

# The Modelling of Biological Growth: a Pattern Theoretic Approach

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# Dedication

This research work is dedicated to my PhD co-supervisor

Dr. Ulf Grenander, the founder of Pattern Theory

Division of Applied Mathematics, Brown University

Providence, Rhode Island, USA.

<http://www.dam.brown.edu/ptg/>

# Outline

- 1 Mathematical foundations of computational anatomy
- 2 Growth models in computational anatomy
- 3 A link between anatomical models and the GRID model
- 4 GRID view of growth on a fine time scale
- 5 GRID equation of growth on a coarse time scale (macroscopic growth law)
- 6 Image inference of growth properties of the *Drosophila* wing disc
- 7 Summary, concluding remarks and future perspectives
- 8 Current work

# Mathematical foundations of computational anatomy

Computational anatomy<sup>1</sup> focuses on the precise study of the biological variability of brain anatomy.

D'Arcy Thompson laid out the vision of this discipline in his treatise “On Growth and Form”<sup>2</sup>. In 1917 he wrote

*“In a very large part of morphology, our essential task lies in the comparison of related forms rather than in the precise definition of each; and the deformation of a complicated figure may be a phenomenon easy of comprehension, though the figure itself may be left unanalyzed and undefined.”*

D'Arcy Thompson introduced the Method of Coordinates to accomplish the process of comparison.

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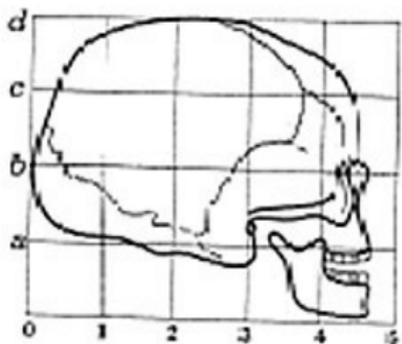
<sup>1</sup> *Computational anatomy: An Emerging Discipline* by U. Grenander, M. I. Miller, *Quart. Appl. Math.*, **56(4)** 617-694 (1998)

<sup>2</sup> *On Growth and Form*, by D'Arcy Wentworth Thompson, Univeristy Press, 1917, 793 pages

# Mathematical foundations of computational anatomy

The Method of Coordinates reveals the phenomenon of correlation in regards to form within the family (e.g., primates).

Example: Evolution of the human skull shape<sup>3</sup>



**Figure:** Human Skull

Skull of chimpanzee

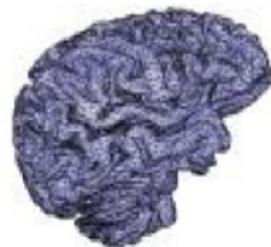
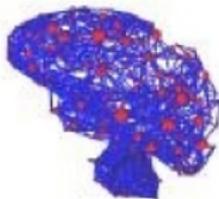
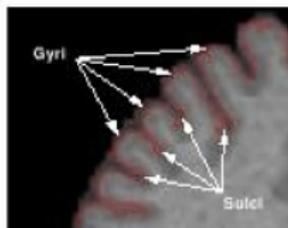
Skull of baboon

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# Mathematical foundations of computational anatomy

Thompson's vision has been cast into a precise mathematical form by Ulf Grenander and Michael Miller.

The anatomical configuration is a collection of 0,1,2,3-dimensional submanifolds with variabilities accommodated via random transformations (a [probabilistically deformable template](#)<sup>4</sup>).



**Figure:** Gyri and sulci in a brain slice image, Sulcal landmarks and lines  
Triangulated graph of a brain surface

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<sup>4</sup>*General Pattern Theory: A Mathematical Study of Regular Structures* by Ulf Grenander, Oxford University Press Inc., New York, NY, 1993

# Mathematical foundations of computational anatomy

Comparison of brain structures within a given anatomical population is achieved by means of **diffeomorphic transformations** (1-1 and onto, differentiable with differentiable inverse).

Importance of diffeomorphisms:

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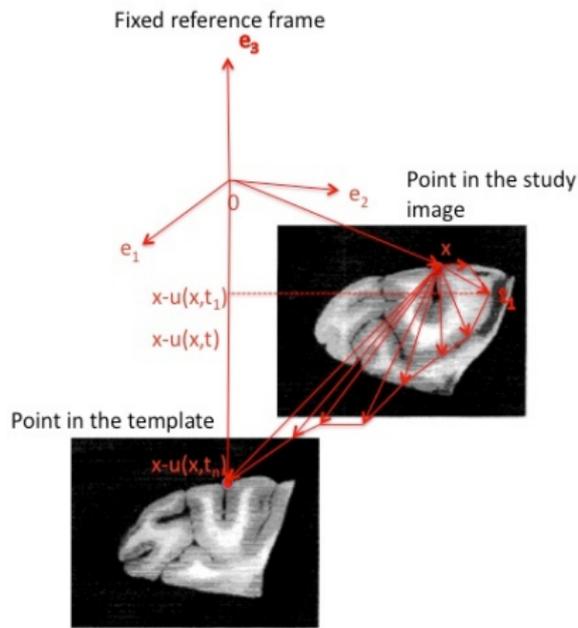
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## Importance of diffeomorphisms:

- Connected sets remain connected
- Submanifolds such as surfaces are mapped as surfaces
- The global relationships between structures are preserved
- The geometric features of individual anatomies (Gaussian curvature, Riemannian length, surface area) are maintained.

# Mathematical foundations of computational anatomy

Illustration of a large deformation diffeomorphic map.



**Figure:** The monkey cortex cryosection,  $\mathcal{I}_{temp}$ , and the second monkey slice,  $\mathcal{I}$ .  $\vec{u}(x, t)$  is a time-dependent map  $\mathcal{I}_{temp}(x - \vec{u}(x, t)) \rightarrow \mathcal{I}(x)$ .

# Mathematical foundations of computational anatomy

## Diffeomorphic flows for large deformations are

- generated by continuum mechanics equations of motion

$$\vec{v} = \frac{d\vec{u}}{dt} = \frac{\partial\vec{u}}{\partial t} + \sum_{i=1}^d v_i \frac{\partial\vec{u}}{\partial x_i}$$

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- constrained to the set of transformations consistent with the material properties of brain anatomy under study (elastic, visco-elastic, etc.)

$$\hat{v}(x, T) = \arg \min_{\vec{v}} E(\vec{v}(x, T), \vec{u}(x, T)) \quad (1)$$

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- $E_2(\vec{v}(x, T)) = \frac{1}{2\sigma^2} \int_{[0, T]} \int_{\Omega} |\mathcal{I}_{temp}(x - \vec{u}(x, t)) - \mathcal{I}(x)|^2 dx dt$  is the observation energy needed to register template and study images.

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- The solution  $\vec{u}(x, t), t \in [0, T]$  maximizes the posterior distribution  $p(\vec{u}|\mathcal{I})$  written in Gibbs form

$$p(\vec{u}|\mathcal{I}) \propto p(\mathcal{I}|\vec{u}) \cdot p(\vec{u}) \quad (3)$$

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- $E$  is the Gibbs potential, the sum of the prior energy  $E_1(\vec{v})$  and the Gaussian log-likelihood  $E_2(\vec{u})$ .

# Growth models in computational anatomy

- The equations of motion from mechanics have been used for computation of growth-induced shape changes seen in medical images.

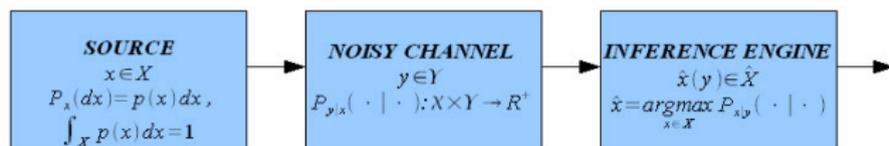
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- The equations of motion from mechanics have been used for computation of growth-induced shape changes seen in medical images.
- Bayesian interpretation of transformations provides a strong mathematical basis for image and landmark matching algorithms.
- The goal of these algorithms is to infer growth deformation fields determined by changes in pixel values.

# Growth models in computational anatomy



EXAMPLE IN COMPUTATIONAL ANATOMY

**DIFFEOMORPHIC  
MAPPING**  
 $\tilde{u}(x, t):$   
 $I_{template}(\tilde{x} - \tilde{u}(\tilde{x}, t)) \rightarrow I_{stud\phi}(\tilde{x})$

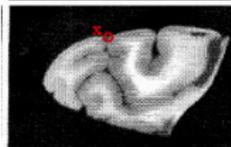
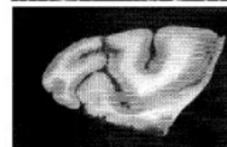
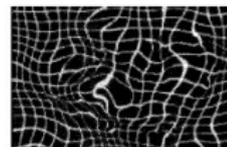


IMAGE PAIR

$(I_{template}(\tilde{x} - \tilde{u}(\tilde{x}, t)), I_{stud\phi}(\tilde{x}))$



INFERENCE RESULTS

$\hat{\tilde{u}}(\tilde{x}, T), \hat{I}_{stud\phi}$

**Figure:** The growth model in computational anatomy as Bayesian paradigm separating source from noisy observations.

(Images reproduced from *Deformable templates using large deformation kinematics* by R. D. Rabbitt, G. E. Christensen and M. I. Miller, IEEE Transactions on Image Processing, **5(10)** 1433-1447 (1996) )

# Growth models in computational anatomy

- Computational anatomy equations for growth generate very realistic structures.

# Growth models in computational anatomy

- Computational anatomy equations for growth generate very realistic structures.
- However, they do not reflect the underlying biology of shape change.

# A link between anatomical models and the GRID model

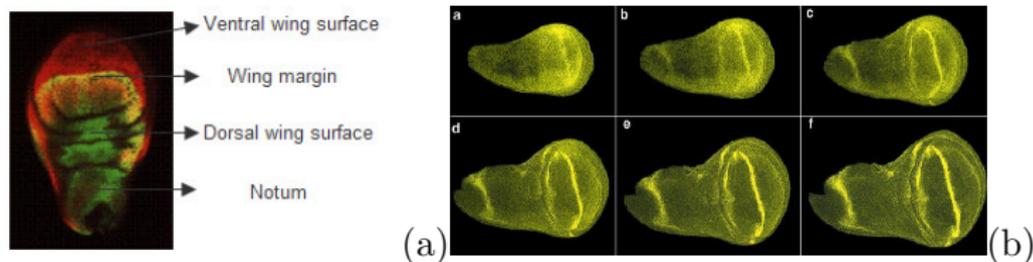
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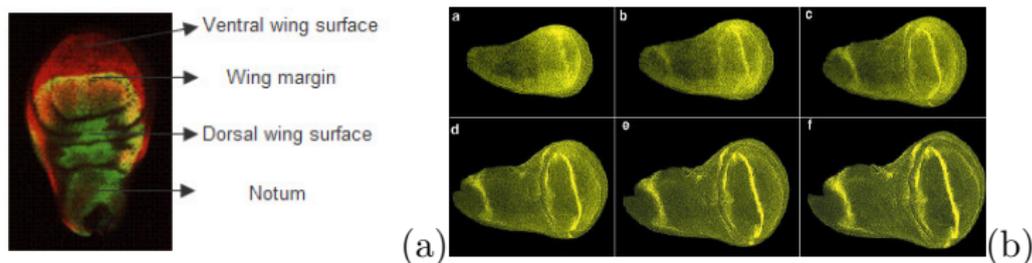
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- The genetic program of development unfolds in the form of spatial-temporal distribution of densities of gene products.



**Figure:** (a) Overlapping of the Vestigial and Apterous expression patterns, (b) Dynamics of the Wingless expression pattern during larval growth [ $\approx 48h$ ,  $\approx 120h$  after egg laying].

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- At this level of small populations of cells a certain deformation is assigned.

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The GRID model is **the first of its kind, genetically-based** mathematical model for a biological growth.

We are led to the dynamical model of growth as a sequence of genetically controlled transformations.

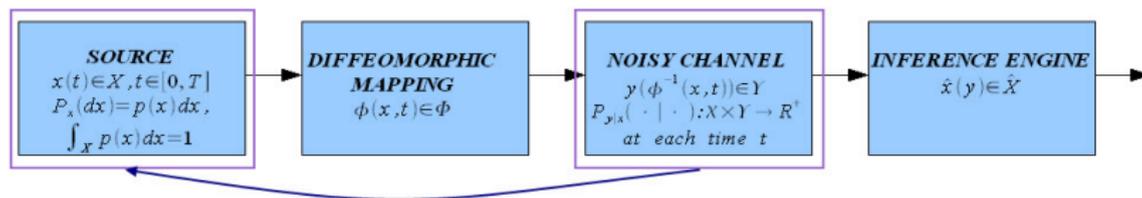


Figure: Schematic illustration of the GRID model.

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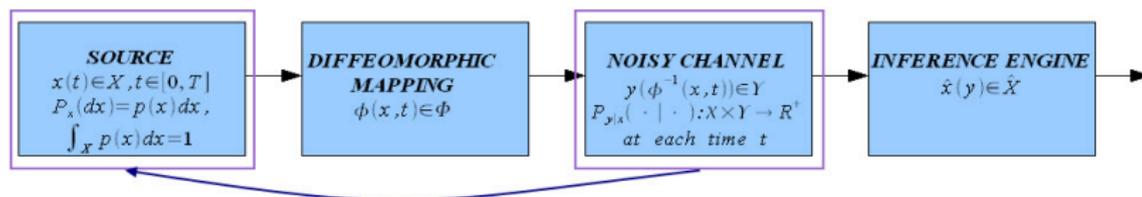


Figure: Schematic illustration of the GRID model.

We are looking for

- a smaller, more structured space  $\Phi$  of diffeomorphisms appropriate to modeling biological deformations,
- unknown structures hidden deeper in given observations of growth.

# GRID view of growth on a fine time scale

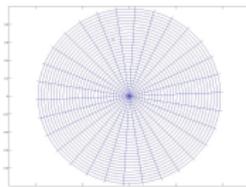
The **growth pattern** is a cumulative growth deformation composed of elementary deformations  $\phi^{(\xi_{seed}, t_i)}$

$$X(\xi, t_n) = \phi^{(\xi_{seed\sigma_n}, t_n)} \circ \phi^{(\xi_{seed\sigma_{n-1}}, t_{n-1})} \circ \dots \circ \phi^{(\xi_{seed\sigma_1}, t_1)} X(\xi, t_0).$$

# GRID view of growth on a fine time scale

Construction of the  $\phi$ -map:

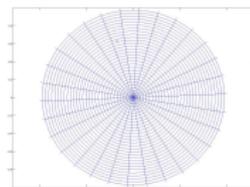
- Place a *seed* on a Darcyan grid according to a Poisson process.



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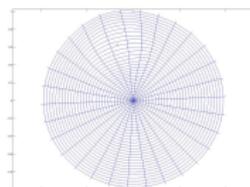
- Place a *seed* on a Darcyan grid according to a Poisson process.



- Deform the neighborhood around the seed

$\phi(x(\xi, t)) = x(\xi, t) + k(\tau)\mathcal{R}(x(\xi, t) - x(\xi_{seed}, t))$ , where

$$\mathcal{R}(\cdot) = (x(\xi, t) - x(\xi_{seed}, t)) \exp\left(-\frac{\|x(\xi, t) - x(\xi_{seed}, t)\|^2}{s^2}\right)$$

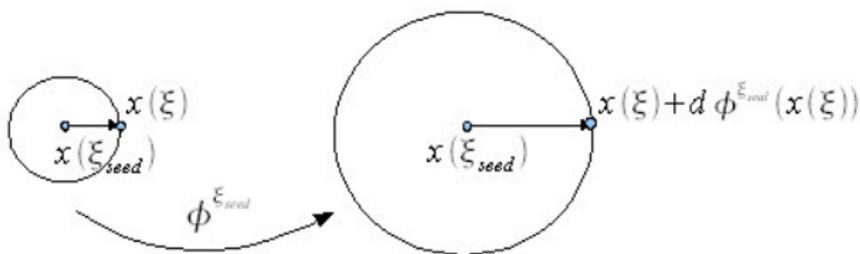


## Isotropic deformation patterns

$$\phi(x(\xi, t)) = x(\xi, t) + k(\tau)\mathcal{R}(x(\xi, t) - x(\xi_{seed}, t)).$$

If  $k(\tau) = \text{const}$  then the local deformation is **isotropic**.

The isotropic GRID transformation of a disk of radius  $s$  centered at the seed deforms it into a bigger or smaller disk.



# Isotropic deformation patterns

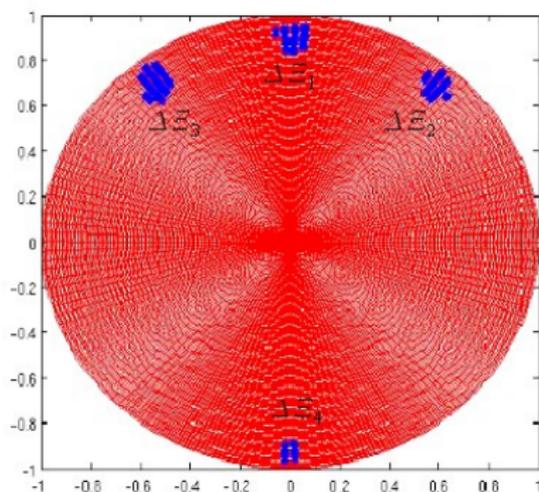


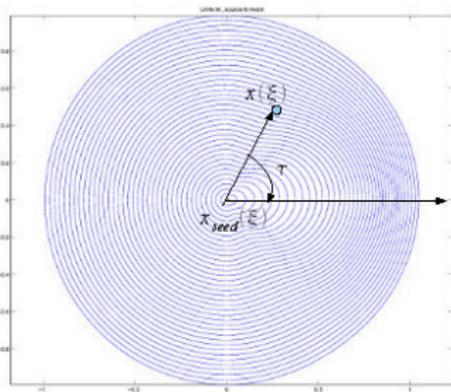
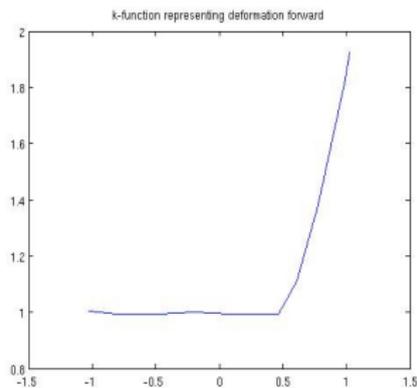
Figure: Isotropic locally expansive growth with active gene sets  $\bigcup_{i=1}^4 \Delta \Xi_i$ .

Click on an image to play a movie.

# Anisotropic deformation patterns

$$\phi(x(\xi, t)) = x(\xi, t) + k(\tau)\mathcal{R}(x(\xi, t) - x(\xi_{seed}, t)).$$

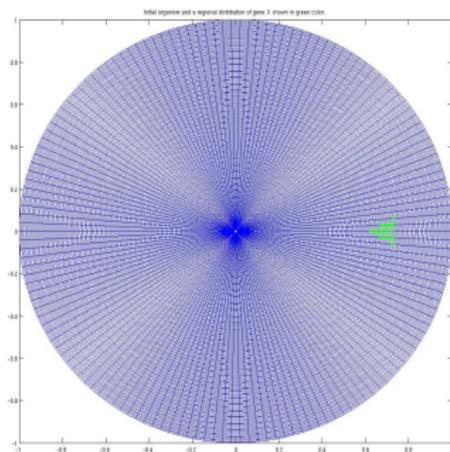
If  $k(\tau)$  is angle-dependent, then the deformation  $\phi^{\xi_{seed}, t}$  is anisotropic with one or more preferred directions of growth or decay.



**Figure:** Angular deformation function  $k(\cos(\tau))$  and the corresponding deformation type “unipolar\_source\_forward”.

## Anisotropic deformation patterns

We specify gene activity region and build a growth pattern out of several elementary “uni-source-forward” maps.

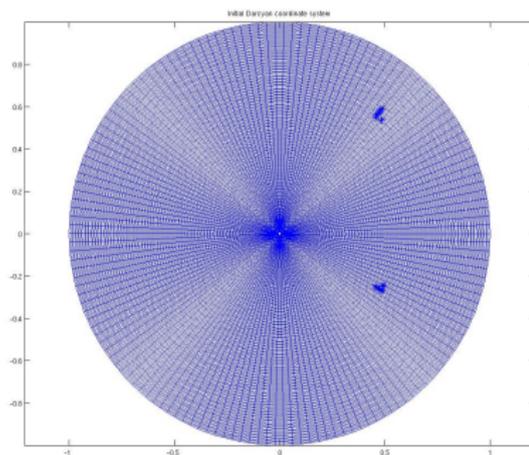


**Figure:** Gene activity region, unipolar source growth pattern and evolution of the Jacobian of the transformation with respect to the initially polar grid.

Click on an image to play a movie.

## Anisotropic deformation patterns

Similarly, we build a growth pattern out of several elementary “uni-sink-forward” maps.



**Figure:** Gene activity regions, unipolar sink growth pattern and evolution of the Jacobian of the transformation with respect to the initially polar grid.

[Click on an image to play a movie.](#)

## Anisotropic deformation patterns

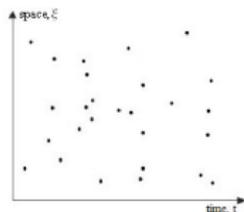
**Figure:** Two consecutive phases of chick wing development, “arm” and “forearm” with preferential directions of growth  $\tau = \pi/2$  and  $\tau = \pi/4$  correspondingly.

## Stochastic version of the isotropic GRID model

Imagine a growing organism as an evolution of a discrete particle configuration in absolute space-time driven by the inhomogeneous Poisson point process of seed activations.

Such a growth pattern  $\{x(\xi, t), t > t_0, \xi \in \Xi\}$  is a **Poisson-driven Markov process** described by the stochastic differential equation

$$dx = \int_{\xi_{t_j} \in \Xi} y^{\xi_{t_j}}(x) \mu(d\xi, dt) \text{ subject to } x(\xi, t_0) = x_0(\xi).$$



**Figure:** Spatial-temporal Poisson point process,  $\xi$ , spatial coordinate,  $t$ , time coordinate.

# Stochastic version of the isotropic GRID model

Experimental study of the Poisson-driven Markov process suggests the diffusive nature of interior seed paths.

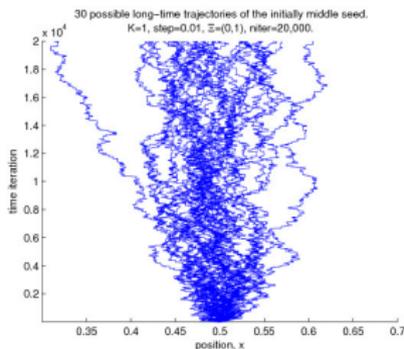


Figure: 30 realizations of 1D long-time Poisson-driven process.

## Stochastic version of the isotropic GRID model

We approximate the jump process by the diffusion process.

Namely, we derive the Fokker-Planck equation (FPE) describing the probability density of the 1D diffusive stochastic flow

$$\frac{\partial f(x, t)}{\partial t} = -\frac{\partial}{\partial x} (f(x, t) \cdot a(x)) + \frac{1}{2} \frac{\partial^2}{\partial x^2} (f(x, t) \cdot b(x))$$

with initial conditions  $f(x, t_0) = \sigma(x - \xi_0)$ .

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FPE coefficients  $a(x)$  and  $b(x)$  reveal the space-dependent average velocity and the diffusion rate of the stochastic flow.

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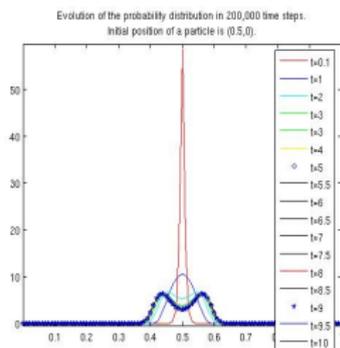
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FPE time-dependent solutions reveal bimodal distribution of a random seed trajectory in space-time.



Evolution of the probability density  $f(x, t)$  of seed trajectories in time-space.

## Stochastic version of the isotropic GRID model

Future applications of the 2D Fokker-Planck equation include computation of macroscopic properties of the stochastic flow.

- Evolution of the mean seed trajectories in time.

$$\frac{d}{dt} \langle x(t) \rangle = \langle a(x(t)) \rangle .$$

- Evolution of the variance of seed trajectories in time.

$$\frac{d}{dt} \langle \langle x(t) \rangle \rangle = \langle b(x, t) \rangle + 2 \langle [x(t) - \langle x(t) \rangle] a(x(t)) \rangle$$

Maintaining the condition of independency of seed trajectories we can claim that these equations are meaningful macroscopic equations of growth on a fine time scale.

# GRID equation of growth on a coarse time scale

Motivation: A multitude of elementary biological events (cell divisions/deaths, enlargements and movements) results in visible shape and interior changes of a growing organism seen in images.



It seems natural to represent an underlying biological transformation by a diffeomorphic flow that evolves in time as a collective effect of a large number of cell decisions.

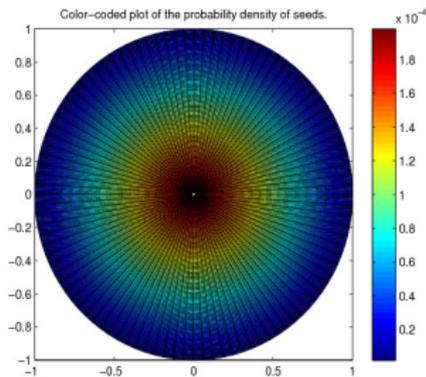


Figure: Macroscopic growth with space-dependent Poisson intensity.

## GRID equation of growth on a coarse time scale

The GRID equation of growth on a coarse time scale<sup>5</sup> is a continuum mechanics equation of motion with the velocity resulting from an infinite number of seed activations.

$$\frac{\partial x(\xi, t)}{\partial t} = \int_{\xi_{seed} \in \Xi} \Delta x^{\xi_{seed}}(\xi, t) \lambda(x(\xi_{seed}, t)) d\xi_{seed},$$

where  $\Delta x^{\xi_{seed}}(\xi, t)$  is an elementary deformation field due to a single seed placement at  $x(\xi_{seed})$   
 $\lambda(x(\xi_{seed}, t))$  is the Poisson intensity of seed placements.

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<sup>5</sup>N. Portman, E.R. Vrscay, *Existence and Uniqueness of Solutions to the GRID Macroscopic Growth Equation*, Appl.Math. Comput. (2011), doi:10.1016/j.amc201.03.021, in press

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$$\frac{\partial x(\xi, t)}{\partial t} = \int_{\xi_{seed} \in \Xi} \Delta x^{\xi_{seed}}(\xi, t) \lambda(x(\xi_{seed}, t)) d\xi_{seed},$$

Growth is approximated by a diffeomorphic flow  $x(\xi, t)$  that depends on

- the Poisson intensity of seed placements  $\lambda(x(\xi_{seed}, t))$
- and the relative rate of expansion/contraction  $k(x(\xi, t))$  (the source).

We use the GRID macroscopic growth equation for image inference of the source of the diffeomorphic flow.

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<sup>5</sup>N. Portman, E.R. Vrscay, *Existence and Uniqueness of Solutions to the GRID Macroscopic Growth Equation*, Appl.Math. Comput. (2011), doi:10.1016/j.amc201.03.021, in press

# Larval development of the *Drosophila* wing disc

**Biological facts** that have been taken into the 2D GRID model of the wing disc growth:

1. The observed dynamics of Wingless gene expression is tightly linked to the biological process of cell divisions.
2. Cells divide randomly and uniformly throughout the wing disc at larval stage of development.
3. Cell number doubles on average every 9 hours during the second and early third instar.
4. Most cell movements are due to passive displacements (newborn cells pushing extant ones).
5. The disc epithelium is one cell thick.

# Estimation of the intensity of cell decisions

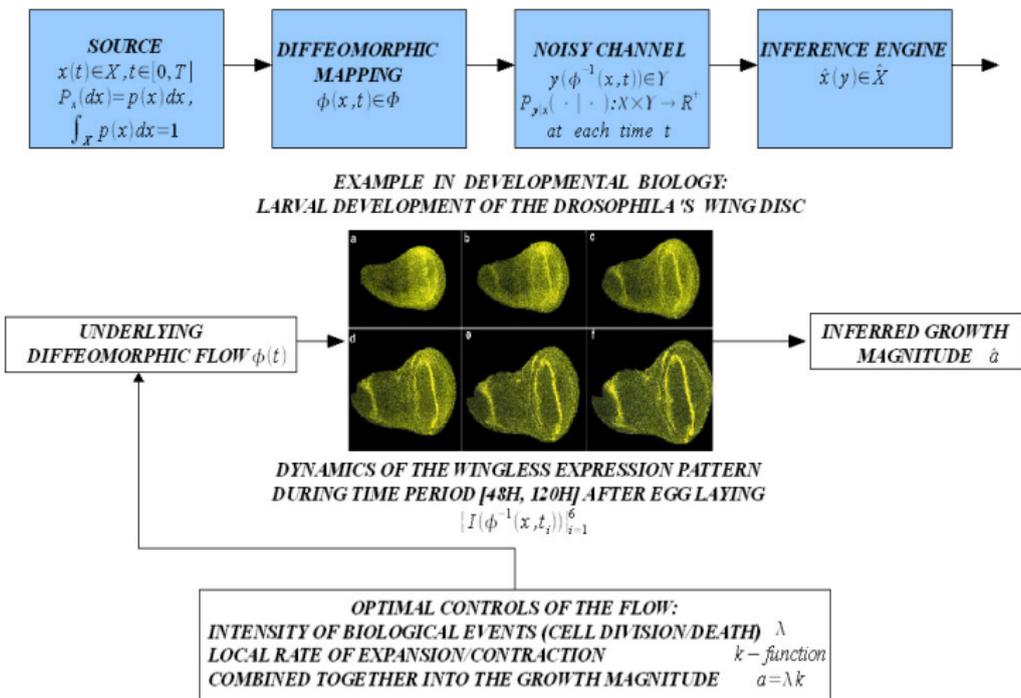


Figure: Inference of the GRID magnitude parameter from sensor data.

## Estimation of the intensity of cell decisions

The growth magnitude  $a(\xi_{seed}, t) = k(x(\xi_{seed}, t))\lambda(x(\xi_{seed}, t))$  is the unknown source of a biological deformation.

### Assumption.

- The absolute value of the local rate of expansion/contraction  $k(x(\xi_{seed}, t))$  is constant. It varies in sign throughout the cellular field.
- Let  $k(x(\xi_{seed}, t))$  be  $\pm 1$  and let  $\lambda$  absorb this constant for simplicity.
- The Poisson intensity of events in the Darcyan space is  $|\lambda(\xi_{seed}, t)|$ .

We would like to infer  $\lambda$ -field directly from image data.

## Estimation of the intensity of cell decisions

Using Bayes theorem we find a *maximum a posteriori* (MAP) estimate of  $\lambda(\xi, T)$

$$\arg \min_{\lambda \in R^N \times [0, T]} E_{post}(\lambda(\xi, T)) = \arg \min_{\lambda \in R^N \times [0, T]} [E_{likelihood}(\lambda(\xi, T)) + E_{prior}(|\lambda(\xi, T)|) + \Phi(\lambda(\xi, T))]$$

$E_{likelihood}(\cdot)$  relates observed pixel values with the growth parameter  $\lambda(\xi, T)$ ,

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$E_{prior}(\cdot)$  measures cell activities as represented by the Poisson intensity  $|\lambda(\xi, T)|$ ,

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$\Phi(\cdot)$  increases smoothness of  $\lambda(\xi, T)$  in the organism's domain.

$$\Phi(\lambda) = \|\nabla \lambda\|_2^2 = \int_{\xi \in \Xi} |\nabla \lambda(\xi, T)|^2 d\xi.$$

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subject to the discretized macroscopic growth equation

$$x(\xi, T) - x(\xi, 0) = \sum_{t=1}^T \sum_{\xi_{seed} \in \Xi} (x(\xi, t) - x(\xi_{seed}, t)) e^{\frac{-\|x(\xi, t) - x(\xi_{seed}, t)\|^2}{s(x(\xi_{seed}, t))^2}} \cdot \frac{1}{J(x(\xi_{seed}, (t-1)))} \lambda(\xi_{seed}, t)$$

with the initial conditions  $\lambda(\xi) = \frac{1}{N}$  ( $N$  is the total number of Darcyan seeds). This is the **optimal control problem** formulation.

# Prior models of the intensity field

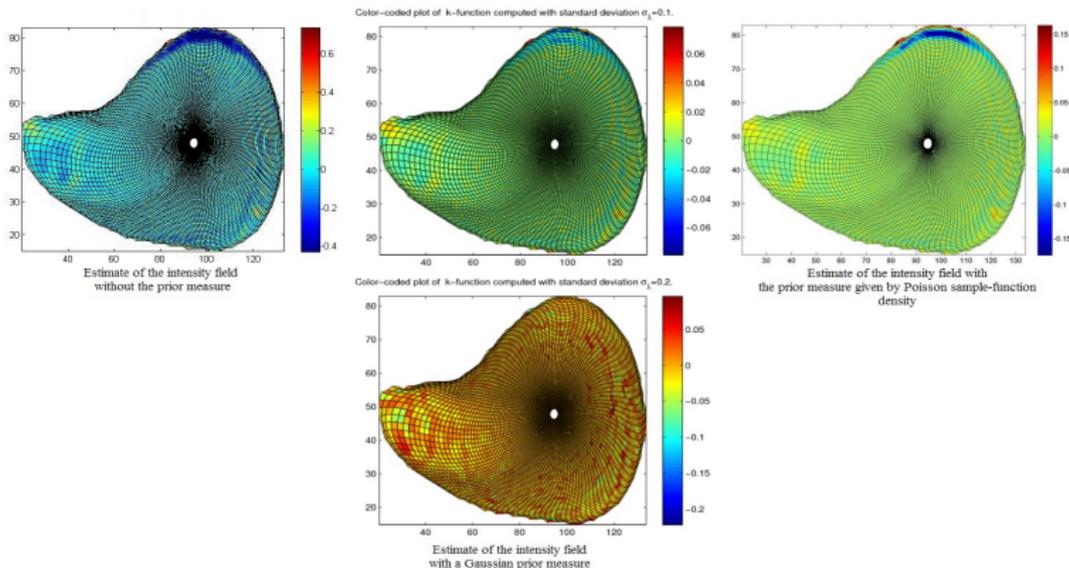
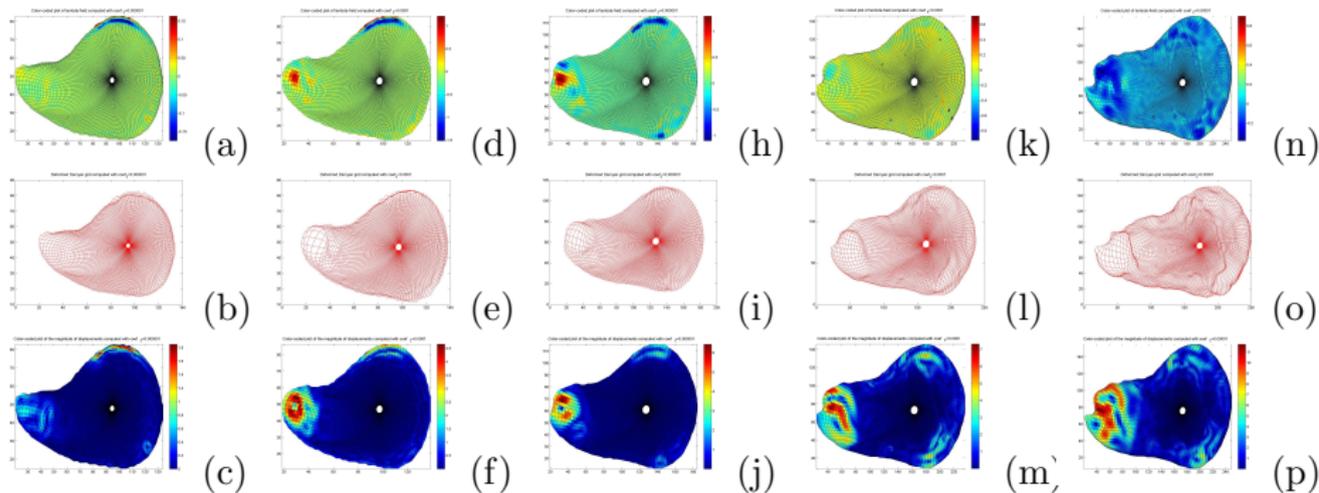


Figure: Left: no prior model,

middle: Gaussian prior  $E_{prior}(\lambda(\xi, t)) = \frac{1}{2\sigma_\lambda^2} \cdot \sum_{\xi \in \Xi} (\lambda(\xi, t) - \frac{1}{N})^2$ ,

right: Poisson prior  $E_{prior}(\lambda(\xi, t)) = - \sum_{[i=1]}^N \ln |\lambda(\xi_i, t)| + \sum_{[i=1]}^N |\lambda(\xi_i, t)|$

Inferred growth patterns of the *Drosophila* wing disc<sup>6</sup>.

**Figure:** Estimated  $\lambda(\xi)$  (top panel), deformed Darcyan grid of the wing disc generated by  $x(\xi, t)$  (middle panel) and magnitude of the displacements (bottom panel) for image pairs  $(I_1, I_2)$  (a-c),  $(I_2, I_3)$  (d-f),  $(I_3, I_4)$  (h-j),  $(I_4, I_5)$  (k-m),  $(I_5, I_6)$  (n-p).

<sup>6</sup>Portman N., Grenander U., Vrscay E., *GRID Macroscopic Growth Law and its Application to Image Inference*, Quarterly of Applied Mathematics, Vol. LXIX(2), 227–260 (2011)

# Hidden growth patterns of the *Drosophila* wing disc

**Figure:** The diffeomorphic flow  $x(\xi, t)$  of the Darcyan grid of the wing disc and the corresponding evolution of the pixel intensities  $I_1(x(\xi, t))$ .

Click on an image to play a movie.

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    - It allows *maximum a posteriori* estimation of the intensity of elementary biological events underlying observed dynamics of levels of gene expression.
- The diffeomorphic flow corresponding to the optimal value of the  $\lambda$ -field does not fully register source and target images.

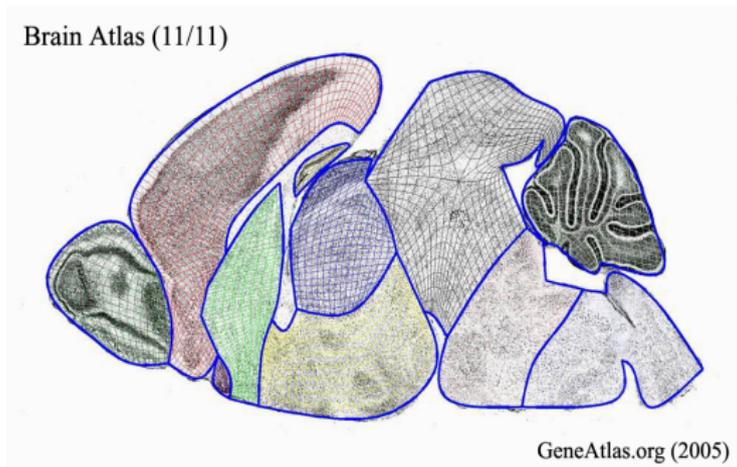
## Concluding remarks

This research has contributed to the development of

- a genetically-based model of a biological growth in quantitative biology,
- new computational methods in grid generation,
- optimization methods in image analysis,
- a new application of image analysis to the field of confocal microscopy.

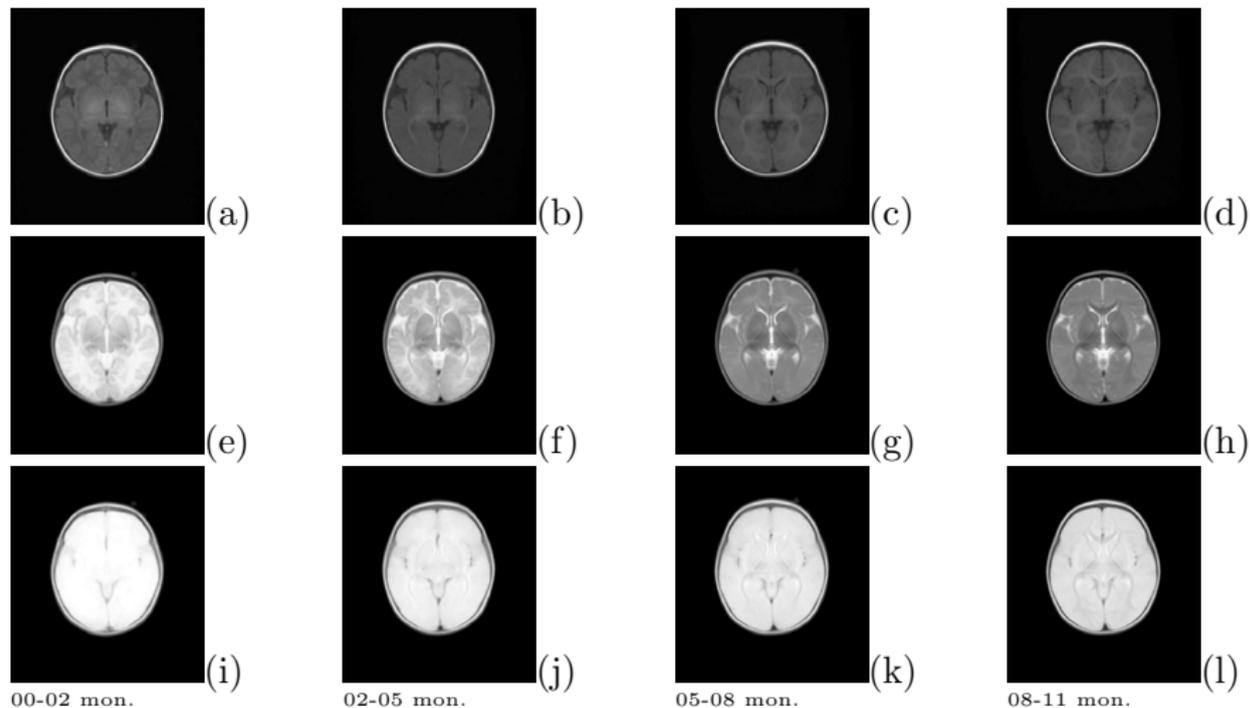
## Future perspectives

The study of a link between gene expression patterns and generation of shape in a developing mouse brain.



**Figure:** Brain atlas of a postnatal (day 7) mouse brain sagittal slice with the gene expression data (gene atlas) attached onto it. Cells expressing genes in anatomical subregions of the brain are stained in dark, [www. geneatlas. org ].

# Current work



**Figure:** Axonal myelination during infant brain development affecting MRI signal. (a)-(d) T1-, (e)-(h) T2- and (i-l) proton density-weighted templates

## Current work

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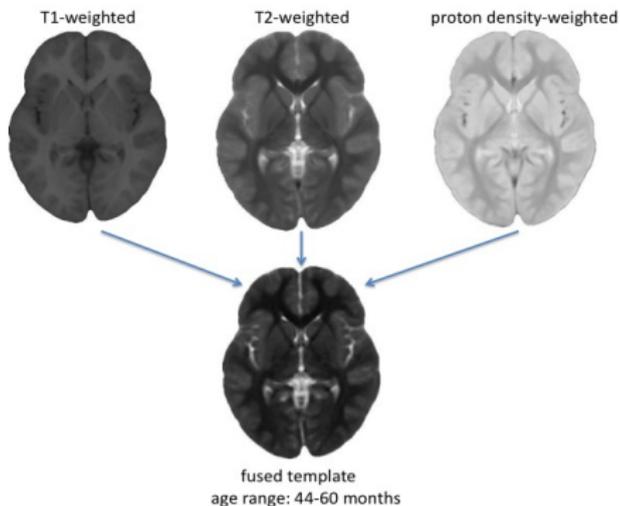
- Most longitudinal studies have been limited to T1-weighted images only.
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- Most longitudinal studies have been limited to T1-weighted images only.
- As a result, the automated image segmentation and cortical surface extraction procedures are hard to implement due to poor and highly variable grey/white matter contrast.
- It is reasonable to combine information from all three MR anatomical images in the form of fused images with enhanced detail.
- This way uniqueness and fidelity of deformation fields induced by developmental process to all three types of MRI data can be established.

# Current work



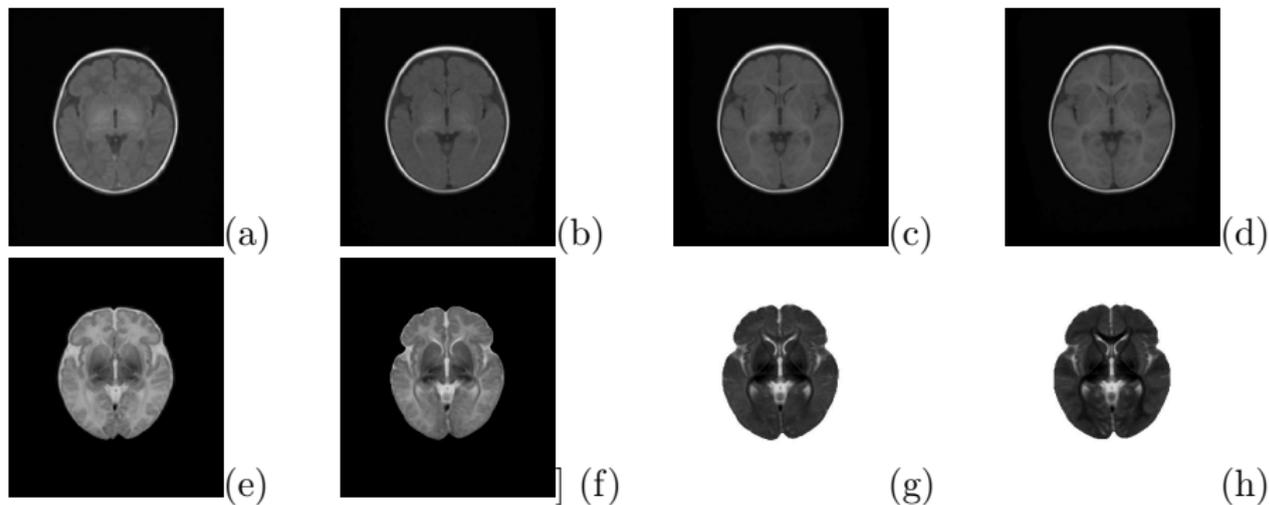
**Figure:** Fused template (44-60 mon.) obtained from T1-, T2- and PD-weighted templates <sup>7 8</sup> using wavelet-based approach.

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<sup>7</sup> Alan C. Evans and Brain Development Cooperative Group, *The NIH MRI study of normal brain development*, NeuroImage 30 (2006), 184-202.

<sup>8</sup> V. Fonov, Ilana R. Leppert, B. Pike, D. L. Collins and the Brain Development cooperative Group, *MRI models of normal pediatric brain development from birth to 4.5 years: Part 1: Anatomical Templates* to be submitted to NeuroImage.

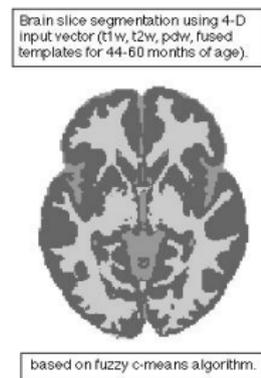
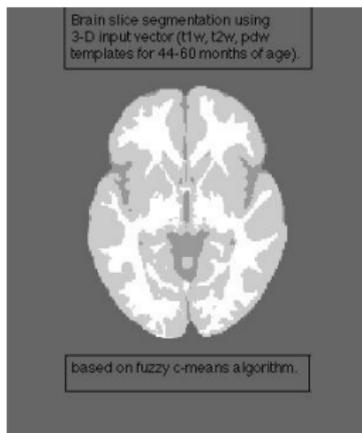
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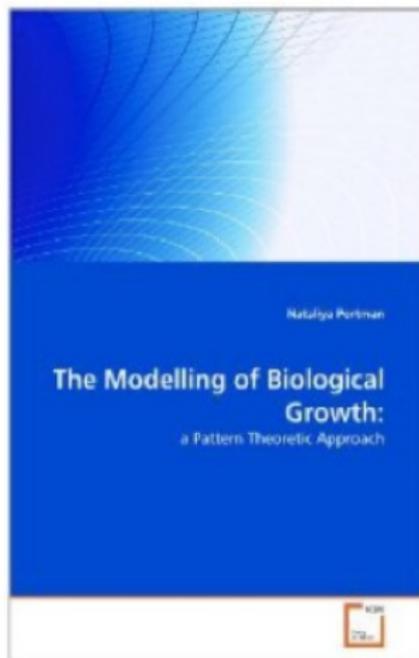
**Figure:** (a)-(d) T1-weighted atlas of normal early brain development and (e)-(h) its fused version.

# Current work

Adding a fused image to the existing three anatomical imaging modalities improves image segmentation.



# Literature



N. Portman, *The Modelling of Biological Growth: a Pattern Theoretic Approach*, VDM Verlag (May 2011), ISBN-10:3639303857, 304 pages, available at [www.amazon.ca](http://www.amazon.ca)

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