Important terms & concepts for **discrete random variables**

- Probability Mass Function (PMF)
- ***<u>Cumulative Distribution Function (CDF)</u>***
- ***<u>Complementary Cumulative Distribution Function (CCDF)</u>***
- ***<u>Expected value</u>***
- ***<u>Mean</u>***
- ***<u>Variance</u>***
- ***<u>Standard deviation</u>***

<u>Boldface and underlined</u> are the same for continuous distributions

Which distribution is this?

$$\binom{n}{x} p^x (1-p)^{n-x}$$

A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Which distribution is this?

$$\binom{n}{x} p^x (1-p)^{n-x}$$

A. Uniform
B. $\boxed{\text{Binomial}}$
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Which distribution is this?

$$\binom{x-1}{r-1}(1-p)^{x-r}p^r$$

A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Which distribution is this?

$$\binom{x-1}{r-1}(1-p)^{x-r}p^r$$

A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Which distribution is this?

$$\frac{e^{-\lambda}\lambda^{x}}{x!}$$

A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Which distribution is this?

$$\frac{e^{-\lambda}\lambda^{x}}{x!}$$

A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
E. Poisson

Get your i-clickers

Name	Probability Distribution	Mean	Variance
Discrete			
Uniform	$\frac{1}{n}, a \leq b$	$\frac{(b+a)}{2}$	$\frac{(b-a+1)^2-1}{12}$
Binomial	$\binom{n}{x} p^x (1-p)^{n-x}$, $x = 0, 1, \ldots, n, 0 \leq p \leq 1$	np	$np(1-p)$
Geometric	$(1-p)^{x-1} p$, $x = 1, 2, \ldots, 0 \leq p \leq 1$	$1/p$	$(1-p)/p^2$
Negative binomial	$\binom{x-1}{r-1} (1-p)^{x-r} p^r$ $x = r, r+1, r+2, \ldots, 0 \leq p \leq 1$	r/p	$r(1-p)/p^2$
Poisson	$\frac{e^{-\lambda}\lambda^x}{x!}, x = 0, 1, 2, \ldots, 0 < \lambda$	λ	λ

What distributions we learn

- Uniform distribution
- Bernoulli distribution/trial
- Binomial distribution
- Poisson distribution
- Geometric distribution
- Negative binomial distribution

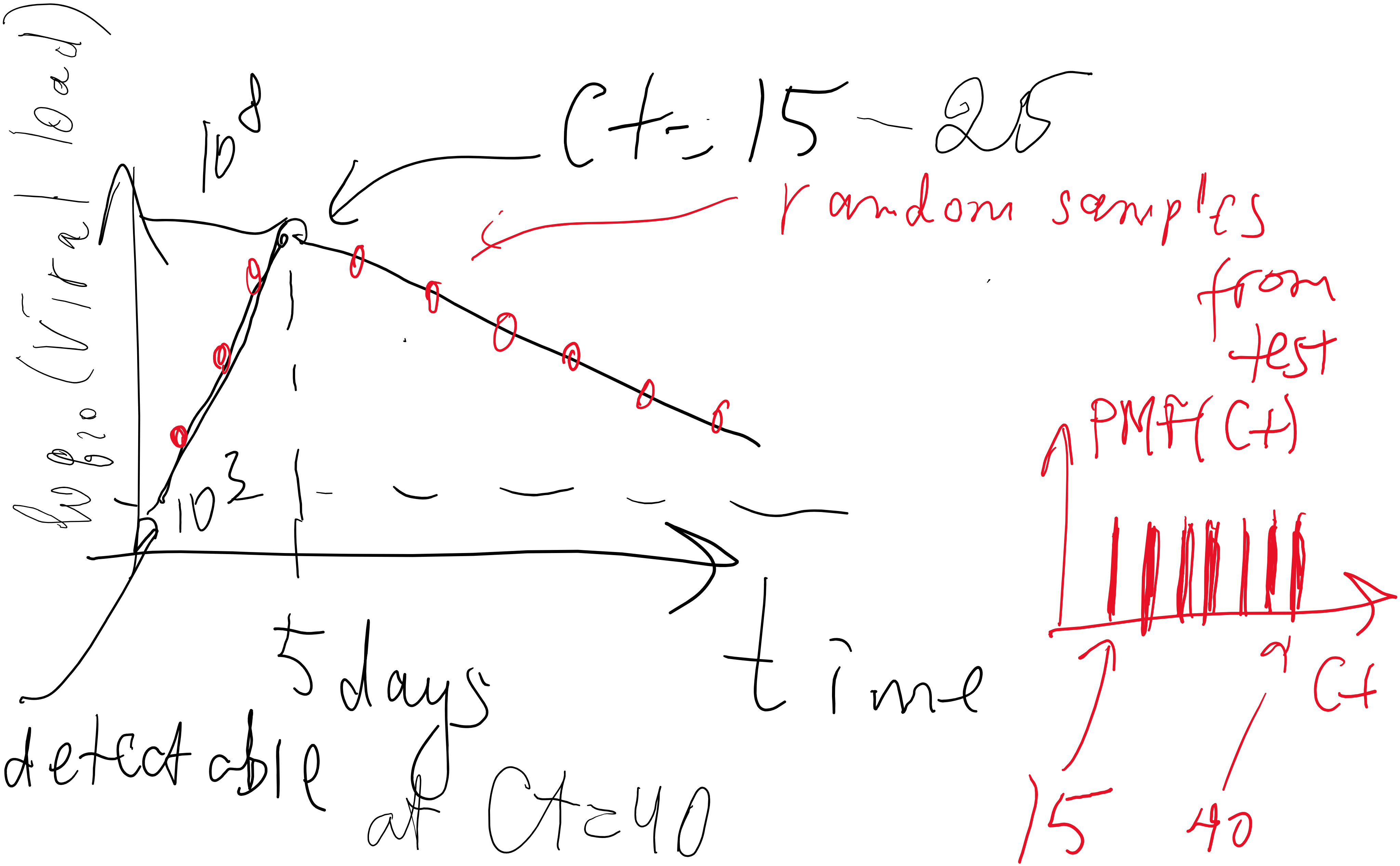
Why do we need to know these simple distributions?

Ways to use statistics

- To process your experimental data
  - What do you need? Mean, Variance, Standard deviation. No need to know any textbook distributions
- To plan experiments
  - Need to know distributions, e.g., Poisson to plan how much redundancy to use for genome assembly
- To learn biological processes behind your data
  - Need to know distributions to compare empirical distributions in your data to what you expect based on a simple hypothesis

Uniform distribution

Why Ct distribution should it be uniform?



Examples of uniform distribution: Ct value of PCR test of a virus

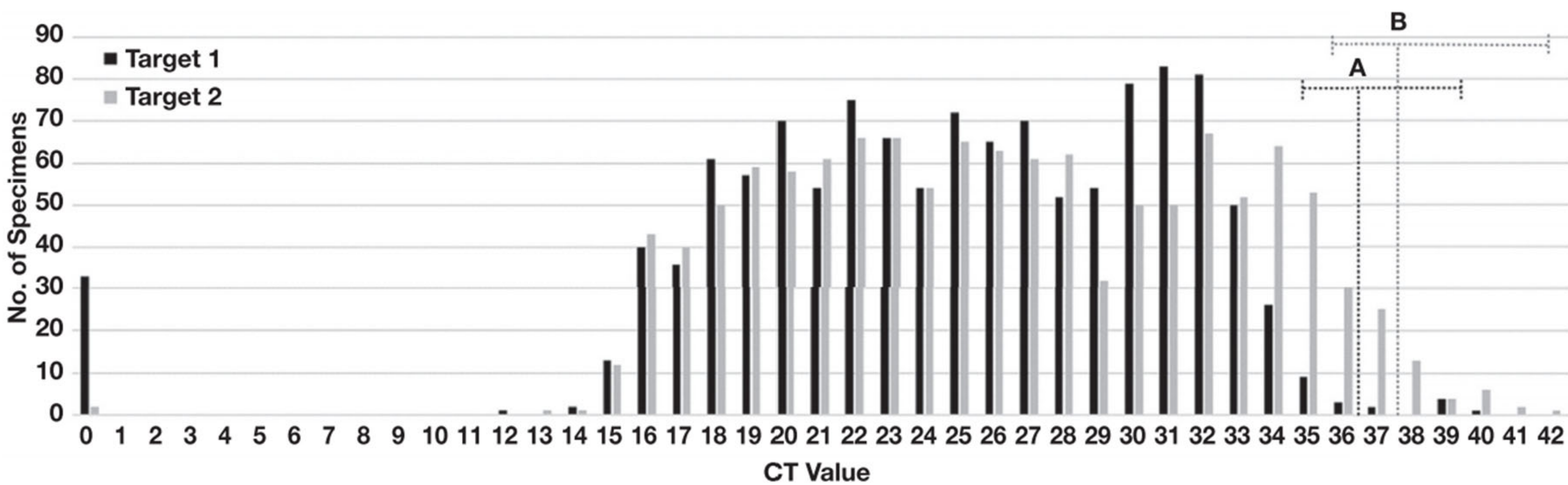
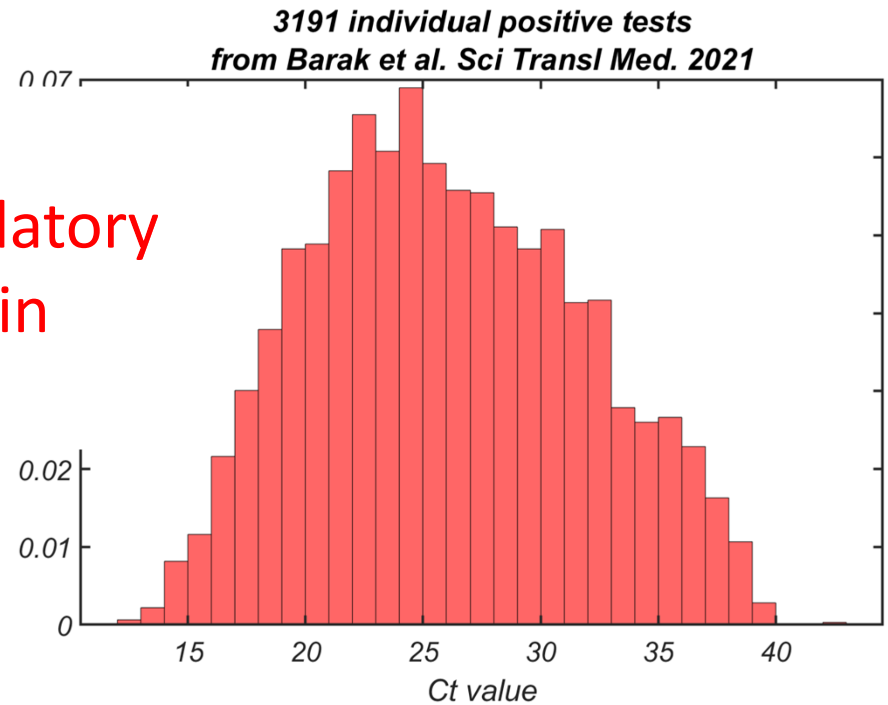


Figure 3 Distribution of cycle threshold (CT) values. The total number of specimens with indicated CT values for Target 1 and 2 are plotted. The estimated limit of detection for (A) Target 1 and (B) Target 2 are indicated by vertical dotted lines. Horizontal dotted lines encompass specimens with CT values less than 3× the LoD for which sensitivity of detection may be less than 100%. This included 19/1,180 (1.6%) reported CT values for Target 1 and 81/1,211 (6.7%) reported CT values for Target 2. Specimens with Target 1 or 2 reported as "not detected" are denoted as a CT value of "0."

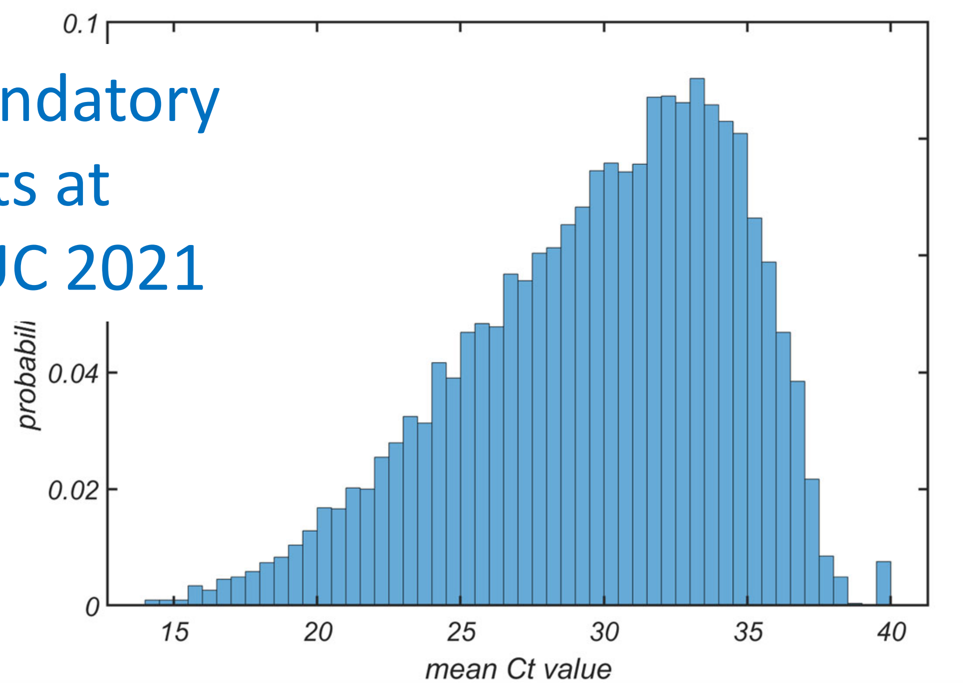
Distribution of SARS-CoV-2 PCR Cycle Threshold Values Provide Practical Insight Into Overall and Target-Specific Sensitivity Among Symptomatic Patients
Blake W Buchan, PhD, Jessica S Hoff, PhD, Cameron G Gmehlin, Adriana Perez, Matthew L Faron, PhD, L Silvia Munoz-Price, MD, PhD, Nathan A Ledeboer, PhD *American Journal of Clinical Pathology*, Volume 154, Issue 4, 1 October 2020, https://academic.oup.com/ajcp/article/154/4/479/5873820

Why should we care?

Non-mandatory tests in Israel



Mandatory tests at UIUC 2021



- High Ct value means we identified the infected individual early, hopefully before transmission to others
- When testing is mandatory, and people are tested frequently – Ct value is skewed towards high values

Negative binomial distribution

Statistics of cancer incidence vs age

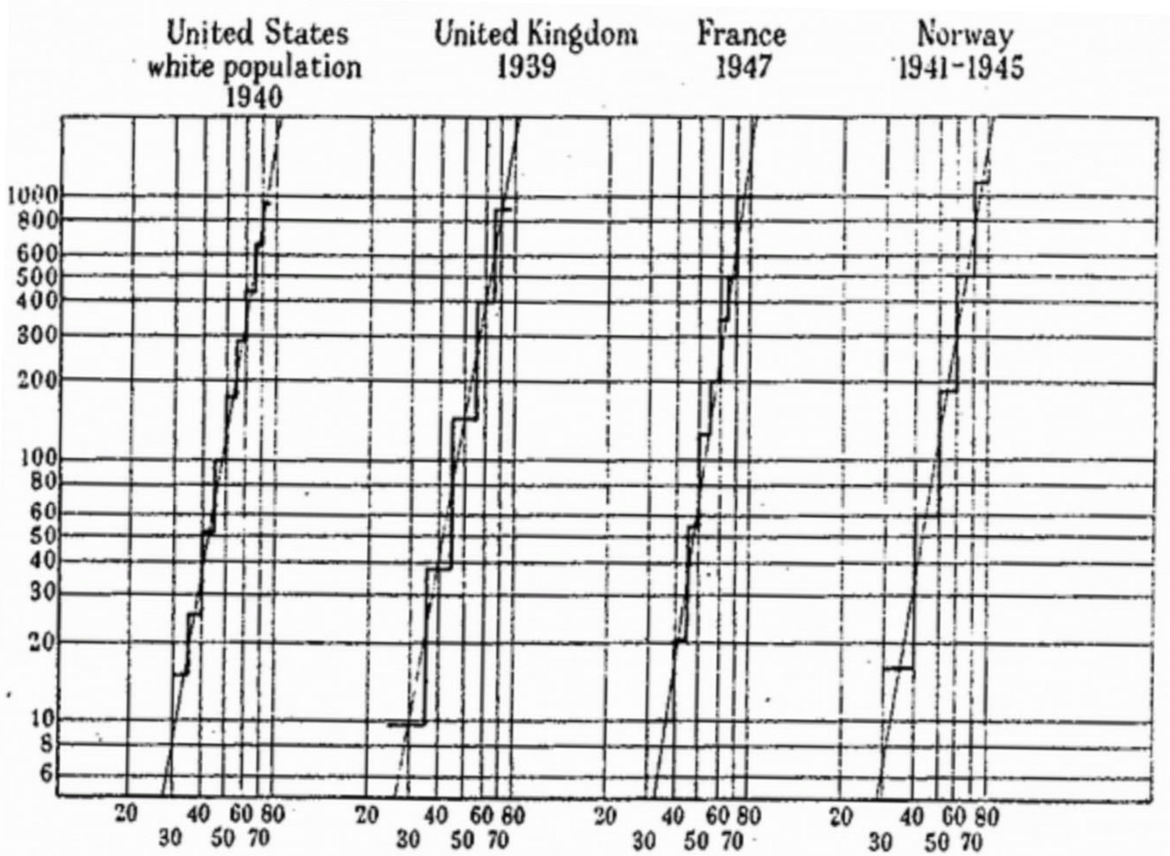


FIG. 1.—Diagram drawn to double logarithmic (log/log) scale showing the cancer death-rate (in the case of the United Kingdom, the carcinoma death-rate) in males at different ages. Deaths per 100,000 males are shown on the vertical scale, age figures on the horizontal scale.

Multi-mutation theory of cancer:
Carl O. Nordling (British J. of Cancer, March 1953):

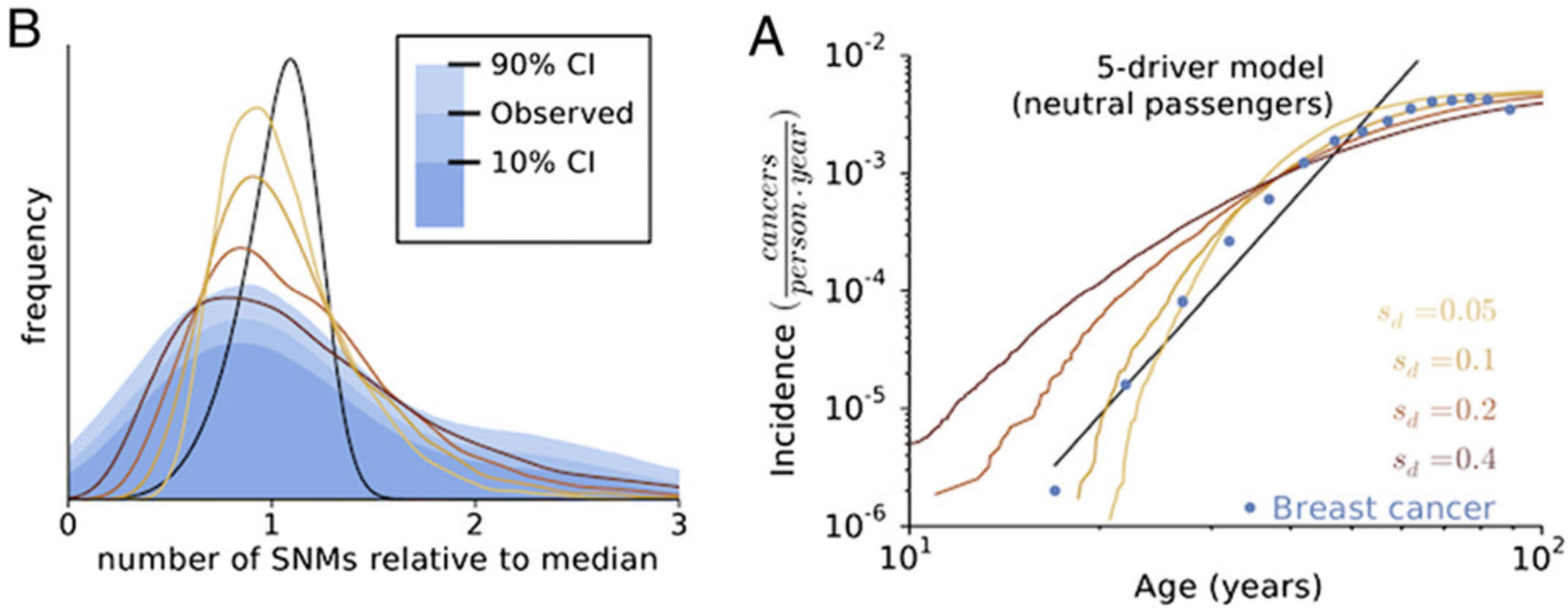
Cancer death rate $\sim$ (patient age)^6

It suggests the existence of k=7 driver genes

$$P(T_{cancer} \leq t) \sim (u_1 t)(u_2 t)..(u_k t) \sim u_1 u_2..u_k\, t^k$$

$$P(T_{cancer} = t) \sim \frac{d}{dt}(u_1 t)(u_2 t)..(u_k t) \sim k\, u_1 u_2..u_k\, t^{k-1}$$

Can we prove/quantify it using statistics?



Assume: growth rate of cancer=$(1+s_d)^{Nd}/(1+s_p)^{Np}$

$\mu=10^{-8}$, Target$_d$=1,400, Target$_p$=10^7, s_d=0.05 to 0.4, s_p=0.001

s_p/s_d for breast: 0.0060±0.0010;

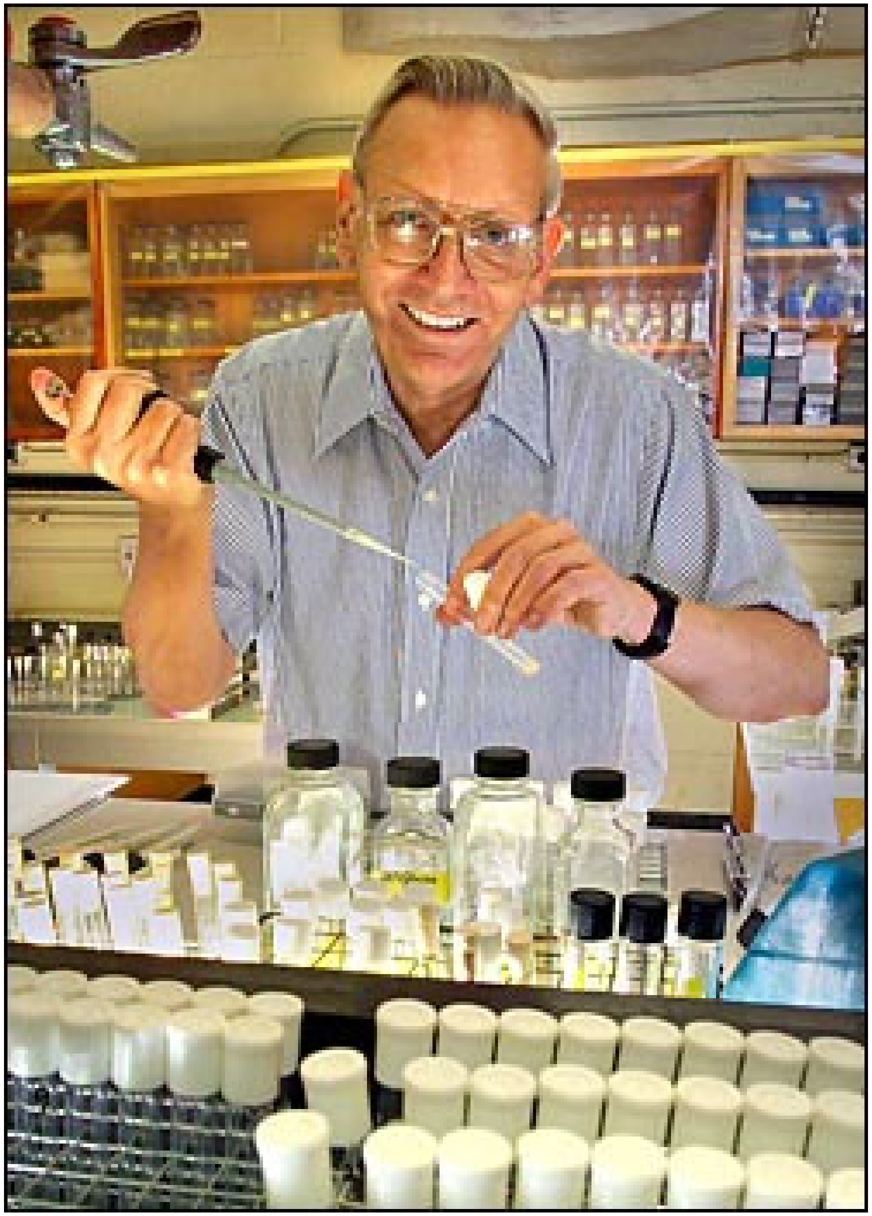
melanoma: 0.016±0.003; lung: 0.0094±0.0093;

Blue - data on breast cancer: incidence; non-synonymous mutations

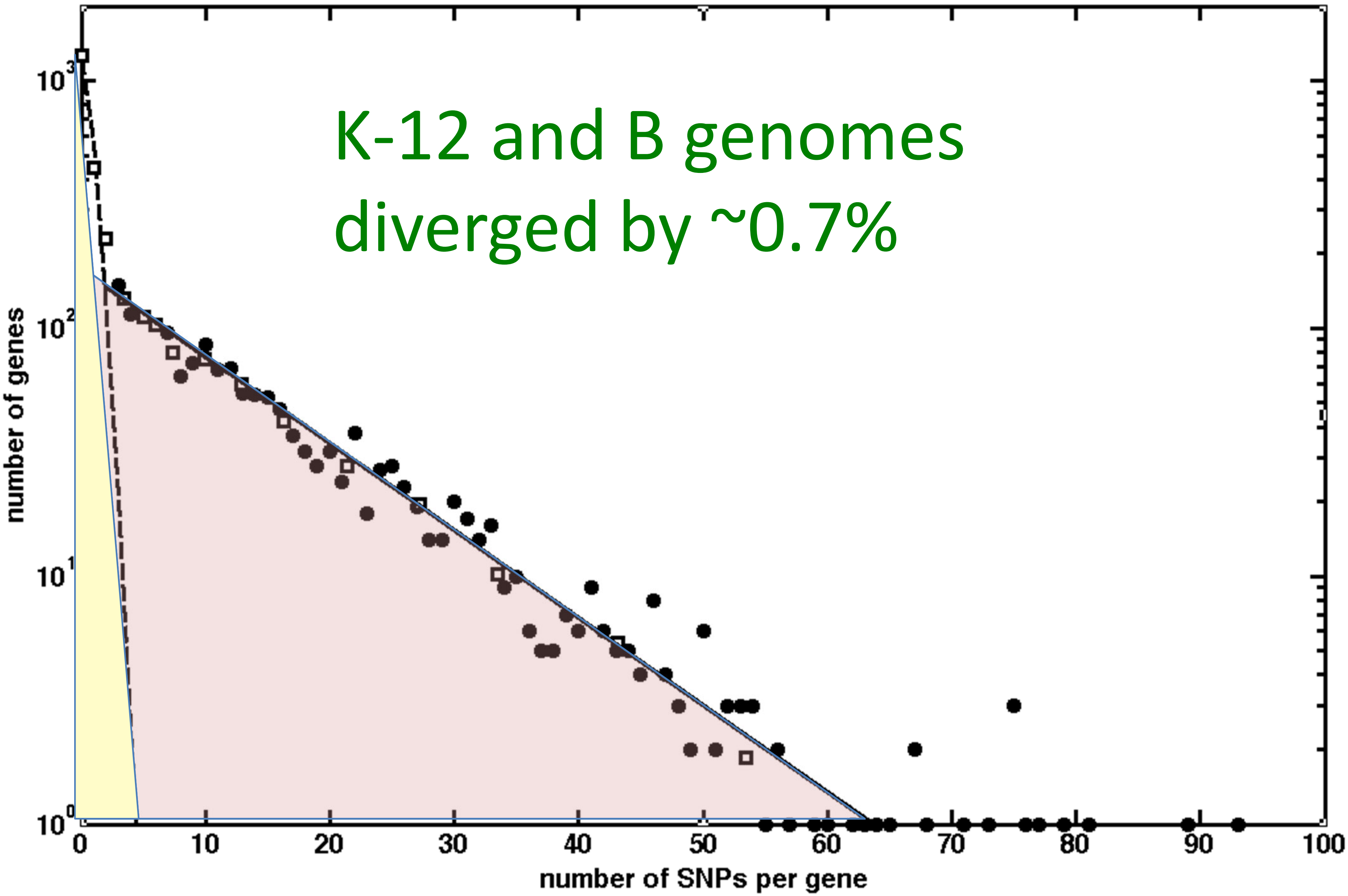
Poisson and Exponential Distributions

F. William Studier

- Worked at Brookhaven National Laboratory, Long Island, NY since 1964
- Inventor of **slab gel electrophoresis in 1970** (not patented- back then no incentive to patent work if you are supported by the US givernment)
- Inventor of T7 phage expression system for **fast production of proteins**. Licensed by over 900 companies, generated over $55 million for the lab https://en.wikipedia.org/wiki/T7_expression_system

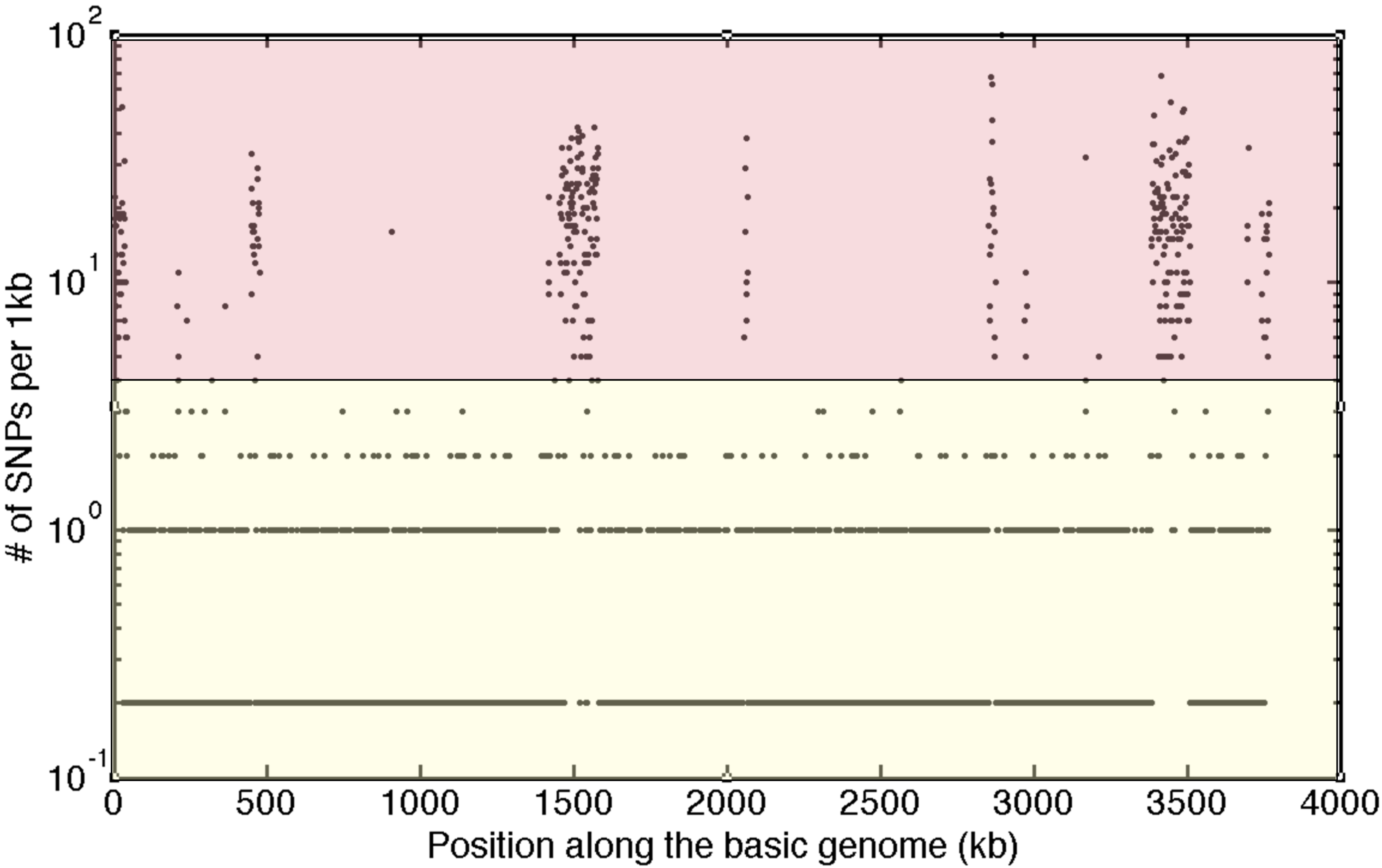


K-12 vs BL21(DE3) strains of E. coli



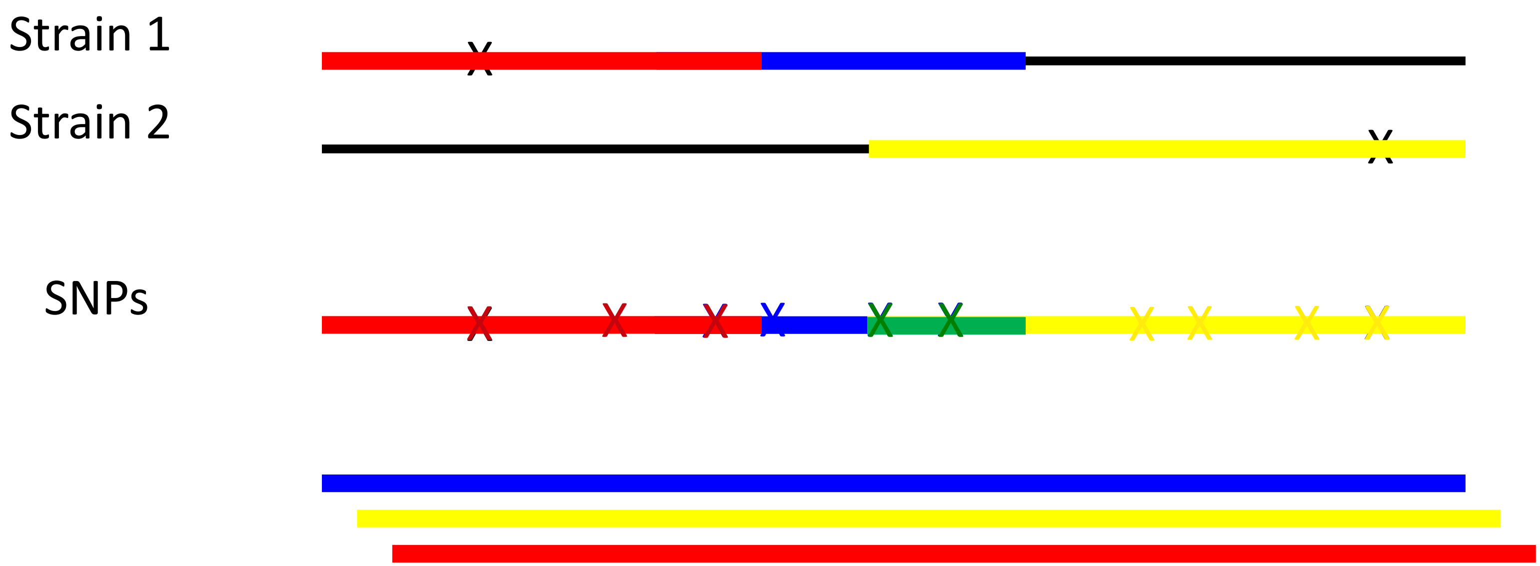
Studier FW, Daegelen P, Lenski RE, **Maslov S**, Kim JF, J. Mol Biol. (2009)

Highly variable segments are clustered



K-12 vs UMNF18 diverged by ~0.18%

Model of bacterial evolution by mutations and homologous recombination



- Mutation rate μ (bp/generation)
- Recombination rate ρ (bp/generation)
- l_R- average length of recombined segments
- $\theta = 2\mu N_e$ depending on N_e – (effective) population size
- δ_{TE} transfer efficiency: Prob(successful transfer + recombination): ~ $\exp(-\delta/\delta_{TE})$

Dixit P, Pang TY, Studier FW, **Maslov S,** PNAS (2015); arXiv:1405.2548

Why exponential tail?

- Empirical data for E. coli: Prob(δ)=exp(-δ/0.01)
  Similar slopes in other species as distant as B. subtilis
- Theory 1: PopGen 101 coalescence time distribution:
  - Prob(T) ~ exp(-T/N_e) →
    Prob(δ) ~ exp(- δ/ 2μN_e) = exp(- δ/θ)
    θ =2μN_e~0.01, μ~10^{-10} → N_e~10^8
- Theory 2: biophysics of homologous recombination:
  - Requires perfect matches of L=30bp on each side →
    Prob(δ)=$(1- δ)^{2L}$=exp(-60•δ)=exp(-δ/0.016)=exp (-δ/$δ_{TE}$)
- Both mechanisms likely to work together:
  biophysics of recombination affects the effective population size

Continuous Probability Distributions

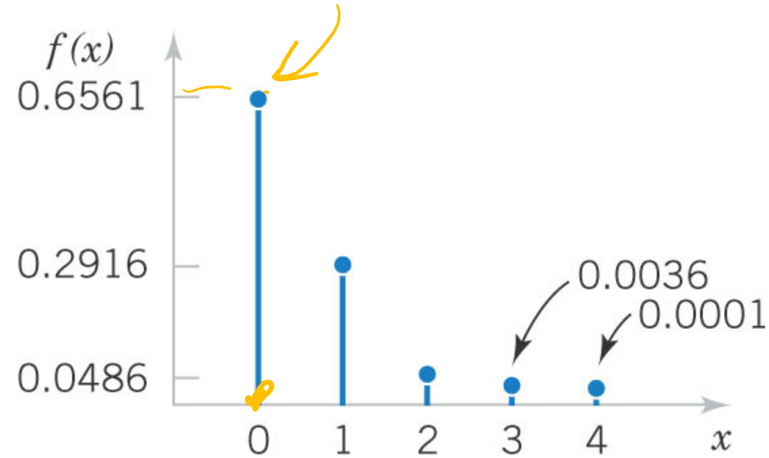
Uniform Distribution

Continuous & Discrete Random Variables

- A discrete random variable is usually integer number
  - N – the number of proteins in a cell
  - D- number of nucleotides different between two sequences
- A continuous random variable is a real number
  - C=N/V – the concentration of proteins in a cell of volume V
  - Percentage D/L*100% of different nucleotides in protein sequences of different lengths L (depending on set of L's may be discrete but dense)

Probability Mass Function (PMF)

- *X* – discrete random variable



Probability Mass Function for the # of mismatches in 4-mers

- Probability Mass Function: f(x)=P(X=x) – the probability that X is exactly equal to x

P(*X* =0) =	0.6561
P(*X* =1) =	0.2916
P(*X* =2) =	0.0486
P(*X* =3) =	0.0036
P(*X* =4) =	0.0001
Σ_x P(X=x)=	1.0000

Probability Density Function (PDF)

Density functions, in contrast to mass functions, distribute probability continuously along an interval

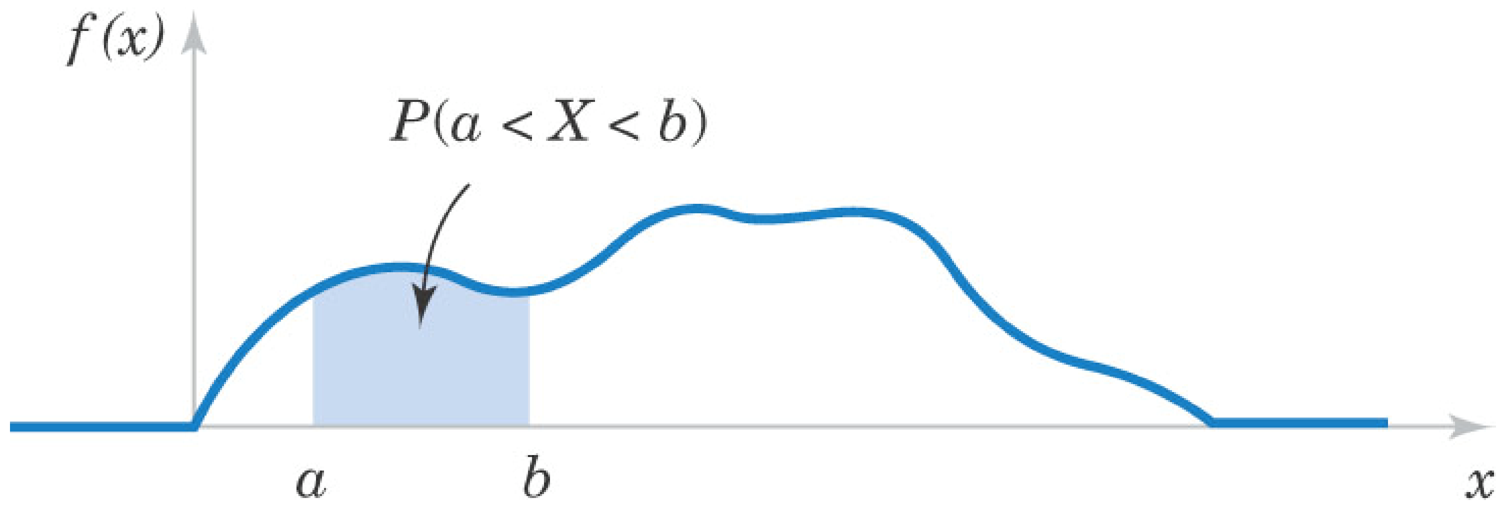


Figure 4-2 Probability is determined from the area under $f(x)$ from a to b.

Probability Density Function

For a continuous random variable X,
a probability density function is a function such that

(1) $f(x) \geq 0$ means that the function is always non−negative.

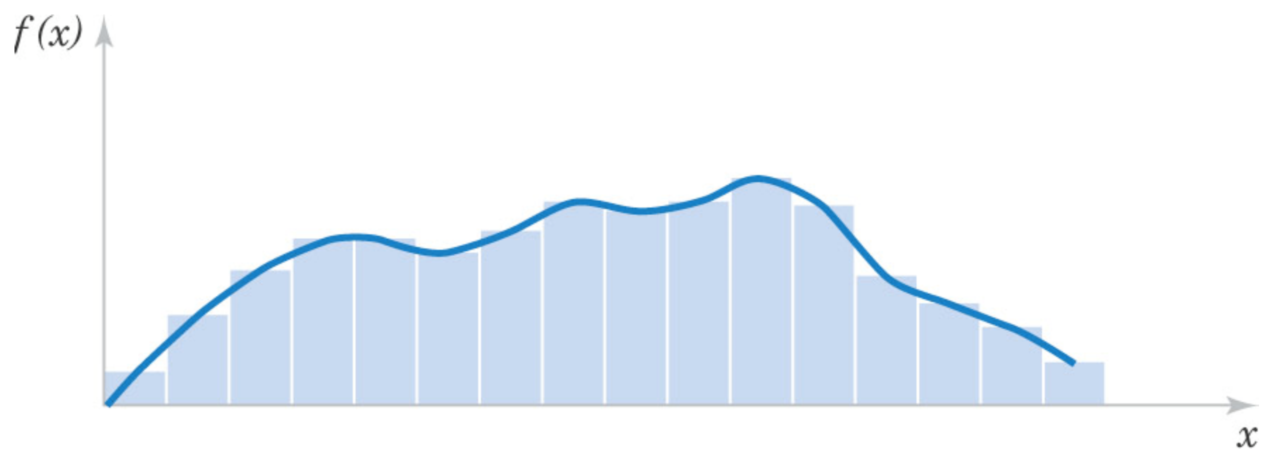
(2) $$\int_{-\infty}^{\infty} f(x)\, dx = 1$$

(3) $P(a \leq X \leq b) = \int_{a}^{b} f(x)dx =$ area under $f(x)dx$ from a to b

Normalized histogram approximates PDF

A histogram is graphical display of data showing a series of adjacent rectangles. Each rectangle has a base which represents an interval of data values. The height of the rectangle is a number of events in the sample within the base.

When base length is narrow, the histogram could be normalized to approximate PDF (f(x)):
height of each rectangle =
=(# of events within base)/(total # of events)/width of its base.



Normalized histogram approximates a probability density function.

Cumulative Distribution Functions (CDF & CCDF)

The cumulative distribution function (CDF) of a continuous random variable X is,

$$F(x) = P(X \leq x) = \int_{-\infty}^{x} f(u)du \text{ for } -\infty < x < \infty \quad (4\text{−}3)$$

One can also use the inverse cumulative distribution function or complementary cumulative distribution function (CCDF)

$$F_{>}(x) = P(X > x) = \int_{x}^{\infty} f(u)du \text{ for } -\infty < x < \infty$$

Definition of CDF for a continous variable is the same as for a discrete variable

Density vs. Cumulative Functions

- The probability density function (PDF) is the derivative of the cumulative distribution function (CDF).

$$f(x) = \frac{dF(x)}{dx} = -\frac{dF_{>}(x)}{dx}$$

as long as the derivative exists.

Mean & Variance

Suppose X is a continuous random variable with probability density function $f(x)$. The mean or expected value of X, denoted as μ or $E(X)$, is

$$\mu = E(X) = \int_{-\infty}^{\infty} xf(x)dx \qquad (4\text{–}4)$$

The variance of X, denoted as $V(X)$ or σ^2, is

$$\sigma^2 = V(X) = \int_{-\infty}^{\infty} (x-\mu)^2 f(x)dx = \int_{-\infty}^{\infty} x^2 f(x)dx - \mu^2$$

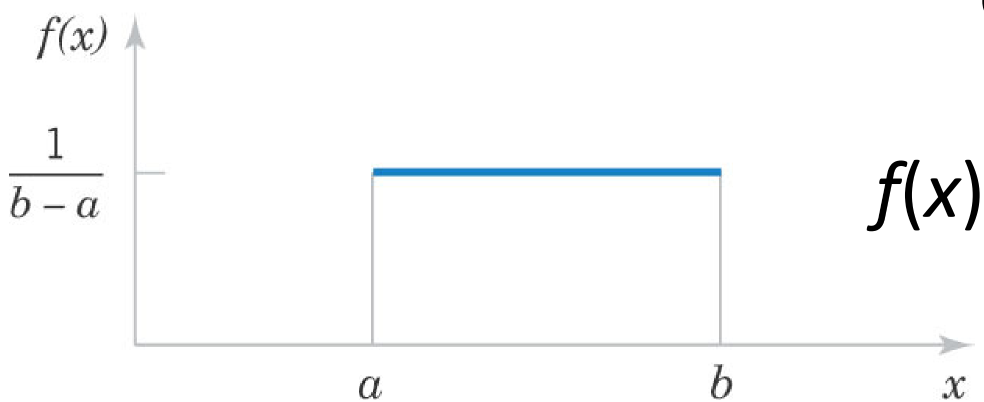
The standard deviation of X is $\sigma = \sqrt{\sigma^2}$.

Gallery of Useful
Continuous Probability Distributions

Continuous Uniform Distribution

- This is the simplest continuous distribution and analogous to its discrete counterpart.
- A continuous random variable X with probability density function

$$f(x) = 1 \,/\, (b - a) \text{ for } a \le x \le b \qquad (4\text{-}6)$$



Compare to discrete

$f(x) = 1/(b-a+1)$

Figure 4-8 Continuous uniform PDF

Comparison between Discrete & Continuous Uniform Distributions

Discrete:

- PMF: $f(x) = 1/(b\text{-}a+1)$
- Mean and Variance:

$\mu = E(x) = (b+a)/2$

$\sigma^2 = V(x) = [(b\text{-}a+1)^2 – 1]/12$

Continuous:

- PMF: $f(x) = 1/(b\text{-}a)$
- Mean and Variance:

$\mu = E(x) = (b+a)/2$

$\sigma^2 = V(x) = (b\text{-}a)^2/12$

X is a continuous random variable with a uniform distribution between 0 and 3.

What is Probability(X=1)?

A. 1/4
B. 1/3
C. 0
D. Infinity
E. I have no idea

Get your i-clickers

X is a continuous random variable with a uniform distribution between 0 and 3.

What is $P(X=1)$?

A. 1/4
B. 1/3
C. 0
D. Infinity
E. I have no idea

Get your i-clickers

X is a continuous random variable with a uniform distribution between 0 and 3.

What is $P(X<1)$?

A. 1/4
B. 1/3
C. 0
D. Infinity
E. I have no idea

Get your i-clickers

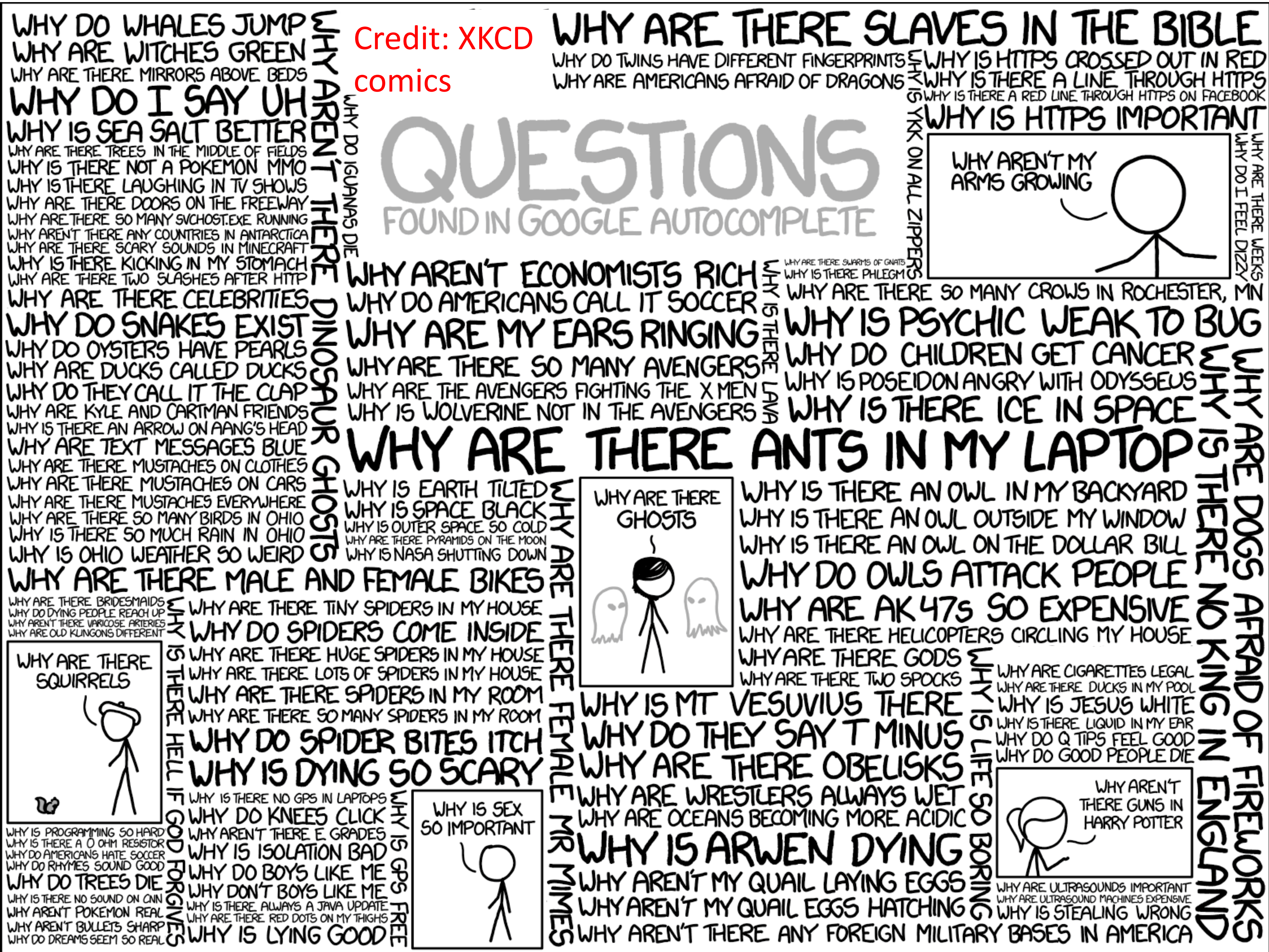
X is a continuous random variable with a uniform distribution between 0 and 3.

What is $P(X<1)$?

A. 1/4
B. $\boxed{1/3}$
C. 0
D. Infinity
E. I have no idea

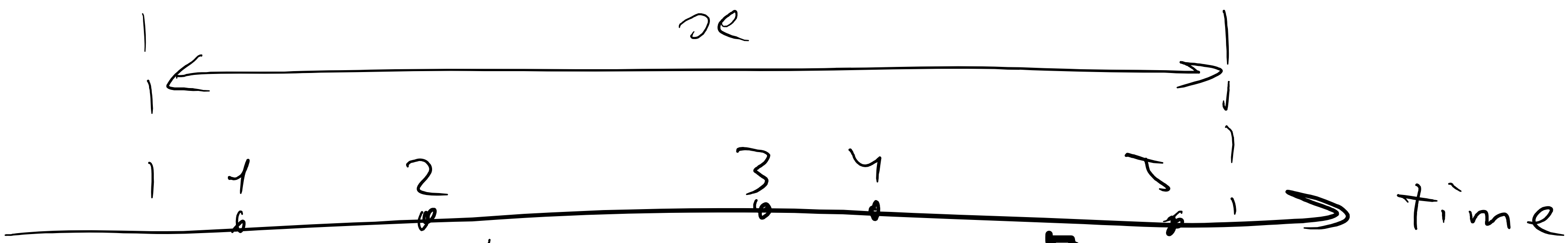
Get your i-clickers

Credit: XKCD comics



Constant rate (Poisson) process

Constant rate (Poisson) process



discrete events happen at rate Γ

Expected number of events in time x is Γx

The actual number of events N_x is a Poisson distributed discrete random variable

$$\boxed{P(N_x = n) = \frac{(\Gamma x)^n}{n!} e^{-\Gamma x}}$$

Why Poisson? Divide x into many tiny intervals of length Δx

$p = \Gamma \Delta x$

$L = x/\Delta x$

$E(N_x) = pL = \Gamma x$

$$\text{Prob}(N = n) = \binom{L}{n} p^n (1-p)^{L-n}$$

$\downarrow$ $\quad p \sim \Delta x \to 0, \; L \sim 1/\Delta x \to \infty$

Poisson

Constant rate (AKA Poisson) processes

- Let's assume that proteins are produced by ribosomes in the cell at a rate r per second.
- The expected number of proteins produced in x seconds is $r \cdot x$.
- The actual number of proteins N_x is a discrete random variable following a Poisson distribution with mean $r \cdot x$:

$$P_N(N_x=n)=\exp(-r\cdot x)(r\cdot x)^n/n! \qquad E(N_x)= rx$$

- Why Discrete Poisson Distribution?
  - Divide time into many tiny intervals of length $\Delta x \ll 1/r$
  - The probability of success (protein production) per internal is small: $p\_success=r\Delta x \ll 1$,
  - The number of intervals is large: $n= x/\Delta x \gg 1$
  - Mean is constant: $r=E(N_x)=p\_success \cdot n= r\Delta x \cdot x/\Delta x = r\cdot x$
  - In the limit $\Delta x \ll x$, p_success is small and n is large, thus Binomial distribution → Poisson distribution

Exponential Distribution Definition

Exponential random variable X describes interval between two successes of a constant rate (Poisson) random process with success rate r per unit interval.

The probability density function of X is:

$$f(x) = re^{-rx} \quad \text{for} \quad 0 \leq x < \infty$$

Closely related to the discrete geometric distribution

$$f(x) = p(1-p)^{x-1} = \mathrm{p}\, \mathrm{e}^{(\mathrm{x}-1)\ln(1-\mathrm{p})} \approx \mathrm{p}e^{-\mathrm{px}} \quad \text{for small p}$$

To summarize constant rate processes:

r - rate per unit of time length 1D

$N(x)$ — disrete number of events in time x

Poisson: $\boxed{P(N(x)=n) = \frac{(r \cdot x)^n}{n!} e^{-r \cdot x}}$

Time interval X between successive events is a continuously distributed random variable

Its PDF is $\boxed{f(x) = e^{-rx}}$

What is the interval X between two successes of a constant rate process?

- X is a continuous random variable
- CCDF: $P_X(X>x) = P_N(N_X=0) = \exp(-r \cdot x)$.
  - Remember: $P_N(N_X=n) = \exp(-r \cdot x)\,(r \cdot x)^n/n!$
- PDF: $f_X(x) = -dCCDF_X(x)/dx = r \cdot \exp(-r \cdot x)$
- We started with a discrete Poisson distribution where time x was a parameter
- We ended up with a continuous exponential distribution

Exponential Mean & Variance

If the random variable X has an exponential distribution with rate r,

$$\mu = E(X) = \frac{1}{r} \quad \text{and} \quad \sigma^2 = V(X) = \frac{1}{r^2} \qquad (4\text{–}15)$$

Note that, for the:

- Poisson distribution: mean= variance
- Exponential distribution: mean = standard

deviation = variance$^{0.5}$