

# A model for transfer phenomena in structured populations

*Peter Hinow*<sup>1</sup>, *Pierre Magal*<sup>2</sup>, *Glenn F. Webb*<sup>3</sup>

<sup>1</sup>Institute for Mathematics and its Applications, University of Minnesota, Minneapolis, MN 55455, USA; <sup>2</sup>Department of Mathematics, University of Le Havre, France; <sup>3</sup>Department of Mathematics, Vanderbilt University, Nashville, TN 37240, USA

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# Overview of the talk

- ▶ introduction to the biological background
  - ▶ multidrug resistance, the role of P-gp
  - ▶ intercellular transfer of transmembrane proteins
- ▶ formulation of the mathematical models and analytical results
  - ▶ the simple transfer model
  - ▶ production of P-gp and cell division
- ▶ numerical simulations
- ▶ outlook, conclusion

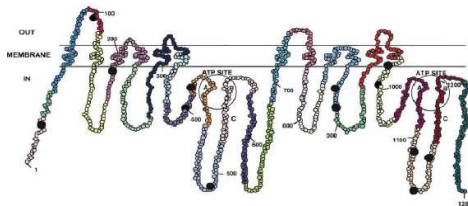
# Cancer treatment options

- ▶ surgery
- ▶ radiotherapy
- ▶ cytotoxic chemotherapy
- ▶ newer strategies: immune therapy, oncolytic viruses ...
- ▶ combinations of these

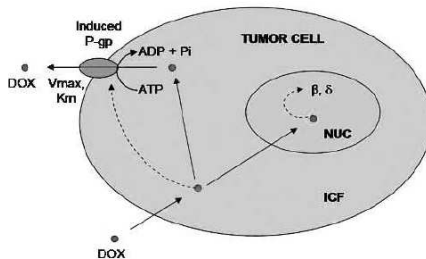
Chemotherapy is the treatment of choice for  $\approx 50\%$  of all cancers (in particular cancers of the blood and metastatic tumors).

However, the appearance of multidrug resistance (MDR) minimizes the effectiveness of such therapy in a large number of patients.

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



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

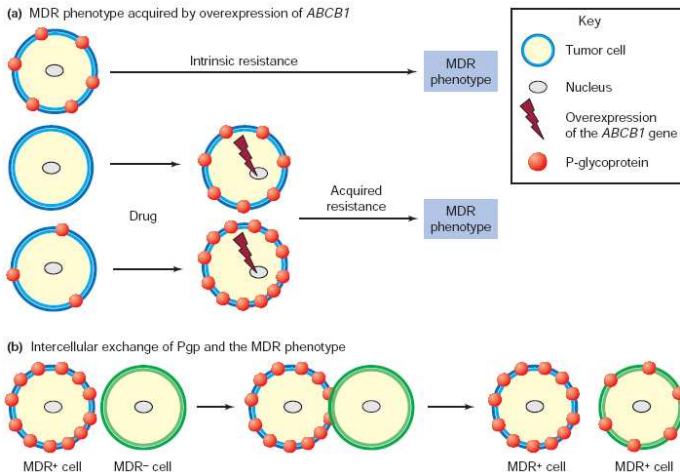


Luu & Uchizono, *Pharmaceutical Research* **22**, 2005

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

- ▶ P-gp is an ATP-dependent pump that is able to remove many cytotoxic substances such as doxorubicin, daunorubicin, vinblastin, vincristin, etoposide and others from the cytoplasm of a cell.
- ▶ 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.

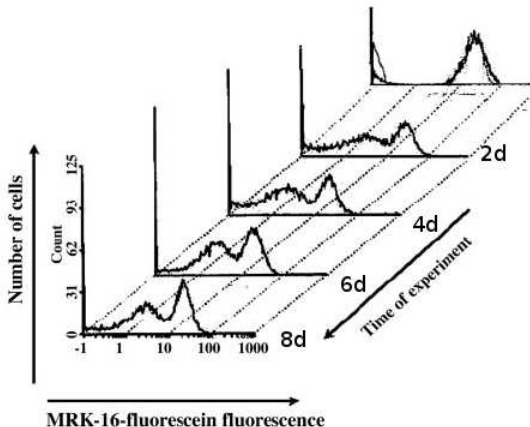
# The pathways to multidrug resistance (MDR)



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 a fluorescent antibody to measure the level of P-gp expression



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

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

$$E_n(u) = \int_0^1 p^n u(p) \, dp$$

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

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  $T : L_+^1(0, 1) \rightarrow L_+^1(0, 1)$  is given by  $T(0) = 0$  and for  $u \neq 0$  by

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

# The transfer equation

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

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

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.

## Theorem

The operator  $T$  maps  $L_+^1(0, 1)$  into itself and has the following properties:

1.  $T$  is positive 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  $n = 0, 1$

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

# 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 globally Lipschitz continuous  $F$ . The solution has the representation

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

and the positivity of  $u$  follows. □

# 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*

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

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

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

# Convergence of the moments

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

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

a linear functional  $w$  by

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

and extend this to a linear functional  $w \in C[0, 1]'$  by the Weierstrass approximation theorem. □

# Can we do better?

## Theorem

*If the transfer fraction  $f$  is constant, 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*

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

*as  $t \rightarrow \infty$ .*

# 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

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

# Convergence towards a Dirac measure

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

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

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
- ▶ a random fluctuations in the P-gp content of a cell (i.e. a diffusion term)
- ▶ proliferation and/or death of cells, which may depend on their P-gp content.

$$\begin{aligned}\frac{\partial u}{\partial t} - D^2 \frac{\partial^2 u}{\partial p^2} + \frac{\partial}{\partial p}(h(p)u) &= (c(p) - \mathcal{L}(u))u + 2\tau(T(u) - u), \\ D^2 \frac{\partial u}{\partial p} &= h(p)u(p, t), \quad p = 0, 1, \\ u(p, 0) &= u_0(p),\end{aligned}\tag{2}$$

where  $h \in W^{1,\infty}(0, 1)$  is the convection field,  $c \in L^\infty(0, 1)$  the combined proliferation and death rate and  $\mathcal{L} : L^1(0, 1) \rightarrow \mathbb{R}$  a positive linear functional that models effects of crowding.

## Theorem

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

*Proof (sketch).* The operator  $Au = D^2u'' - (hu)'$  is the generator of a strongly continuous positive semigroup  $\{T(t)\}_{t \geq 0}$  on  $L^1(0, 1)$ . The existence of a solution follows from standard theory for Lipschitz perturbations of linear problems (A. Pazy, *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Springer, 1983).  $\square$

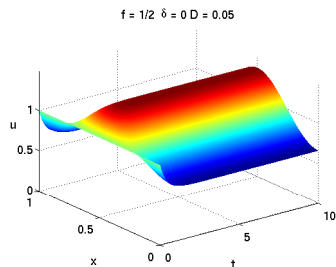
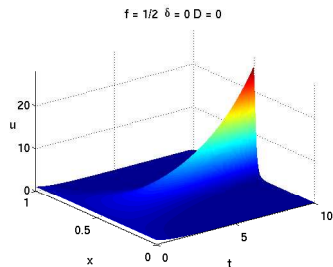
## Theorem

For every  $\tau \approx 0$ , equation (2) has a unique globally asymptotically stable steady state  $u_\tau^* \in L_+^1(0, 1)$ .

*Proof (sketch).* The existence can be shown by a computation in case  $\tau = 0$  (no transfer). For  $\tau$  sufficiently small, one can apply a perturbation theorem by Smith and Waltman (Proc. Amer. Math. Soc. **127**, 1999).

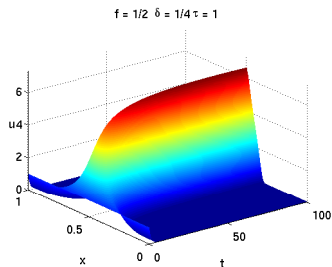
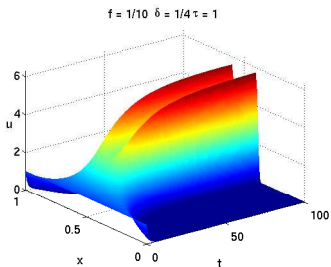
This was proved for a similar model by Magal and Webb (Discr. Contin. Dyn. Sys. **6**, 2000). □

# 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).

# Numerical simulations

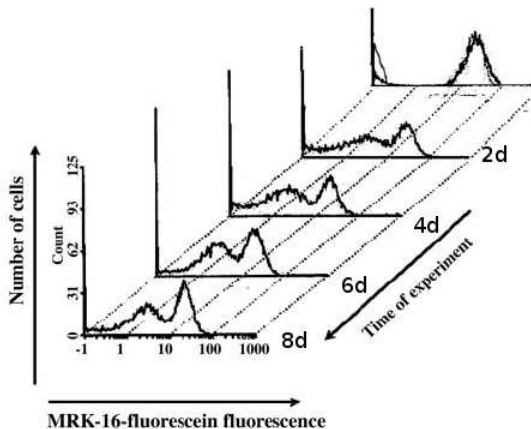


The numerical solution of the pure transport equation (1) with

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

using  $\delta = \frac{1}{4}$  and  $f = \frac{1}{10}$  (left) respectively  $f = \frac{1}{2}$  (right).

# Recall...



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

# Transfer limited to “nonvanishing” differences

Consider again the pure transfer model (1) 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).

## 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  $\text{diam supp } u_\infty \leq \delta$  such that (in  $L^1_+(0, 1)$ )

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

## Topics of future research

- ▶ How important is P-gp transfer for the development of multidrug resistance *in vivo*?
- ▶ Do the sensitive and resistant populations have different growth rates (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.
- ▶ A spatial component will be introduced (transfer takes place only between cells in close proximity).
- ▶ The model has to be complemented with experimental work (Frank Le Foll, University of Le Havre, France).

## More examples for transfer processes

- ▶ inelastic interacting particles exchanging kinetic energy
- ▶ economically interacting populations exchanging assets
- ▶ bacteria transferring genetic material

# Acknowledgments

- ▶ the IMA
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Thank you for your attention