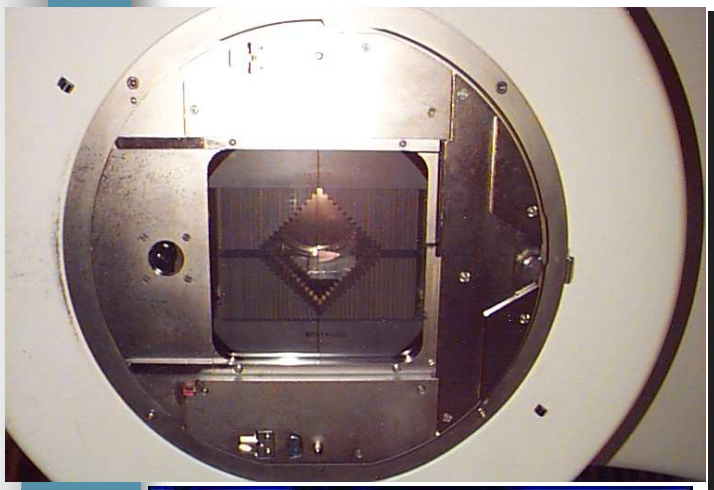
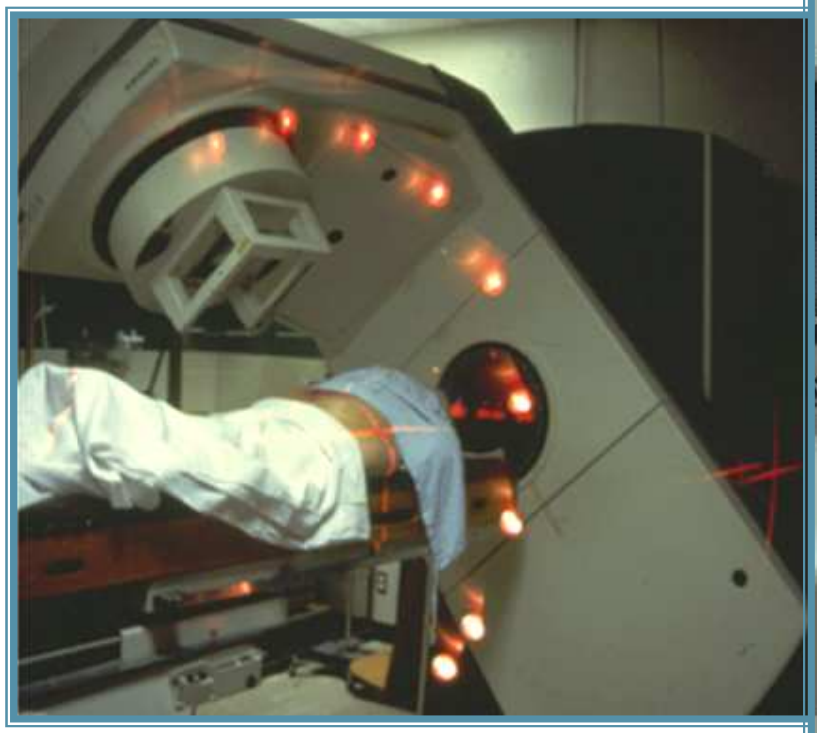
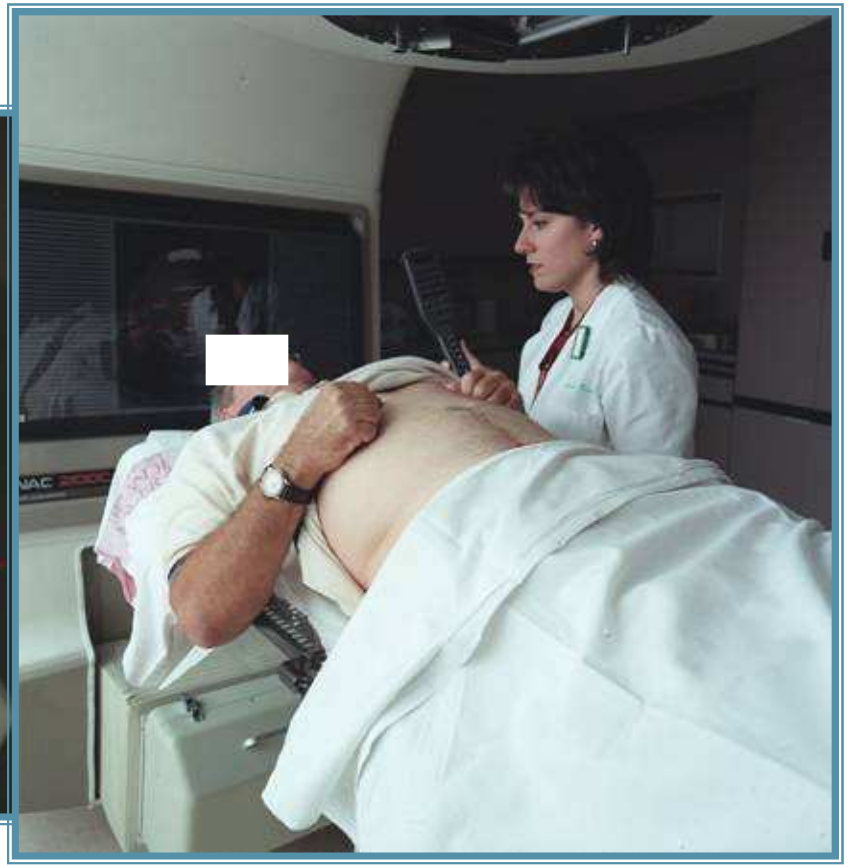
Modern Radiation Therapy: Computer-Controlled Linac and Multileaf Collimator (MLC)



Isocentric Patient Radiation Therapy

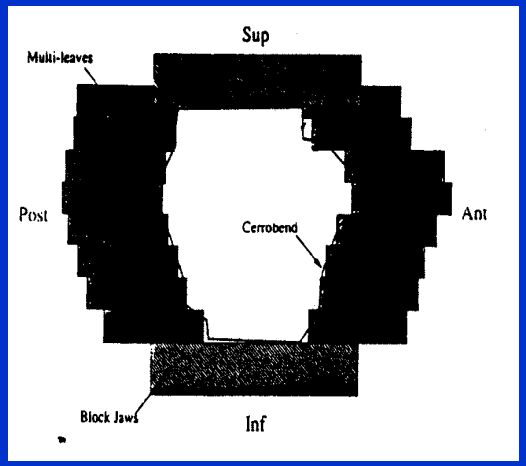




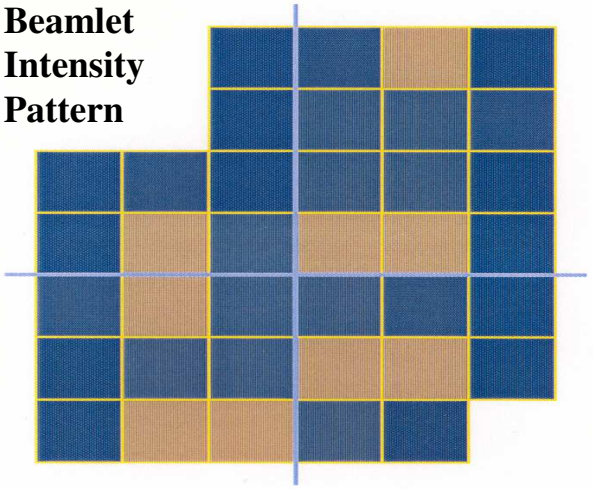
Intensity Modulated Radiation Therapy

Fig 1a

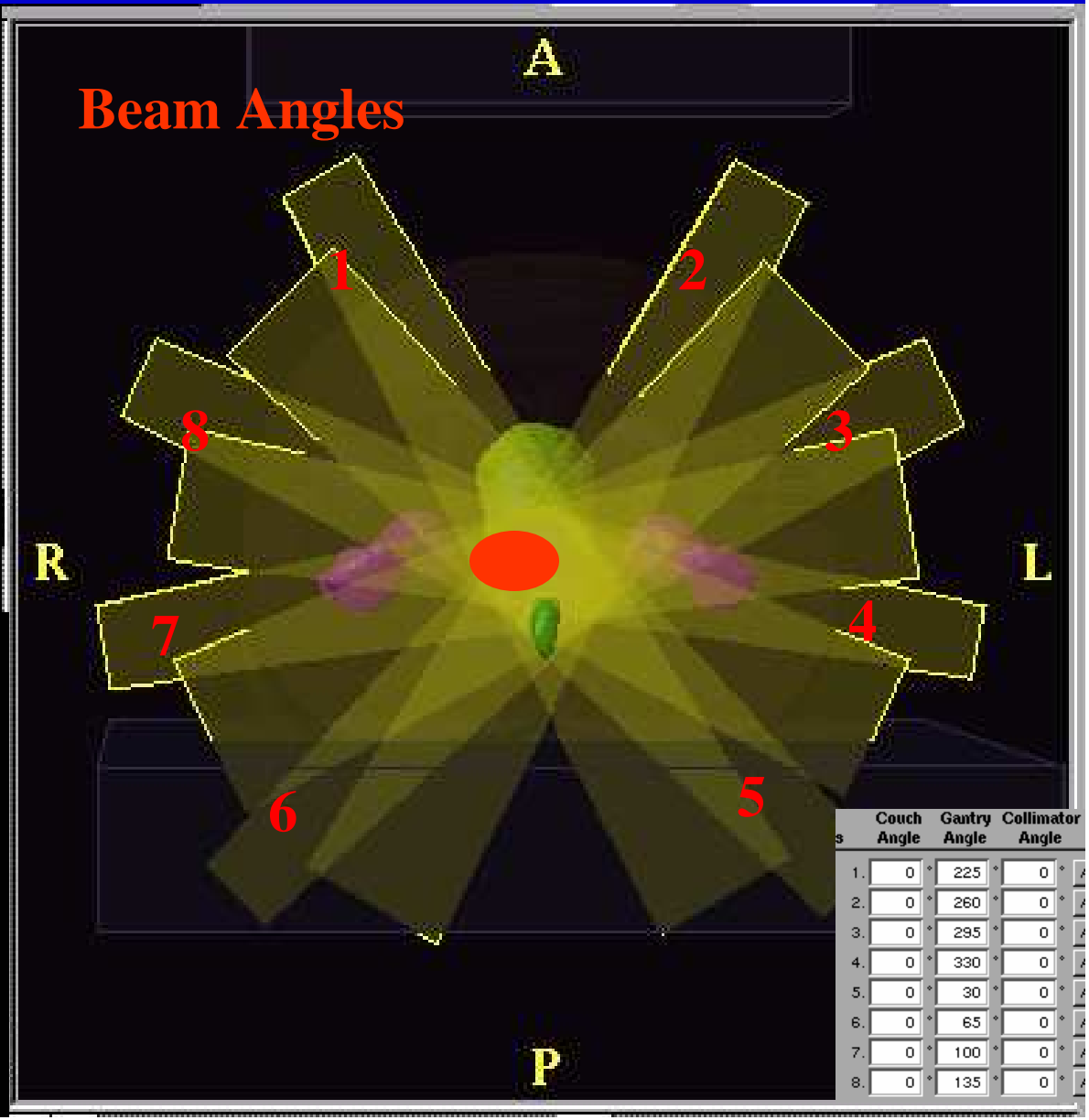
Multileaf Collimator



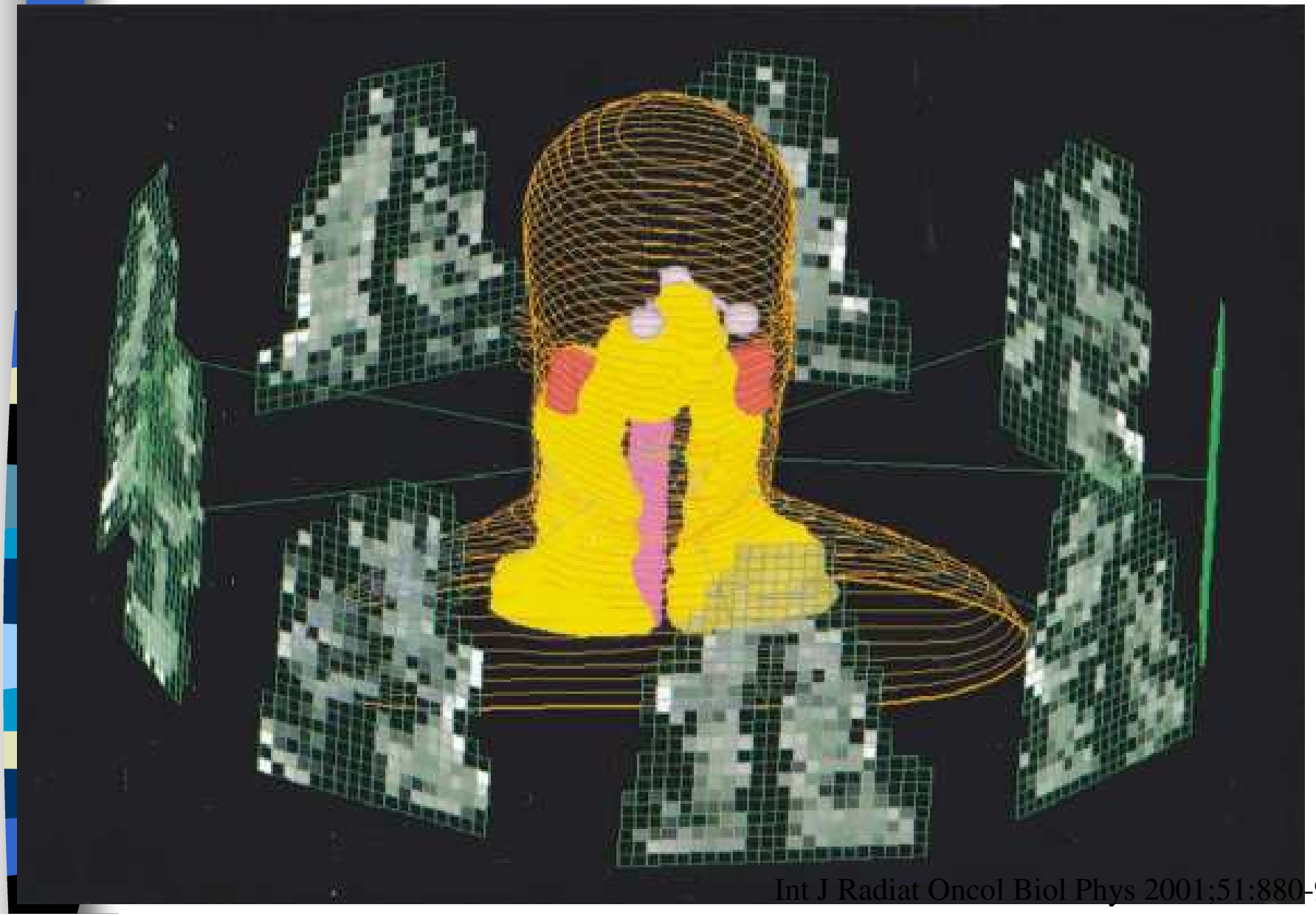
Beamlet Intensity Pattern



Beam Angles

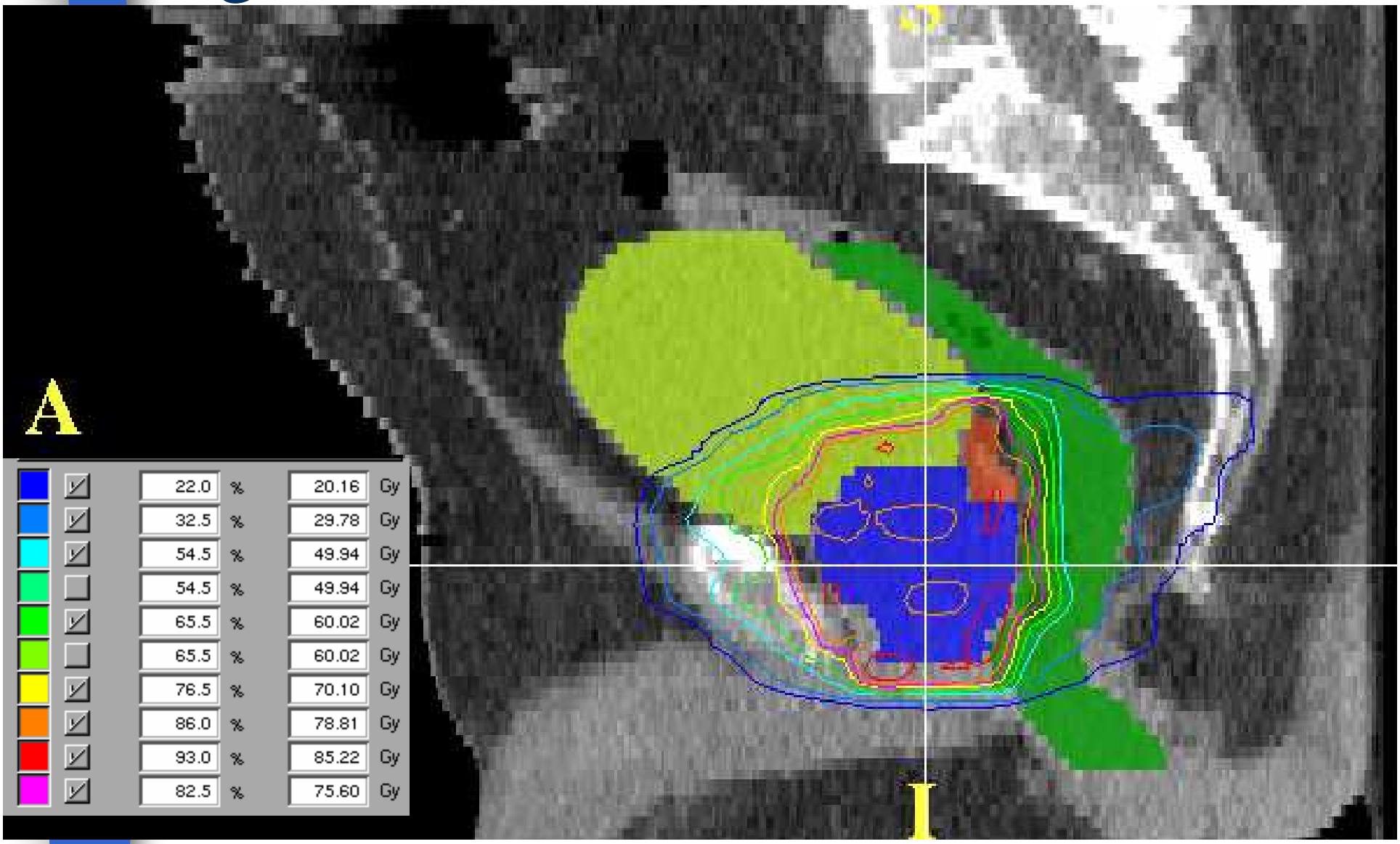


9-Field Head & Neck IMRT Case

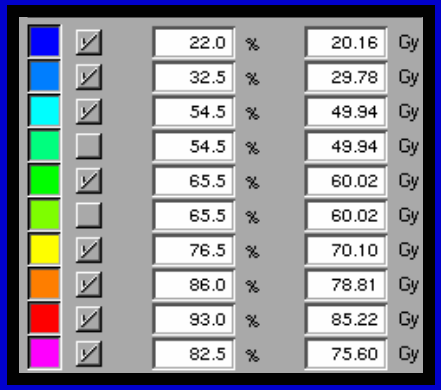


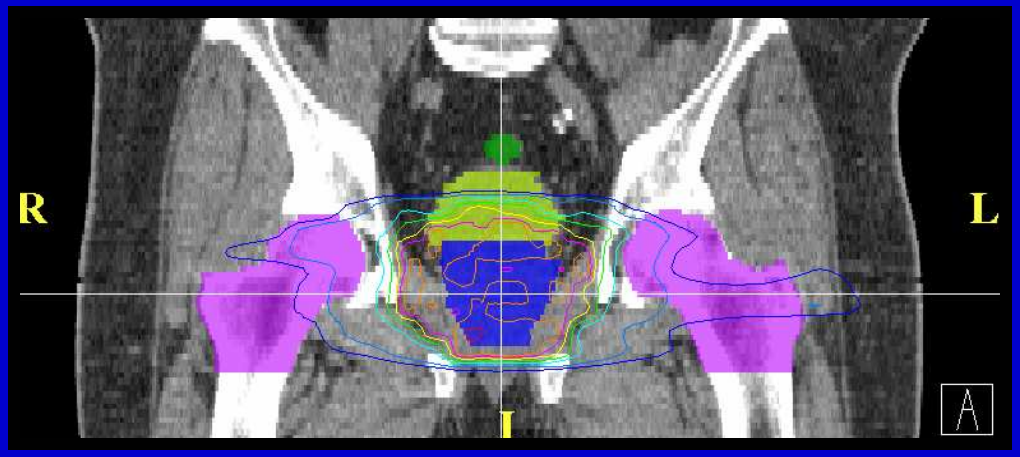
Int J Radiat Oncol Biol Phys 2001;51:880-914

Sagittal Dose Distribution



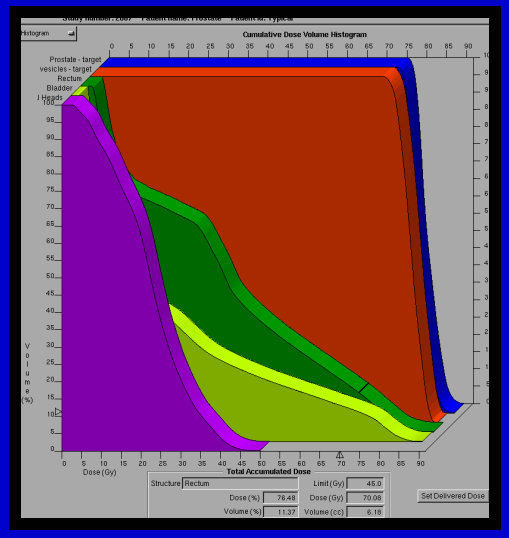
Doses Represented

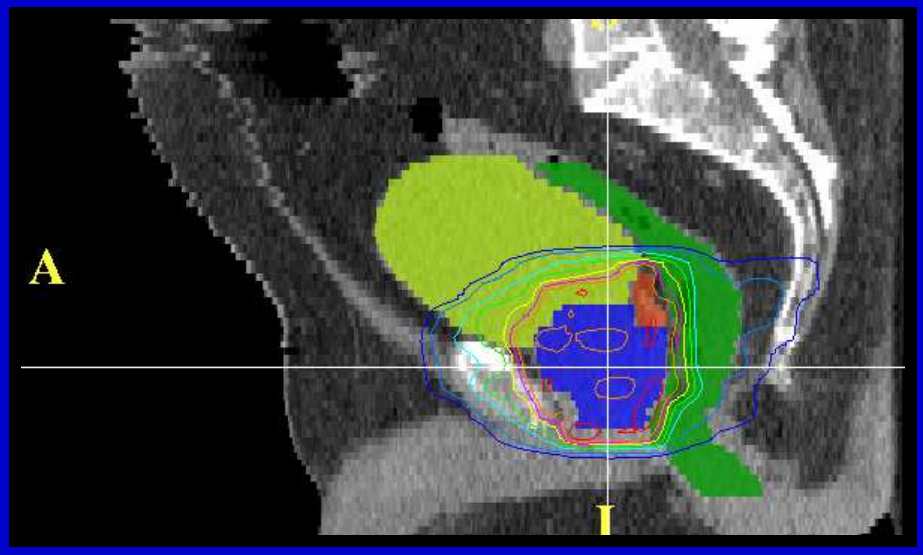




Coronal Dose Distribution

Dose-Volume Histogram





Sagittal Dose Distribution

Figure 1b

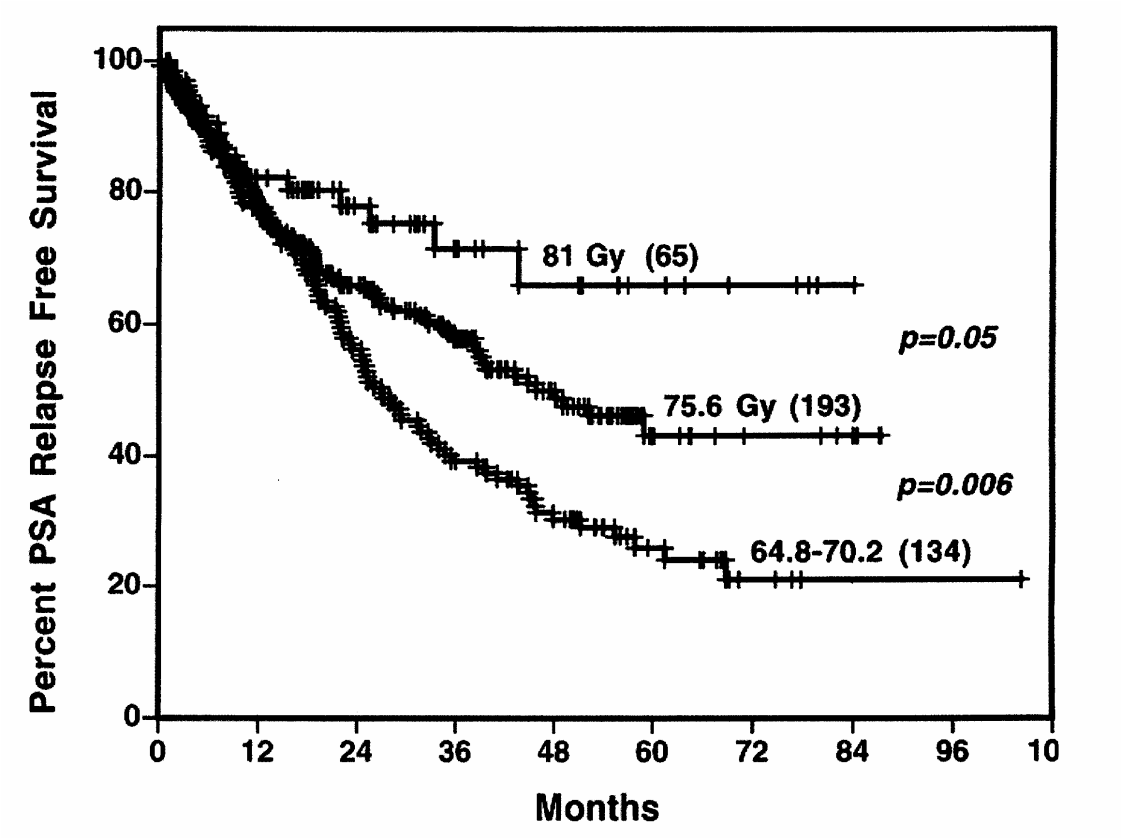

Percent PSA Relapse Free Survival
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
10
Months
81 Gy (65)
p=0.05
75.6 Gy (193)
p=0.006
64.8-70.2 (134)

Figure 3

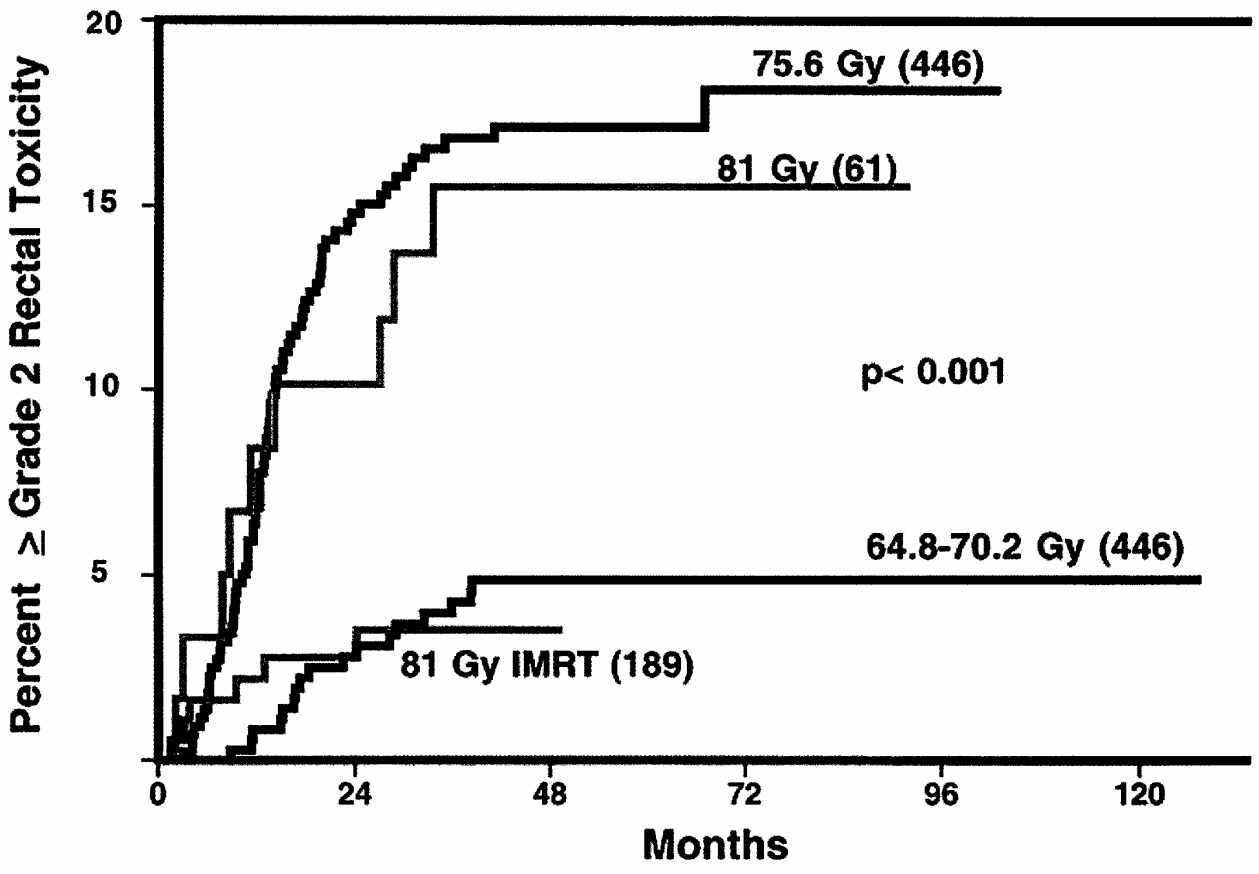

Percent ≥ Grade 2 Rectal Toxicity
20
15
10
5
0
24
48
72
96
120
Months
75.6 Gy (446)
81 Gy (61)
p< 0.001
64.8-70.2 Gy (446)
81 Gy IMRT (189)

Figure 4

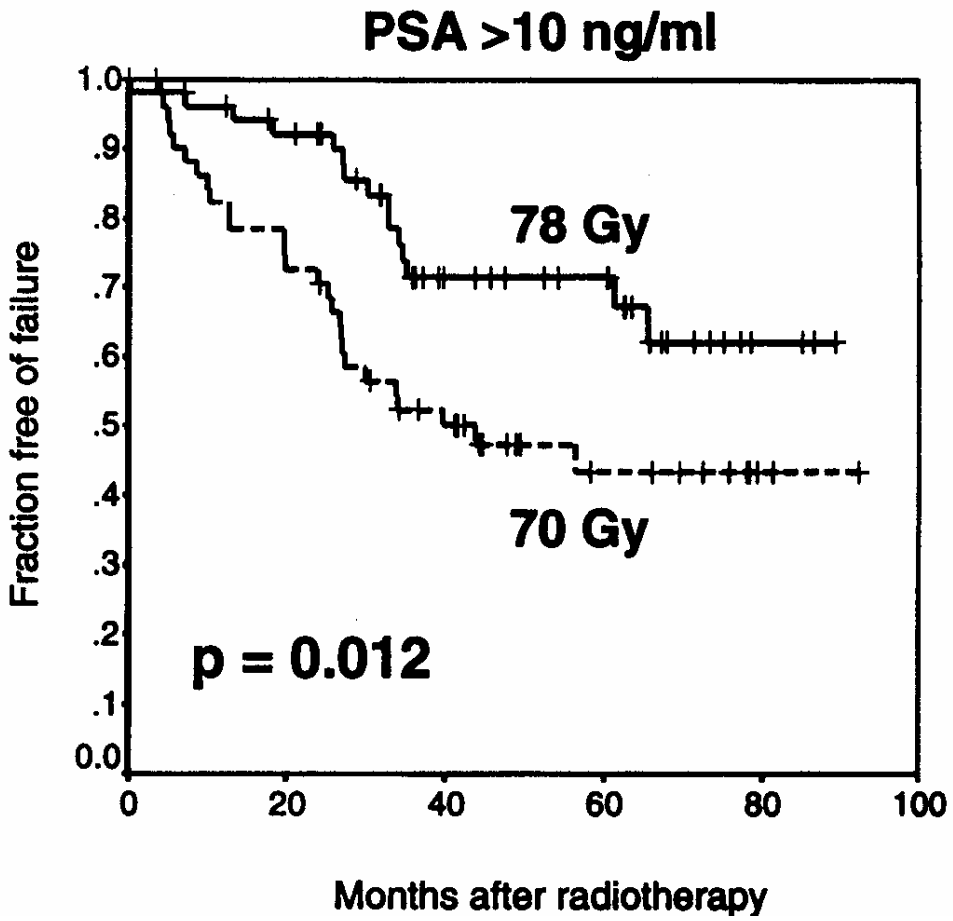

PSA >10 ng/ml
Fraction free of failure
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0.0
78 Gy
70 Gy
p = 0.012
0
20
40
60
80
100
Months after radiotherapy

Figure 2

Fractionated Radiotherapy: Dose

Survivi

- α depends on the LET of the radiation (photons and electrons are low LET, heavy charged particles and neutrons are high LET)
- β increases with increasing dose rate and decreasing LET

Fractionated Radiotherapy: Dose

- Hypothesis: NTCP depends on secondary organization of target cells into “functional subunits” (FSUs) e.g. nephrons (kidney)
- The probability that an FSU will be killed by a given dose depends on the number *N* and sensitivity of target cells in each FSU

$$\text{prob}\{F$$

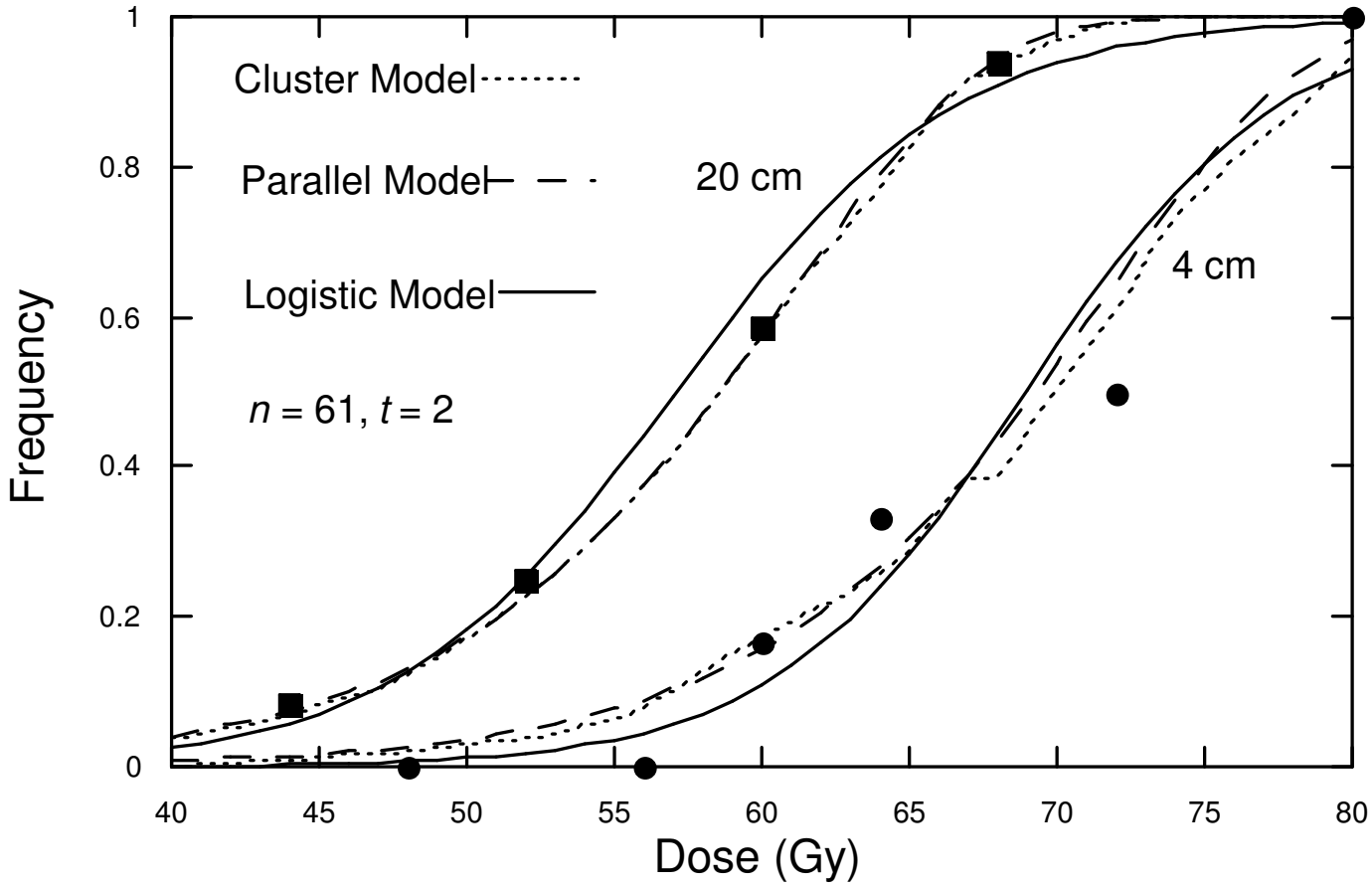
Fractionated Radiotherapy: Dose

- Modern EBRT is delivered with low-LET photons and electrons, at high dose rates. Therefore for homogeneously irradiated normal tissues (x constant) the density of sterilized FSUs d = prob{FSU sterilization} can be modeled with 2 parameters (A and B)
- Modern EBRT is however also characterized by highly inhomogeneous dose distributions, in which case d would be modeled with 3 parameters A, α, and β.

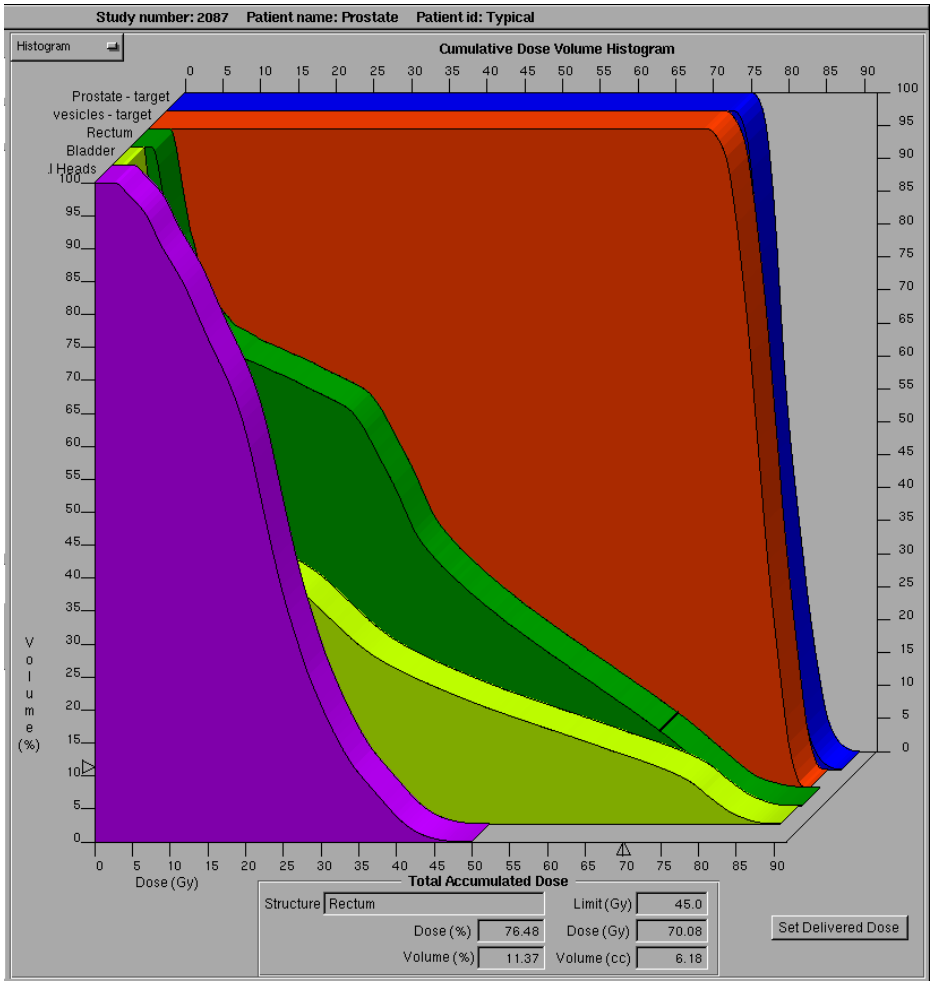
Fractionated Radiotherapy: Volume

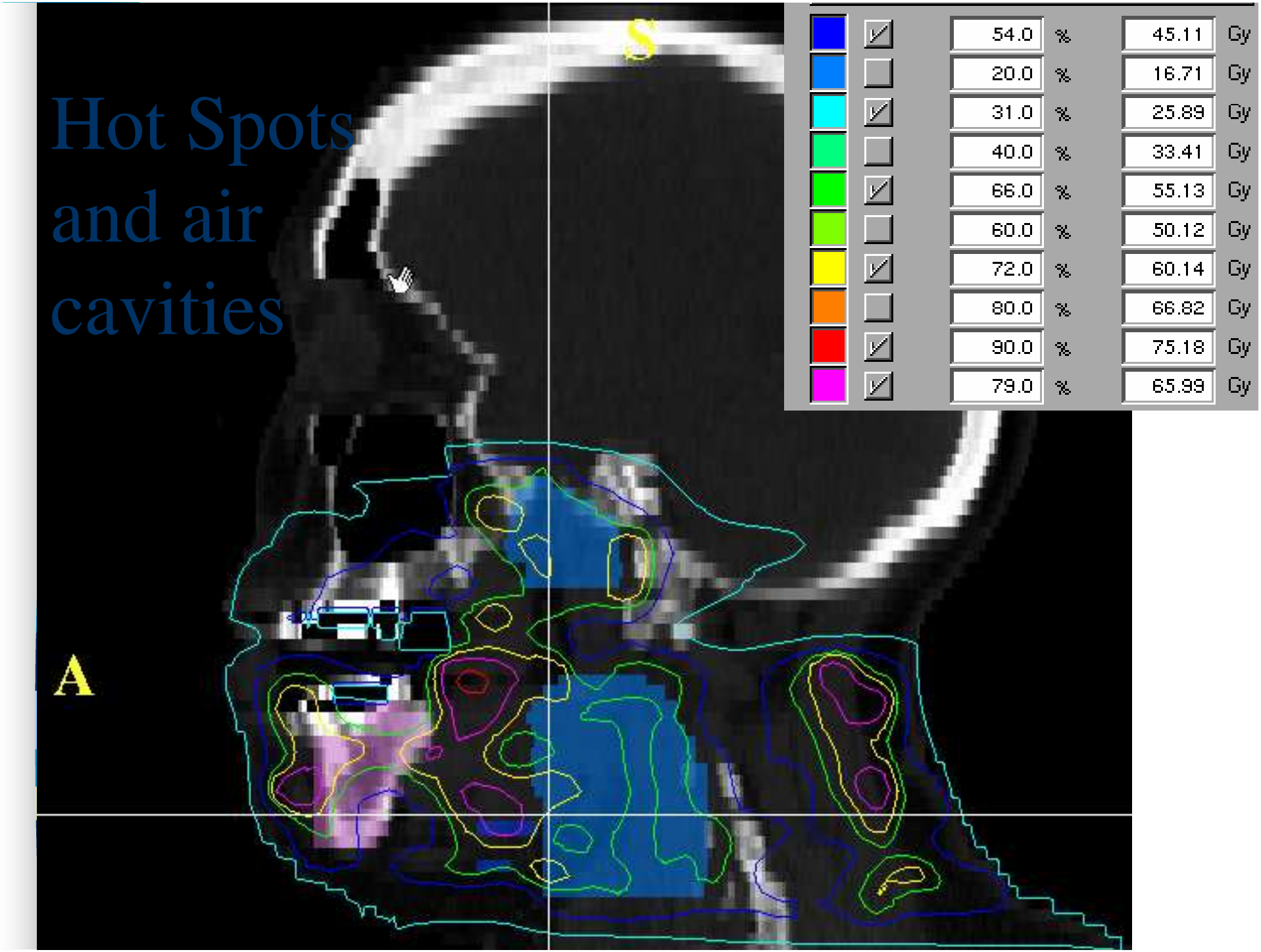
- When the same dose is delivered to different volumes (areas, lengths) of normal tissue such as the spinal cord (in the treatment of lung cancer) or the rectal wall (in the treatment of prostate cancer), NTCP is higher in the larger of the two volumes (the “volume effect”)
- Example: uniformly irradiated lengths (4 and 20 cm) of canine spinal cord (Powers et al. 1998):

Fractionated Radiotherapy: Volume



Dose-volume histogram




Hot Spots and air cavities
S
A
54.0 % 45.11 Gy
20.0 % 16.71 Gy
31.0 % 25.89 Gy
40.0 % 33.41 Gy
66.0 % 55.13 Gy
60.0 % 50.12 Gy
72.0 % 60.14 Gy
80.0 % 66.82 Gy
90.0 % 75.18 Gy
79.0 % 65.99 Gy

Site Percolation Theory

- Let $M = (m_{ij})$ be a random n x n binary matrix with
  $m_{ij} = 1$ with probability p and 0 with probability $1 - p$
  m_{ij} and m_{kl} are independent if $(i,j) \neq (k,l)$
- An s-cluster is an isolated grouping of s adjacent 1s in M, where adjacency means horizontal or vertical neighbors (not diagonal). For example:

has one 1-cluster, two 2-clusters, and one 4-cluster for p=9/16.

Site Percolation Theory

- Mean cluster size: $\sigma_4(p) = (1+2+2+4)/4 = 9/4$
- The critical probability or percolation threshold p_c is defined in terms of

by

Site Percolation Theory

- That is, the critical probability is the unique value of p for which an ∞-cluster appears in the infinite square lattice
- The case of one dimension is of no interest since the ∞-cluster only occurs when p=1
- For site-percolation models on the square lattice there are rigorous bounds (but no closed-form expressions):

$$0.556 < p_c < 0.679492$$

and calculations indicate that $p_c = 0.5928$

Site Percolation Theory

Let $c_2(n,p)$ denote the mean maximum cluster size for the n x n two-dimensional lattice. Asymptotic estimates

where $S = 91/48 = 1.896...$ is called the scaling exponent. That $S < 2$ implies that the maximum cluster at the percolation threshold is a fractal.

Site Percolation Theory: Applications

- Forest fires: the forest is modeled by a square lattice, where a tree on fire will ignite its nearest neighbor in a cluster. How long does the fire last? For small or large values of p, that is, above and below p_c, not long: the maximum duration of the fire occurs when $p = p_c$.
- Epidemics in orchards: similar to above, with probability p that a healthy tree will be infected by a neighboring blighted tree, where p is known as a function of distance. Lattice spacing that prevents an epidemic: $p < p_c$.

Site Percolation Theory: Applications

- Ferromagnetism: magnetization of a metal is measured in terms of oscillations in an applied external field. The temperature of the metal is increased from 0 to T, then decreased to 0. If T is sufficiently large the metal retains no magnetization whereas if T is lower than the critical temperature T_c the metal keeps some of its induced magnetization.
- Other: Polymerization, Productivity of oil fields, Extreme market share (0 or 100%) in the media industry, Wafer-scale integration in the manufacture of microchips

Cluster models of dose-volume effects

- Hypothesis: a normal-tissue complication occurs when there are sufficiently large aggregates of adjacent sterilized FSUs. Different volumes (areas, lengths) of irradiated tissue are modeled by lattices of correspondingly different sizes. The critical feature is mean maximal cluster size.
- Differences: cluster models vs. percolation models
  - Emphasis on max. cluster size in finite lattices, not mean cluster size in infinite lattices
  - One-dimensional cluster models are nontrivial
  - More highly compact clusters (that result from increasing the local connectivity) are used in the modeling

Cluster models of dose-volume effects

Dose-dependent density d of sterilized FSUs:

$$1$$

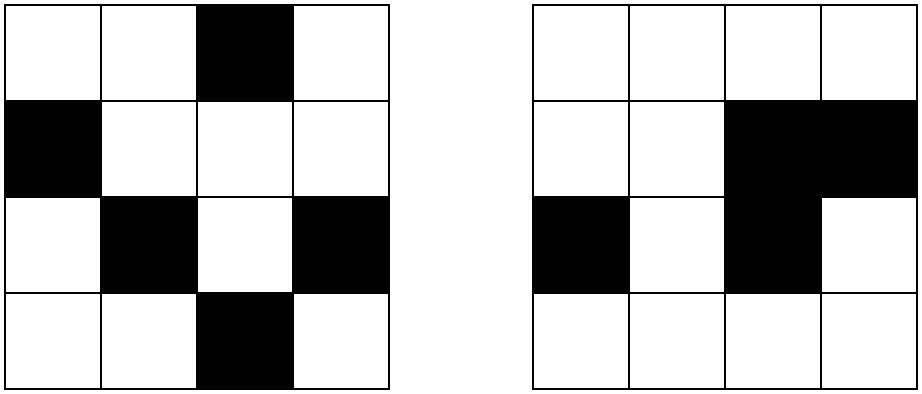
Additional parameters: n (size) and t (complication threshold)

Consequences of random radiation-induced cell killing:

(1) The *number* of sterilized FSUs is binomially distributed about the mean e.g. $n^2\ d$

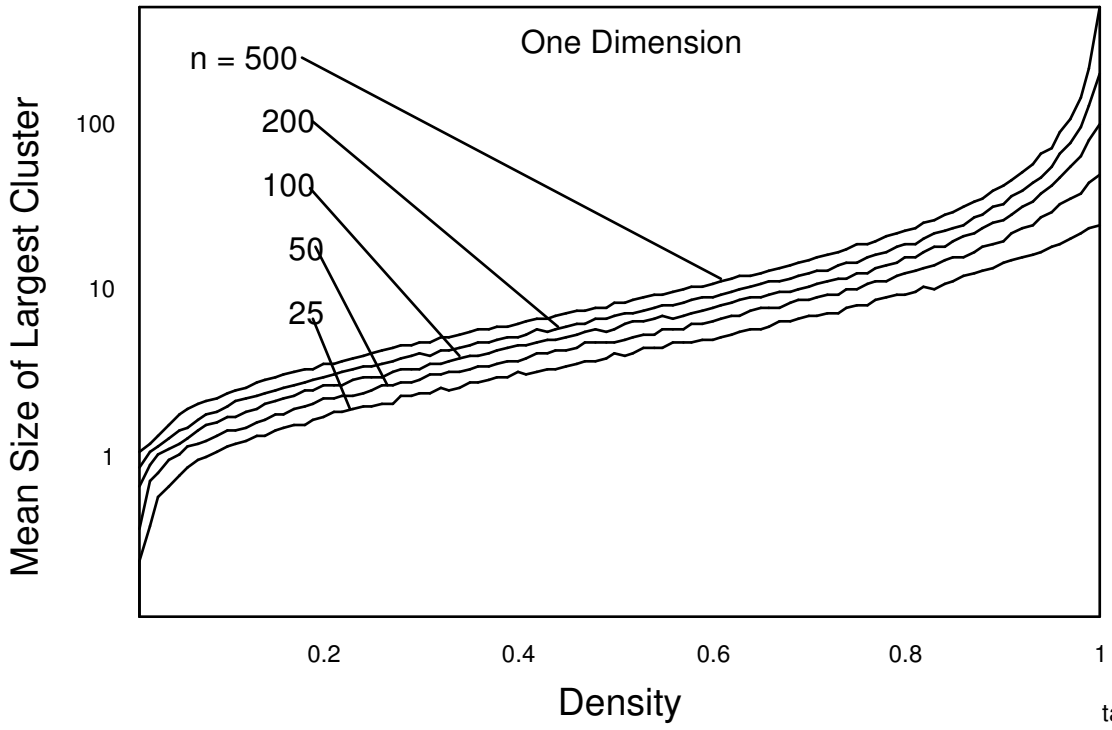
(2) The *location* of sterilized FSUs is randomly distributed throughout the irradiated volume (area,length)

Cluster models of dose-volume effects

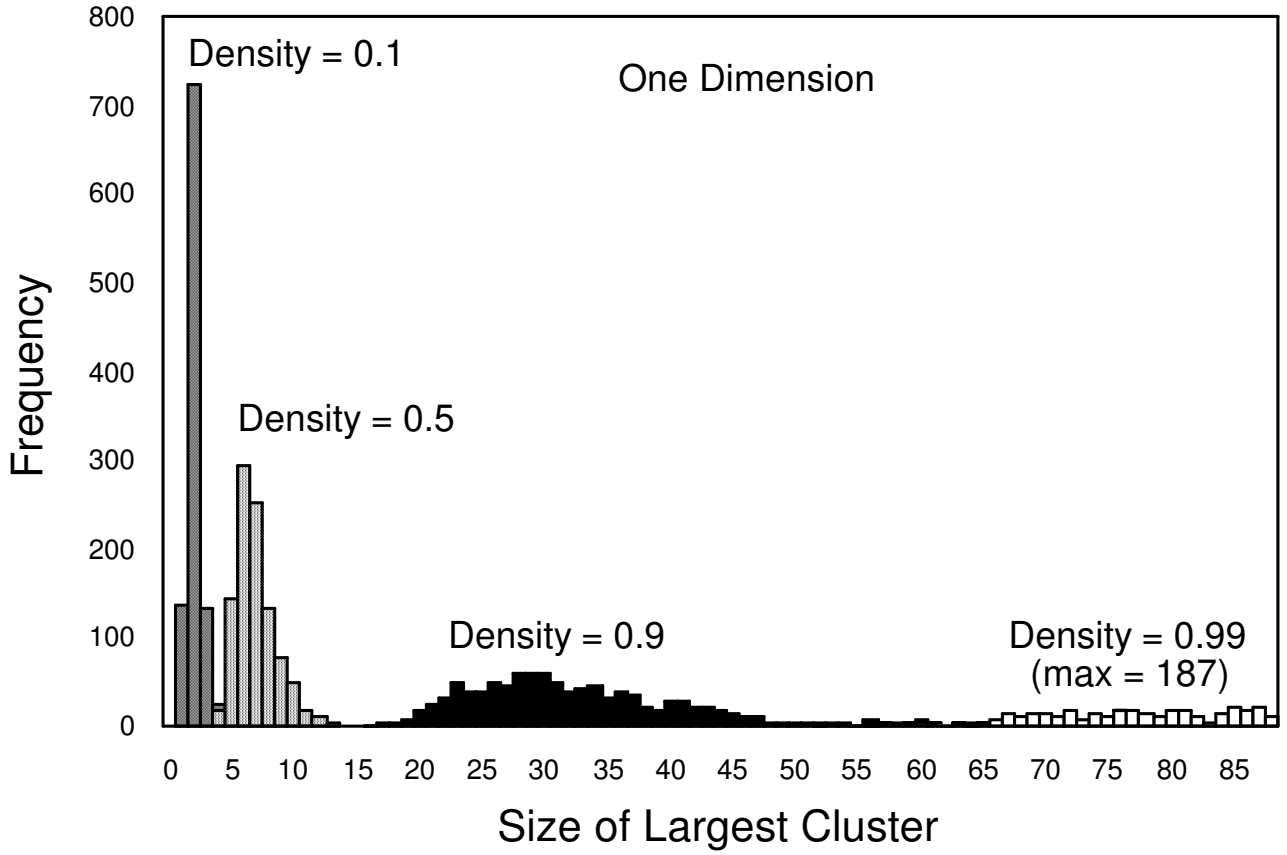


One-dimensional models

- Maximum cluster size = length of longest uninterrupted string of black intervals
- Percolation threshold occurs at $p_c = 1$

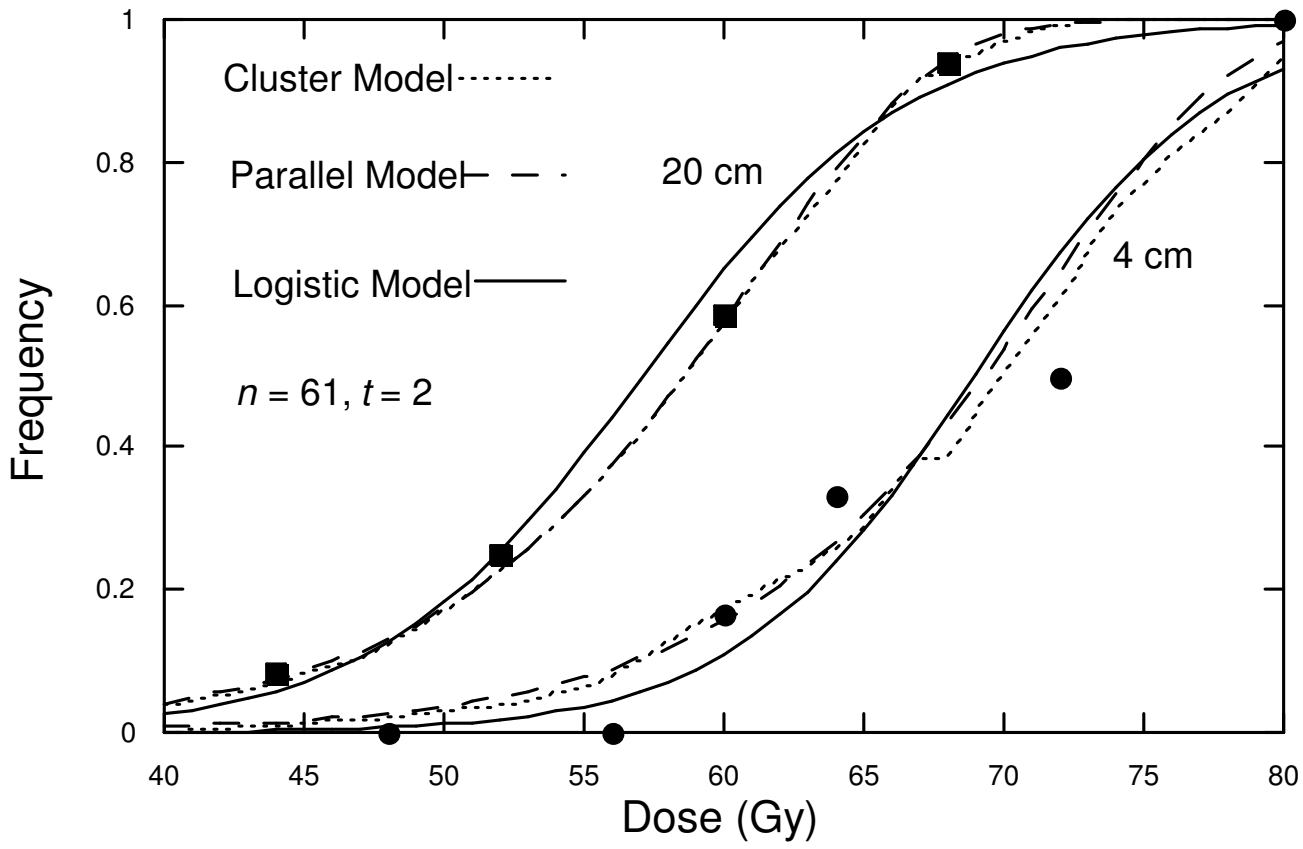


One-dimensional models

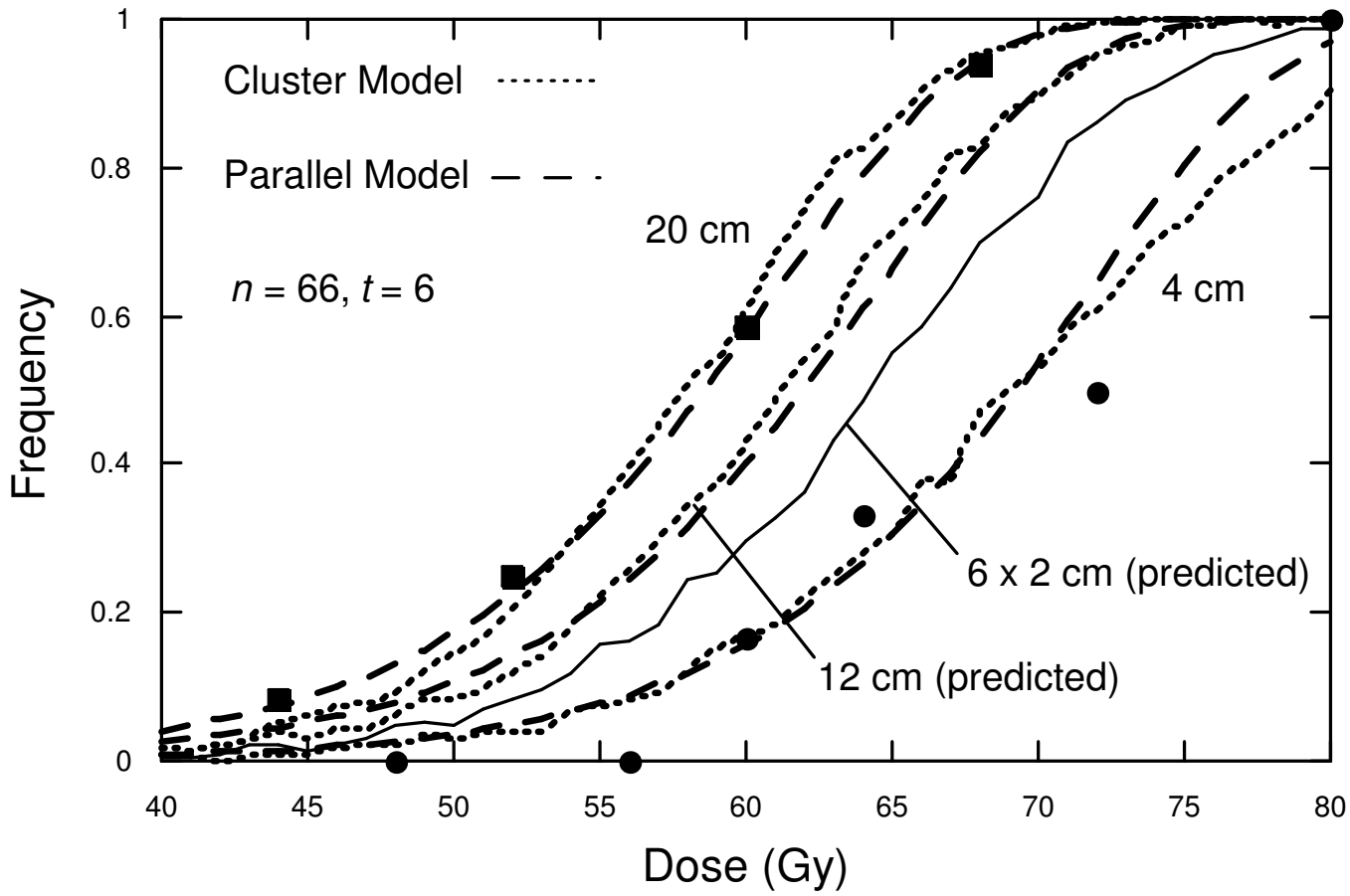


kvalues1

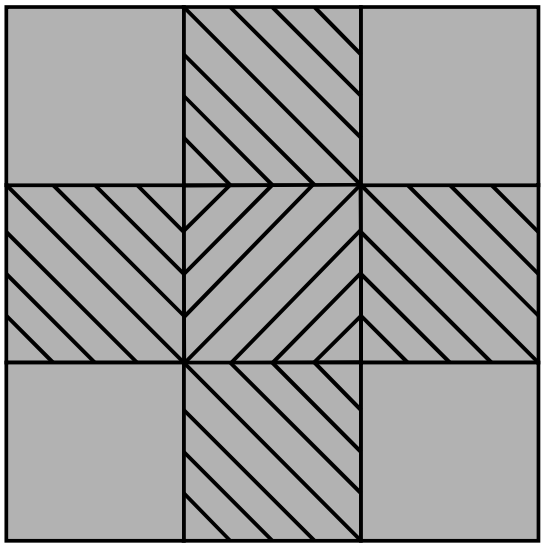
One-dimensional models



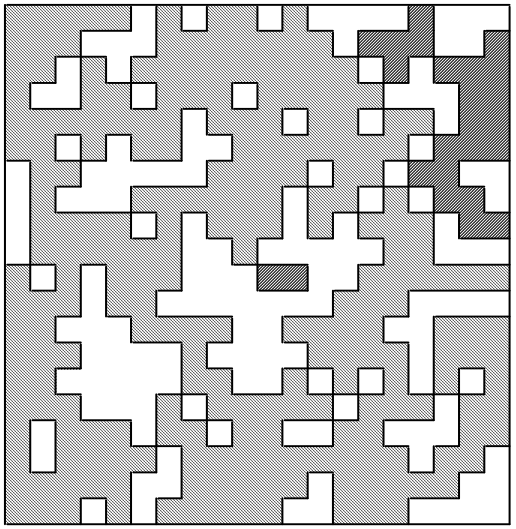
One-dimensional models



Two-dimensional models: 1-connectivity

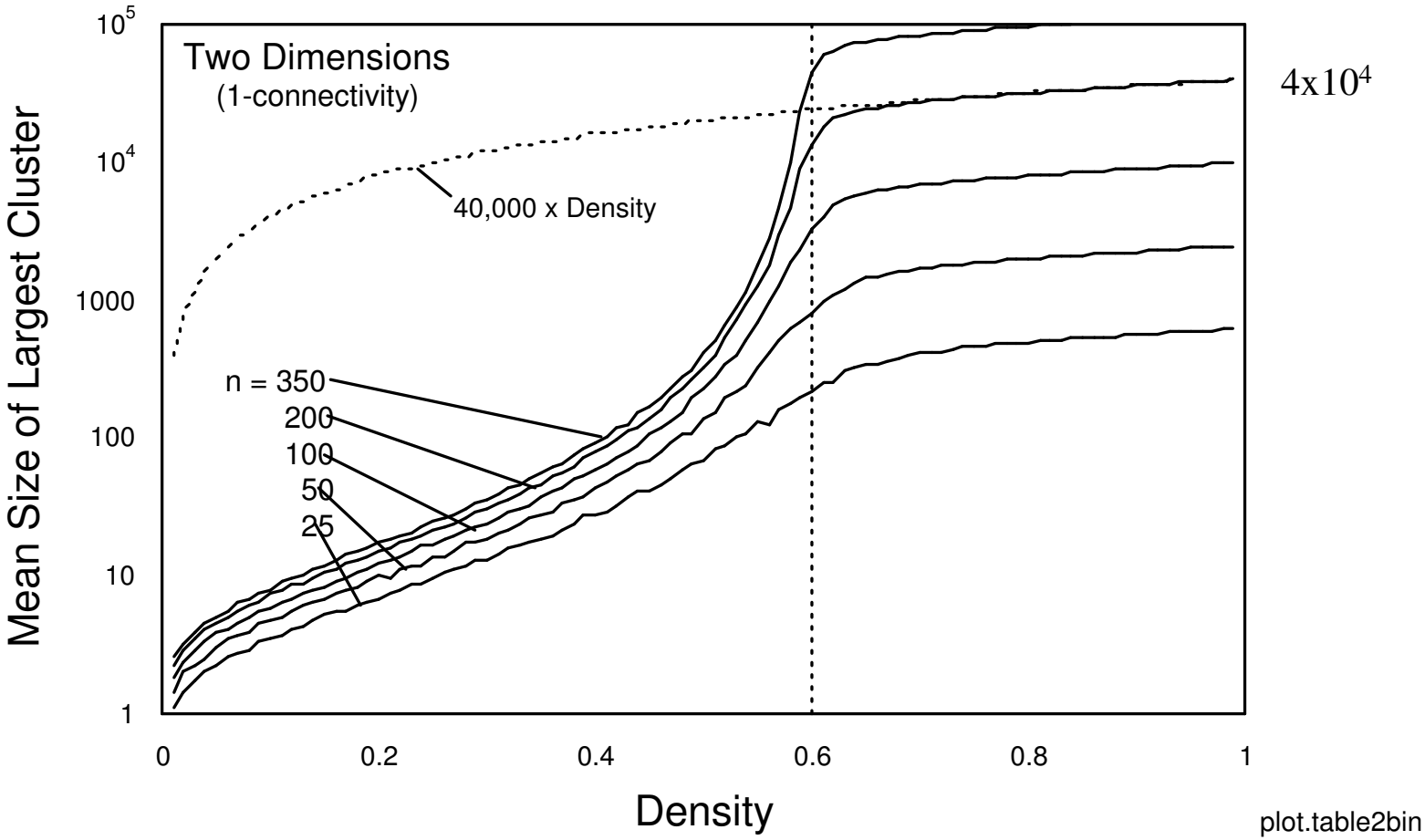


A

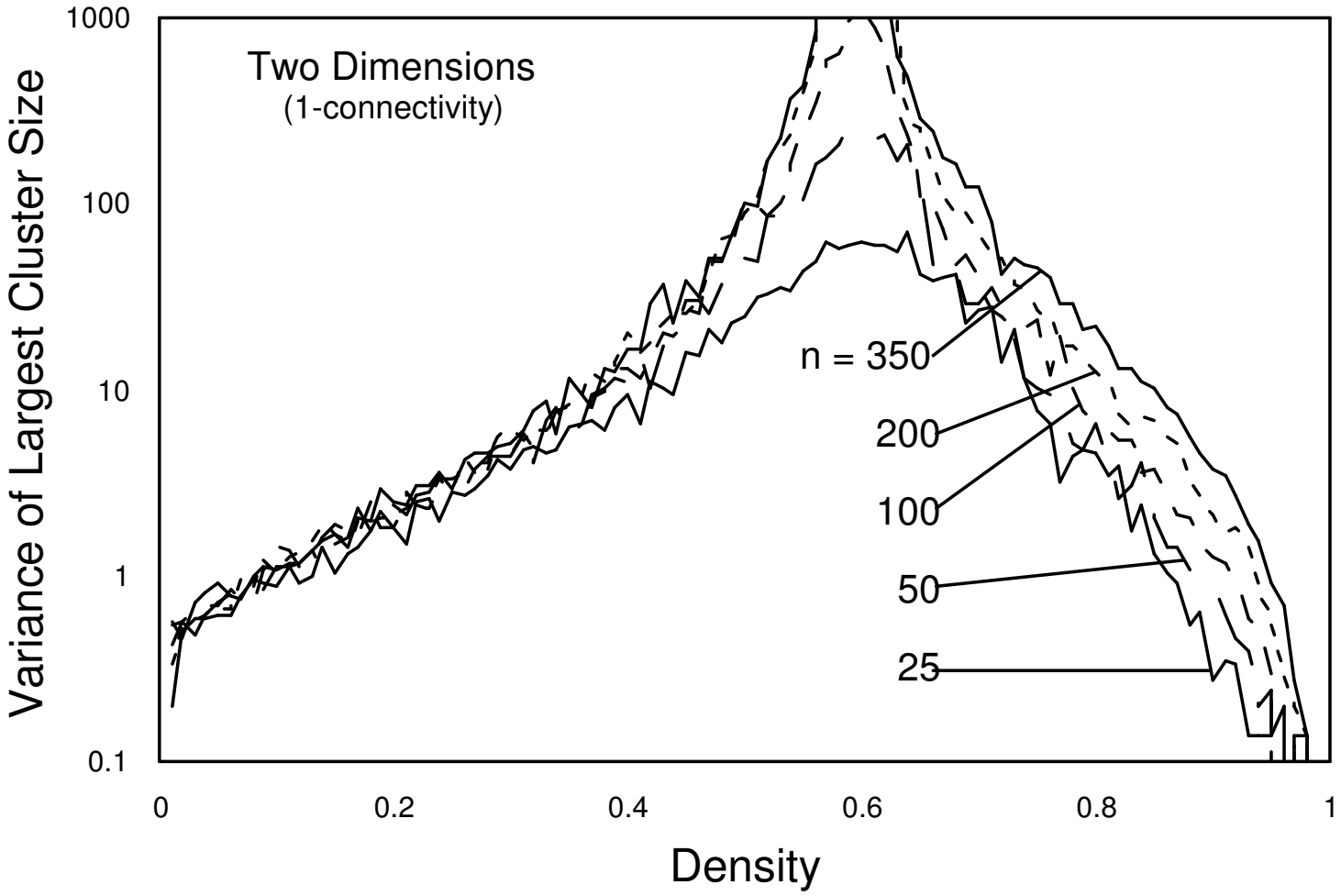


B

Two-dimensional models: 1-connectivity

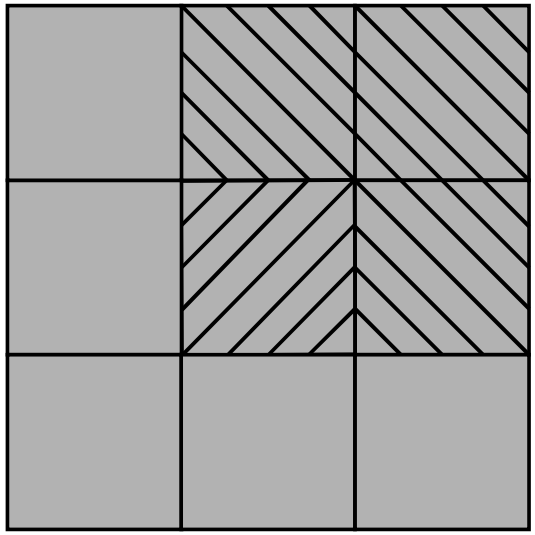


Two-dimensional models: 1-connectivity



vtable2

Two-dimensional models: 2-connectivity



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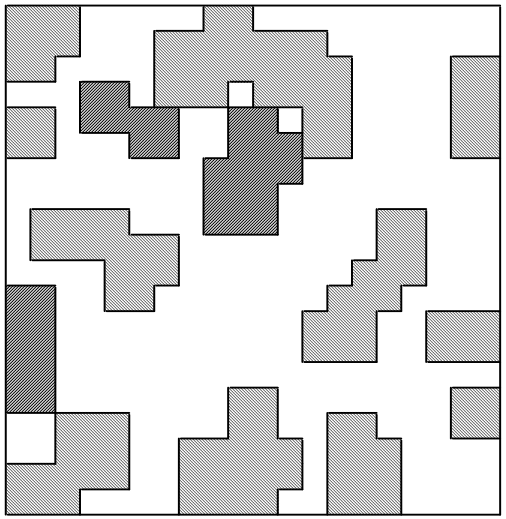
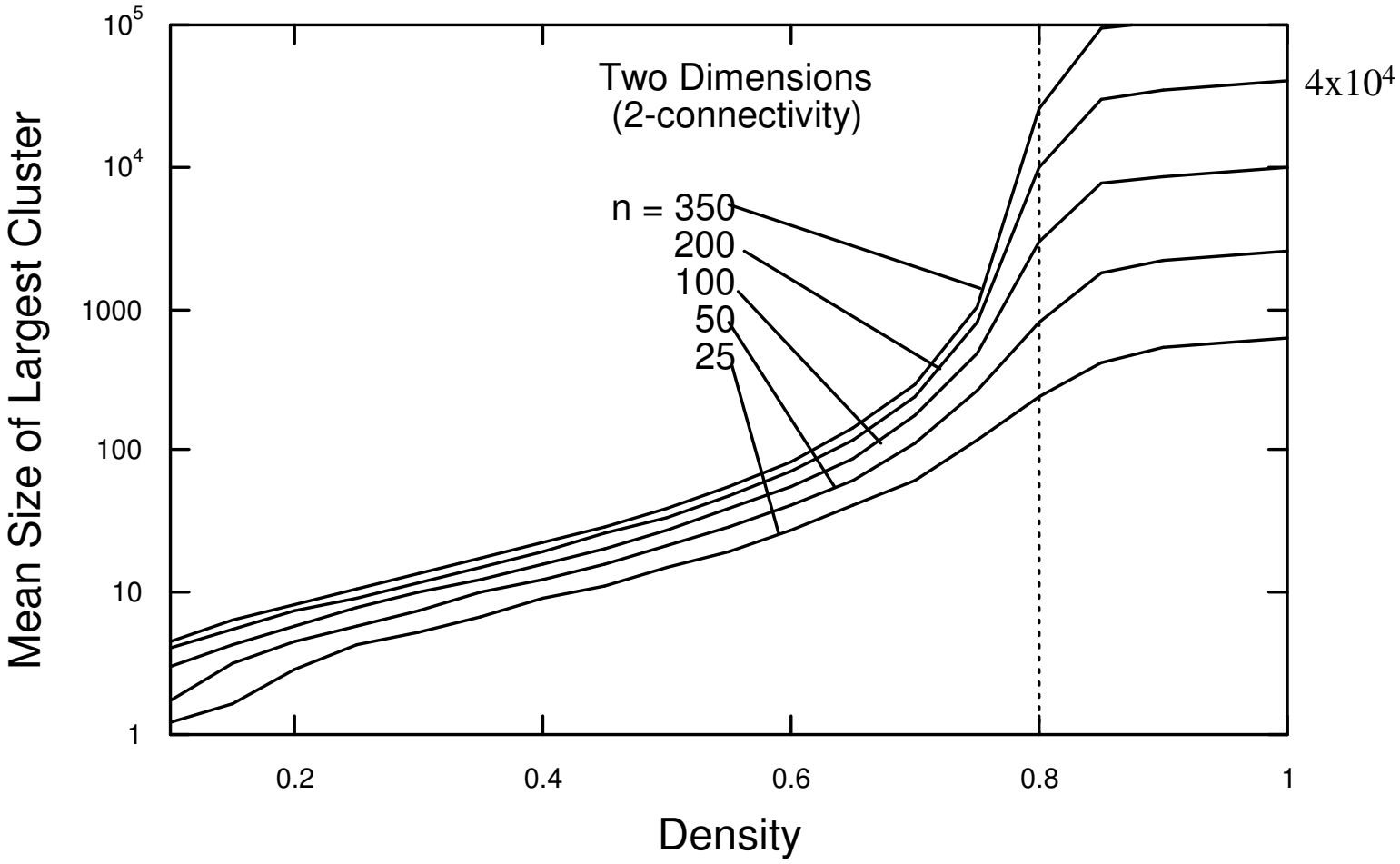
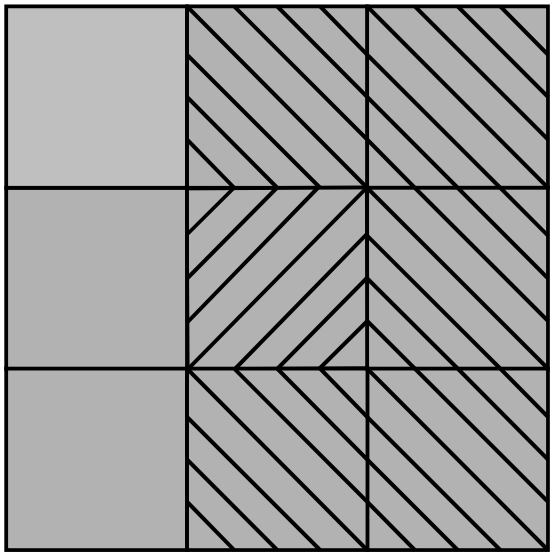


D

Two-dimensional models: 2-connectivity



Two-dimensional models: 3-connectivity



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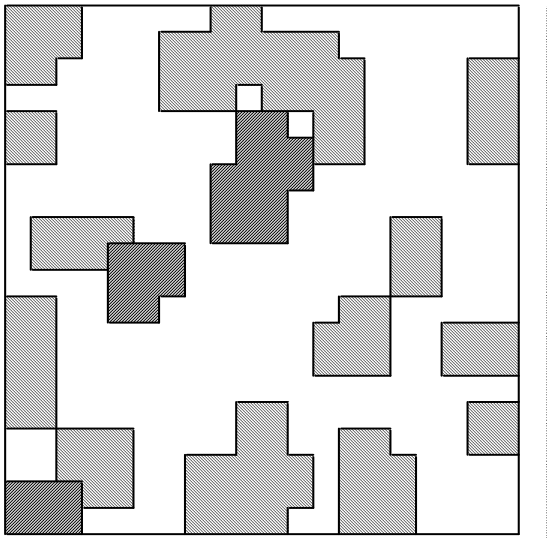
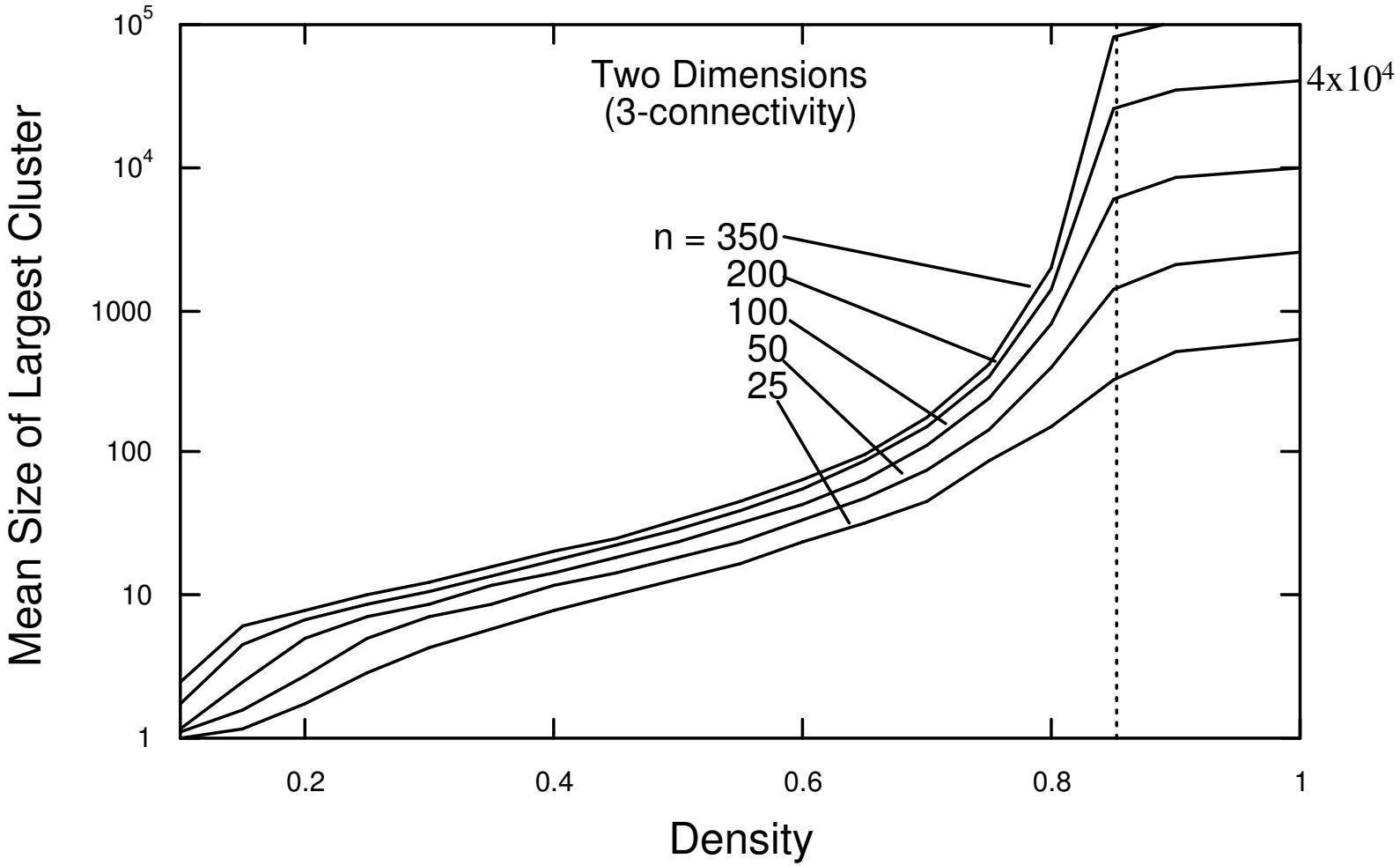


F

Two-dimensional models: 3-connectivity



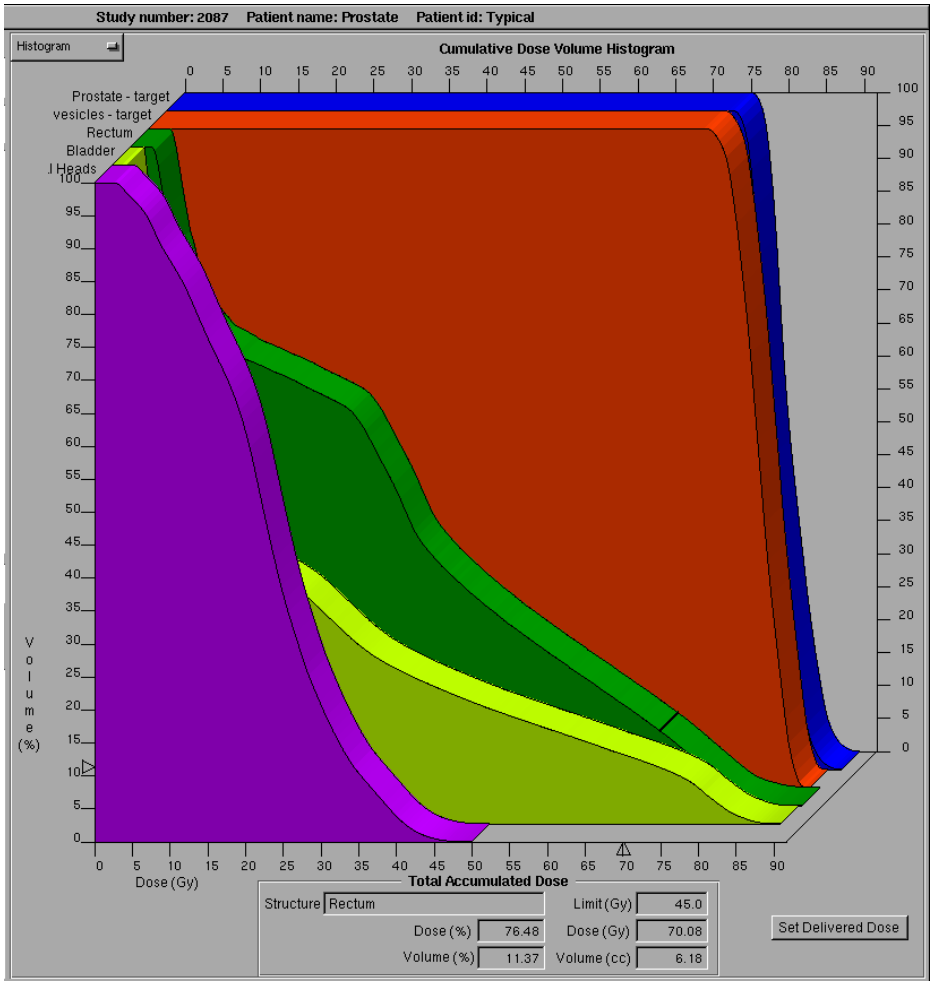
Model Validation

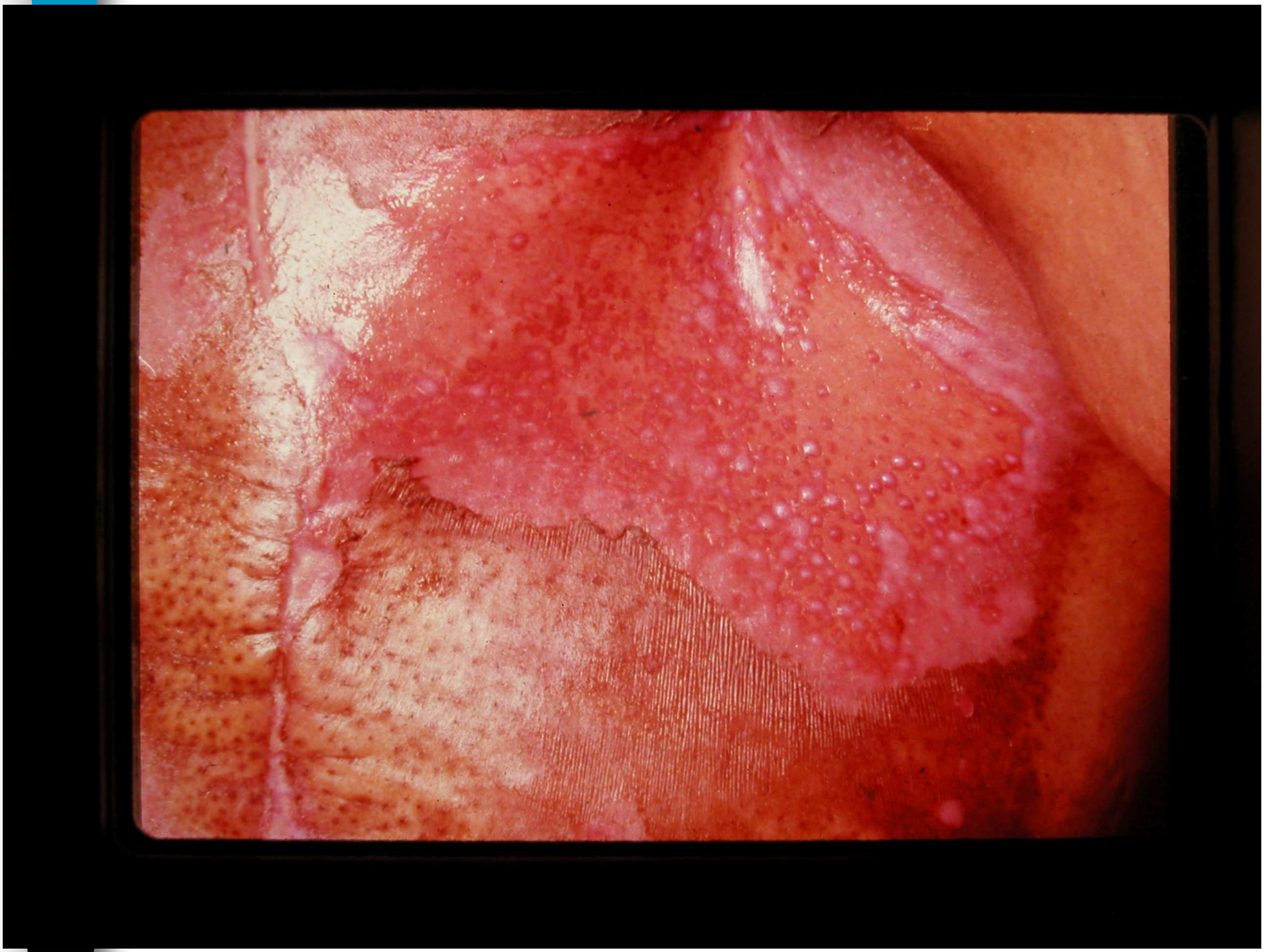
- "Grid Therapy"
- Differences in maximum cluster size for different dose distributions with identical DVHs
- Existence of a "percolation dose"

Grid Therapy

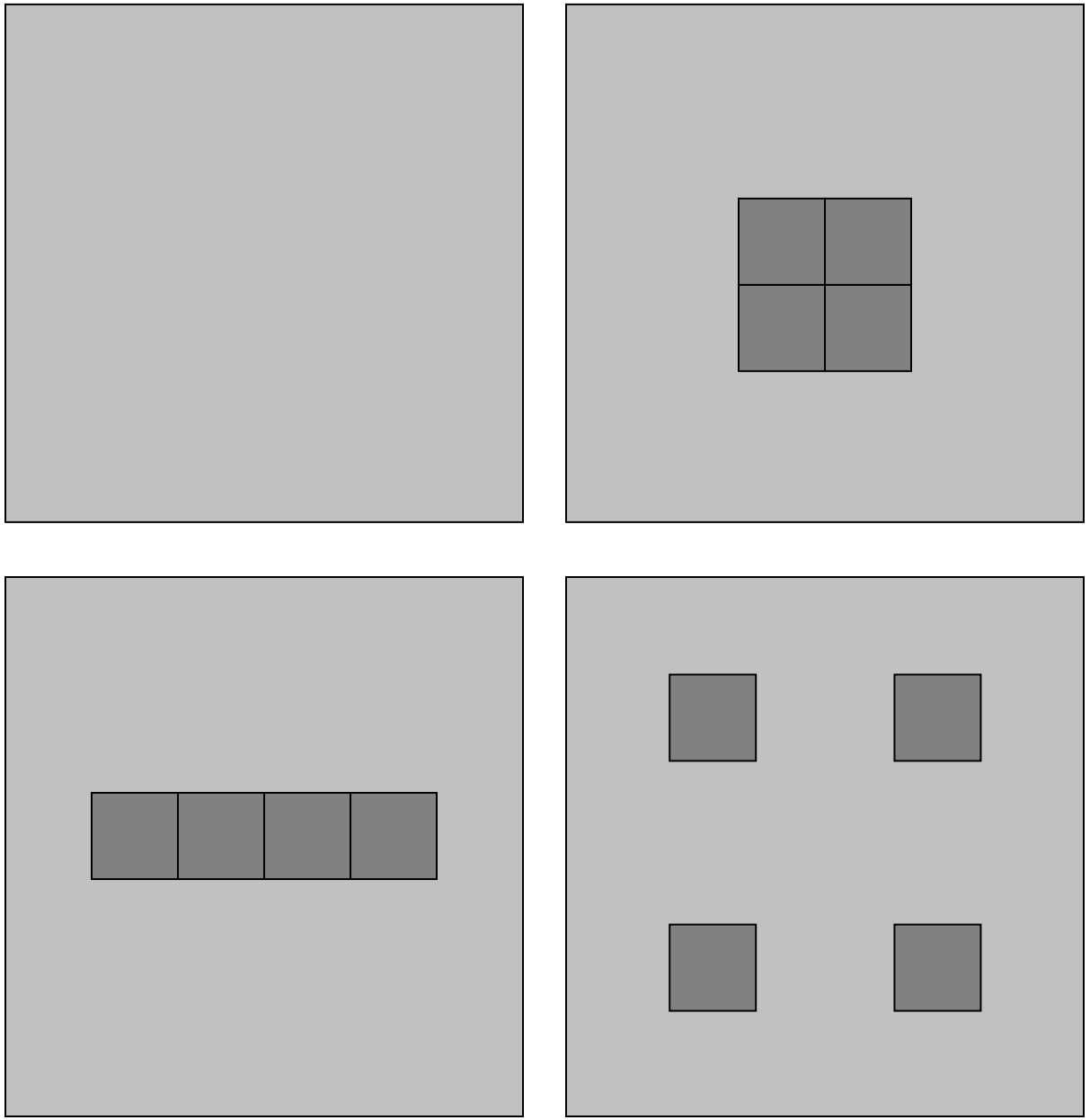
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Dose-volume histogram

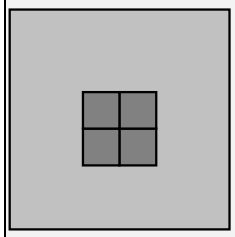
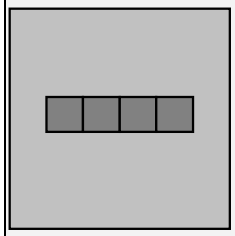
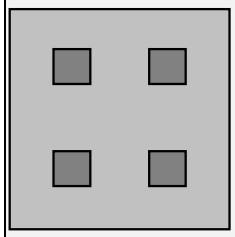




Different Cluster Distributions Arise from Same DVH



Different Cluster Distributions Arise from Same DVH: Mean Size of Largest Cluster (d_1=0.1)

Dose Distribution	d_2			
	0.5	**0.6**	**0.7**	**0.8**
	27.7	56.7	178	3160
	27.6	57.3	176	2290
	27.1	54.7	161	1190

Percolation dose

Asymptotic dependence of $c_2(n,d)$ on n:

where p_c=0.5928 for the 2-lattice (1-connectivity).

How rapidly does NTCP change when the irradiated area n^2 is increased at constant dose (density)? Assuming a continuous sigmoidal form near the threshold t...

Percolation dose

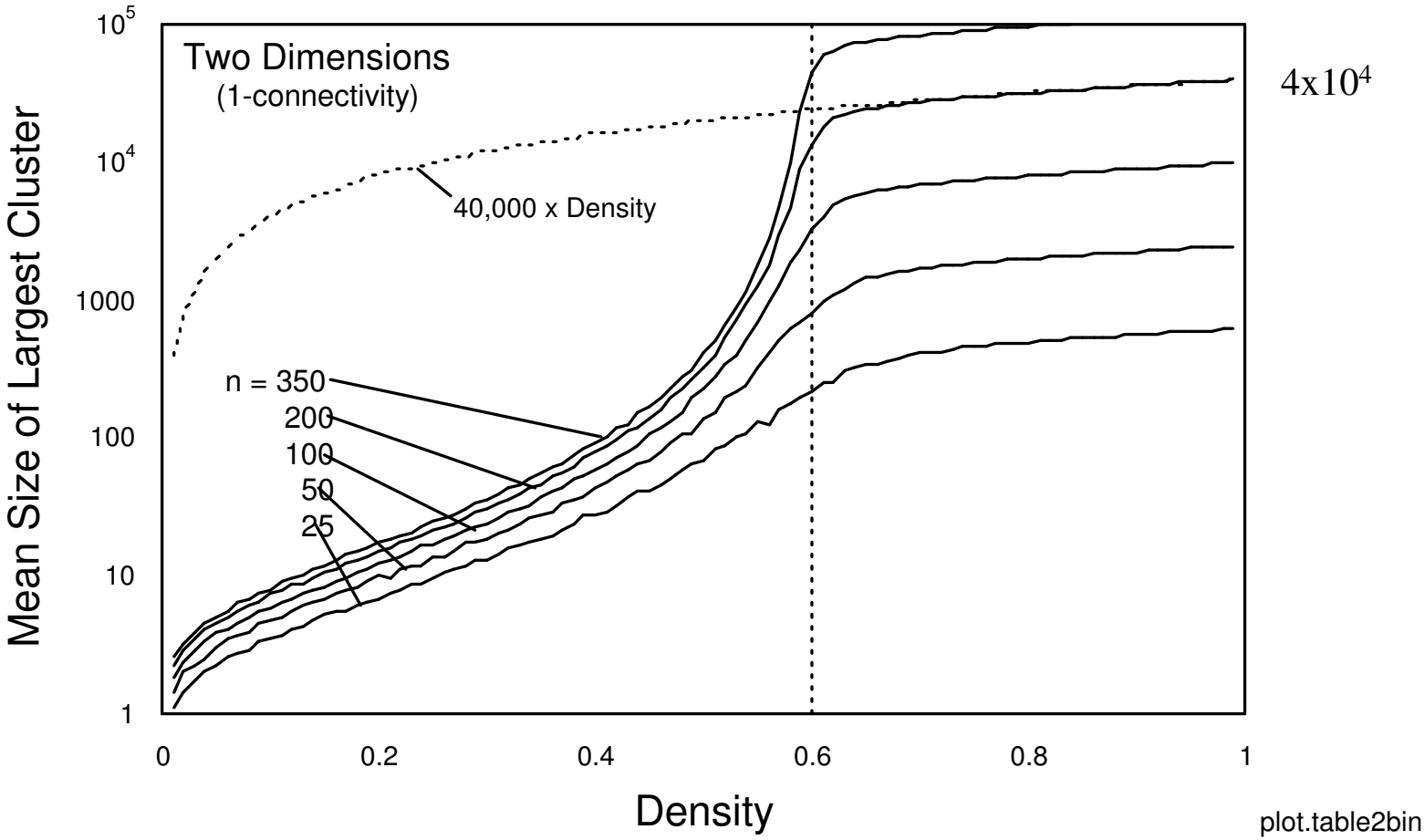
$$dN'$$

Conjecture

There is a “percolation dose” D_p defined by

such that for $D < D_p$ NTCP is a weak function of area irradiated, whereas for $D > D_p$ NTCP is a very strong function of area irradiated

Two-dimensional models: 1-connectivity



Conclusions

- The increasing conformality of external-beam radiotherapy treatments, realized by new technologies like IMRT, will result in increasing heterogeneity of dose distributions to normal tissues, and DVHs may not contain enough information to describe NTCP accurately
- Cluster models, a finite realization of percolation models, offer an alternative approach based on the complete 3-D dose distribution matrix
- Cluster models await validation from clinical data

What's needed...

- Cancer research: prospective dose-escalation studies of normal-tissue complications (comparable to RTOG 96-01 for rectal toxicity after EBRT for prostate ca)
- Applied mathematics: asymptotics for 2- and 3-D lattices with 2-connectivity at below-percolation densities

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