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Lability of nanoparticulate metal complexes at a macroscopic metal responsive (bio)interface : expression and asymptotic scaling laws

Reference:

Duval Jérôme F.L., Town Raewyn M., van Leeuwen Herman P.- Lability of nanoparticulate metal complexes at a macroscopic metal responsive (bio)interface : expression and asymptotic scaling laws
The journal of physical chemistry : C : nanomaterials and interfaces - ISSN 1932-7447 - 122:11(2018), p. 6052-6065
Full text (Publisher's DOI): <https://doi.org/doi:10.1021/ACS.JPCC.7B11982>
Full text (Publisher's DOI): <https://doi.org/10.1021/ACS.JPCC.7B11982>
To cite this reference: <https://hdl.handle.net/10067/1500800151162165141>

Article

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J. Phys. Chem. C, **Just Accepted Manuscript** • DOI: 10.1021/acs.jpcc.7b11982 • Publication Date (Web): 19 Feb 2018

Downloaded from <http://pubs.acs.org> on February 25, 2018

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**Lability of Nanoparticulate Metal Complexes at a
Macroscopic Metal Responsive (Bio)Interface: Expression
and Asymptotic Scaling Laws**

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Abstract.

The lability of metal complexes expresses the extent of the dissociative contribution of the complex species to the flux of metal ions toward a macroscopic metal-responsive (bio)interface, *e.g.* an electroodic sensor or an organism. While the case of molecular ligands is well established, it is only recently that a definition was elaborated for the lability of metal complexes with nanoparticles (NPs) in aqueous dispersions. The definition includes the thickness of the non-equilibrium reaction layer operational at the (bio)interface and the extent of geometrical exclusion of NPs therefrom. In this work, an explicit expression is derived for the lability of nanoparticulate metal complexes (M-NP) towards a macroscopic reactive (bio)interface. Interpretation accounts for the M-NP chemodynamic properties that depend on NP size, electrostatics, metal diffusion and dehydration rates, and density of metal binding sites for various NPs types, *i.e.* soft/core-shell and hard NPs having volume and surface sites distribution, respectively. Computational examples under practical conditions illustrate how these factors jointly determine the remarkable non-monotonous dependence of M-NP lability parameter on NP size. The analysis is supported by the formulation of asymptotic scaling laws clarifying how local M-NP dissociation dynamics affect the lability parameter for M-NP complexes at the scale of the macroscopic (bio)interface.

1. Introduction.

The nanoparticle (NP) size domain has been shown to exhibit unique reactivity features towards target ions and small molecules.¹⁻³ The modified reactivity of various target species upon their association with NPs has broad significance for *e.g.* robust risk assessments of NPs,^{4,5} and design of NPs with tailored uptake/release kinetics for application in *e.g.* drug delivery.⁶⁻¹⁰ The interpretation calls for coupling the physicochemical features of NPs, *e.g.* size, charge density, chemical functionality, with their chemodynamic behaviour under the conditions encountered in environmental and biological media. The conceptual framework we develop herein quantitatively describes the reactivity of NP-target associates at a fundamental mechanistic level. The concepts are applicable to any target species: without loss of generality, we take the example of metal ion (M) complexes with negatively charged NPs.

Recent work has elaborated a conceptual framework for evaluation of the chemodynamics of (nano)particulate metal complexes, *i.e.* the dynamics of interconversion between free and complexed metal forms.^{1,2,11-17} The work extends the original Eigen mechanism¹⁸ for formation of complexes between M and molecular ligands to the more intricate situation of charged complexing agents with nanoparticulate and colloidal dimensions. The confinement of metal binding sites within the volume of the permeable particle body or shell (3D soft/core-shell NPs) or at the particle surface (2D hard NPs) leads to metal complex chemodynamics that generally involve a balance between chemical reaction kinetic and diffusive metal transport contributions.^{1,2,11-17} Several reports demonstrated that these contributions are strongly affected by the electrostatic conditions prevailing in the vicinity, at the surface and/or in the volume of the NP body.² Depending on medium salinity, NP charge and size, the particulate electric field may lead to a significant increase of the concentration of metal ions at the surface or in the volume of the NPs, and subsequently to a kinetics of M-NP complex formation that may be several orders of magnitude faster than that for complexes with molecular ligands.¹

Given this knowledge on the chemodynamic properties of M-NP complexes, it was recently possible to elaborate a definition of their lability at a metal-responsive macroscopic interface such as a sensing electrode or the surface of an organism.¹³ The lability parameter is a measure of the extent to which the dissociation of the complexes contributes to the flux of metal ions toward the reactive sensing interface.¹³ Such formulation of M-NP lability is mandatory for *e.g.* a proper evaluation of the bioavailability of metal ions to organisms in the presence of complexants,¹⁹ for interpreting measurements obtained by dynamic metal speciation techniques such as various voltammetries²⁰⁻²² and Diffusive Gradients in Thin Films (DGT),²³⁻²⁵ as well as in predicting release kinetics in the context of nanodrug formulations.⁷ At the labile limit, complexation of metal ions by nanoparticulate ligands is at equilibrium for any position from the sensing surface so that the overall flux of metal to the sensor results from the coupled diffusion-controlled transport of M-NP and free M.¹³ In the other limit of non-labile complexes, the complexation equilibrium

is not maintained and the relevant metal flux to the sensor is governed by the rate at which metal ions are released from the particle body.¹³ For intermediate situations, the lability parameter is determined by the ratio between the kinetic dissociation flux of complexes and the coupled diffusion flux of M-NP and M (**Figure 1**). A convenient way to formulate the dissociative kinetic flux of M-NP complexes at the sensor surface is to invoke the concept of a reaction layer, originally developed by Heyrovský and Brdička²⁶⁻²⁸ for molecular complexing ligands and recently detailed for nanoparticulate ligands.²⁹ The thickness of this reaction layer, $\bar{\lambda}$, basically derives from the relative mobilities of free and complexed metal species in the medium and their respective lifetimes as determined by the rate of re-association of M with NPs and the rate of M-NP dissociation.^{2,29} In turn, the spatial zone lying within a distance $\bar{\lambda}$ from the sensor defines a non-labile region where metal release from the complexes to the macroscopic interface is operational, *i.e.* $\bar{\lambda}$ denotes an effective reaction layer thickness at the macroscopic reactive interface.^{2,29} By its very nature, a reaction layer can only exist in the presence of complexing sites.^{13,30} Accordingly, for the case of NP complexants, the reaction layer at the sensing surface is an operational one that is related to the time-averaged presence of particle body volume/surface area and the corresponding time-averaged complexing site concentration. Unlike molecular ligands,²⁵⁻²⁸ the dissociation kinetic flux of M-NP complexes, or for that matter, the reaction layer thickness $\bar{\lambda}$, generally depends on the degree of geometrical exclusion of the complexing NP's body from the reaction layer, *i.e.* on the fraction of metal binding sites effectively involved in the dissociation of the complexes at the metal-sensing interface.^{2,13,29} Recent successful confrontation between the above lability framework and electrochemical data collected for Cd(II) in a dispersion of polymer nanoparticles evidenced the paramount importance of NP exclusion effects for a proper assessment of the lability of the nanoparticulate metal complexes considered.^{2,29} In contrast, the application of the conventional reaction layer approach - which neglects such effects²⁵⁻²⁸ - was shown to overestimate the lability parameter of the complexes by more than 3 orders of magnitude.²⁹

In the present work, an expression is developed for the lability parameter of M-NP complexes at a macroscopic metal sensor with *explicit* integration of the local M-NP chemodynamic features in conjunction with the macroscopic scale kinetic and transport-mediated exchange of metal species at the sensor interface. Such elaboration generalizes previous work¹³ and is further complemented by the derivation of useful tractable asymptotic scaling laws for analysis of the cumbersome dependence of lability of nanoparticulate complexes on their size. In turn, the results allow for a clear identification of the multi-factorial processes that control the magnitude of the M-NP lability parameter over the practical range of particle size as a function of *e.g.* the particle electrostatic features, the density of metal binding sites located within the volume or at the surface of the particle, the dehydration kinetics of the complexing metal ion (Eigen type association) and the intrinsic stability of the nanoparticulate metal complex.

2. Theory: setting the stage.

In the following, we consider charged spherical nanoparticles of radius r_p dispersed in a medium containing aqueous metal ions M (valence z_M) with bulk concentration c_M^* and ions from a monovalent background electrolyte in large excess over M. In line with usual practice, the electric potential profile at the NP/medium interface is assumed to be pre-established by the indifferent electrolyte ions.² The binding of metal ions to NPs occurs *via* reactive sites S, that are present in excess over the metal ions in solution, and distributed either at the NP surface or within the particle body. The former case refers to 2D hard complexing NPs with surface local site density denoted as Γ_s and the latter to soft/permeable and core-shell particulate systems with intraparticulate volume site density c_s .^{17,29} We introduce the ratio $z = a / r_p$ with a being the NP core radius so that soft, core-shell and hard complexing NPs refer to $z = 0$, $0 < z < 1$ and $z = 1$, respectively. The volume fraction of particles in dispersion is denoted as ϕ . For many practical cases with $\phi \ll 1$, there is no overlap between diffusion layers and electric double layers of neighbouring particles.²⁹ For the sake of readability, a list of the symbols (with corresponding units) used in this work is provided at the end of the manuscript.

Chemodynamics of nanoparticulate metal complexes. In the high charge density regime where the separation distance ℓ_c between structural charges carried by NPs is smaller than the electric Debye layer thickness $1/\kappa$,¹⁴ the formation of M-NP complexes basically comprises the following successive steps:^{2,13-17,29-30} (a) the conductive diffusion of $M_{aq}^{z_M+}$ from the bulk solution to the charged particle body (3D NPs) or surface (2D NPs), and the subsequent incorporation of $M_{aq}^{z_M+}$ as a free hydrated ion within the particle shell volume (relevant for 3D NP type) (step (i) in **Figure 1** with rate constant $k_{a,p}$ expressed in $\text{mol}^{-1} \text{m}^3 \text{s}^{-1}$); (b) the fast electrostatic pairing of $M_{aq}^{z_M+}$ with S, which leads to an outer-sphere $M \bullet S$ associate; and finally (c) the formation of an inner-sphere MS complex following the loss of water of hydration by $M_{aq}^{z_M+}$ and the creation of a chemical bond with S (step (ii) in **Figure 1** with rate constant k_a^{is} in $\text{m}^3 \text{mol}^{-1} \text{s}^{-1}$). The dissociative counterparts of steps (i) and (ii) are shown schematically in **Figure 1** with the corresponding rate constants $k_{d,p}$ and k_d^{is} (both in s^{-1}), respectively. Depending on a number of physicochemical parameters pertaining to the properties of the NP (size, site density, electrostatics), to the free metal ion (dehydration kinetics, valency) and to the stability of the complex MS, the rates for overall

formation and dissociation of M-NP complexes may be kinetically determined by step (i), step (ii) or by both. The conceptual framework has been extensively detailed in preceding theoretical reports, together with supporting experimental data.^{1,2,12-17} The composite rate constants k_a ($\text{mol}^{-1} \text{m}^3 \text{s}^{-1}$) and k_d (s^{-1}) for the *overall* association (step (i) to (ii) in **Figure 1**) and dissociation (step (ii) to (i)) thus generally involve both chemical kinetic and diffusive transport contributions according to $k_a = \left(1/k_a^{\text{is}} + 1/k_{a,p}\right)^{-1}$ and $k_d = \left(1/k_d^{\text{is}} + 1/k_{d,p}\right)^{-1}$, respectively. It is stressed that the intraparticulate diffusion of metal ions M has been shown to be fast compared to extraparticulate diffusion³¹ so that the former can often be neglected with respect to the latter. In turn, $k_{a,p}$ and $k_{d,p}$ effectively represent the transport of M to and from the sites S, respectively.

Lability of nanoparticulate metal complexes at a macroscopic metal-responsive (bio)interface. A macroscopic metal sensor (with curvature radius r_o much larger than r_p) converts or accumulates the free metal ions M (**Figure 1**). Examples of such sensors include bacteria,³²⁻³⁴ algae,³⁵⁻³⁶ gill surfaces,³⁷⁻³⁸ electrodes,²⁰ polymeric gel layers and other ion-exchange resins.³⁹⁻⁴⁶ The conversion or accumulation of M at the sensor surface or biointerface creates a concentration gradient of M from the bulk solution towards the sensor surface. Depending on the rate of interconversion between free and complexed metal forms as compared to the conversion/accumulation timescale, complexes may dissociate within the diffusion layer at the reactive sensor/medium interface (**Figure 1**), thus releasing M ions that enhance the metal transport flux towards the sensor. The lability parameter $\mathcal{L}$ for the nanoparticulate metal complexes at the metal-responsive (bio)interface is defined as the ratio between the maximum kinetic flux, J_{kin} , arising from the rate of dissociation of the complexed species, and the maximum diffusive flux, J_{diff} , that represents the rate at which free *and* complexed metal species arrive at the macroscopic reactive (bio)interface (**Figure 1**).² The expression of the maximum kinetic flux J_{kin} for chemical dissociation of M-NP complexes may be written in the form^{2,13,29}

$$J_{\text{kin}} = k_d^{\text{is}} \bar{c}_{\text{MS}}^{\lambda} \bar{\lambda} \quad (1)$$

, where $\bar{\lambda}$ is the thickness of the macroscopic reaction layer at the medium side of the sensor/medium interface operational for nanoparticulate metal complexes,²⁹ and $\bar{c}_{\text{MS}}^{\lambda}$ is the concentration of MS complexes *averaged* of the entire dispersion volume (indicated by the overbar notation in $\bar{c}_{\text{MS}}^{\lambda}$) with proper consideration of NP geometrical exclusion from the reaction layer (indicated by the superscript λ in $\bar{c}_{\text{MS}}^{\lambda}$, see §3).^{13,29} Alternatively, $\bar{c}_{\text{MS}}^{\lambda}$ represents the averaged (maximum) concentration of MS species

within the macroscopic reaction layer volume. The meanings of the ‘overbar’ and ‘superscript λ ’ notations as adopted in $\bar{c}_{MS}^\lambda$ also apply for the concentration term $\bar{c}_s^\lambda$ introduced below. Following the original idea by Koutecký and Koryta for molecular complexing ligands,⁴⁷⁻⁴⁸ the length scale $\bar{\lambda}$ derives from the diffusion coefficient D_M of free metal M in the electrolyte medium, its mean free lifetime $1/(k_{a,p}\bar{c}_s^\lambda)$ with $\bar{c}_s^\lambda$ the concentration of metal binding sites S smeared-out over the entire dispersion volume and corrected for the extent to which NP reactive shell/surface is excluded from the reaction layer (**Figure 1**), and from the diffusion coefficient D_p and mean lifetime $1/k_d$ of the M-NP complex, with D_p the particle diffusion coefficient. Taking all this together, we can write^{2,29}

$$\bar{\lambda} = 1 / \sqrt{k_{a,p}\bar{c}_s^\lambda / D_M + k_d / D_p} \quad (2)$$

, where $k_{a,p}$, $\bar{c}_s^\lambda$, k_d and D_p depend on particle size as detailed in previous reports.^{17,29}

The total steady state maximum diffusive flux J_{diff} of *all metal forms* from bulk medium to the sensor is given by^{2,13,29}

$$J_{\text{diff}} = \frac{D_M c_M^* + D_p (\bar{c}_M + \bar{c}_{MS})}{\bar{\delta}_0} \quad (3)$$

, where $\bar{c}_M$ and $\bar{c}_{MS}$ denote the concentrations of free and complexed metal forms associated to the NP and averaged over the entire dispersion volume (indicated by the overbar notation in $\bar{c}_M$ and $\bar{c}_{MS}$), respectively and $\bar{\delta}_0$ refers to the thickness of the macroscopic diffusion layer at the sensor/medium interface (indicated by the overbar notation similarly to $\bar{\lambda}$).² A system is denoted as labile when $J_{\text{kin}} \gg J_{\text{diff}}$ ($\mathcal{L} \gg 1$), *i.e.* the metal flux at the sensor surface is determined by coupled diffusion of M and M-NP, whereas the inequality $J_{\text{kin}} \ll J_{\text{diff}}$ ($\mathcal{L} \ll 1$) applies to situations where it is the rate of dissociation of M-NP complexes that kinetically controls the contribution of M-NP to the flux of M. Equations (1)-(3) are valid for perfect metal sink condition at the sensor surface. However, previous report⁴⁹ evidenced that boundary conditions do not influence the lability and relative contributions of metal species. It could be anticipated that this feature, derived for the case of molecular ligands L, also holds for the situation of NP complexants. Firm conclusion on this issue will be provided in a forthcoming study where the lability parameter evaluated from eqs. (1)-(3) will be compared to that derived from the numerical solving of the differential equations detailing the reactive transfers of M and NP at the sensor/solution interface.

Analogy with the situation of molecular ligands homogeneously distributed over the entire solution volume. Prior to further developments, it is useful to recall the basis of eqs (1)-(3) by drawing an analogy with the situation of molecular ligands (denoted as L hereafter) homogeneously distributed over the entire solution volume (in contrast to the binding sites S carried by the NP complexants, **Figure 1**). For such a situation, van Leeuwen unequivocally showed⁵⁰ that in the limit of labile complexes the metal flux expression at the sensor surface - as derived from rigorous solution of the relevant diffusion equation corrected for chemical kinetic terms - can be expressed in the form $J_{\text{diff}} = \bar{D}^{1/2} (c_M^* + c_{\text{ML}}^*) / (\pi t)^{1/2}$ with c_M^* and c_{ML}^* the bulk concentration of free M and ML complexes and $\bar{D}$ an operational diffusion coefficient defined by the sum of the diffusion coefficient of M (D_M) and ML (D_{ML}) weighted by the M and ML concentrations across the diffusion layer. The concentrations c_M^* and c_{ML}^* are interrelated via the stability constant $Kc_L^* = c_{\text{ML}}^* / c_M^*$ with c_L^* the bulk concentration of ligands L in excess over M. Under steady-state transport conditions, J_{diff} can be rearranged in the form $J_{\text{diff}} = \bar{D} (c_M^* + c_{\text{ML}}^*) / \bar{\delta}_0$ where $\bar{\delta}_0 = (\pi \bar{D} t)^{1/2}$ is the thickness of the steady-state diffusion layer at the macroscopic sensor surface. For NP complexants hosting metal binding sites S within their body (soft NP case) or at their surface (hard NP), the term $c_M^* + c_{\text{ML}}^*$ in the expression $J_{\text{diff}} = \bar{D} (c_M^* + c_{\text{ML}}^*) / \bar{\delta}_0$ above is replaced by $c_M^* + \bar{c}_M + \bar{c}_{\text{MS}}$ where $\bar{c}_M$ and $\bar{c}_{\text{MS}}$ are defined below eq. (3). As both M and MS are confined within/at the reactive NP volume/surface, they diffuse toward the macroscopic reactive surface with the diffusion coefficient D_p of the NP metal carrier. Following the analogy with the molecular ligand situation, the effective diffusion coefficient $\bar{D}$ introduced above then becomes for the case of NP complexants $\bar{D} = (D_M c_M^* + D_p (\bar{c}_M + \bar{c}_{\text{MS}})) / (c_M^* + \bar{c}_M + \bar{c}_{\text{MS}})$. Altogether, these elements lead to eq. (3).

Van Leeuwen further showed⁵⁰ that for molecular ligands L taken in the extreme $Kc_L^* \gg D_M / D_{\text{ML}}$, the metal flux at the macroscopic surface in the non-labile limit is given by $J_{\text{kin}} = k_d c_{\text{ML}}^* (D_M / k_a')^{1/2}$ with $k_a' = k_a c_L^*$. The latter expression is generally written $J_{\text{kin}} = k_d c_{\text{ML}}^* \mu$ where $\mu = (D_M / k_a')^{1/2}$ is the thickness of the conventional reaction layer involving the kinetic constant k_a' for M association with L, and k_d identifies with k_d^{is} according to Eigen association scheme between M and L.¹⁸ In the case where the transport of the released M from inside to outside of the NP is rate-limiting the overall M-NP

dissociation process, the system is labile, as argued in previous work.³⁰ This expression of J_{kin} can be used for the situation of NP complexants *provided that* c_{ML}^* is replaced by $\bar{c}_{\text{MS}}^\lambda$, the concentration of inner-sphere complexes MS averaged over the entire dispersion volume with account of the only fraction of the reactive shell volume located within the reaction layer of thickness $\bar{\lambda}$ (**Figure 1**, see §3). This thickness is the pendant of μ defined above for molecular L (see §3).^{2,13,29} It is important to realize that the condition $Kc_{\text{L}}^* \gg D_{\text{M}} / D_{\text{ML}}$ argued to derive J_{kin} (and subsequent μ) is generally not satisfied for NP complexants because NP diffusion coefficient D_{p} (the analogue of D_{ML}) is lower than D_{M} to an extent that depends on the NP radius r_{p} . This implies that the *dissociative* term $D_{\text{M}} / k_{\text{a}}'$ alone is not sufficient for defining the reaction layer thickness $\bar{\lambda}$ relevant for NP complexants at a reactive sensor/solution interface. In turn, an MS formation term should be included in the definition of $\bar{\lambda}$ to account for the association between free M and S. This additional (*associative*) term corresponds to $k_{\text{d}} / D_{\text{p}}$ in eq. (2). In that equation, k_{d} (the reciprocal life time of MS) is the composite kinetic constant $k_{\text{d}} = \left(1 / k_{\text{d}}^{\text{is}} + 1 / k_{\text{d,p}}\right)^{-1}$ that should be considered in order to cover the entire range of M-NP dissociation dynamics, *i.e.* from slowly (*e.g.* Ni) to rapidly (*e.g.* Pb) dehydrating metal ions.^{12,17} Finally, the *dissociative* term $D_{\text{M}} / k_{\text{a}}'$ involved in the defining expression of μ should be replaced - for the NP case - by $D_{\text{M}} / \left(k_{\text{a,p}} \bar{c}_{\text{s}}^\lambda\right)$. This term involves the concentration $\bar{c}_{\text{s}}^\lambda$ of binding sites effectively present within the reaction layer (see §3) and smeared out over the entire dispersion volume, and the diffusion-component $k_{\text{a,p}}$ for M-NP association. It is stressed here that it is $k_{\text{a,p}}$ and not the composite constant k_{a} that must be considered because the relevant timescale is the one required to get M inside the volume of the NP complexant (**Figure 1**). All these elements motivate the form of eq. (2) that defines $\bar{\lambda}$.

It is further emphasized that the original paper⁵¹ that elaborated an extended definition of the reaction layer thickness used a notation based on the involved rate constants, which has carried into subsequent work.^{2,17,29} Herein we adopt a process-based nomenclature and define the association reaction layer thickness as $\left(k_{\text{d}} / D_{\text{p}}\right)^{-1/2}$ and dissociation layer thickness as $\left(D_{\text{M}} / \left(k_{\text{a,p}} \bar{c}_{\text{s}}^\lambda\right)\right)^{1/2}$. The latter enters the original Heyrovsky formulation²⁶ of the kinetic flux due to *dissociation* of MS. The former involves k_{d} that defines the lifetime of the complex MS. The corresponding flux is an *associative* one because it counts the total production of MS in the layer of thickness $\left(k_{\text{d}} / D_{\text{p}}\right)^{-1/2}$.

Finally, the basis of eqs. (1)-(3) is supported by the excellent agreement between the lability parameter measured by electrochemistry for Cd(II)-latex particles (Table 3 in Ref. [29], and Figure 10 in Ref. [2]) and the treatment of the lability parameter outlined above for NP complexants at a macroscopic metal sensor surface. It is stressed that this treatment did not require any adjustable parameters given the known physicochemical properties of the latex NPs considered, both in terms of size and density of sites S derived from independent electrokinetic analysis.^{2,29} In particular, the comparison between experiments and theory highlighted the dramatic impact of the geometric exclusion of NP from the reaction layer (thickness $\bar{\lambda}$) on the lability parameter $\mathcal{L}$. Adopting the standard reaction layer formulation $\mu = (D_M / k_a')^{1/2}$ with ignoring NP exclusion process, $\mathcal{L}$ was found to exceed by more than 3 orders of magnitude the experimental value. In addition, evaluation of $\mathcal{L}$ for Cd-latex NP from eqs. (1)-(3) with arbitrarily ignoring the $D_M c_M^*$ term in eq. (3) results in a lability parameter that is *ca.* 4 times larger than the experimental value. These elements further comfort our defining expressions here for J_{kin} , J_{diff} and $\bar{\lambda}$. Within the context of lability evaluation for molecular complexes ML, some authors⁵² define J_{diff} as the maximum diffusive supply of the complexes without any contribution from free M (*i.e.* $D_M c_M^* = 0$ in eq. (3)). As previously argued, such definition would lead to a poorer comparison to experimental data on Cd-latex NP system, and to ignoring the necessarily coupled diffusions of free M and complexed metal species to the sensor surface as evidenced by van Leeuwen.⁵⁰ Last, other operational definitions of the reaction layer thickness are proposed in the literature for the case of molecular ligands.²⁵ At this stage, it is difficult to appreciate whether or not the proposed definitions can be easily transposed to the intricate situation of NP complexants with proper integration of their defining physicochemical features and of *e.g.* the paramount contribution of NP exclusion from the reaction layer.^{2,29} The solution proposed in this report and elsewhere^{2,13,29} achieves such a transition between molecular to NP complexant situations.

In the sections below (§3-4), starting from the eqs. (1)-(3) an expression for the lability parameter $\mathcal{L} = J_{\text{kin}} / J_{\text{diff}}$ of M-NP complexes at a reactive (bio)interface is explicitly derived as a function of (i) the relevant physicochemical features of the nanoparticulate ligands, which includes their size, their electrostatic characteristics and the density of metal binding sites S they carry, (ii) the metal diffusion and dehydration kinetic properties, and (iii) the stability of the intraparticulate or surface metal complexes MS. For that purpose, differentiation is made between the case of 3D soft/core-shell complexing nanoparticles (§3) and that of 2D hard nanoparticulate ligands (§4). It is emphasized that the developments below hold for cases in line with the applicability of the generalized Eigen

scheme^{1,2,12,14,16,17} (**Figure 1**) in the high NP charge density regime ($\kappa\ell_c \ll 1$) and for metal binding sites S homogeneously distributed within the reactive NP shell (3D case) or at the NP surface (2D). In addition, dilute NP suspensions are exclusively considered ($\varphi \ll 1$).

Figure 1. Schematic representation of a soft nanoparticle metal complex M-NP (radius r_p) in the vicinity of a metal (bio)interface that is reactive toward aqueous metal ions $M_{aq}^{z_M+}$ (M for short). The chemodynamic processes governing the formation/dissociation of the M-NP complexes are schematically depicted with the corresponding rate constants (see text for details). The volume component of the nanoparticle body lying within the operational reaction layer of thickness $\bar{\lambda}$ is indicated in grey shading. The figure clarifies the typical concentration profiles for free metal ions M and for NP-supported MS complexes from bulk solution to the responsive (bio)interface. Meaning of symbols and nomenclature are detailed in the text.

3. Theory: Lability of nanoparticle metal complexes M-NP at a (bio)interface which is reactive towards the free metal ion M.

3.1. The case of 3D (soft/core-shell) nanoparticle ligands.

The averaged concentrations $\bar{c}_{MS}^\lambda$ and $\bar{c}_S^\lambda$ involved in the definition of the kinetic flux J_{kin} (eqs. (1)-(2)) depend on the NP volume fraction φ in the entire dispersion according to

$$\bar{c}_i^\lambda = c_i \varphi (1 - \gamma) (1 - z^3) \quad (4)$$

, where the index i refers to MS or S. c_{MS} and c_S represent the concentrations of MS and S in the NP shell volume and the dimensionless term $1 - \gamma$ specifies the averaged fraction of nanoparticle shell

volume within the reaction layer zone (**Figure 1**).²⁹ It is noted that the concentrations $\bar{c}_S^\lambda$ is related to the concentration of S averaged over the entire dispersion, denoted as $\bar{c}_S$, via $\bar{c}_S^\lambda = \bar{c}_S(1-\gamma)$ so that eq. (2) can equally be written in the form $\bar{\lambda} = 1/\sqrt{k_{a,p}\bar{c}_S(1-\gamma)/D_M + k_d/D_p}$ given in eq. (2) of Ref. [29]. As demonstrated in Ref. [29], in the absence of interactions between the NP and the sensor surface, γ solely depends on the ratios $\bar{\lambda}/r_p \equiv \Lambda$ and $z = a/r_p$. Qualitatively, γ increases from 0 to 1 with increasing Λ^{-1} with the limits $\gamma = 0$ and $\gamma = 1$ corresponding to situations where the geometrical exclusion of the reactive volume of the NPs from the reaction layer is insignificant ($\Lambda^{-1} \ll 1$) and complete ($\Lambda^{-1} \gg 1$), respectively. The magnitude of $1-\gamma$ is obtained from numerical evaluation of the NP shell volume lying in the reaction layer and averaged over all positions of the particle centre from the sensor, *i.e.*²⁹

$$\gamma(\Lambda, z) = 1 - \frac{\Lambda^3}{4(1-z^3)} \int_0^1 F(\Lambda, z, x) dx \quad (5)$$

, where the cumbersome function F was derived in Ref. [29] and is recalled in Supporting Information (eq. (S1) therein, §I), $x = H/\bar{\lambda}$ and H is the separation distance between the NP and the (bio)interface as specified in **Figure 1**. In turn we obtain $J_{\text{kin}} = k_d^{\text{is}} c_{\text{MS}} \varphi(1-z^3) [1-\gamma(\Lambda, z)] \bar{\lambda}$ with $\bar{\lambda} = \Lambda r_p$. Further realizing that the concentrations $\bar{c}_M$ and $\bar{c}_{\text{MS}}$ involved in the expression of the diffusion flux J_{diff} (eq. (3)) are defined by $\bar{c}_M = c_M \varphi(1-z^3)$ and $\bar{c}_{\text{MS}} = c_{\text{MS}} \varphi(1-z^3)$, respectively, the lability parameter $\mathcal{L} = J_{\text{kin}}/J_{\text{diff}}$ may be rearranged according to

$$\mathcal{L} = \frac{k_d^{\text{is}} c_{\text{MS}} \varphi(1-z^3) [1-\gamma(\Lambda, z)]}{D_M c_M^* \left(1 + \frac{\ell}{r_p} \varphi(1-z^3) \sum_{j=\text{MS}, \text{M}} \frac{c_j}{c_M^*} \right)} r_p \bar{\delta}_0 \Lambda \quad (6)$$

, where the index j refers here to MS and M species, $\ell = k_B T / (6\pi\eta D_M)$ is the length scale defined by $\ell/r_p = D_p/D_M$ with D_p provided by the Stokes-Einstein equation, and η is the dynamic viscosity of the medium. We define the intrinsic stability constant of the inner-sphere complexes MS in terms of the intraparticulate conditions, *i.e.* $K_{\text{int}} = k_a^{\text{is}}/k_d^{\text{is}} = c_{\text{MS}}/(c_M c_s)$ (in $\text{mol}^{-1} \text{m}^3$). Recalling that in the high charge density regime $\kappa \ell_c \ll 1$ and for a relaxed electric field (large excess of background electrolyte),

c_M is related to the bulk concentration c_M^* via $c_M = c_M^* \bar{f}_B$ with $\bar{f}_B$ the Boltzmann *equilibrium* partitioning factor averaged over the particle shell volume,^{12,53} we obtain after some rearrangements

$$\mathcal{L} = \frac{k_a^{\text{is}} c_s \phi \bar{f}_B (1-z^3) [1-\gamma(\Lambda, z)]}{D_M \left(1 + \frac{\ell}{r_p} \phi \bar{f}_B (1-z^3) (1 + K_{\text{int}} c_s) \right)} r_p \bar{\delta}_o \Lambda. \quad (7)$$

In details, the quantity $\bar{f}_B$ corresponds to the integral average of the position-dependent Boltzmann factor termed f_B according to $\bar{f}_B = \int_a^{r_p} 4\pi r^2 f_B(r) dr / V_{\text{shell}}$ with V_{shell} the shell volume. Under Donnan condition, this expression reduces to $\bar{f}_B = f_B = \exp(-z_M F \psi^D / RT)$ with ψ^D the applicable Donnan potential.

Equation 7 involves the rate constant for formation of inner-sphere complex MS (**Figure 1**), k_a^{is} , expressed in terms of the intraparticle conditions by^{17,29}

$$k_a^{\text{is}} = \frac{3D_M}{\ell_a^2 c_s} \quad (8)$$

, where we define $\ell_a = \sqrt{3D_M / (k_w V^{\text{os}} N_{\text{Av}} c_s)}$ (m) as the thickness of an intraparticle dissociation reaction layer ('dissociation' qualification given here on a process-based nomenclature and not on the kinetic constant-based nomenclature adopted in earlier work^{17,29}) defined as the average distance travelled by a free M within the NP shell at zero intraparticle potential (*i.e.* in the absence of electrostatic conduction contribution) before it (re)associates with a site S to form MS, k_w (s⁻¹) is the metal dehydration rate constant (tabulated values are available for a number of metal ions⁵⁴), V^{os} is the outer sphere volume and N_{Av} is the Avogadro number.

Combining eqs. (7)-(8), the final result for $\mathcal{L}$ reads as

$$\mathcal{L} = 3\phi \bar{f}_B (1-z^3) [1-\gamma(\Lambda, z)] \frac{r_p \bar{\delta}_o}{\ell_a^2} \Lambda \left(1 + \frac{r_p^*}{r_p} \right)^{-1} \quad (9)$$

, where $\gamma(\Lambda, z)$ is defined by eq. (5) and we introduced the length scale $r_p^* = \phi \bar{f}_B \ell (1-z^3) (1 + K_{\text{int}} c_s)$

for dimensioning the diffusive flux according to $J_{\text{diff}} = (D_M c_M^* / \bar{\delta}_o) (1 + r_p^* / r_p)$.

The remaining task is the formulation of the dimensionless macroscopic reaction layer thickness $\Lambda = \bar{\lambda} / r_p$ operative at the sensor/medium interface. Starting from eq. (2) and substituting therein the expressions of $k_{a,p}$ and k_d derived elsewhere^{2,17} for core-shell particles with a given c_s , it is shown that $\Lambda = \bar{\lambda} / r_p$ identifies with the physical root of the transcendental equation²⁹

$$\Lambda^2 \Phi_{el,a} \left\{ 1 - \gamma(\Lambda, z) + \left\{ \ell r_p^{-1} \Phi_B \left[1 + \left(\frac{\mu_d}{r_p} \right)^2 \right] \right\}^{-1} \right\} - 1 = 0 \quad (10)$$

, with $\Phi_{el,a} = 3\varphi \bar{f}_{el,a}$, $\Phi_B = \varphi \bar{f}_B / (1 + K_{int} c_s)$ (both dimensionless). The length scale

$$\mu_d = \sqrt{\frac{3D_M(1 + K_{int} c_s) K_{int}}{k_w V^{os} N_{Av}}} \bar{f}_{el,d} \text{ in eq. (10) corresponds to the thickness of the } intraparticulate \text{ reaction}$$

layer (corrected for particle electrostatics on transport rates) with regard to the association process (process-based nomenclature). It is straightforward to realise that for zero electrostatic potential within the

NP shell, we have $\mu_d / \ell_a = \sqrt{(1 + K_{int} c_s) K_{int} c_s}$ or $\mu_d / \ell_a = K_{int} c_s$ for $K_{int} c_s \gg 1$. Previous work^{17,29}

elaborated diagnosis for chemodynamic behaviour for M-NP association and dissociation from criteria involving the ratios ℓ_a / r_p and μ_d / r_p , respectively. Unlike the choice originally made in Ref. [17], the

term $\sqrt{(1 + K_{int} c_s) K_{int} c_s}$ could have been left outside the defining expression of μ_d , then resulting in

$\mu_d / \ell_a = 1$. The dimensionless scalars $\bar{f}_{el,a}$ involved in $\Phi_{el,a}$ and $\bar{f}_{el,d} = \bar{f}_{el,a} / \bar{f}_B$ appearing in μ_d

correct the convergent (subscript 'a') or divergent (subscript 'd') diffusion of M to or from the NPs for particle electrostatic effects, respectively. Quantitatively, these scalars are obtained from solution of the

non-linear Poisson-Boltzmann equation as detailed elsewhere,^{17,53} and their deviation from unity indicates

the extent to which diffusion of M is accelerated or impeded by the particle electric double layer field. For

practical situations where NPs are negatively charged, in contrast to the behaviour of $\bar{f}_B$, the factor $\bar{f}_{el,a}$

does not exceed *ca.* one order of magnitude,^{12,17} so that the inequality $\Phi_{el,a} \ll 1$ is always satisfied in the

limit of dilute NP dispersions ($\varphi \ll 1$).²⁹

The set of eqs. (5), (9) and (10) fully defines the lability parameter of a given nanoparticulate metal complex and elegantly pinpoints the nature of the various physicochemical terms that come into play both at the local nanoparticulate (NP) and the macroscopic (sensor) levels. The nonlinear coupling between the exclusion factor γ (eq. (5)) and the dimensionless reaction layer thickness $\Lambda = \bar{\lambda} / r_p$ (eq. (10)) makes it impossible to formulate general expressions for γ , Λ and $\mathcal{L}$ as a function of particle size. Such a

formulation is however possible for the specific case of soft nanoparticulate ligands, as shown in the next section. In the following, the symbol ‘ $\propto$ ’ means ‘scales with’.

3.2. Asymptotic scaling laws for the lability parameter of soft nanoparticulate metal complexes *versus* particle size.

For soft NPs devoid of impermeable core component ($z = 0$), eq. (5) exactly reduces to²⁹

$$\gamma(\Lambda, z = 0) = \begin{cases} 1 + \frac{\Lambda^2}{4} \left(\frac{\Lambda}{4} - 1 \right), & \text{for } \Lambda < 2 \\ \Lambda^{-1}, & \text{for } \Lambda \geq 2 \end{cases} \quad (11)$$

Substituting eq. (11) into eq. (10) and subsequently solving of the so-obtained polynomial equations in $\Lambda = \bar{\lambda} / r_p$ in the practical limit of dilute NP suspensions (*i.e.* $\varphi \ll 1$ or $\Phi_{el,a} \ll 1$),²⁹ we obtain the expressions for the reaction layer thickness $\bar{\lambda}$ elaborated elsewhere²⁹ (Table S1 therein) and rearranged here in the concise form

$$\bar{\lambda} = \begin{cases} r_p \left(1 + \sqrt{1 + 4 / \Phi_{el,a}} \right) / 2, & \text{for } r_p \ll r_{p,max} \\ r_{p,int}^{3/2} / \sqrt{r_p}, & \text{for } r_{p,max} \ll r_p \ll \mu_d \\ \sqrt{\tilde{r}_p r_p}, & \text{for } r_p \gg \mu_d \end{cases} \quad (12)$$

, where the length scales $r_{p,max} = \left(2\ell\Phi_B\mu_d^2 \right)^{1/3}$, $r_{p,int} = \left(\ell\Phi_B\mu_d^2 / \Phi_{el,a} \right)^{1/3}$ ($> r_{p,max}$) and $\tilde{r}_p = \ell\Phi_B / \Phi_{el,a}$ are introduced for proper dimensioning and reduction of eq. (12). As shown below, these length scales offer a pragmatic way to rationalise and parameterize the multifactorial lability parameter of nanoparticulate metal complexes at macroscopic reactive (bio)interfaces and, in particular, explain the non-monotonous dependence of $\mathcal{L}$ on NP size. It is stressed that no tractable analytical solution exists for $\Lambda = \bar{\lambda} / r_p$ (and thus for $\mathcal{L}$) over the whole range of particle size r_p .

Equation 12 highlights the existence of three distinct asymptotic regimes for the dependence of $\bar{\lambda}$ on particle size.²⁹ Briefly, the linear increase of $\bar{\lambda}$ with r_p for $r_p \ll r_{p,max}$ corresponds to a reaction layer that is primarily governed by the term $k_{a,p}\bar{c}_s^{\bar{\lambda}} / D_M$ in eq. (2). Here, the exclusion process impacts on the extension of the reaction layer at the sensor/medium interface to an extent that depends on the deviation of $2^{-1}\sqrt{\Phi_{el,a}} \left(-1 + \sqrt{1 + 4\Phi_{el,a}^{-1}} \right)$ from unity.²⁹ In the regime $r_p \gg \mu_d$, $\bar{\lambda}$ increases with particle size according to the power law $r_p^{1/2}$ and the associative term k_d / D_p in eq. (2) now significantly exceeds

$k_{a,p}\bar{c}_s^\lambda / D_M$, so that the exclusion process (γ -dependent term in eq. (2)) is immaterial for the magnitude of $\bar{\lambda}$ in this range of r_p . In the intermediate regime, *i.e.* $r_{p,\max} \ll r_p \ll \mu_d$, $\bar{\lambda}$ decreases with r_p according to $r_p^{-1/2}$ and both association and dissociation of M-NP complexes then contribute to $\bar{\lambda}$. The dependence of $\bar{\lambda}$ on particle size is therefore generally marked by the presence of a maximum at $r_p = r_{p,\max}$ and a minimum at $r_p = \mu_d$.²⁹ Depending on *e.g.* the stability of MS complexes and the magnitude of the intraparticulate potential (as subsumed in the term Φ_B), these extrema are more or less pronounced or may even disappear.²⁹ In this latter situation, $\bar{\lambda}$ monotonously increases with r_p from $\bar{\lambda} \propto r_p$ to $\bar{\lambda} \propto r_p^{1/2}$ at sufficiently small and large NPs, respectively. The existence of extrema in $\bar{\lambda}$ *versus* r_p is tied to the generic condition $\mu_d / (\Phi_B \ell) > 54$ applicable for $r_{p,\max} / \mu_d \ll 1$ (see Table S3 in Ref. [29]).

With the dependence of $\bar{\lambda}$ (or Λ) on r_p clarified, the way in which the exclusion factor γ varies with r_p can be explicitly formulated after substitution of eq. (12) into eq. (11). These expressions may then be exploited in combination with eq. (9) to define the sought asymptotic scaling laws for the lability parameter $\mathcal{L}$ *versus* particle size. The results collected in **Table 1** systematically demonstrate the power-law dependence of $\mathcal{L}$ on r_p depending on the magnitude of r_p compared to the characteristic length scales $r_{p,\max}$, $\tilde{r}_p$, $r_{p,\text{int}}$, r_p^* and μ_d . For the sake of completeness, the corresponding expressions of Λ and γ are further detailed in **Table 1** for the various asymptotic limits identified therein. It is emphasized that the electrostatic features of the NPs, the particle volume fraction, the stability of the MS complexes and the M-NP chemodynamic properties are all subsumed in the aforementioned length scales.

Figure 2A displays the typical dependence of the lability parameter $\mathcal{L}$ for M-NP complexes towards a macroscopic sensor on particle size. The practical conditions $\{K_{\text{int}}, c_s, D_M, \bar{f}_B, \bar{f}_{\text{el,a}}, k_w, \varphi, \bar{\delta}_o\}$ adopted are specified in the caption and the corresponding $r_{p,\max}$, $\tilde{r}_p$, $r_{p,\text{int}}$, r_p^* and μ_d are indicated in **Figure 2A** by vertical lines. The results are derived from rigorous solution of eqs. (5), (9) and (10) and further compared to predictions (i) from the applicable asymptotic power-law expressions reported in **Table 1**, and (ii) with ignoring the exclusion of NP body from the reaction layer, *i.e.* by arbitrarily setting $\gamma = 0$ in eqs. (9) and (10). For the sake of *formal comparison* between exact and approximate asymptotic results over the *whole range* of chemodynamic M-NP dissociation features, $\mathcal{L}$ is given as a function of r_p

normalized by the intraparticulate reaction layer μ_d . The regimes $r_p / \mu_d \ll 1$, $r_p / \mu_d \gg 1$ and $r_p / \mu_d \approx 1$ correspond indeed to an overall M-NP complex dissociation rate constant k_d determined by inner-sphere complex MS dissociation ($k_d \rightarrow k_d^{is}$), by the conductive diffusion of M into the medium ($k_d \rightarrow k_{d,p}$) and by both ($k_d = (1/k_d^{is} + 1/k_{d,p})^{-1}$), respectively.¹⁷ This typology of M-NP dissociation chemodynamics stems from the expression $k_d^{is} / k_{d,p} = (r_p / \mu_d)^2$ that applies for 3D soft/core-shell NPs of given c_s :¹⁷ it compares the characteristic timescale for M diffusion from the intraparticulate NP reactive volume ($1/k_{d,p}$) to that for the chemical dissociation of MS complexes ($1/k_d^{is}$). It is stressed that the extreme $r_p / \mu_d \ll 1$ does not represent a physically realistic reaction shell layer (with thickness μ_d) at the NP/medium interface as it would then extend well beyond the physical shell with thickness $d = r_p - a$. Under the condition $r_p / \mu_d \ll 1$, the whole particle shell is then contributing evenly to the dissociation of MS.

Particle size range	Lability $\mathcal{L}$	$\Lambda = \bar{\lambda} / r_p$ and γ
$r_p \ll r_{p,max}$ $\begin{cases} r_p \ll r_p^* \text{-----} \textcircled{1} \\ r_p \gg r_p^* \text{-----} \end{cases}$	$\begin{cases} 3 \left(\Phi_{el,a}^{-1/2} - \frac{1}{2} \right) \phi \bar{f}_B \frac{\bar{\delta}_o r_p^2}{\ell_a^2 r_p^*} \\ 3 \left(\Phi_{el,a}^{-1/2} - \frac{1}{2} \right) \phi \bar{f}_B \frac{\bar{\delta}_o r_p}{\ell_a^2} \end{cases}$	$\Lambda = \frac{1}{2} \left(1 + \sqrt{1 + 4 \Phi_{el,a}^{-1/2}} \right)$ $\gamma = \Lambda^{-1}$
$r_{p,max} \ll r_p \ll \mu_d$ $\begin{cases} r_p \ll r_{p,int} \begin{cases} r_p \ll r_p^* \text{-----} \textcircled{2} \\ r_p \gg r_p^* \text{-----} \end{cases} \\ r_p \gg r_{p,int} \begin{cases} r_p \ll r_p^* \text{-----} \textcircled{3} \\ r_p \gg r_p^* \text{-----} \end{cases} \end{cases}$	$\begin{cases} 3 \phi \bar{f}_B \frac{\bar{\delta}_o r_{p,int}^{3/2} r_p^{1/2}}{\ell_a^2 r_p^*} \\ 3 \phi \bar{f}_B \frac{\bar{\delta}_o r_{p,int}^{3/2} r_p^{-1/2}}{\ell_a^2} \\ 3 \phi \bar{f}_B \frac{\bar{\delta}_o r_{p,int}^{9/2} r_p^{-5/2}}{4 \ell_a^2 r_p^*} \\ 3 \phi \bar{f}_B \frac{\bar{\delta}_o r_{p,int}^{9/2} r_p^{-7/2}}{4 \ell_a^2} \end{cases}$	$\Lambda \sim \left(\frac{r_{p,int}}{r_p} \right)^{3/2}$ $\begin{cases} \Lambda \gg 2 \\ \gamma = \Lambda^{-1} \end{cases}$ $\begin{cases} \Lambda \ll 2 \\ \gamma = 1 + \frac{1}{4} \Lambda^2 \left(\frac{\Lambda}{4} - 1 \right) \end{cases}$

$r_p \gg \mu_d \begin{cases} r_p \ll \tilde{r}_p \\ r_p \gg \tilde{r}_p \end{cases}$	$\begin{aligned} r_p \ll \tilde{r}_p &\begin{cases} r_p \ll r_p^* & \dots 3\phi \bar{f}_B \frac{\bar{\delta}_o \tilde{r}_p^{1/2} r_p^{3/2}}{\ell_a^2 r_p^*} \\ r_p \gg r_p^* & \dots 3\phi \bar{f}_B \frac{\bar{\delta}_o \tilde{r}_p^{1/2} r_p^{1/2}}{\ell_a^2} \end{cases} \\ r_p \gg \tilde{r}_p &\begin{cases} r_p \ll r_p^* & \textcircled{4} \dots 3\phi \bar{f}_B \frac{\bar{\delta}_o \tilde{r}_p^{3/2} r_p^{1/2}}{4\ell_a^2 r_p^*} \\ r_p \gg r_p^* & \textcircled{5} \dots 3\phi \bar{f}_B \frac{\bar{\delta}_o \tilde{r}_p^{3/2} r_p^{-1/2}}{4\ell_a^2} \end{cases} \end{aligned}$	$\Lambda \sim \left(\frac{\tilde{r}_p}{r_p} \right)^{1/2}$ $\begin{aligned} \Lambda &\begin{cases} \Lambda \ll 2 \\ \Lambda \gg 2 \end{cases} \\ \gamma &\begin{cases} \gamma = \Lambda^{-1} \\ \gamma = 1 + \frac{1}{4}\Lambda^2 \left(\frac{\Lambda}{4} - 1 \right) \end{cases} \end{aligned}$
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Table 1. Asymptotic expressions of the lability parameter $\mathcal{L}$ in various regimes of soft particle radius r_p ($z = 0$) and corresponding expressions of the (dimensionless) macroscopic reaction layer thickness $\Lambda = \bar{\lambda} / r_p$ and of the factor γ for geometrical exclusion of NP volume from the reaction layer. The indications **1**, **2**, **3**, **4** and **5** correspond to the particle size domains identified in **Figure 2A**. The length scales $r_{p,\max}$, $r_{p,\text{int}}$, $\tilde{r}_p$, r_p^* and μ_d are defined by $r_{p,\max} = (2\ell\Phi_B\mu_d^2)^{1/3}$, $r_{p,\text{int}} = (\ell\Phi_B\mu_d^2/\Phi_{\text{el},a})^{1/3}$, $\tilde{r}_p = \ell\Phi_B/\Phi_{\text{el},a}$, $r_p^* = \phi\bar{f}_B\ell(1+K_{\text{int}}c_s)$ and $\mu_d = \sqrt{\frac{3D_M(1+K_{\text{int}}c_s)K_{\text{int}}}{k_wV^{\text{os}}N_{\text{Av}}}}\bar{f}_{\text{el},d}$ with $\bar{f}_{\text{el},d} = \bar{f}_{\text{el},a}/\bar{f}_B$, respectively. See text for details.

Figure 2. Typical dependence of the lability parameter $\mathcal{L}$ on particle radius r_p (normalized in panel A by the intraparticle reaction layer thickness μ_d). (A) $K_{\text{int}} = 10 \text{ mol}^{-1} \text{ m}^3$ (typical for Cu(II)-humic acid NPs for a degree of reactive site coverage of 0.03),⁵⁵ $c_s = 7 \times 10^2 \text{ mol m}^{-3}$ (typical for humic acid NPs),⁵⁶ $D_M = 7 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$,⁵⁷ $\bar{f}_B = 10^{4.2}$ (reached for humic acids under salinity conditions between 1 and 10 mM),¹² $\bar{f}_{\text{el,a}} = 1$,^{12,17} $z = 0$ (soft NPs), $k_w = 10^9 \text{ s}^{-1}$ (relevant for Cu(II)),⁵⁴ $V^{\text{OS}} = 0.38 \text{ nm}^3$,¹⁴ $\varphi = 5 \times 10^{-4}$, $\bar{\delta}_0 = 2 \text{ }\mu\text{m}$. The positioning of the key length scales $\tilde{r}_p$, r_p^* , $r_{p,\text{max}}$, $r_{p,\text{int}}$ and μ_d is explicitly indicated together with the applicable asymptotic (power-law) regimes in $\mathcal{L}$ (**Table 1**) and with the associated domains 1 to 5 detailed in the text, §3. For the sake of illustration the dependence of $\mathcal{L}$ on r_p / μ_d is provided with ignoring NPs volume exclusion effects (*i.e.* $\gamma = 0$, black dashed line). Dependence of $\mathcal{L}$ on r_p for various values of φ (B), for values of k_w ($= 3 \times 10^4 \text{ s}^{-1}$, $7 \times 10^7 \text{ s}^{-1}$, $3 \times 10^8 \text{ s}^{-1}$, 10^9 s^{-1} and $7 \times 10^9 \text{ s}^{-1}$ for Ni(II), Zn(II), Cd(II), Cu(II) and Pb(II), respectively)⁵⁴ (C), for values of $z = a / r_p$ (D), K_{int} (in $\text{mol}^{-1} \text{ m}^3$) (E) and $\bar{f}_B$ (F), other model parameters as in (A). In all cases, the relevant characteristic asymptotic regimes in $\mathcal{L}$ (see **Table 1**) are given. In order to simplify the analysis of the impact of k_w on $\mathcal{L}$ (panel C), it is stressed that K_{int} is kept constant for all metal ions tested, which refers to model rather than practical situations.

Figure 2A highlights that the non-monotonous variation of $\mathcal{L}$ with particle size closely follows that predicted on the basis of the relevant asymptotic power-law expressions listed in **Table 1** given the applicable sequence $\tilde{r}_p < r_{p,\max} < r_{p,\text{int}} < \mu_d < r_p^*$. Namely, 5 domains of particle sizes may be formally distinguished (see **Figure 2A**): domain 1 with $\mathcal{L} \propto r_p^2$ for $r_p \ll r_{p,\max}$, domain 2 with $\mathcal{L} \propto r_p^{1/2}$ over the restricted range $r_{p,\max} \ll r_p \ll r_{p,\text{int}}$, domain 3 with $\mathcal{L} \propto r_p^{-5/2}$ for $r_{p,\text{int}} \ll r_p \ll \mu_d$, domain 4 with $\mathcal{L} \propto r_p^{1/2}$ for $\mu_d \ll r_p \ll r_p^*$, and finally domain 5 with $\mathcal{L} \propto r_p^{-1/2}$ for $r_p^* \ll r_p$. Qualitatively, the intricate evolution of $\mathcal{L}$ from domain 1 to 4 is reminiscent of that previously discussed for the macroscopic reaction layer thickness $\bar{\lambda}$ because here $\mathcal{L}$ exhibits a local maximum and a minimum in the vicinity of $r_p = r_{p,\max}$ and $r_p = \mu_d$, respectively. The dependence of $\mathcal{L}$ on r_p thus basically reflects that of $\bar{\lambda}$ detailed by eq. (10). The shift between the two in the r_p -domains 1 to 4 stems from the contribution of the term $(1-\gamma)r_p$, which is inferred from eq. (9) taken in the limit $r_p \ll r_p^*$. It is stressed that the lability parameter measured and successfully predicted from eqs (1)-(3) for the system Cd(II)-latex NP (71 nm in radius)^{2,29} corresponds to domain 3 identified above. Recognizing that domain 1 corresponds to the expected increase of $\mathcal{L}$ upon moving from the molecular to nanoparticulate ligand situations (due to decreasing J_{diff} that follows decreasing D_p), the maximum between domains 1-2 and 3 is supported by experimental finding.

In detail, comparison to predictions obtained with $\gamma = 0$ reveals that domain 1 is not affected by the exclusion of the NP body volume from the reaction layer. This feature is in agreement with the magnitude of $1-\gamma \ll 1$ at such low r_p and with the poor dependence of Λ on γ in this particle size regime given $\Phi_{\text{el,a}} \ll 1$.²⁹ Exclusion becomes significant only for $r_p > r_{p,\max}$ via the term $1-\gamma$ in the lability expression (eq. (9)). This arises because exclusion has become immaterial in defining the reaction layer thickness (or Λ), i.e. with increasing the particle size the term k_d/D_p becomes the only significant one in eq. (2). Domain 5 ($r_p/r_p^* \gg 1$) originates from the fact that the diffusion flux J_{diff} then becomes independent of r_p and reduces to the maximum achievable limiting flux $D_M c_M^* / \bar{\delta}_0$, which is, in fact, the limiting non-labile flux. The contribution of the metal-NP carriers to J_{diff} thus becomes immaterial due to their sluggish diffusion at such large r_p within the time scale of M accumulation at the sensor (i.e. NP

diffusive transport is effectively ‘frozen’ in this time window). Accordingly, the dependence of the lability parameter on r_p in domain 5 becomes solely dictated by that of the kinetic flux, *i.e.* $J_{\text{kin}} \propto (1-\gamma)\bar{\lambda} \propto r_p^{-1/2}$. It is noted that in the extreme $D_p \rightarrow 0$ reached at sufficiently large (infinite) r_p (upper limit of domain 5), $\mathcal{L}$ would go to infinity if the free metal contribution to J_{diff} in eq. (3) is ignored (the intuitive labile limit). However, in such an extreme case, the NP exclusion from the reaction layer of thickness $\bar{\lambda}$ is quasi-complete²⁹ and the kinetic flux J_{kin} should tend to zero (the reasoning discards the obvious impact of particle sedimentation at $D_p \rightarrow 0$ or equivalently $r_p \rightarrow \infty$). In turn, the lability parameter $\mathcal{L}$ becomes mathematically ill-defined in the limit $D_p \rightarrow 0$ when ignoring the term $D_M c_M^*$ in eq. (3). The current formulation with integration of the term $D_M c_M^*$ does not reproduce such ill-defined lability parameter at $D_p \rightarrow 0$. This feature, together with the elements provided in §2, further support the correctness of eqs. (1)-(3).

3.3. Dependence of the lability of soft/core-shell nanoparticulate metal complexes on the physicochemical and chemodynamic factors pertaining to M-NP complexes.

In this section, the particle size-dependent lability parameter of soft/core-shell M-NP complexes is analysed over a range of practical values for relevant physicochemical NP characteristics involved in eq. (9) (*e.g.* $\bar{f}_B$) and of the factors therein that determine M-NP chemodynamics (*e.g.* k_w). For the sake of comparison between these various conditions, the corresponding $\mathcal{L}$ is now represented as a function of r_p and not r_p / μ_d (as in **Figure 2A**) because the reaction layer thickness μ_d itself depends on these conditions (see §3.1). The analysis is therefore restricted to NP size from 1 nm to 1 μm , which does not necessarily cover the whole spectrum of r_p / μ_d values with all lability domains identified in **Figure 2A**.

The extent to which the lability parameter of M-NP complexes at the macroscopic sensor/medium interface is affected by the NP volume fraction φ depends on the particle size (**Figure 2B**). In domain 1 identified in **Figure 2A** ($\mathcal{L} \propto r_p^2$), increasing φ leads to a loss of lability in line with $\mathcal{L} \propto 3(\Phi_{\text{el,a}}^{-1/2})\varphi / r_p^* \propto \varphi^{-1/2}$ (see **Table 1** with $r_p^* \propto \varphi$ and $\Phi_{\text{el,a}} \propto \varphi$). Qualitatively, this feature applies to the lability of molecular complexes ML upon increasing φ or, equivalently, upon increasing the bulk concentration of ligands L, c_L^* . The decreasing lability parameter with increasing φ basically originates

from the associated decrease in the dissociation reaction layer thickness $\left(D_M / (k_{a,p} \bar{c}_s^\lambda)\right)^{1/2}$, recalling that $\bar{c}_s^\lambda \propto \varphi$ in domain 1 where $\gamma \neq 0$ (eq. (4) and **Figure 2A**). In domains 2 and 3, $\mathcal{L}$ is independent of φ (**Table 1**) and the transition between domains 1 and 3 takes the form of a sharp maximum with increasing φ . The onset of domain 4 is reached for $r_p > \mu_d$ (≈ 200 nm under the conditions of **Figure 2B**) and for sufficiently large φ ($\geq 10^{-4}$). In this domain, $\mathcal{L}$ is nearly independent of φ , which is in agreement with the asymptotic result in **Table 1**. For decreasing φ below 10^{-4} and $r_p > 200$ nm, the onset of domain 5 appears as domain 4 becomes immaterial due to the decreasing applicability of the inequality $r_p \ll r_p^*$ (recalling that $r_p^* \propto \varphi$) in the particle size range $r_p > \mu_d$ (see **Table 1**). Altogether, at sufficiently large particle size, a gain in lability is achieved with increasing φ . The opposite impacts of φ on $\mathcal{L}$ at sufficiently low (domain 1) and large particle sizes (domain 5) are explained by the differentiated dependences of J_{diff} and J_{kin} on φ in these respective size windows: $J_{\text{kin}} \propto \varphi^{1/2} \left(\bar{c}_s^\lambda \right)^{-1/2} \times \bar{c}_{\text{MS}}^\lambda$ and $J_{\text{diff}} \propto \varphi \left(\bar{c}_{\text{M,MS}} \right)$ in domain 1, whereas $J_{\text{kin}} \propto \varphi \left(\bar{c}_{\text{MS}}^\lambda \right)$ in domain 5 (where the associative reaction layer term k_d / D_p dominates) with J_{diff} independent of φ in this latter domain (the limiting non-labile flux).

Figure 2C highlights the modification of the dependence of the lability parameter of metal complexes on r_p for the metal sequence Ni(II), Zn(II), Cd(II), Cu(II), Pb(II) with increasing values of the dehydration rate constant k_w from 3×10^4 to $7 \times 10^9 \text{ s}^{-1}$.⁵⁴ Obviously domain 1, where we have $\mathcal{L} \propto r_p^2$, is shifted to lower particle sizes as k_w increases from the Ni(II) to the Pb(II) case. In line with **Table 1**, this shift is due to the decrease of $r_{p,\text{max}} = \left(2\Phi_B \mu_d^2 \ell\right)^{1/3}$ with k_w having in mind that $\mu_d^2 \propto 1/k_w$ (§C1). At sufficiently low r_p where domain 1 applies over the complete metal sequence examined, the lability of M-NP complexes increases from Ni(II) to Pb(II), which is consistent with $\mathcal{L} \propto 1/\ell_a^2$ (**Table 1**) and $1/\ell_a^2 \propto k_w$ (§3.1), and in qualitative agreement with data from literature.⁵⁸ From a physicochemical point of view, the larger is k_w , the faster is the rate constant $k_d^{\text{is}} (= k_a^{\text{is}} / K_{\text{int}} \propto k_w)$ for chemical dissociation of MS complexes, and thus the larger is the dissociation kinetic flux J_{kin} (eq. (1)) compared to J_{diff} and

hence the greater is the lability parameter of the complexes. Putting aside the case of Ni(II) ions, the aforementioned increase in lability with increasing k_w is qualitatively observed in domain 4 ($\mathcal{L} \propto r_p^{1/2}$) which is reached at sufficiently large r_p values as compared to μ_d . This point marks the position of the local minimum in $\mathcal{L}$. In domain 3 ($\mathcal{L} \propto r_p^{-5/2}$) that makes the transition between domains 1-2 and 4, the lability decreases with increasing k_w . This finding may be counter-intuitive given that an increase in k_w results in increasing values of k_d^{is} ,¹³ from which it could be anticipated that $\mathcal{L}$ increases due to increasing J_{kin} . Instead, the observed decrease of $\mathcal{L}$ with k_w is in agreement with the scaling $\mathcal{L} \propto k_w^{-1/2}$ obtained after substituting the k_w -dependent expressions of $r_{p,int}$ and ℓ_a in the asymptotic result displayed in **Table 1** for domain 3. The physicochemical basis for this ‘reversed’ dependence of $\mathcal{L}$ on k_w in domains 1,4 and in domain 3 lies in the distinct variations of the exclusion factor γ with changing k_w in these respective NP size regimes. In domains 1 and 4, NP exclusion is independent of k_w because the limits of insignificant and complete NP exclusion from the macroscopic reaction layer are nearly reached, respectively. In contrast, domain 3 is that where γ increases with k_w . Indeed, the larger is k_w (or the smaller is μ_d) for this range of r_p , the thinner is the reaction layer thickness $\bar{\lambda}$ ²⁹ (see Figure 6 in Ref. [29]) and thus the more significant becomes the NP exclusion from that layer. In turn, this leads to a noticeable decrease of the kinetic flux J_{kin} and consequently of the lability of the metal complexes. This decrease overwhelms the k_w -mediated increase of J_{kin} and $\mathcal{L}$ which governs the trends found in domains 1 and 4. For very slowly dehydrating Ni(II) ions, the corresponding k_w value leads to a domain 3 that does not overlap the ones pertaining to the other metal ions, and to a domain 4 that is unachievable over the range of particle sizes analyzed.

The impact of the core to particle radius ratio $z = a/r_p$ on M-NP lability is illustrated in **Figure 2D**. Qualitatively, the lability parameter $\mathcal{L} \propto 1 - \gamma$ (eq. (9)) increases with increasing z in the intermediate domain 3 identified for soft NPs in **Figure 2A** mainly because the extent of NP exclusion from the macroscopic reaction layer decreases from soft ($z = 0$) to hard NP ($z = 1$) types at fixed r_p .²⁹ Since domain 1 is independent of γ (**Figure 2A**), lability is not impacted by z provided that r_p is sufficiently small compared to $r_{p,max}$. In domain 3, $\mathcal{L}$ further evolves from $\propto r_p^{-5/2}$ for soft NPs (**Table 1**) to $\propto r_p^{-1}$ for $z \rightarrow 1$. The latter scaling is in agreement with the results given in §4 for hard NPs in the relevant size

regime $r_{p,\max} \ll r_p \ll \mu_d$, $r_p \gg r_{p,\text{int}}$ and $r_p \ll r_p^*$ (see **Table 2**, §4). At sufficiently large r_p well beyond $1\ \mu\text{m}$, $\mathcal{L}$ becomes independent of z (not shown) essentially because the asymptotic limit $\gamma \rightarrow 1$ is reached regardless of the NP type considered. Under the conditions of **Figure 2C**, the above influence of z -dependent NP exclusion on lability dominates the impact of the term $1 - z^3$ that appears in eq. (9) following the required averaging of intraparticulate M and MS concentrations over the whole dispersion volume.

The way in which the stability constant K_{int} of MS affects $\mathcal{L}$ is displayed in **Figure 2E**. The reported trends are basically similar to those detailed in **Figure 2C** where the effects observed upon *increasing* k_w from Zn(II) to Pb(II) are qualitatively recovered in **Figure 2E** for *decreasing* values of K_{int} . The reason for such an equivalence is explained by realizing that $k_d^{\text{is}} = k_a^{\text{is}} / K_{\text{int}} \propto k_w$ in eq. (9). The transitions between domains 1-2, 3 and 4 (if applicable) are determined by the shifts of $r_{p,\max}$, $r_{p,\text{int}}$, μ_d and r_p^* that all depend on K_{int} (§3.1 and §3.2). **Figure 2F** shows how increasing values of the Boltzmann partitioning factor $\bar{f}_B$ (with $\bar{f}_B > 1$, *i.e.* negatively charged NPs are considered) significantly increase M-NP complex lability, especially at large r_p values (*i.e.* in domains 3, and 4 or 5 depending on the shift of $r_{p,\max}$, $r_{p,\text{int}}$, μ_d and r_p^* with $\bar{f}_B$) where $J_{\text{diff}} = (D_M c_M^* / \bar{\delta}_o) (1 + r_p^* / r_p)$ poorly depends on $r_p \propto \bar{f}_B$. After analysing the contributions of all $\bar{f}_B$ -dependent terms in eq. (9), it is found that this lability feature at large r_p originates from the increase of J_{kin} with $\bar{f}_B$ due to the associated increase in (i) the intraparticulate MS concentration that follows a significant electrostatically-mediated accumulation of M in the NP body, and (ii) the mean path $(D_p / k_d)^{1/2} \approx \bar{\lambda}$ of M-NP complexes due to retardation of the divergent diffusion of M away from the NP body with increasing $\bar{f}_B$ (we recall here that $k_d \rightarrow k_{d,p} \propto 1 / \bar{f}_B$ at sufficiently large r_p , see Ref. [17]). Finally, the change in $\mathcal{L}$ with increasing concentration of metal binding sites density c_s at fixed $\bar{f}_B$ (not shown) is found to qualitatively follow the trend discussed in **Figure 2F** with decreasing $\bar{f}_B$ at fixed c_s . Indeed, both situations lead to decreasing reaction layer thickness $(D_p / k_d)^{1/2} \approx \bar{\lambda}$ at large r_p where $k_d \rightarrow k_{d,p} \propto 1 + K_{\text{int}} c_s$,¹⁷ *i.e.* a decrease in J_{kin} and a loss of M-NP lability.

4. Theory: The case of 2D (hard) nanoparticulate ligands.

Following the methodology detailed in §3.1 for 3D soft/core-shell NPs, and considering the proper chemodynamic properties of metal complexes formed with 2D hard NPs type ($z=1$) as derived elsewhere,¹⁷ we obtain after some algebra (see Supporting Information, §II, for details) the reduced expression of the lability parameter $\mathcal{L}$ for M-(2D hard) NP complexes

$$\mathcal{L} = 3\phi f_B [1 - \gamma(\Lambda)] \frac{\bar{\delta}_o}{\ell_a} \Lambda \left[1 + \left(\frac{r_p^*}{r_p} \right)^2 \right]^{-1} \quad (13)$$

, where r_p^* is now defined by $r_p^* = \left(3\phi f_B \ell K_H \frac{1 + K_{\text{int}}^{(z=1)} \Gamma_s}{K_{\text{int}}^{(z=1)} \Gamma_s} \right)^{1/2}$ with $K_{\text{int}}^{(z=1)}$ ($\text{mol}^{-1} \text{m}^2$) the intrinsic stability constant of MS surface complexes, K_H (m) the Henry adsorption coefficient for M at the NP surface, and $\ell_a = D_M / (k_w V^{\text{os}} N_{\text{Av}} \Gamma_s)$.¹⁷ The exclusion factor γ remains defined by eq. (5) in the limit $z \rightarrow 1$ ²⁹ and the dimensionless reaction layer $\Lambda = \bar{\lambda} / r_p$ by eq. (10) after systematic replacement of the quantities $\bar{f}_{\text{el},a}$, $\bar{f}_B$, K_{int} and $K_{\text{int}} c_s$ by their 2D equivalents $f_{\text{el},a}$, f_B , K_H / Γ_s and $K_{\text{int}}^{(z=1)} \Gamma_s$, respectively.²⁹ We specify that the reaction layer thickness ℓ_a relevant at the 2D NP level should be here conceived as the thickness of the reaction layer inside the surface layer containing all binding sites and where M may move freely in between the sites S in the 2D lattice layer.¹⁷ In that respect, it is stressed that the ‘surface layer’ in case of hard NPs has generally a given thickness. The volume of that layer is defined by two concentric surfaces defining the mean position of the outer binding sites (facing the outer electrolyte solution) and the inner binding sites close to the hard NP surface. The existence of such a surface layer with finite thickness is tied to the non-ideality of hard NPs due to their roughness (that varies with *e.g.* NP aging). Best experimental evidence of this feature is the fact that the electrophoretic properties of supposedly hard NPs are actually in line with that expected for soft NPs with nanometric shell layer permeable to ions and water.^{59,60}

It is further found that the general expression eq. (5) defining γ simplifies for 2D hard NPs according to²⁹

$$\gamma(\Lambda, z=1) = \begin{cases} 1 - \frac{\Lambda}{4}, & \text{for } \Lambda < 2 \\ \Lambda^{-1}, & \text{for } \Lambda \geq 2 \end{cases} \quad (14)$$

For the practical limit $\Phi_{\text{el,a}} \ll 1$ (*i.e.* $\varphi \ll 1$) where the exclusion factor γ may impact on the reaction layer thickness only at sufficiently small particle size r_p ,²⁹ $\bar{\lambda}$ further remains approximated for 2D hard NP types by eq. (12) pending use of the equivalence invoked above between factors involved in the chemodynamics of metal complexes formed with 3D soft/core-shell NPs and 2D hard NPs. As in §3.2, these analytical expressions for γ (eq. (14)) and $\bar{\lambda}$ (or equivalently $\Lambda = \bar{\lambda} / r_p$) are then substituted into eq. (13) to derive the sought scaling laws for the lability parameter $\mathcal{L}$ for surface metal complexes at a macroscopic medium/sensor interface. The results are collected in **Table 2** and may be used in conjunction with the rigorous eq. (13) to decipher the contributions of all processes governing $\mathcal{L}$ along the lines detailed in **Figure 2** for 3D soft/core-shell NPs. Given the strong analogy mentioned earlier between 3D and 2D NP cases, the results obtained for 2D hard NPs are provided in Supporting Information (**Figure S1**, §III). We report here **Figure 3** that supports the derivation of the exact (eq. (13)) and approximate (**Table 2**) lability expressions evaluated under the realistic conditions detailed in the figure caption. Comparison with predictions where geometrical exclusion of NP from the macroscopic reaction layer is discarded is further given and conclusions given in **Figure 2A** concerning the paramount importance of that exclusion process still hold for 2D hard NPs. The conditions adopted in **Figure 3** are in line with shallow extrema of $\bar{\lambda}$ at $r_p = r_{p,\text{max}}$ and $r_p = \mu_d$, which explains the absence of extrema in the dependence of $\mathcal{L}$ on r_p in domains 1 to 3 identified in **Figure 3**. Again, the domain reached at large particle size ($r_p \gg r_p^*$) corresponds to that where $J_{\text{diff}} \rightarrow (D_M c_M^* / \bar{\delta}_o)$.

Particle size range	Lability $\mathcal{L}$	$\Lambda = \bar{\lambda}/r_p$ and γ
$r_p \ll r_{p,\max}$ <div> $r_p \ll r_p^* \dots\dots\dots \textcircled{1}$ $r_p \gg r_p^* \dots\dots\dots$ </div>	$3 \left(\Phi_{\text{el},a}^{-1/2} - \frac{1}{2} \right) \phi f_B \frac{\bar{\delta}_o r_p^2}{\ell_a r_p^{*2}}$ $3 \left(\Phi_{\text{el},a}^{-1/2} - \frac{1}{2} \right) \phi f_B \frac{\bar{\delta}_o}{\ell_a}$	$\Lambda = \frac{1}{2} \left(1 + \sqrt{1 + 4 \Phi_{\text{el},a}^{-1/2}} \right)$ $\gamma = \Lambda^{-1}$
$r_{p,\max} \ll r_p \ll \mu_d$ <div> $r_p \ll r_{p,\text{int}}$ <div> $r_p \ll r_p^* \dots\dots\dots \textcircled{2}$ $r_p \gg r_p^* \dots\dots\dots$ </div> $r_p \gg r_{p,\text{int}}$ <div> $r_p \ll r_p^* \dots\dots\dots$ $r_p \gg r_p^* \dots\dots\dots$ </div> </div>	$3 \phi f_B \frac{\bar{\delta}_o r_{p,\text{int}}^{3/2} r_p^{1/2}}{\ell_a r_p^{*2}}$ $3 \phi f_B \frac{\bar{\delta}_o r_{p,\text{int}}^{3/2} r_p^{-3/2}}{\ell_a}$ $3 \phi f_B \frac{\bar{\delta}_o r_{p,\text{int}}^3 r_p^{-1}}{4 \ell_a r_p^{*2}}$ $3 \phi f_B \frac{\bar{\delta}_o r_{p,\text{int}}^3 r_p^{-3}}{4 \ell_a}$	$\Lambda \sim \left(\frac{r_{p,\text{int}}}{r_p} \right)^{3/2}$ $\Lambda \gg 2$ $\gamma = \Lambda^{-1}$ $\Lambda \ll 2$ $\gamma = 1 - \frac{\Lambda}{4}$
$r_p \gg \mu_d$ <div> $r_p \ll \tilde{r}_p$ <div> $r_p \ll r_p^* \dots\dots\dots$ $r_p \gg r_p^* \dots\dots\dots$ </div> $r_p \gg \tilde{r}_p$ <div> $r_p \ll r_p^* \dots\dots\dots \textcircled{3}$ $r_p \gg r_p^* \dots\dots\dots \textcircled{4}$ </div> </div>	$3 \phi f_B \frac{\bar{\delta}_o \tilde{r}_p^{1/2} r_p^{3/2}}{\ell_a r_p^{*2}}$ $3 \phi f_B \frac{\bar{\delta}_o \tilde{r}_p^{1/2} r_p^{-1/2}}{\ell_a}$ $3 \phi f_B \frac{\bar{\delta}_o \tilde{r}_p r_p}{4 \ell_a r_p^{*2}}$ $3 \phi f_B \frac{\bar{\delta}_o \tilde{r}_p r_p^{-1}}{4 \ell_a}$	$\Lambda \sim \left(\frac{\tilde{r}_p}{r_p} \right)^{1/2}$ $\Lambda \gg 2$ $\gamma = \Lambda^{-1}$ $\Lambda \ll 2$ $\gamma = 1 - \frac{\Lambda}{4}$

Table 2. Asymptotic expressions of the lability parameter $\mathcal{L}$ in various regimes of hard particle radius r_p ($z = 1$) and corresponding expressions of the (dimensionless) macroscopic reaction layer thickness $\Lambda = \bar{\lambda}/r_p$ and of the factor γ for exclusion of the NPs from the reaction layer. The indications **1**, **2**, **3** and **4** correspond to the particle size domains identified in **Figure 3**. The length scales $r_{p,\max}$, $r_{p,\text{int}}$, $\tilde{r}_p$, r_p^* and μ_d are defined by

$$r_{p,\max} = \left(2 \ell \Phi_B \mu_d^2 \right)^{1/3}, \quad r_{p,\text{int}} = \left(\ell \Phi_B \mu_d^2 / \Phi_{\text{el},a} \right)^{1/3}, \quad \tilde{r}_p = \ell \Phi_B / \Phi_{\text{el},a}, \quad r_p^* = \left(3 \phi f_B \ell K_H \frac{1 + K_{\text{int}}^{(z=1)} \Gamma_s}{K_{\text{int}}^{(z=1)} \Gamma_s} \right)^{1/2} \quad \text{and}$$

$$\mu_d = \sqrt{\frac{3 D_M K_H \left(1 + K_{\text{int}}^{(z=1)} \Gamma_s \right)}{k_w V^{\text{os}} N_{\text{Av}} \Gamma_s}} f_{\text{el},d} \quad \text{with } f_{\text{el},d} = f_{\text{el},a} / f_B, \text{ respectively. See text for details.}$$

Figure 3. Typical dependence of the lability parameter $\mathcal{L}$ on hard particle radius r_p normalized by the intraparticle reaction layer thickness μ_d . $K_{\text{int}}^{(z=1)} = 10^5 \text{ mol}^{-1} \text{ m}^2$, $K_H = 2 \times 10^{-4} \text{ m}$, $\Gamma_s = 1.7 \times 10^{-7} \text{ mol m}^{-2}$ (*i.e.* 1 site S per 10 nm^2), $D_M = 7 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$,⁵⁷ $\bar{f}_B = 10^{3.5}$,¹² $\bar{f}_{\text{el,a}} = 1$,^{12,17} $k_w = 10^9 \text{ s}^{-1}$ (relevant for Cu(II)),⁵⁴ $V^{\text{os}} = 0.38 \text{ nm}^3$,¹⁴ $\varphi = 5 \times 10^{-4}$, $\bar{\delta}_0 = 2 \text{ }\mu\text{m}$. The positioning of the key length scales $\tilde{r}_p$, r_p^* , $r_{p,\text{max}}$, $r_{p,\text{int}}$ and μ_d is explicitly indicated together with the applicable asymptotic regimes in $\mathcal{L}$ (Table 2) associated with the domains 1 to 4 identified in Table 2. For the sake of illustration the dependence of $\mathcal{L}$ on r_p / μ_d is provided with ignoring NPs volume exclusion effects (*i.e.* $\gamma = 0$, black dashed line).

5. Conclusion.

In this work, reduced expressions are provided to describe the lability parameter of nanoparticulate metal complexes at a macroscopic metal-sensing (bio)interface. The analysis is supported by tractable scaling laws derived for the lability parameter $\mathcal{L}$ as a function of particulate ligand size in the extremes of volume and surface binding site distributions applicable for 3D soft NPs and 2D hard NPs, respectively. This rationale allows the identification of the respective contributions of the various factors that control the lability of M-NP complexes, namely: the (intertwined) exclusion of the NP reactive body/surface from the reaction layer, the chemodynamics of M-NP dissociation, the extension of the macroscopic reaction layer from the sensor surface, the defining NP physicochemical properties and the NP volume fraction in the dispersion. The results evidence that the lability parameter of M-NP complexes is generally *not* an increasing function of particle size, a trend that could be anticipated on the sole basis of the associated decrease in the diffusion flux of the particulate metal-carriers. This major remarkable result is a fundamental consequence of the geometric exclusion of the NP from the reaction layer. This phenomenon dramatically affects the dissociative flux of M released by the NP complexant to the sensor/medium interface. The exclusion process is a characteristic feature of NP complexants for which the metal binding sites are inherently confined within/at particle body/surface. Such phenomena were obviously not included in the conventional Koutecký-Koryta reaction layer approach that was developed for molecular systems.

In a forthcoming study, the here-detailed concepts leading to the derivation of the lability parameter for a M-NP system at a metal-responsive sensor surface will be compared with rigorous solution of the coupling between Nernst-Poisson-Planck equations formulated at the NP scale and corrected for chemical kinetic terms over the relevant intraparticulate shell spatial region, *and* at the scale of the solution adjacent to the macroscopic sensor. Such comparison could lead to *e.g.* refinement of the expression for the reaction layer thickness relevant for the M-NP system at the sensor/medium interface. The formulation proposed here offers a way to implement this difficult scaling from the relevant nanometric to macroscopic scales.

To date, attempts to describe the impact of NPs on biota are generally restricted to elaborations of *ad hoc* empirical or statistical relationships between measured bio-indicators and bulk metal concentrations.⁶¹⁻⁶³ Such formulations ignore the fundamental interplay between nanometric and macroscopic kinetic- and transport-determining processes that are intimately connected to the physicochemical features of the complexing nanoparticles or colloids. The theoretical lability framework detailed herein opens perspectives for understanding - on a *mechanistic* level - the extent by which environmental or anthropogenic nanoparticles and colloids in natural waters control (i) the speciation and bioavailability of metal ions toward biological organisms or compartments (*e.g.* bacteria, algae, fish gills, etc) and (ii) therewith, the magnitude of metal biouptake and ensuing bioavailability of essential or therapeutic compounds, or deleterious effects in the case of toxic compounds. The results reported here have thus far-reaching implications for understanding the reactivity of NPs in environmental and biological media beyond the trivial perspective of their large specific surface area.

Supporting Information

I. Definition of the function F involved in eq. (5). II. Detailed derivation of eq. (13). III. Illustrative dependence of the lability parameter of hard nanoparticulate metal complexes on the physicochemical and chemodynamic factors pertaining to M-(2D)NP complexes (Figure S1). The Supporting Information is available free of charge on the ACS Publications website.

Conflicts of interest.

There are no conflicts of interest to declare.

Acknowledgements.

RMT conducted this work within the framework of the EnviroStress Center of Excellence at the University of Antwerp and with financial support from the BELSPO AquaStress and the UA IOF-SBO Waterside projects. JFLD acknowledges the financial support from the French national programme EC2CO-Ecodyn/MicrobiEen (TOXSCALE project).

Glossary of main symbols

Latin

a Particle core radius [m]

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2
3 d Particle shell thickness [m]
4 c_s Density of binding sites S within the particle shell volume (applicable for 3D NP complexants) [mol m⁻³]
5 $\bar{c}_s$ Density of binding sites S smeared-out over the sample volume [mol m⁻³]
6
7 c_M^* Bulk concentration of metal ions M [mol m⁻³]
8 c_M Concentration of intraparticulate free metal ions M [mol m⁻³]
9 $\bar{c}_M$ Concentration of intraparticulate free metal ions smeared-out over the sample volume [mol m⁻³]
10 c_{MS} Concentration of intraparticulate complex metal species MS [mol m⁻³]
11 $\bar{c}_{MS}$ Concentration of complexes MS smeared-out over the sample volume [mol m⁻³]
12
13 D_M Diffusion coefficient of M [m² s⁻¹]
14
15 D_p Diffusion coefficient of the nanoparticle [m² s⁻¹]
16
17 $f_{el,a}$ Factor for conductive diffusion of M to the surface of 2D hard nanoparticulate complexant
18 $\bar{f}_{el,a}$ Factor for conductive diffusion of M to the reactive component of 3D nanoparticulate complexant
19 $f_{el,d}$ Factor for conductive diffusion of M from the surface of hard nanoparticulate complexant
20 $\bar{f}_{el,d}$ Factor for conductive diffusion of M from the reactive volume of 3D nanoparticulate complexant
21
22 f_B Factor for Boltzmann accumulation of M at the surface of 2D nanoparticulate complexant
23 $\bar{f}_B$ Factor for volume-averaged Boltzmann accumulation of M in the reactive component of 3D nanoparticulate
24 complexant
25 J_{kin} Kinetic flux arising from the rate of dissociation of complexed species [mol m² s⁻¹]
26 J_{diff} Diffusive flux arising from the diffusion of all forms of the metal towards a reactive macrointerface [mol m² s⁻¹]
27 k_a Kinetic constant for M-NP formation [mol⁻¹ m³ s⁻¹]
28 k_d Kinetic constant for M-NP dissociation [s⁻¹]
29 k_a^{is} Kinetic constant for inner-sphere MS formation [mol⁻¹ m³ s⁻¹]
30 k_d^{is} Kinetic constant for inner-sphere MS dissociation [s⁻¹]
31 $k_{a,p}$ Kinetic constant for M conductive diffusion to intraparticulate or surface binding sites S [mol⁻¹ m³ s⁻¹]
32 $k_{d,p}$ Kinetic constant for M conductive diffusion from intraparticulate or surface binding sites S [s⁻¹]
33
34 k_w Kinetic constant for inner-sphere dehydration of M^{z+} [s⁻¹]
35 $K_{int}, K_{int}^{(z=1)}$ Intrinsic stability constant for inner-sphere metal complexes in 3D complexing nanoparticles [mol⁻¹ m³] or at the
36 surface of 2D nanoparticles (superscript ‘ $z=1$ ’, [mol⁻¹ m²])
37 K_H Henry coefficient for adsorption of M at the surface of 2D complexing nanoparticles [m]
38 $\mathcal{L}$ Lability parameter of metal complexes (defined as the ratio between J_{kin} and J_{diff})
39 ℓ Defined by $\ell = k_B T / (6\pi\eta D_M)$ (derived from Stokes-Einstein equation)
40 ℓ_a Thickness of intraparticulate dissociation reaction layer devoid of electrostatic contribution [m]
41 ℓ_c Characteristic separation distance between structural charges carried by NPs [m]
42 M Metal ion
43 M-NP Metal-nanoparticle complex
44 MS Inner-sphere complex
45 NP Nanoparticulate complexant
46 r_p Particle radius $a + d$ [m]
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60

$r_{p,\max}$ Defined by $r_{p,\max} = \left(2\ell\Phi_B\mu_d^2\right)^{1/3}$ [m]

r_p^* Defined by $r_p^* = \varphi\bar{f}_B\ell\left(1-z^3\right)\left(1+K_{\text{int}}c_s\right)$ [m] for $0 \leq z < 1$ and $r_p^* = \left(3\varphi\bar{f}_B\ell K_H \frac{1+K_{\text{int}}^{(z=1)}\Gamma_s}{K_{\text{int}}^{(z=1)}\Gamma_s}\right)^{1/2}$ [m]

for $z = 1$

$r_{p,\text{int}}$ Defined by $r_{p,\text{int}} = \left(\ell\Phi_B\mu_d^2 / \Phi_{\text{el},a}\right)^{1/3}$ [m]

$\tilde{r}_p$ Defined by $\tilde{r}_p = \ell\Phi_B / \Phi_{\text{el},a}$ [m]

S Metal binding site

V^{os} Outer-sphere volume per site S [m^3]

z_M Valence of M

z Defined by the ratio a / r_p

Greek

γ Factor for NP body exclusion from the macroscopic reaction layer ($0 \leq \gamma \leq 1$)

Γ_s Surface density of metal binding sites S (applicable for 2D complexing nanoparticles)

$\bar{\delta}_0$ Thickness of the macroscopic diffusion layer at the sensor/medium interface

$1/\kappa$ Thickness of extraparticulate electric double layer [m]

$\bar{\lambda}$ Macroscopic reaction layer thickness [m]

Λ Dimensionless ratio defined by $\bar{\lambda} / r_p$

μ_d Intraparticulate reaction layer thickness with regard to association process (including NP electrostatic effects)[m]

φ Particle volume fraction

$\Phi_{\text{el},a}; \Phi_B$ Dimensionless numbers involved in the expressions of $\bar{\lambda}$ and Λ

References.

- (1) van Leeuwen, H. P.; Buffle, J.; Duval, J. F. L.; Town, R. M. Understanding the extraordinary ionic reactivity of aqueous nanoparticles. *Langmuir* **2013**, 29 (33), 10297–10302.
- (2) Leeuwen, H. P. van; Duval, J. F. L.; Pinheiro, J. P.; Blust, R.; Town, R. M. Chemodynamics and bioavailability of metal ion complexes with nanoparticles in aqueous media. *Environ. Sci. Nano* **2017**, 4 (11), 2108–2133.
- (3) Díaz, S. A.; Sen, S.; Boeneman Gemmill, K.; Brown, C. W.; Oh, E.; Susumu, K.; Stewart, M. H.; Breger, J. C.; Lasarte Aragonés, G.; Field, L. D.; Deschamps, J. R.; Král, P.; Igor L. Medintz, I. L. Elucidating surface ligand-dependent kinetic enhancement of proteolytic activity at surface-modified quantum dots. *ACS Nano* **2017**, 11 (6), 5884–5896.
- (4) Martín-de-Lucía, I.; C. Campos-Mañas, M.; Agüera, A.; Rodea-Palomares, I.; Pulido-Reyes, G.; Leganés, F.; Fernández-Piñas, F.; Rosal, R. Reverse trojan-horse effect decreased wastewater toxicity in the presence of inorganic nanoparticles. *Environ. Sci. Nano* **2017**, 4 (6), 1273–1282.
- (5) Rahban, M.; Divsalar, A.; Saboury A. A.; Golestani A. Nanotoxicity and spectroscopy studies of silver nanoparticle: calf thymus DNA and K562 as targets. *J. Phys. Chem C* **2010**, 114 (13), 5798–5803.
- (6) Adair, J. H.; Parette, M. P.; Altinoğlu, E. İ.; Kester, M. Nanoparticulate alternatives for drug delivery. *ACS Nano* **2010**, 4 (9), 4967–4970.

- (7) Decuzzi, P. Facilitating the Clinical Integration of Nanomedicines: The roles of theoretical and computational scientists. *ACS Nano* **2016**, *10* (9), 8133–8138.
- (8) Dong, H.; Parekh, H. S.; Xu, Z. P. Particle size- and number-dependent delivery to cells by layered double hydroxide nanoparticles. *J. Colloid Interface Sci.* **2015**, *437* (Supplement C), 10–16.
- (9) Yuan, L.; Tang, Q.; Yang, D.; Zhang, J. Z.; Zhang, F.; Hu, J. Preparation of pH-responsive mesoporous silica nanoparticles and their application in controlled drug delivery. *J. Phys. Chem. C* **2011**, *115* (20), 9926–9932.
- (10) Consiglio, G.; Di Pietro, P.; D’Urso, L.; Forte, G.; Grasso, G.; Sgarlata, C.; Cossement, D.; Snyders, R.; Satriano, C. Surface tailoring of polyacrylate-grafted graphene oxide for controlled interactions at the biointerface. *J. Colloid Interface Sci.* **2017**, *506* (Supplement C), 532–542.
- (11) van Leeuwen, H. P.; Buffle, J. Chemodynamics of aquatic metal complexes: from small ligands to colloids. *Environ. Sci. Technol.* **2009**, *43* (19), 7175–7183.
- (12) Town, R. M.; Buffle, J.; Duval, J. F. L.; van Leeuwen, H. P. Chemodynamics of soft charged nanoparticles in aquatic media: fundamental concepts. *J. Phys. Chem. A* **2013**, *117* (33), 7643–7654.
- (13) Town, R. M.; Pinheiro, J. P.; van Leeuwen, H. P. Chemodynamics of soft nanoparticulate metal complexes: from the local particle/medium interface to a macroscopic sensor surface. *Langmuir* **2017**, *33* (2), 527–536.
- (14) van Leeuwen, H. P.; Town, R. M.; Buffle, J. Chemodynamics of soft nanoparticulate metal complexes in aqueous media: basic theory for spherical particles with homogeneous spatial distributions of sites and charges. *Langmuir* **2011**, *27* (8), 4514–4519.
- (15) van Leeuwen, H. P.; Buffle, J.; Town, R. M. Electric relaxation processes in chemodynamics of aqueous metal complexes: from simple ligands to soft nanoparticulate complexants. *Langmuir* **2012**, *28* (1), 227–234.
- (16) Town, R. M.; Duval, J. F. L.; Buffle, J.; van Leeuwen, H. P. Chemodynamics of metal complexation by natural soft colloids: Cu(II) binding by humic acid. *J. Phys. Chem. A* **2012**, *116* (25), 6489–6496.
- (17) Duval, J. F. L. Chemodynamics of metal ion complexation by charged nanoparticles: a dimensionless rationale for soft, core-shell and hard particle types. *Phys. Chem. Chem. Phys.* **2017**, *19* (19), 11802–11815.
- (18) Eigen, M. Fast elementary steps in chemical reaction mechanisms. *Pure Appl. Chem.* **1963**, *6* (1), 97–116.
- (19) Alemani, D.; Buffle, J.; Zhang, Z.; Galceran, J.; Chopard, B. Metal flux and dynamic speciation at (bio)interfaces. Part III: MHEDYN, a general code for metal flux computation; application to simple and fulvic complexants. *Environ. Sci. Technol.* **2008**, *42* (6), 2021–2027.
- (20) Bard, A. J.; Faulkner, L. R. *Electrochemical methods: fundamentals and applications*, 2nd edition.; John Wiley & Sons Inc, 2000.
- (21) Molina, Á.; Laborda, E.; González, J. The reaction layer at microdisks: a cornerstone for the analytical theoretical treatment of homogeneous chemical kinetics at non-uniformly accessible microelectrodes. *Electrochem. Commun.* **2016**, *71*, 18–22.
- (22) Molina, Á.; González, J.; Soto, C. M. Reaction layer thickness of a catalytic mechanism under transient and stationary chronopotentiometric conditions. *J. Electroanal. Chem.* **2011**, *655* (2), 173–179.
- (23) Davison, W.; Zhang, H. Progress in understanding the use of diffusive gradients in thin films (DGT) – Back to Basics. *Environ. Chem.* **2012**, *9* (1), 1–13.
- (24) Galceran, J.; Puy, J. Interpretation of diffusion gradients in thin films (DGT) measurements: a systematic approach. *Environ. Chem.* **2014**, *12* (2), 112–122.
- (25) Salvador, J.; Puy, J.; Cecilia, J.; Galceran, J. Lability of complexes in steady-state finite planar diffusion. *J. Electroanal. Chem.* **2006**, *588* (2), 303–313.
- (26) Heyrovský, J.; Kůta, J. *Principles of polarography*; Academic Press, 1966.
- (27) Brdicka, R.; Wiesner, K. Polarographic determination of the rate of the reaction between ferrohem and hydrogen peroxide. *Collect. Czech. Chem. Commun.* **1947**, *12*, 39–63.
- (28) Brdicka, R.; Wiesner, K. Rate of recombination of ions derived from polarographic limiting currents due to the reduction of acids. **1947**, *12*, 138–149.

- (29) Duval, J. F. L.; Town, R. M.; Van Leeuwen, H. P. Applicability of the reaction layer principle to nanoparticulate metal complexes at a macroscopic reactive (bio)interface: a theoretical study. *J. Phys. Chem. C* **2017**, *121*, 19147-19161.
- (30) Leeuwen, H. P. van; Town, R. M. Lability of nanoparticulate metal complexes in electrochemical speciation analysis. *J. Solid State Electrochem.* **2016**, *20* (12), 3255-3262.
- (31) Crank, J. *The Mathematics of Diffusion*; Clarendon Press, 1979.
- (32) Worms, I.; Simon, D. F.; Hassler, C. S.; Wilkinson, K. J. Bioavailability of trace metals to aquatic microorganisms: importance of chemical, biological and physical processes on biouptake. *Biochimie* **2006**, *88* (11), 1721-1731.
- (33) Klaus-Joerger, T.; Joerger, R.; Olsson, E.; Granqvist, C.-G. Bacteria as workers in the living factory: metal-accumulating bacteria and their potential for materials science. *Trends Biotechnol.* **2001**, *19* (1), 15-20.
- (34) Rotureau, E.; Billard, P.; Duval, J. F. L. Evaluation of metal biouptake from the analysis of bulk metal depletion kinetics at various cell concentrations: theory and application. *Environ. Sci. Technol.* **2015**, *49*, 990-998.
- (35) Fortin, C.; Campbell, P. G. C. Silver uptake by the green alga *chlamydomonas reinhardtii* in relation to chemical speciation: influence of chloride. *Environ. Toxicol. Chem.* **2000**, *19* (11), 2769-2778.
- (36) Lavoie, M.; Fortin, C.; Campbell, P. G. C. Influence of essential elements on cadmium uptake and toxicity in a unicellular green alga: the protective effect of trace zinc and cobalt concentrations. *Environ. Toxicol. Chem.* **2012**, *31* (7), 1445-1452.
- (37) Pagenkopf, G. K. Gill surface interaction model for trace-metal toxicity to fishes: role of complexation, PH, and Water Hardness. *Environ. Sci. Technol.* **1983**, *17* (6), 342-347.
- (38) Grosell, M.; Wood, C. M. Copper uptake across rainbow trout gills: mechanisms of apical entry. *J. Exp. Biol.* **2002**, *205* (8), 1179-1188.
- (39) Alfaro-De la Torre, M. C.; Beaulieu, P.-Y.; Tessier, A. In situ measurement of trace metals in lakewater using the dialysis and DGT techniques. *Anal. Chim. Acta* **2000**, *418* (1), 53-68.
- (40) Zhuang, Y.; Yu, F.; Ma, J.; Chen, J. Enhanced adsorption removal of antibiotics from aqueous solutions by modified alginate/graphene double network porous hydrogel. *J. Colloid Interface Sci.* **2017**, *507* (Supplement C), 250-259.
- (41) Feng, Y.; Wang, Y.; Wang, Y.; Zhang, X.-F.; Yao, J. In-situ gelation of sodium alginate supported on melamine sponge for efficient removal of copper ions. *J. Colloid Interface Sci.* **2018**, *512* (Supplement C), 7-13.
- (42) Weng, L.; Van Riemsdijk, W. H.; Temminghoff, E. J. M. Kinetic aspects of donnan membrane technique for measuring free trace cation concentration. *Anal. Chem.* **2005**, *77* (9), 2852-2861.
- (43) Weng, L.; Van Riemsdijk, W. H.; Temminghoff, E. J. M. Effects of lability of metal complex on free ion measurement using DMT. *Environ. Sci. Technol.* **2010**, *44* (7), 2529-2534.
- (44) Viana, M. M. O.; da Silva, M. P.; Agraz, R.; Procopio, J. R.; Sevilla, M. T.; Hernandez, L. Comparison of two kinetic approaches for copper speciation using ion-exchange columns and ion-exchange modified carbon paste electrodes. *Anal. Chim. Acta* **1999**, *382* (1), 179-188.
- (45) Muller, F. L. L.; Kester, D. R. Kinetic approach to trace metal complexation in seawater: application to zinc and cadmium. *Environ. Sci. Technol.* **1990**, *24* (2), 234-242.
- (46) Procopio, J. R.; Viana, M. M. O.; Hernandez, L. Microcolumn ion-exchange method for kinetic speciation of copper and lead in natural waters. *Environ. Sci. Technol.* **1997**, *31* (11), 3081-3085.
- (47) Koutecký, J.; Koryta, J. The general theory of polarographic kinetic currents. *Electrochimica Acta* **1961**, *3* (4), 318-339.
- (48) Koryta, J.; Dvorak, J.; Kavan, L. *Principles of Electrochemistry*, 2 edition.; Wiley: Chichester, 1993.
- (49) Zhang, Z.; Alemani, D.; Buffle, J.; Town, R. M.; Wilkinson, K. J. Metal flux through consuming interfaces in ligand mixtures: boundary conditions do not influence the lability and relative contributions of metal species. *Phys. Chem. Chem. Phys.* **2011**, *13*, 17606-17614.
- (50) van Leeuwen, H. P. Revisited: the conception of lability of metal complexes. *Electroanalysis* **2001**, *13*, 826-830.

- (51) Zhang, Z.; Buffle, J.; van Leeuwen, H. P. Roles of dynamic metal speciation and membrane permeability in metal flux through lipophilic membranes: general theory and experimental validation with nonlabile complexes. *Langmuir* **2007**, *23*, 5216-5226.
- (52) Salvador, J.; Puy, J.; Galceran, J.; Cecilia, J.; Town, R. M.; van Leeuwen, H. P. Lability criteria for successive metal complexes in steady-state planar diffusion. *J. Phys. Chem. B* **2006**, *110*, 891-899.
- (53) Duval, J. F. L.; van Leeuwen, H. P. Rates of ionic reactions with charged nanoparticles in aqueous media. *J. Phys. Chem. A* **2012**, *116* (25), 6443-6451.
- (54) Morel, F. M. M.; Hering, J. G. *Principles and Applications of Aquatic Chemistry*, 1st edition.; Wiley-Interscience: New York, 1993.
- (55) Town, R. M.; van Leeuwen, H. P. Intraparticulate metal speciation analysis of soft complexing nanoparticles. The intrinsic chemical heterogeneity of metal-humic acid complexes. *J. Phys. Chem. A* **2016**, *120* (43), 8637-8644.
- (56) van Leeuwen, H. P.; Town, R. M. Electric condensation of divalent counterions by humic acid nanoparticles. *Environ. Chem.* **2016**, *13*, 76-83.
- (57) Stackelberg, M. V.; Pilgram, M.; Toome, V. Bestimmung von Diffusionskoeffizienten einiger Ionen in wässriger Lösung in Gegenwart von Fremdelektrolyten. I. *Z. Für Elektrochem. Berichte Bunsenges. Für Phys. Chem.* **1953**, *57* (5), 342-350.
- (58) van Leeuwen, H. P.; Town, R. M.; Buffle, J.; Cleven, R. F. M. J.; Davison, W.; Puy, J.; van Riemsdijk, W. H.; Sigg, L. Dynamic speciation analysis and bioavailability of metals in aquatic systems *Environ. Sci. Technol.* **2005**, *39*, 8545-8556.
- (59) Duval, J. F. L.; Farinha, J. P. S.; Pinheiro, J. P. Impact of electrostatics on the chemodynamics of highly charged metal-polymer nanoparticle complexes. *Langmuir* **2013**, *29*, 13821-13835.
- (60) Skvarla, J. Hard versus soft particle electrokinetics of silica colloids. *Langmuir* **2007**, *23*, 5305-5314.
- (61) Fourches, D.; Pu, D.; Tassa, C.; Weissleder, R.; Shaw, S. Y.; Mumper, R. J.; Tropsha, A. quantitative nanostructure-activity relationship modeling. *ACS Nano* **2010**, *4* (10), 5703-5712.
- (62) Gajewicz, A.; Jagiello, K.; D. Cronin, M. T.; Leszczynski, J.; Puzyn, T. Addressing a bottle neck for regulation of nanomaterials: quantitative read-across (Nano-QRA) algorithm for cases when only limited data is available. *Environ. Sci. Nano* **2017**, *4* (2), 346-358.
- (63) Baalousha, M.; Cornelis, G.; J. Kuhlbusch, T. A.; Lynch, I.; Nickel, C.; Peijnenburg, W.; Brink, N. W. van den. Modeling nanomaterial fate and uptake in the environment: current knowledge and future trends. *Environ. Sci. Nano* **2016**, *3* (2), 323-345.

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