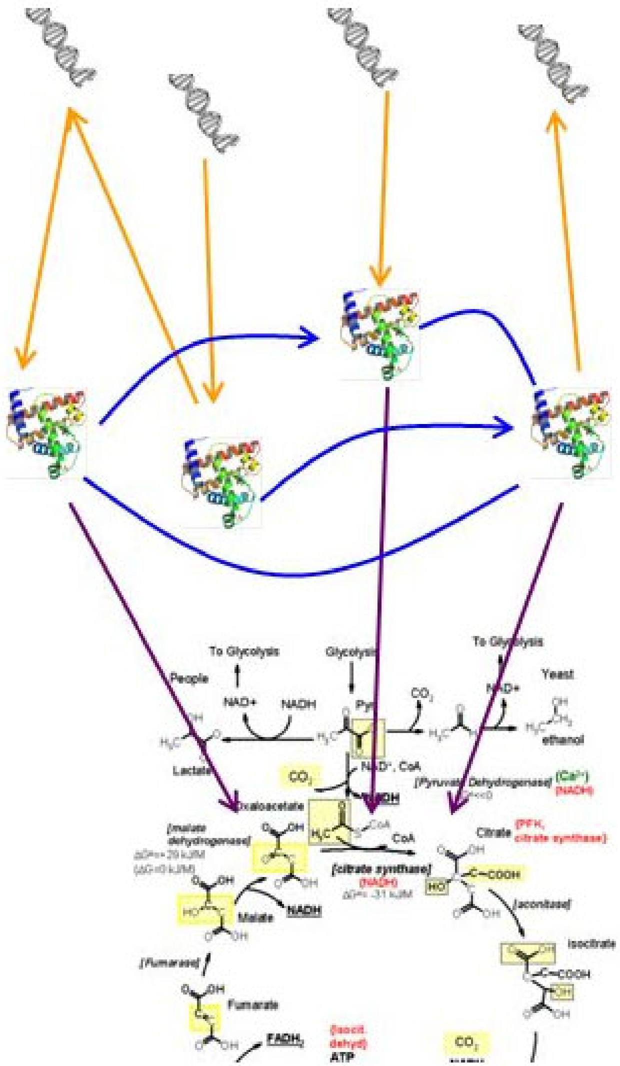
Fitting a Gaussian distribution: a biological example

Molecular binding is used at multiple levels

Each level has its own molecular interaction network



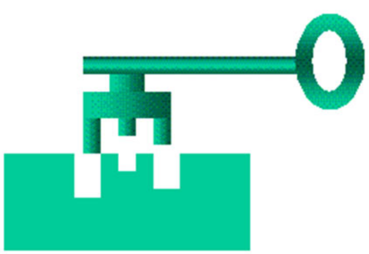
Regulatory network:
RNA-level regulation
By DNA-binding Proteins

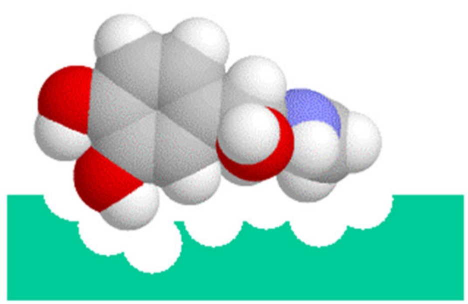
Protein-Protein (binding) Interaction Network

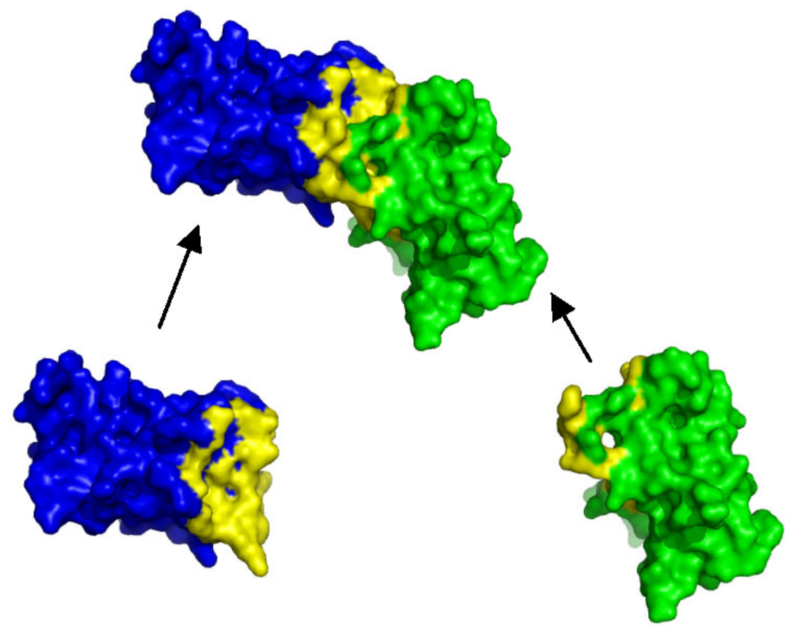
Protein-Metabolite Interactions:
Metabolic network

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







PNAS

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

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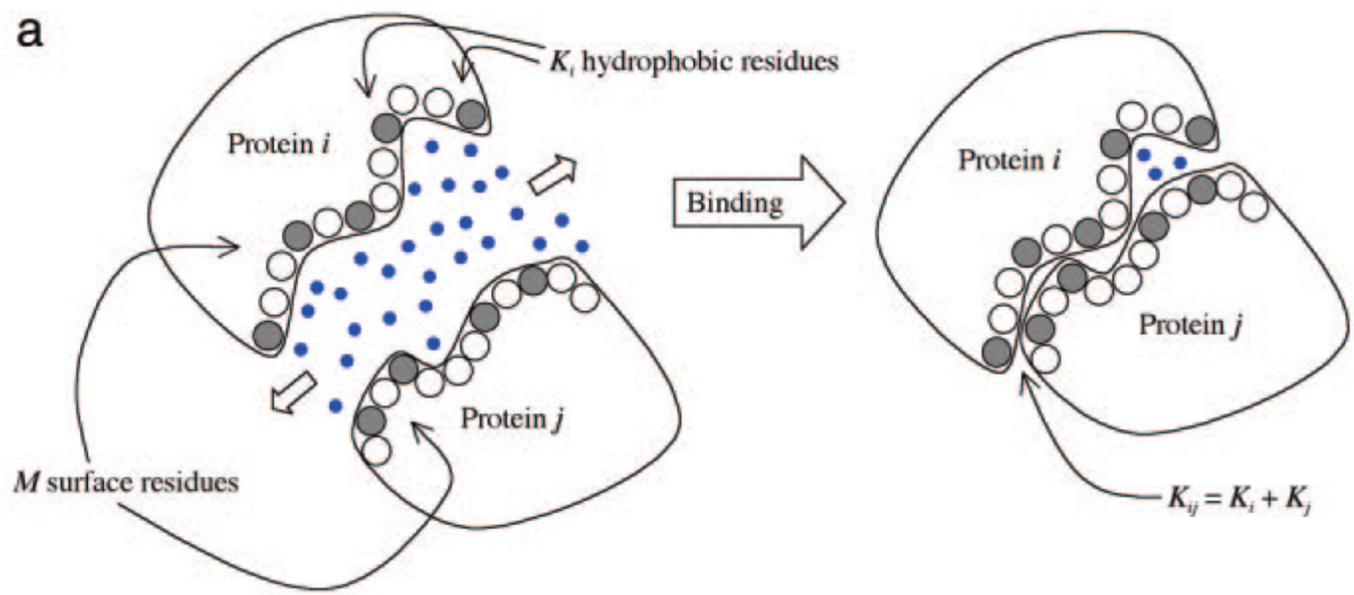
It has recently been demonstrated that many biological networks exhibit a "scale-free" topology, for which the probability of observing a node with a certain number of edges (k) follows a power law: i.e., $p(k) \sim k^{-\gamma}$. This observation has been reproduced by

(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

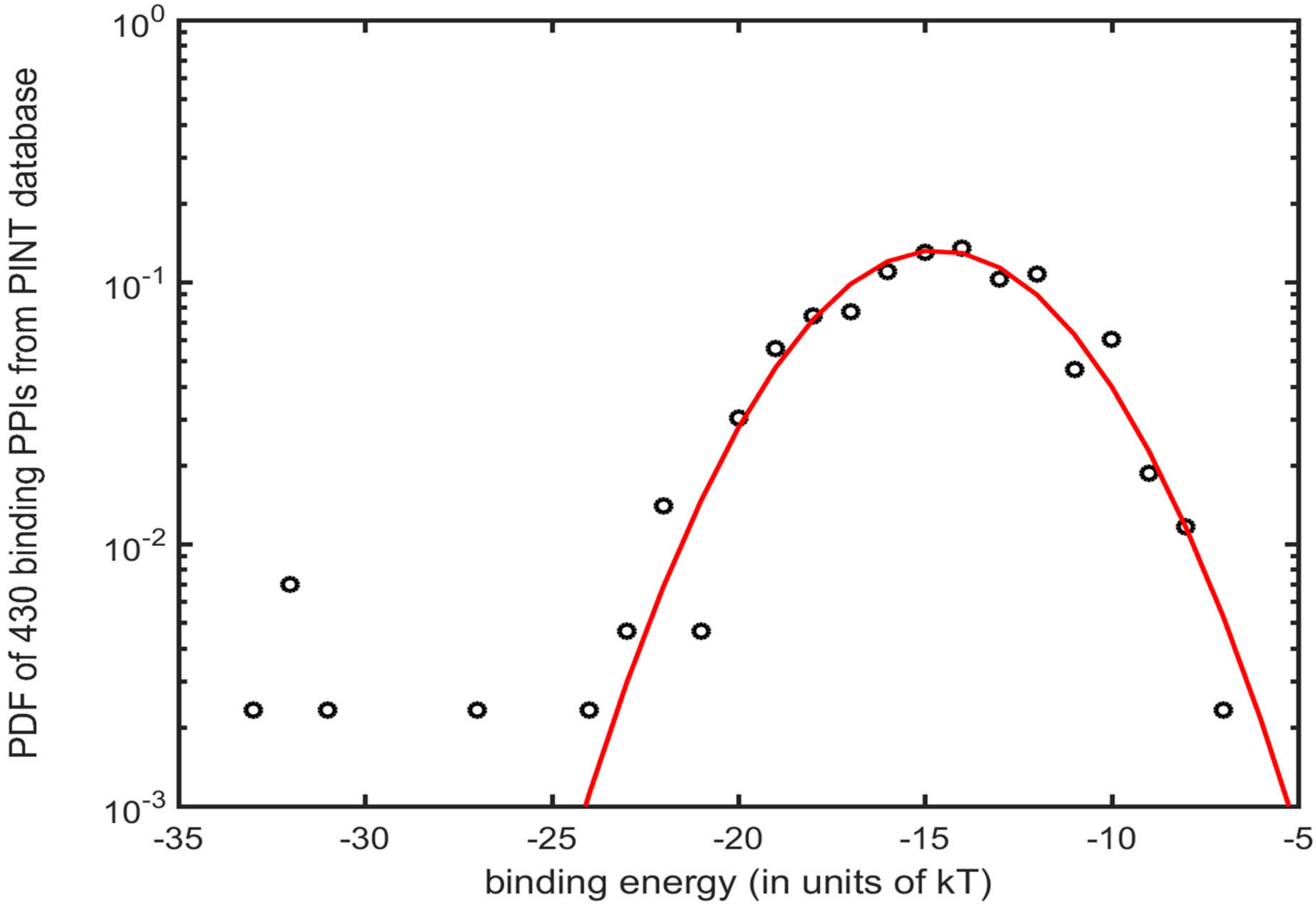


Predicted Gaussian distribution: PDF(E_{ij}=E)– because E_{ij} – sum of hydrophobicities of many independent residues

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

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

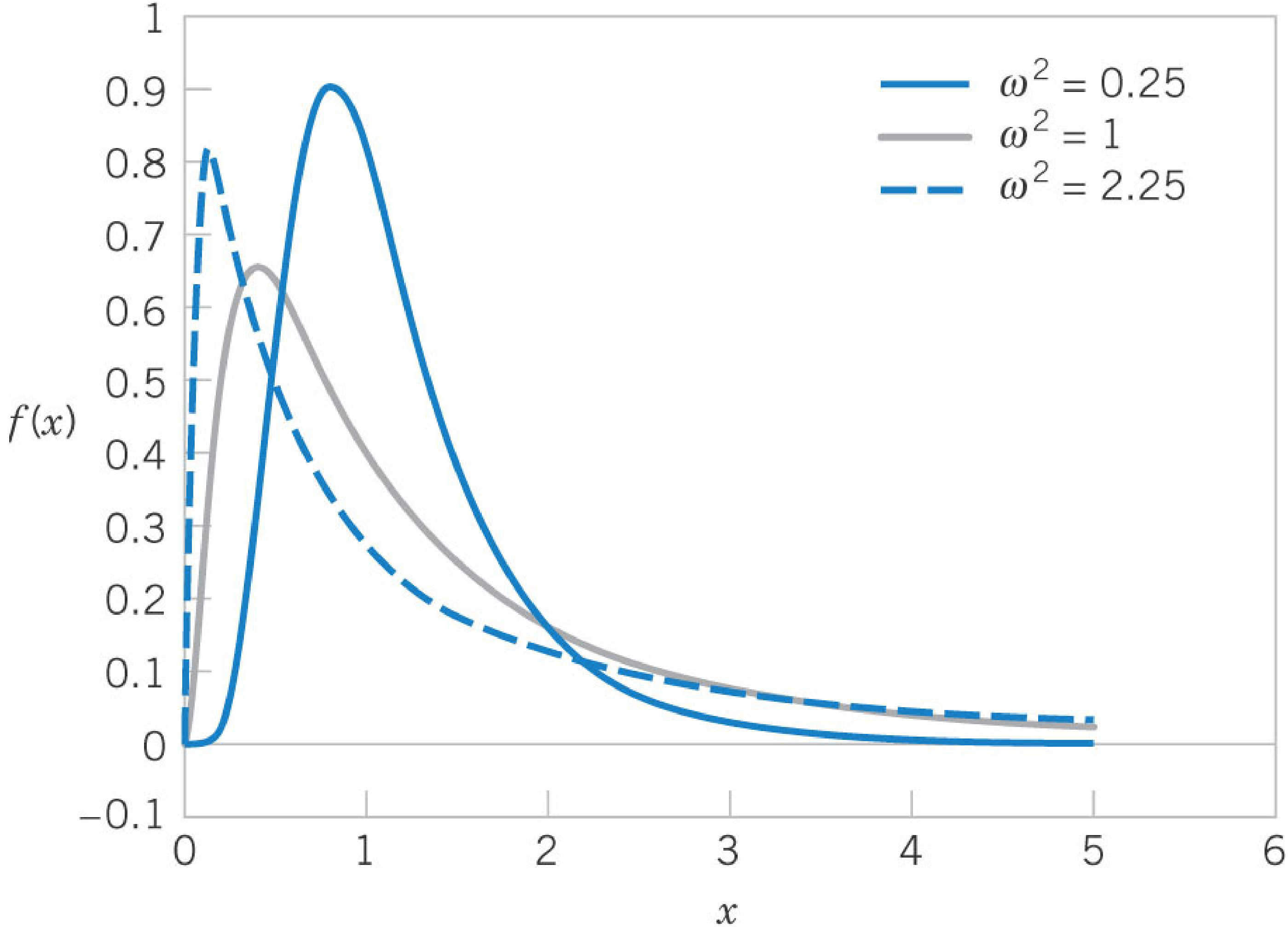
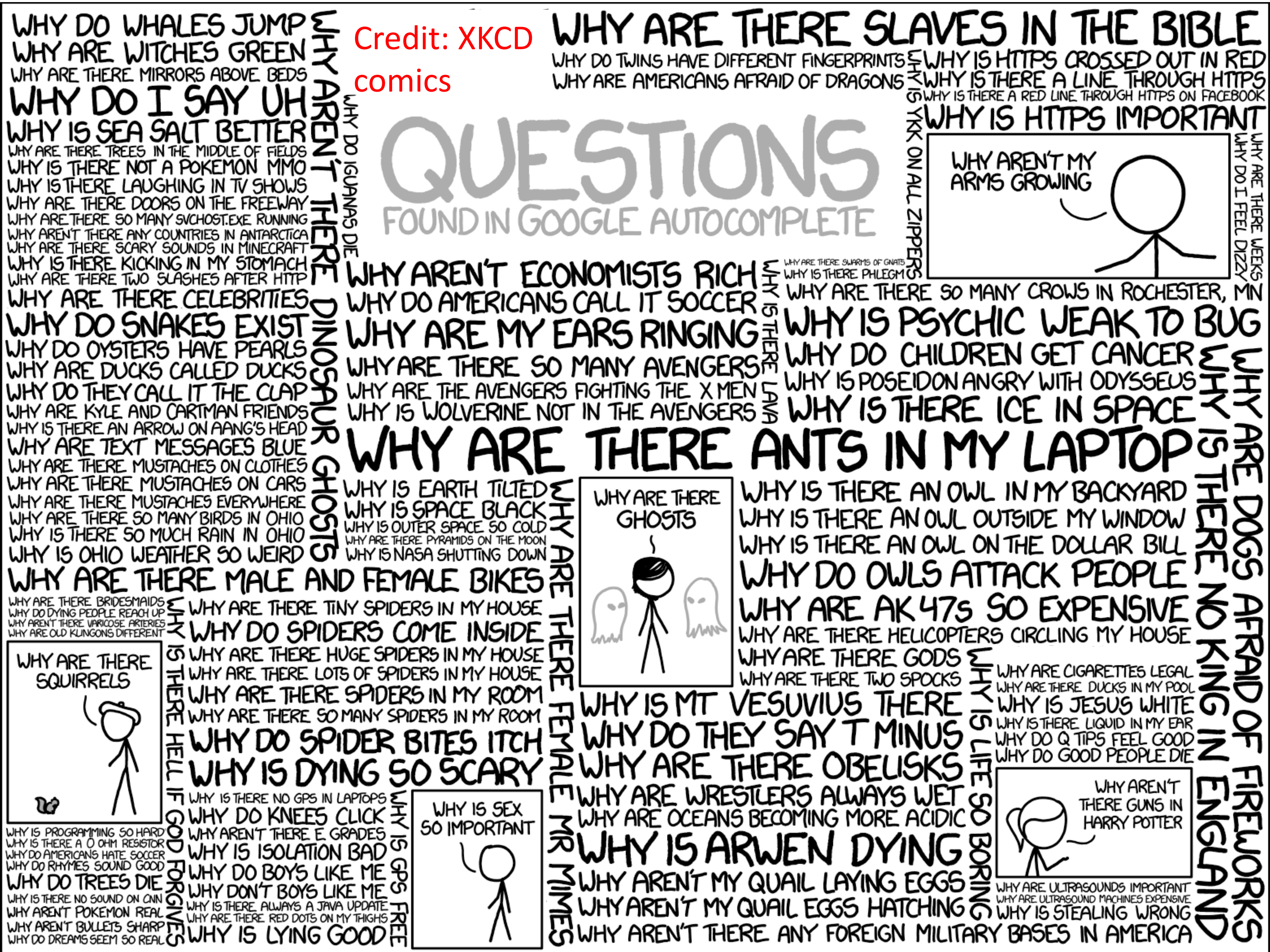


Figure 4-27 Lognormal probability density functions with $\theta = 0$ for selected values of ω^2.

Credit: XKCD comics



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

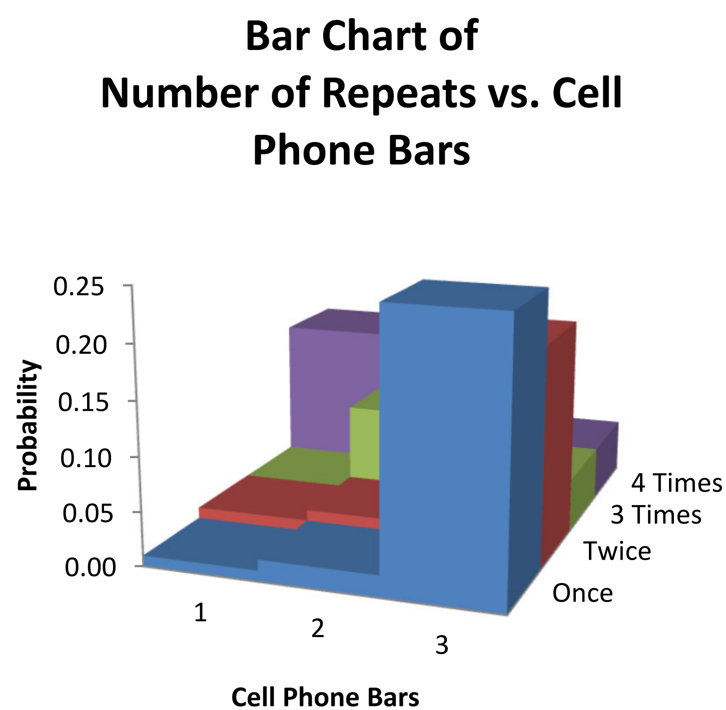


Figure 5-1 Joint probability distribution of X and Y. The table cells are the probabilities. Observe that more bars relate to less repeating.

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 $P(B|A) = \dfrac{P(A \cap B)}{P(A)}$

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

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

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

X and Y are Bernoulli variables

	Y=0	Y=1
X=0	2/6	1/6
X=1	2/6	1/6

Are they independent?

A. yes
B. no
C. I don't know

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X and Y are Bernoulli variables

	Y=0	Y=1
X=0	1/2	0
X=1	0	1/2

Are they independent?

A. yes
B. no
C. I don't know

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