Direct and indirect control of drug resistant cancer populations

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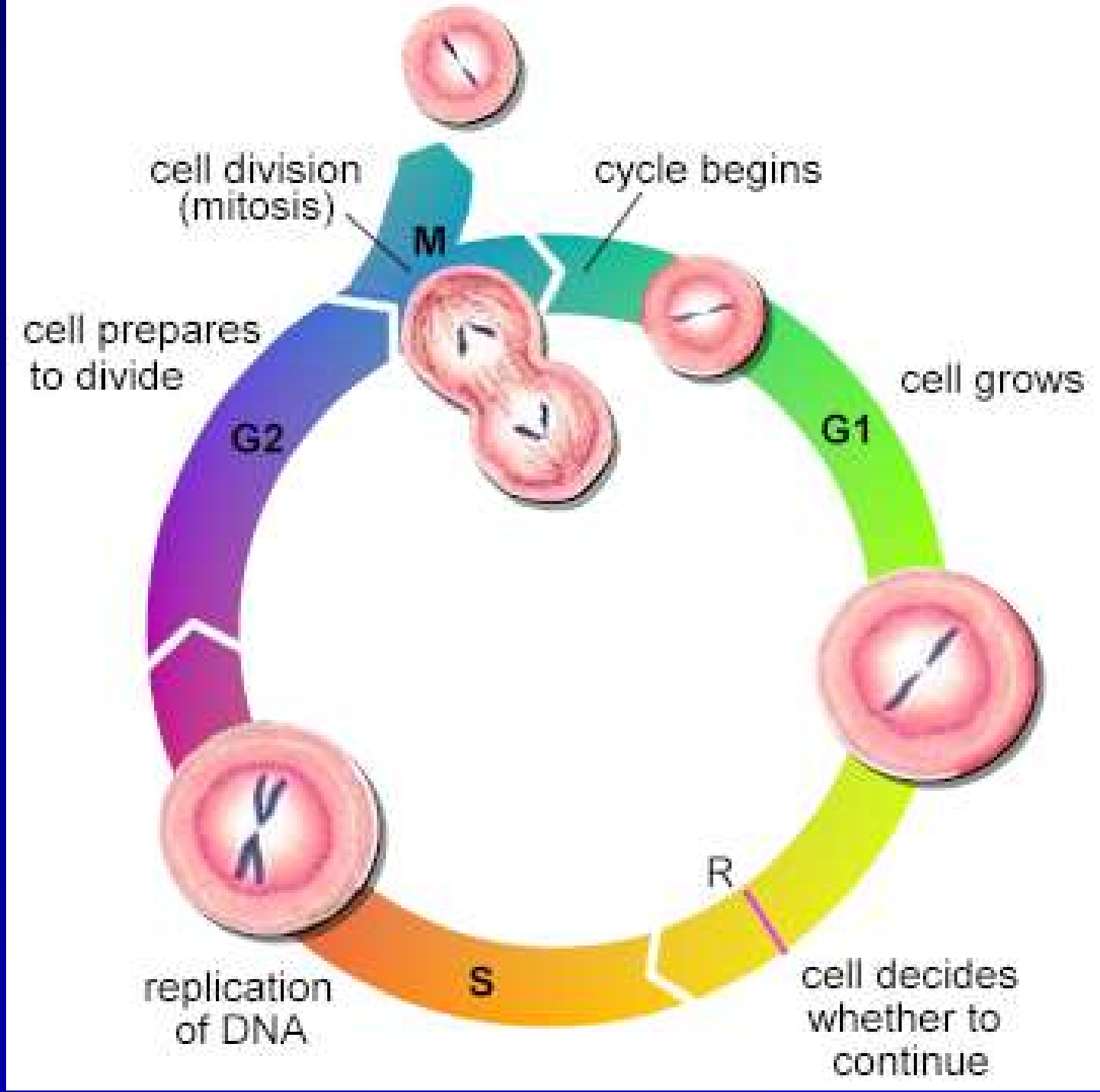
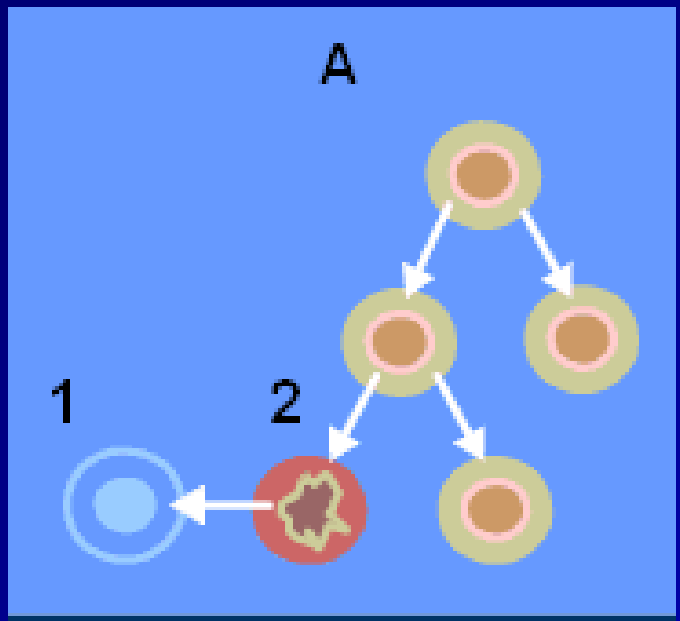
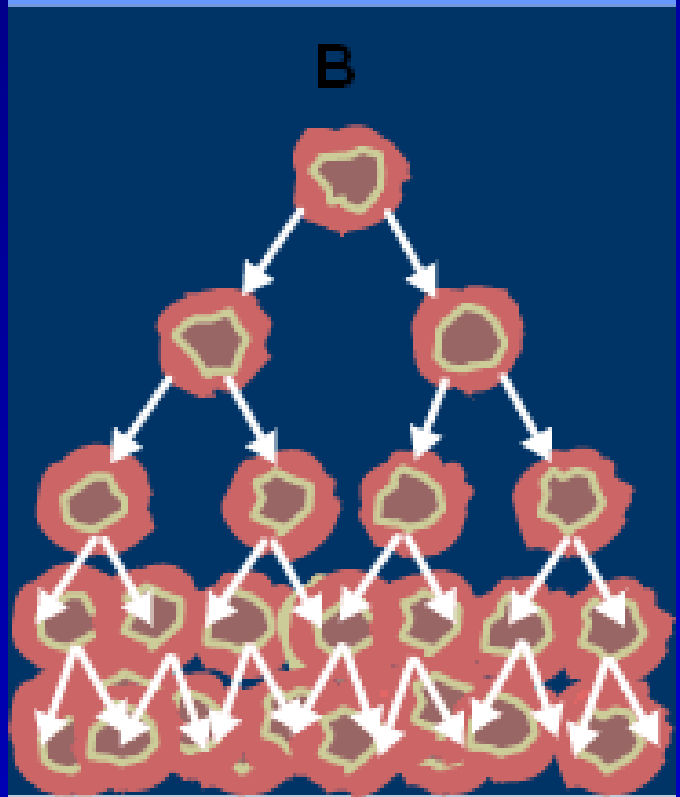
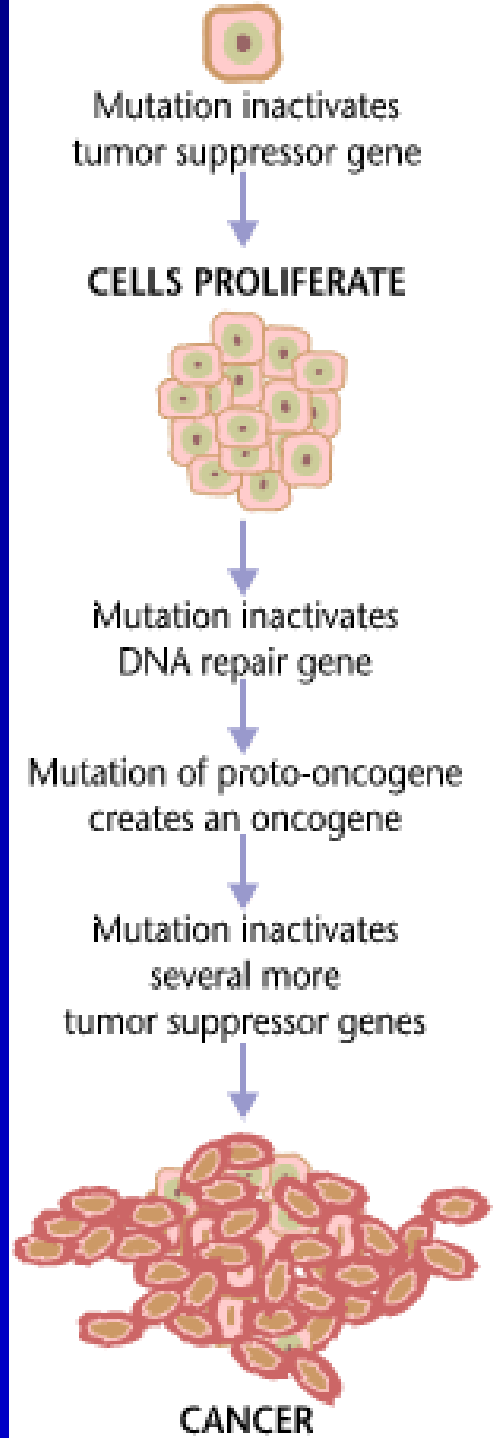
Outline of the talk:

- cell cycle as an object of direct control
- simplest models of tumor growth
- compartmental models – phase specificity of anticancer drugs
- use of maximum principle in protocols optimization
- drug resistance – modeling and analysis
- optimization of chemotherapy protocols
- tumor angiogenesis
- antiangiogenic therapy as an indirect control class
- combined direct and indirect control

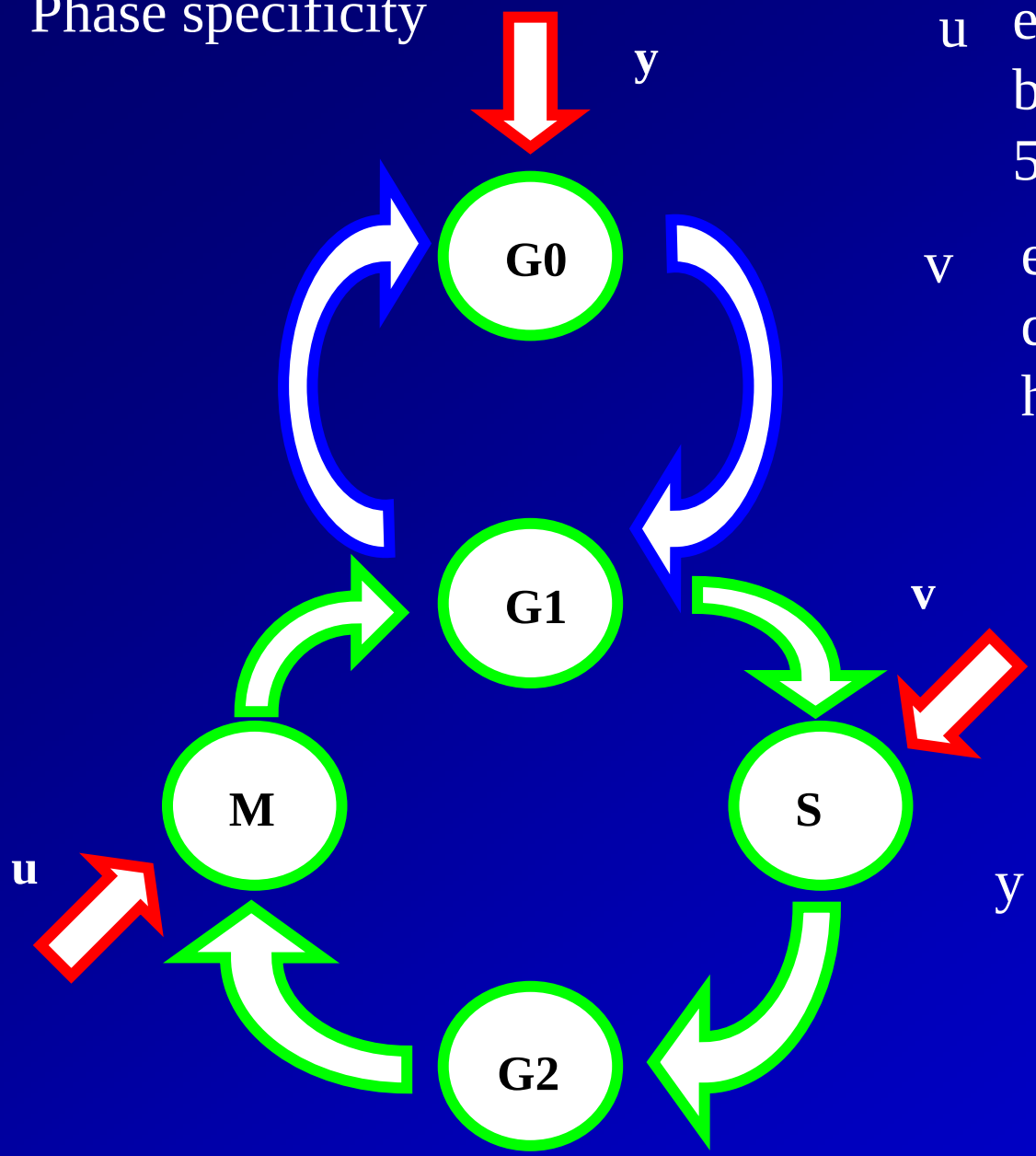

cell division
(mitosis)
M
cycle begins
cell prepares
to divide
G2
cell grows
G1
R
replication
of DNA
S
cell decides
whether to
continue


A
1
2


B


Mutation inactivates
tumor suppressor gene
CELLS PROLIFERATE
Mutation inactivates
DNA repair gene
Mutation of proto-oncogene
creates an oncogene
Mutation inactivates
several more
tumor suppressor genes
CANCER

Phase specificity



u e.g.vincristine,vinblastine, bleomycine,taxol, 5-fluorouracil

v e.g.adriamycin,daunomycin, dexorubin,idarudicin, hydroxyurea

y e.g.granulocyte colony stimulation factors, interleukin-3 combined with human cloned stem cell factor

3 types of action:

1. Killing (u)

$$\dot{N}_i = -a_i N_i + a_{i-1} N_{i-1}$$

$$\dot{N}_{i+1} = a_i (1-u) N_i - a_{i+1} N_{i+1} \qquad u \in [0,1]$$

2. Blocking (v) – synchronization

$$\dot{N}_i = -a_i v N_i + a_{i-1} N_{i-1}$$

$$\dot{N}_{i+1} = a_i v N_i - a_{i+1} N_{i+1} \qquad v \in [v_{\min}, 1]$$

3. Alteration of transit time (y)

$$\dot{N}_i = a_{i-1} N_{i-1} - y a_i N_i$$

$$\dot{N}_{i+1} = y a_i N_i - a_{i+1} N_{i+1}$$

$$\overline{\Delta \tau_i^*} = \frac{\overline{\Delta \tau_i}}{y} \qquad a_i^* = y a_i \qquad y > 1 \longleftarrow \textbf{recruitment}$$

Therapy goal:

$$TCP = \exp(-f\theta N(T_k)) \rightarrow \max$$

f Clonogenic fraction θ Tumor cell density

$$Min \leftarrow N_\Sigma(T) = \sum_i N_i(T)$$

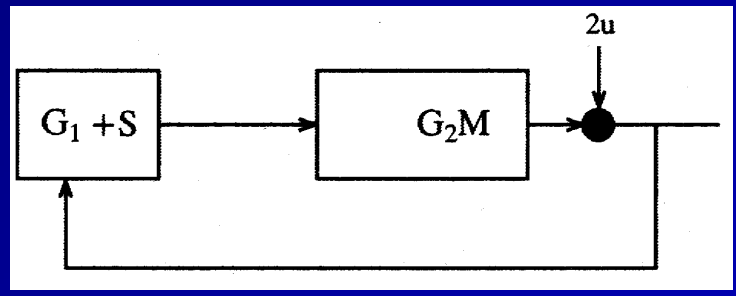
under constraints on cumulative negative effect on normal tissues

$$\int_0^T u dt \leq \Xi$$

Performance index:

$$J = \sum_i N_i(T) + r\int_0^T u dt$$

2 compartment model



$$\dot{N}_1 = -a_1 N_1 + 2(1-u)a_2 N_2 \quad N_1(0) = N_{10} > 0$$

$$\dot{N}_2 = -a_2 N_2 + a_1 N_1 \quad N_2(0) = N_{20} > 0$$

$$J = \sum_{i=1}^{2} r_i N_i(T) + \int_0^T u(t)dt$$

$$H = u + p'(A+uB)N \rightarrow \min$$

Maximum principle

Two point boundary value problem.

a) conjugate equations:

$$\dot{N}(t) = [A + Bu(t)]N(t),$$
$$\dot{p}(t) = -[A + Bu(t)]' p(t),$$

b) switching rule:

Switching function f_s

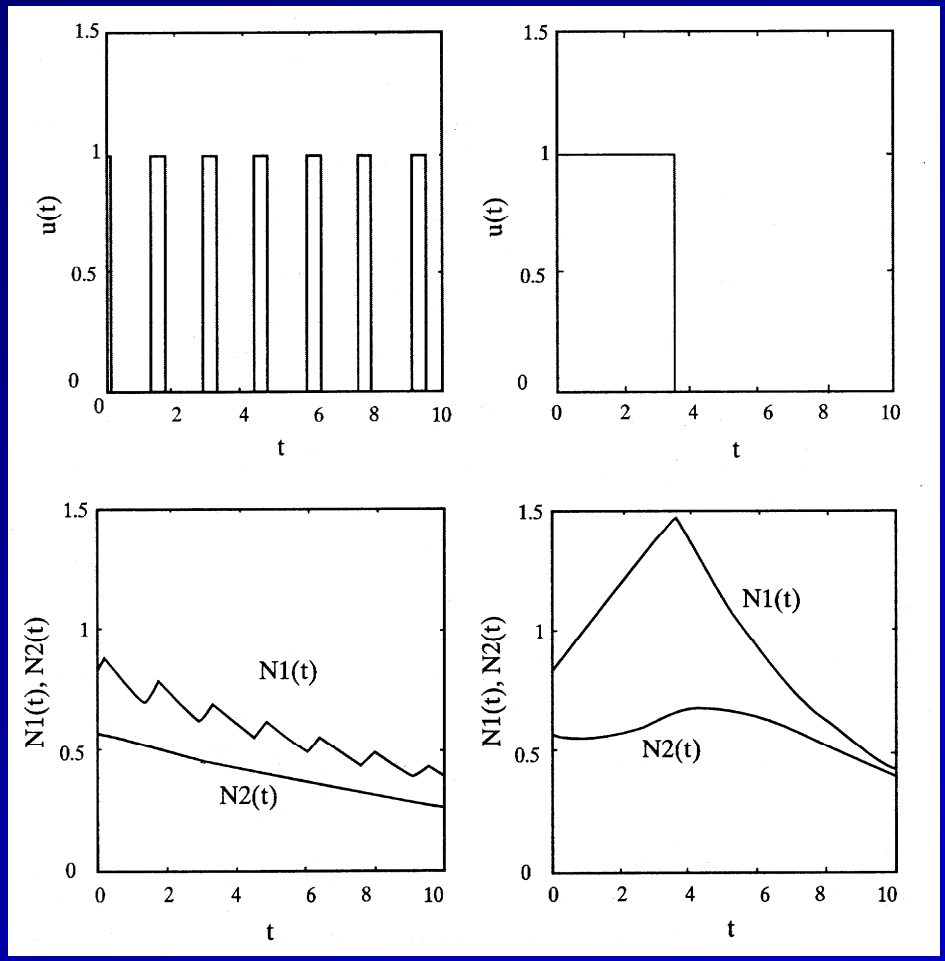
$$u(t) = \begin{cases} 0 & if \quad p'(t)BN(t) + 1 > 0, \\ 1 & if \quad p'(t)BN(t) + 1 < 0, \end{cases}$$

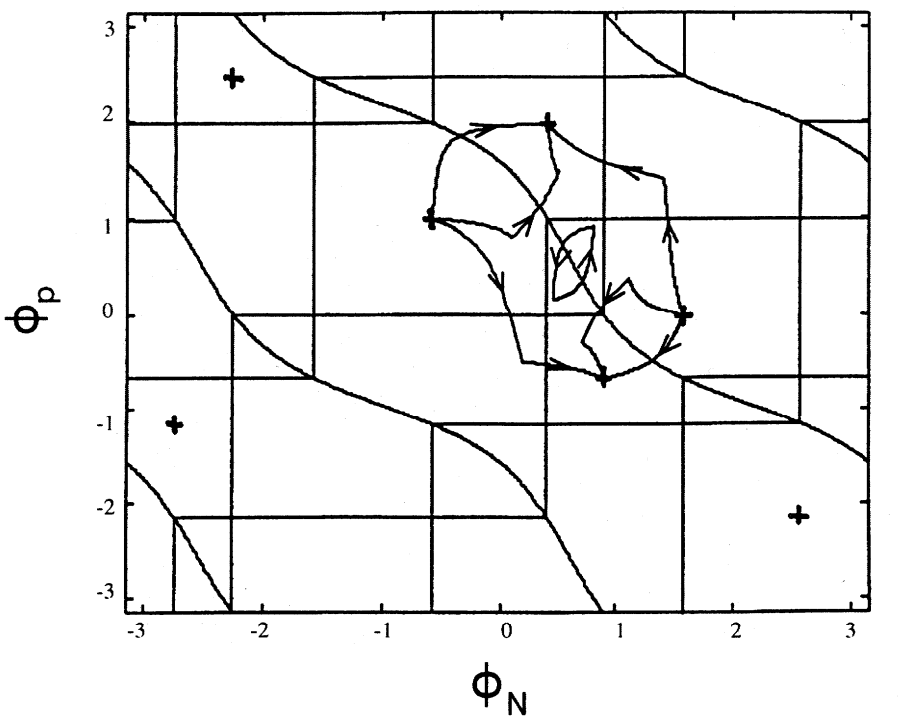
c) boundary conditions:

$$N(0) = N_0, \quad p(T) = r.$$

N belongs to positively invariant set,
p belongs to negatively invariant set

trajectories





Singular control

Legendre-Clebsch condition:

$$(-1)^k \frac{\partial}{\partial u} \frac{d^{2k}}{dt^{2k}} f_s \geq 0$$

r = 2k (for linear in control problem r should be even) in the r-th order derivative of the switching function u appears explicitly k-order of the singular arc

In this case k = 1,

but

$$\frac{df_s}{dt} = p'[A,B]N = 0,$$

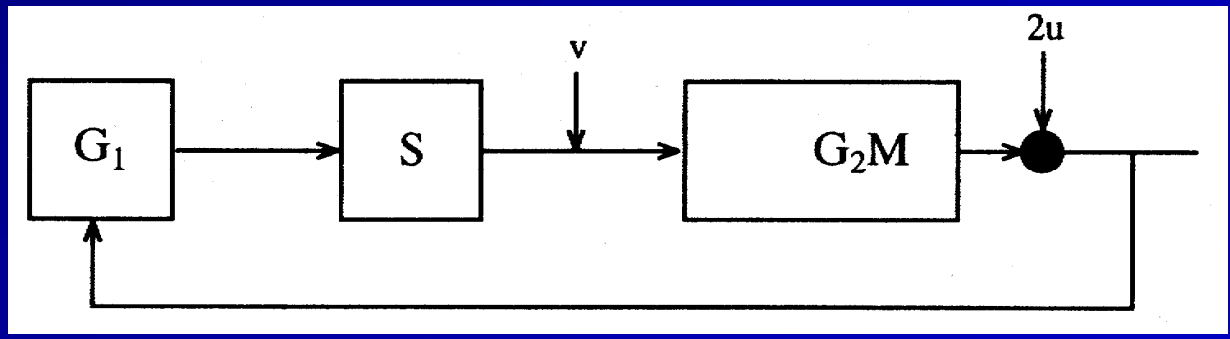
$$\frac{d^2 f_s}{dt^2} = p'[A,[A,B]]N + up'[B,[A,B]]N$$

$$\frac{\partial}{\partial u} \frac{d^2}{dt^2} f_s = p'[B,[A,B]]N = -4a_1 a_2 p'BN = 4a_1 a_2 > 0$$

The condition is violated

3 compartment models

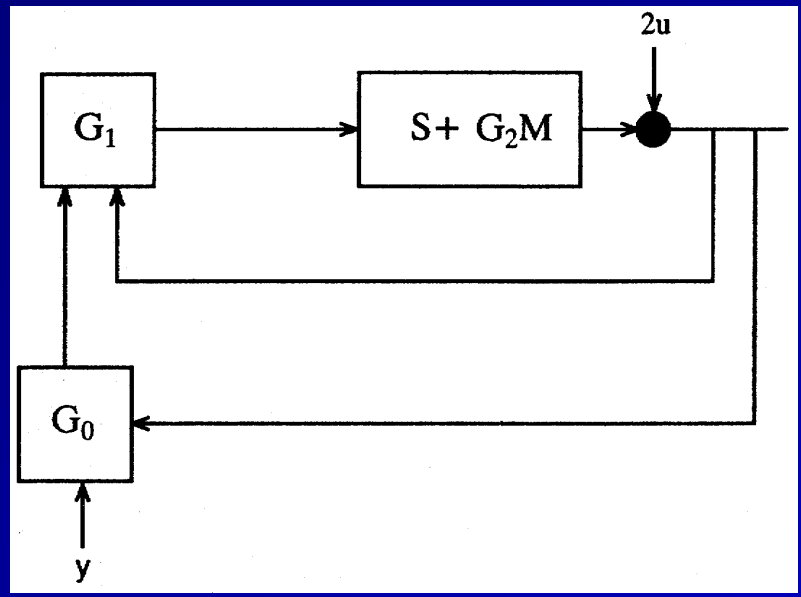
synchronization



$$\dot{N}_1 = -a_1 N_1 + 2(1-u)a_3 N_3, \qquad N_1(0) = N_{10} > 0$$
$$\dot{N}_2 = -v a_2 N_2 + a_1 N_1, \qquad N_2(0) = N_{20} > 0$$
$$\dot{N}_3 = -a_3 N_3 + v a_2 N_2, \qquad N_3(0) = N_{30} > 0$$

$$J = \sum_{i=1}^{3} r_i N_i(T) + \int_0^T u(t)dt$$

recruitment



$$\dot{N}_0 = -ya_0N_0 + 2b_0(1-u)a_2N_2, \qquad N_0(0) = N_{00} > 0$$

$$\dot{N}_1 = -a_1N_1 + ya_0N_0 + 2b_1(1-u)a_2N_2, \qquad N_1(0) = N_{10} > 0$$

$$\dot{N}_2 = -a_2N_2 + a_1N_1, \qquad N_2(0) = N_{20} > 0$$

$$\dot{N}(t) = [A + B_1u(t) + B_2v(t)]N(t),$$

$$\dot{p}(t) = -[A + B_1u(t) + B_2v(t)]' p(t),$$

N is in positively invariant set

p is in negatively invariant set

Necessary conditions

synchronization

$$u = \begin{cases} 0; & 2a_3 N_3 p_1 < 1 \\ 1; & 2a_3 N_3 p_1 > 1 \end{cases}$$

$$v = \begin{cases} v_m; & p_2 < p_3 \\ 1; & p_2 > p_3 \end{cases}$$

$$\begin{aligned} \dot{p}_1 &= a_1(p_1 - p_2), & p_1(T) &= r_1 \\ \dot{p}_2 &= a_2(p_2 - p_3)v, & p_2(T) &= r_2 \\ \dot{p}_3 &= a_3(p_3 - 2p_1(1-u)), & p_3(T) &= r_3 \end{aligned}$$

recruitment

$$u = \begin{cases} 0; & 2a_2 N_2 (b_0 p_0 - b_1 p_1) < 1, \\ 1; & 2a_2 N_2 (b_0 p_0 - b_1 p_1) > 1, \end{cases}$$

$$y = \begin{cases} 1; & p_1 > p_0, \\ 0; & p_1 < p_0. \end{cases}$$

$$\dot{p}_0 = y a_0 (p_0 - p_1), \qquad p_0(T) = r_0$$

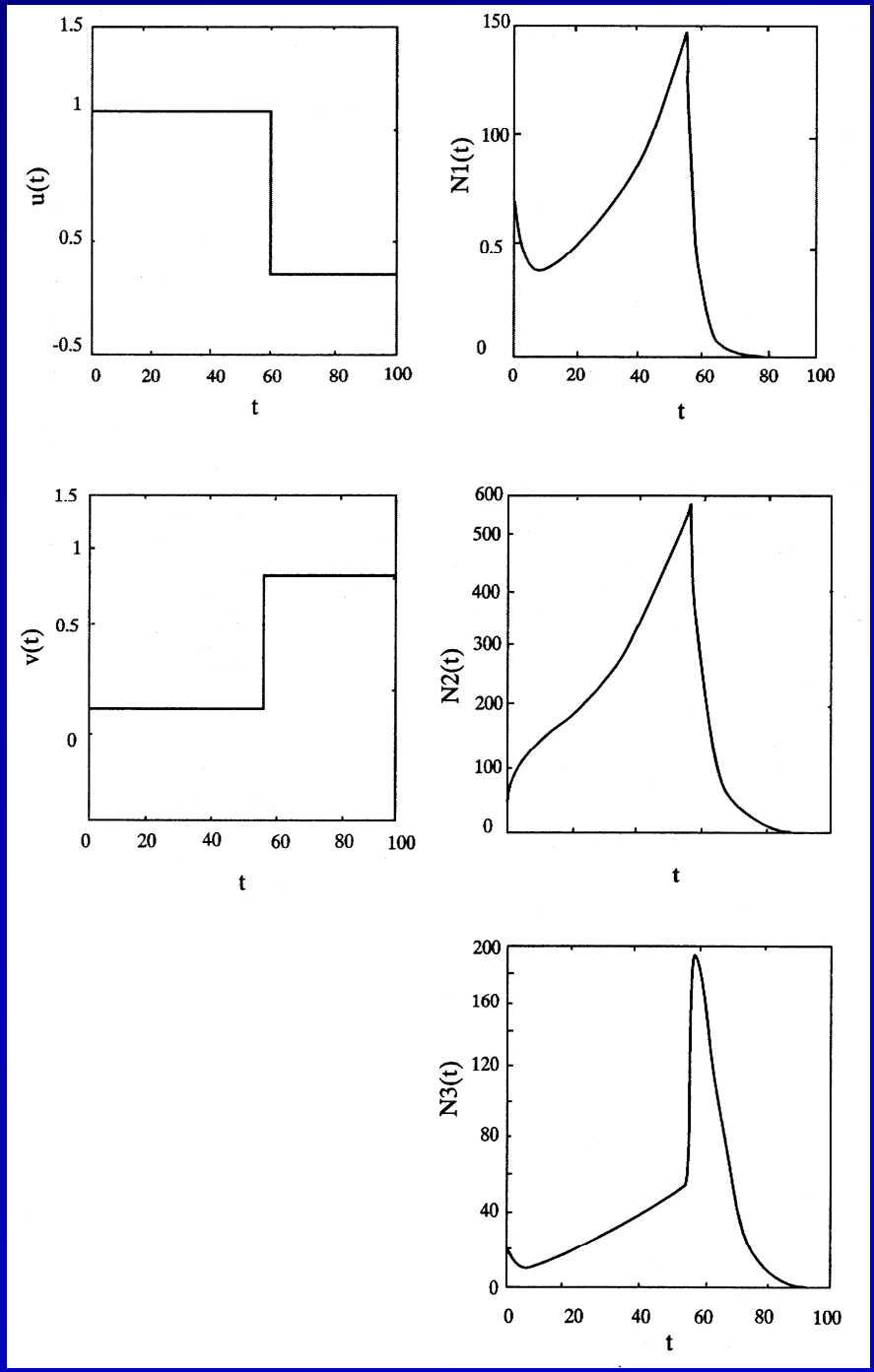
$$\dot{p}_1 = a_1 (p_1 - p_2), \qquad p_1(T) = r_1$$

$$\dot{p}_2 = a_2 [p_2 - 2(1-u)(b_0 p_0 - b_1 p_1)], \qquad p_2(T) = r_2$$

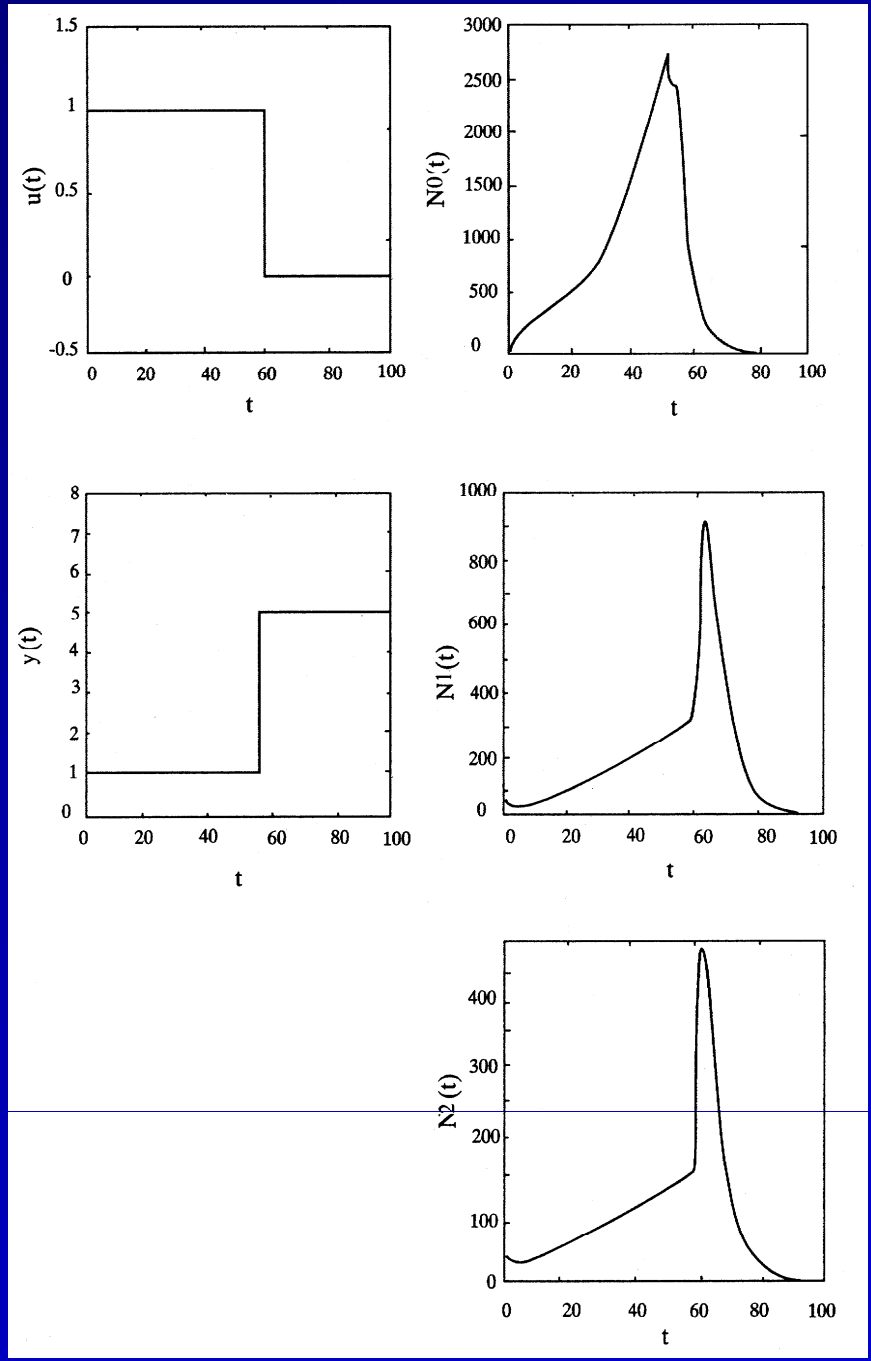
In both cases singular arcs are eliminated using Clebsch –Legendre and Goh conditions

Numerical results

Synchronization
with cell arrest

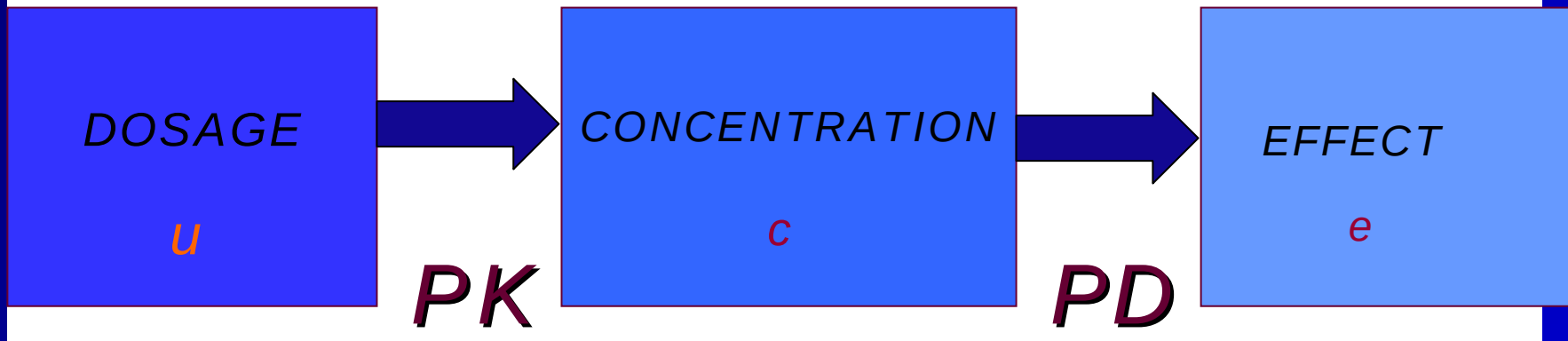


Recruitment from G0



Pharmacokinetics and Pharmacodynamics (PK/PD)

in previous models: *dosage = concentration = effect*



$$\dot{N}(t) = (A + s(c)B)\,N, \qquad N(0) = N_0$$
$$\dot{c}(t) = -(f + ug)c + hu, \qquad c(0) = 0$$

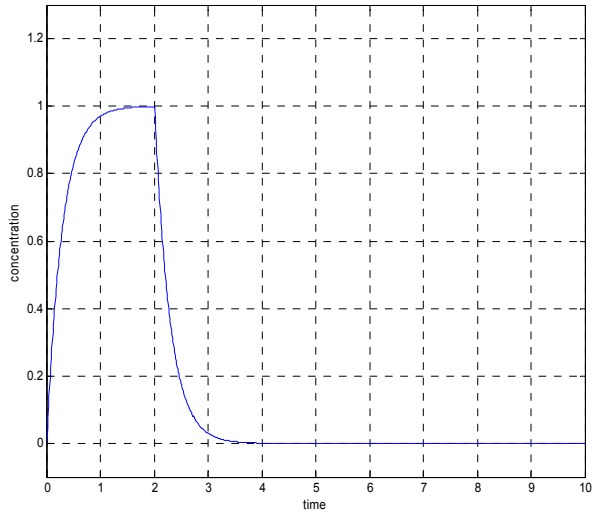
Models for PK

- Often unknown specifics
- Common approach - linear model (exponential growth/ decay)-Bellman's model

$$\dot{c} = -fc + hu, \quad c(0) = 0$$

f, h

positive constants



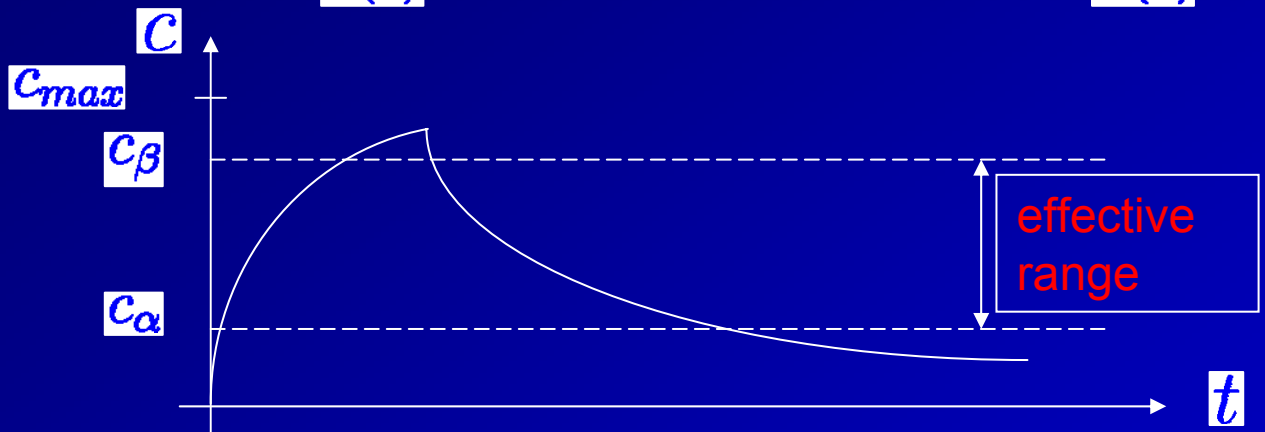
$$f = h = 5ln(2)$$

Pharmacodynamics

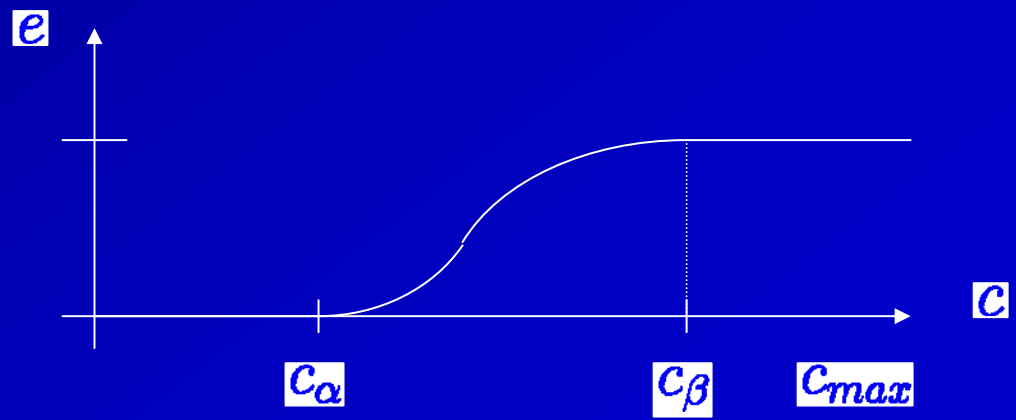
concentration → PD → effect

$c(t)$ → PD → $e(t)$

$e = s(c)$



saturation models

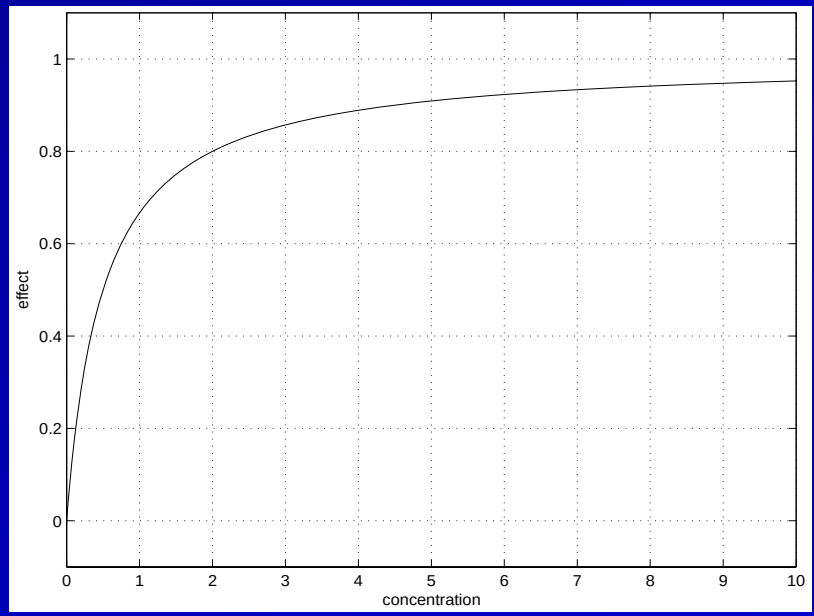


Models for PD: Michaelis-Menten Model

$$s_2(c) = \frac{E_{max} c}{EC_{50} + c},$$

EC_{50}

- Menten constant
- smooth saturation at maximum effect
- immediate effects

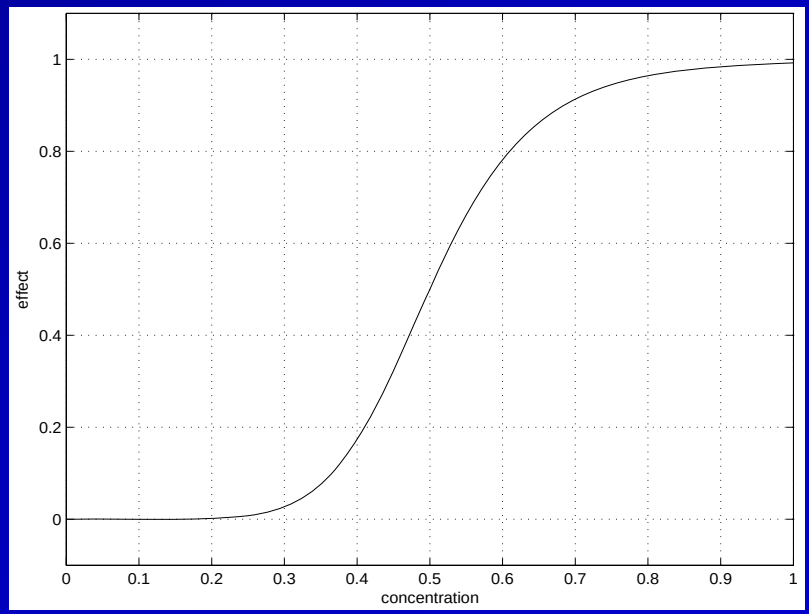


Models for PD: Sigmoidal Model

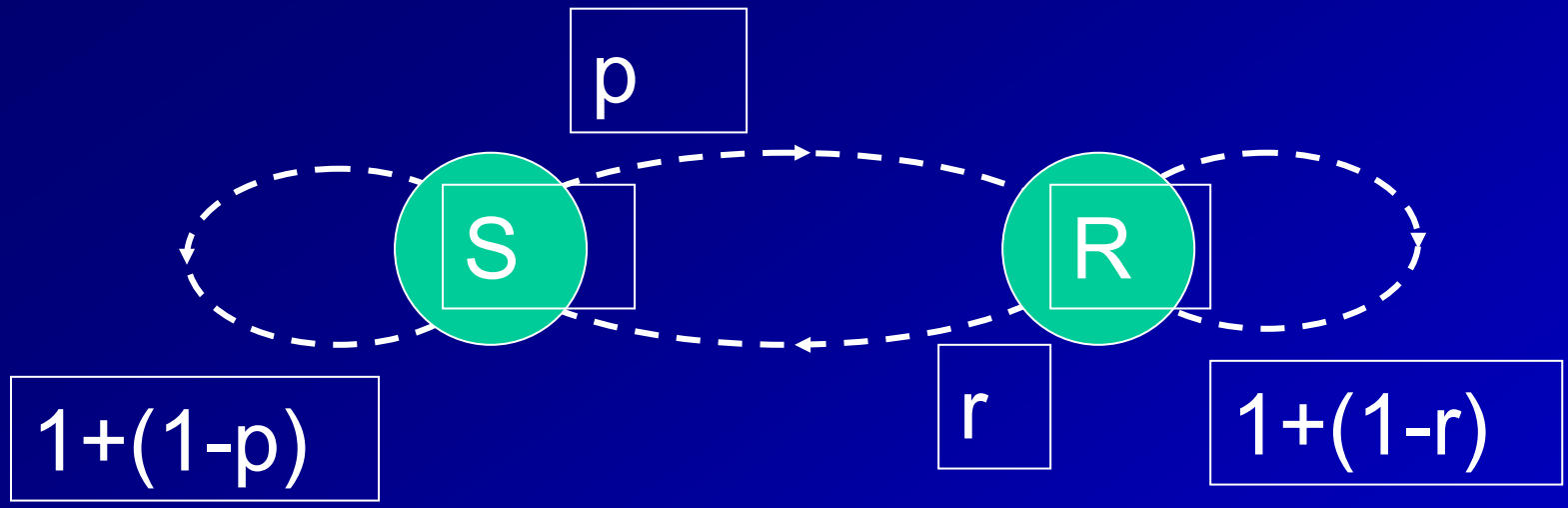
$$s_3(c) = \frac{E_{max}c^n + E_{min}(EC_{50})^{n\log_{10}c}}{(EC_{50}^n + c^n)},$$

$$s_4(c) = \frac{E_{max}c^n}{(EC_{50}^n + c^n)},$$

- smooth upper saturation
- delay effect

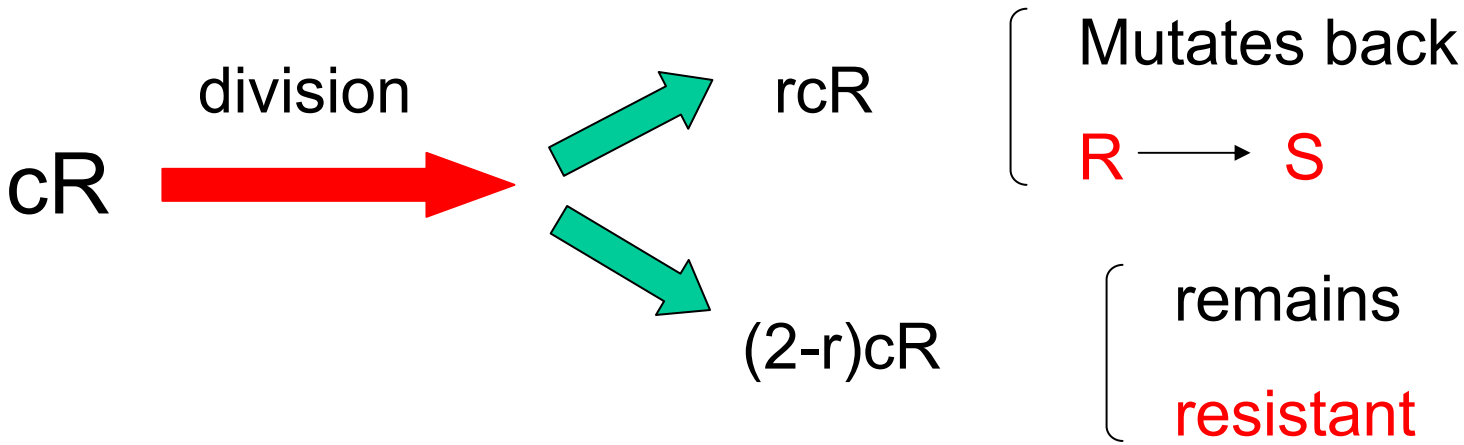


Drug resistance (1)



- S – average number of cells in sensitive compartment
- R – average number of cells in resistant compartment
- $0 < p < 1$ probability of a daughter cell of a sensitive cell to become resistant
- $0 \leq r < 1$ probability of a daughter cell of a resistant cell to become sensitive
  - r=0 stable gene amplification
  - r>0 unstable gene amplification

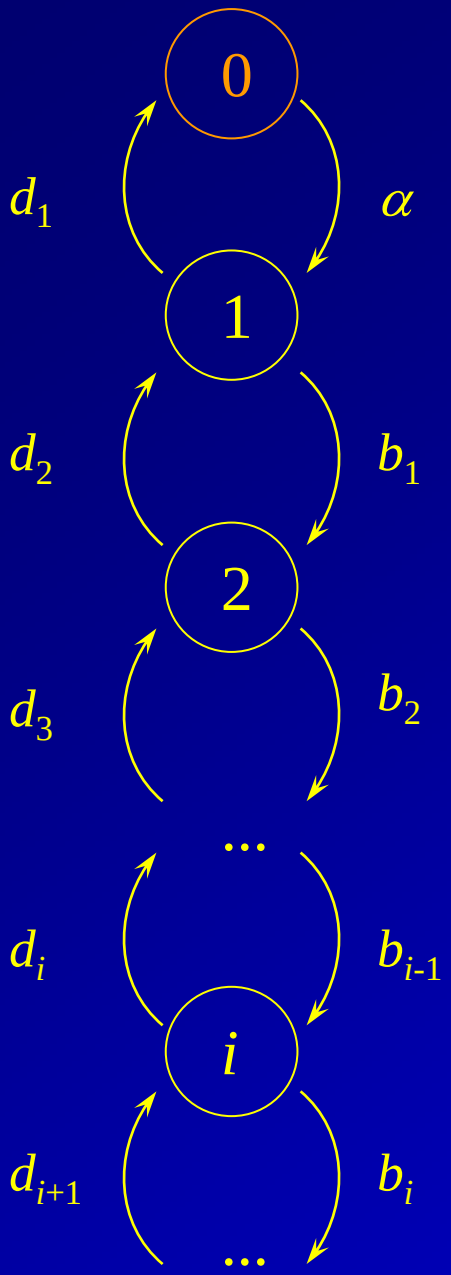
- cR(t) – outflow of resistant cells



- dynamics

$$\begin{aligned} \dot{S} &= -aS + (2-p)(1-u)aS + rcR, \\ \dot{R} &= -cR + (2-r)cR + p(1-u)aS. \end{aligned}$$

Drug resistance model (2)



$$\dot{N}_0(t) = \lambda_0 N_0(t) - \alpha N_0(t) + d_1 N_1(t)$$

$$\dot{N}_1(t) = \lambda_1 N_1(t) - (b_1 + d_1) N_1(t) + \alpha N_0(t) + d_1 N_2(t)$$

$$\dot{N}_2(t) = \lambda_2 N_2(t) - (b_2 + d_2) N_2(t) + b_1 N_1(t) + d_3 N_3(t)$$

$N_i(t)$ – number of cells with i additional gene copies responsible for drug removement and metabolisation,
λ_i – cell lifespans, $b<d$ (amplification < deamplification)

$$\dot{N}_i(t) = \lambda_i N_i(t) - (b_i + d_i) N_i(t) + d_{i+1} N_{i+1}(t) + b_{i-1} N_{i-1}(t)$$

Drug resistance model (3)

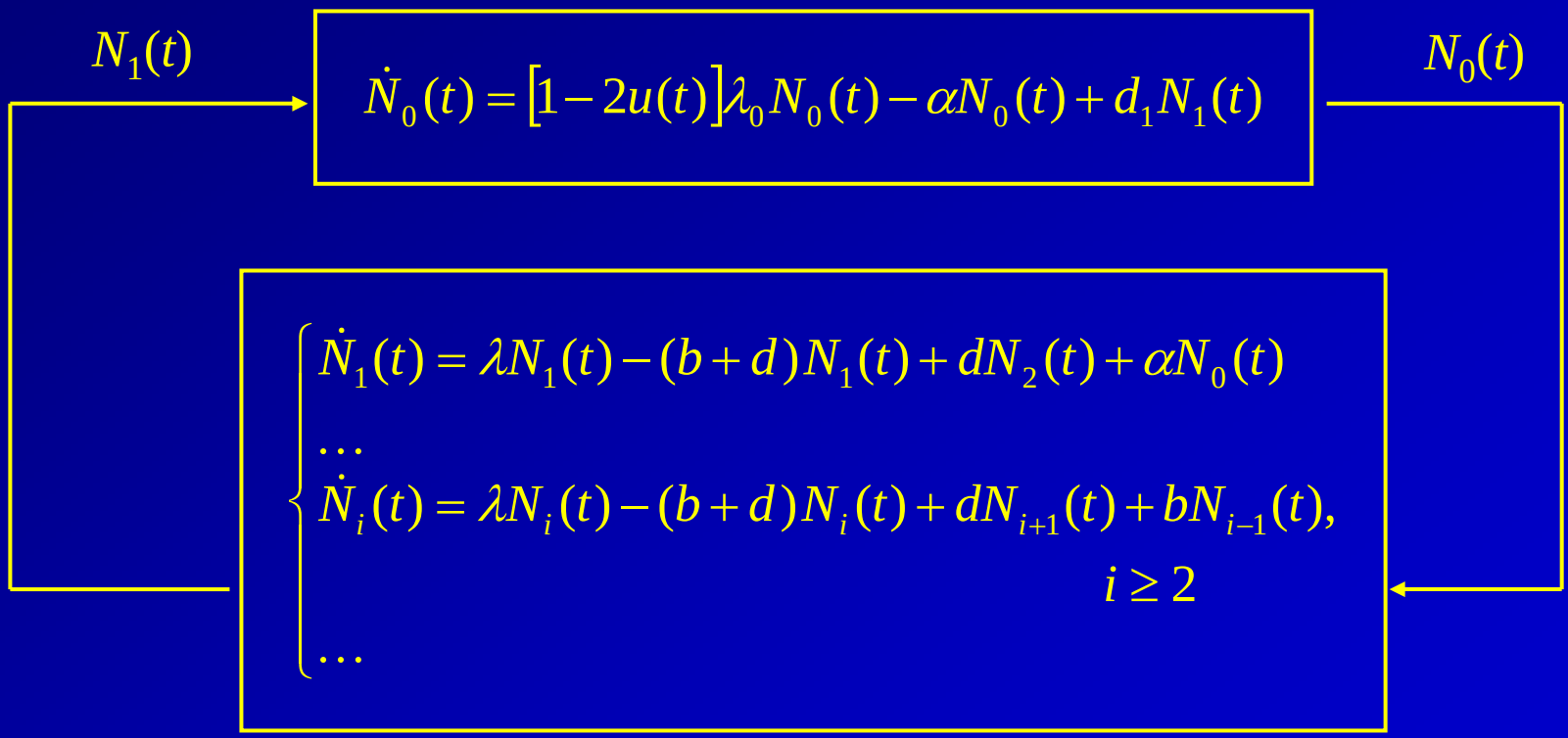
Model of cancer cells evolution, taking into account increasing drug resistance

Simplifying assumptions:

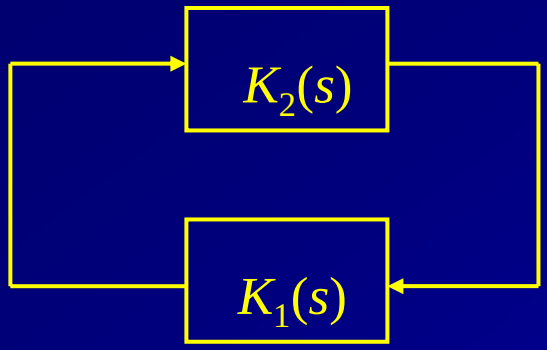
- the resistant cells are insensitive to drug's action ⟶ $u(t)$ only in 0 comp.
- there are no differences between parameters of cells of different type ⟶ $\lambda_i = \lambda,\ b_i = b,\ d_i = d$

$$\begin{cases} \dot{N}_0(t) = [1-2u(t)]\lambda N_0(t) - \alpha N_0(t) + dN_1(t) \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) + dN_2(t) + \alpha N_0(t) \\ \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), i \geq 2 \\ \dots \end{cases}$$

Block diagram



Stability conditions (for constant u)



$$K_1(s) = \alpha \frac{s - \lambda + b + d - \sqrt{(s - \lambda + b + d)^2 - 4bd}}{2bd}$$

$$N_\Sigma(t) = \sum_{i \geq 1} N_i(t) = \exp[\lambda t] \cdot \left[1 - \left(\sqrt{\frac{d}{b}} \right) \int_0^t \frac{I_1\left(2\sqrt{bd}\ \tau\right)}{\tau} \exp[-(b+d)\tau] d\tau \right]$$

$$N_\Sigma(t) = \sum_{i \geq 1} N_i(t) \sim \left[1 - \frac{\min(b,d)}{b} \right] e^{\lambda t} + \frac{d}{2\sqrt{\pi} \sqrt[4]{(bd)^3} \left(\sqrt{d} - \sqrt{b}\right)^2} t^{-3/2}\, e^{[\lambda - (\sqrt{d} - \sqrt{b})^2]t}$$

$$b < d \qquad \sqrt{d} - \sqrt{b} > \sqrt{\lambda}$$

Moreover:

$$u > \frac{1}{2} + \frac{\alpha}{d} \cdot \frac{1}{d - b - \lambda + \sqrt{(b + d - \lambda)^2 - 4bd}}$$

Optimization of chemotherapy protocols

$$\min_{u} \leftarrow J = \sum_{k \geq 0} N_k(T) + r \int_0^T u(\tau) d\tau$$

$$\min_{u} \leftarrow J = N_0(T) +$$

$$+ \int_0^T \left[r_1 \alpha N_\Sigma(T-\tau) N_0(\tau) + r u(\tau) \right] d\tau$$

For the simplified model and nonexisting initial drug resistant population:

$$\dot{N}_0(t) = (1-2u(t))\lambda N_0(t) - \alpha N_0(t) + d\alpha \int_0^t \phi_1(t-\tau) N_0(\tau) d\tau$$

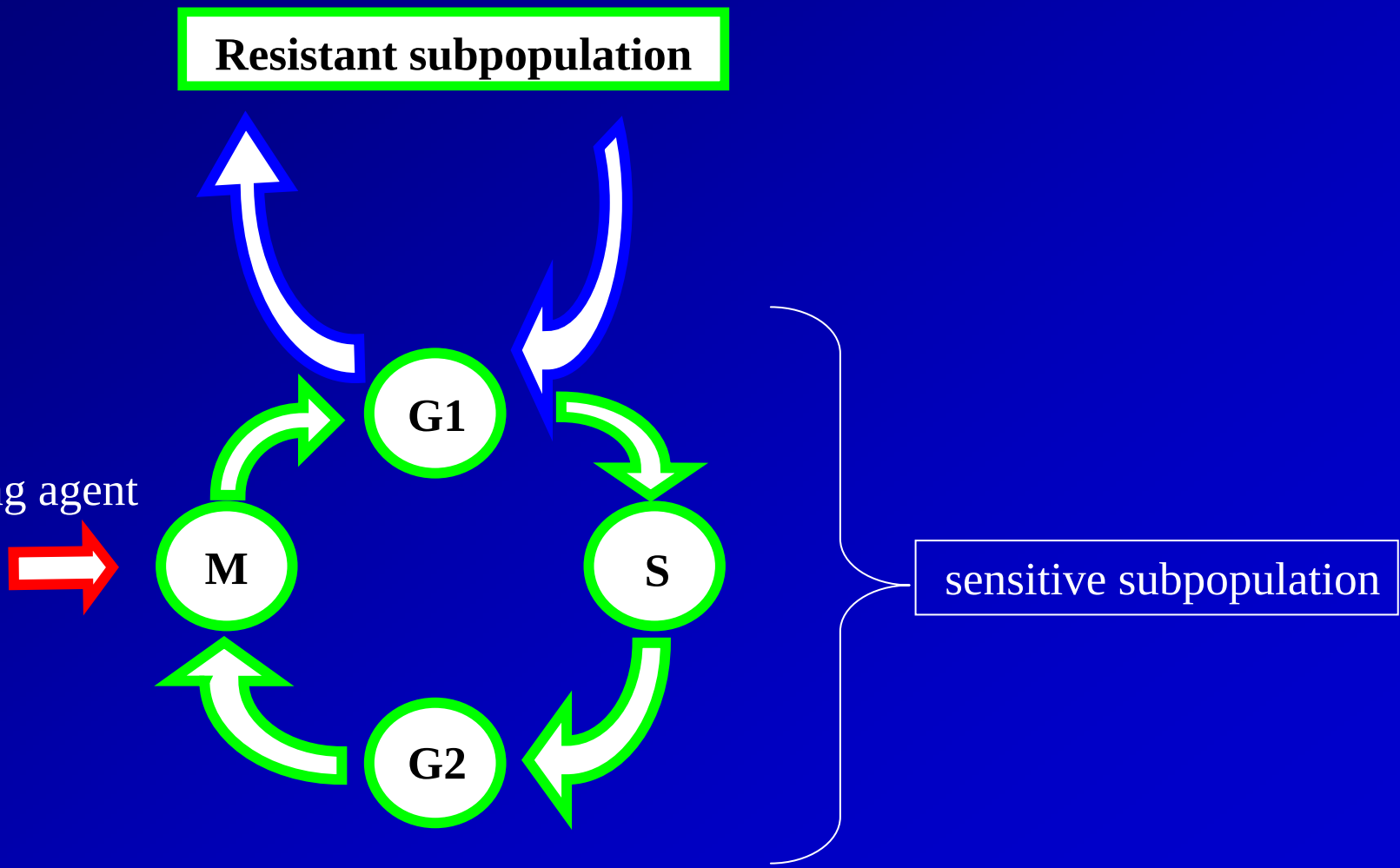
$$\phi_1(t) = \left(\sqrt{\frac{1}{bd}}\right) \frac{I_1\left(2\sqrt{bd}t\right)}{t} e^{-(b+d)t}$$

$$u^{opt}(t) = \arg\min\left[\left(r - 2p(t)\lambda N_0(t)\right)u(t)\right]$$

$$\dot{p}(t) = -\left[r_1 \alpha N_\Sigma (T-t) + p(t)\left((1-2u)\lambda - \alpha\right) + d\alpha \int_t^T p(\tau)\phi_1(t-\tau)d\tau \right] \qquad p(T) = 1$$

$$u(t) = \begin{cases} 0 & for \quad r - 2p(t)\lambda N_0(t) > 0 \\ 1 & for \quad r - 2p(t)\lambda N_0(t) < 0 \end{cases}$$

Combined model (1)



Cells in phases $S+G_1$

Cells in phase G_2M

$$\dot{N}_0(t) = -\lambda_0 N_0(t) + (2-\alpha)\left[1-u(t)\right]\lambda_1 N_1(t) + dN_2(t)$$

$$\dot{N}_1(t) = \lambda_0 N_0(t) - \lambda_1 N_1(t)$$

$$\dot{N}_2(t) = \lambda_2 N_2(t) - (b+d)N_2(t) + \alpha\lambda_1 N_1(t) + dN_3(t)$$

$$\cdots$$

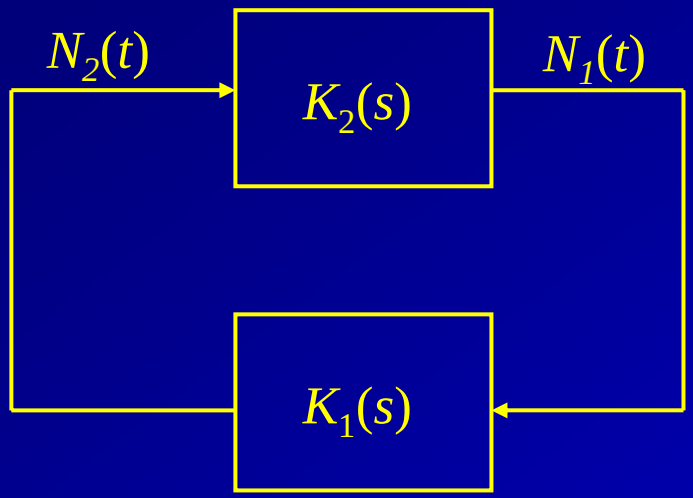
$$\dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 3$$

$$\cdots$$

Drug resistant cells

$$J = \sum_{i=0}^{1} N_i(T) + r_1 \sum_{i=2}^{\infty} N_i(T) + \int_0^T \left[r_2 u(\tau)\right] d\tau$$

Transfer functions



$$K_2(s) = \frac{d\lambda_0}{s^2 + (\lambda_0 + \lambda_1)s + ((\alpha - 2\lambda_1)(1-u) + \lambda_1)\lambda_0}$$

(u constant)

$$K_1(s) = \alpha \frac{s - \lambda + b + d - \sqrt{(s - \lambda + b + d)^2 - 4bd}}{2bd}$$

$$\dot{N}_0(t) = -\lambda_0 N_0 + (1-u(t))(2\lambda_1 - \alpha)N_1(t) + d\alpha \int_0^t \phi_1(t-\tau)N_1(\tau)d\tau$$

$$\dot{N}_1(t) = \lambda_0 N_0(t) - \lambda_1 N_1(t)$$

$$u^{opt}(t) = \arg\min\left[\left(r_2 - (2\lambda_1 - \alpha)\, p(t)\lambda N_1(t)\right)u(t)\right]$$

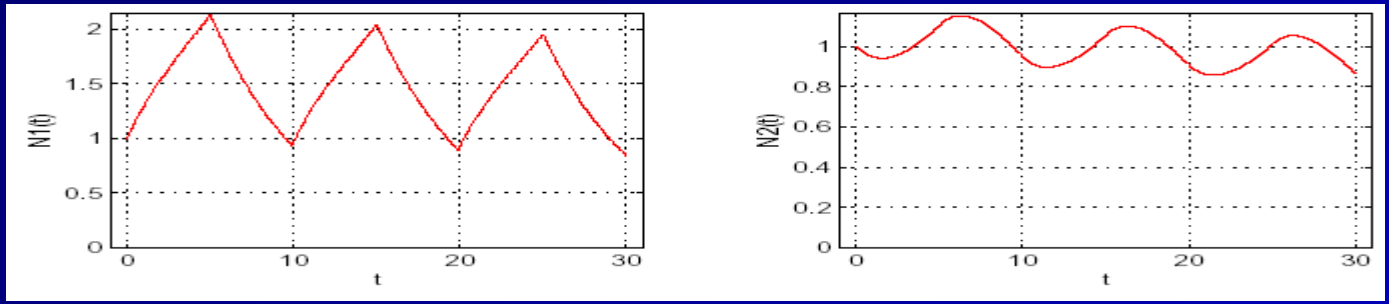
$$\dot{p}(t) = \lambda_0(p\ (t) - p_1(t))$$

$$p(T) = 1$$

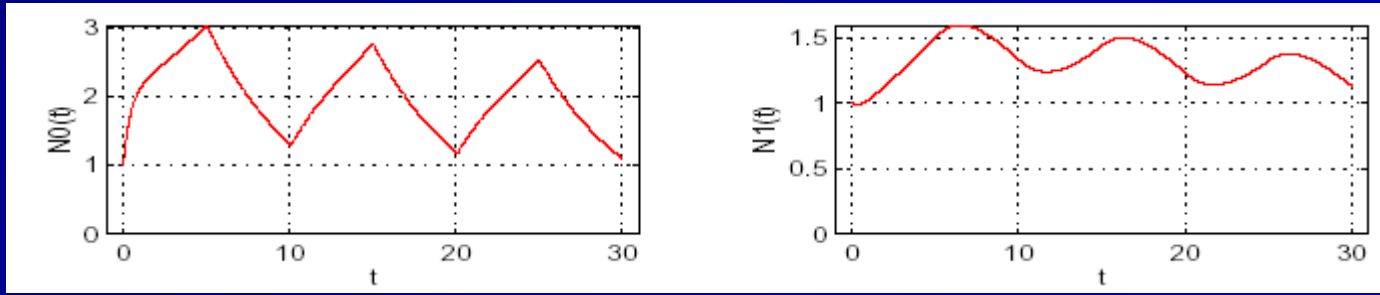
$$\dot{p}_1(t) = -\left[\alpha r_1 N_\Sigma(T-t) + p(t)\left((1-u)(2\lambda_1 - \alpha) + d\alpha \int_t^T p(\tau)\phi_1(t-\tau)d\tau \right]\right] + \lambda_1 p_1$$

$$p_1(T) = 1$$

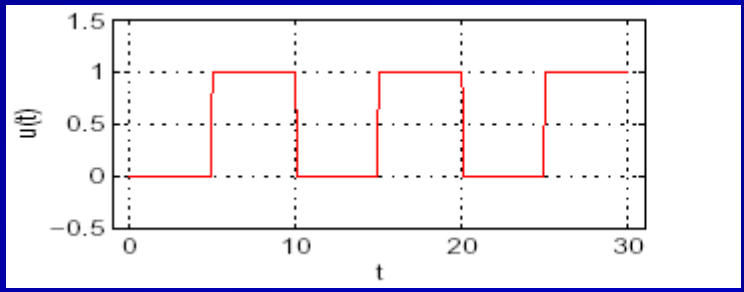
Numerical example



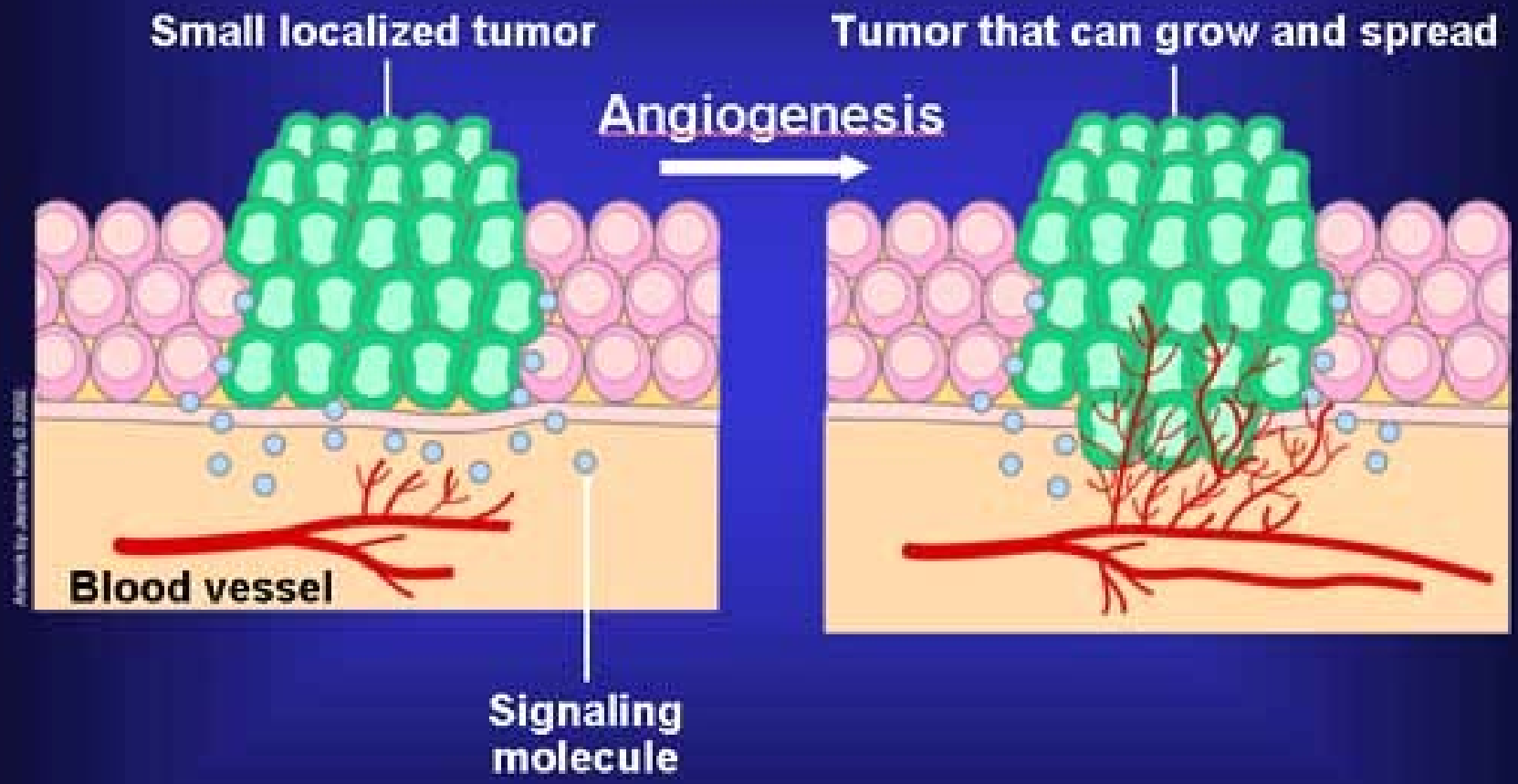
Without gene amplification



With gene amplification

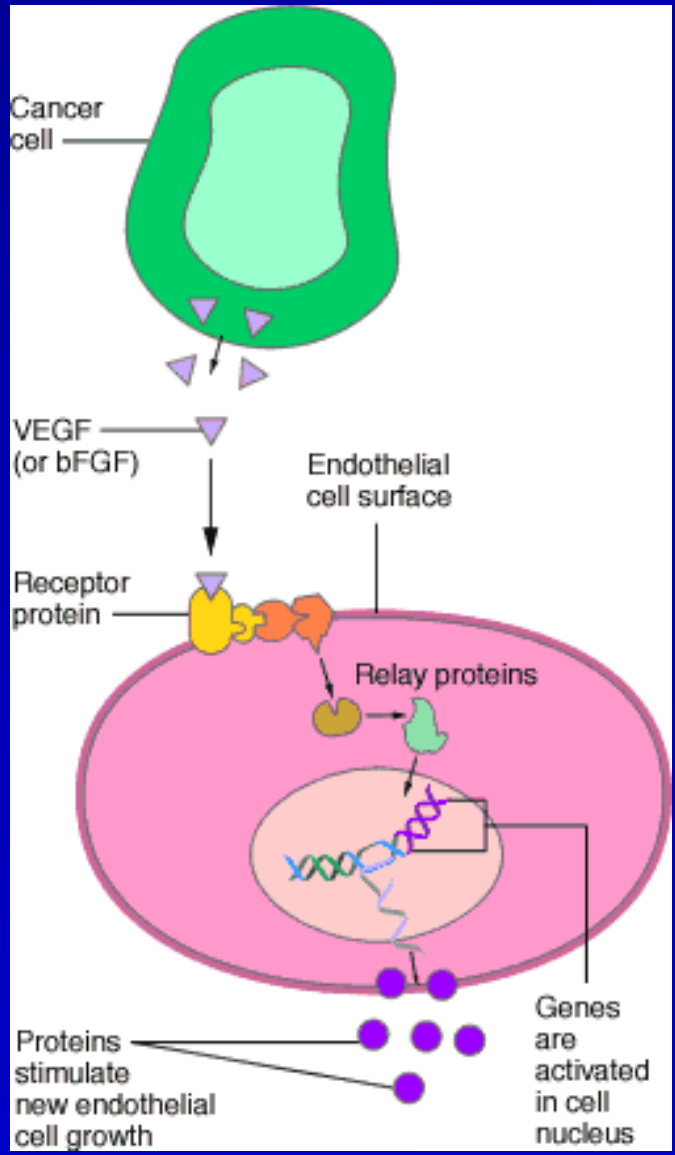


What Is Tumor Angiogenesis?

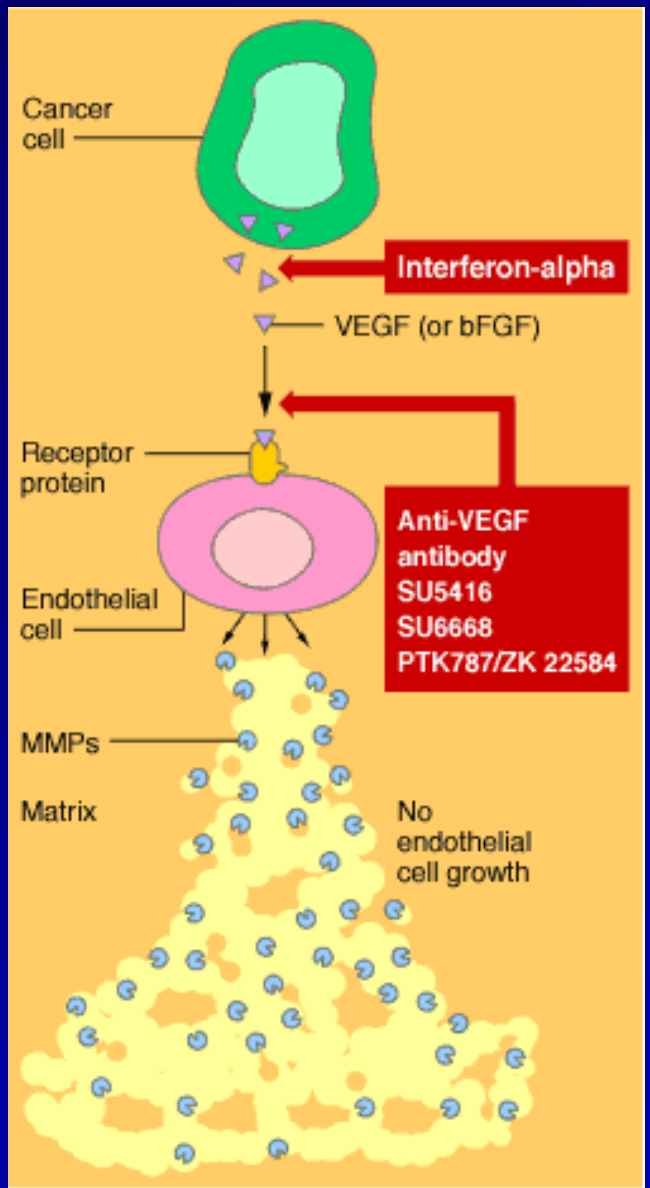


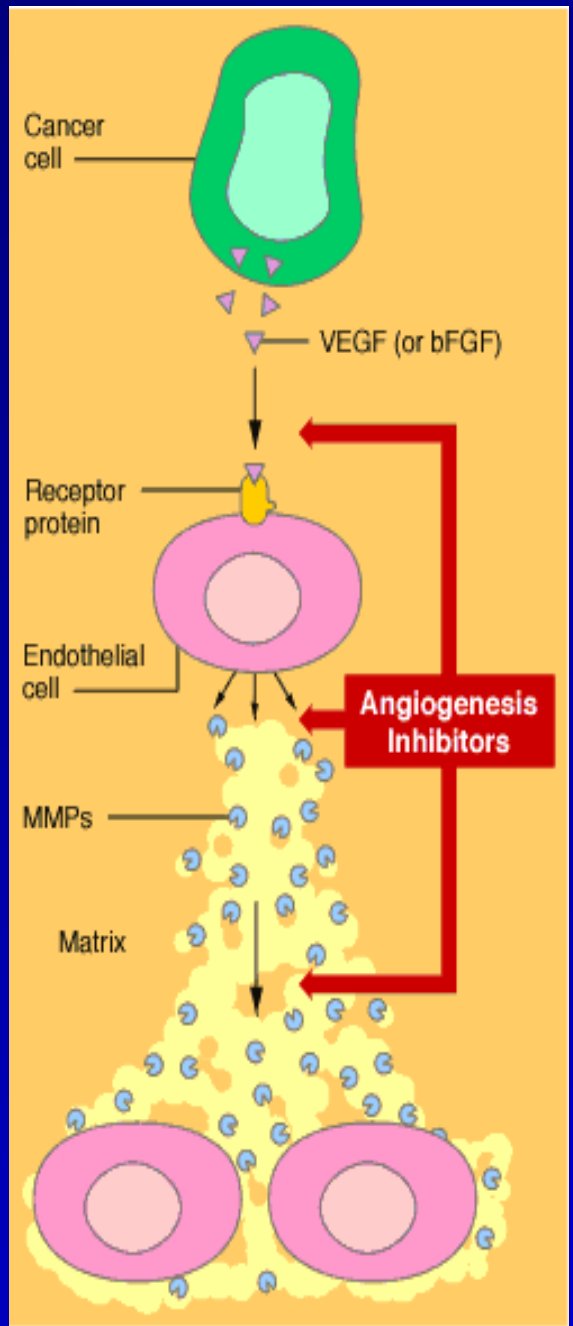
Cascade of angiogenic signals

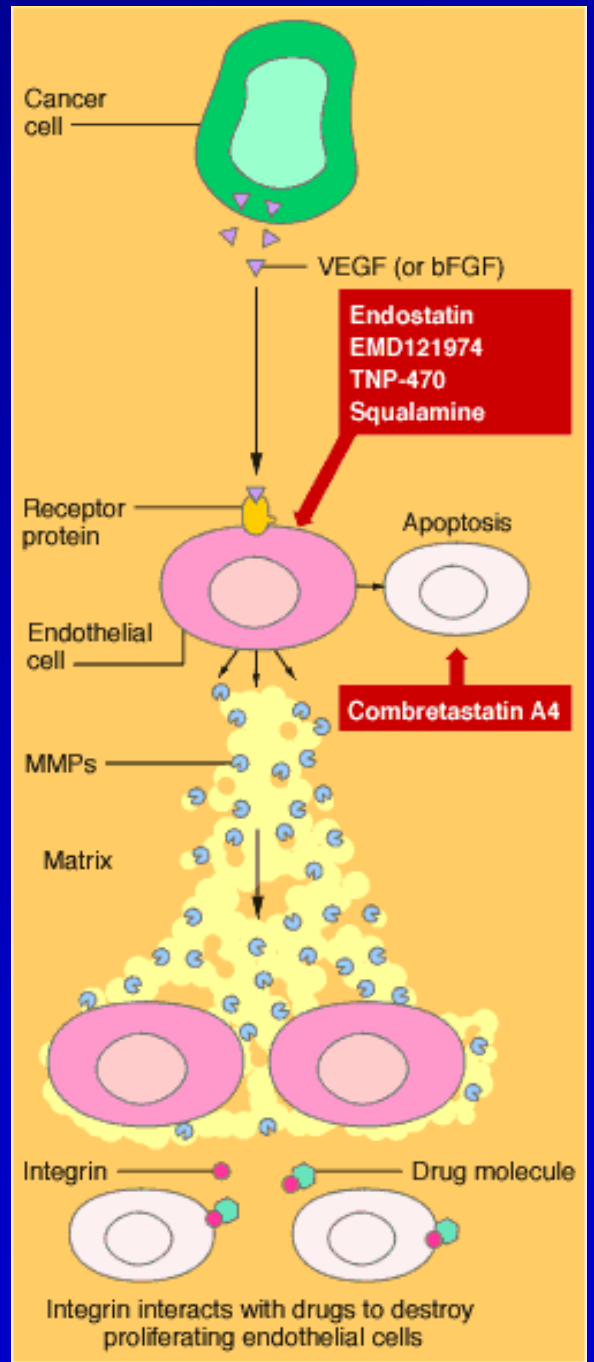
To initiate the process of angiogenesis cancer cells must release factors which will stimulate endothelial cells to more intensive proliferation, e.g.EGF – vascular endothelial growth factor, and bFGF – basic fibroblast growth factor. They are discovered by receptors upon the surface of endothelial cells which in turn activate some genes in the cell nucleus. Their upregulation leads to activation of factors necessary for increasing growth of endothelium (e.g. by destroying the structure of extracellular cell matrix - ECM).



Therapy – where to attack?







Models of tumor growth

$$\frac{dN}{dt} = \dot{N} = aN, N(0) = N_0 \Rightarrow$$

$$N = N_0 e^{at}, a = \ln 2 / PDT$$

$$\frac{\dot{N}}{N} = a = const.$$

Gompertzian growth

$$\dot{N} = a(t)N, N(0) = N_0,$$

$$\dot{a} = -\beta a, a(0) = \alpha \Rightarrow$$

$$N = N_0 e^{\alpha/\beta(1-e^{-\beta t})}$$

$$N_\infty = N_0 e^{\alpha/\beta}$$

Equivalent nonlinear Gompertz model:

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

Incorporation of angiogenesis in the model (Hahnfeldt):

$$N_{\infty} = K$$

K– effective vascular support (carrying capacity)

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)

The dynamics of the growth of volume K 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*).

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

$$IF/SF = K^b N^c$$

$$b + c \approx 2/3$$

Originally

d'Onofrio-Gandolfi

$$b = 1, c = -1/3$$

$$b = 0, c = 2/3$$

$$IF \approx CR^2, SF \approx const, MF \approx const, R \approx \sqrt[3]{N}$$

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

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

Similarly for logistic growth (Pearl-Verhulst equation)

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

Stability conditions

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

- Equillibrium points (for $\gamma > \mu$) :

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

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

$$x' = y - x,$$

$$y' = \vartheta(1 - e^{2/3x})$$

local asymptotic stability

Lyapunov function:

$$V(x,z) = 0.5z^2 + \vartheta \int_0^x (e^{2/3\xi} - 1) d\xi,$$

$$V' = -z^2 < 0$$

$$z = y - x,$$
$$x' = z,$$
$$z' = -z - \vartheta\,(e^{2/3x} - 1)$$

$$(e^{2/3\xi} - 1)\xi > 0 \Rightarrow V > 0,$$
$$V \to \infty, \|z, x\| \to \infty$$

Global asymptotic stability

The effect of therapy:

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

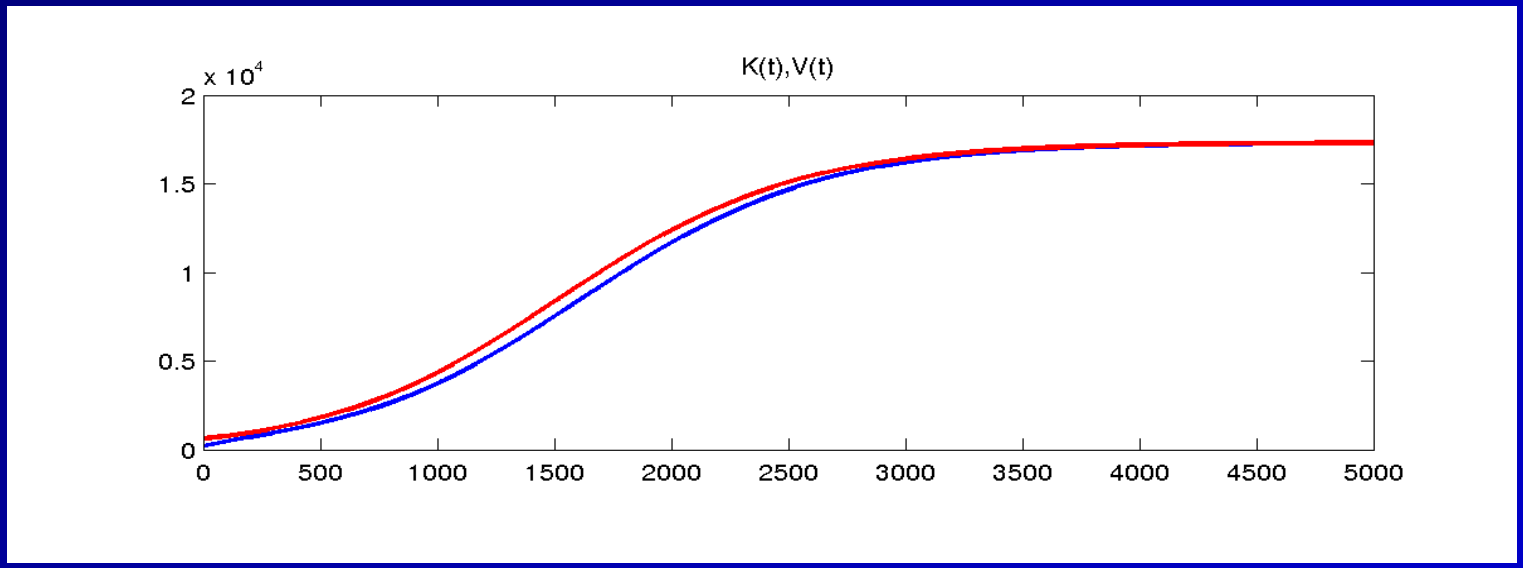
Constant dose: *u(t)=U=const.*

$$N^* = K^* = ((\gamma - \mu - \eta U) / \lambda)^{3/2}$$

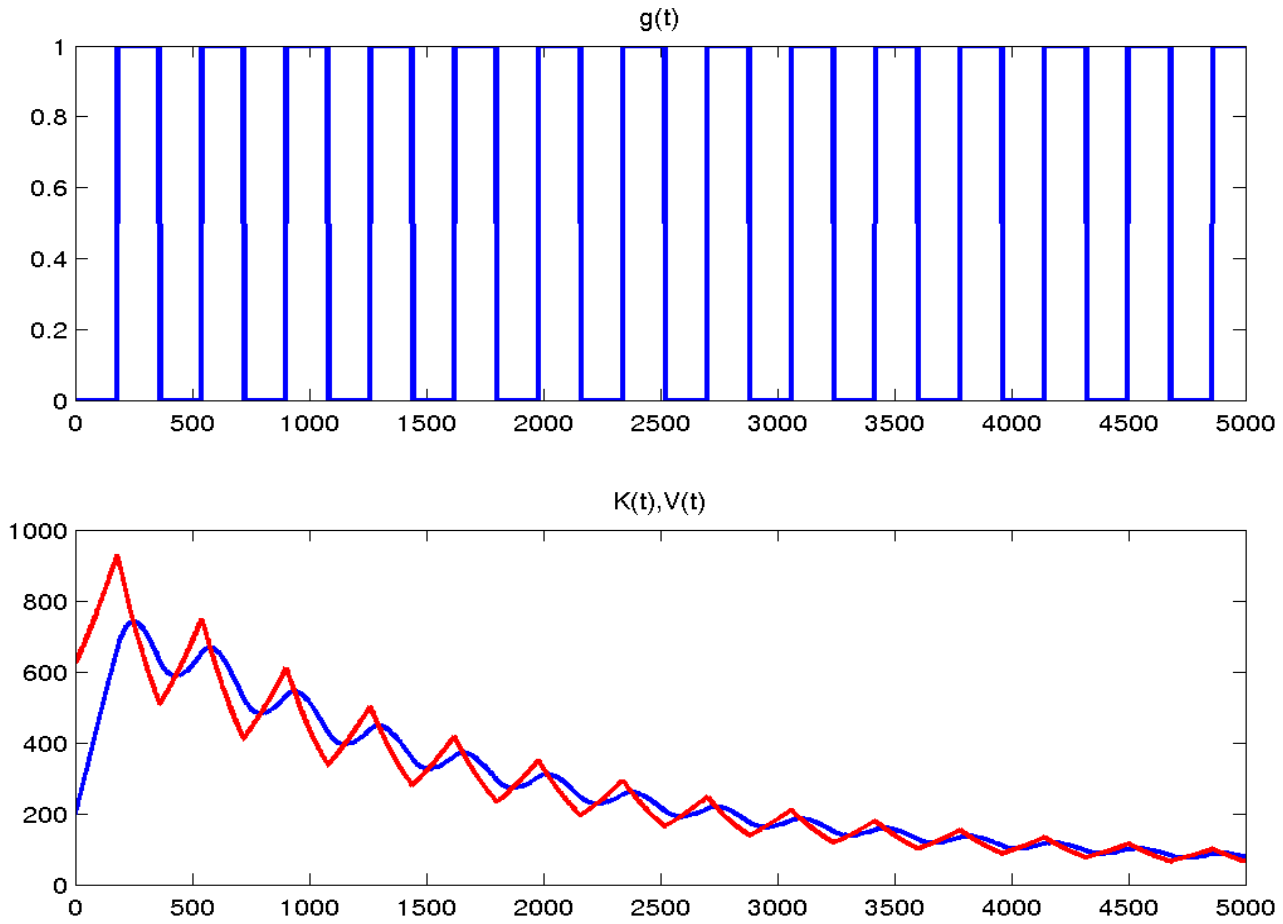
$$\eta U \approx \gamma - \mu \Rightarrow K^* \to 0$$

Similarly for periodic u(t) with average U

Simulation for the model without therapy



With periodic therapy



Optimization of therapy

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

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

$$TCP = \exp(-f\theta N(T_k)) \rightarrow \max$$

$$\min_{u} \leftarrow J = N(T_k); \int_0^{T_k} u(t)dt \leq \Xi$$

$$0 \leq u \leq U_m$$

Modified optimization problem

$$I = gx(T_f) + hy(T_f) + r\int_0^{T_f} u(\tau)d\tau$$

$$0 \le u \le 1, T_f = T_k\beta$$

$$x' = y - x,$$

$$y' = \vartheta(1 - e^{2/3x}) - \nu u$$

$$\nu = \eta / \vartheta$$

$$H = ru - \nu qu + p(y - x) + q\vartheta(1 - e^{2/3x})$$

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

$$q' = -p, q(T_f) = h$$

Switching function

$$q = r / v > 0$$

$$u = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min \quad H$$

Bang-bang control, no singular arcs

$$q'' - q' + 2/3 q \vartheta e^{2/3x} = 0,$$

$$q(T_f) = h, q'(T_f) = -g$$

Let's return to original Hahnfeldt model:

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

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

Equilibrium points the same and stability analysis similar with the same log transmormation.

Define: $Z = \ln KN^{\theta}, \theta = \gamma / \beta$

We have:

$$\dot{N} / N = \beta(1 - N^{\theta+1} / e^{Z})$$

$$\dot{Z} = \gamma - \lambda N^{2/3} - \mu - \eta u$$

By introducing performance index:

$$I = gN(T_k) + r\int_0^{T_k} u(\tau)d\tau$$

$$0 \le u \le 1$$

Necessary conditions are:

$$H = ru - \eta qu + p(\beta N(1 - N^{\theta+1} / e^{Z})) + q(\gamma - \mu - \lambda N^{2/3})$$

$$\dot{p} = -\beta p(1 - e^{-Z}(\theta + 2)N^{\theta+1}) + (2/3)q\lambda N^{-1/3}$$

$$\dot{q} = -\beta p N^{\theta+2} e^{-Z}$$

$$p(T_k) = g,$$

$$q(T_k) = 0$$

$$q = r / \eta > 0$$

$$u = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H$$

Switching function

Bang-bang control, no singular arcs

Combined antiangiogenic and chemo-therapy

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

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

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

$$N^* = ((\gamma - \mu - \eta U - \xi V) / \lambda)^{3/2}$$

$$K^* = N^* e^{\xi V / \beta}$$

$$\eta U + \xi V = \gamma - \mu \Rightarrow K^* \to 0, N^* \to 0$$

Optimization of combined therapy

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

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

$$TCP = \exp(-f\theta N(T_k)) \rightarrow \max$$

$$\min_{u,v} \leftarrow J = N(T_k); \int_0^{T_k} u(t)dt \le \Xi; \int_0^{T_k} v(t)dt \le \Omega$$

$$0 \le u \le U_m, 0 \le v \le V_m$$

Modified optimization problem

$$x' = y - x - \varepsilon v,$$
$$y' = \vartheta(1 - e^{2/3x}) + \sigma u + \zeta v$$

$$I = gx(T_f) + hy(T_f) + r\int_0^{T_f} u(\tau)d\tau + s\int_0^{T_f} v(\tau)d\tau$$
$$0 \le u \le 1, T_f = T_k\beta$$

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

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

Switching conditions

$$q = -r/\sigma$$

$$u = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H$$

$$p = s/\varepsilon + q\zeta/\varepsilon$$

$$v = \begin{cases} 1 \\ 0 \end{cases} \Leftarrow \min H$$

$$q'' - q' + 2/3q\vartheta e^{2/3x} = 0,\ p = -q'$$

$$q(T_f) = h, q'(T_f) = -g = -p(T_f)$$

Singular control

No singular arcs for u
cause q = const
Is not a solution

Singular solution
is not optimal, for v
Clebsch-Legendre
condition:

$$\frac{\partial}{\partial u}\frac{d^2}{dt^2} f_s = \frac{4}{9} q\varepsilon^2 \beta\vartheta e^{\frac{2}{3}x} > 0$$

is not satisfied

More realistic model

$$\dot{S} = -aS + (1 - v)(2 - q)aS + rcR$$

$$\dot{R} = -cR + (2 - r)cR(1-R/K) + (1 - v)\, qS.$$

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

Conclusion

- Modelling cell cycle may be useful for understanding and combating cancer
- Compartmental models may be used in analysis and synthesis of phase specific protocols of anticancer therapy
- Compartmental modelling may be also applied to overcome drug resistance
- It is possible to decrease and even eridicate the modelled tumor for constant and periodic therapies by controling vascular network formated in the angiogenesis
- Model optimization leads to necessary conditions in the form of bang-bang control
- Control theory provides very attractive tools also in other problems of modern oncology e.g class prediction and pattern discovery basing on microarray data, modelling and identification of regulatory pathways etc.

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