Controllability and Sensitivity of Models of Combined Anticancer Therapy

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Combined therapy:

Chemotherapy (direct) + antiangiogenic therapy (indirect)

Problems : drug resistance, side effects, slowly growing tumors, necessity of intra-tumor delivery

Advantages: general efficiency, especially for fast growing tumors

Problems : difficulty in observation of effects, fast growing tumors, problems with wound healing, diabetes, menstruation

Advantages: resistant to resistance, efficient for slowly growing tumors, effect of "prunning"

Antiangiogenic resistance



Chaotic behavior of the vascular network created in the process of tumor angiogenesis



The Biology of Cancer (© Garland Science 2007) - Figure 13.34a



Konerding et al. In Molls and Vaupel, Blood Perfusion and Microenvironment of Human Tumors, 2002



Combined therapy: effect of prunning



Fig 1. Proposed role of vessel normalization in the response of tumors to antiangiogenic therapy.

R. K. Jain, "Normalization of tumor vasculature and microenvironment in antiangiogenic therapies," ASCO AnnualMeeting, pp. 412–417, 2007.

Combined therapy (efficiency)

ClinicalTrials.gov	Antiangiogenic drugs	Cytostatic drugs	Progression-free
			survival
NCT00219557	Axitinib	Gemcitabine	116 days
			(109 to 160)
	-	Gemcitabine	(68 to 205)
NCT00532155	Aflibercept	Docetaxel	5.19 months (4.37 to 5.55)
	-	Docetaxel	4.11 months (3.52 to 4.34)
NCT00434252	Bevacizumab	Carboplatin, Paclitaxel	5.6 months (4.21 to 6.80)
	-	Carboplatin, Paclitaxel	4.2 months (2.83 to 5.36)
NCT00687297	Vandetanib 4 cycles with continuation of treatment	Docetaxel, Carboplatin	4.5 months (3.3 to 5.8)
	Vandetanib 4 cycles, without continuation of treatment	Docetaxel, Carboplatin	4.2 months (2.8 to 4.9)
NCT00130728	Erlotinib, Bevacizumab	-	3.4 months (2.79 to 4.27)
	Bevacizumab	-	1.7 months (1.48 to 2.53)

Therapy – where to attack?







The problem of controllability:

Roughly speaking controllability of a dynamical control system means that it is possible to drive this system from an arbitrary initial state to an arbitrary final state in finite time using the set of admissible controls. For linear timeinvariant systems the notions of controllability in a given time interval, controllability at a given initial time, controllability and uniform controllability are equivalent. Controllability is strongly related to the notion of attainable set.

Linear time-invariant systems of order n.

$$\underline{x}'(t) = A\underline{x}(t) + B\underline{u}(t)$$

Necessary and sufficient condition of controllability for linear time-invariant system is the so called Kalman rank condition (Kalman, 1960):

rank[
$$B, AB, A^2B, ..., A^{n-1}B$$
]= n

Linear time-invariant systems with constrained controls

Suppose that the set of admissible controls is a cone U_c with vertex at zero and a nonempty interior in the *m* dimensional space. Then the system is globally controllable if and only if (Brammer 1972):

1) it is controllable without constraints i.e. the rank condition is satisfied

rank[
$$B, AB, A^2B, ..., A^{n-1}B$$
]= n

2) there is no real eigenvector $w \in \mathbb{R}^n$ of the matrix A^{tr} satisfying inequalities:

 $w^{tr}B\underline{u} \leq 0$, for all $\underline{u} \in U_c$.

Sensitivity

Two most frequently discussed types of sensitivity:

1) Parametric sensitivity: local - reaction of the system for infinitesimal changes of parameters, and global - reaction of the system to finite changes of parameters

2) Structural sensitivity: dependence of system characteristics on the form of model within assumed family of models (considered in this talk)

Family of models

Gompertzian model of tumor growth:

$$\dot{N}/N = -\beta \ln N/N_{\infty} \approx 1/PDT$$

$$N_{\infty} = K$$

K – effective vascular support (carrying capacity)

Incorporation of angiogenesis in the model (Hahnfeldt)

Similarly for logistic growth (Pearl-Verhulst equation)

$$\dot{N}/N = \beta(1 - N/K)$$

K – effective vascular support (carrying capacity)

The dynamics of the growth of this volume represented by its *PDT* depends on the stimulators of angiogenesis (*SF*), inhibitory factors secreted by tumor cells (*IF*) and natural mortality of the endothelial cells (*MF*)

Hypotheses (Hahnfeldt et al.)

$$1/PDT_k = MF + SF + IF$$

$$IF/SF = K^b N^c \qquad b+c \approx 2/3$$

Original (1999)
$$b = 1, c = -1/3$$
d'Onofrio-Gandolfi (2004) $b = 0, c = 2/3$ Ergun et al. (2003) $b = 2/3, c = 0$

A. (original Hahnfeldt model)

$$N/N = -\beta \ln N/K$$

$$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu)$$

B. (Hahnfeldt model with logistic growth)

 $\dot{N}/N = \beta(1 - N/K)$ $\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu)$

C. (D'Onofrio-Gandolfi model with Gompertz-type growth)

$$\dot{N} / N = -\beta \ln N / K$$
$$\dot{K} / K = \gamma - (\lambda N^{2/3} + \mu)$$

D. (D'Onofrio-Gandolfi model with logistic growth)

$$N/N = \beta(1 - N/K)$$

 $\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu)$

Ergun's model

$\dot{N}/N = \beta(1 - N/K) \dot{N}/N = -\beta \ln N/K$

$$\dot{K} = \gamma K^{2/3} - \lambda K^{4/3}$$

Some other modifications: Agur et al., 2004 Foryś et al., 2005 D'Onofrio – Gandolfi, 2009 (delays resulting from mitotic division)

Simulation for the model without therapy





Hahnfeldt model with logistic growth, N(0) = K(0) = 200



D'Onofrio-Gandolfi model with Gompertz-type growth, N(0) = K(0) = 200

$$\dot{N}/N = \dot{K}/K = 0 \Longrightarrow N^* = K^* = \left(\left(\gamma - \mu\right)/\lambda\right)^{3/2}$$
$$\gamma > \mu$$

$$x = \ln N / N^*, y = \ln K / K^*, x^* = y^* = 0,$$

$$\tau = \beta t, \vartheta = (\gamma - \mu) / \beta, x' = dx / d\tau, y' = dy / d\tau$$

$$x' = y - x$$
,
 $y' = \mathcal{G}(e^{x-y} - e^{2/3x})$
Semilinear system
local asymptotic
stability (model A)

$$x' = y - x,$$

$$y' = (\vartheta/3)x - \vartheta y$$

A)

Stability condition insensitive structurally (global stability may be proved using direct Lyapunov method).

Combined antiangiogenic and chemo-therapy

$$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu + \eta u + \xi v),$$

$$\dot{N}/N = -\beta \ln N/K - \varphi v$$

Constant drug doses: u(t)=U=const, v(t)=V=const

We assume for simplicity $\mu=0$ (as in Ergun et al. model)

$$\eta U + \xi V = \gamma e^{-\varphi V/\beta} \Longrightarrow K^* \to 0, N^* \to 0$$

Periodic therapy (d'Onofrio et al.2004) (for B,C,D: NSC, for A only NC)

$$U = 1/T \int_{0}^{T} u(t)dt, f(t) = u(t) - U, F(t) = \eta \int_{0}^{t} f(\tau)d\tau$$
$$V = 1/T \int_{0}^{T} v(t)dt, g(t) = v(t) - V, G(t) = \xi \int_{0}^{t} g(\tau)d\tau$$

Structurally sensitive

$$\eta U + \xi V \ge \gamma e^{-\varphi V},$$

Optimization (for C)
$$\dot{N} / N = -\beta \ln N / K - \varphi v(t)$$

$$\dot{K}/K = \gamma - (\lambda N^{2/3} + \mu + \eta u(t) + \xi v(t)),$$

$$TCP = \exp(-f\theta N(T_k)) \to \max$$
$$\min_{u,v} \leftarrow J = N(T_k); \int_0^{T_k} u(t)dt \le \Xi; \int_0^{T_k} v(t)dt \le \Omega$$
$$0 \le u \le U_m, 0 \le v \le V_m$$

Modified optimization problem

$$\begin{aligned} x' &= y - x - \varepsilon v, \\ y' &= 9(1 - e^{2/3x}) + \sigma u + \zeta v \end{aligned} \qquad \sigma &= -\eta \beta / (\gamma - \mu) \end{aligned}$$

$$= gx(T_f) + hy(T_f) + r \int_{0}^{T_f} u(\tau) d\tau + s \int_{0}^{T_f} v(\tau) d\tau$$

$$\leq u, v \leq 1, T_f = T_k \beta$$

 $H = ru + \sigma qu + \varsigma qv + sv - \varepsilon pv + p(y - x) + q \mathcal{G}(1 - e^{2/3x})$

$$p' = p + 2/3q \mathcal{P}e^{2/3x}, p(T_f) = g$$
$$q' = -p, q(T_f) = h$$

Switching conditions

$$q = -r/\sigma$$
$$u = \begin{cases} 1 \\ 0 \\ \end{bmatrix} \iff minH$$

$$p = s / \varepsilon + q\zeta / \varepsilon$$
$$v = \begin{cases} 1 \\ 0 \\ \end{bmatrix} \iff H$$

$$q'' - q' + 2/3q \, \vartheta e^{2/3x} = 0, \, p = -q'$$
$$q(T_f) = h, q'(T_f) = -g = -p(T_f)$$

Similarly for B and D but for A there exist optimal singular arcs (Ledzewicz, Schaettler) - structural sensitivity .

Semilinear systems and linear associated systems

$$\underline{x}'(t) = A\underline{x}(t) + F(\underline{x}(t)) + B\underline{u}(t)$$

$$\underline{z}'(t) = C\underline{z}(t) + D\underline{u}(t)$$

$$C = A + F_x(0), D = B$$

With delays

 $\underline{x}'(t) = A\underline{x}(t) + F(\underline{x}(t)) + B\underline{u}(t) + G\underline{u}(t-h)$





Sufficient condition of local constrained controllability for semilinear dynamical system with many inputs (Klamka):

If the associated linear dynamical system is 1. controllable without any constraints i.e. (satisfies Kalman rank condition):

rank[$D, CD, C^2D, ..., C^{n-1}D$] = nand

2. there is no real eigenvector $w \in \mathbb{R}^n$ of the matrix C^{tr} satisfying inequalities:

 $w^{tr}D\underline{u} \leq 0$, for all $\underline{u} \in U_c$.

then the semilinear stationary dynamical control system (17) is U_c -locally controllable in [0, T].

We have for model A

$$x' = y - x - \varepsilon v,$$

$$y' = \vartheta(e^{x-y} - e^{2/3x}) - \sigma u - \varsigma v$$

The linear associated system has a form:

$$x' = y - x - \varepsilon v,$$
$$y' = \frac{1}{3} \vartheta x - \vartheta y - \sigma u - \varsigma v$$

The rank condition is always satisfied

$$P(s) = \det(sI - C^{tr}) = \det\begin{bmatrix}s+1 & -\frac{1}{3}\mathcal{9}\\-1 & s+\mathcal{9}\end{bmatrix} =$$

 $= s^{2} + s(1+\vartheta) + \frac{2}{3}\vartheta \qquad --$

No complex eigenvalues

Real negative eigenvalues only

$$w_1^{tr} D\underline{u} = -(\vartheta + s_1)^{-1} \sigma u + (\varepsilon - (\vartheta + s_1)^{-1} \varsigma)v > 0$$

$$w_2^{tr} D\underline{u} = -(\vartheta + s_2)^{-1} \sigma u + (\varepsilon - (\vartheta + s_2)^{-1} \varsigma) v > 0$$

For some combination of admissible controls

Thus the system is locally constrained controllable.

- In the case of monotherapy (e.g. only antiangiogenic therapy) the sufficient condition of local controllability is simplified: If the associated linear dynamical system is controllable without any constraints i.e. satisfies the rank condition:
- $\operatorname{rank}[D, CD, C^2D, \dots, C^{n-1}D] = n,$
- and its state matrix has only complex eigenvalues then the semilinear dynamical system is locally constrained controllable in time interval [0,T].
- Thus in this case the system does not satisfy the necessary conditions of constrained local controllability since the eigenvalues are real.
- Since for logistic type model of tumor growth (model B) the associated linear system is the same thus we have the same conditions of controllability and the same conclusions could be formulated.

For models C and D controllability conditions could be checked in similar way. For example for model C:

$$x' = y - x - \varepsilon v,$$

$$y' = \mathcal{G}(1 - e^{2/3x}) - \sigma u - \varsigma v$$

The linear associated system has a form:

$$x' = y - x - \varepsilon v,$$

$$y' = -2\vartheta / 3x - \sigma u - \varsigma v$$

$$P(s) = \det(sI - C^{tr}) = \det\begin{bmatrix} s+1 & \frac{2}{3}\mathcal{9} \\ -1 & s \end{bmatrix} =$$

$$= s^{2} + s + \frac{2}{3} \mathcal{G}$$
1) $\mathcal{G} > \frac{3}{8}$ Complex eigenvalues

2) $\mathcal{G} < \frac{3}{8}$ Real eigenvalues

$$w_1^{tr} B \underline{u} = -s_1^{-1} \sigma u + (\varepsilon - s_1^{-1} \xi) v > 0$$

$$w_2^{tr} B \underline{u} = -s_2^{-1} \sigma u + (\varepsilon - s_2^{-1} \xi) v > 0$$

Now we can introduce delays in controls due to PK/PD effects and some conditions imposed on treatment protocols related for example to the prunning effect.

In the simplest case we have

$$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu + \eta u(t) + \xi v(t-h)),$$

$$\dot{N}/N = -\beta \ln N/K - \varphi v(t-h)$$

Such model is suitable for example for combination of angiogenic inhibitor Sunitinib with Cisplatin

Two types of controllability could be defined: relative and absolute depending on the definition of the state of the system. The relative controllability is related to the instataneous state and the absolute one - to the complete state of the system combining the instant-aneous state and delayed control functions (x(t) and v(s), $s \in [t-h, t)$).

We have for modified model A

$$x' = y - x - \varepsilon v(t - h),$$

$$y' = \vartheta(e^{x - y} - e^{2/3x}) - \sigma u(t) - \varsigma v(t - h)$$

The linear associated system has a form:

$$x' = y - x - \varepsilon v(t - h),$$

$$y' = \frac{1}{3} \vartheta x - \vartheta y - \sigma u(t) - \varsigma v(t - h)$$

Sufficient condition of local constrained relative controllability for semilinear dynamical system with many inputs:

If the associated linear dynamical system is controllable without any constraints i.e.

 $\operatorname{rank}[D, CD, C^2D, \dots, C^{n-1}D] = n$

and

there is no real eigenvector $w \in \mathbb{R}^n$ of the matrix C^{tr} satisfying inequalities:

 $w^{tr}D\underline{u} \leq 0$, for all $\underline{u} \in U_c$.

then the semilinear stationary dynamical control system (17) is U_c -locally controllable in [0, *T*] for T > h.

But it means that the conditions will be the same as before if T > h.

Two different angiogenic inhibitors

$\dot{K}/K = \gamma N/K - (\lambda N^{2/3} + \mu + \eta u(t) + \xi v(t-h) + \omega u(t-h_1))$

$$\dot{N}/N = -\beta \ln N/K - \varphi v(t-h)$$

Such model is suitable for example for combination of two angiogenic inhibitors e.g. Bevacizumab and Angiostatin with Cisplatin.

We have

$$x' = y - x - \varepsilon v(t - h),$$

$$y' = \vartheta(e^{x - y} - e^{2/3x}) - \sigma u(t) - \varsigma v(t - h) - \chi u(t - h_1)$$

The linear associated system has a form:

$$x' = y - x - \varepsilon v(t - h),$$

$$y' = \frac{1}{3} \vartheta x - \vartheta y - \sigma u(t) - \varsigma v(t - h) - \chi u(t - h_1)$$



Hahnfeldt et al. model with Gompertz-type growth under combined therapy .Values of parameters chosen for simulation: $\eta = 0.7$, $\psi = 0.7$, $\xi = 0.5$, $\varpi = 0.2$, $h_1 = 18.6$, h = 1.84.

Credits

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