Lability Criteria for Successive Metal Complexes in Steady-State Planar Diffusion

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The lability of sequential metal complexes, ML, ML$_2$, ML$_3$, ... , up to a general 1:n metal/ligand stoichiometric ratio is considered for the case of metal ions (M) being accumulated at a surface (analytical sensor or organism). The analytical solution for the steady-state diffusion of M within a sequential complexation scheme allows quantification of the contribution from the dissociation of all of the complex species to the metal flux through the so-called lability degree, ξ. A lability degree for each sequential complexation step is also defined which, due to the sequential character of the complexation scheme, depends not only on the proper kinetic constants of the given complexation step but also on the kinetics of the previous ones. When all contributions from the complexes are diffusion limited, the system is fully labile and $\xi = 1$. To provide simple lability criteria, the reaction layer approximation is extended to specifically deal with this sequential complexation scheme, so that a reaction layer thickness is defined when the existence of one particular rate-limiting step is assumed. Expressions for the classical lability parameter, L, are formulated using the reaction layer approximation. The change of the lability of the system as the diffusion layer thickness is modified is analyzed in detail. The contribution of the complex flux reflects the evolution of the system from labile to inert as the thickness of the sensor is appropriately decreased.

1. Introduction

Interactions between soluble species and surfaces mediate a wide variety of processes. Substrate–receptor bindings between soluble ligands and cell surface receptors are present in immune, neurological, and cell growth processes.[1–3] Industrial processes of gas separation, chromatography, and colloid and polymer science, in general, are also impacted by interactions between soluble ligands and surfaces.[4,5] In aquatic ecosystems, the availability of metal species to an analytical sensor or an accumulating organism is generally influenced by interactions between ligands in the medium and the surface and hence by the kinetics of interconversion of metal species, transport, and internalization phenomena.[6–8]

We adhere here, without any loss of generality, to the terminology of metal availability in an aquatic system. Lability refers to the contribution of the complex species to metal fluxes,[9–11] and lability criteria, based on the evaluation of an inequality, allow an a priori knowledge of these contributions in terms of kinetic constants, bulk concentration values, diffusion coefficients, time scale of the experiment, relevant size of the sensor, and so forth.

Although lability criteria have been established for a range of different situations, they usually consider complexes of only 1:1 stoichiometry.[12] Under general transient conditions, a recent work[13] considered complexes of 1:2 stoichiometry, when the mechanism implies sequential complexation. In this case, either the first or the second step in the dissociation process could be rate-limiting. Analytical expressions for the lability criterion were obtained by use of the reaction layer approximation, while numerical simulation of the corresponding model allowed a quantitative and accurate prediction of the lability degree. However, in many systems with monodentate ligands (e.g., monocarboxyl) or simple ligands such as Cl$^-$ and NO$_3^-$, complexes of higher stoichiometry are formed. For the general case of complexes with 1:n stoichiometry, the increased number of species present renders the rigorous numerical simulation of the complete transient response increasingly difficult. Moreover, analytical expressions based on the reaction layer approximation become more inaccurate, since different dissociation steps may exhibit similar rates and the behavior of the system is not necessarily determined by only one limiting step. Here, we present an analysis of the lability of complexes of a general 1:n metal-to-ligand stoichiometry under ligand excess and steady-state conditions reached under planar diffusion in a finite domain. These conditions typically apply to sensors such as permeation liquid membranes,[14,15] diffusive gradients in thin film (DGT),[16,17] or gel-integrated microelectrodes[18,19] which have emerged as powerful techniques in the measurement of metal fluxes and in the assessment of the fate and environmental impact of metal complexes in natural media. The analysis presented herein aims at defining a specific lability criterion for a sequential complexation scheme and also at quantifying the degree of lability of the system by means of a mathematical procedure previously applied to consider mixtures of ligands.[20] Moreover, as some techniques incorporate a gel layer, through which metal species diffuse toward an accumulating phase or

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surface, the effect of variation of the thickness of the diffusion layer is considered in detail.

2. Mathematical Formulation

We consider the following sequential complexation scheme:

$$ML_{i-1} + L \underset{k_{d,i}}{\overset{k_{a,i}}{\rightleftharpoons}} ML_i \qquad i = 1, \ldots, n \qquad (1)$$

and assume that the ligand is present in the system in a great excess with respect to the metal so that $c_L \approx c_L^*$ (where the asterisk denotes bulk solution values). The concentration ratio, Q_i, is defined as

$$Q_i = \frac{c_{ML_i}}{c_{ML_{i-1}} c_L} \qquad (2)$$

which equals the corresponding stability constant, K_i, when equilibrium conditions are attained:

$$K_i' = \frac{k_{a,i}'}{k_{d,i}} = \frac{c_{ML_i}^*}{c_{ML_{i-1}}^*} \qquad i = 1, \ldots, n \qquad (3)$$

where $K_i' = K_i c_L^*$, $k_{a,i}' = k_{a,i} c_L^*$, and K_i, $k_{a,i}$, and $k_{d,i}$ are the equilibrium, association, and dissociation rate constants of the complexation step i (seen in eq 1) from ML_{i-1} to ML_i, respectively.

For steady-state diffusion toward a planar active surface, we can write

$$D_M \frac{d^2 c_M}{dx^2} + k_{d,1} c_{ML} - k_{a,i}' c_M = 0 \qquad (4)$$

$$D_{ML} \frac{d^2 c_{ML}}{dx^2} + k_{d,2} c_{ML_2} + k_{a,1}' c_M - k_{a,2}' c_{ML} - k_{d,1} c_{ML} = 0 \quad (5)$$

$$D_{ML} \frac{d^2 c_{ML_n}}{dx^2} + k_{a,n}' c_{ML_{n-1}} - k_{d,n} c_{ML_n} = 0 \qquad (6)$$

where, for simplicity, it has been assumed that all of the complex metal species share a common diffusion coefficient, D_{ML}.

Notice that, under ligand excess conditions, the kinetics of interconversion of ML_{i-1} and ML_i are pseudo-first-order and the system of eqs 4−6 becomes linear.

In the case where only the free metal ion (M) is being consumed at the interface, the boundary conditions corresponding to the maximum metal flux are given by

$$x = 0$$

$$c_M = 0; \left(\frac{dc_{ML}}{dx}\right)_{x=0} = \left(\frac{dc_{ML_2}}{dx}\right)_{x=0} = \ldots = \left(\frac{dc_{ML_n}}{dx}\right)_{x=0} = 0 \quad (7)$$

$$x = g \qquad c_M = c_M^*; c_{ML} = c_{ML}^*, \ldots, c_{ML_n} = c_{ML_n}^* \qquad (8)$$

where g is the thickness of the diffusion domain. For instance, in the case of DGT, it would be the thickness of the gel layer if one can assume that hydrodynamic conditions render concentration polarization in the external solution phase (i.e., $x > g$) negligible. As has been pointed out,[11] when g is of the order of the thickness of the concentration polarization layer in the external solution phase, the boundary condition (eq 8) is not suitable.

By a procedure based on uncoupling the system of differential eqs 4−6, and using the boundary conditions in eqs 7 and 8, we obtain, as outlined in the appendix, the concentration profiles of all of the species and the limiting metal flux at the accumulating surface:

$$J_M = D_M \left(\frac{dc_M}{dx}\right)_{x=0} \qquad (9)$$

3. Lability

Our purpose now is to quantify the extent of the indirect contribution of the complexes to the interfacial metal flux. When the metal is consumed at a surface, a metal concentration profile develops, and the depletion of the metal concentration shifts the complex equilibria to net dissociation. Lability refers to the capacity of the complexes to increase the metal flux with respect to the flux arising in an inert system. Let us define this increase as the complex contribution to the metal flux and denote it by $J_{complex}$. Thus,

$$J_M = J_{complex} + J_{free} \qquad (10)$$

where J_{free} is the diffusive flux due to free metal only, which, under the specific conditions considered here, is simply given by

$$J_{free} = \frac{D_M c_M^*}{g} \qquad (11)$$

Notice that $J_{complex}$, the actual kinetic flux, is different from the hypothetical maximum kinetic flux, which has been denoted in the literature with the label J_{kin} (see section 4 below). When this capacity (J_{kin}) is limiting the metal flux available at the active surface, we say that the system is under kinetic control, that is, partially labile or nonlabile; however, when this capacity is well over the maximum diffusive supply of the complex (J_{dif}), the system behaves as a diffusion-controlled system and we say that it is labile. This comparison is classically assessed by means of the evaluation of the lability parameter, L,

$$L \equiv \frac{J_{kin}}{J_{dif}} \qquad (12)$$

Then, the application of the lability criteria corresponds to $L \gg 1$ for a labile complex and $L \ll 1$ for a nonlabile one.

Here, we aim at defining a specific lability criterion for the complexation scheme depicted in eq 1 but also at quantifying the degree of lability of the system. Accordingly, we define a lability degree by comparing the actual contribution of the complexes with its maximum contribution to the metal flux (which is then diffusion-controlled), as arising in (fully) labile conditions:

$$\xi = \frac{J_M - J_{free}}{J_{labile} - J_{free}} \qquad (13)$$

To analyze the particular contribution of the different complexes $ML, \ldots, ML_n$, we first add all of the conservation eqs 4−6 and divide by D_M, which gives

$$\frac{d^2}{dx^2}\left[c_M(x) + \sum_{i=1}^{n} \epsilon c_{ML_i}(x)\right] = 0 \qquad (14)$$

where $\epsilon = D_{ML}/D_M$.

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Integration under boundary conditions as given by eqs 7 and 8 leads to

$$c_M(x) + \sum_{i=1}^{n}\epsilon c_{ML_i}(x) = \sum_{i=1}^{n}\epsilon c^0_{ML_i} + [c^*_M + \sum_{i=1}^{n}\epsilon(c^*_{ML_i} - c^0_{ML_i})]\frac{x}{g} \quad (15)$$

where $c^0_{ML_i}$ denotes the concentration of the complex ML_i at the limiting surface $x = 0$.

Recalling that $(dc_{ML_i}/dx)_{x=0} = 0$, differentiation of eq 15 yields

$$\frac{d}{dx}[c_M(x) + \sum_{i=1}^{n}\epsilon c_{ML_i}(x)]_{x=0} = \left(\frac{dc_M}{dx}\right)_{x=0} = \frac{c^*_M + \sum_{i=1}^{n}\epsilon(c^*_{ML_i} - c^0_{ML_i})}{g} \quad (16)$$

Thus,

$$J_M = D_M\left(\frac{dc_M}{dx}\right)_{x=0} = D_M\frac{c^*_M}{g} + \sum_{i=1}^{n}D_{ML_i}\frac{c^*_{ML_i}}{g}\xi_i \quad (17)$$

with

$$\xi_i = \left(1 - \frac{c^0_{ML_i}}{c^*_{ML_i}}\right) \quad (18)$$

As $0 < \xi_i < 1$, eq 17 indicates that ξ_i is the fraction of the maximum diffusive flux of ML_i with which this complex is contributing to the metal flux; ξ_i can then be defined as the degree of lability of complex ML_i.[7,10,20,21] Notice that, for the system with only one complex, that is, $n = 1$, the lability degree of this complex, ξ_1, necessarily coincides with the lability degree of the system, ξ (as defined in eq 13). Equation 17 also indicates that the maximum contribution of the complexes to the metal flux, that is, the actual maximum kinetic flux, corresponds to $\xi_i = 1 \ \forall i$, amounting to

$$J_{labile} - J_{free} = D_{ML}\sum_{i=1}^{n}\frac{c^*_{ML_i}}{g} \quad (19)$$

This expression for the maximum kinetic flux has been obtained under steady-state conditions (reached when g is fixed), but it also holds for the transient regime (with a time-dependent diffusion layer thickness, δ, instead of g) of systems with $D_{ML} = D_M$, which was the original case considered by Koutecký and Koryta.[22]

The degree of lability of the system, ξ, defined in eq 13 can then be expressed in terms of ξ_i as

$$\xi = \frac{D_{ML}\sum_{i=1}^{n}\frac{c^*_{ML_i}}{g}\xi_i}{D_{ML}\sum_{i=1}^{n}\frac{c^*_{ML_i}}{g}} = \frac{\sum_{i=1}^{n}c^*_{ML_i}\xi_i}{\sum_{i=1}^{n}c^*_{ML_i}} = \frac{\sum_{i=1}^{n}[\xi_i(\prod_{j=1}^{i}K'_j)]}{\sum_{i=1}^{n}[\prod_{j=1}^{i}K'_j]} \quad (20)$$

which indicates that the degree of lability of the system is a weighted average of the degrees of lability of all of the complexes with weighting factors given by the respective

fraction of the corresponding bulk concentration over the bulk concentration of total metal bound. Since for most of the cases of interest $K'_j \gg 1 \ \forall j$, $c^*_{ML_n}$ is the only relevant bulk concentration and the global degree of lability reduces to $\xi \cong \xi_n$.

The evaluation of ξ has to be done once the system of eqs 4−6 is solved. Once this is achieved (see Appendix A), the $c^0_{ML_i}$ values are known, the particular degree of lability of a given complex, ξ_i, can be determined from eq 18, and ξ can be computed from eq 20. In terms of ξ, as defined in eq 13 or 20, a system becomes more labile as $\xi \rightarrow 1$.

Obviously, the most extensive dissociation of the complexes corresponds to reaching equilibrium conditions. In labile systems, there is equilibrium between all of the metal species. However, the attainment of equilibrium conditions between some complex species does not imply that the whole system is labile in a scheme of successive complexation. For instance, in the system depicted in eq 1, some complexes can be in equilibrium with preceding metal complexes

$$(e.g., ML_3 \underset{k_{a,3}}{\overset{k_{d,3}}{\rightleftharpoons}} ML_2 + L)$$
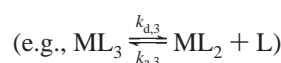
without the possibility of full contribution to the metal flux whenever another subsequent dissociation step

$$(e.g., ML \underset{k_{a,1}}{\overset{k_{d,1}}{\rightleftharpoons}} M + L)$$
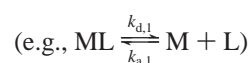
in the dissociation to free metal is rate-limiting. Lability of the entire system requires equilibrium conditions between free metal and *each* one of the metal complex species.

4. Reaction Layer Approximation and the Lability Criteria

For the simplest system, $M + L \rightleftharpoons ML$, under an excess of ligand, the reaction layer approximation relies on assuming steady-state conditions and a flat complex concentration profile. In this way, the diffusion equation for the metal becomes uncoupled from the transport equation of ML and can easily be solved. The analytical solution with $c_{ML}(x) = c^*_{ML}$ allows quantification of the hypothetical maximum contribution of the complex to the metal flux by means of a parameter called the reaction layer thickness, whose expression for one complex in planar semi-infinite diffusion, $\sqrt{D_M/k_a c^*_L}$, was derived by Koutecký and Brdicka.[23] It can be seen that, in planar geometry with an excess of only one ligand, the expression $\sqrt{D_M/k_a c^*_L}$ stands for (i) an operational parameter, μ, to reproduce the kinetic flux (when c_{ML} takes everywhere its bulk value),[24] (ii) the effective thickness of the disequilibration layer,[22] or (iii) the distance traveled by the metal ion before reassociation.[25] When changing the system (e.g., the stoichiometry, the geometry, etc.) or other conditions, these three concepts do not coincide in just one mathematical expression and we have to decide which of the three concepts (see p 346 in ref 26) is labeled "reaction layer". In this work, we adhere to the operational definition i.[21,24] In this perspective, the reaction layer thickness is a parameter (different for different scenarios) related to the hypothetical maximum kinetic flux, that is, without any limitation due to the diffusion of the complex.

Uncoupling the metal transport equation for the present case of successive complexes is more involved than in the simple $M + L \rightleftharpoons ML$ system. The assumption that $c_{ML} = c^*_{ML}$ is quite restrictive because it means that just the first complexation step $M + L \rightleftharpoons ML$ is the rate-limiting one in the dissociation of the

ML_n complexes. Although this is the more common situation for the dissociation of successive metal complexes in aqueous systems,[13] we shall consider here, for the sake of generality, that an arbitrary kinetic step, j, is the rate-limiting one. We also consider equilibrium conditions for the preceding steps, so that the addition of the steady-state diffusion equations for the free metal, eq 4, ML, eq 5, and successively up to that corresponding to the complex ML_j yields

$$\frac{d^2c_j}{dx^2} = \frac{1}{(\mu_j^\infty)^2}\left(c_j - \frac{c_{ML_j}}{c_{ML_j}^*}c_j^*\right) \tag{21}$$

where

$$c_j = c_M + c_{ML} + ... + c_{ML_j-1} \tag{22}$$

is the total concentration of labile metal in the system and μ_j^∞ denotes

$$\mu_j^\infty = \sqrt{\frac{D_j c_j^*}{k_{d,j}c_{ML_j}^*}} \tag{23}$$

It will be shown below in eq 37 that μ_j^∞ is the reaction layer thickness for this sequential complexation scheme but under semi-infinite diffusion conditions. D_j is the average diffusion coefficient for the labile part of the system, given by

$$D_j = \frac{D_M + D_{ML}\sum_{k=2}^{j}\prod_{i=1}^{k-1}K_i'}{1 + \sum_{k=2}^{j}\prod_{i=1}^{k-1}K_i'} \tag{24}$$

For the most common case in which the rate-limiting step is $M + L \rightleftharpoons ML$, that is, for $j = 1$, eq 24 reduces to $D_1 = D_M$.

Within the most simple application of the reaction layer approximation, the steady-state concentration of ML_j is assumed equal to the bulk value, that is, $c_{ML_j} \cong c_{ML_j}^*$. This condition means that the dissociation of the species ML_j is rate-limiting and the other steps are in equilibrium. Moreover, assuming that $c_{ML_j} \cong c_{ML_j}^*$ is a way of assessing the hypothetical maximum kinetic flux in the absence of diffusion limitation for this complex j.

The integration of eq 21 with $c_{ML_j} \cong c_{ML_j}^*$ and the boundary conditions

$$x = 0 \qquad c_j = 0 \tag{25}$$

$$x = g \qquad c_j = c_j^* \tag{26}$$

leads to

$$\left(\frac{dc_j}{dx}\right)_{x=0} = \frac{c_j^*}{\mu_j^\infty}\coth\left(\frac{g}{\mu_j^\infty}\right) \tag{27}$$

Notice that when all of the complexes of a stoichiometry lower than j are labile, the metal flux (see eq 9) has to be written as

$$J_M = D_j\left(\frac{dc_j}{dx}\right)_{x=0} \tag{28}$$

J_M can be split into the hypothetical kinetic component in the absence of diffusion limitation for ML_j (we are using $c_{ML_j} \cong c_{ML_j}^*$) and a contribution from the original free metal in the samples given in eqs 10 and 11, respectively. The kinetic component can be written as

$$J_{kin} = \sum_{i=1}^{j-1}D_{ML}\frac{c_{ML_i}^*}{g} + J_{kin,j} \tag{29}$$

where the first term is the diffusion contribution from all of the complexes with a stoichiometry lower than j (considered to be labile) and $J_{kin,j}$ represents the hypothetical contribution of the complex species with stoichiometry ML_j. Adhering to the operational definition of the reaction layer,[21,24] we can define μ_j so that

$$J_{kin,j} = k_{d,j}\, c_{ML_j}^*\mu_j \tag{30}$$

Then,

$$D_j\frac{c_j^*}{\mu_j^\infty}\coth\left(\frac{g}{\mu_j^\infty}\right) = D_j\frac{c_j^*}{g} + k_{d,j}\, c_{ML_j}^*\mu_j \tag{31}$$

which leads to an expression for μ_j, the reaction layer thickness for the case where j is the rate-limiting step, given by

$$\mu_j = \mu_j^\infty\left(\coth\left(\frac{g}{\mu_j^\infty}\right) - \frac{\mu_j^\infty}{g}\right) \tag{32}$$

Equation 32 defines the pertaining reaction layer thickness for the present complexation scheme, yielding the following expression for the lability parameter:

$$L_j = \frac{J_{kin}}{\sum_{i=1}^{n}J_{dif,ML_i}} = \frac{\frac{D_{ML}}{g}\sum_{i=1}^{j-1}c_{ML_i}^* + k_{d,j}\, c_{ML_j}^*\mu_j}{\sum_{i=1}^{n}D_{ML}\frac{c_{ML_i}^*}{g}} \tag{33}$$

Due to the sequential complexation scheme studied, the ability of the complexes to produce a metal flux is limited by the slowest step, j. Accordingly,

$$L \approx L_j \tag{34}$$

Then, the corresponding lability criterion for a labile system becomes

$$L_j > 1 \tag{35}$$

Recalling that for cases of practical interest K_i' ($i = 1, ... , n$) is well above unity, $(D_{ML}/g)\sum_{i=1}^{j-1}c_{ML_i}^* \ll k_{d,j}\, c_{ML_j}^*\mu_j$ and eq 33 comes to

$$L_j = \frac{k_{d,j}\, c_{ML_j}^*\mu_j}{D_{ML}\frac{c_{ML_n}^*}{g}} = \frac{k_{d,j}\mu_j g}{D_{ML}\prod_{i=j+1}^{n}K_i'} \tag{36}$$

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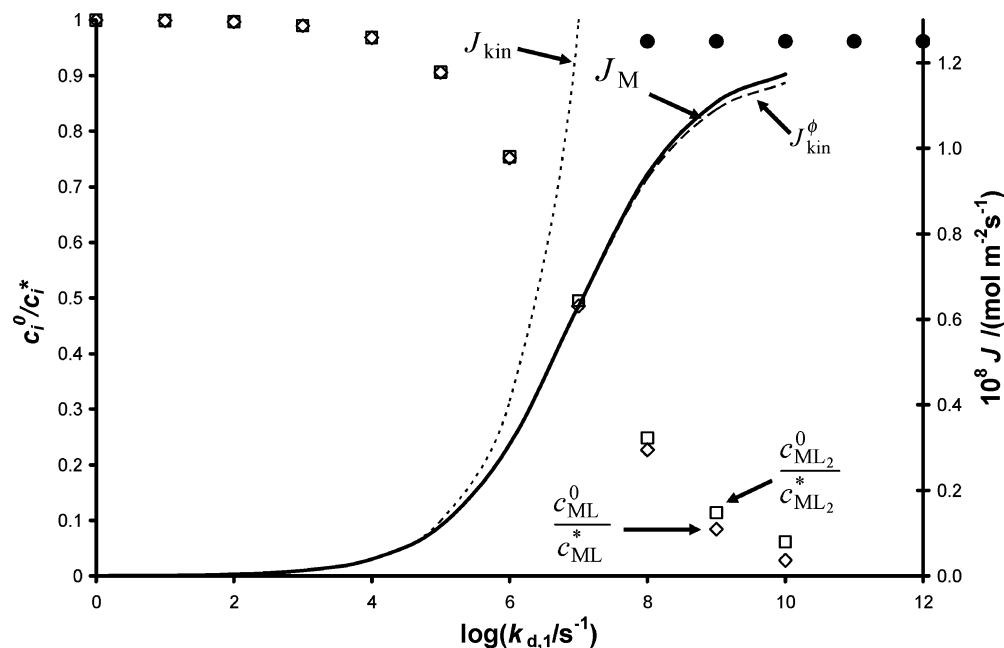*J. Phys. Chem. B, Vol. 110, No. 2, 2006* **895**

Figure 1. Metal flux at the consuming surface $x = 0$, J_M (continuous line), the kinetic flux, J_{kin} (short dashed line), and J_{kin}^ϕ (long dashed line), referred to the right ordinate axis and c_{ML}^0/c_{ML}^* (diamond marker), and $c_{ML_2}^0/c_{ML_2}^*$ (square marker) referred to the left ordinate axis as functions of the dissociation kinetic constant $\log(k_{d,1}/s^{-1})$. Parameters: total metal concentration 0.1 mol m^{-3}, total ligand concentration 3.0 mol m^{-3}, $K_1 = 100$ m^3 mol^{-1}, $K_2 = 50$ m^3 mol^{-1}, $K_3 = 10$ m^3 mol^{-1}, $K_4 = 5$ m^3 mol^{-1}, $k_{d,2} = 2 \times 10^6$ s^{-1}, $k_{d,3} = 10^7$ s^{-1}, $k_{d,4} = 2 \times 10^7$ s^{-1}, $g = 8 \times 10^{-4}$ m, $D_M = 10^{-9}$ m^2 s^{-1}, and $\epsilon = 0.1$. At each point, $k_{a,1}$ takes the value required to maintain a fixed K_1. The horizontal bullets on the right side indicate the metal flux for the labile case.

which is a simple general expression. A further simplification can be obtained when $g \gg \mu_j^\infty$. Under this limiting condition,

$$\lim_{g/\mu_j^\infty \to \infty} \mu_j = \mu_j^\infty \qquad (37)$$

which confirms that μ_j^∞, as given in eq 23, is the extension of the Koutecký–Brdicka expression[23] for the reaction layer thickness suitable for the present case (step j is rate-limiting, while the previous ones are under equilibrium conditions) but corresponding to semi-infinite diffusion. The lability parameter in eq 36 when $g \gg \mu_j^\infty$ is given by

$$L_j \approx \frac{k_{d,j}\,\mu_j^\infty\, g}{D_{ML}\displaystyle\prod_{i=j+1}^{n} K_i'} \approx \frac{g}{D_{ML}^{1/2}\displaystyle\prod_{i=j+1}^{n} K_i'}\sqrt{k_{d,j}} \qquad (38)$$

In addition to yielding the lability criteria, eq 30 can also be expected to give accurate values of the actual contribution of the complexes to the metal flux at low enough $k_{d,j}$ when the system is almost nonlabile. As the degree of lability increases, J_{kin} overestimates the actual metal flux, since the ML$_j$ concentration at the reaction layer, which can be approximated by $c_{ML_j}^0$, is less than that in the bulk solution, $c_{ML_j}^*$. Previous work[12,13,27] has shown that the reaction layer approximation can still provide accurate values for the actual metal flux by using the concentrations at $x = 0$ as an estimate of the average concentration over $0 \leq x \leq \mu_j$. This result follows from the fact that eq 21, once $c_{ML_j}^*$ is replaced by $c_{ML_j}^0$, can be integrated in the disequilibration layer domain, and the procedure outlined above leads to an implicit equation for μ_j for which eq 32 gives an accurate approximate solution. This value will be labeled J_{kin}^ϕ, which is an estimation of the contribution of the complexes to the metal flux, labeled $J_{complex}$ in this work.

5. Specific Illustration for $n = 4$

The case $n = 2$ has been presented in detail[13] and verified experimentally.[28] To exemplify the results obtained in the present work, we will consider now a system with $n = 4$. The most likely case will be considered, that is, M + L $\rightleftharpoons$ ML as the rate-limiting step in the overall dissociation of metal complexes. The case of rate limitation by another intermediate step follows similar reasoning.

For M + L $\rightleftharpoons$ ML as the rate-limiting step, the rigorous metal flux can be computed from eq 9, while the ability of the dissociation processes to contribute to the metal flux, J_{kin}, is computed from eqs 29 and 30. The approximation to the complex flux based on the reaction layer, J_{kin}^ϕ, is functionally identical to J_{kin} but uses $c_{ML_j}^0$, instead of the bulk concentration, $c_{ML_j}^*$. Notice that J_{kin}^ϕ has no predictive value, since $c_{ML_j}^0$ is obtained only after the rigorous solution of eqs 4–8. In fact, computation of J_{kin}^ϕ serves only for checking the accuracy of the reaction layer approximation. Similarly, $J_{kin,j}^\phi$, analogous to eq 30, becomes

$$J_{kin,j}^\phi = k_{d,j}\, c_{ML_j}^0\, \mu_j \qquad (39)$$

Figure 1 shows the behavior of J_M, J_{kin}, and J_{kin}^ϕ when $k_{d,1}$ is scanned to cover the range from no dissociation to equilibrium regimes for the step M + L $\rightleftharpoons$ ML. The kinetic constants of the other steps are high enough for equilibrium to be established between the species ML, ML$_2$, ML$_3$, and ML$_4$, at any relevant spatial position and time. The fulfillment of equilibrium between ML and ML$_2$ is evidenced in Figure 1 by the coincidence of both normalized concentrations at $x = 0$:

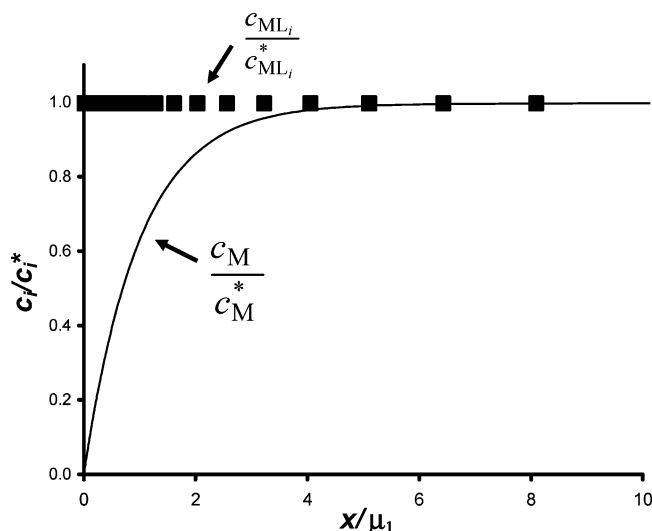$$\frac{c_{ML}^0}{c_{ML}^*} = \frac{c_{ML_2}^0}{c_{ML_2}^*} \qquad (40)$$

Figure 2. Normalized concentration profiles, c_i/c_i^*, of M (continuous line) and ML, ML_2, ML_3, and ML_4 (square marker) (all of them converge so that we have used only one marker), as a function of the distance to the active surface measured as x/μ_1. $k_{d,1} = 10^2$ s^{-1}, and the rest of the parameters are the same as those listed in the Figure 1 caption.

Since J_{free} can be neglected for the chosen set of parameters, Figure 1 also shows that J_M (eq 9) and J_{kin}^ϕ are in good agreement over the complete $k_{d,1}$ range, which indicates the accuracy of the reaction layer approximation. Conversely, J_{kin} diverges from J_M for $k_{d,1} > 10^5$ s^{-1} when c_{ML}^0 clearly differs from c_{ML}^*, and J_{kin} overestimates the metal flux.

As $\epsilon K_i' \gg 1$, assuming step 1 as the rate-limiting step, the lability parameter, L, as defined in eq 36 reads

$$L_1 = \frac{J_{kin}}{J_{dif,ML} + J_{dif,ML_2} + ... + J_{dif,ML_4}} \approx \frac{k_{d,1}\mu_1 g}{K_2'K_3'K_4'D_{ML}} \approx$$

$$\frac{k_{d,1}^{1/2} g}{K_2'K_3'K_4'D_{ML}^{1/2}} \quad (41)$$

Notice the increase of the denominator in eq 41 as the maximum stoichiometric relation M/L increases. Since for the cases of interest $K_i' > 1$, the increase of the denominator as n increases indicates a lower degree of lability of the system, so that higher kinetic dissociation constants of step 1 would be required to reach lability. Accordingly, Figure 1 shows that, for $k_{d,1} = 10^6$ s^{-1}, ξ is around 0.25, while, for the same value of the kinetic constants, a system with $n = 2$ would be labile ($L \gg 1$). Actually, $k_{d,1}$ values of the order of 10^{10} s^{-1} are required to reach labile conditions in the present case of Figure 1. From a physical point of view, this fact reflects the increasing effective stability of complex ML_n as n increases whenever $K_i' > 1$.

As expected from the behavior of J_{kin} seen in Figure 1, the lability parameter, L, of the real rate-limiting step is close to the global lability degree, ξ, for low dissociation rate constants ($J_{kin} \approx J_{complex}$ up to $k_{d,1} \approx 10^5$ in Figure 1), reproducing satisfactorily the lability of the system up to around 30%.

If we examine the concentration profiles in Figure 2, corresponding to $k_{d,1} = 10^2$ s^{-1} in Figure 1, we can see that, while the metal concentration profile is depleted close to $x = 0$, the other normalized concentration profiles collapse to the value $(c_{ML_i}(x)/c_{ML_i}^*) \approx 1$. This indicates the fulfillment of equilibrium conditions for all of the kinetic steps except step 1 which is rate-limiting. Thus, although we have high kinetic
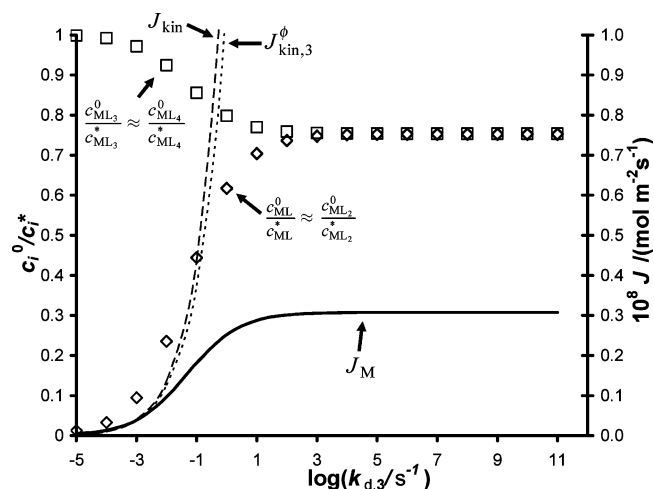

Figure 3. Metal flux at the active surface, J_M (continuous line), J_{kin} (long dashed line), and $J_{kin,3}^\phi$ (short dashed line), referred to the right ordinate axis. The normalized concentrations are referred to the left ordinate axis: c_{ML}^0/c_{ML}^* and $c_{ML_2}^0/c_{ML_2}^*$ almost coincide (share diamond marker); $c_{ML_3}^0/c_{ML_3}^*$ practically coincides with $c_{ML_4}^0/c_{ML_4}^*$ (and share square marker). In abscissas: the dissociation kinetic constant $\log(k_{d,3}/$s^{-1}). $k_{d,1} = 10^6$ s^{-1}, $k_{d,2} = 2 \times 10^6$ s^{-1}, and $k_{d,4} = 2 \times 10^7$ s^{-1}, and the rest of the parameters are the same as those listed in the Figure 1 caption. In each point, $k_{a,3}$ takes the value required to maintain a fixed K_3.

constants for step 2, step 3 and so on, these complexes, which reach equilibrium conditions, do not contribute to the metal flux due to the limiting effect of step 1.

Other combinations of the kinetic parameters lead to conditions without one unique limiting step. This situation can arise in many cases and is beyond one reaction layer formulation. A clear example is depicted in Figure 3. At low enough $k_{d,3}$ values, J_M and $J_{kin,3}^\phi$ converge and dissociation of ML_3 is the rate-limiting step. Accordingly, $(c_{ML_2}^0/c_{ML_2}^*)$ and (c_{ML}^0/c_{ML}^*) are close to zero, indicating equilibrium between the free metal and these complexes at the limiting surface, while $(c_{ML_3}^0/c_{ML_3}^*)$ is close to 1, which indicates that equilibrium is not attained between ML_3 and M. Upon increasing $k_{d,3}$, $c_{ML_3}^0$ decreases from $c_{ML_3}^*$ to around 75% of this bulk value, but $J_{kin,3}^\phi$ diverges from J_M in contrast to what would be expected for step 3 being rate-limiting. This behavior can be justified by the concomitant increase of c_{ML}^0 and $c_{ML_2}^0$ which reflects the loss of equilibrium of step 1, $M + L \rightleftharpoons ML$, and denotes that step 3 is no longer rate-limiting; rather, step 1 is now the rate-limiting one in the dissociation of the complex species. Accordingly, when $k_{d,3}$ increases, the system does not tend to be labile but rather reaches only 24.6% of the maximum kinetic contribution to the metal flux at the highest $k_{d,3}$ value in Figure 3. The (c_{ML}^0/c_{ML}^*) value reached at high $k_{d,3}$ values is consistent with this maximum attained degree of lability.

5.1. Diagnostic Criteria for the Rate-Limiting Step. In a system with a complex of 1:1 stoichiometry, the change of a parameter of the system, like the thickness of the diffusion layer, that modifies the contribution of the complex to the metal flux,[12] can shift the system from labile, with a diffusion-controlled complex contribution, to an intermediate situation where the complex contribution is rate-limiting. The final limiting situation occurs when there is no complex contribution, that is, the system is inert.

When a general system with sequential complexes of 1:n metal/ligand stoichiometry is considered, we have seen that new partially labile situations arise. The prediction of the degree of

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TABLE 1: Global Degree of Lability, ξ (Rightmost Column Computed via eq 13) of a System with Parameters of Figure 3 Can Be Approximated by the Lowest Lability Parameter (L_j Computed with eq 36) of the Four Individual Steps for Low ξ Values

$k_{a,3}/mol^{-1} m^3 s^{-1}$	L_1 (%)	L_2 (%)	L_3 (%)	L_4 (%)	ξ (%)
10^{-4}	35.3	100	0.15	100	0.41
10^{-3}	35.3	100	0.91	100	1.07
10^{-2}	35.3	100	3.5	100	3.10
10^{-1}	35.3	100	11.7	100	7.71
1	35.3	100	37.9	100	14.5
10^1	35.3	100	100	100	20.2
10^2	35.3	100	100	100	23.0
10^3	35.3	100	100	100	24.1
10^4	35.3	100	100	100	24.5
10^5	35.3	100	100	100	24.6
10^6	35.3	100	100	100	24.6
10^7	35.3	100	100	100	24.6
10^8	35.3	100	100	100	24.6
10^9	35.3	100	100	100	24.6
10^{10}	35.3	100	100	100	24.6
10^{11}	35.3	100	100	100	24.6
10^{12}	35.3	100	100	100	24.6

Figure 4. Metal flux at the active surface, J_M (continuous line), the actual kinetic flux, $J_{complex}$ (full square marker), and J_{labile} (short dashed line), referred to the left ordinate axis and the lability degree, ξ, of the system (full triangle) (in %), and ξ_i defined in eq 18 referred to the right ordinate axis as a function of $\log(g/m)$: ξ_1 (open circle), ξ_2 (full circle), ξ_3 and ξ_4 (both sharing full triangle). $k_{d,1} = 8 \times 10^6 \ s^{-1}$, $k_{d,2} = 2 \times 10^5 \ s^{-1}$, $k_{d,3} = 10^{-1} \ s^{-1}$, and $k_{d,4} = 2 \times 10^6 \ s^{-1}$, and the rest of the parameters are the same as those listed in the Figure 1 caption.

lability of the system should then take into account these new situations. While eqs 13 or 20 still predict rigorously the current degree of lability for any situation, the application of lability criteria in the successive complexation scheme analyzed has to be deduced from examination of each one of the L_j parameters and is determined by the lowest L_j value. Let us compute these L_j parameters for the data of Figure 3. As can be seen in Table 1, for low $k_{d,3}$ values, $L_3 < 1$ indicates the nonlability of the system. Actually, step 3 is rate-limiting and L_3 approaches the actual degree of lability, ξ, of the system, calculated by means of eq 13. Upon increasing $k_{d,3}$, step 1 becomes rate-limiting and the lability parameter L_1 produces the lowest L_j value which is close to the actual lability of the system predicted by eq 13.

A complementary identification of which step in the sequential complexation scheme is the rate-limiting one can be achieved from the dependence of the measured lability on c_L^* and comparison of it with that predicted by the lability criterion for a given potentially rate-limiting step. For example, the analytical expression for the lability criterion for the $n = 2$ case, with $j = 1$ as the rate-limiting step, is[13]

$$L_1 = \frac{k_{d,1} D_M^{1/2} g}{k_{a,1}'^{1/2} K_2' D_{ML_2}} \gg 1 \qquad (42)$$

Thus, if this criterion holds, low L values should follow a $c_L^{*-3/2}$ dependence. This has been observed experimentally for several ML_2 systems,[28] confirming the nature of the rate-limiting step.

6. Dependence of the Degree of Lability on g

It has been seen shown[12] that all of the systems tend to be inert as g decreases, independent of the value of the kinetic constants.

Figure 4 shows the behavior of a general system with $n = 4$ when g is varied. At high g values ($g > 10^{-2}$ m), J_M and J_{labile} converge, indicating that lability is approached. When g decreases, J_{labile} increases, while J_M reaches a plateau in the range 10^{-3} m $> g > 10^{-5}$ m due to the decrease in the lability degree, ξ_3, corresponding to $ML_3 \rightarrow ML_2 + L$ (and that of complexes with higher stoichiometry). The kinetic contribution to the metal flux is now limited by the rate of dissociation of step 3. We can also see the convergence between J_M and $J_{complex}$,
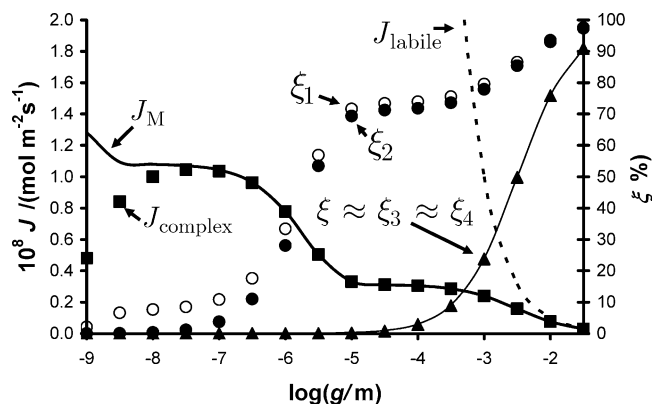
indicating that J_{free} is negligible in this spatial range. The approximately flat interval of J_M is then the typical[12] shoulder exhibited by J_M when some complex becomes nonlabile. However, in the present case, a further decrease of g increases the metal flux up to a new plateau in the range 10^{-7} m $> g > 10^{-8}$ m. This new increase of J_M is due to the increase of the actual kinetic flux (we see the concomitant increase of $J_{complex}$ in the figure) due to the residual concentrations of metal complexes with a stoichiometry lower than 3. Although these concentrations are low ($K_i' > 1$), the small diffusion layer reached yields an appreciable contribution from these complexes. When this contribution drops (recognized by the decrease of ξ_2 and ξ_1, which happens at not very different g values as both constants do not differ very much, $k_{d,1} = 8 \times 10^6 \ s^{-1}$, $k_{d,2} = 2 \times 10^5 \ s^{-1}$), J_M exhibits a new plateau and finally begins to increase, just at the leftmost part of the plot, due to the increase of the inert flux associated with the decrease of g.

The thickness of the different shoulders exhibited by J_M can be assessed by the computation of the difference in the g value required for J_{free} (given by eq 13) and J_{labile} (which can be computed with eq 19). Simple algebra gives this difference as

$$\Delta(\log g) = \log(\epsilon \prod_{i=1}^4 K_i') = \log \epsilon + \sum_{i=1}^4 \log K_i' \qquad (43)$$

which for the data of the figure holds for more than 6 units and lies outside the range depicted. An estimation of the beginning of this shoulder can be obtained by equating eq 36 to 1 for the j value of the limiting kinetic step (i.e., that with the lowest L value).

7. Conclusions

The analytical solutions of the concentration profiles and metal flux arising in systems with successive complexes under steady-state conditions and an excess of ligand have been derived. In this way, the degree of lability of the system can be rigorously predicted and quantified from the kinetic constants and the physical dimensions of the accumulating surface. The developed methodology can be applied to any system in which the metal ion participates in several sequential processes leading to a coupled system of linear diffusion differential equations with only one relevant spatial coordinate under steady-state conditions.

A global lability degree of the system and particular degrees of lability for each metal complex species are used to quantify the contribution of all of the metal complex species to the metal flux. For a general ML_n system, under the conditions of interest ($K_i' > 1$), the system tends to be more inert as n increases. That is, when $M + L \rightleftharpoons ML$ is the rate-limiting step in the dissociation of metal complex species, a greater value of n means that a higher dissociation constant for the ML species is required to reach labile conditions.

The reaction layer approximation has been used to formulate simple lability criteria for these systems based on the comparison of the hypothetical maximum metal flux that could be obtained in the absence of diffusion limitation for the complexes (J_{kin}) with the maximum diffusional supply of the complexes (J_{dif}), as given in eq 12. The formulation of these lability criteria requires knowledge of the reaction layer thickness which is obtained in this work for the particular system analyzed. On the basis of the assumption of a particular complexation step as the rate-limiting one in the dissociation processes, we can compute as many lability parameters as there are kinetic steps. The lowest L_j value thus obtained indicates the lability character of the whole system.

As the thickness of the diffusion layer decreases, the system becomes more inert and the actual kinetic contribution follows a peaked behavior. Parallel to the arising of this maximum in $J_{complex}$, J_M develops a shoulder from values close to J_{labile} to J_{free}. The rigorous expression for the lability degree and the approximation suggested in this work provide different ways to estimate the thickness of the diffusion layer required for a given contribution of the metal complexes to the metal flux; that is, it provides a tool for sensor optimization.

Appendix A: Rigorous Solution of the System of eqs 4−8

Introducing the change of variables

$$z = x/\sqrt{D_M} \tag{A-1}$$

the set of eqs 4−6 can be rewritten in matrix form as

$$\nabla^2[\vec{C}(z)] + \mathbf{A} \cdot \vec{C}(z) = 0 \tag{A-2}$$

with $\vec{C}(z) = (c_M(z), c_{ML}(z), \dots , c_{ML_n}(z))^T$ and $\mathbf{A}$ being a square matrix of dimensions $((n + 1), (n + 1))$

$$\mathbf{A} =$$

$$\begin{vmatrix} -k_{a,1}' & k_{d,1} & 0 & 0\dots\dots & 0 & 0 & 0 \\ \dfrac{k_{a,1}'}{\epsilon} & -\dfrac{k_{a,2}' + k_{d,1}}{\epsilon} & \dfrac{k_{d,2}}{\epsilon} & 0\dots\dots & 0 & 0 & 0 \\ 0 & \dfrac{k_{a,2}'}{\epsilon} & -\dfrac{k_{a,3}' + k_{d,2}}{\epsilon} & \dfrac{k_{d,3}}{\epsilon}\dots\dots & 0 & 0 & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ 0 & 0 & 0 & 0\dots\dots & \dfrac{k_{a,n-1}'}{\epsilon} & -\dfrac{k_{a,n}' + k_{d,n-1}}{\epsilon} & \dfrac{k_{d,n}}{\epsilon} \\ 0 & 0 & 0 & 0\dots\dots & 0 & \dfrac{k_{a,n}'}{\epsilon} & -\dfrac{k_{d,n}}{\epsilon} \end{vmatrix}$$

$$\tag{A-3}$$

where

$$\epsilon = D_{ML}/D_L \tag{A-4}$$

It can be proven that matrix $\mathbf{A}$ can be diagonalized and is semidefinite negative (one eigenvalue is zero, while the others are negative), so that it can be expressed as

$$\mathbf{A} = \mathbf{P} \cdot \mathbf{D} \cdot \mathbf{P}^{-1} \tag{A-5}$$

where $\mathbf{D}$ is a diagonal matrix (made from the eigenvalues) and $\mathbf{P}$ is the change of the basis and is made of the eigenvectors.

If we define

$$\vec{y}(z) = \mathbf{P}^{-1} \cdot \vec{C}(z) \tag{A-6}$$

the system A-2 can be written as

$$\nabla^2[y_i(z)] + n_i y_i(z) = 0, \quad i = 1, 2, \dots , n + 1 \tag{A-7}$$

Since all of the eigenvalues, n_i, are negative or zero, we define

$$\omega_i = \sqrt{-n_i} \tag{A-8}$$

and

$$\nabla^2[y_i(z)] - \omega_i^2 y_i(z) = 0 \Rightarrow y_i''(z) - \omega_i^2 y_i(z) = 0,$$
$$i = 1, 2, \dots , n + 1 \tag{A-9}$$

with $\omega_{n+1} = 0$.

The general solution of eq A-9 is

$$y_i(z) = A_{1,i} \exp(\omega_i z) + A_{2,i} \exp(-\omega_i z) \qquad i = 1, \dots , n$$

$$y_{n+1}(z) = A_{1,n+1} z + A_{2,n+1} \tag{A-10}$$

The set of integration constants $A_{1,i}$ and $A_{2,i}$ have to be determined from the boundary conditions. Let us obtain the boundary conditions at the bulk for y_i. The bulk concentration values verify $\mathbf{A} \cdot \vec{C}^* = 0$, and recalling that $\mathbf{A} = \mathbf{P} \cdot \mathbf{D} \cdot \mathbf{P}^{-1}$ and eq A-6

$$\mathbf{D} \cdot \vec{y} = 0 \tag{A-11}$$

or in terms of y

$$y_i^* = 0, \quad i = 1, 2, \dots , n \tag{A-12}$$

$$y_{i+1}^* = \frac{c_M^*}{P_{1,n+1}} = \frac{c_{ML}^*}{P_{2,n+1}} = \dots = \frac{c_{ML_n}^*}{P_{n+1,n+1}}$$

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Appendix B: Table of the Most Relevant Symbols

symbol	meaning	equation
g	thickness of the diffusion domain	8
$J_{complex}$	contribution of the complexes to the metal flux	10
J_{dif,ML_i}	maximum diffusive flux due to complex ML_i	33
J_{free}	flux if the complexes were inert (i.e., due to free M)	10, 11, 13
J_{kin}	hypothetical maximum kinetic contribution if there was no limitation from the diffusion of the complexes	29, 33
J_{kin}^{ϕ}	approximation to the actual kinetic flux using reaction layer concentrations	$J_{kin}^{\phi} = \sum_{i=1}^{j-1} D_{ML}(c_{ML_i}^*/g) + k_{d,j}c_{ML_j}^0\mu_j$
$J_{kin,j}$	J_{kin} arising only from the complex with stoichiometry ML_j	29, 30
$J_{kin,j}^{\phi}$	approximation to the contribution of complex ML_j to the metal flux using reaction layer concentrations	39
J_{labile}	flux if the complexes were labile	13
J_M	total metal flux at $x = 0$	9, 10, 13, 17
L	lability parameter comparing J_{kin} and the maximum diffusional flux of the complexes	12, 34
L_j	lability parameter when j is the rate-limiting step	33, 35, 36, 38, 41
μ_j	diffusion layer thickness for j being the rate-limiting step in finite diffusion	32, 36
μ_j^{∞}	diffusion layer thickness for j being the rate-limiting step in semi-infinite diffusion	23, 32
ξ	global degree of lability	13, 20
ξ_i	degree of lability of the complex ML_i	17, 18, 20

Using eq A-12, the n first components of eq A-10 can be written as

$$y_i(z) = B_i \sinh[\omega_i(z^* - z)] \qquad (A\text{-}13)$$

while for $i = n + 1$

$$y_{n+1}(z) = y_{n+1}^* + B_{n+1}(z^* - z) \qquad (A\text{-}14)$$

where

$$z^* = \frac{g}{\sqrt{D_M}} \qquad (A\text{-}15)$$

With the definition

$$\vec{f}(z) = (\sinh[\omega_1(z^* - z)], \ldots , \sinh[\omega_n(z^* - z)], z^* - z)^T \qquad (A\text{-}16)$$

and recalling that $\vec{y}(z) = \mathbf{P}^{-1}\cdot\vec{C}(z)$, the concentrations of the ML_i species are rewritten as

$$c_{ML_i}(z) = \sum_{j=1}^{n+1} P_{ij}B_jf_j(z) + c_{ML_i}^* \qquad (A\text{-}17)$$

where the remaining undetermined constants, B_j, have to be obtained from the boundary conditions at $z = 0$.

The boundary conditions (9) for $z = 0$ lead to

$$\begin{vmatrix} P_{1,1}f_1(0) & P_{1,2}f_2(0) & P_{1,n+1}f_{n+1}(0) \\ P_{2,1}f_1'(0) & P_{2,2}f_2'(0) & P_{2,n+1}f_{n+1}'(0) \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ P_{n+1,1}f_1'(0) & P_{n+1,2}f_2'(0) & P_{n+1,n+1}f_{n+1}'(0) \end{vmatrix} \begin{pmatrix} B_1 \\ B_2 \\ \cdot \\ \cdot \\ \cdot \\ B_{n+1} \end{pmatrix} = \begin{pmatrix} -c_M^* \\ 0 \\ \cdot \\ \cdot \\ \cdot \\ 0 \end{pmatrix} \qquad (A\text{-}18)$$

which determine the unknown constants, B_i.

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