Growth Patterns of Microscopic Brain Tumors

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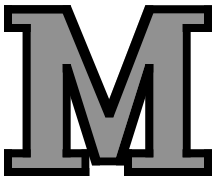

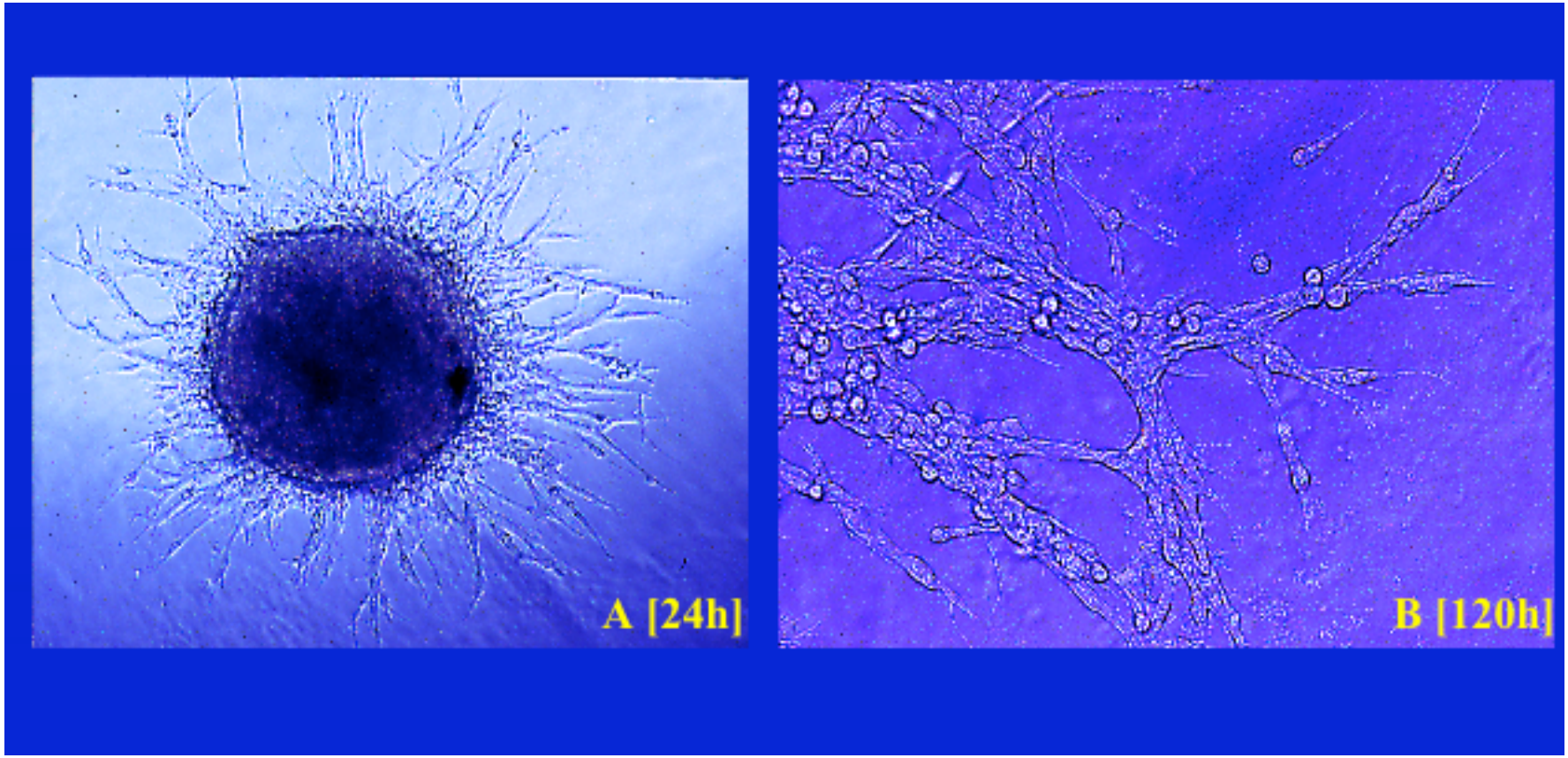

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Background

• Highly malignant brain tumors such as Glioblastoma Multiforme form complex growth patterns:invasive cells organize in tenuous branches.

• The pattern consists of *proliferation* followed by *invasive spread.*

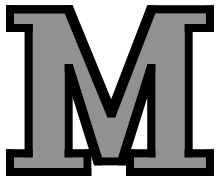
-In the initial stages the tumor grows symmetrically forming a central multicellular tumor spheroid (MTS).

- Then there is rapid invasion of surrounding tissue by mobile tumor cells, which are shed by the MTS and form branching chains of single cells.

The rapid invasion of brain parenchyma surrounding the main macroscopic tumor makes this terrible disease very difficult to treat.

• Our information comes from experiments in transparent gel (Matrigel): an MTS is seeded and an invasive zone forms. (Deisboeck, et al.)

• Our interest is to try to understand the mechanism for the formation of the branching structures.



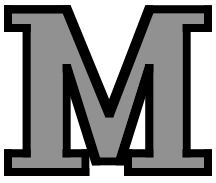
Similar Patterns

Other biological patterns *look* like GBM tumors, e.g. bacteria colonies:

But, the mechanism for branching here is that of DLA, the *proliferation of the tips* due to excess nutrient far from the center.

This may account for the pattern of cancers other than brain tumors.

For GBM invasive cells don't proliferate, but *move*. Most of the new cells are produced at the surface of the MTS, and then invade the surrounding tissue.



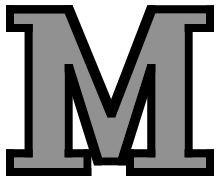
Two Elements of our Model

(i) *Chemotaxis:* motion along the gradient of nutrient concentration.

In the experiment, a (non-replenished) nutrient medium is mixed with the bio-gel, and it is consumed by the growing tumor. This, alone, would merely lead to an expanding cloud of mobile cells.

(ii) *Homotype attraction*: cells secrete a soluble agent (paracrine production) which attracts other cells.

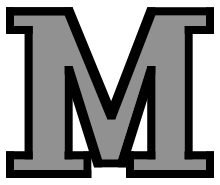
There also may be tissue damage by the invading cells, which gives rise to pathways which other cells can follow more easily. (We will look at experiments about the pathways at the end of the talk).



Results:

• In continuum model we get branch formation from a combination of heterotype and homotype attraction (*both are necessary*).

• For a discrete model for the invasive cells we get regimes of branch formation rather like the experiment.



Continuum Modeling

The mobile tumor cells are shed from the MTS and, in the absence of other forces, undergo *random motion*. In addition, there is *chemotaxis*, i.e. directed active motion along chemical gradients.

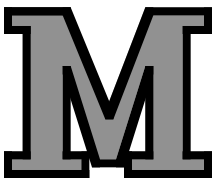
c= tumor cell concentration
n= nutrient concentration
h= homotype factor

1.) Tumor cells:

$$\partial c/\partial t = \nabla[D_c(\mathbf{r})\nabla c] \quad -\nabla[c\,\chi(n,\mathbf{r})\nabla n] \quad -\nabla[c\,\rho\nabla h]$$

diffusion *drift from ∇n* *drift from∇h*

Chemotaxis coefficient: $\chi = \chi(\mathbf{r})n_o^2/(n_o+n)^2$ (receptor law)
$n_o \sim 0.2\ g/l$



2.) Nutrient:

$$\partial n / \partial t = D_n \nabla^2 n - \lambda(n)c$$

diffusion *consumption of n*

D_n = 6.7 x 10^{-7} cm^2/sec has been measured.

Consumption of nutrient by the cells also has been measured:

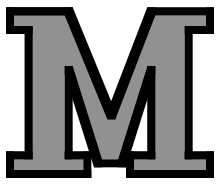
$\lambda(n) = \lambda_0 n/n_1 \quad n \le n_1; \qquad \lambda_0 \quad n > n_1$

$n_1 \sim 0.2$ *g/l* λ_0 = 1.6 pg/cell/min

3. Homotype factor (almost nothing is known about this)

$$\partial h / \partial t = D_h \nabla^2 h - \mu h + \alpha c$$

diffusion *decay* *production by tumor cells*



Unknown Parameters:

We *guess* $D_c \sim 10^{-12}$ cm^2/sec

The only value in the literature is *much larger*, $\sim 10^{-9}$

Burgess P. K., P. M. Kulesa, J. D. Murray, and E. C. Alvord. *The interaction of growth rates and diffusion coefficients in a three-dimensional mathematical model of gliomas*. J. Neuropath. Exp. Neurol. **56**,704-713 (1997).

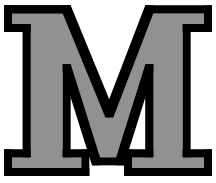
However, the analysis is based on proliferation throughout the invasive zone, and *no chemotaxis*.

Almost everything about the homotype factor is unknown. Basically we use the following as fitting parameters:

$\square$ and $\square$ (give the steady-state concentration of *h*.)

D_h, the diffusion coefficient of h. To fit the pattern $D_h < D_c$.

$\square$ gives the attraction of cells to the homotype factor.



Stability Analysis

Use Eq. 1, 2, 3 above (for *c, n, h)* to show that there is a *branch-forming instability*: start with uniform growth along a channel, and show that the tumor cells tend to clump along a line.

We should note that for our purposes the equation for *n* may simplified because the time scale for the diffusion of the nutrient is *much* faster than that of the tumor cells. So set $\partial n/\partial t = 0$. Thus, for $n>n_o$:

$$\nabla^2 n = [\lambda_o / D_n]c$$

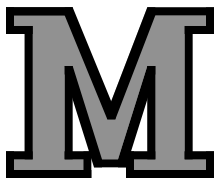
Also note that the MTS consumes nutrient. We take *n=0* in the central tumor.

Solution: $c= c_o(1+C)$ $h= h_o(1+H)$

where *C, H,* are small deviations from the steady state. Linearize the three equations in terms of these variables.

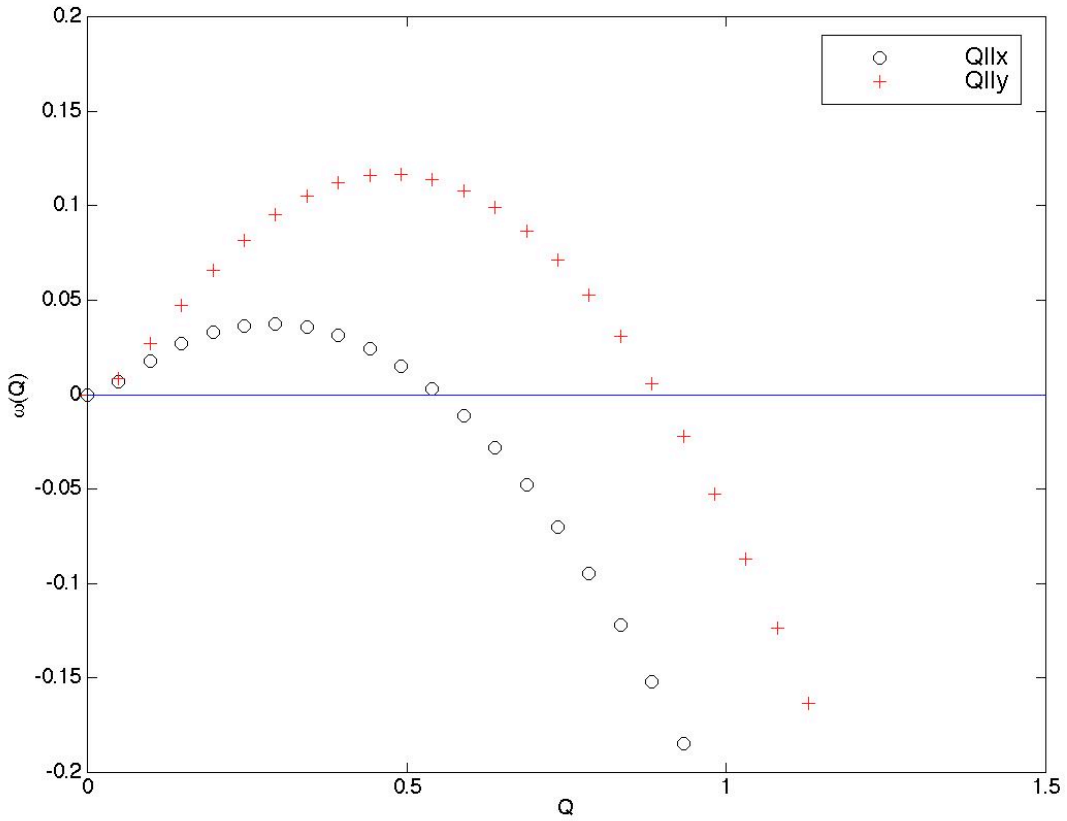
Standard solution: $C, H \sim exp (\omega T - i\mathbf{Q}\cdot\mathbf{r})$
$\mathbf{r}= a\rho$, using *a,* the cell diameter, to rescale spatial variables;

$t= (a^2 /D_c)T$, scaling time by the jump time of tumor cells.

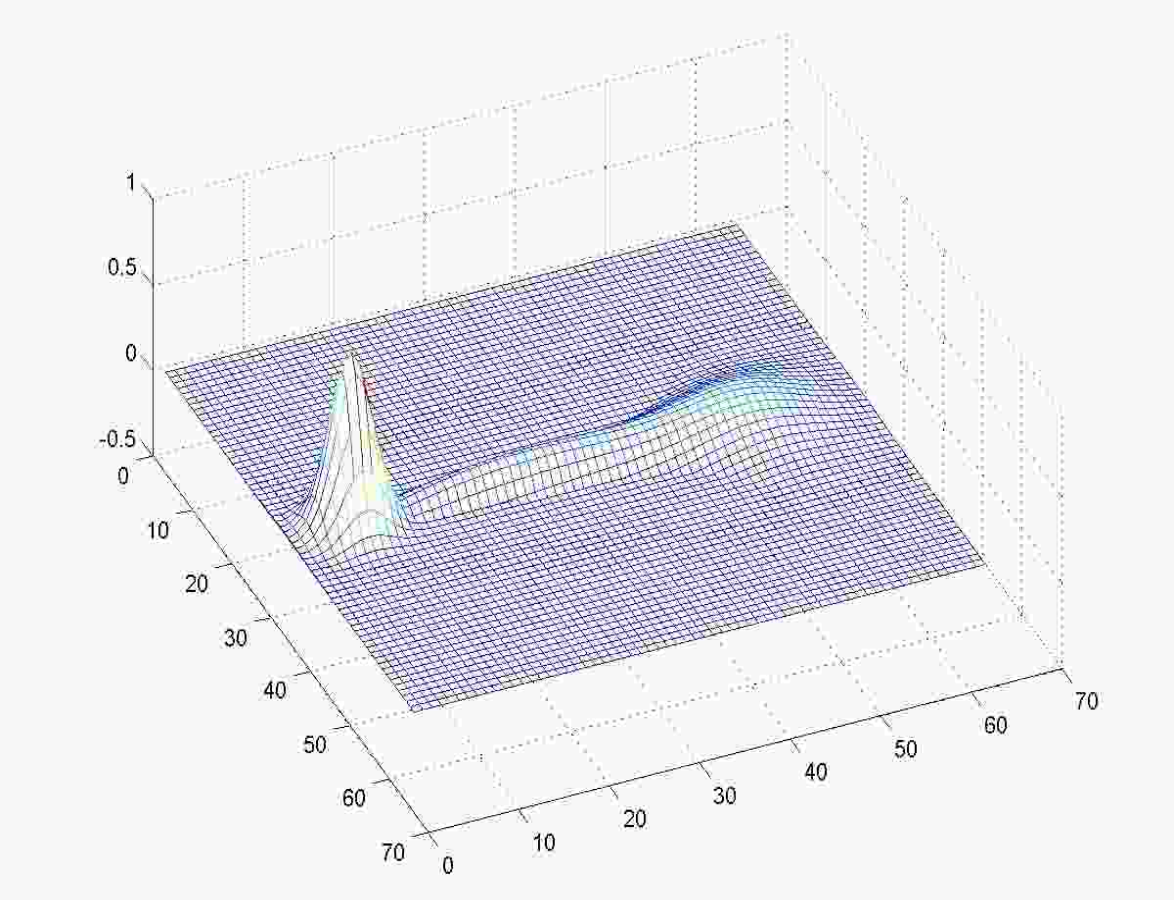


Results

Dispersion relation: $\omega(Q)$.



Development of an initial instability:



Discrete Simulation Model

Here we treat the tumor cells as agents on a lattice. Their motion is a discrete, biased random walk, as above.

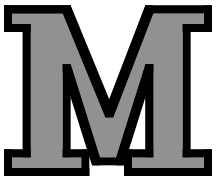
We take an extreme form of homotype attraction, assuming that the cells, in effect, damage or consume the gel as they move.

In our model, everywhere where a cell has been, the jump rate is larger by a large factor.

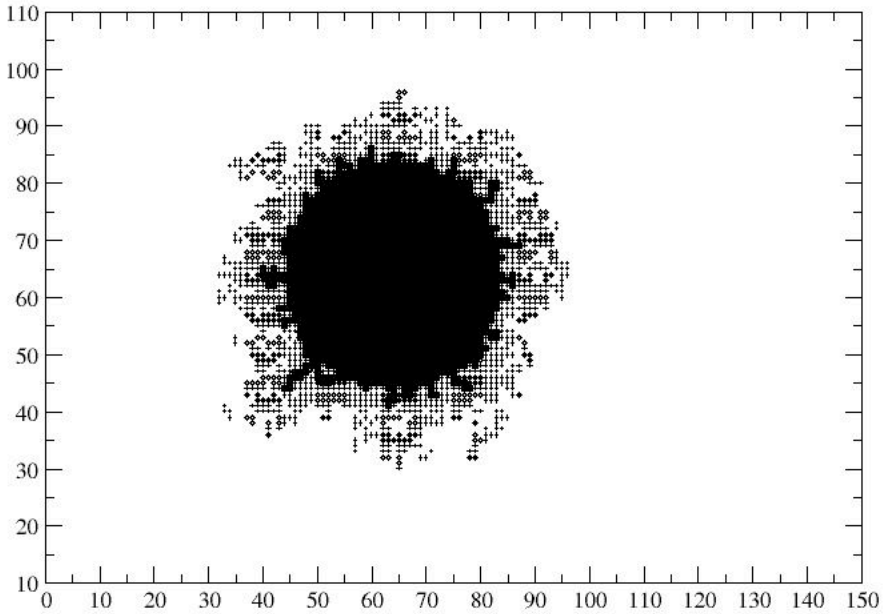
In all cases we started with a tumor core of a radius of 20 cells, and liberated 100 cells to start invasion. We allow the MTS to continue to grow an occupy a lattice site where the mobile cells have move away.

We will show three regimes for the pattern:

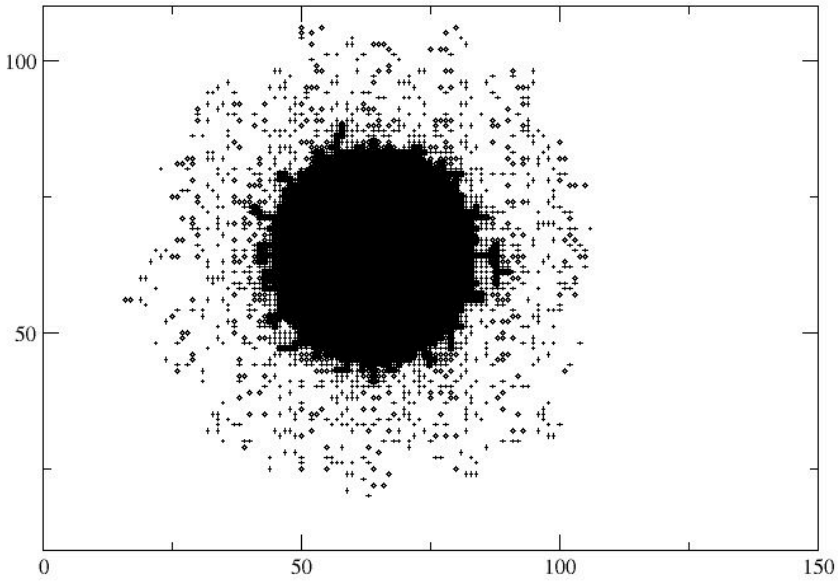
1. Weak chemotaxis, weak homotype attraction.
2. Strong chemotaxis, weak homotype attraction.
3. Both very strong.



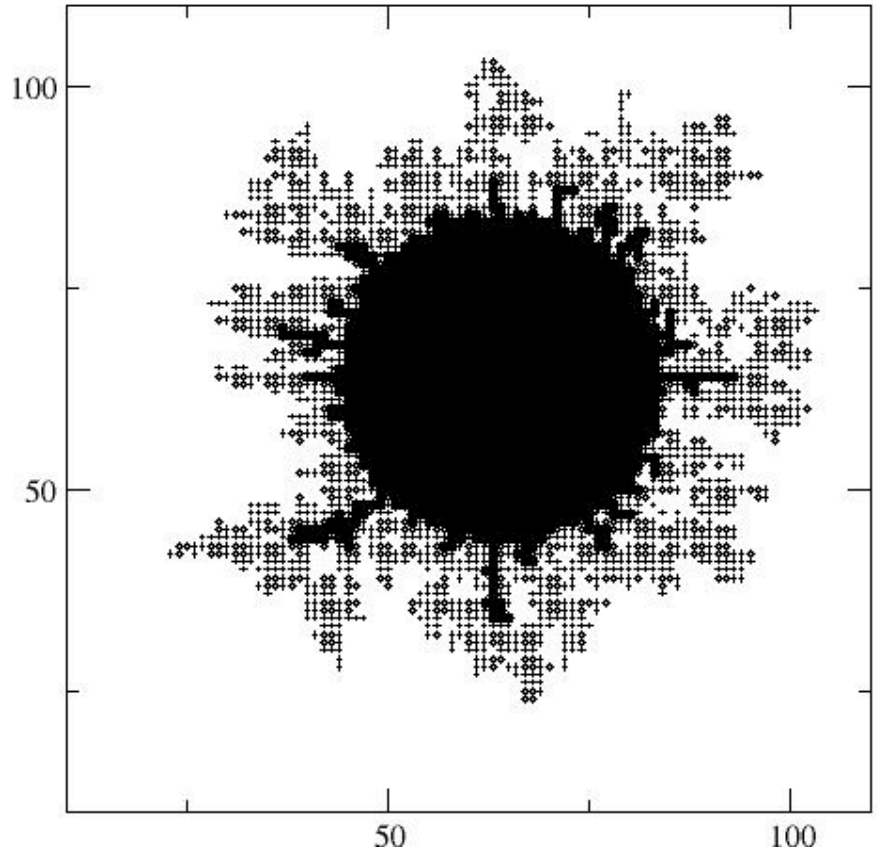
Weak chemotaxis, homotype attraction:



Strong chemotaxis:



Very strong chemotaxis, homotype attraction:



Our model *seems* to have the right ingredients.

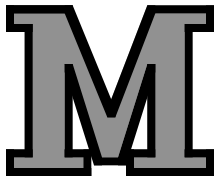
However, we don't know in detail how the cells interact with the medium, how they move, what is the nature of the 'pathways'.

Questions:
What do the cells do to the medium as they invade? How do they form pathways?

1.)They mechanically deform the gel, and possibly tear it.

2.) They can rearrange the fibers – remodel the gel

3.) They can degrade the gel via proteolytic enzymes.



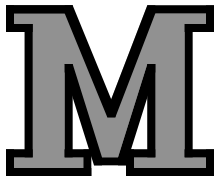
Experiments by the Weitz group at Harvard:

Measuring the Mechanical Stress Induced by an Expanding Multicellular Tumor System: A Case Study

(in press)

V. D. Gordon , M. T. Valentine , M. L. Gardel , D. Andor-Ardó, S. Dennison , A. A. Bogdanov , D. A. Weitz and T. S. Deisboeck

Seed the Matrigel with beads to serve as markers for the stress in the medium. Track motion of beads near tumor: blue early, red late.



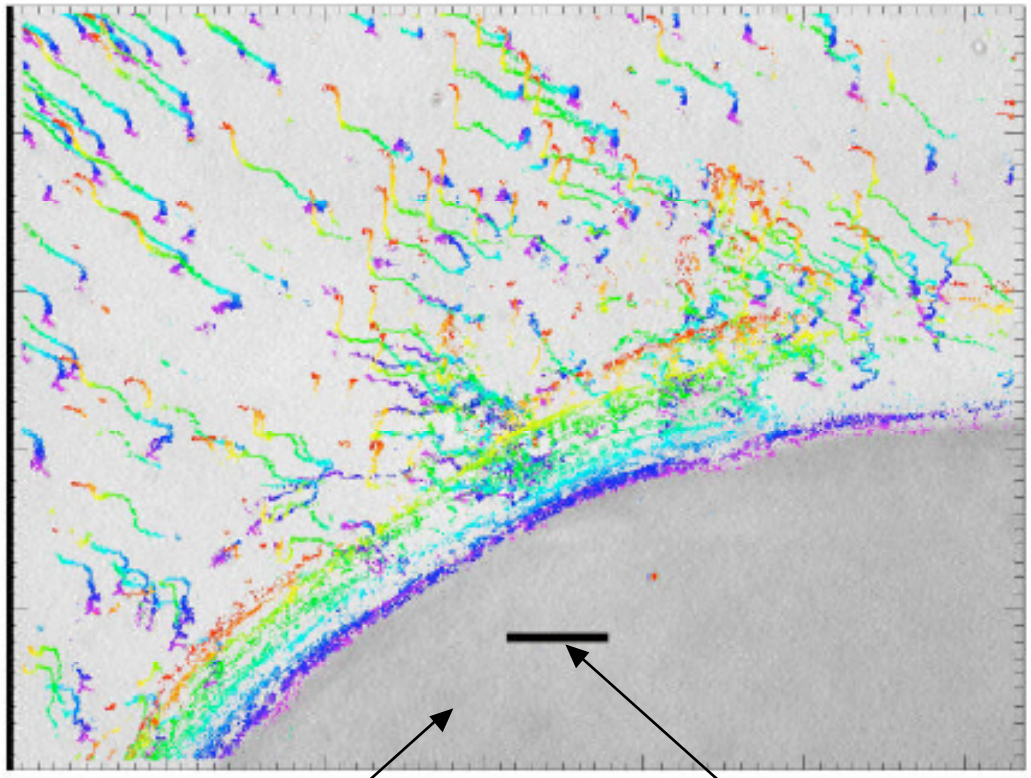


Figure 5

Stress experiments (cont.)

But, near the invasive cells, the stress is reversed: the cells *pull* on the fibers in the gel.

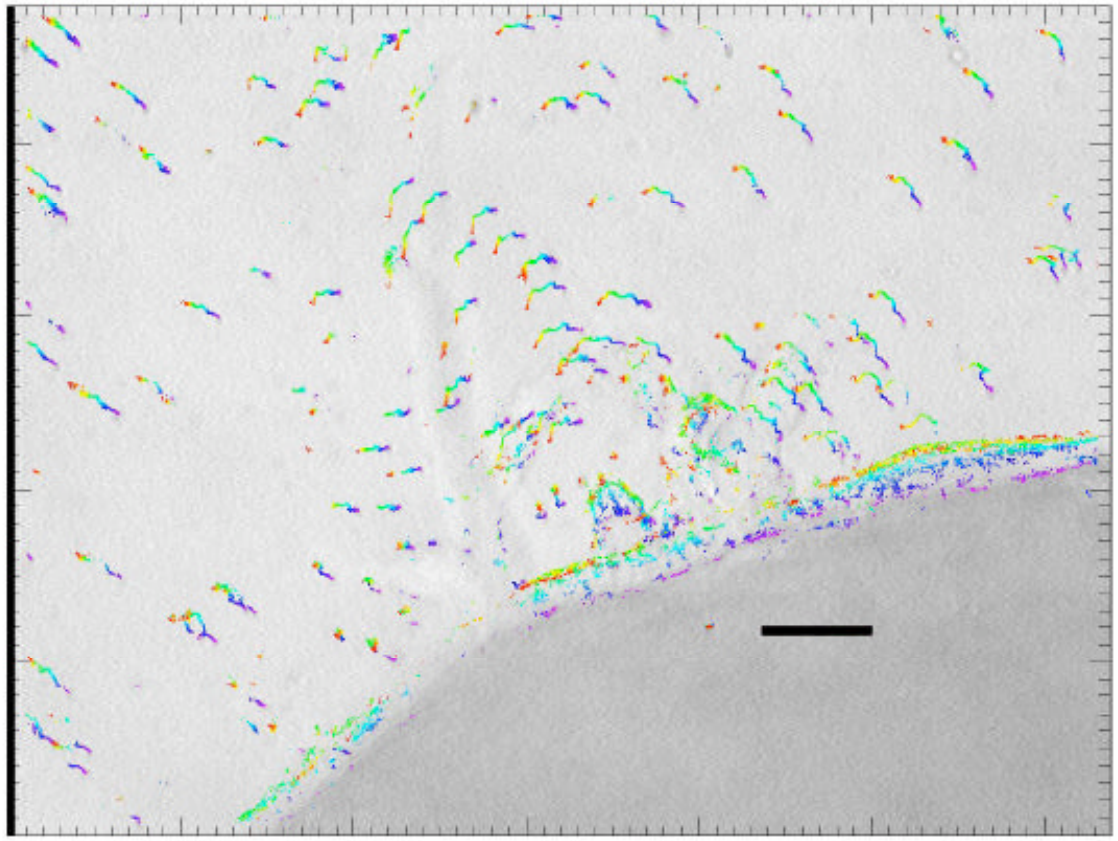


Figure 6

Arrow marks a single cell. Note dipole pattern.

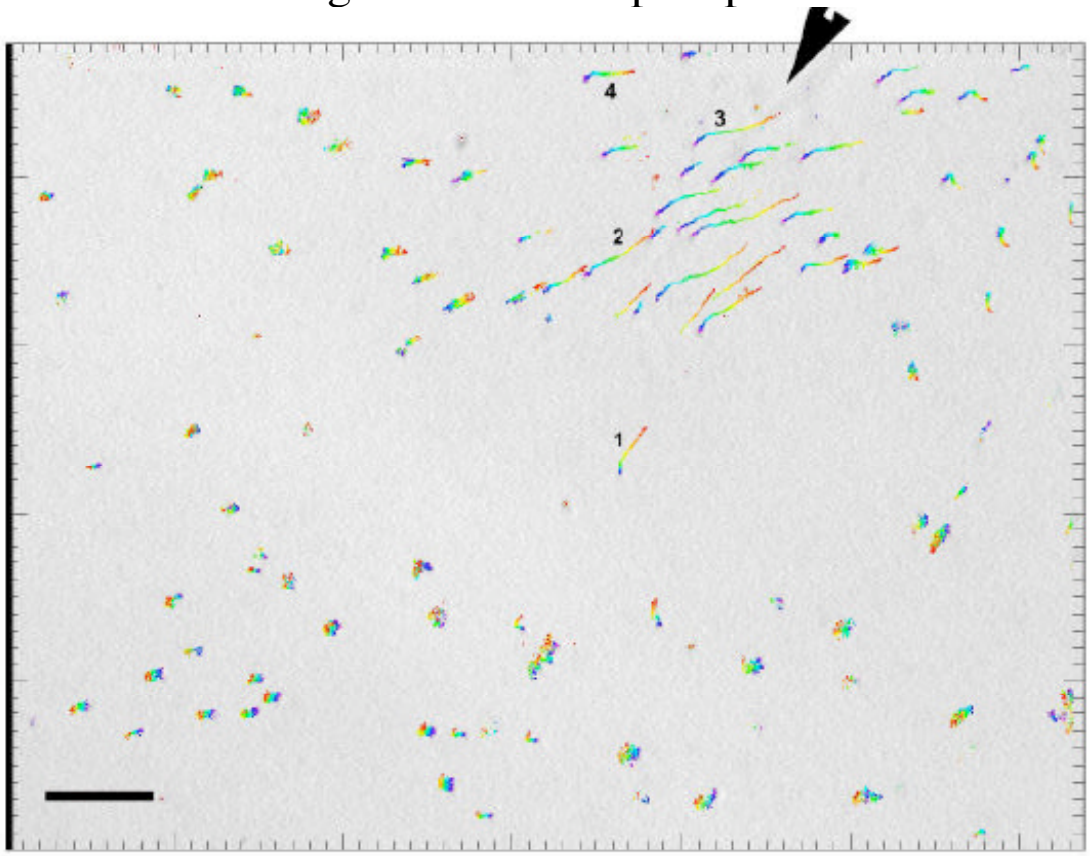
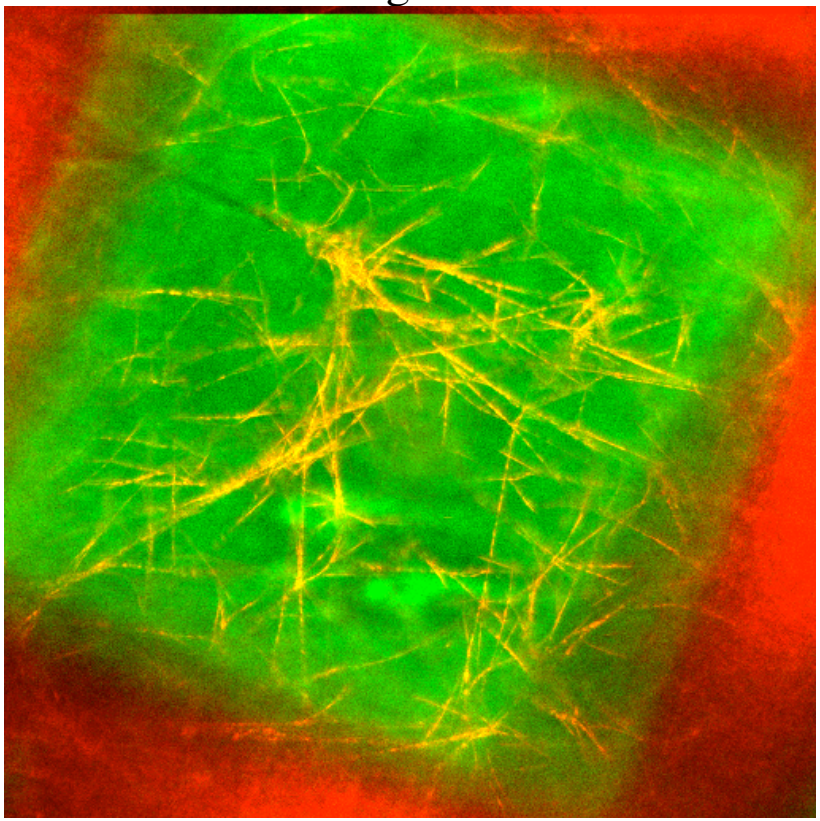


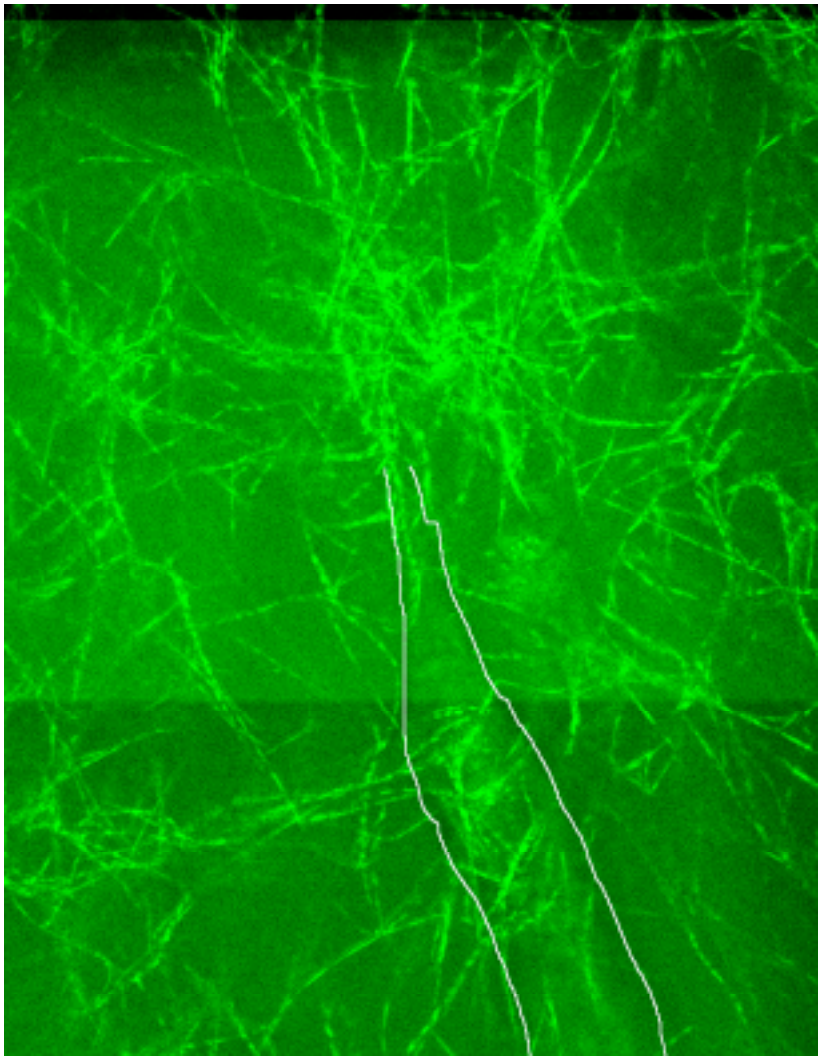
Figure 7

New experiments

V. Gordon, L. Kaufman, E. Filippindi, D. Weitz, T. Deisboeck

One result of the traction of the cells on the gel is a *reorientation* of the fibers.





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Implications for cell mobility and modeling

• Cells crawl on the collagen fibers in the medium, and apply stresses. The stresses are large, and are near the yield stress of the (rather fragile) Matrigel. Thus there could be a kind of *fracture* to form a pathway for cell invasion.

NB: The ECM of the brain is probably more robust.

• The cells have been shown to digest collagen via the expression of various proteolytic enzymes.

• The actual interaction of the invasive cells with the ECM is thus rather complex – it is not clear that any simple reaction-diffusion equation will capture the important features. This remains to be sorted out.