Information Optimal Control for Single Particle Tracking Microscopy

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Abstract

We consider the problem of designing a control policy for a laser scanning microscope (LSM) which will minimize the estimation uncertainty when identifying the state and motion model of a fluorescent biological particle. Using the information optimal design framework we pose an optimization problem which seeks to maximize the Fisher information of the particle’s state. We then apply optimal control methods to determine the laser trajectory that maximizes a criterion based on the Fisher information. The resulting optimal control policy is a Bang-Singular control which moves the laser to the set of measurement locations that maximize the rate of information accumulation. Simulations demonstrate the ability of the resulting control system to position the laser to measure the particles location with a minimum uncertainty.

Keywords

Information Theory; Optimal Control; Optimal Experimental Design; Microscopes; Parameter Estimation; Single Particle Tracking

1. INTRODUCTION

In cellular biology it is important to identify the models describing biomolecular motion to explore mechanisms of transport, assembly, and conformation changes of single molecules and organelles inside the cell. These building blocks are collectively called particles, and they combine into complex networks of processes that underlie cellular behavior and function. Studying these processes at the single particle level allows biophysicists to understand a variety of biological phenomena and to explore heterogeneity of behavior across cells. The class of tools for investigating these systems are collectively referred to as Single Particle Tracking (SPT) microscopes and continues to be incredibly impactful in probing biomolecular and cellular systems as evidenced by their role in, for example, the development of pharmaceuticals (Ruthardt et al., 2011), understanding pathways of viral infection (Brandenburg and Zhuang, 2007), and investigating synaptic function and neuropathological disease (Bannai et al., 2020). These techniques offer nanometer-scale accuracy and precision in inferring the state of a particle and the resulting trajectories can

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be used in identifying biophysical model parameters (Manzo and Garcia-Parajo, 2015; Shen et al., 2017; von Diezmann et al., 2017). While these tools continue to be successful, their development in general has not considered how the design of the microscope system affects the quality of the collected data to identify the state and model parameters. In this paper we consider the problem of designing a control policy for a laser scanning microscope (LSM) that can optimally accumulate information to enable identification with minimal uncertainty, using optimal control methods to determine the trajectory that maximizes a criterion based on the Fisher information.

An SPT experiment uses an optical microscope to observe the motion of a particle over time. The particles of interest are sub-diffraction limit in size and thus not detectable using standard optical microscopy. This is overcome by attaching a fluorescent label (or collection of labels) to the particle of interest; these reporters act as a beacon conveying information about the location and state of the single particle. An SPT microscope, diagrammed in Fig. 1, focuses a laser (blue) into the sample, and then collects and transmits the emitted light (green) to a photodetector which then measures the signal. The detection process can be described as a spatio-temporal random signal, where information about the particle’s state is embedded in noise. By applying an information theoretic framework from estimation theory to this process, one can quantify the amount of information the recorded optical signal carries about the particle’s position (Ram et al., 2006), motion model parameters (Vahid et al., 2020), and conformational dynamics (Watkins and Yang, 2004) through the Fisher information matrix (FIM) (Kay, 2012). In this framework, the detected signal is described as a random process carrying information about an underlying set of parameters to be estimated, θ. The Cramer-Rao lower bound (CRLB), given by the main diagonal elements of the FIM inverse, gives the minimum variance achievable in estimation.

While this framework has been applied as a means of comparing different SPT microscope designs (von Diezmann et al., 2017; Zhou et al., 2019), it has seen limited use beyond this, and optimal information gathering remains relatively unexplored in the SPT domain. There are three exceptions to this. In the first (Ober et al., 2004) the optimal pixel size for a digital camera was found that minimized the CRLB for position estimation when the optical signal had shot noise and the camera added Gaussian distributed read noise. The second (Gallatin and Berglund, 2012) determined the information optimal measurement locations for a laser scanning microscope (LSM) by applying matrix means to the FIM and optimizing over all measurement locations. This gave a set of measurement locations with the highest sensitivities to changes in the particle’s position. Finally, Shechtman et al. (2014) designed an optical phase mask that allows for estimation of a particle’s 3-dimensional position from a 2-dimensional image with the minimum estimation variance in all three axes. They did this by optimizing the design of the phase mask with a cost functional that is the sum of the square root of the CRLBs.

The goal of this paper is to develop a framework that combines the information optimal methods encoded in the FIM and CRLB together with optimal control theory to design SPT methods (Section 2) and to apply this paradigm to the problem of determining the path of an LSM that minimizes the estimation variance for determining the location of a single particle (Section 3). We demonstrate the LSM solution through simulations (Section 4) and conclude
with a discussion of challenges to practical implementation. The two main contributions of this work lie in the concise statement of the information optimal microscope design paradigm and in the solution to the information optimal problem applied to a feedback driven LSM.

2. INFORMATION OPTIMAL DESIGN

In designing information optimal SPT techniques, we follow a five step process of engineering optimal systems: (1) define the goal, (2) translate the goal into an objective function, (3) identify the design variables, (4) solve the resulting constrained optimization problem, and (5) validate the solution (Arora, 2016). For SPT, the specific experimental goals clearly depend on the biological questions being asked. However, the questions of interest can be broadly classified as: (1) where is the particle, (2) what is the model of particle behavior, and (3) when does the model or its parameters change? In each case, the experimental goal can be formulated as an estimation problem with an associated FIM and CRLB. Adding practical constraints encountered in microscope design and actuator dynamics, we arrive at the generic optimization problem,

$$\min_{x, u(\cdot)} \mathbb{E}[\|F(t, r_l, r_p, \theta)\| + L(t, r_l, u)]$$

subj. to $$\dot{r}_l = f(r_l, u), \quad u \in U,$$

$$dr_p = g(t, r_p; \theta) dt + \sigma(t, r_p; \theta) dW,$$

where $F(t, r_l, r_p, \theta)$ is the FIM, $\| \cdot \|$ is a norm capturing the optimality criterion applied to the FIM, $\mathbb{E}$ is the expected value with respect to the distribution induced by the stochastic motion of the particle, $L(t, r_l, u)$ captures auxiliary control objectives, $r_p$ is the state of the particle, $r_l$ is the state of the laser, $u$ is the control inputs to the laser in the set of admissible controls $U$, $W$ is a standard Wiener process, and $\theta$ is an unknown parameter vector. This optimization formulation encodes the wealth of complexity present in this application, however, it is generally non-convex, and challenging to solve. The remainder of the paper considers the simpler and feasible problem of a fixed particle with linear laser scanning dynamics. Also note that the particle state $r_p$ is not known nor directly observed. Details of the measurements depend on the specific experimental setup and are delayed until Section 3 where we consider the specific setting of LSM.

The behavior of the optimal control signal and the resulting system depends, of course, on the choice of the norm that takes the FIM and produces the scalar cost. In this work, we turn to the field of optimal experimental design which uses several different metrics based on the information matrices, each of which has nice properties for optimization (Pukelsheim, 2006). Standard examples are the trace criterion (T-optimal), determinant criterion (D-optimal), average-variance criterion (A-optimal), and the smallest-eigenvalue criterion (E-optimal). Each one prioritizes different aspects of the information matrix resulting in a potentially different solution. T-optimality is the one we pursue here. The reason for this choice is two-fold. First, by maximizing the Fisher information we simultaneously minimize the CRLB allowing us to achieve our aim of minimizing estimation uncertainty. Second, T-optimality is linear and results in a local cost functional in a form where we can apply Euler-Lagrange methods.
3. INFORMATION OPTIMAL LSM

There have been numerous examples of laser scanning microscopes designed for SPT experiments. In these instruments, light from a laser is focused into the sample to excite the fluorescent label. This beam is actuated relative to a global frame and the resulting intensity is captured by a photodetector such as a charge coupled device camera (see Fig. 1). LSM designs for SPT include scanning along a circular pattern (known as an orbital scan) (Enderlein, 2000; Levi and Gratton, 2007), through a fixed measurement constellation such as a cross (Shen and Andersson, 2012; Gwosch et al., 2020), along a knight’s tour (Hou et al., 2017), or guiding the laser using extremum seeking control (Ashley et al., 2016a). In each of these methods a laser is scanned in a way that modulates the emitted fluorescent signal and a feedback controller is used to center the scan pattern on the particle. The motion of the laser, however, is not optimized to maximize the information acquired to determine particle location or identify the motion model parameters. Our goal here is to apply the information optimal design paradigm to this class of microscope.

As described in Section 2, the first step of the design process is to select an experimental goal. In many applications of SPT, the goal is to measure the location of a (fixed) particle over time with the smallest estimation uncertainty. While estimation in three dimensions is possible (see, e.g., (Sage et al., 2019)), the description of the optics and the measurement process becomes significantly more complicated than in the planar setting. For simplicity of exposition, then, here we focus on localizing the particle in two dimensions.

In this setting, the unknown parameter is \( \theta = (x_p, y_p) \) representing the particle location in the \( x \) and \( y \) directions respectively. The FIM for this process, \( F(\theta) \), applied to a laser scanning fluorescent microscope is given by (Gallatin and Berglund, 2012)

\[
F(\theta) = \int_{t_0}^{t_1} \frac{1}{\Lambda} \left( \frac{\partial \Lambda}{\partial \theta} \right)^T d\tau,
\]

(2)

where \( \Lambda \) is the mean photon detection rate and \( T \) represents the transpose operation. The mean photon detection rate for a LSM can be modeled in two dimensions as

\[
\Lambda = \Lambda_0 \exp \left( -\frac{\epsilon_x^2 + \epsilon_y^2}{\omega^2} \right),
\]

(3)

where \( \Lambda_0 \) is the peak detected photon rate and \( \omega \) is the width of the laser, \( r_l = (x_l, y_l)^T \) is the position of the laser, and \( \epsilon = (\epsilon_x, \epsilon_y)^T \) is the relative position between the particle and the laser. By combining (2) and (3) we arrive at the FIM for estimating the position of the particle,

\[
F(\theta) = \frac{16}{\omega^3} \int_{t_0}^{t_1} \Lambda \left[ \begin{array}{cc} \epsilon_x^2 & \epsilon_x \epsilon_y \\ \epsilon_x \epsilon_y & \epsilon_y^2 \end{array} \right] d\tau.
\]

(4)
The next step in this process is to map the FIM to a scalar cost function; as noted in Section 2 we use the trace criterion, though other choices are possible. Finally, we describe the actuation of the laser beam using a simple single integrator model with bounds on the control input representing limits on the actuators. The resulting information optimal design problem is then

$$\min_{u_x(\cdot), u_y(\cdot)} J = -\frac{16}{\omega^4} \int_0^{T_1} \Lambda(\epsilon^2_x + \epsilon^2_y) d\tau$$

subject to

$$\dot{x}_l = u_x, \quad u_x \in [u_x^-, u_x^+]$$

$$\dot{y}_l = u_y, \quad u_y \in [u_y^-, u_y^+]$$

$$r_p(t) = r_p$$

(5)

where $u^x_\pm, u^y_\pm$ are the bounds for the input for the control of the laser and $r_p = (x_p, y_p)^T$ is the position of the particle. In general we assume the control bounds are symmetric about zero with $u^x_\pm = -u^x_{\max}$ and $u^x_\pm = u^x_{\max}$.

This problem then becomes an optimal control problem which can be analyzed using Pontryagin’s Minimum Principle (PMP) (Bryson, 1975). We first apply this to the one dimensional (1D) case (taken to be the $x$-axis) to provide insight into the solution process before considering the 2D problem. In 1-D, the cost function becomes

$$\min_{u_x(\cdot)} J = -\frac{16}{\omega^4} \int_0^{\infty} \Lambda\epsilon^2_x d\tau$$

(6)

The integrand of this function is the first time derivative of the Fisher information. As a result, the laser trajectory that minimizes the cost function maximizes the information accumulation rate. Note that this cost function has neither a terminal cost nor any constraint on the final location of the laser. Below we show that this implies that the optimal control is to steer to a set we refer to as the information optimal set.

Following the PMP, the costate dynamics, $\dot{p}$, of this system can be shown to be given by

$$\dot{p} = \frac{\partial \dot{F}}{\partial x_l} = \frac{32 \epsilon_x A}{\omega^4} \left( \frac{2 \epsilon^2_x}{\omega^2} - 1 \right)$$

(7)

where $\dot{F}$ is the rate of information accumulation. The costate can be interpreted as representing how the system’s capacity to accumulate information changes with changes in laser position. As our cost functional does not depend explicitly on the control input, PMP shows that the optimal control is a bang-singular strategy defined by the sign of the costate,

$$pu^* \leq pu$$

(8)

with the resulting control policy
\[ u^* = \begin{cases} -u_{x}^{\text{max}} & p > 0, \\ 0 & p = 0, \\ u_{x}^{\text{max}} & p < 0. \end{cases} \] (9)

In general, the PMP does not tell us what the optimal control is on the information optimal set. Singular arcs are defined to be those states for which \( p = 0 \), and in this application, the singular arc is synonymous with the information optimal set. In order for the system to reside on a singular arc, we need both \( p \) and all its time derivatives to be zero. We define the information optimal set as those states where the costate stays constant. From (7), this set is given by

\[ \epsilon_x = \pm \frac{\omega}{\sqrt{2}}. \] (10)

Note that in the 1D case, the information optimal set corresponds to two distinct points to the left and right of the particle. Consider now the second time derivative of the costate,

\[ \ddot{p} = \frac{32}{\omega^4}u_x A \left( \frac{8\epsilon_x^4}{\omega^2} - \frac{10\epsilon_x^2}{\omega^2} + 1 \right) = 0. \] (11)

Using (10) in (11) shows that \( u_x = 0 \) on the information optimal set. This allows us to give the complete optimal control law in feedback form as

\[ u^* = u_{x}^{\text{max}} \text{sgn}(\epsilon_x) \text{sgn}(2\epsilon_x^2 - \omega^2) \] (12)

where \( \text{sgn}(\cdot) \) represents the signum function. The optimal control is thus to move as quickly as possible to one of the singular points. Placing the laser at either of these locations achieves the goal of this work, measuring an optical signal that is maximally sensitive to changes in the particle’s position, which also minimizes uncertainty in estimating the particles position. This uncertainty is bounded by the CRLB, given by

\[ \text{CRLB}_{1D} = \frac{\omega^2 e}{8 A_0 t_1} \] (13)

where \( t_1 \) is the time horizon of scanning.

Building on the insights gained through consideration of the 1D problem, we now consider the more practical 2D setting. The solution to this case follows the same steps as the 1D case, however, now we must balance the competing goals of estimating the particles position in the \( x \) and \( y \) directions. The costate dynamics are given by

\[ \ddot{p}_x = \sum_{i=1}^{2} \frac{\partial \tilde{F}_{ii}}{\partial x_i} \frac{32}{\omega^4} \epsilon_x A \left( \frac{2(\epsilon_x^2 + \epsilon_y^2)}{\omega^2} - 1 \right). \] (14)
\[ \dot{y} = \sum_{i=1}^{2} \frac{\partial F}{\partial y_i} = \frac{32}{\omega^3} \mathcal{C}_y A \left( \frac{2(e_x^2 + e_y^2)}{\omega^2} - 1 \right). \]  

(15)

giving a minimum information point at \((\epsilon_x, \epsilon_y) = (0, 0)\), and the information optimal set which is the circle

\[ e_x^2 + e_y^2 = \frac{\omega^2}{2}. \]  

(16)

The optimal control to get to this singular set can be stated in feedback form as

\[ u_x^* = u_{x\max} \text{sgn}(\epsilon_x) \text{sgn}(2(\epsilon_x^2 + \epsilon_y^2) - \omega^2), \]  

(17)

\[ u_y^* = u_{y\max} \text{sgn}(\epsilon_y) \text{sgn}(2(\epsilon_x^2 + \epsilon_y^2) - \omega^2). \]  

(18)

To understand the optimal control on the singular set, we set the second time derivative of the costate to 0,

\[ \ddot{\rho} = -\frac{128}{\omega^6} A \epsilon_x \epsilon_y (\epsilon_x u_x + \epsilon_y u_y) = 0, \]  

(19)

From this, we have the relationship

\[ \epsilon_x \dot{\epsilon}_x + \epsilon_y \dot{\epsilon}_y = 0, \]  

(19)

which needs to be satisfied while on the information optimal set. One solution to this is given by

\[ \epsilon_x(t) = \frac{\omega}{\sqrt{2}} \sin(\phi(t)), \quad \epsilon_y(t) = \frac{\omega}{\sqrt{2}} \cos(\phi(t)), \]  

(20)

where \(\phi\) is an arbitrary function, implying that the optimal scanning strategy is not unique. Further constraints must be imposed in order to uniquely specify an optimal control. Useful constraints to enforce include requiring the FIM to be invertible, enforcing an equal CRLB in \(x\) and \(y\) position estimation, and practical constraints such as scanning the laser at a constant speed. Applying this combination of constraints leads to the control policy

\[ \epsilon_x(t) = \frac{\omega}{\sqrt{2}} \sin \left( \frac{\sqrt{2} v t}{\omega} \right), \]  

(21a)

\[ \epsilon_y(t) = \frac{\omega}{\sqrt{2}} \cos \left( \frac{\sqrt{2} v t}{\omega} \right). \]  

(21b)
where \( v \) is a user-selected velocity of the laser scanning. To equalize the CRLB in \( x \) and \( y \), the velocity should be chosen so that over the time horizon \( t \) the laser scans an integer multiple of a half orbit, leading to the CRLB for localization given by

\[
\text{CRLB}_{2D} = \frac{\omega^2 e}{4A_{0f1}} = \frac{\sqrt{2} \omega v e}{4\pi A_0}.
\]

(22)

4. SIMULATIONS

Simulations in Matlab were performed to demonstrate the information optimal control of LSM. The basic scheme of the simulation control system is shown in the block diagram in Fig. 2. The controller implemented a state machine which switched between the optimal control, given by (12) and (17) for the 1-D and 2-D cases respectively, which drives the laser to the information optimal set, and the optimal control on this set. The optimal control law requires the particle position in order to calculate the optimal control. This is of course not known a priori and while the information is encoded in the measurements, those measurements are simply the intensity time series collected along the laser trajectory. The best way to combine estimation with the control scheme online is a subject of ongoing research. Here, we used a maximum likelihood estimator (MLE) and applied a certainty equivalence-type scheme wherein the controller used the MLE estimate as if it were ground truth. Our MLE used the 10 most recent measurements, and found the global maximum of the log likelihood function through an iterative grid search. The particle position was initialized randomly with a uniform density function from \(-5 \mu m\) to \(5 \mu m\). The laser position was initialized to a random position within \(2\omega\) of the particle’s location. At each time step, the number of photons detected was a realization of a Poisson random process with a mean given by (3). Fig. 3 and Fig. 4 show typical results of applying the information optimal control simulations in 1-D and 2-D respectively. In these simulations, the parameters were set to values that are typical in the biophysical setting. Specifically, we chose: \(A_0 = 100\) photons per millisecond, \(\omega = 1 \mu m\), 1 ms control horizon, a receding measurement horizon of 10 ms, an infinite prediction horizon and \(u_{\text{max}} = 50 \mu m/s\). Each of these simulations exhibit the expected behavior of the optimal control, namely, first proceeding toward the information optimal set and then either staying fixed (relative to the estimation location) in the 1-D setting, or moving around the corresponding circle in the 2-D setting. In Fig. 4d we show the evolution of the CRLB as information is acquired over the trajectory.

While not shown here, we did observe that if the laser was initialized too far from the particle, initial position estimates will be poor potentially causing the laser to fail to converge to the information optimal set. While this is not unexpected as the signal level drops off exponentially as the laser moves away from the particle, a detailed exploration of the limits of this approach are the topic of future work.

5. DISCUSSION AND CONCLUSIONS

Information optimal control is a very promising approach for reducing uncertainty of localization and model identification in SPT. This paradigm offers a general framework
for both improving existing SPT measurement systems and for designing new ones. The results shown for LSM systems provide optimal trajectories that maximize the FIM (thereby minimizing the CRLB) for estimating the particle’s state. The information optimal control for a fixed particle takes on a Bang-Singular form which results in a seek and orbit scanning strategy for an arbitrary initial state of the particle and laser. Interestingly, many of the early SPT systems implemented an orbital scanning strategy. The performance of these systems were very good for slowly diffusing particles, but became very poor as the rate of diffusion increased. Once the particle’s motion becomes too fast, the orbital strategy was unable to track the particles. Alternative policies, such as following a Knight’s tour over a fixed area in general perform better than orbital methods for tracking a fast diffusing particle; determining the information optimal strategy under this setting is a subject of ongoing work.

While the paradigm we introduce in this work is powerful, it does have limitations. Perhaps chief among these is that it relies on being able to obtain an expression for the FIM. Depending on the experimental aim, a closed-form expression for the FIM that is amenable to direct mathematical analysis may not be available. This is particularly true when there are multiple non-Gaussian noise sources present. When simplifying assumptions are made, it is important to understand the limitations of the subsequent analysis for real-world application. For example, the form of the FIM in this paper neglected both background light and detector noise sources, limiting our results to the high signal-to-noise setting.

A second difficulty is the fact that the FIM depends on the true location of the particle. This is, of course unknown, and an online estimator is needed. However, in general the likelihood function exhibits local maxima. For example, LSM in the 1D case, the symmetry of the situation leads to a likelihood function with two global maxima equidistant from the laser’s current location. Symmetry in the 2D case leads to an entire circle of maxima centered on the laser’s location. This symmetry is broken through motion of the laser but may cause issues with the controller structure described here. In addition, MLE estimation is often solved numerically and can be computationally expensive. For example, the present work relies on a grid search while prior results of one of the authors uses the expectation maximization algorithm, coupled with sequential Monte Carlo methods to handle the nonlinearities (Ashley and Andersson, 2015; Lin and Andersson, 2019). However, the time scale of the motion of the laser, especially to track a moving particle, can easily be on the sub-millisecond time scale. One of the authors overcame these issues through an extremum-seeking controller (Ashley et al., 2016b) that exhibits a seek and orbit character. That approach could be linked to the present results by setting the parameters of the controller such that the orbit has a radius that matches that of the information optimal set, providing near-optimal results without the need for an online estimator.

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Fig. 1.
Illustration of a single particle tracking microscope tracking a virus particle.
Fig. 2.
Implemented control system
Fig. 3.  
1-D simulation. (a) (blue) Path of the laser, (black) true particle location, and (cyan) estimated location over the duration of the simulation run. (b) Measured intensity during the run. Note the fluctuations in signal due to the shot noise process.
Fig. 4.
2-D simulation. (a) (blue) Path of the laser, (black line) true information optimal set, and (black diamond) position of the particle. (b) Measured intensity during the run. (c) $X$ trajectory of the (blue) laser, (cyan) estimate, and (black) particle. (d) CRLB of the (black) $X$ estimate and (blue) $Y$ estimate.