A Stochastic Partial Differential Equation for Biological Growth with Genetically Controlled Cells[1]

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1 Background

Much recent work in CA employs diffeomorphisms that deform templates into observed images. See Christensen, Rabbit, Miller (1994), Beg, Miller,Trouve, and Younes (2003), Mumford (2002), Miller, Trouve and Younes (2002). Further reference can be found at www.cis.jhu.edu and in Grenander,Miller (1998). This work has used a *static* approach, biological time does not enter the discussion, only algorithmic time, but now, when we are studying biological growth, the diffeomorphisms will represent the *dynamics of growth/decay* in biological time, and this will have important consequences for the model building.

We have used models as the one in (1), and several variations of it,

$$\frac{\partial \phi(x,t)}{\partial t} = v[\phi(x] + n(x,t); x = (x_1, x_2, x_3) \in X; t \in [0,1] \tag{1}$$

with $X = [0, l_1] \times [0, l_2] \times [0, l_3]$, time unit perhaps a week, $n(\cdot,\cdot)$ means random noise representing biological variation, and perhaps terms on the right hand side to represent landmark constraints. This induces maps

$$I_{temp} \rightarrow I^{\mathcal{D}} = \phi^{(-1)} \circ I_{temp} \tag{2}$$

where I is a template image and ϕ is the diffeomorphism. Here the velocity of deformation $v(\cdot)$ is a function of the moving point x in absolute space X, but this setup corresponds poorly to what happens during biological growth, since only relative space is meaningful in this context. We must construct biologically meaningful models, so that they express *growth tendencies of the cells* as governed by genes and modifications of genes. This relates to the cells themselves, not to their position in absolute spece X. Hence, we should adopt the point of view in GPT, section 4.3.8, where growth pressure is related to the cells (generators) of the organism.

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We add in passing that we may have concentrated too much on diffeomorphic mappings. Many biological processes exhibit destruction of topology, say in mitosis or, closer to our current interest, in pathological growth and decay. Better keep this in mind for future use.

Returning to the above discussion, we are atually confronted with the question of choosing an intrinsic coordinate system. Although equations of motions are usually simpler to write down in Eulerian formulations, here we will have equations with more Langrangian components relating to the cells along the trajectory. The growth tendency should be expressed in such Lagrangian coordinates. This will lead to some unavoidable mathematical complications, but we believe that we will be able able to cope with them.

2 An SPDE for growth.

More concretely, let the trajectories in absolute space be denoted by $x(t) = \phi(\xi, t)$ where ξ enumerates the trajectories with the initial values $x(\xi, 0) = \xi \in \Xi$. We could start with the PDE for incompressible Navier-Stokes,

$$SPDE : \frac{Dv}{Dt} = -grad\ p + \mu \Delta v \tag{3}$$

but with the *growth pressure* p being a given function of ξ, not of x, and with a parameter μ that plays a role similar to that of viscosity for fluids. For example, cells belonging to the hippocampus may have different values for the pressure $p(\cdot)$ than cells in the frontal cortex due to genetic control. The gradient of $p(\cdot)$ drives the organism to expand or contract according to the genetic information stored in the cells. We will also have random terms representing biological variability, but that will be discussed later. The term Δv and the viscosity μ are introduced to ensure enough smoothness for the case to be studied later on when we also have random forces acting on the cell growth.

This model will not be adequate for describing growth processes since the assumed incompressibilty contradicts growth. It will therefor be modified and we shall try the following. Note also the discussion in Mumford (2002), section 4.3, in terms of geodesics in homogeneous spaces.

With standard notation

$$\dot{f} = \frac{\partial}{\partial t}\ for\ fixed\ \xi \tag{4}$$

$$f_t = \frac{\partial}{\partial t}\ for\ fixed\ x \tag{5}$$

we can write $v = \dot{\phi}$ and introduce the deformation gradient as the function $F = \frac{\partial \phi}{\partial \xi}$ taking 3×3 matrices as values. Assuming that the map $\phi : \Xi \to X$ can be inverted with an inverse

$\Phi : X \to \Xi$, which will be the case at least for sufficiently small values of t, we also get the inverse $G = \frac{\partial \Phi}{\partial x}, G = F^{-1}$.

Then we can write the momentum equation concisely as

$$(v_i)_t = \sum_{j=1}^{3} \frac{\partial T_{ij}}{\partial x_j} \tag{6}$$

with the Cauchy stress matrix

$$T_{ij} = \mu \frac{\partial v_i}{\partial x_j} - p(\xi)\delta_{ij} \tag{7}$$

Following a suggestion by Constantine Dafermos we will proceed as follows. Start from the form of the momentum equation

$$(v_i)_t + \sum_{j=1}^{3} \frac{\partial v_i v_j}{\partial x_j} = \sum_{j=1}^{3} \frac{\partial T_{i,j}}{\partial x_j} + \ randomness \tag{8}$$

and the mass equation

$$\rho_t + \sum_{j=1}^{3} \frac{\partial (\rho v_i v_j)}{\partial x_j} = 0 \tag{9}$$

and reduce expressions with derivatives w.r.t. x's to expressions involving derivatives w.r.t. ξ's using the Jacobian matrices F and G. This leads to the following system of stochastic PDE's

$$\dot{G_{\beta j}} = - \sum_{i,\alpha=1}^{3} G_{\beta,i} \frac{\partial v_i}{\partial \xi_\alpha} G_{\alpha,j} \tag{10}$$

$$\dot{v_i} = \sum_{\alpha=1}^{3} \frac{\partial S_{i,\alpha}}{\partial \xi_\alpha} + n_i \tag{11}$$

where we have introduced the matrix-valued function S with components

$$S_{i,\alpha} = \frac{1}{det\ (G)} [\mu \sum_{\beta,j=1}^{3} G_{\alpha,j} \frac{\partial v_i}{\partial \xi_\beta} G_{\beta,j} - p(\xi) G_{\alpha,i}] \tag{12}$$

and n_i is the random term corresponding to biological variability.

With vector-matrix notation one can write (8) and (9) as

$$\dot{G} = -\frac{\partial v}{\partial \xi} G G^T \tag{13}$$

and

$$\dot{v} = \frac{\partial S}{\partial \xi} + n \tag{14}$$

This system has 12 equations (9 in (12), 3 in (13)) and 12 unknown functions (3 components in the vector v and 9 components in the matrix G) , note that $p(\cdot)$ is assumed to be known in advance. Equations (8) and (9)form our SPDE. We will probably use Neumann boundary conditions along the sides bounding the box X and initial values

$$v(\xi, 0) = 0, G(\xi, 0) = I \tag{15}$$

This PDE does not seem to have any accepted name. Perhaps it could be called MICKEY'S LAW.

If this growth model turns out to be realistic we will be confronted by several questions:

1) In order to judge the performance of the model we ought to synthesize it applying it to some of the MRI's we already have. There does not (?) seem to exist any software specialized for this set up, but it may be possible to use programs of general nature and specialize it to MICKEY. I am looking into this problem. It appeared troubling that the observed displacement fields seemed to have fairly chaotic divergence, but this was late explained as a computational artefact due to landmark constraints.

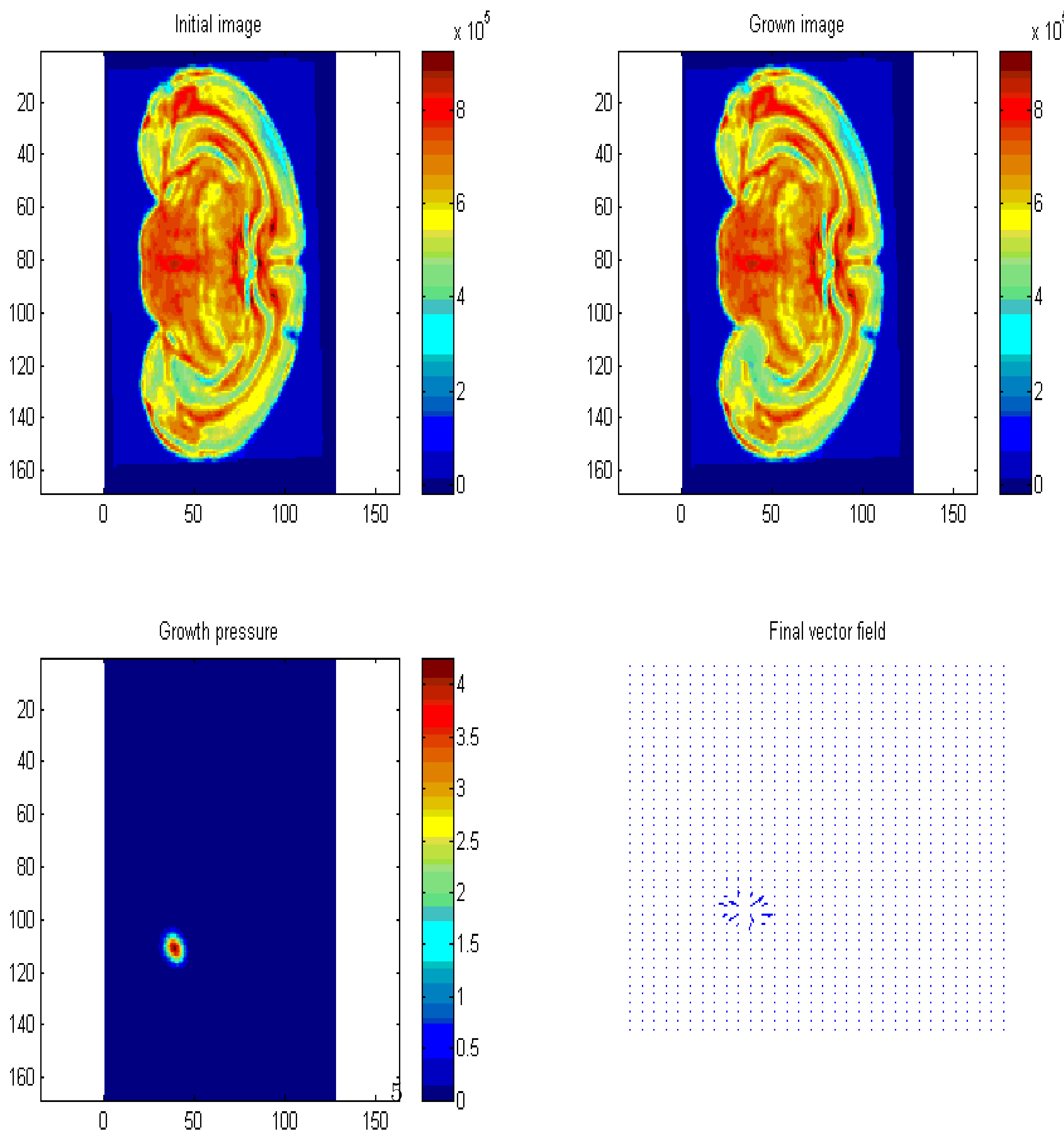
2) Using our existing data for template + image and already computed diffeomorphisms for the duration one week, how do we estimate the variation of $p(\cdot)$ over Ξ ? Perhaps we could use some simple time-averaging behavior, but a full ML solution would require a careful examination of the form of the likelihood function involving a Jacobian.

3) How would a minimum energy derivation of the solution to MICKEY'S LAW be organized ? Too early to say yet.

4) If we can handle 1) - 3) we can use the results in FANOVA as discussed in earlier reports.

3 Simulating the SPDE.

Waiting for 3D software to solve the SPDE we have developed MATLAB code for the 2D case. It uses a rough difference scheme for integrating the differential equation. We get for example



Initial image
x 10^5
Grown image
x 10^5
Growth pressure
Final vector field

Figure 1

The structure at location (45,125) in the upper left panel has grown as is seen in the upper right panel. The lower left panel shows the growth pressure and the right lower one presents the resulting deplacement field.

In Figure 2 we see a growth area at (50,80) and a decay area at (80,0),resulting in the structure in the right upper panel.

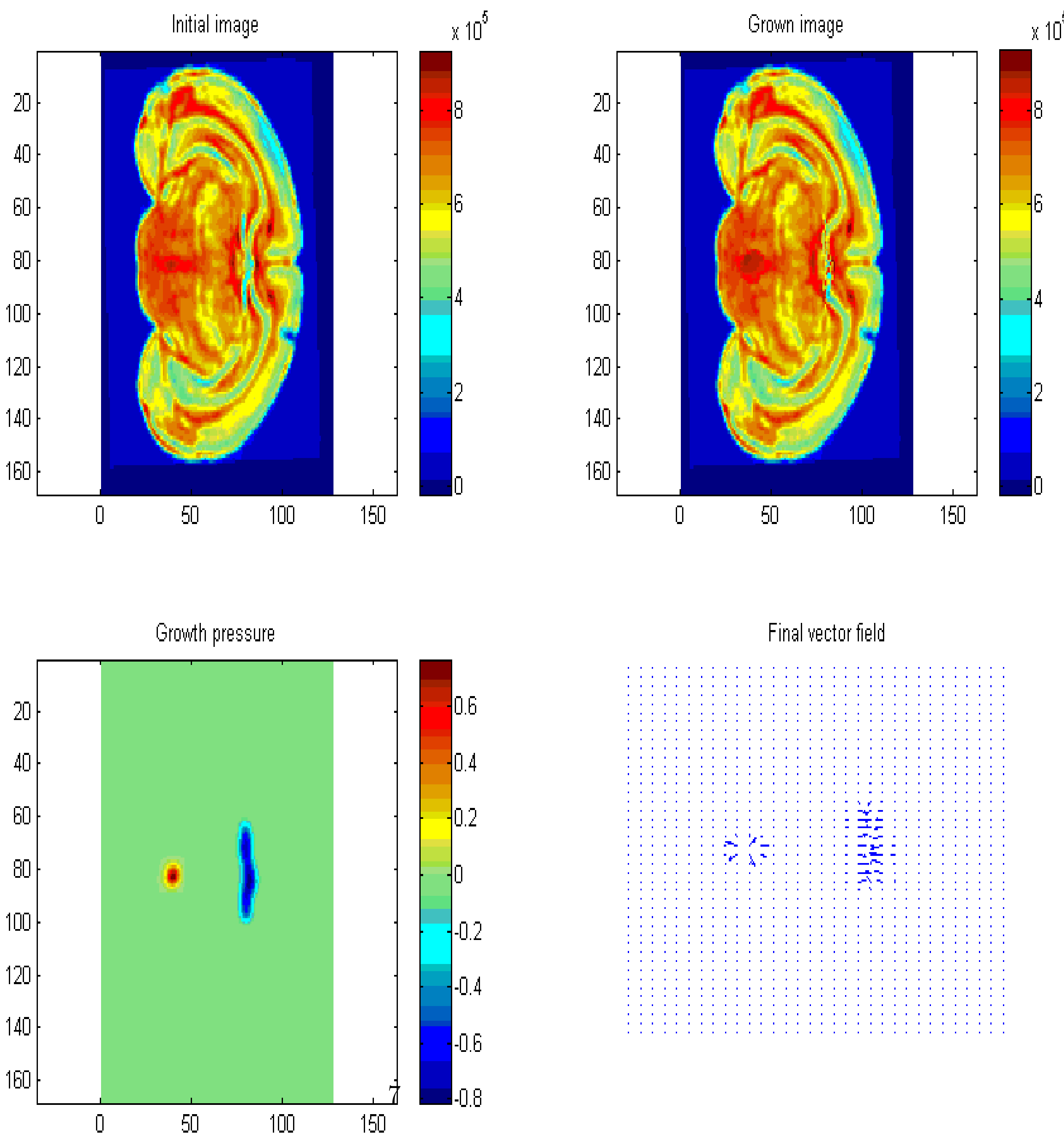


Figure 2

We have seen similar phenomina before, see Grenander, Miller (1998), but they were not based on a biologically motivated models as are Figures 1 and 2.

We mention parenthetically that if we leave out the viscosity term in (12) we get a simpler model, both analytically and computationally, but numerical experiments have convinced us that the growth then tends to be non-cohesive which contradicts experience. Therefore we have not pursued this alternative.

The SPDE has a regular solution for suffiently small durations, but nothing guarantees that this holds for long durations. Indeed, the non-linear form of the flow can very well lead to shockwaves and other singularities. If shockwaves occur this may have interesting biological interpretations, but this remains to be seen.

The paradigm of fluid flows of images has served us well, but biological growth is different from mechanical flow, so that we ought to be open to non-mechanical models for growth.

4 How to estimate the growth pressure?

If it turns out that the SPDE is indeed useful for our purpose, the question arises how the $p(\cdot)$-function can be estimated. We offer the following crude attempt that should be understood only as a first approximation.

If we neglect the viscosity term in (12) as well as the local variability of the deformation tensor G, we see that $\dot{v} \propto \ grad\ p$ where the degree of approximation is in doubt. Integrating this approximate proportionality relation we get

$$v(\xi,1)=\int_{t=0}^{1}\dot{v}\ (\xi,t)dt\ \ \propto\ \ (grad\ p)(\xi) \tag{16}$$

Now recall that a vector field $F=\{f(x);x\in X\}$ can be expressed via Helmholz' theorem as a sum

$$F=F_1+F_2=gradE+curlF \tag{17}$$

in terms of a scalar potential E and a vector potential F, so that the first term in the sum is irrotational, $curlF_1=0$, and the second term is solenoidal, $divF_2=0$. Apply div to both sides of (17)

$$divF=div\ gradE=\Delta E \tag{18}$$

It seems reasonable to state $E(x)=0;x\in\partial X$ so that with these boundary conditions

$$E=\Delta^{-1}divF \tag{19}$$

since the operator Δ is invertible on the subpace of functions vanishing on ∂X. Hence the ratio, for example with L_2 norm,

$$r_{irroot} = \frac{\|V_1\|}{\|V\|} \tag{20}$$

expresses the degree to which the velocity field is irrotational. Apply (16) and (19) to data, using classical over relaxation to determine the inverse of the Laplacian Δ, we get the estimate of the growth pressure

$$p^*(\xi) = (\Delta^{-1} div\ v)(\xi, 1) \tag{21}$$

Look at the artificial growth data in Figure 3. The growth pressure is positive in the upper part of the organism (expansion) and negative in the lower part (compression) as is seen in the upper right panel.

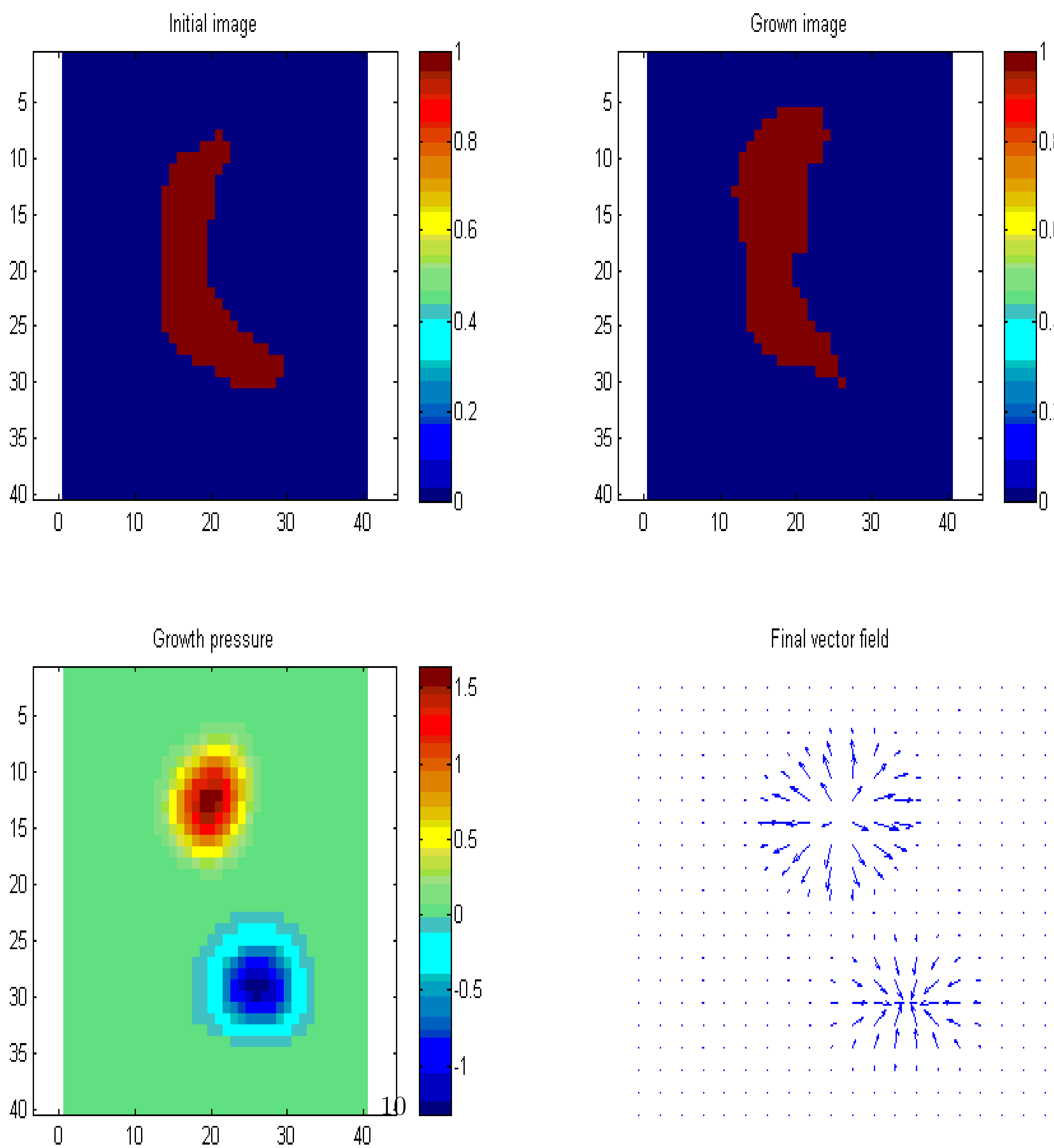


Figure 3

Compute the estimate in (21); the result is shown in the right panel of Figure 4. It does not look too bad, but we had better exercise caution keeping in mind that experimenting with artificial data often leads to misleadingly good result.

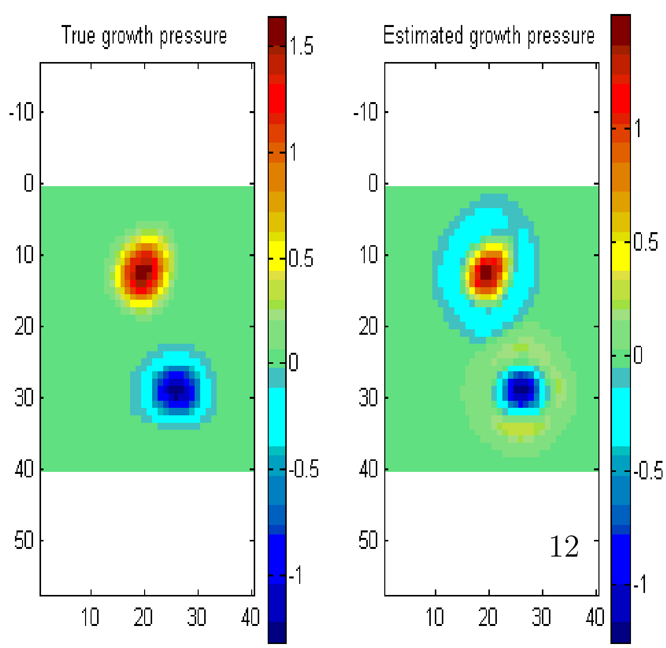


Figure 4

A more ambitious approach, perhaps using (21) as an initial attempt, could be based on ML estimation, but it remains to be seen how this could be done.

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5 REFERENCES

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