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## Nanoparticles in bodily tissues: predicting their equilibrium distributions

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Nanoparticles (NPs) interact within organisms via various biochemical interactions which can bring benefits to society. Classically, fate/distribution of substances is assessed via phase (octanol-water) based partitioning. A decade ago, Praetorius famously stated that phase-based partitioning for NPs is "a road to nowhere". While (in vivo) experiments are cumbersome, reliable partitioning values are of utmost importance given a wealth of medicinal/toxicological and environmental exposure assessments. In this communication, we describe calculus for distribution in human tissues. We applied surface free energy components for NPs, cell membranes/vesicles, plasma and protein describing (van de Waals and Lewis acid-base) interactions amongst tissue and blood constituents. We considered neutral and charged NPs, and various tissues for statistical evaluation. Comparison to experiments showed that predictions are acceptable ( $R^2 \ge 0.7$ ). Depending on surface functionality, phagocyte-rich and cancerous tissues accumulate NPs distinctly from 'normal' tissue, via e.g., receptor (lectin/ cadherin) binding. Our modeling study aids and supplements experiments to quantify the interactions, tissues concentrations and transport of NPs with(in) organs, to unravel mechanisms of human exposures. It provides a reference for partitioning to benchmark upcoming medical applications (e.g., PBPK) and human/ecological risk assessments, enabling experimentalists more efficient monitoring, data interpretation, and reduces cost/ time-intensive medicinal and toxicological campaigns.

## 1. Introduction

Nanoparticles (NPs)1,2 have a wide range of applications in chemical industry and in medicine.3,4 NPs are, e.g., used therapeutically to target tumor cells. NPs however, also come with environmental risks<sup>5,6</sup> depending on non-targeted

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#### **Environmental significance**

Current study in our research group deals with the prediction of distribution of nanoparticles in humans. This is crucial, but not adequately covered by current fate models. In this study surface-driven models were developed capable of predicting partitioning of structurally diverse nanoparticles. The developed models can be used to predict distribution in various tissues. The methods developed in our study are the first of its kind that allow for robust predictions that were not possible previously. We believe Environmental Science: Nano readers will benefit from the results outlined in this study as it aids their further research and policy decisions.

biochemical interactions.<sup>7,8</sup> As NPs come in different materials and sizes, quantifying the impact of surface coating<sup>9</sup>/functionalization on NPs cellular transport has important implications in toxicology.

For decades, fate and accumulation of small organic compounds have been benchmarked using phase-behavior/ partitioning. 10 Oil-water 11,12 and octanol-water partition coefficient  $(K_{ow})$  have been used to predict NP accumulation/ transformation in environments 13,14 and organisms. 10,15 However, NPs interact with bio-membrane surfaces, 16 preventing dispersion. 17,18 Interactions between NPs and biological matrices are difficult to characterize due to adsorption and (irreversible) agglomeration.

Pauli, markedly said, "God made the bulk; the surface was invented by the devil". 19 In a bulk phase, elements are surrounded by other similar elements. Surface elements interact either with elements from the same surface, or with elements located just below, above or beyond it. Therefore, properties of a phase and its energies differ depending upon location, making phase-partitioning inadequate to describe exposure. As NP interactions are surface-driven, Praetorius stated that "assessing NP fate via Kow is a road to nowhere". 17

Fully empirical (i.e., 'black box')<sup>20</sup> methods, evaluate cellular equilibria of NPs without regard for mechanism and have confined applicability due to lack of understanding. Instead, mechanistic insights are needed to describe NPbiological interactions semi-empirically. Current semi-

empirical methods<sup>21,22</sup> apply mechanisms but still have limited applicability to other exposure regimes.

Interaction with tissue components is at the basis of (NP) accumulation. 23,24 Transport of NPs in(to) cells 25 depend on uptake pathway, possible via passive diffusion into/through the cytoplasm, adhesion to endoplasmic reticulum<sup>26</sup> or Golgi apparatus<sup>27</sup> to be encapsulated by membranes and vesicles, 28-30 (e.g., non-endocytic pathways for red blood cells<sup>31</sup>). NP can agglomerate in vesicles, to be excreted by cells.<sup>29</sup> NPs transport and accumulation (agglomeration) in/to lysosomes<sup>17</sup> enables acid-catalyzed degradation, <sup>7,30,32,33</sup> altering their surfaces.34

Transport by vesicles<sup>35</sup> drives NP exo/endocytosis. Upon cytosis, cell membranes and vesicles deform to fuse and release/trap NPs.36 Therefore, past research predicted transport based on membrane energies like crossing, deformation, 37,38 encapsulation and combination. 39 Recent work40 linked NP properties to traits of cells to assess interaction energy and predict cellular uptake and elimination. Properties of NPs, e.g., charge (density<sup>41</sup>) and cell traits influence NP transport, but it remains difficult to characterize binding to vesicles. Identifying the probability/ frequency of binding and transport42 enable assessing NP

Relationships between surface physico-chemical properties and cell behavior at the interface have been hypothesized. 43-46 We specify this hypothesis by considering NP properties and tissue/cells traits to assess partitioning in organs, Fig. 1. In this communication, we quantify exposure by using interaction energies between NPs and membranes. We consider the fraction/frequency of NPs bound/ encapsulated by/in organ(elles). We focus on polar (Lewis

acid-base) and Van de Waals forces. We assessed our model with experimental data for various tissues and explored the effect of NP properties on partitioning.

### 2. Methods

#### 2.1. Tissue compositions

Tissue partitioning (K) is affected by the amount of membrane in a cell, and how many cells of a type an organ tissue contains. E.g., cancerous cells express enhanced intracellular signaling via vesicles. 48-52 As the concentration of cells and their membranes is in excess to NP concentration, we take that sorption is linear in NP concentration, and that K is a summation function over Boltzmann partitioning ( $e^{-\Delta G_i/RT}$ ) among cell types (i), weighted by their proportion in the tissue:

$$K_{\text{tissue/blood}} = a \cdot \sum_{1}^{i} \left( \frac{[i]}{[\text{tot}_i]} \cdot e^{\frac{-\Delta G_{\text{membr}(i)/\text{water}}}{RT}} \right) + b$$
 (1)

We take proportions of cell types from Table 1. We calculate binding energy changes  $\Delta G_i$  from surface energies  $\gamma$ , section 2.3. Apart from membranes, proteins influence distribution of NPs. We take serum protein concentration independent of tissue type (equal among capillary bloods), and describe its influence in section 2.2. Knowing how much water organs contain, we extrapolate  $e^{-\Delta G_{\text{(tissue/water)}/RT}}$  to  $e^{-\Delta G_{\text{(organ/water)}/RT}}$ . Table 1.

#### 2.2. Membrane-protein-water partitioning

We calculate  $K_i$  via Boltzmann, via  $\Delta G$ : values for free energy of binding. Fig. 1 depicts the influence of G

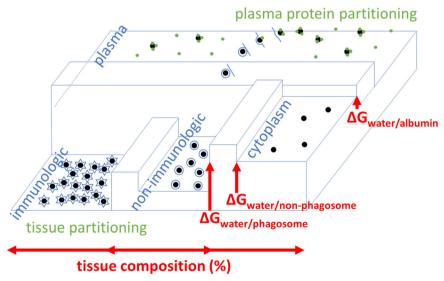


Fig. 1 Example distribution of NPs throughout/around tissues, influenced by energy G. Plasma = extracellular serum (saline water + protein). Difference between dividing beams (barriers) are  $\Delta G = \Delta G_{\text{on}}^{\ddagger} - \Delta G_{\text{off}}^{\ddagger}$ , i.e.,  $K = \frac{k_{\text{on}}}{k_{\text{off}}}$  denotes equilibrium which is attained after long-term exposure. Intracellular vesicle-free NPs exist. 47 Low G means high NP concentration: [NP] across compartments i (horizontal) [NP] $_{ij}$ /[NP] $_{total} = e^{-\Delta G_{np-j}/RT}$ ; depending on properties, accumulation in phagocytes/lysosomes.

Table 1 Simple representative composition (%) of healthy human organ tissues by generic celltype. Colors denote dominant contribution to energy (red = hydrophobic, blue = Lewis basic, green = Lewis acidic). We combined compositions with surface energy data (Table 2). Membrane types have varying degrees of immunological (Fig. 1) relevance<sup>53–70</sup>

Membrane cell type i <sup>a</sup>	Liver	Bone; <sup>b</sup> spine	Skin	Spleen <sup>e</sup>	Adipos e	Tumor	Mucus	Blood	Lymph	Brain barrier <sup>d</sup> testis barrier	Lung; kidney;
Keratinocytes, %	0	0	59	0	0	0	0	0	0	0	0
Epith/endoth, %	5	1	40	5	0	0		0	0	100	99
Hepatocytes, %	70	0	0	0	0	0	0	0	0	0	0
Osteocytes, %	0	98	0	0	0	0	0	0	0	0	0
Phagocytes, <sup>c</sup> %	25	1	1	25	0	0	0	0.1	100	0	1
Lipocytes, %	0	0	0	0	100	0	0	0		0	0
Cancerous, %	0	0	0	0	0	100	0	0	0	0	0
Erythrocytes, %	0	0	0	70	0	0	0	99.9	0	0	0
Mucous cell, %	0	0	0	0	0	0	100	0	0	0	0
Total, %	100	100	100	100	100	100	100	100	100	100	100
Water, % (ref. 53)	72	31; 69	64	75	21	80	98	90	96	70	83; 82; 75
References	54–61	61–64	61	61, 65–68	_	_	69	61, 70	61	_	61

<sup>&</sup>lt;sup>a</sup> Representative functional cell; <sup>b</sup> excluding bone marrow; <sup>c</sup> assuming the majority of immunological cells is phagocytosic, <sup>d</sup> BBB consists of tightly packed endothelial cells. <sup>e</sup> White pulp (25% of splenictissue) structurally similar to lymph.<sup>7</sup>

(vertical) across different surfaces/compartments (horizontal). The lower G, the higher the partitioning therein/on. The ability of NPs to partition onto membranes depend on their bio-availability, i.e., interaction with endemic serum proteins, 46,72,73 Fig. 1. We define partitioning of NPs between water (w) and membranes (m) as function of serum plasma protein coating in two additive terms:

$$e^{\frac{-\Delta G_{\text{membr(i)/water}}}{RT}} = \frac{e^{-\Delta G_{\text{water-membr(serum)}}/RT}}{\left(1 + \alpha \cdot e^{-\Delta G_{\text{serum-water(NP)}}/RT}\right)} + \frac{e^{-\Delta G_{\text{water-membr(NP)}}/RT}}{\left(1 + \alpha \cdot e^{-\Delta G_{\text{water-serum(NP)}}/RT}\right)}$$
(2)

where we take that a NP is either covered or uncovered by serum proteins (p), analogous to small organic molecules.  $\alpha$  is a dimensionless frequency of NP-encounters, proportional to plasma protein amount (7%); inversely proportional to the NPs (surface area) acting as a plasma protein scavenger,  $\alpha = \frac{0.07}{\left(\frac{[\text{NP}]}{[\text{serum}]}\right) + 1}$ . RT is gas constant;

temp.

Serum contains 60-80 g L<sup>-1</sup> plasma protein (35-50 g  $L^{-1}$  albumin), with MW of ~150 kg mol<sup>-1</sup>, thus (70/  $150000) \times 6.02 \times 10^{23} = 2.8 \times 10^{20}$  proteins per L (size  $d_{\text{serum}} = 6 \text{ nm}$ ), of which  $(1000/(6 \times 6) = )$  28 can adsorb on 1000 nm<sup>2</sup> NP surface. Thus, protein concentration is in excess to NPs dosing concentration [NP] in any practical scenario ( $10^6$ – $10^{12}$  NPs L<sup>-1</sup> (ref. 74)). We thus disregard homo-/heteroaggregation/agglomeration, taking  $\alpha = 0.07$ .

#### 2.3. Free energy changes

We obtained different binding free energy changes  $\Delta G$  via:

$$\Delta G_{\text{water} \rightarrow \text{membrane}(\text{serum})}$$
  
=  $A \cdot (\gamma_{\text{serum-plasma-membr}}^{\text{AB}} + \gamma_{\text{serum-plasma-membr}}^{\text{LW}})$ 

$$\Delta G_{\text{water} \rightarrow \text{membrane(NP)}} = A \cdot (\gamma_{\text{NP-plasma-membr}}^{\text{AB}} + \gamma_{\text{NP-plasma-membr}}^{\text{LW}})$$

$$\Delta G_{\rm water \rightarrow serum(NP)} = A \cdot \left( \gamma_{\rm NP-plasma-protein}^{\rm AB} + \gamma_{\rm NP-plasma-serum}^{\rm LW} \right)$$

$$\Delta G_{\rm serum \rightarrow water(NP)} = -A \cdot \left( \gamma_{\rm NP-plasma-serum}^{\rm AB} + \gamma_{\rm NP-plasma-serum}^{\rm LW} \right) \ \ (3)$$

In 'classical phase partitioning' (for small organic compounds) A is the solvent accessible molecular surface

area. NP partitioning is geometry-driven;<sup>75</sup> we assume only partial wrapping of surface area (*e.g.*, bending/deformation negligible to AB/LW forces or compensated by receptor-ligand binding<sup>76</sup>) estimating the interaction area (m<sup>2</sup>) A from molar volume<sup>77</sup> (here, the ethylene glycol monomer of PEG). We involved Vande Waals (LW)/polar Lewis acid–base (AB) forces<sup>40,78</sup> taking distances in equilibrium by born repulsion, 0.157 nm.<sup>78</sup>

We calculated  $\gamma^{AB}$  and  $\gamma^{LW}$  (mJ m $^{-2}$ ) from effective surface energy components  $\gamma^{LW}$ ,  $\gamma^+$  and  $\gamma^-$  (electron acceptor and donor) for each species: NPs, membranes, serum plasma protein and water; details in ref. 78 and 79, substantiated by multiple cell lines (macrophage, endothelial cancer, fibroblast, etc.).  $^{80,81}$  We take for  $\gamma^+_{\rm protein}$ ,  $\gamma^-_{\rm protein}$ ,  $\gamma^L_{\rm protein}$  of serum protein 0.002, 20, and 41 mJ m $^{-2}$ , taken to resemble dry albumin at pH 7,  $^{79,82}$  and for  $\gamma^+_{\rm plasma}$ ,  $\gamma^L_{\rm plasma}$ ,  $\gamma^L_{\rm plasma}$  of plasma 25.5, 25.5 and 21.8, mJ m $^{-2}$ , taken to resemble water. For NP  $\gamma^+_{\rm NP}$ ,  $\gamma^L_{\rm NP}$ ,  $\gamma^L_{\rm NP}$  we took 0, 45, and 43 mJ m $^{-2}$ , taken to be polyethylene glycol.

#### 2.4. Cell membrane types

While carbohydrate contents in membrane surfaces do not (greatly) differ between cell types,  $^{83-87}$  differentiation involves glycosylation:  $^{88-90}$  phagocyte have glycosylated protein receptors (lectins  $^{90,91}$ ) with binding motifs specific to ( $\beta$ -) glucan-chitin copolymers  $^{92-94}$  recognizing foreign particles. Liver (Kupffer)  $^{92,95,96}$  and cancer cell  $^{97,98}$  membranes are lectin-rich. Immunological (mucus/phagocytic/cancerous)

cells have enhanced metabolism over 'tranquil'/'sluggish', *e.g.*, endothelial cells.<sup>7,81,99,100</sup>

Via abnormal metabolism cancer cells produce e.g., lactate acidifying tissues,  $^{101}$  affecting bio-adsorption.  $^{102,103}$  Metastatic cancer cells migrate/proliferate to tissues via the blood,  $^{104,105}$  depending on hydrophilicity (i.e.,  $\gamma^{AB}$ ). Cells contain many surfaces: Golgi apparatus/vesicles/lysosomes/endoplasmic reticulum. Liver macrophages internalize NPs  $^{106-108}$  and entail acid-rich lysosomes, attacking particles.  $^{109,110}$  pH can alter/affect surface activity, tension ( $\gamma^{111}$  and 'biocollisions'.  $^{112}$ 

Membranes thereby differ in characteristic 'surface acidity', <sup>113</sup> analogous to  $pK_a/pH$  functionalities among organic compounds ( $pK_a$ 's on surfaces). <sup>114</sup> We characterize cell membrane type by energy of surfaces  $\gamma$ . Adipocytes contain more lipid (with specific  $\gamma$ ). <sup>85,115</sup> Table 2 lists  $\gamma^+_{\text{membrane}}$ ,  $\gamma^-_{\text{membrane}}$ ,  $\gamma^-_{\text{membrane}}$  values that we used to effectuate aforementioned factors, substantiated by relationships between phagocytosis/contact angle (*i.e.*,  $\gamma$ ). <sup>43</sup>

#### 2.5. Testing using experimental tissue partitioning.

We evaluate accuracies of K from eqn (1)–(3) by comparison with experimentally-derived K from  $in\ vivo$  concentration data<sup>133,134</sup> (open literature). We neglect biotransformation, and disregard elimination via faeces/urine. We focus on large exposure times t, e.g., months, <sup>133</sup> so organs continuously take in/eliminate NPs (4, 13, 100 nm, coated with PEG) with equal rates. By analogy, barriers in Fig. 1 are sufficiently low. Then, dividing uptake and elimination gives K for organ tissues:

Table 2 Energy components of membrane surfaces in cell types (mJ m $^{-2}$ ). Ranges are variabilities across exp. setups. Colors denote dominant contribution to  $\gamma$  (red = hydrophobic, blue = basic polar, green = acidic polar). Octanol is a reference to phase partitioning<sup>44,116-131</sup>

Membrane biomaterial type i	$\gamma_{ m membrane}^{ m LW}$	$\gamma_{ m membrane}^+$	y_membrane	References
Keratinocyte <sup>a</sup>	32–36	0.0-1.3	7.5–14.5	116, 117
Epith/endoth <sup>b</sup>	37.6	0.00-1.05	59.6–76.7	118, 119
Hepatocyte <sup>c</sup>	39	0.00-1.05	54	120
Osteocyte <sup>d</sup>	42	0.2-0.3	39.1-60.6	121–124
Phagocyte <sup>e,f</sup>	28–30	5.3–7.7	18–23	44
Lipocyte	24.0–27.1	0	0	125–127
Cancerous <sup>f,g</sup>	36.0	1.23-1.70	50.9–53.7	118
Erythrocyte	35.2	0.01	46.2	128
Mucin/mucus	37.26/6.92	3.19/49.17	9.55/7.84	129, 130
Octanol	27.5	0	18.0	131

<sup>&</sup>lt;sup>a</sup> Values represent untreated keratinous skin, keratin <85% of differentiated keratinocytes. Human endothelial cellline HUVEC. Values unknown,  $\gamma^{\text{LW}}$  taken for a generic cell, taken as range for non-immune cells,  $\gamma^-$  taken corresponding to maximum binding. For bone/osteocytes, membranes surface reflects hydroxyapatite, values represent untreated (hydrophilic) hydroxyapatite (>70% crystalline) and collagen. Phagocytic cell lines THP-1, HL-60. Local tissue/organelle pH enhances γ: linear/exponential extrapolations imply  $\gamma^+$  = 1.2–6.0 mJ m<sup>-2</sup>, substantiating values reported. Breast cancer cell line MCF-7.

$$\frac{k_{\rm in}}{k_{\rm out}} \cdot \left(1 - e^{-k_{\rm out} \cdot t}\right) = \frac{[\rm NP]_{\rm organ}}{[\rm NP]_{\rm blood}} = K_{\rm tissue/blood} \tag{4}$$

assuming that experiments reflect equilibrium. Section 4.2–4.4 discusses accuracy of the assumption.

## 3. Results

#### 3.1. Interaction between NPs, membranes and serum

Table 2 shows energies for interaction between PEG-NPs and membrane biomaterial membrane surfaces ( $\gamma$  and  $\Delta G$ ). Interaction energies are either positive or negative. The larger the hydrophobicity and Lewis acidic character of the membrane, the more negative the energy values for interaction. The  $\Delta G$  did not differ between differently sized PEG-NPs (4–100 nm) as the PEG coating groups are similarly sized.

The  $\Delta G_{\rm NP}$  range from -4.4 to +5.1 kJ mol<sup>-1</sup>, which is an energy range of 9.5 kJ mol<sup>-1</sup>. If  $\Delta G_{\rm albumin}$  were taken into account also, the summed  $\Delta G$  is a range of -11.5 to +7.8 kJ mol<sup>-1</sup>. This shows that albumin has a differentiating effect on cell type. Based on these values, via eqn (1)–(3), ratios were calculated for partitioning of PEG-NPs between serum and membranes. Predicted K was highest for non-polar lipocyte surfaces, and lowest for endothelial/epithelial cells. Again, the larger the hydrophobicity/Lewis acidic character of the membrane surface, the larger the predicted K.

#### 3.2. Partitioning of NPs in organ tissues

Experimentally derived (eqn (4))  $K_{\rm tissue/blood}$  for PEG-NPs range from 0.044 to 2600; these K's are independent of time within 7 days to 6 months. Other data for starch/dextran coated NPs<sup>135</sup> and eqn (4) imply a 3 day apparent tissue/blood/K is  $\geq 7$  for phagocyte-rich tissues (e.g., liver/spleen); for phagocyte-poorer tissues,  $K_{\rm tissue/blood} \geq 0.3.^{135}$  These values appear low compared to longer exposure times > 7 days-6 months. This indicates absence of equilibrium or steady state. We did not see a statistically significant effect of NP size on the  $K_{\rm exp}$ ,  $^{133}$  Fig. 1. Surface functionality does influence partitioning, with 6 day  $K_{\rm liver/blood} > K_{\rm spleen/blood}$  for cationic CTAB-NPs, but  $K_{\rm liver/blood} < K_{\rm spleen/blood}$  for neutral PEG-NPs.  $^{134}$ 

#### 3.3. Prediction of NP partitioning

Fig. 2 depicts predicted K, eqn (1)–(3) and experimentally derived K (eqn (4)) for PEG-NP partitioning in different organ tissues, with reference to blood ( $K_{\rm tissue/blood}$ ). For 4 nm PEG-NPS, the Pearson correlation coefficient  $R^2$  = 0.69 and p = 0.0004 (2SD). For 13 nm,  $R^2$  = 0.75, p = 0.0001 (2SD) and for 100 nm  $R^2$  = 0.70, p = 0.0004 (2SD). For 4, 13 and 100 nm grouped together,  $R^2$  = 0.68, p < 0.00001 (2SD). The p values of these four linear regressions are all lower than 0.05 (SD), denoting statistically significant relationships.  $R^2$  values are all higher than 0.6, which is often considered the minimally

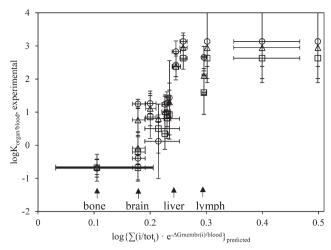


Fig. 2 Predicted (x-axis, eqn (1)–(3)) vs. experiment-derived partitioning between organ tissue (Table 1) and blood of PEG-NPs (Cho et al. 133 data, N=42, eqn (4)). Circle  $\bigcirc=4$  nm, triangle  $\triangle=13$  nm, square  $\square=100$  nm. Variance between same symbols due to difference in organ tissue composition (Table 1). Adipose tissue (log  $K_{\rm pred}=1.3$ ) shown as 0.5. Horizontal error bars propagate variabilities in  $\bar{\gamma}_{\rm membrane}$  (Table 2); vertical error bars are 1SD based on 4 datapoints.  $\Delta G$  in 2.303 RT.

accepted prediction precision for (environmental) risk assessment.  $^{136}$ 

The slope a of the linear regression (*i.e.*,  $\log K_{\rm organ/bloodsexp} = a \cdot \log K_{\rm pred} + b$ ) is approximately  $15 \pm 3$  (2SD), significantly larger than 1. The offset b is  $-2 \pm 1$  (2SD). Regression fits ( $R^2$ ) were slightly higher for a log-logistic fit, as compared to a linear fit. As adipose tissue appears out of domain, it was not taken into account in regressions. Values for predicted K for partitioning of PEG-NPs from blood into skin and adipose tissue were relatively high,  $\geq 0.4$ . Values for  $K_{\rm pred}$  and  $K_{\rm exp}$  for bone and brain were lowest. We did not observe any apparent outliers. Though we took data in Fig. 2 from 1 literature source,  $^{133}$  other sources  $^{134,137-139}$  show similar trends for PEG. eqn (1)–(3) correctly predict that albumin adsorption for cationic NPs is higher than for anionic NPs.  $^{134}$ 

$$\begin{split} \log \textit{K}_{\text{organ/blood,experimental}} &= 15(\pm 3) \cdot log\{\sum (i/tot_i) \cdot e^{-\Delta G_{\text{membrane}(i)/blood}}\}_{\text{predicted}} - (2 \pm 1) \end{split}$$

## 4. Discussion

#### 4.1. Energy considerations

Eqn (1)–(3) have a mechanistic basis. High/low K can be explained by many experimental phenomena. Cationic NPs (high  $\gamma^+$ ) are cleared from blood (hence, organs) faster than neutral or anionic NPs,  $^{137}$  presumably via enhanced binding to serum protein (high  $\gamma^-$ ). Eqn (3) predicts this, which constitutes a basis for tissue partitioning. Organs rich in phagocytes show enhanced K; indeed, NPs accumulate in lymph nodes.  $^{140}$  Instead of polar headgroups (AB interaction), NPs may interact with lipid tails (micelle-like

system, involving differing  $\gamma$  (ref. 126 and 141)), as enhancing concentrations in adipose tissues (Fig. 2).

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Across tissues,  $\Delta G$  ranges from -4.4 to +5.1 kJ mol<sup>-1</sup>, a range of 9.5 kJ mol<sup>-1</sup>, equal to around 5-10 hydrogen (H) bonds. H-bonds need to be broken in order for surface molecules to interact. This number, ~10 kJ mol<sup>-1</sup>, was associated to the difference between active and passive uptake mechanisms:  $^{142,143}$  cells with high positive  $\Delta G$ (Table 3) take up PEG-NPs passively; cells with lower  $\Delta G$  also take up PEG-NPs actively. The number of PEG chains on the (4 nm) NP surface would be  $\sim 40$ , <sup>144–146</sup> but a limited number need interact with biomembranes. Molecular initiating interaction events (MIE) between substance and biomolecule/ system (e.g., ~7 kJ mol<sup>-1</sup> (ref. 147)) lead to outcome pathways. The MIE involves a limited/single functional group on the NP surface.

Though (e.g., lung) tissue contains only  $\sim 1\%$  phagocytes, these contain up to 83% of all (PEG) NPs in tissue. 148 This implies a NP macrophage/tissue partitioning K = (100) $[pha]\cdot([NP_{tot}]/[NP_{pha}] - 1)$ , i.e.  $(100/[1])\cdot([100]/[83] - 1) = 20$ . This 20-fold enhancement matches higher receptor densities<sup>149</sup> and activities<sup>150</sup> of macrophages. Moving 1 mol of a substance across a 20-fold gradient at 25 °C is  $\Delta G$  =  $(8.315 \text{ J mol}^{-1} \text{ K}^{-1}) \cdot (298 \text{ K}) \cdot \ln(20/1) = 7.4 \text{ kJ mol}^{-1} \cdot 151 \text{ It is}$ therefore unlikely that slope = 15, larger than 1 (Fig. 2), stems from inaccurate  $\gamma$  (eqn (1)-(3), Table 2). If our  $\Delta G$  is fully precise and exact, slope (Fig. 2) should be 1 (according to Boltzmann). The difference between expected (1) and observed (~15) may relate (partially) to unanticipated wrapping/bending or (geometry-)specific ligand-receptor energies  $^{152-154}$  contributing to  $\gamma$ , not reflected by Table 2, which may refine K. After phagocytosis, a cell minimizes its surface tension ( $\gamma$ ) by smoothening.<sup>155</sup>

#### 4.2. Cell signaling

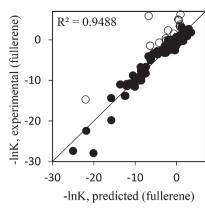
Not the full NP surface area interacts with the biomembrane surface. Indeed,  $K_{\text{exp}}$  does not differ between NP sizes<sup>133</sup>(-Fig. 2). Log-logistic fits are slightly better than linear fits between  $K_{\text{exp}}$  and  $K_{\text{pred}}$  (levelling off in Fig. 2), implying a crowding/shielding/saturation. This may refer to interaction area A (eqn (3)), which varies depending on strength of interaction ( $\Delta G$ ).  $\Delta G$  depends on polymer size, but approaches (per monomer unit) zero at higher MW. 156 Chemical potential of an atom/molecule depends on its surrounding, larger on convex surfaces than on flat surfaces, in turn larger than under concaves. 157 While size/geometry can affect y, 158,159 interaction with serum/cytoplasmic constituents and geometric restrictions may offset the effect. The slope ( $\sim$ 15) is thus not a size-effect *per se*.

The slope (Fig. 2) may entail information on frequency,  $\alpha$ in eqn (2) or i in eqn (1). Under steady state, it implies higher phagocytic activity. By analogy, in (eco)toxicology, IC<sub>50</sub>/EC<sub>50</sub> values (in log-logistic curves) describe induction of biological response. Indeed, high (toxic) pressures instigate aggrupation of phagocytes (granuloma) at sites of NPs (increasing i/toti for phagocytes, eqn (1)). We assumed that one NP binds to/ within one vesicle<sup>42,160</sup> ignoring (intracellular) aggregation.<sup>33</sup> This is sometimes not true: spleen phacocytes cluster (bioconcentrate) PEG-NPs in lysosomes; 133 Kupffer macrophages engorge NP-aggregates. 161 Aggregation changes the properties of the NP cluster.

A 10-fold increase in the average number of NPs per lysosome, implies an effective 'bioconcentration factor' of 10. Bioaccumulation (in organisms), rather, involves multiple uptake steps by different signaling pathways. Detecting bioactive substances enhances local internal

Table 3 Surface energies changes for adsorption interaction of albumin and PEG-NPs onto membranes biomaterials i, and for sorption of albumin onto PEG-NPs. Corresponding membrane-serum partitioning ratio K (eqn (2)) also shown.  $\gamma_{NP}^{\text{water} \rightarrow \text{albumin}} = 4.2 \text{ mJ m}^{-2}$ 

Membrane biomaterials type i	$\gamma_{\text{albumin}}^{\text{water}  ightarrow \text{membrane}}$ , mJ m <sup>-2</sup>	$\gamma_{\mathrm{NP}}^{\mathrm{water}  ightarrow \mathrm{membrane}}$ , mJ m $^{-2}$	$\Delta G_{ m albumin}^{ m water  ightarrow membrane} \; , \ { m kJ \; mol^{-1}}$	$\Delta G_{ m NP}^{ m water  ightarrow membrane} \; , \ { m kJ \; mol^{-1}}$	Predicted K membrane/serum, eqn (1)–(3)
Keratinocyte	-26.3	-7.8	-3.2	-1.0	5.0
Epith/endoth	+21.9	+41.2	+2.7	+5.1	0.5
Hepatocyte	+12.5	+31.7	+1.5	+3.9	0.7
Osteocyte	+8.7	+28.7	+1.1	+3.5	0.9
Phagocyte	-10.6	+0.3	-1.3	0.0	2.6
Lipocyte	-57.7	-35.7	-7.1	-4.4	23.0
Cancerous	+12.7	+29.6	+1.6	+3.7	0.7
Erythrocyte	+7.4	+29.3	+0.9	+3.6	0.9
Mucus	-13.2	-21.5	-1.6	-2.7	4.7



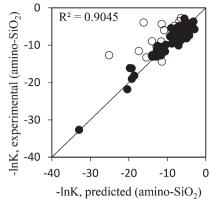


Fig. 3 Experimental vs. predicted partitioning for 155 biomolecules between water and fullerene  $C_{60}$  (left) and amino-functionalized SiO<sub>2</sub> NPs (right). Experimental values characterize partitioning of NPs onto (within) biomolecules and water. Data from ref. 215. Open symbols are (incompletely characterized mixtures of large) flexible molecules that minimize energy by molecular reorientation (oligonucleotides, small proteins). Interaction with  $C_{60}$  ( $\gamma_{LW}$ ,  $\gamma^+$ ,  $\gamma^-$  = 25, 2, 17 mJ m<sup>-2</sup>) via polarization and electron donation; with (cationic) SiO<sub>2</sub>-NH<sub>3</sub> ( $\gamma_{LW}$ ,  $\gamma^+$ ,  $\gamma^-$  = 0, 50, 0.1 mJ m<sup>-2</sup>) via electron accepting.

concentrations.  $^{162-164}$  BAFs along (cell signaling  $^{94,165}$ ) pathways may be  $\sim 100$  times higher than BCF for the same substance.  $^{166}$  Bioaccumulation  $K_{\rm BAF}$  may be described as  $K_{\rm BCF} \cdot K_{\rm BCF} \cdot K_{\rm BCF} \cdot ...$  etc., involving multiple concentrating steps (after the MIE).

Such steps may involve Ca2+, affecting lectin binding capacity,  $^{91,165,167}$  which  $\gamma$  (Table 2) not captures. Cancer cells lack Ca<sup>2+</sup>-dependent cadherin<sup>168-170</sup> enhancing repulsion. Saline solutions effectuate different  $\gamma$  than pure water<sup>75,129</sup> (eqn (3)). Amine-binding is key to pathogen detection and immune response, 171–174 with electron-acceptor/donor interactions central to lectin binding to chitin ( $\gamma^{LW} = 41$ ,  $\gamma^{+} =$ 1.3,  $y^- = 17.1 \text{ mJ m}^{-2}$  (ref. 175)) via the N-acetyl group. <sup>176</sup> Ca<sup>2+</sup> complexation (bridging) affects its  $\Delta G$ . This explains the high slope (Fig. 2) because Ca<sup>2+</sup> is only relevant in those (i.e., immunological) tissues. 181 For phagocytes, a decrease by Ca2+ in  $\Delta G_{NP}^{\text{water} \rightarrow \text{membrane}}$  from 0 (Table 3) by a representative –25 kJ  $\text{mol}^{-1}$  (ref. 182 and 183) increases predicted  $\log K$  for e.g., the liver to  $\sim$ 2.9, agreeing with experiment (2.4–2.8, Fig. 2).

#### 4.3. Tissue inhomogeneities

Stronger correlations may imply a more homogeneous tissues or uniform binding mechanism. Inhomogeneities (*e.g.*, layering) in tissues affect K (hence,  $R^2$ , Fig. 2) via local increased exposures. Penetration of PEG-NPs through skin depends on hydration status. Mucus epithelial tissue (mouth/stomach) cells produce (N-)glycosylated proteins rotecting organisms by binding (trapping) foreign material. This explains marked accumulation of NPs in (Ca<sup>2+</sup>-augmented) mucin (Table 3), 189,190 having distinct  $\gamma$  (Table 1).

We cannot always assume the barriers in Fig. 1 are sufficiently low; inhibition of transport limits tissue partitioning. Macrophages (microglia) account for 10–15% of brain cells, 191 and would readily take up NPs. 192 However, the brain's blood vessels are lined with endothelial cells

wedged tightly together, creating a boundary. Likewise, microvascular endothelial cells form the blood–spinal cord barrier; Sertoli cells constitute the blood–testis barrier. Pores sizes of  $\sim$ 5 nm may complicate measuring a K in kidney.

We characterized each individual membrane surface (and serum protein) by a single  $\gamma$  set, implying that e.g., vesicles share the characteristics of cell surfaces, which combine during cytosis. y<sub>membrane</sub> characterizes weighted averages of membrane receptors/proteins, components: lipids, counterions, etc. However, generic description of  $\gamma$  may not apply. Inhomogeneity in tissues is apparent from e.g. markedly different  $\gamma$  for bile in the liver ( $\gamma^{LW} = 23-26$ ,  $\gamma^+ = 36-46$ ,  $\gamma^- = 8-15$  mJ m<sup>-2</sup>, <sup>193</sup> and  $\gamma^+ = 10-13$ ,  $\gamma^- = 35-41$ ,  $\gamma^{LW} = 25-41$ 27 mJ m<sup>-2</sup> (ref. 194)) and hydroxyapatite ( $\gamma^{LW} = 2.2, \gamma^{+} = 19.8,$  $y^- = 73.2 \text{ mJ m}^{-2}$  (ref. 195)), differing from Table 2. In reality, differs across cell membranes. Pending γmembrane (experimental) data, implementing distributions of  $\gamma_{\text{membrane}}$ for inhomogeneous surfaces renders predictions more precise.

NP distribution depend on interaction with (intra) cellular/tissue compartments, other than in Table 1.196,197 A diversity of proteins in biological media 198,199 may differentially functionalize NPs (and membranes) affecting  $\gamma$ , but was ignored. Tissue composition (Table 1) may be dependent on NP concentration, characterizable by healthy/ affected tissues, in terms of phagocytes.200 Differences in body/organ weights and composition exist. 163,201 We presume that inter-202 and intraspecies 86 differences in lectin contribute to variance in NP distribution. Human physiology is not an exact science; assessments need customization. Standardization helps to benchmark exposures and tailor assessments.

#### 4.4. Outlook and conclusion

Performance of eqn (1)–(3) is appreciable,  $R^2 = 0.68$ , and statistically significant p < 0.00001 (2SD). In comparison,

different labs monitoring in vivo concentration routinely yield a variability scatter of >20-40%. 138 Variance in experimental log K (e.g., 7 days or 6 months) is 20–100% depending on tissue. <sup>133</sup> ~70% of white blood cells are phagocytes, hence, representability of Table 1 entries introduces errors of ~30%. Whether *K* reflects equilibrium (section 2.5) is uncertain due to experimental limits (colloids preventing dispersion). Barriers/ inhomogeneities complicate in vivo measuring (local equilibria). K may increase/decrease via size-exclusion or immune response by aggrupation (clustering) of macrophages. Uncertain geometry of protein/vesicle/cell/tissue surfaces impacts y, within 5%. 203 Additional experiments on (de/at) tachment NPs aid assessment of tissue trafficking.

chemistry, 103,204,205 Depending lysosomes/ autophagosomes<sup>206</sup> degrade ionizable/polarizable NPs, <sup>26,207</sup> affecting y, but does not affect model results for inert PEG-NPs (Fig. 2).  $\gamma$  is a function of surface morphology (shape), 155,208 but applicability to non-spherical NPs remains speculation, needing further study. Long-term exposures to various NPs/coatings (PbO, TiO2, QDs, C60, citrate 61,209-214) show distributions similar to Fig. 2 and values, e.g. Kliver/blood  $\approx 10^{3,212}$  are comparable. Moreover, Fig. 3 ascertains flexibility of our 'generic' model by showing applicability to other NPs/biomolecules:

Eqn (3) uses  $\gamma$  of NP and cell membrane (biomolecules), either experimental (if available) or predicted (i.e., computed<sup>80</sup>). We used  $\gamma$  (ref. 216 and 217) to describe adhesion of surfaces, avoiding shortcomings of  $K_{ow}$ . Relationships (Fig. 2) depend on standardizing doses/ exposures and sample processing (tissue-specific digestion/ fixation/drying rates).  $\gamma$  (Table 2) is subject to test liquids (analogous to octanol). Surface energy components ( $\gamma^{LW}$ ,  $\gamma^{AB}$ ) describe small organic compounds (e.g., polar surface area); cations are electron-poor Lewis acids, anions are electronrich Lewis donors. For NP surfaces with limited/uniform polarizability, we can obtain  $\gamma_{\rm NP}^{\rm LW}$ ,  $\gamma_{\rm NP}^+$  and  $\gamma_{\rm NP}^-$  from partial charged surface area/density. 40,80 This unifies descriptions for NPs and small organic molecules:  $^{218}$  both  $\gamma$  for NPs and charged surface areas of small molecules drive their partitioning; both find use in risk assessment. 214,219,220

Our calculus for various NP types successfully yields partitioning in(to) many tissues/organs, by cells40,81 and biomolecules. These data find use in PBPK modeling with extensions via scaling. 201,214,221 Existing PBPK models parametrize partitioning without (much) regard for mechanism:<sup>222</sup> higher K in non-phagocytotic organ tissues.<sup>223</sup> Ideally, all parameters ought be mechanism-based to allow extrapolation across NPs/tissues. To our knowledge, a theoretical framework did not yet exist for tissue partitioning of NPs. We are happy to attribute complex behaviors to simple properties and traits and expand concepts for small molecules to NPs. Regressions between predicted/ experimental K are useful to obtain tissue partitioning without experiments. We instigated future research for implementing biodistributions of particles in medical and toxicological applications.

## Conflicts of interest

There are no conflicts to declare.

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