# A model for transfer phenomena in biological populations

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December 11, 2008

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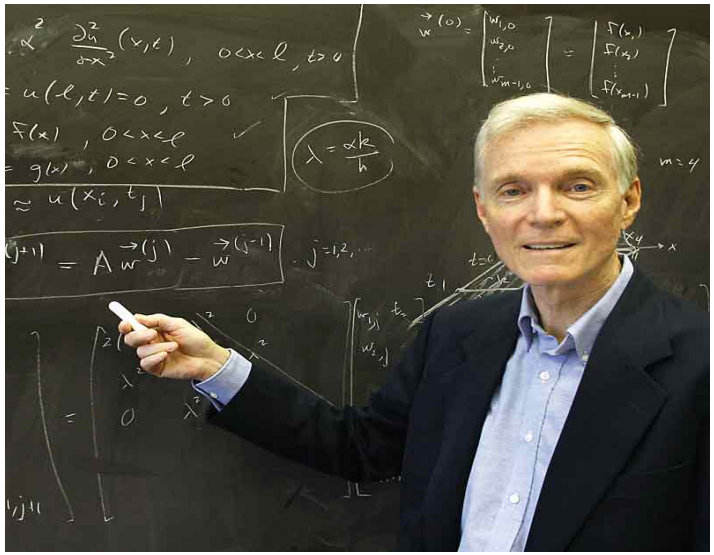


Glenn Webb, Vanderbilt University

# Overview of the talk

- introduction to the biological background
  - cancer disease and its treatment
  - multidrug resistance (MDR) and the role of P-gp
  - intercellular transfer of transmembrane proteins
- formulation of the mathematical models and analytical results
  - the simple transfer model (only transfer between individuals is considered)
  - the model with production of P-gp, cell division and cell death
- numerical simulations
- outlook, conclusion

# Cancer and its treatment

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Treatment options consist of

- surgery
- radiotherapy
- cytotoxic (cell-killing) chemotherapy
- newer strategies: immune therapy, oncolytic viruses ...
- combinations of these

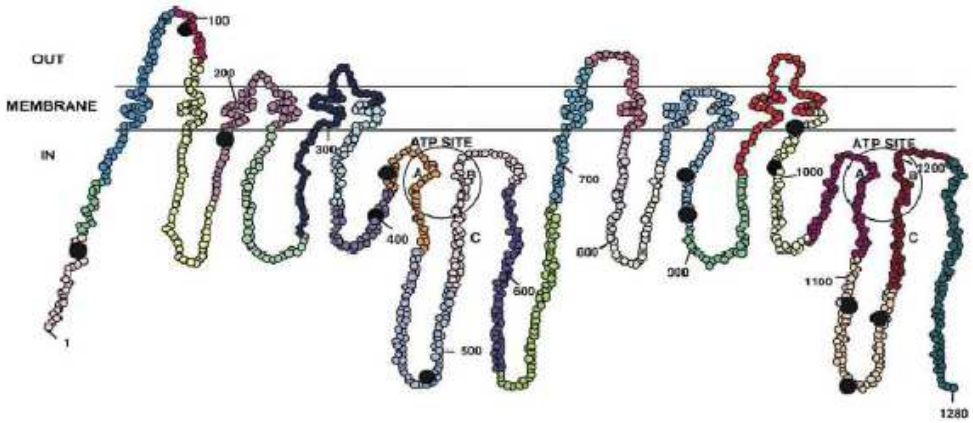
Chemotherapy is the treatment of choice for $\approx 50\%$ of all cancers. In particular, cancers of the blood (such as leukemia) and metastatic tumors require chemotherapy.

# Chemotherapy and resistance to it

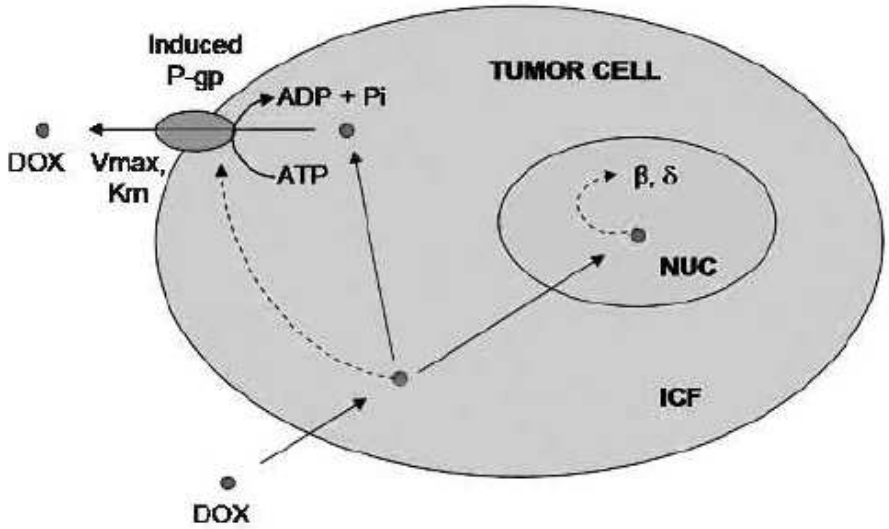
Cytotoxic drugs (such as cisplatin, taxol, doxorubucin) kill rapidly dividing cells, cancer cells just as healthy dividing cells.

However, the appearance of multidrug resistance (MDR) minimizes the effectiveness of such therapy in a large number of patients. Here, resistance applies to not just one, but a wide panel of cytotoxic drugs. One mechanism responsible for multidrug resistance is an increased efflux of drug from the cell.

# The role of P-glycoprotein (P-gp)




Ambudkar *et al.*, Oncogene **22**, 2003

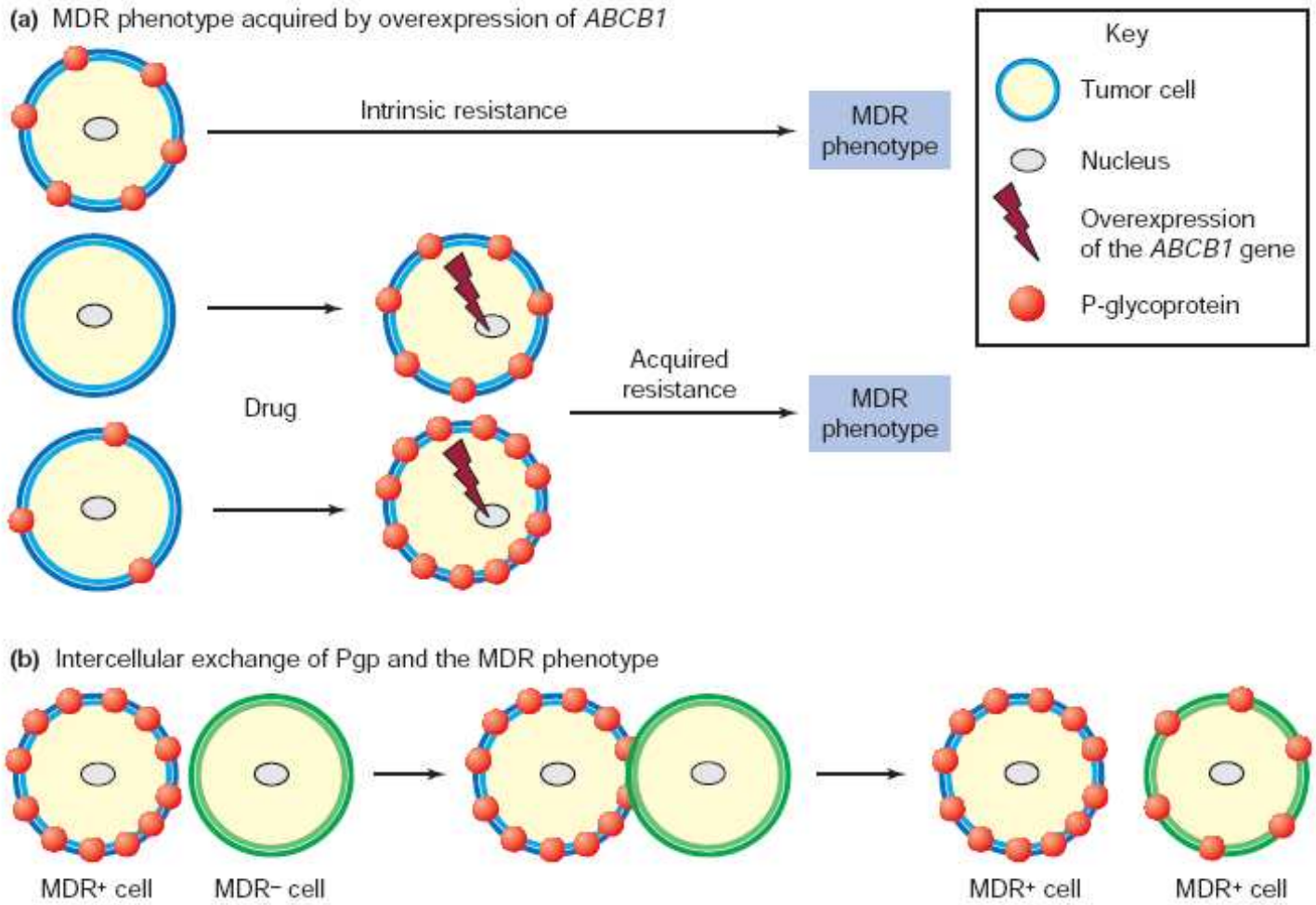



Luu & Uchizono, Pharmaceutical Research **22**, 2005

# The role of P-glycoprotein (P-gp)

- P-gp (also known as ABCB1) is an ATP-dependent pump located in the cell membrane that is able to remove a wide panel of cytotoxic substances such as from the cytoplasm of a cell.
- P-gp requires chemical energy in the form of ATP and hence can pump the cytotoxic substances against a gradient.
- Thus anticancer drugs cannot accumulate to sufficiently high levels and the cell is protected from death.
- The expression of P-gp has been documented in breast cancers, sarcomas, neuroblastomas, leukemias and others and is generally associated with a poor prognosis.

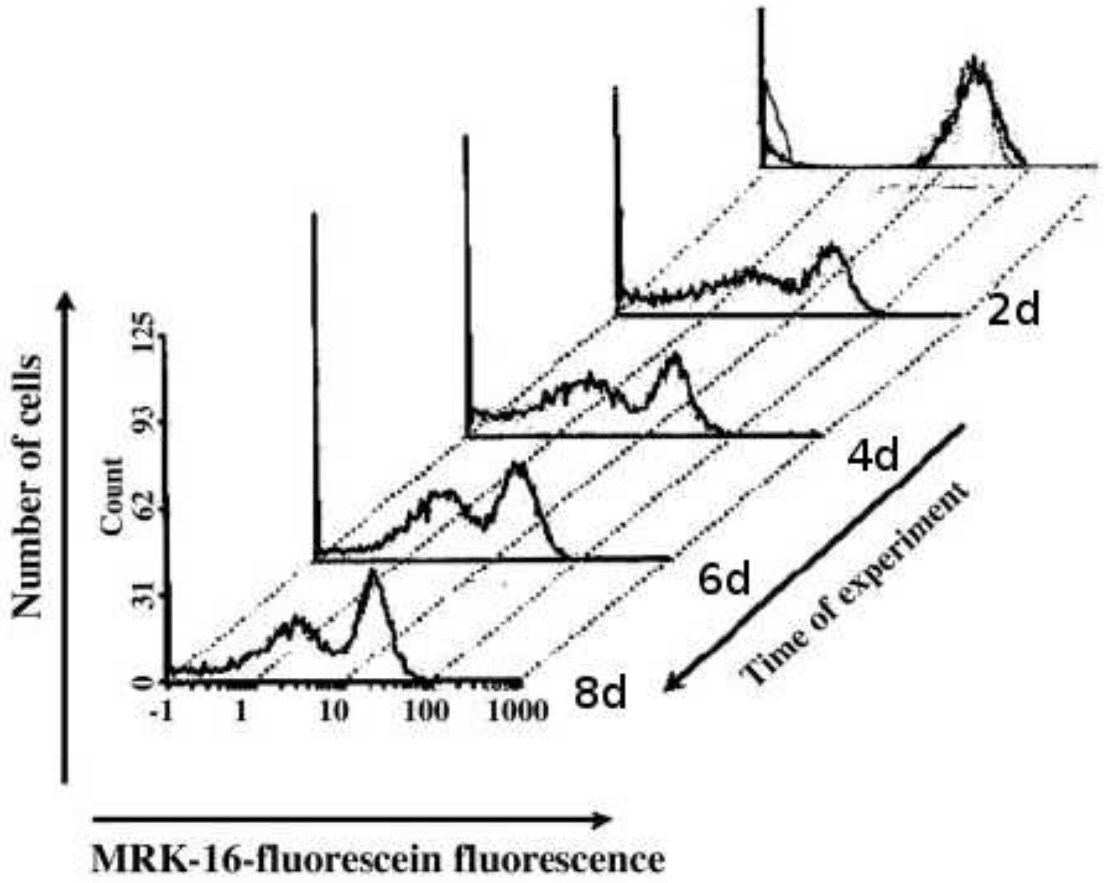
# The pathways to multidrug resistance (MDR)




Ambudkar *et al.*, Trends in Pharmacological Sciences **26**, 2005

# Intercellular transfer of P-gp

Levchenko *et al.* cocultured sensitive and resistant cancer cells and used fluorescent antibodies to measure the level of P-gp expression




Levchenko *et al.*, Proc. Nat. Acad. Sci. USA **102**, 2005

# Summary

Cancer cells can have the multidrug resistant (MDR) phenotype by

1. being intrinsically resistant
2. expression of P-gp under exposure to cytotoxic drug
3. through transfer from P-gp rich resistant cells (shown both *in vitro* and *in vivo*).

We will introduce a model for processes 3 and 2 & 3.

# The model

Let $p \in [0,1]$ denote the scalar quantity and let $u(p,t)$ denote the population density of individuals having quantity $p$ at time $t$. We work in the space $L^1[0,1]$ with positive cone $L^1_+[0,1]$. Define

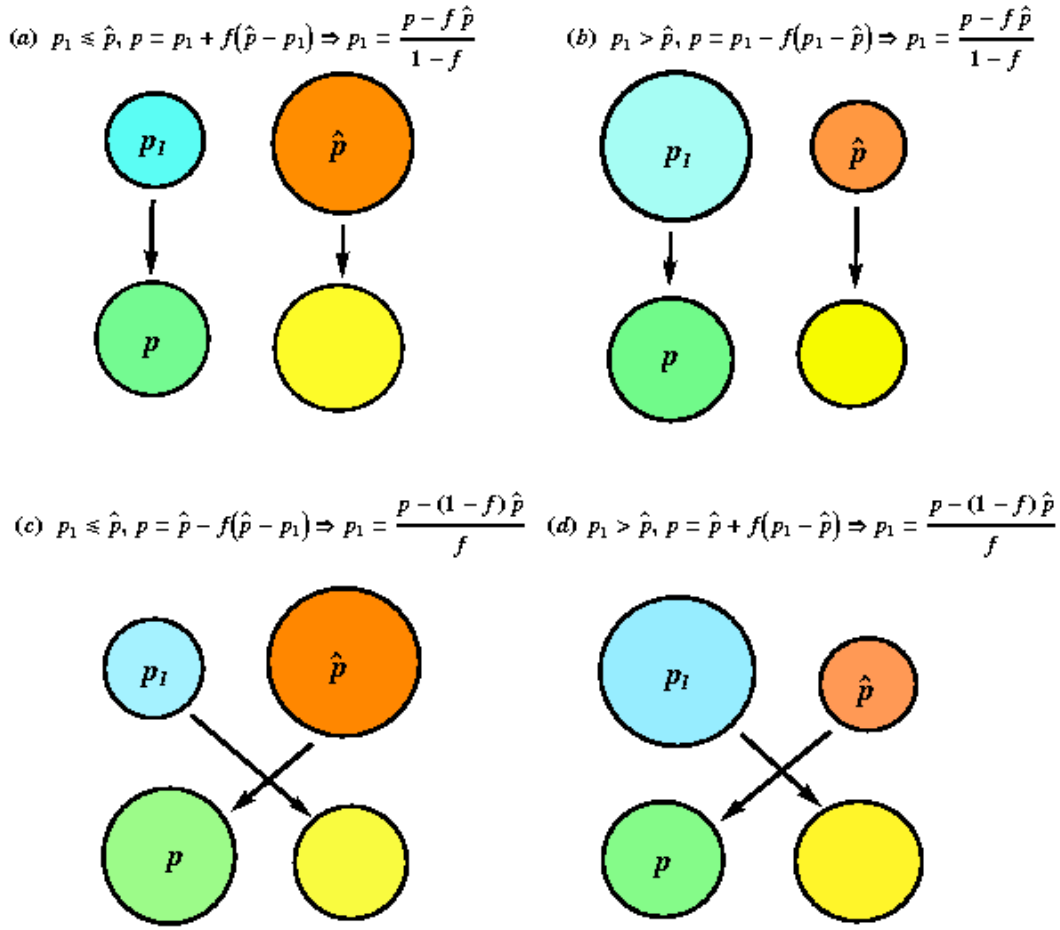
$$E_n(u) = \int_0^1 p^n u(p)\,\mathrm{d}p$$

for the $n$-th moment. $E_0(u) = ||u||$ is the total number of individuals and $E_1(u)$ is the total amount of the quantity $p$ in all individuals.

# The transfer process

1. The probability that a pair of two individuals is involved in a transfer event is independent of their $p$ values and the pairing is chosen randomly from all individuals.
2. The time between two transfer events follows an exponential law with mean $\tau^{-1} > 0$ (alternatively, $\tau$ is the rate of transfer per unit time).
3. Let $f \in L^{\infty}[0,1]$ with $0 \leq f \leq 1$. If 2 individuals whose difference in quantity is $\hat{p}$ are involved in a transfer, then the one with higher value loses $f(|\hat{p}|)$ times the difference of their $p$ values and the one with lower $p$ value gains exactly this amount.

# The transfer process




The four possibilities of transfer to a cell with value $p$ after a transfer event.

# The transfer process

Let two individuals have values $p_1$ and $p_2$ before the transfer and $\bar{p}_1$ and $\bar{p}_2$ afterwards. Then by assumption 3 we obtain

$$p_1 \mapsto \bar{p}_1 = p_1 + f(|\hat{p}|)(p_2 - p_1)$$

and

$$p_2 \mapsto \bar{p}_2 = p_2 - f(|\hat{p}|)(p_2 - p_1)$$

where $\hat{p} = p_1 - p_2$. Thus,

$$p_1 = \bar{p}_1 + f(|\hat{p}|)\hat{p} \text{ and } p_2 = \bar{p}_1 - (1 - f(|\hat{p}|))\hat{p}.$$

# The transfer operator

For any function $\phi$ defined on $[0,1]$ we denote by $\bar{\phi}$ its trivial extension by zero outside $[0,1]$. The transfer operator $T : L^1_+[0,1] \to L^1_+[0,1]$ is given by $T(0) = 0$ and for $u \neq 0$ by

$$T(u)(p) = \frac{1}{||u||_1} \int_{-\infty}^{\infty} \bar{u}(p + \bar{f}(|\hat{p}|)\hat{p})\bar{u}(p - (1 - \bar{f}(|\hat{p}|))\hat{p})\,\mathrm{d}\hat{p}.$$

# The transfer equation

A particle of size $p$ is lost when it is either the donor or the acceptor in a transfer.

$$\begin{aligned} \frac{du}{dt} &= 2\tau \left( T(u(t)) - u(t) \right), \\ u(0) &= u_0 \in L^1_+ (0,1). \end{aligned} \tag{1}$$

The transfer rate $\tau$ must be multiplied by 2 as transfer involves two individuals (a particle that emerges with quantity $p$ may have been the smaller or larger partner in the transfer event).

Notice the formal similarity to an equation of Boltzmann type.

# Basic properties of the transfer operator

**Theorem**

*The operator $T$ maps $L^1_+[0,1]$ into itself and has the following properties:*

1. *$T$ is positively homogeneous, $T(cu) = cT(u)$ for all $c > 0$,*
2. *$T$ is globally Lipschitz continuous,*
3. *We have for $u \in L^1_+[0,1]$ and $n = 0, 1$*

$$E_n(T(u)) = E_n(u),$$

*Proof.* By calculation. □

# Basic properties of the transfer model

**Theorem**

*For each initial datum* $u_0 \in L^1_+[0,1]$, *equation* (1) *has a global positive solution. Moreover, for all* $t > 0$ *and* $n = 0, 1$

$$E_n(u(t)) = E_n(u_0).$$

# Basic properties of the transfer model

*Proof.* This is a standard result for an ordinary differential equation $y' = F(y)$ in a Banach space with gobally Lipschitz continuous $F$. The solution has the representation

$$u(t) = e^{-2\tau t} u_0 + 2\tau \int_0^t e^{-2\tau(t-s)} T(u(s)) \, \mathrm{d}s,$$

and the positivity of $u$ follows. The conservation of the zeroth and first moment follows from the corresponding property of the transfer operator. □

# Convergence of the solution

Let $u(t)$ be the solution of equation (1) with initial value $u_0 \in L^1_+[0,1] \setminus \{0\}$.

**Theorem**

*There exists a Radon measure $w$ on $[0,1]$ such that*

$$\lim_{t\to\infty} \langle u(t), \phi \rangle = \langle w, \phi \rangle$$

*for every $\phi \in C[0,1]$.*

$\langle \cdot, \cdot \rangle$ denotes the pairing of $C[0,1]$ with its dual space

$$\langle w, \phi \rangle = \int_0^1 \phi(p)\, w(\mathrm{d}p).$$

# Convergence of the moments

*Proof.* We show first that the moments $E_n(u(t))$, $n \geq 1$ are decreasing along a trajectory and since they are all $\geq 0$, their limits $E_n^\infty(u_0)$ as $t \to \infty$ exist. Then we define for a polynomial

$$\varrho(x) = \sum_{n=0}^{m} a_n x^n$$

a linear functional $w$ by

$$\langle w, \varrho \rangle = \sum_{n=0}^{m} a_n E_n^\infty.$$

# Convergence of the moments

By the Weierstrass approximation theorem, the space of polynomials $\mathcal{P}[0,1]$ is dense in the space of continuous functions $C[0,1]$ and so $w$ extends uniquely to an element of the dual space $C[0,1]'$.

By the Riesz representation theorem the linear functional $w$ can be identified with a Radon measure supported on $[0,1]$. $\square$

# Can we do better?

Unfortunately not...

**Theorem**

*If the transfer fraction $f$ is constant, i.e. $f(|p|) = f$, then for each $u_0 \in L^1_+[0,1] \setminus \{0\}$, the solution of the transfer model (1) converges to a Dirac measure in the weak$^*$ topology. More precisely let $m = \frac{E_1(u_0)}{E_0(u_0)}$ be the mean of the initial datum, then*

$$u(t) \overset{*}{\rightharpoonup} E_0(u_0)\delta_m$$

*as $t \to \infty$.*

# Convergence towards a Dirac measure

*Proof.* Assume without loss of generality that $E_0(u_0) = 1$. We have the following system of ordinary differential equations for the moments $x_n(t) = E_n(u(t))$

$$\frac{dx_n(t)}{dt} = \sum_{k=0}^{n} \binom{n}{k} f^k (1-f)^{n-k} x_k(t) x_{n-k}(t) - x_n(t),$$
$$x_n(0) = E_n(u_0).$$

From this, one can show that

$$\lim_{t \to \infty} x_n(t) = x_1(0)^n.$$

# Convergence towards a Dirac measure

This implies that for every polynomial $\varrho \in \mathcal{P}[0,1]$

$$\lim_{t\to\infty} \langle u(t), \varrho \rangle = \delta_{E_1(u_0)}(\varrho).$$

Again this result extends to every $\phi \in C[0,1]$ by the Weierstrass approximation theorem. □

# The model with expression of P-gp and proliferation

We add to our model

- production or loss of P-gp by the cells, at a rate $h$ depending on $p$
- random fluctuations in the P-gp content of a cell (a diffusion term)
- proliferation and death of cells, depending on their P-gp content.

The proliferation of cells saturates as a certain carrying capacity is reached (logistic growth).

# The full model

$$\frac{\partial u}{\partial t} \underbrace{-D^2\frac{\partial^2 u}{\partial p^2} + \frac{\partial}{\partial p}(h(p)u)}_{\textit{fluctuations and production}} = \underbrace{(c(p) - \mathcal{L}(u))u}_{\textit{birth and death}} + \underbrace{2\tau(T(u) - u)}_{\textit{transfer}},$$

$$\begin{aligned} D^2\frac{\partial u}{\partial p} &= h(p)u(p,t), \quad p = 0,\ 1, \\ u(p,0) &= u_0(p), \end{aligned} \tag{2}$$

where $h \in C^1[0,1]$ is the convection field, $c \in L^\infty[0,1]$ the combined proliferation and death rate and $\mathcal{L} : L^1[0,1] \to \mathbb{R}$ a positive linear functional that models effects of crowding (for example $\mathcal{L}(u) = \gamma||u||_1$).

### Definition

A *one-parameter strongly continuous semigroup* $(S(t))_{t\geq 0}$ on the Banach space $X$ is a family of linear bounded operators such that

- $S(0) = I$,
- $S(t+s) = S(t)S(s)$, and
- for every $x \in X$, $\lim_{t\to 0+} S(t)x = x$.

The *infinitesimal generator* $A$ of the semigroup $S(t)$ is the linear operator defined by

$$Ax := \lim_{t\to 0+} \frac{S(h)x - x}{h}$$

whose domain $D(A)$ is the set of $x \in X$ for which the limit exists.

# Global existence result

**Theorem**

*For every* $u_0 \in L^1_+[0,1]$, *equation* (2) *has a unique global solution in* $L^1_+[0,1]$.

*Proof.* The operator $Au = D^2u'' - (hu)'$ is the infinitesimal generator of a positive, compact and analytic semigroup $\{S_A(t)\}_{t\geq 0}$ on $L^1[0,1]$ (H. Amann, Israel J. Math. **45**, 1983).

The operator $B = A + c$ is a bounded perturbation of $A$ and is the infinitesimal generator of a positive, compact semigroup $\{S_B(t)\}_{t\geq 0}$. (A. Pazy, *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Springer, 1983).

# Global existence result

The operator $B$ (diffusion, transport and growth) has a simple eigenvalue $\lambda_0(B) \in \mathbb{R}$.

The existence of a solution to the nonlinear problem follows from the theory for Lipschitz perturbations of linear problems. $\square$

# Global asymptotic stability

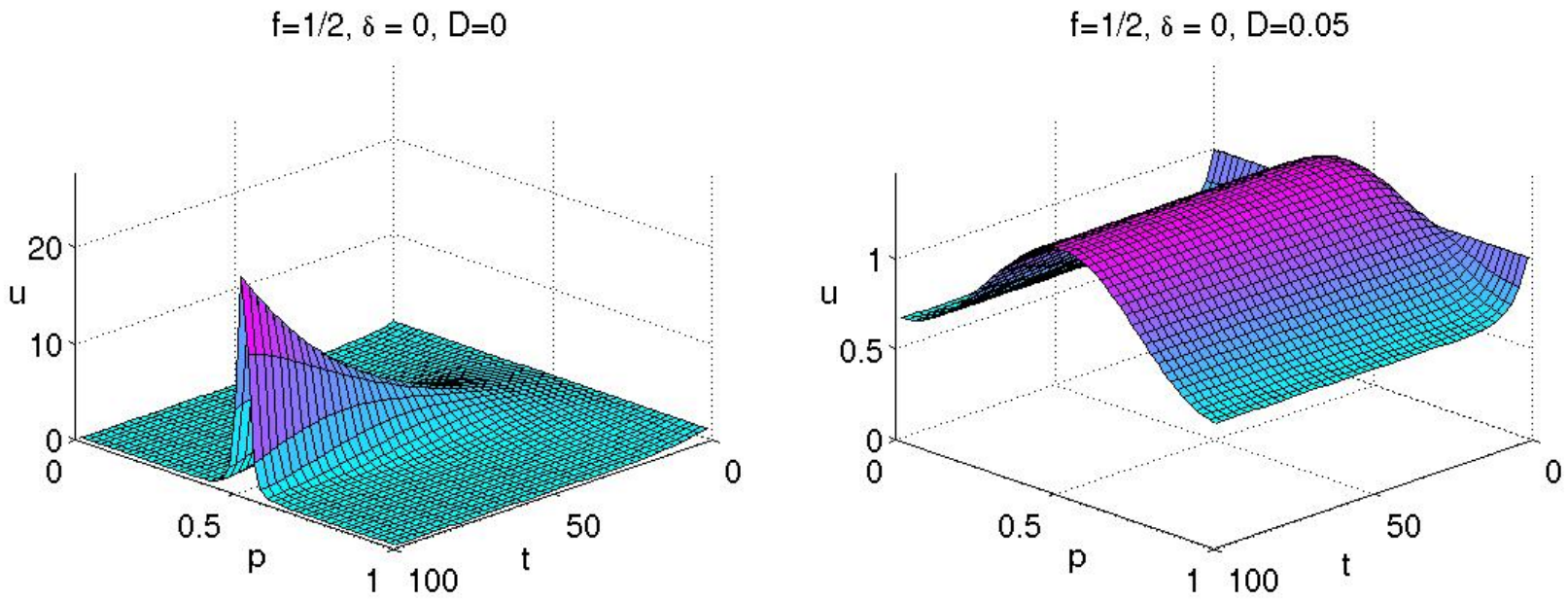
**Theorem**

*Provided that* $\lambda_0(B) > 0$, *there exists* $\tau^* > 0$ *such that for every* $\tau \in [0, \tau^*]$, *equation* (2) *has a unique globally asymptotically stable steady state* $u_\tau \in L^1_+[0,1]$.

*Proof.*

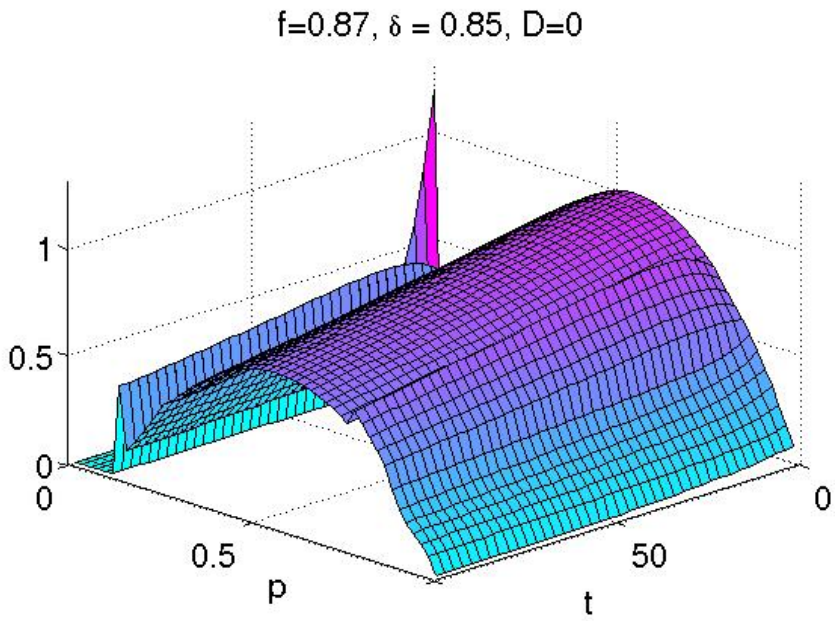
This was proved by Magal and Webb (Discr. Contin. Dyn. Sys. **6**, 2000), and Magal (Discr. Contin. Dyn. Sys. B **2**, 2002). □

# Numerical simulations




The numerical solution of the full model (2) with $f \equiv \frac{1}{2}$, $h \equiv 0$ and $D = 0$ (left) respectively $D = 0.05$ (right). The solution remains bounded when diffusion is present.

# Numerical simulations

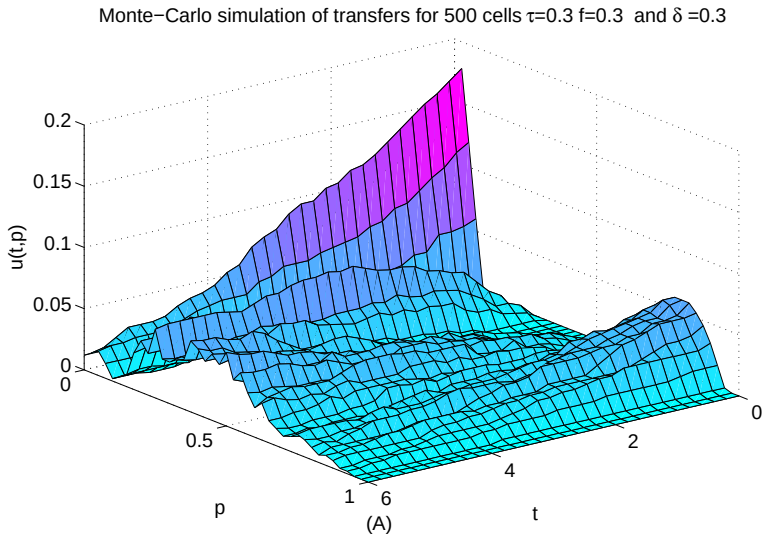


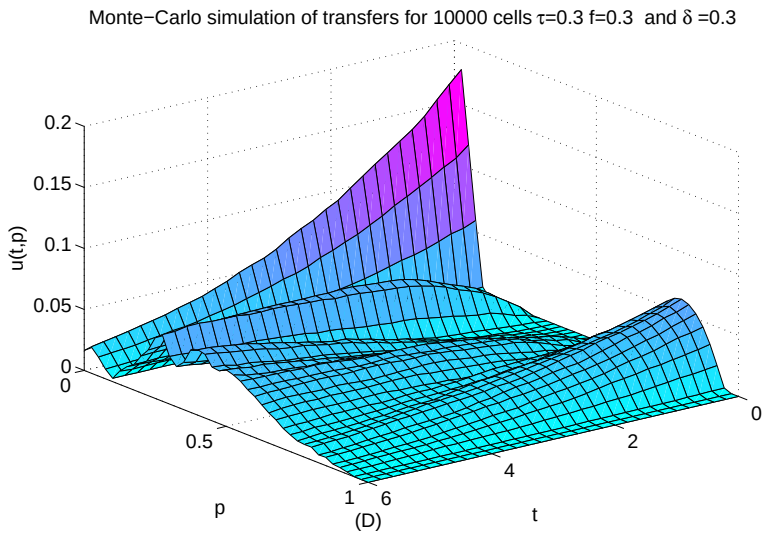

The numerical solution of the pure transport equation (1) with

$$f(|p|) = \begin{cases} f & \text{if } |p| \geq \delta, \\ 0 & \text{otherwise} \end{cases}$$

using $\delta = 0.85$ and $f = 0.87$.

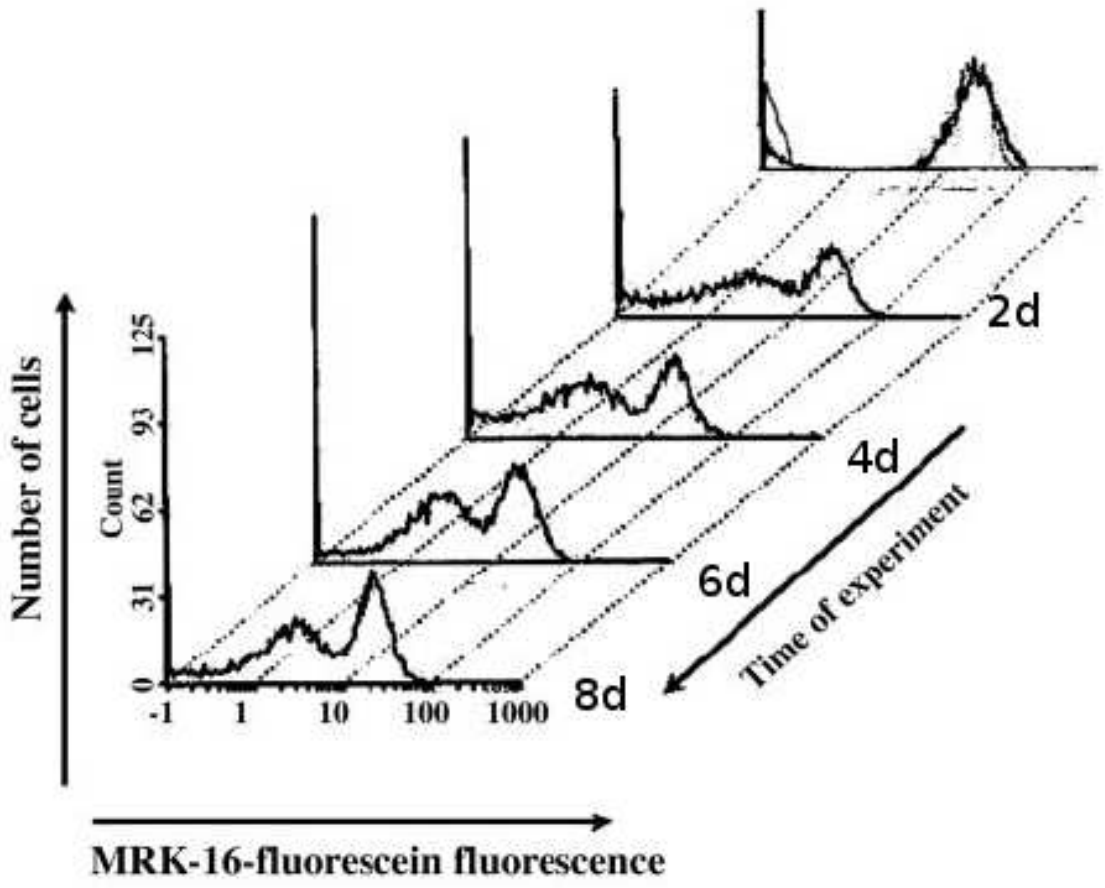
# Numerical simulations




The Monte Carlo simulations of the pure transport process with 500 respectively 10000 individual cells.

# Recall. . .




Levchenko *et al.*, Proc. Nat. Acad. Sci. USA **102**, 2005

# Transfer limited to nontrivial differences

Consider again the pure transfer model (1) (without production and diffusion) and assume there exists a $\delta > 0$ such that $f|_{[0,\delta]} = 0$ (i.e. transfer takes place only if the difference in quantity exceeds a certain threshold). Highly concentrated populations are steady states of (1).

## Lemma

*Let $u \in L^1[0,1]$ with diam supp $u \leq \delta$. Then $u$ is a steady state of the pure transfer model (1).*

# Transfer limited to nontrivial differences

Based on our numerical experiments, we state the following

## Conjecture

*Let $u(t)$ be a solution of equation (1) with $u(0) \in L^\infty[0,1]$. Then there exists a function $u_\infty \in L^\infty[0,1]$ with $E_0(u_\infty) = E_0(u_0)$, $E_1(u_\infty) = E_1(u_0)$ and diam supp $u_\infty \leq \delta$ such that (in $L^1_+[0,1]$)*

$$\lim_{t\to\infty} u(t) = u_\infty.$$

# Outlook

Topics of future research

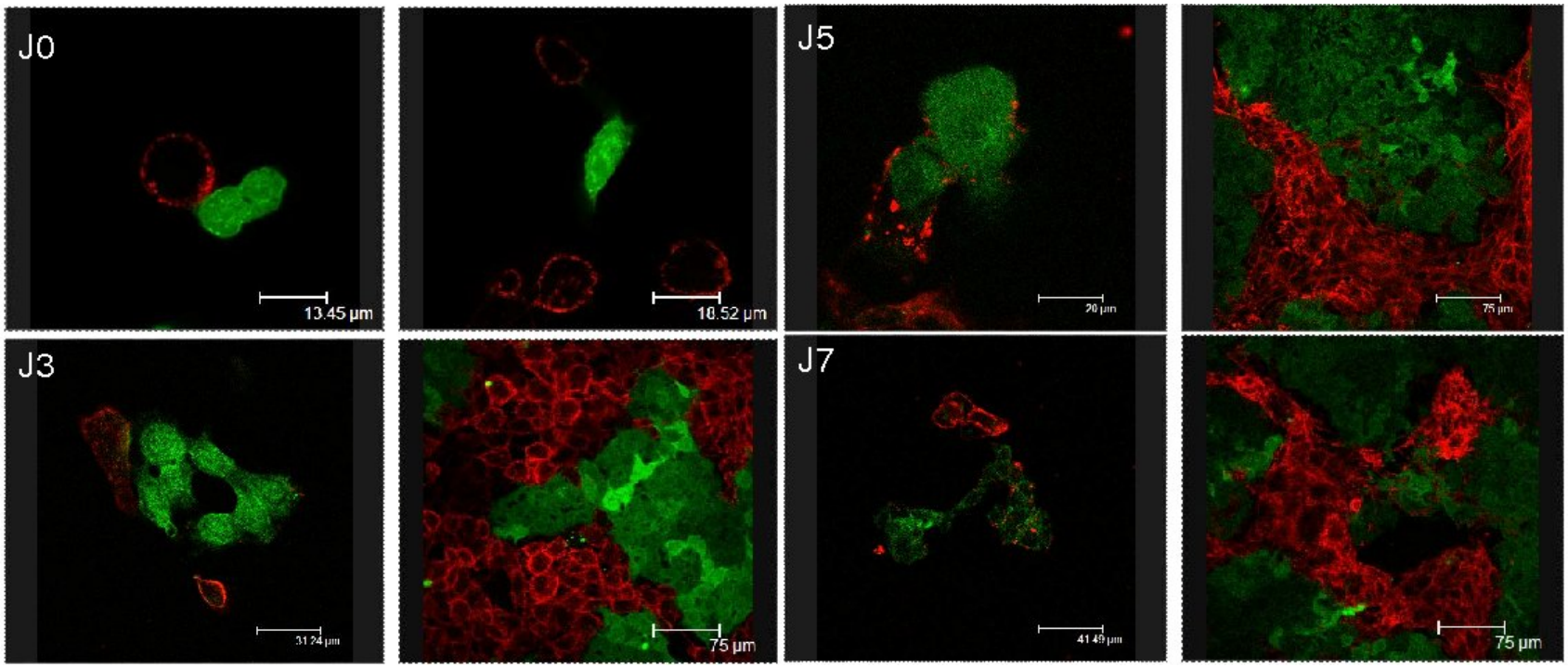
- How important is P-gp transfer for the development of multidrug resistance *in vivo*?
- Does the resistant population have a slower growth rate than the sensitive population (indicated by Levchenko *et al.*) and could this be exploited?
- P-gp may not remove all kinds of cytotoxic drugs with the same efficiency. There is room for better scheduling of combination chemotherapy protocols.

# Outlook

Topics of future research (continued)

- A spatial component will be introduced such that the transfer efficiency decreases with the distances between cells.
- The model has to be complemented with experimental work and parameters have to be determined.

# Outlook




green: sensitive cells, red: P-gp on the surface of resistant cells; increase in red staining in the membrane of green cells (J="jour")

Jennifer Pasquier and Frank Le Foll, University of Le Havre, France

# Outlook

More examples for transfer processes

- inelastic interacting particles exchanging kinetic energy (Ben Naim et al., Aranson & Tsimring)
- economically or socially interacting populations exchanging assets or opinions (compromise processes)
- bacteria transferring genetic material (Novozhilov et al., Webb & Blaser)

# Acknowledgments


- the IMA
- Vanderbilt Integrative Cancer Biology Center
- CIRM Luminy, Marseille, France
- Dr. Marta Lewicka (School of Mathematics, University of Minnesota)

Thank you for your attention

P. Hinow, P. Magal, G. F. Webb and F. Le Foll. A model for transfer phenomena in biological populations. *SIAM J. Appl. Math., to appear* (2008)