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A Bayesian hierarchical model for maximizing the vascular adhesion of nanoparticles

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Abstract

The complex vascular dynamics and wall deposition of systemically injected nanoparticles is regulated by their geometrical properties (size, shape) and biophysical parameters (ligand-receptor bond type and surface density, local shear rates). Although sophisticated computational models have been developed to capture the vascular behavior of nanoparticles, it is increasingly recognized that purely deterministic approaches, where the governing parameters are known a priori and conclusively describe behaviors based on physical characteristics, may be too restrictive to accurately reflect natural processes. Here, a novel computational framework is proposed by coupling the physics dictating the vascular adhesion of nanoparticles with a stochastic model. In particular, two governing parameters (i.e. the ligand-receptor bond length and the ligand surface density on the nanoparticle) are treated as two stochastic quantities, whose values are not fixed a priori but would rather range in defined intervals with a certain probability. This approach is used to predict the deposition of spherical nanoparticles with different radii, ranging from 750 to 6,000 nm, in a parallel plate flow chamber under different flow conditions, with a shear rate ranging from 50 to 90 sec⁻¹. It is demonstrated that the resulting stochastic model can predict the experimental data more accurately than the original deterministic model. This approach allows one to increase the predictive power of mathematical models of any natural process by accounting for the experimental and intrinsic biological uncertainties.

Keywords

Bayesian Inference; Nanomedicine; Vascular Adhesion; Uncertainty Quantification

1 Introduction

Nanotechnology is at the forefront of the current initiative for targeted therapies in medicine [1,2]. Nanoparticles, smaller than the size of a red blood cell, can be injected in the vasculature and pushed by the blood flow to reach virtually any site within the host organism. Their size, shape, and surface properties can be tailored during the synthesis process to deliver with high efficiency several therapeutic and imaging molecules to the biological target (i.e. a tumor mass, arteriosclerotic plaque, a damaged vessel, and so on) [3–5]. Ensuring nanoparticles recognize their specific target, while avoiding the non-specific sequestration by filtering organs, such as the liver, spleen, and kidneys, is part of their rational design [6]. This will indeed increase the amount of drug molecules accumulating within the target tissue while reducing the risk of side effects and damage to surrounding healthy tissues.

For vascular targeted nanoparticles, the complex dynamics of blood transport and adhesion to the vessel walls dictate their ability to reach and accumulate at the diseased site [7–10]. More specifically, the delivery and adhesion processes involve dynamic interactions between the vascular environment and the surfaces of the particle which are regulated by specific interaction (ligand-receptor bond formation) and non-specific interaction (colloidal forces). Sophisticated deterministic models have been developed to describe such multifaceted interplay [11,8,12–14]. However, it has been increasingly recognized that deterministic models, where model parameters are known and conclusively describe behaviors based on physical characteristics, may be too restrictive to accurately reflect natural processes. The uncertainty in the actual, realistic quantification of these governing parameters is challenging and, additionally, such values could be patient specific or vary within a patient spatially and temporally. Therefore, models including a stochastic component would allow for the uncertainty on parameter estimates, as well as experimental variability and experimental error. Indeed, this quantification of variation is unattainable in deterministic models and would complement the latter.

The use of stochastic modeling has become of increasing interest in the bioengineering field. For example, [15] develop a method of recovering relationships between genes from microarray data with Bayesian networks. A computational package introduced in [16] exploits Bayesian phylogenetic analyses to incorporate information from different data sources evolving under different stochastic evolutionary models. [17] provides an overview of efforts to model in vivo reactions by assuming that observed random fluctuations are a consequence of the small number of reacting molecules. See also [18] for a review of the foundations of stochastic differential equations, with applications in oncology and agronomy. [19] develop a computational framework to predict nanoparticle dispersion and transport characteristics in the microvasculature with a combination of computer simulations, experimental data, and quantitative predictions. Our method is most similar to the approach in [19]; we not only take advantage of stochastic models for our specific

problem (here, vascular adhesion of nanoparticles), but have the advantage of biologically sound foundations, via a theoretical physical model.

Our goal is to identify the optimal nanoparticle configuration to maximize the probability of adhesion to vessel walls under flow. To this end, we develop a computational framework, coupling the physics dictating the biological processes with a stochastic model. Here, this approach focuses on the investigation of the effects of two parameters, one including the length of the bond of one particle and one incorporating the surface density of the particle [20]. Essentially, the two parameters exemplify the possibility of a particle to attach and the strength of the bond. These parameters are customarily assumed to be known, fixed quantities. Nonetheless, we would expect some uncertainty in these values given the dynamics of the environment.

The remainder of the article is organized as follows. Discussion regarding the development of the modeling framework and inferential objectives are presented in Section 2. Results are provided in Section 3, and conclusions in Section 4.

2 Materials and Methods

2.1 Theoretical model of adhesion

In the vascular adhesion of nanoparticles, the concept of the probability of adhesion, P_a , was introduced in [20] as a means to quantify the strength of adhesion of a nanoparticle to the vessel wall under flow. Accordingly, P_a is the probability of at least one ligand-receptor bond forming. The adhesion probability is determined through the probabilistic kinetic formulation of [21]

$$P_a \simeq m_r m_l K_a^0 A_c \exp \left\{ -\frac{\lambda f}{k_B T} \right\}, \quad (1)$$

where m_r is the receptor density on the substrate surface, m_l is the surface density of ligands, K_a^0 is the association constant of ligand-receptor pair at zero load, A_c is the contact area of the particle, f is the force per unit ligand-receptor pair, λ is the characteristic length of the ligand-receptor bond, and $k_B T$ is the Boltzman thermal energy ($4.14 \times 10^{-21} J$).

Further, we can approximate the area of interaction, A_c , as πr_0^2 , with r_0 the radius of the circular section of the spheroid at h_0 above the substrate. By using the equation for the intersection of a spheroid with a constant plane, we have

$$A_c \simeq \pi r_0^2 = \pi a^2 \left[1 - \left(1 - \frac{h_0 - \delta_{eq}}{a} \gamma \right)^2 \right]. \quad (2)$$

Here, γ is the aspect ratio (for spherical particles, $\gamma = 1$), a is the radius of the particle, δ_{eq} is the distance between substrate and particle, and h_0 is the max distance between spheroid and substrate at which a bond can be formed.

Finally, the force per unit ligand-receptor pair, f , can be expressed as the ratio between the total dislodging force, F_{dis} , and the product of the area of interaction A_c and the surface density of receptors, m_r (i.e., $f = F_{dis}/m_r$). The dislodging force is a combination of the drag force, F , along the flow direction and the torque, T , which, in turn, are affected by the radius of the particle (a), the separation distance from the substrate, and the shear stress at the wall, μS . Assuming F is uniformly shared across the ligand-receptor bonds and T is shared uniformly within those ligand-receptor pairs which are stretched, it follows that

$$\begin{aligned} F_{dis} &= F + 2T/r_0 \\ &= 6\pi a(a + \delta_{eq})\mu S F^S + 8\pi a^3\mu S T^S / r_0. \end{aligned} \quad (3)$$

Thus, by combining the previous equations, we can obtain an explicit expression for the probability of adhesion,

$$P_a(S, a, \theta) = \pi r_0^2 \exp \left\{ -\frac{\lambda}{k_B T} \left[6(a + \delta_{eq})F^S + 8\frac{a^2}{r_0}T^S \right] \times \frac{a}{r_0^2} \frac{\mu S}{m_r} \right\} (m_r m_l K_a^0), \quad (4)$$

where the use of the notation $P_a(S, a, \theta)$ explicitly highlights that such probability is primarily a function of the shear rate, S , the radius of the particle, a , and other (non-constant) physical parameters, θ . More specifically, we assume

$\theta = (m_r, m_l, K_a^0, \lambda, \delta_{eq}, h_0, r_0)$ in (4). In the following, we set the equilibrium separation distance, δ_{eq} , to $5 \times 10^{-9}m$ and $h_0 = 10^{-8}m$. The remaining parameters (λ, K_a^0, m_r, m_l) are particularly important in explaining the probability of adhesion. The underlying physics gives a range of plausible values for these parameters. However, arbitrarily fixing the values of these parameters may be too restrictive to accurately describe the reality of observed data. Our framework provides a way to estimate these parameters on the basis of available data, while also accounting for experimental variability.

2.2 Hierarchical model formulation

Mathematically, learning the values of all four parameters of interest is impossible. This is due to the fact that these parameters occur in combinations. That is, holding all parameters constant, multiple values of λ and m_r produce equivalent ratios λ/m_r . In the same vein, the same value of $m_r m_l K_a^0$ can be produced with different combinations of the three parameter values. In equation 4, two governing parameters can be uniquely identified, namely, $\beta_1 = \lambda/m_r$ and $\beta_2 = m_r m_l K_a^0$. Since β_1 is the ratio between the characteristic bond length, λ and the surface density of receptors m_r , it can be considered a measure of the bond strength. Indeed, the chemical bond between receptors and ligands is stronger as β_1 increases. Similarly, β_2 can be considered as a measure of the strength of vascular adhesion in that it depends on the surface density of receptors, m_r , and ligands, m_l , as well as the ligand-receptor affinity constant K_a^0 . as β_2 gets larger, the higher is the vascular adhesion. Plausible ranges for $\beta_1 \in [1 \times 10^{-25}m^3, 1 \times 10^{-23}m^3]$ and $\beta_2 \in [0, 1 \times 10^{16}m^{-2}]$ are found through the possible values for each parameter. These simplifications propagate to the adhesion probability, which can be written as follows

$$P_a(S, a, \boldsymbol{\theta}) = \pi r_0^2 \beta_2 \exp \left\{ -\beta_1 \left[6(a + \delta_{eq}) F^S + 8 \frac{a^2}{r_0} T^S \right] \times \frac{a}{r_0^2} \frac{\mu S}{k_B T} \right\}, \quad (5)$$

where, with some abuse of notation, we now indicate $\boldsymbol{\theta} = (\beta_0, \beta_1, \delta_{eq}, h_0, r_0)$. As β_1 and β_2 are unknown, we formulate appropriate distributional assumptions on the values of each parameter. These assumptions can be derived from the literature, previous experimental data, or the physical properties of the combined parameters. For example, here we use the theoretical range of plausible values for the physical parameters to determine the location and scale of each prior distribution. In other words, the distributional assumptions correspond to a set of prior beliefs regarding the parameters of interest and will be used as prior distributions in a fully Bayesian hierarchical setting. Accordingly, these prior distributions are updated on the basis of the observed experimental data in order to obtain posterior inference on β_1 and β_2 .

Let X_{sa} denote the number of adhered particles with radius a at shear rate S . A natural approach would be to assume the observations arise from a Binomial distribution with probability of success $P_a(S, a, \boldsymbol{\theta})$ and size 10^6 . Under this formulation, the assumptions imply independence of each experiment, and also each trial within an experiment. That is, the model assumes that each of the nanoparticles adheres independently of the rest. To move away from this unreasonable notion, we consider the data, Y_{sa} , as the *proportion* of nanoparticles of radius a that adhere at shear rate S . We may consider the log transform of the proportion of adhered particles, then propose a Gaussian likelihood. Given the possibility of extending this framework to more complex models, we choose to instead keep the proportions and use a Beta likelihood. Note, however, that results for the experimental data are comparable under both of these formulations.

Thus, given $P_a(S, a, \boldsymbol{\theta})$ (as given in 5) and a precision parameter ϕ , we assume

$$Y_{sa} | S, a, \boldsymbol{\theta}, \phi \stackrel{ind}{\sim} \text{Beta}(P_a(S, a, \boldsymbol{\theta})\phi, (1 - P_a(S, a, \boldsymbol{\theta}))\phi), \quad (6)$$

where we use the representation of the Beta distribution in terms of the mean and a scale parameter, with $E(Y_{sa} | S, a, \boldsymbol{\theta}, \phi) = P_a(S, a, \boldsymbol{\theta})$ and $\text{Var}(Y_{sa} | S, a, \boldsymbol{\theta}, \phi) = (P_a(S, a, \boldsymbol{\theta})(1 - P_a(S, a, \boldsymbol{\theta}))) / (1 + \phi)$. Here, we introduce uncertainty in two ways: first, we fully account for the experimental error, i.e. the deviance between the theoretical value of $P_a(S, a, \boldsymbol{\theta})$ and the observed data; and second, we do not fix any predetermined values for β_1 and β_2 . We conduct our estimation using a Bayesian framework and are able to incorporate existing knowledge about the current values of the parameters into the estimation procedure. We place independent Gaussian priors on both β_1 and β_2 , truncated below at 0. The mean and standard deviations of the truncated Gaussian distributions are chosen to correspond to their theoretical physical range. Namely, the truncated Gaussian prior for β_1 has a mean of $1 \times 10^{-24} m^3$ and a standard deviation of $5 \times 10^{-24} m^3$ and the prior for β_2 has a mean of $1 \times 10^{13} m^{-2}$ and a standard deviation of $5 \times 10^{13} m^{-2}$.

The precision parameter, ϕ , controls how much experimental error to allow. The standard deviation of the beta likelihood distribution captures the experimental error of the data. In Table 1, we give the standard deviation of the beta distribution as a function of ϕ and P_a . As ϕ increases, the experimental error decreases. Furthermore, for any fixed value of ϕ , the variance is larger for values of P_a close to 0.5. This follows from the consideration that values of the probability of adhesion near the middle of the interval $[0, 1]$ do not provide much predictive information on the final behavior of a nano particle when injected into a vessel. Note that the variance is symmetric around 0.5; i.e. its value is the same for, say, $P_a = 0.2$ and $P_a = 0.8$.

As ϕ is positive valued and unknown before data collection, we assign it a Gamma prior distribution with a mean of about 20 and most of its mass concentrate in the range $(0, 100)$. Consequently, the full vector of parameters of the model can be represented as $\Theta = (\beta_1, \beta_2, \phi)$. The likelihood of the data (6) and the collection of prior distributions define a multilevel/hierarchical Bayesian model on the observed data, Y_{sa} , which can be represented in summary by the following set of equations,

$$Y_{sa} \sim B(\phi P_a(S, a, \theta), \phi(1 - P_a(S, a, \theta))) \\ (\beta_1, \beta_2, \phi) \sim N^+(\beta_1; m_1, s_1) \times N^+(\beta_2; m_2, s_2) \times \text{Gamma}(\phi; c, b),$$

where P_a is as in 5 and $(m_1, s_1, m_2, s_2, c, b)$ are fixed and determined on the basis of the available information as discussed above. Here, $N^+(m, s)$ denotes the Gaussian distribution with mean m and standard deviation s truncated below at 0 and $\text{Gamma}(c, b)$ denotes the Gamma distribution with shape parameter c and scale parameter b . Posterior estimates of β_1 , β_2 , and ϕ are obtained by updating the prior knowledge based on the observed data.

2.3 Parallel plate flow chamber experiments

Polystyrene fluorescent particles (Fluoresbrite®, Polysciences, Warrington, PA) of different sizes were purchased, namely 0.75, 1.0, 2.0, 4.5, and 6.0 μm (nominal diameter). Particle number and diameter were measured using a Multisizer 4 Coulter Counter and a size analyzer (Beckman Coulter, Fullerton, CA) with a 100 μm aperture. Particles were suspended in a balanced electrolyte solution (ISOTON II Diluent, Beckman Coulter) and counted. The adhesion experiments were conducted in a parallel plate flow chamber (Glycotech, Rockville, MD) consisting of a Plexiglass flow deck, with inlet and outlet holes, a 35 mm borosilicate cover slip, and a silicon gasket, installed between the flow deck and the cover slip. The parallel plate flow chamber was connected to a syringe pump (Harvard Apparatus, Holliston, MA) through plastic tubing to control the flow rate precisely. The chamber channel was 5 mm wide (w), 20 mm long (l), and 254 μm high (h). After connecting the chamber to the pump, the apparatus was placed on the stage of an inverted fluorescent microscope (Nikon TE-2000). A schematic of the apparatus is presented in Figure 1. For each experiment, 106 fluorescent polystyrene particles in 1 mL of solution were injected at different shear rates ($S = 50, 75$, and 90 sec^{-1}), controlled through the syringe pump flow rate Q following the relationship $S = 6Q/(h^2w)$. Images of the fluorescent particles adhering to the substrate within the chamber were captured at regions of interest using a 20 $\times$ dry

objective and were saved to a computer for storage. Multiple regions of interest were chosen in the middle of the channel to limit flow disturbance due to the side walls and inlet/outlet effects. The still images were saved to a computer for storage using a Nikon DQC-FS digital camera (Tokyo, Japan), and exported as TIF files into ImageJ, a freeware software from the National Institutes of Health (<http://rsb.info.nih.gov/ij/>), for post-processing. The 35 mm borosilicate dishes were coated with collagen type I solution from rat tails (Sigma-Aldrich Corporation, St Louis, MO). The collagen solution with a concentration of 4 mg/mL was diluted in double-distilled water to obtain a surface coverage of about 10 $\mu\text{g}/\text{cm}^2$.

3 Results

3.1 Experimental Results

Previously analyzed in [22], we consider experiments using polystyrene fluorescent spherical particles of different sizes, 0.75, 1.0, 2.0, 4.5, and 6.0 μm in diameter. For each experiment, 10^6 fluorescent particles in 1 mL of solution were injected at different shear rates ($S = 50, 75$, and 90 sec^{-1}). After injection into the parallel plate flow chamber system, the number of particles adhering per unit area to the collagen substrate was measured using fluorescence microscopy under different hydrodynamic conditions (wall shear rate S) and particle diameter (d). Figure 2 shows the results. The x -axis represents the diameter of the particle and the y -axis is the proportion of adhering particles. The data at the three shear rates are delineated via point type. In general, as the shear rate increases, the number of adhering particles decreases. Across the range of diameters, the change in the number of adhering particles depends on the shear rate.

3.2 Posterior Analysis

To update our prior beliefs about the parameters of interest via the data, we obtain posterior inference on θ and $P_a(S, a, \theta)$ by way of Markov chain Monte Carlo (MCMC) methods. This is a powerful technique used to perform numerical integration. Our model, as is the case in many Bayesian models, is analytically intractable, and therefore requires an algorithm to estimate the posterior distribution of the unknown parameters (see Appendix A for details). This is done by first choosing starting values for each of our parameters. Then, for each iteration of the algorithm, sample new values of the parameters based on the data, the likelihood, and the parameter values from the previous iteration. This process builds a Markov chain of random draws. When the Markov chain reaches convergence after a so called "burn-in" period, the draws are theoretically independent from the starting values of each parameter, and effectively represent samples from the posterior distribution of the parameters of interest. Multiple chains can be used to assess convergence when the likelihood is multimodal and there is a possibility that a single chain may be stuck in a local mode [23].

The posterior samples so obtained can be used to provide posterior estimates of the parameters of interest, as well as highest posterior credible intervals. For example, the MCMC sample average provides an ergodic estimate of the posterior expected value of a parameter. Let $\beta^{(b)}$, $b = 1, \dots, B$, indicate the posterior draws of β after burn-in. Then

$$E(\beta|\text{data}) \approx \frac{1}{B} \sum_{b=1}^B \beta^{(b)}.$$

The accuracy of the estimate will increase as B , the length of the

chain, increases. In most problems of medium complexity, $B = 10,000$ may produce good estimates. Similarly, we can acquire 95% posterior credible intervals of the parameters by estimating the posterior density of the MCMC draws and determining the corresponding 2.5% and 97.5% quantiles.

For the spherical data, we fit the hierarchical Bayesian model. Figure 3 gives posterior densities for $\beta_1 = \lambda/m_r$ (top panel), $\beta_2 = m_r m_l K_0^a$ (middle panel), and the precision parameter, ϕ (bottom panel). The mean for β_1 is $1.48 \times 10^{-24} m^3$ with standard deviation $0.147 \times 10^{-24} m^3$. The posterior mean of β_2 is $1.38 \times 10^{13} m^{-2}$ and a standard deviation of $1.12 \times 10^{12} m^{-2}$. Finally, the mean for the variance term, ϕ , is 15.5 and a standard deviation of 2.81. As ϕ is a precision parameter, larger values imply less experimental error. This estimate averages over all observed data points, and a larger sample size is customarily associated to greater precision and less experimental error.

Figure 4 plots point estimates (posterior means) and 95% interval estimates for the probability of adhesion in (5) at the three observed shear rates, $S = 50 \text{sec}^{-1}$, 75sec^{-1} , and 90sec^{-1} , as a function of radius. Here, the range of values for the radius of the particle ranges from $0.05 \mu m$ to $5 \mu m$. The theoretical model follows the general pattern of the experimental data, rising from close to zero for small particles to a point around the mid-point of the range of diameters then falling off as the particles get larger. The general structure of the underlying, theoretical model for the probability of adhesion closely resembles what is observed in experimental data. By placing prior distributions on the two governing parameters (β_1 and β_2), we account for our uncertainty in these parameters, which then propagates to the probability of adhesion. The posterior uncertainty bands are increasing in width as particle radius increases, and decrease slightly as the shear rate increases. As the radius increases and moves farther from the observed values, the uncertainty in the probability of adhesion grows. For all values of the radius, observed or unobserved, we have a distribution of possible values for the probability of adhesion.

3.3 Prediction Results

A key inferential objective is the estimation of the optimal particle radius. Note that the nature of the function in (5) forces the probability of adhesion to increase as the shear rate decreases, thus the optimal shear rate is always be the smallest possible. Hence, we fix the shear rate and determine the optimum diameter under that condition. To this end, posterior draws of the optimal values of a_0 are obtained by numerically inverting the posterior realization of $P_a(S_0, a_0, \theta)$ at each iteration of the MCMC.

To assess the variability inherent to experimentation, the posterior mean (solid lines) and 95% credible intervals (dashed lines) for the posterior predictive distribution are shown in Figure 5. The overall shape is comparable to the posterior mean for the probability of adhesion, but includes wider interval estimates to account for experimental error. The majority of the realized values fall within the 95% intervals at each of the observed shear rates. As there are only 3 or 4 data points at each shear rate/radius combination, the predictive variability is large but not unreasonable. Thereby, the model assumptions,

including the functional form of the probability of adhesion, are supported by the experimental data.

Finally, we obtain inference for the optimal radius at three shear rates, the smallest observed ($S = 50\text{sec}^{-1}$) and two unobserved ($S = 30\text{sec}^{-1}$ and $S = 40\text{sec}^{-1}$). The distributions for the optimum are shown in Figure 6. The observed shear rate, $S = 50\text{sec}^{-1}$, imparts a mean optimal radius of $2.82\mu\text{m}$ with a 95% interval of $[2.46\mu\text{m}, 3.19\mu\text{m}]$. As the shear rate decreases from the observed values, the means increase and the uncertainty associated with the value increases. That is, the mean optimum at $S = 40\text{sec}^{-1}$ is $3.27\mu\text{m}$ with a 95% interval of $[2.87\mu\text{m}, 3.68\mu\text{m}]$, and specifying $S = 30\text{sec}^{-1}$ results in an optimum of $3.96\mu\text{m}$ and a 95% interval of $[3.49\mu\text{m}, 4.50\mu\text{m}]$.

4 Conclusions

A computational model for predicting the vascular deposition of blood-borne nanoparticles has been presented that accounts for the intrinsic uncertainties of the problem. A stochastic description for two independent, governing parameters, namely the ligand-receptor bond length and the surface density of ligands over the nanoparticle, has been included in the original mathematical adhesion model. In particular, the non-monotonic behavior of the probability of adhesion as a function of the particle size as well as the contribution of the shear rate appear to be captured quite accurately by our modeling framework, especially considering the limited amount of experimental data available. It is demonstrated that the stochastic computational framework can more accurately predict the complex vascular dynamics and wall deposition of the nanoparticles. The approach can be easily extended to describe other biological parameters as stochastic variables, rather than deterministic, fixed parameters. These would include, for instance, the surface charge of the nanoparticles; the local hemodynamic conditions and vascular architecture; and many others. The proposed computational framework could be effectively employed to predict and interpret experimental data deriving from in vivo experiments, where the precise value of the governing parameters is not known a priori and can only be estimated with a certain probability.

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A MCMC details

Since the posterior distribution of the parameters of interest cannot be computed in closed form, we require the use of MCMC methods for inference. Specifically, lacking closed form full conditional distributions, we employ Metropolis-Hastings steps for each of the three parameters of interest. Briefly, the Metropolis-Hastings algorithm can be used to obtain samples from any target probability distribution, say $p(x)$, provided it is possible to compute the value of a function, $q(x)$, proportional to $p(x)$. The sample values are produced iteratively, as part of a Markov Chain, with the distribution of the next sample being dependent only on the current sample value. At each iteration of the algorithm, candidate value is proposed. Then, with some probability, the candidate is either accepted or rejected. If accepted, the candidate value is used in the next iteration; otherwise, the candidate value is discarded, and the current value is retained for the next iteration. The probability of acceptance is determined by comparing the likelihoods of the current and candidate sample values with respect to the target distribution $p(x)$. For the purposes of this algorithm, we have simplified this probability by proposing candidates from the prior distributions.

At iteration b , to update $\beta_1^{(b)}$, the candidate, β_1^* is generated from a Gaussian distribution, truncated below at 0, with mean 1×10^{-24} and standard deviation 5×10^{-24} . The candidate is accepted probability given by the minimum of 1 and the following ratio

$$\frac{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^*, \beta_2^{(b-1)}) \phi^{(b-1)}, (1 - P_a(S, a, \beta_1^*, \beta_2^{(b-1)})) \phi^{(b-1)} \right)}{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^{(b-1)}, \beta_2^{(b-1)}) \phi^{(b-1)}, (1 - P_a(S, a, \beta_1^{(b-1)}, \beta_2^{(b-1)})) \phi^{(b-1)} \right)}$$

For the update of $\beta_2^{(b)}$, the candidate, β_2^* is generated from a Gaussian distribution, truncated below at 0, with mean 1×10^{13} and standard deviation 5×10^{13} . The candidate is accepted probability given by the minimum of 1 and the following ratio

$$\frac{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^{(b)}, \beta_2^*) \phi^{(b-1)}, (1 - P_a(S, a, \beta_1^{(b)}, \beta_2^*)) \phi^{(b-1)} \right)}{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^b, \beta_2^{(b-1)}) \phi^{(b-1)}, (1 - P_a(S, a, \beta_1^b, \beta_2^{(b-1)})) \phi^{(b-1)} \right)}$$

Finally, the precision parameter, $\phi^{(b)}$, is updated through a proposal ϕ^* from a Gamma distribution with shape 2 and scale 0.05. The proposal is accepted with probability given by the minimum of 1 and the following ratio

$$\frac{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^b, \beta_2^{(b)}) \phi^*, (1 - P_a(S, a, \beta_1^b, \beta_2^{(b)})) \phi^* \right)}{\prod_s \prod_a \text{Beta} \left(y_{sa}; P_a(S, a, \beta_1^{(b)}, \beta_2^{(b)}) \phi^{(b-1)}, (1 - P_a(S, a, \beta_1^{(b)}, \beta_2^{(b)})) \phi^{(b-1)} \right)}$$

Fig. 1.

The experimental apparatus includes an inverted epi-fluorescent microscope connected to a computer for data acquisition and storage; a syringe pump for infusing the nanoparticles and controlling the shear rate within the chamber; and the actual parallel plate flow chamber.

Fig. 2. Spherical particle data: each point represents one trial, where the x -coordinate representing the diameter of the particle, the y -coordinate gives the proportion of particles adhering per unit area, and the point type providing the shear rate (∇ for $S = 50\text{sec}^{-1}$, $\times$ for $S = 75 \text{ sec}^{-1}$, and $\diamond$ for $S = 90 \text{ sec}^{-1}$)

Fig. 3. Posterior densities of the three parameters of interest; β_1 (top panel), β_2 (middle panel), and ϕ (bottom panel). Prior distributions are shown as dashed lines.

Fig. 4.
For each of the observed shear rates, posterior mean (solid lines) and 95% interval estimates (dashed lines) for the probability of adhesion, overlaid on plot of the data.

Fig. 5.
For each of the observed shear rates, posterior mean (solid lines) and 95% interval estimates (dashed lines) for the predictive distribution, overlaid on plot of the data.

Fig. 6. The posterior densities of the optimal particle radius at three shear rates, $S = 30\text{sec}^{-1}$, $S = 40\text{sec}^{-1}$, and $S = 50\text{sec}^{-1}$.

Table 1

The standard deviation of the beta distribution, $B(\phi P_a, \phi(1 - P_a))$, as a function of P_a and ϕ . Such a standard deviation captures the experimental error, which decreases as ϕ increases.

	$P_a = 0.2$	$P_a = 0.3$	$P_a = 0.4$	$P_a = 0.5$
$\phi = 5$	0.1633	0.1871	0.2000	0.2041
$\phi = 10$	0.1206	0.1382	0.1477	0.1508
$\phi = 30$	0.0718	0.0823	0.0880	0.0898
$\phi = 50$	0.0560	0.0642	0.0686	0.0700
$\phi = 100$	0.0398	0.0456	0.0487	0.0498