

Patient specific differences in setup error variability and its effect on treatment margins in fractionated radiotherapy

Marcel van Herk and Marnix Witte

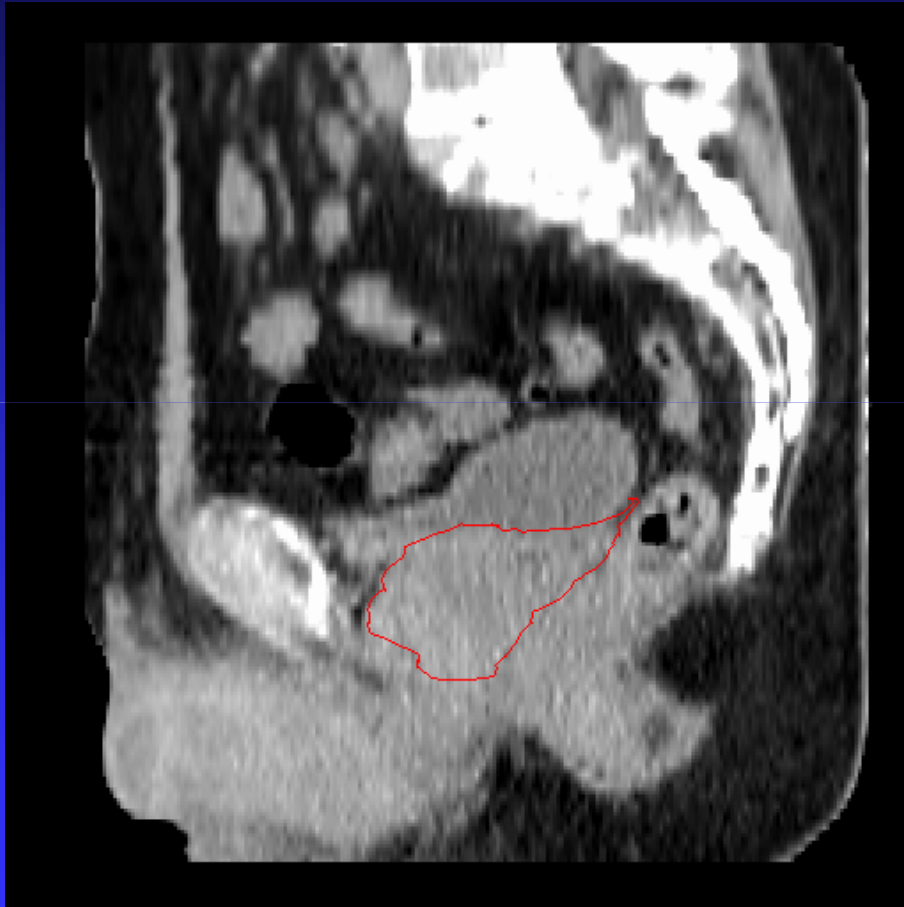
Netherlands Cancer Institute, Amsterdam, The Netherlands

This work was sponsored by the Dutch Cancer Society

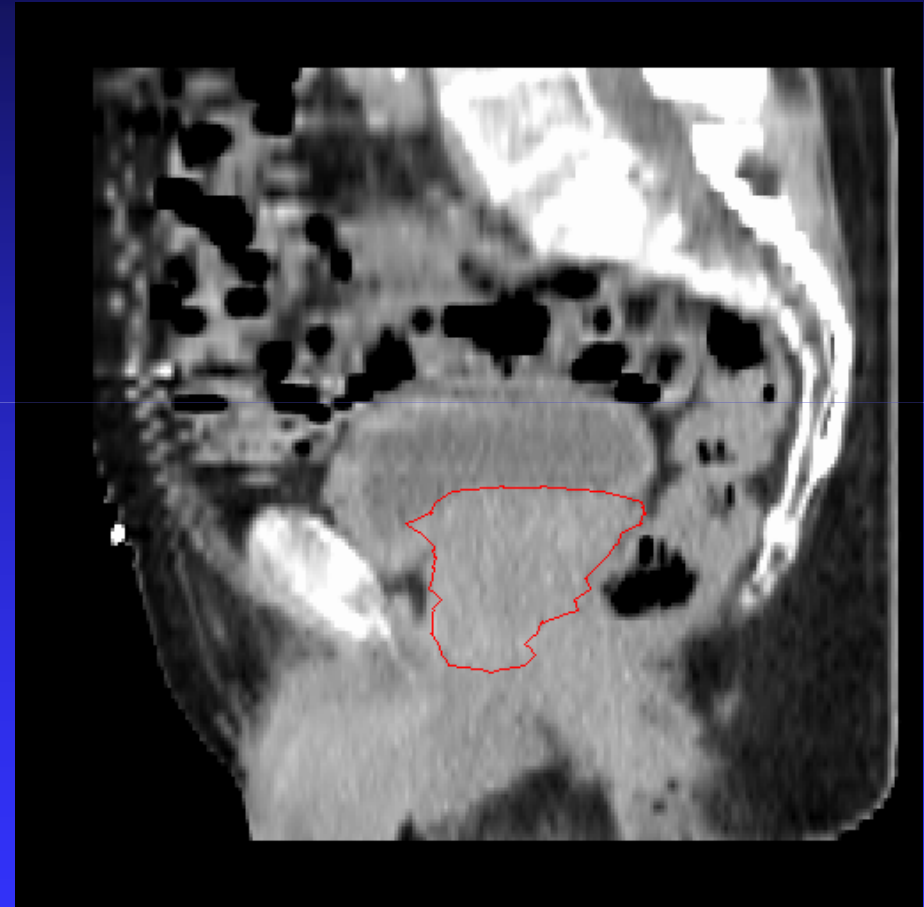
Introduction

- It is often assumed that the mobility (setup error and/or organ motion standard deviation) differs from patient to patient
- However, this is difficult to prove because there are often only few measurements (fractions) per patient
- Aims:
 - 1) quantify the statistics of patient-specific differences in mobility by analysis of data from a large group of patients
 - 2) Analyze the effect of any variability on population-based margins

Are patients comparable? (in terms of setup error or organ motion)



sd = 1mm



sd = 5mm

12 daily scans showing prostate motion

Common analysis of (setup) error (random and systematic)

	patient 1	patient 2	patient 3	patient 4
fraction 1	0.5	0.0	0.2	0.7
fraction 2	0.6	-0.5	0.3	0.2
fraction 3	0.9	0.2	0.2	-0.4
fraction 4	1.3	-1.1	0.3	-0.1
mean	0.8	-0.4	0.3	0.1
sd	0.3	0.6	0.1	0.5

Intra-fraction
0.0
0.3
0.4
0.1
0.3
Mean = 0.2
RMS of SD = σ_f

{ mean = M
 { SD = Σ
 { RMS = σ

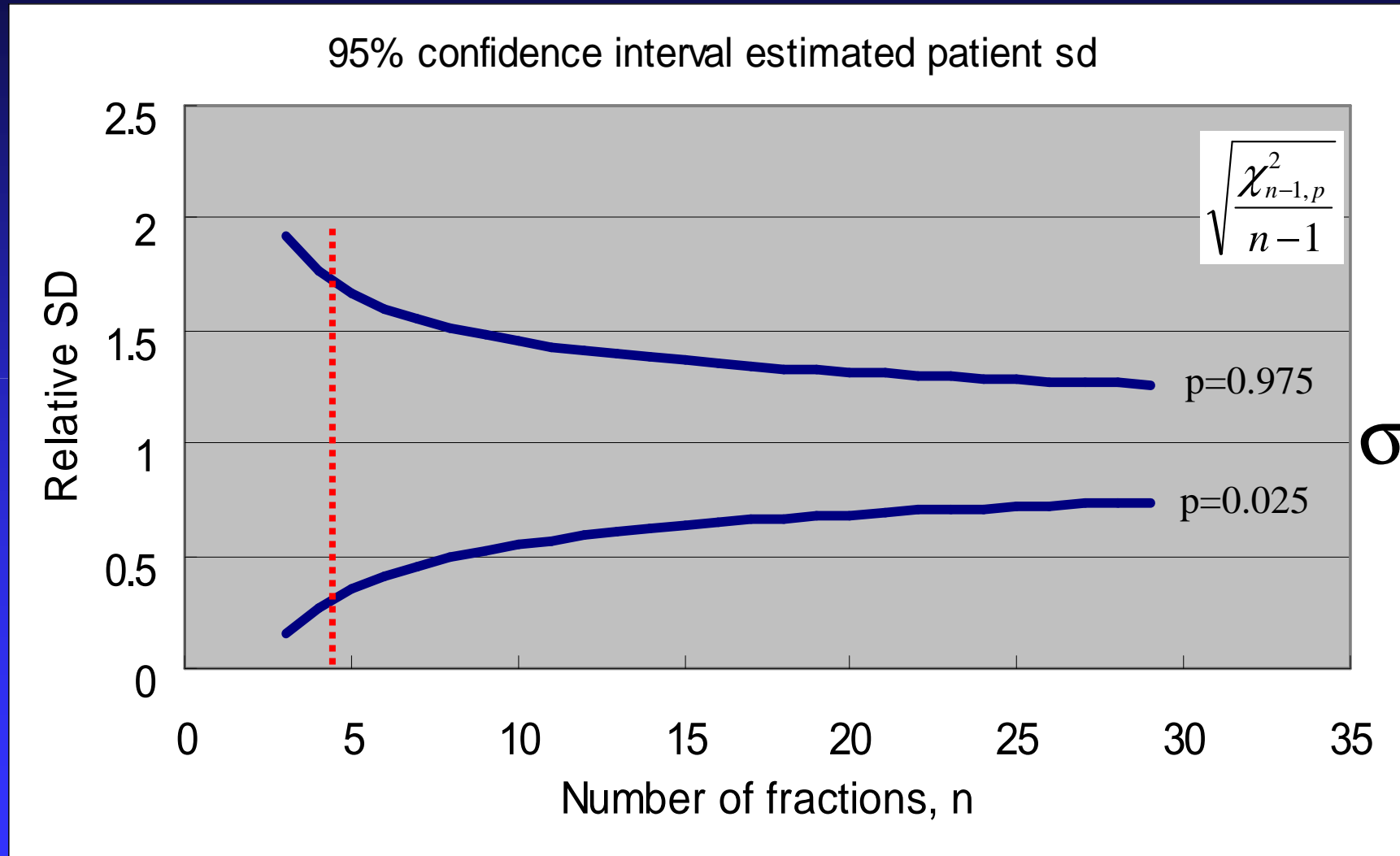
DIFFERENT ?

- M = group systematic error
- Σ = SD systematic error
- σ = SD random error (mobility)
- σ_f = SD intra-fraction motion

SD should be calculated using the "nonbiased" or "n-1" method

van Herk et al, Sem Rad Onc 2004

Measurement error in SD - does patient sd deviate from population σ ?



For N=4, expect observed SD between 0.27σ and 1.77σ

Extended analysis of (setup) error

	patient 1	patient 2	patient 3	patient 4
fraction 1	0.5	0.0	0.2	0.7
fraction 2	0.6	-0.5	0.3	0.2
fraction 3	0.9	0.2	0.2	-0.4
fraction 4	1.3	-1.1	0.3	-0.1
mean	0.8	-0.4	0.3	0.1
sd	0.3	0.6	0.1	0.5

Intra-fraction
0.0
0.3
0.4
0.1
0.3
Mean = 0.2
RMS of SD = σ_f

$\left\{ \begin{array}{l} \text{mean} = M \\ \text{SD} = \Sigma \\ \text{RMS} = \sigma \end{array} \right.$
 $\left\{ \begin{array}{l} \text{SD} = \text{sdsd} \end{array} \right.$


NEW!

M = group systematic error
 Σ = SD systematic error
 σ = SD random error (mobility)
 σ_f = SD intra-fraction motion
 sdsd = SD of mobility –

with large measurement error because of few fractions

Prostate setup error data from EPID

470 patients with average 8.5 fractions per patient
(setup corrections removed)

N=470	M (mm)	Σ (mm)	σ (mm) <i>Mean sd</i>	sdsd (mm) <i>SD sd</i>
LR	0.2	2.5	2.0	0.8
SI	0.4	1.5	1.2	0.4 
AP	0.6	2.3	1.8	0.6

NEW!

Data courtesy of Wilma Heemsbergen, TKZ group NKI/AVL

Even if all patients are the same, $sdsd \neq 0$
 → correct for measurement error in sd

N=470	sdsd (mm)	SD measurement error, 8.5 samples (mm)	$\sigma_{\sigma} = \text{True variability (mm)}$
LR	0.8	0.6	0.5
SI →	0.4	0.3	0.2
AP	0.6	0.5	0.3

} 0.26 σ

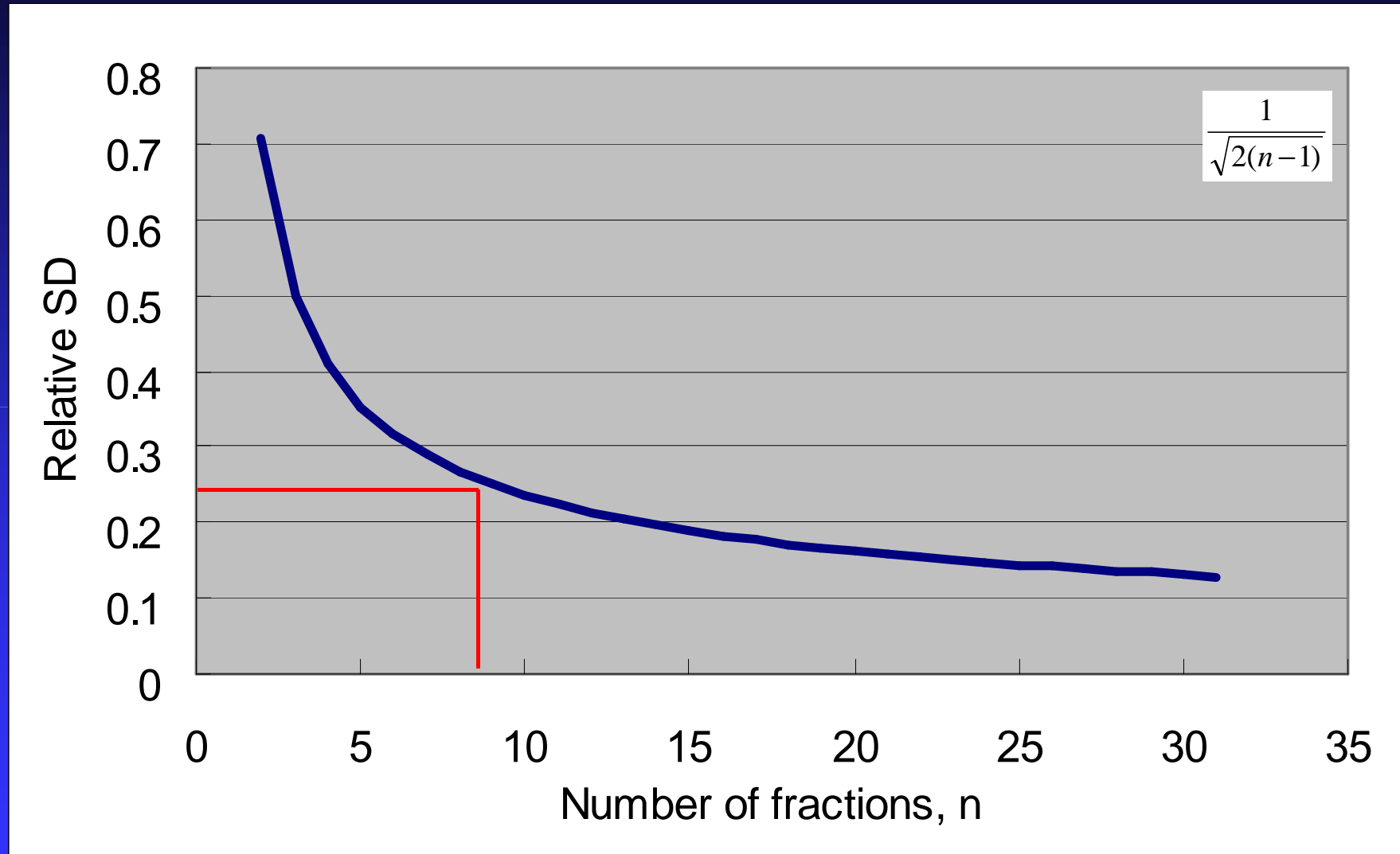
} $\approx 0.22 \sigma$

raw data

statistics

$\sqrt{\text{raw data}^2 - \text{statistics}^2}$

Error in sd (estimator of σ)



0.26 σ for 8.5 fractions

Inter-patient variability in organ motion

N=19	σ (mm, °)	sdsd (mm, °)	SD measurement error N=11	σ_{σ} = True variability (mm, °)
T _{LR}	0.9	0.5	0.2	0.4
T _{SI}	2.1	0.6	0.4	0.5
T _{AP}	3.2	1.4	0.7	1.2
R _{LR}	3.5	1.3	0.7	1.1
R _{SI}	1.9	0.8	0.4	0.7
R _{AP}	1.5	0.6	0.3	0.6

} 0.41 σ

} $\approx 0.3 \sigma$

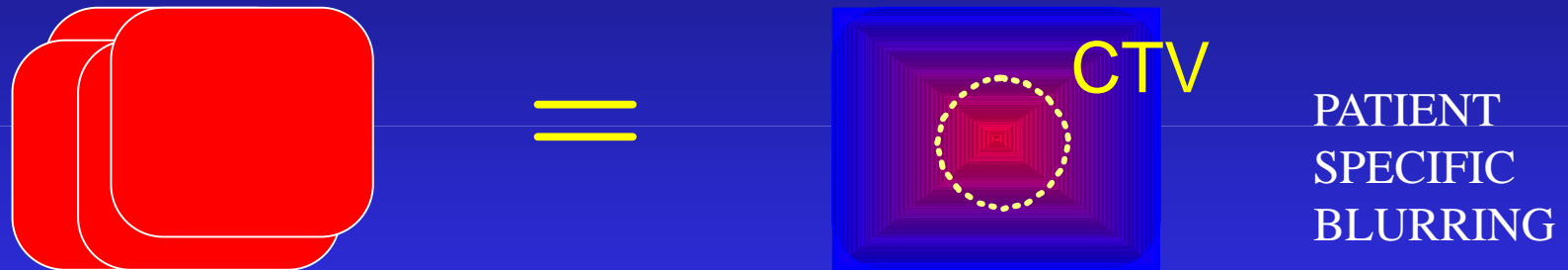
raw data

statistics

$\sqrt{\text{raw data}^2 - \text{statistics}^2}$

What is the effect of geometrical errors on the CTV dose ?

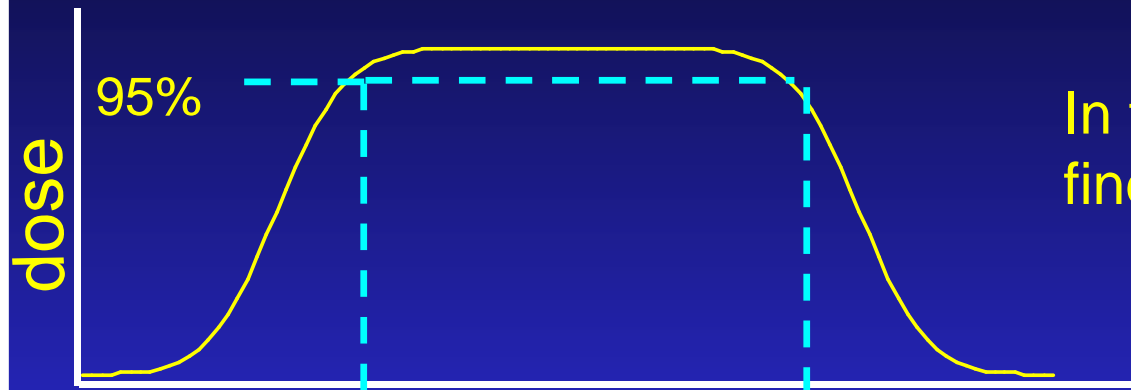
Treatment execution (random) errors blur the dose distribution



Preparation (systematic) errors shift the dose distribution



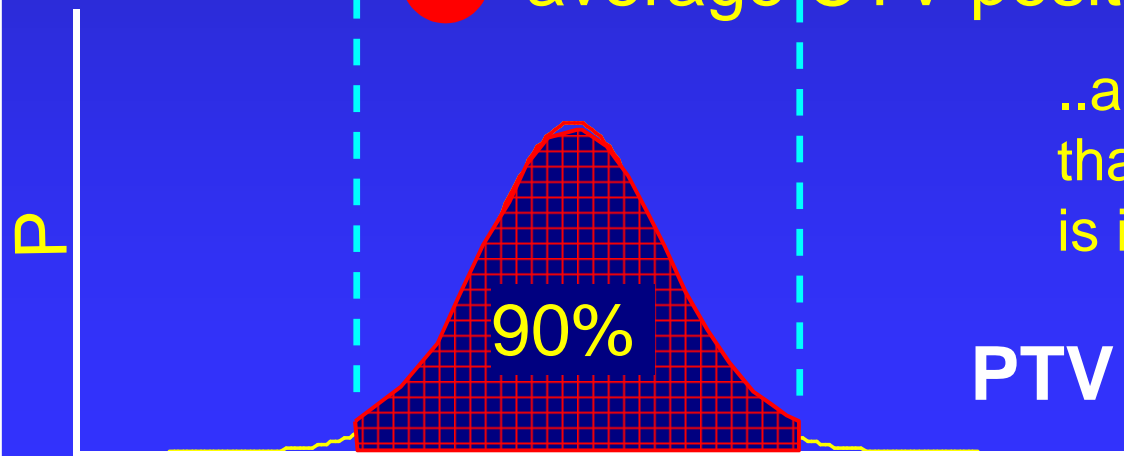
Computation of the dose probability for a small CTV in 1D



In the cumulative (blurred) dose, find where the dose > 95%

x →

● average CTV position

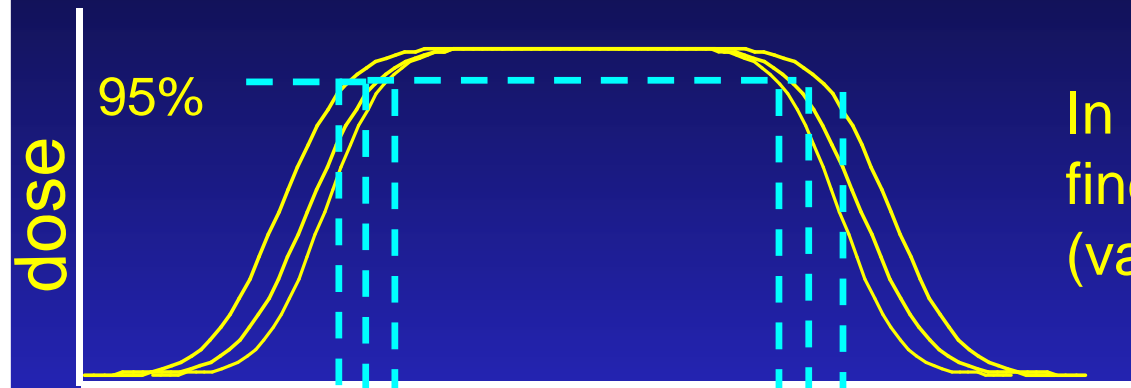


..and compute the probability that the average CTV position is in this area

$$\text{PTV margin} = 2.5 \Sigma + 0.7 \sigma$$

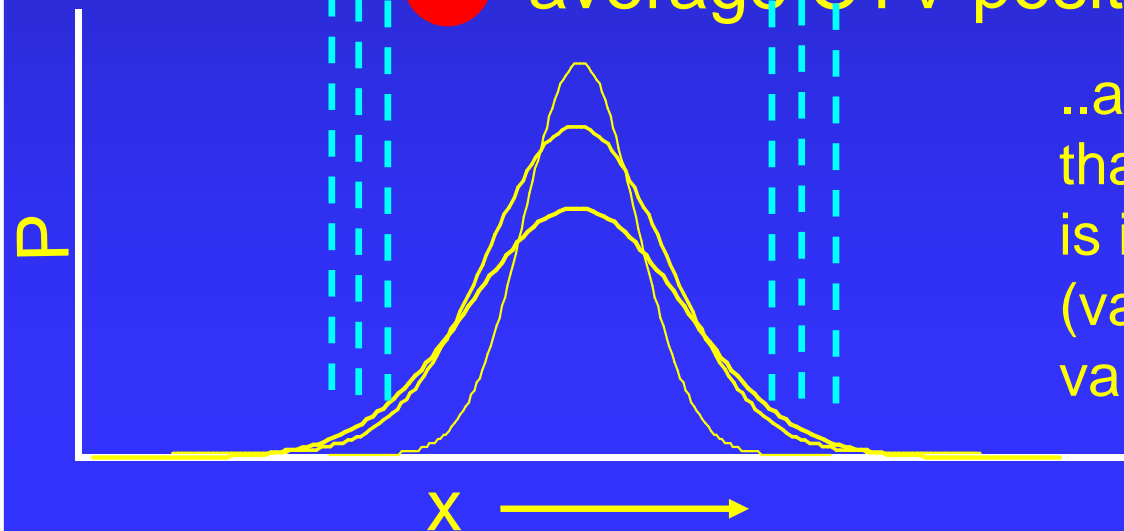
x →

Computation of dose probability with patient specific σ and Σ



In the cumulative (blurred) dose, find where the dose $> 95\%$
(variable, 22% variability in σ)

x \longrightarrow
● average CTV position



..and compute the probability that the average CTV position is in this area
(variable), assuming 22% variability in Σ (same process)

Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95%
isodose :

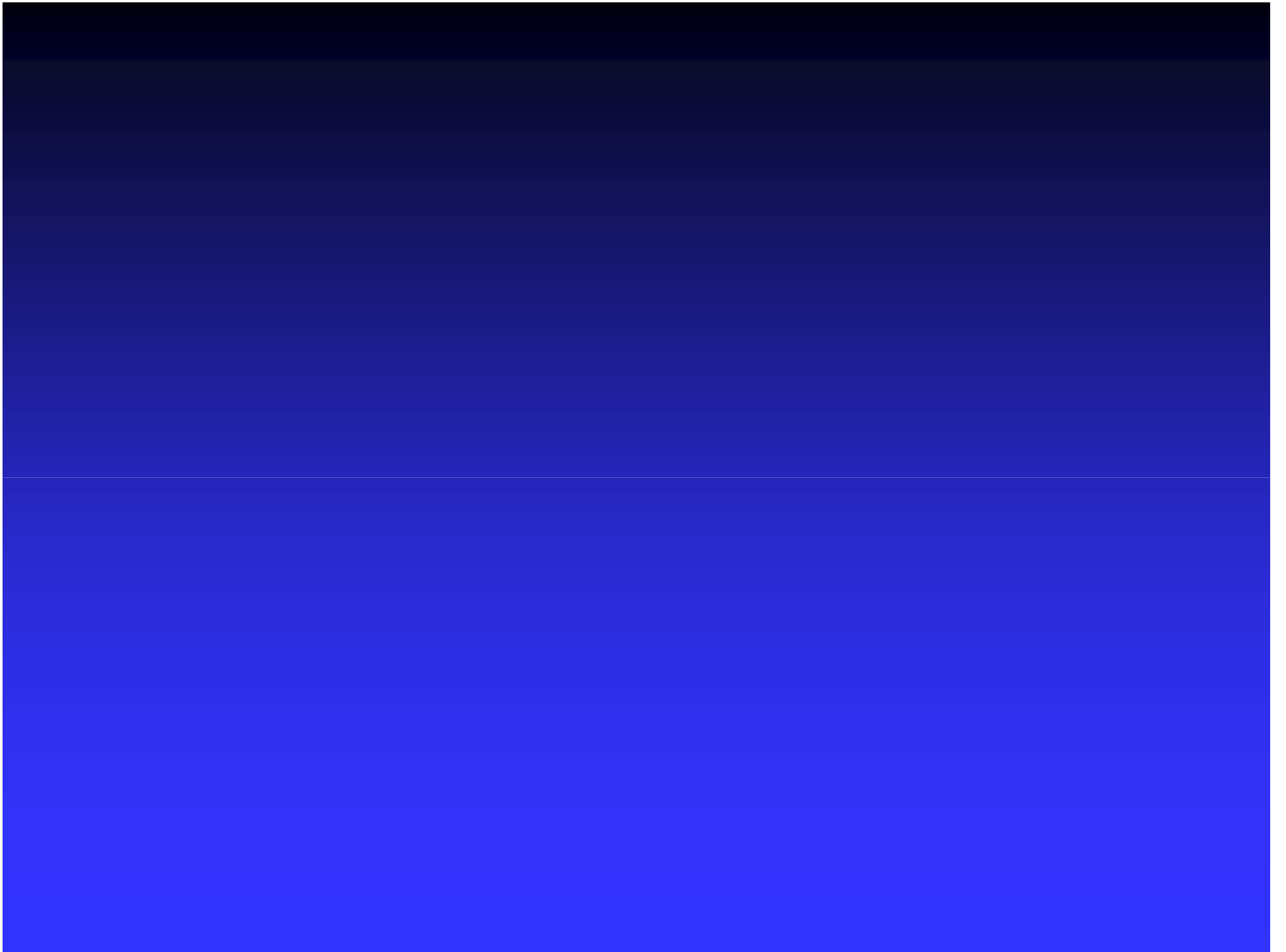
Σ and σ variable: PTV margin = $\alpha \Sigma + 0.7 \sigma$

$\sigma_{\sigma}/\sigma, \sigma_{\Sigma}/\Sigma$	α
0	2.5
0.1	2.55
0.22	2.74
0.3	2.87

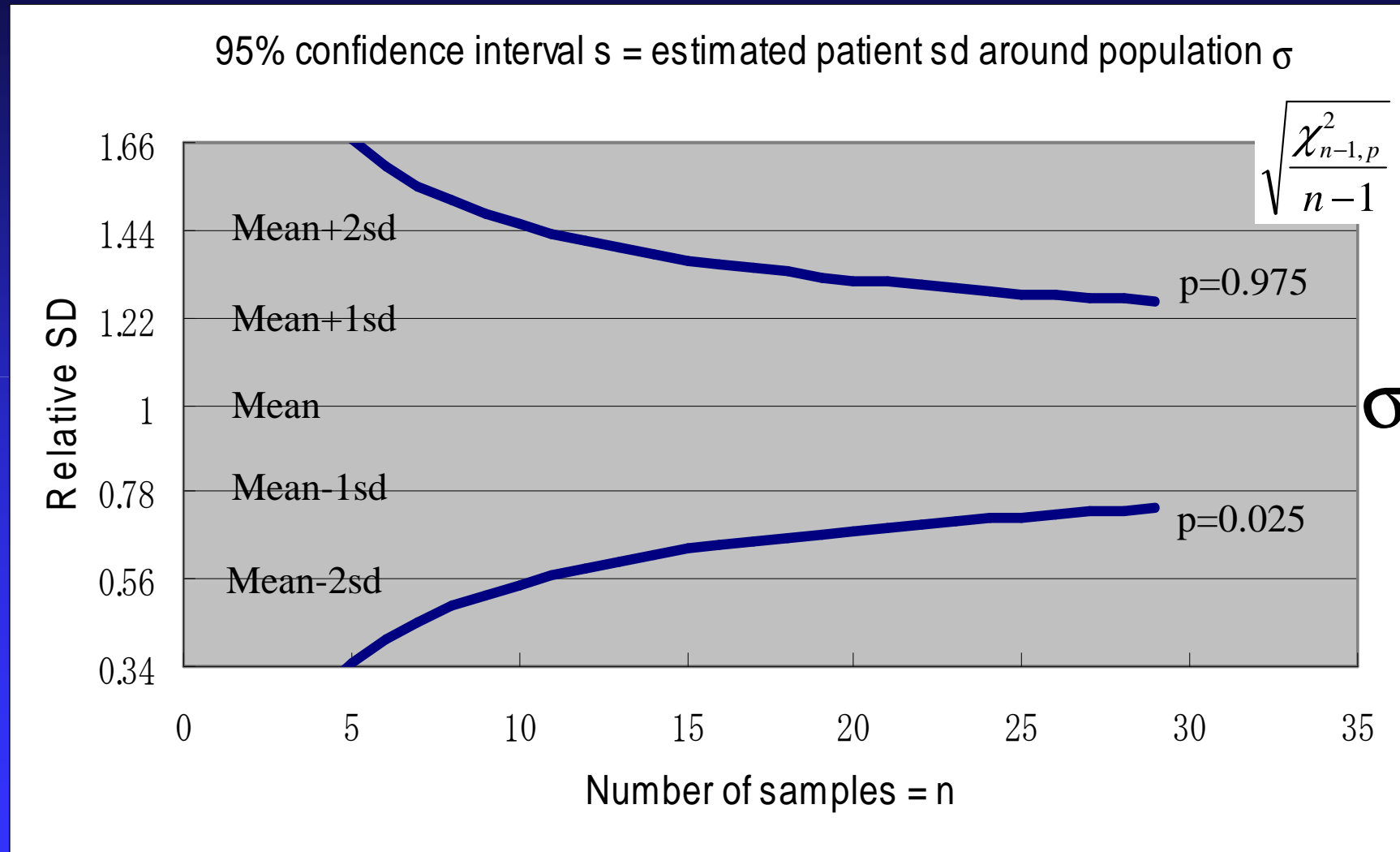


Conclusions

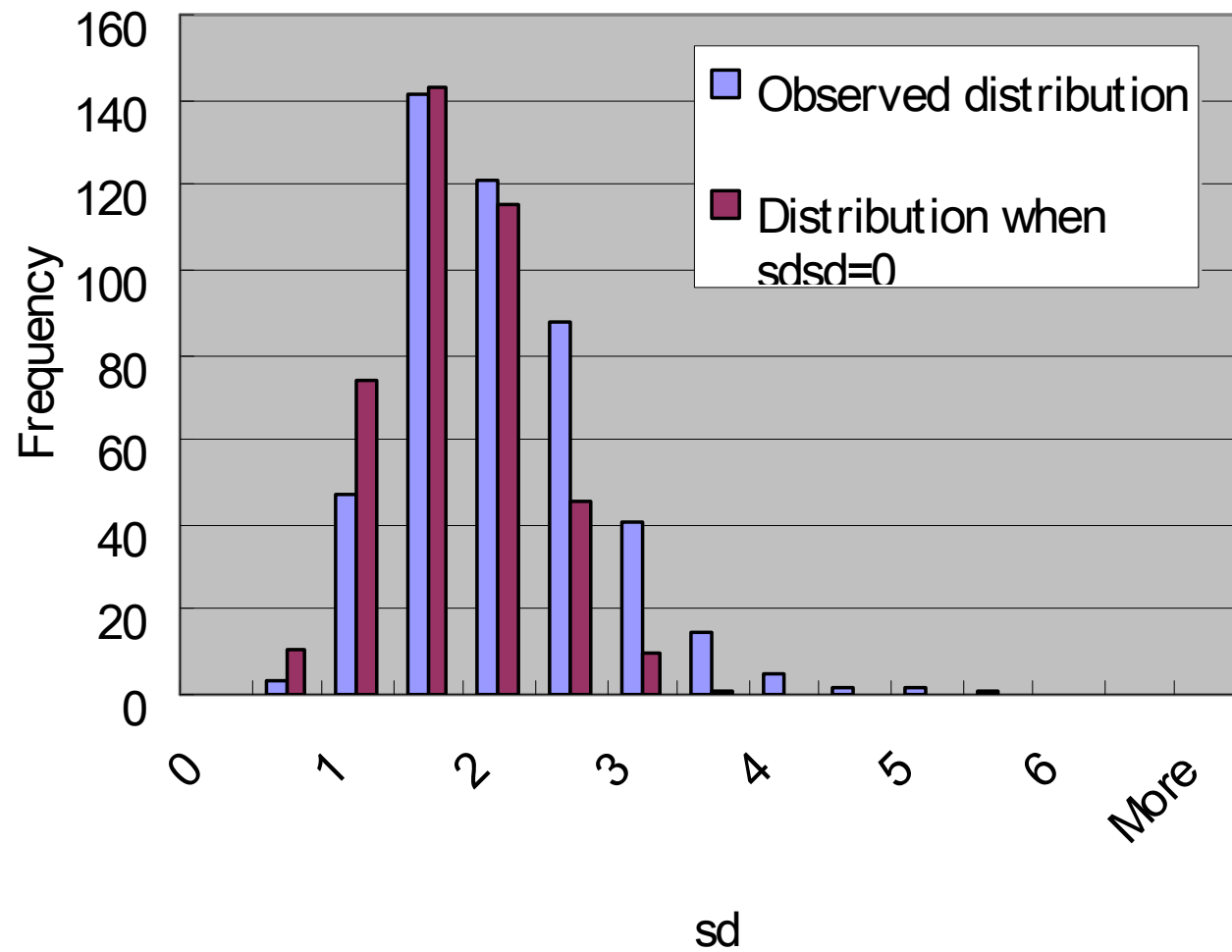
- Inter-patient variability in mobility exists (22% in setup error in our population, +/- 30% for organ motion)
- Inter-patient variability is hard to prove for individual patients: you need at least 10 samples to pick out outliers at $2\sigma_{\sigma}$
- Inter-patient variability very slightly increases margin requirements
- Be very careful when basing margins on SD measurements in individual patients – large probability that you are wrong

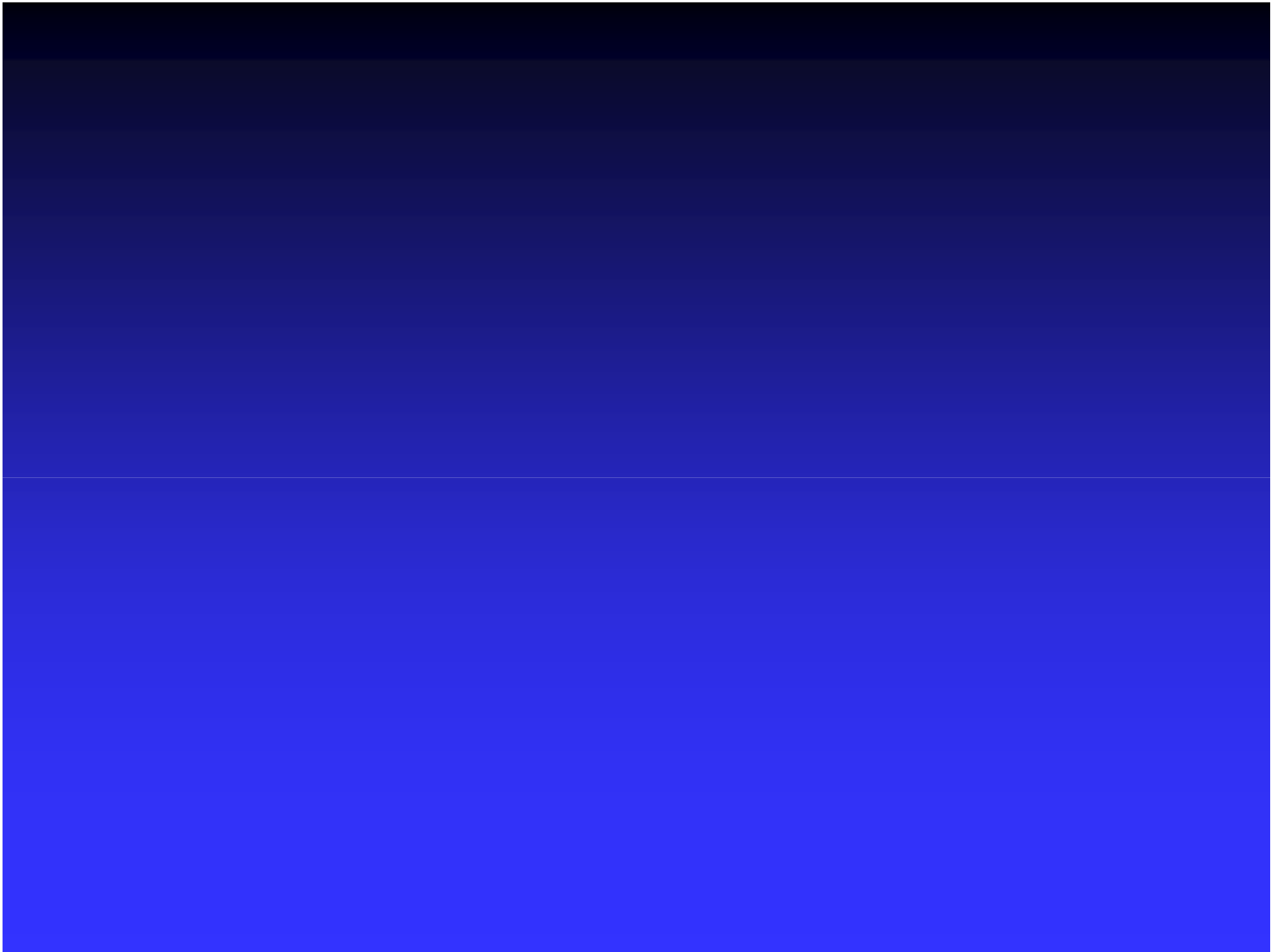


Measurement uncertainty in SD - does a patient deviate from population ?



For N=10, any observed SD between $\sigma - 2\sigma_\sigma$ and $\sigma + 2\sigma_\sigma$ is expected





Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) :

$$\Sigma \text{ and } \sigma \text{ constant: PTV margin} = 2.5 \Sigma + 0.7 \sigma$$

Σ = quadratic sum of SD of all preparation (systematic) errors

σ = quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

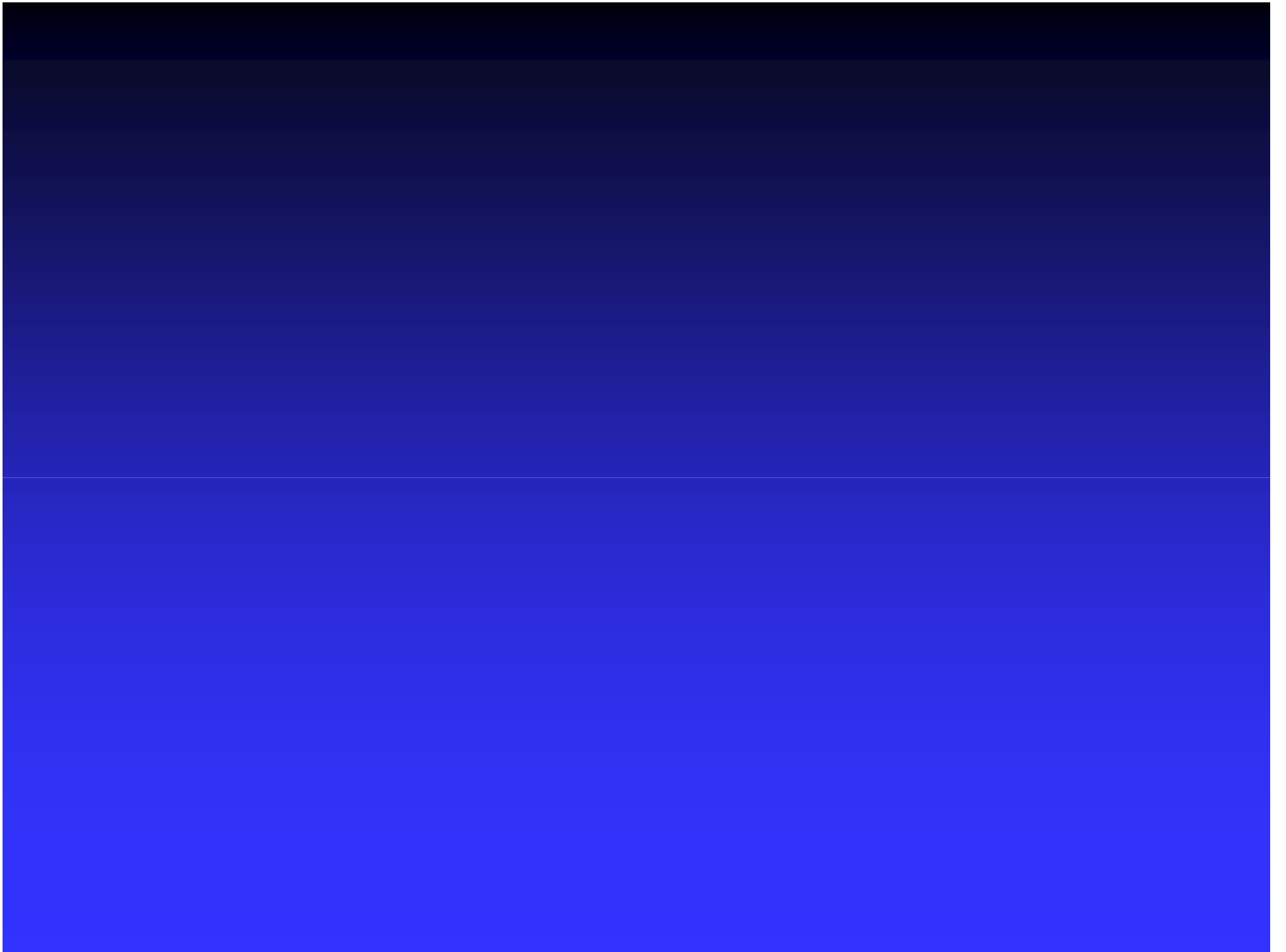
*For a big CTV with smooth shape, penumbra 5 mm

Analysis of CTV dose probability

- Blur planned dose distribution *with all execution (random) errors* to estimate the cumulative dose distribution
- For a given *dose level*:
 - Find region of space where the cumulative dose exceeds the given level
 - Compute *probability* that the CTV is in this region

Analysis of CTV dose probability

- Blur planned dose distribution *with all execution (random) errors* to estimate the cumulative dose distribution – *blurring patient specific*
- For a given *dose level*:
 - Find region of space where the cumulative dose exceeds the given level (*patient specific*)
 - Compute *probability* that the CTV is in this region (*patient specific*)



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Aims:

- 1) quantify the statistics of patient-specific differences in mobility by analysis of data from a large group of patients
- 2) Analyze the effect of any variability on population-based margins

Extended analysis of (setup) error

Look at differences in sd between patients

	patient 1	patient 2	patient 3	patient 4
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RMS of SD = σ_f

$\left\{ \begin{array}{l} \text{mean} = M \\ \text{SD} = \Sigma \\ \text{RMS} = \sigma \\ \text{SD} = \text{sdsd} \end{array} \right.$

NEW!

M = group systematic error

Σ = standard deviation of the systematic (preparation) error

σ = standard deviation of the random (execution) error

σ_f = standard deviation of the intra-fraction motion

sdsd = standard deviation of patient specific mobility – *diluted by large measurement error in sd because of low number of fractions*

Correction of the observed sdsd for measurement error in sd

470 patients	sdsd (mm)	SD estimation error, 8.5 samples (mm)	$\sigma_{\sigma} = \text{True variability (mm)}$
X (LR)	0.8	0.6	0.5
Y (SI)	0.4	0.3	0.2
Z (AP)	0.6	0.5	0.3

} 0.26 σ

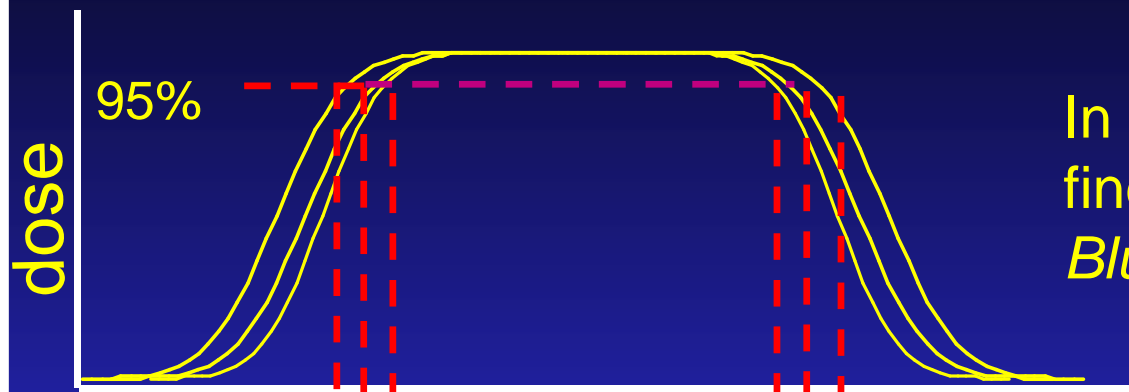
} 0.22 σ

raw: raw data

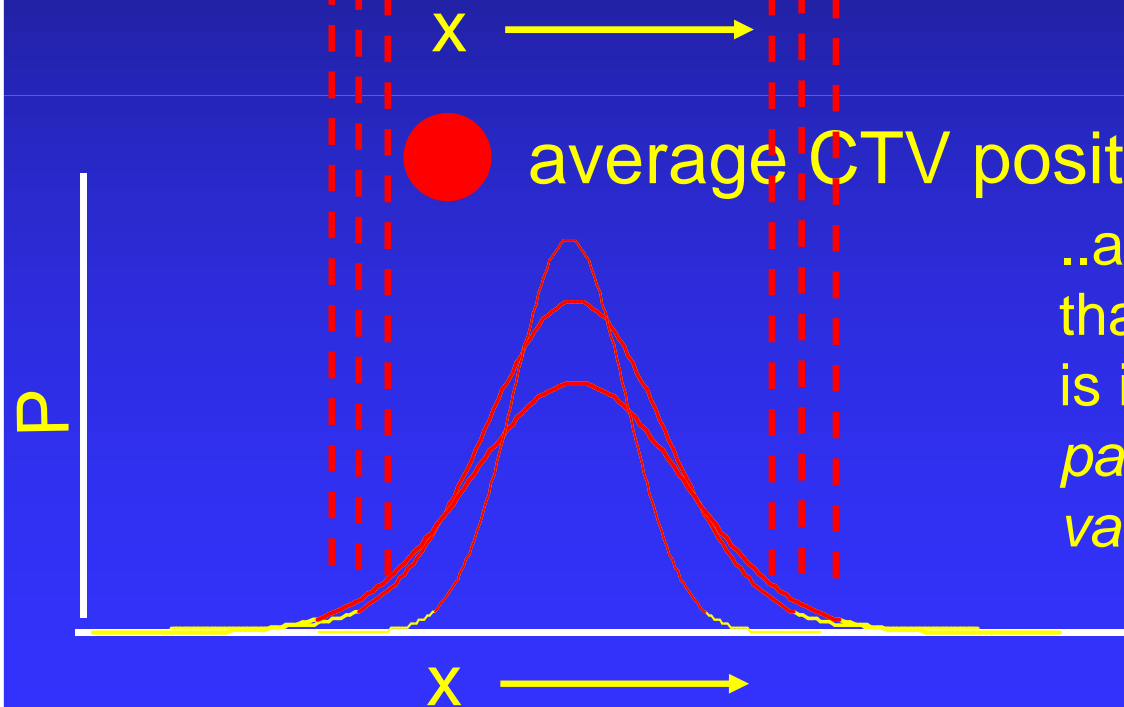
error: measurement error

$\text{Sqrt}(\text{raw}^2 - \text{error}^2)$

Effect of patient specific σ and Σ



In the cumulative (blurred) dose, find where the dose > 95%
Blurring patient specific



..and compute the probability that the average CTV position is in this area *for all sorts of patients* → also assuming 22% variability in Σ (same process)

Required margin increases from $2.5\Sigma + 0.7\sigma$ to $2.7\Sigma + 0.7\sigma$

Conclusions

- Inter-patient variability in mobility exists (22% in setup error in our population)
- Inter-patient variability is hard to prove for individual patients: you need at least 10 samples to pick out outliers at $2\sigma_\sigma$
- Inter-patient variability very slightly increases margin requirements
- Be very careful when basing margins on SD measurements in individual patients – large probability that you are wrong