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

- Probability Mass Function (PMF)
- ***Cumulative Distribution Function (CDF)***
- ***Complementary Cumulative Distribution Function (CCDF)***
- ***Expected value***
- ***Mean***
- ***Variance***
- ***Standard deviation***
- ***Skewness***

Boldface and underlined are the same for continuous distributions

What distributions did we learn?

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

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. 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

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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

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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

Why do we need to know these simple distributions?

Ways to use probability and 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

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

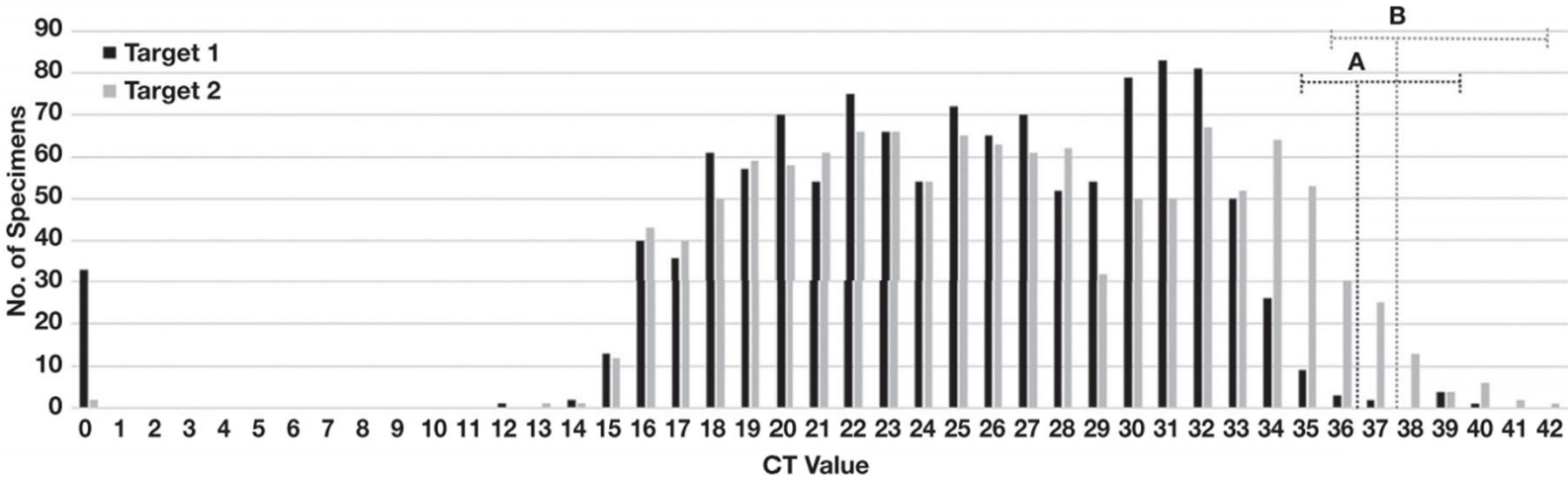


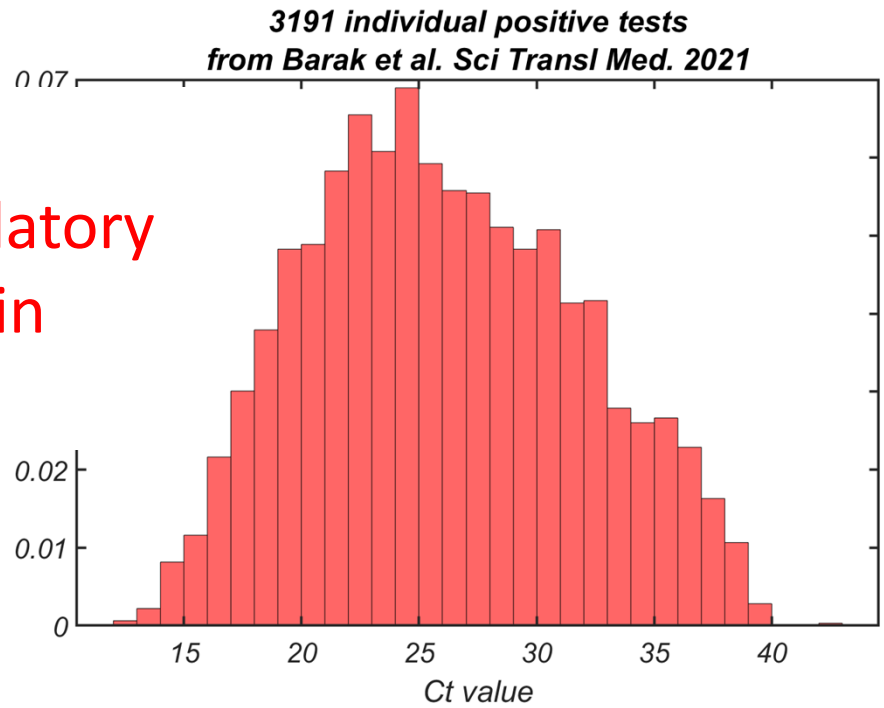
Figure 3 Distribution of cycle threshold (CT) values. The total number of specimens with indicated CT values for Target 1 and 2 are plotted. The estimated limit of detection for (A) Target 1 and (B) Target 2 are indicated by vertical dotted lines. Horizontal dotted lines encompass specimens with CT values 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

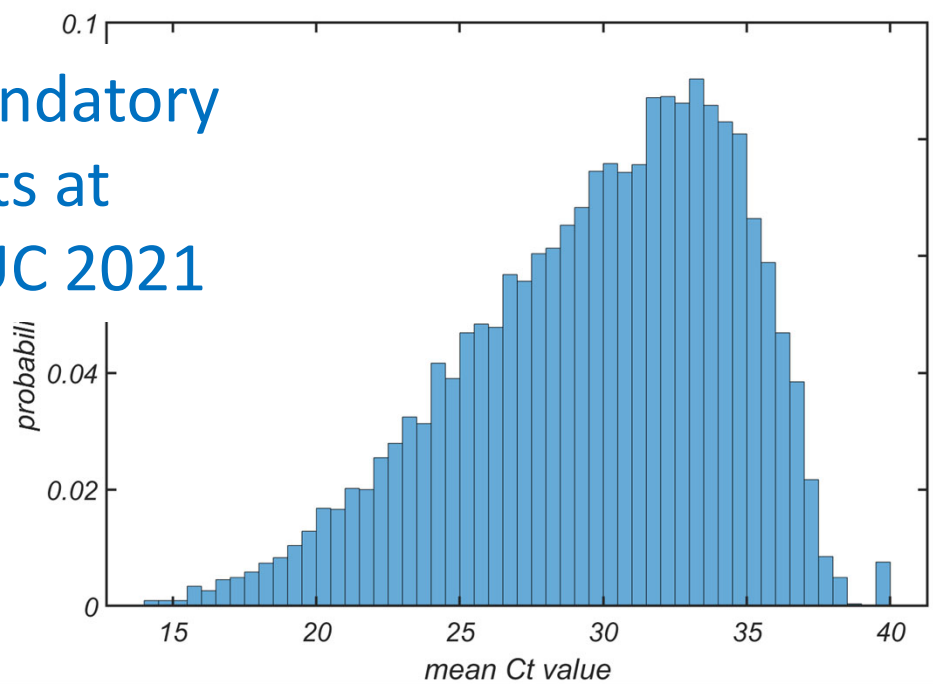
Blake W Buchan, PhD, Jessica S Hoff, PhD, Cameron G Gmehlin, Adriana Perez, Matthew L Faron, PhD, L Silvia Munoz-Price, MD, PhD, Nathan A Ledeboer, PhD *American Journal of Clinical Pathology*, Volume 154, Issue 4, 1 October 2020, https://academic.oup.com/ajcp/article/154/4/479/5873820

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

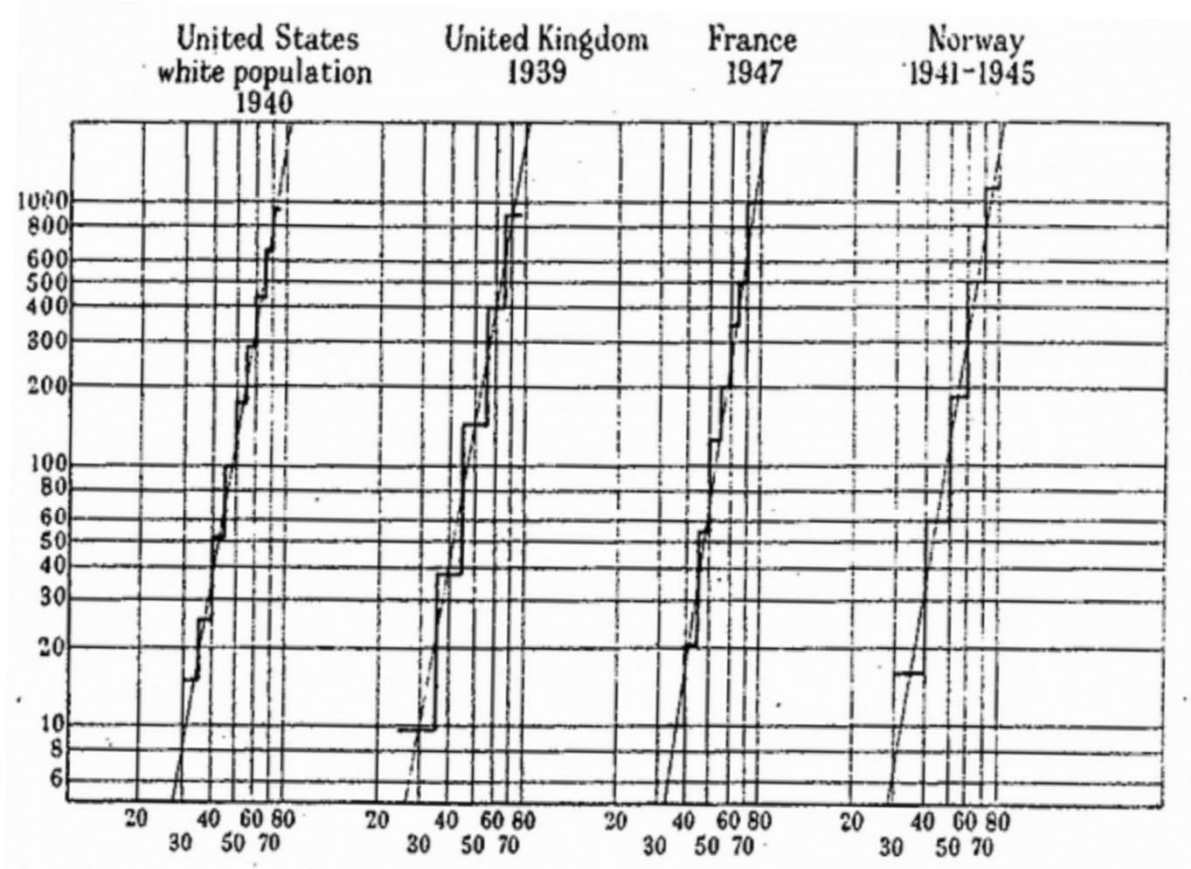


FIG. 1.—Diagram drawn to double logarithmic (log/log) scale showing the cancer death-rate (in the case of the United Kingdom, the carcinoma death-rate) in males at different ages. Deaths per 100,000 males are shown on the vertical scale, age figures on the horizontal scale.

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

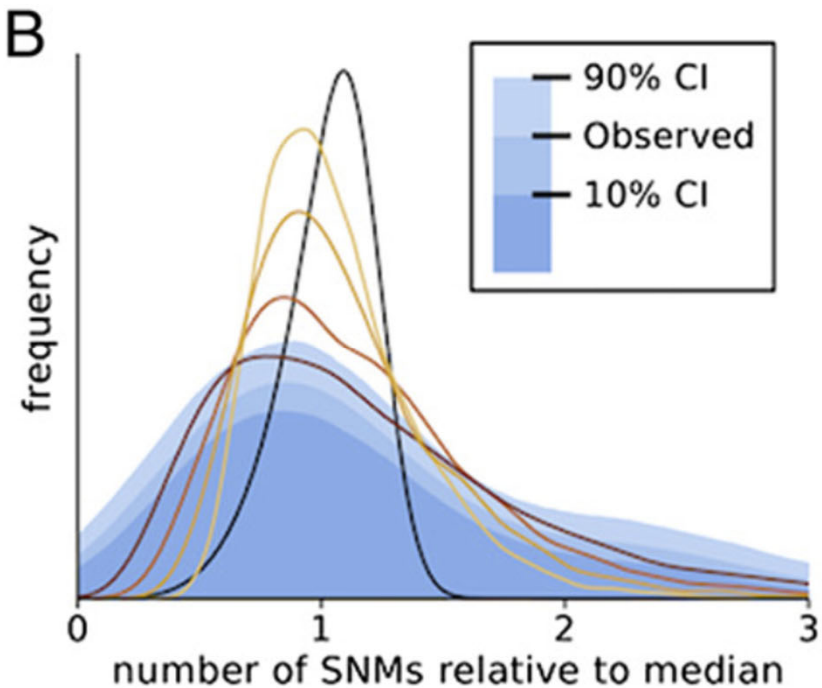
Cancer death rate
~ (patient age)^6

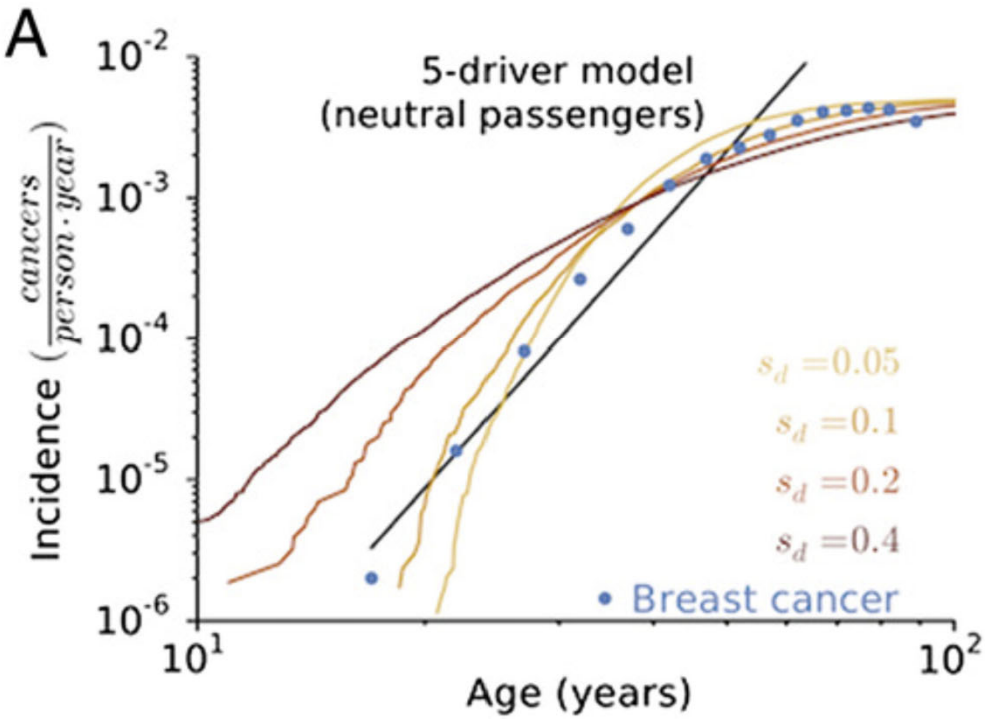
It suggests the existence of
k=7 driver genes

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

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

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 government)
- 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
- In 2024 he was awarded $400,000 Merkin Prize in Biomedical Technology (Broad Institute of MIT and Harvard) "for development of widely used protein- and RNA-production platform" https://merkinprize.org/2024-pr

K-12 and B are the most common lab strains of E. coli

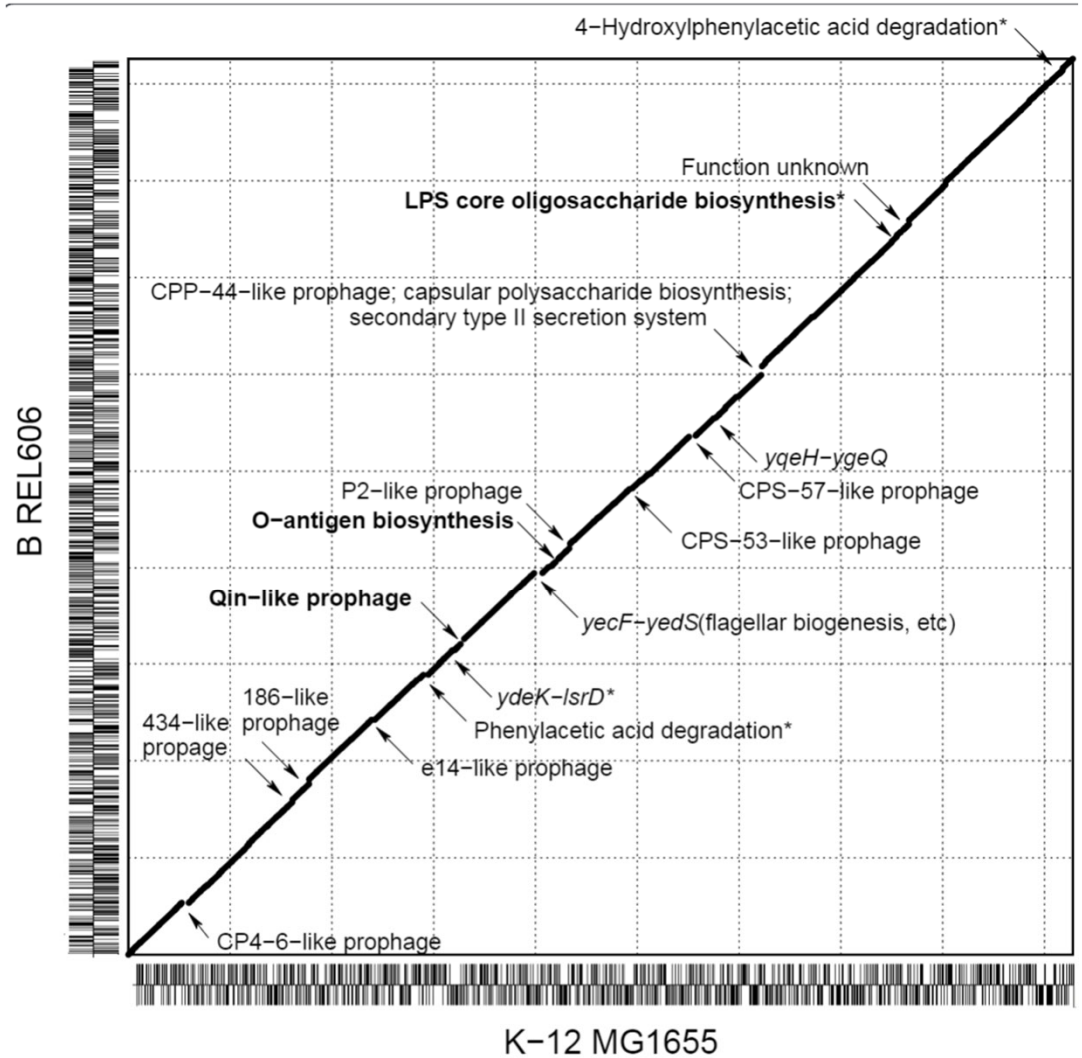


Figure 1 Whole genome comparison of *E. coli* B REL606 and *E. coli* K-12 MG1655. Strain-specific regions are indicated by discontinuities or the diagonal line (those >10 kb are marked by arrows). Short vertical lines on each axis represent coding sequences that reside on the forward or reverse strand. Segments that occupy the same location on each genome and encode equivalent functions but are highly dissimilar are shown in bold. Except for those marked with asterisks, all the strain-specific regions coincide with genomic islands that were identified by genomic anomalies. Ticks are marked every 500 kb.

- B strain can be traced back to d'Hérelle(Lambda-phage), Pasteur Institute, Delbruck, Rockefeller U., Studier and Rich Lenski LTEE
- K-12 was isolated in 1922 at Palo Alto hospital. First sequenced genome
- Both have ~4000 genes in roughly the same order

Yoon *et al. Genome Biology* 2012, **13**:R37
http://genomebiology.com/2012/13/5/R37

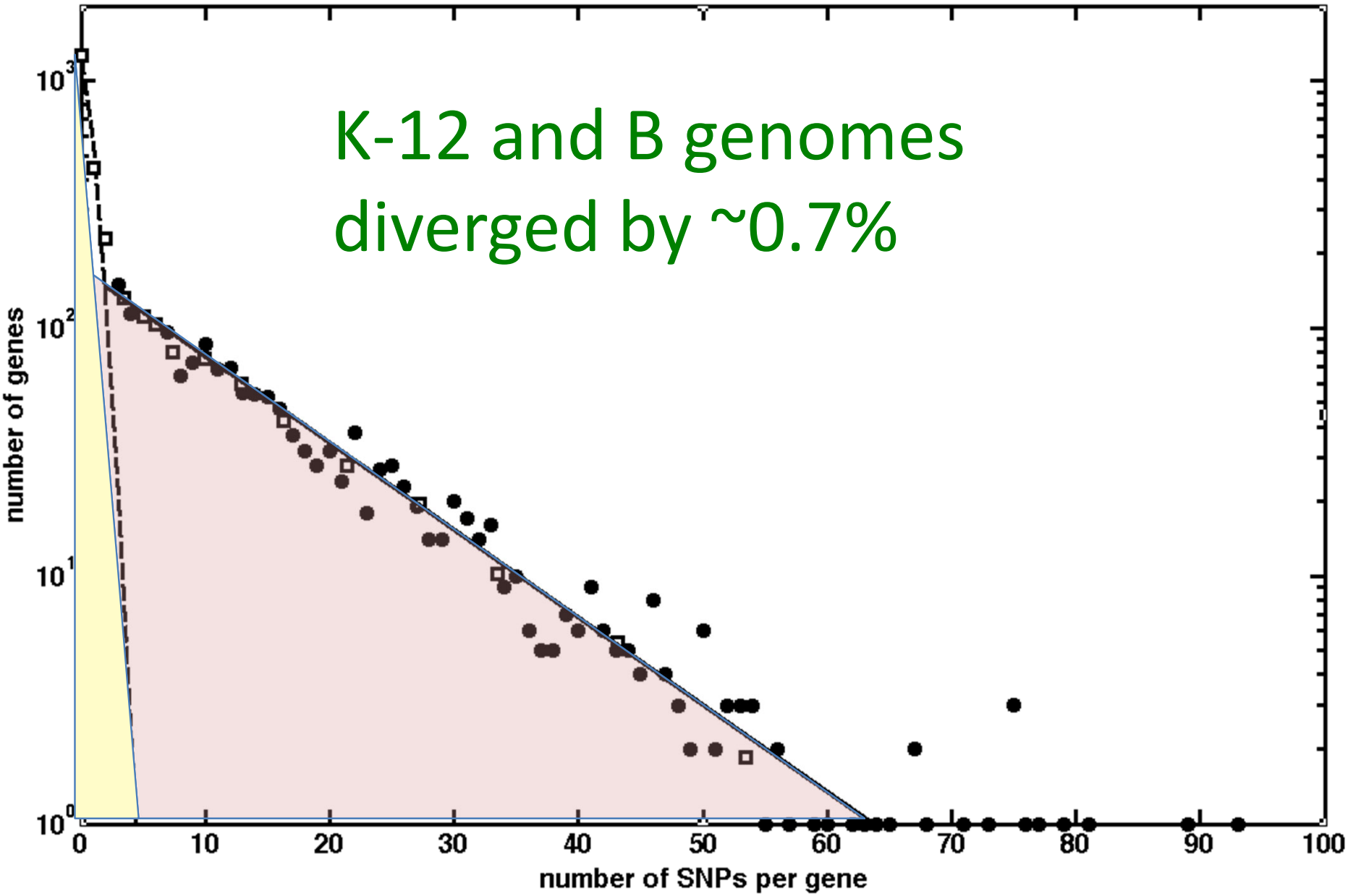
Genome Biology

RESEARCH Open Access

Comparative multi-omics systems analysis of *Escherichia coli* strains B and K-12

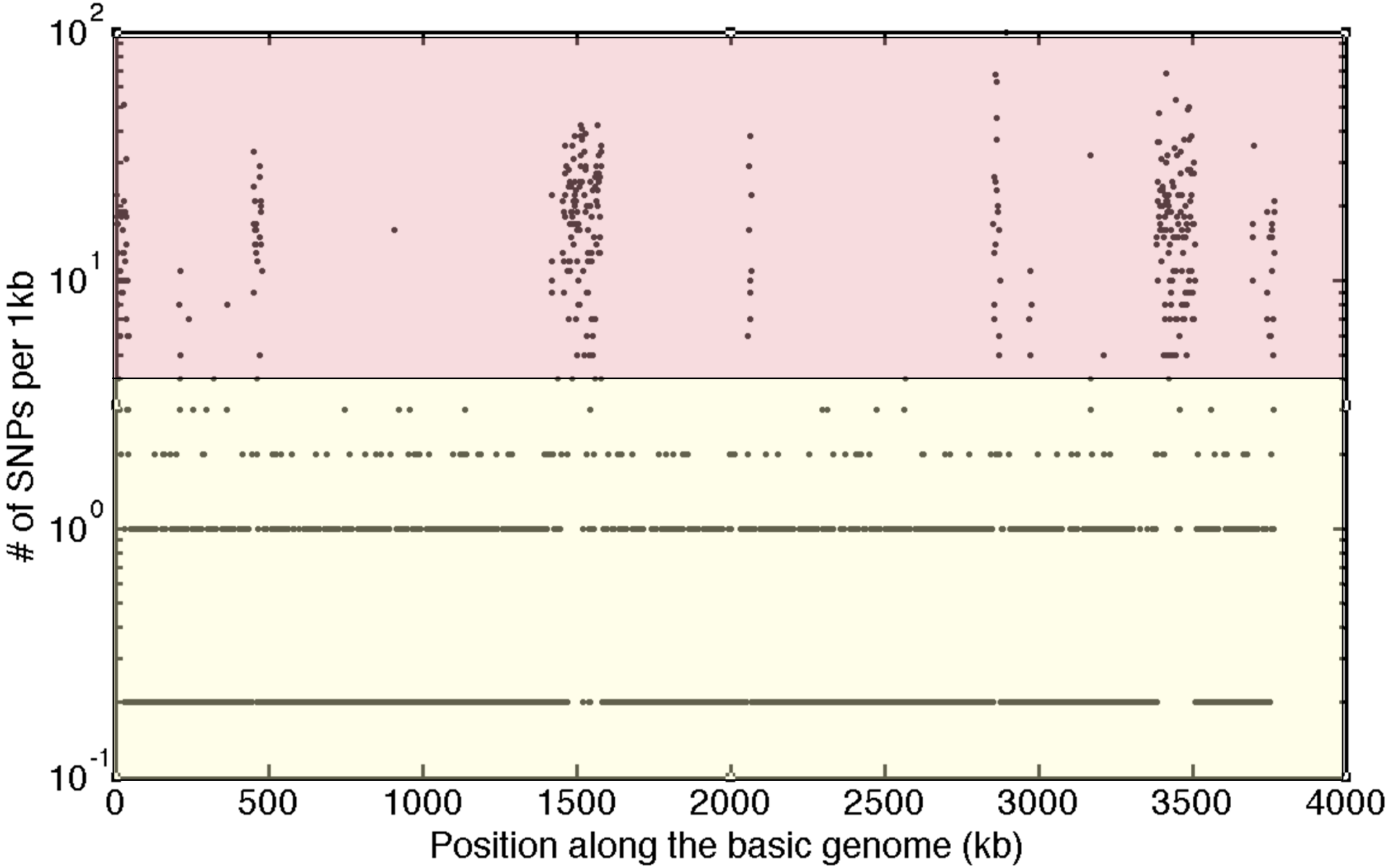
Sung Ho Yoon[1], Mee-Jung Han[2,3], Haeyoung Jeong[1], Choong Hoon Lee[1,4,5], Xiao-Xia Xia[2], Dae-Hee Lee[1], Ji Hoon Shim[1], Sang Yup Lee[2,6], Tae Kwang Oh[7] and Jihyun F Kim[1,5*]

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



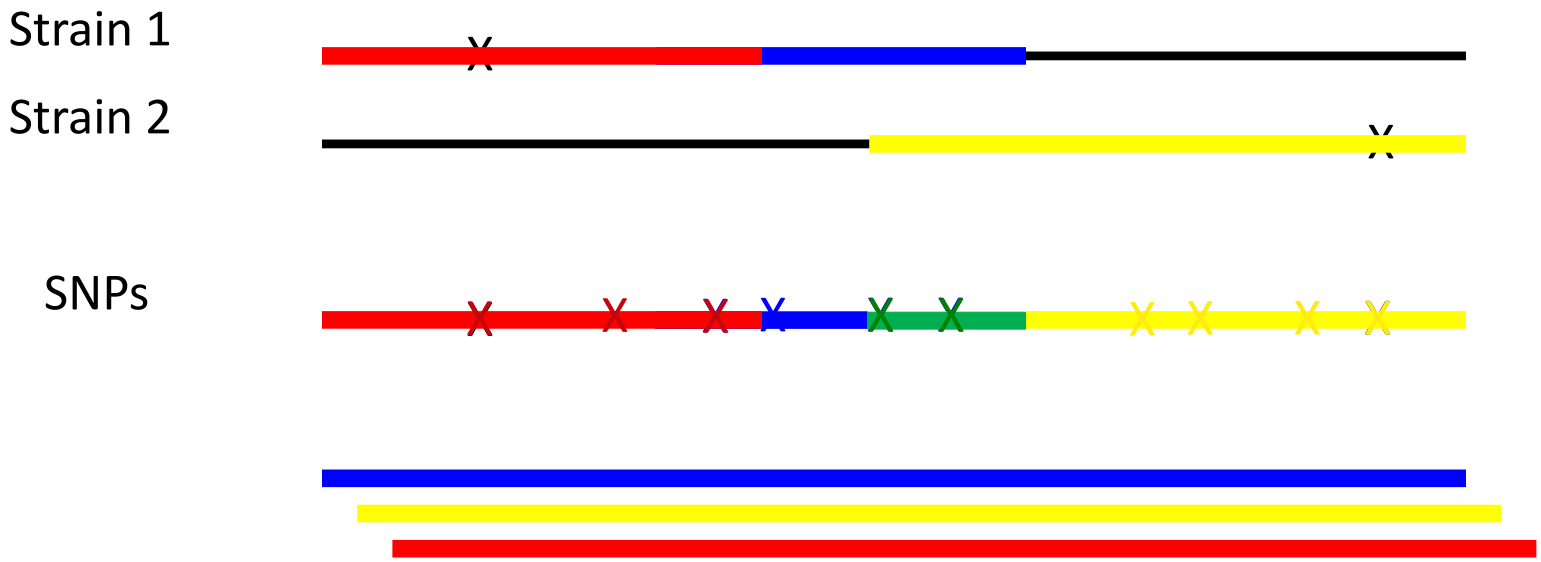
Studier FW, Daegelen P, Lenski RE, **Maslov S**, Kim JF, J. Mol Biol. (2009)

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)=$(1- \delta)^{2L}$=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

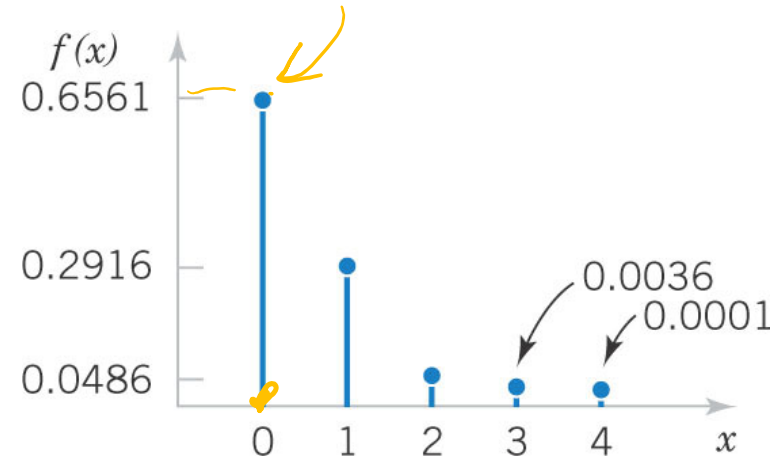
Uniform Distribution

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
$\sum_x$ P(X=x)=	1.0000

Probability Density Function (PDF)

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

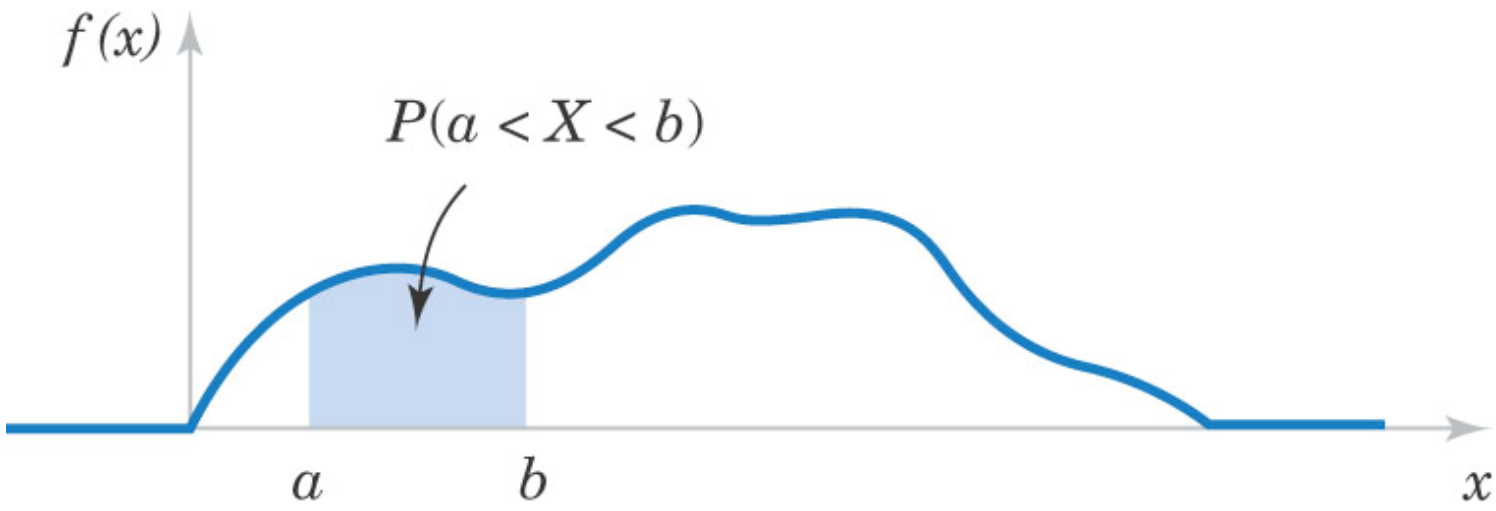


Figure 4-2 Probability is determined from the area under $f(x)$ from a to b.

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

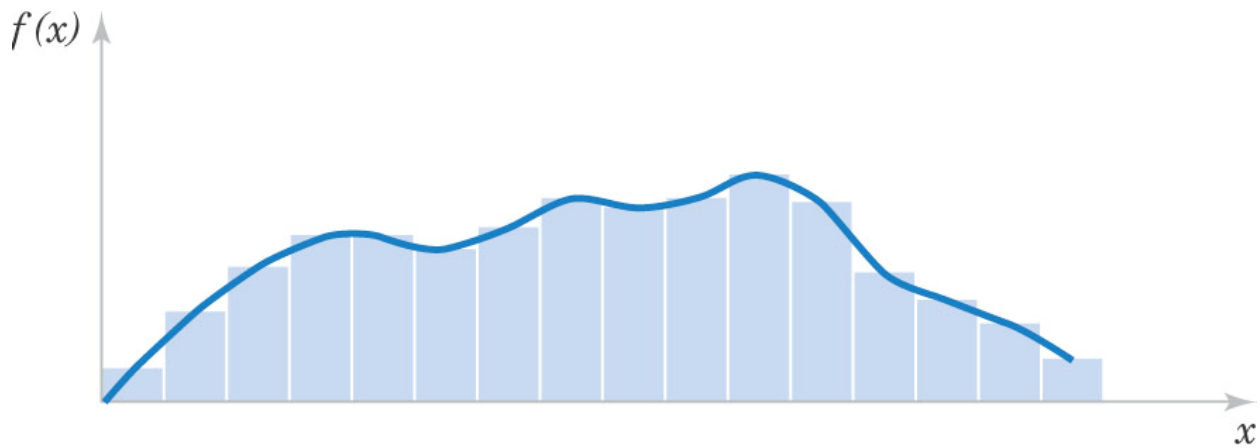
Normalized histogram approximates PDF

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,

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

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

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

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

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

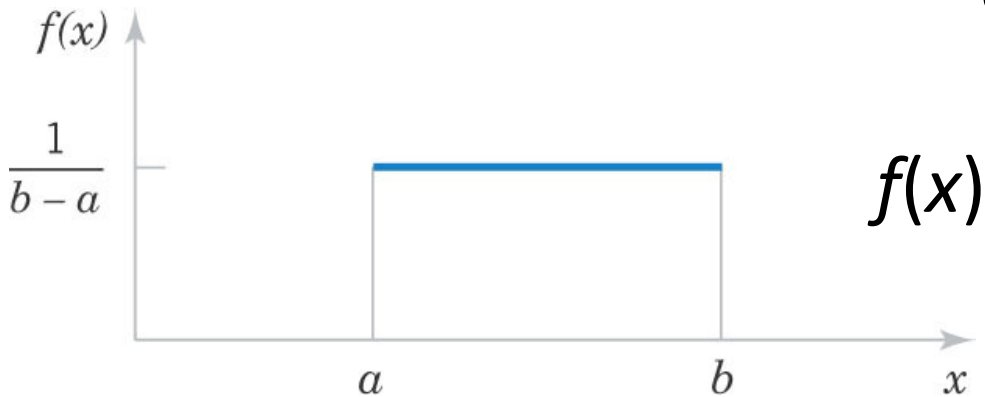


Figure 4-8 Continuous uniform PDF

Comparison between Discrete & Continuous Uniform Distributions

Discrete:

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

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

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

Continuous:

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

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

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

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

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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

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Get your i-clickers

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

What is the skeweness of X?

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

Get your i-clickers

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C. 0
D. Infinity
E. I have no idea

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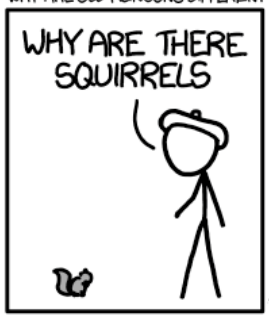
Credit: XKCD comics

QUESTIONS
FOUND IN GOOGLE AUTOCOMPLETE

WHY DO WHALES JUMP
WHY ARE WITCHES GREEN
WHY ARE THERE MIRRORS ABOVE BEDS
WHY DO I SAY UH
WHY IS SEA SALT BETTER
WHY ARE THERE TREES IN THE MIDDLE OF FIELDS
WHY IS THERE NOT A POKEMON MMO
WHY IS THERE LAUGHING IN TV SHOWS
WHY ARE THERE DOORS ON THE FREEWAY
WHY ARE THERE SO MANY SVCHOST.EXE RUNNING
WHY AREN'T THERE ANY COUNTRIES IN ANTARCTICA
WHY ARE THERE SCARY SOUNDS IN MINECRAFT
WHY IS THERE KICKING IN MY STOMACH
WHY ARE THERE TWO SLASHES AFTER HTTP
WHY ARE THERE CELEBRITIES
WHY DO SNAKES EXIST
WHY DO OYSTERS HAVE PEARLS
WHY ARE DUCKS CALLED DUCKS
WHY DO THEY CALL IT THE CLAP
WHY ARE KYLE AND CARTMAN FRIENDS
WHY IS THERE AN ARROW ON AANG'S HEAD
WHY ARE TEXT MESSAGES BLUE
WHY ARE THERE MUSTACHES ON CLOTHES
WHY ARE THERE MUSTACHES ON CARS
WHY ARE THERE MUSTACHES EVERYWHERE
WHY ARE THERE SO MANY BIRDS IN OHIO
WHY IS THERE SO MUCH RAIN IN OHIO
WHY IS OHIO WEATHER SO WEIRD
WHY ARE THERE MALE AND FEMALE BIKES
WHY ARE THERE BRIDESMAIDS
WHY DO DYING PEOPLE REACH UP
WHY AREN'T THERE VARICOSE ARTERIES
WHY ARE OLD KLINGONS DIFFERENT

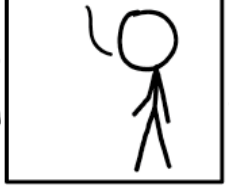
WHY ARE THERE SQUIRRELS



WHY IS PROGRAMMING SO HARD
WHY IS THERE A 0 OHM RESISTOR
WHY DO AMERICANS HATE SOCCER
WHY DO RHYMES SOUND GOOD
WHY DO TREES DIE
WHY IS THERE NO SOUND ON CNN
WHY AREN'T POKEMON REAL
WHY AREN'T BULLETS SHARP
WHY DO DREAMS SEEM SO REAL

WHY ARE THERE TINY SPIDERS IN MY HOUSE
WHY DO SPIDERS COME INSIDE
WHY ARE THERE HUGE SPIDERS IN MY HOUSE
WHY ARE THERE LOTS OF SPIDERS IN MY HOUSE
WHY ARE THERE SPIDERS IN MY ROOM
WHY ARE THERE SO MANY SPIDERS IN MY ROOM
WHY DO SPIDER BITES ITCH
WHY IS DYING SO SCARY
WHY IS THERE NO GPS IN LAPTOPS
WHY DO KNEES CLICK
WHY AREN'T THERE E GRADES
WHY IS ISOLATION BAD
WHY DO BOYS LIKE ME
WHY DON'T BOYS LIKE ME
WHY IS THERE ALWAYS A JAVA UPDATE
WHY ARE THERE RED DOTS ON MY THIGHS
WHY IS LYING GOOD

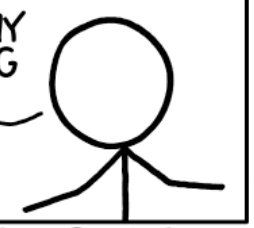
WHY IS SEX SO IMPORTANT



WHY DO IGUANAS DIE
WHY ARE THERE DINOSAUR GHOSTS
WHY IS THERE HELL IF GOD FORGIVES
WHY IS GPS FREE

WHY ARE THERE SLAVES IN THE BIBLE
WHY DO TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY IS HTTPS CROSSED OUT IN RED
WHY IS THERE A LINE THROUGH HTTPS
WHY IS THERE A RED LINE THROUGH HTTPS ON FACEBOOK
WHY IS HTTPS IMPORTANT
WHY IS YKK ON ALL ZIPPERS

WHY AREN'T MY ARMS GROWING



WHY ARE THERE WEEKS
WHY DO I FEEL DIZZY
WHY ARE THERE SWARMS OF GNATS
WHY IS THERE PHLEGM
WHY AREN'T ECONOMISTS RICH
WHY DO AMERICANS CALL IT SOCCER
WHY ARE MY EARS RINGING
WHY ARE THERE SO MANY AVENGERS
WHY ARE THE AVENGERS FIGHTING THE X MEN
WHY IS WOLVERINE NOT IN THE AVENGERS
WHY IS THERE LAVA
WHY ARE THERE SO MANY CROWS IN ROCHESTER, MN
WHY IS PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE
WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND
WHY ARE THERE ANTS IN MY LAPTOP
WHY IS EARTH TILTED
WHY IS SPACE BLACK
WHY IS OUTER SPACE SO COLD
WHY ARE THERE PYRAMIDS ON THE MOON
WHY IS NASA SHUTTING DOWN
WHY ARE THERE FEMALE MR MIMES

WHY ARE THERE GHOSTS

WHY IS THERE AN OWL IN MY BACKYARD
WHY IS THERE AN OWL OUTSIDE MY WINDOW
WHY IS THERE AN OWL ON THE DOLLAR BILL
WHY DO OWLS ATTACK PEOPLE
WHY ARE AK 47s SO EXPENSIVE
WHY ARE THERE HELICOPTERS CIRCLING MY HOUSE
WHY ARE THERE GODS
WHY ARE THERE TWO SPOCKS
WHY IS MT VESUVIUS THERE
WHY DO THEY SAY T MINUS
WHY ARE THERE OBELISKS
WHY ARE WRESTLERS ALWAYS WET
WHY ARE OCEANS BECOMING MORE ACIDIC
WHY IS ARWEN DYING
WHY AREN'T MY QUAIL LAYING EGGS
WHY AREN'T MY QUAIL EGGS HATCHING
WHY AREN'T THERE ANY FOREIGN MILITARY BASES IN AMERICA
WHY IS LIFE SO BORING
WHY ARE CIGARETTES LEGAL
WHY ARE THERE DUCKS IN MY POOL
WHY IS JESUS WHITE
WHY IS THERE LIQUID IN MY EAR
WHY DO Q TIPS FEEL GOOD
WHY DO GOOD PEOPLE DIE

WHY AREN'T THERE GUNS IN HARRY POTTER

WHY ARE ULTRASOUNDS IMPORTANT
WHY ARE ULTRASOUND MACHINES EXPENSIVE
WHY IS STEALING WRONG