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Abstract

The injection of fluids loaded with a precise number of particles, polymers, and other solutes is common in many areas of chemical engineering. By definition, injection of these fluids is meant to occur over the shortest possible duration. This raises the question that is answered in this note: *At what concentration should a fluid be loaded in order to inject that fluid fastest?* A similar question has been addressed for flows of Newtonian fluids in biophysical and physiological studies. We generalize that analysis. We show for Newtonian fluids containing a single suspended component that the optimal loading is determined from a common tangent construction for the viscosity as a function of concentration. We extend this formulation to describe optimal injection of a multi-component Newtonian fluid. Additionally, we study the injection problem for a simple, model non-Newtonian fluid carrying a single suspended component. Finally, we discuss applications for optimally loaded injections.

Introduction

The problem of engineering a batch injection can be defined in the following way: blend a prescribed dose of some solute(s) in some quantity of solvent(s) such that the time to inject the solution is minimal. There is an equivalent engineering problem for continuous injection: maximize the steady molar flow rate of some solute(s) in some solvent(s) down a pipe at a fixed pressure drop by varying the solution composition. The viscosity of solutions changes and generally increases with the addition solutes to a solvent. Thus, increasing the solute concentration will increase the solution viscosity and reduce the volumetric flow rate

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volumetric flow rate can accompany either an increase or a reduction in the molar flow rate of the solute. The solution composition that minimizes the duration of injection resides at the transition between increasing and decreasing molar solute flow rate. In principle, the design choices for optimizing batch or continuous injection include the geometry of the injection apparatus, the pressure drop applied to drive the injection, and the composition of the solution. In this work, we focus on how the composition of the solution should be chosen in order to minimize the duration of the injection. This optimal composition is determined with minimal assumptions about the flow geometry, but allowing for some non-trivial forms for the rheological response of the fluid. Some examples drawn from the literature and recent research from our own group is used to demonstrate the utility of the expressions we derive.

The term "injection" obviously connotes pharmaceutical injections: a batch process in which an active agent is dispersed in a solvent and injected via a syringe into a living host. A problem of recent interest in this area has been the injection of aqueous solutions of globular proteins (monoclonal antibodies) at high protein concentrations – for which the solutions become hundreds of times more viscous than water [1]. The problem of finding the optimal composition for a pharmaceutical injection is important and has a non-trivial solution. Injections into living hosts can only occur humanely over a finite duration, typically about one second. Similarly, most injections via syringe are powered by forces exerted by human thumbs. With these two practical constraints on the process, a pharmaceutical injection can be engineered in two steps. First, one finds the composition of medication that minimizes the injection duration and the volume of that optimal solution that delivers the desired dose. Then, one sizes the bore of the syringe needle so that this minimal injection duration at the maximal possible applied force matches or falls below the limiting duration. To our knowledge, such a process is not employed currently, but in this work we provide methods for estimating the optimal composition of such pharmaceutical formulations.

One example of continuous (or semi-batch) injection in which the composition of the solution is a free design variable while the molar flow rate of the solute(s) is maximized is the pumping of concrete [2]. Concrete consists of a combination of aggregate, cement powder, and water. The powder and aggregate are mixed in precise ratios to engineer the strength of the final product. Some water is needed for the hydration reaction that converts minerals in the cement powder into the cement binder that bridges the aggregates. However, much more water is used in this process in order make the mixture flow, and too much added water can lead to concrete with reduced compressive strength. An engineering problem that is addressed partly through the inclusion of additives that increase flowability of concrete, is determining the composition of the concrete mixture that delivers the prescribed mass ratio of concrete powder to aggregate at the highest

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possible rate. Such an optimal composition must reside within a region of design space that still meets the final specifications for the poured concrete. That is, there must be enough water to complete the hydration reaction and not so much that the concrete is weakened. While we will not address optimization of injection with constraints of this sort here, one could easily modify the present calculations to incorporate this feature.

Adaptations of natural systems to enable efficient transport of solutes have been studied extensively in the physiology and bio-fluid mechanics literature. A key question asked in these studies is whether certain natural systems are operating optimally. For example, the hematocrit of of human blood is about 45%. Past work in physiology has argued that this loading of blood with red blood cells maximizes the flux of oxygen delivered to the body and have analyzed empirical models of blood viscosity to justify these arguments[3,4,5,6]. Likewise, the idea that nature optimizes fluxes of a single solute in a Newtonian fluid under different mechanical constraints has been explored in other contexts including the delivery of nutrients in plants and the sipping of nectar from flowers by hummingbirds[7,8,9]. While there is some overlap between the present work and these past efforts, we will abstract away from the natural context to the artificially engineered one. We will derive expressions for the optimal composition of single and multi-component Newtonian fluids that are independent of any model for the dependance of viscosity on solution composition, and even apply those same methods to analyze the optimal injection of certain non-Newtonian fluids. This model-free approach will be leveraged to develop some graphical methods for approximating the optimal composition of solutions from experimental data and to offer some suggestions for how to prepare solutions optimized for injection experimentally. As with these past efforts in physiology and bio-fluid mechanics, we will apply some empirical models for the viscosity as a function of composition in new contexts in order to suggest how to improve several different artificially engineered systems.

The article is organized as follows. First, we derive expressions for the optimal composition of two component fluids (one solvent and one solute) which have Newtonian and non-Newtonian rheological responses respectively. Then, we derive the optimal composition for injection of a multi-component fluid (many solvents and solutes) with Newtonian rheology. Finally, we discuss these derivations in the context of several practical examples from the literature and our own research on nanocrystal synthesis.

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Modeling Optimal Injection

Two component, Newtonian fluids

Consider a fluid consisting of two components: a solvent and a suspended solute. On increasing the concentration of the solute in the solvent, c, the viscosity of the fluid, $\eta(c)$, is typically expected to increase. Assume that the resistance to flow of this fluid during injection is laminar and dominated by a region length L and driven by a pressure differential $|\Delta P|$. Then, to a good approximation the volumetric flow rate of the fluid can be written as:

$$Q = \frac{V}{t} = \frac{N}{ct} = \frac{|\Delta P|}{L}\left(\frac{A}{\eta(c)}\right), \tag{1}$$

where N is the amount of the suspended component in the fluid, V is the volume of the fluid so that $c = N/V$, t is the duration of the injection, and A is a purely geometric factor. For steady, unidirectional, laminar flow in a pipe with a circular cross section of radius R, the Hagen-Poiseuille formula gives: $A = \pi R^4/8$. For flow in a rectangular channel with height H much smaller than its width W, $A = H^3 W/12$. Similar geometric factors can easily be derived for Newtonian fluids in the same flow conditions but transported by pipes with more complicated cross sections. In the present work, the units of the dose N are left arbitrary. If number of solutes is chosen for this unit, then c is the number density. If mass is chosen for this unit, then c is the mass density. If volume is chosen for this unit, then c is the volume fraction. For the present purposes, the distinction between these measures is irrelevant. The injection problem is defined by the shortest duration to deliver an amount of solute, N.

The relevant optimization problem for injection is a minimization of the duration t with respect to the concentration c while holding the amount of solute N fixed. From equation 1 it is clear that:

$$\frac{dt}{dc} = \frac{N}{Ac}\left(\frac{L}{|\Delta P|}\right)\left(\eta'(c) - \frac{\eta(c)}{c}\right), \tag{2}$$

with N held constant. A locally minimal duration, t^*, occurs at an optimal concentration, c^* for which $dt/dc = 0$ and $d^2t/dc^2 > 0$, which means the optimal concentration satisfies the equality:

$$\eta'(c^*) = \frac{\eta(c^*)}{c^*}, \tag{3}$$

and the inequality: $\eta''(c^*) > 0$. This equality defining an optimal concentration merely states that the shortest injection duration occurs at a concentration for which a line through the origin is tangent to the

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viscosity on a plot of $\eta(c)$ versus c (see Figure 1).

Among the set of any local minima, $\{(c_i^*, t_i^*)\}$, equation 1 requires that

$$t_i^* = \eta'(c_i^*)\frac{NL}{|\Delta P|A}. \tag{4}$$

Therefore, the globally minimal duration occurs for the loading having the smallest possible value in $\{\eta'(c_i^*)\}$. Many two component fluids have a viscosity that is a convex function of c, so this set of minima is likely to contain only a single element. The local minimum is the global minimum. In practice, the viscosity may not be known as a smooth function of concentration. Figure 1 suggests a graphical method for estimating the optimal loading when only experimental data for $\eta(c)$ are available.

Two component, non-Newtonian fluids

For non-Newtonian fluids, whose viscosity depends on the stress, τ, during deformation, an application of this same approach incorporating some mild approximations can be used to define similar conditions for optimality. For simplicity, assume that the flow dominating the resistance during injection is steady, unidirectional and in a pipe with a circular cross-section of radius R. Non-Newtonian fluids are susceptible to instabilities that yield unsteady flow, but those circumstances are still active areas of research and would make estimating the minimal injection duration difficult. One should check that the optimal injection conditions determined using these mild assumptions (steady unidirectional flow) are not unstable via experiment. The steady shear viscosity of a two component fluid that exhibits non-Newtonian behavior will depend on both the concentration of the suspended component and the magnitude of the shear stress, so that it can be expressed as $\eta(c, |\tau|)$. Integrating the axial momentum balance along the radial direction in the pipe yields:

$$\tau(r) = \eta(c, |\tau(r)|)\dot{\gamma}(r) = \frac{1}{2}\frac{|\Delta P|}{L}r, \tag{5}$$

where r is the distance from the pipe center to the pipe wall. When imposing no-slip boundary conditions at the pipe wall, the volumetric flow rate can be written as:

$$Q = 2\pi\left|\int_0^R v(r)r\,dr\right| = \pi\left|\int_0^R \frac{d}{dr}(v(r)r^2) - \dot{\gamma}(r)r^2\,dr\right| = \frac{\pi}{2}\frac{|\Delta P|}{L}\int_0^R \frac{r^3}{\eta(c, |\tau(r)|)}\,dr. \tag{6}$$

The optimal loading is defined by the concentration and pressure drop that minimizes the duration of the injection. Setting $Q = N/(ct)$ as in the previous examples, computing dt/dc and $dt/d|\Delta P|$ with fixed N,

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and then setting these quantities equal to zero produces the necessary conditions for optimal injection of a non-Newtonian fluid:

$$\frac{\partial t}{\partial c} = 0 \rightarrow \int_0^R \frac{r^3}{\eta(c^*, |\tau(r)|)^2} \left(\frac{\partial}{\partial c} \eta(c, |\tau(r)|) \Big|_{c=c^*} - \frac{\eta(c^*, |\tau(r)|)}{c^*} \right) dr = 0, \tag{7a}$$

$$\frac{\partial t}{\partial |\Delta P|} = 0 \rightarrow \int_0^R \frac{r^3}{\eta(c^*, |\tau(r)|)^2} \left(\frac{1}{2} \frac{\partial}{\partial \sigma} \eta(c^*, \sigma) \Big|_{\sigma=|\tau(r)|} \frac{|\Delta P^*|}{L} r - \eta(c^*, |\tau(r)|) \right) dr = 0, \tag{7b}$$

$$|\tau(r)| = \frac{1}{2} \frac{|\Delta P^*|}{L} r, \tag{7c}$$

where the variable σ is simply being used as a dummy variable for the radially dependent shear stress. From these expressions, one can see right away that the optimally loaded two component Newtonian fluid will have a concentration that satisfies $\eta'(c^*) = \eta(c^*)/c^*$. For non-Newtonian fluids, however, the terms in parentheses cannot be made equal to zero in general (at all values of r simultaneously) and it is the integrals themselves that must be zero for the optimal loading. With sufficient knowledge of the rheology, a concentration for which this equation is satisfied might be identified. However, such detailed knowledge is difficult to acquire experimentally. With some further approximations of the rheology, analytical conditions for optimal injection can be derived.

A common rheology observed in non-Newtonian fluids is a steady shear viscosity that changes from one value at low stress, $\eta_0(c) = \eta(c, 0)$ to another value at large stress $\eta_\infty(c) = \eta(c, \tau \to \infty)$[10]. Typically this transition happens near a critical value of the stress $\hat{\tau}(c) > 0$. In general, this transition happens over a range of stresses in this neighborhood, but for the present purposes we will make a simplifying assumption that the fluid has only a low and a high stress state characterized by different fluid viscosities. For shear thinning fluids, $\eta_0(c) > \eta_\infty(c)$[11], while for shear thickening fluids $\eta_\infty(c) > \eta_0(c)$[12]. To analyze this approximation model, the viscosity is represented as the piece-wise constant function of the stress:

$$\eta(c, |\tau|) = \begin{cases} \eta_0(c), & |\tau| < \hat{\tau}(c) \\ \eta_\infty(c), & |\tau| \geq \hat{\tau}(c) \end{cases}. \tag{8}$$

When this model is applied to the present flow problem, there emerges a critical length scale $\hat{R}(c, |\Delta P|/L) = 2\hat{\tau}(c)L/|\Delta P|$ that divides the pipe into two regions with different viscosity. For $r < \hat{R}(c, |\Delta P|/L)$, the viscosity is $\eta_0(c)$. For $\hat{R}(c, |\Delta P|/L) < r < R$, the viscosity is $\eta_\infty(c)$. In order to realize this outer annulus of fluid, the pipe radius must exceed $\hat{R}(c, |\Delta P|/L)$.

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With this simple two state model of the viscosity, the volumetric flow rate can be written as:

$$Q = \frac{N}{ct} = \frac{\pi}{32} \frac{|\Delta P|}{L} \left\{ \frac{R^4}{\eta_0(c)} + \left(R^4 - \hat{R}(c, |\Delta P|/L)^4 \right) \left(\frac{1}{\eta_\infty(c)} - \frac{1}{\eta_0(c)} \right) H(R - \hat{R}(c, |\Delta P|/L)) \right\}, \quad (9)$$

where $H(x)$ is the Heaviside step function. For this model, an optimal injection is defined by the concentration and the pressure drop that minimizes the injection time. The necessary conditions defining the optimal concentration and pressure drop are the equations:

$$\frac{\partial t}{\partial c} = 0 \rightarrow \frac{R^4}{\eta_0(c^*)^2} \left(\eta_0'(c^*) - \frac{\eta_0(c^*)}{c^*} \right) + (R^4 - \hat{R}(c^*, |\Delta P^*|/L)^4)$$
$$\times \left[\frac{1}{\eta_\infty(c^*)^2} \left(\eta_\infty'(c^*) - \frac{\eta_\infty(c^*)}{c^*} \right) - \frac{1}{\eta_0(c^*)^2} \left(\eta_0'(c^*) - \frac{\eta_0(c^*)}{c^*} \right) \right.$$
$$\left. + \frac{4\hat{R}(c^*, |\Delta P^*|/L)^4}{R^4 - \hat{R}(c^*, |\Delta P^*|/L)^4} \left(\frac{\hat{\tau}'(c^*)}{\hat{\tau}(c^*)} \right) \left(\frac{1}{\eta_\infty(c^*)} - \frac{1}{\eta_0(c^*)} \right) \right] H \left(R - \hat{R}(c^*, |\Delta P^*|/L) \right) = 0, \quad (10a)$$

$$\frac{\partial t}{\partial |\Delta P|} = 0 \rightarrow \frac{R^4}{\eta_0(c^*)} + (R^4 + 3\hat{R}(c^*, |\Delta P^*|/L)^4) \left(\frac{1}{\eta_\infty(c^*)} - \frac{1}{\eta_0(c^*)} \right) H \left(R - \hat{R}(c^*, |\Delta P^*|/L) \right) = 0. \quad (10b)$$

For a shear thinning fluid, the solution to these equations is the largest possible pressure drop so that $\hat{R}(c^*, |\Delta P^*|/L) \ll R$, and the viscosity across the channel is the lower of the two limiting viscosities: $\eta_\infty(c)$. Then the optimal loading is just given by the same expression as for a Newtonian fluid with the high stress viscosity: $\eta_\infty'(c^*) = \eta_\infty(c^*)/c^*$. For a shear thickening suspension, the optimal conditions are more complicated. A lower bound on the pressure drop is given by that for which $R = \hat{R}(c^*, |\Delta P^*|/L)$, which would make the viscosity across the channel the low stress viscosity. If the thickening is strong enough that adding any more pressure would reduce the flow rate, then locally optimal concentration corresponding to this pressure is defined by $\eta_0'(c^*) = \eta_0(c^*)/c^*$. It may be that the shear thickening is mild enough that a higher pressure still reduces the flow rate. In which case, the locally optimal concentation and pressure are given by the solutions to equations 10a and 10b with unity substituted for the value of the Heaviside step function.

One peculiarity of this model formulation with a shear thickening fluid arises because the pressure drop driving the flow is an unbounded quantity. This means that the global minimum of injection duration is given by a diverging pressure drop and a concentration satisfying: $\eta_\infty'(c^*) = \eta_\infty(c^*)/c^*$. That is, the fluid is driven as hard as possible and the viscosity across the pipe is the high stress viscosity. This is the same solution as found for the shear thinning fluid. However, in practice this global minimum may result in stresses that are not physically realizable. In that case, a fluid driven to flow with $R \approx \hat{R}(c^*, |\Delta P^*|/L)$, and

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$\eta_0'(c^*) = \eta_0(c^*)/c^*$ is likely to give the physically reachable solution to the optimization problem.

Multi-component, Newtonian fluids

The analysis of a two component Newtonian fluid can be easily extended to a multi-component fluid, though some more care is needed to define the optimization problem. Let the fluid be composed of one set, $\mathcal{N}$, of N different components which are to be delivered in a precise quantity and another set, $\mathcal{S}$, of S different components whose quantity can be adjusted to minimize the injection time. In the previous two component example, the set $\mathcal{S}$ included only the solvent whose amount in the fluid was freely adjustable while the set $\mathcal{N}$ included only the solute for which a prescribed quantity, N was to be delivered. Now, let $\mathbf{N} \in \mathbb{R}^N$ be the quantities of compounds in the set $\mathcal{N}$ and $\mathbf{S} \in \mathbb{R}^S$ be the quantity of compounds in the set $\mathcal{S}$. The relevant optimization problem minimizes the duration of injection by changing $\mathbf{S}$ at a fixed dose $\mathbf{N}$.

Assuming ideal mixing, the volume of the multi-component fluid is: $V = \hat{\boldsymbol{V}}_S^T \mathbf{S} + \hat{\boldsymbol{V}}_N^T \mathbf{N}$, where $\hat{\boldsymbol{V}}_N \in \mathbb{R}^N$ and $\hat{\boldsymbol{V}}_S \in \mathbb{R}^S$ are vectors of the specific volumes of the compounds in set $\mathcal{N}$ and $\mathcal{S}$, respectively. The shear viscosity $\eta(\mathbf{c}_N, \mathbf{c}_S)$ can only depend explicitly on intensive quantities; therefore, it is an explicit function of the concentration vectors $\mathbf{c}_N = \mathbf{N}/V$ and $\mathbf{c}_S = \mathbf{S}/V$. Following equation 1, the duration of injection is:

$$t = \frac{1}{A}\left(\frac{L}{|\Delta P|}\right)\left(\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}\right)\eta(\mathbf{c}_S, \mathbf{c}_N), \tag{11}$$

and the duration is minimized when: $dt/dS_i = 0$ for $i = 1, \ldots, S$ and the Hessian of t with respect to $\mathbf{S}$ is positive definite. It follows that the necessary condition defining the optimal amounts, $\mathbf{S}^*$, is:

$$\nabla_{\mathbf{c}_S}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) = -\left[\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) - (\mathbf{c}_N^*)^T\nabla_{\mathbf{c}_N}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) - (\mathbf{c}_S^*)^T\nabla_{\mathbf{c}_S}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*)\right]\hat{\boldsymbol{V}}_S, \tag{12}$$

where $\mathbf{c}_S^* = \mathbf{S}^*/(\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}^*)$ and $\mathbf{c}_N^* = \mathbf{N}/(\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}^*)$. Such a condition may prove useful for formulating optimal fluids if a smooth and continuous expression for the viscosity as a function of composition is known.

Although it may be difficult to measure the viscosity of fluids across a broad composition space with a typical rheometer, methods of microrheology and microfluidics have been combined to rapidly formulate and characterize the rheology of complex mixtures[13]. The result of such experiments would be the viscosity at many discrete points in an $N \times S - 1$ dimensional space of concentrations. If the viscosity is known at a discrete set of points, then the optimization problem can be posed differently. A Delaunay triangulation of the composition space using the points at which the viscosity was measured can be used to construct a

piece-wise linear approximation of the viscosity as a function of $\mathbf{c}_S$ and $\mathbf{c}_N$, denoted $\hat{\eta}(\mathbf{c}_S, \mathbf{c}_N)$. With this approximation, the minimum duration injection is given by the solution of the optimization problem:

$$\mathbf{S}^* = \arg\min_{\mathbf{S}} (\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}) \hat{\eta} \left(\frac{\mathbf{S}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}}, \frac{\mathbf{N}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}} \right) \tag{13}$$

$$\text{s.t. } S_i \geq 0$$

$$\frac{\mathbf{S}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}} \in \mathcal{C}_S$$

$$\frac{\mathbf{N}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}} \in \mathcal{C}_N,$$

where $\mathcal{C}_S$ and $\mathcal{C}_N$ are the convex hulls of the composition space over which the piece-wise linear approximation of the viscosity is valid. Although the optimal formulation design is challenging to describe analytically, numerical solutions to this problem are feasible. For example, well-known sub-gradient descent methods are routinely applied to constrained optimization problems over this sort of non-smooth objective function [14].

Discussion of Applications and Experimental Examples

The simplest two component fluid was investigated by Einstein [15,16]. In the limit that the solute is sufficiently diluted, he proposed that the viscosity scales linearly with the solute concentration: $\eta(c) = \eta(0)(1 + [\eta]c)$, where $[\eta]$ is the so called intrinsic viscosity. For rigid, impenetrable spherical particles, c describes the volume fraction of spheres and $[\eta] = 5/2$. At higher concentrations strong deviations from this linear trend appear. *For a variety of constitutive models and experiments, the optimal concentration for injection appears to live near where the deviation from this linear model become apparent.*

For example, many polymer solutions have a viscosity that scales linearly with concentration in the dilute limit. However, there exists a so called "overlap concentration" beyond which polymer chains begin to interact strongly with one another and power law scaling of the viscosity with concentration emerges [17]. The particular power law depends on the topological and chemical details of the polymer, but this transition is generic [10]. Figure 2 plots on logarithmic axes the viscosity as a function of concentration for such polymer solutions. In this circumstance, it is clear that the viscosity as a function of concentration has a tangent line through the origin right at the overlap concentration. Physically, this is the highest polymer concentration accessible before the viscosity begins to grow rapidly with c. Thus, an optimal injection of a fixed number of polymers will be formulated at the overlap concentration.

For particle suspensions, the viscosity is expected to diverge as the concentration approaches the point of maximum packing. The Krieger-Dougherty model is commonly used to represent this behavior [18]:

$$\eta(c) = \eta(0) \left(1 + \frac{c}{c_{\max}}\right)^{-[\eta]c_{\max}},\tag{14}$$

where $c_{\max}$ is the maximum concentration below which the fluid has a finite viscosity. The relationship between the power-law exponent and the intrinsic viscosity in equation 14 is purely heuristic, but this expression has been found to provide an adequate description of many loaded fluids. In suspensions of hard, nearly spherical particles, one finds that $[\eta]c_{\max} \approx 2$ describes many experimental data sets quite well [19]. Such power law scaling can even be justified in analytical models of mono-disperse suspensions of spheres [20]. If such a particle-filled fluid exhibits Newtonian behavior or has Newtonian plateaus at low and high stress that show similar power law scaling [21], then the optimal loading predicted by equation 3 is given by an incredibly simple expression:

$$c^* = \frac{c_{\max}}{1 + [\eta]c_{\max}}.\tag{15}$$

This result suggests an experimental procedure for finding the optimal formulation of a Krieger-Dougherty-like fluid. First solvent is added to the prescribed dose of suspended component until the mixture just becomes flowable. This point identifies the concentration $c_{\max}$. Then the fluid is further diluted with solvent to a concentration of approximately $c_{\max}/3$ at which point the duration of injection should be nearly minimized.

A simple example involving a two component, Newtonian fluid is the injection of fixed quantity of glycerol dispersed in a variable quantity of water. Glycerol injections are used as a nerve block to treat symptoms of chronic pain. The viscosity of pure glycerol at room temperature is hundreds of times that of water. Figure 3a) depicts experimental measurements of the viscosity of glycerol-water solutions at 30°C over a broad range of molar concentrations [22]. A tangent line through the origin determines the optimal concentration for injection, which is the equivalent of approximately 30% glycerol by weight. Of course for medical treatment there may be other constraints on the process including a limit on the maximum injectable volume, but these constraints are easily accounted for by altering the formulation of the optimization problem.

As a related example, consider the problem of formulating solutions of globular proteins for subcutaneous injection. Particularly for the case of monoclonal antibodies, the problem of injectability poses a major challenge. Depending on the viscosity of an antibody solution loaded with a prescribed dose, injection in a fixed amount of time may require pressure drops so large that forces supplied by human hands are not

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sufficient to complete the injection. *A potential solution to this problem is understanding how the minimal injection duration at a human appliable pressure drop could be shifted by engineering different factors in the antibody solution.* A heuristic model commonly applied to antibody solutions is the so-called Mooney equation[1]:

$$\eta(c) = \eta(0) \exp\left(\frac{[\eta]c}{1 - c/c_{\max}}\right), \tag{16}$$

which describes a viscosity that diverges exponentially as the concentration approaches $c_{\max}$. Figure 3b) depicts the viscosity of two proprietary antibodies suspended in identical buffer solutions measured by scientists at Pfizer as well as fits to the Mooney equation[1]. For this model, the optimal loading is given by:

$$c^* = c_{\max}\left[1 - \frac{1}{2}[\eta]c_{\max}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)\right], \tag{17}$$

and the minimal injection duration, t^*, depends on the model parameters through its linear proportionality with the derivative of the viscosity:

$$t^* \sim \eta'(c*) = \frac{4\eta(0)}{[\eta]c_{\max}^2}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)^{-2}\exp\left[\frac{[\eta]c_{\max}}{2}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)\right]. \tag{18}$$

An intuitive conclusion justified by these calculations is that the duration of injection at the optimal concentration can be made smaller by engineering a solution with a larger $c_{\max}$ and fixed $[\eta]$. That is, without changing the dilute hydrodynamic characteristics of the protein, a shorter duration can be achieved when the optimal concentration is further from maximum packing. Perhaps less intuitive is the correlation for the intrinsic viscosity. A shorter duration for the optimal injection can also be achieved by decreasing the intrinsic viscosity at fixed $c_{\max}$. That is, maintaining the packing limits of the molecule, but reducing its effective hydrodynamic size in the dilute limit will also speed up the injection.

The product $[\eta]c_{\max}$ is approximately the relative viscosity given by extrapolating the linear model of the viscosity in the dilute region to the concentration at maximum packing. It appears that this factor exerts the strongest influence on the optimal duration of injection both the Mooney and the Krieger-Dougherty models. It is not clear to what extent this product can be engineered in suspensions of proteins or particles. For the examples in figure 3b), $[\eta]c_{\max} \approx 10$, and it is typically much smaller for hard particles. This at least suggests that engineering the "efficiency" of the solute packing is possible and can be used to optimize the injection duration via molecular design. Some recent experiments have shown that adding arginine to solutions of antibodies results in a viscosity that diverges at higher concentrations[23]. From the perspective

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of the optimal injection duration, one must ask whether the addition of arginine can change the molecular interactions in a way that shifts $[\eta]c_{\max}$ favorably. Certainly, this detailed analysis of the injection problem signals that $[\eta]c_{\max}$ is an interesting target for decreasing the optimal injection duration or equivalently increasing the optimal molar flow rate of a suspended component.

Finally, in recent experiments we have scaled up the batch synthesis of PbS nanocrystals via burst nucleation and found this framework for optimizing injection an indispensable tool[24]. In this synthetic procedure, a concentrated solution of sulfur precursor suspended in oleylamine is injected by hand using a 20 mL syringe into a solution of lead chloride precursor being stirred at 120°C[25]. The nanocrystals grow in solution before the reaction is quenched. Our original synthetic procedure would yield ∼75 mg of nanocrystals. In order to perform neutron scattering experiments on concentrated solutions of PbS nanocrystals, the yield of the synthetic procedure would need to be scaled up by two orders of magnitude while maintaining low size dispersity in the batch[26]. The size dispersity is strongly influenced by the duration of injection for the sulfur precursor solution. In order to successfully scale up the synthesis, it was essential to minimize the duration of injection. The volume of the sulfur solution needed for the scaled-up synthesis well exceeds the capacity of a 20 mL syringe. As such, we used a pressure-driven injection in which the sulfur solution is held in a pressurized volumetric funnel and injected into the reaction vessel containing the lead chloride solution, which is held under a mild vacuum[27].

The optimization procedure follows the serial dilution methodology described for a Krieger-Dougherty fluid. In the experimental apparatus, a funnel holding the sulfur solution is positioned vertically above the reaction vessel and held back by a stop cock with a large orifice. The applied pressure drop driving the fluid into the vessel vastly exceeds the gravitational load on the fluid so that equation 1 is appropriate for describing the fluid flow. We use a mass basis so that N is the mass of sulfur to be injected, c is the sulfur mass concentration, and $\eta(c)$ is the viscosity as a function of mass concentration. We measured the injection duration for 0.65 g sulfur suspended in different volumes of oleylamine from 15 to 180 mL. Figure 4 shows these durations. Using the measured durations, we fit for the geometric prefactor, A and $c_{\max}$ using a Krieger-Doughtery viscosity model with $[\eta]c_{\max} = 2$ and an unloaded viscosity $\eta(0) = 4.93$ cP for oleylamine at 25°C[28]. We find $c_{\max} = 101$ mg/mL and $A = 2107$ s^2/m^2. Figure 4 shows the viscosity profile predicted by the timing measurements and the geometric tangent construction corresponding to the optimal injection concentration. The optimal concentration for injection is then found to be 33.7 mg/mL. Using this concentration for the sulfur precursor solution, we were able to obtain multiple grams of 6.1 nm diameter PbS nanocrystals with a size dispersity of 3.4%, on par with the lowest size dispersity samples obtainable in

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the small scale synthesis.

This procedure is both simple to implement and provides valuable insight into the shape of the objective function. No rheological measurements were required for this optimization. It is only required to measure the duration of injection of a few solutions at different concentration formulated by serial dilution. Figure 4 plots the injection duration from these experiments. At low concentration, too much volume is required to deliver the requisite mass and the injection time is large. At high concentration, the solution viscosity has climbed large enough that the injection time increases. The optimal injection concentration occurs where the viscosity profile departs from a linear approximation. Additionally, we note the injection time function is relatively flat near the optimal concentration. That is, the injection time will not change significantly if there is small error in the sulfur solution preparation for these experimental parameters. If the geometric prefactor were larger, as would be the case for larger pressure differentials, more injected mass, or smaller stopcock radii, then the injection time profile would be sharper and it would be more important to precisely prepare a precursor solution to match the optimal concentration.

Conclusions

Inspired by past work in modeling biophysical systems with Newtonian fluids, we have derived new formulas representing the solution to an optimization problem describing the optimal formulation for delivering a solute at the maximal rate in multicomponent fluids. The framework employed in this work allowed for graphical or numerical determination of the optimal formulation of single and multicomponent Newtonian fluids using a limited number of experimental measurements of the viscosity as a function of composition. Additionally, we showed how model shear thinning and shear thickening fluids transporting a single solute should be loaded in order to achieve the maximum delivery rate. For this model fluid, there is a simple transition between two limiting viscous states at low and high applied stresses, but the same approach could be applied to fluids with more complex rheology. We showed that the optimal injection of these fluids must control both the formulation and the pressure drop applied. For a shear thinning fluid, the optimally loaded fluid is the one that maximizes the rate of solute delivery in the high stress branch of the viscosity while using the highest accessible pressure drop to drive the flow. For a shear thickening fluid, the situation is more complicated. A locally optimal solution can be found when the fluid is loaded to maximize the delivery rate in the low stress branch of the viscosity with the pressure drop restricted so that the fluid throughout the flow channel has rheology drawn from this same low stress branch. A globally optimal delivery rate is

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always found as the pressure drop diverges, but such solutions may not be physically accessible in real world injection scenarios with shear thickening fluids. We demonstrate how these calculations can be applied to the delivery of chemical solutes in a burst nucleation experiment for the growth of quantum dots, but we expect that there are many more applications for such optimal flow scenarios beyond this context or the biophysical systems explored in past works. One area in which rapid injection is essential is in pharmaceuticals. The derivation of an optimization problem for multicomponent Newtonian formulations may find use in this particular area where macromolecular species are often the target injectable, but various excipients can be added to solution as viscosity modifiers and solubilizers. This multicomponent formulation of the injection problem enables a principled way of designing human injectable solutions that expose patients to a minimal injection duration.

Acknowledgements

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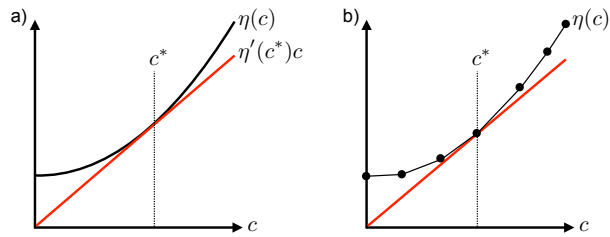
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Figure 1: Tangent line construction for finding optimal composition. a) For a two component, Newtonian fluid having an increasing viscosity with respect to the concentration of a solute, the injection of a fixed dose of solute with minimal duration occurs where a line through the origin forms a tangent with the viscosity. b) A simple graphical method for determining the optimal loading for injection involves determining where a line through the origin intersects just once the piece-wise linear approximation of the viscosity formed from connecting experimental data with lines.
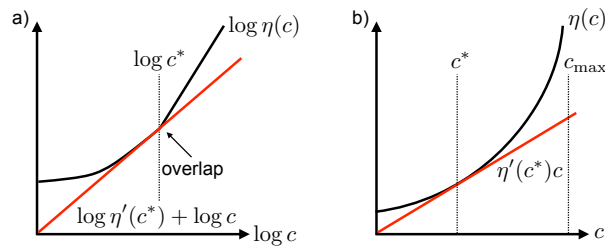
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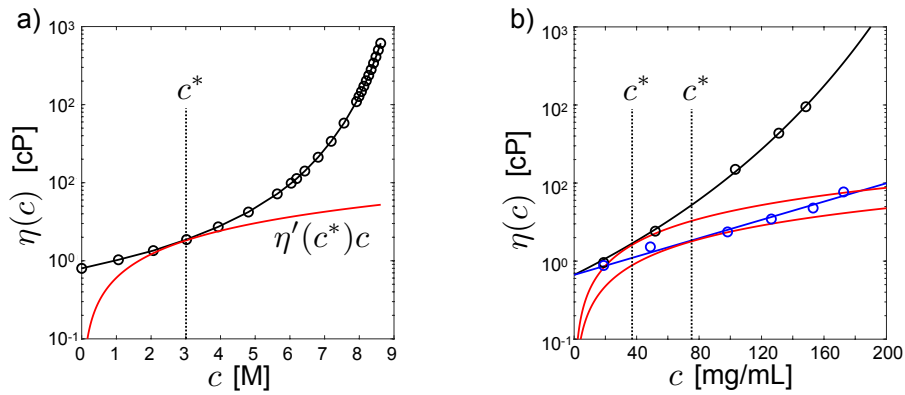
Figure 3: Optimization of medical injections. a) The viscosity of glycerol-water mixtures as a function of the molar concentration of glycerol. Following the procedure in Figure 1b), the line through the origin just touching an experimental data point determines an approximation for the concentration of the fluid with minimal injection duration. The optimal concentration is equivalent to a glycerol weight fraction of 30%. b) The viscosity as a function of concentration for two monoclonal antibody solutions produced by Pfizer (blue and black circles). The blue and black curves are fits of the Mooney equation to the data, and the red curves are lines through the origin that are tangent to the model.
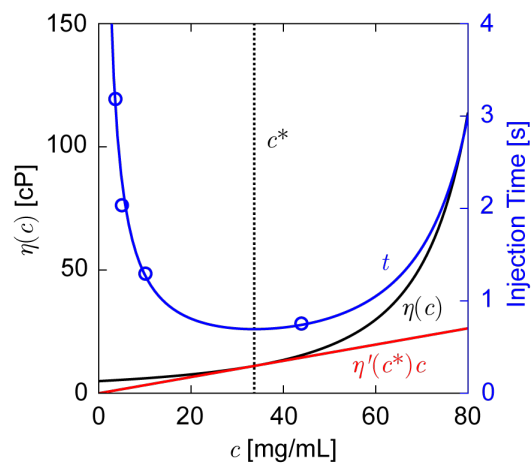
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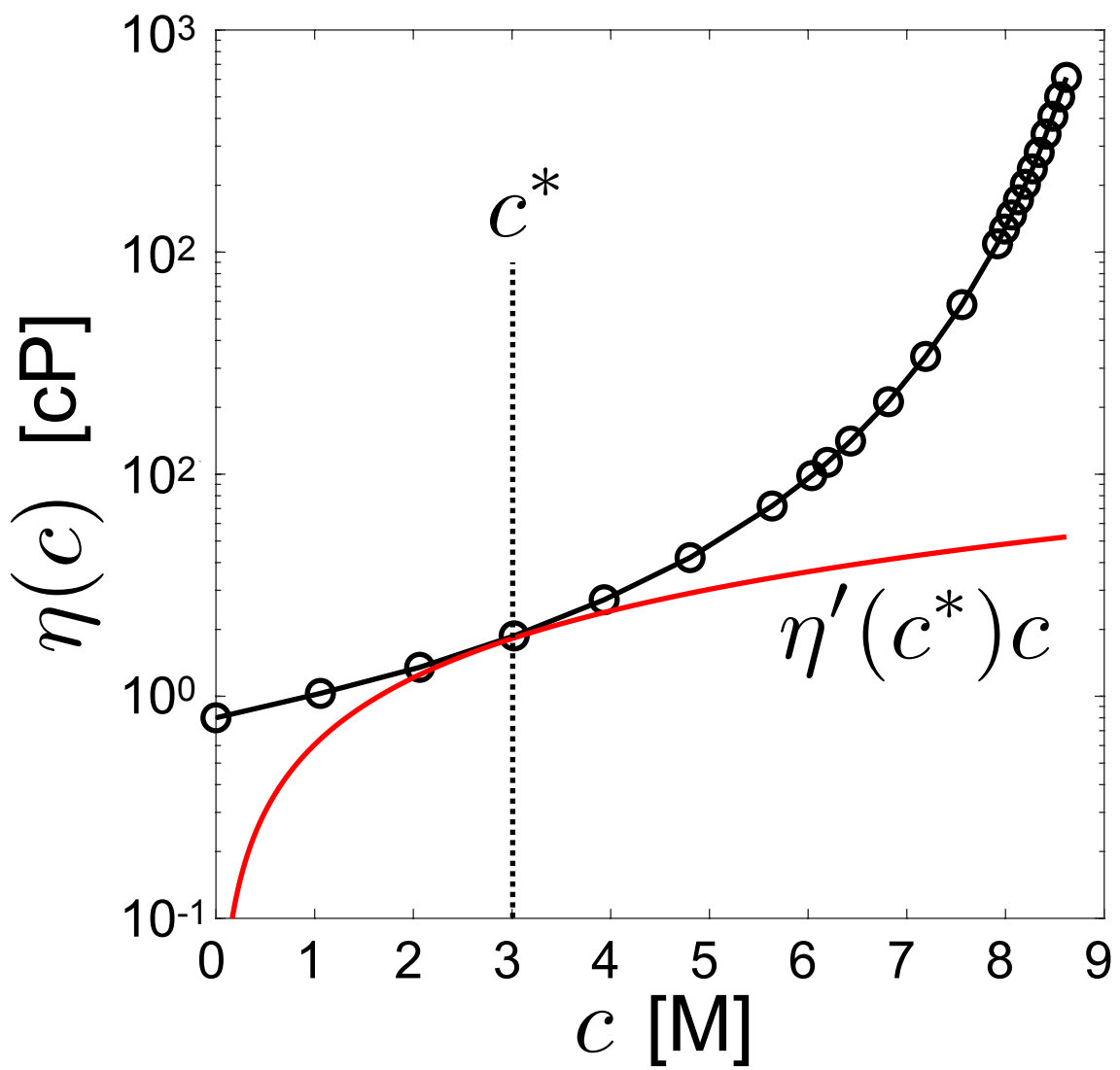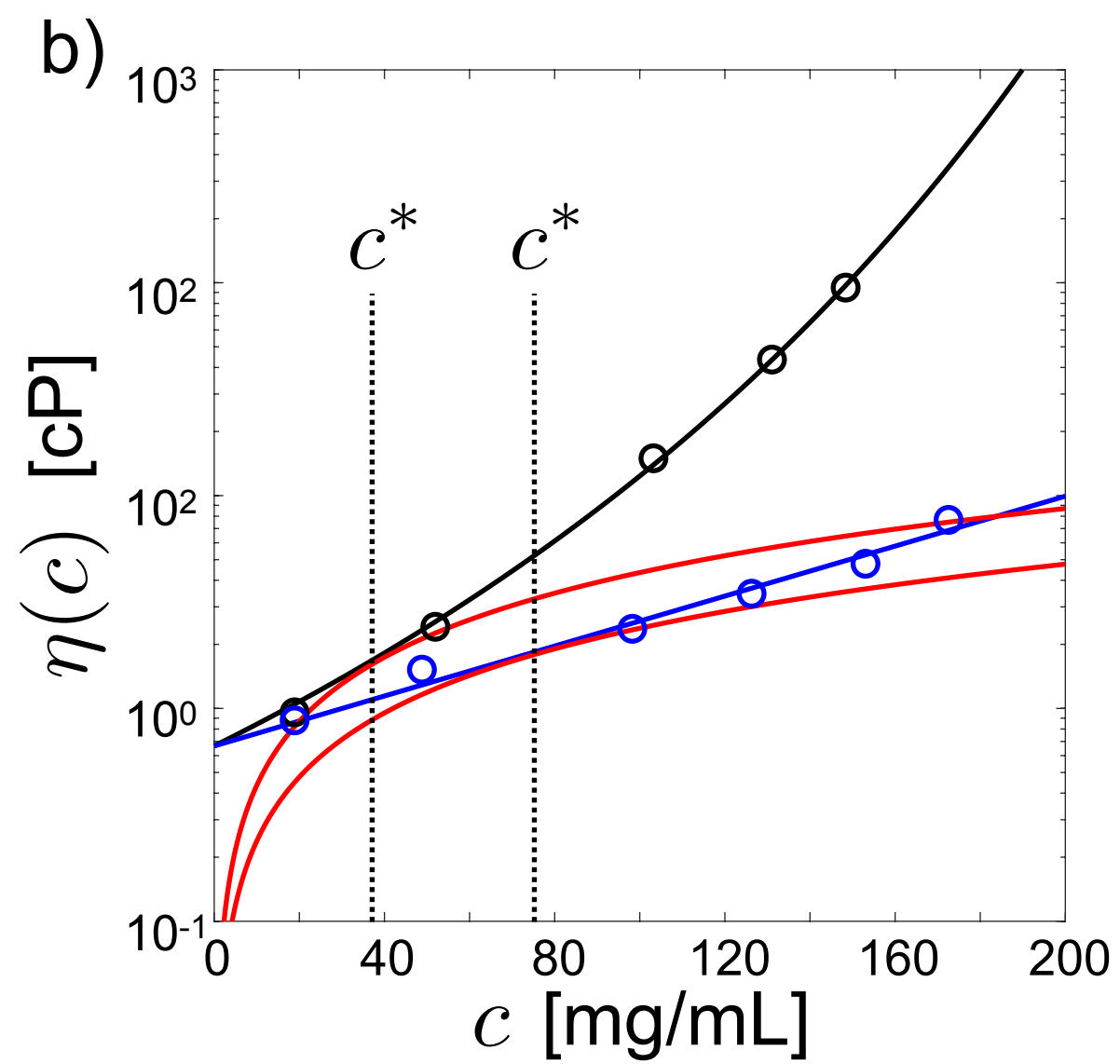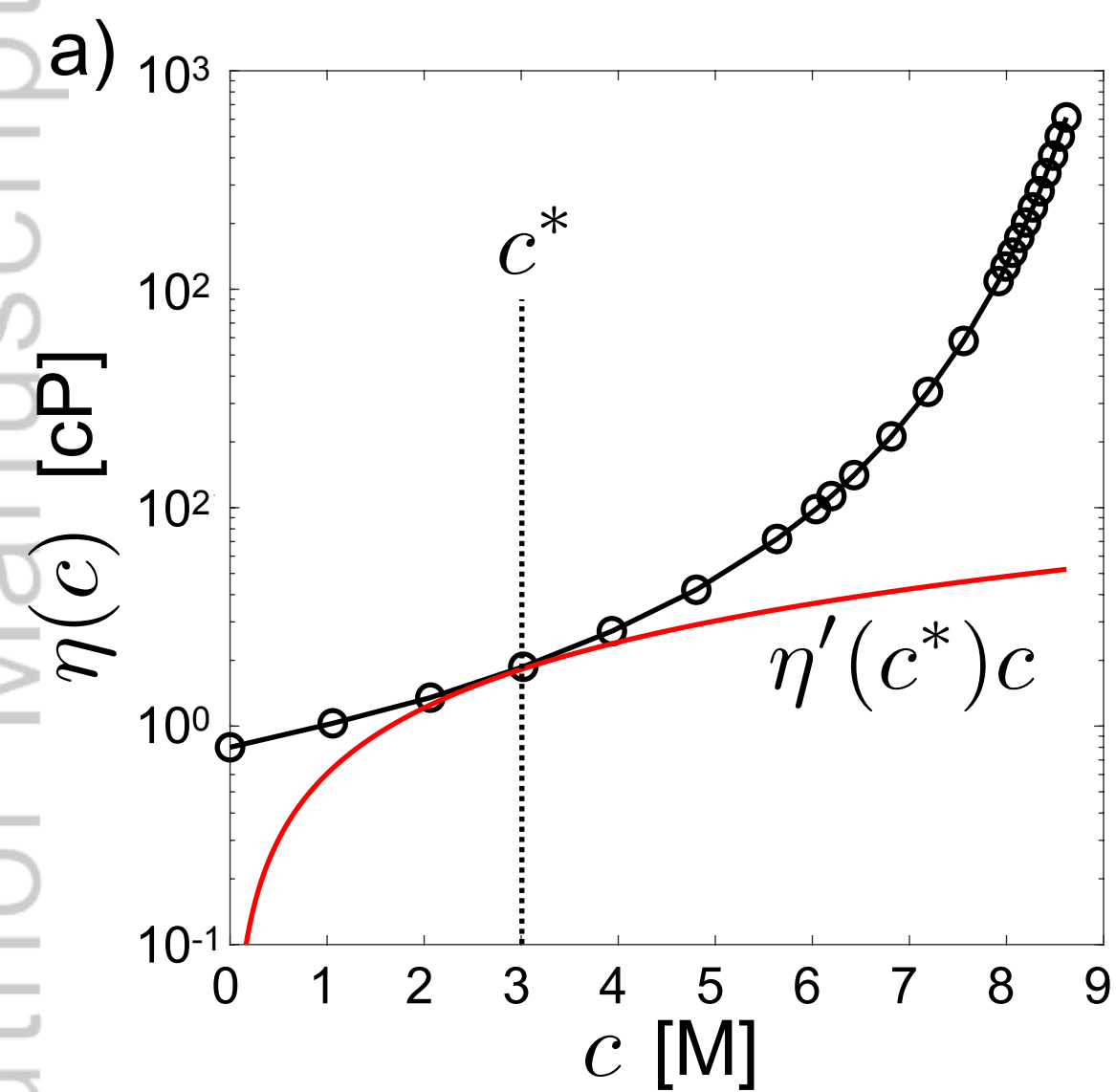
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a)

c^*

$\eta'(c^*)c$

$\eta(c)$ [cP]

c [M]

b)

c^* c^*

$\eta(c)$ [cP]

c [mg/mL]

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October 7, 2020

To: AICHE Journal Editors
From: James W. Swan

Dear Editors,

      Will Tisdale, Sam Winslow, and I have complete revisions of our manuscrip "Optimal Loading for Injection." We believe the manuscript is ready for publication now.

Respectfully,

James W. Swan
Associate Professor

Optimal Loading for Injection

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Abstract

The injection of fluids loaded with a precise number of particles, polymers, and other solutes is common in many areas of chemical engineering. By definition, injection of these fluids is meant to occur over the shortest possible duration. This raises the question that is answered in this note: *At what concentration should a fluid be loaded in order to inject that fluid fastest?* A similar question has been addressed for flows of Newtonian fluids in biophysical and physiological studies. We generalize that analysis. We show for Newtonian fluids containing a single suspended component that the optimal loading is determined from a common tangent construction for the viscosity as a function of concentration. We extend this formulation to describe optimal injection of a multi-component Newtonian fluid. Additionally, we study the injection problem for a simple, model non-Newtonian fluid carrying a single suspended component. Finally, we discuss applications for optimally loaded injections.

Introduction

The problem of engineering a batch injection can be defined in the following way: blend a prescribed dose of some solute(s) in some quantity of solvent(s) such that the time to inject the solution is minimal. There is an equivalent engineering problem for continuous injection: maximize the steady molar flow rate of some solute(s) in some solvent(s) down a pipe at a fixed pressure drop by varying the solution composition. The viscosity of solutions changes and generally increases with the addition solutes to a solvent. Thus, increasing the solute concentration will increase the solution viscosity and reduce the volumetric flow rate for the injection. Depending on the relationship between solute concentration and viscosity, this decrease in

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volumetric flow rate can accompany either an increase or a reduction in the molar flow rate of the solute. The solution composition that minimizes the duration of injection resides at the transition between increasing and decreasing molar solute flow rate. In principle, the design choices for optimizing batch or continuous injection include the geometry of the injection apparatus, the pressure drop applied to drive the injection, and the composition of the solution. In this work, we focus on how the composition of the solution should be chosen in order to minimize the duration of the injection. This optimal composition is determined with minimal assumptions about the flow geometry, but allowing for some non-trivial forms for the rheological response of the fluid. Some examples drawn from the literature and recent research from our own group is used to demonstrate the utility of the expressions we derive.

The term "injection" obviously connotes pharmaceutical injections: a batch process in which an active agent is dispersed in a solvent and injected via a syringe into a living host. A problem of recent interest in this area has been the injection of aqueous solutions of globular proteins (monoclonal antibodies) at high protein concentrations – for which the solutions become hundreds of times more viscous than water [1]. The problem of finding the optimal composition for a pharmaceutical injection is important and has a non-trivial solution. Injections into living hosts can only occur humanely over a finite duration, typically about one second. Similarly, most injections via syringe are powered by forces exerted by human thumbs. With these two practical constraints on the process, a pharmaceutical injection can be engineered in two steps. First, one finds the composition of medication that minimizes the injection duration and the volume of that optimal solution that delivers the desired dose. Then, one sizes the bore of the syringe needle so that this minimal injection duration at the maximal possible applied force matches or falls below the limiting duration. To our knowledge, such a process is not employed currently, but in this work we provide methods for estimating the optimal composition of such pharmaceutical formulations.

One example of continuous (or semi-batch) injection in which the composition of the solution is a free design variable while the molar flow rate of the solute(s) is maximized is the pumping of concrete [2]. Concrete consists of a combination of aggregate, cement powder, and water. The powder and aggregate are mixed in precise ratios to engineer the strength of the final product. Some water is needed for the hydration reaction that converts minerals in the cement powder into the cement binder that bridges the aggregates. However, much more water is used in this process in order make the mixture flow, and too much added water can lead to concrete with reduced compressive strength. An engineering problem that is addressed partly through the inclusion of additives that increase flowability of concrete, is determining the composition of the concrete mixture that delivers the prescribed mass ratio of concrete powder to aggregate at the highest

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possible rate. Such an optimal composition must reside within a region of design space that still meets the final specifications for the poured concrete. That is, there must be enough water to complete the hydration reaction and not so much that the concrete is weakened. While we will not address optimization of injection with constraints of this sort here, one could easily modify the present calculations to incorporate this feature.

Adaptations of natural systems to enable efficient transport of solutes have been studied extensively in the physiology and bio-fluid mechanics literature. A key question asked in these studies is whether certain natural systems are operating optimally. For example, the hematocrit of of human blood is about 45%. Past work in physiology has argued that this loading of blood with red blood cells maximizes the flux of oxygen delivered to the body and have analyzed empirical models of blood viscosity to justify these arguments[3,4,5,6]. Likewise, the idea that nature optimizes fluxes of a single solute in a Newtonian fluid under different mechanical constraints has been explored in other contexts including the delivery of nutrients in plants and the sipping of nectar from flowers by hummingbirds[7,8,9]. While there is some overlap between the present work and these past efforts, we will abstract away from the natural context to the artificially engineered one. We will derive expressions for the optimal composition of single and multi-component Newtonian fluids that are independent of any model for the dependance of viscosity on solution composition, and even apply those same methods to analyze the optimal injection of certain non-Newtonian fluids. This model-free approach will be leveraged to develop some graphical methods for approximating the optimal composition of solutions from experimental data and to offer some suggestions for how to prepare solutions optimized for injection experimentally. As with these past efforts in physiology and bio-fluid mechanics, we will apply some empirical models for the viscosity as a function of composition in new contexts in order to suggest how to improve several different artificially engineered systems.

The article is organized as follows. First, we derive expressions for the optimal composition of two component fluids (one solvent and one solute) which have Newtonian and non-Newtonian rheological responses respectively. Then, we derive the optimal composition for injection of a multi-component fluid (many solvents and solutes) with Newtonian rheology. Finally, we discuss these derivations in the context of several practical examples from the literature and our own research on nanocrystal synthesis.

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Modeling Optimal Injection

Two component, Newtonian fluids

Consider a fluid consisting of two components: a solvent and a suspended solute. On increasing the concentration of the solute in the solvent, c, the viscosity of the fluid, $\eta(c)$, is typically expected to increase. Assume that the resistance to flow of this fluid during injection is laminar and dominated by a region length L and driven by a pressure differential $|\Delta P|$. Then, to a good approximation the volumetric flow rate of the fluid can be written as:

$$Q = \frac{V}{t} = \frac{N}{ct} = \frac{|\Delta P|}{L}\left(\frac{A}{\eta(c)}\right), \tag{1}$$

where N is the amount of the suspended component in the fluid, V is the volume of the fluid so that $c = N/V$, t is the duration of the injection, and A is a purely geometric factor. For steady, unidirectional, laminar flow in a pipe with a circular cross section of radius R, the Hagen-Poiseuille formula gives: $A = \pi R^4/8$. For flow in a rectangular channel with height H much smaller than its width W, $A = H^3 W/12$. Similar geometric factors can easily be derived for Newtonian fluids in the same flow conditions but transported by pipes with more complicated cross sections. In the present work, the units of the dose N are left arbitrary. If number of solutes is chosen for this unit, then c is the number density. If mass is chosen for this unit, then c is the mass density. If volume is chosen for this unit, then c is the volume fraction. For the present purposes, the distinction between these measures is irrelevant. The injection problem is defined by the shortest duration to deliver an amount of solute, N.

The relevant optimization problem for injection is a minimization of the duration t with respect to the concentration c while holding the amount of solute N fixed. From equation 1 it is clear that:

$$\frac{dt}{dc} = \frac{N}{Ac}\left(\frac{L}{|\Delta P|}\right)\left(\eta'(c) - \frac{\eta(c)}{c}\right), \tag{2}$$

with N held constant. A locally minimal duration, t^*, occurs at an optimal concentration, c^* for which $dt/dc = 0$ and $d^2t/dc^2 > 0$, which means the optimal concentration satisfies the equality:

$$\eta'(c^*) = \frac{\eta(c^*)}{c^*}, \tag{3}$$

and the inequality: $\eta''(c^*) > 0$. This equality defining an optimal concentration merely states that the shortest injection duration occurs at a concentration for which a line through the origin is tangent to the

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viscosity on a plot of $\eta(c)$ versus c (see Figure 1).

Among the set of any local minima, $\{(c_i^*, t_i^*)\}$, equation 1 requires that

$$t_i^* = \eta'(c_i^*)\frac{NL}{|\Delta P|A}. \tag{4}$$

Therefore, the globally minimal duration occurs for the loading having the smallest possible value in $\{\eta'(c_i^*)\}$. Many two component fluids have a viscosity that is a convex function of c, so this set of minima is likely to contain only a single element. The local minimum is the global minimum. In practice, the viscosity may not be known as a smooth function of concentration. Figure 1 suggests a graphical method for estimating the optimal loading when only experimental data for $\eta(c)$ are available.

Two component, non-Newtonian fluids

For non-Newtonian fluids, whose viscosity depends on the stress, τ, during deformation, an application of this same approach incorporating some mild approximations can be used to define similar conditions for optimality. For simplicity, assume that the flow dominating the resistance during injection is steady, unidirectional and in a pipe with a circular cross-section of radius R. Non-Newtonian fluids are susceptible to instabilities that yield unsteady flow, but those circumstances are still active areas of research and would make estimating the minimal injection duration difficult. One should check that the optimal injection conditions determined using these mild assumptions (steady unidirectional flow) are not unstable via experiment. The steady shear viscosity of a two component fluid that exhibits non-Newtonian behavior will depend on both the concentration of the suspended component and the magnitude of the shear stress, so that it can be expressed as $\eta(c, |\tau|)$. Integrating the axial momentum balance along the radial direction in the pipe yields:

$$\tau(r) = \eta(c, |\tau(r)|)\dot{\gamma}(r) = \frac{1}{2}\frac{|\Delta P|}{L}r, \tag{5}$$

where r is the distance from the pipe center to the pipe wall. When imposing no-slip boundary conditions at the pipe wall, the volumetric flow rate can be written as:

$$Q = 2\pi\left|\int_0^R v(r)r\,dr\right| = \pi\left|\int_0^R \frac{d}{dr}(v(r)r^2) - \dot{\gamma}(r)r^2\,dr\right| = \frac{\pi}{2}\frac{|\Delta P|}{L}\int_0^R \frac{r^3}{\eta(c, |\tau(r)|)}\,dr. \tag{6}$$

The optimal loading is defined by the concentration and pressure drop that minimizes the duration of the injection. Setting $Q = N/(ct)$ as in the previous examples, computing dt/dc and $dt/d|\Delta P|$ with fixed N,

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and then setting these quantities equal to zero produces the necessary conditions for optimal injection of a non-Newtonian fluid:

$$\frac{\partial t}{\partial c} = 0 \rightarrow \int_0^R \frac{r^3}{\eta(c^*, |\tau(r)|)^2} \left(\frac{\partial}{\partial c} \eta(c, |\tau(r)|) \Big|_{c=c^*} - \frac{\eta(c^*, |\tau(r)|)}{c^*} \right) dr = 0, \tag{7a}$$

$$\frac{\partial t}{\partial |\Delta P|} = 0 \rightarrow \int_0^R \frac{r^3}{\eta(c^*, |\tau(r)|)^2} \left(\frac{1}{2} \frac{\partial}{\partial \sigma} \eta(c^*, \sigma) \Big|_{\sigma = |\tau(r)|} \frac{|\Delta P^*|}{L} r - \eta(c^*, |\tau(r)|) \right) dr = 0, \tag{7b}$$

$$|\tau(r)| = \frac{1}{2} \frac{|\Delta P^*|}{L} r, \tag{7c}$$

where the variable σ is simply being used as a dummy variable for the radially dependent shear stress. From these expressions, one can see right away that the optimally loaded two component Newtonian fluid will have a concentration that satisfies $\eta'(c^*) = \eta(c^*)/c^*$. For non-Newtonian fluids, however, the terms in parentheses cannot be made equal to zero in general (at all values of r simultaneously) and it is the integrals themselves that must be zero for the optimal loading. With sufficient knowledge of the rheology, a concentration for which this equation is satisfied might be identified. However, such detailed knowledge is difficult to acquire experimentally. With some further approximations of the rheology, analytical conditions for optimal injection can be derived.

A common rheology observed in non-Newtonian fluids is a steady shear viscosity that changes from one value at low stress, $\eta_0(c) = \eta(c, 0)$ to another value at large stress $\eta_\infty(c) = \eta(c, \tau \rightarrow \infty)$[10]. Typically this transition happens near a critical value of the stress $\hat{\tau}(c) > 0$. In general, this transition happens over a range of stresses in this neighborhood, but for the present purposes we will make a simplifying assumption that the fluid has only a low and a high stress state characterized by different fluid viscosities. For shear thinning fluids, $\eta_0(c) > \eta_\infty(c)$[11], while for shear thickening fluids $\eta_\infty(c) > \eta_0(c)$[12]. To analyze this approximation model, the viscosity is represented as the piece-wise constant function of the stress:

$$\eta(c, |\tau|) = \begin{cases} \eta_0(c), & |\tau| < \hat{\tau}(c) \\ \eta_\infty(c), & |\tau| \geq \hat{\tau}(c) \end{cases}. \tag{8}$$

When this model is applied to the present flow problem, there emerges a critical length scale $\hat{R}(c, |\Delta P|/L) = 2\hat{\tau}(c)L/|\Delta P|$ that divides the pipe into two regions with different viscosity. For $r < \hat{R}(c, |\Delta P|/L)$, the viscosity is $\eta_0(c)$. For $\hat{R}(c, |\Delta P|/L) < r < R$, the viscosity is $\eta_\infty(c)$. In order to realize this outer annulus of fluid, the pipe radius must exceed $\hat{R}(c, |\Delta P|/L)$.

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With this simple two state model of the viscosity, the volumetric flow rate can be written as:

$$Q = \frac{N}{ct} = \frac{\pi}{32} \frac{|\Delta P|}{L} \left\{ \frac{R^4}{\eta_0(c)} + \left(R^4 - \hat{R}(c, |\Delta P|/L)^4 \right) \left(\frac{1}{\eta_\infty(c)} - \frac{1}{\eta_0(c)} \right) H(R - \hat{R}(c, |\Delta P|/L)) \right\}, \quad (9)$$

where $H(x)$ is the Heaviside step function. For this model, an optimal injection is defined by the concentration and the pressure drop that minimizes the injection time. The necessary conditions defining the optimal concentration and pressure drop are the equations:

$$\frac{\partial t}{\partial c} = 0 \rightarrow \frac{R^4}{\eta_0(c^*)^2} \left(\eta_0'(c^*) - \frac{\eta_0(c^*)}{c^*} \right) + (R^4 - \hat{R}(c^*, |\Delta P^*|/L)^4)$$
$$\times \left[\frac{1}{\eta_\infty(c^*)^2} \left(\eta_\infty'(c^*) - \frac{\eta_\infty(c^*)}{c^*} \right) - \frac{1}{\eta_0(c^*)^2} \left(\eta_0'(c^*) - \frac{\eta_0(c^*)}{c^*} \right) \right.$$
$$\left. + \frac{4\hat{R}(c^*, |\Delta P^*|/L)^4}{R^4 - \hat{R}(c^*, |\Delta P^*|/L)^4} \left(\frac{\hat{\tau}'(c^*)}{\hat{\tau}(c^*)} \right) \left(\frac{1}{\eta_\infty(c^*)} - \frac{1}{\eta_0(c^*)} \right) \right] H \left(R - \hat{R}(c^*, |\Delta P^*|/L) \right) = 0, \quad (10a)$$

$$\frac{\partial t}{\partial |\Delta P|} = 0 \rightarrow \frac{R^4}{\eta_0(c^*)} + (R^4 + 3\hat{R}(c^*, |\Delta P^*|/L)^4) \left(\frac{1}{\eta_\infty(c^*)} - \frac{1}{\eta_0(c^*)} \right) H \left(R - \hat{R}(c^*, |\Delta P^*|/L) \right) = 0. \quad (10b)$$

For a shear thinning fluid, the solution to these equations is the largest possible pressure drop so that $\hat{R}(c^*, |\Delta P^*|/L) \ll R$, and the viscosity across the channel is the lower of the two limiting viscosities: $\eta_\infty(c)$. Then the optimal loading is just given by the same expression as for a Newtonian fluid with the high stress viscosity: $\eta_\infty'(c^*) = \eta_\infty(c^*)/c^*$. For a shear thickening suspension, the optimal conditions are more complicated. A lower bound on the pressure drop is given by that for which $R = \hat{R}(c^*, |\Delta P^*|/L)$, which would make the viscosity across the channel the low stress viscosity. If the thickening is strong enough that adding any more pressure would reduce the flow rate, then locally optimal concentration corresponding to this pressure is defined by $\eta_0'(c^*) = \eta_0(c^*)/c^*$. It may be that the shear thickening is mild enough that a higher pressure still reduces the flow rate. In which case, the locally optimal concentation and pressure are given by the solutions to equations 10a and 10b with unity substituted for the value of the Heaviside step function.

One peculiarity of this model formulation with a shear thickening fluid arises because the pressure drop driving the flow is an unbounded quantity. This means that the global minimum of injection duration is given by a diverging pressure drop and a concentration satisfying: $\eta_\infty'(c^*) = \eta_\infty(c^*)/c^*$. That is, the fluid is driven as hard as possible and the viscosity across the pipe is the high stress viscosity. This is the same solution as found for the shear thinning fluid. However, in practice this global minimum may result in stresses that are not physically realizable. In that case, a fluid driven to flow with $R \approx \hat{R}(c^*, |\Delta P^*|/L)$, and

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$\eta'_0(c^*) = \eta_0(c^*)/c^*$ is likely to give the physically reachable solution to the optimization problem.

Multi-component, Newtonian fluids

The analysis of a two component Newtonian fluid can be easily extended to a multi-component fluid, though some more care is needed to define the optimization problem. Let the fluid be composed of one set, $\mathcal{N}$, of N different components which are to be delivered in a precise quantity and another set, $\mathcal{S}$, of S different components whose quantity can be adjusted to minimize the injection time. In the previous two component example, the set $\mathcal{S}$ included only the solvent whose amount in the fluid was freely adjustable while the set $\mathcal{N}$ included only the solute for which a prescribed quantity, N was to be delivered. Now, let $\mathbf{N} \in \mathbb{R}^N$ be the quantities of compounds in the set $\mathcal{N}$ and $\mathbf{S} \in \mathbb{R}^S$ be the quantity of compounds in the set $\mathcal{S}$. The relevant optimization problem minimizes the duration of injection by changing $\mathbf{S}$ at a fixed dose $\mathbf{N}$.

Assuming ideal mixing, the volume of the multi-component fluid is: $V = \hat{\boldsymbol{V}}_S^T \mathbf{S} + \hat{\boldsymbol{V}}_N^T \mathbf{N}$, where $\hat{\boldsymbol{V}}_N \in \mathbb{R}^N$ and $\hat{\boldsymbol{V}}_S \in \mathbb{R}^S$ are vectors of the specific volumes of the compounds in set $\mathcal{N}$ and $\mathcal{S}$, respectively. The shear viscosity $\eta(\mathbf{c}_N, \mathbf{c}_S)$ can only depend explicitly on intensive quantities; therefore, it is an explicit function of the concentration vectors $\mathbf{c}_N = \mathbf{N}/V$ and $\mathbf{c}_S = \mathbf{S}/V$. Following equation 1, the duration of injection is:

$$t = \frac{1}{A}\left(\frac{L}{|\Delta P|}\right)\left(\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}\right)\eta(\mathbf{c}_S, \mathbf{c}_N), \tag{11}$$

and the duration is minimized when: $dt/dS_i = 0$ for $i = 1, \ldots, S$ and the Hessian of t with respect to $\mathbf{S}$ is positive definite. It follows that the necessary condition defining the optimal amounts, $\mathbf{S}^*$, is:

$$\nabla_{\mathbf{c}_S}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) = -\left[\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) - (\mathbf{c}_N^*)^T\nabla_{\mathbf{c}_N}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*) - (\mathbf{c}_S^*)^T\nabla_{\mathbf{c}_S}\eta(\mathbf{c}_N^*, \mathbf{c}_S^*)\right]\hat{\boldsymbol{V}}_S, \tag{12}$$

where $\mathbf{c}_S^* = \mathbf{S}^*/(\hat{\boldsymbol{V}}_N^T\mathbf{N} + \hat{\boldsymbol{V}}_S^T\mathbf{S}^*)$ and $\mathbf{c}_N^* = \mathbf{N}/(\hat{\boldsymbol{V}}_N^T\mathbf{N} + \hat{\boldsymbol{V}}_S^T\mathbf{S}^*)$. Such a condition may prove useful for formulating optimal fluids if a smooth and continuous expression for the viscosity as a function of composition is known.

Although it may be difficult to measure the viscosity of fluids across a broad composition space with a typical rheometer, methods of microrheology and microfluidics have been combined to rapidly formulate and characterize the rheology of complex mixtures[13]. The result of such experiments would be the viscosity at many discrete points in an $N \times S - 1$ dimensional space of concentrations. If the viscosity is known at a discrete set of points, then the optimization problem can be posed differently. A Delaunay triangulation of the composition space using the points at which the viscosity was measured can be used to construct a

piece-wise linear approximation of the viscosity as a function of $\mathbf{c}_S$ and $\mathbf{c}_N$, denoted $\hat{\eta}(\mathbf{c}_S, \mathbf{c}_N)$. With this approximation, the minimum duration injection is given by the solution of the optimization problem:

$$\mathbf{S}^* = \arg\min_{\mathbf{S}} (\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S})\hat{\eta}\left(\frac{\mathbf{S}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}}, \frac{\mathbf{N}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}}\right) \tag{13}$$

$$\text{s.t.}\, S_i \geq 0$$

$$\frac{\mathbf{S}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}} \in \mathcal{C}_S$$

$$\frac{\mathbf{N}}{\hat{\boldsymbol{V}}_N^T \mathbf{N} + \hat{\boldsymbol{V}}_S^T \mathbf{S}} \in \mathcal{C}_N,$$

where $\mathcal{C}_S$ and $\mathcal{C}_N$ are the convex hulls of the composition space over which the piece-wise linear approximation of the viscosity is valid. Although the optimal formulation design is challenging to describe analytically, numerical solutions to this problem are feasible. For example, well-known sub-gradient descent methods are routinely applied to constrained optimization problems over this sort of non-smooth objective function [14].

Discussion of Applications and Experimental Examples

The simplest two component fluid was investigated by Einstein [15,16]. In the limit that the solute is sufficiently diluted, he proposed that the viscosity scales linearly with the solute concentration: $\eta(c) = \eta(0)(1 + [\eta]c)$, where $[\eta]$ is the so called intrinsic viscosity. For rigid, impenetrable spherical particles, c describes the volume fraction of spheres and $[\eta] = 5/2$. At higher concentrations strong deviations from this linear trend appear. *For a variety of constitutive models and experiments, the optimal concentration for injection appears to live near where the deviation from this linear model become apparent.*

For example, many polymer solutions have a viscosity that scales linearly with concentration in the dilute limit. However, there exists a so called "overlap concentration" beyond which polymer chains begin to interact strongly with one another and power law scaling of the viscosity with concentration emerges [17]. The particular power law depends on the topological and chemical details of the polymer, but this transition is generic [10]. Figure 2 plots on logarithmic axes the viscosity as a function of concentration for such polymer solutions. In this circumstance, it is clear that the viscosity as a function of concentration has a tangent line through the origin right at the overlap concentration. Physically, this is the highest polymer concentration accessible before the viscosity begins to grow rapidly with c. Thus, an optimal injection of a fixed number of polymers will be formulated at the overlap concentration.

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For particle suspensions, the viscosity is expected to diverge as the concentration approaches the point of maximum packing. The Krieger-Dougherty model is commonly used to represent this behavior [18]:

$$\eta(c) = \eta(0) \left(1 + \frac{c}{c_{\max}} \right)^{-[\eta]c_{\max}}, \tag{14}$$

where $c_{\max}$ is the maximum concentration below which the fluid has a finite viscosity. The relationship between the power-law exponent and the intrinsic viscosity in equation 14 is purely heuristic, but this expression has been found to provide an adequate description of many loaded fluids. In suspensions of hard, nearly spherical particles, one finds that $[\eta]c_{\max} \approx 2$ describes many experimental data sets quite well [19]. Such power law scaling can even be justified in analytical models of mono-disperse suspensions of spheres [20]. If such a particle-filled fluid exhibits Newtonian behavior or has Newtonian plateaus at low and high stress that show similar power law scaling [21], then the optimal loading predicted by equation 3 is given by an incredibly simple expression:

$$c^* = \frac{c_{\max}}{1 + [\eta]c_{\max}}. \tag{15}$$

This result suggests an experimental procedure for finding the optimal formulation of a Krieger-Dougherty-like fluid. First solvent is added to the prescribed dose of suspended component until the mixture just becomes flowable. This point identifies the concentration $c_{\max}$. Then the fluid is further diluted with solvent to a concentration of approximately $c_{\max}/3$ at which point the duration of injection should be nearly minimized.

A simple example involving a two component, Newtonian fluid is the injection of fixed quantity of glycerol dispersed in a variable quantity of water. Glycerol injections are used as a nerve block to treat symptoms of chronic pain. The viscosity of pure glycerol at room temperature is hundreds of times that of water. Figure 3a) depicts experimental measurements of the viscosity of glycerol-water solutions at 30°C over a broad range of molar concentrations [22]. A tangent line through the origin determines the optimal concentration for injection, which is the equivalent of approximately 30% glycerol by weight. Of course for medical treatment there may be other constraints on the process including a limit on the maximum injectable volume, but these constraints are easily accounted for by altering the formulation of the optimization problem.

As a related example, consider the problem of formulating solutions of globular proteins for subcutaneous injection. Particularly for the case of monoclonal antibodies, the problem of injectability poses a major challenge. Depending on the viscosity of an antibody solution loaded with a prescribed dose, injection in a fixed amount of time may require pressure drops so large that forces supplied by human hands are not

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sufficient to complete the injection. *A potential solution to this problem is understanding how the minimal injection duration at a human appliable pressure drop could be shifted by engineering different factors in the antibody solution.* A heuristic model commonly applied to antibody solutions is the so-called Mooney equation[1]:

$$\eta(c) = \eta(0) \exp\left(\frac{[\eta]c}{1 - c/c_{\max}}\right), \tag{16}$$

which describes a viscosity that diverges exponentially as the concentration approaches $c_{\max}$. Figure 3b) depicts the viscosity of two proprietary antibodies suspended in identical buffer solutions measured by scientists at Pfizer as well as fits to the Mooney equation[1]. For this model, the optimal loading is given by:

$$c^* = c_{\max}\left[1 - \frac{1}{2}[\eta]c_{\max}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)\right], \tag{17}$$

and the minimal injection duration, t^*, depends on the model parameters through its linear proportionality with the derivative of the viscosity:

$$t^* \sim \eta'(c*) = \frac{4\eta(0)}{[\eta]c_{\max}^2}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)^{-2}\exp\left[\frac{[\eta]c_{\max}}{2}\left(\sqrt{\frac{4}{[\eta]c_{\max}} + 1} - 1\right)\right]. \tag{18}$$

An intuitive conclusion justified by these calculations is that the duration of injection at the optimal concentration can be made smaller by engineering a solution with a larger $c_{\max}$ and fixed $[\eta]$. That is, without changing the dilute hydrodynamic characteristics of the protein, a shorter duration can be achieved when the optimal concentration is further from maximum packing. Perhaps less intuitive is the correlation for the intrinsic viscosity. A shorter duration for the optimal injection can also be achieved by decreasing the intrinsic viscosity at fixed $c_{\max}$. That is, maintaining the packing limits of the molecule, but reducing its effective hydrodynamic size in the dilute limit will also speed up the injection.

The product $[\eta]c_{\max}$ is approximately the relative viscosity given by extrapolating the linear model of the viscosity in the dilute region to the concentration at maximum packing. It appears that this factor exerts the strongest influence on the optimal duration of injection both the Mooney and the Krieger-Dougherty models. It is not clear to what extent this product can be engineered in suspensions of proteins or particles. For the examples in figure 3b), $[\eta]c_{\max} \approx 10$, and it is typically much smaller for hard particles. This at least suggests that engineering the "efficiency" of the solute packing is possible and can be used to optimize the injection duration via molecular design. Some recent experiments have shown that adding arginine to solutions of antibodies results in a viscosity that diverges at higher concentrations[23]. From the perspective

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of the optimal injection duration, one must ask whether the addition of arginine can change the molecular interactions in a way that shifts $[\eta]c_{\max}$ favorably. Certainly, this detailed analysis of the injection problem signals that $[\eta]c_{\max}$ is an interesting target for decreasing the optimal injection duration or equivalently increasing the optimal molar flow rate of a suspended component.

Finally, in recent experiments we have scaled up the batch synthesis of PbS nanocrystals via burst nucleation and found this framework for optimizing injection an indispensable tool[24]. In this synthetic procedure, a concentrated solution of sulfur precursor suspended in oleylamine is injected by hand using a 20 mL syringe into a solution of lead chloride precursor being stirred at $120°C$[25]. The nanocrystals grow in solution before the reaction is quenched. Our original synthetic procedure would yield ~75 mg of nanocrystals. In order to perform neutron scattering experiments on concentrated solutions of PbS nanocrystals, the yield of the synthetic procedure would need to be scaled up by two orders of magnitude while maintaining low size dispersity in the batch[26]. The size dispersity is strongly influenced by the duration of injection for the sulfur precursor solution. In order to successfully scale up the synthesis, it was essential to minimize the duration of injection. The volume of the sulfur solution needed for the scaled-up synthesis well exceeds the capacity of a 20 mL syringe. As such, we used a pressure-driven injection in which the sulfur solution is held in a pressurized volumetric funnel and injected into the reaction vessel containing the lead chloride solution, which is held under a mild vacuum[27].

The optimization procedure follows the serial dilution methodology described for a Krieger-Dougherty fluid. In the experimental apparatus, a funnel holding the sulfur solution is positioned vertically above the reaction vessel and held back by a stop cock with a large orifice. The applied pressure drop driving the fluid into the vessel vastly exceeds the gravitational load on the fluid so that equation 1 is appropriate for describing the fluid flow. We use a mass basis so that N is the mass of sulfur to be injected, c is the sulfur mass concentration, and $\eta(c)$ is the viscosity as a function of mass concentration. We measured the injection duration for 0.65 g sulfur suspended in different volumes of oleylamine from 15 to 180 mL. Figure 4 shows these durations. Using the measured durations, we fit for the geometric prefactor, A and $c_{\max}$ using a Krieger-Doughtery viscosity model with $[\eta]c_{\max} = 2$ and an unloaded viscosity $\eta(0) = 4.93$ cP for oleylamine at $25°C$[28]. We find $c_{\max} = 101$ mg/mL and $A = 2107$ s^2/m^2. Figure 4 shows the viscosity profile predicted by the timing measurements and the geometric tangent construction corresponding to the optimal injection concentration. The optimal concentration for injection is then found to be 33.7 mg/mL. Using this concentration for the sulfur precursor solution, we were able to obtain multiple grams of 6.1 nm diameter PbS nanocrystals with a size dispersity of 3.4%, on par with the lowest size dispersity samples obtainable in

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the small scale synthesis.

This procedure is both simple to implement and provides valuable insight into the shape of the objective function. No rheological measurements were required for this optimization. It is only required to measure the duration of injection of a few solutions at different concentration formulated by serial dilution. Figure 4 plots the injection duration from these experiments. At low concentration, too much volume is required to deliver the requisite mass and the injection time is large. At high concentration, the solution viscosity has climbed large enough that the injection time increases. The optimal injection concentration occurs where the viscosity profile departs from a linear approximation. Additionally, we note the injection time function is relatively flat near the optimal concentration. That is, the injection time will not change significantly if there is small error in the sulfur solution preparation for these experimental parameters. If the geometric prefactor were larger, as would be the case for larger pressure differentials, more injected mass, or smaller stopcock radii, then the injection time profile would be sharper and it would be more important to precisely prepare a precursor solution to match the optimal concentration.

Conclusions

Inspired by past work in modeling biophysical systems with Newtonian fluids, we have derived new formulas representing the solution to an optimization problem describing the optimal formulation for delivering a solute at the maximal rate in multicomponent fluids. The framework employed in this work allowed for graphical or numerical determination of the optimal formulation of single and multicomponent Newtonian fluids using a limited number of experimental measurements of the viscosity as a function of composition. Additionally, we showed how model shear thinning and shear thickening fluids transporting a single solute should be loaded in order to achieve the maximum delivery rate. For this model fluid, there is a simple transition between two limiting viscous states at low and high applied stresses, but the same approach could be applied to fluids with more complex rheology. We showed that the optimal injection of these fluids must control both the formulation and the pressure drop applied. For a shear thinning fluid, the optimally loaded fluid is the one that maximizes the rate of solute delivery in the high stress branch of the viscosity while using the highest accessible pressure drop to drive the flow. For a shear thickening fluid, the situation is more complicated. A locally optimal solution can be found when the fluid is loaded to maximize the delivery rate in the low stress branch of the viscosity with the pressure drop restricted so that the fluid throughout the flow channel has rheology drawn from this same low stress branch. A globally optimal delivery rate is

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always found as the pressure drop diverges, but such solutions may not be physically accessible in real world injection scenarios with shear thickening fluids. We demonstrate how these calculations can be applied to the delivery of chemical solutes in a burst nucleation experiment for the growth of quantum dots, but we expect that there are many more applications for such optimal flow scenarios beyond this context or the biophysical systems explored in past works. One area in which rapid injection is essential is in pharmaceuticals. The derivation of an optimization problem for multicomponent Newtonian formulations may find use in this particular area where macromolecular species are often the target injectable, but various excipients can be added to solution as viscosity modifiers and solubilizers. This multicomponent formulation of the injection problem enables a principled way of designing human injectable solutions that expose patients to a minimal injection duration.

Acknowledgements

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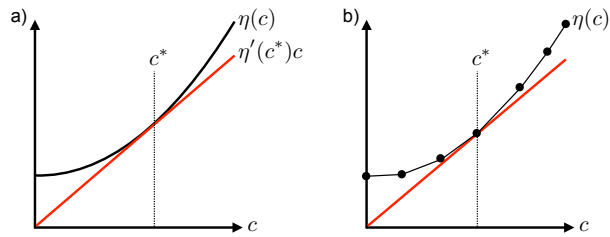
Figure 1: Tangent line construction for finding optimal composition. a) For a two component, Newtonian fluid having an increasing viscosity with respect to the concentration of a solute, the injection of a fixed dose of solute with minimal duration occurs where a line through the origin forms a tangent with the viscosity. b) A simple graphical method for determining the optimal loading for injection involves determining where a line through the origin intersects just once the piece-wise linear approximation of the viscosity formed from connecting experimental data with lines.

Figure 2: Typical scaling of solution viscosity with concentration. a) A schematic of the viscosity of a polymer solution as a function of polymer concentration. On increasing the concentration past the overlap concentration a new power law trend in the viscosity emerges. The optimal loading for injection resides at this overlap concentration and can be found by shifting a line with unit slope vertically until it just intersect the viscosity curve on a log-log plot of viscosity versus concentration. b) A schematic of the viscosity dependence described by the Krieger-Dougherty model. The optimal loading for Krieger-Dougherty models typically resides near $c_{\max}/3$.

Figure 3: Optimization of medical injections. a) The viscosity of glycerol-water mixtures as a function of the molar concentration of glycerol. Following the procedure in Figure 1b), the line through the origin just touching an experimental data point determines an approximation for the concentration of the fluid with minimal injection duration. The optimal concentration is equivalent to a glycerol weight fraction of 30%. b) The viscosity as a function of concentration for two monoclonal antibody solutions produced by Pfizer (blue and black circles). The blue and black curves are fits of the Mooney equation to the data, and the red curves are lines through the origin that are tangent to the model.

Figure 4: Optimizing a scaled-up hot-injection synthesis of PbS nanocrystals. Measured injection times to deliver 0.65 g sulfur in oleylamine are shown in blue with a fit to equation 4 using a Krieger-Doughtery viscosity model. The predicted viscosity profile is shown in black with the geometric construction of Equation 3 in red. The optimal concentration for injection is found to be 33.7 mg/mL with $c_{\max} = 101$ mg/mL.
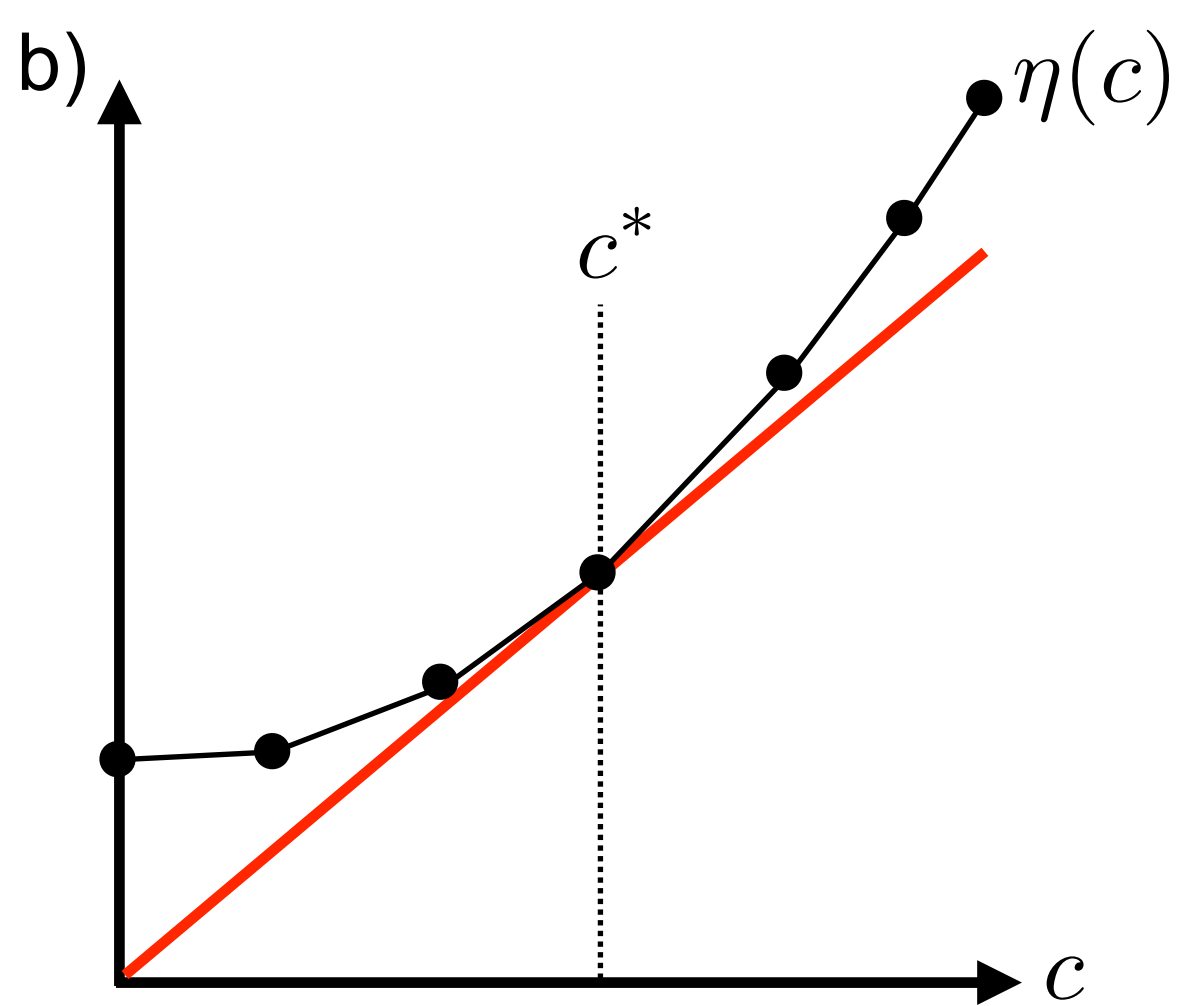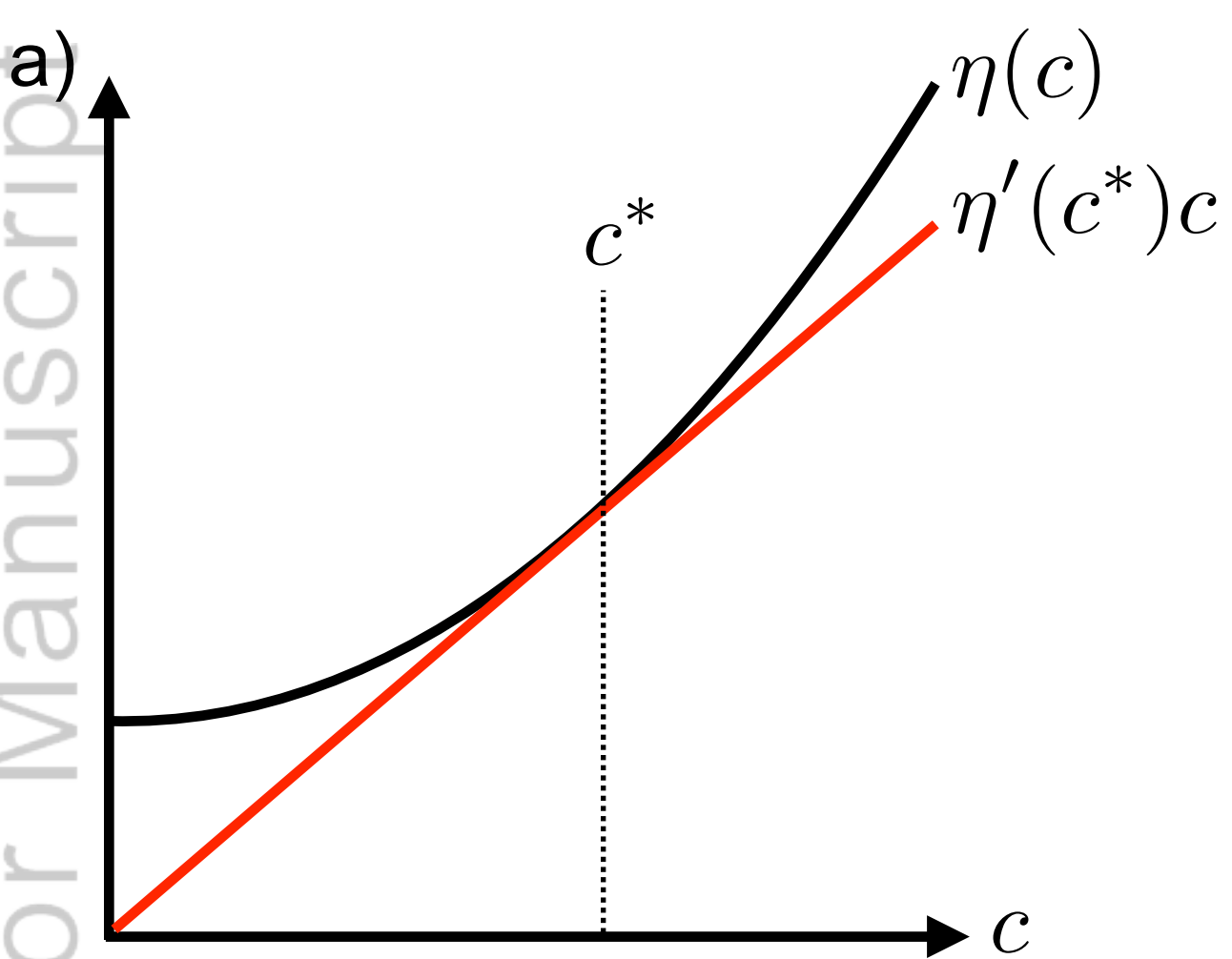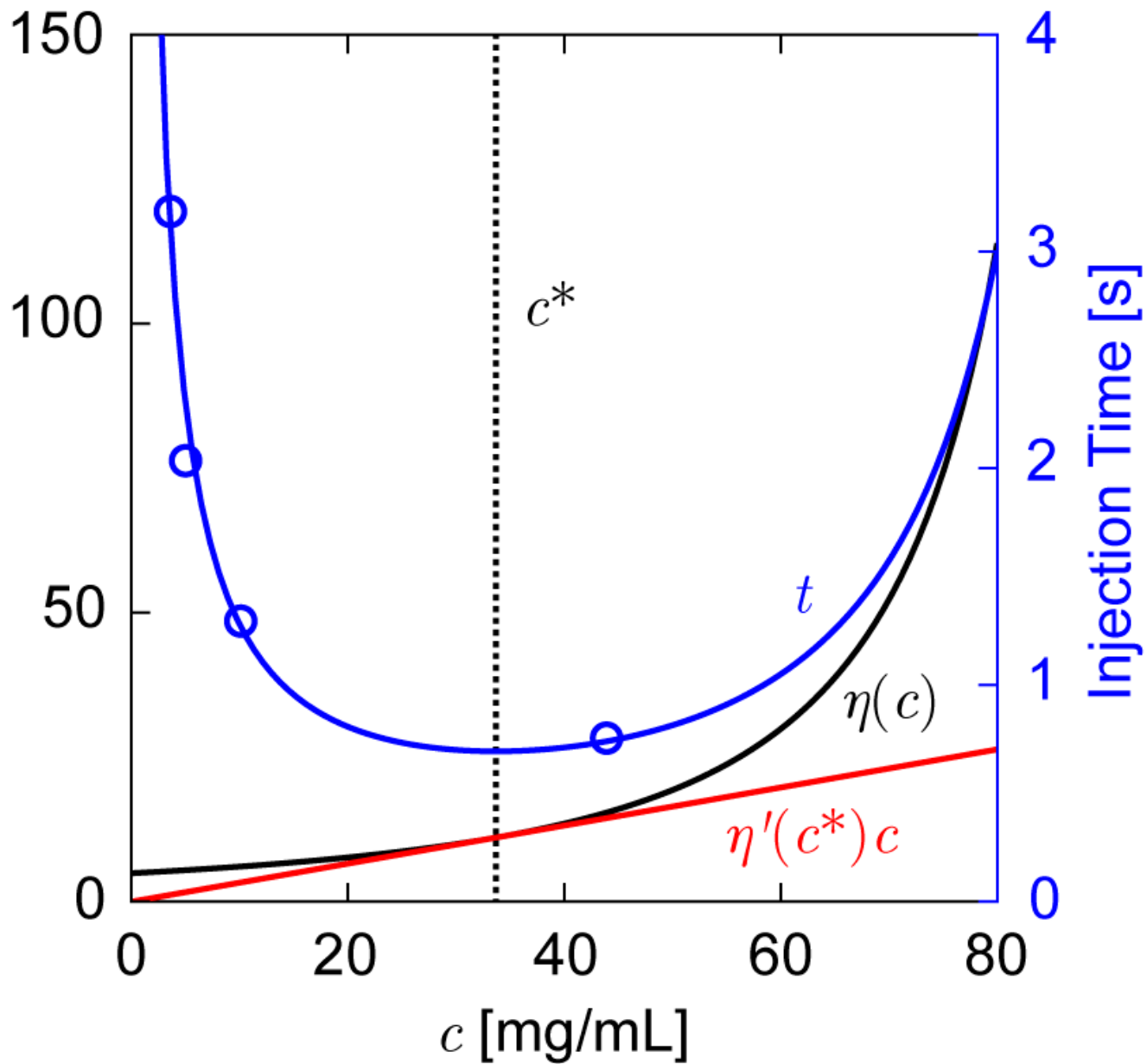
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AIC_17102_PbS_injection-01.png

a)

$\log \eta(c)$

$\log c^*$

overlap

$\log \eta'(c^*) + \log c$

$\log c$

b)

$\eta(c)$

c^*

$c_{\max}$

$\eta'(c^*)c$

c
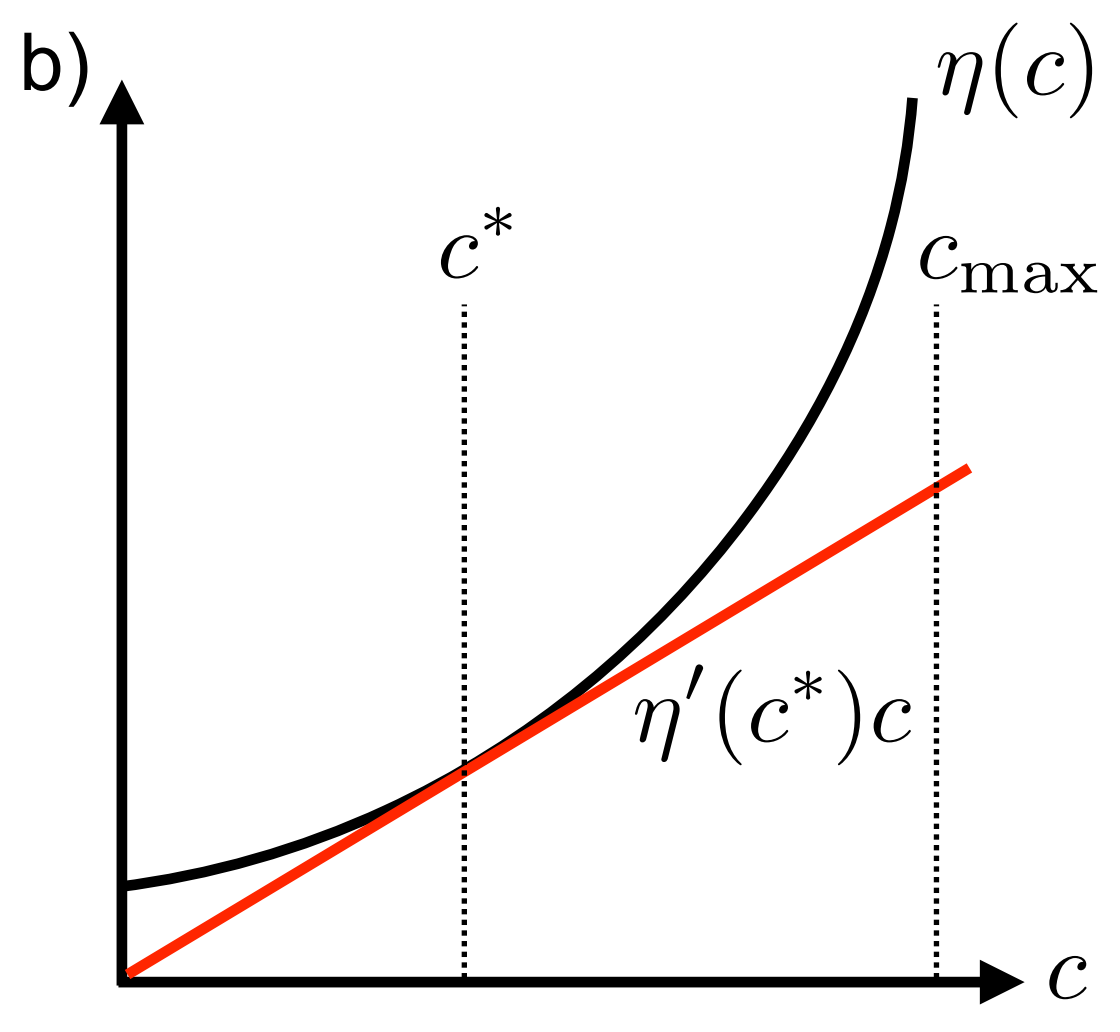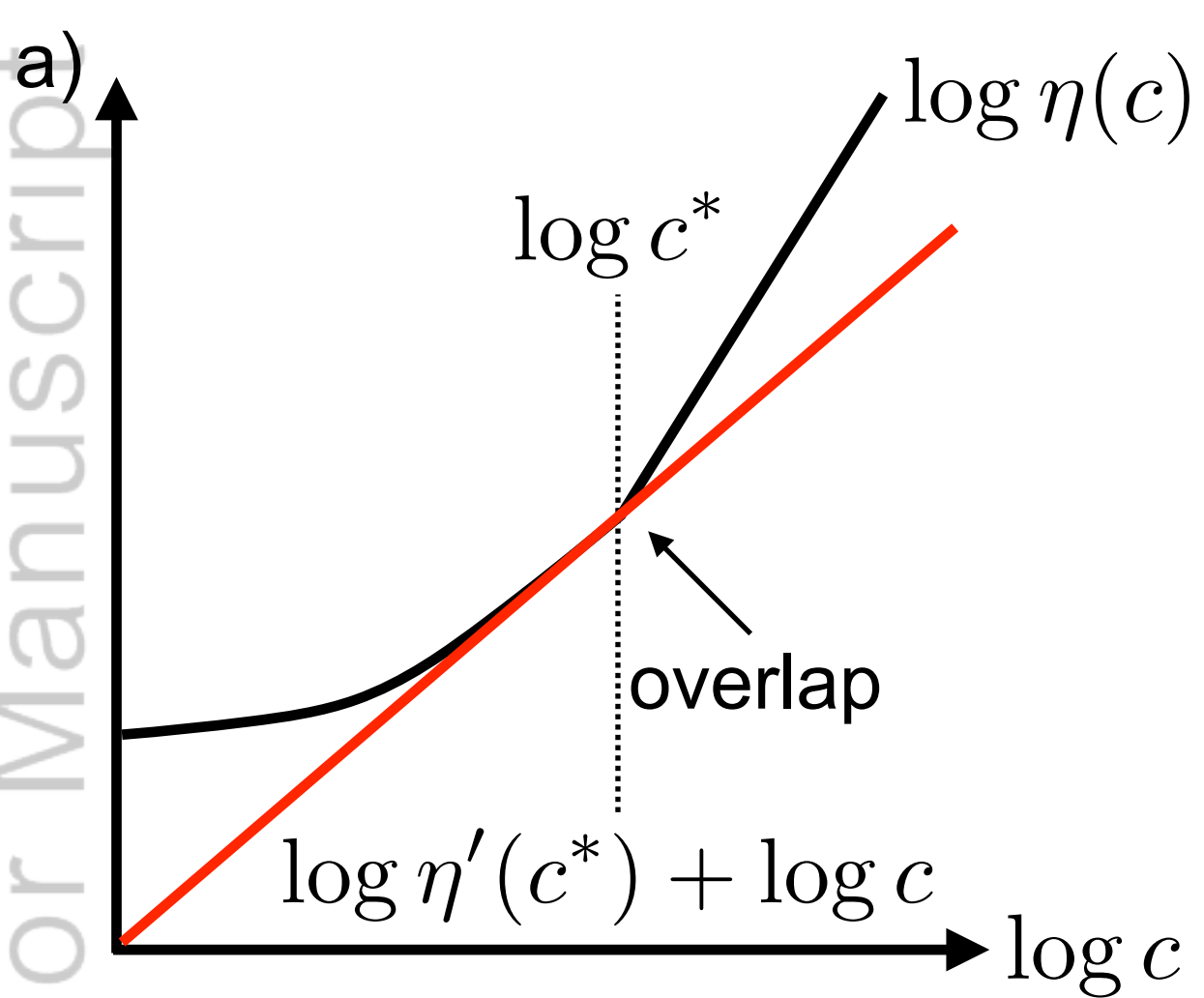
Response to reviewer 1

Dear reviewer,

We thank you for your comments.

Response to reviewer 2

Dear reviewer,

We thank you for your comments and have revised the abstract as you suggested.