BIOE 505:
Computational Bioengineering

What this class is all about?

Instructor

- Name: Sergei Maslov

- Professor of Bioengineering, Physics, Carl R. Woese Institute for Genomic Biology, and National Center for Supercomputing Applications

- Office: 3103 Carl Woese Institute for Genomic Biology
and sometimes 3146C Everitt Laboratory (both by appointment)

- E-mail: maslov@illinois.edu

- Phone: 217-265-5705

Questions and Suggestions:

maslov@Illinois.edu

Start subject with [BIOE505]

Grading

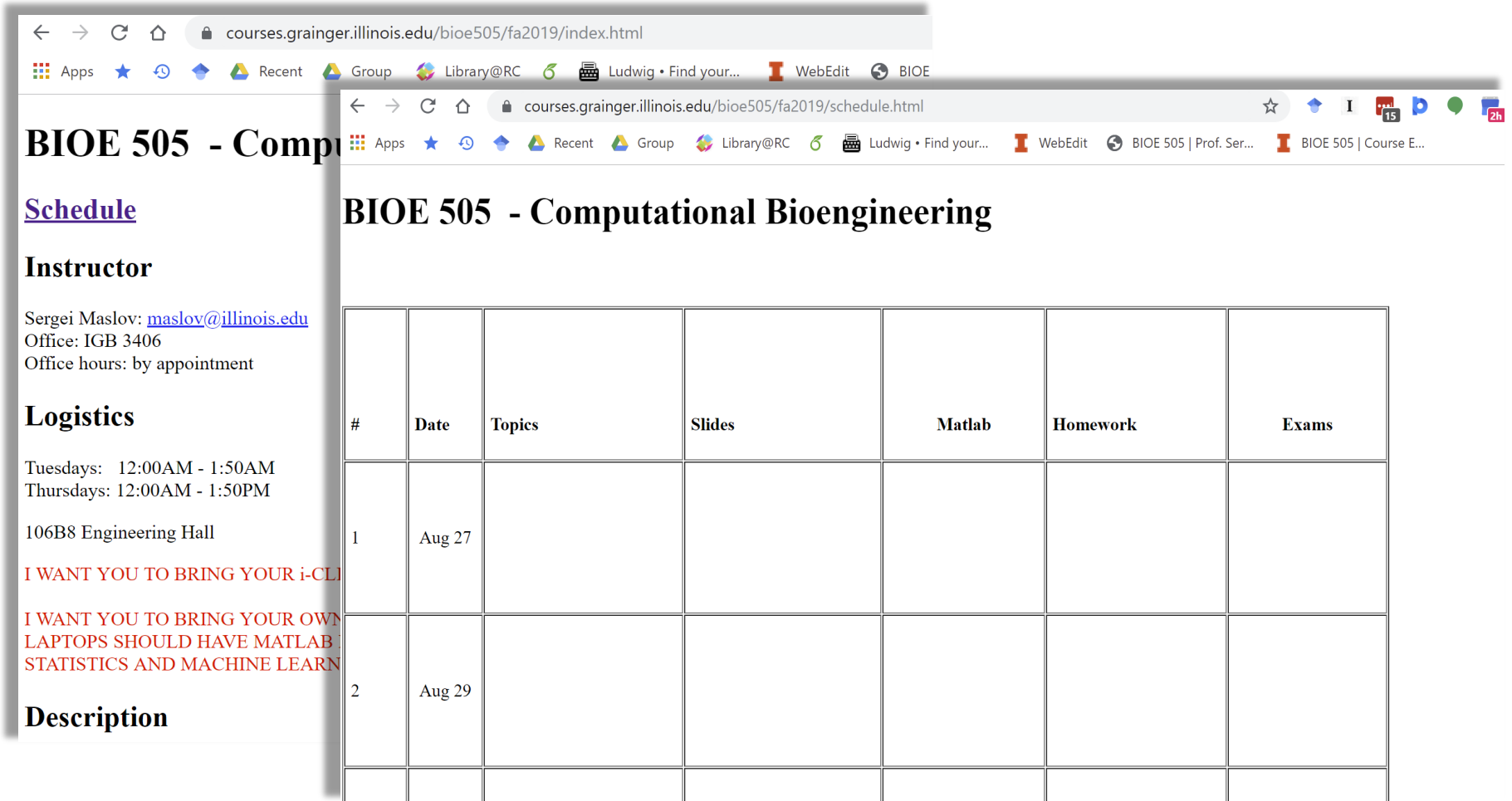
- Midterm exam 40%
- Final exam 60%
- Homework (ungraded) will be posted online. Solutions will be posted in a week.
- Homework will build on topics covered in lectures and will consist of problem sets related to topics covered in lectures
- Useful to prepare for exams

Course Website

https://courses.engr.illinois.edu/bioe505

Grades will be on

https://my.bioen.illinois.edu/gradebook



courses.grainger.illinois.edu/bioe505/fa2019/index.html

Apps Recent Group Library@RC Ludwig • Find your... WebEdit BIOE

BIOE 505 - Compu

Schedule

Instructor

Sergei Maslov: maslov@illinois.edu
Office: IGB 3406
Office hours: by appointment

Logistics

Tuesdays: 12:00AM - 1:50AM
Thursdays: 12:00AM - 1:50PM

106B8 Engineering Hall

I WANT YOU TO BRING YOUR i-CL

I WANT YOU TO BRING YOUR OWN
LAPTOPS SHOULD HAVE MATLAB
STATISTICS AND MACHINE LEARN

Description

courses.grainger.illinois.edu/bioe505/fa2019/schedule.html

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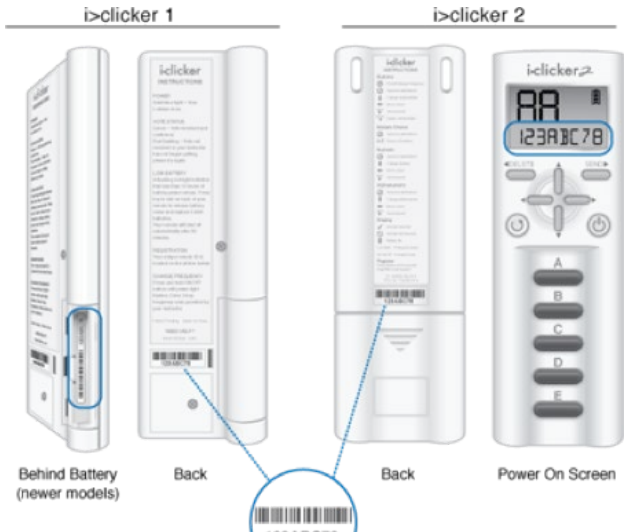
BIOE 505 - Computational Bioengineering

#	Date	Topics	Slides	Matlab	Homework	Exams
1	Aug 27					
2	Aug 29					

Bring your iClickers to my lectures

- **Who knows what is an iClicker?**
- **Show of hands: who has an iClicker?**
- **I would like you all to have an iClicker and bring it to every class. On amazon.com a new iClicker (1st generation is OK) costs around $40. It is also sold at UIUC Bookstore. The used ones are cheaper.**
- **An alternative solution is using a mobile app: https://www.iclicker.com/students/apps-and-remotes/apps**
- **Your answers WILL NOT be used for grading. I need them to see if I lost some of you and what could I rephrase to better explain the material**



Who has Matlab?

A. Already have it installed on my laptop
B. Will install it (starting this year **it is free**!)
C. Plan to access it on EWS via CITRIX
D. I don't know yet
E. I will never use Matlab!

Why don't we use Python?

Get your i-clickers

We will use Matlab in class

- Bring your laptops to class
- Need to have Matlab installed and know the basic user interface (inline commands, plotting)
- We will use Statistics and Machine Learning Toolbox and Bioinformatics Toolboxes
- Good news! Now all faculty and graduate students get Matlab **for free.** See offering on the WebStore site and follow the detailed instructions.
- .m files and .mat with Matlab commands and data will be on the website after the lecture

Possible alternative to purchasing Matlab and toolboxes is to use campus resources.

Both Engineering Workstations (EWS) and ACES computers have Matlab.
I don't think all of them offer the statistics and bioinformatics toolboxes
(EWS should, ACES computers may not..).

See the following to access:

Citrix for EWS, Matlab, and ACES computers -- links for all
https://it.engineering.illinois.edu/ews/lab-information/remote-connections/connecting-citrix
https://it.engineering.illinois.edu/services/instructional-services/remote-connections-citrix

Accessing Engineering Workstations (EWS)
https://it.engineering.illinois.edu/ews

Accessing ACES Academic Computing Workstations
http://acf.aces.illinois.edu/remote/
http://acf.aces.illinois.edu/remote/pc.html

To access off campus use:

CISCO Virtual Private Network -- For off-campus access to campus computer and network resources (software programs, files saved on the network, etc.)
https://techservices.illinois.edu/services/virtual-private-networking-vpn/download-and-set-up-the-vpn-client

CISCO VPN CLIENT
https://webstore.illinois.edu/shop/product.aspx?zpid=2600

CISCO AnyConnect VPN
https://webstore.illinois.edu/shop/product.aspx?zpid=1222

What will you learn in this course?

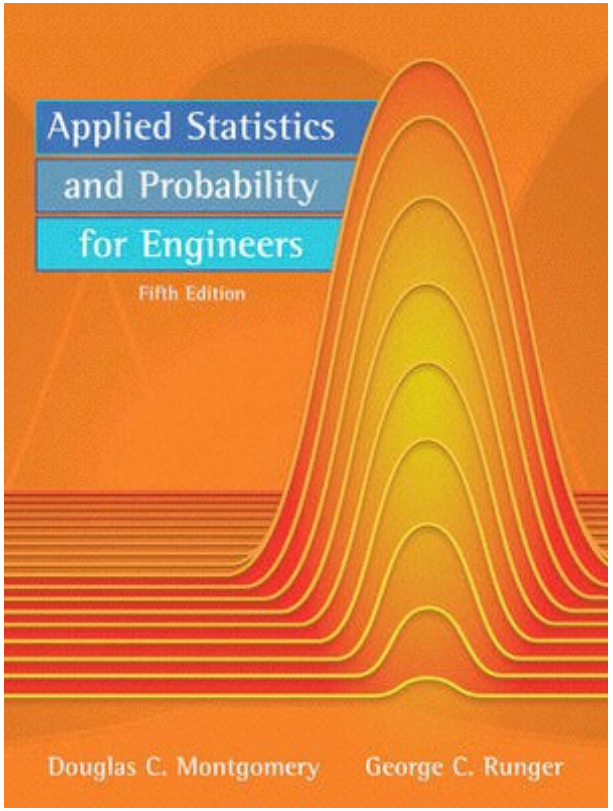
- Basics of probability and statistics
  - Basic concepts of probability, Bayes theorem
  - Discrete and continuous probability distributions
  - Multivariate statistics
  - Sampling distributions
  - Parameter estimation
  - Hypothesis testing
  - Regression
- How it is applied to biological data
  - Basics of genomics
  - Systems biology (gene expression, networks)

The main Probability/Statistics Textbook

Applied Statistics and Probability for Engineers, 5th Edition
D. C. Montgomery and G. C. Runger
John Wiley & Sons, Inc. (2011)

You can also use other editions from 4th (2007) to 6th (2014)

5th edition is available for free at our library



Problems for our main Probability/Statistics Textbook

Student Solutions Manual Applied Statistics and Probability for Engineers, 5th Edition
D. C. Montgomery and G. C. Runger
John Wiley & Sons, Inc. (2010)

You can also use other editions from 4th (2007) to 6th (2014)

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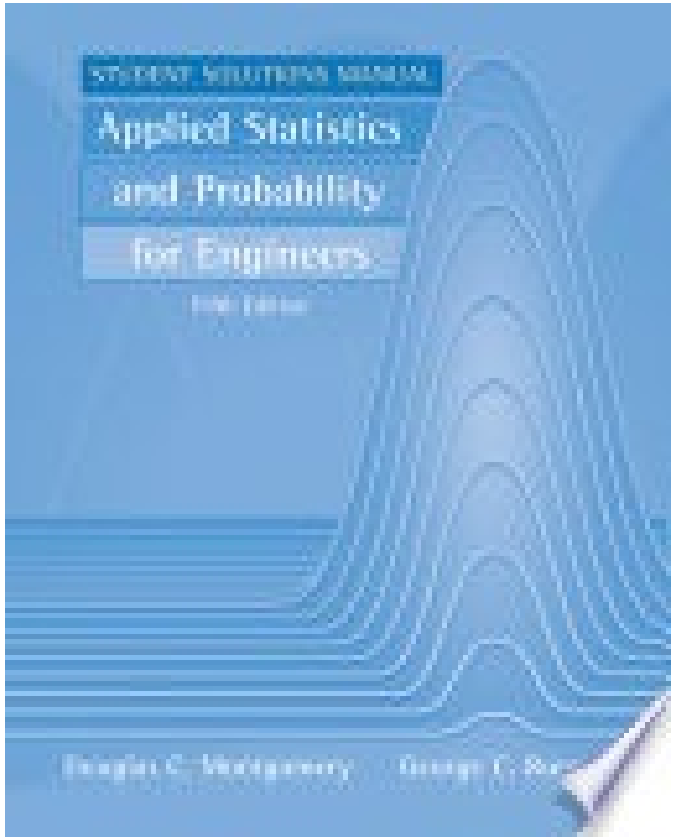
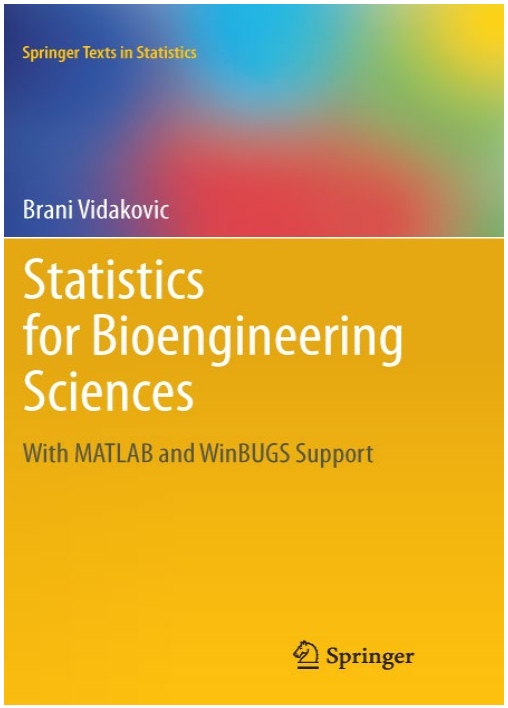


Probability/Statistics for Bioengineering with Matlab exercises

Statistics for Bioengineering Sciences
with MATLAB and WinBUGS Support

Brani Vidakovic
Department of Biomedical Engineering, Georgia Tech
(2011) Springer, New York
It is constantly updated with the newest version at the link below.

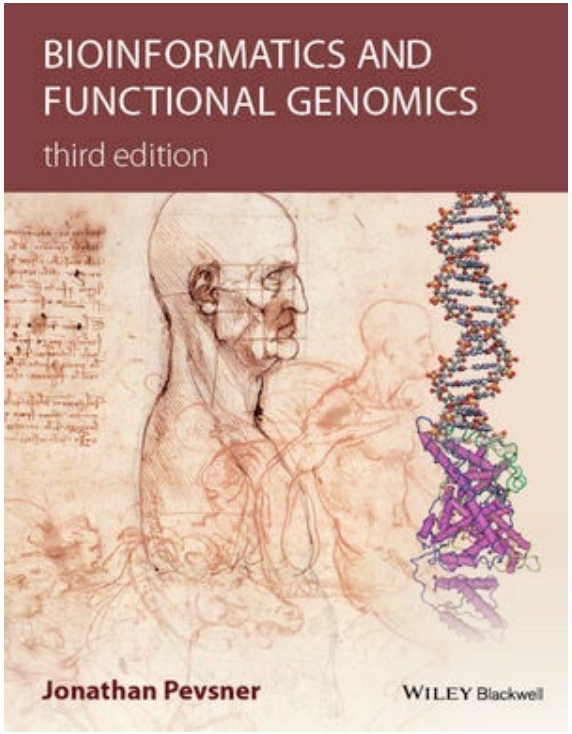


Free as a PDF eBook at
http://statbook.gatech.edu/statb4.pdf
Matlab exercises and datasets are at
http://springer.bme.gatech.edu

Genomics/Systems Biology Textbook

- *J Pevsner*
  Bioinformatics and functional genomics
Wiley-Blackwell,
2nd edition [2009] exists in electronic form
3rd edition [2015] has up-to-date information on NGS: RECOMMENDED
(about $60 on amazon)

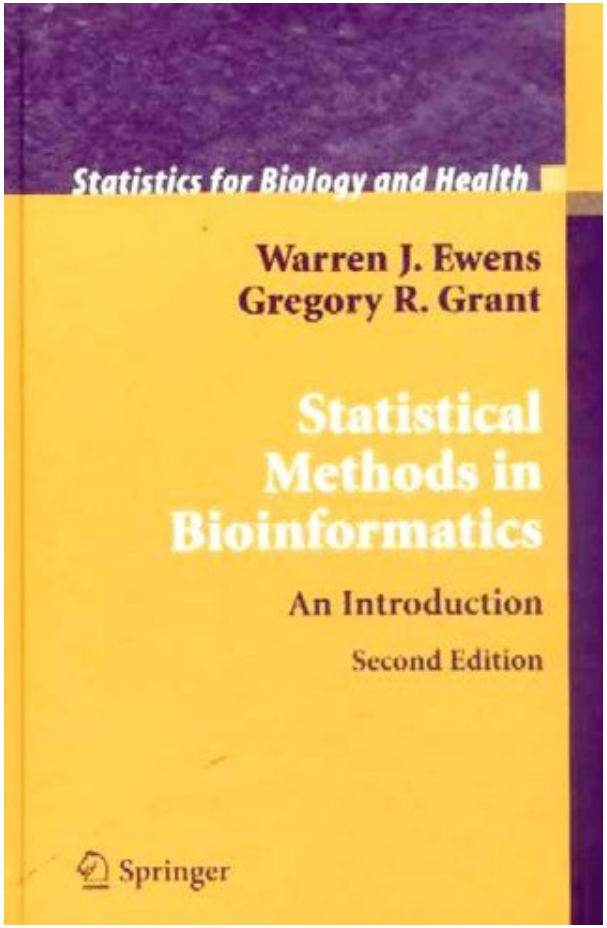
- *2nd edition is available for free in electronic form in our library*



Another Bioinformatics/Statistics Textbook

- *Ewens, WJ and Grant, GR* **Statistical Methods in Bioinformatics: An Introduction,** *2nd ed, Springer, 2005.*

- *2nd edition as PDF eBook*

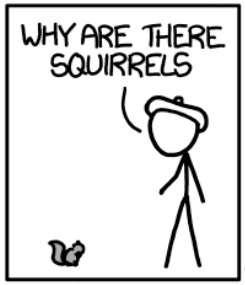


Credit: XKCD comics

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 TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY ARE THERE SLAVES IN THE BIBLE
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 SWARMS OF GNATS
WHY IS THERE PHLEGM
WHY ARE THERE SO MANY CROWS IN ROCHESTER,
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 PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE
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 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 ARE MY BOOBS ITCHY
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 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 AREN'T THERE GUNS IN HARRY POTTER

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

WHY DO IGUANAS DIE
WHY AREN'T THERE DINOSAUR GHOSTS
WHY IS THERE HELL IF GOD FORGIVES
WHY IS GPS FREE
WHY IS THERE FEMALE MR MIMES
WHY IS YKK ON ALL ZIPPERS
WHY ARE THERE WEEKS
WHY DO I FEEL DIZZY
WHY IS THERE LAVA
WHY IS THERE NO KING IN ENGLAND
WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS LIFE SO BORING

This course is about biological data and probability theory, and statistics concepts needed for its analysis

What biological data will be discussed?

Will be covered in lectures or Matlab exercises:

- Genomic data: strings of letters ACGT
- Gene Expression data: messenger RNA copy numbers transcribed from genes
- Proteomic data: protein abundances
- Network data: pairs of interacting genes or proteins and protein-protein interaction strengths

Will not be covered:

- Imaging data such as e.g. fMRI brain scans,
  Brain connectome data, Ecosystem dynamics data

Why do you need
probability and statistics
to analyze
modern biological data?

Definition of probability theory by Encyclopedia Britannica

a branch of mathematics concerned with the analysis of random phenomena

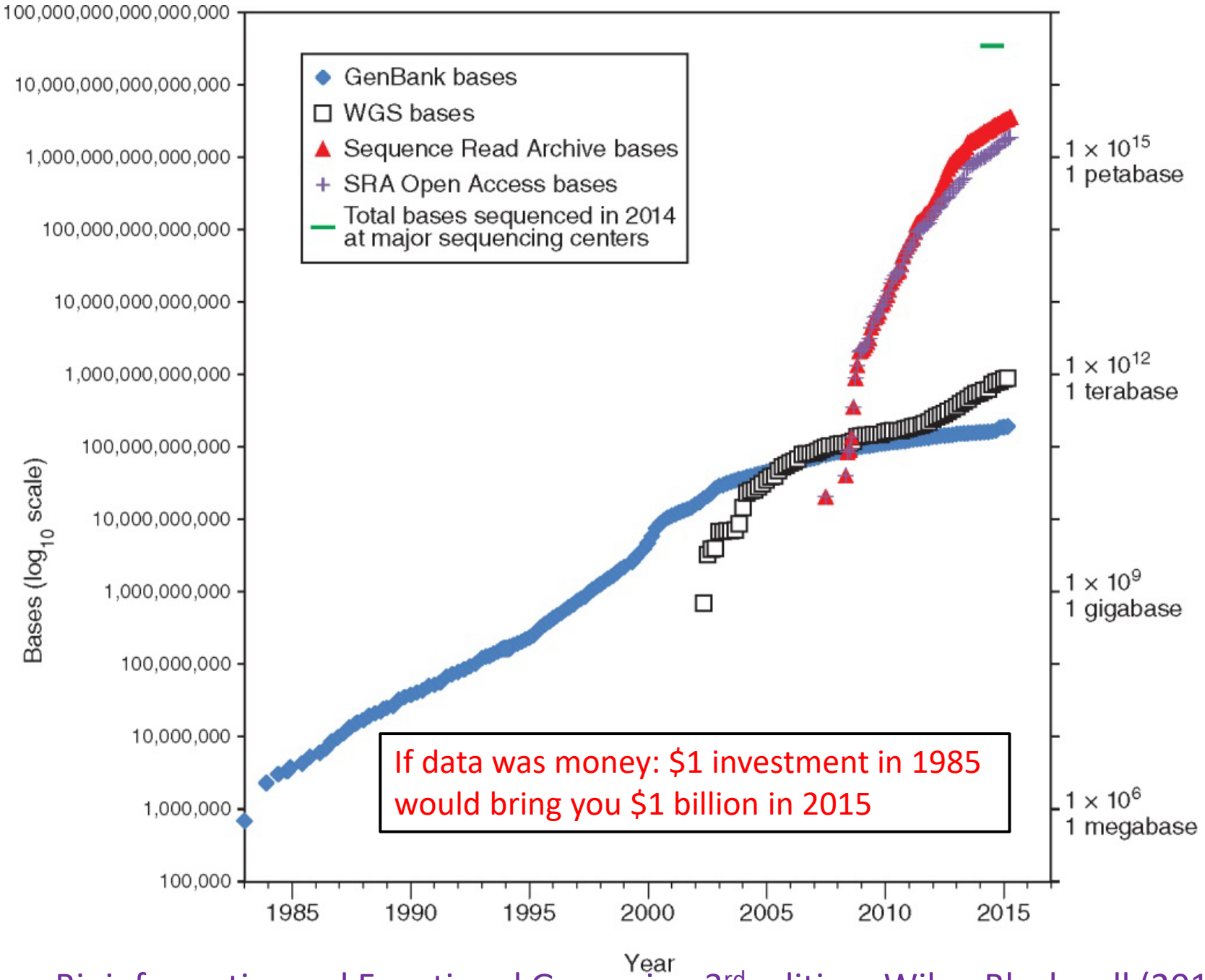
Definition of *statistics* by Merriam-Webster

1 : a branch of mathematics dealing with the collection, analysis, interpretation, and presentation of masses of numerical data

…

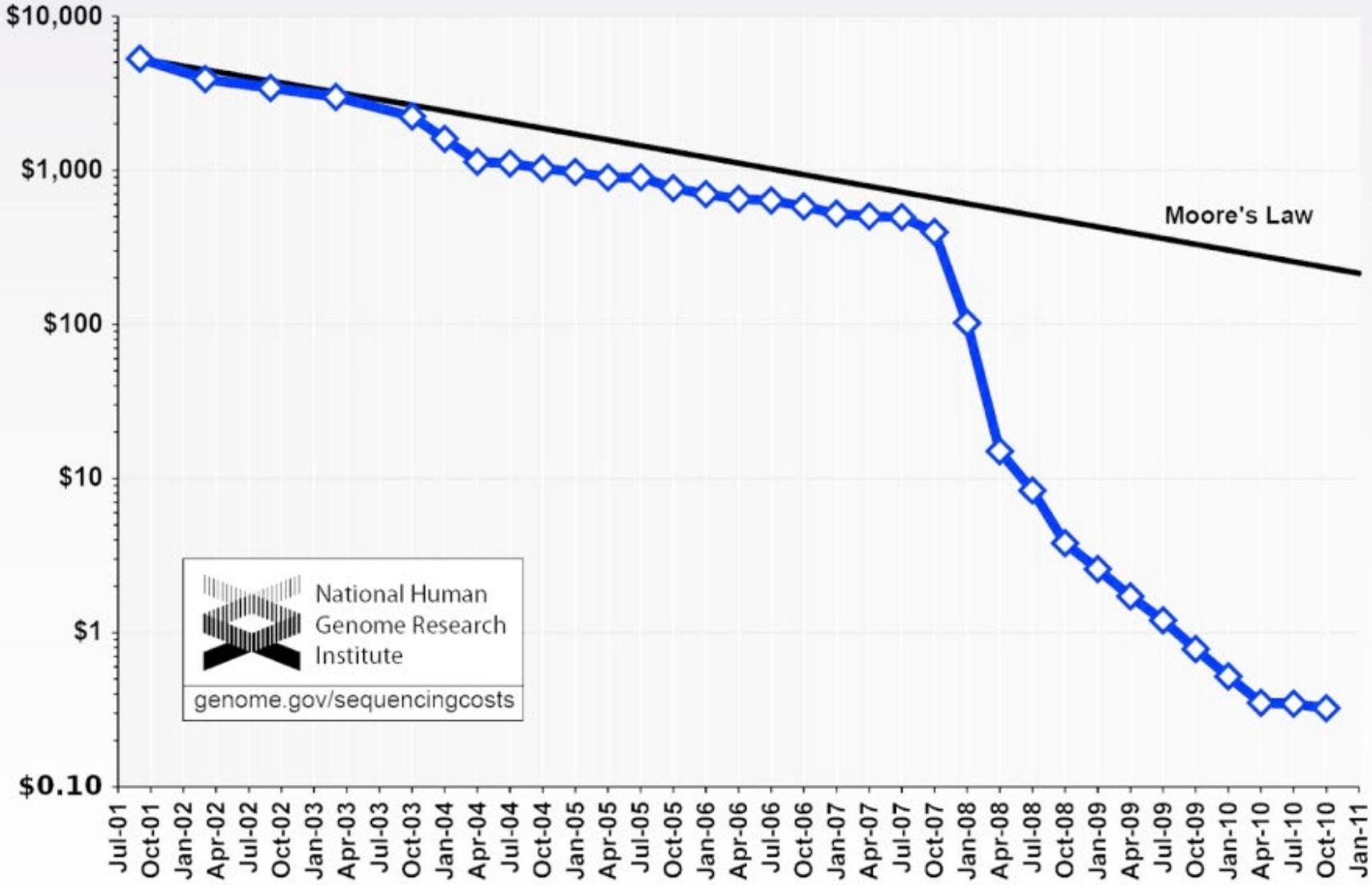
Why do you need
probability and statistics
to analyze
modern biological data?

Reason 1:
Biology now has Lots of Data



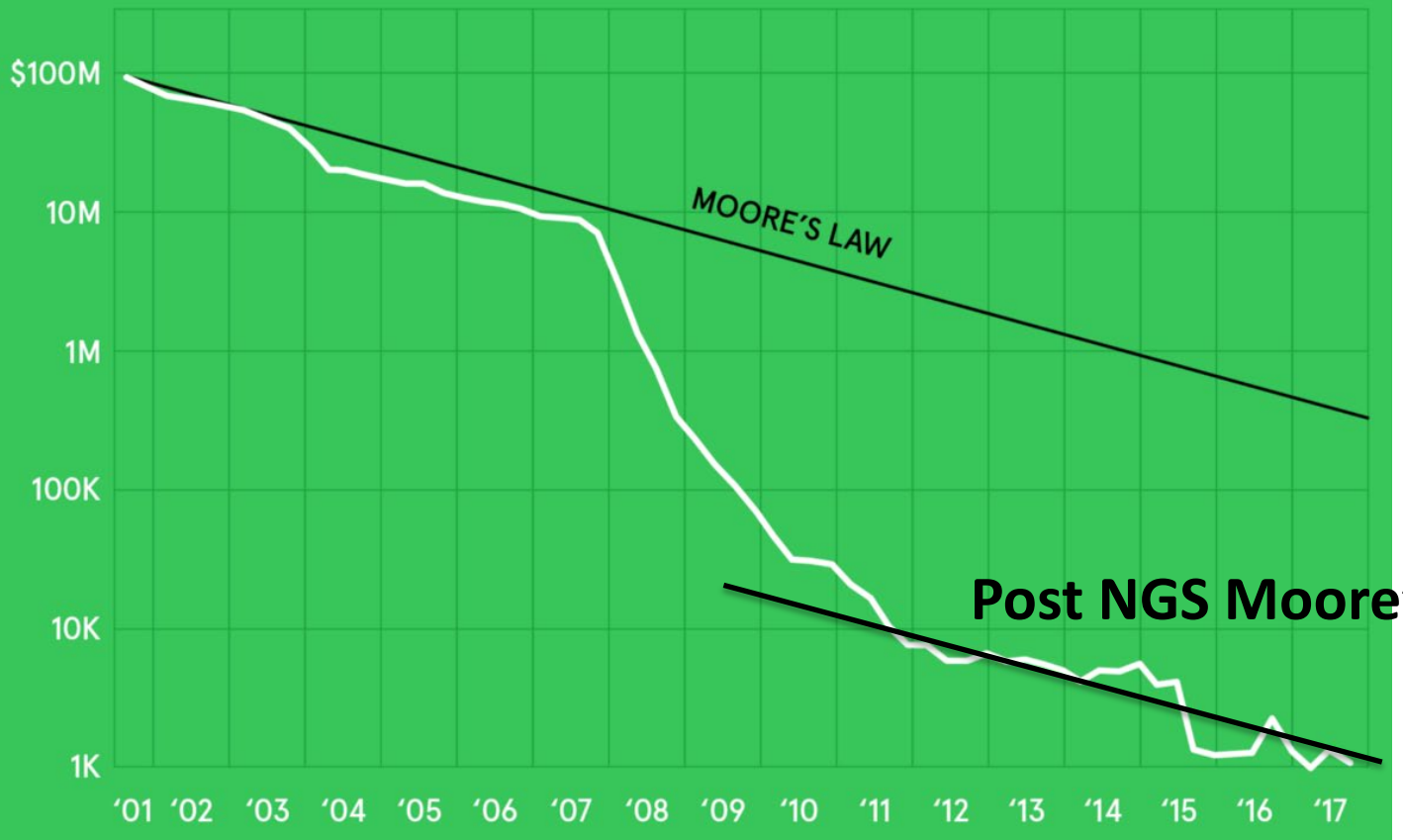
J. Pevsner, Bioinformatics and Functional Genomics, 3rd edition, Wiley-Blackwell (2015)

Cost per Megabase of DNA Sequence



Cost per Genome Sequenced

The cost of sequencing a human genome compared with the reductions that would be expected at the rate Moore's law predicts for computer chips. Over the past decade, next-generation sequencing and cloud computing drove the figure down. The average bumped higher in recent years because of brief slowdowns in production.



Who will have bigger data by 2025?

Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year

Peta=10^{15} Exa=10^{18} Zetta=10^{21}

Z. Stephens, S. Lee, F. Faghri, R. Campbell, C. Zhai, M. Efron, R. Iyer, M. Schatz, S. Sinha, and G. Robinson (2015) PLoS Biol 13: e1002195.

Base pairs	Unit	Abbreviation	Example
1	1 base pair	1 bp	A, C, G, T = 2 bits = 0.25 bytes
1000	1 kilobase pair	1 kb	
1,000,000	1 megabase pair	1 Mb	
10^9	1 gigabase pair	1 Gb	
10^{12}	1 terabase pair	1 Tb	
10^{15}	1 petabase pair	1 Pb	

Size	Abbreviation	No. bytes	Examples
Bytes	–	1	1 byte is typically 8 bits, used to encode a single character of text
Kilobytes	1 kb	10^3	Size of a text file with up to 1000 characters
Megabytes	1 MB	10^6	Size of a text file with 1 million characters
Gigabytes	1 GB	10^9	600 GB: size of GenBank (uncompressed flat files) ftp://ftp.ncbi.nih.gov/genbank/gbrel.txt (WebLink 2.84)
Terabytes	1 TB	10^{12}	385 TB: United States Library of Congress web archive (http://www.loc.gov/webarchiving/faq.html) (WebLink 2.85)
			464 TB: Data generated by the 1000 Genomes Project (http://www.1000genomes.org/faq/how-much-disk-space-used-1000-genomes-project) (WebLink 2.86)
Petabytes	1 PB	10^{15}	1 PB: size of dataset available from The Cancer Genome Atlas (TCGA)
			5 PB: size of SRA data available for download from NCBI
			15 PB: amount of data produced each year at the physics facility CERN (near Geneva) (http://home.web.cern.ch/about/computing) (WebLink 2.87)
Exabytes	1 EB	10^{18}	2.5 exabytes of data are produced worldwide (Lampitt, 2014)

J. Pevsner, Bioinformatics and Functional Genomics, 3rd edition, Wiley-Blackwell (2015)

What makes genomic data so big?

- There are ~9 millions species each with its own genome
- Each of us humans (7.5 billions and counting) has unique DNA: we want to compare them all to each other
- Each cell has just 1 genome (DNA) but multitude of transcriptomes (RNA levels) and proteomes (protein levels)
- Cancer cells acquire mutations in their genomes: need to track multiple lineages in a tumor vs time to understand cancer
- DNA was proposed as a long-term storage medium of information

Farfetched? Storage standards evolve fast but DNA standard remained unchanged for 4 billion years

Note: Nature article started the comparison with a hard drive and flash memory skipping the floppy disk

nature International weekly journal of science

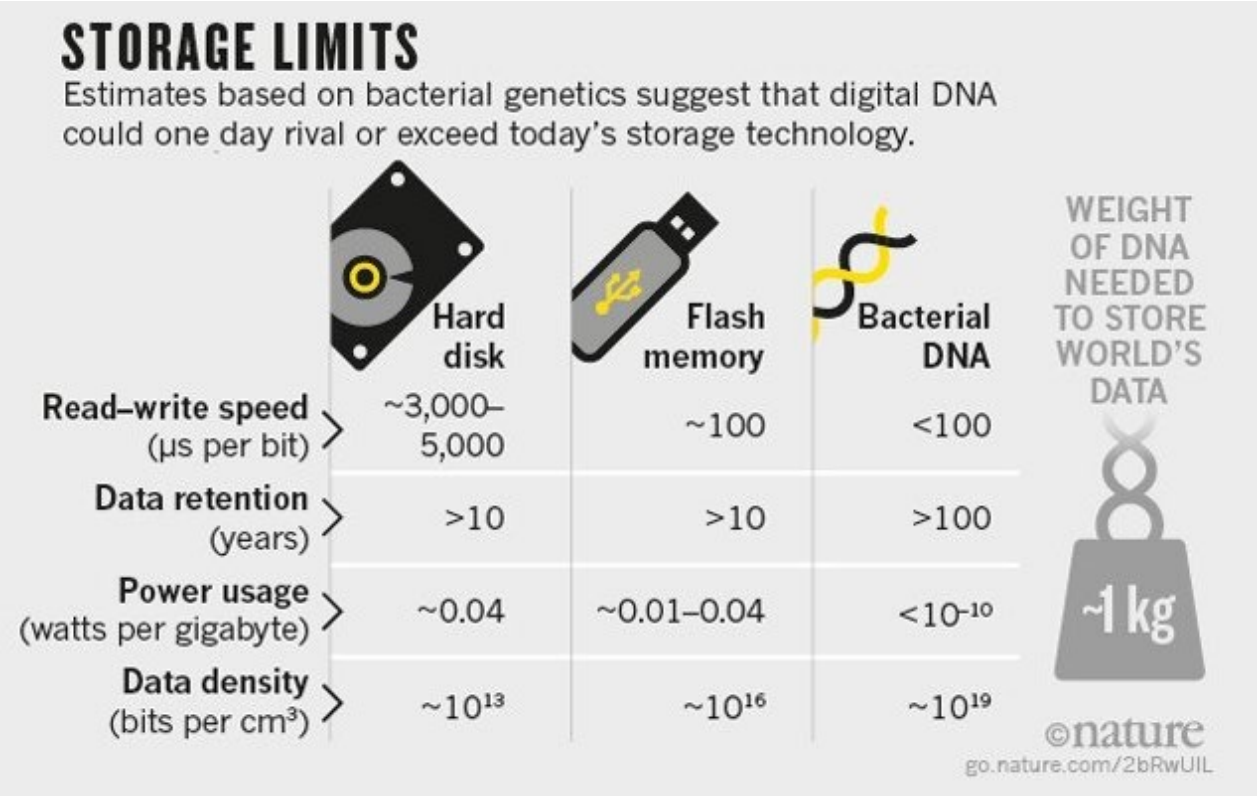
NATURE | NEWS FEATURE

How DNA could store all the world's data

Modern archiving technology
may hold an answer to that pr

Andy Extance

31 August 2016

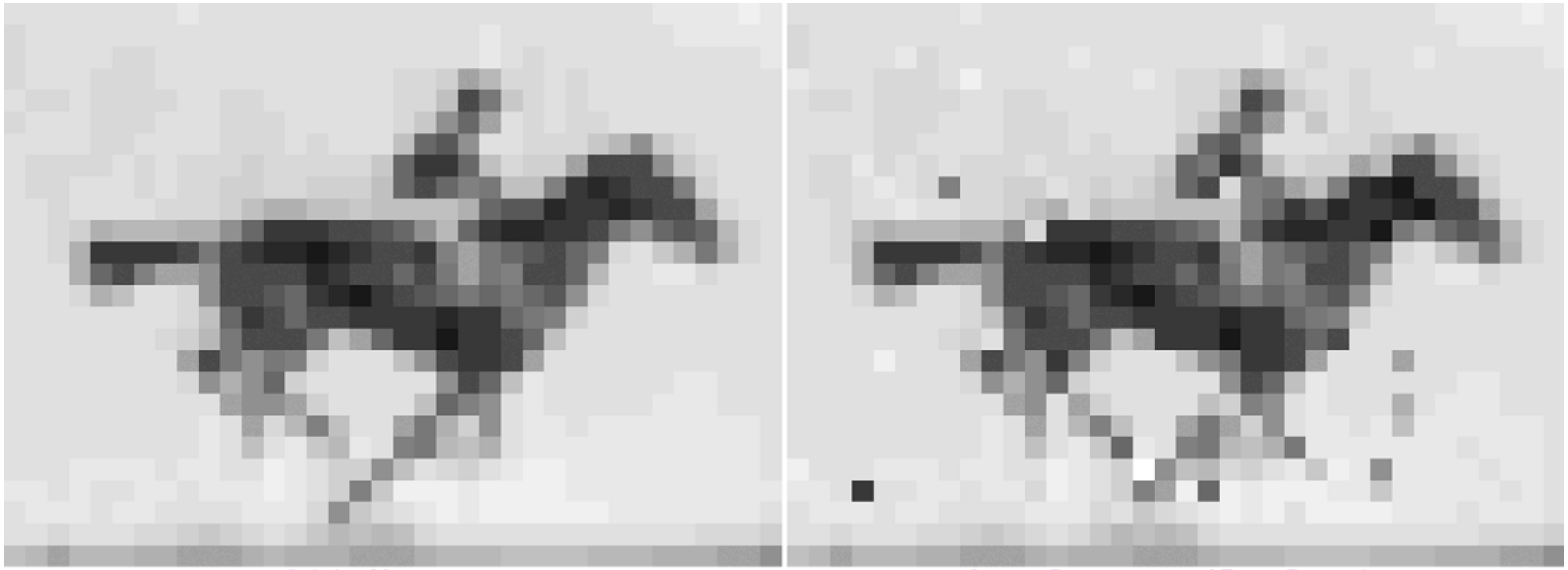


- Prof Olgica Milenkovic from Electrical and Computer Engineering UIUC is a local expert on this topic

- Profs. George Church and Sri Kosuri (Harvard Medical School) explains a potential use of DNA as storage medium in 2012

- https://www.youtube.com/watch?v=IJAdqAVjQqY

Fast-forward from 2012 to 2017



Original Image

Image Reconstructed From Bacteria

Shipman SL, Nivala J, Macklis JD, Church GM.
CRISPR–Cas encoding of a digital movie into the genomes
of a population of living bacteria. Nature. 2017;547: 345–349. doi:10.1038/nature23017

Why do you need
probability and statistics
to analyze
modern biological data?

Reason 2:
Life is random and messy

Show video
“Cell organelles”

- Made at the Walter and Eliza Hall Institute of Medical Research at Victoria, Australia
- Animated by award-winning artist Dr. Drew Berry
- Go to https://www.wehi.edu.au/wehi-tv for other videos

Life is messy, random, and noisy

Yet it is beautifully complex
and has many parts
(see statistics)

Why life is so random?

- Biomolecules are very small (nano- to micro-meters) → Brownian noise
- # molecules/cell is often small → Large cell-to-cell variations
- Genomic data comes from biological evolution
  - the Mother of all random processes
- Genomic data involves (random) samples
  - We have genomes of some (not all) organisms
  - We have tissue samples of some (not all) cancer patients

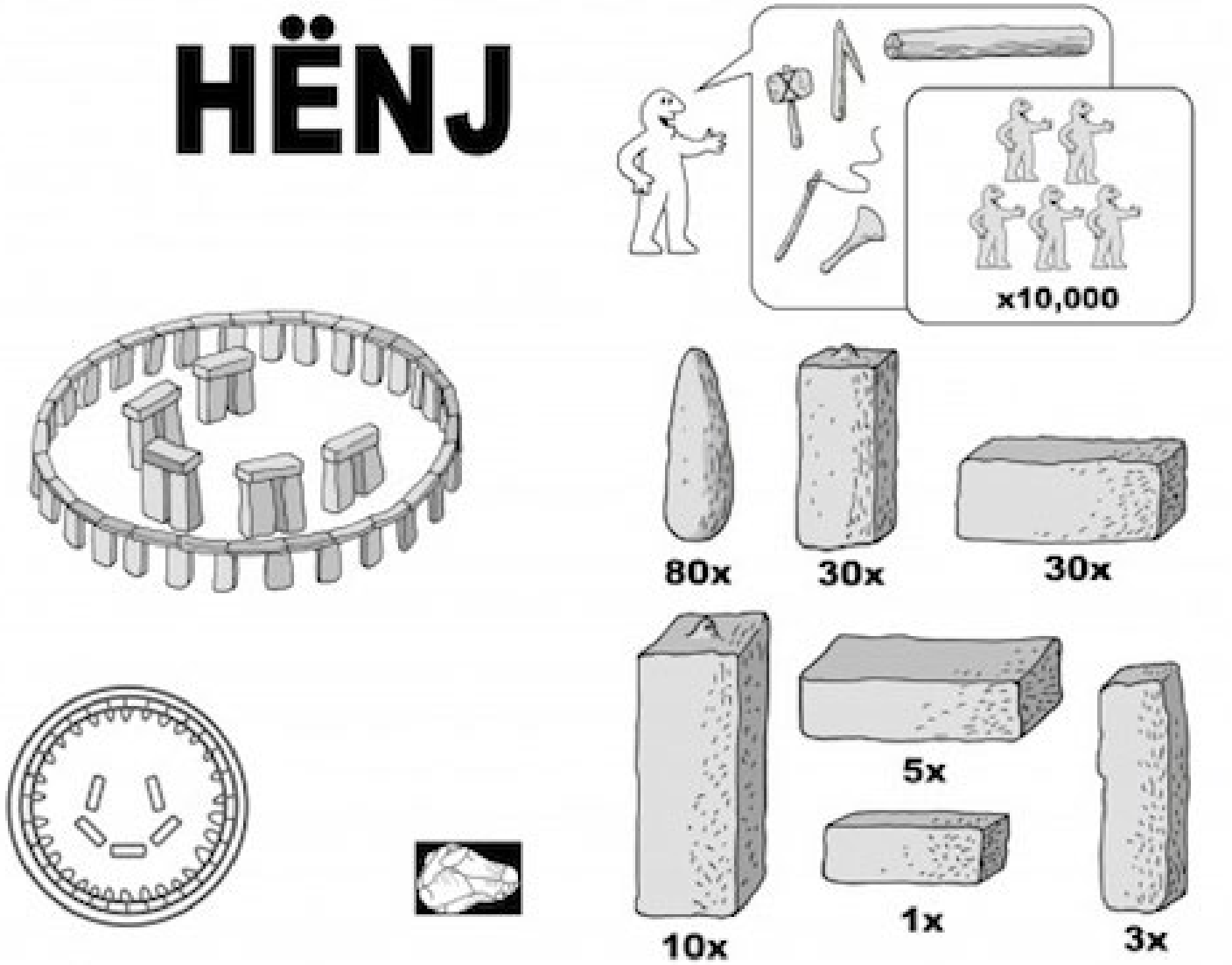
Why life is so complex?

Primer on complex system

Complex systems have many interacting parts

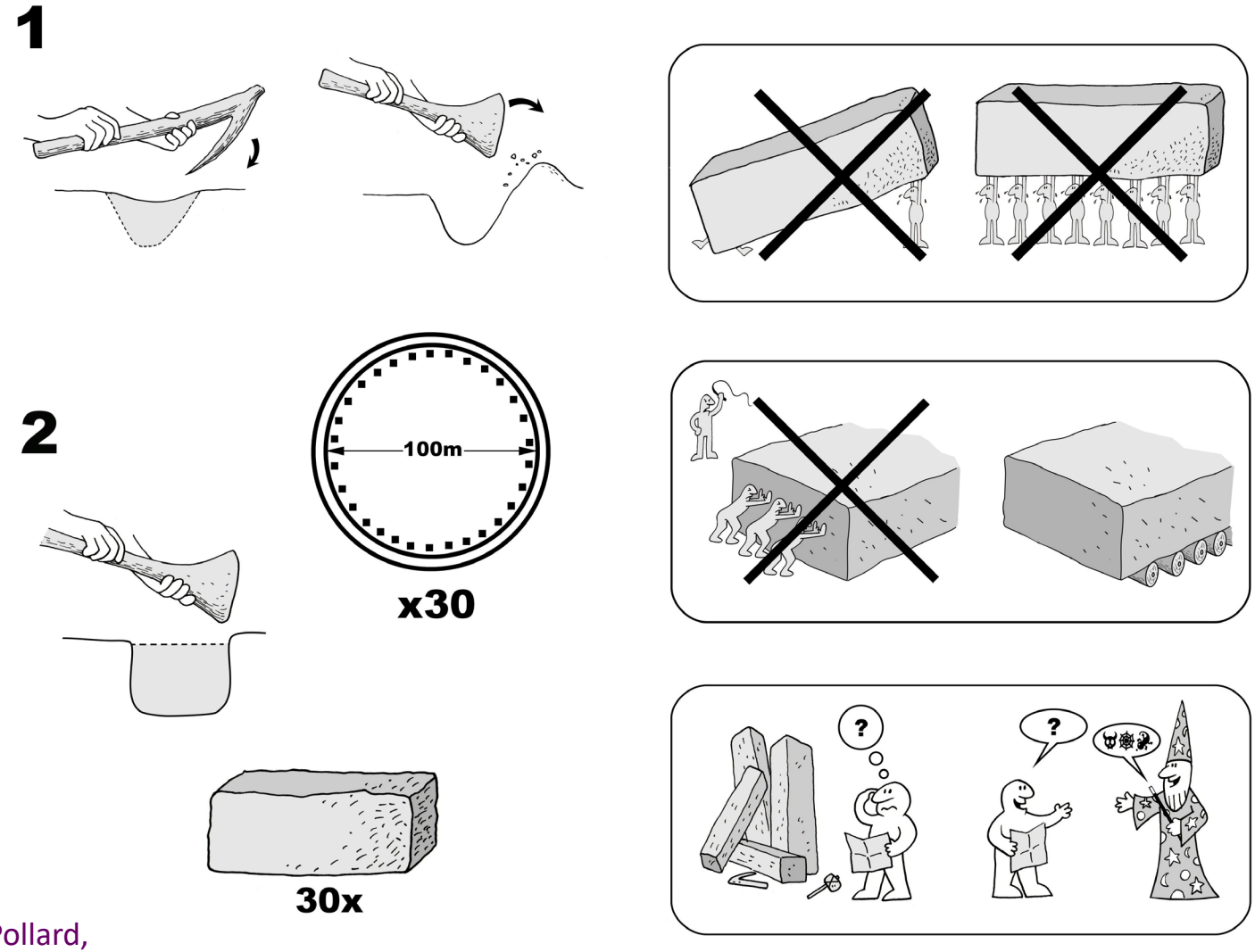
- All parts are different from each other
  - 10s thousands (10^4) types of proteins in an organism
  - 100 thousands (10^5) organizations (AS) in the Internet
  - 1 billion (10^9) people on Facebook
  - 10 billion (10^{10}) web pages in the WWW
  - 100 billion (10^{11}) neurons in a human brain
  - NOT 10^{23} electrons or quarks studied by physics: they are all the same and boring!
- Yet they share the same basic design
  - All proteins are strings of the same 20 amino acids
  - All WWW pages use HTML, JavaScript, etc.
  - All neurons generate and receive electric spikes

Example: a complex system with many parts



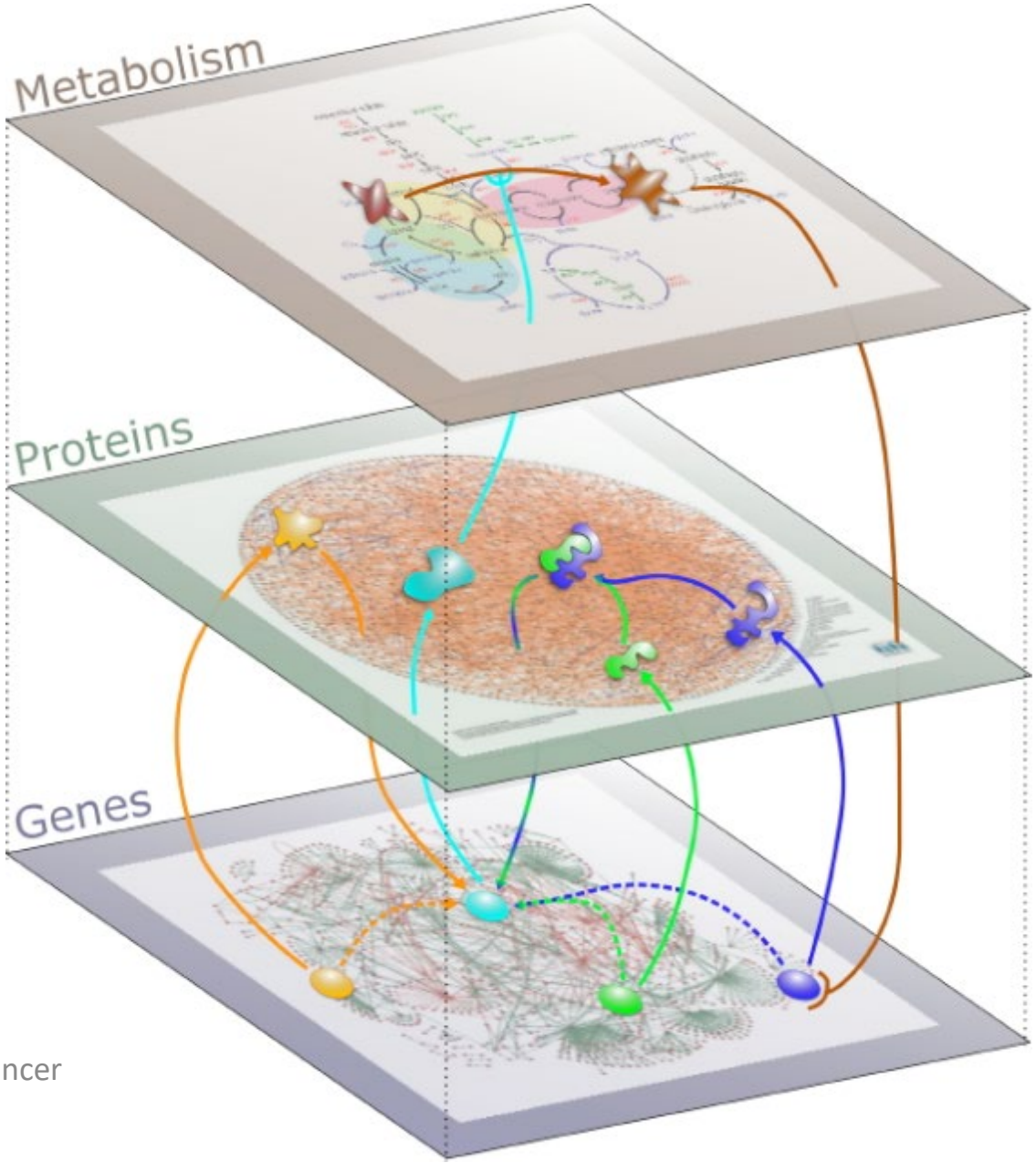
Justin Pollard,
http://www.designboom.com

Parts interact →
they need to be assembled to work



Justin Pollard,
http://www.designboom.com

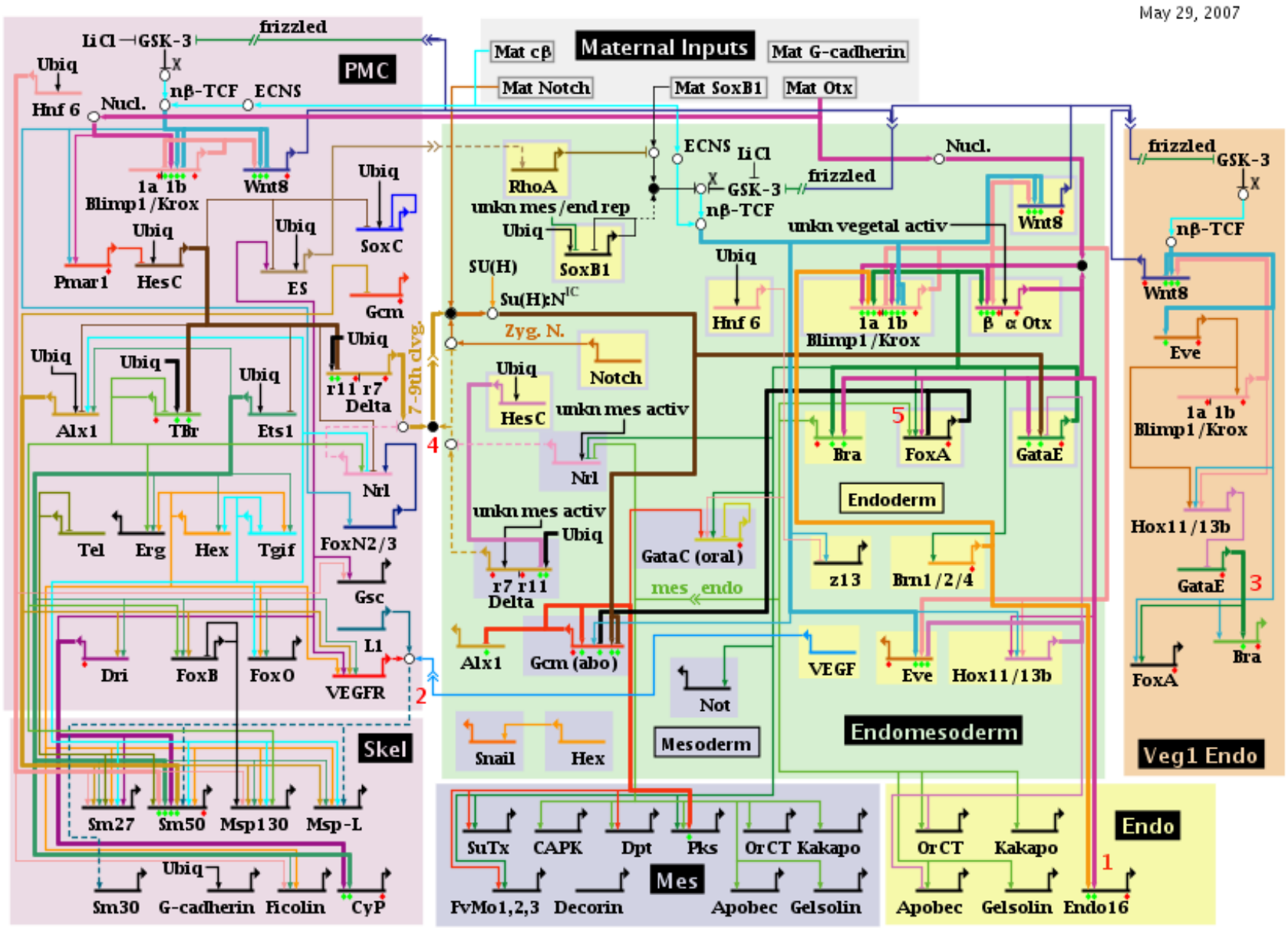
Intra-cellular Networks operate on multiple levels



Slides by Amitabh Sharma, PhD

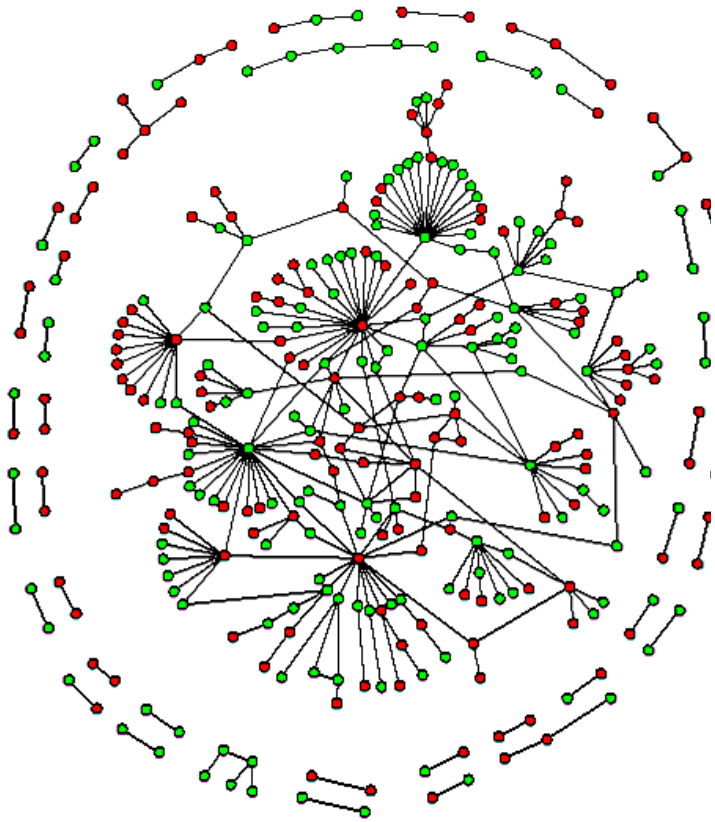
Northeastern University & Dana Farber Cancer Institute

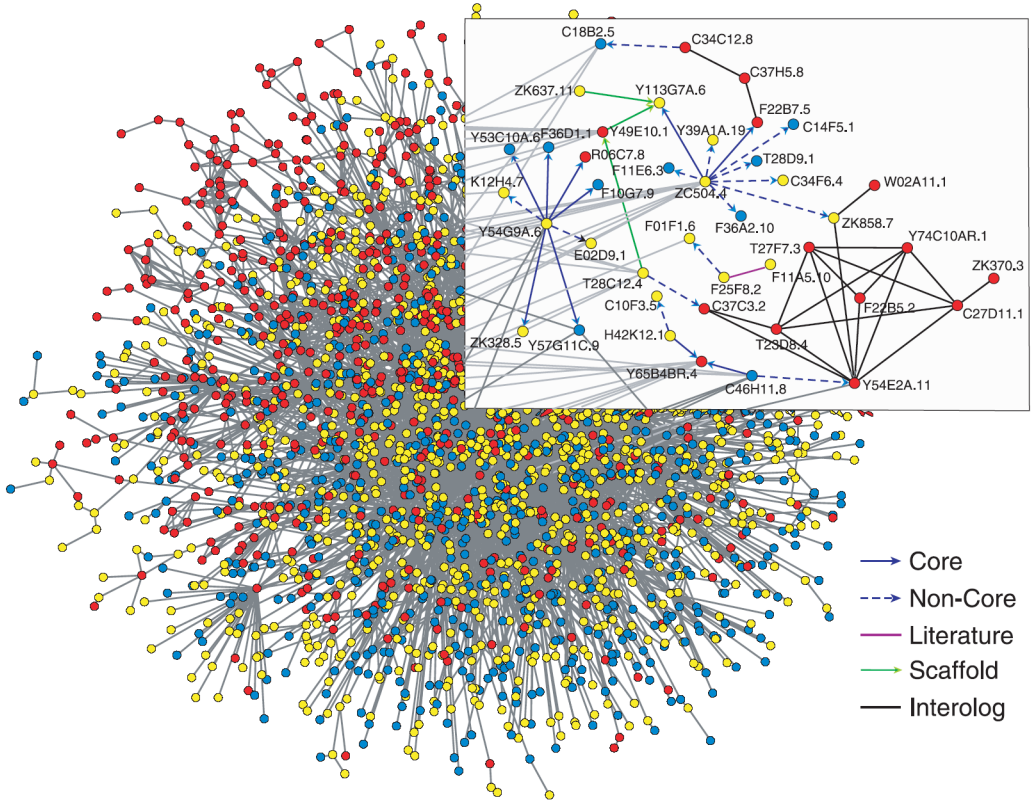
Sea urchin embryonic development (from endomesoderm up to 30 hours) by Davidson's lab



Ubiq=ubiquitous; Mat = maternal; activ = activator; rep = repressor;
unkn = unknown; Nucl. = nuclearization; χ = β-catenin source;
nβ-TCF = nuclearized b-β-catenin-Tcf1; ES = early signal;
ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

Protein-Protein binding
IntAct Database (Dec 2015)
Interactions: 577,297 Proteins: 89,716

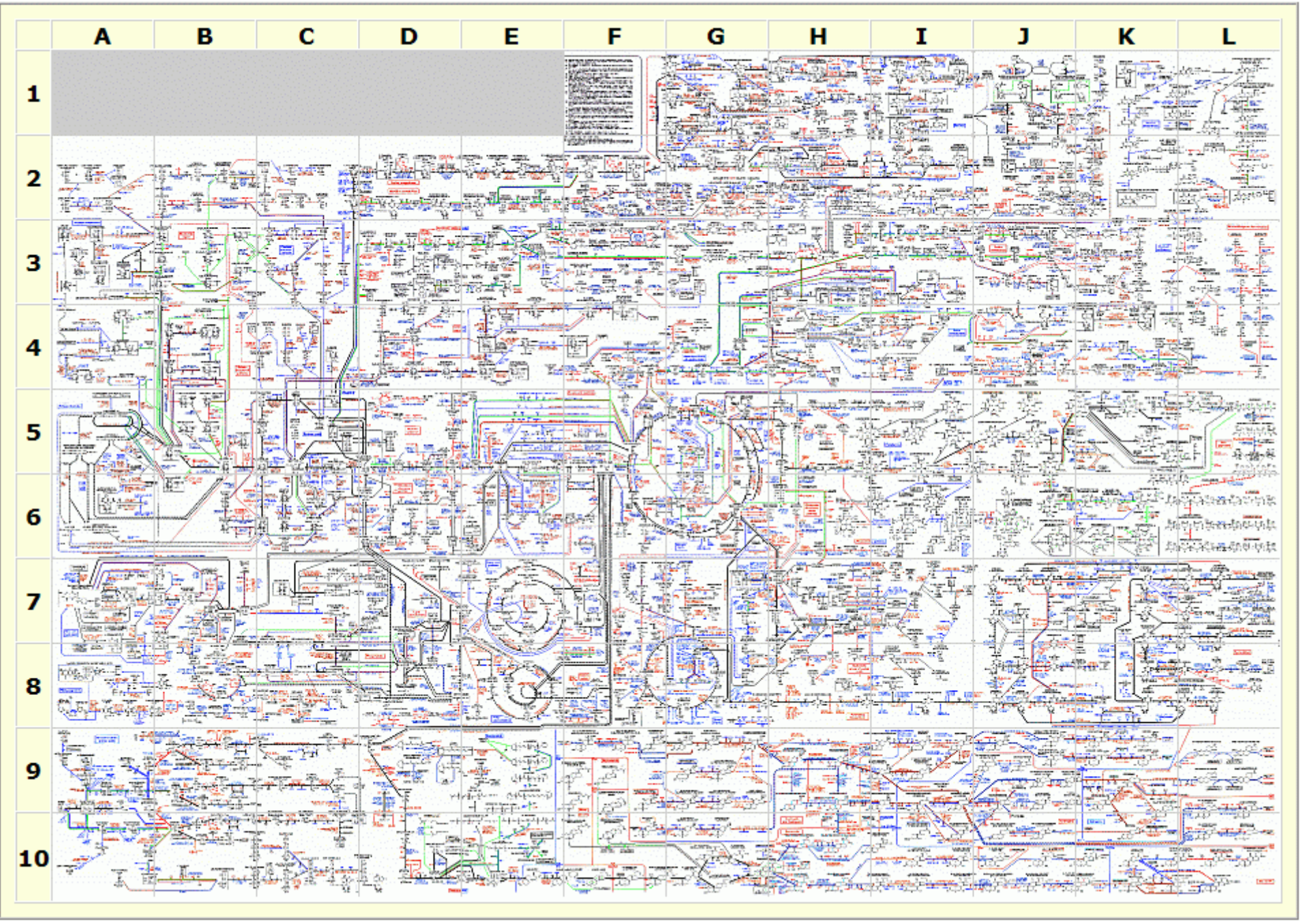




Baker's yeast *S. cerevisiae* (only nuclear proteins shown)
From S. Maslov, K. Sneppen, Science 2002

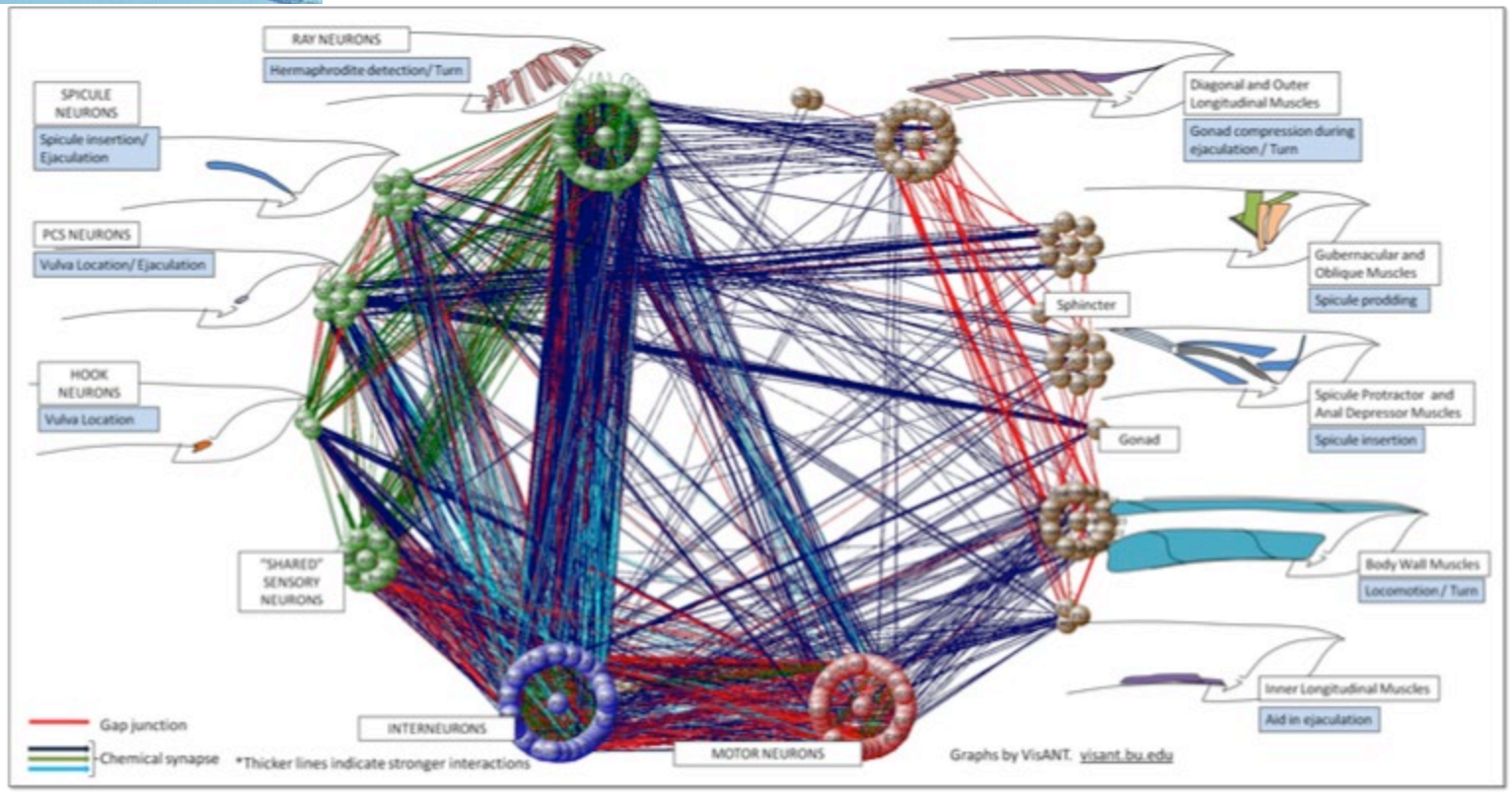
Worm *C. elegans*
From S. Lee et al , Science 2004

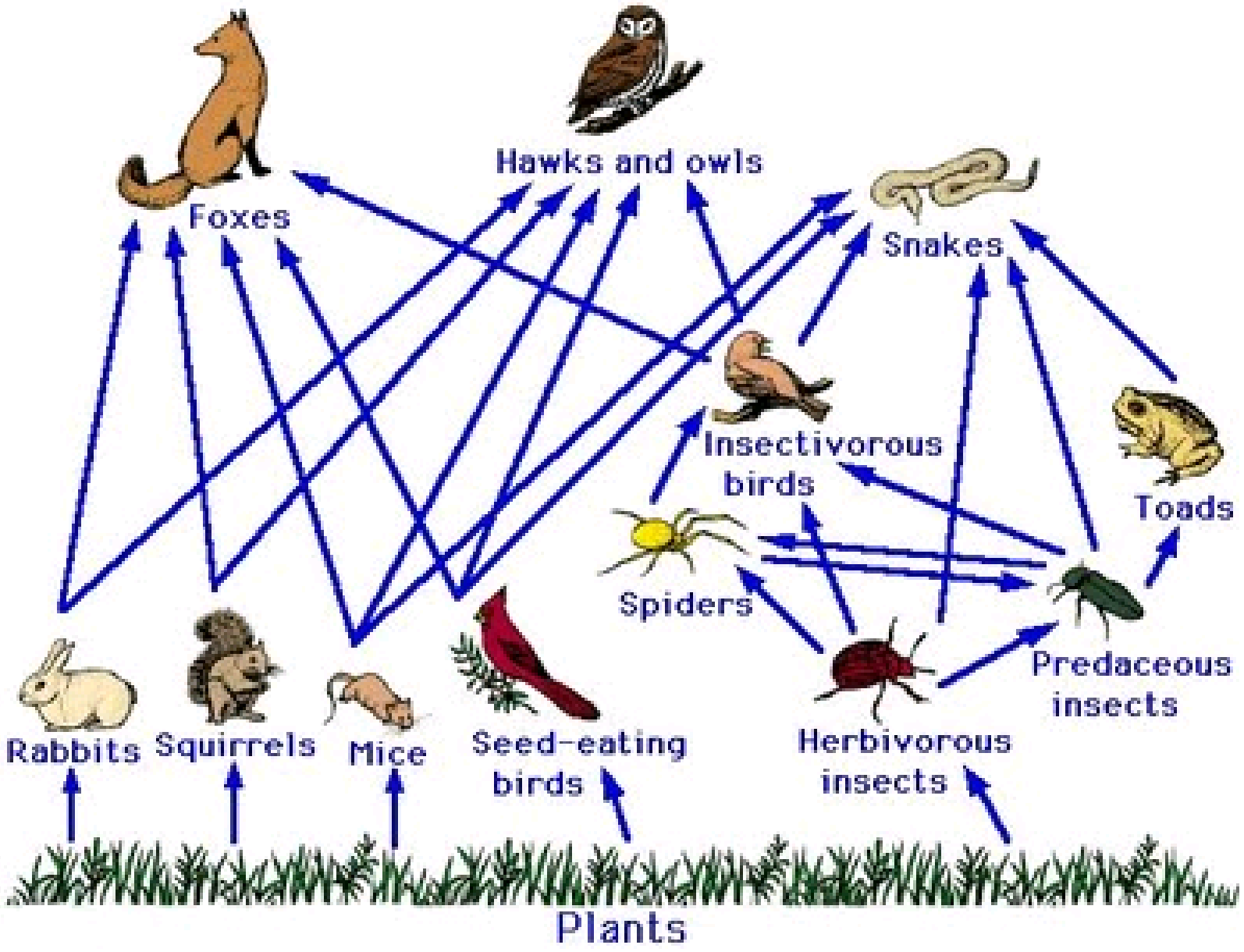
Metabolic pathway chart by ExPASy: **5702 reactions as of December 2015**

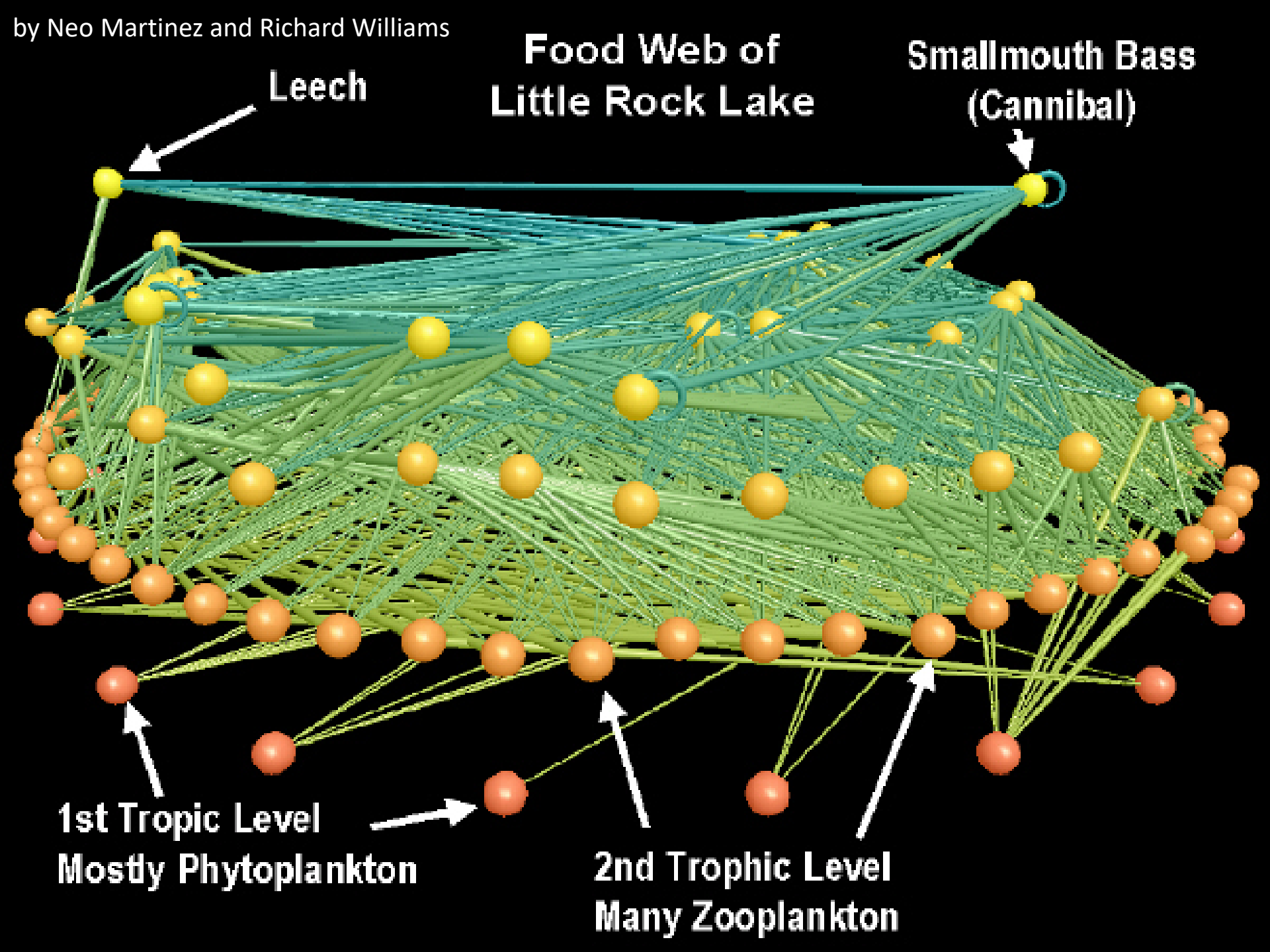


Brain and nerves of a worm

- Worm (C. elegans) has 302 neurons
- Our brain has 100 billion (10^{11}) neurons




Foxes
Hawks and owls
Snakes
Insectivorous birds
Toads
Spiders
Predaceous insects
Rabbits
Squirrels
Mice
Seed-eating birds
Herbivorous insects
Plants


by Neo Martinez and Richard Williams
Food Web of
Little Rock Lake
Leech
Smallmouth Bass
(Cannibal)
1st Tropic Level
Mostly Phytoplankton
2nd Trophic Level
Many Zooplankton

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 ARE THERE FEMALE MR MIMES
WHY IS THERE LAVA
WHY IS LIFE SO BORING
WHY ARE TREES TALL
WHY IS YKK ON ALL ZIPPERS
WHY ARE THERE WEEKS
WHY DO I FEEL DIZZY
WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND

WHY DO TESTICLES MOVE
WHY ARE THERE PSYCHICS
WHY ARE HATS SO EXPENSIVE
WHY IS THERE CAFFEINE IN MY SHAMPOO
WHY DO YOUR BOOBS HURT

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 AREN'T MY ARMS GROWING

WHY ARE THERE SWARMS OF GNATS
WHY IS THERE PHLEGM
WHY ARE THERE SO MANY CROWS IN ROCHESTER,
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 PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE

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 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 ARE MY BOOBS ITCHY
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 IS THERE A LINE THROUGH HTTPS

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 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 AREN'T THERE GUNS IN HARRY POTTER

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

Credit: XKCD comics