST using a struc-
tural alignment prior performed just about 10% better than the MSQ
using sequence alone. This similarity in the performance of alignment
priors is expected as both are one-dimensional decompositions of the
three-dimensional structure. Overall, the best results for KScons were
obtained using the MST structural evolutionary prior with the MP
posterior estimate, although the MSQ-MP prior performs reasonably
well. Compared to the EC methods of PSICOV and CoinDCA,
KScons MST-MP exhibits marked improvement on this dataset.
In each of the categories from the PSICOV test set (Table 2), the KScons
MST-MP predictions improve prediction accuracy by 0.3 or 30%
over EC methods like PSICOV (Jones et al., 2012) and CoinDCA
(Ma et al., 2015) that leverage significantly more sequence data than
KScons. Generally, the performance trends shown in Table 2 were
consistent across each test set (see supplement). For these reasons,
farther comparisons to the CASP10 and CASP11 test sets in Tables 3
and 4, respectively, are from the MST-MP KScons models, although
complete tables are shown in the supplement.

Regarding contact predictions in the more challenging CASP10
set (Table 3), KScons MST-MP is again comparable to the best EC
approaches of PSICOV and CoinDCA. KScons performs markedly
better than PSICOV. In this instance however, KScons MST-MP
contact predictions are just 7% on average better than CoinDCA,
which is within the equivalence of the standard deviation. The
supervised learning methods of MetaPSICOV and CoinDCA-NN are
both about 30% better than the KScons MST-MP. For the most
recent CASP11, KScons MST-MP contact prediction accuracies are
lower by 6%, but show similar improvement over the strictly EC
methods of PSICOV and CoinDCA. Again, the supervised learning
MetaPSICOV and CoinDCA-NN programs are about 45% better.
The CONSIP2 server using MetaPSICOV (Kosciolek and Jones,
2015) had the strongest showing in CASP11 for contact prediction
(Monastyrskyy et al., 2015). CONSIP2 is an implementation of
MetaPSICOV, a supervised machine learning approach combining
a number of EC methods. Only the L/10 and L/5 values were re-
ported, so our discussion is limited to these prediction accuracies.
Also, KScons was tested on all 89 structures, while the CONSIP2
server results are only for 36. KScons MST-MP generally did not
perform as well as the CONSIP2 server results, especially for short
and medium range contacts. Additionally, the CASP11 set contained
many targets that did not have many homologs (Monastyrskyy
et al., 2015). The present implementation of KScons MST-MP needs
homologs to make accurate predictions. In general, current super-
vised learning methods are more accurate than our implementation
of the knob-socket approach due to this requirement for structural
homologs. Even so, results from all three datasets are impressive
considering that the KScons approach is based primarily on model-
ing structural data using the simple knob-socket construct. The
supervised learning methods are more complex in there using hun-
dreds of inputs and furthermore, do not provide insight on their suc-
nesses or failures. On the other hand, the knob-socket construct
allows us to investigate the performance of this approach.

To better understand the current strengths and limitations of the
knob-socket implementation in KScons, the classification precision
and recall for γ were calculated. Complete tables for all 6 variations
are given in the supplement, while Table 5 shows the values over the
3 tests sets for the MST-MAP and MST-MP implementations of
KScons. Precision is defined as the percentage of actual sockets that
are correctly estimated over all predicted sockets. Consistent
with previous methods, the precision results showed that many false posi-
tives are predicted, which has been a recognized problem in contact
prediction (Monastyrskyy et al., 2015). The improvement of the MP
test set was clear in the precision and can be seen especially
for the CASP11 set, where the MP identified more true contacts
than the MAP. Recall is defined as the percentage of sockets that are
correctly estimated over all actual sockets. In comparison, the MSQ
and MST priors improved the recall of true contacts, but more false
positives were found. Comparing the posterior estimates in Table 5,
the MAP predicted fewer true contacts and more contacts that were
false than the MP. These results indicate the need for homologs for
accurate predictions in this implementation of KScons. Because the

### Table 4. Means of contact prediction accuracy achieved by our method with MST prior and MP posterior estimation, PSICOV, CoinDCA, MetaPSICOV, CoinDCA-NN and CONSIP2 in the CASP11 set

<table>
<thead>
<tr>
<th></th>
<th>Short range</th>
<th></th>
<th>Medium range</th>
<th></th>
<th>Long range</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/10</td>
<td>L/5</td>
<td>L/2</td>
<td>L/10</td>
<td>L/5</td>
<td>L/2</td>
</tr>
<tr>
<td>KScons</td>
<td>0.462</td>
<td>0.425</td>
<td>0.305</td>
<td>0.395</td>
<td>0.350</td>
<td>0.268</td>
</tr>
<tr>
<td>PSICOV</td>
<td>0.190</td>
<td>0.144</td>
<td>0.112</td>
<td>0.196</td>
<td>0.163</td>
<td>0.115</td>
</tr>
<tr>
<td>CoinDCA</td>
<td>0.452</td>
<td>0.391</td>
<td>0.286</td>
<td>0.430</td>
<td>0.365</td>
<td>0.254</td>
</tr>
<tr>
<td>MetaPSICOV</td>
<td>0.680</td>
<td>0.582</td>
<td>0.419</td>
<td>0.555</td>
<td>0.492</td>
<td>0.407</td>
</tr>
<tr>
<td>CoinDCA-NN</td>
<td>0.685</td>
<td>0.584</td>
<td>0.423</td>
<td>0.585</td>
<td>0.526</td>
<td>0.432</td>
</tr>
</tbody>
</table>
MAP predicts contacts only using the isolated preference of knobs with sockets without context, the predictions produce many false positives and fewer true negatives. Therefore, certain knob-socket combinations that have high frequency in the ALN library of structures will always be predicted. The MP uses the homolog and structural topology to provide context and attenuate the highly preferred knob-sockets of the MAP to make more correct predictions.

More specifically, an analysis of contact prediction accuracy based on a three state description of secondary structure between CASP10 and CASP11 sets further confirms the strengths and limitations of KScons MST-MP. Table 5 shows the accuracy of prediction using a 3 state description of secondary structure. The improved performance of KScons MST-MP in the CASP10 dataset over the CASP11 dataset involves not just identifying fewer correct contacts, but also more false positives and false negatives. For KScons MST-MP, the strength is that the knob-sockets are able to pull significant information from the packing of the structural homologs. For both datasets, the trend is that helices are the most accurately predicted contacts above 59%. With a drop to about 20% for true positives, a significant fall off is seen in accuracy of predicting sheets. Coil is just a little worse with just over 18% true positives. The lack of homologs in CASP11 compared to CASP10 shows that helical predictions suffer from more false positives, while the sheets and coil have more false negatives. Helices are well represented in the training ALN set with a local socket and non-local knob-socket. For helices, the decrease in accuracy between CASP10 and CASP11 is mainly due to a 4% increase in the false positives. A closer look at the more complete analysis in the supplement shows the helical contact predictions in the CASP11 dataset make many more false positives. Therefore, KScons’s difficulty with helical contact prediction is inclusion of more incorrect long-range contacts without homologs or poor knob-socket predictions. Sheet sockets and knob-sockets are both non-local and problematic for the knob-socket construct. For sheets, the decrease in accuracy is due to a 4% increase in false negatives. Looking at the more detailed breakdown, this increase is primarily due to more false negatives from long-range contacts in the CASP11 dataset. The coil contacts are local, but random sockets, while knob-sockets are long-range. Like sheet predictions, the coil contacts are difficult to model with very low accuracies. The 2% increase in false positives seen in coil predictions also mirrors the difficulties with long-range interactions.

### 6 Conclusion

As a complement to current EC and supervised learning approaches to residue contact prediction, the knob-socket construct allows the direct statistical modeling of structure into sequence space (Fig. 1). Therefore, the purpose of this work has been to develop a Bayesian statistical model using knob-socket information that maximizes contact prediction accuracy from a combination of priors and posteriors. The resulting program was then compared over three different and difficult test sets to gauge the overall performance on contact predictions against current leading methods. This article is a natural extension of our preliminary work (Li et al., 2014), where we proposed a Bayesian model to predict 2-state structure from 1-state structure based on the knob-socket model of protein packing in 2-state structure.

The combinations and comparisons revealed that a simple implementation of the knob-socket preferences requires known homologs to guide correct predictions. Testing 3 priors and 2 posterior estimates revealed that the multiple structure alignment prior and a marginal probability posterior (MST-MP) combination maximized KScons prediction accuracy. Without the MP, the knob-socket preferences from the ALN training set are too dominant and lead to decreased contact prediction accuracy because of the inclusion of more false positives and false negatives. In other words, KScons MST-MP improved the prediction true positives and also true negatives. While KScons MST-MP demonstrated greater contact prediction accuracy in comparison to EC methods over the PSICOV dataset, the more challenging CASP10 and CASP11 revealed that KScons MST-MP performs better than EC methods without the need for deep sequence alignments, but also has the same need for homologs. For proteins with no homologs, the supervised learning methods are the most accurate. Even so, this initial implementation of the knob-socket model performs well in extracting correct contact predictions using a simple and intuitive construct, as opposed to the complicated amalgamation of hundreds of inputs needed in the supervised learning approaches.

Because the knob-socket construct maps a direct correspondence between sequence and structure space, the strengths and weaknesses of the current implementation in contact prediction can be identified. This analysis provides a clear path to method improvement. Further work will be to understand how to improve the MAP that uses only the preferences from a protein structure training set. In particular, the goal is to identify how to decrease the false positives for helical contacts and the false negatives for sheet and coil contacts. Our objective is to provide a structural explanation based on knob-socket patterns for prediction of residue contacts in the cases of no sequence data.

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### Conflict of Interest

none declared.

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