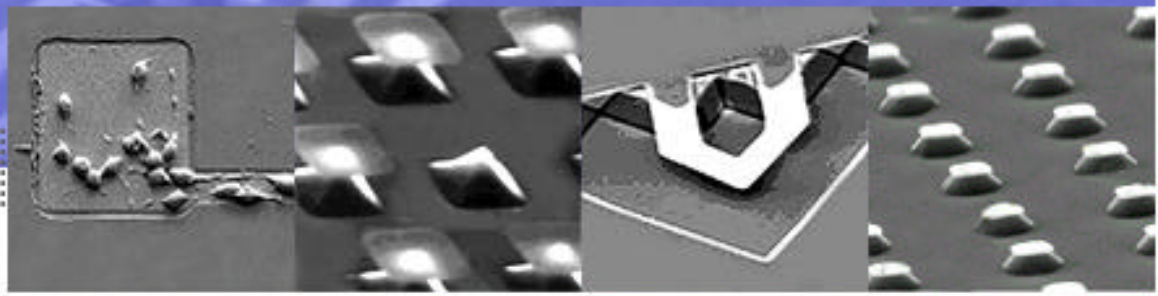
PURDUE UNIVERSITY

LIBNA

LIBNA is focused on research in BioMEMS & Bionanotechnology, in the areas of interface between micro, nanoengineering & life sciences



Introduction to BioMEMS & Bionanotechnology
Lecture 1

R. Bashir

Laboratory of Integrated Biomedical Micro/Nanotechnology and Applications (LIBNA), Discovery Park

School of Electrical and Computer Engineering,

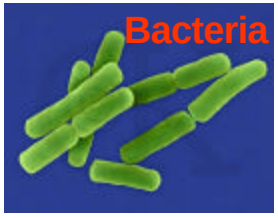
Weldon School of Biomedical Engineering,

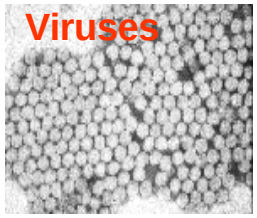
Purdue University, West Lafayette, Indiana

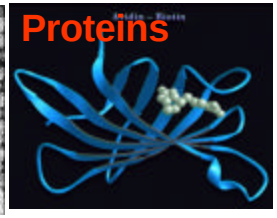
http://engineering.purdue.edu/LIBNA

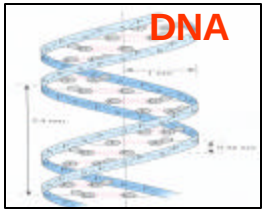
Key Topics

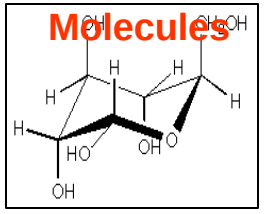
- **Biochips/Biosensors and Device Fabrication**
- **Cells, DNA, Proteins**
- **Micro-fluidics**
- **Biochip Sensors & Detection Methods**
- **Micro-arrays**
- **Lab-on-a-chip Devices**











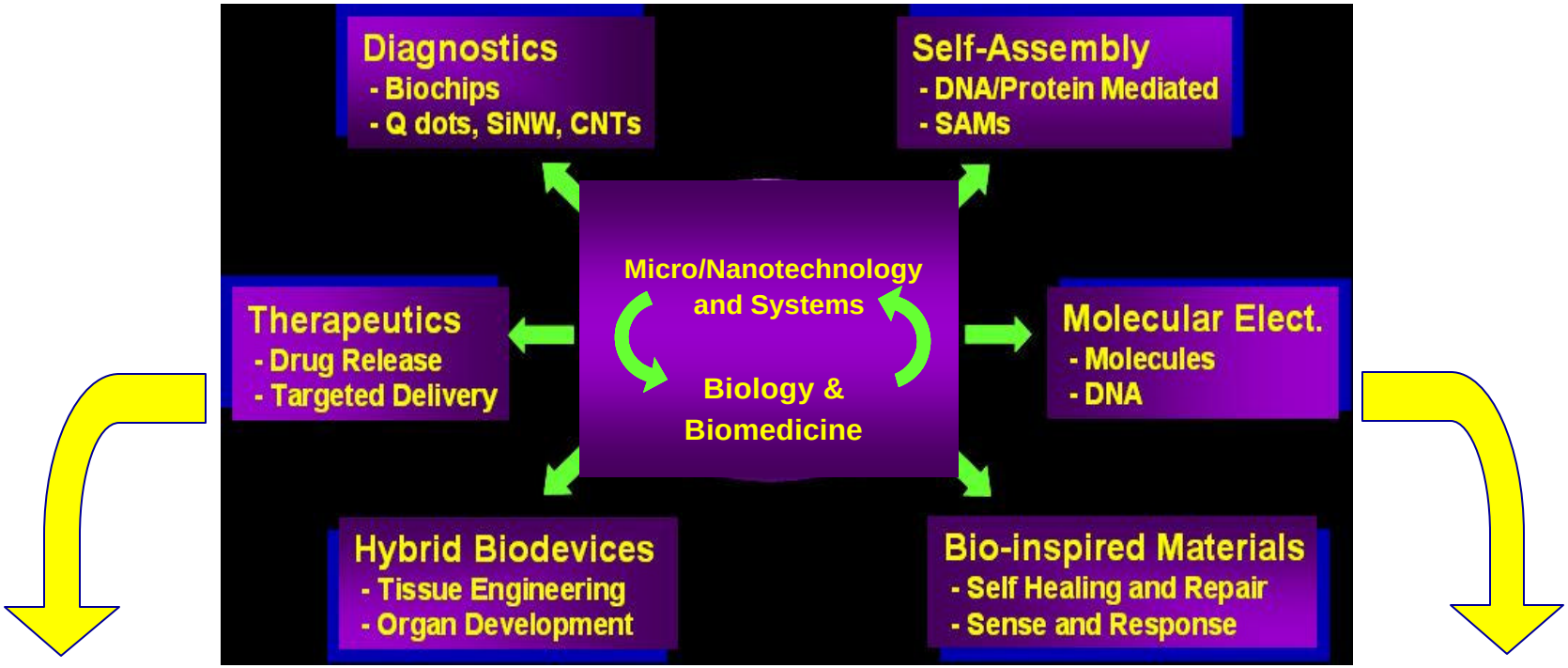
Definitions

- BioMEMS are biomedical or biological applications of MEMS (micro electro mechanical systems)

- BioNanotechnology is biological applications of nanotechnology (science and technology of miniaturization at scales of <100nm)

BioMEMS and Bionanotechnology

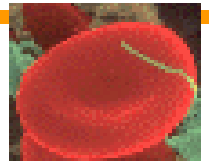
Apply micro/nano-technology to develop novel devices and systems that have a biomedical impact or are bio-inspired



Novel Solutions for Frontiers in Medicine and Biology

Novel Solutions for Frontiers in Materials and Information Processing

On Size and Scale !



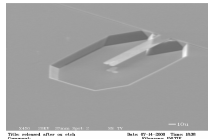
Top-down

100µm

Plant and Animal Cells

10µm

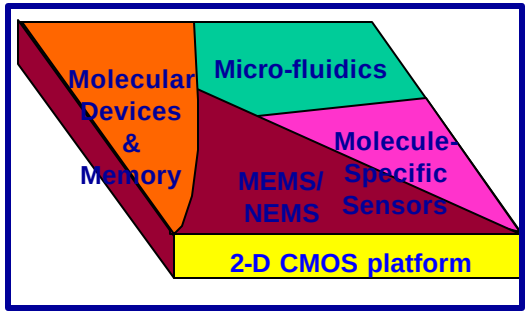
MEMS



Most Bacteria

1µm

MicroElectronics & MEMS

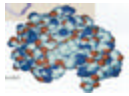


100nm

Virus

Min Feature of MOS-T (in 2004)

10nm

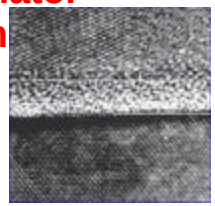


Proteins

One Helical Turn of DNA

1nm

Gate Insulator for 100nm MOS-T

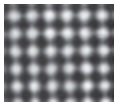


Nanoscale functional elements

Integrated BioChips (Macro, Micro, Nano)

0.1nm

Atoms



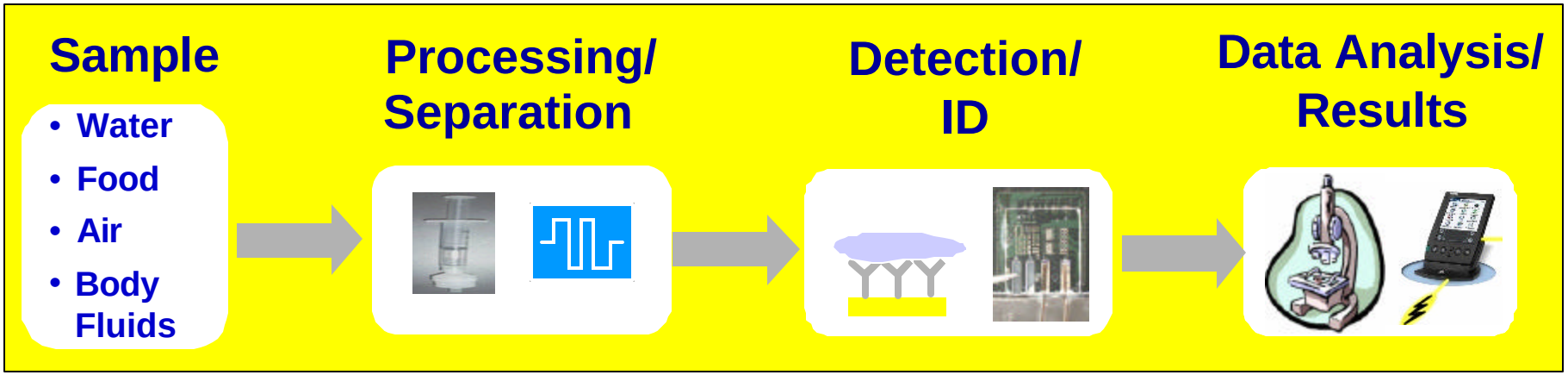
Bottoms-Up

More Definitions

- Biosensors are ‘analytical devices that combine a biologically sensitive element with a physical or chemical transducer to selectively and quantitatively detect the presence of specific compounds in a given external environment’ [Vo-Dinh and Cullum, 2000].

- Biochips can be defined as ‘*microelectronic-inspired* devices that are used for delivery, processing, analysis, or detection of biological molecules and species’ [Bashir, 2004]. These devices are used to detect cells, microorganisms, viruses, proteins, DNA and related nucleic acids, and small molecules of biochemical importance and interest.

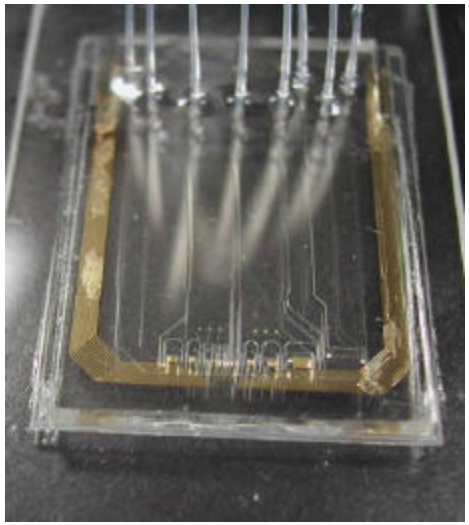
Overview of Biosensor System



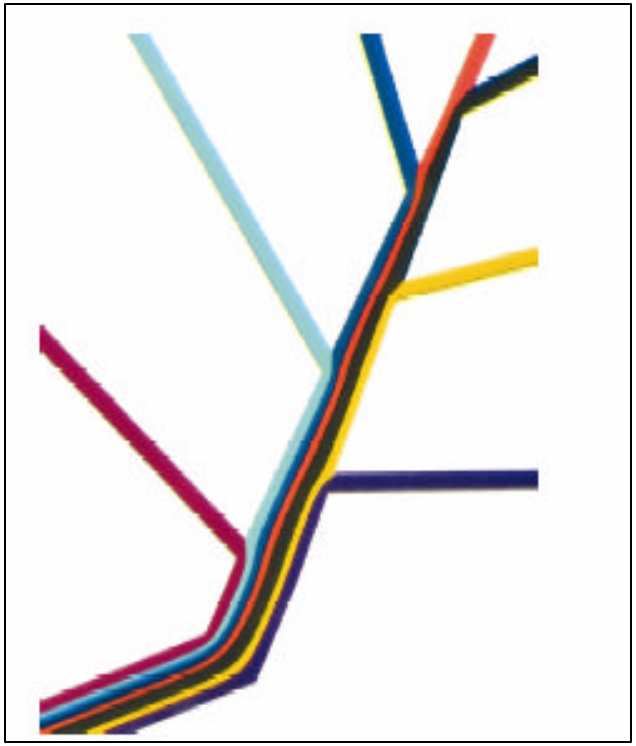
Introduction

Key Attributes of Biochips

1. Small length scale
2. Small thermal mass
3. Laminar flow, Re < 1
4. High surface-to-volume ratio



W.J. Chang, D. Akin, M. Sedlek, M. Ladisch, R. Bashir, *Biomedical Microdevices*, vol. 5, no. 4, pp. 281-290, 2003.



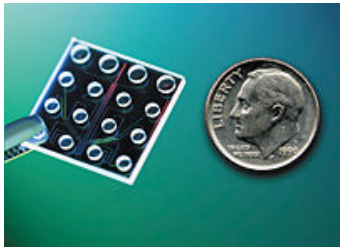
Whitesides Harvard University

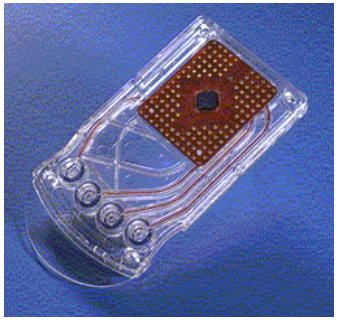
Reasons for Miniaturization

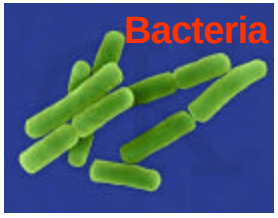
- In general, the use of micro and nano-scale detection technologies is justified by,
  - (i) reducing the sensor element to the scale of the target species and hence providing a higher sensitivity → single entity/molecule
  - (ii) reduced reagent volumes and associated costs,
  - (iii) reduced time to result due to small volumes resulting in higher effective concentrations,
  - (iv) amenability of portability and miniaturization of the entire system
  - (v) point-of-care diagnostic,
  - (vi) Multi-agent detection capability
  - (vii) Potential for use *in vitro* as well as *in vivo*

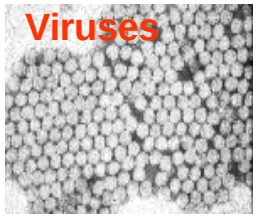
Biochips for Detection

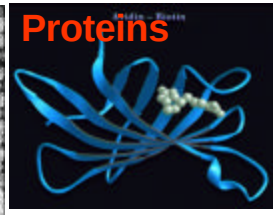
- Applications
  - Medicine
  - Pharmaceuticals
  - Food Safety
  - Homeland Security, etc.
- Integrated, Sensitive, Rapid, Cost x Performance
- Commercialized; Nanogen, Affymetrix, Caliper, Others….

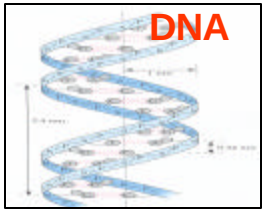


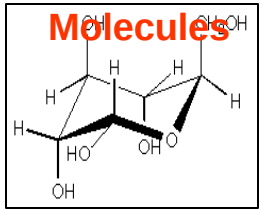






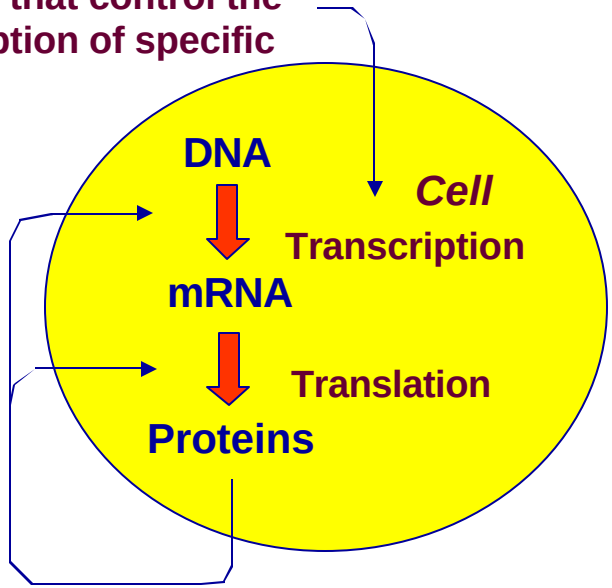


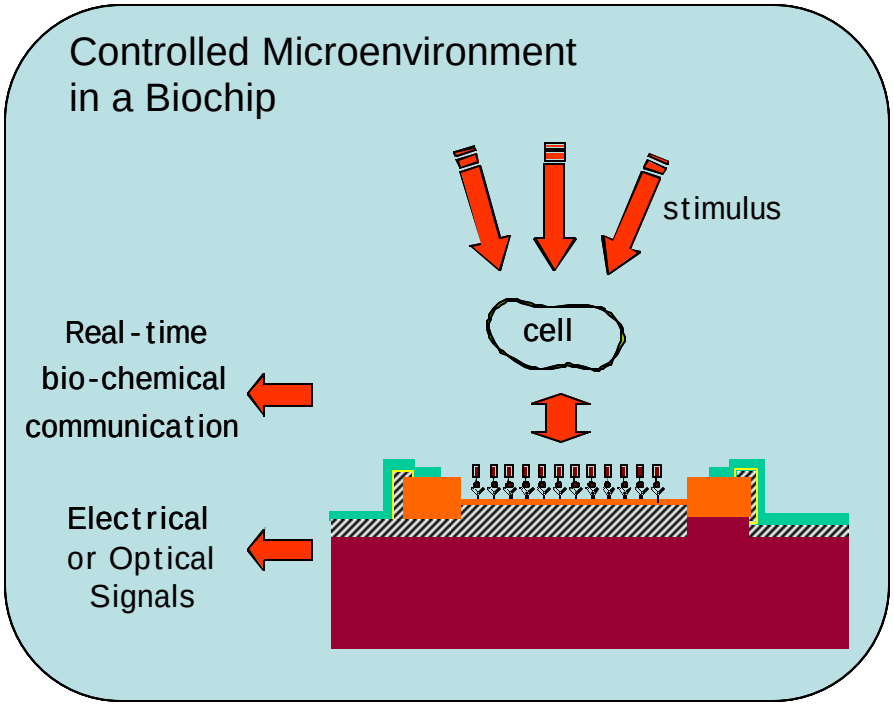




Novel Tools for NanoBiology

Transcription factors:
Proteins that control the transcription of specific genes





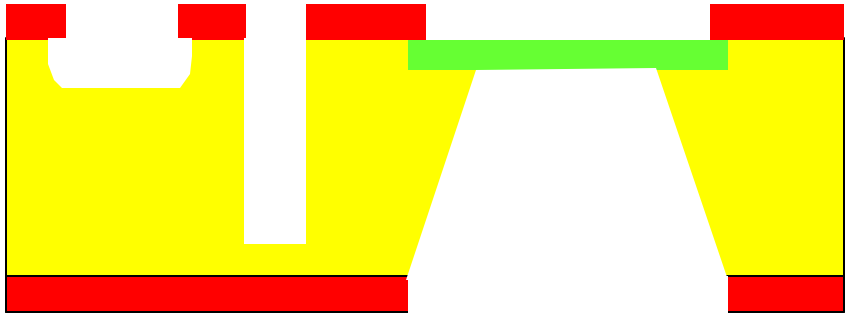
- **Analysis of single cells and the study of their function in real time.**
- **Increase understanding of signaling pathways inside the cell.**
- **Basic cell functions such as differentiation, reproduction, apoptosis, etc. and their implications on various disease states.**
- **Focus of the post-genomic era and systems biology**

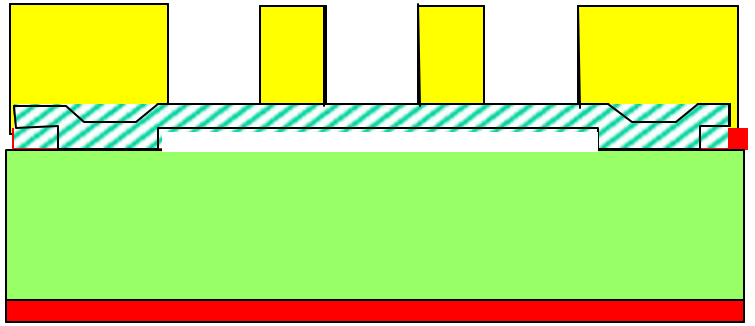
BioChip/BioMEMS Materials

- Silicon and microelectronic materials
- Glass, Quartz
- Polymers
  - Poly (dimethylsiloxane) (PDMS)
  - Poly (methyl methacrylate) (PMMA)
  - Teflon, etc.
- Biological Entities
  - Cells, Proteins, DNA
  - Frontier of BioMEMS !

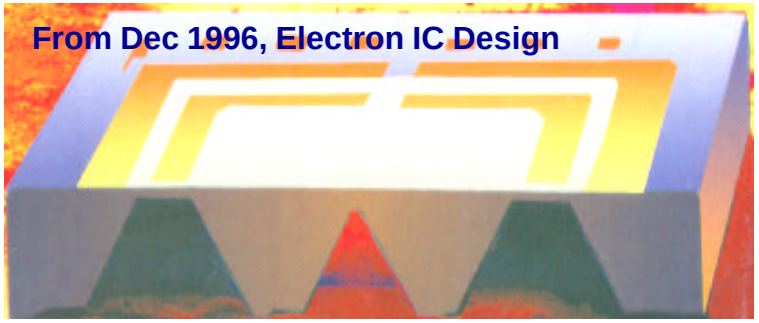
Introduction to Device Fabrication

- MEMS/NEMS Silicon Fabrication
  - Formation of structures that could be used to form sensors and actuators.
  - Processing of electrical or non-electrical signals.
  - Conventional and new semiconductor processing technology modules are used.
  - Etching, Deposition, Photolithography, Oxidation, Epitaxy, etc.
  - Deep RIE, Thick Plating, etc
- Bulk and Surface Micromachining

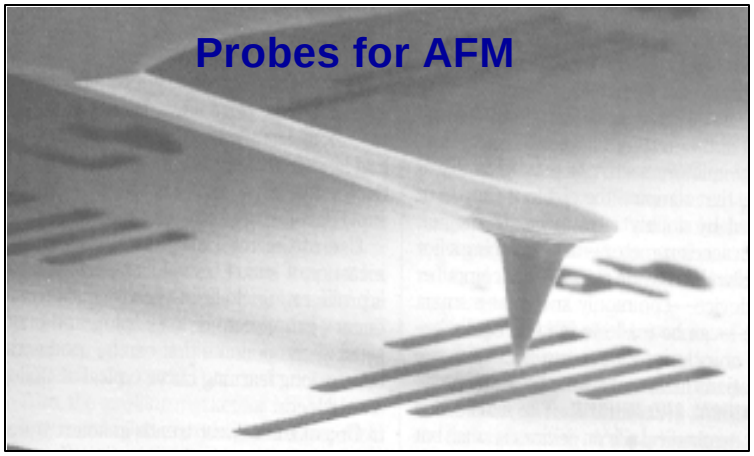




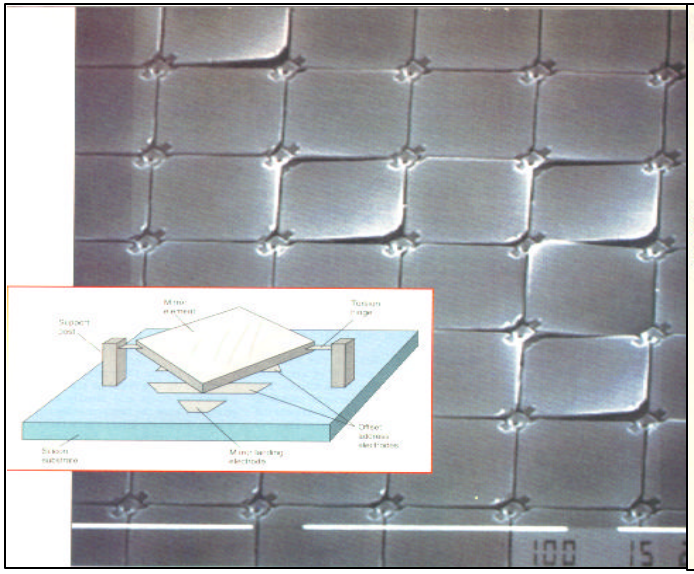
MEMS Examples

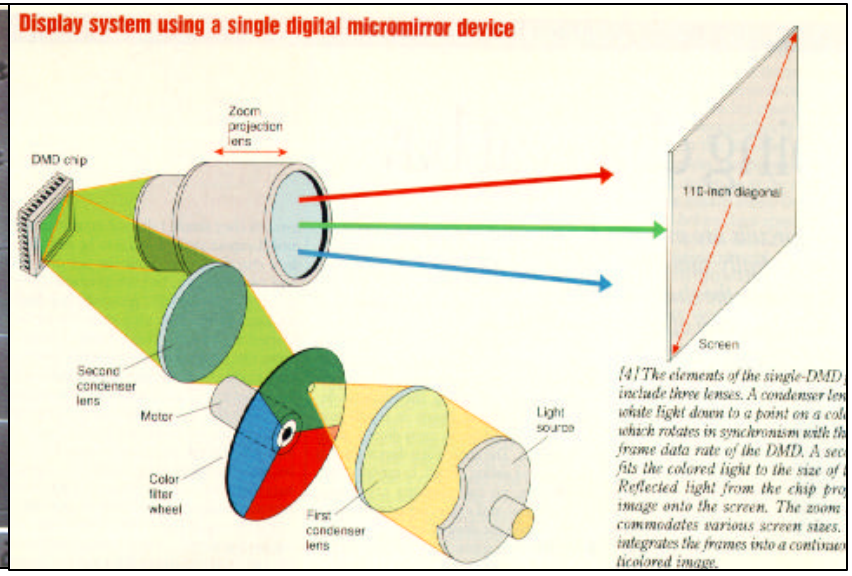


Bulk Micromachined Accelerometer from Silicon Microstructures. Inc.



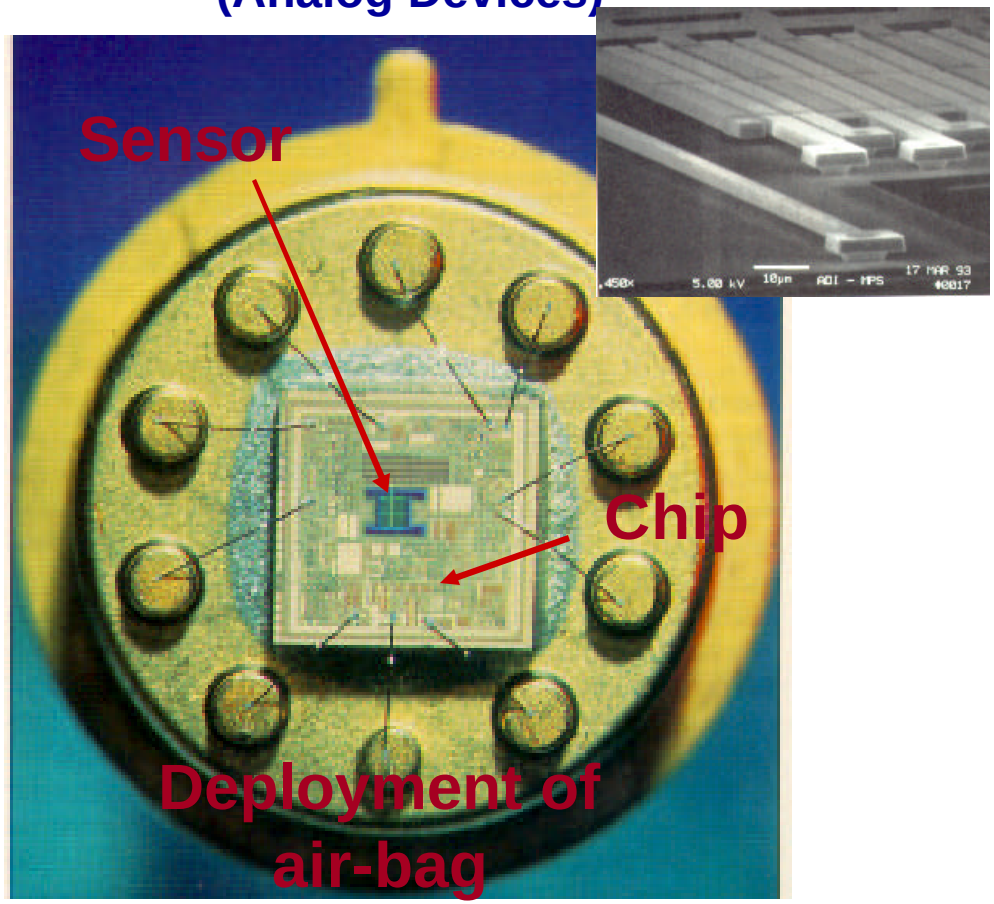
DMD Chip from Texas Instruments



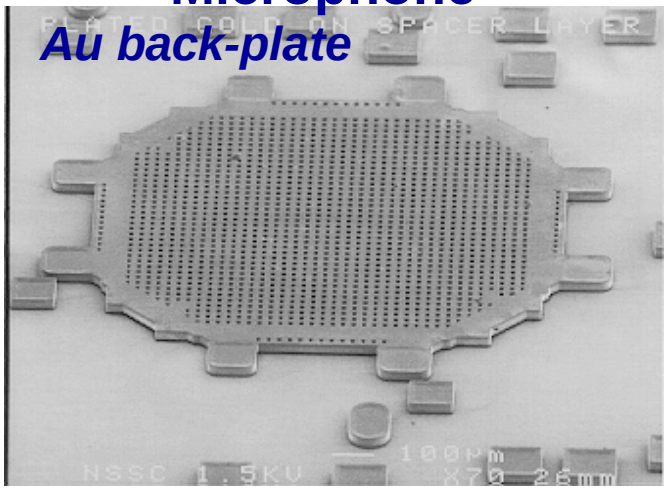


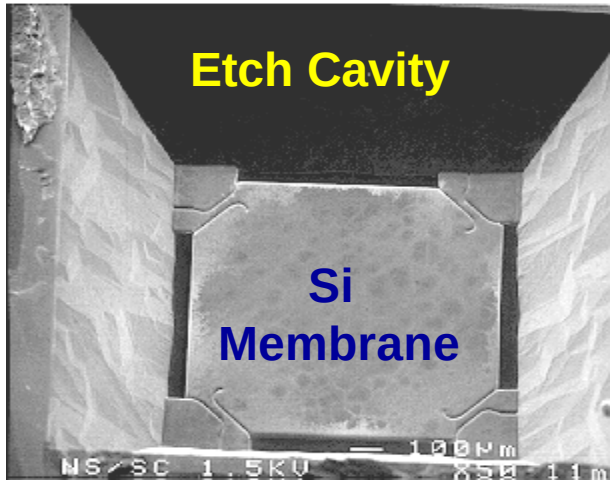
MEMS Examples

Single Chip Accelerometer (Analog Devices)



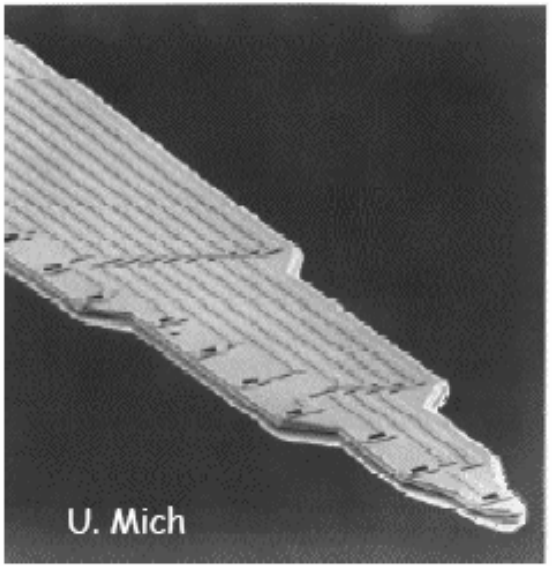
Single Chip Microphone

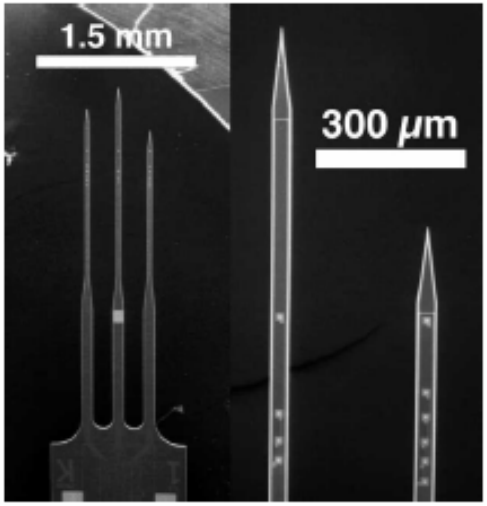




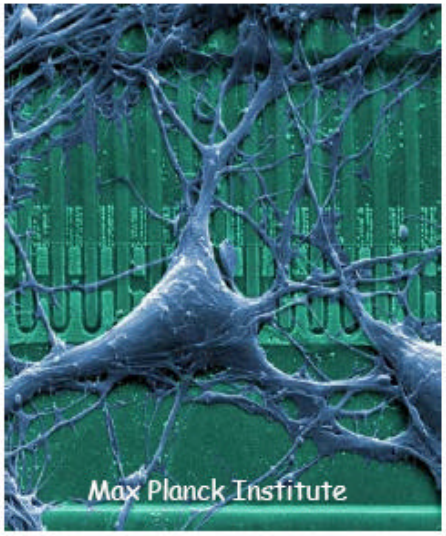
Draper Labs,
National Semiconductor, 1998

Silicon BioMEMS Examples

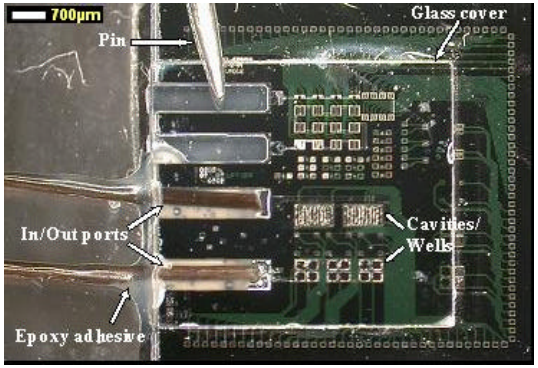




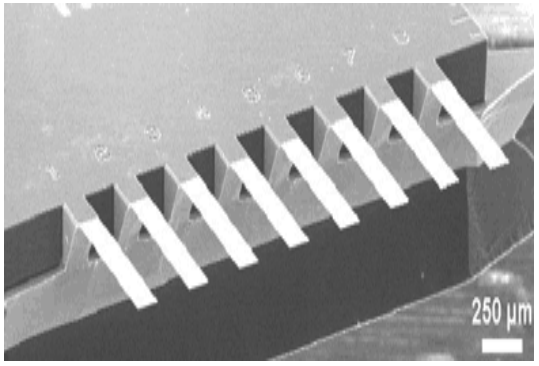
Stanford Neuro Probe



Kumetrix



Purdue Silicon BioChip

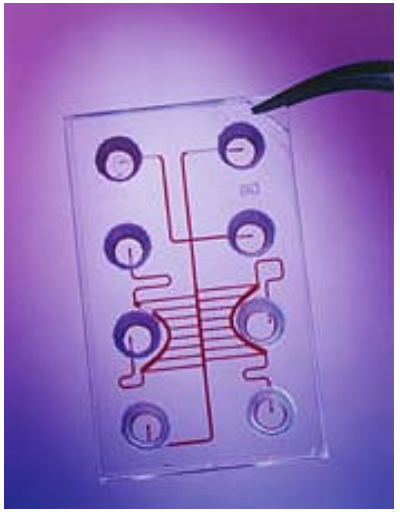


IBM Zurich Research

BioMEMS/Biochip Fabrication

- In addition to Silicon….
- Biocompatibility, ideal for biomedical devices
- Transparent within the visible spectrum
- Rapid fabrication
- Photo-definable
- Chemically modifiable
- Possible choices
  - PDMS - polydimethylsiloxane,
  - Hydrogels – PMAA,
  - Teflon
  - SU-8, etc.

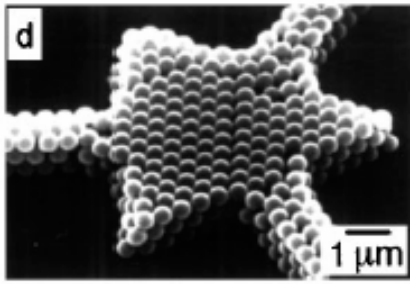
Immunochip (Aclara)

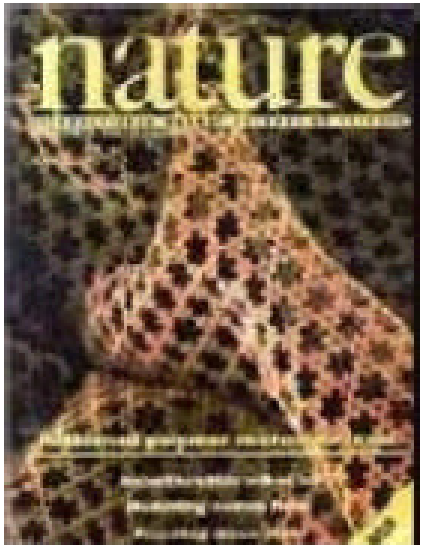


Lab on Chip (Caliper)

Alternative Fabrication Methods

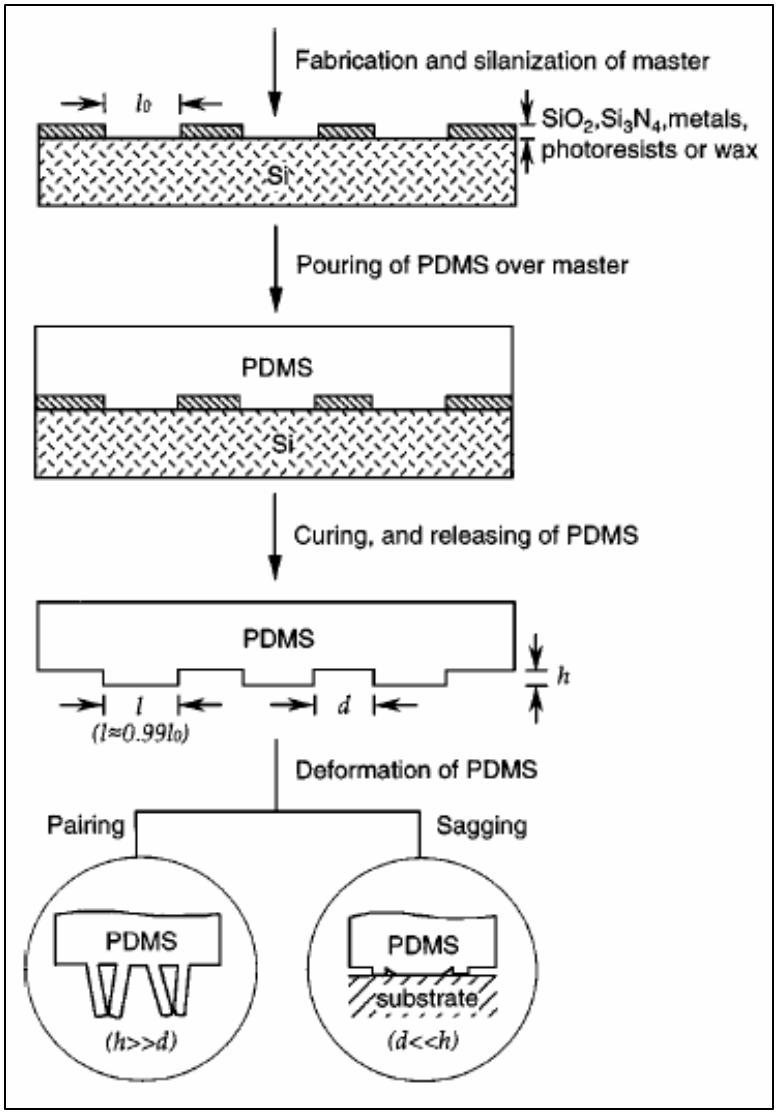
- Soft Lithography
  - Replication and molding
  - Micro-contact printing
  - Micro-molding in capillaries
  - Micro-transfer molding
  - Solvent assisted micro-molding
  - Dip Pen Lithography
- Compression Molding
  - Hot Embossing
  - Injection Molding
- Inkjet Printing





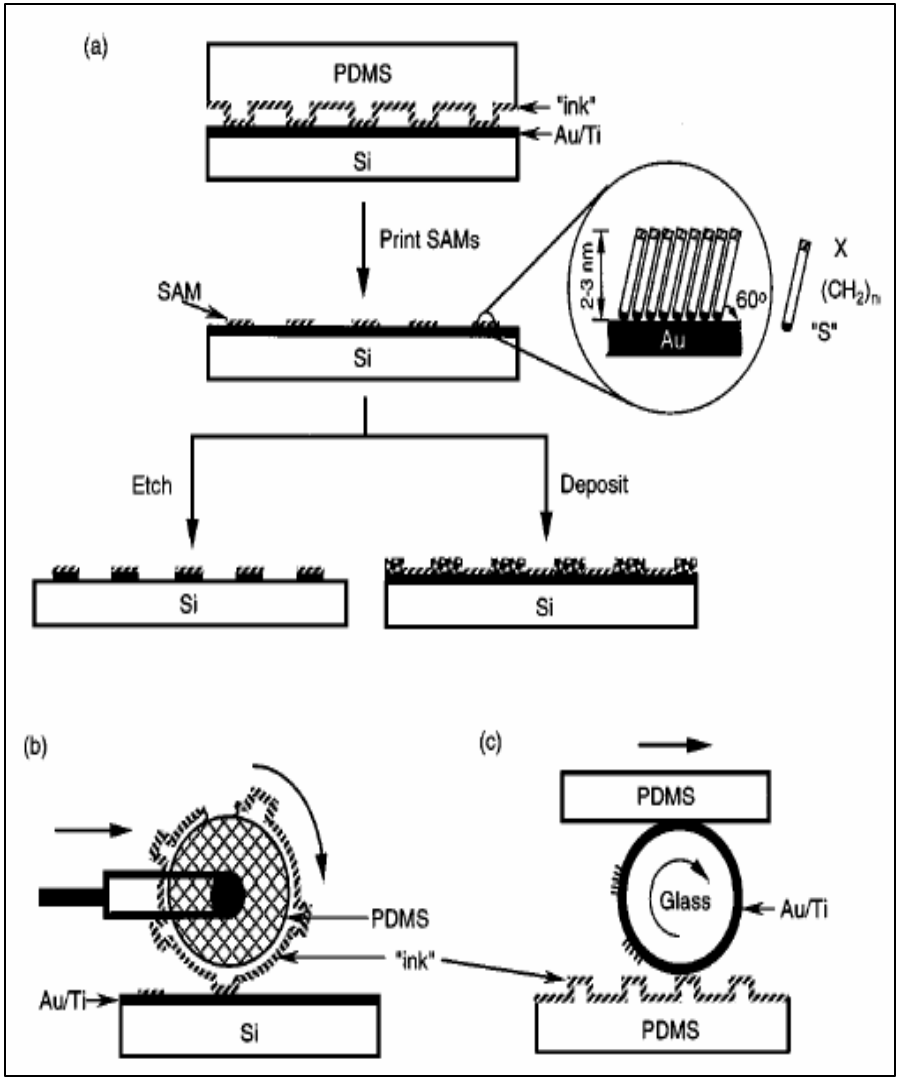
Replication and Molding

- Master mold made from silicon, glass, metal, SU-8
- Surface treatment of master
- Pour PDMS (mix, oligomer, and CL agent)
- Cure (~60C, 1 hr)
- Peel off PDMS structure
- Mold can be used again
- **Y. Gia, and G. M. Whitesides, Annu. Rev. Mater. Sci. 1998, 28, 153-84**

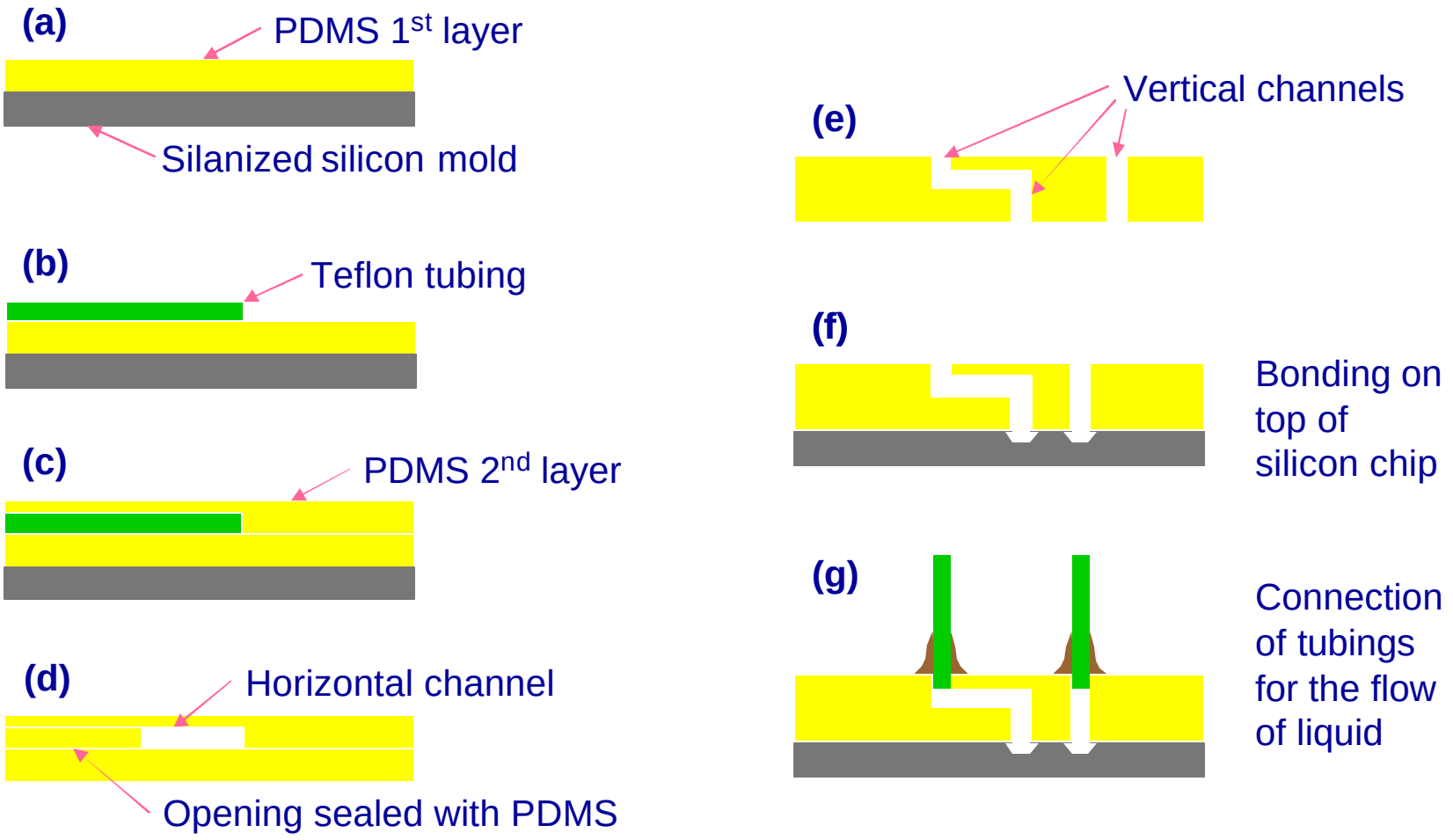


μ-Contact Printing

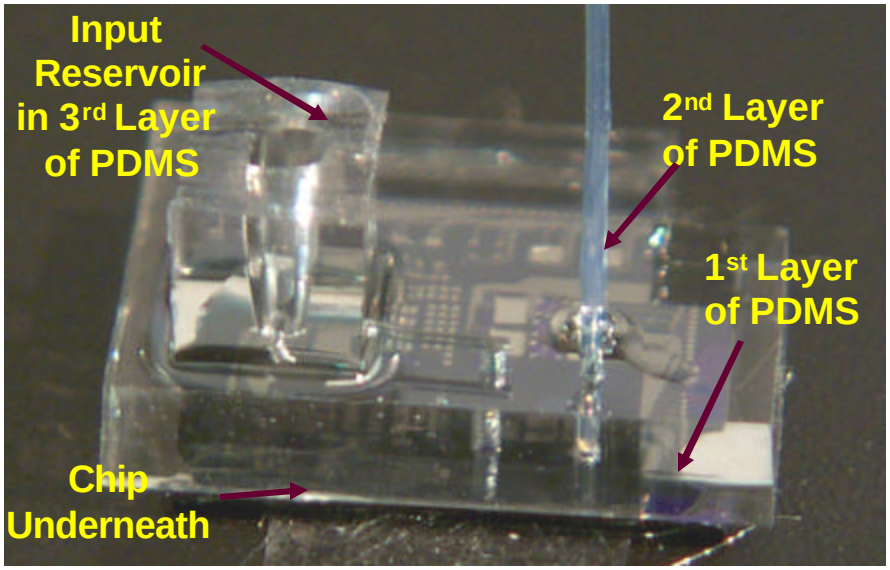
- Ink the PDMS structure with molecules (alkylthiols, proteins, DNA, etc.)
- Transfer the layer through physical contact (optimize time)
- Inking is performed via covalent binding on substrate
- Can be performed on flat surface or curved surface

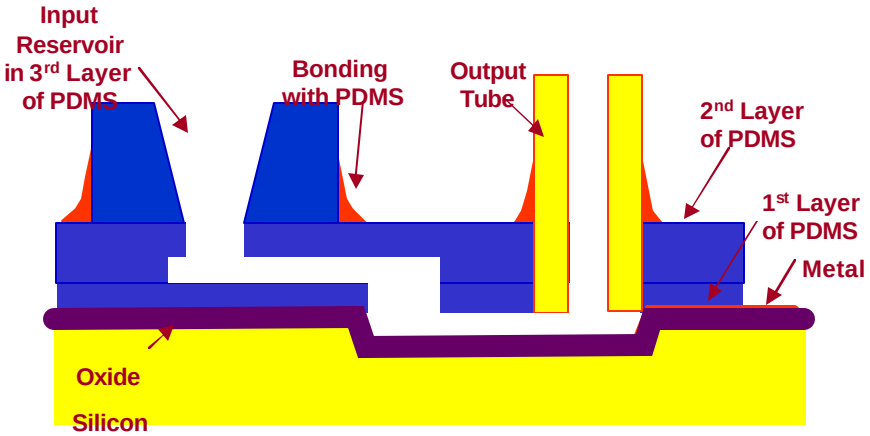


PDMS/Glass (Silicon) Hybrid Biochip

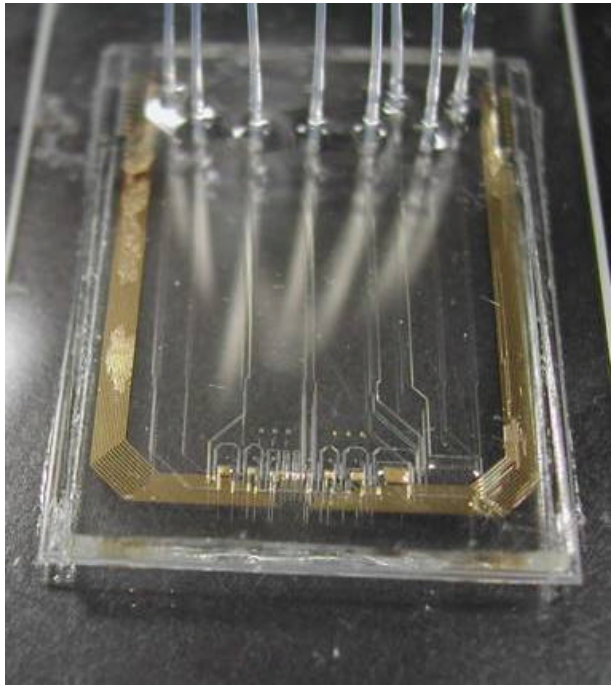


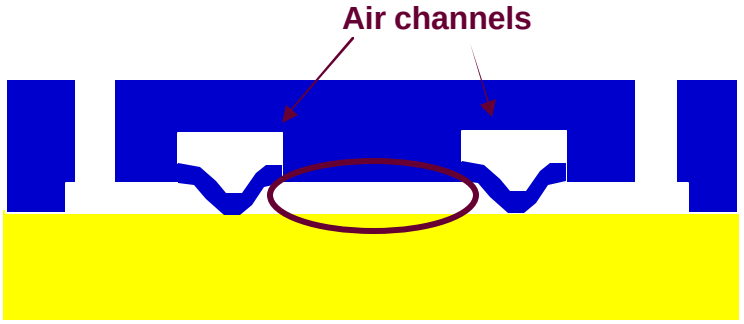
Silicon Base, 3 PDMS layers, Top I/O port





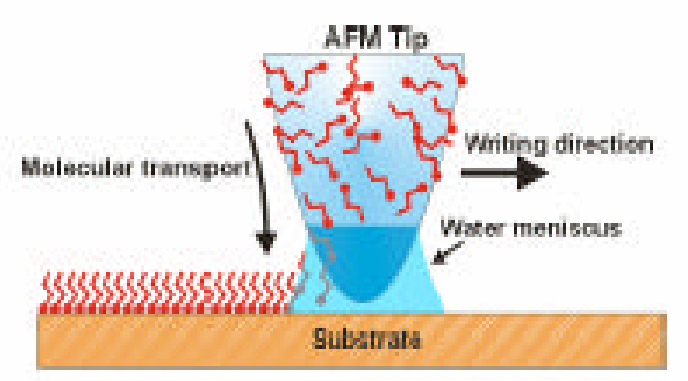
Glass Base, 3 PDMS layers, Top I/O port, Valves

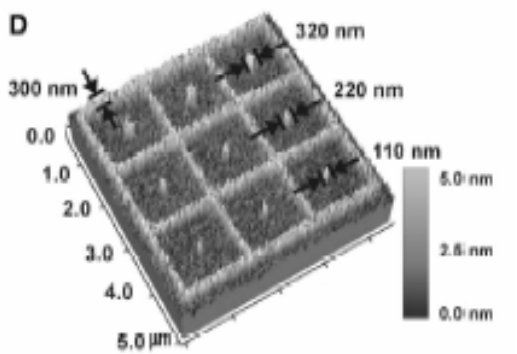


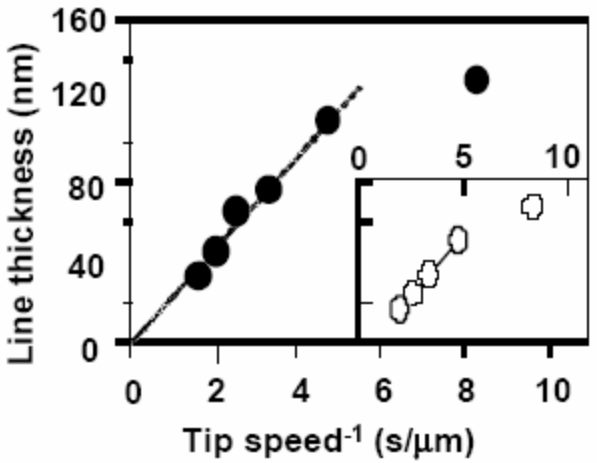


Dip Pen Lithography

- AFM Tip used to ‘write’ molecules
- Being commercialized by Nanoink, Inc.
- SAMs, DNA, Proteins, etc.
- Serial (need array of cantilevers for parallel writing)
- Continuous source of molecules – microfluidics !





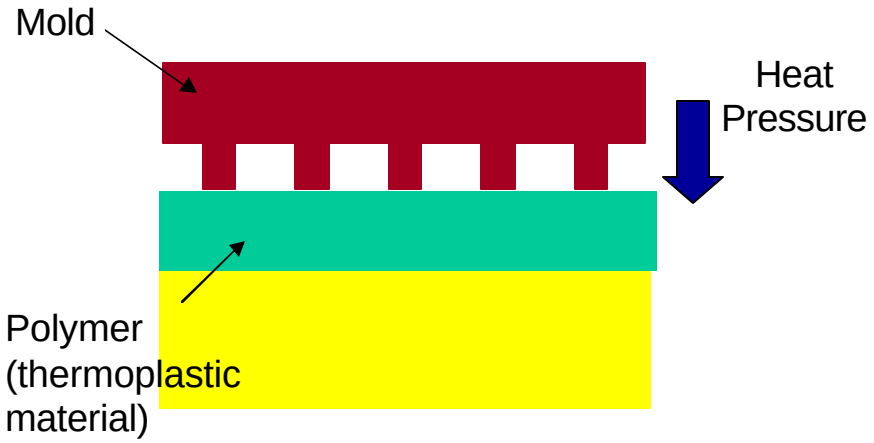


C. S. Mirkin, et. al, Science, **283**, 661 (1999); Science **286**, 523 (1999); **288**, 1808 (2000).

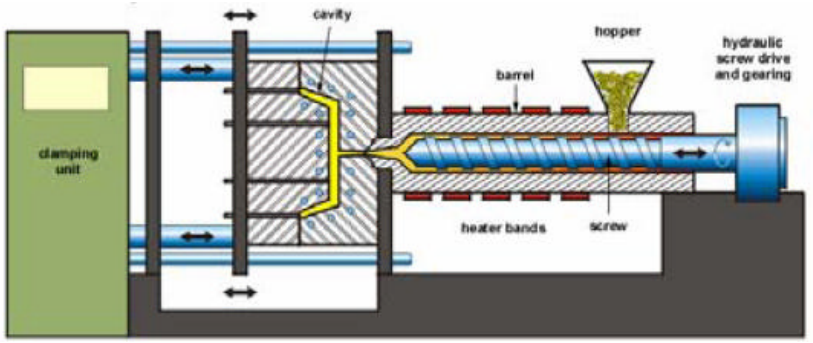
Lee, K.B.; Park, S.J.; Mirkin , C.A. ; Smith, J.C.; Mrksich, M. Protein nanoarrays generated by dip-pen nanolithography Science 2002 , 295, 1702-1705.

Compression Molding

Hot Embossing



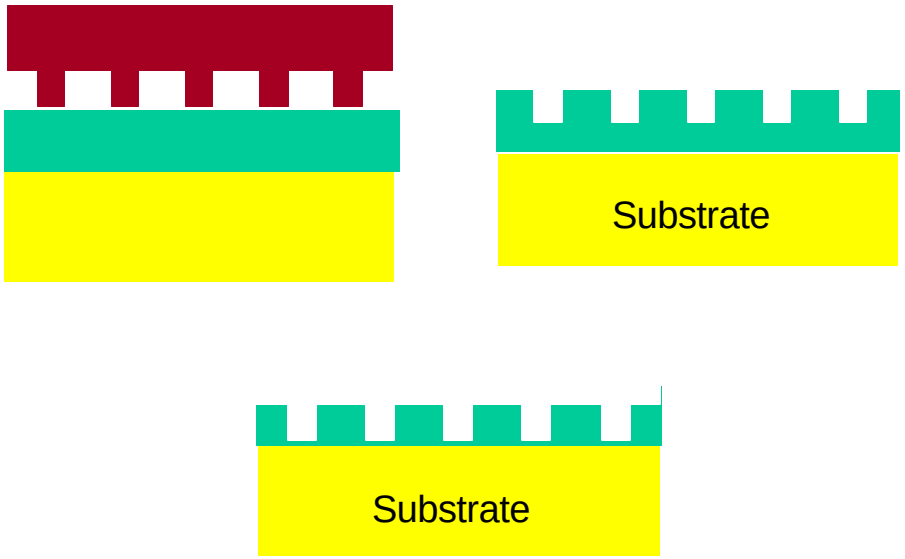
Precision Injection Molding



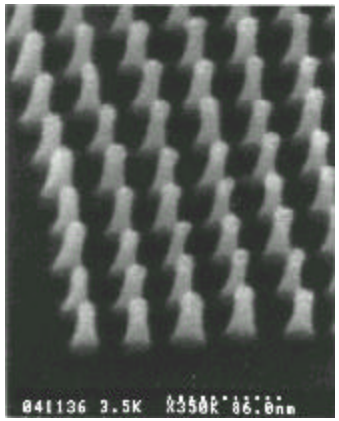
Features down to 0.1um deep and 0.6um wide (for CD-R)

Immunochip (Aclara)

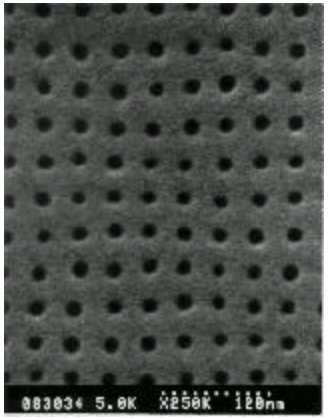
Nano-Imprint Lithography



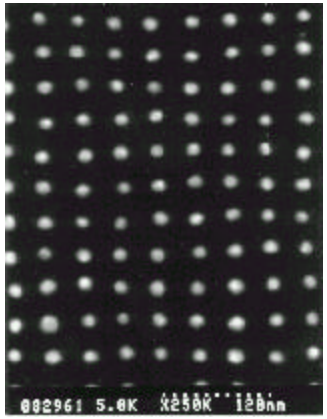
Imprint mold with 10nm diameter pillars



10nm diameter holes imprinted in PMMA



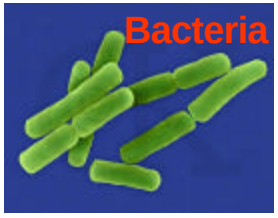
10nm diameter metal dots

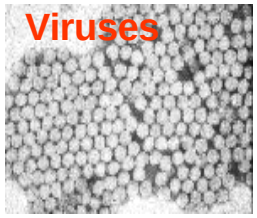


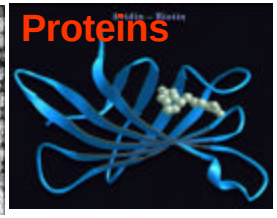
- Nano-scale extension of hot embossing
- Need a nano-scale master mold
- Added to ITRS Roadmap

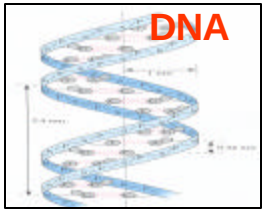
Key Topics

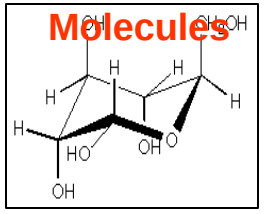
- Biochips/Biosensors and Device Fabrication
- **Cells, DNA, Proteins**
- Micro-fluidics
- Biochip Sensors & Detection Methods
- Micro-arrays
- Lab-on-a-chip Devices





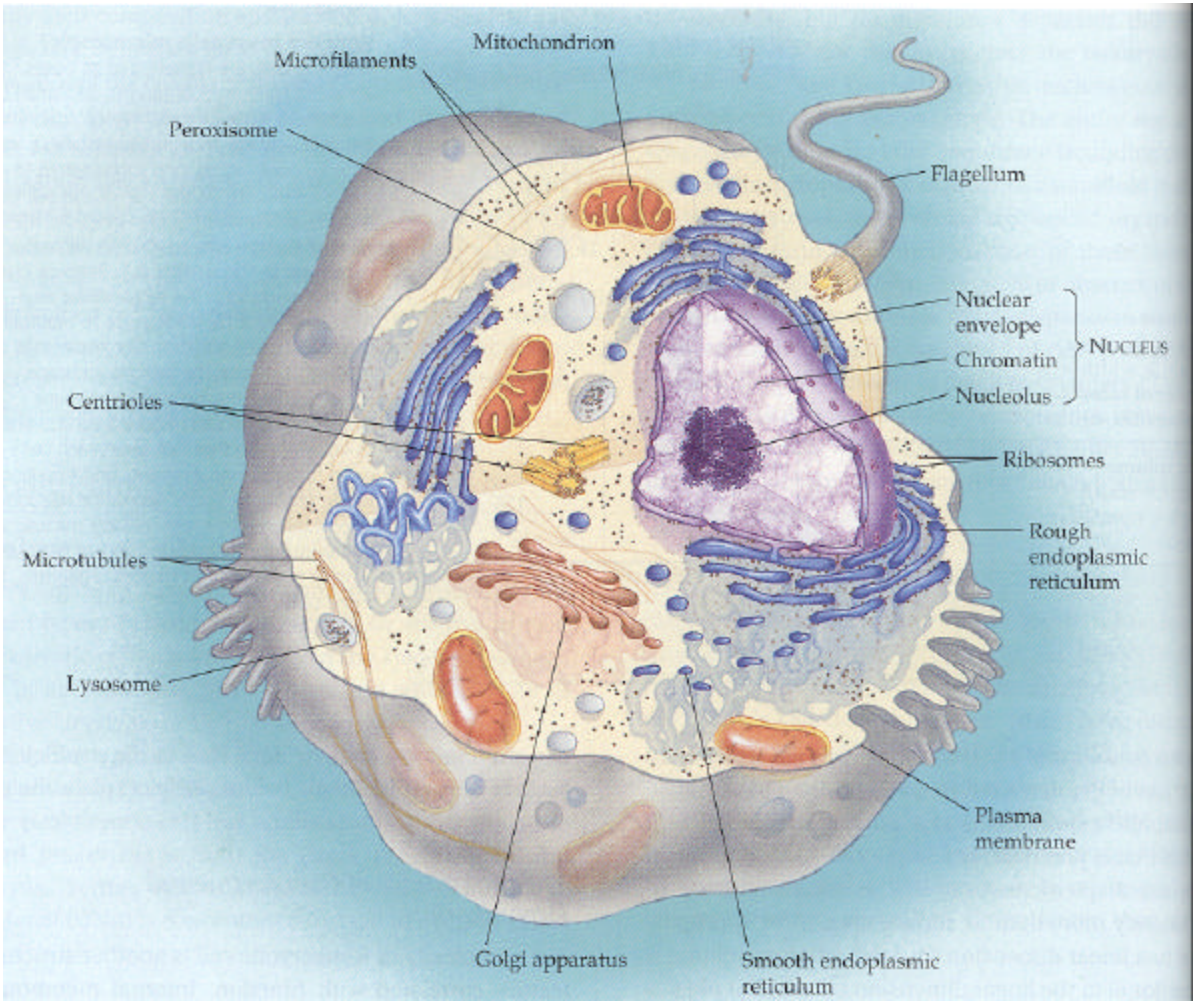






Cells – Brief Overview

- Genetic information is contained in chromatin (a diffused mass which distinguishes to a chromosome when cell is ready to divide)
- Humans have 46 chromosomes in each cell (except in reproductive cells)
- Chromosomes are long, uninterrupted, packed, super-coiled linear polymer strands of DNA (deoxyribonucleic acid) - 6 cm long when extended
- In humans, each chromosome is 50-400 x 10^6 units long



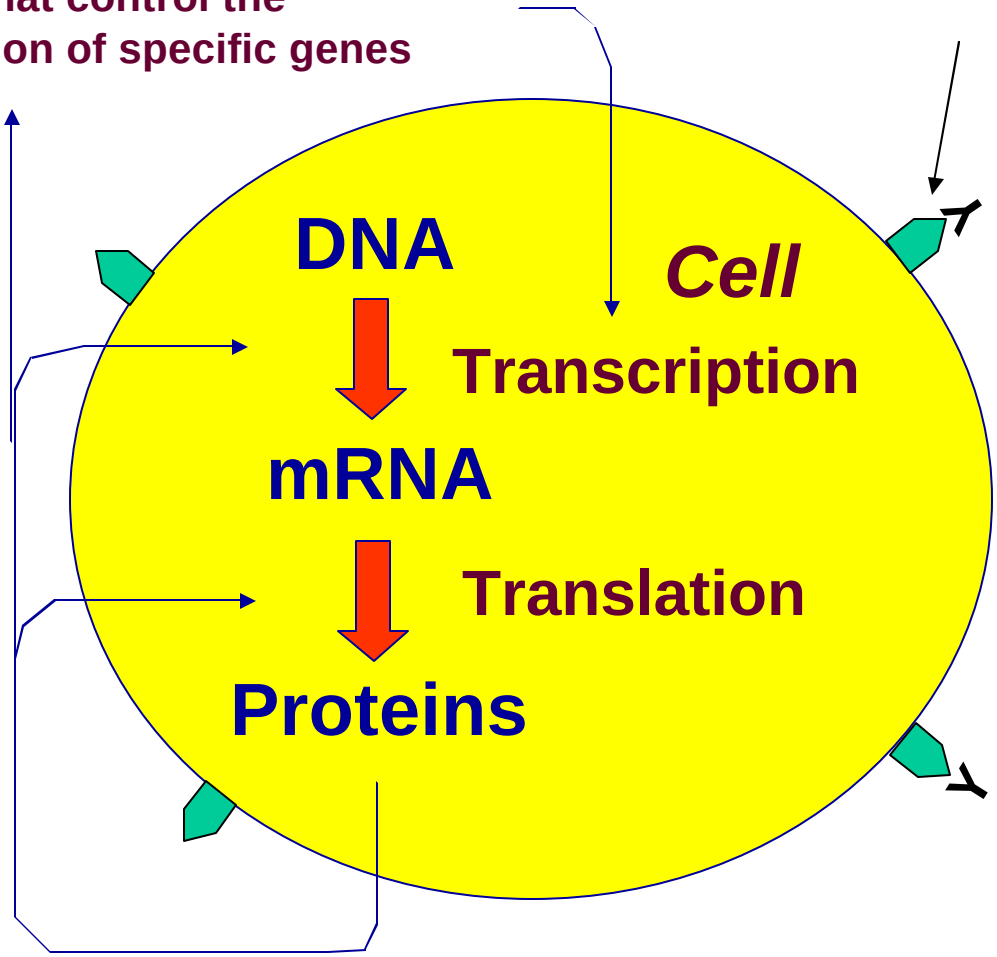
From: Biology, 4th Edition by Campbell

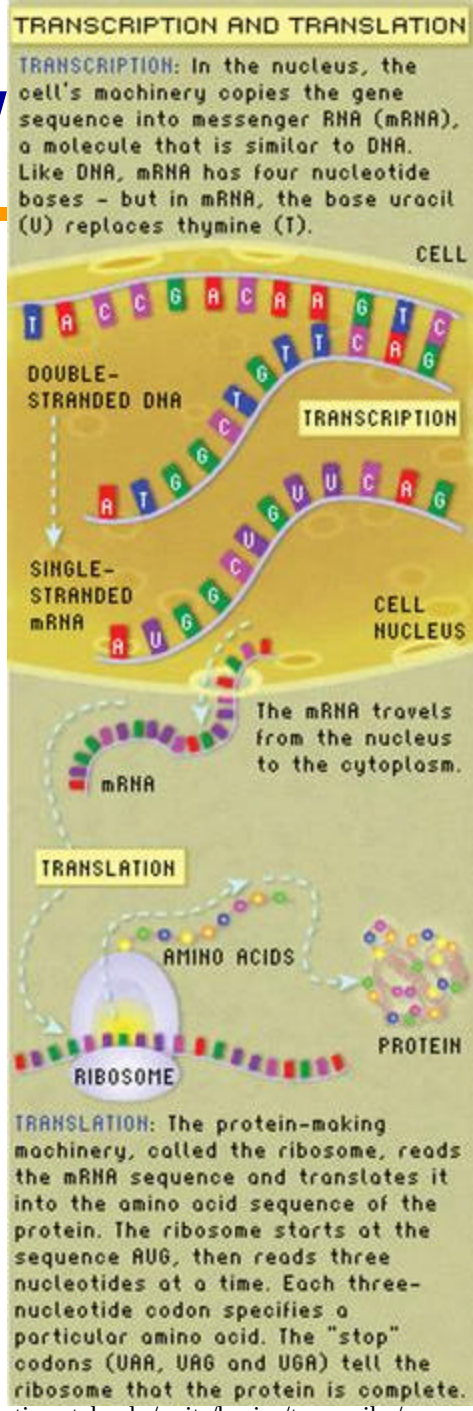
PURDUE UNIVERSITY

Cells – Brief Overview

Transcription factors:
Proteins that control the transcription of specific genes

Surface Proteins
(could be specific to cells)





http://gslc.genetics.utah.edu/units/basics/transcribe/

DNA to Proteins

- Transcription
  - double stranded DNA is converted to a single stranded mRNA
  - RNA polymerase synthesizes the mRNA
- Translation
  - Ribosomes ‘translate’ the sequence of bases in the mRNA to proteins.
  - These proteins than perform various functions inside and outside the cell

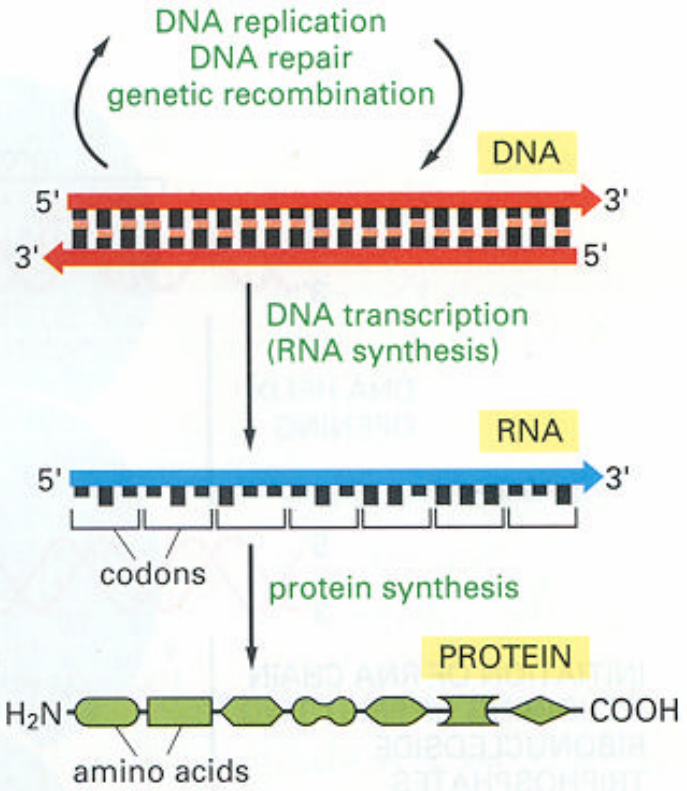
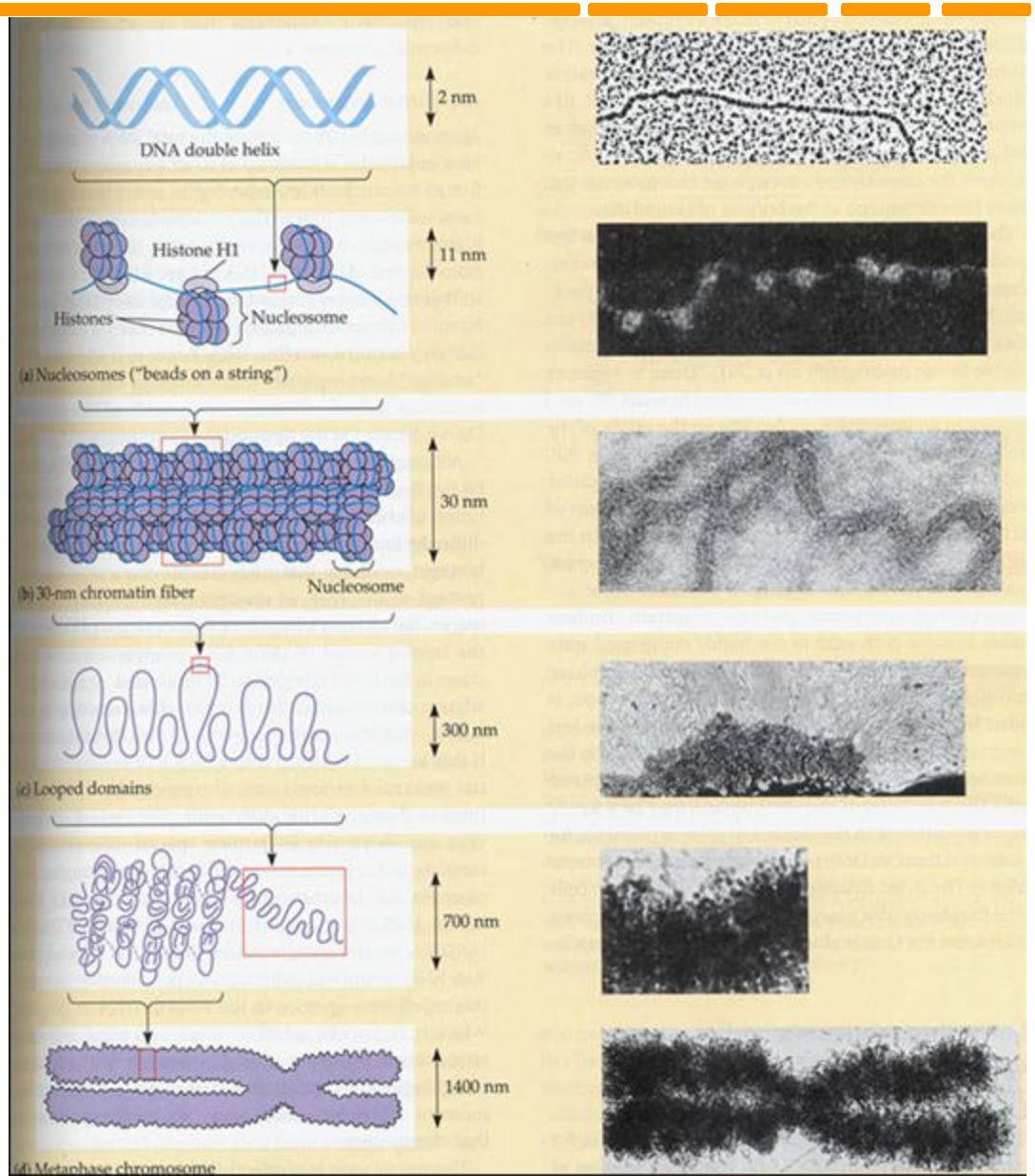


Figure 6–1 The basic genetic processes. The processes shown here are thought to occur in all present-day cells. Very early in the evolution of life, however, much simpler cells probably existed that lacked both DNA and proteins (see Figure 1–11). Note that a sequence of three nucleotides (a codon) in an RNA molecule codes for a specific amino acid in a protein.

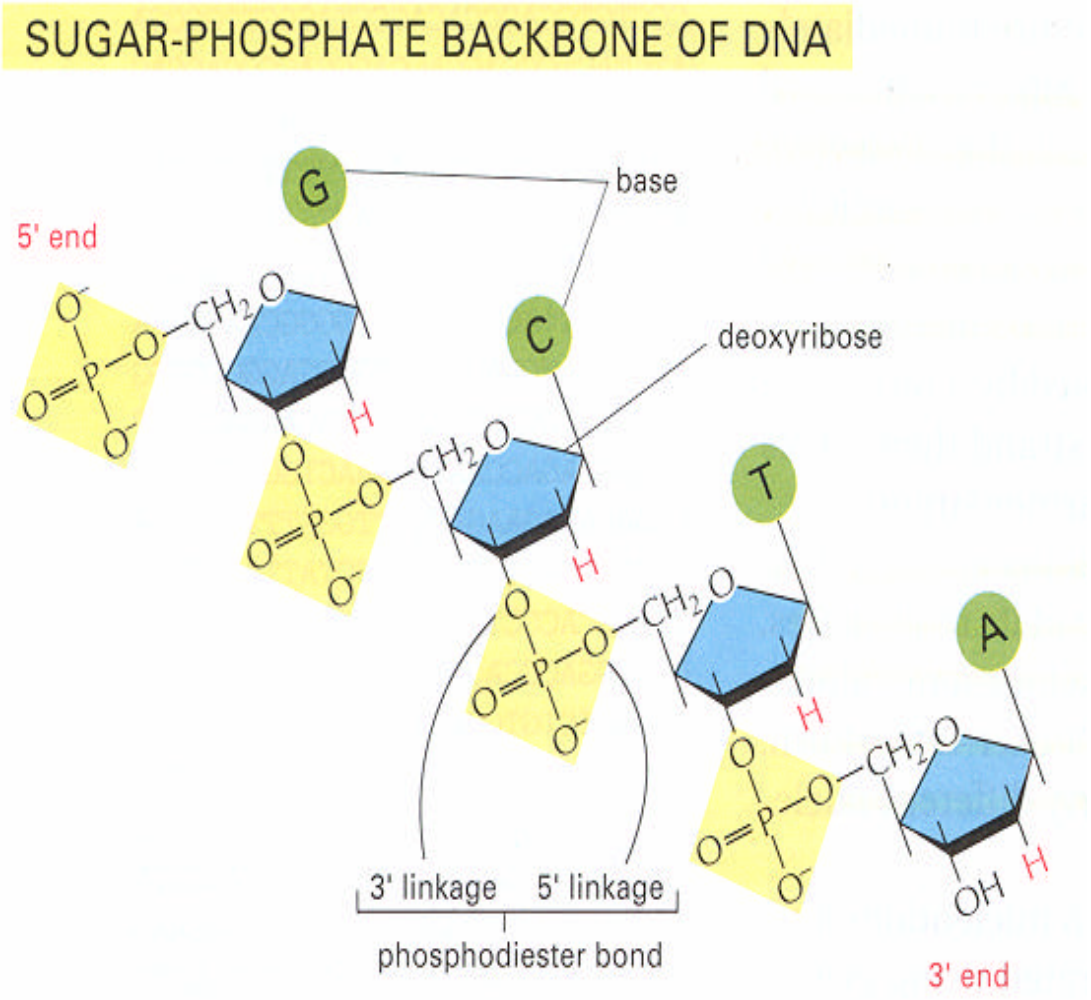
Chromosomes → DNA

Decreasing complexity



Structure of DNA

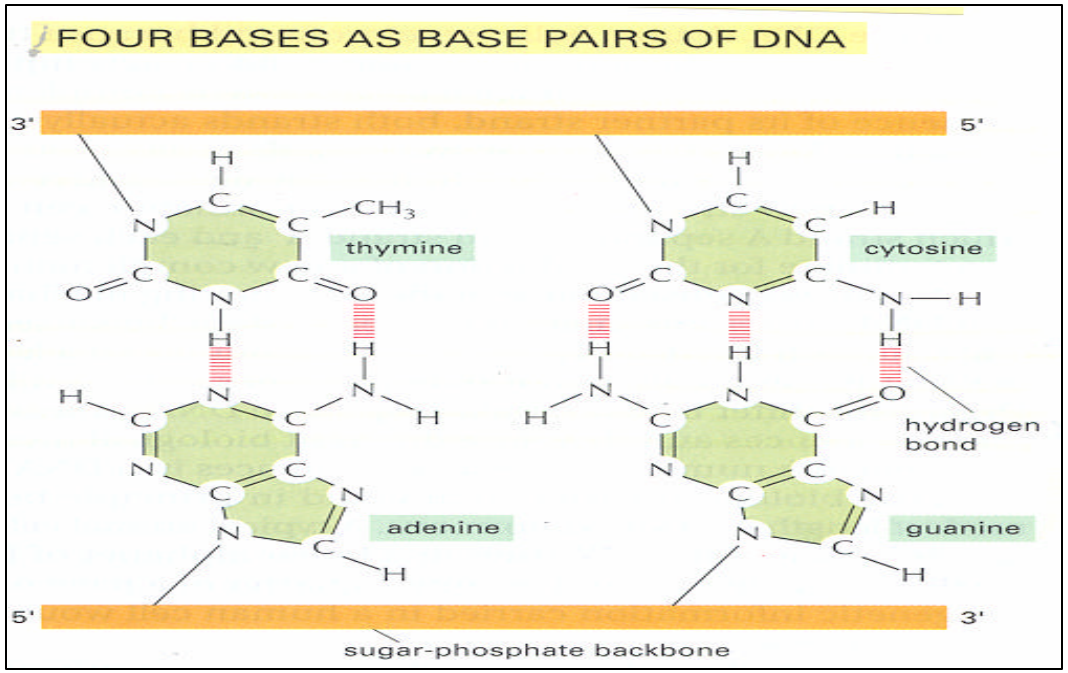
- DNA is composed of;
  - a phosphate back-bone where each phosphate radical has a negative charge
  - a Deoxyribose (D in DNA) sugar
  - 4 types of bases or nucleotides. These are adenine (A), thymine (T), cytosine (C), Guanine (G)
- A binds to T and G binds to C - complementary base pairs

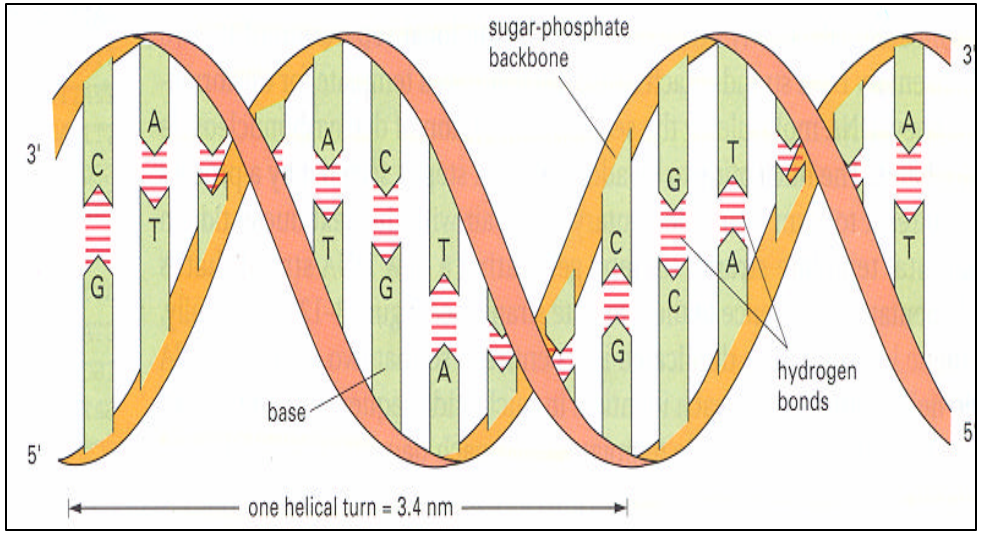


Structure of DNA

Pyrimidines (T, C) 1 ring

Purines (A, G) 2 rings

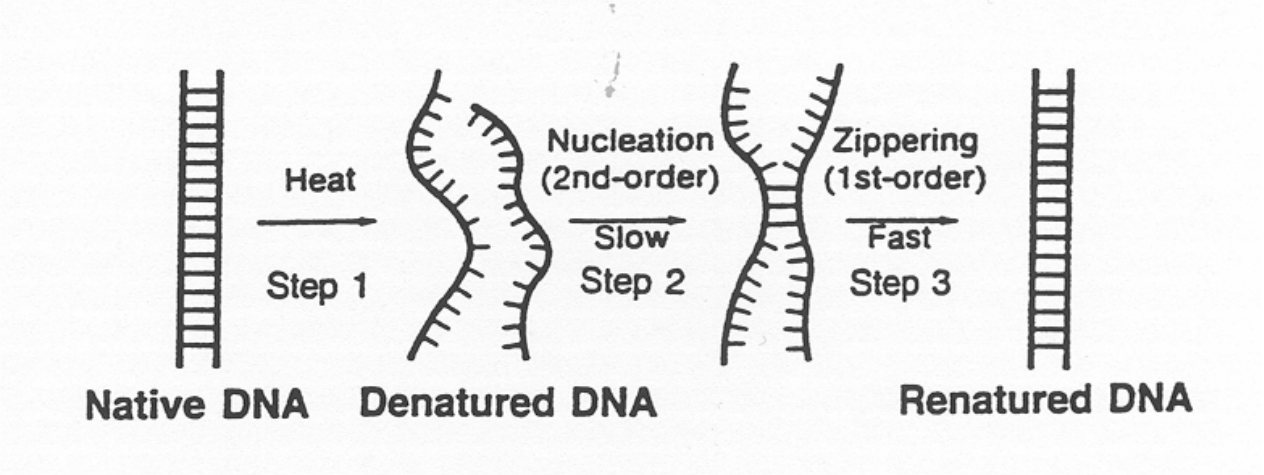


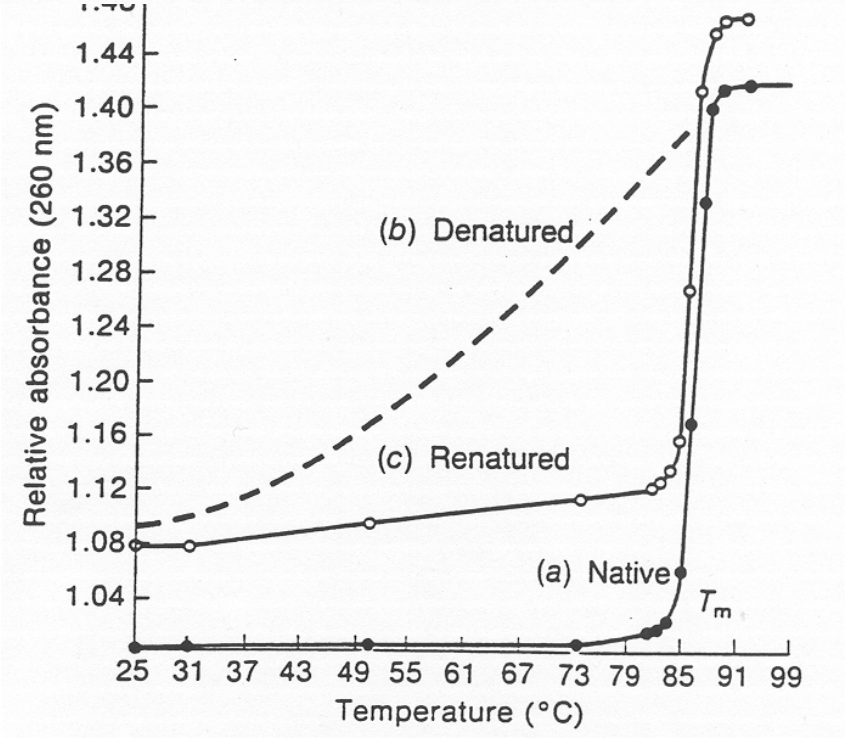


DNA Hybridization

- When DNA is heated to a temperature (~>90°C) or exposed to pH > ~12, the complementary strands dissociates - *DNA denaturation*
- Process is reversible (exposure to a melting temperature T_m > 65°C) and 2 complementary ssDNA will *hybridize* to each other and join to form dsDNA
- Hybridization can happen between any two complementary single stranded molecules (DNA/DNA, DNA/RNA, RNA/RNA)
- Can provide a very sensitive means to detect specific nucleotide sequences
- Factors affecting hybridizaton : temperature, Salt and buffer concentration, G & C content - T_m can be calculated
- Rate of hybridization is proportional to concentration of target and probe and limited by the lower concentration material

DNA Hybridization

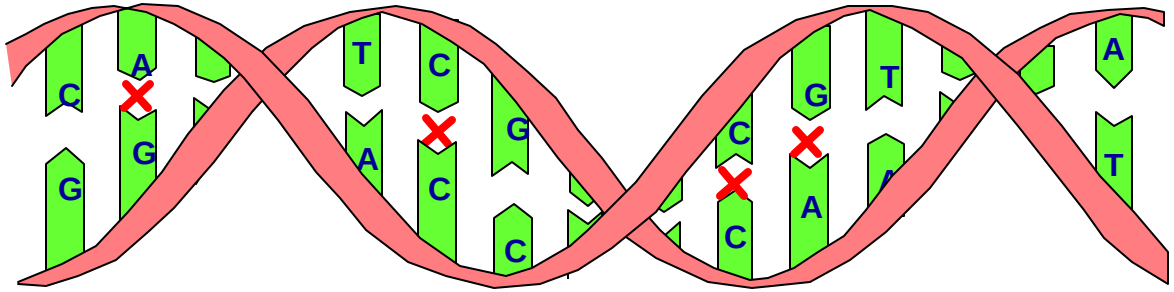




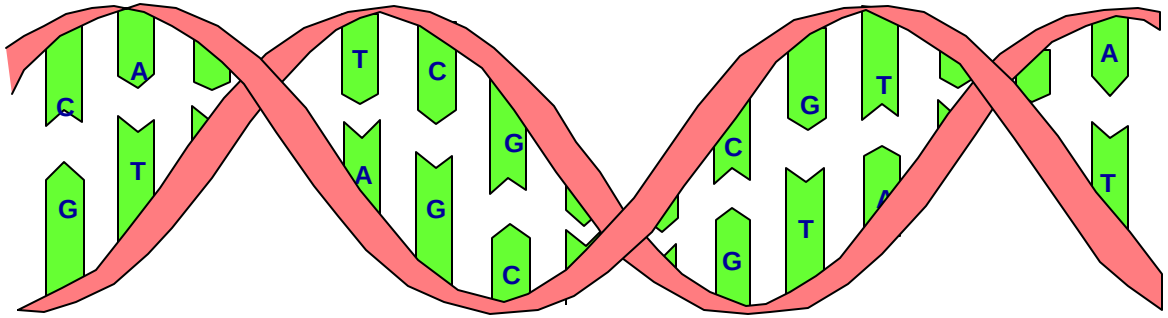
DNA Hybridization

Stringency

Reduced Stringency Hybridization



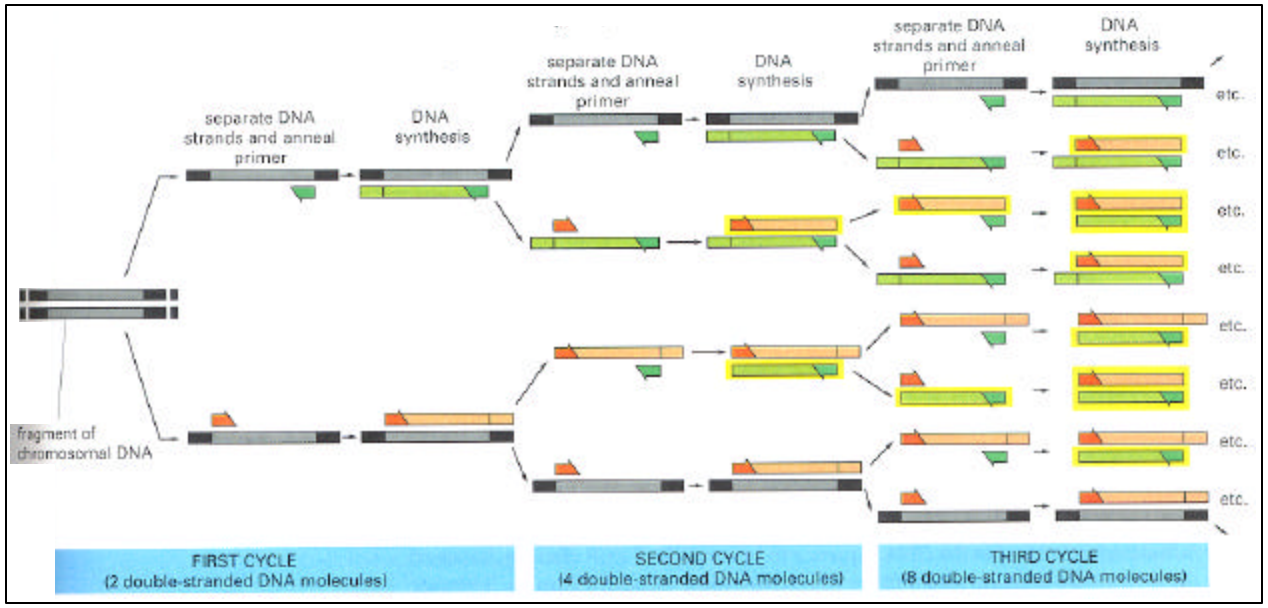
Stringent Hybridization

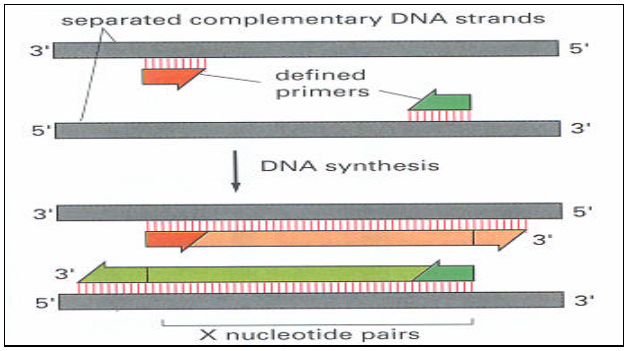


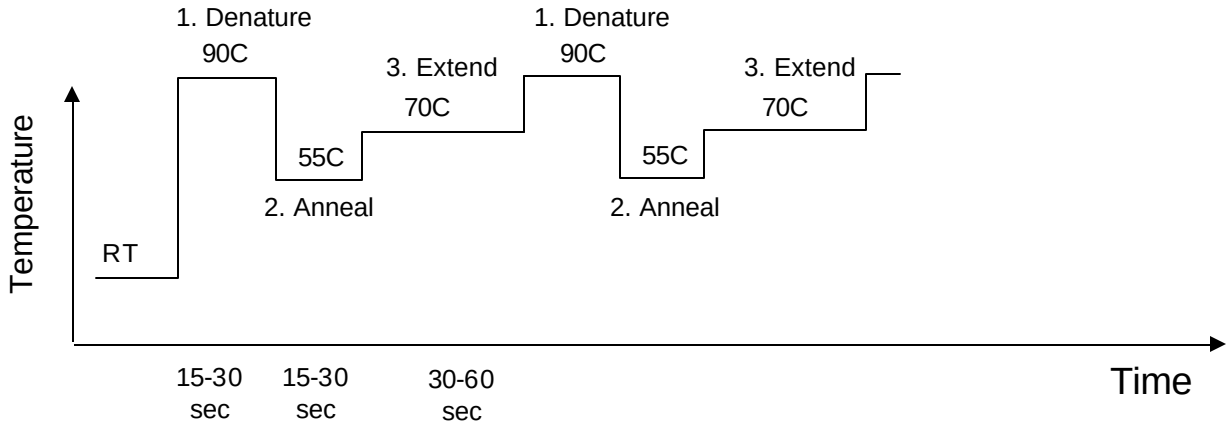
PCR - Polymerase Chain Reaction

- **Technique to amplify (make multiple copies) of known DNA molecules - invented in 1985**
- **Use enzyme called DNA polymerase and primers (short ssDNA strands)**
- **Billions of copies can be made within hours in laboratory**
- **Very useful in research, diagnosis, forensics, etc where large samples are required from very small concentrations.**

PCR Sequence

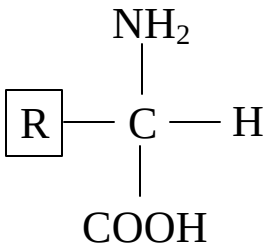


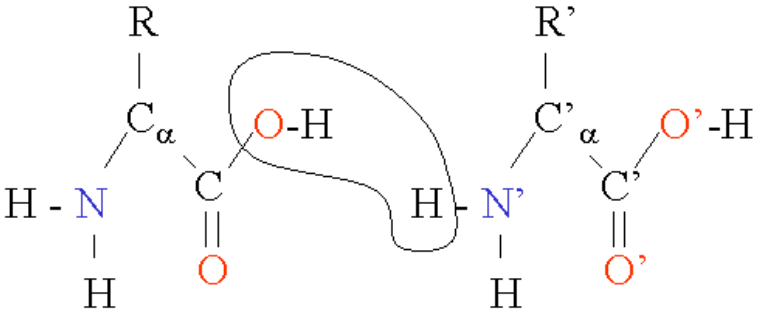


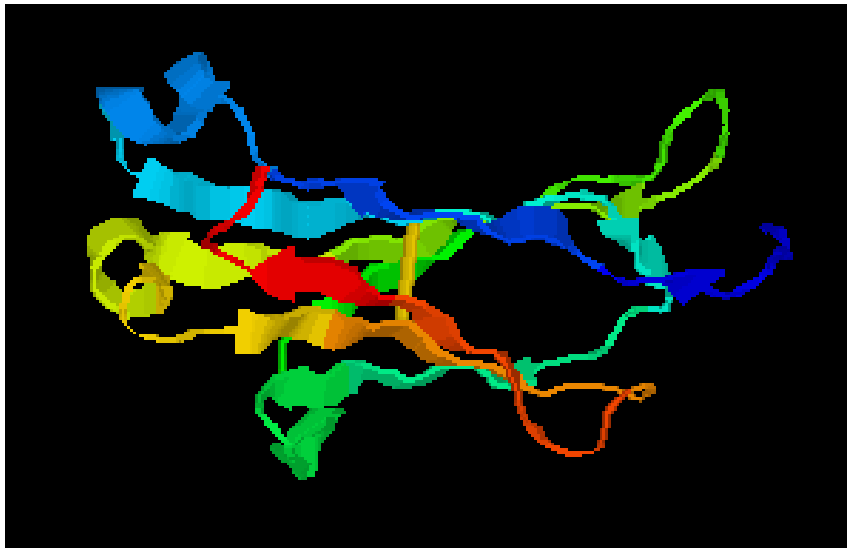


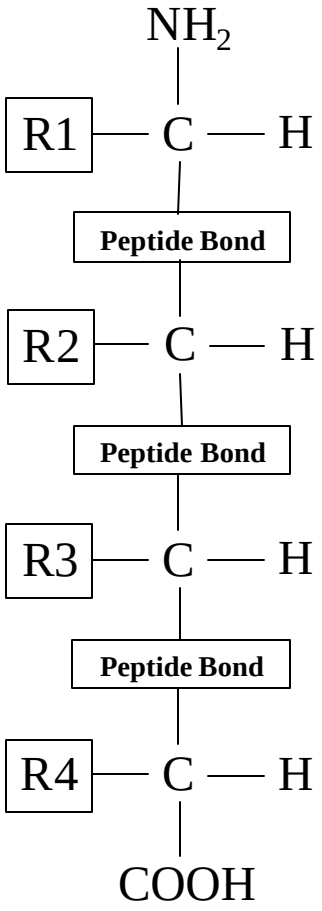
- Primers are short strands of nucleotides which are complementary to specific regions of the target DNA to the amplified - hence the 'end' sequence of short regions of the target DNA to be copied is needed
- DNA Polymerase is an enzyme which takes nucleotides from the ambient solution and starts to construct the complementary sequence
- An adequate supply of nucleotides are needed (dNTPs - deoxyribonucleose triphosphates - dATP, dCTP, dGTP, dTTP)

Protein Structure









http://www.umass.edu/microbio/rasmol/rotating.htm

http://www.umass.edu/microbio/chime/antibody/