ハイブリッドシミュレーション ～数理腫瘍学の基本ツール

2015. 12. 24

鈴木　貴

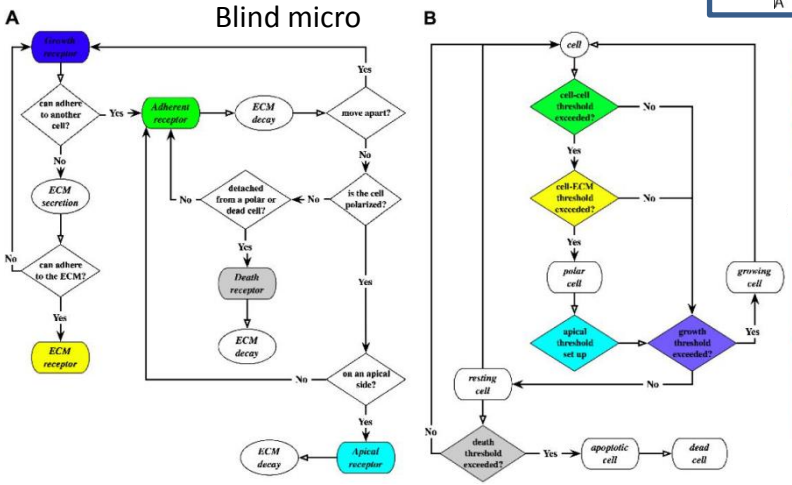
Integrative Mathematical Oncology

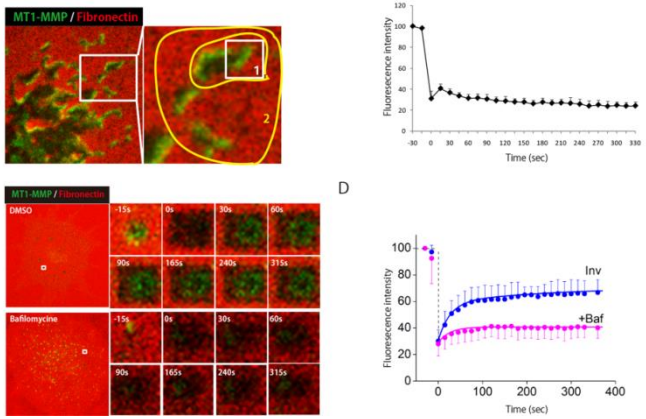
Bio-Informatics — Cell Biology — Data Science — Bio-Statistics

Systems Biology

Mathematical Modeling

Blind micro





$n = n(x,t)$: CANCER

$c = c(x,t)$: ECM

$f = f(x,t)$: MMP

$\Rightarrow$

$$n_t = d_n \nabla^2 n - \gamma \nabla \cdot (n \nabla c)$$

$$c_t = -\eta f c$$

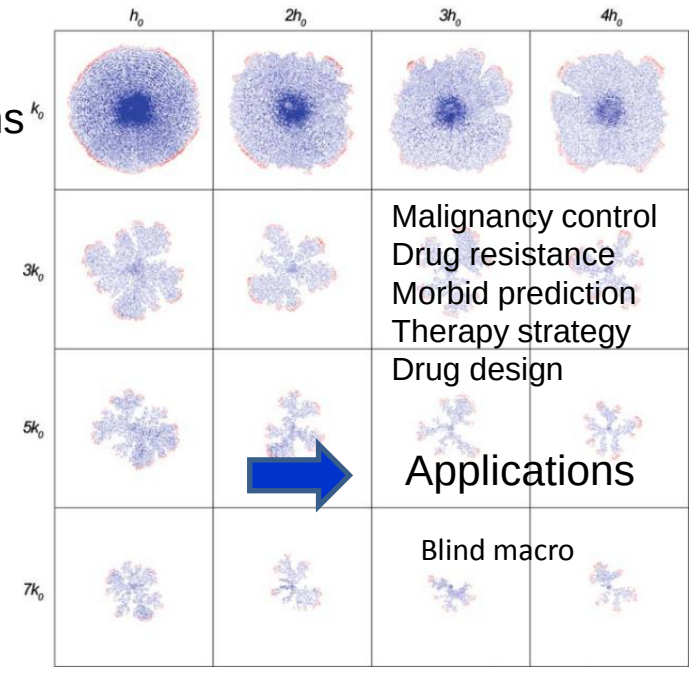
$$f_t = d_f \nabla^2 f + \alpha n - \beta f$$

C. Lopez et. al.

Hybrid Simulation with Fluctuations

M. Chaplain (Andrews Univ.)

V. Quaranta (Vanderbilt Univ.)



A. Anderson et. al.

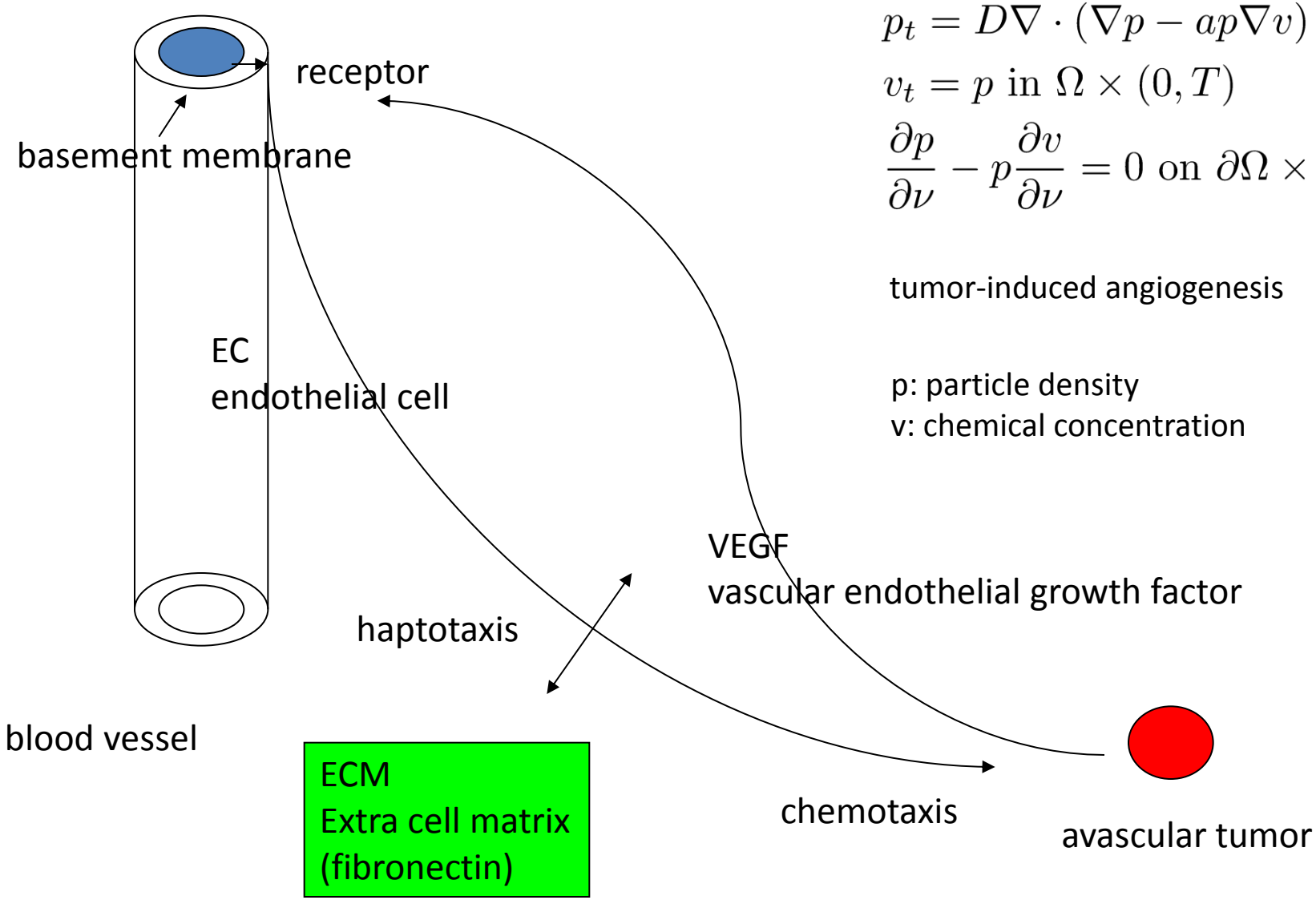
1. Angiogenesis

Levine-Sleeman 1997

$$p_t = D\nabla \cdot (\nabla p - ap\nabla v)$$
$$v_t = p \text{ in } \Omega \times (0,T)$$
$$\frac{\partial p}{\partial \nu} - p\frac{\partial v}{\partial \nu} = 0 \text{ on } \partial\Omega \times (0,T)$$

tumor-induced angiogenesis

p: particle density
v: chemical concentration



Anderson-Chaplain Model 1998

$D_n, \chi_0, k_1, \rho_0 > 0$: experimental data

$$F = -D_n \nabla n + \rho_0 n \nabla f + \chi(c) n \nabla c$$

$$\chi(c) = \frac{\chi_0 k_1}{k_1 + c}$$

$\Rightarrow$

$$\frac{\partial n}{\partial t} + \nabla \cdot F = 0 \ldots \text{ mass conservation}$$

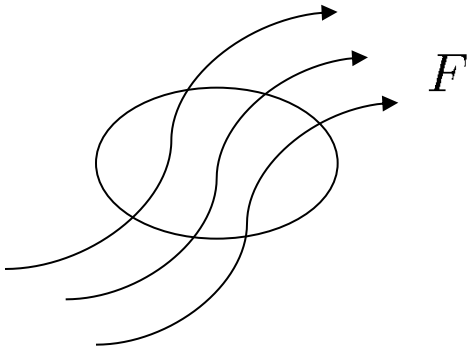
$$\frac{\partial f}{\partial t} = \beta n - \gamma n f, \quad \frac{\partial c}{\partial t} = -\eta n c$$

$\beta, \gamma, \eta > 0$, constants

n: density of EC (endotherial cells)
F: flux of n

$\Rightarrow$

$n \mapsto$ diffusion
f: fibronection concentration $\mapsto$ chemotaxis
c: TAF concentration $\mapsto$ haptotaxis



Mathematical structure

$f_0 > \frac{\beta}{\gamma} \Rightarrow c, f \ldots$ monotone decreasing in t

$$\frac{\partial c}{\partial t} = -\eta n c, \quad \frac{\partial f}{\partial t} = \beta n - \gamma n f$$

$\Rightarrow$

$$-\frac{1}{\eta}\frac{\partial}{\partial t}\log c = n, \quad -\frac{1}{\gamma}\frac{\partial}{\partial t}\log|\beta - \gamma| = n$$

$\Rightarrow$

$$n_t = \nabla \cdot (\nabla n - n \nabla \varphi(v, w)), \ \ v_t = p, \ \ w_t = q$$

$\varphi = \varphi(v, w) \ldots$ sensitivity function

$$v = -\eta^{-1} \log c, \ \ w = -\frac{1}{\gamma}\log|\beta - \gamma f|$$

$\Rightarrow$

$$n_t = \nabla \cdot (\nabla n - n \nabla \varphi(v))$$
$$v_t = n \quad \text{in } \Omega \times (0, T)$$
$$\frac{\partial n}{\partial \nu} - n \frac{\partial \varphi(v)}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, T)$$
$$(n, v)|_{t=0} = (n_0, v_0)$$

A Finite Difference Scheme for $\Omega = (0,1)$

uniform space mesh h, $N = \dfrac{1}{h}$

non-uniform time mesh $\{\tau_p\}_{p=0}^{M-1}$

$t_{p+1} = t_p + \tau_p$, $t_0 = 0$

main and sub-lattices in space

$\{x_i = (i - \frac{1}{2})h \mid i = 1, 2, \ldots, N\}$

$\{\hat{x}_i = ih \mid i = 0, 1, \ldots, N\}$

$\Rightarrow$

$n_i^p \approx n(x_i, t_p)$

$c_i^p \approx c(\hat{x}_i, t_p)$

$f_i^p \approx f(\hat{x}_i, t_p)$,

recall the barrier model

$v = \nabla c$, $w = \nabla f \mapsto F$: flux of n approximated on $\{x_i\}$

v, w, upwind finite diffenece

n, center finite difference

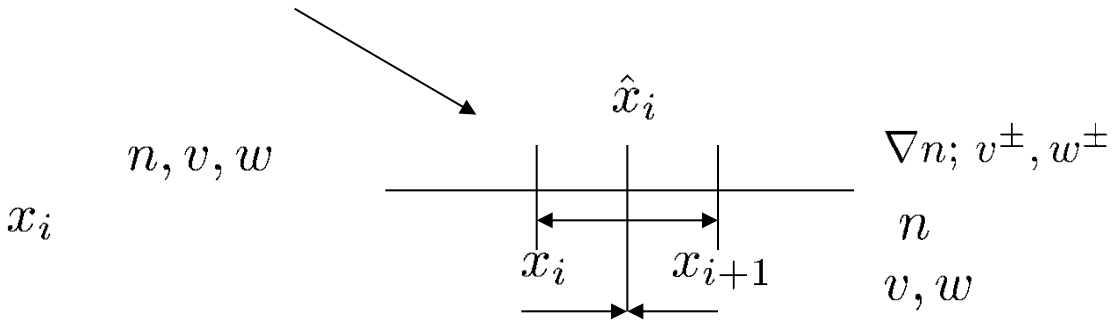
$\Rightarrow$

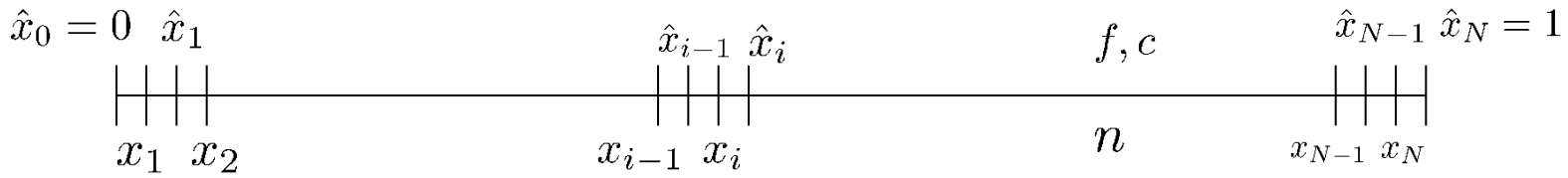
$F_i^p \approx F(\hat{x}_i, t_p)$

$v_i^p \approx v(x_i, t_p)$

$w_i^p \approx w(x_i, t_p)$

c.f. barrier model





$$v_i^p = \frac{c_i^p - c_{i-1}^p}{h},\ w_i^p = \frac{f_i^p - f_{i-1}^p}{h}$$

$$v_i^{\pm,p} = \max\{0, \pm v_i^p\},\ w_i^{\pm,p} = \max\{0, \pm w_i^p\},$$

$1 \le i \le N$, define

$$F_i^p = -d\frac{n_{i+1}^p - n_i^p}{h} + \frac{\chi}{1+\alpha c_i^p}.$$

$$(v_i^{+,p} n_i^p - v_{i+1}^{-,p} n_{i+1}^p) + \rho(w_i^{+,p} n_i^p - w_{i+1}^{-,p} n_{i+1}^p)$$

$1 \le i \le N-1$

Require $F_0^p = F_N^p = 0$.

F, n discretized on $\{\hat{x}_i\}$

mixed method to t, $0 < \theta < 1$

$$\frac{n_i^{p+1} - n_i^p}{\tau_p} = -\theta\frac{F_i^{p+1} - F_{i-1}^{p+1}}{h}$$

$$-(1-\theta)\frac{F_i^p - F_{i-1}^p}{h},\ 1 \le i \le N$$

c, f discretized on on $\{\hat{x}_i\}$

interpolation of n defined on $\{x_i\}$

$$n(\hat{x}_i, t_p) = \begin{cases} n_1^p & (i=0) \\ \frac{n_{i+1}^p + n_i^p}{2} & (1 \le i \le N-1) \\ n_N^p & (i=N) \end{cases}$$

explicit method to t

$$\frac{c_i^{p+1} - c_i^p}{\tau_p} = -\eta n(\hat{x}_i, t_p) c_i^p$$

$$\frac{f_i^{p+1} - f_i^p}{\tau_p} = \beta n(\hat{x}_i, t_p) - \gamma n(\hat{x}_i, t_p) f_i^p$$

$0 \le i \le N$

well-posedness, positivity, mass conservation of n if

$$\tau_p < \min\left\{\frac{h^2}{(1-\theta)(d+h\hat{H})}, \frac{h}{4\theta\hat{H}}, \frac{1}{\eta\hat{n}^p}, \frac{1}{\gamma\hat{n}^p}\right\}$$

$$\hat{H} = \frac{\chi}{1+\alpha\hat{c}^p}\hat{v}^p + \rho\hat{w}^p,\ \hat{c}^p = \max_{0\le i\le N} c_i^p$$

$$\hat{n}^p = \max_{1\le i\le N} n_i^p,\ \hat{v} = \max_{1\le i\le N} v_i^p,\ \hat{w}^p = \max_{1\le i\le N} w_i^p$$

Saito-S. 05

A numerical scheme realizing

$n > 0$... positivity

$\|n(t)\|_1 = \|n_0\|_1$

... total mass conservation

Tools:

1. sub-lattice
2. upwind difference
3. mass lumping

→

The discretization scheme to n...

$$n_i^{p+1} = P_i^{0,p} n_i^p + P_{i+1}^{-,p} n_{i+1}^p + P_{i-1}^{+,p} n_{i-1}^p$$

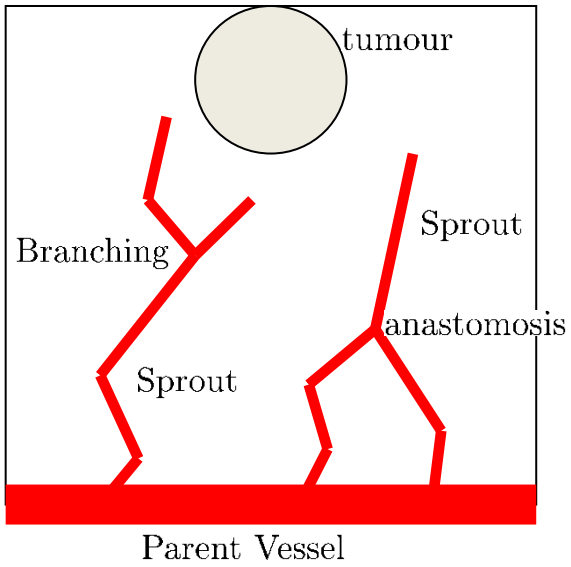
$$2 \leq i \leq N$$

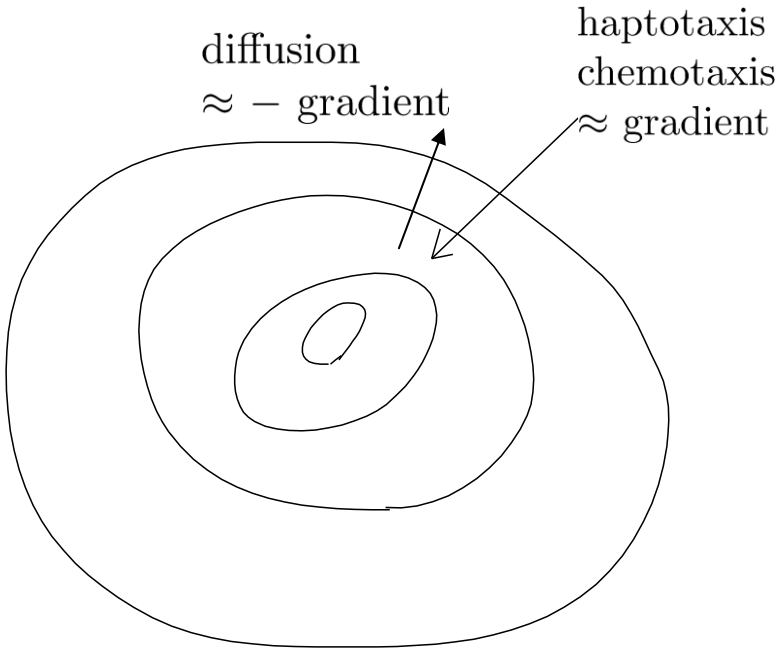
$$P_i^{0,p} > 0,\ P_i^{0,p} + P_i^{-,p} + P_i^{+,p} = 1$$

$\Rightarrow$

$P_i^{0,p}$, $P_i^{+,p}$, $P_i^{-,p}$
regarded as transient probablities

hybrid simulation between individual – continuous objects





Hybrid discrete-continuous model

Anderson et.al. 2006 on tumor morphology space - time discrete description

1. Fundamental equations described by MDE, MM, and oxygen, involved by a *tumor cell indicator*
2. **Mobile probabilities** of tumor cells described by an intrinsic unbiased motility and MM concentration combined with rate parameters
3. Mutation schemes by cacer cell life to change *phenotype*, i.e., several parameters updated

Medication simulation

$2d$: the initial medication
d: medicated after
T_d: time period

$$\frac{dm_i}{dt} = -\mu m_i$$
$$i = 1, \cdots, [T/T_d]$$

$$\Rightarrow$$

$$m_i(t) = m(t)|_{(i-1)T_d < t \leq iT_d}$$
$$m_1|_{t=0} = 2d$$
$$m_i|_{t=(i-1)T_d} = m_{i-1}|_{t=(i-1)T_d} + d$$
$$2 \leq i \leq T/T_d$$

Numerical results $\Rightarrow$

1. medication attacking to EC not efficient
2. that to TAF medicable