The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific and
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Workshop on Biomedical Applications of High Energy Ion Beams

Co-sponsored by: ICGEB and University of Surrey

12-16 February 2007

Venue:
Adriatico Guest House Giambiagi Lecture Hall
ICTP, Trieste, Italy

Cell Cycle Models and Modelling Cellular Response to Radiation

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14:00 – 15:30 Cell Cycle Models And Modelling Cellular Response To Radiation

Dr. Norman Kirkby, University of Surrey, U.K.

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Talk Outline

- Ground Rules
- Introduction
- Cell Cycle Modelling: CelCyMUS
- Modelling Cell Survival
- Example Application
- Questions

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Plato's Academy

The inscription above the door read:

"Let no one ignorant of geometry enter here"

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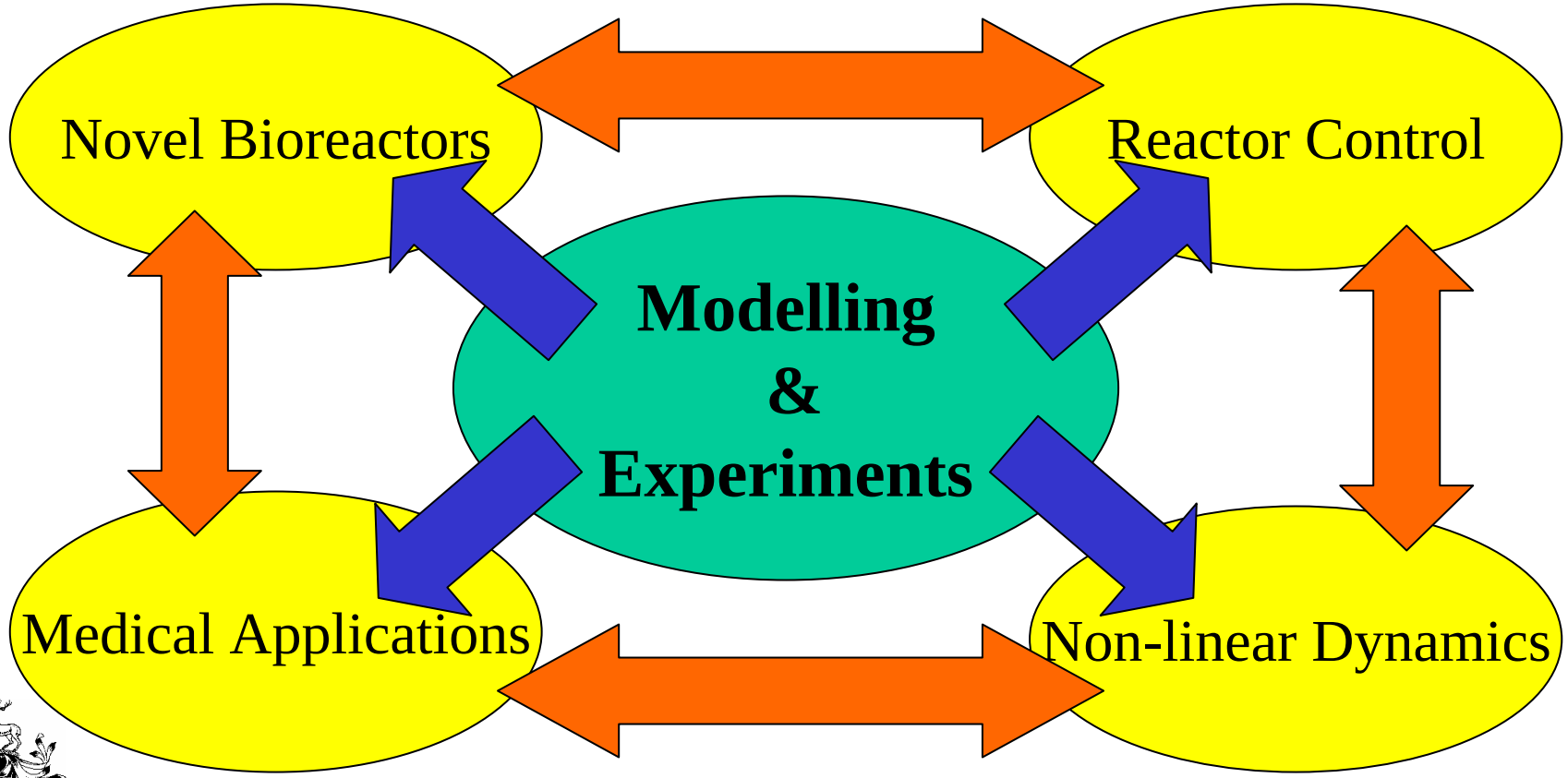
The Bioprocess Engineering Group



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Introduction to Mathematical Modelling

- Encode knowledge
- Design and operation of processes such as radiotherapy
- Fundamental to scientific method

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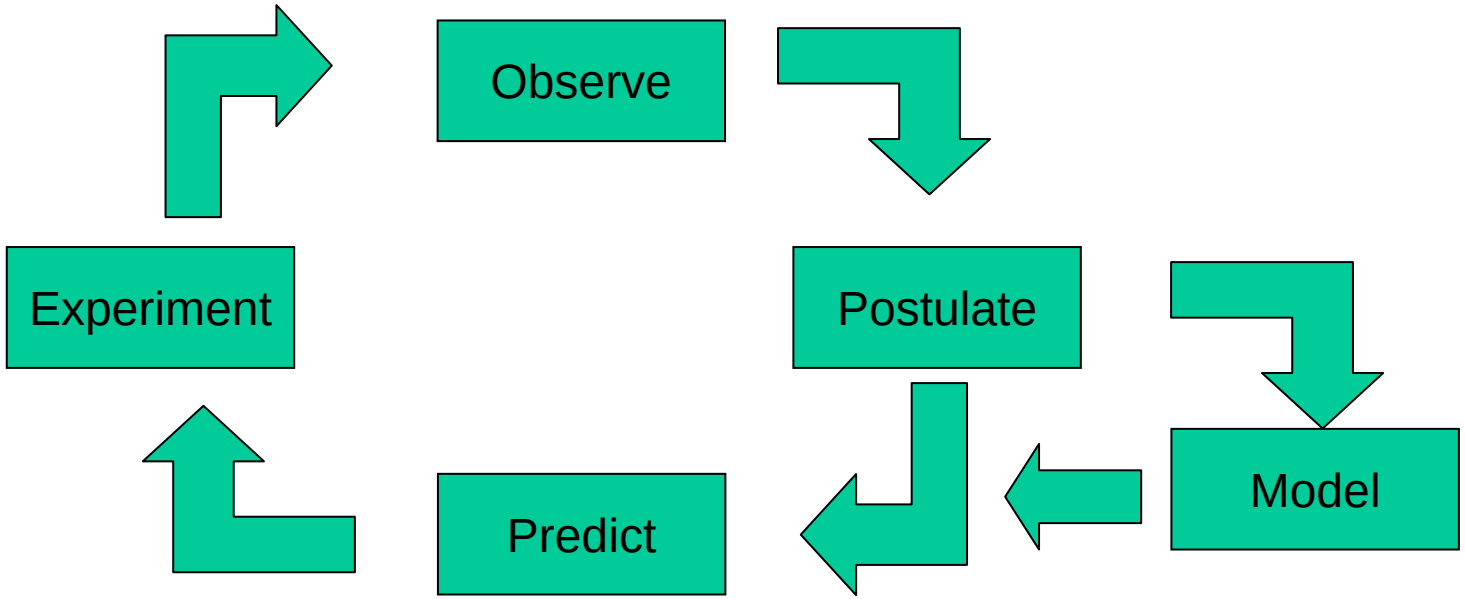
Introduction to Mathematical Modelling



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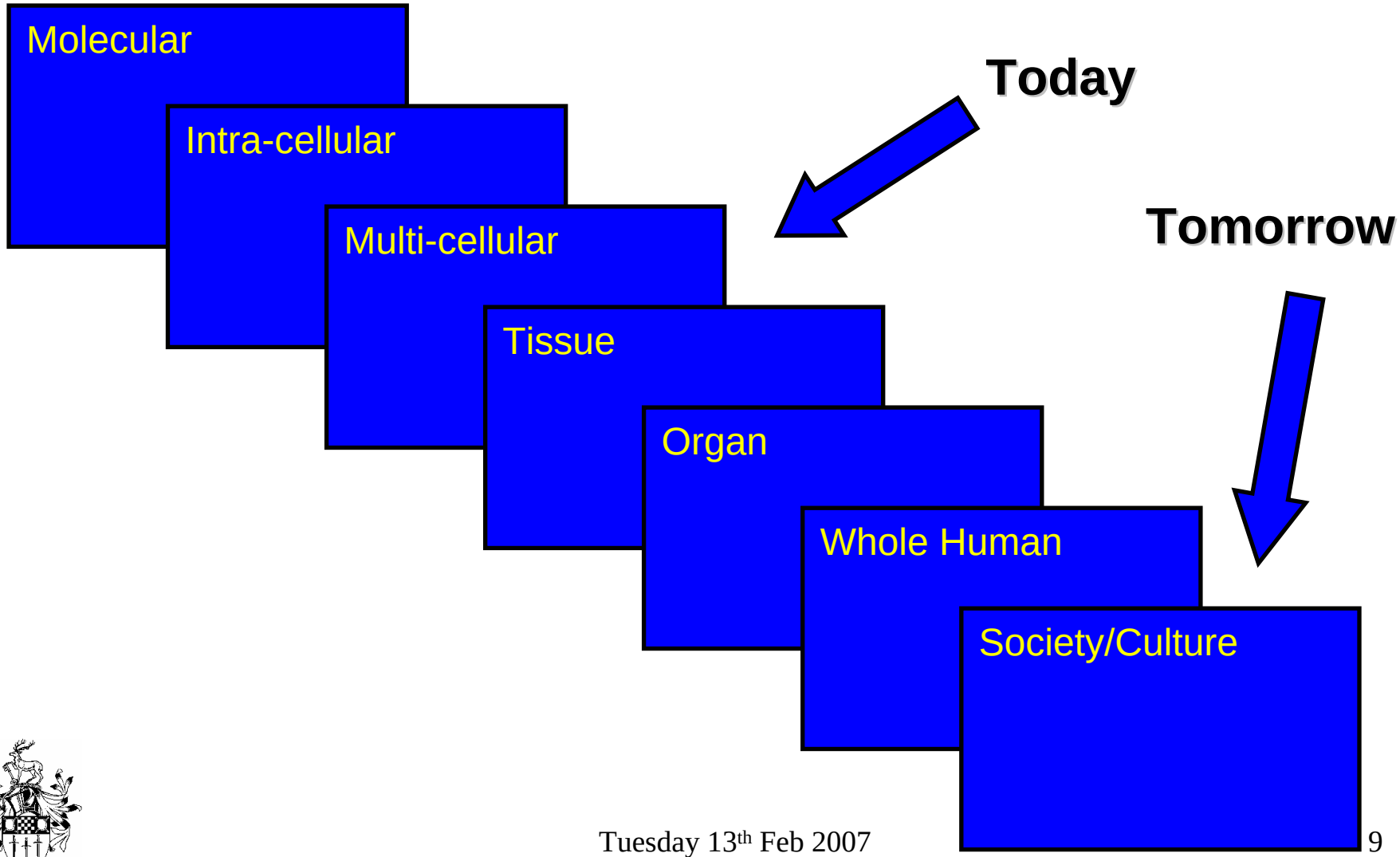
Mathematical Models



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Mathematical Models of Cells

- Cell Cycle Model University of Surrey CellCyMUS
- A model that treats cells as individuals!
- Cells are born, grow, divide, die etc
- A cyclic sequence of growth phases

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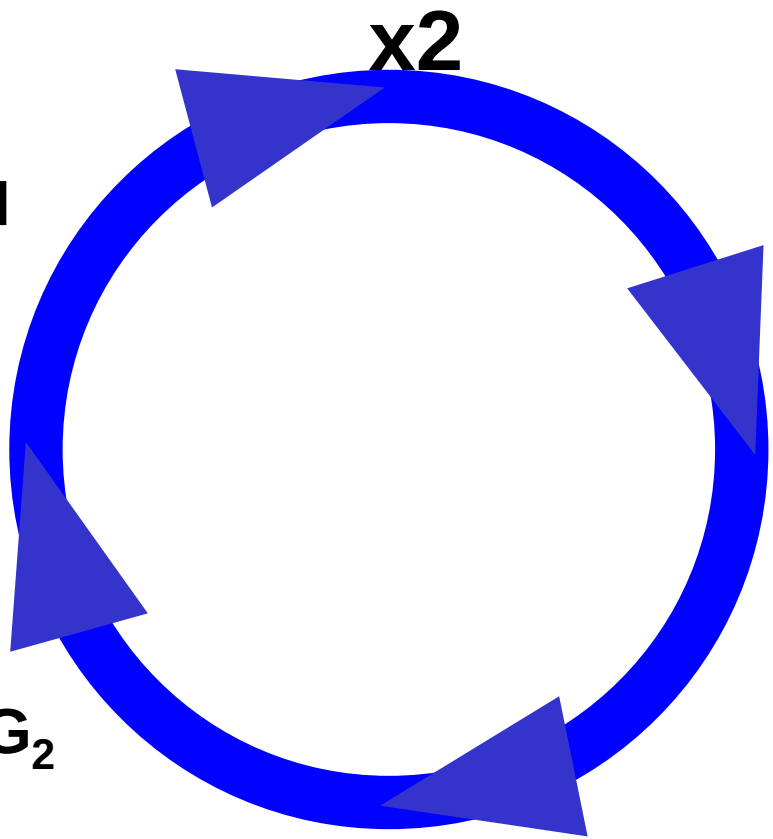
The Cell Cycle



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CelCyMUS

- A generic model
- PYO phases etc
- To build specific models of specific organisms
- Cells get older
- Cells move on to other phases
- Cells wash out of the reactor...

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CelCyMUS Notation / Equations

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- n_x is population density in phase x, per unit volume of space = Cells/m^3/hr
- Time, t, & age within phase x is τ_x
- $n_x d\tau_x$ is the number of cells per unit volume with ages between τ_x and $\tau_x + d\tau_x$

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About Population Balances

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- A number balance on a control volume, V.
- This volume is assumed to be well mixed
- Flow rate F(t) through the system – solvent/serum
- N_{xi} is the population age distribution being convected into the control volume

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About Population Balances

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- Accumulation with respect to time
- Population dynamics
- E.g. how the number of teenagers is varying with time

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About Population Balances

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- The difference between inlet and outlet
- Transition to other phases, e.g. the operation of checkpoints
- Rate of change of population with respect to age

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About Population Balances

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- Variations of population density with age
  - Previous changes in birth rate
  - Age-related transitions

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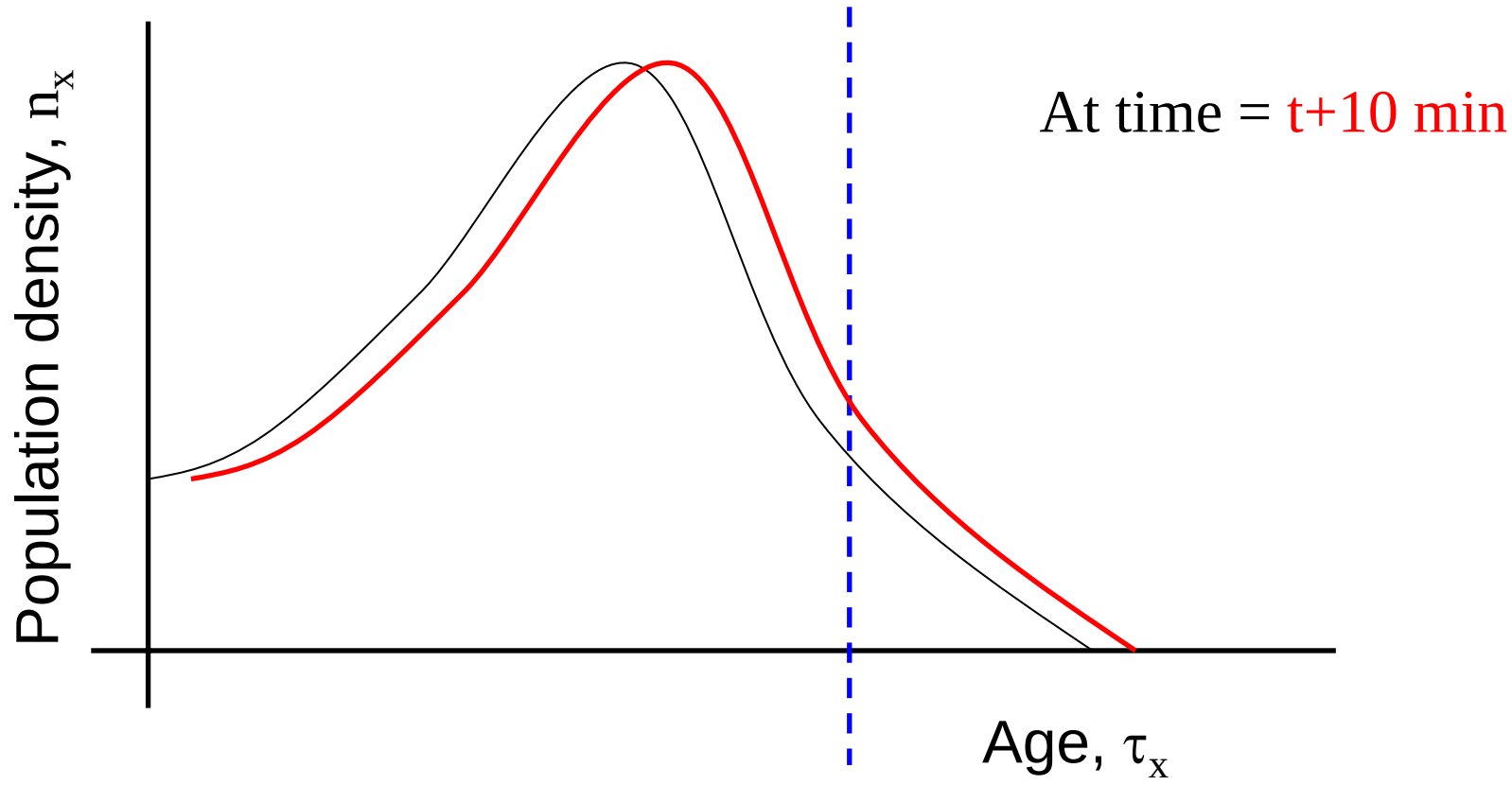
About Population Balances



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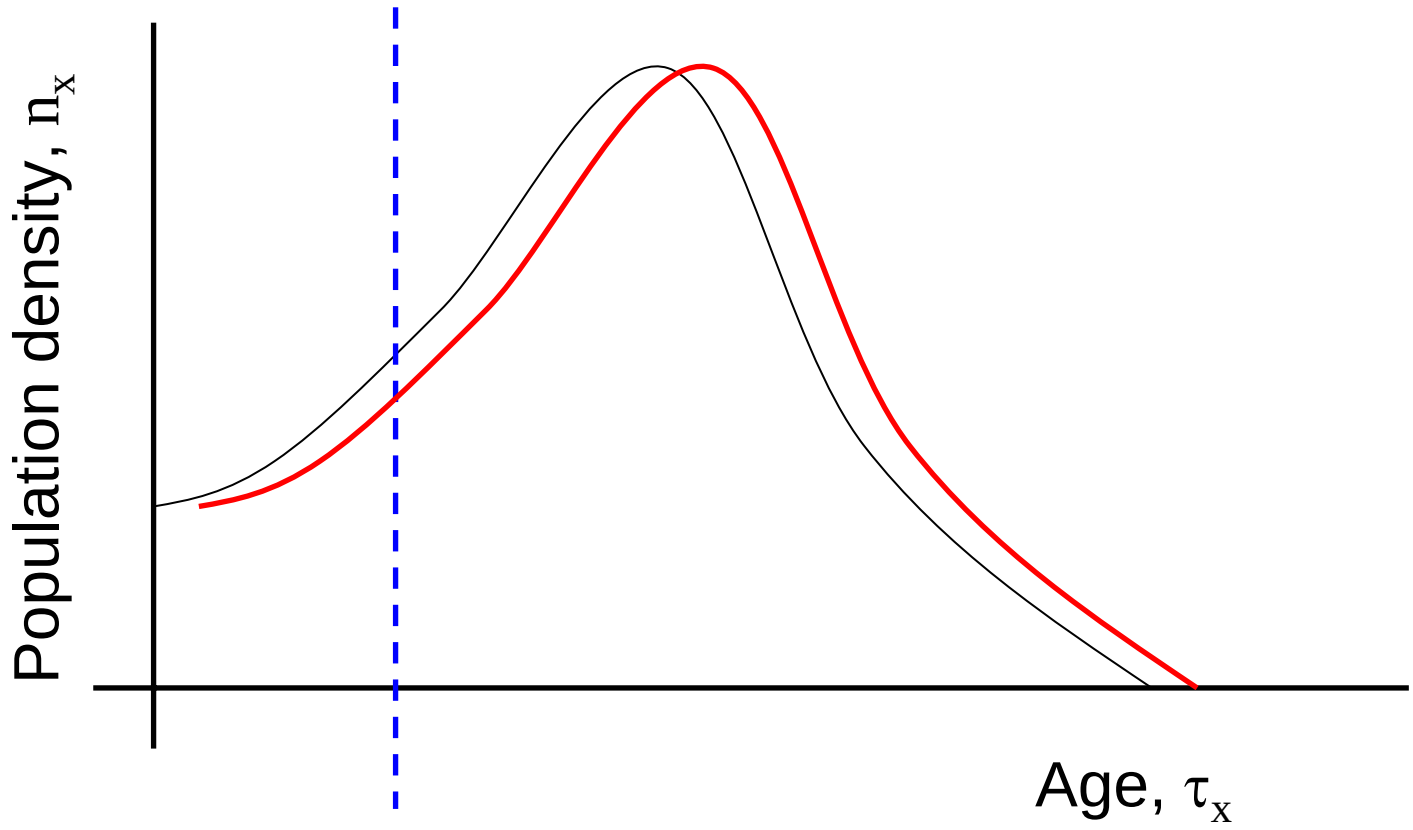
About Population Balances



About Population Balances

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \frac{F(t)}{V}\left(n_x(t,\tau_x) - n_{xi}(t,\tau_x)\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x(t,\tau_x)}{\partial \tau_x}$$

- Variations of population density with age
  - When population density decreases with age accumulation wrt time will be positive if all else is frozen
  - When population density increases with age accumulation wrt time will be negative if all else is frozen

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Transition Rules

$$\frac{\partial n_x(t,\tau_x)}{\partial t} = \ldots_x(t,\tau_x) - \sum_{j=1}^{G_x} r_{jx}(\tau_x, n_x(t,\tau_x), \mathbf{C}_c(t,\tau_x), \mathbf{C}_s(t)) - \frac{\partial n_x(t,\tau_x)}{\partial \tau}$$

G_x rules

$$\sum_{j=1}^{G_x} r_{jx}(\tau_x, n_x(t,\tau_x), \mathbf{C}_c(t,\tau_x), \mathbf{C}_s(t))$$

Popul… den…

Cell S…

Substrate

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Transition Rules

- Operation of checkpoints
- Cell death
  - Starvation
  - Mechanical damage
  - Apoptosis
- Changes of cell state
  - Damage by radiation

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What have we forgotten?

- Position
  - We assume the population is homogeneous in the control volume
- Cell diffusion
  - Fickian
  - Motility, e.g. chemotaxis

Method of Solution

- $n_x(t,\tau_x)$ is a function of time and age
- Apply the chain rule:

$$dn_x = \left(\frac{\partial n_x}{\partial t}\right)dt + \left(\frac{\partial n_x}{\partial \tau}\right)d\tau$$

Method of Solution

- Rearrange for the ‘total derivative’

$$\frac{Dn_x}{Dt} = \left(\frac{\partial n_x}{\partial t}\right) + \left(\frac{\partial n_x}{\partial \tau}\right)\frac{d\tau}{dt}$$

- And compare to our population balance

$$\frac{\partial n_x}{\partial t} = \frac{F(t)}{V}\left(n_x - n_{xi}\right) - \sum_{j=1}^{G_x} r_{jx} - \frac{\partial n_x}{\partial \tau_x}$$

Method of Solution

- Rearrange for the 'total derivative'

$$\frac{Dn_x}{Dt} = \left(\frac{\partial n_x}{\partial t}\right) + \left(\frac{\partial n_x}{\partial \tau}\right)\frac{d\tau}{dt}$$

- And compare to our population balance

$$\frac{F(t)}{V}\left(n_x - n_{xi}\right) - \sum_{j=1}^{G_x} r_{jx} = \frac{\partial n_x}{\partial t} + \frac{\partial n_x}{\partial \tau_x}$$

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Method of Characteristics

- Firstly we note, (with relief…)

$$\frac{d\tau_x}{dt} = 1$$

- We have reduced one PDE to two ODEs
- The total derivative applies along these trajectories

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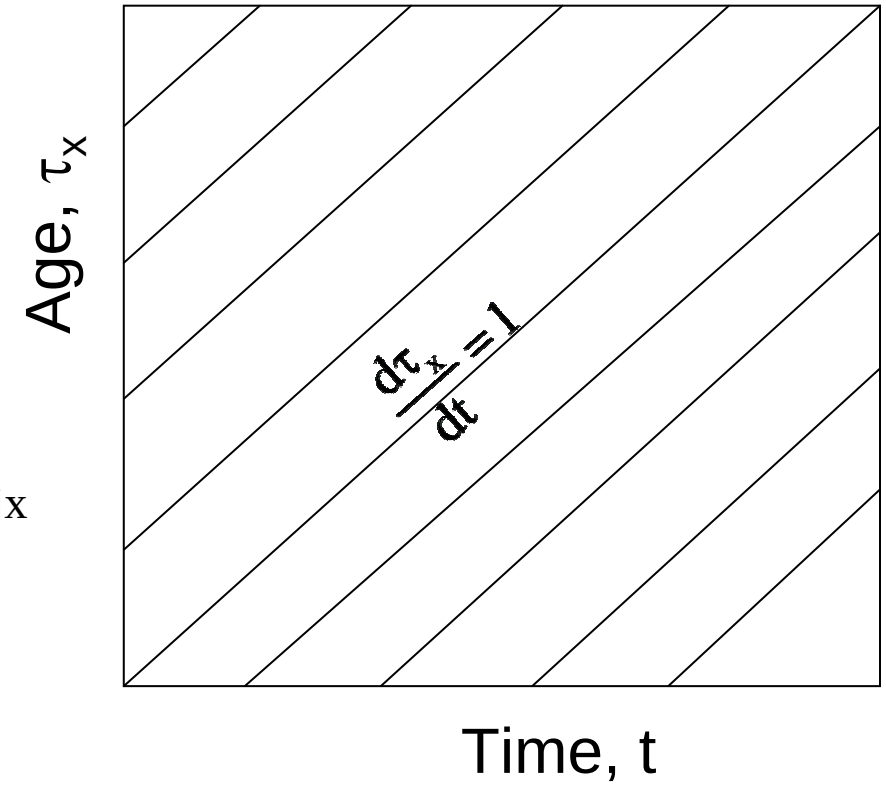
Method of Characteristics

- Along the characteristic ground curves

$$\frac{Dn_x}{Dt} = \frac{F(t)}{V}\left(n_x - n_{xi}\right) - \sum_{j=1}^{G_x} r_{jx}$$



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Numerical Solution

- Integrate the total derivative numerically
- Intermediate function evaluations are expensive
- Currently use Euler

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Cytological State Vector, $\mathbf{C_c}$

- We require rate expressions for input & output.
- We use either simple mass transfer for nutrients, or enzyme kinetics
- Each cell is a batch reactor

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Medium State Vector, $\mathbf{C_s}$

- We write dynamic material balances for each component in the medium
- We calculate uptake (or production) by summation of the rates for every cell

In = Out + Acc wrt time + Destroyed by cells + Destroyed by reaction

$$FC_{sF} = FC_s + V\frac{dC_s}{dt} + V\sum_{i=1}^{i=N_X}\left\{\int r_{si} n_i d\tau_i\right\} + Vr_s'$$

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Simulations

- Computer program input
  - Initial age distribution
  - Parameters of each transition rule, for every cell cycle phase
  - Cell destination from each transition rule

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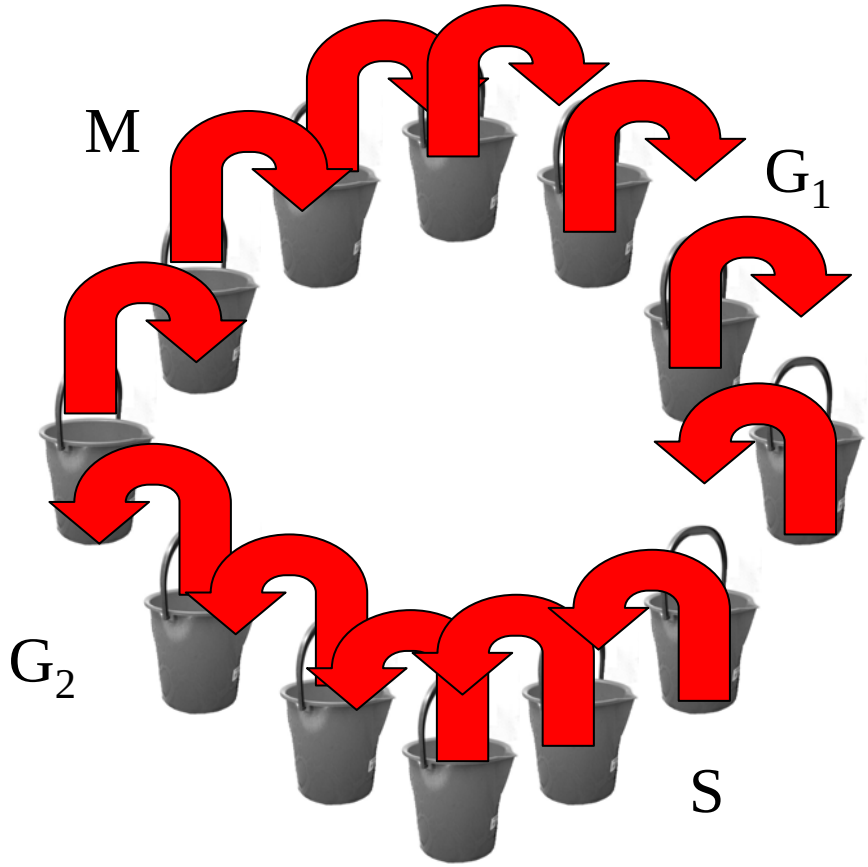
Simulations



Each bucket contains cells of a different age

At each time step cell move from one bucket to the next

Unless they are removed or destroyed

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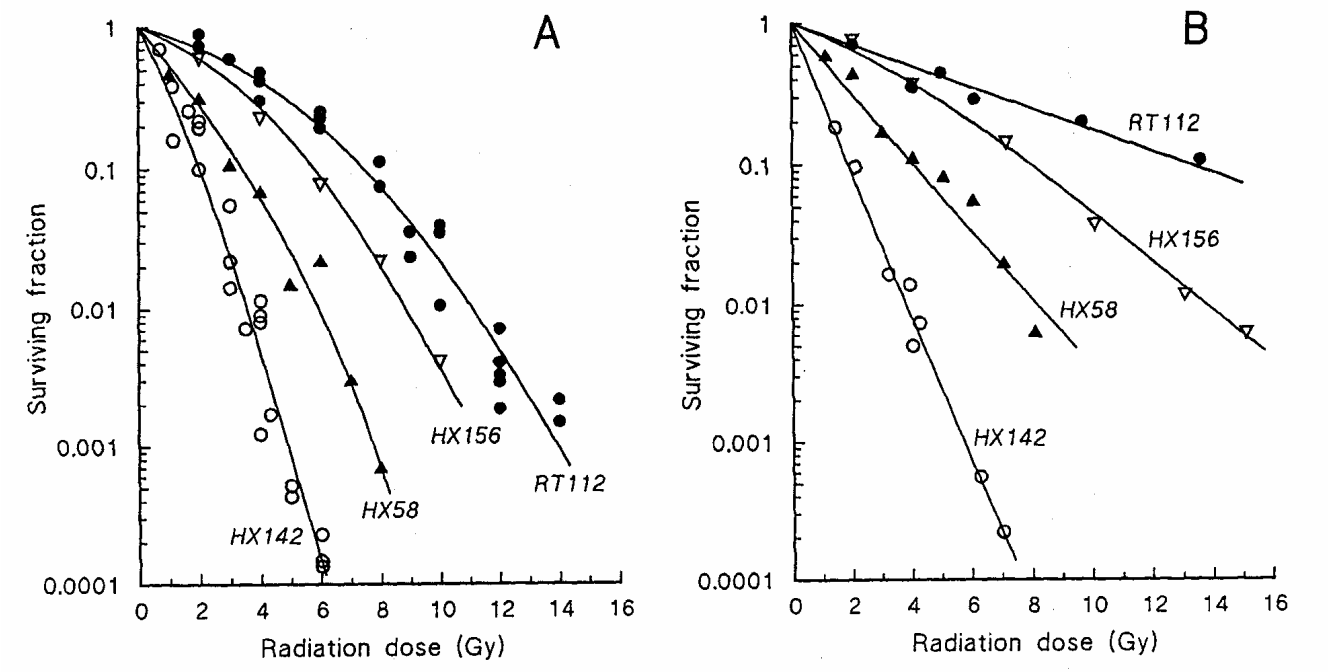
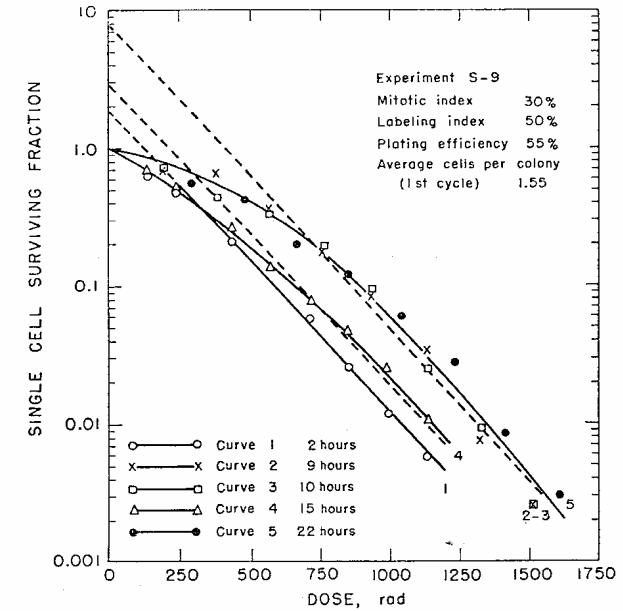
Modelling the Effect of Radiation

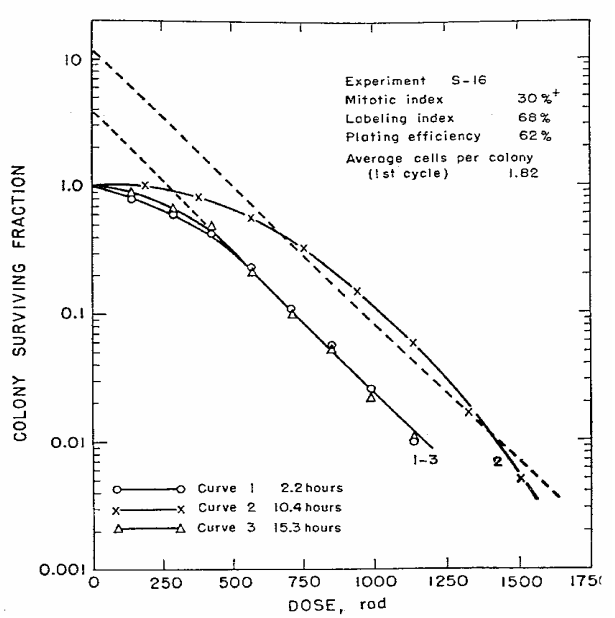
- Cell survival depends on cell line



Modelling the Effect of Radiation

- Cell survival depends on location in cell cycle
  - Sinclair and Morton 1965





Radiation Models

- Linear quadratic

$$S_f = \exp(-\alpha D - \beta D^2)$$

- Low dose hypersensitivity

$$S_f = \exp(-\alpha_R \left\{1 + \left(\frac{\alpha_R}{\alpha_S}\right) \exp\left(\frac{-D}{D_c}\right)\right\} D - \beta D^2)$$

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Morgiane's Model

- Below some critical dose, Dc, any given cell follows a 'sensitive' LQ
- Above the critical dose, the same cell would follow a 'resistant' LQ
- The critical dose is normally distributed in a population of cells

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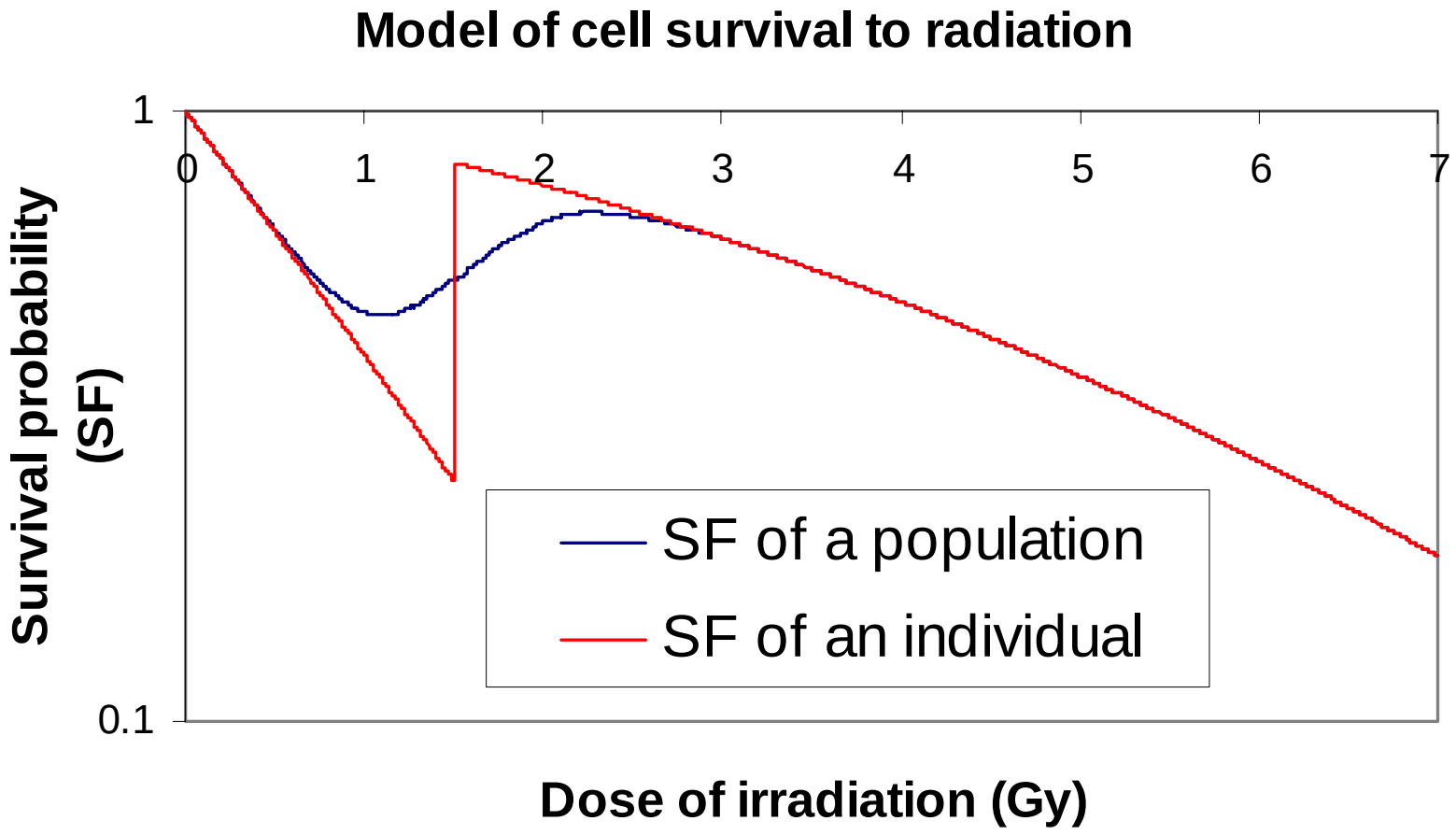
Low-Dose Hypersensitivity



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Worked Example

- Cell cycle model for ‘normal’ and ‘irreparably-damaged’ cells
- Cell cycle data for distribution of SF vs dose around the cell cycle
- Real and proposed radiation fractionation schedules

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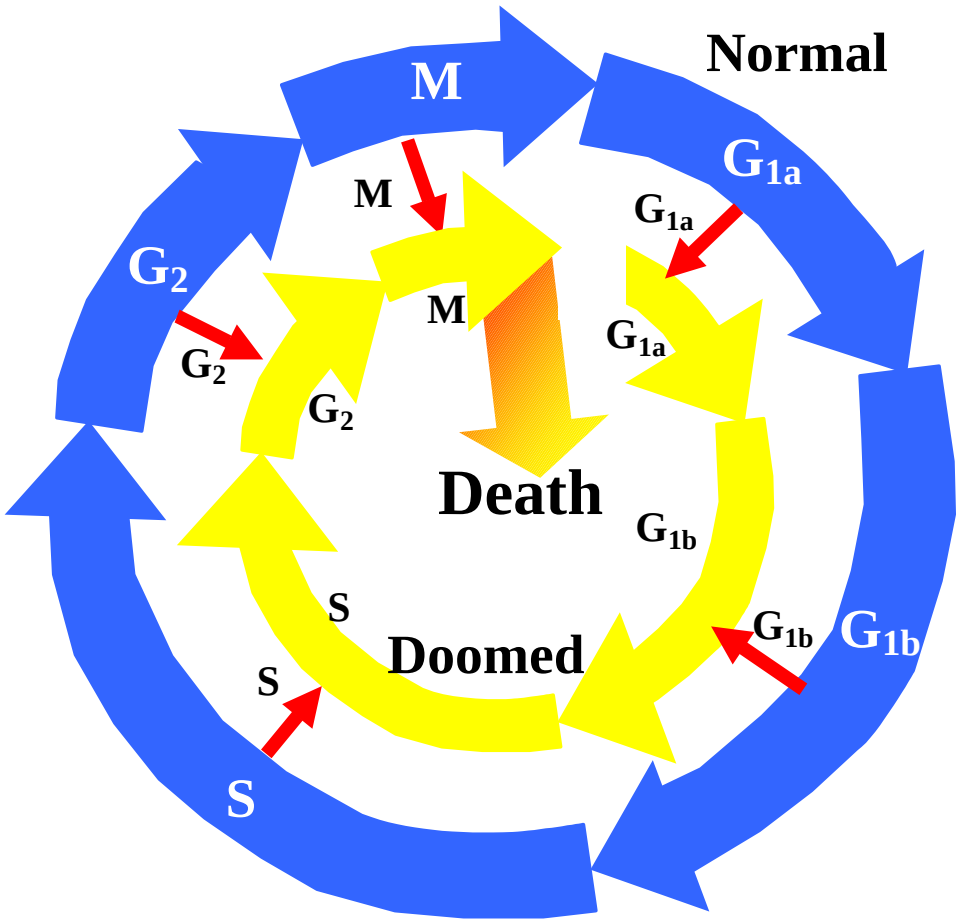
The Cell Cycle



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Controlling Growth Rate

- No diffusion or nutritional limitations
- Phase durations could be extended
- Use proliferation factor
  - not all daughters are viable
  - some detach from the tumour
  - some attacked by immune system ...

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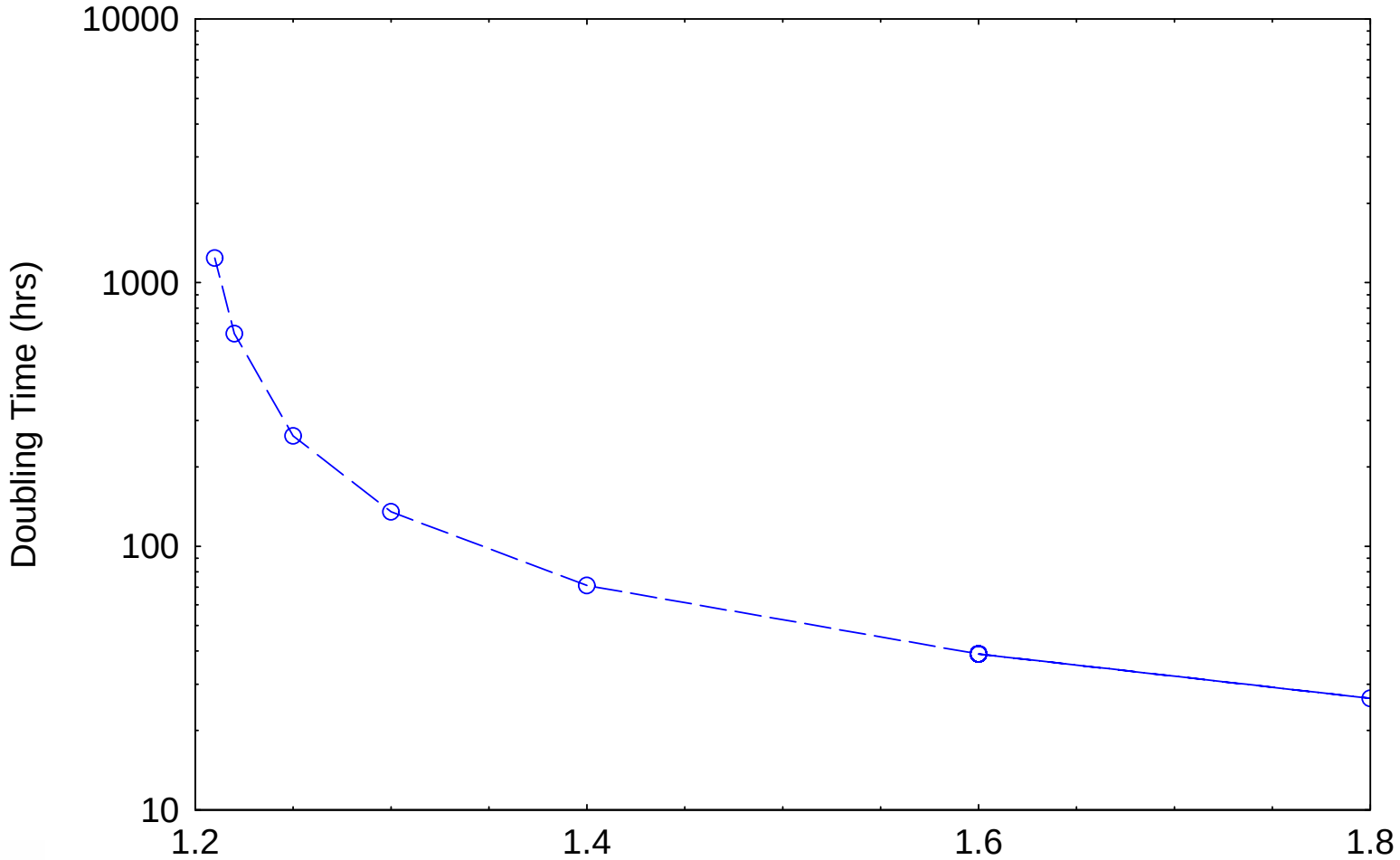
Controlling Growth Rate



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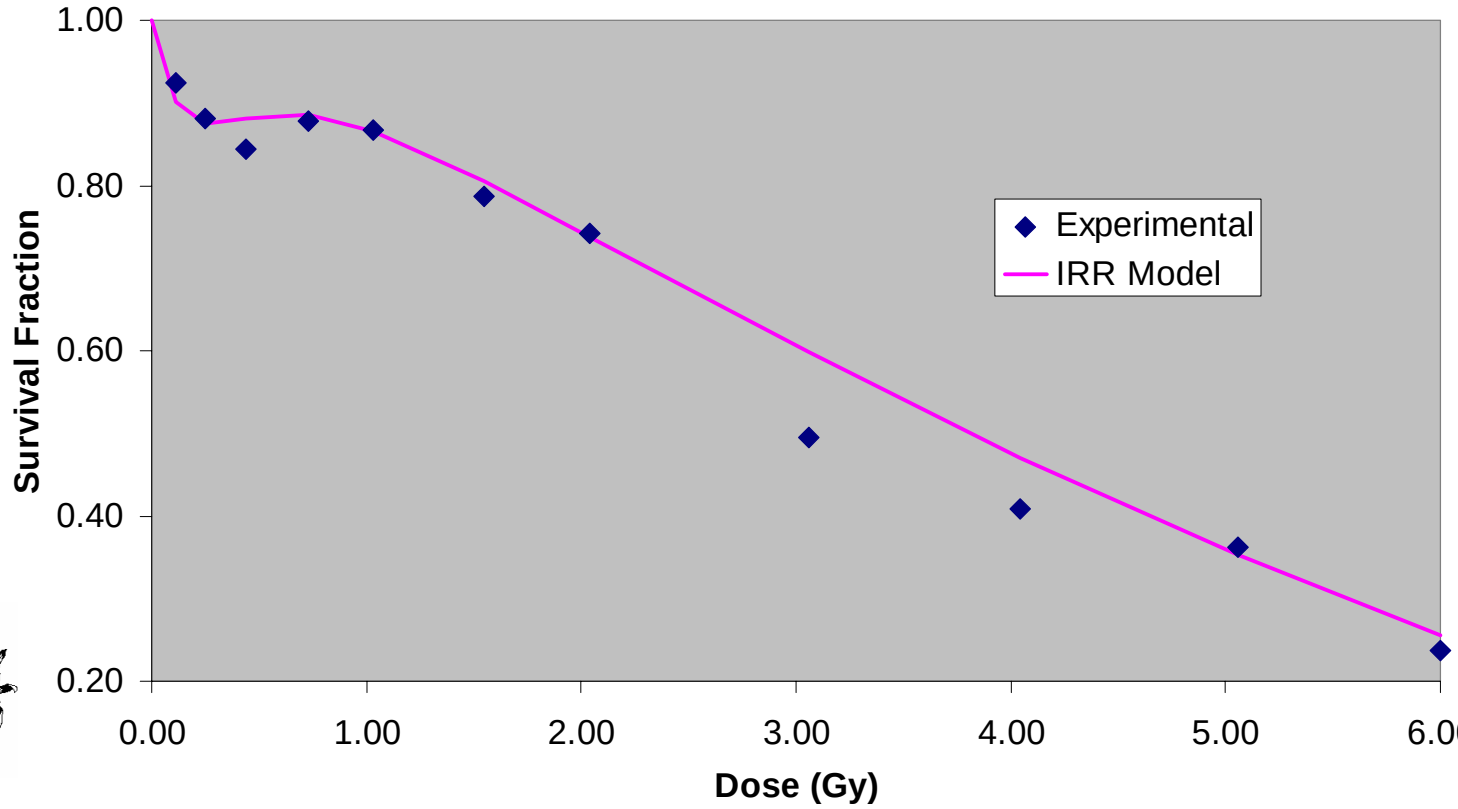
Experimental Data for T98G

- Whole population
  - Expt data from Short, Mitchell, Boulton, Woodcock & Joiner, Int J Rad Biol,1999, 75(11),pp1341 - 1348. IRR fitted to whole population



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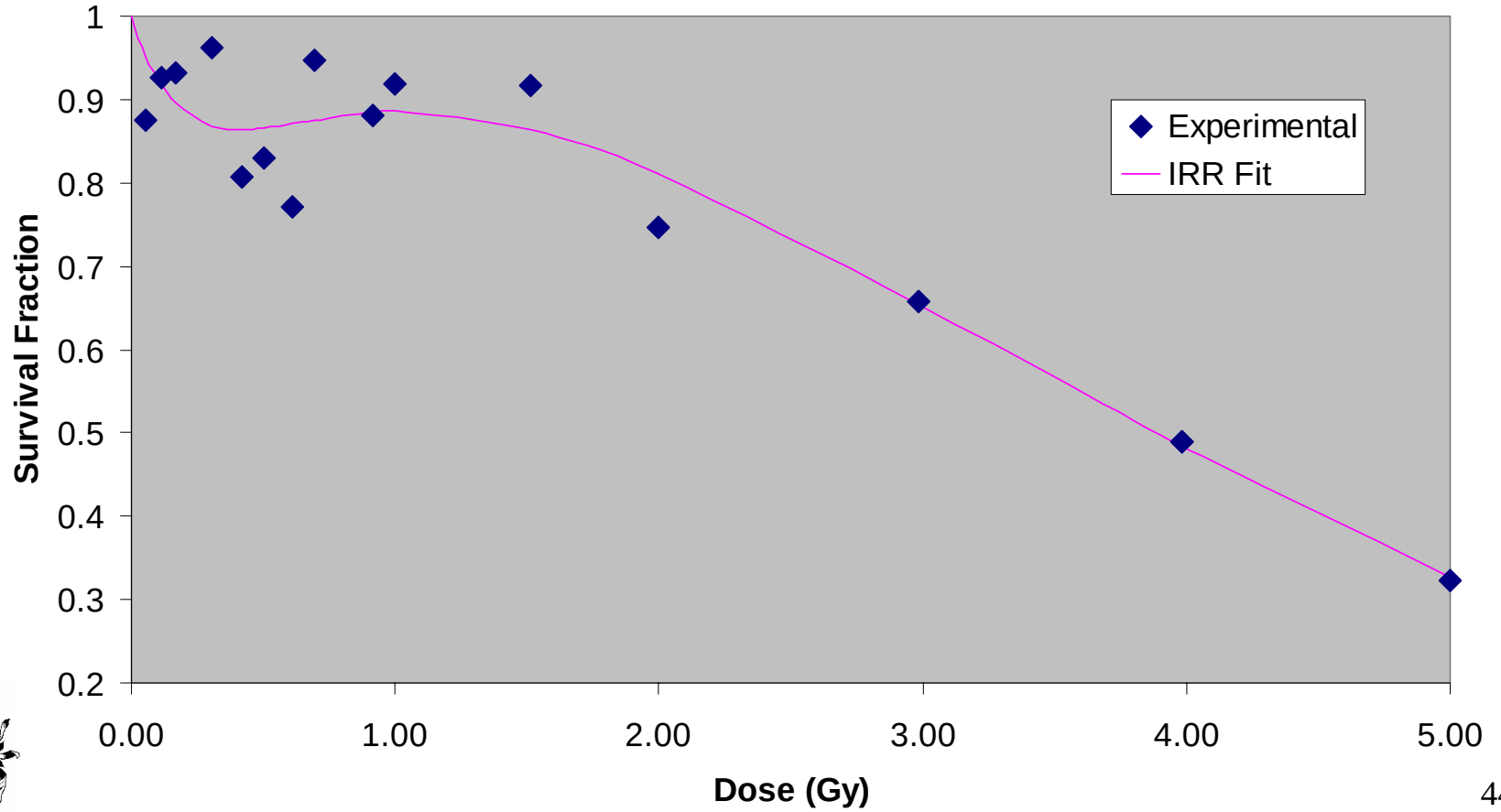
Data for Phases of T98G

- experimental and fitted curves for G1 phase



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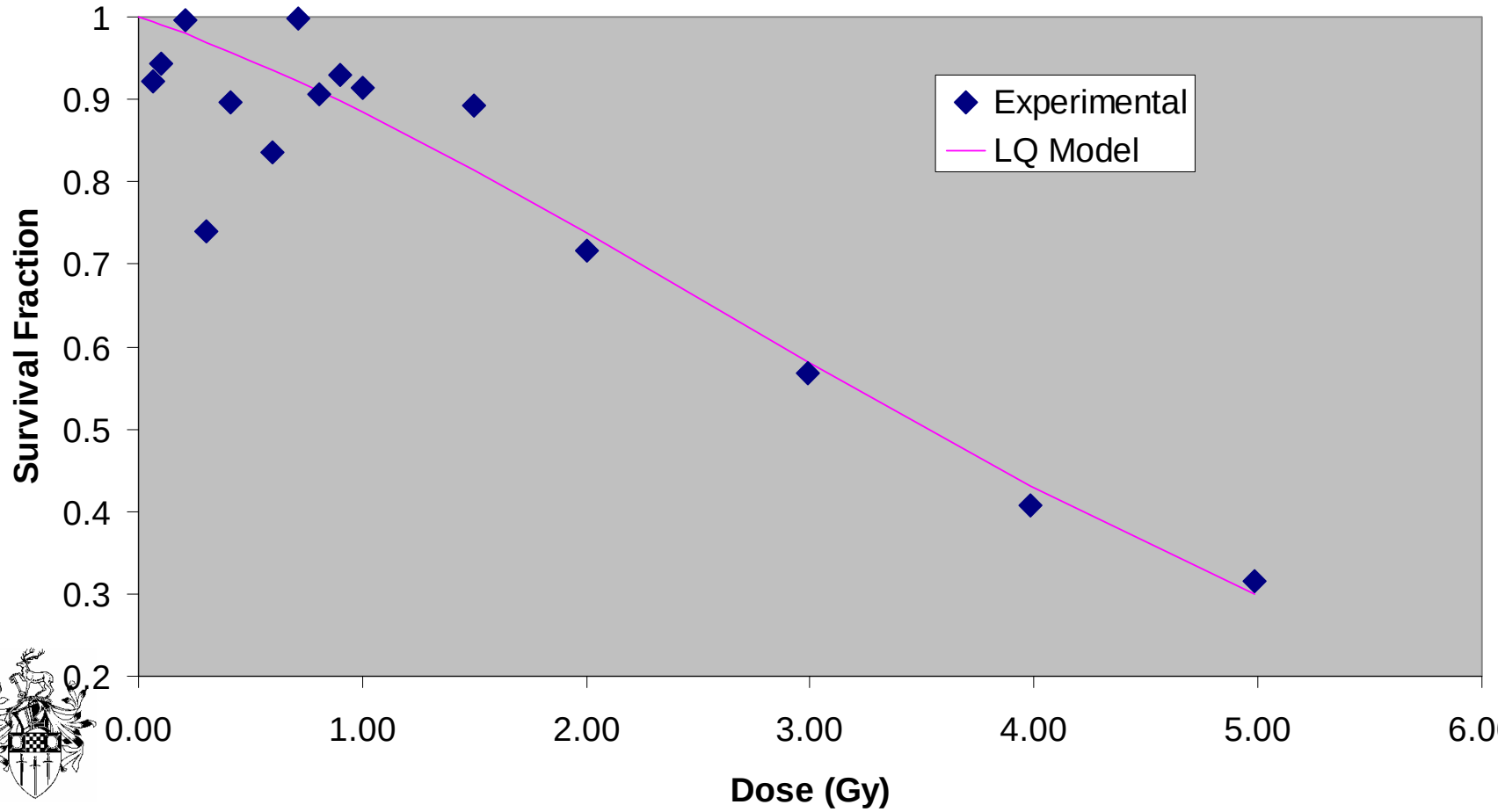
Data for Phases of T98G

- experimental and fitted curves for S phase



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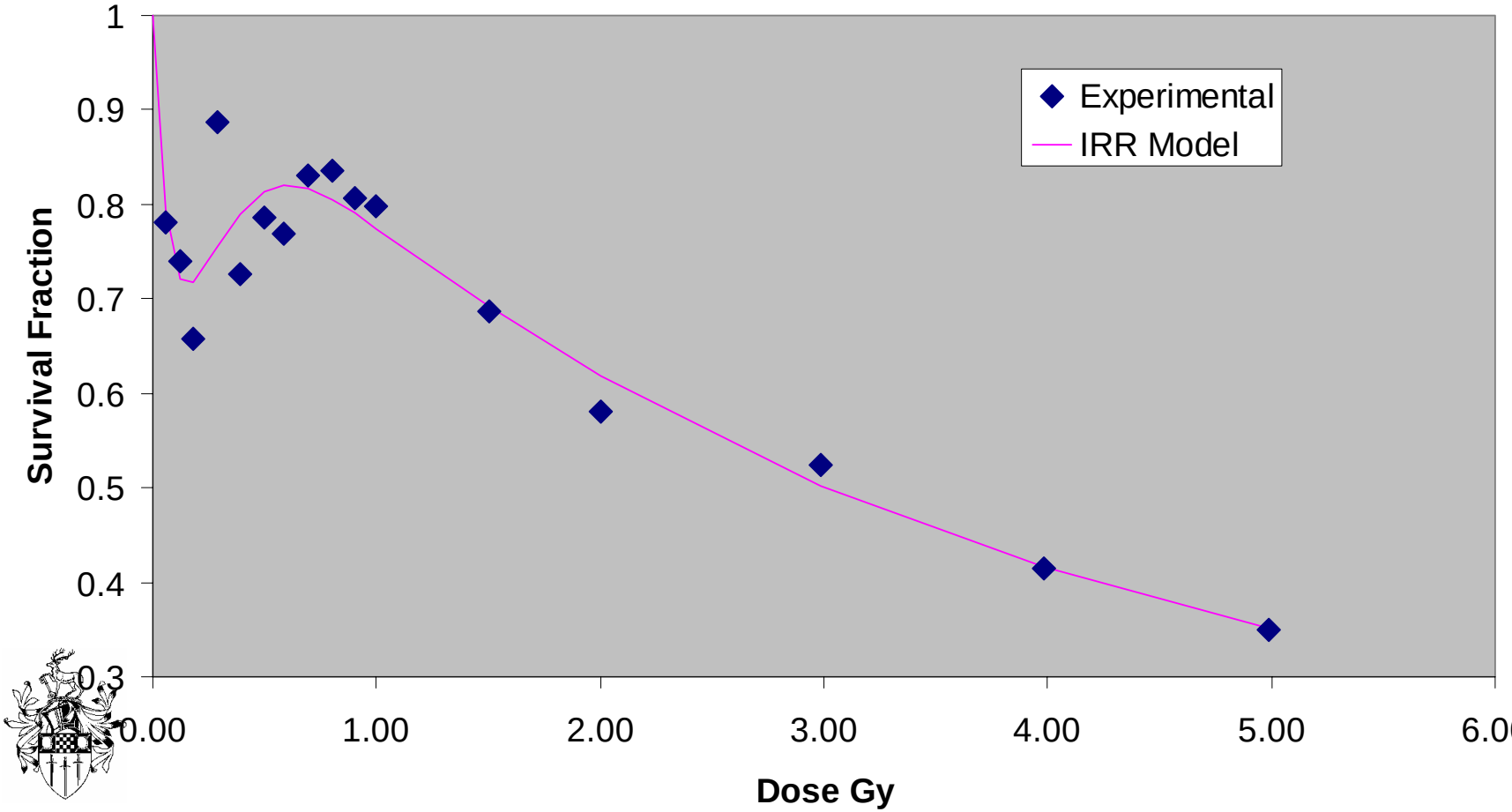
Data for Phases of T98G

- experimental and fitted curves for G2 & M



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Clinical Treatment Strategies

- Conventional
  - 2 Gy/day in one fraction
  - Monday - Friday
  - 6 weeks = 60 Gy total
- CHART - Continuous Hyperfractionated Accelerated Radio Therapy
  - 3 fractions/day of 1.5 Gy each (08.00, 14.00, 20.00)
  - Every day (incl Saturday and Sunday)
  - for 12 days = 54 Gy total

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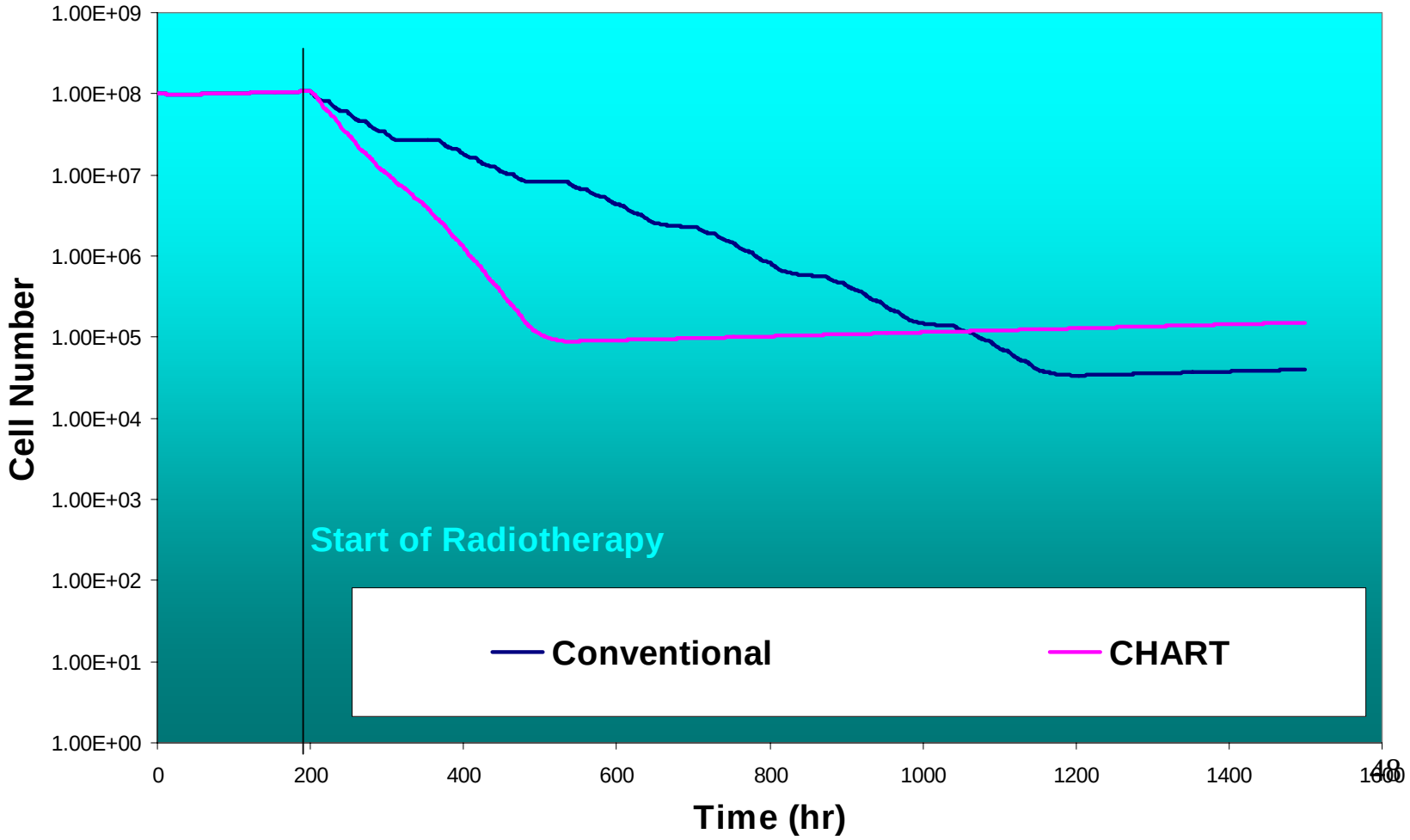
Slow Growing T98g Response To Radiotherapy



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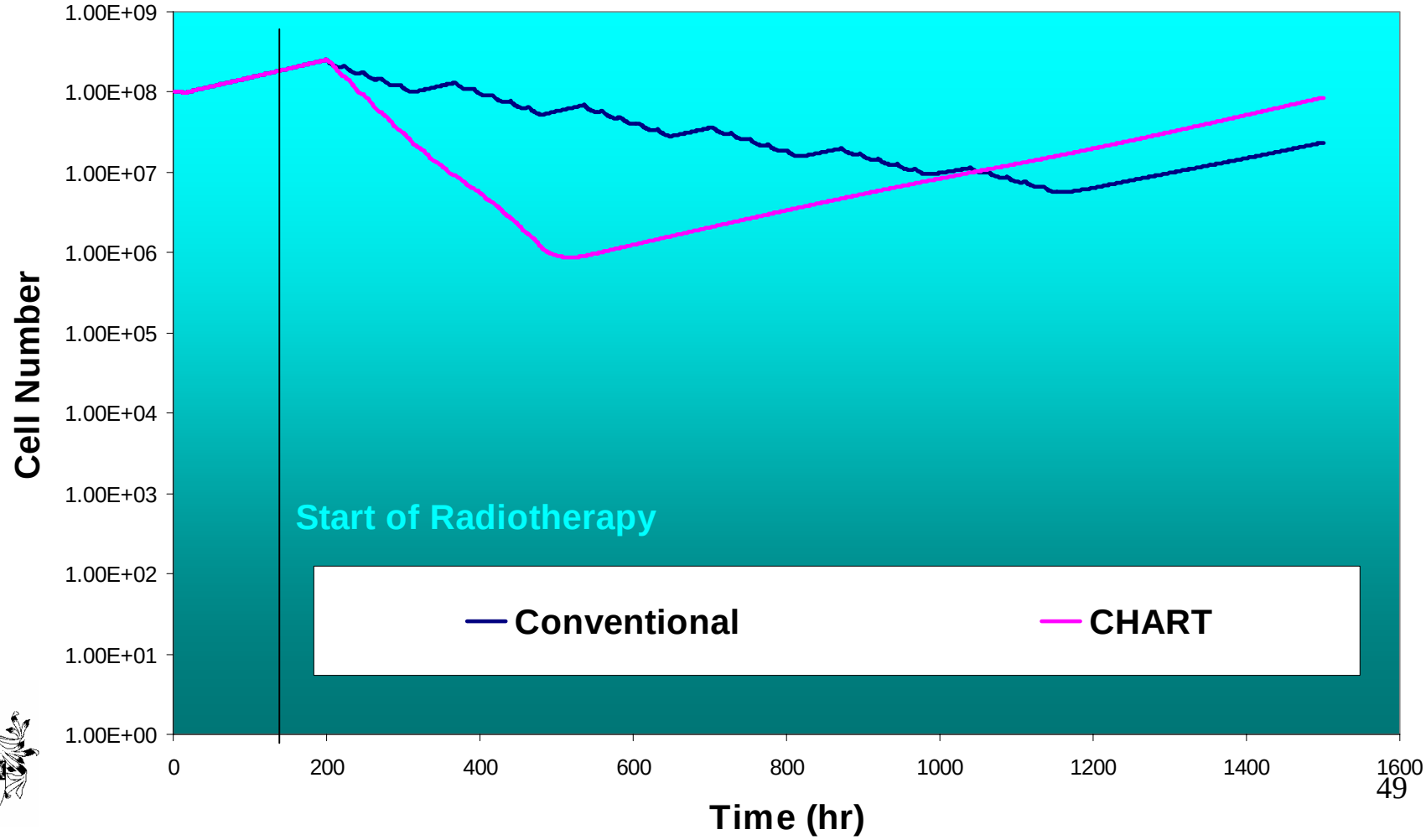
Fast Growing T98g Response To Radiotherapy



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Discussion

- Slow T98G tumour has higher chance of complete cure with conventional strategy
- Fast T98G tumour has a better chance of complete cure with CHART
- If cure not achieved CHART leaves the larger T98G tumour in the long run.

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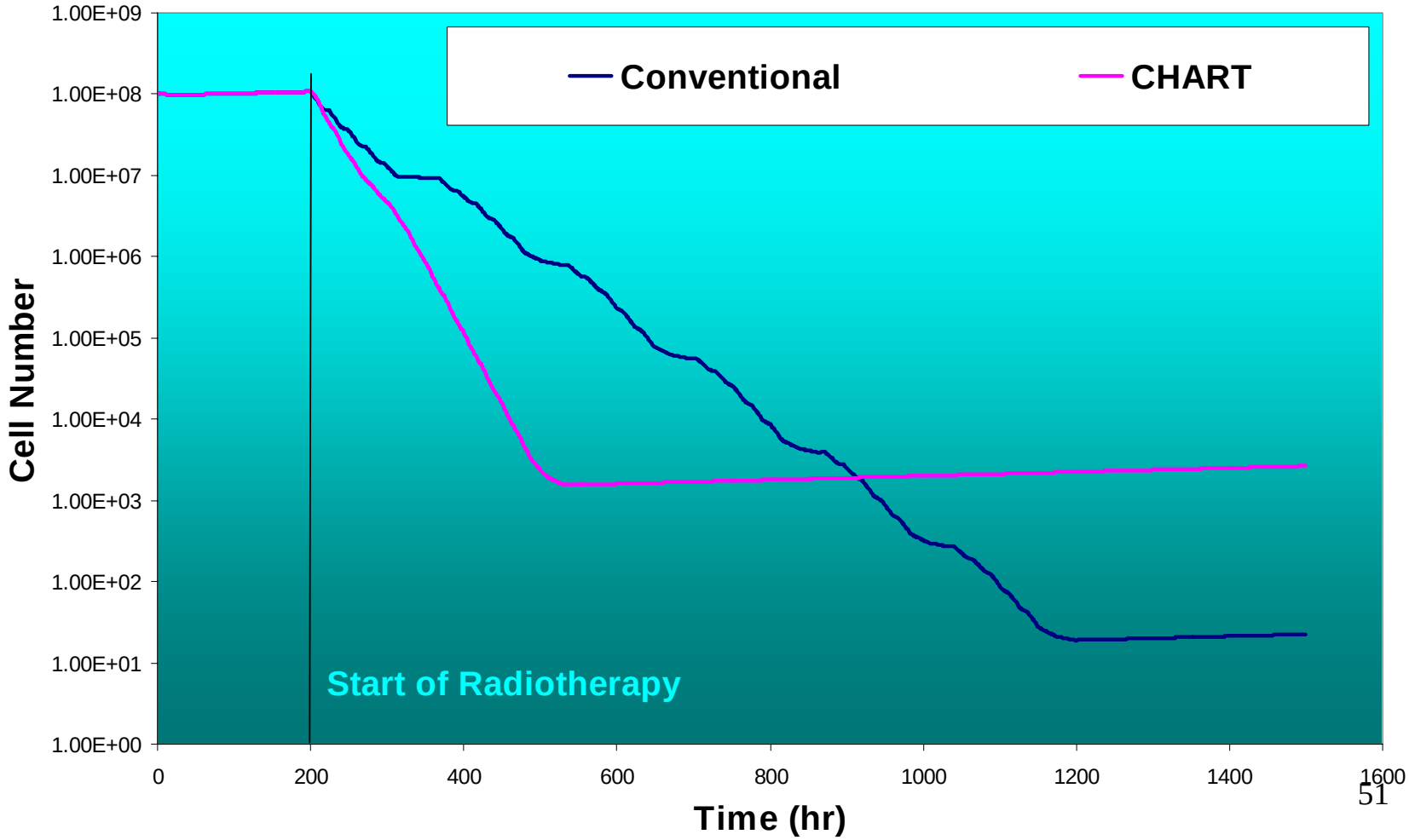
Slow Growing U373 Response To Radiotherapy



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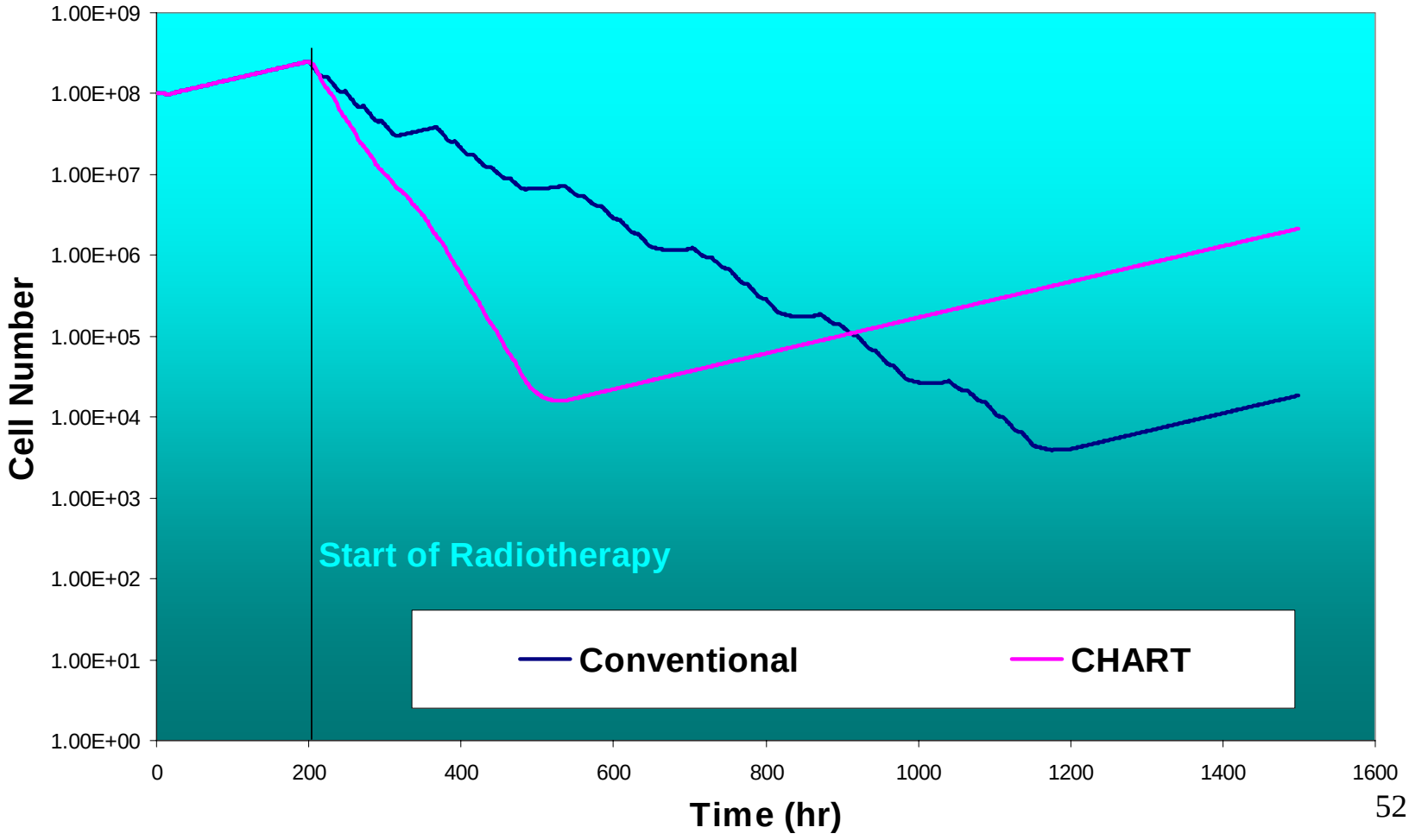
Fast Growing U373 Response To Radiotherapy



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Discussion

- Slow and fast U373 tumour has higher chance of complete cure with conventional strategy
- If cure not achieved CHART leaves the larger U373 tumour in the long run.

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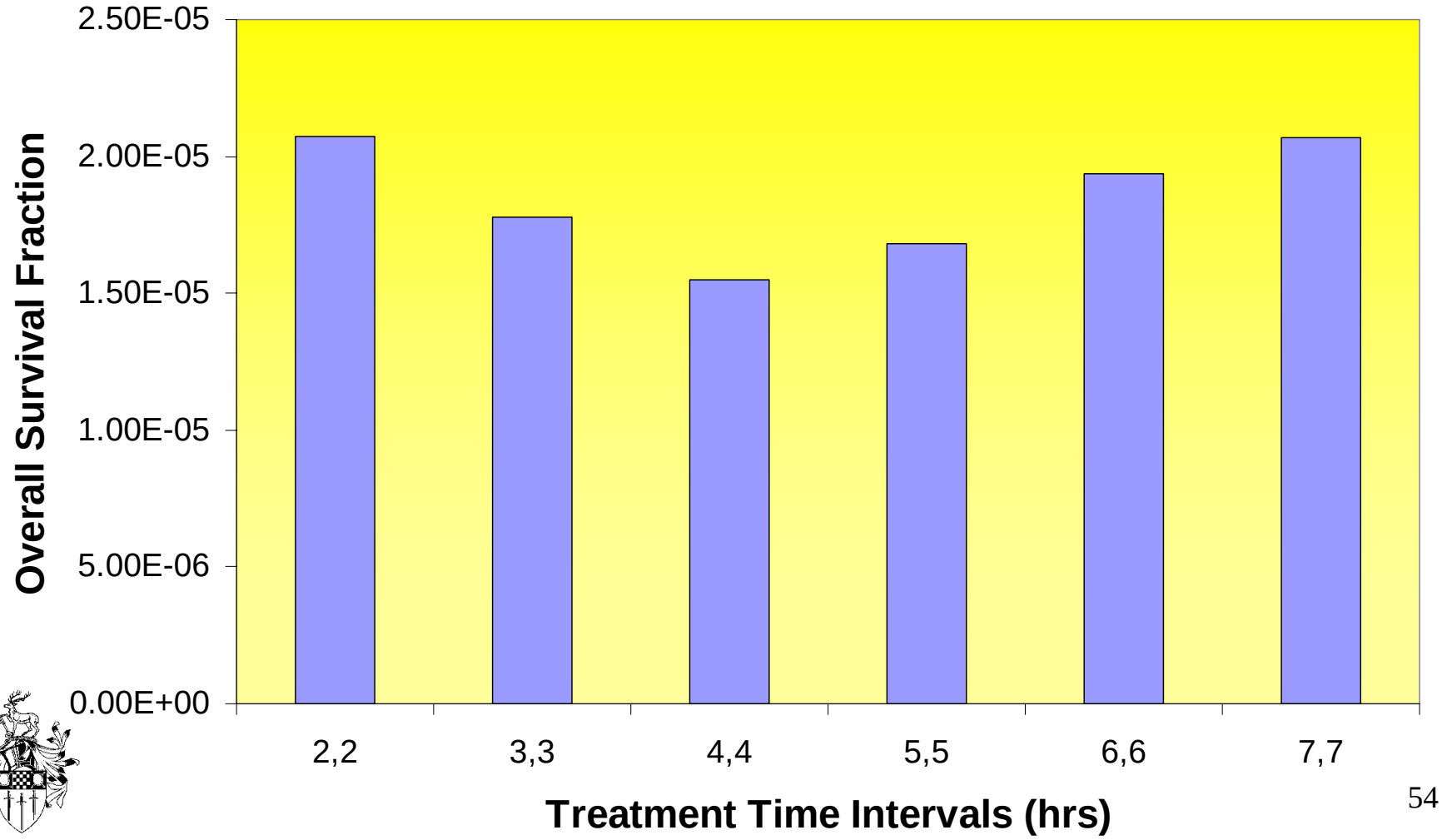
Effect of CHART intervals



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Conclusions

- We have assembled a flexible and general model for simulation of radio-therapy
- We can already simulate known, existing clinical features of conventional radio therapy and CHART

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Future Work

- Add structure in space & diffusion of oxygen, nutrients and cells
- Add hypoxic and necrotic phases
- Refine survival models incorporating dose rate
- Refine survival models for HRS
- Add survival models for ion beam therapy
- Stem cell populations

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Summary

- Cell populations can be modelled to include cell cycle effects
- Simulation is a powerful tool to check understanding, completeness and consistency of data

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Deficiencies and Disadvantages

- There is no simple way to allow the development or destruction of spatially organised tissue
  - Cellular automata are the future…

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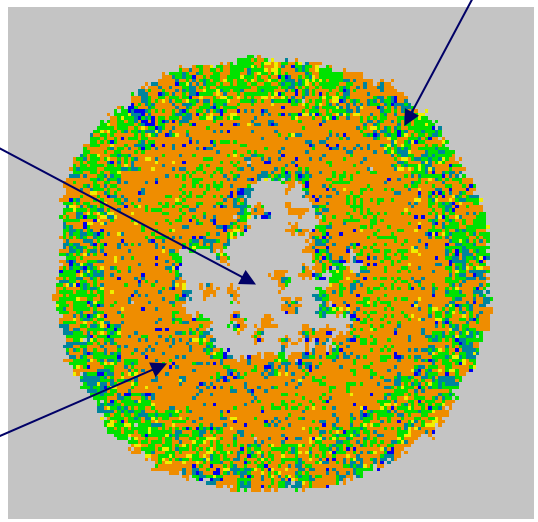
Cellular Automata Models

Growth of glioma cells at 72 days

Proliferative rim

Necrotic core

Quiescent cells



660μm

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Deficiencies and Disadvantages

- There is no direct ‘patient outcome’ that can be related to clinical trials
  - But this I will cover tomorrow!

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Collaborators

- Paul Hayter
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- David Faraday
- Sónia Araújo
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- Tigran Arzumanov
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- Kevin Prise
- Melvyn Folkard
- Roger Webb
- Karen Kirkby

- M Eng Projects
  - Roos Wulan
  - Graham Moffat
  - Anthony Skadorwa
  - Femi Oluboyede
  - Malak Hamden
  - Asli Tamer
  - Ollie Jones

Lab Manager: Bryan Underwood

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- Marie Curie Research Training Network "Cellion"
- The Gray Cancer Institute
- Surrey Ion Beam Centre
- School of Engineering, Surrey

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Thank you for listening

Questions

"All models are wrong but some are useful"
G. E. P. Box