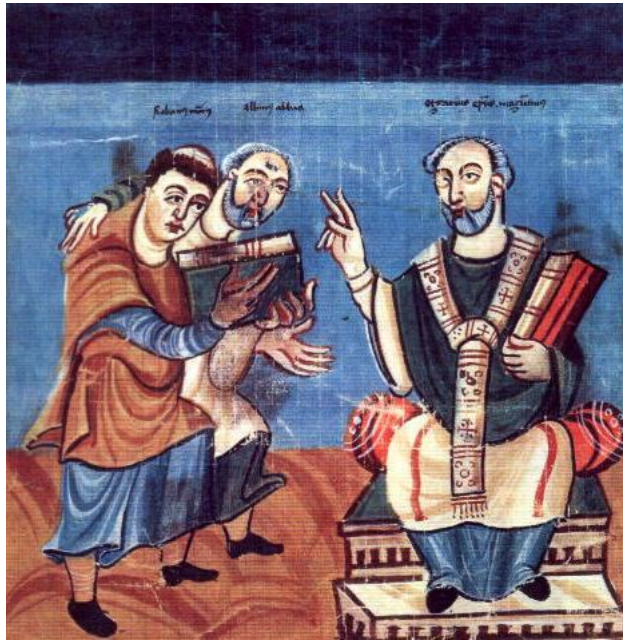


# How evolution designs living matter

Ard Louis





## *Propositiones ad acuendos iuvenes* “Problems to sharpen the young”

- Problem 13:

*“A king ordered his servant to collect an army from 30 manors, in such a way that from each manor he would take the same number of men he had collected up to then. The servant went to the first manor alone; to the second one he went with one other; to the next he took three with him, How many were collected from the 30 manors?”*

Alcuin of York  
735-804

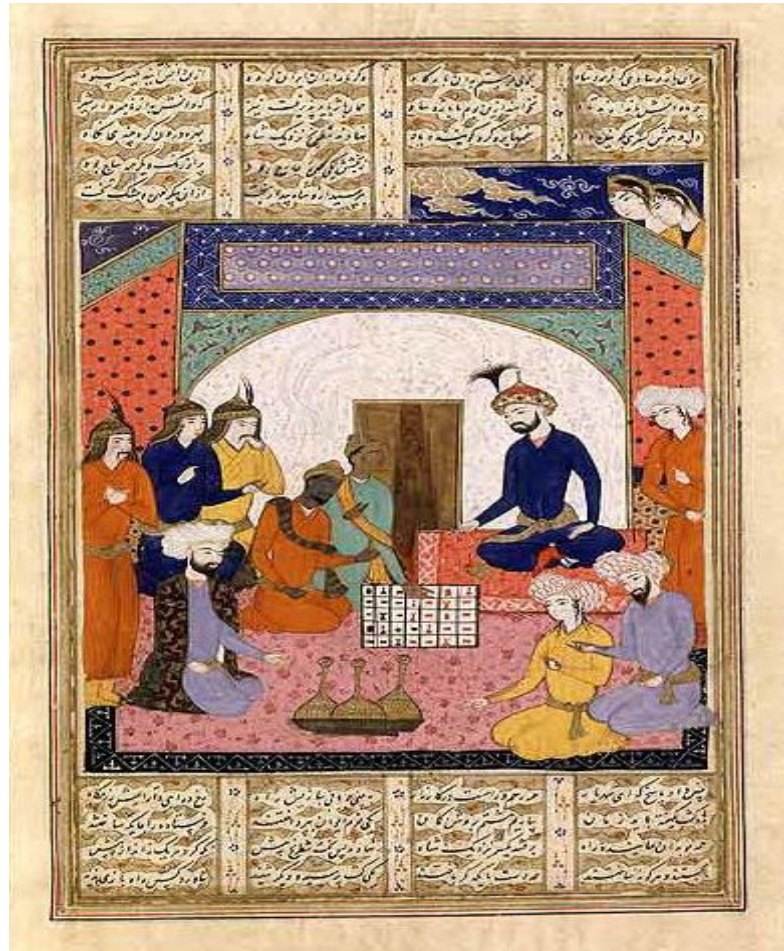
$2^{30}-1= 1,073,741,823$  (1 billion) soldiers,



A barley-corn: to a single  
barley-corn I increased,  
2 barley-corns in the 1st day;  
4 barley-corns in the 2nd day;  
8 barley-corns in the 3rd day;  
..  
..  
30 2 'thousand' 7 'hundred' 37  
talents 1/2 mina 2 1/3 shekels 4  
barley-corns in the 30th day.

Mari 08613 tablet  
(Old Babylonian. 1900-1600 BC)

$$2^{64}-1= 18,446,744,073,709,551,615$$

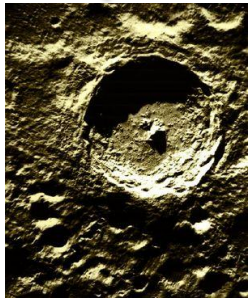
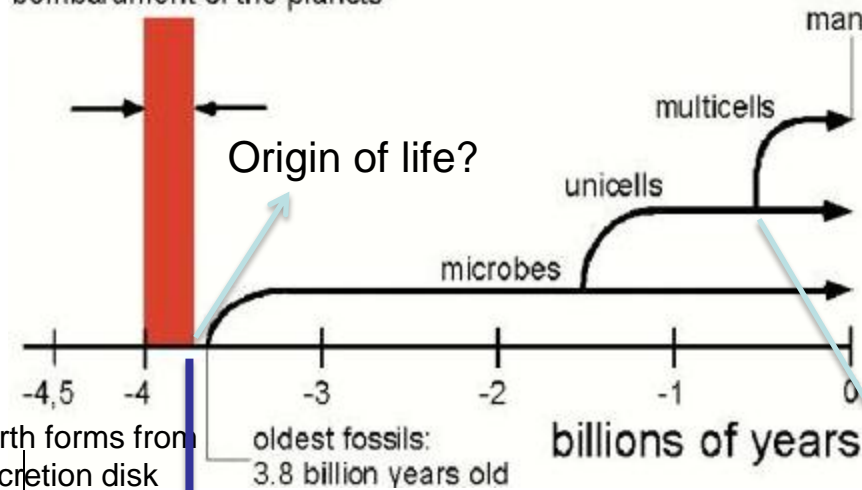


Shah-nama (Persian: شاهنامه Šāhnāmeḥ, "The Book of Kings")  
by Ferdowsi(فردوسی) 940 – 1020

# History of life on earth

## the evolution of life

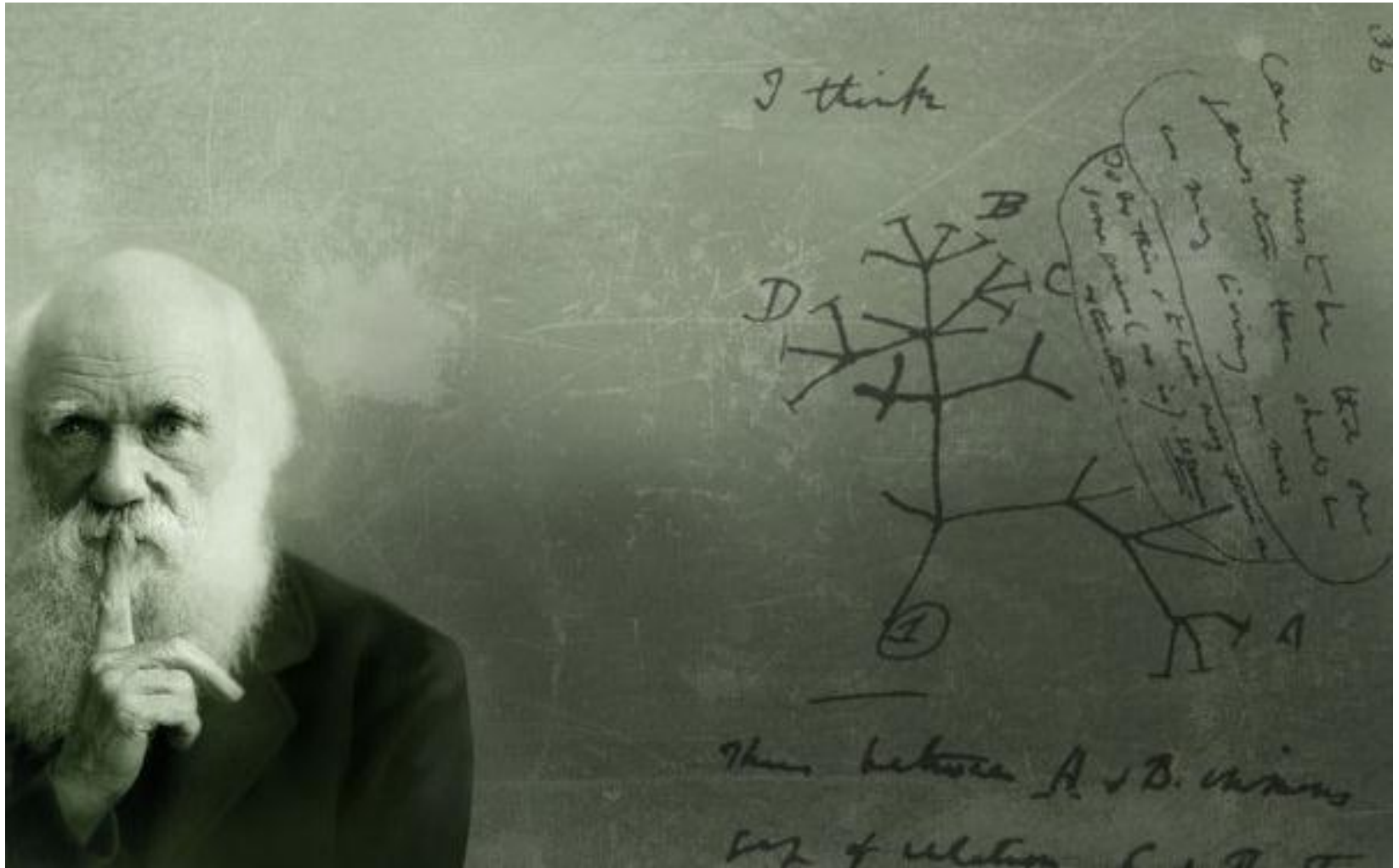
bombardment of the planets



Late heavy bombardment

era	time (millions of years ago)	important events
Cenozoic	0.0	present time
	less than 0.1	advent of modern humans
	2.4	ice age
Mesozoic	66.4	mass extinction
	141	first flowering plants
	195	birds evolve from reptiles
	230	first dinosaurs and mammals
	245	mass extinction
Paleozoic	280	mass extinction
	340	reptiles appear
	360	first insects
	370	amphibians appear
	420	plants colonize land
	540	mass extinction
Precambrian	700	simple multicellular organisms evolve
	2,100	oldest eukaryotic fossils
	2,500	oxygen begins to accumulate in atmosphere
	3,500	oldest prokaryotic fossils

# 1859: Variation and Natural Selection



# Arrival of the fittest?

where does variation come from?

“Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest.”

*Species and Varieties. Their Origin by Mutation.* Chicago: Open Court (1904)



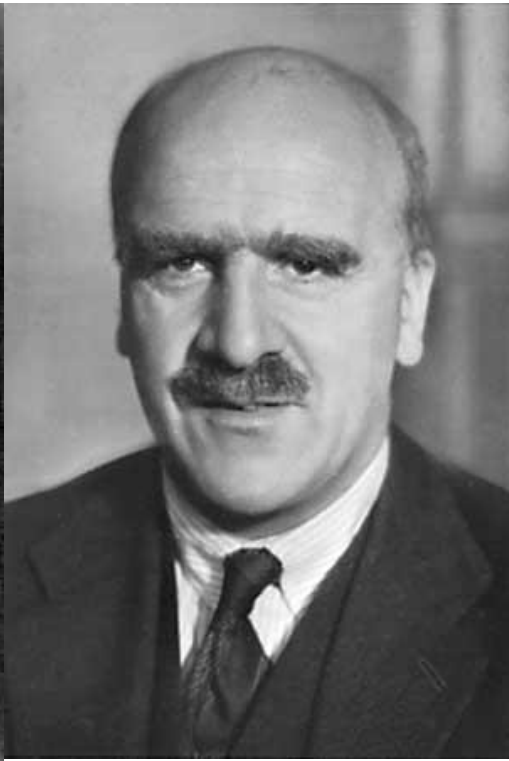
Natural selection as a sieve?

Hugo de Vries 1848-1935

# Modern Synthesis



R.A. Fisher  
1890 – 1962



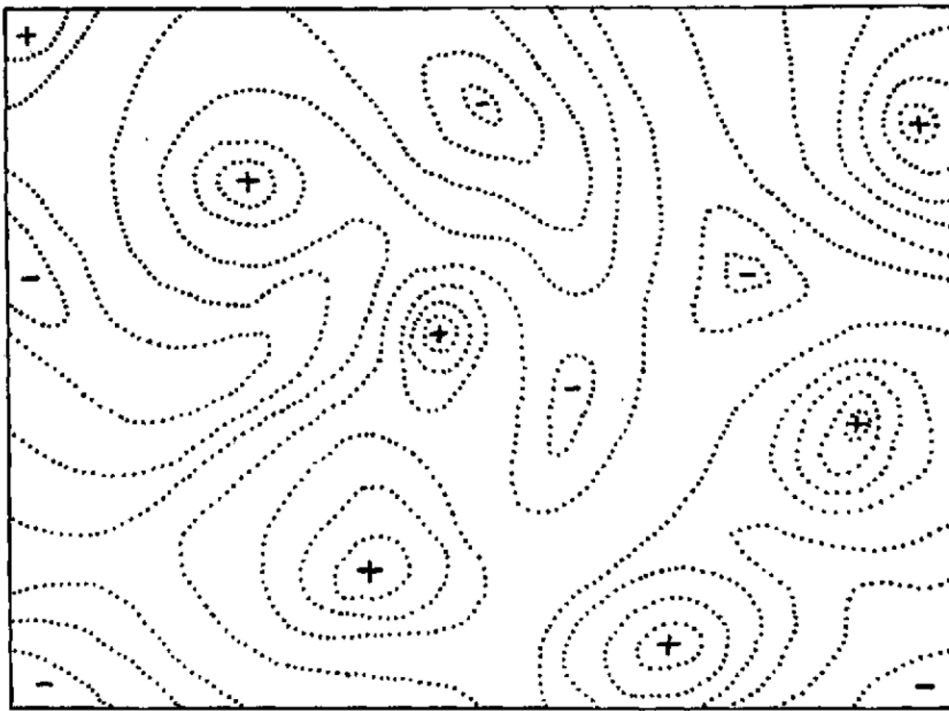
JBS Haldane  
1892 – 1964



Sewall Wright  
1889 – 1988



How big is evolutionary  
search space?



Sewell Wright

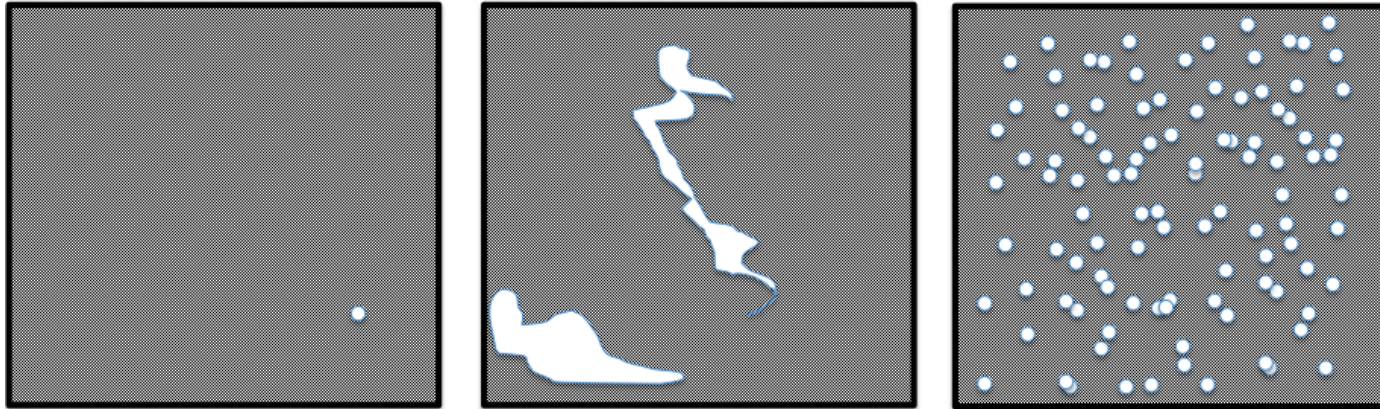
FIGURE 2.—Diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands. Dotted lines represent contours with respect to adaptiveness.

Estimates of the total number of genes in the cells of higher organisms range from 1000 up ... With 10 alleomorphs in each of 1000 loci, the number of possible combinations is  $10^{1000}$  which is a very large number. It has been estimated that the total number of electrons and protons in the whole visible universe is much less than  $10^{100}$ "

↑  
hyperastronomical

*“The population is thus confined to an infinitesimal portion of the field of possible gene combinations”*

1. Nature can only explore an unimaginably small fraction of all theoretically possible genomes.



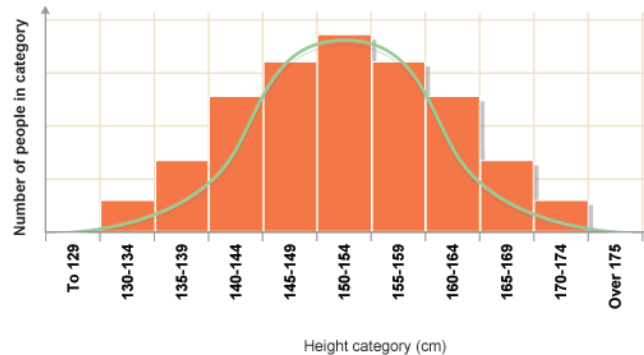
*“The chance that a random combination is as adaptive as those characteristic of the species may be as low as  $10^{-100}$  and still leave room for  $10^{800}$  separate peaks [adaptive gene combinations], each surrounded by  $10^{100}$  more or less similar combinations. “*

2. The current instantiation of genetic possibilities (life as we know it) is largely contingent, since it could just have well occupied a different part of genotype space.

*“... under biparental reproduction a very low rate of mutation balanced by moderate selection is enough to maintain a practically infinite field of possible gene combinations within the species “*

3. The variation for natural selection to act on is abundant.

4. Variation does not introduce a significant bias in evolutionary trajectories

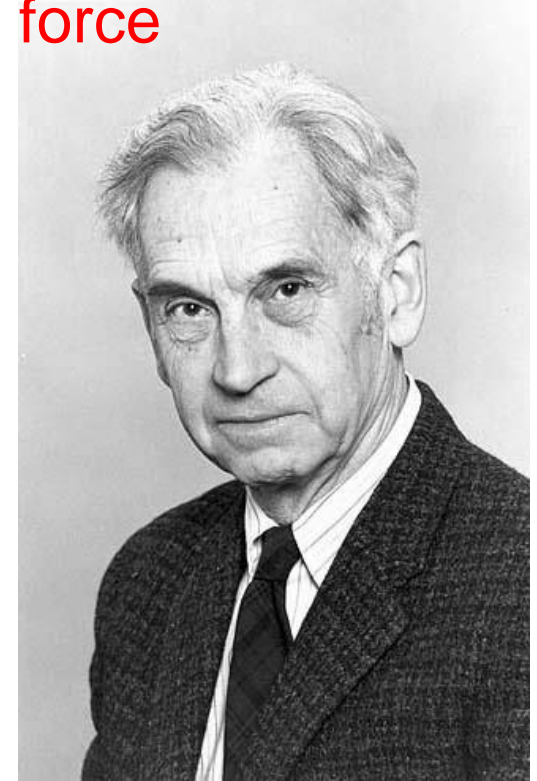


# Where does evolutionary novelty come from?

MS: selection (not variation) is primary causal force

*Evolution is not primarily a genetic event. Mutation merely supplies the gene pool with genetic variation; it is selection that induces evolutionary change.*

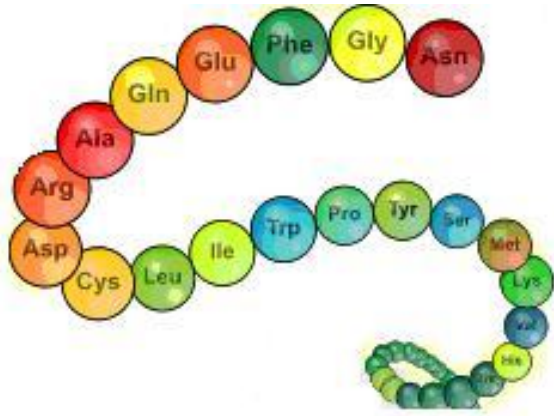
-- Ernest Mayr, *Animal Species and Evolution*, HUP 1963)



Ernest Mayr – 1904-2000

# Evolution and hyper-astronomical numbers

Proteins: linear chains made from an alphabet of 20 amino acids



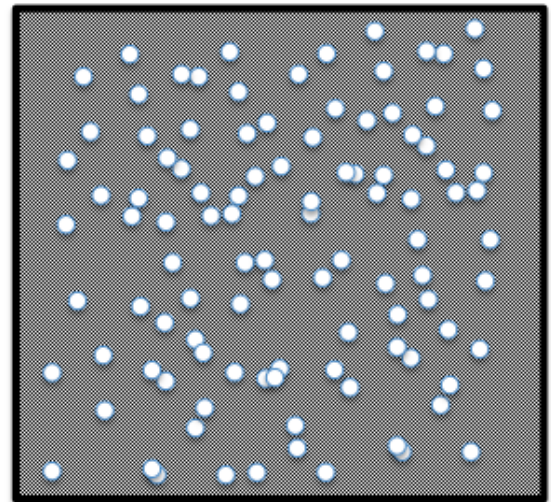
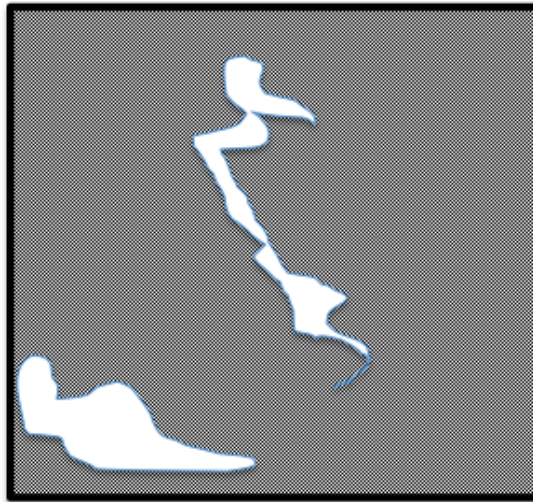
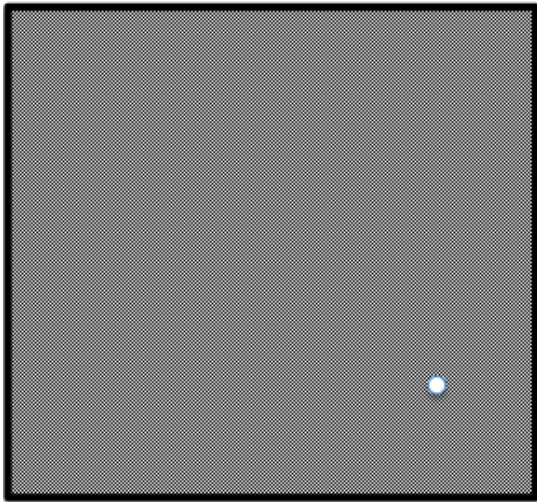
## Hoyle Paradox

all combinations of length  
100 proteins would weigh  
more than the visible  
universe.



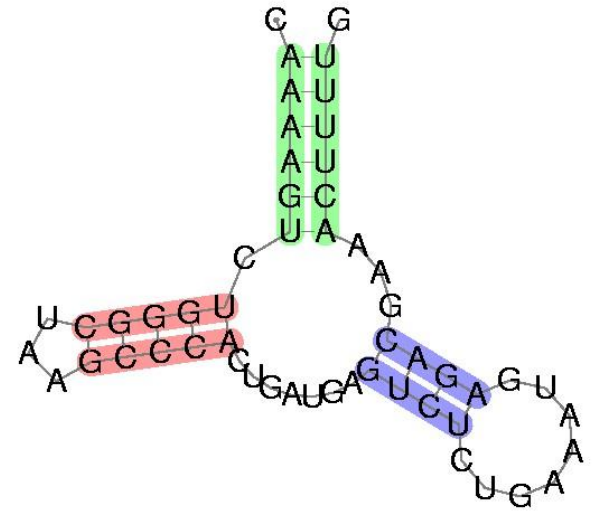
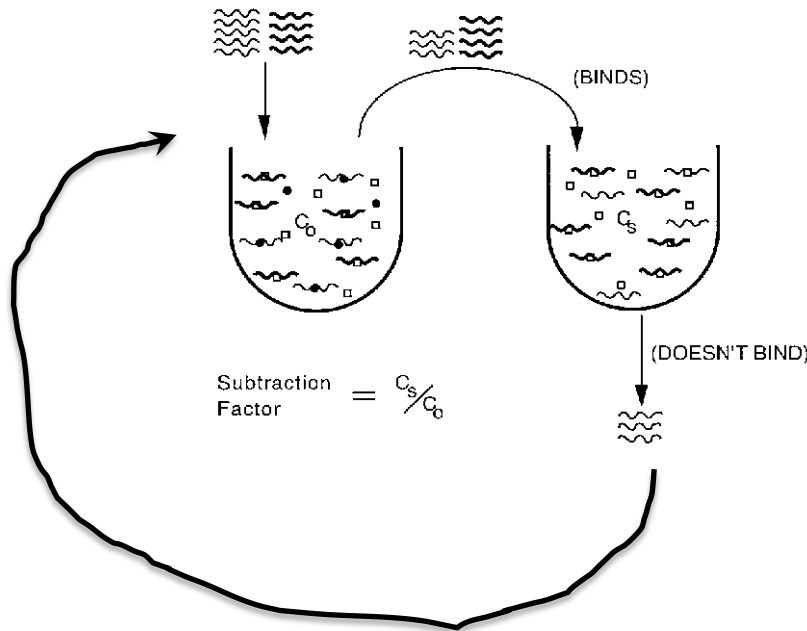
Fred Hoyle 1915-2001

what does search space look like?



# Convergent Evolution?

Hammerhead ribozyme keeps emerging from SELEX in-vitro evolution



RNA: alphabet of 4 nucleotides, so  $L=55$  means  $4^{55} \sim 10^{33}$

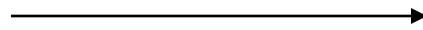
Salehi-Ashtiani K, Szostak JW. In vitro evolution suggests multiple origins for the hammerhead ribozyme. *Nature*. 2001 Nov 1;414(6859):82-4.



# Convergent Evolution?

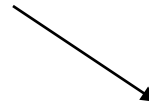
North America:

Placental Sabre-toothed cat



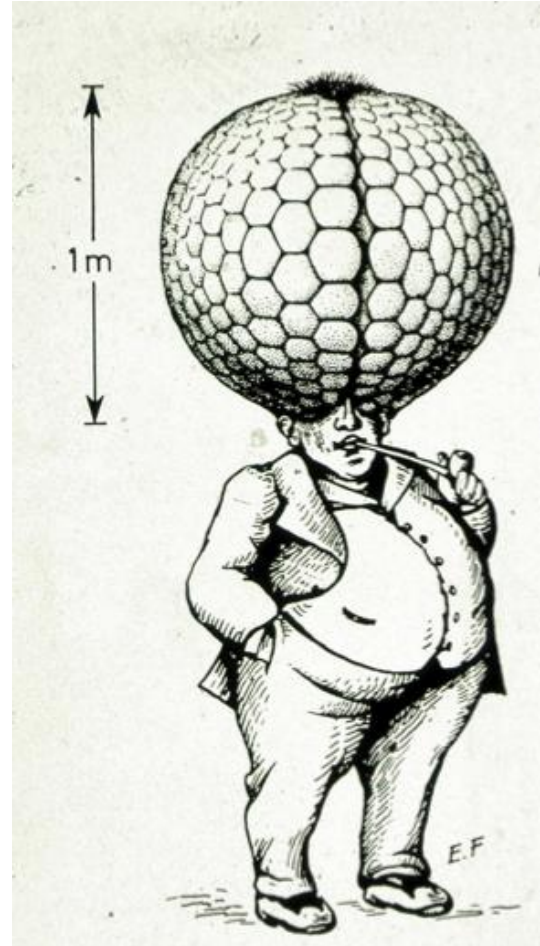
South America”

Marsupial Sabre-toothed cat

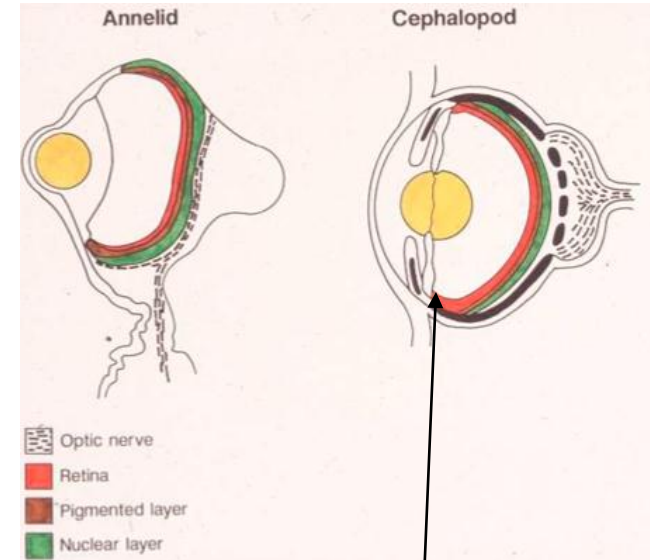


# Convergent Evolution?

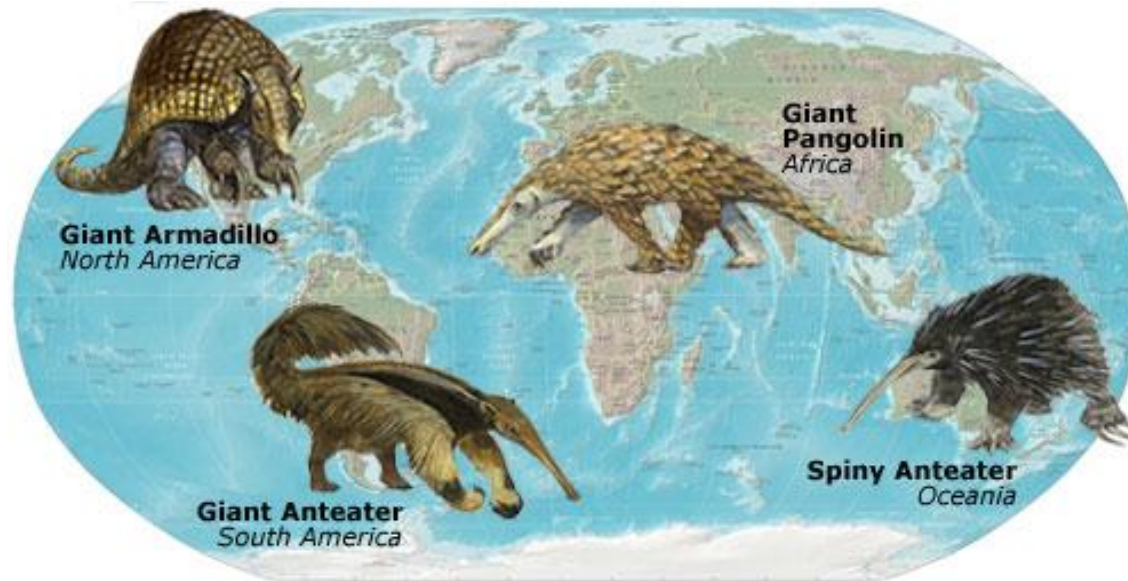
compound eye



camera eye



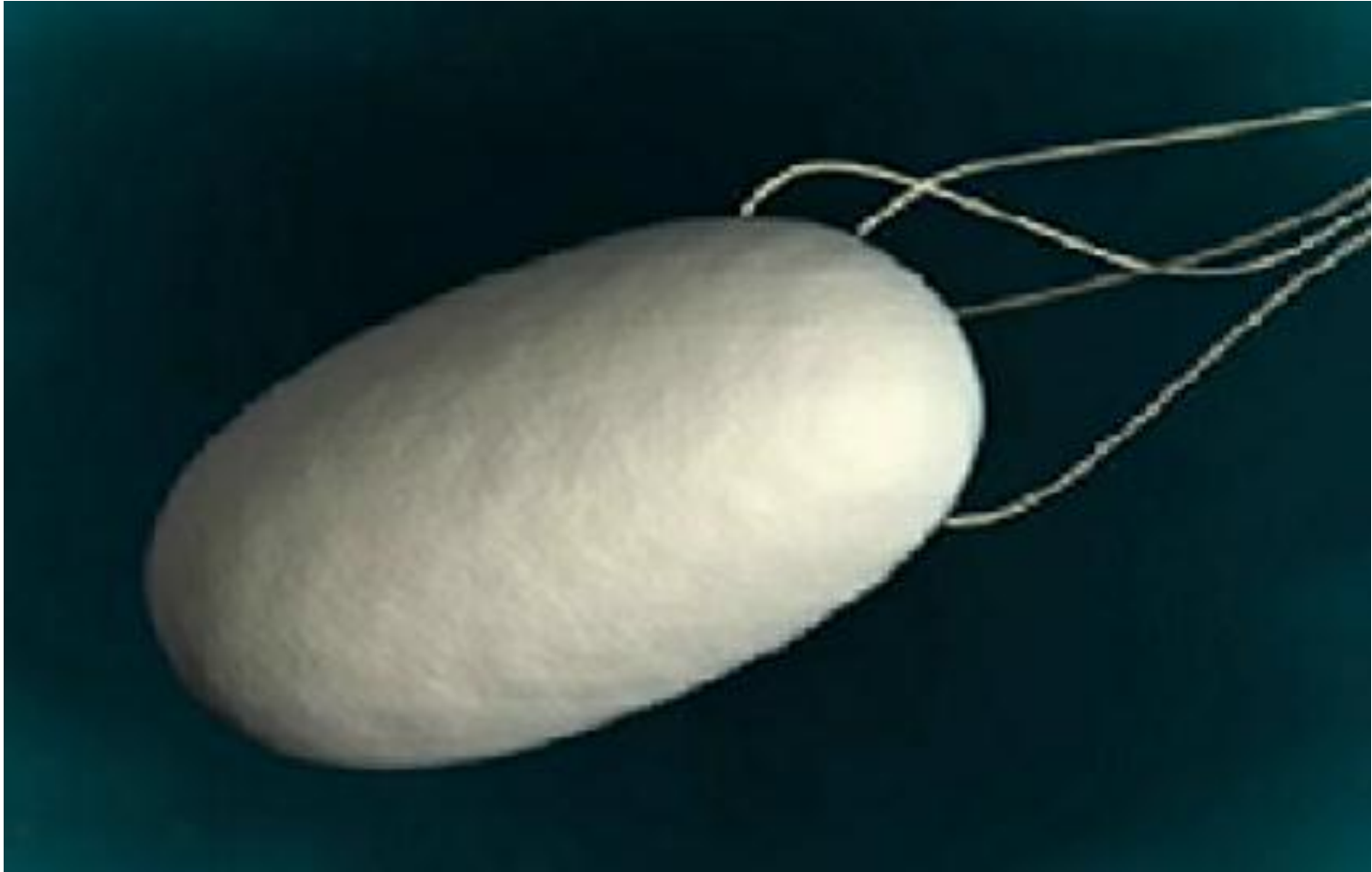
# Convergent Evolution?



- Enormous number of examples ... from proteins to vision up to societies to intelligence.
- <http://www.mapoflife.org>
- **Why all this convergence? variation or selection or something else?**

The principal aim of this book has been to show that the constraints of evolution and the ubiquity of convergence make the emergence of something like ourselves a near-inevitability. Simon Conway Morris, "Life's Solution", (CUP 2003) pp328

# Biological self-assembly



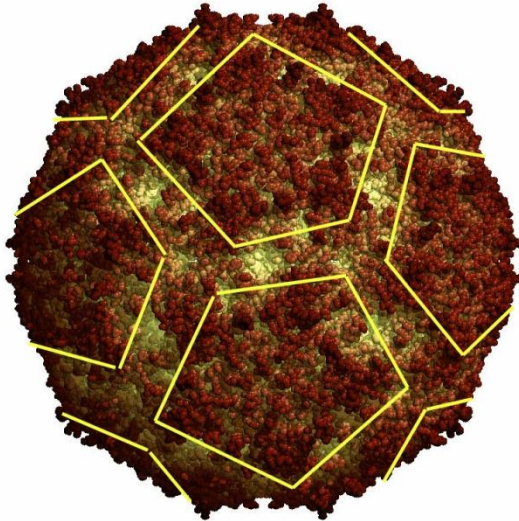
Movie from: Keiichi Namba, Osaka ERATO  
project?

- Can we understand?
  - Self-assembly
  - Evolution
- Can we emulate (nanotechnology?)

# Virus self-assembly

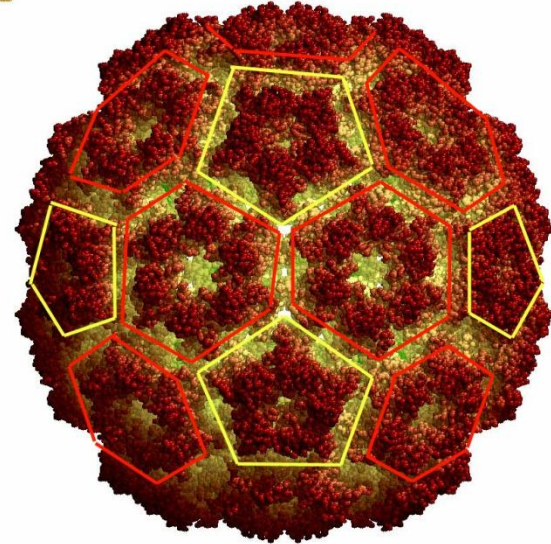
20Å

**Galleria mellonella densovirus PDB\_ID: 1DNV**



20Å

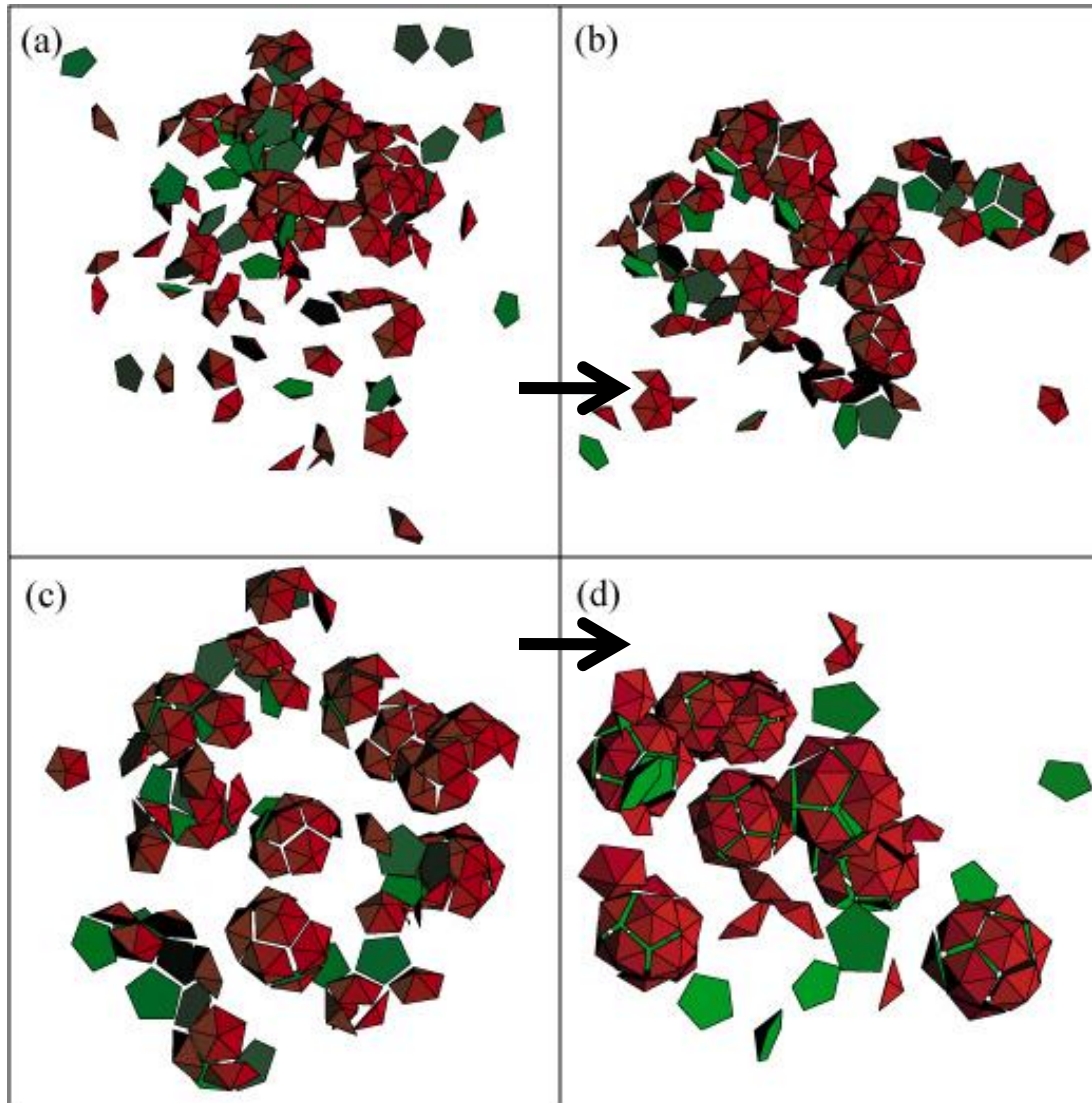
**Cucumber mosaic virus PDB\_ID: 1F15**



viruses

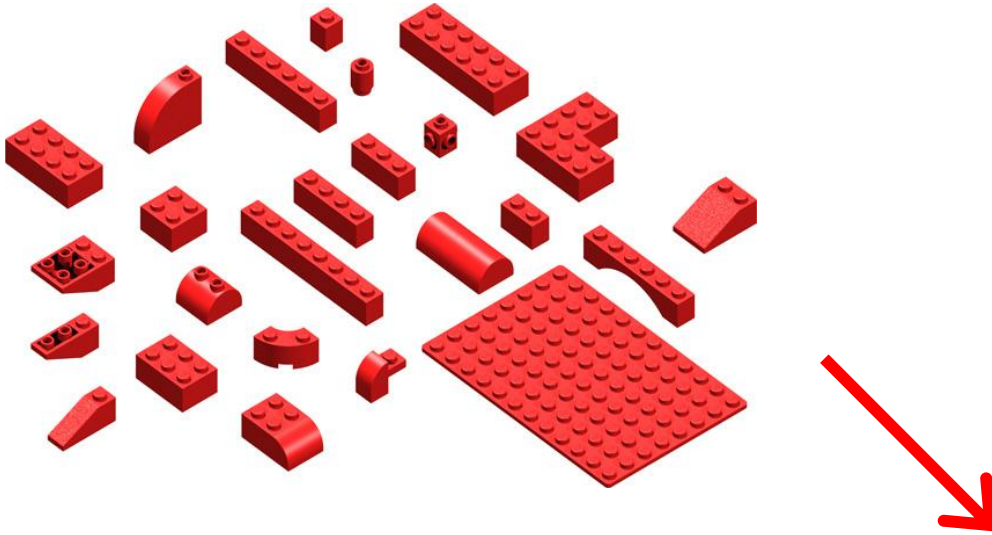
viruses assemble from identical capsomeric units

# “computer virus” self-assembly

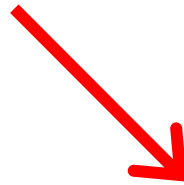
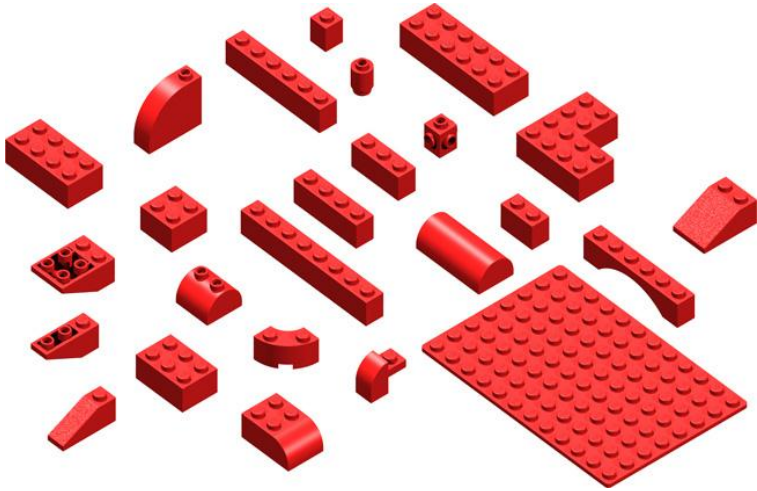


Computer viruses?

# Biological self-assembly



# Science is fun!





# Protein folding (self-assembly)



## Levinthal Paradox (1968):

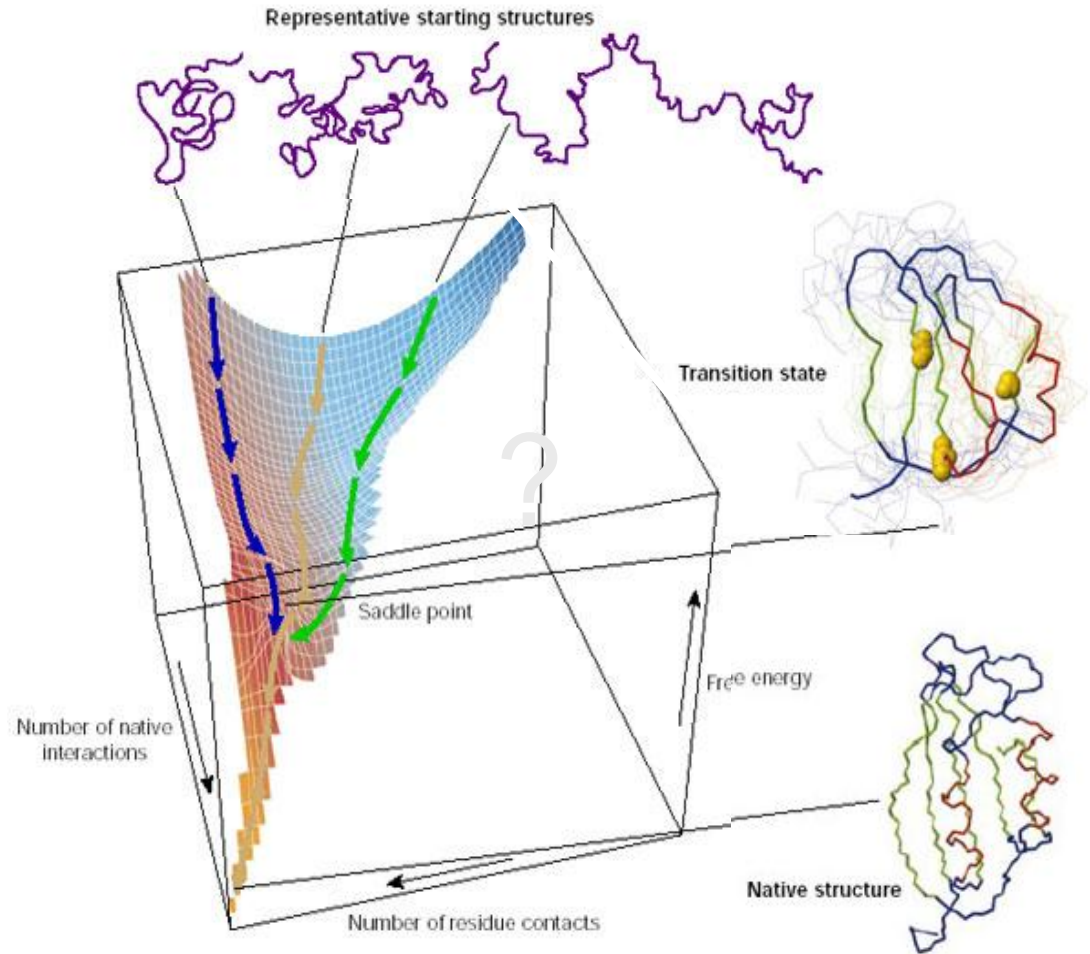
150 amino acids

~10 angles between them

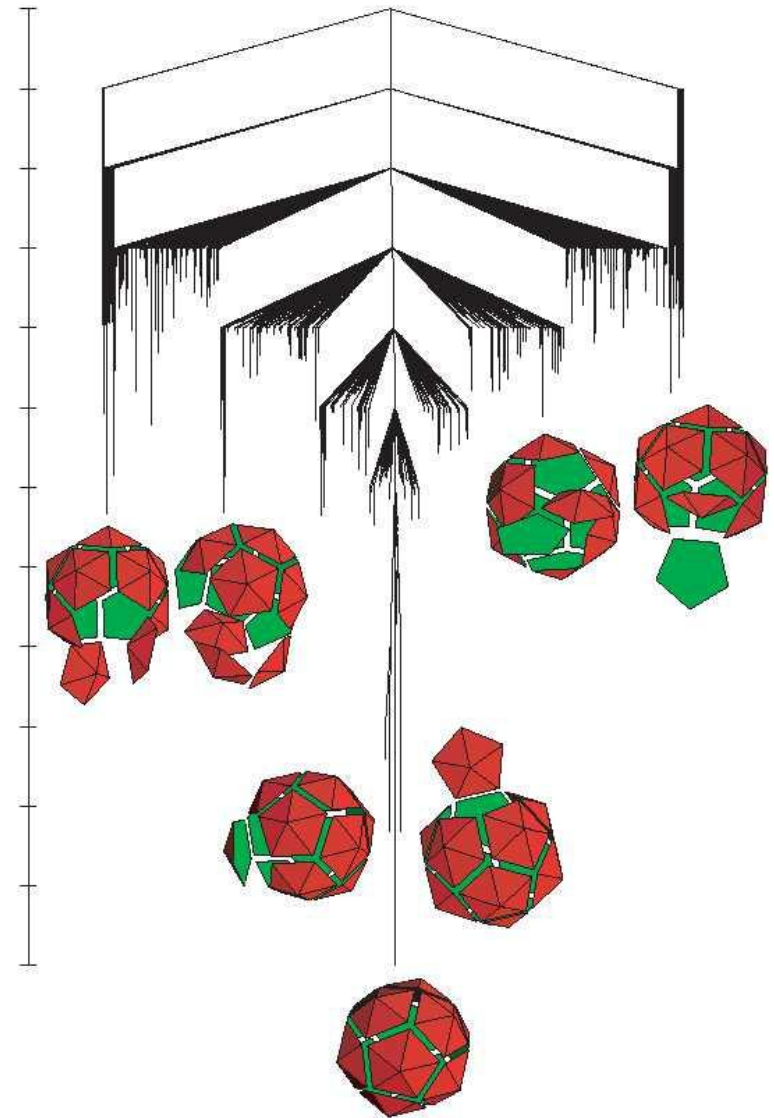
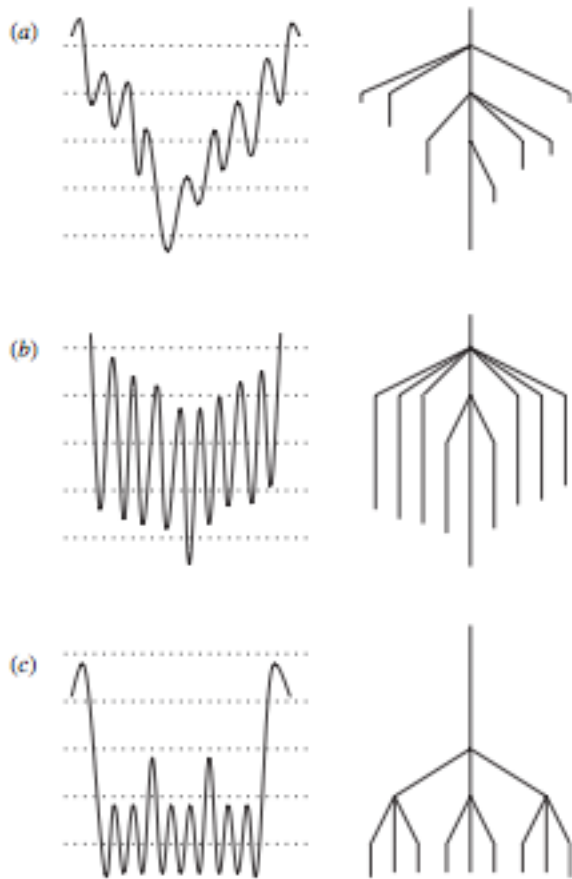
~ $10^{150}$  different states.

How does protein find its folded native structure?

**The search is not random!**



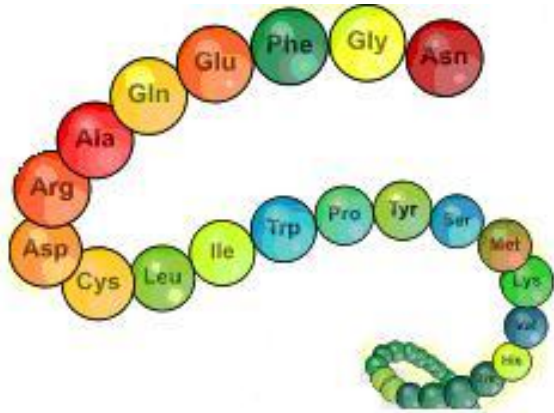
# Energy landscape for a virus capsid



**The search is not random!**

# Evolution and hyper-astronomical numbers

Proteins: linear chains made from an alphabet of 20 amino acids



## Hoyle Paradox

100 residue protein; 20 amino acids => combinations would weigh more than all the atoms in the visible universe.



Fred Hoyle 1915-2001

# how are genotypes distributed over phenotypes?

$$N_G \gg N_P$$

Neutral theory of evolution:

Kimura 1968

King and Jukes 1969

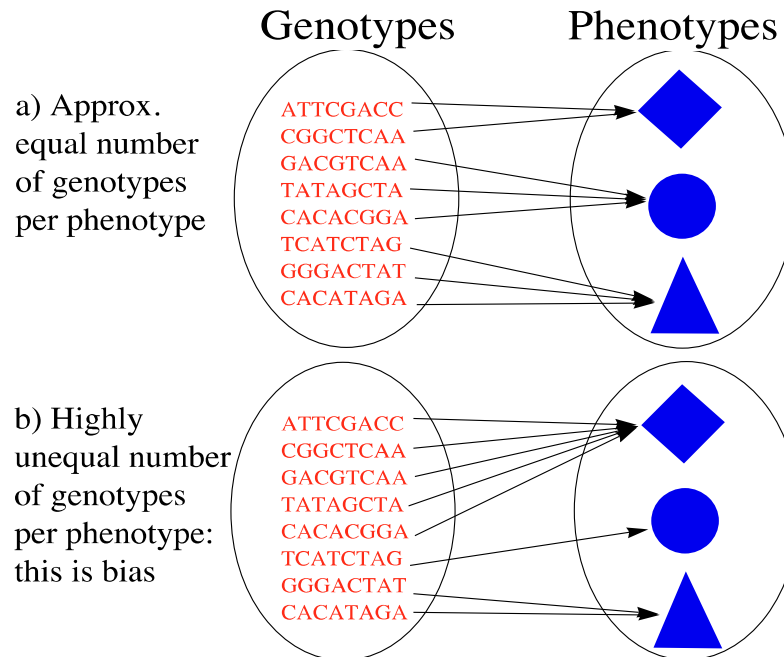
Lots of mutations are neutral ...  
e.g. proteins can have the same  
function with > 50% sequence  
dissimilarity



Motoo Kimura  
1924-1994

# how are genotypes distributed over phenotypes?

$$N_G \gg N_P$$

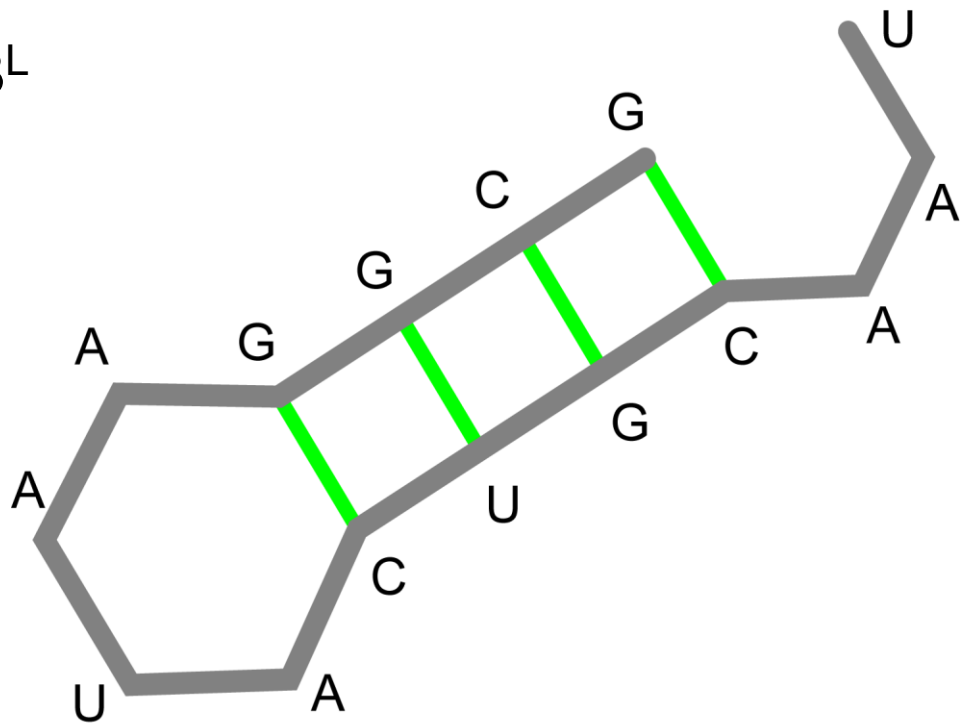


# Model GP map: RNA secondary structures

$$N_G = 4^L$$

$$N_P = 0.02 \times 1.93^L$$

$$N_G \gg N_P$$

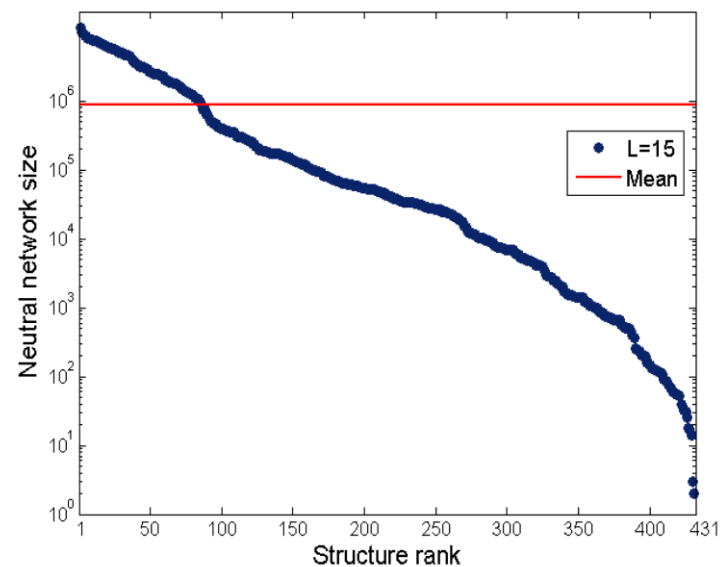
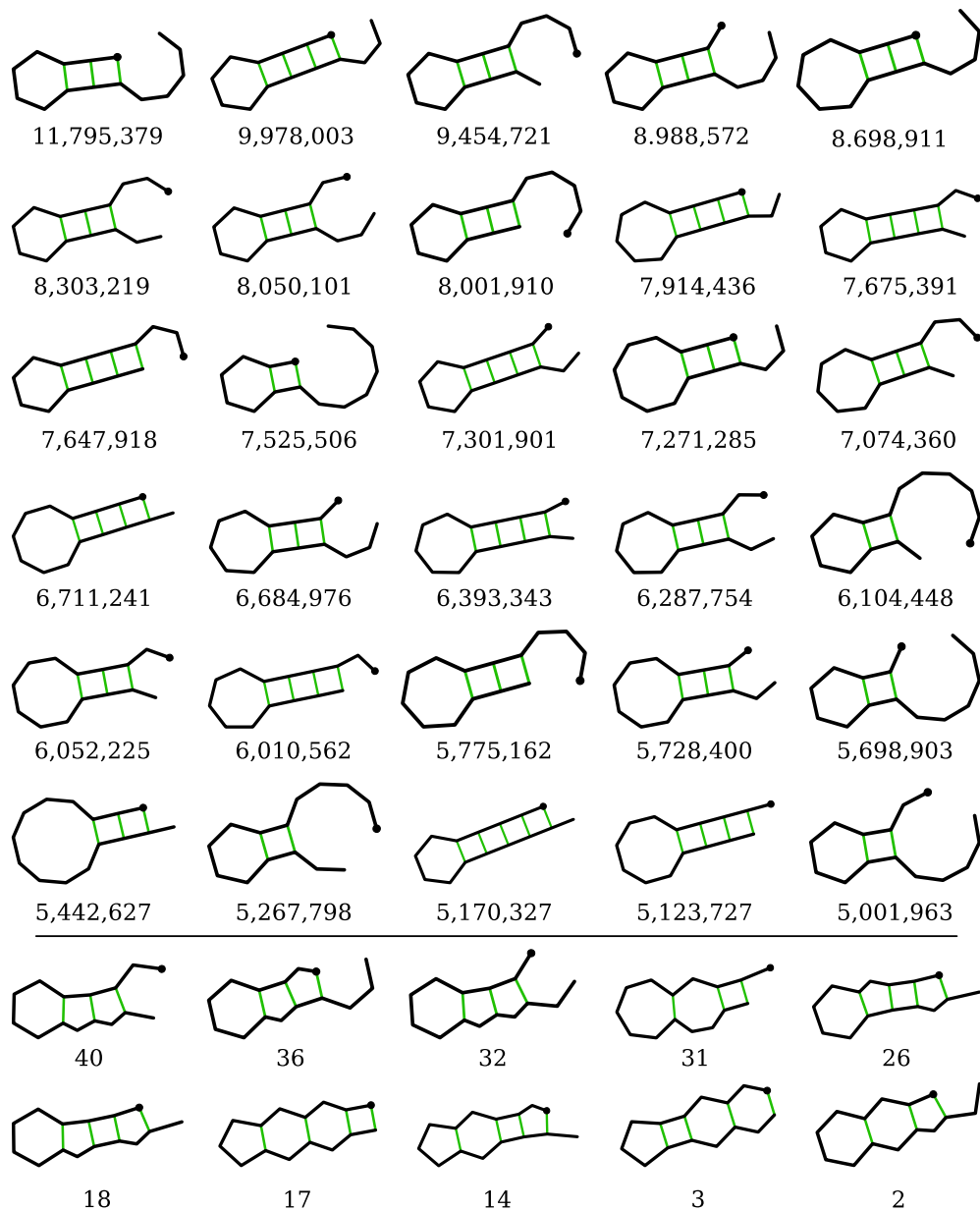


Genotype  
Phenotype

GCGGAAUACUGCAAU  
((( (. . . ))) . . .

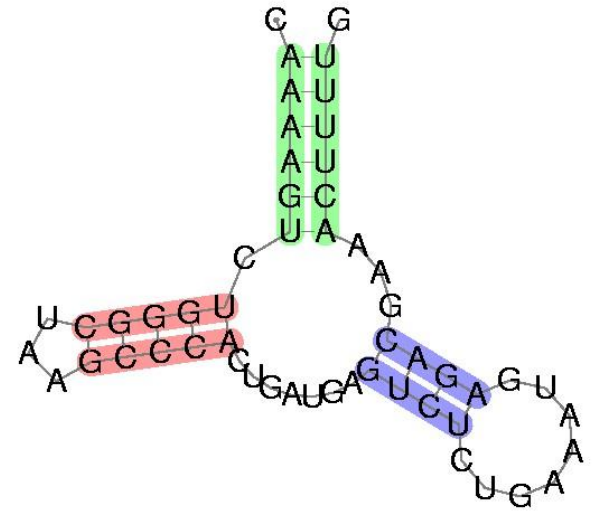
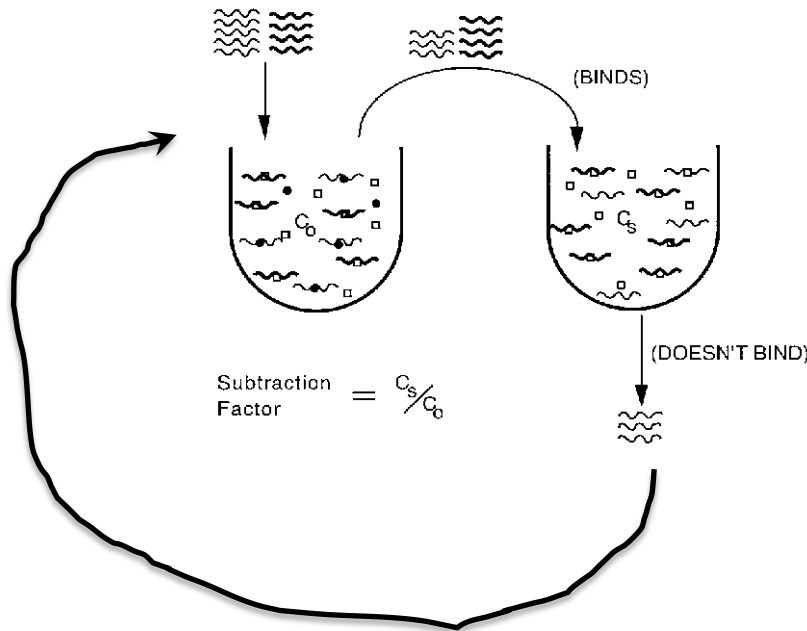
Sequence  
Structure

**L=15:  $4^{15} \sim 1 \times 10^9$  sequences -- 431 phenotypes – but 26/431 take up 50% of G-s**



# Convergent Evolution?

Hammerhead ribozyme keeps emerging from SELEX in-vitro evolution



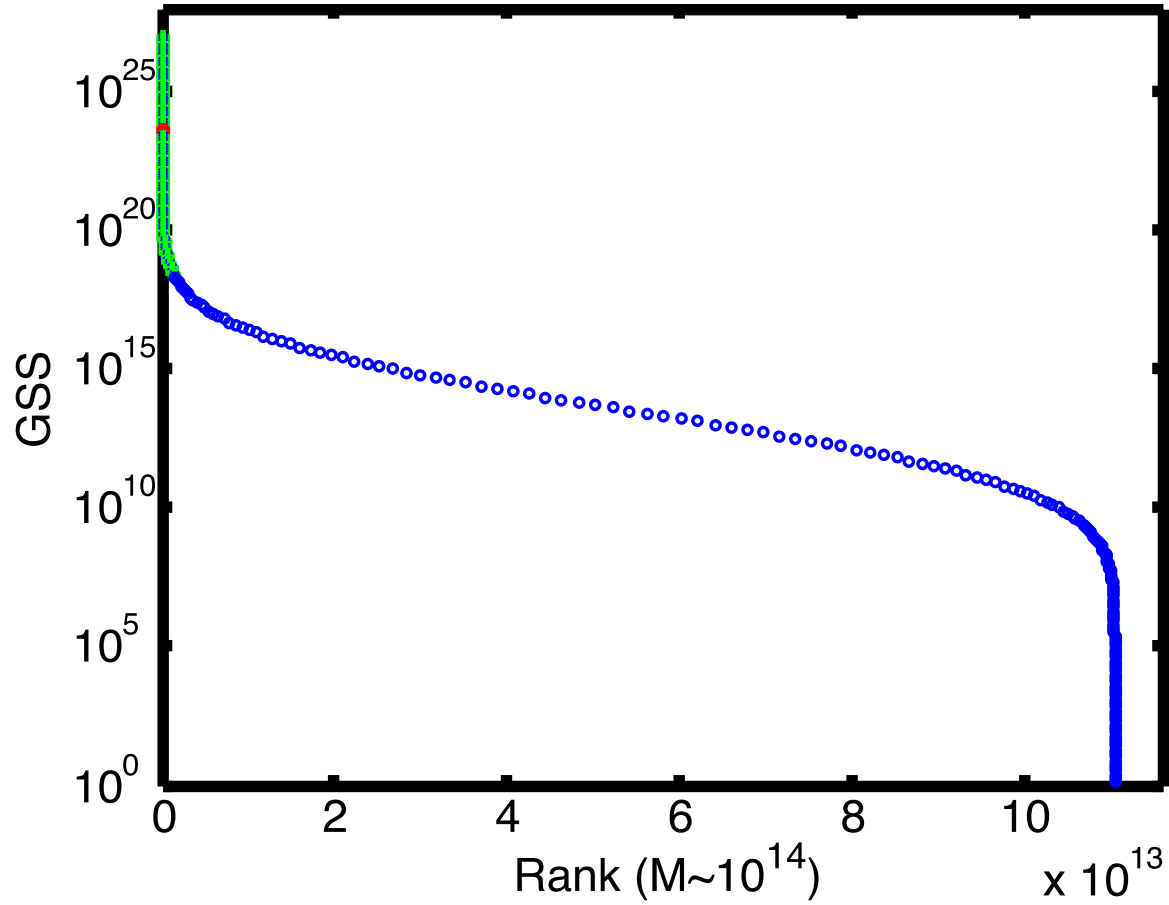
RNA: alphabet of 4 nucleotides, so  $L=55$  means  $4^{55} \sim 10^{33}$

Salehi-Ashtiani K, Szostak JW. In vitro evolution suggests multiple origins for the hammerhead ribozyme. *Nature*. 2001 Nov 1;414(6859):82-4.

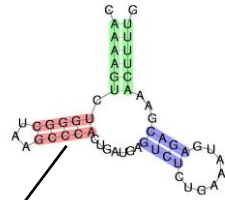


# larger RNA?

RNA GSS-rank plot, L=55

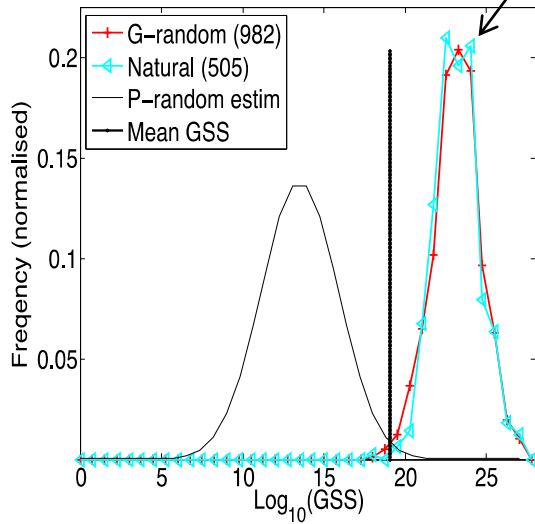


# RNA topology dominated by variation

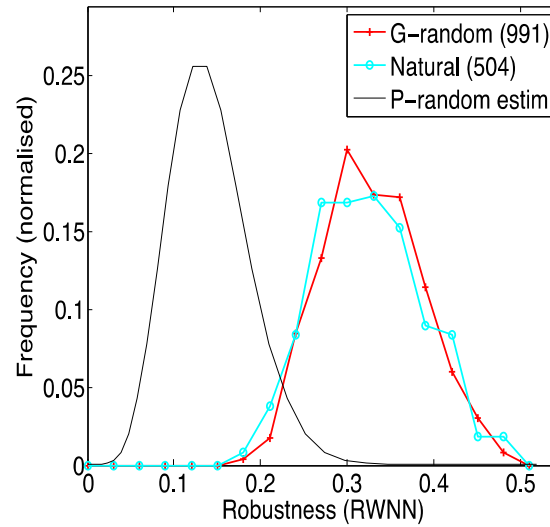


## hammerhead ribozyme

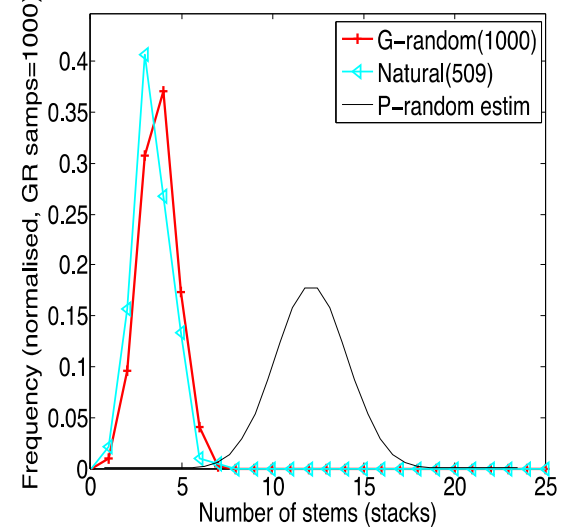
GSS for natural and sampled RNA L=55, param=33, binsize=0.75



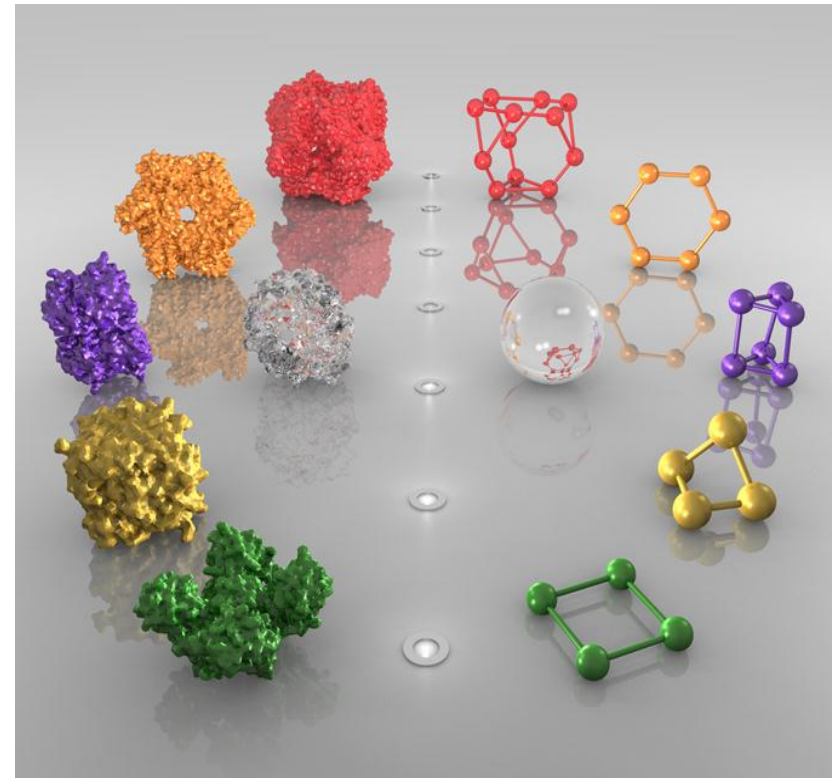
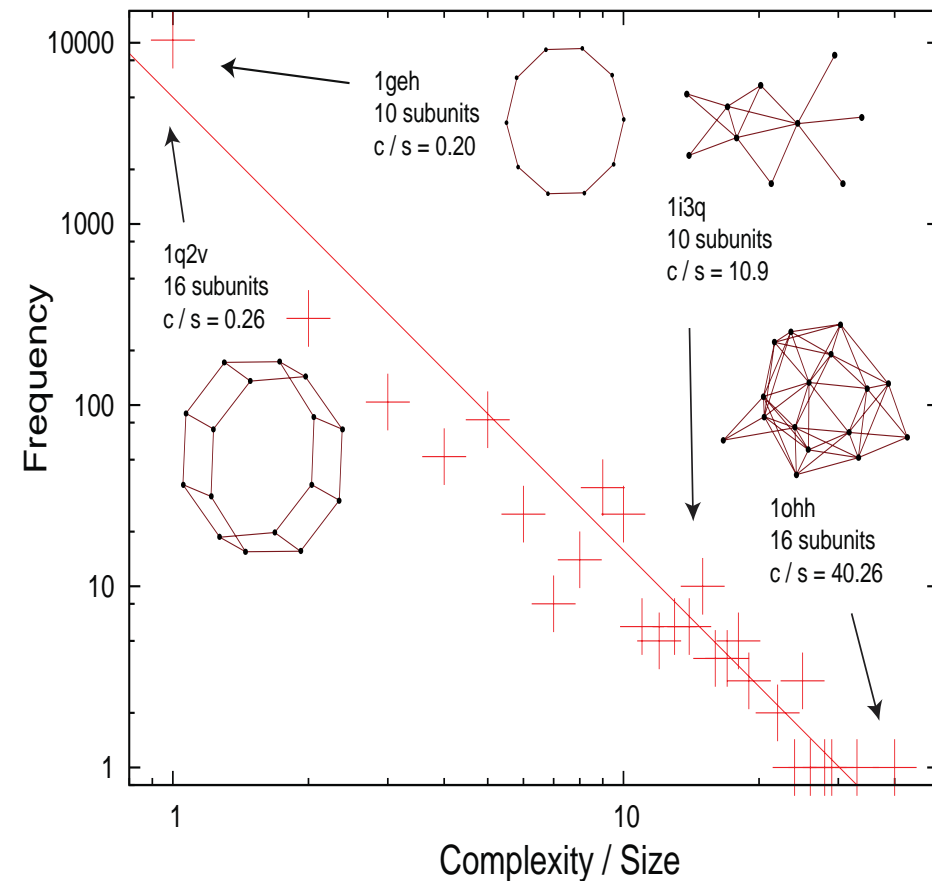
Robustness, RNA L=55



Number of stems in natural and random RNA SS, L=55



# protein quaternary structure



# Proteins self-assemble into quaternary structure



Movie from: Keiichi Namba, Osaka ERATO project

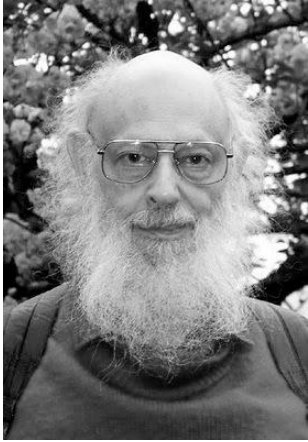
- Can we understand?
  - Assembly
  - Evolution ?
- Can we emulate?

# Neutral Space Topology

- 1)  $N_G \gg N_P$  (number of genotypes  $\gg$  number of phenotypes)
- 2) Genotype set (GS) size per phenotype is highly skewed

Why the skew??





R. Solomonoff  
1926-2009

# Universal probability and the algorithmic nature of the world

$$P(x) = \sum_l 2^{-l} \approx 2^{-k}$$

$P(x)$  = probability that a random sequence, fed into a universal Turing machine, produces the output  $x$

The sum is over all halting programs of length  $l$  that produce  $x$

**intuitively**: simpler outputs are found more often.

Coding Theorem by Solomonoff and Levin.

deep connections to Occam's razor and Bayes priors.

W. Kircher, M. Li, and P. Vitanyi, *The Miraculous Universal Distribution*, *The Mathematical Intelligencer*, 19:4, 7–15, 1997.

# The Oxford crew ...





# Biological networks: interacting many-body systems

Why are there so few genes?

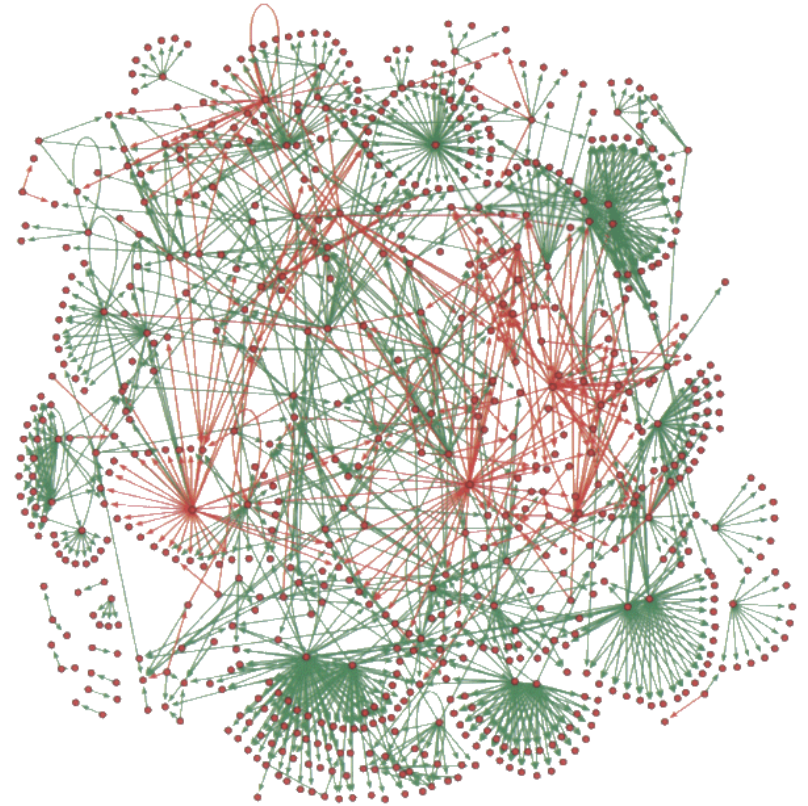
complexity comes from the interactions (systems biology)

model as networks of differential equations? .

Random Matrix Theory

What are the collective modes?

How do they evolve



transcriptional network for yeast:  
*Saccharomyces cerevisiae*