**FORWARD-BACKWARD SPLITTING IN DEFORMABLE IMAGE REGISTRATION: A DEMONS APPROACH**


¹Wellcome / EPSRC Centre for Interventional and Surgical Sciences, UCL, London, UK  
²Translational Imaging Group, CMIC, University College London (UCL), London, UK

**ABSTRACT**

Efficient non-linear image registration implementations are key for many biomedical imaging applications. By using the classical demons approach, the associated optimization problem is solved by an alternate optimization scheme consisting of a gradient descent step followed by Gaussian smoothing. Despite being simple and powerful, the solution of the underly ring relaxed formulation is not guaranteed to minimize the original global energy. Implicitly, however, this second step can be recast as the proximal map of the regularizer. This interpretation introduces a parallel to the more general forward gradient descent and proximal step. By shifting entirely to FBS, we can take advantage of the recent advances in FBS methods and solve the original, non-relaxed deformable registration problem for any type of differentiable similarity measure and convex regularization associated with a tractable proximal operator. Additionally, global convergence to a critical point is guaranteed under weak restrictions. For the first time in the context of image registration, we show that Tikhonov regularization breaks down to the simple use of B-Spline filtering in the proximal step. We demonstrate the versatility of FBS by encoding spatial transformation as displacement fields or free-form B-Spline deformations. We use state-of-the-art FBS solvers and compare their performance against the classical demons, the recently proposed inertial demons and the conjugate gradient optimizer. Numerical experiments performed on both synthetic and clinical data show the advantage of FBS in image registration in terms of both convergence and accuracy.

**1. INTRODUCTION**

Efficient non-linear image registration implementations are essential in the fields of medical and biomedical imaging to allow for both timely and accurate modern image analysis. In its general formulation, image registration aims at finding a (non-linear) registration transform $T$ which best aligns a fixed with a moving image, denoted by $F$ and $M$, respectively. This is typically framed as the optimization of a global energy

$$ E(T) := \text{Sim}(F, M \circ T) + \text{Reg}(T) $$

consisting of a similarity measure Sim and an additional regularization term Reg to better constrain the otherwise ill-posed problem. Given the difficulty of solving the (in most applications of interest) non-convex problem (1) directly, in the demons algorithm, the relaxed formulation,

$$ \tilde{E}(S, T) := \text{Sim}(F, M \circ S) + \lambda \|S - T\|^2 + \text{Reg}(T) $$

with $\lambda > 0$, is optimized instead by solving iteratively for the spatial transformations $S$ and $T$ [1, 2, 3]. In the first step of this demons approach, $T$ is being fixed and the optimization of Sim($F, M \circ S$) + $\lambda \|S - T\|^2$ with respect to $S$ is approximated by a gradient descent step. Then, the updated $S$ is fixed and the optimization of $\lambda \|S - T\|^2 + \text{Reg}(T)$ with respect to $T$ is performed with a simple Gaussian filter applied to $S$. Both steps are then repeated until convergence. Despite its simplicity, it has been shown to be a very powerful approach in practice. Much work has been invested to further extend the demons approach. For instance, in [3] the incorporation of diffeomorphic transformations was suggested to enforce preservation of topology and, more recently, it was suggested to incorporate an additional inertial term to improve overall convergence speed and accuracy [1]. The diffusion-like Gaussian regularization was extended to bilateral filtering to allow for deformation discontinuities in [4] and a duality-based Total Variation (TV) approach for optical flow was proposed in [5] to solve a convex approximation of form (2). Thus, a wide range of algorithms typically solve a relaxed formulation which is not guaranteed to obtain an optimal solution of the original formulation (1). In contrast, gradient descent and conjugate gradient methods have been applied to directly solve the original problem (1) for a variety of cost functions and regularizers, e.g. [6]. However, some form of relaxation is typically employed in case the regularizing term is non-differentiable as in the setting of TV regularization.

In this paper, we want to highlight a numerical framework which indeed is able to solve the deformable registration problem (1) in its original form. As an active field of research, Forward-Backward Splitting (FBS) methods have been developed to solve convex and, more recently, non-convex problems of the form

$$ \min_{u \in \mathbb{R}^N} (f(u) + g(u)) $$

where $f(u)$ is a non-convex function.
2.1. Forward-Backward Splitting Methods

In case the associated proximal operator of $g$, i.e.,

$$
\text{prox}_g(u, \tau) := \arg\min_{v \in \mathbb{R}^N} \left( \|u - v\|^2 + 2\tau g(v) \right),
$$

(4)

with $\tau > 0$ is easy to compute, FBS methods break down the iterative solution of (3) into two simple, iterative steps: a forward gradient descent step on $f$ and a so-called proximal, backward gradient descent step. Their advantage, however, lies in their sound mathematical basis, proof of algorithmic convergence to a critical point, simplicity to use and their richness of possible functions $f$ and $g$.

In this work, (i) we propose using a guaranteed-to-converge FBS framework to solve directly for non-linear registration problems of the form (1); (ii) we demonstrate their advantage to efficiently implement various kinds of regularizers vital for medical image registration; (iii) we specifically illustrate that Tikhonov regularization breaks down to simple B-Spline filtering in the proximal step; (iv) we showcase both the fast iterative shrinkage/thresholding algorithm (FISTA) [7] and the recently proposed inertial proximal algorithm for non-convex optimization (iPiano) [8] as FBS instances; (v) we illustrate the versatility of FBS by relying on a combination of displacement fields, free-form B-Spline transformation, sum of squared differences (SSD) and normalized mutual information (NMI) in conjunction with second-order Tikhonov regularization; and (vi) we evaluate the performance of both FISTA and iPiano against the classical demons, the recently proposed inertial demons [1] and the conjugate gradient method within NIFTYREG [6].

2. FORWARD-BACKWARD SPLITTING FOR IMAGE REGISTRATION

2.2. Forward Step in Image Registration

Given a differentiable (possibly non-convex) function $f$ and a convex (possibly non-differentiable) function $g$, problems of the form (3) can efficiently be solved by FBS methods in cases where the proximal operator (4) of $g$ can be evaluated easily. In case of a convex $f$, the basic FBS algorithm guarantees the convergence of $u_k$ to a critical point $\tilde{u}$ of (3) for $k \to \infty$ for an appropriate step size $0 < \tau_k < 2/L(\nabla f)$, which depends on the Lipschitz constant of the gradient on $f$ only [7, 8]. The recently proposed FBS-variant called “inertial proximal algorithm for non-convex optimization” (iPiano) extends this statement even to non-convex functions $f$ [8]. In practice, however, it can be very challenging to estimate the Lipschitz constant $L(\nabla f)$ beforehand. By using backtracking, the Lipschitz constant and, hence, the step sizes $\tau_k$ can be estimated automatically. Several variants of FBS have been proposed to speed up the convergence of potentially slow FBS. For the numerical experiments we will use both FISTA [9] and iPiano [8] with their basic iterations shown in Algs. 1 and 2, respectively.

Algorithm 1: FISTA algorithm [9]

\[
\begin{align*}
\tilde{v}_{k+1} &:= u_k - \tau_k \nabla f(u_k) \quad \text{(Forward step)} \\
v_{k+1} &:= \text{prox}_g(\tilde{v}_{k+1}, \tau_k) \quad \text{(Proximal step)} \\
\alpha_{k+1} &:= (1 + \sqrt{1 + 4\alpha_k^2})/2 \quad \text{(Acceleration parameter)} \\
\xi_{k+1} &:= \nabla f(u_k) + \alpha_{k+1} (v_{k+1} - v_k) \quad \text{(Prediction step)}
\end{align*}
\]

Algorithm 2: Generic iPiano algorithm [8]

\[
\begin{align*}
u_{k+1} &:= u_k - \tau_k \nabla f(u_k) + \beta (u_k - u_{k-1}) \quad \text{(Forward step with inertia)} \\
u_{k+1} &:= \text{prox}_g(u_{k+1}, \tau_k) \quad \text{(Proximal step)}
\end{align*}
\]

FISTA is based on a predefined sequence of acceleration parameters and is characterized by its lack of tuning parameter in addition to its good worst-case performance. The correct step size can be estimated even without knowing the Lipschitz constant by using backtracking line search. Using non-monotone backtracking has the advantage of not discarding iterates with a higher objective value which might still be closer to the minimizer. This is especially useful in case of poorly conditioned problems and alleviates the computational burden since non-monotone line search conditions are less likely to be violated. Generally, FISTA also performs well on non-convex problems although global convergence is not guaranteed. Building on FISTA, the recent iPiano algorithm has been specifically designed for non-convex problems. Its rigorous mathematical analysis ensures favorable properties and guarantees global convergence also for non-convex $f$ under very weak restrictions. As opposed to FISTA, additional tuning parameters are required. This includes the inertial weight $\beta \in [0, 1)$ and the parameters $\eta, \epsilon > 1$ which adaptively tune the step size $\tau_k$ during run time to achieve fast convergence.

In the context of (non-linear) image registration (1) the framework of FBS is ideal for dealing with a wide range of composite objective functions. Here, $f$ will typically correspond to the (differentiable) similarity measure $\text{Sim}$ and $g$ to the (convex) regularizer $\text{Reg}$.

2.2. Forward Step in Image Registration

To illustrate the use of forward step in FBS, we focus on SSD as the similarity measure and displacement fields as the spatial transformation model. Nonetheless, we highlight and
demonstrate in Section 3 that FBS allows for both parametric, e.g. free-form B-Spline, and non-parametric spatial transformations. The forward step is based on the gradient of \( f(u) = \text{Sim}(u) = \text{SSD}(u) = \frac{1}{2}\|F - M \circ u\|^2 \) with vector field \( u \). Explicitly written, this reads
\[
\nabla_u f(u(x)) = (M \circ u(x) - F(x)) J_{u(x)}(x)
\]
(5) with \( J_{u(x)} = \nabla_u M(u(x)) \) or \( J_{u(x)} = \frac{1}{2} \left( \nabla_u M(u(x)) + \nabla F(x) \right) \) in case symmetric forces are applied at a point \( x \) [3]. Moreover, any other differentiable, parametric or non-parametric spatial transform can be incorporated without restriction. This includes the exponential map vital for image registration on the Lie algebra of diffeomorphisms [10, 11, 3].

2.3. Proximal Step in Image Registration

An explicit or easy-to-solve proximal map \( \text{prox}_g \) is critical for the efficient computation of the proximal step in FBS. We discuss important examples for image registration.

It is well known that Gaussian blurring \( G_\sigma \) with standard deviation \( \sigma > 0 \) used in the demons algorithm corresponds to applying diffusion-like regularization. Based on the relationship between Gaussian smoothing and solving the heat equation established in [12] we infer the closed-form solution for the proximal operator for diffusion-like regularization, i.e.
\[
G_\sigma \ast u = \arg\min_v \left( \|u - v\|^2 + \sum_{i,j=1}^{\infty} \frac{\sigma_{2k}^2}{2\kappa^2} \left\| \frac{\partial^k}{\partial x_i^k} v_j \right\|^2 \right)
\]
(6) with \( g_\sigma^k(v) = \frac{1}{2\pi} \sum_{i,j=1}^{D} \sum_{k=1}^{\infty} \frac{\sigma_{2k}^2}{2\kappa^2} \left\| \frac{\partial^k}{\partial x_i^k} v_j \right\|^2 \) whereby \( v = (v_{ij})_{i,j=1}^{D} : \mathbb{R}^D \to \mathbb{R}^D \) and \( D \) denoting the dimension of space. Hence, Gaussian filtering corresponds to using the function \( g_\sigma^k \) as regularizer and using a step size \( \tau_k = \tau \) for its proximal operator. With a view to FBS where the same step size is used for both the forward and proximal step, this means that adjusting the step size \( \tau_k \) at FBS iterations implicitly corresponds to an adaptive scaling of the objective function according to \( f + g_\sigma^k = f + \frac{1}{\sigma} g_\sigma^k \) in (3). However, proofs of convergence are based on a fixed \( g \) and, hence, the strong mathematical statement of guaranteed algorithmic convergence of FBS to a critical point would be lost. Note that (6) corresponds to the second step in the classical demons approach too.

Another class of important closed-form proximal maps are related to the application of Tikhonov regularization. Based on the insights in [13], we explicitly state the proximal operator for \( r \)-th order Tikhonov regularization, i.e. \( g_\lambda^r(v) = \frac{1}{2} \sum_{i,j=1}^{D} \left\| \frac{\partial^r}{\partial x_i^k} v_j \right\|^2 \) with regularization parameter \( \lambda > 0 \), as
\[
B_{2r-1,\tau\lambda}(v) = \arg\min_v \left( \|u - v\|^2 + \tau\lambda \sum_{i,j=1}^{D} \left\| \frac{\partial^r}{\partial x_i^k} v_j \right\|^2 \right)
\]
(7) whereby \( B_{2r-1,\tau\lambda} \) denotes the B-Spline smoothing filter of order \( 2r - 1 \) and smoothing parameter \( \tau\lambda \). Varying step sizes \( \tau_k \) for adaptive FBS schemes can easily be incorporated by scaling the smoothing parameter for the filtering without changing the original objective function, in contrast to Gaussian smoothing. Importantly, second-order Tikhonov regularization represents a cubic spline smoothing for the proximal step which can be efficiently implemented using \( 15D \) operations per voxel by recursive infinite impulse response (IIR) filters [13].

Moreover, more complicated regularizers can easily be wrapped into the FBS framework. For example, isotropic TV regularization leads to a proximal step of
\[
\text{prox}_g(u, \tau_k) = \arg\min_v \left( \|u - v\|^2 + 2\tau_k \lambda TV_{iso}(v) \right)
\]
(8) which corresponds to a TV denoising step. By using its dual formulation, isotropic TV regularization can be solved via a nested FBS scheme in which a FBS is applied also for the minimization in the proximal step (8) [7].

3. EXPERIMENTS

3.1. Circle to C

\begin{center}
\textbf{Fig. 1.} Convergence comparison of solvers for the non-linear registration of the classical "Circle to C" with markers indicating every 500 iterations.
\end{center}

To examine the ability for the proposed FBS framework to perform large deformations, we chose the classical "Circle to C" experiment. We compare both FISTA and iPiano against the additive demons and the recently proposed inertial demons [1]. Based on the similarity measure \( \text{SSD}(u) = \frac{1}{2}\|F - M \circ u\|^2 = f(u) \), we parameterized the inertial demons as proposed in [1] and implemented the Efficient Second-order Minimization (ESM) [3] based gradient in (5), set the inertial weight \( \alpha = 0.9 \) and the maximal step to 0.5 voxels for the demons algorithms. The corresponding Gaussian smoothing was performed using \( \sigma = 1 \). FISTA and iPiano were implemented as outlined in [7, Alg. 3] and [8, Alg. 4], respectively, whereby second-order Tikhonov (TK2) regularization was applied using cubic B-Spline filtering for the proximal step. The TK2-regularization parameter \( \lambda = 0.5 \) was set.
based on the relationship $\sigma^2 = \sqrt{2\lambda}$ to the Gaussian standard deviation $\sigma$ established experimentally in [14]. The step size parameter $\tau_0$ was arbitrarily initialized as in [7] by ensuring a value higher than $2/L(\nabla f)$ from where backtracking line search took care of finding the adequate step size for the FBS variants. For iPiano the inertial weight $\beta$ was set to 0.95 in conjunction with $c = 1.05$ and $\eta = 1.2$ to adaptively tune the step size parameter during runtime. The identity deformation was provided as the initial value for all solvers.

Fig. 1 shows that both FISTA and iPiano outperform the demons and inertial demons algorithm in terms of computational speed and numerical accuracy converging about four times faster than their demons counterparts. The oscillations of FISTA at the beginning can be attributed to the non-monotone backtracking line search to ensure that iterates with higher objective values, but possibly closer to the minimizer, are not discarded.

### 3.2. 3D Anatomical MRI

![Fig. 2. 3D-Comparison of FISTA and iPiano against the conjugate gradient (CG) solver based on overall 1180 registrations. The Dice scores represent the mean of all propagated labels for each registration. All FBS results, apart from NMI, are statistically significantly better ($p < 10^{-6}$) than the CG ones based on the Wilcoxon signed rank test.](image-url)

In the 3D experiment, we assessed the proposed FBS framework by registering 35 T1-weighted brain MRIs as provided by Neuromorphometrics for the MICCAI 2012 Grand Challenge on label fusion and propagated their respective parcellations holding 143 labels. Each brain was registered to the remaining 34 brains in either direction summing up to overall 1190 registrations for each method. In order to evaluate the performance of the actual numerical solvers in this task, we embedded both FISTA and iPiano as additional optimizers into the NIFTYREG registration framework [6] which is based on a cubic B-Spline parameterization. As similarity measure, we chose normalized mutual information. Including a TK2-regularization term in the objective function, the conjugate gradient (CG) solver could be applied to the overall cost function (1). This could then directly be compared against the performance of both FISTA and iPiano using cubic B-Spline filtering for the proximal operator. For the regularization parameter $\lambda$ we chose 0.05. The step size for both FBS solvers was fixed and set experimentally to avoid its possible re-computation during the backtracking at each iteration and $\beta$ was set to 0.95 for iPiano. The registration was performed within a multi-resolution framework with 2 levels. The FBS solvers ran for the total amount of 500 iterations whereas the CG solver was terminated earlier in case the stopping condition was met as implemented in NIFTYREG.

Fig. 2 summarizes the corresponding registration results. Both FBS solvers reached statistically significantly better figures for overall similarity (NMI $- \lambda$TK2), smoothness (TK2), and Dice scores. However, 68 values were detected as outliers with higher values in the TK2 term for iPiano. Further analysis needs to be done but, presumably, this can be attributed to a possibly too high inertial weight $\beta$ used in the experiment.

### 4. DISCUSSION

In this paper, we present and demonstrate the capability of Forward-Backward Splitting schemes to be efficiently used in the challenging problem of deformable image registration. The advantage of FBS lies in their general framework to solve for arbitrary differentiable similarity measures in conjunction with any kind of convex regularizer associated with an easy-to-compute proximal operator. In addition, the use of FBS comes with a proven algorithmic convergence to a critical value of the original problem (1). We provide explicit forward and proximal steps for several similarity and regularization terms of benefit for (medical) image registration thereby allowing for efficient solutions via FBS. Additionally, and for the first time, we show the possibility to incorporate Tikhonov regularization in image registration by the mere application of B-Spline filtering in the proximal step which can be efficiently implemented by recursive IIR filters. We showcase two important instances of FBS solvers, FISTA and iPiano, and obtain statistically significantly better results in our numerical experiments than those obtained by the conjugate gradient method in NIFTYREG. Overall, we recommend the use of FBS methods to efficiently solve deformable registration problems due to their favorable theoretical properties, simplicity to use and general applicability to a wide range of similarity measures and regularizers. Future work could include the investigation of obtained deformation fields using FBS and a comparison with Quasi-Newton optimization methods.

### 5. ACKNOWLEDGEMENTS

This work is partially funded by the UCL EPSRC Centre for Doctoral Training in Medical Imaging (EP/L016478/1), the Innovative Engineering for Health award (Wellcome Trust [203145Z/16/Z, WT101957] and EPSRC [NS/A000027/1]), and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.
6. REFERENCES


