Liquid Nebulization-Ion Mobility Spectrometry Based Quantification of Nanoparticle-Protein Conjugate Formation

Seongho Jeon[1], Derek R. Oberreit[2], Gary Van Schooneveld[3], & Christopher J. Hogan Jr.[1,*]

[1]Department of Mechanical Engineering, University of Minnesota, Minneapolis, MN, USA
[2]Kanomax-FMT, St Paul, MN USA
[3]CT Associates, Inc., Eden Prairie, MN USA

Supporting Information

***To whom correspondence should be addressed: hogan108@ umn.edu, Tel: 1-612-626-8312, Fax: 1-612-625-6069.**

INFORMATION AVAILABLE

- Description of Langmuir-like sorption model and derivation of P_i.
- Description of a constant number Monte Carlo approach to predict the size distribution functions of nanoparticle-protein conjugates considered both the Langmuir-like sorption model and an irreversible condensation model.

The Langmuir-Like Sorption Model and Derivation of P_i

Noted in the main text, the mean diameter of a nanoparticle-conjugate size distribution function can be predicted using an equilibrium binding model and with prior knowledge of the bare nanoparticle size distribution function via the equation:

$$d_{p,ave} = \frac{\int_{-\infty}^{\infty} \frac{dn}{dlog_{10}d_{p,0}}\Big|_0 (\sum_{i=0}^{\infty} d_{p,i}P_i) dlog_{10}d_{p,0}}{\int_{-\infty}^{\infty} \frac{dn}{dlog_{10}d_{p,0}}\Big|_0 dlog_{10}d_{p,0}} \quad \text{(S1)}$$

Equations for P_i, which is defined as the probability that a nanoparticle have *i* proteins bound to it, are provided in the main text. Our purpose in this section is to provide a derivation for the provided expressions, which is similar to the derivation provided for this expression in related IMS studies.[1,2] First, we note that P_i can be expressed as:

$$P_i = \frac{n_i}{\sum_{k=0}^{k=\infty} n_k} = \frac{\frac{n_i}{n_0}}{1.0+\sum_{k=1}^{k=\infty}\frac{n_k}{n_0}} \quad \text{(S2)}$$

where n_i is the number concentration of nanoparticles with *i* proteins adsorbed onto their surfaces, and n_o is the number concentration of bare nanoparticles. At equilibrium, the ratio $\frac{n_i}{n_0}$ (or $\frac{n_k}{n_0}$) in equation (S2) can be linked to the dimensionless equilibrium binding coefficients $\left[K_{eq}\right]_{j-1\to j}$ for the reaction: $n_{j-1} + n_a \rightleftharpoons n_j$ via the equation:

$$\frac{n_i}{n_0} = \frac{n_1}{n_0}\frac{n_2}{n_1} \ldots \frac{n_{i-1}}{n_{i-2}}\frac{n_i}{n_{i-1}} = \prod_{j=1}^{i}\left[K_{eq}\right]_{j-1\to j} \quad \text{(S3)}$$

Assuming that each nanoparticle has $[X]\pi d_{p,0}^2$ specific sites where proteins can bind ([X] is the assumed size-independent site surface density or maximum surface coverage), that the effective protein concentration above a site is n_{eff}, and that the protein adsorption and desorption rate coefficients are exactly equal in magnitude (i.e. they are diffusion limited reactions), $\left[K_{eq}\right]_{i-1\to i}$ can be expressed as:

$$\left[K_{eq}\right]_{j-1\to j} = \frac{n_a[X]\pi d_{p,0}^2 - j + 1}{j n_{eff}} \quad \text{(S4)}$$

Substitution of equations (S3-4) into equation (S2) leads to:

$$P_0 = \frac{1.0}{1.0+\sum_{k=1}^{k=[X]\pi d_{p,0}^2}\left(\left(\frac{n_a}{n_{eff}}\right)^k \prod_{j=1}^{j=k}\left(\frac{\left[[X]\pi d_{p,0}^2 - j + 1\right]}{j}\right)\right)} \quad \text{(S5)}$$

$$P_i = \frac{\left(\frac{n_a}{n_{eff}}\right)^i \Pi_{j=1}^{i}\left(\frac{\left[[X]\pi d_{p,0}^2 - j + 1\right]}{j}\right)}{1.0 + \sum_{k=1}^{k=[X]\pi d_{p,0}^2}\left(\left(\frac{n_a}{n_{eff}}\right)^k \Pi_{j=1}^{j=k}\left(\frac{\left[[X]\pi d_{p,0}^2 - j + 1\right]}{j}\right)\right)} \qquad i \geq 1 \qquad \text{(S6)}$$

Equations (S5) & (S6) are derived using the same assumptions as the Langmuir adsorption model (but applied for discrete numbers of proteins, hence it differs slightly from the traditional Langmuir model). They are identical to equations (2a) & (2b) of the main text. Figure S1 displays P_i values a at different n_a/n_{eff} ratios with $d_{p,0}$ = 30.0 nm and [X] = 0.060 # nm^{-2}, showing the as n_a/n_{eff} increases the mode P_i value increases.

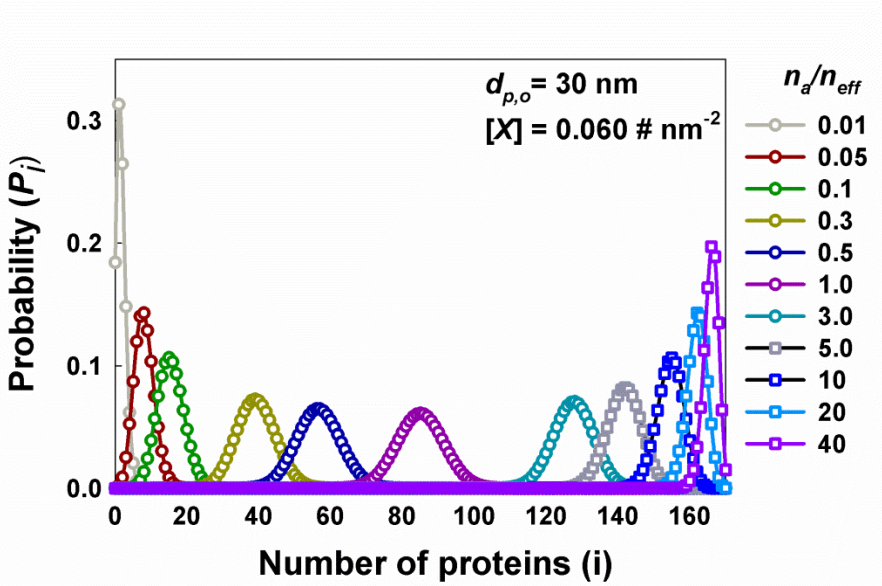

Figure S1. The probability P_i that a nanoparticle has i proteins bound (at equilibrium) predicted by the Langmuir-like model at various n_a/n_{eff} ratios ($d_{p,o}$ = 30.0 nm and [X] = 0.060 # nm^{-2}).

Constant Number Monte Carlo Simulations

The constant number Monte Carlo simulation approach, developed by Smith and Matsoukas,[3] is a relatively simple and accurate method for monitoring the evolution of particle size distribution functions. Here, we adapt it to make predictions about the size distribution functions of originally lognormally distribution particles as noted in the main text. For the Langmuir-like sorption model, evolution of the distribution function in time need not be considered. Instead, 10^5 nanoparticle diameters are sampled from the lognormal distribution. For each sampled nanoparticle, using the noted equations for P_i and with prescribed values of *[X]* and n_a/n_{eff}, an integer number of proteins bound (i) is also sampled. The bare nanoparticle diameter, number of proteins bound, and protein diameter (assumed) are then used to calculate the conjugate diameters. Binning of conjugate diameters enables construction of a size distribution function. In addition to the examples in the main text, Figure S2 displays plots of constant number Monte Carlo inferred size distribution functions for lognormally distributed particles with variable values of n_a/n_{eff}.

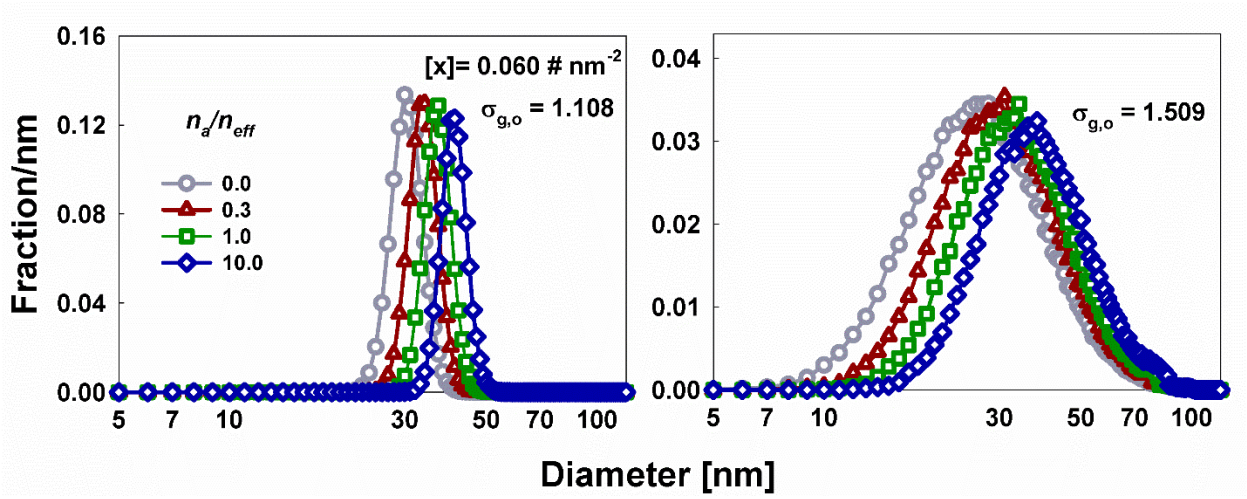

Figure S2. Simulated size distribution functions with the constant number Monte Carlo algorithm considering the Langmuir-like binding model with the noted input parameters. The bare nanoparticle geometric mean diameter was 31.1 nm.

The size distribution functions of nanoparticles upon *irreversible* protein binding events (termed condensation here) were also simulated by applying constant number Monte Carlo simulation. The key differences with the Langmuir-like binding model are that (1) binding can occur indefinitely, i.e. there is no maximum surface coverage, and (2) protein dissociation from the conjugate is not considered. For this procedure we again selected 10^5 nanoparticle diameters from prescribed size distribution functions. Subsequently, at each timestep 100 of these nanoparticles were sampled to undergo protein binding/condensation with the probability of selection proportional to the diffusion limited binding rate between protein and nanoparticle/nanoparticle-protein conjugate. The rate coefficient, k_i, for this reaction, is expressed as:

$$k_i = 2\pi(d_{p,i} + d_{pro})(D_{p,i} + D_{pro}) \quad \text{(S7)}$$

where D denotes the diffusion coefficient for conjugates and isolated proteins (equivalent to $\frac{kT}{3\pi\mu d}$, where k is Boltzmann's constant, T is temperature, μ is the solvent's dynamic viscosity, and d is the diameter of the entity in question). The probability of condensation $P_{c,i}$ is calculated as:

$$P_{c,i} = \frac{k_i}{\sum_{j=1}^{j=N} k_j} \quad \text{(S8)}$$

where N is the total number of sampled nanoparticles. After condensation, nanoparticle diameters are increased, and the procedure is repeated. The size distribution function hence evolves over time, with the true rate proportional to the number concentrations in suspension. Sample results considering irreversible condensation onto lognormally distributed particles, are shown in Figure S3.

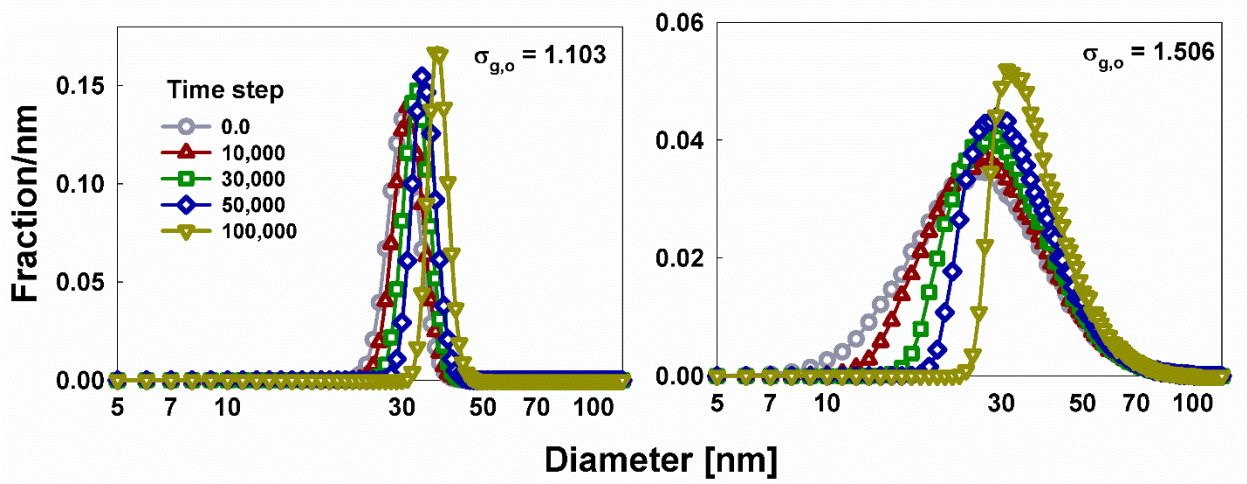

Figure S3. Simulated size distribution functions with the constant number Monte Carlo algorithm considering irreversible condensation.

References

(1) Oberreit, D.; Rawat, V. K.; Larriba-Andaluz, C.; Ouyang, H.; McMurry, P. H.; Hogan, C. J. *The Journal of Chemical Physics* 2015, *143*, 104204.
(2) Rawat, V. K.; Vidal-de-Miguel, G.; Hogan, C. J. *Analyst* 2015, *140*, 6945-6954.
(3) Smith, M.; Matsoukas, T. *Chemical Engineering Science* 1998, *53*, 1777-1786.