The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific and
Cultural Organization

IAEA
International Atomic Energy Agency

310/1828 310/9

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

Modelling Patient Outcomes to Radiotherapy

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11:00 – 12:30 Modelling Patient Outcomes to Radiotherapy

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

The Abdus Salam International Centre for Theoretical Physics

United Nations Educational, Scientific and Cultural Organization

International Atomic Energy Agency

Wednesday 14th Feb 2007

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Talk Contents

- Background
- BJJK model
  - Model of a patient & treatment
  - Model of a population of patients
  - Optimisation: fitting to clinical trials
- Results
- Conclusions and Future Work
- Questions

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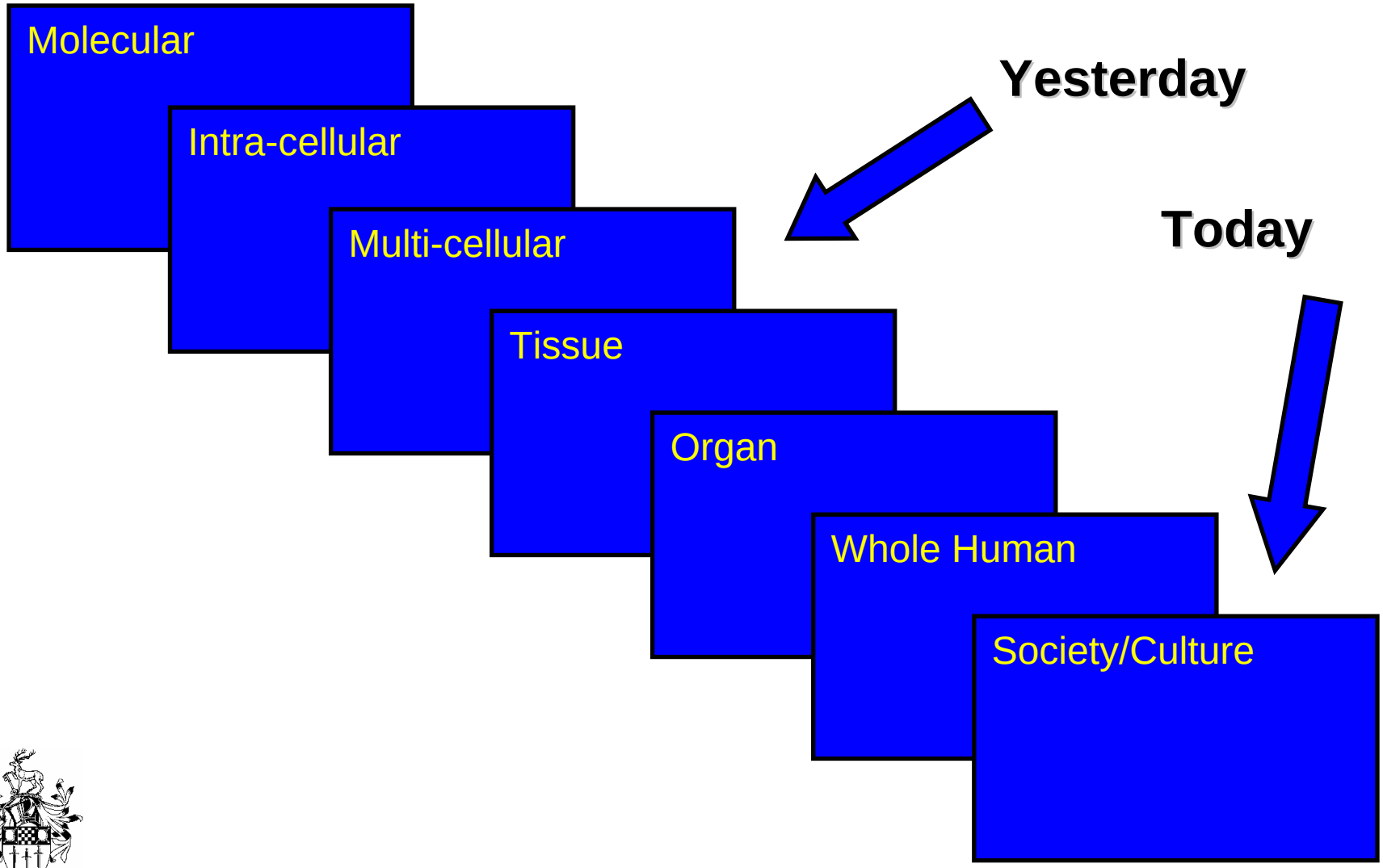
Mathematical Models



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EPSRC
Engineering and Physical Sciences Research Council

Background

- Discipline Hopping grant from the Life Sciences Interface of the Engineering and Physical Sciences, BBSRC and MRC
- One year working ‘out of discipline’
- What can I take to the new discipline
- What can I return with from the experience?

MRC Medical Research Council

bbsrc

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"What committee in its right mind would take a Chemical Engineer and use tax-payers money to put him in a clinical neuro-oncology team for a year?"

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Cancer

- There are about 350,000 new cases of cancer in the UK per annum
- Lung, breast, colorectal and prostate account for the vast majority.
- There are about 4000 new cases per year of brain cancer of which 2000 are grade 4 glioblastoma.
- Average years of life lost per patient is higher for GBM than any other cancer
- 50% patients are dead in 9 months

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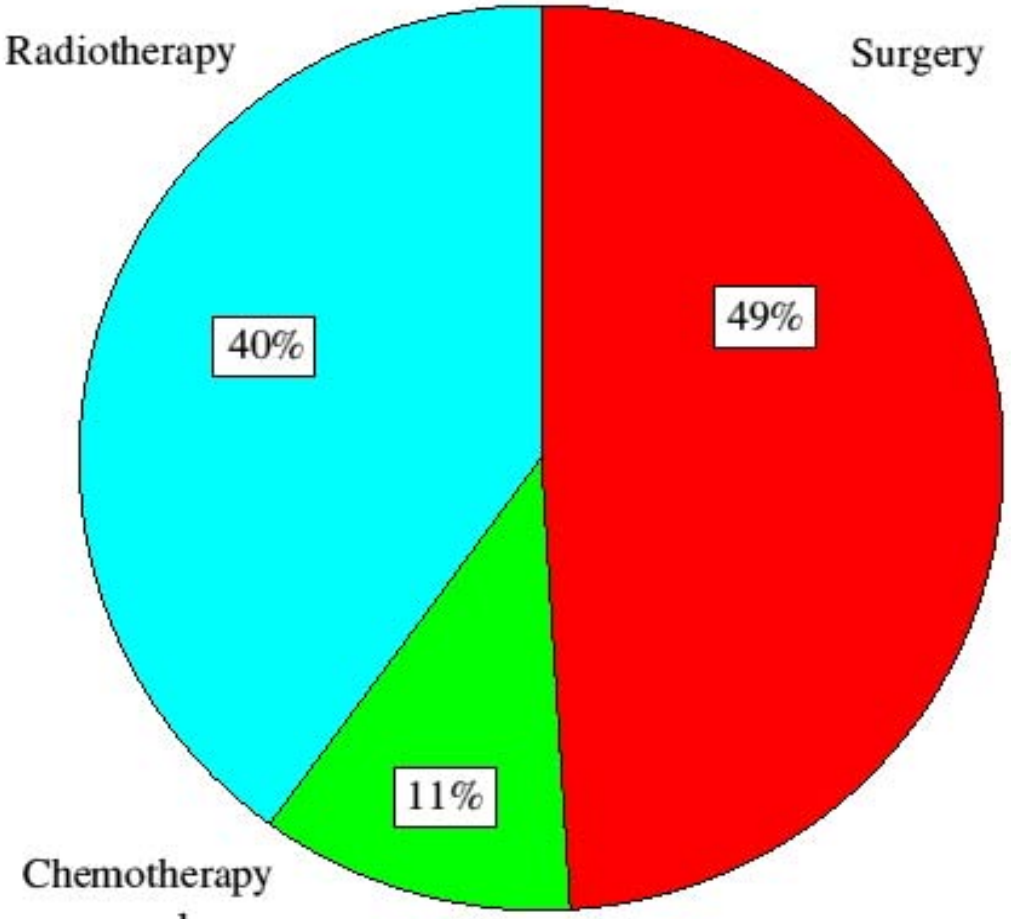
Treatment Cures



Chemotherapy
- alone
- with surgery
- with radiotherapy

Reference
Cancer Services Collaborative 2002
www.nhs.uk/npat

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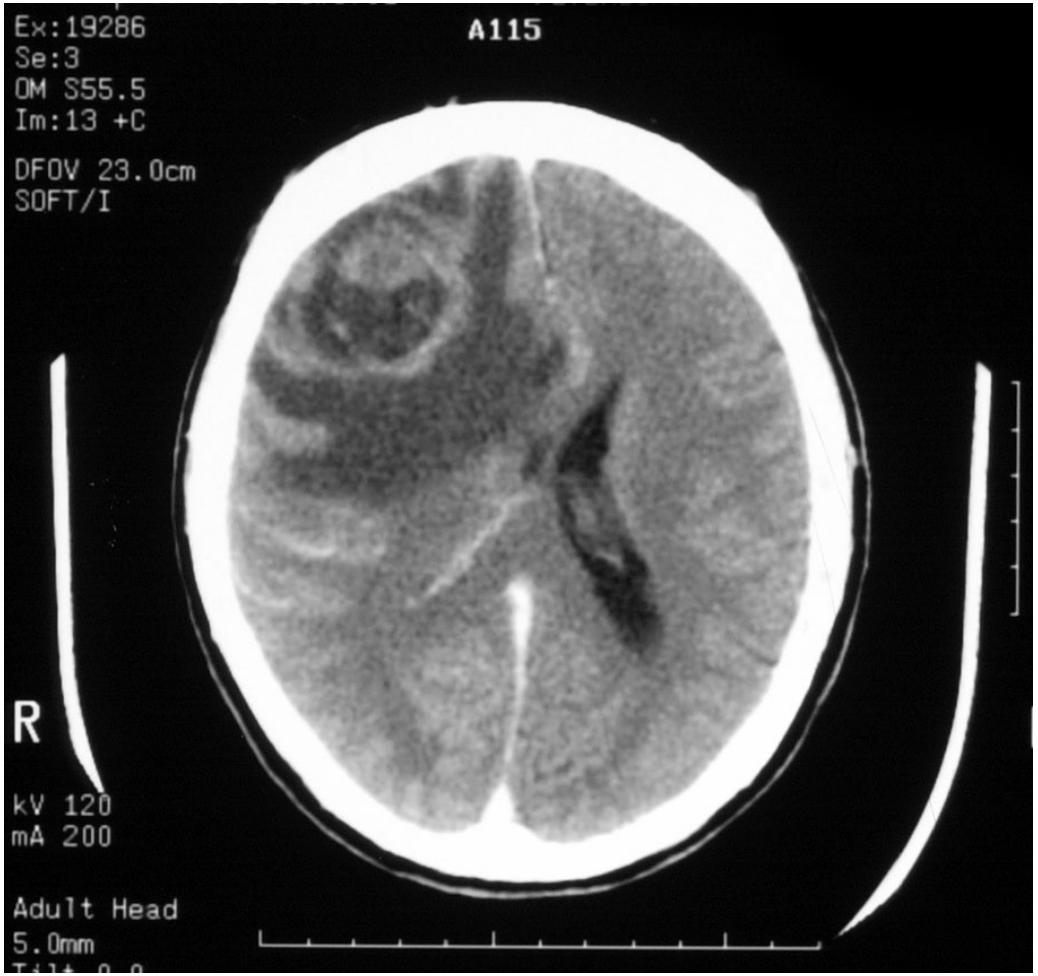
Typical GBM (Grade 4 glioma)



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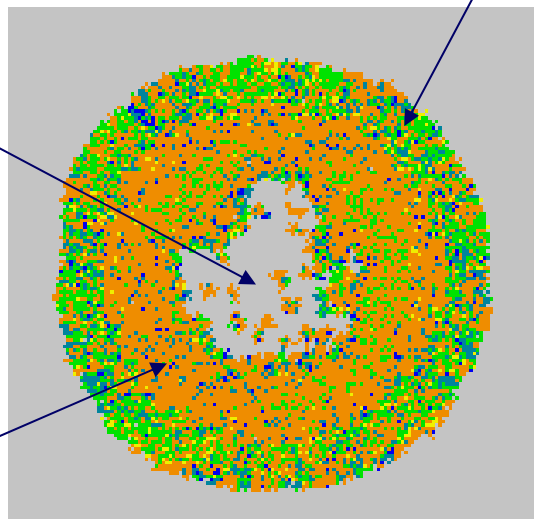
Cellular Automata Models

Growth of glioma cells at 72 days

Proliferative rim

Necrotic core



Quiescent cells

660μm

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GBM Patients

- The outcome has hardly changed over a long period of time
- Median survival < 300 days
- Long-term survival < 3%
- Average years of life lost per patient is highest for all main cancers
- Spending on research is low…

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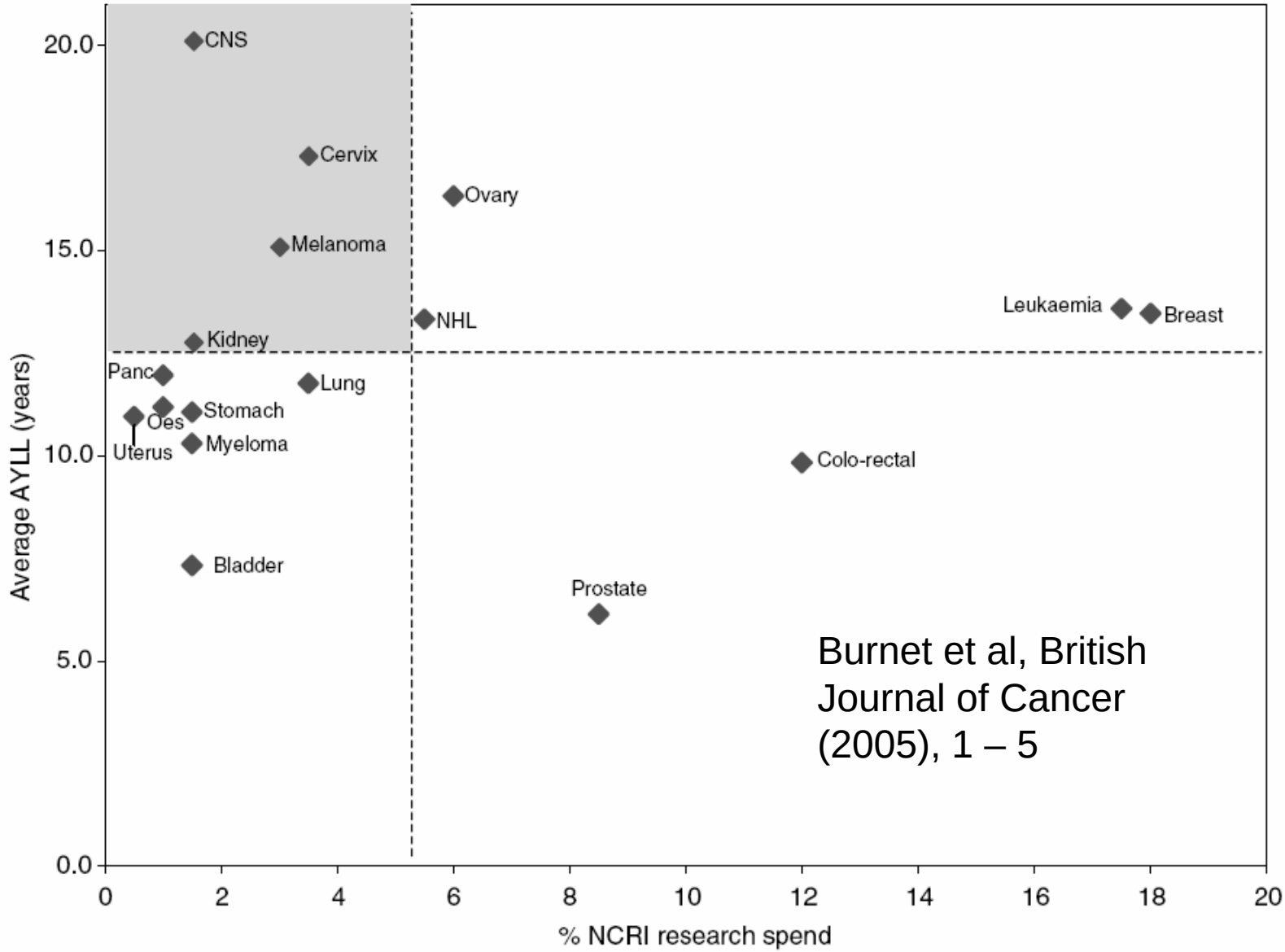
AYLL vs Spend



Burnet et al, British Journal of Cancer (2005), 1 – 5

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GBM Patients

- Symptoms at presentation: headache, neurological impairment, fits.
- Metastatic spread is rare
- Recurrence at original site is common
- Proliferative rim includes invasion of normal brain

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GBM Patients: Cause of Death

- Intra-cranial pressure
- Destruction of vital section of normal brain
- Toxic burden of necrosis?
- Other?

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Patient Outcome Models

- A model to address direct clinical issues
- What total dose to give?
- How to fractionate?
  - Given finite resources, waiting lists etc
- How to plan therapy?
- How to control side effects?
- Can we extract biological data from clinical studies?

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Approach

- A model of ‘a patient’
  - Tumour growth
  - Normal brain cell damage
  - Response to radiotherapy
  - Delay before treatment
- Monte Carlo simulation to generate a population of patients
- Simulated annealing to fit onto clinical data

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Model of a Patient

- Some reaction engineering…
- Normal brain cells, n_n
- Cancer cells, n_c

Tumour Growth

$$C \xrightarrow{k_c} 2C \qquad r_c = k_c n_c$$

Destruction of Normal Brain

$$N + C \xrightarrow{k_n} C \qquad r_n = k_n n_c n_n$$

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First Approximation

- Exceedingly crude tumour growth kinetics
- Does damage to the normal brain continue if the tumour is not getting any bigger
- A better approximation might be to make damage related to growth rate

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Model of a Patient

- Patient presents with some tumour, n_{c0}, and some brain left, n_{n0}
- When n_n drops below n_{ncrit} the patient dies
- We assume radiotherapy reduces n_c but has no effect on n_n.
- We assume no other loss of normal brain cells, e.g. with age.

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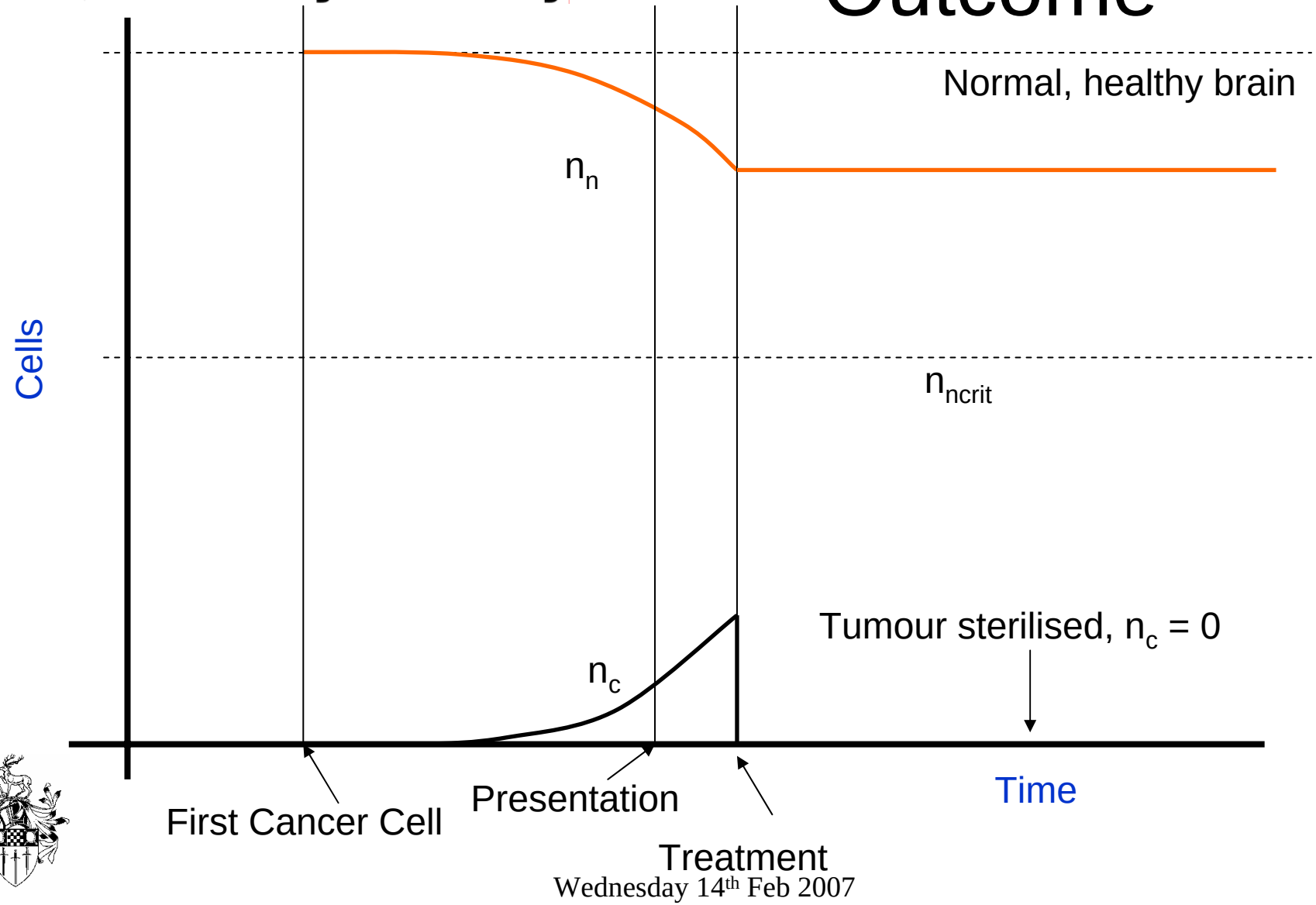
Model of a Model Outcome



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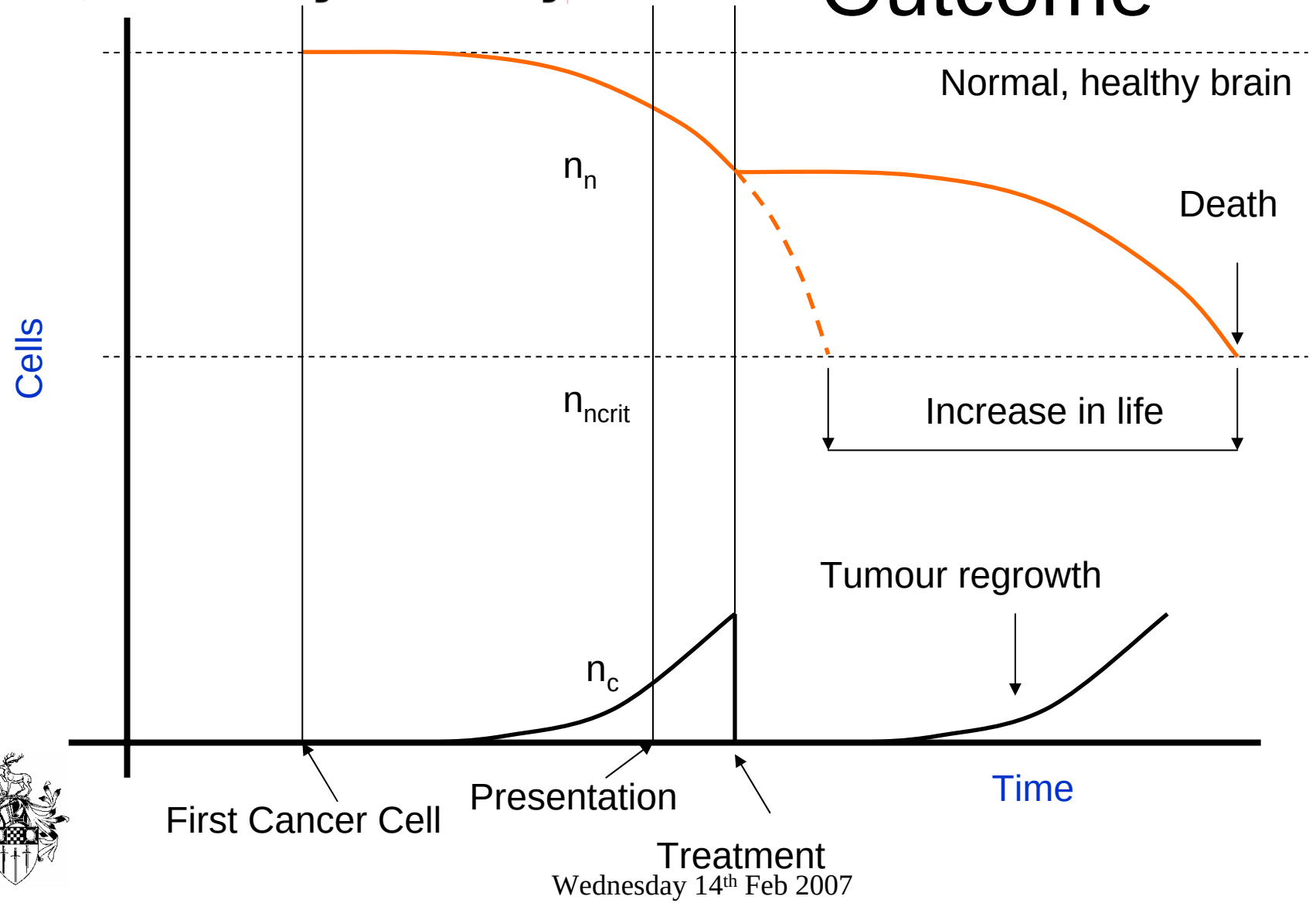
Model of a Model Outcome



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Model of a Patient

- Assume the tumour is a closed system
- Perform a number balance on the system

$$\frac{dn_c}{dt} = r_c = k_c n_c$$ Tumour

$$\frac{dn_n}{dt} = -r_n = -k_n n_n n_c$$ Normal brain

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Model of a Patient

- Solve analytically

Tumour

$$n_c(t) = n_{c0} \exp(k_c t)$$

Normal brain

$$\ln\left(\frac{n_n}{n_{n0}}\right) = -\frac{k_n n_{c0}}{k_c}\left(\exp(k_c t) - 1\right)$$

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Model of a Patient

- From this we can calculate when a patient will die if untreated:

$$\ln\left(\frac{n_{ncrit}}{n_{n0}}\right) = -\frac{k_n n_{c0}}{k_c}\left(\exp\left(k_c t_{death,untreated}\right) - 1\right)$$

$$t_{death,untreated} = \frac{1}{k_c}\ln\left(1 - \frac{k_c}{k_n n_{c0}}\ln\left(\frac{n_{ncrit}}{n_{n0}}\right)\right)$$

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Size of Tumour at Presentation

- n_{c0} is not an independent parameter
- It can be calculated from n_{n0}, k_c, k_n and n_{nbrain} (the number of normal cells in a complete brain)
- The state space is given by

$$\ln\left(\frac{n_n}{n_{n0}}\right) = -\frac{k_n}{k_c}\left(n_c - n_{c0}\right), \text{ hence}$$

$$n_{c0} = \frac{k_c}{k_n}\ln\left(\frac{n_{nbrain}}{n_{n0}}\right)$$

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Age of Tumour at Presentation

- Using the state space
- Given the size of tumour at presentation
- The age of the tumour is…

$$t_{age} = \frac{1}{k_c} \ln\left(n_{c0}\right)$$

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Treating the Patient

- Select the patient for a therapy
  - Radical
  - Palliative
  - Best nursing care
- Wait for treatment machine to become available, t_{delay}
- Treat instantaneously
  - Use no radiobiology, just survival fraction

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Treating the Patient

$$n_c\left(t^{+}_{delay}\right) = n_c\left(t^{-}_{delay}\right) x_s^j$$

- If cell number in tumour < 1 deem tumour to be sterilised
- Otherwise calculate new survival time
- Give j fractions of radiotherapy, each has tumour cell survival fraction x_s
- Assume we know x_s for each patient

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Survival After Treatment

- We can calculate how long the normal brain will now take to drop to only n_{crit} cells left.
- Hence we have calculated the patient survival time
- We can impose a clinical trial time and censor surviving patients if necessary

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Summary of the Patient

- Tumour growth rate constant, k_c
- Normal brain interaction constant, k_n
- Normal brain at presentation, n_{n0}
- Normal brain at death, n_{crit}
- Delay to start treatment, t_{delay}
- Survival fraction in response to each fraction, x_s

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Populations of Patients

- Monte Carlo Simulation:
- Random generation of each of the parameters that characterise a patient
- Calculate their survival time, etc
- Analyse the statistics for the results
- Input distributions have to be plausible, if not measured.

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Populations of Patients

Distributions for

- Normal brain cells at presentation
- Critical cells number left at death
- Tumour doubling time
- Delay to treatment
- Tumour/Normal cell interaction constant
- Survival fraction to a single dose of radiation

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Distributions

- Normal distributions

$$p(k) \propto \exp\left(-\left(\frac{k-\bar{k}}{\sigma}\right)^2\right)$$

- Skewed distribution for survival fraction

$$p(x_s) \propto x_s^{\,n}\left(1-x_s\right)^m \exp(-\alpha x_s)$$

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Constructing a Population of Patients

- Know, estimate or determine by fitting 13 parameters:
- Mean and standard deviations for
  - k_c, k_n, n_{n0}, n_{ncrit}, t_{delay}
- Survival fraction parameters
  - n, m, α

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Methods for Generating Distributions

- The Normal distribution is easy:
  - Method of Box GEP and Muller ME 'A note on the generation of random normal deviates, Ann. Math. Statist., 29, 610-611, 1958
  - **call RANDOM_NUMBER(r)**
  - **call RANDOM_NUMBER(theta)**
  - **Theta = two_pi*theta**
  - **R = SQRT(-two * log(r))**
  - **x = R*SIN(Theta)*var%std+var%mean**
  - **y = R*COS(Theta)*var%std+var%mean**

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Methods for Generating Distributions

- The Survival Fraction Distribution is not so easy:
  - Use an acceptance/rejection test
  - It is iterative
- Care is required to check that the desired distribution is being generated

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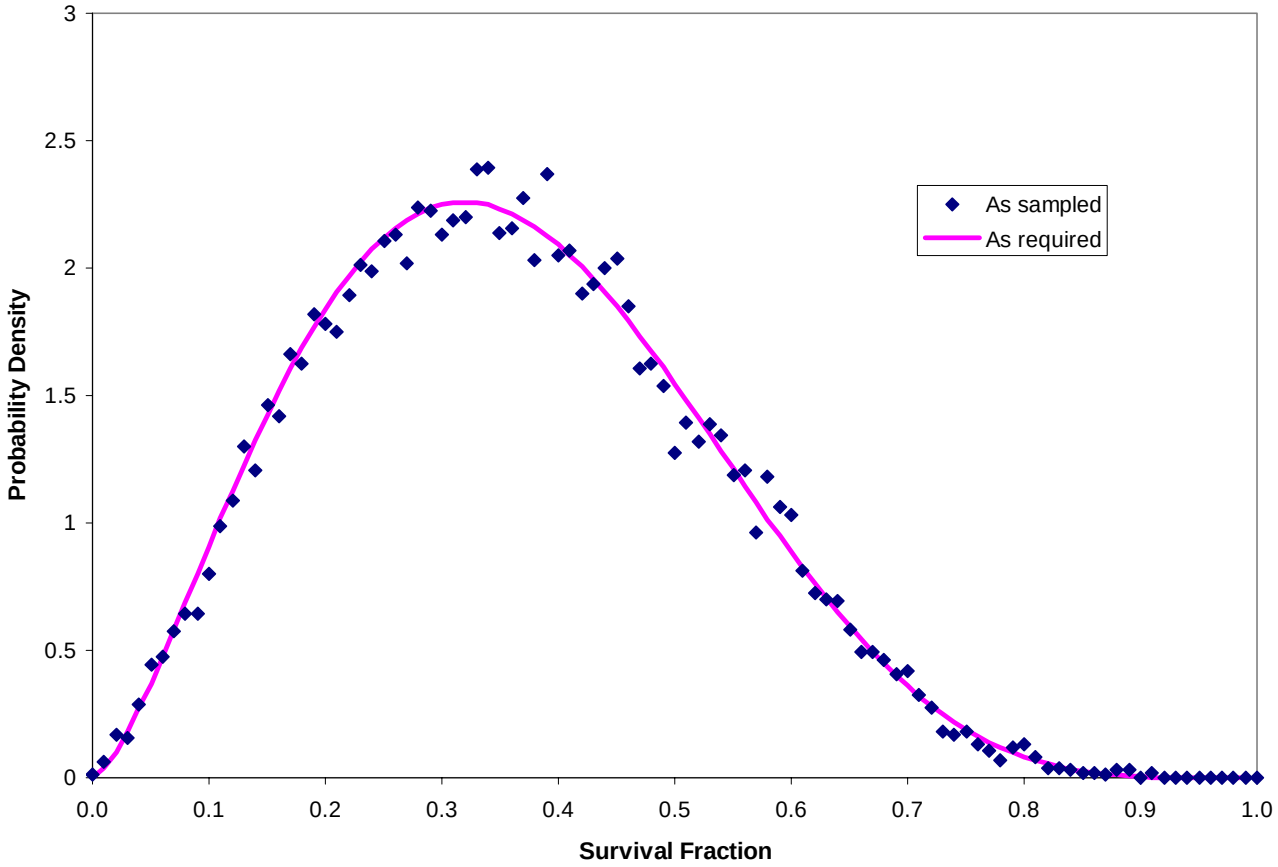
Methods for Generating Distributions



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Disadvantages of x_s Distribution

- Specify n, m, and α
- Have to compute numerically:
  - Mean
  - Variance
  - Skewness
  - Kurtosis etc
- Integrate numerically for the normalisation constant

$$p(x_s) = k_{x_s} x_s^{\,n} (1 - x_s)^m \exp(-\alpha x_s)$$

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Clinical Patient Selection

- Some patients, with parameters selected at random, are dead at presentation, die before treatment etc
- Clinicians use WHO performance status to select patients
- We invented the ‘too poorly laws’

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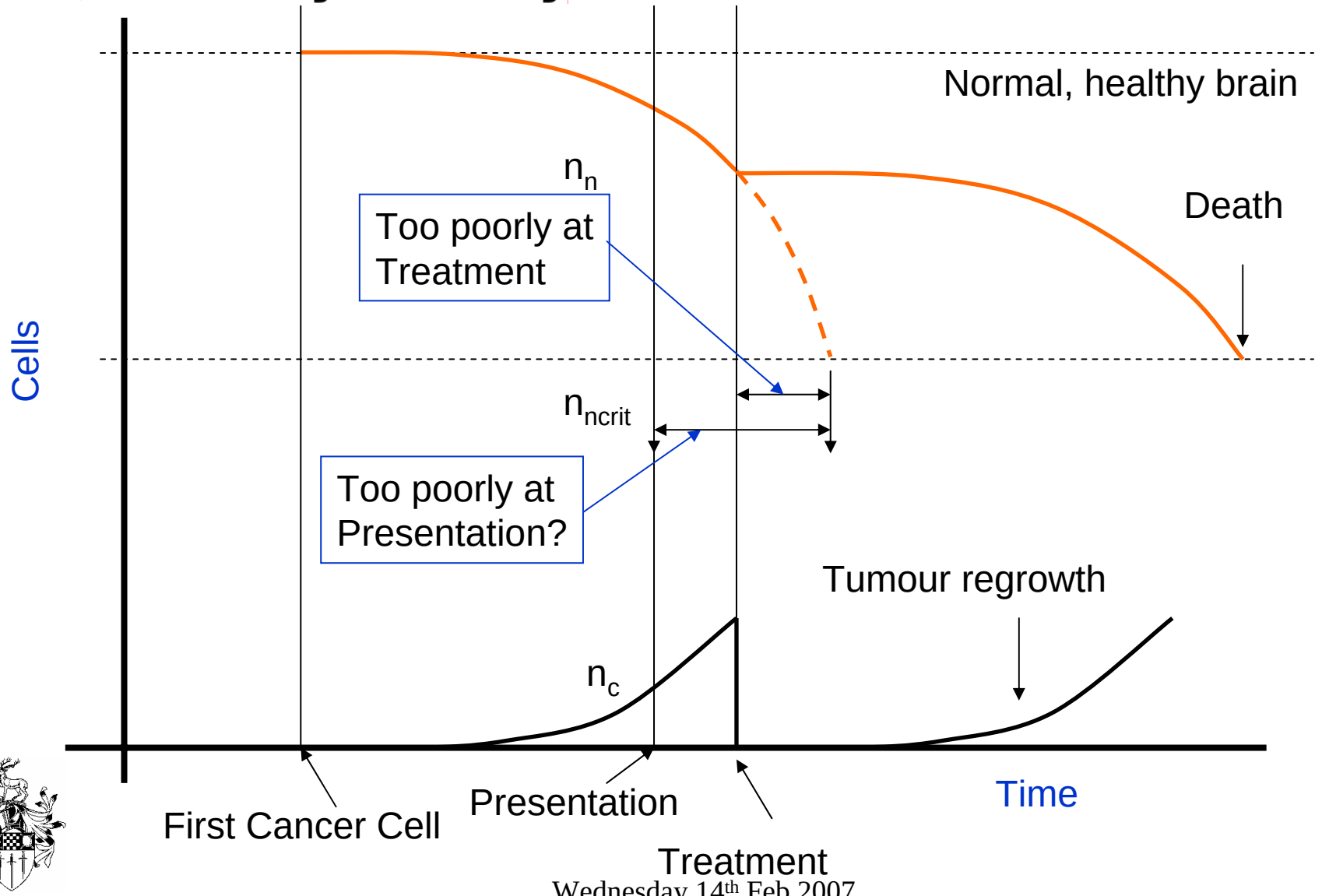
Too Poorly Laws



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Modelling Clinicians

- Our model clinicians know when a patient will die if untreated
- Our model clinicians do not know the waiting time to commence treatment
- Both are wrong!
- Both flatter real clinicians!

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Treatment Selection

- If $t_{untreated} < t_1$
  - Best nursing care, too poorly for any treatment
- If $t_2 > t_{untreated} > t_1$
  - Palliative treatment
  - Short planning and waiting time
- If $t_2 < t_{untreated}$
  - Radical treatment
  - Longer planning and waiting time

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Assessment at Presentation

- Given that we pretend we do not know the waiting time…
- Patients can be too poorly to treat when they arrive for treatment – and they are turned away.
- Conclude…
- A large number of patients may have to be generated in order to get enough to actually treat

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Fitting the Model to Data

- Some parameters we know ahead of time – e.g. distribution of waiting times
- Some have to be obtained by fitting
- Optimisation routines can be very slow and can home in on local minima
- We used a simulated annealing/ folding polygon hybrid.

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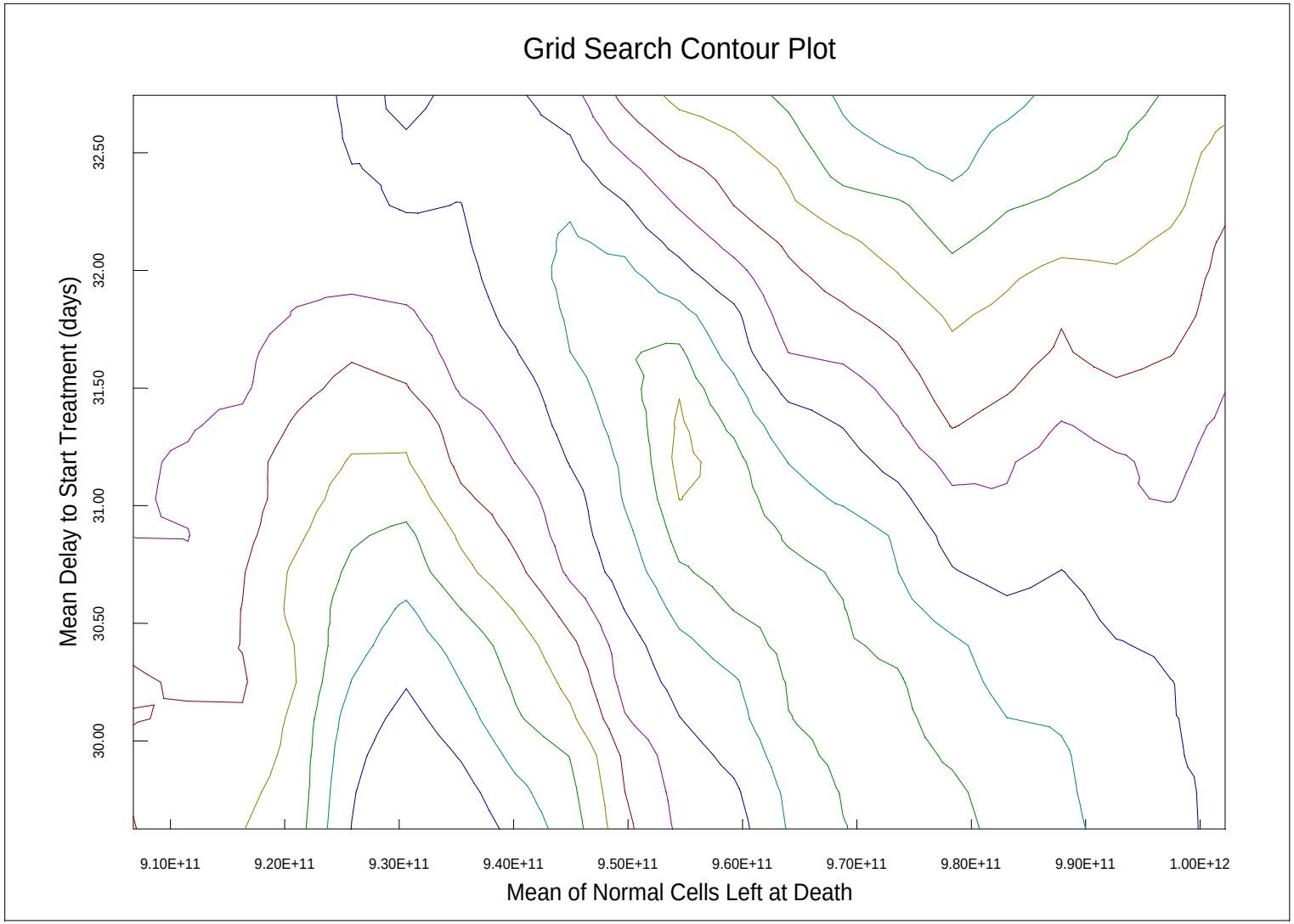
Problems Fitting



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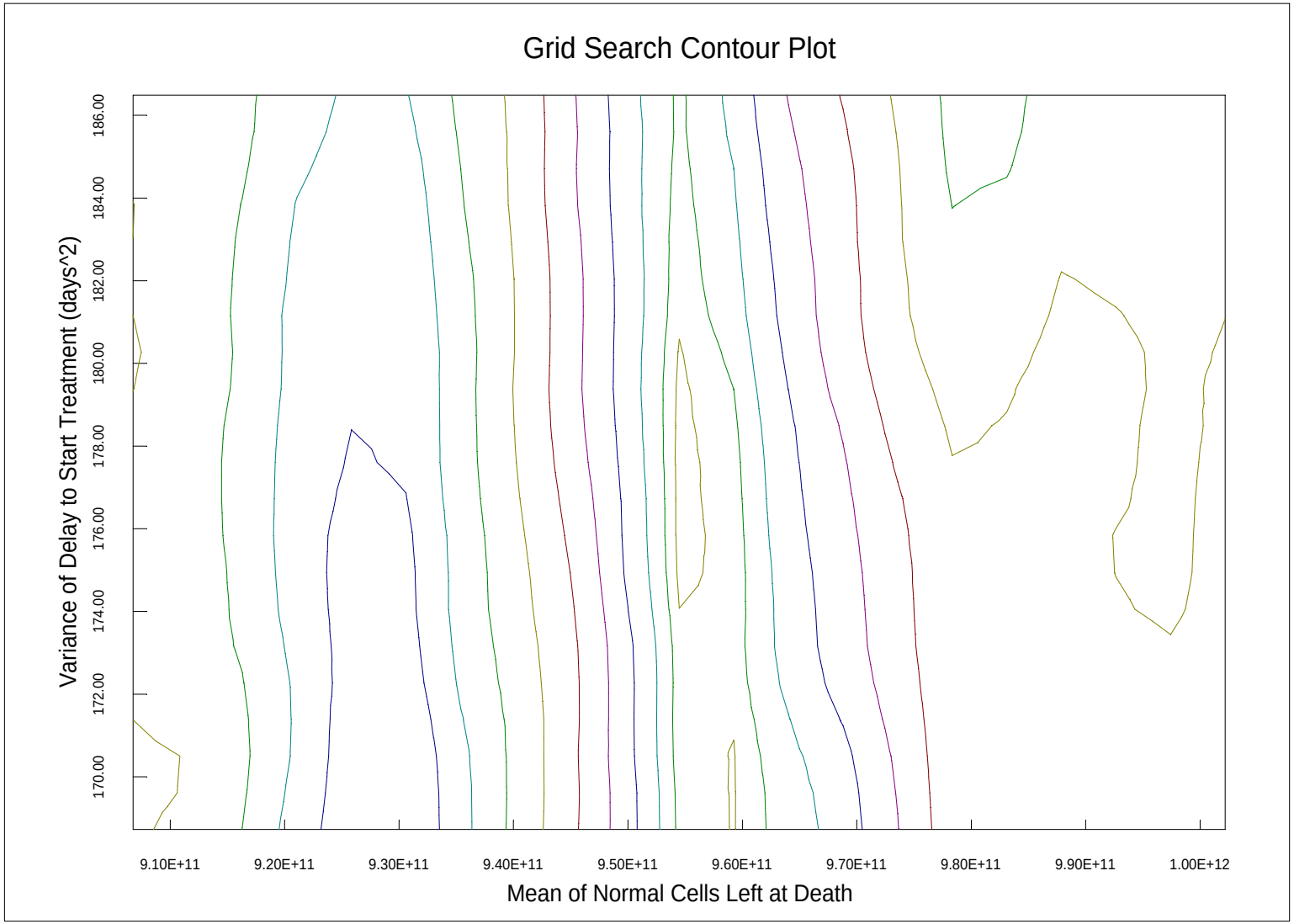
Problems Fitting



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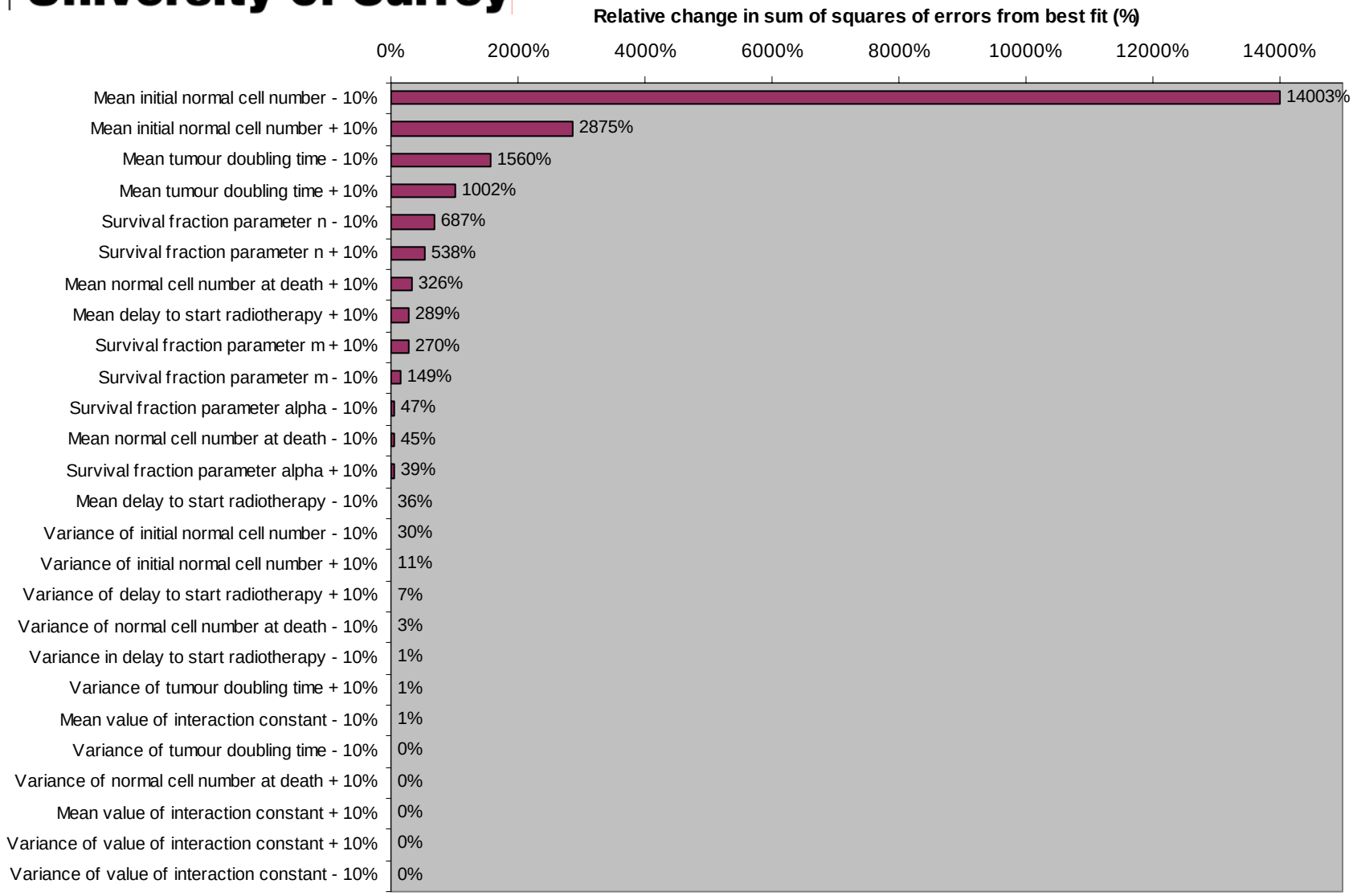
Sensitivity Analysis



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Sensitivity Analysis

- Recall that this model currently has a log(log()) term, recall…

$$t_{death,untreated} = \frac{1}{k_c} \ln\left(1 - \frac{k_c}{k_n n_{c0}} \ln\left(\frac{n_{ncrit}}{n_{n0}}\right)\right)$$

- So it is not surprising that the sensitivities are widely spread.
- Variances are covariant

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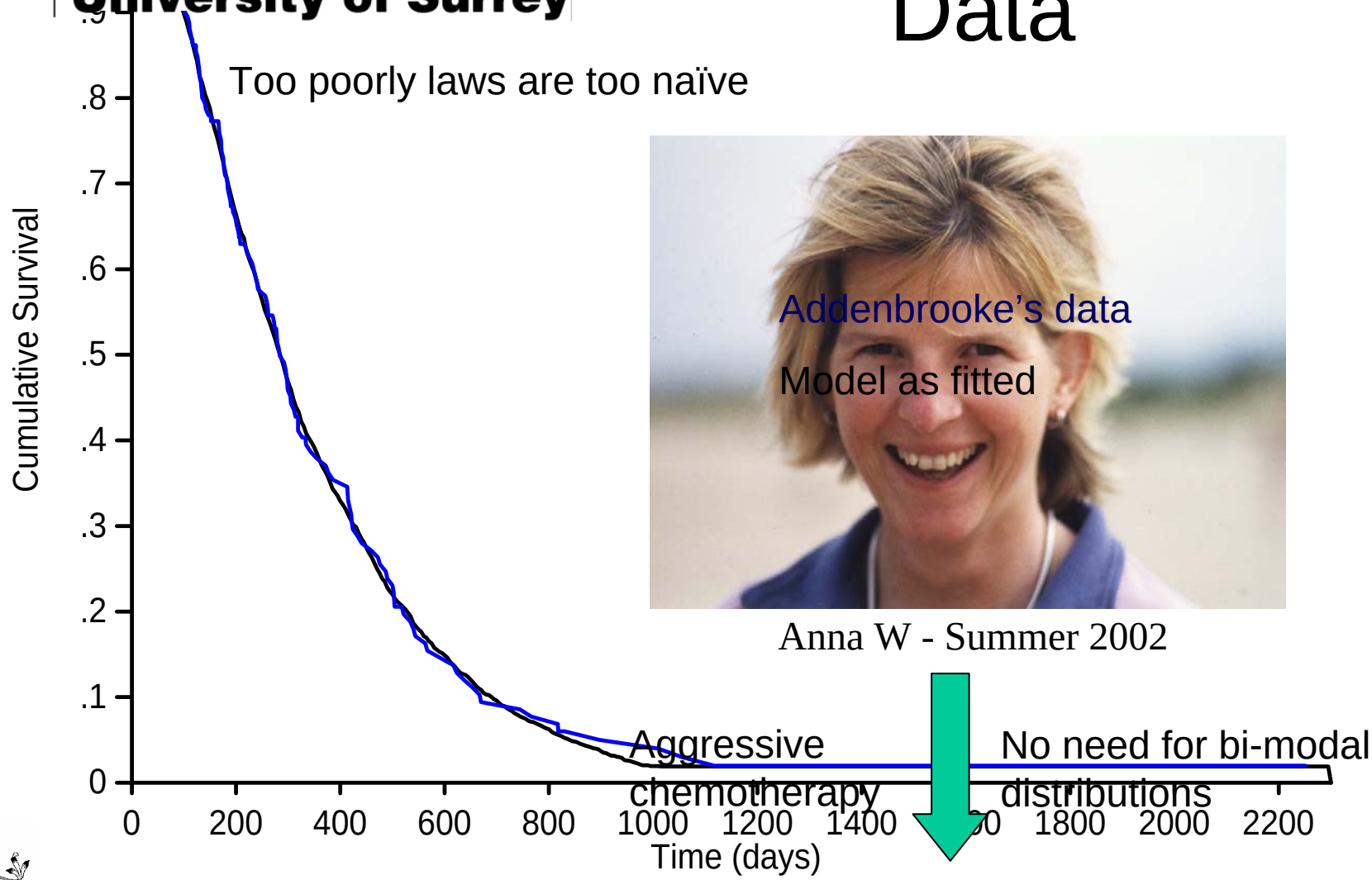
Fitting to Clinical Data



Anna W - Summer 2002

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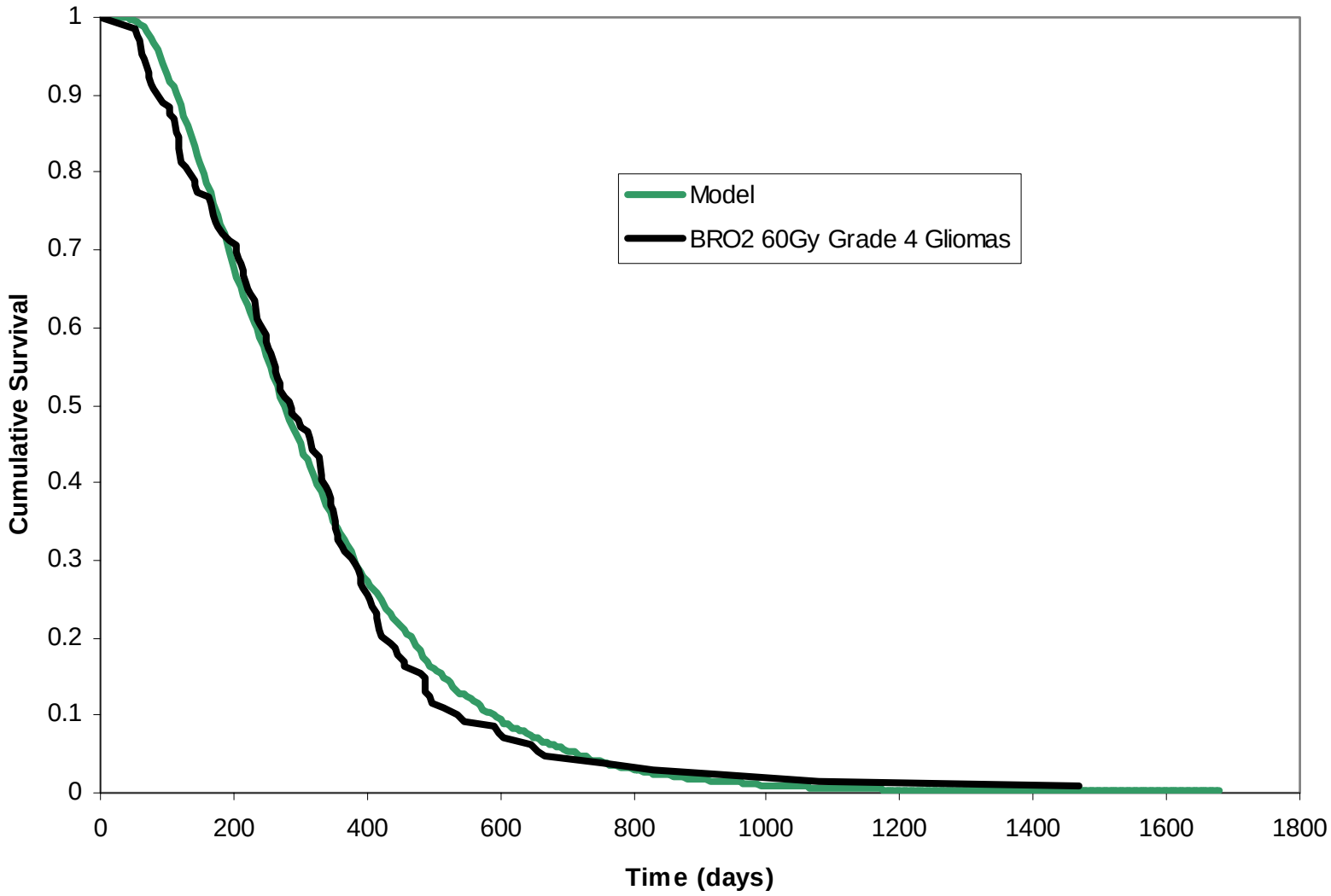
Fit to BRO2 Results



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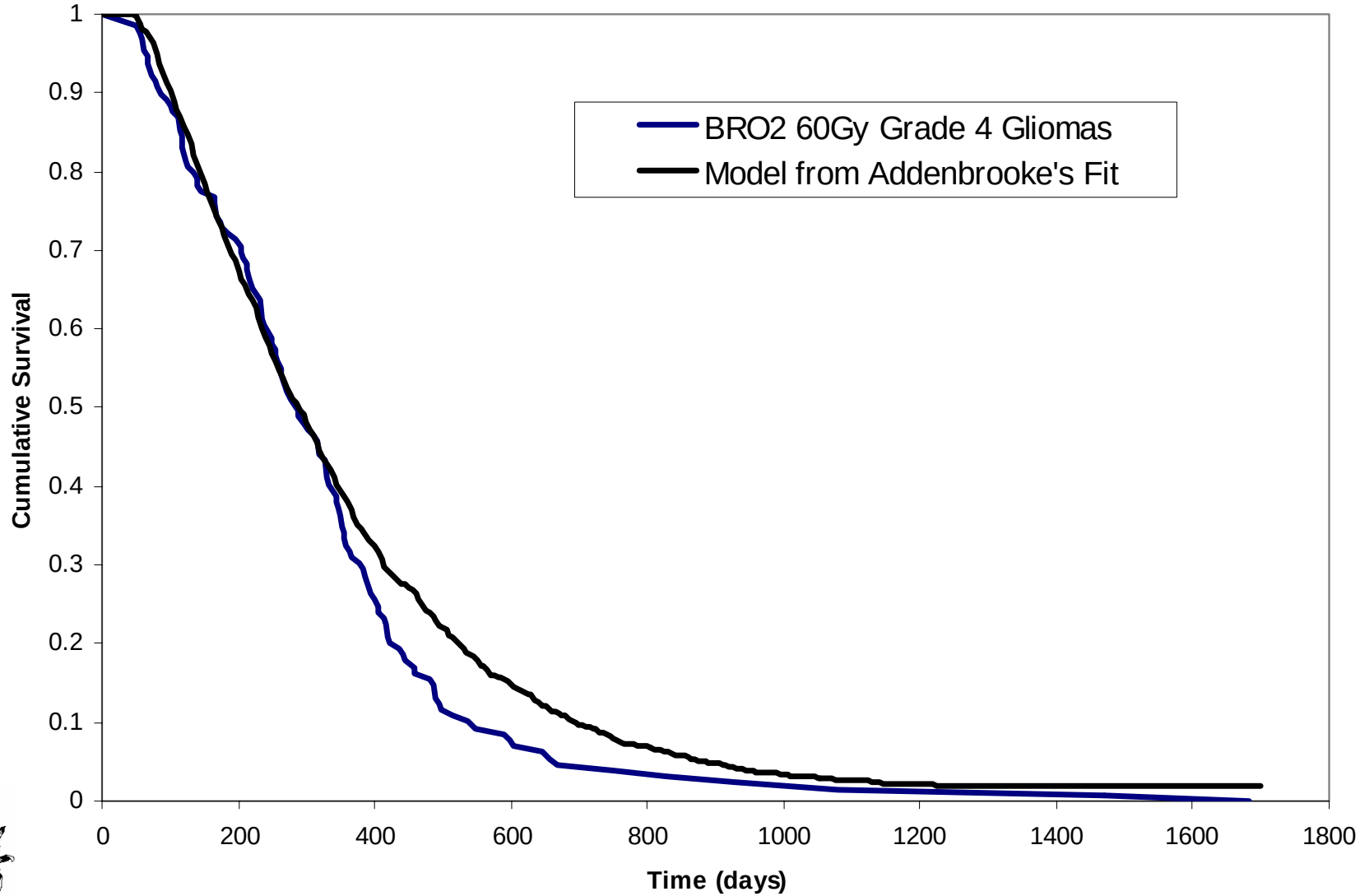
Predict BRO2 Trial



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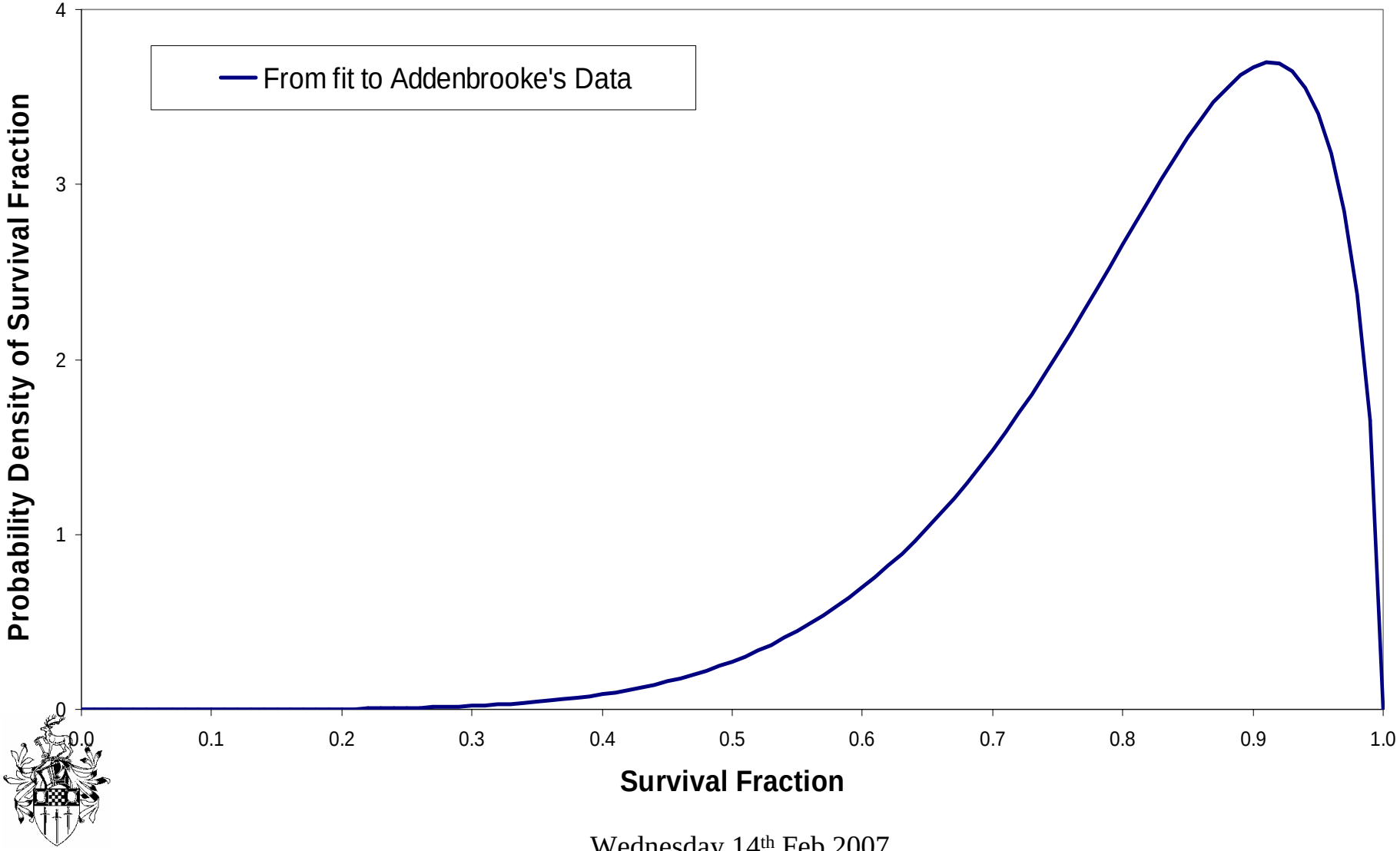
Intriguing Consequences



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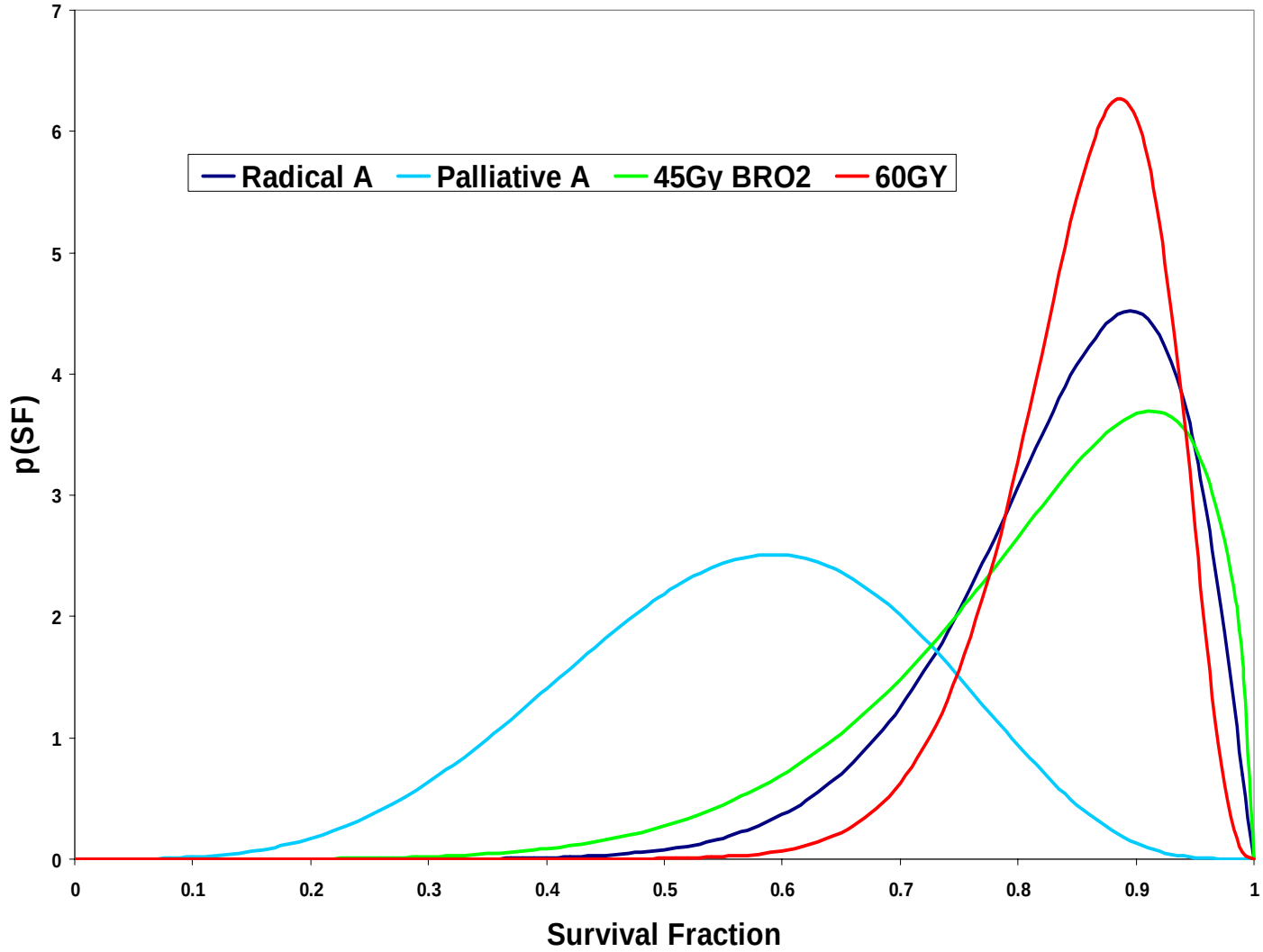
Radical & Palliative



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Distribution of SF

- What we predict here is consistent with measured SF at these doses
- The mean α/β is about right
- Can we drive these distributions to the left with the high RBE of carbon ions?
- Can radiosensitising drugs help?

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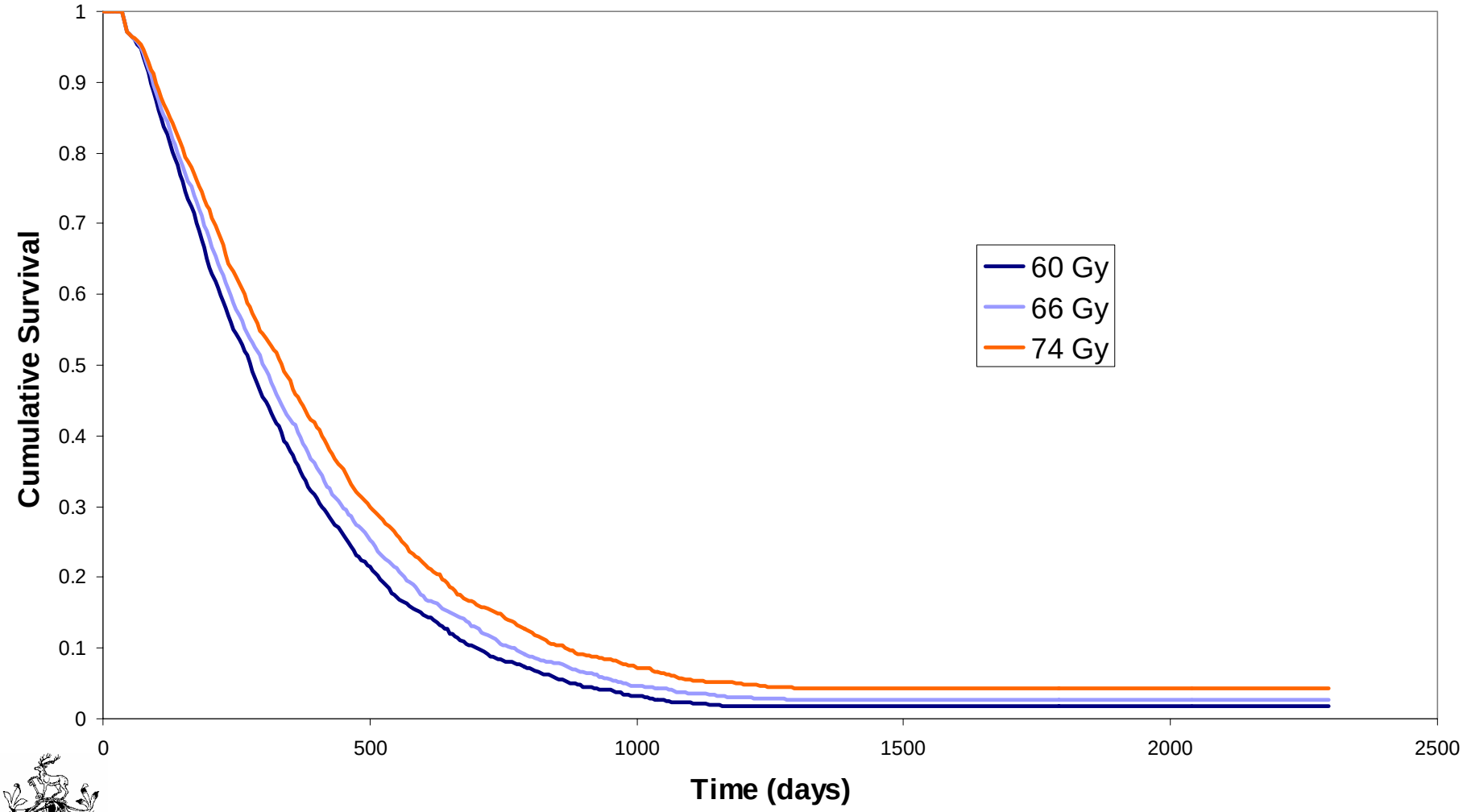
Dose Escalation



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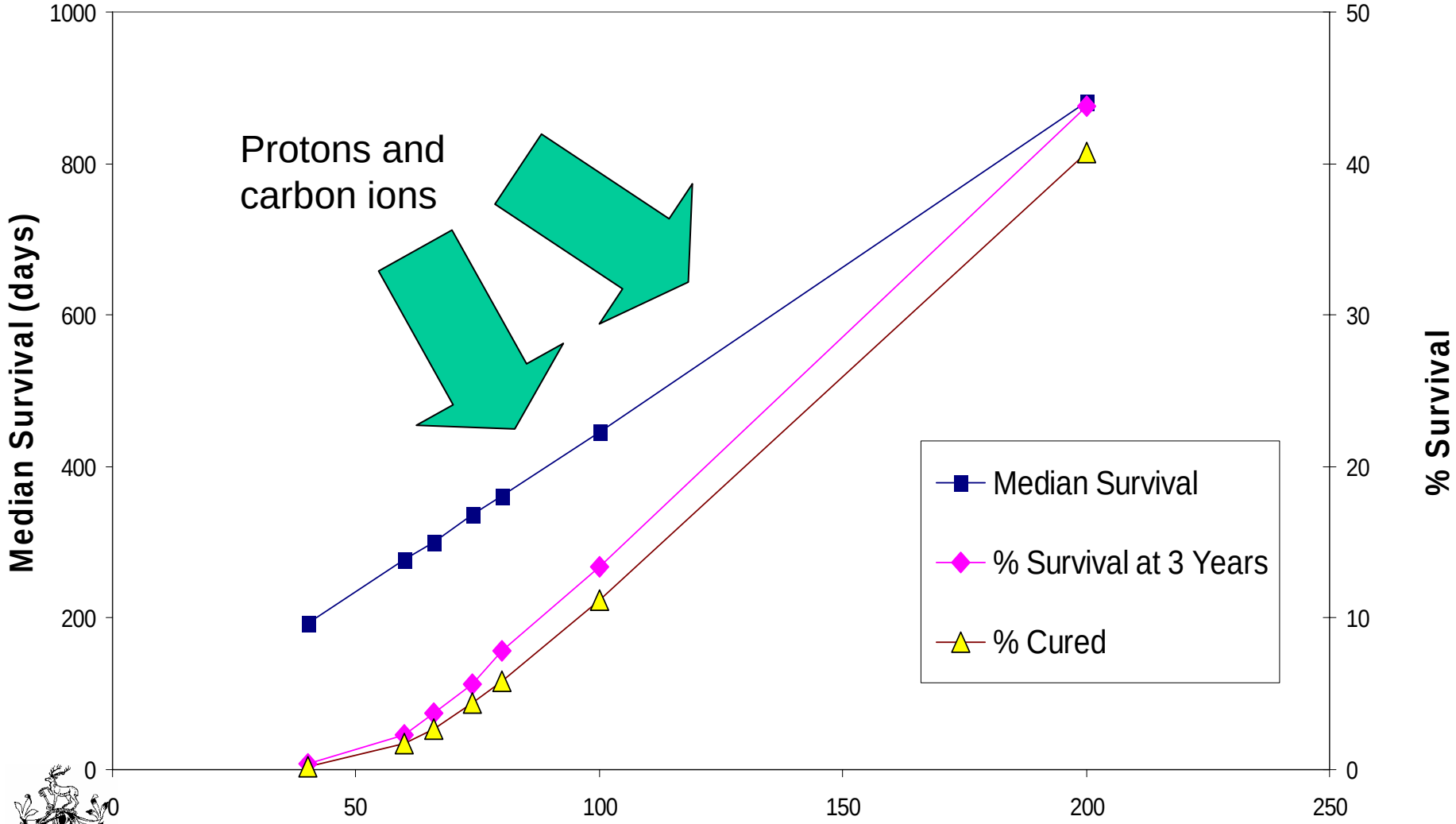
Dose Escalation



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Design of Clinical Trials?

- How many patients do we need to recruit in order that the effects of a given dose escalation can be seen at a conclusive level of statistical significance.
- Can this model help design trials?

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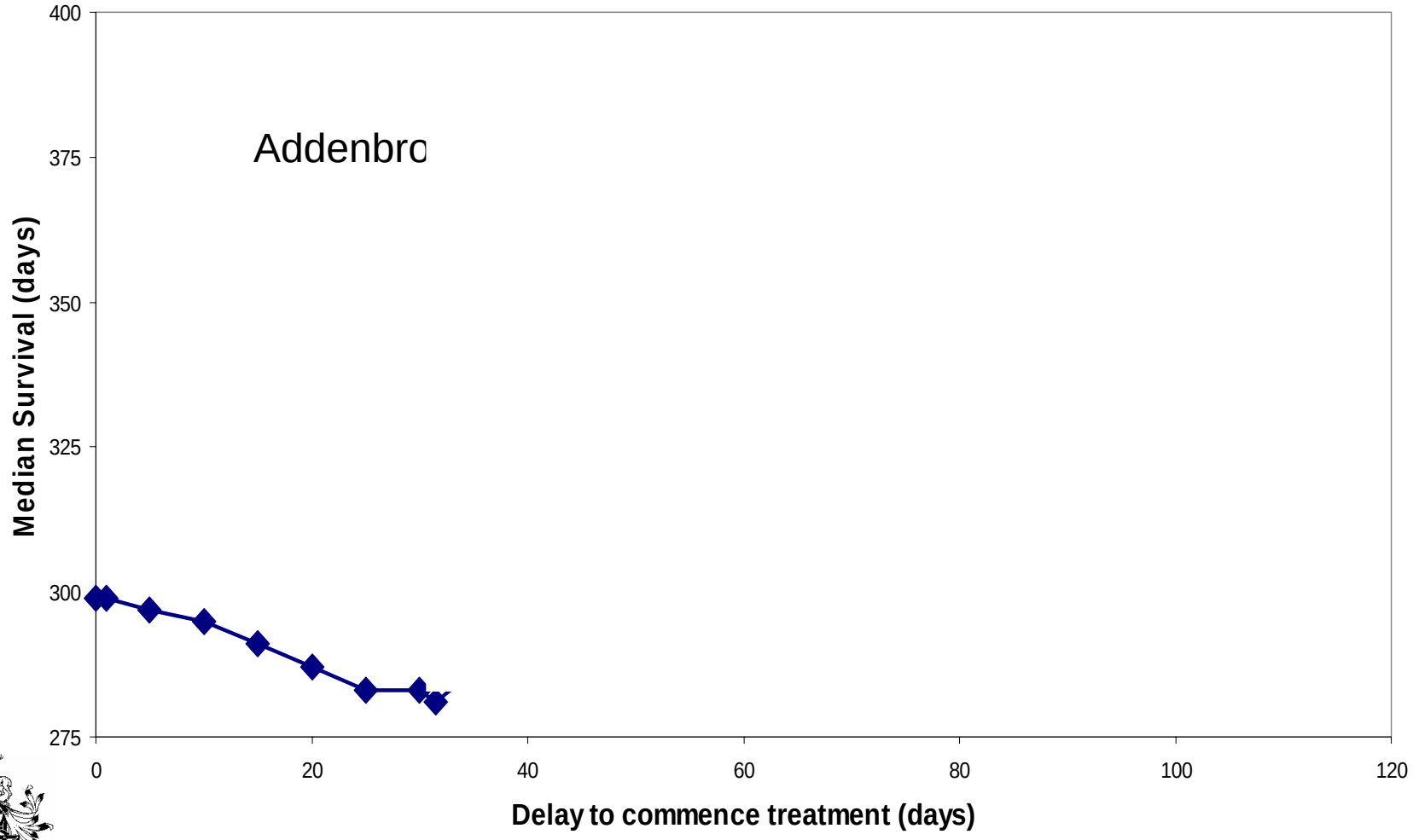
Effect of Treatment Delays



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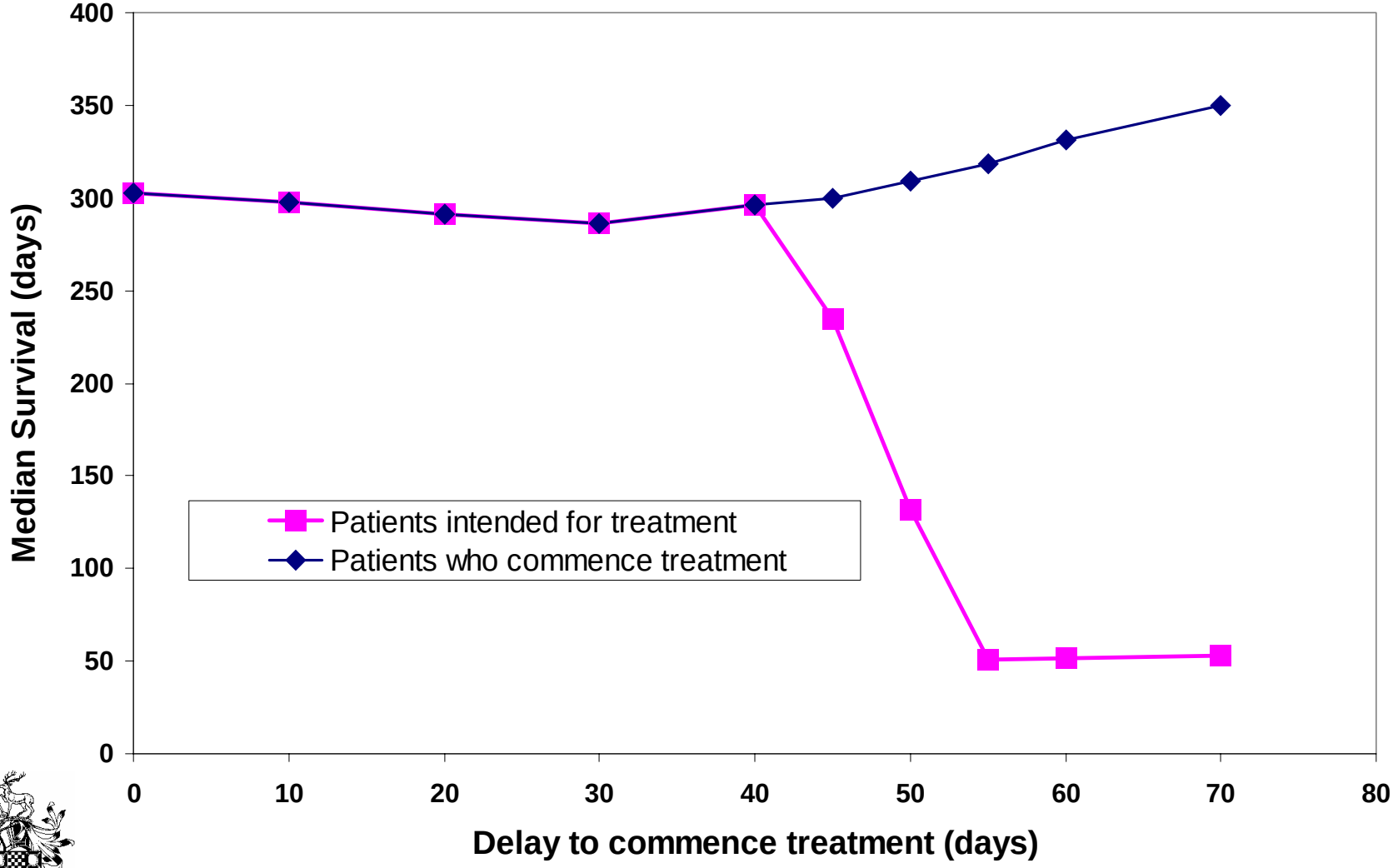
Effect of Treatment Delays



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Waiting Times

- Political Issue in UK
- Effects seem to be highly dependent on too poorly laws
- Do and Barton study, but very few others – evidence difficult to interpret
- What effect would a proton facility in the UK have on waiting times?

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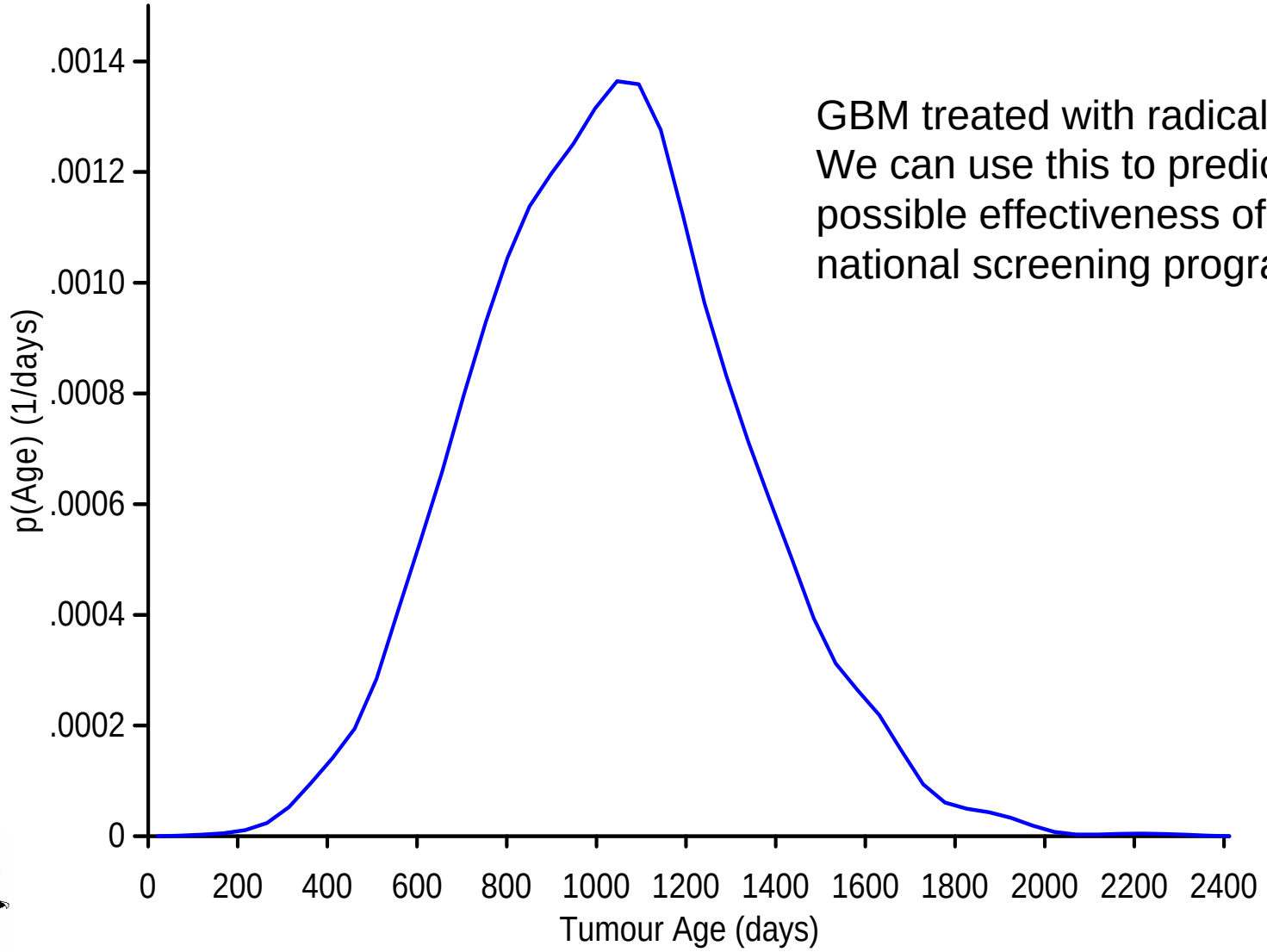
Tumour Age Distribution



GBM treated with radical intent. We can use this to predict the possible effectiveness of a national screening programme

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Tumour Age Distribution

- Very difficult to measure
- Real GBM distribution is probably younger (k_c decreases with size and nutrient limitation)
- Early diagnosis does not seem to help in GBM

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Conclusions

- We have made a start
- Formulating the model has caused us to ask some interesting and difficult questions.
- The model has been used to guide the design of a clinical trial
  - Which is now in progress

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Future Work

- Multi-processor Fortran and Migration to Super-computer
- Optimisation Methodologies to exploit Cluster or Grid capabilities
- Radiobiology, e.g. SF related to dose
- Effect on normal tissue
- Low dose and bystander effect
- Time distributed treatment
- Conventional treatments
- Missing appointments

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Future Work

- Concurrent/Adjuvant chemotherapy
- temozolomide
- "Chemo as a second, isolated treatment"
- Time dependent interactions between the treatments
- Chemo - normal brain interactions
- Question: difference between concurrent vs adjuvant chemotherapy

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Future Work

- Grade 3 Gliomas
- Analysis of data on grade 3 from BRO2 and other trials
- Analysis of the effects of chemo
- Clinical and Anatomical Aspects
- Age and WHO performance status
- Normal brain interactions
- Tumour location in brain
- Other tumour cites, e.g. cervix

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Future Work

- Distributions in clinician decision making
- Question: how does this effect Do and Barton - waiting times?
- Improved growth kinetics
- Simple diffusion and reaction model
- Cell cycle-based growth kinetics
- Cell cycle-based radiosensitivity
- Novel and enhanced treatment strategies
- New radiotherapy schedules
- Protons and carbon ions
- New drugs (e.g. AQ4N?)

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Take-home Message

- Currently, the main value in these models is in the creative process of formulation,
- Perhaps not in the results yet!
- Modelling is a potent catalyst for constructive dialog

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Thank you for listening

Questions

"All models are a compromise with reality"

Octave Levenspiel

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