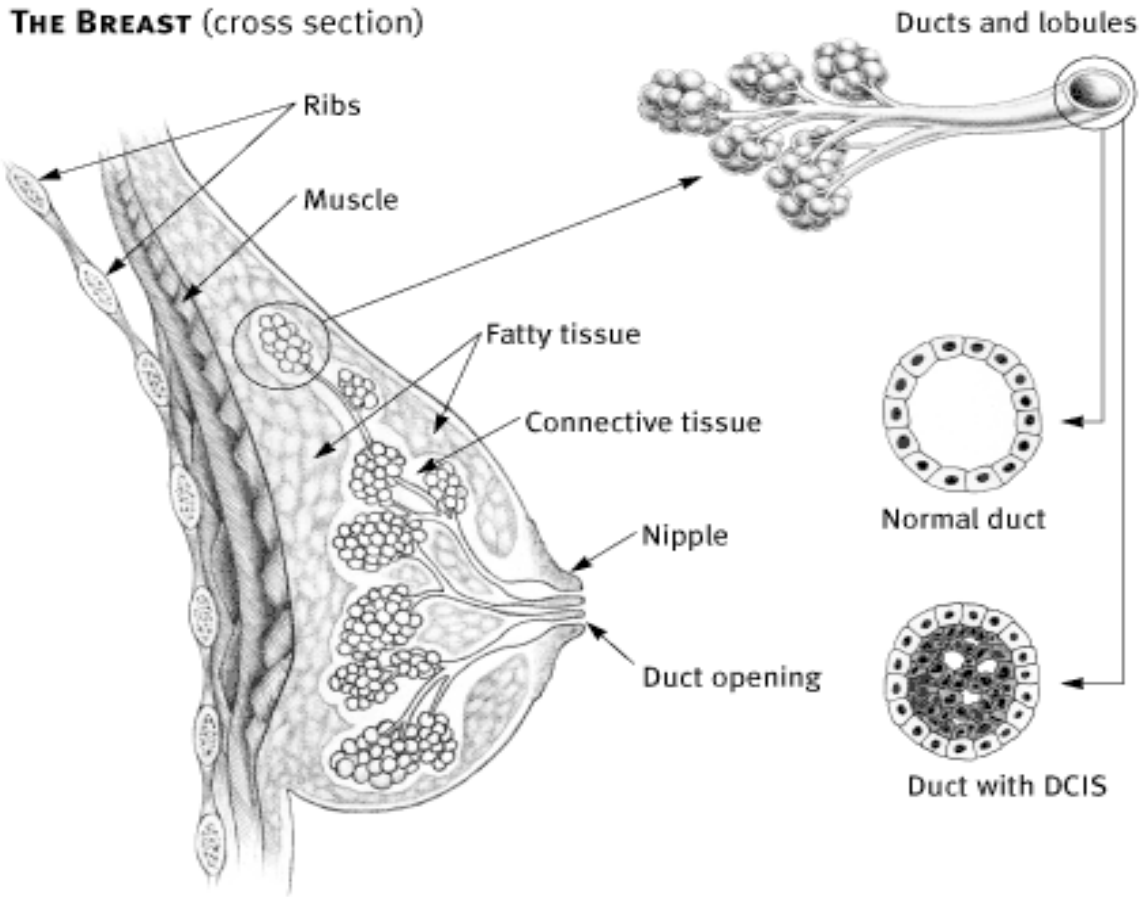
A PDE Model of Cancer and related inverse problems

Yongzhi Steve Xu

Department of Mathematics

University of Louisville

Ductal carcinoma in situ



--- From http://www.accv.org.au/

we consider a free boundary problem model of tumor growth that consists a continuum of cells in three states: proliferating, quiescent, or necrotic.

- Let p, q, n and ρ be the densities of proliferating cells, quiescent cells, necrotic cells, and the surrounding fluid, respectively.
- Let the quiescent cells become proliferating at a rate $K_{qp}(c)$, and become necrotic at a rate $K_{qn}(c)$;
- the proliferating cells become quiescent at a rate $K_{pq}(c)$, and have proliferating rate $K_p(c)$;
- the necrotic cells be removed from the tumor at a constant rate K_n.
- $\mathbf{v}$ be the local velocity of cells.

We assume that $K_{qp}(c)$ and $K_p(c)$ are positive-valued monotone increasing function of the nutrient concentration c; $K_{qn}(c)$ and $K_{pq}(c)$ are positive-valued monotone decreasing function of the nutrient concentration c.

By the law of conservation of mass, we have the following equations:

$$\frac{\partial p}{\partial t} + div(p\mathbf{v}) = [K_p(c) - K_{pq}(c)]p + K_{qp}(c)q, \tag{1.1}$$

$$\frac{\partial q}{\partial t} + div(q\mathbf{v}) = K_{pq}(c)p - [K_{qp}(c) + K_{qn}(c)]q, \tag{1.2}$$

$$\frac{\partial n}{\partial t} + div(n\mathbf{v}) = K_{qn}(c)q - K_n n. \tag{1.3}$$

$$\frac{\partial \rho}{\partial t} + div(\rho\mathbf{v}) = 0. \tag{1.4}$$

The nutrient concentration c satisfies a reaction-diffusion equation:

$$\frac{\partial c}{\partial t} + \bigtriangledown \cdot (c\mathbf{v}) = D \bigtriangleup c + \delta k_\rho(c)\rho - \gamma k_p(c)p. \tag{1.5}$$

Following Ward and King [100] [101], we modify the Michaelis-Menten kinetics which are often used to model cell kinetics (Lin, [76], McElwain, [83]) and cellular nutrient consumption in tumors (Casciari et al. [33]; Hlatky et al, [69]; Li, [77]), to assume that

$$K_{qp}(c) = \frac{A_{qp}c^{m_{qp}}}{c_1 + \alpha_{qp}c^{m_{qp}}}, \quad K_p(c) = \frac{A_p c^{m_p}}{c_2 + \alpha_p c^{m_p}}, \tag{1.6}$$

$$K_{pq}(c) = B_{pq}\left(1 - \frac{A_{pq}c^{m_{pq}}}{c_3 + \alpha_{pq}c^{m_{pq}}}\right), \quad K_{qn}(c) = B_{qn}\left(1 - \frac{A_{qn}c^{m_{qn}}}{c_4 + \alpha_{qn}c^{m_{qn}}}\right), \tag{1.7}$$

$$K_\rho(c) = \frac{A_\rho c^{m_\rho}}{c_5 + \alpha_\rho c^{m_\rho}}, \tag{1.8}$$

where the positive exponents m_{qp}, m_p, m_{pq}, m_{qn}, and m_ρ govern the sharpness of change near the critical concertrations c_1, c_2, c_3, c_4 and c_5.

For simplification, we may assume that the exponents $m_\cdot = 1$, and the parameters $\alpha_\cdot = 0$. Then The rates $K_\cdot(c)$ are linear functions of c.

$$K_{qp}(c) = A^0_{qp}c, \quad K_p(c) = A^0_p c, \quad K_{pq}(c) = B^0_{pq}(1 - A^0_{pq}c), \tag{1.9}$$

$$K_{qn}(c) = B^0_{qn}(1 - A^0_{qn}c), \quad K_\rho(c) = A^0_\rho c. \tag{1.10}$$

The simplified equation for nutrient concentration c becomes

$$\frac{\partial c}{\partial t} + \bigtriangledown \cdot (c\mathbf{v}) = D \bigtriangleup c - (\delta A_\rho^0 \rho - \gamma A_p^0 p)c. \tag{1.11}$$

We assume that the tumor tissue is a porous medium so that, by Darcey's law,

$$\mathbf{v} = - \bigtriangledown \sigma, \quad \sigma = \text{pressure}. \tag{1.12}$$

We also assume that all cells are of the same volume and density and that the total density of cells is uniform throughout the tumor. Then $p + q + n = B = constant$. Adding equations (2.1)-(2.3), we have

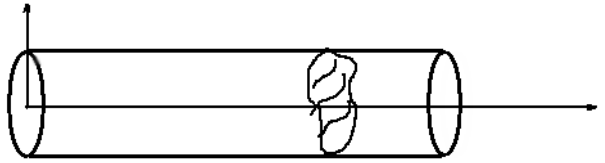
$$B \bigtriangledown \cdot \mathbf{v} = K_p(c)p - K_n(c)n = (K_p(c) + K_n(c))p + K_n(c)q - K_n(c)B. \tag{1.13}$$

From (2.12),

$$\bigtriangleup \sigma = -\frac{1}{B} \left[(K_p(c) + K_n(c))p + K_n(c)q - K_n(c)B \right]. \tag{1.14}$$

Initial and boundary conditions, as well as free boundary conditions will be imposed to model the growth of DCIS. These conditions are rather complicated. For the sake of simplying discussion, we will only present them for some particular cases in the later parts of the paper.

2 Preliminary results



From (1.11), assuming $\mathbf{v}=\mathbf{0}$, and $\lambda(x) = -(\delta A_\rho^0 \rho - \gamma A_p^0 p)$, we have

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{1}{r^2}\frac{\partial^2 c}{\partial \theta^2} + \frac{\partial^2 c}{\partial z^2}\right) + \lambda c, \quad \text{in } B(t), t > 0. \tag{2.1}$$

where

$$B(t) = \{(r,\theta,z) | 0 < z < s(r,\theta,t), 0 \le r < r_0, 0 \le \theta \le 2\pi\}$$

at each time t; the growing boundary of the tumour is given by $z = s(r,\theta,t)$, an unknown function of r, θ and t.

In the DCIS case, we assume that $c(r,\theta,z,t)$ satisfies following boundary conditions.

$$\frac{\partial c}{\partial r} + \alpha(c_B - c) = \gamma_1, \text{ when } r = r_0, \tag{2.2}$$

$$\frac{\partial c}{\partial z} + \beta(c_B - c) = \gamma_2, \text{ when } z = 0, \tag{2.3}$$

$$c(r,\theta,s(r,\theta,t),t) = c_1, \tag{2.4}$$

$$c(r,\theta,z,0) = c_0(r,\theta,z), \text{ in } B(0); \tag{2.5}$$

where $B(0) = \{(r,\theta,z) | 0 < z < s_0(r,\theta), 0 \le r < r_0, 0 \le \theta \le 2\pi\}$ is the initial region of the tumour with $s_0(r,\theta)$ given. $c_0(r,\theta,z)$ is the initial nutrient concentration. α, β, γ_1 and γ_2 are constants that reflect the properties of the duct. The smoothness of c implies that

$$\frac{\partial c}{\partial r} = 0, \text{ when } r = 0, \tag{2.6}$$

$$c(r,\theta,z,t) = c(r,\theta+2\pi,z,t). \tag{2.7}$$

The mass conservation consideration implies the relation ([?])

$$\frac{d}{dt}\left[\int_0^{2\pi}\int_0^{r_0} s(r,\theta,t) r dr d\theta\right] = \int_0^{2\pi}\int_0^{r_0}\int_0^{s(r,t)} p(c) r dz dr d\theta \tag{2.8}$$

where $p(c)$ denotes the cell proliferation rate within the tumour.

Case 1: Cancer Cells fill the duct

One typical type of DCIS is that cancer cells completely fill the affected breast duct (solid type).

It is shown in [?] that under some general assumptions we know that if $c_1 > \tilde{c} > 0$, the free boundary problem has an unique unstable stationary solution $z = z_s$. A stationary solution of one-dimensional model is shown in Figure 2(a).

Case 2: Cancer Cells do not fill the duct

Assuming the free boundary is flat and using separation of variables, we find that solution has the form

$$c(r,z) = R(r)Z(z) = ACJ_0(\xi r)\left[\cos(\sqrt{-\lambda-\xi^2}z) + \frac{\beta}{\sqrt{-\lambda-\xi^2}}\sin(\sqrt{-\lambda-\xi^2}z\right] \tag{2.9}$$

where

$$AC = \frac{\frac{1}{2}r_0^2 z_s \tilde{c}}{\int_0^{r_0} J_0(\xi r)rdr \int_0^{z_s}\left[\cos(\sqrt{-\lambda-\xi^2}z) + \frac{\beta}{\sqrt{-\lambda-\xi^2}}\sin(\sqrt{-\lambda-\xi^2}z\right]dz}.$$

The patterns of this solution depend on the signs of two parameters, ξ^2 and $\tau^2 = -\lambda-\xi^2$, where $\lambda = \Gamma+\lambda_0$ is known. The parameter ξ and the stationary free boundary z_s satisfy

$$\tan(\sqrt{-\lambda-\xi^2}z_s) = -\frac{\sqrt{-\lambda-\xi^2}}{\beta}, \tag{2.10}$$

and

$$\xi J_1(\xi r_0) + \alpha J_0(\xi r_0) = 0. \tag{2.11}$$

Equations (2.9), (2.10) and (2.11) represent the patterns of stationary solutions with flat free boundary. We can use their different combinations to show possible patterns of DCIS.

There are four different combinations of ξ and $\tau := \sqrt{-\lambda-\xi^2}$. One typical solution of each case is shown in Figure 2 (b)-(e). That is,

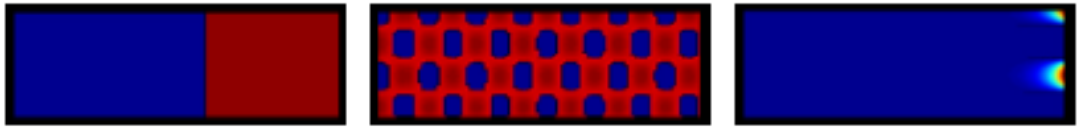
Case 2a: $\xi^2 \geq 0$ and $\tau \geq 0$ in Figure 2(b).

Case 2b: $\xi^2 \geq 0$ and $\tau = i|\tau|$ in Figure 2(c).

Case 2c: $\xi = i|\xi|$ and $\tau > 0$ in Figure 2(d).

Case 2d: $\xi = i|\xi|$ and $\tau = i|\tau|$ in Figure 2(e).

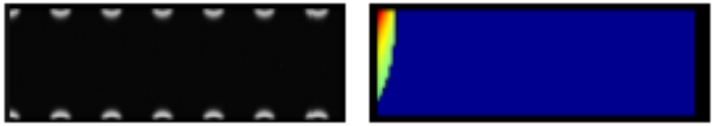
Figure 2: Computational results of DCIS patterns



(a) Solid DCIS

(b) Cribiform DCIS

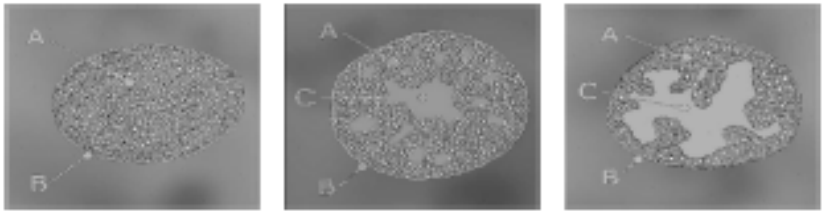
(c) Tumor moving but not growing



(d) Papillary DCIS

(e) Tumor neither moving nor growing

Figure 3: Typical paterns of DCIS

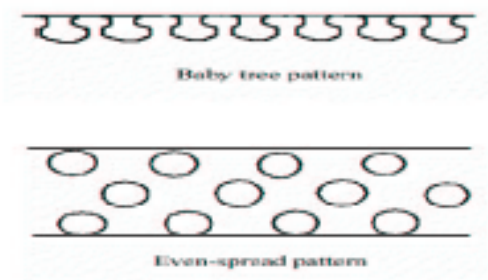


(a) Solid DCIS

(b) Cribiform DCIS

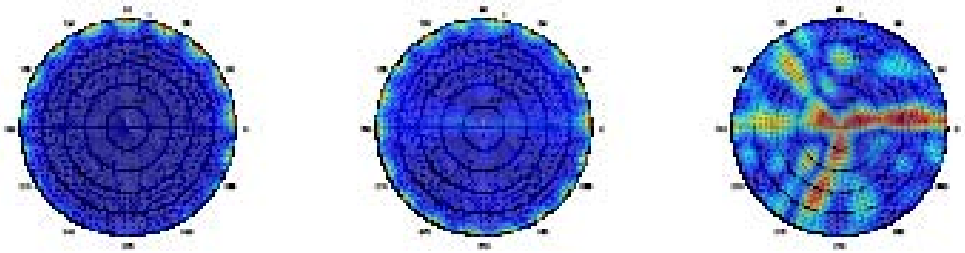
(c) Papillary DCIS

Figure 4: Edgerton drawed typical paterns of DCIS



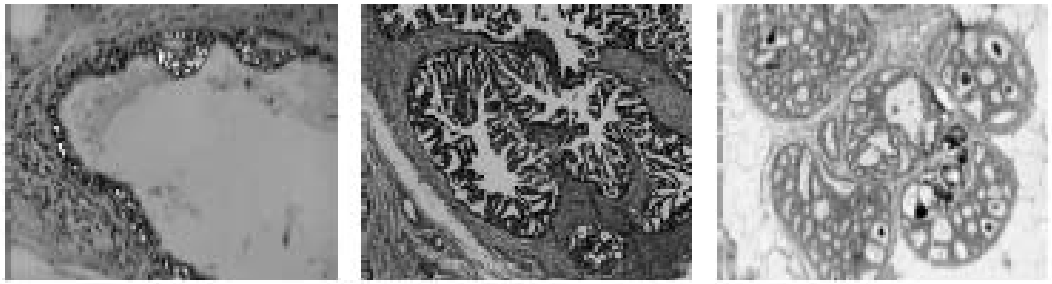
2.1 Typical three-dimensional patterns of DCIS

Figure 5: Some computational paterns of DCIS



(a) Pattern 1 (b) Pattern 2 (c) Pattern 3

Figure 6: Some paterns of DCIS



(a) Micropapillary DCIS, from ccm.ucdavis.edu (b) Papillary DCIS, from www.breastdiseases.com (c) Cribiform DCIS, from ccm.ucdavis.edu

3 A free boundary problem of parabolic equation with integral condition

We consider a free boundary problem of parabolic equation with integral condition on the unknown free boundary:

$$\frac{\partial u}{\partial t} - a\frac{\partial^2 u}{\partial x^2} + b(x,t)\frac{\partial}{\partial x}u - c(x,t)u = f(x,t),\ 0 < x < s(t), t > 0. \tag{3.1}$$

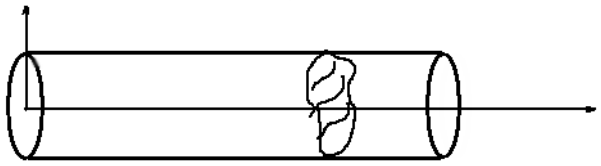
$$u(x,0) = 0,\ t > 0, \tag{3.2}$$

$$u(s(t),t) = 0,\ t > 0, \tag{3.3}$$

$$u(x,0) = u_0(x),\ 0 < x < s(0), \tag{3.4}$$

$$\frac{\partial s}{\partial t} = \mu \int_0^{s(t)} (u(x,t) - \hat{u})dx,\ t > 0, \tag{3.5}$$

where $a > 0$ is a constant, $x = s(t)$ is the free boundary to be determined. $u_0(x)$ is a given function, μ and $\tilde{u}$ are known constants.



4 Inverse problems related to cancer diagnose

4.1 The direct Free boundary problem of DCIS

$$c\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial x^2} - \lambda(x)\sigma, \ \text{ in } B(t), t > 0. \tag{4.1}$$

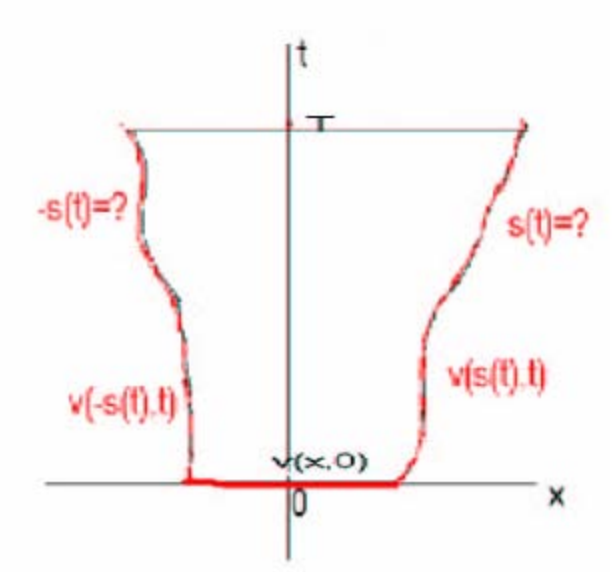
$$\sigma(-s(t)/2, t) = \sigma_1, \ t > 0, \tag{4.2}$$

$$\sigma(s(t)/2, t) = \sigma_1, \ t > 0, \tag{4.3}$$

$$\sigma(x, 0) = \sigma_0(x), \ \text{in } B(0); \tag{4.4}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-s(t)/2}^{s(t)/2} (\sigma - \tilde{\sigma}) dx, \ s(0) = s_0, \tag{4.5}$$

Figure 7: Free boundary problem



4.2. Inverse Problems

(1) Clinical data is obtained by one incisional biopsy.

When noticing possible breast cancer, one opts to do an incisional biopsy to find out the DCIS pattern along with the changing rate at the moment. Since no information is available before, we can assume no initial data given, instead we assume that two conditions are given at terminal time $t = T$.

The problem is as follows: find $(\sigma(x,t),\ \lambda(x),\ s(t))$ such that

$$c\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial x^2} - \lambda(x)\sigma, \ \text{ in } B(t),\ 0 < t < T, \tag{4.6}$$

$$\sigma(-\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.7}$$

$$\sigma(\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.8}$$

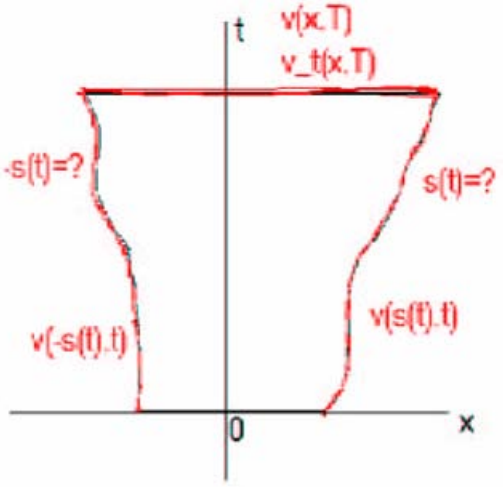
$$\sigma(x,T) = \sigma_T(x),\ -\frac{s(t)}{2} < x < \frac{s(t)}{2}, \tag{4.9}$$

$$\sigma_t(x,T) = \eta_T(x),\ -\frac{s(t)}{2} < x < \frac{s(t)}{2}, \tag{4.10}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-\frac{s(t)}{2}}^{\frac{s(t)}{2}} \tilde{\sigma}) dx,\ s(T) = s_T, \tag{4.11}$$

The problem (4.6)-(4.11) is denoted by IP1.

Figure 13: IP1



(2) Clinical data is obtained by a sequence of needle biopsy.

When noticing possible breast tumor, but it may be benign, one opts to do a sequence of needle biopsy over a time interval to find out the DCIS pattern change in the time interval. In this case we assume that we know initial data, and data at a internal point over time interval $[0, T]$.

The problem is as follows: find $(\sigma(x,t),\ \lambda(x),\ s(t))$ such that

$$c\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial x^2} - \lambda(x)\sigma, \quad \text{in } B(t),\ 0 < t < T, \tag{4.12}$$

$$\sigma(-\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.13}$$

$$\sigma(\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.14}$$

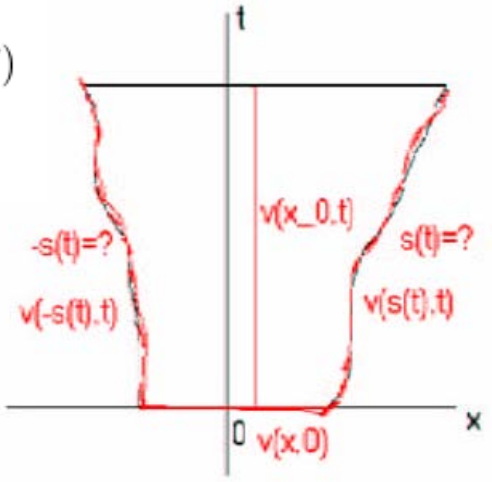
$$\sigma(x, 0) = \sigma_0(x),\ -\frac{s(0)}{2} < x < \frac{s(0)}{2}, \tag{4.15}$$

$$\sigma(x_0, t) = \sigma_2(t), \quad 0 < t < T, \tag{4.16}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-\frac{s(t)}{2}}^{\frac{s(t)}{2}} (\sigma(s(t), t) - \tilde{\sigma})dx,\ s(0) = s_0, \tag{4.17}$$

The problem (4.12)-(4.17) is denoted by IP2.

Figure 14: IP2



(3) Clinical data is obtained by a sequence of tomograph.

When noticing possible breast tumor, but it may be benign, one opts to do a sequence of tomograph over a time interval to find out the DCIS pattern change in the time interval. In this case we assume that we know initial data and the tumor boundary over time interval $[0, T]$.

The problem is as follows: find ($\sigma(x,t)$ and $\lambda(x)$) such that

$$c\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial x^2} - \lambda(x)\sigma, \ \text{ in } B(t),\ 0 < t < T, \tag{4.18}$$

$$\sigma(-\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.19}$$

$$\sigma(\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.20}$$

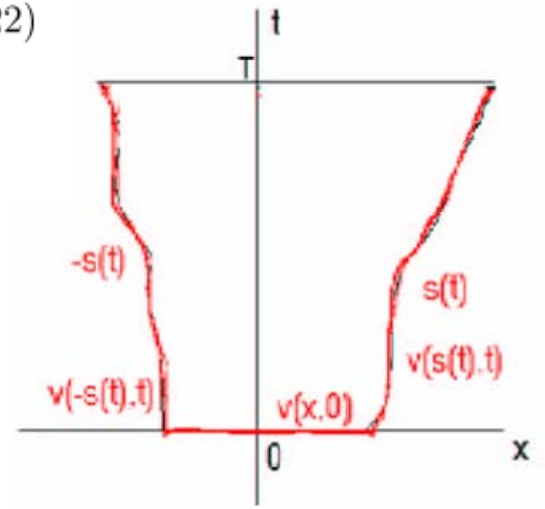
$$\sigma(x, 0) = \sigma_0(x),\ -\frac{s(0)}{2} < x < \frac{s(0)}{2}, \tag{4.21}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-\frac{s(t)}{2}}^{\frac{s(t)}{2}} (\sigma(s(t), t) - \tilde{\sigma})dx,\ s(0) = s_0, \tag{4.22}$$

where $s(t)$ for $0 < t < T$ is given.

The problem (4.18)-(4.22) is denoted by IP3.

Figure 15: IP3



(4) Clinical data is obtained by an initial and a follow-up tests.

When noticing possible breast tumor, but it may be benign, one opts to do second check-up after a while. In this case we assume that we know the initial data at $t = 0$ and the terminal data when $t = T$.

The problem is as follows: find $(\sigma(x,t),\ \lambda(x),\ s(t))$ such that

$$c\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial x^2} - \lambda(x)\sigma, \ \text{ in } B(t),\ 0 < t < T, \tag{4.23}$$

$$\sigma(-\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.24}$$

$$\sigma(\frac{s(t)}{2}, t) = \sigma_1,\ 0 < t < T, \tag{4.25}$$

$$\sigma(x,0) = \sigma_0(x),\ -\frac{s(0)}{2} < x < \frac{s(0)}{2},\ s(0) = s_0 \tag{4.26}$$

$$\sigma(x,T) = \sigma_T(x),\ -\frac{s(T)}{2} < x < \frac{s(T)}{2},\ s(T) = s_T, \tag{4.27}$$

$$\frac{\partial s}{\partial t} = \mu \int_{-\frac{s(t)}{2}}^{\frac{s(t)}{2}} \tilde{\sigma}) dx, \tag{4.28}$$

The problem (4.23)-(4.28) is denoted by IP4.