Modelling of physiological and pathological processes

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Lecture 1

Some books and papers…

•Y.C. Fung: *Biomechanics (Volumes 1, 2 & 3)* Springer

•H. Kleinstreuer: *Biofluids*, CRC Press

•S.A. Berger: *Introduction to Bioengineering*, Oxford University Press

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•A. C. Guyton & J. E. Hall, *Textbook of Medical Physiology*, Elsevier

•G. Batchelor, *An Introduction to Fluid Dynamics,* Cambridge University Press

•Papoulis G, *Probability, Random Variables, and Stochastic Processes*, 3rd ed. McGraw-Hill. 1991. ISBN 0-07-100870-5

…more books and papers…

Numerical Analysis

Elementary numerical analysis
(Atkinson)

•Numerical analysis
(Burden/Faires)

•Fundamentals of computer numerical analysis
(Friedman/Kandel)

•Numerical recipes in (Fortran, F90, C etc.)

•Theoretical numerical analysis:
a functional analysis framework
(Atkinson/Han)

Dynamical Systems

Chance and chaos
(Ruelle)

•Exploring complexity : an introduction
(Nicolis/Prigogine)

•The fractal geometry of nature
(Mandelbrot)

•Universality in chaos
(Cvitanovic)

•Turbulence, strange attractors, and chaos
(Ruelle)

•Nonlinear dynamics and chaos
(Thompson/Stewart)

•From equilibrium to chaos : practical bifurcation and stability analysis
(Seydel)

•Chaotic evolution and strange attractors
(Ruelle)

Numerical Analysis:

Research depended on Theory and Experiment.
Now a third approach is available for looking into the physical world: **Simulation & Modeling**

YV

Simulation means expressing the governing physical laws of a system in equations and solving them on the computer

Modeling means admitting our inability either to cast the physics in equations or to solve the “true” equations. In this case, what we solve of the computer is either a simplification, or something that looks realistic and representative. There is a hidden hypothesis when modeling is performed.

A new trend in Biology research involves **testing** a hypothesis through computational “virtual” experiments

Modeling of Complex Systems in Biology, Medicine and Life Sciences:

- Models that carry all the relevant physics
- Adequate numerical methods
- Validation
- Efficient postprocessing
- Open mind

A sometimes impossible compromise:
Mathematical Elegance vs. Biological Relevance

Why simulation?

When we apply Computational Simulation techniques in vascular pathologies, we encounter four elements that correspond to unique strengths of the *in silico* approach:

+ **Can predict**

+ **Can do multiphysics, if we choose to**

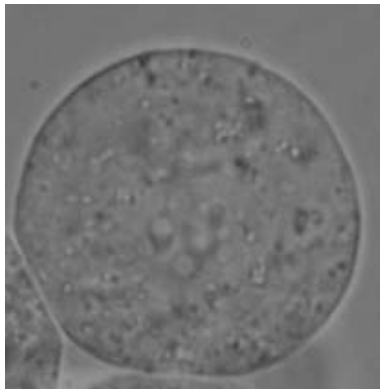
+ **Offers detailed description**

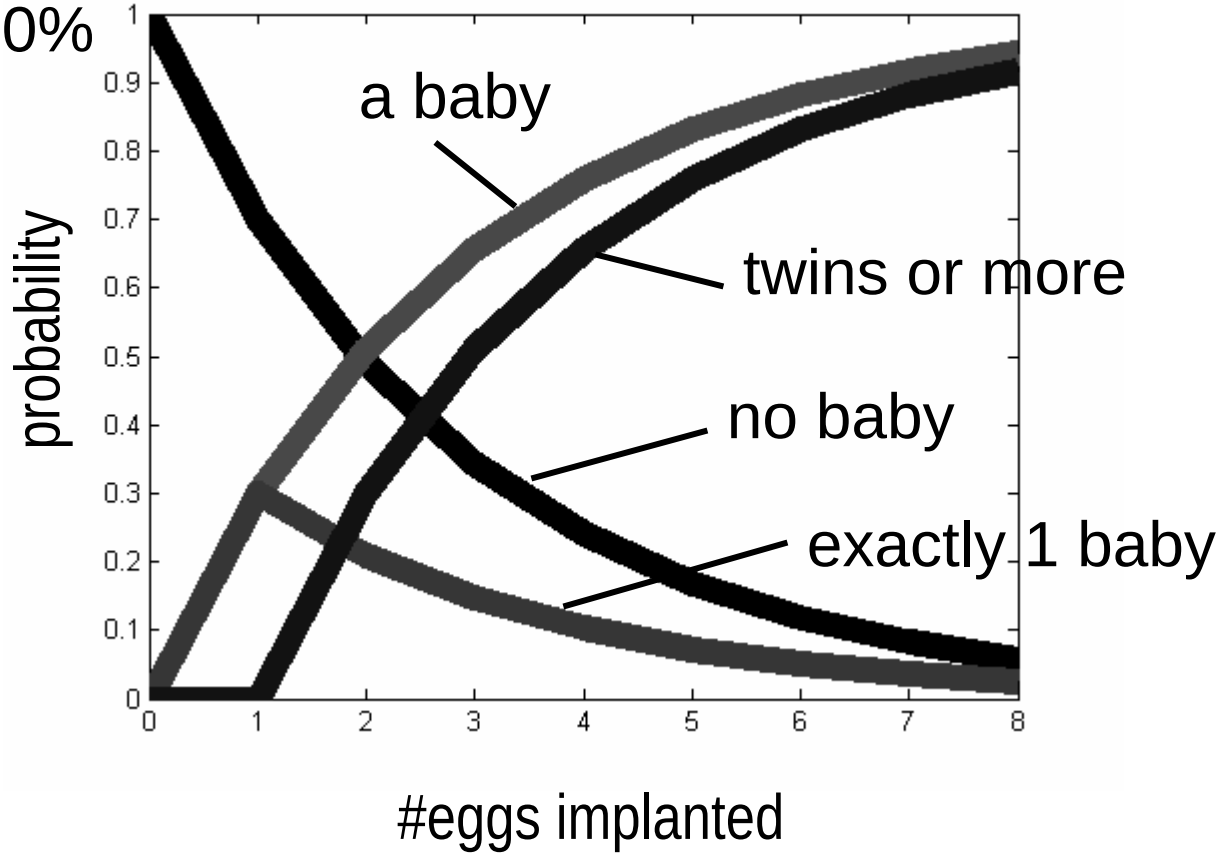
+ **Can speculate and confirm/refute**

- We also encounter the **necessity of validation**, but we know how to do that…

Motivation: *A priori* viability test of oocytes in IVF

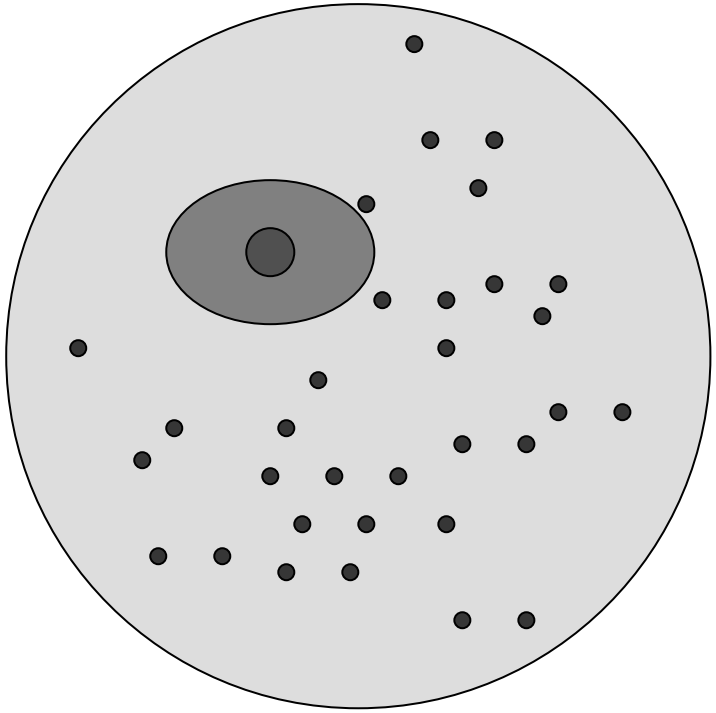
Viability of an egg: 30%

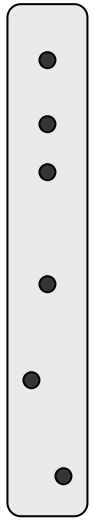


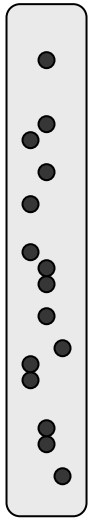


Spent Culture Medium Concentration for Viability

Measure certain parameters after fertilization indicating the viability, e.g. the amount of secreted or consumed components in the culture medium.



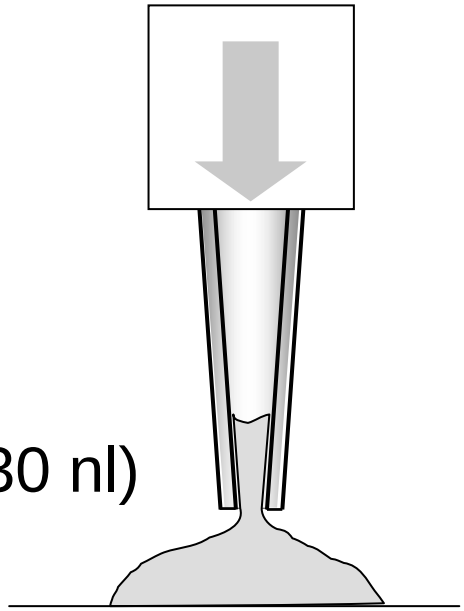




- Metabolite (e.g. lactate)

$C(t_1)$ $C(t_2)$

Protocol Step 1:
Pipette incubation drop



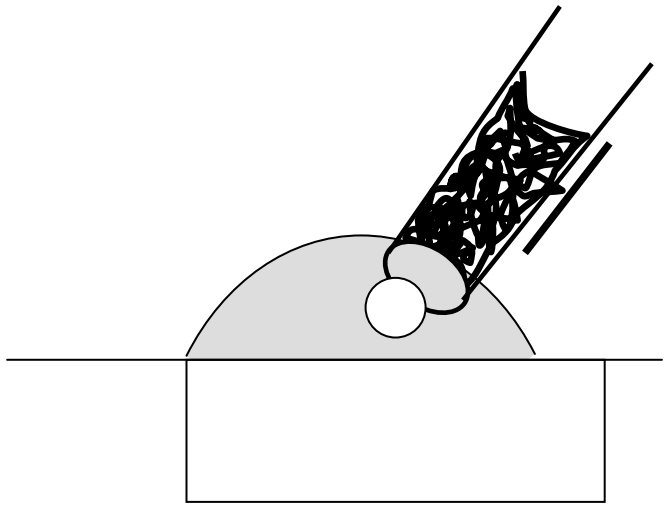
(e.g. 30 nl)

Source of uncertainty

Initial incubation drop pipette imprecision

(see slide on volume-dependent pipetting errors below)

Protocol Step 2:
Add embryo

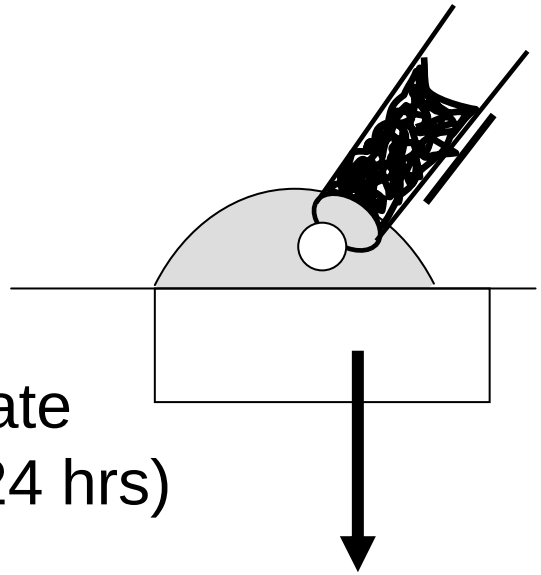


Source of uncertainty

Variation in volume of media accompanying embryo:

30 nl +/- 10 nl

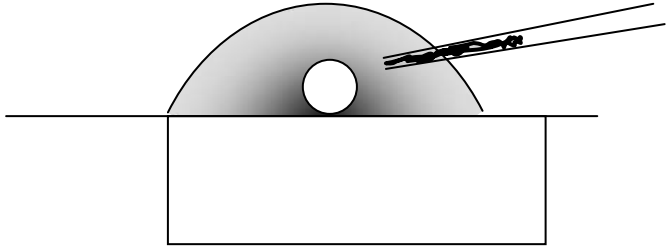
Protocol Step 3:
Incubate



Incubate
(e.g. 24 hrs)

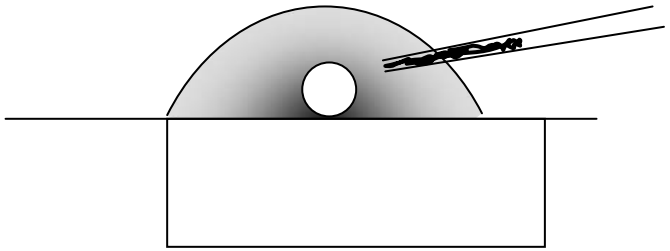
Source of uncertainty

Inconsistencies in incubation duration



e.g. 24 h +/- 1 h

Protocol step 4:
Sampling of medium

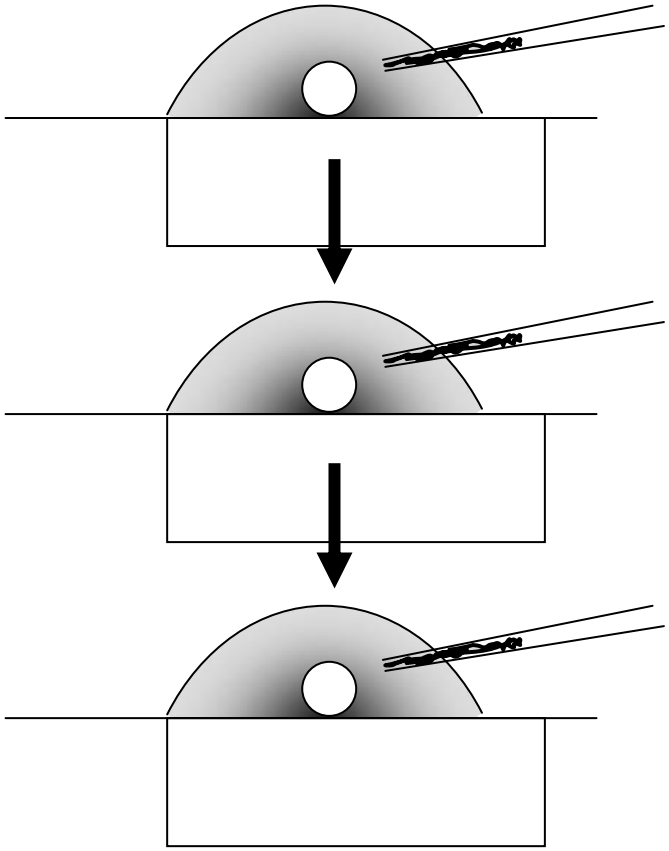


Source of uncertainty

Imprecision in obtaining small analysis samples

(see slide on volume-dependent pipetting errors below)

Other uncertainties associated with serial sampling



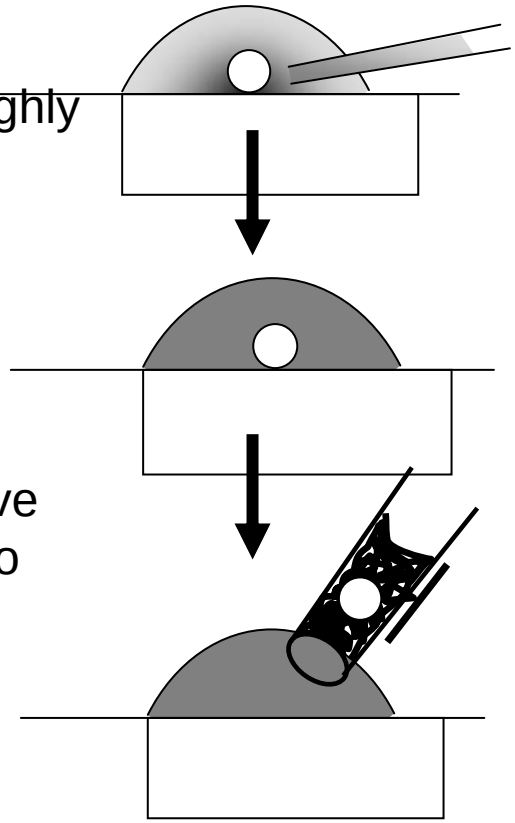
Sampling from a gradient around embryo

Dilution of sample during analysis

Variance introduced by serial sampling (volume changes and incubation duration imprecision)

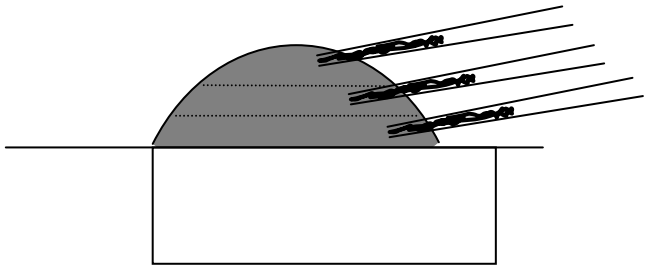
We can neglect them in the following protocol

Mix thoroughly



Remove embryo

Parallel sampling



A simple model for the concentration measurement

Variation in n (rate in metabolite consumption or secretion) is a measure for embryo viability

$$C = \frac{nT}{I + E}$$

Medium concentration before sampling.

I : incubation volume
E : medium volume accompanying embryo
T : incubation time

$$\hat{N} = C \cdot S$$

Number of sampled metabolites

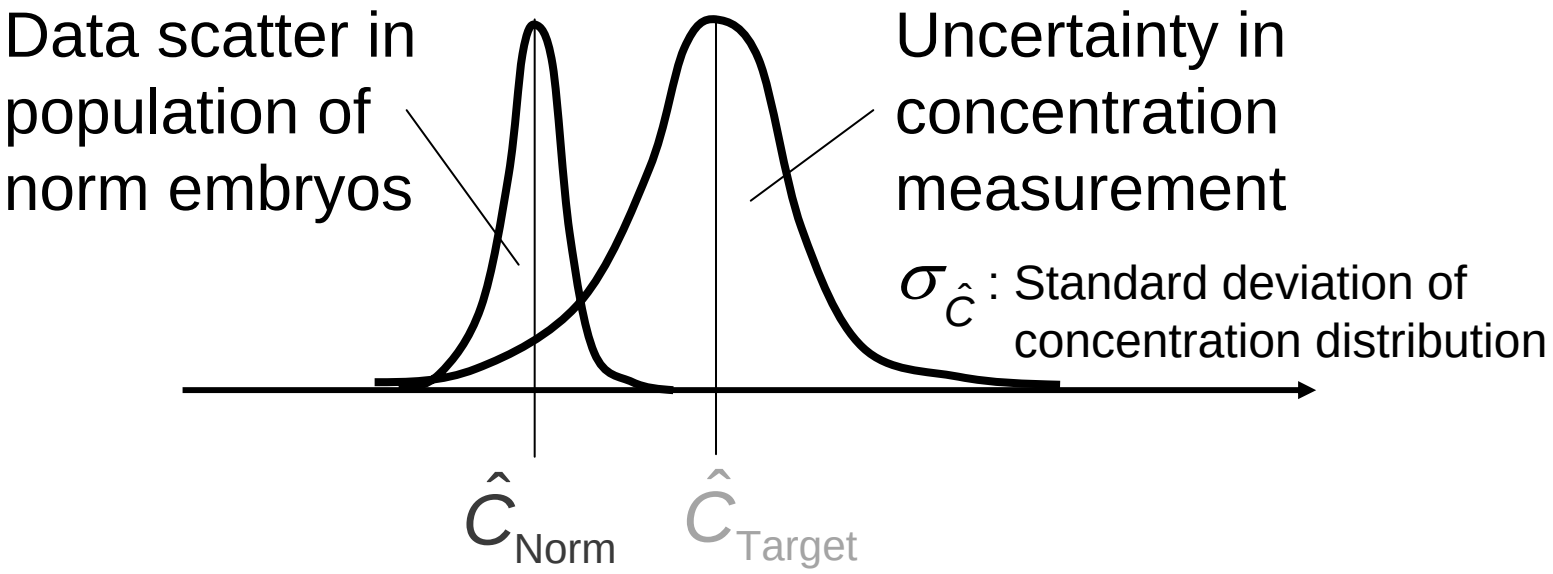
S : actual sampling volume

$$\hat{C} = \hat{N} / S_0 = \frac{nT}{I + E} \cdot \frac{S}{S_0}$$

Measured concentration

S_0 : nominal sampling volume

Viability test based on comparison between target and norm embryo



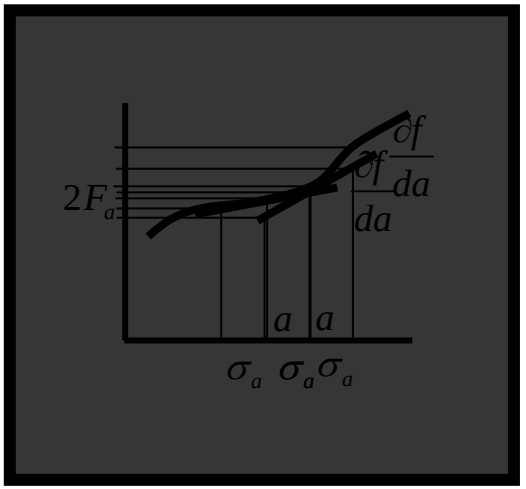
Is $\left\| \hat{C}_{Target} - \hat{C}_{Norm} \right\|$ significant? Minimize $\sigma_{\hat{C}}$

What is the uncertainty of the concentration measurement?

Recall Gauss' law of error propagation:

$$y = f(x)$$

$$\sigma_y^2 = \left(\frac{\partial f}{\partial x_1}\right)^2 \sigma_{x_1}^2 + \cdots + \left(\frac{\partial f}{\partial x_u}\right)^2 \sigma_{x_u}^2$$



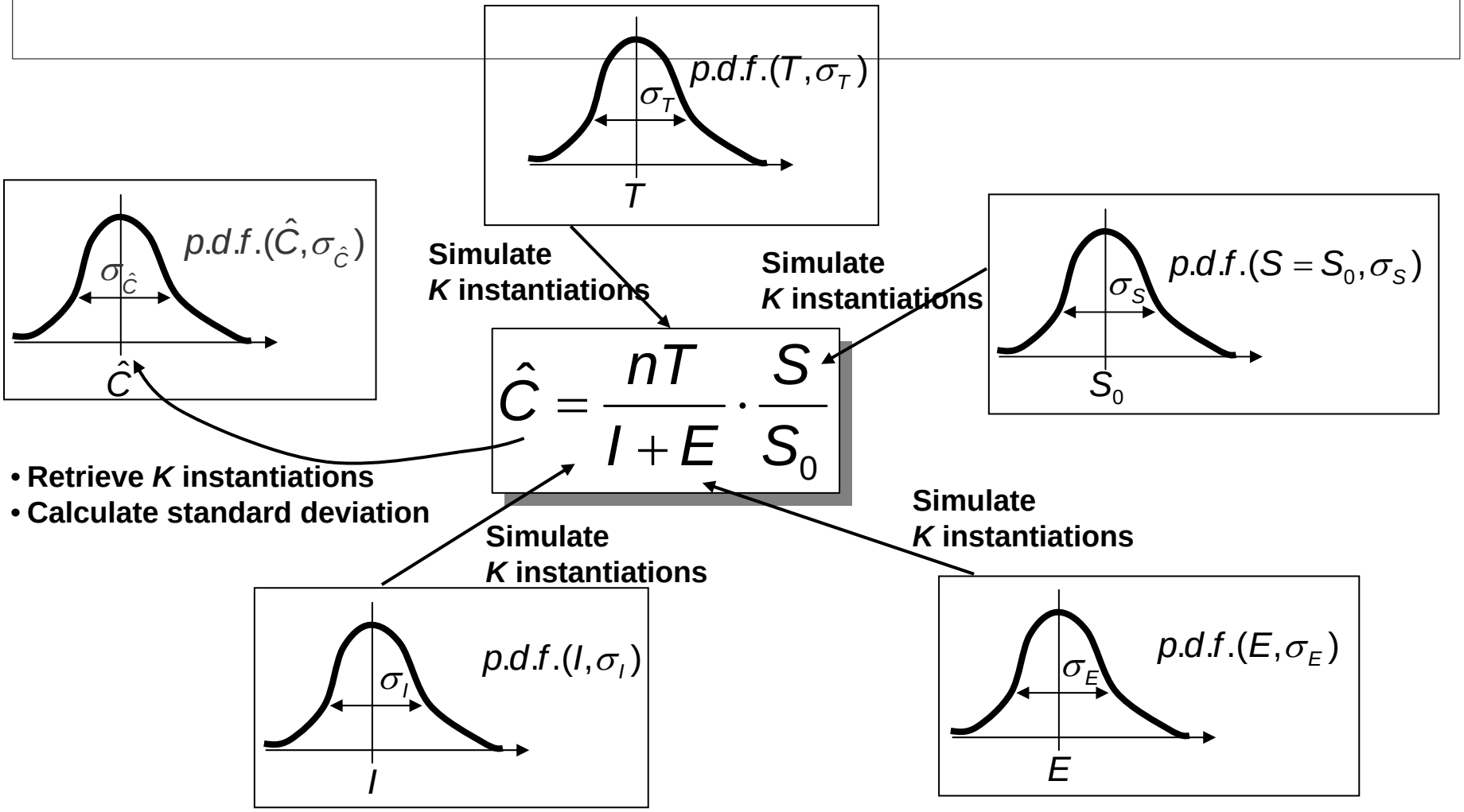
Analytical solution:

$$\sigma_{\hat{C}}^2 = \underbrace{\left(\frac{C}{T}\right)^2 \sigma_T^2}_{F_T^2} + \underbrace{\left(\frac{C}{I+E}\right)^2 \left(\sigma_I^2 + \sigma_E^2\right)}_{F_I^2 + F_E^2} + \underbrace{\left(\frac{C}{S}\right)^2 \sigma_S^2}_{F_S^2}$$

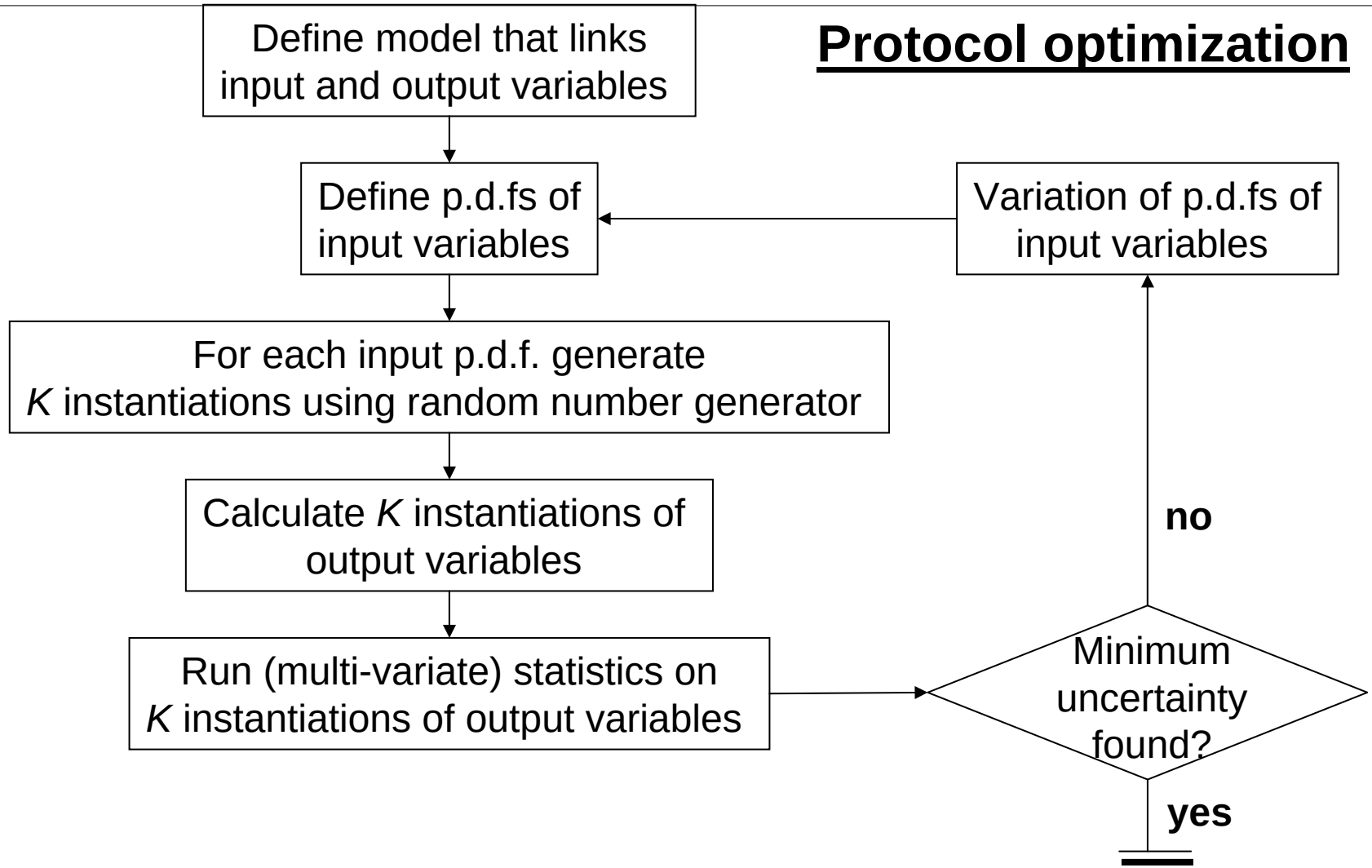
Influence factor of time uncertainty

Influence factor of volume uncertainties

An alternative method to calculate the uncertainty



An algorithm for Monte Carlo experiments

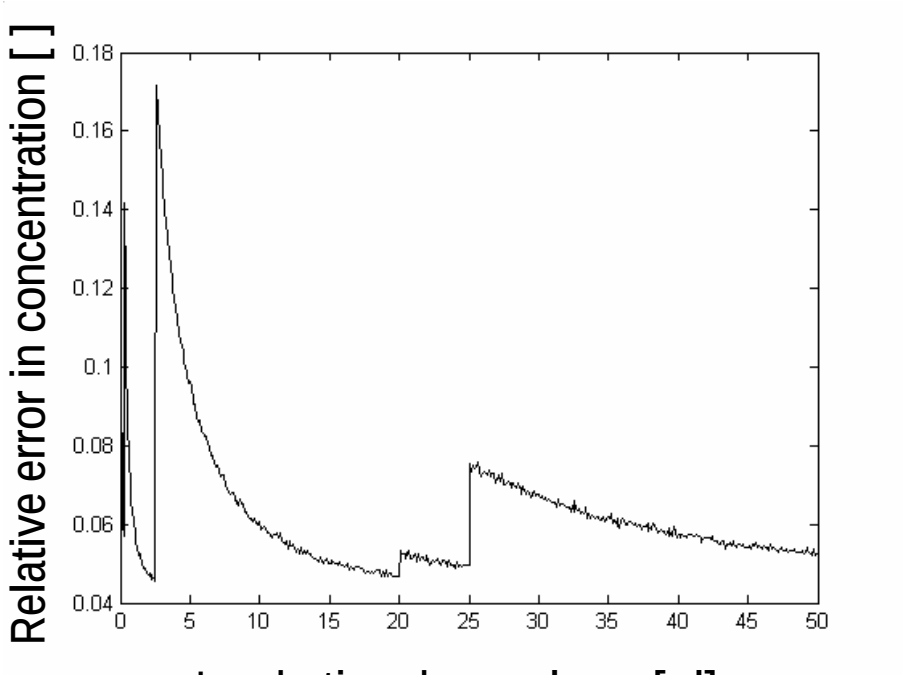


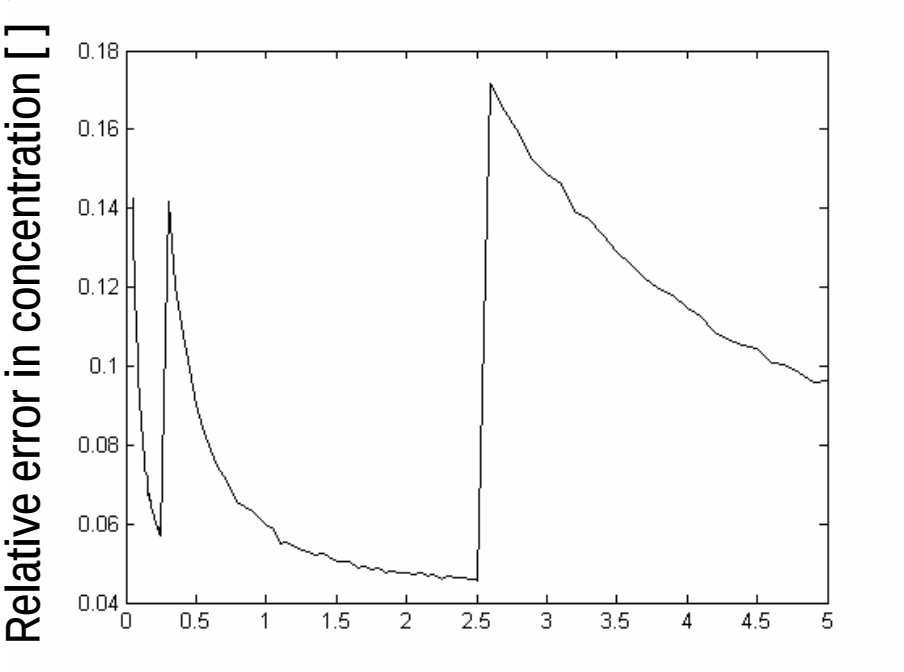
Uncertainty of pipette volumes

Get values from the manufacturer (or measure it yourself), e.g. www.eppendorf.com

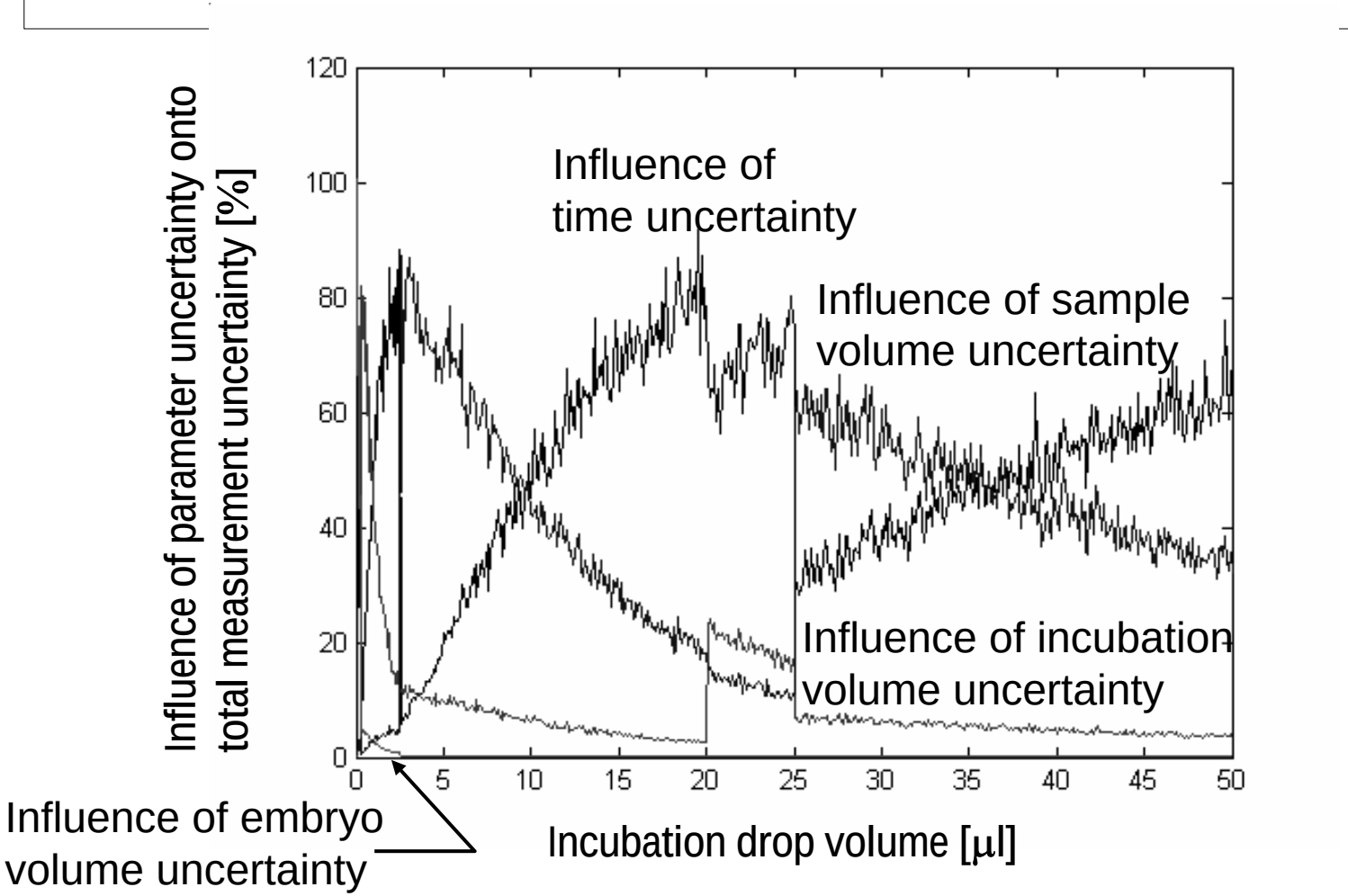
Pipette volume	Imprecision No handling errors!
5 – 250 nl	+/- 1%
0.25 – 2.5 µl	+/- 0.04 µl
2.5 – 20 µl	+/- 0.15 µl
20 – 50 µl	+/- 0.5 µl

It does matter which pipette you use!

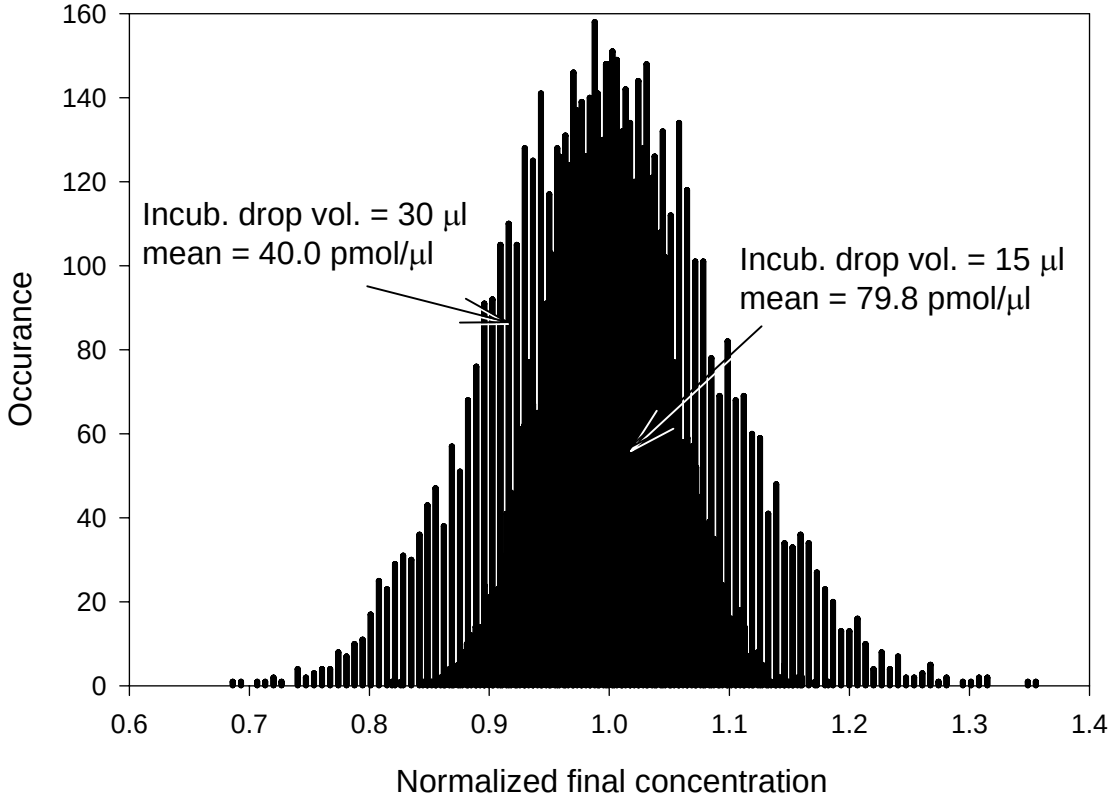




The influence of the parameters vary



Monte Carlo simulated distribution of lactate concentration after 24h incubation



Propagation of p.d.fs of input variables into p.d.f. of output variables

Even for functions $\Re^1 \rightarrow \Re^1$ there is often no closed form solution. For $\Re^n \rightarrow \Re^m$ it is impossible to propagate the distribution analytically.

The Kolmogorov-Smirnov non-parametric test allows you to compare an empirical c.d.f with a theoretical c.d.f

Obtain an empirical data set by running *K* MC experiments

↓

Calculate empirical cumulative distribution function

$$W_K(y_i) = P(y \le y_i) = \frac{\text{rank}(y_i \in \text{sort}(y))}{K}$$

↓

Hypothesis for a distribution F_0

↓

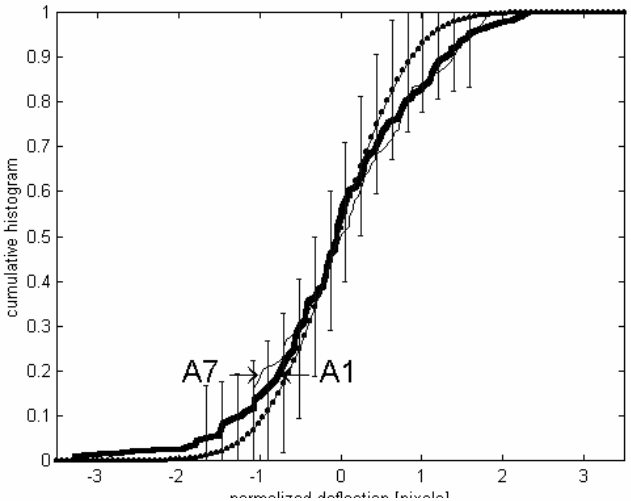
$$d = \sup_{y_1 < y \le y_K} \left\| W_K(y) - F_0(y) \right\|$$

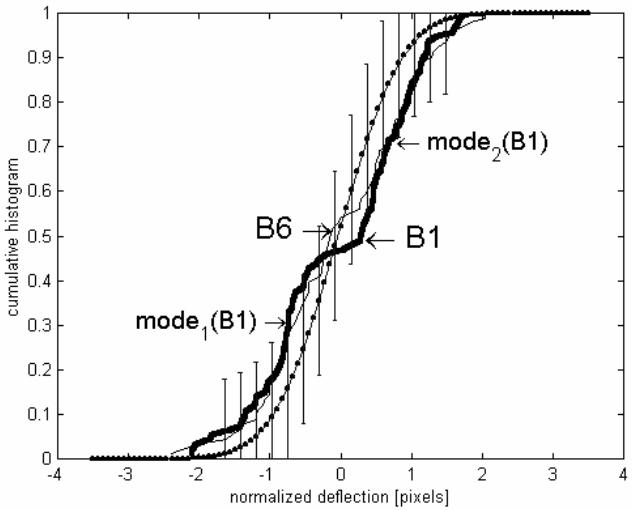
$$\lim_{K \to \infty} P(d \cdot \sqrt{K} < \lambda) = \sum_{i=-\infty}^{\infty} (-1)^i e^{-2i^2\lambda^2} = 1 - \alpha$$

Given α determine λ_0

$H_0 : W_K \equiv F_0$ if $d \le \lambda_0$

$H_A : W_K \ne F_0$ otherwise





Danuser *et al. J. Microscopy* 198(1):34-53. 2000