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Applicability of the Reaction Layer Principle to Nanoparticulate Metal Complexes at a Macroscopic Reactive (Bio)Interface: a Theoretical Study

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Abstract.

The reaction layer concept is commonly adopted to estimate the contribution of metal complexes to the flux of free metal ions (M) towards a macroscopic M-accumulating (bio)interface, *e.g.* a biosurface (microorganism) or a sensor (electrode). This concept is well-established for molecular ligands homogeneously distributed in solution. However, the case of (nano)particulate complexants carrying metal binding sites within their body or at their surface has so far received scant attention. In this study, a formalism is elaborated to evaluate the thickness $\bar{\lambda}$ of the reaction layer that is operational for (nano)particulate metal complexes at a macroscopic metal-sensing (bio)interface. The theory integrates the relevant chemodynamic properties of nanoparticulate metal complexes as governed by the interplay between M conductive diffusion to/from the nanoparticulate complexants and the dissociation kinetics of inner-sphere complexes between M and particle-supported binding sites. The intricate dependence of $\bar{\lambda}$ on particle size, particle type, particle charge, the density/number of metal binding sites, and the nature of the metal ion is physically interpreted with the aid of computational illustrations. Analytical formulations are further derived in the extremes where reaction layer properties are dominated by either diffusion-controlled or kinetically-controlled dissociation of nanoparticulate metal complexes. The results constitute a solid physicochemical basis for elaboration to lability of nanoparticulate complexes at macroscopic reactive (bio)interfaces, a central theme in biouptake and toxicity of metals. In particular, the here-reported formalism is shown to successfully predict the lability of metal-polymer nanoparticle complexes as determined from voltammetric measurements. It is further evidenced that conventional approaches ignoring particle body exclusion from the reaction layer may dramatically overestimate, by several orders of magnitude, the true kinetic flux arising from the rate of dissociation of nanoparticulate metal species at a macroscopic reactive interface.

1. Introduction.

The majority of the metal load in environmental and biological systems is associated with complexing agents that span a wide range of sizes and chemical functionalities. It is long recognized that the comprehensive understanding of the bioavailability of complex metal species requires knowledge of their chemodynamic features, *i.e.* the rates of interconversion between free metal ions ($M_{\text{aq}}^{z_M+}$) and their complexed forms.^{1,2,3} In most cases, the free metal ion is the predominant bioreactive form, and thus it is crucial to have the means to analyse the rate at which $M_{\text{aq}}^{z_M+}$ can be released from its complexed forms. To this end, a suite of dynamic speciation techniques have been developed that provide a measure of the fluxes and reactivities of metal species.⁴ Each technique has an effective timescale, governed by the applicable characteristic diffusion length. For example, in electrochemical techniques the timescale is determined by the thickness of the linear diffusion layer in solution for macroscopic electrodes and the radial diffusion layer in the case of spherical microelectrodes,⁵ whilst for diffusive gradients in thin film (DGT), the thickness of the diffusive gel layer is generally the relevant dimension.^{6,7} The metal speciation techniques comprise a reactive interface (*e.g.* an electrode, an ion-exchange resin, a polymer) that converts and/or accumulates the target species, typically $M_{\text{aq}}^{z_M+}$. The process of conversion/accumulation at a dynamic sensor surface or a biointerface lowers the local concentration of $M_{\text{aq}}^{z_M+}$ and sets up a flux of $M_{\text{aq}}^{z_M+}$ from the bulk sample solution towards the interface. Depending on the chemodynamic features of the metal complexes and the operational timescale of the accumulation process, the complexed forms may dissociate within the diffusion layer at the reactive interface. The subsequently released $M_{\text{aq}}^{z_M+}$ is then available to participate in the diffusive transport towards the sensor or organism. The concept of lability provides a quantitative description of the dissociative contribution of metal complex species to the flux of the free metal ion. So-called lability criteria are formulated as the ratio between the kinetic flux, J_{kin} , arising from the rate of dissociation of complexed species, and the diffusive flux, J_{diff} , of all forms of the metal towards a reactive interface. A system is denoted as labile when $J_{\text{kin}} \gg J_{\text{diff}}$. Such criteria are well established for molecular scale complexes with complexant dimensions much smaller than the thickness of the nonequilibrium reaction layer that extends continuously over the sensing interface.^{4,8,9} The interpretation framework often incorporates the Koutecký-Koryta (KK) approximation¹⁰⁻¹³ which divides the concentration profiles of free and complexed metal species in the diffusion layer into a labile and nonlabile region, with the boundary between the two regions lying at a distance from the sensing interface that identifies with the reaction layer thickness. The concept of a reaction layer derives from the relative

mobilities and lifetimes of the various metal species in the medium. That is, the mobility of the free $M_{aq}^{z_M+}$ in the medium and its mean free lifetime (governed by the rate of re-association), together with the mobility of the complexed form and its mean free lifetime (governed by the rate of dissociation). Typically for molecular complexants, situations of practical interest fulfill the criterion $\varepsilon K' \gg 1$, where ε is the ratio of diffusion coefficients for the complex and the free $M_{aq}^{z_M+}$, and K' is the dimensionless product of the stability constant of the complex and the binding site concentration. In such cases the so-called association reaction layer thickness is the pertinent parameter, denoted by μ , and J_{kin} is given by the product of the dissociation rate constant, the concentration of the complexed form and μ . The KK approach has demonstrated great utility in describing labilities of complex systems for a range of molecular complexes and operational timescales.¹³⁻¹⁷

In recent years the chemodynamic features of metal ion complexes with nanoparticles (NPs) have been analysed in some detail and a comprehensive framework to describe the overall association/dissociation kinetics of nanoparticulate complexes has been established.¹⁸⁻²³ This has already been used as the primary basis for extending the lability analysis to the case of soft nanoparticulate metal ion complexes.^{24,25} A typical elementary aspect is that the reaction layer concept only has physical meaning in the presence of complexing sites, and thus the classical reaction layer for complexing NPs necessarily is an *intraparticulate* feature.²⁴ Furthermore, due to the lower diffusion coefficient of the complexed metal as compared to that of the free ion, the condition $\varepsilon K' \gg 1$ is more demanding for nanoparticulate complexes. A proper description of the dissociative contribution of nanoparticulate complexes to the flux of free $M_{aq}^{z_M+}$ towards a macroscopic sensing interface thus requires coupling of the local particulate processes of metal association/dissociation and diffusion to/from the particle with metal ion fluxes towards the sensor/medium interface. The first steps towards establishing a conceptual framework for the lability of nanoparticulate metal complexes have been made by invoking the established KK approximation together with an *operational* reaction layer thickness at the macroscopic interface.²⁵ The effective thickness of this operational reaction layer derives from the time-averaged presence of particle body volume, in turn corresponding to a time-averaged complexing site concentration. In doing so, it was shown that the characteristics of the supposedly spherical NP generally give rise to a certain extent of exclusion of their body volume (depletion) near the macrosurface with consequences for the local concentration of complexing sites, the magnitude of J_{kin} , and the ensuing lability of the nanoparticulate metal species.²⁵

Herein the conceptual framework for spherical NPs is extended to quantify the influence of the molecular, nanoparticulate and macroscopic factors that contribute to the magnitude of the reaction layer

that is operational at a macroscopic reactive (bio)surface. Following this more rigorous approach, the properties of the reaction layer are formulated in dimensionless form for (i) charged 3D soft/core-shell nanoparticles that carry metal binding sites within the volume of the permeable particle body or shell, respectively, and (ii) 2D hard complexing nanoparticles that comprise an impermeable particle body with metal binding sites at their surface. For each type of nanoparticulate ligand, the physicochemical characteristics of the reaction layer are derived as a function of the defining properties of the nanoparticles, which includes their size, their electrostatic features and their density/number of metal binding sites S . In addition, the way in which the (metal-dependent) dissociation kinetics of intraparticulate or surface MS complexes (3D soft/core-shell NP and 2D NP case, respectively) and their thermodynamic stabilities impact on the thickness of the macroscopic reaction layer is highlighted and discussed in detail.

2. Theory.

2.1. Description of the problem.

In the following, we consider a dispersion of spherical, charged core-shell nanoparticles (NPs) of radius $r_p = a + d$, with a the core radius and d the shell thickness, in an aqueous medium containing metal ions $M_{aq}^{z_M+}$ (M for short) at bulk concentration c_M^* . Fully permeable 3D NPs have $r_p = d$ and $a = 0$, whilst at the other extreme the impermeable 2D NPs have $r_p = a$ and $d = 0$. A glossary of the symbols (with corresponding units) used in this work is provided at the end of the manuscript. In line with practical situations, sufficiently dilute NP dispersions are considered so that there is no overlap between the individual electric double layers and/or the diffusion layers of different NPs. Accordingly, for particle radius r_p much larger than the electric double layer thickness (denoted as $1/\kappa$), the range of particle volume fractions adopted in this work necessarily satisfies $\varphi < \varphi_{\max}$ with $\varphi_{\max} \approx 0.13$ which corresponds to the extreme where adjacent NPs are separated by a distance $2r_p$ with r_p the typical thickness of their steady-state M diffusion layer. In the more general case (*i.e.* at any κr_p value), $\varphi_{\max}$ is provided by $\varphi_{\max} = \min(0.13, [\kappa r_p / (1 + \kappa r_p)]^3)$ where $[\kappa r_p / (1 + \kappa r_p)]^3$ is the particle volume fraction where electric double layer overlap between neighbouring particles sets in. For the sake of convenience, we introduce the ratio $z = a / r_p$ so that $d = r_p(1 - z)$ and $a = r_p z$. The NPs are generally defined by a spatial confinement of electric charges with density denoted as ρ_0 , and of N_s metal binding sites S , the concentration of which is denoted c_s . Thus, the situation of fully soft porous particles is met for $z = 0$ and the other extreme of hard particles corresponds to $z = 1$. For the latter particles type, the applicable

surface densities of charges and binding sites are denoted as σ_0 and Γ_s , respectively. The confinement of the binding sites S within the particle body or at the particle surface generates a spatial heterogeneity of the sites within the whole sample volume.¹⁸⁻²³ In turn, the dynamics of formation/dissociation of nanoparticulate metal complexes differs significantly from that of their molecular equivalents defined with the sites S *homogeneously* distributed in solution. The primary reason for this difference in reactivity is that the electrostatic conditions prevailing in the intraparticulate or particle surface compartments differ from those in the surrounding medium, which modifies the concentration of metal ion reactants in/at the particulate volume/surface. Negatively charged NPs may thus generate rates of reactions with positively charged metal ions that are orders of magnitudes larger than those typically observed for their molecular counterparts.¹⁹

This study focuses on the non-equilibrium processes taking place at the interface between a dispersion of reactive NPs and a macroscopic metal-responsive (bio)interface that accumulates or converts free metal ions. Examples of such (bio)interfaces include metal-accumulating (micro)organisms such as bacteria²⁶ or algae,²⁷ electrodes,²⁸ catalytic surfaces²⁹ or (bio)sensor surfaces.³⁰ The concept of a reaction layer is a promising tool to quantify the lability of M-NP complexes at such macroscopic reactive (bio)interfaces.²⁵ As compared to the well-established situation of molecular complexing agents,¹³⁻¹⁷ the unique features of nanoparticulate complexants require proper formulation of the coupling between dynamics of metal complex formation/dissociation processes relevant at the *nanoparticulate level*, and the M-NP chemodynamic features effective in the vicinity of the *macroscopic* (bio)interface. In view of the paramount importance of nanoparticulate matter in governing *e.g.* biouptake and toxicity of metallic species in biological media,^{1,2} the present exhaustive and in-depth analysis of the properties of the reaction layer applicable for M-NP complexes at a macroscopic M-sensing (bio)interface is most timely. To set the scene, we first recall the chemodynamic properties of M-NP complexes in terms of the physicochemical conditions relevant for the local intraparticulate or particle surface environments.²³

2.2. Chemodynamics of nanoparticulate metal complexes.

In line with preceding developments,¹⁸⁻²³ we consider below the usual practical case in which the NP dispersion is equilibrated with the background electrolyte (*i.e.* the electric field at the NP/solution interface is set), the bulk concentration of M (c_M^*) is well below the concentration of the here-considered monovalent background electrolyte (c^∞) and the binding sites S are well in excess over the metal species M within the sample volume. These conditions are typically met for the case of trace metal ions in environmental and biological media. Furthermore, various particle charge-density regimes can be defined:¹⁸ the high-charge density regime corresponds to the case where the average structural charge

separation, ℓ_C , is sufficiently small so that $\kappa_p \ell_C \ll 1$, where κ_p is the intraparticle screening length.^{31,32} In this case the potential field arises from the cooperative electrostatic forces of the charged sites. If additionally the radius of the charged particle is much larger than κ_p , then a Donnan potential difference ψ_D is established between the bulk of the soft particulate phase and the bulk aqueous medium. At the other extreme, the low charge density regime corresponds to the situation where $\kappa_p \ell_C \gg 1$ and the relevant potential field is the local one around each charged site.

The association of M with an individual complexing nanoparticle can be described by an extended Eigen mechanism^{18-23,33} that generally comprises the following successive steps (**Figure 1**): (i) conductive diffusion of M from the bulk solution to the charged particle body (3D soft/core-shell NPs) or surface (2D NPs), (ii) incorporation of $M_{aq}^{z_M+}$ as a free hydrated ion within the particle shell volume (relevant for 3D NP type), (iii) electrostatic pairing of $M_{aq}^{z_M+}$ with S, which leads to an outer-sphere $M \bullet S$ complex, and (iv) the formation of 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. The dissociative counterparts of steps (i), (ii), (iii) and (iv) are also shown schematically in **Figure 1**.

For 3D soft/core-shell nanoparticulate systems with a sufficiently high water content, M diffusion within the NP body is *ca.* an order of magnitude faster than extraparticle diffusion and thus it is not rate-limiting for the overall formation/dissociation of nanoparticulate metal complexes.³⁴ In the high charge density regime, a similar conclusion holds for step (iii) that pertains to the interconversion between intraparticle free $M_{aq}^{z_M+}$ and outer-sphere $M \bullet S$ because there is practically no potential difference between these two species.^{24,25} In turn, the rate of overall formation/dissociation of M-(3D)NP complexes (**Figure 1**) is either determined by the dynamics of M conductive diffusion to/from the NP body (steps (i)-(ii)) or the kinetics of inner-sphere association/dissociation (step (iv)), or by both. Denoting the diffusion-controlled rates for M-(3D)NP association and dissociation as $k_{a,p}$ and $k_{d,p}$, respectively, and introducing the kinetically-controlled rates k_a^{is} and k_d^{is} for inner sphere complex association/dissociation (**Figure 1**), the composite rate constants $k_a = \left(1/k_a^{is} + 1/k_{a,p}\right)^{-1}$ and $k_d = \left(1/k_d^{is} + 1/k_{d,p}\right)^{-1}$ for the overall association (subscript 'a', step (i) to (iv) in **Figure 1**) and dissociation

Figure 1. Schematic representation of the volume exclusion of (negatively charged) 3D soft (A) and core-shell (B) nanoparticles (NP) in the vicinity of a macroscopic metal (M)-sensing (bio)interface. The volume component of the nanoparticle body lying within the operational reaction layer of thickness $\bar{\lambda}$ (eqs 2, 3 and 9) is indicated in grey shading (the remaining particle volume thus corresponds to that excluded from the reaction layer). The various geometrical parameters used in the theoretical developments are specified. In (A), the processes (i)-(iv) involved in the formation/dissociation of nanoparticulate metal complexes are indicated together with the corresponding rate constants. Panel (B) inventories the different configurations encountered in terms of overlap between reaction layer and reactive component of 3D core-shell NPs. See text for details.

(subscript ‘d’, step (iv) to (i)) of nanoparticulate metal complexes, may be written in the generic dimensionless form²³

$$k_{a/d} / k_{a/d}^{\text{is}} = 1 / \left(1 + \Lambda_{a/d} \left(\frac{r_p}{\ell_{a/d}} \right)^{n_{a/d}} \right) \quad (1)$$

, where subscript ‘a/d’ denotes either the association or dissociation process, $n_{a/d}$ are integers, and $\Lambda_{a/d}$ corrects $k_{a/d}$ for the presence of electric charges within the reactive particle volume and for the presence of a core component, as extensively detailed in Ref. [23]. Briefly, particle electrostatics impacts chemodynamics of metal complexes *via* Boltzmann accumulation of metal ions within the reactive particle component and *via* acceleration (or retardation depending on the sign of the particle charge) of extra-particulate metal diffusion to/from the particle due to the presence of an electric double layer field at

the particle/solution interface. The magnitude of $n_{a/d}$ further originates from the power-law dependence of $k_{a/d,p}$ and $k_{a/d}^{is}$ on particle radius and it changes depending on whether the density or the number of binding sites S per particle is constant with r_p .²³ The parameters $\ell_{a/d}$ and $\ell_{a/d}\Lambda_{a/d}^{-1/n_{a/d}}$ correspond to the thicknesses of the relevant *intraparticulate* association/dissociation reaction layers operative at the NP/medium interface without and with account of nanoparticle electrostatics, respectively.²³ The association reaction layer is defined as the mean distance covered by the intraparticulate free M before it reassociates with molecular S , and the dissociation reaction layer is determined by the characteristic timescale for complex dissociation within the particle body.^{23,24} Accordingly, the intraparticulate reaction layer should not be confused with the reaction layer of thickness $\bar{\lambda}$ that is operational at the macroscopic scale of the metal-sensing (bio)interface (**Figure 1**). Formulations of $n_{a/d}$, $\Lambda_{a/d}$ and $\ell_{a/d}$ involved in eq 1 were derived for the practical cases where either the number N_s or the density c_s of binding sites S remains constant upon changing particle size r_p and/or particle core dimension.²³ The analysis detailed in Ref. [23] further demonstrates that eq 1 is also valid for the overall rates of association/dissociation of M -(2D) NP complexes provided that $n_{a/d}$, $\Lambda_{a/d}$ and $\ell_{a/d}$ are replaced by the corresponding expressions applicable under either constant N_s or constant Γ_s conditions.

Equation (1) holds for a fully relaxed ion distribution at the NP/solution interphase, in the high charge density regime, under Donnan conditions (3D NP case) and for thin extraparticulate double layers (2D NP case) as achieved for $\kappa_p d \gg 1$ and $\kappa a \gg 1$, respectively, where $\kappa_p^{-1} = \kappa^{-1} / \sqrt{\cosh(y_D)}$ is the intraparticulate screening Debye length, κ^{-1} is the extraparticulate electric double layer thickness and the dimensionless equilibrium Donnan potential is defined by $y_D = e\psi_D / k_B T$ (e , k_B and T have their usual meanings). For the sake of completeness, the expressions of $n_{a/d}$, $\Lambda_{a/d}$ and $\ell_{a/d}$ as derived in Ref. [23] for 3D and 2D particulate complexants, are summarized in **Table 1**. These expressions are based on the rate constants $k_{a/d}^{is}$ expressed in terms of the local intraparticulate (or surface) metal concentrations.

A 3D soft or core-shell complexing NPs (0 ≤ z < 1)						
Constant c _s			Constant N _s			
n _a	Λ _a	ℓ _a	n _a	Λ _a	ℓ _a	
2	$\frac{1-z^3}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M}{k_w V^{os} N_{Av} c_s}}$	-1	$\frac{1}{\bar{f}_{el,a}}$	$\frac{k_w V^{os} N_s}{4\pi D_M}$	
n _d	Λ _d	ℓ _d	n _d	Λ _d	ℓ _d	
2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M(1+K_{int}c_s)}{k_w V^{os} N_{Av} K_{int}^{-1}}}$	2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M K_{int}}{k_w V^{os} N_{Av}}}$	for $r_p \gg \frac{r_{int}}{(1-z^3)^{1/3}}$
			5	$\frac{\bar{f}_B(1-z^3)}{\bar{f}_{el,a}}$	$\left(\frac{9D_M N_s K_{int}^2}{4\pi k_w V^{os} N_{Av}^2}\right)^{1/5}$	for $r_p \ll \frac{r_{int}}{(1-z^3)^{1/3}}$
B 2D hard complexing NPs (z = 1)						
Constant Γ _s			Constant N _s			
n _a	Λ _a	ℓ _a	n _a	Λ _a	ℓ _a	
1	$\frac{1}{\bar{f}_{el,a}}$	$\frac{D_M}{k_w V^{os} N_{Av} \Gamma_s}$	-1	$\frac{1}{\bar{f}_{el,a}}$	$\frac{k_w V^{os} N_s}{4\pi D_M}$	
n _d	Λ _d	ℓ _d	n _d	Λ _d	ℓ _d	
2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M(1+K_{int}^{(z=1)}\Gamma_s)}{k_w V^{os} N_{Av} \Gamma_s K_H^{-1}}}$	0	$\frac{k_w V^{os} N_s}{12\pi \bar{f}_{el,d} D_M K_H}$	<i>not applicable</i>	for $r_p \gg r_{int}^{(z=1)}$
			2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M K_{int}^{(z=1)}}{k_w V^{os} N_{Av} K_H^{-1}}}$	for $r_p \ll r_{int}^{(z=1)}$

Table 1. Expressions of $n_{a/d}$, $\ell_{a/d}$ and $\Lambda_{a/d}$ involved in eq 1 and in the definition of the Damkohler numbers $Da_{a/d} = \Lambda_{a/d} (r_p / \ell_{a/d})^{n_{a/d}}$ for 3D soft/core-shell (A) and 2D hard (B) complexing NPs.²³ These expressions are obtained from derivations of the relevant chemical kinetic/transport rate constants written in terms of local intraparticulate or surface metal concentrations.²³ Distinction is made between situations where the volume or surface density (c_s or Γ_s , respectively) of metal binding sites and number N_s of sites S per particle remain constant with varying particle radius r_p and/or core dimension a . Meanings of symbols are detailed in the text and summarised in the glossary. The length scales r_{int} (A) and $r_{int}^{(z=1)}$ (B) are defined by $r_{int} = [3K_{int}N_s / (4\pi N_{Av})]^{1/3}$ and $r_{int}^{(z=1)} = [K_{int}^{(z=1)}N_s / (4\pi N_{Av})]^{1/2}$, respectively.²³

Briefly, for 3D nanoparticulate systems and fully relaxed electric fields in/around the NPs, $\Lambda_{a/d}$ depends on the dimensionless quantities $\bar{f}_{el,a}$ and $\bar{f}_{el,d} = \bar{f}_{el,a} / \bar{f}_B$ whose deviations from unity reflect the extent by which the particle electrostatics accelerate or impede the convergent (subscript 'a') or divergent (subscript 'd') diffusion of M to/from the nanoparticles. The overbar notation in $\bar{f}_{el,a}$, $\bar{f}_{el,d}$ and $\bar{f}_B$ denotes that the parameter corresponds to the integral average value over the pertaining particle volume.³⁵ $\Lambda_{a/d}$ may further depend on the metal Boltzmann accumulation factor $\bar{f}_B$ (dimensionless) for M within the shell volume (**Table 1**). The equivalents of $\bar{f}_{el,a}$, $\bar{f}_{el,d}$ and $\bar{f}_B$ for 2D complexing particles are denoted as $f_{el,a}$, $f_{el,d}$ and f_B , respectively. Following the work by Debye,³⁶ under given electric field conditions at the NP/solution interface, these electrostatic quantities are derived from solution of the non-linear Poisson-Boltzmann equation³⁵ or from tractable expressions available in the limits $\kappa_p d \gg 1$ (3D NP case) and $\kappa a \gg 1$ (2D NP case).²³ The *intrinsic* thicknesses $\ell_{a/d}$ (*i.e.* devoid of electrostatic contributions) of the intraparticulate association/dissociation reaction layers are determined by the rate constant k_w of metal dehydration (step (iv) in **Figure 1**), by the outer-sphere volume V^{os} per site S, by the metal diffusion coefficient D_M within the particle, by the volume/surface densities (or number) of binding sites S, and by the *intrinsic* stability constants of inner-sphere MS complexes (*i.e.* free from electrostatic contributions to the binding) denoted as K_{int} and $K_{int}^{(z=1)}$ for 3D and 2D NP cases, respectively (**Table 1**).²³ Using eq 1, full diagnosis of M-NP chemodynamic behaviour may be formulated on the basis of the intraparticulate (or NP surface) association and dissociation Damkohler numbers defined by $Da_a = k_a^{is} / k_{a,p}$ and $Da_d = k_d^{is} / k_{d,p}$, respectively, or, equivalently, by $Da_{a/d} = \Lambda_{a/d} (r_p / \ell_{a/d})^{n_{a/d}}$.²³ The results are summarized in **Figure 2**. The reader is referred to Ref. [23] for a detailed representation and discussion of the chemodynamic portraits of M-NP complexes corresponding to the distinct situations listed in **Figure 2**.

Figure 2. Diagnosis for chemodynamic behaviour of M-NP association and dissociation (subscript ‘a’ and ‘d’, respectively) formulated in terms of $Da_{a/d} = \Lambda_{a/d} (r_p / \ell_{a/d})^{n_{a/d}}$ with the expressions of $n_{a/d}$, $\ell_{a/d}$ and $\Lambda_{a/d}$ listed in **Table 1**. For *e.g.* M-NP dissociation (subscript ‘d’), cases $r_p \ll \ell_d \Lambda_d^{-1/n_d}$, $r_p \approx \ell_d \Lambda_d^{-1/n_d}$ and $r_p \gg \ell_d \Lambda_d^{-1/n_d}$ correspond to $k_d \rightarrow k_d^{is}$, $k_d^{is} \approx k_{d,p}$ and $k_d \rightarrow k_{d,p}$ for $n_d > 0$, with k_d , $k_{d,p}$ and k_d^{is} indicated in **Figure 1A**.

2.3. Dimensionless formulation of macroscopic operational reaction layer thickness for M-NP complexes at a metal-sensing (bio)interface.

Description of processes at the macroscopic level, *i.e.* the flux of metal species towards a reactive (bio)interface, requires the rate expressions to be formulated in terms of concentrations averaged over the entire volume of the dispersion. The same fundamental approach as that used for the well-known situation of molecular complexing ligands³⁷ is applied to define the thickness $\bar{\lambda}$ of the reaction layer that is operative for nanoparticulate metal complexes at a macroscopic M-sensing (bio)interface. That is, $\bar{\lambda}$ derives from the diffusion coefficient D_M of free metal M, its mean free lifetime $1 / (k_{a,p} \bar{c}_s^\lambda)$ relevant at the macroscopic scale with $\bar{c}_s^\lambda$ the smeared-out concentration of metal binding sites S located *within* the reaction layer (**Figure 1**), and the mobility D_p and mean lifetime $1 / k_d$ of the M-NP complex, with D_p the particle diffusion coefficient. In turn, we obtain

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

, where $\bar{c}_s$ is the concentration of *all* binding sites S present in the particle dispersion and smeared-out over the sample volume. The dimensionless term $1-\gamma$ specifies the averaged fraction of nanoparticle shell volume (or surface for the 2D case) that is operative within the reaction layer zone (**Figure 1**). The limits $\gamma=0$ and $\gamma=1$ correspond to cases where exclusion of the reactive volume or surface of the NPs from the reaction layer is insignificant (*i.e.* $r_p \ll \bar{\lambda}$) or complete ($\bar{\lambda} \ll r_p$), respectively. In intermediate situations, the exclusion factor γ depends on the magnitude of the ratio $\bar{\lambda}/r_p$, as detailed in the next section. Inspection of eq 2 shows that only the associative term contains the effective binding site concentration, *i.e.* exclusion effects are obviously immaterial if the dissociative term dominates the magnitude of $\bar{\lambda}$. The associative component of $\bar{\lambda}$ in eq 2 refines the formulation reported elsewhere²⁵ in the sense that it involves only the relevant diffusion-controlled contribution $k_{a,p}$ for the evaluation of the mean lifetime of free M *outside* the reactive particle volume or surface. For 3D soft and core-shell particulate ligand types ($0 \leq z < 1$), at given particle volume fraction φ and density c_s of binding sites S we have $\bar{c}_s = c_s \varphi (1 - z^3)$ while the relationship $\bar{c}_s = 3\Gamma_s \varphi / r_p$ applies for 2D hard complexing particles ($z=1$) at fixed φ and Γ_s . Under constant N_s and φ conditions, the relationship $\bar{c}_s = 3N_s \varphi / (4\pi N_{Av} r_p^3)$ is applicable for both types of particulate ligands ($0 \leq z \leq 1$), with N_{Av} the Avogadro number. Using eq 1, and after proper formulation of M-NP association/dissociation kinetics in terms of metal concentrations smeared-out over the sample volume,^{20,25} eq 2 may be rewritten in the dimensionless form (**Supporting Information, SI, eqs s1-s3**)

$$\Lambda^2 \overline{Da}_a \left[1 - \gamma(\Lambda) + \frac{D_M}{D_p(r_p)} \frac{k_d^{is}}{k_a^{is} \bar{c}_s} \frac{Da_a(r_p)}{1 + Da_d(r_p)} \right] - 1 = 0 \quad (3)$$

, where we introduced the convenient dimensionless spatial variable $\Lambda = \bar{\lambda}/r_p$. Equation 3 holds for 3D soft and core-shell NPs ($0 \leq z < 1$) with the applicable expressions of $Da_a = \Lambda_a (r_p/\ell_a)^{n_a}$ and $Da_d = \Lambda_d (r_p/\ell_d)^{n_d}$ listed in **Table 1A**. For the sake of clarity, eq 3 makes explicit that $Da_{a/d}$ and particle diffusion coefficient D_p depend on particle radius r_p , and that γ is a function of $\Lambda = \bar{\lambda}/r_p$ (see §2.4). For 2D hard complexing particles ($z=1$), eq 3 remains correct with considering the pertaining $Da_{a/d}$ defined in **Table 1B**. The dimensionless associative Damkohler number $\overline{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$, relevant at the macroscopic scale, compares the characteristic M diffusion timescale r_p^2 / D_M with the

mean lifetime $1/(k_{a,p}\bar{c}_s)$ of free M within the *whole* sample volume. The ratio k_a^{is}/k_d^{is} in eq 3 reflects the intrinsic stability of the inner-sphere MS complexes with $k_a^{is}/k_d^{is} = K_{int}$ and $k_a^{is}/k_d^{is} = K_H / \Gamma_s$ (mol⁻¹ m³) for 3D soft/core-shell and 2D hard complexing particles, respectively, with K_H the Henry adsorption coefficient of M at the NP surface.²³ Equation 3 highlights the multiscale nature of the reaction layer whose thickness $\bar{\lambda}$ (or Λ) is determined by *local* dynamics of M-NP association/dissociation processes *via* $Da_{a/d}$, $k_{a,p}$ and k_a^{is}/k_d^{is} , and by the smeared-out concentration $\bar{c}_s$ of binding sites S over the reaction layer volume. The next section is devoted to the formulation of the geometrical exclusion factor γ involved in eq 3.

2.4. Exclusion of nanoparticle body/surface from a macroscopic reaction layer volume.

For the sake of simplicity, it is assumed here that there are no physicochemical interactions between the NPs and the macroscopic M-sensing (bio)interface. The intricate account for M-NP/(bio)interface interactions will be tackled in a forthcoming analysis. Under the conditions adopted here, and focusing first on the case of 3D soft and core-shell NPs ($0 \leq z < 1$), γ is given by

$$\text{For } 0 \leq z < 1: \gamma(\Lambda) = 1 - \frac{V_{\text{cap}}(\bar{\lambda})}{4\pi r_p^3(1-z^3)/3} \quad (4)$$

, where $V_{\text{cap}}(\bar{\lambda})$ is the effective complexing NP *shell volume* lying within the reaction layer of thickness $\bar{\lambda}$ and *averaged* over all possible positions of the particle center from the (bio)interface (**Figure 1**) and $4\pi r_p^3(1-z^3)/3$ is the volume of the particle shell hosting metal binding sites S. In turn, eq 4 can be rewritten in the integral form

$$\text{For } 0 \leq z < 1: \gamma(\Lambda) = 1 - \frac{\Lambda^3}{4(1-z^3)} \int_0^1 F(\Lambda, z, x) dx \quad (5)$$

, where F is a conditional function, detailed in the **Supporting Information (SII, eq s6)**, that depends on the dimensionless spatial variables $\Lambda = \bar{\lambda}/r_p$, $z = a/r_p$ and $x = H/\bar{\lambda}$ with H the NP-(bio)interface separation distance specified in **Figure 1**. After some developments that include integration of the excluded NP volume over all possible NP positions H with respect to the reactive surface (**Figure 1A**), it is shown that for a 3D soft particulate ligand type ($z = 0$), eq 5 reduces to (**Supporting Information, details in SII below eq s5**)

$$\text{For } z=0: \gamma(\Lambda) = \begin{cases} 1 + \frac{\Lambda^2}{4} \left(\frac{\Lambda}{4} - 1 \right), & \text{for } \Lambda < 2 \\ \Lambda^{-1}, & \text{for } \Lambda \geq 2 \end{cases} \quad (6)$$

For the more involved case of core-shell NPs ($0 < z < 1$), after lengthy algebraic developments that rationalize γ for the various NP configurations illustrated in **Figure 1B** (see details in **Supporting Information, SII**), it is demonstrated that γ defined by eq 5 is approximated by

$$\text{For } 0 < z < 1: \gamma(\Lambda) = \begin{cases} 1 + \frac{\Lambda^2}{4} \left(\frac{\Lambda}{4} - 1 \right) (1 - z^3)^{-1}, & \text{for } \Lambda < 1 - z < 1/X_{\min}(z) \\ 1 - \frac{6(1+z) - 4(1-z)(1+2z)\Lambda^{-1} + \Lambda^{-2}(1-z)^2(1+3z)}{16\Lambda^{-1}(1+z+z^2)}, & \text{for } 1 - z \leq \Lambda < 1/X_{\min}(z) \\ \Lambda^{-1}, & \text{for } \Lambda \geq 1/X_{\min}(z) \end{cases} \quad (7)$$

, where $X_{\min}(z) = \left[\frac{z^2}{2} \left(\frac{z+11/3}{z+1} \right) + \frac{17}{6} \right]^{-1/2}$ is a decreasing function of z varying between $X_{\min}(0) \approx 0.59$ and $X_{\min}(1) = 1/2$, and satisfying $1/X_{\min}(z) > 1 - z$. Equation 7 is rigorous except for $\Lambda^{-1} = X_{\min}(z)$ where the error is *ca.* 2% for $z \rightarrow 0$ and this error monotonously decreases with increasing z to become 0 for $z \rightarrow 1$.

For 2D hard complexing particles ($z = 1$), rewriting eqs 4-5 in terms of the spherical cap of surface area $A_{\text{cap}}(\bar{\lambda})$ defined from the intersection between NP and reaction layer of thickness $\bar{\lambda}$, and averaged over the various NP positions from the (bio)interface, we obtain the exact expression for γ (see details in the **Supporting Information, SII, eq s7 and below**)

$$\text{For } z=1: \gamma(\Lambda) = \begin{cases} 1 - \frac{\Lambda}{4}, & \text{for } \Lambda < 2 \\ \Lambda^{-1}, & \text{for } \Lambda \geq 2 \end{cases} \quad (8)$$

Finally, starting from the piecewise eq 7 and identifying the ranges of Λ that are physically applicable in the extremes of 3D soft and 2D hard particulate complexants, it is verified that eq 7 taken in the limits $z \rightarrow 0$ and $z \rightarrow 1$ correctly simplifies into eqs 6 and 8, respectively, with setting $X_{\min}(0) \equiv 1/2$. It is thus concluded *a posteriori* that eq 5 is also applicable for the 2D case with z tending asymptotically to 1.

Figure 3. (A) Dependence of the exclusion factor γ on normalized particle radius $r_p / \bar{\lambda} = \Lambda^{-1}$ for 3D soft nanoparticulate ligands ($z=0$). Points: numerical evaluation of the integral eq 5; dotted lines: predictions from analytical eq 6 for $r_p / \bar{\lambda} < 1/2$ (red) and $r_p / \bar{\lambda} \geq 1/2$ (blue). (B) Dependence of γ on $r_p / \bar{\lambda} = \Lambda^{-1}$ at different values of z (indicated). Solid lines: eq 5; dotted line: limit $\gamma = r_p / \bar{\lambda}$ applicable for $r_p / \bar{\lambda} < X_{\min}(z)$. In inset: zoom of the behaviour of γ for $r_p / \bar{\lambda} \geq X_{\min}(z)$, and corresponding expressions applicable at $z=0$ (blue) and $z=1$ (red).

Figure 3 displays the dependence of the exclusion factor γ on the ratio $r_p / \bar{\lambda}$ ($= \Lambda^{-1}$) for soft NPs ($z=0$, **Figure 3A**) and for different values of z covering the situations of soft, core-shell and hard particulate ligand types ($0 \leq z \leq 1$, **Figure 3B**). For all cases examined, in-line with intuition, γ increases from 0 to 1 with increasing $r_p / \bar{\lambda}$. That is, the larger is the particle size relative to $\bar{\lambda}$, the lower is the concentration of intraparticulate or surface metal binding sites S that effectively contribute to the mean lifetime of free M within the reaction layer. **Figure 3** shows the concordance between the results obtained from numerical evaluation of the integral eq 5 according to Romberg's method³⁸ and from the piecewise analytical formulations of γ defined by eq 7 and used for $z=0$ (**Figure 3A**) and for $0 \leq z \leq 1$ (**Figure 3B**). **Figure 3B** further demonstrates that the geometrical exclusion of core-shell and hard particles differs from that of soft NPs only for $r_p / \bar{\lambda} > 1/2$, and that complete exclusion ($\gamma \rightarrow 1$) is reached for all particle types at sufficiently large $r_p / \bar{\lambda}$. As expected from simple geometric considerations, at fixed values of $r_p / \bar{\lambda}$ above $1/2$, γ decreases with increasing z , *i.e.* the exclusion of NPs from the reaction layer is more pronounced for a 3D site distribution as compared to a 2D one. In line with this result, the

threshold value of $r_p / \bar{\lambda}$ where the limit $\gamma \rightarrow 1$ is reached increases with z . On a quantitative level, the difference between the extent of exclusion for soft ($z=0$) and hard ($z=1$) nanoparticles from the reaction layer reaches a maximum for $r_p / \bar{\lambda} \approx 1.31$ with a corresponding γ at $z=0$ that is about 9% larger than that at $z=1$, which reflects a modest impact of particle core on γ . This latter result moderates the conclusion given elsewhere²⁵ where the expression of $A_{\text{cap}}(\bar{\lambda})$ derived for hard particles (eq 23 in Ref. [25]) is not averaged over the ensemble of distances separating particle and (bio)interface. The current section §2.4 completes the results of Ref. [25] because it tackles the case of core-shell particles (eq 7) and further formulates γ for all particulate ligand types over the *entire range* of $r_p / \bar{\lambda}$ values. In particular, the expression of $V_{\text{cap}}(\bar{\lambda})$ reported for soft porous particles in Ref. [25] (eq 22 therein) strictly applies for $r_p / \bar{\lambda} > 1/2$ and correctly corresponds to eq 6 that defines γ in this specific $r_p / \bar{\lambda}$ domain.

2.5. Evaluation of the ratio $\bar{\lambda} / r_p$.

In this section, we evaluate and interpret $\Lambda = \bar{\lambda} / r_p$ in terms of the associative contribution $\overline{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$ and of its dissociative counterpart defined by $\overline{Da}_d = k_d r_p^2 / D_p$ ($\overline{Da}_{a/d}$ are both independent of Λ) so that eqs 2-3 simply become

$$\Lambda^2 \overline{Da}_a (1 - \gamma(\Lambda) + \overline{Da}_d / \overline{Da}_a) - 1 = 0 \quad (9)$$

, to be solved in Λ with $\gamma(\Lambda)$ defined by eq 5. Comparison between eqs 9 and 3 shows that $\overline{Da}_{a/d}$ and

$\overline{Da}_{a/d}$ are interrelated via $\overline{Da}_d / \overline{Da}_a = \frac{D_M}{D_p} \frac{k_d^{\text{is}}}{k_a^{\text{is}} \bar{c}_s} \frac{Da_a}{1 + Da_d}$. It will be apparent in §3 that the analysis of

Λ detailed below (**Figure 4**) according to the $(\overline{Da}_a, \overline{Da}_d)$ representation is useful and decisive for rationalizing the complex dependence of $\bar{\lambda}$ on particle size, particle type and on the other key determinants of M-NP chemodynamics (eqs 1 and 3). After substitution of eqs 6, 7 or 8 into eq 9 and algebraic rearrangements, it is demonstrated that the searched Λ corresponds to the physically-relevant root of the $\overline{Da}_{a/d}$ -dependent quadratic, cubic or quintic polynomial equations $P(\Lambda)$ detailed in **Supporting Information (SI-III-(A), eqs s8-s10)** for soft, core-shell and hard nanoparticles. For fixed values of $\overline{Da}_{a/d}$ and given z , we systematically verified that this root, numerically obtained by Muller's method,³⁹ corresponds to that derived from eqs 9 and 5. For some cases, it is possible to elaborate

tractable analytical expressions of Λ , as detailed in **SIH-(B)** of the **Supporting Information (Table S1 therein)**.

Figure 4. (A) Dependence of the normalized reaction layer thickness $\bar{\lambda}/r_p$ on dimensionless Damkohler number $\bar{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$. Solid line: numerical solution of eqs 9 and 5; Dotted lines: predictions from $\bar{\lambda}/r_p \sim (\bar{Da}_a + \bar{Da}_d)^{-1/2}$ (curve (a), red) and $\bar{\lambda}/r_p \sim \sqrt{2} (\bar{Da}_a)^{-1/4}$ (curve (b), blue). Model parameters: $\log(\bar{Da}_d) = -3$. In inset, simulations are provided for various values of $\log(\bar{Da}_d)$ (indicated). (B) Dependence of $\bar{\lambda}/r_p$ on $\bar{Da}_a$ for various values of $z = a/r_p$ (indicated). Curve (a): as in in panel (A). The slopes $-1/4$ and $-1/3$ refer to the behaviour of $\bar{\lambda}/r_p$ at large $\bar{Da}_a$ for $z = 0$ and $z = 1$, respectively.

Figure 4A reports the dependence of $\Lambda = \bar{\lambda}/r_p$ on $\bar{Da}_a$ for various values of $\bar{Da}_d$ (inset) at $z = 0$ (soft NPs). Starting from $\bar{Da}_a \rightarrow 0$, $\bar{\lambda}/r_p$ decreases with increasing $\bar{Da}_a$ according to the power law $\bar{\lambda}/r_p \sim (\bar{Da}_a + \bar{Da}_d)^{-1/2}$ (**SIH-(B)** in **Supporting Information**). Simple inspection of eq 9 reveals that this decrease in $\bar{\lambda}/r_p$ is not affected by the NP exclusion process (*i.e.* $\gamma \rightarrow 0$). Realizing that $\bar{Da}_{a/d} \sim r_p^2$, the situation corresponds simply to that where $\bar{\lambda}$ is solely controlled by the balance between associative and dissociative components of the reaction layer in a way that is qualitatively similar to that which applies to molecular MS complexes with moderate stability in line with $K_{\text{int}} \bar{c}_s \approx 1$. Upon further

increase of $\overline{Da}_a$, the decrease in $\bar{\lambda}/r_p$ becomes weaker and at sufficiently large $\overline{Da}_a$ ($\gg \overline{Da}_d$) it follows the power law $\bar{\lambda}/r_p \sim \sqrt{2}(\overline{Da}_a)^{-1/4}$ (SIII-(B) in **Supporting Information**), which is independent of $\overline{Da}_d$ (inset): the association contribution then outweighs the dissociation term involved in the expression of $\bar{\lambda}/r_p$. In this second regime, geometrical exclusion of the NP from the reaction layer contributes to $\bar{\lambda}/r_p$. Indeed, the decrease in $\bar{\lambda}/r_p$ as a sole result of increasing $\overline{Da}_a$ is necessarily accompanied by a significant increase in γ (**Figure 3**). In turn, NP exclusion together with $\overline{Da}_a$ concurrently affect the ratio $\bar{\lambda}/r_p$. The underlying NP exclusion-mediated increase in $\bar{\lambda}/r_p$ as compared to the $\gamma = 0$ case (**Figure 4A**, red dotted line), is the direct consequence of the increase of the mean lifetime $1/(k_{a,p}\bar{c}_s(1-\gamma))$ of free M in the vicinity of the reaction layer. The crossover between the two regimes identified above at small and large $\overline{Da}_a$ can be defined from the intersection of their respective asymptotic expressions, leading to $\overline{Da}_a + \overline{Da}_d = 1/4$ and $\bar{\lambda}/r_p = 2$, *i.e.* the value of $\Lambda = \bar{\lambda}/r_p$ marking the transition between behaviour of γ at $\gamma < 1/2$ and $\gamma > 1/2$ (see eq 6 and **Figure 3**). Obviously, the decrease in $\bar{\lambda}/r_p$ observed in **Figure 4A** at sufficiently low $\overline{Da}_a$ gradually disappears with increasing the ratio $\overline{Da}_d/\overline{Da}_a$ to leave place to a constant plateau $\bar{\lambda}/r_p \sim (\overline{Da}_d)^{-1/2}$ (inset **Figure 4A**). In such a situation, the regime $\bar{\lambda}/r_p \sim \sqrt{2}(\overline{Da}_a)^{-1/4}$ operative at large $\overline{Da}_a$ sets in for *ca.* $\overline{Da}_a > 4(\overline{Da}_d)^2$, in line with the simulations provided in the inset.

Figure 4B extends the results obtained in panel **A** by displaying the dependence of $\bar{\lambda}/r_p$ on $\overline{Da}_a$ at various values of $z = a/r_p$ from 0 (3D soft NPs) to 1 (2D hard NPs). In agreement with the above arguments, the contribution of γ to the ratio $\bar{\lambda}/r_p$ appears at sufficiently large values of $\overline{Da}_a$ where the decrease in $\bar{\lambda}/r_p$ depends on z according $\bar{\lambda}/r_p \sim \sqrt{2} \left[(1-z^3)/\overline{Da}_a \right]^{1/4}$ for $0 \leq z < 1$ and $\bar{\lambda}/r_p \sim (4/\overline{Da}_a)^{1/3}$ for $z \rightarrow 1$ (SIII-(B) in **Supporting Information**). In line with the results of **Figure 3B**, the exclusion of NPs from the reaction layer is less significant with increasing z at fixed $\bar{\lambda}/r_p$ value below ~ 2 . In turn, the decrease in $\bar{\lambda}/r_p$ displayed in **Figure 4B** for $\bar{\lambda}/r_p < 2$ is stronger for hard particle types as compared to that for their soft homologues. The effects of $\overline{Da}_d$ on $\bar{\lambda}/r_p$ for $0 \leq z \leq 1$ is

qualitatively similar to that discussed in the inset of panel (A) (not shown). For a given $\overline{Da}_d$ such that $\overline{Da}_d \gg \overline{Da}_a$, the transition between the regime $\lambda / r_p \sim (\overline{Da}_d)^{-1/2}$ and that where $\bar{\lambda} / r_p$ decreases with increasing $\overline{Da}_a$ (see inset **Figure 4A**) is reached for $\overline{Da}_a \approx 4(\overline{Da}_d)^{3/2}$ at $z = 1$.

On the basis of the results detailed in the preceding sections, the processes governing the evolution of the macroscopic reaction layer thickness $\bar{\lambda}$ with varying particle size r_p can be established *e.g.* as a function of the particle type considered and of the relevant transport and chemical kinetic rate constants that determine local M-NP chemodynamic properties (**Figure 2**). This feature is exploited in the following section where cases corresponding to constant density or constant number of metal binding sites are discriminated.

3. Physicochemical determinants of the reaction layer: Results and Discussion.

3.1. The case of 3D nanoparticulate ligands ($0 \leq z < 1$) with a given density c_s of metal binding sites.

For 3D soft and core-shell complexing nanoparticles with a given density c_s of intraparticulate metal binding sites S , the relevant expressions for $n_{a,d}$, $\ell_{a,d}$ and $\Lambda_{a,d}$ involved in $Da_{a/d} = \Lambda_{a/d} (r_p / \ell_{a/d})^{n_{a/d}}$ are detailed in **Table 1A** (left column). After substitution into eq 3 and rearrangements, eq 3 reduces to the elegant form (**SIV-(A)** in **Supporting Information, eqs s11-s13**)

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

, with $\Phi_{el,a} = 3\phi \bar{f}_{el,a}$ and $\Phi_B = \phi \bar{f}_B / (1 + K_{int} c_s)$ (both dimensionless) and $\mu_d = \ell_d \Lambda_d^{-1/2} = \ell_d \sqrt{\bar{f}_{el,a} / \bar{f}_B}$ is the thickness of the *intraparticulate* dissociation reaction layer corrected for particle electrostatics under conditions of a fully relaxed electric field. $\ell = k_B T / (6\pi\eta D_M)$ is the length scale defined by $\ell / r_p = D_p(r_p) / D_M$ with D_p provided by the Stokes-Einstein equation, and η is the dynamic viscosity of the medium. For metal ions such as Ni(II), Zn(II), Cd(II), Cu(II) and Pb(II) with $D_M \approx 10^{-9} \text{ m}^2 \text{ s}^{-1}$,⁴⁰ at $T = 295 \text{ K}$, we have $\ell \approx 0.23 \text{ nm}$. Equation 10 clarifies how the macroscopic reaction layer thickness $\bar{\lambda} = \Lambda \times r_p$ is intimately connected to (i) the chemodynamics of M-NP complexes dissociation, as reflected by the magnitude of the ratio r_p / μ_d compared to unity (see **Figure 2**), (ii) the

particle electrostatic features subsumed in $\bar{f}_{\text{el},a}$ and $\bar{f}_B$, (iii) the dimensionless stability constant $K_{\text{int}}c_s$ for inner-sphere MS complexes, and (iv) the particle volume fraction φ in the dispersion. The nature of the metal ion M also comes into play *via* the diffusion coefficient D_M and the contribution of the metal dehydration kinetic rate constant,⁴¹ k_w , which are both involved in ℓ_d (**Table 1A**). For given values of $\Phi_{\text{el},a}$, Φ_B and μ_d , Λ is numerically obtained over the relevant range of particle size $1 \text{ nm} < r_p < 1 \mu\text{m}$ following the strategy adopted for solving eq 9, and the searched $\bar{\lambda}$ is subsequently derived from $\bar{\lambda} = \Lambda \times r_p$. Analytical expressions of $\bar{\lambda}$ can be obtained from those derived for Λ in §2.5 within the ($\bar{D}a_a, \bar{D}a_d$) representation (eq 9) upon substituting therein $\bar{D}a_a$ and $\bar{D}a_a / \bar{D}a_d$ by their developed expressions $\Phi_{\text{el},a}$ and $\ell r_p^{-1} \Phi_B \left[1 + (\mu_d r_p^{-1})^2 \right]$, respectively, inferred from direct comparison between eqs 9 and 10. For practical values of φ (§2.1) and $\bar{f}_{\text{el},a}$,^{20,23} $\Phi_{\text{el},a}$ is systematically (well) below unity, whereas μ_d / r_p may adopt values well below or above 1 depending on the M-NP chemodynamic behaviour (**Figure 2**).²³ Similarly we have $0 < \Phi_B < \infty$ depending on particle attributes $\bar{f}_B$ ^{18,21} and c_s , and the MS stability constant K_{int} . It is noted that Φ_B corresponds to the ratio $\bar{D}a_a / \bar{D}a_d$ in the specific case where particle radius r_p satisfies $\ell r_p^{-1} \left[1 + (\mu_d r_p^{-1})^2 \right] \approx 1$.

Figure 5. (A) Dependence of $\bar{\lambda}$ on particle size r_p for different values of $\log(\Phi_B)$ (indicated), with $\log(\Phi_{el,a}) = -2$, $\mu_d = 100$ nm, $z = 0$. Blue and red dotted lines correspond to the expressions applicable in the diffusion-controlled M-NP dissociation regime $r_p \gg \mu_d$ (i.e. $k_d \rightarrow k_{d,p}$) and kinetically-controlled M-NP dissociation regime $r_p \ll r_{p,max} (< \mu_d)$ (i.e. $k_d \rightarrow k_d^{is}$). The graph further details the regime $r_p = \mu_d$ (i.e. $k_d^{is} = k_{d,p}$) where both chemical kinetics and M diffusion govern the chemodynamics of M-NP dissociation. (B) As in panel (A) with varying $\log(\Phi_{el,a})$ (indicated) for $\log(\Phi_B) = 1$, $\mu_d = 100$ nm, $z = 0$. Results refer to the situation of 3D soft NPs with fixed density c_s of metal binding sites S.

3.1.1. Impact of Φ_B on $\bar{\lambda}$. **Figure 5A** shows the dependence of $\bar{\lambda}$ on the size r_p of 3D soft particles ($z = 0$) for distinct values of Φ_B at fixed $\Phi_{el,a}$ and μ_d . For sufficiently small particle sizes $r_p \ll r_{p,max}$ (with $r_{p,max}$ indicated in the figure), $\bar{\lambda}$ increases linearly with r_p , then reaches a local maximum $\bar{\lambda}_{max}$ at $r_p = r_{p,max}$, goes through a minimum $\bar{\lambda}_{min}$ at $r_{p,min} = \mu_d$ and increases for $r_p \gg \mu_d$. It is shown from eq 10 that the increase in $\bar{\lambda}$ for $r_p \gg \mu_d$ obeys the power law $\bar{\lambda} \sim \sqrt{\Phi_B \ell r_p / \Phi_{el,a}}$ (**SIV-(A)** in **Supporting Information**). In this regime, the dissociative term in $\bar{\lambda}$ dominates the associative one ($\overline{Da_a} / \overline{Da_d} \ll 1$) and the situation is therefore the analogue of the specific case $\bar{\lambda} / r_p \sim (\overline{Da_d})^{-1/2}$ identified in the inset of **Figure 4A** within the $(\overline{Da_a}, \overline{Da_d})$ representation with $\overline{Da_d} \sim \Phi_{el,a} r_p / (\ell \Phi_B)$. For $r_p \ll r_{p,max} (< \mu_d)$, eq 10 simplifies into (**SIV-(A)** in **Supporting Information**)

$$\left\{ \begin{array}{l} \text{For } \Phi_{el,a} < \frac{X_{min}^2(z)}{1 - X_{min}(z)}: \bar{\lambda} \sim r_p \left(1 + \sqrt{1 + 4 / \Phi_{el,a}} \right) / 2 \\ \text{For } \Phi_{el,a} > \frac{X_{min}^2(z)}{1 - X_{min}(z)}: \left\{ \begin{array}{l} \bar{\lambda} \sim r_p \sqrt{2} (1 - z^3)^{1/4} \Phi_{el,a}^{-1/4} \text{ for } \bar{\lambda} / r_p < 1 - z \\ \bar{\lambda} \sim r_p \left[\frac{8}{3} \left(\frac{1 + z + z^2}{1 + z} \right) \right]^{1/3} \Phi_{el,a}^{-1/3} \text{ for } \bar{\lambda} / r_p > 1 - z \end{array} \right. \end{array} \right. \quad (11)$$

, which is consistent with the unit slope (red dotted line) indicated in the double logarithmic representation of **Figure 5A** where $z = 0$. The regime described by eq 11 solely depends on $\overline{Da_a} = \Phi_{el,a}$. It thus corresponds to a macroscopic reaction layer thickness that is now independent of the dissociation contribution (i.e. $\overline{Da_a} / \overline{Da_d} \gg 1$), as detailed in **Figure 4**. That is, the associative term dominates eq 2 and thus it is in this regime that the NP exclusion factor may come into play in determining the magnitude of $\bar{\lambda}$ depending on the magnitude of $\overline{Da_a}$, as discussed in **Figure 4B**. The presence of the maximum

and minimum in $\bar{\lambda}$ at $r_{p,\max}$ and $r_{p,\min} (> r_{p,\max})$ (**Figure 5A**) basically reflect the modulation of the ratio $\overline{Da}_a / \overline{Da}_d$ with changing particle size r_p . Expressions for $r_{p,\max}$, $\bar{\lambda}_{\max}$ and $\bar{\lambda}_{\min}$ are provided in the **Supporting Information (SIV-(B), Table S2** therein) as a function of the relevant $\Phi_{el,a}$, Φ_B and μ_d . For well-defined minima in $\bar{\lambda}$, *i.e.* for $r_{p,\min} \gg r_{p,\max}$, it can be shown that the decrease in $\bar{\lambda}$ from $\bar{\lambda}_{\max}$ to $\bar{\lambda}_{\min}$ follows the power law $\bar{\lambda} \sim \sqrt{\Phi_B \Phi_{el,a}^{-1} \ell \mu_d^2 / r_p}$ (green dotted line in **Figure 5A**). **Figure 5A** shows that increasing Φ_B at fixed particle size results in an increase of $\bar{\lambda}$. This trend is qualitatively in line with the discussion in §2.5 (inset **Figure 4A**). An increase in Φ_B leads indeed to a decreasing contribution of the dissociation term $\overline{Da}_d$, recalling that $\overline{Da}_a / \overline{Da}_d = \ell r_p^{-1} \Phi_B \left[1 + (\mu_d r_p^{-1})^2 \right]$. In turn, at sufficiently large Φ_B where the inequality $\overline{Da}_a / \overline{Da}_d \gg 1$ is satisfied, the dependence of $\bar{\lambda}$ on particle size becomes dictated, over the *whole* range of r_p , by the limit defined by eq 11. The gradual increase of Φ_B is therefore accompanied by a shift of $r_{p,\max}$ to larger r_p values and to extrema in $\bar{\lambda}$ that become progressively less pronounced until they vanish for $\Phi_B \gg 1$ (**Figure 5A**). A criterion for the presence/absence of maximum and minimum in $\bar{\lambda}$ *versus* r_p can be formulated in terms of $\Phi_{el,a}$, Φ_B and μ_d on the basis of the expressions reported in **Supporting Information** for $\bar{\lambda}_{\max}$ and $\bar{\lambda}_{\min}$. The reader is referred to **SIV-(C)** of the **Supporting Information (Table S3** therein) for details.

Altogether, **Figure 5A** makes the explicit connection between the spatial scales pertaining to M-NP chemodynamics expressed in terms of local intraparticulate conditions (*i.e.* r_p and μ_d) and those relevant for M-NP chemodynamics at the macroscopic scale (*i.e.* r_p and $\bar{\lambda}$). Namely, for conductive diffusion-controlled M-NP dissociation (*i.e.* $r_p \gg \mu_d$ or, equivalently, $k_d \rightarrow k_{d,p}$, see **Figure 2** with the here applicable $n_d = 2$), the dissociation term in the expression of $\bar{\lambda}$ dominates ($\overline{Da}_d / \overline{Da}_a \gg 1$) as a result of sluggish NP diffusion to the (bio)interface, thus rendering the NP exclusion process immaterial for defining the macroscopic reaction layer thickness. In the other limit $r_p \ll \mu_d$ (*i.e.* $k_d \rightarrow k_d^{is}$) corresponding to kinetically-controlled M-NP dissociation, it is the association term in $\bar{\lambda}$ that mediates the extension of the layer ($\overline{Da}_a / \overline{Da}_d \gg 1$) and, depending on the magnitude of $\overline{Da}_a$, NP exclusion may be significant. For intermediate situations where both chemical kinetics and conductive diffusion controlled M-NP dissociation count ($r_p = \mu_d$, *i.e.* $k_d^{is} = k_{d,p}$), $\bar{\lambda}$ exhibits a local minimum provided that

$\Phi_{\text{el,a}}$, Φ_{B} and μ_{d} obey the conditional expression detailed in **Supporting Information (SIV-(C), Table S3)**.

3.1.2. Impact of $\Phi_{\text{el,a}}$ on $\bar{\lambda}$. **Figure 5B** shows that increasing $\overline{Da}_{\text{a}} = \Phi_{\text{el,a}}$ at fixed Φ_{B} and μ_{d} leads to a decrease in $\bar{\lambda}$ for given particle size r_{p} . This trend corresponds to that detailed in **Figure 4A**. Qualitatively, all the features detailed in **Figure 5A** that define the dependence of $\bar{\lambda}$ on r_{p} , are preserved for $\Phi_{\text{el,a}} \ll 1$ (*i.e.* existence of the limiting regimes $r_{\text{p}} \gg \mu_{\text{d}}$ and $r_{\text{p}} \ll \mu_{\text{d}}$ and presence of local extrema in $\bar{\lambda}$). It is only when $\Phi_{\text{el,a}}$ reaches its maximum practical value (*i.e.* *ca.* unity) that $r_{\text{p,max}}$ slightly decreases. These findings are in agreement with the expressions provided for $r_{\text{p,max}}$ in **Supporting Information (SIV-(B), Table S2)**. The decrease observed for $\bar{\lambda}$ with increasing $\Phi_{\text{el,a}}$ is further in agreement with the power law $\bar{\lambda} \sim \Phi_{\text{el,a}}^{-1/y}$ (with $y = 2, 3$ or 4) as derived from eq 11 (valid for $r_{\text{p}} \ll r_{\text{p,max}} (< \mu_{\text{d}})$) applied in the limit $\Phi_{\text{el,a}} \ll 1$, and from the expression $\bar{\lambda} \sim \sqrt{\Phi_{\text{B}} \ell_{\text{p}} / \Phi_{\text{el,a}}}$ relevant for $r_{\text{p}} \gg \mu_{\text{d}}$.

3.1.3. Impact of μ_{d} on $\bar{\lambda}$. **Figure 5** mainly shows how the interplay between particle electrostatics, particle volume fraction and MS stability, as subsumed in the dimensionless quantities $\Phi_{\text{el,a}}$ and/or Φ_{B} , determine the extension $\bar{\lambda}$ of the macroscopic reaction layer from the (bio)interface.

Figure 6. As in **Figure 5** with varying μ_d (indicated) at fixed $\log(\Phi_{\text{el,a}}) = -2$ and $\log(\Phi_B) = 1$.

Figure 6 focuses on the contribution of the intraparticle reaction layer thickness μ_d . Unlike $\Phi_{\text{el,a}}$ and Φ_B , μ_d involves the rate constant k_w for inner sphere dehydration of M. The magnitude of k_w significantly varies depending on the nature of the metal ion, *e.g.* it ranges from $3 \times 10^4 \text{ s}^{-1}$ to $7 \times 10^9 \text{ s}^{-1}$ over the metal sequence Ni(II), Zn(II), Cd(II), Cu(II) and Pb(II).⁴¹ As k_w increases, μ_d decreases (all other parameters being constant), *i.e.* the overall M-NP dissociation becomes increasingly rate-limited by diffusion of M from the NP body (step (i) in **Figure 1**).²³ The larger is μ_d , *i.e.* the smaller k_w , the broader is the range of particle sizes r_p where $\bar{\lambda}$ is defined by eq 11 which corresponds to a dominating contribution of $\overline{Da_a}$ to $\bar{\lambda}$. On the other hand, the faster is inner-sphere MS dehydration kinetics, the larger is the particle size window where $\bar{\lambda}$ is determined by the dissociation term $\overline{Da_d}$, *i.e.* $\bar{\lambda} \sim \sqrt{\Phi_B \ell r_p / \Phi_{\text{el,a}}}$. In line with the preceding developments, the minimum in $\bar{\lambda}$ is positioned at $r_{p,\text{min}} = \mu_d$, and the maximum is shifted to lower r_p with decreasing μ_d , which again conforms to the expression of $r_{p,\text{max}}$ given in **Supporting Information (SIV-(B), Table S2)**.

3.1.4. Quantifying the contribution of the NP exclusion process to $\bar{\lambda}$. Following the discussion in §3.1.1, depending on the magnitude of $\overline{Da_a} = \Phi_{\text{el,a}}$ NP exclusion (*i.e.* γ) is significant in defining $\bar{\lambda}$ only within the regime $r_p \ll \mu_d$. Accordingly, the impact of this exclusion can be quantitatively addressed upon evaluation of the ratio $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ where $\bar{\lambda}(\gamma)$ is provided by eq 11 and $\bar{\lambda}(\gamma=0)$ is defined

by $\bar{\lambda}(\gamma=0) = r_p / \sqrt{\Phi_{\text{el},a}}$ which is derived from eq 10 in the limits $r_p \ll \mu_d$ and $\gamma=0$. It is straightforward to verify that this ratio $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ is independent of r_p and is solely determined by the magnitude of $\Phi_{\text{el},a}$ and z (**Figure 7**). At fixed z , $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ (≤ 1) decreases with increasing the contribution of the associative term $\overline{Da}_a = \Phi_{\text{el},a}$ in eq 10, in line with the conclusions drawn from **Figure 4**. That is, the NP exclusion process generates an increased extension of the macroscopic reaction layer and this increase is more pronounced for large $\overline{Da}_a = \Phi_{\text{el},a}$. Two regimes may be distinguished: (i) for $\Phi_{\text{el},a} < X_{\min}^2(z)/(1-X_{\min}(z))$, $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ is independent of z , which corresponds to the range of $\overline{Da}_a = \Phi_{\text{el},a}$ values where γ identifies to $r_p/\bar{\lambda}$ (eqs 6-7); (ii) for $\Phi_{\text{el},a} > X_{\min}^2(z)/(1-X_{\min}(z))$, $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ (slightly) increases with z , which originates from the moderate z -dependence of γ detailed in **Figure 4B**. As $X_{\min}^2(z)/(1-X_{\min}(z))$ varies between 0.87 and

Figure 7. Ratio $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ applying in the regime $r_p \ll \mu_d$ (see eq 11), as a function of $\Phi_{\text{el},a}$ for various values of z (indicated). The ratio is independent of z for $\Phi_{\text{el},a}$ lower than $X_{\min}^2(z)/(1-X_{\min}(z))$, this boundary is indicated by the shaded red area. See text for details.

0.5 for $0 \leq z < 1$ (shaded red zone in **Figure 7**), practical values of $\Phi_{\text{el},a} (< 1)$ basically correspond to situations where the presence of a core within the 3D NP body does not impact on $\bar{\lambda}$ (z appears in eq 10 only through the γ term). In addition, the inspection of **Figure 7** reveals that under the $\Phi_{\text{el},a}$ conditions adopted in **Figure 5B**, the exclusion of NPs from the reaction layer leads to a *ca.* 40% increase of $\bar{\lambda}$ for

$\Phi_{\text{el},a} = 1$ as compared to the situation $\gamma = 0$, and this contribution decreases to 5% for $\Phi_{\text{el},a} = 10^{-2}$. To summarize, the extent by which γ affects the reaction layer thickness $\bar{\lambda}$ at any value of $\Phi_{\text{el},a}$ in line with the practical condition $\Phi_{\text{el},a} < 1$, is tied to deviation of $2^{-1}\sqrt{\Phi_{\text{el},a}}\left(-1 + \sqrt{1 + 4\Phi_{\text{el},a}^{-1}}\right)$ (≤ 1) from unity, which directly follows from the expression of $\bar{\lambda}(\gamma=0)/\bar{\lambda}(\gamma)$ applicable for $r_p \ll \mu_d$ and $\Phi_{\text{el},a} \ll 1$.

3.2. The case of 2D hard particulate ligands ($z=1$) with a given surface density Γ_s of metal binding sites.

For situations of 2D hard complexing particles with fixed surface density Γ_s of binding sites S, the development of eq 3 with use of the relevant expressions for $n_{a/d}$, $\ell_{a/d}$ and $\Lambda_{a/d}$ collected in **Table 1B** (left column) and of the relation $\bar{c}_s = 3\Gamma_s\varphi/r_p$ leads to a defining expression of $\Lambda = \bar{\lambda}/r_p$ that is identical to eq 10 with $\Phi_{\text{el},a} = 3\varphi f_{\text{el},a}$, $\Phi_B = \varphi f_B / \left(1 + K_{\text{int}}^{(z=1)}\Gamma_s\right)$ and $\mu_d = \ell_d\Lambda_d^{-1/2} = \ell_d\sqrt{f_{\text{el},a}/f_B}$. The situation tackled here is therefore completely analogous to that detailed in §3.1 for 3D NPs with fixed c_s provided that the 3D-relevant quantities $\bar{f}_{\text{el},a}$, $\bar{f}_B$, K_{int} and $K_{\text{int}}c_s$ are replaced by their 2D equivalents $f_{\text{el},a}$, f_B , K_H/Γ_s and $K_{\text{int}}^{(z=1)}\Gamma_s$, respectively, and that proper expression of γ applicable for 2D hard particles is considered (**Figure 3**). This similarity is subject to the assumption that the water content in 3D soft/core-shell NPs is sufficiently large so that intraparticulate diffusion is not rate limiting the overall association/dissociation of nanoparticulate metal complexes.²³ All conclusions and expressions provided in §3.1 for the particle size regimes $r_p \ll r_{p,\text{max}} (< \mu_d)$ and $r_p \gg \mu_d$ therefore remain applicable with use of these equivalencies. This parallel between reactivities of 3D soft NPs under constant c_s condition and 2D hard NPs with fixed Γ_s in the vicinity of a macroscopic (bio)interface is similar to that identified elsewhere²³ within the framework of chemodynamics of metal ion complexation by these particulate ligands.

For the sake of conciseness, the situations of 3D soft/core-shell particulate ligands ($0 \leq z < 1$) and 2D hard particulate ligands ($z=1$) defined by a given number N_s of metal binding sites (*i.e.* N_s is independent of particle radius r_p) are detailed in **sections SV** and **SVI** of the **Supporting Information**, respectively. The analogues of eq 10 in such situations are provided and the ensuing characteristic dependence of the reaction layer thickness $\bar{\lambda}$ on particle size r_p is extensively detailed. In the following

section, experimental data are collated with the theoretical framework detailed in §3.1 and comparison between experiments and theory evidences the sound physico-chemical basis of the formalism. In particular, it highlights the importance of considering particle body exclusion from the reaction layer for a proper evaluation of the lability of nanoparticulate metal complexes at reactive (bio)interfaces.

3.3. Practical illustrations.

The primary parameter of interest in the context of the present work is the magnitude of the kinetic flux, J_{kin} , for M-NP entities at a reactive (bio)interface. Knowledge of J_{kin} is fundamental to interpretation of data from various dynamic metal speciation sensors and for predictions of bioavailability. Accordingly, the practical relevance of the theory presented in §3.1 is demonstrated by comparing the magnitude of J_{kin} computed for metal complexes with 3D soft and core-shell NPs using (i) a conventional approach with an associative reaction layer only ($K_{\text{int}}\bar{c}_s \gg 1$), and (ii) the present treatment with both an associative and a dissociative reaction layer included, taking into account exclusion of particle body from the reaction layer. We stress that even for cases where the magnitude of $\bar{\lambda}$ (eq 2) is dominated by the dissociation term (so that $\bar{c}_s(1-\gamma)$ is immaterial), the exclusion factor $1-\gamma$ does impact on the concentration of inner-sphere complexes, MS, that lies within the reaction layer of thickness $\bar{\lambda}$, i.e. $\bar{c}_{\text{MS}}(1-\gamma)$. Hence the extent to which NPs are excluded from the macroscopic reaction layer can have a significant effect on the magnitude of J_{kin} .

Conventionally J_{kin} is given by:

$$J_{\text{kin}} = k_{\text{d}}^{\text{is}} \bar{c}_{\text{MS}} \mu \quad (12)$$

, where $\bar{c}_{\text{MS}}$ is the smeared-out concentration of inner-sphere complexes MS over the sample volume, $\mu = (k_{\text{a}}\bar{c}_s / D_{\text{M}})^{-1/2}$ is the association reaction layer, and possible exclusion of particle body from the reaction layer is ignored.

Using the theory detailed in the preceding sections, we can write:

$$J_{\text{kin}} = k_{\text{d}}^{\text{is}} \bar{c}_{\text{MS}} (1-\gamma) \bar{\lambda} \quad (13)$$

The J_{kin} values computed on the basis of eqs 12 and 13 are compared in **Table 2** for Cu(II) complexes with 3D humic acid (HA) particles⁴² and Cd(II) complexes with core-shell carboxyl functionalized latex NPs.⁴³ Humic acids (HAs) are soft NPs that carry a high negative charge at near neutral pH;⁴⁴ they are ubiquitous in environmental systems and complex a range of trace metal ions of biological relevance. The core-shell latex NPs typify the properties of many engineered impermeable NPs that carry a thin layer of reactive sites at their surface.⁴⁵

NP type	r_p / nm	a / nm	d / nm	$1-\gamma$	μ / m	$\bar{\lambda} / \text{m}$	$J_{\text{kin}} (\mu)$ $\text{mol m}^{-2} \text{s}^{-1}$	$J_{\text{kin}} (\bar{\lambda})$ $\text{mol m}^{-2} \text{s}^{-1}$
3D(soft) ^b	80	0	80	0.005	1.5×10^{-6}	1.1×10^{-8}	7.0×10^{-4}	2.7×10^{-8}
core-shell ^c	71	70	1	0.035	5.0×10^{-7}	1.0×10^{-8}	7.6×10^{-5}	5.4×10^{-8}

Table 2. Kinetic flux, J_{kin} , for soft and core-shell NPs: comparison of approach with dedicated reaction layer, $J_{\text{kin}} (\bar{\lambda})$, with the conventional smeared-out approach, $J_{\text{kin}} (\mu)$.^a

^a k_w for $\text{Cu}(\text{H}_2\text{O})_6^{2+}$ is $1 \times 10^9 \text{ s}^{-1}$ and k_w for $\text{Cd}(\text{H}_2\text{O})_6^{2+}$ is $3 \times 10^8 \text{ s}^{-1}$,⁴¹ $D_{\text{Cu}} = 7.2 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$, $D_{\text{Cd}} = 7.0 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$.

^b Cu-HA at pH 6, solution ionic strength = 10 mol m^{-3} , $K_{\text{int}} = 10 \text{ m}^3 \text{ mol}^{-1}$, density of negatively charged reactive sites in the soft particle body = 700 mol m^{-3} , $D_p = 2.74 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$.⁴² Computations are performed for a particle volume fraction of 10^{-3} and a degree of reactive site coverage of 0.03, *i.e.* 3% of the reactive sites are occupied by M. In addition, $\bar{f}_B = 5 \times 10^3$ and $\bar{f}_{\text{el,a}} = 1$ (see Refs [20] and [42]).

^c Cd-latex at pH 6.5, solution ionic strength = 10 mol m^{-3} , $K_{\text{int}} = 2.25 \text{ m}^3 \text{ mol}^{-1}$, density of negatively charged reactive sites in the soft shell = 1014 mol m^{-3} , $D_p = 3.09 \times 10^{-12} \text{ m}^2 \text{ s}^{-1}$.⁴³ Computations are performed for a particle volume fraction of 5.9×10^{-3} (which corresponds to a particle shell volume fraction of *ca.* 2.5×10^{-4}) and a degree of reactive site coverage of 0.02 with $\bar{f}_B = 140.5$ and $\bar{f}_{\text{el,a}} = 1.16$ (derived from the electrostatic NP features reported in Ref. [45]).

The results in **Table 2** show that, as expected, the exclusion effect has a greater impact on the 3D case. For both types of particles the conventional approach overestimates J_{kin} by 3 orders of magnitude for the core-shell NPs and by more than 4 orders of magnitude for the 3D NPs. Such discrepancies can be highly significant in the context of dynamic metal speciation analysis, *e.g.* voltammetric measurements, and for predictions of bioavailability. The contribution of metal ions released from nanoparticles to the overall flux of metal species towards a reactive (bio)interface derives from the relative magnitudes of J_{kin} , the diffusive flux, J_{diff} , and the operational timescale of the interfacial process of interest, *e.g.* as determined by the thickness of the macroscopic diffusion layer.⁴ The concept of lability describes the interplay between these features. The formulation of lability criteria for nanoparticulate complexes will be comprehensively explored in our forthcoming work. Here we give a brief illustration to underscore the applicability of the theoretical framework developed herein. Lability is a well-accepted and extensively documented feature in the electrochemistry of metal complexes for more than half a century.¹⁰⁻¹³ Taking the example of electrochemical reduction of free metal ions from a dispersion of M-NP complexes, the

lability of the M-NP species corresponds to the ratio of the measured current and the current corresponding to the purely diffusive flux. The latter is obtained from measurement of a metal-only solution and accounting for the applicable diffusion coefficient difference.⁴³ The theoretical lability criterion, $\mathcal{L}$, is given by the ratio of the kinetic and diffusive fluxes; $\mathcal{L} \gg 1$ corresponds to a labile complex. Voltammetric measurements have been reported for the core-shell Cd(II)-latex system given in **Table 2**.⁴³ The $\mathcal{L}$ values derived from experiment and theory are compared in **Table 3**. The new theoretical framework, with a dedicated reaction layer, $\bar{\lambda}$, and accounting for exclusion of the particle body from the reaction layer at the electrode surface, is shown to provide excellent agreement with the experimental data. In contrast, the conventional approach overestimates $\mathcal{L}$ by more than 3 orders of magnitude. This strikingly highlights the paramount importance of considering particle body exclusion from reaction layer for a proper derivation of metal complex lability diagnosis at reactive (bio)interfaces.

$I_{\text{meas}} / \text{nA}$	$I_{\text{labile}} / \text{nA}$	$\mathcal{L}_{\text{expt}}$	$\mathcal{L}_{\text{calc}} (\mu)$	$\mathcal{L}_{\text{calc}} (\bar{\lambda})$
0.68	1.3	0.52	1.858×10^3	0.55

Table 3. Comparison of the lability criteria derived from voltammetric measurements, $\mathcal{L}_{\text{expt}}$, with theoretically predicted values, $\mathcal{L}_{\text{calc}}$, computed using (i) the conventional association reaction layer thickness μ and ignoring possible exclusion of the particle body from the reaction layer at the electrode surface, and (ii) the dedicated reaction layer thickness $\bar{\lambda}$ together with exclusion of the particle body from the reaction layer. The voltammetric currents, I , were measured by differential pulse polarography, under the conditions given in Table 2 for the core-shell Cd(II)-latex system.⁴³

4. Conclusions and future developments.

This work reports a comprehensive elaboration of the concept of a non-equilibrium reaction layer adjacent to a macroscopic metal responsive (bio)interface in contact with an aqueous dispersion of nanoparticulate metal complexes. The analysis integrates the intricate coupling between (i) the chemodynamics of nanoparticulate metal complexes, as determined by the physicochemical conditions prevailing in the local intraparticulate or particle surface environment, (ii) the purely geometrical exclusion of part of the NP body/surface from the reaction layer, which modifies the averaged concentration of metal binding sites effective for the reactivity of free metal ions at the surface of the macroscopic sensing (bio)interface, and (iii) the very different mobilities of free metal ions and metal complexes in solution, as fixed by their respective Brownian diffusion coefficients. The expressions for

the macroscopic reaction layer thickness are derived as a function of nanoparticle properties (size, electrostatic features, 3D soft/core-shell or 2D hard types, density/number of binding sites), dehydration kinetic features of the metal ion, stability of molecular inner-sphere metal complexes, and particle volume fraction in the dispersion. The contributions of these various molecular, particulate and macroscopic factors to the magnitude of the operational reaction layer at the (bio)interface are rationalized *via* the introduction of convenient dimensionless parameters together with the applicable intraparticulate dissociation reaction layer thickness. Computational illustrations, supported by analytical expressions, quantitatively capture the multi-scale nature of the reaction layer operational for nanoparticulate metal complexes reactivity in the vicinity of macroscopic (bio)interface. The outcome can differ drastically from that obtained using a conventional approach as illustrated by the example cases of Cu(II) complexes with soft NPs and Cd(II) complexes with core-shell NPs.

The formalism provides the relevant physicochemical dynamic elements for a proper rationale of the lability of M-NP complexes towards a reactive macroscopic interface. This step is mandatory for defining the contribution of particulate complex dissociation to the overall flux of metal to *e.g.* microorganisms, and thereby is implicated in quantifying the role of complexes in mediating metal toxicity effects. The current theory further paves the way for a range of developments that shall be addressed in forthcoming work, including (i) comparison of the steady-state approach considered herein with analysis of the transient and depletion features of M-NPs inside the macroscopic diffusion layer computed *via* coupled transient Nernst-Planck equations applicable at the macroscopic and nano-scales, (ii) the implications of NP exclusion for the ensuing lability of M-NP complexes by comparison of the applicable kinetic and diffusive fluxes at various reactive interfaces, (iii) the impacts of colloidal interactions (*e.g.* electrostatics and van der Waals) between the macroscopic (bio)interface and metal complexes on the lability of the latter, and (iv) extension of the concepts to incorporate the physical and chemical heterogeneity typical of NPs in environmental and biological media, as well as mixtures of metal ions: precedents for mixture-type effects exist in the molecular literature.⁴⁶ Each of these developments is challenging in its own right and shall pave the way for rigorous interpretation of the chemodynamic features of nanoparticulate metal species in environmental and biological systems.

Supporting Information.

SI. Demonstration of eq 3. **SII.** Expression of the conditional function F involved in eq 5 and demonstrations of eqs 6-8. **SIIL.** (A) Expressions of the quadratic, cubic and quintic polynomial functions $P(\Lambda)$ derived from combining eq 9 with eqs 6, 7 or 8. (B) Approximate solutions for Λ within the framework of the $(\overline{Da}_a, \overline{Da}_d)$ representation introduced in §2.5. **SIV.** (A) Derivation of eq 10 and solutions thereof in the limits $r_p \gg \mu_d$ and $r_p \ll r_{p,max} (< \mu_d)$. (B) Expressions of $r_{p,max}$, $\bar{\lambda}_{max}$ and $\bar{\lambda}_{min}$ as a function of the relevant $\Phi_{el,a}$, Φ_B and μ_d for 3D soft/core-shell particles under constant c_s

condition. (C) Quantitative criterion for the presence/absence of maximum and minimum in $\bar{\lambda}$ versus r_p for 3D soft/core-shell particles under constant c_s condition. **SV. (A)** The case of 3D soft/core-shell particulate ligands ($0 \leq z < 1$) with a given number N_s of metal binding sites. **(B)** Demonstration of the pendant of eq 10 for 3D particulate soft/core-shell ligands ($0 \leq z < 1$) with a given number N_s of metal binding sites. **(C)** Dependence of $\bar{\lambda}$ on particle size r_p for different values of $z = a/r_p$ and μ_d for 3D soft/core-shell particles under constant N_s condition. **SVI. (A)** The case of 2D hard particulate ligands ($z = 1$) with a given number N_s of metal binding sites. **(B)** Expressions of Λ (or $\bar{\lambda}$) in some practical limits of particle size r_p for 2D hard particulate ligands ($z = 1$) with fixed N_s .

Glossary of main symbols

a Particle core radius [m]

d Particle shell thickness [m]

c_s Density of binding sites S within the particle shell volume (applicable for 3D NP complexants) [mol m⁻³]

$\bar{c}_s$ Density of binding sites S smeared-out over the sample volume [mol m⁻³]

c_M^* Bulk concentration of metal ions M [mol m⁻³]

$\bar{c}_{MS}$ Density of inner-sphere complexes smeared-out over the sample volume [mol m⁻³]

c^∞ Bulk electrolyte concentration [mol m⁻³]

D_M Diffusion coefficient of M [m² s⁻¹]

D_p Diffusion coefficient of the nanoparticle [m² s⁻¹]

$Da_{a/d}$ Damkohler numbers pertaining to M-NP formation and dissociation (subscript 'a' and 'd', respectively)

$\overline{Da}_{a/d}$ Damkohler numbers defined by $\overline{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$ and $\overline{Da}_d = k_d r_p^2 / D_p$

$f_{el,a}$ Factor for conductive diffusion of M to the surface of 2D hard nanoparticulate complexant

$\bar{f}_{el,a}$ Factor for conductive diffusion of M to the reactive component of 3D nanoparticulate complexant

$f_{el,d}$ Factor for conductive diffusion of M from the surface of hard nanoparticulate complexant

$\bar{f}_{el,d}$ Factor for conductive diffusion of M from the reactive volume of 3D nanoparticulate complexant

f_B Factor for Boltzmann accumulation of M at the surface of 2D nanoparticulate complexant

$\bar{f}_B$ Factor for volume-averaged Boltzmann accumulation of M in the reactive component of 3D nanoparticulate complexant

J_{kin} Kinetic flux arising from the rate of dissociation of complexed species [mol m² s⁻¹]

J_{diff}^1 Diffusive flux arising from the diffusion of all forms of the metal towards a reactive macrointerface [mol m² s⁻¹]

k_a Kinetic constant for M-NP formation [mol⁻¹ m³ s⁻¹]

k_d Kinetic constant for M-NP dissociation [s⁻¹]

k_a^{is} Kinetic constant for inner sphere MS formation [mol⁻¹ m³ s⁻¹]

k_d^{is} Kinetic constant for inner sphere MS dissociation [s⁻¹]

$k_{a,p}$ Kinetic constant for M conductive diffusion to intraparticulate or surface binding sites S [mol⁻¹ m³ s⁻¹]

$k_{d,p}$ Kinetic constant for M conductive diffusion from intraparticulate or surface binding sites S [s⁻¹]

k_w Kinetic constant for inner-sphere dehydration of M^{z+} [s^{-1}]
 $K_{int}, K_{int}^{(z=1)}$ Stability constant for inner sphere metal complexes in 3D complexing nanoparticles [$mol^{-1} m^3$] or at the surface of 2D nanoparticles (superscript ' $z = 1$ ', [$mol^{-1} m^2$])
 K_H Henry coefficient for adsorption of M at the surface of 2D complexing nanoparticles [m]
 $\mathcal{L}$ Lability of metal complexes (defined as the ratio between J_{kin} and J_{diff}).
 $\ell_{a/d}$ Thickness of intraparticulate association/dissociation reaction layers devoid of electrostatic contributions (subscript 'a' and 'd', respectively) [m]
M Metal ion
M-NP Metal-nanoparticle complex
MS Inner-sphere complex
 N_s Number of metal binding sites S per particle
NP Nanoparticulate complexant
 $n_{a/d}$ Integer numbers involved in eq 1
 r Radial coordinate [m]
 $r_{int}, r_{int}^{(z=1)}$ Length scales that depend on MS stability constants K_{int} and $K_{int}^{(z=1)}$, respectively [m]
 r_p Particle radius $a + d$ [m]
S Metal binding site
 V^{OS} Outer-sphere volume per site S [m^3]
 γ_D Dimensionless Donnan potential
 z_M Valence of M
 z Defined by the ratio a / r_p

Greek symbols

φ Particle volume fraction
 $\Phi_{el,a}; \Phi_B$ Dimensionless numbers involved in the expressions of $\bar{\lambda}$ and Λ
 Γ_s Surface density of metal binding sites S (applicable for 2D complexing nanoparticles)
 $1 / \kappa_p$ Thickness of intraparticulate electric double layer [m]
 $1 / \kappa$ Thickness of extraparticulate electric double layer [m]
 $\Lambda_{a/d}$ Dimensionless numbers in eq 1 that correct $k_{a/d}$ for particle electrostatics and particle ligand type
 γ Factor that mirrors the extent of NP exclusion from the macroscopic reaction layer ($0 \leq \gamma \leq 1$)
 Λ Dimensionless ratio defined by $\bar{\lambda} / r_p$
 ψ_D Donnan potential [V]
 $\bar{\lambda}$ Macroscopic reaction layer thickness [m]
 μ_d Intraparticulate dissociation reaction layer thickness [m]
 μ Conventional macroscopic association reaction layer thickness [m]
 ρ_o Volume charge density of 3D nanoparticles [$C m^{-3}$]
 σ_o Surface charge density of 2D nanoparticles [$C m^{-2}$]

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Figure 2

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Figure 3

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Figure 4

254x190mm (96 x 96 DPI)

Figure 5

254x190mm (96 x 96 DPI)

Figure 6

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Figure 7

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A 3D soft or core-shell complexing NPs ($0 \leq z < 1$)								
Constant c_s						Constant N_s		
n_a	Λ_a	ℓ_a	n_a	Λ_a	ℓ_a			
2	$\frac{1-z^3}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M}{k_wV^{os}N_{Av}c_s}}$	-1	$\frac{1}{\bar{f}_{el,a}}$	$\frac{k_wV^{os}N_s}{4\pi D_M}$			
n_d	Λ_d	ℓ_d	n_d	Λ_d	ℓ_d			
2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_M(1+K_{int}c_s)}{k_wV^{os}N_{Av}K_{int}^{-1}}}$	2	$\frac{\bar{f}_B}{\bar{f}_{el,a}}$	$\sqrt{\frac{3D_MK_{int}}{k_wV^{os}N_{Av}}}$	for $r_p \gg \frac{r_{int}}{(1-z^3)^{1/3}}$		
			5	$\frac{\bar{f}_B(1-z^3)}{\bar{f}_{el,a}}$	$\left(\frac{9D_MN_sK_{int}^2}{4\pi k_wV^{os}N_{Av}^2}\right)^{1/5}$	for $r_p \ll \frac{r_{int}}{(1-z^3)^{1/3}}$		

Table 1

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B 2D hard complexing NPs ($z = 1$)						
Constant Γ_s			Constant N_s			
n_a	Λ_a	ℓ_a	n_a	Λ_a	ℓ_a	
1	$\frac{1}{f_{el,a}}$	$\frac{D_M}{k_w V^{os} N_{Av} \Gamma_s}$	-1	$\frac{1}{f_{el,a}}$	$\frac{k_w V^{os} N_s}{4\pi D_M}$	
n_d	Λ_d	ℓ_d	n_d	Λ_d	ℓ_d	
2	$\frac{f_B}{f_{el,a}}$	$\sqrt{\frac{3D_M(1+K_{int}^{(z=1)}\Gamma_s)}{k_w V^{os} N_{Av} \Gamma_s K_H^{-1}}}$	0	$\frac{k_w V^{os} N_s}{12\pi f_{el,d} D_M K_H}$	<i>not applicable</i>	for $r_p \gg r_{int}^{(z=1)}$
			2	$\frac{f_B}{f_{el,a}}$	$\sqrt{\frac{3D_M K_{int}^{(z=1)}}{k_w V^{os} N_{Av} K_H^{-1}}}$	for $r_p \ll r_{int}^{(z=1)}$

Table 1 (follow up)

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NP type	r_p / nm	a / nm	d / nm	$1-\gamma$	μ / m	$\bar{\lambda}$ / m	$J_{\text{kin}}(\mu)$ mol m ⁻² s ⁻¹	$J_{\text{kin}}(\bar{\lambda})$ mol m ² s ⁻¹
3D(soft) ^b	80	0	80	0.005	1.5x10 ⁻⁶	1.1x10 ⁻⁸	7.0x10 ⁻⁴	2.7x10 ⁻⁸
core-shell ^c	71	70	1	0.035	5x10 ⁻⁷	1.0x10 ⁻⁸	7.6x10 ⁻⁵	5.4x10 ⁻⁸

Table 2

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$I_{\text{meas}} / \text{nA}$	$I_{\text{labile}} / \text{nA}$	$\mathcal{L}_{\text{expt}}$	$\mathcal{L}_{\text{calc}} (\mu)$	$\mathcal{L}_{\text{calc}} (\bar{\lambda})$
0.68	1.3	0.52	1.858×10^3	0.55

Table 3

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Figure 1 is a log-log plot showing the relationship between the reaction layer thickness (nm) on the y-axis and the soft particle radius (μm) on the x-axis. The y-axis ranges from 1 nm to 100 nm, and the x-axis ranges from 1 nm to 1 μm. Two curves are shown: a red curve labeled 'kinetically-controlled complex dissociation' and a blue curve labeled 'diffusion-controlled complex dissociation'. The red curve has a slope of 1, and the blue curve has a slope of 1/2. An inset diagram illustrates the reaction layer, metal-sensitized (bio)interface, and complexing nanoparticles, with arrows indicating diffusion and chemical kinetics.

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SUPPORTING INFORMATION

Applicability of the Reaction Layer Principle to Nanoparticulate Metal Complexes at a Macroscopic Reactive (Bio)Interface: a Theoretical Study

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NB. The references indicated in this document are those of the main text. All symbols, unless otherwise specified, are defined in the main text (see glossary therein).

SI. Demonstration of eq 3.

Equation 2 in the main text may be rewritten in the form of eq 9, *i.e.*

$$\Lambda^2 \overline{Da}_a \left[1 - \gamma(\Lambda) + \overline{Da}_d / \overline{Da}_a \right] - 1 = 0 \quad (s1)$$

, where $\Lambda = \bar{\lambda} / r_p$, $\overline{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$ and $\overline{Da}_d = k_d r_p^2 / D_p$. The ratio $\overline{Da}_d / \overline{Da}_a$ involved in eq s1 directly follows from the defining expressions of $\overline{Da}_a$ and $\overline{Da}_d$ that involve the rate constants $k_{a,p}$ and k_d with the result $\overline{Da}_d / \overline{Da}_a = k_d D_M / (k_{a,p} \bar{c}_s D_p)$. Using eq 1, the latter ratio $\overline{Da}_d / \overline{Da}_a$ can be recast in the form

$$\overline{Da}_d / \overline{Da}_a = \frac{D_M}{D_p \bar{c}_s} \frac{k_d^{is} / k_a^{is}}{1 + k_d^{is} / k_{d,p}} \frac{1}{k_{a,p} / k_a^{is}}. \quad (s2)$$

Recalling that the Damkohler numbers $Da_d = \Lambda_d (r_p / \ell_d)^{n_d}$ and $Da_a = \Lambda_a (r_p / \ell_a)^{n_a}$ identify to $k_d^{is} / k_{d,p}$ and $k_a^{is} / k_{a,p}$, respectively,²³ eq s2 becomes

$$\overline{Da}_d / \overline{Da}_a = \frac{D_M}{D_p} \frac{k_d^{is}}{k_a^{is} \bar{c}_s} \frac{Da_a}{1 + Da_d}. \quad (s3)$$

Substituting eq s3 into eq s1, we obtain eq 3 in the main text.

SII. Expression of the conditional function F involved in eq 5 and demonstrations of eqs 6-8.

Let us first consider the situation depicted in **Figure 1A** that applies for a 3D soft particle. The particle volume lying within the reaction layer of thickness $\bar{\lambda}$ is given by $\pi L^2(3r_p - L)/3$ where L is specified in **Figure 1A**. This expression can be rearranged according to $\pi \bar{\lambda}^3(1 - H/\bar{\lambda})^2(3r_p/\bar{\lambda} - 1 + H/\bar{\lambda})/3$ where we introduced the distance $H = \bar{\lambda} - L$ separating the M-sensing (bio)interface and the soft nanoparticulate complexant (see **Figure 1A**). Averaging this expression over all possible positions of the particle center from the (bio)sensor surface, or, equivalently, over the separation distance H , we obtain for $V_{\text{cap}}(\bar{\lambda})$ involved in eq 4

$$V_{\text{cap}}(\bar{\lambda}) = \frac{\pi \bar{\lambda}^3}{3} \int_0^1 (1-x)^2 (3\Lambda^{-1} + x - 1) dx \quad (\text{s4})$$

, with $\Lambda = \bar{\lambda}/r_p$ and $x = H/\bar{\lambda}$ ($0 \leq x \leq 1$). Obviously, $V_{\text{cap}}(\bar{\lambda}) = 4\pi r_p^3/3$ (i.e. $\gamma = 0$) for $H + 2r_p \leq \bar{\lambda}$ (i.e. $0 \leq x \leq 1 - 2\Lambda^{-1}$) and $V_{\text{cap}}(\bar{\lambda}) = 0$ (i.e. $\gamma = 1$) for $x > 1$. The latter situation is not encountered within the integration domain relevant in eq s4. In turn, eq 4 combined with eq s4 leads to

$$\gamma(\Lambda) = 1 - \frac{\Lambda^3}{4} \int_0^1 F(\Lambda, z=0, x) dx \quad (\text{s5})$$

, with $F(\Lambda, z=0, x) = 4\Lambda^{-3}$ for $0 \leq x \leq 1 - 2\Lambda^{-1}$, $F(\Lambda, z=0, x) = (1-x)^2(3\Lambda^{-1} + x - 1)$ for $1 - 2\Lambda^{-1} < x \leq 1$. This formulation defines the conditional function $F(\Lambda, z, x)$ involved in eq 5 for the specific case of soft complexing NPs ($z = 0$). In the limit $\Lambda^{-1} \ll 1$ (i.e. $r_p \ll \bar{\lambda}$ or, equivalently, $x \approx 1$),

$V_{\text{cap}}(\bar{\lambda})$ is provided by $V_{\text{cap}}(\bar{\lambda}) \approx 4\pi r_p^3/3 - \pi \bar{\lambda}^{-1} \int_0^{2r_p} h^2(3r_p - h) dh/3$ with $h = 2r_p - L$, which yields

after calculation $\gamma(\Lambda) = \Lambda^{-1}$. In the other extreme $\Lambda^{-1} \gg 1$, we have

$V_{\text{cap}}(\bar{\lambda}) = \pi \bar{\lambda}^{-1} \int_0^{\bar{\lambda}} h^2(3r_p - h) dh/3$, which provides $\gamma(\Lambda) = 1 + \Lambda^2(\Lambda/4 - 1)/4$. Numerical evaluation of

eq s5, comparison with the aforementioned analytical results obtained in the limits $\Lambda^{-1} \ll 1$ and $\Lambda^{-1} \gg 1$ and further analysis of continuity of $\gamma(\Lambda)$ and $d\gamma(\Lambda)/d\Lambda$ at $\Lambda^{-1} = 1/2$ demonstrate the applicability of the conditional eq 6 formulated in the main text and illustrated in **Figure 3A**.

The above strategy can be applied for the general situation of 3D core-shell NPs ($0 < z < 1$) with (i) a proper consideration of the various positioning of the particle core relative to the boundary $\bar{\lambda}$ of the

reaction layer (**Figure 1B**), and (ii) the replacement of eq s5 by eq 5 that adequately reflects the absence of metal binding sites S within the NP core component. After lengthy algebra, the conditional function $F(\Lambda, z, x)$ now reads as

$$F(\Lambda, z, x) = \begin{cases} 4(1-z^3)\Lambda^{-3}, & \text{for } 0 \leq x < 1-2\Lambda^{-1} \\ (1-x)^2(3\Lambda^{-1}+x-1)-4(z\Lambda^{-1})^3, & \text{for } 1-2\Lambda^{-1} \leq x < 1-(1+z)\Lambda^{-1} \\ (1-x)^2(3\Lambda^{-1}+x-1)-[1-x-(1-z)\Lambda^{-1}]^2[x-1+(1+2z)\Lambda^{-1}], & \text{for } 1-(1+z)\Lambda^{-1} \leq x < 1-(1-z)\Lambda^{-1} \\ (1-x)^2(3\Lambda^{-1}+x-1), & \text{for } 1-(1-z)\Lambda^{-1} \leq x \leq 1 \end{cases} \quad (\text{s6})$$

Similarly to the soft NP case, derivation of analytical expressions for $V_{\text{cap}}(\bar{\lambda})$ (and thus γ) is possible for core-shell complexants in the extremes $\Lambda^{-1} \ll 1$ and $\Lambda^{-1} \gg 1$, with distinction in this latter limit of the situations $d < \bar{\lambda}$ (or $\Lambda > 1-z$) and $d > \bar{\lambda}$ (or $\Lambda < 1-z$). The results are detailed in eq 7. Inspection of these analytical results and comparison with the numerical outcome of eq 5 with $F(\Lambda, z, x)$ defined by eq s6, shows that eq 7 reproduces the whole dependence of γ on Λ and z (**Figure 3B**) upon introduction

of the function $X_{\min}(z) = \left[\frac{z^2}{2} \left(\frac{z+11/3}{z+1} \right) + \frac{17}{6} \right]^{-1/2}$ that marks the transition between the Λ domains

where the γ -expressions pertaining to $\Lambda^{-1} \ll 1$ and $\Lambda^{-1} \gg 1$ can be applied.

Last, the methodology outlined in the preceding developments can be followed to tackle the 2D hard NP case for which γ is now defined by

$$\gamma(\Lambda) = 1 - \frac{A_{\text{cap}}(\bar{\lambda})}{4\pi r_p^2} \quad (\text{s7})$$

, where $A_{\text{cap}}(\bar{\lambda}) \approx 4\pi r_p^2 - \bar{\lambda}^{-1} \int_0^{2r_p} 2\pi h r_p dh$ for $\Lambda^{-1} \ll 1$ and $A_{\text{cap}}(\bar{\lambda}) = \bar{\lambda}^{-1} \int_0^{\bar{\lambda}} 2\pi h r_p dh$ for $\Lambda^{-1} \gg 1$,

leading to the analytical expressions $\gamma(\Lambda) = \Lambda^{-1}$ and $\gamma(\Lambda) = 1 - \Lambda/4$, respectively (**Figure 3B**). These results correspond to eq 8 that properly reproduces -over the whole range of Λ - the outcome of eq 5 taken in the limit $z \rightarrow 1$ with $F(\Lambda, z, x)$ defined by the conditional expressions in eq 7 and applicable for $z \rightarrow 1$, that is $0 \leq \Lambda < 1/X_{\min}(1)$ and $\Lambda \geq 1/X_{\min}(1)$ with $X_{\min}(1) = 1/2$.

SIIL. (A) Expressions of the quadratic, cubic and quintic polynomial functions $P(\Lambda)$ derived from combining eq 9 with eqs 6, 7 or 8.

Substituting eq 6, 7 or eq 8 into eq 9, we obtain after some rearrangements the following polynomial expressions in Λ that depend on $\overline{Da}_a$, $\overline{Da}_d$ and z

$$\text{For } z = 0: \begin{cases} \Lambda^5 - 4\Lambda^4 + 16\overline{Da}_a^{-1}(1 - \overline{Da}_d\Lambda^2) = 0, \text{ for } \Lambda \leq 2 \\ \Lambda^2 - (\overline{Da}_a + \overline{Da}_d)^{-1}(1 + \overline{Da}_a\Lambda) = 0, \text{ for } \Lambda > 2 \end{cases} \quad (\text{s8})$$

$$\text{For } 0 < z < 1: \begin{cases} \Lambda^5 - 4\Lambda^4 + 16\overline{Da}_a^{-1}(1 - z^3)(1 - \overline{Da}_d\Lambda^2) = 0, \text{ for } \Lambda \leq 1 - z < 1/X_{\min}(z) \\ 3\Lambda^3(1+z) + \left[8\frac{\overline{Da}_d}{\overline{Da}_a}(1+z+z^2) + 2(2z+1)(z-1) \right] \Lambda^2 + \\ \frac{(3z+1)(z-1)^2}{2} \Lambda - \frac{8(1+z+z^2)}{\overline{Da}_a} = 0, \text{ for } 1-z < \Lambda \leq 1/X_{\min}(z) \\ \Lambda^2 - (\overline{Da}_a + \overline{Da}_d)^{-1}(1 + \overline{Da}_a\Lambda) = 0, \text{ for } \Lambda > 1/X_{\min}(z) \end{cases} \quad (\text{s9})$$

$$\text{For } z = 1: \begin{cases} \frac{\overline{Da}_a}{4} \Lambda^3 + \overline{Da}_d \Lambda^2 - 1 = 0, \text{ for } \Lambda \leq 2 \\ \Lambda^2 - (\overline{Da}_a + \overline{Da}_d)^{-1}(1 + \overline{Da}_a\Lambda) = 0, \text{ for } \Lambda > 2 \end{cases} \quad (\text{s10})$$

In line with the discussion provided in the main text eqs s8, s9 and s10 for $\Lambda > 2$ ($= 1/X_{\min}(1)$) are identical over the whole range of z values. In addition, eq s9 for $\Lambda \leq 1 - z < 1/X_{\min}(z)$ reduces to eq (s8) in the domain $\Lambda \leq 2$ when taken in the limit $z = 0$ (recalling that $1/X_{\min}(0) \approx 1.7$). Finally, eq s9 for $1 - z < \Lambda \leq 1/X_{\min}(z)$ with $z = 1$ correctly reduces to eq s10 within the domain $\Lambda \leq 2$. Therefore, it is sufficient to derive analytical solutions of eq s9, when possible, to cover all types of NP complexants with $0 \leq z \leq 1$. These solutions are provided in the next section and, where necessary, the approximations underlying their validity are specified.

(B) Approximate solutions for Λ within the framework of the $(\overline{Da}_a, \overline{Da}_d)$ representation introduced in §2.5.

Following the arguments exposed in the previous section, rigorous or approximate analytical solutions of eq s9 are collected in **Table S1**.

Expressions for $\Lambda = \bar{\lambda}/r_p$ in $(\bar{D}a_a; \bar{D}a_d)$ representation

Domains of validity	Expression
$\Lambda \leq 1 - z < \frac{1}{X_{\min}(z)}$ $(0 \leq z < 1)$	<p>Rigorous formulation $\Lambda^5 - 4\Lambda^4 + 16\bar{D}a_a^{-1}(1 - z^3)(1 - \bar{D}a_d\Lambda^2) = 0$</p> <p>Approximate solution for $\Lambda^5 \ll 1$ $\Lambda = \sqrt{2 \frac{\bar{D}a_d}{\bar{D}a_a}(1 - z^3)} \sqrt{-1 + \sqrt{1 + \frac{\bar{D}a_a \bar{D}a_d^{-2}}{1 - z^3}}}$</p>
$1 - z < \Lambda \leq \frac{1}{X_{\min}(z)}$ $(0 < z \leq 1)$	<p>Rigorous formulation</p> $3\Lambda^3(1 + z) + \left[8 \frac{\bar{D}a_d}{\bar{D}a_a}(1 + z + z^2) + 2(z - 1)(2z + 1) \right] \Lambda^2 + \frac{(z - 1)^2(3z + 1)}{2} \Lambda - \frac{8}{\bar{D}a_a}(1 + z + z^2) = 0$ <p>Approximate solution for $z \rightarrow 1$ and $\bar{D}a_a / \bar{D}a_d \gg 1$ $\Lambda = \left[\frac{8}{3} \left(\frac{1 + z + z^2}{1 + z} \right) \bar{D}a_a^{-1} \right]^{1/3}$</p>
$\Lambda > \frac{1}{X_{\min}(z)}$ $(0 \leq z \leq 1)$	<p>Rigorous formulation</p> $\Lambda^2 - (\bar{D}a_a + \bar{D}a_d)^{-1}(1 + \bar{D}a_a\Lambda) = 0$ <p>Rigorous solution</p> $\Lambda = \frac{1}{2(1 + \bar{D}a_d / \bar{D}a_a)} \left[1 + \sqrt{1 + \frac{4(1 + \bar{D}a_d / \bar{D}a_a)}{\bar{D}a_a}} \right]$

Table S1. Approximate or rigorous solutions $\Lambda = \bar{\lambda}/r_p$ of eqs s8-s10 within the framework of the $(\bar{D}a_a, \bar{D}a_d)$ representation. It is stressed that the inequality $\Lambda \leq 1 - z < \frac{1}{X_{\min}(z)}$ (first line) strictly holds for $z \neq 1$, i.e. $0 \leq z < 1$. For $z = 1$ (2D hard particle case), we end up with $\Lambda \leq 0 < \frac{1}{X_{\min}(z)}$, which is obviously physically irrelevant as Λ refers to a positive quantity. For the specific hard particle case $z = 1$, this is therefore the range $1 - z < \Lambda \leq \frac{1}{X_{\min}(z)}$ that should be considered, as mentioned in Table S1 (second line) *via* the precision $0 < z \leq 1$.

Referring to **Table S1** (third line), it is straightforward to realize that $\Lambda = \bar{\lambda}/r_p$ follows the power law $\bar{\lambda}/r_p \sim (\bar{D}a_a + \bar{D}a_d)^{-1/2}$ for $\bar{D}a_a \rightarrow 0$. At sufficiently large $\bar{D}a_a \gg \bar{D}a_d$ and low $\Lambda = \bar{\lambda}/r_p$, $\Lambda = \bar{\lambda}/r_p$ decreases with $\bar{D}a_a$ according to $\bar{\lambda}/r_p \sim \sqrt{2} \left[(1 - z^3) / \bar{D}a_a \right]^{1/4}$ for $0 \leq z < 1$ and to $\bar{\lambda}/r_p \sim (4 / \bar{D}a_a)^{1/3}$ for $z \rightarrow 1$, which are obtained from the expressions reported in the first and second line of **Table S1**. These expressions are in line with those indicated in §2.5 of the main text.

SIV. (A) Derivation of eq 10 and solutions thereof in the limits $r_p \gg \mu_d$ and $r_p \ll r_{p,\max} (< \mu_d)$.

From §2.2, we have $Da_{a/d} = \Lambda_{a/d} (r_p / \ell_{a/d})^{n_{a/d}}$ that refer to the Damkohler numbers for M-NP association and dissociation (subscript ‘a’ and ‘d’, respectively). For the case of 3D soft/core-shell NPs with fixed c_s , we have $Da_d = (r_p / \mu_d)^2$ where $\mu_d = \ell_d \Lambda_d^{-1/2}$ and ℓ_d and Λ_d are specified in **Table 1** of the main text. In addition, $Da_a = (r_p / \mu_a)^2$ with $\mu_a = \ell_a \Lambda_a^{-1/2}$ (with ℓ_a and Λ_a also specified in **Table 1**). In turn, recalling that $\bar{c}_s = c_s \varphi (1 - z^3)$ and $k_a^{\text{is}} / k_d^{\text{is}} = K_{\text{int}}$, we obtain

$$\overline{Da}_a / \overline{Da}_d = \left[\frac{D_M}{D_p(r_p)} \frac{\Lambda_a}{K_{\text{int}} c_s \varphi \ell_a^2 (1 - z^3)} \frac{r_p^2}{1 + (r_p / \mu_d)^2} \right]^{-1} \quad (\text{s11})$$

Substituting $\Lambda_a = (1 - z^3) / \bar{f}_{\text{el},a}$ (**Table 1**), eq s11 becomes after some rearrangements

$$\overline{Da}_a / \overline{Da}_d = \left(\frac{D_p(r_p)}{D_M} K_{\text{int}} c_s \varphi \right) \left[1 + \left(\frac{\mu_d}{r_p} \right)^2 \right] \frac{\bar{f}_{\text{el},a} \ell_a^2}{\mu_d^2} \quad (\text{s12})$$

, with $\frac{\bar{f}_{\text{el},a} \ell_a^2}{\mu_d^2} = \frac{\bar{f}_B}{(1 + K_{\text{int}} c_s) K_{\text{int}} c_s}$ which is obtained from the expressions of μ_d and ℓ_a reported in

Table 1. In turn, substitution of eq s12 in eq 9 and further introducing $\ell / r_p = D_p(r_p) / D_M$ (see main text), it comes

$$\Lambda^2 \overline{Da}_a \left\{ 1 - \gamma(\Lambda) + \left\{ \ell r_p^{-1} \frac{\varphi \bar{f}_B}{(1 + K_{\text{int}} c_s)} \left[1 + \left(\frac{\mu_d}{r_p} \right)^2 \right] \right\}^{-1} \right\} - 1 = 0. \quad (\text{s13})$$

Finally, $\overline{Da}_a = k_{a,p} \bar{c}_s r_p^2 / D_M$ can be recast in the form $\overline{Da}_a = k_a^{\text{is}} c_s \varphi \bar{f}_{\text{el},a} \ell_a^2 / D_M$, which is obtained with using $\bar{c}_s = c_s \varphi (1 - z^3)$ and $k_{a,p} / k_a^{\text{is}} = Da_a^{-1}$. Developing the latter expression of $\overline{Da}_a$ with aid of the defining expression of ℓ_a and $k_a^{\text{is}} = k_w V^{\text{os}} N_{A_V}$,²³ we obtain $\overline{Da}_a = 3\varphi \bar{f}_{\text{el},a}$. Finally, eq s13 identifies to eq 10 of the main text with $\overline{Da}_a = \Phi_{\text{el},a} = 3\varphi \bar{f}_{\text{el},a}$ and $\Phi_B = \varphi \bar{f}_B / (1 + K_{\text{int}} c_s)$.

In the limit of sufficiently large $r_p (>> \mu_d)$, we necessarily have $\overline{Da_d} / \overline{Da_a} >> 1$ so that exclusion becomes immaterial and eq s13 reduces to $\Lambda^2 \sim \frac{\ell \Phi_B}{r_p \Phi_{el,a}}$, i.e. $\bar{\lambda} \sim \sqrt{\Phi_B \ell r_p / \Phi_{el,a}}$, in agreement with the statement in the main text. In the other extreme of sufficiently small $r_p (<< r_{p,max} (< \mu_d))$, we have $\overline{Da_d} / \overline{Da_a} << 1$. In this situation where Λ is dominated by the associative term $\overline{Da_a}$, eq 11 in the main text directly follows from the expressions provided in **Table S1** taken in the limit $\overline{Da_a} / \overline{Da_d} >> 1$. The value $1/X_{min}(z)$ marking the transition between the Λ -domains where the expressions for $\Lambda > 1/X_{min}(z)$ and $\Lambda < 1/X_{min}(z)$ (with therein the subcases $\Lambda < 1-z$ and $\Lambda > 1-z$) are applicable, satisfies the relationship $X_{min}^{-2}(z) - X_{min}^{-1}(z) + 1/\overline{Da_a} = 0$ that originates from the expression indicated in the third line of **Table S1** in the limit $\overline{Da_a} / \overline{Da_d} >> 1$. The critical value of $\overline{Da_a} = \Phi_{el,a}$ satisfying this equality is simply defined by $X_{min}^2(z)/(1 - X_{min}(z))$, which explains the conditional expressions indicated in eq 11 in terms of $\overline{Da_a} = \Phi_{el,a}$.

(B) Expressions of $r_{p,max}$, $\bar{\lambda}_{max}$ and $\bar{\lambda}_{min}$ as a function of the relevant $\Phi_{el,a}$, Φ_B and μ_d for 3D soft/core-shell particles under constant c_s condition.

Starting from eq 10 and making use of the analytical expressions provided in **Table S1**, the extrema in $\bar{\lambda}$ displayed in **Figure 5A** of the main text can be identified upon inspection of the r_p -values where the first derivative $d\bar{\lambda}/dr_p$ is zero. The results are collected in **Table S2**.

Expressions for minima and maxima in $\bar{\lambda}$ versus r_p (constant c_s)

Domains of validity	Expression
$\Phi_{el,a} << \frac{X_{min}^2(z)}{1 - X_{min}(z)}$	$\begin{cases} r_{p,min} = \mu_d \\ \bar{\lambda}_{min} = \sqrt{2 \frac{\Phi_B}{\Phi_{el,a}} \mu_d \ell} \quad \text{for } \mu_d / \ell >> \Phi_B \\ \\ r_{p,max} = (2\Phi_B \mu_d^2 \ell)^{1/3} \\ \bar{\lambda}_{max} = \frac{\sqrt{3}}{3} \sqrt{\frac{1}{\Phi_{el,a}}} (2\Phi_B \mu_d^2 \ell)^{1/3} \end{cases} \quad \text{for } r_{p,max} / \mu_d << 1$

Expressions for minima and maxima in $\bar{\lambda}$ versus r_p (constant c_s)

Domains of validity	Expression
$\Phi_{el,a} \gg \frac{X_{min}^2(z)}{1 - X_{min}(z)}$	$\begin{cases} r_{p,min} = \mu_d \\ \bar{\lambda}_{min} = \sqrt{\frac{(1-z^3)\mu_d^3}{\Phi_B \ell}} \sqrt{1 + \frac{(1-z^3)^{-1}}{\Phi_{el,a}} \left(\frac{2\Phi_B \ell}{\mu_d}\right)^2} - 1 \end{cases} \quad \text{for } z \neq 1$
	$\begin{cases} r_{p,max} = 2^{1/3} \left[5(1-z^3) \Phi_{el,a} \right]^{-1/6} (\Phi_B \mu_d^2 \ell)^{1/3} \\ \bar{\lambda}_{max} = 32^{1/6} (1-z^3)^{1/12} (5\Phi_{el,a})^{-5/12} (\Phi_B \mu_d^2 \ell)^{1/3} \end{cases} \quad \text{for } \begin{cases} r_{p,max} / \mu_d \ll 1 \\ \frac{\bar{\lambda}_{max}}{r_{p,max}} < 1 - z \end{cases}$
	$\begin{cases} r_{p,max} \approx (\Phi_{el,a})^{-1/9} \left[\frac{8(1+z+z^2)}{3(1+z)} \right]^{-2/9} (\Phi_B \mu_d^2 \ell)^{1/3} \\ \bar{\lambda}_{max} \approx (\Phi_{el,a})^{-4/9} \left[\frac{8(1+z+z^2)}{3(1+z)} \right]^{1/9} (\Phi_B \mu_d^2 \ell)^{1/3} \end{cases} \quad \text{for } \begin{cases} r_{p,max} / \mu_d \ll 1 \\ z \rightarrow 1 \\ \overline{Da}_a / \overline{Da}_d \gg 1 \text{ at} \\ r_p = r_{p,max} \end{cases}$

Table S2. Expressions of extrema in $\bar{\lambda}$ versus particle size for NP complexants at fixed c_s .

(C) Quantitative criterion for the presence/absence of maximum and minimum in $\bar{\lambda}$ versus r_p for 3D soft/core-shell particles under constant c_s condition.

Using the expression provided in **Table S2**, it is straightforward to derive a criterion for the vanishing of the extrema in $\bar{\lambda}$ versus r_p plot. This criterion reads as $\bar{\lambda}_{min} = \bar{\lambda}_{max}$ and it converts into the expressions detailed in **Table S3** as a function of the key quantities $\Phi_{el,a}$, Φ_B , ℓ , z and μ_d .

Condition for $\bar{\lambda}_{\min} = \bar{\lambda}_{\max}$ (vanishing of maximum, constant c_s)

Domains of validity	Expression
$\Phi_{\text{el,a}} \ll \frac{X_{\min}^2(z)}{1 - X_{\min}(z)}$	$\frac{\mu_d}{\Phi_B \ell} \approx 54 \text{ for } r_{\text{p,max}} / \mu_d \ll 1$
$\Phi_{\text{el,a}} \gg \frac{X_{\min}^2(z)}{1 - X_{\min}(z)}$	$\left[\begin{array}{l} \frac{\mu_d}{\Phi_B \ell} \approx \frac{25\sqrt{5}}{4\sqrt{(1-z^3)}\Phi_{\text{el,a}}} \quad \text{for } \left\{ \begin{array}{l} r_{\text{p,max}} / \mu_d \ll 1 \\ \bar{\lambda}_{\max} < 1 - z \\ r_{\text{p,max}} \end{array} \right. \\ \frac{\mu_d}{\Phi_B \ell} \approx 2 \left[\frac{3(1+z)}{(1+z+z^2)\sqrt{\Phi_{\text{el,a}}}} \right]^{2/3} \quad \text{for } \left\{ \begin{array}{l} r_{\text{p,max}} / \mu_d \ll 1 \\ z \rightarrow 1 \\ \overline{Da_a} / \overline{Da_d} \gg 1 \text{ at } r_p = r_{\text{p,max}} \end{array} \right. \end{array} \right.$

Table S3. Condition for vanishing of the extrema in $\bar{\lambda}$. The condition for the *presence* of a maximum and a minimum in $\bar{\lambda}$ versus r_p is given by the conditions provided in Table S3 after replacing the sign ‘ $\approx$ ’ by ‘ $>$ ’.

SV. (A) The case of 3D soft/core-shell particulate ligands ($0 \leq z < 1$) with a given number N_s of metal binding sites.

The applicable expressions for $n_{\text{a/d}}$, $\ell_{\text{a/d}}$ and $\Lambda_{\text{a/d}}$ are collated in **Table 1A** (right column) in the limits of sufficiently weak and strong inner-sphere MS complexes ($r_p \gg r_{\text{int}}(1-z^3)^{-1/3}$ and $r_p \ll r_{\text{int}}(1-z^3)^{-1/3}$, respectively, with $r_{\text{int}} = [3K_{\text{int}}N_s / (4\pi N_{\text{Av}})]^{1/3}$).²³ Starting from the rigorous expression detailed in Ref. [23] (eq 17 therein) that gives rise to these limits, and following the methodology adopted to derive eq 10, it is shown that the dimensionless reaction layer thickness $\Lambda = \bar{\lambda} / r_p$ under the examined condition of constant N_s is given by (see demonstration in **Supporting Information, SV-(B)**)

$$\Lambda^2 \Phi_{\text{el,a}} \left\{ 1 - \gamma(\Lambda) + \left\{ \ell r_p^{-1} \Phi_B \left(\frac{\mu_d}{r_p} \right)^2 \left[1 + \frac{(r_p / \mu_d)^2}{1 + (1-z^3)^{-1} (r_{\text{int}} / r_p)^3} \right] \right\}^{-1} \right\} - 1 = 0 \quad (\text{s14})$$

, where the intraparticle reaction layer is now given by $\mu_d = \ell_d \sqrt{\bar{f}_{el,a} / \bar{f}_B}$ with $\ell_d = \sqrt{\frac{3D_M K_{int}}{k_w V^{os} N_{Av}}}$, and the dimensionless quantities $\Phi_{el,a}$ and Φ_B are now defined by $\Phi_{el,a} = 3\varphi \bar{f}_{el,a}$ (as in §3.1) and $\Phi_B = \varphi \bar{f}_B$. The latter expression identifies with that of Φ_B given in §3.1 provided that $K_{int} c_s \ll 1$. The defining expressions of the association and dissociation terms $\bar{D}a_a$ and $\bar{D}a_d$ straightforwardly follow from comparing eq s14 with eq 9.

Figure S1. Dependence of $\bar{\lambda}$ on particle size r_p for different values of $r_{int} = [3K_{int}N_s / (4\pi N_{Av})]^{1/3}$ (indicated) with $\log(\Phi_{el,a}) = -2$, $\log(\Phi_B) = 0$, $\mu_d = 10$ nm, $z = 0$. Blue and red dotted lines correspond to the expressions applicable in the diffusion-controlled M-NP dissociation regime $r_p \gg \max(\mu_d, r_{int})$ (i.e. $k_d \rightarrow k_{d,p}$) and kinetically-controlled M-NP dissociation regime $r_p \ll r_{p,max} (< \mu_d)$ (i.e. $k_d \rightarrow k_d^{is}$), respectively. Green dotted line corresponds to mixed transport-chemical kinetics determined M-NP dissociation. Results refer to the situation of 3D soft NPs with a fixed number N_s of metal binding sites S. See text for details.

It is verified that for sufficiently weak inner-sphere MS complexes ($K_{int} c_s \ll 1$ or, equivalently, $r_p \gg r_{int}$ at fixed z), eq s14 exactly matches eq 10: *all the results* obtained in §3.1 under constant c_s conditions are then applicable here within this range of particle size. **Figure S1** shows how the dependence of $\bar{\lambda}$ on r_p is modified over the whole range of particle size with varying r_{int} (i.e. the strength of intraparticle MS complexes) at fixed $\Phi_{el,a}$, Φ_B and μ_d . Analysis reveals that the new feature compared to **Figure 5** is the position of the well-defined minimum in $\bar{\lambda}$, as $r_{p,min}$ may now significantly exceed μ_d depending on the magnitude of r_{int} (**Figure S1**). It can be shown that for cases where $r_{p,min} \gg \mu_d$, the decrease in $\bar{\lambda}$ with increasing r_p in the range $\mu_d < r_p < r_{p,min}$ obeys the power-law $\bar{\lambda} \sim \sqrt{\Phi_B \Phi_{el,a}^{-1} (\ell \mu_d^2 / r_p)}$ (green dotted line in **Figure S1**). The consequence of a pronounced minimum in $\bar{\lambda}$ at $r_p = r_{p,min}$ is the strong increase of $\bar{\lambda}$ with increasing r_p from $r_{p,min}$ to values

$r_p \gg r_{\text{int}}$ where the dissociation contribution in eq s14 dominates with the result $\bar{\lambda} \sim \sqrt{\Phi_B \ell r_p / \Phi_{\text{el,a}}}$ (blue dotted line in **Figure S1**). The major implication of a treatment where N_s is constant with r_p stems from the corresponding decrease of the density $c_s \propto r_p^{-3}$ of sites S in the shell upon increasing particle size. For sufficiently strong MS complexes (*i.e.* $K_{\text{int}} c_s \gg 1$ or $r_p \ll r_{\text{int}}$) and *e.g.* soft NPs ($z = 0$), this leads to a decreasing contribution of the dissociation term $\overline{Da_d} \propto r_p^3 / (1 + \Lambda_d r_p^5)$ in eq s14 with increasing r_p , as compared to the increase of $\overline{Da_d} \propto r_p^3 / (1 + \Lambda_d r_p^2)$ that holds under constant c_s condition. It is this feature that is the origin of the strong decrease in $\bar{\lambda}$ for r_p in the range $r_{p,\text{max}} < r_p \ll r_{\text{int}}$ (**Figure S1**). It is further verified that (i) the position of the maximum in $\bar{\lambda}$ remains basically unchanged with changing r_{int} , (ii) the impacts of Φ_B and $\Phi_{\text{el,a}}$ on $\bar{\lambda}$ qualitatively correspond to those detailed in §3.1.1 and §3.1.2, respectively, and (iii) that the purely association regime $r_p \ll \mu_d$ remains defined by $\bar{\lambda} \sim r_p (1 + \sqrt{1 + 4 / \Phi_{\text{el,a}}}) / 2$ for practical values of $\Phi_{\text{el,a}}$. Following (iii), the evaluation of the contribution of the NP exclusion process is then subjected to the estimation of the same criterion as that invoked in §3.1.4 for $\Phi_{\text{el,a}} < 1$ (**Figure 7**). The impact of z is transparent from inspection of eq s14 and it solely stems from the increase of the density $c_s \propto (1 - z^3)^{-1}$ of sites S in the shell with increasing particle core dimension at fixed r_p . Accordingly, the presence of a core component within the NP body manifests itself in a shift of $r_{p,\text{min}}$ with increasing z (**Supporting Information, SV-(C), Figure S2**). For the sake of completeness, the shift of the extrema in $\bar{\lambda}$ with increasing μ_d is illustrated in **Figure S3** of the **Supporting Information (SV-(C))**, which constitutes the pendant of **Figure 6** for constant N_s condition.

(B) Demonstration of eq s14 (pendant of eq 10 for 3D soft/core-shell particulate ligands ($0 \leq z < 1$) with a given number N_s of metal binding sites).

We start from eq s1 (or eq 9) with $\overline{Da_a} = k_{a,p} \bar{c}_s r_p^2 / D_M$ and $\overline{Da_d} = k_d r_p^2 / D_p$. For 3D particulate ligands ($0 \leq z < 1$) with fixed number N_s of metal binding sites, which is the situation of interest here, we have $\bar{c}_s = 3N_s \varphi / (4\pi N_{\text{Av}} r_p^3)$ and $k_{a,p} = k_a^{\text{is}} / Da_a = k_a^{\text{is}} / \left[(r_p / \ell_a)^{-1} / \bar{f}_{\text{el,a}} \right]$, as derived from **Table**

1A. In turn, we obtain $\overline{Da}_a = \frac{3k_a^{\text{is}} \bar{f}_{\text{el},a} N_s \varphi}{4\pi N_{\text{Av}} D_M \ell_a}$ which, after substitution of the expression of ℓ_a relevant for

the case tackled here (**Table 1A**) and after use of $k_a^{\text{is}} = k_w V^{\text{os}} N_{\text{Av}}$,²³ simplifies into $\overline{Da}_a = 3\varphi \bar{f}_{\text{el},a}$. In addition, the rigorous expression detailed in Ref. [23] for the overall M-(3D)NP dissociation rate constant k_d under constant N_s condition is given, after adaption of the notations, by

$$k_d / k_d^{\text{is}} = 1 / \left\{ 1 + \left(\frac{r_p}{\mu_d} \right)^2 \left[1 + \left(1 - z^3 \right)^{-1} \left(\frac{r_{\text{int}}}{r_p} \right)^3 \right]^{-1} \right\} \quad (\text{s15})$$

$\mu_d = \ell_d \sqrt{\bar{f}_{\text{el},a} / \bar{f}_B}$ with $\ell_d = \sqrt{\frac{3D_M K_{\text{int}}}{k_w V^{\text{os}} N_{\text{Av}}}}$. Then, we obtain for $\overline{Da}_d = k_d r_p^2 / D_p$

$$\overline{Da}_d = \frac{k_d^{\text{is}}}{1 + \left(\frac{r_p}{\mu_d} \right)^2 \left[1 + \left(1 - z^3 \right)^{-1} \left(\frac{r_{\text{int}}}{r_p} \right)^3 \right]^{-1}} r_p^2 / D_p \quad (\text{s16})$$

It comes, with $\overline{Da}_a = \frac{3k_a^{\text{is}} \bar{f}_{\text{el},a} N_s \varphi}{4\pi N_{\text{Av}} D_M \ell_a}$,

$$\frac{\overline{Da}_a}{\overline{Da}_d} = \frac{D_p}{D_M} \frac{1}{r_p^2} \left\{ 1 + \left(\frac{r_p}{\mu_d} \right)^2 \left[1 + \left(1 - z^3 \right)^{-1} \left(\frac{r_{\text{int}}}{r_p} \right)^3 \right]^{-1} \right\} \frac{3K_{\text{int}} \bar{f}_{\text{el},a} N_s \varphi}{4\pi N_{\text{Av}} \ell_a} \quad (\text{s17})$$

, where we used $k_a^{\text{is}} / k_d^{\text{is}} = K_{\text{int}}$. Realising that $\frac{3K_{\text{int}} \bar{f}_{\text{el},a} N_s \varphi}{4\pi N_{\text{Av}} \ell_a} = \left(\frac{3K_{\text{int}} D_M}{k_w V^{\text{os}} N_{\text{Av}}} \frac{\bar{f}_{\text{el},a}}{\bar{f}_B} \right) \varphi \bar{f}_B = \mu_d^2 \varphi \bar{f}_B$, we infer

$$\frac{\overline{Da}_a}{\overline{Da}_d} = \ell r_p^{-1} \varphi \bar{f}_B \left(\frac{\mu_d}{r_p} \right)^2 \left\{ 1 + \left(\frac{r_p}{\mu_d} \right)^2 \left[1 + \left(1 - z^3 \right)^{-1} \left(\frac{r_{\text{int}}}{r_p} \right)^3 \right]^{-1} \right\} \quad (\text{s18})$$

, where we used $D_p / D_M = \ell / r_p$. Finally, after substitution of eq s18 into eq s1 (or eq 9) and recalling

that $\overline{Da}_a = 3\varphi \bar{f}_{\text{el},a}$, we end up with

$$\Lambda^2 \Phi_{\text{el},a} \left\{ 1 - \gamma + \left\{ \ell r_p^{-1} \Phi_B \left(\frac{\mu_d}{r_p} \right)^2 \left[1 + \frac{\left(r_p / \mu_d \right)^2}{1 + \left(1 - z^3 \right)^{-1} \left(r_{\text{int}} / r_p \right)^3} \right]^{-1} \right\} \right\} - 1 = 0 \quad (\text{s19})$$

, with $\Phi_{\text{el,a}} = 3\varphi\bar{f}_{\text{el,a}}$ and $\Phi_{\text{B}} = \varphi\bar{f}_{\text{B}}$. Equation s19 identifies with eq s14.

(C) Dependence of $\bar{\lambda}$ on particle size r_p for different values of $z = a/r_p$ and μ_d (Figure S2 and S3, respectively) for 3D soft/core-shell particles under constant N_s condition.

Figure S2. Dependence of $\bar{\lambda}$ on particle size r_p for different values of $z = a/r_p < 1$ (indicated). Model parameters: $\log(\Phi_{\text{el,a}}) = -2$, $\log(\Phi_{\text{B}}) = 0$, $\mu_d = 10$ nm, $r_{\text{int}} = 100$ nm. Meanings of blue, red and green dotted lines: as in **Figure S1**. Simulations are performed for 3D soft/core-shell particulate ligands under constant N_s condition.

Figure S3. Dependence of $\bar{\lambda}$ on particle size r_p for different values of μ_d (indicated). Model parameters: $\log(\Phi_{\text{el,a}}) = -2$, $\log(\Phi_{\text{B}}) = 0$, $r_{\text{int}} = 100$ nm, $z = 0$. Meanings of blue, red and green dotted lines: as in **Figure S1**. Simulations are performed for 3D soft particulate ligands under constant N_s condition.

SVI. (A) The case of 2D hard particulate ligands ($z = 1$) with a given number N_s of metal binding sites.

Starting from eq 3, and realizing that expressions of n_a , ℓ_a and Λ_a provided in **Table 1B** for 2D hard NP complexants with fixed N_s are similar to those specified in **Table 1A** for 3D soft/core-shell NPs under constant N_s conditions, we have $\overline{Da}_a = \Phi_{el,a} = 3\varphi f_{el,a}$. In addition, the rigorous expression detailed in Ref. [23] for the overall M-(2D) NP dissociation rate constant k_d under constant N_s condition is given by

$$k_d / k_d^{is} = 1 / \left\{ 1 + \omega \frac{f_B}{f_{el,a}} \left[1 + \left(\frac{r_{int}^{(z=1)}}{r_p} \right)^2 \right]^{-1} \right\} \quad (s20)$$

, where $\omega = \frac{k_w V^{os} N_s}{12\pi D_M K_H}$. Accordingly, we obtain for $\overline{Da}_d = k_d r_p^2 / D_p$

$$\overline{Da}_d = \frac{k_d^{is}}{1 + \omega \frac{f_B}{f_{el,a}} \left[1 + \left(\frac{r_{int}^{(z=1)}}{r_p} \right)^2 \right]^{-1}} r_p^2 / D_p \quad (s21)$$

Using $\overline{Da}_a = \frac{3k_a^{is} f_{el,a} N_s \varphi}{4\pi N_{Av} D_M \ell_a}$, $k_a^{is} / k_d^{is} = K_H / \Gamma_s$ (the latter expression applies for 2D hard NPs as argued

in §2.3 of the main text), $\Gamma_s = N_s / (N_{Av} 4\pi r_p^2)$ and $\ell_a = \frac{k_w V^{os} N_s}{4\pi D_M}$ (**Table 1B**), it comes

$$\frac{\overline{Da}_a}{\overline{Da}_d} = \frac{D_p}{D_M} \left\{ 1 + \omega \frac{f_B}{f_{el,a}} \left[1 + \left(\frac{r_{int}^{(z=1)}}{r_p} \right)^2 \right]^{-1} \right\} \frac{1}{\omega} \frac{f_{el,a}}{f_B} f_B \varphi \quad (s22)$$

It is straightforward to realize that $\omega \frac{f_B}{f_{el,a}}$ identifies with the ratio $\left(r_{int}^{(z=1)} / \mu_d \right)^2$ with

$\mu_d = \ell_d \Lambda_d^{-1/2} = \ell_d \sqrt{f_{el,a} / f_B}$ and ℓ_d defined in **Table 1B**. Then, eq s22 becomes

$$\frac{\overline{Da}_a}{\overline{Da}_d} = \ell_r^{-1} f_B \varphi \left(\frac{\mu_d}{r_{int}^{(z=1)}} \right)^2 \left\{ 1 + \left(r_{int}^{(z=1)} / \mu_d \right)^2 \left[1 + \left(\frac{r_{int}^{(z=1)}}{r_p} \right)^2 \right]^{-1} \right\} \quad (s23)$$

Defining $\Phi_{el,a} = 3\varphi f_{el,a}$ and $\Phi_B = \varphi f_B$, eq s23 combined with eq 3 then leads to

$$\Lambda^2 \Phi_{\text{el,a}} \left\{ 1 - \gamma(\Lambda) + \left[\ell r_p^{-1} \Phi_B \left(\frac{\mu_d}{r_{\text{int}}^{(z=1)}} \right)^2 \left(1 + \frac{\left(r_{\text{int}}^{(z=1)} / \mu_d \right)^2}{1 + \left(r_{\text{int}}^{(z=1)} / r_p \right)^2} \right) \right]^{-1} \right\} - 1 = 0 \quad (\text{s24})$$

, where $\gamma(\Lambda)$ is defined by eq 8 and μ_d is here defined by the expressions $\Phi_{\text{el,a}} = 3\varphi f_{\text{el,a}}$, $\Phi_B = \varphi f_B$

and $\mu_d = \ell_d \Lambda_d^{-1/2} = \ell_d \sqrt{f_{\text{el,a}} / f_B}$ with $\ell_d = \sqrt{\frac{3D_M K_{\text{int}}^{(z=1)}}{k_w V^{\text{os}} N_{\text{Av}} K_H^{-1}}}$.

It is stressed that $r_{\text{int}}^{(z=1)} = \left[K_{\text{int}}^{(z=1)} N_s / (4\pi N_{\text{Av}}) \right]^{1/2}$ involved in eq s24 is the 2D analogue of the length scale r_{int} relevant for the 3D case. Unlike the situations previously examined, there are no limiting cases where eq s24 takes the form of eq 10 with an Φ_B factor that would solely depend on φ , f_B and $K_{\text{int}}^{(z=1)}$ (or $r_{\text{int}}^{(z=1)}$). **Figure S4** displays the basic features underlying the dependence of $\bar{\lambda}$ on r_p as numerically obtained from eq s24 for different values of the ratio $r_{\text{int}}^{(z=1)} / \mu_d$ at fixed Φ_B , $\Phi_{\text{el,a}}$ and μ_d . Regardless of the magnitude of these different parameters, the extension of the reaction layer from the macroscopic bio(interface) now continuously increases with particle size over the whole range of r_p and, unlike the cases detailed in §3.1 and §3.2, there are no extrema in $\bar{\lambda}$. On a quantitative level, the magnitude of the increase of $\bar{\lambda}$ with r_p strongly depends on the ratio $r_{\text{int}}^{(z=1)} / \mu_d$. For $r_{\text{int}}^{(z=1)} / \mu_d < 1$, two distinct regimes can be identified, namely $\bar{\lambda} \sim r_p$ (red dotted line in **Figure S4**) and $\bar{\lambda} \sim \sqrt{r_p}$ (blue dotted

line) applying for $r_p / r_p^* \ll 1$ and $r_p / r_p^* \gg 1$, respectively, where $r_p^* = 4\ell \frac{\Phi_B}{\Phi_{\text{el,a}}} \left(\frac{\mu_d / r_{\text{int}}^{(z=1)}}{1 + \sqrt{1 + 4 / \Phi_{\text{el,a}}}} \right)^2$ (see

Supporting Information, SVI-(B)). These correspond to a reaction layer thickness that is dominated by the association and dissociation terms $\overline{Da}_a$ and $\overline{Da}_d$, respectively, whose expressions directly follow from comparison between eq s24 and eq 9. For $r_{\text{int}}^{(z=1)} / \mu_d \gg 1$, the increase in $\bar{\lambda}$ with r_p successively follows the power laws $\bar{\lambda} \sim r_p$, $\bar{\lambda} \sim \sqrt{r_p}$, $\bar{\lambda} \sim r_p^{3/2}$ (green dotted line in **Figure S4**) and $\bar{\lambda} \sim \sqrt{r_p}$ for $r_p / r_p^* \ll 1$, $r_p^* < r_p < \mu_d$, $\mu_d < r_p < r_{\text{int}}^{(z=1)}$ and $r_p \gg r_{\text{int}}^{(z=1)}$, respectively (**Supporting Information, SVI-(B)**). In **Figure S4**, only the three last regimes in line with $r_p^* < r_p$ are observable for practical ranges

of particle sizes. The presence/absence and/or relative extensions of the regimes $\bar{\lambda} \sim \sqrt{r_p}$ and $\bar{\lambda} \sim r_p^{3/2}$ applying over the intermediate range of r_p values is intimately connected to the magnitude of $\Phi_B / \Phi_{el,a}$ which affects the ratios r_p^* / μ_d and $r_p^* / r_{int}^{(z=1)}$ (not shown). The reader is referred to **Supporting Information (SVI-(B))** for the exact expressions of the asymptotic regimes invoked above. Finally, it is straightforward to verify that NP volume exclusion does not contribute to Λ under conditions in line with $\overline{Da_d} / \overline{Da_a} \gg 1$. For cases where Λ is dominated by the associative term $\overline{Da_a}$, the exclusion process affects $\bar{\lambda}$ so long as the condition $2^{-1} \sqrt{\Phi_{el,a}} \left(-1 + \sqrt{1 + 4\Phi_{el,a}^{-1}} \right) < 1$ is obeyed, a result that is similar to that obtained in §3.1.4 for 3D soft/core-shell NPs under constant c_s condition.

Figure S4. Dependence of $\bar{\lambda}$ on particle size r_p for different values of the ratio $r_{int}^{(z=1)} / \mu_d$ (indicated) with $\log(\Phi_{el,a}) = -1$, $\log(\Phi_B) = 1$, $\mu_d = 10$ nm. Blue, green and red dotted lines correspond to the distinct asymptotic regimes detailed in the text of SVI-(A). Results refer to the situation of 2D hard NPs with fixed number N_s of metal binding sites S. See text for details.

(B) Expressions of Λ (or $\bar{\lambda}$) from solution of eq s24 in some practical limits of particle size r_p for 2D hard particulate ligands ($z = 1$) with fixed N_s :

After some algebra, it is shown that the asymptotic solutions $\bar{\lambda}$ of eq s24 are defined by

$$\frac{r_{int}^{(z=1)}}{\mu_d} < 1 : \begin{cases} \text{For } r_p \ll r_p^* : \bar{\lambda} \sim r_p \left(1 + \sqrt{1 + 4 / \Phi_{el,a}} \right) / 2 \\ \text{For } r_p \gg r_p^* : \bar{\lambda} \sim \sqrt{r_p} \sqrt{\frac{\ell \Phi_B \left[1 + \left(\mu_d / r_{int}^{(z=1)} \right)^2 \right]}{\Phi_{el,a}}} \end{cases} \quad (s25)$$

$$\frac{r_{\text{int}}^{(z=1)}}{\mu_d} \gg 1: \left\{ \begin{array}{l} \text{For } r_p << r_p^*: \bar{\lambda} \sim r_p \left(1 + \sqrt{1 + 4 / \Phi_{\text{el},a}}\right) / 2 \\ \text{For } r_p^* < r_p < \mu_d: \bar{\lambda} \sim \sqrt{\frac{\Phi_B \ell r_p}{\Phi_{\text{el},a}}} \left(\frac{\mu_d}{r_{\text{int}}^{(z=1)}} \right) \\ \text{For } \mu_d < r_p < r_{\text{int}}^{(z=1)}: \bar{\lambda} \sim \sqrt{\frac{\Phi_B \ell r_p^3}{\Phi_{\text{el},a} \left(r_{\text{int}}^{(z=1)}\right)^2}} \\ \text{For } r_p \gg r_{\text{int}}^{(z=1)}: \bar{\lambda} \sim \sqrt{r_p} \sqrt{\frac{\ell \Phi_B}{\Phi_{\text{el},a}}} \end{array} \right. \quad (\text{s26})$$

, where $r_p^* = 4\ell \frac{\Phi_B}{\Phi_{\text{el},a}} \left(\frac{\mu_d / r_{\text{int}}^{(z=1)}}{1 + \sqrt{1 + 4 / \Phi_{\text{el},a}}} \right)^2$, which is obtained from the r_p -intersect of the asymptotic

regimes defined by eq s24 for $r_p << r_p^*$ and $r_p^* < r_p < \mu_d$.