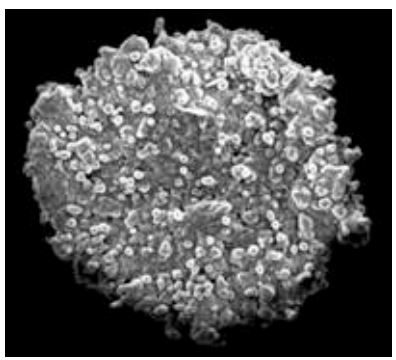
Using High Fidelity Numerical Simulation & GA Search to find Better Radiation Therapies for Cancer



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Agenda

Aims: The 'Emerald City'

Step 1: a high fidelity numerical model of tumour growth

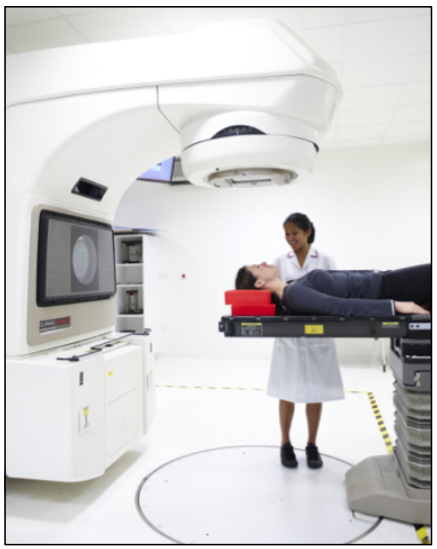
Step 2: a high fidelity model of tumour growth *and response to single-dose irradiation*

Step 3: a high fidelity model of tumour growth *and response to multi-dose irradiation*

Step 4: *Apply GA search to find better multi-dose irradiation protocols by numerical simulation*

Some reflections on the journey.

The Emerald City



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

About 4 in 10 people presently receive radiotherapy as part of their treatment;

Majority of treatments delivered as a 'multi-fraction' protocol (a sequence of low-dose fractions applied once- or twice- a day) (often nothing on the weekend);

But exploration of alternative protocols (timing, dose, or dose+timing) is effectively non-existent ...

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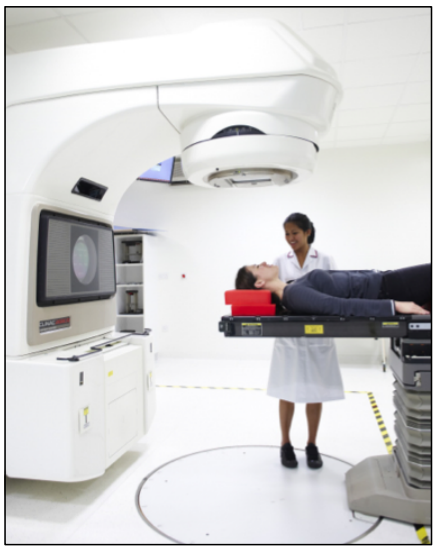
The Emerald City



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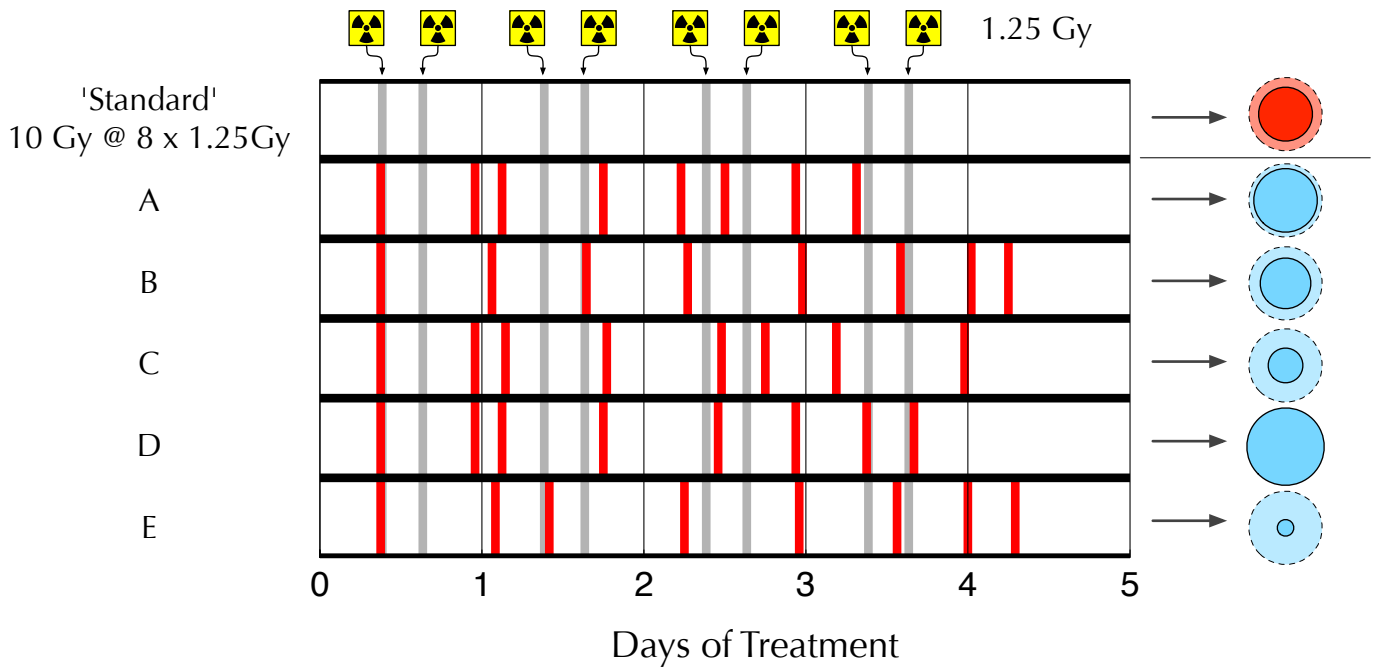

A '10 fraction' program, with time-gaps in {18,18.5,...,29.5,30}h can be constructed in over 95 trillion ways.

*Can we find a better protocol, simply by changing the **timing** of the fractions?*

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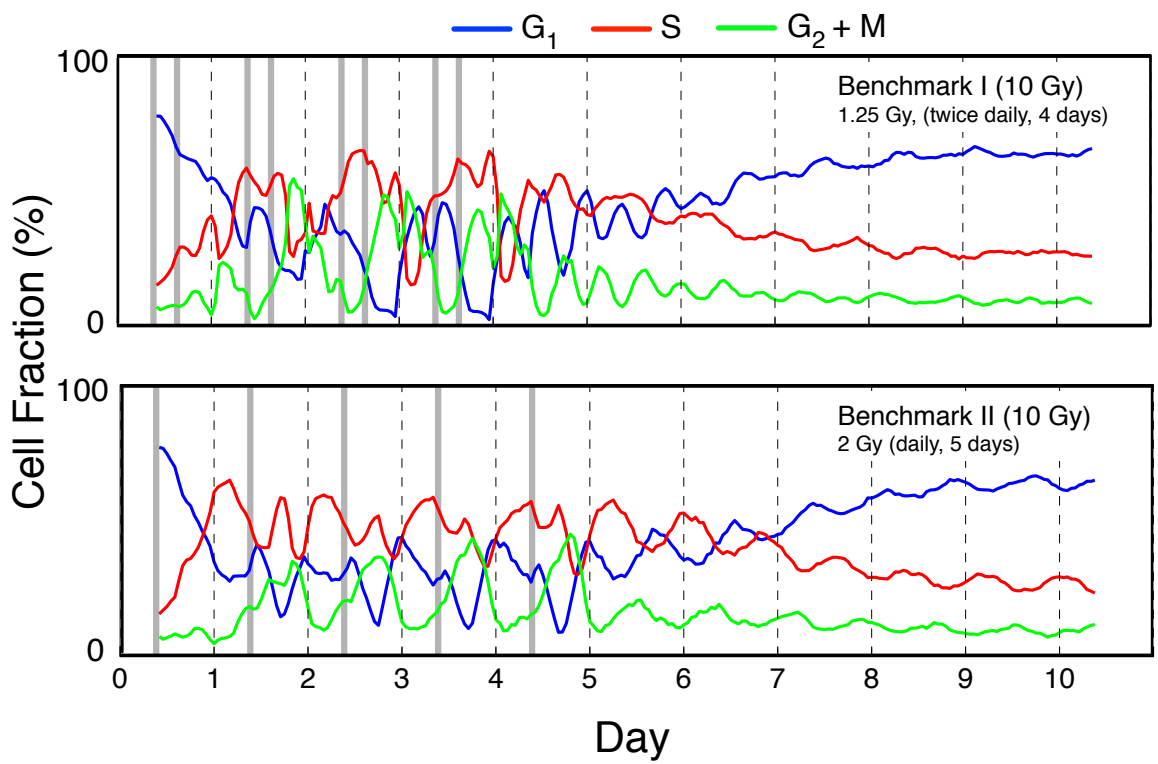
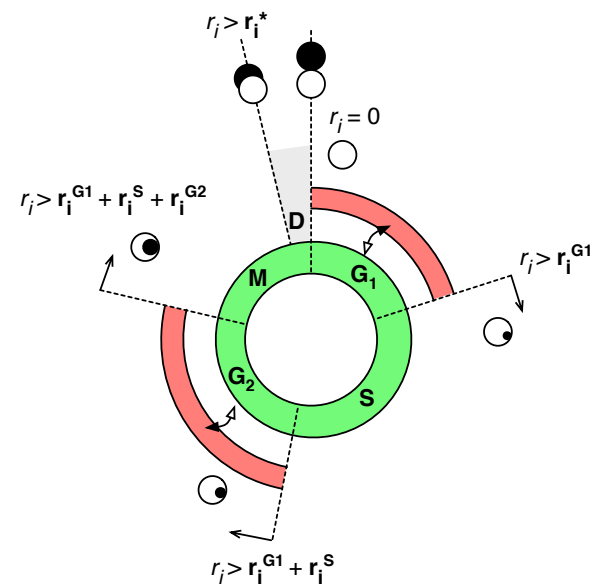
The Emerald City: the hypothesis





*Well timed fractions might exploit the **dynamical cell-phase response** of the cells, leading to greater impact **at no additional radiation burden**, possibly due to **synchronisation** of cell-phases.*

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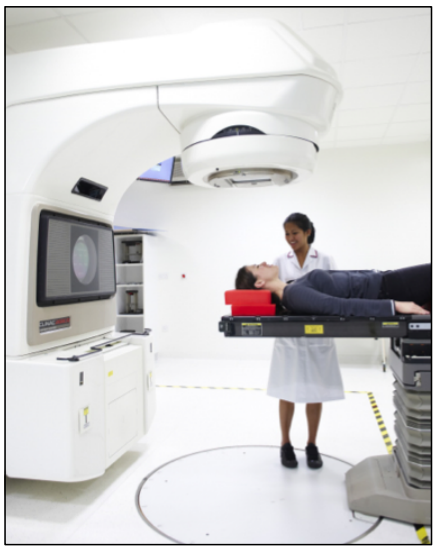
Some reflections on the journey.

The Approach



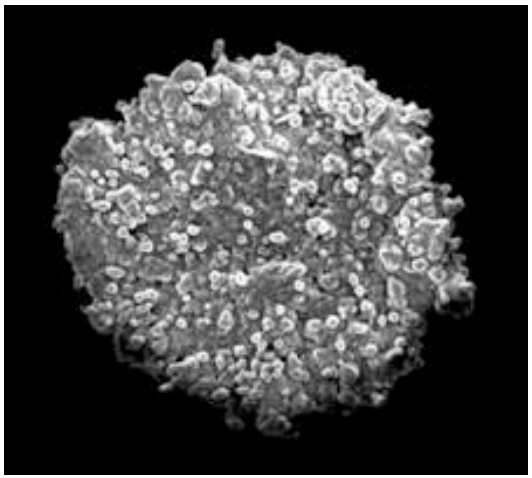
Source: [1] Cancer Research UK, 'Radiotherapy Briefsheet', Aug. 2010.

High Fidelity: the highest probability of translation to the lab / clinic

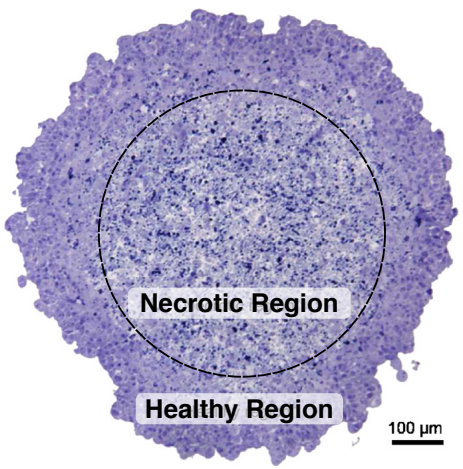
Single Cell-line Focus: the most available data for calibration and validation (choose EMT6/Ro)

'Better': establish benchmarks results of standard protocols for statistical comparison to establish any benefit (again: translational outcomes)

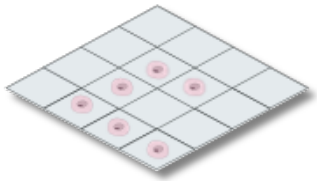
Spatial Considerations



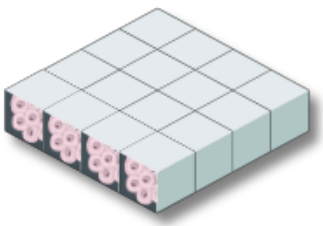
Source: Senavirathna et al. (2013), Theranostics 3(9):687-691.



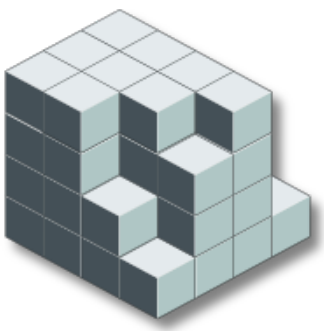
Source: Yu et al. (2007), 3-d video holography through biological tissue.



2D

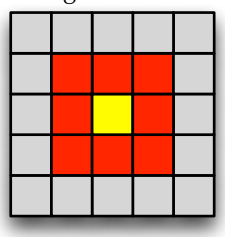


Quasi-2D



3D

Moore (8) Neighbourhood



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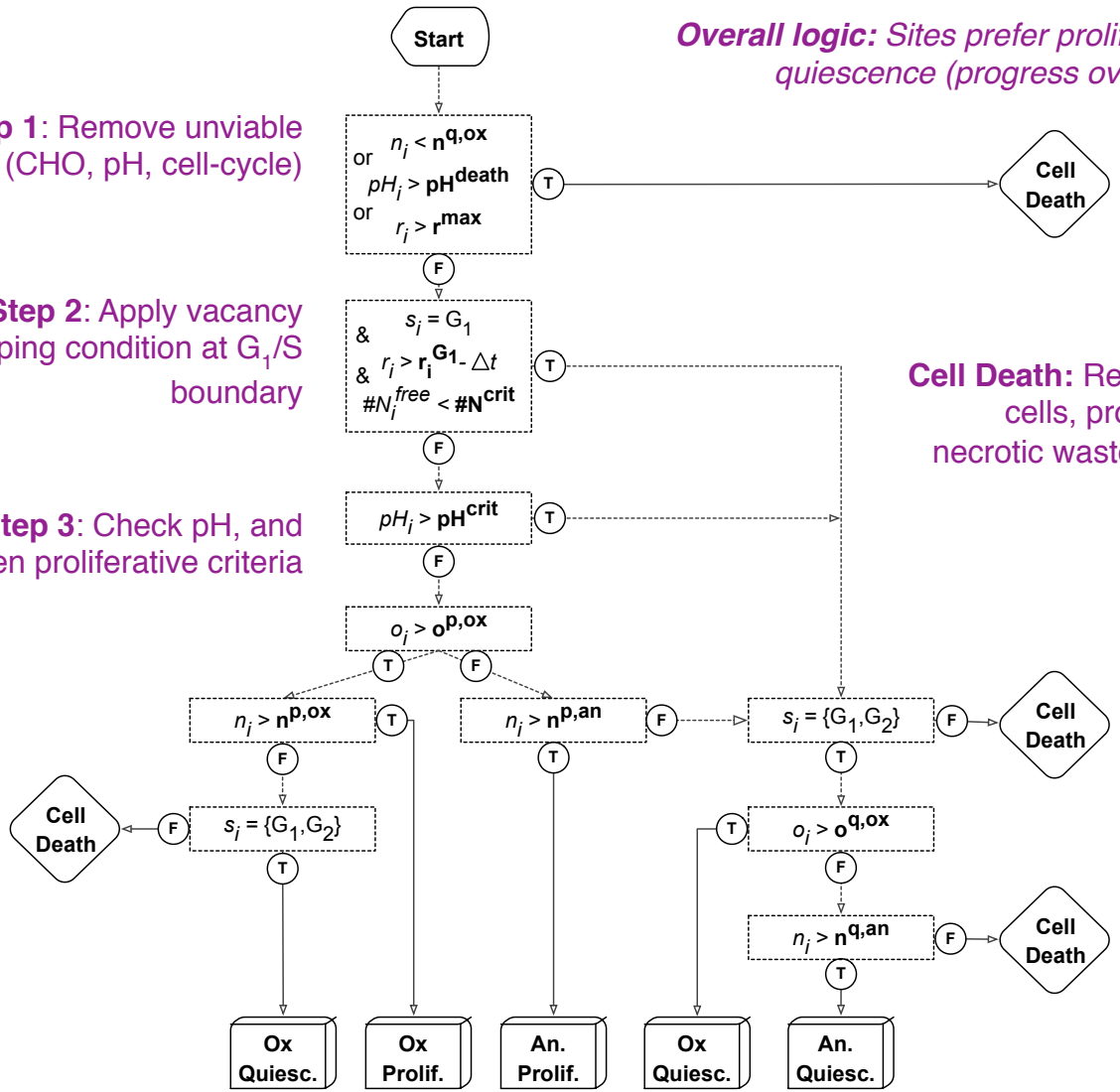
Metabolism Algorithms

Overall logic: *Sites prefer proliferation > quiescence (progress over stasis)*

Step 1: Remove unviable sites (CHO, pH, cell-cycle)

Step 2: Apply vacancy stopping condition at G_1/S boundary

Step 3: Check pH, and then proliferative criteria



Cell Death: Remove cells, produce necrotic waste (H^+)

Substrate:
We match experimental conditions [FS1985] ...
[CHO] = 5.5 *mM*
$[O_2]$ = 0.28 *mM*
pH = 7.4

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Parameters (…yes!)

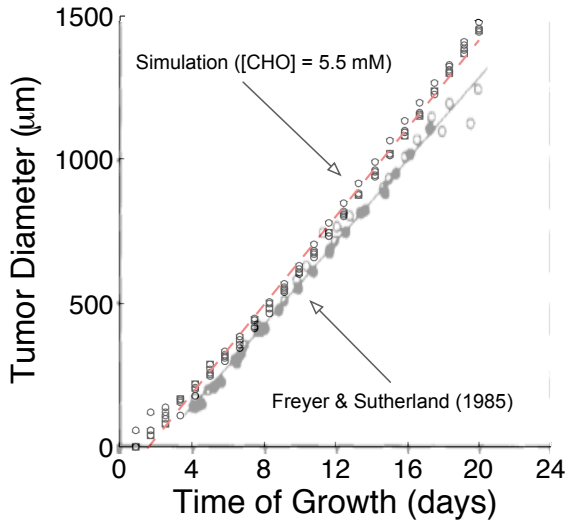
Model parameters with references.

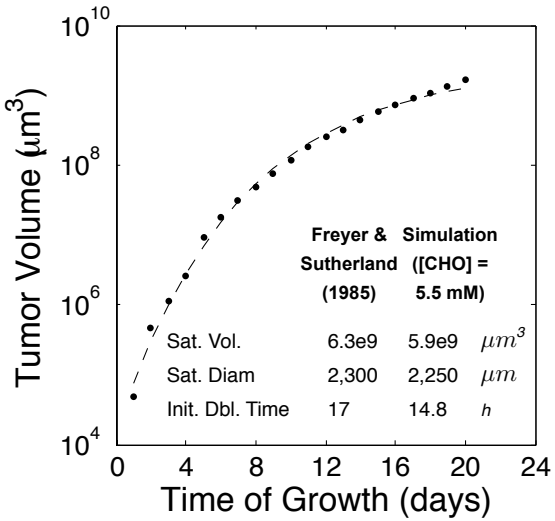
Description	Symbol	Value	Units	Ref[a]
Cell packing density	ρ	4×10^8	cell cm^{-3}	Freyer and Sutherland (1985)
Number of cells per site	N	20	cell site^{-1}	Calib.
Unit side-length	u	38.8	µm	Calc.
Update time-step	Δt	6	s	Set
Diffusion time-step	τ	0.25	s	Set
Cell cycle				
Av. G_1 phase dur. (s.d.)	$\bar{r}^{G_1}(\sigma_0^{G_1})$	6(1)	h	Zacharaki et al. (2004)
Av. S phase dur. (s.d.)	$\bar{r}^{S}(\sigma_0^{S})$	10(2)	h	Zacharaki et al. (2004)
Av. G_2 phase dur. (s.d.)	$\bar{r}^{G_2}(\sigma_0^{G_2})$	2(0)	h	Zacharaki et al. (2004)
Av. M phase dur. (s.d.)[b]	$\bar{r}^{M}(\sigma_0^{M})$	2(0)	h	Zacharaki et al. (2004)
Av. D phase dur. (s.d.)[b]	$\bar{r}^{D}(\sigma_0^{D})$	0.1(0)	h	Est.
Maximal cell cycle time	r^{max}	20.1	h	Est., Freyer and Sutherland (1980, 1985), Jiang et al. (2005)
Medium				
Medium [CHO]	n_{ex}	5.5	mM	Freyer and Sutherland (1985), Luk and Sutherland (1987), Kelley et al. (1981)
Medium [O_2] conc.	o_{ex}	0.28	mM	Freyer and Sutherland (1985), Luk and Sutherland (1987), Kelley et al. (1981)
Medium pH level	pH_{ex}	7.4		Freyer and Sutherland (1985), Luk and Sutherland (1987), Kelley et al. (1981)
Crit. pH: prolif.→quiesc.	pH^{crit}	6.4		Casciari et al. (1992)
Crit. pH: quiesc.→death	pH^{death}	6.0		Dairkee et al. (1995)
Diffusion coef.				
CHO diffusion coef.	D_n	9.5×10^{-6}	cm^2 s^{-1}	Calib.
O_2 diffusion coef.	D_o	1.82×10^{-5}	cm^2 s^{-1}	Venkatasubramanian et al. (2006)
H^+ diffusion coef.	D_w	1.1×10^{-5}	cm^2 s^{-1}	Crone and Levitt (1984)
Proliferating cells				
Aer. prol. CHO cons. rt.	$n^{p,ox}$	18×10^{-17}	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
An. prol. CHO cons. rt.	$n^{p,an}$	52×10^{-17}	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
Aer. prol. O_2 cons. rt.	$o^{p,ox}$	8.3×10^{-17}	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
An. prol. O_2 cons. rt.	$o^{p,an}$	0	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
Aer. prol. H^+ prod. rt.	$w^{p,ox}$	1×10^{-5}	mM (s)$^{-1}$	Patel et al. (2001)
An. prol. H^+ prod. rt	$w^{p,an} = 2n^{p,an}$	104×10^{-17}	mol (cell s)$^{-1}$	Est.
Quiescent cells				
Aer. quiesc. CHO cons. rt.	$n^{q,ox}$	15×10^{-17}	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
An. quies. CHO cons. rt.	$n^{q,an} = \frac{n^{p,an}}{n^{p,ox}} n^{q,ox}$	43×10^{-17}	mol (cell s)$^{-1}$	Est., Freyer and Sutherland (1985)
Aer. quiesc. O_2 cons. rt.	$o^{q,ox}$	5.5×10^{-17}	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
An. quiesc. O_2 cons. rt.	$o^{q,an}$	0	mol (cell s)$^{-1}$	Freyer and Sutherland (1985)
Aer. quiesc. H^+ prod. rt.	$w^{q,ox}$	0.05×10^{-5}	mM (s)$^{-1}$	Patel et al. (2001)
An. quiesc. H^+ prod. rt.	$w^{q,an} = 2n^{q,an}$	86×10^{-17}	mol (cell s)$^{-1}$	Est.
Dead cells				
Dead cells CHO cons. rt.	n^{death}	0	mol (cell s)$^{-1}$	Est.
Dead cells O_2 cons. rt.	o^{death}	0	mol (cell s)$^{-1}$	Est.
Necrotic material prod.	w^n	9.0×10^{-4}	mM (site)$^{-1}$	Est.

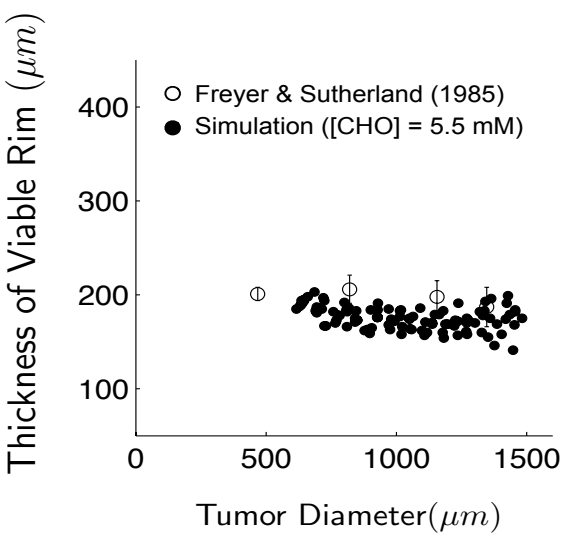
[a] 'calib.': parameter was defined by calibrating to empirical literature; 'est.': parameter and/or relationship assumed; and 'calc.': parameter the result of algebraic calculation of other parameters.

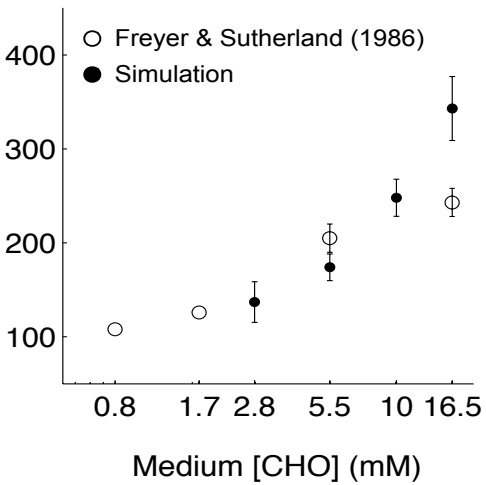
[b] The biological duration of M phase is given by $\bar{r}_M(\sigma_0^{r_M}) + \bar{r}_D(\sigma_0^{r_D})$.

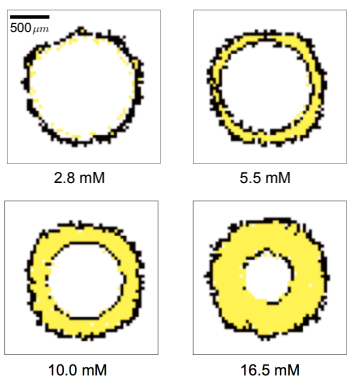
Bulk Tumour Dynamics, Comparison to Exp.











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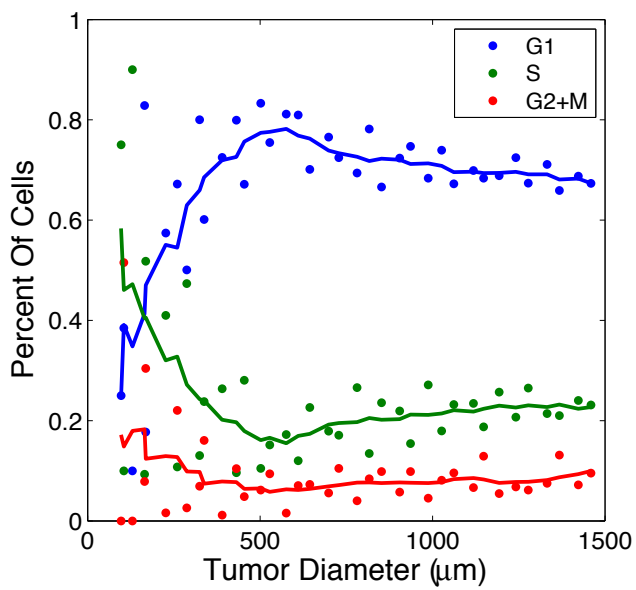
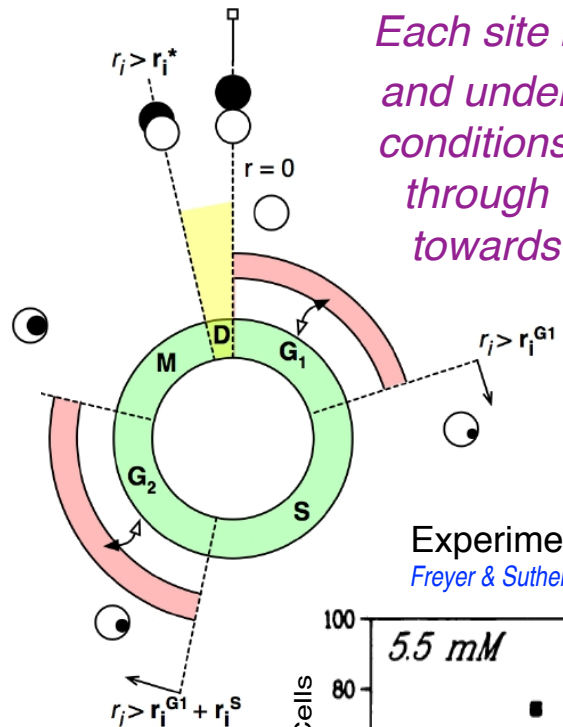
Cell Phase Dynamics, Comparison to Exp.

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.

Simulation

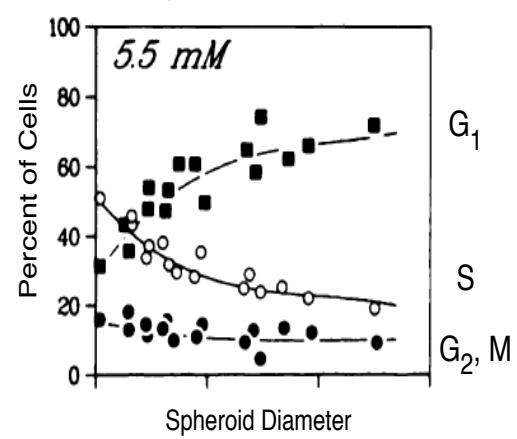




Each site begins in G_1, and under proliferative conditions, progresses through the cell cycle towards Division (D).

Experiment

Freyer & Sutherland (1986)



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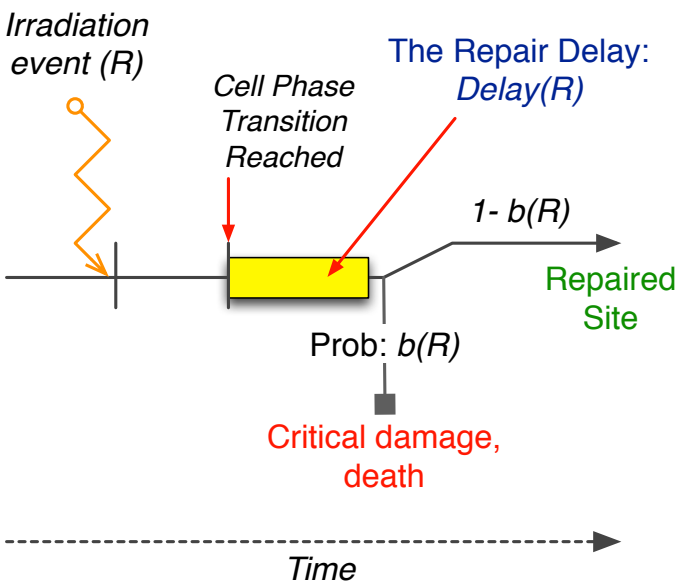
Some reflections on the journey.

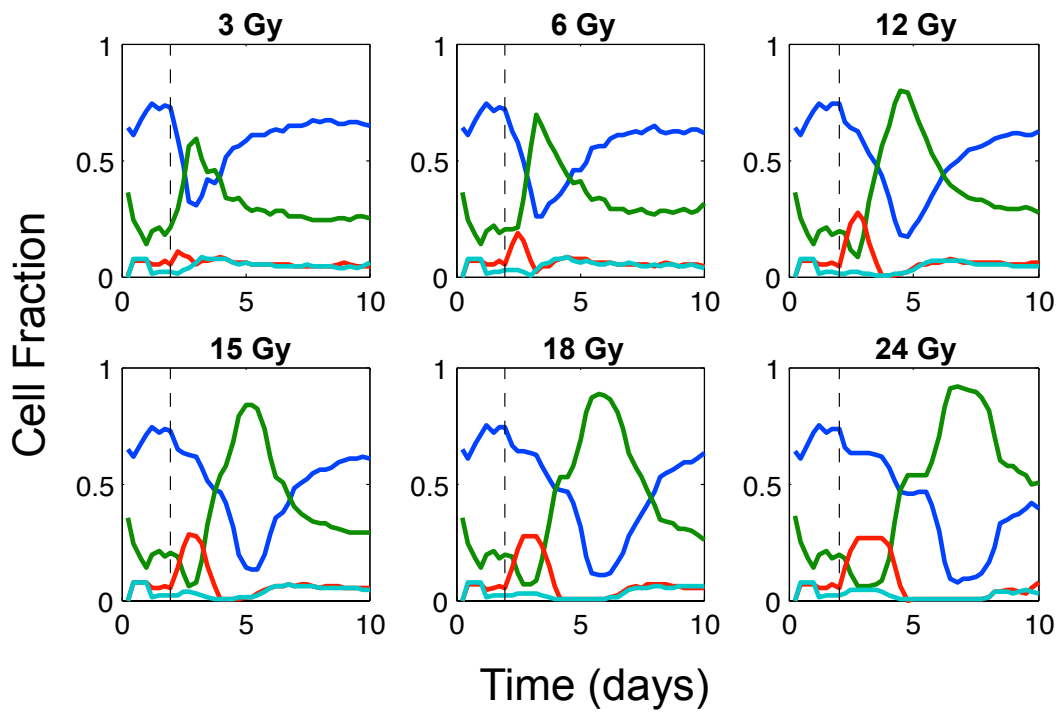
Introducing Single-dose X-Irradiation



Two functions to identify:

Delay(R)

b(R)



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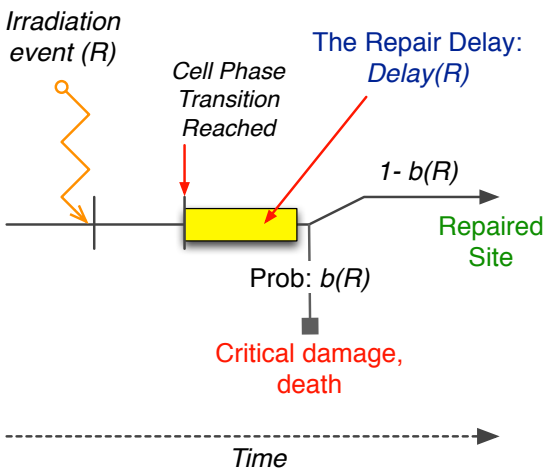
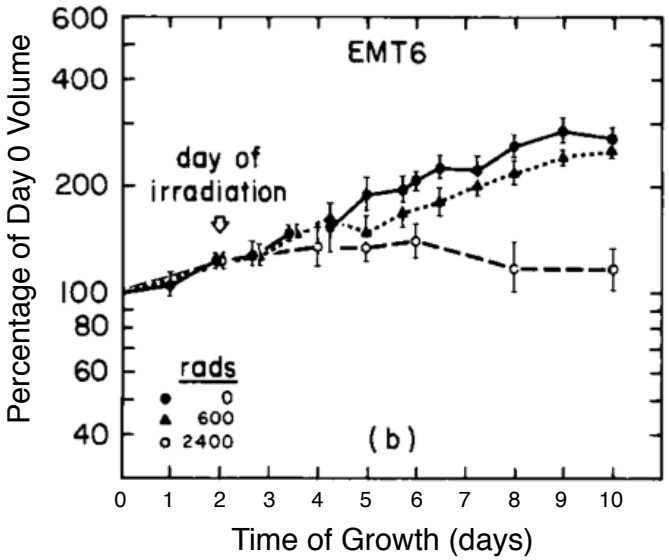
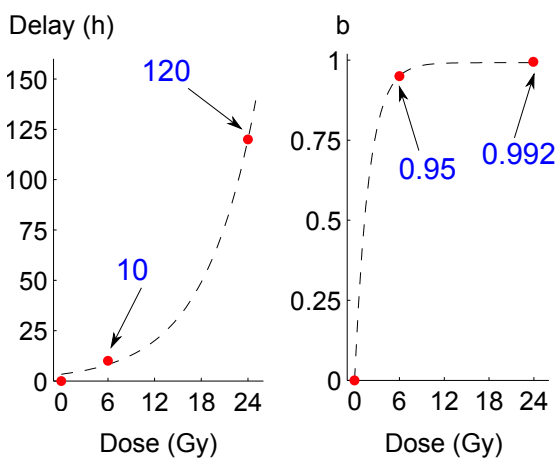
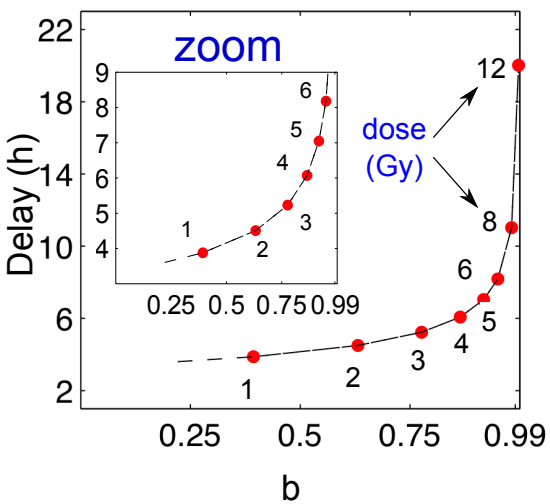
Single-dose X-Irradiation



Kelley et al. (1981)







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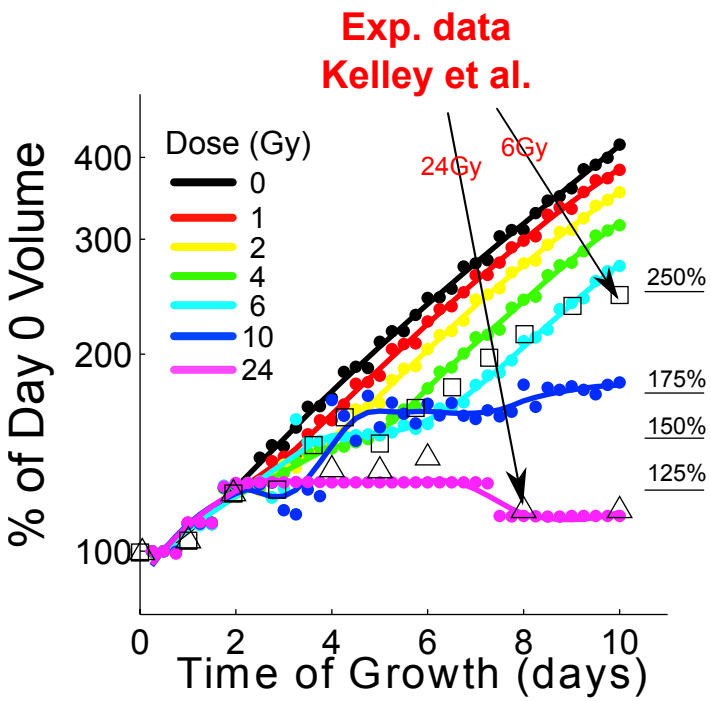
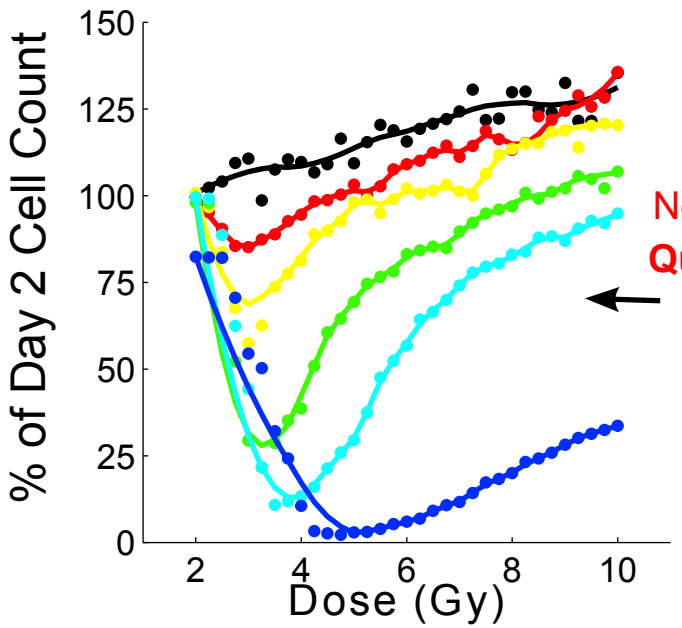
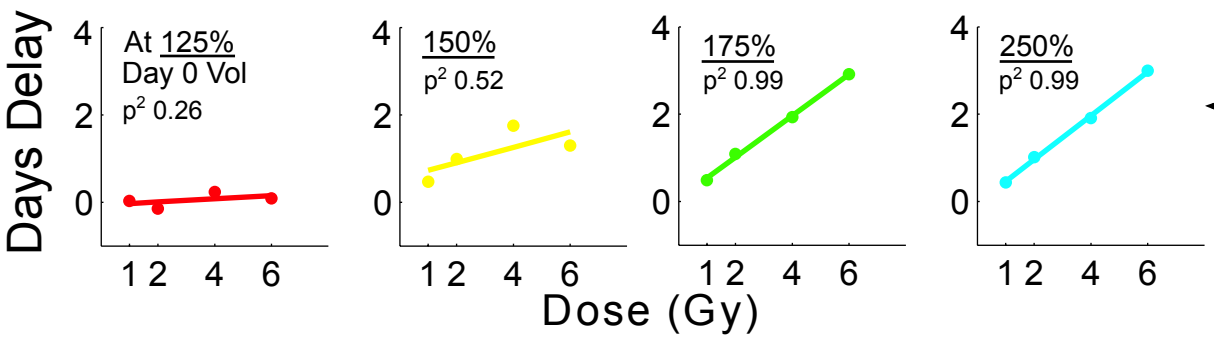
Comparison to Exp. Data





No EMT6/Ro exp. data

Qualitative agreement with R1H data Jung et al.



Agreement with EMT6/Ro exp. data Rockwell&Kallman

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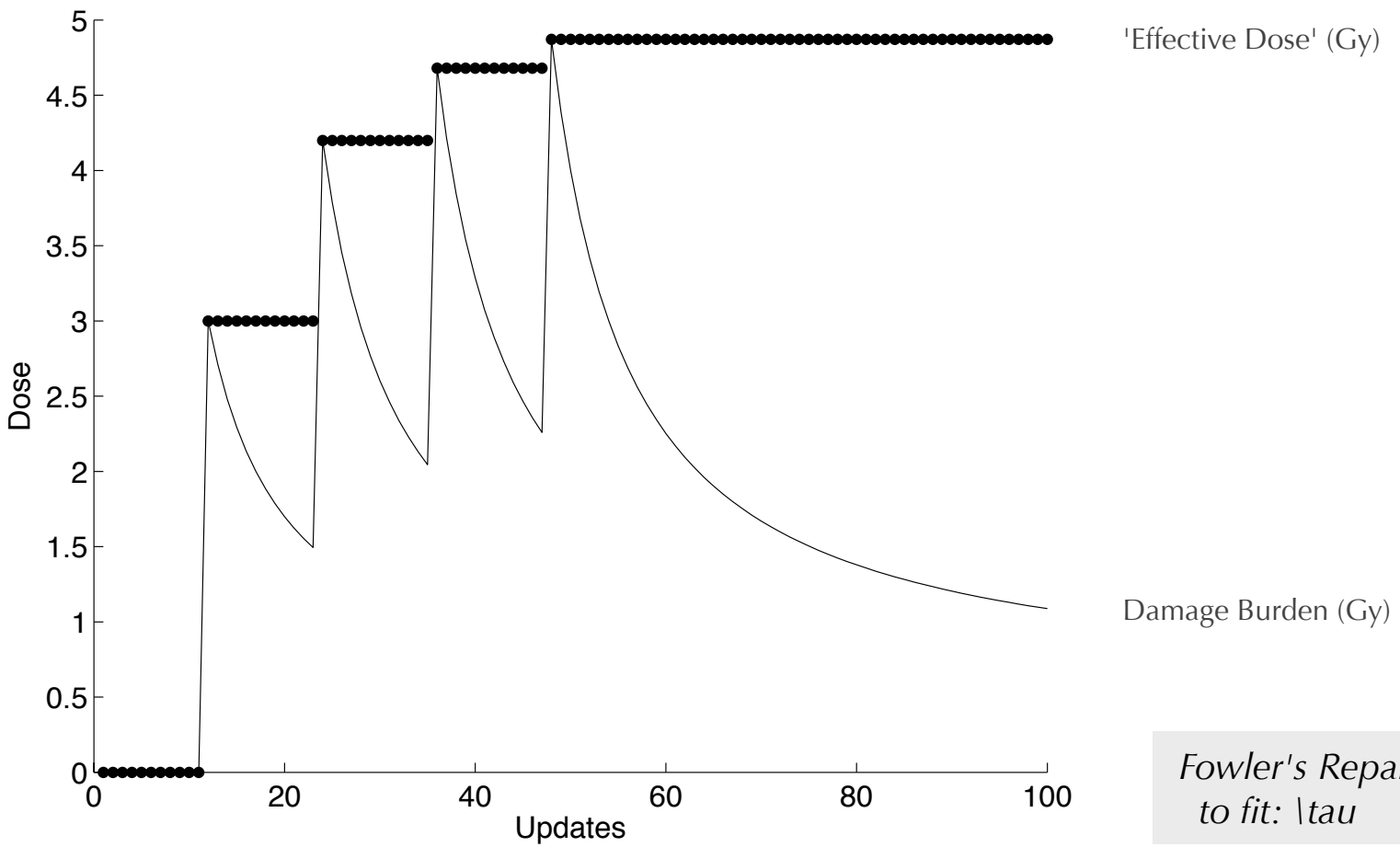
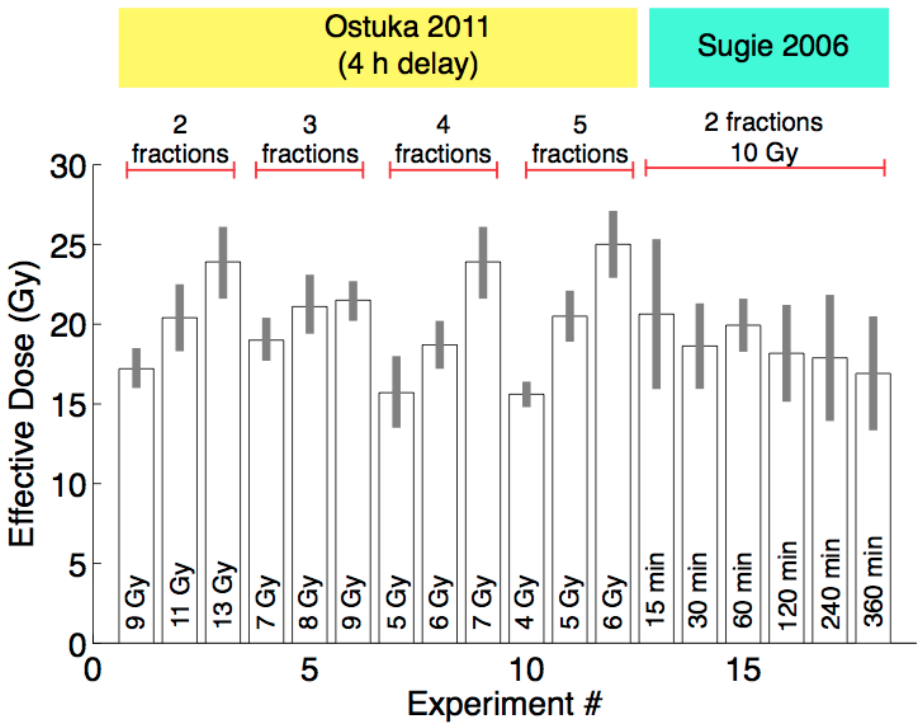
Some reflections on the journey.

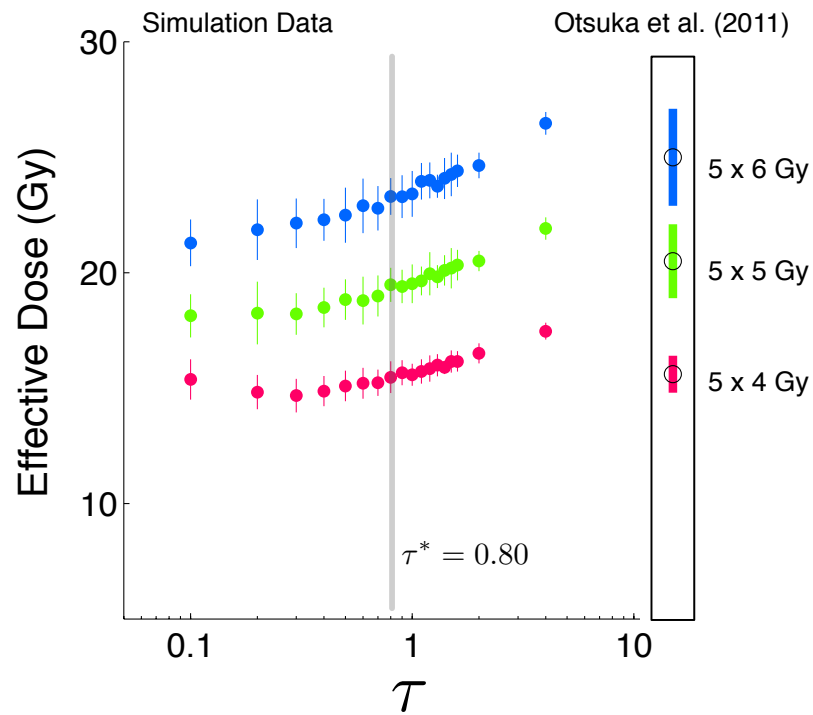
Multi-Dose Irradiation

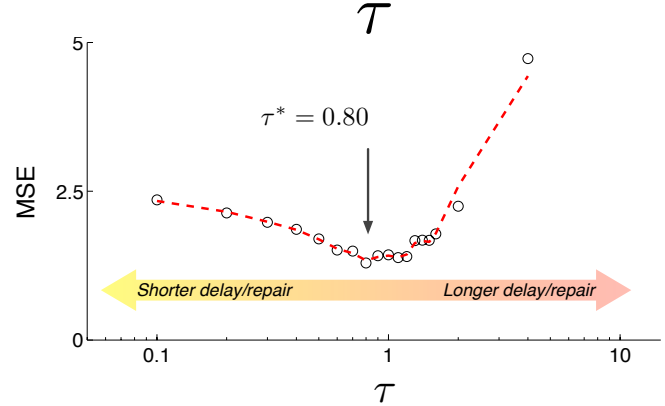


Fowler's Repair Model:
to fit: \tau

Calibration of \tau

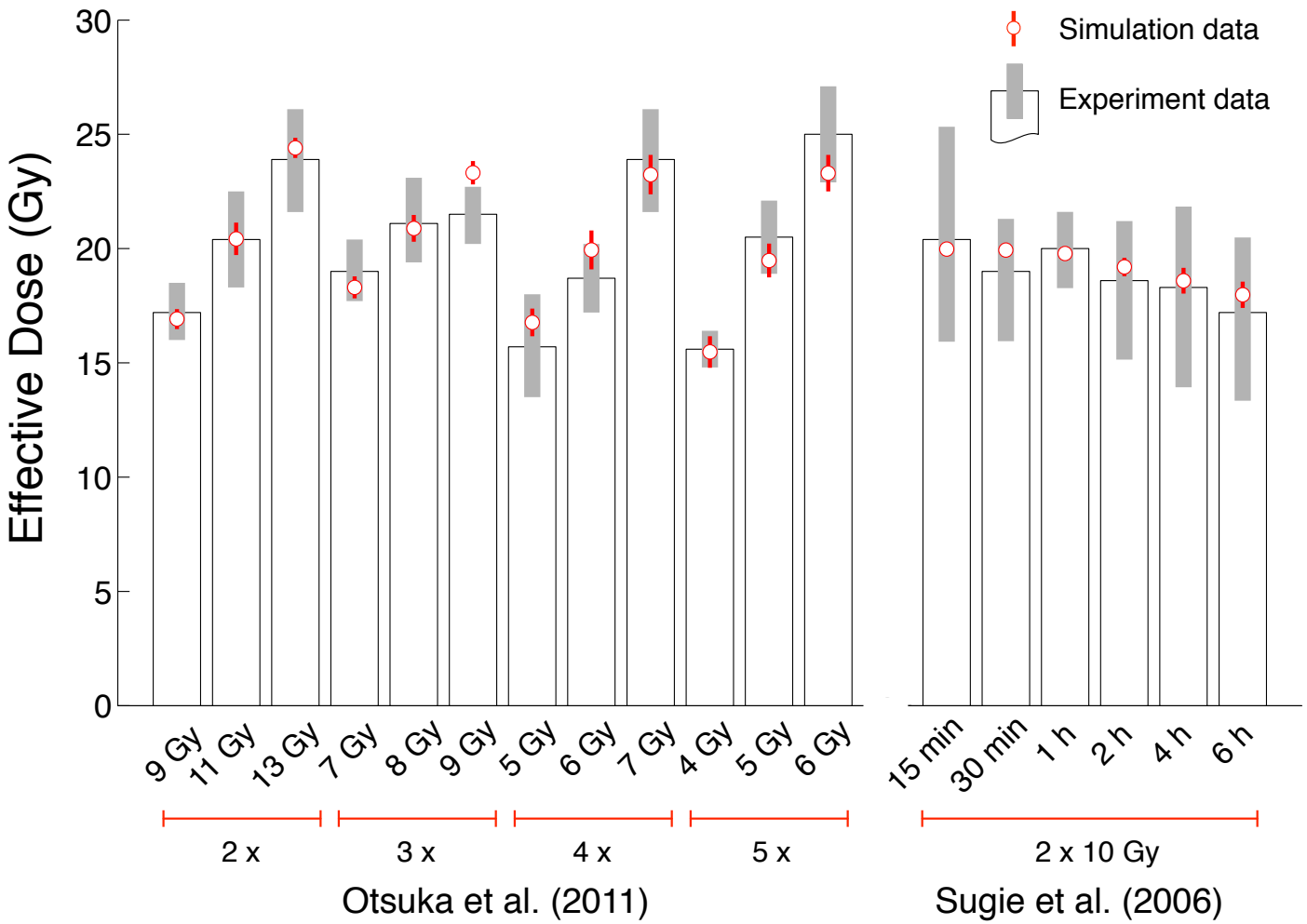






Calibration: an ensemble of 18 Independent Multi-fraction Experiments

Optimal Calibration: Comparison to Experiment



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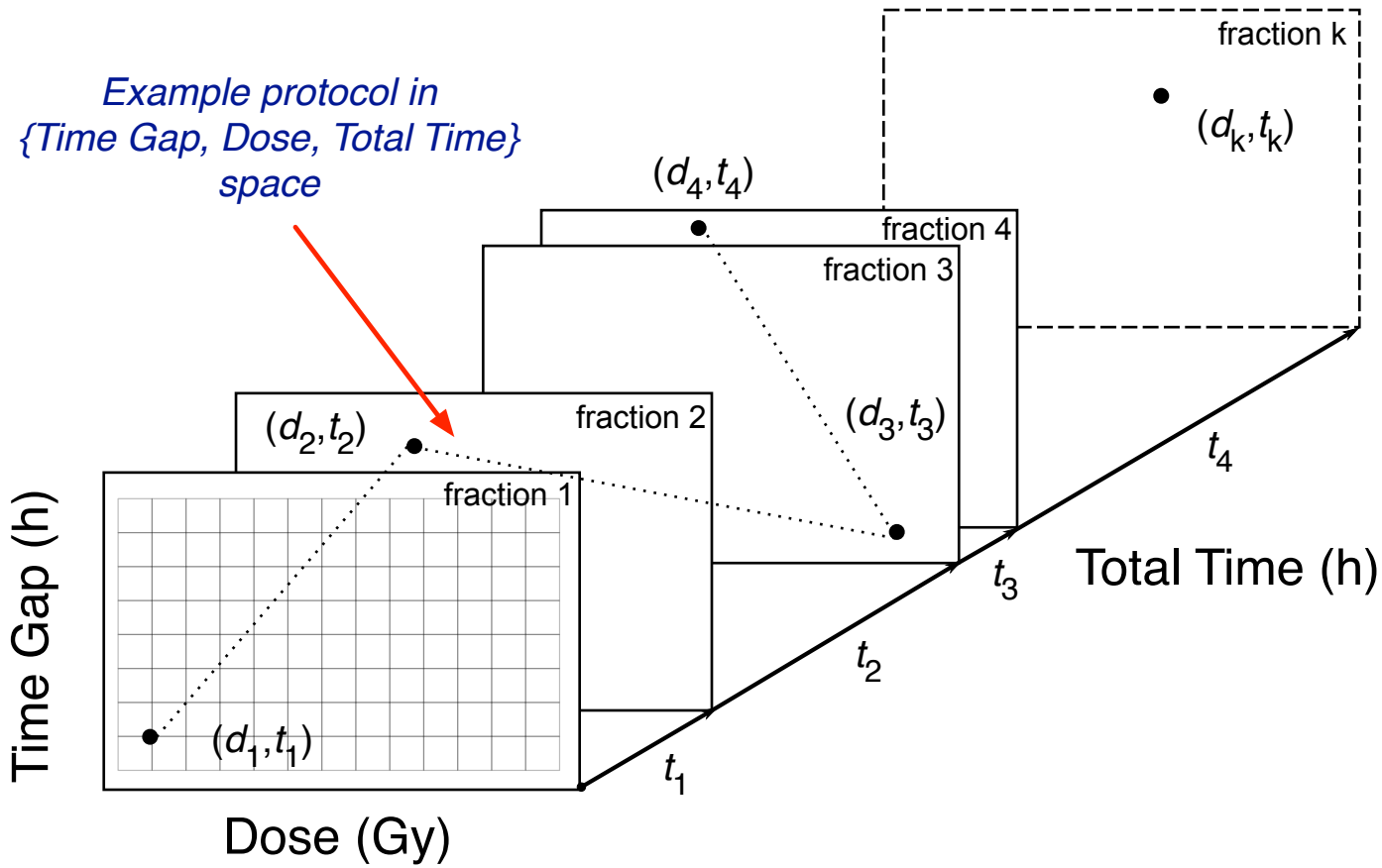
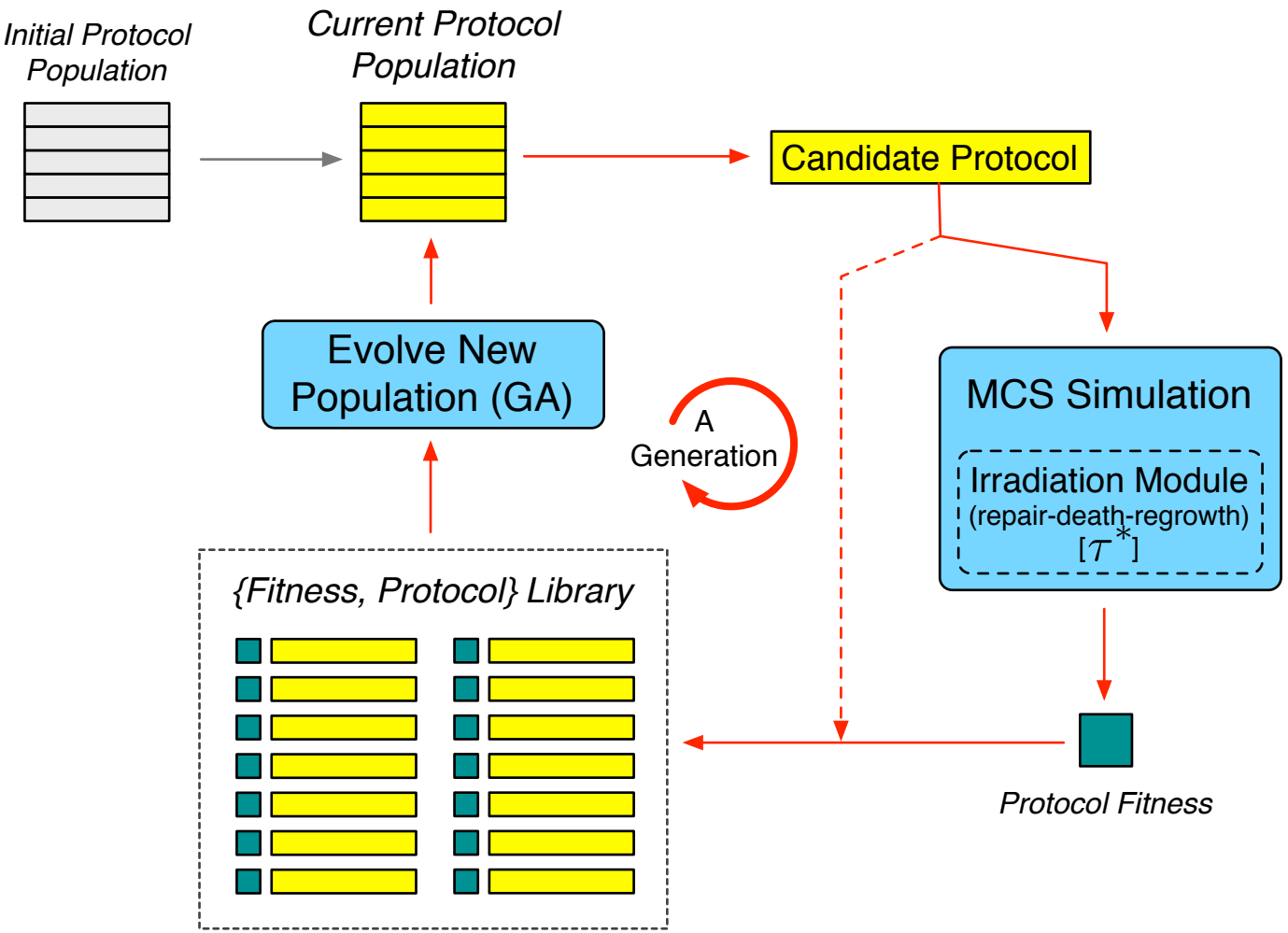
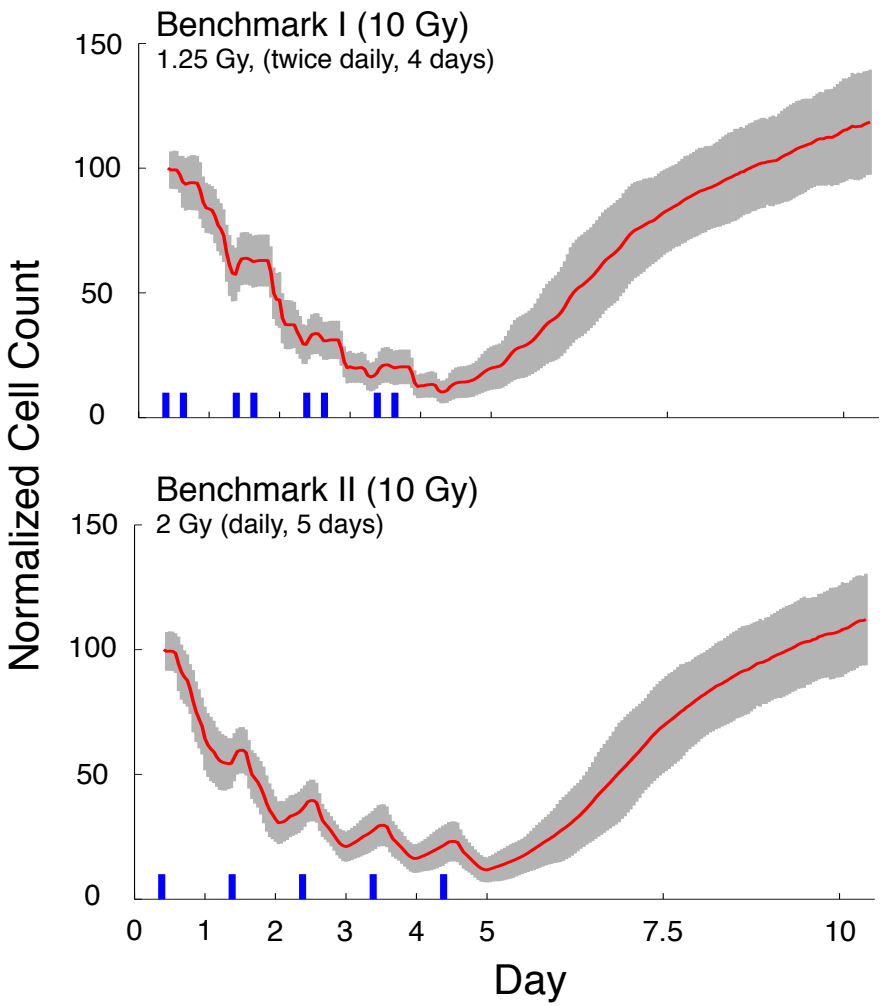
Visualising 'Protocol Space'



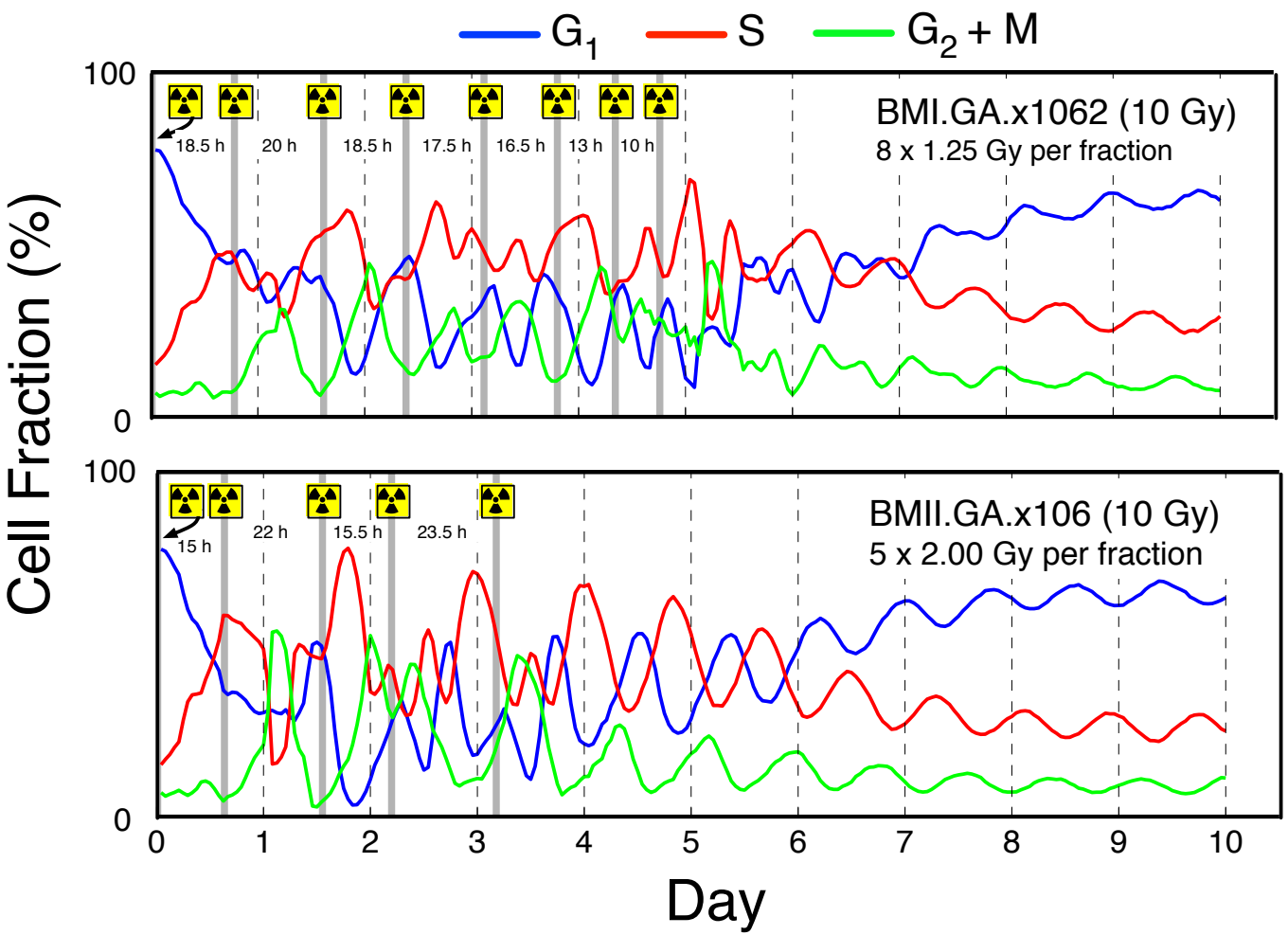
The GA Search Architecture



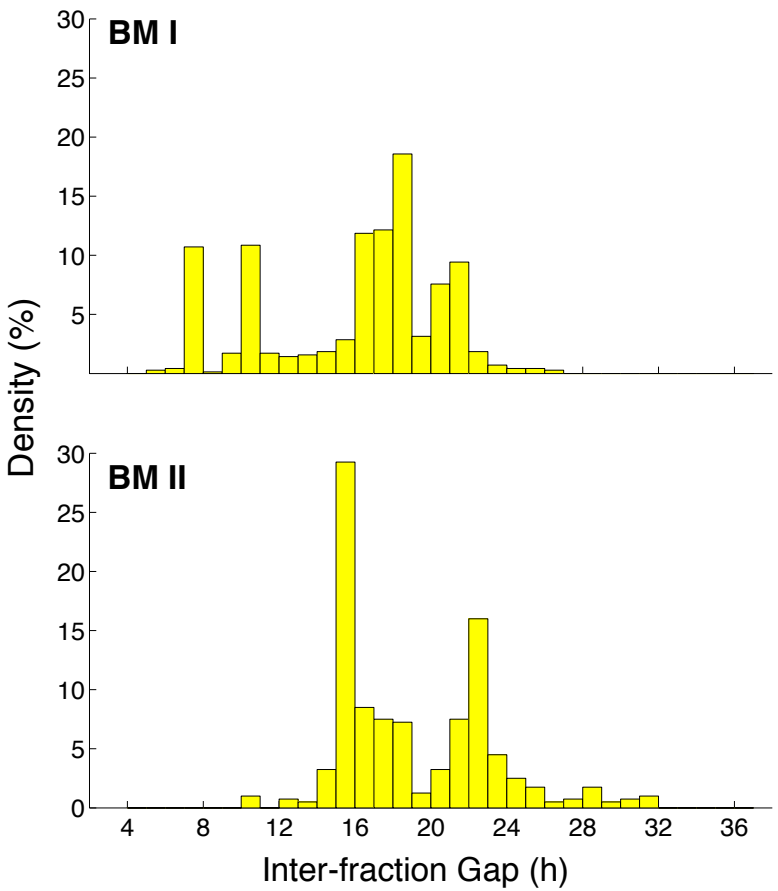
'Better': Establishing the Benchmarks

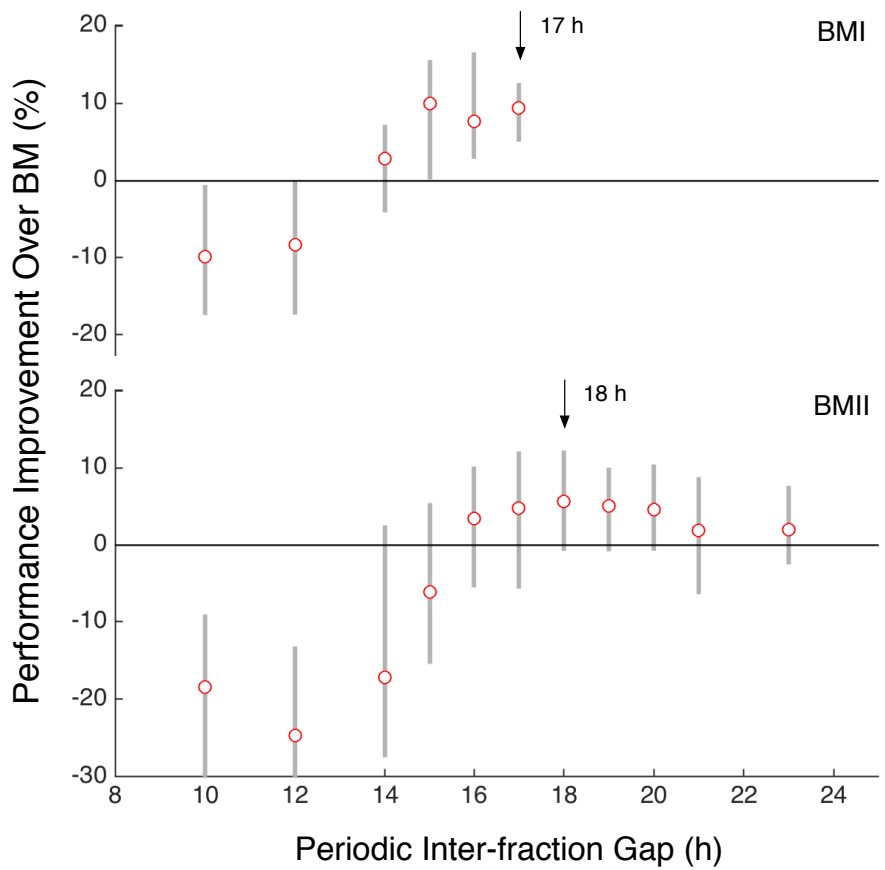


After the GA (40,000 CPU h!)



After the GA: Temporal Synchronicity?





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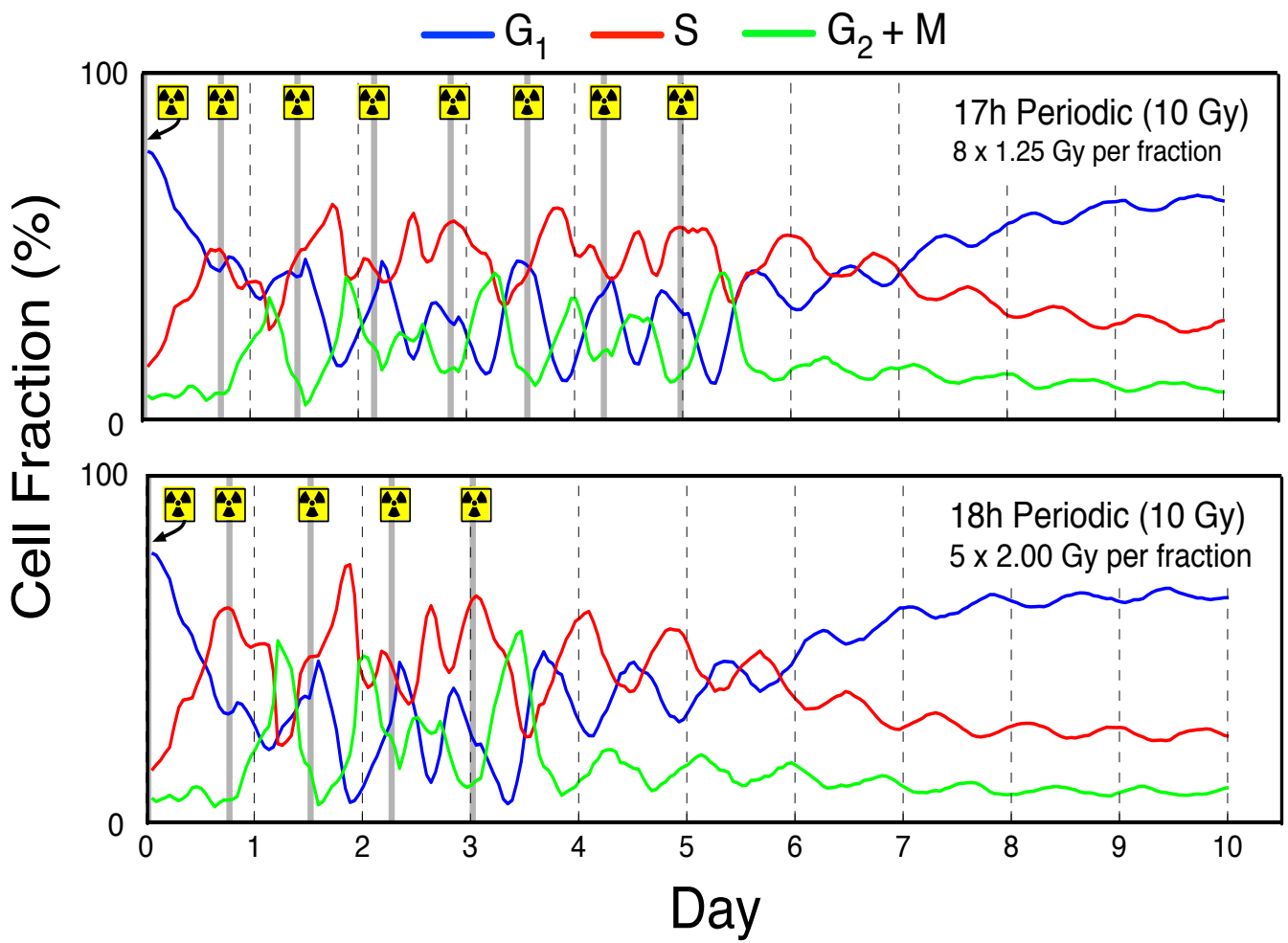
Hand-Crafted Periodic Protocols



Reflections

'**Emerald City**'? .. avg. benefit: 9.4% or 7.1% .. max benefit: 16.5% or 13.3%

- Only **1 week** of treatment (most treatments over 4+ weeks)
- Only searching **timing** (what about dose? dose & timing?)
- Very conservative approach .. high possibility for translational benefit.

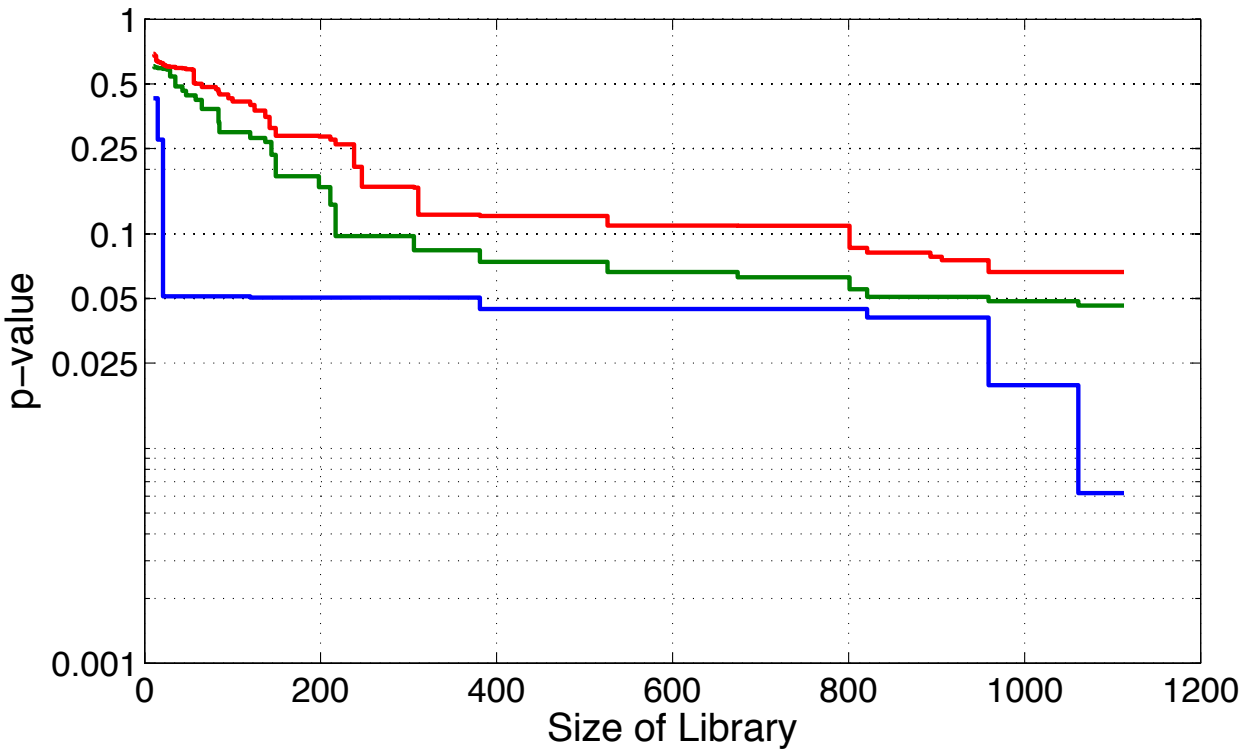
Inputs: 300 man-hours from SA alone; almost 100,000 CPU hours .. about 6 years of collaboration

Intangibles: expertise, skills, knowledge, collaboration

Learnings: good data for calibration + validation consistent feature (run out now?) .. publication between/across disciplines?

Appendices

GA Performance with Size of Library



Example Candidate -- Benchmark Comparison

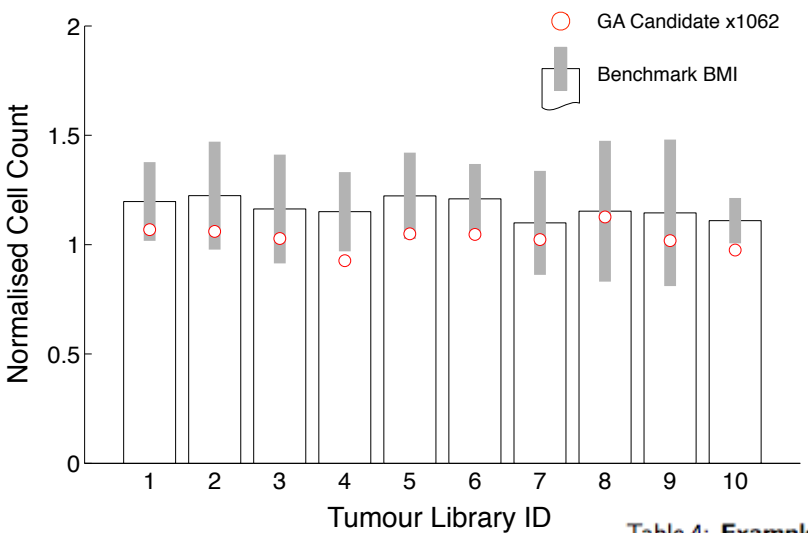


Table 4: **Example data used to derive the fitness score of a candidate.** Here, candidate x1062 is measured by normalised cell count against the same for the BMI protocol, allowing the calculation of relative score vector (col 3).

Tumor Library ID (j)	Norm. Cell Count		Relative Score
	Benchmark n'^{BMI^j}	Candidate x1062 $n'^{\rho^j_{\mathrm{x1062}}}$	s^j_{x1062}
1	1.20	1.07	13
2	1.22	1.06	16
3	1.16	1.03	13
4	1.15	0.93	22
5	1.22	1.05	17
6	1.21	1.05	16
7	1.10	1.02	8
8	1.15	1.13	2
9	1.15	1.02	13
10	1.11	0.97	14

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Comparison of Basic Model to Experiment

Table 2: **Characteristics of the 10 day, 10 tumor, library used in the present study.** A comparison is provided to available *in vitro* literature for EMT6/Ro under equivalent medium conditions though over 14 and ~ 20 days.

Measure	10 Day Library (for BM I, II)	*in vitro*[†] (at 14 or ~20 days)	Units
Bulk & necrotic properties			
Final Tumor diameter	840 (±11)	est. 1050[a] - 1250[c]	μm
Diameter growth rate	77.3 (±0.4)	60[b] - 79[a]	μm/day
Diameter at onset of necrosis	638 (±28)	413[c]	μm
Viable rim (post necrosis)	185 (±12)	207 (±13)[b]	μm
Gompertz fit properties			
Est. doubling time (vol.)	20.1	17[c] - 18[d]	h
Saturation volume	3.72×10^9	$6.3^c - 11.0^d \times 10^9$	μm^3
Saturation cell count	6.91×10^5	$7.0^c - 9.8^d \times 10^5$	
Cell phase fractions			
G_1	76.8 (±2.6)	60.1 (±5.3)[b] - 76 (±3)[c]	%
S	14.8 (±3.0)	16 (±3)[c] - 27.4 (±0.5)[a]	%
$G_2 + M$	8.5 (±1.9)	9 (±3)[c] - 13.1 (±2.1)[b]	%

Notes:

[†] Experimental literature ranges given where available. Importantly, experimental values only available for tumors grown in the same media for 14 days or ~ 20 days as follows: 14 days {[a] [9], [b] [3]}, and ~ 20 days { [c] [10], [d] [11], and [e] [12] }.