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Mechanistic Linear-Quadratic-Linear (LQL) Model for Large Doses Per Fraction

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Background

- Stereotactic Body Radiation Therapy (SBRT) is increasingly common for treatment of several tumor sites.
- SBRT = single dose or small number of high dose fractions.
- The question arises:

How do we model large fraction doses?
Is the Linear-Quadratic(LQ) model valid?

Is the Linear-Quadratic(LQ) model valid at large doses per fraction?

Answer: all over the place

1. ASTRO 2008: we don't know.
   (Educational session, W. McBride, PhD, UCLA)
2. Brenner (and others): Yes of course.
   (Seminars of Rad. Oncology, Oct 2008, etc).
3. Other authors: no, not really.
   (several alternative models proposed,)
4. Our answer: …coming soon

Alternative models

- Over the years many models have been proposed
  (Parks *et al* (2008), others: e. g. Charlie Ma 2012)
- Lethal-Potentially-Lethal (LPL)
  (Fan Y and Paliwal B AAPM 2003
  Curtis 1986).

LQ too good to let go

• Decades of success: LQ model gives good description of fractionation effects for low doses per fraction (e.g. 2Gy).

• Few and established parameters: α/β ratios well known for many tissues, repair times also.

• Mathematical simplicity

• Mechanistic (e.g. Dale 1985, others)

• Can include 4 Rs. (e. g. Brenner 1995, others)

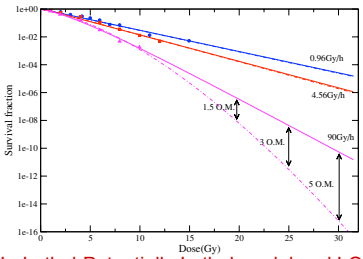
What do we know about LQ at high doses?

•LQ model has a continuously bending survival curve at high doses versus linear behavior observed at least in some cell lines (logarithmic scale).

• LQ model matches other more sophisticated models like the Lethal-Potentially-Lethal model (LPL) only at low doses and dose-rates but not at high doses. (Brenner *et al* 1998)

Our linear-quadratic-linear (LQL) model addresses these two issues

HX118 melanoma cells survival curves LQ(dashed) and LPL(solid) model fits (Steel *et al* 1987)



LPL=Lethal-Potentially-Lethal model and LQ fits are indistinguishable for low doses and dose-rates but what about higher doses????

Guerrero and X. Allen Li, *Phys. Med. Biol.* **49,** 4825–4835 (2004)

Can the LQ model match the LPL at high doses?

- LQ Survival curve:

$$S_{LQ}=\exp(-\alpha D-\beta D^2 G(\mu T))$$

G(μT) is the Lea-Catcheside factor ➔increased survival due to repair, dose rate effect (μ=repair rate, T= treatment time)

$$0<G(x)<1 \qquad G(x)=\frac{2}{x^2}\left(x-1+e^{-x}\right)$$

Can the LQ model match the LPL at high doses?

- LQL Survival curve:

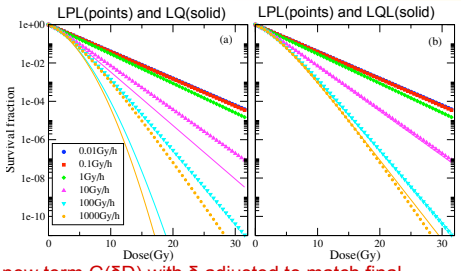
$$S_{LQL}=\exp(-\alpha D-\beta D^2 G(\mu T+\delta D))$$

- Acute dose: μT<<1 G=1 for LQ but for LQL G(δD) remains for acute doses:

$$S_{LQL}=\exp(-\alpha D-\beta D^2 G(\delta D))$$

- Introduces a new parameter δ [Gy^{-1}].

LQL matches LPL survival for ALL doses and dose-rates

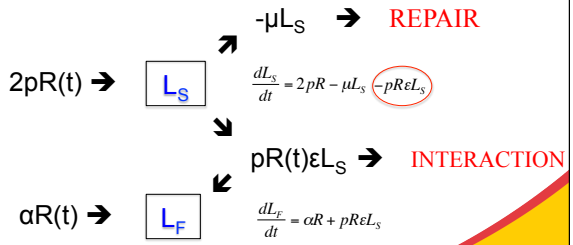


The new term G(δD) with δ adjusted to match final slope, makes the LQL equivalent to LPL with advantage of familiarity and knowledge of parameters α and β.

Guerrero and X. Allen Li, *Phys. Med. Biol.* **49,** 4825–4835 (2004)

Compartmental LQL formulation (Carlone et al) (based on Dale's 1985 LQ formulation)

L_S= sub-lethal lesions L_F=fatal lesions R(t)=dose-rate p=yield of L_S per unit dose ε=probability of interaction



M. Carlone, D. Wilkins, and P. Raaphorst *Phys. Med. Biol.* **50**, L9–L15 (2005)

Linear-Quadratic-Linear(LQL) solution

- New factor in solution for acute doses

$$S=\exp(-\alpha D-\beta D^2 G(\delta D)) \quad \delta=p\varepsilon$$

p=yield of L_S per unit dose ε=probability of interaction

- Interpretation of G(δD): reduction in survival due to interaction between lesions.

Linear-Quadratic-Linear(LQL) solution

- For large doses S~exp(-(α+β/2δ)D) (linear behavior).
- LQL agrees with LPL model at all doses and dose-rates
- Mechanistic formulation

Test the models at high dose? Isoeffect equations using BED

D= total dose
d=dose per fraction
n=number of fractions

BED= biologically effective dose
=D(1+d/(α/β))

LQ: $$\frac{1}{D}=\frac{1}{BED}+\frac{1}{BED\cdot(\alpha/\beta)}d$$

LQL: $$\frac{1}{D}=\frac{1}{BED}+\frac{1}{BED\cdot(\alpha/\beta)}d\cdot G(\delta d)$$

Fe-plots: for a certain isoeffect plot 1/D vs d
LQ predicts linear behavior

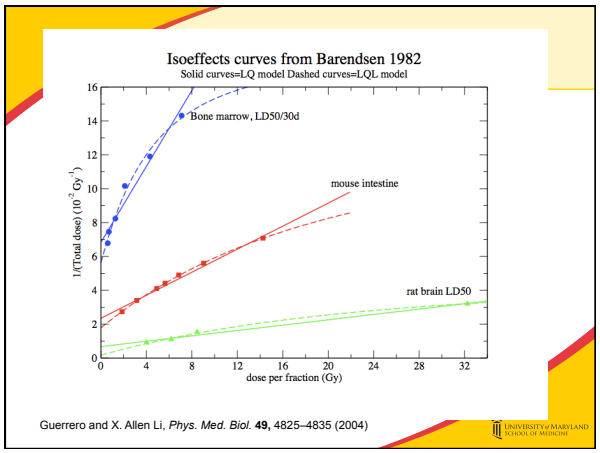
LQ vs LQL Test: Re-analyze isoeffect data

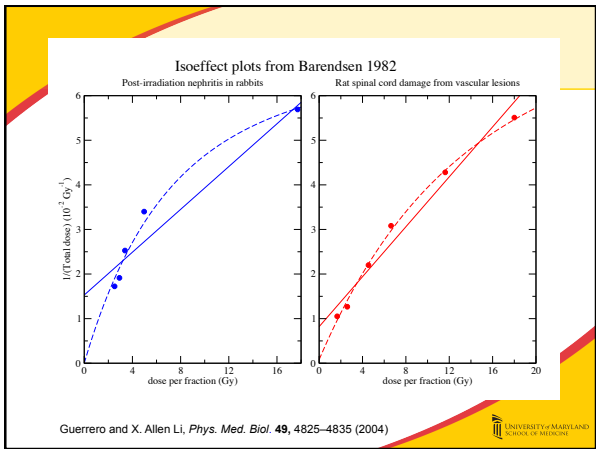
Barendsen 1982, Red Journal

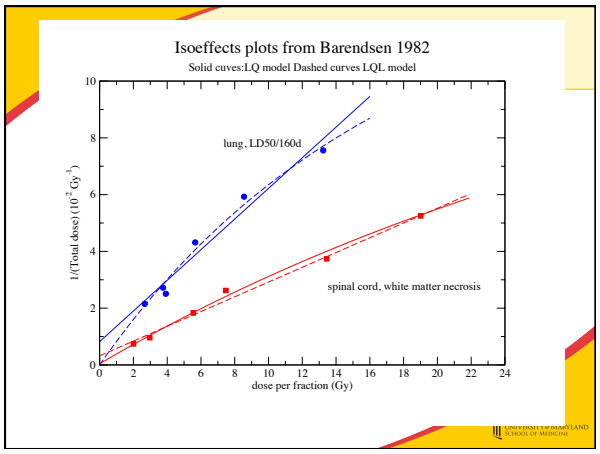
"Dose fractionation, dose rate and iso-effect relationships for normal tissue responses"

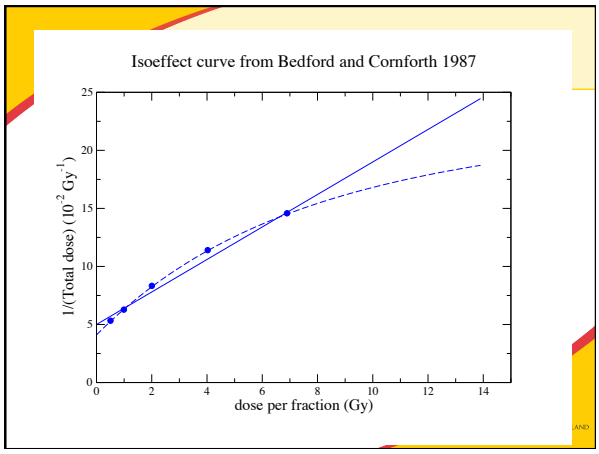
Seminal work for LQ model
cited over 500 times

Fit of isoeffect curves from animal experiments with LQ formula


Isoeffects curves from Barendsen 1982
Solid curves=LQ model Dashed curves=LQL model
Bone marrow, LD50/30d
mouse intestine
rat brain LD50
1/(Total dose) (10^-2 Gy^-1)
dose per fraction (Gy)
Guerrero and X. Allen Li, Phys. Med. Biol. 49, 4825–4835 (2004)


Isoeffect plots from Barendsen 1982
Post-irradiation nephritis in rabbits
Rat spinal cord damage from vascular lesions
1/(Total dose) (10^-2 Gy^-1)
dose per fraction (Gy)
Guerrero and X. Allen Li, Phys. Med. Biol. 49, 4825–4835 (2004)


Isoeffects plots from Barendsen 1982
Solid cuves:LQ model Dashed curves LQL model
lung, LD50/160d
spinal cord, white matter necrosis
1/(Total dose) (10^-2 Gy^-1)
dose per fraction (Gy)


Isoeffect curve from Bedford and Cornforth 1987
1/(Total dose) (10^-2 Gy^-1)
dose per fraction (Gy)

13 Isoeffect plots analysis
LQ vs. LQL fits with χ^2/n value

	LQ		LQL		
Experiment	α/β (Gy)	χ^2/n	α/β (Gy)	δ (Gy^{-1})	χ^2/n
Bone marrow LD50/30 days*	6.1	0.435	2.23	0.39	0.16
Mouse jejunum crypt death*	6.9	0.034	3.25	0.09	0.0075
Mouse foot skin desquamation	10.0	0.0047	9.90	<0.04	0.0052
Rat brain LD50/1 year*	8.6	0.023	0.89	0.08	0.01
Mouse kidney histopathologic changes	0.73	0.095	–	0.049	0.08
Rabbit post-irradiation nephritis*	6.4	0.26	–	0.25	0.082
Rat spinal cord (vascular lesions)*	3.0	0.094	0.14	0.13	0.01
Rat spinal cord (radiculopathy)	4.5	0.019	3.86	0.01	0.02
Mouse lung LD50*	1.5	0.2	–	0.096	0.13
Mouse spinal cord white matter necrosis*	1.2	0.041	0.11	0.045	0.035
Mouse skin contraction	5.1	0.007	4.34	<0.04	0.009
Mouse spinal cord myelopathy	4.9	0.010	5.0	<0.04	0.013
In vitro AG1522 cells in plateau phase*	3.6	0.29	1.7	0.23	0.0029

Guerrero and X. Allen Li, *Phys. Med. Biol.* **49,** 4825–4835 (2004)

Isoeffects summary

- Of 13 isoeffects curves studied, the LQL significantly improved the quality of the curve fit in 8 of them.
- Values of δ ranged from 0.04 to 0.4 Gy^{-1}
- Dose values were the LQ loses accuracy ~ δ^{-1}= 2.5Gy to 22Gy or larger.

Is the Linear-Quadratic(LQ) model valid at large doses per fraction?

Answer: all over the place

- Our answer:

Only sometimes: depending on the end point, tissue type and the dose level the LQ model may or may not be sufficient.

δ can be estimated from known parameters α, β and the final slope D_0

$$\delta = \frac{2\beta D_0}{1 - \alpha D_0}.$$

Cell line	α (Gy^{-1})	β (Gy^{-2})	D_0 (Gy)	δ (Gy^{-1})	D^* (Gy)
T-1	0.18	0.050	1.1	0.137	7.3
R-1	0.18	0.037	1.3	0.126	7.9
RUC-1	0.12	0.023	1.5	0.084	11.9
RUC-2	0.08	0.010	2.2	0.053	18.7
ROS-1	0.18	0.036	1.6	0.162	6.2
RMS-1	0.22	0.054	1.1	0.157	6.4
MLS-1	0.36	0.025	1.2	0.106	9.4
Gioblastomas (5)	0.241	0.029	1.44	0.128	7.8
Melanomas (19)	0.255	0.053	1.04	0.150	6.7
Squamous cell carcinomas (6)	0.273	0.045	1.28	0.177	5.6
Adenocarcinomas (6)	0.311	0.055	1.04	0.169	5.9
Lymphomas (7)	0.451	0.051	1.48	0.452	2.2
Oat cell carcinomas (6)	0.650	0.081	1.51	13.2	0.076

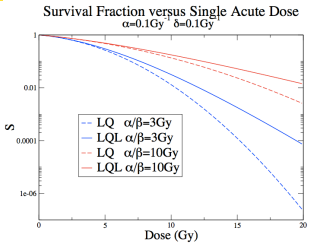
Barendsen 1982, Malaise *et al* 1986

δ can be estimated from known parameters

	LPL				LQL			
Cell line	η_L (Gy^{-1})	η_{PL} (Gy^{-1})	ϵ	$T_{1/2}$ (h)	α (Gy^{-1})	β (Gy^{-2})	δ (Gy^{-1})	D^* (Gy)
HX34	0.27	1.81	27	0.11	0.27	0.061	0.11	9.91
HX118	0.32	0.98	6.8	0.16	0.32	0.070	0.22	4.6
HX58	0.45	3.12	88	0.82	0.45	0.055	0.050	18.8
HX156	0.30	2.82	156	0.54	0.30	0.026	0.027	37.7
RT112	0.10	1.65	40	0.86	0.10	0.034	0.062	16.16
GCT127	0.45	2.04	46	0.31	0.45	0.045	0.067	15.03
HX142	0.11	1.74	1.54	0.54	0.11	0.98	1.69	0.6

Average value for $\delta \approx 0.1 Gy^{-1}$

Clinical application: SBRT fractionation Interplay of parameters



LQL Survival Curve: reduction in survival more pronounced for smaller α/β ratio

Prostate and lung SBRT and Hypofractionation

Prostate hypofractionation (review by Ritter *et al*)

- -Moderate fractionation (d=2-4.3Gy)
- -Extreme hypofractionation(d=6.7-10.5Gy)
- -α/β=1.5, 3Gy or 10Gy.

Lung SBRT (review by Silva *et al*)

- -α/β=10Gy for lung
- -α/β=3Gy for normal tissue

Important quantities

Biologically effective dose (BED) for fractionated treatments:
d=dose per fraction D=total Dose

$$BED_{LQ} = D \cdot \left[1 + \frac{d}{(\alpha/\beta)}\right] \qquad BED_{LQL} = D \cdot \left[1 + \frac{d \cdot G(\delta d)}{(\alpha/\beta)}\right]$$

Equivalent dose in 2 Gy fractions EQD2

$$EQD2_{(LQ)} = BED_{LQ} / \left(1 + 2/(\alpha/\beta)\right)$$

$$EQD2_{(LQL)} = BED_{LQL} / \left(1 + 2 \cdot G(\delta 2)/(\alpha/\beta)\right)$$

Prostate Cancer Equivalent Dose at 2Gy/fr
Extreme hypofractionation

α/β=1.5Gy δ=0.1Gy^{-1}

d(Gy)	D(Gy)	$EQD2_{LQ}$	$EQD2_{LQL}$	%diff.
1.8	75.6	71.3	71.6	0.5
6.1	42.7	92.7	82.6	
6.7	33.5	78.5	68.8	
7.3	36.3	90.6	78.2	
7.0	35.0	85.0	73.8	11-21%
9.5	47.5	149.3	121.0	
10.0	50.0	164.3	131.3	
10.5	52.5	180.0	141.9	

Lung cancer BED

δ=0.1Gy^{-1}

α/β(Gy)	d(Gy)	D(Gy)	BED_{LQ}	BED_{LQL}	%diff
10.0	26	26	93.6	59.5	8-34%
	12	36	79.2	66.1	
	10	30	60.0	52.1	
	6	48	76.8	71.8	
	7	28	47.6	43.7	
3.0	26	26	251.3	137.6	14-45%
	12	36	180.0	136.2	
	10	30	130.0	103.6	
	6	48	144.0	127.4	
	7	28	93.3	80.4	

Mechanistic formulation allows other dose-rates
Ex: Split dose- recovery ratio RR

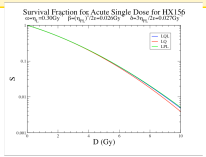
- Two fractions of size d separated by an interval of time T.

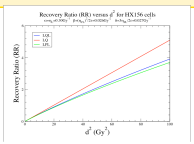
- Experiments look at recovery ratio RR=S(T)/S(T=0) as T goes to infinity.

$$RR_{LQ} = e^{2\beta d^2} \rightarrow RR_{LQL} = e^{2\beta F(\delta d) d^2} \qquad F(x) = \frac{(1-e^{-x})^2}{x^2}$$

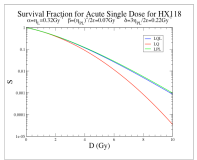
- LQL predicts reduced recovery ratio.

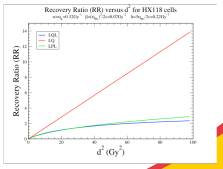
δ=0.03 Gy^{-1}





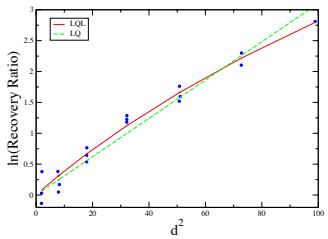
δ=0.22 Gy^{-1}





Guerrero and Carlone, Med. Phys. 37, 4173-81 (2010)

Recovery Ratio of HF19 cells in plateau phase Alsbeih et al



The LQL gives a better fit of the recovery ratio as a function of dose per fraction

Guerrero and Carlone, Med. Phys. 37, 4173-81 (2010)

LQL split dose prediction

If survival for a single fraction deviates from LQ model and follows LQL, then a similar deviation is seen in the RR for split dose experiments and the size of the deviations are related.

Limitations of LQL

- LQL assumes that damage is based on cell survival but other mechanisms (e.g. vascular damage) may be at play at large doses per fraction
- The LQL only presents part of the story and does not address other potential differences between standard fractionation and SBRT (e.g 4R's).

Final thoughts

- The LQL model is an extension of the LQ model with one additional parameter that comes into play at high doses.
- LQL model matches the LPL for large doses.
- LQL is mechanistic and can make predictions for arbitrary dose-rates.
- LQL gives better fit than LQ model for many in-vivo isoeffect experiments and recovers the LQ model at low doses.
- LQL can be used to estimate BED for clinical SBRT schedules (δ has been characterized for different types of tissues)

Thank you!

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References

-Guerrero and Carlone, Med. Phys. 37, 4173-81 (2010)
-Guerrero and X. Allen Li, *Phys. Med. Biol.* **49,** 4825–4835 (2004).
-M. Carlone, D. Wilkins, and P. Raaphorst *Phys. Med. Biol.* **50**, L9–L15 (2005).
-M. Guerrero and X. A. Li, *Phys. Med. Biol.* **50**, L13–L15 (2005).
-W. Barendsen, *Int. J. Radiat. Oncol. Biol. Phys.* **8**,1981–1997 (1982).
-R. G. Dale, Br. J. Radiol. **58**, 515–528 (1985).
-D. E. Lea, *Actions of Radiations on Living Cells (*Cambridge University Press, Cambridge, 1946).
-R. K. Sachs, P. Hahnfeld, and D. J. Brenner, *Int. J. Radiat. Biol.* **72**, 351–374 (1997).
-S. B. Curtis,*Radiat. Res.* **106**, 252–270 (1986); Erratum in: *Radiat Res* **119**(3): 584 (1989).
-G. G. Steel, *Radiother. Oncol.* **9**, 299–310 (1987).
-R. G. Dale, *Br. J. Radiol.* **62**, 241–244 (1989).
-M. G. Alsbeih, B. Fertil, C. Badie, and E. P. Malaise, *Int. J. Radiat. Biol.* **67**, 453–460 (1995).