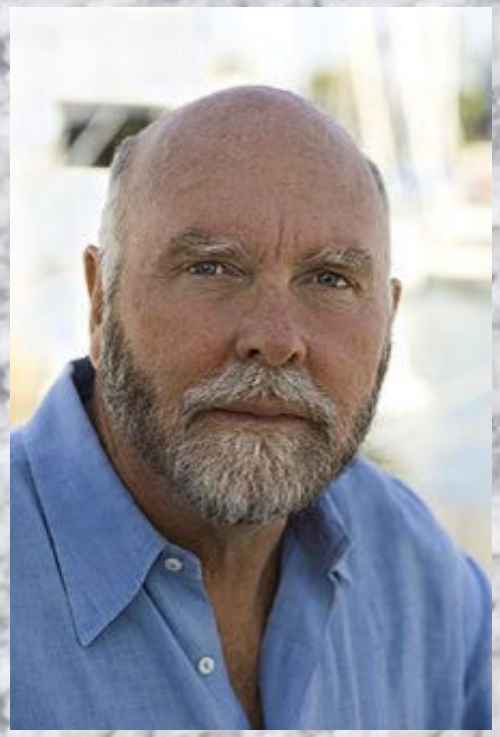
Будет ли наука в эпоху технологии?

(How much is your science?)

Craig Venter



- 1975 – PhD. degree in physiology and pharmacology from the University of California, San Diego
- 1984 – NIH, EST studies
- 1995-2000 – Human Genome Project competitor in Celera Genomics Group

J. Craig Venter™
INSTITUTE

Human diploid genome

The first publication of a diploid human genome from one person: A step closer to truly individualized genomic medicine.

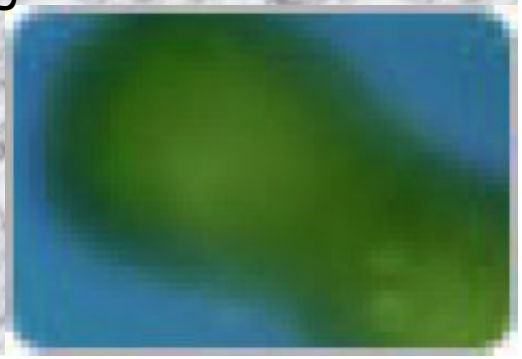
Global Ocean Sampling expedition

The world around us teems with life. But what we see with our eyes is not all that's there, nor all that is important. The unseen world is invisible to us,but its importance is immeasurable. The microbes in the sea, land, and air sustain our life on Earth.

HMP

Human Microbiome Project (HMP)

The NIH Human Microbiome Project (HMP) was initiated to help determine the core human microbiome, to understand the changes in the human microbiome



First Self-Replicating Syntetic Bacterial cell

Genomic science has greatly enhanced our understanding of the biological world. It is enabling researchers to "read" the genetic code of any organism

Sciencexpress Research Article

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

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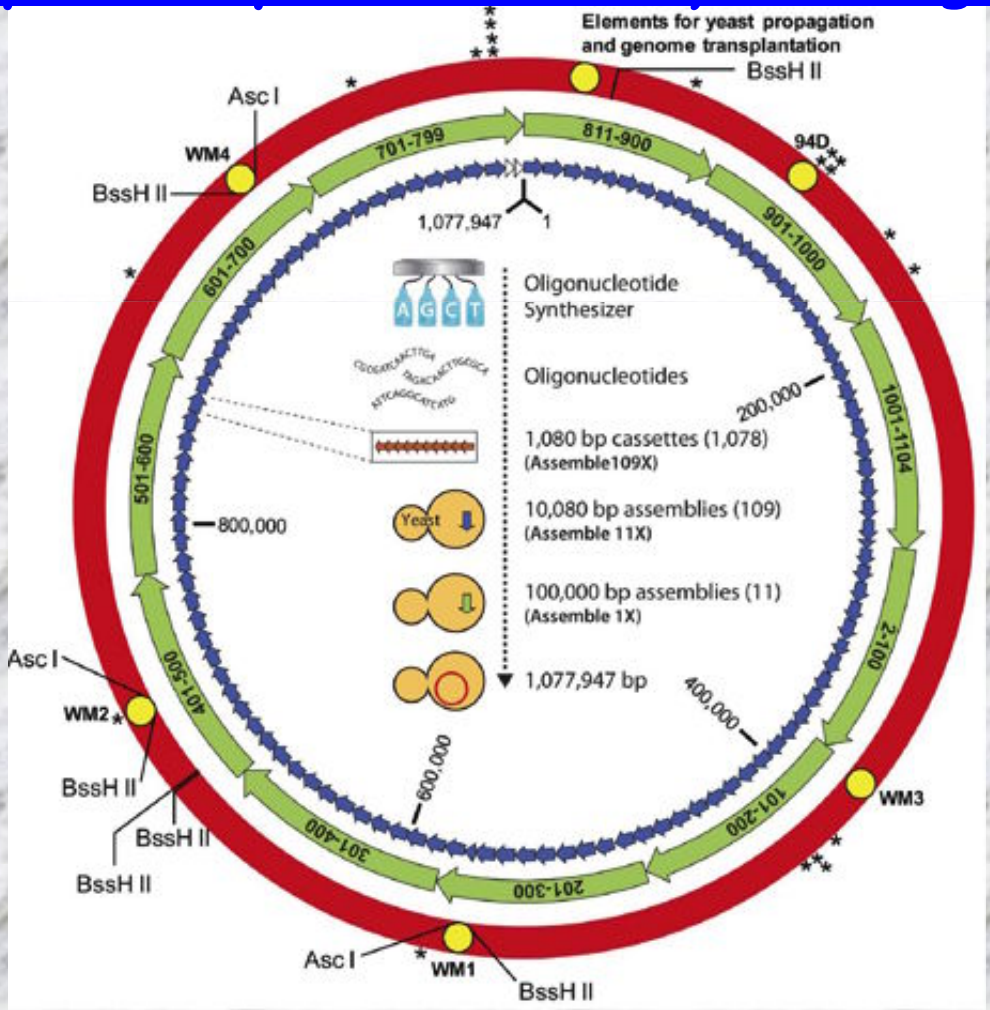
In 1977, Sanger and colleagues determined the complete genetic code of phage φX174, the first DNA genome to be completely sequenced. Eighteen years later, in 1995, our team was able to read the first complete genetic code of a selfreplicating bacterium, Haemophilus influenzae. Efforts to understand all this new genomic information have spawned numerous new computational and experimental paradigms, yet our genomic knowledge remains very limited.

- No single cellular system has all of its genes understood in terms of their biological roles.
- Even in simple bacterial cells, do the chromosomes contain the entire genetic repertoire?
- If so, can a complete genetic system be reproduced by chemical synthesis starting with only the digitized DNA sequence contained in a computer?

The assembly of a synthetic *M. mycoides* genome in yeast

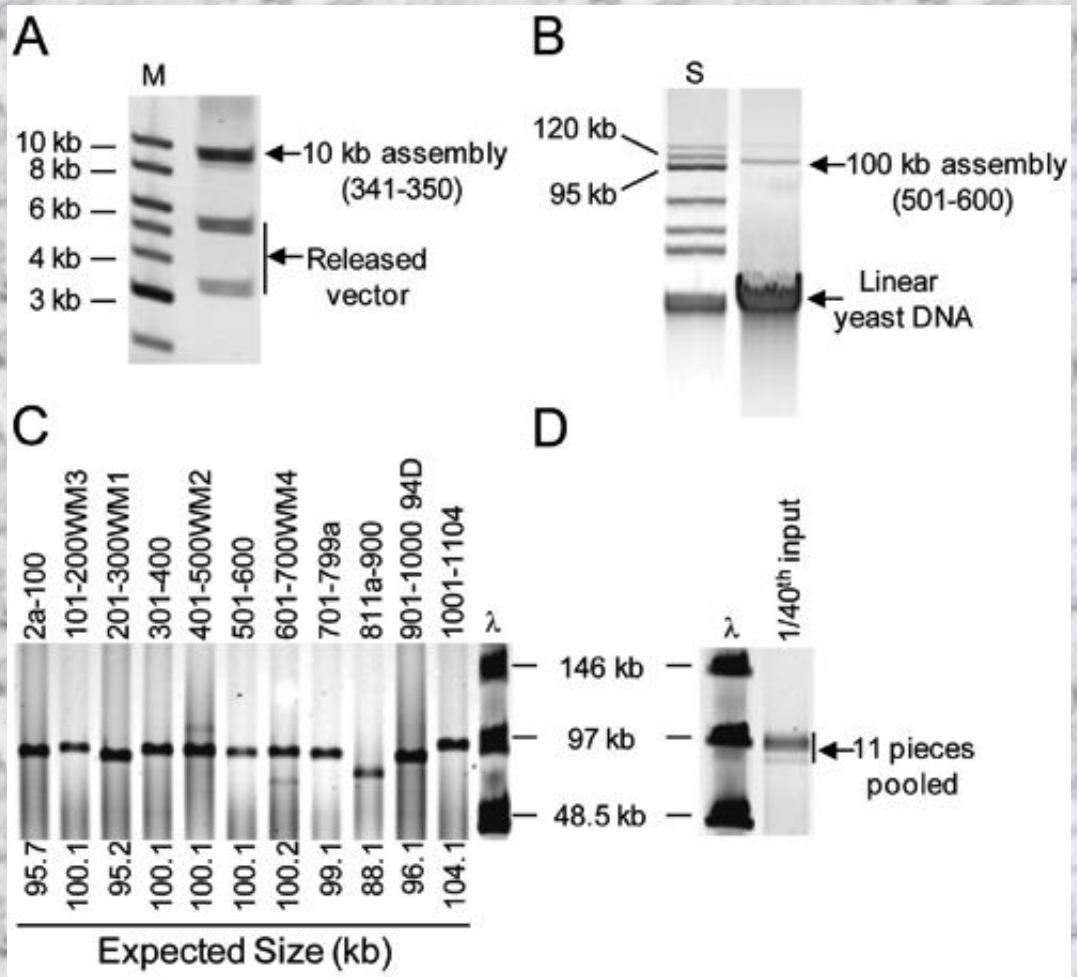


A synthetic *M. mycoides* genome was assembled from 1,078 overlapping DNA cassettes in three steps. In the first step, 1,080-bp cassettes (orange arrows), produced from overlapping synthetic oligonucleotides, were recombined in sets of 10 to produce one hundred nine ~10-kb assemblies (blue arrows). These were then recombined in sets of 10 to produce eleven ~100-kb assemblies (green arrows). In the final stage of assembly, these eleven fragments were recombined into the complete genome (red circle).

Major variations from the natural genome are shown as yellow circles. These include 4 watermarked regions (WM1-WM4), a 4-kb region that was intentionally deleted (94D), and elements for growth in yeast and genome transplantation. In addition, there are 20 locations with nucleotide polymorphisms (asterisks).

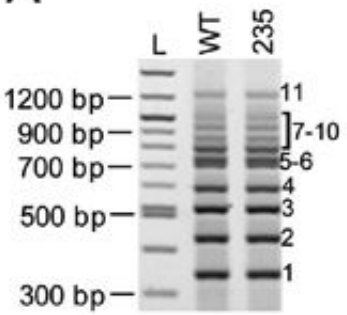
The designed sequence is 1,077,947 bp. The locations of the Asc I and BssH II restriction sites are shown.

Analysis of Assembly Intermediates



Characterization of SyntGenome isolated from yeast

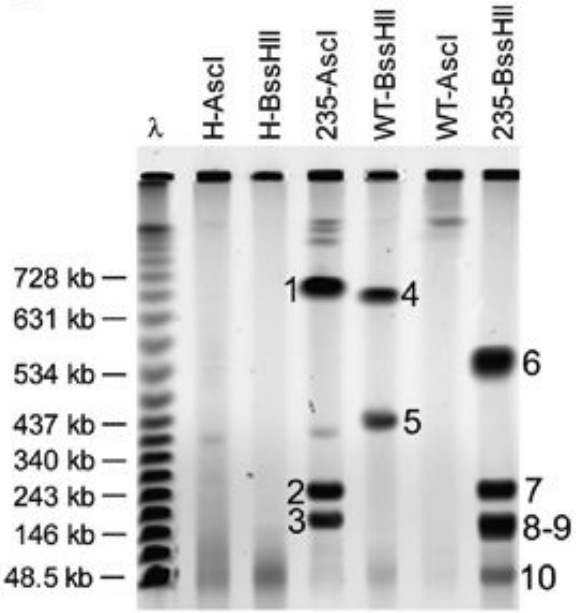
A



B

Strain	Digest	Fragment # and size (kb)
WT	AscI	No sites
WT	BssHII	(4) 668 (5) 419
Syn235	AscI	(1) 685 (2) 233 (3) 160
Syn235	BssHII	(6) 533 (7) 233 (8) 152 (9) 126 (10) 34

C

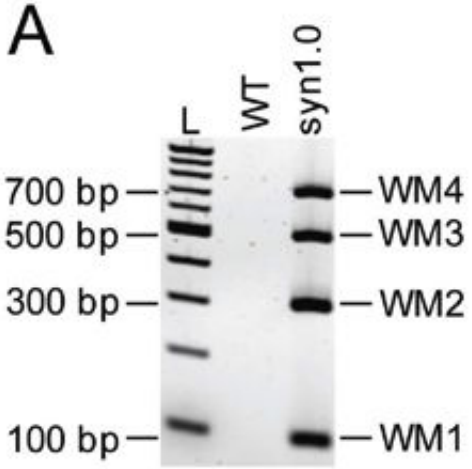


A – multiplex PCR

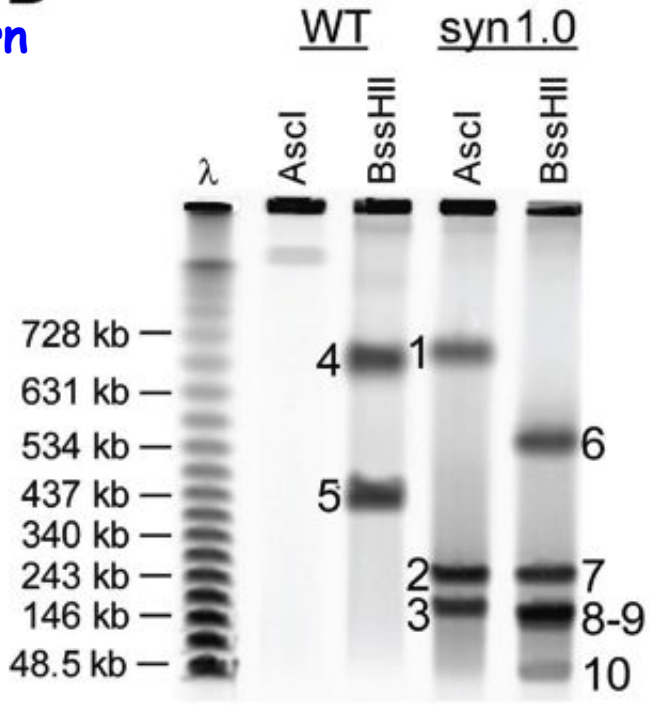
B,C – restriction pattern

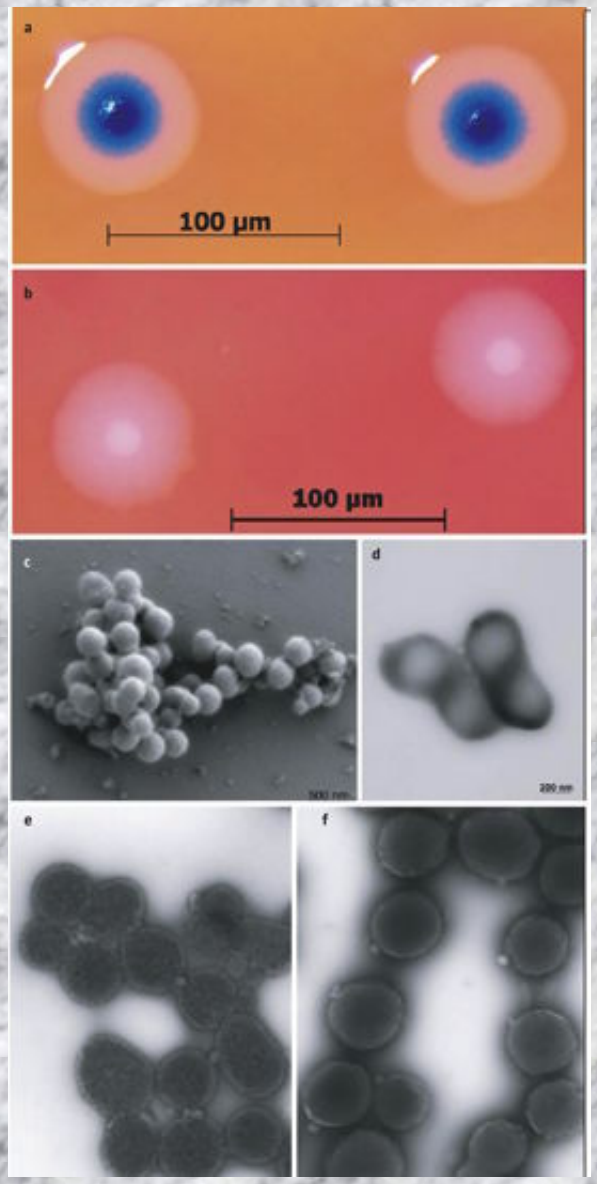
Characterization of the transplantants

A



B





a,c,d,e JCVI-syn1.0

b,f Wild Type

We have been driving the ethical discussion concerning synthetic life from the earliest stages of this work.

As synthetic genomic applications expand, we anticipate that this work will continue to raise philosophical issues that have broad societal and ethical implications.

We encourage the continued discourse.

Guenter Albrecht-Buehler

- 1972. Ph.D. in physics from the Technische Universitaet, Munich

- 1972-1973. Post-doctoral work on cell motility at the Friedrich Miescher Institute, Basel Switzerland

- Northwestern University medical School, Dep of Cellular and Molecular Biology, Robert Laughlin Rea Professor

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 8288–8292, September 1992
Cell Biology

Rudimentary form of cellular "vision"

(BHK cells/infrared light/cell polarity/cell–cell communication)

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Communicated by Howard Green, June 1, 1992

Experimental Cell Research **279**, 167–176 (2002)
doi:10.1006/excr.2002.5602

Water Structuring Centers of Mammalian Cell Surfaces

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Genomics 90 (2007) 297–305

GENOMICS

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Inversions and inverted transpositions as the basis for an almost universal "format" of genome sequences

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Received 21 March 2007; accepted 21 May 2007
Available online 20 June 2007

Functional genomics & bioinformatics DOI 10.1002/bies.080081

The spectra of point mutations in vertebrate genomes

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Materials and methods

The genome sequences of human, chimpanzee, rat, mouse, pufferfish, zebrafish, and sea squirt were obtained from the UCSC site.

The analysis program, "dnaorg.exe", was written by G.A.-B. using Visual C++ (Microsoft, Redmond, WA).

Results

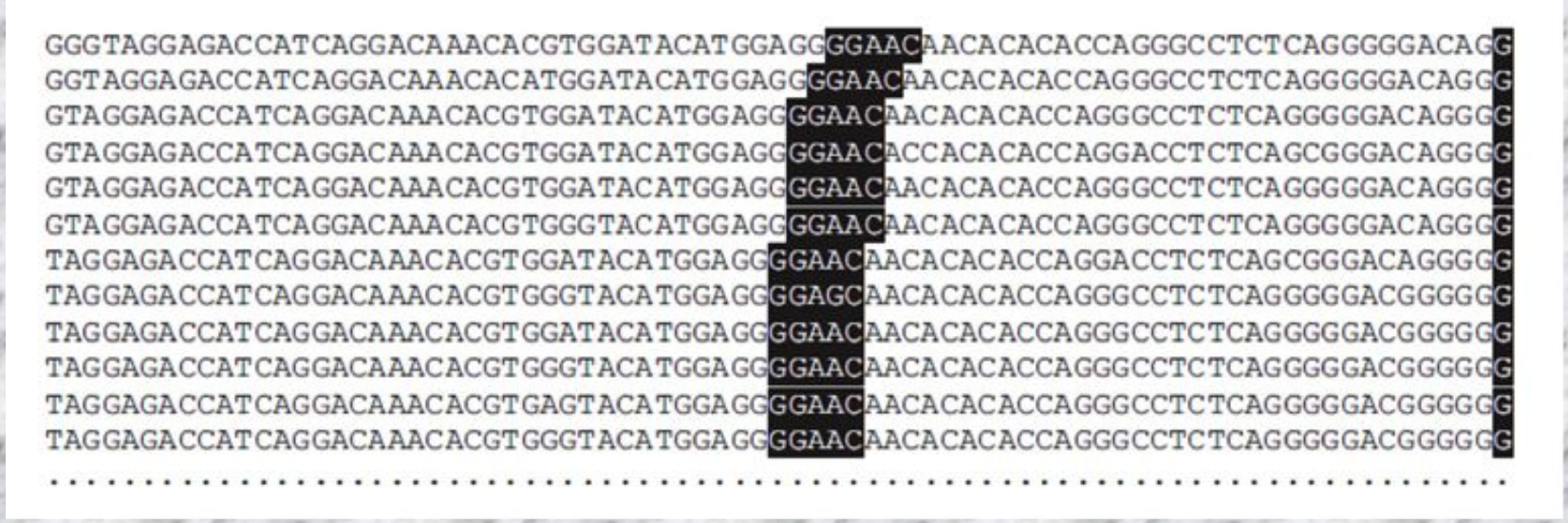
Point mutation spectrum

The remaining 12 possible point mutations are

[C → A], [T → A], [G → A], [A → C], [T → C], [G → C],
[A → T], [C → T], [G → T], [A → G], [C → G], [T → G].

[A → T], [C → T], [G → T], [A → G], [C → G], and [T → G].

Example 1a: punctuated sequence in human chromosome 1 starting at position 643,635



Example 1b: example of a point mutation [T→C] in a vertical column of an aligned inter-punctuation segment

```
..GGGTAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
...GGTAGGAGACCATCAGGACAAACACATGGATACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
....GTAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
....GTAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACACCACACACCAGGACCTCTCAGCGG...
....GTAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
....GTAGGAGACCATCAGGACAAACACGTGGGTACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
.....TAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACAACACACACCAGGACCTCTCAGCGG...
.....TAGGAGACCATCAGGACAAACACGTGGGTACATGGAGGGGAGCAACACACACCAGGGCCTCTCAGGGG...
.....TAGGAGACCATCAGGACAAACACGTGGATACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
.....TAGGAGACCATCAGGACAAACACGTGGGTACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
.....TAGGAGACCATCAGGACAAACACGTGAGTACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
.....TAGGAGACCATCAGGACAAACACGTGGGTACATGGAGGGGAACAACACACACCAGGGCCTCTCAGGGG...
.....................................................................
```

Example 1c: identification of point mutations in the manually aligned inter-punctuation segments of Example 1a

```
GCACCACCACCACCATCACCACCATCATAACCA
TTACCATCACTACCATCATCATCACCACCACCA
CCATCACCCCTACCACCACCACCATCATCACCA
CCACCACCACCACCACCATCACCACCACCATCA
CCACCACCACCATCACTACCACCACCACCACCA
CCCCCATCACTACCACTCATCATCACCACCACA
CCATCACCACCATCACCACCACCACCACCACCA
CCATCACCACCACCACCATCACTACCACCACCA
CCACCCCCATCACTACCATCATCATCACCACCA
CCACCATCACCACCATCACCACCACCACCATCA
TCACCACCACCATCACCACCACCACCACCACCA
CCACCAGCACCACCACCATCACCACCACCACCA
TCACCACCACCACCACCACCACCCCCACTACCA
.....................................
```

Example 2: almost repetitive stretch of tri-nucleotides "XYA" in human Chromosome 7 with highlighted punctuating base "A" and point mutations

Spectra of point mutations

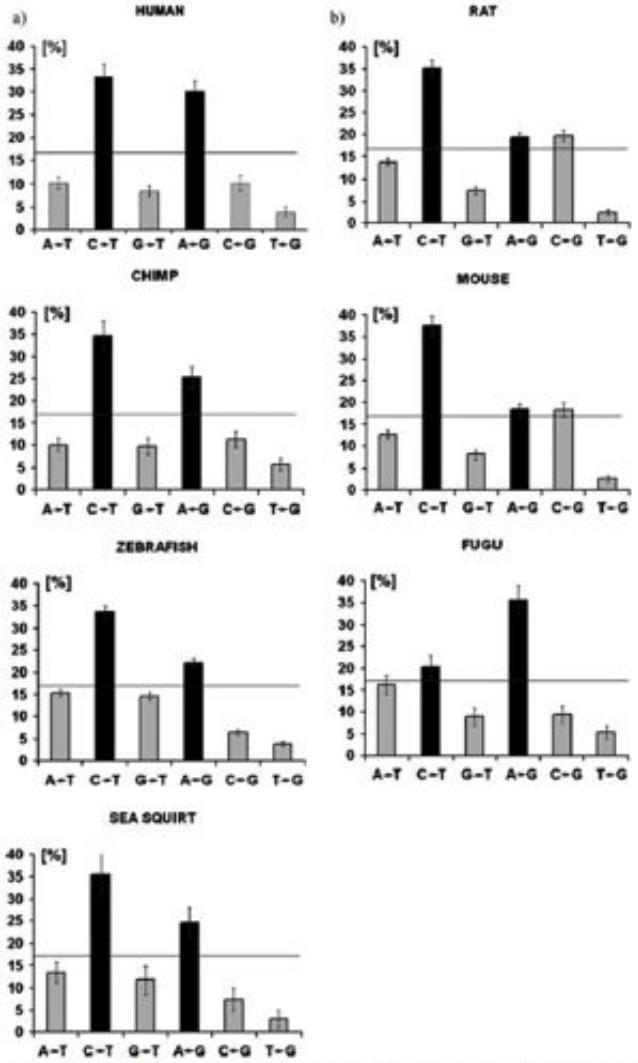


Figure 2. a: Normalized spectra of point mutations S([X → Y]) found in the punctuated sequences of the complete genomes of human (8,103 point mutations), chimpanzee (3,098 point mutations), zebrafish (17,914 point mutations), and sea squirt (1,419 point mutations). Axes as in Fig. 1. The horizontal lines are drawn at the average level of frequency = 1/6. The error bars represent standard errors of the counts. For better visualization of the patterns, the largest peaks were rendered black. b:Normalized spectra of point mutations S([X → Y]) found in the punctuated sequences of the complete genomes of rat (10,106 point mutations), mouse (8,039 point mutations), and pufferfish (fugu) (2,393 point mutations). Axes and labels as in Fig. 2a.

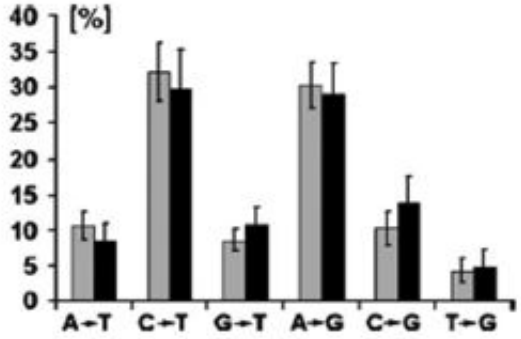


Figure 1. Comparison of the spectra of the point mutations S([X → Y]) found in the punctuated sequences of human chromosomes 1, 2, 3, 4, 5, 6, 7, 17, and X with (gray columns; 3,766 point mutations) and without (black columns; 2,005 point mutations) tandem sequences. The abscissa shows the six essential point mutations [X → Y] (see (2)). The error bars represent standard errors of the counts.

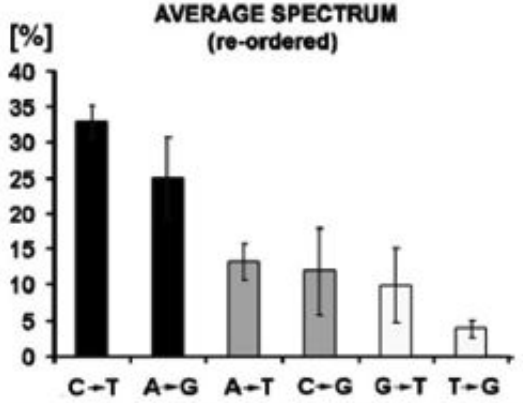


Figure 3. Average spectrum of the spectra S([X → Y]) shown in Fig. 2a and b ordered by amplitude. Error bars indicate standard deviations of the averages. As described in the Discussion, the grouping of the six essential point mutations into the two most frequent (black columns), two intermediate frequent (gray columns) and the two least frequent (white columns) mutations, may help identify different underlying mechanisms.

(I) The two largest peaks at [C->T] and [A->G] may be the result of enzymatic inter-conversion such as the deaminationof 5-methyl-cytosine or the de-methylation of 2-aminated-adenine.

(II) The two next smaller peaks at [A->T] and [C->G] are in effect single base pair inversions. For example, if A is changed into T on one strand, then there was initially a complementary T on the opposite strand that was subsequently changed into A, which means that the AT-pair effectively flipped around. Therefore, in order to explain these peaks, I make the ad hoc assumption that there are natural mechanisms of single base-pair inversions.
Of course, the base pairs must not physically flip around, as their 5'-ends would collide with 5'-ends and their 3'-ends with 3'-ends. Hence, the flipping around must be effectively the excision of an AT- or GC-pair followed by the insertion of the corresponding inverted pair. There is **no generally known mechanism** of single pair inversion. However, each of the four possible cases, namely [A->T],(13,14) [T->A],(15) [C->G],(16) and [G->C](17) have been observed as naturally occurring gene mutations related to human disease.

(III) The two remaining peaks [G->T],and [T->G] can be explained as the result of a combination of the two described mechanisms, namely an inter-conversion followed by a single base-pair inversion.

The article emphasizes the auto-mutagenic character of the suggested mechanisms of point mutations because it could help explain the high speed of evolution. If genomes would, indeed, mutate themselves vigorously not only by countless transpositions but also by self-created point mutations, the number of mutations, especially in the germ line, could be much larger than currently accepted exogenous mutation mechanism such as cosmic radiation can account for.