An optimal control approach to cell tracking

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Abstract: Cell tracking is of vital importance in many biological studies, hence robust cell tracking algorithms are needed for inference of dynamic features from (static) *in vivo* and *in vitro* experimental imaging data of cells migrating. In recent years much attention has been focused on the modelling of cell motility from physical principles and the development of state-of-the art numerical methods for the simulation of the model equations. Despite this, the vast majority of cell tracking algorithms proposed to date focus solely on the imaging data itself and do not attempt to incorporate any physical knowledge on cell migration into the tracking procedure. In this study, we present a mathematical approach for cell tracking, in which we formulate the cell tracking problem as an inverse problem for fitting a mathematical model for cell motility to experimental imaging data. The novelty of this approach is that the physics underlying the model for cell migration is encoded in the tracking algorithm. To illustrate this we focus on an example of Zebrafish (*Danio rerio's larvae*) Neutrophil migration and contrast an ad-hoc approach to cell tracking based on interpolation with the model fitting approach we propose in this study.

Keywords: cell tracking, optimal control of PDEs, chemotaxis, cell motility

1 Introduction

Cell migration is a fundamental process in cell biology and is tightly linked to many important physiological and pathological events such as the immune response, wound healing, tissue differentiation, metastasis, embryogenesis, inflammation and tumour invasion [2]. Advances in experimental techniques means that we now have access to both *in vivo* and *in vitro* imaging data of migrating cells. Cell tracking is concerned with the development of methods to track and analyse dynamic cell shape changes from static imaging data (see for example [10] for a review), with level set or electrostatic based methods among the most widely used. One feature of the aforementioned methods is that the trajectories they generate are not physical in nature rather they are designed with the goal of achieving nice geometric properties, e.g., equidistribution of vertices, smoothness of the trajectories, etc. On the other hand a major focus of current research is the derivation of mathematical models for cell migration based physical principles, e.g., [4]. Furthermore, such models appear to show good qualitative and quantitative agreement with experimental observations of migrating cells. Recently we investigated fitting parameters in such models to experimental imaging data of migrating cells where observations of both the position of the cells and the concentrations of cell-resident proteins related to motility were available [3].

In this study we focus on the setting, more prevalent in cell tracking problems, where only the position of the cell, specifically the cell membrane, at a series of discrete times is available and no further biological information

is given. To this end, we derive a mathematical model based on physical principles for cell migration and then formulate an inverse problem, which takes the form of a PDE constrained optimisation problem, for fitting the model to the experimental observations. To solve the optimisation problem we propose an algorithm based on previous studies on the optimal control of geometric evolution laws [5]. Finally, we apply the algorithm to some experimental data on the migration of neutrophils and contrast the results of our approach with a simple cell tracking algorithm based on interpolation.

Due to space constraints we eschew technical details in the subsequent discussion focussing on the general idea of our approach and contrasting it with a more standard cell tracking approach in a biological application of *in vivo* migration. For further details on the methodology see [1].

2 An optimal control approach to cell tracking

In this section we present a numerical method for cell tracking based on optimal control theory. Our method is inspired by the work of Haußer et al. [5], who use an optimal control approach to control the shape evolution of nanoscale islands with electric fields.

As previously stated our approach seeks to fit a mathematical model to experimental data. The model we consider describes the movement of the cell by proposing an evolution law for the motion of the cell membrane which we denote by $\Gamma_t, t \in [0,T]$, where $\Gamma_t \subset \mathbb{R}^n, n = 2,3$ is assumed to be a closed $n-1$ dimensional hypersurface. Given an initial surface Γ_0 our model for the evolution law takes the form of mean curvature with forcing

$$\vec{v}(\vec{x},t) = -\sigma H(\vec{x},t) + \eta(\vec{x},t) + \lambda(t) \quad \vec{x} \in \Gamma_t, t \in (0,T], \tag{1}$$

where $\vec{v}$ is the normal velocity, H is the sum of the principle curvatures, λ is a spatially uniform forcing term enforcing volume conservation and the forcing function η drives the movement of the cell. Such models may be derived by assuming a force balance on the cell membrane where the various force contributions accounted for are the resistance of the cell membrane to stretching, a hydrostatic pressure that conserves the enclosed volume, a viscous force opposing the motion and protrusive and retractive forces arising due to actin polymerisation or myosin mediated contraction (for further information on the derivation of the model and the inclusion of other forces see [4]).

We now assume we are given some experimental observations of the position of the cell membrane $\{\hat{\Gamma}_i\}_{i=0,\ldots,N}$ where $N > 0$. The idea of the cell tracking algorithm we propose in this study is to find a forcing function function η such that the solution to the model equations is close (c.f., (3)) to the experimental data. The initial data for the model is given by the initial experimental observation i.e., $\Gamma_0 := \hat{\Gamma}_0$. We approximate the geometric evolution equation with a phase field model (conserved Allen-Cahn with forcing) of the form

$$\varepsilon \partial_t \varphi(\vec{x},t) = \varepsilon \Delta \varphi(\vec{x},t) - \frac{1}{\varepsilon} G'(\varphi(\vec{x},t)) + c_w(\eta(\vec{x},t) + \lambda(t)), \tag{2}$$

for the phase field function φ of the curve with initial condition $\varphi(\vec{x},t) = \varphi_0(\vec{x})$ and zero flux boundary conditions on a rectangular domain Ω in $\mathbb{R}^2$. We take $G(\varphi) = \frac{1}{4}(\varphi^2 - 1)^2$ a double well potential, ε a small length parameter of the interfacial thickness and c_w a scaling constant dependent on the double well potential. We also approximate the sharp interface observations of the experimental data ($\hat{\Gamma}_i$'s) with diffuse interfaces defined on the same domain Ω and using the same value of ε (see [3] for details).

As in [5] we formulate the problem of fitting to the experimental data as the following minimisation problem: given an initial phase field function $\varphi(\vec{x},0)$ at time $t = 0$, and a desired final phase field $\varphi_{des}(\vec{x},T)$, find a suitable control function $\eta(\vec{x},t) : \Omega \times [0,T] \to \mathbb{R}^2$ which minimises:

$$J(\varphi(\vec{x},t), \eta(\vec{x},t)) = \frac{1}{2}\int_\Omega (\varphi(\vec{x},T) - \varphi_{des}(\vec{x}))^2 \, d\vec{x} + \frac{\gamma}{2}\int_0^T \int_\Omega \eta^2(\vec{x},t) d\vec{x} dt \tag{3}$$

subject to the constraints given by (2), where γ is a positive regularisation parameter. For simplicity we have assumed $N = 1$, i.e., we are attempting to fit to a single observation using a previous observation as data. $\phi(\vec{x},0)$ and $\phi(\vec{x},T)$ are the diffuse interface representations of the initial and final data respectively. We adopt an optimal control approach for the solution of the minimisation problem, formally deriving the first order necessary conditions and employing a simple gradient update scheme for the control. To solve the forward equation (2) and the adjoint equation (for efficient computation of the gradient) we employ a finite element method.

3 Application to experimental data

To contrast the cell tracking approach proposed above with a more standard algorithm, we apply the optimal control based algorithm to the problem of tracking *in vivo* migration of neutrophils in zebrafish larvae and compare it with an approach based on interpolation. Neutrophil migration as observed in zebrafish larvae is a popular model to study the cellular inflammatory response mainly due to the transparent nature of the zebrafish in the developmental stage and the capacity to reproduce *in vivo* conditions of inflammation similar to those in humans [9].

Experimental Setup

In the interests of space we only briefly state the details of the experimental setup. For the experimental methodology and that used to generate and segment the imaging data we refer to [6]. Zebrafish were maintained according to standard protocols, tail-fin transection was performed at 3 days post fertilisation, then mounted on melting point agarose, and images were captured using an UltraVIEWVoX spinning disk confocal microscope (PerkinElmer Life and Analytical Sciences) as previously described [9]. The biological data sets were acquired from transgenic Tg(mpx:eGFP)i114 zebrafish larvae in which neutrophils specifically express Green Fluorescent Protein (GFP). We selected eight observations of the migration of a single neutrophil as shown in Figure 1(a). The observations were obtained in MATLAB format from the open-source software PhagoSight [8]

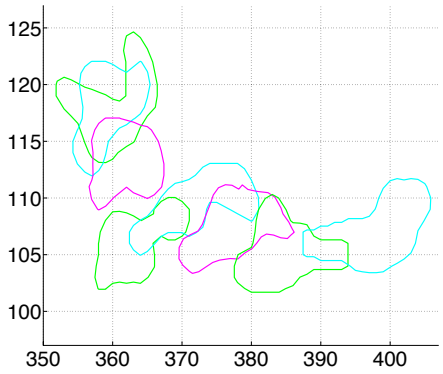
The biological data sets were acquired from transgenic Tg(mpx:eGFP)i114 zebrafish larvae in which neutrophils specifically express Green Fluorescent Protein (GFP). We selected eight observations of the migration of a single neutrophil as shown in Figure 1(a). The orientation is such that tail-fin (which is the direction of expected migration) is to the right of the neutrophils.

A simple interpolation based approach to cell tracking

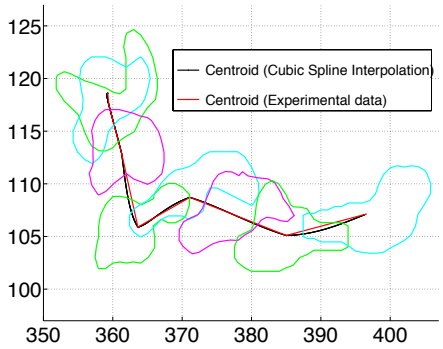
To contrast the optimal control approach with a cell tracking method that is purely geometric in nature (i.e., the trajectories are non-physical) we implemented a simple algorithm for cell tracking based on cubic spline interpolation. Here, following Madzvamuse et al. [7], given experimental observations of the cell membrane we use cubic splines to generate a series of intermediate cell-surface boundaries with the interpolation chosen such that the point trajectories are smooth (C^2). To do this given two successive observations of the cell membrane (that consist of a series of points on the cell membrane) we first manually select a single point on the first surface to be mapped to a specific point on the second surface which uniquely determines the entire mapping of every point as it is assumed the mapping preserves the connectivity (topology).

Results

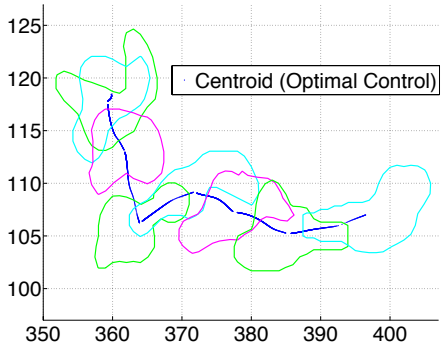
In Figure 1 we report on the results of the two tracking algorithms applied to the experimental data. We see that the cubic spline interpolation algorithm (as expected) and the optimal control based algorithm both generate centroid trajectories that are significantly smoother than those obtained by linear interpolation of the cell centroids alone. The usual measures of chemotaxis persistence length, chemotactic indices, maximum velocities etc. have been computed and exhibit significant variation using the different approaches but are not reported on due to space constraints. For this example the area of the cell is not conserved in the experimental data therefore we take the linear interpolant of the area of the experimental data to be the target area and determine the λ term in (2) such that it (weakly) penalises deviations from this target area (see [3] for details). In Figure 1(d) we clearly observe good agreement between the target area (green line) and the area of the cell using the optimal control approach while the area of the cell using the cubic spline interpolation approach is significantly smaller than the area of the cell away from the end points of the interval. In Figure 1(e) we plot one example of the optimal control based approach fitting between the fourth and fifth (from the left) snapshot of Figure 1(a). We observe good agreement between the final position with the computed optimal control and the experimental data we also above strong contractile forces in the rear of the cell away from the chemoattractant and strong protrusive forces in the front of the cell that points towards the chemoattractant (the chemoattractant concentration is expected to increase from left to right).



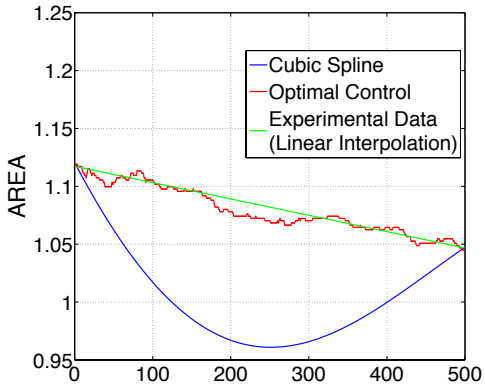
(a) 2*d* experimental data of migrating zebrafish neutrophils *in vivo*



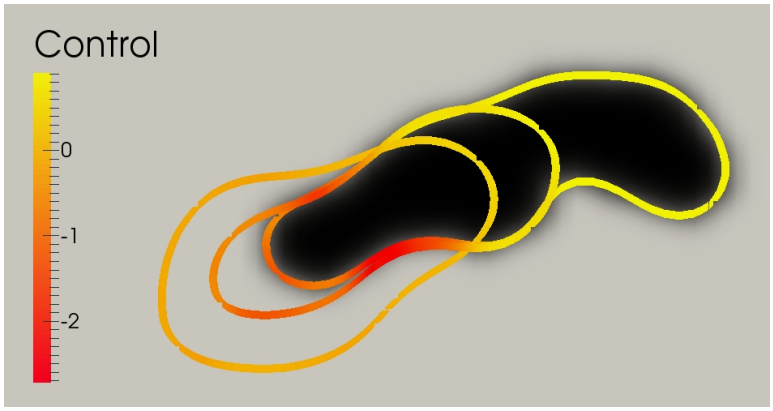
(b) Centroid trajectories, linear interpolation and cubic spline interpolation



(c) Centroid trajectories, optimal control based tracking



(d) Enclosed area



(e) The zero level set of the phase field function shaded by the value of the control is shown at $t = 0, T/2$ and T the background indicates the diffuse interface representation of of the experimental data at $t = T$ (i.e., the desired shape).

Figure 1. *(a) Experimental data. (b)-(c) Experimental data and centroids computed with the different cell tracking algorithms. (d) area of the cell, the green line indicates the linear interpolant of the area of the observations, the blue line the area using cubic spline interpolation and the red line the area using the optimal control approach. (e) An example of intermediate morphologies obtained with the optimal control algorithm.*

4 Conclusion

In recent years, the rapid development in microscopy and imaging techniques has generated a huge amount of data on migrating cells *in vivo* and *in vitro*. A key challenge is to study from discrete observed snapshots, quantities of interest, such as trajectories of material points on the membrane, velocities and geometric quantities [3]. In this study we have proposed an alternative to the purely geometric widely used cell tracking approaches for the estimation of such quantities in which the estimated trajectories correspond to those generated by a physical model for the evolution and thus may be more physically meaningful than those obtained previously.

While this proof of concept application to experimental data focused on 2-dimensional observations each of the algorithms is immediately applicable to 3-dimensional data sets. Moreover while we specifically focussed on the case where minimal information regarding the biology is available, in theory our approach is applicable to models where more biology is included. In particular models for the dynamics of actin and myosin as well as other motility related species within the cell and on the membrane may be included and the evolution law may be modified to take into account the dependence of the movement of the cell on these species, see for example [4]. We also believe the optimal control/inverse problem approach we present in this study could be a useful framework within which to investigate other biological questions beyond cell tracking such as the inference of chemotactic fields during *in vivo* chemotaxis [6]. Finally we remark that data on the morphology, curvature, normal velocity, etc., may be easily extracted using the optimal control based approach which may be useful in applications.

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