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Map analysis of ligand binding to a linear lattice

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Abstract

A one-dimensional mapping of the binding properties of a linear lattice offers an exact analytical solution for the site-specific properties of the lattice once the length N and the parameter for nearest neighbor interactions are specified. The solution is derived independent of the definition of the partition function or the transfer matrix, nor does it involve combinatorial arguments. This result provides a simple and effective way of analyzing experimental data for protein-ligand interactions and broadens our understanding of site-specific properties in biological macromolecules.

Keywords: Cooperativity; Ising problem; Maps; Thermodynamics

1. Introduction

Ligand binding to a linear lattice encapsulates features that are relevant to a variety of biological phenomena and has been subject to extensive theoretical analysis [1–5]. These treatments, focusing on the global properties of the lattice, have been complemented by the analysis of binding events occurring locally at individual sites [6]. The classical approach to the problem of ligand binding to a linear lattice is based on the definition of a transfer matrix [1–5]. This approach is very powerful and can also be extended to the analysis of a number of two-dimensional problems [7], or to any case for which the eigenvalues of the transfer matrix can be obtained in closed form.

Ligand binding to a linear lattice is the simplest one-dimensional incarnation of the more general Ising problem [8]. Solutions of this problem have been offered in one dimension and in the two-dimensional case when the lattice has infinite size and is subject to periodic boundary conditions. In view of the extraordinary complexity of this problem in general and specifically in those cases most relevant to biology where the size of the lattice is finite and devoid of periodic boundary conditions [6], alternative methods of solution that do not depend on the transfer matrix, combinatorial arguments or the specific details of the partition function would be extremely useful. Not only will these methods broaden our understanding of the statistical thermodynamics of the Ising problem, but they may actually offer a solution under conditions where the transfer matrix is hopeless to manipulate analytically. A promising approach has recently been developed within the framework of site-specific thermodynamics [6] and has provided new insights into the Ising problem [9]. Here we extend this approach by casting the problem

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of ligand binding to a linear lattice within the framework of a map dynamics. This dynamics is sufficient to trace in detail how the binding probability to the end site of the lattice evolves as a function of the lattice length. The solution so obtained is exact and analytic. The treatment may be considered paradigmatic of extension to more elaborate lattices.

2. General considerations

A basic property of a linear lattice of length N is that its individual binding sites are functionally nonequivalent, since they are flanked by a different number of sites depending on the position along the lattice. As a consequence, the binding probability at each site is different and a treatment of binding processes in terms of site-specific effects becomes justified and often necessary to deal with experimental data. This is in contrast with the presence of periodic boundary conditions that lead to closure of the linear lattice, in which case, all sites become equivalent as does the binding probability at any site. We assume that K is the equilibrium binding constant of each site in the linear lattice and x is the ligand activity. The two variables are conveniently merged into a scaled activity variable $\omega = Kx$. When two bound ligands contact each other in the lattice, they experience an interaction quantified by the dimensionless parameter σ, which denotes positive ($\sigma > 1$) or negative ($\sigma < 1$) coupling between neighbor sites.

The binding probability, ${}^{L}X_{j(N)}$, to a given site, j, along the lattice is derived from a basic result of site-specific thermodynamics as [6]

$$ {}^{L}X_{j(N)} = 1 - \frac{{}^{0,L}\Psi_{j(N)}}{{}^{L}\Psi_{(N)}} \tag{1} $$

where ${}^{L}\Psi_{(N)}$ is the partition function of the lattice and ${}^{0,L}\Psi_{j(N)}$ is the contracted form of ${}^{L}\Psi_{(N)}$ containing all configurations with site j kept unligated. When site j is kept unligated, the original lattice is cut into two smaller lattices containing $j-1$ and $N-j$ sites respectively. This is a consequence of the stated interaction rule under which the behavior of the lattice is independent of unligated sites [6]. Hence, ${}^{0,L}\Psi_{j(N)} = {}^{L}\Psi_{(j-1)}\,{}^{L}\Psi_{(N-j)}$ and

$$ {}^{L}X_{j(N)} = 1 - \frac{{}^{L}\Psi_{(j-1)}\,{}^{L}\Psi_{(N-j)}}{{}^{L}\Psi_{(N)}} \tag{2} $$

The expected symmetry of the lattice around the midpoint $M = (N+1)/2$ is evident from Eq. (2). Sites equidistant from M have the same binding curve, since the replacement $j \rightarrow N-j+1$ leaves Eq. (2) unchanged. The binding curve of the end site ($j = 1, N$) is particularly important because it provides a connection between the partition function of the lattice and that of a lattice one unit shorter according to

$$ {}^{L}X_{N(N)} = 1 - \frac{{}^{L}\Psi_{(N-1)}}{{}^{L}\Psi_{(N)}} \tag{3} $$

If the properties of the end site of the lattice are known, then the properties of any other site can be derived. In fact,

$$ {}^{L}X_{j(N)} = 1 - \frac{\left(1-{}^{L}X_{N-j+1(N-j+1)}\right)\left(1-{}^{L}X_{N-j+2(N-j+2)}\right)\cdots\left(1-{}^{L}X_{N(N)}\right)}{\left(1-{}^{L}X_{1(1)}\right)\left(1-{}^{L}X_{2(2)}\right)\cdots\left(1-{}^{L}X_{j-1(j-1)}\right)} \tag{4} $$

Summation over the index j in Eq. (4) yields the global binding curve of the lattice [6]. Hence, all the information about the binding properties of the lattice is encapsulated by the binding curve of the end site, to which we now turn our attention.

3. A mathematical map for the properties of the end site

The probe theorem [6,9] implies that the binding curve of the end site of the lattice obeys the following basic relation

$$ {}^{L}X_{N(N)} = {}^{L}X_{1(1)}\frac{1+(\sigma-1)\,{}^{L}X_{N-1(N-1)}}{1+(\sigma-1)\,{}^{L}X_{1(1)}\,{}^{L}X_{N-1(N-1)}} \tag{5} $$

Introducing the variable $\theta_j = {}^{L}X_{j(j)}$ to denote the binding curve of the end site in a lattice of length j yields the map

$$ \theta_N = \theta_1\frac{1+(\sigma-1)\,\theta_{N-1}}{1+(\sigma-1)\,\theta_1\theta_{N-1}} \quad (\theta_0 = 0) \tag{6} $$

The value of θ_1 is uniquely defined by the scaled activity variable through

$$\theta_1 = \frac{\omega}{1+\omega} \tag{7}$$

The map in Eq. (6) is illustrated in Fig. 1 as a next-amplitude plot. The solution of Eq. (6) in the form

$$\theta_N = \theta_N(N, \sigma, \theta_1) \tag{8}$$

yields the value of θ_N once σ, N and θ_1 are specified. In what follows, we show that this solution is obtained in closed form.

The solution in the limit of an infinite lattice ($N \to \infty$) is the positive fixed point of the map

$$\theta_\infty = \theta_1 \frac{1+(\sigma-1)\theta_\infty}{1+(\sigma-1)\theta_1\theta_\infty} \tag{9}$$

or

$$\theta_\infty = \frac{(\sigma-1)\theta_1 - 1 + \sqrt{[(\sigma-1)\theta_1 - 1]^2 + 4(\sigma-1)\theta_1^2}}{2(\sigma-1)\theta_1} \tag{10}$$

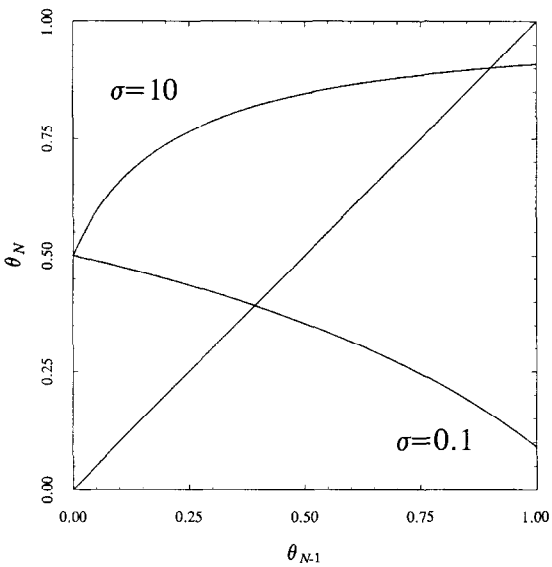

Fig. 1. Next amplitude plot expressing the mapping of the binding curve of the end site of the linear lattice, for $\theta_1 = 0.5$ and two possible values of the interaction parameter σ. The fixed point of the map is given by the intersection with the straight line and is always stable (see Eq. (11)). Absence of interactions between neighbor sites ($\sigma = 1$) gives a straight line parallel to the abscissa (not shown) and provides the boundary between positive and negative interactions.

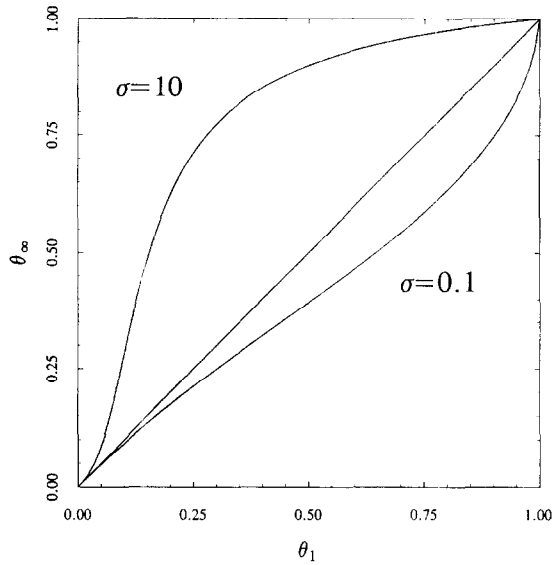

Fig. 2. Binding probability of the end site as a function of the length of the lattice. Curves were obtained according to Eq. (16) with parameter values $\sigma = 1000$ (continuous line) and $\sigma = 200$ (discontinuous line).

which depends solely on θ_1 and σ. A plot of θ_∞ versus θ_1 is shown in Fig. 2. This fixed point of the map is stable since the derivative

$$\lim_{N\to\infty} \frac{d\theta_N}{d\theta_{N-1}} = \alpha = \frac{(\sigma-1)(1-\theta_1)\theta_\infty}{[1+(\sigma-1)\theta_\infty][1+(\sigma-1)\theta_1\theta_\infty]} \tag{11}$$

is less than 1 in absolute value, as it can be verified from Eq. (10). This is also illustrated in the next-amplitude plot in Fig. 1. The mapping can be expressed with respect to the stable fixed point as

$$\theta_N = \theta_\infty + \epsilon_N \tag{12}$$

so that

$$\epsilon_N = \frac{\dfrac{(\sigma-1)\theta_\infty}{1+(\sigma-1)\theta_\infty} - \dfrac{(\sigma-1)\theta_1\theta_\infty}{1+(\sigma-1)\theta_1\theta_\infty}}{1+\dfrac{(\sigma-1)\theta_1}{1+(\sigma-1)\theta_1\theta_\infty}\epsilon_{N-1}}\epsilon_{N-1} = \frac{\alpha\epsilon_{N-1}}{1+\beta\epsilon_{N-1}} \tag{13}$$

with

$$\beta = \frac{(\sigma - 1)\theta_1}{1 + (\sigma - 1)\theta_1\theta_\infty} \tag{14}$$

Iteration of Eq. (13) leads to

$$\begin{aligned}\epsilon_N &= \frac{\alpha^2\epsilon_{N-2}}{1 + \beta(1+\alpha)\epsilon_{N-2}} \\ &= \frac{\alpha^3\epsilon_{N-3}}{1 + \beta(1+\alpha+\alpha^2)\epsilon_{N-3}} = \dots \\ &= \frac{\alpha^N\epsilon_0}{1 + \beta\dfrac{1-\alpha^N}{1-\alpha}\epsilon_0} = -\frac{\alpha^N\theta_\infty}{1 - \beta\dfrac{1-\alpha^N}{1-\alpha}\theta_\infty}\end{aligned} \tag{15}$$

Hence,

$$\theta_N = \theta_\infty\left(1 - \frac{\alpha^N}{1 - \beta\dfrac{1-\alpha^N}{1-\alpha}\theta_\infty}\right) \tag{16}$$

where α and β are defined in Eqs. (11) and (14) respectively. Eq. (16) is the desired solution for the binding curve of the end site of the lattice.

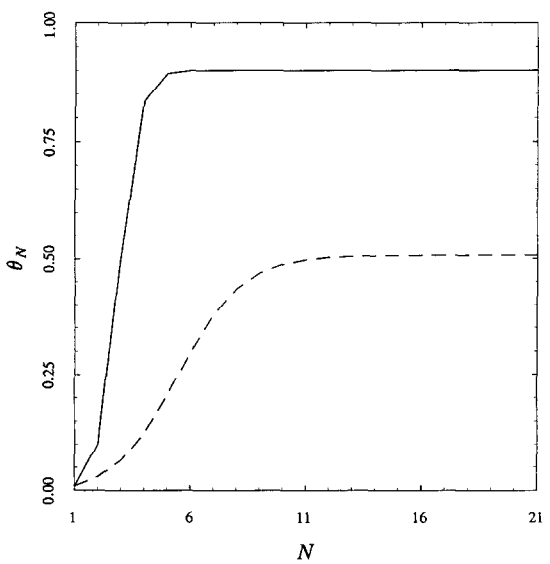

Fig. 3. Binding probability of the end site as a function of the length of the lattice. Curves were obtained according to Eq. (16) with parameter values $\sigma = 1000$ (continuous line) and $\sigma = 200$ (discontinuous line).

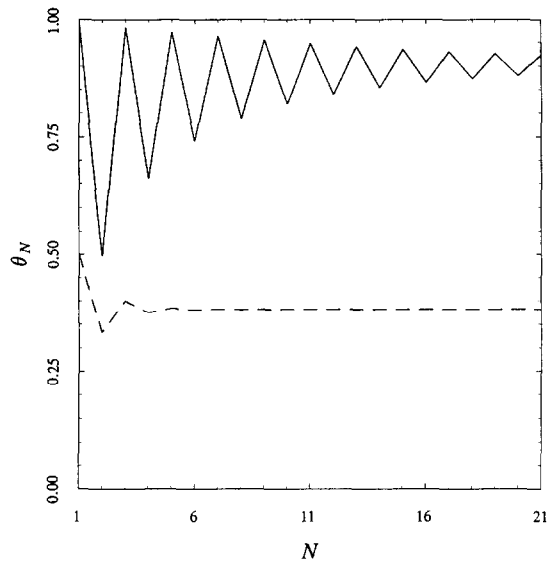

Fig. 4. Binding probability of the end site as a function of the length of the lattice. Curves were obtained according to Eq. (16) with $\sigma = 0$ and two different values of θ_1. The oscillatory behavior of the function θ_N is more graphically illustrated when $\theta_1 \to 1$ (continuous line).

The properties of θ_N are illustrated in Figs. 3 and 4. When $\sigma > 1$, characteristic of positive interactions between neighbor sites, the binding probability increases monotonically and progressively with the length of the lattice. For $\sigma < 1$, characteristic of negative interactions between neighbor sites, the binding probability decreases with the length of the lattice in an oscillatory manner. The oscillations are damped asymmetrically, with the upper envelope of the decay showing a smaller amplitude. The transition from monotonic to damped oscillatory behavior originates from the fact that α in Eq. (16) goes from positive ($\sigma > 1$) to negative ($\sigma < 1$).

4. Conclusion

The binding probability to the end site of a linear lattice is expressed by Eq. (3) and encapsulated by the map in Eq. (6), whose solution is Eq. (16). This solution provides the building blocks for deducing the binding probability to any other site of the lattice according to Eq. (4). Hence, all binding properties of a linear lattice can be derived directly from the map

in Eq. (6), without a need for defining the partition function or the transfer matrix. Notwithstanding their simplicity, nonlinear maps are conducive to extraordinarily complex dynamics and have been used to describe a variety of physical and chemical phenomena [10]. To our knowledge, maps have never been used before to describe the behavior of equilibrium systems, like ligand binding to a one-dimensional lattice. The present study suggests that map formulations derived from site-specific thermodynamics may provide an alternative approach to ligand binding to more elaborate lattices where matrix methods prove difficult or intractable.

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