

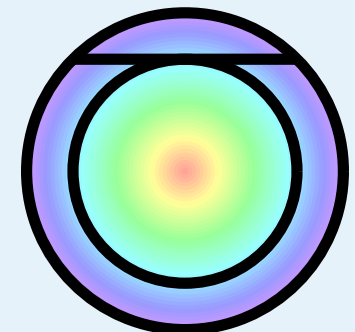
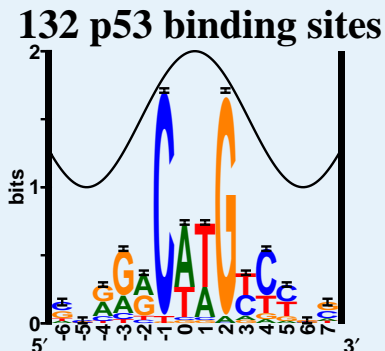


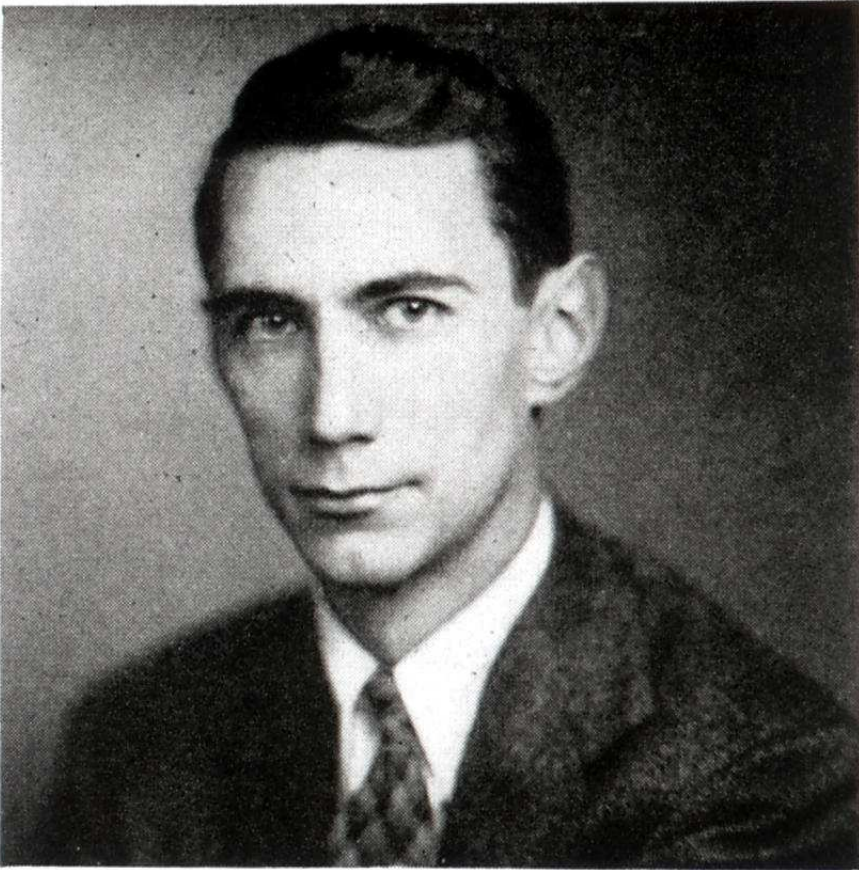
# Why Do Restriction Enzymes Prefer 4 and 6 Base DNA Sequences?

Thomas D. Schneider, Ph.D.  
Vishnu Jejjala, Ph.D.

Molecular Information Theory Group  
Center for Cancer Research  
RNA Biology Laboratory  
National Cancer Institute  
Frederick, MD 21702-1201

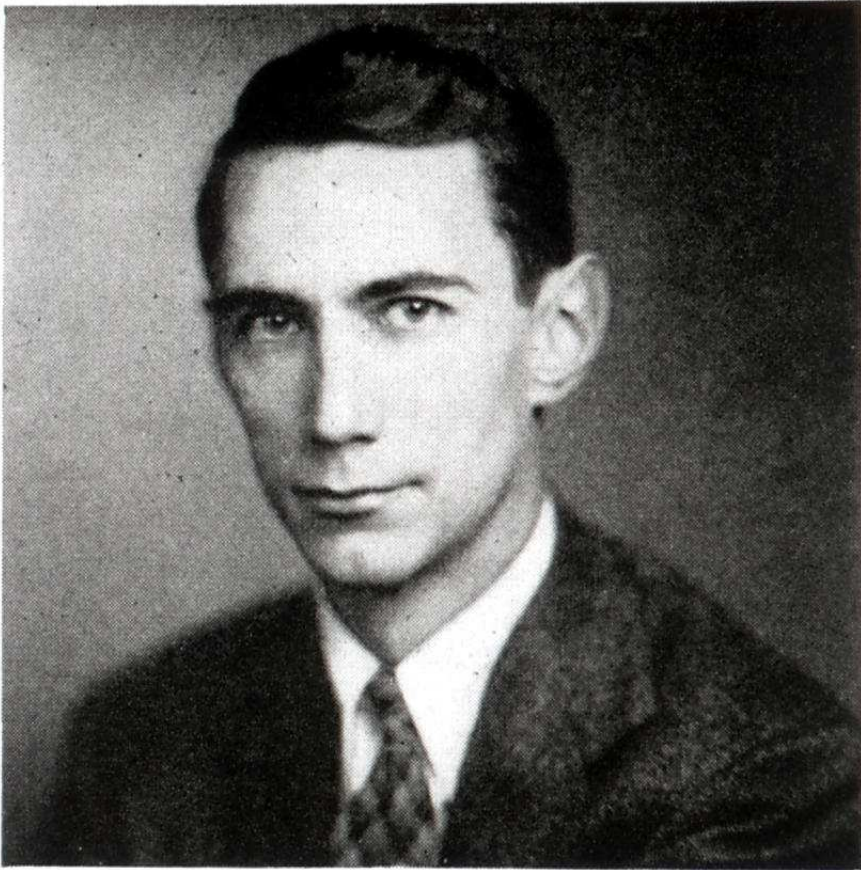
and  
University of the Witwatersrand  
Johannesburg, South Africa





**CLAUDE E. SHANNON**

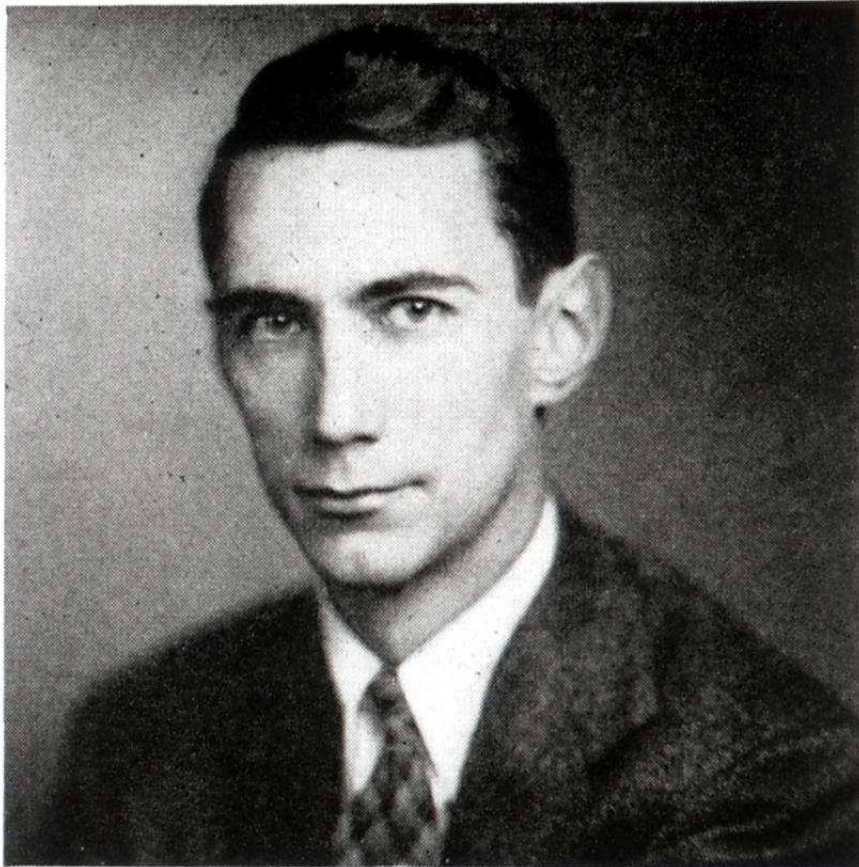
- April 30, 1916 - February 24, 2001



## CLAUDE E. SHANNON

- April 30, 1916 - February 24, 2001
- Founded Information Theory

# Information Theory - History



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- April 30, 1916 - February 24, 2001
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- Important papers: 1948

### A Mathematical Theory of Communication

By C. E. SHANNON

#### INTRODUCTION

THE recent development of various methods of modulation such as PCM and PPM which exchange bandwidth for signal-to-noise ratio has intensified the interest in a general theory of communication. A basis for such a theory is contained in the important papers of Nyquist<sup>1</sup> and Hartley<sup>2</sup> on this subject. In the present paper we will extend the theory to include a number of new factors, in particular the effect of noise in the channel, and the savings possible due to the statistical structure of the original message and due to the nature of the final destination of the information.

The fundamental problem of communication is that of reproducing at one point either exactly or approximately a message selected at another point. Frequently the messages have *meaning*; that is they refer to or are correlated according to some system with certain physical or conceptual entities. These semantic aspects of communication are irrelevant to the engineering problem. The significant aspect is that the actual message is one *selected from a set* of possible messages. The system must be designed to operate for each possible selection, not just the one which will actually be chosen since this is unknown at the time of design.

If the number of messages in the set is finite then this number or any monotonic function of this number can be regarded as a measure of the information produced when one message is chosen from the set, all choices being equally likely. As was pointed out by Hartley the most natural choice is the logarithmic function. Although this definition must be generalized considerably when we consider the influence of the statistics of the message and when we have a continuous range of messages, we will in all cases use an essentially logarithmic measure.

The logarithmic measure is more convenient for various reasons:

1. It is practically more useful. Parameters of engineering importance such as time, bandwidth, number of relays, etc., tend to vary linearly with the logarithm of the number of possibilities. For example, adding one relay to a group doubles the number of possible states of the relays. It adds 1 to the base 2 logarithm of this number. Doubling the time roughly squares the number of possible messages, or doubles the logarithm, etc.
2. It is nearer to our intuitive feeling as to the proper measure. This is closely related to (1) since we intuitively measure entities by linear comparison with common standards. One feels, for example, that two punched cards should have twice the capacity of one for information storage, and two identical channels twice the capacity of one for transmitting information.
3. It is mathematically more suitable. Many of the limiting operations are simple in terms of the logarithm but would require clumsy restatement in terms of the number of possibilities.

The choice of a logarithmic base corresponds to the choice of a unit for measuring information. If the base 2 is used the resulting units may be called binary digits, or more briefly *bits*, a word suggested by J. W. Tukey. A device with two stable positions, such as a relay or a flip-flop circuit, can store one bit of information.  $N$  such devices can store  $N$  bits, since the total number of possible states is  $2^N$  and  $\log_2 2^N = N$ . If the base 10 is used the units may be called decimal digits. Since

$$\begin{aligned}\log_2 M &= \log_{10} M / \log_{10} 2 \\ &= 3.32 \log_{10} M,\end{aligned}$$

<sup>1</sup>Nyquist, H., "Certain Factors Affecting Telegraph Speed," *Bell System Technical Journal*, April 1924, p. 324; "Certain Topics in Telegraph Transmission Theory," *A.I.E.E. Trans.*, v. 47, April 1928, p. 617.

<sup>2</sup>Hartley, R. V. L., "Transmission of Information," *Bell System Technical Journal*, July 1928, p. 535.

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The fundamental properties of a message to or are correlated aspects of communication message is one selection, not selection, not selection.

If the number of messages can be regarded as a function of choices being equally function. Although the statistics of the message are essentially logarithmic. The logarithmic message

1. It is practically the number of relays, etc., adding one relay logarithm of this doubles the logarithm.
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## Communication in the Presence of Noise

CLAUDE E. SHANNON, MEMBER, IRE

### Classic Paper

A method is developed for representing any communication system geometrically. Messages and the corresponding signals are points in two "function spaces," and the modulation process is a mapping of one space into the other. Using this representation, a number of results in communication theory are deduced concerning expansion and compression of bandwidth and the threshold effect. Formulas are found for the maximum rate of transmission of binary digits over a system when the signal is perturbed by various types of noise. Some of the properties of "ideal" systems which transmit at this maximum rate are discussed. The equivalent number of binary digits per second for certain information sources is calculated.

### I. INTRODUCTION

A general communications system is shown schematically in Fig. 1. It consists essentially of five elements.

1) *An Information Source:* The source selects one message from a set of possible messages to be transmitted to the receiving terminal. The message may be of various types; for example, a sequence of letters or numbers, as in telegraphy or teletype, or a continuous function of time  $f(t)$ , as in radio or telephony.

2) *The Transmitter:* This operates on the message in some way and produces a signal suitable for transmission to the receiving point over the channel. In telephony, this operation consists of merely changing sound pressure into a proportional electrical current. In telegraphy, we have an encoding operation which produces a sequence of dots, dashes, and spaces corresponding to the letters of the message. To take a more complex example, in the case of multiplex PCM telephony the different speech functions must be sampled, compressed, quantized and encoded, and finally interleaved properly to construct the signal.

3) *The Channel:* This is merely the medium used to transmit the signal from the transmitting to the receiving point. It may be a pair of wires, a coaxial cable, a band of radio frequencies, etc. During transmission, or at the receiving terminal, the signal may be perturbed by noise or distortion. Noise and distortion may be differentiated on the basis that distortion is a fixed operation applied to the signal, while noise involves statistical and unpredictable

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Publisher Item Identifier S 0018-9219(98)01299-7.

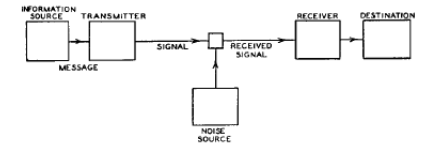


Fig. 1. General communications system.

perturbations. Distortion can, in principle, be corrected by applying the inverse operation, while a perturbation due to noise cannot always be removed, since the signal does not always undergo the same change during transmission.

4) *The Receiver:* This operates on the received signal and attempts to reproduce, from it, the original message. Ordinarily it will perform approximately the mathematical inverse of the operations of the transmitter, although they may differ somewhat with best design in order to combat noise.

5) *The Destination:* This is the person or thing for whom the message is intended.

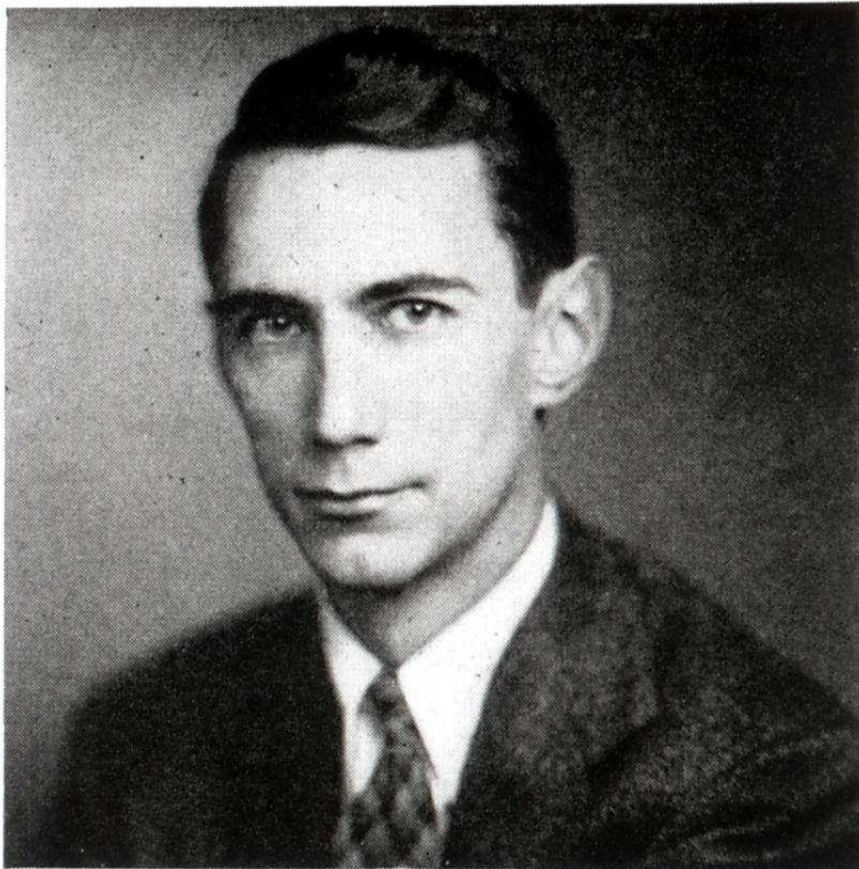
Following Nyquist<sup>1</sup> and Hartley,<sup>2</sup> it is convenient to use a logarithmic measure of information. If a device has  $n$  possible positions it can, by definition, store  $\log_2 n$  units of information. The choice of the base  $b$  amounts to a choice of unit, since  $\log_b n = \log_b c \log_c n$ . We will use the base 2 and call the resulting units binary digits or bits. A group of  $m$  relays or flip-flop circuits has  $2^m$  possible sets of positions, and can therefore store  $\log_2 2^m = m$  bits.

If it is possible to distinguish reliably  $M$  different signal functions of duration  $T$  on a channel, we can say that the channel can transmit  $\log_2 M$  bits in time  $T$ . The rate of transmission is then  $\log_2 M/T$ . More precisely, the channel capacity may be defined as

$$C = \lim_{T \rightarrow \infty} \frac{\log_2 M}{T} \quad (1)$$

<sup>1</sup>H. Nyquist, "Certain factors affecting telegraph speed," *Bell Syst. Tech. J.*, vol. 3, p. 324, Apr. 1924.

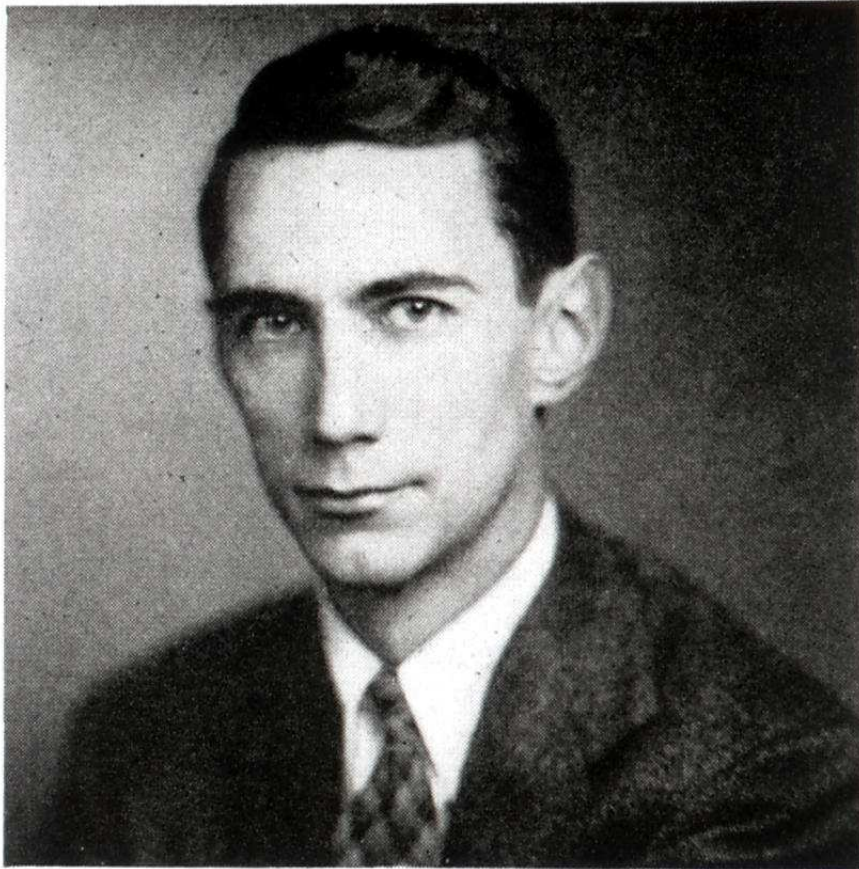
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# Information Theory - History



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- Important papers: 1948 , 1949
- Result: modern communications!

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The fundamental problem is to represent a message to or are correlated aspects of communication message is one selection, not a selection. If the number of messages can be regarded as a function of the number of choices being equally function. Although the statistics of the message are essentially logarithmic. The logarithmic measure of the number of choices is called the entropy of the message.

1. It is practically not possible to add one relay channel to a system of relays, etc., adding one relay channel to a system of relays, etc., doubling the logarithm of the number of choices.
2. It is nearer to our intuitive measure of the number of binary digits than the number of channels.
3. It is mathematically simpler than the number of channels.

The choice of a logarithm base 2 is used throughout the paper. A device which transmits  $N$  bits of information per second. If the base 10 is used it is called the number of channels.

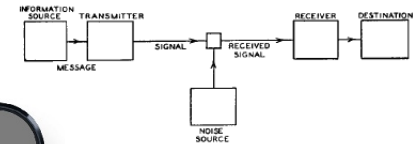
<sup>1</sup>Nyquist, H., "Certain Factors Affecting Telegraph Speed," *Bell Syst. Tech. J.*, p. 324, Apr. 1924.  
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General communications system.



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# Information Theory: One-Minute Lesson

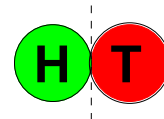
number of symbols	number of bits	example
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**M**

**B**

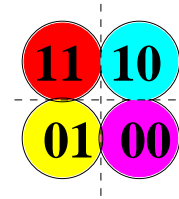
**2**

**1**



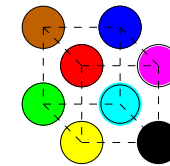
**4**

**2**



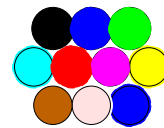
**8**

**3**



$$M=2^B$$

$$B=\log_2 M$$



# Information Theory: One-Minute Lesson

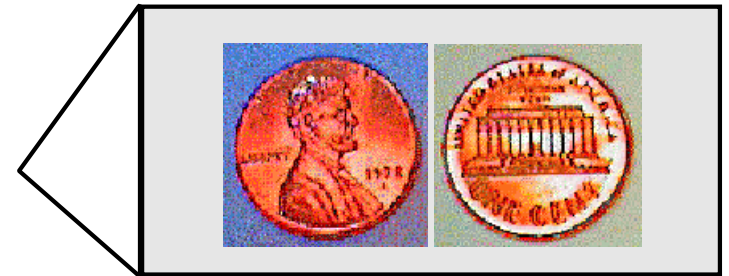
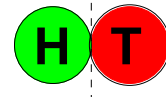
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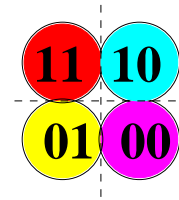
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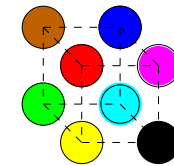
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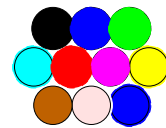
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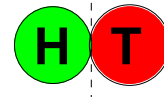
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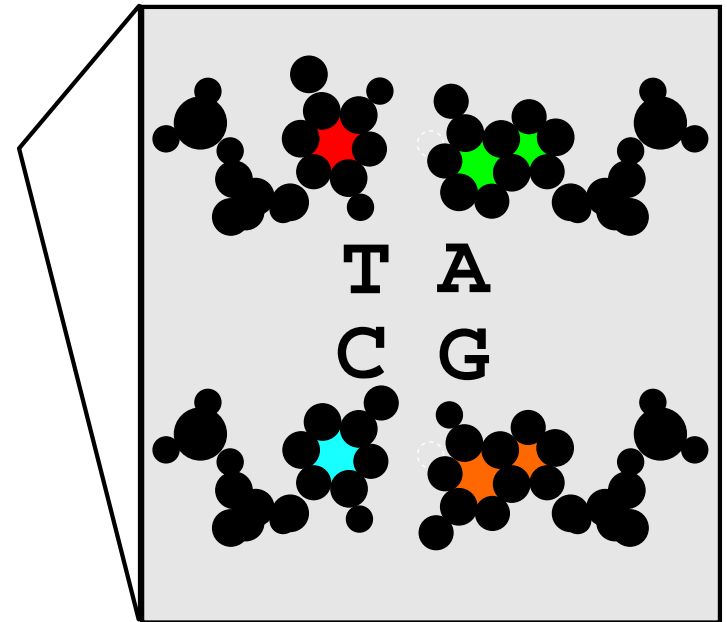
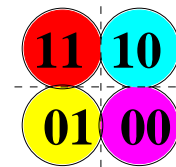
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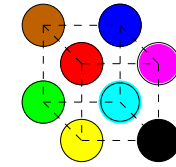
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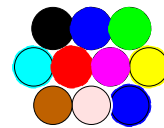
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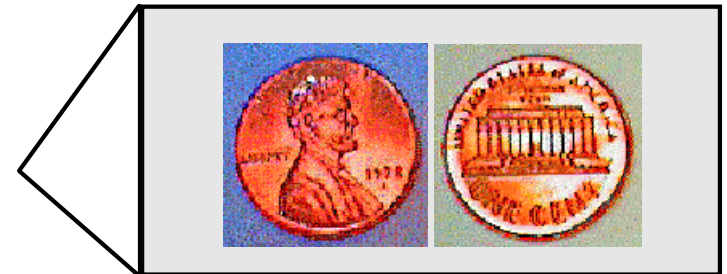
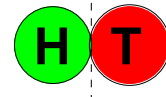
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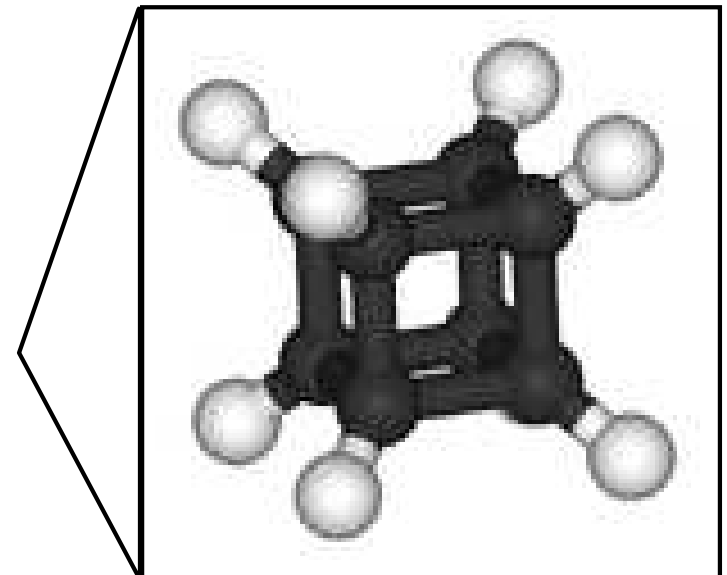
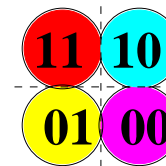
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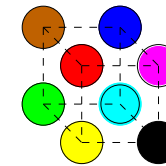
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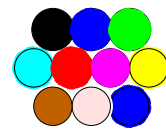
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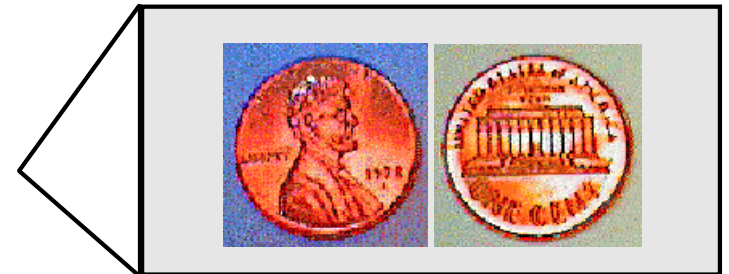
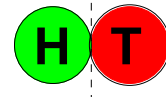
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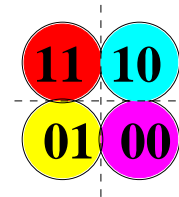
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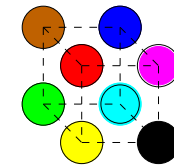
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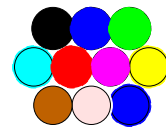
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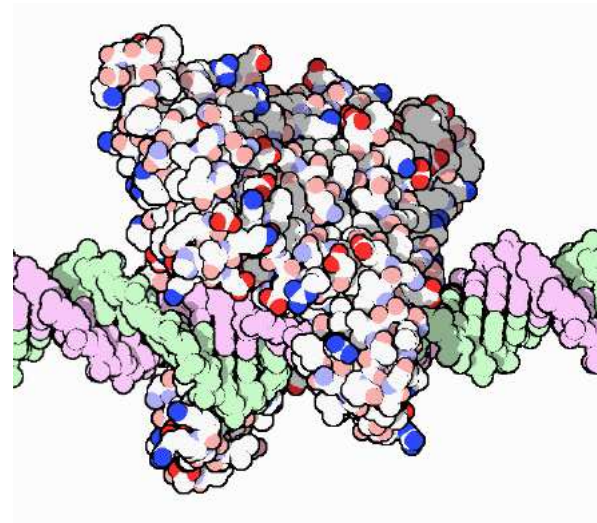
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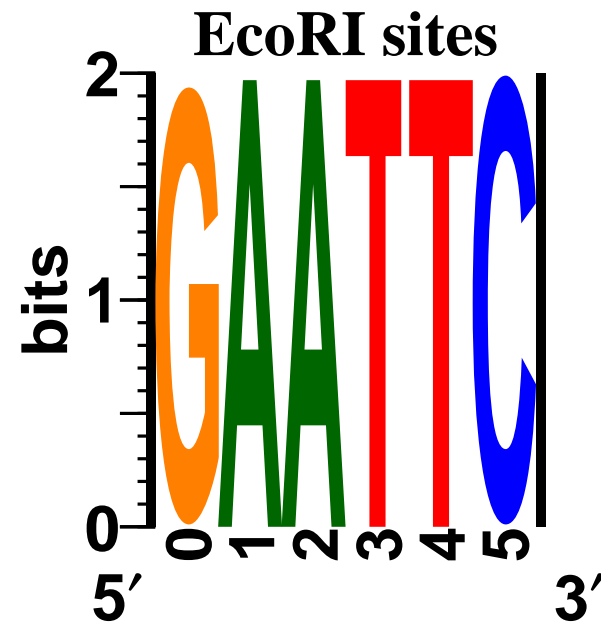
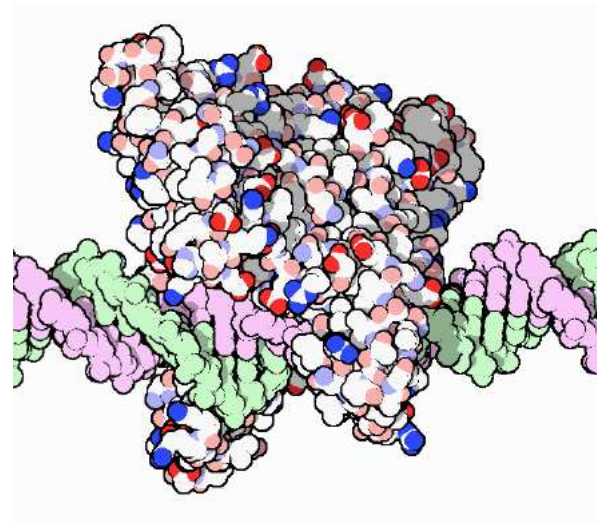
# Information of EcoRI DNA Binding

- EcoRI - restriction enzyme



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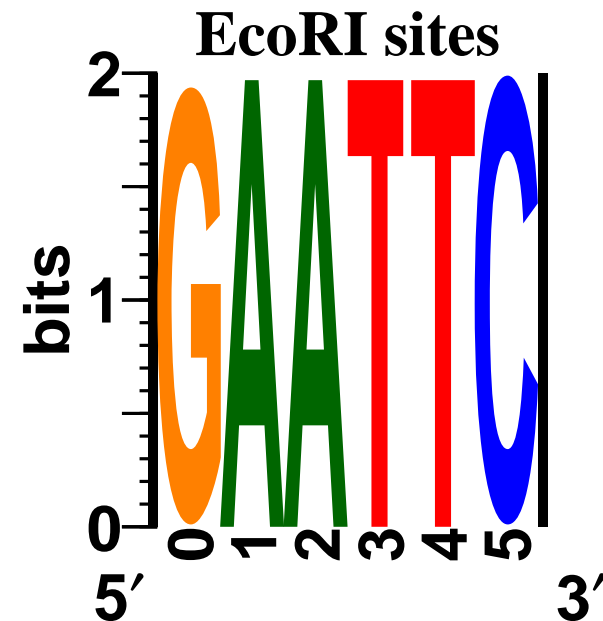
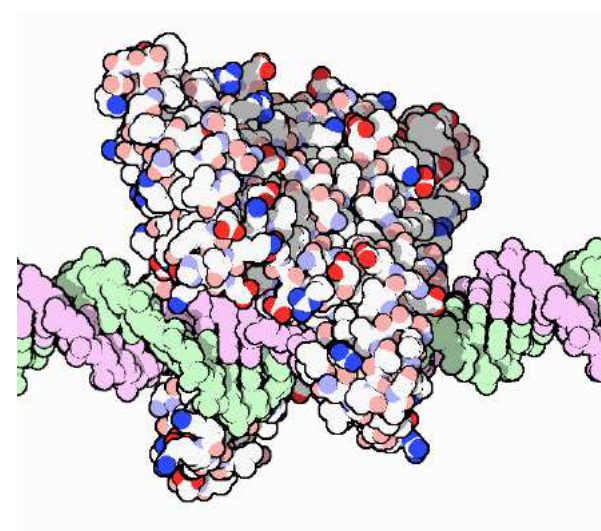
- EcoRI - restriction enzyme
- EcoRI binds DNA at 5' GAATTC 3'



# Information of EcoRI DNA Binding

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- information required:

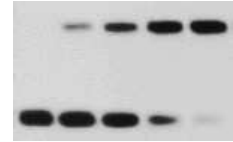
$$6 \text{ bases} \times 2 \text{ bits per base} = \boxed{12 \text{ bits}}$$



# Energy Dissipation by EcoRI

- Measured specific binding constant:

$$K_{spec} = 1.6 \times 10^5$$



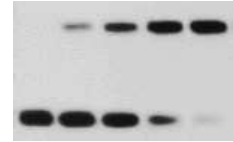
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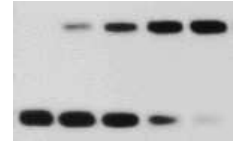
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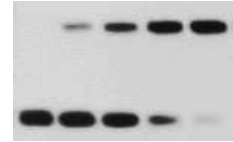
$$\mathcal{E}_{min} = k_B T \ln 2 \quad (\text{joules per bit})$$



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- Number of bits that could have been selected:

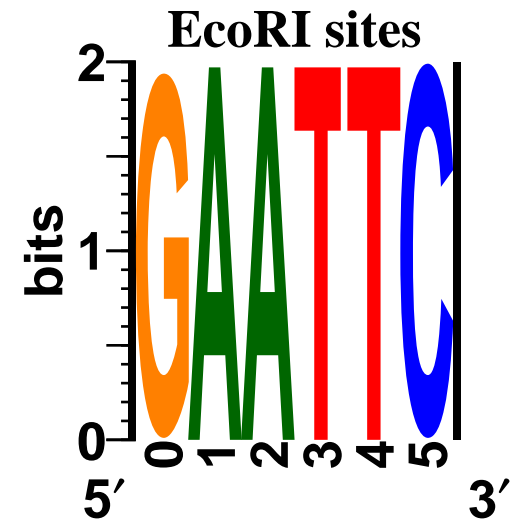
$$\begin{aligned} R_{energy} &= -\Delta G^{\circ} / \mathcal{E}_{min} \\ &= k_B T \ln K_{spec} / k_B T \ln 2 \\ &= \log_2 K_{spec} \quad \Leftarrow \text{SO SIMPLE!} \\ &= \boxed{17.3 \text{ bits per binding}} \end{aligned}$$

# Information/Energy = Efficiency of EcoRI

EcoRI could have made 17.3 binary choices

# Information/Energy = Efficiency of EcoRI

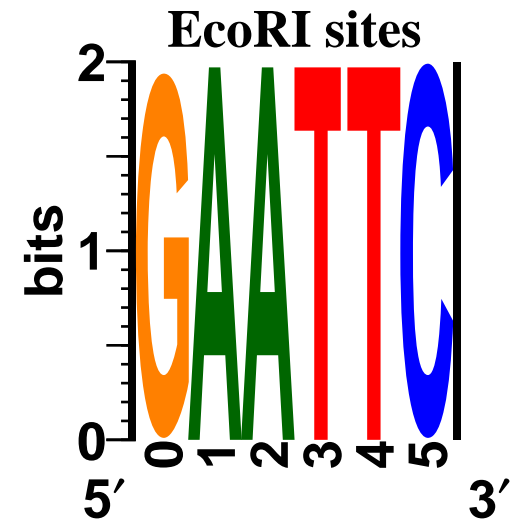
EcoRI could have made 17.3 binary choices  
...but it only made 12 choices.



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Efficiency is  
'WORK' DONE / ENERGY DISSIPATED

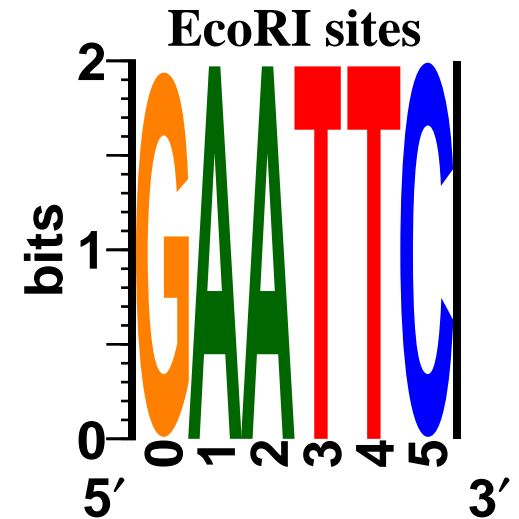


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$$\frac{12 \text{ bits per binding}}{17.3 \text{ bits per binding}} = 0.7$$



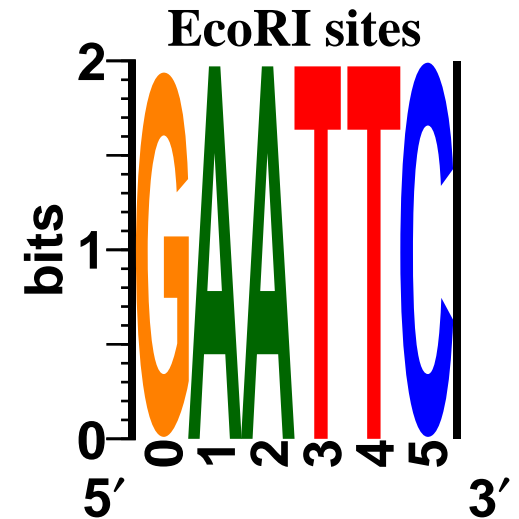
# Information/Energy = Efficiency of EcoRI = 70%

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**The efficiency is 70%.**



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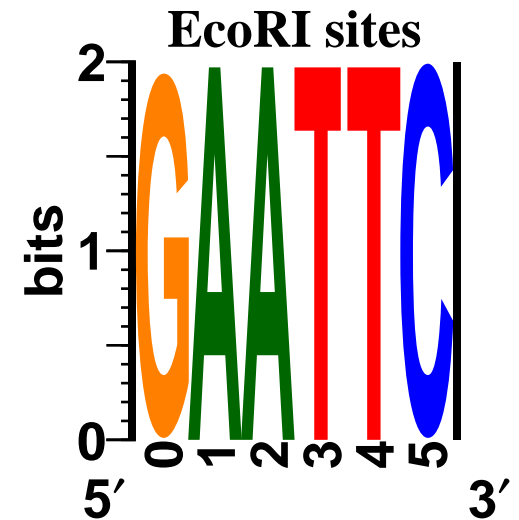
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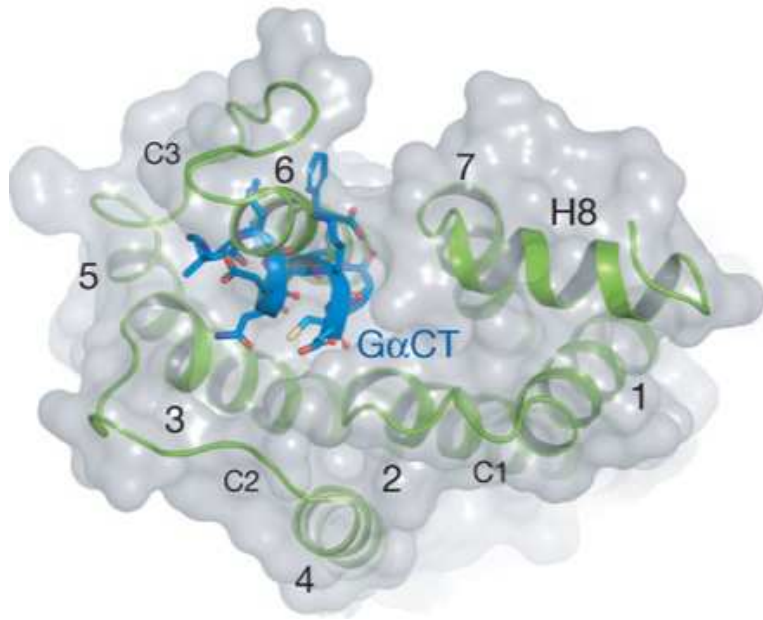
**18 out of 19 DNA binding proteins give ~70% efficiency.**





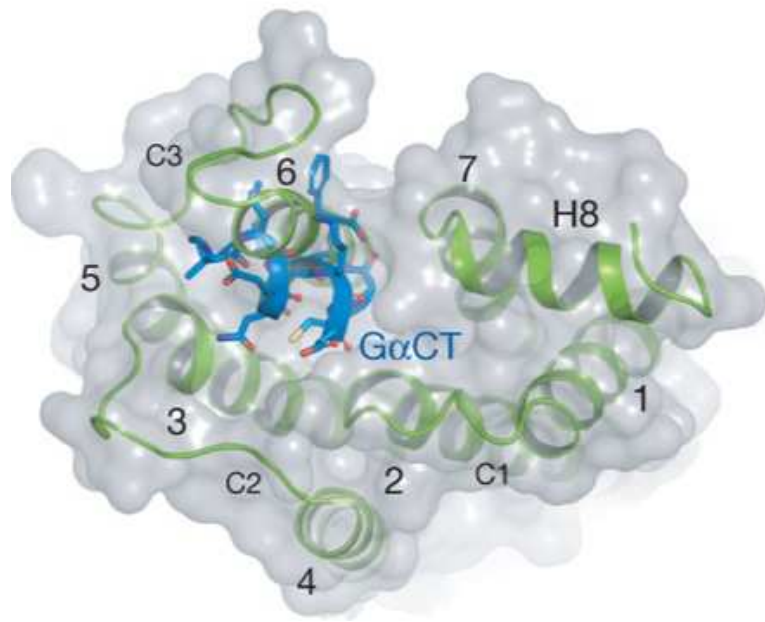
# Rhodopsin Shape Change

Dark State



# Rhodopsin Shape Change

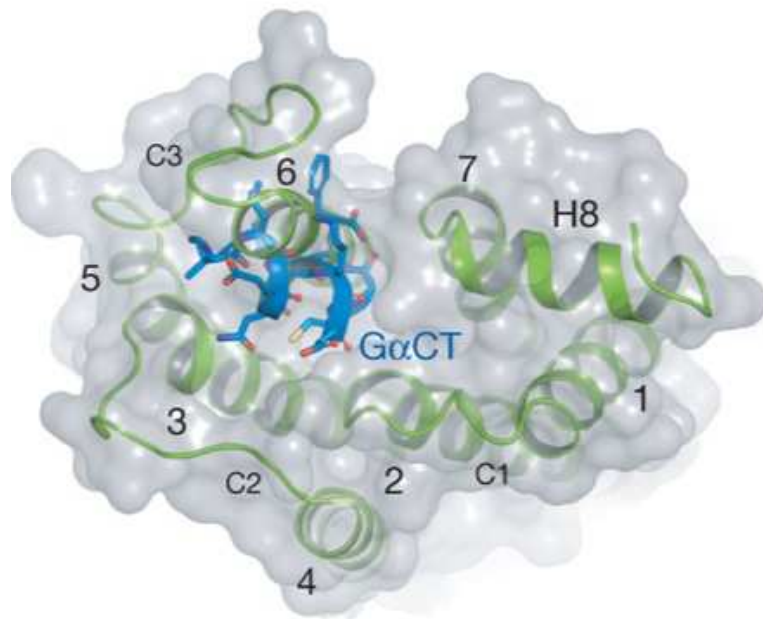
Dark State



$h\nu$

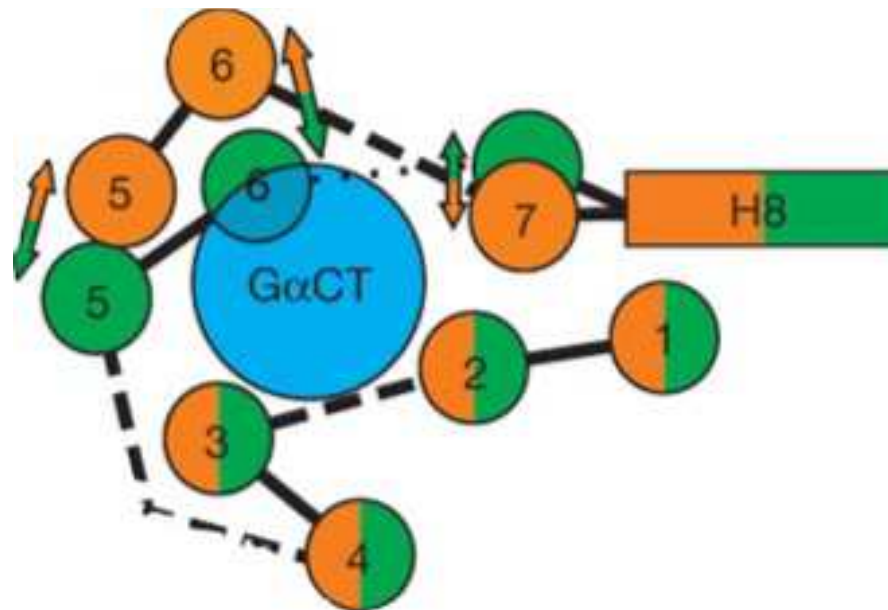
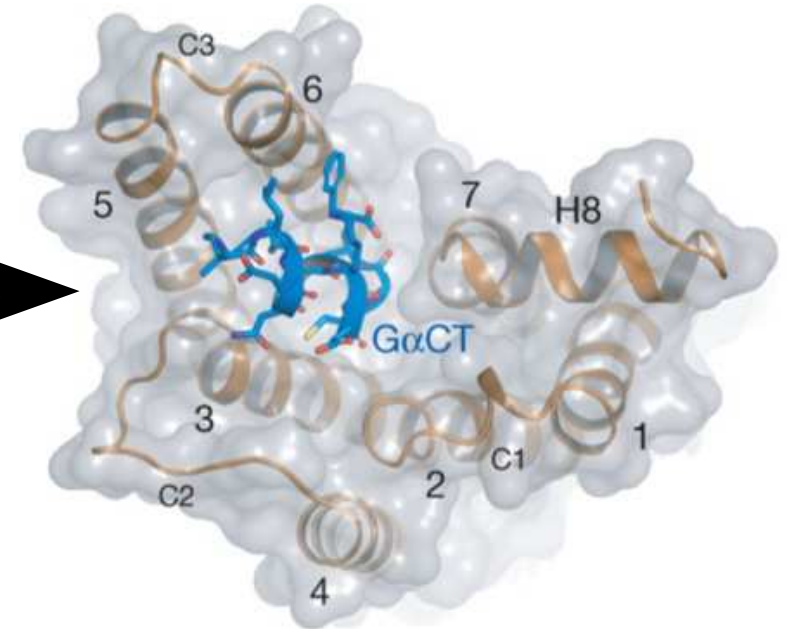
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Dark State



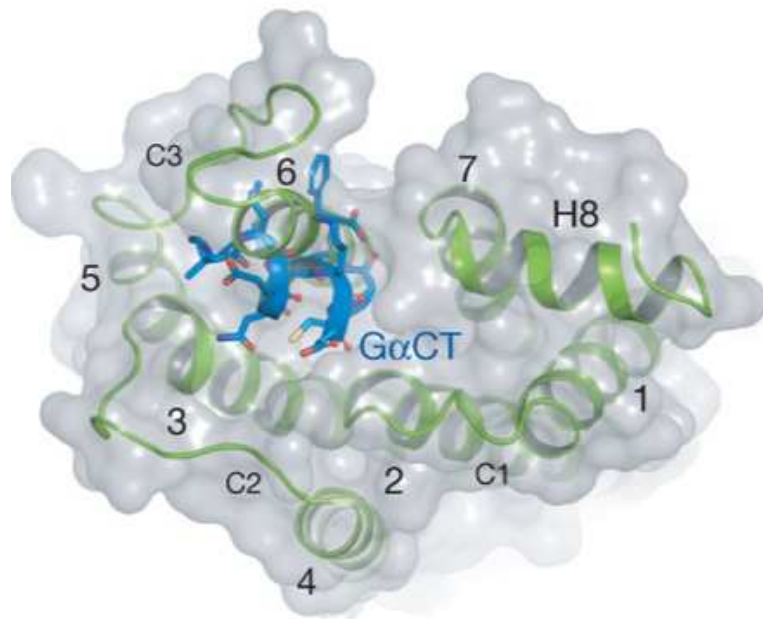
$h\nu$

After Photon - Light State

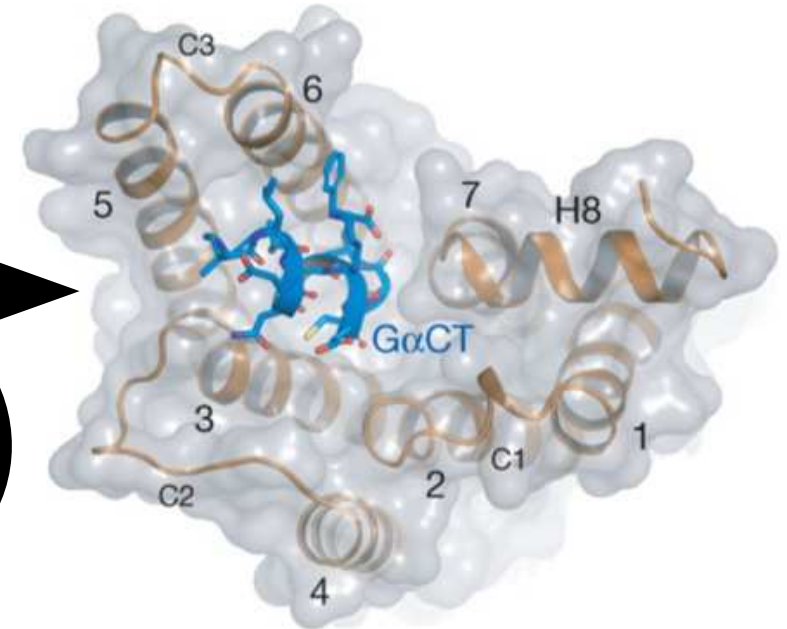


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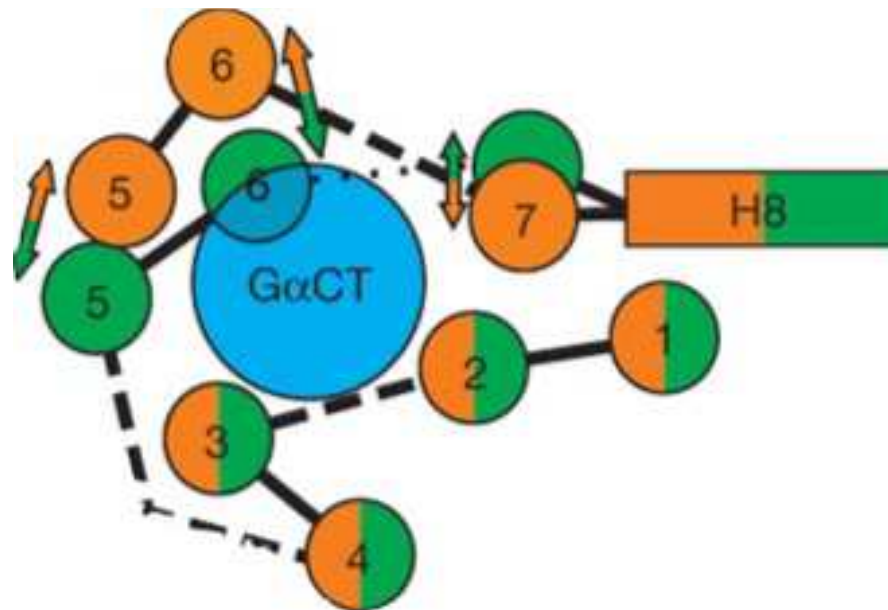
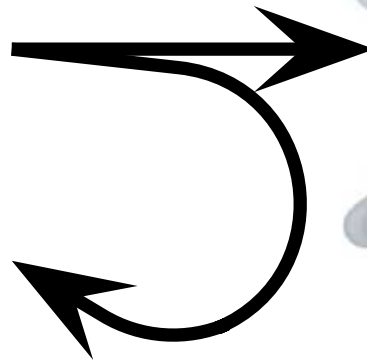
Dark State



After Photon - Light State

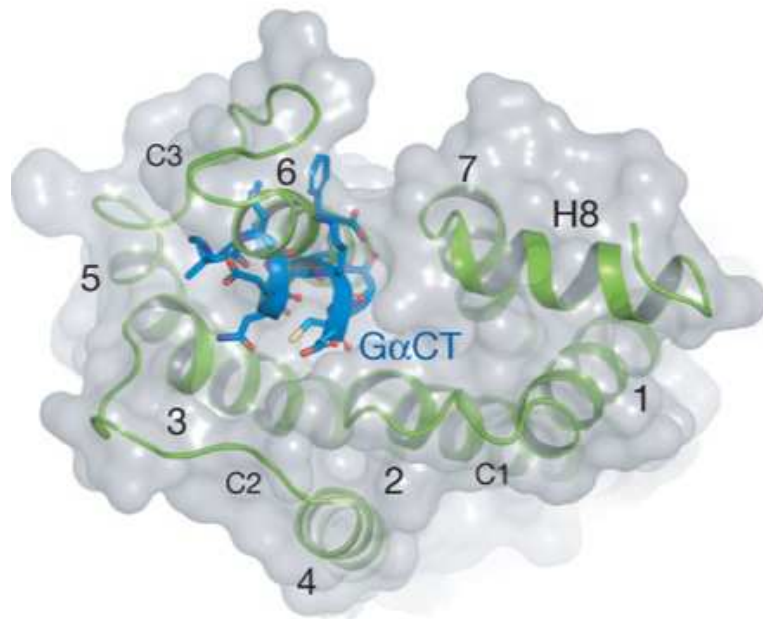


$h\nu$

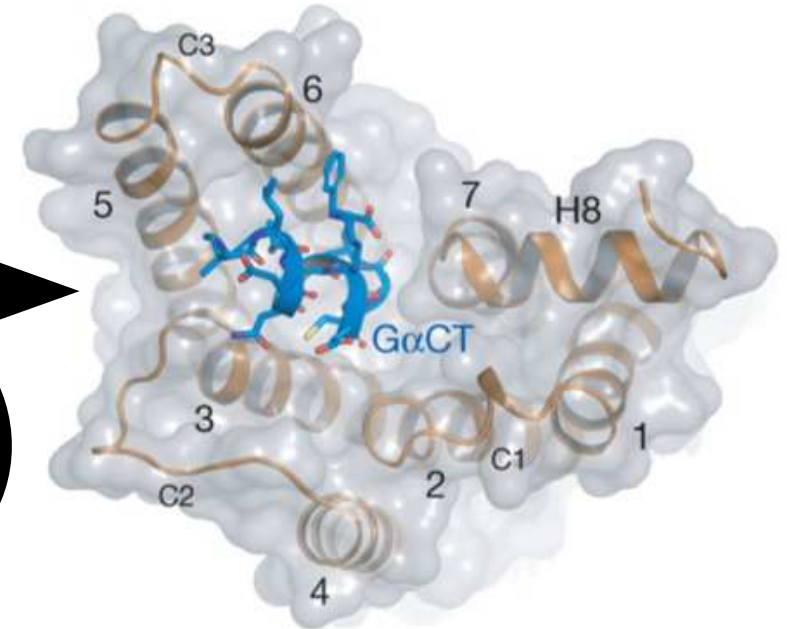


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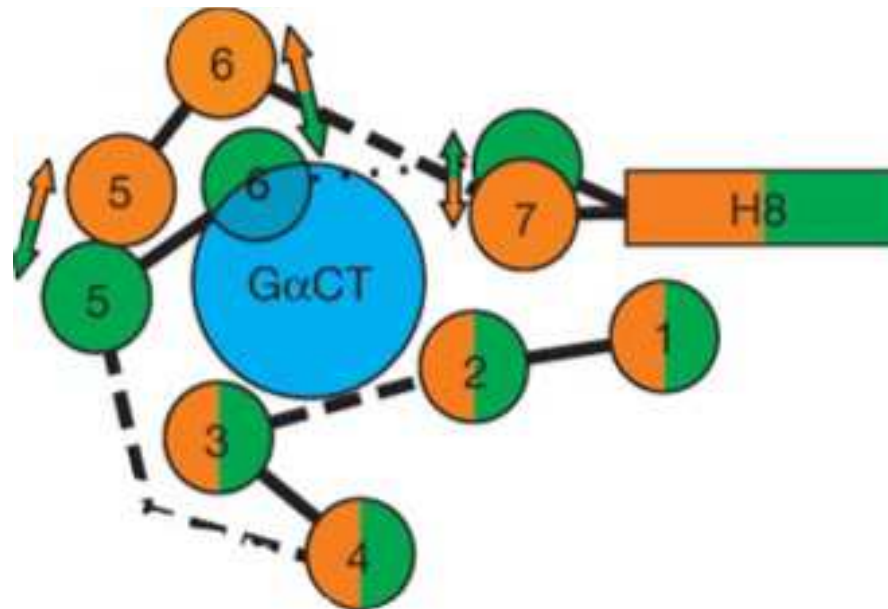
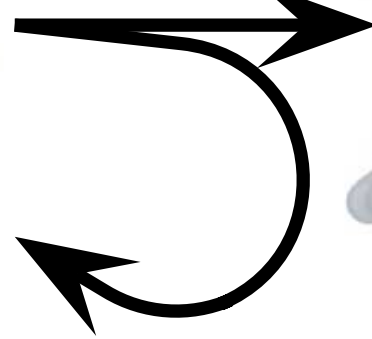
Dark State



After Photon - Light State

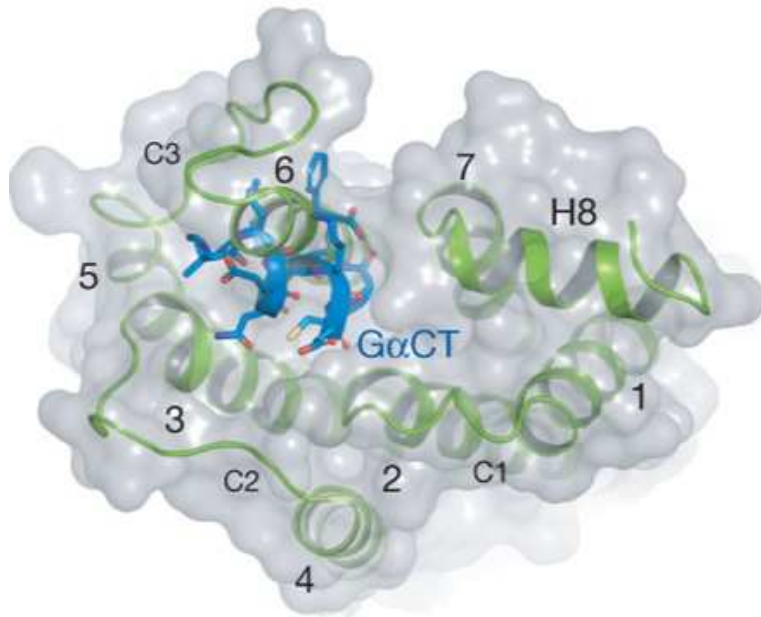


$h\nu$   
70%

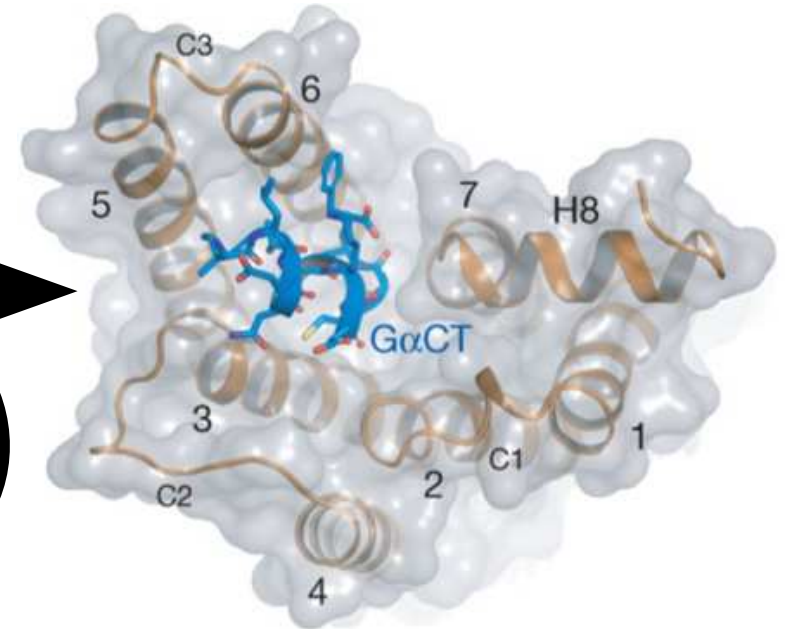


# Rhodopsin Shape Change

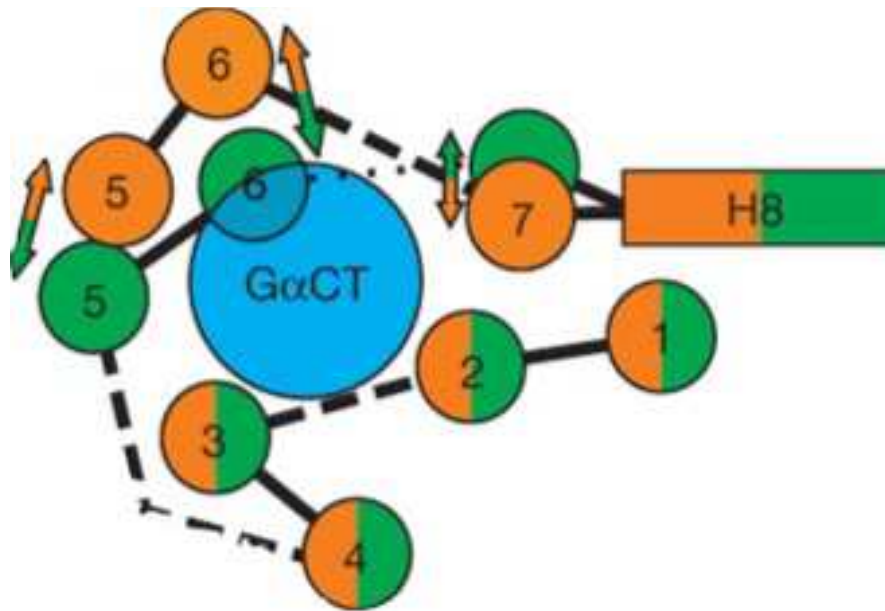
Dark State



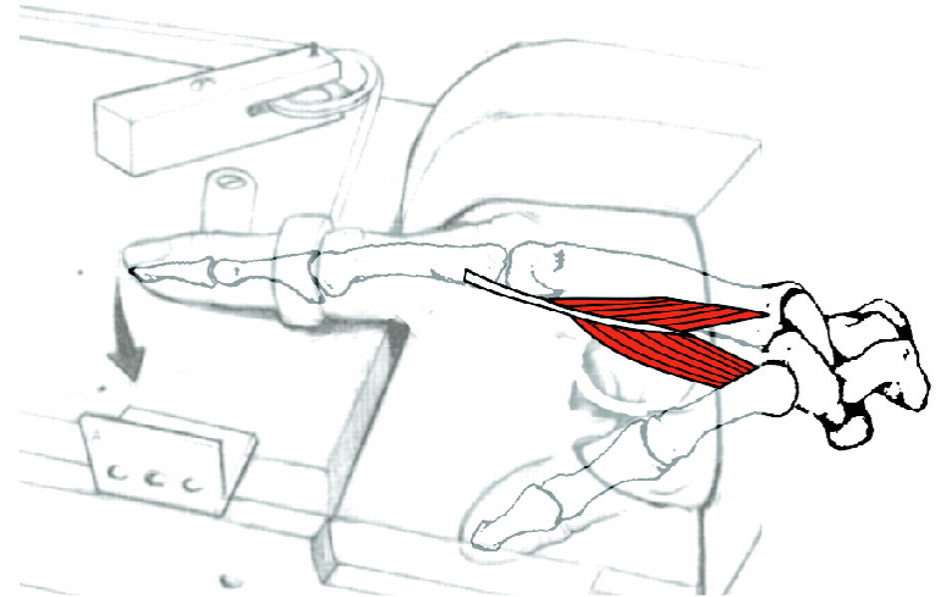
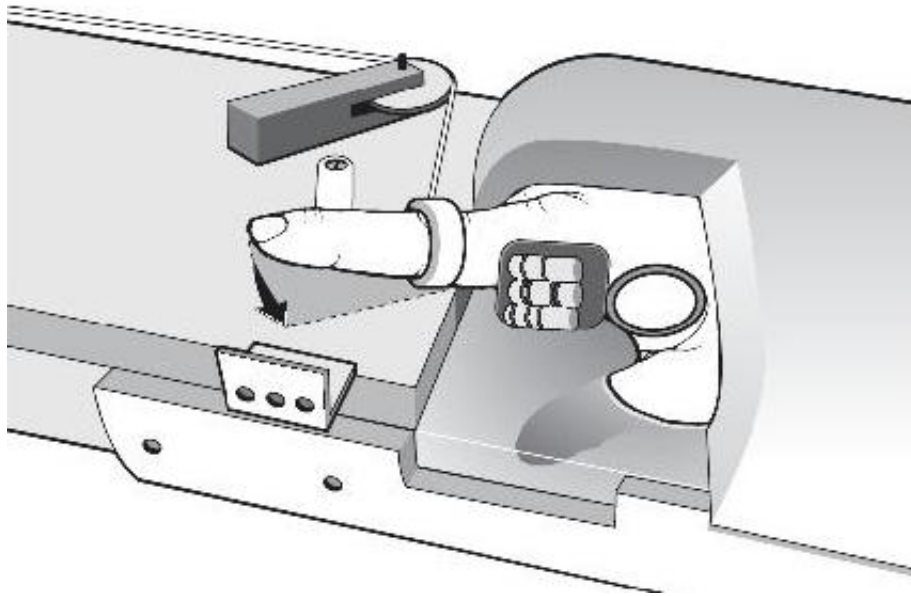
After Photon - Light State



$h\nu$   
70%  
30%

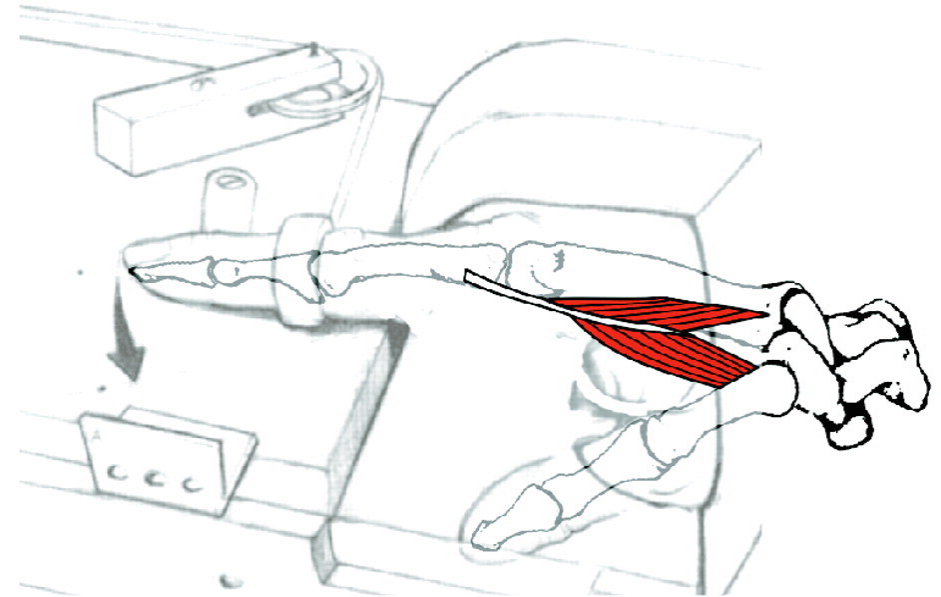
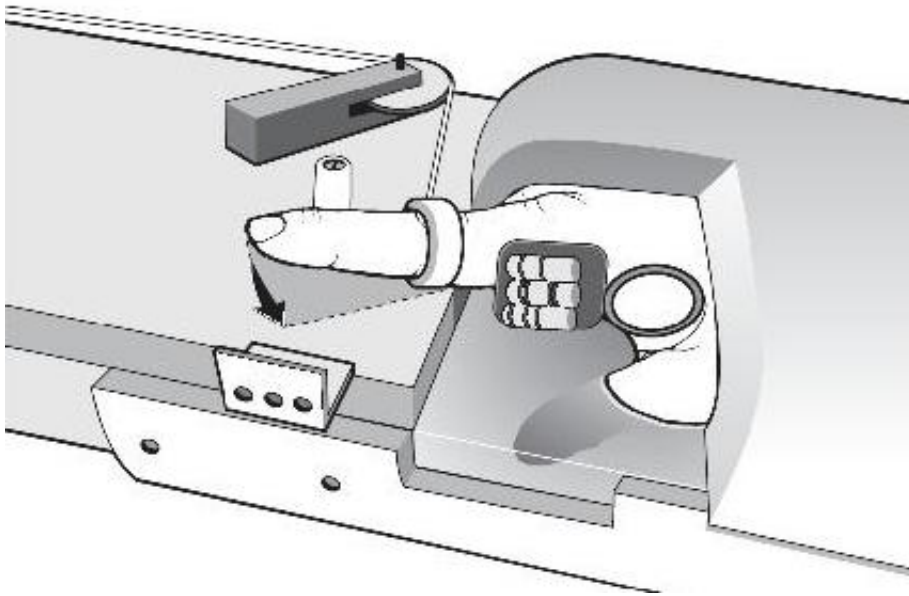


# Efficiency of Muscle



- Experiments by Kushmerick's lab since (at least) 1969

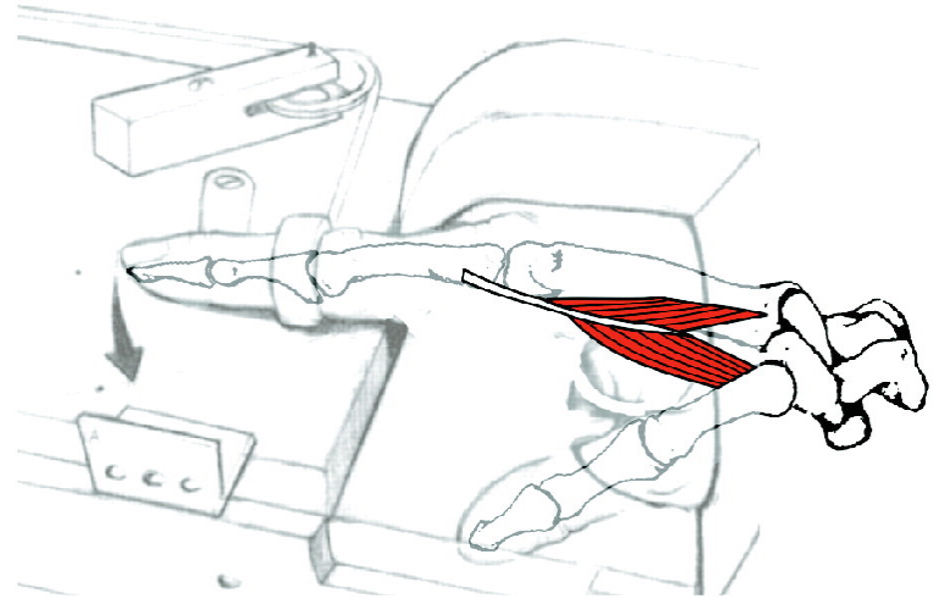
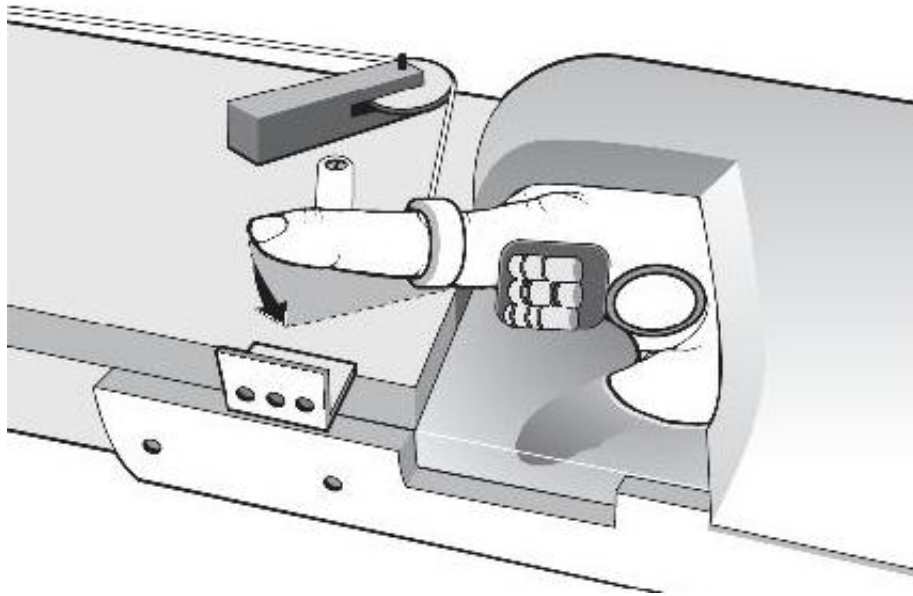
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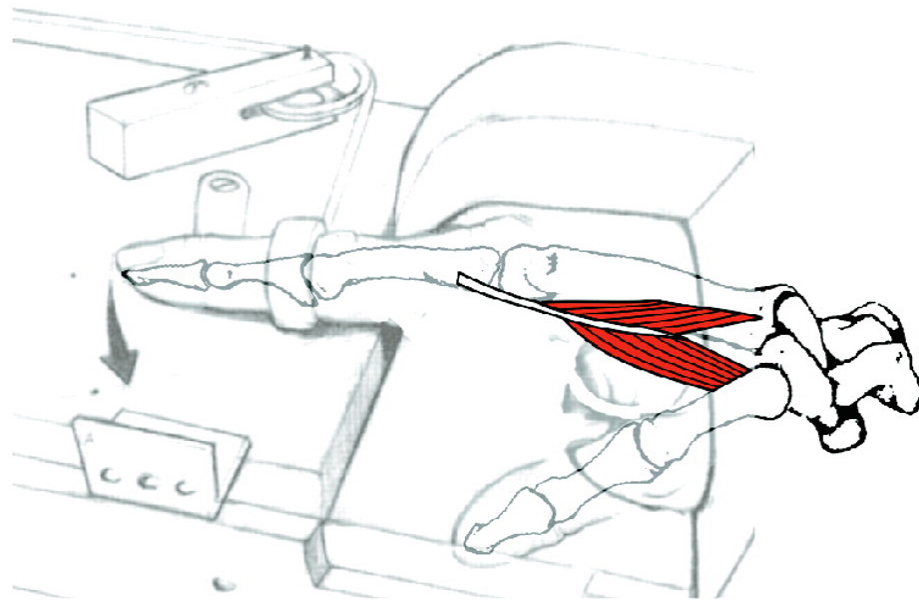
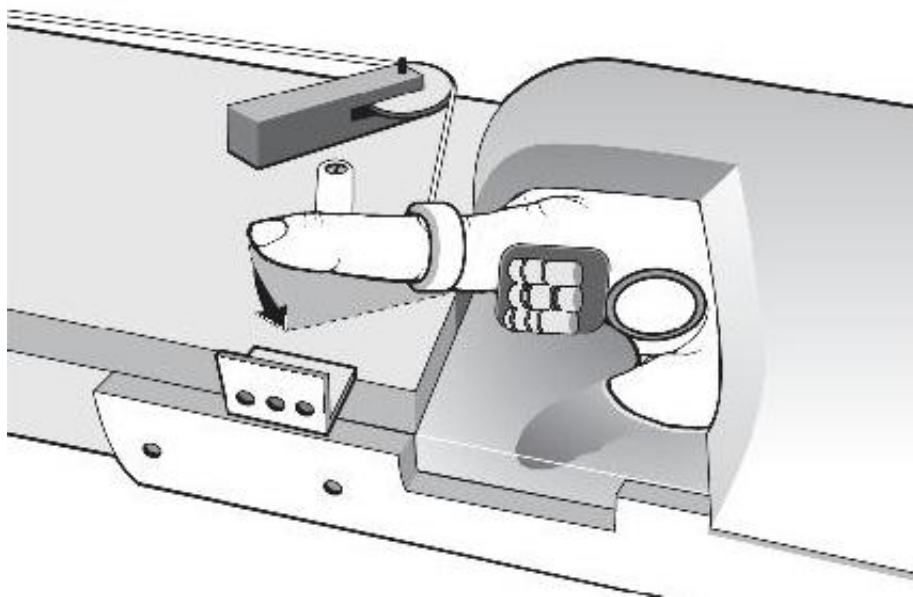


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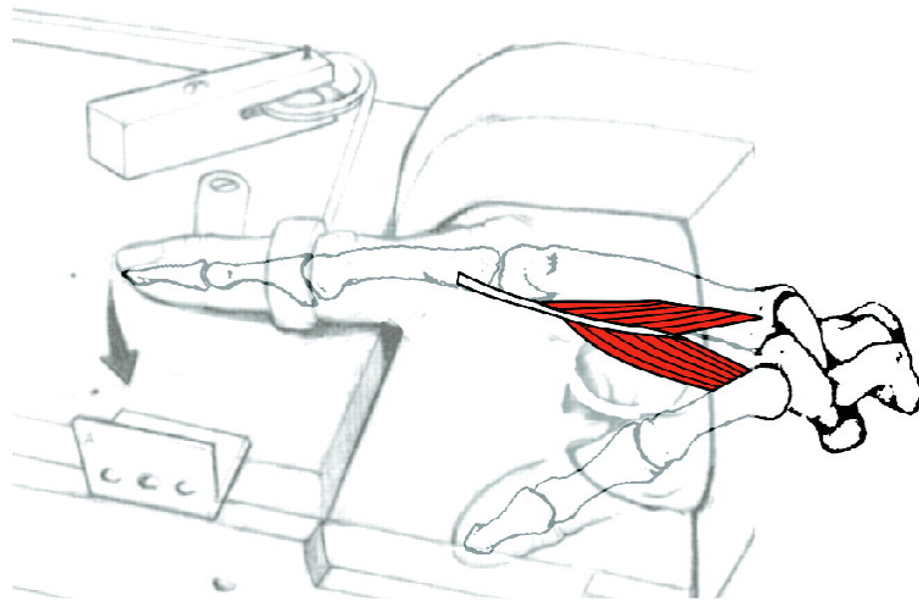
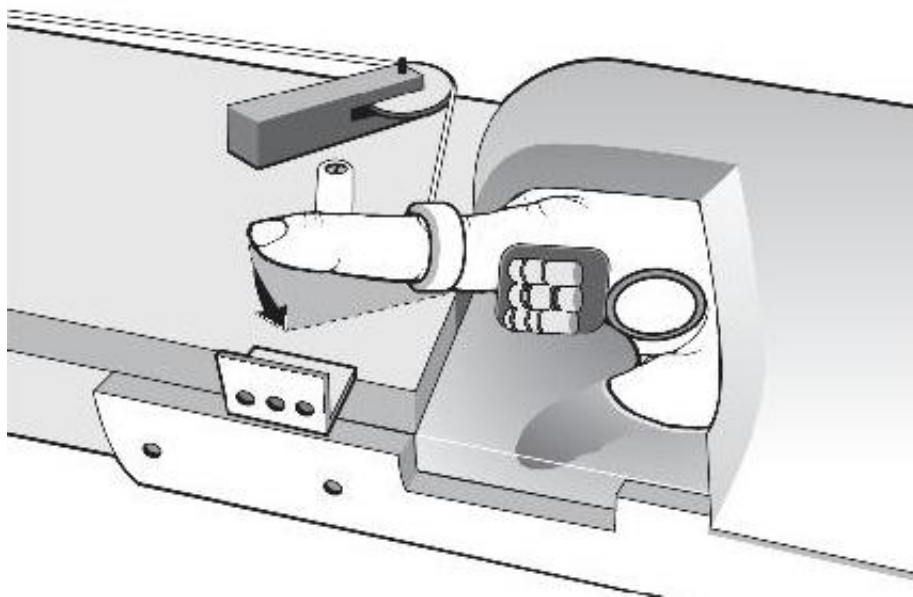
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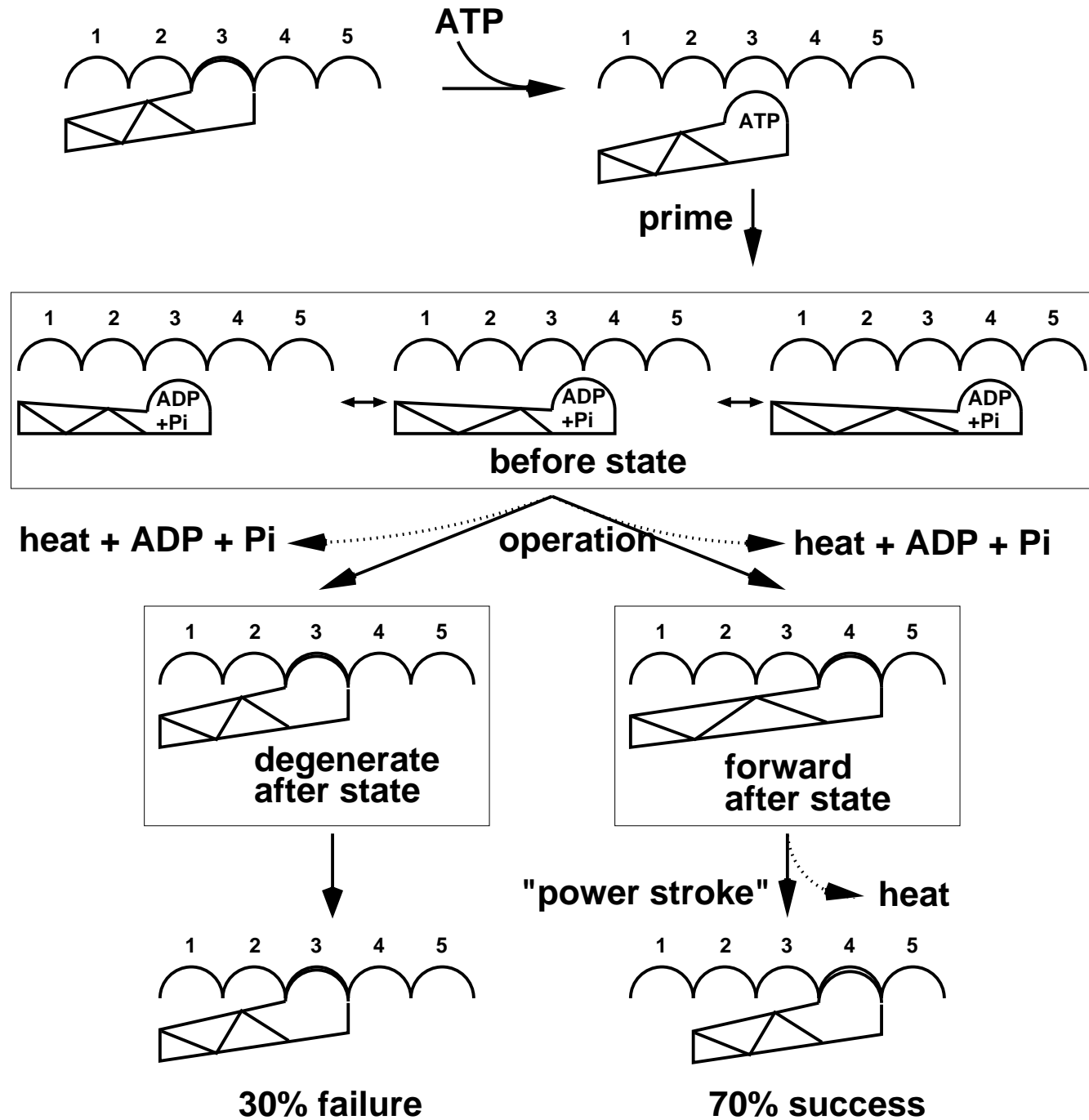
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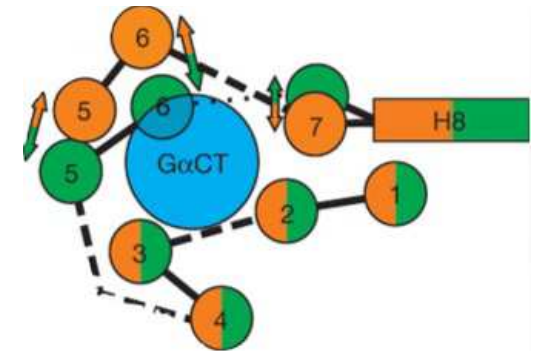
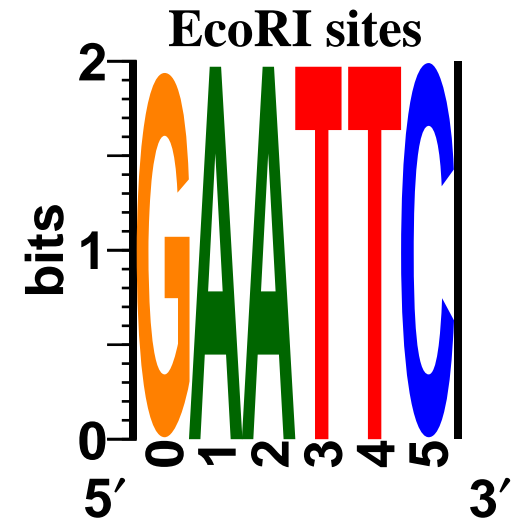
- Experiments by Kushmerick's lab since (at least) 1969
- new work: 2008, 2011
- Weight lifting gives work done
- NMR coil gives ATP = energy used
- **Efficiency:  $0.68 \pm 0.09$**

# Tom's Model of Muscle Mechanism



# Why are molecular machines 70% efficient?

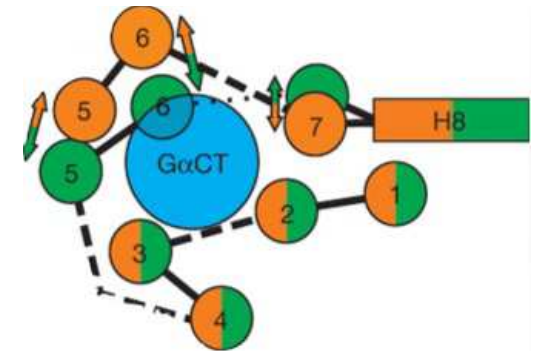
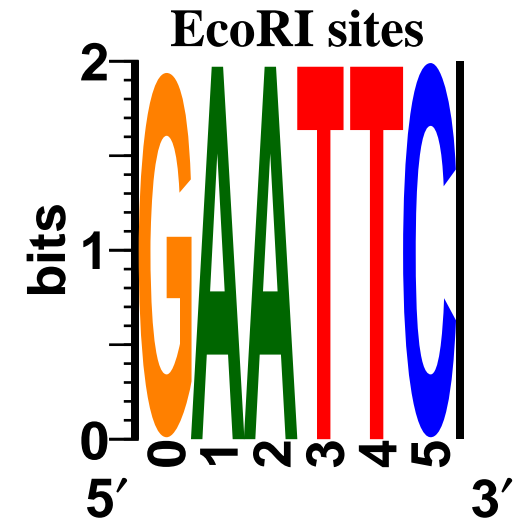
70% efficiency appears widely in biology:



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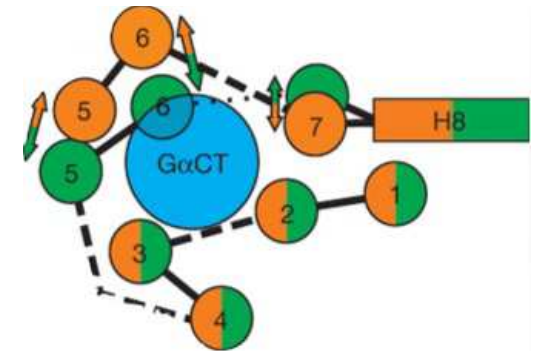
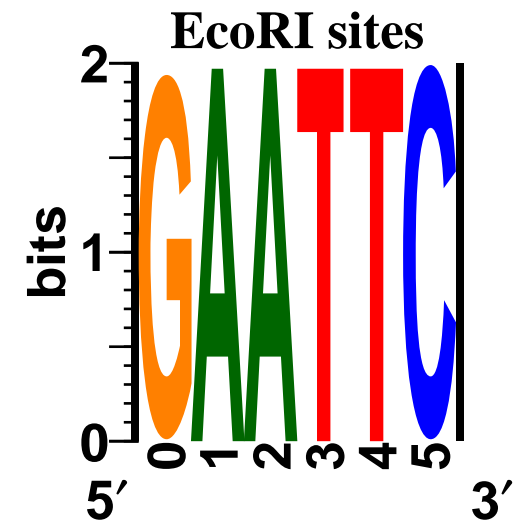
- DNA - protein binding



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70% efficiency appears widely in biology:

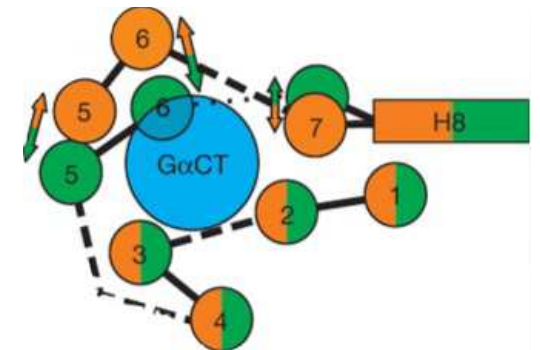
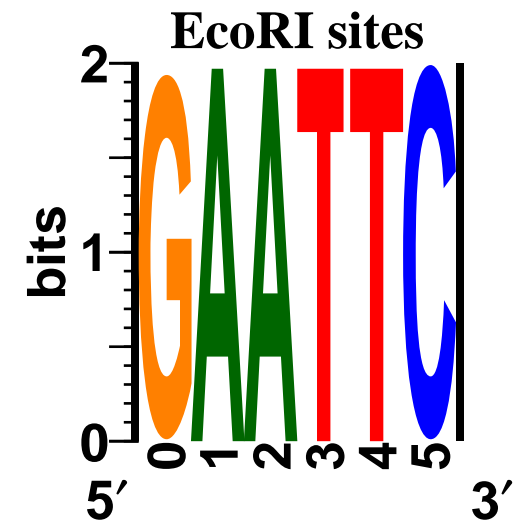
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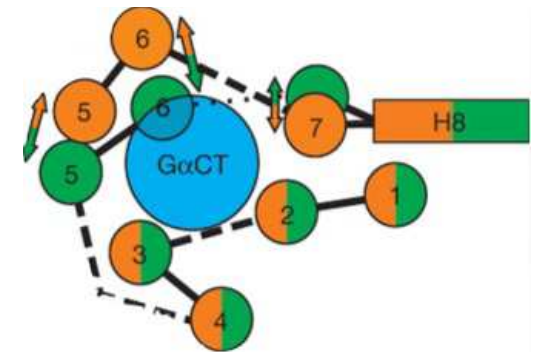
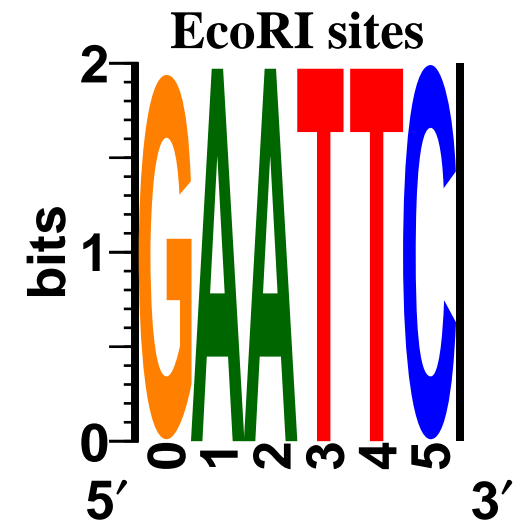




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- other systems

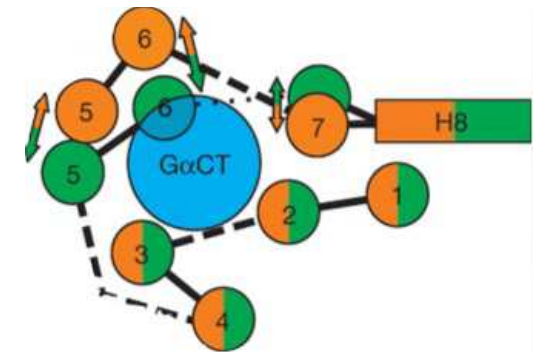
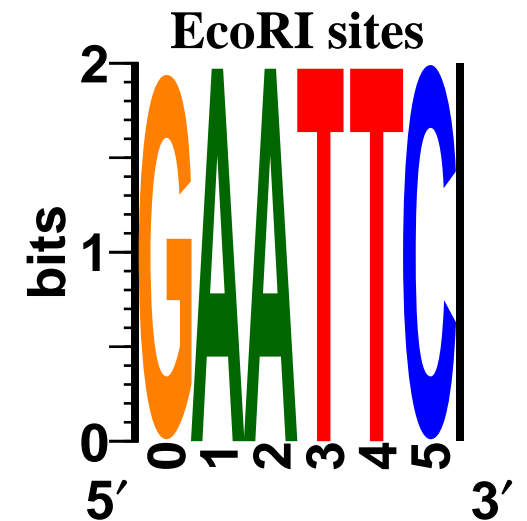


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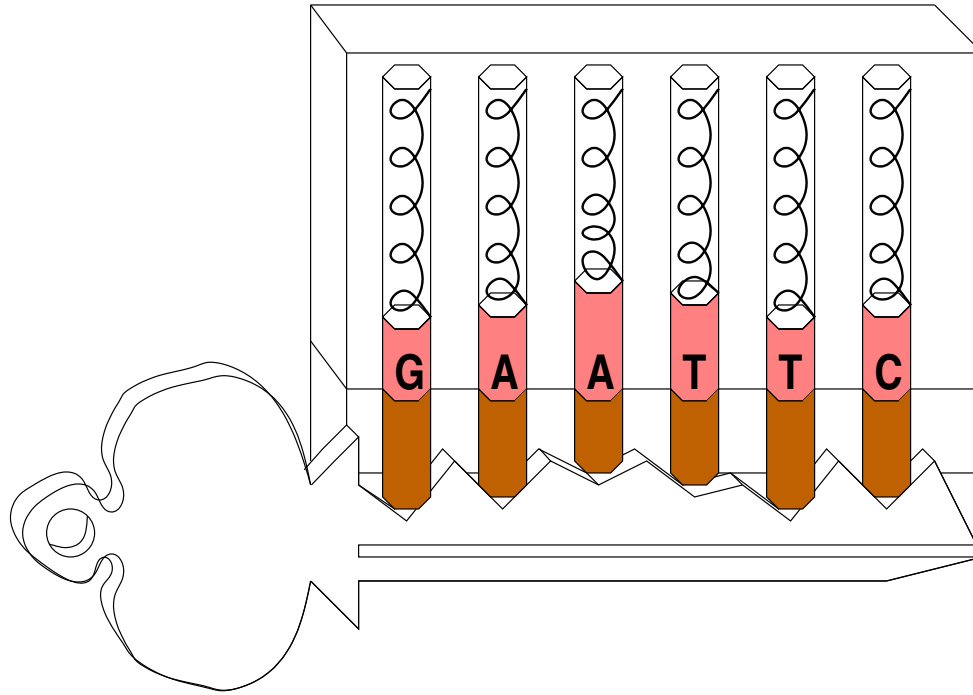
70% efficiency appears widely in biology:

- DNA - protein binding
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- muscle
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**Why 70% efficiency?**



# Lock and Key

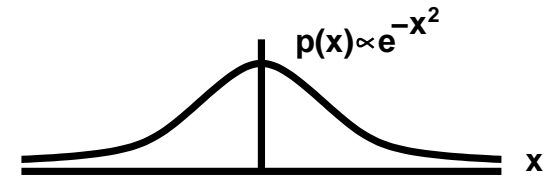


**Like a key in a lock  
which has many independent pins,  
it takes many numbers  
to describe the vibrational state  
of a molecular machine**

# Gaussians

- Pin motion  $x$  has a Gaussian distribution:

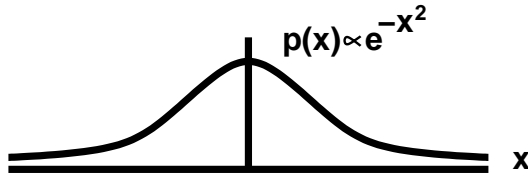
$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$



$\mu$  = mean,  $\sigma$  = standard deviation

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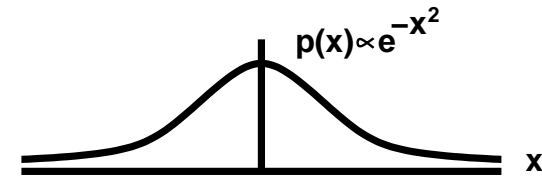
$\mu =$  mean,  $\sigma =$  standard deviation

- Gaussian distributions are generated by the sum of many small random variables

# Gaussians

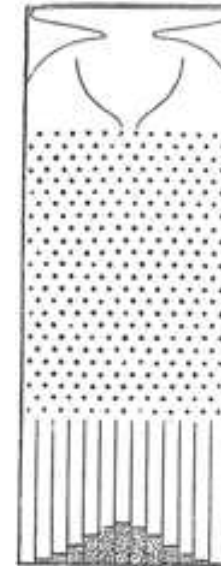
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$\mu$  = mean,  $\sigma$  = standard deviation

- Gaussian distributions are generated by the sum of many small random variables
- Drunkard's walk: Galton's quincunx device!



# Two Gaussians

$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \quad (1)$$

$$p(y) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(y-\mu)^2}{2\sigma^2}} \quad (2)$$

# Two Gaussians

$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \propto e^{-x^2} \quad (1)$$

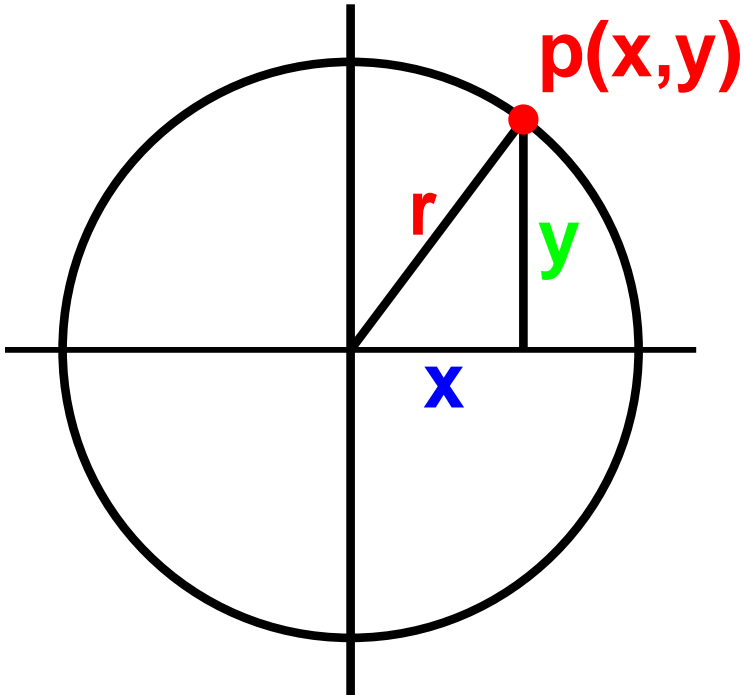
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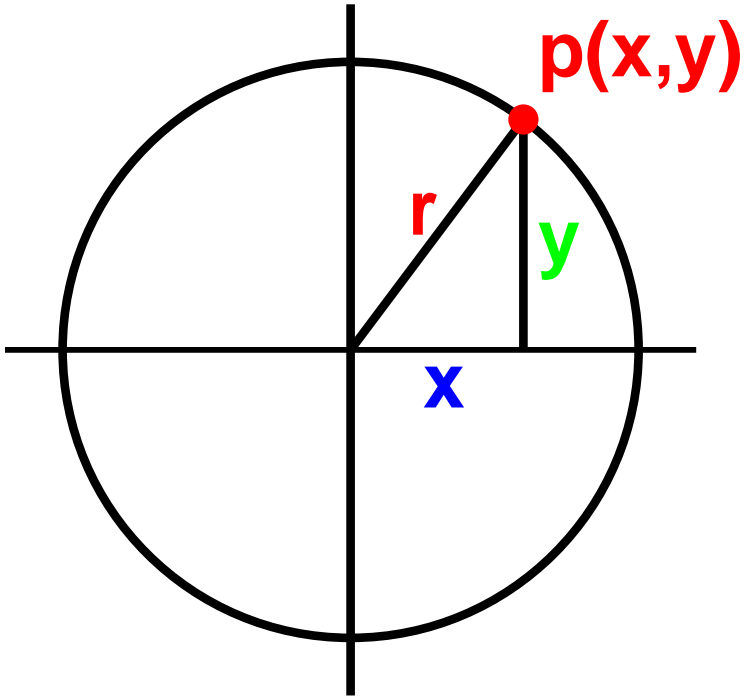


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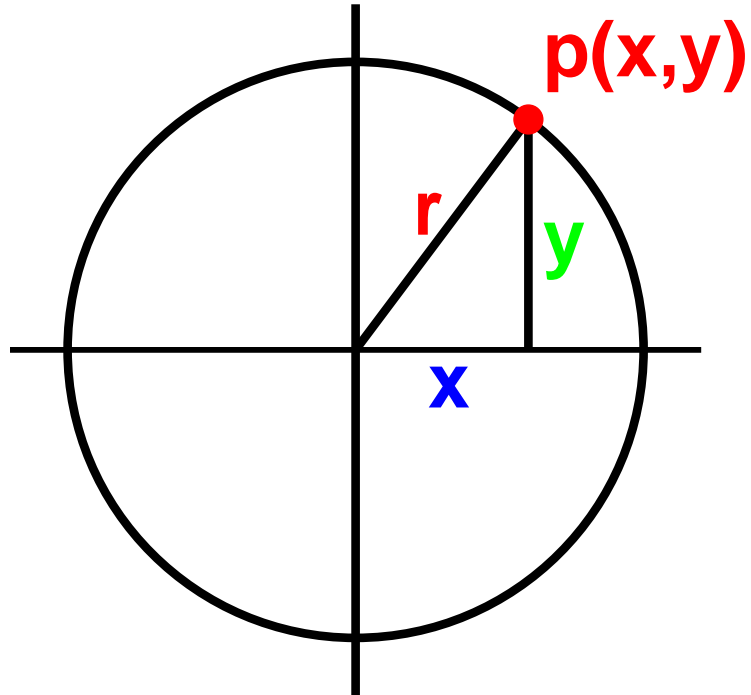
$$p(x, y) = p(x) \times p(y) \quad (3)$$



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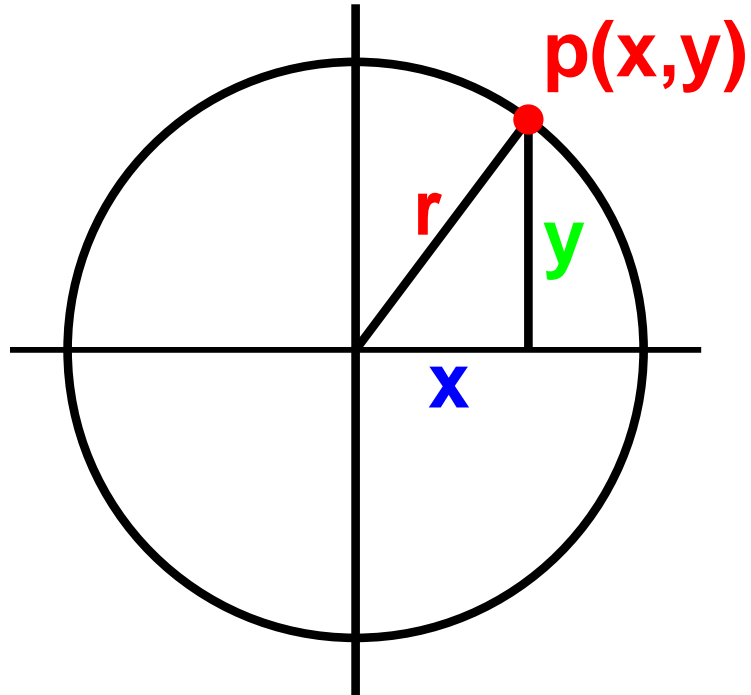
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$$p(x, y) = p(x) \times p(y) \quad (3)$$

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$$\propto e^{-(x^2+y^2)} \quad (5)$$

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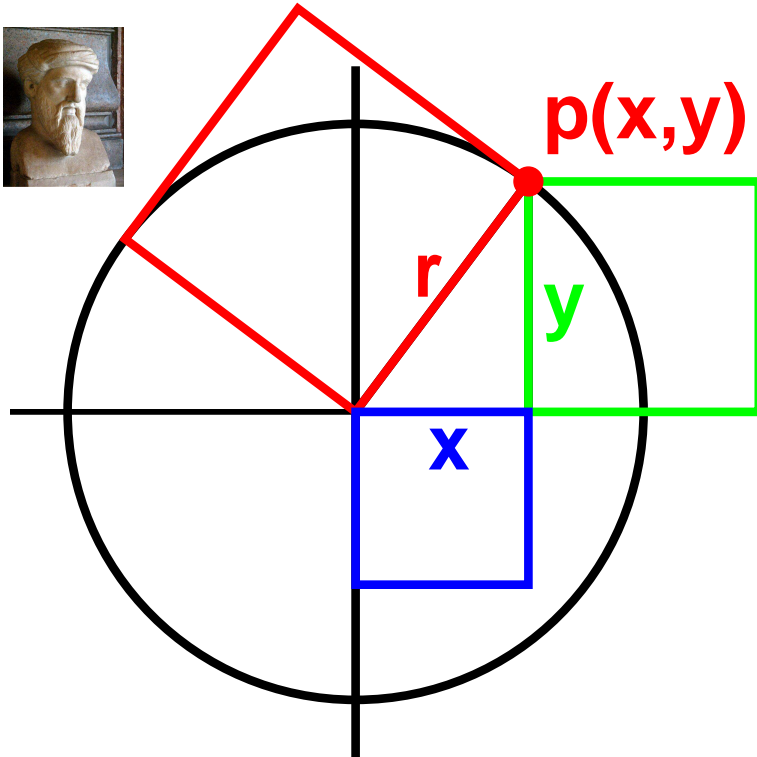
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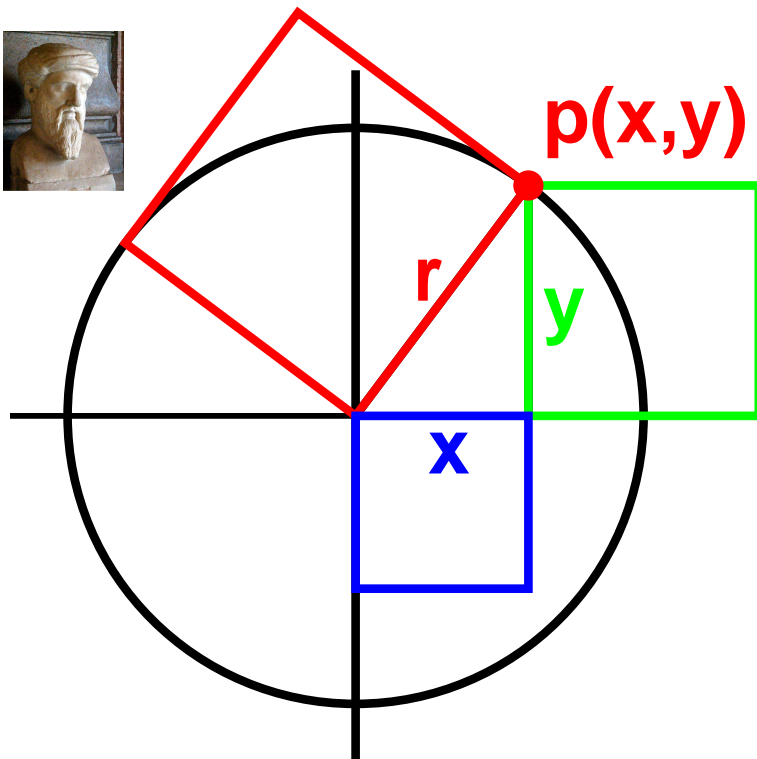
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$$\propto e^{-r^2} \quad (6)$$

If  $p(x, y)$  is a constant,  
then  $r$  is a constant.



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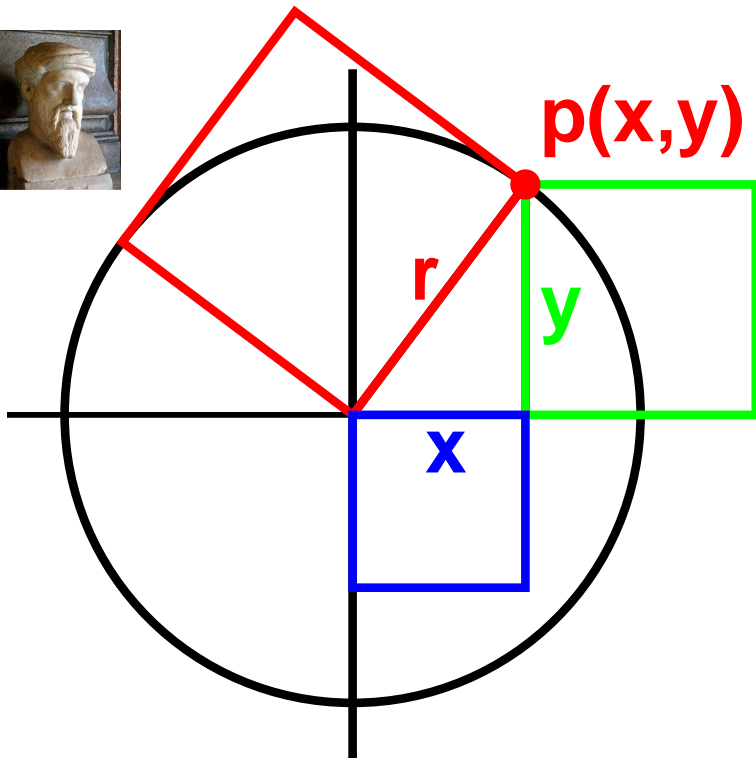
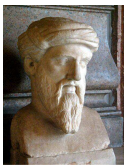
$$\propto e^{-x^2} \times e^{-y^2} \quad (4)$$

$$\propto e^{-(x^2+y^2)} \quad (5)$$

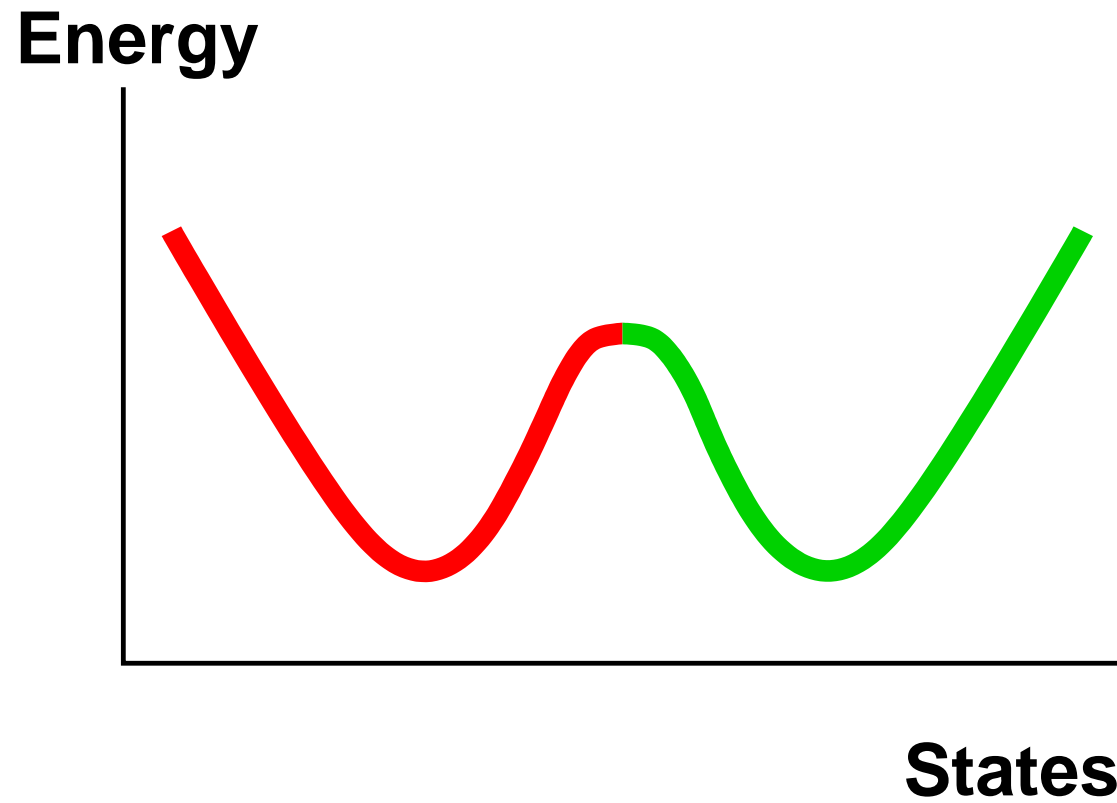
$$\propto e^{-r^2} \quad (6)$$

If  $p(x, y)$  is a constant,  
then  $r$  is a constant.

**Circular distribution!**



# 1 Dimension



**1 dimension is too simple!**



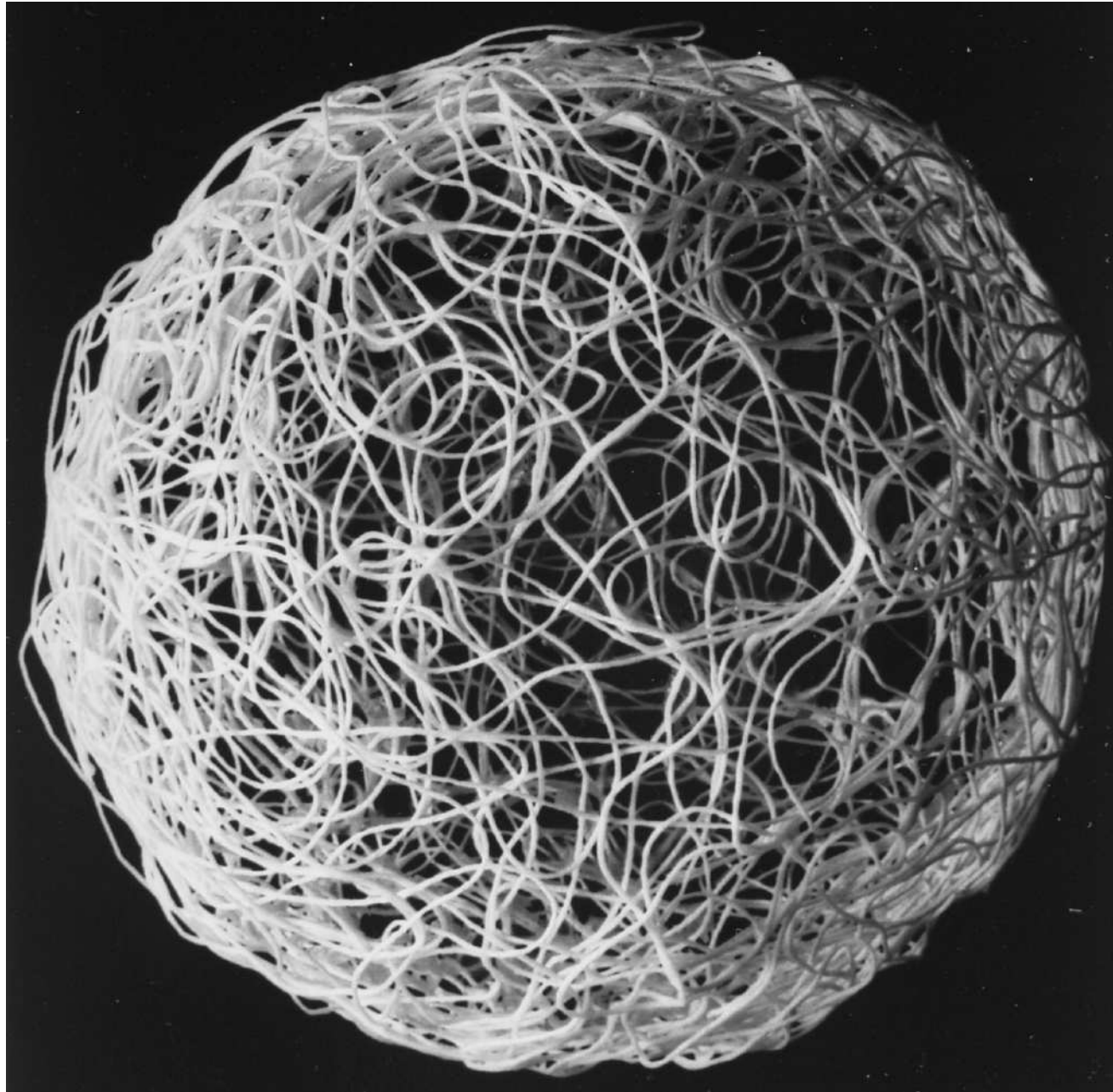
# Bowls in 2 Dimensions



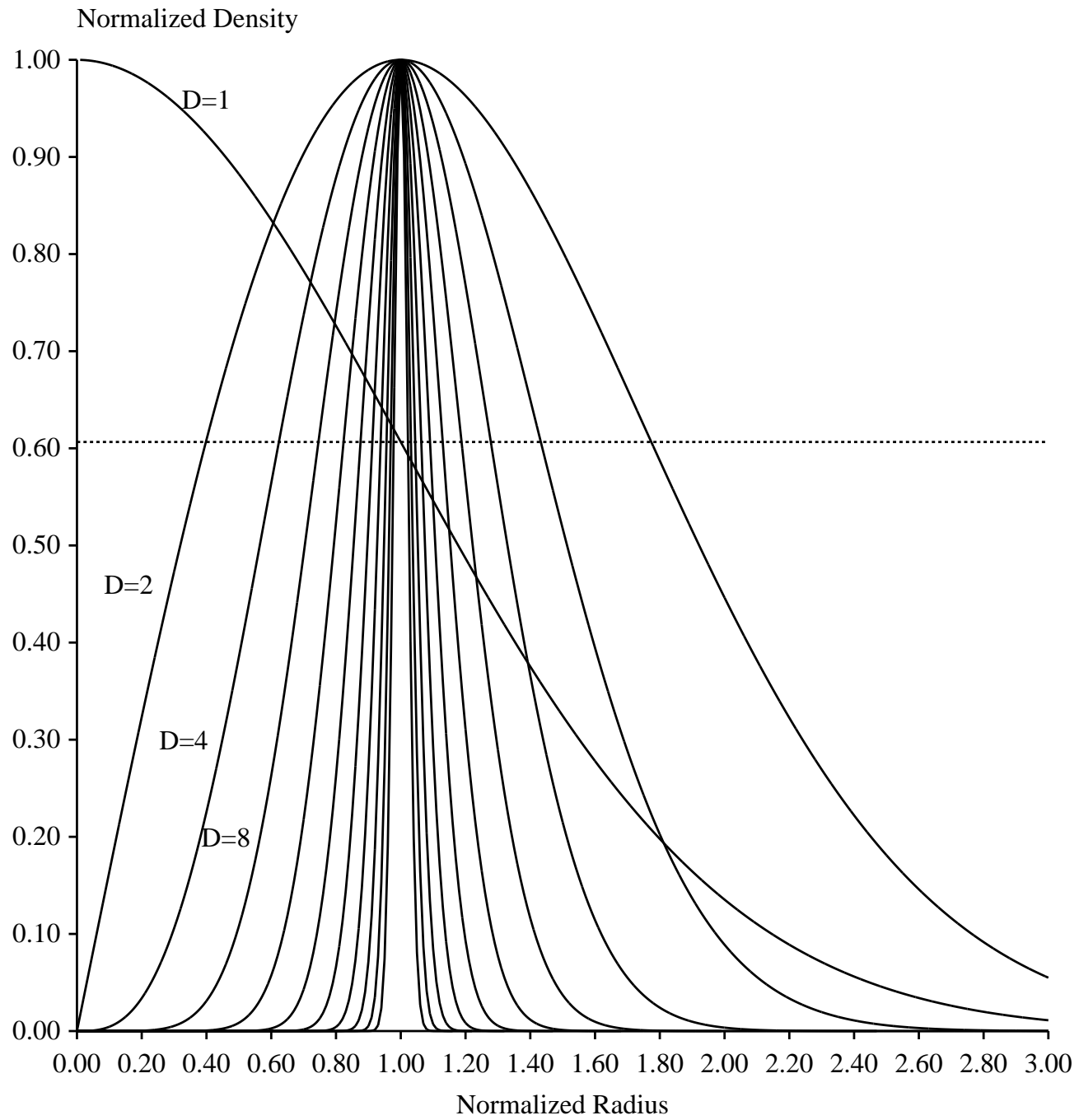
# Spheres in 3 Dimensions



# N Dimensional Sphere



# Spheres tighten in high dimensions



# Good Sphere Packing



- Good packing of spheres gives a molecule the capacity to make selections efficiently

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- Good packing of spheres gives a molecule the capacity to make selections efficiently
- Shannon's 1949 paper: each gumball is a message

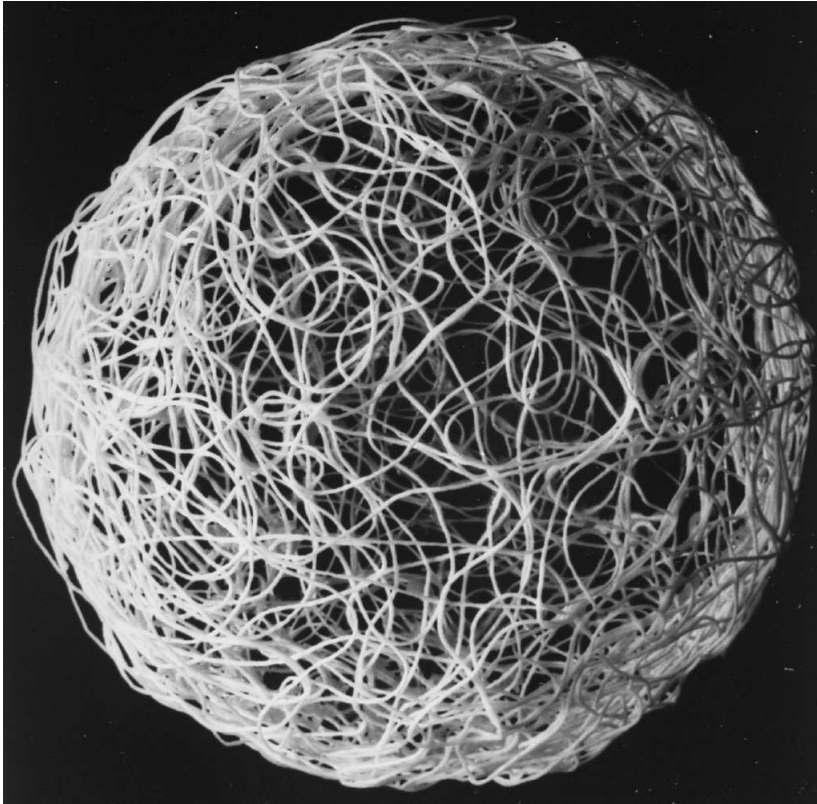
# Good Sphere Packing



- Good packing of spheres gives a molecule the capacity to make selections efficiently
- Shannon's 1949 paper: each gumball is a message
- For a molecule each gumball is a state

# N Dimensional Sphere Separation

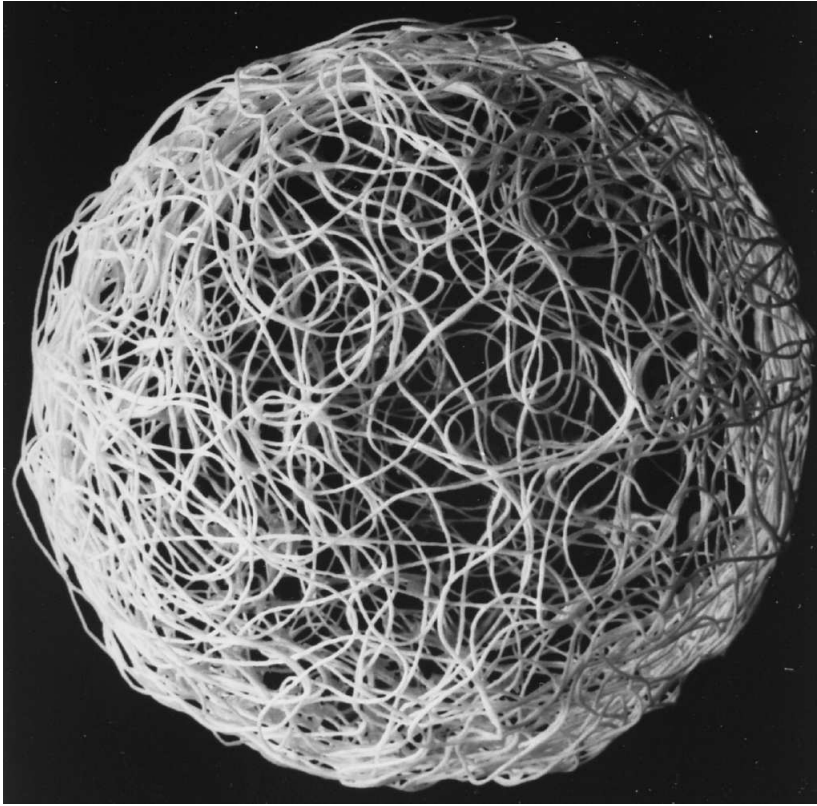
Degenerate Sphere



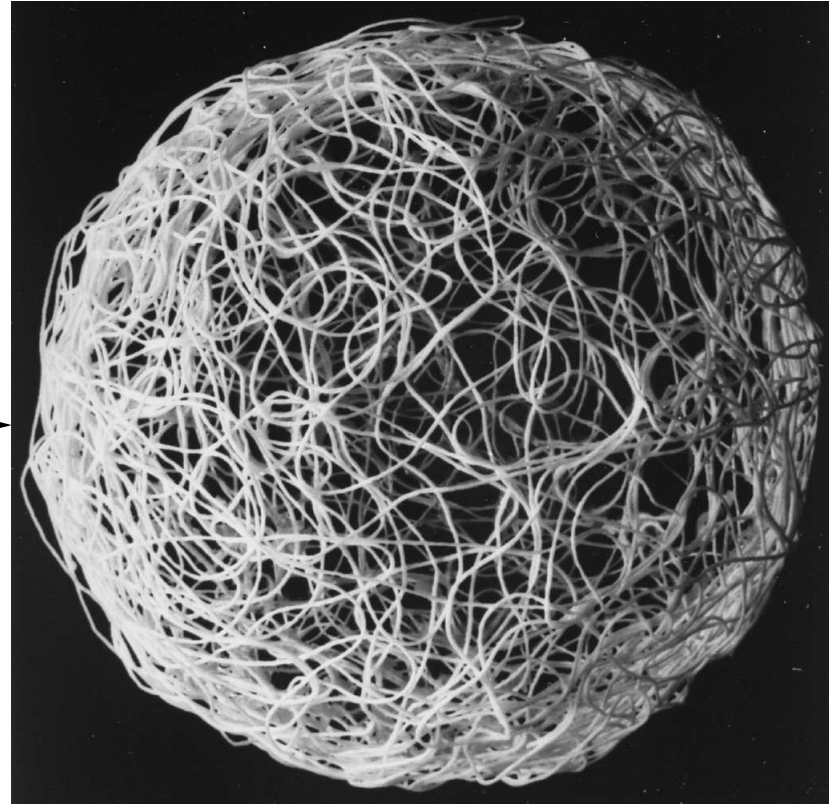


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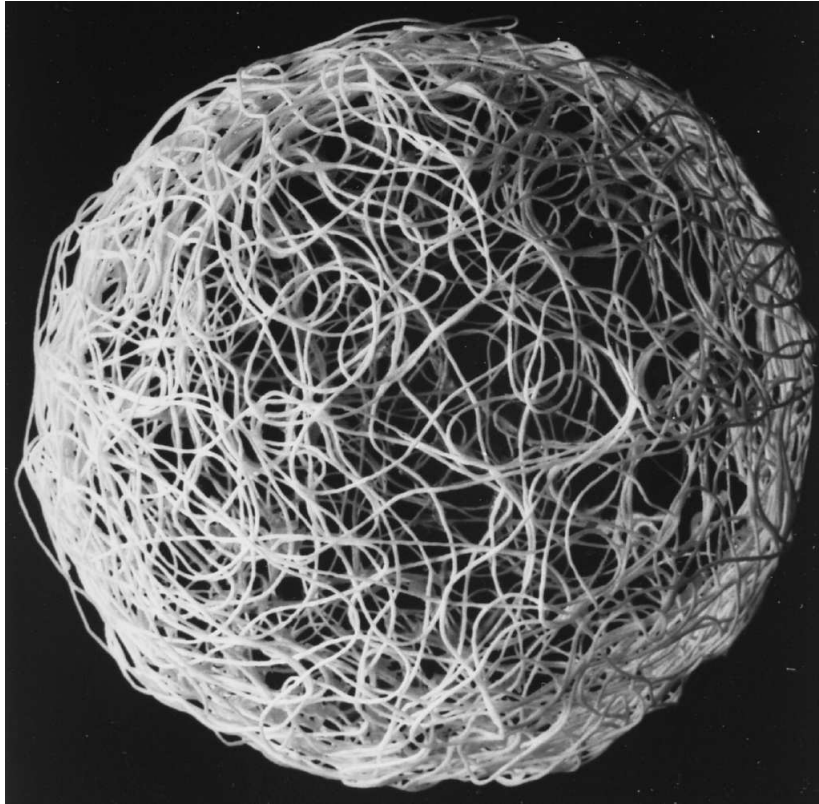


Forward Sphere

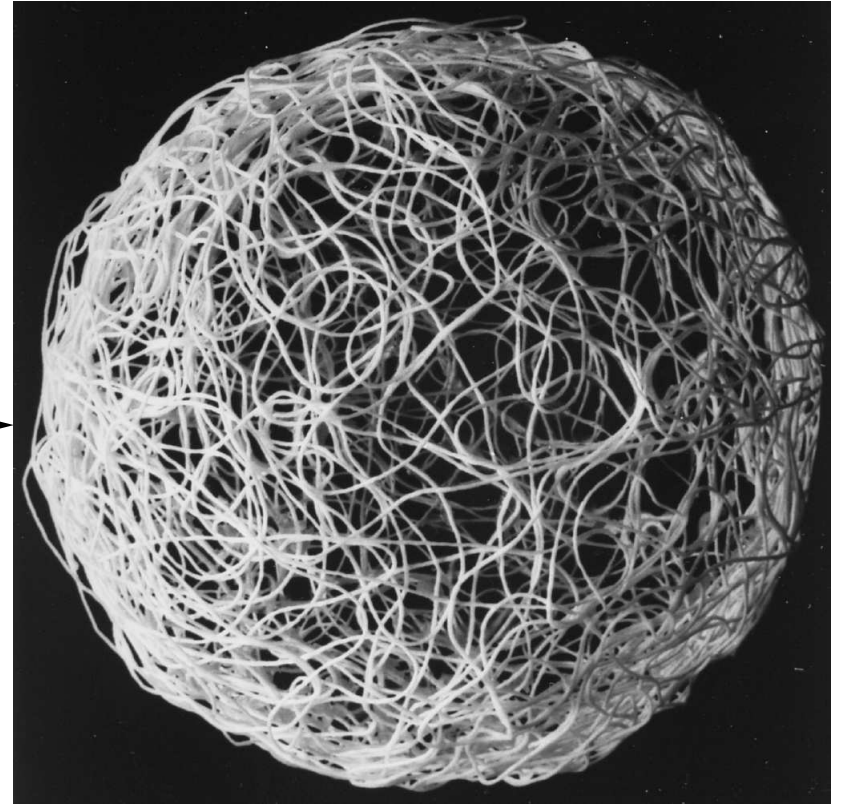


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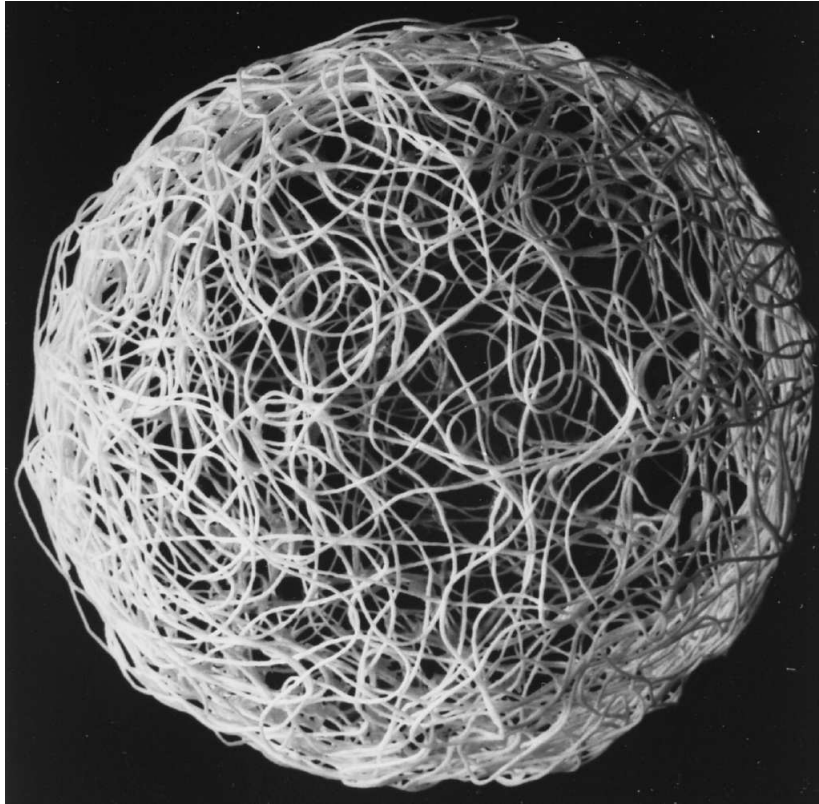
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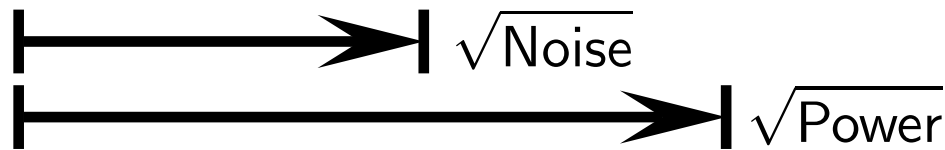
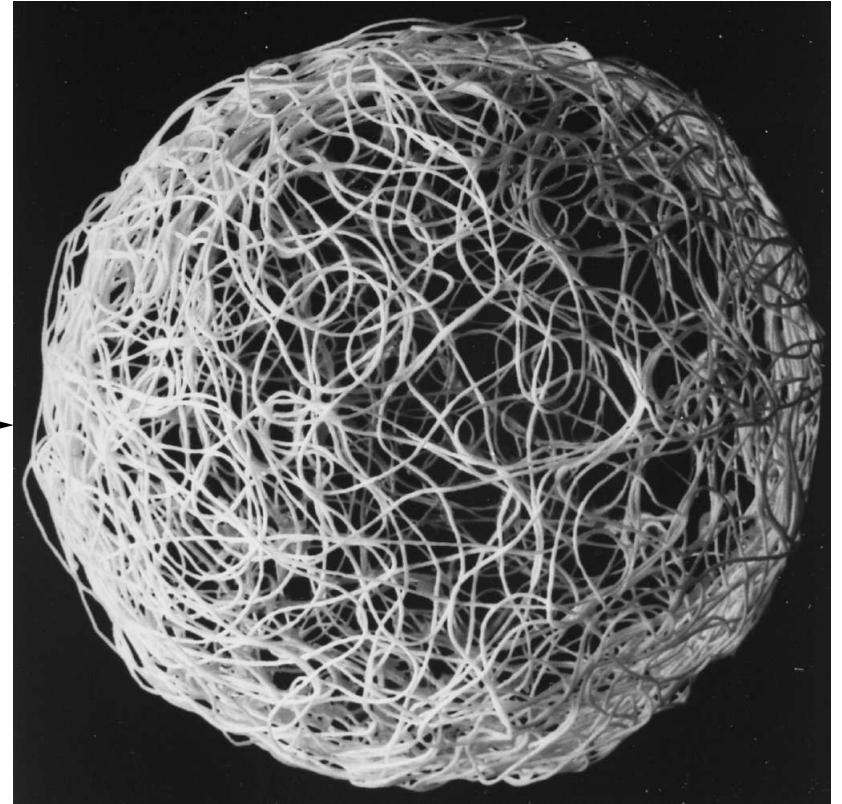
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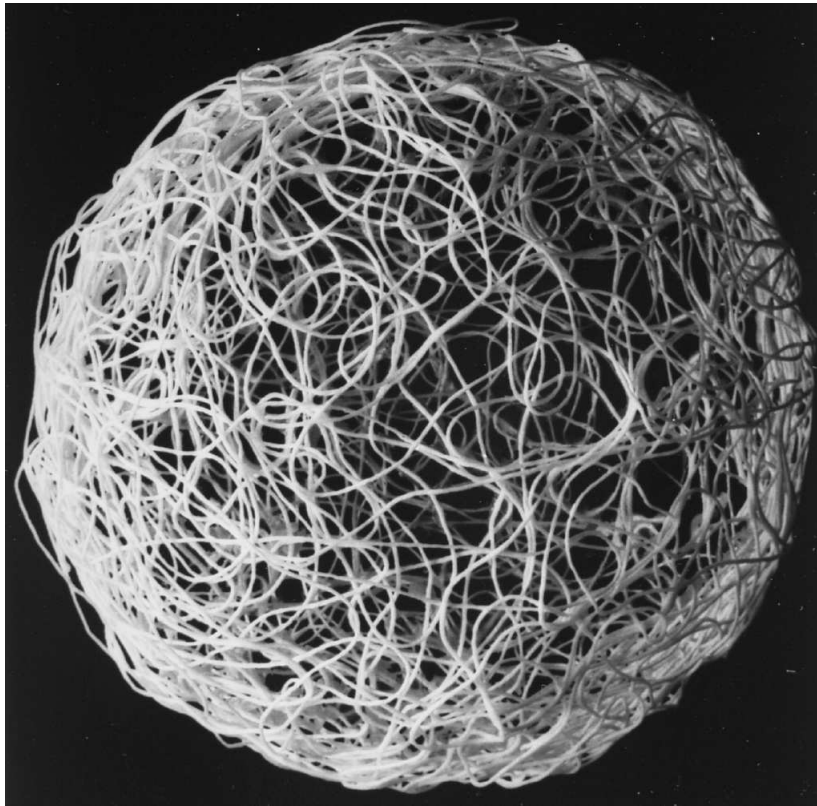


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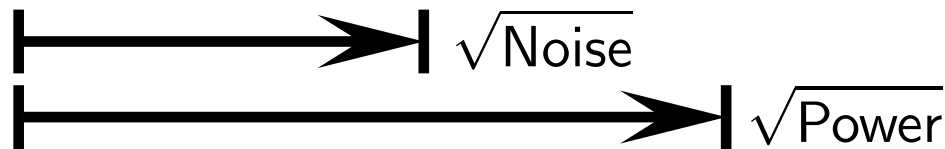
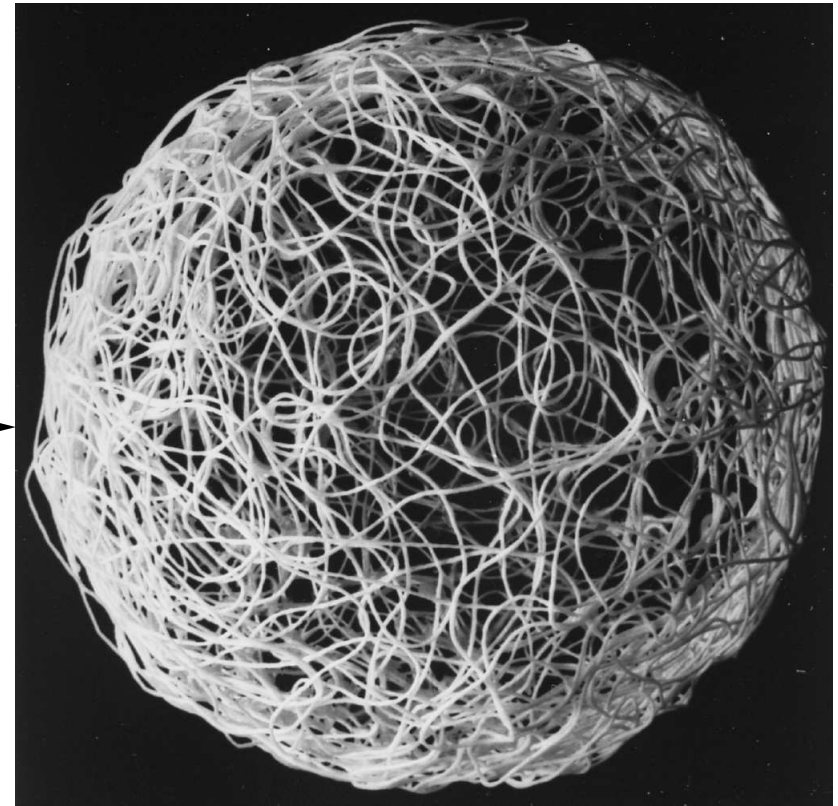


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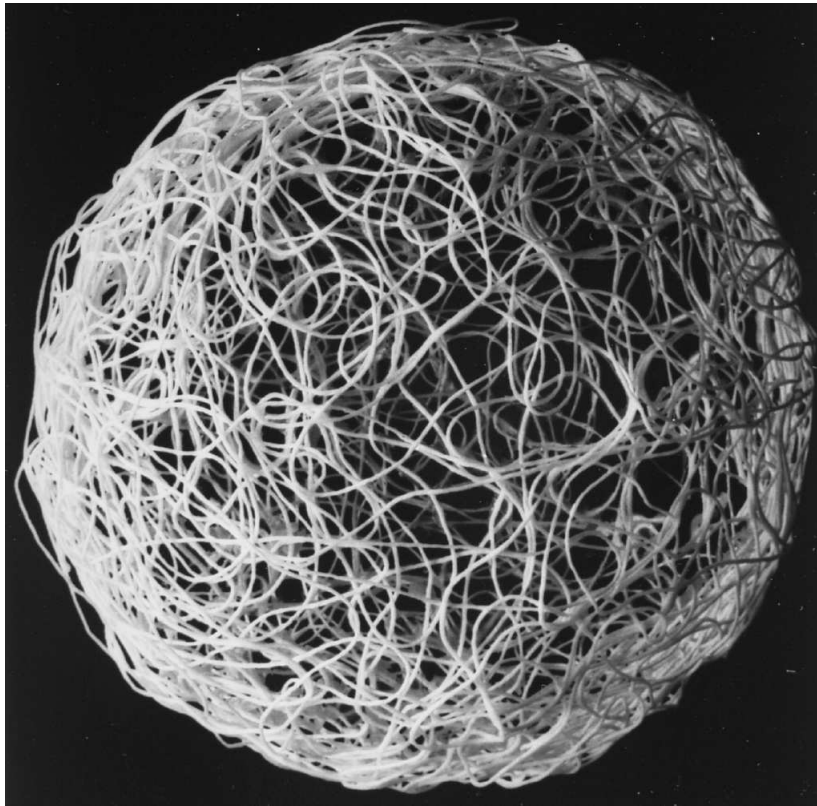
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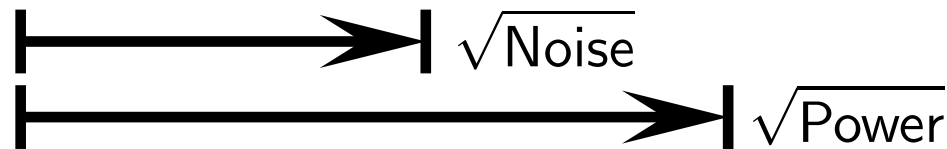
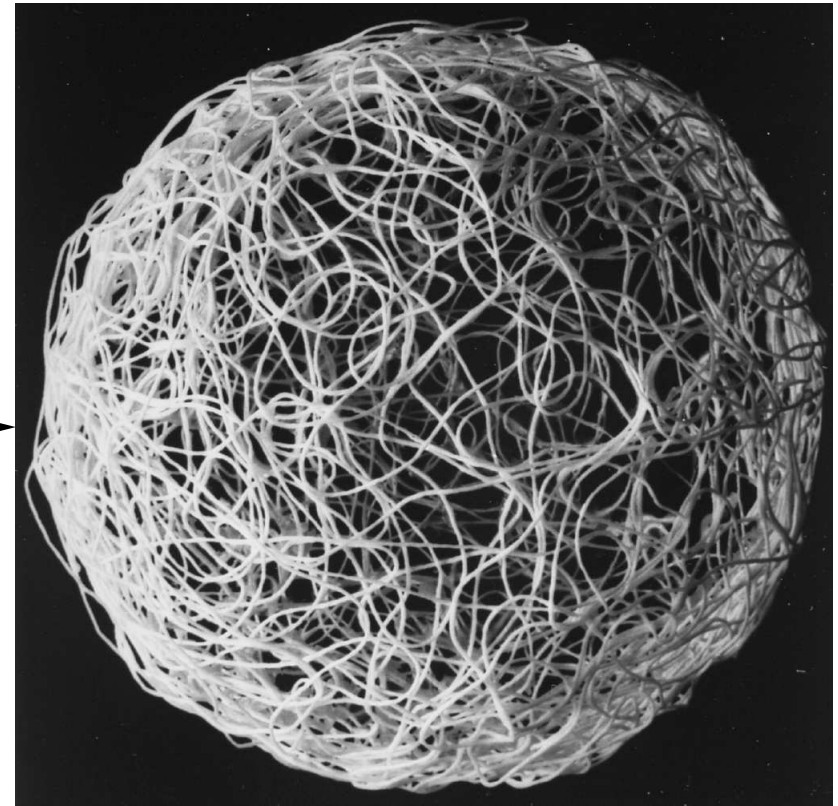
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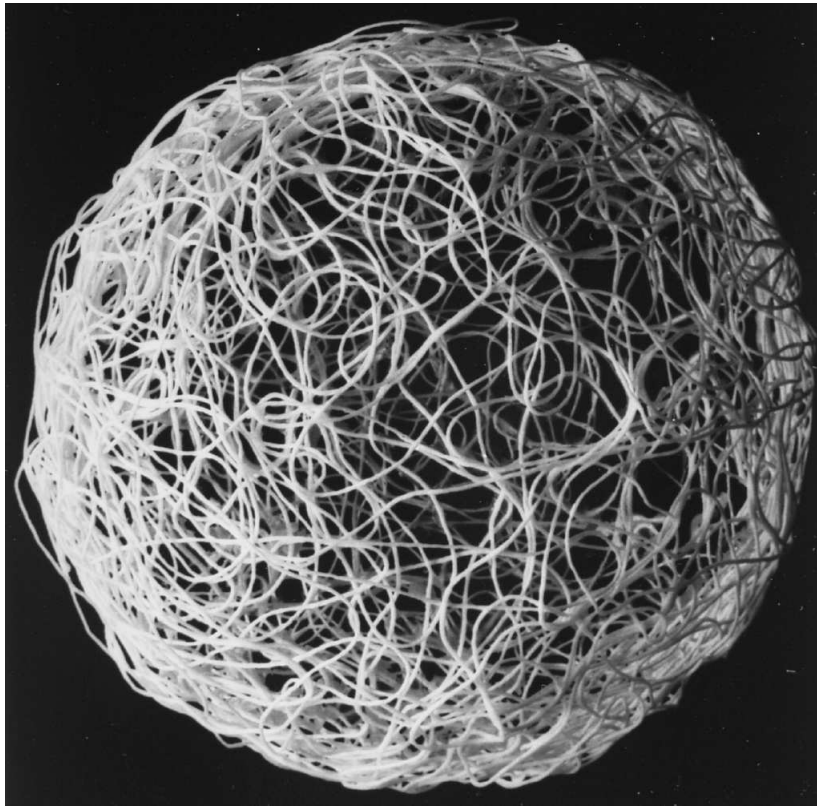


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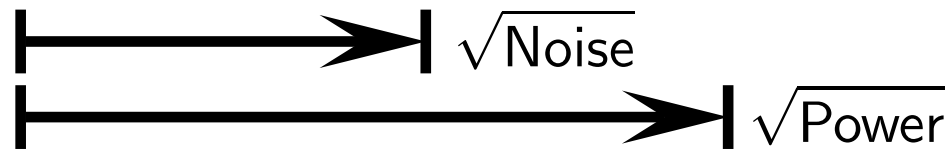
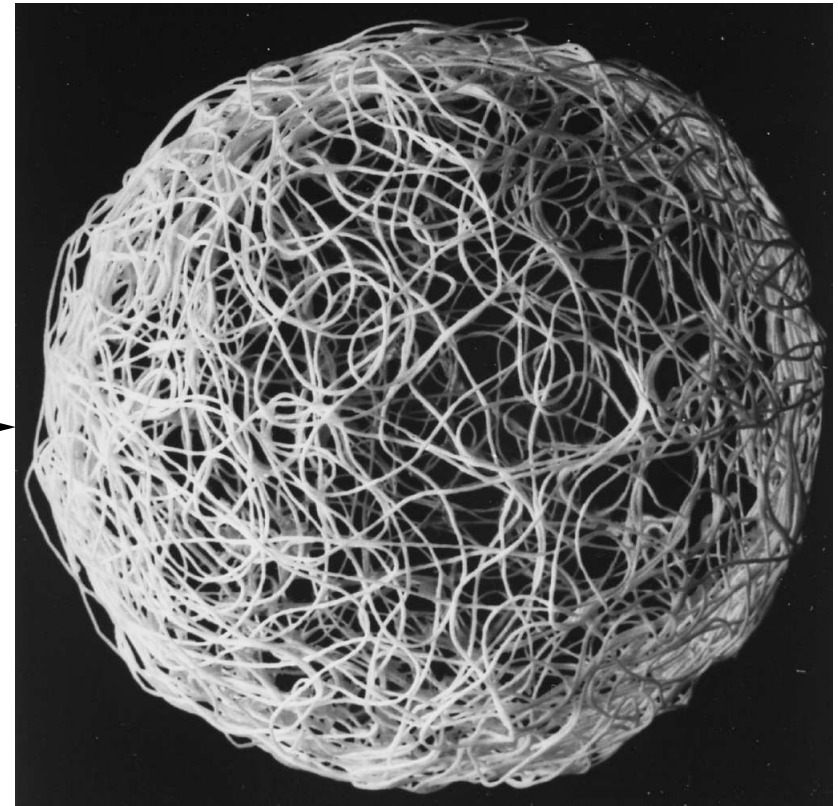
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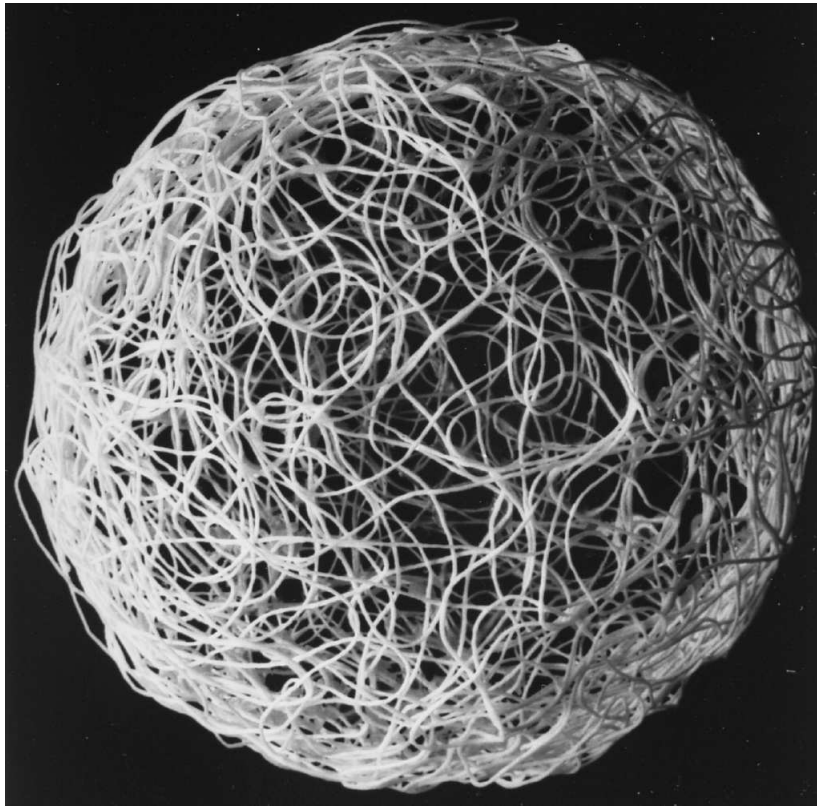


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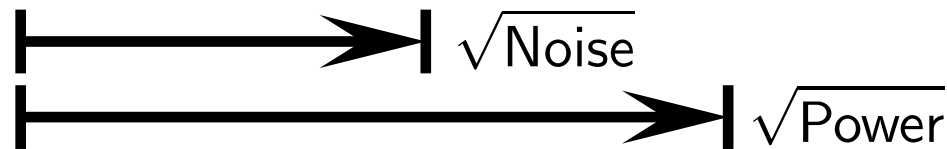
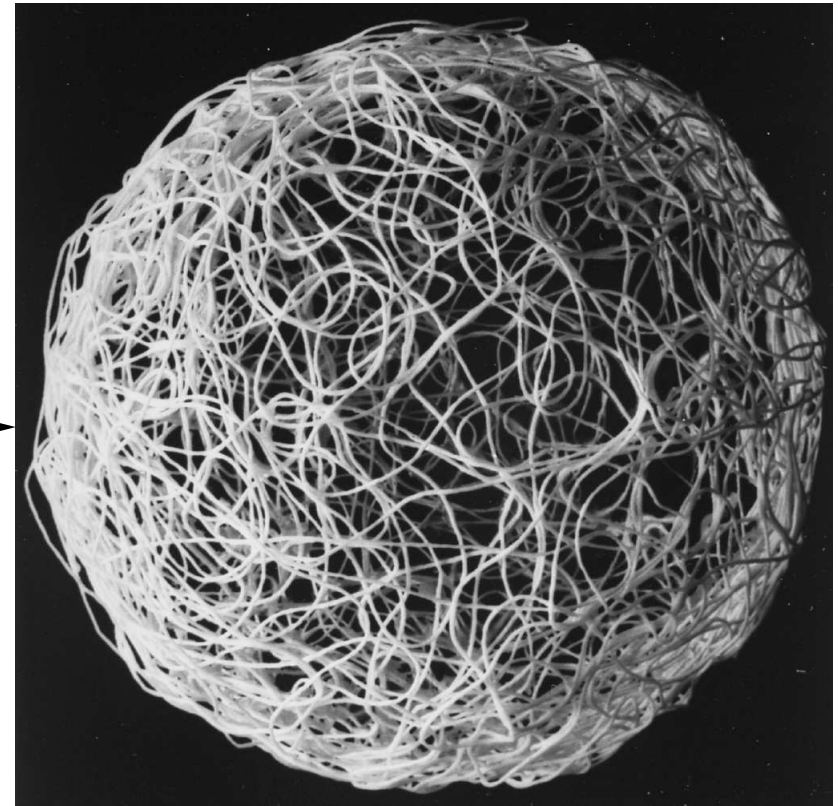
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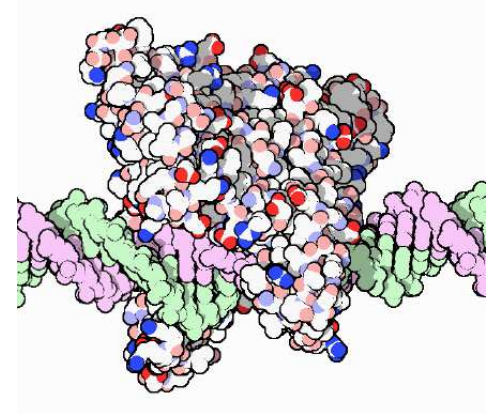
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# Theoretical Isothermal Efficiency

- For molecular states of molecules with  $d_{space}$  'parts'  $P$  energy is dissipated for noise  $N$  and

$$C = d_{space} \log_2(P/N + 1) \leftarrow \text{machine capacity}$$



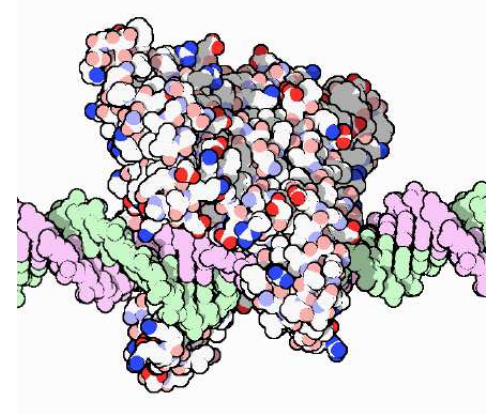


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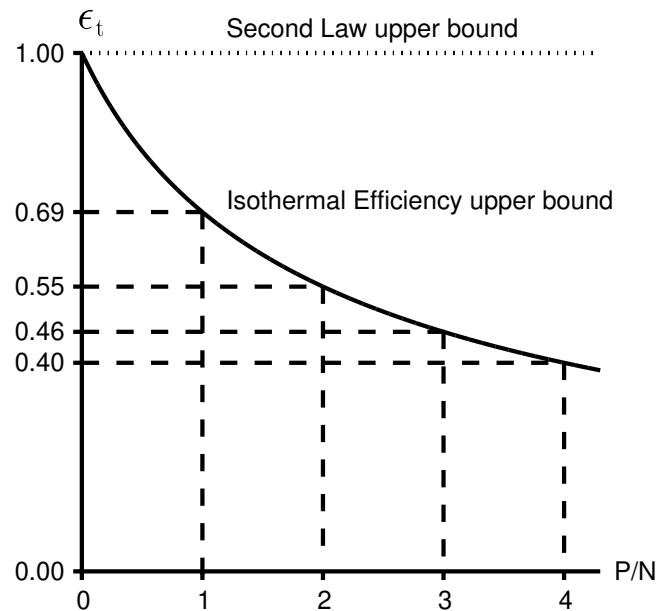
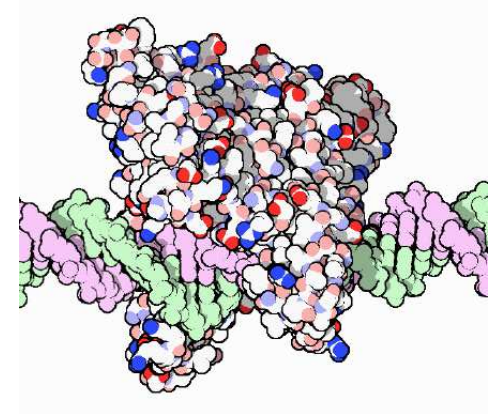


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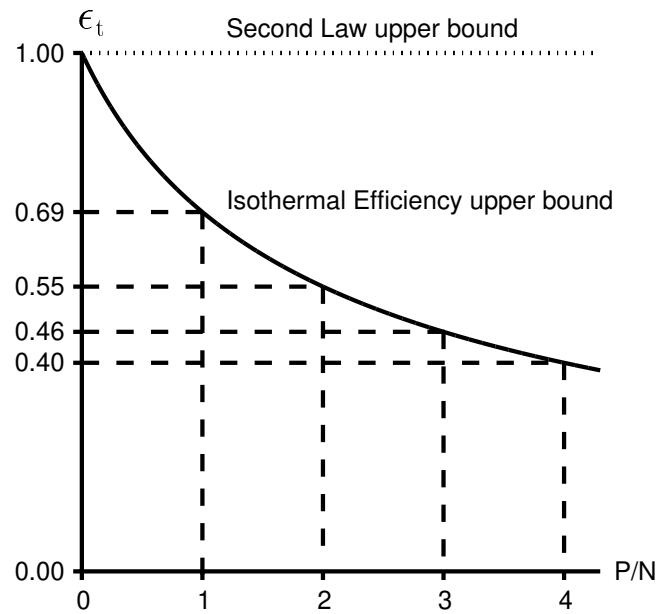
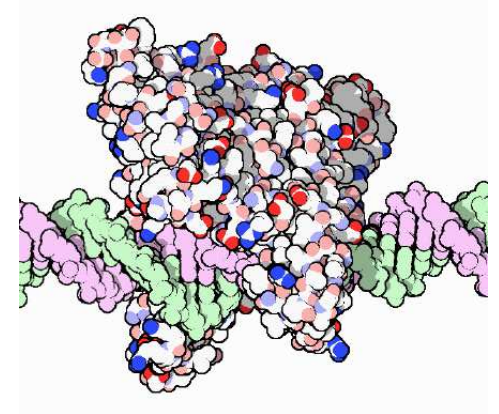
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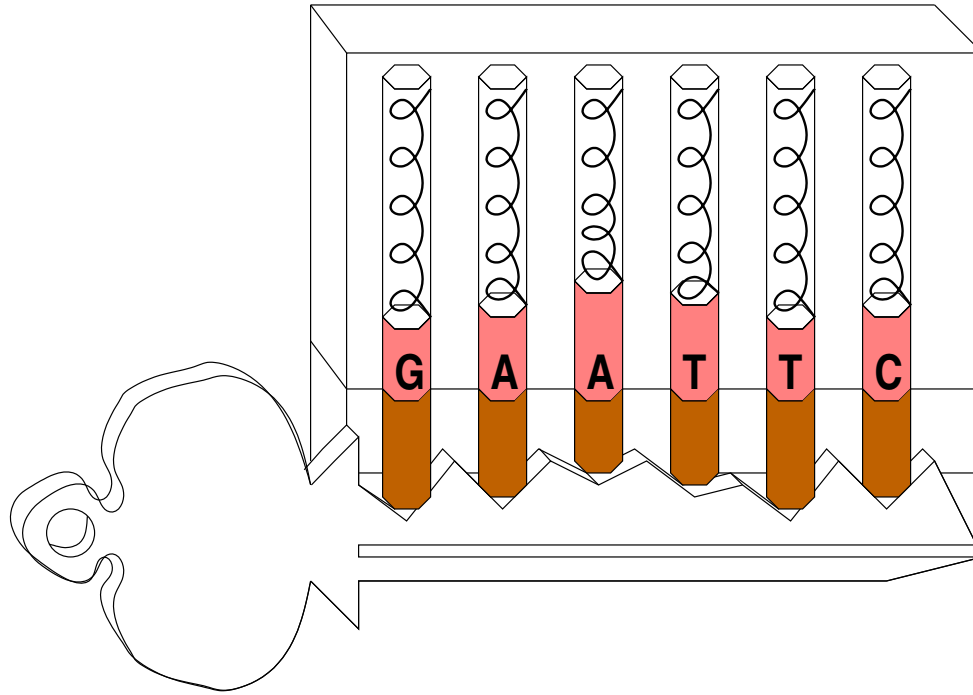
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The curve is an upper bound

- If  $P/N = 1$  the efficiency is 70%!

# Dimensionality



**Like a key in a lock  
which has many independent pins,  
it takes many numbers  
to describe the vibrational state  
of a molecular machine**

# A Dimensionality Equation

Channel capacity of molecular machine:

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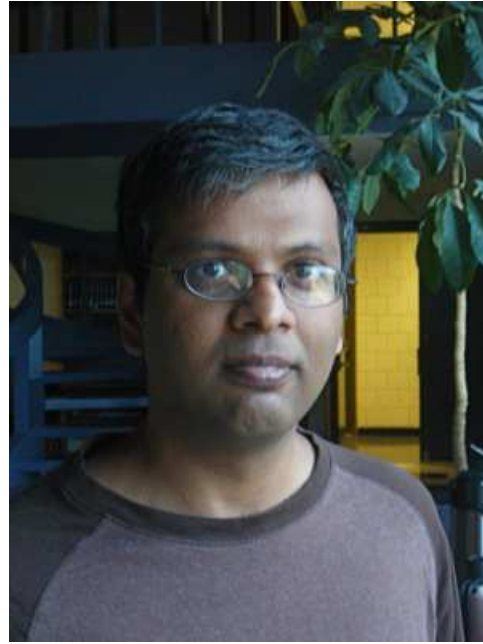
since there are both a phase and an amplitude for each of the independent oscillator pins that describe the motions of a molecule at thermal equilibrium.

Combining equations (7), (8) and (9) gives a lower bound for the dimensionality:

$$D \geq \frac{2R}{\log_2 \left( \frac{P}{N} + 1 \right)}. \quad (10)$$

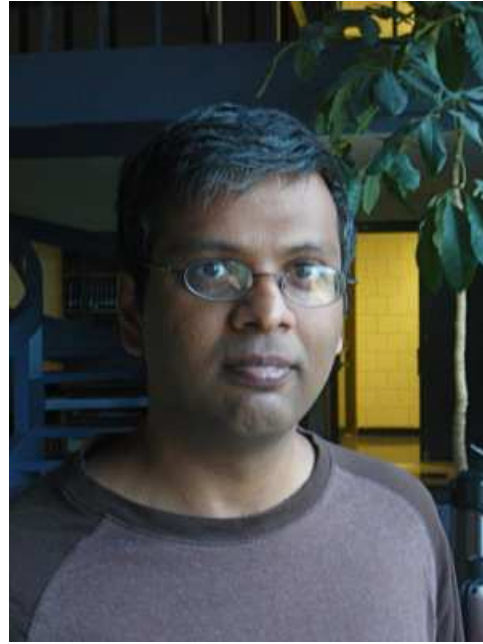


# Vishnu's Observation



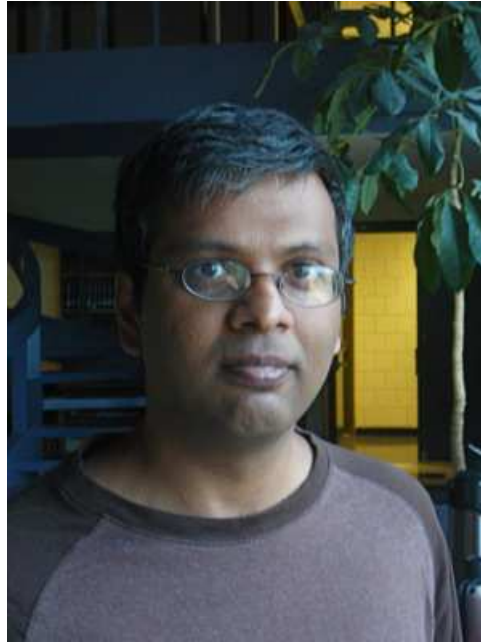
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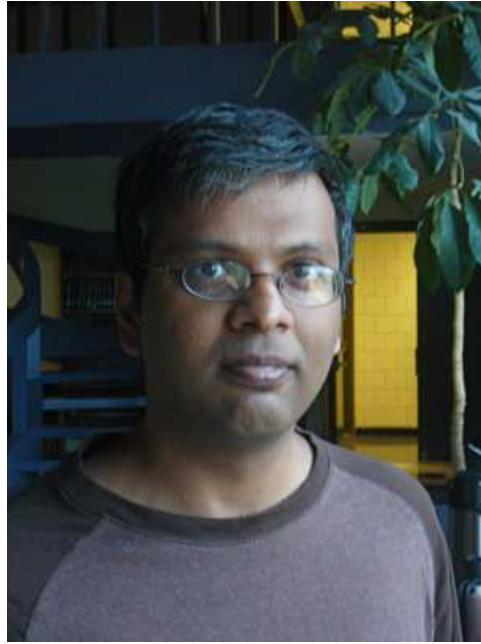
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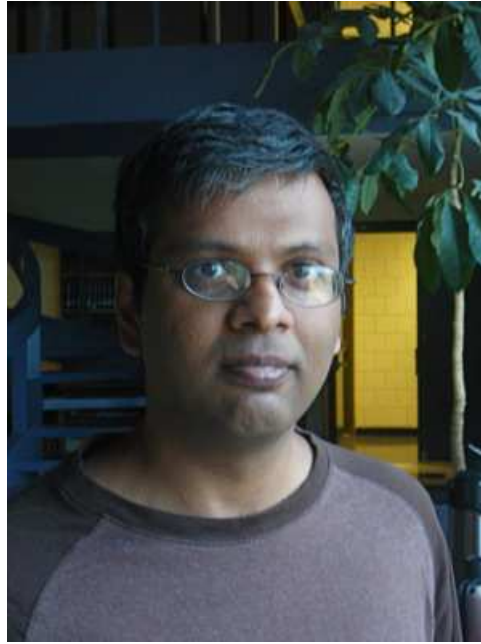
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- **He did not succeed.**



18 years later ...

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- Tom already had this equation in 1991!

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**Vishnu was right!**  
**There is an equation**  
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- A measured isothermal efficiency,  $\epsilon_r < \epsilon_t$ , is defined by the information gained,  $R$ , versus the information that could be gained for the given energy dissipation,  $R_{energy}$ :

$$\epsilon_r = R / R_{energy} \quad (18)$$

- combining equations (15) to (18) gives

$$P = \mathcal{E}_{min} R_{energy} \quad (19)$$

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- Equation (22) is an

upper bound on the dimensionality as a function of the information gain  $R$  and the isothermal efficiency  $\epsilon_r$ .

# Bounds on the dimensionality of molecular machines

- Combining the lower bound (10) with the upper bound (22)

$$\frac{2R}{\log_2 \left( \frac{P}{N} + 1 \right)} \leq D < \frac{2R \ln 2}{\epsilon_r} \quad (23)$$

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- So

$$\frac{2R \ln 2}{\ln(\rho + 1)} \leq D < \frac{2R \ln 2}{\epsilon_r} \quad (24)$$


A beautifully symmetrical equation!

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$$\rho \rightarrow 1$$

$$\epsilon_r \rightarrow \ln(2)$$

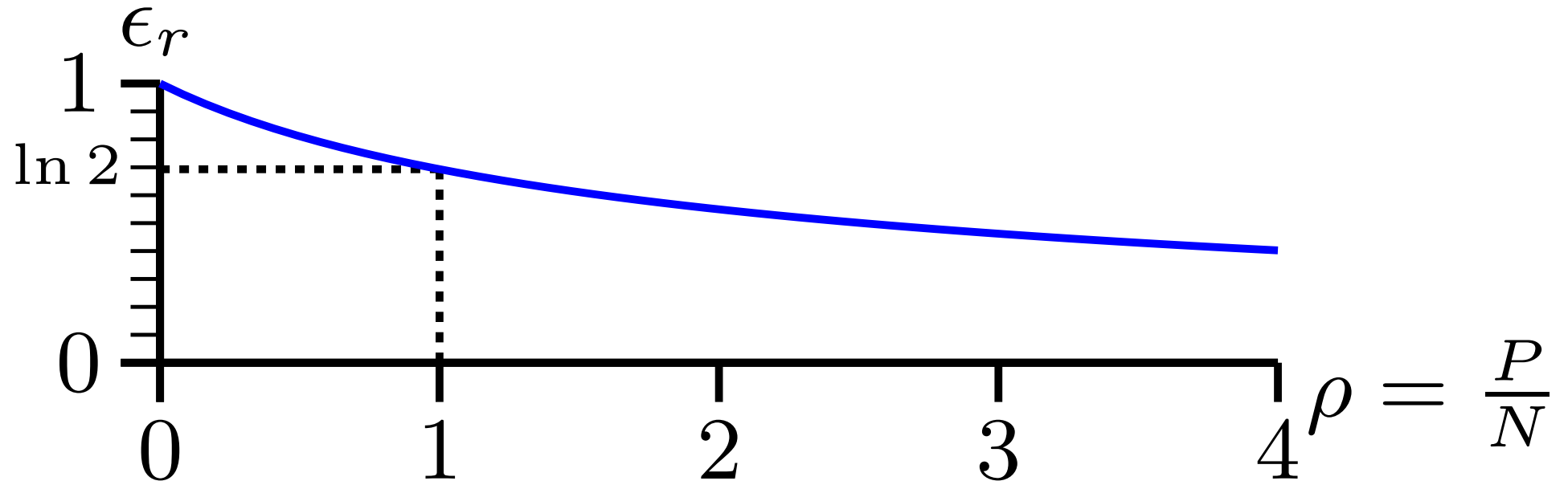
The left hand side converges to  $2R$ .

The right hand side converges to  $2R$ .

**BOTH SIDES converge to  $2R$ !**

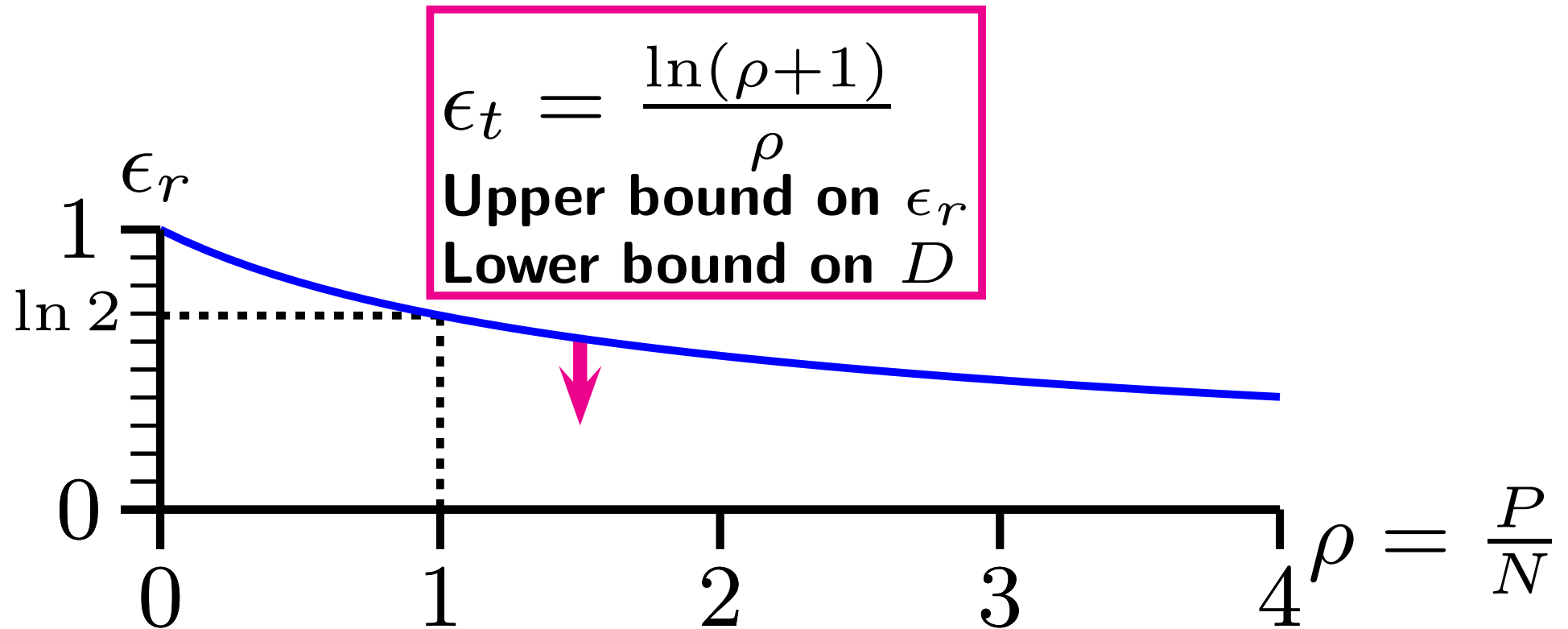
Vishnu was right  
about the convergence!

# Efficiency curve bounds

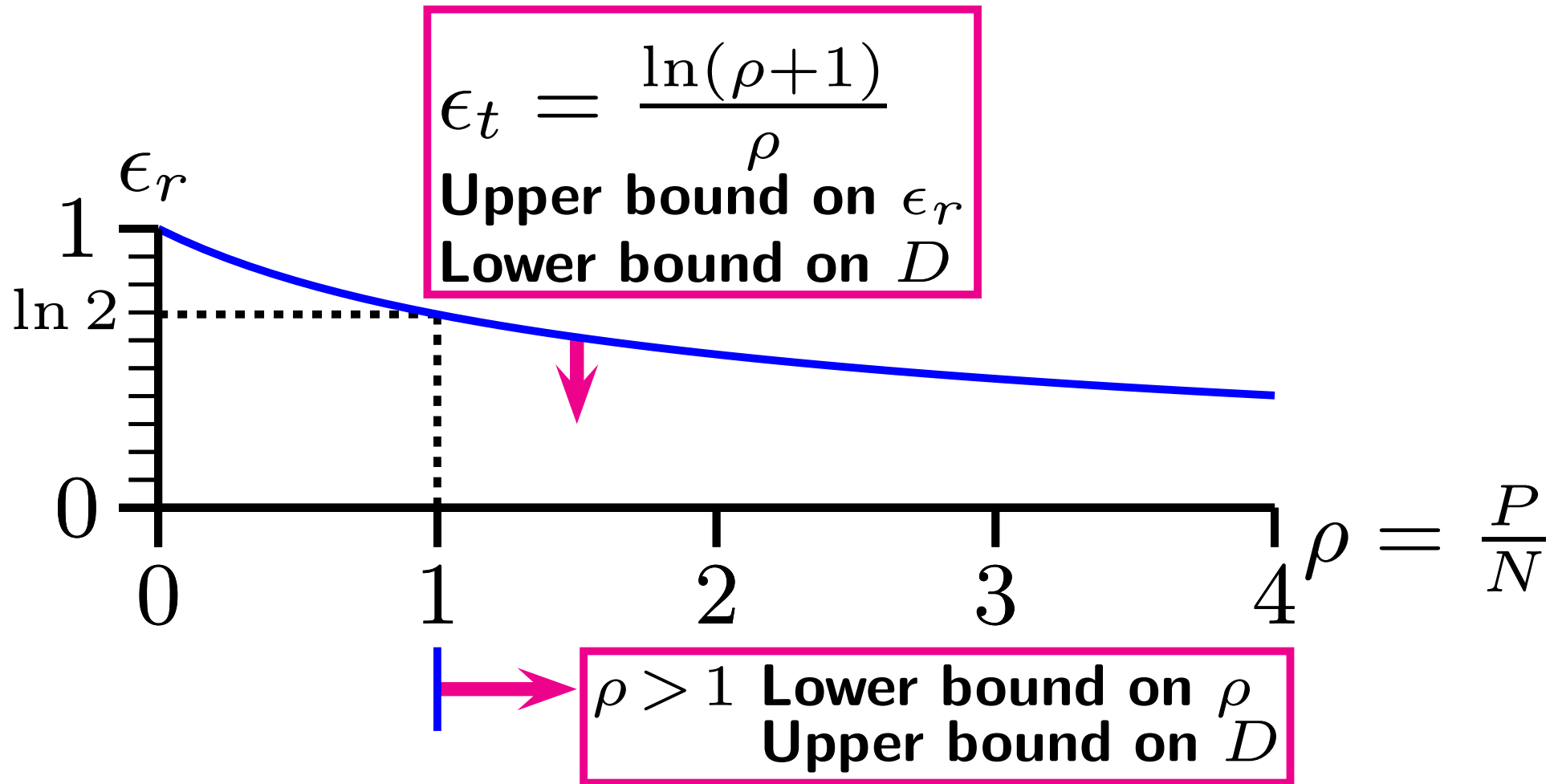




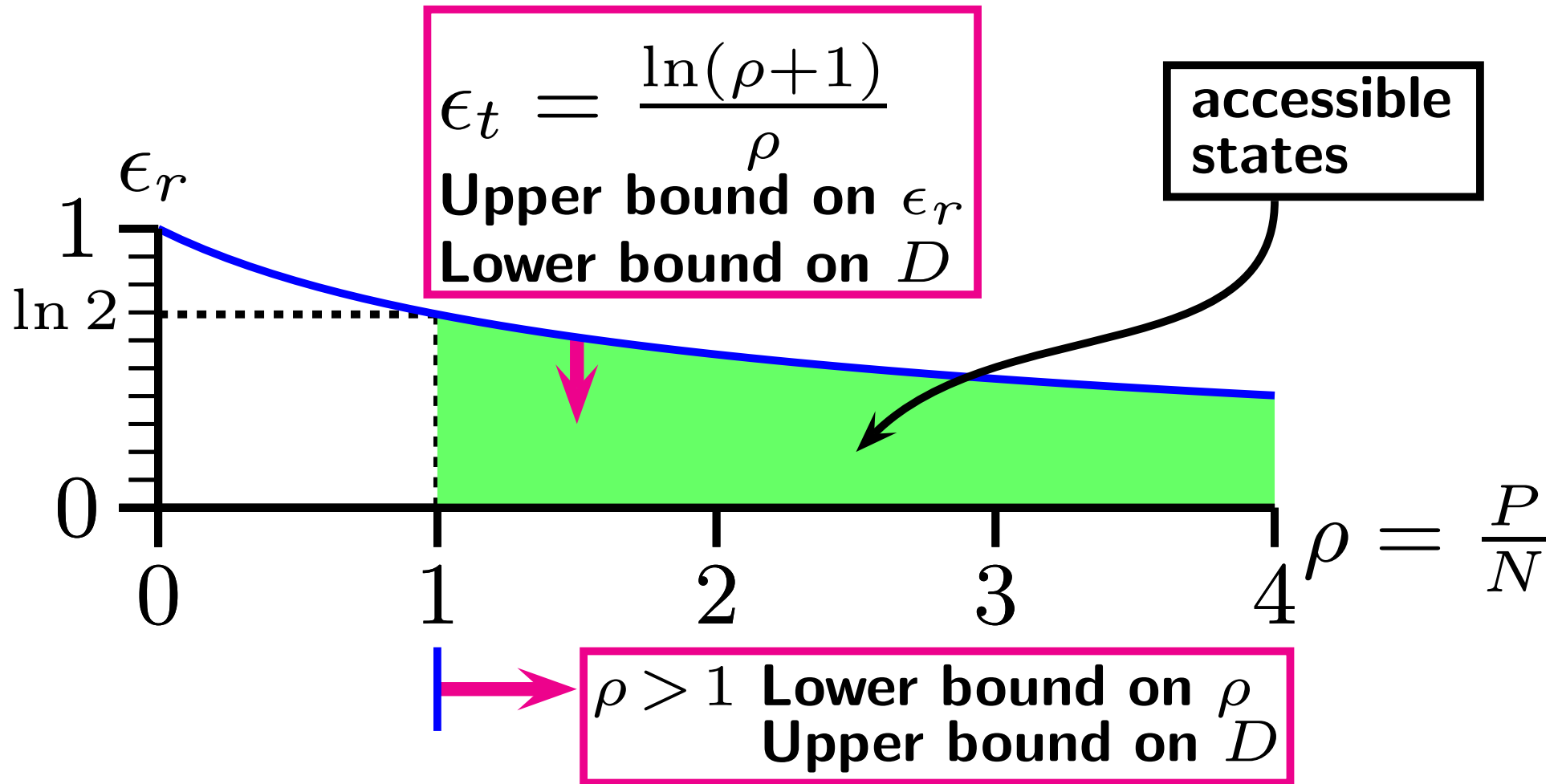
# Efficiency curve bounds



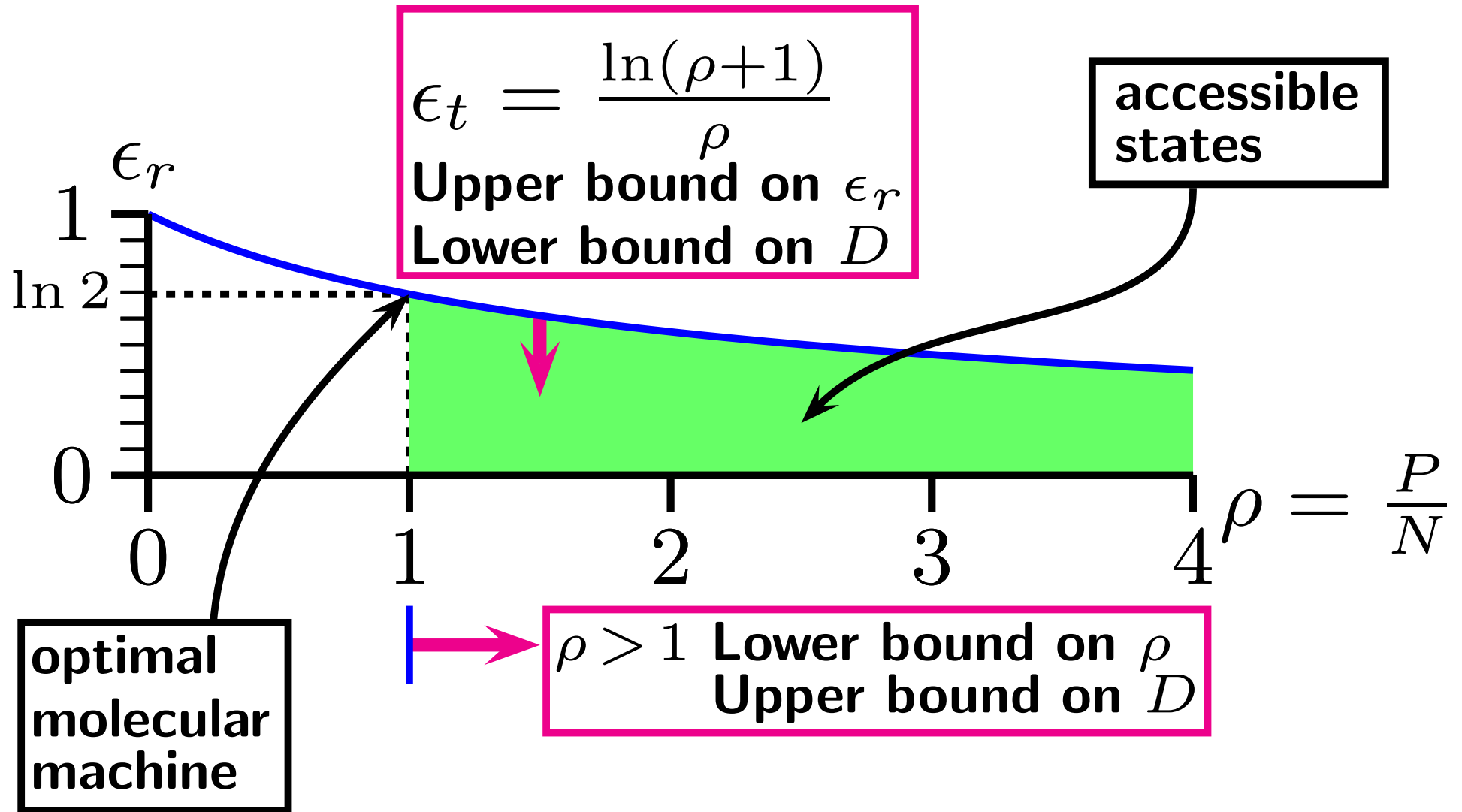
# Efficiency curve bounds



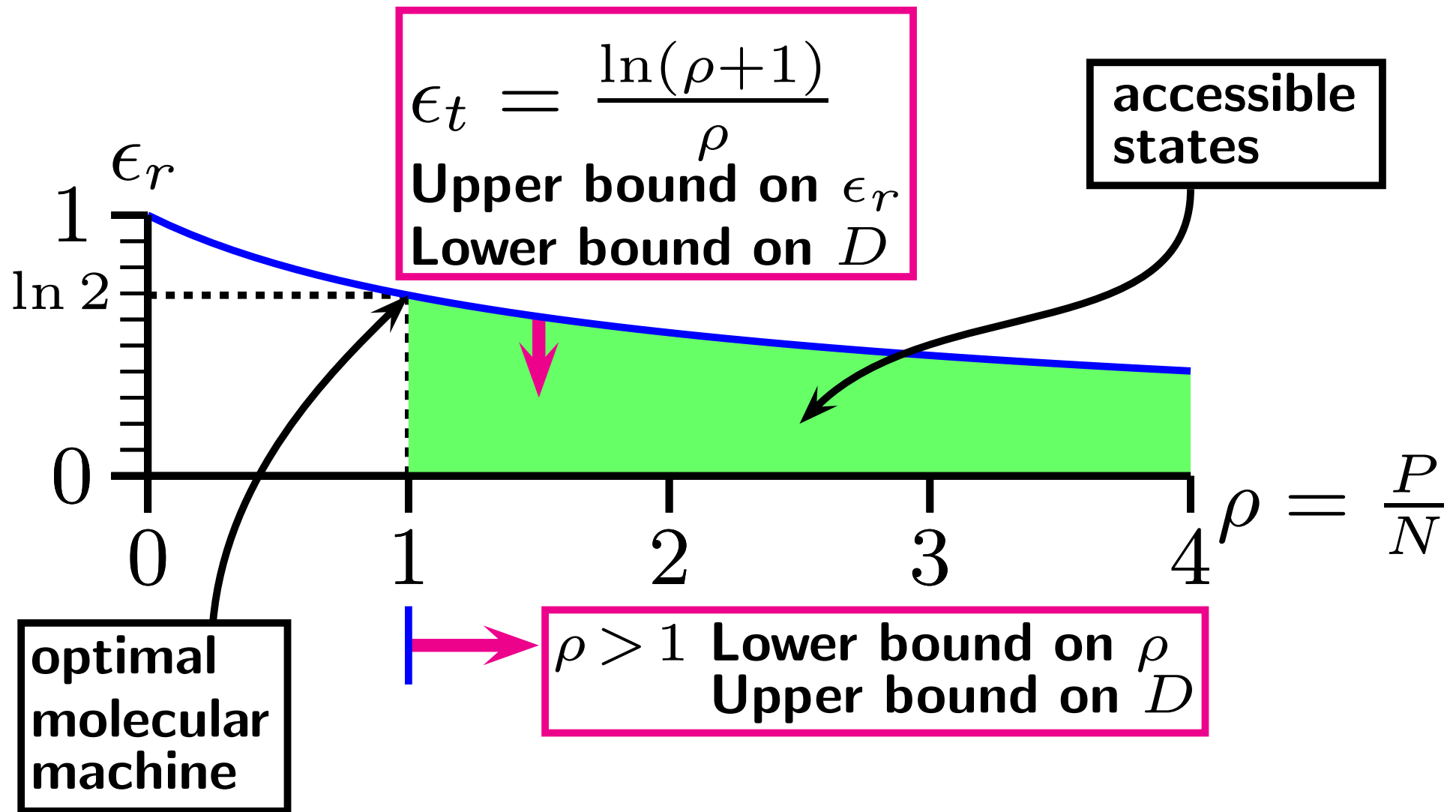
# Efficiency curve bounds



# Efficiency curve bounds



# Efficiency curve bounds



$D = 2R$  when the molecular machine is optimal

If a molecular machine has evolved to optimum, then the dimensionality is

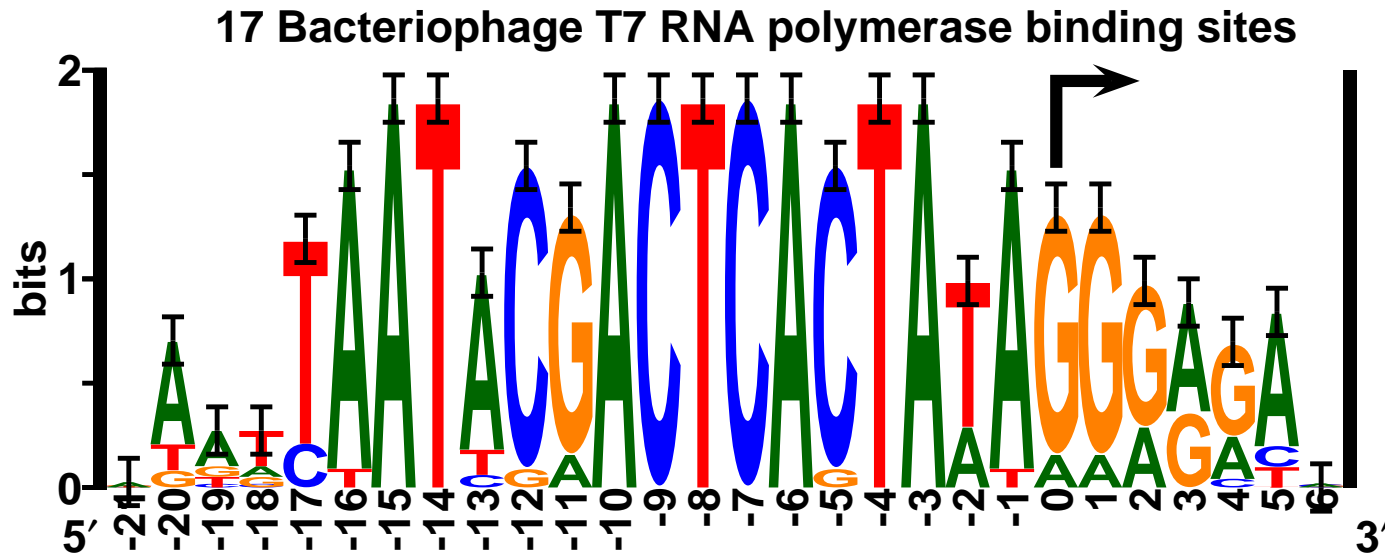
$$D = 2R$$

If a molecular machine has evolved to optimum, then the dimensionality is

$$D = 2R$$

Let's calculate  $D$  for restriction enzymes!

# Sequence Logo



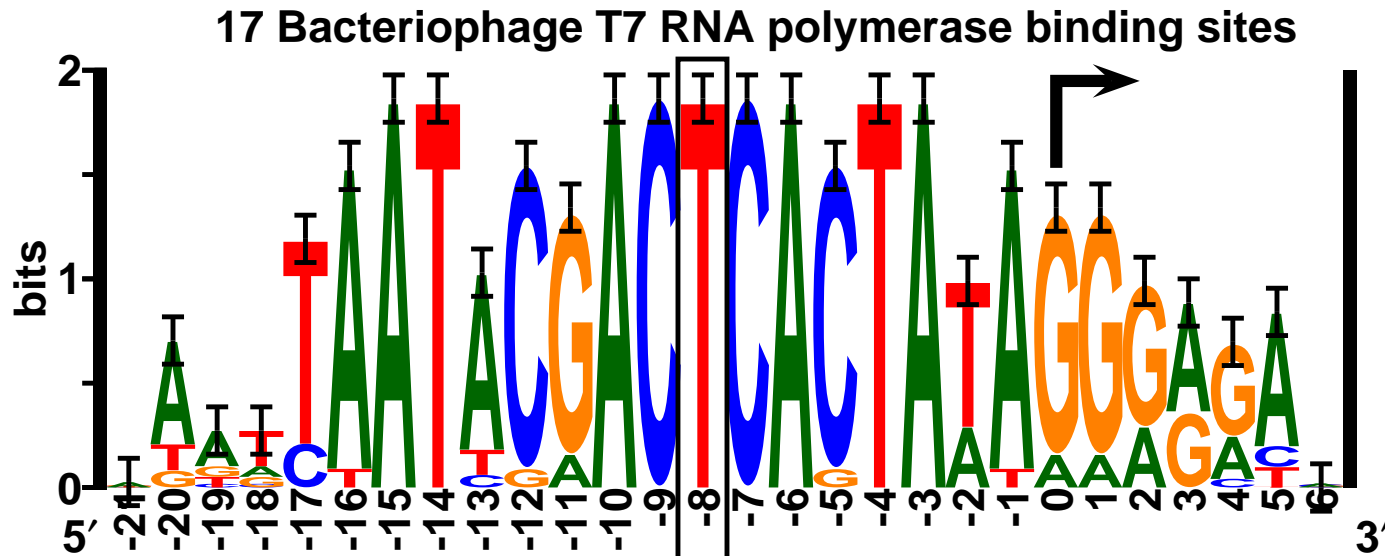
Schneider &  
Stephens  
*Nucl. Acids Res.*  
18: 6097-6100  
1990

```
1 ttattaatacaactcactataaggagag
2 aaatcaatacgaactcactatagaggac
3 cggttaatacgaactcactataggagaac
4 gaagtaatacgaactcagtatagggacaa
5 taattaattgaactcactaaaggggagac
6 cgcttaatacgaactcactaaagggagaca
```

6 of 17 sites



# Sequence Logo

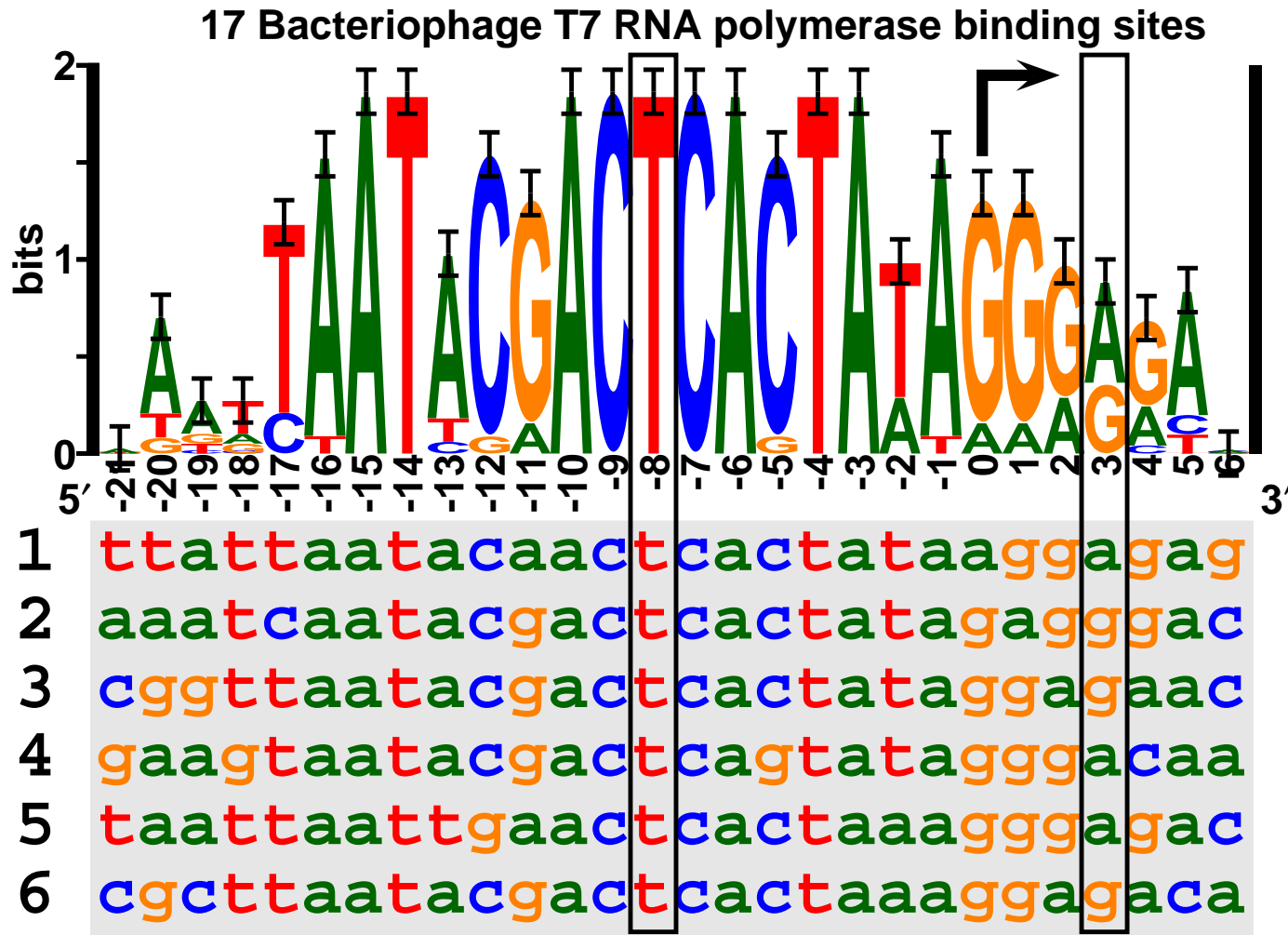


Schneider &  
Stephens  
*Nucl. Acids Res.*  
18: 6097-6100  
1990

1	t	t	a	t	a	a	t	a	c	a	a	c	t	c	a	c	t	a	t	a	a	g	g	a	g	a	g	
2	a	a	a	t	c	a	a	t	a	c	g	a	c	t	c	a	c	t	a	t	a	g	a	g	g	g	a	c
3	c	g	g	t	t	a	a	t	a	c	g	a	c	t	c	a	c	t	a	t	a	g	g	a	a	a	c	
4	g	a	a	g	t	a	a	t	a	c	g	a	c	t	c	a	g	t	a	t	a	g	g	g	a	c	a	
5	t	a	a	t	t	a	a	t	t	g	a	a	c	t	c	a	c	t	a	a	a	g	g	g	a	g	a	c
6	c	g	c	t	t	a	a	t	a	c	g	a	c	t	c	a	c	t	a	a	a	g	g	a	g	a	c	a

6 of 17 sites

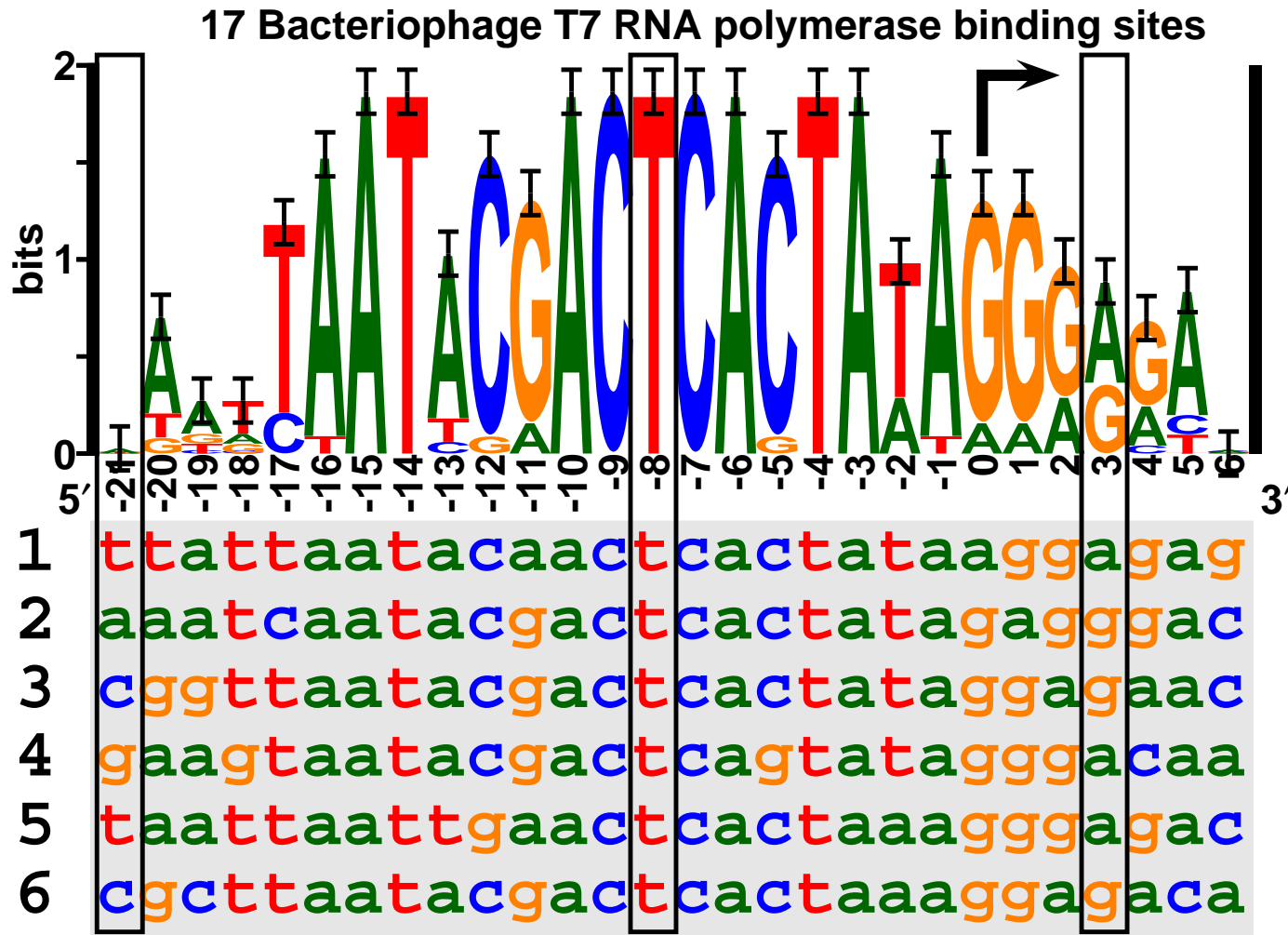
# Sequence Logo



Schneider &  
Stephens  
*Nucl. Acids Res.*  
18: 6097-6100  
1990

6 of 17 sites

# Sequence Logo



Schneider &  
Stephens  
*Nucl. Acids Res.*  
**18:** 6097-6100  
1990

6 of 17 sites

Example:

Example:

- EcoRI

Example:

- EcoRI

- 5' G↓AATTC 3'

Example:

- EcoRI
- 5' G↓AATTC 3'
- 6 bases: selecting 1 in 4.

## Example:

- EcoRI
- 5' G↓AATTC 3'
- 6 bases: selecting 1 in 4.
- Uncertainty **before** binding: 2 bits
- Uncertainty **after** binding: 0 bits
- Decrease in uncertainty: 2 bits



## Example:

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- 5' G↓AATTC 3'
- 6 bases: selecting 1 in 4.
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- Decrease in uncertainty: 2 bits
- $6 \times (2 - 0) = 12$  bits

## Example:

- EcoRI
- 5' G↓AATTC 3'
- 6 bases: selecting 1 in 4.
- Uncertainty **before** binding: 2 bits
- Uncertainty **after** binding: 0 bits
- Decrease in uncertainty: 2 bits
- $6 \times (2 - 0) = 12$  bits
- $12 \times 2 = 24$  dimensions

Example:

Example:

- 5' GTY↓RAC 3' HincIII

Example:

● 5' GTY↓RAC 3' HincIII

● 5' GT AC 3'

● GT AC :  $(2 - 0) \times 4 = 8$  bits

total = 8

Example:

- 5' GTY↓RAC 3' HincIII

- 5' GTY↓RAC 3'

- GT AC :  $(2 - 0) \times 4 = 8$  bits

- Y↓R :  $(2 - 1) \times 2 = 2$  bits

total = 8 + 2

Example:

- 5' GTY↓RAC 3' HincIII

- 5' GTY↓RAC 3'

- GT AC :  $(2 - 0) \times 4 = 8$  bits

- Y↓R :  $(2 - 1) \times 2 = 2$  bits

total = 8 + 2 = 10 bits

## Example:

- 5' GTY↓RAC 3' HincIII

- 5' GTY↓RAC 3'

- GT AC :  $(2 - 0) \times 4 = 8$  bits

- Y↓R :  $(2 - 1) \times 2 = 2$  bits

total = 8 + 2 = 10 bits

- 10 bits / 2 = 5 compressed bases



## Example:

- 5' GTY↓RAC 3' HincIII

- 5' GTY↓RAC 3'

- GT AC :  $(2 - 0) \times 4 = 8$  bits

- Y↓R :  $(2 - 1) \times 2 = 2$  bits

total = 8 + 2 = 10 bits

- 10 bits / 2 = 5 compressed bases

- 10 bits × 2 = 20 dimensions

Example:

Example:

- 5' VCW 3' RlaI

Example:

- 5' VCW 3' Rlal

- 5' C 3'

- C :  $2 - 0 = 2$  bits

total = 2

Example:

- 5' VCW 3' R|al

- 5' CW 3'

- C :  $2 - 0 = 2$  bits

- W = A/T :  $2 - 1 = 1$  bit

total = 2 + 1

Example:

- 5' VCW 3' R|al

- 5' V CW 3'

- C :  $2 - 0 = 2$  bits

W = A/T:  $2 - 1 = 1$  bit

V = A,C,G:

$2 - \log_2 3 \approx 0.42$  bits

total =  $2 + 1 + 0.42$

Example:

- 5' VCW 3' R|al

- 5' V CW 3'

- C :  $2 - 0 = 2$  bits

W = A/T:  $2 - 1 = 1$  bit

V = A,C,G:

$2 - \log_2 3 \approx 0.42$  bits

total =  $2 + 1 + 0.42 = 3.42$  bits

Example:

- 5' VCW 3' RlIaI

- 5' **V****C****W** 3'

- **C** :  $2 - 0 = 2$  bits

- **W** = A/T:  $2 - 1 = 1$  bit

- **V** = A,C,G:

$2 - \log_2 3 \approx 0.42$  bits

total =  $2 + 1 + 0.42 = 3.42$  bits

- $3.42$  bits / 2 = 1.71 compressed bases



Example:

- 5' VCW 3' RlIaI

- 5' **V****C****W** 3'

- **C** :  $2 - 0 = 2$  bits

- **W** = A/T:  $2 - 1 = 1$  bit

- **V** = A,C,G:

$2 - \log_2 3 \approx 0.42$  bits

total =  $2 + 1 + 0.42 = 3.42$  bits

- $3.42$  bits / 2 = 1.71 compressed bases

- $3.42$  bits  $\times 2 = 6.83$  dimensions

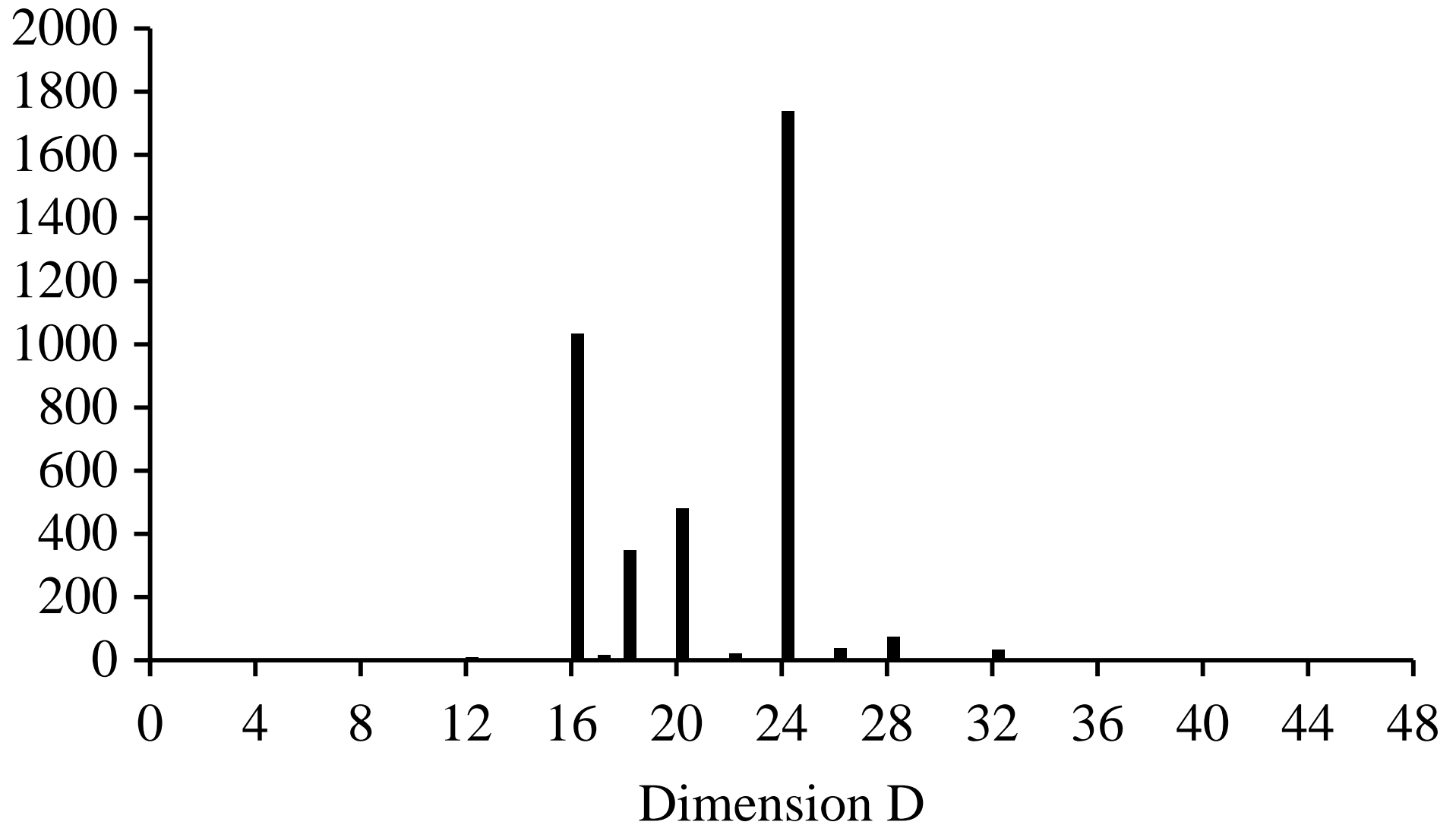
# Restriction Enzyme Coding Space Dimensionality

Example Restriction Enzyme	Sequence	Compressed Bases, $\lambda = R/2$	Bits $R$ (pins)	Dimension $D = 2R$	Number $N$
MspJI	CNNR(9/13)	1.50	3.00	6.00	1
⇒ RlaI	VCW	1.71	3.42	6.83	1
SgeI	CNNGNNNNNNNNN↓	2.00	4.00	8.00	5
AspBHI	YSCNS(8/12)	2.50	5.00	10.00	1
SgrTI	CCDS(10/14)	2.71	5.42	10.83	2
CviJI	RG↓CY	3.00	6.00	12.00	9
LpnPI	CCDG(10/14)	3.21	6.42	12.83	1
M.NgoMXV	GCCHR	3.71	7.42	14.83	1
TaqI	T↓CGA	4.00	8.00	16.00	1034
Bsp1286I	GDGCH↓C	4.42	8.83	17.66	15
Avall	G↓GWCC	4.50	9.00	18.00	346
Hin4I	(8/13)GAYNNNNNVTC(13/8)	4.71	9.42	18.83	1
⇒ HincII	GTY↓RAC	5.00	10.00	20.00	480
PpuMI	RG↓GWCCY	5.50	11.00	22.00	20
⇒ EcoRI	G↓AATTC	6.00	12.00	24.00	1738
PspXI	VC↓TCGAGB	6.42	12.83	25.66	1
RsrII	CG↓GWCCG	6.50	13.00	26.00	37
SgrAI	CR↓CCGGYG	7.00	14.00	28.00	73
KpnBI	CAAANNNNNNRTCA	7.50	15.00	30.00	2
SfiI	GGCCNNNN↓NGGCC	8.00	16.00	32.00	34

3802 restriction enzymes from Rich Roberts' Restriction Enzyme Database, REBASE

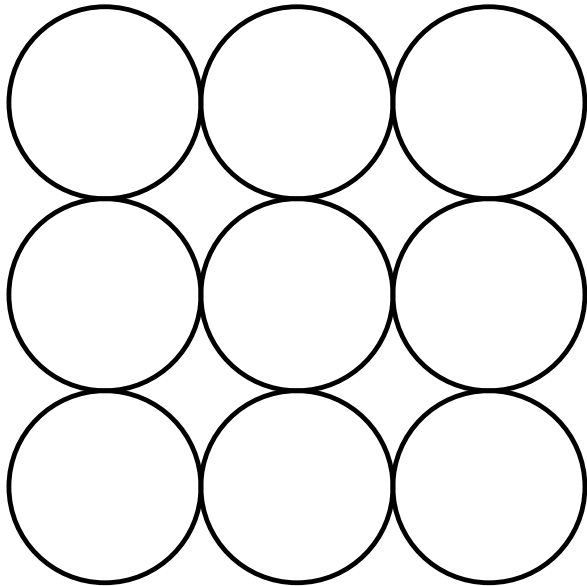
# Restriction Enzyme Dimensionalities

Number of Restriction Enzymes



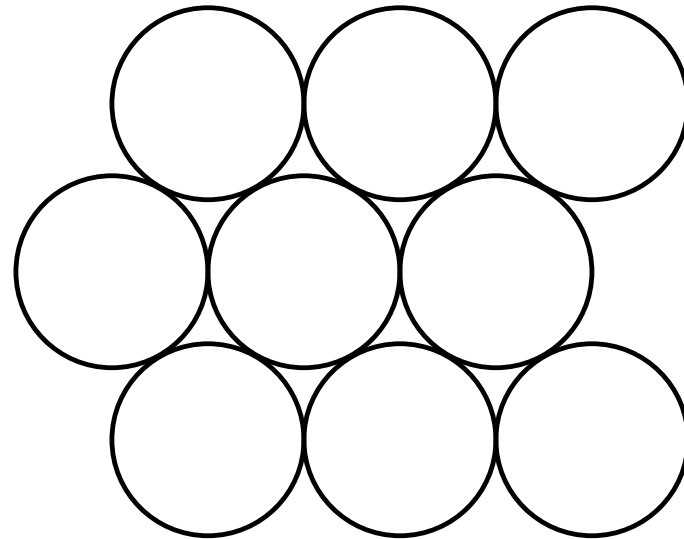
# Packing in 2 Dimensions

## Square Packing



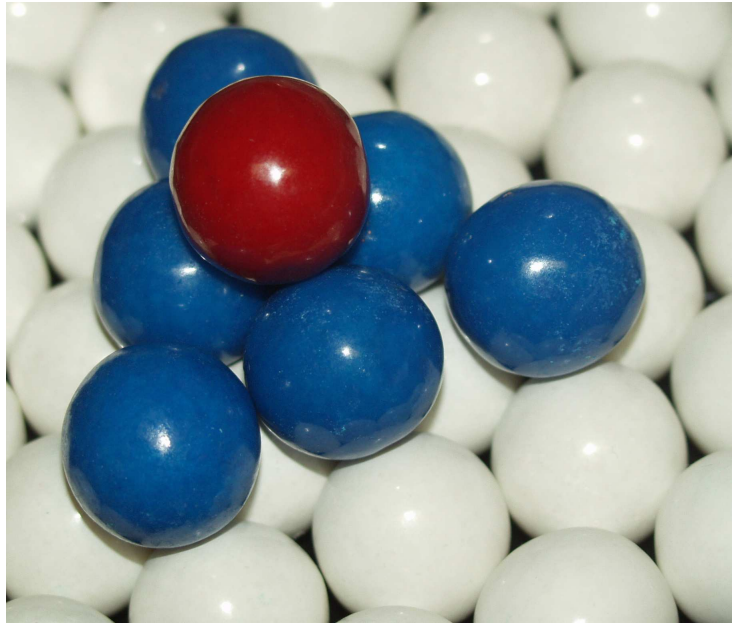
$\pi r^2 / (2 \times r)^2 = 79\%$   
of the plane filled

## Hexagonal Packing



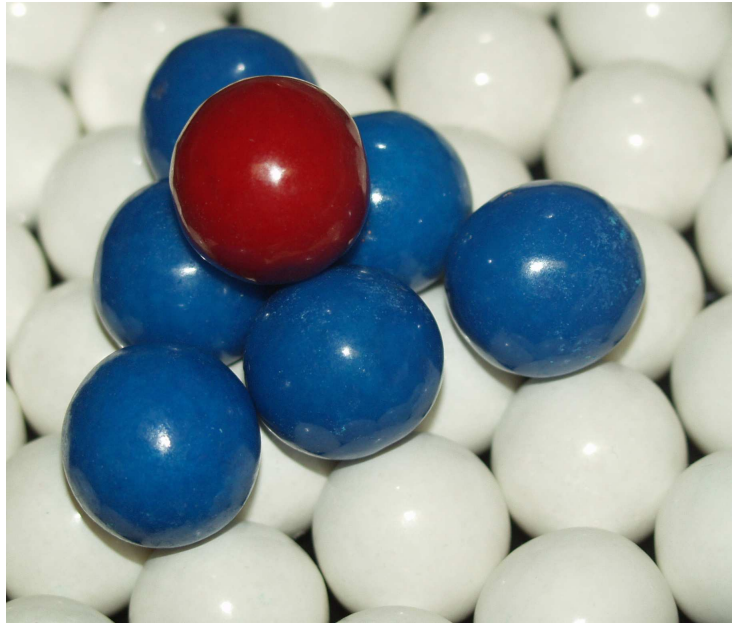
$\pi / \sqrt{12} = 91\%$   
of the plane filled

# Packing in 3 Dimensions



hexagonal sphere packing

# Packing in 3 Dimensions

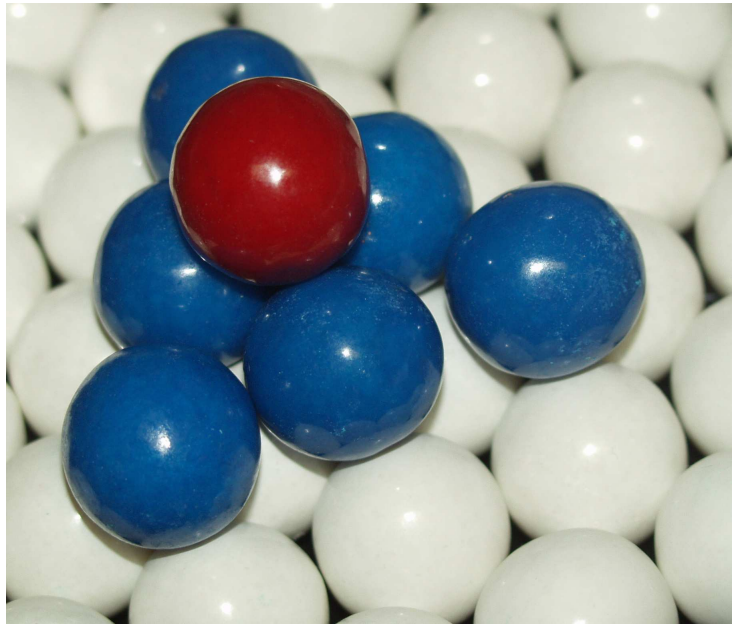


hexagonal sphere packing

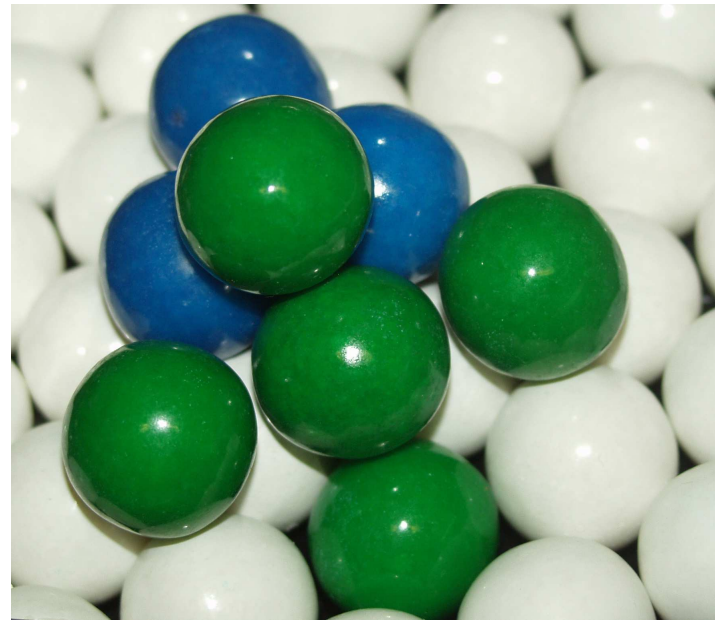


green balls reveal square packing

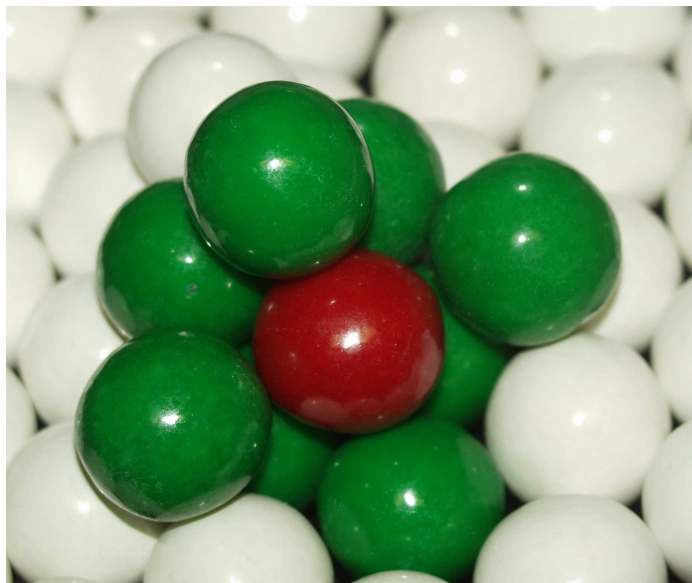
# Packing in 3 Dimensions



hexagonal sphere packing

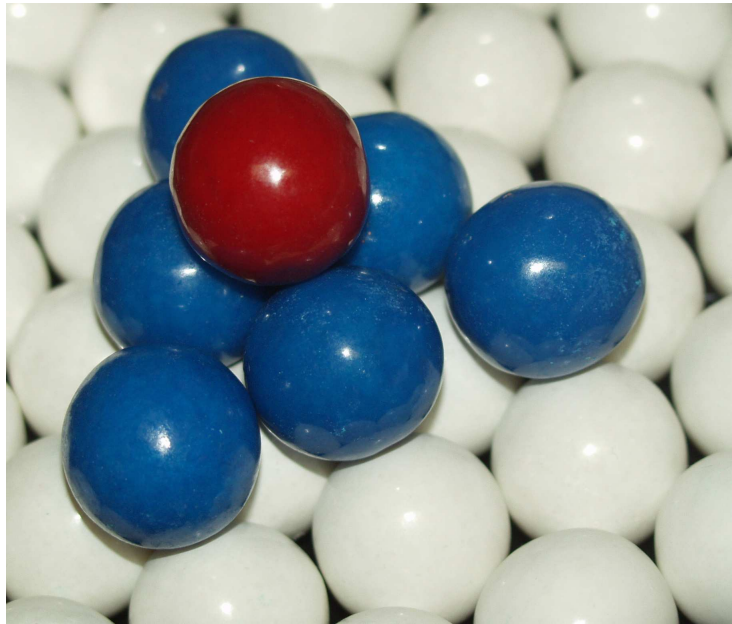


green balls reveal square packing



face centered cubic packing

# Packing in 3 Dimensions



hexagonal sphere packing



green balls reveal square packing



face centered cubic packing



more spheres show square packing



# Higher Dimensional Sphere Packing?



What happens  
in higher  
dimensions?

# Discovery of the Leech Lattice

Leech, John (1964), "Some sphere packings in higher space", Canadian Journal of Mathematics 16: 657-682

## SOME SPHERE PACKINGS IN HIGHER SPACE

JOHN LEECH

**Introduction.** This paper is concerned with the packing of equal spheres in Euclidean spaces  $[n]$  of  $n > 8$  dimensions. To be precise, a *packing* is a distribution of spheres any two of which have at most a point of contact in common. If the centres of the spheres form a lattice, the packing is said to be a *lattice packing*. The densest lattice packings are known for spaces of up to eight dimensions (1, 2), but not for any space of more than eight dimensions. Further, although non-lattice packings are known in [3] and [5] which have the same density as the densest lattice packings, none is known which has greater density than the densest lattice packings in any space of up to eight dimensions, neither, for any space of more than two dimensions, has it been shown that they do not exist.

In Part 1 the densest lattice packings in [4] and [8] are generalized to packings, not all lattice packings, in  $[2^m]$ , in which each sphere touches

$$(2 + 2)(2 + 2^2)(2 + 2^3) \dots (2 + 2^m)$$

others. This gives packings in [16] in which each sphere touches 4320 others, which may be the densest in this space. For  $m > 4$  the corresponding packings are unlikely to be the densest, though they seem to be the densest yet constructed.

In Part 2 some different analogies to the densest lattice packing in [8] are considered, which lead to new packings in [12] and [24]. In [12] this does not lead to any packing as dense as  $K_{12}$  (5), though it leads to new co-ordinates for some known packings. In [24] a dense lattice packing is found in which each sphere touches 98256 others. Other packings in up to 23 dimensions are found as sections of this packing in [24].

In Part 3 the densities of these packings are compared with Rogers' upper bound (10). This comparison is also made for the known densest lattice packings in up to eight dimensions for which it has not been made before. The numbers of spheres touched are compared with Coxeter's upper bound (4). For the packings in  $[2^m]$  the density and the number of spheres touched are of a much smaller order of magnitude than Rogers' and Coxeter's upper bounds as  $m \rightarrow \infty$ . The packings in up to 24 dimensions are closer to the upper bounds, though not so close as in from 3 to 8 dimensions, that in [8] being especially close.

Received June 26, 1963.

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Leech, John (1967), "Notes on sphere packings", Canadian Journal of Mathematics 19: 251-267

## NOTES ON SPHERE PACKINGS

JOHN LEECH

These notes are to supplement my paper (4), and should be read in conjunction with it. Both are divided into three parts, and in these notes the section numbers have a further digit added; thus §1.41 here supplements §1.4 of (4). References by section numbers are always to (4) or to the present notes, but references to other papers are numbered independently.

The principal results of these notes are the following. New sphere packings are given in  $[2^m]$ ,  $m \geq 6$ , and in [24], which are twice as dense as those of §§1.6, 2.3. Others are given in  $[2^m]$ ,  $m \geq 5$ , with the same density as those of §1.6, but in which each sphere touches fewer other spheres than in the earlier packings. Acknowledgment is made of lattice packings in  $[2^m]$  given by Barnes and Wall (2) in anticipation of §1.6 (in which the packings were lattice packings only for  $m \leq 6$ ). Denser packings than those of §2.4 are given for [11], as a section of  $K_{12}$ , and for [22] and [23], as sections of the new packing in [24]; that in [11] is due to Barnes (1). A proof is given that the packing in [16] (§1.2) is a section of those in [24] (§2.3 or §2.31). Table I supersedes those of (4), giving values of Rogers' bound for the density of packings, and Coxeter's bound for the number of spheres that may touch any one, for spaces of up to 24 dimensions, in comparison with the best figures achieved by known packings in these spaces.

### 1. Packings in $[2^m]$

**1.31.** This section and the next two are preliminary to the constructions of sphere packings in §§1.61-1.63 below. It was shown in §1.3 that any two rows of  $2^m$  binary digits having  $k$ -parity differ in at least  $2^k$  places. It follows that any row having exactly  $k$ -parity differs in at least  $2^k$  places from any row having  $(k+1)$ -parity. We now investigate whether there exist rows differing in more than  $2^k$  places from every row having  $(k+1)$ -parity.

For  $k=0$  there is clearly no such row, since every row either has 1-parity (simple even parity) or can be altered in any one place so as to give it 1-parity. There is also no such row for  $k=1$ . If a row does not have 1-parity, then it can be altered in one place to give it 2-parity; we reverse the digit whose position, when expressed as an integer in the binary scale, has 1's in just those positions whose significance corresponds to those binary constituent rows (§1.3) of the given row which do not have 1-parity. If a row has 1-parity, we can alter it in two places so as to give it 2-parity; one may be chosen arbitrarily, and the other is then uniquely determined as above for a row not having 1-parity.

Received June 30, 1965. Revised version received August 5, 1966.

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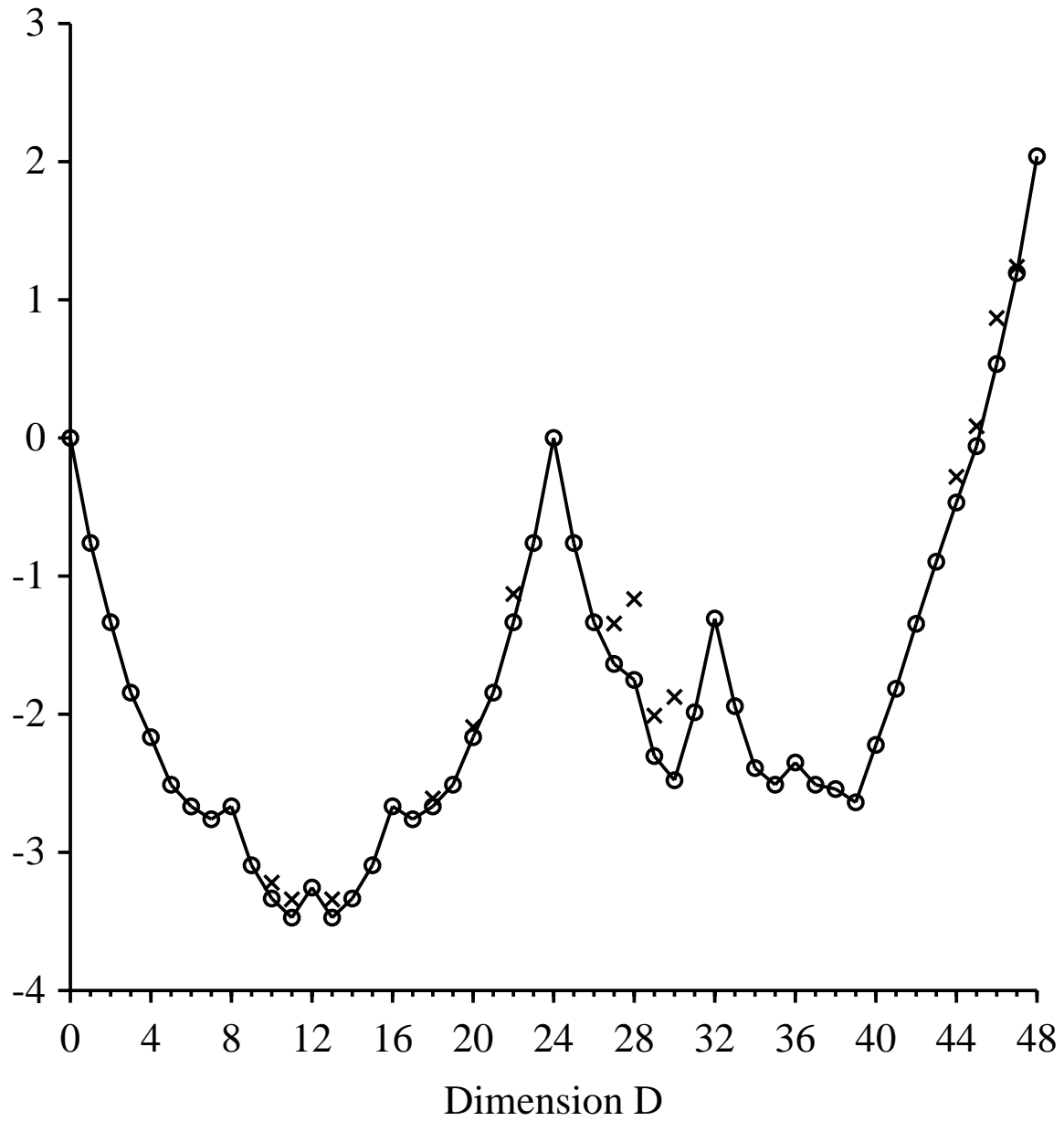
Received June 30, 1965. Revised version received August 5, 1966.

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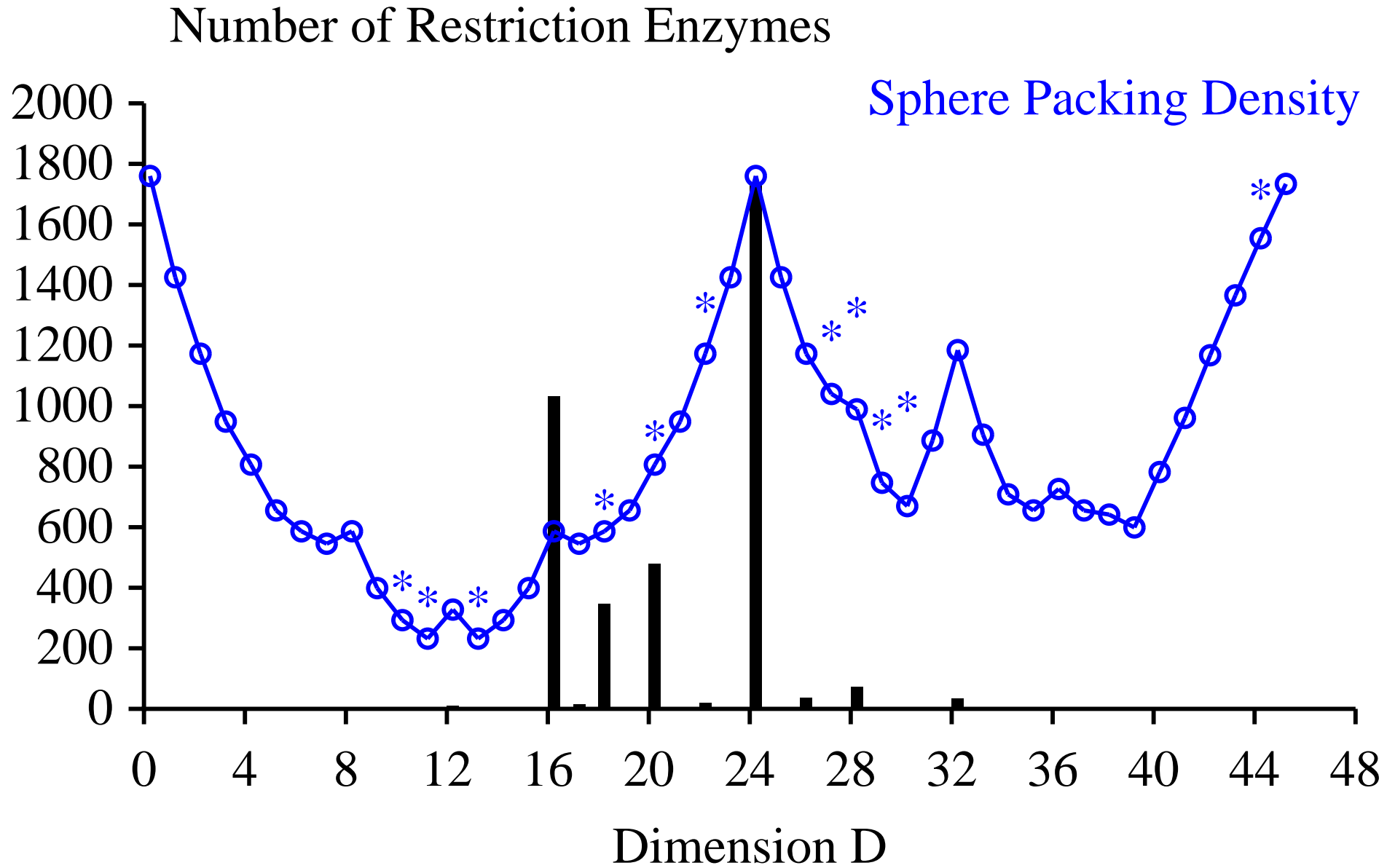
The Best Sphere Packing is in 24 dimensions!

# Best Sphere Packing

Rescaled Sphere Packing Center Density



# Restriction Enzyme Dimensions & Best Packing



# Leech Lattice Modem

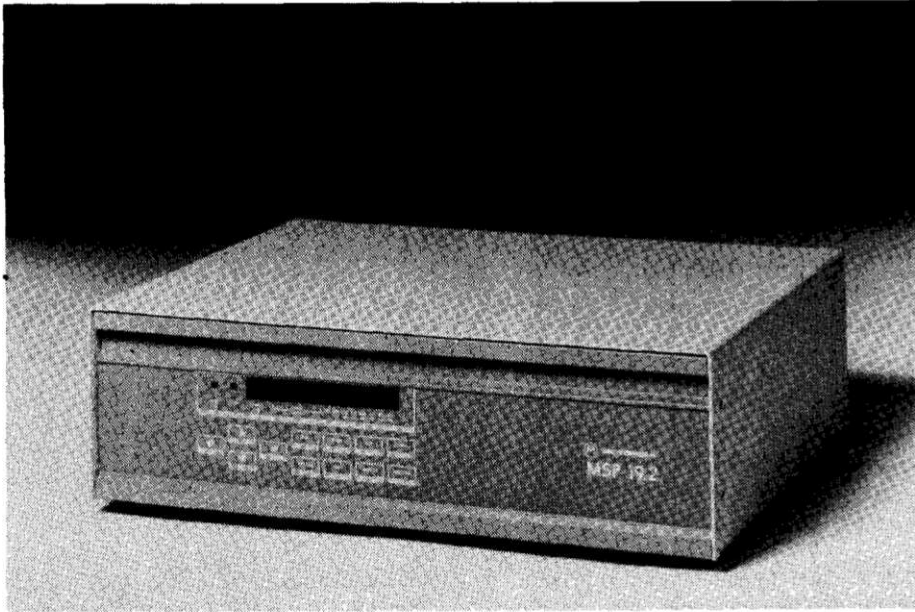


Fig. 1. A hardware prototype of the 19 200 bit/s Leech modem.

# Leech Lattice Modem

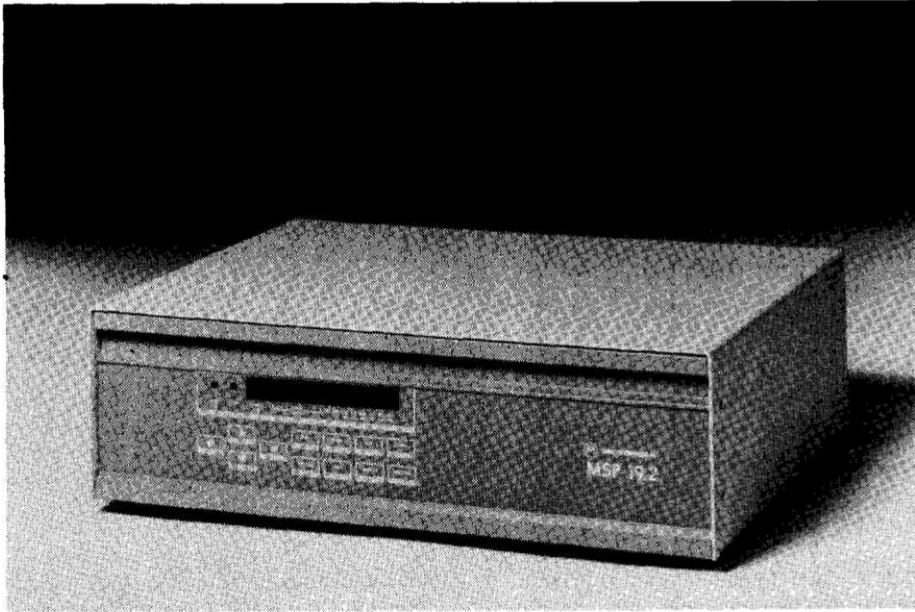


Fig. 1. A hardware prototype of the 19 200 bit/s Leech modem.

- Leech Lattice 19,200 bit/sec modem built by Motorola

# Leech Lattice Modem

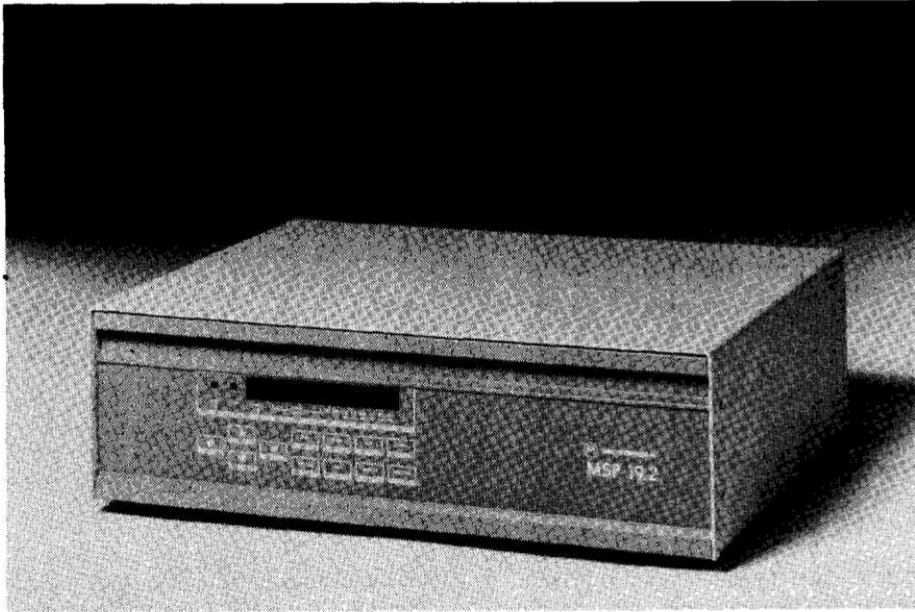
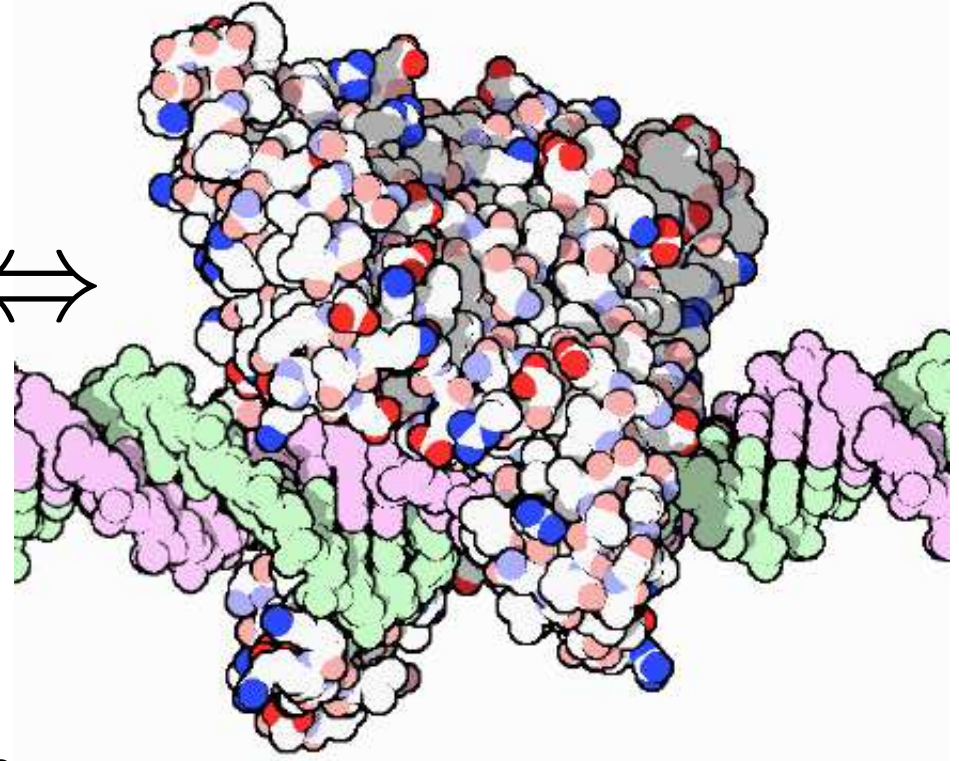
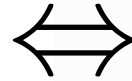


Fig. 1. A hardware prototype of the 19 200 bit/s Leech modem.



- Leech Lattice 19,200 bit/sec mode
- EcoRI decodes one of 4096 patterns probably using the Leech Lattice



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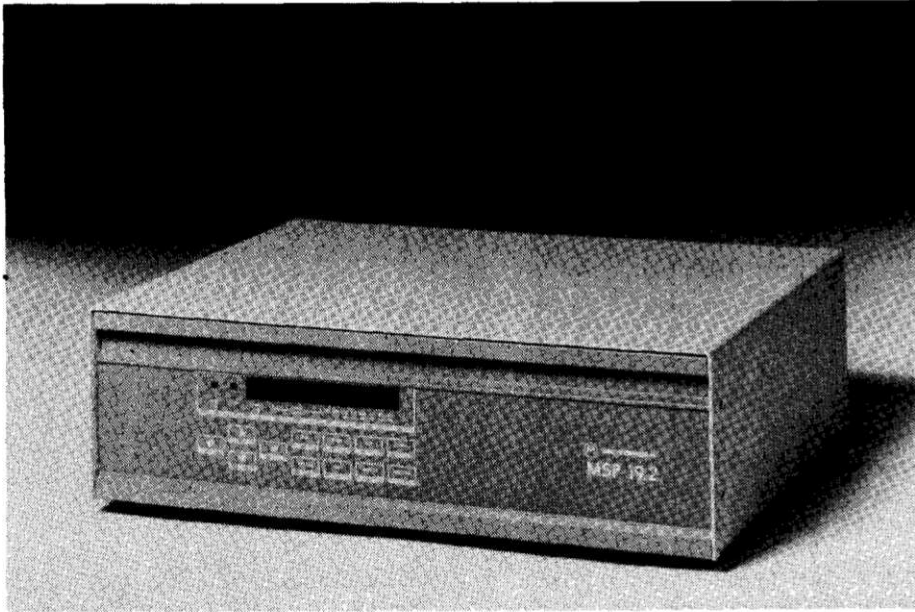
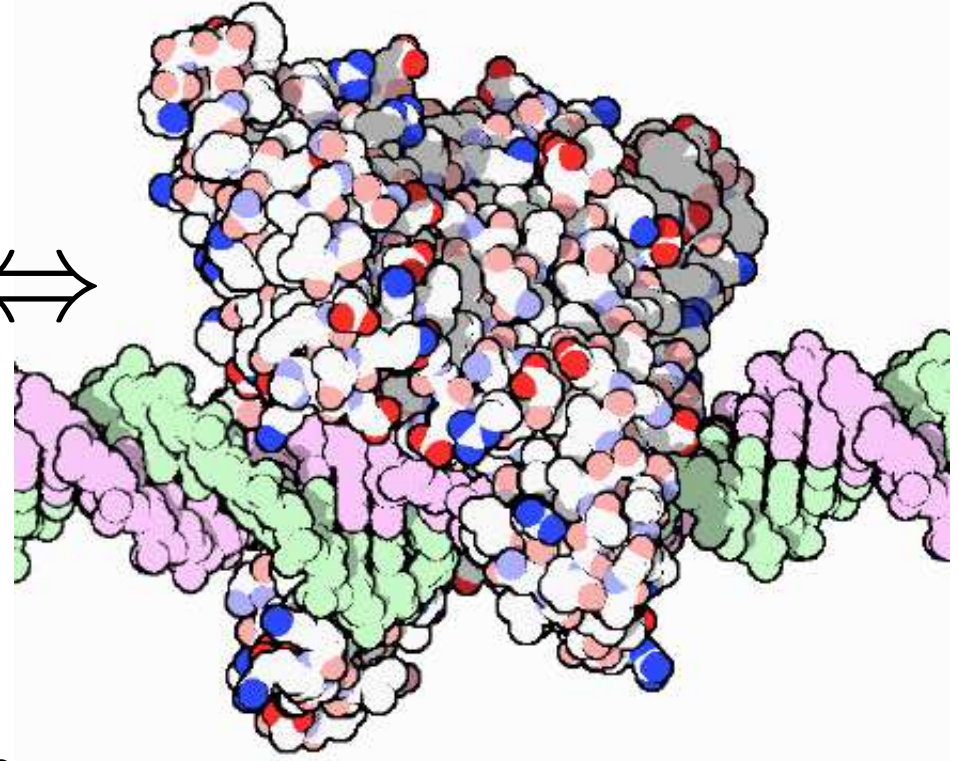
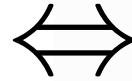
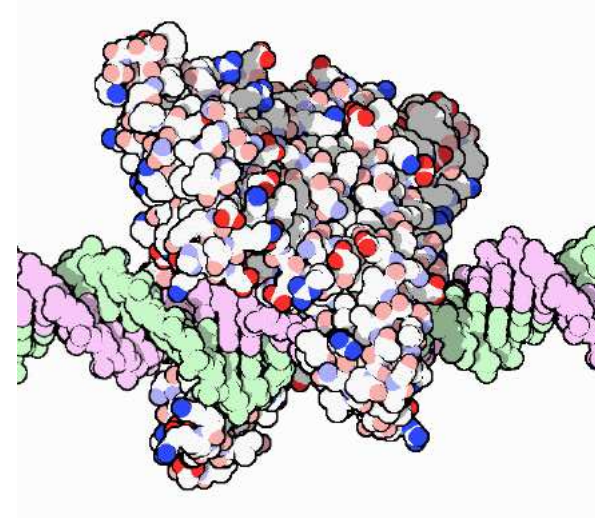
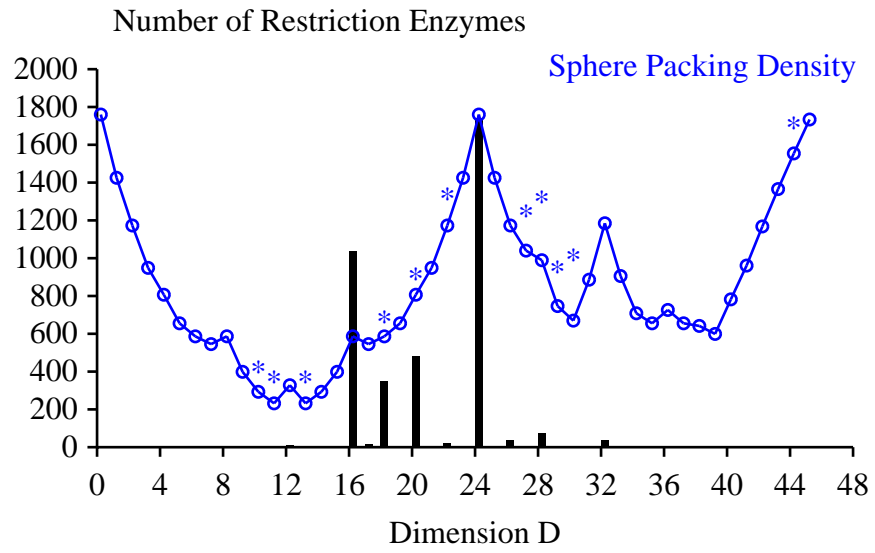


Fig. 1. A hardware prototype of the 19 200 bit/s Leech modem.

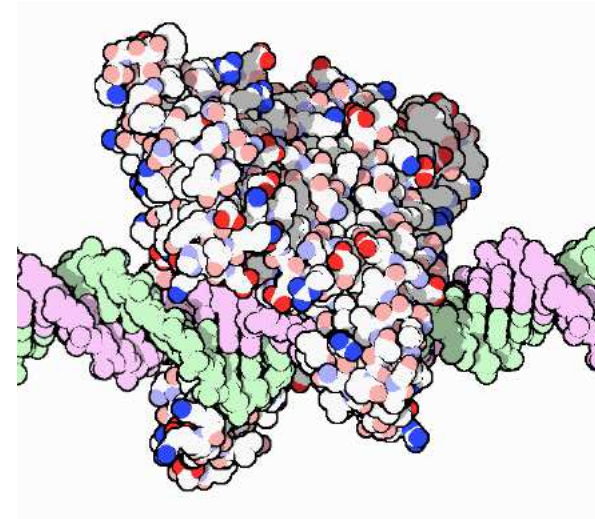
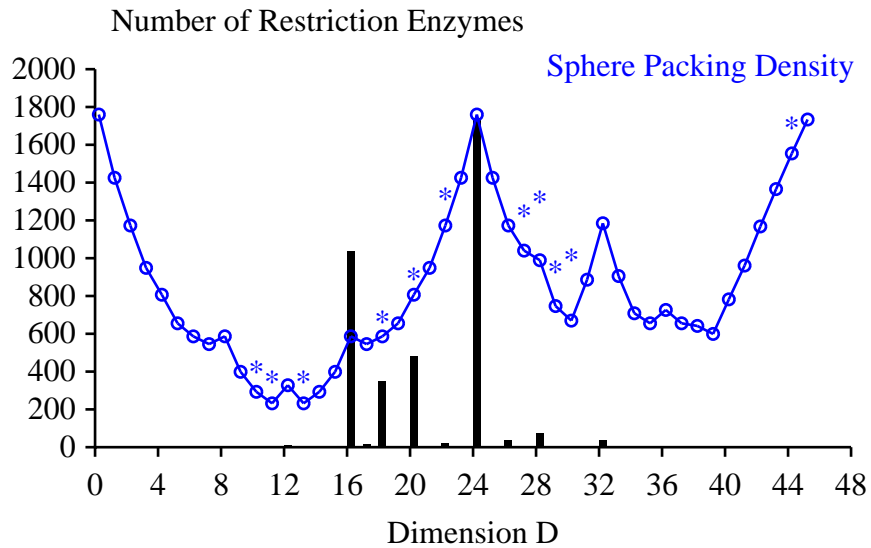


- Leech Lattice 19,200 bit/sec mode
- EcoRI decodes one of 4096 patterns probably using the Leech Lattice
- Single molecules could be used to build a modem, in theory.

# Conclusions

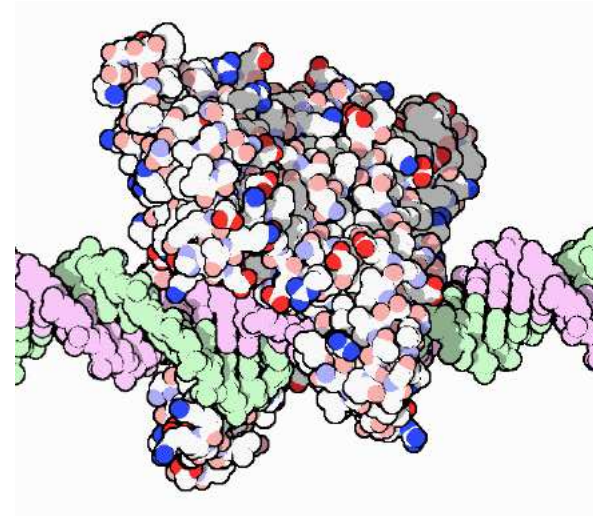
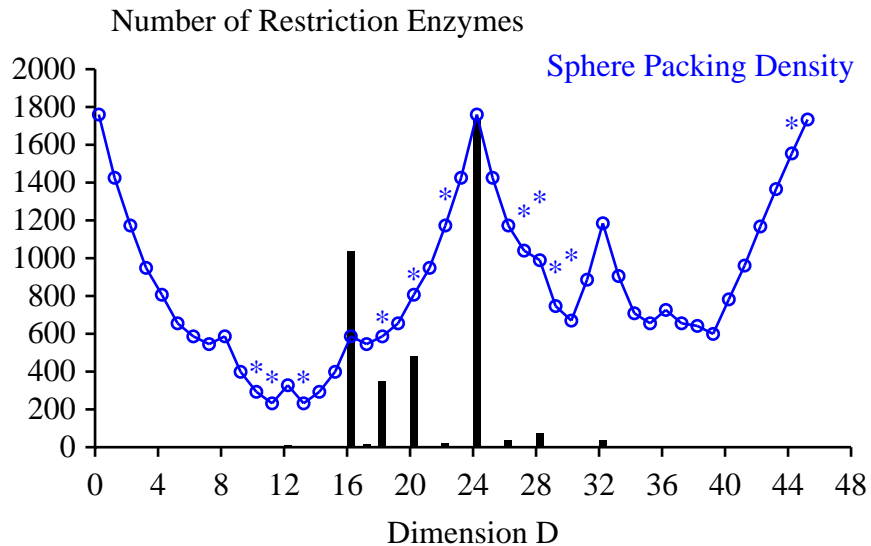


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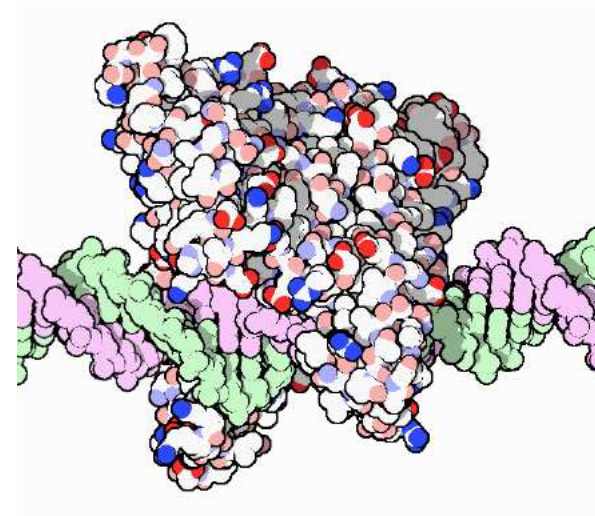
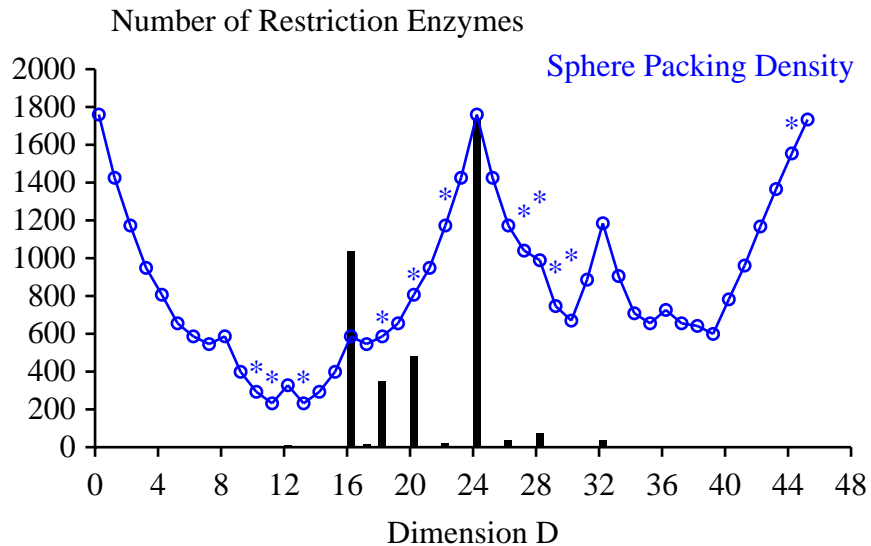
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- 4 base cutting restriction enzymes work in 16 dimensions
- Both have good lattice packings.

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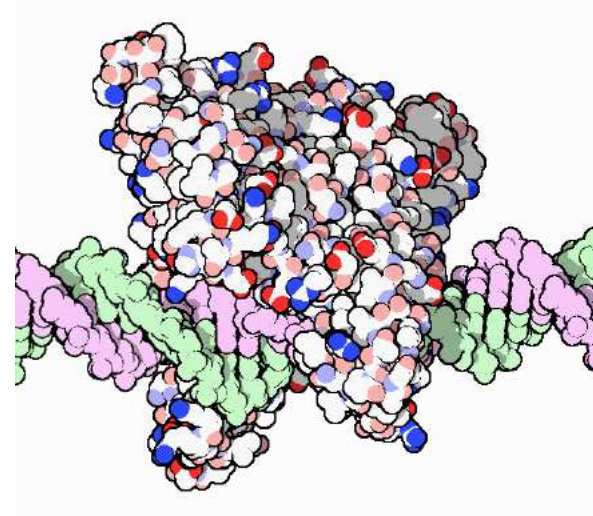
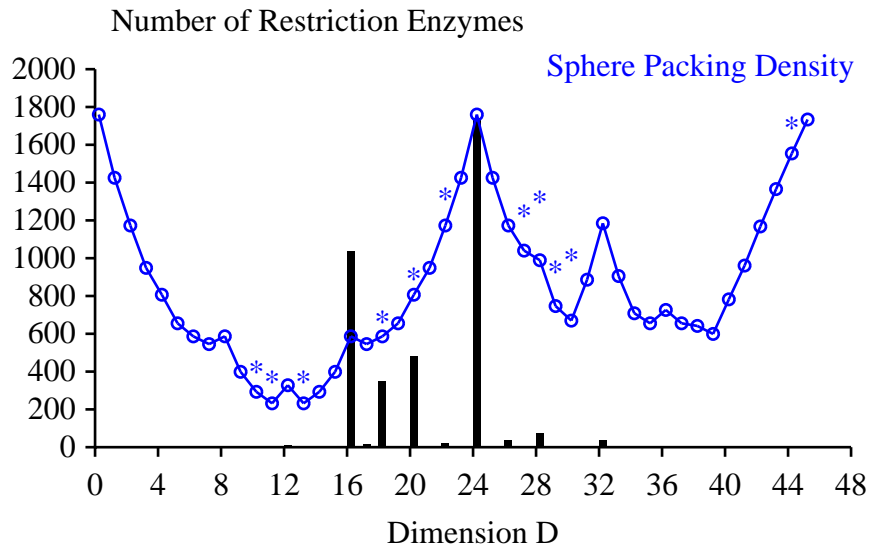
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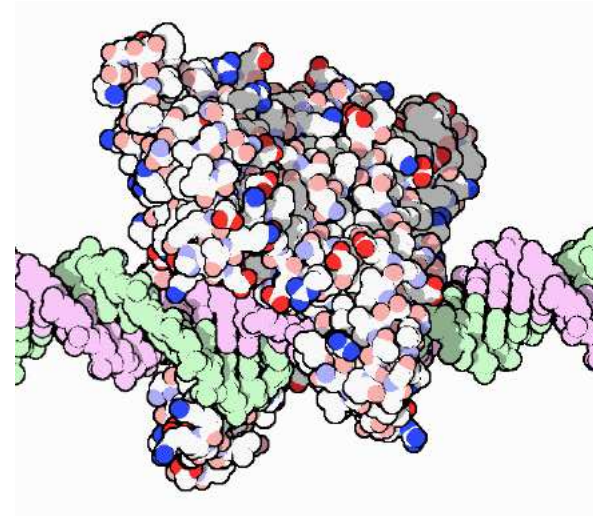
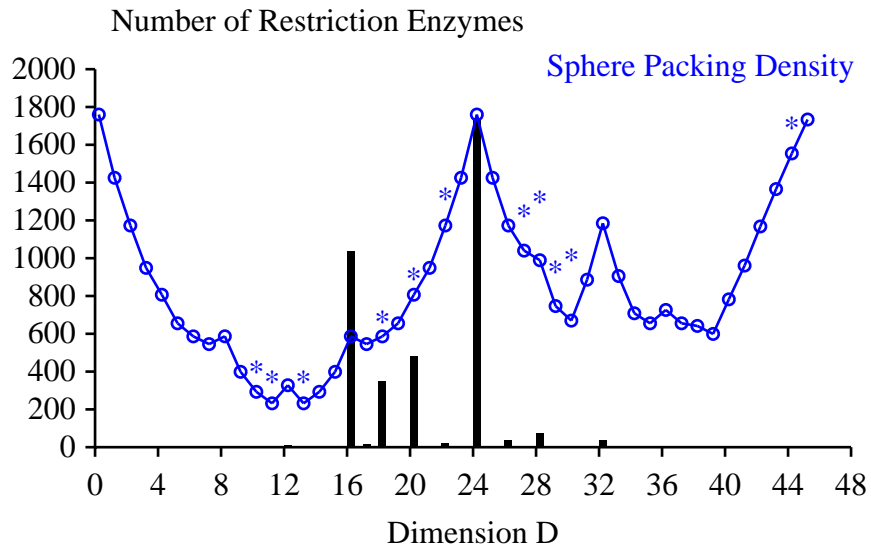
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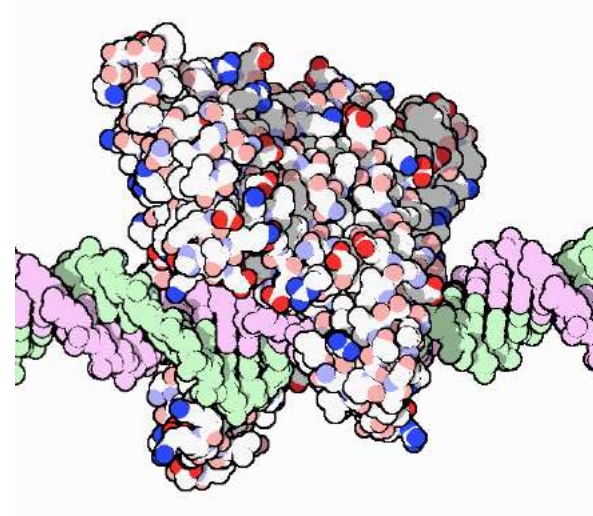
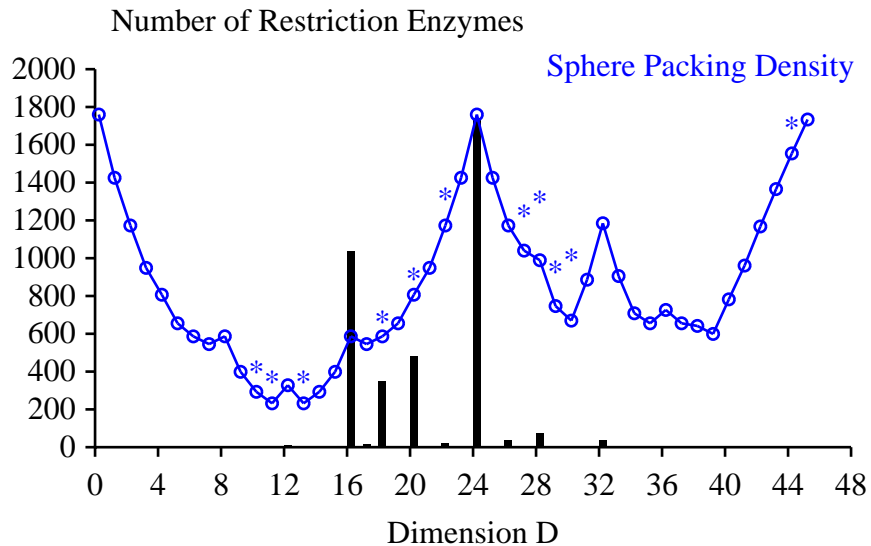
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- Restriction Enzymes probably use the 24 dimensional Leech Lattice
- Good packing can explain why restriction enzymes are so precise
- Dimensionality is a clue to mechanism
- Leech Lattice coding is used for modern communications
- Single molecules probably can be used to do communications!



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# Version

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