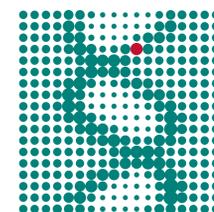


# Automatic Fusion of 3D staining patterns from mouse embryo tomograms

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MPIMG



SMP-RNA | NGFN

## Abstract

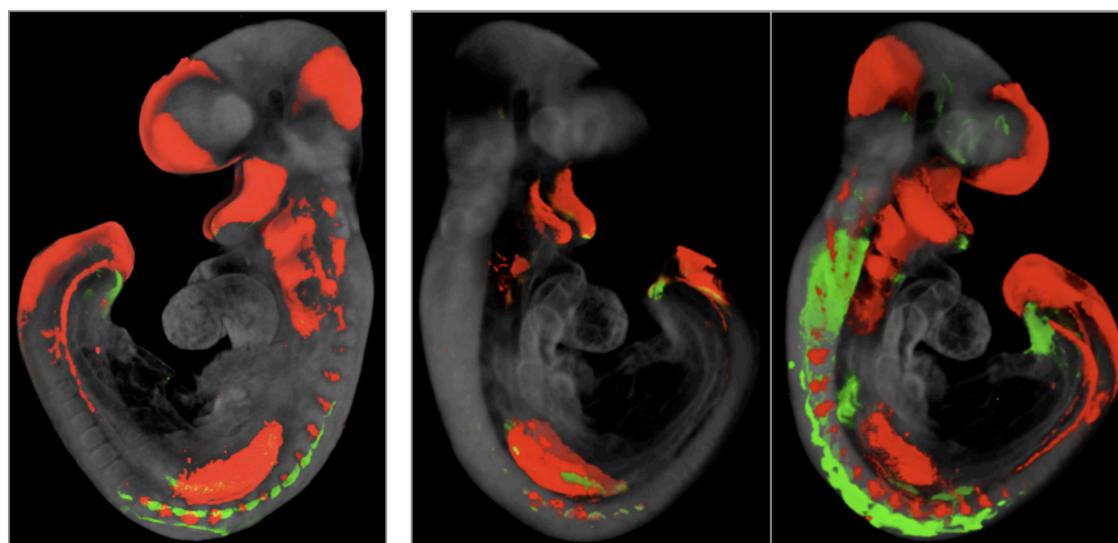
The spatial distribution of molecular staining patterns, e.g. from gene expression or proteins, is important to understand developmental processes on the molecular level.

The information when, where and under which condition gene expression or protein concentrations are present in an organism can be recorded from in-situ and staining experiments and result in images of the subject containing specific patterns. When scanning a whole catalogue of genes for a hypothesis one typically needs to compare a large set of transcriptional patterns, which is a time-consuming process. Furthermore this type of analysis does not lead to a quantitative understanding of the processes.

This leads us to the formulation of an image registration problem, that can be stated as finding a mapping of one image to another similar image, such that their difference is minimized. Similarity is measured on the level of intensities of the images. Our method first searches for a best affine match and derives then from the similarity measure a driving force, that deforms the images over time into a matching state. Our computational method for the fusion of 3D staining patterns from whole, intact mouse embryo images is non-parametric and does neither require user input nor a segmentation.

We exemplify in our results the success of our method by validating the co- and differentially expressed regions of the genes *Cdx1* and *Spry1* in mouse embryos of Theiler stage 15.

## Detection of Syn- and Differential Expression



Fused Patterns in one anatomy

Syn Expression | Differential Expression

## Registration Method

### Model Equation 1: Global Robust Registration

$$\mathbf{a}^* = \arg \min_{\mathbf{a}} \int_{\Omega} (R(x) - T(U_G(x) - x))^2 dx$$

### Model Equation 2: Variational Symmetric Demons Curvature Registration

$$\underbrace{f(\mathbf{x})}_{\text{data term (force)}} - \alpha \cdot \underbrace{\Delta^2 u(\mathbf{x})}_{\text{regularizer}} = 0 \quad \forall \mathbf{x}$$

$$\mathbf{f}(\mathbf{x}) = \frac{2 \cdot (R(x) - T(x - u(x))) \cdot (\nabla R(x) + \nabla T(x - u))}{\sqrt{R(x) - T(x - u(x))} \cdot \|\nabla R(x) + \nabla T(x - u(x))\|_2^2}$$

### Algorithm 1 Automatic Registration Algorithm

```

Fuse Pattern and Anatomy Channels by voxelwise max
Match Histograms
//Diffusion Smoothing
K ← 0.9
τ ← 0.0625
C(x) := e(-|x|/K)
I(x, 0) = I0(x)
for time t = 0 to 4 do
    Compute flux It = div(C(x, t)∇I(x))
end for
//Steepest Descent Global Registration
Calculate Gaussian Pyramids on It
Initialize: s, a0 ← I + 0, τ ← 0.1
for level l = 0 to 4 do
    a0 ← 0
    for k = 1 to nl do
        ak+1 = - (∇DSSD(ak) · τ · ∇DSSD(ak)) / (s · ||∇DSSD(ak)||22 + ak)
        if (∇DSSD(ak+1), ∇DSSD(ak)) < 0 then
            τ ← τ/2 //Relaxation
        end if
    end for
    τ = τ/2
end for
//Variational Deformable Registration
//Calculate affine vector field U from estimated parameters ak
U(x) = Ax + t - x
for level l = 0 to 4 do
    x1 ← U(x)
    Initialize: τ ← 1.0, α ← 1.0
    for k = 1 to Nl do
        //Compute symmetric demon force:
        fk+1(x) = fk(x, uk)
        //Solve curvature equation
        ∂tuk+1(x, t) - αΔ2uk+1(x, t) = f(x, uk)
        k = k + 1
    end for
end for
Resample image
return uk
    
```

## Towards Regulatory Networks

The detection of syn- and differentially expressed transcripts in high resolution in an intact 3D mouse embryo is an important method for the identification of a candidate list of genes forming a regulatory network, but arguably more information needs to be integrated to *reconstruct* a network. Although our mid term goal is a quantitative atlas of fused expression patterns of mouse embryos, a first step towards the elucidation of regulatory networks, will be an integrated analysis of microarray and *in situ* image data [1].

## Literature

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- [4] L. Neidhardt, S. Gasca, K. Wertz, F. Obermayr, S. Worpenberg, H. Lehrach and B.G. Herrmann, (2000), Large-scale screen for genes controlling mammalian embryogenesis, using high-throughput gene expression analysis in mouse embryos, *Mechanisms of Development*, **2**, 77-93
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Mouse Embryo with Spry1 Pattern

Mouse Embryo with Cdx1 Pattern

After Registration

Example Slice

