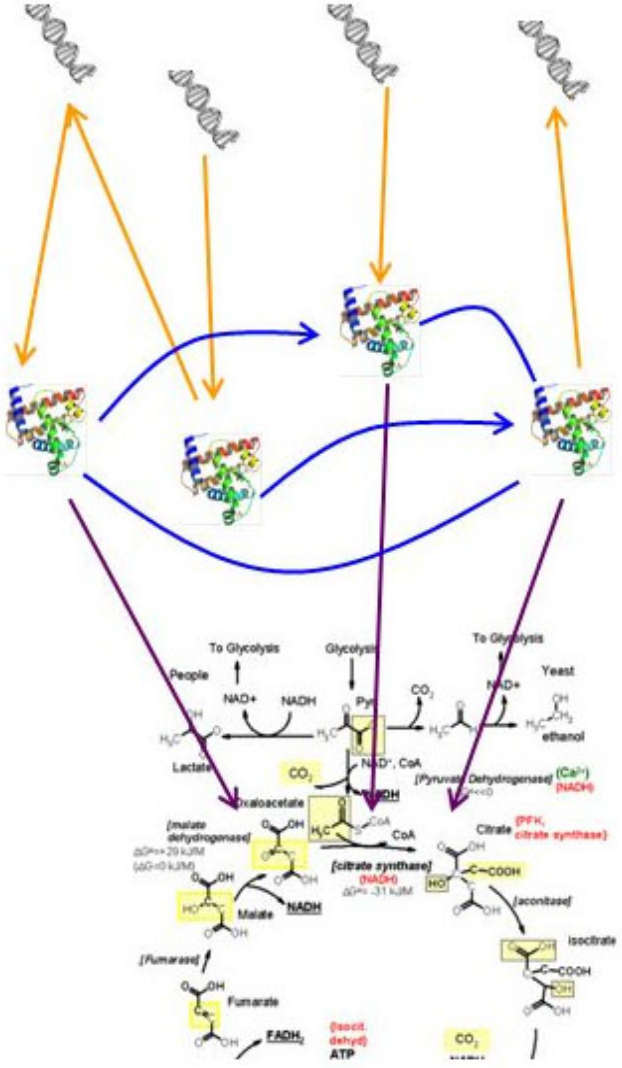
Fitting a Gaussian distribution: a biological example

Molecular binding is used at multiple levels

Each level has its own molecular interaction network



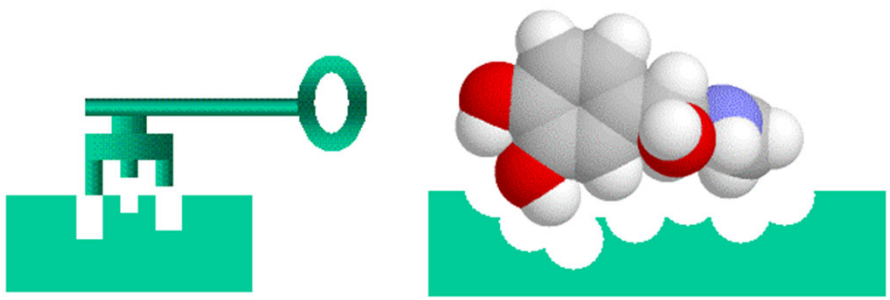
Regulatory network:
RNA-level regulation
By DNA-binding Proteins

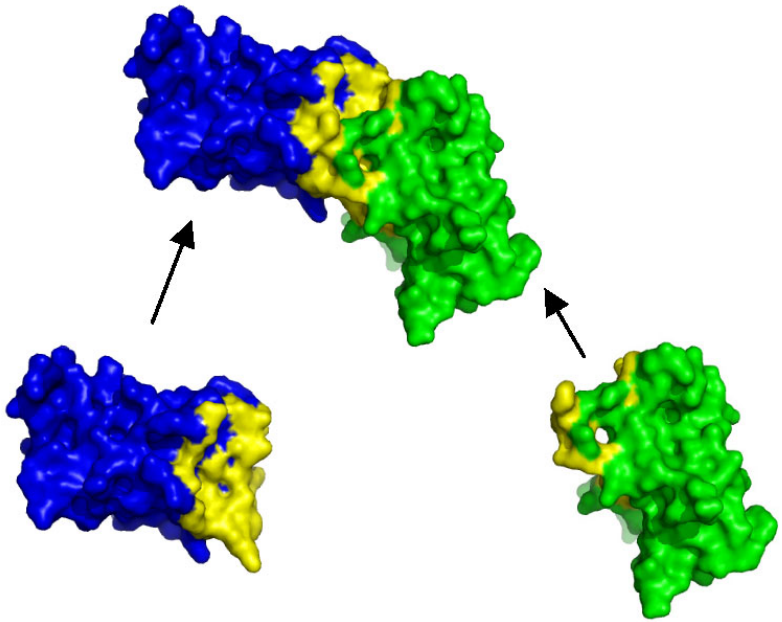
Protein-Protein (binding) Interaction Network

Protein-Metabolite Interactions: Metabolic network

Biological example of a Gaussian: Energy of Protein-Protein Binding Interactions

- Proteins and other biomolecules (metabolites, drugs, DNA) specifically (and non-specifically) bind each other
- For specific bindings: Lock-and-Key theory
- For non-specific bindings: random contacts





A simple physical model for scaling in protein–protein interaction networks

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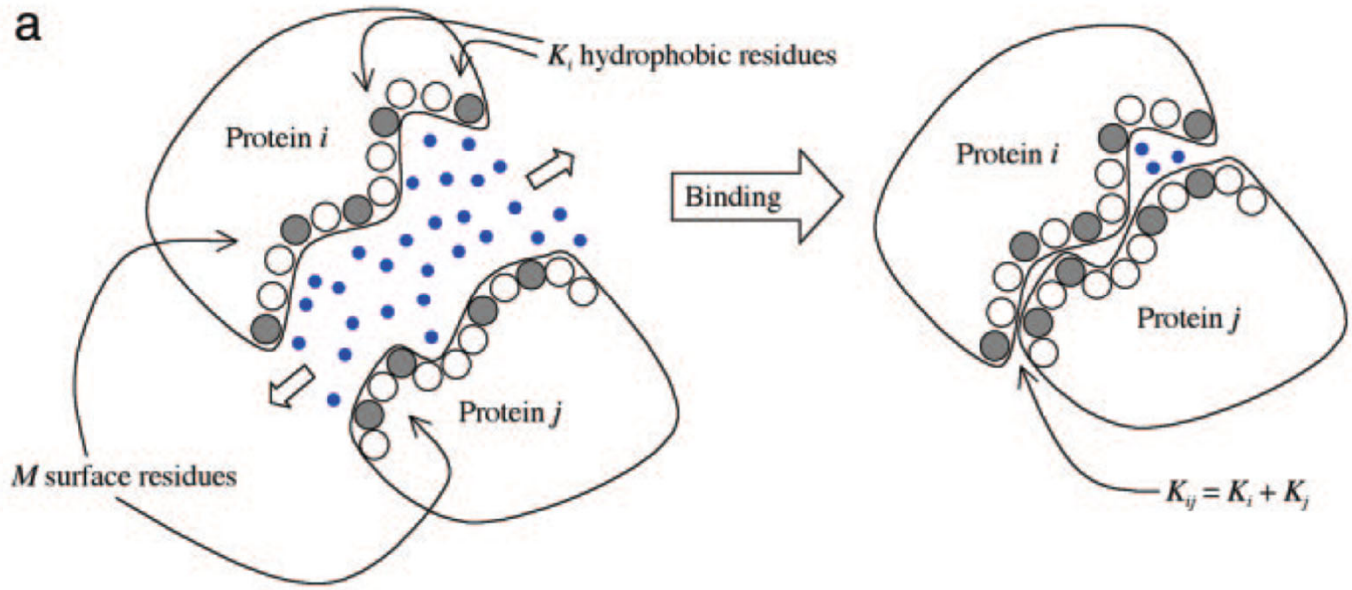
It has recently been demonstrated that many biological networks exhibit a "scale-free" topology, for which the probability of observing a node with a certain number of edges (k) follows a power law: i.e., $p(k) \sim k^{-\gamma}$. This observation has been reproduced by

(19–22). Indeed, when the two major *S. cerevisiae* p protein interaction (PPI) experiments are compared w another, one finds that only ≈150 of the thousands of tions identified in each experiment are recovered in th

Most Binding energy is due to hydrophobic amino-acid residues being screened from water

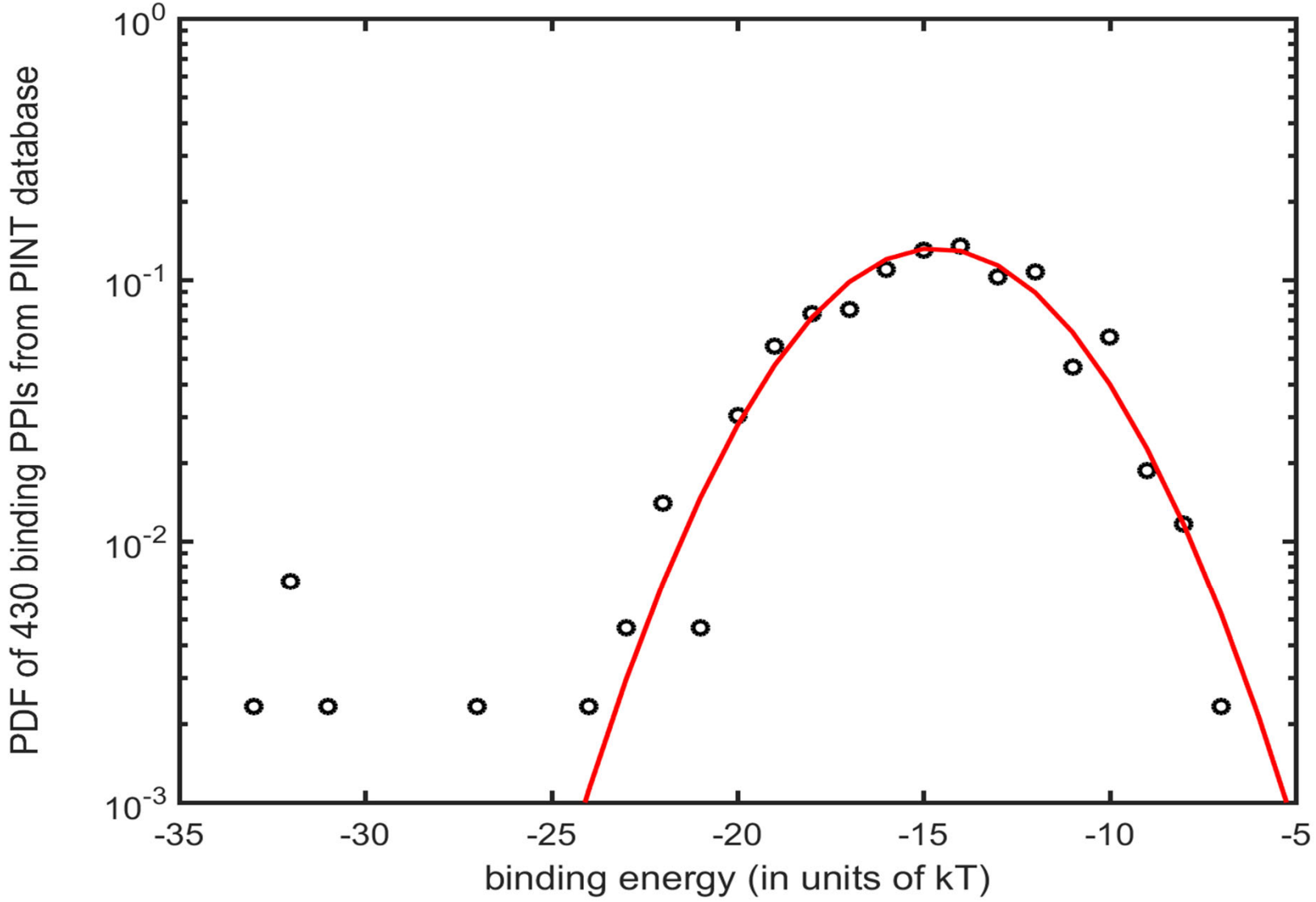


Predicted Gaussian distribution: PDF(E_{ij}=E)– because E_{ij} – sum of hydrophobicities of many independent residues

Matlab exercise

- In Matlab load PINT_binding_energy.mat with binding energy E_{ij} (in units of kT at room temperature) for 430 pairs of interacting proteins from human, yeast, etc.
- Data collected in 2007 from the PINT database http://www.bioinfodatabase.com/pint/
  and analyzed in J. Zhang, **S. Maslov**, E. Shakhnovich, Molecular Systems Biology (2008)
- Fit Gaussian to the distribution of E_{ij} using dfittool
- Use "Exclude" button to generate the new exclusion rule to drop all points with X<-23 from the fit
- Use "New Fit" button to generate the new "Normal" fit with the exclusion rule you just created
- Find mean (mu) and standard deviation (sigma)
- Select "probability plot" from "Display type" dropdown menu to evaluate the quality of the plot. Where does the probability plot deviate from a straight line?

How does it compare with the experimental data ?



J. Zhang, **S. Maslov**, E. Shakhnovich,
Nature/EMBO Molecular Systems Biology (2008)

Data on binding interactions
from PINT database

Dissociation constant

- Interaction between two molecules (say, proteins) is usually described in terms of dissociation constant
  $K_{ij}=1M \exp(-E_{ij}/kT)$
- Law of Mass Action: the concentration D_{ij} of a heterodimer formed out of two proteins with free (monomer) concentrations C_i and C_j : $D_{ij}=C_iC_j/K_{ij}$
- What is the distribution of K_{ij}?
- Answer: it is called log-normal since the logarithm of K_{ij} is the binding energy $-E_{ij}/kT$ which is normally distributed

$X = Y^2$ or $Y = \sqrt{X}$

Y – uniform distribution between $[0, 1]$

$P(Y < y) = y$

$P(X < x) = P(\sqrt{X} < \sqrt{x}) =$

$= P(Y < \sqrt{x}) = \sqrt{x}$

Prob. desity $(x) = \frac{d}{dx} P(X < x) = \frac{1}{2\sqrt{x}}$

Let $X = \exp(W)$ and

W is $N(\theta, \omega^2)$

$$P(X > x) = P(W > \ln(x)) =$$

$$= \int_{\ln(x)}^{+\infty} \frac{1}{\sqrt{2\pi}\,\omega} \exp\left(-\frac{(\ln(y)-\theta)^2}{2\omega^2}\right) d\ln y$$

$$= \int_{\ln(x)}^{+\infty} \frac{1}{\sqrt{2\pi}\,\omega} \exp\left(-\frac{(\ln(y)-\theta)^2}{2\omega^2}\right) \frac{dy}{y}$$

$$PDF = \frac{1}{\sqrt{2\pi}\,\omega\, y} \exp\left(-\frac{(\ln y-\theta)^2}{2\omega^2}\right)$$

Lognormal Distribution

- Let *W* denote a normal random variable with mean of θ and variance of ω^2, i.e., $E(W) = \theta$ and $V(W) = \omega^2$
- As a change of variable, let $X = e^W = \exp(W)$ and $W = \ln(X)$
- Now X is a lognormal random variable.

$$F(x) = P[X \le x] = P[\exp(W) \le x] = P[W \le \ln(x)]$$

$$= P\left[Z \le \frac{\ln(x) - \theta}{\omega}\right] = \Phi\left[\frac{\ln(x) - \theta}{\omega}\right] = \quad \text{for} \quad x > 0$$

$$= 0 \quad \text{for} \quad x \le 0$$

$$f(x) = \frac{dF(x)}{dx} = \frac{1}{x\omega\sqrt{2\pi}} e^{-\left[\frac{\ln(x)-\theta}{2\omega}\right]^2} \qquad \text{for } 0 < x < \infty$$

$$E(X) = e^{\theta+\omega^2/2} \qquad \text{and} \qquad V(X) = e^{2\theta+\omega^2}\left(e^{\omega^2} - 1\right) \qquad (4\text{-}22)$$

Lognormal Graphs

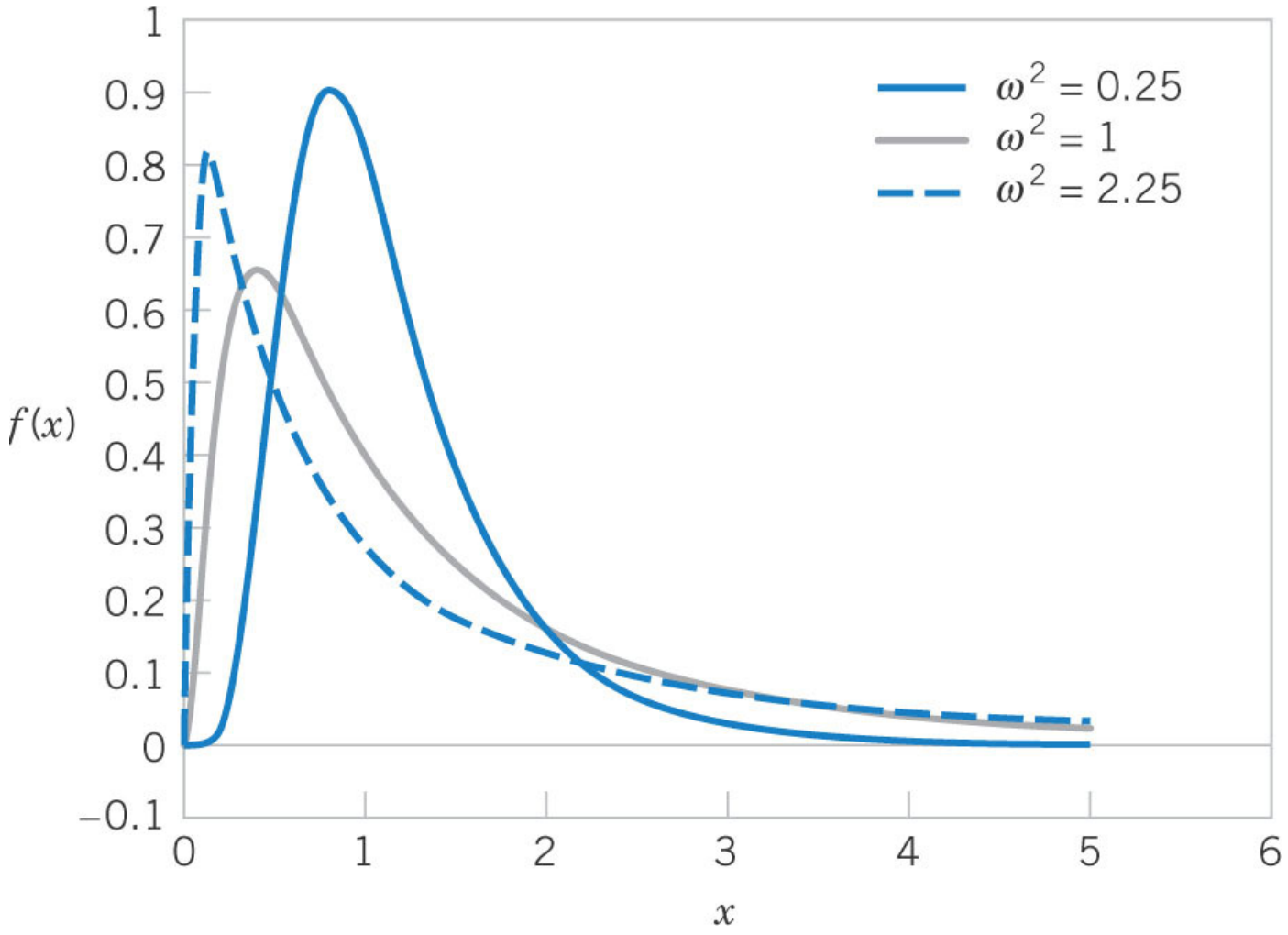


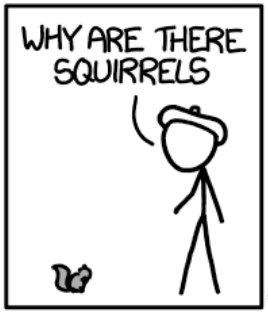
Figure 4-27 Lognormal probability density functions with θ = 0 for selected values of ω^2.

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 DO IGUANAS DIE
WHY AREN'T THERE DINOSAUR GHOSTS
WHY IS THERE HELL IF GOD FORGIVES
WHY IS GPS FREE

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 ARE THERE SLAVES IN THE BIBLE
WHY DO TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY IS YKK ON ALL ZIPPERS
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 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 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 THERE NO KING IN ENGLAND
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

Multiple random variables, Correlations

What we learned so far…

- Random Events:
  - Working with events as sets: union, intersection, etc.
    - Some events are simple: Head vs Tails, Cancer vs Healthy
    - Some are more complex: 10<Gene expression<100
    - Some are even more complex: Series of dice rolls: 1,3,5,3,2
  - Conditional probability: $P(A|B)=P(A \cap B)/P(B)$
  - Independent events: $P(A|B)=P(A)$ or $P(A \cap B)= P(A)*P(B)$
  - Bayes theorem: relates $P(A|B)$ to $P(B|A)$
- Random variables:
  - Mean, Variance, Standard deviation. How to work with E(g(X))
  - Discrete (Uniform, Bernoulli, Binomial, Poisson, Geometric, Negative binomial, Power law);
    PMF: f(x)=Prob(X=x); CDF: F(x)=Prob(X≤x);
  - Continuous (Uniform, Exponential, Erlang, Gamma, Normal, Log-normal);
    PDF: f(x) such that Prob(X inside A)= $\int_A f(x)dx$; CDF: F(x)=Prob(X≤x)
- Next step: work with **multiple random variables** measured together in the same series of random experiments

Concept of Joint Probabilities

- Biological systems are usually described not by a single random variable but by many random variables
- Example: The expression state of a human cell: 20,000 random variables X_i for each of its genes
- A joint probability distribution describes the behavior of several random variables
- We will start with just two random variables X and Y and generalize when necessary

Joint Probability Mass Function Defined

The joint probability mass function of the
discrete random variables X and Y,
denoted as $f_{XY}(x,y)$, satifies:

(1) $f_{XY}(x,y) = P(X{=}x, Y{=}y)$

(2) $f_{XY}(x,y) \geq 0$ All probabilities are non−negative

(3) $\sum_x \sum_y f_{XY}(x,y) = 1$ The sum of all probabilities is 1

Montgomery Runger 5th edition Equation (5−1)

Example 5-1: # Repeats vs. Signal Bars

You use your cell phone to check your airline reservation. It asks you to speak the name of your departure city to the voice recognition system.

- Let Y denote the number of times you have to state your departure city.
- Let X denote the number of bars of signal strength on you cell phone.

y = number of times city name is stated	x = number of bars of signal strength		
	1	2	3
1	0.01	0.02	0.25
2	0.02	0.03	0.20
3	0.02	0.10	0.05
4	0.15	0.10	0.05

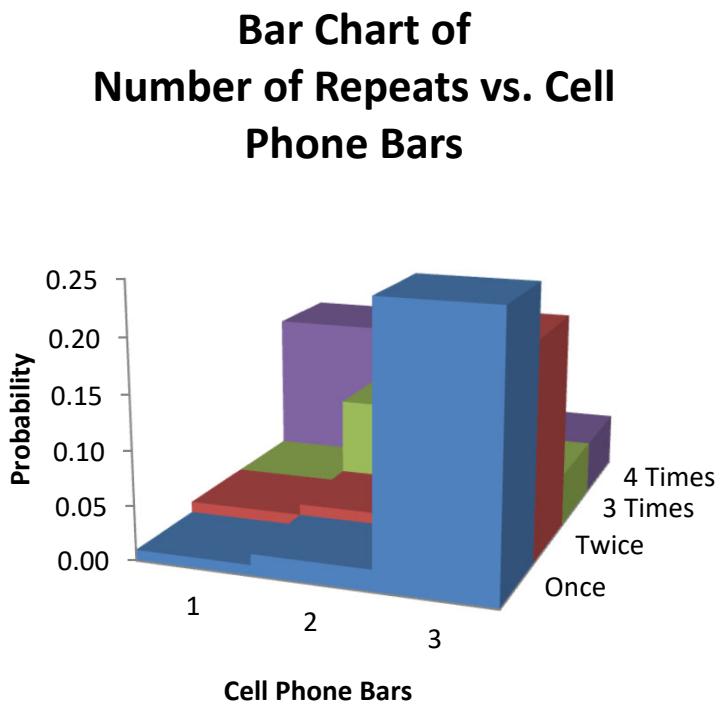


Figure 5-1 Joint probability distribution of X and Y. The table cells are the probabilities. Observe that more bars relate to less repeating.

Marginal Probability Distributions (discrete)

For a discrete joint PDF, there are marginal distributions for each random variable, formed by summing the joint PMF over the other variable.

$$f_X(x) = \sum_y f_{XY}(x,y)$$

$$f_Y(y) = \sum_x f_{XY}(x,y)$$

Called marginal because they are written in the margins

y = number of times city name is stated	x = number of bars of signal strength			
	1	2	3	$f_Y(y)$ =
1	0.01	0.02	0.25	0.28
2	0.02	0.03	0.20	0.25
3	0.02	0.10	0.05	0.17
4	0.15	0.10	0.05	0.30
$f_X(x)$ =	0.20	0.25	0.55	1.00

Figure 5-6 From the prior example, the joint PMF is shown in green while the two marginal PMFs are shown in purple.

Mean & Variance of X and Y are calculated using marginal distributions

y = number of times city name is stated	x = number of bars of signal strength					
	1	2	3	$f(y)=$	$y*f(y)=$	$y^2*f(y)=$
1	0.01	0.02	0.25	0.28	0.28	0.28
2	0.02	0.03	0.20	0.25	0.50	1.00
3	0.02	0.10	0.05	0.17	0.51	1.53
4	0.15	0.10	0.05	0.30	1.20	4.80
$f(x)=$	0.20	0.25	0.55	1.00	2.49	7.61
$x*f(x)=$	0.20	0.50	1.65	2.35		
$x^2*f(x)=$	0.20	1.00	4.95	6.15		

$\mu_X = E(X) = 2.35$; $\sigma_X^2 = V(X) = 6.15 - 2.35^2 = 6.15 - 5.52 = 0.6275$

$\mu_Y = E(Y) = 2.49$; $\sigma_Y^2 = V(Y) = 7.61 - 2.49^2 = 7.61 - 16.20 = 1.4099$

Conditional Probability Distributions

Recall that $P(B|A) = \frac{P(A \cap B)}{P(A)}$

$$P(Y=y|X=x)=P(X=x,Y=y)/P(X=x)=$$
$$=f(x,y)/f_X(x)$$

From Example 5-1

$P(Y=1|X=3) = 0.25/0.55 = 0.455$

$P(Y=2|X=3) = 0.20/0.55 = 0.364$

$P(Y=3|X=3) = 0.05/0.55 = 0.091$

$P(Y=4|X=3) = 0.05/0.55 = 0.091$

Sum = *1.00*

y = number of times city name is stated	x = number of bars of signal strength			
	1	2	3	$f_Y(y)$ =
1	0.01	0.02	0.25	0.28
2	0.02	0.03	0.20	0.25
3	0.02	0.10	0.05	0.17
4	0.15	0.10	0.05	0.30
$f_X(x)$ =	0.20	0.25	0.55	1.00

Note that there are 12 probabilities conditional on *X*, and 12 more probabilities conditional upon *Y*.

Reminder

Statistically independent events

Always true: $P(A \cap B) = P(A|B) \cdot P(B) = P(B|A) \cdot P(A)$

- **Two events**

Two events are **independent** if any one of the following equivalent statements is true:

(1) $P(A|B) = P(A)$

(2) $P(B|A) = P(B)$

(3) $P(A \cap B) = P(A)P(B)$

- **Multiple events**

The events $E_1, E_2, \ldots, E_n$ are independent if and only if for any subset of these events $E_{i_1}, E_{i_2}, \ldots, E_{i_k}$,

$$P(E_{i_1} \cap E_{i_2} \cap \cdots \cap E_{i_k}) = P(E_{i_1}) \times P(E_{i_2}) \times \cdots \times P(E_{i_k})$$

Joint Random Variable Independence

- Random variable independence means that knowledge of the value of X does not change any of the probabilities associated with the values of Y.

- Opposite: Dependence implies that the values of *X* are influenced by the values of *Y*

Independence for Discrete Random Variables

- Remember independence of events (slide 13 lecture 4) : Events are independent if any one of the three conditions are met:
  1) $P(A|B)=P(A \cap B)/P(B)=P(A)$ or
  2) $P(B|A)= P(A \cap B)/P(A)=P(B)$ or
  3) $P(A \cap B)=P(A) \cdot P(B)$

- Random variables independent if **all events** A that $Y=y$ and B that $X=x$ are independent if any one of these conditions is met:
  1) $P(Y=y|X=x)=P(Y=y)$ for any x or
  2) $P(X=x|Y=y)=P(X=x)$ for any y or
  3) $P(X=x, Y=y)=P(X=x)\cdot P(Y=y)$
  for every pair x **and** y