McMaster University | Integrated Biomedical Engineering & Health Sciences Program

IBEHS - 4QZ3
Modelling of Biological Systems

Lecture 1

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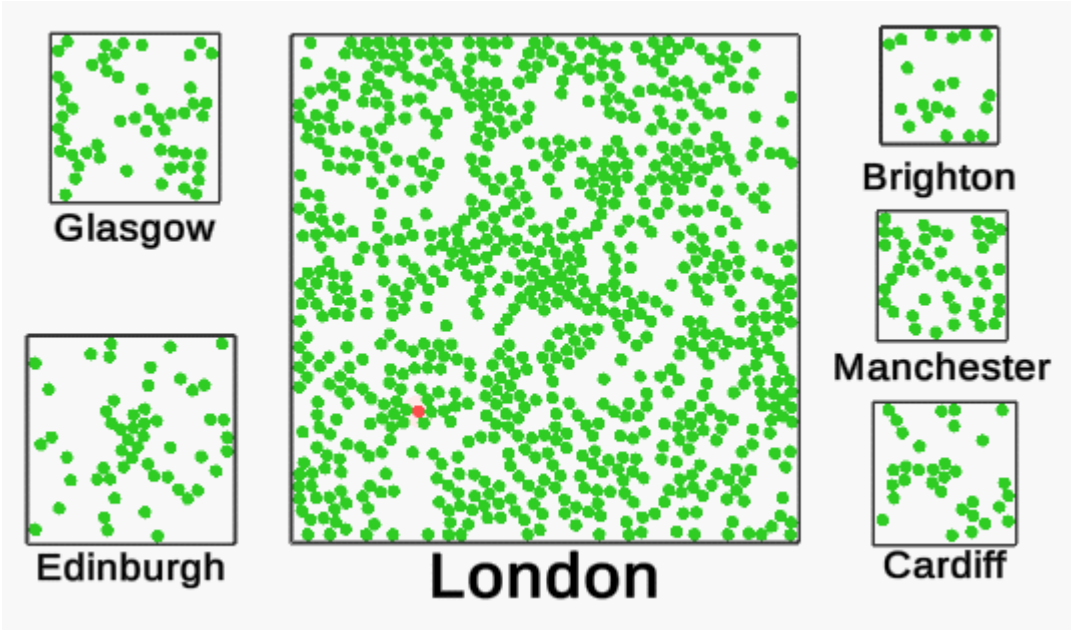
Todays Aims…

What is Biological Modelling?

Why do we do it?

How do models compare to the real data?

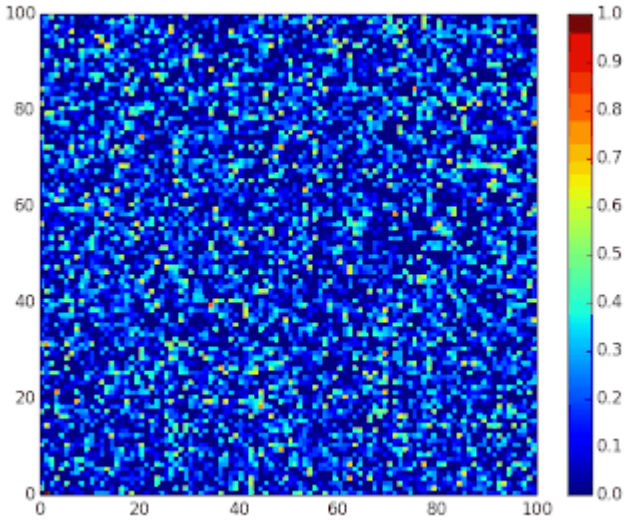


https://www.alanzucconi.com/2020/03/30/mathematics-epidemics/

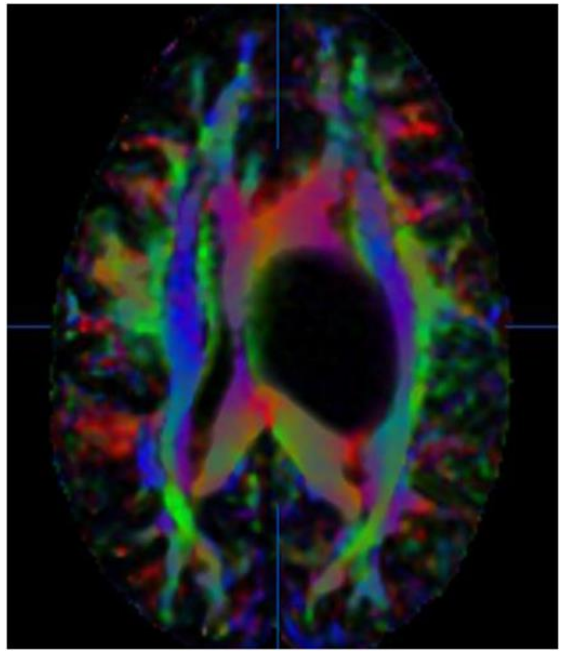
Special Issue
CHEMOMETRICS
Received: 12 September 2007, Revised: 11 December 2007, Accepted: 1 February 2008, Published online in Wiley Interscience: 14 May 2008
(www.interscience.wiley.com) DOI: 10.1002/cem.1143

Dynamic contrast-enhanced MRI diagnostics in oncology via principal component analysis

Mark-John Bruwer[a], John F. MacGregor[a]* and Michael D. Noseworthy[b,c,d]



https://en.wikipedia.org/wiki/Epidemic_models_on_lattices



https://www.frontiersin.org/articles/10.3389/fneur.2017.00660/full

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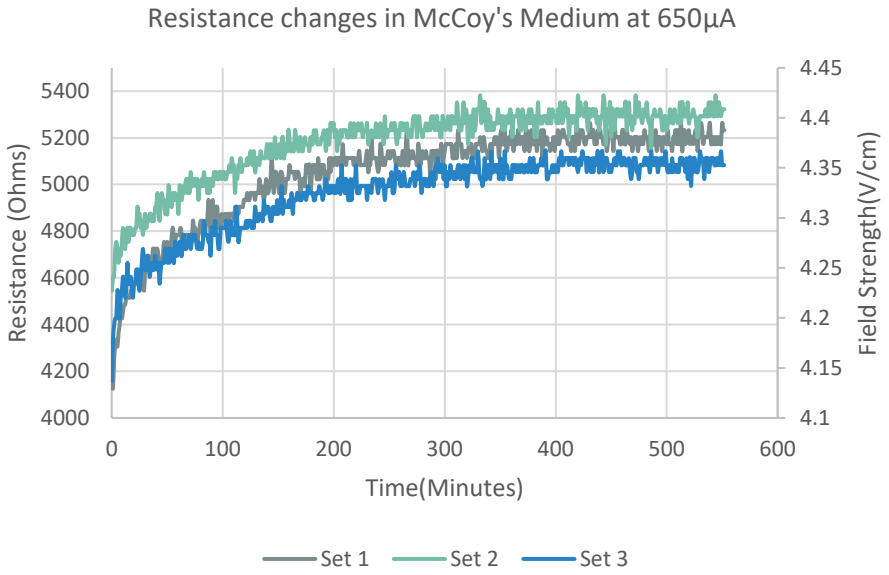
RESEARCH ARTICLE

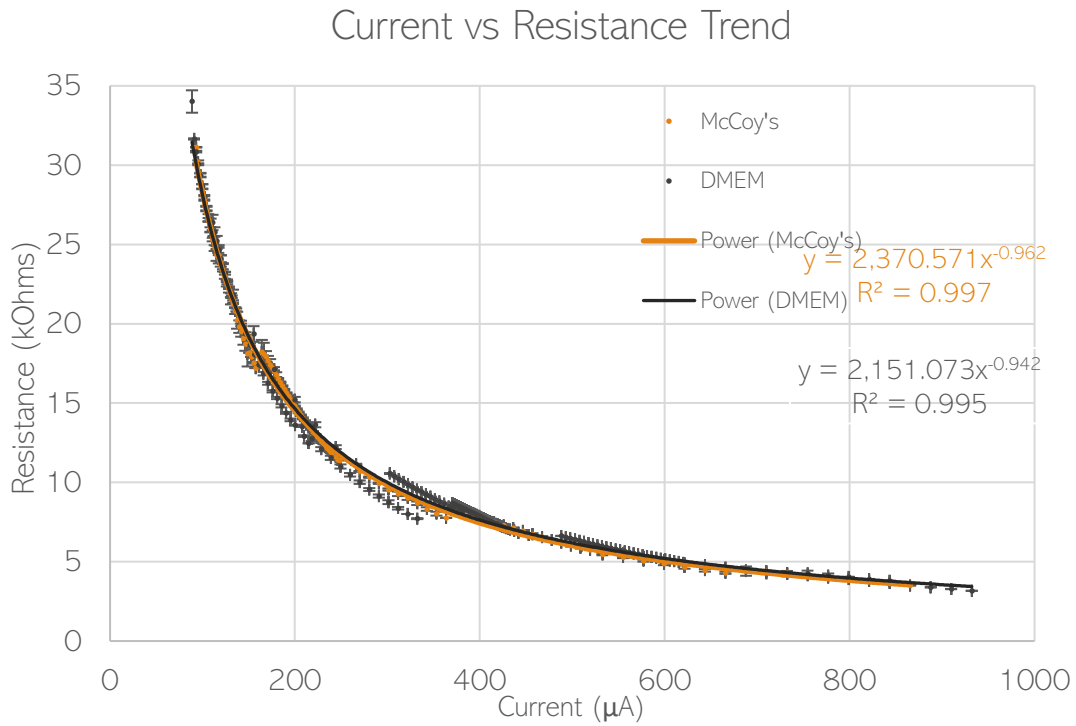
Fractal Analysis of Brain Blood Oxygenation Level Dependent (BOLD) Signals from Children with Mild Traumatic Brain Injury (mTBI)

Olga Dona, Michael D. Noseworthy, Carol DeMatteo, John F. Connolly

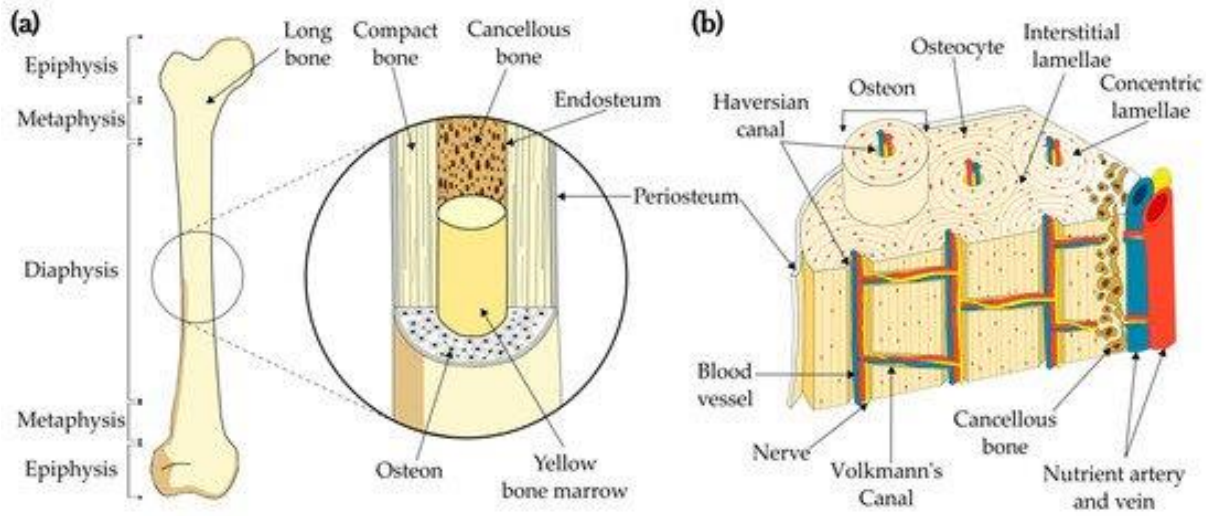
Published: January 10, 2017 • https://doi.org/10.1371/journal.pone.0169647

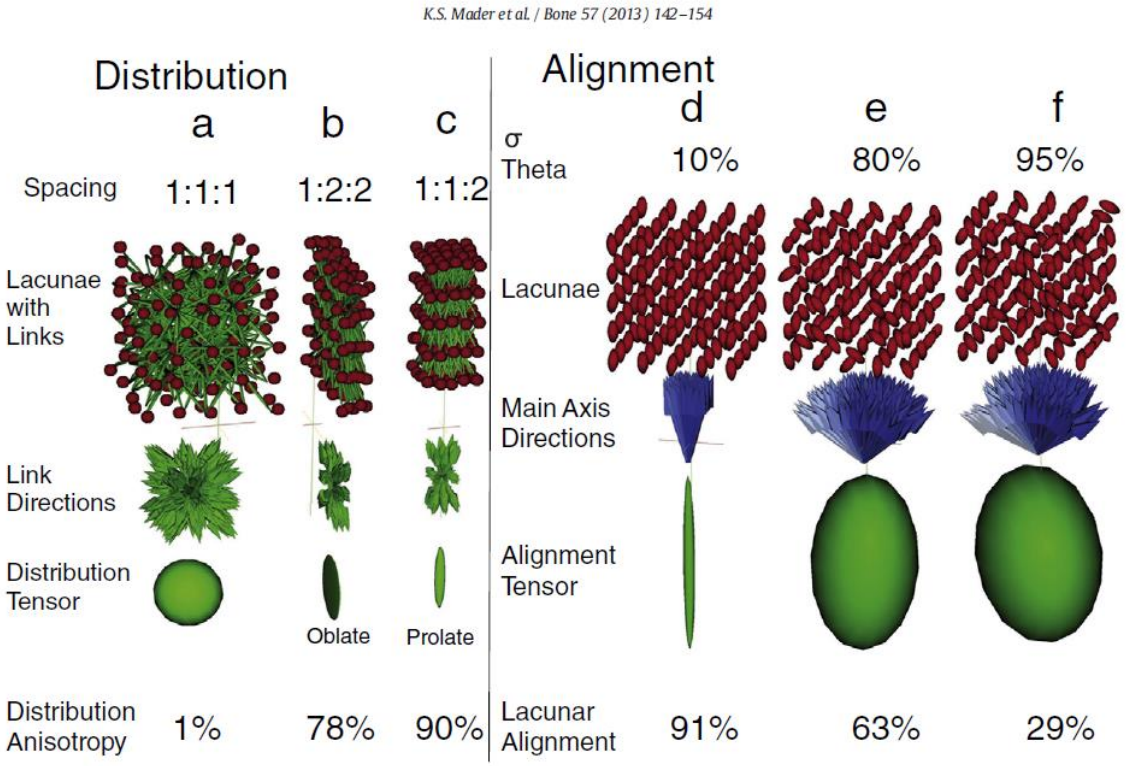
Electrical Properties of Cell Culture Media





Modelling of Osteocyte-Lacunocanalicular network





Model Types

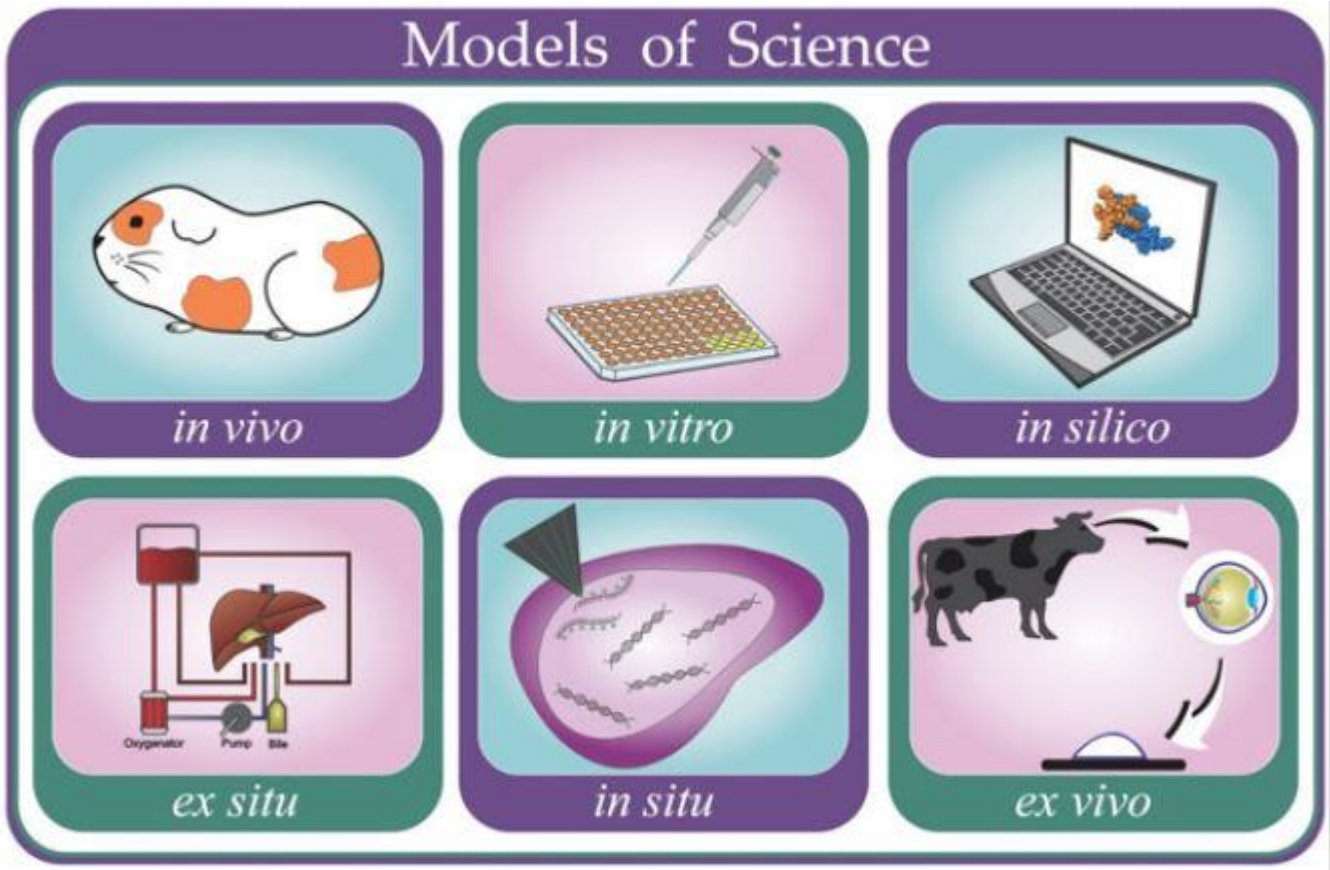
In Silico – "in silicon" - computer model

In Vitro – "in the glass" – cell model

In Vivo – "in the living" – whole organisms - plants animals

In Situ – "on site"

Computer model --> Cell model --> Small Animal Model--> Large Animal Model--> Human Trials



https://biomedscis.com/fulltext/research-models-in-biomedical-sciences-advantages-and-limitations.ID.000197.php

1) What do you want to study?? <u>Create a model</u>
   - based on some *a priori* understanding of the system to test
   - build a model based on physical/physiological/chemical characteristics
   - consider inclusion of assumptions and constraints to help simplify things

2) Test the model (part 1)
   - computer simulation
   - programming
3) Test the model (part 2)
   - build the system to test
   - mock system
   - can control many variables
   - hardest to get data from, but easiest to interpret!

4) Test the model (part 3)
   - the REAL thing → your biological system!!
   - the easiest to get data from, but hardest to interpret!

ELEMENTS

WHAT ARE THE ODDS WE ARE LIVING IN A

Elon Musk says we may live in a simulation. Here's how we might tell if he's right

Scientists are looking for ways to put this mind-bending idea to the test.

The posthuman future has never been easier to imagine—especially for those who work at the forefront of technology.

PHOTOGRAPH BY JANUS FILMS/EVERETT

Simulation

- a comprehensive method for studying systems
- refers to an entire process which includes:
  - choosing a model
  - finding a way to efficiently implement the model on a computer
  - calculating output of the algorithm
  - and visualizing and studying the resultant data

Simulation Types

Equation Based Simulation

A set of equations that describe the system

Executing the model is solving the series of equations

Commonly ordinary differential equations (ODE) or over time and space partial differential equations (PDE)

i.e. simulation of fluid flow

Agent Based Simulation

Simulates the interactions of autonomous agents

Used in behavioural and social sciences where studying network interactions of individuals

i.e. n-many discrete particles

Simulation Types

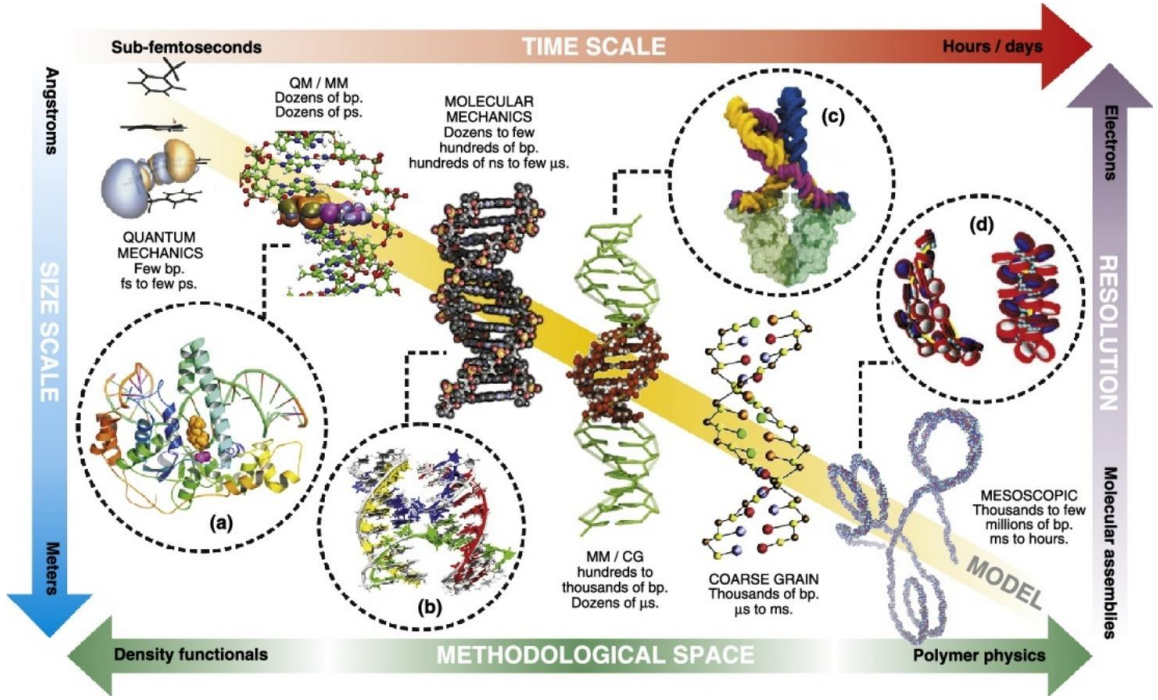
Multi-scale simulations

Multiple models at various scales are used together to describe the system

Monte Carlo Simulations

System that uses randomness to generate a model/outcome

Used to look at predictability of models



https://www.sciencedirect.com/science/article/abs/pii/S0959440X15001761

http://plato.stanford.edu/entries/simulations-science/

Computer Simulations

- assist in the design, creation, and evaluation of complex systems to understand and evaluate 'what if' case scenarios.

Benefits:

- Gain better understanding of a process or group of interconnected processes. Also used to identify problem areas
- Evaluate effect of systems or process changes such as demand, resources, supply, and constraints. This could help in cost assessment, disease prediction, etc.
- Identify actions needed upstream or downstream relative to a given operation, organization, or activity to either improve or mitigate processes or events
- Evaluate impact if a change in the system occurs

Computer Simulations

Cons:

Have to have a very thorough understanding of our system before starting

- Initial conditions
- Parameters
- Variability?

Can make mistakes while creating the model

Have to find a way to interpret the results

Research Ethics

Essentiality
- Scrutinized by external body (Animal committee, ethics board etc.)

voluntariness, informed consent, and community agreement
- Participants should be made aware of risks and benefits

non-exploitation
- Participants should be made aware of all danger

privacy and confidentiality
- Records are kept confidential

precaution and risk minimization
- Minimal risk to participants at all phases of the study

Research Ethics cont.

professional competence
- Conducted by qualified people

accountability and transparency
- Research done in a fair, honest, impartial, and transparent manner

maximization of the public interest and of distributive justice
- Research should benefit all, not just socially better off

public domain
- Findings should be public domain

Should all be considered when doing any biological study

Research Ethics - HeLa

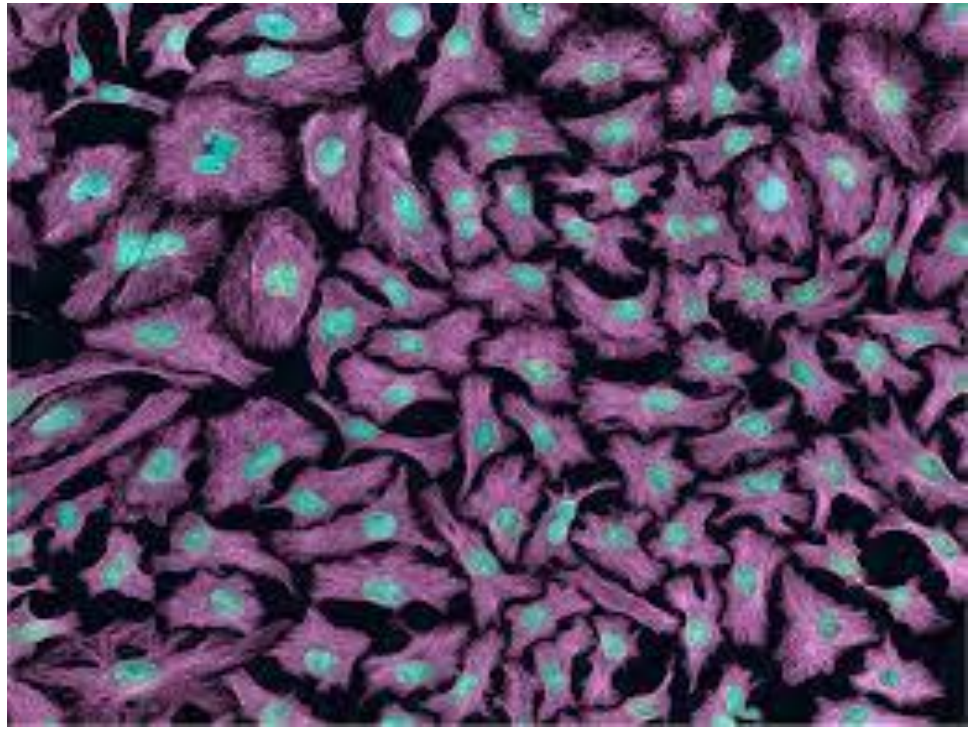
Most used immortal cell line

1st successful human in vitro line

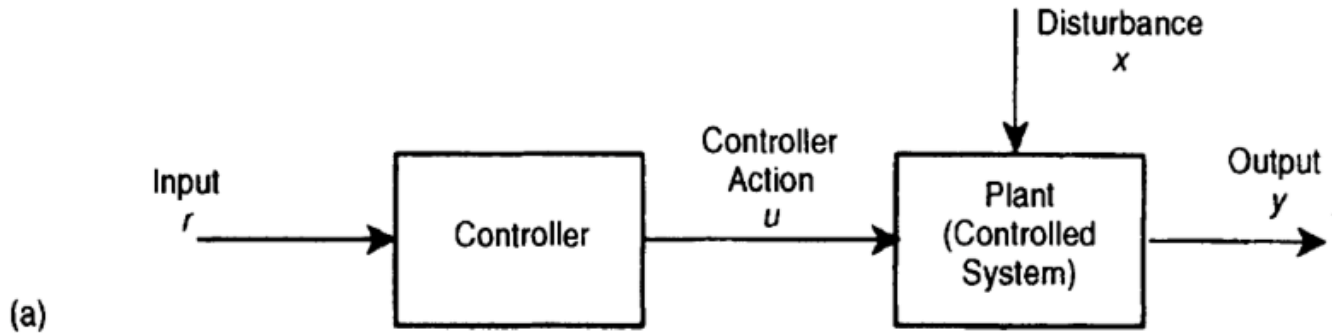
Taken from cervical cancer of Henrietta Lacks

No consent was given, ante or post-mortem…

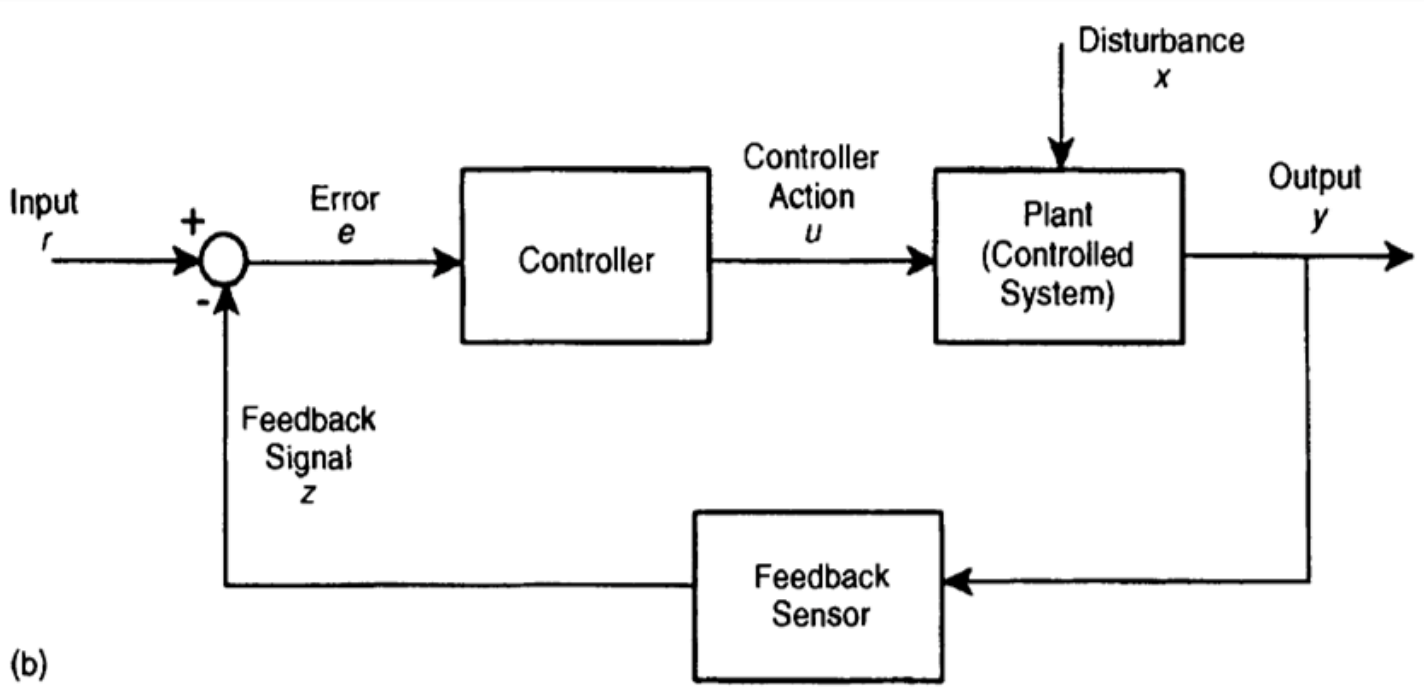
No anonymity



Biological Systems as Controlled System: Open Loop



Biological Systems as Controlled System: Closed Loop

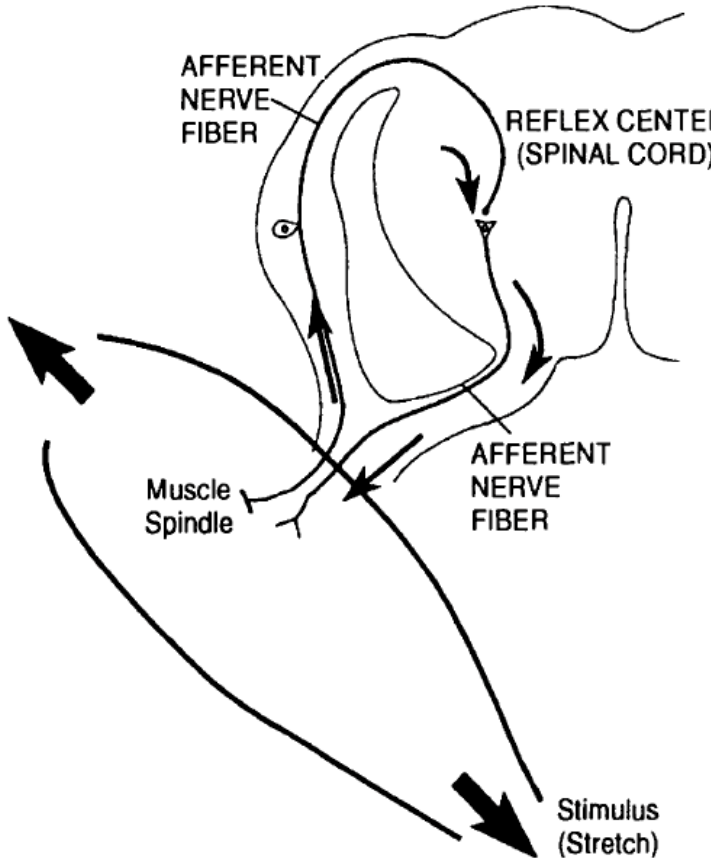


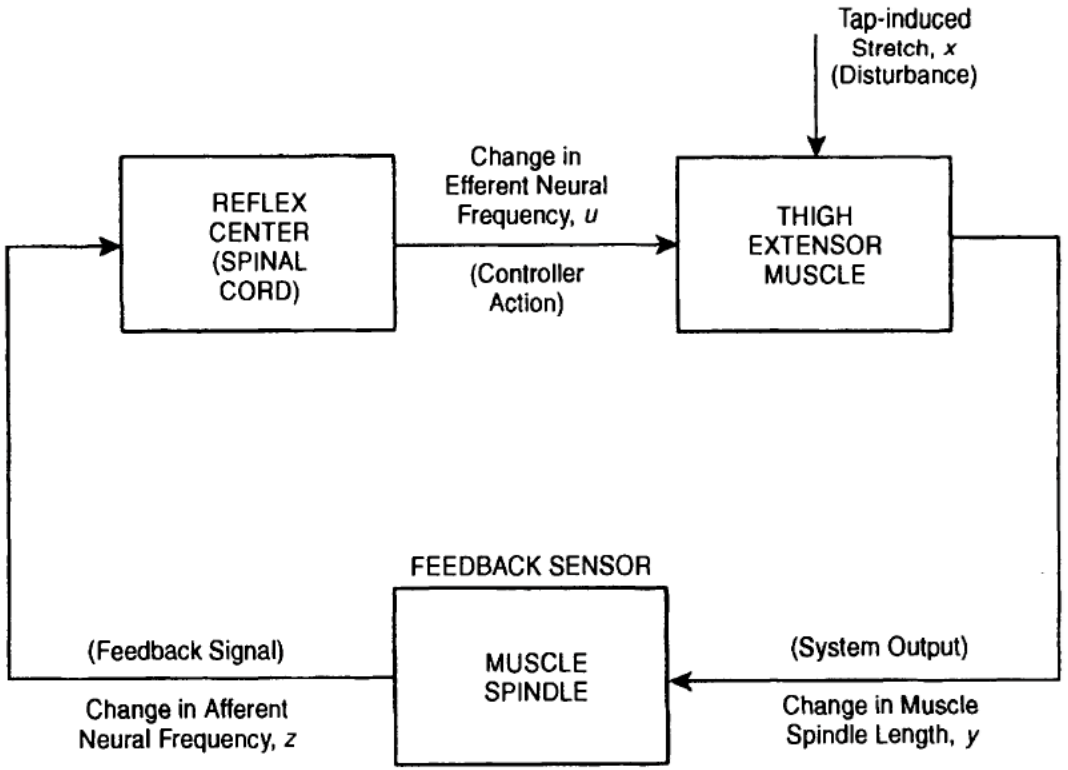
Biological Examples

- body temperature (homeothermic vs. poikilothermic)

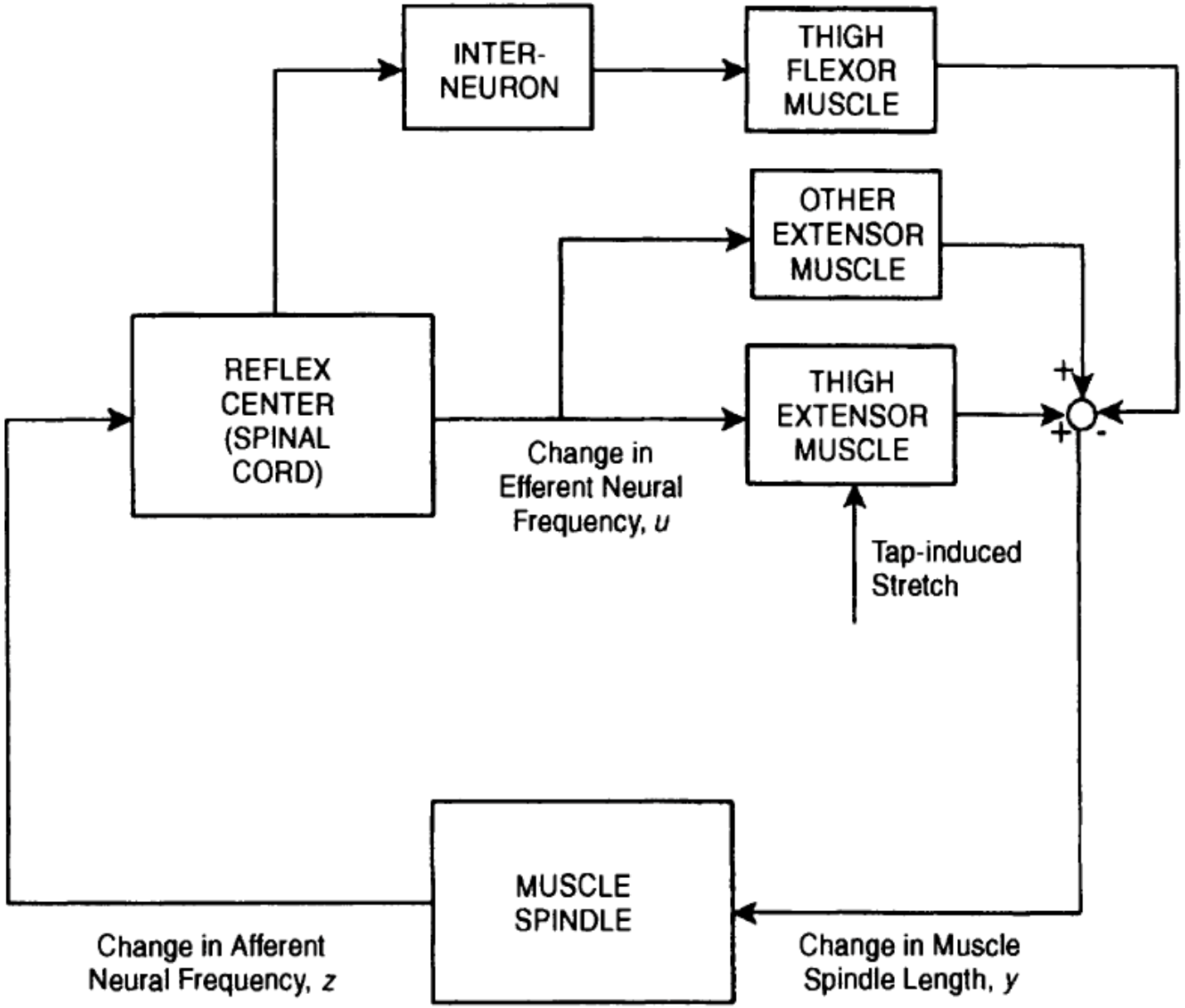
- heart rate

(sympathetic vs. parasympathetic)





More thorou


INTER-
NEURON
THIGH
FLEXOR
MUSCLE
OTHER
EXTENSOR
MUSCLE
REFLEX
CENTER
(SPINAL
CORD)
THIGH
EXTENSOR
MUSCLE
+
+
-
Change in
Efferent Neural
Frequency, u
Tap-induced
Stretch
MUSCLE
SPINDLE
Change in Afferent
Neural Frequency, z
Change in Muscle
Spindle Length, y

Engineering Control vs. Biological Control System

First Difference

Engineering

- accomplish a defined task with extensively optimized, fine-tuned parameters.
- Will perform its task "optimally" manner (at least, under the circumstances in which it is tested).

Biological

- built for versatility and may be capable of serving several different functions.
- e.g. primary purpose of the respiratory system is gas exchange, a secondary but also important function is to facilitate the elimination of body heat.

Engineering Control vs. Biological Control System

Second Difference

Engineering

- built by the designer
- characteristics of various components are generally known.

Biological

- consists of components that are unknown and difficult to analyze.
- Need to apply system identification techniques to determine how these various subsystems behave before proceeding to analyzing the overall control system.

Engineering Control vs. Biological Control System

Third Difference

Engineering

- Tend to be as straightforward as possible

Biological:

- extensive degree of cross-coupling or interaction among different physiological control systems.
  - e.g. cardiovascular system has a large dependence on interactions with the respiratory, renal, endocrine, and other organ systems.

Engineering Control vs. Biological Control System

Fourth Difference

Biological:

- Physiological control systems, in general, are adaptive.
- Thus a system may be able to offset any change in output not only through feedback but also by allowing the controller or plant characteristics to change.

Engineering:

- Can be designed to be adaptive
- In general, conditions are set and system follows those conditions

Engineering Control vs. Biological Control System

Fifth Difference

Biological:

- Feedback in biological systems is often embedded.
- Not always a simple sensor that provides negative feedback

Engineering

- In engineering this is often a sensor that imposes –ve feedback (say through subtraction) to the system.,

Engineering Control vs. Biological Control System

Sixth Difference

Biological:

- Generally nonlinear,

Engineering:

- Can be linear or nonlinear.
- Frequently, an engineer prefers to design or use linear system components since they have properties that are well-behaved and easy to predict.

Before we model… what does our Data look like?

Data Types

Different Types of data demand different types of analysis

Quantitative

Discrete (integer, ordinal)

(e.g. # of petals on flower)

Continuous (interval)

(weight, height, depth, etc.)

Qualitative

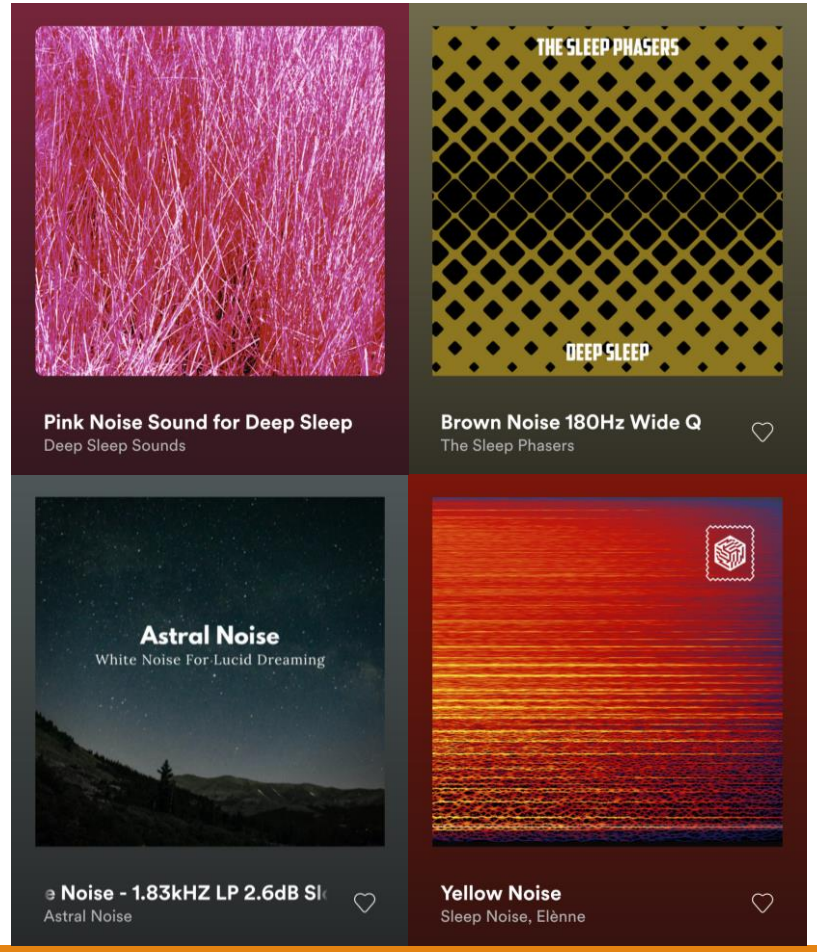
Discrete (nominal)

(classified, bins, ethnic background, sex)

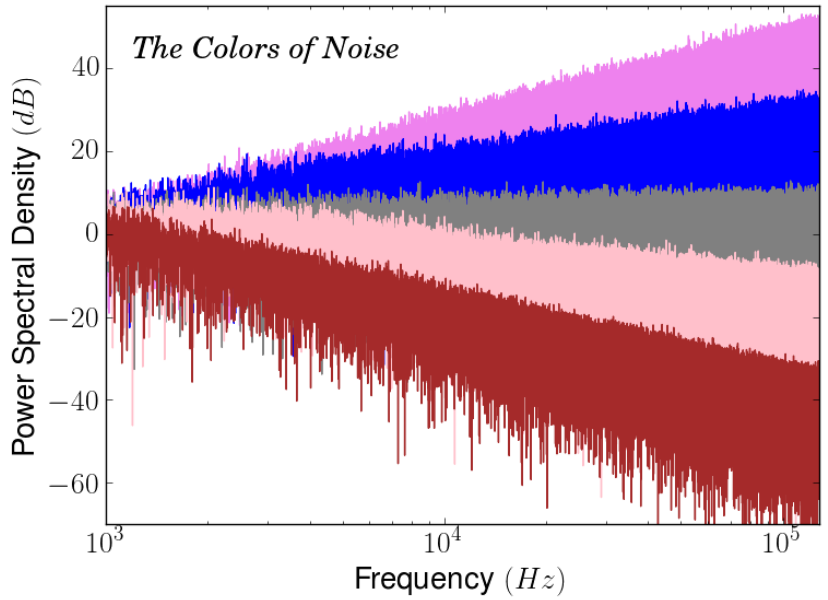
Noise

- An obstacle/interference to your message/signal/data
- Any unwanted data that doesn't help explain the relationship or feature you're looking for
- Types of biomedical noise
  - physiological variability
  - environmental noise or interference
  - transducer-induced noise
  - electronic noise

Noise Colour



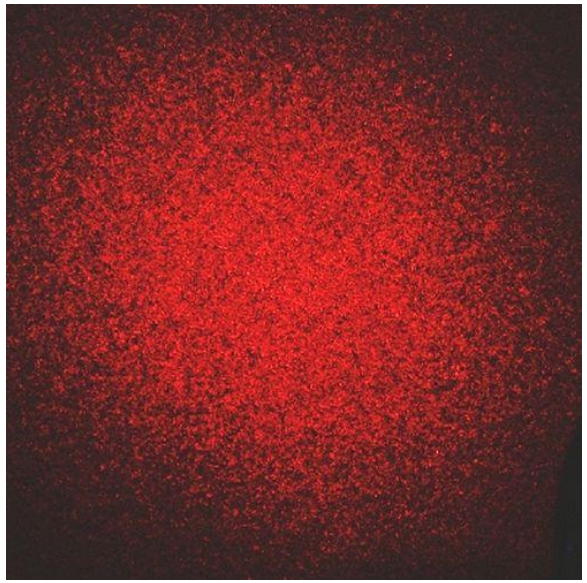
- White noise – uniform noise, random error
- Pink noise – 1/f pattern – intensity decreases with frequency
- Red noise – more low frequency than average
- Blue – more high frequency than average
- Most follows normal distribution, but it doesn't have to



https://en.wikipedia.org/wiki/Colors_of_noise

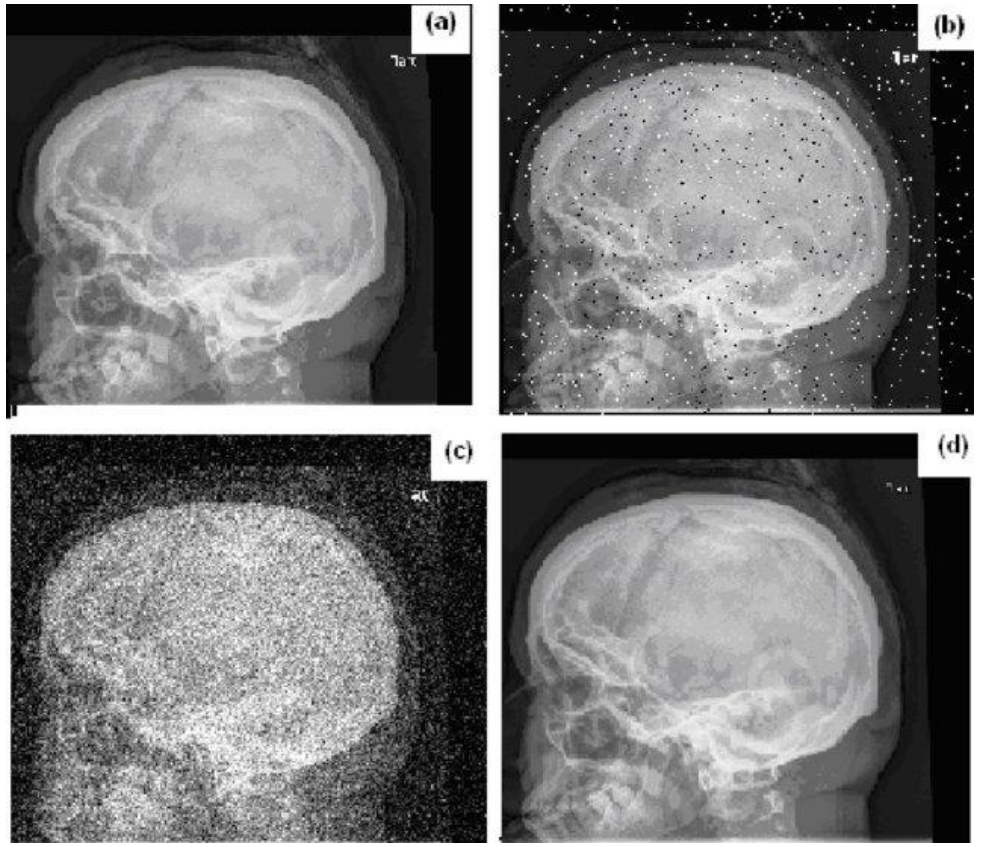
Image Noise

Speckle noise - ultrasound



https://www.wikiwand.com/en/Speckle_pattern

(a) Original Image,
(b) Salt and Pepper Noisy Image
(c) Gaussian Noisy Image
(d) Poisson Noisy Image



https://www.researchgate.net/publication/239735322_Computed_radiography_skull_image_enhancement_using_Wiener_filter

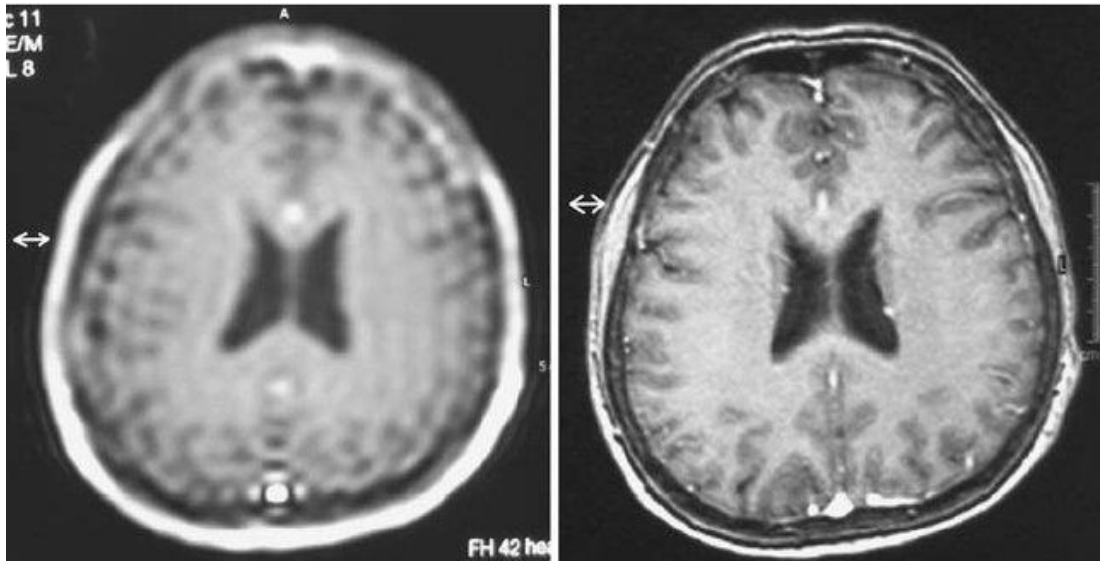
Artifact vs noise

Artifact

- appears to be a feature in the image
- Error in perception of information

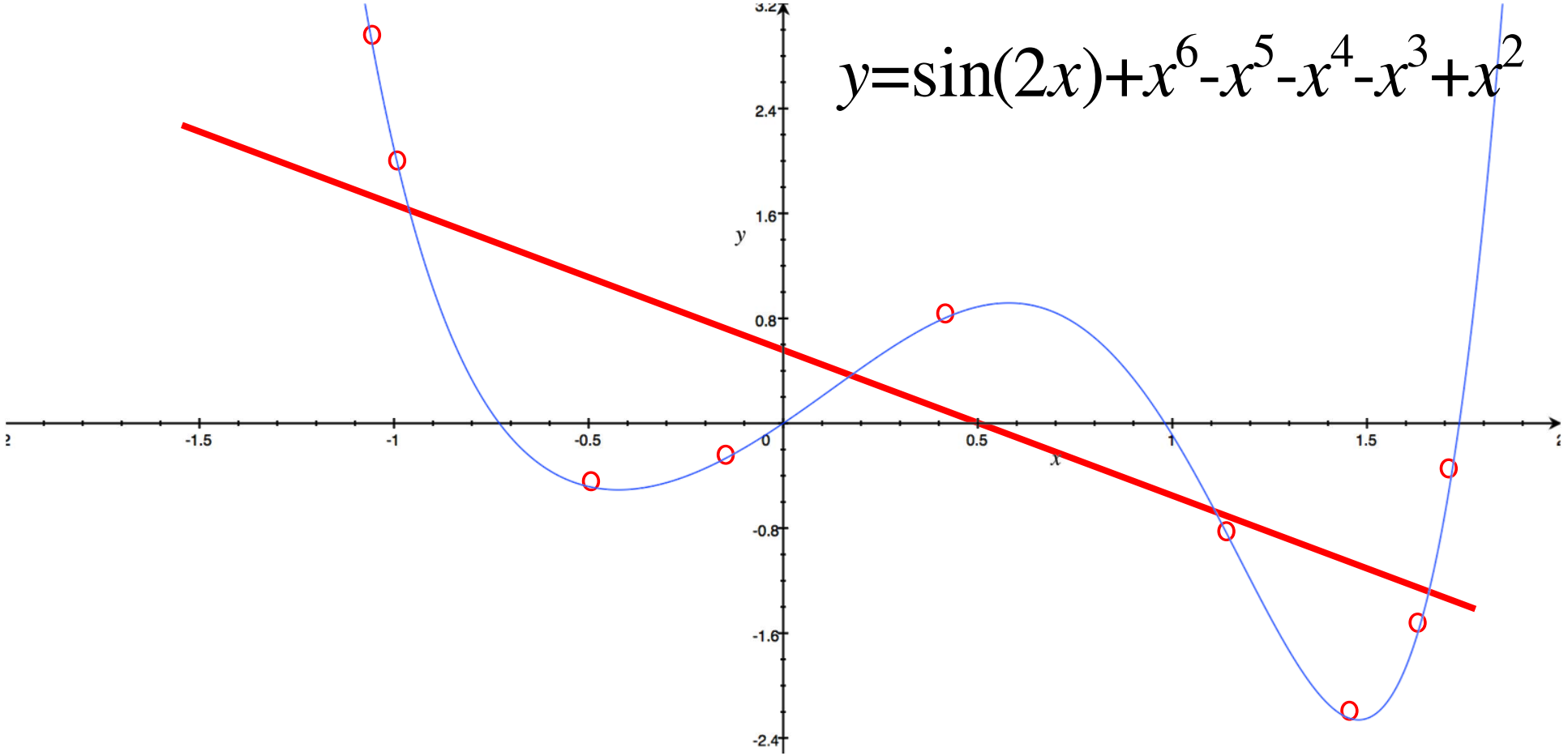
Noise

- obscures features
- generally random over frequencies or across image



https://www.researchgate.net/publication/6649032_Artifacts_in_body_MR_imaging_Their_appearance_and_how_to_eliminate_them/figures?lo=1

What is the Appropriate Mathematical Model: How to choose??



How do we prove our model is good?

Statistics?

1) Computer simulation

   - do we need statistics?

2) Mock System

   - do we need statistics?

3) The Biological System

   - so we need statistics?

Consider adding noise (colour?) or tolerance to see how model behaves

YES! How do we deal with multiple devices? Errors add in quadrature

YES! Absolutely essential- biological variability AND device tolerance + system noise demands the need for statistics

Types of Statistical Analysis

- Parametric vs. Non-parametric
- regression; minimizing least squares
- fit analysis/quality, e.g. R^2, χ^2 tests
- test differences between a number of specified treatments

Errors

The difference between the observed and the true value

Illegitimate errors

- true mistakes
- ballpark errors, wrong equations etc.

Systematic errors

- difficult to spot
- faulty calibration, observer bias, observation parallax etc.

Random errors

- Experimental accuracy, precision

Error Propagation

Also known as **Propagation of Uncertainty**

Effect the uncertainty of a variable has on the uncertainty of the function it is used in

Due to measurement errors/observation errors

Calculus used to calculate combined error from multiple components

Used to estimate true error/uncertainty in a system

Why is error propagation important?

Kersten Blunder

- Vigor space probe
- Inches to mm conversion was off (0.9mm)
- Probe completely missed Venus and was lost in space

Space Mountain Tokyo

- Roller-coaster axle broke mid ride due to an error converting from imperial to metric

Air Canada Gimli Glider

- Measurement error by pilot for fuel requirement for the flight
- Used up all fuel halfway through flight

Error in using a tape measure?

Human error

Instrument error

- Tick error
- Hook error

TAPE MEASURES	TOLERANCE MM ACCORDING TO EU STANDARDS		
	ACCURACY CLASS I	ACCURACY CLASS II	ACCURACY CLASS III
3 METRES	±0,4	±0,9	±1,8
5 METRES	±0,6	±1,3	±2,6
8 METRES	±0,9	±1,9	±3,8

Example: Dimensions of a box

Example: What is the volume of a box of dimensions L, W and H ?

Easy:

But how do the uncertainties in these measurements result in uncertainty of the final result, V_0?

Note: ignore higher order terms in expansion which is equivalent to neglecting the fact the partial derivatives are not constant over the ranges of L, W, and H. But if errors are large need to include 2^{nd} partial derivatives and cross derivatives!

Example: Dimensions of a box

Assuming someone is building a 1m3 box of wood and assuming they know how to use a tape measure…

Error Propagation Equations

They look worse than they are

Look for ways to simplify

- Neglect insignificant terms that make negligible contributions to the final uncertainty
- Rule of thumb: ignore error terms that make final contributions that are less than 10% of the largest contribution.
- But take care with this as many small uncertainties can add up!

Understanding what can be ignored takes practice!

Error Analysis Continued

→ Consider: we want to determine a quantity x that is a function of at least 2 measured variables u and v

$$x = f(u, v, \ldots)$$

Although not exact consider the most probable value for x is:

$$\bar{x} = f(\bar{u}, \bar{v}, \ldots)$$

The uncertainty in x can be determined by considering the spread of values in x resulting from the individual measurements in u_i and v_i:

$$x_i = f(u_i, v_i, \ldots)$$

Error Propagation Equation

In the limit of infinite measurements the mean of the distribution coincides with x with variance described by:

Recall volume calculation example, where V was a function of the deviations in the calculated dimensions, express deviations in x in terms of deviations in u and v:

Error Propagation Equation

Each partial derivative is evaluated with all the other variables fixed at their mean values.

Combine Equations:

$$\sigma_x^2 = \lim_{N\to\infty}\left[\frac{1}{N}\sum (x_i - \bar{x})^2\right]$$

$$x_i - \bar{x} \simeq (u_i - \bar{u})\left(\frac{\partial x}{\partial u}\right) + (v - \bar{v})\left(\frac{\partial x}{\partial v}\right) + \cdots$$

Error Propagation Equation

This allows expression of variance for x in terms of variances for the variables u, v, ,.... (i.e. whatever was measured)

$$\sigma_x^2 \simeq \lim_{N\to\infty} \frac{1}{N} \sum \left[(u_i - \bar{u}) \left(\frac{\partial x}{\partial u} \right) + (v_i - \bar{v}) \left(\frac{\partial x}{\partial v} \right) + \cdots \right]^2$$

$$\simeq \lim_{N\to\infty} \frac{1}{N} \sum \left[(u_i - \bar{u})^2 \left(\frac{\partial x}{\partial u} \right)^2 + (v_i - \bar{v})^2 \left(\frac{\partial x}{\partial v} \right)^2 \right.$$

$$\left. + 2(u_i - \bar{u})(v_i - \bar{v}) \left(\frac{\partial x}{\partial u} \right) \left(\frac{\partial x}{\partial v} \right) + \cdots \right]$$

Error Propagation Equation

The first 2 terms are simple:

$$\sigma_u^2 = \lim_{N\to\infty}\left[\frac{1}{N}\sum(u_i - \bar{u}_i)^2\right] \qquad \sigma_v^2 = \lim_{N\to\infty}\left[\frac{1}{N}\sum(v_i - \bar{v}_i)^2\right]$$

The 3rd term may be replaced by a covariance term:

$$\sigma_{uv}^2 \equiv \lim_{N\to\infty}\left[\frac{1}{N}\sum[(u_i - \bar{u})(v_i - \bar{v})]\right]$$

Error Propagation Equation

Substituting 3 terms back into original equation:

$$\sigma_x^2 \simeq \sigma_u^2 \left(\frac{\partial x}{\partial u}\right)^2 + \sigma_v^2 \left(\frac{\partial x}{\partial v}\right)^2 + \cdots + 2\sigma_{uv}^2 \left(\frac{\partial x}{\partial u}\right)\left(\frac{\partial x}{\partial v}\right) + \cdots$$

- the first 2 terms are the averages of the squares of deviations weighted by the squares of the partial derivatives

Error Propagation Equation

$$\sigma_x^2 \simeq \sigma_u^2 \left(\frac{\partial x}{\partial u}\right)^2 + \sigma_v^2 \left(\frac{\partial x}{\partial v}\right)^2 + \cdots + 2\sigma_{uv}^2 \left(\frac{\partial x}{\partial u}\right)\left(\frac{\partial x}{\partial v}\right) + \cdots$$

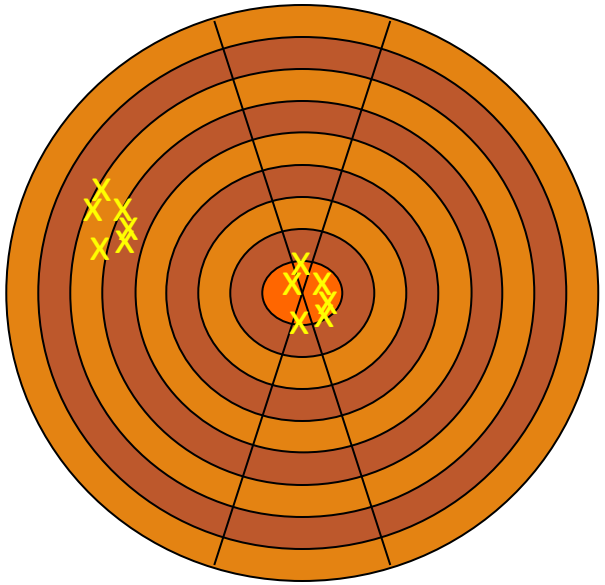
- If fluctuations in u and v are uncorrelated, then one would expect equal distribution of +ve and –ve values for this term and hence it would vanish with increased numbers of randomly selected observations. The equation then reduces to:

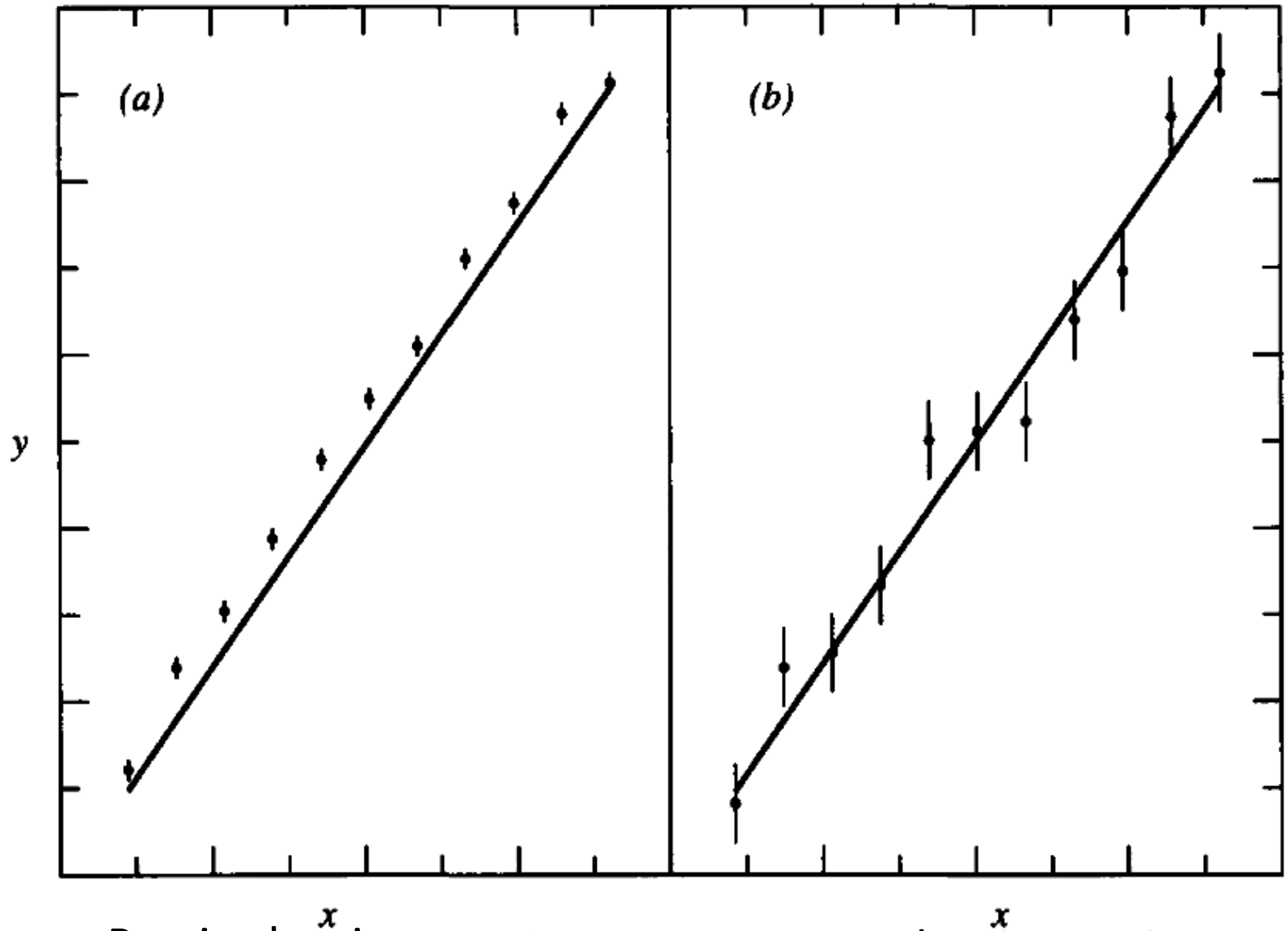
$$\sigma_x^2 \simeq \sigma_u^2 \left(\frac{\partial x}{\partial u}\right)^2 + \sigma_v^2 \left(\frac{\partial x}{\partial v}\right)^2 + \cdots$$

Accuracy versus Precision

Accuracy: how close to the true value did we get.

Precision: how exact are the measurements repeatability





Precise but inaccurate

Accurate but imprecise

"TRUE" = straight line

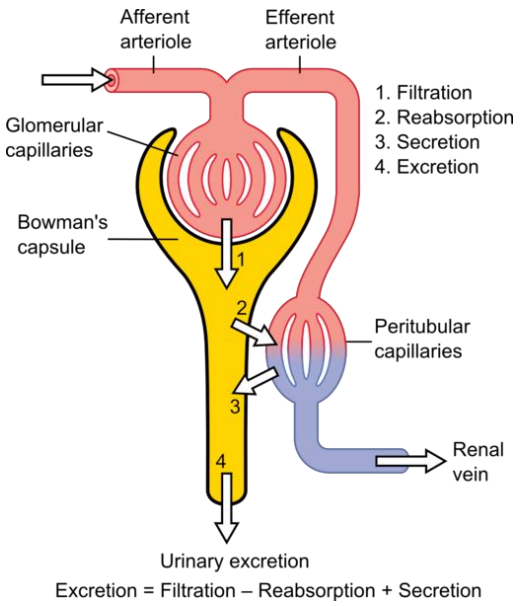
Is this Important to Know for Biological Modelling??

Consider measuring Glomerular Filtration Rate (GFR) an indication of renal function

$$GFR = 141 \times \min(SCr/k, 1)^{a} \times \max(SCr/k, 1)^{-1.209} \times 0.993^{Age} \times [1.018] \times [1.159]$$

If female

If African



SCr = serum creatinine (mg/dL)
k = 0.7 (females) or 0.9 (males)
a = -0.329 (females) or -0.411 (males)
min = minimum of SCr/k or 1 (whichever is least)
max = maximum of SCr/k or 1 (whichever is maximum)