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Matrix formalism for site-specific binding of unstructured proteins to multicomponent lipid membranes‡

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Abstract: We describe a new approach to calculate the binding of flexible peptides and unfolded proteins to multicomponent lipid membranes. The method is based on the transfer matrix formalism of statistical mechanics recently described as a systematic tool to study DNA–protein–drug binding in gene regulation. Using the energies of interaction of the individual polymer segments with different membrane lipid species and the scaling corrections due to polymer looping, we calculate polymer adsorption characteristics and the degree of sequestration of specific membrane lipids. The method is applied to the effector domain of the MARCKS (myristoylated alanine rich C kinase substrate) protein known to be involved in signal transduction through membrane binding. The calculated binding constants of the MARCKS(151–175) peptide and a series of related peptides to mixed PC/PS/PIP2 membranes are in satisfactory agreement with *in vitro* experiments. Copyright © 2008 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: natively unstructured protein; flexible peptide; polymer–membrane interaction; mixed lipid membrane; lattice models; equilibrium binding; peptide–membrane; MARCKS protein

INTRODUCTION

Protein binding to the cell membrane is a key step in many biological signal transduction pathways [1–5]. In addition, membrane-active peptides are increasingly used in pharmaceutical applications [6]. Both systems emphasize the need for a quantitative treatment of membrane–peptide binding. Here, we consider the transfer matrix formalism as a potentially general tool for the quantitative treatment of interactions of membrane lipids with unstructured peripheral proteins or peptides. We focus on amphitropic biopolymers that may be localized either in the aqueous cell compartments or on the surface of the plasma membrane [2].

The cell membrane is a two-dimensional liquid of multiple lipid species, some of which, e.g. phosphatidylinositol 4,5-bisphosphate (PIP2), in addition to their structural roles, are also the precursors of second messengers [4]. Protein binding to the membrane surface may involve both nonspecific hydrophobic and electrostatic interactions, as well as the recognition of specific lipids. Given the hydrophobic and amphiphilic properties of the individual amino acids [7,8], one can try to predict the preferred peptide conformations on a membrane. However, the computations required to solve a 3D protein structure are obviously enormous. Furthermore, the computational complexity is substantially amplified by the fact that more than one molecule is usually involved in each elementary event of signal transduction. The situation is somewhat simpler in the case of unstructured peptides or proteins. Many protein segments may adopt an extended, unfolded conformation upon interaction with the membrane, while the others are intrinsically unfolded in a native protein state (for example, clusters of charged residues). The binding behavior of such unstructured biopolymers is encountered, for instance, in the membrane adsorption of small signaling proteins such as MARCKS (myristoylated alanine rich C kinase substrate) and its analogs [3]. In this work, we propose a method for calculation of the membrane binding and unbinding behavior of unstructured proteins and peptides. The method takes into account both the membrane composition and polymer sequence.

The idea is to combine one-dimensional lattice models of the type widely used in molecular biology of DNA and actin [9–12] with the scaling approaches of polymer physics [13,14]. Lattice models allow us to concentrate on site-specific effects abstracting from the 3D structure, while scaling arguments enable the introduction of simple corrections to the binding affinities arising from conformational (entropic) constraints. The latter corrections result in nonadditive binding energies of individual binding sites. For example, when two binding sites are separated by an unbound polymer segment, polymer looping should be taken into account (Figure 1). The effective binding constant of a polymer is thus determined by the binding constants of the individual segments, and their

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positions along the sequence, as well as the membrane lipid composition.

Our methodology is based on the transfer matrix formalism previously described as a general tool for the calculation of DNA–protein binding in gene regulation [11]. In the context of protein–DNA interactions, the method allows to solve many complex scenarios of cooperative assembly of proteins on the DNA molecule, which may loop and form compact structures. On the other hand, in the membrane–protein interaction, the flexible protein is the 1D analog of DNA, and the binding ligands are the (mobile) lipids embedded in the 2D membrane. Assuming that the membrane is much larger than the unstructured polymer in its vicinity, we may center on the polymer and implement one-dimensional equilibrium models.

An important system characterized by such unstructured binding is the MARCKS protein that acts at the inner leaflet of the plasma membrane [1–5]. MARCKS participates in signal transduction by adsorbing to the membrane, sequestering PIP2, and then releasing this lipid in response to local signals, such as an increased concentration of Ca^{2+}/calmodulin or the activation of protein kinase C (PKC) [3]. MARCKS binding is enhanced through anchoring of the myristoylated terminus, which inserts into the hydrophobic membrane core, and the basic 25-amino acid 'effector domain' that contains 13 Lys and 5 Phe residues that interact with the membrane electrostatically and hydrophobically. Three of four serine residues inside the effector domain may be phosphorylated by PKC, thus changing the binding pattern and leading to protein desorption from the membrane. Several other signal proteins act in a similar way [3].

Binding of MARCKS and related proteins and peptides to a lipid membrane has been studied previously by solving the Poisson–Boltzmann equation [15,16] and using Monte Carlo simulations [17,18]. Here, we apply a transfer matrix approach to this system. We perform calculations for the peptides corresponding to the effector domain of the human MARCKS protein, and consider the effects of changes in its sequence and in membrane composition.

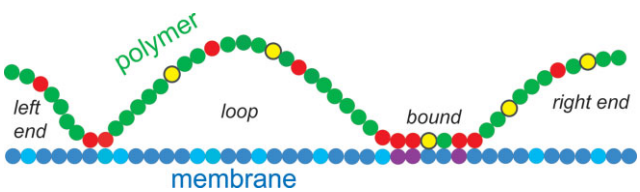

Figure 1 A schematic view of a polymer on a membrane. Different colors correspond to different types of polymer amino acids and membrane lipids.

GENERAL METHODOLOGY

In the transfer matrix formalism, the polymer is treated as a one-dimensional array of units (binding sites, residues, segments), where each unit is characterized by a matrix of statistical weights corresponding to all its possible states [9,11]. The polymer's one-dimensionality means that only adjacent segments physically interact, and there are no interactions between segments situated far from each other along the sequence. However, since polymer segments are connected, the state of a given segment depends on the states of all other segments through global changes in the configurational entropy due to formation of loops and tails. The product of transfer matrices corresponding to all polymer units gives the partition function. The general methodology consists of enumerating all possible states of the elementary unit, constructing the corresponding transfer matrices and building the partition function. Then, we calculate the maps of binding or binding curves and other related structural and thermodynamic properties [11].

The Elementary Unit

We model the protein or peptide molecule as a linear lattice of N units labeled $n = 1 \ldots N$. Throughout this article we will assume that the elementary unit of the polymer is one amino acid residue interacting with membrane lipids via electrostatic and/or hydrophobic potentials. The elementary unit of the membrane is one lipid molecule.

Enumeration of States

Our next step is to list all available states for each elementary polymer unit. Figure 1 illustrates one possible polymer–membrane configuration. We assume that the size of the lipids allows one amino acid to cover one lipid, reasonably consistent with the membrane lipids geometry [19]. A given unit of the bound polymer may either be in contact with a lipid molecule, reside inside a polymer 'loop' (between the membrane-bound regions), or belong to one of the two polymer tails. Table 1 lists the possible states for each individual polymer unit of the polymer interacting with a membrane containing three different lipid species.

Transfer Matrix Construction

The element $Q_n(i,j)$ of the transfer matrix Q_n expresses the statistical weight corresponding to the nth polymer unit in state i, followed by the next unit in state j. Note that only specific combinations of states i and j are allowed. The allowed states are characterized by statistical weights depending on the concentrations and energetic interaction parameters, as detailed below.

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Table 1 Enumeration of the states of a polymer segment interacting with a membrane containing three lipid species in the framework of the transfer matrix formalism

State	Description	
1	Bound to the membrane	Bound to lipid 1
2		Bound to lipid 2
3		Bound to lipid 3
3 + 1	Belongs to the polymer loop attached to the membrane	0 units before next lipid
3 + 2		1 unit before next lipid
2 + N		$N - 2$ units before next lipid
3 + N	Left polymer end	Unbound
4 + N	Right polymer end	Unbound

Forbidden states are characterized by zero statistical weights.

A free polymer in 3D may be found in one of $C_{3D} \times (S_{3D})^N$ conformations, where N is the polymer length, C_{3D} is a constant that depends on the physical properties of the chain, and S_{3D} is the number of possible orientations of a given polymer segment relative to its preceeding segment in a lattice model. We set the energy of a free polymer as a reference 'zero' level.

Bound Polymer Segments

The weights of the polymer units in the bound states are given within our model as $K_{ig}^{(n)} \times \boldsymbol{c_{og}} \times w_{gh} \times S_{2D}$. Here $K_{ig}^{(n)}$ is the binding constant for the nth polymer unit of type i and a lipid of type g. In the model, for noninteracting neighbor residues, $K_{ig}^{(n)}$ depends only on the type of the nth polymer unit. However, in the case of interactions between all nearest neighbor lipids and polymer residues (e.g. Debye–Hückel interactions as in our model below), $K_{ig}^{(n)}$ is determined also by the type of the previous and next polymer residues. c_{og} is the relative concentration (mole fraction) of g-type lipids in the membrane, and w_{gh} is the cooperativity constant determined by the interactions between the neighboring lipids of types g and h ($w_{gh} = 1$ if g and h do not interact) [11]. S_{2D} is the coordination number of the 2D lattice model describing the membrane. In our calculations, we imply hexagonal lattices with $S_{2D} = 6$ nearest neighbors in 2D and $S_{3D} = 12$ in 3D. Because the behavior of the system is determined by the ratio S_{3D}/S_{2D} rather than by their absolute values, we may set $S_{3D} = 1$ and $S_{2D} = 0.5$.

Loops and Tails

The statistical weight of a polymer loop of length j can be adequately accounted for by the expression $(S_{3D})^j \times C_{LOOP} \times j^{-\alpha}$, where C_{LOOP} is a constant that depends on the loop flexibility, while the exponent α depends on the geometry of the system. For an ideal flexible chain, we use $\alpha = 1.5$ and $C_{LOOP} = 0.6$ assuming the Gaussian distribution of the distances between the loop ends [14]. Similar to end-grafted polymers, the membrane-bound polymer has one or two free ends. The weight of the free polymer end of length j is given by $(S_{3D})^j \times j^{-\beta}$, where $\beta = 0.3$ for impenetrable membranes [13]. The statistical weight of a polymer loop starting and ending on the membrane surface should also take into account the fact that the membrane is impenetrable. Thus, the correct statistical weight of a first unit starting the membrane-bound polymer loop of length j is $(S_{3D})^j \times C_{LOOP} \times j^{-(\alpha+\beta)}$.

Boundary Conditions

Close to the polymer ends, the transfer matrices change according to the boundary conditions. For example, the loop cannot propagate beyond the polymer ends – thus the loop of length j cannot start within the last $j - 1$ polymer units. Our boundary conditions also imply that the first transfer matrix is preceded by the vector (1, 1, ... 1), and the last transfer matrix is followed by the vector $(1, 1, \ldots 1)^T$ [11]. This is required to get a scalar value of the partition function as a final result of the matrix multiplications.

Calculating Binding Probabilities

The partition function Z and its derivatives are calculated using recursive multiplication of all transfer matrices according to the polymer sequence [10,11]. The probability c_{ng} that the nth polymer segment is bound to a lipid molecule of type g is given by:

$$c_{ng} = \frac{\partial Z}{\partial K_{ig}^{(n)}} \times \frac{K_{ig}^{(n)}}{Z}$$

The whole set of c_{ng} values determines the map of lipid binding to the polymer [11]. The probability c_n that the nth polymer unit is bound to the membrane (to any membrane lipid) is $c_n = \sum_g c_{ng}$, and the number of sequestered g-type lipids is $c_g = \sum_n c_{ng}$.

The membrane–polymer binding constant (also known as the partition coefficient) is given by the ratio between the partition functions of free and bound polymer conformations: $K = Z_{bound}/Z_{free}$, where Z_{bound} is the partition function calculated as described above, and Z_{free} is the partition function calculated for the polymer of the same length, setting all the energies of polymer–lipid interaction equal to zero.

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MODEL CALCULATIONS

Our model system is based on the signal protein MARCKS described in the introduction. The human MARCKS consists of 331 amino acids, but many experiments have been reported for the peptide corresponding to the MARCKS effector domain, MARCKS(151–175), and several other peptides with similar sequence. Here, we report representative calculations for the effector domain, postponing calculations that address the whole sequence of MARCKS to a future report (Teif *et al.*, in preparation).

The following peptides have been studied:

MARCKS(151–175), *KKKKKRFSFKKSFKLSGFSFKKNKK*; FA-MARCKS(151–175), MARCKS(151–175) with 5 Phe substituted by Ala; KA-MARCKS(151–175), MARCKS(151–175) with 13 Lys substituted by Ala; S*-MARCKS(151–175), MARCKS(151–175) triply phosphorylated by PKC, KKKKKRF**S**FKK**S**FKLSGF**S**FKKNKK; Lys13, *KKKKKKKKKKKKK*; Lys13Phe5, *KKKKKKKKKKKKKFFFFF*.

All peptides above consist of four types of residues: $i = 1$ – neutral non-aromatic (Leu, Ser, Gly, Ala), $i = 2$ – basic (Lys and Arg, charge $= +1$), $i = 3$ – aromatic (Phe), $i = 4$ – phosphorylated Ser (charge $= -2$). We focus on cell membranes composed of three types of lipids: $g = 1$ – neutral phosphatidyl choline (PC), $g = 2$ – monovalent phosphatidyl serine (PS), (charge $= -1$), $g = 3$ – multivalent PIP2 (charge varies from -3 to -5 in different experiments; we take charge $= -4$ corresponding to the physiological pH range.

We set to zero the interaction energy of neutral nonaromatic polymer units with the membrane. Based on experiments [18,20], we assume that aromatic phenyl rings of bound peptides are buried in the hydrophobic core of the membrane, while the charged units remain primarily in the water phase. The Phe residues bind membranes with an energy ranging from 0.2 kcal/mol [20] to 1.3 kcal/mol [7], depending on experimental conditions. The value of the Phe-membrane insertion energy used in our calculations is determined by fitting the adsorption isotherms to experiment.

We assume that the distance between the centers of lipid head groups is $d = 8.66$ Å, which is also used to model the bond length between the neighboring polymer segments [17]. The charged Lys and Arg residues interact with charged membrane lipids through the Debye–Hückel potential [17]. Charged polymer residues interact with a lipid molecule directly underneath as well as with its six nearest neighbors. Conversely, the membrane lipids interact with the polymer segment directly above, as well as with its two nearest neighbor residues. The strength of the electrostatic interaction depends on our choice of the effective dielectric constant near the membrane (ranging between $\varepsilon = 78$ in water to $\varepsilon = 2$ inside the membrane).

We assume that all lipid head groups are of the same size and that the PS and PIP2 lipids interact with the charged peptide units according to their charges, -1 for PS and -4 for PIP2. Note that while we set the PIP2 charge equal to -4, in fact the charge can vary from -3 to -5 depending on experimental conditions [4]. We know from experiments that PIP2 but not PS is sequestered by the MARCKS(151–175) peptide [21]. PIP2 sequestration transfers a molecule from the membrane region of average concentration c_{03} to a membrane region covered by the bound peptide raising its concentration to c_{03}^*. This changes the lipid's entropy by $\Delta S = -\ln(c_{03}^*/c_{03})$ [17]. Correspondingly, the binding constant decreases by a factor of c_{03}^*/c_{03}. We find c_{03}^* self-consistently, changing c_{03}^* until it converges to c_3 given by our calculations. This gives $c_{03}^* \sim 0.16 = 4/25$ corresponding to about four PIP2 molecules sequestered by the 25-residue peptide, consistent with the experimental results [3,4].

Figure 2 shows the experimental results and model calculations corresponding to MARCKS(151–175) binding to mixed membranes of different lipid composition. Line 1 shows the peptide binding constant calculated for a PC/PS membrane as a function of PS content. The value at 0% PS may be interpreted as a purely hydrophobic interaction, implying that the energy of insertion of a phenol ring on this peptide into the membrane is 0.8 kcal/mol/Phe residue. The slope of the line is determined mainly by electrostatic interactions. By fitting the calculated line to the experimental results, we find an effective dielectric constant $\varepsilon = 55$. We use these values of electrostatic and hydrophobic interactions in all other calculations without further fitting. The choice of the reference experimental dataset does not affect the relative changes in the binding affinities arising due to the changes in membrane composition and polymer sequence.

Line 2 in Figure 2 is calculated for MARCKS(151–175) binding to a PC/PS/PIP2 membrane containing 1% PIP2, which is close to the physiological concentration of this lipid. Adding PIP2 increases the peptide binding constant by about four orders of magnitude. For a membrane containing no PS, the beginning of the line coincides with the experimental point [23]. The slope of the line is smaller than that for the PC/PS membrane, because PS competes with PIP2. Our calculations show that in the absence of PS, about 4 PIP2 molecules are sequestered by the peptide – more than enough to neutralize its 13 Lys residues. Monte Carlo simulations yield similar results (Tzlil and Ben-Shaul, in preparation).

Figure 3 shows the effect of altering peptide sequence on the binding to a PC/PS membrane. Line 1 shown here for reference is identical to line 1 in Figure 2. Line 2 is calculated for Lys13. This peptide bears the same charge as MARCKS(151–175), but the absence of hydrophobic residues makes its binding constant an

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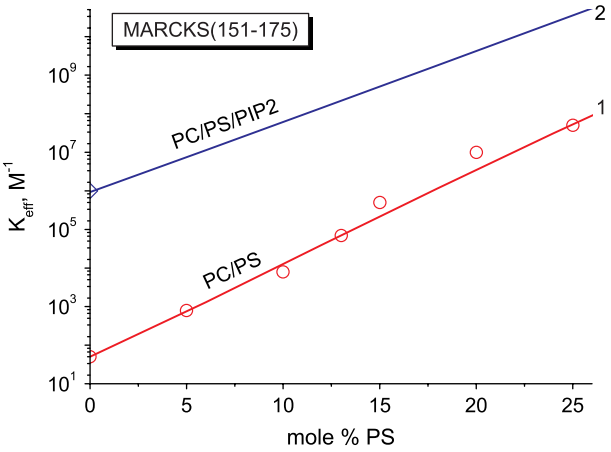

Figure 2 MARCKS(151–175) binding to a mixed lipid membrane with different PS composition. 1 – PC/PS membrane; 2 – PC/PS/PIP2 membrane, 1% PIP2. Circles – experimental data for bovine MARCKS(151–175) binding to PC/PS membranes, pH = 7 [22]; square – experimental data for bovine MARCKS(151–175) binding to PC/PS/PIP2 membranes, pH = 7 [23]. Solid lines are calculated as described in the text. This figure is available in colour online at www.interscience.wiley.com/journal/jpepsci.

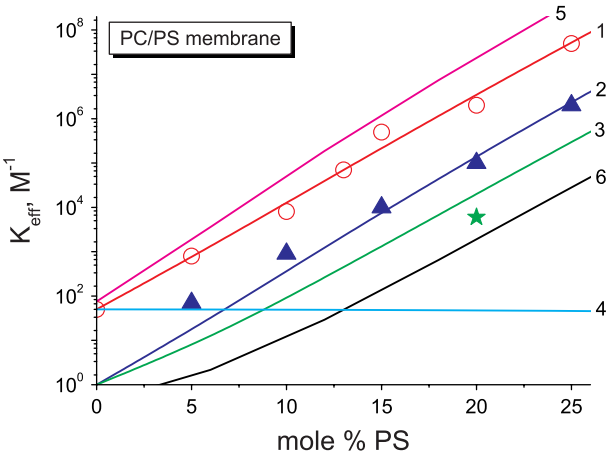

Figure 3 The effect of peptide sequences on the affinity to a mixed PC/PS membrane. The solid lines are calculated as described in the text. 1 – MARCKS(151–175); 2 – Lys13; 3 – FA-MARCKS(151–175); 4 – LA-MARCKS(151–175); 5 – Lys13Phe5; 6 – SF-MARCKS(151–175). Circles – experimental data for MARCKS(151–175) [22]; triangles – experimental data for Lys13 [21]; asterisk – an experimental point corresponding to FA-MARCKS(151–175) [25].

order of magnitude weaker. The agreement between the Lys13 line and the experimental data [21] is satisfactory except at small PS values. This discrepancy may be due to nonelectrostatic contributions in Lys binding that we neglect in these calculations. The fact that the electrostatic and hydrophobic interactions are not simply additive has been confirmed experimentally [24]. Thus, although electrostatic models give reasonable estimates, the use of phenomenological experimental values for all amino acid–lipid interactions [7] would be preferable for this type of calculations.

Line 3 is calculated for FA-MARCKS (151–175). Here, five Phe residues are substituted by Ala. This peptide has the same number of charged residues as Lys13, but has a different length (25 vs 13) and arrangement of Lys residues along the sequence. Energetically, we expect similar characteristics for the Lys13 and FA-MARCKS(151–175) peptide. However, lines 2 and 3 do not coincide because of the entropic effects, reflecting different polymer lengths and looping behavior. The impact of looping entropy becomes more dramatic for long unstructured proteins (data not shown). Line 4 is calculated for KA-MARCKS(151–175) peptide. Here, all Lys residues are substituted by neutral Ala, and the binding, which is now due only to Phe residues, is essentially independent of the membrane composition. Line 5 is calculated for the Lys13Phe5 peptide, which contains the same number of charged and aromatic residues as MARCKS(151–175). However, since the length and arrangements of different polymer units do not coincide with the natural peptide, the lines are distinguishable.

Finally, line 6 is calculated for the S*-MARCKS (151–175) peptide, where three of four Ser residues inside the effector domain of MARCKS(151–175) are phosphorylated, thus reducing its net charge from +13 to +7. This phosphorylation mimics the action of PKC in signal transduction mediated by MARCKS–membrane binding, sometimes referred to as the 'electrostatic switch' [3,26]. Our calculations predict that after phosphorylation, the binding constant decreases by about 1000 times, which implies negligible binding for physiological concentrations of the protein. This result is consistent with *in vitro* experiments [3,4,26].

CONCLUSION

We have presented a general method for calculating sequence-specific binding of flexible peptides and unstructured proteins to mixed lipid membranes. The calculations for the MARCKS effector domain and related peptides allowed us to determine relative changes in the binding constant arising due to the changes in peptide sequence and membrane composition, in agreement with experiments. The matrix method may be easily extended to consider the binding of second layer molecules to the proteins already bound to the membrane [11]. We therefore hope that it is not only applicable to the study of signal transduction through single-protein binding to a membrane but may also be extended in future to include multiprotein assemblies on the membrane. This could help to study, for example, the membrane-cytoskeleton attachment [27], and its regulation by binding of small ligands such as ATP and Ca^{2+}.

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Multilayer matrix models may be also applicable to lipid-templated amyloid-type protein fibril formation [28,29].

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