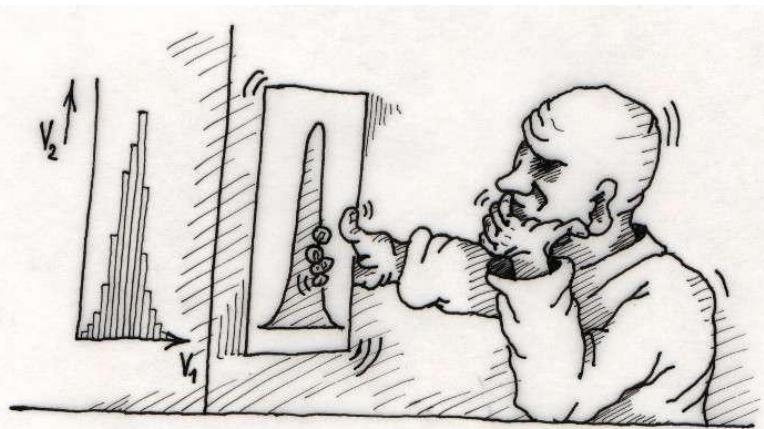


生物统计学： 生物信息中的概率统计模型

2020年秋



有关信息

- 授课教师：宁康
 - Email: ningkang@hust.edu.cn
 - Office: 华中科技大学东十一楼504室
 - Phone: 87793041, 18627968927
- 课程网页
 - <http://www.microbioinformatics.org/teach/#>
 - QQ群:

考评

课程成绩

=

课堂讨论 (10%)

+课后作业&随堂测验 (20%)

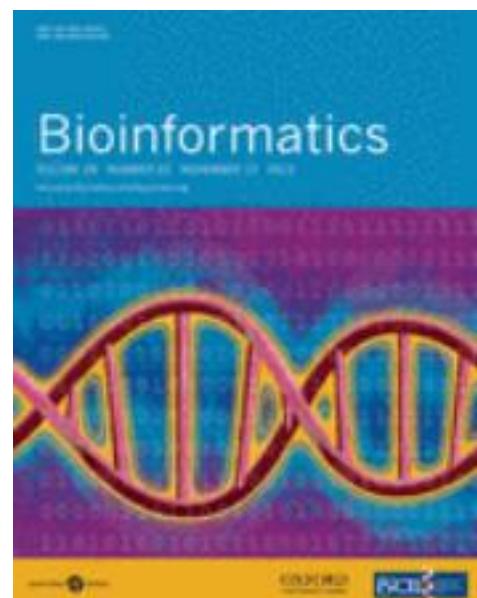
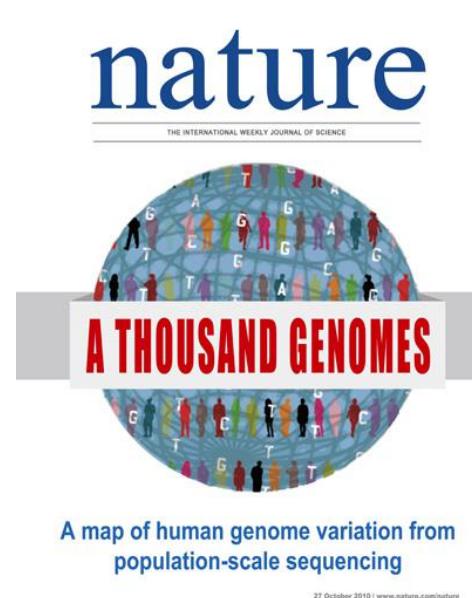
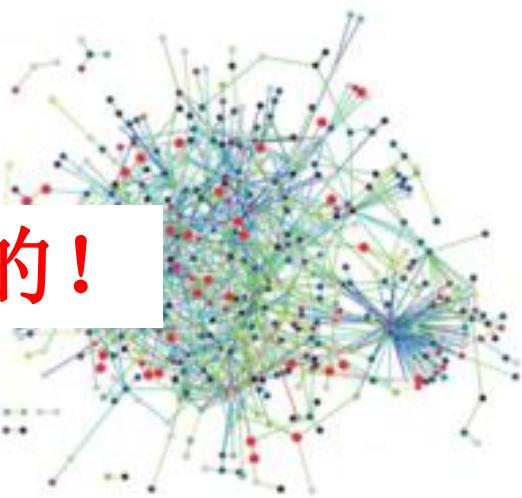
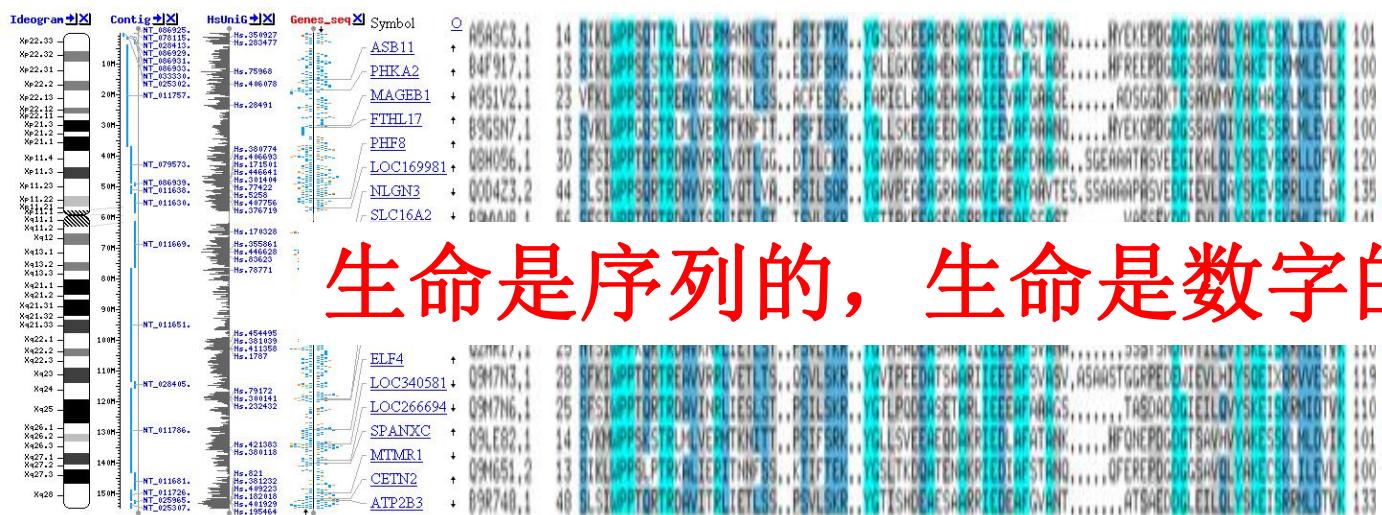
+终结性考试 (70%)

生物统计学：生物学视角

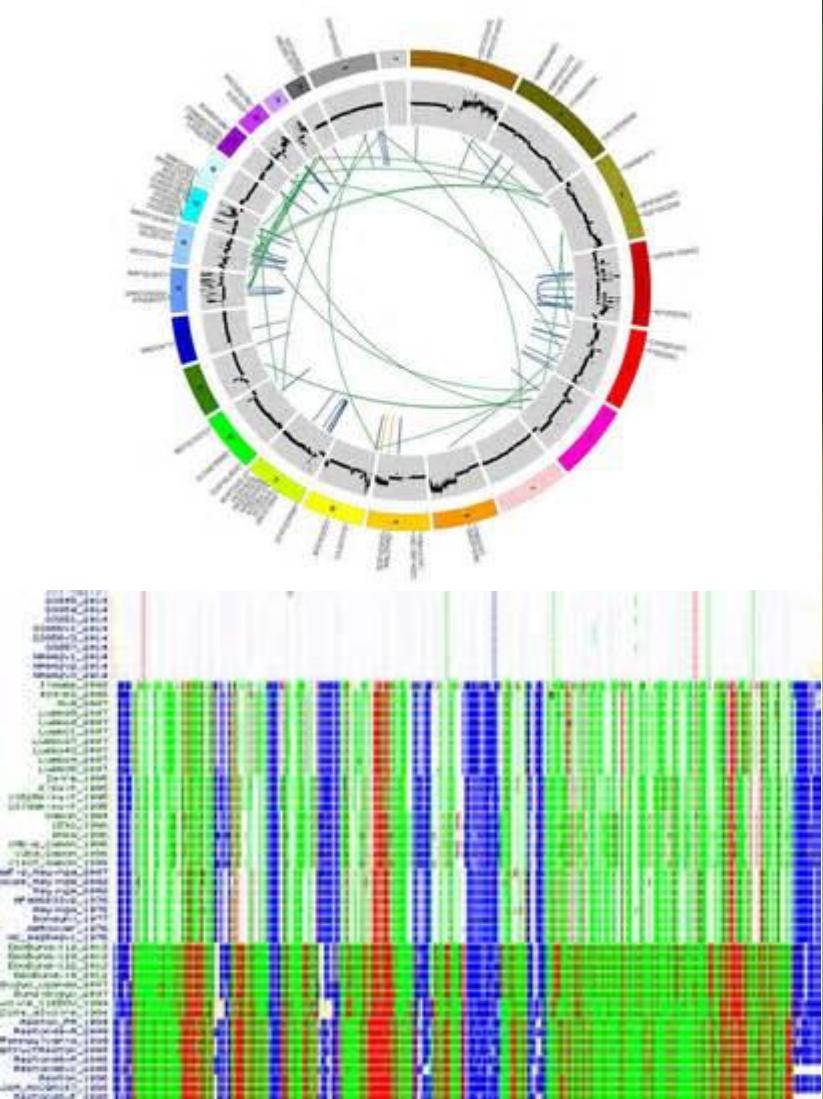


生物信息学@HUST

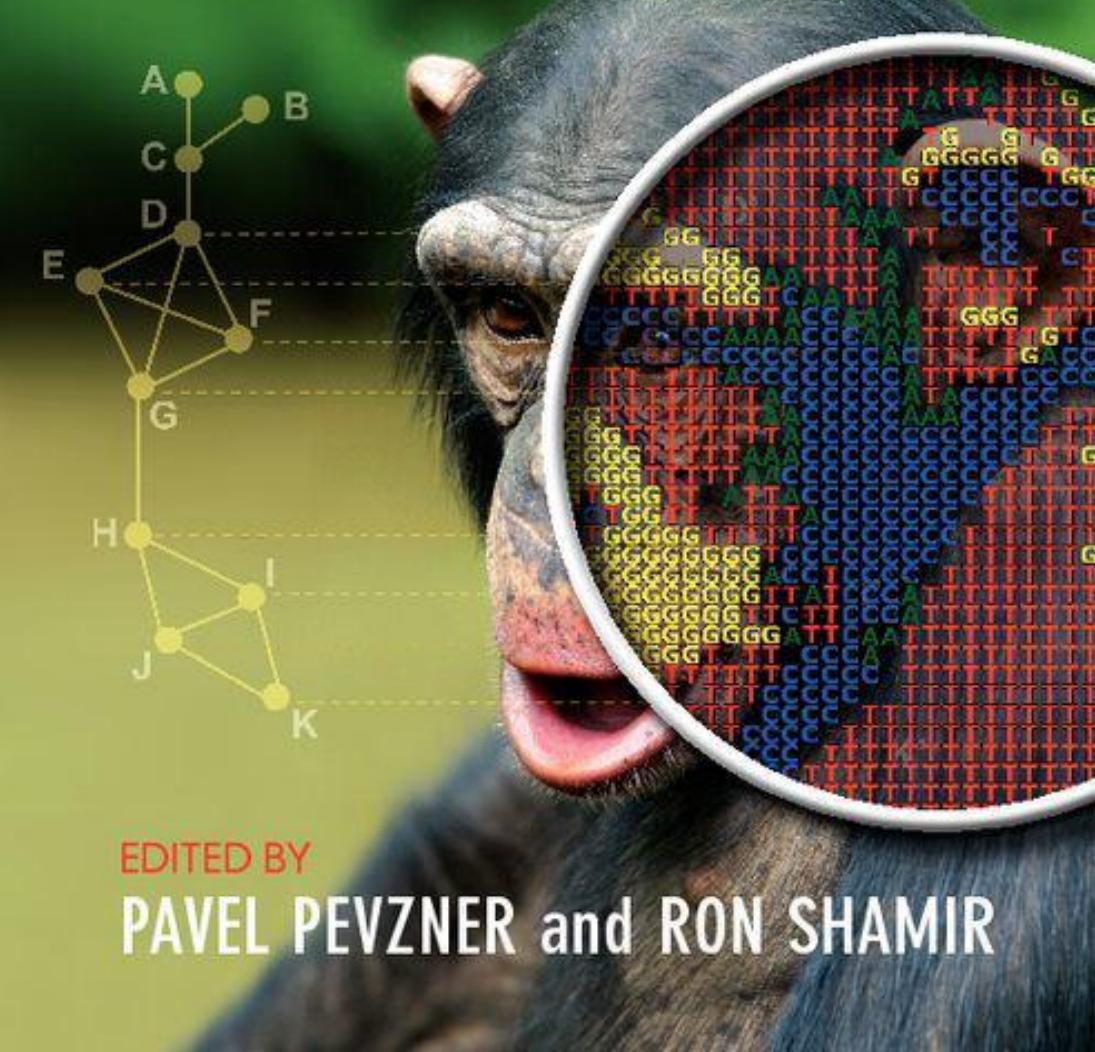
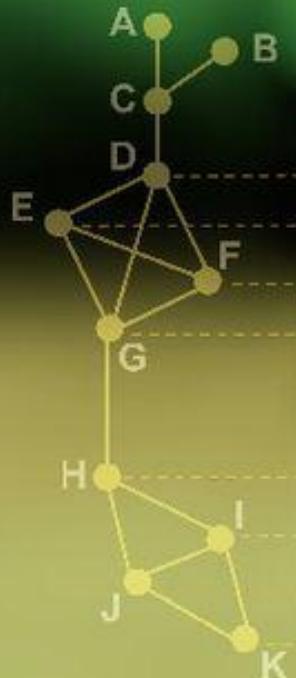
生命是序列的，生命是数字的！



生命是序列的，
生命是数字的！



BIOINFORMATICS FOR BIOLOGISTS

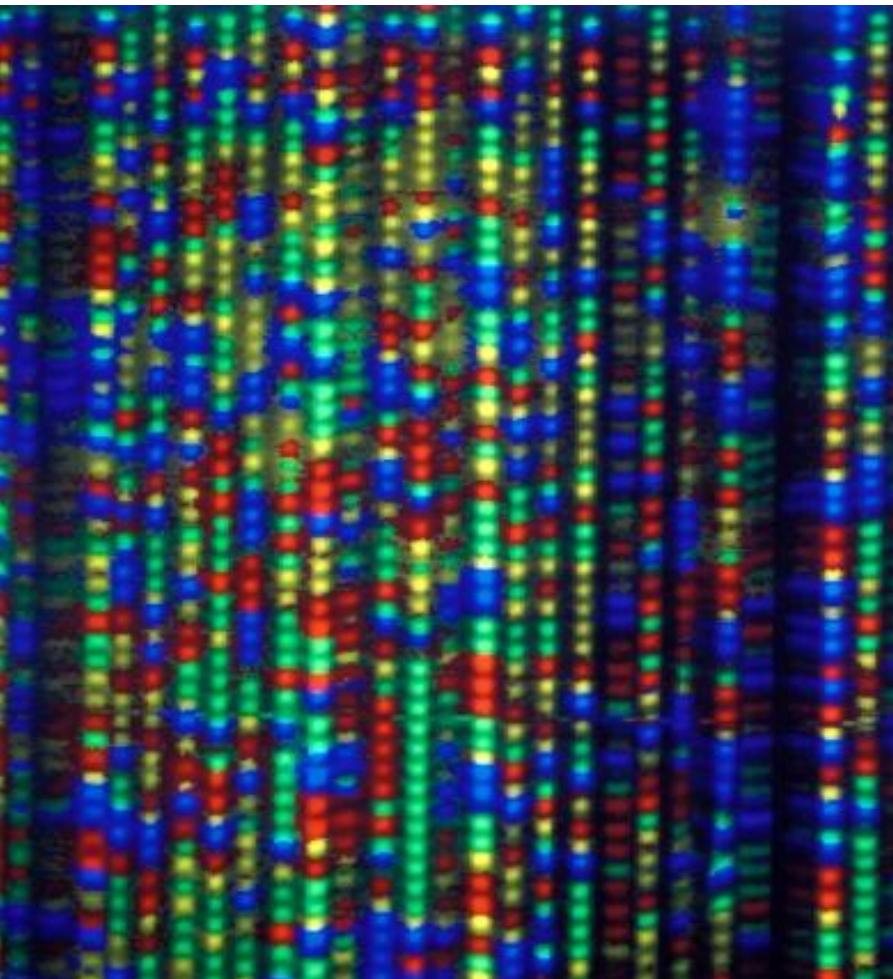
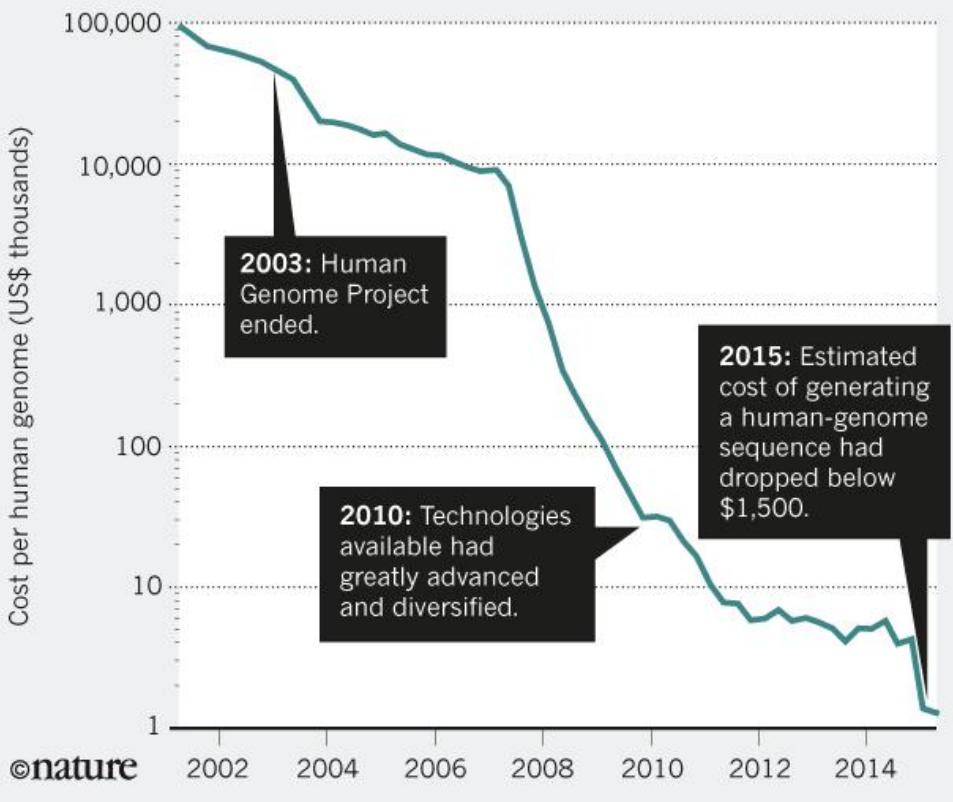


DNA sequencing and bioinformatics



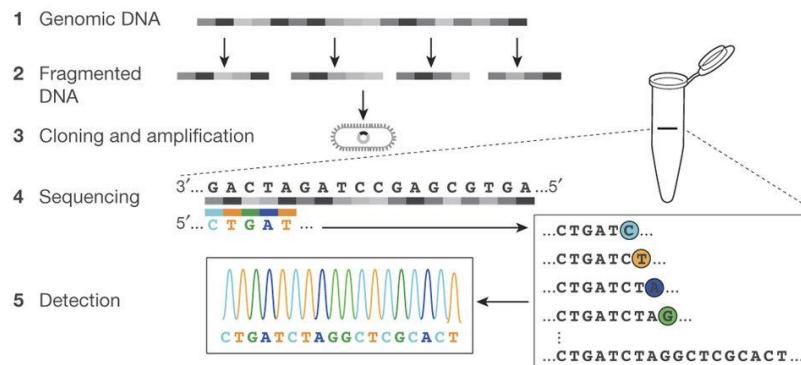
BETTER, CHEAPER, FASTER

The cost of DNA sequencing has dropped dramatically over the past decade, enabling many more applications.

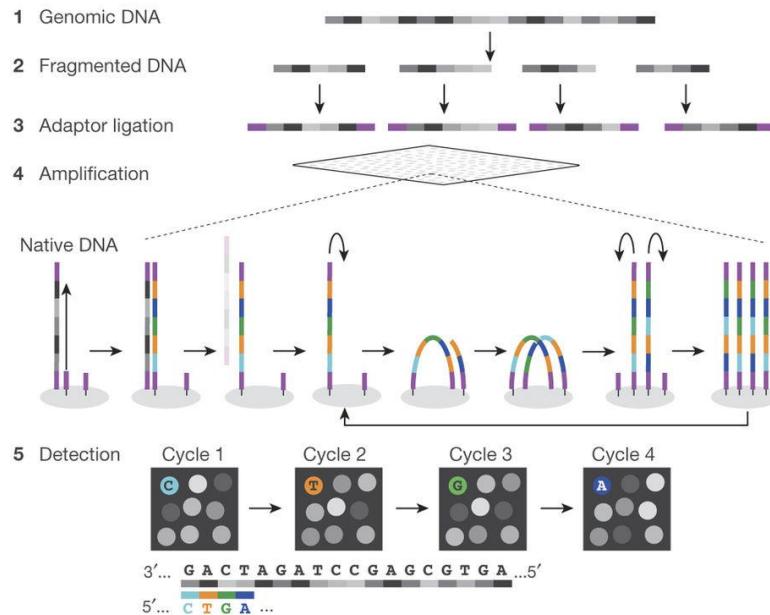


DNA Sequencing

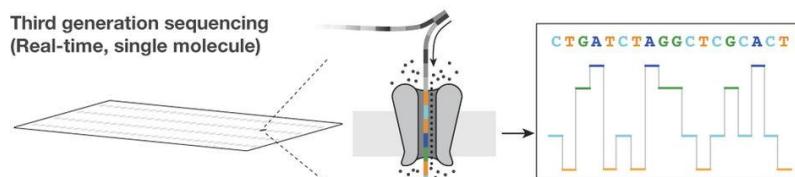
First generation sequencing (Sanger)



Second generation sequencing (massively parallel)

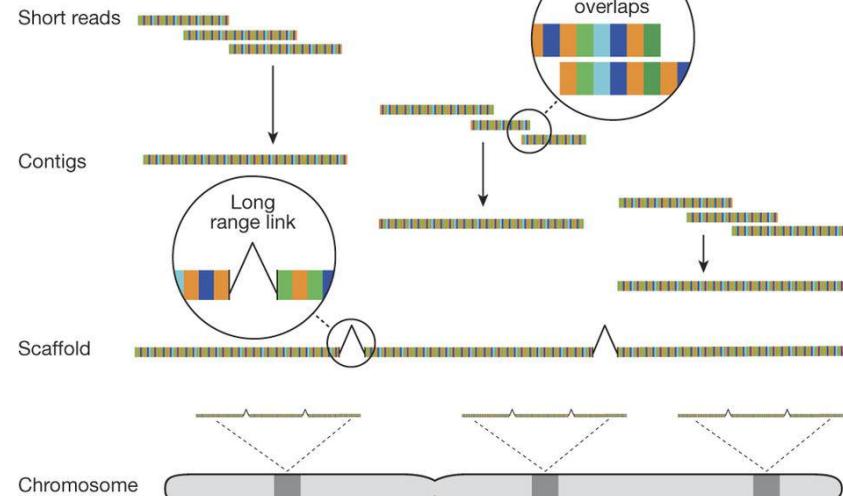


Third generation sequencing (Real-time, single molecule)



Sequencing applications

De novo genome assembly



Genome resequencing

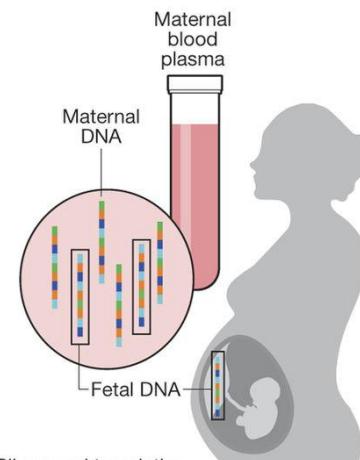
Individual

1 G A C T A G A T C C G A G C G T G A
 2 G A C T A G A T A C G A G C G T G A
 3 G A C G A G A T C C G C G C G T G A
 ...
 7.5 billion G A C T A G A T C C G A G C G C G A

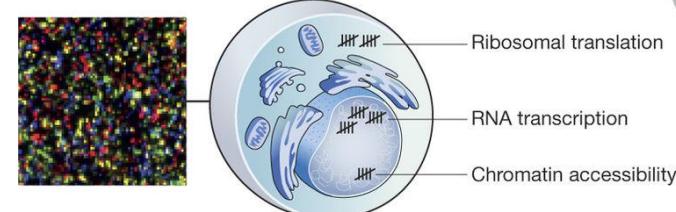
Sites of variation

G A C T A G A T C C G A G C G T G A

Clinical applications (NIPT)



Sequencers as counting devices



在今天，DNA测序技术已经在诸多方面达到了临床应用的具体要求。

科学家估计，全世界每年大约有四百万到六百万孕妇正在通过外周血游离DNA对胎儿的21三体综合征进行诊断，而十年之内，这个数字将超过1500万。

在高收入国家，基因组测序已经广泛用于多种疾病的产前诊断，可以揭示大约30%的出生缺陷，同时，这一数字也正随着数据解读能力的成熟而逐渐上升。

在肿瘤学领域，液体活检在最近几年已经成为了肿瘤相关学术，产业以及投资界的新宠。基于DNA测序的液体活检被认为正逐步发展为癌症诊断与预后评估的标准方法，能够在可知的时间内逐步补充甚至取代传统的创伤性癌症诊断技术。

同样，手持DNA测序仪等设备的开发也使得流行病学家甚至能够在最为偏远的地区高效完成对人类样本，动物以及昆虫病原载体甚至是空气，水，食物的基因检测。

流行病学家和公共卫生专家也开始讨论如何通过对城市垃圾中微生物的DNA测序辅助传染性疾病的预防与控制。

海洋生物学家也正在通过宏基因组学技术来对海洋的生态健康进行监测与研究。

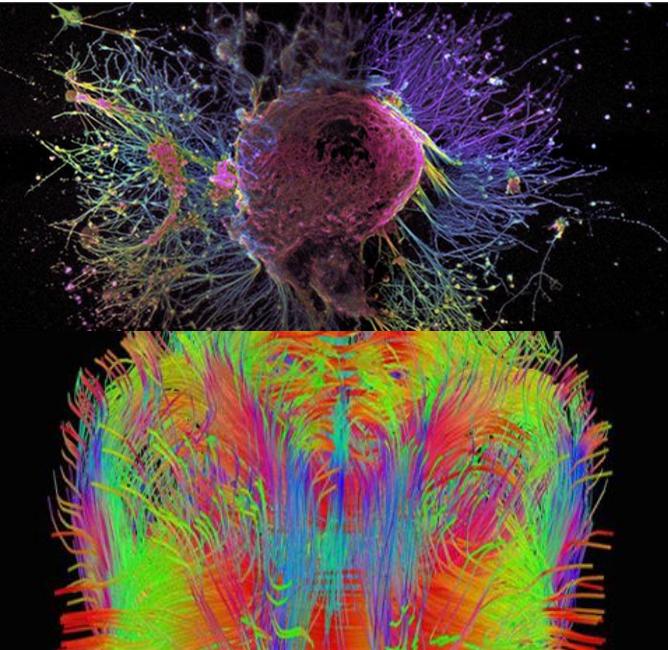
在法医领域，便携式DNA测序仪可以将DNA分析带出法医实验室，使其成为一线警务工作人员的随身工具。帮助警方即使通过DNA监测确定嫌疑人，发展成为诸如酒精探测器一类的便捷工具。

在人们的家里，DNA测序设备或许也可以成为下一个“智能”或“连接”设备，一些评论者甚至认定厕所是通过实时DNA测序监测家庭成员健康的理想场所。



生物信息学@HUST

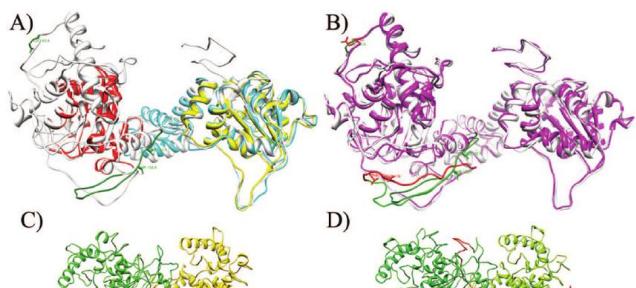
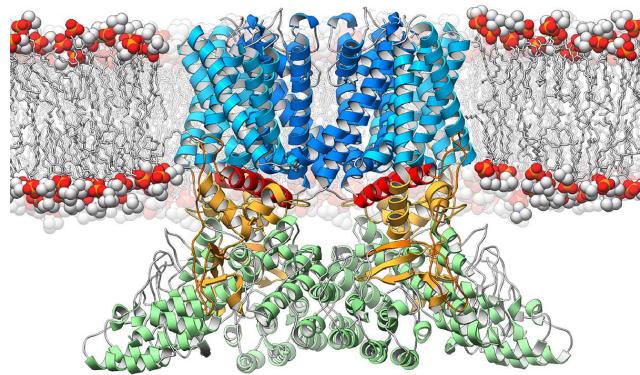
生命不只是序列的，但是生命始终是数字的！

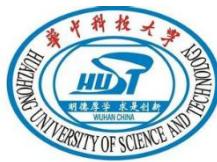


- 结构生物学
(Structure biology)

- 生物图像
(Bio-imaging)

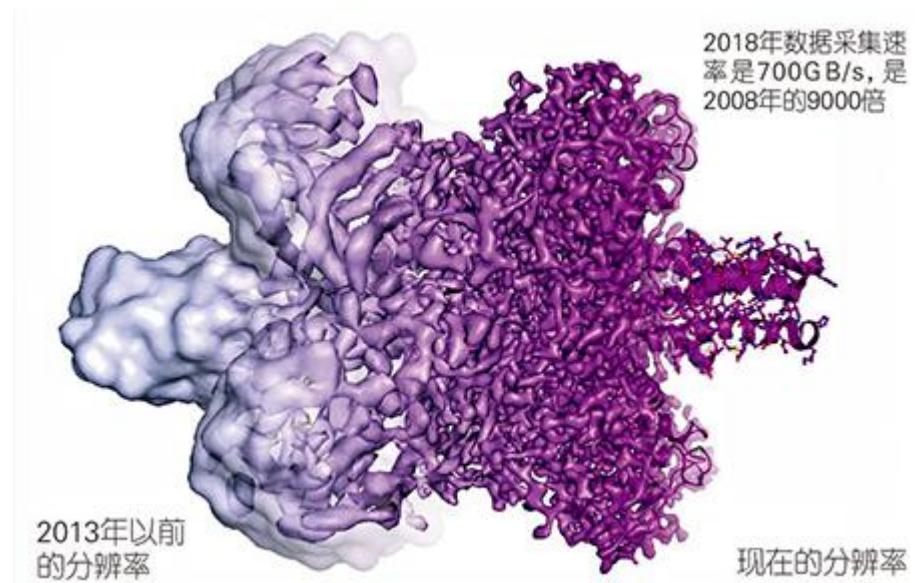
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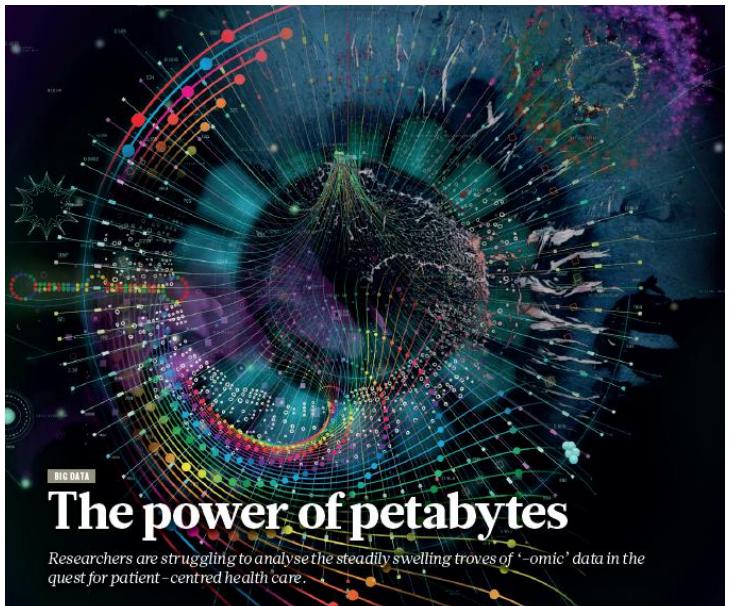


生物信息学@HUST

生命不只是序列的，但是生命始终是数字的！

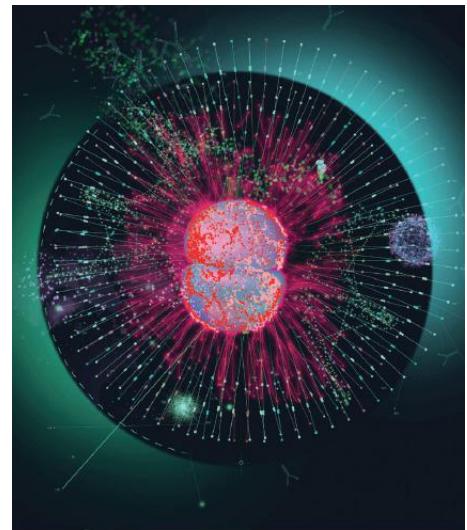


Big-data become popular...



Smartphone fitness apps enable researchers to gather health data from large numbers of people.

MOBILE DATA
Made to measure

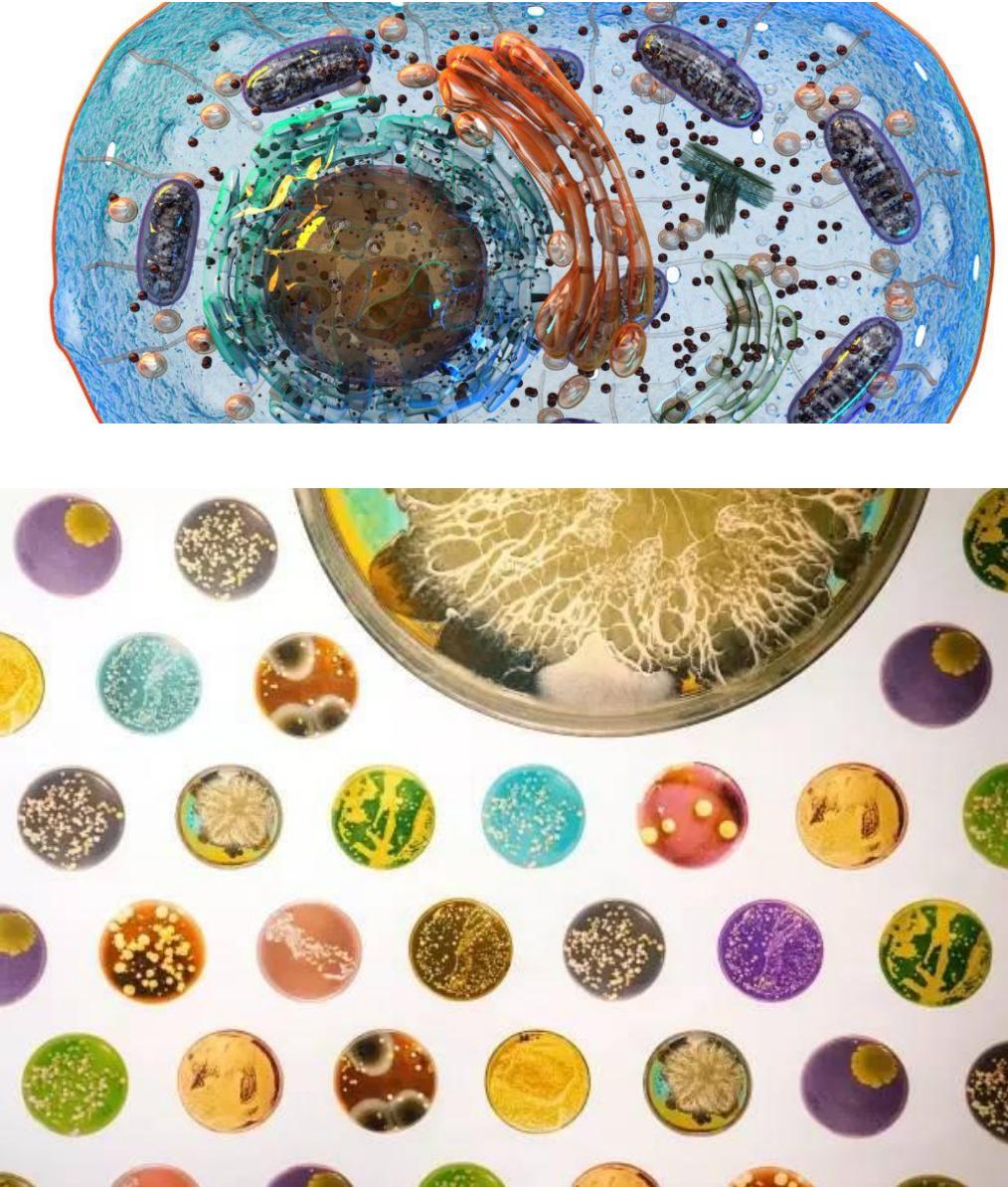


Nature, 2015/11/05 collection on “Big-data in biomedicine”

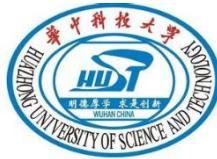
Microbiome and big-data...



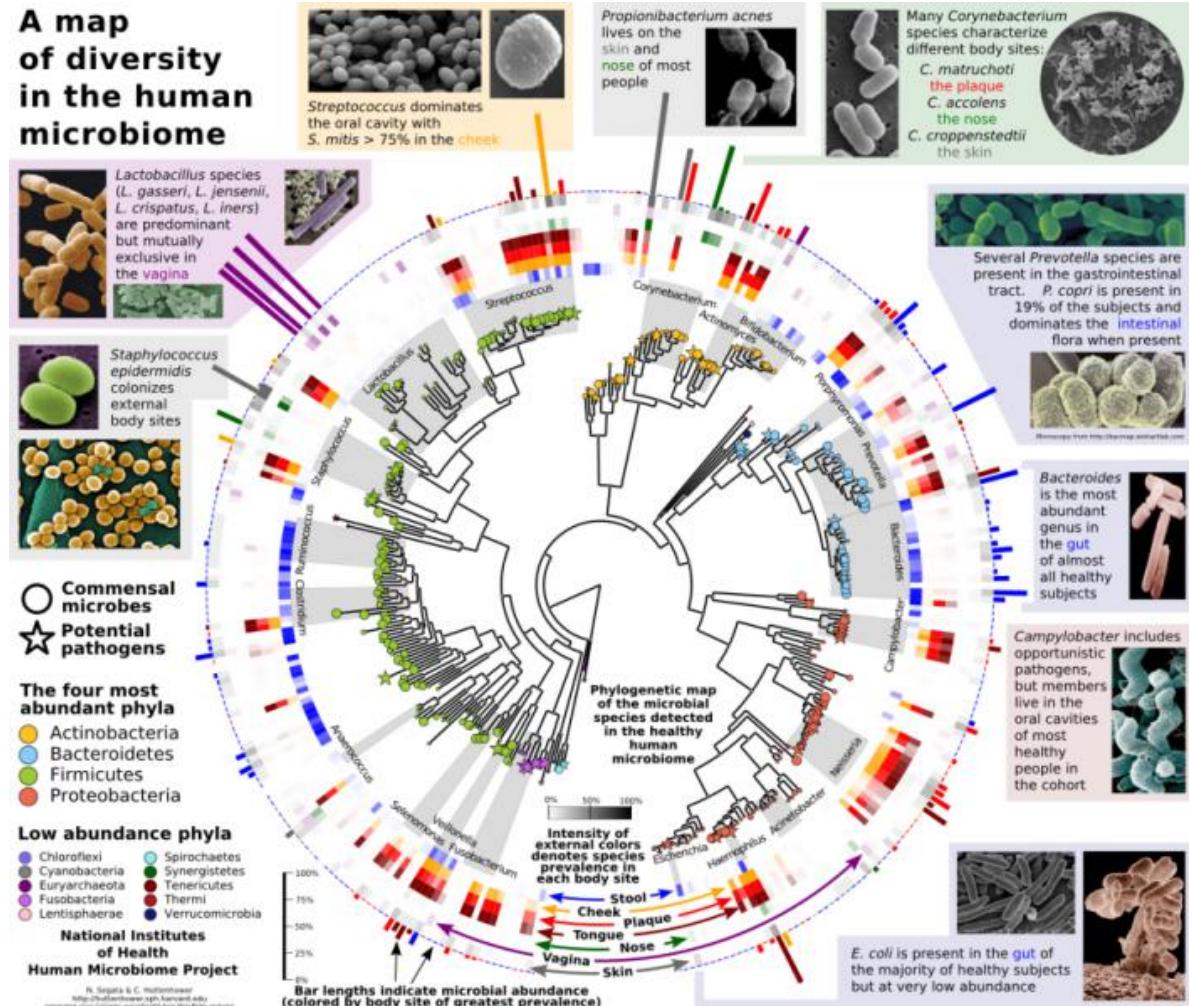
- A cell is already very complex
- 一个细胞已经非常复杂了
- A microbial community is much more complex than a cell
- 一个微生物群落就更为复杂了
- But much more big-data
- 但是也代表了更多的数据

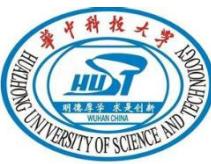


Microbiome and big-data...



在生物信息眼里，这全是大数据。。。。





Microbiome and big-data...



Larry Smarr

Founding Director of the
California Institute for
Telecommunications and
Information Technology (Calit2)

PUBLICATIONS

LARRY'S LATEST PAPERS

[Large Memory High Performance Computing Enables Comparison Across Human Gut Microbiome Of Patients With Autoimmune Diseases And Healthy Subjects](#)

Published in the XSEDE 2013 Proceedings of the Conference on Extreme Science and Engineering Discovery Environment: Gateway to Discovery, Article No. 25 (<http://dl.acm.org/citation.cfm?doid=2484762.2484828>)

[Quantifying Your Body: A How-to Guide From A Systems Biology Perspective](#)

Larry Smarr, Biotechnol. J. 2012, 7, 980-991

[Supporting Information For Quantifying Your Body: A How-to Guide From A Systems Biology Perspective](#)

Supporting Information for DOI 10.1002/biot.201100495

[Essay: An Evolution Toward A Programmable Universe](#)

Larry Smarr, Dec 5, 2011, The New York Times

[Quantified Health: A 10-year Detective Story Of Digitally Enabled Genomic Medicine](#)

Larry Smarr, with commentary by Mark Anderson, published as a Special Letter in the Strategic News Service Newsletter, September 30, 2011.

[How I Improved My Health By Changing My Eating, Exercise, And Stress Management Habits: An Annotated Reading List](#)

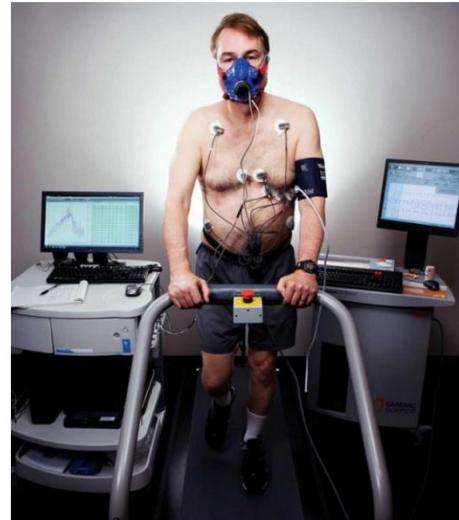
Larry Smarr, Requested by Mark Anderson, CEO Strategic News Service For Distribution to the Future in Review 2011 Attendees

Biomedicine

The Patient of the Future

Internet pioneer Larry Smarr's quest to quantify everything about his health led him to a startling discovery, an unusual partnership with his doctor, and more control over his life.

by Jon Cohen February 21, 2012



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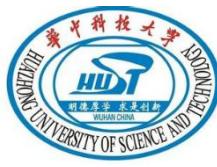
Blog



Larry Smarr

Can you coordinate the dance of your body's 100 trillion microorganisms?

Biomedical big-data...

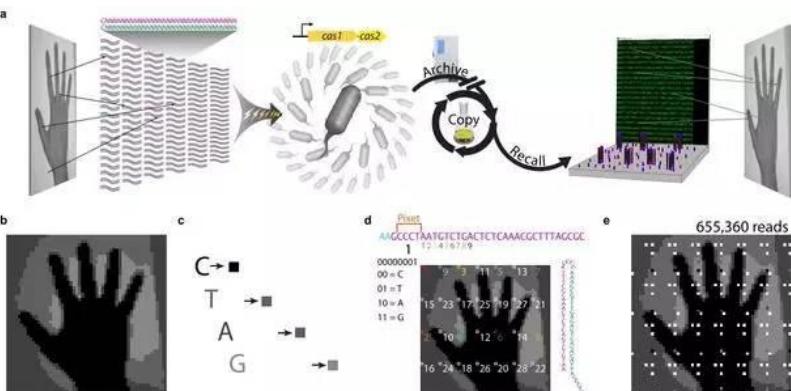
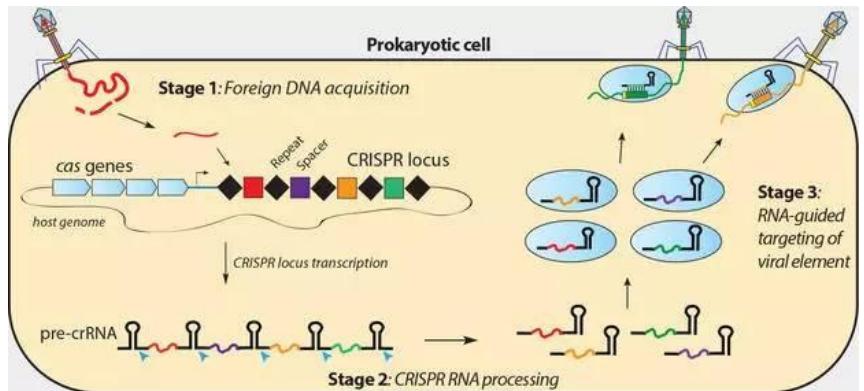


"Have you ever figured how information-rich your stool is?" Larry asks me with a wide smile, his gray-green eyes intent behind rimless glasses. "There are about 100 billion bacteria per gram. Each bacterium has DNA whose length is typically one to 10 megabases—call it 1 million bytes of information. **This means human stool has a data capacity of 100,000 terabytes of information stored per gram.** That's many orders of magnitude more information density than, say, in a chip in your smartphone or your personal computer. So your stool is far more interesting than a computer."

-- Larry Smarr



Understand it, create it!



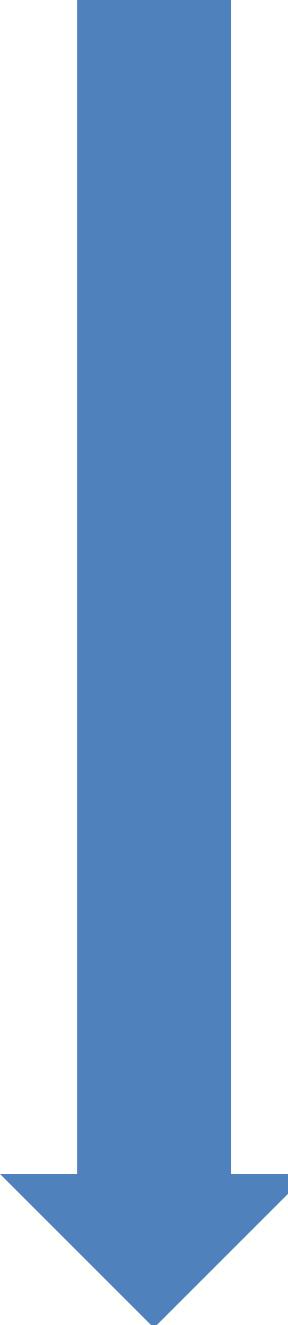
Original Image

原始图像

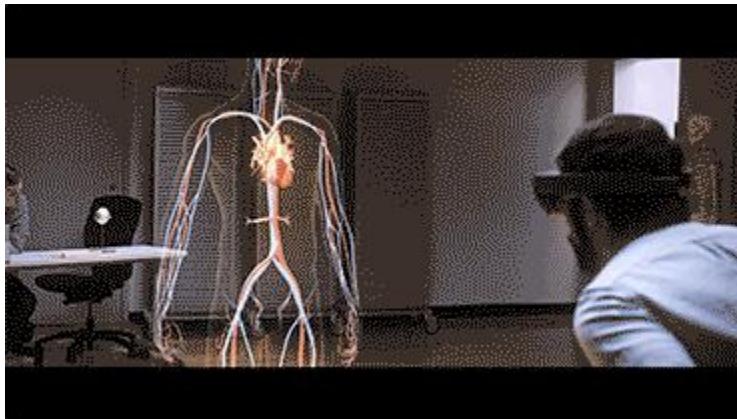


Image Reconstructed From Bacteria

从细菌DNA还原的图像



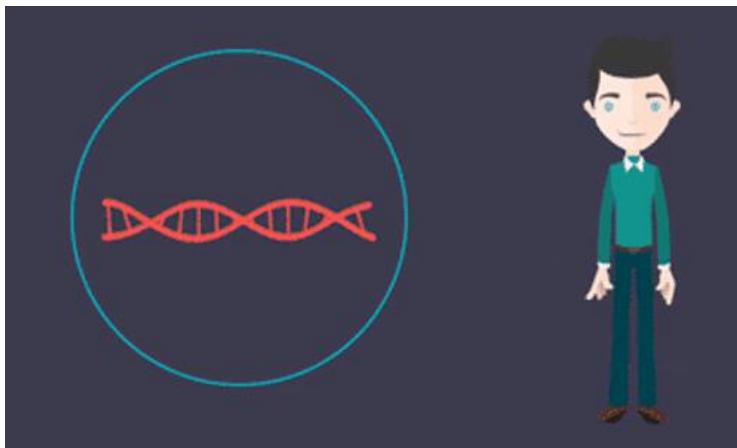
See it!



Understand it!



Create it!



生物统计学：计算科学视角

Donald Knuth (高德纳)



Donald Knuth, the "father of the analysis of algorithms."



The Art of Computer Programming (计算机程序设计艺术)
)

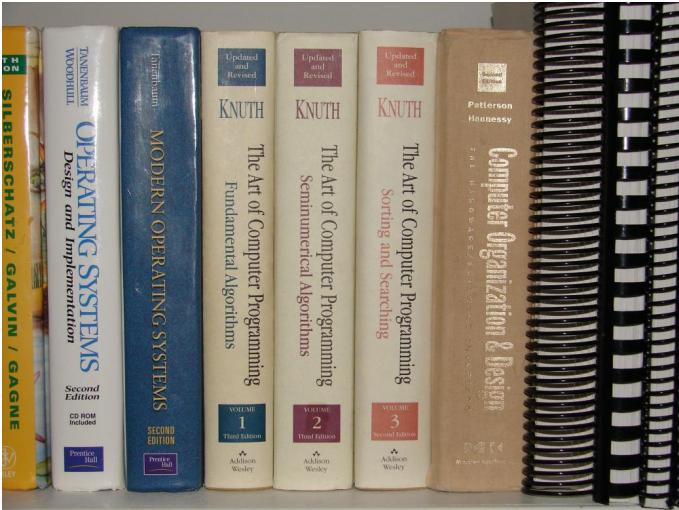
Markup

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The quadratic formula is $-b \pm \sqrt{b^2 - 4ac} \over 2a$ \bye
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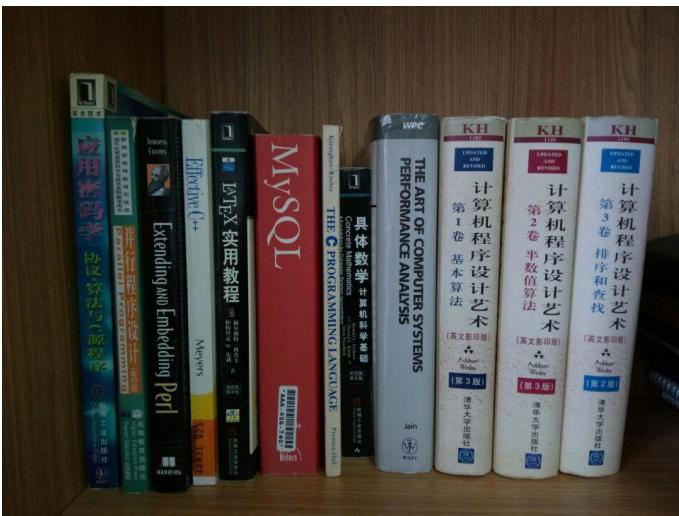
Renders as

$$\text{The quadratic formula is } \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

“生物信息学为算法研究提供了500年的问题” – Don Knuth

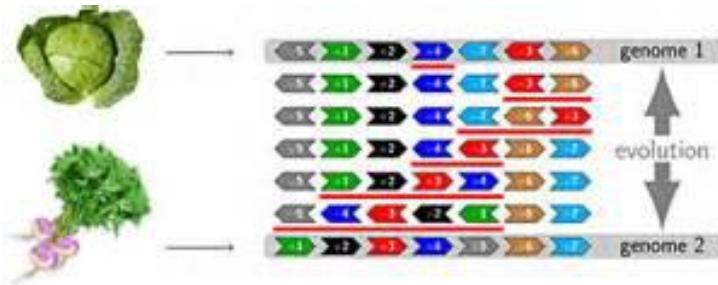


“definitely send me a résumé if you finish this fiendishly difficult book” – Bill Gates



“definitely come to talk about algorithm if you read half of this book” – Kang Ning

Bill Gates (比尔盖茨)



比尔盖茨:下个世界首富出自基因检测领域

Sorting by reversal problem

Discrete Mathematics 27 (1979) 47-57.
© North-Holland Publishing Company

BOUNDS FOR SORTING BY PREFIX REVERSAL

William H. GATES
Microsoft, Albuquerque, New Mexico

Christos H. PAPADIMITRIOU^{*}†
Department of Electrical Engineering, University of California, Berkeley, CA 94720, U.S.A.

Received 18 January 1978
Revised 28 August 1978

For a permutation σ of the integers from 1 to n , let $f(\sigma)$ be the smallest number of prefix reversals that will transform σ to the identity permutation, and let $f(n)$ be the largest such $f(\sigma)$ for all σ in the symmetric group S_n . We show that $f(n) \leq (5n+5)/3$, and that $f(n) \geq 17n/16$ for n a multiple of 16. If, furthermore, each integer is required to participate in an even number of reversed prefixes, the corresponding function $g(n)$ is shown to obey $3n/2 - 1 \leq g(n) \leq 2n + 3$.

1. Introduction

We introduce our problem by the following quotation from [1]

The chef in our place is sloppy, and when he prepares a stack of pancakes they come out all different sizes. Therefore, when I deliver them to a customer, on the way to the table I rearrange them (so that the smallest winds up on top, and so on, down to the largest at the bottom) by grabbing several from the top and flipping them over, repeating this (varying the number I flip) as many times as necessary. If there are n pancakes, what is the maximum number of flips (as a function $f(n)$ of n) that I will ever have to use to rearrange them?

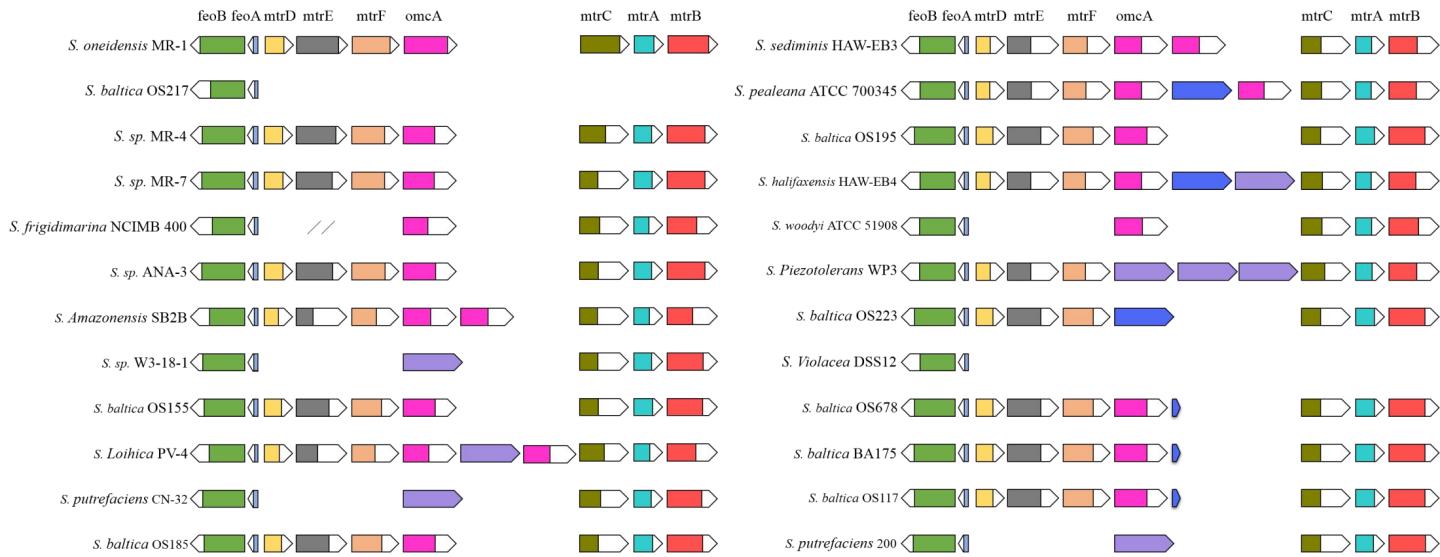
In this paper we derive upper and lower bounds for $f(n)$. Certain bounds were already known. For example, consider any stack of pancakes. An adjacency in this stack is a pair of pancakes that are adjacent in the stack, and such that no other pancake has size intermediate between the two. If the largest pancake is on the bottom, this also counts as one extra adjacency. Now, for $n \geq 4$ there are stacks of n pancakes that have no adjacencies whatsoever. On the other hand, a sorted stack must have all n adjacencies and each move (flip) can create at most one adjacency. Consequently, for $n \geq 4$, $f(n) \geq n$. By elaborating on this argument, M.R. Garey, D.S. Johnson and S. Lin [2] showed that $f(n) \geq n + 1$ for $n \geq 6$.

For upper bounds—algorithms, that is—it was known that $f(n) \leq 2n$. This can be seen as follows. Given any stack we may start by bringing the largest pancake on top and then flip the whole stack: the largest pancake is now at the bottom,

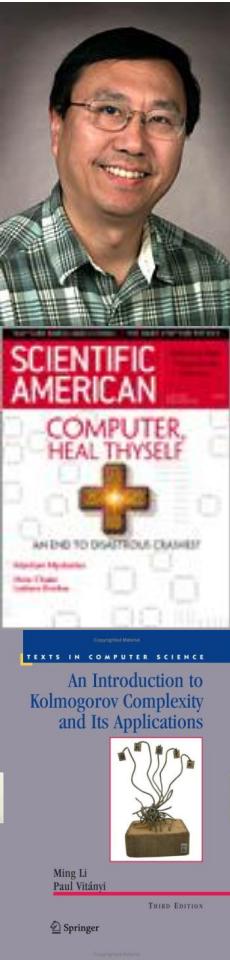
* Research supported by NSF Grant MCS 77-61193.

† Current address: Laboratory for Computer Science, Massachusetts Institute of Technology, Cambridge, Ma 02139, USA.

How many reversal steps for this REAL case?



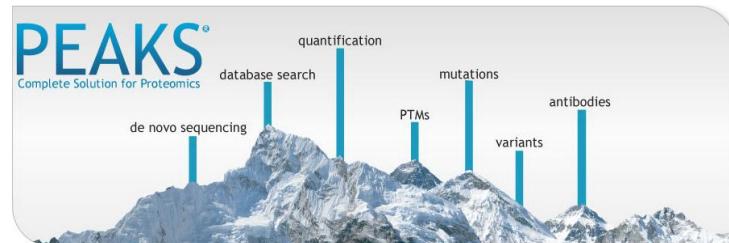
Ming Li (李明)



滑铁卢大学是微软招聘毕业生最多的学校之一



PatternHunter, ExonHunter, ...



理论、生物信息、应用都重要！

Ming Li (李明) & Tao Jiang (姜涛)



SIAM J. COMPUT.
Vol. 24, No. 5, pp. 1122–1139, October 1995

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012

ON THE APPROXIMATION OF SHORTEST COMMON SUPERSEQUENCES AND LONGEST COMMON SUBSEQUENCES*

TAO JIANG[†] AND MING LI[‡]

Abstract. The problems of finding shortest common supersequences (SCS) and longest common subsequences (LCS) are two well-known NP-hard problems that have applications in many areas, including computational molecular biology, data compression, robot motion planning, and scheduling, text editing, etc. A lot of fruitless effort has been spent in searching for good approximation algorithms for these problems. In this paper, we show that these problems are inherently hard to approximate in the worst case. In particular, we prove that (i) SCS does not have a polynomial-time linear approximation algorithm unless $P = NP$; (ii) There exists a constant $\delta > 0$ such that, if SCS has a polynomial-time approximation algorithm with ratio $\log^\delta n$, where n is the number of input sequences, then NP is contained in $DTIME(2^{\text{polylog } n})$; (iii) There exists a constant $\delta > 0$ such that, if LCS has a polynomial-time approximation algorithm with performance ratio n^δ , then $P = NP$. The proofs utilize the recent results of Arora et al. [*Proc. 23rd IEEE Symposium on Foundations of Computer Science*, 1992, pp. 14–23] on the complexity of approximation problems.

In the second part of the paper, we introduce a new method for analyzing the average-case performance of algorithms for sequences, based on Kolmogorov complexity. Despite the above nonapproximability results, we show that near optimal solutions for both SCS and LCS can be found on the average. More precisely, consider a fixed alphabet Σ and suppose that the input sequences are generated randomly according to the uniform probability distribution and are of the same length n . Moreover, assume that the number of input sequences is polynomial in n . Then, there are simple greedy algorithms which approximate SCS and LCS with expected additive errors $O(n^{0.707})$ and $O(n^{1/2+\epsilon})$ for any $\epsilon > 0$, respectively.

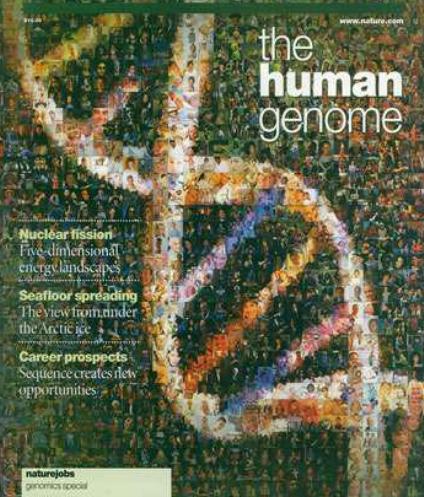
Incidentally, our analyses also provide tight upper and lower bounds on the expected LCS and SCS lengths for a set of random sequences solving a generalization of another well-known open question on the expected LCS length for two random sequences [K. Alexander, *The rate of convergence of the mean length of the longest common subsequence*, 1992, manuscript], [V. Chvatal and D. Sankoff, *J. Appl. Probab.*, 12 (1975), pp. 306–315], [D. Sankoff and J. Kruskall, eds., *Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison*, Addison-Wesley, Reading, MA, 1983].

Key words. shortest common supersequence, longest common subsequence, approximation algorithm, NP-hardness, average-case analysis, random sequence

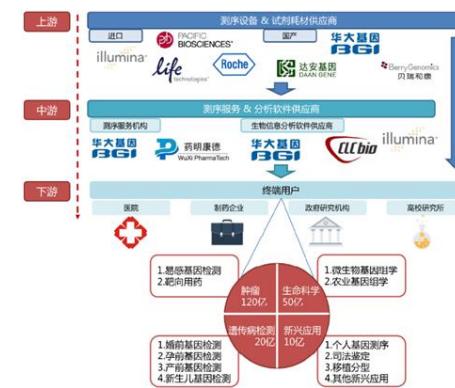
Current status (现今态势)



1 February 2001
nature
the human genome



很难找到
与生物信息学和生物统计学
没有关系的
生物学与生物工程
研究和应用领域了。 . .



Alphabet (谷歌)

Google 的基因组学梦想



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CORRESPONDENCE

23andMe and the FDA

N Engl J Med 2014; 370:2248-2249 | June 5, 2014 | DOI: 10.1056/NEJMc1404692

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To the Editor:

In their Perspective article (March 13 issue),¹ Annas and Elias state that the conflict between the genetic-testing company 23andMe and the Food and Drug Administration (FDA) concerns analytic and clinical validity, clinical utility, and ethical, legal, and social issues. However, their discussion is limited to a domestic U.S. perspective. After a person's raw genetic data have been determined from a DNA sample, the data are stored remotely and can be accessed easily anywhere in the world. For example, in Japan, maternal blood samples from Japanese mothers undergoing



FDA approves 23andMe gene carrier test

Nature Biotechnology 33, 435 (2015) | doi:10.1038/nbt0515-435a

Published online 12 May 2015

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23andMe, based in Mountain View, California, has received word from the US Food and Drug Administration (FDA) that their Bloom syndrome carrier screening test was approved as a class II device. The approval came in February, 15 months after the personal genomics company received a cease and desist letter from the regulator for its genetic tests because the company was dispensing health-related information to consumers without having obtained marketing clearance. The FDA website lists class II devices as moderate risk, requiring some regulatory controls, putting carrier screening tests in the same category as condoms. This turnaround follows the company's

Future (未来)

Cancer informatics Gene regulation
Personalized medicine Protein modeling
Computational biology Gene expression analysis
Image analysis Genomics and proteomics
Comparative genomics Gene expression databases
Epidemic models Computational drug discovery

Bioinformatics

Sequence analysis Bio-ontologies and semantics
Evolution and phylogenetics Structure prediction
Cheminformatics Next generation sequencing
Computational intelligence
Biomedical engineering Amino acid s
Structural bioinformatics Medical
Microarrays
Visualization

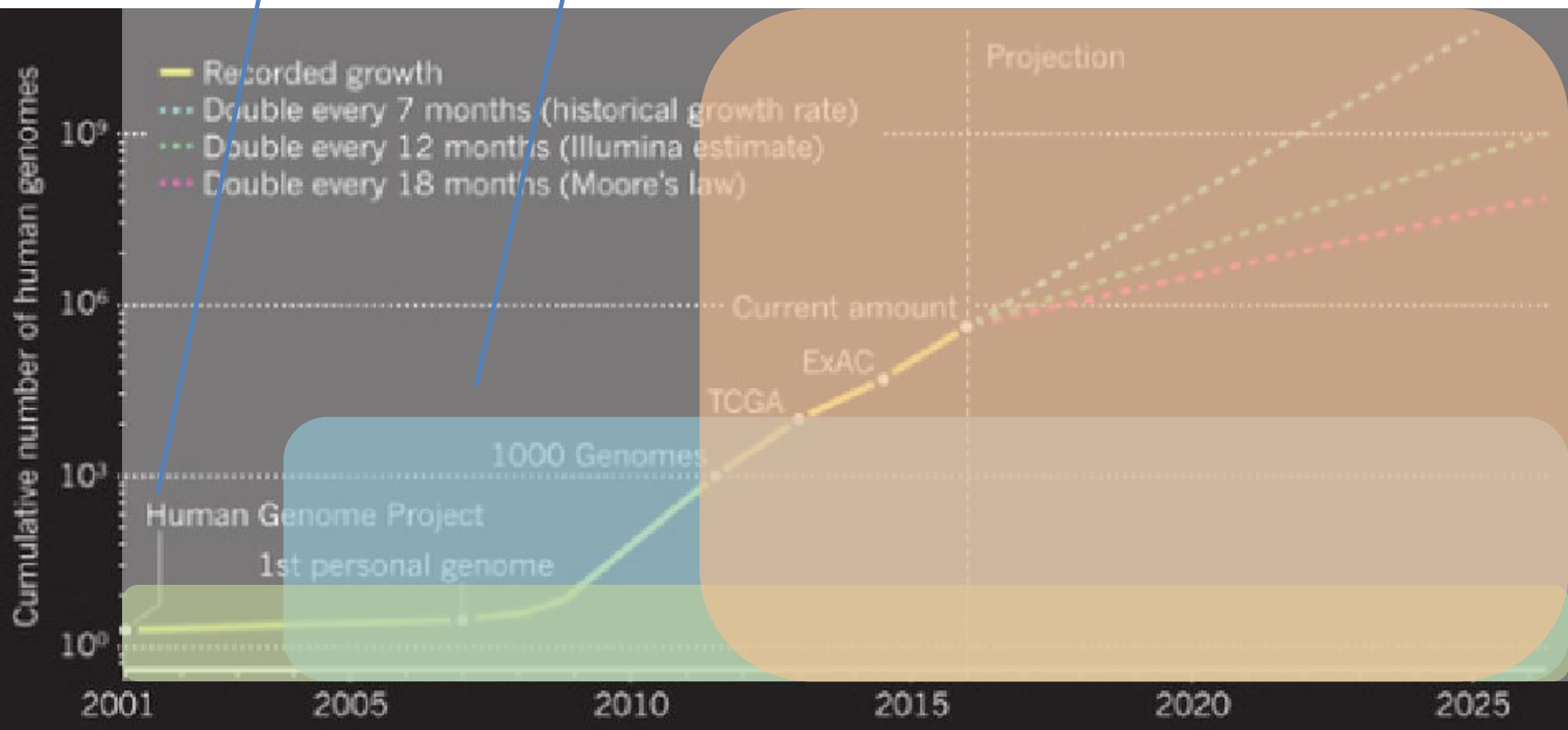


Biostatistics

生物统计和深度学习
处理范围

湿实验
可验证范围

传统生物信息
处理范围



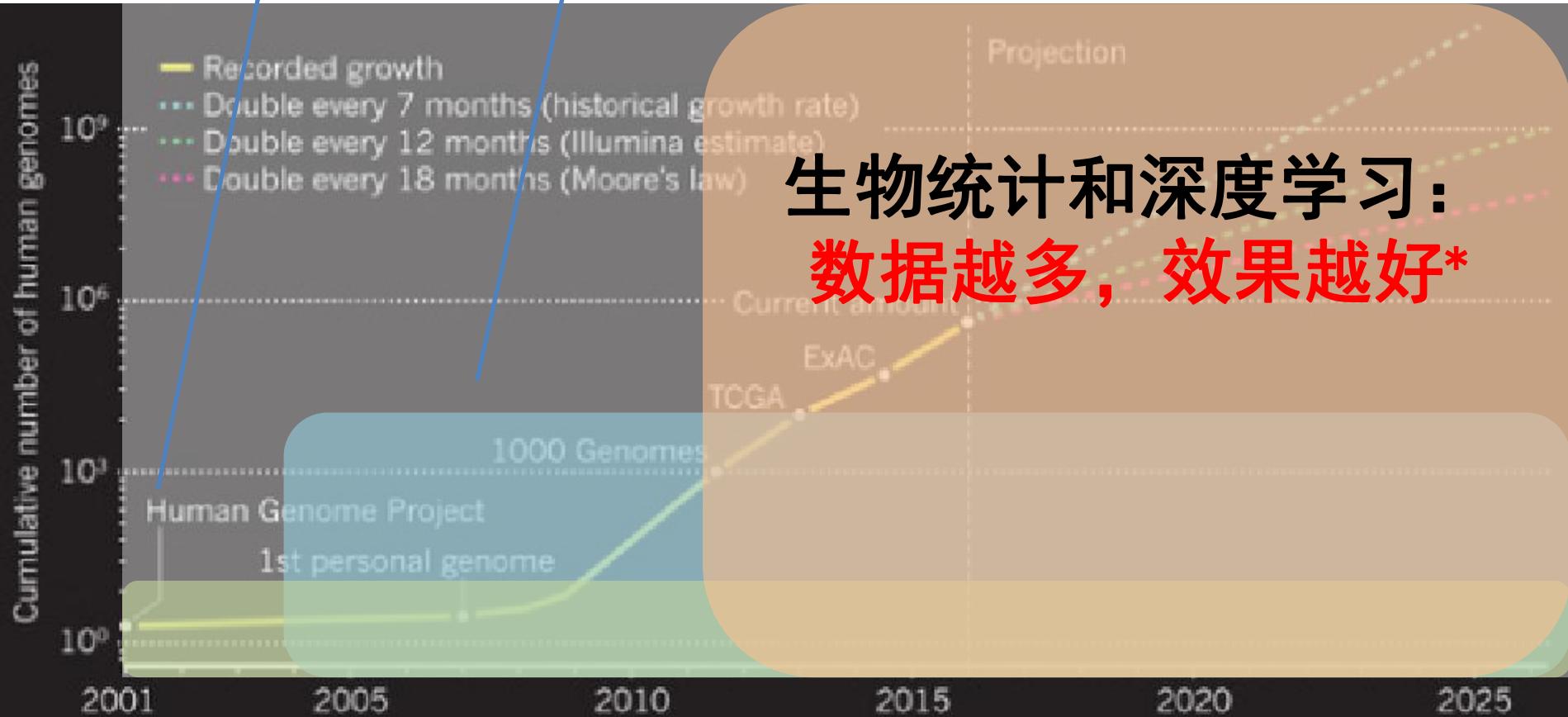
Biostatistics

生物统计和深度学习
处理范围

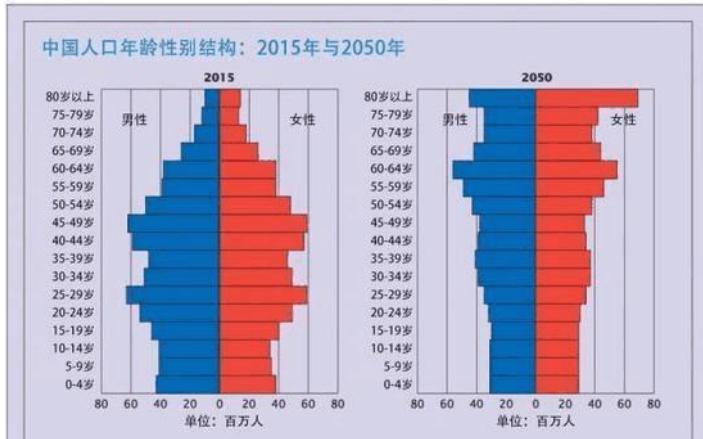
湿实验
可验证范围

传统生物信息
处理范围

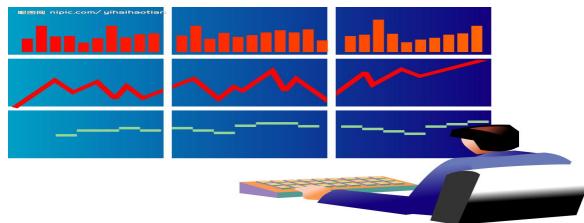
生物统计和深度学习：
数据越多，效果越好*



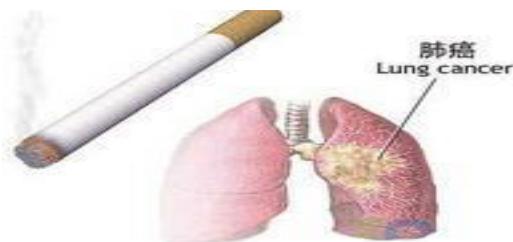
统计学：让数字说话！



人口数量和结构可以预测吗？

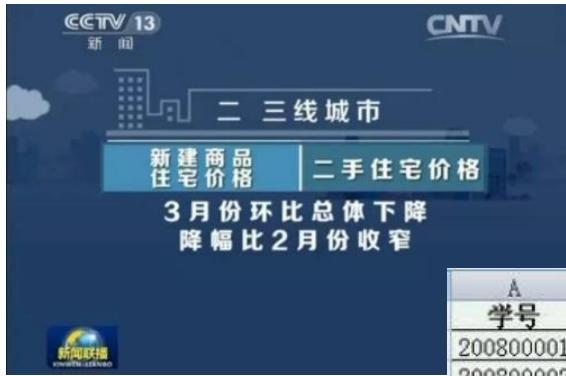


股市可以预测吗？



吸烟可以致癌？新药测试？

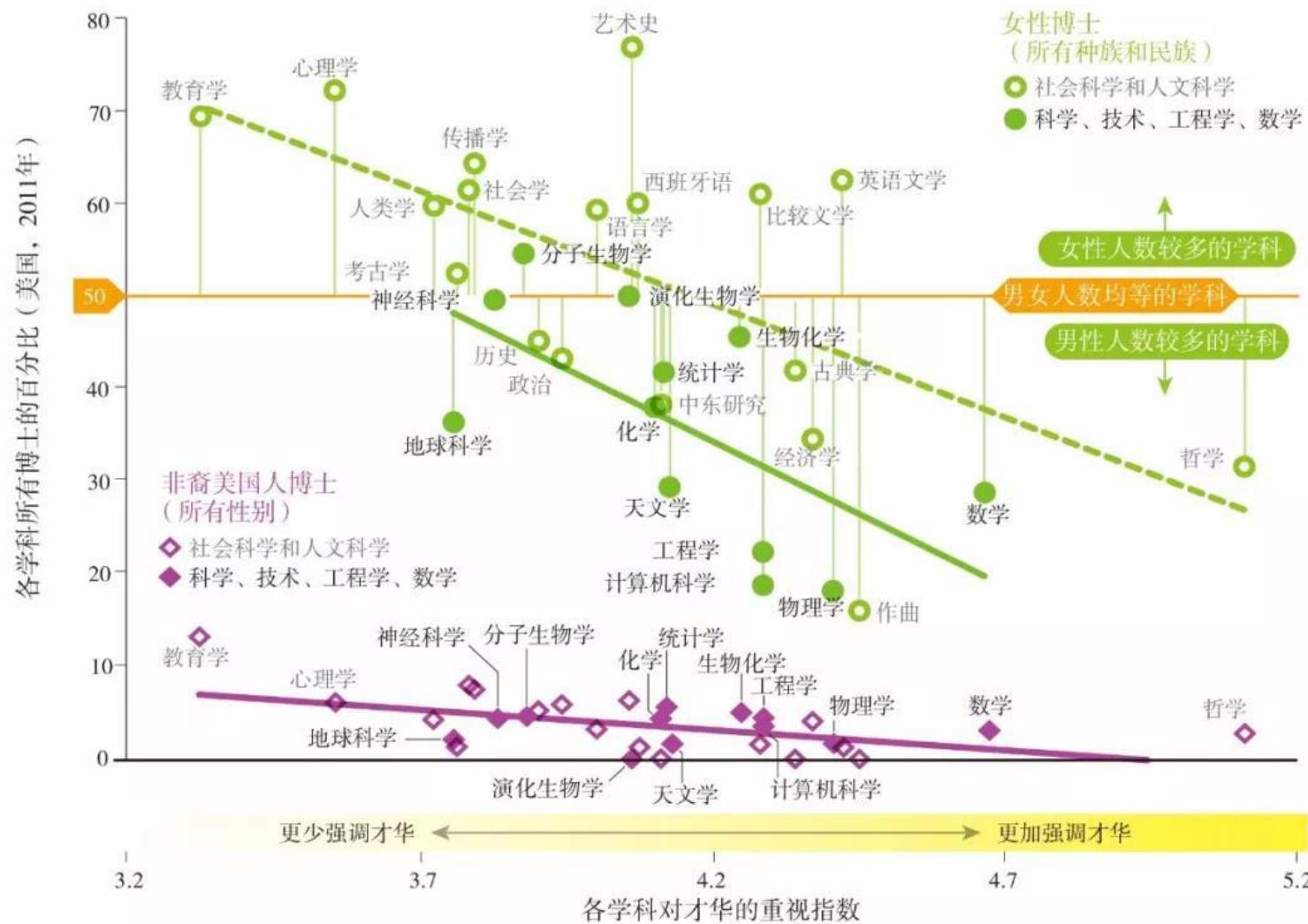
统计学：无处不在！



A	B	C	D	E	F	G
学号	姓名	语文	数学	英语	平均分	名次
200800001	狮子王	89	65	56	70.00	13
200800002	米老鼠	96	80	98	91.33	1
200800003	花木兰	83	82	83	82.67	9
200800004	唐老鸭	91	90	87	89.33	3
200800005	阿童木	93	92	88	91.00	2
200800006	灰姑娘	90	86	80	85.33	6
200800007	大力士	94	79	91	88.00	4
200800008	跳跳虎	83	43	94	73.33	10
200800009	小蚂蚁	89	91	82	87.33	5
200800010	皮诺曹	48	95	76	73.00	11
200800011	爱丽丝	87	83	85	85.00	7
200800012	睡美人	82	79.5	90	83.83	8
200800013	大力士	81	54	80	71.67	12



统计学：无处不在！



统计学：无处不在！

习近平说：中国是世界第二大经济体，有13亿多人口的大市场，有960多万平方米的国土，中国经济是一片大海，而不是一个小池塘。大海有风平浪静之时，也有风狂雨骤之时。没有风狂雨骤，那就不是大海了。狂风骤雨可以掀翻小池塘，但不能掀翻大海。经历了无数次狂风骤雨，大海依旧在那儿！经历了5000多年的艰难困苦，中国依旧在这儿！面向未来，中国将永远在这儿！

概率：

$$P(\text{掀翻} \cap \text{狂风骤雨} | \text{小池塘}) = \text{high}$$

$$P(\text{掀翻} \cap \text{小雨} | \text{小池塘}) = \text{low}$$

$$P(\text{掀翻} \cap \text{狂风骤雨} | \text{大海}) = \text{low}$$

$$P(\text{掀翻} \cap \text{小雨} | \text{大海}) = \text{low}$$

$$P(\text{掀翻} | \text{大海}) = P(\text{掀翻} \cap \text{狂风骤雨} | \text{大海}) + P(\text{掀翻} \cap \text{小雨} | \text{大海})$$

贝叶斯推断：

$$P(\text{掀翻} | \text{大海}) = P(\text{大海} | \text{掀翻}) * P(\text{掀翻}) / P(\text{大海}) = \text{low}$$

vs.

$$P(\text{掀翻} | \text{小池塘}) = P(\text{小池塘} | \text{掀翻}) * P(\text{掀翻}) / P(\text{小池塘}) = \text{high}$$



统计学：产生价值！



基于大数据统计分析的防控平台 (社会效益)



基于大数据统计分析的决策平台 (经济效益)

统计学：产生价值！

[公司文件] 加强与国内大学合作，吸纳全球优秀人才，共同推动中国基础研究
——任总与中国科学技术大学包信和校长座谈的讲话

2018-12-13 17:59 6799 113

只看楼主

总裁办电子邮件

电邮讲话【2018】128号

签发人：任正非

加强与国内大学合作，吸纳全球优秀人才，共同推动中国基础研究

——任总与中国科学技术大学包信和校长座谈的讲话

2018年11月19日

在高校学科设置上，我特别支持你们重视统计学。计算机科学不仅仅是技术，还应该以统计学为基础。大数据需要统计学，信息科学需要统计学，生命科学也需要统计学。国家要搞人工智能，更要重视统计学。统计学不是一个纯粹的学科，而是每一个学科都要以统计学为基础。

统计学：概率不等于事实！

盖洛普民意测验与美国总统大选关联度一览表（1936—2000）

年代	候选人	盖洛普最后 民意测验结果 (%)	总统选举真 实结果 (%)	盖洛普 误差 (%)
2000	布什	48.0	47.9	+0.1
1996	克林顿	52.0	49.2	+2.8
1992	克林顿	49.0	43.3	+5.7
1988	老布什	56.0	53.9	+2.1
1984	里根	59.0	59.2	-0.2
1980	里根	47.0	50.8	-3.8
1976	卡特	48.0	50.1	-2.1
1972	尼克松	62.0	61.8	+0.2
1968	尼克松	43.0	43.5	-0.5
1964	约翰逊	64.0	61.3	+2.7
1960	肯尼迪	51.0	50.1	+0.9
1956	艾森豪威尔	59.5	57.8	+1.7
1952	艾森豪威尔	51.0	55.4	-4.4
1948	杜鲁门	44.5	49.5	-5.0
1944	罗斯福	51.5	53.8	-2.3
1940	罗斯福	52.0	55.0	-3.0
1936	罗斯福	55.7	62.5	-6.8



盖洛普民意测验创始人
乔治·盖洛普

统计学： 历史和地位！



it's a long long story

人口普查

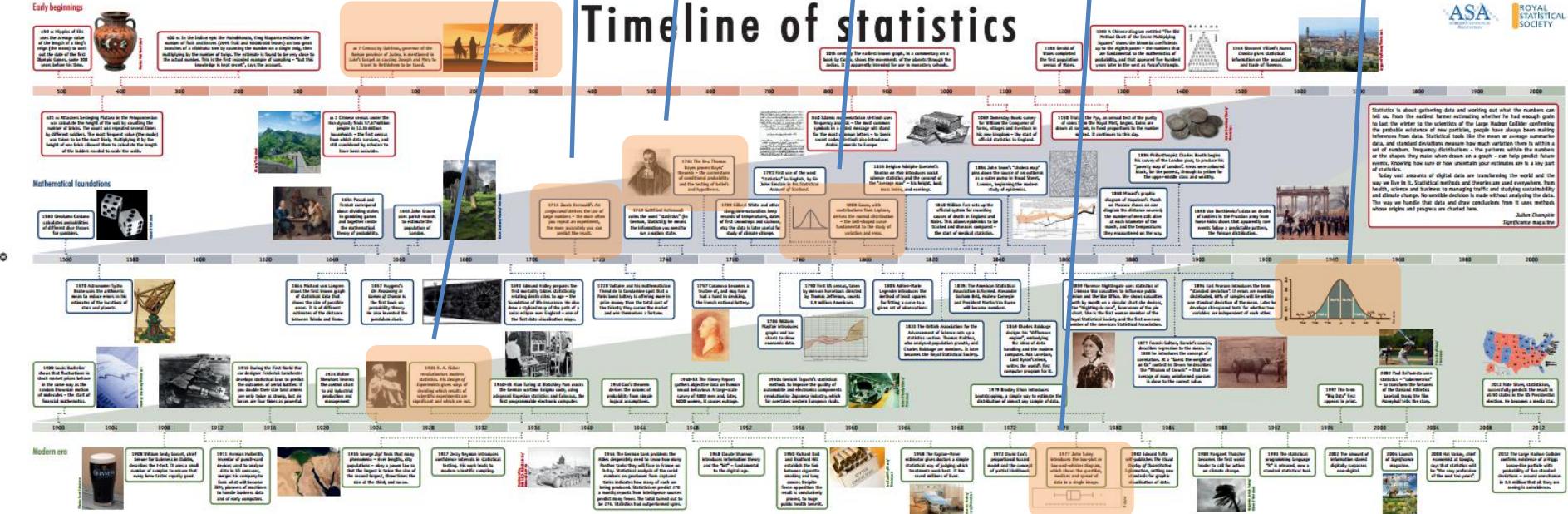
F检验

大数定理

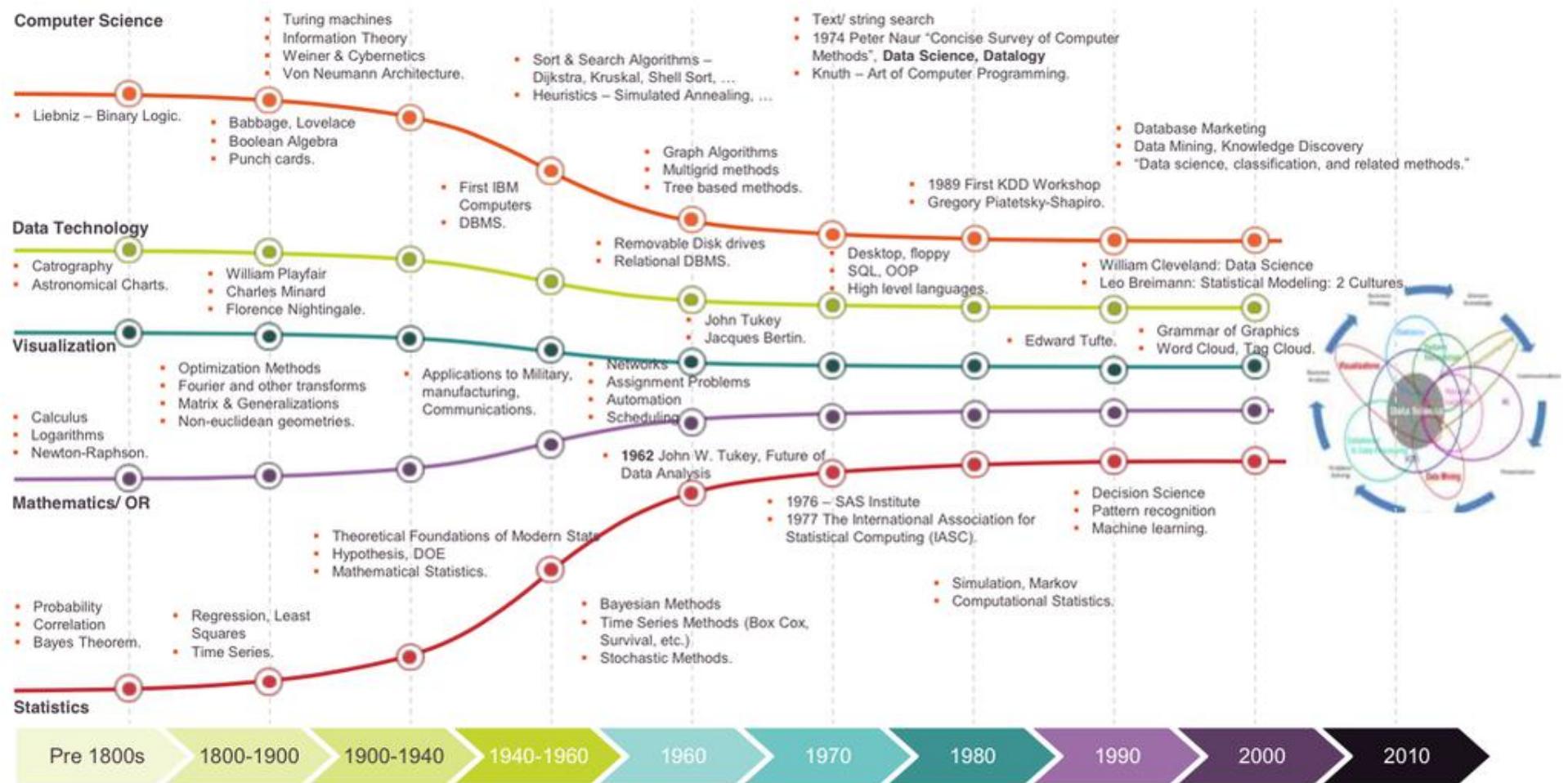
贝叶斯推断

正态分布

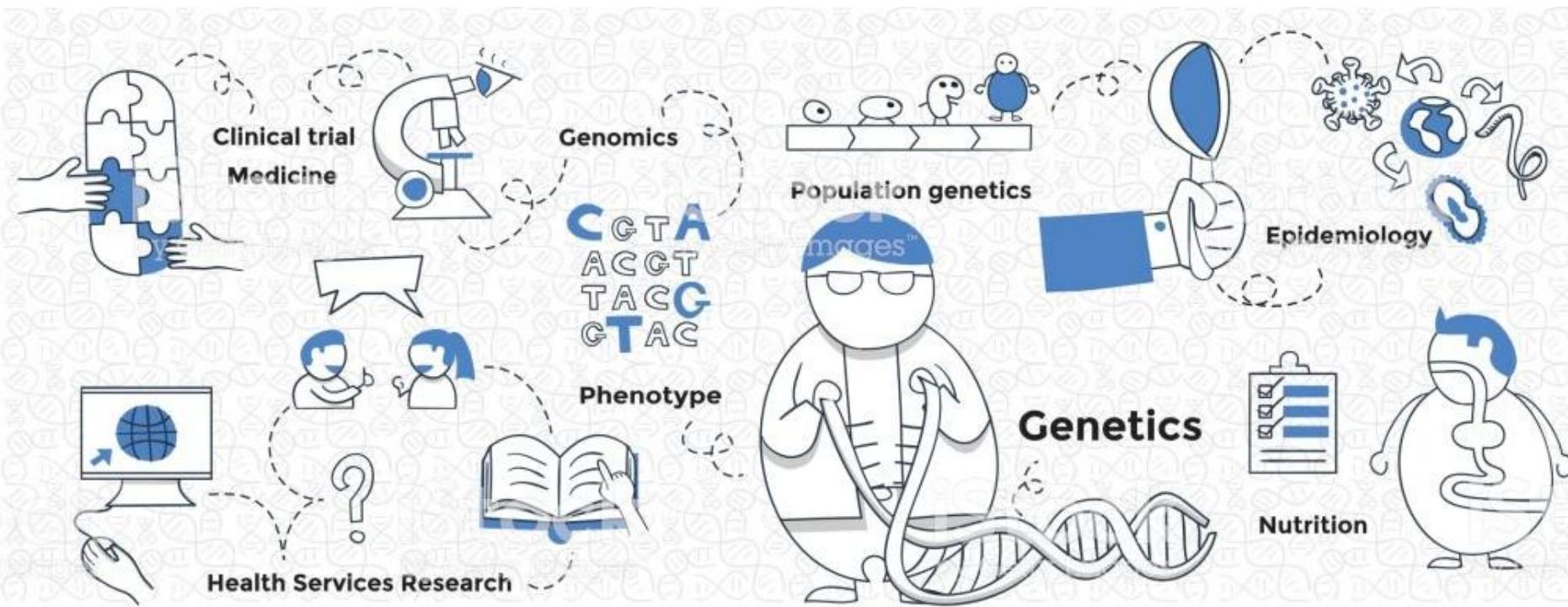
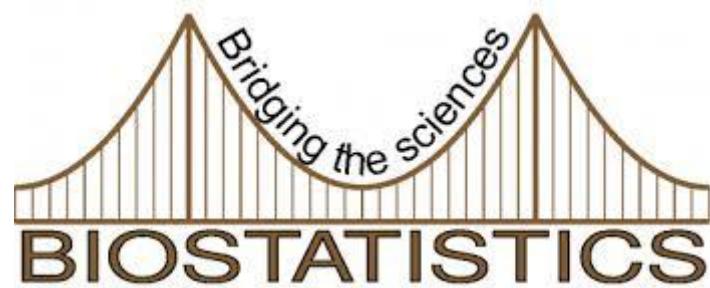
方差



统计学：历史和地位！



统计学：生物统计学！



为什么要学习生物统计学

两品种小麦的对比

转基因小麦



一株转基因小麦各项指标都优于另一株非转基因小麦，是否可以确定转基因小麦产量提高？

实际情况可能是：



所选转基因小麦是实验田中长得最好的，而所选非转基因小麦是麦田中非常普通的一株。

怎样才能确认转基因小麦更优呢？



选取所有的
小麦进行比
较？

如何选取



摘取多少小麦才能更好地保证对
比结果的准确性呢？

为什么要学习生物统计学

阿司匹林对抗癌的疗效



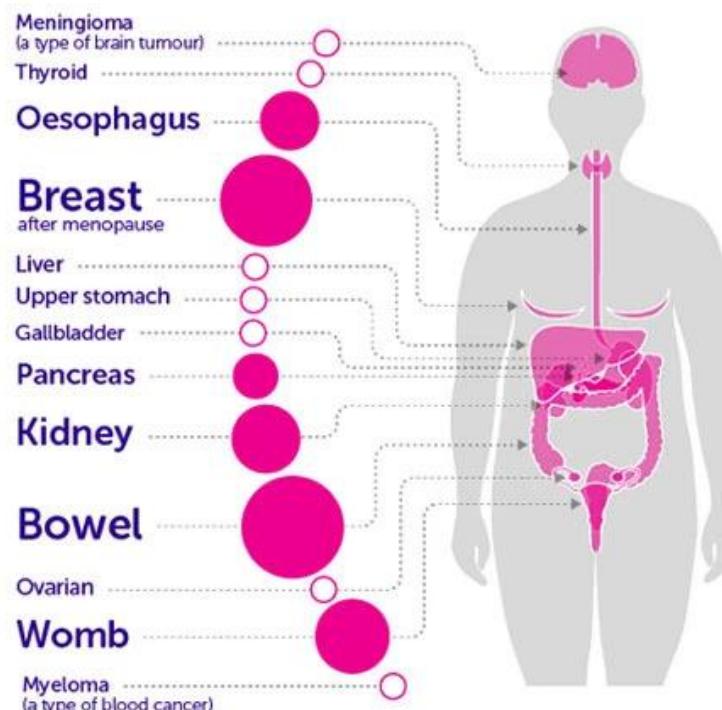
口服阿司匹林，可能有助于治疗好多种癌症。

是真的吗？

BEING OVERWEIGHT CAN CAUSE 13 TYPES OF CANCER

● Larger circles indicate cancers with more UK cases linked to being overweight or obese

○ Number of linked cases are currently being calculated and will be available in 2017



实际情况可能是：

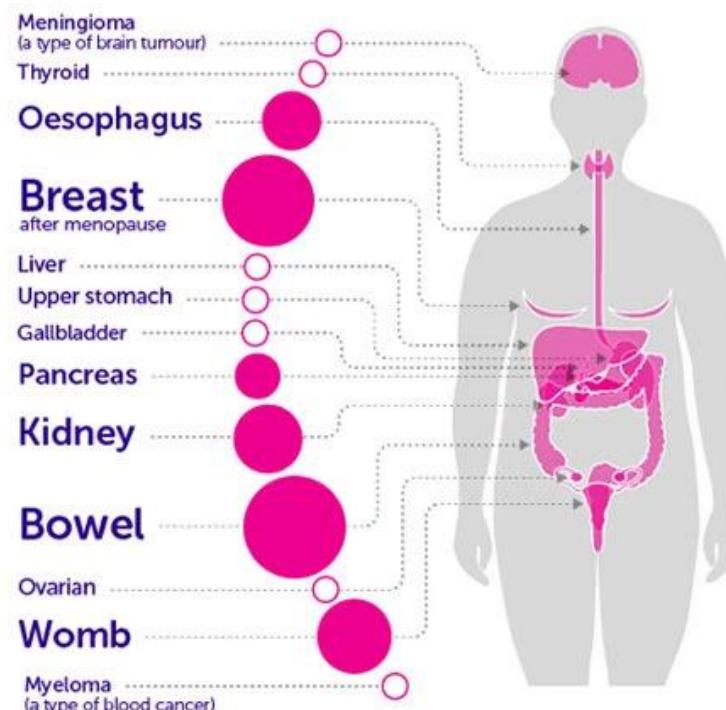


口服阿司匹林的同时，可能也口服了其它抗癌药物。 . .

BEING OVERWEIGHT CAN CAUSE 13 TYPES OF CANCER

● Larger circles indicate cancers with more UK cases linked to being overweight or obese

○ Number of linked cases are currently being calculated and will be available in 2017

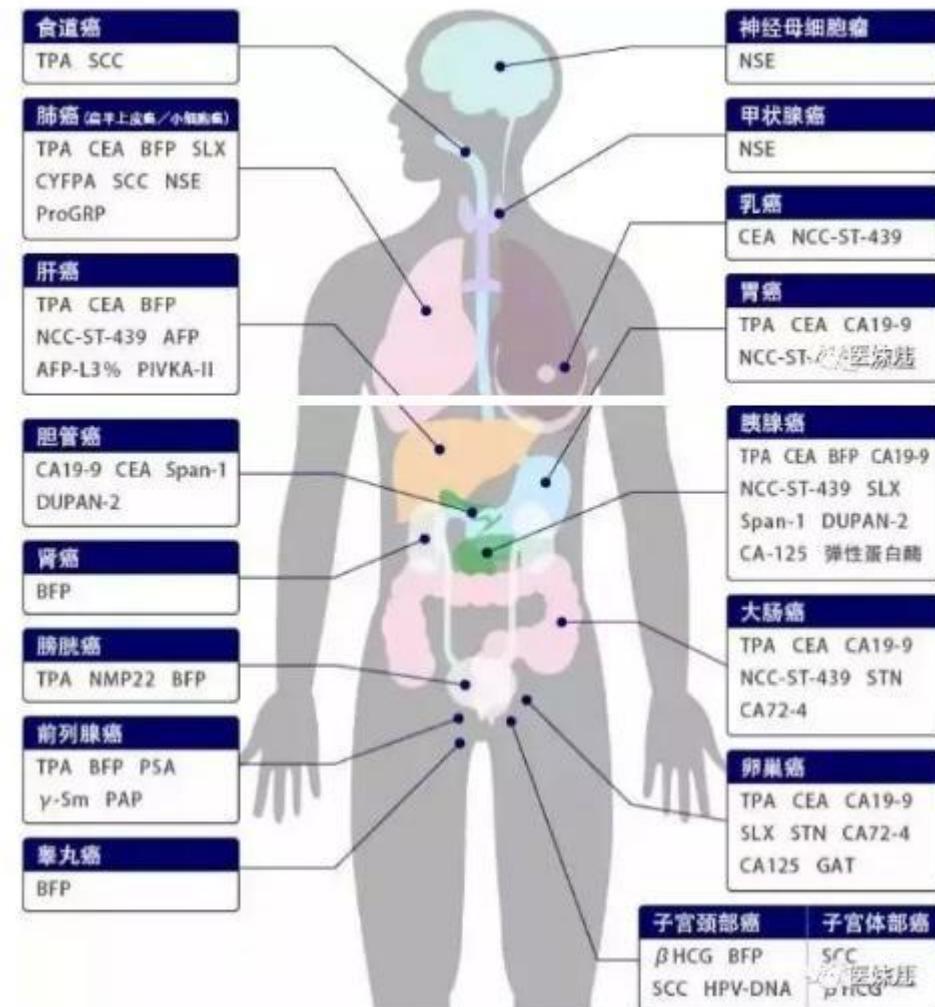


如何选取

要评估口服阿司匹林的效果，必须做好实验设计，控制单变量，评估其影响。

造成假阳性的坏家伙们

泛筛选干扰化合物（PAINS）可能会包括上百种类型的化合物，不过其中有一些的出现频率会远高于其他的类型。在这其中，最常带来麻烦的就是以下几种（关键结构用红色和紫色标出）。如果拥有这些结构的分子在筛选试验中出现，就要格外当心。



如何确立可靠的关联性



为什么要学习生物统计学

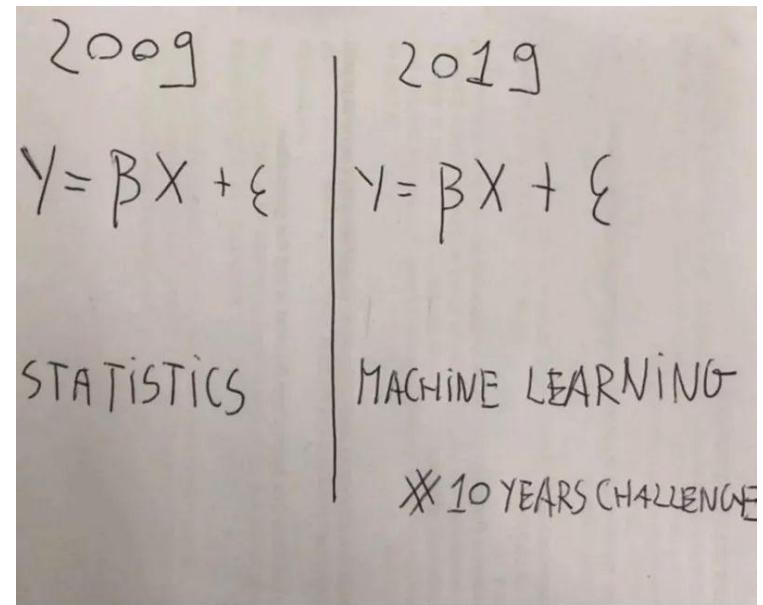
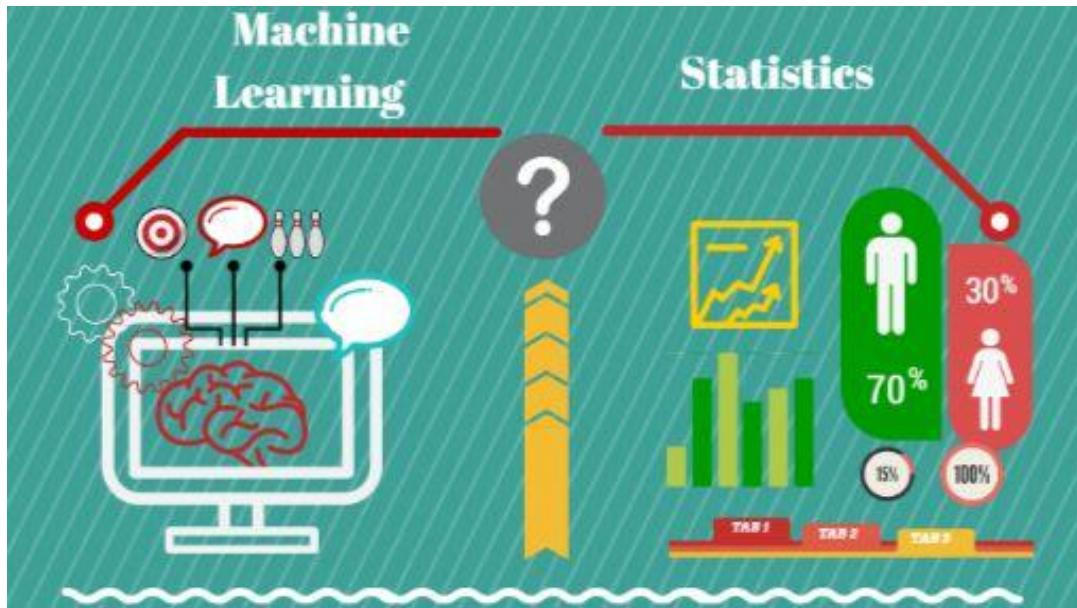
- 生物统计学是生物科学研究的基本工具
 - 生物现象的特点：
 - 变异性：个体之间存在差异
 - 不确定性（随机性）：变异不能准确推算
 - 复杂性：影响因素众多，有些是未知的

常规的数学方法不能解决问题

为什么要学习生物统计学

- 必须利用生物统计学才能回答的问题
 - 疾病已经进入哪个阶段了？
 - 哪些基因在疾病发生发展中起到关键作用？
 - 基因和环境是否有关？
 - 新药物是否更有效？
 - 遗传与环境哪个更重要？
 -

为什么要学习生物统计学

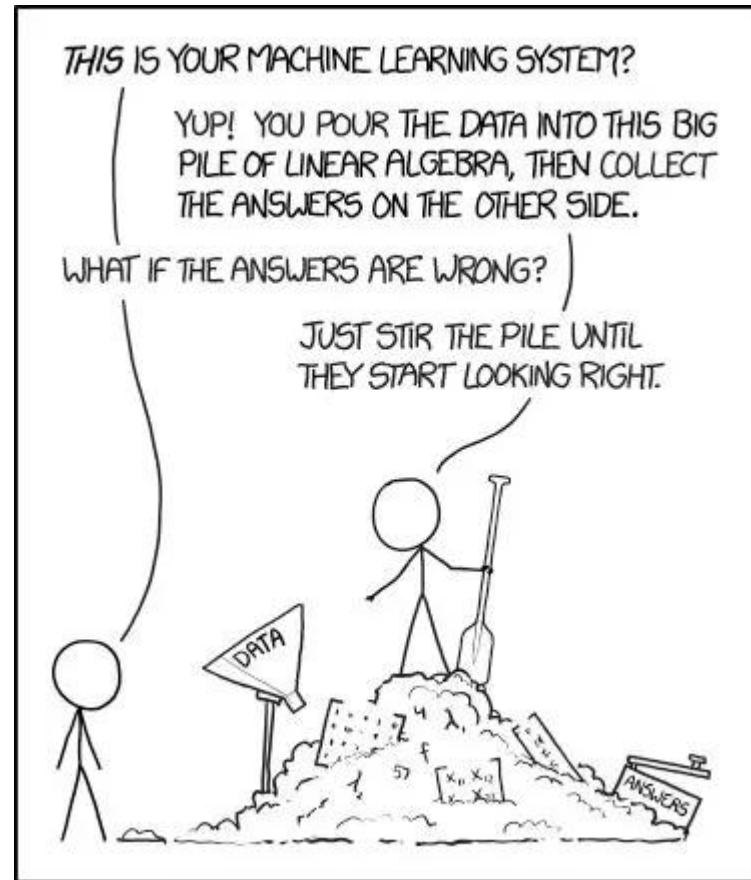


<https://mp.weixin.qq.com/s/xCJBowXS89UIHA07R8WNuw>

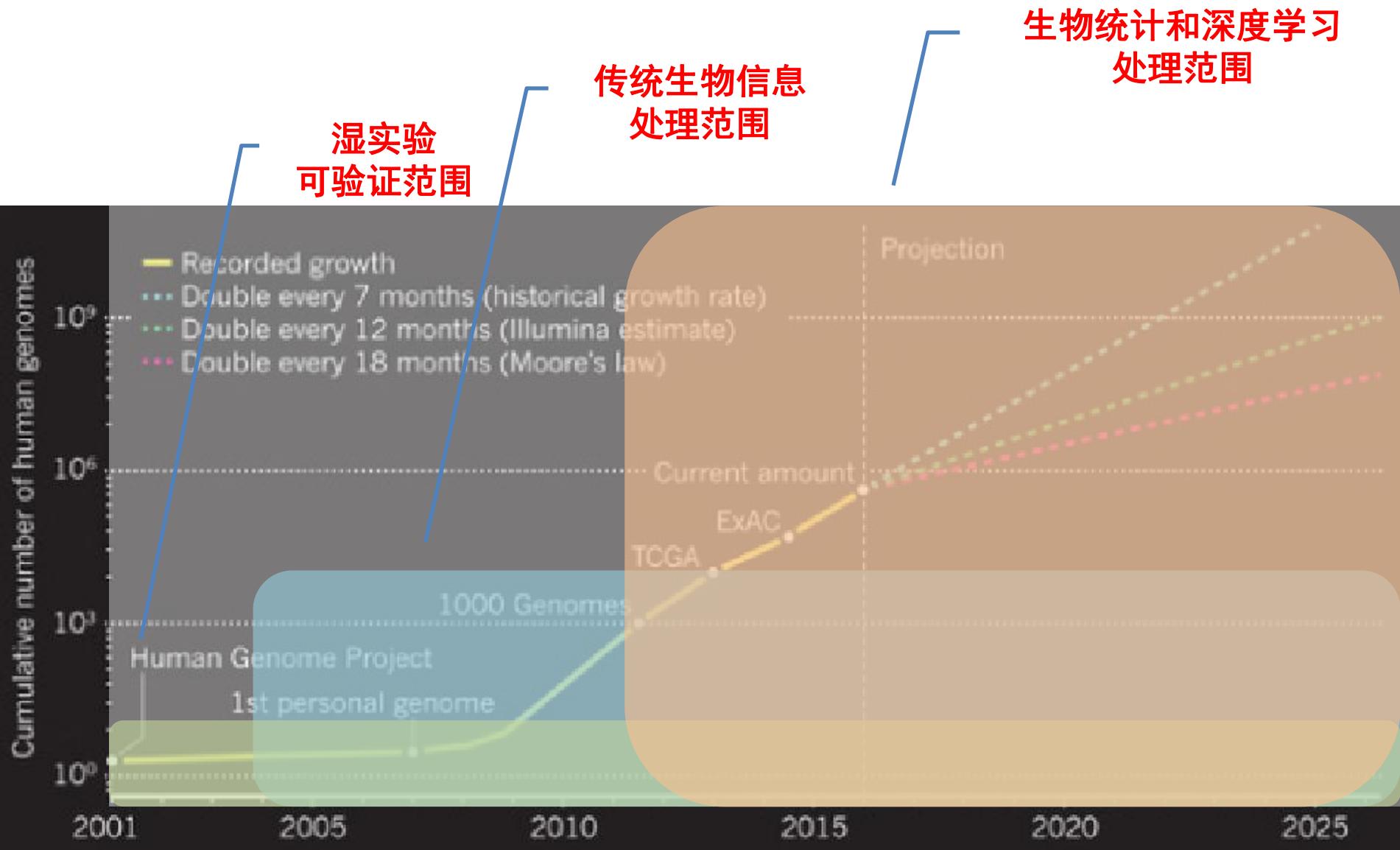
<https://towardsdatascience.com/the-actual-difference-between-statistics-and-machine-learning-64b49f07ea3?gi=412e8f93e22e>

为什么要学习生物统计学

- 如果你只是想从数据中找出哪类人更容易得某种疾病，机器学习可能是更好的选择。
- 如果你希望找出变量之间的关系或从数据中得出推论，选择统计模型会更好。

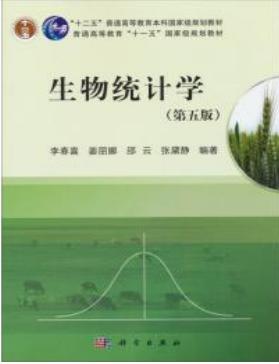


为什么要学习生物统计学



学习方法与要求

- 要弄懂统计的基本原理和基本公式；
- 要认真做好习题作业，加深对公式及统计步骤的理解，达到能熟练地应用统计方法；
- 注意培养科学的统计思维方法，理论联系实际，结合专业，了解统计方法的实际应用。



教材及参考书目

- **教学参考书:**

- 《生物统计学》(第5版), 普通高等教育十二五国家级规划教材). 科学出版社. 2013年6月出版. 李春喜, 姜丽娜, 邵云, 张黛静编著.
- 《生物序列分析》(第1版). 科学出版社. 2010年8月出版. R. Durbin等编著, 王俊等主译.

- **课外文献阅读:**

- 《生物统计学》(第4版). 高等教育出版社. 2013年12月出版. 杜荣骞主编.
- 《生物统计学》(普通高等院校生命科学类十二五规划教材). 华中科技大学出版社. 2015年3月出版. 彭明春, 马纪主编.

课程范围

- 生物统计学的范围
 - 一切和生物相关数据的分析有关的统计
- 面向生物信息和大数据挖掘的生物统计学特点
 - 兼容并包、同时注重方法和应用
- 生物统计学的应用
 - 精准医学的应用

课程结构

- 生物统计学基础；
- 生物信息中的算法设计与概率统计模型；
- 生物大数据和深度学习。

Biostatistics

Biostatistics is the application of statistics to a wide range of topics in biology.

The science of biostatistics encompasses **the design of biological experiments**, especially in medicine, pharmacy, agriculture and fishery; **the collection, summarization, and analysis of data from those experiments**; and **the interpretation of, and inference from, the results**.

A major branch of this is medical biostatistics, which is exclusively concerned with medicine and health.

Bioinformatics

Bioinformatics is the research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data;

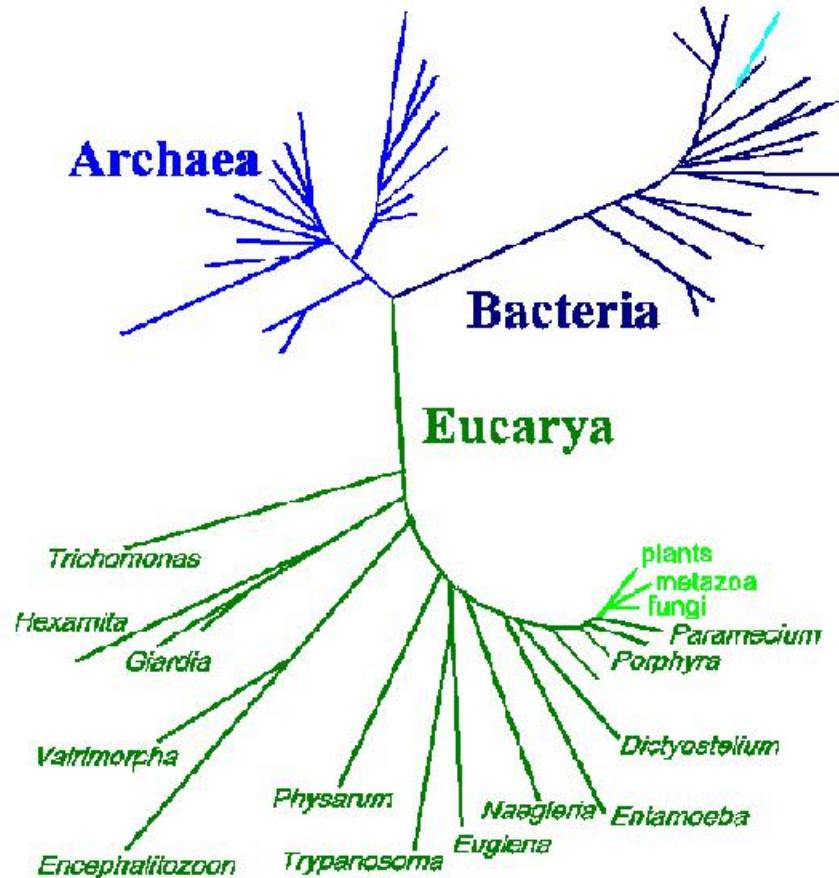
Computational biology is the development and application of data-analytical and theoretical methods, mathematical modeling and computational simulation techniques to the study of biological, behavioral, and social systems.

Bioinformatics

- Overlay of **Biology, Computer science and Statistics.**
- Topics:
 - Sequence alignment
 - Protein folding
 - Gene finding
 - Functional annotation
 - Network inference

研究对象: 生物序列, 进化树, 生物网络, 基因表达...

Tree of Life



modified from N.R. Pace, ASM News 62:464, 1996

Molecules of Life

- DNA
- RNA
- Protein

DNA

- Deoxyribonucleic acid(脱氧核糖核酸)
- Consist of four nucleotides
 - A Adenine(腺嘌呤)
 - C Cytosine(胞嘧啶)
 - G Guanine(鸟嘌呤)
 - T Thymine(胸腺嘧啶)

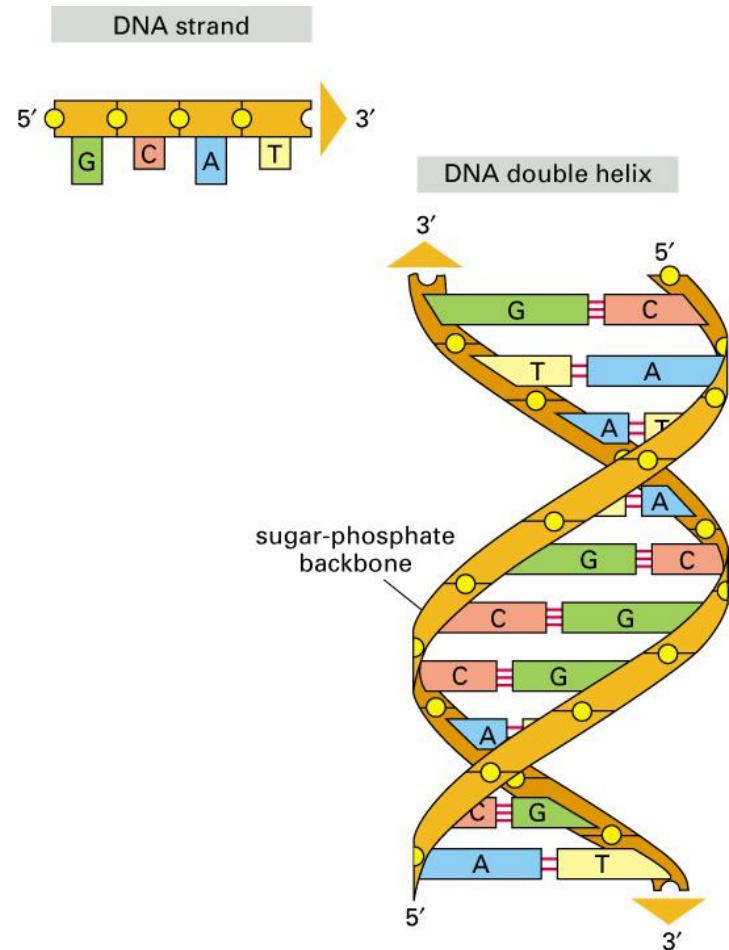


Figure 4-3 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

RNA

- Ribonucleic acid (核糖核酸)
 - mRNA: Messenger RNAs, code for proteins
 - rRNA: Ribosomal RNAs, form the basic structure of the ribosome and catalyze protein synthesis.
 - tRNA: Transfer RNAs, central to protein synthesis as adaptors between mRNA and amino acids.

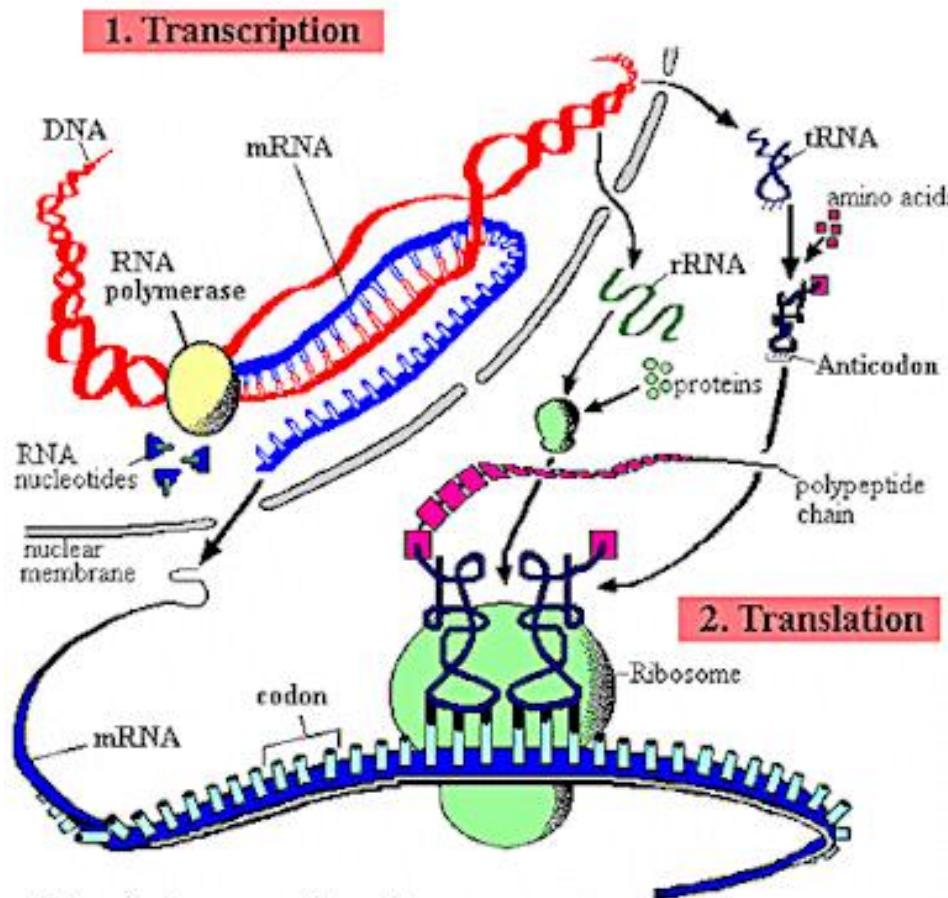
Proteins

Main building blocks and functional molecules,
take up ~20% of eukaryotic cell's weight.

- Structural proteins
- Enzymes
- Antibodies
- Transmembrane proteins

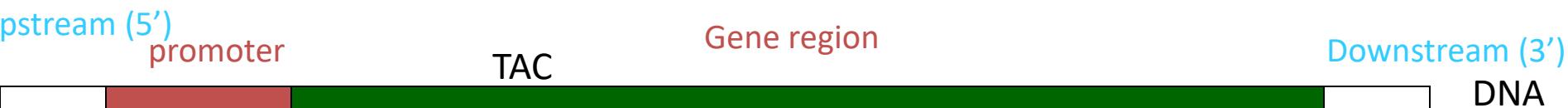
The Central Dogma

DNA → RNA → Protein



Prokaryotic Genes

Prokaryotes (intronless protein coding genes)



↓
Transcription (gene is encoded on minus strand .. And the reverse complement is read into mRNA)



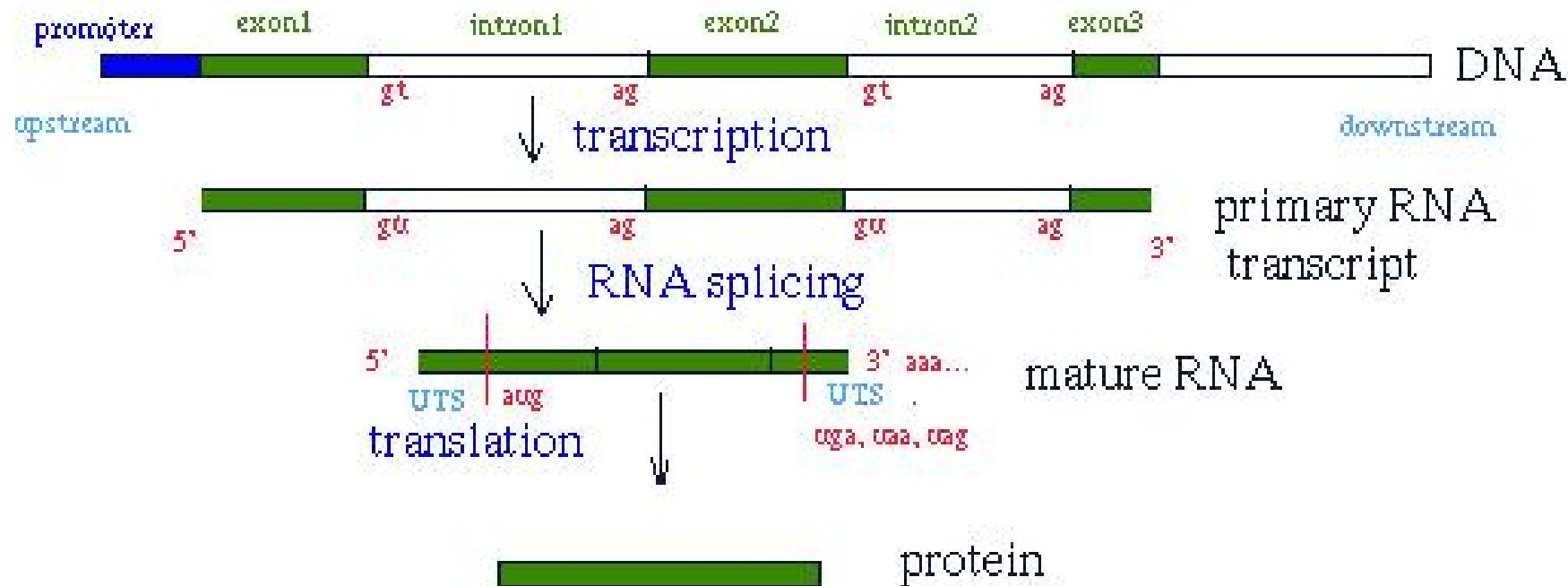
ATG

Translation: tRNA read off each codons, 3 bases at a time,
starting at start codon until it reaches a STOP codon.

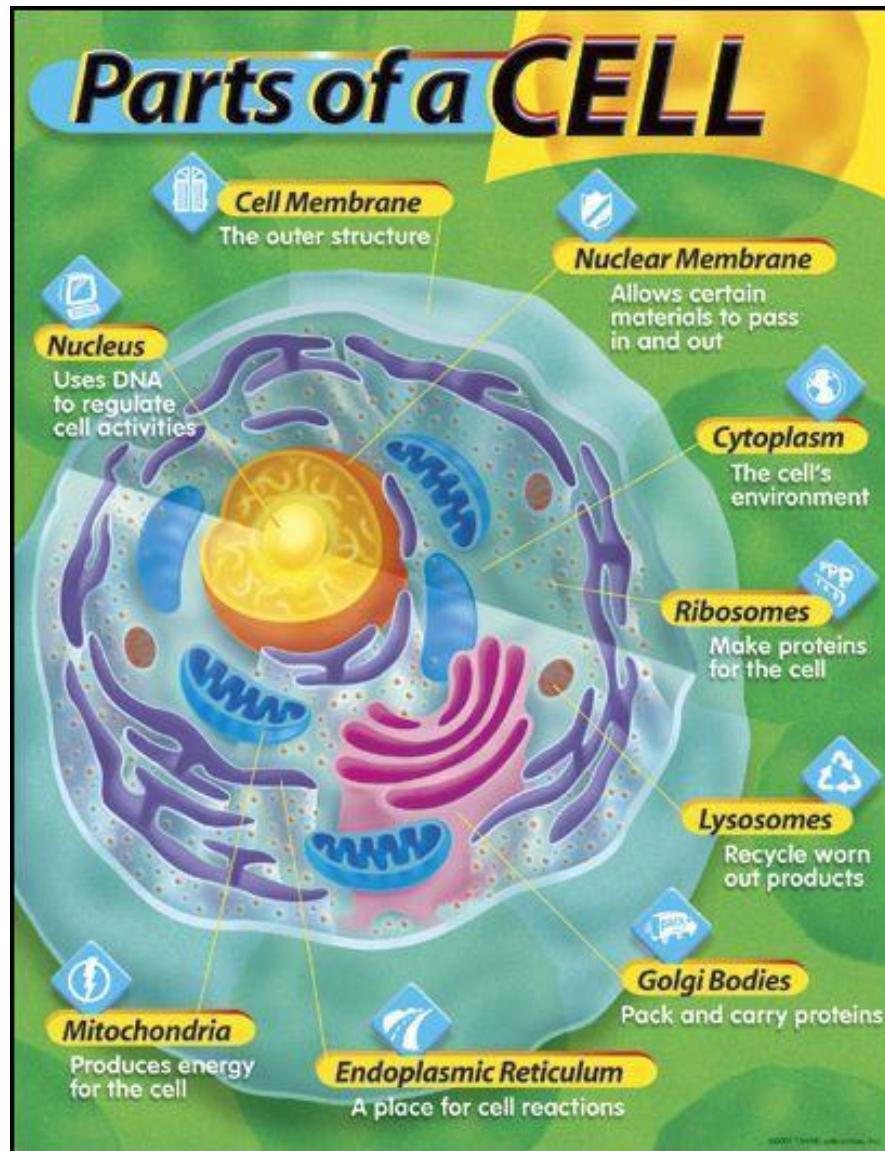


protein

Eukaryotic Genes



Cell structure



Cell structure

Zooming In

In 1664, English scientist Robert Hooke viewed a thin slice of cork through an early microscope. Cork looked to him as if it were constructed of dozens of tiny rectangular compartments. He called them *cells*, from the Latin *cella*, meaning small room.

At first, scientists couldn't see much within a cell and thought it was just filled with jelly. They called that jelly *protoplasm*. But improved microscopes slowly changed that view. We know now that each cell is really a complex part of life.

What's in a Cell?

Each cell is different, but all cells have features similar to this **HUMAN CELL** ➔

Ingredients of Cells



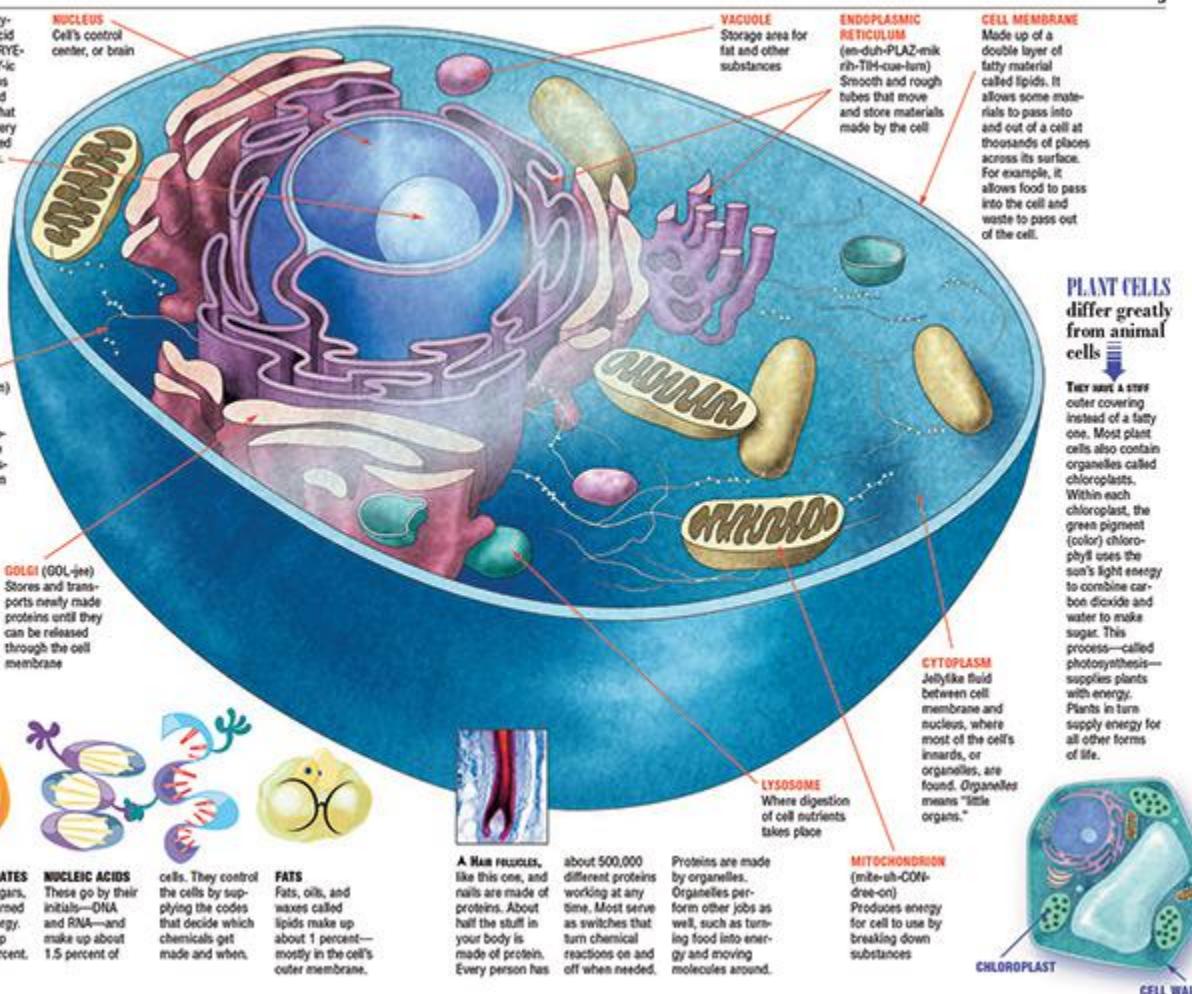
WATER
Water makes up about 90 percent of a cell's weight. Here's what's in the other 10 percent:

PROTEINS
About 5 percent are protein molecules, which in turn are made up of chemicals called amino acids.

CARBOHYDRATES
These are sugars, which are burned for quick energy. They make up about 2.5 percent.

NUCLEIC ACIDS
These go by their initials—DNA and RNA—and make up about 1.5 percent of cells. They control the cells by supplying the codes that decide which chemicals get made and when.

FATS
Fats, oils, and waxes called lipids make up about 1 percent—mostly in the cell's outer membrane.



Biostatistics

Case 1: 基因表达数据分析

- 差异表达基因分析
- 基因共表达分析
- 基因表达数据的聚类和分类
- 基因集分析
- 基因调控网络

Biostatistics

Case 2: 基因集合分析

- 通过测序，找到了一批“interesting”的基因
 - ✿ 差异表达基因
 - ✿ 不做差异基因鉴定，直接做基因集分析
- 生物学功能上是否存在关联？
 - ✿ 某种功能是否显著？
- 计算分析方法
 - ✿ 基因本体 (Gene Ontology)
 - ✿ KEGG (Kyoto Encyclopedia of Genes and Genomes)
 - ✿ 超几何分布

Biostatistics

Case 3: 微生物组生态数据分析

- 物种的富集分析
- 功能的富集分析
- MWAS分析

人工智能与机器学习、深度学习的关系

AI

人工智能(AI)：

让计算机能够象人一样思考

ML

机器学习(ML)：

提升计算机模拟人类思考能力的方法

DL

深度学习(DL)：

通过神经网络方式进行机器学习的方法

基础

计算机

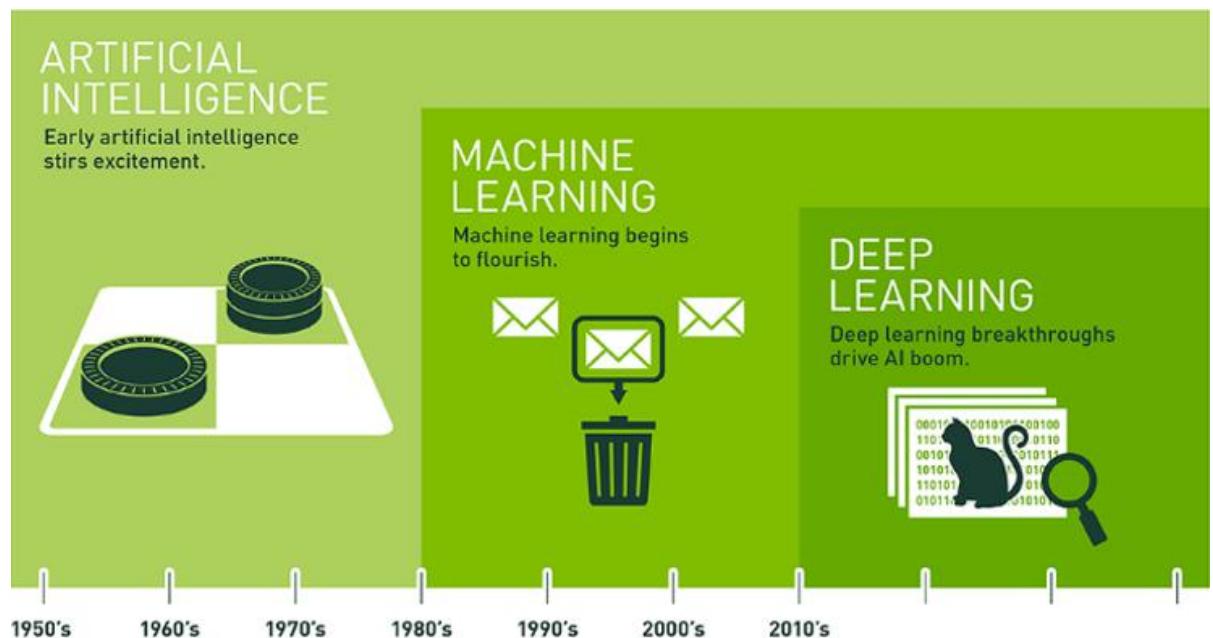
统计学

行业知识

知识工程

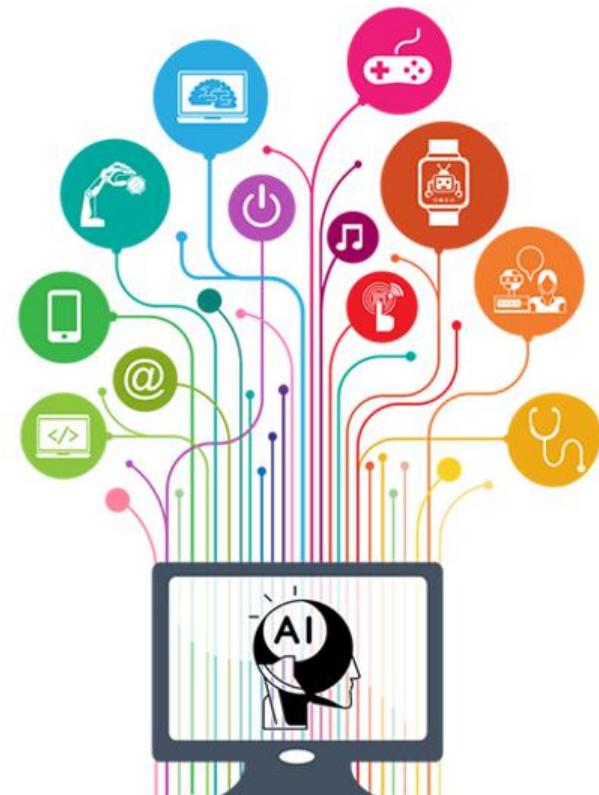
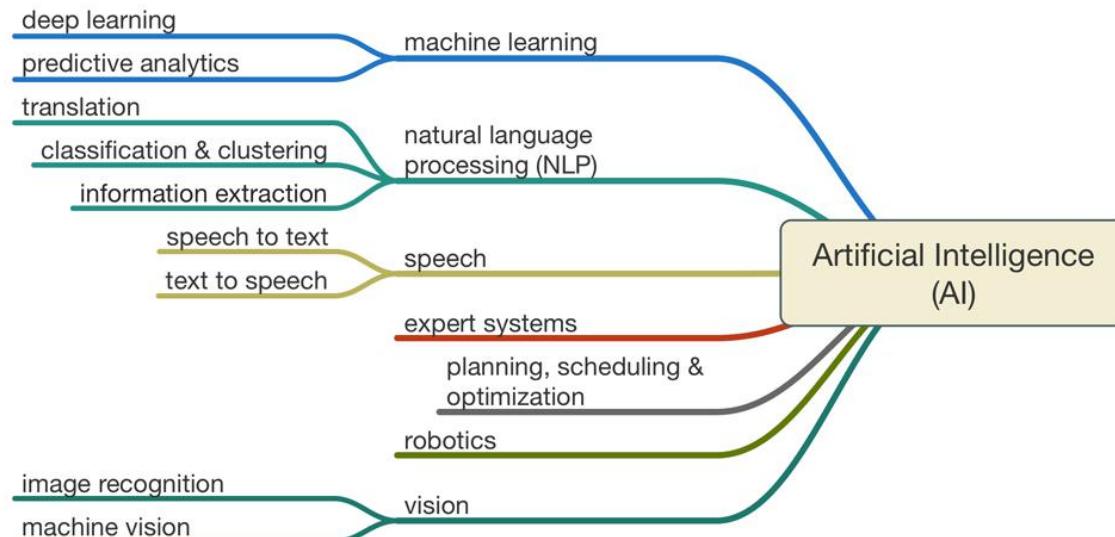
Introduction

- Artificial Intelligence
- Machine learning
- “Deep” learning



Artificial Intelligence

Artificial intelligence (AI, also machine intelligence, MI) is intelligence displayed by machines, in contrast with the natural intelligence (NI) displayed by humans and other animals.



Hatley, L. (2016). Presentation, New Designs for Learning: Games and Gamification
https://en.wikipedia.org/wiki/Applications_of_artificial_intelligence

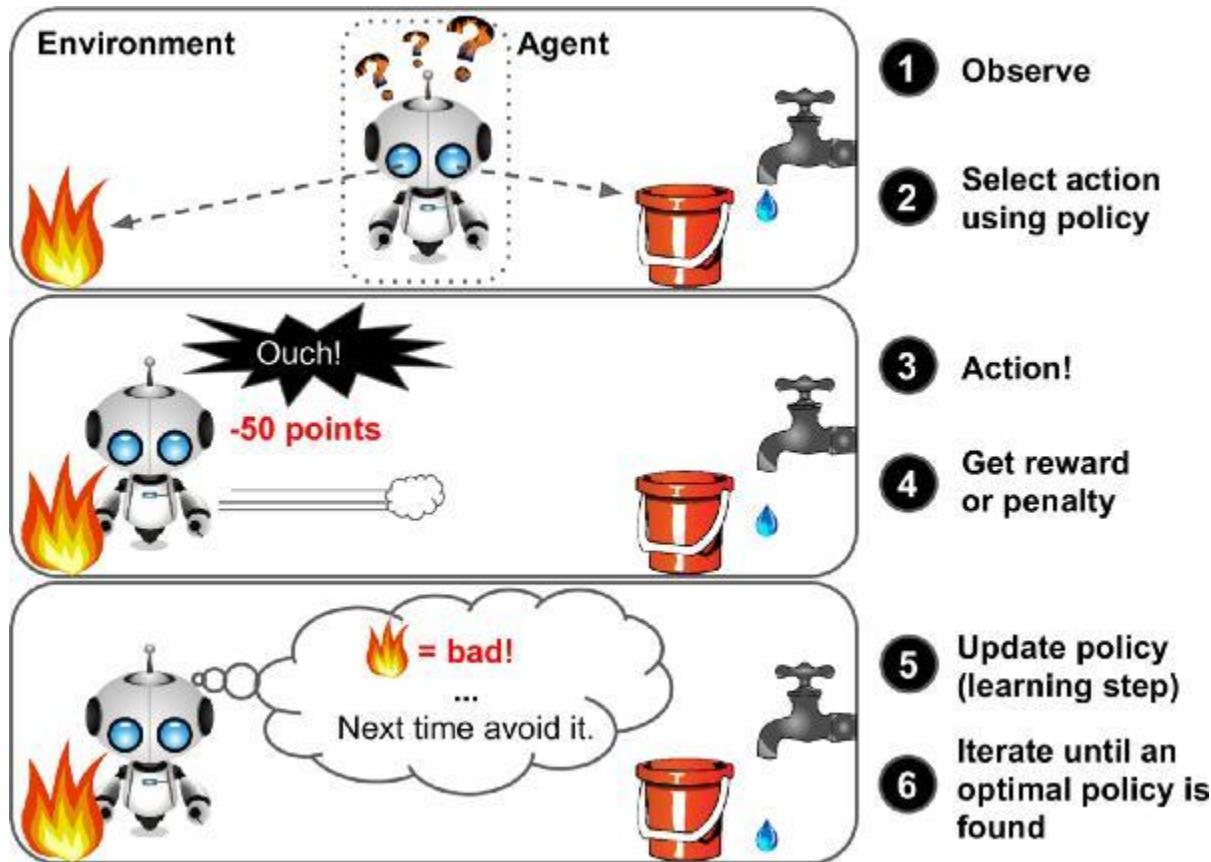
Big-data + Deep learning

Big-data is a term for data sets that are so large or complex that traditional data processing application software is inadequate to deal with them. Challenges include capture, storage, analysis, data curation, search, sharing, transfer, visualization, querying, updating and information privacy.

Deep learning is part of a broader family of machine learning methods based on learning representations of data. Research in this area attempts to make better representations and create models to learn these representations from large-scale unlabeled data.

Big-data + Deep learning

Reinforcement Learning

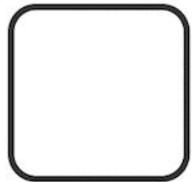


Big-data + Deep learning

Markov chain

Stochastic Process

Random Variable

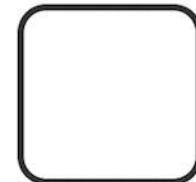


Possible States: ● ● ●



Markov Chain

Random Variable



Possible States: ● ● ●



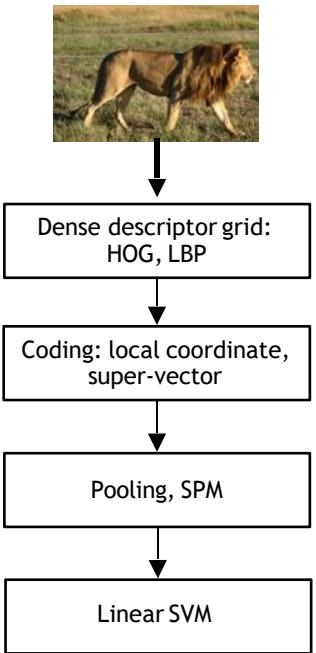
“The future is independent of the past given the present!”

Big-data + Deep learning

IMAGENET Large Scale Visual Recognition Challenge

Year 2010

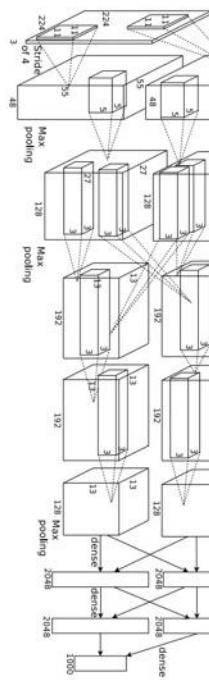
NEC-UIUC



[Lin CVPR 2011]

Year 2012

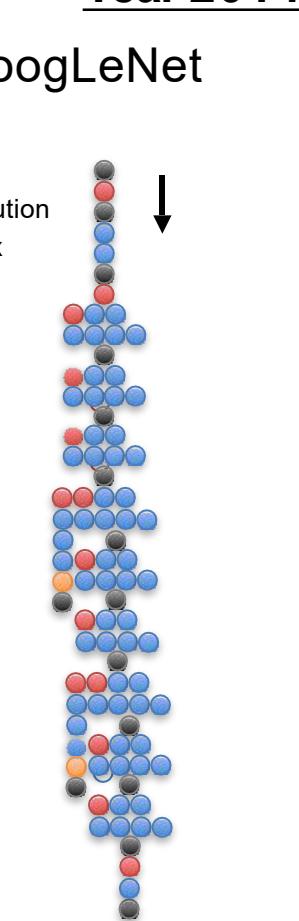
SuperVision



[Krizhevsky NIPS 2012]

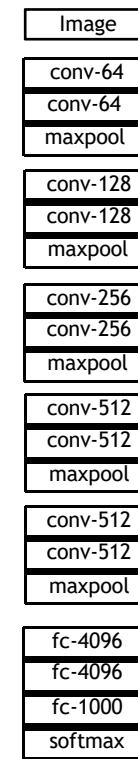
Year 2014

GoogLeNet



[Szegedy arxiv 2014]

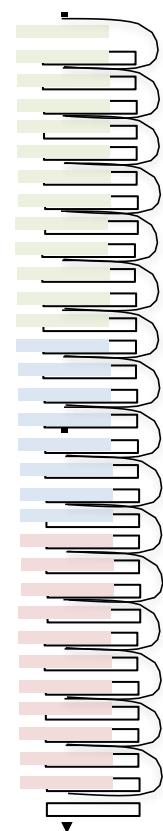
VGG



[Simonyan arxiv 2014]

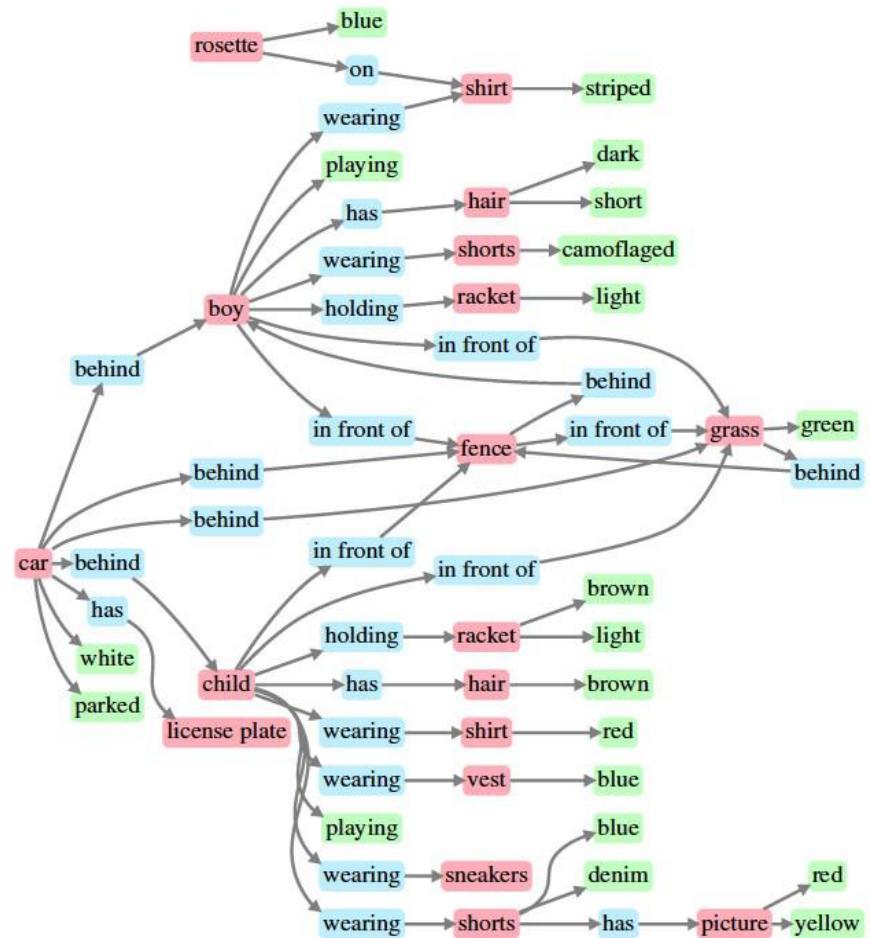
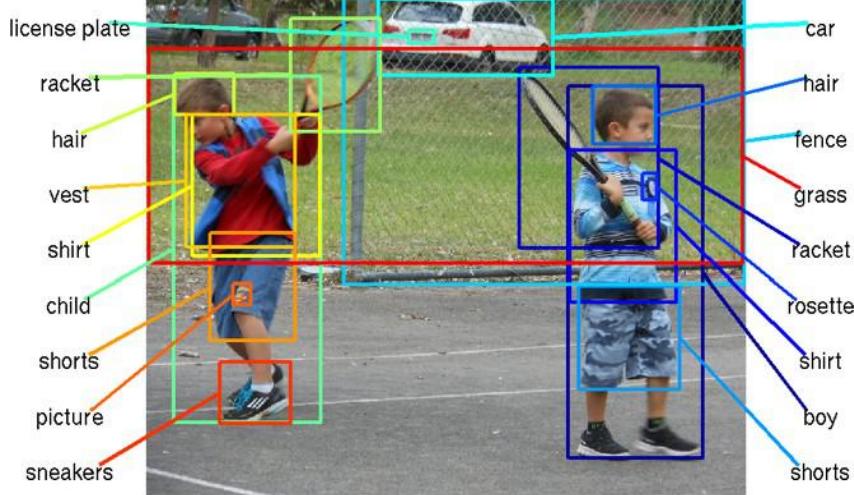
Year 2015

MSRA



[He ICCV 2015]

Big-data + Deep learning



Johnson *et al.*, “Image Retrieval using Scene Graphs”, CVPR 2015

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Big-data + Deep learning

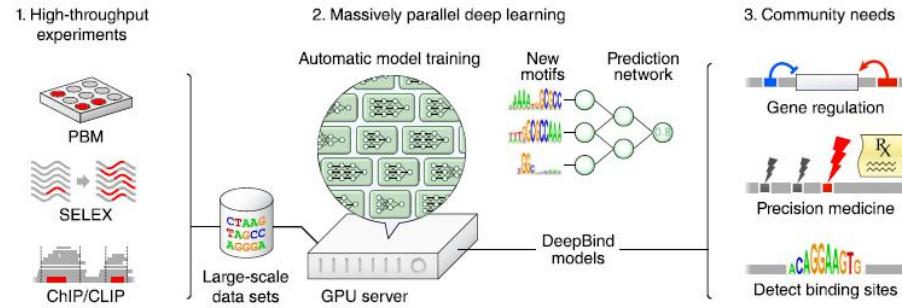


Figure 1 DeepBind's input data, training procedure and applications. 1. The sequence specificities of DNA- and RNA-binding proteins can now be measured by several types of high-throughput assay, including PBM, SELEX, and ChIP- and CLIP-seq techniques. 2. DeepBind captures these binding specificities from raw sequence data by jointly discovering new sequence motifs along with rules for combining them into a predictive binding score. Graphics processing units (GPUs) are used to automatically train high-quality models, with expert tuning allowed but not required. 3. The resulting DeepBind models can then be used to identify binding sites in test sequences and to score the effects of novel mutations.

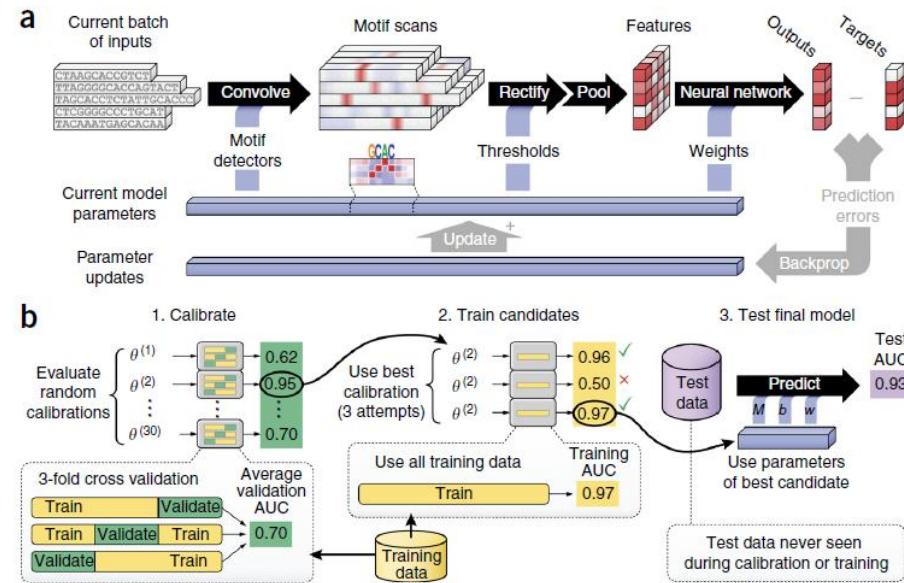
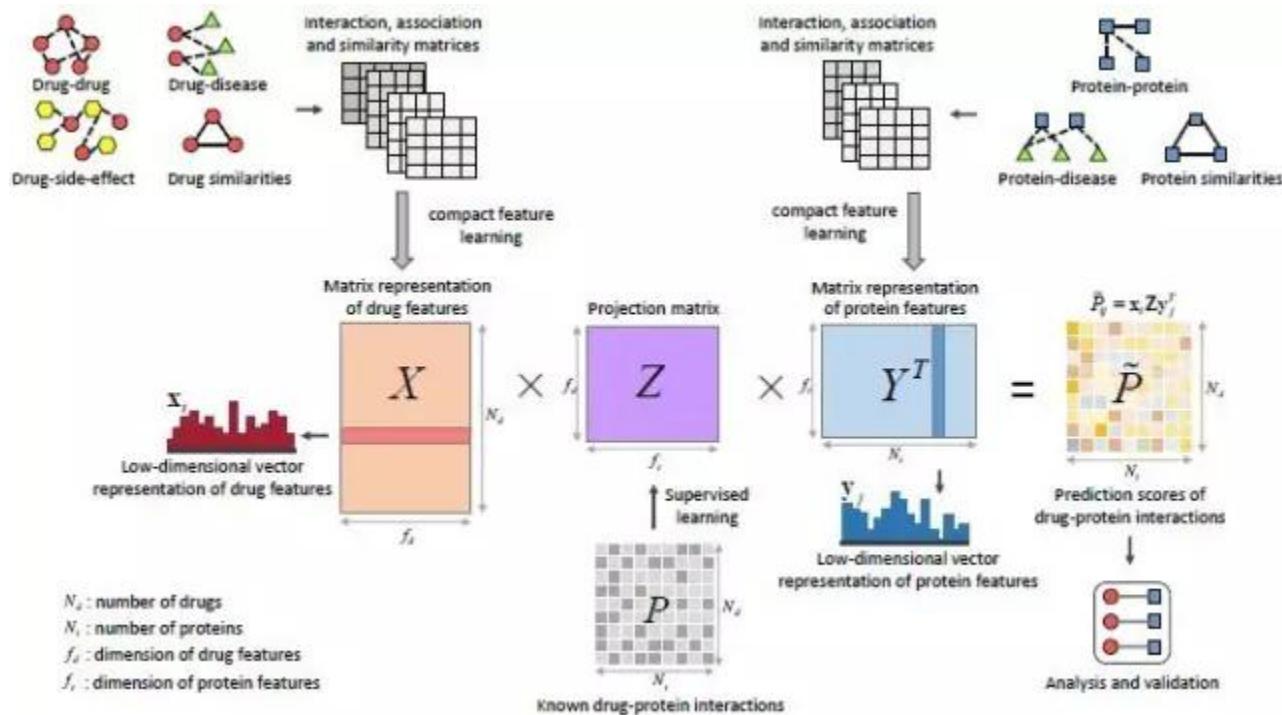


Figure 2 Details of inner workings of DeepBind and its training procedure. (a) Five independent sequences being processed in parallel by a single DeepBind model. The convolve, rectify, pool and neural network stages predict a separate score for each sequence using the current model parameters (*Supplementary Notes*, sec. 1). During the training phase, the backprop and update stages simultaneously update all motifs, thresholds and network weights of the model to improve prediction accuracy. (b) The calibration, training and testing procedure used throughout (*Supplementary Notes*, sec. 2).

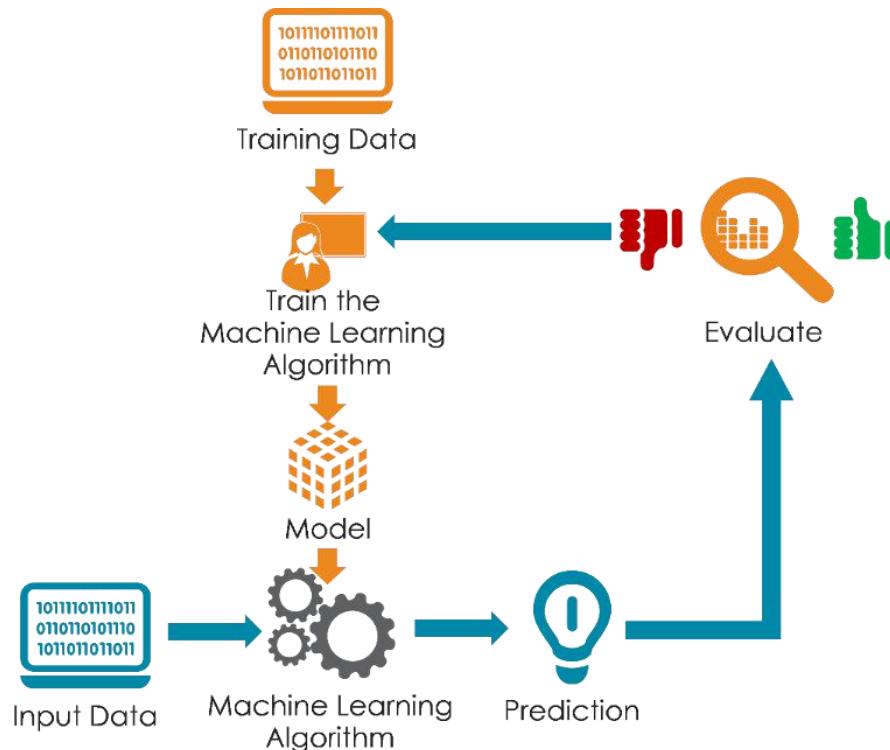
Big-data + Deep learning



Jianyang Zeng *et al.*, Nature Communications, 2017

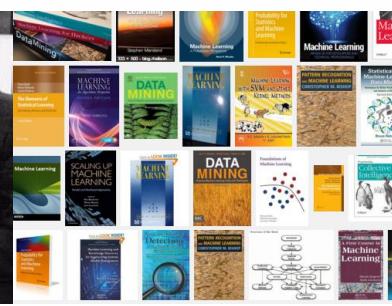
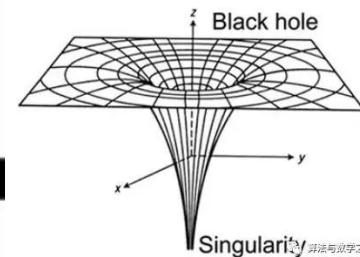
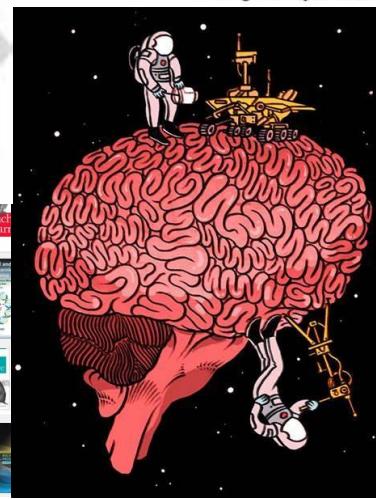
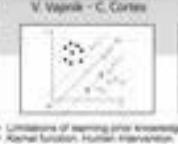
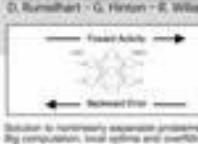
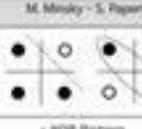
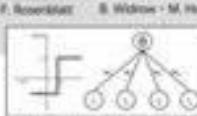
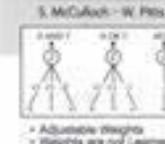
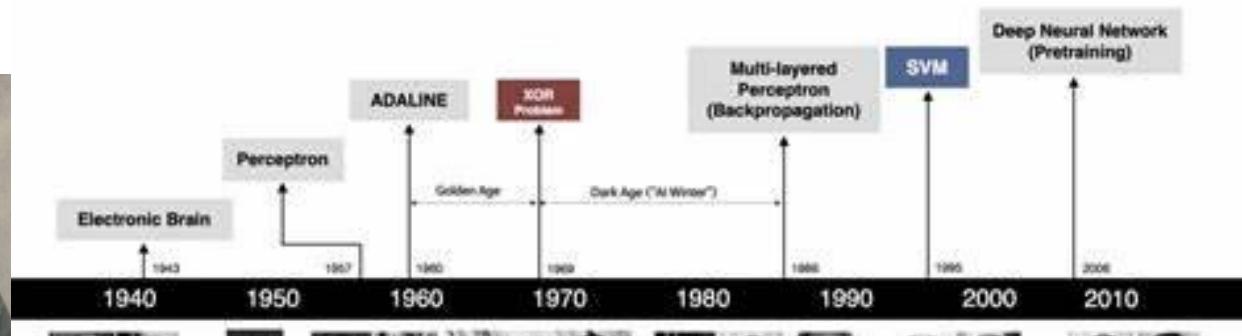
Machine Learning

Machine learning is the science of getting computers to act without being explicitly programmed.

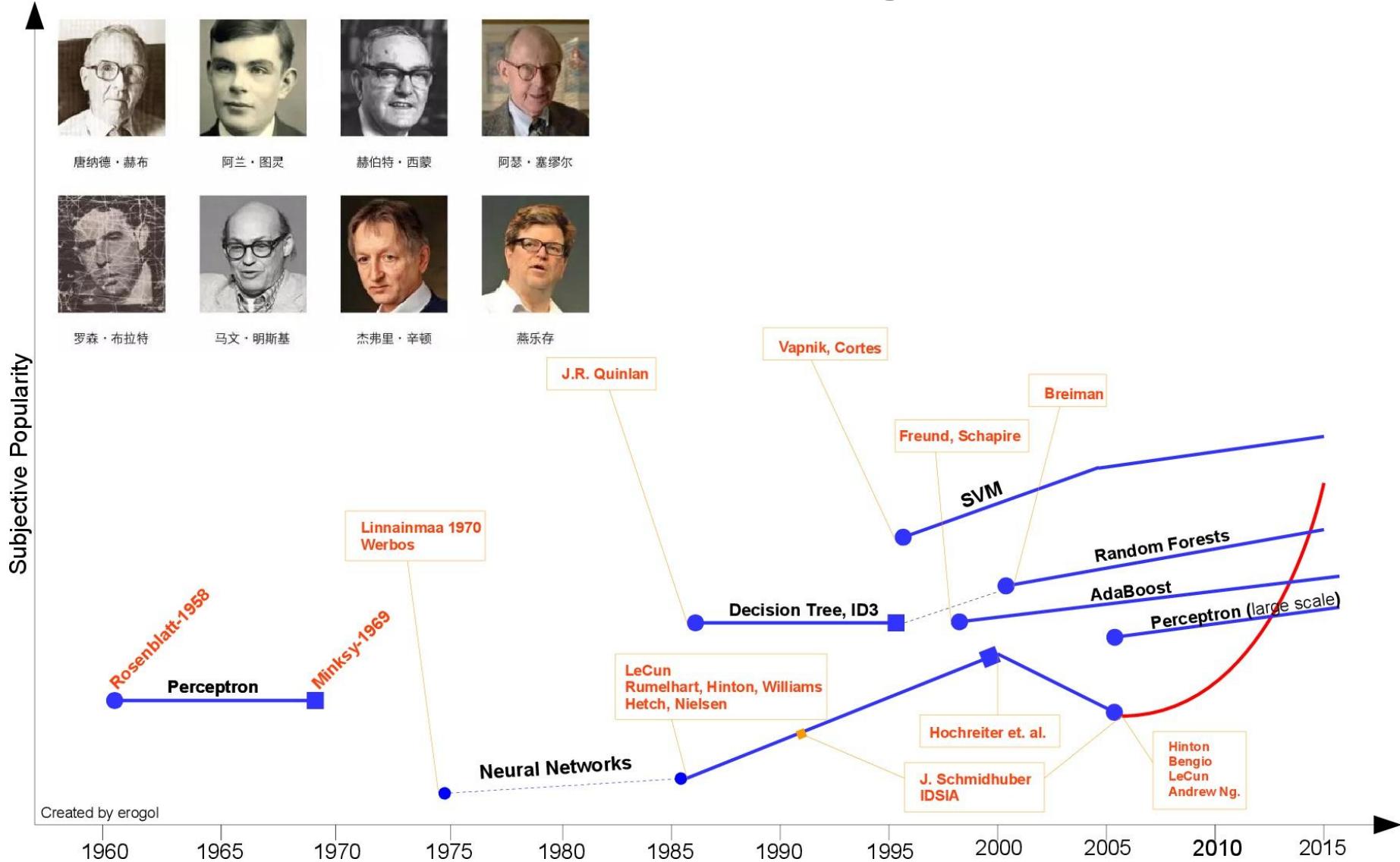


General workflow of Machine Learning

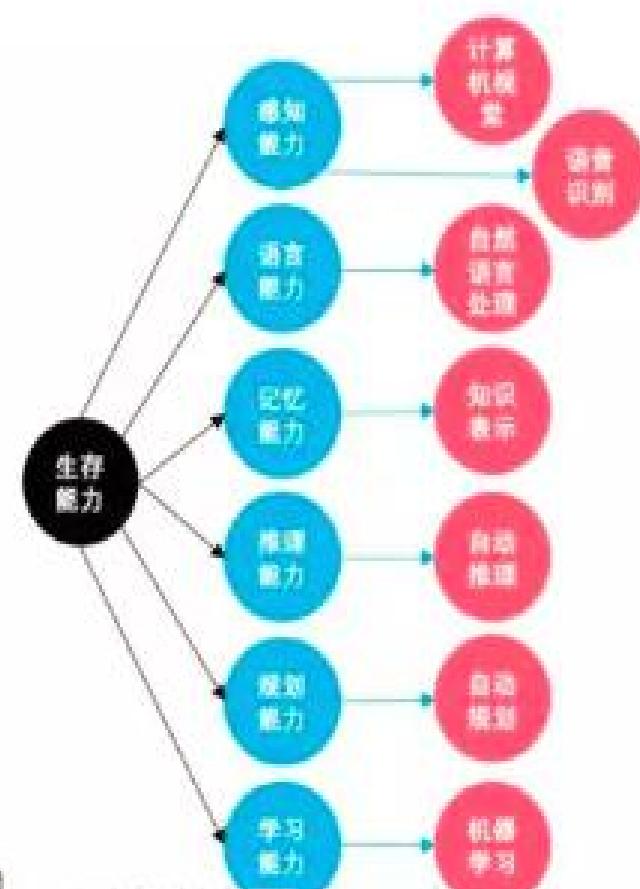
Machine Learning



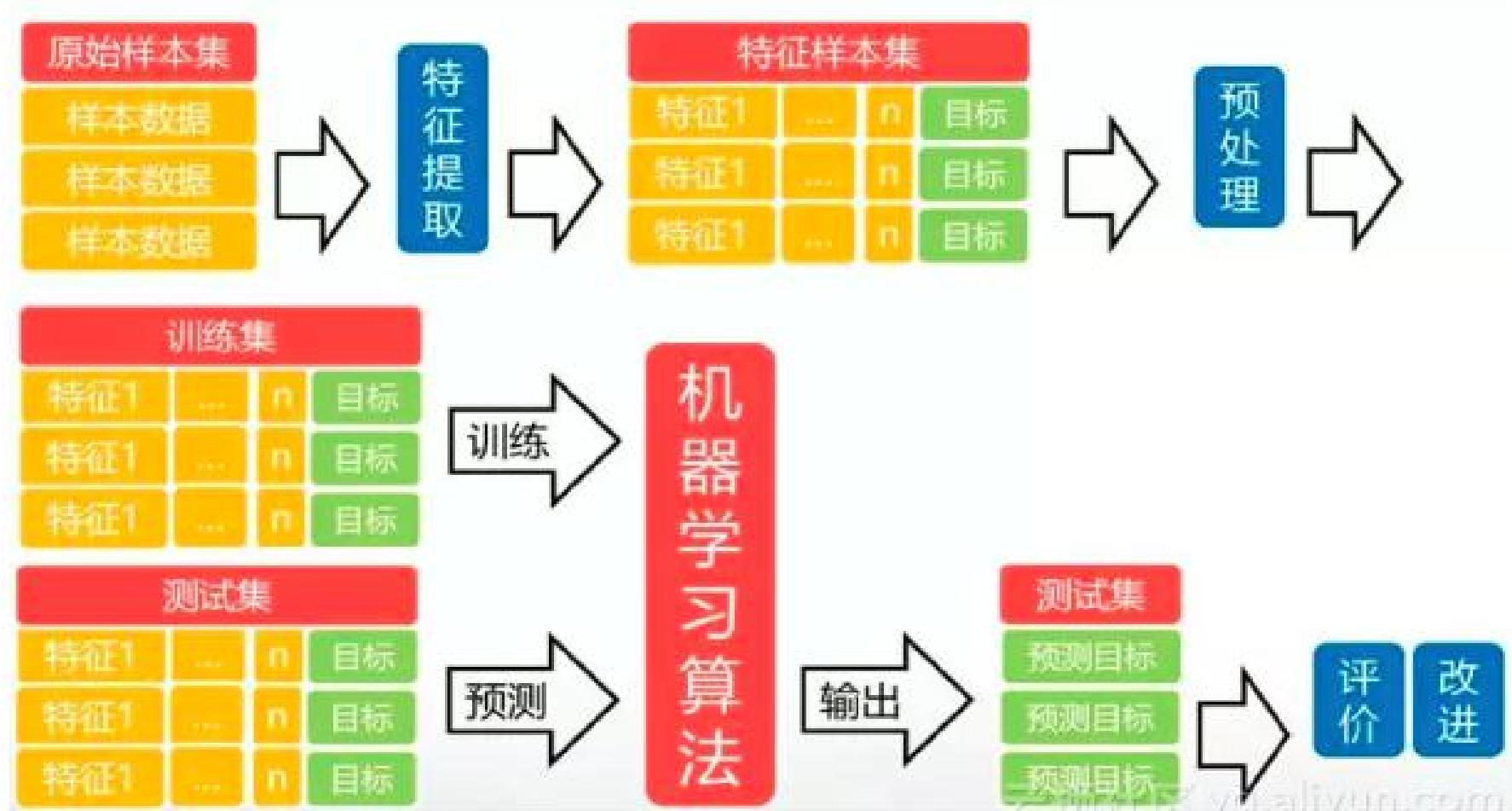
Machine Learning



拥抱人工智能从机器学习开始

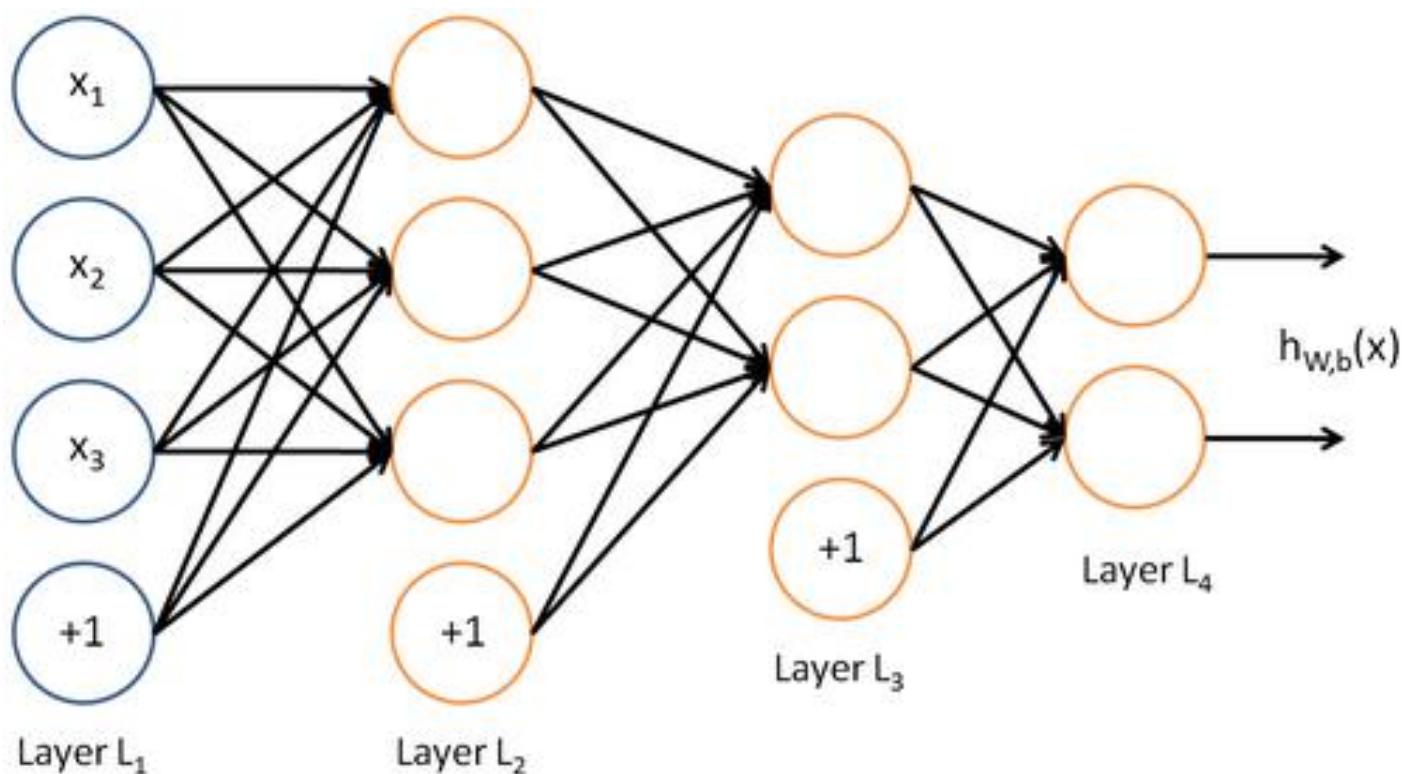


- 机器学习最大的特点是利用数据而不是指令来进行各种工作，其学习过程主要包括：数据的特征提取、数据预处理、训练模型、测试模型、模型评估改进等几部分。



机器学习算法是使计算机具有智能的关键

- 算法是通过使用已知的输入和输出以某种方式“训练”以对特定输入进行响应。代表着用系统的方法描述解决问题的策略机制。人工智能的发展离不开机器学习算法的不断进步。



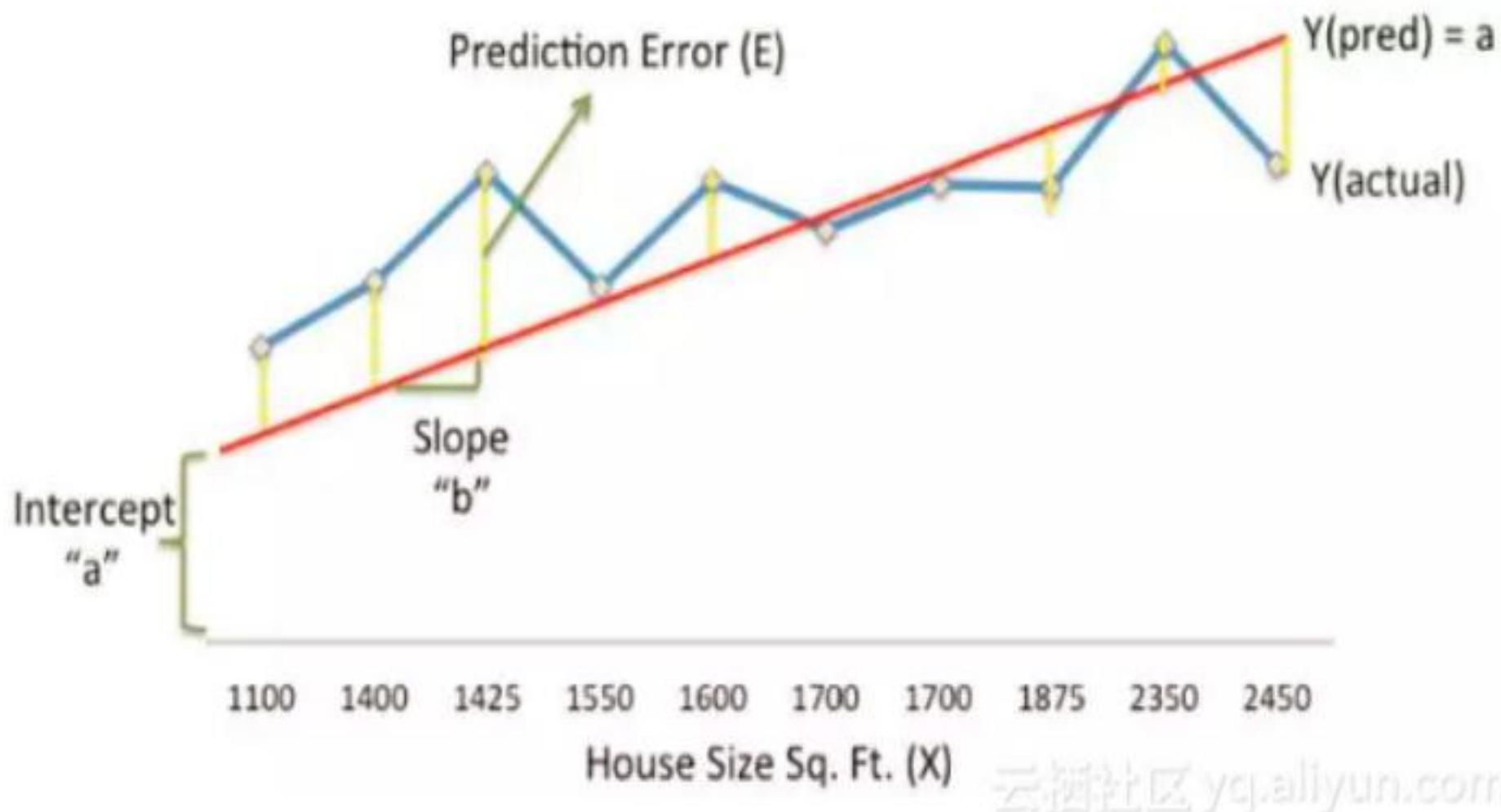
机器学习算法分类



1. 线性回归：找到一条直线来预测目标值

- 一个简单的场景：已知房屋价格与尺寸的历史数据，问面积为2000时，售价为多少？

House Size sq.ft (X)	1400	1600	1700	1875	1100	1550	2350	2450	1425	1710
House Price \$ (Y)	245,000	312,000	279,000	308,000	199,000	219,000	405,000	324,000	319,000	255,000

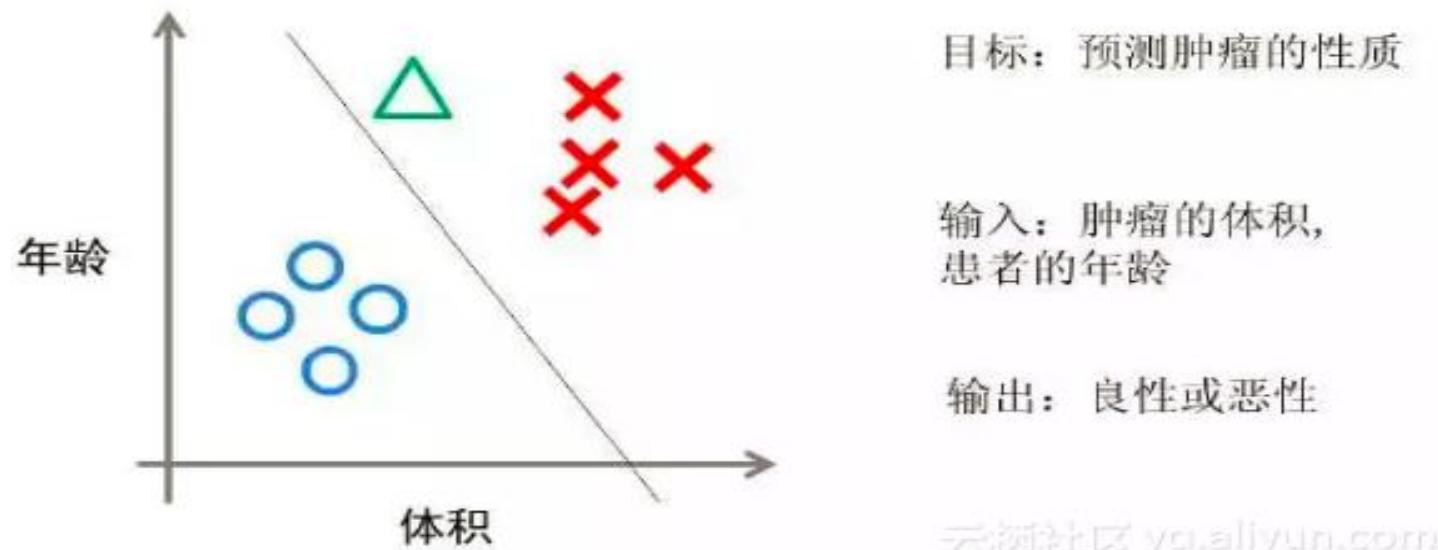


线性回归的应用

- **预测客户终生价值：** 基于老客户历史数据与客户生命周期的关联关系，建立线性回归模型，预测新客户的终生价值，进而开展针对性的活动。
- **机场客流量分布预测：** 以海量机场WiFi数据及安检登机值机数据，通过数据算法实现机场航站楼客流分析与预测。
- **货币基金资金流入流出预测：** 通过用户基本信息数据、用户申购赎回数据、收益率表和银行间拆借利率等信息，对用户的申购赎回数据的把握，精准预测未来每日的资金流入流出情况。
- **电影票房预测：** 依据历史票房数据、影评数据、舆情数据等互联网公众数据，对电影票房进行预测。

2. 逻辑回归：找到一条直线来分类数据

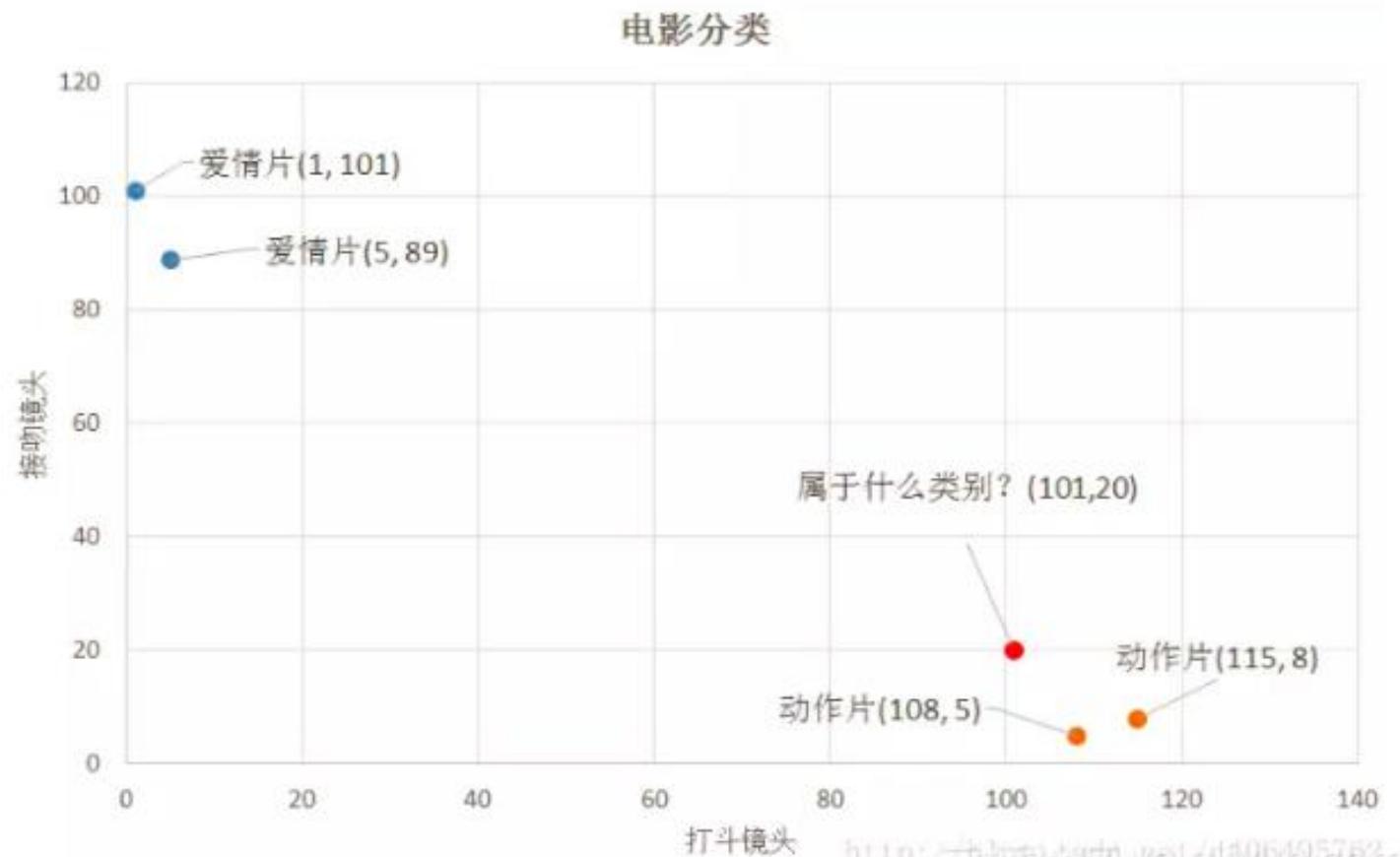
- 逻辑回归虽然名字叫回归，却是属于分类算法，是通过 Sigmoid函数将线性函数的结果映射到Sigmoid函数中，预估事件出现的概率并分类。



逻辑回归从直观上来说是画出了一条分类线。位于分类线一侧的数据，概率 >0.5 , 属于分类A；位于分类线另一侧的数据，概率 <0.5 , 属于分类B。

3. K-近邻：用距离度量最相邻的分类标签

- 一个简单的场景：已知一个电影中的打斗和接吻镜头数，判断它是属于爱情片还是动作片。当接吻镜头数较多时，根据经验我们判断它为爱情片。那么计算机如何进行判别呢？



4. 朴素贝叶斯：选择后验概率最大的类为分类标签

- 一个简单的场景：一号碗(C1)有30颗水果糖和10颗巧克力糖，二号碗(C2)有水果糖和巧克力糖各20颗。现在随机选择一个碗，从中摸出一颗糖，发现是水果糖。
- 问这颗水果糖(x)最有可能来自哪个碗？

$$P(\omega_j | x) = \frac{p(x | \omega_j) P(\omega_j)}{p(x)}$$

似然函数 $p(x | \omega_j)$ 和 先验概率 $P(\omega_j)$ 是分子的组成部分。
后验概率 $P(\omega_j | x)$ 是整个表达式的结果。
证据因子 (evidence) $p(x)$ 是分母的组成部分，可以通过以下公式计算：

$$p(x) = \sum_{j=1}^2 p(x | \omega_j) P(\omega_j)$$

例如上面的例子中： $P(X)$: 水果糖的概率为 $5/8$

$P(X|C1)$: 一号碗中水果糖的概率为 $3/4$

$P(X|C2)$: 二号碗中水果糖的概率为 $2/4$

$P(C1)=P(C2)$: 两个碗被选中的概率相同，为 $1/2$

则水果糖来自一号碗的概率为：

$$P(C1|X) = P(X|C1)P(C1)/P(X) = (3/4)(1/2)/(5/8) = 3/5$$

水果糖来自二号碗的概率为：

$$P(C2|X) = P(X|C2)P(C2)/P(X) = (2/4)(1/2)/(5/8) = 2/5$$

$$P(C1|X) > P(C2|X)$$

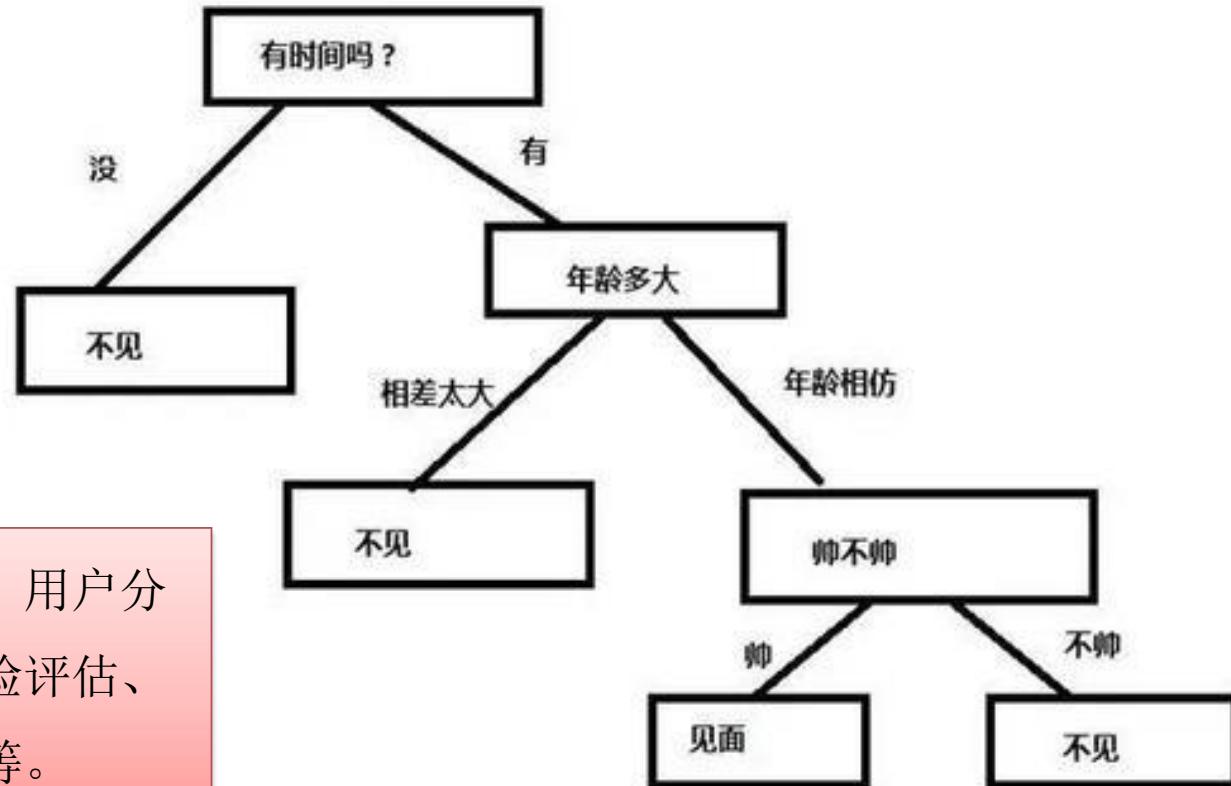
因此这颗糖最有可能来自一号碗。

朴素贝叶斯的主要应用有文本分类、垃圾文本过滤，情感判别，多分类实时预测等。

5. 决策树：构造熵值下降最快的分类树

- 一个简单的场景：

相亲时，可能首先检测相亲对方是否有时间。如果有，则考虑进一步接触，再观察其是否有上进心，如果没有，直接Say Goodbye。如果有，则在看帅不帅，帅的可以列入候选名单。

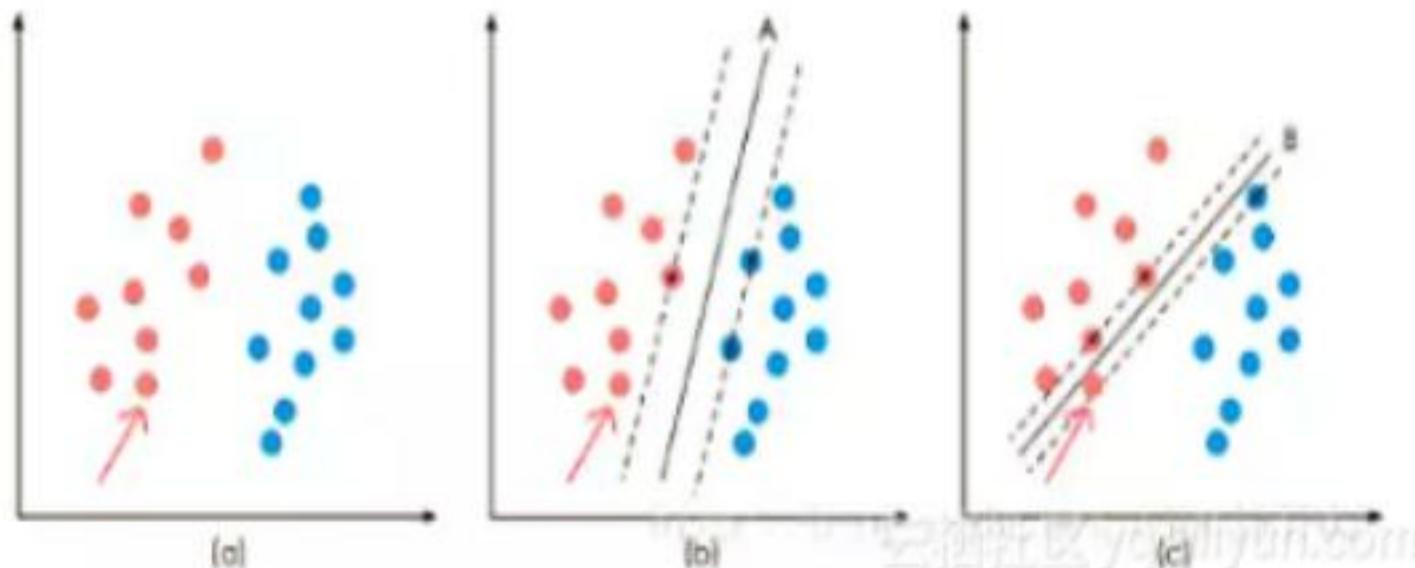


决策树可以应用于：用户分级评估、贷款风险评估、选股、投标决策等。

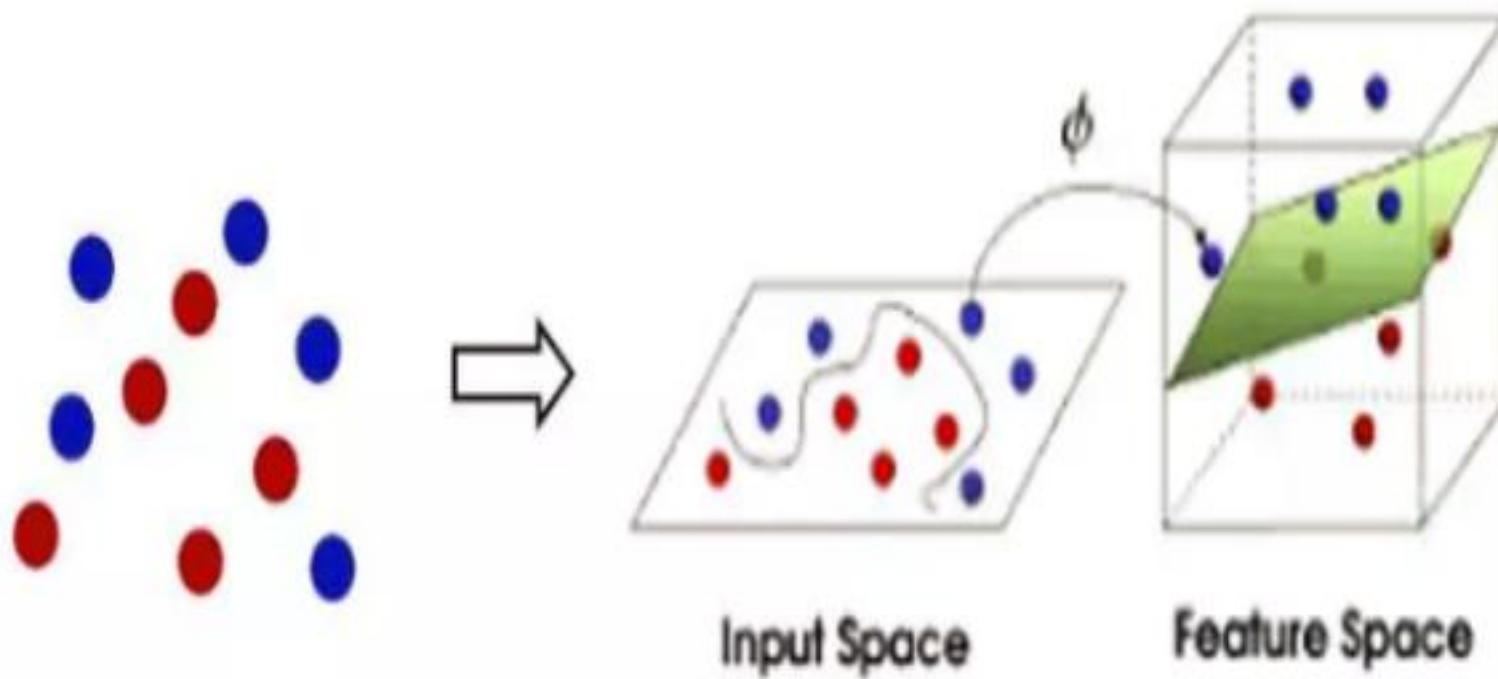
6. 支持向量机 (SVM)：构造超平面，分类非线性数据

一个简单的场景：

要求用一根线将不同颜色的球分开，要求尽量在放更多球之后，仍然适用。A、B两条线都可以满足条件。再继续增加球，线A仍可以将球很好的分开，而线B则不可以。



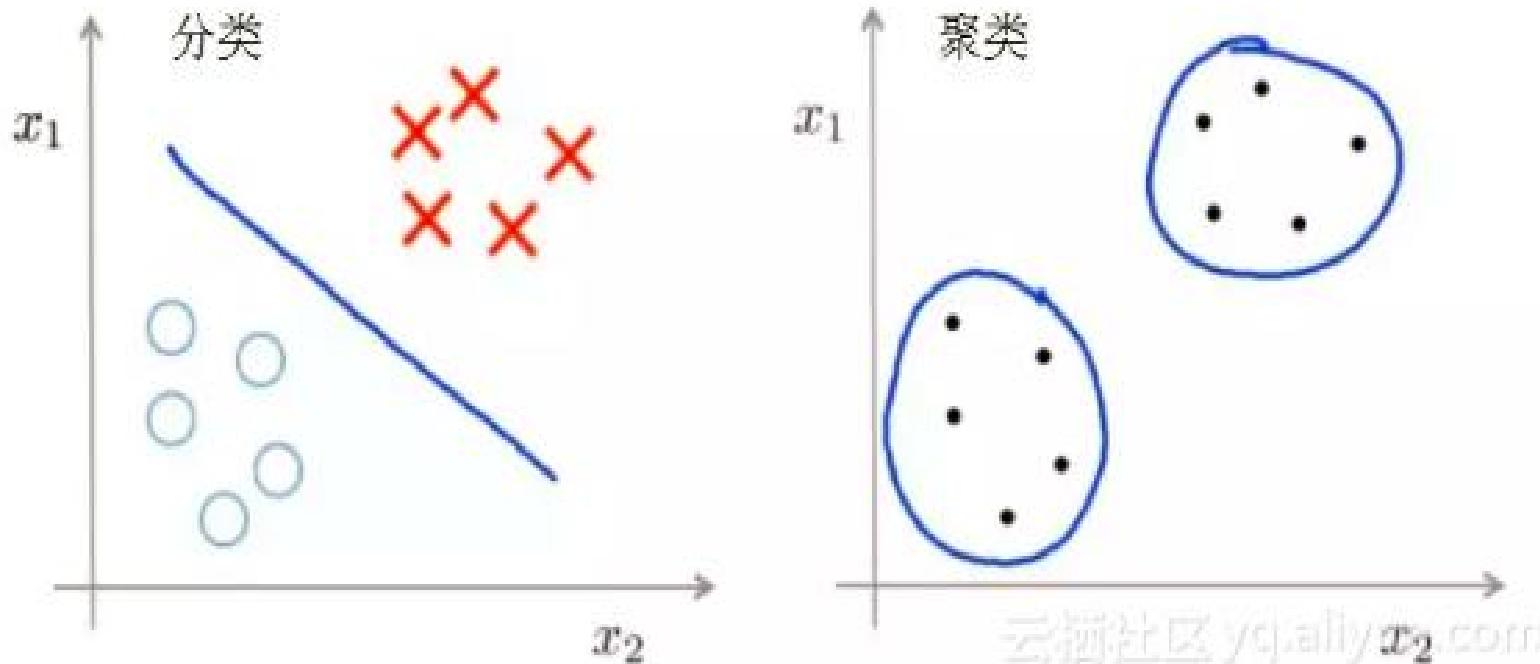
进一步增加难度，当球没有明确的分界线，用一条直线已经无法将球分开，该怎么解决？



SVM 可应用于垃圾邮件识别、手写识别、文本分类、选股等。

7. K-means: 计算质心，聚类无标签数据

- 在上面介绍的分类算法中，需要被分类的数据集已经有标记，例如数据集已经标记为○或者×，通过学习出假设函数对这两类数据进行划分。而对于没有标记的数据集，希望能有一种算法能够自动的将相同元素分为紧密关系的子集或簇，这就是聚类算法。

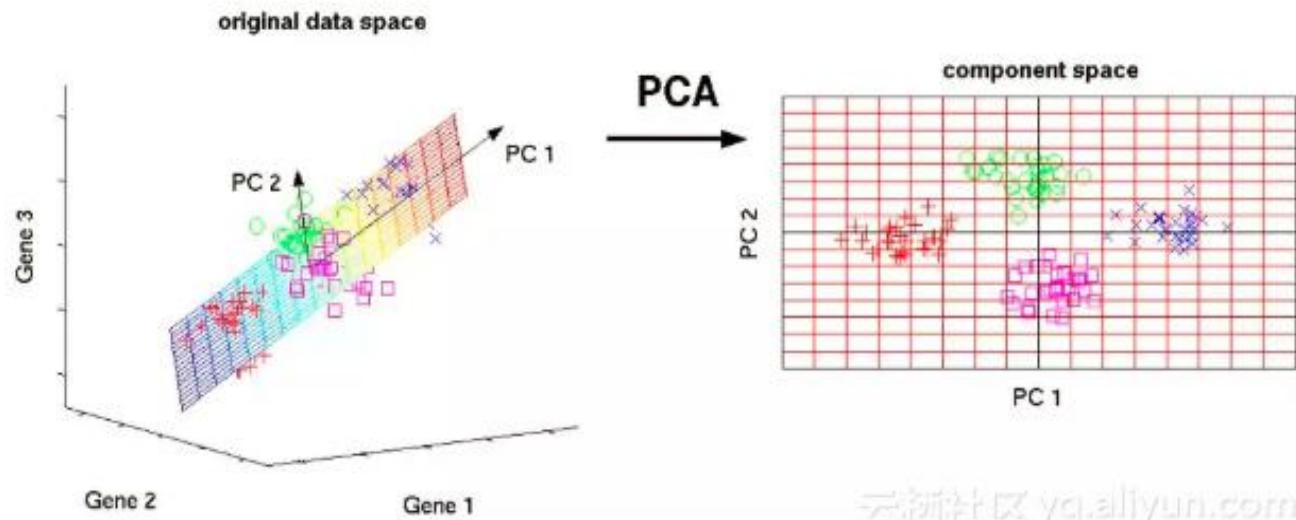


• 8. 关联分析：挖掘啤酒与尿布（频繁项集）的关联规则

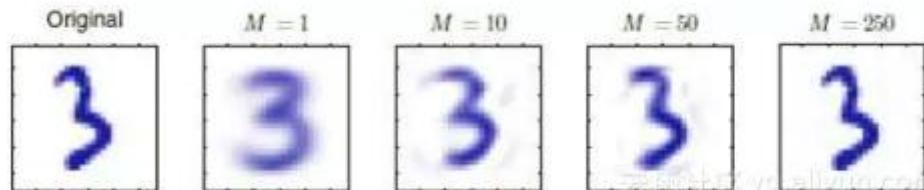
- 算法中几个相关的概念：
 - **频繁项集：**在数据库中大量频繁出现的数据集合。例如购物单数据中{'啤酒'}、{'尿布'}、{'啤酒', '尿布'}出现的次数都比较多。
 - **关联规则：**由集合 A，可以在某置信度下推出集合 B。即如果 A 发生了，那么 B 也很有可能会发生。例如购买了{'尿布'}的人很可能会购买{'啤酒'}。
 - **支持度：**指某频繁项集在整个数据集中的比例。假设数据集有 10 条记录，包含{'啤酒', '尿布'}的有 5 条记录，那么{'啤酒', '尿布'}的支持度就是 $5/10 = 0.5$ 。
 - **置信度：**有关联规则如{'尿布'} -> {'啤酒'}，它的置信度为 {'尿布'} -> {'啤酒'}
假设{'尿布', '啤酒'}的支持度为 0.45，{'尿布'}的支持度为 0.5，则{'尿布'} -> {'啤酒'}的置信度为 $0.45 / 0.5 = 0.9$ 。

9. PCA降维：减少数据维度，降低数据复杂度

- 降维是指将原高维空间中的数据点映射到低维度的空间中。因为高维特征的数目巨大，距离计算困难，分类器的性能会随着特征数的增加而下降；减少高维的冗余信息所造成的误差，可以提高识别的精度。



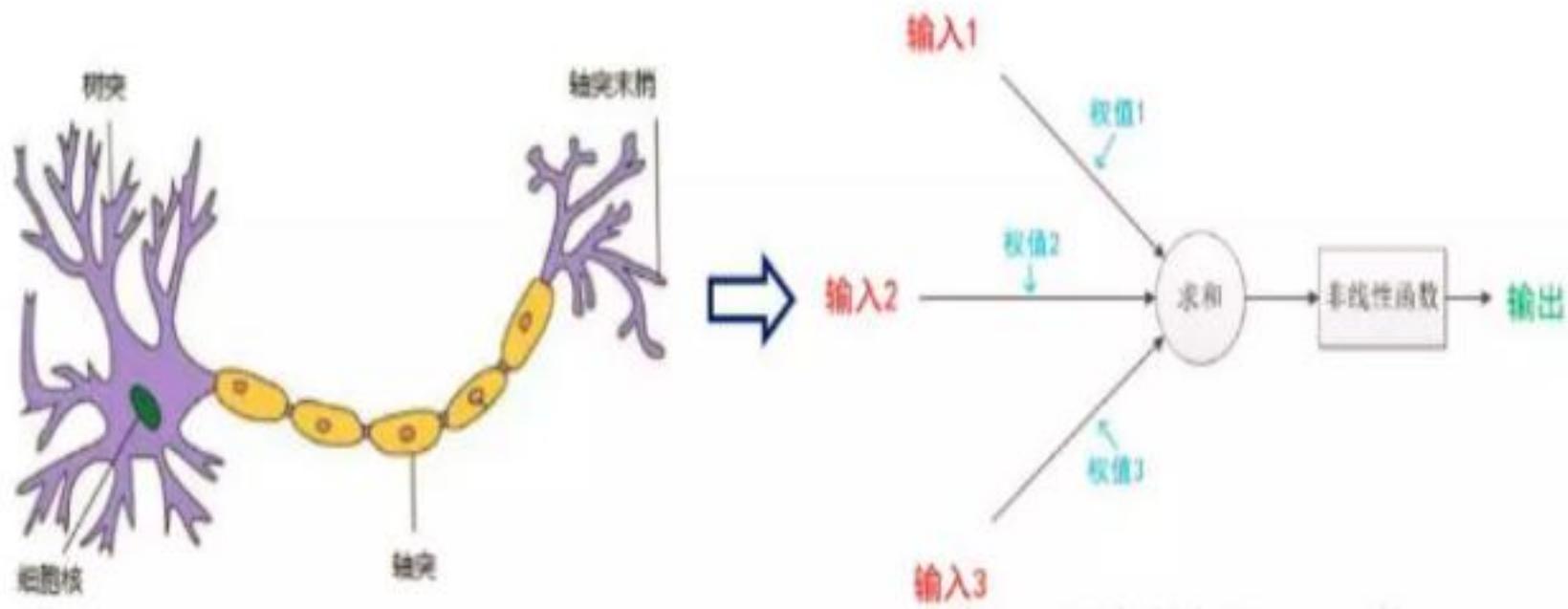
云栖社区 yq.aliyun.com



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10. 人工神经网络：逐层抽象，逼近任意函数

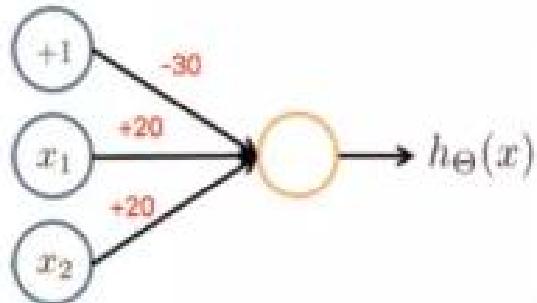
- 前面介绍了九种传统的机器学习算法，现在介绍一下深度学习的基础：人工神经网络。它是模拟人脑神经网络而设计的模型，由多个节点（人工神经元）相互联结而成，可以用来对数据之间的复杂关系进行建模。



- 例如利用单层神经网络实现逻辑与门和同或门

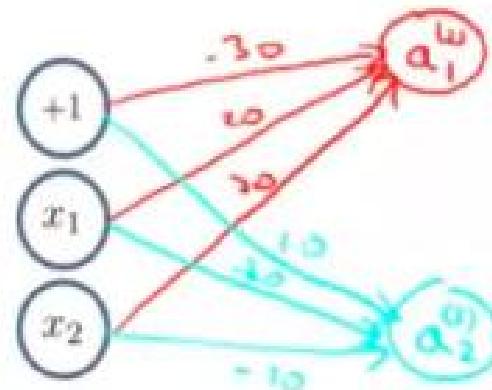
与门AND

$$h_{\Theta}(x) = g(-30 + 20x_1 + 20x_2)$$



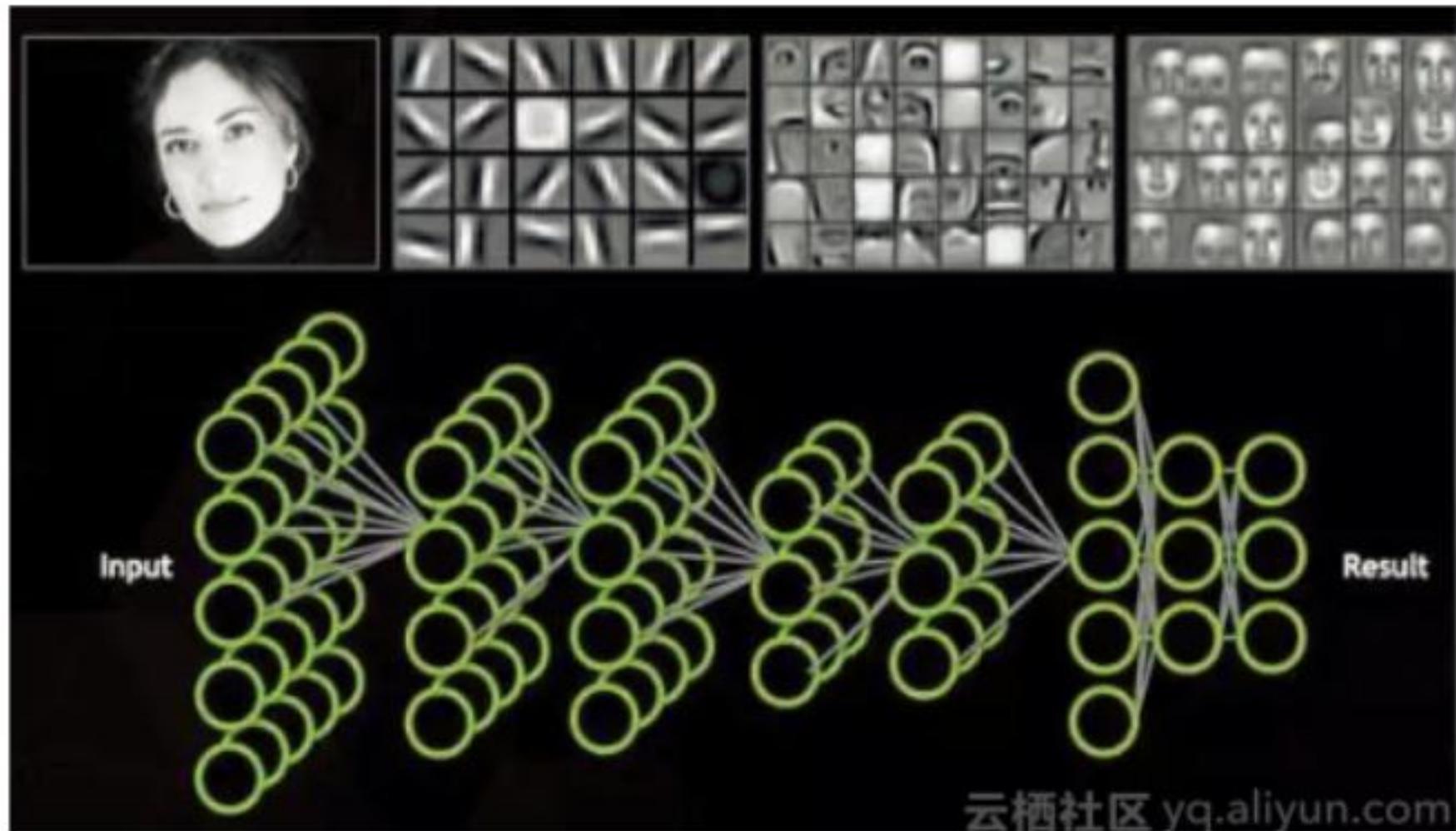
x1	x2	$h_{\Theta}(x)$
0	0	$g(-30) \approx 0$
0	1	$g(-10) \approx 0$
1	0	$g(-10) \approx 0$
1	1	$g(10) \approx 1$

同或门XNOR



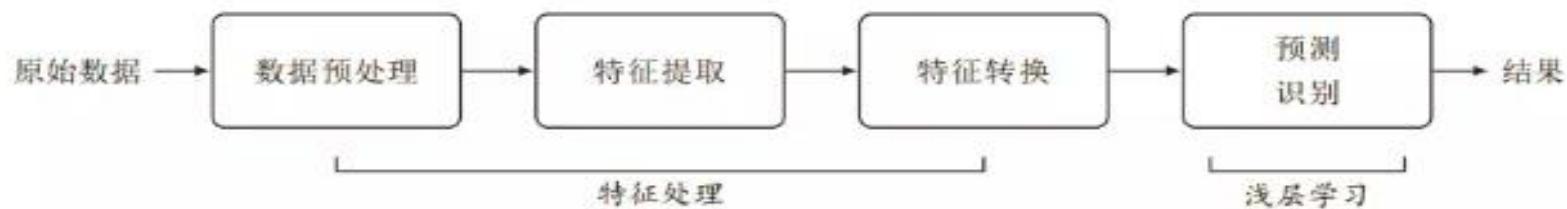
x1	x2	a1(2)	a2(2)	$h_{\Theta}(x)$
0	0	0	1	1
0	1	0	0	0
1	0	0	0	0
1	1	1	0	1

- 多层神经网络的每一层神经元学习到的是前一层神经元值的更抽象的表示，通过抽取更抽象的特征来对事物进行区分，从而获得更好的区分与分类能力。

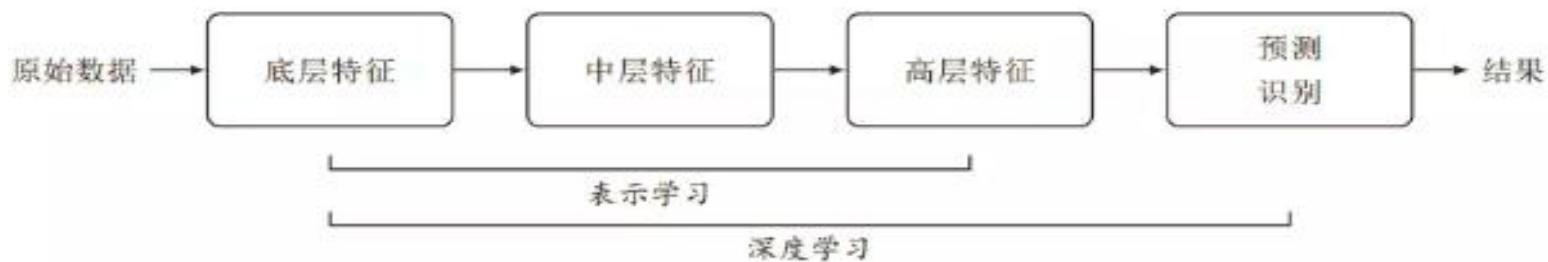


11. 深度学习：赋予人工智能以璀璨的未来

- 深度学习就是一种基于对数据进行表征学习的方法，使用多层网络，能够学习抽象概念，同时融入自我学习，逐步从大量的样本中逐层抽象出相关的概念，然后做出理解，最终做出判断和决策。通过构建具有一定“深度”的模型，可以让模型来自动学习好的特征表示（从底层特征，到中层特征，再到高层特征），从而最终提升预测或识别的准确性。



传统机器学习的数据处理流程。



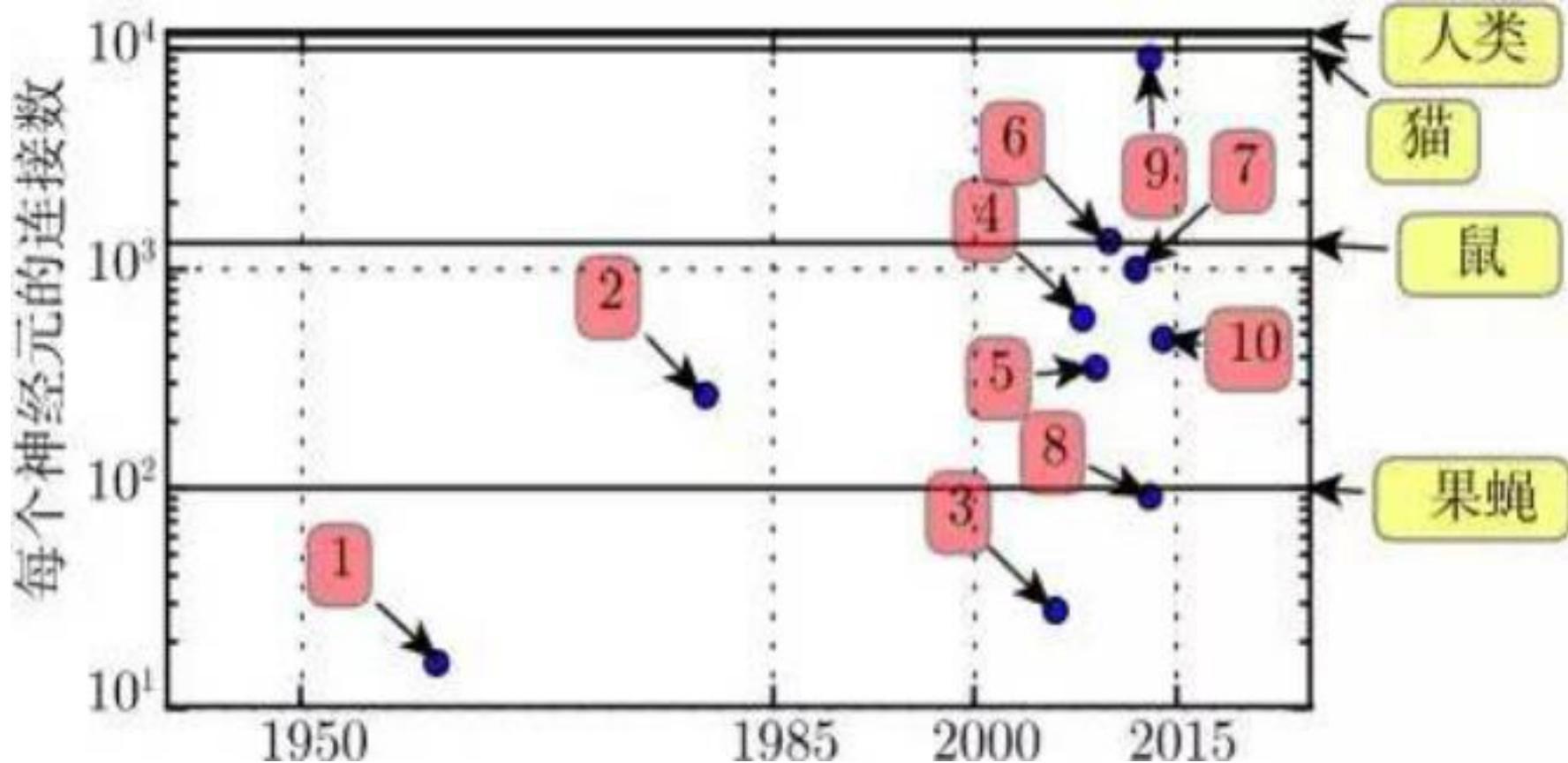
深度学习的数据处理流程。

深度学习的历史变迁：

深度学习经历了三次浪潮：

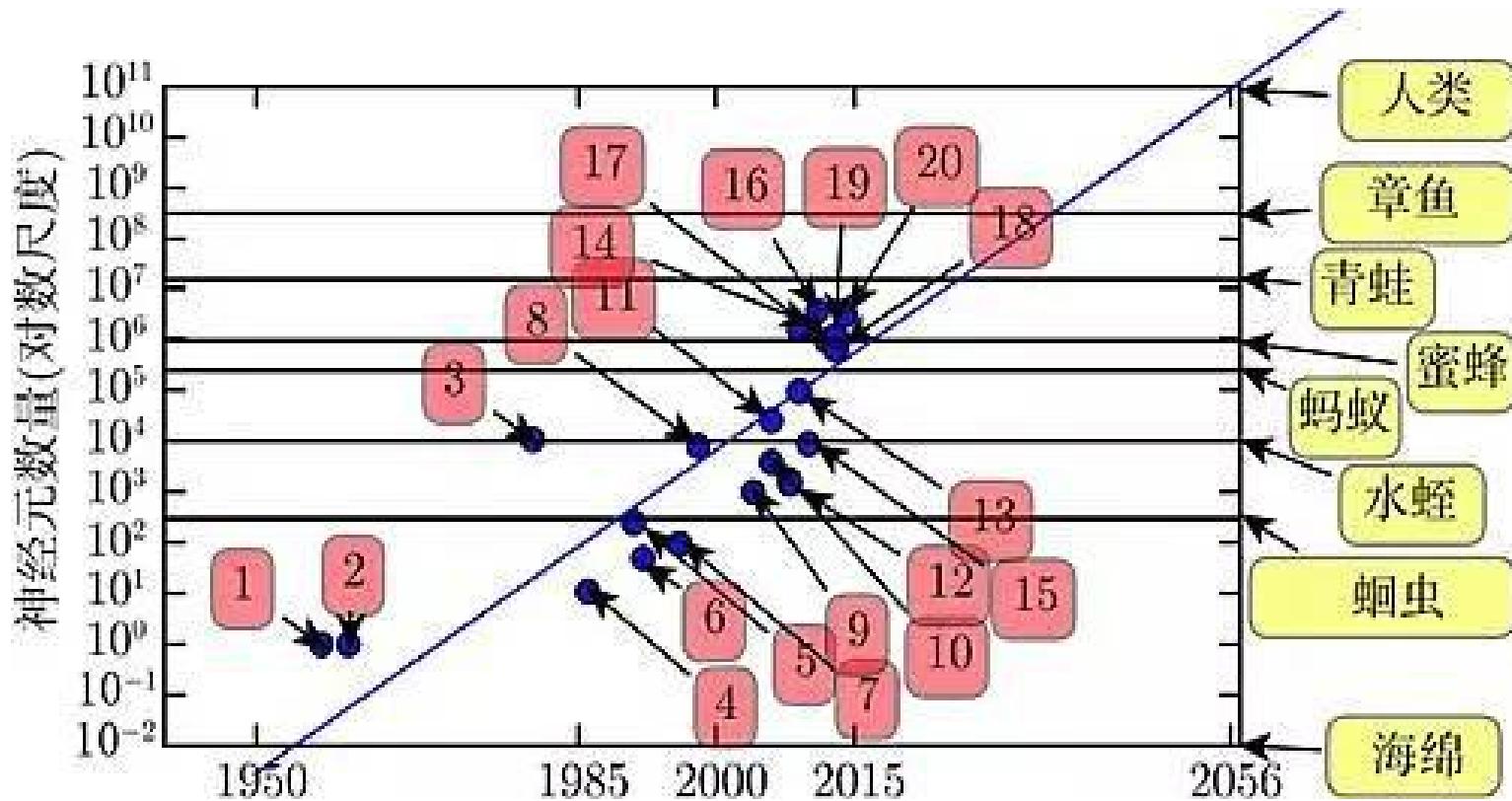
- 20世纪40年代～60年代，深度学习的雏形出现在控制论中；
 - 20世纪80年代～90年代，深度学习表现为联结主义；
 - 2006年以后，正式以深度学习之名复兴。
-
- 第一次浪潮：以感知机和线性模型为代表
不能解决与或问题
 - 第二次浪潮：以多层感知机和BP模型为代表
以统计学为基础，应用核函数和图模型的支持向量机算法（SVM算法）等各種浅层有监督的机器学习模型广泛应用，且深度神经网络不可训练
 - 第三次浪潮：以无监督学习为代表。
解决了深层神经网络的计算能力问题；解决了深度神经网络后向误差反馈梯度消失的问题。

与日俱增的每个神经元的连接数



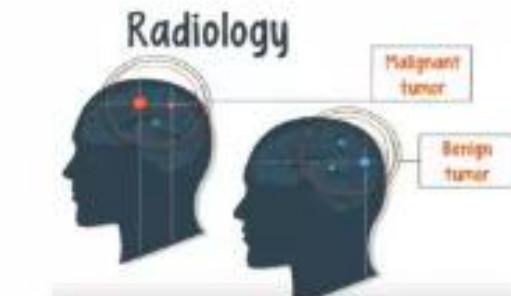
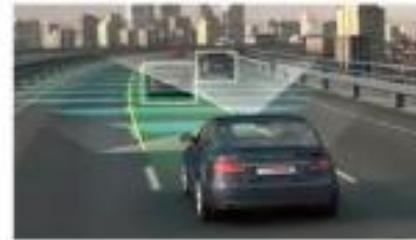
- 最初，人工神经网络中神经元之间的连接数受限于硬件能力。而现在，神经元之间的连接数大多是出于设计考虑。一些人工神经网络中每个神经元的连接数与猫一样多，并且对于其他神经网络来说，每个神经元的连接数与较小哺乳动物（如小鼠）一样多，这种情况是非常普遍的。甚至人类大脑每个神经元的连接数也没有过高的数量。
- 1. 自适应线性单元 (Widrow and Hoff, 1960)； 2. 神经认知机 (Fukushima, 1980)； 3. GPU 加速卷积网络 (Chellapilla et al., 2006)； 4. 深度玻尔兹曼机 (Salakhutdinov and Hinton, 2009a)； 5. 无监督卷积网络 (Jarrett et al., 2009b)； 6. GPU- 加速多层感知机 (Ciresan et al., 2010)； 7. 分布式自编码器 (Le et al., 2012)； 8. Multi-GPU 卷积网络 (Krizhevsky et al., 2012a)； 9. COTS HPC 无监督卷积网络 (Coates et al., 2013)； 10. GoogLeNet (Szegedy et al., 2014a)

与日俱增的神经网络规模



- 自从引入隐藏单元，人工神经网络的规模大约每 2.4 年翻一倍。
- 1. 感知机 (Rosenblatt, 1958, 1962)；2. 自适应线性单元 (Widrow and Hoff, 1960)；3. 神经认知机 (Fukushima, 1980)；4. 早期后向传播网络 (Rumelhart et al., 1986b)；5. 用于语音识别的循环神经网络 (Robinson and Fallside, 1991)；6. 用于语音识别的多层感知机 (Bengio et al., 1991)；7. 均匀场 sigmoid 信念网络 (Saul et al., 1996)；8. LeNet5 (LeCun et al., 1998c)；9. 回声状态网络 (Jaeger and Haas, 2004)；10. 深度信念网络 (Hinton et al., 2006a)；11. GPU- 加速卷积网络 (Chellapilla et al., 2006)；12. 深度玻尔兹曼机 (Salakhutdinov and Hinton, 2009a)；13. GPU 加速深度信念网络 (Raina et al., 2009a)；14. 无监督卷积网络 (Jarrett et al., 2009b)；15. GPU- 加速多层感知机 (Ciresan et al., 2010)；16. OMP-1 网络 (Coates and Ng, 2011)；17. 分布式自编码器 (Le et al., 2012)；18. MultiGPU 卷积网络 (Krizhevsky et al., 2012a)；19. COTS HPC 无监督卷积网络 (Coates et al., 2013)；20. GoogLeNet (Szegedy et al., 2014a)

- 目前深度学习的应用十分广泛，例如图像识别、语音识别、机器翻译、自动驾驶、金融风控、智能机器人等。



Machine Learning in biology

↓
Supervised Unsupervised

$x \rightarrow y$

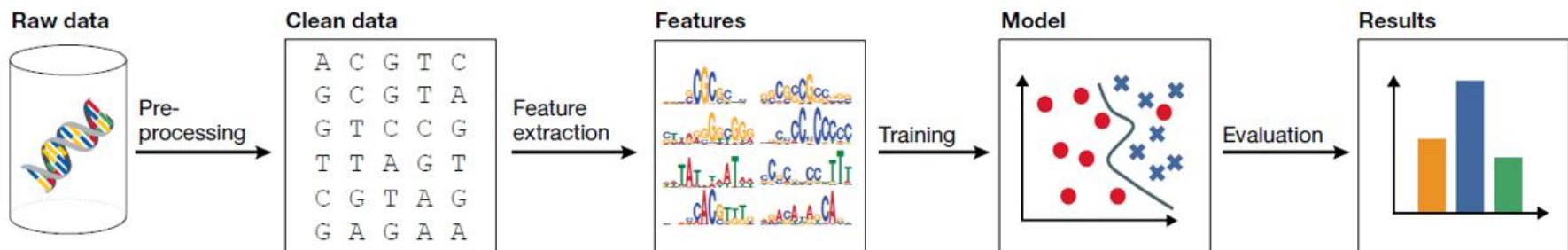


x



- Linear regression
 - Logistic regression
 - Random Forest
 - SVM
 - ...
- PCA
 - Factor analysis
 - Clustering
 - Outlier detection
 - ...

Machine learning algorithm: supervised and unsupervised



An exemplification of Machine learning in biology : classification model

课程安排

- 生物背景和课程简介
- 传统生物统计学及其应用
- 生物统计学和生物大数据挖掘
 - Hidden Markov Model (HMM)及其应用
 - Markov Chain
 - HMM理论
 - HMM和基因识别 (Topic I)
 - HMM和序列比对 (Topic II)
 - 进化树的概率模型 (Topic III)
 - Motif finding中的概率模型 (Topic IV)
 - EM algorithm
 - Markov Chain Monte Carlo (MCMC)
 - 基因表达数据分析 (Topic V)
 - 聚类分析-Mixture model
 - Classification-Lasso Based variable selection
 - 基因网络推断 (Topic VI)
 - Bayesian网络
 - Gaussian Graphical Model
 - 基因网络分析 (Topic VII)
 - Network clustering
 - Network Motif
 - Markov random field (MRF)
 - Dimension reduction及其应用 (Topic VIII)
- 面向生物大数据挖掘的深度学习

研究对象：
生物序列，
进化树，
生物网络，
基因表达
...

方法：
生物计算与生物统计

Topic I: Sequence's Feature Detection

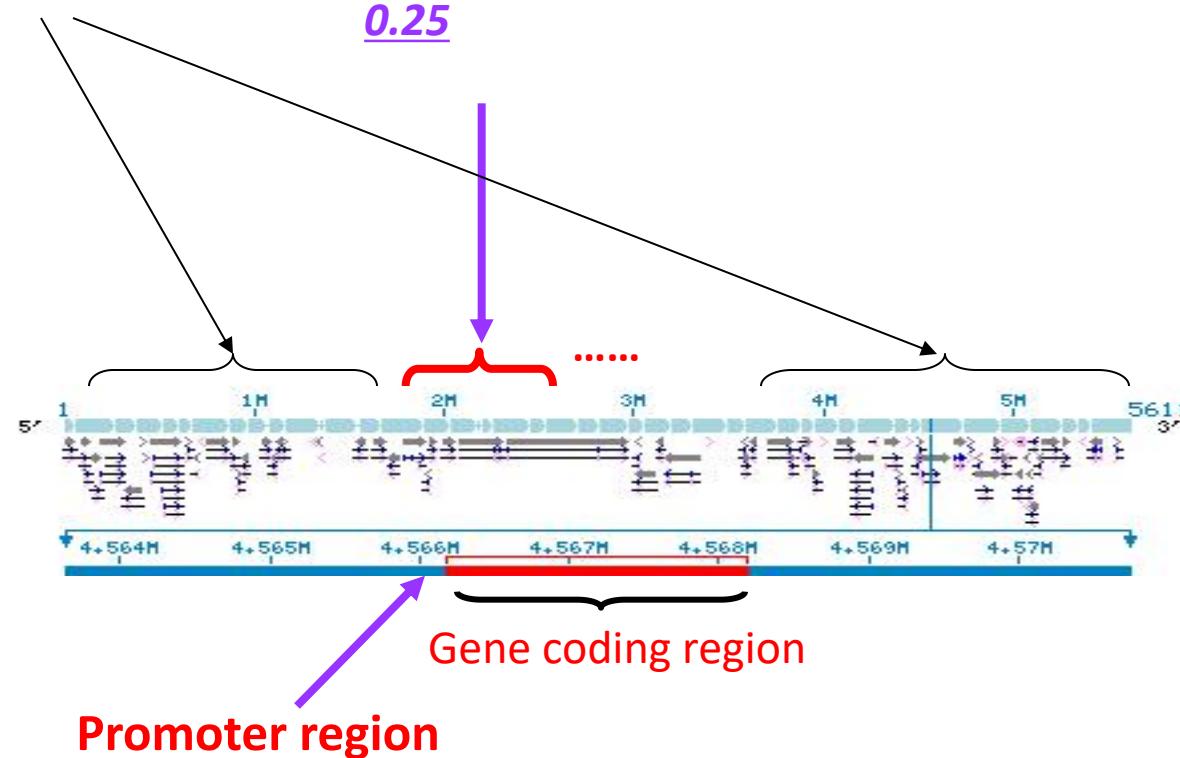
- Problem I: CpG island finding
- Problem II: Gene finding (promoter prediction, Splicing site prediction, Translation Initial Site Prediction etc.)
- Hidden Markov Model is a powerful method for these problem

什么是CpG岛？

CG-poor regions: $P(CG)$

~ 0.07!

CG-rich region: $P(CG) \sim$
0.25



CpG岛的生物学意义

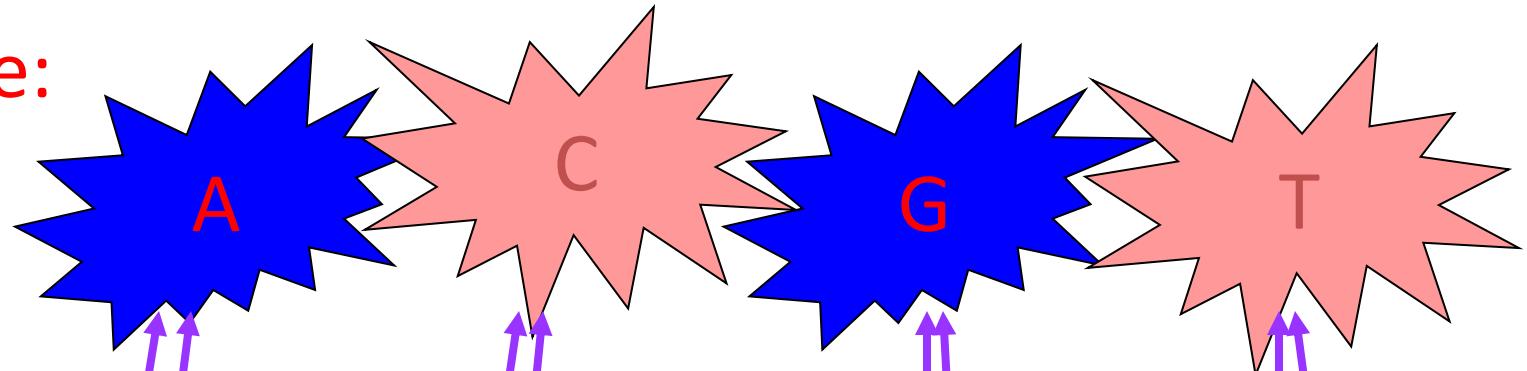
- CpG-rich regions are associated with genes which are *frequently transcribed*.
- Helps to understand gene expression related to *location* in genome.

HMM对于CpG岛识别的意义

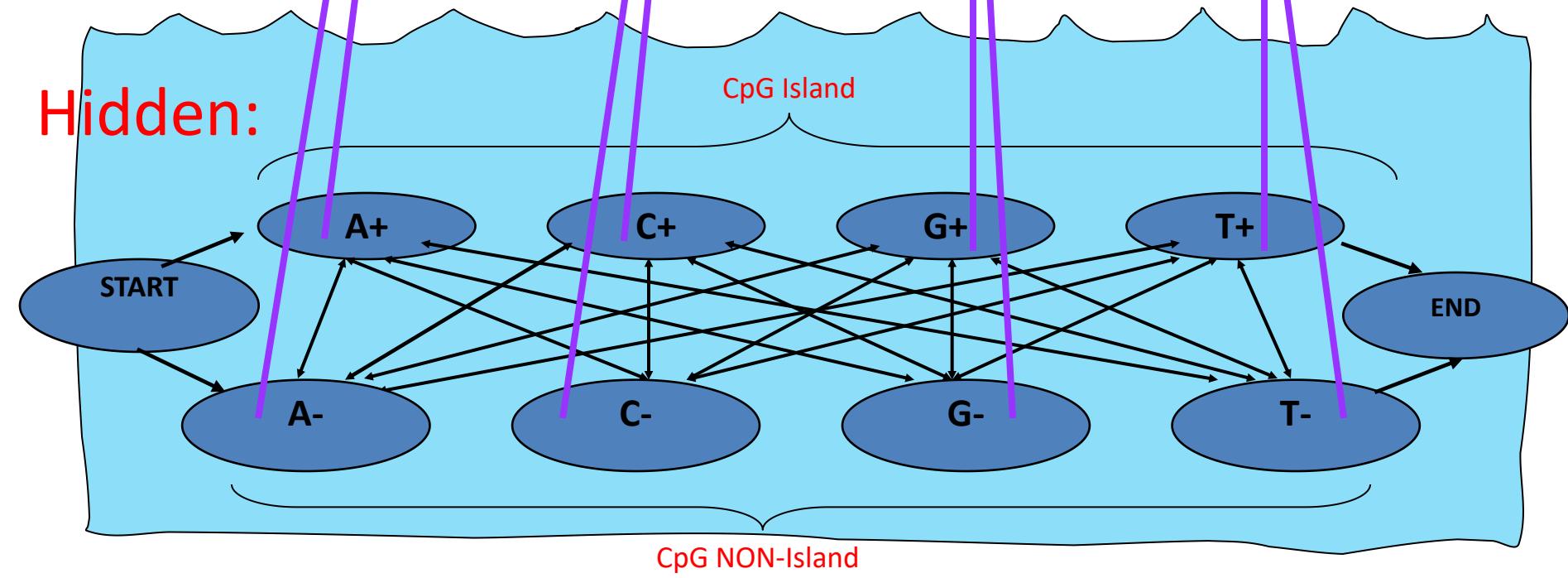
- Q: Why an HMM?
- It can answer the questions:
 - Short sequence: *does it come from a CpG island or not?*
 - Long sequence: *where are the CpG islands?*
- So, what's a good model?
 - Well, we need states for **ISLAND bases** and **NON-ISLAND bases ...**

HMM示意

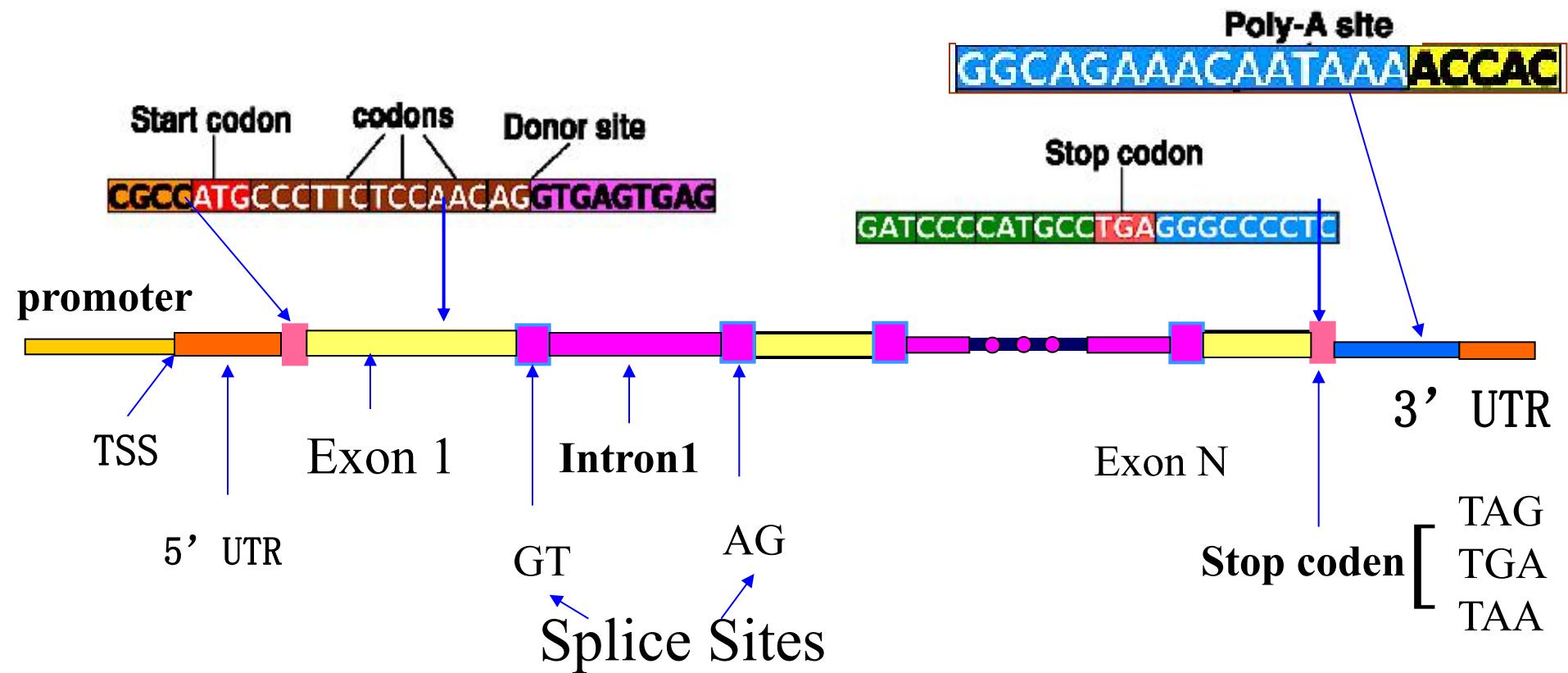
Visible:



Hidden:



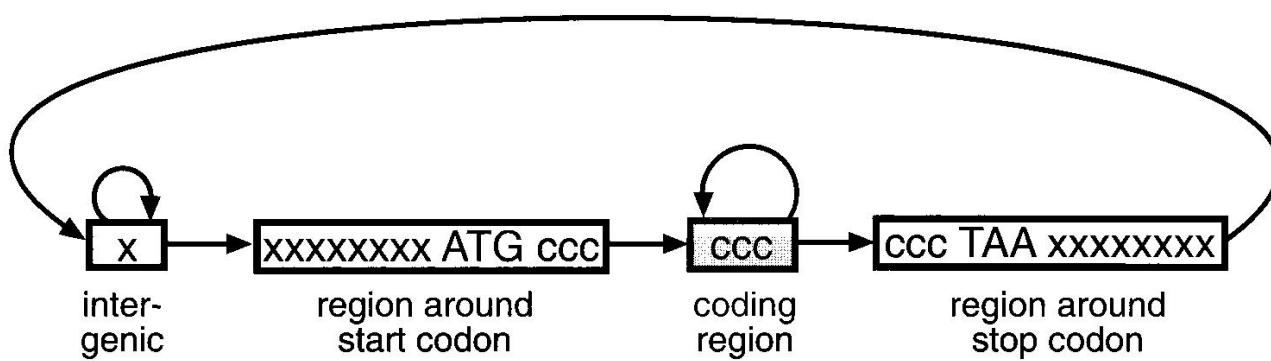
基因的结构



HMMs and Gene Structure

- Nucleotides $\{A, C, G, T\}$ are the observables
- Different states generates generate nucleotides at different frequencies

A simple HMM for unspliced genes:

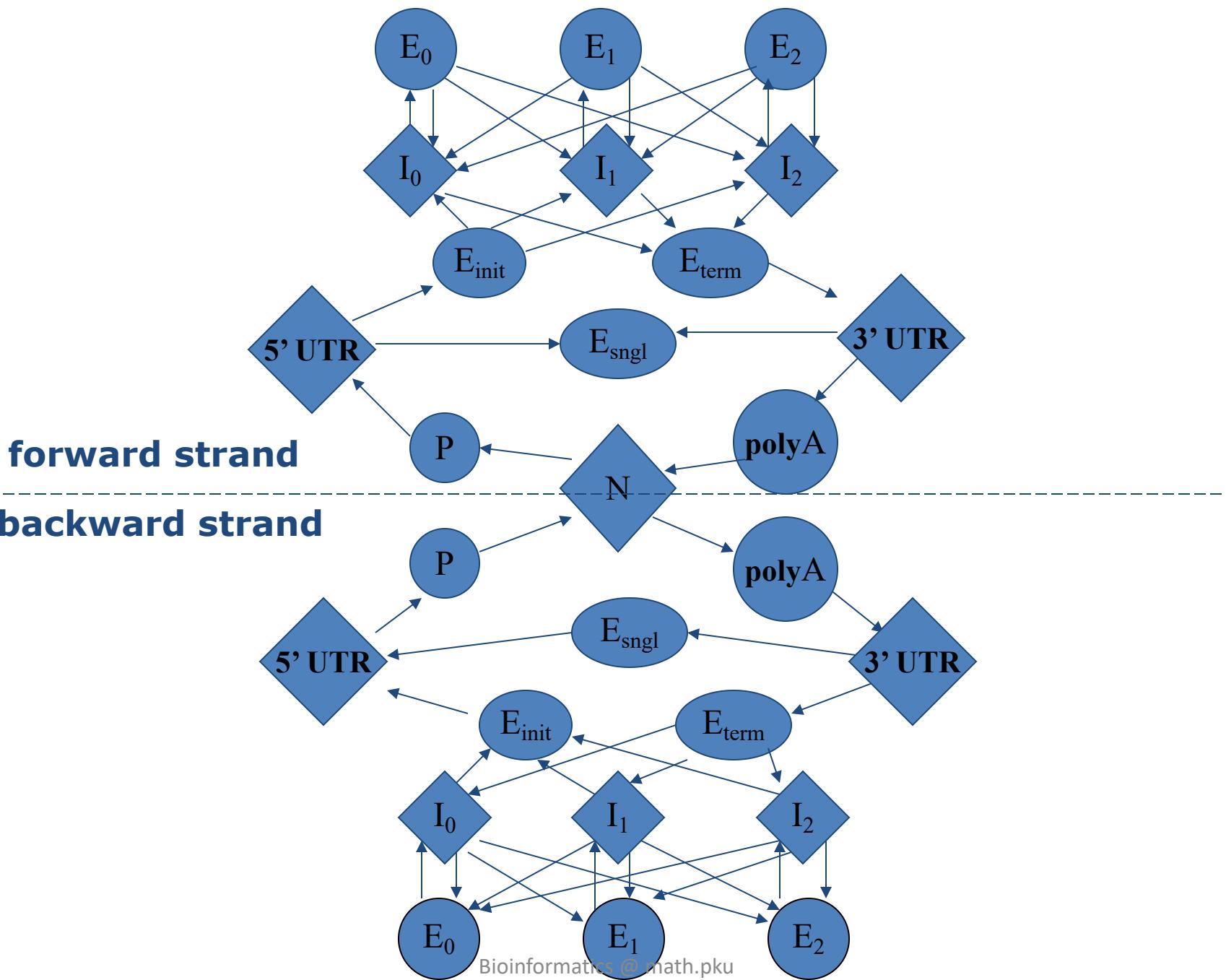


AAAGC **ATG** CAT TTA ACG AGA GCA CAA GGG CTC **TAA** TGCCG

- The sequence of states is an annotation of the generated string – each nucleotide is generated in **intergenic**, **start/stop**, **coding** state

Genscan

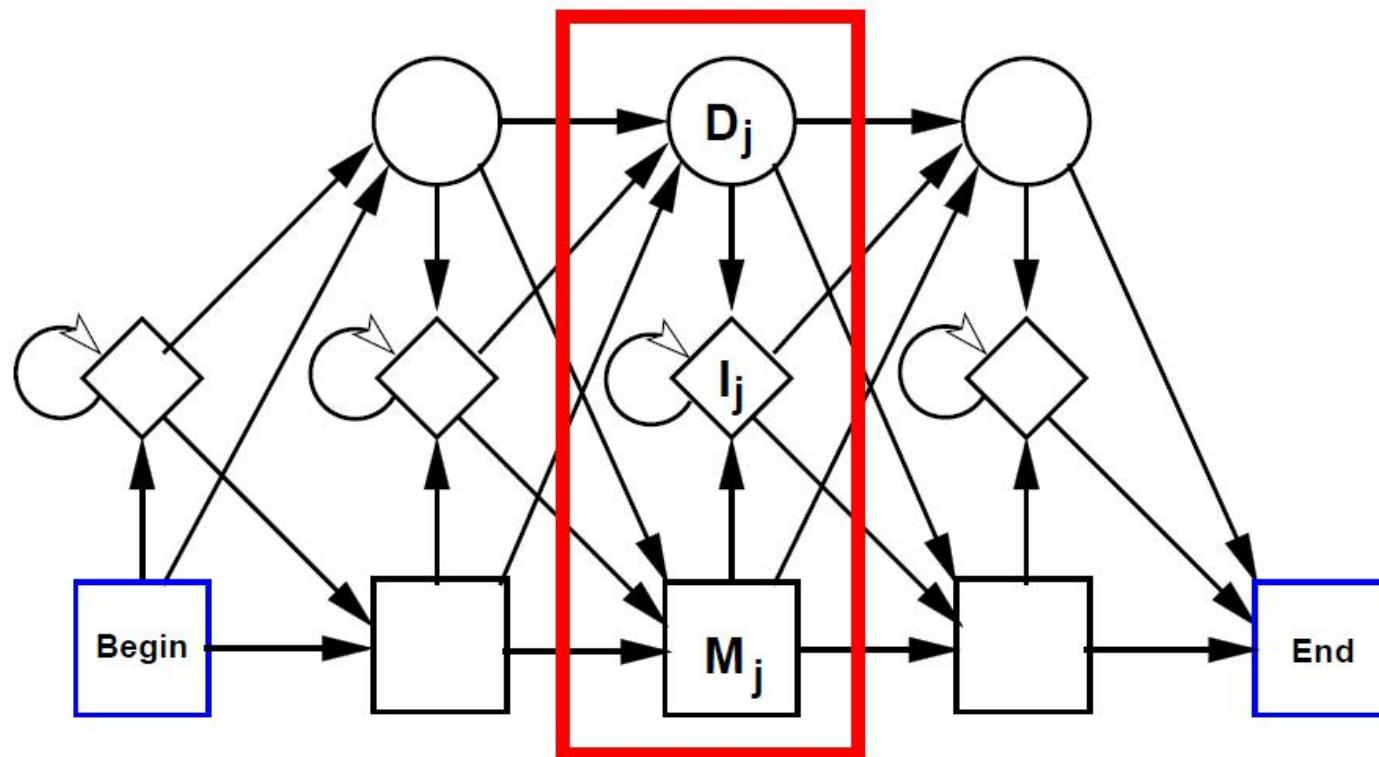
- Developed by Chris Burge 1997
- One of the most accurate *ab initio* programs
- Uses explicit state duration HMM to model gene structure (different length distributions for exons)
- Different model parameters for regions with different GC content



Topic II: Multiple Alignment

	X	X	.	.	.	X
bat	A	G	-	-	-	C
rat	A	-	A	G	-	C
cat	A	G	-	A	A	-
gnat	-	-	A	A	A	C
goat	A	G	-	-	-	C
	1	2	.	.	.	3

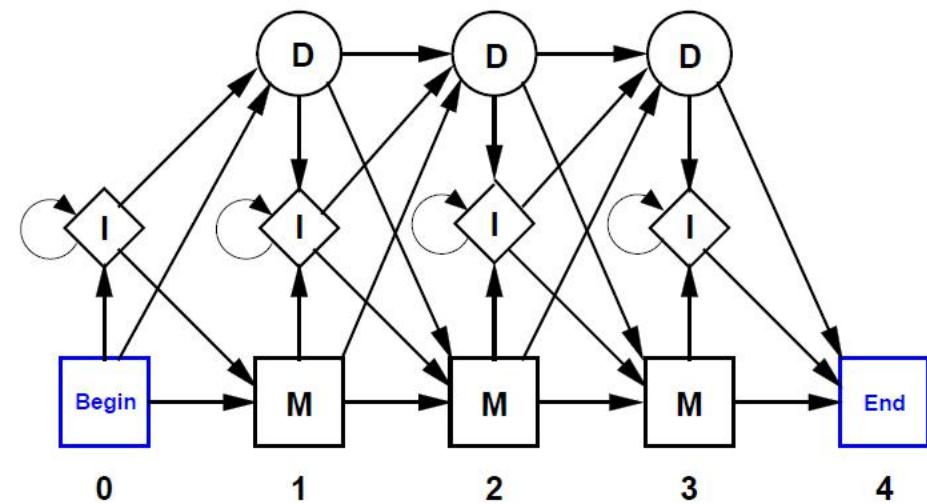
Profiled HMM



Transition structure of a profile HMM

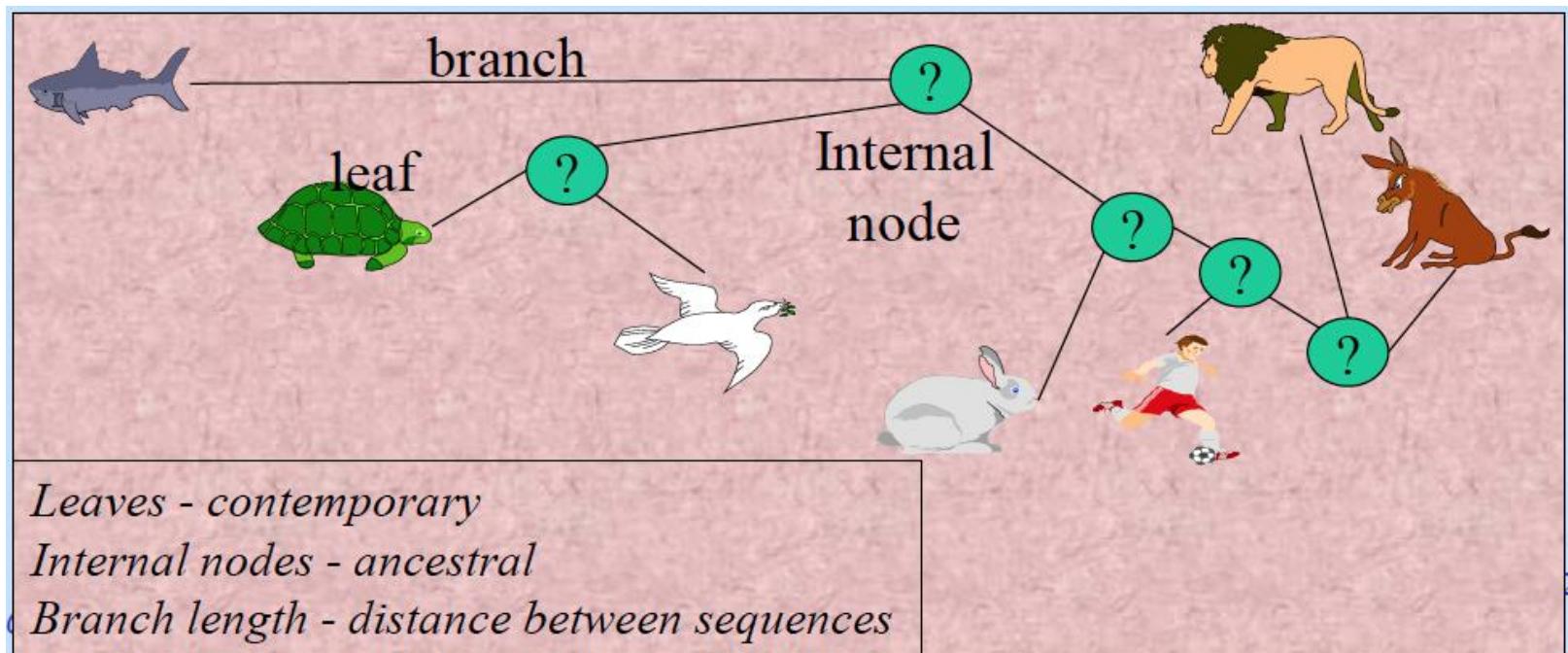
Example of Profile HMM

	X	X	.	.	.	X
bat	A	G	-	-	-	C
rat	A	-	A	G	-	C
cat	A	G	-	A	A	-
gnat	-	-	A	A	A	C
goat	A	G	-	-	-	C
	1	2	.	.	.	3



Topic III: Tree of life

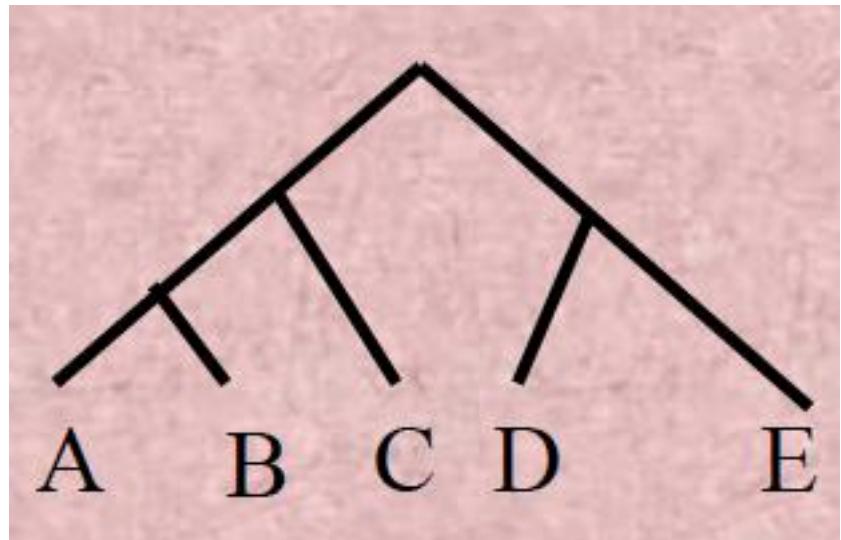
- Phylogeny: the ancestral relationship of a set of species
- Represented by a phylogenetic tree



Inferring a phylogenetic tree

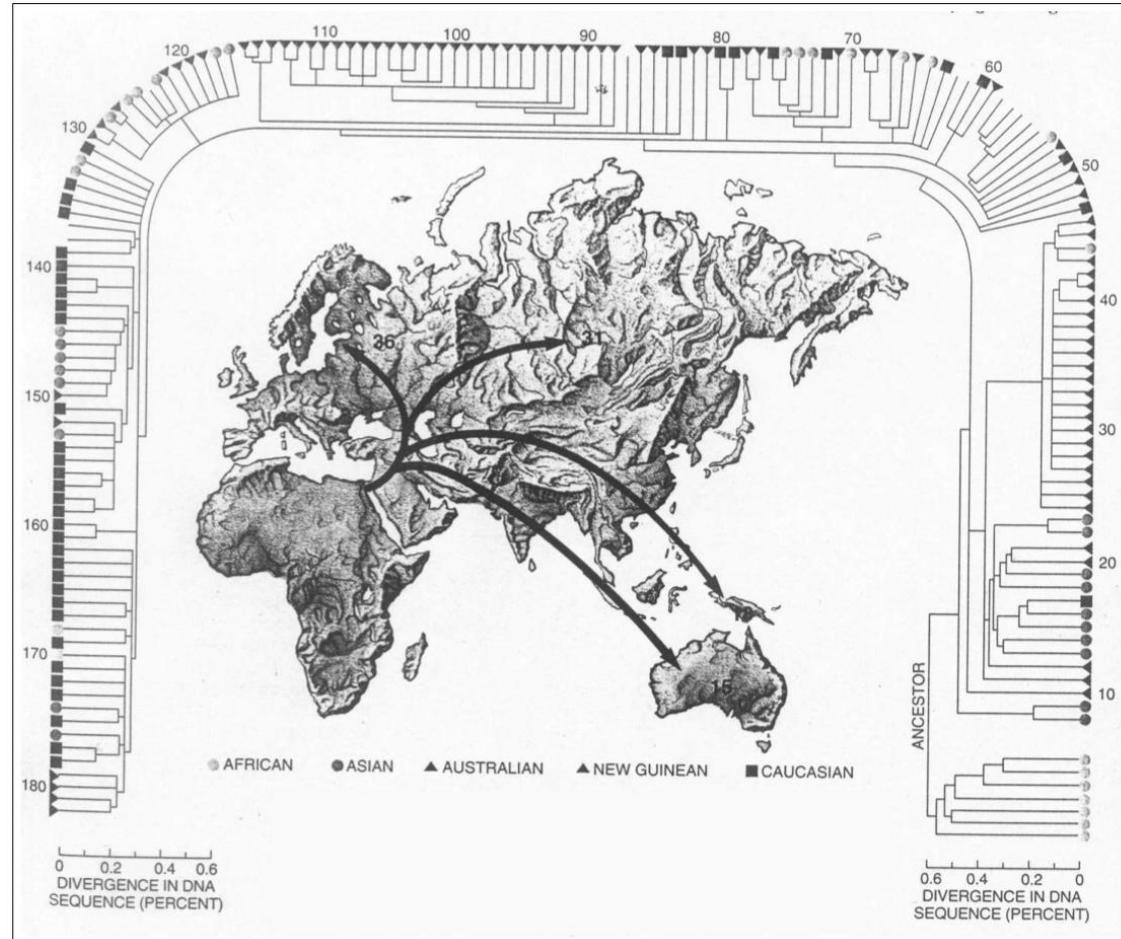
- Classical: morphological characters
- Modern: molecular sequences

A:	CAGGTA
B:	CAGACA
C:	CGGGTA
D:	TGCACT
E:	TGCGTA



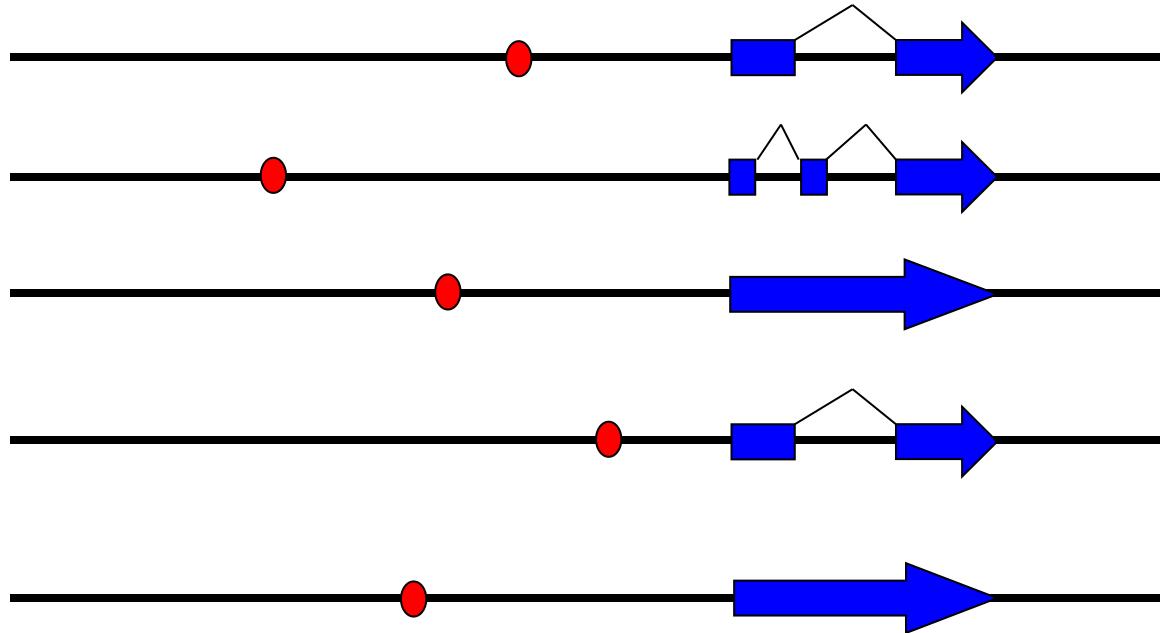
- Approaches: probabilistic model, bootstrap

An example: Out of Africa



Topic IV: Motif Finding

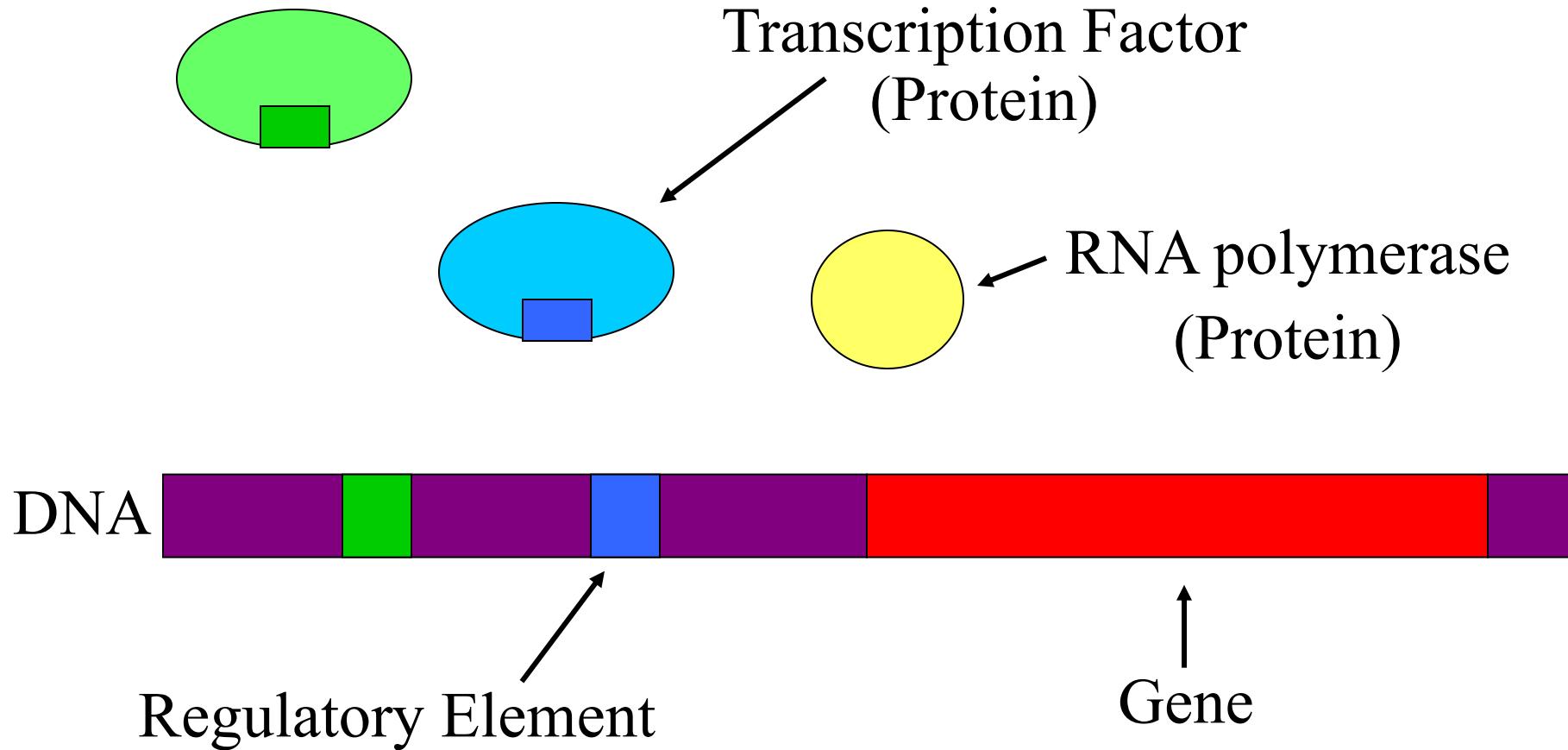
- Find promoter motifs associated with **co-regulated or functionally related genes**



Transcriptional Regulation

- The transcription of each gene is controlled by a regulatory region of DNA relatively near the transcription start site (TSS).
- two types of fundamental components
 - short DNA regulatory elements
 - *gene regulatory proteins* that recognize and bind to them.

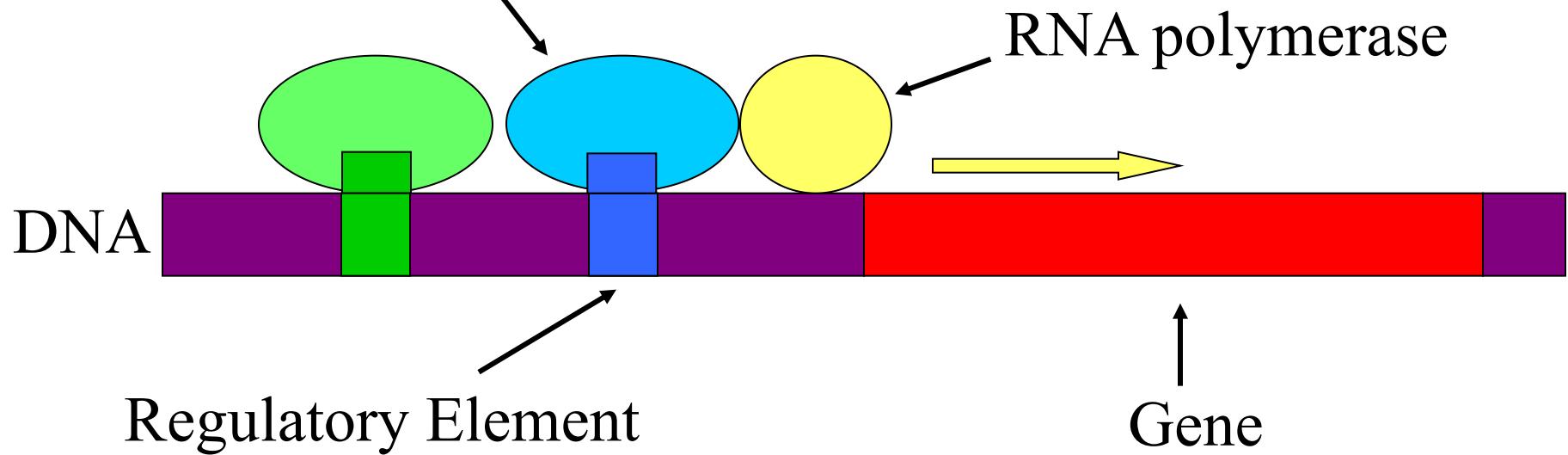
Regulation of Genes



source: M. Tompa, U. of Washington

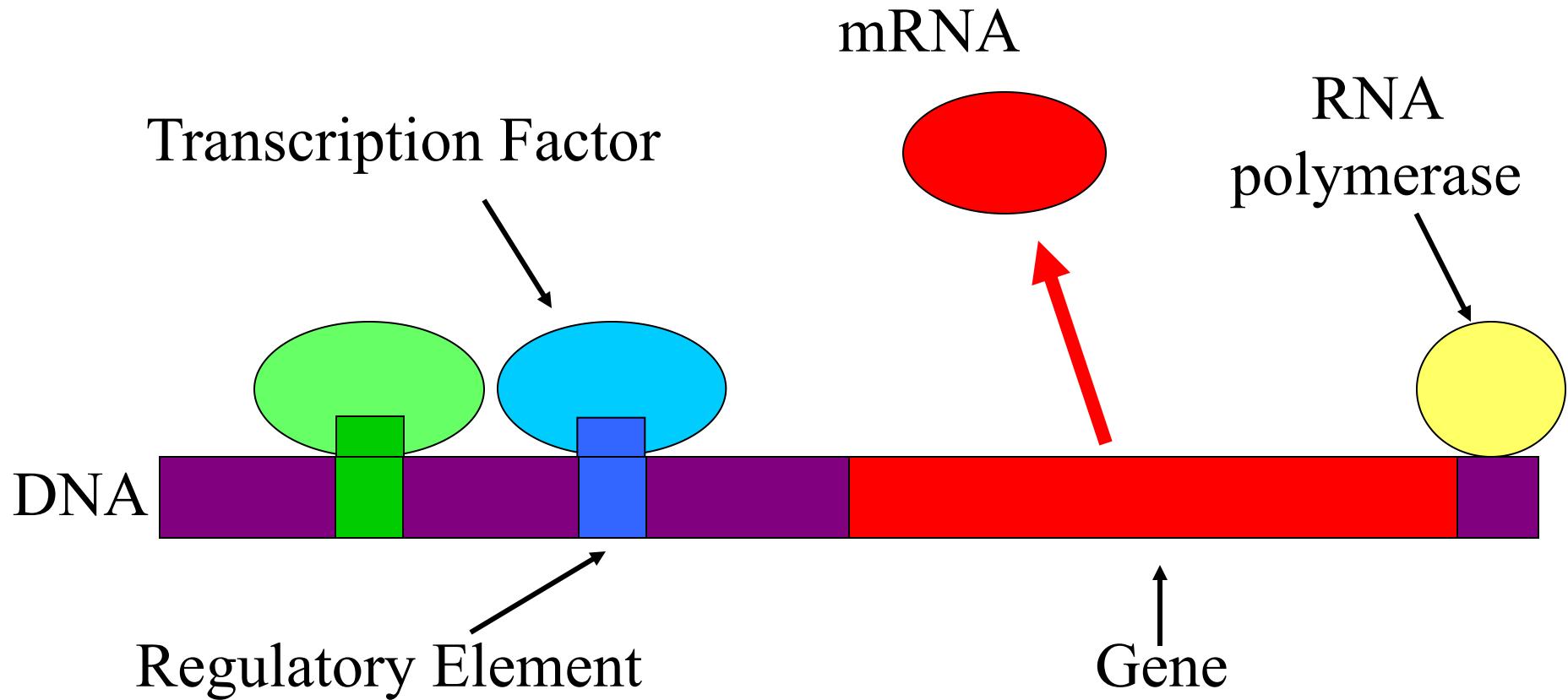
Regulation of Genes

Transcription Factor
(Protein)



source: M. Tompa, U. of Washington

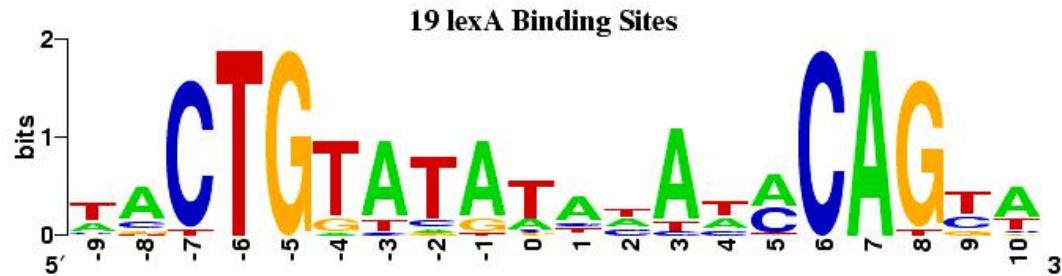
Regulation of Genes



source: M. Tompa, U. of Washington

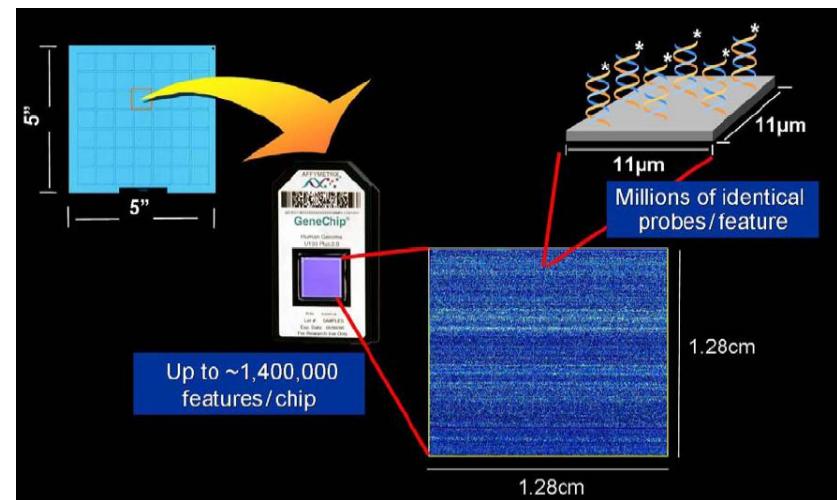
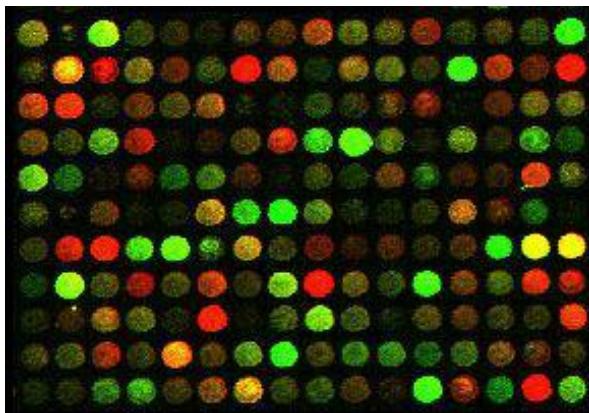
Motif Finding Problem

- Characterizing the motif: Positional weight matrix



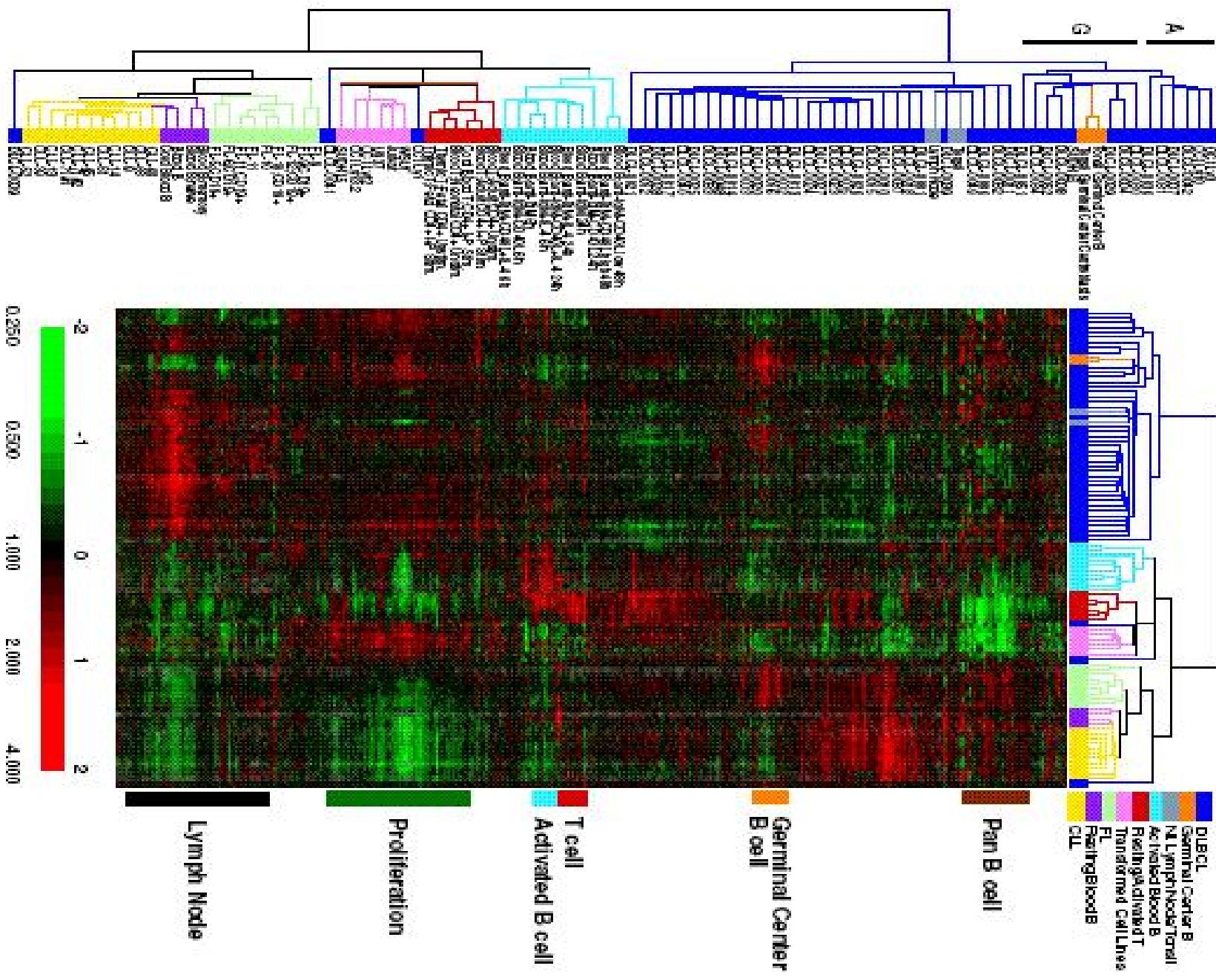
- Finding the motif
 - Gibbs Sampler (AlignACE)
 - EM algorithm (MEME)

Topic V: Gene Expression Data Clustering and Biomarker Discovery



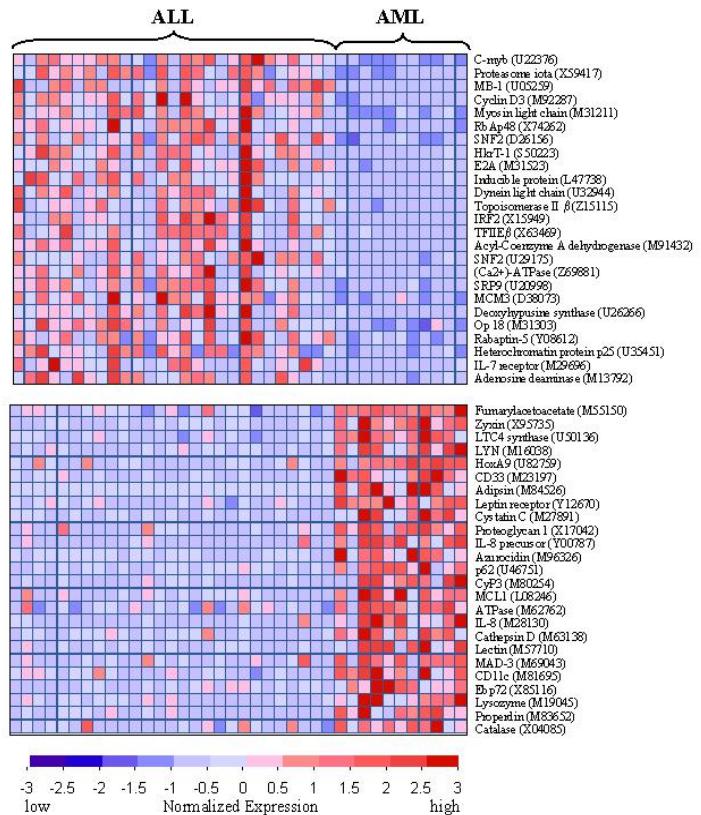
Microarrays

- *DNA microarray* technology rely on the hybridization properties of nucleic acids to monitor DNA or RNA abundance on a genomic scale in different types of cells.

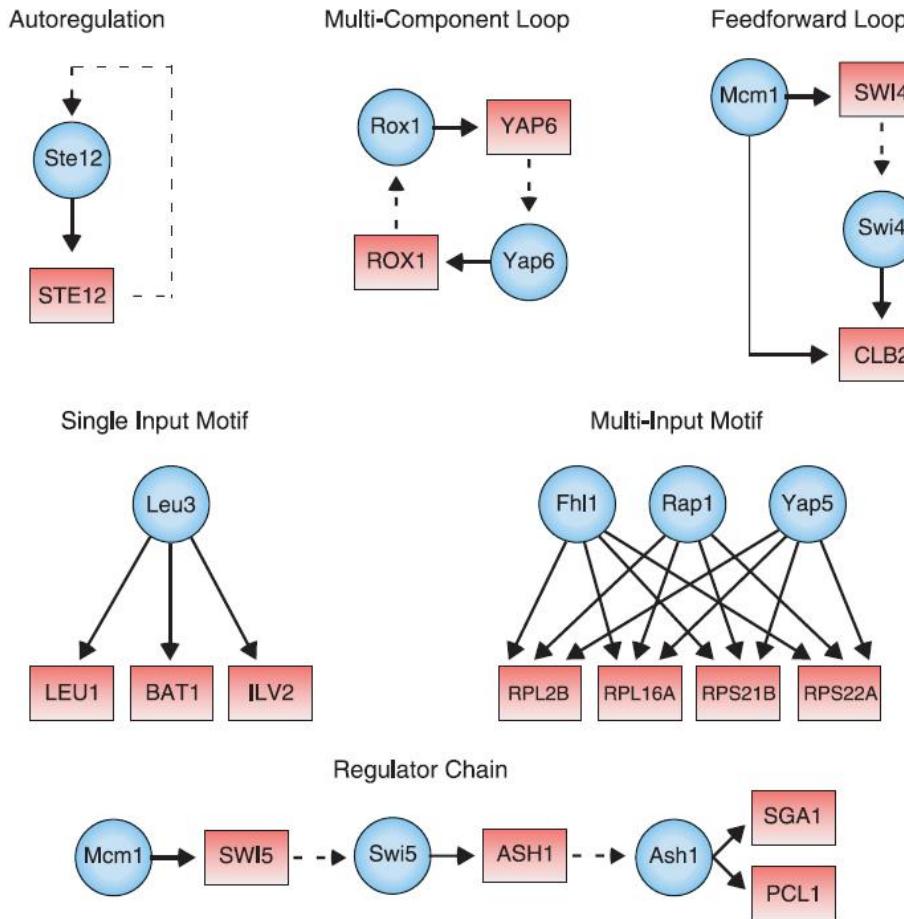


Classification

- Given: the case, control gene expression data
- Find: a set of genes (biomarker) can discriminate two classes.
- Method: variable selection



Topic VI: Regulatory Network Inference from Gene Expression Data



Network Inference: Reverse Engineering

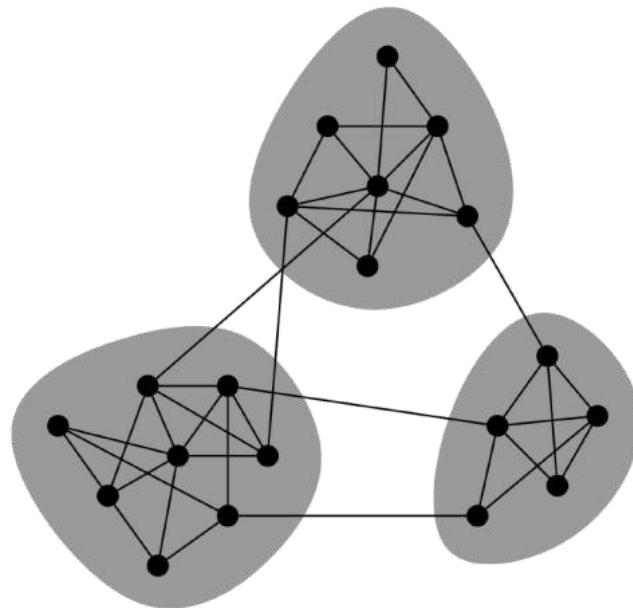
- Given: a large set of gene expression observations
- Find:
 - Wiring diagram
 - Transition rulesTo fit the observation data
- Methods
 - Bayesian Network
 - Gaussian graphical model

Dream Project

- DREAM: Dialogue for Reverse Engineering Assessments and Methods
- <http://dreamchallenges.org/>

Topic VII: Network Analysis

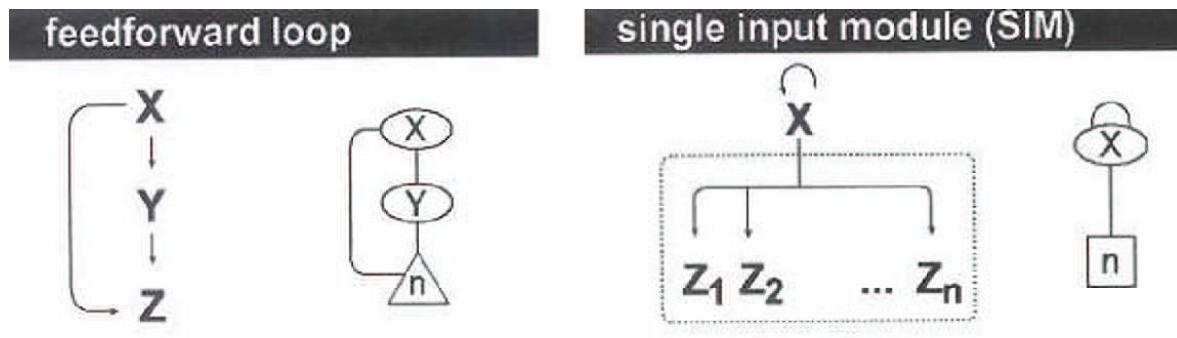
- Network modular (network clustering)



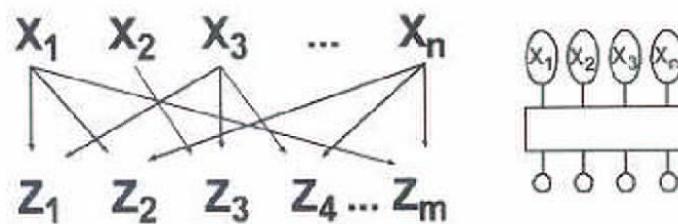
Network Motif

- Definition: Patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks (Milo, R., et. al. *Science* **298**, 824–827)

Network Motifs



dense overlapping regulons (DOR)



Topic VIII: Dimension Reduction

- Curse of dimensionality
- Visualization in low dimension

Curse of Dimensionality

- A major problem is *the curse of dimensionality*.
- If the data x lies in high dimensional space, then an enormous amount of data is required to learn distributions or decision rules.
- Example: 50 dimensions. Each dimension has 20 levels. This gives a total of 20^{50} cells. But the no. of data samples will be far less. There will not be enough data samples to learn.

Curse of Dimensionality

- One way to deal with dimensionality is to assume that we know the form of the probability distribution.
- For example, a Gaussian model in N dimensions has $N + N(N-1)/2$ parameters to estimate.
- Requires $O(N^2)$ data to learn reliably. This may be practical.

Dimension Reduction

- One way to avoid the curse of dimensionality is by projecting the data onto a lower-dimensional space.
- Techniques for dimension reduction:
 - Principal Component Analysis (PCA)
 - Singular value decomposition (SVD)
 - Multi-dimensional Scaling (MDS).

Recap

- a breif summary...
- Think again:
 - Why biostatistics
 - What is biostatistical modeling
 - Where is the applications

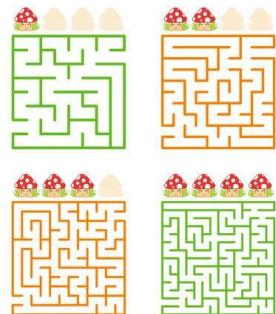
Statistical modeling

数据无处不在，复杂性无处不在。。。。

一天早上我在我的睡衣里打死一只大象，他怎么跑到我睡衣里来的，
我就不知道了。

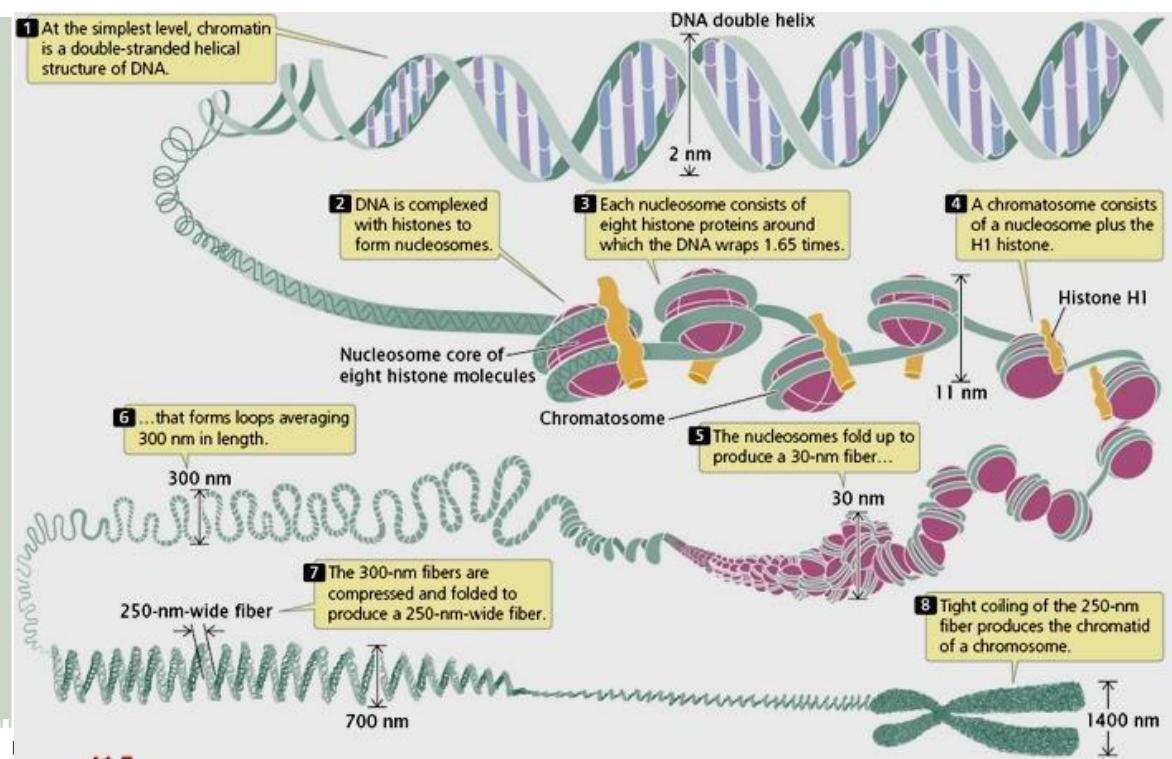
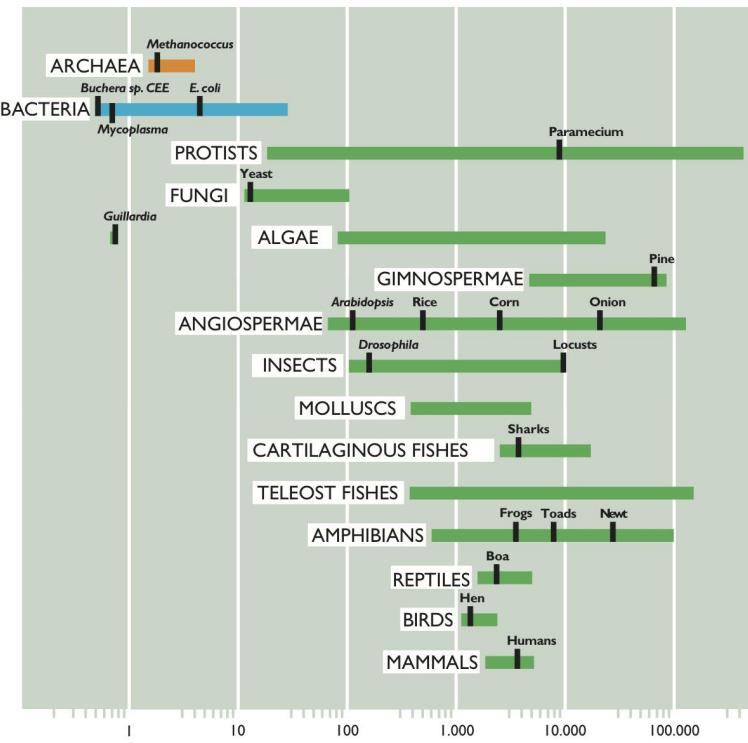
**One morning I shot an elephant in
my pajamas. How he got into my
pajamas I'll never know.**

Groucho Marx



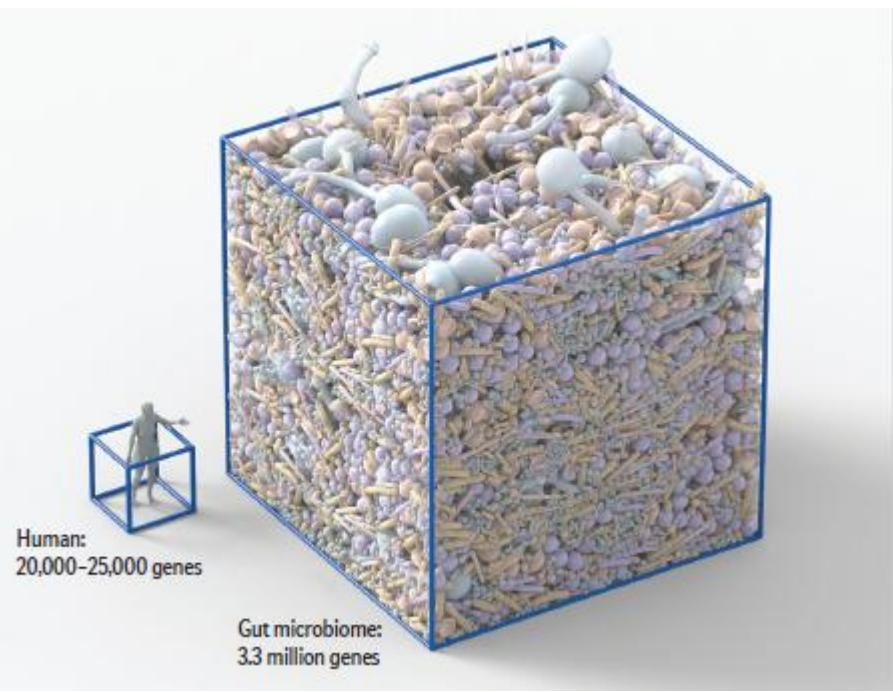
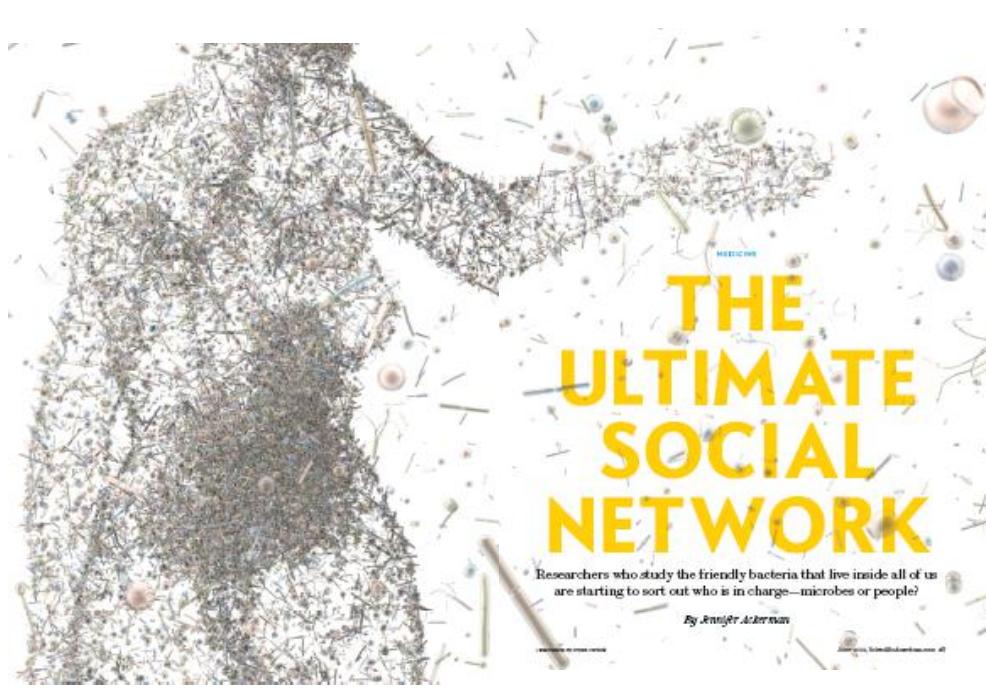
Statistical modeling

数据无处不在，复杂性无处不在。。。。

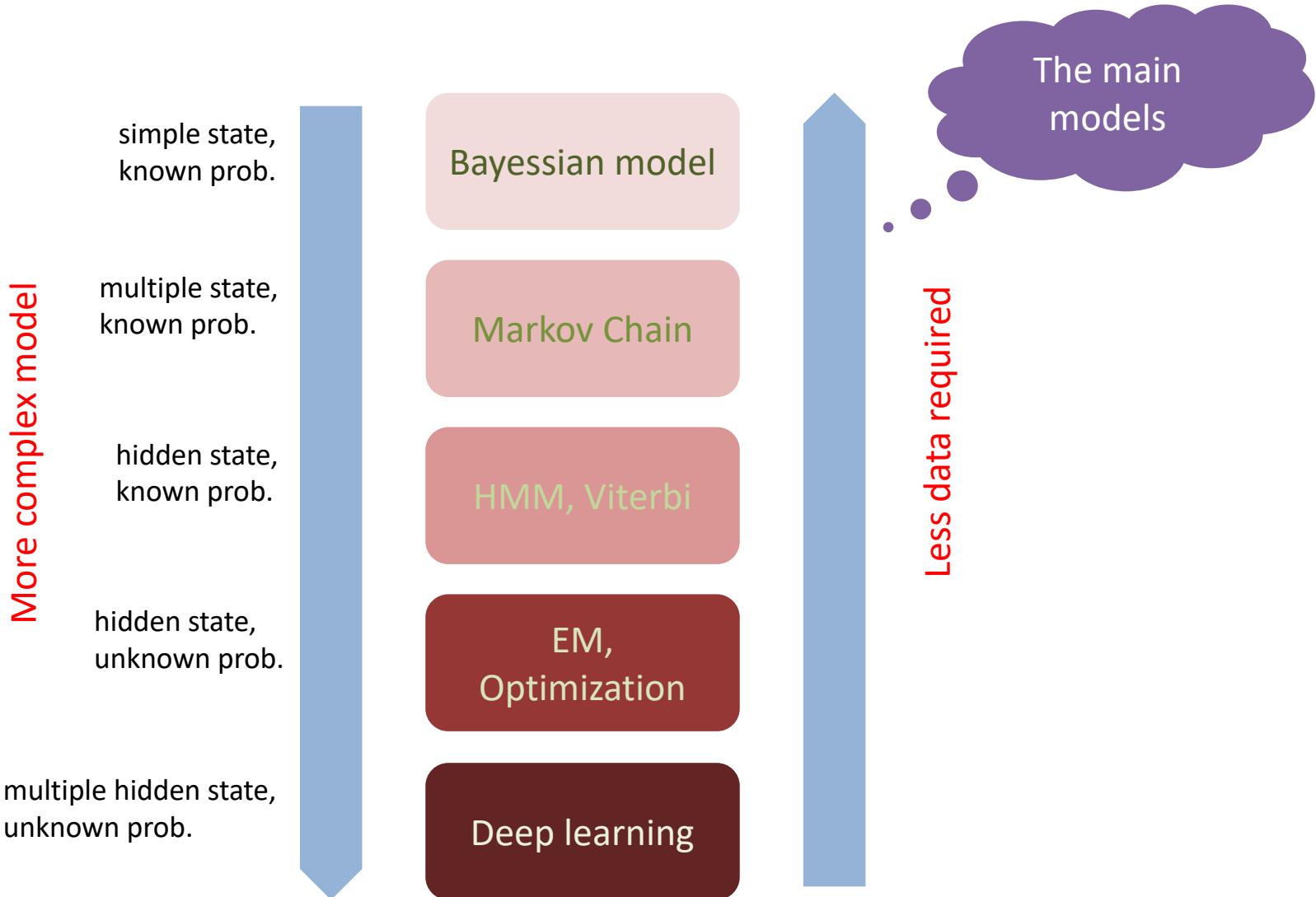


Statistical modeling

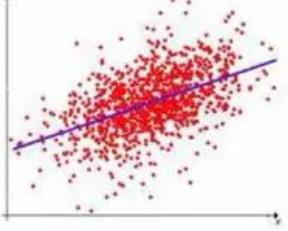
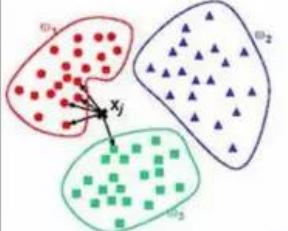
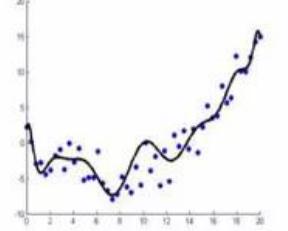
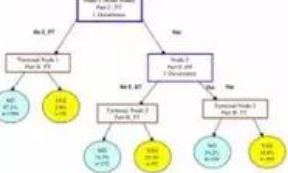
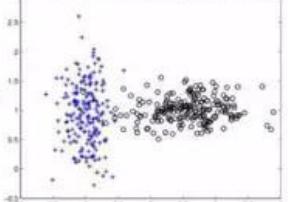
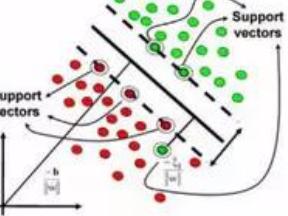
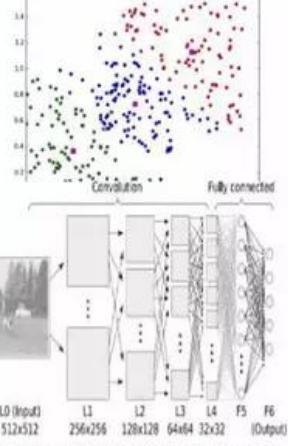
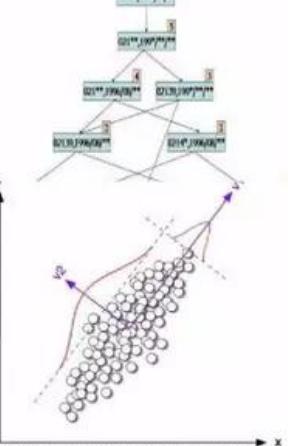
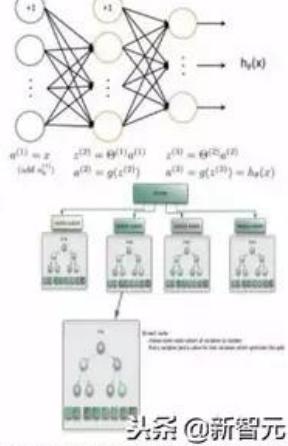
数据无处不在，复杂性无处不在。。。。



Statistical modeling



Statistical modeling

回归算法	基于实例的算法	正则化方法
		
决策树学习	贝叶斯方法	基于核的算法
		
聚类算法	关联规则学习	人工神经网络
		 <p>Diagram illustrating an Artificial Neural Network (ANN) architecture:</p> <ul style="list-style-type: none">Input layer: L_0 (Input) with size 512×512.Hidden layers: L_1 (256x256), L_2 (128x128), L_3 (64x64), L_4 (32x32).Output layer: F_6 (Output). <p>Annotations for the hidden layers show the flow of data through activation functions $g^{(1)}, g^{(2)}, \dots, g^{(4)}$ and weight matrices $\Theta^{(1)}, \Theta^{(2)}, \dots, \Theta^{(4)}$.</p> <p>Bottom right: 头条 @新智元</p>

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 - HMM和基因识别 (Topic I)
 - HMM和序列比对 (Topic II)
 - 进化树的概率模型 (Topic III)
 - Motif finding中的概率模型 (Topic IV)
 - EM algorithm
 - Markov Chain Monte Carlo (MCMC)
 - 基因表达数据分析 (Topic V)
 - 聚类分析-Mixture model
 - Classification-Lasso Based variable selection
 - 基因网络推断 (Topic VI)
 - Bayesian网络
 - Gaussian Graphical Model
 - 基因网络分析 (Topic VII)
 - Network clustering
 - Network Motif
 - Markov random field (MRF)
 - Dimension reduction及其应用 (Topic VIII)
- 面向生物大数据挖掘的深度学习

研究对象：
生物序列，
进化树，
生物网络，
基因表达
...

方法：
生物计算与生物统计

我们有讲义啦

- 《生物统计学：生物大数据的概率统计模型与机器学习方法》，宁康，2020。

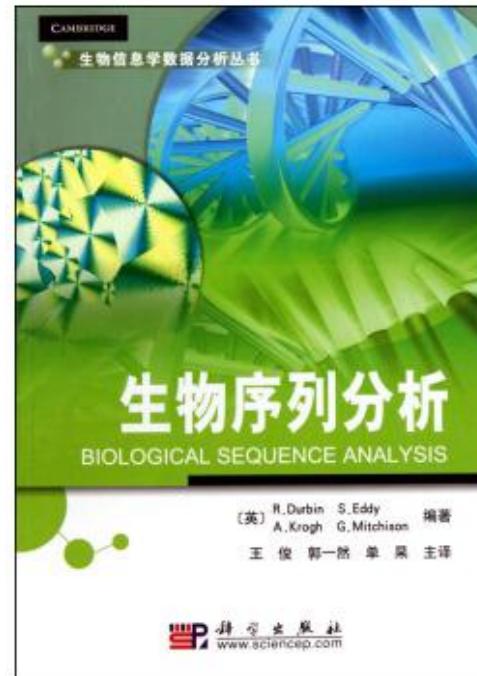
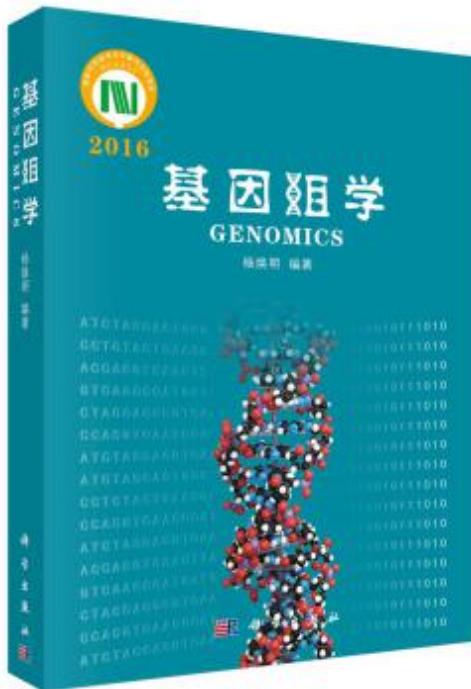
还有配套习题集：

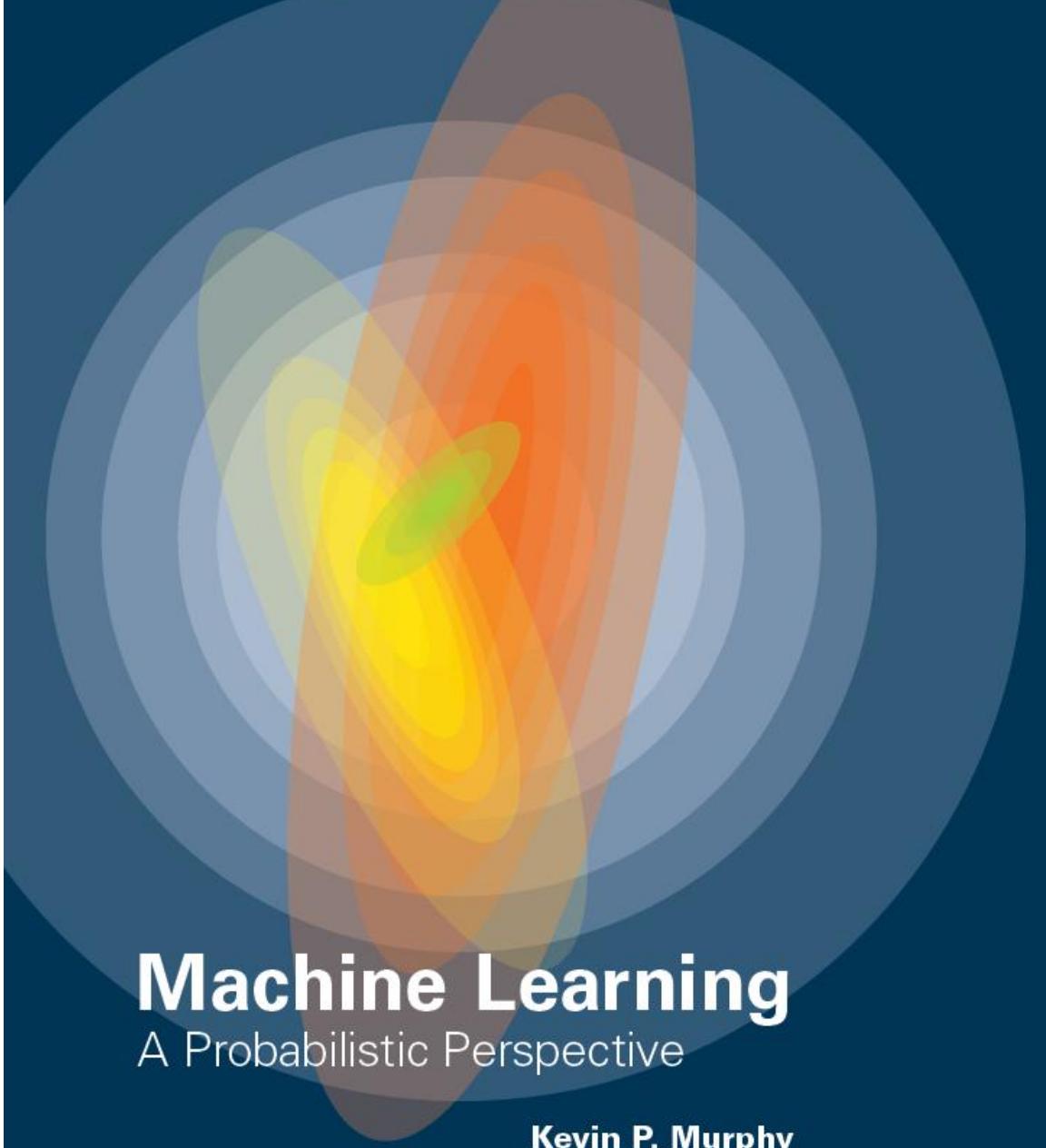
- 《生物统计学习题集》，宁康，2020。

References

- James D. Watson, Tania A. Baker, Stephen P. Bell. Molecular Biology of the Gene. Benjamin-Cummings Publishing Company. 2008.
- Bruce Alberts. Molecular Biology of the Cell. Garland Publishing Inc. 2007.
- Jocelyn E. Krebs, Stephen T. Kilpatrick, Elliott S. Goldstein. Lewin's Genes XI. Jones and Bartlett Publishers, Inc. 2012.

References





Machine Learning

A Probabilistic Perspective

Kevin P. Murphy

DEEP LEARNING

Ian Goodfellow, Yoshua Bengio,
and Aaron Courville



补充知识

生物信息学与生物统计学：

➤两种视角

➤四种技术

➤两类方法

生物信息学与生物统计学： 两种视角，四种技术，两类方法

- 两种视角
 - 生物学视角
 - 计算视角
- 四种技术
 - 算法
 - 数据
 - 超算
 - 深度学习
- 两类方法
 - 经典软件
 - 核心工具

生物信息学：生物学视角

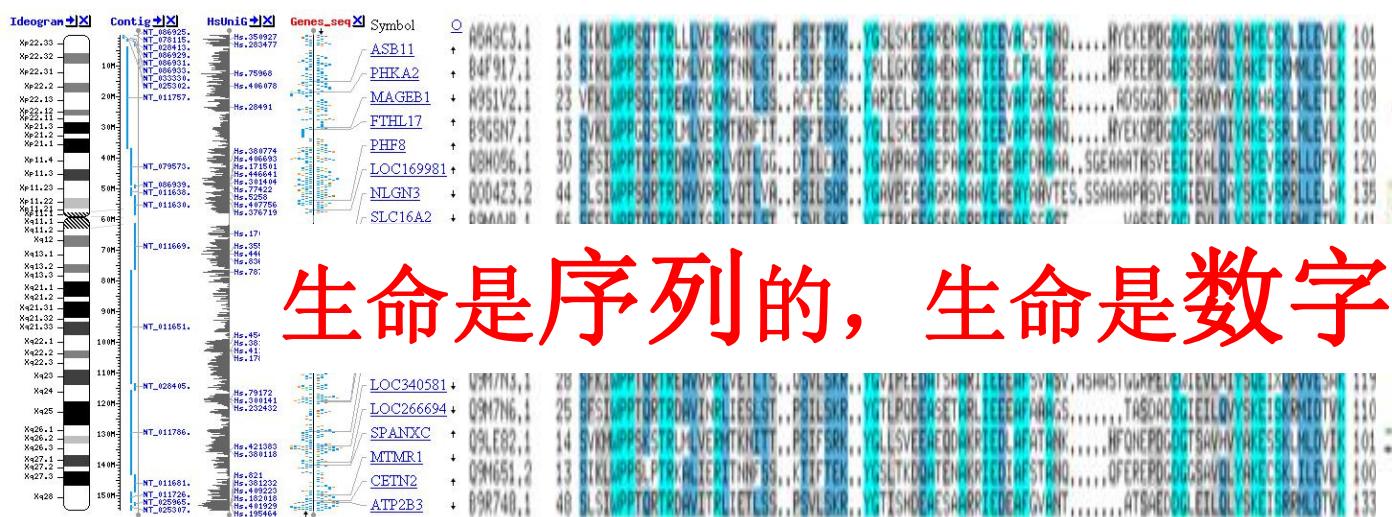


我们是谁？我们从哪里来？我们到哪里去？

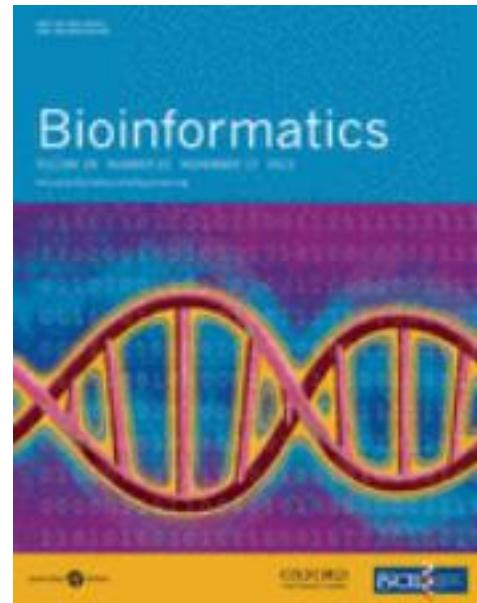
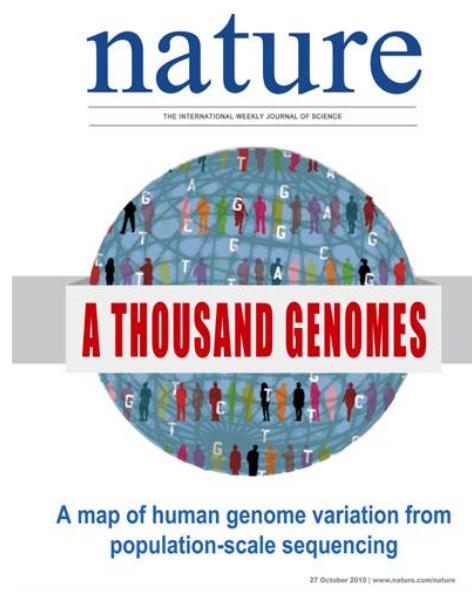


先看视屏！

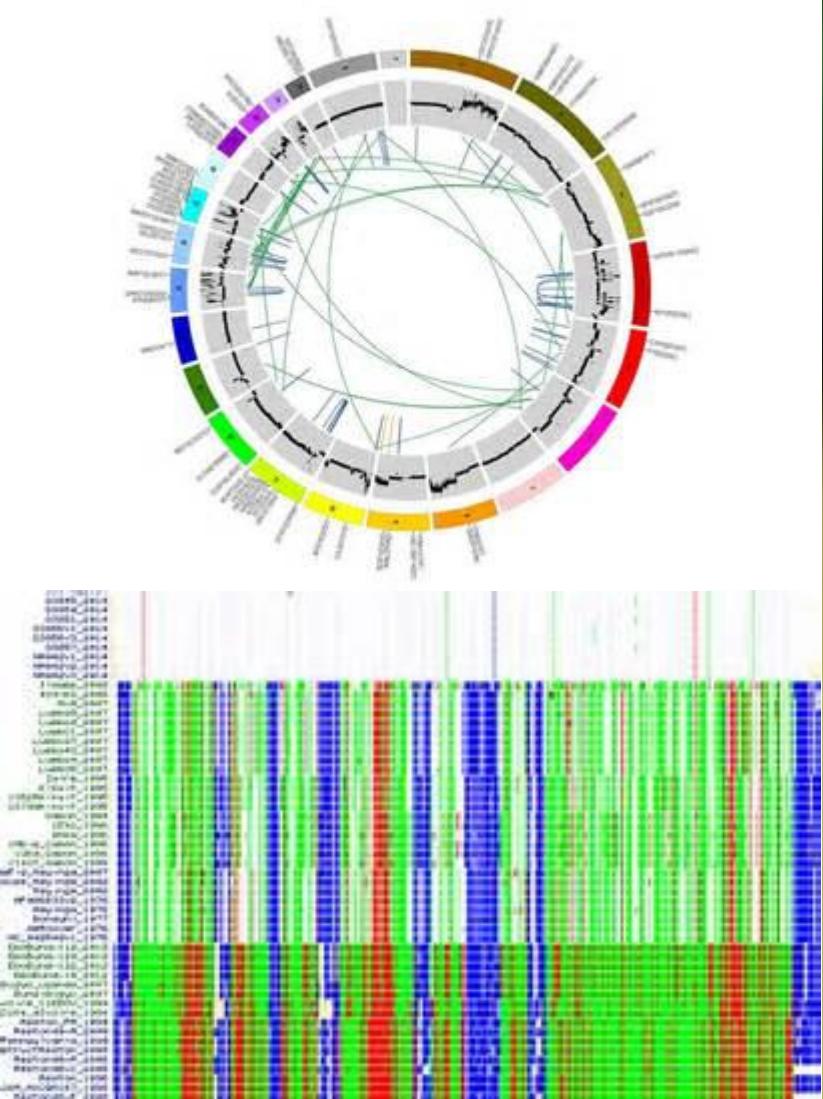
- 开讲啦：如何健康地活到100岁？（汪健@CCTV,
<http://www.biodescover.com/talk/research/103880.html>）
- 基因组学（Barry Schuler@TED, https://www.ted.com/talks/barry_schuler_genomics_101）
- 微生物组学（Rob Knight@TED,
https://www.ted.com/talks/rob_knight_how_our_microbes_make_us_who_we_are）
- 一个IT人的故事（Larry Smarr@TED, <http://www.tedmed.com/talks/show?id=18018>）
- 大数据（Kenneth Cukier@TED,
https://www.ted.com/talks/kenneth_cukier_big_data_is_better_data）



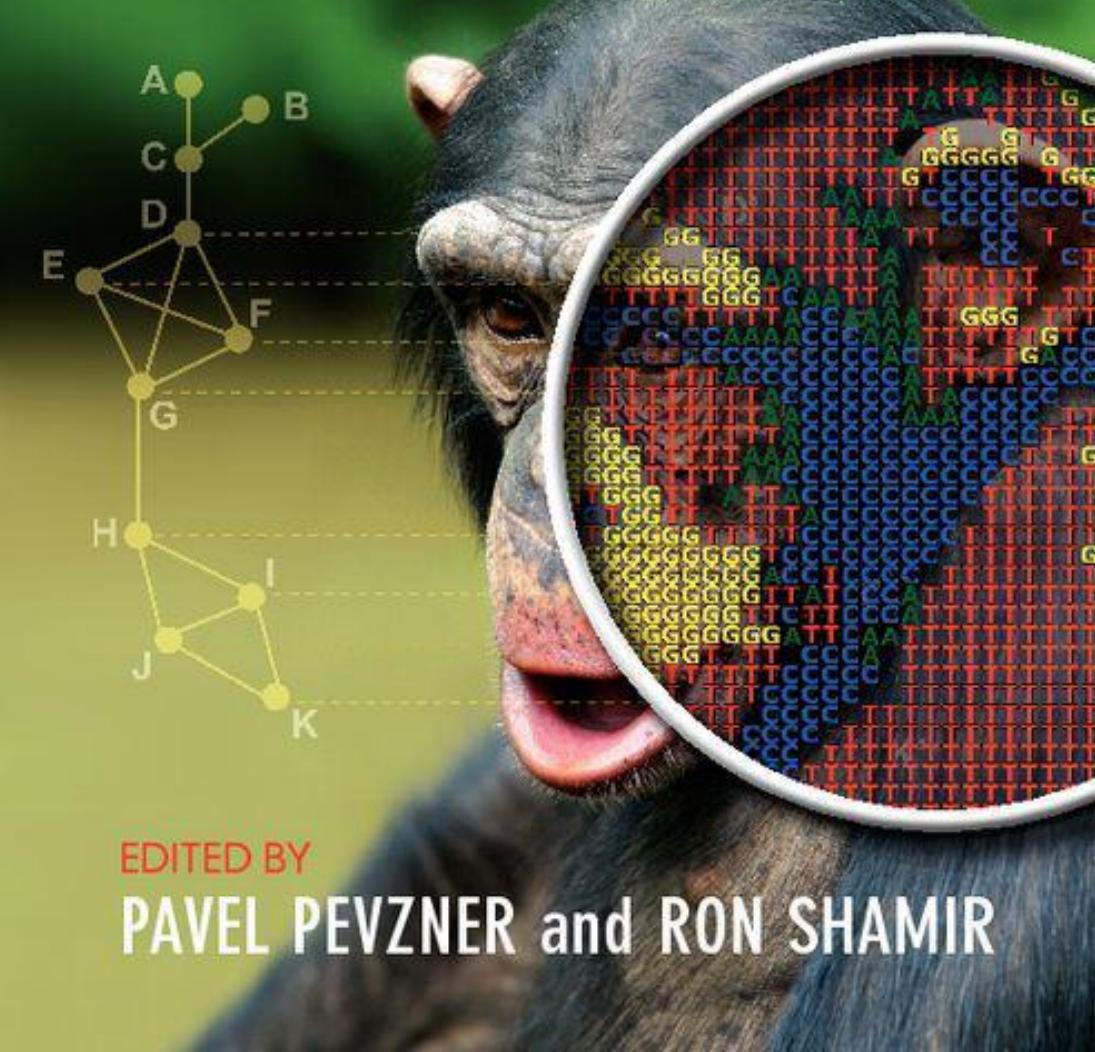
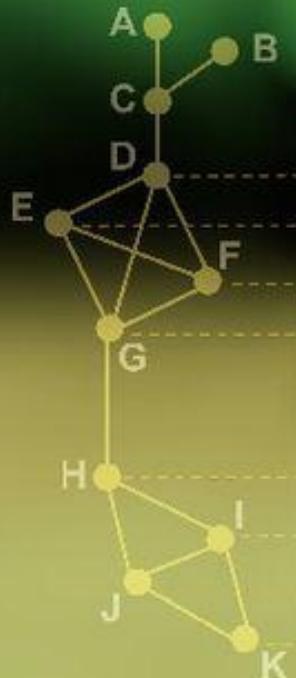
生命是序列的，生命是数字的！



生命是序列的，
生命是数字的！



BIOINFORMATICS FOR BIOLOGISTS

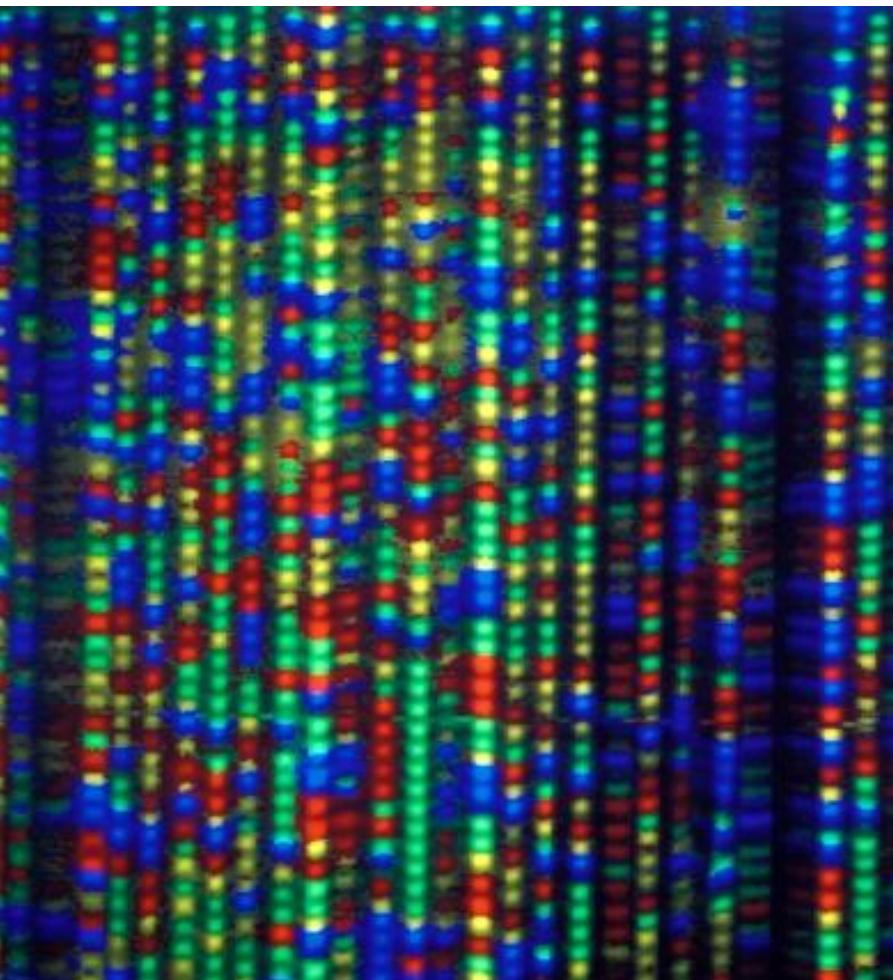
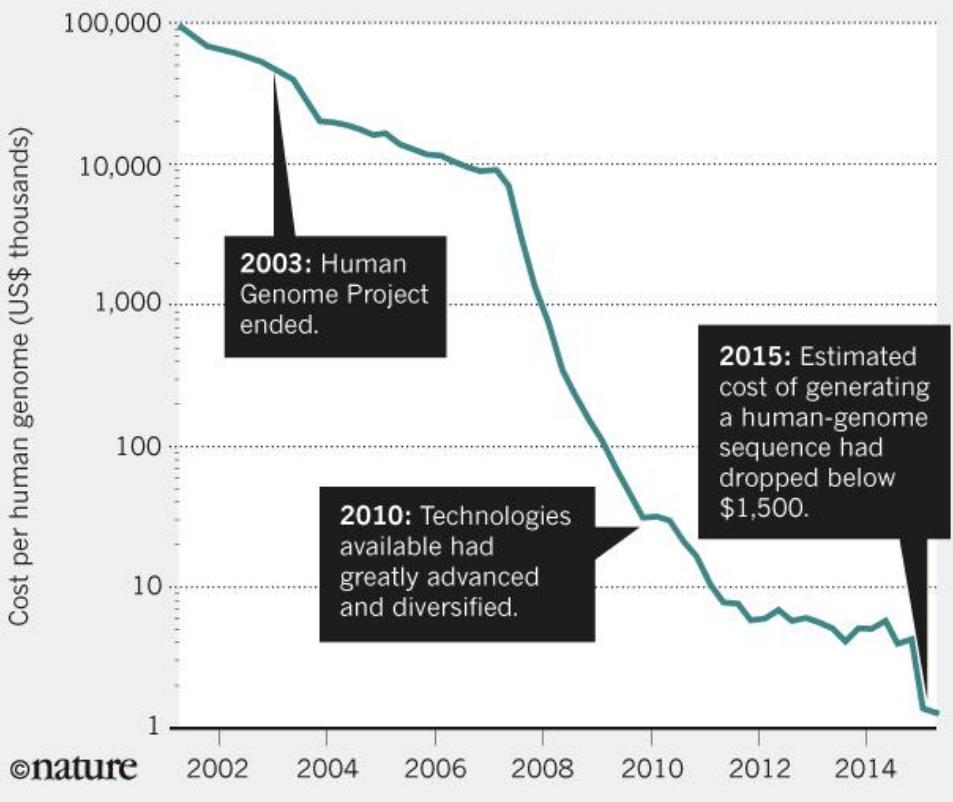


DNA sequencing and bioinformatics



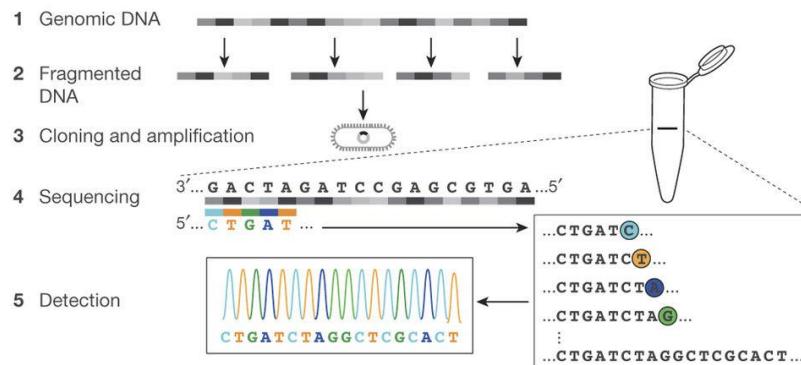
BETTER, CHEAPER, FASTER

The cost of DNA sequencing has dropped dramatically over the past decade, enabling many more applications.

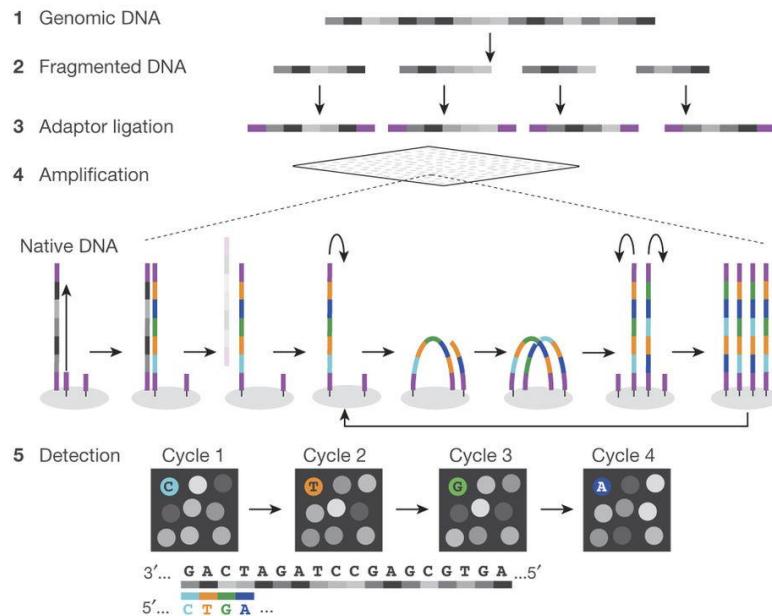


DNA Sequencing

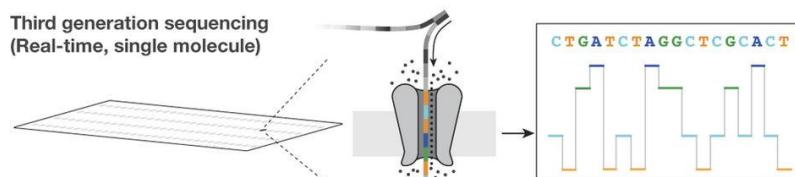
First generation sequencing (Sanger)



Second generation sequencing (massively parallel)

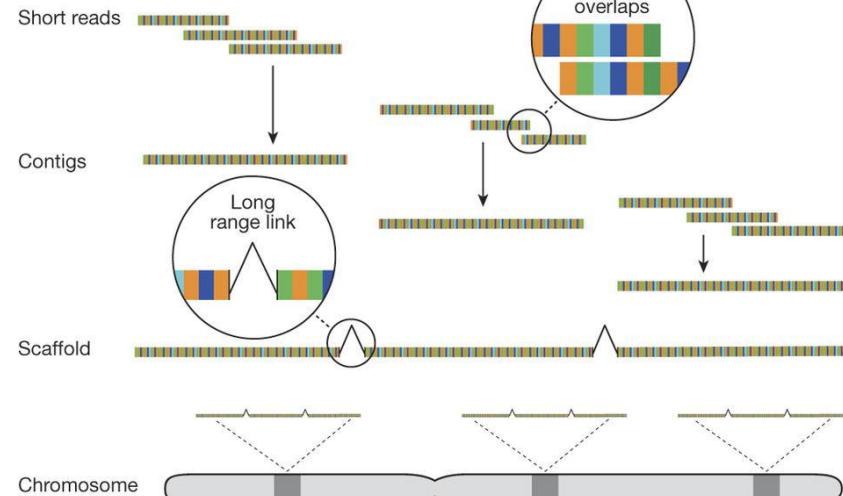


Third generation sequencing (Real-time, single molecule)



Sequencing applications

De novo genome assembly



Genome resequencing

Individual

1 G A C T A G A T C C G A G C G T G A
 2 G A C T A G A T A C G A G C G T G A
 3 G A C G A G A T C C G C G C G T G A
 ...
 7.5 billion G A C T A G A T C C G A G C G C G A

Sites of variation

G A C T A G A T C C G A G C G T G A

Clinical applications (NIPT)

Maternal blood plasma

Maternal DNA

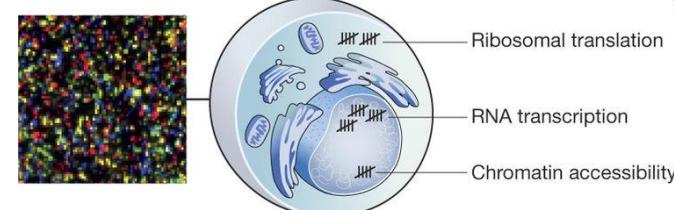
Fetal DNA

Ribosomal translation

RNA transcription

Chromatin accessibility

Sequencers as counting devices



在今天，DNA测序技术已经在诸多方面达到了临床应用的具体要求。

科学家估计，全世界每年大约有四百万到六百万孕妇正在通过外周血游离DNA对胎儿的21三体综合征进行诊断，而十年之内，这个数字将超过1500万。

在高收入国家，基因组测序已经广泛用于多种疾病的产前诊断，可以揭示大约30%的出生缺陷，同时，这一数字也正随着数据解读能力的成熟而逐渐上升。

在肿瘤学领域，液体活检在最近几年已经成为了肿瘤相关学术，产业以及投资界的新宠。基于DNA测序的液体活检被认为正逐步发展为癌症诊断与预后评估的标准方法，能够在可知的时间内逐步补充甚至取代传统的创伤性癌症诊断技术。

同样，手持DNA测序仪等设备的开发也使得流行病学家甚至能够在最为偏远的地区高效完成对人类样本，动物以及昆虫病原载体甚至是空气，水，食物的基因检测。

流行病学家和公共卫生专家也开始讨论如何通过对城市垃圾中微生物的DNA测序辅助传染性疾病的预防与控制。

海洋生物学家也正在通过宏基因组学技术来对海洋的生态健康进行监测与研究。

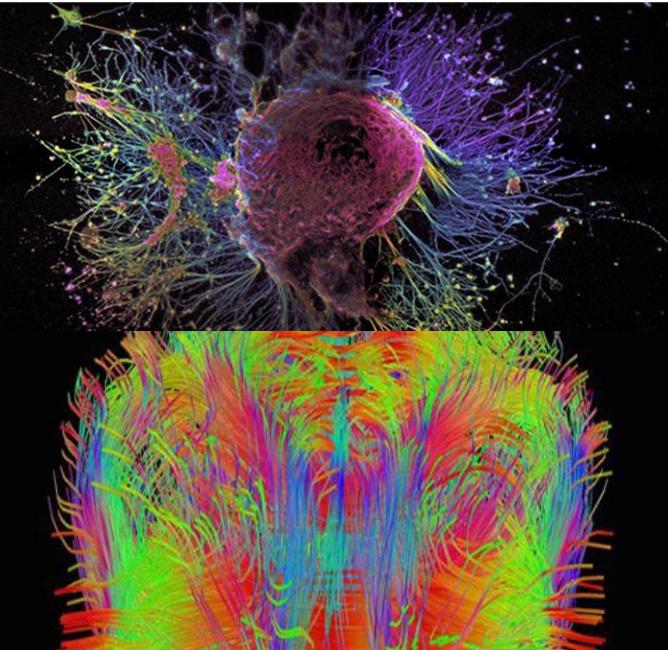
在法医领域，便携式DNA测序仪可以将DNA分析带出法医实验室，使其成为一线警务工作人员的随身工具。帮助警方即使通过DNA监测确定嫌疑人，发展成为诸如酒精探测器一类的便捷工具。

在人们的家里，DNA测序设备或许也可以成为下一个“智能”或“连接”设备，一些评论者甚至认定厕所是通过实时DNA测序监测家庭成员健康的理想场所。



生物信息学@HUST

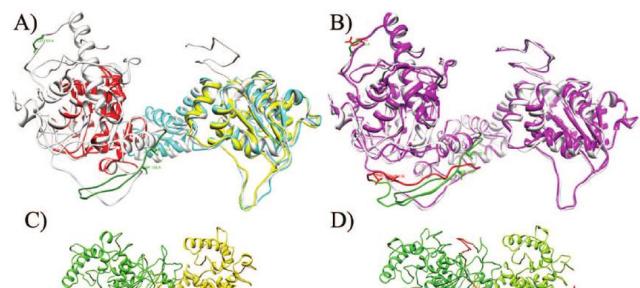
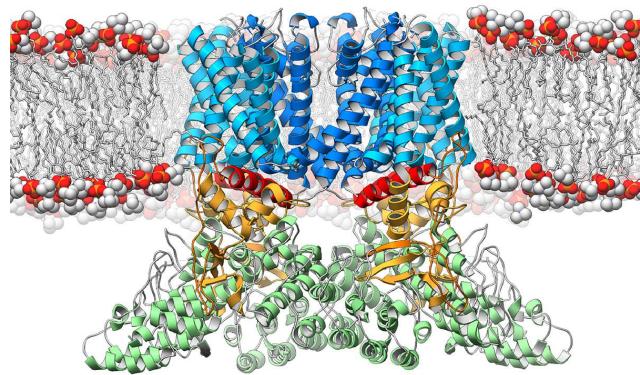
生命不只是序列的，但是生命始终是数字的！



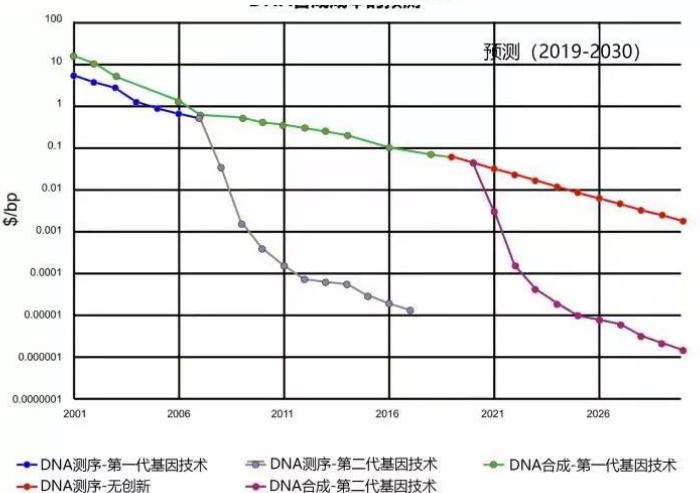
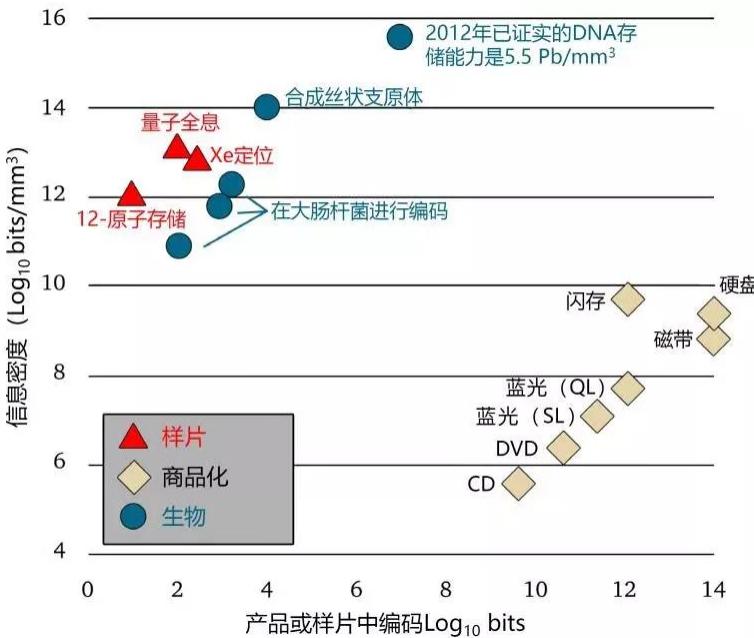
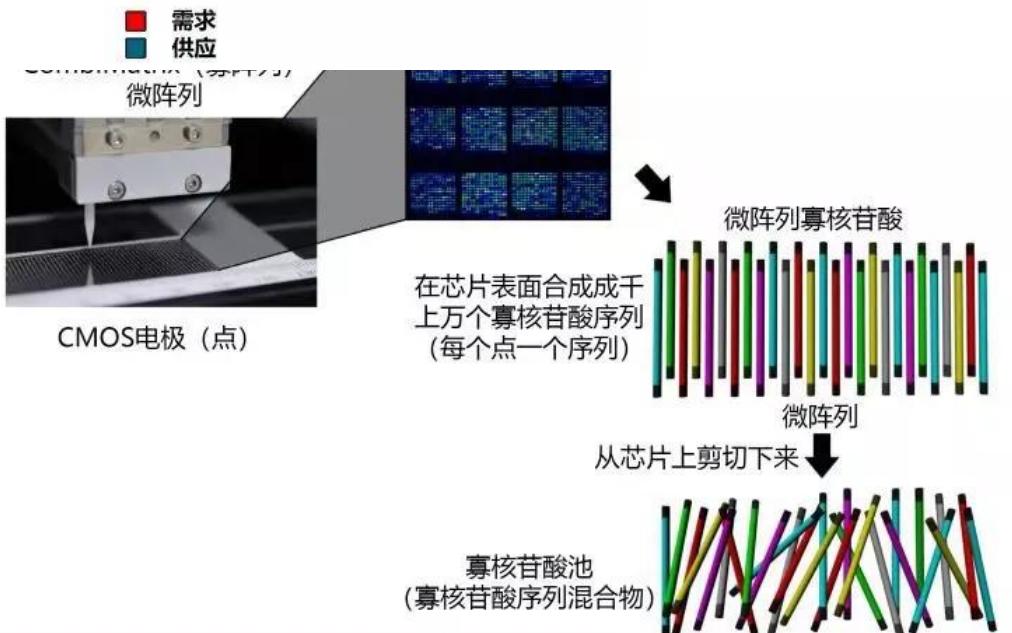
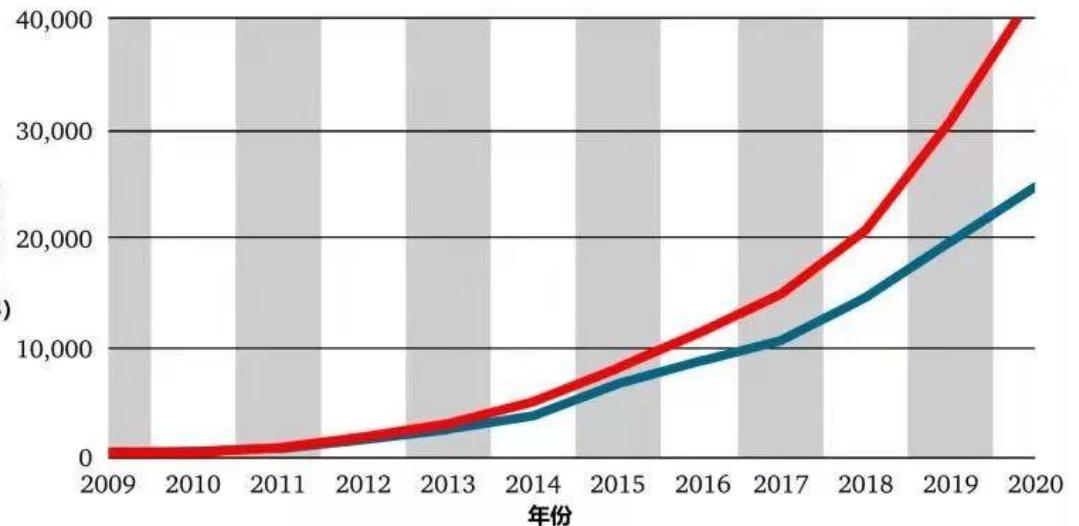
- 结构生物学
(Structure biology)

- 生物图像
(Bio-imaging)

- ○ ○ ○

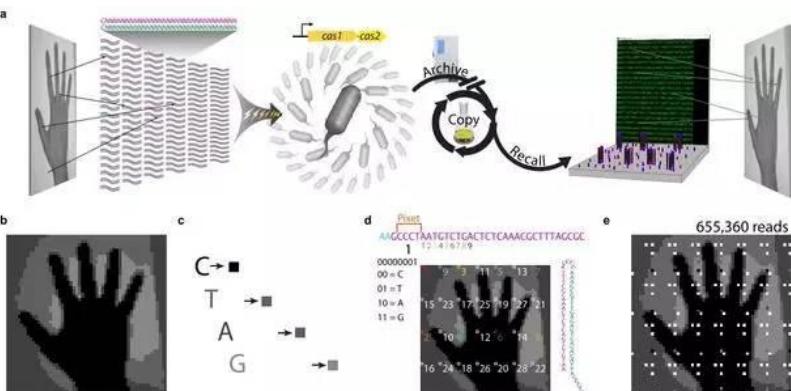
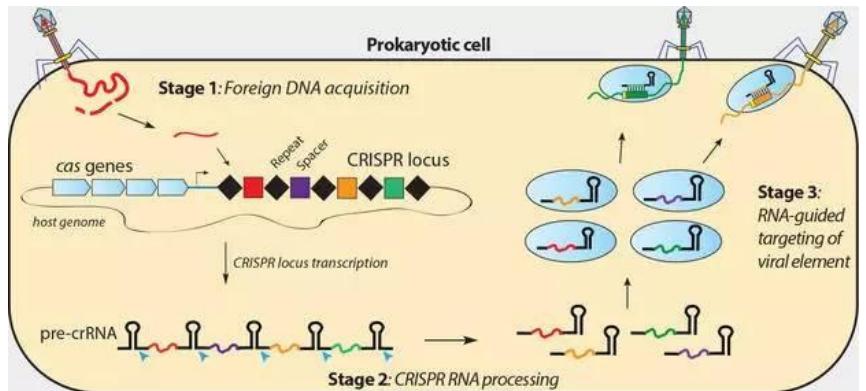


Understand it, create it!



DNA数据存储的现在和未来

Understand it, create it!



Original Image

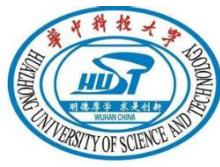
原始图像



Image Reconstructed From Bacteria

从细菌DNA还原的图像

Understand it, create it!



Our test on DNA storage: how can it tolerate mutations?



5% SNPs



2% SNPs



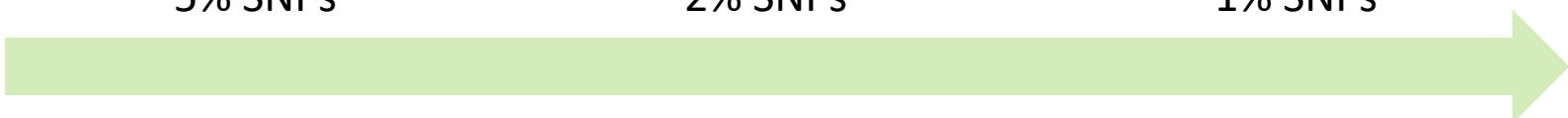
1% SNPs



0.1% SNPs



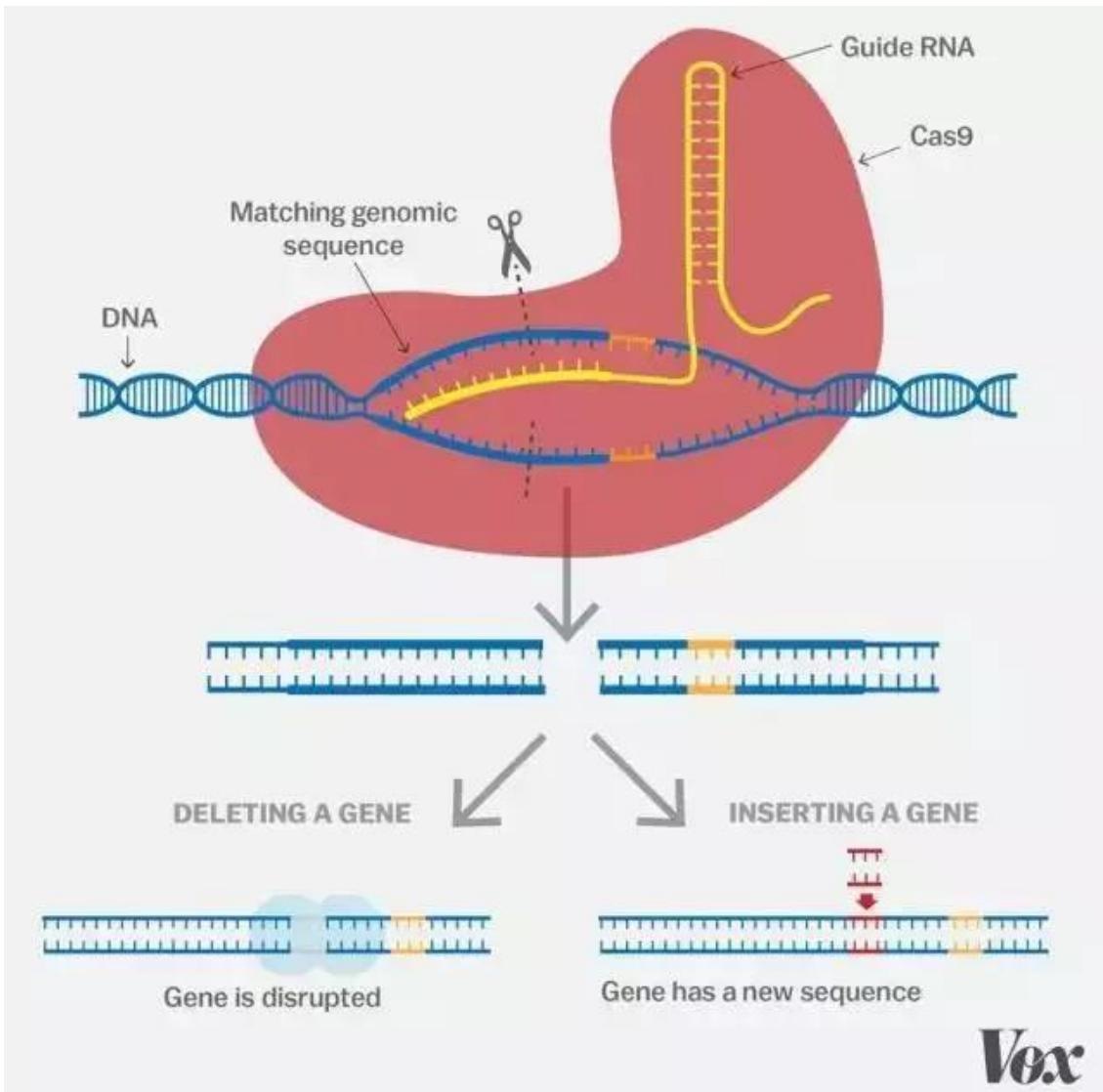
0.05% SNPs

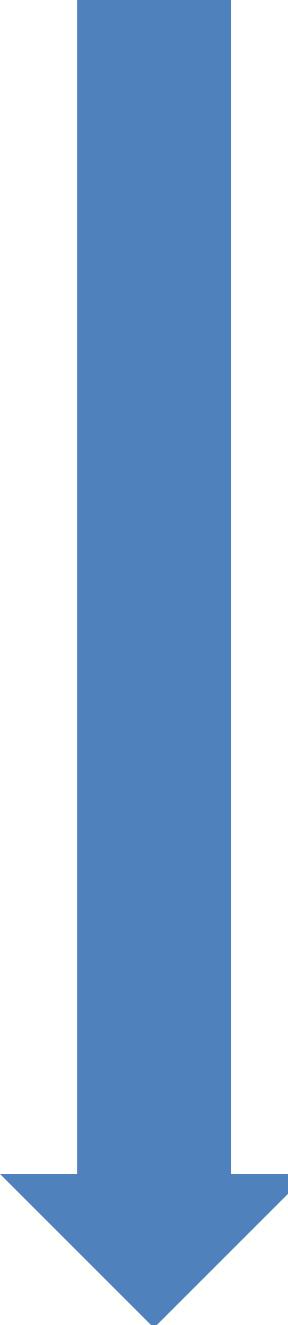


Understand it, create it!

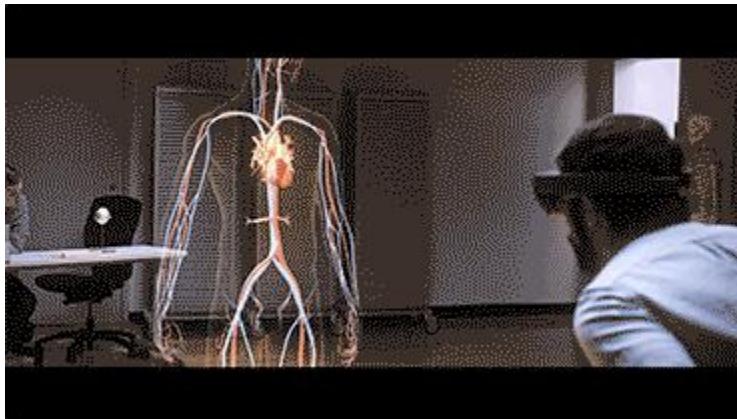


CRISPR-Cas9





See it!



Understand it!



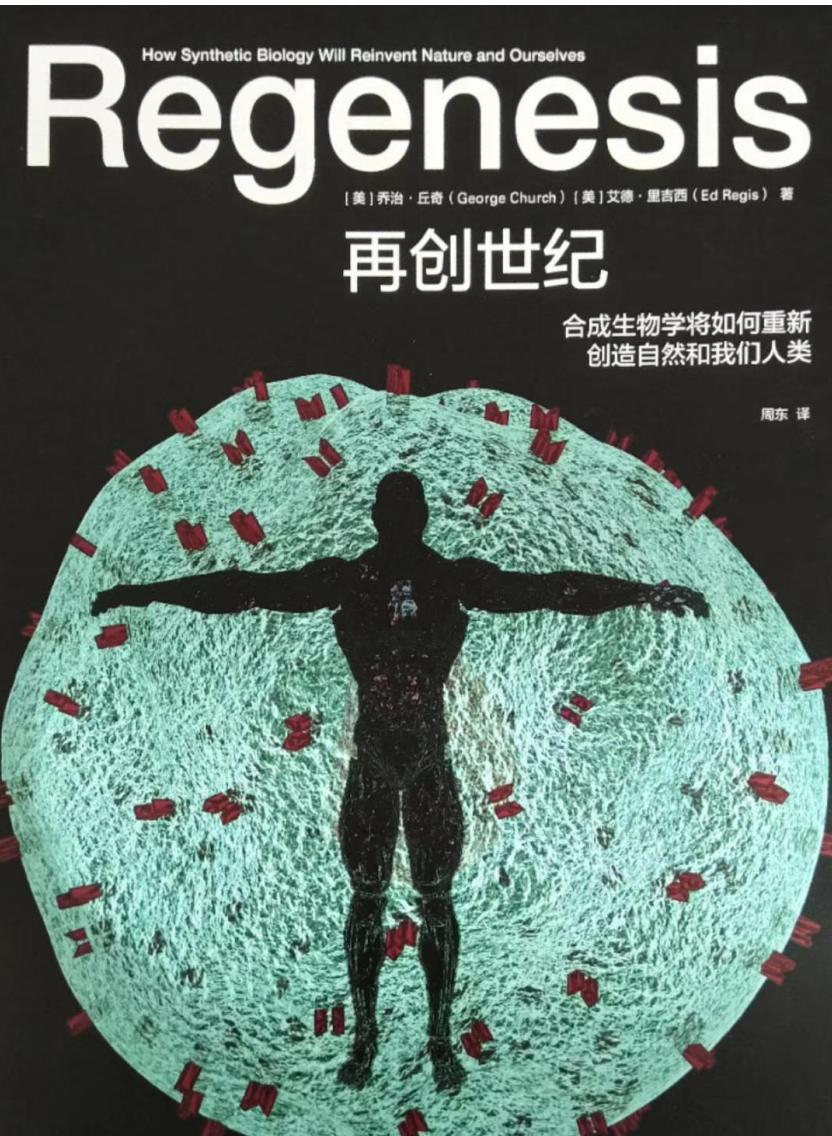
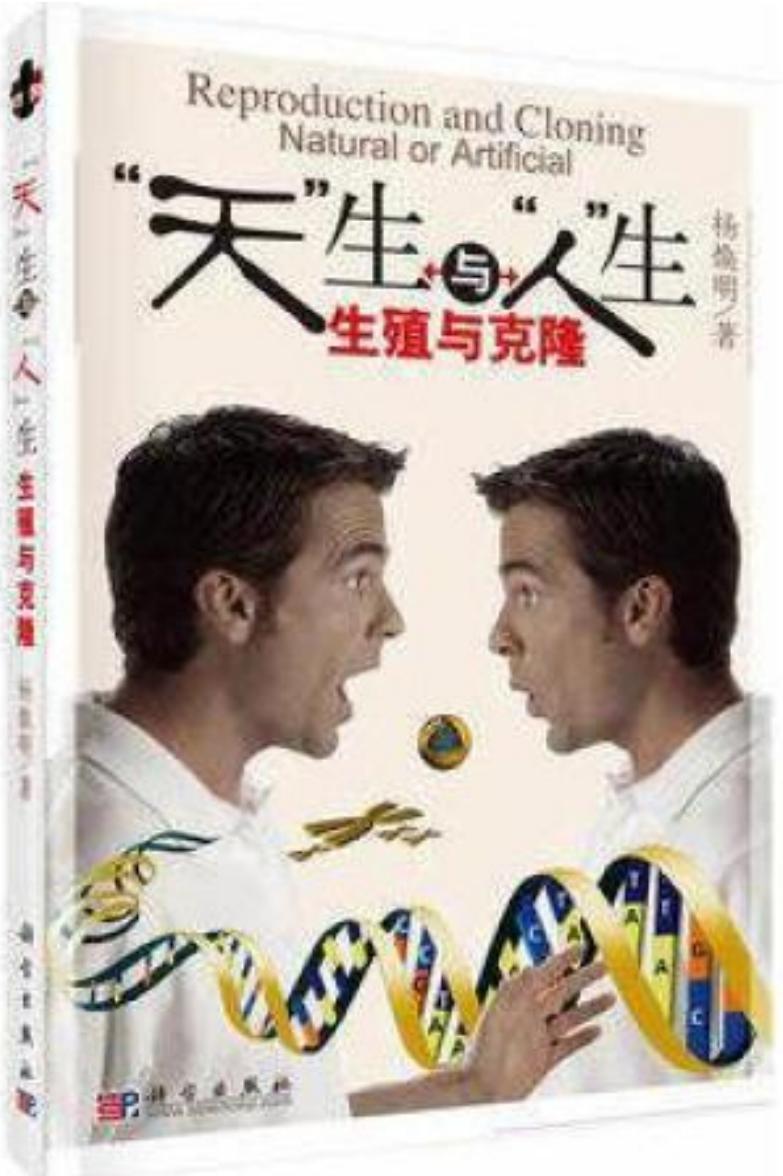
Create it!



Understand it, create it!



读物推荐



Understand it, create it!



The image shows the cover of the October 2014 issue of Discover magazine. The background is a green circuit board pattern. The title "Discover" is written in large, yellow, 3D-style letters. Below it, the subtitle "SCIENCE FOR THE CURIOUS" is in smaller white letters, followed by "October 2014".

TECH
A Spacesuit for Mars p.10

MIND
Never Give Up p.24

COSMOS
The Multiverse Is Real p.62

REWIRED NATURE

How SYNTHETIC BIOLOGY will grow genetic circuits, new drugs and biofuels – and create a sustainable future. p.56

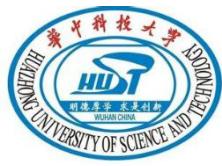
PLUS

Cancer Report
Proton therapy: precision vs. profits p.32

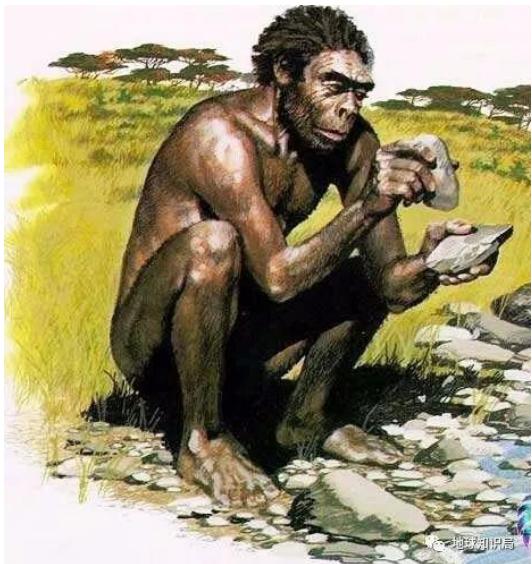
DIY Science
Cool projects YOU can try (and more!) p.5

Hemmmed In
Beefed-up border security endangers desert species p.48

Understand it, create it!



CRISPR和基因编辑技术



OR



CRISPR和基因编辑技术

Are there compelling medical indications?

Disease prevention

- Huntington's
- Tay Sach's
- Cystic Fibrosis
- Sickle cell anemia

Consider alternatives...

- IVF, genetic diagnosis
- Somatic therapy

When no alternative...

- Couples, both affected
- Infertility

Modifying Disease Risk

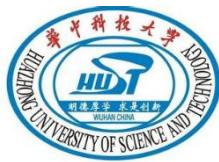
- HIV resistance (CCR5)
- Heart disease (PCSK9)
- Alzheimer's (APP A673T/+)
- Cancer (BRCA1/2)
- Resistance to global pandemics...

"Enhancements"

- Muscularity (MSTN)
- Height, skin color
- Learning and memory
<https://www.dnalc.org/view/1390-Genes-for-Learning-and-Memory.html>

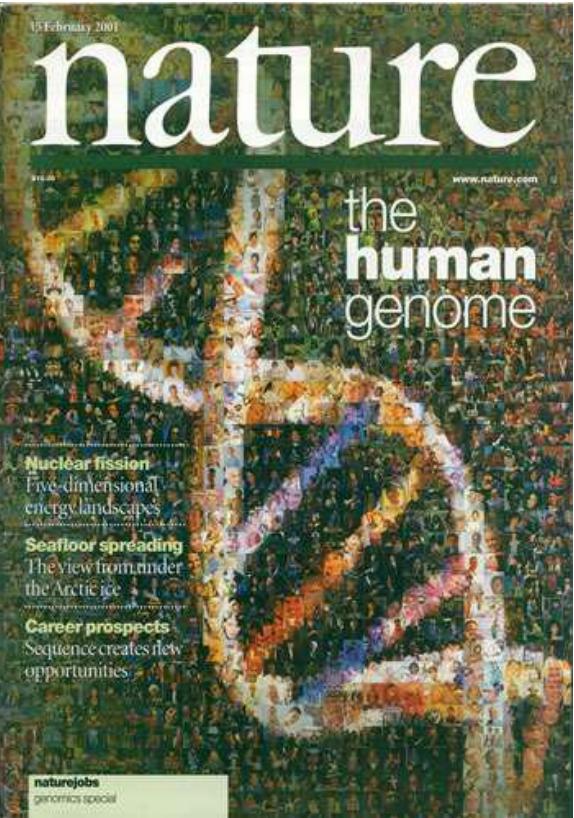
Permissible vs impermissible applications?

生物信息学：计算科学视角

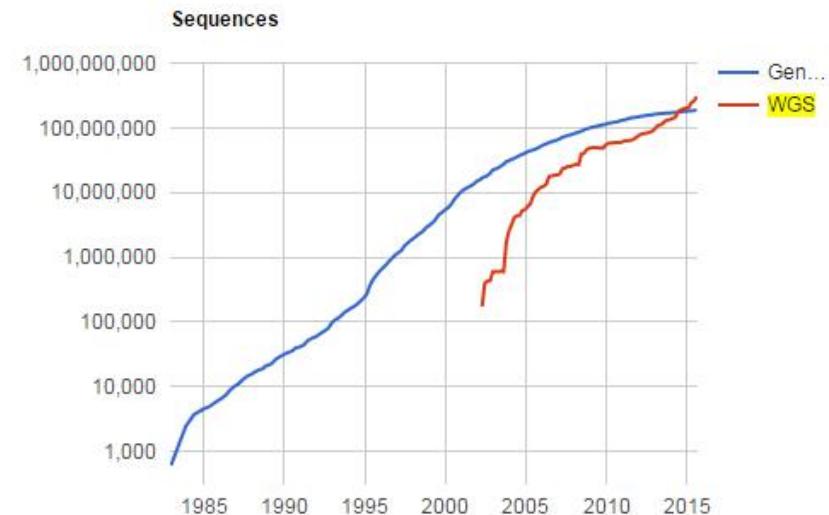
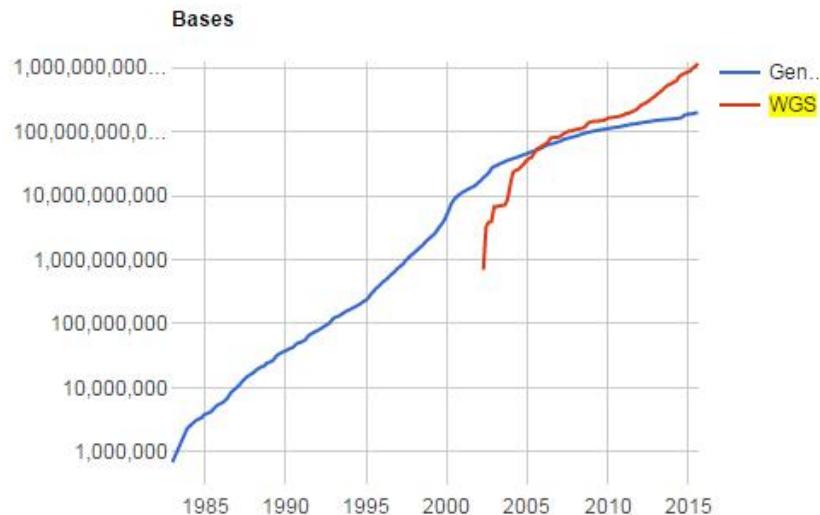
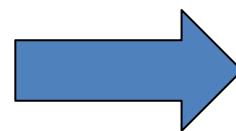
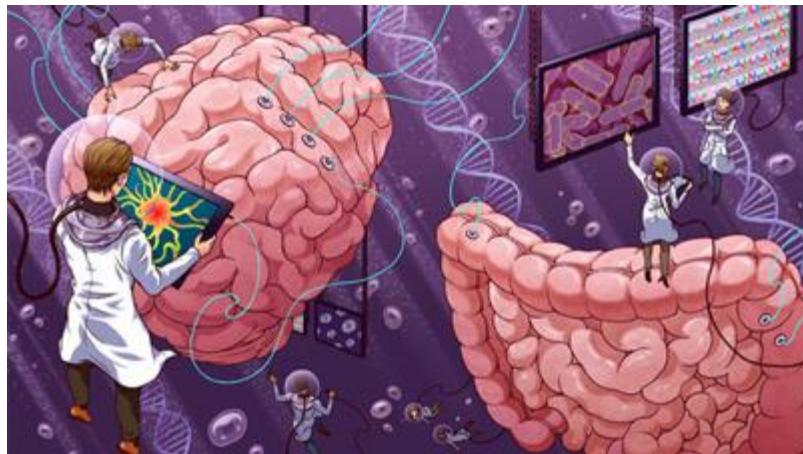


生物信息学@HUST

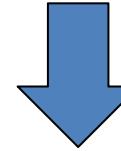
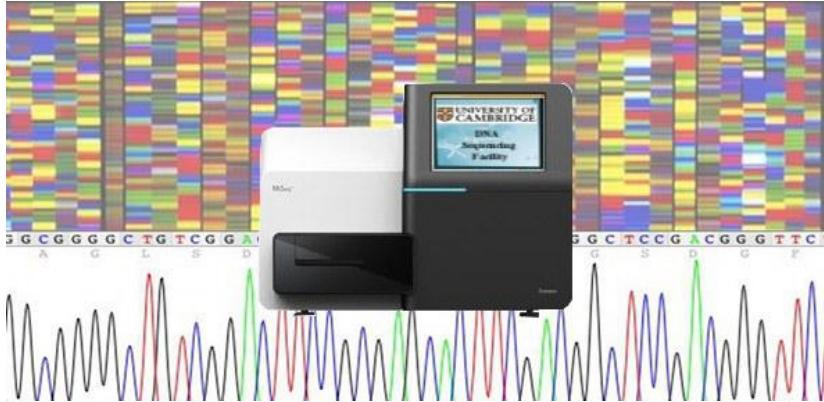
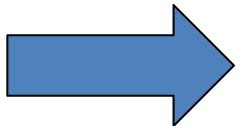
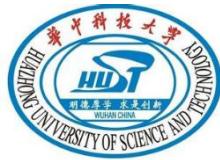
我们是谁？ 我们从哪里来？ 我们到哪里去？



生命科学的前沿 - 生物大数据



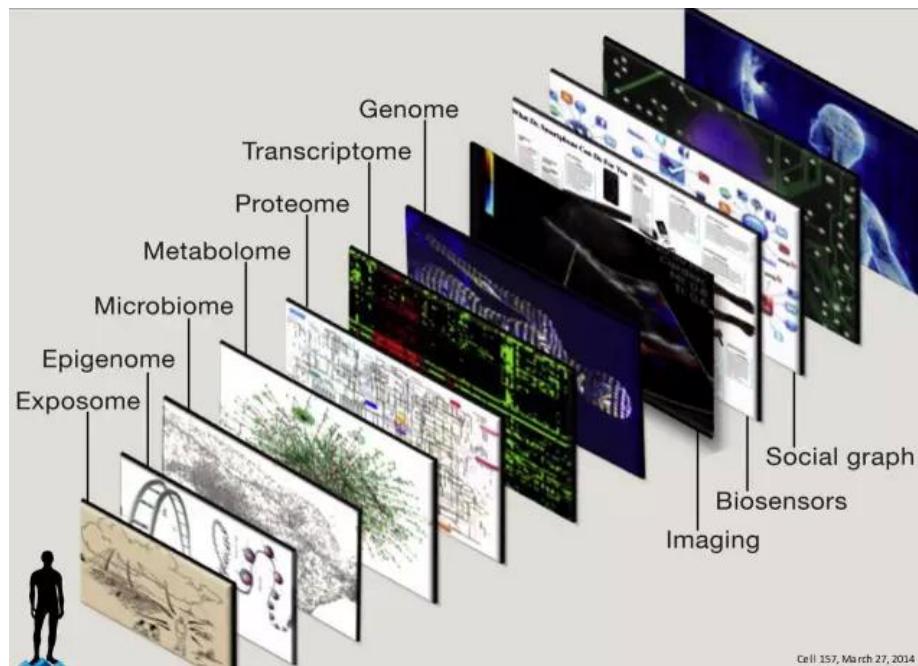
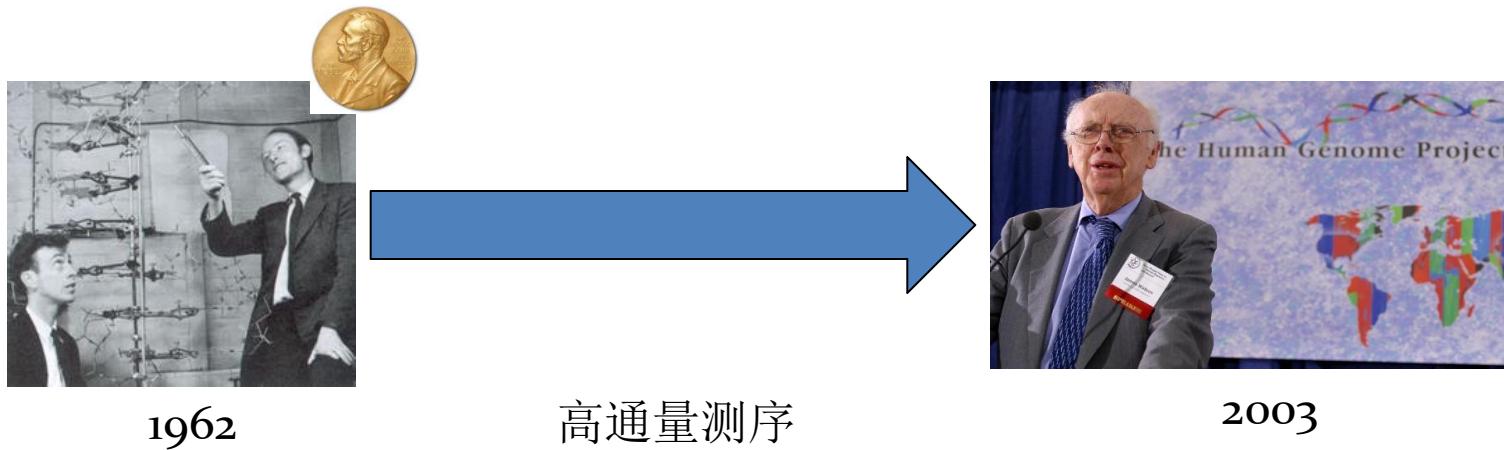
生物大数据 – 机遇与挑战



Next generation sequencing...



大数据的挑战 – 需要高通量的解决方案



大数据的挑战 – 需要高通量的解决方案



1951



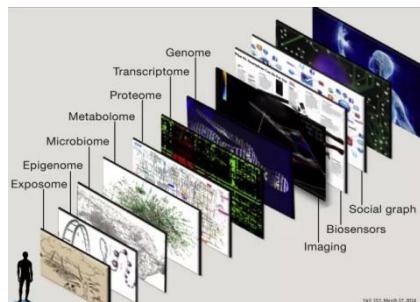
>100候选, >10000实验



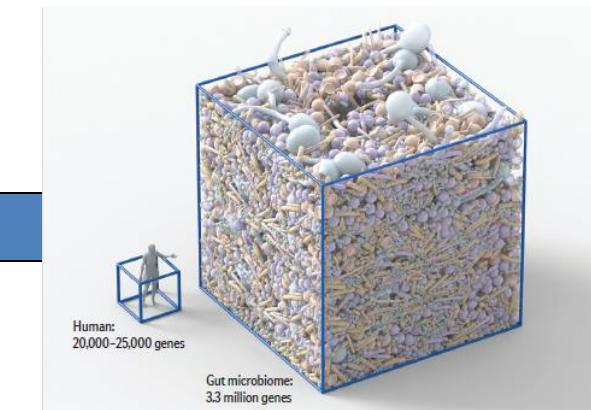
1971



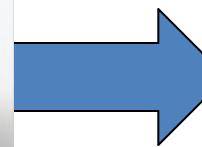
2015



2003



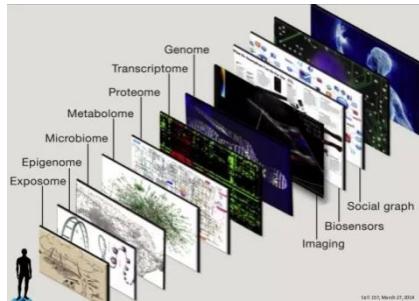
>>60亿研究对象,
>>EB(1000,000TB)数据量



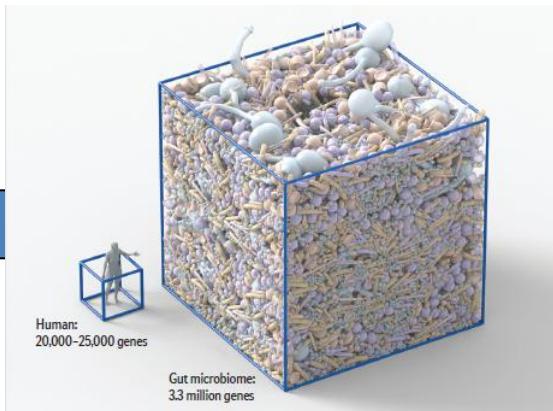
????

如果没有
大数据分析技术...

大数据的挑战 – 需要高通量的解决方案



2003



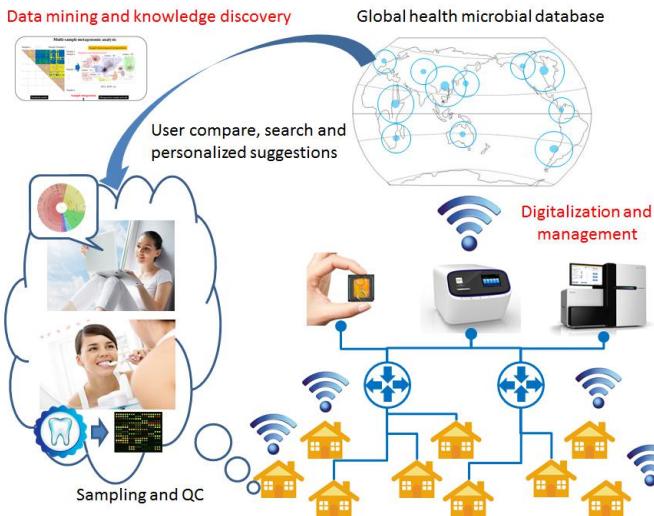
>60亿研究对象，>>EB数据量



!!!!

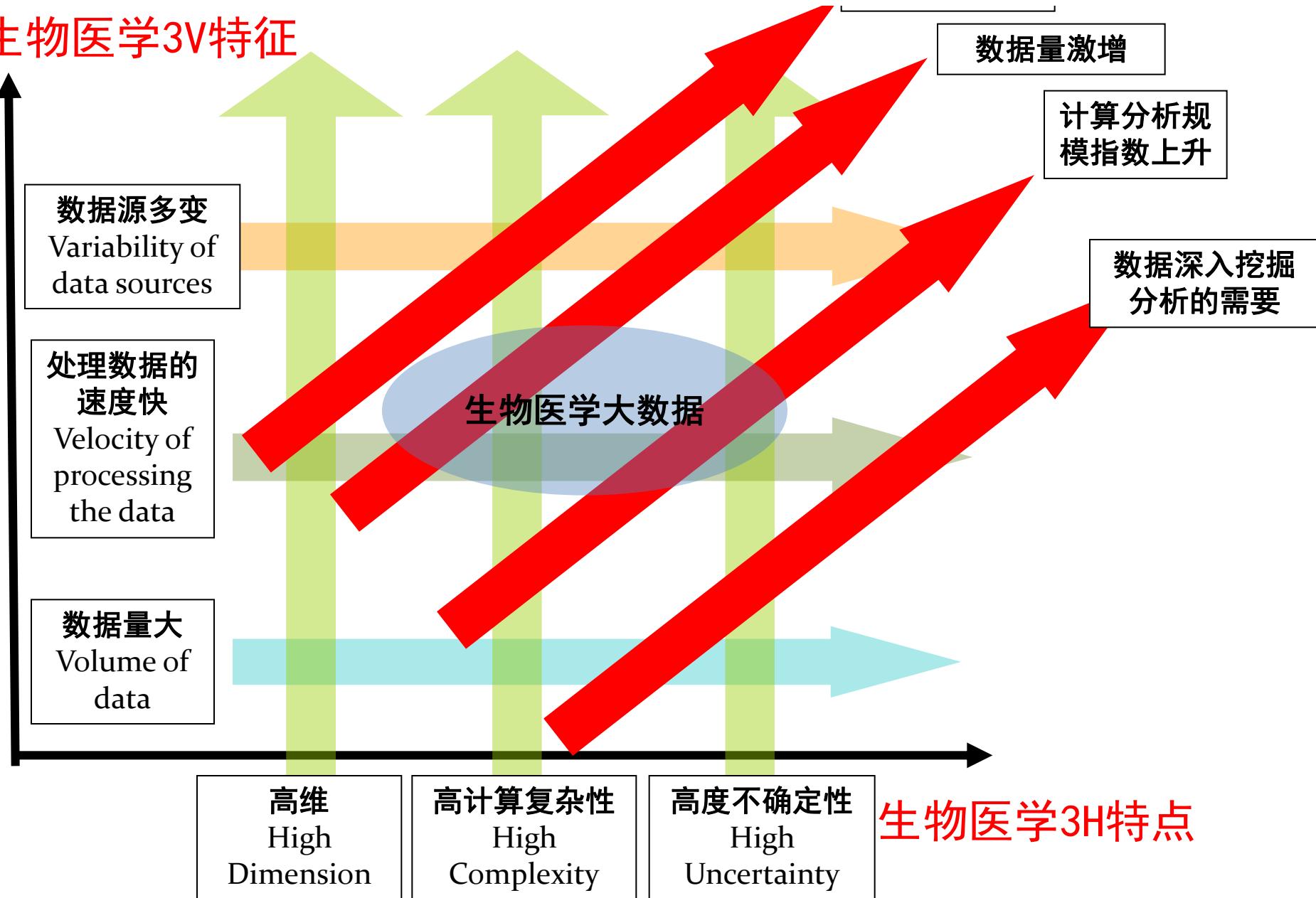
光有机器也枉然...

亟需高性能大数据分析技术...

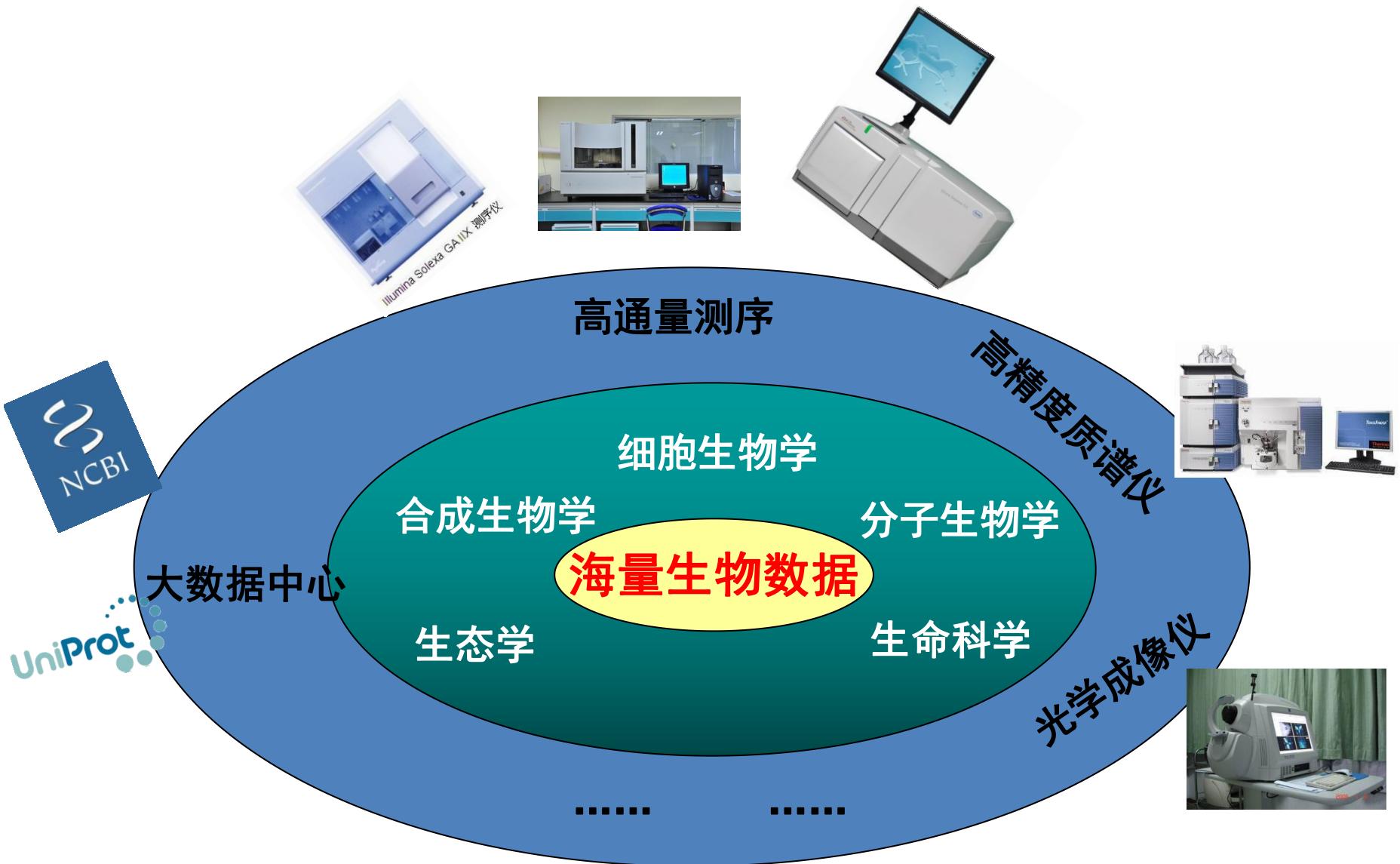


生物医学大数据3V特征

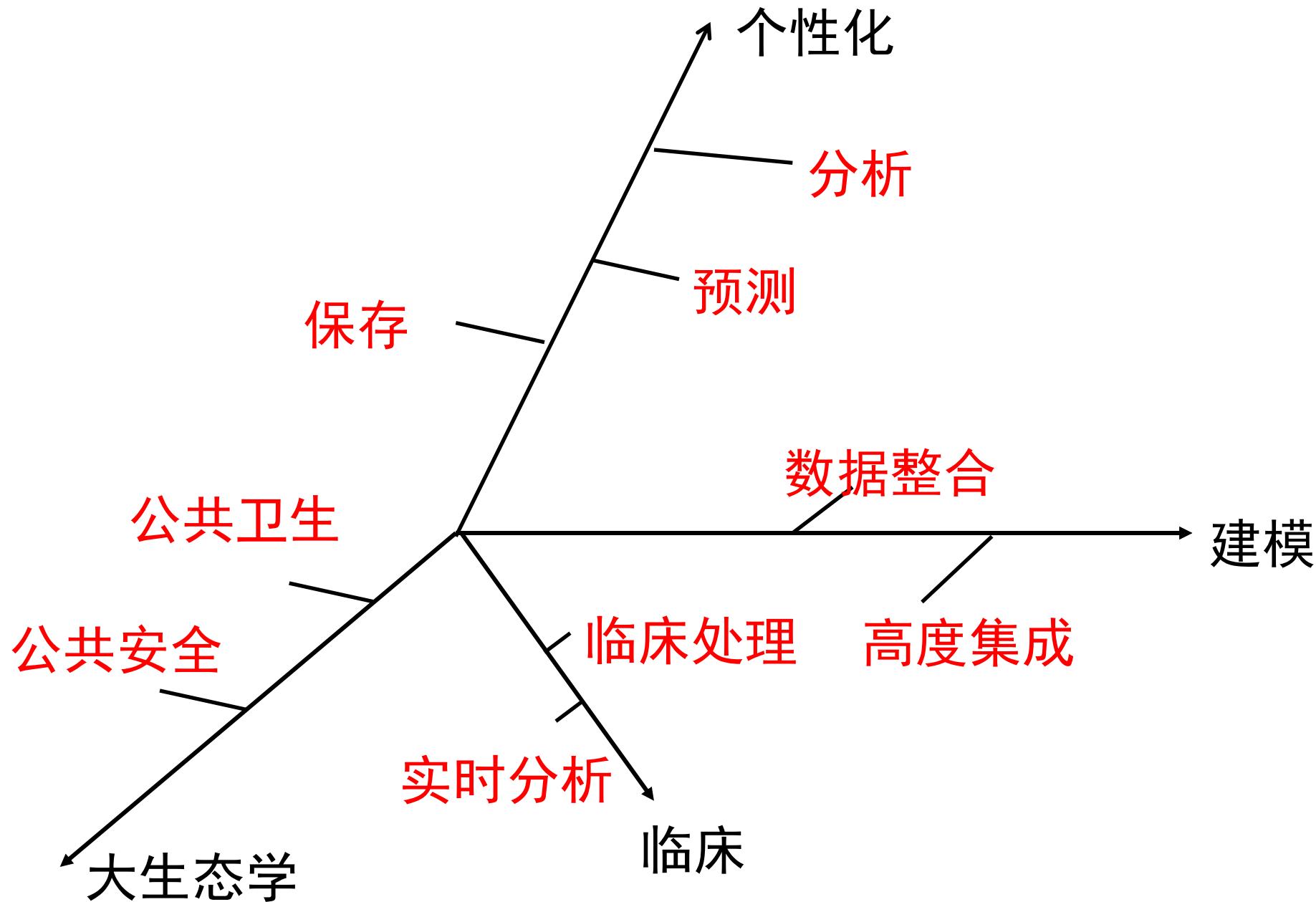
生物医学3V特征



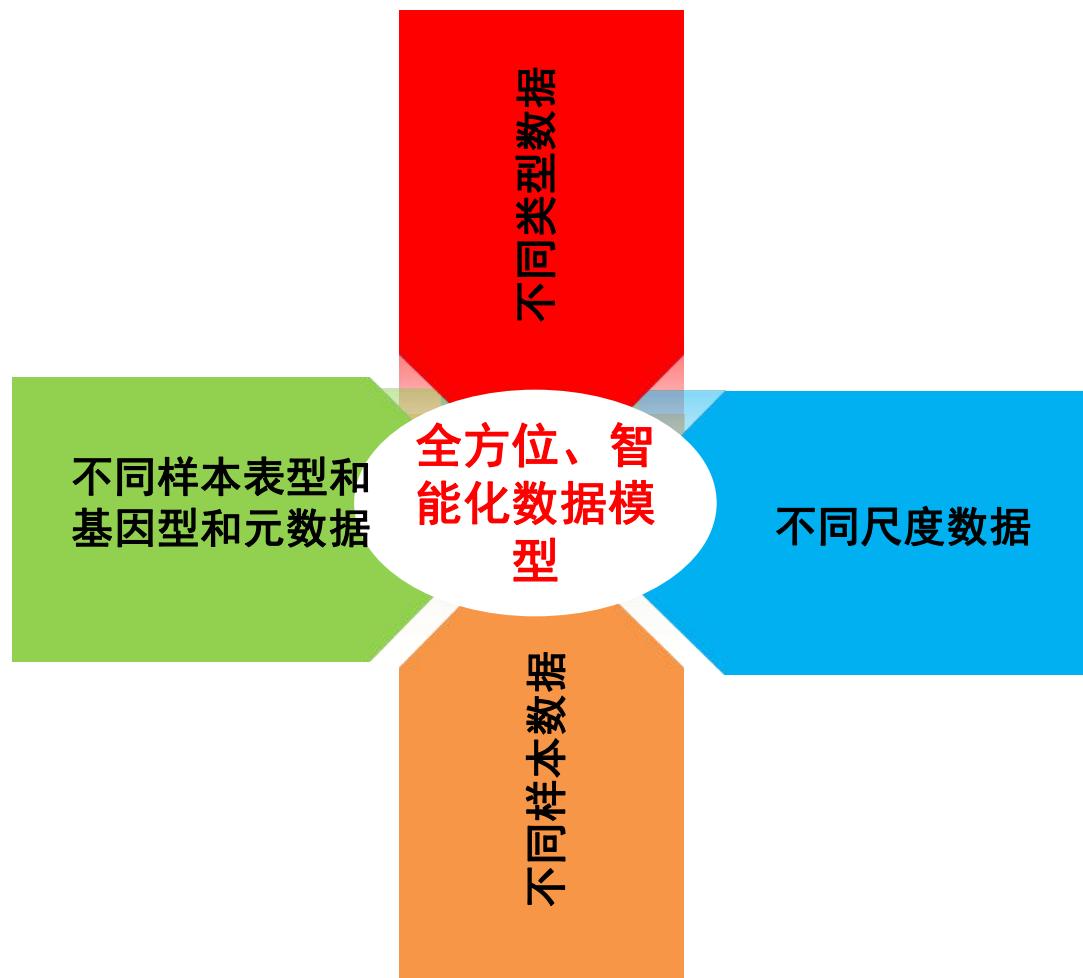
生物医学大数据涉及到广泛的领域



生物医学大数据涉及到完整研究链条



生物医学大数据依赖于大数据的分析方法



Alphabet (谷歌)

Google 的基因组学梦想



HOME ARTICLES & MULTIMEDIA ISSUES SPECIALTIES & TOPICS FOR AUTHORS

CORRESPONDENCE

23andMe and the FDA

N Engl J Med 2014; 370:2248-2249 | June 5, 2014 | DOI: 10.1056/NEJMc1404692

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Article Citing Articles (3) Metrics

To the Editor:

In their Perspective article (March 13 issue),¹ Annas and Elias state that the conflict between the genetic-testing company 23andMe and the Food and Drug Administration (FDA) concerns analytic and clinical validity, clinical utility, and ethical, legal, and social issues. However, their discussion is limited to a domestic U.S. perspective. After a person's raw genetic data have been determined from a DNA sample, the data are stored remotely and can be accessed easily anywhere in the world. For example, in Japan, maternal blood samples from Japanese mothers undergoing



NATURE BIOTECHNOLOGY | NEWS



FDA approves 23andMe gene carrier test

Nature Biotechnology 33, 435 (2015) | doi:10.1038/nbt0515-435a

Published online 12 May 2015

[PDF](#) [Citation](#) [Reprints](#) [Rights & permissions](#) [Article metrics](#)

23andMe, based in Mountain View, California, has received word from the US Food and Drug Administration (FDA) that their Bloom syndrome carrier screening test was approved as a class II device. The approval came in February, 15 months after the personal genomics company received a cease and desist letter from the regulator for its genetic tests because the company was dispensing health-related information to consumers without having obtained marketing clearance. The FDA website lists class II devices as moderate risk, requiring some regulatory controls, putting carrier screening tests in the same category as condoms. This turnaround follows the company's

Future (未来)

Cancer informatics Gene regulation
Personalized medicine Protein modeling
Computational biology Gene expression analysis
Image analysis Genomics and proteomics
Comparative genomics Gene expression databases
Epidemic models Computational drug discovery

Bioinformatics

Sequence analysis Bio-ontologies and semantics
Evolution and phylogenetics Structure prediction
Cheminformatics Next generation sequencing
Computational intelligence
Biomedical engineering Amino acid s
Structural bioinformatics Medical
Microarrays
Visualization

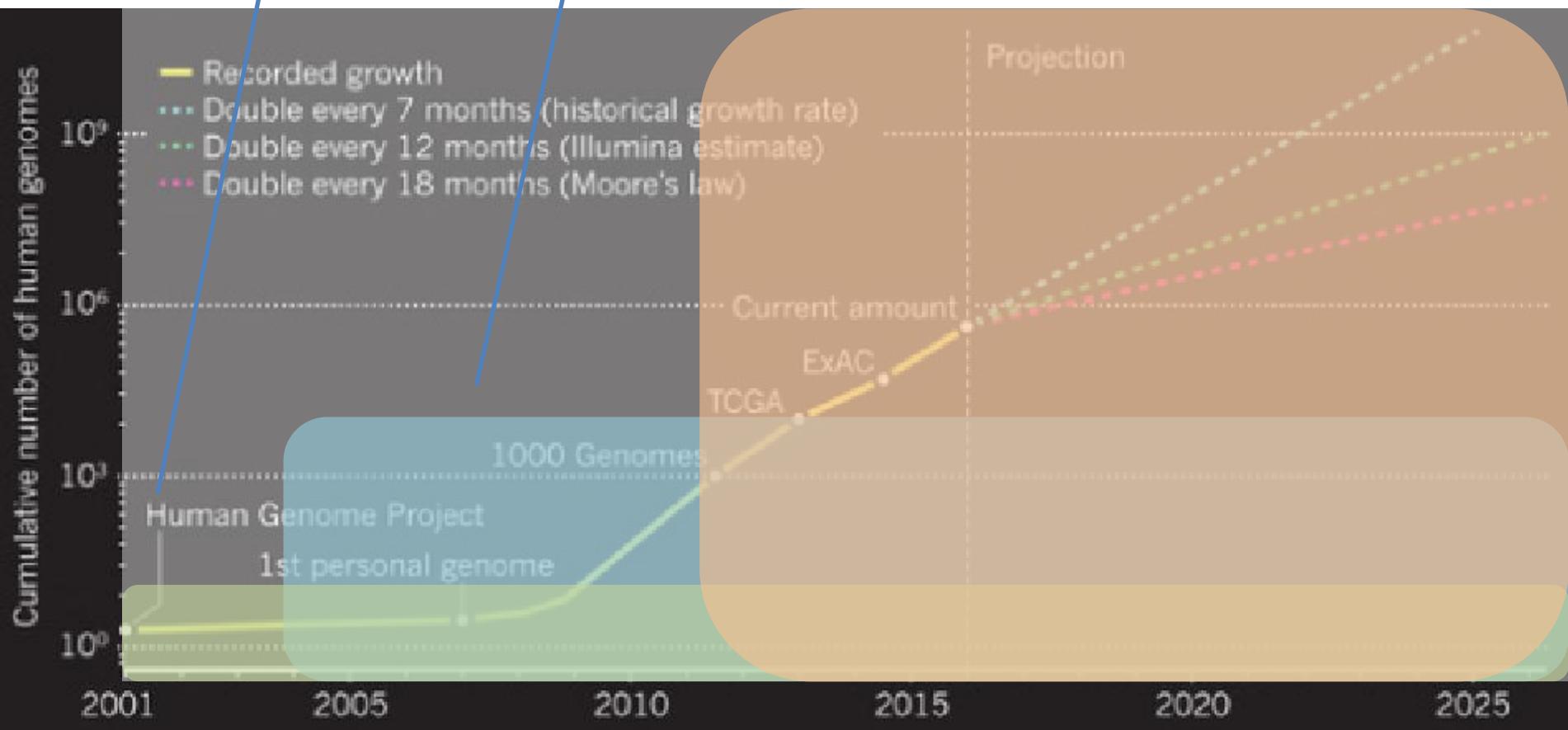


Biostatistics

生物统计和深度学习
处理范围

湿实验
可验证范围

传统生物信息
处理范围



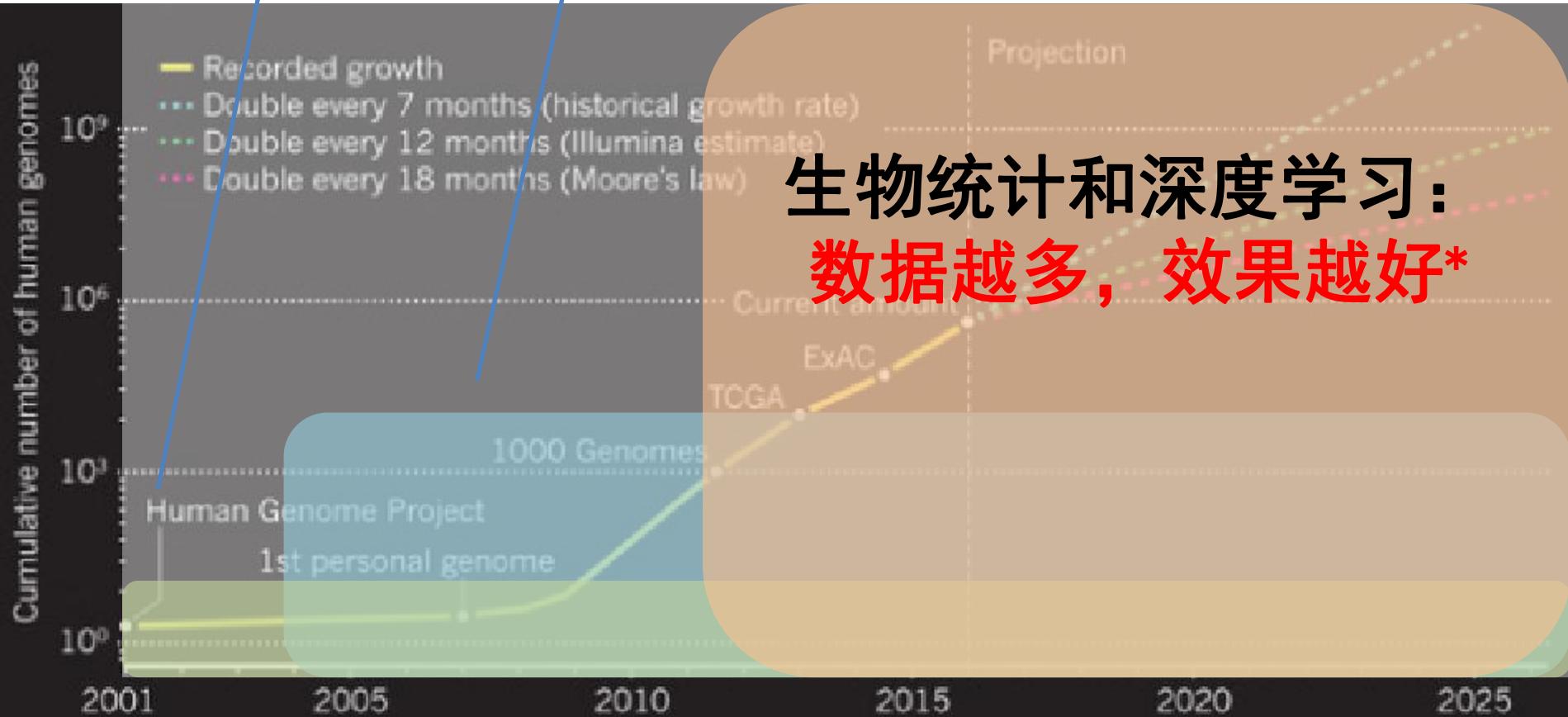
Biostatistics

生物统计和深度学习
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生物统计和深度学习：
数据越多，效果越好*



生物信息学与生物统计学： 两种视角，四种技术，两类方法

- 两种视角
 - 生物学视角
 - 计算视角
- 四种技术
 - 算法
 - 数据
 - 超算
 - 深度学习
- 两类方法
 - 经典软件
 - 核心工具

1. 算法

Donald Knuth (高德纳)



Donald Knuth, the "father of the analysis of algorithms."



The Art of Computer Programming (计算机程序设计艺术)

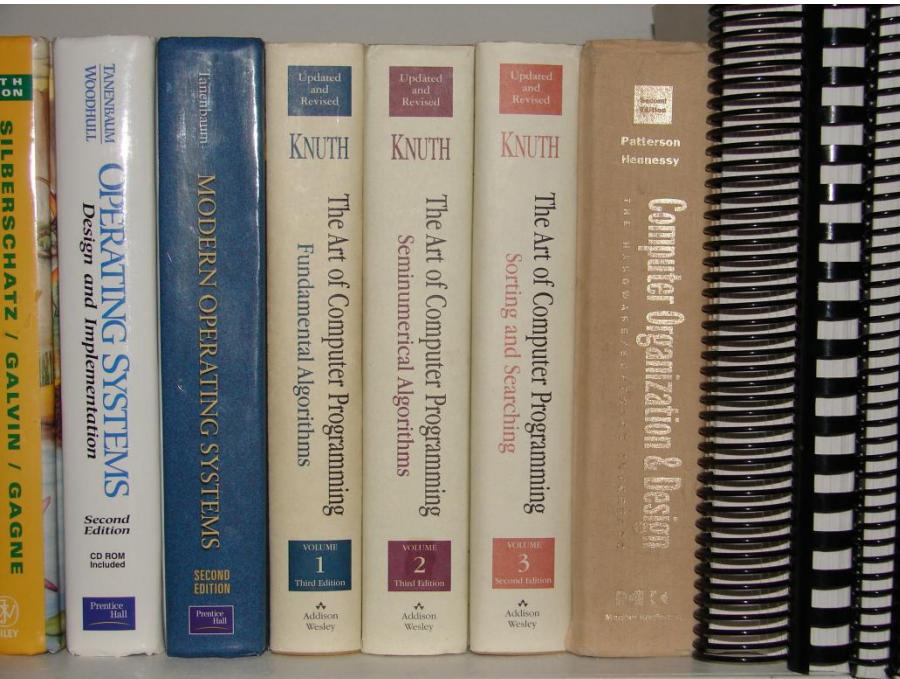
Markup

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The quadratic formula is $-b \pm \sqrt{b^2 - 4ac} \over 2a$ \bye
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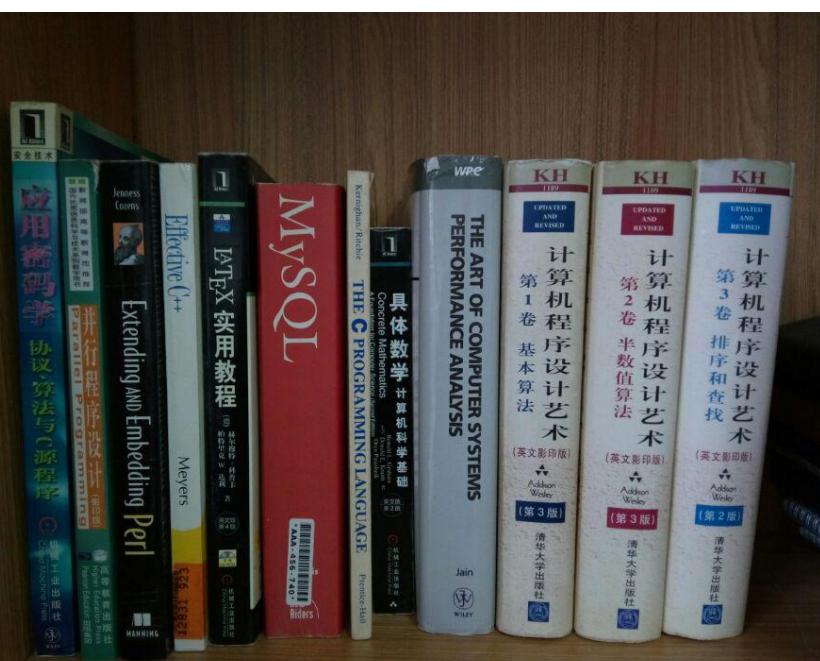
Renders as

$$\text{The quadratic formula is } \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

“生物信息学为算法研究提供了500年的问题” – Don Knuth



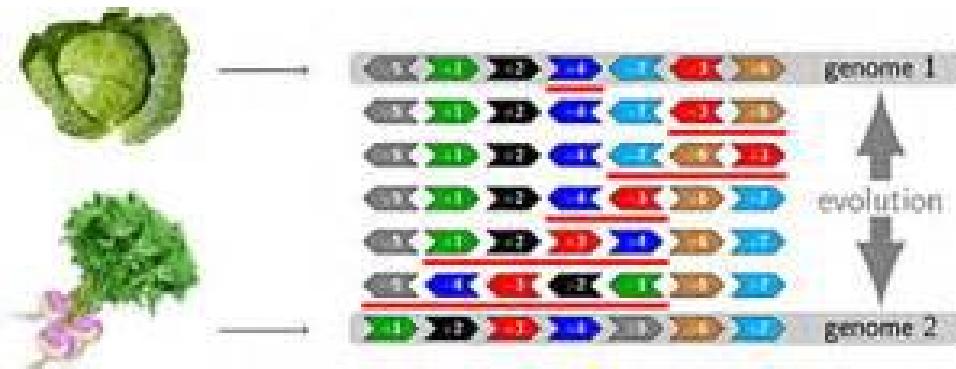
“definitely send me a résumé if you finish this fiendishly difficult book” – Bill Gates



“definitely come to talk about algorithm if you read half of this book” – Kang Ning

Bill Gates (比尔盖茨)

Sorting by reversal problem



比尔盖茨:下个世界首富出自基因检测领域

Discrete Mathematics 27 (1979) 47–57.
© North-Holland Publishing Company

BOUNDS FOR SORTING BY PREFIX REVERSAL

William H. GATES
Microsoft, Albuquerque, New Mexico

Christos H. PAPADIMITRIOU^{*}†
Department of Electrical Engineering, University of California, Berkeley, CA 94720, U.S.A.

Received 18 January 1978
Revised 28 August 1978

For a permutation σ of the integers from 1 to n , let $f(\sigma)$ be the smallest number of reversals that will transform σ to the identity permutation, and let $f(n)$ be the largest such $f(\sigma)$ for all σ in (the symmetric group) S_n . We show that $f(n) \leq (5n + 5)/3$, and that $f(n) \geq 17n/16$ for n a multiple of 16. If, furthermore, each integer is required to participate in an even number of reversed prefixes, the corresponding function $g(n)$ is shown to obey $3n/2 - 1 \leq g(n) \leq 2n + 3$.

1. Introduction

We introduce our problem by the following quotation from [1]

The chef in our place is sloppy, and when he prepares a stack of pancakes they come out all different sizes. Therefore, when I deliver them to a customer, on the way to the table I rearrange them (so that the smallest winds up on top, and so on, down to the largest at the bottom) by grabbing several from the top and flipping them over, repeating this (varying the number I flip) as many times as necessary. If there are n pancakes, what is the maximum number of flips (as a function $f(n)$ of n) that I will ever have to use to rearrange them?

In this paper we derive upper and lower bounds for $f(n)$. Certain bounds were already known. For example, consider any stack of pancakes. An *adjacency* in this stack is a pair of pancakes that are adjacent in the stack, and such that no other pancake has size intermediate between the two. If the largest pancake is on the bottom, this also counts as one extra adjacency. Now, for $n \geq 4$ there are stacks of n pancakes that have no adjacencies whatsoever. On the other hand, a sorted stack must have all n adjacencies and each move (flip) can create at most one adjacency. Consequently, for $n \geq 4$, $f(n) \geq n$. By elaborating on this argument, M.R. Garey, D.S. Johnson and S. Lin [2] showed that $f(n) \geq n + 1$ for $n \geq 6$.

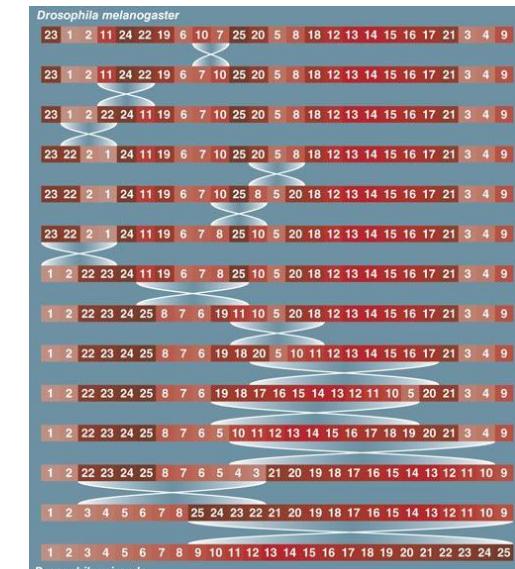
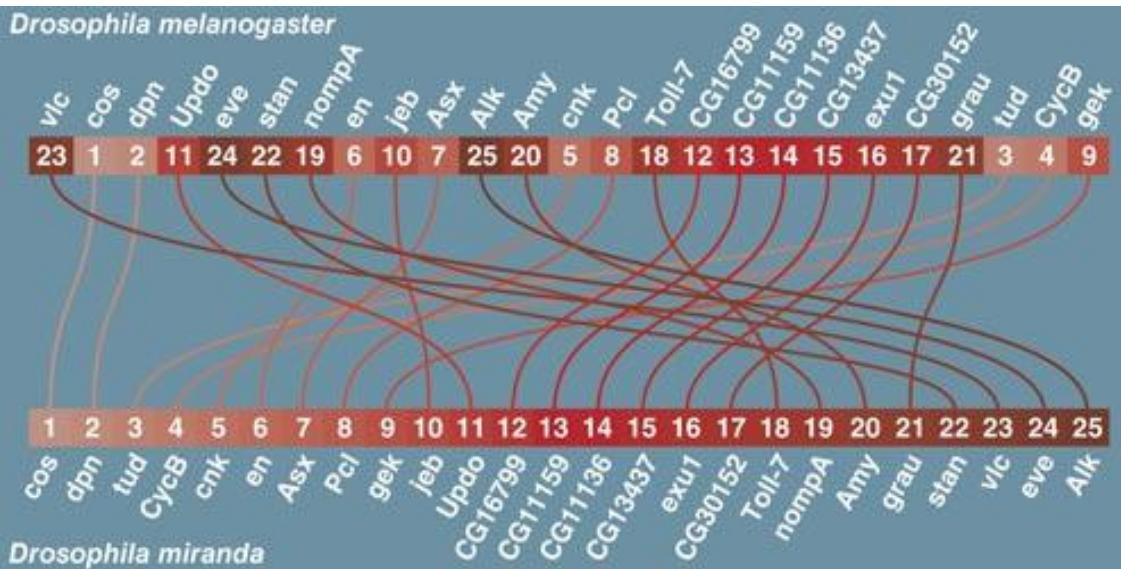
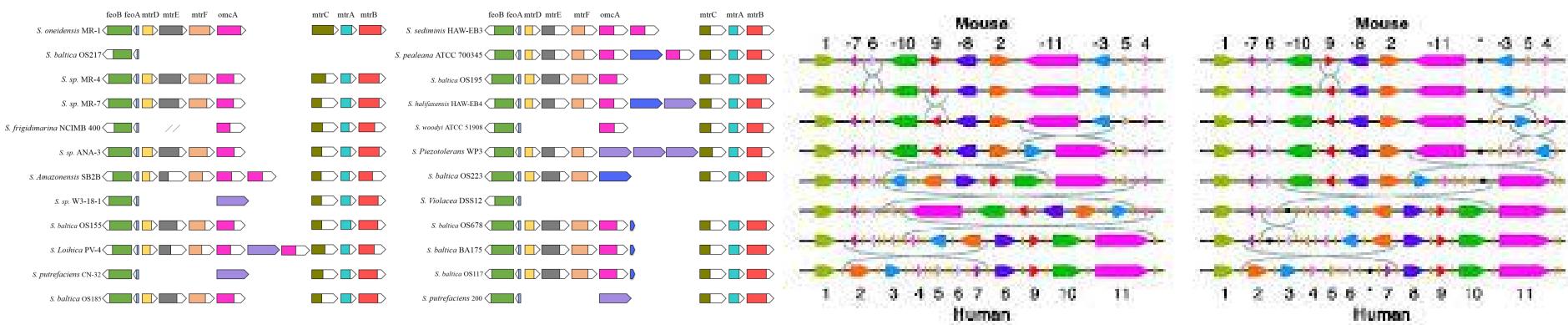
For upper bounds—algorithms, that is—it was known that $f(n) \leq 2n$. This can be seen as follows. Given any stack we may start by bringing the largest pancake on top and then flip the whole stack: the largest pancake is now at the bottom,

* Research supported by NSF Grant MCS 77-01193.

† Current address: Laboratory for Computer Science, Massachusetts Institute of Technology, Cambridge, Ma 02139, USA.

实例

How many reversal steps for this REAL case?



Ming Li (李明) & Tao Jiang (姜涛)



SIAM J. COMPUT.
Vol. 24, No. 5, pp. 1122–1139, October 1995

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012

ON THE APPROXIMATION OF SHORTEST COMMON SUPERSEQUENCES AND LONGEST COMMON SUBSEQUENCES*

TAO JIANG[†] AND MING LI[‡]

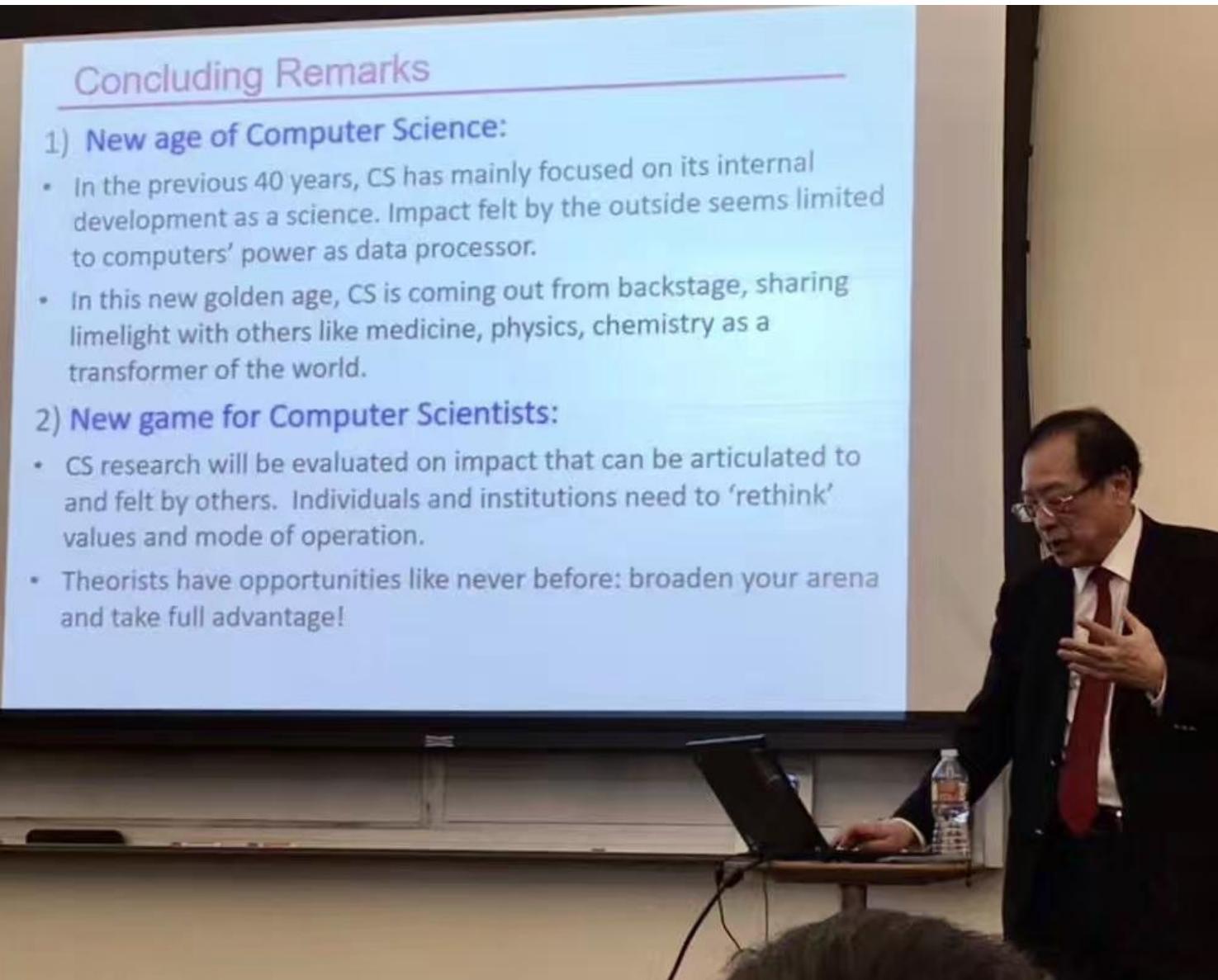
Abstract. The problems of finding shortest common supersequences (SCS) and longest common subsequences (LCS) are two well-known NP-hard problems that have applications in many areas, including computational molecular biology, data compression, robot motion planning, and scheduling, text editing, etc. A lot of fruitless effort has been spent in searching for good approximation algorithms for these problems. In this paper, we show that these problems are inherently hard to approximate in the worst case. In particular, we prove that (i) SCS does not have a polynomial-time linear approximation algorithm unless $P = NP$; (ii) There exists a constant $\delta > 0$ such that, if SCS has a polynomial-time approximation algorithm with ratio $\log^\delta n$, where n is the number of input sequences, then NP is contained in $DTIME(2^{\text{polylog } n})$; (iii) There exists a constant $\delta > 0$ such that, if LCS has a polynomial-time approximation algorithm with performance ratio n^δ , then $P = NP$. The proofs utilize the recent results of Arora et al. [*Proc. 23rd IEEE Symposium on Foundations of Computer Science*, 1992, pp. 14–23] on the complexity of approximation problems.

In the second part of the paper, we introduce a new method for analyzing the average-case performance of algorithms for sequences, based on Kolmogorov complexity. Despite the above nonapproximability results, we show that near optimal solutions for both SCS and LCS can be found on the average. More precisely, consider a fixed alphabet Σ and suppose that the input sequences are generated randomly according to the uniform probability distribution and are of the same length n . Moreover, assume that the number of input sequences is polynomial in n . Then, there are simple greedy algorithms which approximate SCS and LCS with expected additive errors $O(n^{0.707})$ and $O(n^{1/2+\epsilon})$ for any $\epsilon > 0$, respectively.

Incidentally, our analyses also provide tight upper and lower bounds on the expected LCS and SCS lengths for a set of random sequences solving a generalization of another well-known open question on the expected LCS length for two random sequences [K. Alexander, *The rate of convergence of the mean length of the longest common subsequence*, 1992, manuscript], [V. Chvatal and D. Sankoff, *J. Appl. Probab.*, 12 (1975), pp. 306–315], [D. Sankoff and J. Kruskall, eds., *Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison*, Addison-Wesley, Reading, MA, 1983].

Key words. shortest common supersequence, longest common subsequence, approximation algorithm, NP-hardness, average-case analysis, random sequence

姚期智 (Andrew Yao)

A photograph of Andrew Yao, a man with glasses and a dark suit, standing at a podium and gesturing with his hands while speaking. He is positioned to the right of a large projection screen. The screen displays a slide titled "Concluding Remarks" with two main bullet points: "1) New age of Computer Science:" and "2) New game for Computer Scientists:". Each point has several sub-points describing the current state and future challenges of computer science.

Concluding Remarks

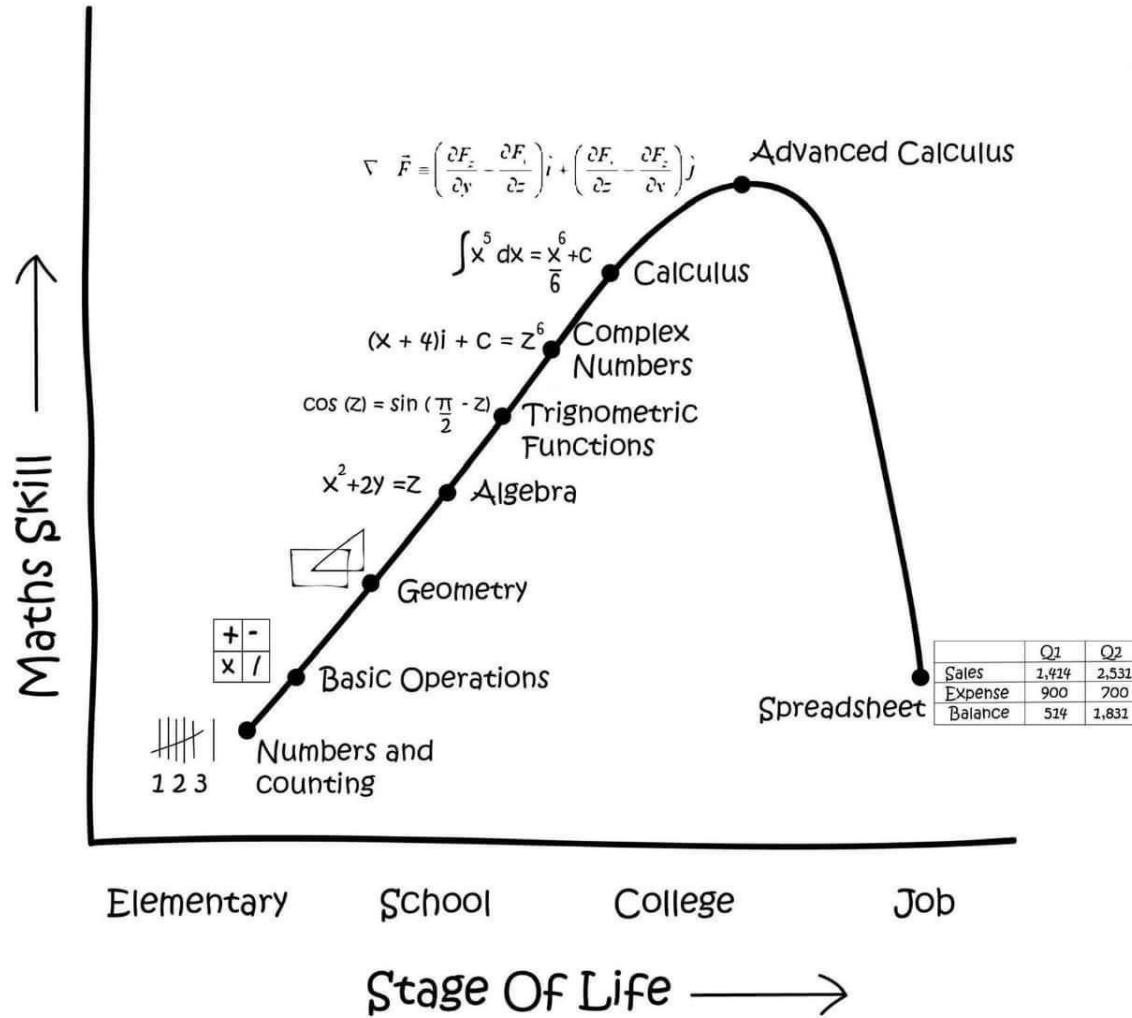
1) **New age of Computer Science:**

- In the previous 40 years, CS has mainly focused on its internal development as a science. Impact felt by the outside seems limited to computers' power as data processor.
- In this new golden age, CS is coming out from backstage, sharing limelight with others like medicine, physics, chemistry as a transformer of the world.

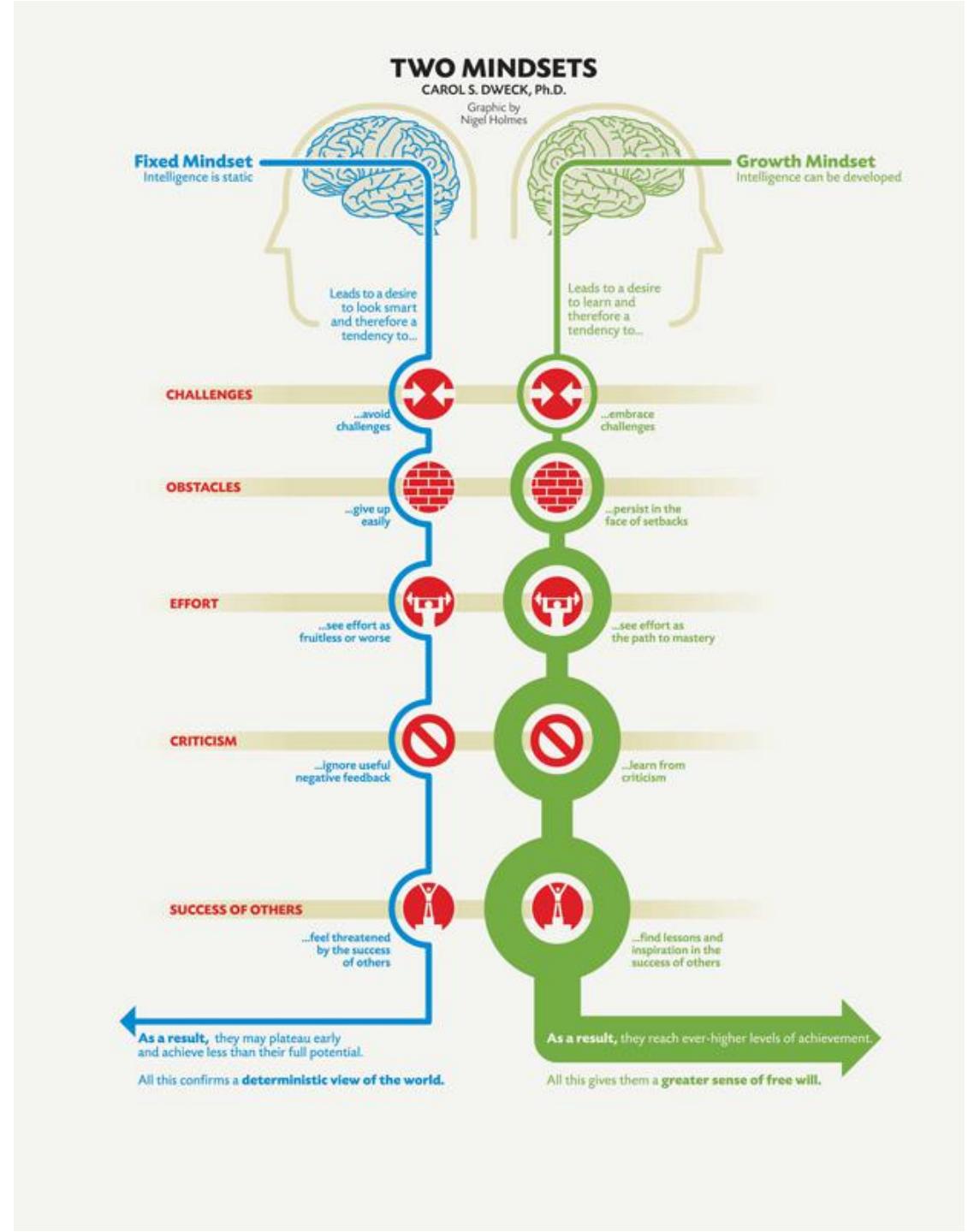
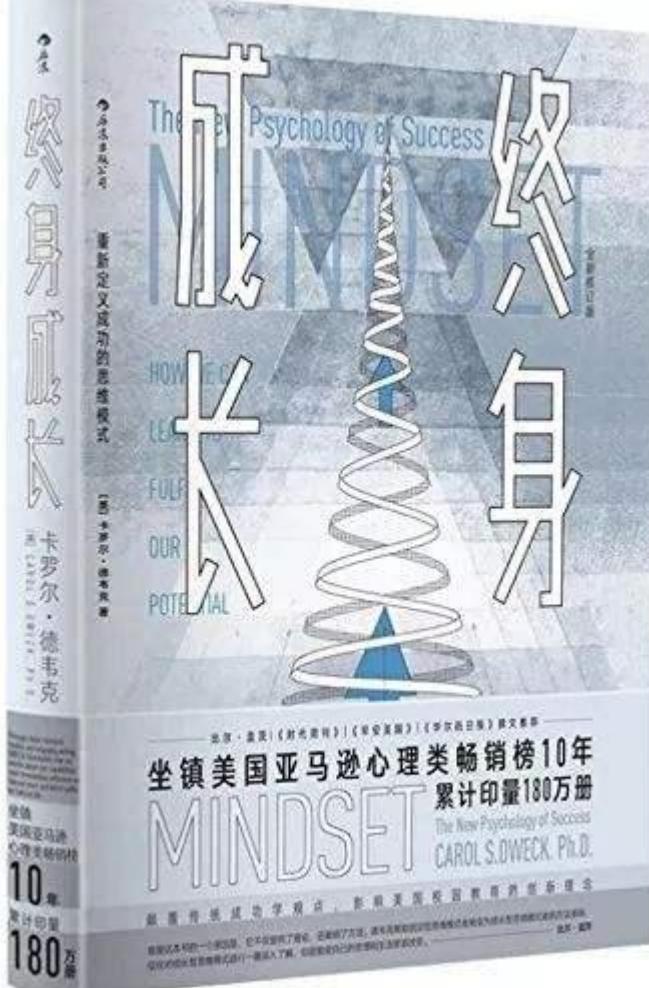
2) **New game for Computer Scientists:**

- CS research will be evaluated on impact that can be articulated to and felt by others. Individuals and institutions need to 'rethink' values and mode of operation.
- Theorists have opportunities like never before: broaden your arena and take full advantage!

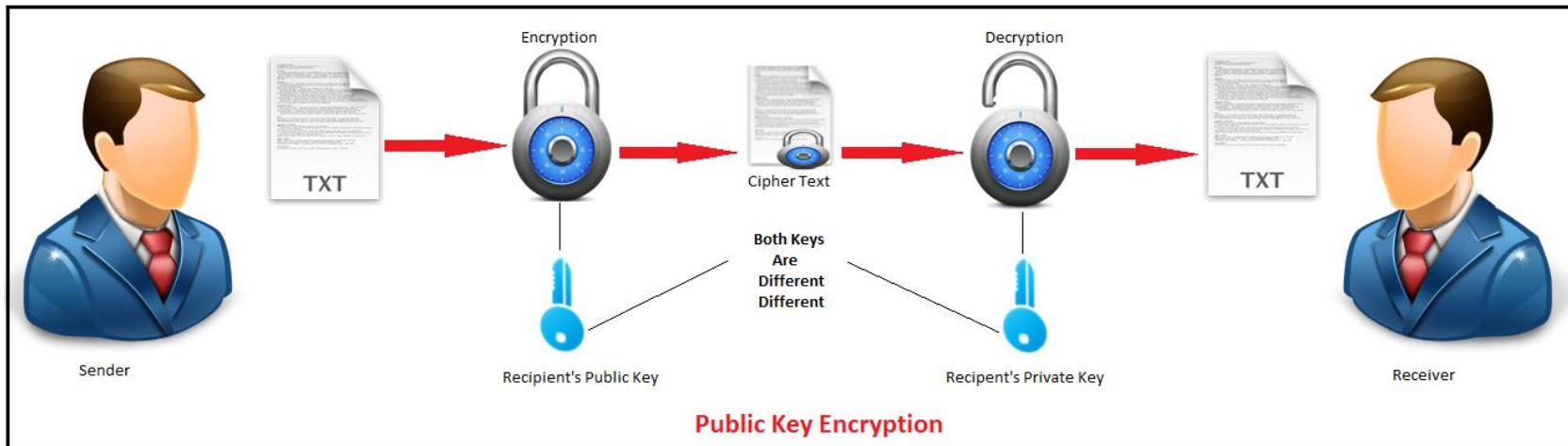
也许觉得算法在今后不会碰到那么多。。。。



终身学习。 . .



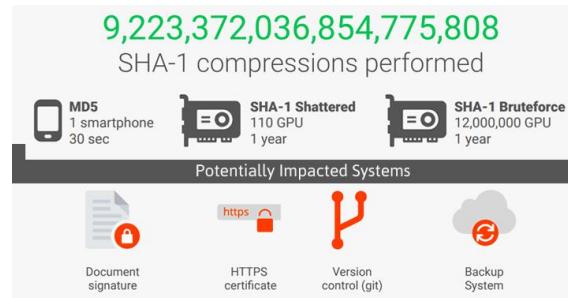
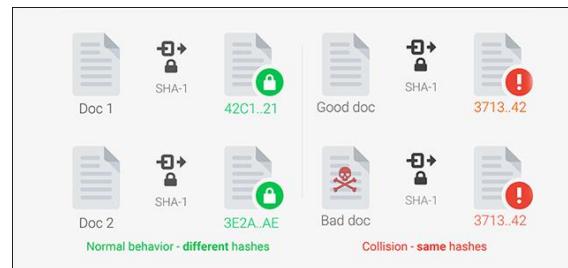
Public key system



RSA algorithm



Adi Shamir, Ron Rivest and Len Adleman
1977



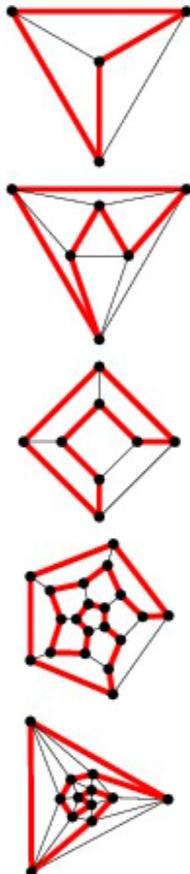
Collision attack



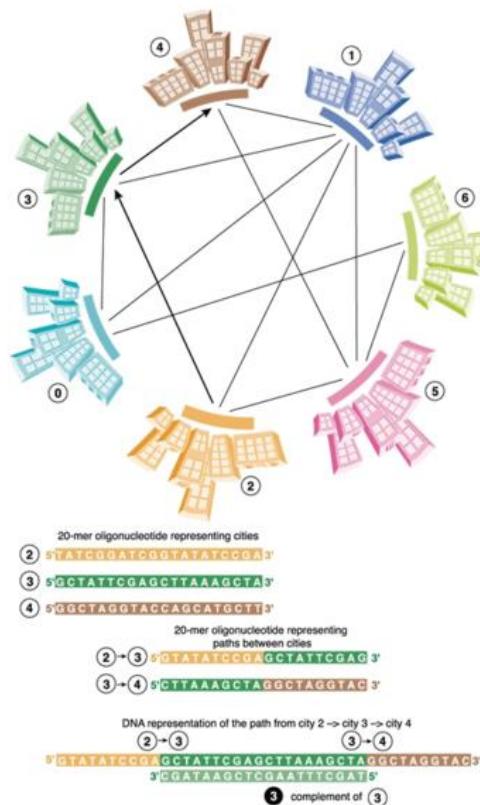
Xiaoyun Wang @ China
2004

Extension: from statistics back to DNA

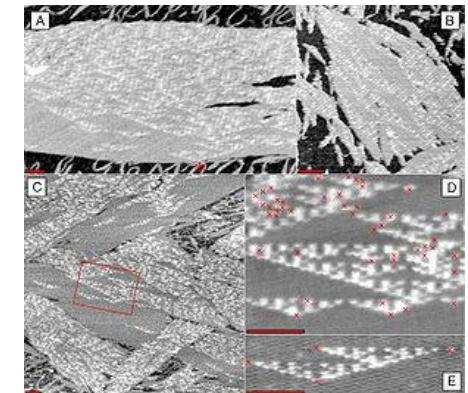
Hamilton path problem



DNA computing



Solution



Leonard Adleman

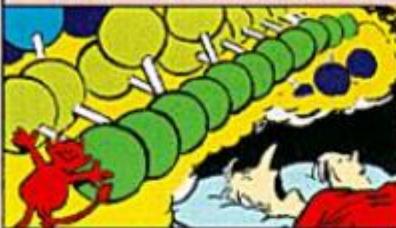


SCIENCE CLASSICS

BY LARRY GONICK



AS COMPUTER COMPONENTS SHRINK YEAR BY YEAR SCIENTISTS DREAM OF THEIR ULTIMATE GOAL A CHEMICAL COMPUTER, WHOSE WORKING PARTS WOULD BE INDIVIDUAL MOLECULES.



BUT THIS HAS REMAINED ONLY A DREAM—UNTIL NOW. LEONARD ADLEMAN OF THE UNIVERSITY OF SOUTHERN CALIFORNIA HAS JUST SHOWN HOW TO DO COMPUTATION USING DNA.



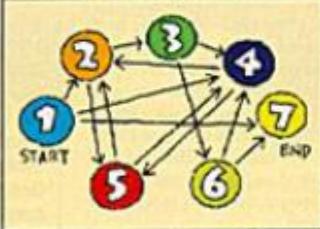
ADLEMAN, A COMPUTER SCIENTIST, CHOSE A TASK THAT REPRESENTS A WHOLE CLASS OF HARD-TO-SOLVE PROBLEMS. COMPUTER GUYS CALL IT THE TRAVELING SALESMAN PROBLEM.



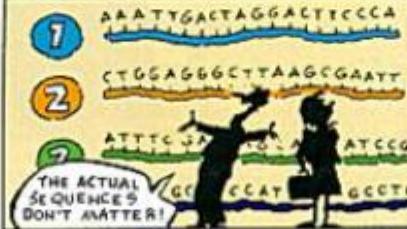
WHEN THE NUMBER OF CITIES IS LARGE—SAY MORE THAN 1000—THIS PROBLEM IS TOO MUCH FOR EVEN THE FASTEST COMPUTER.



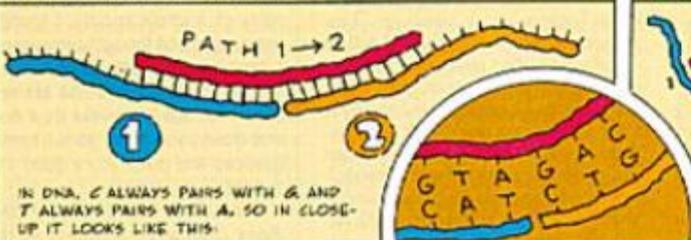
FOR HIS DNA COMPUTATION, APLEMAN
CHOSE THIS SIMPLE ARRANGEMENT
OF 7 CITIES AND #8 STREETS



HE REPRESENTED EACH CITY CHEMICALLY BY A SINGLE STRAND OF DNA 20 BASES LONG, ITS SEQUENCE CHOSEN AT RANDOM.

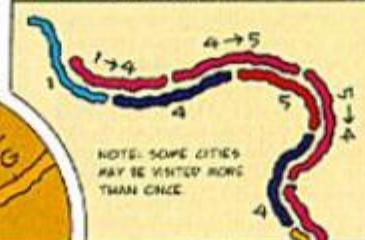


A STREET BETWEEN TWO CITIES IS THE COMPLEMENTARY 2D-BASE STRAND THAT OVERLAPS EACH CITY'S STRAND HALFWAY. THIS STREET LITERALLY JOINS THE TWO CITIES.

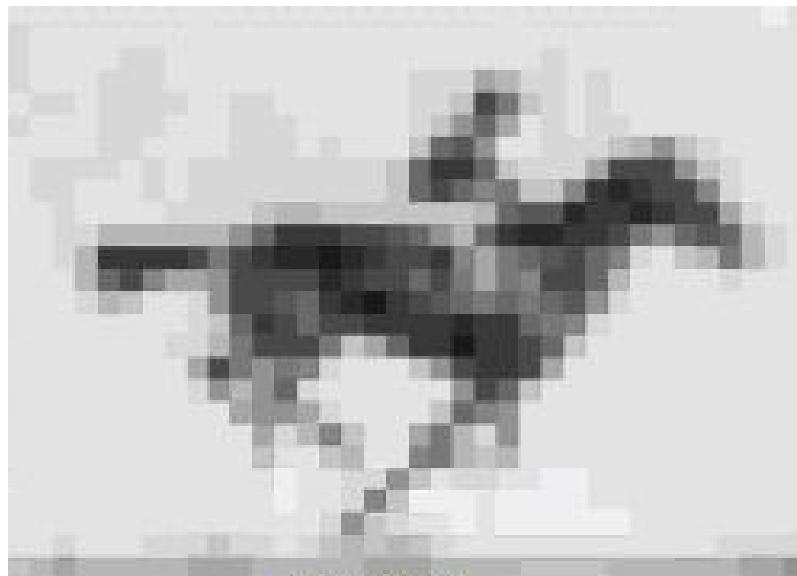
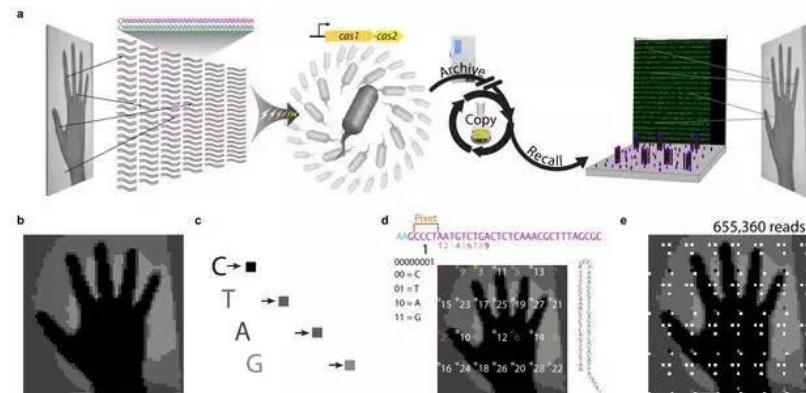
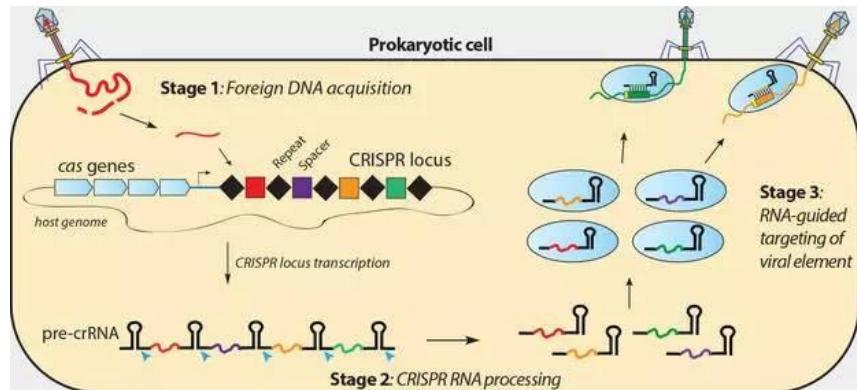


IN DNA, C ALWAYS PAIRS WITH G AND T ALWAYS PAIRS WITH A, SO IN CLOSE-UP IT LOOKS LIKE THIS:

A MULTICITY TOUR BECOMES A PIECE OF DOUBLE-STRANDED DNA, WITH THE CITIES LINKED IN SOME ORDER BY THE STREETS



Understand it, create it!



原始图像

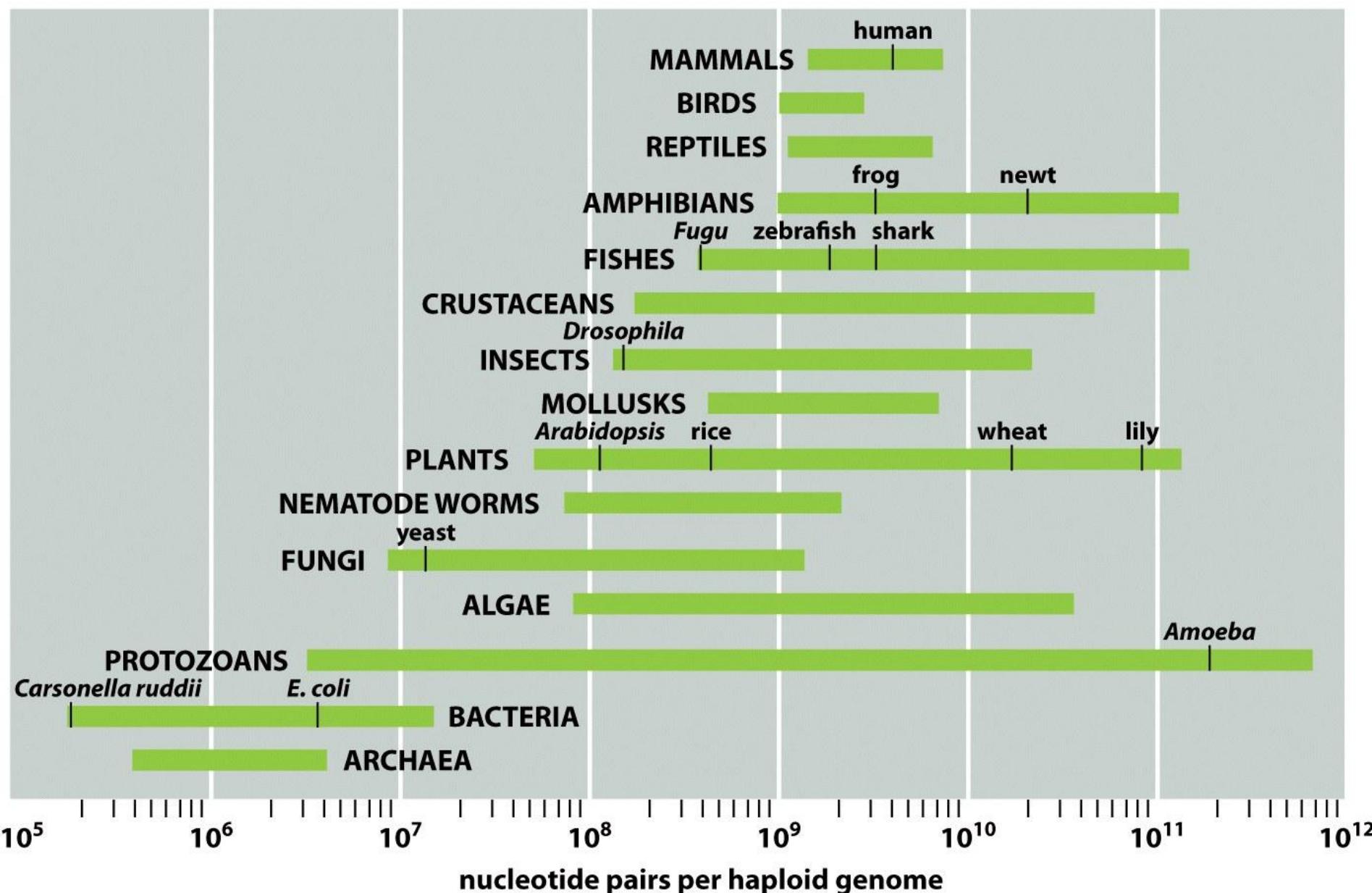


从细菌DNA还原的图像

CRISPR–Cas encoding of a digital movie into the genomes of a population of living bacteria, Nature, 2017

2. 数据

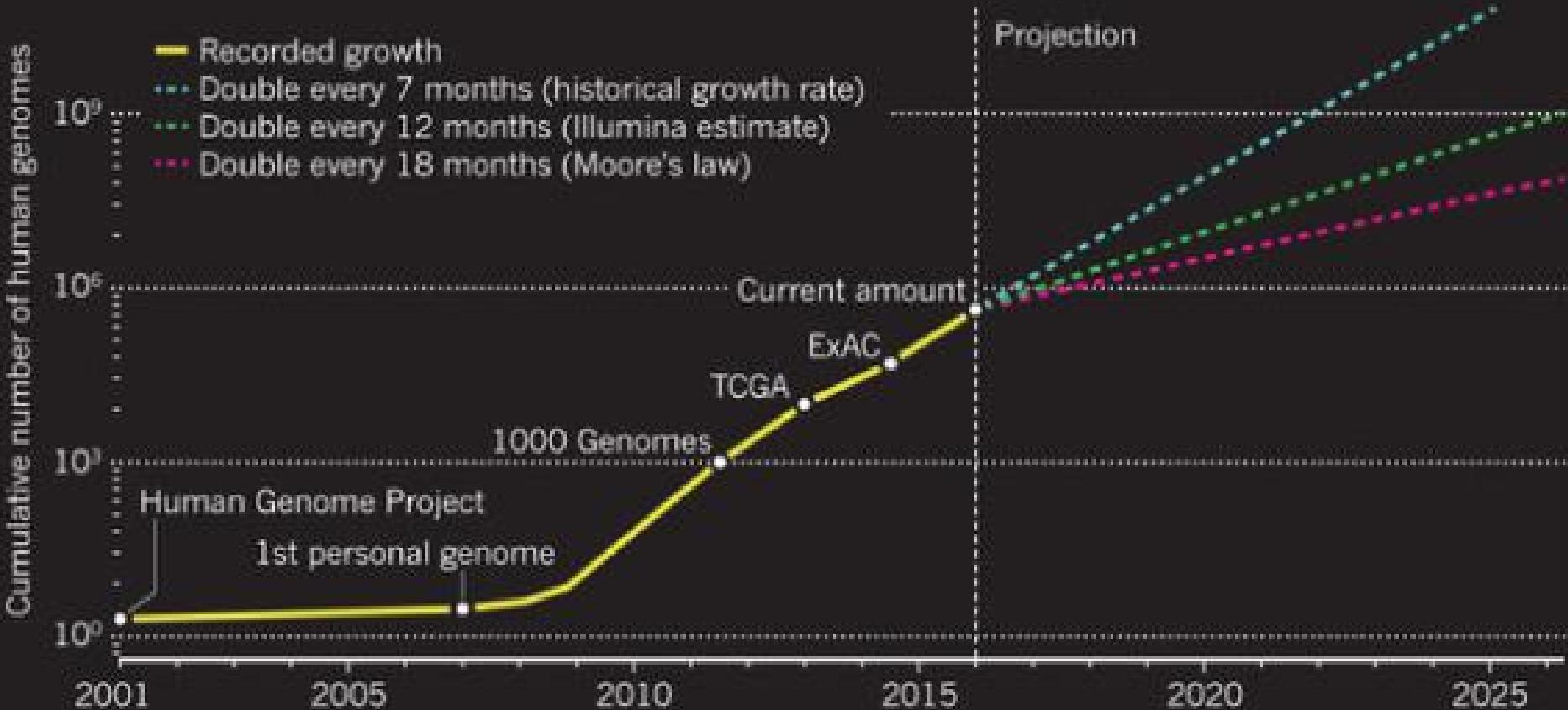
生物数据很大



生物数据很大

DNA SEQUENCING SOARS

Human genomes are being sequenced at an ever-increasing rate. The 1000 Genomes Project has aggregated hundreds of genomes; The Cancer Genome Atlas (TCGA) has gathered several thousand; and the Exome Aggregation Consortium (ExAC) has sequenced more than 60,000 exomes. Dotted lines show three possible future growth curves.

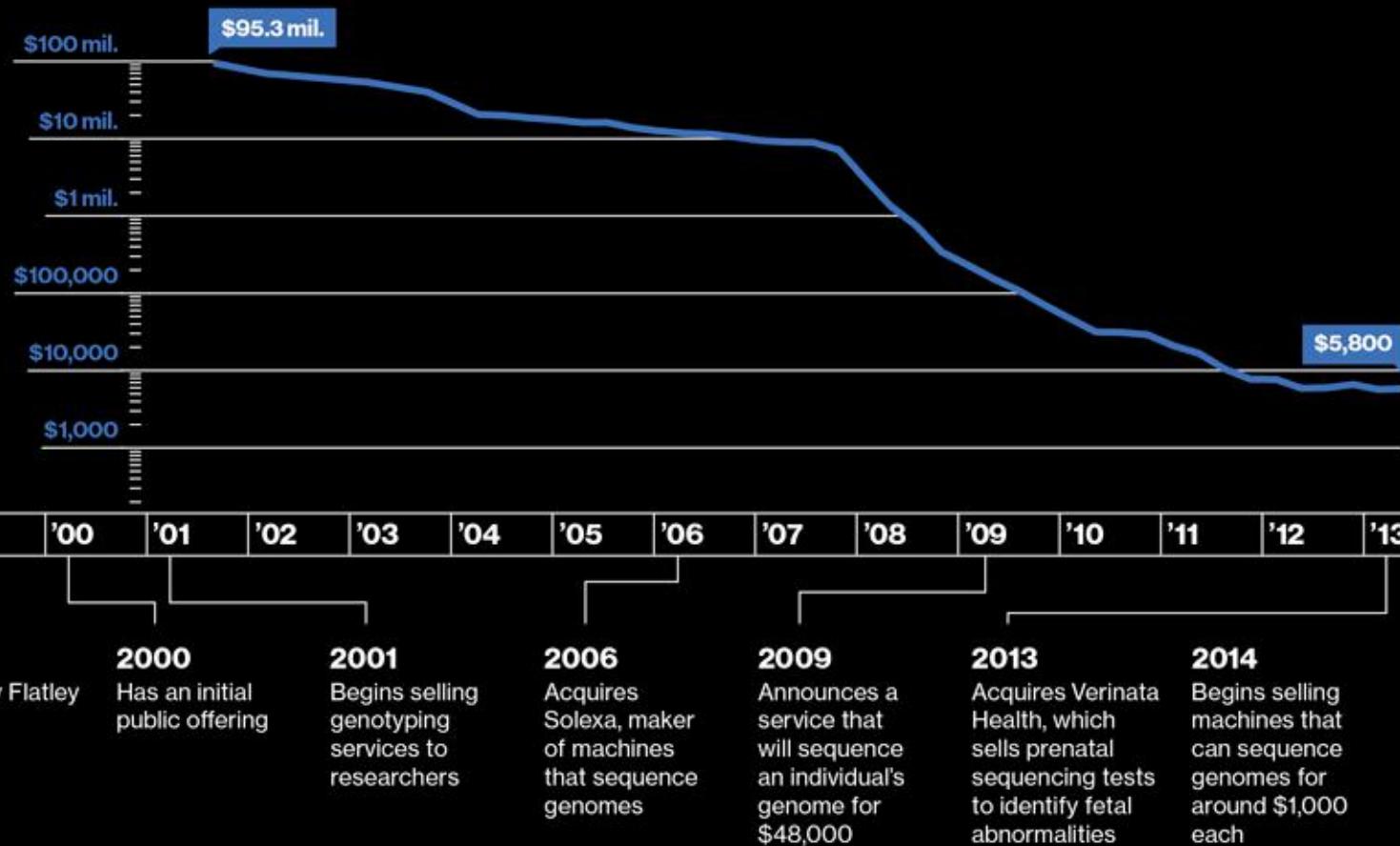


生物数据很大

Genomic Economics

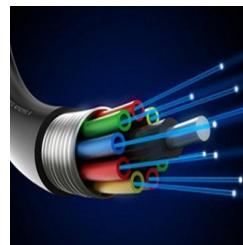
The cost of sequencing has plunged because of technologies that read DNA optically and finish the job in hours rather than days.

COST PER GENOME



制约数据交换的实际是网络

光纤



北京-->武汉： 1Gb/s， 5000元/月

Infiniband



服务器之间： ~50Gb/s， 10万元

快递小哥



北京-->武汉：
 $(4\text{TB} * 20) / (60 * 60 * 24 * 2) = 463\text{MB/s} = \text{3.7Gb/s}$, 200元

他可以多装点，而且次日达可以更快的。。。

3. 超算

超级计算机平台

TOP 10 Sites for June 2017

For more information about the sites and systems in the list, click on the links or view the complete list.

[1-100](#) [101-200](#) [201-300](#) [301-400](#) [401-500](#)

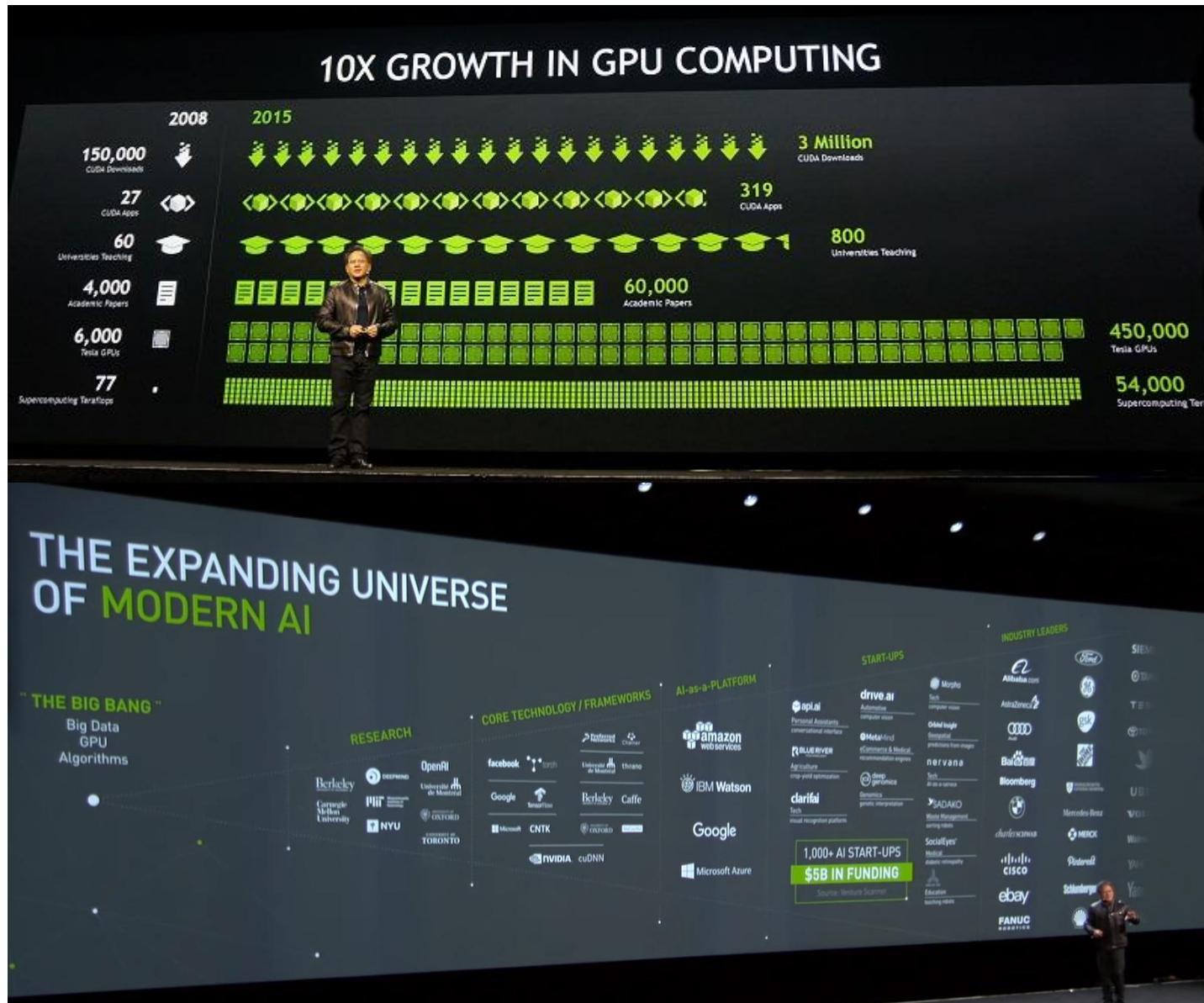
Rank	System	Cores	Rmax [TFlop/s]	Rpeak [TFlop/s]	Power (kW)
1	Sunway TaihuLight - Sunway MPP, Sunway SW26010 260C 1.45GHz, Sunway , NRCPC National Supercomputing Center in Wuxi China	10,649,600	93,014.6	125,435.9	15,371
2	Tianhe-2 (MilkyWay-2) - TH-IVB-FEP Cluster, Intel Xeon E5-2692 12C 2.200GHz, TH Express-2, Intel Xeon Phi 31S1P , NUDT National Super Computer Center in Guangzhou China	3,120,000	33,862.7	54,902.4	17,808
3	Piz Daint - Cray XC50, Xeon E5-2690v3 12C 2.6GHz, Aries interconnect , NVIDIA Tesla P100 , Cray Inc. Swiss National Supercomputing Centre (CSCS) Switzerland	361,760	19,590.0	25,326.3	2,272
4	Titan - Cray XK7, Opteron 6274 16C 2.200GHz, Cray Gemini interconnect, NVIDIA K20x , Cray Inc. DOE/SC/Oak Ridge National Laboratory United States	560,640	17,590.0	27,112.5	8,209
5	Sequoia - BlueGene/Q, Power BQC 16C 1.60 GHz, Custom , IBM DOE/NNSA/LLNL United States	1,572,864	17,173.2	20,132.7	7,890
6	Cori - Cray XC40, Intel Xeon Phi 7250 68C 1.4GHz, Aries interconnect , Cray Inc. DOE/SC/LBNL/NERSC United States	622,336	14,014.7	27,880.7	3,939
7	Oakforest-PACS - PRIMERGY CX1640 M1, Intel Xeon Phi 7250 68C 1.4GHz, Intel Omni-Path , Fujitsu Joint Center for Advanced High Performance Computing Japan	556,104	13,554.6	24,913.5	2,719
8	K computer, SPARC64 VIIIfx 2.0GHz, Tofu interconnect , Fujitsu RIKEN Advanced Institute for Computational Science (AICS) Japan	705,024	10,510.0	11,280.4	12,660

超级计算机平台

Tianhe-2



GPU计算



GPU计算



PLATFORMS ▾ DEVELOPERS ▾ COMMUNITY ▾ SHOP DRIVERS ▾ SUPPORT ABOUT NVIDIA ▾

TESLA

NVIDIA Home > Products > High Performance Computing > Industry Applications > Bioinformatics & Life Sciences

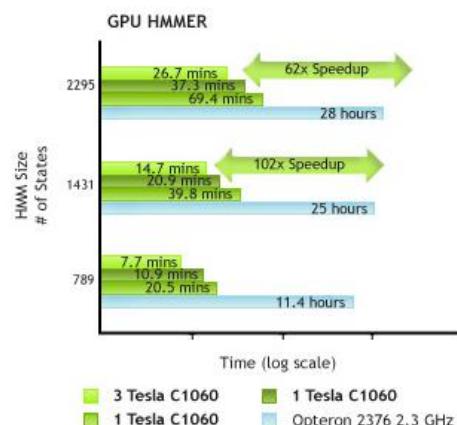
Subscribe

GPU APPLICATIONS

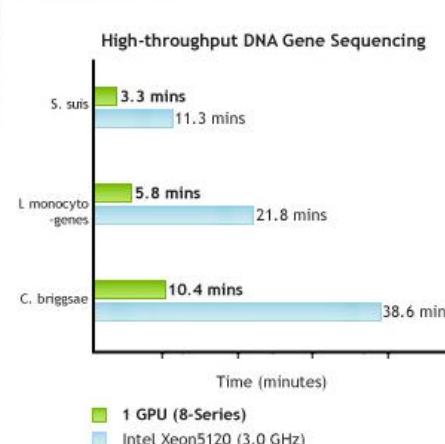
Transforming computational research and engineering

BIOINFORMATICS AND LIFE SCIENCES

Sequencing and protein docking are very compute-intensive tasks that see a large performance benefit by using a CUDA-enabled GPU. There is quite a bit of ongoing work on using GPUs for a range of Bioinformatics and life sciences codes.



Accelerating HMMER using GPUs
Scalable Informatics



MUMmerGPU: High-throughput DNA sequence alignment using GPUs
Schatz, et al

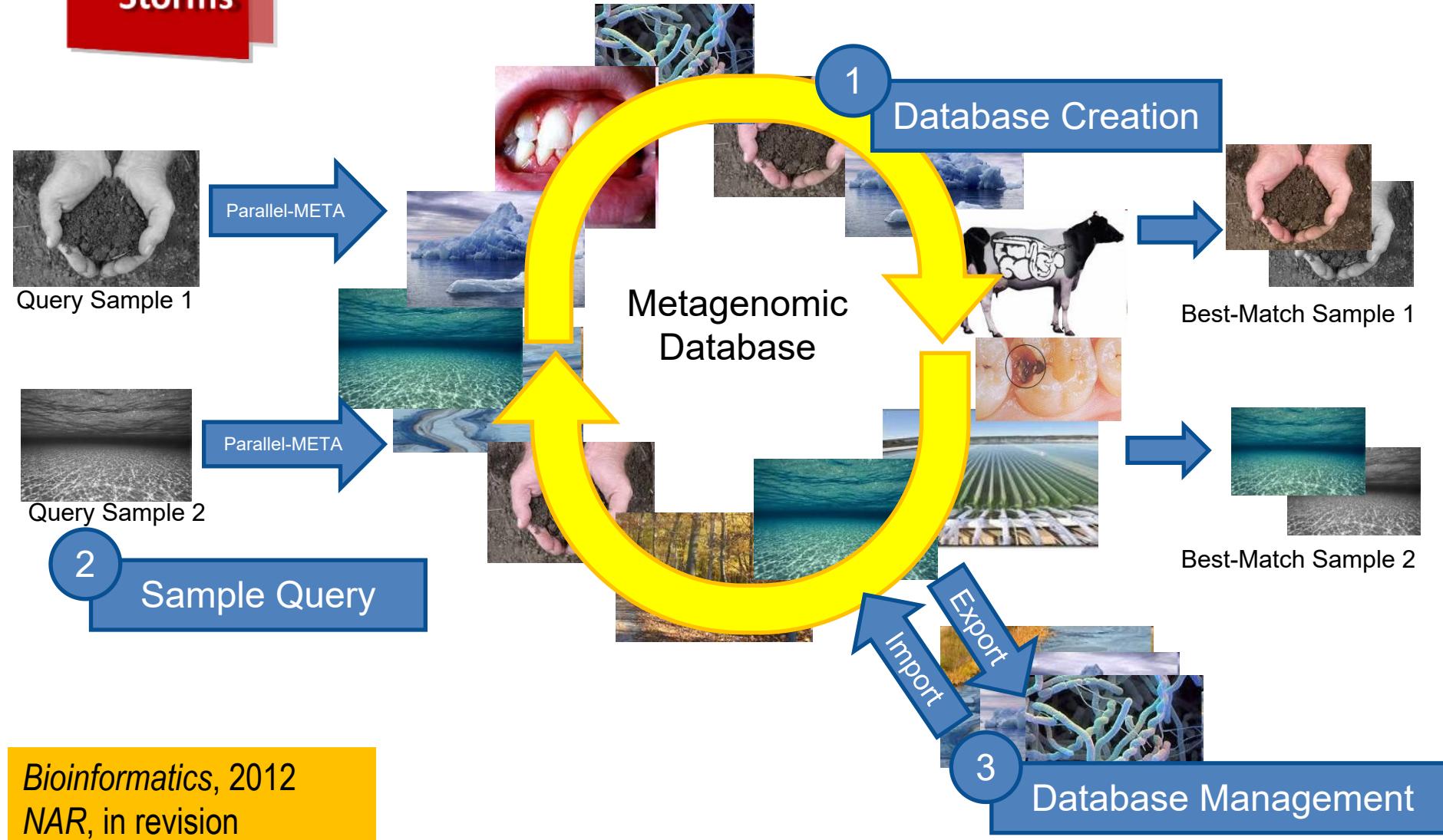
Meta-Storms

高性能的生物计算（蓝色）

HPC



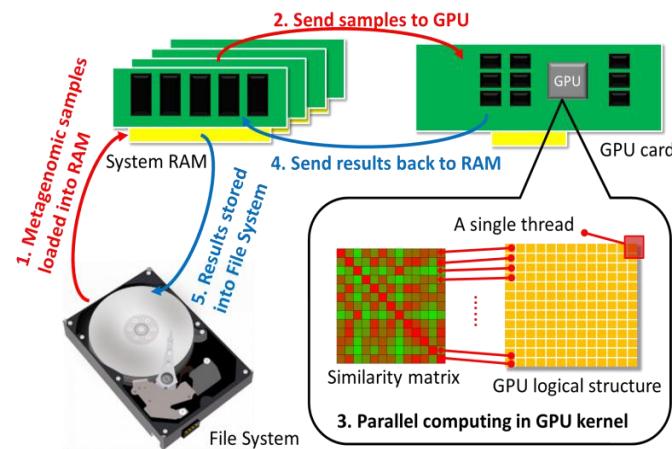
利用先进的数据库和索引技术处理群落比较和搜索



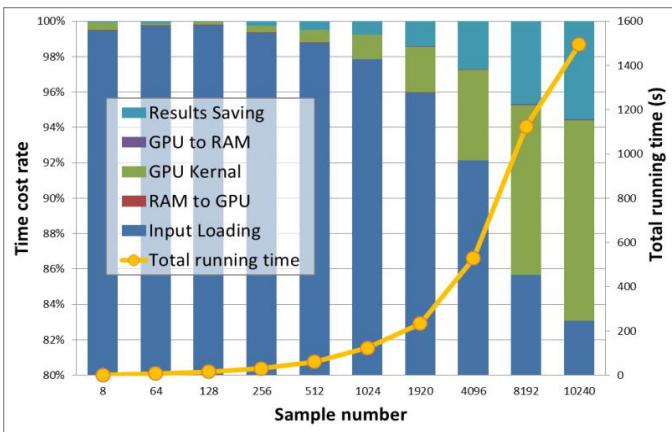
Meta-Storms

高性能的生物计算（蓝色）

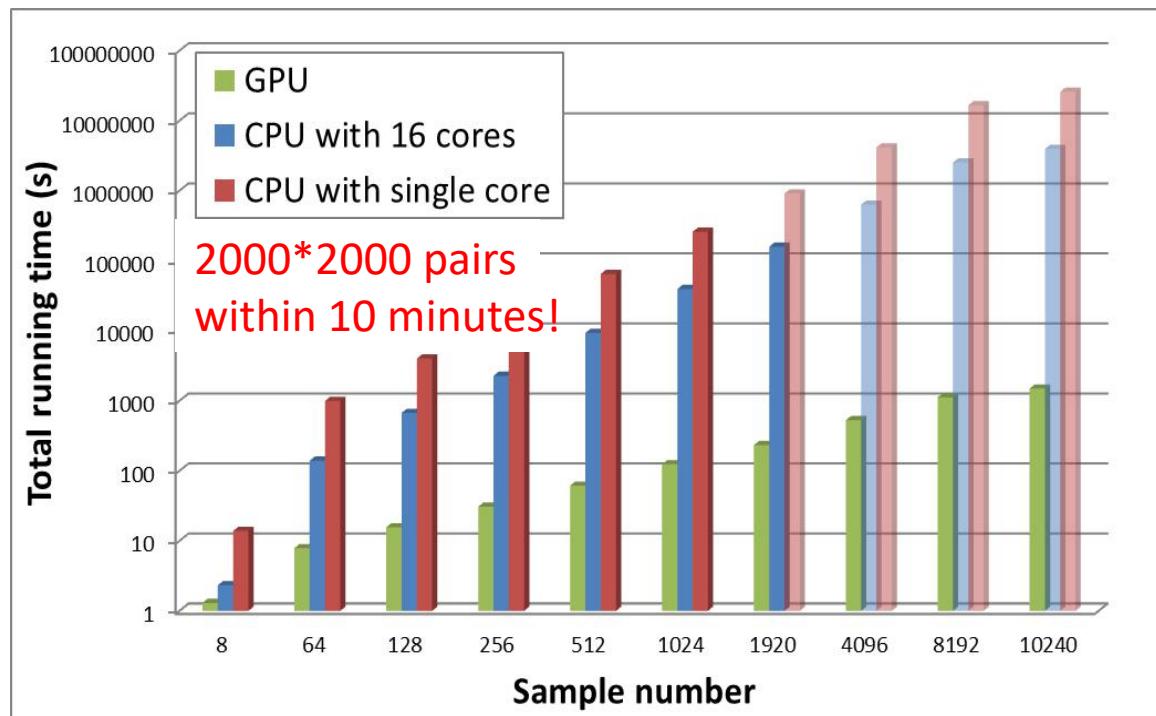
HPC



利用并行计算技术
加速**大规模群落比
较和搜索**

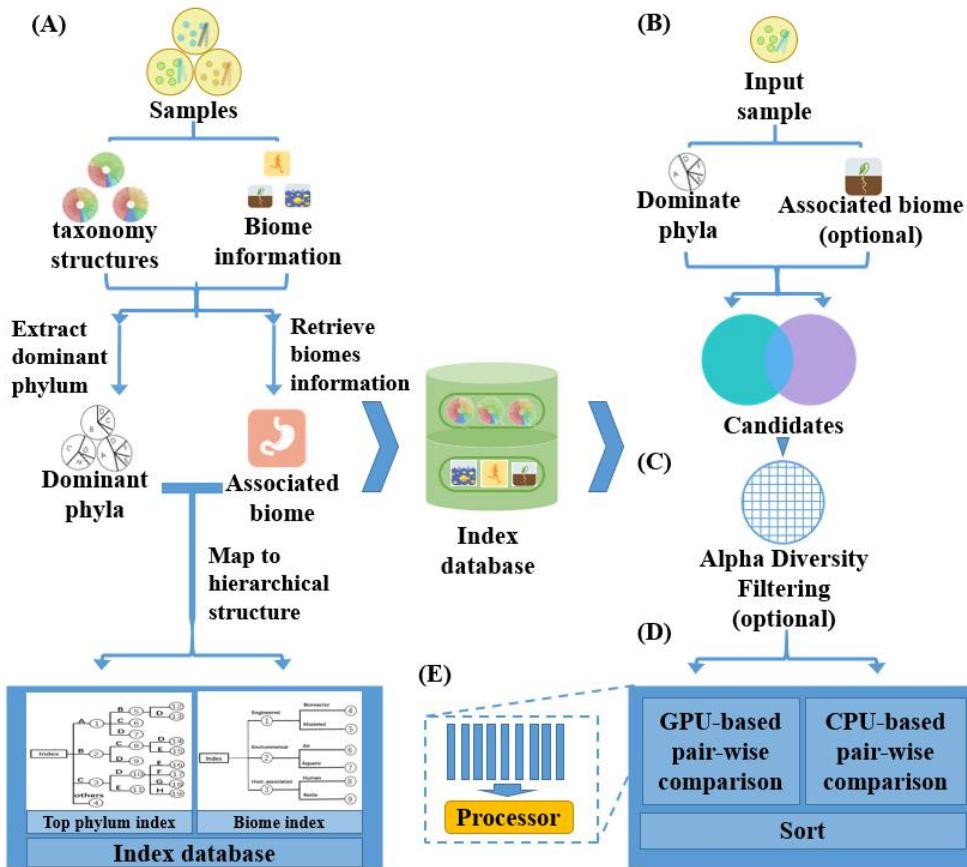


Data source: MG-RAST database

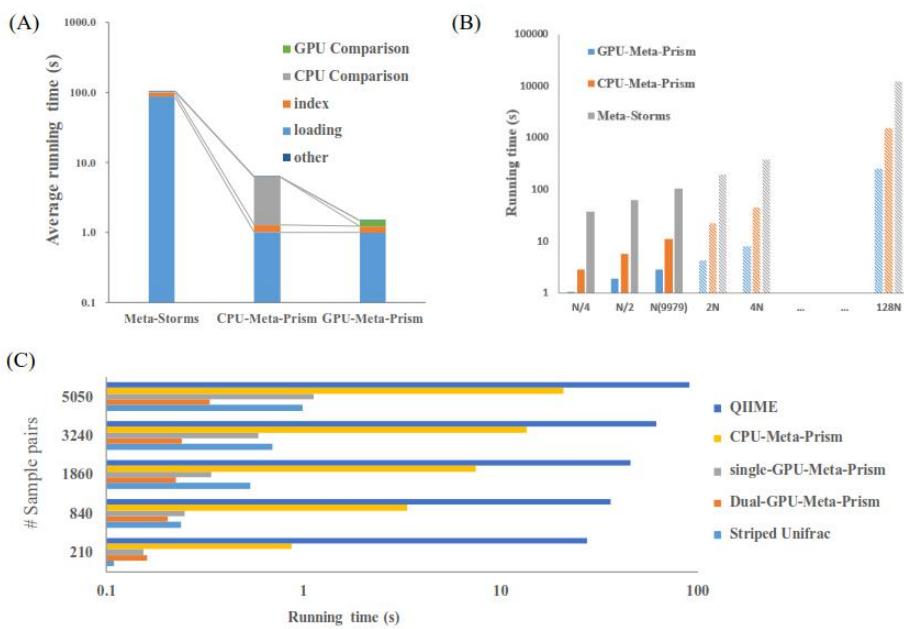


Meta-Prism

高性能的生物计算（蓝色）
HPC



利用双引擎计算，同时提高准确性和运行速度



4. 深度学习

Deep Learning



数据很重要！



算法更重要！

$$\begin{aligned}\frac{d\mathcal{L}}{dW} &= \sum_i \frac{d\mathcal{L}}{da_i} \frac{da_i}{dz_i} \frac{dz_i}{dW} \\&= \frac{1}{N} \sum_i - \left(\frac{y_i}{a_i} - \frac{1-y_i}{1-a_i} \right) \cdot \frac{\exp(-z)}{(1+\exp(-z))^2} \cdot x_i \\&\quad \cancel{\frac{1}{N} \sum_i - \left(\frac{y_i - a_i}{a_i(1-a_i)} \right) \cdot a_i(1-a_i) \cdot x_i} \\&= \frac{1}{N} \sum_i -(y_i - a_i) \cdot x_i\end{aligned}$$

AS WE CAN SEE HERE,
THIS IS OBVIOUS!

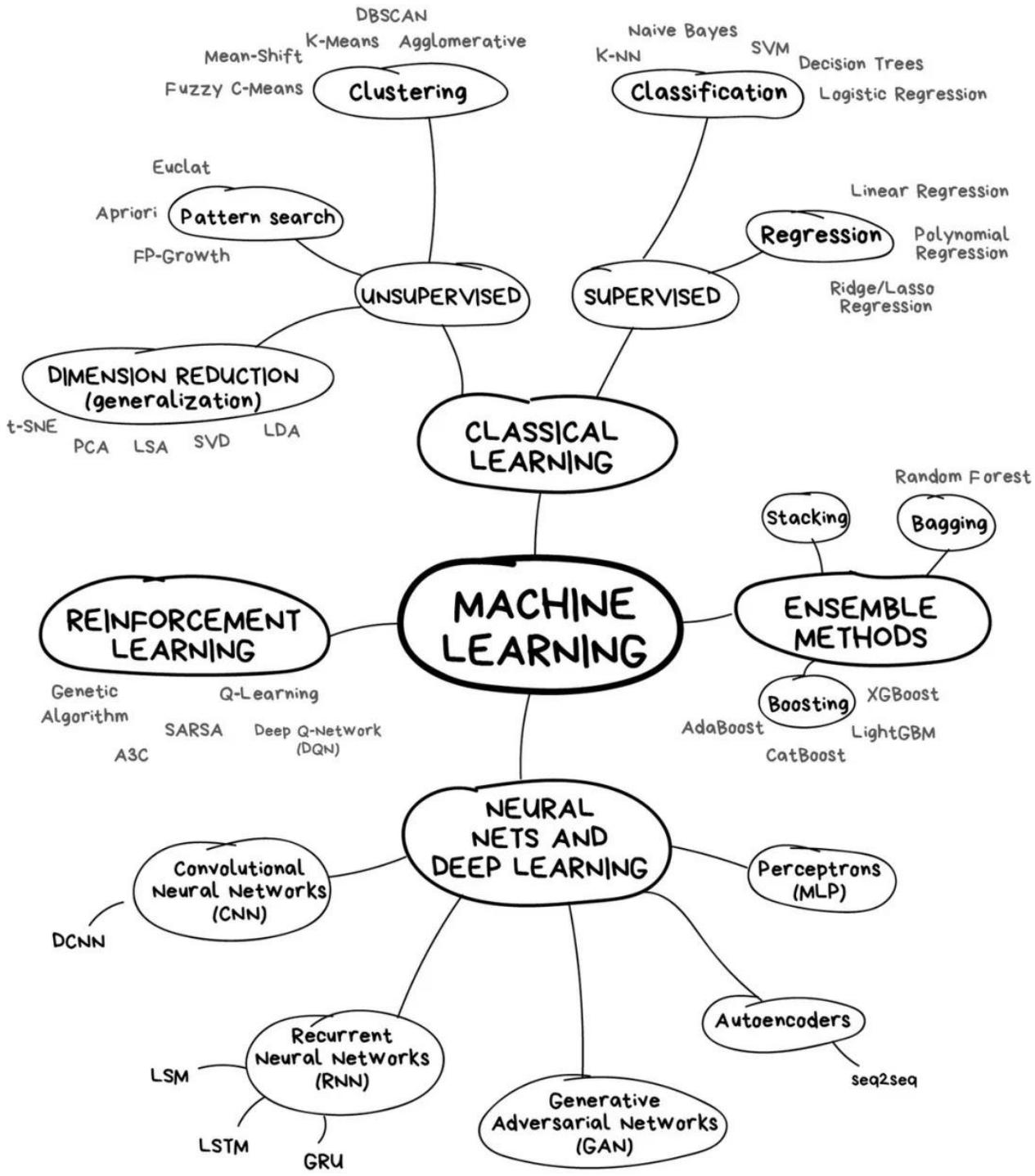


PROGRAMMERS ARE PROGRAMMING!
DATASCIENCE!
PROFESSION OF FUTURE!
IN THE NEXT FIVE YEARS...
EXPONENTIAL GROWTH!!!
SMART MACHINES!
A-A-A-A-A-A-A-A-A-AAA!!!!!!

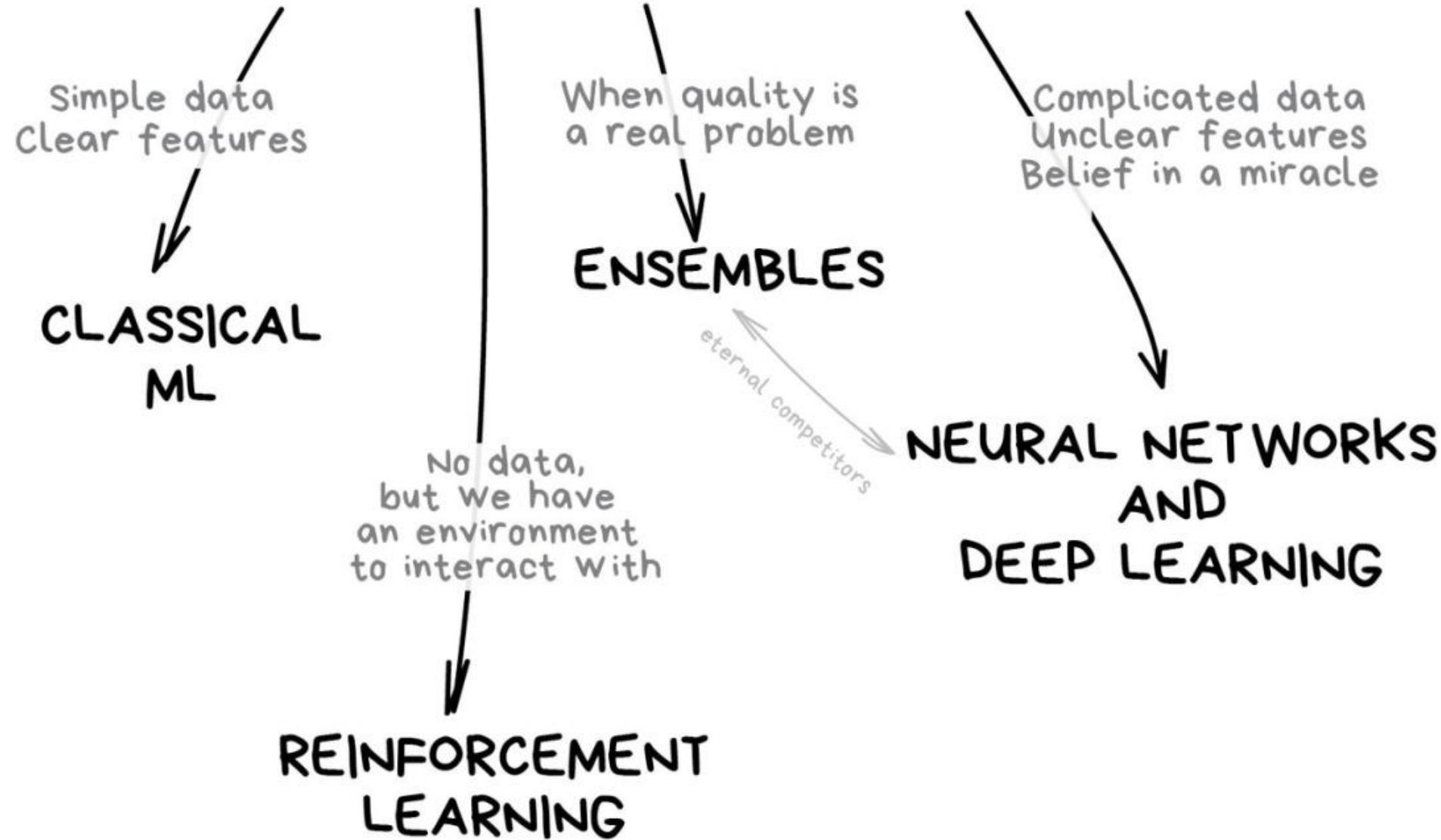




TWO TYPES OF ARTICLES ABOUT MACHINE LEARNING



THE MAIN TYPES OF MACHINE LEARNING



CLASSICAL MACHINE LEARNING

Data is pre-categorized or numerical

SUPERVISED

Predict a category

Predict a number

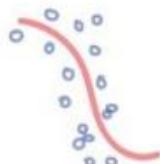
CLASSIFICATION

«Divide the socks by color»



REGRESSION

«Divide the ties by length»



Data is not labeled in any way

UNSUPERVISED

Divide by similarity

CLUSTERING

«Split up similar clothing into stacks»



Identify sequences

ASSOCIATION

«Find what clothes I often wear together»



DIMENSION REDUCTION (generalization)

«Make the best outfits from the given clothes»



hey	... 1829
I'm	... 1710
no	... 1191
where	... 1012
you	... 985
speak	... 873
learn	... 747
one	... 739

good letters

viagra	... 1552
casino	... 1492
100%	... 1320
credit	... 1184
sale	... 985
press	... 873
free	... 747
enlarge	... 739

spam letters

«KITTY»

13 times

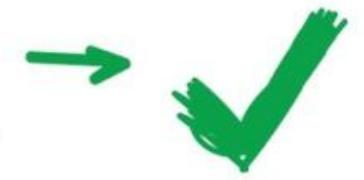
672 times

THE SIMPLEST SPAM-FILTER

(used until 2010)

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

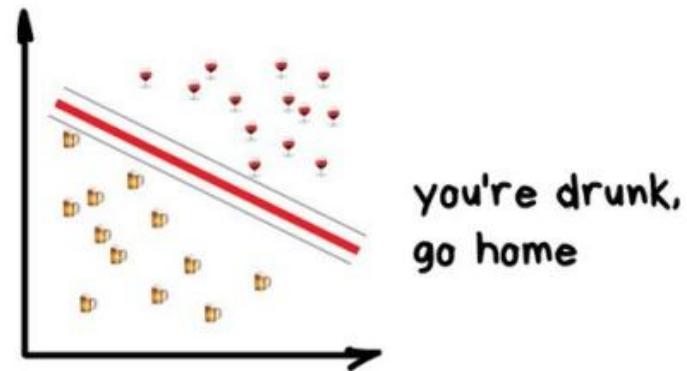
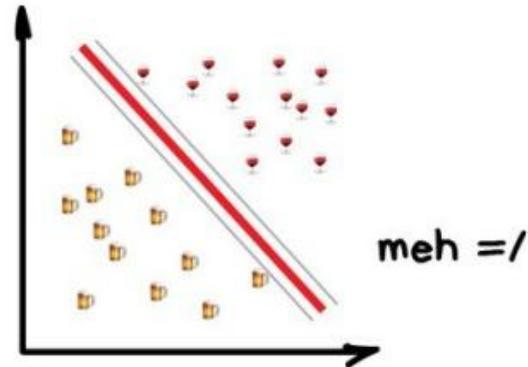
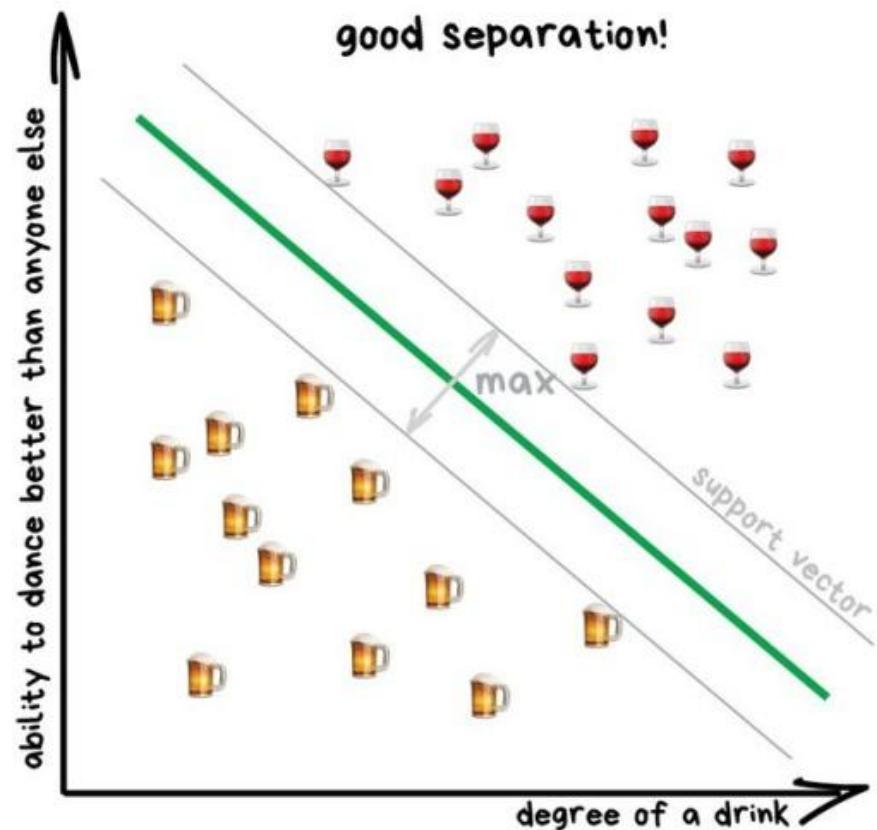
BAYES' THEOREM



NOT SPAM

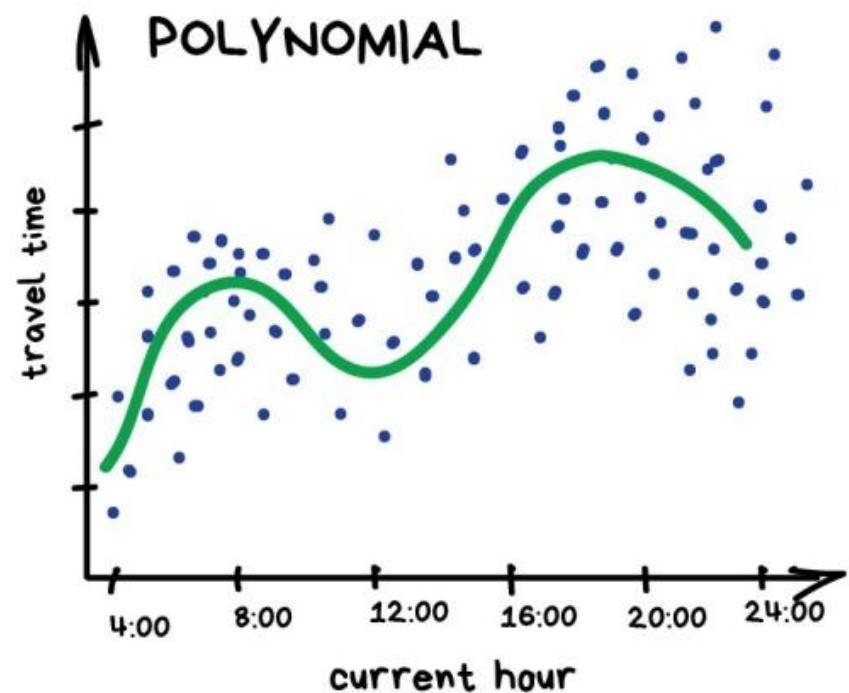
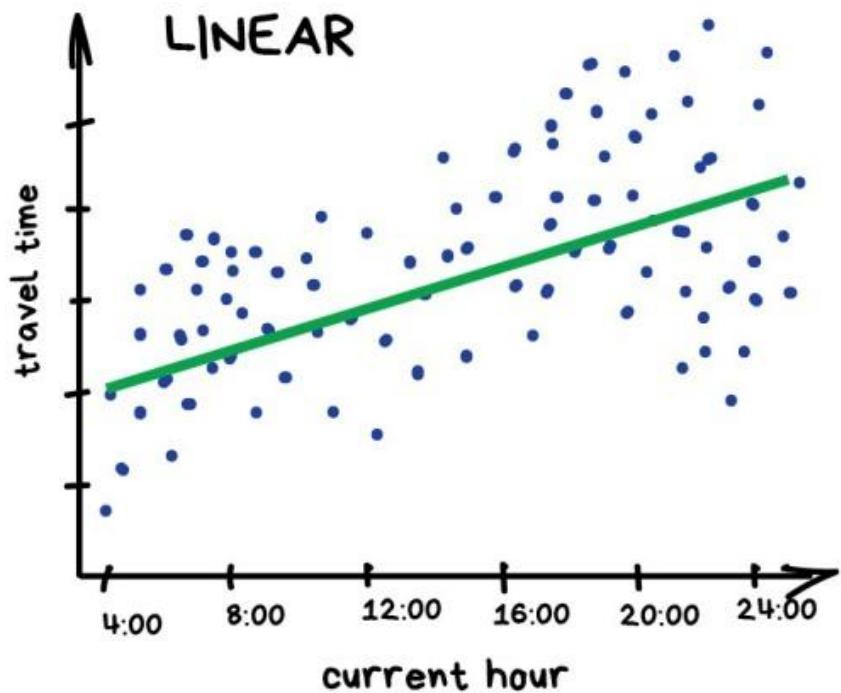
NAIVE BAYES

SEPARATE TYPES OF ALCOHOL



SUPPORT VECTOR MACHINE

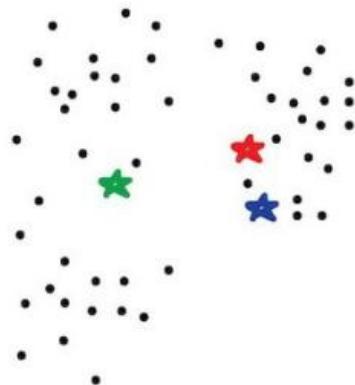
PREDICT TRAFFIC JAMS



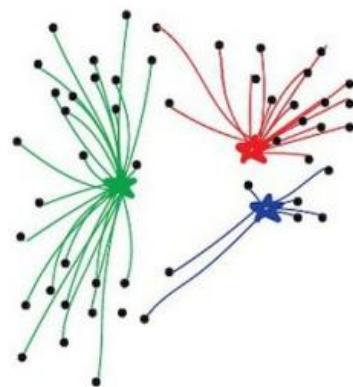
REGRESSION

PUT KEBAB KIOSKS IN THE OPTIMAL WAY

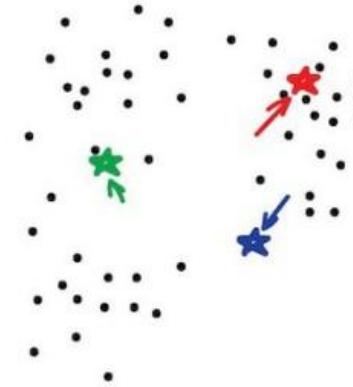
(also illustrating the K-means method)



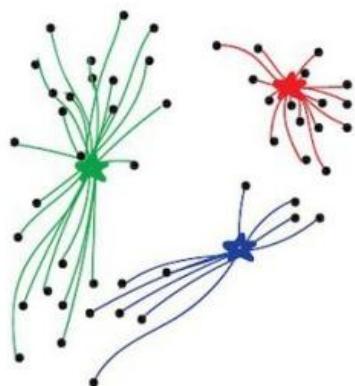
1. Put kebab kiosks in random places in city



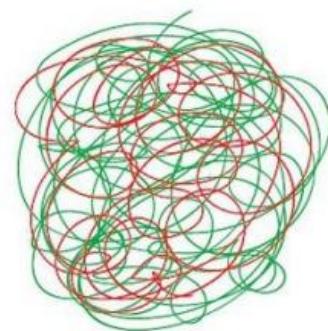
2. Watch how buyers choose the nearest one



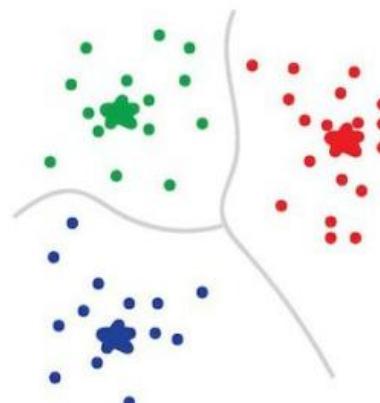
3. Move kiosks closer to the centers of their popularity



4. Watch and move again

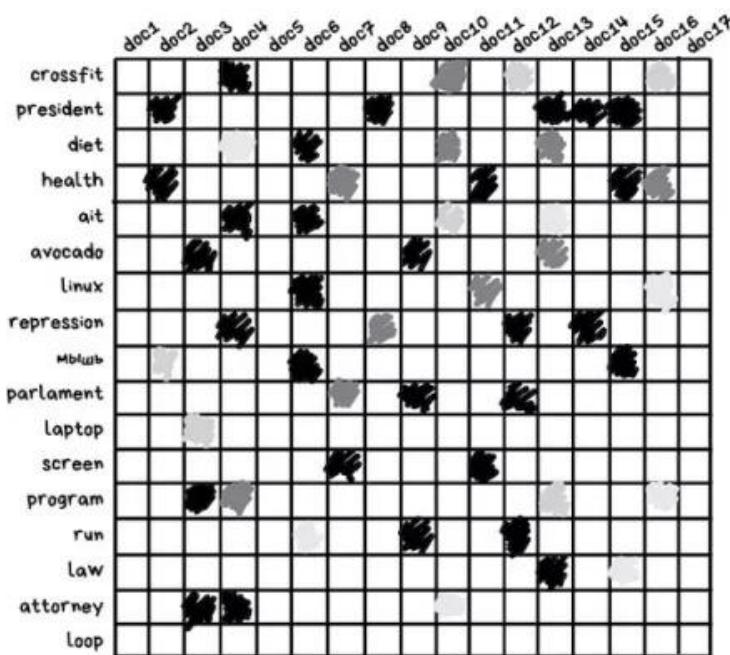


5. Repeat a million times

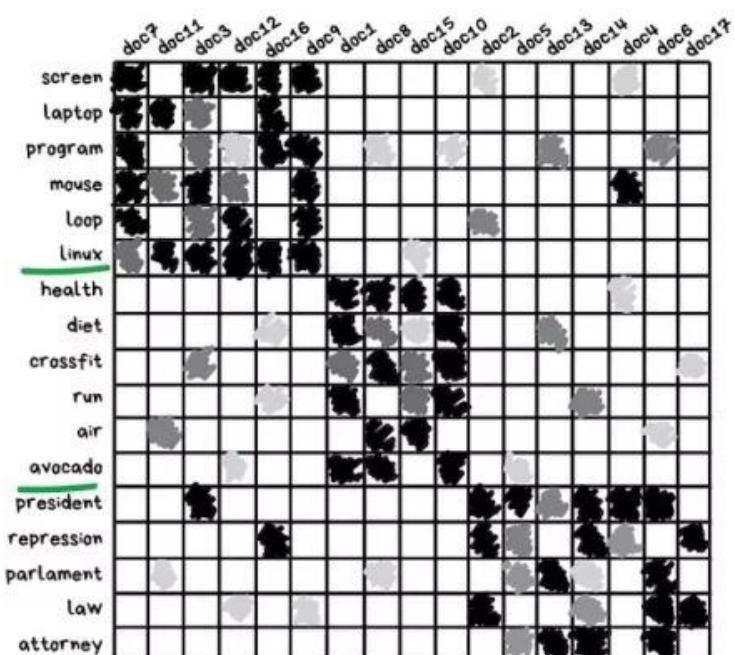


6. Done!
You're god of kebabs!

SEPARATE DOCUMENTS BY TOPIC



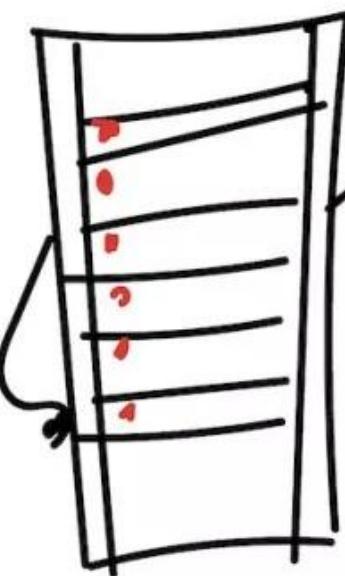
→
SVD
2. Transform



1. Build a matrix of how often each word can be found in each document
(black - more often)

3. Get visual topic clusters.
Even if the words haven't met together

LATENT SEMANTIC ANALYSIS (LSA)



THAT MEATBAG BOUGHT A SOFA



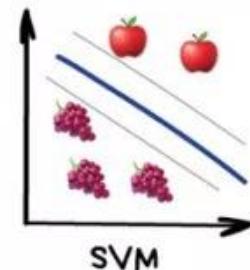
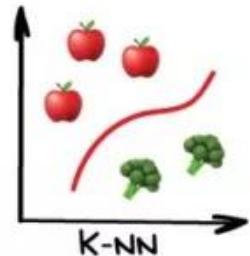
PROBABLY, HE LOVE SOFAS!!!



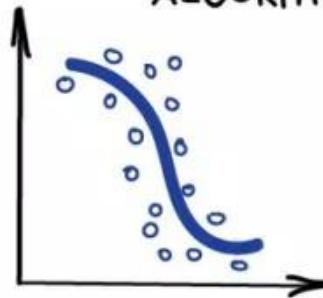
RECOMMEND HIM 148 MORE SOFAS



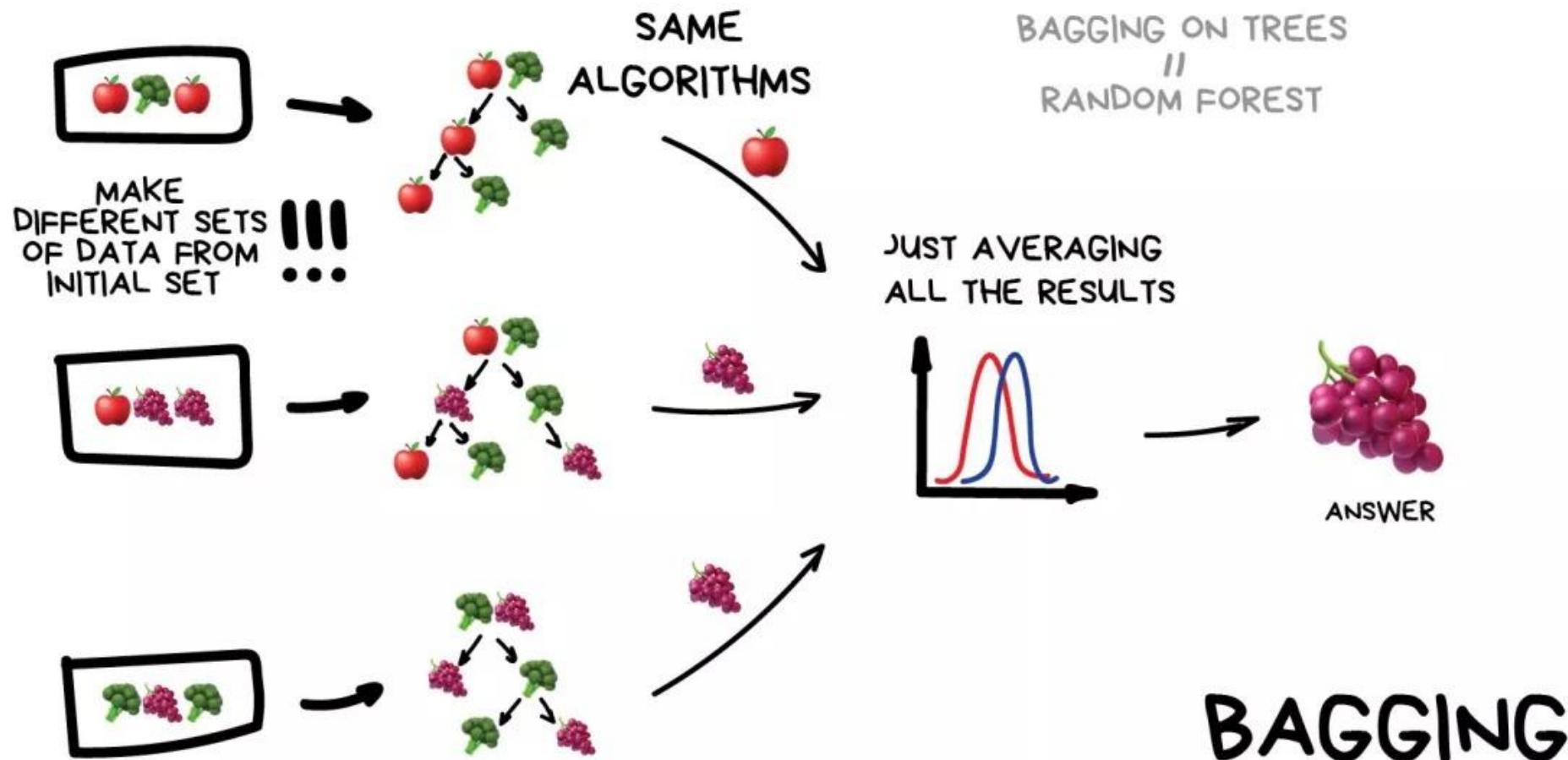
DIFFERENT ALGORITHMS

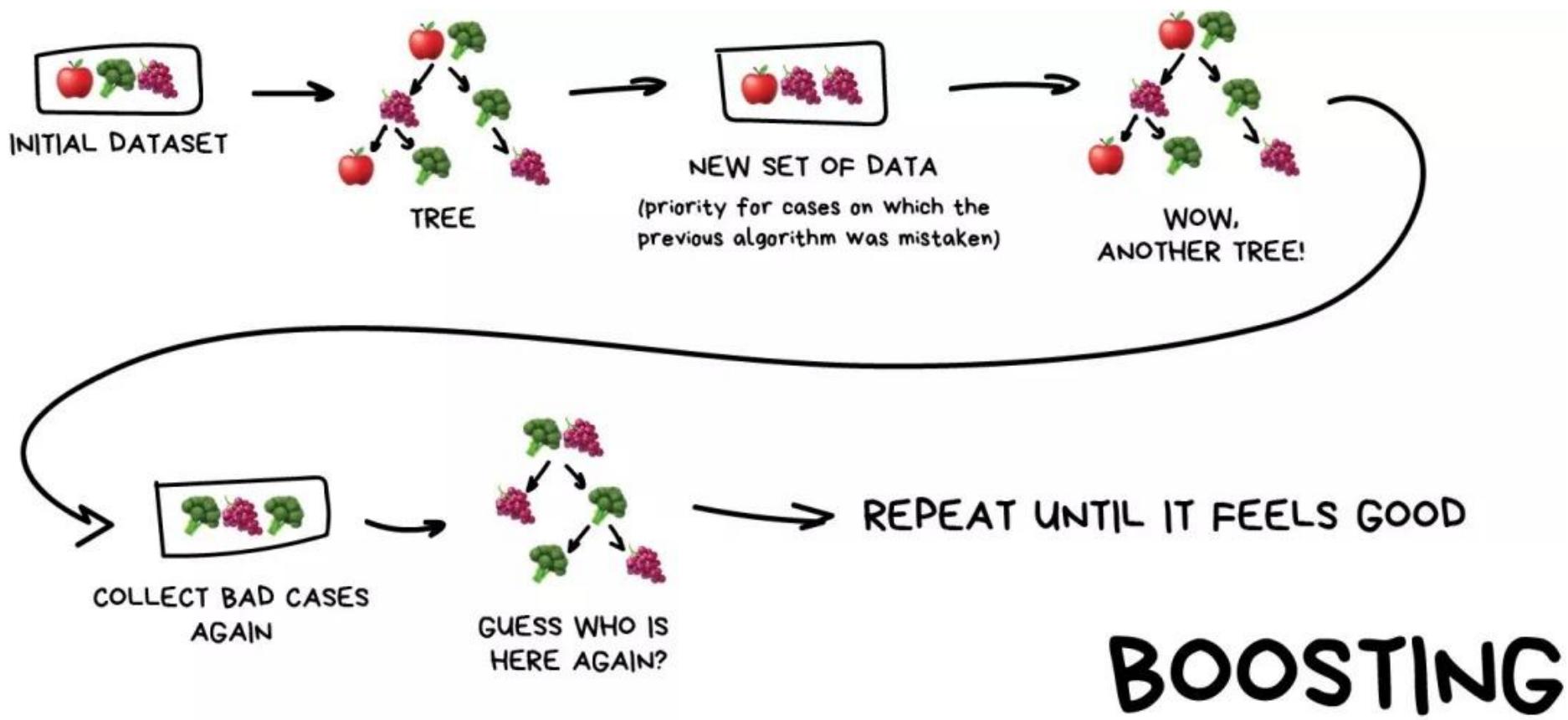


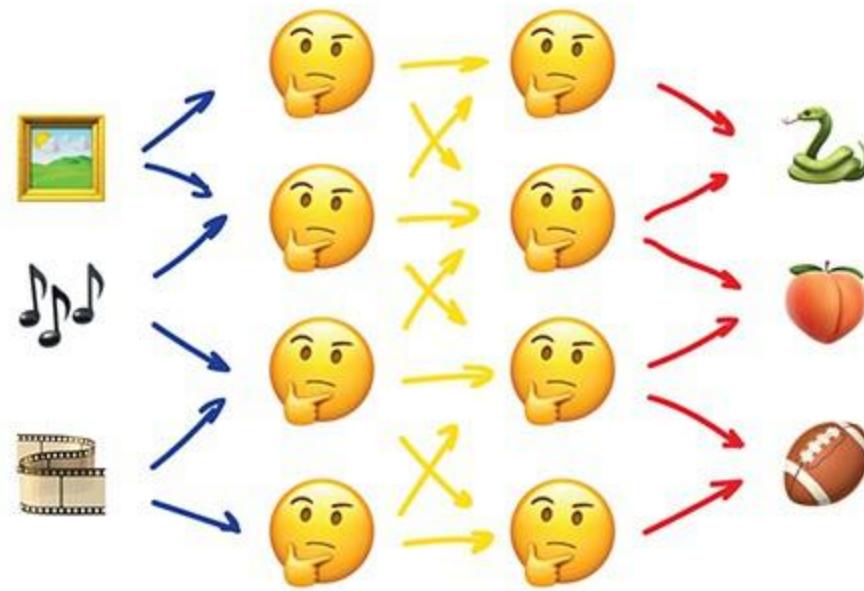
FINAL DECISION ALGORITHM



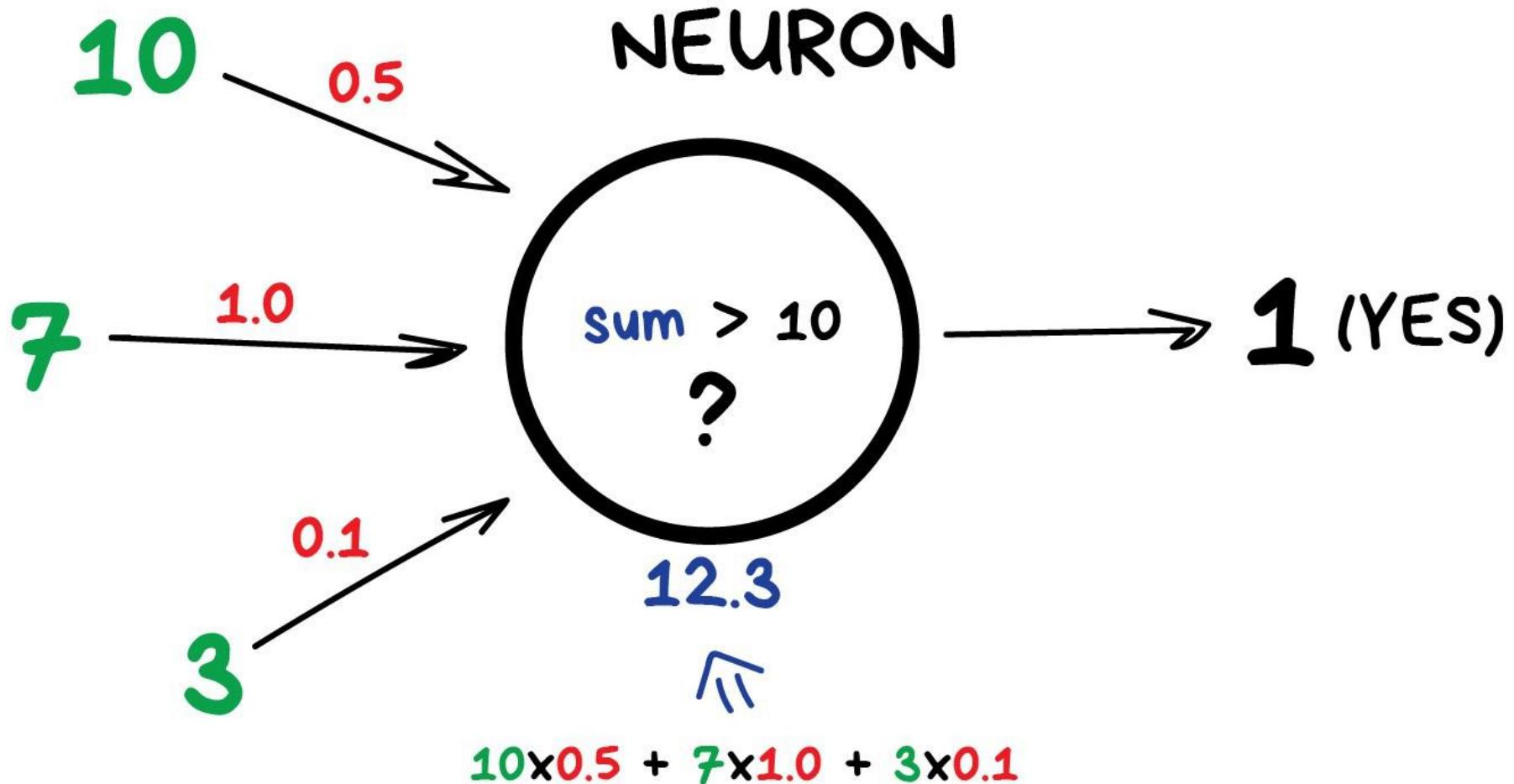
STACKING

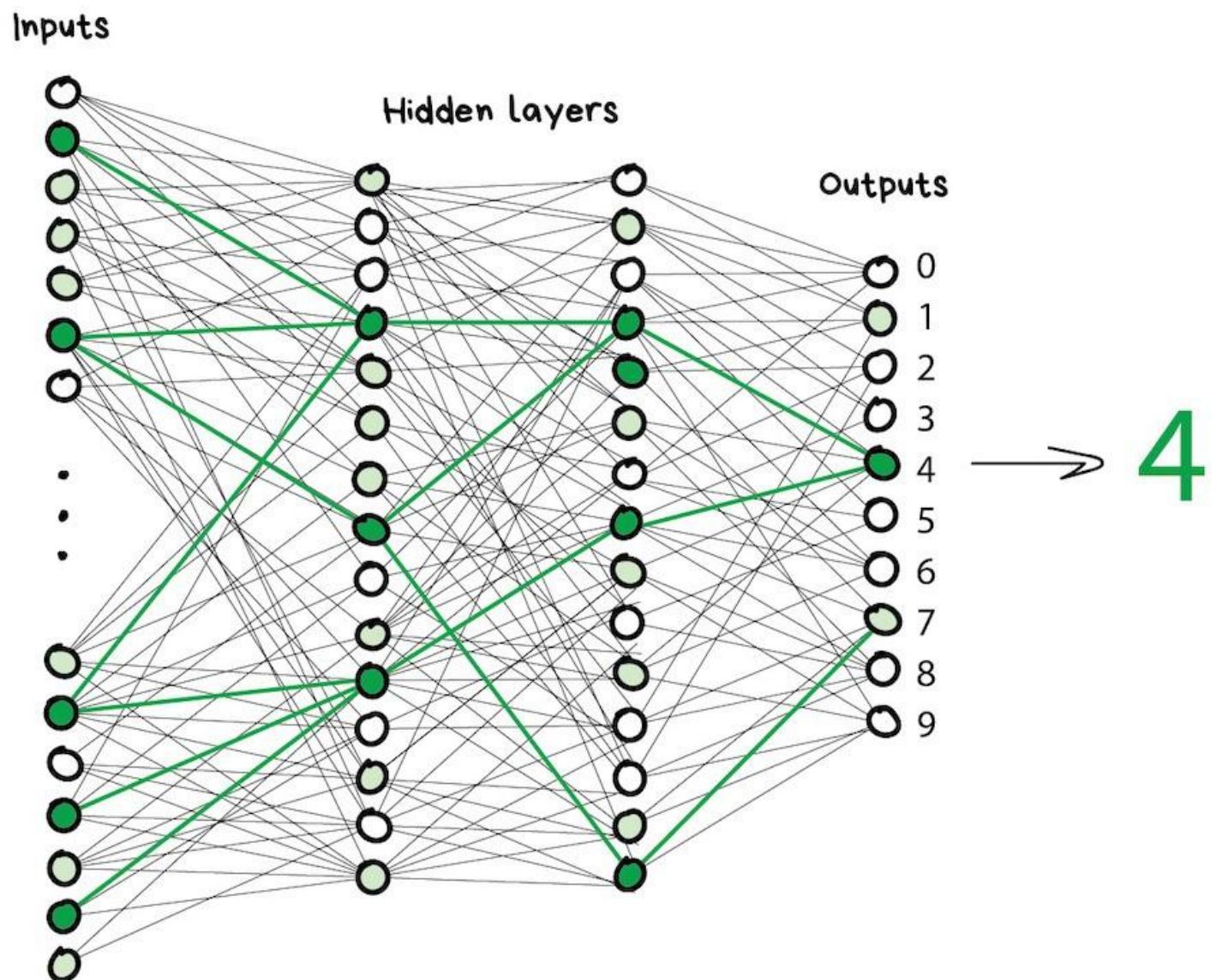
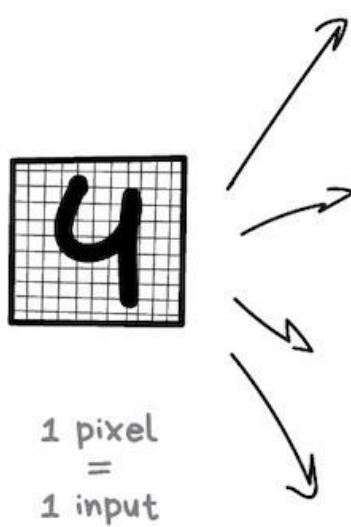




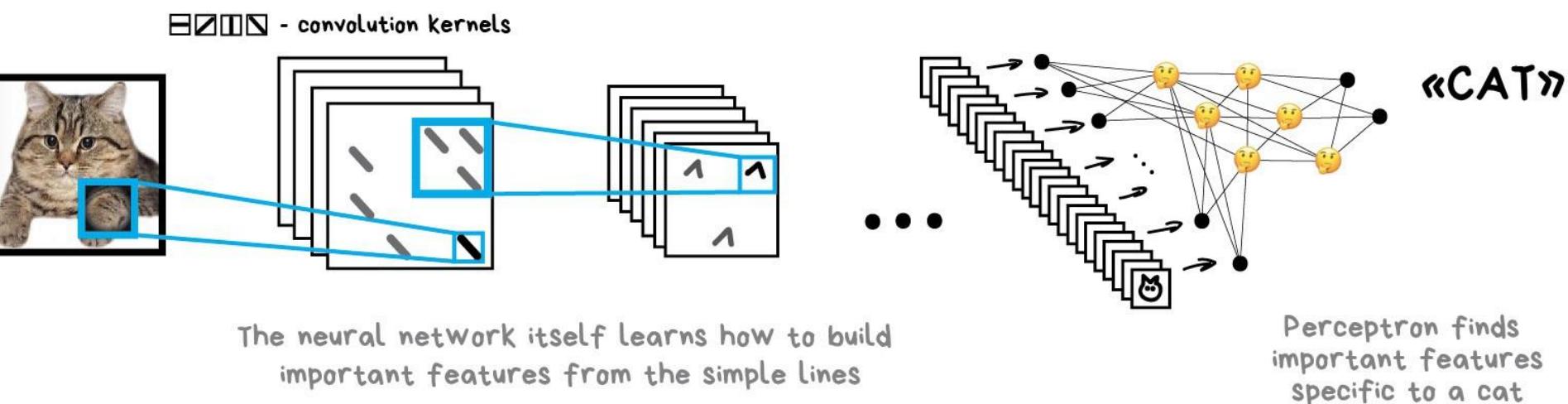
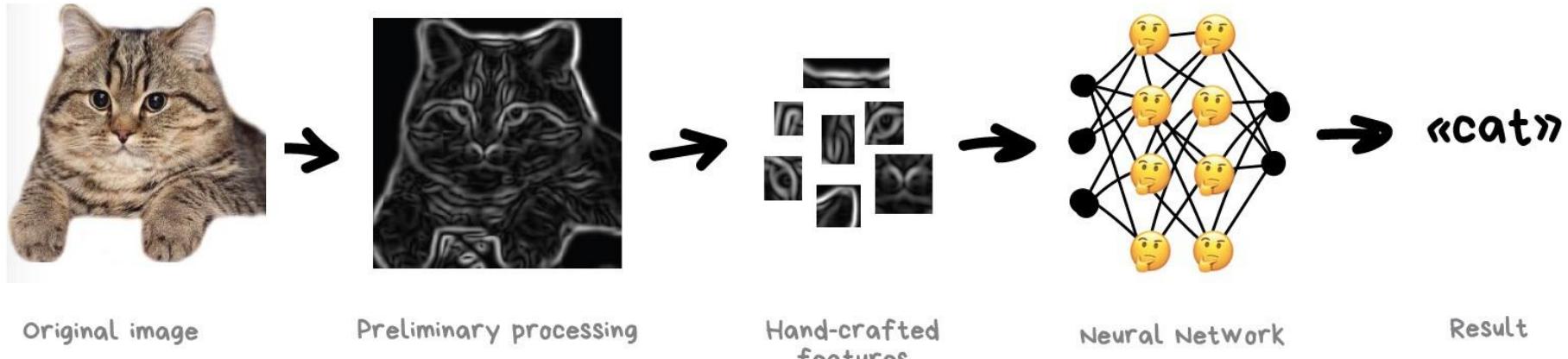


Neural Networks

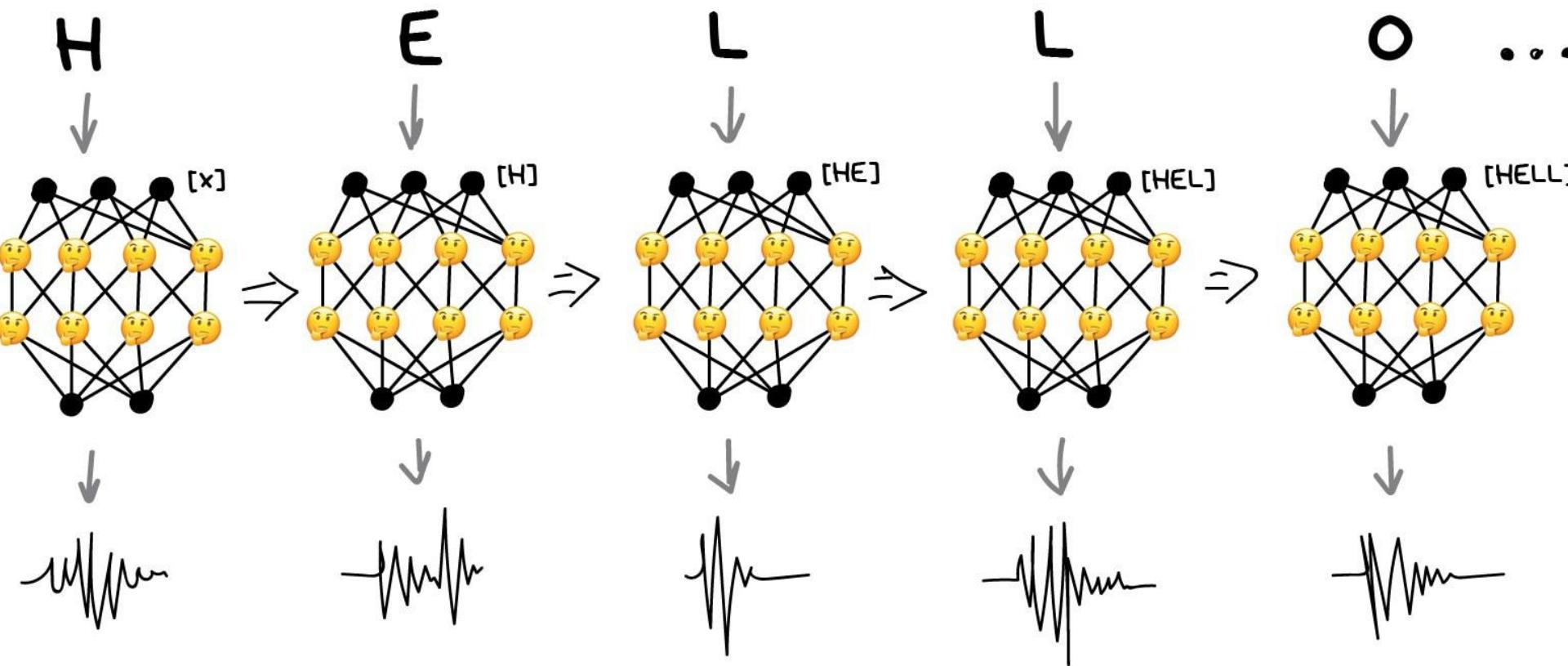




MULTILAYER PERCEPTRON (MLP)



CONVOLUTIONAL NEURAL NETWORK (CNN)

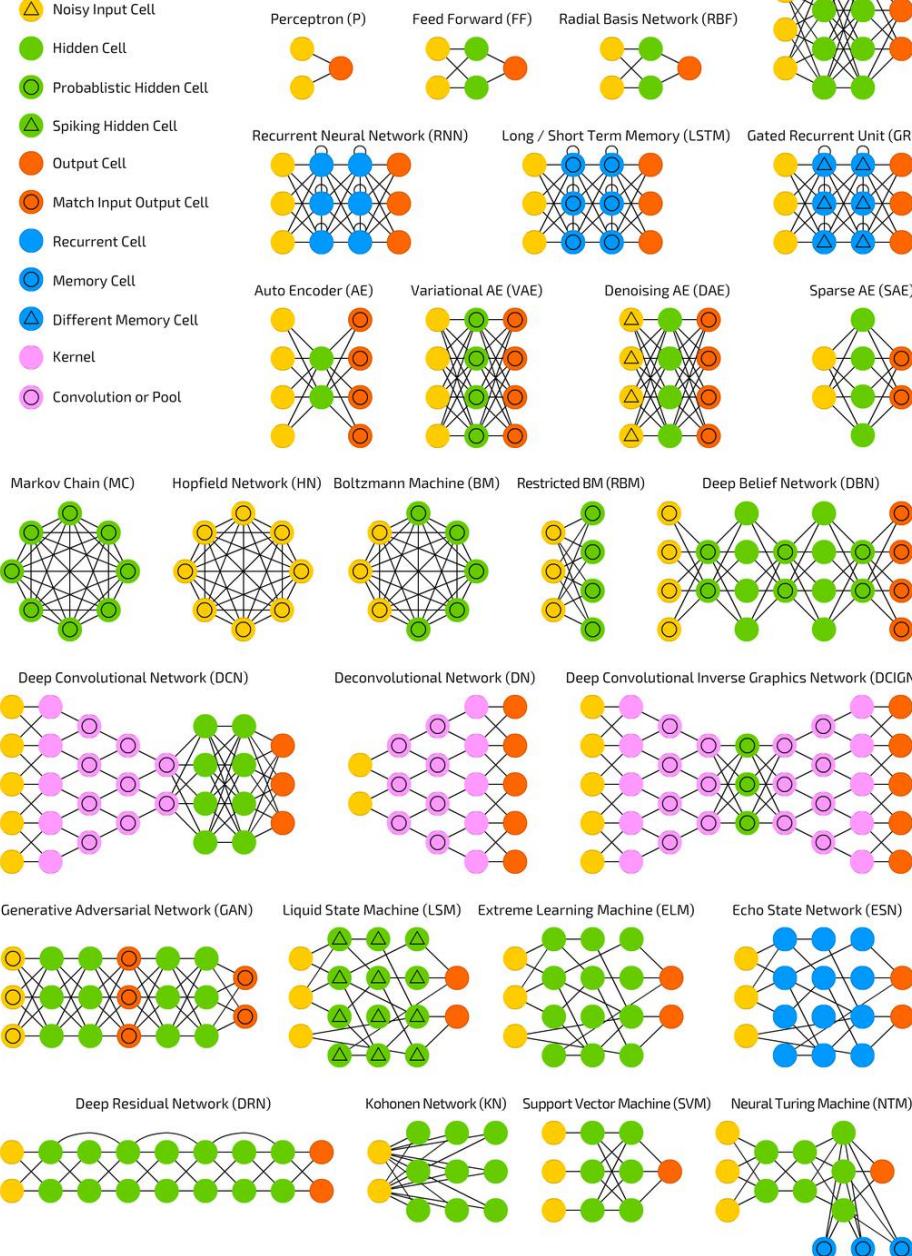


RECURRENT NEURAL NETWORK (RNN)

A mostly complete chart of
Neural Networks

©2016 Fjodor van Veen - asimovinstitute.org

- Backfed Input Cell
- Input Cell
- △ Noisy Input Cell
- Hidden Cell
- Probabilistic Hidden Cell
- △ Spiking Hidden Cell
- Output Cell
- Match Input Output Cell
- Recurrent Cell
- Memory Cell
- △ Different Memory Cell
- Kernel
- Convolution or Pool



Deep Learning



Caffe

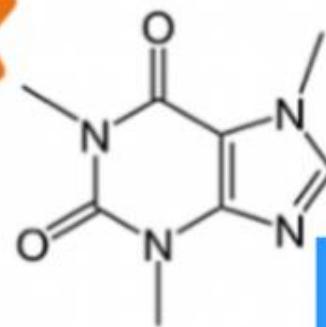


K

Keras



theano

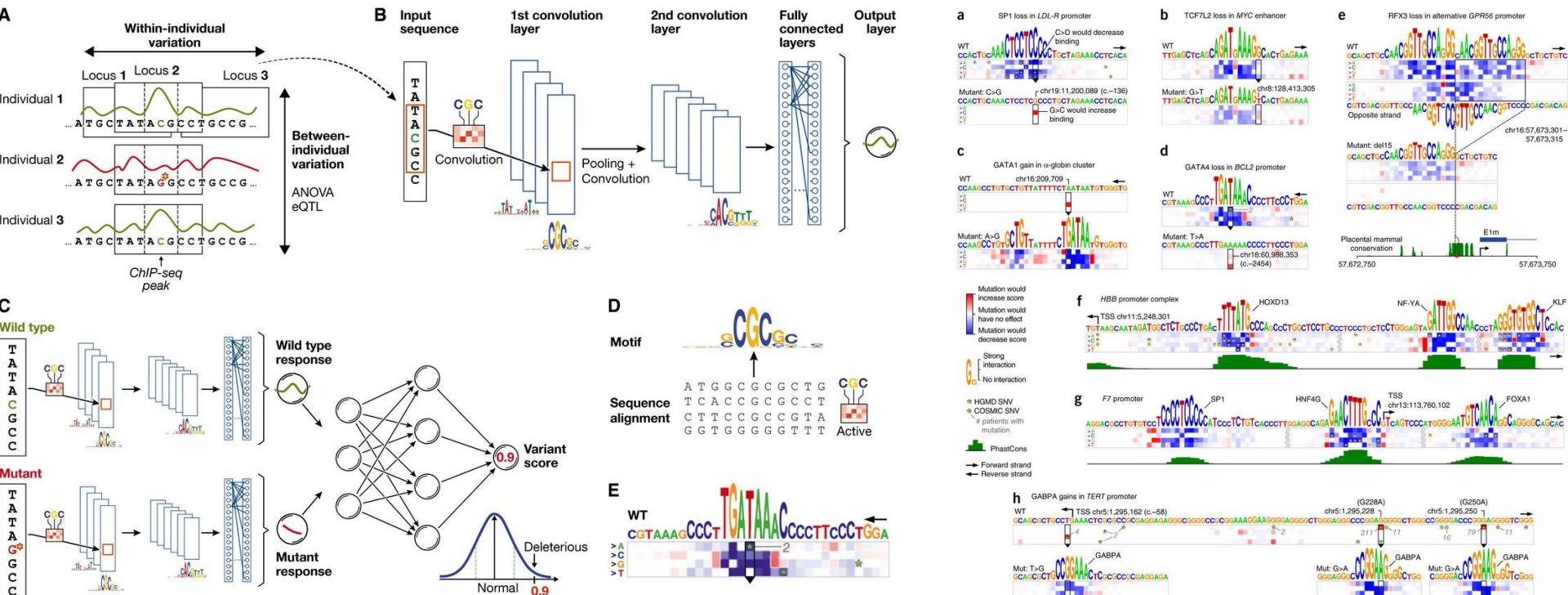
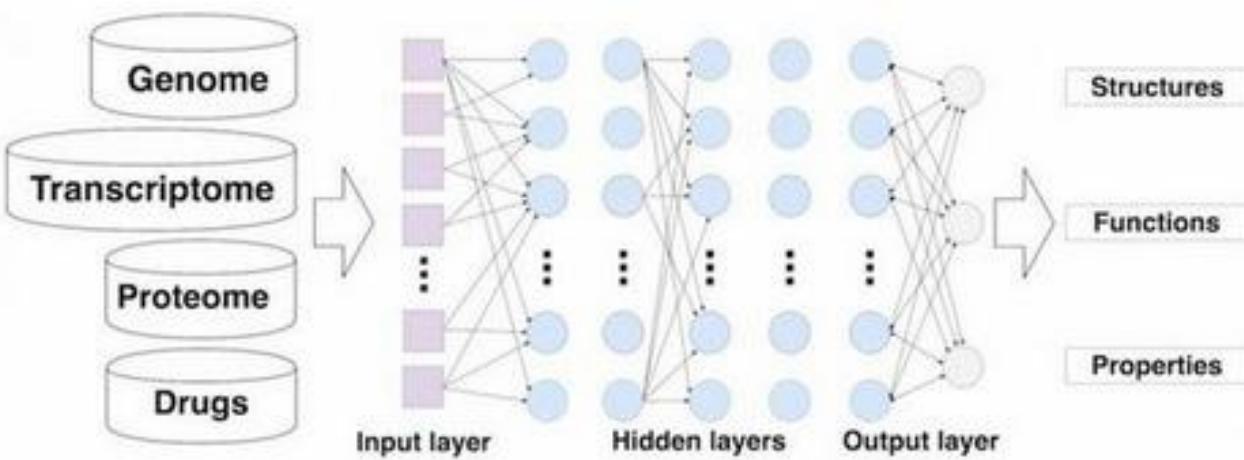


ELK

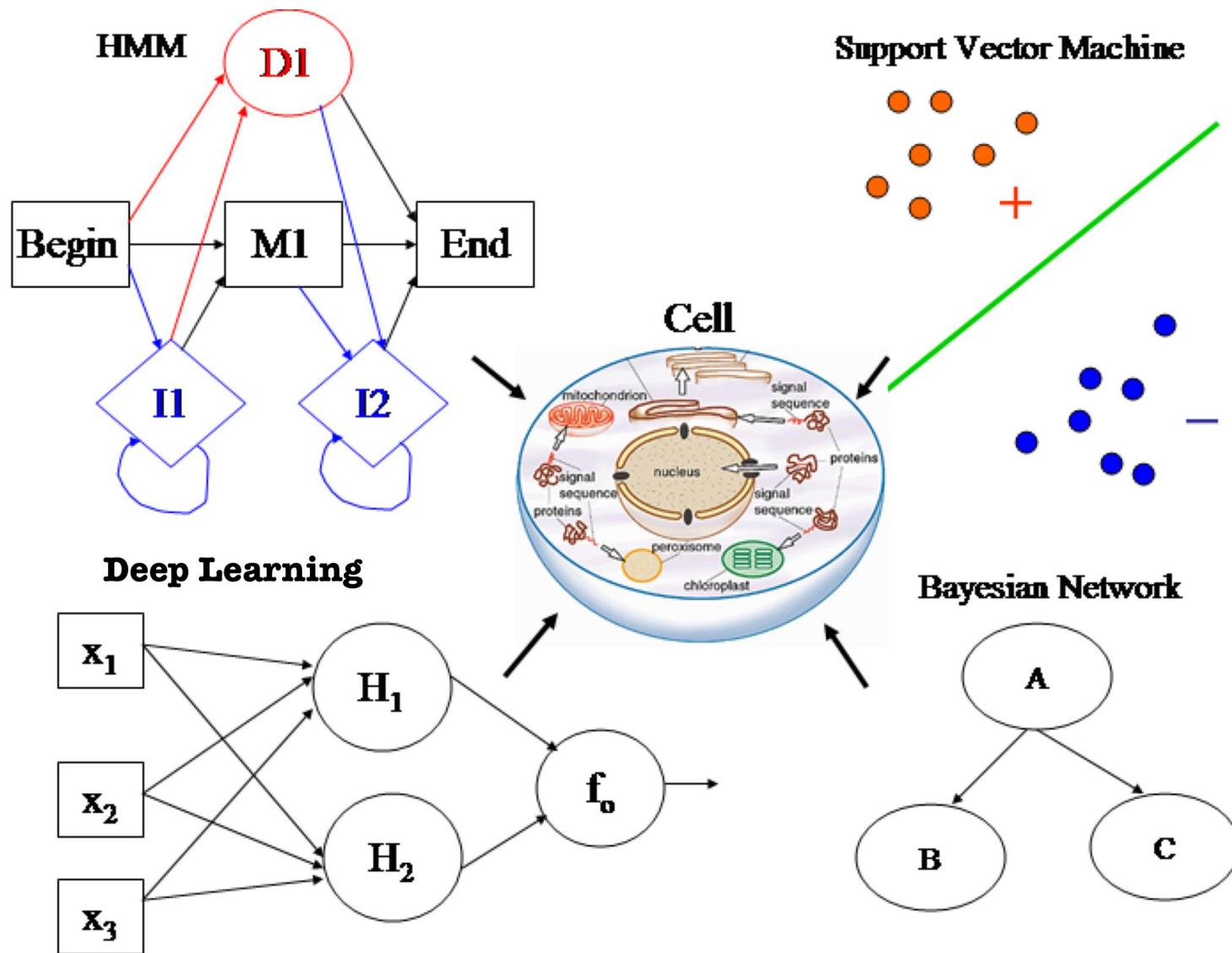


TensorFlow

Deep Learning for Bioinformatics

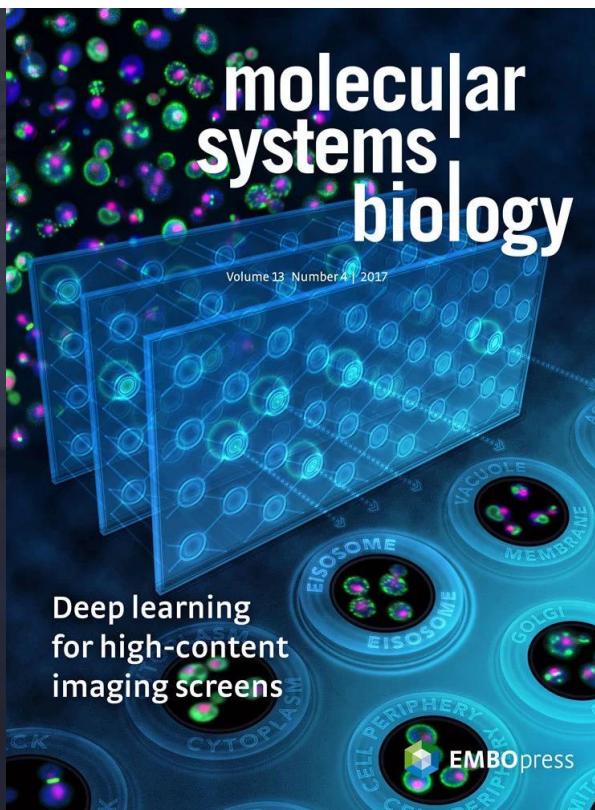


Deep Learning for Bioinformatics



Deep Learning for Bioinformatics

- 高通量测序数据挖掘
- 蛋白和分子对接（药物设计）
- 生物影像分析
- . . .



DEEP LEARNING

Ian Goodfellow, Yoshua Bengio,
and Aaron Courville



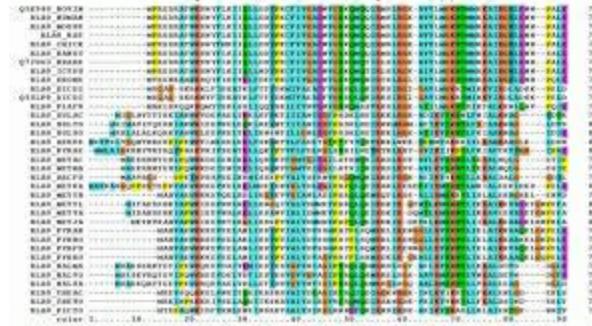
生物信息学与生物统计学： 两种视角，四种技术，两类方法

- 两种视角
 - 生物学视角
 - 计算视角
- 四种技术
 - 算法
 - 数据
 - 超算
 - 深度学习
- 两类方法
 - 经典软件
 - 核心工具

生物统计学经典软件

生物统计经典软件

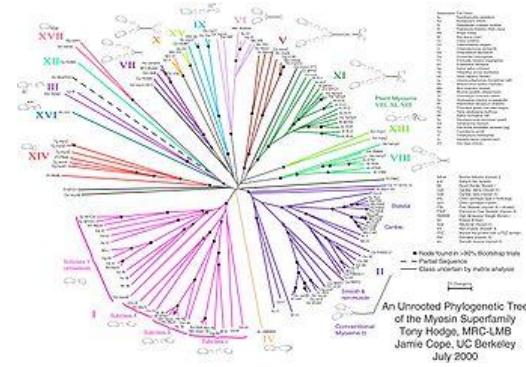
高通量测序数据分析



- MEME: <http://meme-suite.org/>
- GenScan: <http://genes.mit.edu/GENSCAN.html>
- HMMAlign:
<http://www.biology.wustl.edu/gcg/hmmalign.html>

生物统计经典软件

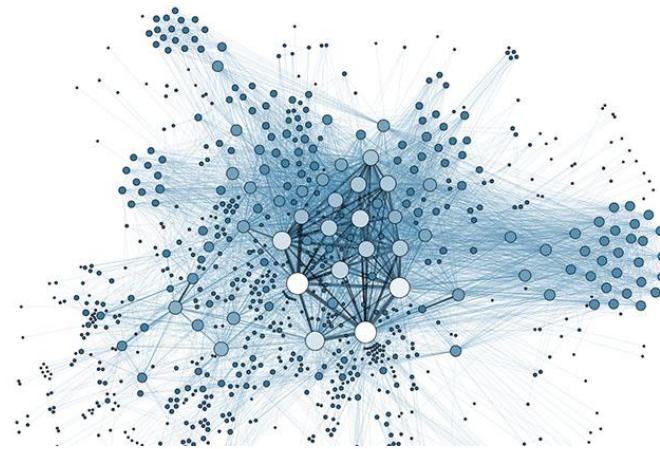
物种和基因进化分析



- iTOL: <https://itol.embl.de/>
 - MEGA: <http://www.megasoftware.net/>

生物统计经典软件

生物分子网络分析



➤ Cytoscape: <http://www.cytoscape.org/>

生物统计经典软件

降维、分子结构等分析

- PCA analysis: <http://biit.cs.ut.ee/clustvis/>
- DREAM Challenge: <http://dreamchallenges.org/>

生物统计经典软件

基因组可视化: Genome Browser, (<http://genome.ucsc.edu/>), (tracks, annotations, etc.)

序列保守性: WebLogo, (<http://weblogo.berkeley.edu/logo.cgi>),

基因预测: MEME, (<http://meme-suite.org/>).

进化树: iTOL, (<https://itol.embl.de/>),

基因调控网络: GeneNetwork, (<http://gn2.genenetwork.org/>), Cytoscape, (<https://cytoscape.org/>),

代谢通路: KEGG, (<https://www.kegg.jp/>); iPATH, (<https://pathways.embl.de/>),

蛋白结构与功能: PDB, (<http://www.rcsb.org>); pFAM, (<http://pfam.xfam.org/>),

微生物组: EBI Magnify. (<https://www.ebi.ac.uk/metagenomics/>),

蛋白和小分子互作数据: STITCH, (<http://stitch.embl.de/>); STRING, (<http://string-db.org>),

药物数据库: DrugBank, (<https://www.drugbank.ca/>),

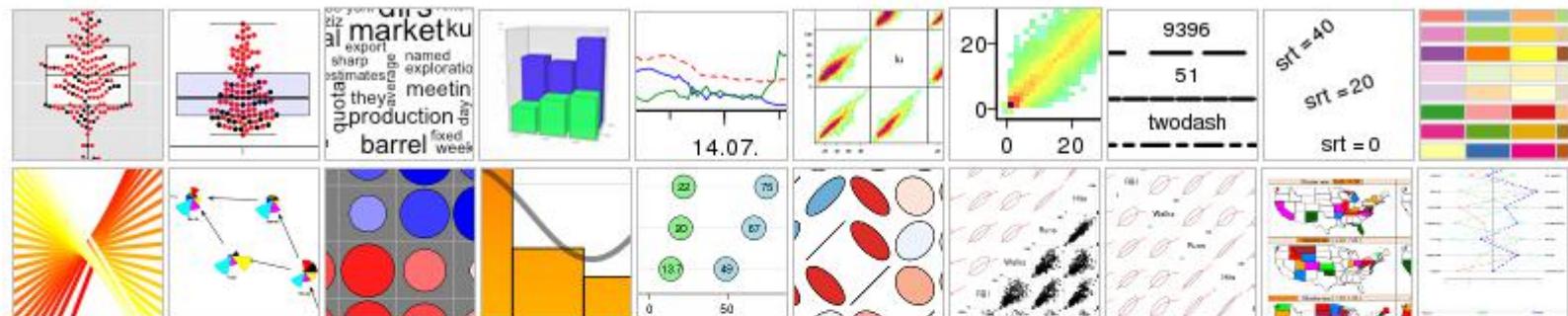
生物数据分析平台: Galaxy, (<https://usegalaxy.org/>),

生物数据可视化: Echart, (<https://www.echartsjs.com/examples/zh/index.html>),

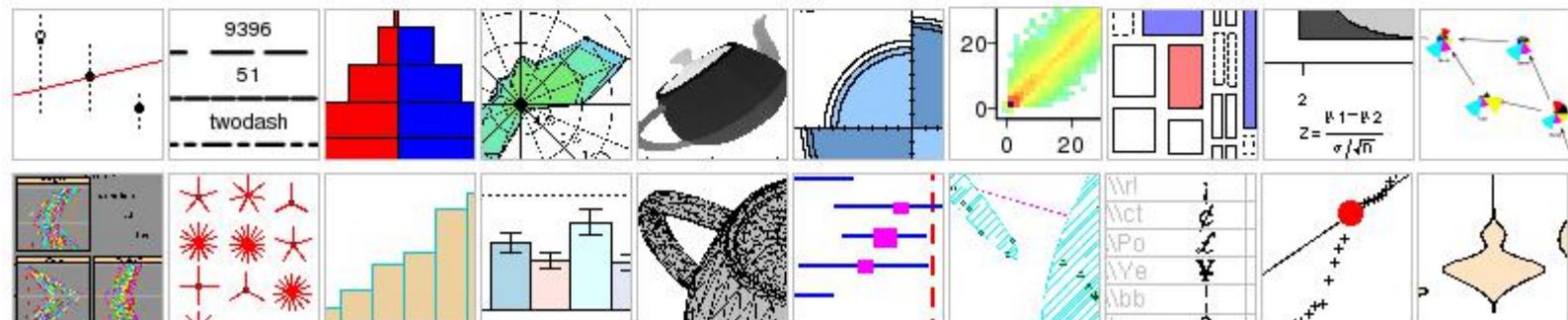
生物统计学核心工具

R: <https://www.r-project.org>

» Last entries ...



» Random entries

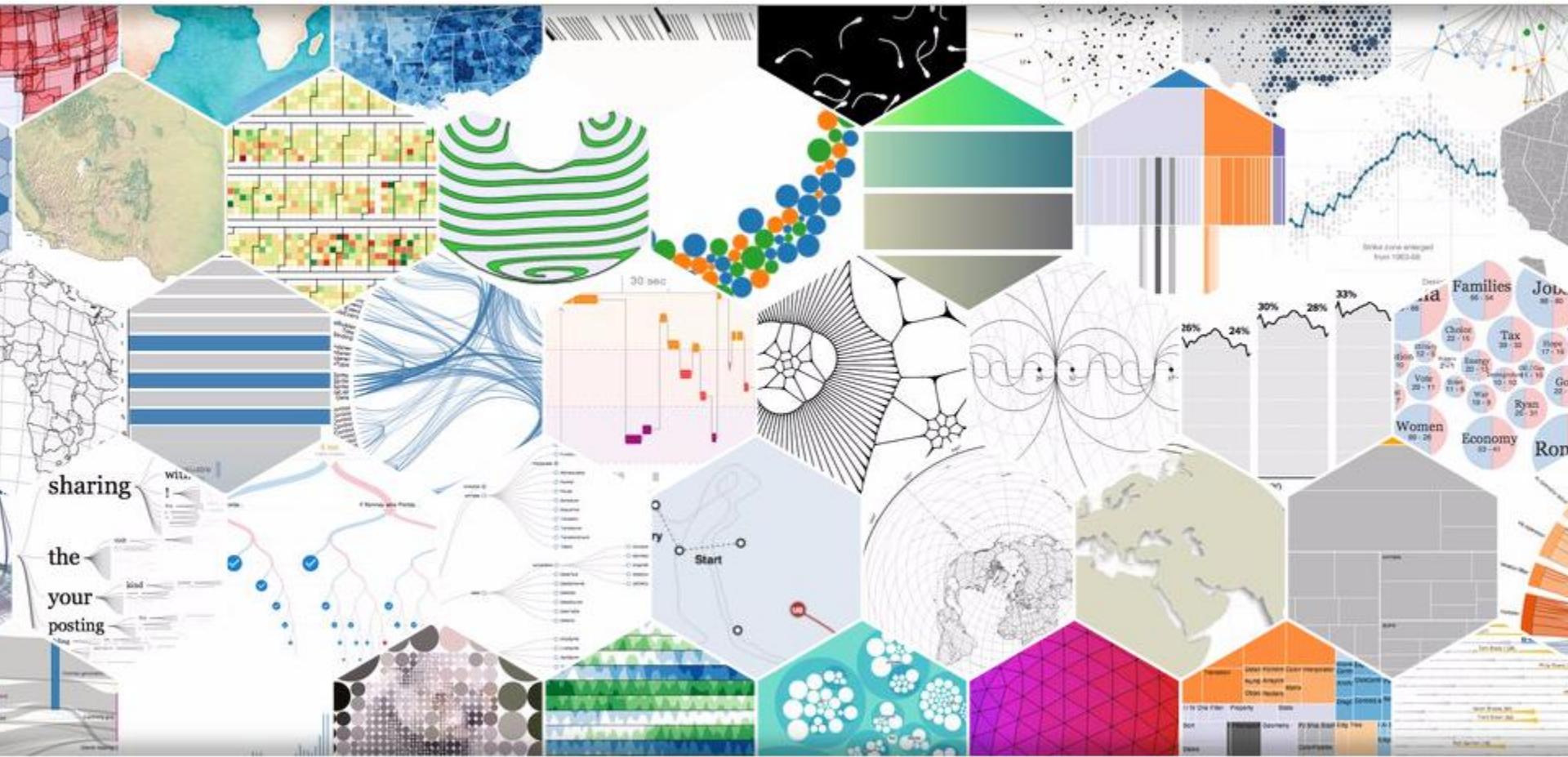


Python and Biopython:

<https://www.python.org/>

<http://biopython.org/>

D3.js for visualization:
<https://d3js.org/>



Echart for visualization:

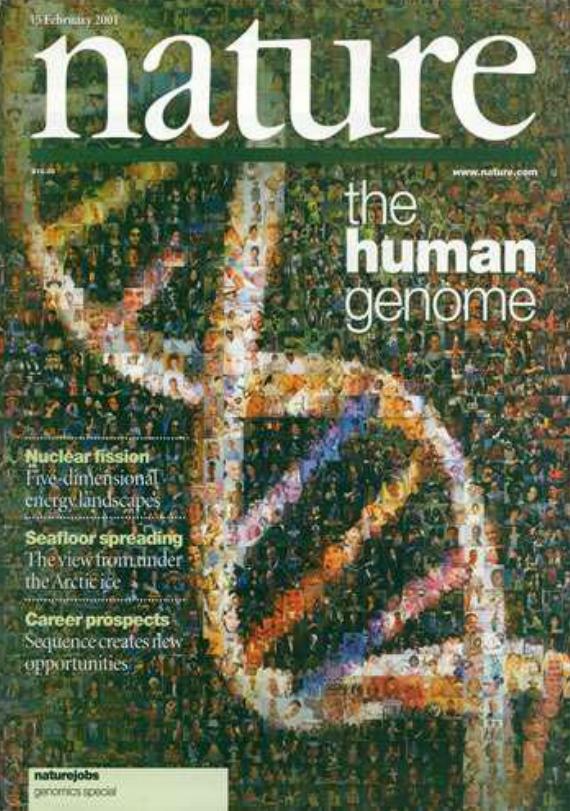
<http://echarts.baidu.com>



Current status (现今态势)



很难找到
与生物信息学没有关系的
生物学和计算科学
研究和应用领域了。。。。。



Alphabet (谷歌)

Google 的基因组学梦想



The NEW ENGLAND
JOURNAL of MEDICINE

HOME ARTICLES & MULTIMEDIA ISSUES SPECIALTIES & TOPICS FOR AUTHORS

CORRESPONDENCE

23andMe and the FDA

N Engl J Med 2014; 370:2248-2249 | June 5, 2014 | DOI: 10.1056/NEJMc1404692

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Article Citing Articles (3) Metrics

To the Editor:

In their Perspective article (March 13 issue),¹ Annas and Elias state that the conflict between the genetic-testing company 23andMe and the Food and Drug Administration (FDA) concerns analytic and clinical validity, clinical utility, and ethical, legal, and social issues. However, their discussion is limited to a domestic U.S. perspective. After a person's raw genetic data have been determined from a DNA sample, the data are stored remotely and can be accessed easily anywhere in the world. For example, in Japan, maternal blood samples from Japanese mothers undergoing

nature
biotechnology

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NATURE BIOTECHNOLOGY | NEWS



FDA approves 23andMe gene carrier test

Nature Biotechnology 33, 435 (2015) | doi:10.1038/nbt0515-435a

Published online 12 May 2015

PDF Citation Reprints Rights & permissions Article metrics

23andMe, based in Mountain View, California, has received word from the US Food and Drug Administration (FDA) that their Bloom syndrome carrier screening test was approved as a class II device. The approval came in February, 15 months after the personal genomics company received a cease and desist letter from the regulator for its genetic tests because the company was dispensing health-related information to consumers without having obtained marketing clearance. The FDA website lists class II devices as moderate risk, requiring some regulatory controls, putting carrier screening tests in the same category as condoms. This turnaround follows the company's

Future (未来)

Cancer informatics Gene regulation
Personalized medicine Protein modeling
Computational biology Gene expression analysis
Image analysis Genomics and proteomics
Comparative genomics Gene expression databases
Epidemic models Computational drug discovery

Bioinformatics

Sequence analysis Bio-ontologies and semantics
Evolution and phylogenetics Structure prediction
Cheminformatics Next generation sequencing
Computational intelligence
Biomedical engineering Amino acid sequence analysis
Structural bioinformatics Medical informatics
Microarrays
Visualization



Future (未来)

我们是谁？ 我们从哪里来？ 我们到哪里去？

