Modelling of Cancer Treatment

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in collaboration with

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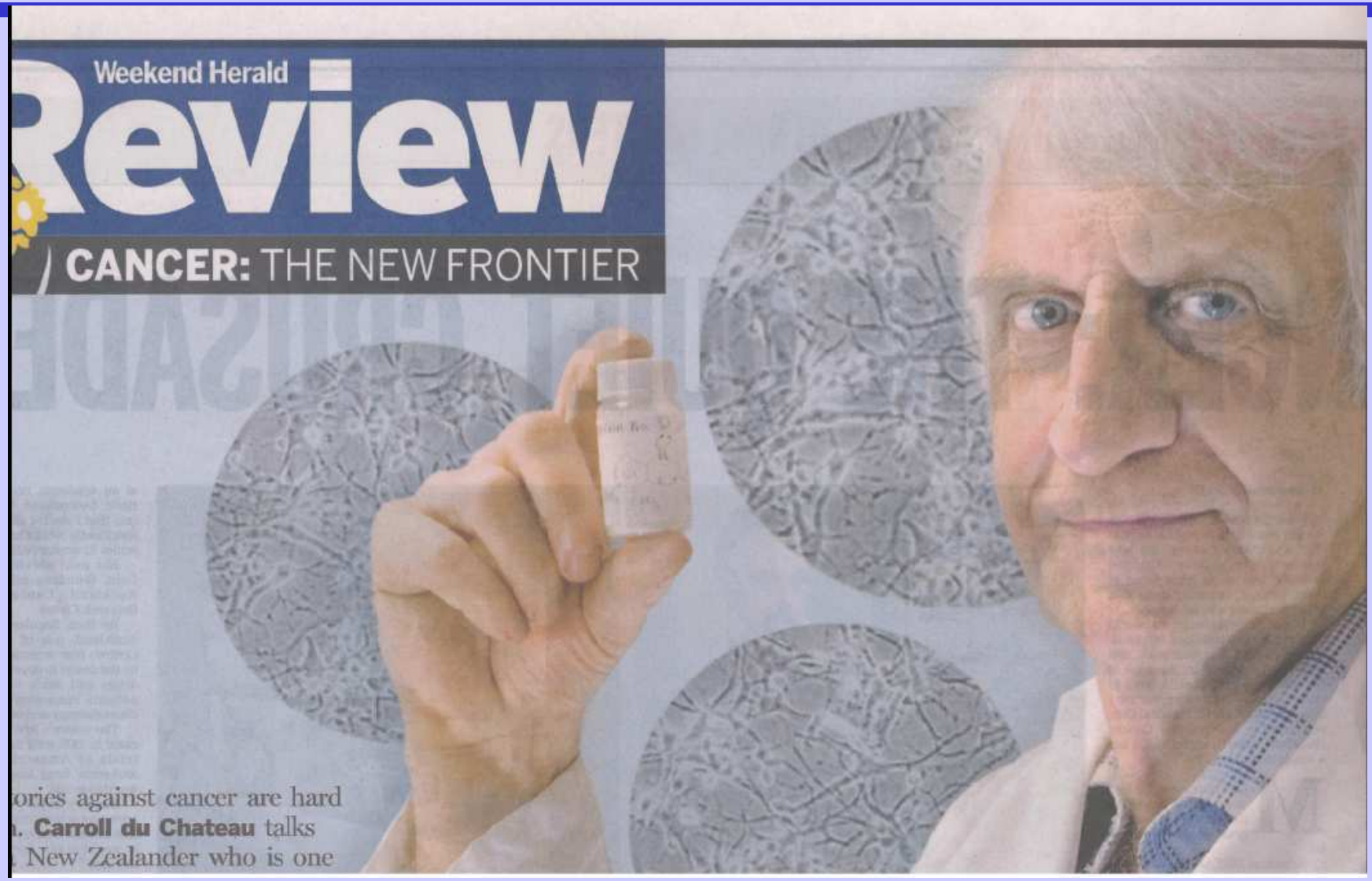
Seminar
June-July 2008

Bruce Baguley; Auckland Cancer Society Professor



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- What is non-local Calculus?

  Occurs when cause and effect are separated.

  * Earlier times affect the present.
  * Action at a distance.

- Test problems:

  $y`(t) = y(t\text{-}1), \quad y((-1,0]) =$ given.

  $y`(x) = \alpha y(\alpha x) - y(x), \quad y(0) = 0, \; y \neq 0.$

What is the solution?

Outline

1. History of the cell-growth model
2. The new mathematics!!!
3. Tumour cell growth
4. Further new maths
5. Modelling cancer treatment **** (main section)
6. Link to other approaches
7. Current work

1. History of the cell-growth model – personal.

1988+: Horticulturists ask me to "provide an understanding of time-series data" which showed that cell populations, structured by size, evolved by simultaneously growing, dividing and dying, evolved to a

"STEADY SIZE DISTRIBUTION"

SSD - first take-out.

This data was for plant-root cells, maize etc.

This result was robust, independent of the initial condition, and in dynamical systems terms, was attracting.

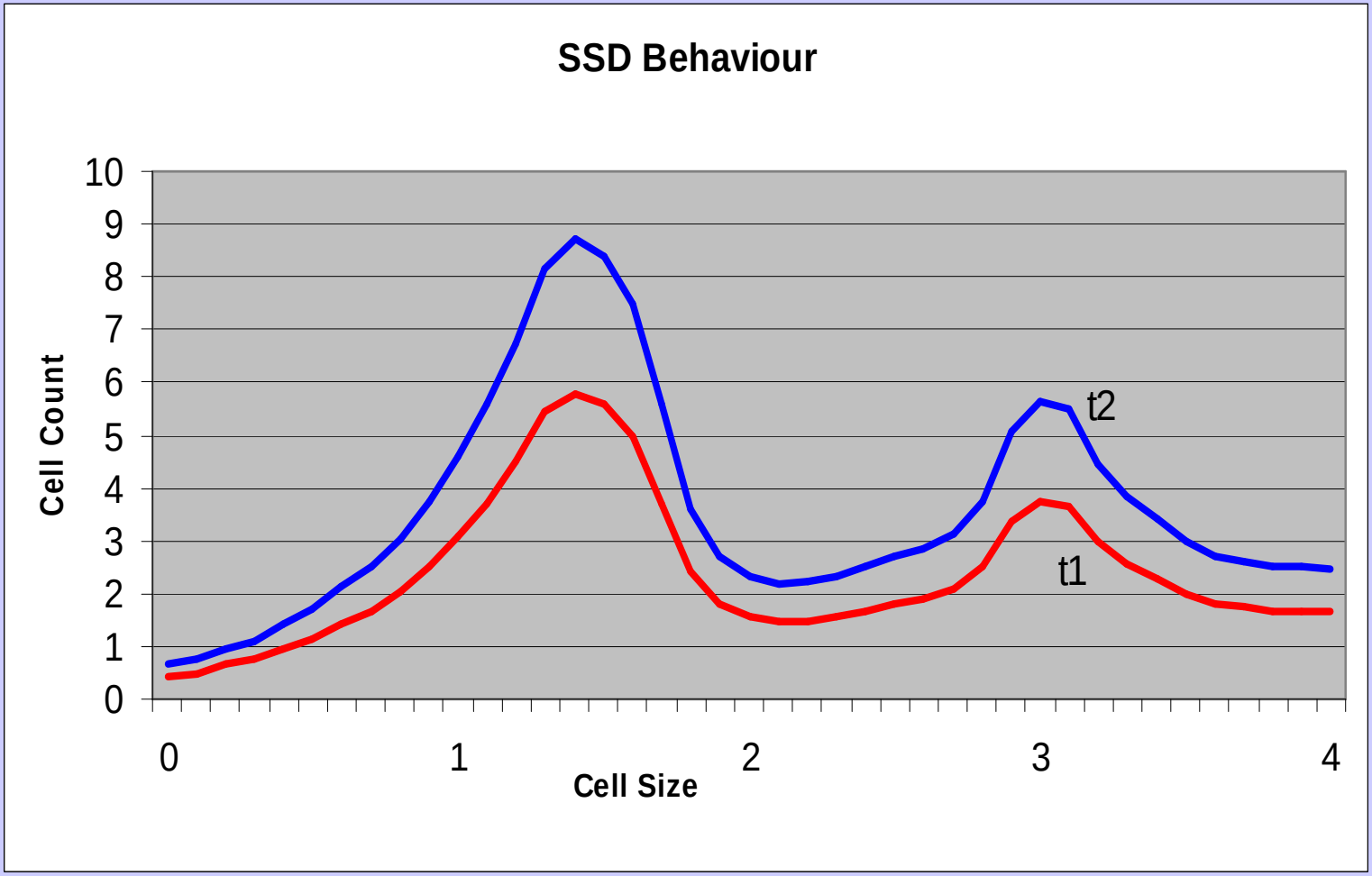
SSDs

- What is a SSD? Introduce $n(x,t)$, the number density of a cell population cohort structured by attributes (x) like:
  * size (say = DNA content) – this is us
  * age
  * time in a given phase….

    etc

Then $\int_a^b n(x,t)\,dx$ = # of cells (biomass) in size interval $[a,b]$, evolving in time.

SSD behaviour: $n(\cdot, t)$ evolves like:



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Core model

- This led to the first cell-growth model:

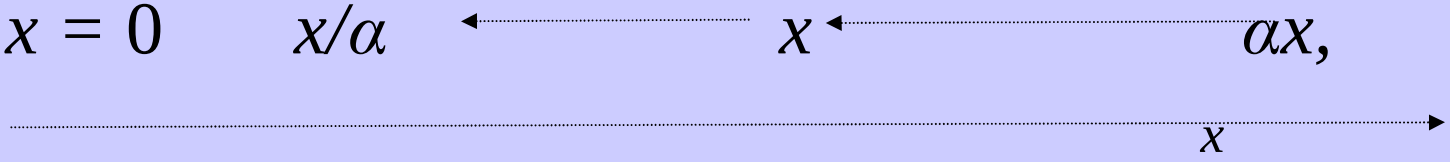
$$n_t = -(gn)_x + b\alpha^2 n(\alpha x,t) - bn - \mu n(x,t), \quad x,t>0,$$

$\alpha > 1$. *Why?*

growth — addition through division — loss through division — death

$n(0,t) = 0$, $n(\infty, t) = 0$, $n(x,0)$ given, $n(x,t) \geq 0$.

The terms are all local except "$n(\alpha x,t)$".



Key questions and answers

- The question then is:

  Are there solutions of the form

  $n(x,t) = N(t)\, y(x) = e^{-\lambda t}\, y(x)$? Q. sign of λ????

Yes there is:

1."A functional differential equation arising in modelling of cell growth". J Australian Math. Soc. Series B, Vol 30.424-435,1989 (A J Hall and G C Wake).

2. "Functional differential equations determining steady size distributions for populations of cells growing exponentially",J.Austr.Math.Ser;B, Vol 31,434-453,1990 (A J Hall and G C Wake).

3. "Steady size distributions for cells in one-dimensional plant tissues" Journal of Mathematical Biology. Vol 30. No 2. pp101-123. 1991 (A J Hall, G C Wake and P W Gandar).

We then added dispersion, see later…

4. “Functional differential equations for cell-growth models with dispersion” Comm. Appl. Anal. **4,** 2000, pp 561-574. (G C Wake, S Cooper, HK Kim, & B van-Brunt).

2. New Mathematics

- The SSD is $y(x)$, which in the no-dispersive case satisfies the interesting non-local equation:

$$y`(x) = a\alpha\, y(\alpha x) - a\, y(x),\ x > 0,$$

$$a = b\alpha/g,$$

$$y(0) = 0,\ y(x) \geq 0\ ,\ \int_0^\infty y(x)\, dx = 1.$$

We prove in Reference 1 that this is well-posed and find $y(x)$ Explicitly. How??

And the $\lambda = \mu - b(\alpha\text{-}1) \lessgtr 0$, in $n(x,t) = e^{-\lambda t}\, y(x)$.

< Therefore this is a healthy growing cohort.

> Therefore this is a decaying cohort

Generic equation

- This is akin to the “pantograph equation”
- Raised in the first MISG in Oxford in 1970
- Is generally ill-posed as an IVP:

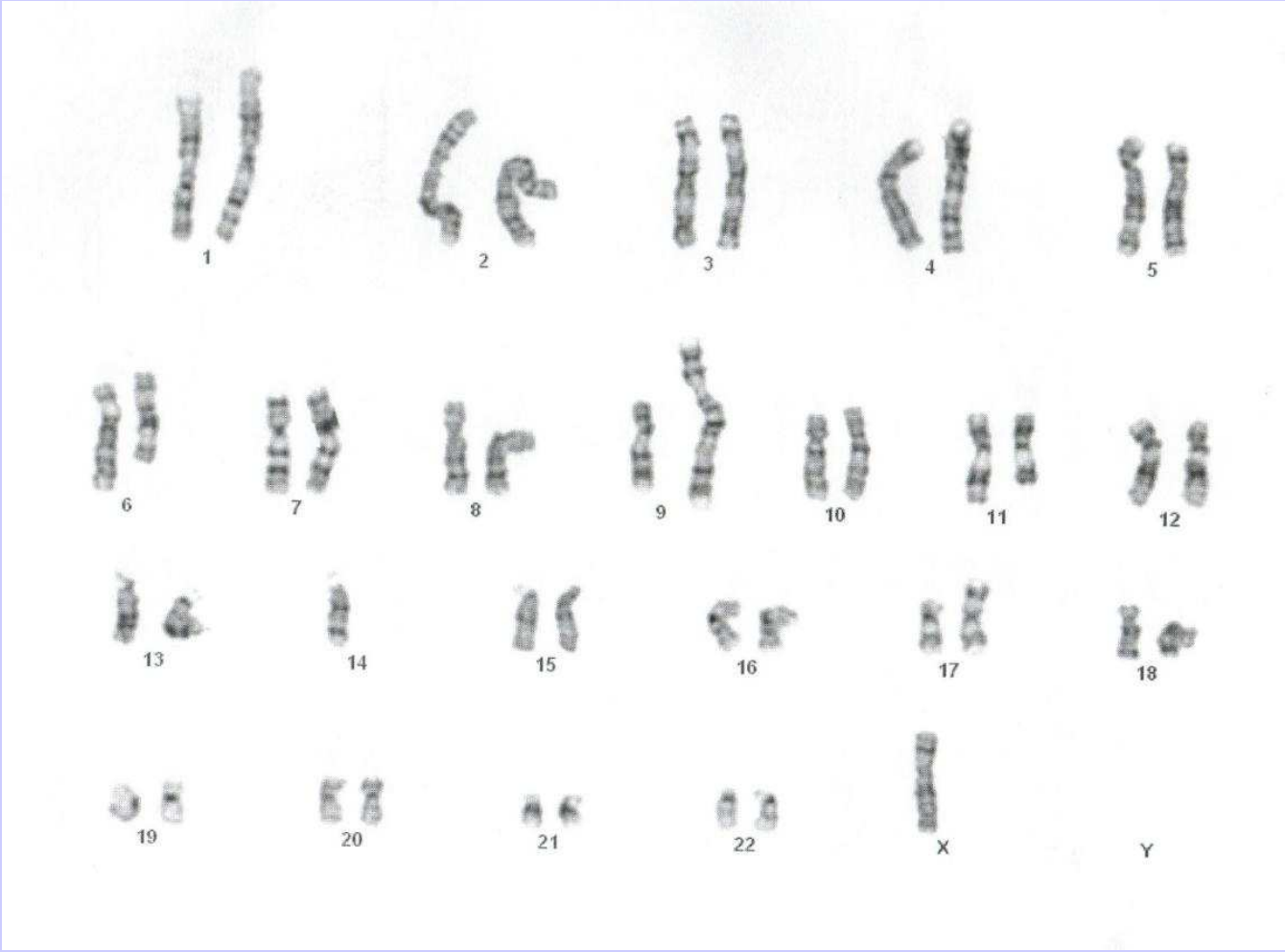
  “the future is dictating the past”

$$y`(x) = a\alpha\, y(\alpha x) - a\, y(x),\ x > 0,\ \alpha > 1,$$

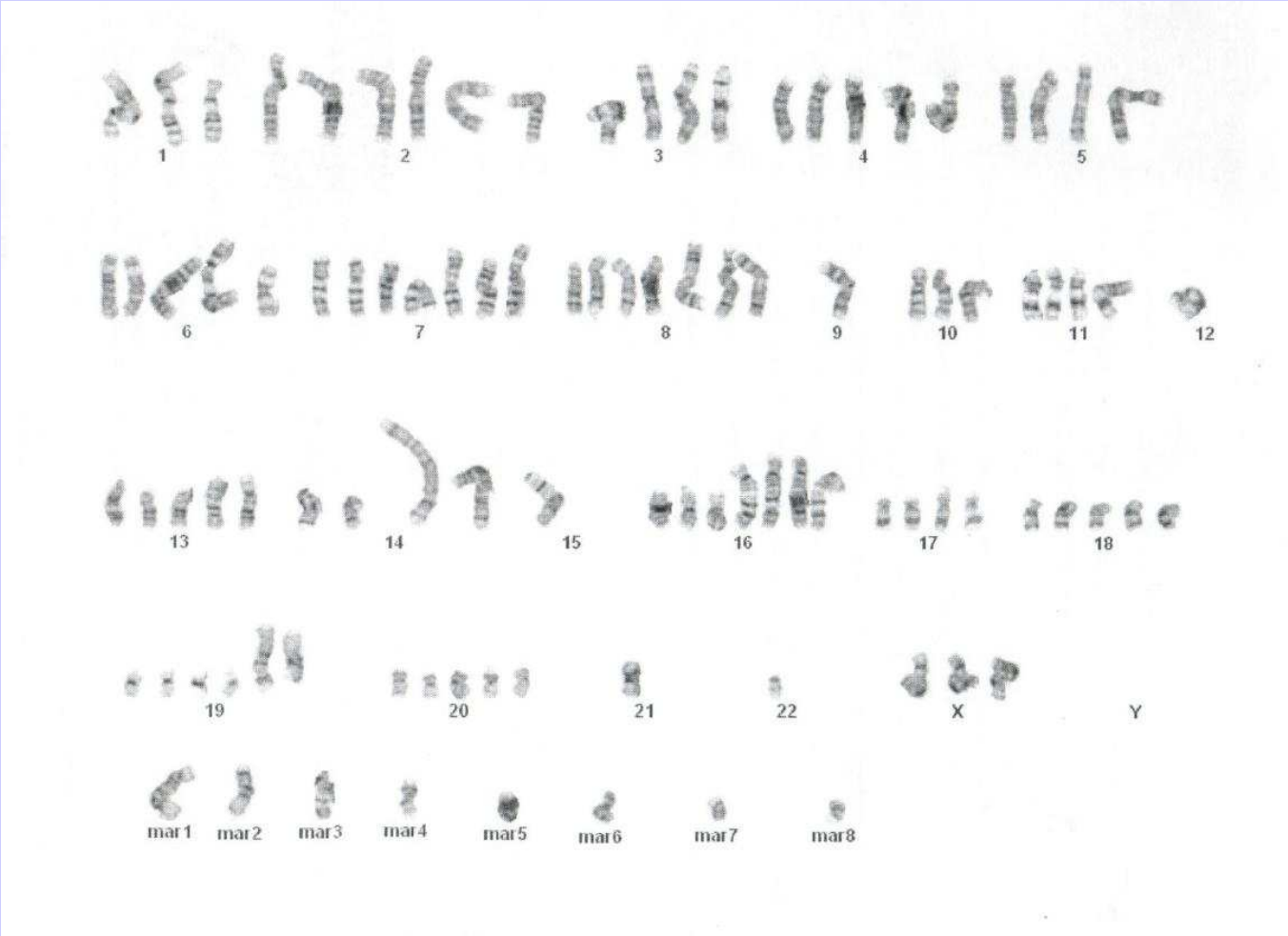
$$y(0) = 0,\ y(\infty) = 0.$$

- For us it is an “eigenvalue problem”, and we are at the principal eigenvalue.

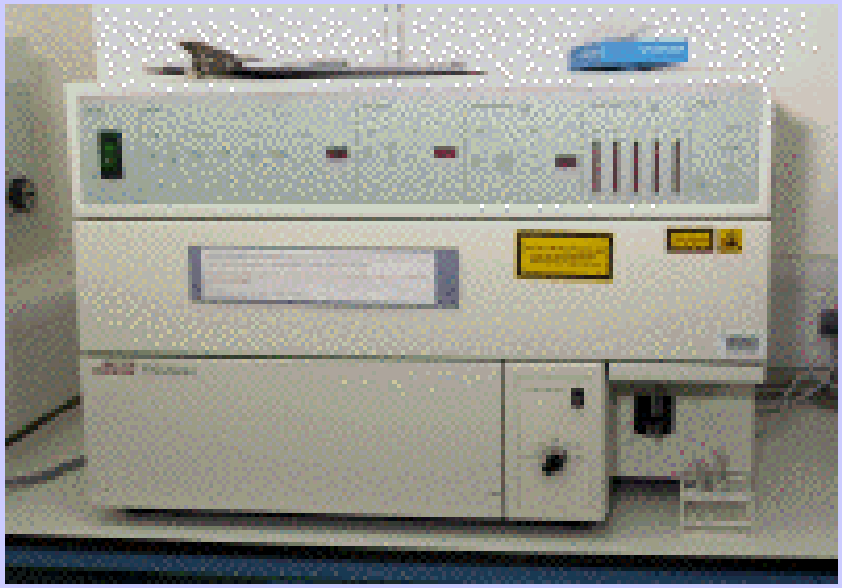
Normal Cells

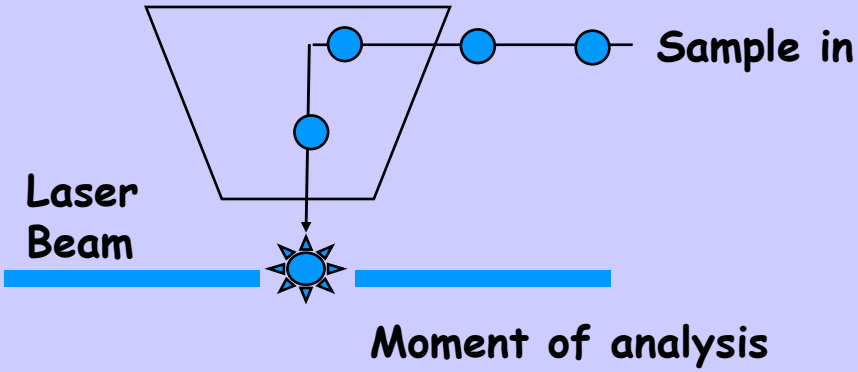


3. Tumour cel1 growth



Flow Cytometry





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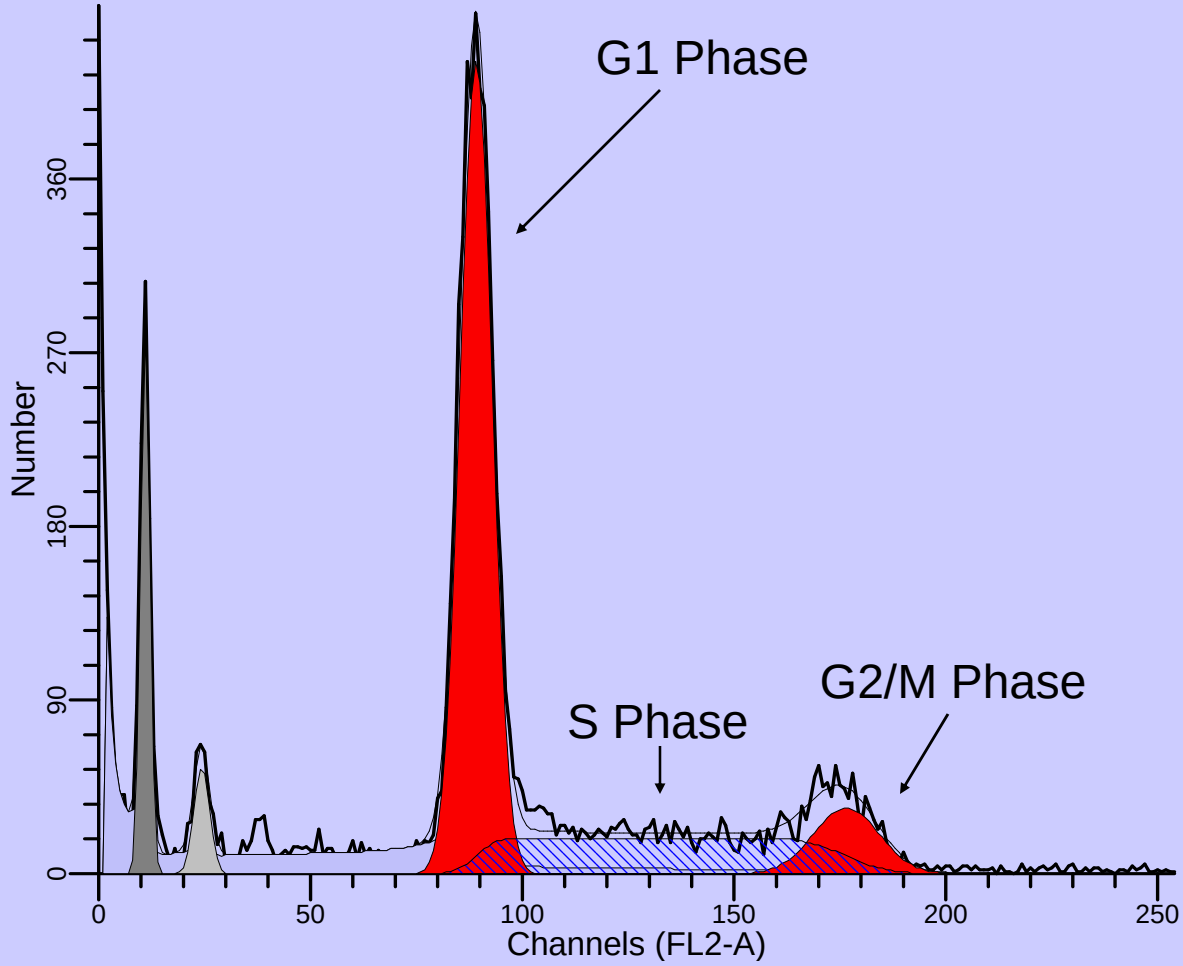
Steady DNA Distribution (SDD)



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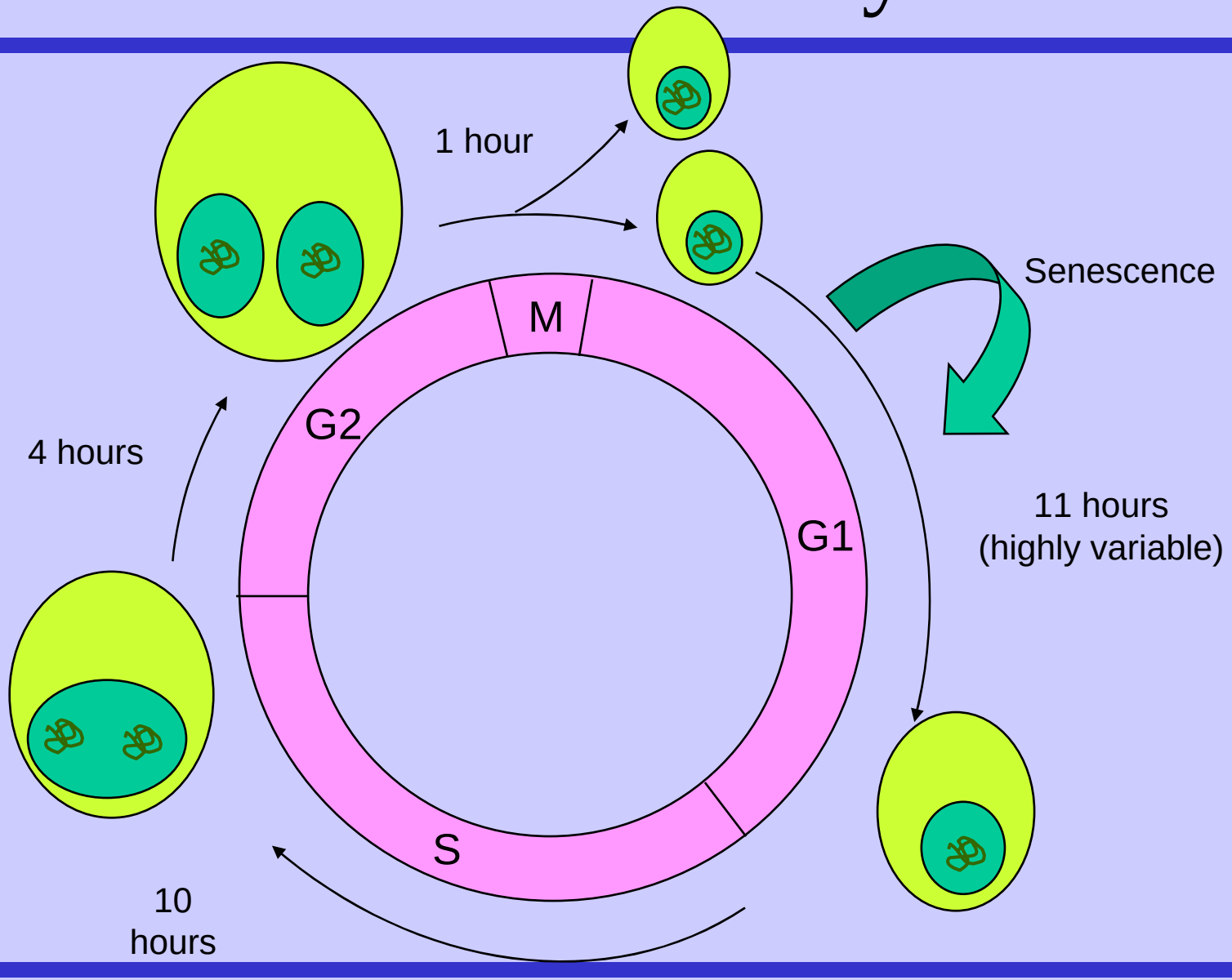
The Human Cell Cycle



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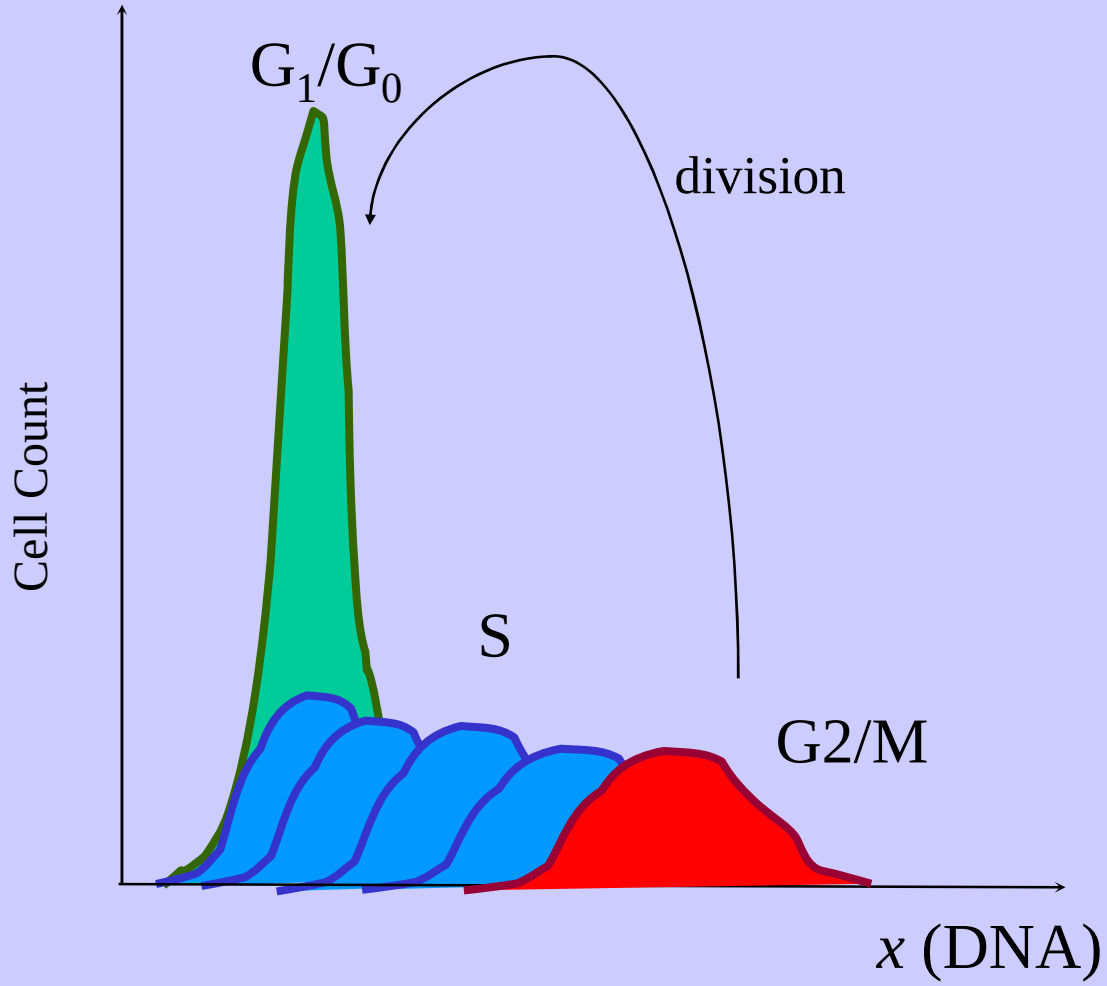
Idea



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Model of a cell line unperturbed by cancer therapy G1-phase

$$\frac{\partial G_1(x,t)}{\partial t} = 4bM(2x,t) - k_1 G_1(x,t), \quad t > 0,\ 0 < x < L,$$

$$G_1(x,t=0) = G_{10}, \quad 0 < x < L,$$

Dispersion

- There is white noise particularly in the S-phase
- Growth $\boldsymbol{dx = g\,dt + \sigma\,dX}$

Deterministic Growth ***White Noise***

- Gives Fokker-Planck Equation

$$S_t = (D\,S)_{xx} - (g\,S)_x + \ldots \quad \text{etc.,}$$

$$D = \sigma^2/2.$$

Model of a cell line unperturbed by cancer therapy S-phase

$$\frac{\partial \bar{S}(x,t;\tau_S)}{\partial \tau_S} = D\frac{\partial^2 \bar{S}(x,t;\tau_S)}{\partial x^2} - g\frac{\partial \bar{S}(x,t;\tau_S)}{\partial x}, \quad t,\tau_S > 0,\ 0 < x < L,$$

$$\bar{S}(x,t;\tau_S = 0) = k_1 G_1(x,t), \quad t > 0,\ 0 < x < L,$$

$$\bar{S}(x,t=0;\tau_S) = \bar{S}_{0\tau_S}, \qquad \tau_S > 0,\ 0 < x < L,$$

$$D\frac{\partial \bar{S}}{\partial x}(x=0,t;\tau_S) - g\bar{S}(x=0,t;\tau_S) = 0, \quad t,\tau_S > 0,$$

$$D\frac{\partial \bar{S}}{\partial x}(x=L,t;\tau_S) - g\bar{S}(x=L,t;\tau_S) = 0, \quad t,\tau_S > 0,$$

$$S(x,t) = \int_0^{T_S} \bar{S}(x,t;\tau_S)\,d\tau_S$$

Model of a cell line unperturbed by cancer therapy G2 & M-phase

$$\frac{\partial G_2(x,t)}{\partial t} = \bar{S}(x,t;T_S) - (k_2 + \mu_{G2})G_2(x,t), \quad t > 0,\ 0 < x < L,$$

$$G_2(x,t=0) = G_{20}, \quad 0 < x < L,$$

$$\frac{\partial M(x,t)}{\partial t} = k_2 G_2(x,t) - bM(x,t), \quad t > 0,\ 0 < x < L,$$

$$M(x,t=0) = M_0, \quad 0 < x < L,$$

$$\frac{\partial \overline{S}(x,t;\tau)}{\partial \tau} = D\frac{\partial^2 \overline{S}(x,t;\tau)}{\partial x^2} - g\frac{\partial \overline{S}(x,t;\tau)}{\partial x}, \quad \overline{S}(x,t;\tau=0) = \overline{S_0}(x,t)$$

$A<x<B$	$\overline{S}(x,t;\tau) = \int_A^B \overline{S}_0(x,t)\gamma(\tau,x,z)dz$
$-\infty < x < \infty$	$\gamma(\tau,x,z) = \frac{1}{2\sqrt{\pi D\tau}} e^{-(x-g\tau-z)^2/4D\tau}$
$0 < x < \infty$ $\overline{S}(x=0,t;\tau) = 0,$	$\gamma(\tau,x,z) = \frac{1}{2\sqrt{\pi D\tau}} e^{g(x-z-g\tau/2)/2D}\left(e^{-(x-z)^2/4D\tau} - e^{-(x+z)^2/4D\tau}\right)$
$0 < x < L$ $\overline{S}(x=0,t;\tau_S) = 0$ $\overline{S}(x=L,t;\tau_S) = 0$	$\gamma(\tau,x,z) = \frac{e^{g(x-z-g\tau/2)/(2D)}}{2\sqrt{\pi D\tau}} \sum_{n=-\infty}^{n=\infty}\left(e^{-(x-z+\lvert n\rvert 2L)^2/4D\tau} - e^{-(x+z-\lvert n\rvert 2L)^2/4D\tau}\right)$
$0 < x < L$	$D\frac{\partial \overline{S}}{\partial x}(0,t;\tau_S) - g\overline{S}(0,t;\tau_S) = 0,$ $D\frac{\partial \overline{S}}{\partial x}(L,t;\tau_S) - g\overline{S}(L,t;\tau_S) = 0,$ $\gamma(\tau,x,z) \cong \frac{1}{2\sqrt{\pi D\tau}} e^{-(x-g\tau-z)^2/4D\tau}$

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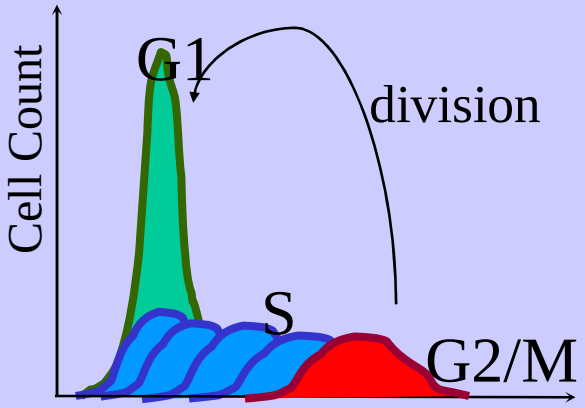
S-phase equations

$$\bar{S}(x,t;\tau_S) = \begin{cases} k_1 G_1(x - g\tau_S, t - \tau_S), & D = 0, \\ \int_0^L k_1 G_1(x, t - \tau_S)\gamma(\tau_S, x, z)dz, & D \neq 0, \end{cases}$$



$$\frac{\partial S(x,t)}{\partial t} = D\frac{\partial^2 S(x,t)}{\partial x^2} - g\frac{\partial S(x,t)}{\partial x} + k_1 G_1(x,t) - \bar{S}(x,t;\tau_S = T_S), \quad t > 0,\ 0 < x < L,$$

$$S(x,t=0) = S_0, \qquad 0 < x < L,$$

$$D\frac{\partial \bar{S}}{\partial x}(x=0,t) - g\bar{S}(x=0,t) = 0, \quad t > 0,$$

$$S(x,t) = k_1 G_1(x,t) + \int_0^{T_S}\int_0^L k_1 G_1(x, t - \tau_S)\gamma(\tau_S, x, z)dz d\tau_S,$$

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4. Further new maths

- *Finite Differences+convolution: Do get SSD's but slow.*
- Look for separable solutions…..

$$G_1(x,t) = N(t)y_1(x)$$
$$S(x,t) = N(t)y_S(x)$$
$$G_2(x,t) = N(t)y_2(x)$$
$$M(x,t) = N(t)y_M(x)$$

If solutions are attracting then
the y's are the SSDs in each phase.

Equations for y_1 the SSD: G1-phase

Delay equation equation:

$$y_1(x-1)=\Lambda y_1\left(\frac{x}{2}\right), \quad x>0, \quad D=0,$$

Solution: $y_1(x) = \delta(x\text{-}1)$, $\Lambda = ½$. Check.
Exam Question on generalised functions?

Fredholm integral equation (non-symmetric):

$$\int_0^L \gamma(T_S, 2x, z)\, y_1(z)\, dz = \Lambda y_1(x), \quad x > 0, \quad D \neq 0$$

$$\Lambda = F(\lambda) = \frac{(\lambda+k_1)(\lambda+k_2)(\lambda+b)e^{\lambda T_S}}{4bk_1k_2}$$

SDD Solutions

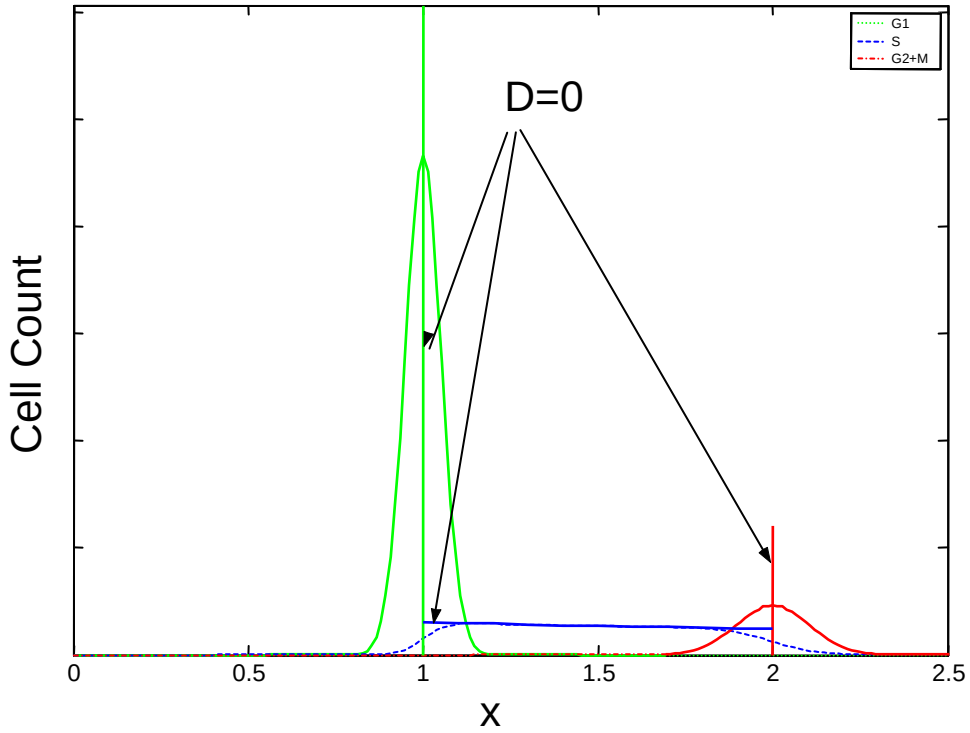
- *Delay equation (D=0): (unique) Point distributions.*

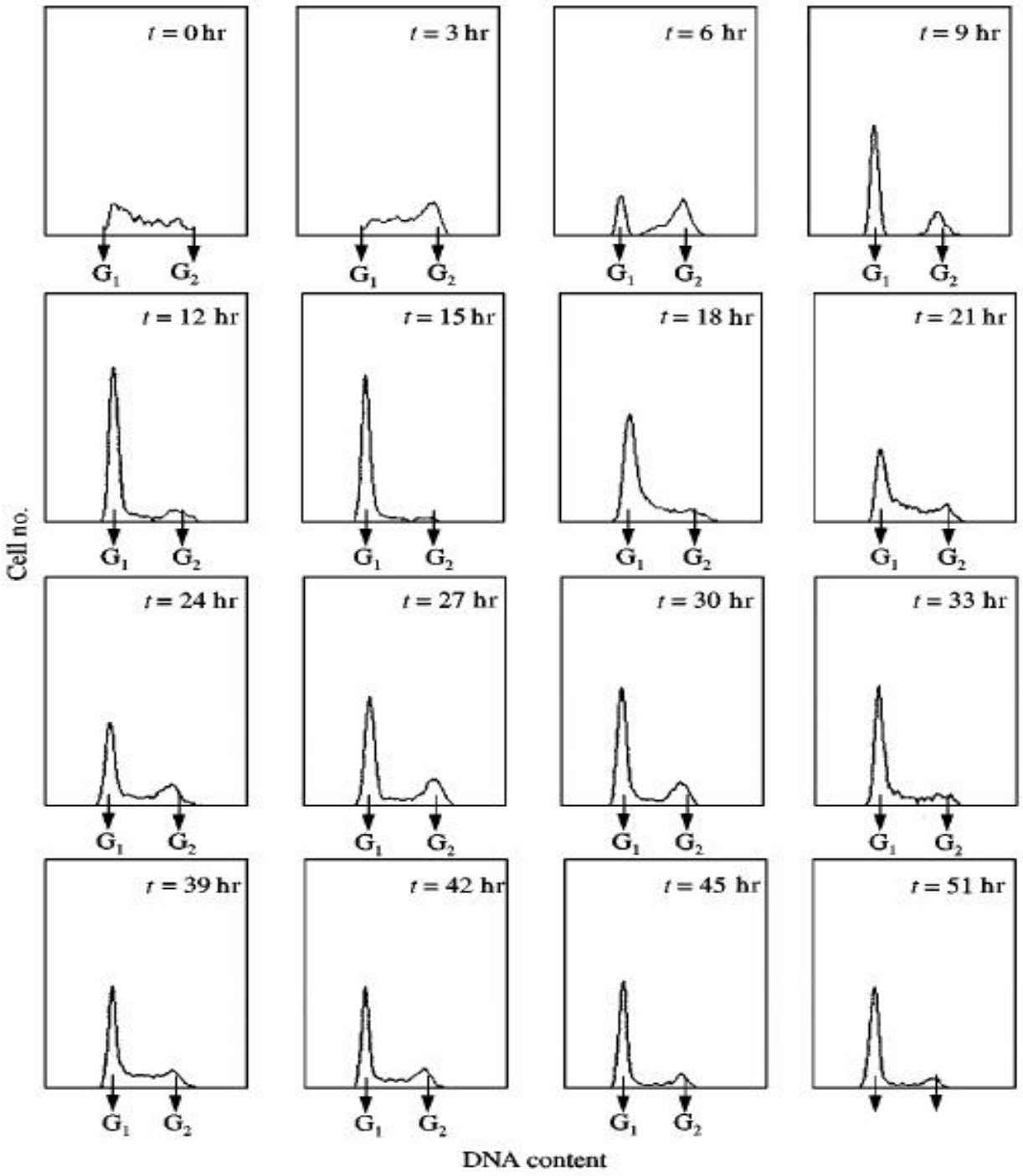
$$y_1(x) \sim \delta(x-1), \quad y_2(x), y_M(x) \sim \delta(x-2),$$

$$y_S(x) \sim H(x-2) - H(x-1)$$

- *Fredholm Integral Equation ($D \neq 0$):*

Numerical methods. Get 1 eigenfunction (there could be others)



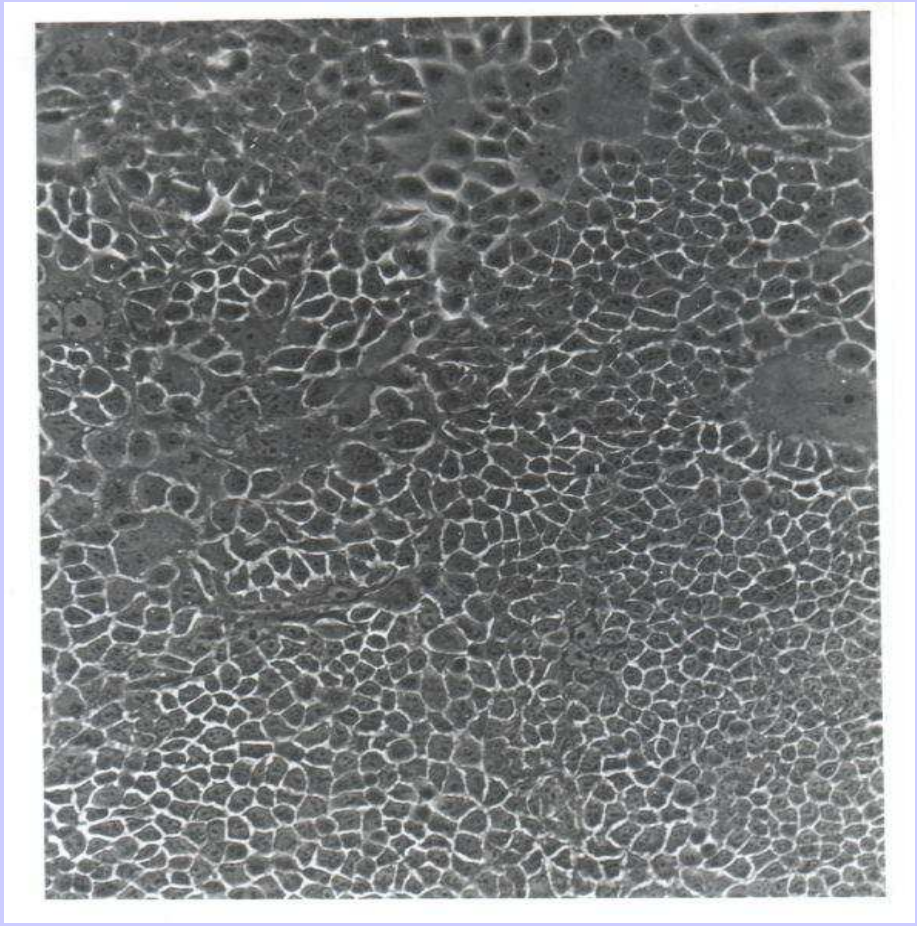


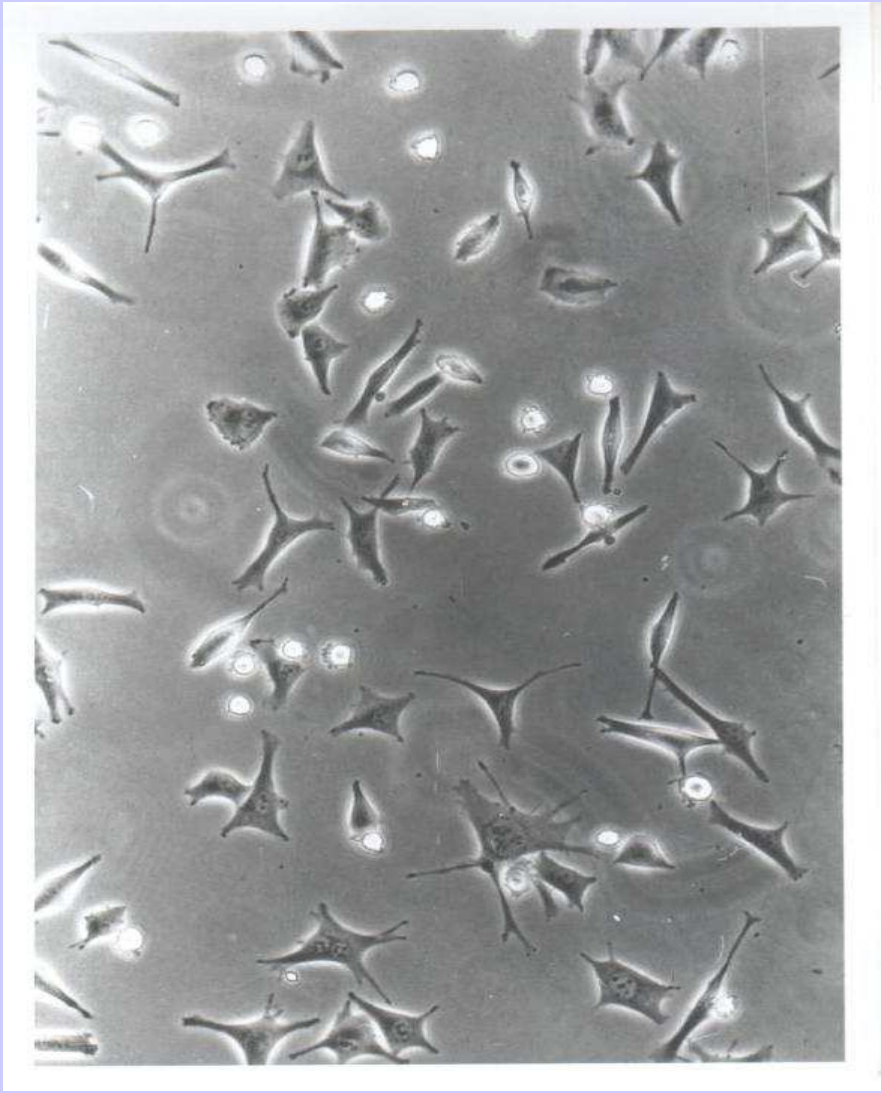
Chiorino et al. *Desyncronization Rate in Cell Populations: Mathematical Modeling and Experimental Data*, J. theor. Biol. (2001) **208**, 185-199

References: Cancer treatment

- Basse B, Baguley BC, Marshall WR, Joseph B, van-Brunt B, Wake GC, & Wall DJN "Modelling cell death in human tumour cell lines exposed to the anticancer drug paclitaxel", Journal Mathematical Biology, **49,** 2004, 329-357**.**
- Basse B, Baguley BC, Marshall E, Wake GC & Wall DJN) “Modelling cell population growth with applications to cancer therapy in human cell lines”, Prog Biophysics Mol Biol, **85,** 2004, pp 353-368**.**

5. Modelling Cancer Treatment: Cell Lines





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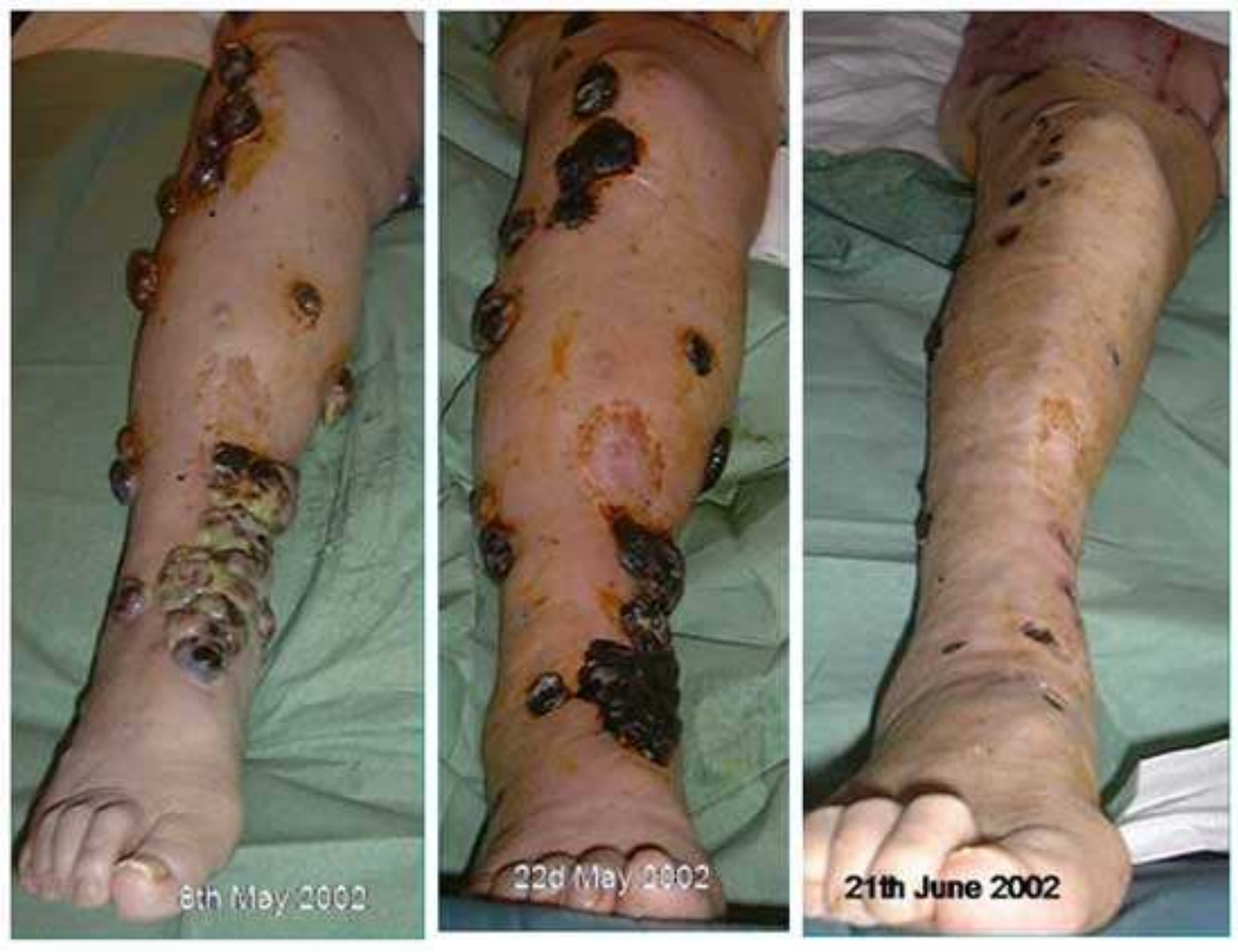
Medical options

- Cure by
  - * poison = chemotherapy
  - * burn = radiotherapy
  - * cut = surgery

Taxol effect: 6 weeks “in vivo”



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Model of a cell line perturbed by paclitaxel

- **Halts cell division**
- **Can induce cell death in G2/M**

$$\frac{\partial G_1(x,t)}{\partial t} = -k_1 G_1(x,t), \quad t > 0,\ 0 < x < L,$$

$$G_1(x,t=0) = G_{10}, \quad 0 < x < L,$$

$$\frac{\partial M(x,t;\tau_M)}{\partial t} = -\mu_M M(x,t;\tau_M), \quad t > 0,\ 0 < x < L,$$

$$M(x,t;\tau_M = 0) = k_2 G_2(x,t), \quad t > 0, \quad 0 < x < L,$$

$$M(x,t=0;\tau_M) = M_0, \quad \tau_M > 0, \quad 0 < x < L,$$

Model of a cell line perturbed by paclitaxel cont…

$$\frac{\partial A(x,t)}{\partial t} = \frac{g_A \partial A(x,t)}{\partial x} + \int_0^\infty \mu_M M(x,t;\tau_M)\, d\tau_M, \quad t > 0,\ 0 < x < L,$$

$$A(x=0,t) = A(x=L,t) = 0, \quad t > 0,$$

$$A(x,t=0) = A_0, \quad 0 < x < L,$$

Parameter Fitting

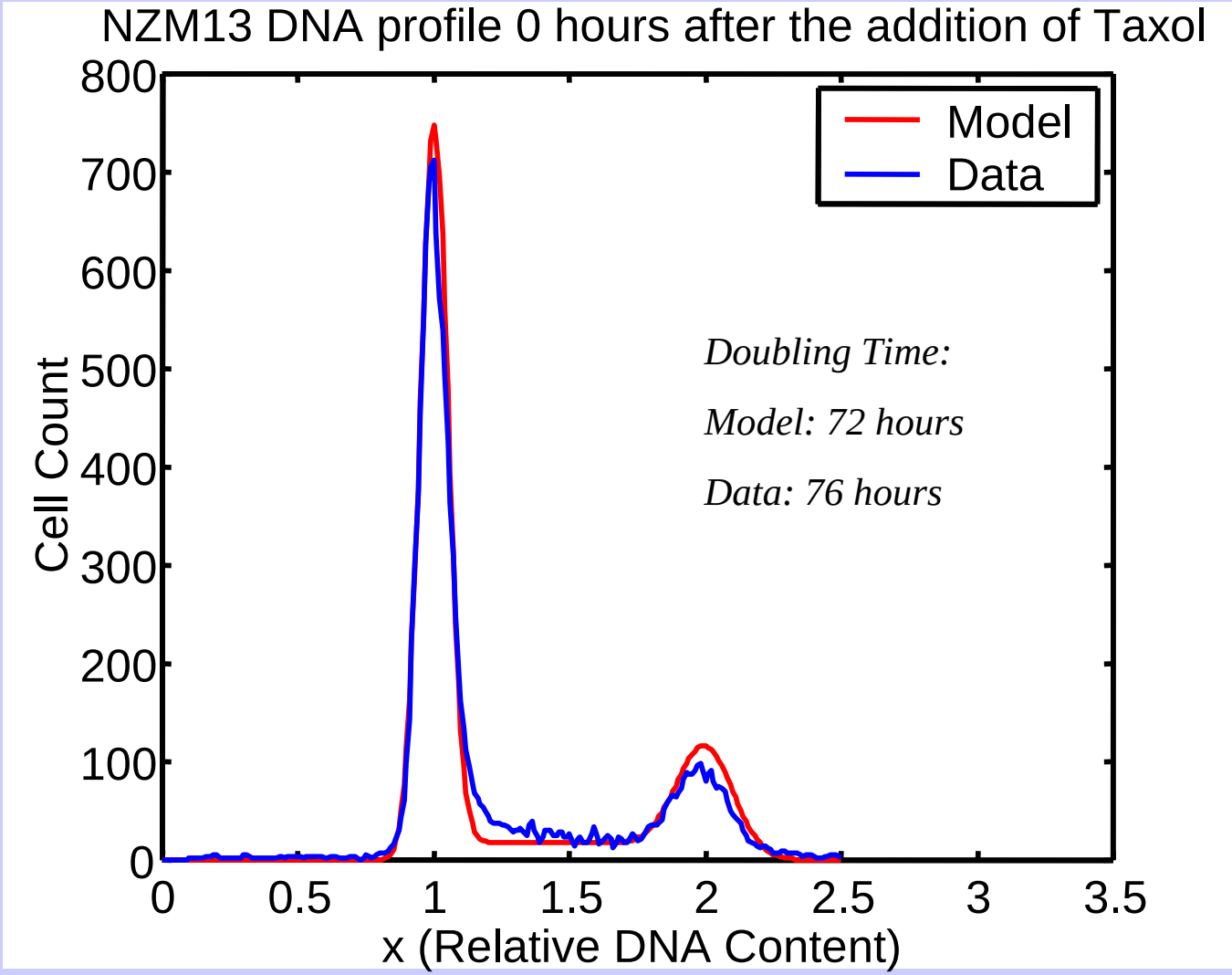
- Minimise $\sum_{j=1}^{J} \left(T(\mathbf{x}, t_j) - D(\mathbf{x}, t_j) \right)^2$

$\beta = (k_1, k_2, T_M, \mu_M, g_A)$

- *Choose a parameter set*
- *Find the model of an unperturbed cell line SDD*
- *Use finite differences and convolution to solve the model of a cell line perturbed by taxol*
- *Calulate the objective function value*

References: Cell-growth; Compartments

- Basse B, Baguley BC, Marshall ES, Joseph WR, van Brunt B Wake GC & Wall DJN. "A mathematical model for analysis of the cell cycle in cell lines derived from human tumours", J Math Biol 2003, **47,** pp 295-312.
- Basse B, Wake GC, Wall DJN, & van-Brunt B. "On a cell-growth model for plankton" Mathematical Medicine and Biology: A Journal of the IMA; **21,** 2004, pp 49-61.



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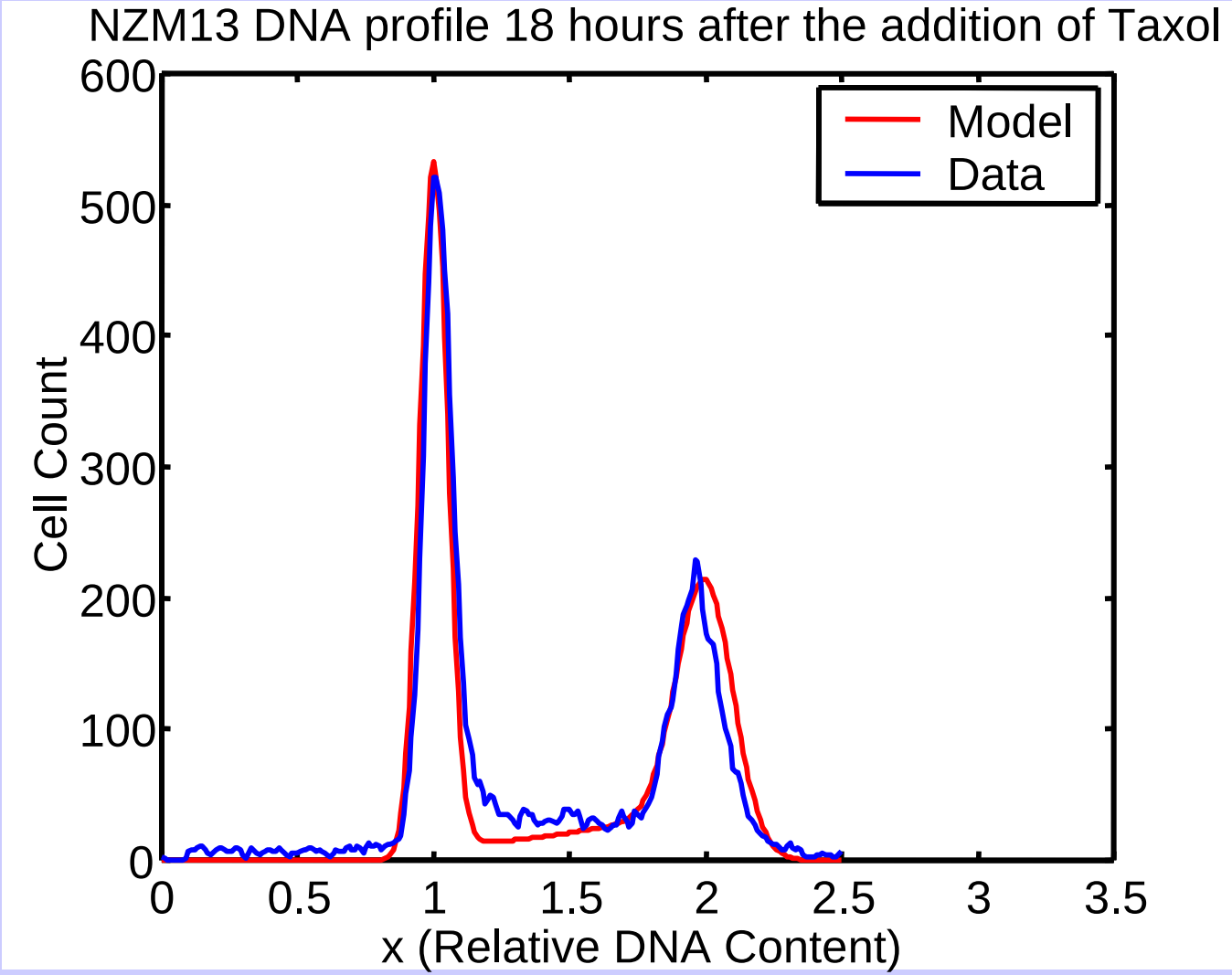

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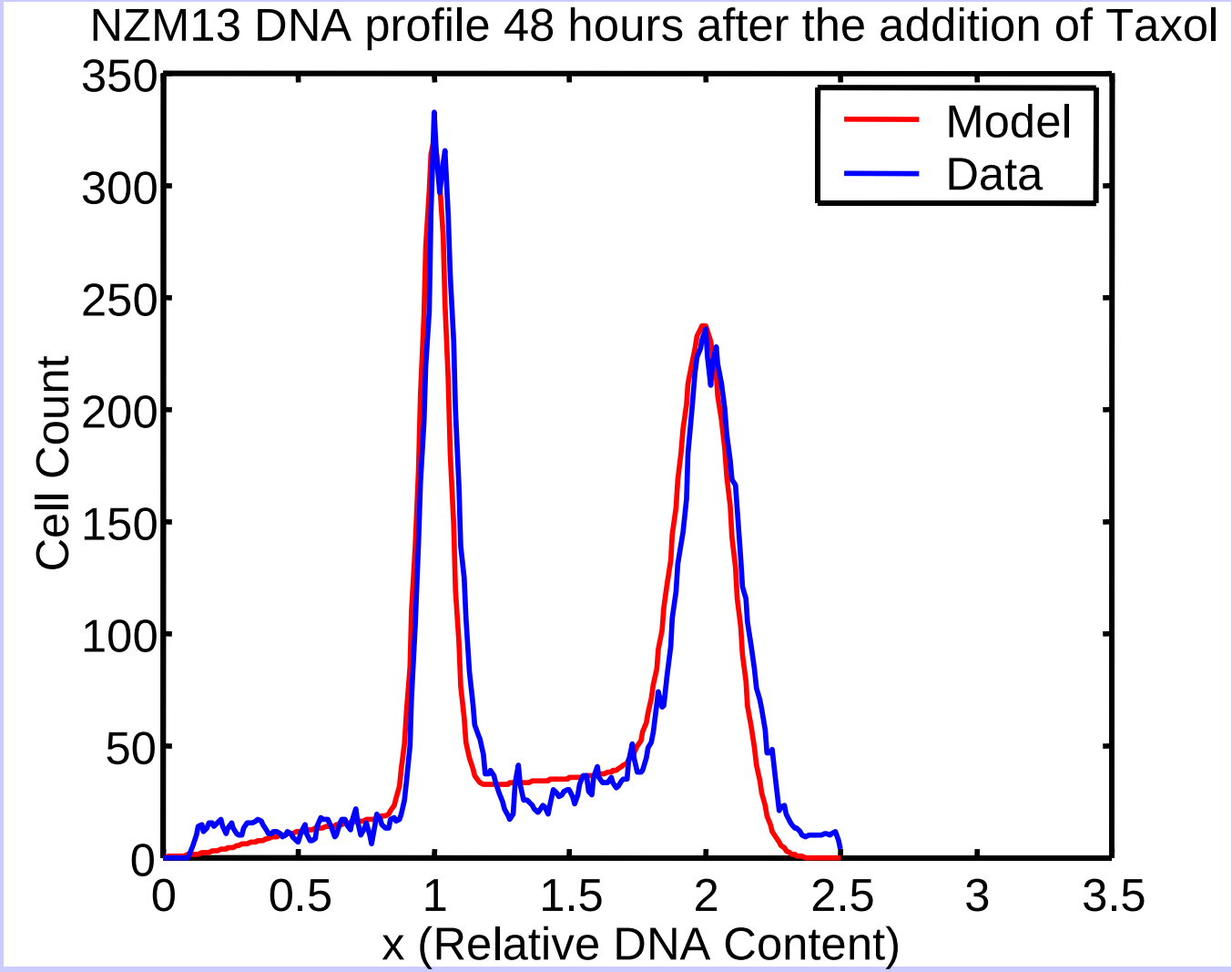

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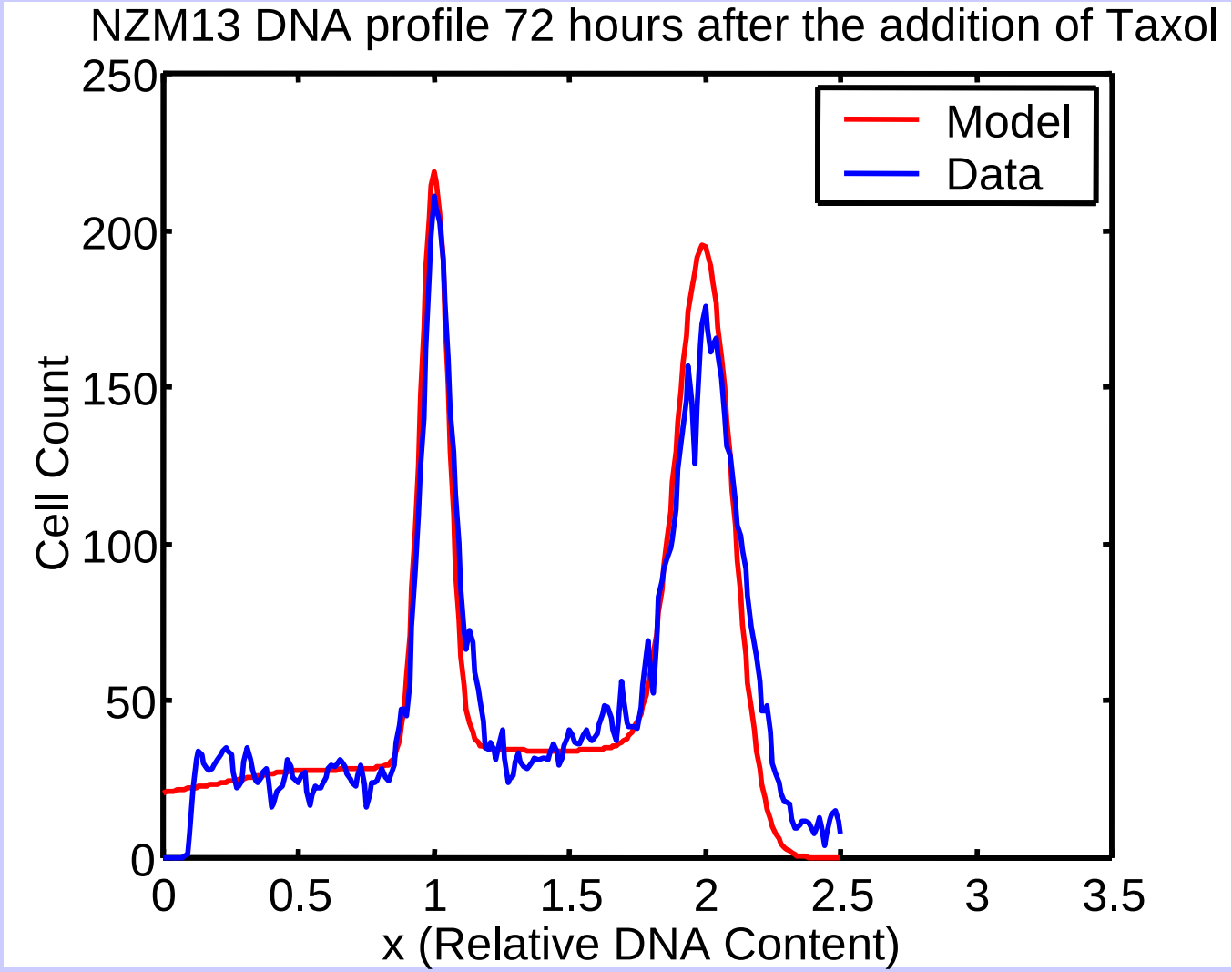

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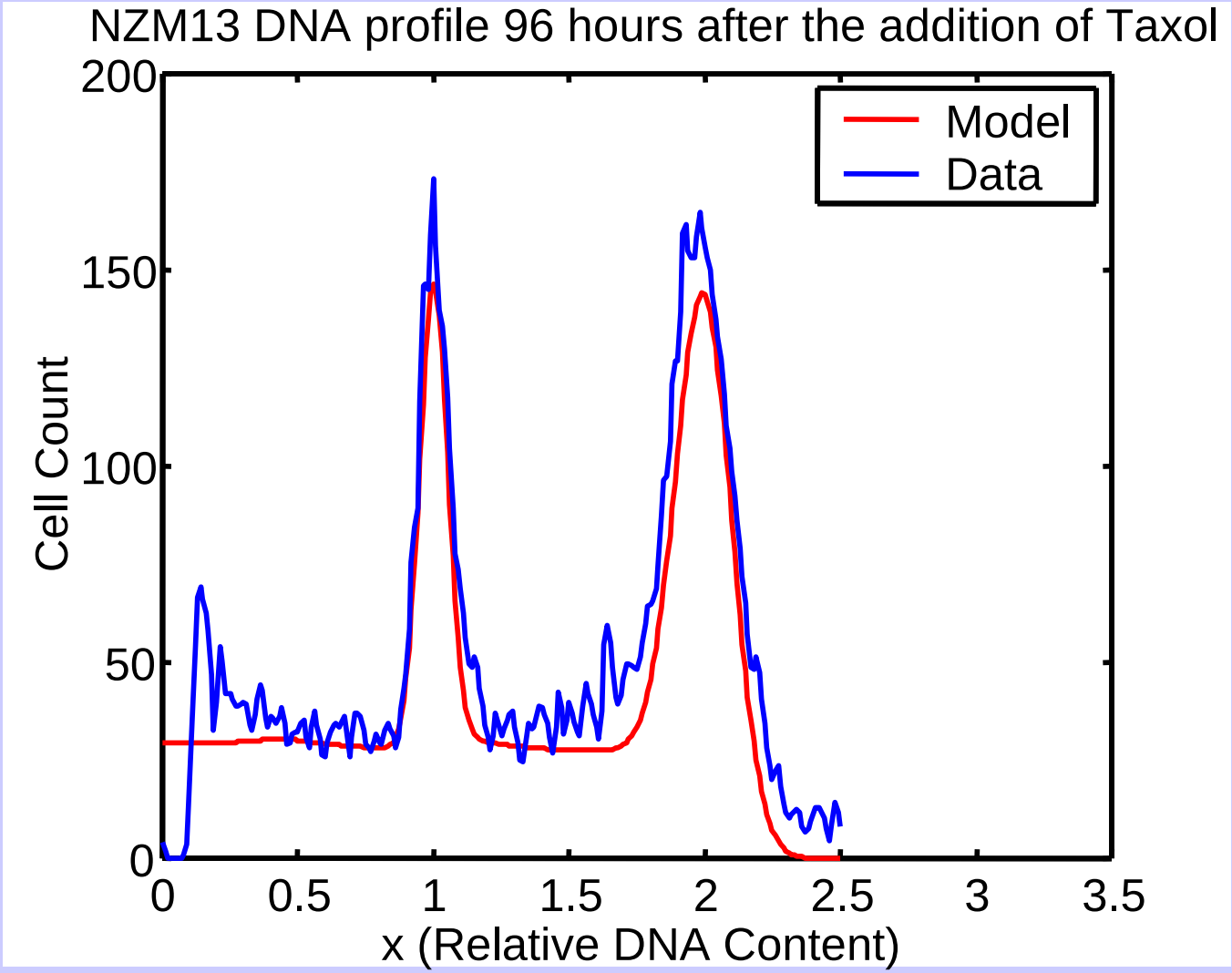

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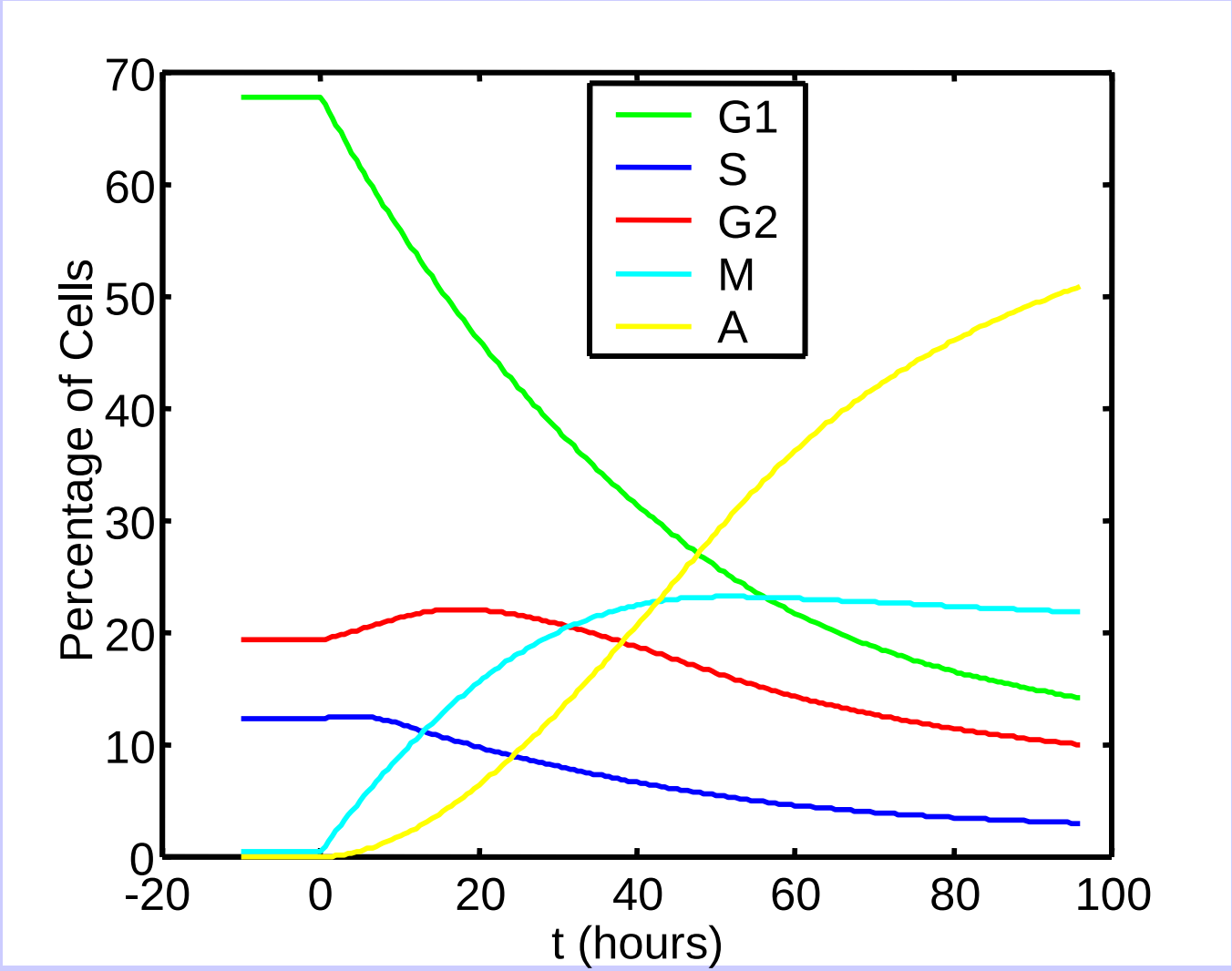
Model Outputs

- DNA profiles
- Percentages in each phase over time
- Absolute numbers in each phase over time
- T_M, the time in M-phase before the onset of apoptosis
- μ_M, the eventual transition rate from M-phase to A-phase
- g_A, the degradation rate in A-phase
- the time it takes for a cell to degrade
- the rate of eventual cell loss from A-phase

Percentages in each phase



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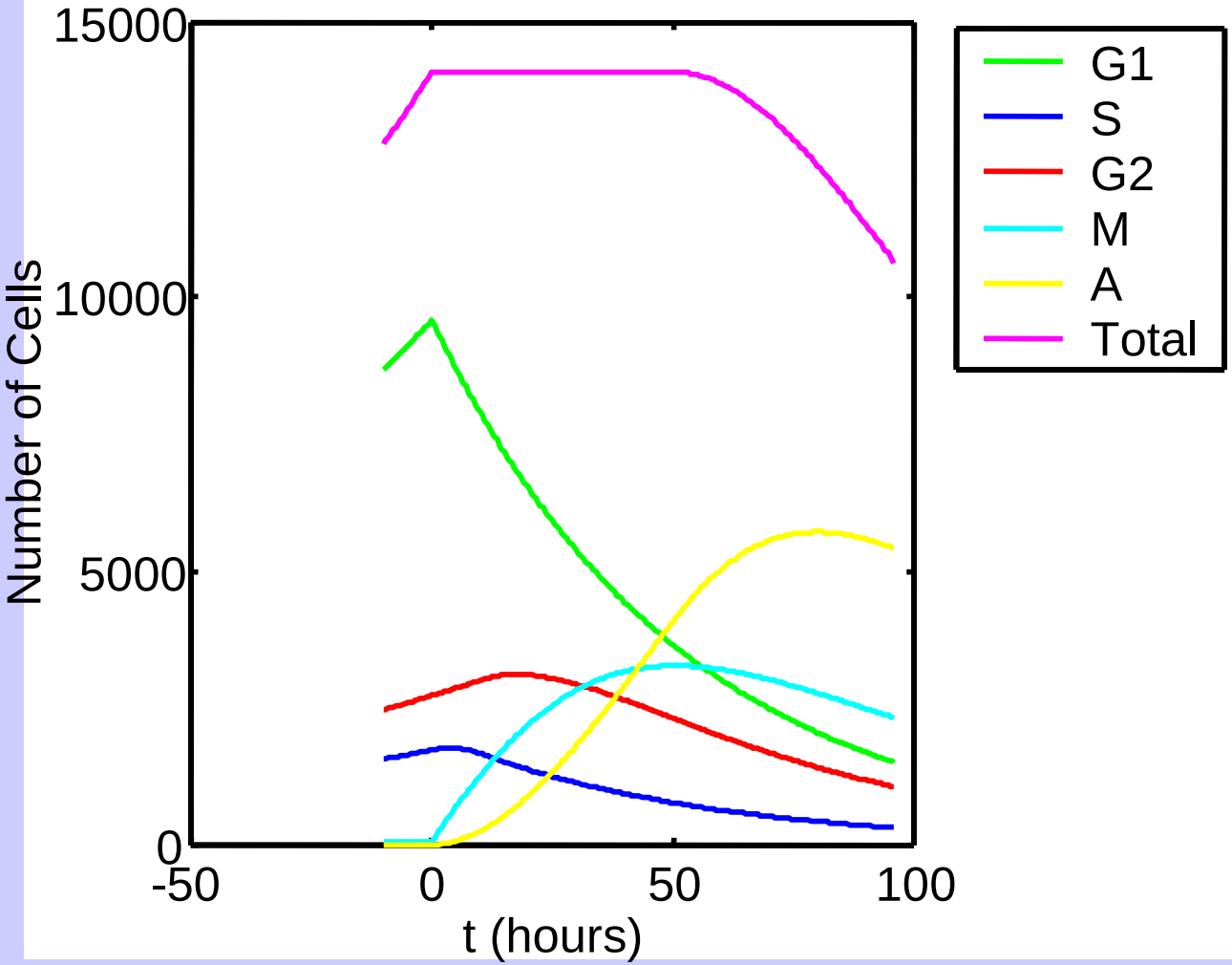
Absolute Cell Number



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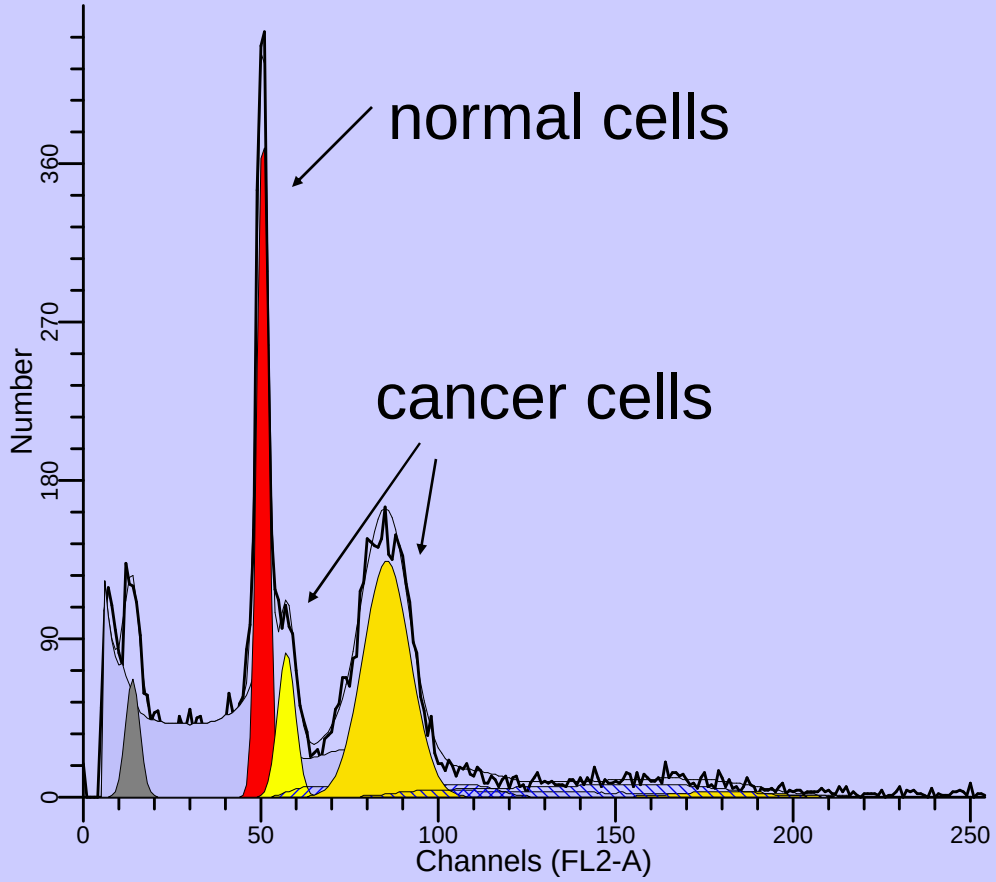
Typical Clinical Sample

Patient with metastatic malignant melanoma



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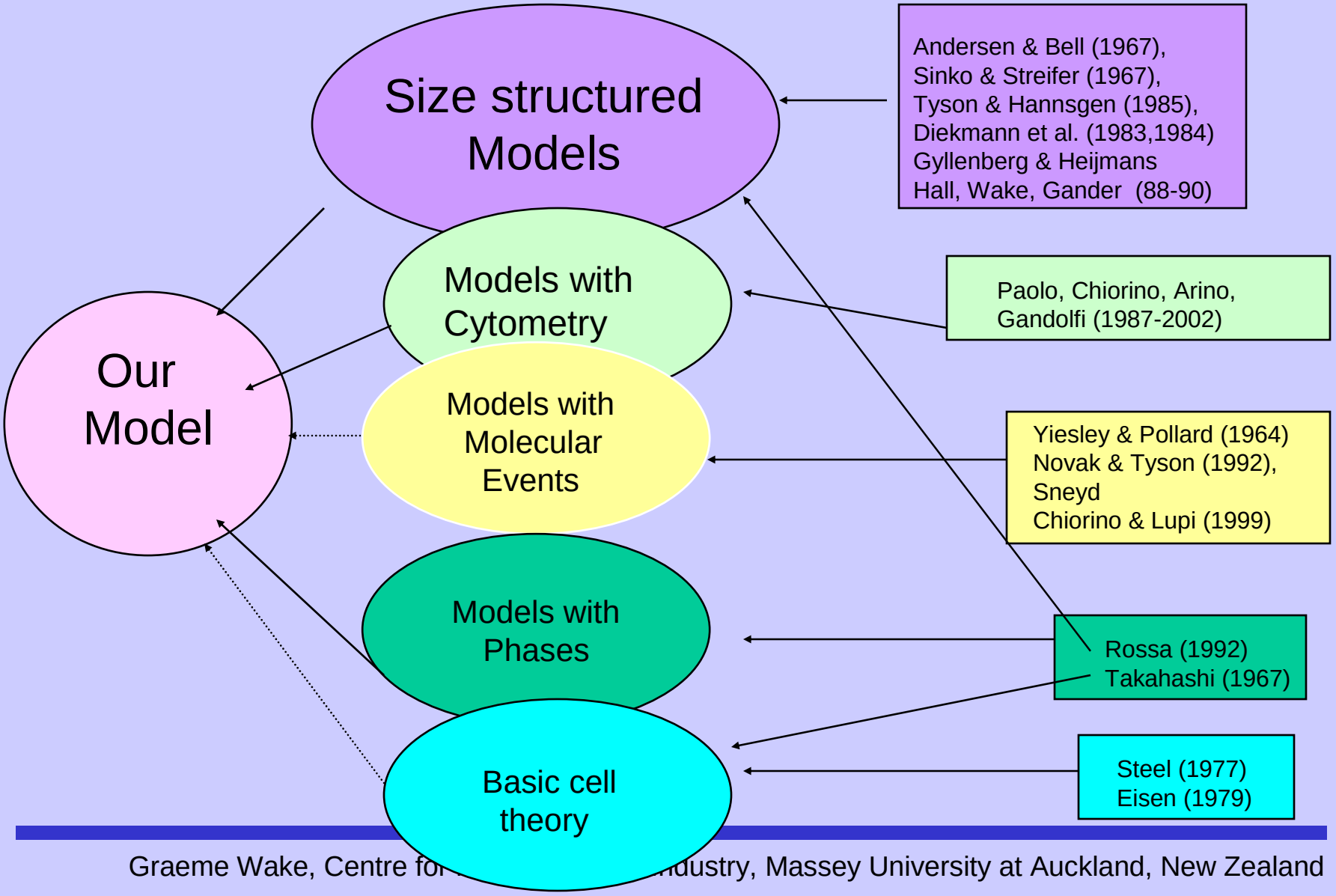
6. Other Models



7(a) Current work -Basse

- *Uniqueness of parameter fitting*
- *Fit other data, compare results*
- *Non-constant degradation rate*
- *Change the concentration of paclitaxel in cell lines*
- *Effects of paclitaxel in vitro (mice) (doesn't stay in the system)*
- *Look at patient tumours*
- *See:* Basse B, Baguley BC, Marshall ES, Wake GC &Wall DJN "Modelling the flow of cytometric data obtained from unperturbed human tumour cell lines: Parameter fitting and comparison", Bulletin of Math Biology, **67, No 4,** 2005, 815 - 830.

7(b) Current work:Transient Models

- Does the transient problem have a solution that (globally) is attracted to SSD behaviour?

- Yes!!!!!!

The model; Single compartment only

$$n_t = (Dn)_{xx} - (gn)_x - \mu n + \alpha^2 B(\alpha x) n(\alpha x, t) - B(x) n(x,t)$$

$$(D(0)n(0,t))_x - g(0)n(0,t) = 0, \qquad t > 0$$

$$n(x,t) \to 0, \qquad x \to \infty \qquad\qquad n_x(x,t) \to 0, \qquad x \to \infty$$

- n(x,t) = density of cells of 'size' x at time t.
- Size is measured by DNA content
- B(x) is the rate of cell division at size x. $B(x) = b\delta(x - l)$
- A cell of size x divides into α daughter cells of size $\frac{x}{\alpha}$
- Of primary interest in this presentation is fixed-size division:

SSD behaviour

- SSD = Steady Size-Distribution
- A model displays SSD behaviour when the shape of the cell-size distribution remains constant while the overall population grows or decays
- This corresponds to a separable solution of the model
- Growth rate is usually exponential
- SSDs are observed to occur in physical cell-cohorts

The D=0 case: no dispersion

Problem: $$n_t = -gn_x - \mu n + \alpha b\,\delta(x - l/\alpha)\,n(l^-,t) - b\,\delta(x-l)\,n(l^-,t),$$

$$n(x,0) = n_0(x), \qquad x > 0,$$

$$n(0,t) = 0, \qquad t > 0.$$

•The limiting shape of the SSDs for the dispersive case as with the requirement of continuity from the left, is a global attractor in this model (in a sense): basically it is the hull that exhibits SSD behaviour

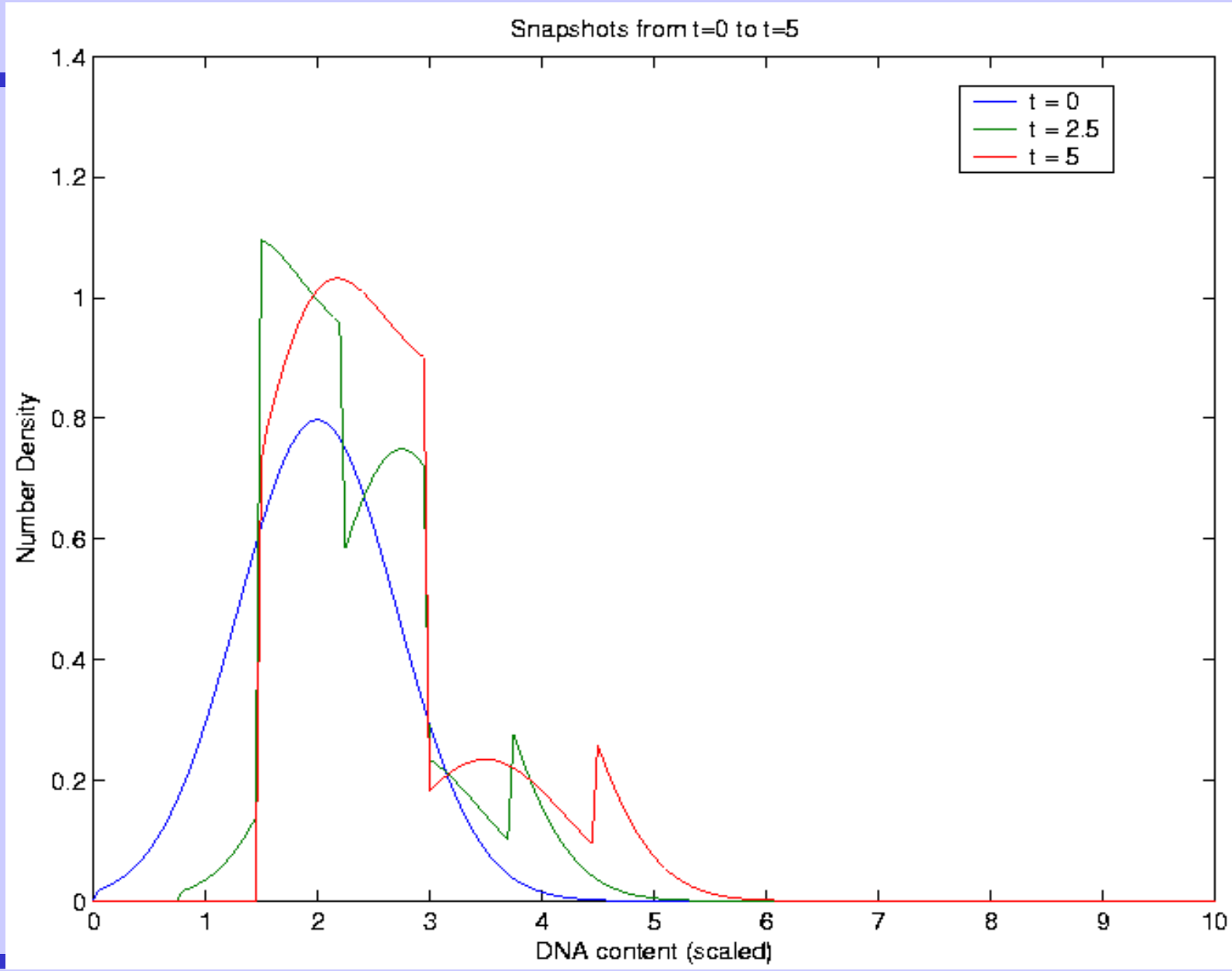
$$n(x,t)\,e^{\lambda t} \sim \max_{t \geq 0} n(x,t) = y(x) \text{ as } D \to 0$$

The solution to the D=0 case: follow characteristics

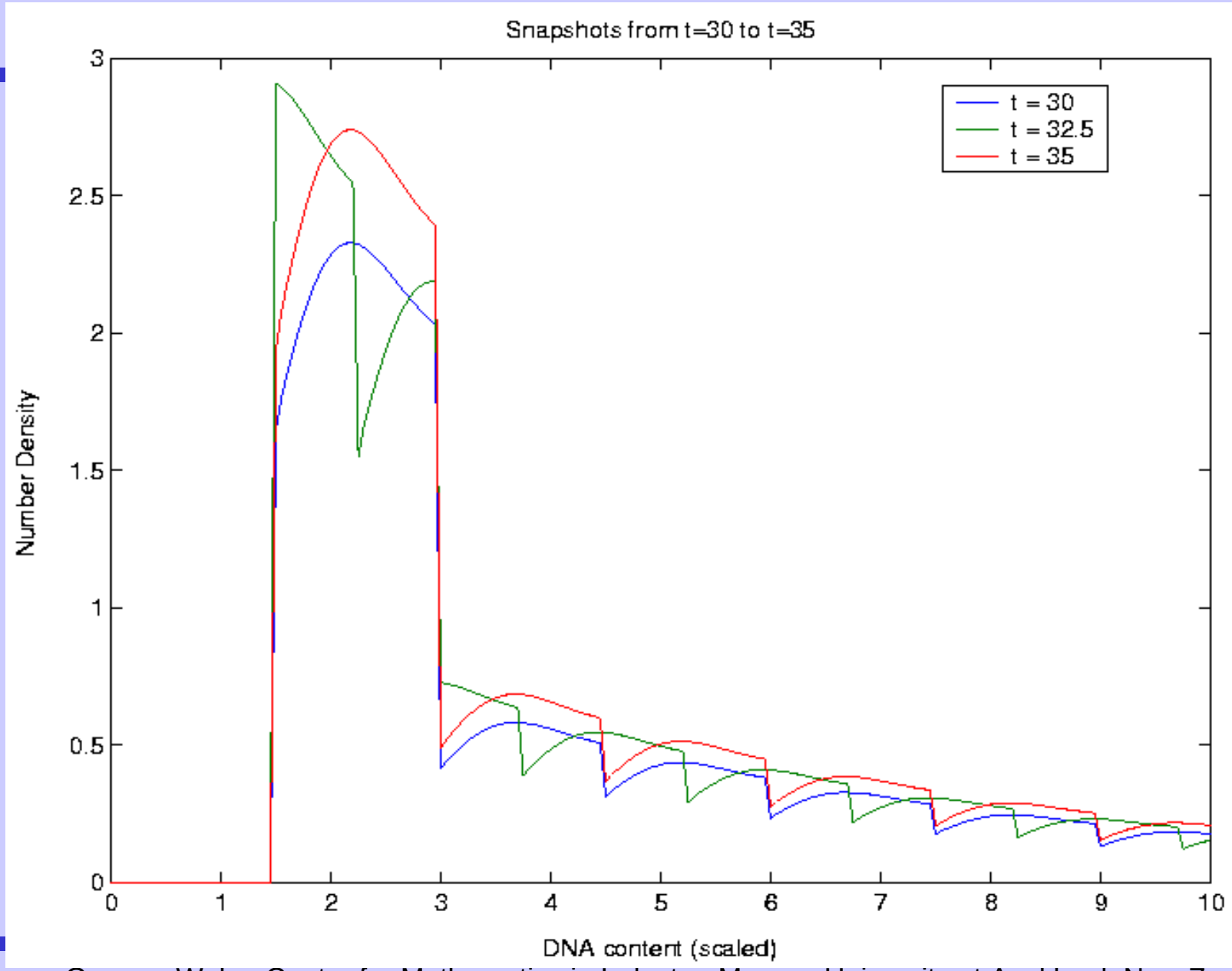
$$n_1(x,t) = n_0(x-gt)e^{-\mu t}H(x-gt), \qquad t>0. \qquad (\alpha = 2)$$

$$n_2(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & \frac{l}{2} < x-gt < l, \\ e^{-\mu t}\left[\lambda^m n_0\left(x-gt+\frac{ml}{2}\right)+\lambda^{m+1}n_0\left(x-gt+\frac{(m+1)l}{2}\right)\right], & \frac{-ml}{2} < x-gt < \frac{-(m-1)l}{2} \end{cases}$$

$$n_3(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & l < x-gt, \\ \left(1-\frac{b}{g}\right)n_2(x,t), & x-gt < l. \end{cases} \qquad \left(\lambda = \frac{\alpha b}{g}\right)$$

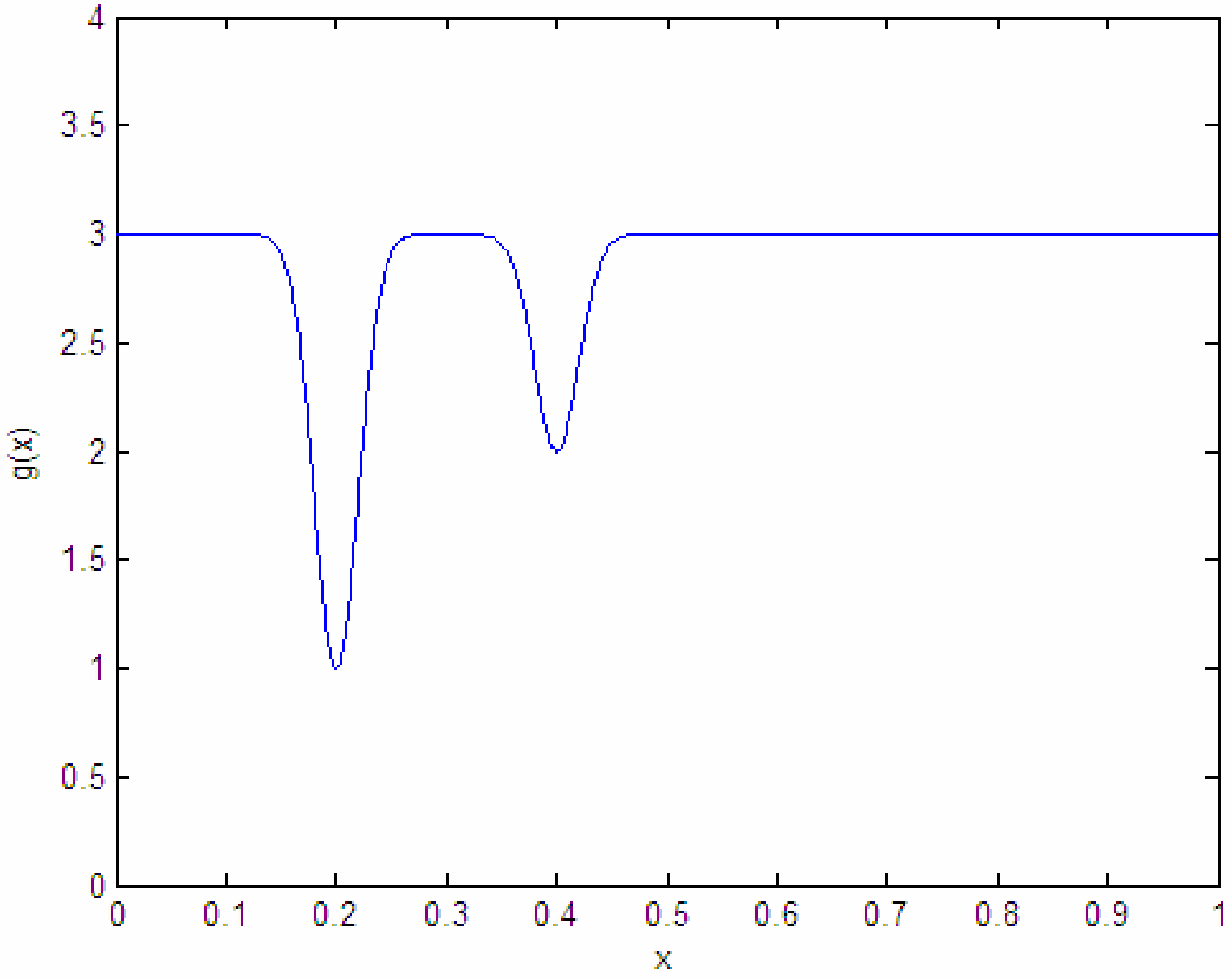


Graeme Wake, Centre for Mathematics in Industry, Massey University at Auckland, New Zealand



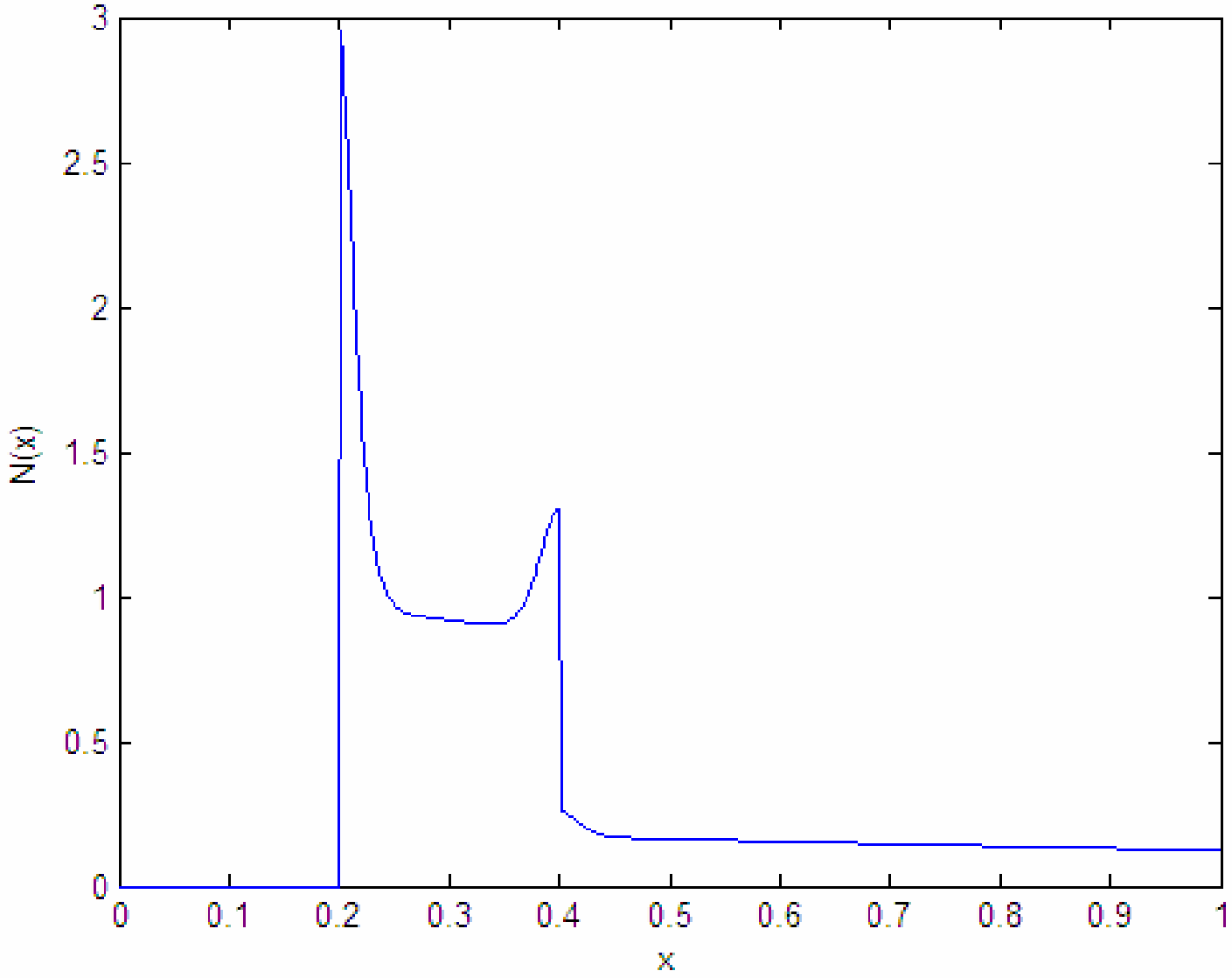
Graeme Wake, Centre for Mathematics in Industry, Massey University at Auckland, New Zealand

A variable growth function



nd

The corresponding hull



Summary

- With D=0, fixed size division the solution exhibited periodic exponential growth

- The hull is a global attractor with the same shape as the limiting SSD as D tends to zero

- A variable growth rate allows the shape of the hull to match observations

- Upper/lower solutions were used to prove a convergence result in a special case (possibly useful in other cases?)

References

R. Begg, G. C. Wake, D. J. N. Wall, *On a functional equation model of transient cell growth*, Math. Med. Biol. **22** (4) (2005) 371-390 (D= 0).

R. Begg, G. C. Wake, D. J. N. Wall, *On the stability of steady size-distributions for a stochastic cell-growth process*, J. Differential and Integral Equations: Vol **21**, Nos. **1-2**, 2008, pp 1-24.(D >0)

The transient problem D > 0, fixed size division

- The problem is:

$$\frac{\partial}{\partial t}n(x,t) = D\frac{\partial^2}{\partial x^2}n(x,t) - g\frac{\partial}{\partial x}n(x,t) + \alpha^2 b\delta(\alpha x - l)n(\alpha x,t) - b\delta(x-l)n(x,t) - \mu n(x,t),$$

$$n(x,0) = n_0(x), \qquad n_0 \in (C \cap L^1 \cap L^\infty)[0,\infty)$$

$$Dn_x(x,t) - gn(x,t)|_{x=0} = 0,$$

$$n(x,t) \to 0, \qquad x \to \infty, \quad t > 0$$

$$n_x(x,t) \to 0, \qquad x \to \infty, \quad t > 0.$$

SSD equation

- This is found to be

equation,

$$\begin{cases} y''(x) - \gamma y'(x) + \alpha^2 \beta \delta(\alpha x - l) y(\alpha x) - (\beta \delta(x - l) + \lambda) y(x) & = 0, \\ y \in (C \cap W^{2,1} \cap L^\infty)[0, \infty), \\ y'(0) - \gamma y(0) = 0, \\ y'(x), y(x) \to 0, \qquad x \to \infty. \end{cases} \tag{3.1.7}$$

where $W^{2,1}[0,\infty)$ is the Sobolev space of functions in $L^1[0,\infty)$ who have weak derivatives up to order 2 also in $L^1[0,\infty)$ (where we consider the δ-distribution to be in $L^1[0,\infty)$ for now); $\gamma = g/D$, $\beta = b/D$ and λ is an eigenvalue of the operator

$$y(\cdot) \to y''(\cdot) - \gamma y'(\cdot) + \alpha^2 \beta \delta(\alpha \cdot - l) y(\alpha \cdot) - \beta \delta(\cdot - l) y(\cdot).$$

If such an eigenvalue exists then there is a separable solution, $N(t)y(x)$

- Trick is to use the dual problem (Ronald Begg found this), where $m(x,t) = n(x,t)e^{\lambda t}$

$$\begin{cases} \psi''(x) + \gamma\psi'(x) + \alpha\beta\delta(x-l)\psi\left(\frac{x}{\alpha}\right) - (\beta\delta(x-l)+\lambda)\psi(x) = 0 \\ \psi'(0) = 0, \qquad 0 < \psi(x) \in (C \cap W^{2,1} \cap L^{\infty})[0,\infty), \qquad \int_0^\infty \psi(x)y(x)\ dx = 1, \end{cases}$$

has two very useful properties which help in proving the stability of the SSD y.

The following convergence result holds:

$$\int_0^\infty \psi(x)|m(x,t) - ky(x)|\ dx \to 0, \qquad t \to \infty.$$

Wish list….

- Extend to splitting at any size…..

  - although the Basse et.al multi-compartment model collapsed to a single compartment seems to be best match by this:

    “splitting at any size”.

Some preliminary results are in:

Begg R, Wake GC & Wall DJN “The steady-states of a multi-compartment, age-size distribution model of cell-growth”; *Euro J of Appl Maths*, Accepted February 2008.

Summary…

- We have a generic set of simple (?)models for cellgrowth/division
- It can be, and is being used to underpin decision support
- There is plenty of “new mathematics” here

Questions/Comments

- Thank you for your attention!!!!