Modelling peptide adsorption energies on gold surfaces with an effective implicit solvent and surface model

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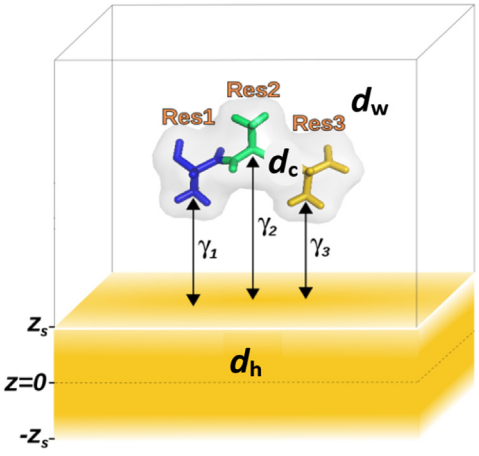
HIGHLIGHTS

- An implicit solvent/implicit surface model parameterization for gold surface.
- Adsorption free energy calculation for amino acids using molecular dynamics (MD).
- In silico evaluation of free energy of adsorption for the set of peptides and gold.
- Comparison and discussion of results obtained with experimental data.

GRAPHICAL ABSTRACT



ABSTRACT

The interaction of proteins and peptides with inorganic surfaces is relevant in a wide array of technological applications. A rational approach to design peptides for specific surfaces would build on amino-acid and surface specific interaction models, which are difficult to characterize experimentally or by modeling. Even with such a model at hand, the large number of possible sequences and the large conformation space of peptides make comparative simulations challenging. Here we present a computational protocol, the effective implicit surface model (EISM), for efficient *in silico* evaluation of the binding affinity trends of peptides on parameterized surface, with a specific application to the widely studied gold surface. In EISM the peptide surface interactions are modeled with an amino-acid and surface specific implicit solvent model, which permits rapid exploration of the peptide conformational degrees of freedom. We demonstrate the parametrization of the model and compare the results with all-atom simulations and experimental results for specific peptides.

Keywords:
Adsorption modelling
Molecular dynamics
Implicit solvent
Implicit surface
Amino acids adsorption
In silico evaluation
Adsorption free energy

1. Introduction

The interaction of proteins/peptides with inorganic surfaces is central to a wide spectrum of biological and chemical phenomena in nature. For example, protein-surface interactions play a pivotal

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role in medical implants, bio-sensors and other functional components at biological/electronic interface [1-3]. For these reasons, a wide range of experimental and theoretical methods are used to investigate these interactions [4]. Many experimental tools have been developed and refined to give insight into peptide/inorganic surface interactions. One of these techniques is the phage display approach [5-7], which allows to identify peptide sequences with specific binding affinity to the investigated surface. The quartz crystal microbalance (QCM) [8,9] and surface plasmon resonance (SPR) [10-12] techniques can be used to measure the adsorption of peptides with inorganic surfaces. Single molecule force microscopy using atomic force microscopy (AFM) [13-15] can be used to monitor the interactions between molecules, surfaces or a molecule and substrate, but these methods cannot directly elucidate the binding mechanism. All of these methods can be used to identify various peptide sequences binding to specific surfaces; however, peptide optimization is difficult because the search space is so large and peptide synthesis still involves complex multistep protocols.

With a limited coverage of sequence space, it is often difficult to identify trends and mechanism from the binding patterns to a particular surface. For these reasons, experimental investigations are increasingly complemented by computational studies to investigate the nature of interactions and to generalize trends [16]. Force field based molecular modelling approaches can help to elucidate interaction mechanisms and to design peptides with specific absorption profiles for relevant surfaces [16-20]. For this accurate model for the intra-molecular interactions and the intermolecular interactions are required. While the models for intra-molecular peptide interactions have been perfected over the last three decades [17,21-24], the development of material specific models for peptide surface interactions remains challenging. Computational efforts are complicated in part by the same complexities that limit experimental investigations. For example, the molecular structure of many inorganic surfaces is insufficiently characterized or structurally and stoichiometric complex or may be process-dependent [25]. One needs to consider the properties of the surface material and the biomolecule as well as those of the buffer solution in which they are immersed. Inorganic surfaces often have defects (adatoms, vacancies, steps, etc.), when they are in contact with liquid water or with proteins. Such defects can be highly reactive and contribute substantially to the surface behaviour even if their population is small. All of these aspects add substantial additional complexity to the development of models to accurately describe the interactions [16,25].

The role of water in the protein-surface interactions is also extremely important, and thus they require an accurate description. Explicit water MD simulations on Au(**111**) [26], rutile [27,28], calcite [30,31], platinum [29] and quartz surfaces [30] show that water restructuring at the aqueous inorganic interface plays a fundamental role in controlling interactions at interfaces. Even when peptides bind directly to the surface, the structure of water close to the surface may play an important role, which is insufficiently described in continuum solvation models for bulk water. Not only water, but also ions concentration also plays a fundamental role in controlling interactions at interfaces [31]. Overall, these examples illustrate the difficulties to parameterize reliable force-fields that describe the affinity of amino acids and proteins with widely used surfaces, such as metals, oxides, polymers, semi-conductors, or carbon-nanostructures.

Other limitations stem from the modelling methodology in general. Extensive sampling of conformational space is another fundamental challenge that must be addressed in protein/peptide-surface MD simulations. In fact, a sufficient sampling of the conformational space is not only needed to properly account for entropic contributions to binding, but also to account for the different protein conformations that may exist in solution, and while in contact with the surface. Unbiased molecular dynamics simulations presently struggle with the time-scales involved in peptide binding, such that generally accelerated methods, like umbrella sampling [32-34] and thermodynamic integration [26,35] or metadynamics simulations [36,37] are used. However, these methods work well only when a well-defined reaction coordinate is available, which is obvious for the relative orientation of substrate and peptide, but much less obvious for the intramolecular degrees of freedom of the peptide. As a result, all-atom explicit solvent molecular-dynamics methods require relatively long simulation times to generate well equilibrated ensembles and even accelerated dynamics methods have difficulty to cope with the issue of peptide conformational change during binding [26]. For this reason we use here a Monte-Carlo protocol, implemented in the SIMONA package, for which we could show that several small proteins and peptides can be folded using the AMBER99IDLN* forcefield in combination with an GB based implicit solvent model [38-40]. It is clearly important to continue to improve the models that describe both the surfaces and the system as a whole in order to obtain better results. However, even when these efforts are successful, the sampling problem remains. In this work we therefore want to test an alternate approach, where an effective model for the interactions of amino acids with a given surface is parameterized on the basis of either experimental or modelling data, which then permit an efficient sampling of peptides and proteins. We have investigated here an effective implicit surface model (EISM) to simplify simulation of the peptide surface interactions. We introduce an implicit model for the surface and the solvent which is augmented by a heuristic solvent-accessible-surface based model for the amino-acid surface interactions that needs to be parameterized either by simulations of small model peptides or by experiment. The advantage of this model is twofold: because the degrees of freedom in the simulation are reduced to the internal degrees of freedom of the peptide and its center-of-mass coordinates the computational effort is significantly reduced, which permits the treatment of larger peptides and or peptide libraries. Secondly, the model can be applied for surfaces and buffer conditions, where microscopic modelling of the realistic system is problematic. This is the case for many surfaces, such as complex iron oxides [16,22,41-43], nanoparticles with undefined or process dependent surface structure or polymeric surfaces of unknown microscopic composition. Its obvious disadvantage is that the model must be parameterized with experimental data or MD simulations for small systems. We here investigate the viability of this approach in principle by studying well defined surfaces, such as gold, silver, titanium and silica, where direct comparison with explicit solvent models is possible.

2. Materials and methods

2.1. Effective implicit surface model

In the following we introduce an implicit solvent / implicit surface force field, the **E**ffective **I**mplicit **S**urface **M**odel (EISM), for fast and efficient *in silico* evaluation of the binding affinity of peptides with inorganic surfaces. In this model the force field of the system comprises the following terms:

$$E = E_{INT} + E_{SLIM} + E_{SLJ} + E_{SASA} + E_{PIT} \quad (1)$$

The term E_{INT} (internal energy) refers to the internal interactions of a peptide i.e., Lennard-Jones (LJ), Coulomb and dihedral terms parametrized by any of the standard force field available. In this investigation we have used the AMBER99IDLN* force field [44].

The second term E_{SLIM} refers to an implicit membrane model SLIM [45] based on a layered Generalized Born model and is used to model the electrostatic interaction of the peptide with the surface. SLIM describes the system in terms of different dielectric regions (Fig. 1), the peptide itself is assigned a dielectric constant d_c ($d_c = 1$), the surface is modelled as a single dielectric slab with dielectric constant d_h ($d_h = 6.8$(gold)),and the solvent region is assigned dielectric constant d_w($d_w = 80$). It must be taking into account that dielectric value for gold is a low-frequency property.

E_{SLJ} (in Eq. (1)) describes the Lennard Jones interactions, between the amino acid residues and the surface.

$$E_{\mathrm{SLJ}} = 8\sum_i \sqrt{\varepsilon_i \varepsilon_S} \times \left(\left(\frac{0.5(\sigma_i + \sigma_S)}{z_i - z_S - \sigma_S} \right)^9 - \left(\frac{0.5(\sigma_i + \sigma_S)}{z_i - z_S - \sigma_S} \right)^3 \right) \quad (2)$$

The z-position of the surface is defined by the parameter Z_S. The sum runs over all peptide atoms i, where σ_i and ε_i are the Lennard-Jones parameters of the peptide's atoms. The parameters $\sigma_S = 3.5$ Å and $\varepsilon_S = 0.1$Kcal/mol characterize the Lennard-Jones interaction of the surface. These empirical parameters account for the presence and position of different atom types contained in the surface. This term is not meant to describe the interaction of the peptide with specific surface atoms, but basically prevents the peptide from entering the surface region and implements a weak non-specific interaction.

All specific interactions of the peptide with the surface are parameterized by a short-range contact potential represented in the third term E_{SASA} in Eq. (1) (solvent accessible surface area) is used to model the interactions of individual amino acids with the surface that are not accounted for by the previously described interactions. The interaction of the peptide and the surface is modelled to be proportional to the solvent accessible surface (SASA) [46] of the peptide with a residue-specific surface tension (units kJ/mol/Å^2), denoted as γ_{aa}.

$$E_{SASA} = \sum_i \gamma_{aa} f(z_i - z_S) A_i + \gamma_w \sum_i A_i \quad (3)$$

Here $A_i$is the SASA for a particular residue as calculated by the PowerSASA method [46]. The strength of this interaction varies with the distance of the atoms i to the surface, as defined by the switching function $f(z_i \quad z_S)$, which varies smoothly by a polynomial from $f(0) = 1$ to $f(z_w) = 0$, and is zero for all arguments larger than z_w. The empirical parameter γ_{aa} determines the maximum strength of the interaction, while the switching function $f(z_i \quad z_S)$ determines the range of the interaction. This term provides an approximate, but quantitative the interaction of an amino acid with the surface. The values γ_{aa} for all 20 amino acids are fitted to the experimental or theoretical data for a given surface and environmental conditions, such as temperature and pH, as discussed below (see the section EISM parameterization). In principle, this amino acid specific term could be chosen to represent the PMF of the amino acid with the surface. However, we want to be able to parameterize the model also using experimental data, where such information is not available. For this reason, we investigate here the simplest model. The E_{PIT} term is the pit potential, which restricts the centre of mass position of each peptide chain to a defined cubic box. If the center of mass is outside of the bounding box, a penalty function is applied that increases quadratically with the distance from the cubic box. All EISM simulations were performed using SIMONA [38,47], a Monte Carlo based molecular simulation software implementing the above mentioned force field. EISM is now part of the SIMONA program, which is freely available to academic users (http://int.kit.edu/nanosim/simona).

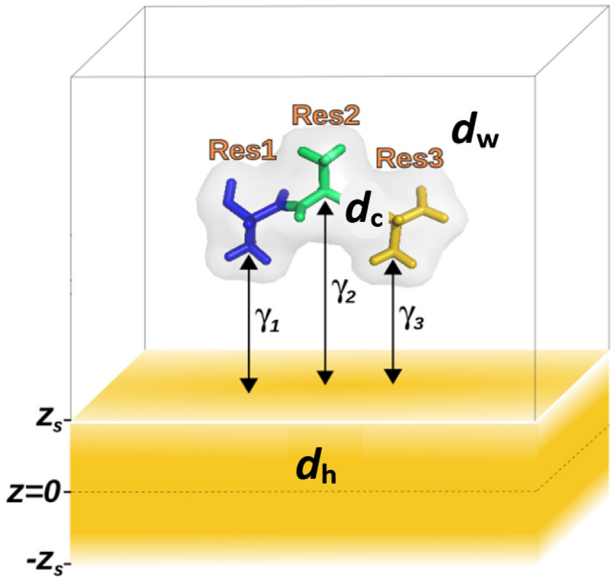

Fig. 1. Sketch of the different regions used in the model for peptide surface interactions. The surface is characterized by dielectric constant d_h and thickness Z_S = 15 Å. The peptide is characterized by dielectric constant $d_c = 1$. Water is assigned a dielectric constant $d_w = 80$.

2.2. Simulation protocol

2.2.1. EISM calculations

We first relaxed the structure of the peptides in the presence of the explicit solvent (in absence of surface) using MD simulation with the AMBER99SB-ILDN [44] force field and SPC water model for 200 ns using the GROMACS 4.6.2 [48] simulation package. The peptides are capped at N- and C-terminal with Acetyl and *N*-methyl group respectively. The Nosé–Hoover thermostat [49,50] was used at 300 K with a coupling constant of 0.1 ps. The pressure was maintained at 1 atm isotropically with the Parinello-Rahman barostat [51] and a coupling constant of 2.0 ps. To investigate the interactions of relaxed peptides with inorganic surfaces we performed Monte Carlo simulations with EISM force-field implemented in the SIMONA package [47] performing 10 K simulation steps per simulation at 300 K using the plugin umbrella sampling protocol PLUMED [52]. To reduce the numerical error, we averaged the free energy of binding curves over twenty independent simulations for every single peptide sequence. The Potential of Mean Force (PMF) curves were calculated using the Weighted Histogram Analysis Method (WHAM) [33].

2.2.2. Classical MD simulations and Umbrella sampling

The Gold (**111**) surface was modelled according to the force field GolP-Charmm developed in [52]. The atomistic model of the amino acids (AAs)/peptides were built using the AMBERTOOLS program. The AAs/peptides were further capped with acetyl at the *N*-terminus and *N*-methyl at the C-terminus using CHARMM-GUI. The capped AAs/peptides were parameterized for molecular dynamics (MD) simulation using the CGenFF program. A simulation box with Gold in one end and AA/peptide in the middle was prepared. The full system was then solvated in a TIP3P water box. Sufficient numbers of Na^+/Cl^- counter ions were added to achieve overall charge neutrality of the system. The system was first energy minimized and then equilibrated in the NVT ensemble. The Gold surface was kept frozen during the simulation and periodic boundary condition was imposed in all three (x,y and z) directions. Nosé–Hoover thermostat was used to maintain the system temperature at 300 K. The equilibrated system was subjected to a series of short NVT simulations with varying the z dimension of the simulation box to achieve the correct density of the water

in the bulk. The system with correct water density was further used for all subsequent MD runs. To generate the configuration for the umbrella sampling (US), the AA/peptide was pulled towards the Gold surface and the overall system is equilibrated again when the AA/peptide was adsorbed to the Gold. The AA/peptide was then pulled off from the Gold surface and a total 50 snapshots of the system were saved for the US run. We used a spring constant of 1000 kJ/mol-nm^2 and the pull rate 0.01 nm/ps for the pulling simulations. The US simulations were further performed with these configurations with the strength of the umbrella potential 1000 kJ/mol-nm^2. Each umbrella sampling window was first equilibrated for 4 ns and then from another 10 ns run we saved the output data for potential of mean force (PMF) generation. All the simulations were performed using the GROMACS simulation package. The PMF curves were calculated using the Weighted Histogram Analysis Method (WHAM) also implemented in GROMACS.

3. Results

3.1. Gold Surface (Au(1 1 1))

Free energy of adsorption for all 20 amino acids was obtained employing classical MD simulations and Umbrella sampling with the simulation protocol described previously. Monte-Carlo simulations with SIMONA program in combination with umbrella sampling, using EISM force field were performed to determine the EISM residue-specific surface tension parameters - γ_{aa} (where *aa* = 20 amino acids) in eq. (3) for all 20 amino acids for the Au (**111**) surface. The results obtained are summarized in the Table 1.

The values obtained for the EISM-γ_{aa} co-efficient from the parameterization set Table 1 clearly show the difficulties interpreting presently available parametrizations, especially for the positively charged amino acid Lysine (Lys). Data from Hoefling et al. [26] suggest Lys will bind strongly to the surface, in contrast to the parametrization by Palafox-Hernandez et al[37]. In correlation with experimentally determined affinities of peptides using phage-display data[53] there is a general trend in binding affinity for aromatic < sulfur containing < positive < polar < aliphatic ~ negative peptides to gold. We note that the EISM- γ_{aa} coefficients, which simply reproduce the ΔG of the MD forcefield, do not reproduce this trend fully.

In order to test the validity of the model, we performed EISM model calculations based on the γ_{aa} parameterization on the data from MD simulations using the protocol described in the methods section for the peptides AYSSGAPPMPPF (A3), WAGAKRLVLRRE (AuBP1), WALRRSIRRQSY (AuBP2), TGIFKSARAMRN (AgBP1), EQLGVRKELRGV (AgBP2), MHGKTQATSGTIQS (GBP1), TGTSVLIATPYV (Midas2), TSNAVHPTLRHL (Pd4), LKAHLPPSRLPS (B1), PPPWLPYMPPWS (QBP1), KHKHWHW(Z1) and RMRMKMK (Z2) [54] for which binding affinities (ΔG) to the Au(**111**) surface have been measured using Quartz Crystal Microbalance (QCM) [54]. The acronyms in the parenthesis were taken from Tang et al. [54] and will be used throughout the paper to identify the peptides. For each peptide we observe a pronounced minimum of the free energy surface and plateau at large distances. We find that the peptide Z1 peptide has the strongest affinity to the Au(**111**) surface, followed by A3, QBP1, and GBP1 peptides, which have medium affinity (see Table 2).

The trends in binding affinity for these peptides can be correlated to the presence of strong binding amino acids, such as Trp, Tyr, Met, Phe, and His. In order to illustrate this trend we divided all amino acids into four differently coloured groups, depending of the value of free adsorption energy – red colour for **W**, **Y**, **C**; yellow one for **M**, **R**, **H**, **G**, **F**; green for **A, S, Q, K, P, L, N, V,** and aqua for

T, I, E, D: **T, I, E, D** ∈ **[10, 20]** kJ/mol;
A, S, Q, K, P, L, N, V ∈ **(20, 30]** kJ/mol;
M, R, H, G, F ∈ **(30, 40]** kJ/mol;
W, Y, C ∈ **(40, 60]** kJ/mol.

The binding affinity of a particular peptide sequence is characterized by the difference in Gibbs free energy between the bound and the unbound state calculated using the EISM model in umbrella sampling simulations. The free energy curves for some of the peptides are illustrated in Fig. 2.

Free energy of adsorption obtained with EISM model corresponds to a single peptide adsorbed on gold, while in the QCM approach a monolayer of peptides at a finite concentration was measured. We have therefore scaled the free energy of adsorption

Table 2
Adsorption free energies (kJ/mol) at the Au (111) aqueous metal interface for a list of peptides calculated using EISM simulations, compared with available experimental data[54] for monolayer and converted values for one peptide.

Name of Peptide	Sequence	QCM, ΔG, (kj/mol) Monolayer	Converted ΔG (kj/mol) One peptide	EISM, ΔG (kj/mol) One peptide
AuBP1	WAGAKRLVLRRE	-37.6 ± 0.9	-69.9	-72.5
GBP1	MHGKTQATSGTIQS	-37.6 ± 1.0	-69.9	-77.2
B1	LKAHLPPSRLPS	-36.6 ± 1.2	-68.0	-69.8
AuBP2	WALRRSIRRQSY	-36.4 ± 0.3	-67.7	-70.3
Midas2	TGTSVLIATPYV	-35.7 ± 1.2	-66.4	-75.3
AgBP2	EQLGVRKELRGV	-35.3 ± 1.2	-65.6	-71.5
Z2	RMRMKMK	-35.0 ± 0.6	-65.1	-75.7
QBP1	PPPWLPYMPPWS	-35.0 ± 1.1	-65.1	-81.4
A3	AYSSGAPPMPPF	-31.8 ± 0.3	-59.1	-82.5
AgBP1	TGIFKSARAMRN	-31.6 ± 0.2	-58.8	-59.8
Z1	KHKHWHW	-31.3 ± 0.1	-58.2	-85.3
Pd4	TSNAVHPTLRHL	-30.3 ± 0.2	-56.3	-65.3

Table 1
Adsorption free energies (kJ/mol) at the Au (**111**) aqueous metal interface for all 20 amino acids and SASA parameter γ_{aa} calculated using EISM simulations.

Amino Acids	ΔG KJ/mol	EISM γ_i	Amino Acids	ΔG KJ/mol	EISM γ_i
ALA (A)	25.8	0.098	LEU (L)	20.1	0.046
ARG (R)	34.5	0.064	LYS (K)	21.2	0.033
ASN (N)	21.8	0.052	MET (M)	37.4	0.089
ASP (D)	10.1	0.006	PHE (F)	34.4	0.079
CYS (C)	37.4	0.136	PRO (P)	25.1	0.078
GLN (Q)	21.7	0.042	SER (S)	24.1	0.079
GLU (E)	11.8	0.006	THR (T)	18.7	0.049
GLY (G)	30.4	0.165	TRP (W)	58.6	0.130
HIS (H)	33.5	0.074	TYR (Y)	49.3	0.117
ILE (I)	18.8	0.043	VAL (V)	23.2	0.066

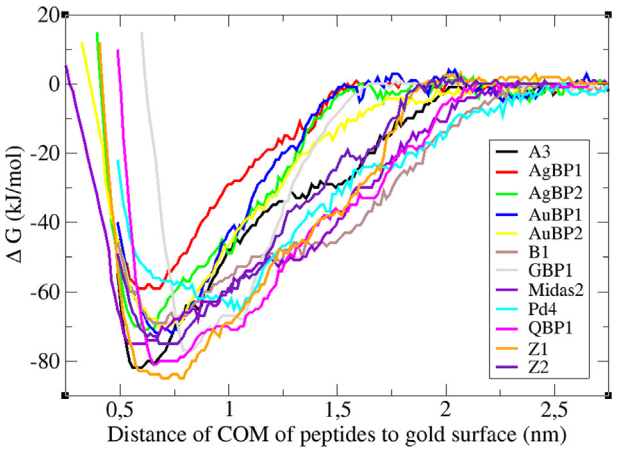

Fig. 2. The free energy curves of adsorption of selected peptides obtained from EISM calculations.

of [52]: authors of the paper perform estimation for AuBP1, and obtained ΔG (AuBP1) = -51.8 ± 18.1 kj/mol for one peptide adsorbed. We expanded this approach for other peptides studied (See Fig. 3.).

We found an overall good correlation with the protocol, which is obviously limited by the accuracy of the MD forcefield and other factors. QBP1, Z1 and A3 deviate significantly from the trend, showing much lower free energy of adsorption obtained with EISM model. It can be easily explained, that model based on AuBP1 contains only one Trp with strong binding affinity and one Gly and two Arg with medium binding affinity. On contrast, QBP1 has two Trp, and one Tyr with strong binding affinity and Met with medium binding affinity. A3 has TYR with strong binding affinity, and Gly, Met, Phe with moderate binding affinity. AgBP1 exhibits the weakest free adsorption energy, that can be explained by the fact, that it contains amino acids with moderate binding and with medium binding affinity. Next, we compare our simulation results for AuBP2, AuBP1 and QBP1 with published data from Corni et al. [55] who used REMD simulations and SPR (surface plasmon resonance spectroscopy to study peptides adsorption at the aqueous Au(**111**) interface. In contrast to Corni et al. [55] we observed strong binding affinity for the QBP1 peptide to Au(**111**) surface, which is in agreement with results from Oren et al. [56], who also find high affinity for QBP1. It is surprising that Corni et al. [55] observed very weak binding of this QBP1 peptide as it contains significant number of amino acids with reported high affinity (2 TRP, 1 MET, and 1 TYR).

Overall EISM appears to slightly overestimate the free energy of adsorption in comparison to the values [52]. However, all peptides studied (apart of GBP1, QBP1, and A3) follow a straight line (green in the figure). In order to rectify this situation, which most likely results from the forcefield, the residue-specific surface tension values - γ_{aa} were slightly decreased (10%) to obtain a better agreement between the results of EISM model and the experiment (see Fig. 4).

The results of this model yield a better agreement with the data (see also Table 3). Peptides GBP1, Z1, AuBP1, are most affected by the change of parameters, losing 6.8 kj/mol (8.81%), 6.1 kj/mol (7.15%), 6.0 kj/mol (8.28%).

The rest of peptides are affected moderately, in comparison to peptides discussed previously. Column 5 exhibits the difference between converted values and data obtained with EISM approach with γ_{aa} decreased by 10%. Peptides GBP1 and AuBP2 shows their free energy of adsorption is almost equal to converted ones. AuBP1, B1, Midas2, AgBP2, AgBP1, Z2, and Pd4 exhibit the difference of free energy between EISM_10 model and converted values is less than 6 kj/mol. If we consider the relative error of the model (column 6 of Table 3) we find that most of the peptides exhibits less than 10% error.

At present, the mechanism of peptide binding to gold surfaces remains not fully understood. There are examples where a large number of anchor residues which high amino acid affinity can confer a strong binding affinity (e.g. QBP1), but there are other sequences that bind equally well in the absence of such sequences. In addition, there are peptides, such as B1 and AgBP1 which have a number of high-affinity amino acids in the sequence but still bind weakly on the Au(**111**) surface. This illustrates the complexities involved in the development of accurate forcefields to predict the affinity of peptides. One option available in the future may be to integrate experimental information into the model. The compar-

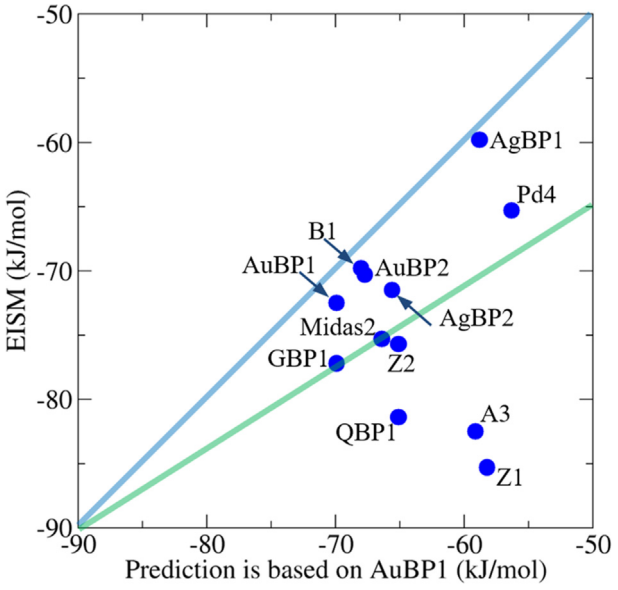

Fig. 3. The comparison of free energy of adsorption obtained via EISM model and converted values based on AuBP1 data. [52]

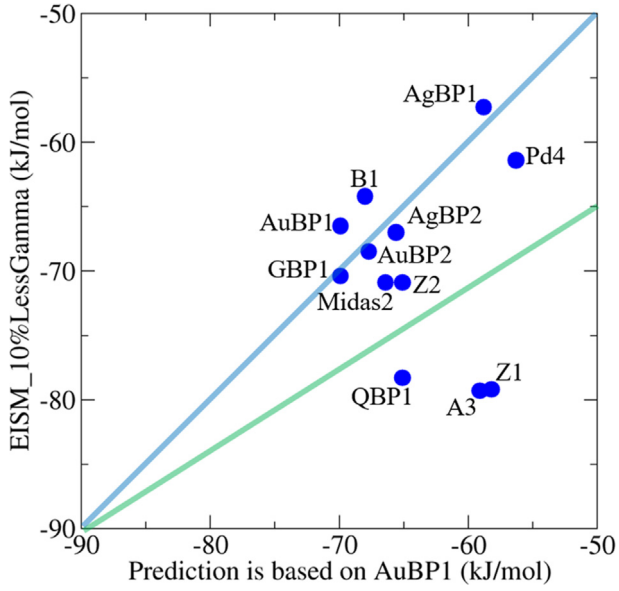

Fig. 4. EISM model with γ_{aa} 10% weaker vs. values based on AuBP1 data[52]: The comparison of free energy of adsorption.

Table 3
Adsorption free energies (kJ/mol) for a list of peptides calculated using EISM simulations with γ decreased by 10%, and compared with original EISM model (third and fourth columns): EISM - EISM_10, (EISM - EISM_10)/EISM*100%. The comparison with converted values is performed as well: Converted - EISM_10%; (Converted - EISM_10%)/Conv*100% (fifth and sixth columns).

Name of Peptide	EISM_10, (kj/mol)	EISM - EISM_10 (kj/mol)	Col_3/ EISM*100% (%)	Converted - EISM_10 (kj/mol)	Col_5/ Converted*100% (%)
AuBP1	66.5	6.0	8.28	3.4	4.86
GBP1	70.4	6.8	8.81	0.5	0.71
B1	64.2	5.6	8.02	3.8	5.89
AuBP2	68.5	1.8	2.56	0.8	1.18
Midas2	70.9	4.4	5.84	4.5	6.77
AgBP2	67.0	4.5	6.29	1.4	2.13
Z2	70.9	4.8	6.34	5.8	8.91
QBP1	78.3	3.1	3.81	13.2	20.28
A3	79.3	3.2	3.88	20.2	34.18
AgBP1	57.3	2.5	4.18	1.5	2.55
Z1'	79.2	6.1	7.15	21	36.08
Pd4	61.4	3.9	5.97	5.1	9.06

Table 4
The comparison of simulation time and adsorption free energy between MD (Gromacs) and SIMONA for ALA and AAAAAA.

System studied	MD + US	ΔG, (kj/mol)	EISM + US	ΔG, (kj/mol)
ALA (21763 atoms in MD)	~231 h	25.8	~10 min	25.8
AAAAAA (27198 atoms in MD)	~286 h	45.9	~20 min	58.7

ison of the simulation time as well as adsorption free energy between MD and the EISM Model (both with Umbrella Sampling) for ALA and AAAAAA is shown in Table 4. The data shows that EISM model calculations are computationally far less costly in comparison to classical molecular dynamics simulations, making calculations of larger peptides feasible. This would also allow to screen the parameter space for the model to better fit a training set of experimental data, but presently not enough consistent experimental data is available. Simulations are performed on 1 node and 64 logical cores at local cluster.

4. Conclusions

In summary, we have demonstrated for gold surface that an implicit solvent/implicit surface model can be parameterized on the basis of the measured or computed affinity of amino acids and can be subsequently used to compute trends in the affinity of peptides to the same surface. Such a model is useful in at least two application scenarios. *First*, the numerical effort of explicit-surface/explicit solvent simulations presently complicates the screening of peptide libraries. *Second*, implicit surface models can be used where atomistic force fields for particular surfaces or environmental conditions are difficult to parameterize, for instance when there is significant surface reconstruction of an unknown extent or if the surface contains many defects. In the latter scenario experimental data for amino acids or small homo-peptides may be used to parameterize the EISM model, which then can be used to study a large library of peptides. Because peptide synthesis is more complex than DNA synthesis and peptide-arrays can be difficult to read out due to signal-to-noise problems implicit surface/solvent models can help to pre-screen peptide libraries and focus the experimental efforts. Future work should focus on this aspect to increase the transferability of the parameters that have been determined for one particular surface and environmental condition. The advantage of the models lies in the fact that they separate the complexity of the peptide-surface interactions from the sampling issues associated with peptides of increasing length and number.

CRediT authorship contribution statement

Mikhail Suyetin: Investigation, Software, Validation, Visualization, Formal analysis, Writing - review & editing. **Saientan Bag:** Investigation. **Priya Anand:** Investigation, Writing - original draft. **Monika Borkowska-Panek:** Investigation. **Florian Gußmann:** Investigation. **Martin Brieg:** Investigation. **Karin Fink:** Investigation, Writing - review & editing. **Wolfgang Wenzel:** Supervision, Conceptualization, Methodology, Software, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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