Using the Semiempirical Quantum Mechanics in Improving the Molecular Docking: A Case Study with CDK2

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Abstract: In this study, we use some modified semiempirical quantum mechanics (SQM) methods for improving the molecular docking process. To this end, the three popular SQM Hamiltonians, PM6, PM6-D3H4X, and PM7 are employed for geometry optimization of some binding modes of ligands docked into the human cyclin-dependent kinase 2 (CDK2) by two widely used docking tools, AutoDock and AutoDock Vina. The results were analyzed with two different evaluation metrics: the symmetry-corrected heavy-atom RMSD and the fraction of recovered ligand-protein contacts. It is shown that the evaluation of the fraction of recovered contacts is more useful to measure the similarity between two structures when interacting with a protein. It was also found that AutoDock is more successful than AutoDock Vina in producing the correct ligand poses (RMSD $\leq$ 2.0 Å) and ranking of the poses. It is also demonstrated that the ligand optimization at the SQM level improves the docking results and the SQM structures have a significantly better fit to the observed crystal structures. Finally, the SQM optimizations reduce the number of close contacts in the docking poses and successfully remove most of the clash or bad contacts between ligand and protein.

Keywords: Molecular docking · Semiempirical quantum mechanics · Ligand optimization · Bad contacts · CDK2

1 Introduction

Molecular docking simulation is an efficient and successful computational tool for the study of ligand–protein binding and is widely used for structure-based drug design in recent years.[1–5] The docking algorithms have been developed for fast prediction of the possible conformations of the ligand within a protein binding site and correct estimation of their relative binding affinities. However, because of various simplifications and approximations used in the docking algorithms for speeding up the calculations, there is always some doubt about the validity of the docking results. Therefore, the accuracy of docking methods must be evaluated in comparison with the known experimental data or the results obtained from sophisticated computational methods such as the hybrid quantum mechanics/molecular mechanics (QM/MM) or the molecular dynamic (MD) simulations.[6–8] Consequently, finding an optimal trade-off between the speed and accuracy of docking is an active area of research in docking development.

Recent developments in the semiempirical quantum mechanics (SQM) methods – including new accurate parameterized models, linear-scaling procedures and modern parallelization techniques – provide opportunities to incorporate the quantum mechanical effects and the electronic properties in ligand–protein binding interactions, such as charge transfer, polarization, and dispersion into the docking calculations and improve the docking performance.[9–12] Two main methodologies have been proposed for the inclusion of the quantum effects in the docking results; one is employing SQM methods in the framework of the scoring functions, in which some parameters and/or individual contributions of the scoring functions are obtained from SQM calculations.[10,13–17] The second is the post-docking SQM calculations, in which the docking results are used for further calculations at the SQM levels.[12,18–20] Many studies on various biomolecular complexes have shown that the use of the SQM methods through each of the methodologies has led to more accurate estimation of complex geometry and binding energy and consequently has increased the docking accuracy.[9–23]

In this study, a post-docking optimization with the different popular corrected SQM Hamiltonians has been performed for the docking results of a series of human cyclin-dependent kinase 2 (CDK2). The CDK2 is a serine/threonine-protein kinase that is activated by binding to a regulatory cyclin protein for the cell cycle progression and transcription. Malfunction or overexpression of CDK2 leads to different kinds of cancer and therefore, targeting CDK2 is...
one of the most successful clinical approaches in cancer therapy.\cite{24–26} Furthermore, from the computational point of view, the adequate availability of complex X-ray crystal structures of CDK2 with various ligands (within the ATP binding site) and their affinity data makes CDK2 a very interesting target for docking studies.\cite{17,20–23,27–30}

2 Methods

2.1 Protein Structure Preparation

The starting point of this study was the preparing 376 crystal structures of CDK2 in the Protein Data Bank (PDB)\cite{31} based on UniProt ID P24941 (for a complete list of the PDB entries see Table S1 in the Supporting Information). The protein structure files were prepared according to the following procedure. First, water molecules, organic solvents (like ethanol, glycerol, and 1,2-ethanediol), metal, small ions (such as trifluoromagnesate, nitrate, and phosphate), and unnecessary chains (like cyclin subunit) were removed from the PDB files.

Second, each cleaned PDB file that contains bound ligands was divided into single chain–ligand complexes. For each of the complexes, the crucial structural information available in its corresponding PDB file was extracted to define the binding site, to identify mutated or modified residues and missing atoms or loops, and to inspect some essential crystallographic data (like resolution and alternate locations). Several common filtering criteria were used to exclude problematic complexes at this stage, which included cases where the receptor had mutated/modified residues (except phosphorylated threonine 160, TPO160), where the binding site contained mutated/modified residues or missing atoms/residues, where there was more than one ligand in the binding site, or where the ligand was incomplete. It is interesting to note that no complexes were retained with a resolution higher than 3.0 Å because of these filtering criteria.

Third, for performing structural alignment, the ATP binding site contained 27 residues were defined based on 26 ATP-bound complexes from the PDB files (See Table S2 in the Supporting Information for a list of residues contributing to the ATP-Binding Site). The receptor structures of remaining complexes were aligned to the ATP binding site Cα atoms of a reference structure (4GCJ chain A, having the highest resolution, 1.42 Å, and without missing non-terminal residues). In addition to the ATP binding site, a general binding site containing 41 residues was defined based on the above-mentioned extracted crystallographic data for computing pairwise RMSD values for each pair of the binding site residues (the list of residues selected for defining the general binding site has been provided in Supporting Information Table S2). The generated pairwise RMSD matrix was employed for choosing representative protein structures using the single-linkage hierarchical agglomerative clustering approach. Membership in clusters depended on the simultaneous fulfillment of two conditions: first that average pairwise RMSD values for each pair of members of one cluster should not be more than 1.0 Å and second that the number of pairwise RMSD values more than 2.5 Å for each pair of residues between members of one cluster should not be more than 3. This clustering procedure yielded a set of 87 clusters that 29 of these clusters correspond to the active state of the receptors, where the CDK2 has been complexed with cyclin subunit. The complexes with the best resolution in each cluster were chosen as representative structures (the representative PDB entries have been highlighted in the Supporting Information Table S1).

Next, in the case of incompletely resolved representative structures (68 out of 87 structures), missing residues and loop segments were rebuilt using the MODELLER program,\cite{32} missing heavy atoms of side chains were guessed using the psfgen plugin of VMD,\cite{33} and missing hydrogen atoms were added to heavy atoms using the Reduce program.\cite{34} It should be added here that the best-modeled loops were selected based on the analysis of interatomic distances between Cα atoms of proteins and modeled loops to ensure that the loops do not interact with the residue of the binding site and have a proper orientation relative to the binding site. Finally, the resulting structures were subjected to 20000 steps of conjugate gradient energy minimization to remove atomic clashes using the NAMD program\cite{35} with the CHARMM27 force field and generalized Born implicit solvent (GBIS).

2.2 Docking Setup

The chemical structures of ligands for performing docking were taken from the Chemical Component Dictionary (CCD)\cite{36} to prevent bias toward sampling the X-ray ligand conformation. The correct protonation and tautomerization state for each ligand were manually assigned based on visual inspection of the X-ray ligand position in its binding pocket. This set of ligands contains only some main chemical elements (including H, C, N, P, O, S, F, Cl, and Br). It has different sizes (molecular weights between 176.2 and 507.2), total charges (of −2 to +2), and flexibilities (the number of active rotatable bonds ranging from 0 to 15).

The initial docking search space (i.e., the docking box) was constructed based on the coordinates of the natural substrate ATP/ADP in the experimental complex structures. Then the box size was extended to optimal size to enclose other bound ligands near the ATP/ADP. The ligands located away from the mass center of the ATP/ADP (more than 7 Å) were ignored for calculating the box. The final docking search space was included in a box of 22.4×17.8×20.0 Å³, centered on the mean of the geometric centers of all ligands.
All of the molecular docking simulations were performed with two well-established docking programs: AutoDock4 (version 4.2.5.1) and AutoDock Vina (version 1.1.2). The ligand conformational search method used in AutoDock was the Lamarckian genetic algorithm with an initial population of 500 individuals, a maximum number of $5 \times 10^5$ energy evaluations, a maximum number of $5 \times 10^4$ generations, and the default settings were used for the other parameters. The grid maps with a spacing of 0.375 Å were calculated for the docking box with the program AutoGrid4. Each AutoDock calculation consists of 200 independent searches (runs). For AutoDock Vina (shortly Vina), the exhaustiveness parameter was set to 500. It seems useful to recall that the default exhaustiveness value is 8, and increasing this to higher values will enhance the probability of finding the proper ligand conformations. Each Vina run generates 20 poses.

2.3 SQM Setup

Some important resulting docking poses were geometrically optimized into their binding pocket with three semi-empirical quantum mechanical (SQM) Hamiltonians, PM6, PM6-D3H4X, and PM7 with the linear scaling MOZYME algorithm implemented in MOPAC2016. For the geometry optimizations, the only ligand was allowed to move, while the protein residues were kept rigid. The possibility of proton transfer from the ligand to the charged residues during the ligand optimization was prevented by locking the hard degrees of freedom of the ligand. For this purpose, the protein and the ligand were defined in freezing Cartesian and internal coordinates with frozen bond lengths and angles, respectively. As a result, the position, orientation, and torsions of the ligand within its binding pocket were relaxed during the optimization.

To reduce the computational cost of SQM calculations, the only protein residues within 8 Å of the ligands were selected, and all the other residues were removed from the complexes. If a single residue atom falls within the cutoff distance of the ligand, then the whole residue is kept in the truncated complex. The dangling bonds were capped with hydrogen atoms. Consequently, the size of resulting complexes from docking (containing about 3000 atoms) reduced to approximately 1000 atoms for truncated complexes on average (minimum of 719 and maximum of 1196), which corresponds to about 65% reduction of the size of the docked complexes.

3 Results and Discussion

3.1 Docking Analysis

In the first part of this section, the performance of two docking programs (AutoDock and Vina) in reproducing the crystallographic binding poses of ligands was evaluated by the symmetry-corrected heavy-atom root mean square deviation (RMSD) to measure the similarity between the reference (experimental) and the predicted (docked) poses. The same RMSD algorithm (as implemented in AutoDock4) was also employed to perform cluster analysis of predicted poses for each docking run.

It is a common strategy to select the top-ranked pose (best-scored pose) or top few poses (according to the scoring function) as the best docking solutions, but it has also been shown that these selected top poses do not always correspond to the correct ligand conformation in experimental structure. Therefore, it is essential to evaluate how similar the selected top poses are to the corresponding reference poses. For this purpose, the RMSD values of the top-ranked poses from each docking run for AutoDock plotted against those for Vina are shown in two different manners in Figure 1. As is apparent from the figure, the top-ranked poses generated with AutoDock have lower RMSDs values and, therefore, are closer to their crystallographic conformations. The AutoDock achieved 32% of the top-ranked poses under 1.0 Å RMSD (26 out of 82 complexes) and 67% under 2.0 Å RMSD (55 out of 82). The corresponding values for Vina are 11% and 37%, respectively. It seems reasonable to conclude that AutoDock is more successful than Vina in producing the correct ligand conformation (RMSD ≤ 2.0 Å) at the first ranking position.

The docking success rate defined as the fraction of correct poses in a subset of ranked poses (based on the scoring function energy) within an RMSD cutoff value. Figure 2 displays the docking success rate for different subsets of ranked poses with an RMSD cutoff of 2.0 Å. The solid brown lines in this figure represent the success rates
for the top 1% of the ranked AutoDock poses (containing the top two poses for each complex). In 50 cases out of 82, both of these top poses generated by AutoDock are within 2.0 Å of the crystal ligand. In 21 cases, neither of the top two poses is within 2.0 Å. Inspection of the top 10% (50%) of AutoDock solutions, which includes top 20 (100) ranked poses for each complex shows that all selected top poses belonging to 41 (20) complexes are within an RMSD of less than 2.0 Å from the corresponding reference structures, and in 10 (5) cases, none of the selected top poses is within 2.0 Å. Considering all possible AutoDock solutions for each complex (solid red lines), there are 8 cases for which all AutoDock poses are within 2.0 Å and only 4 cases for which AutoDock fails to produce any acceptable solutions with RMSD values ≤ 2.0 Å. The corresponding results with an RMSD cutoff of 1.0 Å are displayed in Figure S1 in the Supporting Information.

The success rate of Vina has been depicted as colored dashed lines in Figure 2. With respect to the total number of Vina solutions (20 poses for each run), the top 1%, 10%, 50%, and 100% of the ranked poses include, respectively, the top one, two, ten, and twenty poses for each complex. As can be observed in the figure, for 26 complexes, the top-ranked poses are within 2.0 Å of reference poses (brown dashed lines). For 20 complexes, the top two poses are within 2.0 Å, while for 17 complexes, only one of the top two poses is within 2.0 Å of the crystal ligand pose. Finally, there are no cases in which all Vina solutions (100%) or even half of them (50%) could be close to the experimentally binding modes for the RMSD cutoff (red and blue dashed lines in Figure 2). The corresponding results for Vina solutions with an RMSD cutoff of 1.0 Å are displayed in Figure S1 in the Supporting Information. Consequently, the results show that the success rates in predicting a correct ligand pose among all those produced by Vina are significantly lower than those for AutoDock.

Other criteria used to judge the performance of docking methods is the evaluation of the scoring position of the Best Pose and the Best-Fit Pose in all docking solutions for each complex. The former is characterized by the lowest free energy pose among all correct docking poses with RMSD values ≤ 2.0 Å, and the latter is the closest pose to the crystal conformation, which is detected with the lowest RMSD from the experimental structure for each docking run. The scoring positions of the above-mentioned poses relative to all ranked poses of each run have been displayed in Figure 3. It should be added here that according to the red lines in Figure 2, AutoDock and Vina fail in sampling the correct pose within 2.0 Å of the crystallographic conformations for 4 and 15 of 82 complexes, respectively. Therefore, the results of the Best Poses have been obtained for 78 and 67 complexes, respectively, for AutoDock and Vina.
apparent from Figure 3, the Best Poses got better scores in AutoDock and most of them placed in the top 10% ranked poses, while Vina provided significantly worse results in ranking the Best Poses. The corresponding results with the RMSD values ≤ 1.0 Å can be found in Figure S2 in the Supporting Information.

The different observation was obtained for the Best-Fit Poses. Both docking methods were not able to well rank these poses at the top of the list of generated poses. Of course, Vina is marginally better in ranking the Best-Fit Poses than AutoDock. It is also interesting to note that the RMSD values of the Best-Fit Pose in each docking run had slightly different ranges for AutoDock (from 0.31 Å to 3.71 Å) and Vina (from 0.26 Å to 3.9 Å). Overall, based on these observations, the AutoDock scoring function seems more accurate than the Vina scoring function in ranking the Best Poses and the Best-Fit Poses.

To obtain a small set of representative docking poses, all docking poses for each complex were clustered into structurally similar groups. For performing consistent cluster analysis, the symmetry-corrected heavy-atom RMSD algorithm implemented in AutoDock4 was used with an RMSD cutoff of 1.0 Å for both docking methods. The technical details for performing the cluster analysis can be found in the AutoDock4 manual. The total number of clusters obtained for each complex were summarized in Figure 4. The minimum number of clusters detected for Vina solutions had 7 clusters and the largest cluster contained 20% of total generated poses (4 of 20 poses). Also, most of the clusters included one or two members. Consequently, it seems that Vina systematically produces structurally dissimilar ligand conformations that do not cluster well into groups.

A different behavior was found for AutoDock solutions. Inspection of Figure 4 reveals that for 21 complexes, the number of clusters was less than 10 clusters, and one of these complexes had only one cluster, which means that it is all poses were structurally very similar and clustered into one group. On the other hand, for 6 complexes (including only ATP ligand), the number of clusters was more than 190 clusters, which may be associated with the molecular flexibility of ATP with 15 rotatable bonds. The maximum number of clusters identified for AutoDock solutions contained 197 clusters.

In the following, two important clusters of AutoDock results – the first and the most populated clusters – were selected for further analysis. Since the clusters were ranked based on the lowest-energy poses in the clusters, the first clusters contained the top-ranked poses of each docking run. Figure 5 (a) displays the relative rank of the first cluster if the ranking is based on the cluster population rather than the lowest-energy pose. Based on the figure, the first clusters adopted different sizes, and most of them (except 4 cases) distributed among the top 20% ranked cluster. In 37 and 14 cases, the first clusters corresponded to the largest and second-largest clusters, respectively. The rank order of the most populated clusters has been shown in Figure 5 (b). As is evident from the plot, most of them distributed among the top ten clusters (ranked by energy score). They corresponded to the first- and the second-ranked cluster for 39 and 12 cases, respectively. The RMSD values of the top poses belonging to these two clusters (with the lowest-energy) have been summarized in Figure 5 (c). A similar pattern was found for two clusters. 37% of the top poses from the most populated clusters are under 1.0 Å RMSD (30 out of 82) and 62% under 2.0 Å RMSD (51 out of 82). The corresponding values for the first clusters are 32% and 67%, respectively. Therefore, it is reasonable to conclude that these top poses from the first and the most populated clusters must be chosen as a small set of representative poses for each docking run. Since some of the first clusters corresponded to the most populated clusters (for 37 cases), the total number of this set of top poses contained 127 poses.
3.2 SQM Analysis

The post-docking partial optimizations were carried out on three docking poses for each complex, including top-ranked Vina poses and the lowest-energy poses in the first and the most populated clusters for each AutoDock run. The obtained results were analyzed by two different evaluation metrics: the symmetry-corrected heavy-atom RMSD and the fraction of recovered ligand-receptor contacts. The contacts were identified for interatomic distances less than 4.5 Å between any pair of heavy atoms, one from the ligand and one from the receptor. The difference of less than 1.0 Å between the predicted contact and the corresponding contact in the experimental structure was considered as a correct recovery of the contact. Therefore, the high fraction of recovered ligand-receptor contacts indicate more similarity in contacts pattern.

The numerical values of the two above-mentioned metrics have been presented in Table T3–T5 in the Supporting Information. Inspection of the data in thses tables reveals some important points and observations.

Figure 6 shows the correlation between the RMSD from the crystal structure and the fraction of recovered ligand-receptor contacts; the higher the fraction of recovered contacts, the smaller is the RMSD value. What is interesting is that the RMSD values of less than 1.0 Å always occur when over 75% of ligand-receptor contacts are correctly recovered (the left-up part of the figure) and there is no case with RMSD < 1.0 Å and recovered contacts of less than 75% (the left-down part of the figure). However, the reverse is not true and there exist many cases where successful recovery of contact pattern (over 75%) has been accompanied by the RMSD values of more than 1.0 Å – in some cases, even more than 2.0 Å (the right-up part of the figure). On the other hand, there exist cases where the RMSD values of less than 2.0 Å have been accompanied by recovered contacts of less than 35%. For example, see four cases (a)–(d) in Figure 7, which shows the docked ligands (in black lines) and optimized ligands (in colored lines) with respect to the reference ligand at the crystal structures (in ball-and-stick representation). In the first three cases (a–c), predicted structures had adapted inverse orientations...
relative to the reference structure, and in the last case (d), all predicted structures show a significant left shift relative to the reference structure into the binding pocket. Because of this, they have recovered contacts of less than 35% but their RMSD from the reference structures show values of less than 2.0 Å! These observations can be related to the average nature of the RMSD measure, which does not capture local structural similarity/dissimilarity between two structures. Therefore, it seems that the evaluation of the fraction of recovered contacts is more useful to measure the similarity between two structures when interacting with the receptor.

According to the data in these tables, for most of the cases, the ligand optimization at the SQM level has improved the docking results; with decreasing the RMSD value and increasing fraction of recovered native ligand-receptor contacts. For example, four cases (e)–(h) in Figure 7 clearly show how SQM optimizations have led to a displacement of the docked ligand and an improvement of the docking geometries (black lines) and consequently, SQM structures have a significantly better fit to the observed crystal structure. Of course, it should be added here that the SQM optimization usually finds one of the local energy minimum conformations close to the initial geometry and become trapped in the local minimum and therefore, the optimization is not able to take the molecule to lower energy minima further away from the initial geometry. Because of this, the resulting optimized structures strongly depend on the ligand starting geometry and the SQM optimization does not change much the docking poses.

Another interesting observation from Table T3–T5 is that the large changes in the ligand RMSD values do not always accompany the remarkable changes in contacts pattern. For example, for case (i) in Figure 7, the SQM optimization has led to a significant decrease in the RMSD values of the ATP ligand (up to two-unit change), but has not resulted in an improvement of the docking geometry and consequently, the fraction of recovered ligand-receptor contacts has not altered much in this case. Therefore, a considerable decrease in the RMSD value does not necessarily indicate a significant improvement in the geometry of the ligand. Indeed, this finding has correctly reflected in negligible changes in the fraction of recovered ligand-receptor contacts.

A detailed structural analysis of clash or close ligand-receptor contacts provides a clear picture of the significance of the SQM optimization of ligand docking poses. To this end, the number of close contacts between heavy atoms of protein and ligand has been demonstrated for different distance cutoffs in Figure 8. The first observation from the figure is that all close contacts of less than 2.2 Å between protein and ligand were removed by the docking calculations and the SQM optimizations. The second striking observation is that the number of close contacts in Vina results has diminished considerably in comparison with the number of close contacts in AutoDock results, and the ligand optimizations resulted in a significantly increased number of contacts in Vina results at all SQM methods. In addition, the SQM optimization of AutoDock poses led to an increased number of close contacts within the range of 2.2–2.4 Å and a decreased number of contacts for the larger cutoff of 2.4 Å.

With considering hydrogen atoms, the number of close and very close contacts are observed in the docking results (Figure 9). For all distance ranges, the SQM optimizations have reduced the number of close contacts in the docking poses and have successfully removed most of the clash or bad contacts between ligand and protein (distance values of less than 1.5 Å). The observation of less number of contacts in Vina results than the number of contacts in AutoDock results is similar to the decreased number of heavy atoms contacts for Vina results in Figure 8. It is important to note that for some cases, nonphysical intra-molecular hydrogen–hydrogen contacts (from 1.12 to 1.32 Å) were observed that completely relieved by the SQM
optimizations. The observation of very close or bad inter- and intramolecular contacts in the docking results can be explained by the fact that two employed docking methods use the united atom model to represent the ligands and proteins. In this model, the non-polar hydrogen atoms are merged into the carbon atoms to which they are attached and are treated implicitly during the docking, and consequently, restoring the non-polar hydrogen atoms to modeled complexes causes these unrealistic contacts.

Finally, the planarity of polycyclic conjugated molecular segments (such as the purine core of the ATP ligand), which is a structural feature of aromatic systems, was visually inspected. It was found that the PM7 method keeps the planar scaffolds of the conjugated rings better than two other SQM methods. The deviation of conjugated systems from the planarity conformation can be associated with the parameterization of the PM6 method and the empirical corrections added to PM6 (D3H4X), which enhances the formation of ligand-receptor interactions at the cost of breaking the planarity of the aromatic rings.[11]

4 Conclusion

In this work, we have shown how fast and reliable SQM methods can improve the docking accuracy of AutoDock and Vina. As a case study, a series of 87 CDK2 was carefully prepared using strict criteria for the docking calculations. The evaluation of the docking performance of the two above-mentioned programs demonstrated that AutoDock is more successful than Vina in producing the correct ligand conformation (RMSD \( \leq 2.0 \text{ Å} \)) at the first ranking position. Also, the success rates in predicting a correct ligand pose among all docking solutions produced by AutoDock are significantly higher than those for Vina. Besides, the Best Poses (the lowest binding affinity with RMSD < 2.0 Å of the corresponding experimental pose) got better scores in AutoDock, and most of them placed in the top 10% ranked poses, while Vina provided significantly worse results in ranking the Best Poses. The cluster analysis was performed to select a small set of representative docking poses for post-docking SQM optimizations. Three docking poses for each complex, including top-ranked Vina poses and the lowest-energy poses in the first and the most populated clusters for each AutoDock run were optimized with the three popular SQM Hamiltonians, PM6, PM6-D3H4X, and PM7. The obtained results were analyzed by two different evaluation metrics: the symmetry-corrected heavy-atom RMSD and the fraction of recovered ligand-receptor contacts. For most of the cases, the ligand optimization at the SQM level improved the docking results; decreasing the RMSD value and increasing fraction of recovered native ligand-receptor contacts. Of course, it was shown that the average nature of the RMSD measure does not capture local structural similarity/dissimilarity between two structures and the evaluation of the fraction of recovered contacts is
more useful to measure the similarity between two structures when interacting with a protein. Last but not least, the SQM optimizations reduce the number of close contacts in the docking poses, and successfully remove the clash or bad inter- and intramolecular contacts in the docking results. Research in this line is currently underway in our laboratory.

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