

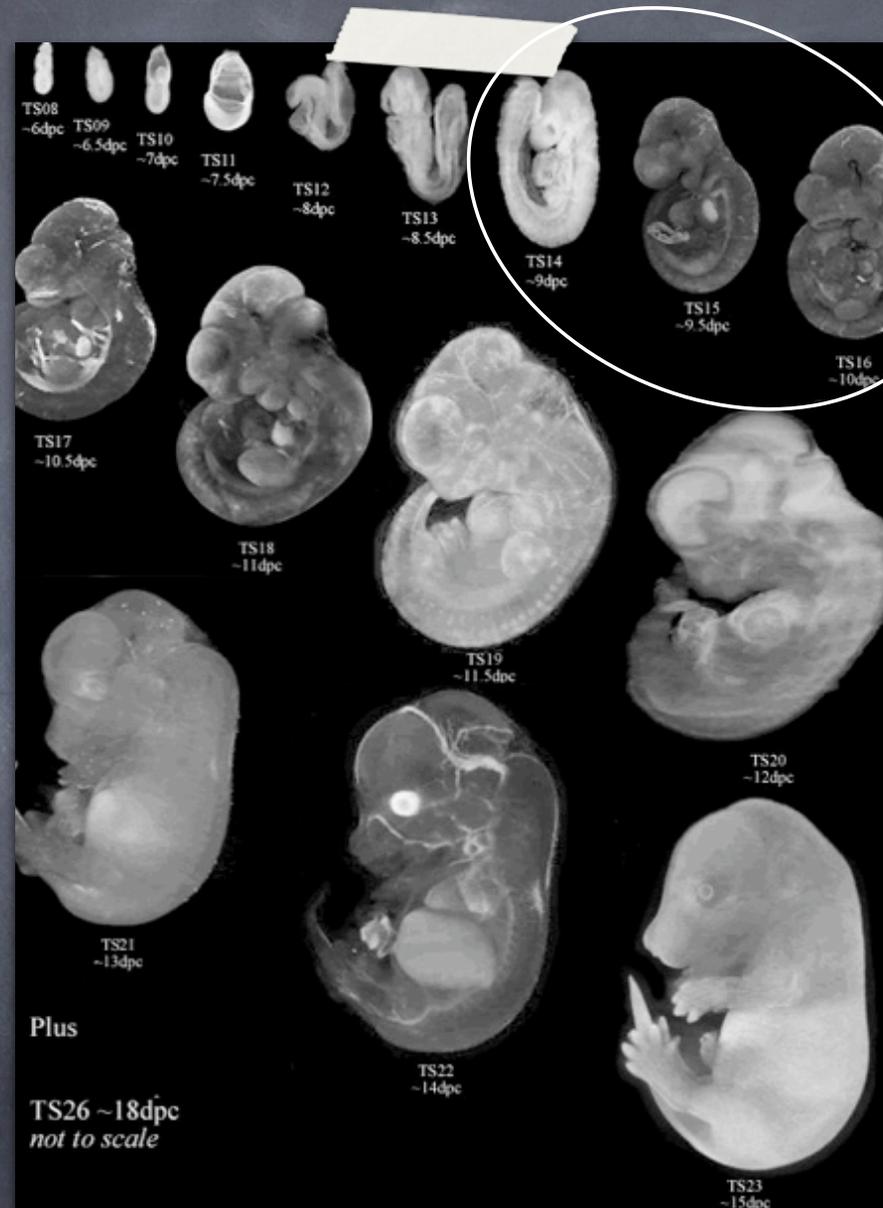
Computational analysis of 3D mouse embryo images

Ruben Schilling
26.11.2008

Introduction

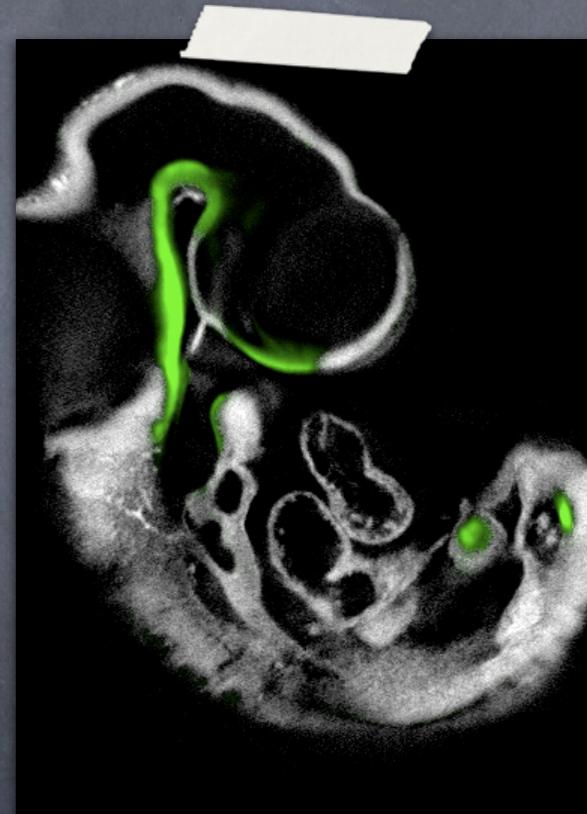
Embryonal stages

- Stage wise registration is meaningful
- Earliest stages are most difficult (inaccurate staging, high flexibility)
- Elderly stages have the more direct impact on medical applications
- Our interest Theiler stage 14-16



In-situ patterns

- Each embryo stained for one gene
- Shows „activity“ of that gene at that time
- Here: sonic hedgehog
- Different markers in use



WNT1

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TS15

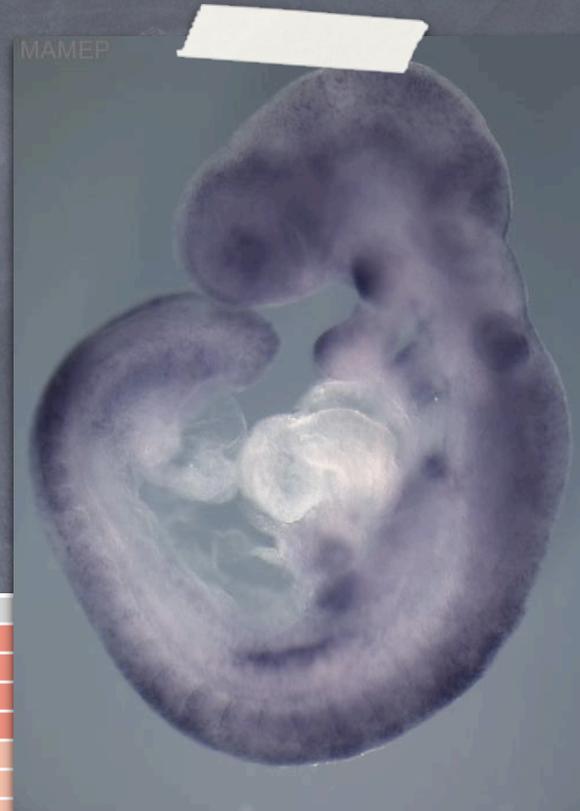
paraxial mesenchyme->somite	strong	regional
forelimb bud->mesenchyme	moderate	regional
tail->mesenchyme	moderate	regional
embryo->branchial arch	weak	regional
future spinal cord->caudal neuropore	weak	graded
future spinal cord->neural plate	weak	graded
future spinal cord->neural tube	possible	graded
central nervous system->future brain	possible	regional

[sequence information](#)

UJ473 (Gradient)

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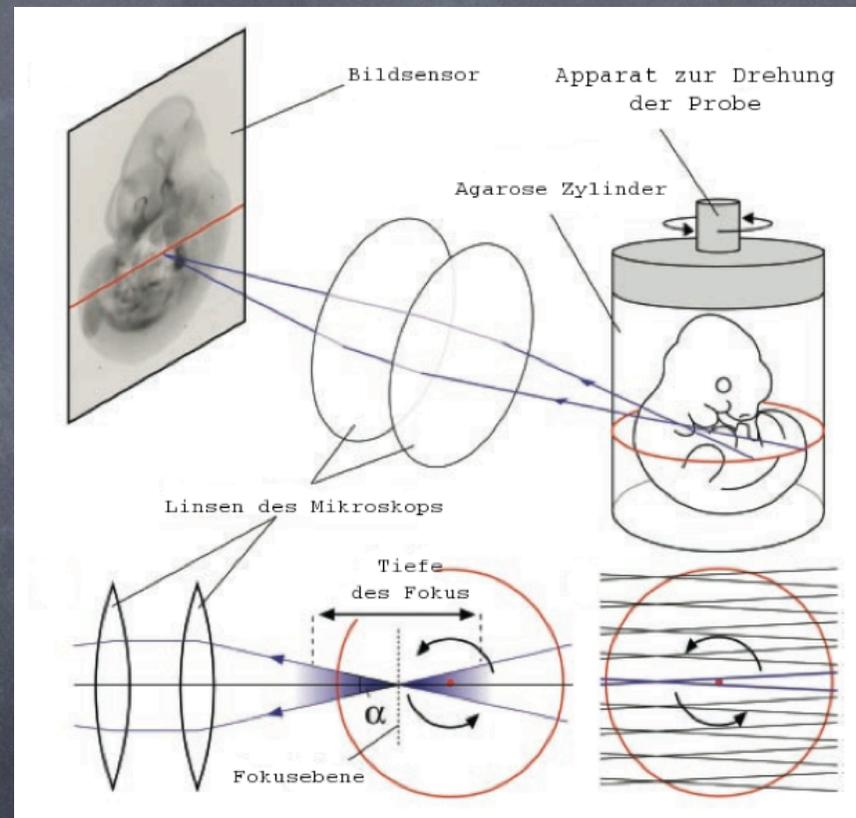
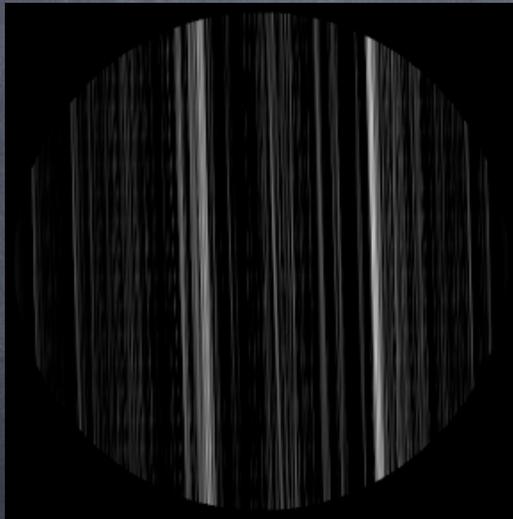
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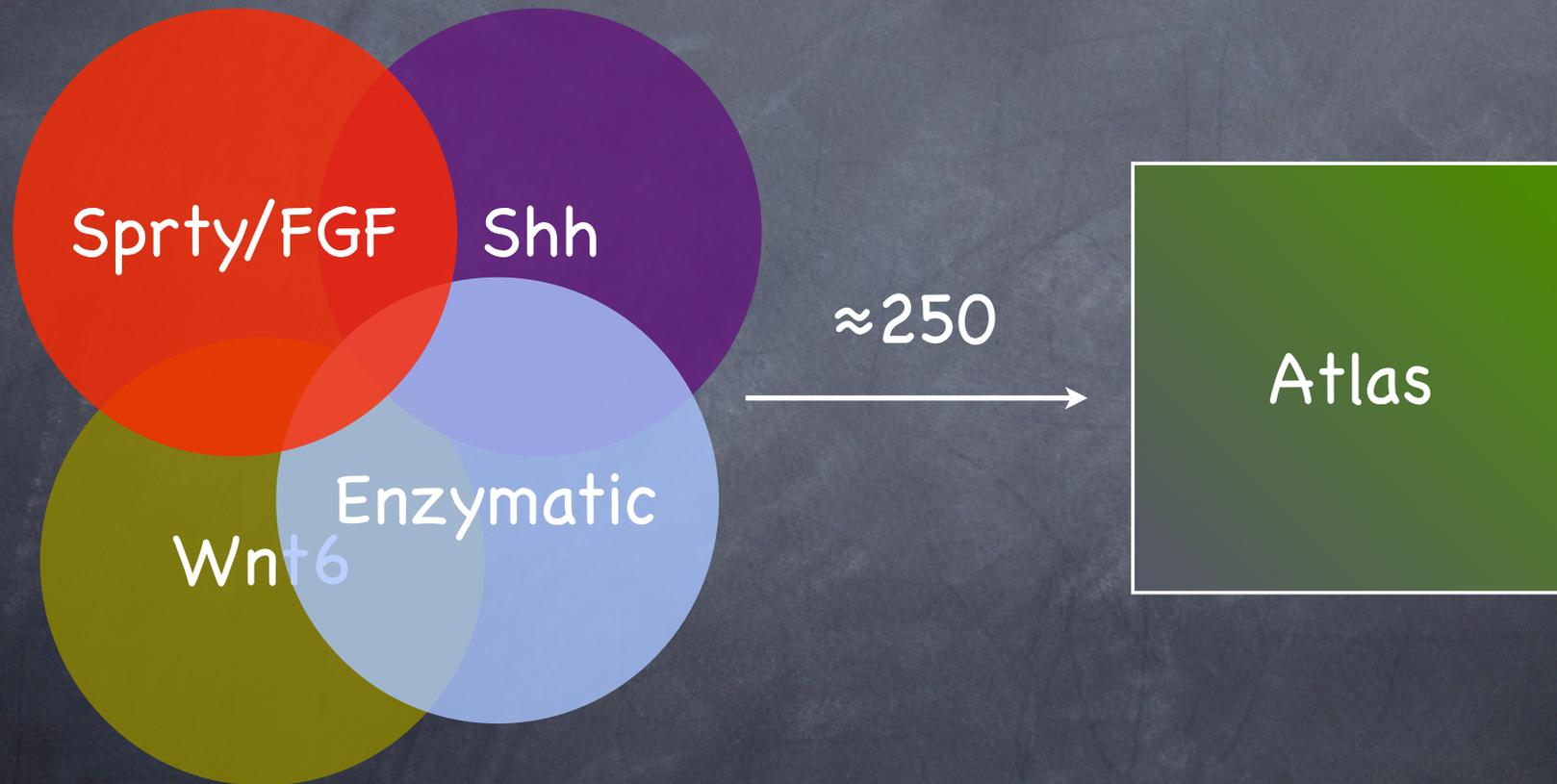
TS15

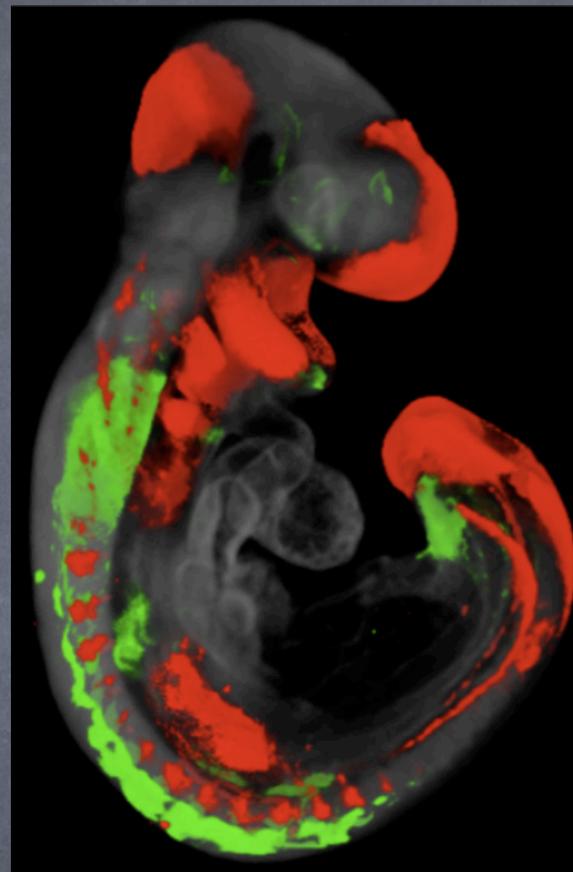
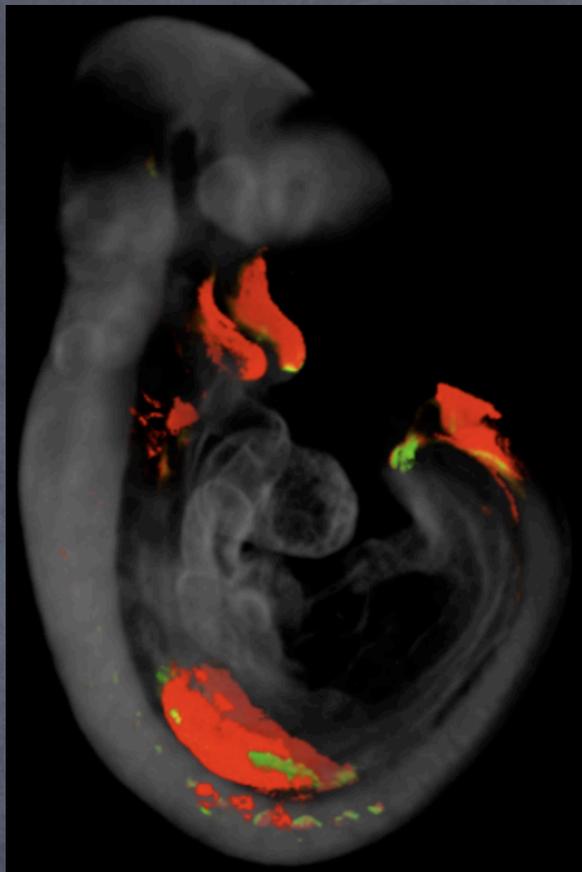
embryo->branchial arch	strong	
forelimb bud->ectoderm	strong	
paraxial mesenchyme->unsegmented mesenchyme	strong	
nose->olfactory placode	strong	
branchial pouch->endoderm	moderate	
future brain->future rhombencephalon	moderate	
midgut->epithelium	moderate	homogeneous
paraxial mesenchyme->somite	moderate	regional
2nd arch->ectoderm	moderate	spotted
future spinal cord->neural tube	moderate	regional
hindgut diverticulum->epithelium	moderate	homogeneous
otocyst->epithelium	moderate	graded
mandibular component->ectoderm	moderate	spotted
future brain->future forebrain	moderate	regional
future spinal cord->caudal neuropore	moderate	homogeneous
respiratory system->lung	moderate	homogeneous
trunk mesenchyme->septum transversum	moderate	regional
central nervous system->future spinal cord	moderate	regional
maxillary component->ectoderm	moderate	spotted
future brain->future midbrain	moderate	regional
oesophageal region->epithelium	moderate	homogeneous
laryngo-tracheal groove->tracheal diverticulum	moderate	regional

OPT imaging modality



Goals: Atlas and functional groups





- Clustering of the patterns
- Spatial co-expression networks
- Automated annotation through one reference

Registration Problem

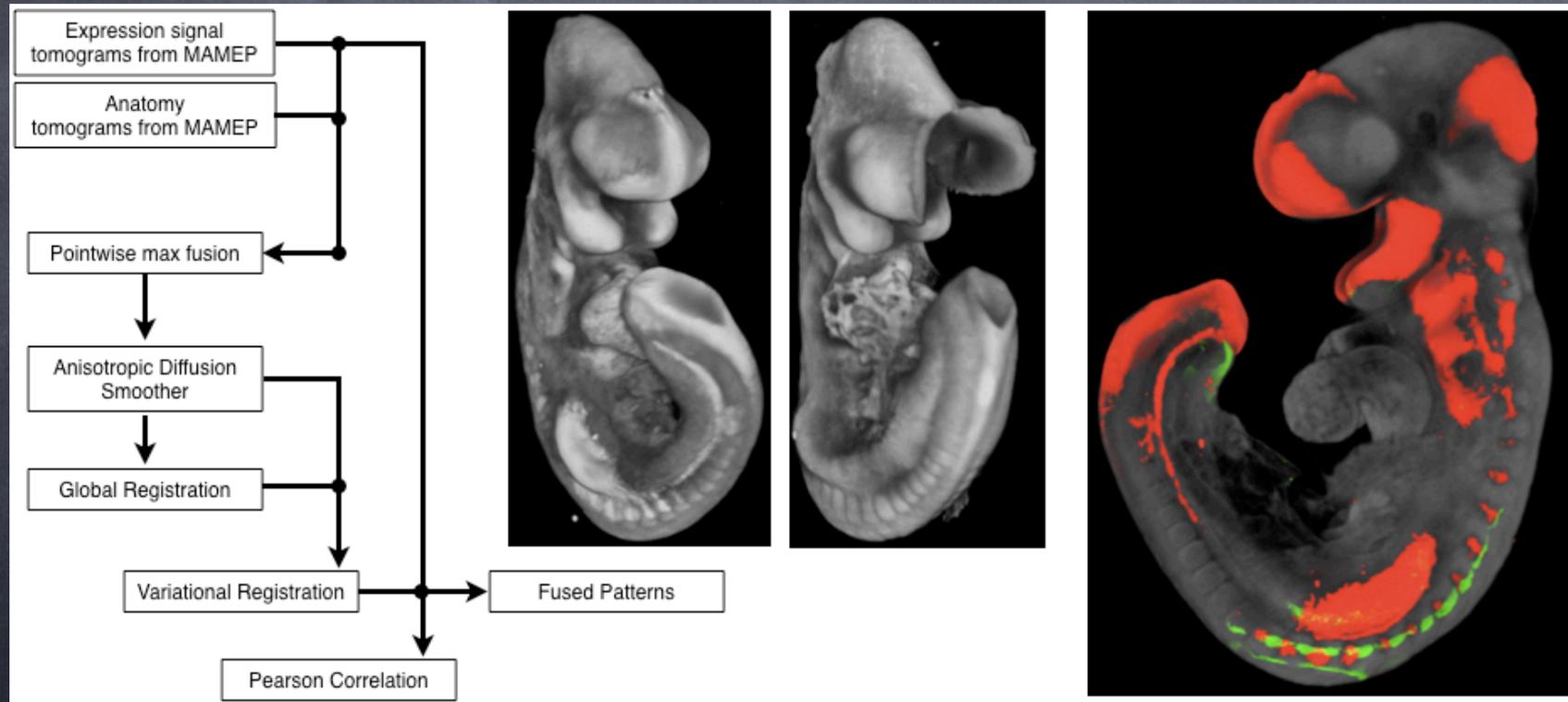
WL: 128 WW: 255

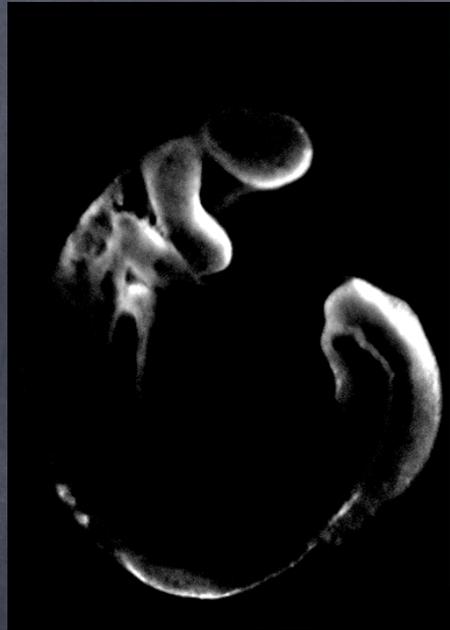


WL: 128 WW: 255

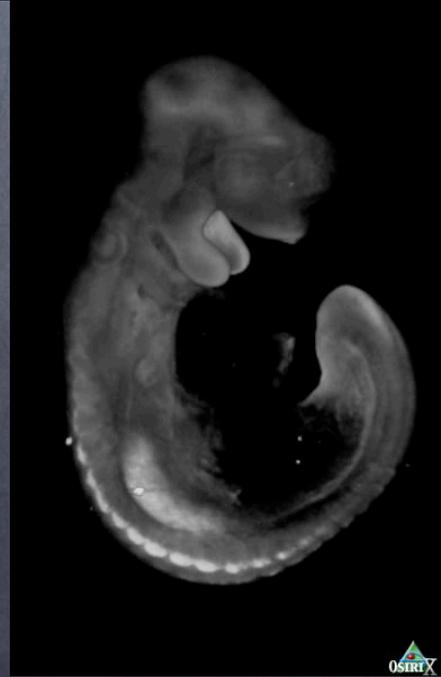


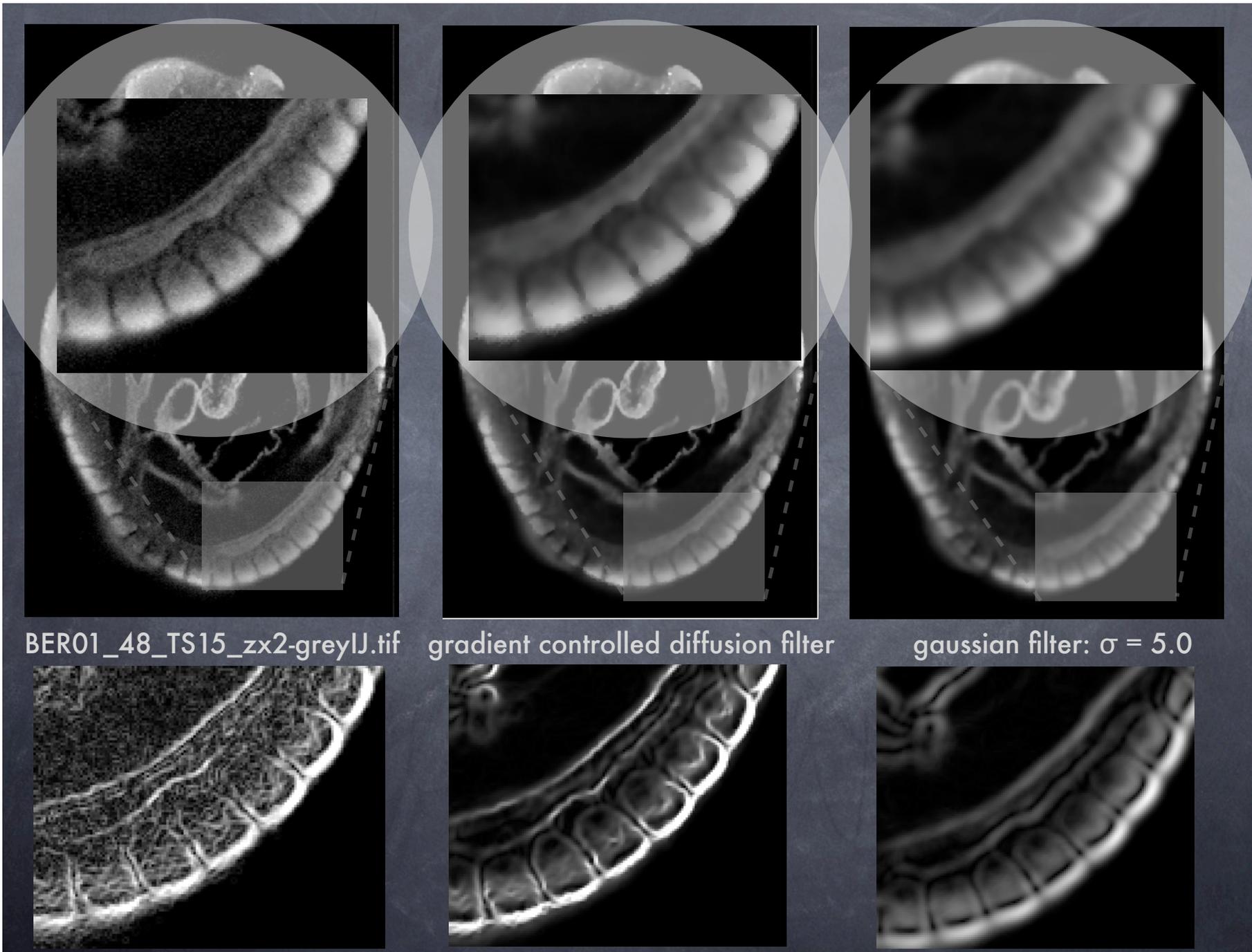
Current pipeline





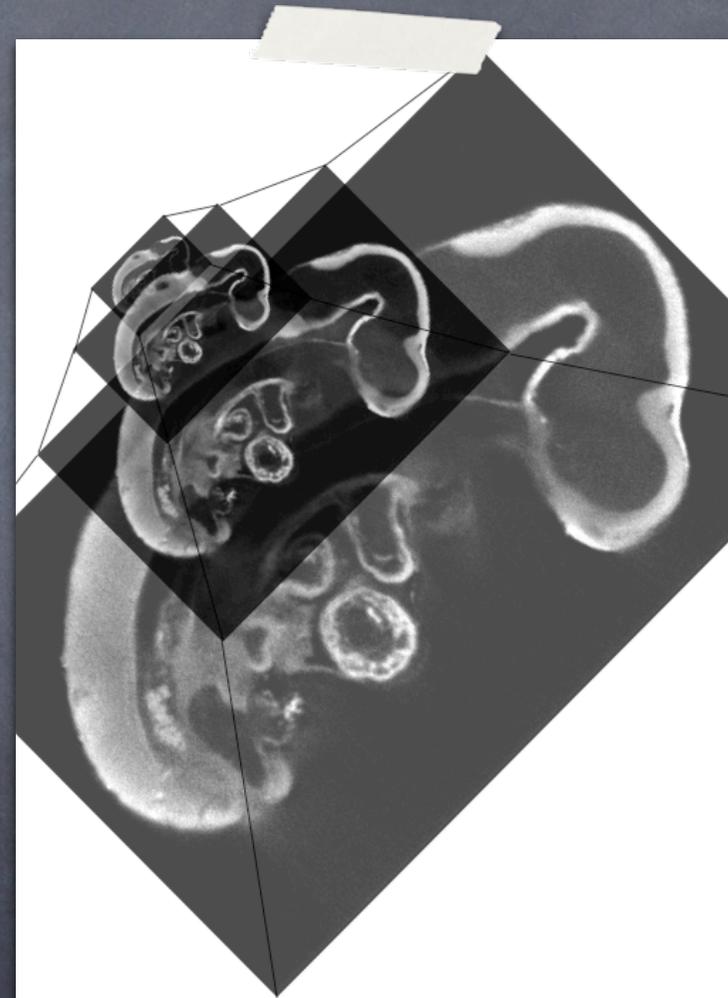
max





MultiResolution

- Gaussian pyramid approach
- 5 levels (powers of 2 scale)
- Smoothing logarithmically proportional to scaling



Preregistration step

- Affine transformation model
 - Weighting of individual parameters possible to tune warps
- Armijo line search for step length
 - Convenient to use (automatic)

Backtracking line search with Armijo condition

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

$$U_G(\mathbf{x}) := \mathbf{A}\mathbf{x} + \mathbf{t} = \begin{pmatrix} a_1 & a_2 & a_3 \\ a_4 & a_5 & a_6 \\ a_7 & a_8 & a_9 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} + \begin{pmatrix} a_{10} \\ a_{11} \\ a_{12} \end{pmatrix}$$



Backtracking Line Search:

Choose $\bar{\tau} > 0, \rho \in (0, 1), c \in (0, 1)$

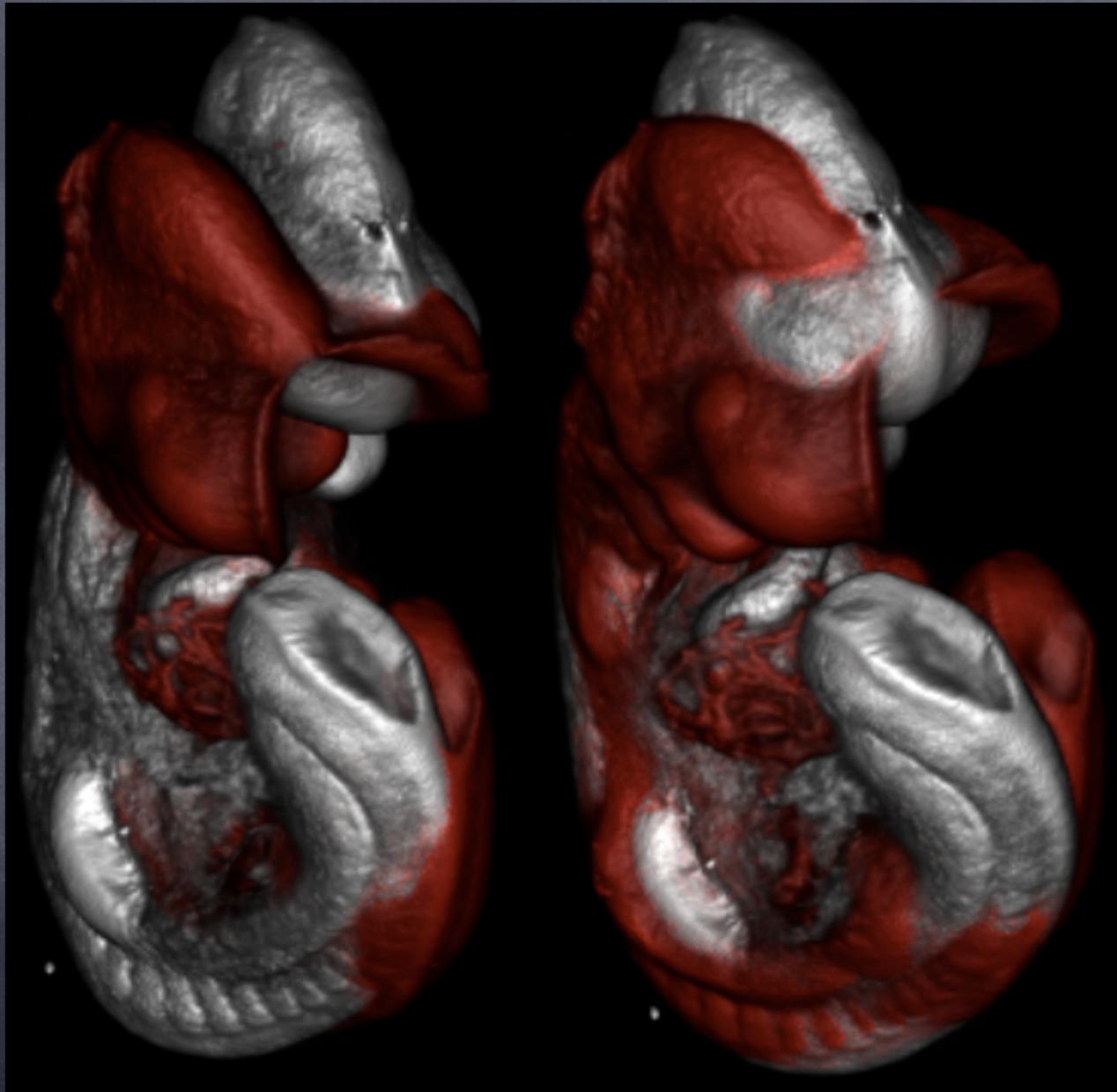
$\tau \leftarrow \bar{\tau}$

while $(!f(x_k + \tau p_k) \leq f(x_k) + c\tau \nabla f_k^T \mathbf{s}^T \cdot \frac{-\nabla f_k}{\|\nabla f_k\|})$

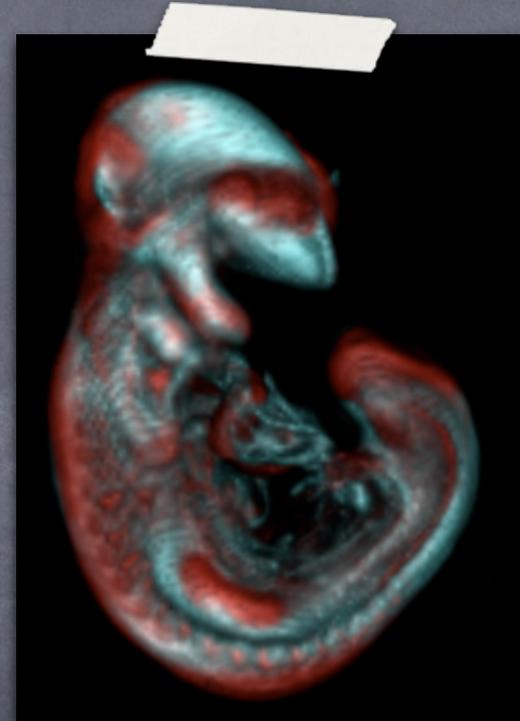
$\tau \leftarrow \rho \cdot \tau$

end

$$\mathbf{a}_{k+1} = -\mathbf{s}^T \cdot \frac{\tau \cdot \nabla f(\mathbf{a}_k)}{\|\nabla f(\mathbf{a}_k)\|_2^2} + \mathbf{a}_k$$



Symmetric Demons + Curvature



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

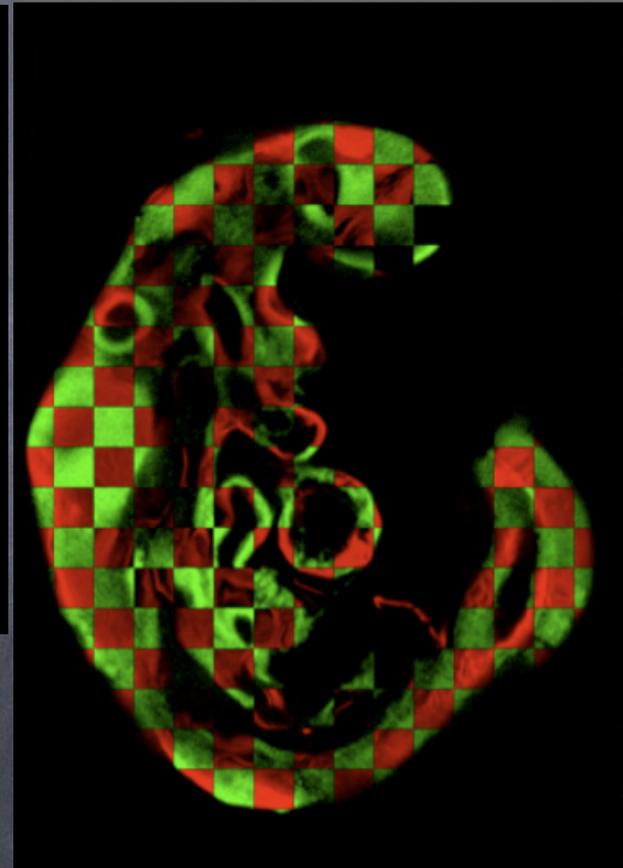
$$f(\mathbf{x}) = \frac{2 \cdot (R(x) - T(x - u(x))) \cdot (\nabla R(x) + \nabla T(x - u))}{\nu \cdot \frac{(R(x) - T(x - u(x)))^2}{\|\nabla R(x) + \nabla T(x - u(x))\|_2^2}}$$

Validation

Structure	Spryt1	Cdx1	Fusion	Error (voxels)
endolymphatic duct (right)	(53, 190, 117)	(64, 189, 87)	(57, 189, 119)	4.5826 ± 3
endolymphatic duct (left)	(62, 206, 175)	(72, 180, 141)	(66, 204, 179)	6 ± 3
Rathke's pouch	(160, 143, 155)	(192, 158, 97)	(159, 151, 151)	9 ± 3
Bucco-Pharyngeal membrane	(136, 171, 151)	(158, 167, 108)	(139, 178, 156)	9.1104 ± 3
Cloacal pouch	(280, 277, 73)	(290, 303, 118)	(285, 292, 79)	16.9115 ± 3
Primitive streak (rostral)	(274, 223, 72)	(304, 248, 117)	(303, 266, 77)	52.1057 ± 3
Lung bud	(151, 378, 111)	(144, 372, 134)	(157, 362, 106)	17.8045 ± 3
Somite C1 (dDM)	(46, 375, 127)	(30, 360, 118)	(30, 330, 80)	67.0075 ± 3
Atrio-ventricular canal	(178, 314, 134)	(186, 310, 141)	(176, 314, 130)	4.4721 ± 3
First branchial pouch (dorsal, left)	(127, 193, 190)	(134, 164, 154)	(119, 191, 197)	10.8167 ± 3
			Median error	9.96 ± 3

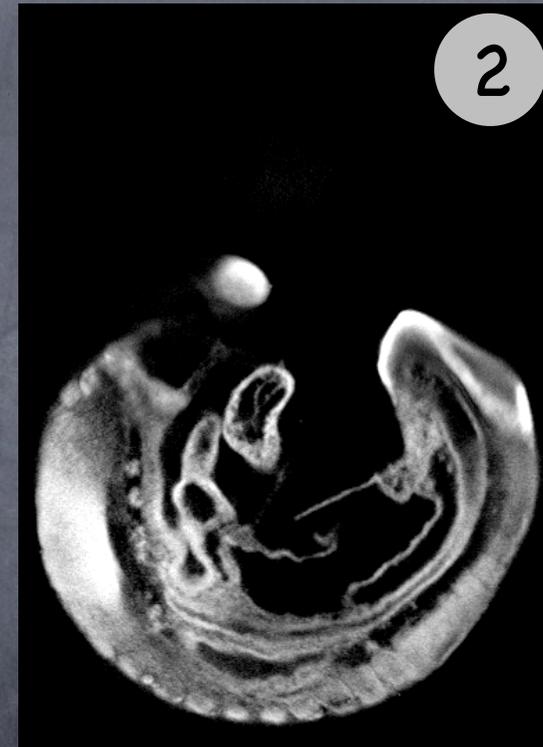
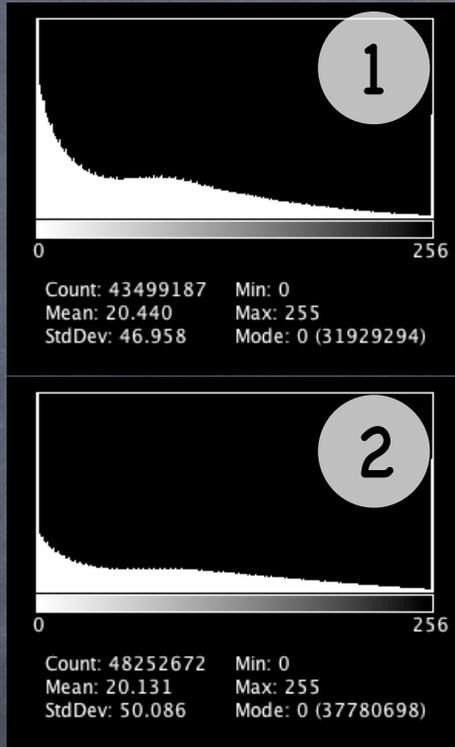
dDM, dorsal dermomyotome; Validation for 10 landmarks, that were passively warped. Two outliers are visible, the remaining landmarks seem to be of expected magnitude in inter-subject registration. The error shown is the hard error, where ± 3 voxels should be conservatively chosen as the soft error accounting for the correct choice of voxel correspondences and the resampling error in the warp.

+ EMAP, MAMEP
literature validation



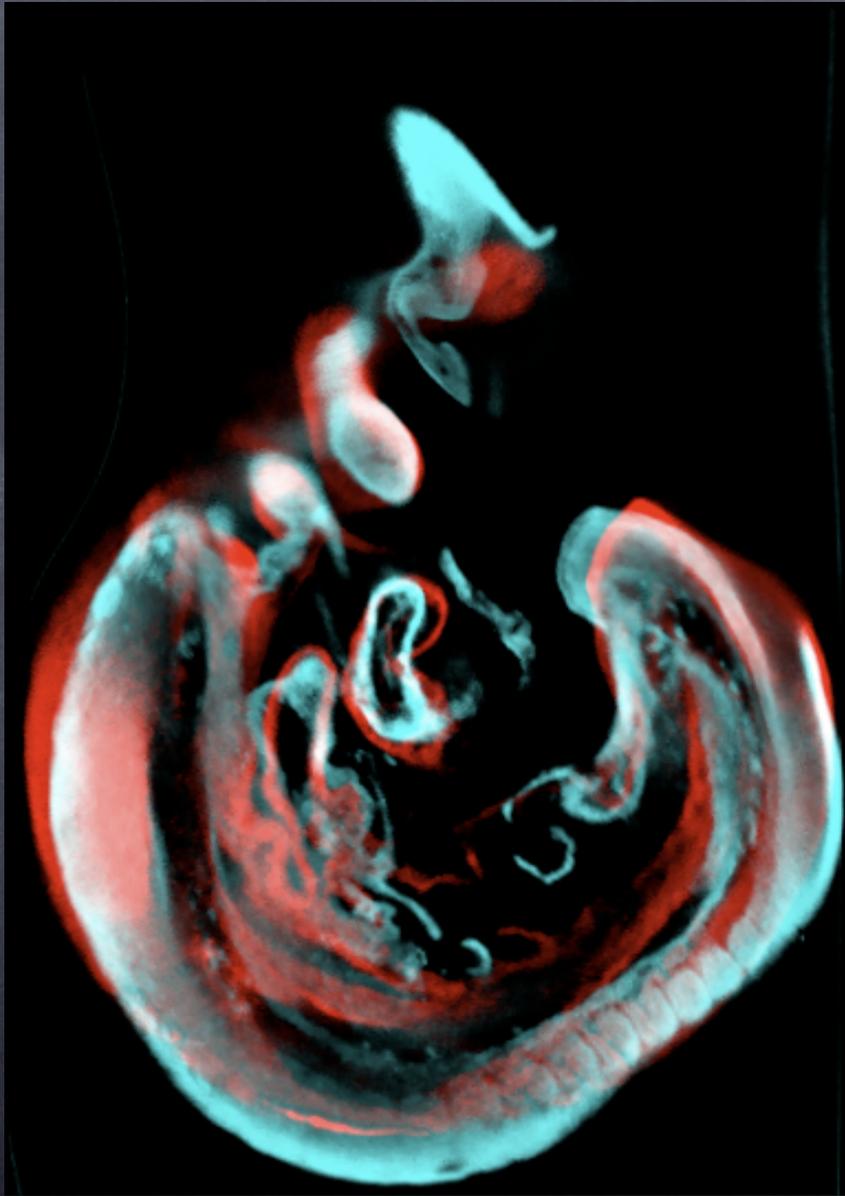
Current Limitations

Problem missing data



Missing data modeling

- Missing data: Occlusions of anatomy through experimental artifacts and noise (simple to detect)
- Idea: Weighting of the decent direction, such that the position of missing data is scored neutrally with regard to our chosen metric
- Two distributions: Missing data & foreground



Current limits of pure intensity based registration



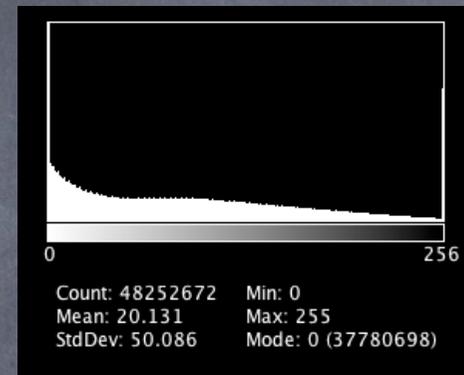
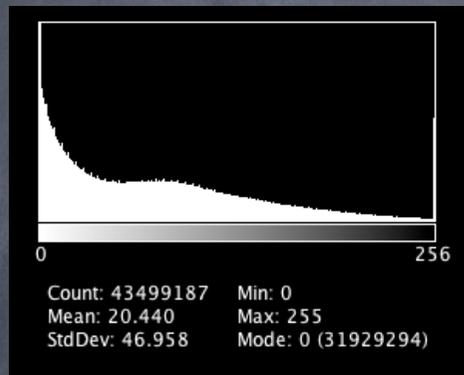
Research Plans

Missing data mixture model

- Specify mixture distributions for images (by means of their histograms)
- Learn parameters of the grayvalue distributions using EM for each image
- -> Weighting for the metric

$$p_1(I_1(x)) \cdot p_2(I_2(x)) \cdot (-f(x, u))$$

Mixture model



$$P(I_1(x|\neg\text{missing})) = \frac{\alpha_1 P_N(I_1(x))}{\alpha_1 P_N(I_1(x)) + (1 - \alpha_1) P_M(I_1(x))}$$
$$\text{fg}(x, \text{offset}, \lambda, \mu, \sigma) = (1 - \pi)e^{-\lambda x} + \pi N(\mu, \sigma, \text{offset} + x)$$
$$\text{missing}(x, \lambda, \text{offset}) = -e^{-\lambda x + \text{offset}}$$
$$\text{mix}(x) = (1 - \pi)\text{fg}(x, \text{offset}, \lambda, \mu, \sigma) + \pi\text{missing}(x, \lambda, \text{offset})$$

CoLD instead of affine registration

$$D[R, T, u] + \alpha S[u] + \beta \int_{\Omega} \Psi(C[u]) dx \rightarrow \min$$

- Landmarks could be manual or from medial axis
- Landmarks should cover the large global deformations

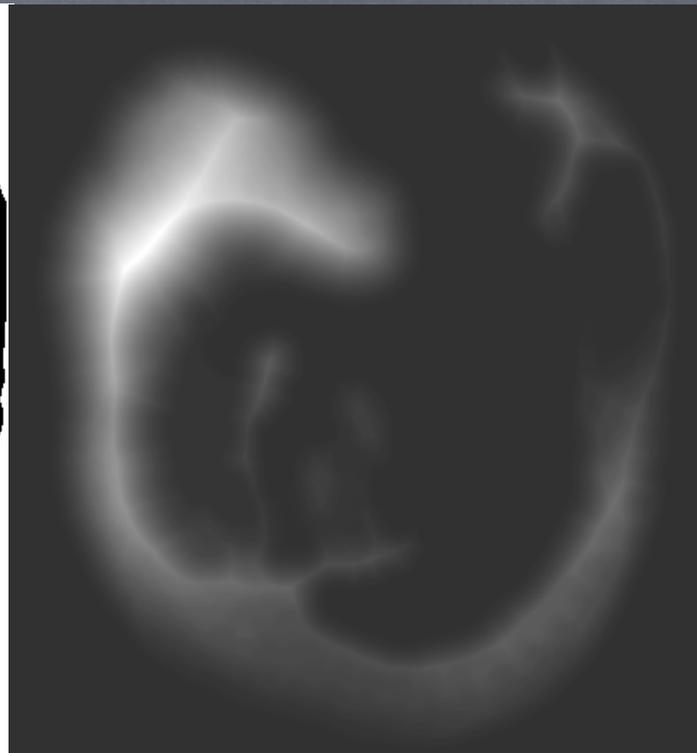
Computing medial axis (1)



Manual
closing

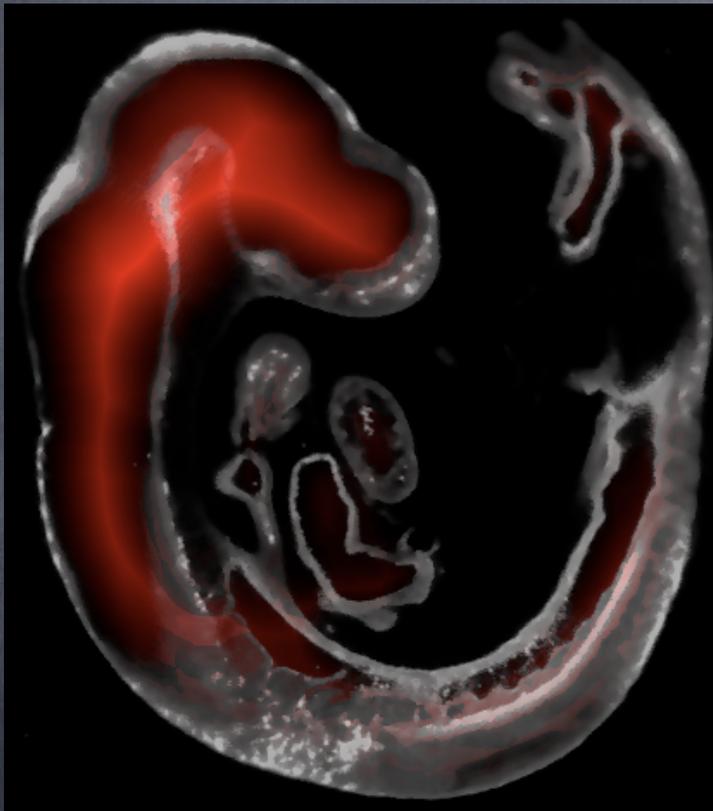


Fill and binarize
the image

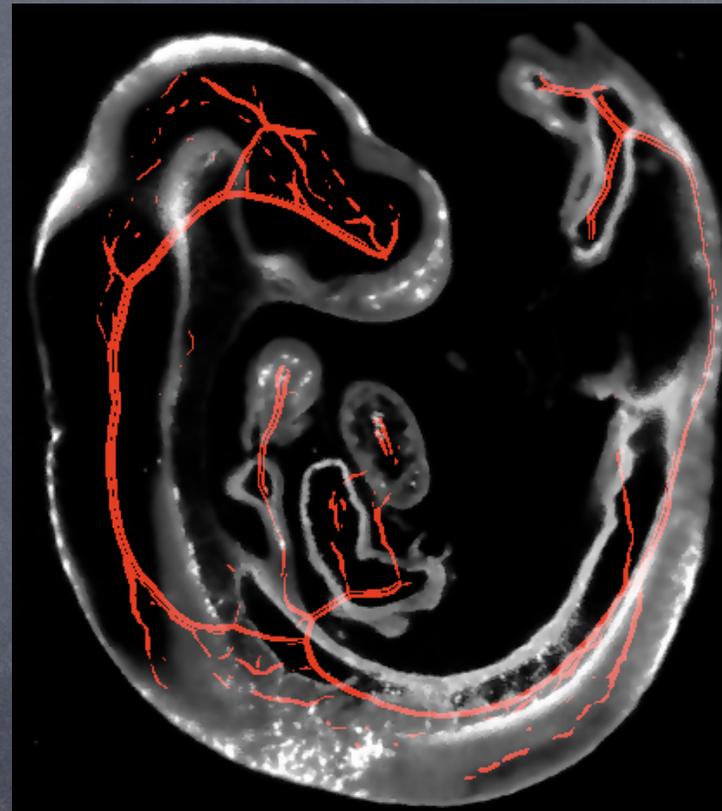


Compute quadratic
distance map

Computing medial axis (2)



Extract saddle points
(the ridge)



Discretize into vertices+edges
compute longest path + prune
branches

Using medial axis for CoLD

- Count nodes along axis to establish correspondences along the whole body
- Semi-automatic, data driven approach
- Unknown if 1D landmark type is sufficient for TPS interpolation

Thank you

Alexander Schliep

Ralf Spörle

Bernhard Herrmann

Martin Vingron

Bernd Fischer