The contribution of age structure to cell population responses to targeted therapeutics

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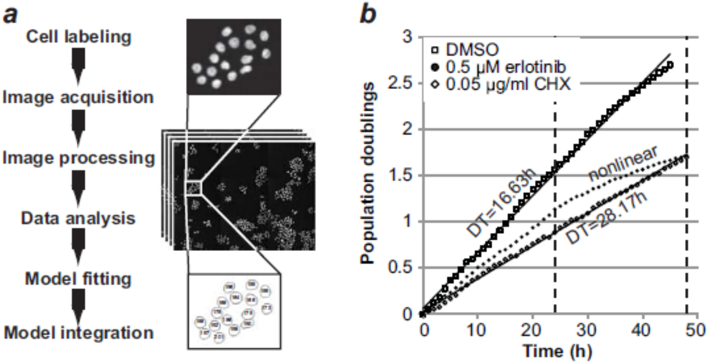
En collaboration avec S. Garbett, D. Tyson and G. Webb (Vanderbilt University)

Séminaire LBBE, Lyon, 31 janvier 2012

ETRAM methodology



D. R. Tyson, S. P. Garbett, P. L. Frick, V. Quaranta

Dynamics vs. end-point assays

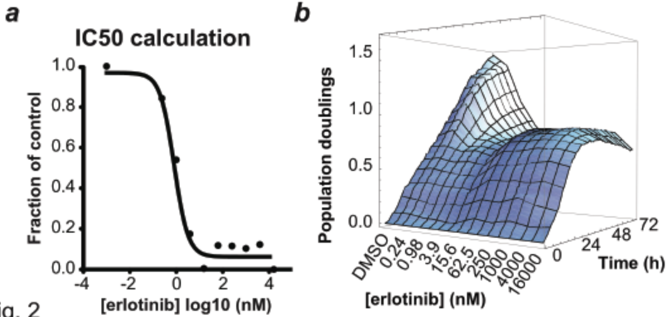
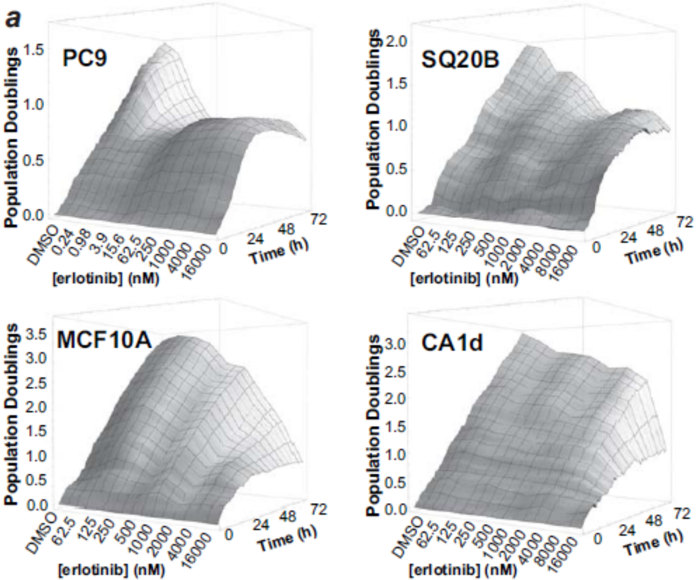


Fig. 2

Different cancer cell lines



ODE model with quiescence

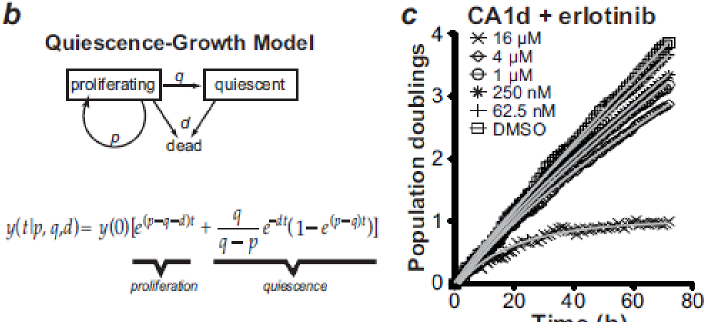


Fig. 3

Estimation of the fraction of quiescent cells

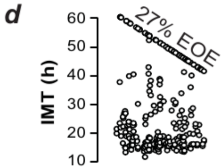
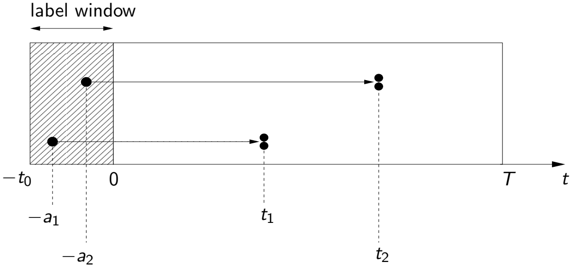


Fig. 4



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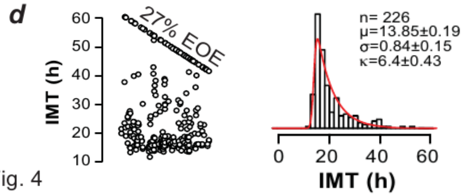
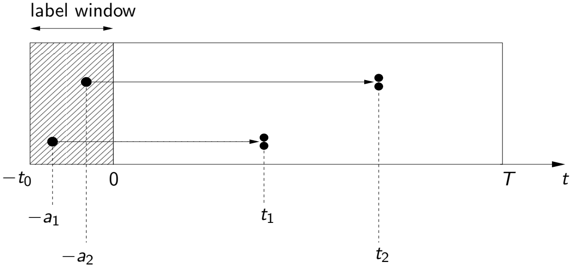


Fig. 4

Cells at EOE that are expected to remain nondivided in future based on EMG distribution:

26% quiescent



Exponentially Modified Gaussian

$$
\begin{aligned}
EMG(x|\lambda,\mu,\sigma) &= \left(\frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(x-\mu)^2}{2\sigma^2}}\right) * \left(\lambda e^{-\lambda x}\right) \\
&= \frac{\lambda}{2}\, Erfc\left(\frac{\mu + \lambda\sigma^2 - x}{\sqrt{2}\sigma}\right)\, e^{\frac{\lambda}{2}(2\mu+\lambda\sigma^2-2x)}
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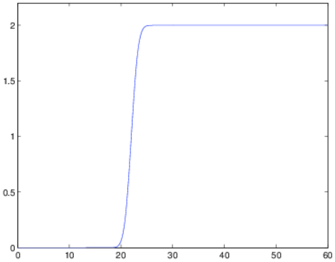

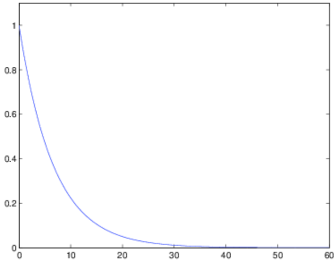

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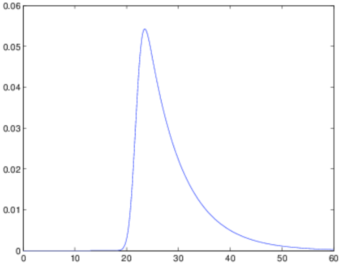
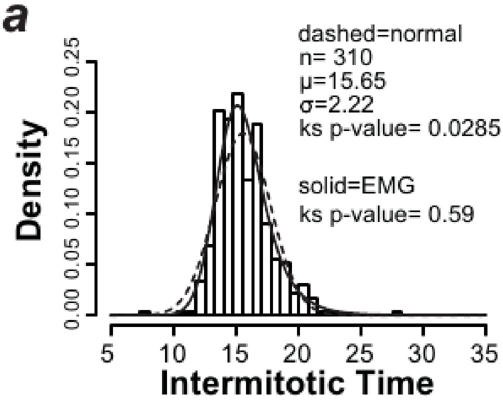


Intermitotic time fitting



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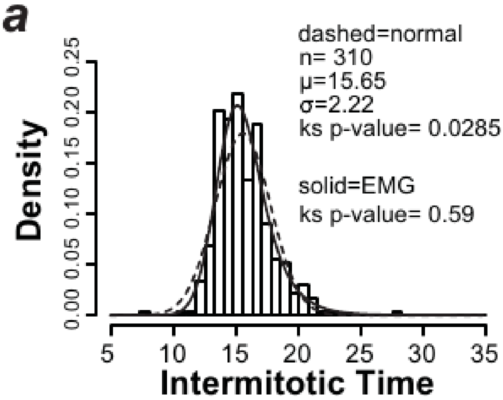

A. Golubev, Exponentially modified Gaussian (EMG) relevance to distributions related to cell proliferation and differentiation, *J. Th. Biol.*

Treatment on PC9 cancer cell

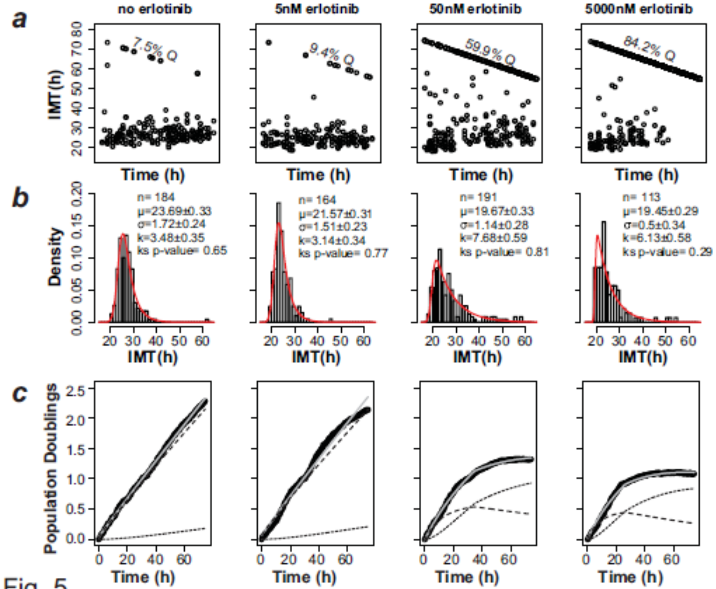

Fig. 5

An age-structured model

We consider the renewal equation with quiescence:

$$\begin{cases} \dfrac{\partial}{\partial t} p(t,a) + \dfrac{\partial}{\partial a} p(t,a) + \beta(a) p(t,a) + \gamma(a)\, p(t,a) + \mu\, p(t,a) = 0, \\ p(t,0) = 2 \displaystyle\int_0^\infty \beta(a) p(t,a)\, da, \\ \dfrac{d}{dt} Q(t) = \displaystyle\int_0^\infty \gamma(a) p(t,a)\, da - \mu Q(t), \end{cases}$$

$p(t,a)$: number of proliferating cells with age $a \geqslant 0$ at time $t \geqslant 0$,

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There exist a positive function $\hat{p}(a)$ and a positive constant λ which depend only on $\beta(a)$, and a constant $C = C(\beta, p_0)$ such that

$$p(t,a) \sim C\,\hat{p}(a)e^{\lambda t}$$

as $t \to \infty$.

The eigenvalue problem

Consider the eigenvalue problem

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There exists a unique solution given by

$$\hat{p}(a) = \hat{p}(0)e^{-\int_0^a(\beta(a')+\lambda)\,da'}$$

where $\lambda > 0$ is the unique solution to the implicit equation

$$1 = 2\int_0^\infty \beta(a)e^{-\int_0^a(\beta(a')+\lambda)\,da'}da,$$

and $\hat{p}(0)$ is chosen to have $\int \hat{p}(a)\,da = 1$.

The intermitotic time distribution

The age-structure of the labelled cells at time $t = 0$ is given by

$$\bar{p}_0(a) = p_0(a)\, \mathbb{1}_{0 \leqslant a \leqslant t_0}.$$

Then we follow this age-distribution along time and obtain for $t > 0$

$$\bar{p}(t,a) = p(t,a)\, \mathbb{1}_{t \leqslant a \leqslant t+t_0}.$$

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According to the age-structured model, the intermitotic time distribution writes

$$I_T(a) := C_T^{-1} \int_0^T \beta(a)\bar{p}(t,a)\, dt$$

where

$$C_T = \int_0^\infty \int_0^T \beta(a)\bar{p}(t,a)\, dt\, dt.$$

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More precisely we prove the convergence

$$\int_0^\infty \left| I_T(a) - I_\infty(a) \right| da \xrightarrow[T \to +\infty]{} 0.$$

Inversion formula

We can recover the division rate from the IMT distribution

$$\beta(a) = \frac{I_\infty(a)}{\int_a^\infty I_\infty(a')\,da'},$$

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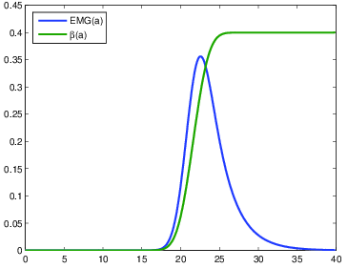
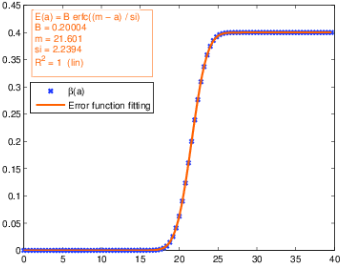
We can recover the division rate from the IMT distribution

$$\beta(a) = \frac{I_\infty(a)}{\int_a^\infty I_\infty(a')\,da'},$$

and the EMG fitting leads numerically to an error-like function:





A first fitting model

Assuming that β is indeed an error function

$$\beta(a) = \beta_0 Erfc\left(\frac{m-a}{\sigma}\right)$$

we obtain a three-parameters model

$$I_\infty(a|\beta_0, m, \sigma) = \beta_0 Erfc\left(\frac{m-a}{\sigma}\right) e^{-\int_0^a \beta_0 Erfc(\frac{m-a'}{\sigma}) da'},$$

which can be used to fit an experimental IMT histogram $(H_i)_{1 \leqslant i \leqslant n}$.

Notice that the integral $\int_0^a \beta_0 Erfc(\frac{m-a'}{\sigma}) da'$ can be explicitely computed in terms of basic functions.

Incorporate the exponential growth rate

When we know experimentaly the value of the exponential growth rate λ, a very important point for applications is to recover a division rate β such that the relation

$$2\int_0^{\infty} \beta(a) e^{-\int_0^a (\beta(a')+\lambda) da'} da = 1$$

is satisfied.

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is satisfied. We remark that this relation writes

$$2\int_0^\infty I_\infty(a) e^{-\lambda a} da = 1$$

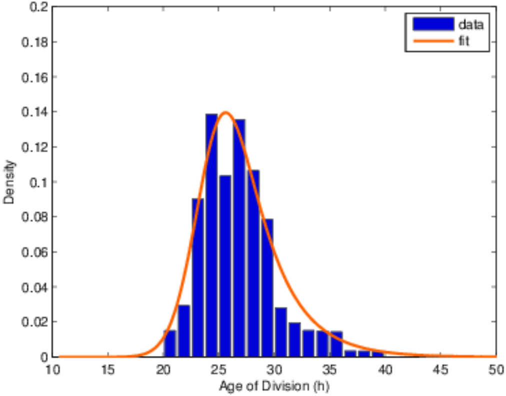
and we use it to improve the fitting method by fitting a modified histogram

$$\widetilde{H}_i = \frac{H_i e^{-\lambda a_i}}{\Delta a \sum_i H_i e^{-\lambda a_i}}$$

with the modified three-parameters model

$$\widetilde{I}_\infty(a) = 2 I_\infty(a) e^{-\lambda a}.$$

Numerical results



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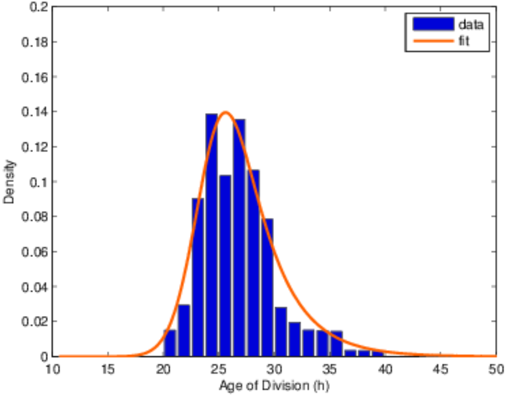

$$\beta(a) \approx 0.14\, Erfc\left(\frac{24.45 - a}{3.34}\right), \quad R^2 = 0.95$$

The fraction rate f

The fraction of quiescent cells among labelled cells

$$F := \frac{Q(0)}{Q(0) + \int_{-t_0}^{0} p(t,0)\,dt}$$

is measured experimentally. But we have with our model

$$Q(0) = \int_{-t_0}^{0} \frac{dQ}{dt}(t)\,dt = 2f \int_{-t_0}^{0} \int_{0}^{\infty} \beta(a)p(t,a)\,dadt$$

and

$$\int_{-t_0}^{0} p(t,0)\,dt = 2(1-f) \int_{-t_0}^{0} \int_{0}^{\infty} \beta(a)p(t,a)\,dadt.$$

Finally we obtain

$$F = \frac{2f}{2f + 2(1-f)} = f.$$

Numerical results