Statistics of cancer incidence vs age

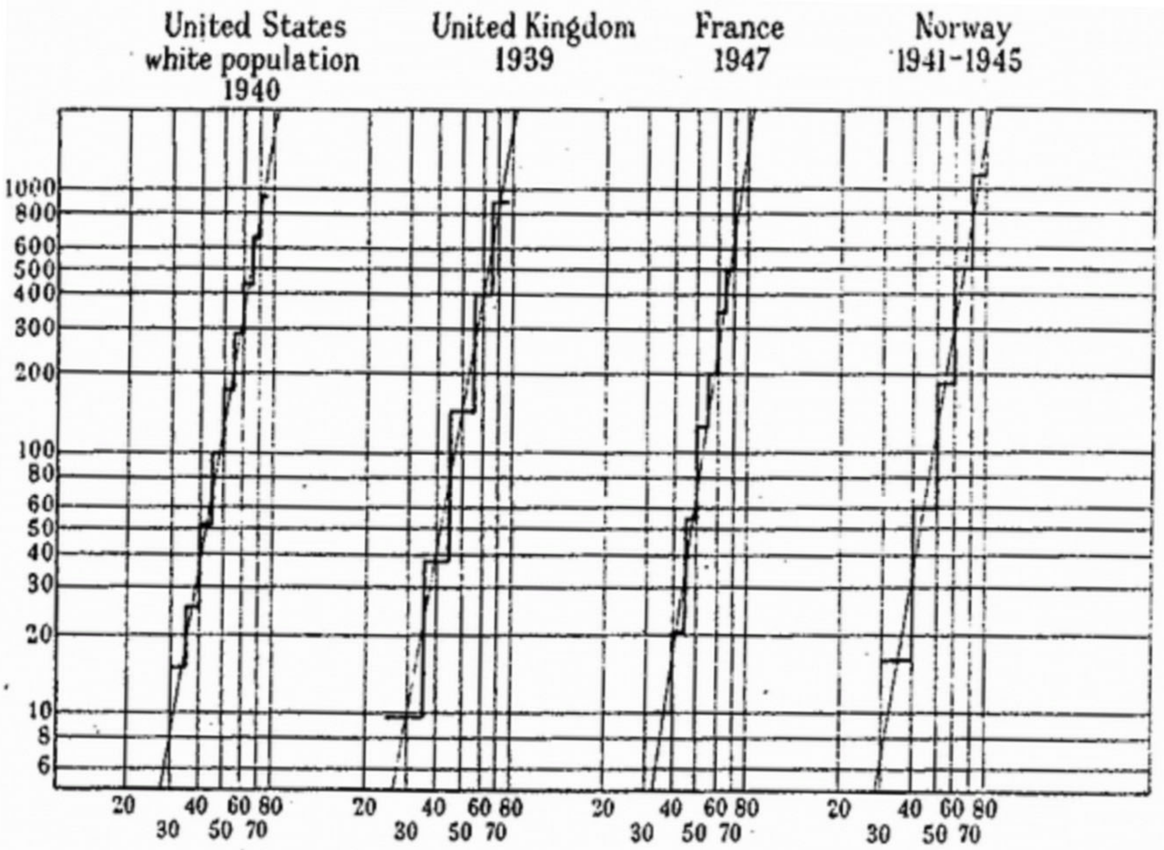


Fig. 1.—Diagram drawn to double logarithmic (log/log) scale showing the cancer death-rate (in the case of the United Kingdom, the carcinoma death-rate) in males at different ages. Deaths per 100,000 males are shown on the vertical scale, age figures on the horizontal scale.

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

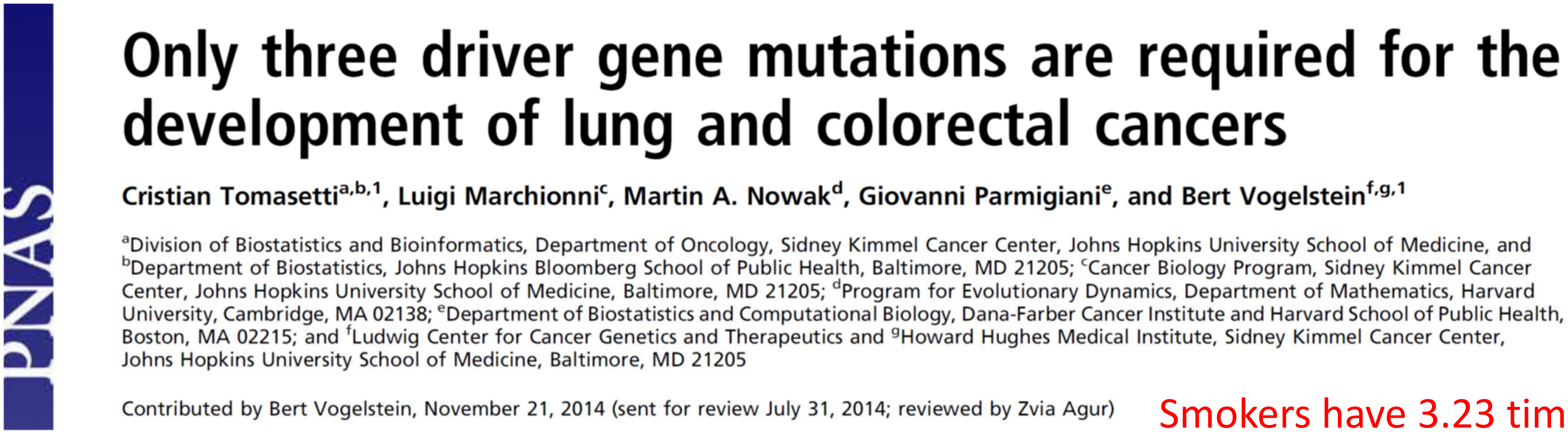
Cancer death rate $\sim$ (patient age)^6

It suggests the existence of k=7 driver genes

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

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

How many driver gene mutations for different types of cancer?



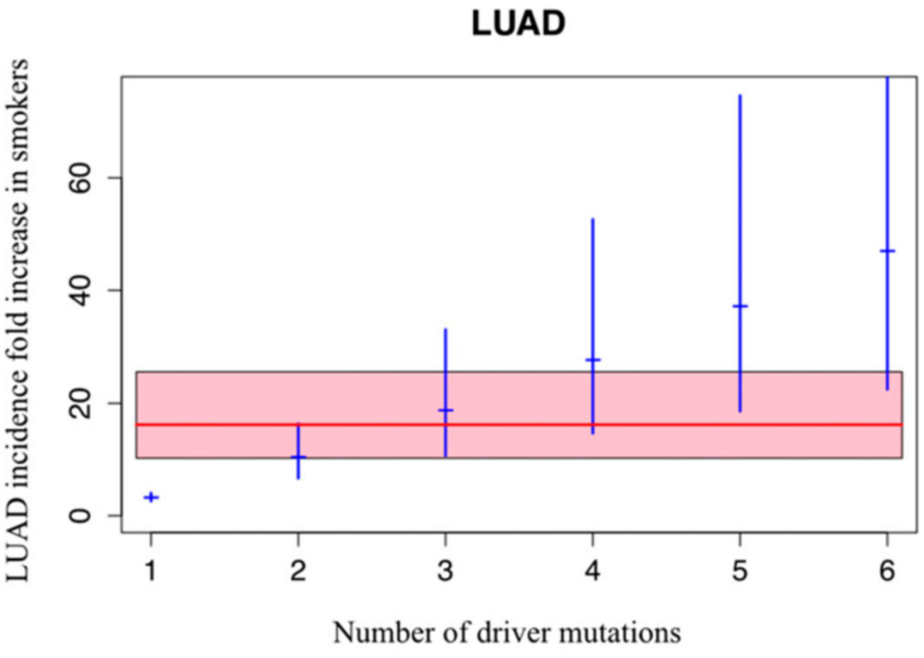
Only three driver gene mutations are required for the development of lung and colorectal cancers

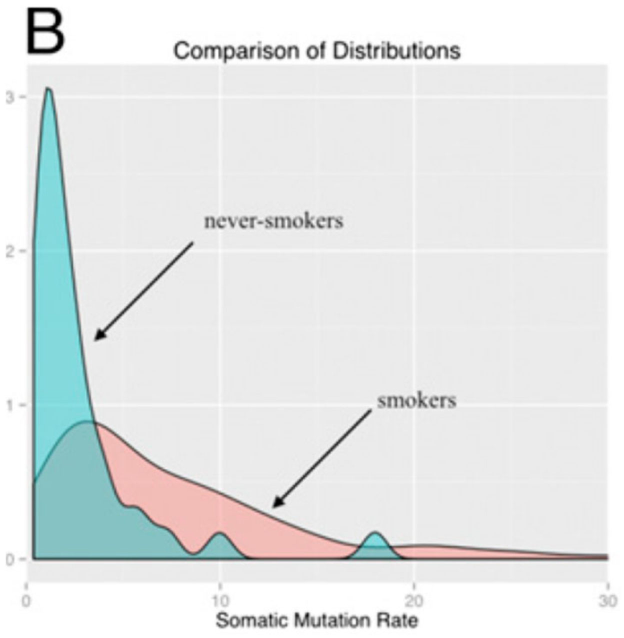
Cristian Tomasetti[a,b,1], Luigi Marchionni[c], Martin A. Nowak[d], Giovanni Parmigiani[e], and Bert Vogelstein[f,g,1]

[a]Division of Biostatistics and Bioinformatics, Department of Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, and [b]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; [c]Cancer Biology Program, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205; [d]Program for Evolutionary Dynamics, Department of Mathematics, Harvard University, Cambridge, MA 02138; [e]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, MA 02215; and [f]Ludwig Center for Cancer Genetics and Therapeutics and [g]Howard Hughes Medical Institute, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205

Contributed by Bert Vogelstein, November 21, 2014 (sent for review July 31, 2014; reviewed by Zvia Agur)

Smokers have 3.23 times more mutations in lungs





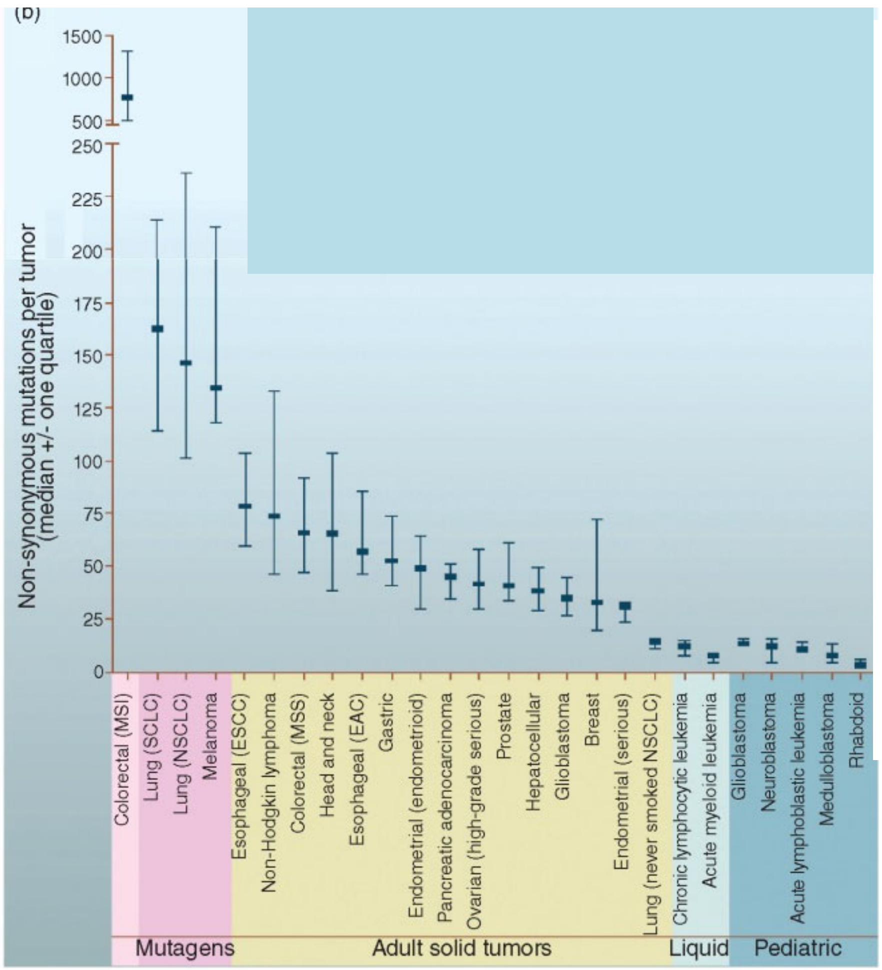
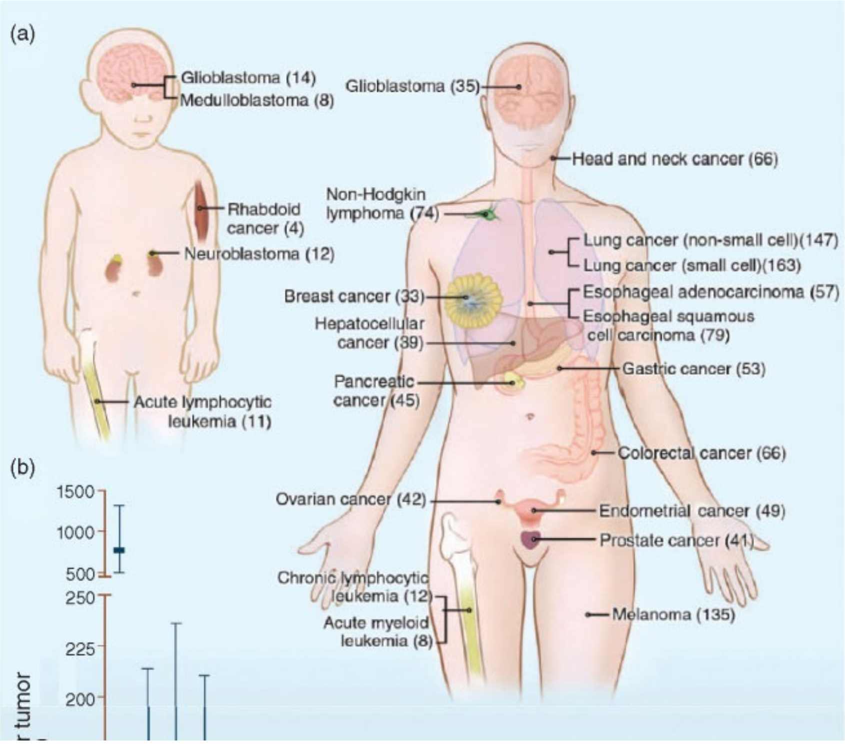


FIGURE 21.10 Somatic mutations in representative human cancers, based on genome-wide sequencing studies. (a) The genomes of adult (right) and pediatric (left) cancers are represented. Numbers in parentheses are the median number of nonsynonymous mutations per tumor. Redrawn from Vogelstein *et al.* (2013). Reproduced with permission from AAAS. (b) Median number of nonsynonymous substitutions per tumor. Horizonal bars indicate the 25% and 75% quartiles. MSI: microsatellite instability; SCLC: small cell lung cancers; NSCLC: non-small cell lung cancers; ESCC: esophageal squamous cell carcinomas; MSS: microsatellite stable; EAC: esophageal adenocarcinomas.

Bioinformatics and Functional Genomics, Third Edition, Jonathan Pevsner.

Companion Website: www.wiley.com/go/pevsnerbioinformatics



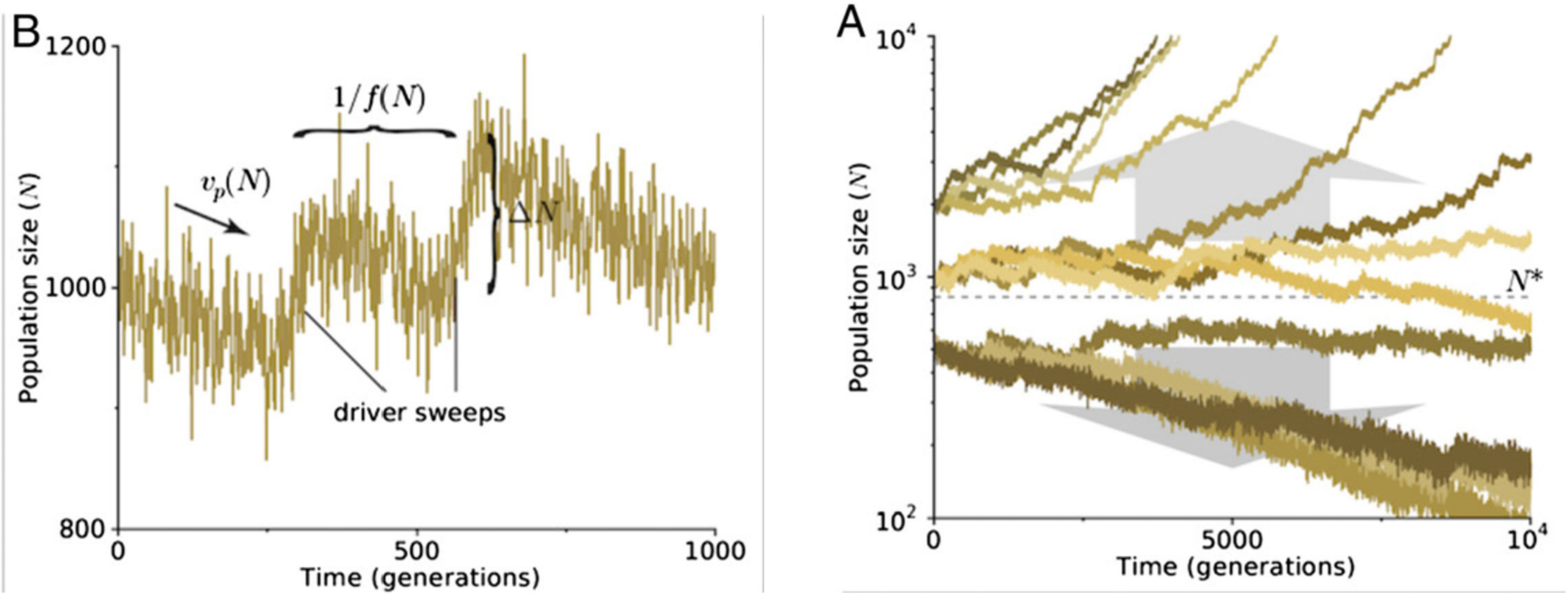
- Cancer cells carry both "Driver" and "Passengers" mutations
- Passenger mutations cause little to no harm (see later for how even little harm matters)
- Both are common as cancers elevate mutation rate

Number of passenger+driver mutations follows negative binomial distribution

- What is the probability to have n_p passenger mutations or (n_p+k) total mutations by the time you are diagnosed with cancer requiring k driver mutations?
- Let p is the probability that a mutation is a driver (p= Genome_target_of_driv/ (Genome_target_of_driv+Genome_target_of_pass) (1-p) – it is a passenger mutation

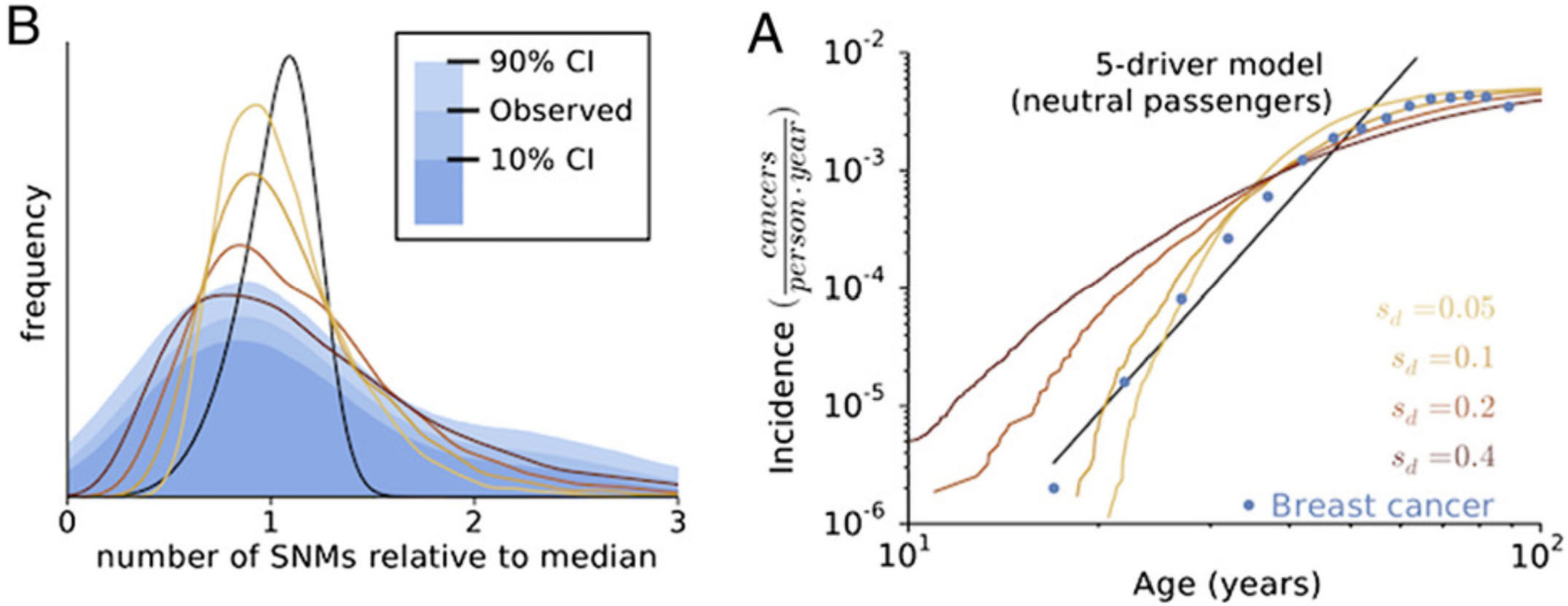
$$P(n_p + k \mid p, k) = \binom{n_p + k - 1}{n_p} (1 - p)^{n_p} p^k$$

What if passenger mutations slow down the growth of cancer tumors?



McFarland CD, Mirny L, Korolev KS, PNAS 2014

Can we prove/quantify it using statistics?



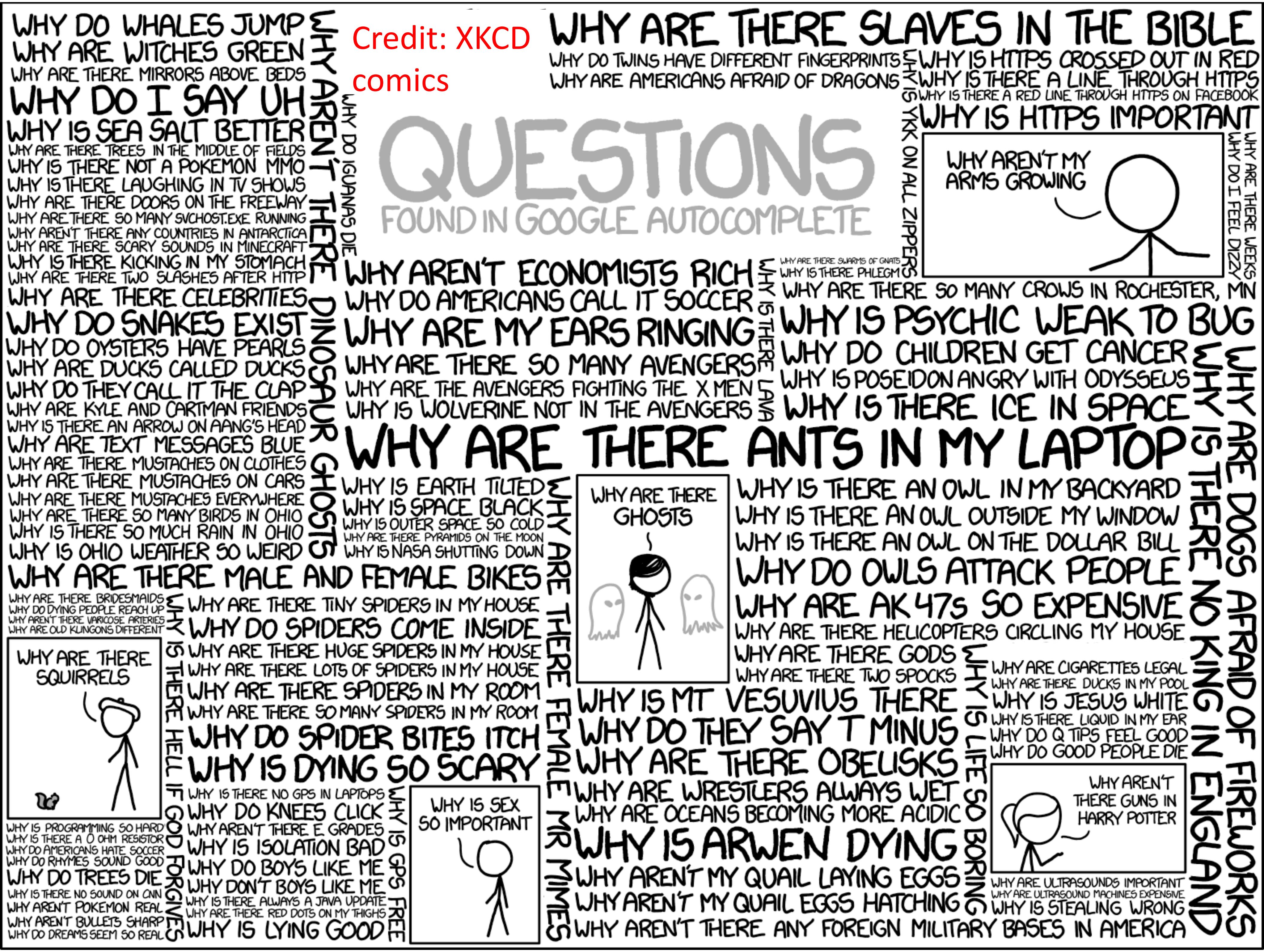
Assume: growth rate of cancer=$(1+s_d)^{Nd}/(1+s_p)^{Np}$

$\mu=10^{-8}$, 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



Credit: XKCD comics

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***

Boldface and underlined 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. 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
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Which distribution is this?

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Which distribution is this?

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

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Which distribution is this?

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A. Uniform
B. Binomial
C. Geometric
D. Negative Binomial
[✓ E. Poisson]

Get your i-clickers

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

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

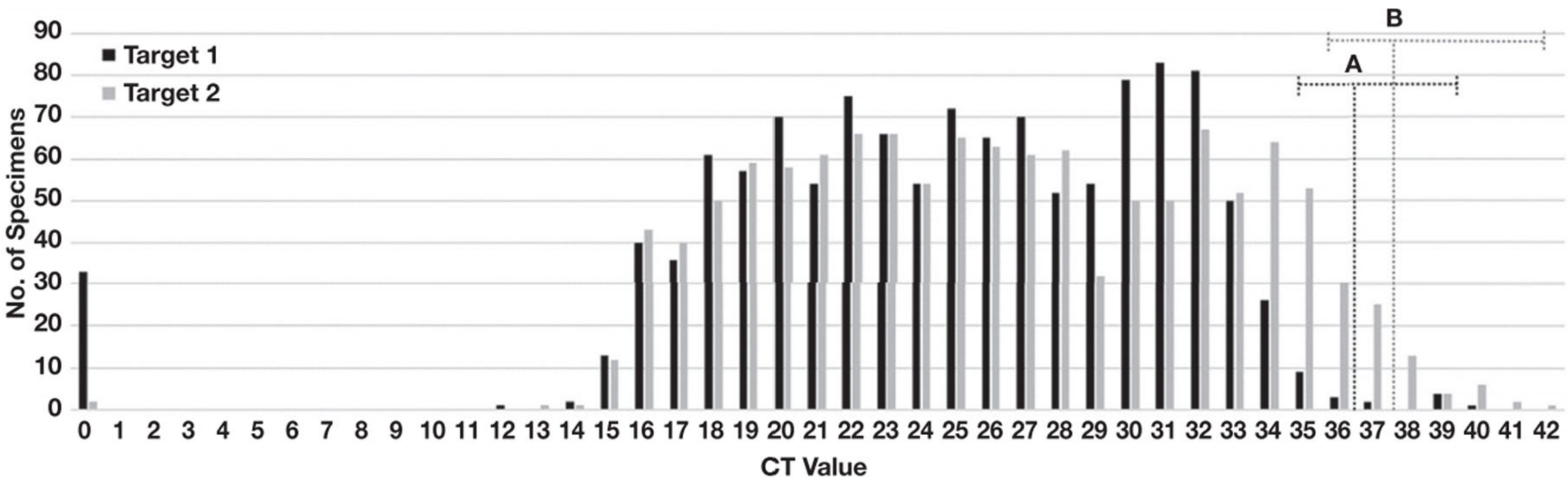
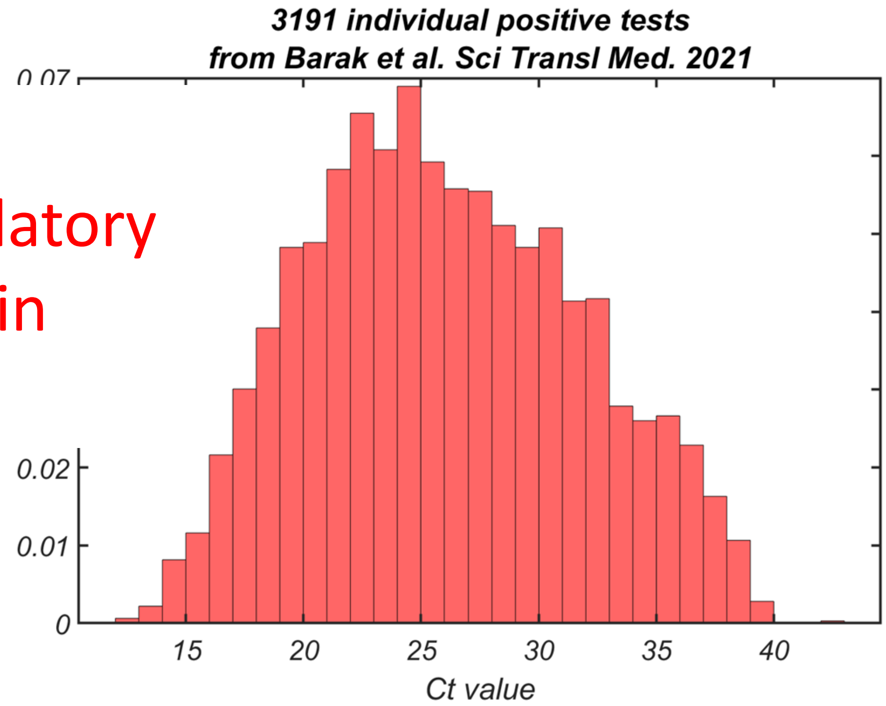


Figure 3 Distribution of cycle threshold (CT) values. The total number of specimens with indicated CT values for Target 1 and 2 are plotted. The estimated limit of detection for (A) Target 1 and (B) Target 2 are indicated by vertical dotted lines. Horizontal dotted lines encompass specimens with CT values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

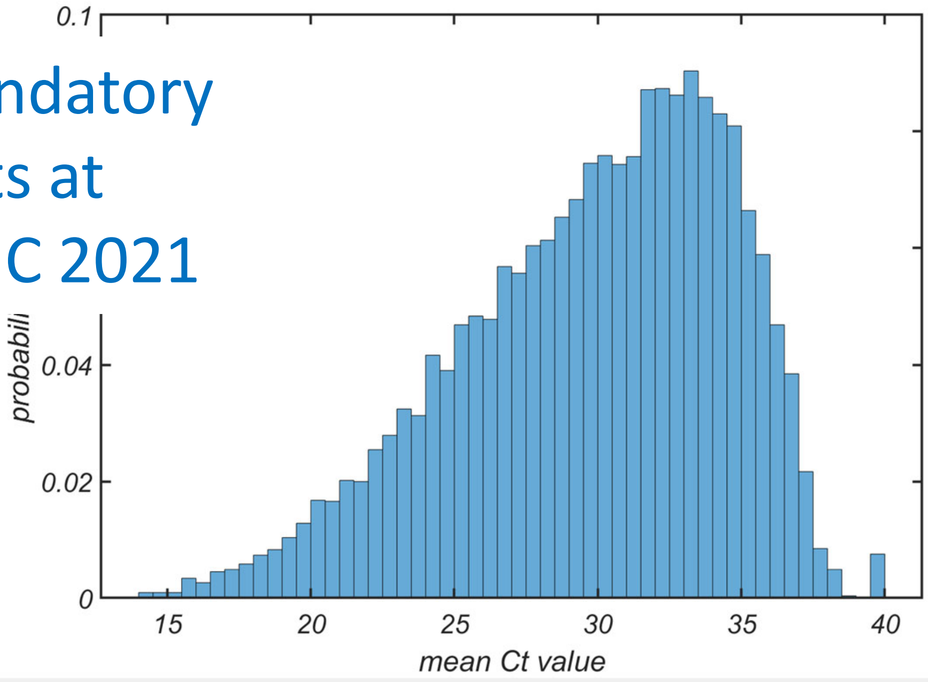
Distribution of SARS-CoV-2 PCR Cycle Threshold Values Provide Practical Insight Into Overall and Target-Specific Sensitivity Among Symptomatic Patients
Blake W Buchan, PhD, Jessica S Hoff, PhD, Cameron G Gmehlin, Adriana Perez, Matthew L Faron, PhD, L Silvia Munoz-Price, MD, PhD, Nathan A Ledeboer, PhD *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


3191 individual positive tests
from Barak et al. Sci Transl Med. 2021

Mandatory tests at UIUC 2021

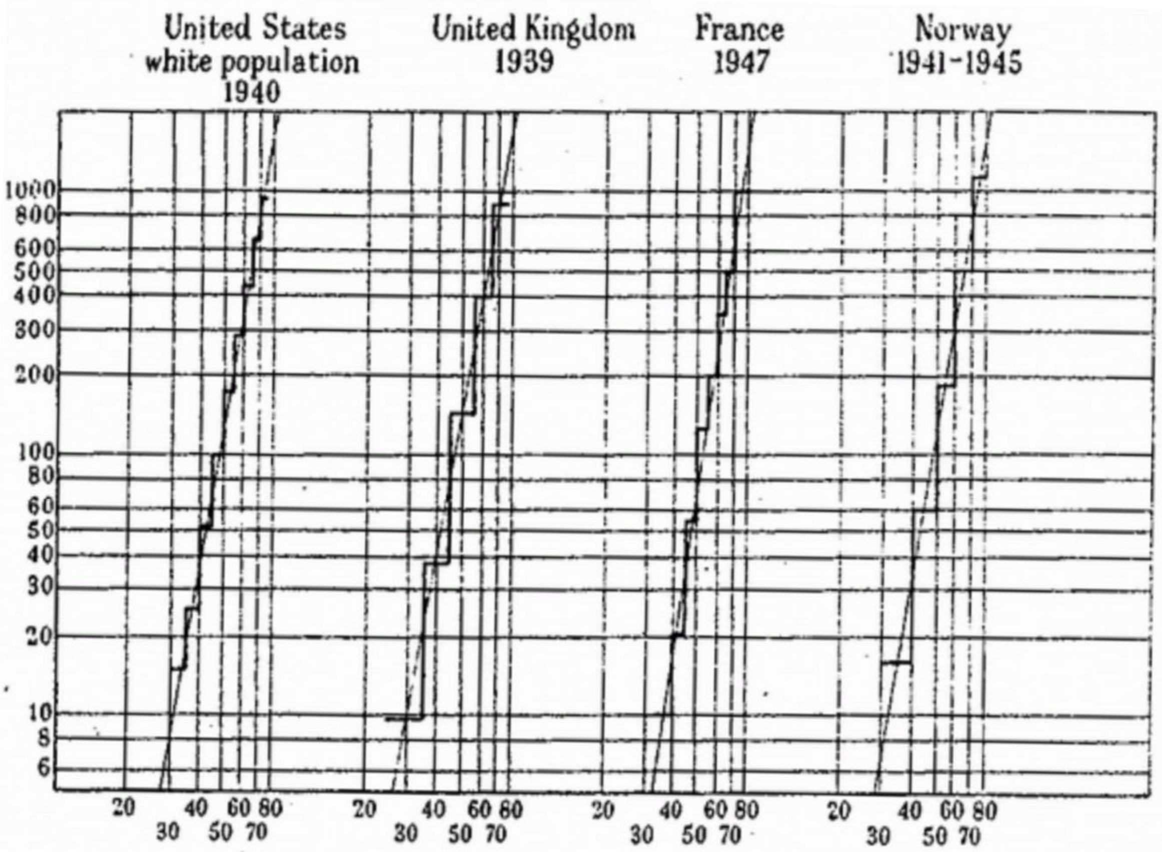


- High Ct value means we identified the infected individual early, hopefully before transmission to others

- 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



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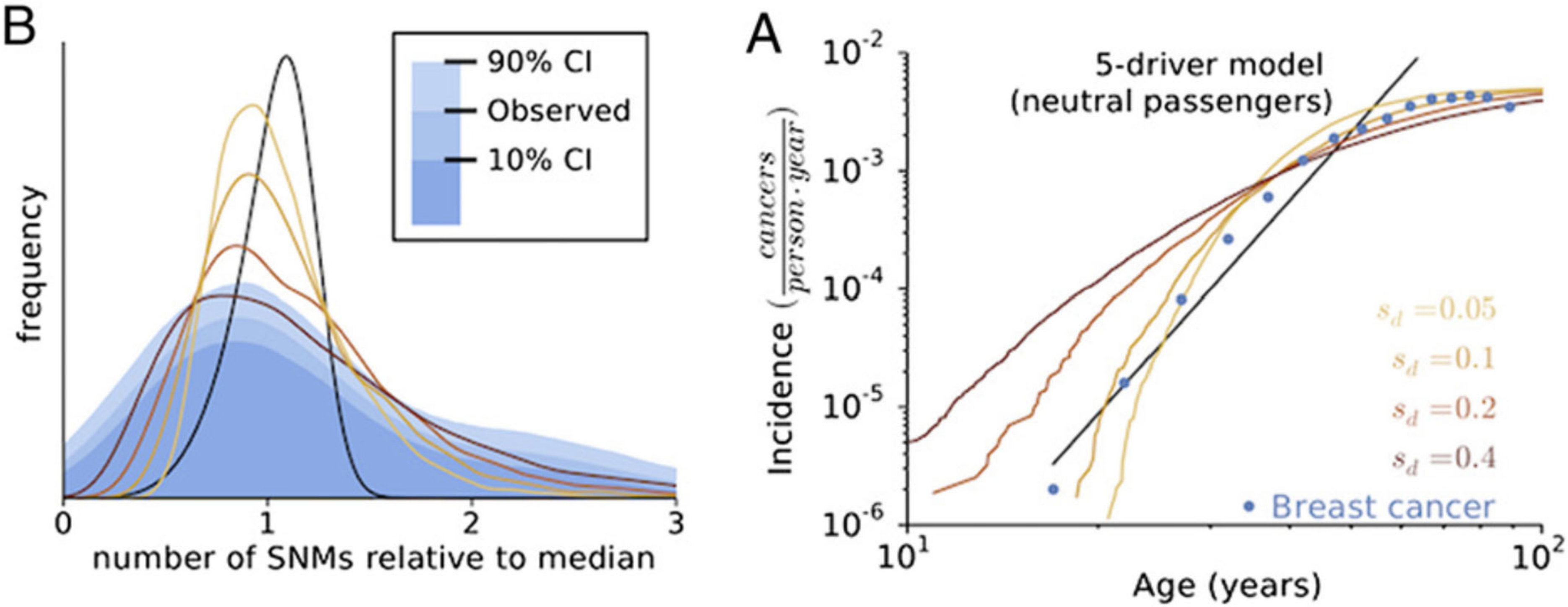

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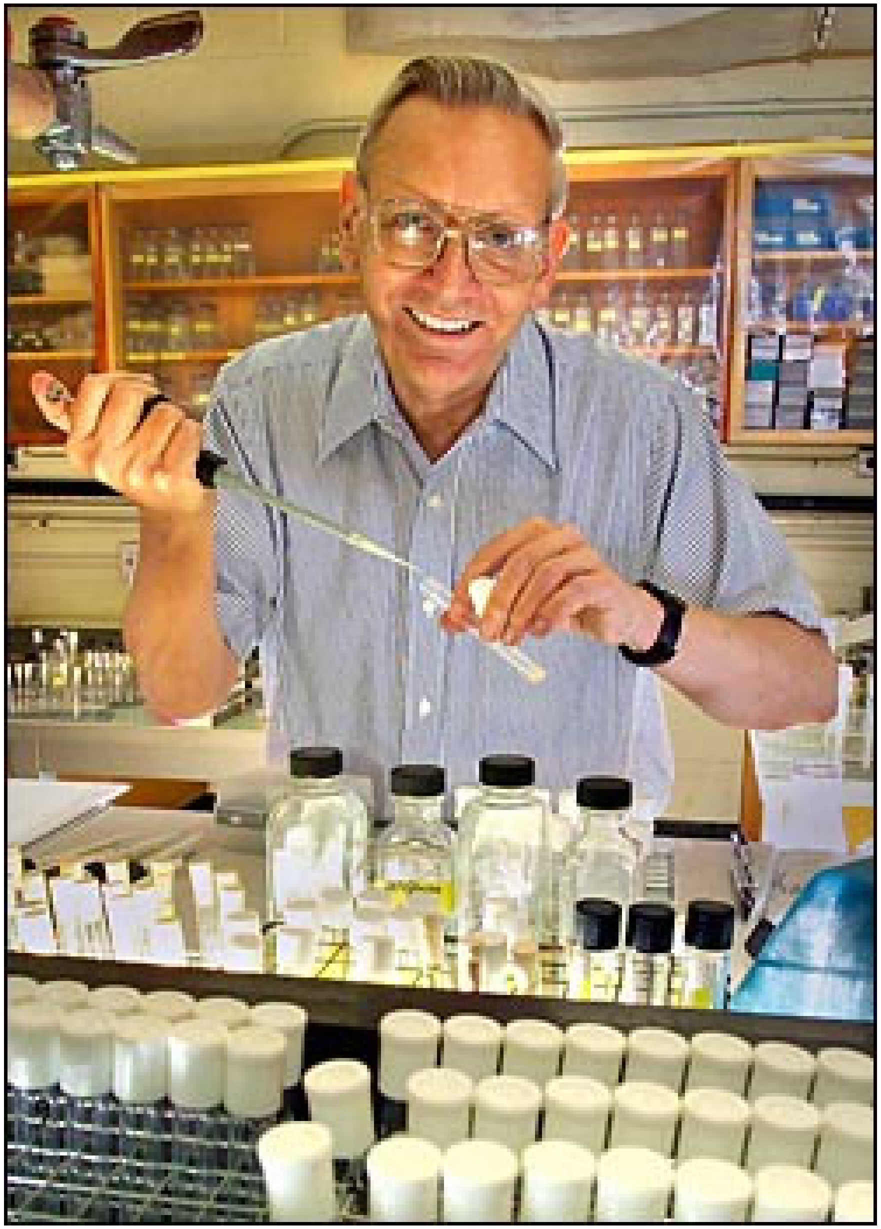
Blue - data on breast cancer: incidence; non-synonymous mutations

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

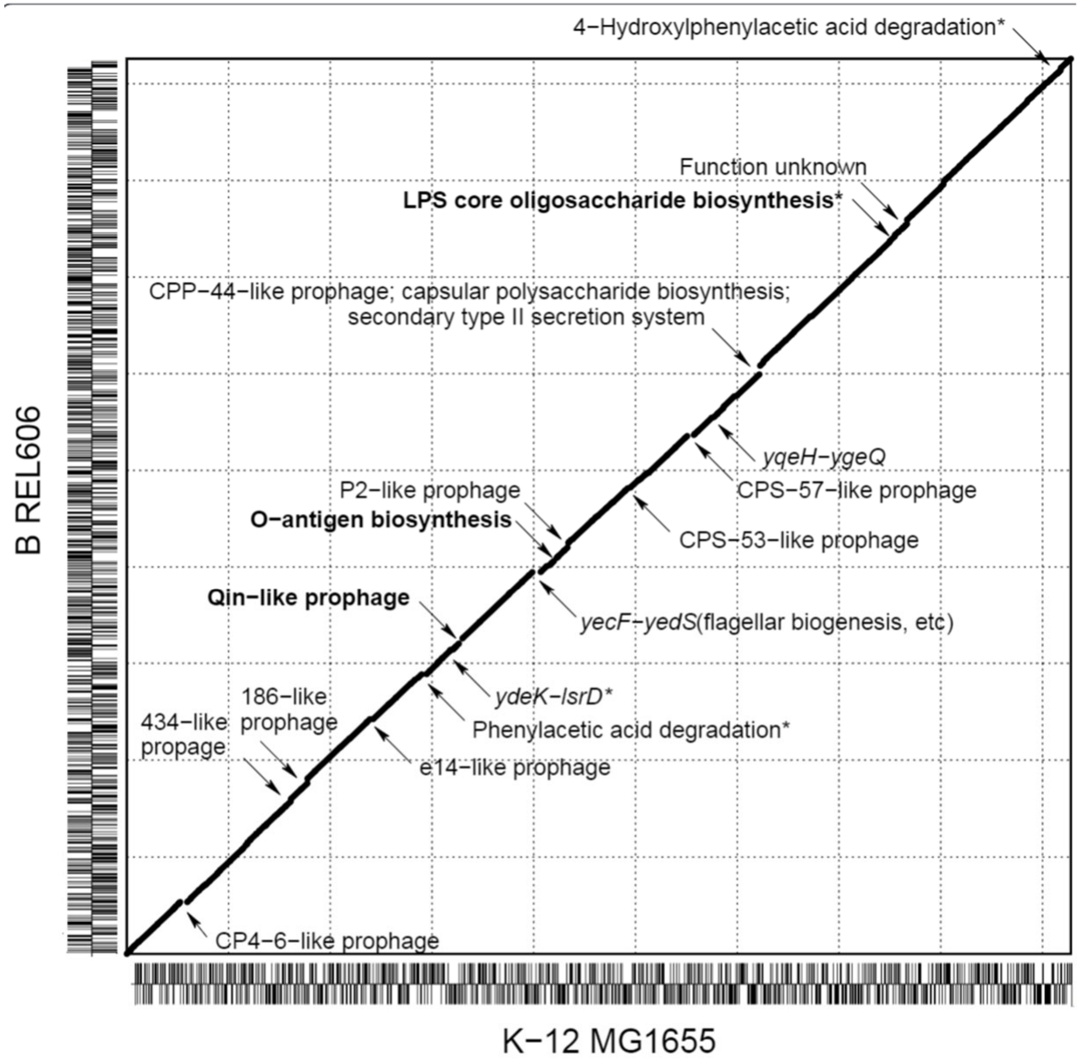
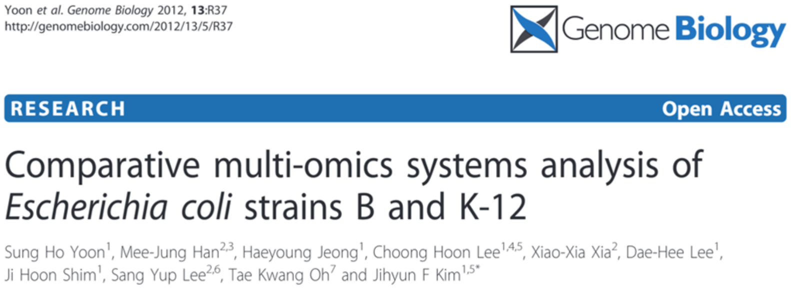


Figure 1 Whole genome comparison of *E. coli* B REL606 and *E. coli* K-12 MG1655. Strain-specific regions are indicated by discontinuities on the diagonal line (those >10 kb are marked by arrows). Short vertical lines on each axis represent coding sequences that reside on the forward or reverse strand. 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

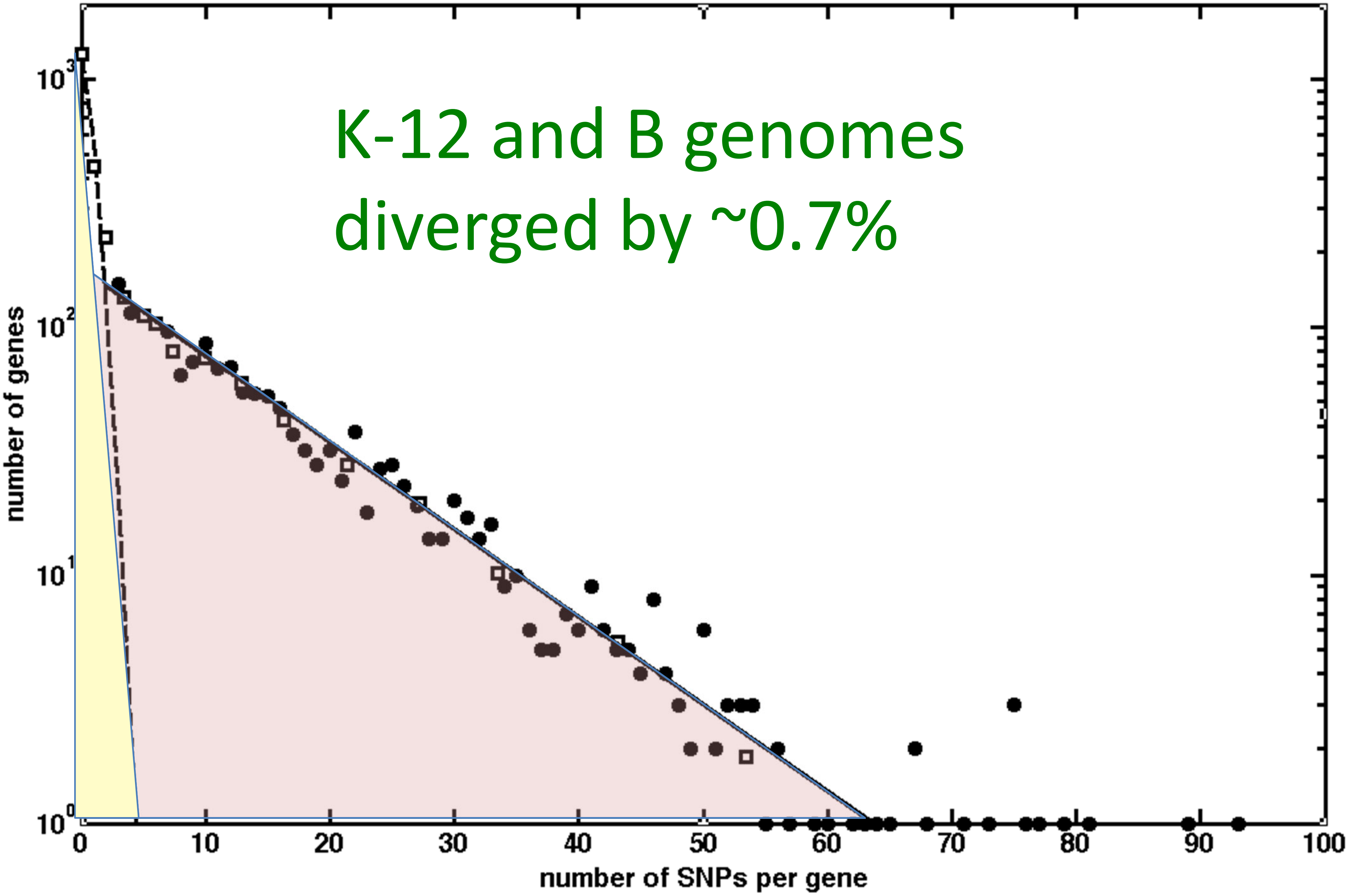
Genome **Biology**

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*]

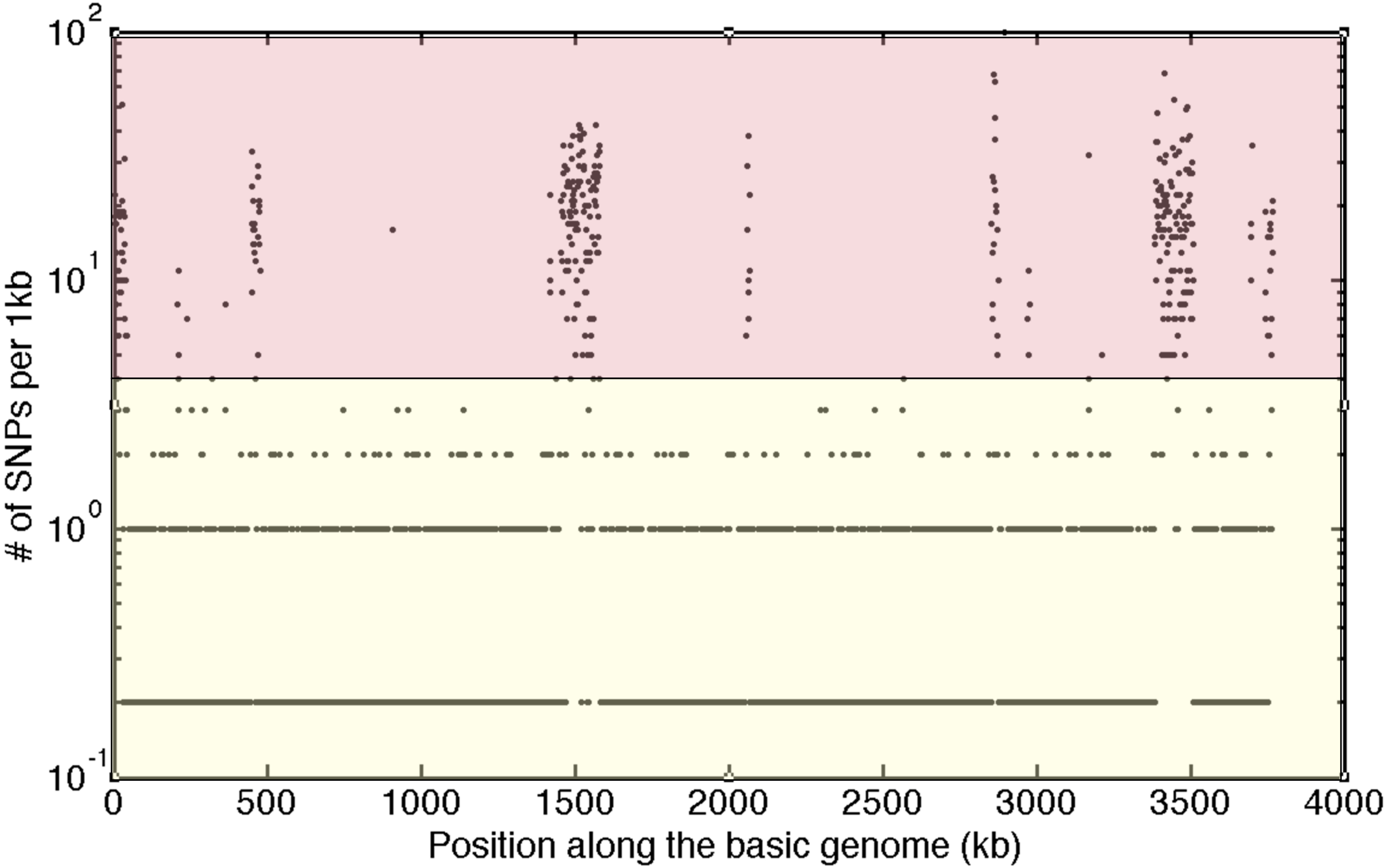
K-12 vs BL21(DE3) strains of E. coli



K-12 and B genomes diverged by ~0.7%

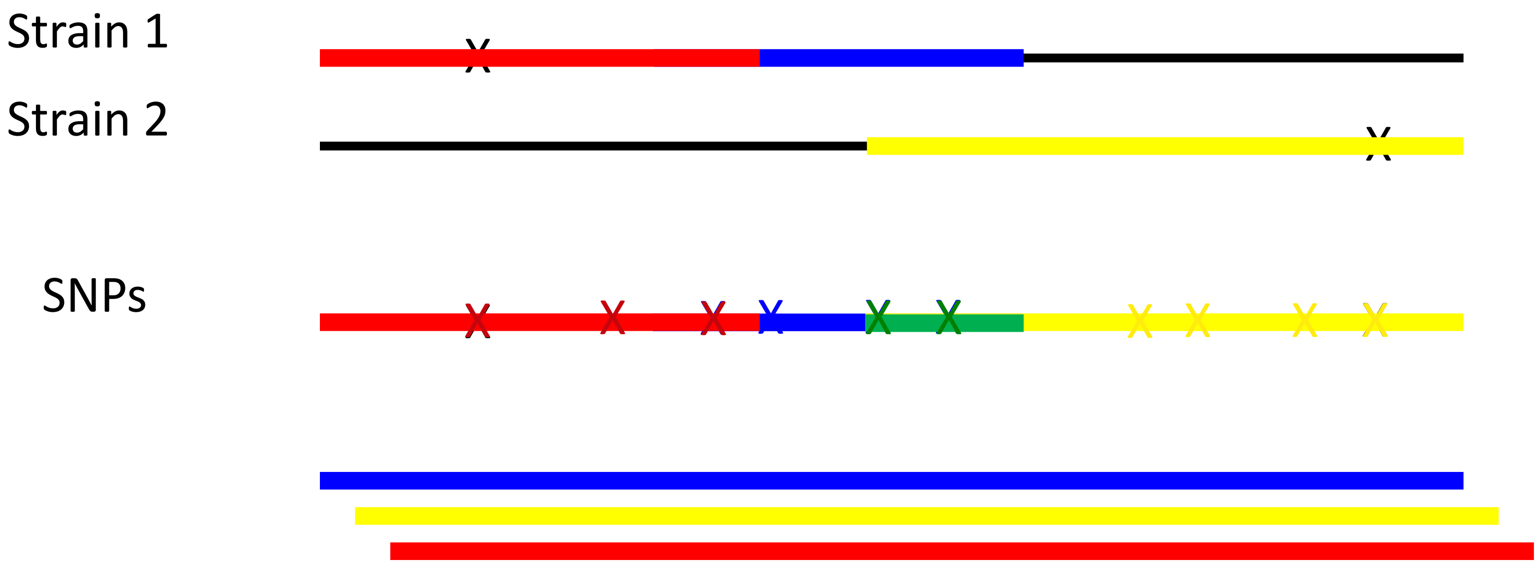
Studier FW, Daegelen P, Lenski RE, **Maslov S**, Kim JF, J. Mol Biol. (2009)

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: $\mathrm{Prob}(\delta)=\exp(-\delta/0.01)$
  Similar slopes in other species as distant as B. subtilis
- Theory 1: PopGen 101 coalescence time distribution:
  - $\mathrm{Prob}(T) \sim \exp(-T/N_e) \rightarrow$
    $\mathrm{Prob}(\delta) \sim \exp(-\delta/2\mu N_e) = \exp(-\delta/\theta)$
    $\theta = 2\mu N_e \sim 0.01$, $\mu \sim 10^{-10} \rightarrow N_e \sim 10^8$
- Theory 2: biophysics of homologous recombination:
  - Requires perfect matches of L=30bp on each side →
    $\mathrm{Prob}(\delta)=(1-\delta)^{2L}=\exp(-60 \bullet \delta)=\exp(-\delta/0.016)=\exp(-\delta/\delta_{TE})$
- Both mechanisms likely to work together:
  biophysics of recombination affects the effective population size

Continuous Probability Distributions

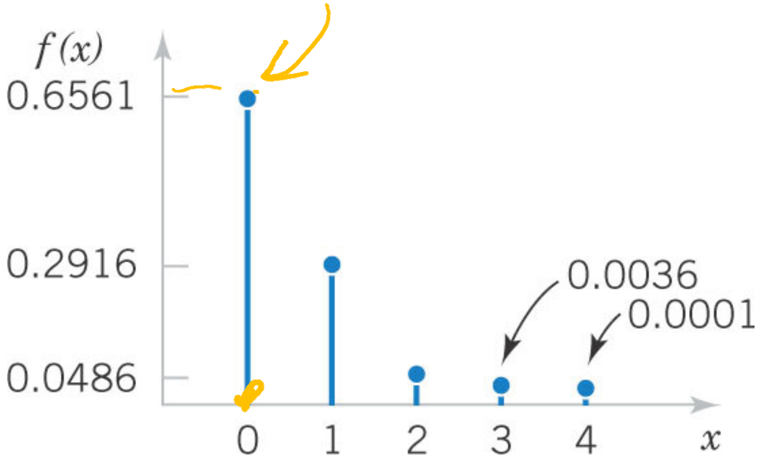
Uniform Distribution

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



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

$P(X=0) =$	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

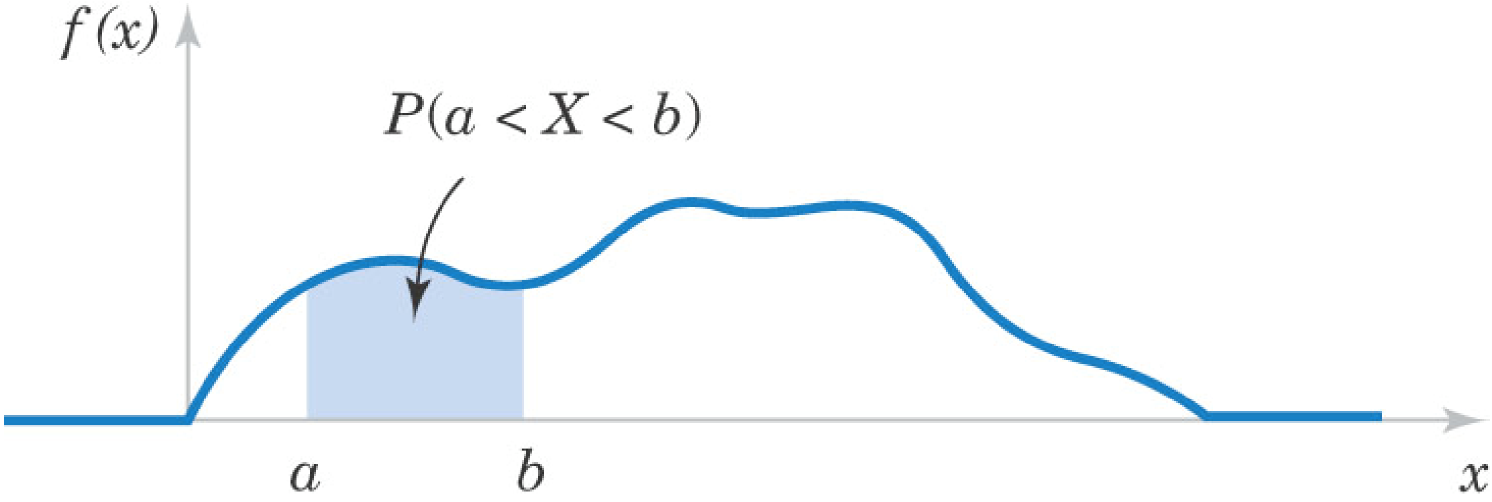


Figure 4-2 Probability is determined from the area under $f(x)$ from a to b.

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.

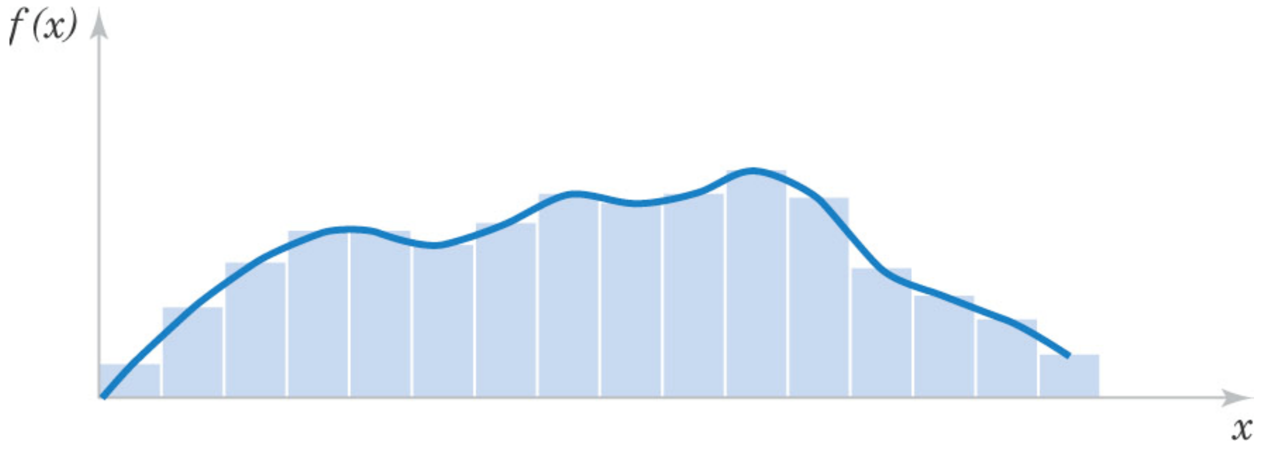
(2) $\int_{-\infty}^{\infty} f(x)\, dx = 1$

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

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

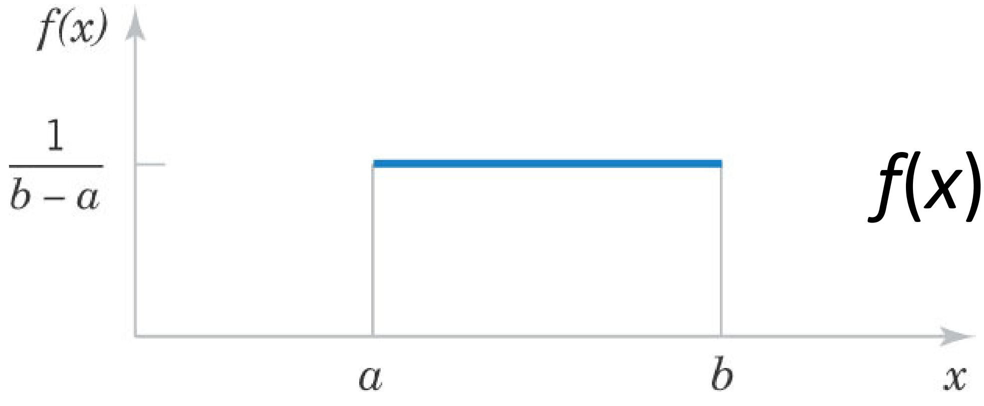
The standard deviation of X is $\sigma = \sqrt{\sigma^2}$.

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

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

What is $P(X=1)$?

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

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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
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D. Infinity
E. I have no idea

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[✓ B. 1/3]
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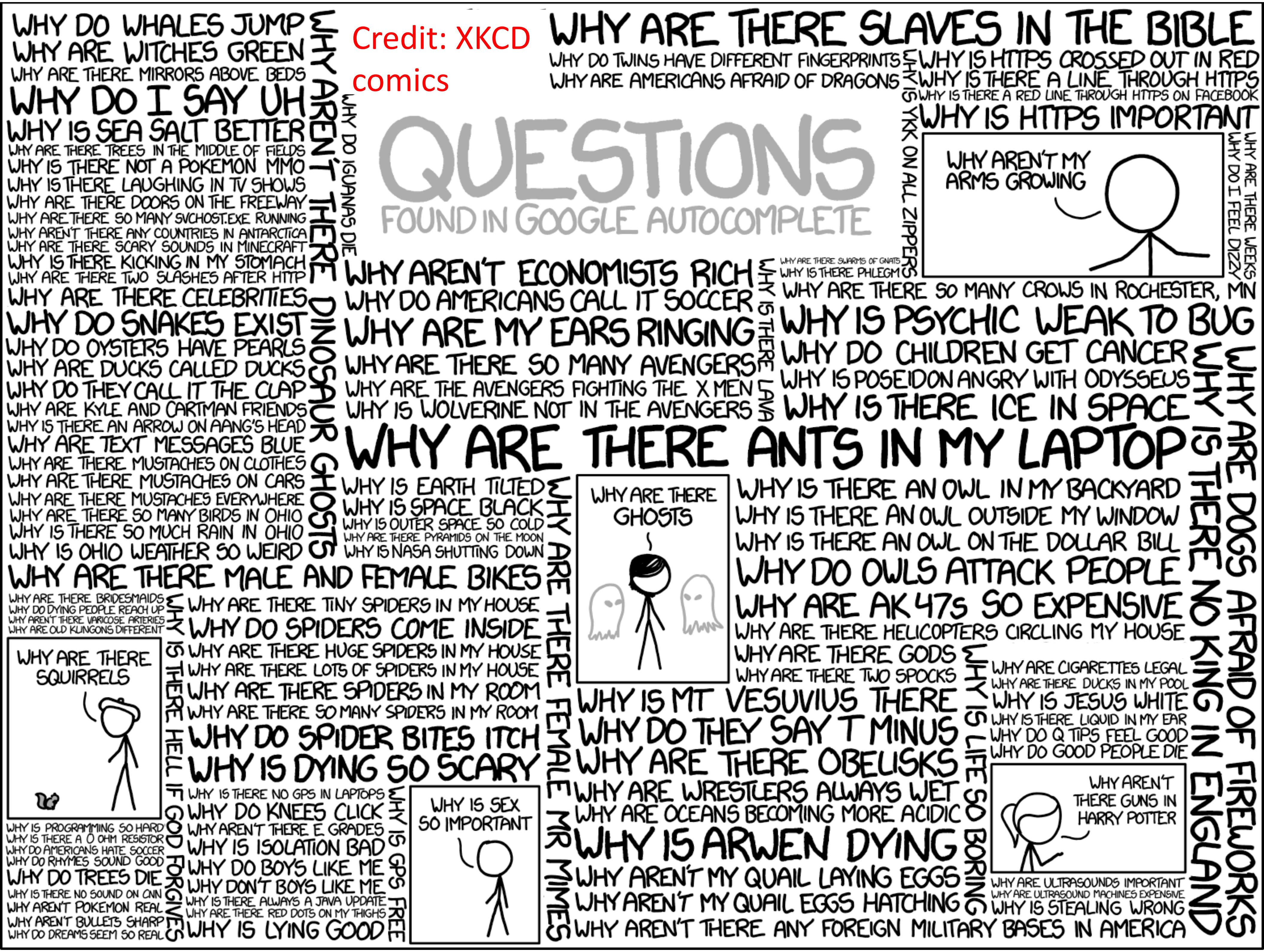

Credit: XKCD comics