Modelowanie wzrostu guzów nowotworowych i wpływu na nie promieniowania

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"Między teorią a zastosowaniami - matematyka w działaniu"
Będlewo 2013

Motivation

The problem

- About 4 in 10 people presently receive radiotherapy as part of their cancer treatment [1];
- But ... variables in 'treatment-space':
  - Number of fractions per day/week;
  - Timing of fractions within a day;
  - Intensity (dosage) of each fraction.
- Choice space for treatments is *vast*!

Source: [1] Cancer Research UK, 'Radiotherapy Briefsheet', Aug. 2010.

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- Current programs are largely *ad-hoc*;
- *No systematic optimisation study of the treatment space ...*

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- Choice space for treatments is *vast*!
- Current programs are largely *ad-hoc*;
- *No systematic optimisation study of the treatment space ...*
- .. Numerical simulation provides an ideal methodology to investigate this space (cost-effective, non-destructive).

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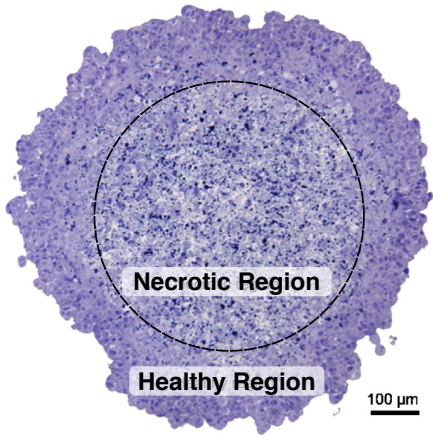
Experimenatl Data: EMT6/Ro Spheroids

Rationale for EMT6/Ro

- EMT6/Ro (mouse mammary tumour cells) are one of the most well-studied (*in vitro*) cell lines;
  - Thus, a good candidate for refinement of numerical simulation.
- We model the bulk tumor dynamics (growth, necrosis, proliferating rim etc.), and, response of EMT6/Ro to X-irradiation.



Source: Yu et al. (2007), 3-d video holography through biological tissue.

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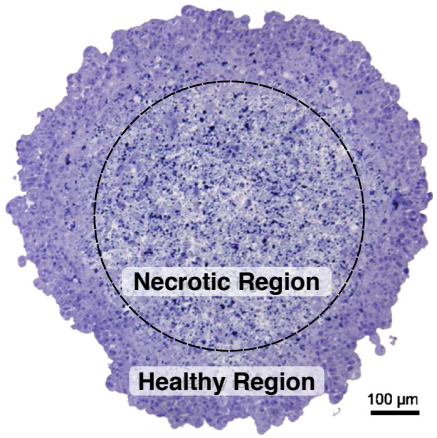
- We model the bulk tumor dynamics (growth, necrosis, proliferating rim etc.), and, response of EMT6/Ro to X-irradiation.
- Calibration (two step):
  1. Step 1: Tumor growth without irradiation;
  2. Step 2: Tumor response to X-irradiation.



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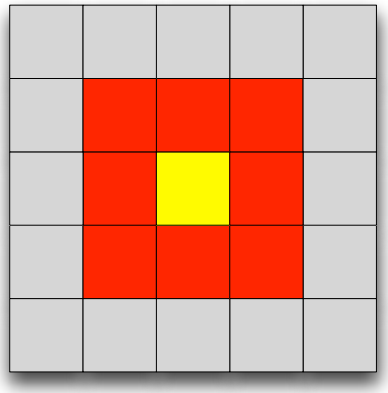
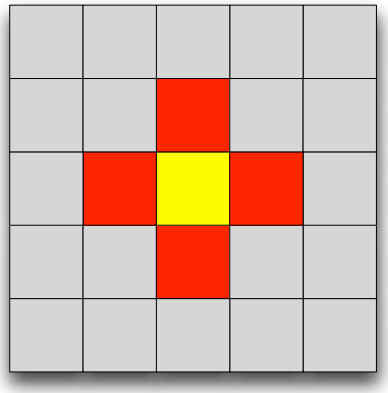
Defining the Cellular Automata (CA)

Moore (8) Neighbourhood

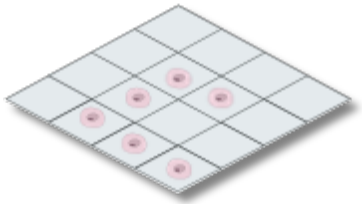


Von Neumann (4) Neighbourhood

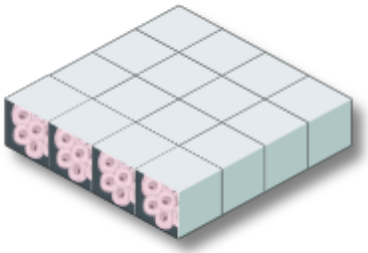


- A discrete model consisting of a regular grid of 'cells';
- Each 'cell' exists in one of a finite number of states;
- Sites update based on interactions with neighbours:
  - Moore (8) neighbourhood (this model);
  - Von Neumann (4) neighbourhood;
  - (or, hexagonal, octagonal lattices).
- Updates: A set of update rules defines transition of each cell from current state to the next;

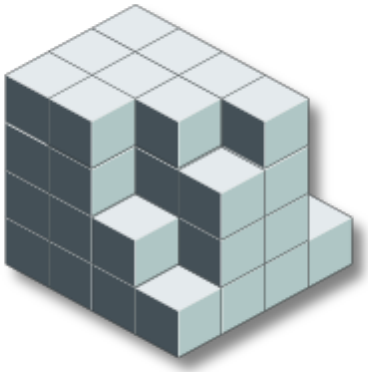
Proposed Cellular Automata (CA)



2D



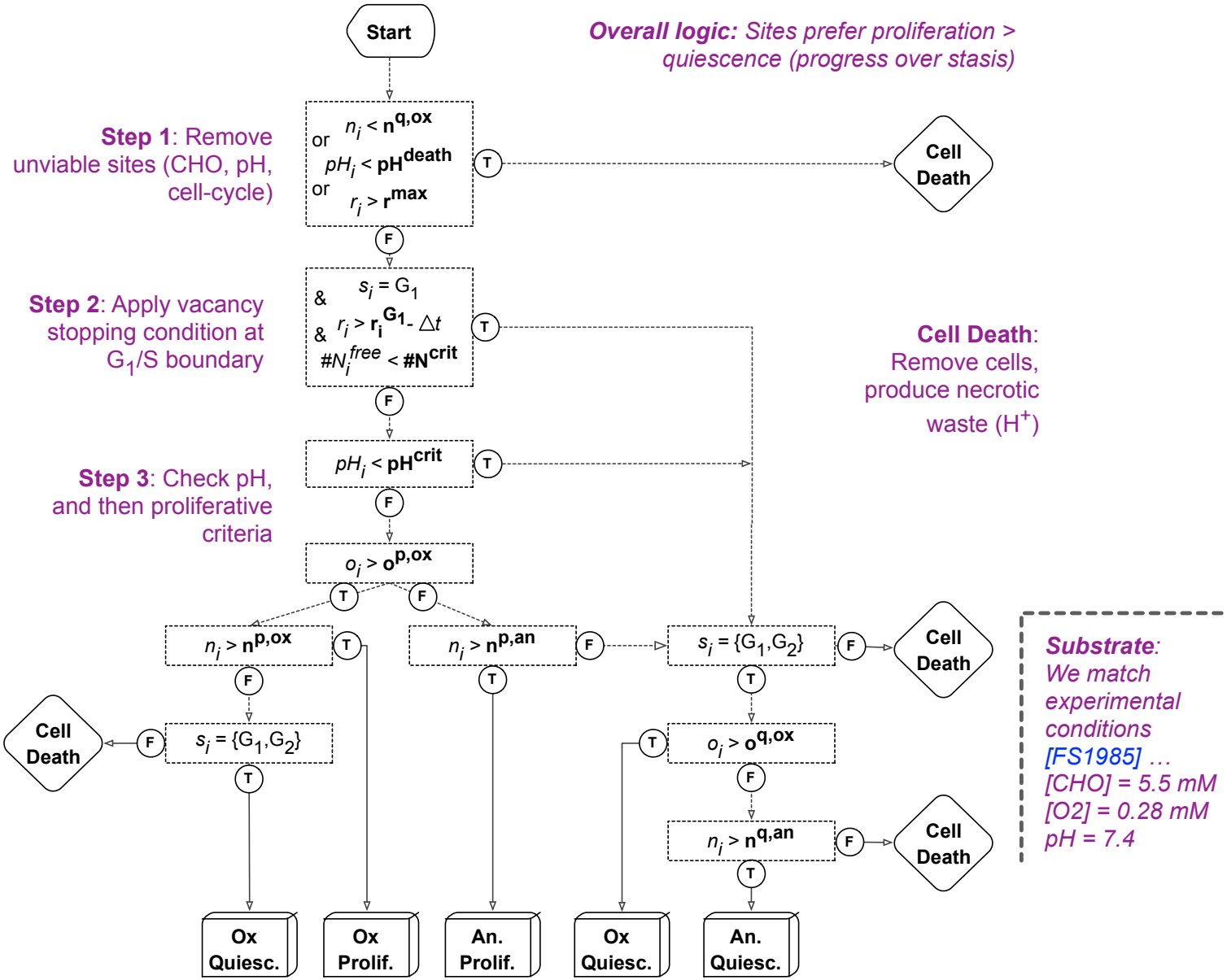
Quasi-2D



3D

- **Grid**: regular;
- **Lattice type**: Quasi-2D;
- **Neighbourhood**: Moore (8);
- **Nutrients/waists**: CHO, O_2, H^+;
- **Updates:** Set of rules defining transition takes into account:
  - concentration of nutrients and waists;
  - cell cycle;
  - cell metabolism;
  - (optional) irradiation does;
  - ...

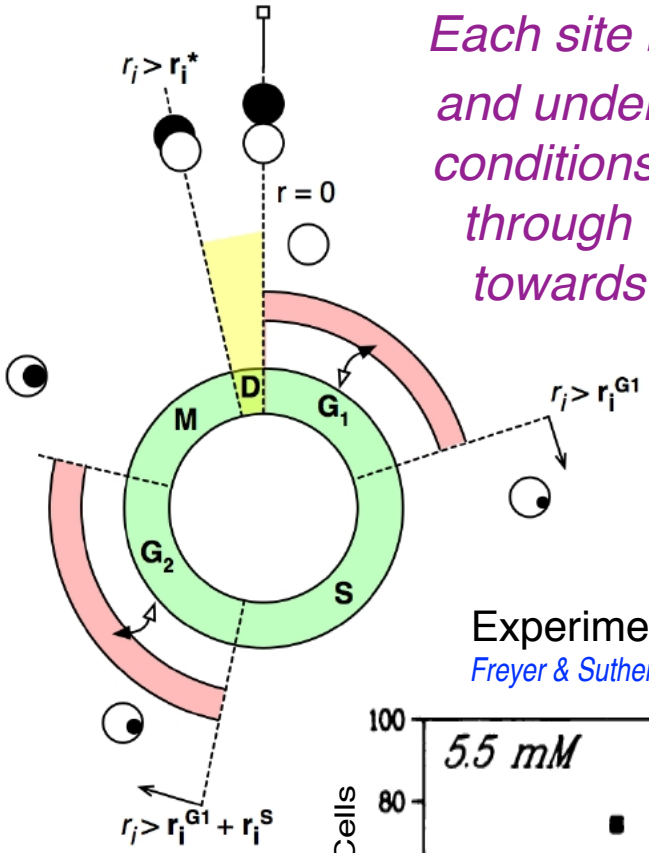
Metabolism: an algorithmic approach



Cell Phase Cycling: checkpoints and progression

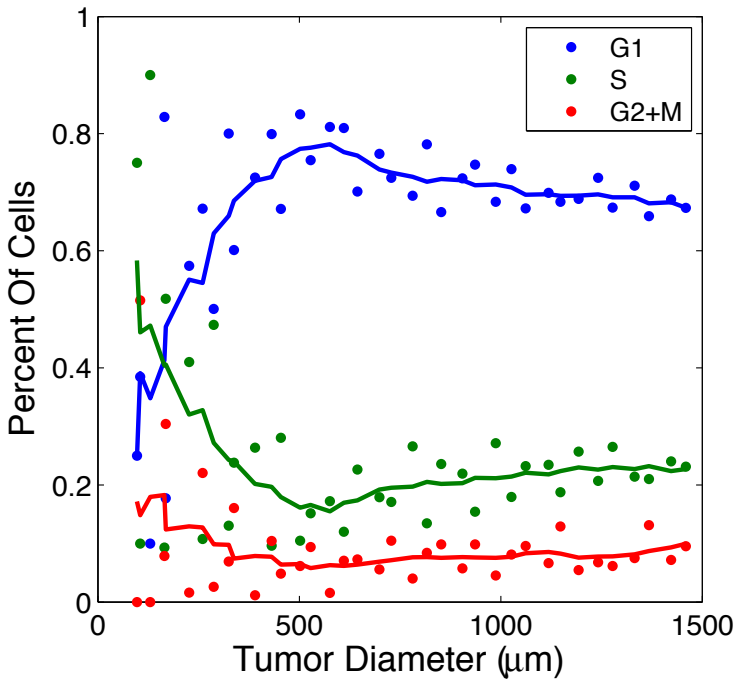
Cell cycle timing (lit.)

Description	Value	Units	Ref.
G_1	6(1)	h	[1]
S	10(2)	h	[1]
G_1	2(0)	h	[1]
M	2(0)	h	[1]
D	0.1(0)	h	ass.



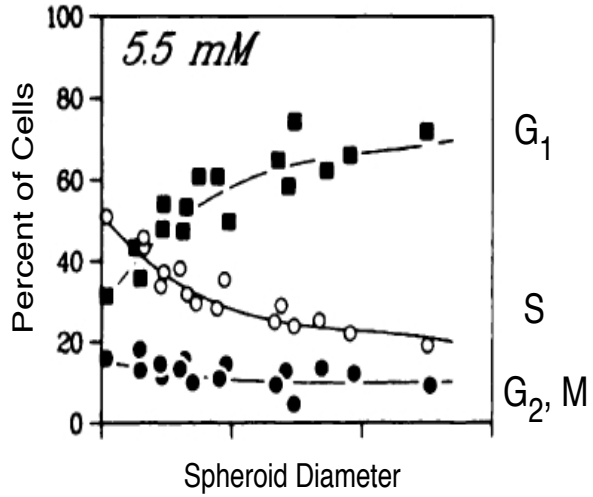
Each site begins in G_1, and under proliferative conditions, progresses through the cell cycle towards Division (D).

Simulation



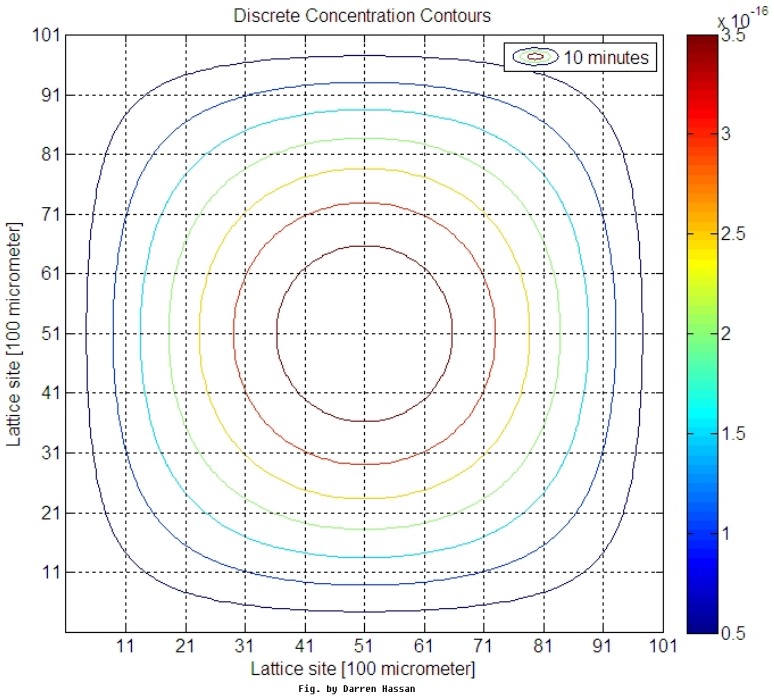
Experiment

Freyer & Sutherland (1986)



Numerical artefacts: geometry problem

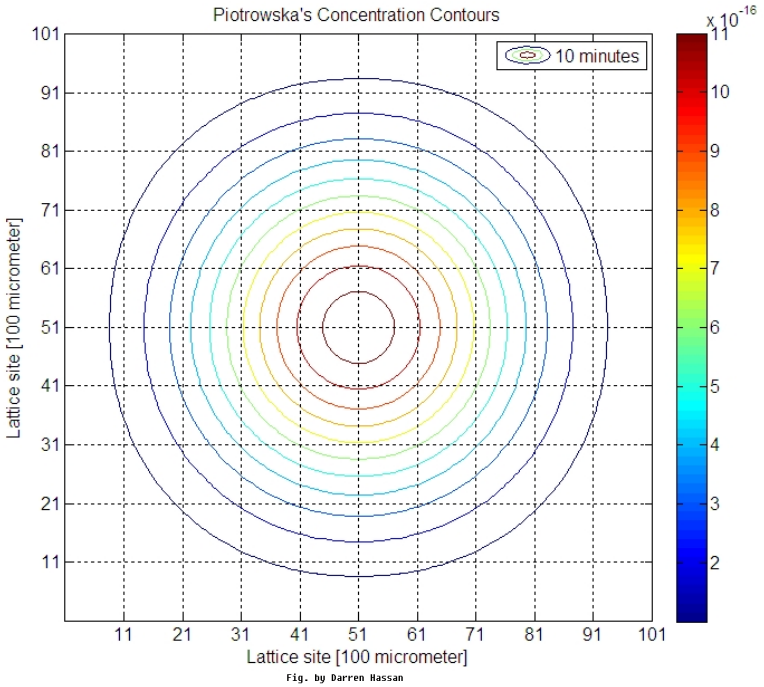
We have a square lattice with Moore neighbourhood.



If diffusion probability is homogeneous on a square lattice, results in anisotropic diffusive frontier

Numerical artefacts: geometry problem

For isotropy, apply heterogeneous diffusion scaling based on geometry of the lattice.

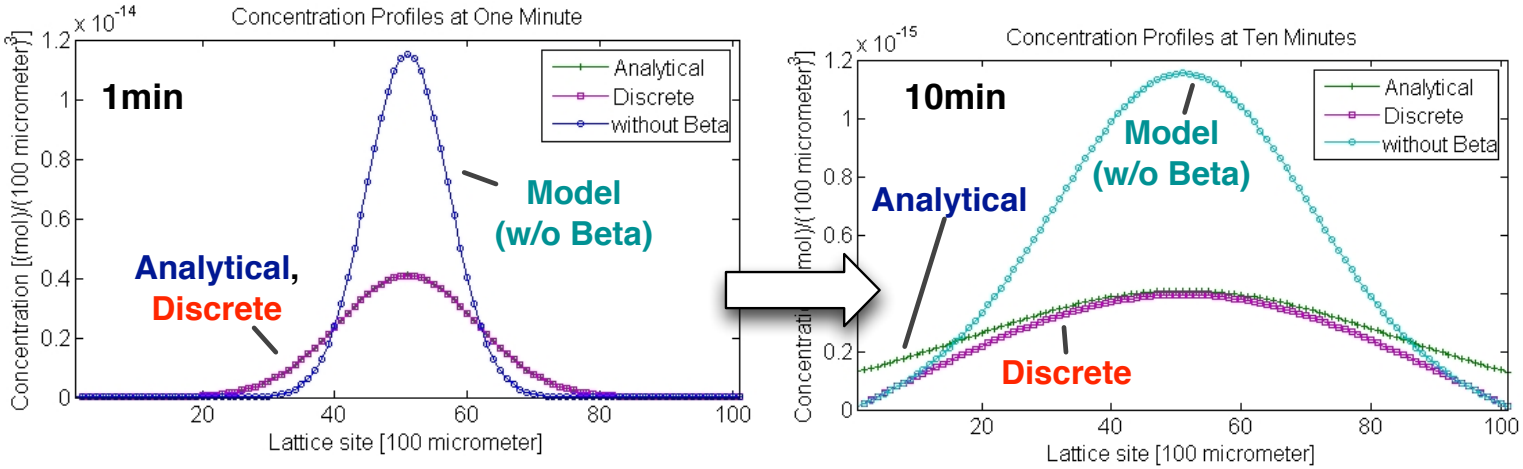


- α scaled diffusion coefficient for considered substances (glucose, oxygen and pH),
- $\beta = 2\sqrt{2}$ correction factor,
- $f = 4 + 2\sqrt{2}$ is the normalising factor,
- τ diffusion step.

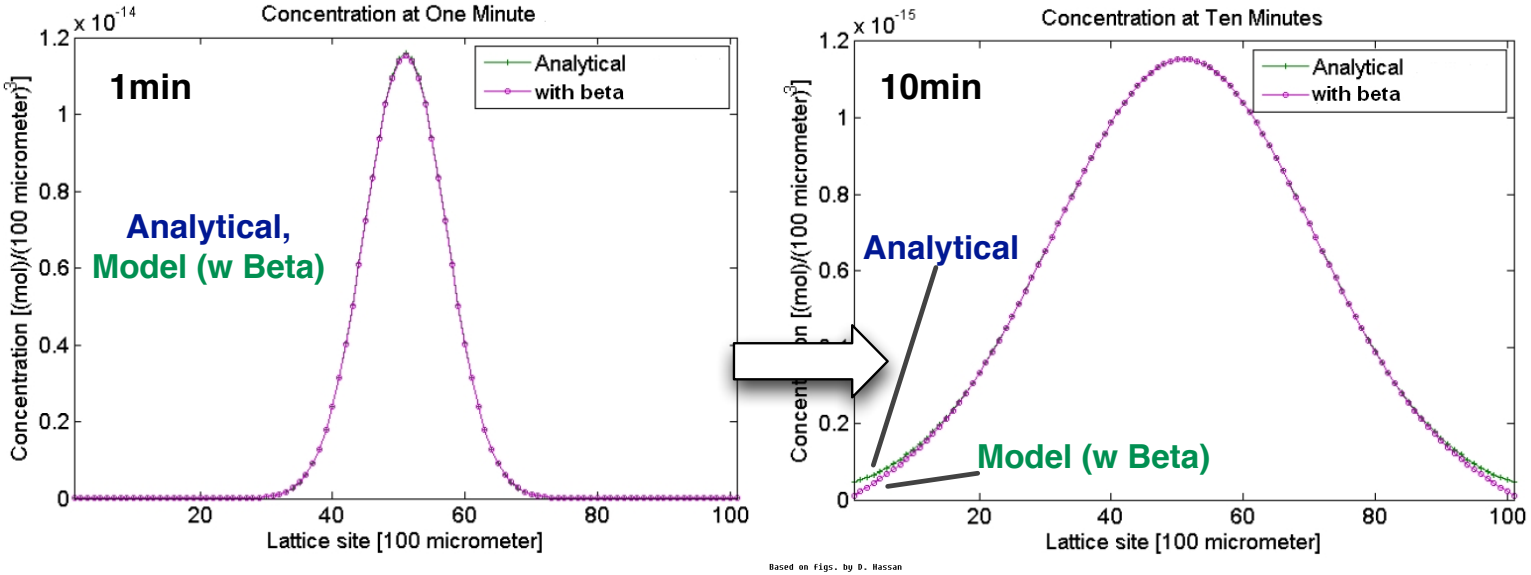
$$x_i^{t+\tau} = \frac{\alpha\beta\tau}{f}\left(\overbrace{\sum_{j\in O^i} x_j^t}^{orthogonal} + \frac{1}{\sqrt{2}}\overbrace{\sum_{j\in D^i} x_j^t}^{diagonal} - f x_i^t\right) + x_i^t$$

Numerical artefacts: numerical accuracy

Without correction factor



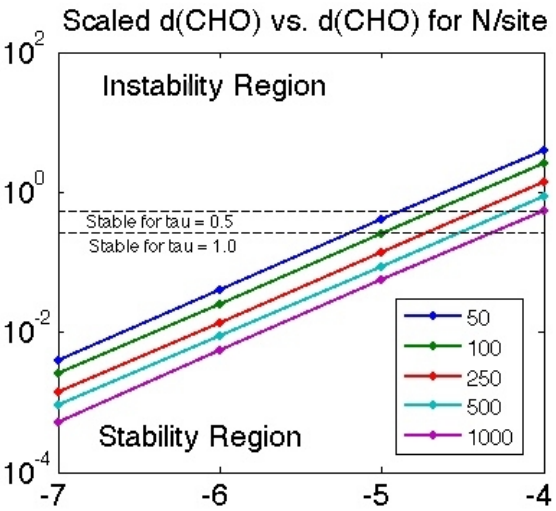
With correction factor

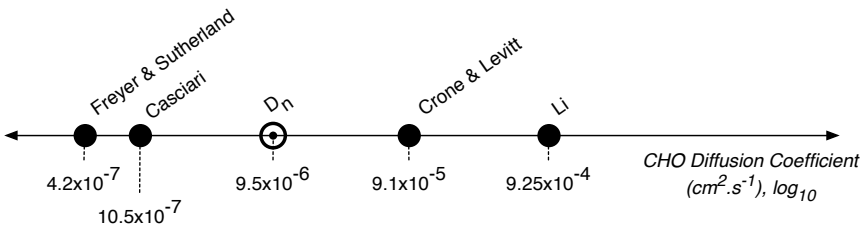


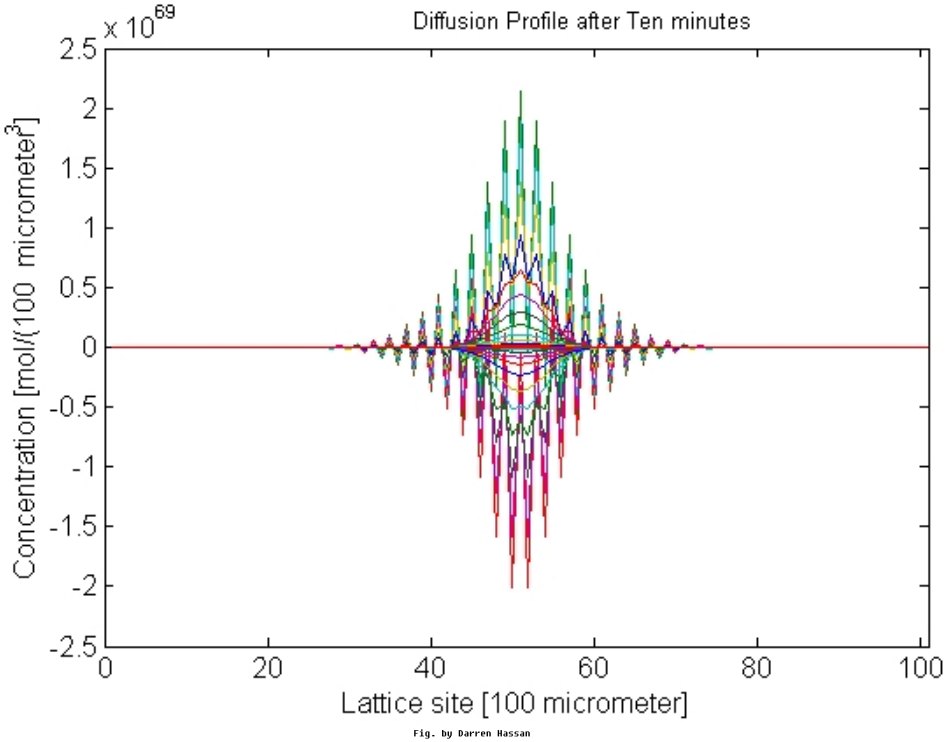
Based on figs. by D. Hassan

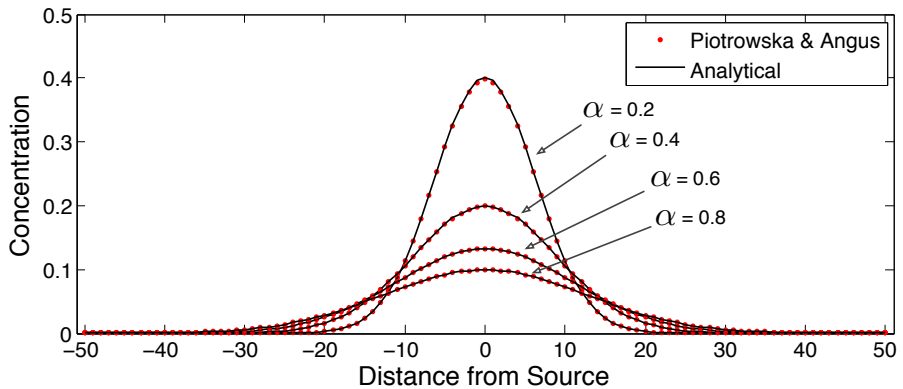
Numerical artefacts: algorithm stability

Discrete diffusion algorithm requires careful choice of τ





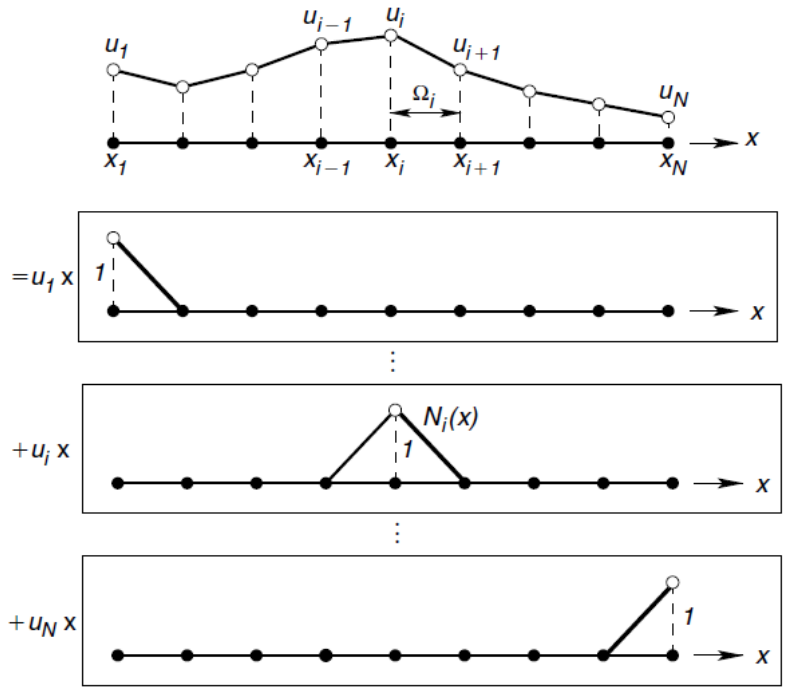




Diffusion algorithm

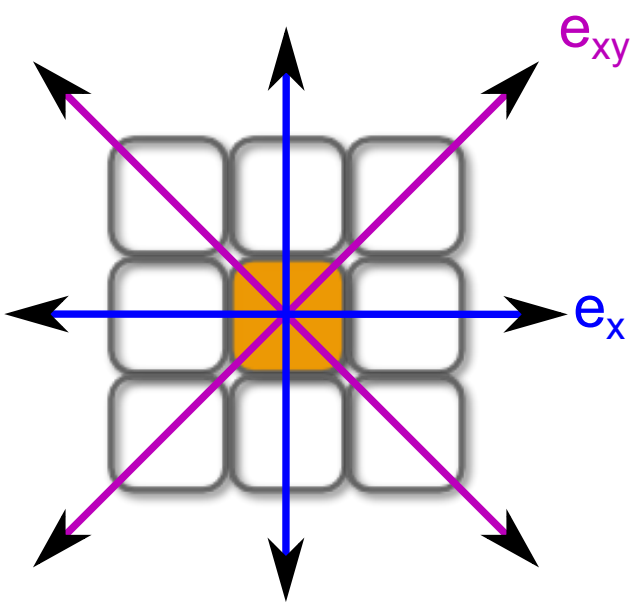
Alternative modelling of **diffusion**:

- Quasi state approximations
- Finite Element Methods (FEM)
  Galerkin method



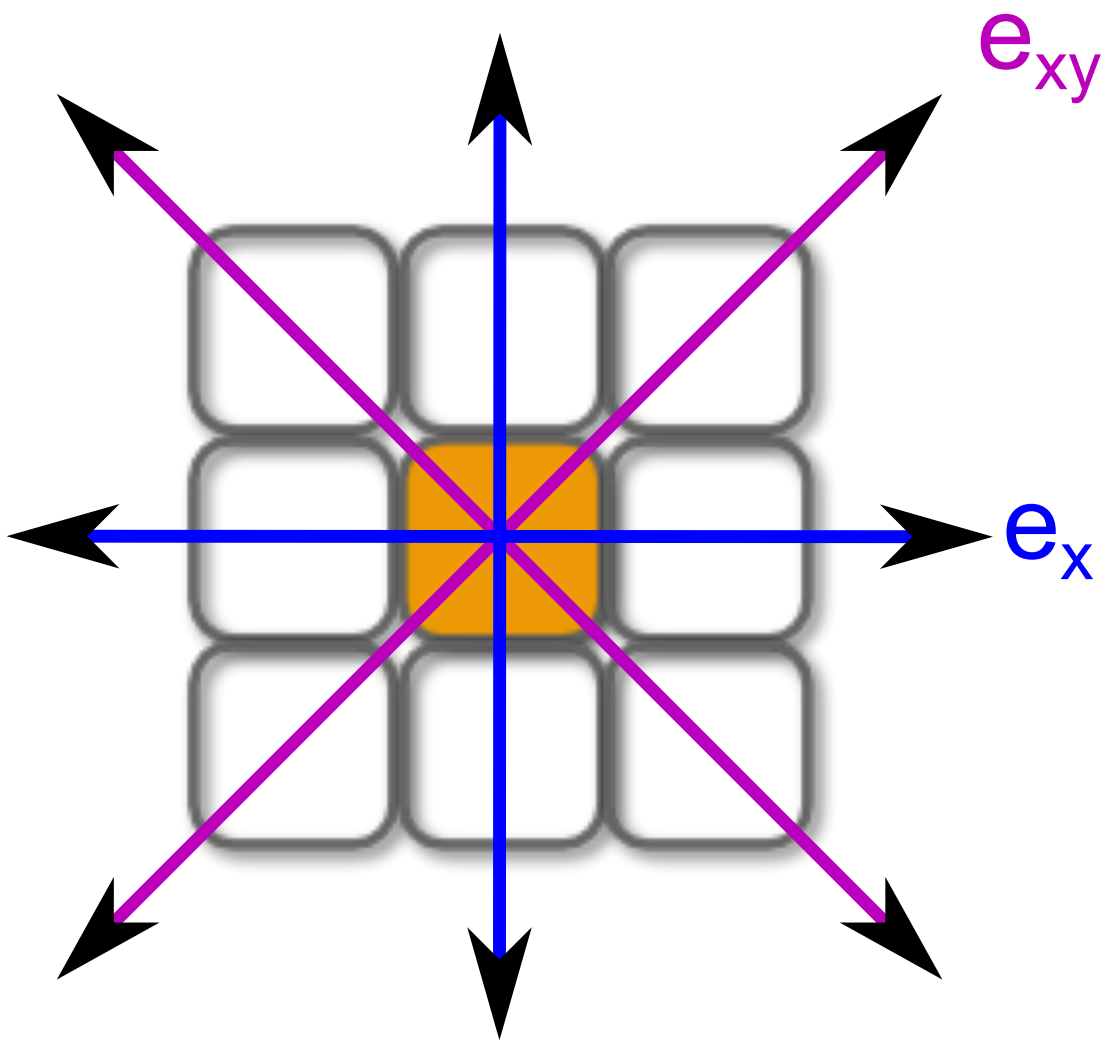
Source: S. Yip (ed.), Handbook of Materials Modeling. Volume I: Methods and Models, 1–32.

Numerical artefacts: location of new cells

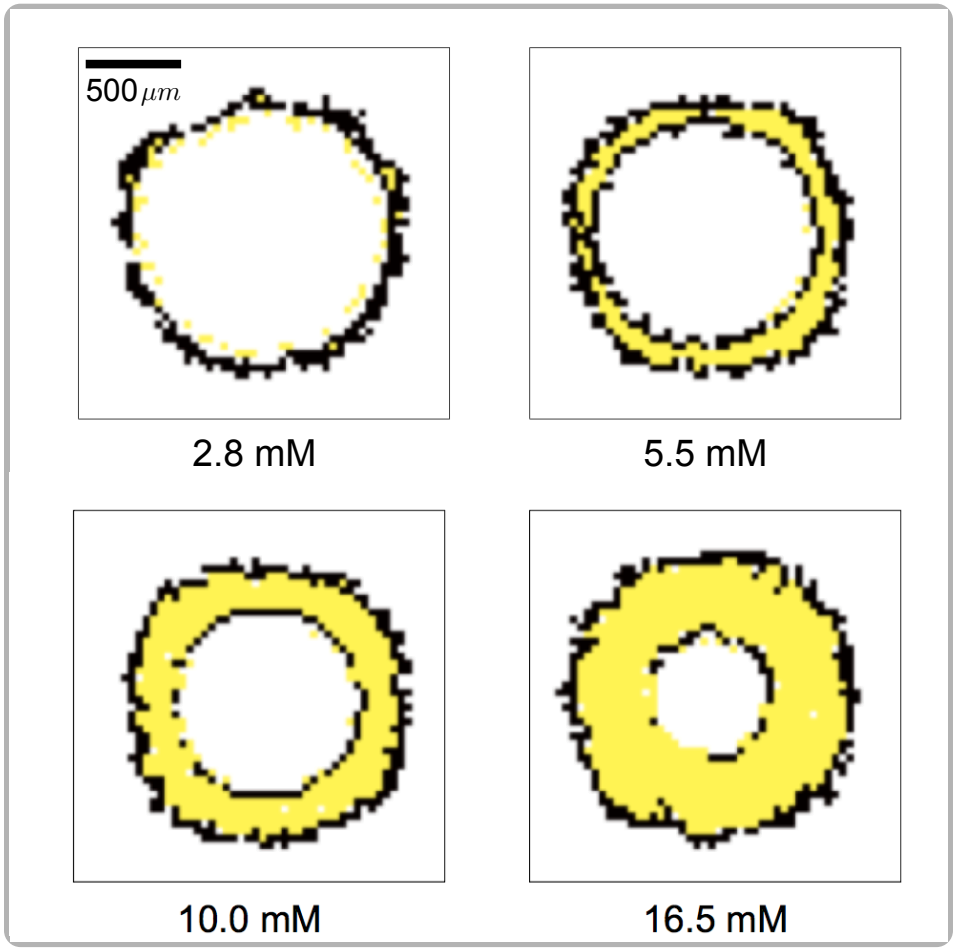


$$\frac{e_{xy}}{e_x} = \frac{\sqrt{2}(\lambda+1)}{2\lambda+1}$$

$$\lambda = \frac{1-\sqrt{2}}{\sqrt{2}-2} \approx 0.7071$$

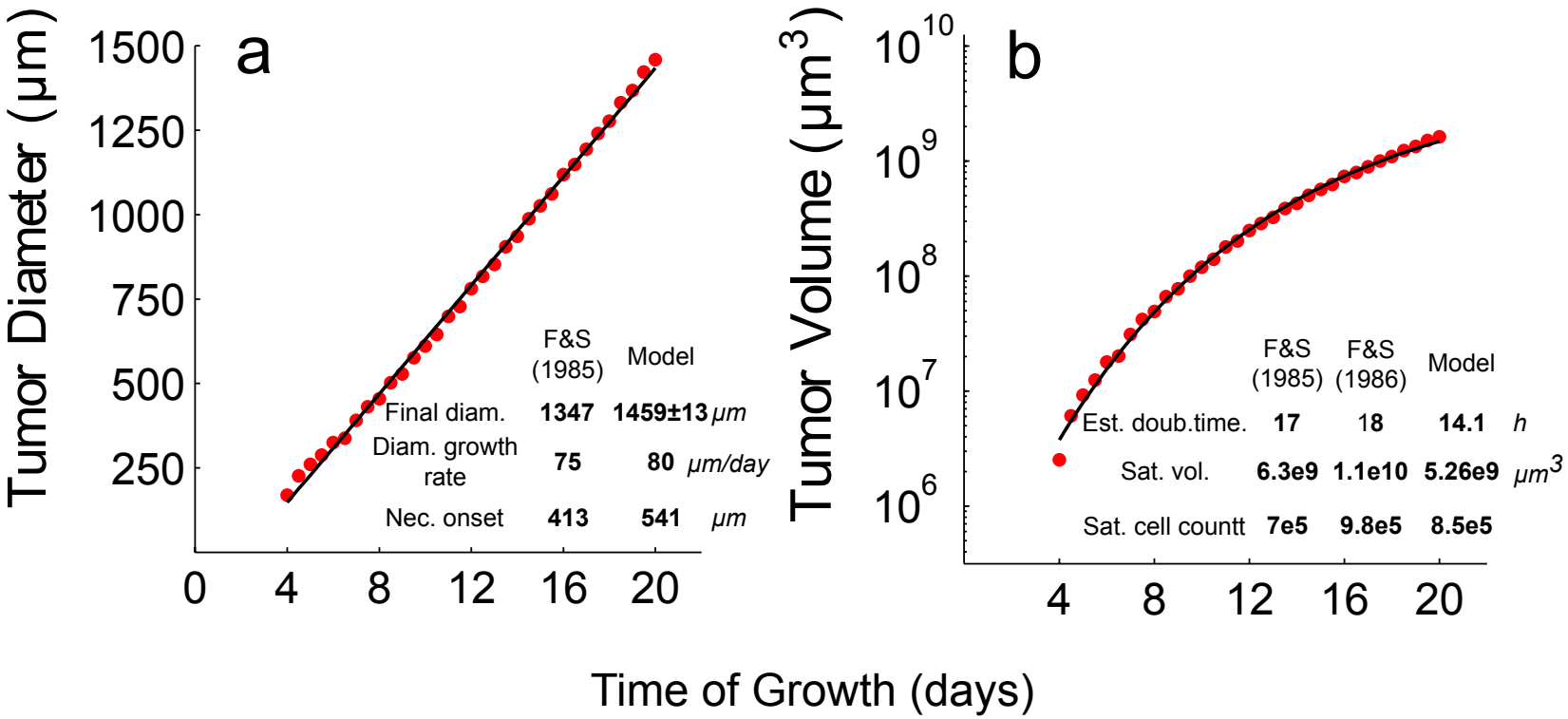


Calibration w/o irradiation: growth properties



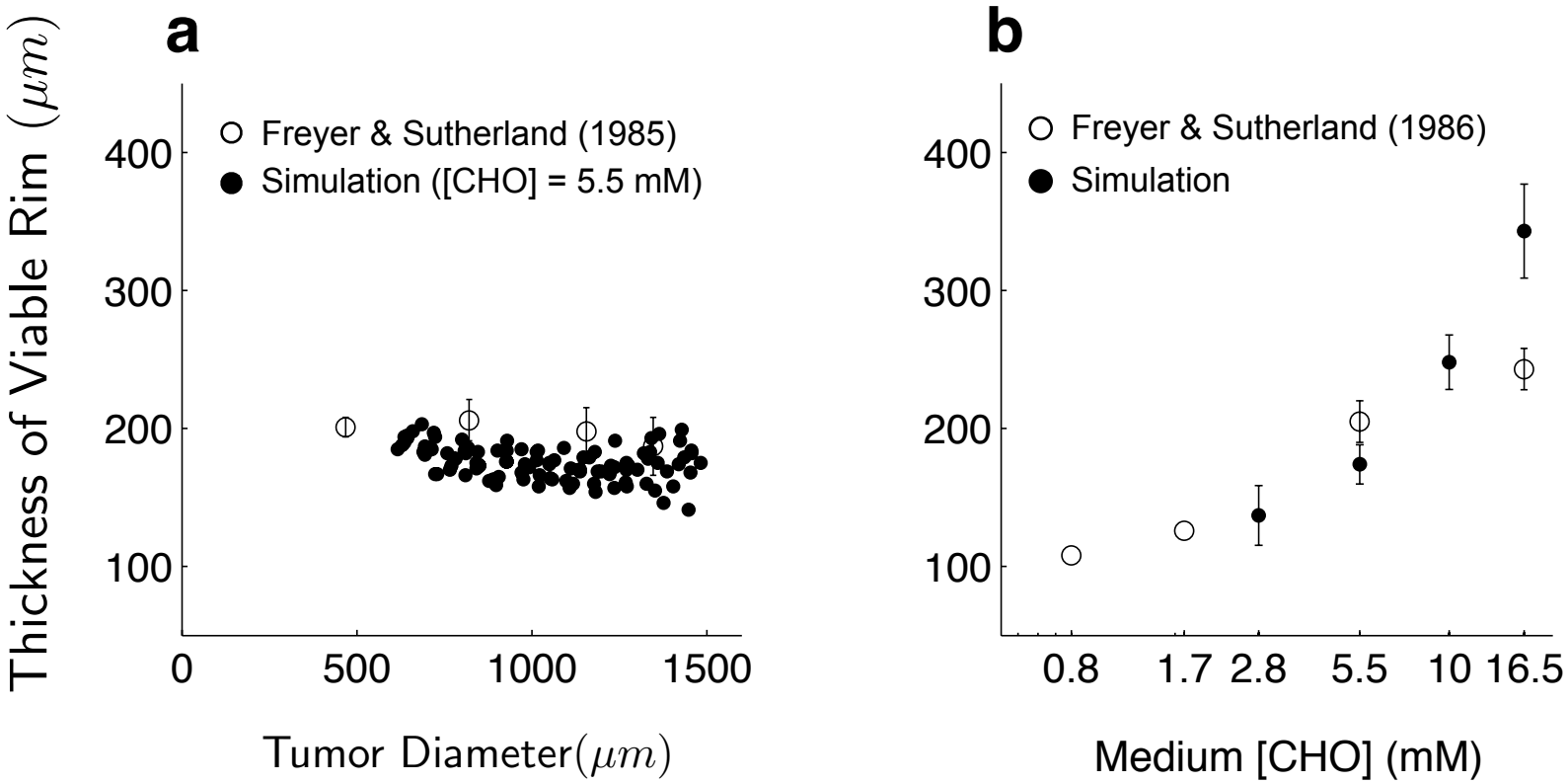
Tumour characteristics at 20 days growth for simulations under varying substrate glucose concentrations at 0.28mM oxygen concentration. Colouring indicates cell metabolism: **proliferative**, quiescent.

Calibration w/o irradiation: bulk measurements



Replication of the Freyer & Sutherland in vitro spheroid glucose trial on EMT6/Ro tumors at 5.5mM substrate CHO concentration for 20 days experiment. Data reported based on Gompertz equation nonlinear fit to data.

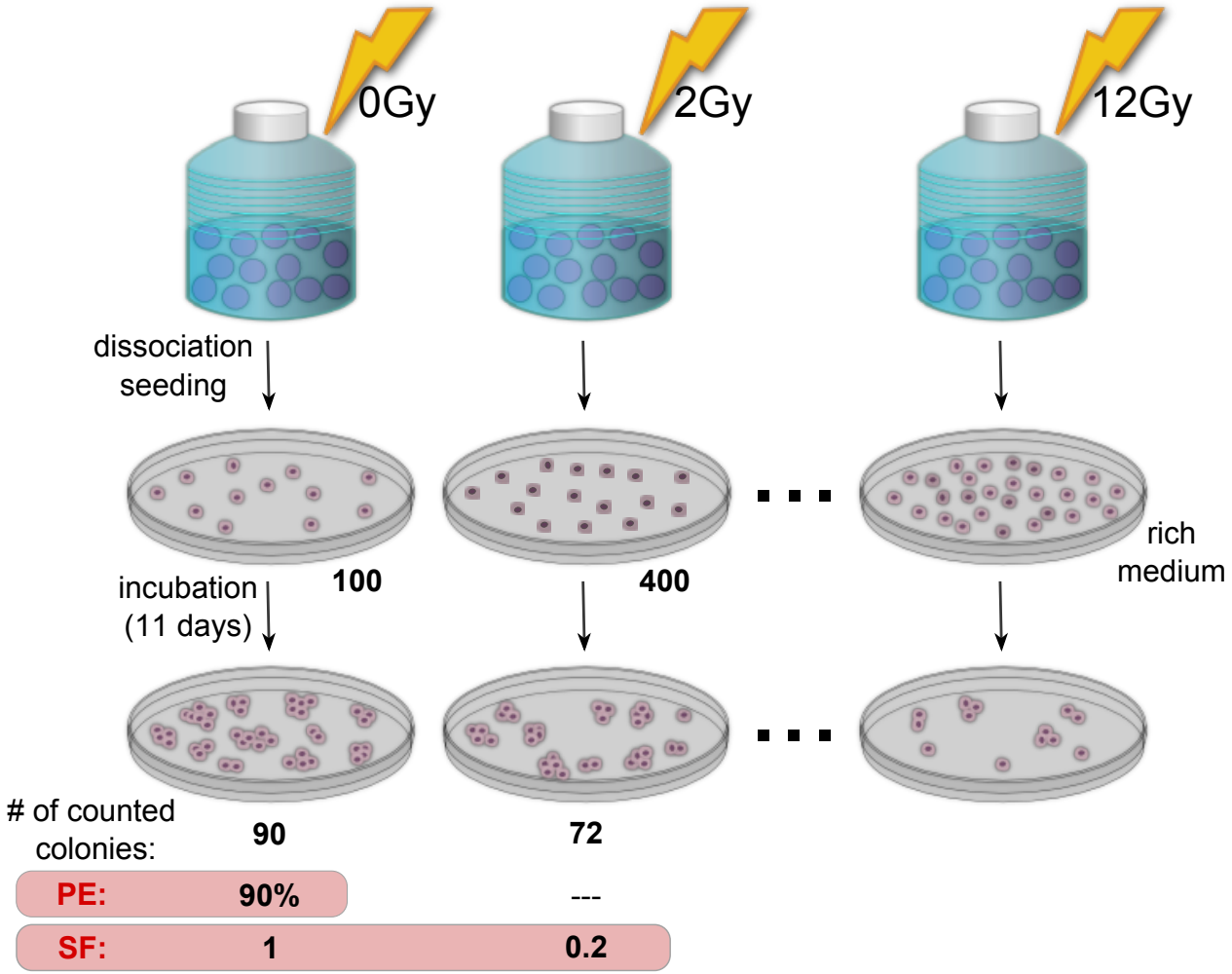
Calibration w/o irradiation: viable rim and [CHO]



(a) Replication of the Freyer & Sutherland 1985 in vitro spheroid glucose trial on EMT6/Ro tumors at 5.5mM substrate [CHO] for 20 days experiment. (b) Thickness of viable cell rim versus medium glucose concentration. Open markers indicate data from the reference, closed markers are simulation outputs.

Surviving Fraction (SF) measurement

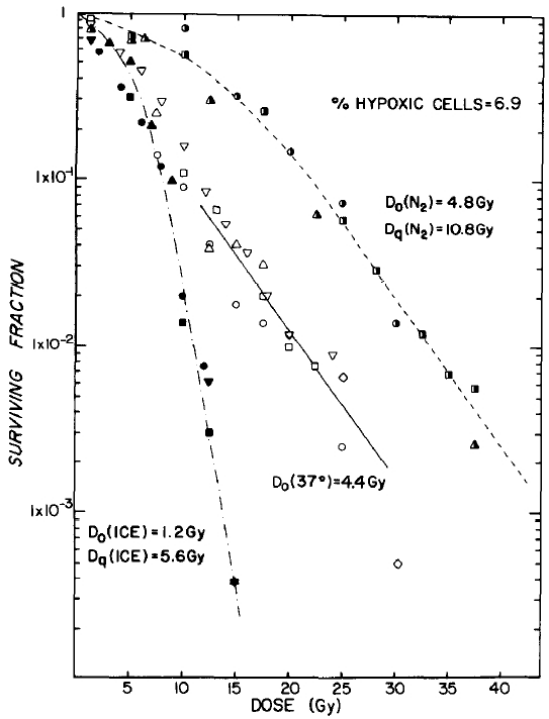
$$SF = \frac{\text{colonies counted}}{\text{cells seeded } x \text{ (PE/100)}} \qquad PE = \frac{\text{colonies observed}}{\text{\# of cells plated}}$$



Surviving Fraction (SF) measurement

LQ model:
$SF = e^{-\alpha R - \beta R^2}$

Luk&Sutherland (1987)



- EMT6/Ro: $SF(R) = 0.8080^R$ (non-log scale),
- Cell might divide many times during the incubation (cell cycle duration $\sim$ 21h);
- Luk et al. (1987) are fully aware that the 11d SF assay will see repair occurring during the incubation period and that this repair will lead to more surviving colonies being counted.

SF data **may underestimate** the true irradiation induced cell death probability

SF data **does not** give us the information on timing

Irradiation modelling: immediate cell death

Hahn et al. (1974):

- There is little or no immediate cell death observed within 6h of irradiation.

Kelley et al. (1981):

- Even for a very high dose (24Gy) there is no immediate change in the tumour volume.

Our trials:

- So long as the immediate death rate from irradiation is smaller than 0.8 the volume will be unchanged for a while.

Irradiation modelling: cell repair time

Hahn et al. (1974):

- Even a small dose of 0.5 Gy can induce delays to mitosis of up to 6h;
- Estimated that the division delay induced by a single 10 Gy dose was over 10 h – approx. 1 min/rad.

Kelley et al. (1981):

- For a large dose (24 Gy) the tumour volume roughly maintains at pre-dose levels for 8 days post-irradiation;
- For a smaller dose (6 Gy) it was estimate that the tumour volume progression is hindered by 50% of the day-0 volume after 8 days.

Wilson (2004):

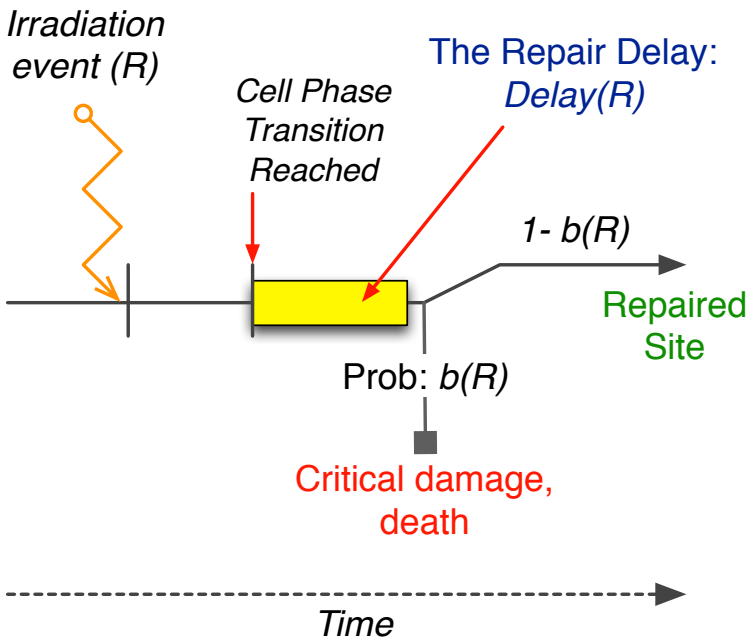
- Points out that repair can occur throughout the cell cycle, and is not confined to one particular check-point.

Irradiation & repair module

Our approach:

- The probability of death immediately upon irradiation is zero;
- Sites undergo repair exclusively at 'check-points' between cell phase cycles (e.g. $G_1|S$, $S|G_2$, etc.), with the exception of the $M|D$ transition where repair is assumed impossible;

- Repair takes an amount of time which is proportional to the irradiation dose, R_i, experienced by the site;
- Repair is not always successful, with probability $b(R_i)$ the site will enter the cell death module.



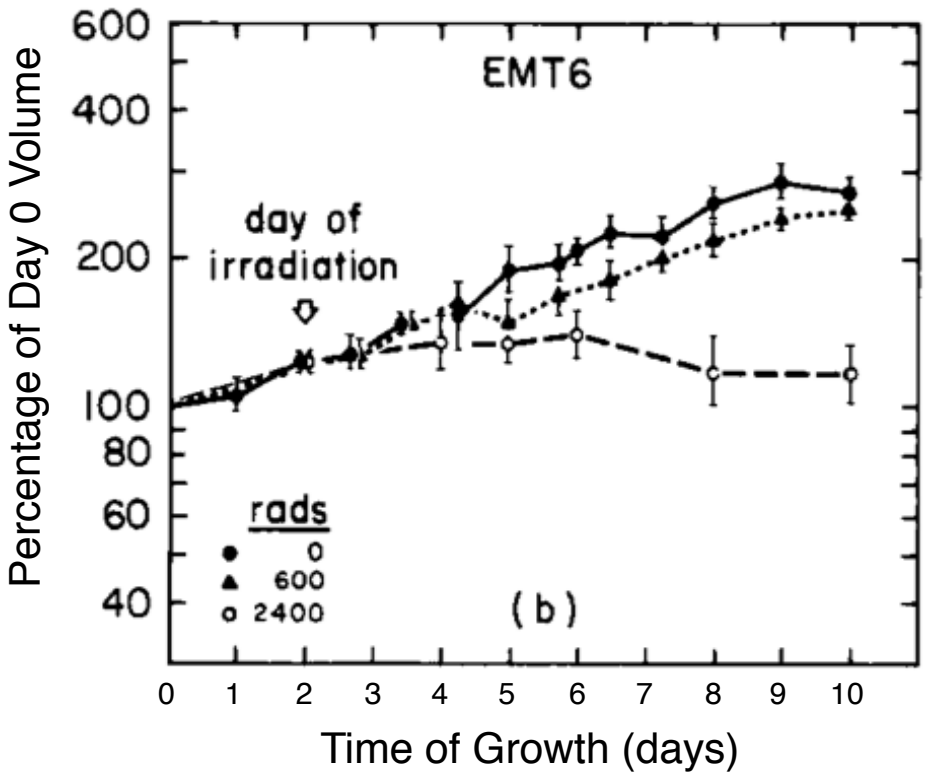
We calibrate the model with the results of Kelley et al. (1981).

Irradiation modelling: setting initial conditions

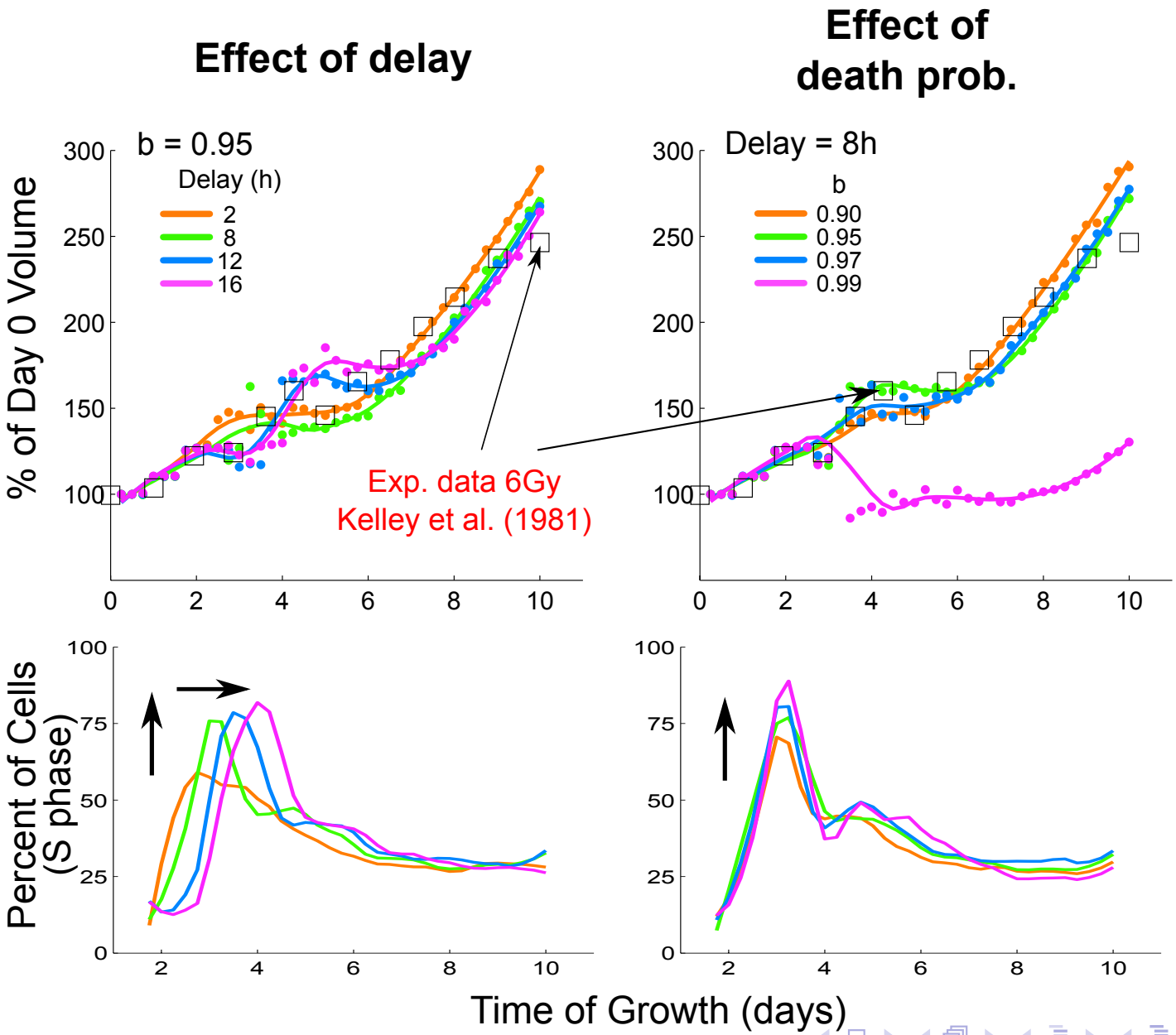
Kelley et al. (1981) lab. exp.:

- Tumours were inoculated at a size of approximately 2×10^4 cells;
- Next tumours grown *in silico* for 2 days, and then at day two the irradiation protocol (at 0Gy, 6Gy or 24Gy) was applied.

Kelley et al. (1981)



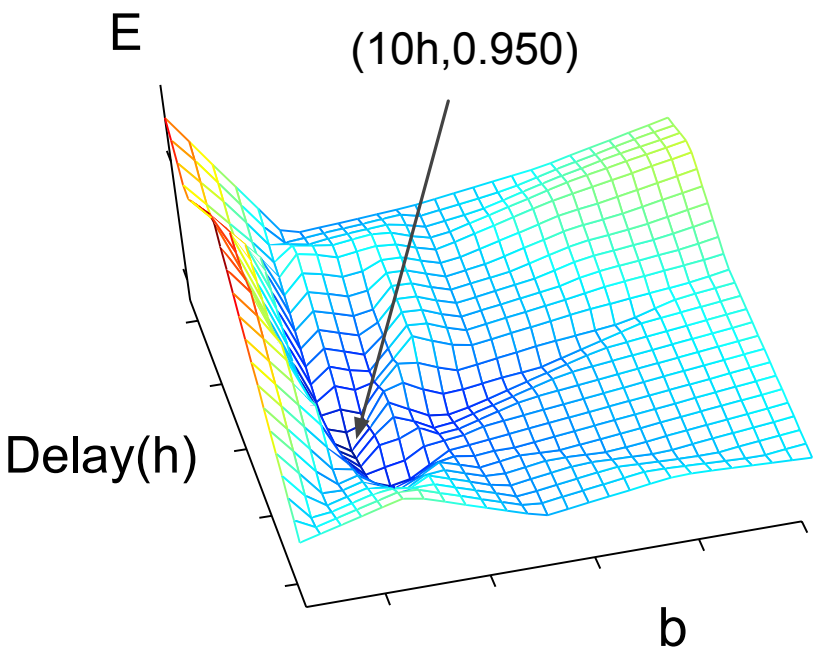
Irradiation modelling: effect of delay and death. prob.



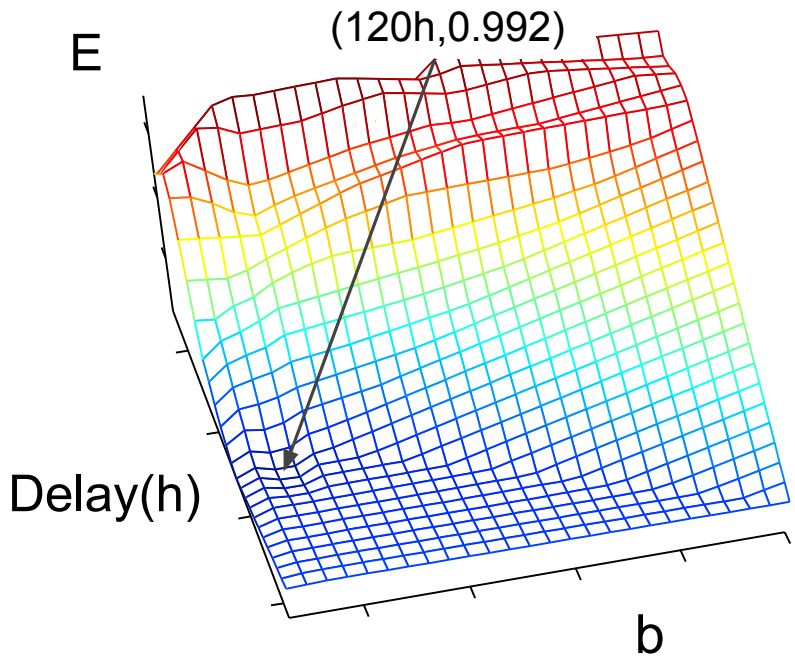
Error surface to Kelley et. al (1981)

Error Score: $$E(i) = \sum_{i}^{n} \left(log_{10} \frac{Mod_i}{Exp_i} \right)^2$$

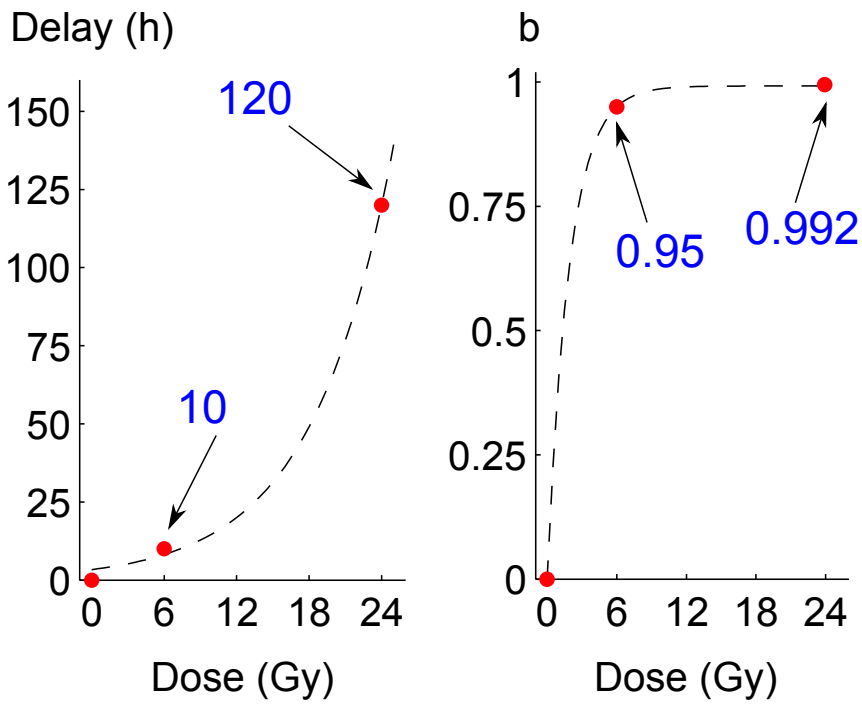
6Gy

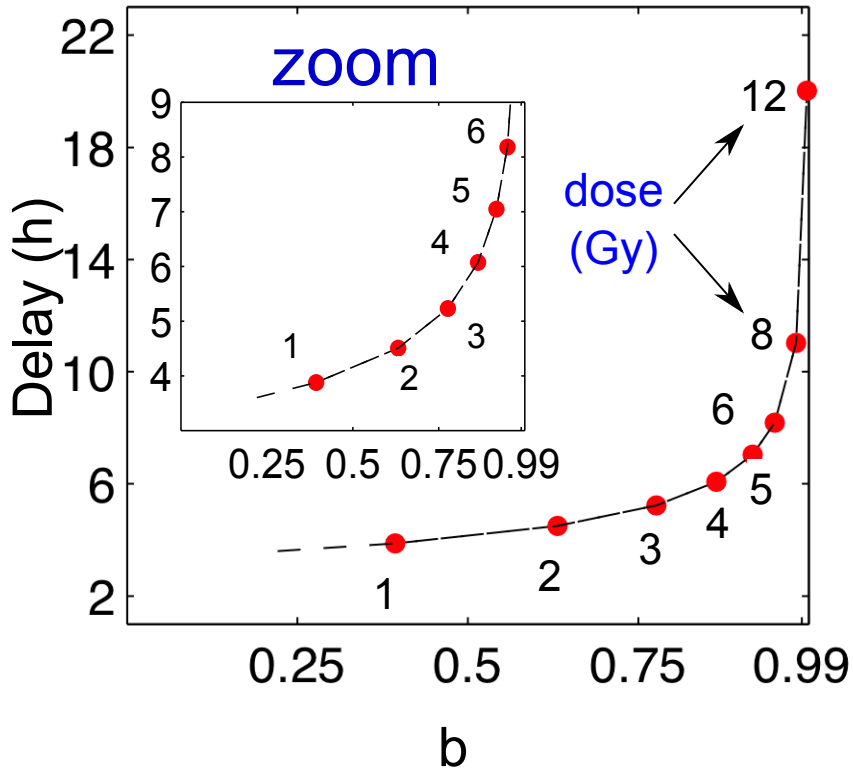


24Gy

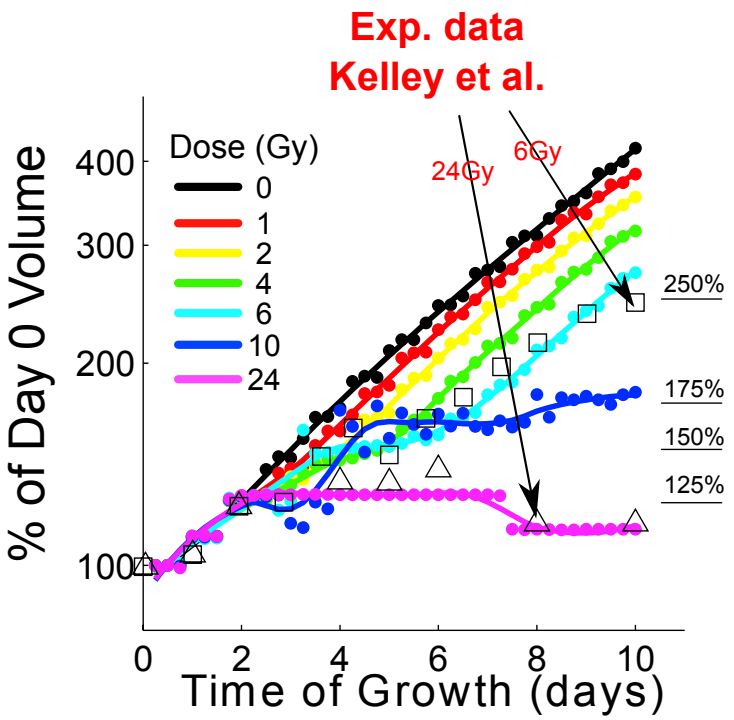


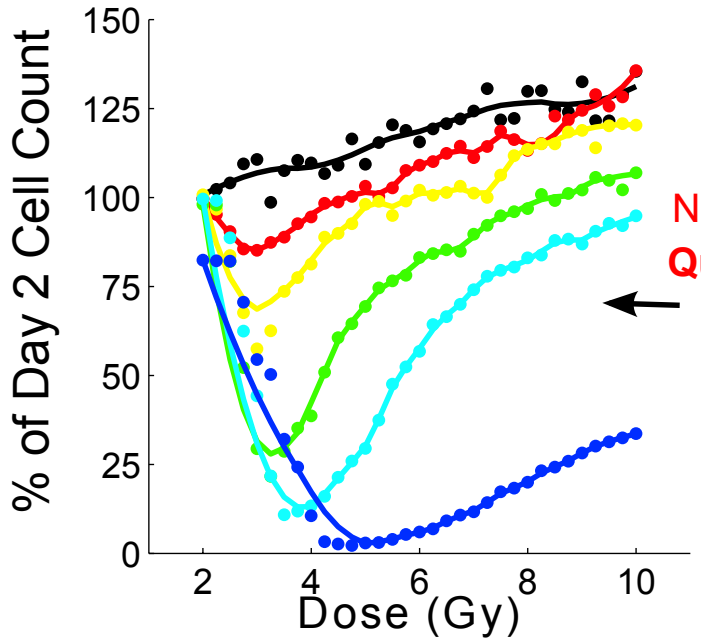
Results: model outputs





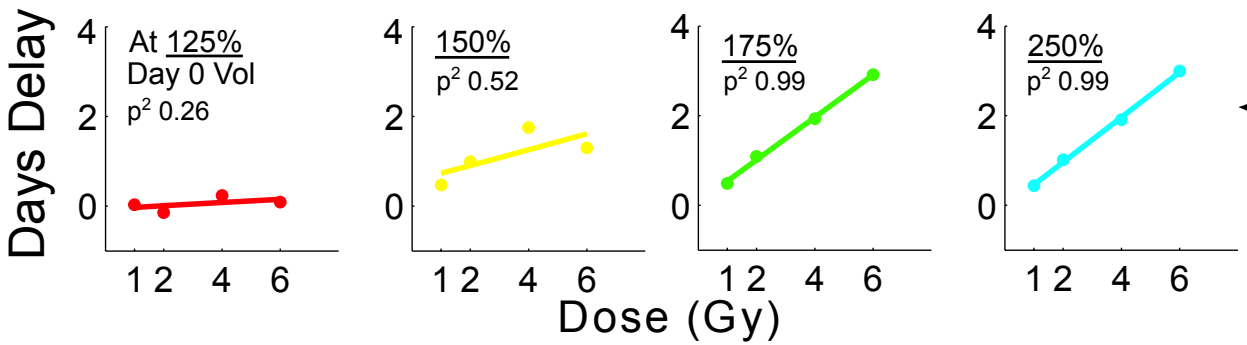
Results: calibrated outputs





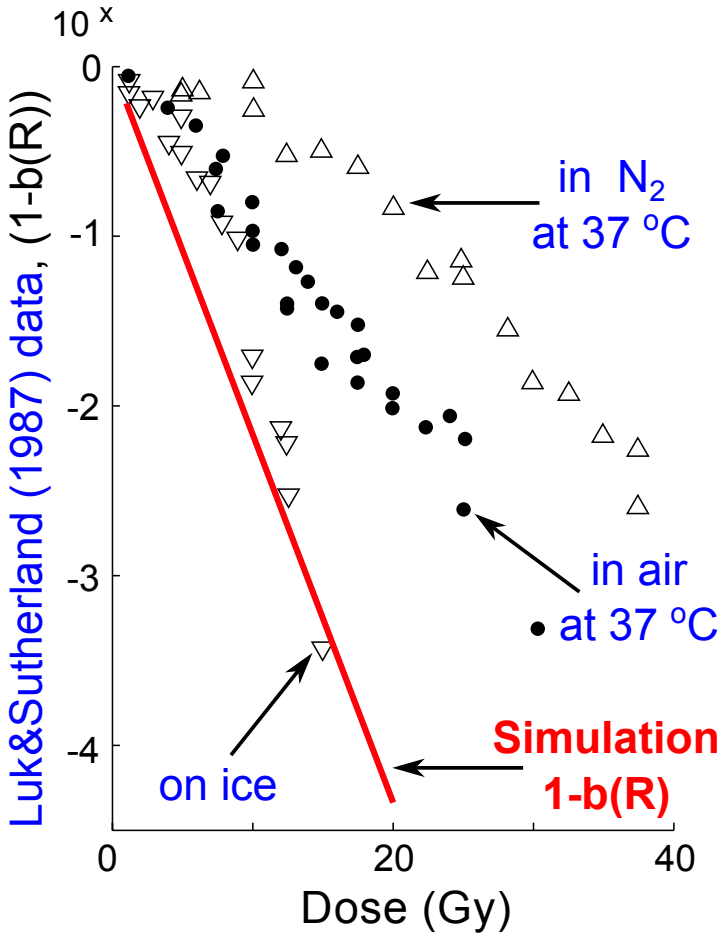
No EMT6/Ro exp. data

Qualitative agreement with R1H data Jung et al.



Agreement with EMT6/Ro exp. data Rockwell&Kallman

Results: calibrated outputs



- CA model estimated direct irradiation survival probability function gives rise to a more severe death rate (steeper gradient);
- Our irradiation probability curve is closer to the EMT6/Ro survival data for irradiation on ice;
- The difference between the two estimates under standard conditions is **more than an order of magnitude**.

Summarising

Key components:

- We have proposed a calibrated, quasi-2D, CA model of EMT6/Ro tumour growth by fitting to existing *in vitro* data:
  1. Bulk growth properties;
  2. Necrotic dynamics;
  3. Cell cycle phase distributions.
- Novel additions:
  1. Irradiation-response module: probabilistic cell death with repair.
  2. Estimation of irradiation survival probability function.
  3. Estimation of cell-cycle delays: due to repair (unavailable as yet, experimentally).

Summarising

Key outcomes:

- New, accurate, estimates of cell phase dynamics after irradiation;
- Our calibrated model shows that cell death probabilities based on survival fraction data used in other computational models may be greatly overestimated;
- For the lab: Predictions on cell-cycle response dynamics (peack in S and G_2 phases);
- For optimised therapy: A new platform to run optimal search over the large radio-therapy treatment space.

Opportunities & Challenges for the work

Opportunities

- CAs are not the perfect models, but are a reasonable choice for tumour dynamics;
- The dynamics of CAs are a good representation of real spheroid dynamics (but *in vivo*?);
- CAs allow investigation of non-experimentally accessible data or data for which experiments are too expensive;
- CAs show good promise for investigation of theory (qualitative & quantitative).

Challenges

- Contingent metabolism needs to be handled carefully (where do you stop? genetic pathways?);
- Mapping from continuous to numerical diffusion not straight-forward (scaled?);
- Migration & metastasis?
- Cell volume considerations?
- Parameters estimation?
- Cell irradiation response?
- Irradiation side effects (of 'optimal' therapies)?

Our publications

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More on our work can be found:

- S.D. Angus, M.J. Piotrowska: 'A numerical model of EMT6/Ro spheroid dynamics under irradiation: calibration & estimation of the underlying irradiation-induced cell survival probability', *Journal of Theoretical Biology*, 320, 2013, 23—32;
- S.D. Angus, M.J. Piotrowska: 'The Onset of Necrosis in a 3D Cellular Automaton Model of EMT6 Multi-Cellular Spheroids', *Applicationes Mathematicae*, 37(1), 2010, 69-88;
- M.J. Piotrowska, S.D. Angus: 'A Quantitative Cellular Automaton Model of in vitro Multicellular Spheroid Tumour Growth', *Journal of Theoretical Biology*, 258, 2009, 165-178.

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