View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by CiteSeerX

D. G. Cole[1]
e-mail: dgcole@pitt.edu

J. G. Pickel
e-mail: jgp2@pitt.edu

Department of Mechanical Engineering and Materials Science,
Swanson School of Engineering,
University of Pittsburgh,
Pittsburgh, PA 15261

Nonlinear Proportional Plus Integral Control of Optical Traps for Exogenous Force Estimation

This article explores nonlinear proportional plus integral (PI) feedback for controlling the position of an object held in an optical trap. In general, nonlinearities in the spatial dependence of the optical force complicate feedback control for optical traps. Nonlinear PI control has been shown to provide all of the benefits of integral control: disturbance rejection, servo tracking, and force estimation. The controller also linearizes the closed-loop system. More importantly, the nonlinear controller is shown to be equivalent to an estimator of the exogenous force. The ability of nonlinear PI control to lower the measurement SNR is evaluated and compared to the variational open-loop case. A simulation demonstrating the performance of the nonlinear PI control is presented. [DOI: 10.1115/1.4004774]

Keywords: nonlinear control, optical traps, optical tweezers, force estimation

1 Introduction

Optical traps use light to exert forces on microscopic objects. Specifically, laser light, focused through a high numerical aperture objective, creates a high intensity focus. As light is diffracted and reflected through dielectric objects, the change in momentum of the light results in a force exerted on the diffracting object, allowing the object to be held near the focus. The scale of these forces is small, from femtonewtons to hundreds of piconewtons, and depends upon the beam's power, the numerical aperture (NA) of the trapping objective, the size of the trapped object, and the quality of the optical system. The ability to generate small forces has made optical traps an important tool for investigating nanoscale phenomena. Of particular importance are single-molecule studies that use trapped microscopic beads as handles; these handles are attached to the molecule of interest, e.g., DNA [1], motor proteins [2], and others [3,4] (see Figs. 1 and 2.) The beads can be manipulated in order to exert desired displacements or forces on the molecule being studied. Also, in the case of motor proteins, the beads can be monitored to measure the generation of force by the motor protein, motor stall force, stepping length, and the motor protein's procession along a substrate molecule, and energy used per step.

A significant challenge in such single-molecule experiments and optical trapping investigations in general, is that all motions at the molecular scale are dominated by Brownian fluctuations, and digging signals of interest out of this Brownian noise is hard. Such signals are often low bandwidth with cut-off frequency ω_b; e.g., molecular stepping of 1 bp (0.34 nm) every 2 s which results in a signal bandwidth dominantly below 0.5 Hz. A typical approach is to trap the beads in a high-stiffness trap,[2] and to filter the measurement with a low-pass filter at or near the signal bandwidth, thus eliminating noise above the low-pass filter's cut-off frequency. A careful analysis of the noise characteristics using this approach shows that the small bandwidth signal-to-noise ratio (SNR) is independent of trapping stiffness [5]. From this result, some researchers have concluded that feedback control, which for simple position feedback has the same effect as increasing the trapping stiffness, cannot improve the SNR [6]. However, this conclusion overlooks the fact that feedback control can frequency shape the response and can reject disturbances while controlling variables of interest. Furthermore, as will be shown in this paper, feedback control can generate an estimate of the exogenous force acting on the trapped bead, and these estimates are a direct and robust measure of the molecular forces of interest. Such capabilities enable optical traps to do more than manipulate objects. Instead, they can be highly versatile platforms for single-molecule investigations.

Linear integral feedback control has been shown to provide advantages over open-loop techniques [5]. The linear theory is appropriate for small displacements of objects within their traps where the linear approximation of the trapping stiffness holds. Integral control can provide measurements with SNR at least as good as open-loop measurements filtered over a low bandwidth. Feedback control, however, provides the advantage that signal SNR can be improved while simultaneously controlling other variables of interest, like the force applied to a molecule. However, many experiments can require the optical trap to generate forces near the peak trapping force. In such cases, Hooke's law for estimating the trapping forces is no longer valid, or more importantly, the bead escapes the trap altogether. A control theory that accounts for the nonlinear characteristic of the trapping force is needed. This paper investigates a nonlinear PI (proportional plus integral) control law that accounts for the spatial nonlinearities of the trapping force.

2 The Optical Trap Equation of Motion

Stable 3D traps can be constructed using high numerical aperture objectives, and several researchers have provided both geometric optic theories [7] and electro-magnetic theories [8–10] for the optical trapping forces. Here, we will consider trapping along a single axis; the extension to the 3D case should be apparent.

Optical trapping forces are generated by the interaction of a dielectric object with the electric field of the focused laser beam. This interaction can be characterized by a potential

$$E(z) = -E_0 \exp\left(-\frac{1}{2}z^2/w_0^2\right) \quad (1)$$

where E_0 is the total depth of the potential, w_0 is a characteristic dimension of the potential related to the beam waist and the size of the trapped object, and z is the relative displacement of the trapped object with respect to the center of the trap. The force acting on the trapped object is

$$f_t(z) = -\nabla E(z) = -kz \exp\left(-\frac{1}{2}z^2/w_0^2\right) \quad (2)$$

[1]Corresponding author.

[2]Here high stiffness implies that the trap's cut-off frequency k/γ is greater than the bandwidth of the signal of interest, so that $k \gg \gamma\omega_b$.

Contributed by the Dynamic Systems Division of ASME for publication in the Journal of Dynamic Systems, Measurement, and Control. Manuscript received August 26, 2010; final manuscript received June 6, 2011; published online December 6, 2011. Assoc. Editor: Won-jong Kim.

Copyright © 2012 by ASME

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

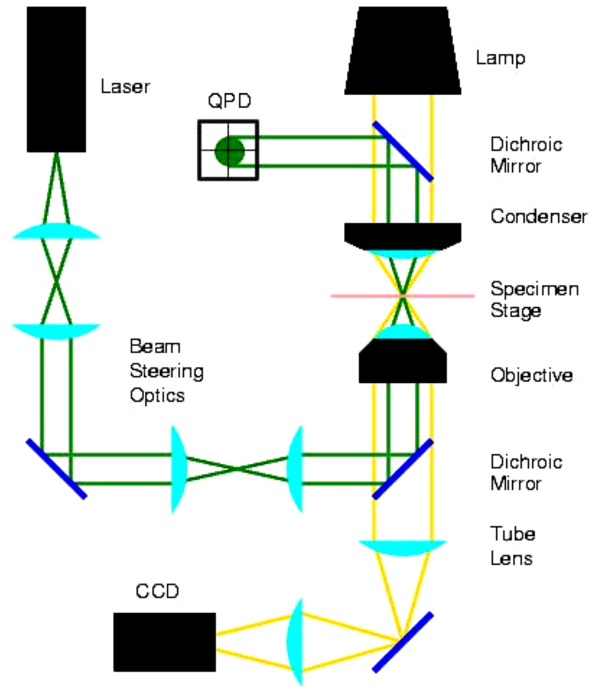

Fig. 1 Optical traps are typically built around a microscope, which provides a high NA objective and a means for imaging trapped objects. A collimated beam is introduced to the microscope at the front focal plane of the objective, making a tight focus at the specimen plane. Diffraction of the light at the focus by dielectric objects results in the optical forces that hold the object. Light from a laser can be steered using various means, and the position of the trapped object within the trap can be sensed using a quadrant photo-diode positioned at the objective's back focal plane.

where $k = E_0/w_0^2$ is the stiffness of the trap. It is apparent that the optical forces are a nonlinear function of the relative position, z. Note that the peak trapping force is $f_{t,\max} = kw_0e^{-1/2} = 0.61kw_0$.

In optical trapping experiments, inertial forces can often be ignored. The dominant force is viscous drag

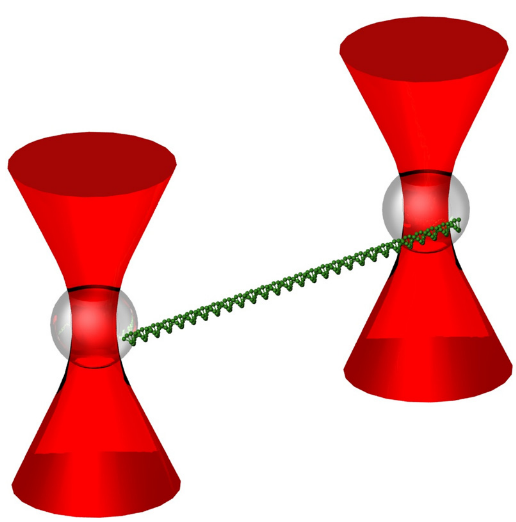

Fig. 2 This schematic illustrates a typical single-molecule experiment. In this two-beam setup, microspheres are held in each trap. A long chain polymer, e.g., DNA, is tethered between the two spheres, and the force on the molecule can be determined by measuring the position of each microsphere in its trap. Feedback control can be used to control the molecule's elongation or the force applied to it.

$$f_d = \gamma\dot{x} = \gamma(\dot{z} + u) \tag{3}$$

where $\gamma = 6\pi\mu r$ is the Stoke's drag coefficient, $\dot{x} = \dot{z} + u$ is the absolute velocity of the bead with respect to the surrounding fluid, and u is the velocity of the trap. The equation of motion is then

$$\gamma\frac{dz}{dt} + kz\exp\left(-\frac{1}{2}z^2/w_0^2\right) = -\gamma u + f_{\text{ex}} \tag{4}$$

where we have included f_{ex} as exogenous forces that include Brownian fluctuations and molecular forces under investigations. The forces can be modulated either by moving the beam (changing u) or by modulating the power of the beam (changing E_0 and k). In this study, the signal u is the control input to the optical trapping system.

3 Open-Loop and Linear Control

Assume the trap is open-loop ($u = 0$). For small motions about $z = 0$, the variational plant is

$$\gamma\frac{dz}{dt} + kz = f_{\text{ex}} \tag{5}$$

This model is appropriate for small deflections about the trap's center. This model is characterized by the stiffness k, which can be calibrated several ways including equipartition, autospectra, and cross-correlation methods, and by the trap's bandwidth (cut-off frequency) $\omega_t = k/\gamma$ [11]. The trap's bandwidth is important because it determines the upper frequency limit for open-loop measurements made using the trap.

The exogenous force includes the molecular forces under investigation and Brownian fluctuations resulting from the collisions of molecules in the surrounding fluid with the trapped object. These Brownian fluctuations are characterized by zero-mean white noise with power spectral density, $s_{\text{ex}} = 2\gamma k_BT$; where, k_B is Boltzmann's constant and T is the absolute temperature of the environment.

A typical strategy for measuring the exogenous force is to estimate the force with Hooke's law, $f_{\text{est}} = kz$. It is straightforward to show that

$$\langle f_{\text{est}}\rangle = k\langle z\rangle = \langle f_{\text{ex}}\rangle \tag{6}$$

so this open-loop approach to measuring f_{ex} results in an unbiased estimator. The variance of this estimate is

$$\text{Var}(f_{\text{est}}) = k^2\text{Var}(z) = k\,k_BT \tag{7}$$

It is well known that $\text{Var}(z) = k_BT/k$ by the equipartition theorem. The broadband SNR is

$$\text{SNR} = \frac{\langle f_{\text{est}}\rangle}{\sqrt{\text{Var}(f_{\text{est}})}} = \frac{\langle f_{\text{ex}}\rangle}{\sqrt{k\,k_BT}} \tag{8}$$

Thus, the SNR improves for a smaller trapping stiffness. In principle, this relationship can be used to determine an acceptably small stiffness so that the SNR meets objectives. However, in practice, as the stiffness gets smaller it is more difficult for trapped objects to remain in the trap. Small disturbances, particularly from Brownian fluctuations, tend to push the objects out of the trap. This is a result of the characteristics of a 3D trap, where reducing the lateral stiffness (e.g., by reducing the trapping laser's power) reduces the longitudinal stiffness to a point that the 3D trap is no longer stable. Thus, there are practical limits on how small the trapping stiffness can be made.

Very often, the signal of interest is band-limited up to a frequency $\omega_b < \omega_t$. In this case, we are interested in the band-limited noise in the force estimate. The small bandwidth variance is

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

$$\mathrm{Var}(f_{\mathrm{est}})_{\omega_b} = \frac{\gamma k_B T \omega_b}{\pi} \tag{9}$$

and the small bandwidth SNR is

$$\mathrm{SNR}_{\omega_b} = \left[\frac{\pi}{\gamma k_B T \omega_b}\right]^{1/2} \langle f_{\mathrm{ex}} \rangle \tag{10}$$

Now, the SNR is independent of the trapping stiffness. The apparent implication of this result is that controlling the trap, which has typically been done using proportional control and has the same effect as increasing trap stiffness, has no effect on the SNR over small bandwidths. However, as will be seen in the remainder of the paper, frequency shaped controllers, like integral control, can result in improved SNR while simultaneously controlling variables of interest.

4 Nonlinear PI Control

The objective here is to synthesize a nonlinear controller that can control the relative position, z, of the particle in the trap. This objective appears in many single-molecule control experiments where the trapping force, $f_t(z)$, is used as a measurement proxy for the exogenous forces (which include the forces from the molecule applied to the bead). Control of z can also be extended to the control of force. A force setpoint $f_{\mathrm{sp}} \in [-f_{\mathrm{peak}}, f_{\mathrm{peak}}]$ can be mapped to a displacement setpoint $z_{\mathrm{sp}} \in [-w_0, w_0]$, which then becomes the setpoint for position regulation. This mapping can be done by iteratively solving $f_t(z_{\mathrm{sp}}) = f_{\mathrm{sp}}$ (see Eq. (2) and Fig. 3).

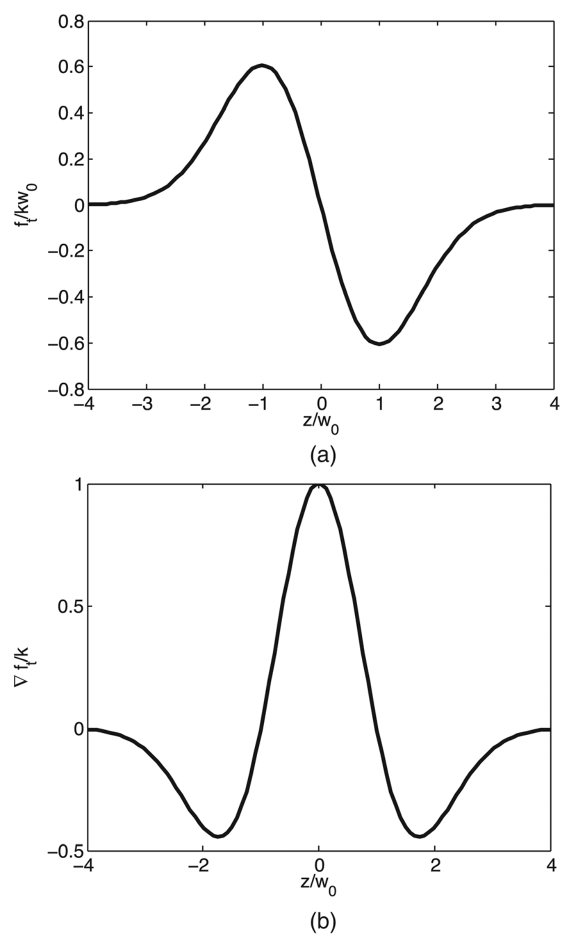

Fig. 3 (*a*) A plot of the normalized optical trapping force, $f_t/(kw_0)$. (*b*) A plot of the normalized local stiffness, f_t/k. The optical force acting on a trapped object is a nonlinear function of the displacement of the object within the trap. Two parameters characterize the trap: the trap stiffness k and the peak trapping force $f_{t,\max} = 0.61kw_0$, where w_0 is a characteristic dimension of the trap.

We will use the method of Wright et al. [12] to generate a nonlinear PI controller with the following criteria:

1. The controller should be first order: This criterion limits controller complexity and facilitates design, which is done by choosing two gains. This criterion matches the linear PI controller which is also first order. The resulting closed-loop system is second order.
2. The controller should possess integral action: Integral action is necessary to drive the steady-state error to zero; improved accuracy is a primary reason for including integral control. The state of the controller is the state of the integrator, although for the nonlinear case, the controller output may depend nonlinearly upon this state.
3. The controller should induce linear closed-loop dynamics: While the first two criteria follow from linear PI controllers, this criteria reflects a desired property of the closed-loop system. A linear closed-loop system is easier to analyze and to predict stability. These features will facilitate the design of the controller.

The following controller meets the given specifications:

$$\frac{d\hat{z}}{dt} = g_1(z_{\mathrm{sp}} - z) \tag{11}$$

$$u = -g_1(z_{\mathrm{sp}} - z) - g_2(\hat{z} - z) - \gamma^{-1} kz \exp\left(-\frac{1}{2}z^2/w_0^2\right) \tag{12}$$

This controller has two tunable parameters: g_1 and g_2. Substituting these into the equation of motion (Eq. (4)), the closed-loop system is linear, as required, with dynamics

$$\frac{d}{dt}\begin{bmatrix} z \\ \hat{z} \end{bmatrix} = \begin{bmatrix} -(g_1+g_2) & g_2 \\ -g_1 & 0 \end{bmatrix}\begin{bmatrix} z \\ \hat{z} \end{bmatrix} + \begin{bmatrix} g_1 \\ g_1 \end{bmatrix} z_{\mathrm{sp}} + \begin{bmatrix} 1/\gamma \\ 0 \end{bmatrix} f_{\mathrm{ex}} \tag{13}$$

It is straightforward to show that the characteristic equation for this linear system is

$$s^2 + (g_1 + g_2)s + g_1 g_2 = 0 \tag{14}$$

and the eigenvalues are $\lambda_{1,2} = \{-g_1, -g_2\}$. Thus, the closed-loop system is characterized by the two time constants, $\tau_1 = 1/g_1$ and $\tau_2 = 1/g_2$.

For now consider the exogenous force to be zero, $f_{\mathrm{ex}} = 0$. This control law forces $\hat{z}$ to match z so that the closed-loop dynamics are linear and first order. We can view $\hat{z}$ as an estimate of the bead displacement z, and the estimation error is

$$\frac{d}{dt}(\hat{z} - z) = -g_2(\hat{z} - z) \tag{15}$$

The position z and its estimate $\hat{z}$ approach each other with time constant τ_2. For $t \gg \tau_2$, $\hat{z} \simeq z$ and Eq. 13 can be simplified to

$$\frac{dz}{dt} = g_1(z_{\mathrm{sp}} - z) \qquad t \gg \tau_2 \tag{16}$$

If we compare this with Eq. (11), we see that once the estimator has converged $\hat{z}$ represents a precalculated estimate of z in the closed-loop.

5 Mean Response and Exogenous Force Estimation

In general, it is desirable to have $\omega_b < g_1 < g_2$ so that the dynamics of the closed-loop system are faster than the signals of interest. Assume also that the exogenous force has an estimated value $\langle f_{\mathrm{ex}} \rangle$ that is band-limited to ω_b; that is, it changes with a time constant $\tau > 1/\omega_b > \tau_1 > \tau_2$. In this case, after sufficiently long time, $t \gg \tau_1$, the expected value of z and $\hat{z}$ can be determined from Eq. (13) to be

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

$$\langle z \rangle = z_{sp} \tag{17}$$

$$\langle \hat{z} \rangle = z_{sp} - \frac{1}{\gamma g_2} \langle f_{ex} \rangle \tag{18}$$

As expected, z tracks z_{sp}, and we see that $\langle f_{ex} \rangle$ does not affect $\langle z \rangle$. Such disturbance rejection is one of the benefits of integral control. Also, we see that $\langle \hat{z} \rangle$ is related to $\langle f_{ex} \rangle$; hence, we can use $\hat{z}$ to calculate an estimate of the exogenous force

$$f_{est} = \gamma g_2 (z_{sp} - \hat{z}) \tag{19}$$

The result in Eq. (18) shows that

$$\langle f_{est} \rangle = \gamma g_2 (z_{sp} - \langle \hat{z} \rangle) = \langle f_{ex} \rangle \tag{20}$$

making this an unbiased estimate of the exogenous force.

The variance of f_{est} depends upon the fluctuations in the system due to Brownian excitations from the surrounding fluid, and is proportional to the variance of $\hat{z}$

$$\text{Var}(f_{est}) = (\gamma g_2)^2 \text{Var}(\hat{z}) \tag{21}$$

To calculate the variance of $\hat{z}$, consider the setpoint to be zero and the exogenous force to be the fluctuating Brownian force resulting from the collision of surrounding molecules with the bead. This force is zero-mean white noise with constant power spectrum; $s_{ex} = 2\gamma k_B T$. The steady-state response due to this fluctuating forces can be found by solving the Lyapunov equation [13]

$$A\Sigma + \Sigma A' + BB' s_{ex} = 0 \tag{22}$$

where

$$A = \begin{bmatrix} -(g_1+g_2) & g_2 \\ -g_1 & 0 \end{bmatrix}, \qquad B = \begin{bmatrix} 1/\gamma \\ 0 \end{bmatrix}, \qquad \Sigma = \begin{bmatrix} \langle z^2 \rangle & \langle z\hat{z} \rangle \\ \langle z\hat{z} \rangle & \langle \hat{z}^2 \rangle \end{bmatrix} \tag{23}$$

with the solution

$$\text{Var}(z) = \frac{k_B T}{\gamma}\left(\frac{1}{g_1+g_2}\right), \quad \text{Var}(\hat{z}) = \frac{k_B T}{\gamma}\frac{g_1}{g_2}\left(\frac{1}{g_1+g_2}\right), \quad \text{Cov}(z,\hat{z}) = 0 \tag{24}$$

The variance of f_{est} is

$$\text{Var}(f_{est}) = (\gamma g_2)^2 \text{Var}(\hat{z}) = \gamma k_B T \frac{g_1 g_2}{g_1+g_2} \tag{25}$$

If we ensure that $g_1 \ll g_2$ then $\text{Var}(f_{est}) \simeq \gamma k_B T g_1$. The signal-to-noise ratio is

$$\text{SNR} = \frac{\langle f_{est} \rangle}{\sqrt{\text{Var}(f_{est})}} = \frac{\langle f_{ex} \rangle}{\sqrt{\gamma k_B T}}\left[\frac{1}{g_1} + \frac{1}{g_2}\right]^{1/2} \simeq \frac{\langle f_{ex} \rangle}{\sqrt{\gamma k_B T g_1}} \tag{26}$$

This result is strikingly similar to Eq. (10), but this is a broadband result. We notice that the SNR is improved as g_1 is reduced, much like reducing the filter bandwidth ω_b in the open-loop case. The advantage here is that feedback control lets us control the relative displacement, z, of the bead within the trap. Since this displacement is directly related to the optical forces, it gives us precise control over the forces applied to single-molecules, for example, something that is not possible in the open-loop case.

5.1 Estimation Sensitivity. The estimation of the exogenous force implicitly depends upon correct knowledge of the trapping stiffness k. The preceding theory assumes that the nominal stiffness, k, is the true trap stiffness, but for off-nominal estimation the true stiffness is $k_{true} = k + \delta k$, which is the appropriate stiffness to use in Eq. (4). The resulting closed-loop equation of motion is

$$\frac{d}{dt}\begin{bmatrix} z \\ \hat{z} \end{bmatrix} = \begin{bmatrix} -(g_1+g_2) & g_2 \\ -g_1 & 0 \end{bmatrix}\begin{bmatrix} z \\ \hat{z} \end{bmatrix} + \begin{bmatrix} g_1 \\ g_1 \end{bmatrix} z_{sp} + \begin{bmatrix} 1/\gamma \\ 0 \end{bmatrix} f_{ex} + \begin{bmatrix} \gamma^{-1}\delta k z \exp\left(-\frac{1}{2}z^2/w_0^2\right) \\ 0 \end{bmatrix} \tag{27}$$

The result of the uncertainty in the stiffness introduces bias in the exogenous force estimate, can affect stability of the system, and affects the achieved SNR. We look at each in turn.

5.1.1 Estimation Bias. With the bandwidth assumptions outlined in Sec. 5, the expected value of z and $\hat{z}$ are

$$\langle z \rangle = z_{sp} \tag{28}$$

$$\langle \hat{z} \rangle = z_{sp} - \frac{1}{\gamma g_2}\langle f_{ex} \rangle + \frac{\delta k}{\gamma g_2}\left\langle z \exp\left(-\frac{1}{2}z^2/w_0^2\right)\right\rangle \tag{29}$$

The effect of the integral control is to maintain the desired setpoint, and it does so by adjusting $\hat{z}$ to account for unknown stiffness; this is a standard robustness result for integral feedback. However, our estimation equation defined in Eq. (20) results in a mean estimated force

$$\langle f_{est} \rangle = \gamma g_2 (z_{sp} - \langle \hat{z} \rangle) = \langle f_{ex} \rangle - \delta k \left\langle z \exp\left(-\frac{1}{2}z^2/w_0^2\right)\right\rangle \tag{30}$$

which results in a biased estimate of the true exogenous force. For small fluctuations, z is normally distributed, $z \sim N(z_{sp}, \sigma^2)$, and the bias is

$$\langle f_{ex} \rangle - \langle f_{est} \rangle = \delta k \left\langle z \exp\left(-\frac{1}{2}z^2/w_0^2\right)\right\rangle = \delta k z_{sp} \exp\left(-\frac{1}{2}z_{sp}^2/w_0^2\right) + O[\sigma^2] \tag{31}$$

We would like the bias to be small compared to the magnitude of the signals we are trying measure. This gives an upper bound on the stiffness error

$$|\delta k| \ll \left|\frac{\langle f_{ex} \rangle}{z_{sp}}\right| \exp\left(\frac{1}{2}z_{sp}^2/w_0^2\right) < 1.649\left|\frac{\langle f_{ex} \rangle}{z_{sp}}\right| \tag{32}$$

where in the second inequality we have assumed the setpoint position is within the bounds of the trap: $|z_{sp}| < w_0$.

5.1.2 Stability. Stability of the off-nominal system can be determined by linearizing Eq. (27) about the mean. For oscillations about the mean, the dynamics matrix becomes

$$A = \begin{bmatrix} -(g_1+g_2+\omega_\delta) & g_2 \\ -g_1 & 0 \end{bmatrix} \tag{33}$$

where the frequency

$$\omega_\delta = \frac{\delta k}{\gamma}\left(1 - \frac{z_{sp}^2}{w_0^2}\right)\exp\left(-\frac{z_{sp}^2}{2w_0^2}\right) \tag{34}$$

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

The quantity ω_δ can be thought of as the error in the trap's bandwidth $\omega_t = k/\gamma$ due to uncertainty in the true stiffness; this error is bounded above by $|\omega_\delta| \le |\delta k|/\gamma$. The characteristic equation is

$$s^2 + (g_1 + g_2 + \omega_\delta)s + g_1 g_2 = 0 \tag{35}$$

A sufficient condition for stability is $|\delta k| < \gamma\,(g_1 + g_2)$.

5.1.3 Achieved SNR. Using Eq. (22) for the off-nominal system, the variance of z and $\hat{z}$ is

$$\begin{aligned}\mathrm{Var}(z) &= \frac{k_B T}{\gamma}\left(\frac{1}{g_1 + g_2 + \omega_\delta}\right),\\ \mathrm{Var}(\hat{z}) &= \frac{k_B T}{\gamma}\frac{g_1}{g_2}\left(\frac{1}{g_1 + g_2 + \omega_\delta}\right), \quad \mathrm{Cov}(z, \hat{z}) = 0\end{aligned} \tag{36}$$

and the variance of f_{est} is

$$\mathrm{Var}(f_{\mathrm{est}}) = (\gamma g_2)^2 \mathrm{Var}(\hat{z}) = \gamma k_B T \frac{g_1 g_2}{g_1 + g_2 + \omega_\delta} \tag{37}$$

The SNR is

$$\mathrm{SNR} = \frac{\langle f_{\mathrm{est}} \rangle}{\sqrt{\gamma k_B T}}\left[\frac{1}{g_1} + \frac{1}{g_2} + \frac{\omega_\delta}{g_1 g_2}\right]^{1/2} \simeq \mathrm{SNR}_0\left(1 + \frac{\omega_\delta}{2g_2}\right) \tag{38}$$

where SNR_0 is the SNR with no uncertainty. We can ensure that the SNR is not affected significantly if $|\omega_\delta| < |\delta k|/\gamma \ll g_2$, or $|\delta k| \ll \gamma g_2$.

6 Discussion

For many single-molecule experiments, the objective is to estimate the exogenous forces, generated by a motor protein attached to the bead. The open-loop approach ($u = 0$) is to measure directly the position of the bead in the trap and to estimate the optical forces using Eq. (2). The assumption here is that the optical forces exactly balance the exogenous force; however, the forces acting on the bead also include fluctuating Brownian forces that result from surrounding water molecules colliding with the bead. Thus, it is necessary to filter the estimated force to a sufficiently low bandwidth to get to the signal of interest.

The measurement of the exogenous force can also be viewed as an estimation problem where the objective is to estimate the exogenous force (which includes molecular forces of interest and Brownian forces) over some bandwidth. This estimated force can then be used in a feedback scheme to drive the difference between the true exogenous force and its estimate to zero; in other words, feedback can be used to make the estimation error small.

The control scheme presented here has two purposes: First, it linearizes the system, making the relationship between the system inputs, z_{sp} and f_{ex}, and the system outputs, z and f_{est}, linear. This greatly simplifies the dynamics of the closed-loop system, facilitating analysis, and it enables the force estimation, which arises naturally through the integral control process.

To see the various parts of this control process, we rewrite the control signal as

$$-\gamma u = -f_t(z) + \gamma(g_1 + g_2)(z_{\mathrm{sp}} - z) - f_{\mathrm{est}} \tag{39}$$

Written this way, we see that the control signal contains three feedback loops (see Fig. 4): Loop 1 cancels the nonlinear optical force; Loop 2 stabilizes the system; and Loop 3 uses integral control for improved tracking, disturbance rejection, and force estimation. We will discuss these in turn.

Loop 1 is positive feedback of the optical force, $f_t(z)$. In principle, this exactly cancels the nonlinear relationship between bead position and the optical force in the bead's equation of motion. After canceling, the bead position is unstable since the resulting equation of motion is for a bead undergoing free diffusion. Direct cancellation of forces that are position dependent is risky since the resulting system could be unstable. In practice, an estimate of the true optical force is used, $\hat{f}_t(z)$, and the optical force is canceled, but possibly not entirely with the possibility of the resulting system being unstable.

Loop 2 uses position feedback to stabilize the system. The resulting closed-loop system is

$$\gamma\frac{dz}{dt} + \gamma(g_1 + g_2)z = \gamma(g_1 + g_2)z_{\mathrm{sp}} + f_{\mathrm{ex}} \tag{40}$$

This system has improved tracking, $z \simeq z_{\mathrm{sp}}$, for higher gains. In principle, this system could be used to estimate the exogenous force with $f_{\mathrm{est}} = \gamma\,(g_1 + g_2)(z - z_{\mathrm{sp}})$. However, the variance of the force estimate is $\mathrm{Var}(f_{\mathrm{est}}) = \gamma k_B T(g_1 + g_2)$, and the SNR $= \langle f_{\mathrm{ex}} \rangle / \sqrt{\gamma k_B T(g_1 + g_2)}$ becomes worse as gains increase. This

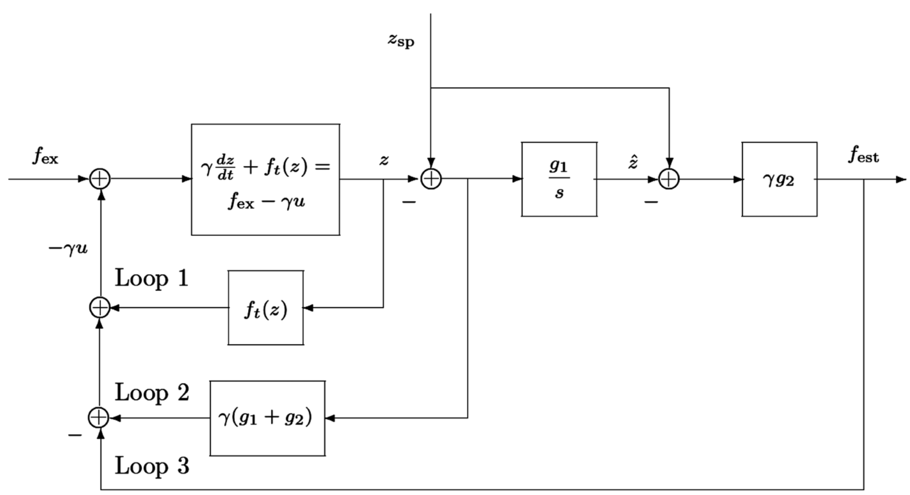

Fig. 4 The controller can also be viewed as an estimator that estimates the exogenous force over some bandwidth. This is done in a feedback scheme to make the estimation error small. The control signal contains three feedback loops: Loop 1 cancels the nonlinear optical force; Loop 2 stabilizes the system; and Loop 3 uses integral control for improved tracking, disturbance rejection, and force estimation.

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

broadband SNR is over the bandwidth of the closed-loop system, $g_1 + g_2$. In many cases, this bandwidth would be much greater than ω_b, the bandwidth of the signals of interest. The open-loop strategy outlined in Sec. 3 could be used on the output of this closed-loop system with the resulting small bandwidth SNR $= \langle f_{ex} \rangle \sqrt{\pi/\gamma k_B T \omega_b}$. This result shows no benefit for position feedback control, a result which has been shown elsewhere [5,6]. Integral feedback, however, can result in improvements in SNR, which is the purpose of Loop 3.

Integral feedback has several advantages: First, it provides good tracking, enabling z to track z_{sp} over a desired bandwidth, and in particular, results in zero steady-state error for a constant z_{sp}; that is, $z_{sp} - z = 0$ for $z_{sp} =$ constant. Second, it provides good disturbance rejection over a desired bandwidth. This bandwidth is presumably ω_b, the bandwidth of the process of interest. The disturbance in this case is the fluctuating Brownian force. Third, the integrator state, $\hat{z}$, is directly related to the exogenous force driving the system away from the setpoint and can be used to form an estimate of those forces over the bandwidth of interest.

The linearized plant (Eq. (40)) in the frequency domain is written as

$$z = \frac{g_1 + g_2}{s + (g_1 + g_2)} z_{sp} + \frac{\gamma^{-1}}{s + (g_1 + g_2)} (f_{ex} - f_{est}) \tag{41}$$

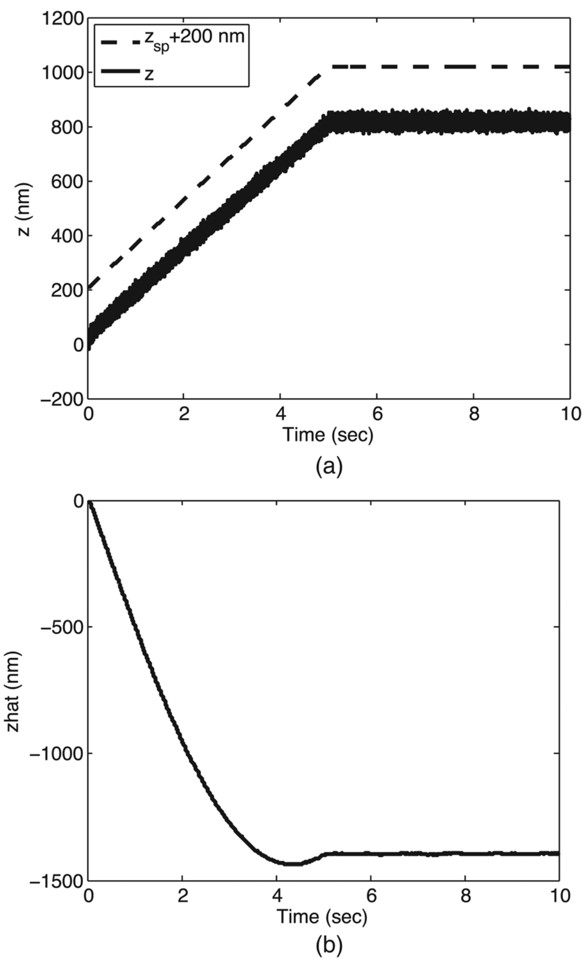

Fig. 5 (*a*) The relative displacement z for a move-and-settle motion with a rise segment (at a constant velocity) to a final setpoint. The final setpoint is chosen to be 817 nm ($0.95w_0$); that is, we require the bead to nearly reach the boundaries of the optical trap. Note: the reference signal z_{sp} has been displaced up 200 nm for clarity. (*b*) The integral state $\hat{z}$ during the move-and-settle motion. Note that in the presence of an exogenous force, $\langle \hat{z} \rangle$ will be different from $\langle z \rangle$ as shown in Eq. (18).

Table 1 The characteristics of the optical trap system and controller used in the simulations.

Parameter	Symbol	Value
Trap stiffness	k	0.13 pN nm^{-1}
Maximum trapping force	$f_{t,\max}$	68 pN
Trap dimension	w_0	860 nm
Bead diameter		1.72 μm
Viscosity of medium	μ	10^{-3} Pa s
Stokes drag coefficient	γ	16.2×10^{-9} N s m^{-1}
Control bandwidth	g_1	18.8 s^{-1} (3 Hz)
Position estimator bandwidth	g_2	1880 s^{-1} (300 Hz)

The estimated force is generated as

$$f_{est} = \gamma g_2 \left(z_{sp} - \frac{g_1}{s}(z_{sp} - z) \right) = \gamma g_2 \frac{g_1}{s} \left(z - \frac{g_1 - s}{g_1} z_{sp} \right) \tag{42}$$

In general, the fact that the estimated force is related to the integral of z_{sp}—z implies that we can think of the forces estimate as proportional to the average difference between z_{sp} and z. In an ideal system with no noise, any difference between z_{sp} and z would be caused by an external force pulling on the bead. The right-half plane zero at $+g_1$ in the above relationship is a bit peculiar, and is there to account for the delay between z_{sp} and z that occurs in the plant. From this, we should expect that at low frequencies, below g_1, the estimated error will be the proportional to the time average of $z - z_{sp}$. Combining Eqs. (41) and (42) gives the closed-loop system

$$f_{est} = \gamma g_2 \frac{s}{s + g_1} z_{sp} + \frac{g_1 g_2}{(s + g_1)(s + g_2)} f_{ex} \tag{43}$$

The result is that $f_{est} \simeq f_{ex}$ at least up to first cut-off frequency g_1. The contributions of the Brownian fluctuations can be minimized by making g_1 suitably small, causing the estimation bandwidth to be low. Furthermore, the effects of a dynamically changing z_{sp} will not be seen in f_{est} at frequencies below g_1, the cut-on frequency of the resulting high-pass filter from z_{sp} and f_{est}; that is, the controller rejects the effects of z_{sp} in f_{est} at low frequencies.

So what are the advantages of using feedback control? Is not the effect of this force estimation the same as the open-loop strategy of low-pass filtering the measured signal over a suitably low bandwidth to reconstruct f_{ex}? The advantage of feedback control is that, while the exogenous force is being measured, variables like molecular elongation or the nominal applied force can be precisely controlled. This is not the situation for the open-loop case. A further advantage of PI control is that the exogenous forces are rejected from the bead's displacement from the trap center. The closed-loop displacement is

$$z = \frac{g_1}{s + g_1} z_{sp} + \frac{s}{(s + g_1)(s + g_2)} f_{ex} \tag{44}$$

Table 2 Statistical results of the simulation about $z = 0$ when $z_{sp} = 0$ and $f_{ex} = 0$. The mean values of z and $\hat{z}$ should be zero. The theoretical variance and covariance are given by Eq. (36). $N = 5{,}000{,}000$ points were used in the calculations (500 s sampled at 10 kHz).

Quantity	Numerical	Theoretical
$\langle z \rangle$	-5.34×10^{-5} nm	0 nm
$\langle \hat{z} \rangle$	-2.6×10^{-3} nm	0 nm
$\mathrm{Var}(z)$	129.3 nm^2	129.6 nm^2
$\mathrm{Var}(\hat{z})$	1.289 nm^2	1.296 nm^2
$\mathrm{Cov}(z, \hat{z})$	-0.0039 nm^2	0 nm^2

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use

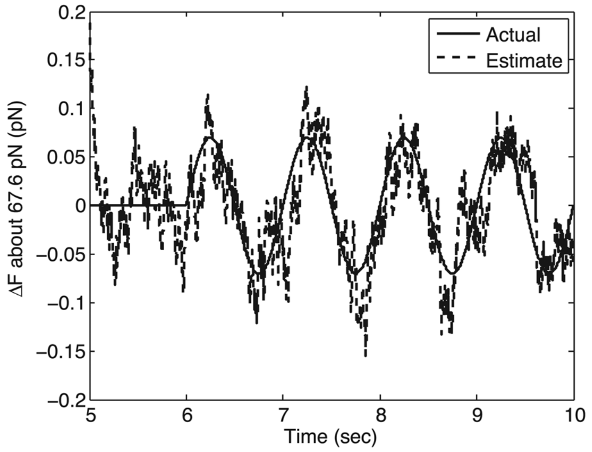

Fig. 6 Shown is the exogenous force and estimated force for a 70 fN variation about the final setpoint of the move-and-settle motion. The SNR for this force estimate is 2 (6 dB).

The effect of closed-loop control is to filter the exogenous force by a high-pass filter with cut-off frequency g_1, the control bandwidth, while the position tracks z_{sp} up to this frequency. Thus, up to the control bandwidth, the exogenous force has little effect on the modal position, which follows the setpoint as required.

7 Simulation

To demonstrate feedback control for single-molecule experiments, we have simulated the response of the system under the action of an exogenous force. A model of the system was constructed in Simulink, and the system equations of motion were solved using solver (ode45) based on an explicit Runge-Kutta (4,5) formula, the Dormand-Prince pair. The sample frequency for the solution was 10 kHz.

To verify the characteristics of the model, an open-loop simulation was done. The mean-squared response was 3.77 pN nm, which compares well with the theoretical value of 4.00 pN nm for an absolute temperature of 290 K; the value depends upon the solver method used. The statistics of the closed-loop response were calculated for the gain values given in Table 1. The closed-loop statistics, shown in Table 2, compare well with theoretical values.

An exogenous force was applied to the bead, and was intended to emulate the force applied to a bead by an attached molecule. We assumed the exogenous force is a function of time and is determined by $f_{ex}(t) = -f_t(z_{sp}(t))$. The setpoint is a move-and-settle motion with a rise segment (at a constant velocity) to a final setpoint. The final setpoint is chosen to be 817 nm ($0.95w_0$); that is, we require the bead to nearly reach the boundaries of the optical trap. The rise lasts for 5 s, making the velocity during the move 163 nm/s. The steady-state optical force at the final setpoint is 67.6 pN.

The strength of optical traps and the nonlinear feedback control of optical traps is that small changes in the exogenous force can be measured in the presence of significant Brownian noise. To demonstrate this, the exogenous force is oscillated with an amplitude of 70 fN about its final setpoint of 67.6 pN. The frequency of this oscillation is 1 Hz. Figure 6 shows the oscillating exogenous force and the estimated force. The achieved SNR is 2 (6 dB).

8 Summary and Conclusions

In an ideal optical trapping system, the measurement of exogenous forces acting on a trapped bead is limited by fluctuations caused by Brownian forces. These Brownian disturbances result in broadband white noise in the measurement, which limits the ability to resolve minute changes in the position of the bead or equivalently small changes in the exogenous force. For open-loop control, this broadband noise can be filtered over a suitably low bandwidth to reveal the signal of interest. However, this open-loop approach does not enable other variables such as molecule elongation or the nominal molecular force to be controlled.

Feedback control provides the benefits of being able to control aspects of the molecule's configuration. Using frequency shaped controllers, like integral control, allows for the closed-loop system to minimize the effects of Brownian fluctuations in frequency ranges of interest. But, in general, nonlinearities in the spatial dependence of the optical force complicate feedback control. In this article, a nonlinear PI control approach has been investigated and has been shown to provide all of the benefits of integral control: disturbance rejection, servo tracking, and force estimation. The nonlinear controller also linearizes the closed-loop system. Finally, it has also been shown to be equivalent to an estimator of the exogenous force.

References

[1] Bustamante, C., Smith, S. B., Liphardt, J., and Smith, D., 2000, "Single-Molecule Studies of DNA Mechanics," Curr. Opin. Struct. Biol., **10**, pp. 279–285.

[2] Michaelis, J., Muschielok, A., Andrecka, J., Kuegel, W., and Moffitt, J. R., 2009, "DNA Based Molecular Motors," Phys. Life. Rev., **6**(4), pp. 250–266.

[3] Svoboda, K., Schmidt, C. K., Schnapp, B. J., and Block, S. M., 1993, "Direct Observation of Kinesin Stepping by Optical Trapping Interferometry," Nature (London), **365**(6448), pp. 721–727.

[4] Svoboda, K., and Block, S. M., 1994, "Biological Applications of Optical Forces," Annu. Rev. Biophys. Biomol. Struct., **23**, pp. 247–285.

[5] Cole, D. G., 2010, "Improving Single-Molecule Experiments With Feedback Control of Optical Traps," J. Dyn. Syst. Meas., Control, Submitted.

[6] Moffitt, J. R., Chemla, Y. R., Izhaky, D., and Bustamante, C., 2006, "Differential Detection of Dual Traps Improves the Spatial Resolution of Optical Tweezers," Proc. Natl. Acad. Sci. U.S.A., **103**(24), pp. 9006–9011.

[7] Gussgard, R., Lindmo, T., and Brevik, I., 1992, "Calculation of Trapping Force in a Strongly Forcused Laser Beam," J. Opt. Soc. Am. B, **9**(10), pp. 1922–1930.

[8] Barton, J. P., Alexander, D. R., and Schaub, S. A., 1989, "Theoretical Determination of Net Radiation Force and Torque for Spherical Particle Illuminated by a Focused Laser Beam," J. Appl. Phys., **66**(10), pp. 4594–4602.

[9] Ren, K. K., Gréha, G., and Gouesbet, G., 1994, "Radiation Pressure Forces Exerted on a Particle Arbitrarily Located in a Gaussian Beam by Using the Generalized Lorenz-Mie Theory, and Associated Resonance Effects," Opt. Commun., **108**, pp. 343–354.

[10] Rohrbach, A., and Stelzer, E. H. K., 2001, "Optical Trapping of Dielectric Particles in Arbitrary Fields," J. Opt. Soc. Am. A, **18**(4), pp. 839–853.

[11] Visscher, K., and Block, S. M., 1998, "Versatile Optical Traps With Feedback Control," Methods Enzymol, **298**, pp. 460–489.

[12] Wright, R. A., Karvaris, C., and Kazantzis, N., 2001, "Model-Based Synthesis of Nonlinear PI and PID Controllers," AIChE J., **47**(8), pp. 1805–1818.

[13] Meditch, J. S., 1969, *Stochastic Optimal Linear Estimation and Control*, McGraw-Hill Book Co, New York.

Downloaded From: https://dynamicsystems.asmedigitalcollection.asme.org on 07/01/2019 Terms of Use: http://www.asme.org/about-asme/terms-of-use