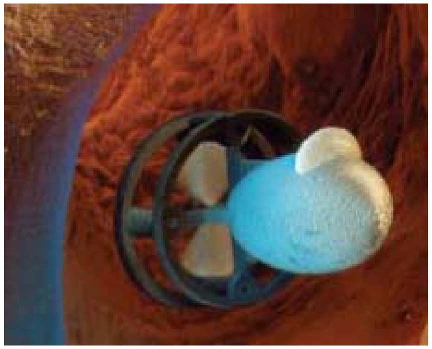
Biomedical sensor technology: state - of the art and future roadmap

Ralph W. Bernstein

SINTEF ICT

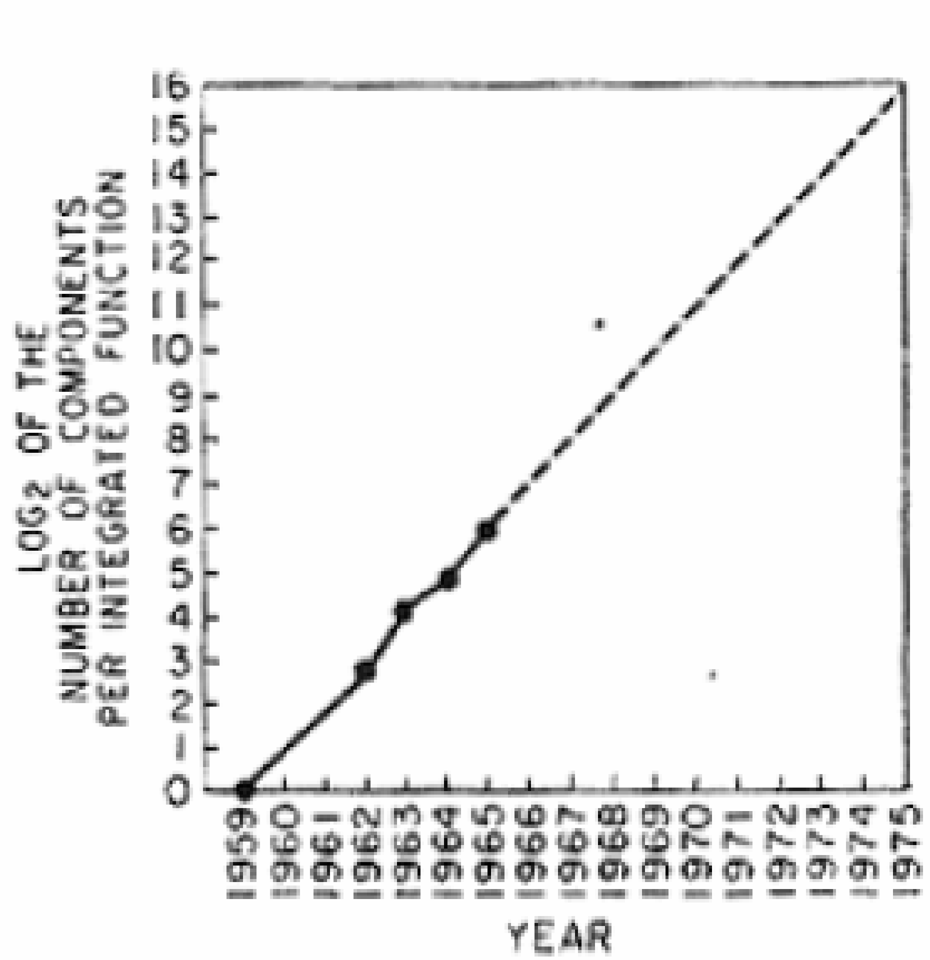
Microsystems and nanotechnology



MiNaLab

- Clean room area:
  SINTEF: 800 m^2
  University of Oslo: 600 m^2
- Micro environments, class 10
- A full silicon processing line for MEMS and radiation detectors
- Capacity of 10.000 6” wafers/year
- Located at the campus of University of Oslo
- 240 MNOK invested in scientific equipment and laboratory infrastructure
- Funded by Norwegian Research Council and SINTEF

Moores law

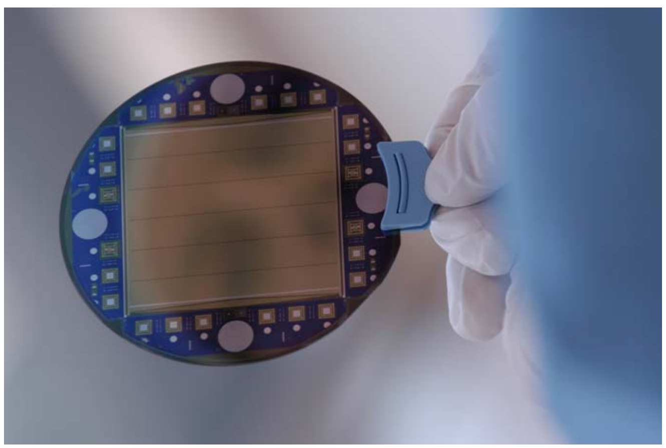


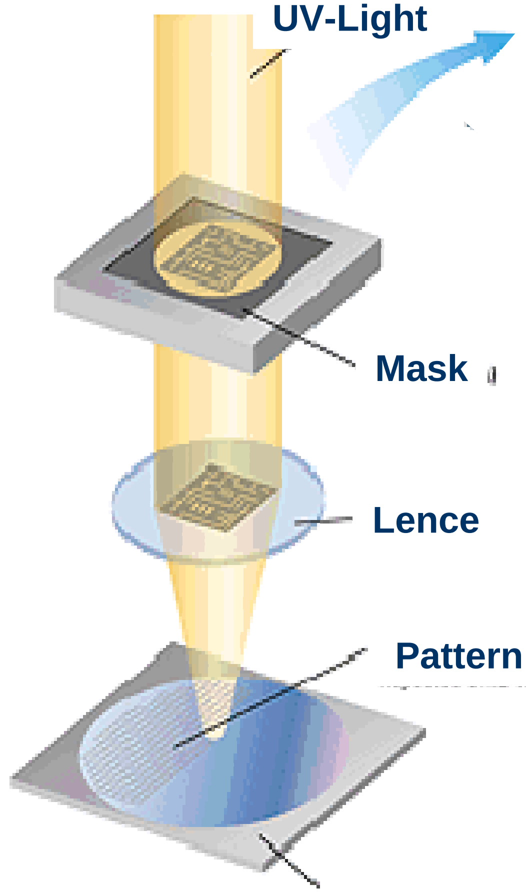
- Gordon Moores observation from 1965: The number of transistors per square inch on an IC doubles every year.
- In subsequent years, the pace has slowed down a bit, but data density has doubled every 18 months.

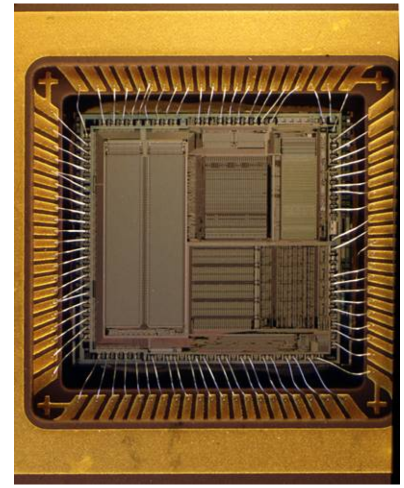
Gordon Moore, Electronics, Volume 38, Number 8, April 19, 1965

Key technologies

- Photo lithography
- Batch production







Micro processor

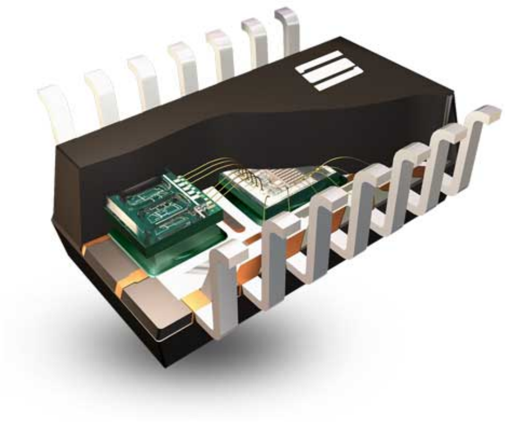
Driving forces

- **Cheaper**
  - Cost per function decreases 25% / year
- **Smaller**
  - Moore's law: bits/chip grow by factor of 4 times every 3 years
- **Faster**
  - 5 times growth every 10 years

Even more important: FUNCTIONALITY !

From the information society towards the instrumentation society

- **Microelectronics** is the first industrial wave based on microtechnology. The next one, microsystems, will have great impact the next 5-10 years.
- **Microsystems** perform measurements, signal conditioning and actuation
- **I the future** the electronics will be connected direct to the environment via sensors => Ambient intelligence
- The keys to this development:
  - ✓ Low cost computer power
  - ✓ Wireless communication
  - ➔ **Modern sensors**
  - ➔ **Distributed power generation**

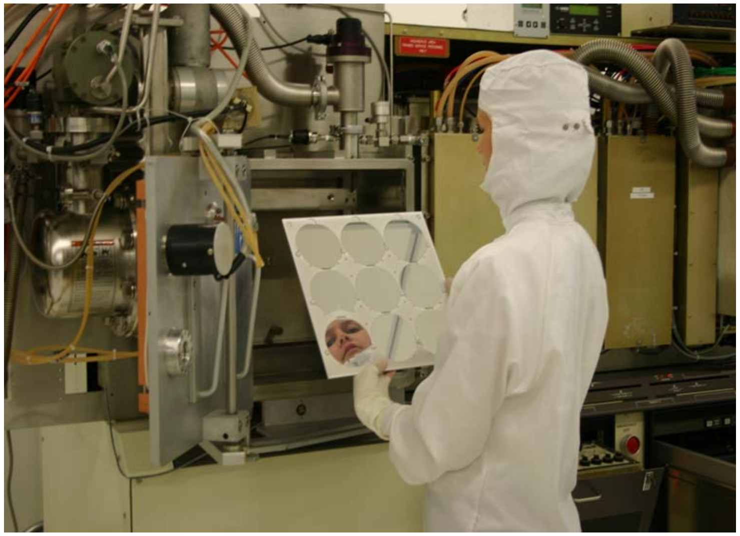


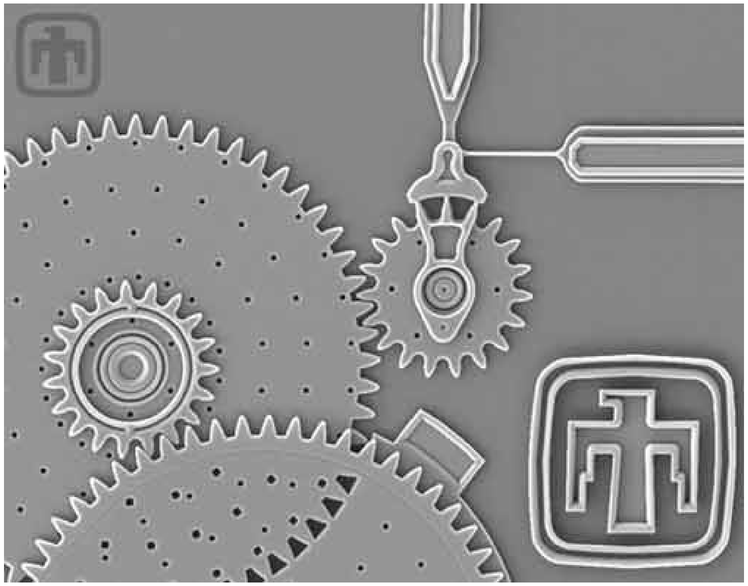
Same challenges for the biomedical area !!

Microsystem technology

- Utilizes the production technology developed for microelectronics to make sensors **(MEMS)**
  - Miniaturization
  - High volume, low cost production
  - Integration with electronics

- Special processes
  - Micromachining
  - Functional thin films
  - Wafer stacking



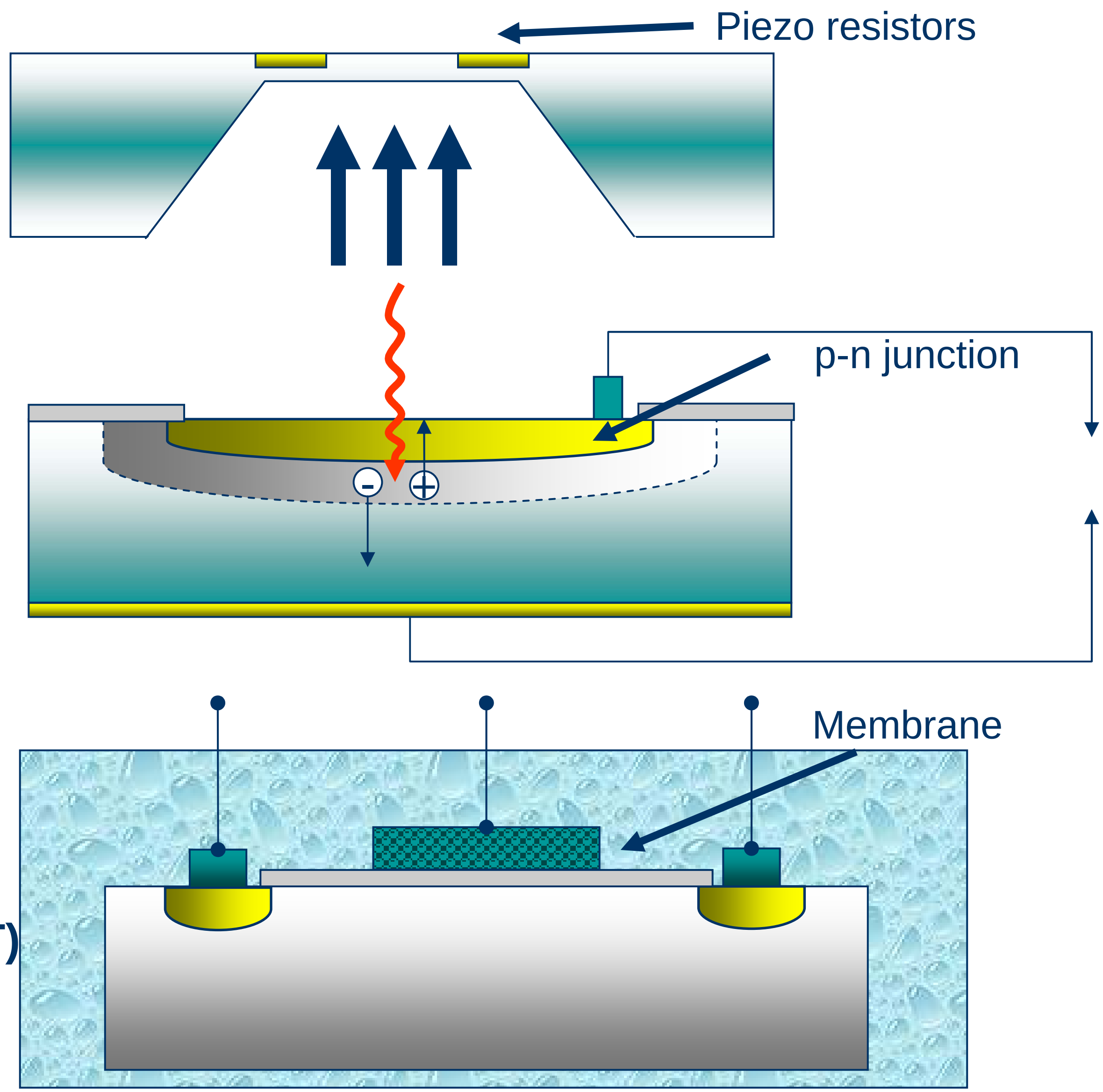


Why silicon technology

- Batch processing => low cost, high volume
- Well established production technology
- Advanced infrastructure, materials and design tools available
- Wide range of sensor principles available
- Silicon has attractive mechanical properties
- Integration with electronics possible

- Polymers are also important

A sensor converts stimuli to electricity



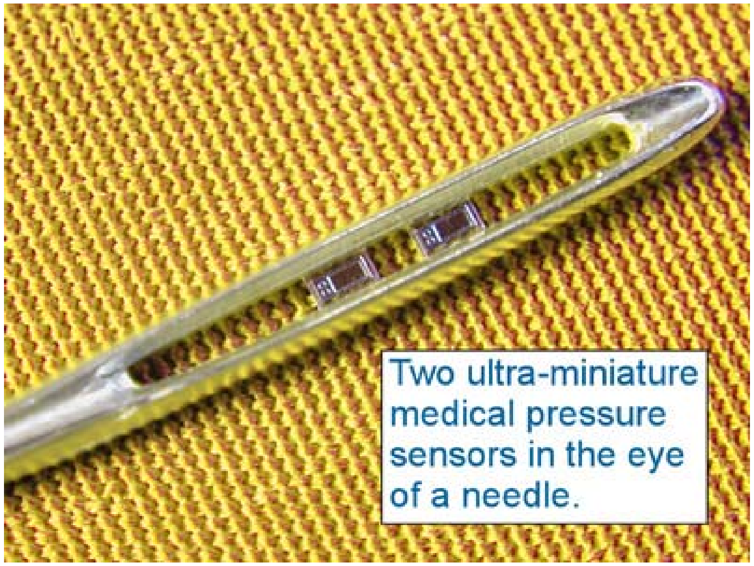
Pressure sensor

Optical sensor

Chemical sensor (ISFET)

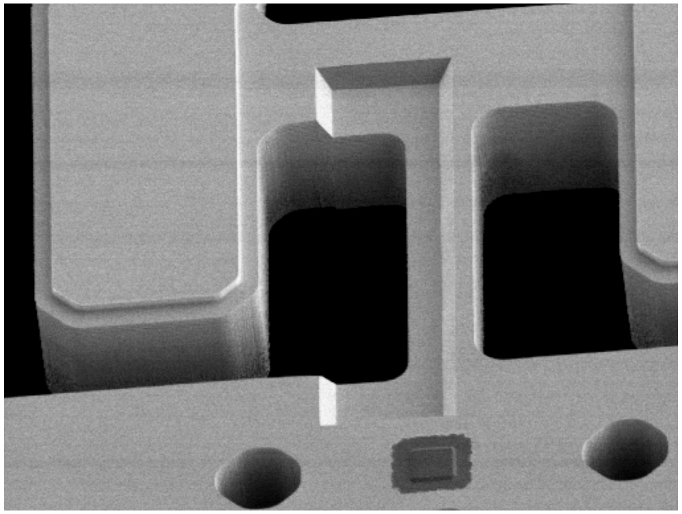
Pressure sensors

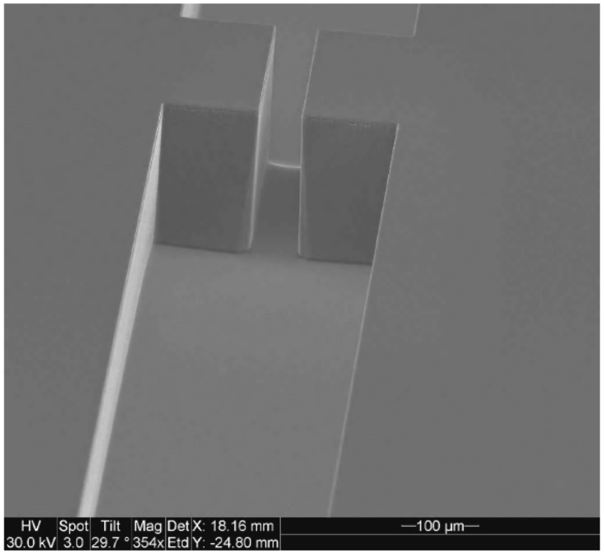
- Measure pressure gradients across heart valves accurately to help assess valve disease
- Diagnose and monitor congestive heart failure
- Measure cardiac output and compliance
- Monitor intracranial pressures in hydrocephalus patients
- Understand glaucoma disease progression and improve patient care
- Improve gastrointestinal tract diagnostic capabilities to help treat gastro esophageal reflux disease (GERD)
- Assist in diagnosis of urological disorders
- Measure drug delivery rate for infusion systems

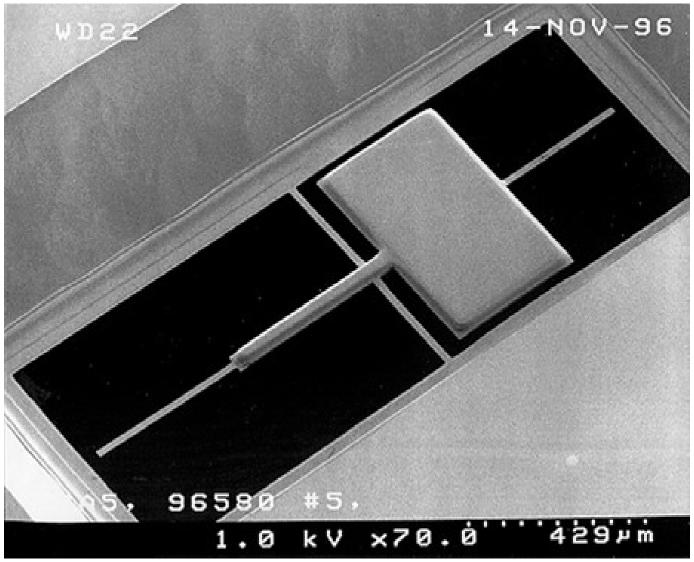


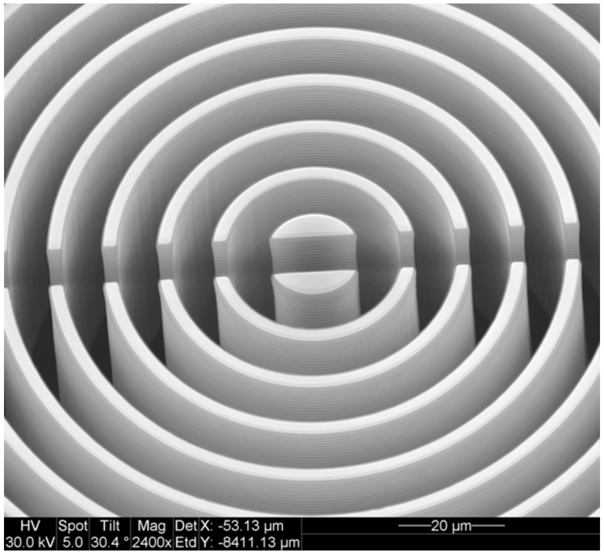
ISSYS INTEGRATED SENSING SYSTEMS

Micromaching of 3D mechanical structures for mechanical sensors

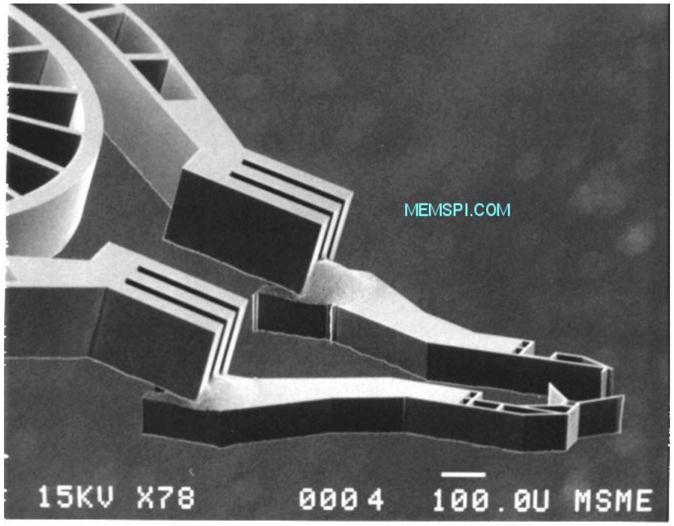




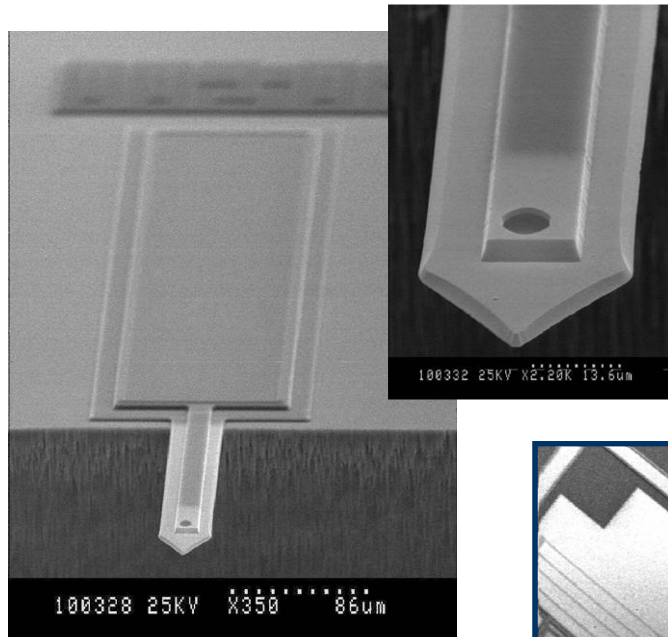




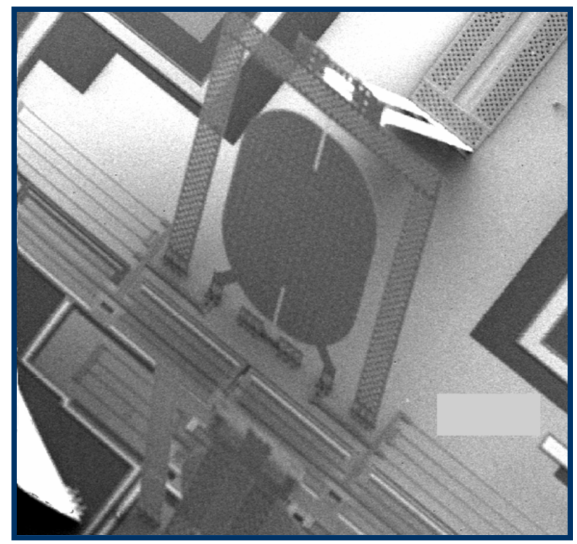
Micro tools



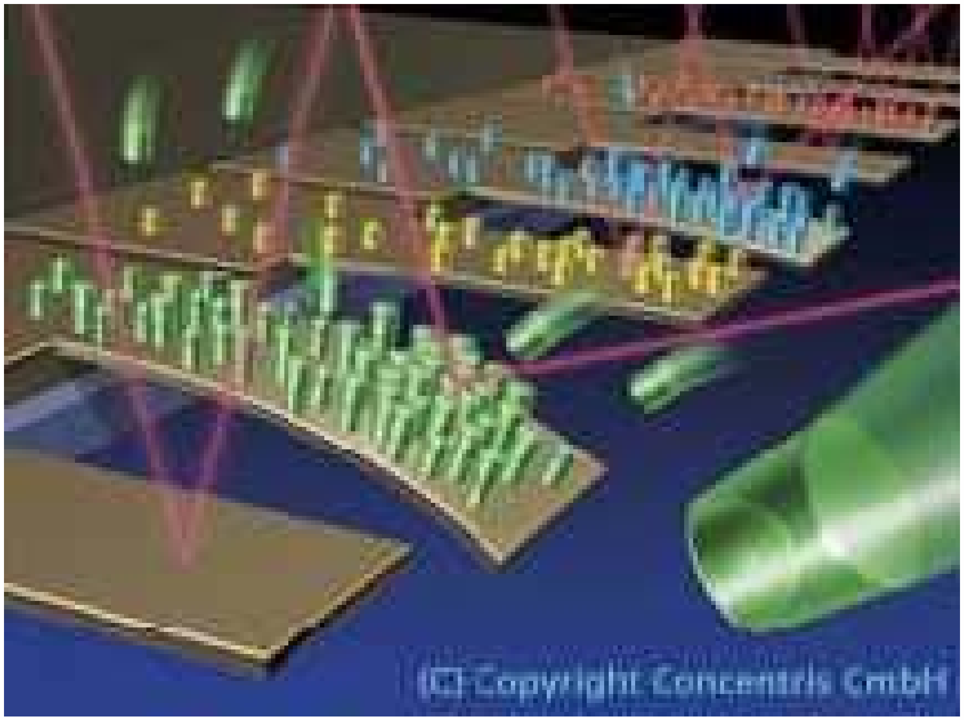
MEMS PI



STANFORD
UNIVERSITY



Micro and nano cantilever sensors



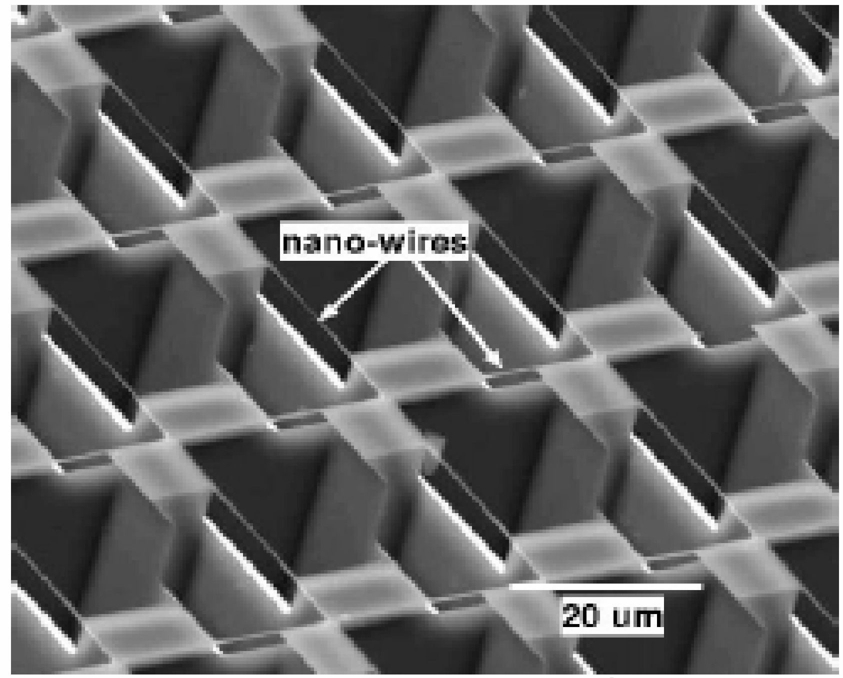
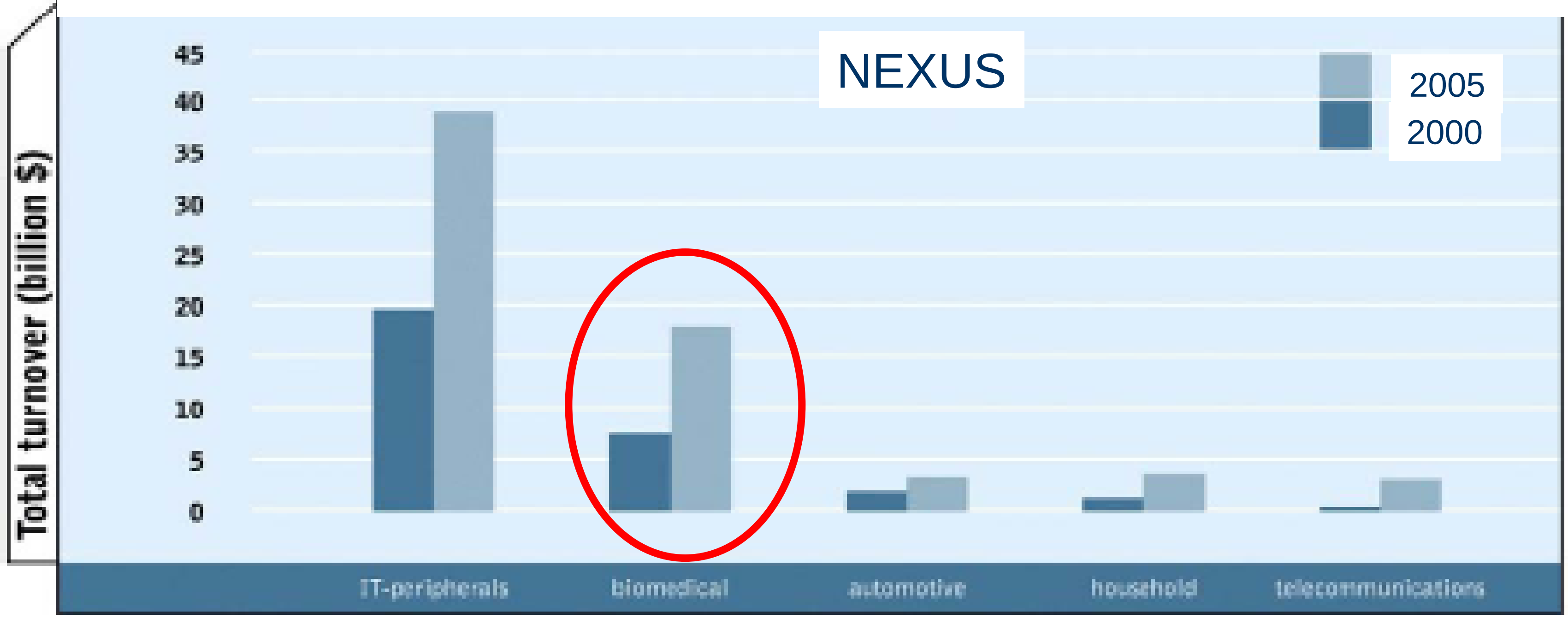


Figure 8: SEM picture of the realized nano-wires: 100 nanonetersin width and from 5 to 15 micrometers in length, according to the mask pattern dimension.

A. Tixier-Mitaa, Y. Mitab and Hiroyuki Fujitaa The University of Tokyo,

Market surveys and roadmaps



Products	2000		2005	
	Units (millions)	$ (millions)	Units (millions)	$ (millions)
In vitro diagnostic		1,250		5,200
Bio chip	30	645	400	4,400
Pressure sensor	130	1,050	310	2,030
Gyroscope	13	340	37	770
Accelerometer	100	470	190	690
Flow sensor	11	230	25	360
Infrared sensor	7	19	20	340
Inclinometer	9	54	20	100
Microspectrometer	0.03	8	0.5	75
Total		4,066		13,965

Open consultation on the European Strategy for nanotechnology (December 2004)

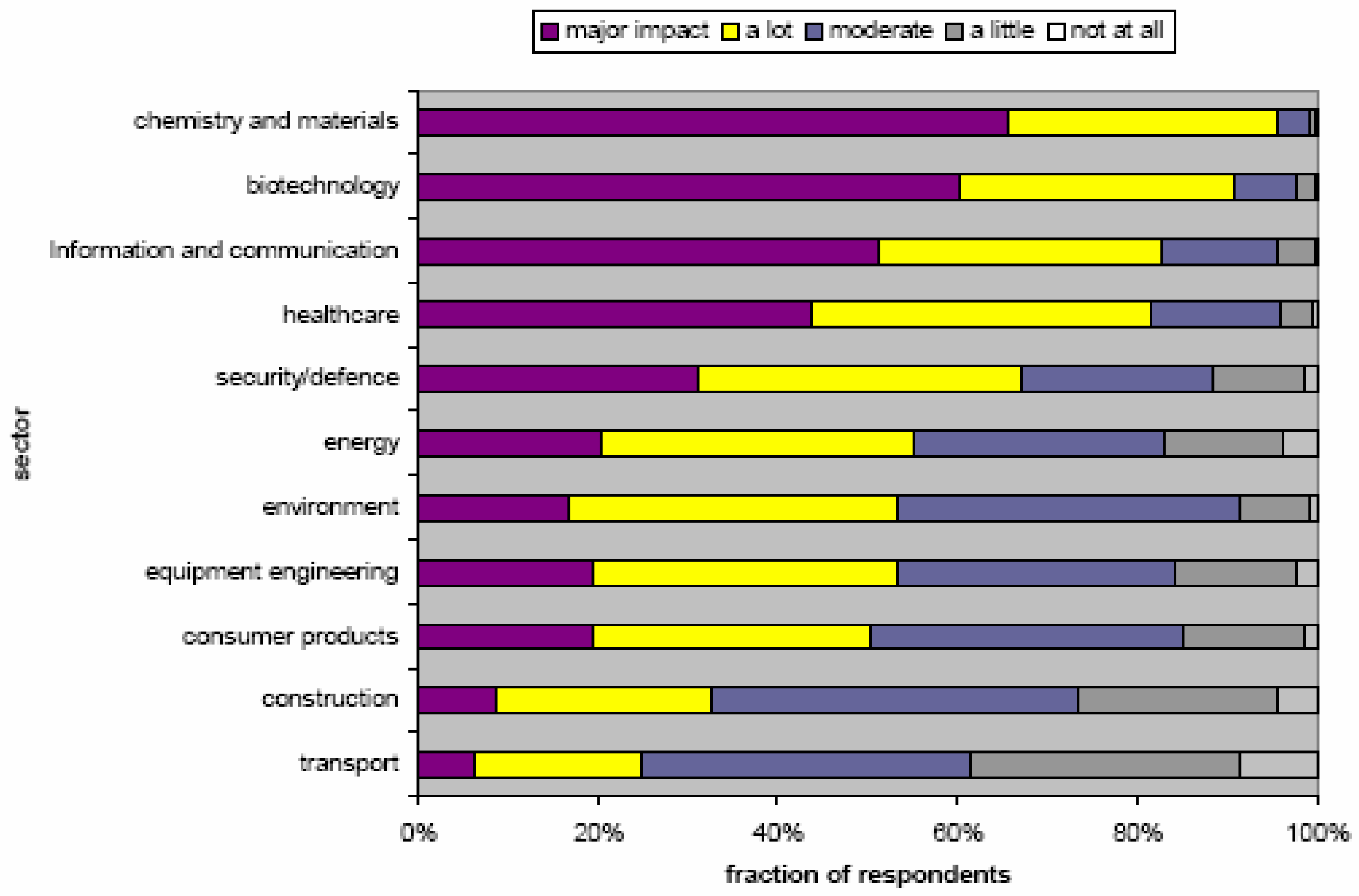
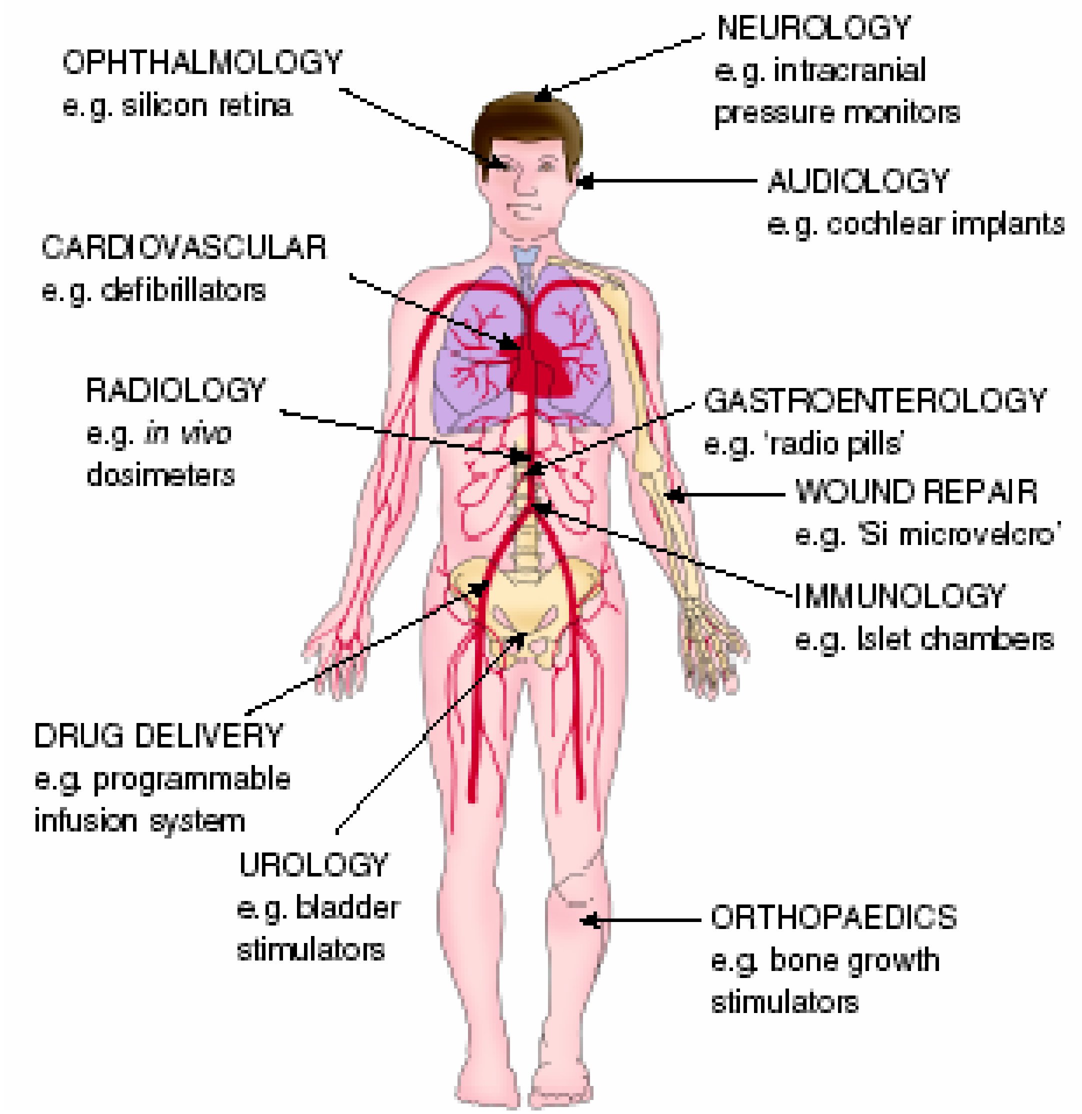


Figure 6 Respondents views on the question "Will nanotechnology have an impact on the following sectors?" Excluded are the respondents who did not express a forecast.

Large R&D focus at implanted sensors

- Reduce Surgical Trauma
- Shorten Patient Recovery Times
- Enhance Patient Quality of Life
- Increase Life Expectancy
- Reduce Healthcare & Social Care Costs

Therapeutic MEMS examples



Current commercial and research status

	Commercial status	Research activity	Potential clinical impact
Cardiovascular	H	H	H
Dentistry	L	L	L
Dermatology	L	L	L
Drug delivery	M	H	H
Endocrinology	M	H	H
Gastroenterology	M	H	H
Genetic engineering & gene therapy	L	M	M
Intensive care	M	L	H
Neurology	H	H	H
Obstetrics & gynaecology	L	L	M
Oncology	M	M	H
Ophthalmology	L	M	M
Orthopaedics	L	M	H
Otology	H	H	H
Paediatrics	L	L	M
Pathology	L	L	L
Physiotherapy	M	M	M
Radiology	M	L	H
Rehabilitative medicine	M	H	H
Respiratory medicine	M	L	M
Surgery (general & minimally invasive)	M	H	H
Sports medicine	L	L	L
Tissue engineering	L	M	M
Transplantation & immunology	L	M	H
Urology	M	M	M
Wound care	L	L	M

Commercial status, commercial availability of MEMS-based implants or devices; Research activity, level of commercial and/or academic research interest; Clinical impact, level of potential impact on mainstream clinical practice.

L, low; M, medium; H, high.

Commercial status

- Most mature MEMS areas
  - Cardiovascular
    - **where pacemakers are gradually being supplemented by other devices such as defibrillators, and ventricular assist devices.**
  - Neurology
    - **where neurostimulators are used to treat a wide range of neurological conditions.**
  - Otology
    - **based primarily on cochlear implants for sensorineural deafness.**
  - Oncology
    - **primarily through the use of programmable drug infusion devices.**
  - Diabetes (endocrinology)
    - **Insulin pumps, mainly**

Highest research activity expected: 8 areas

- Cardiovascular
- Drug delivery
- Endocrinology
- Gastroenterology
- Neurology
- Otology
- Rehabilitative medicine
- Surgery

Research challenges

Table 4.1 – Summary of Generic Issues

Generic issue	Current approach	Potential solution(s)	Future benefit(s)
Interfacing with the body	Hybrid packaging for biocompatibility	Monolithic silicon structures	Further miniaturisation
3D microfabrication	Wafers & planar lithography	Novel lithography or flexible substrates	Shape & complexity
In vivo sensing	Sensor protection via biomembrane	Redundancy via microarrays	Accuracy and stability
In vivo powering	Batteries or inductive coupling	Biofuel cells	Miniaturisation & no surgical replacement
Data transmission	Implantable RF telemetry	Implantable/wearable systems	Well-being monitors and telemedicine

Cardiovascular

Box 5.1: Opportunities for silicon technology in cardiovascular treatment

Opportunities for microelectronic implants in the cardiovascular area include the following:

- **Sensor systems for rate-adaptive pacing**: the addition of one or more sensors to monitor physiological activity and alter cardiovascular parameters accordingly.
- **Smarter and more active catheters and stents**: adaptive catheters and stents which, for example, elute drugs or change position or shape when an attached sensor deems it necessary.
- **Cardiac well-being monitors**: protective rather than therapeutic monitors whose role is to log physiological parameters and provide early warning of disease.
- **One-shot disposable sensors**: low-cost, chip-based systems that can provide physiological parameters after short contact with blood.

Drug delivery

Box 8.1: Opportunities for silicon technology in drug delivery

The recent discovery that the semiconductor can be made biodegradable like polymers such as PLGA and polycaprolactone, opens up the full spectrum of different routes of drug administration to silicon technology. Examples include:

- **Oral 'ticking tablets' for timed delivery to the colon**: tiny electronic timing devices could be combined with electrical control of drug release to deliver to the necessary part of the GI tract.
- **Smarter transdermal patches with on-chip reservoirs**: iontophoretic chip-based systems could have drugs incorporated in a porous reservoir on the inner side and associated electronics/display on the outer side.
- **Micromachined multi-reservoir parenteral depots**: combined micromachining and biodegradability in silicon offers controlled and extended delivery of a cocktail of drugs in a predetermined sequence.
- **Monodisperse microparticles for inhalation therapy**: photolithographic definition of both particle size and shape promises better control over aerosol deposition within the lung.
- **Microtagging of pharmaceutical products**: remotely addressable smart labels for tracking, anti-counterfeiting and improving administration of drugs.

Endocrinology

Box 9.1: Opportunities for silicon technology in endocrinology

Opportunities here focus primarily on advanced sensors and monitoring systems:

- **Minimally invasive glucose monitoring**: one example would be the use of microneedle arrays to extract interstitial fluid in a pain-free manner.
- **Closed-loop glucose monitoring/insulin delivery**: chip-based, implantable system that regulates delivery of insulin by monitoring of blood glucose levels.
- **Immunoisolation chambers for diabetics**: foreign insulin-secreting cells, protected from the patient's immune system by a porous silicon filtration capsule (Figure 9.3).

The diabetes market is immense with a huge, currently unmet, need for less invasive testing. It is also a highly competitive and challenging area. Solutions for other endocrine disorders also look promising.

Gastroenterology

Box 10.1: Opportunities for silicon technology in gastroenterology

In summary, future applications in the gastroenterology area include:

- **Smarter and micromachined tablets**: pills that can be remotely activated to release their drug in a controllable way and at a specific time or location.
- **Swallowable diagnostic microsystems**: there is sufficient room in the GI tract for advanced telemetry pills to incorporate both imaging and sensing capabilities.
- **Electrical stimulation devices**: implantable pulse generators for treating malfunctioning of the digestive process due to diseases such as diabetes, scleroderma, ileus and gastroparesis.

Neurology

Box 13.1: Opportunities for silicon technology in neurology

- **Electrostimulation technology**: implantable microelectronic systems for treating tremor, epilepsy, Parkinson's disease and severe depression.
- **Neuro-interfacing**: microelectrode systems for activity recording that contain integrated sensing and data processing capabilities.
- **Microdialysis**: minimally invasive probes for extracting and analysing cerebrospinal fluid and tissue fluid.

Otology

Box 18.1: Opportunities for silicon technology in otology

Microelectronic implants have had spectacular success in this area but the largest commercial market is undoubtedly that of moderate hearing loss:

- **Further development of middle ear implants**: better nerve interfacing and signal processing.
- **Exploitation of micromachining in ultrasmall microphones**: less and less obtrusive hearing aids.

Rehabilitative medicine

Box 23.1: Opportunities for silicon technology in rehabilitative medicine

- **More closed-loop-like FES systems**: by the linking of motion microsensors to electrical stimulation circuitry, some degree of biofeedback can improve system performance.
- **Implantable multichannel FES systems**: the use of micromachining to integrate multichannel cuff electrodes with multiplexer circuitry and thereby minimise *in vivo* leads.

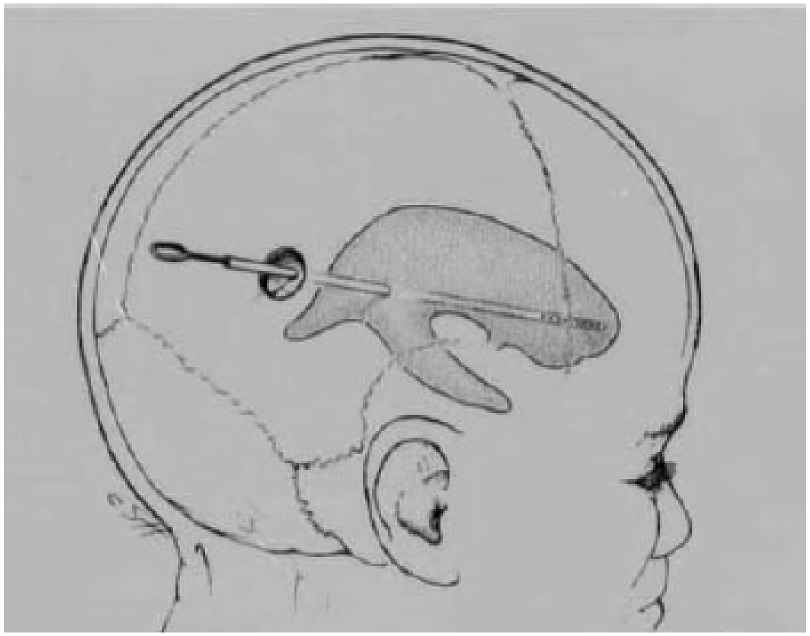
Surgery

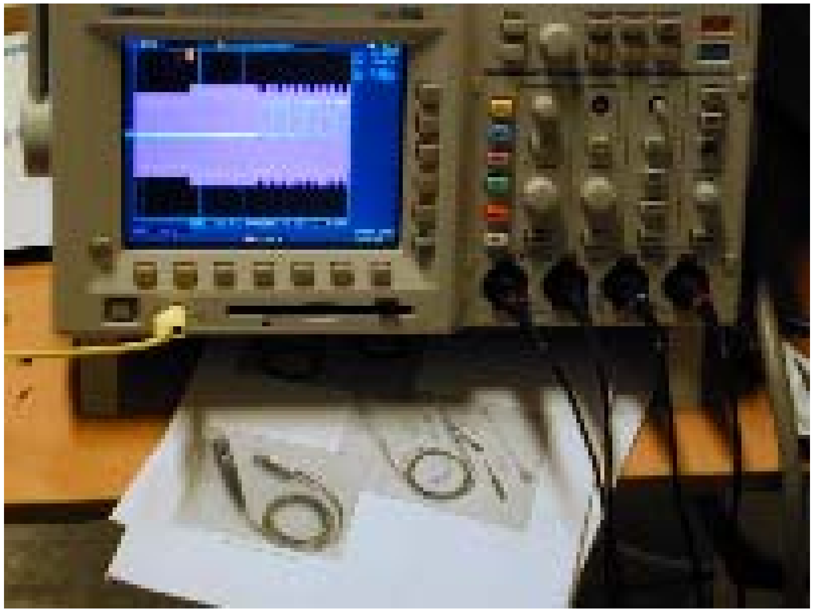
Box 26.1: Opportunities for silicon technology in surgery

- **Smart catheters** enhanced with a variety of sensors, actuators and imaging devices.
- **MOEMS (micro-optical-electromechanical systems)** for various forms of endoscopy.
- **Haptic sensor-incorporated tools**: automated surgical tools with, for example, pressure sensors to provide the surgeon with tactile feedback as to forces being applied.
- **Micromachined tool parts for microsurgery**: precisely engineered tools such as microgrippers, smart scalpels and so on.

Activities at SINTEF ICT.

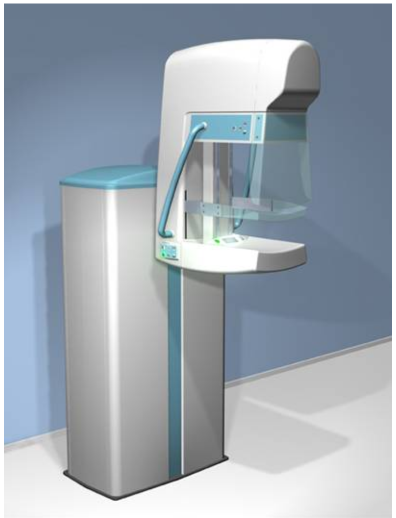
Measurement of inter cranial-pressure



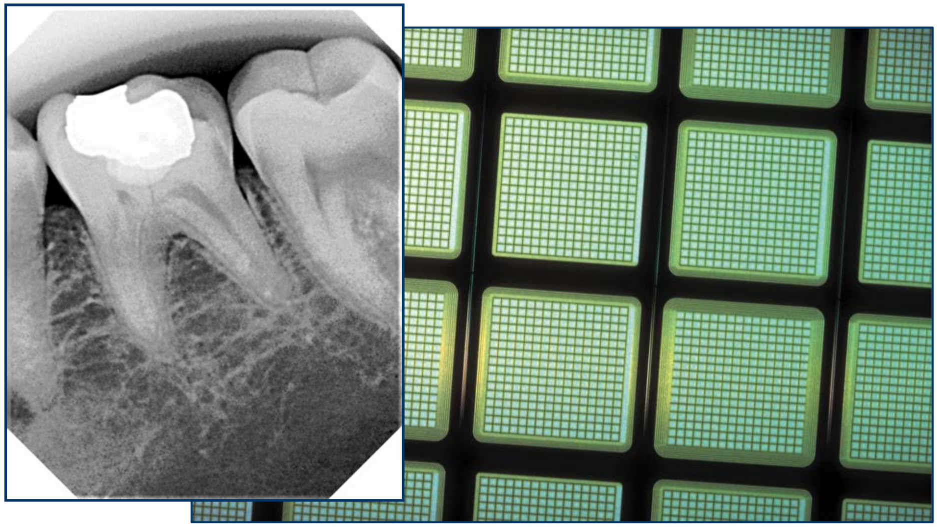


Solid state silicon radiation detectors for medical imaging.

- Micro strip detectors for mammography
- Pixel detectors for dental x-ray
- Pixel detectors for CT scanning.
- Micro strip detectors for screening of isotope labeled nucleotides

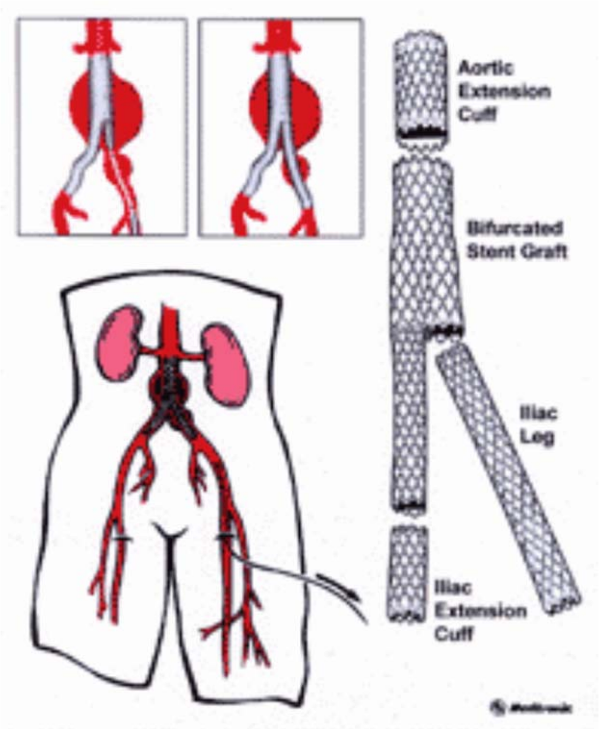


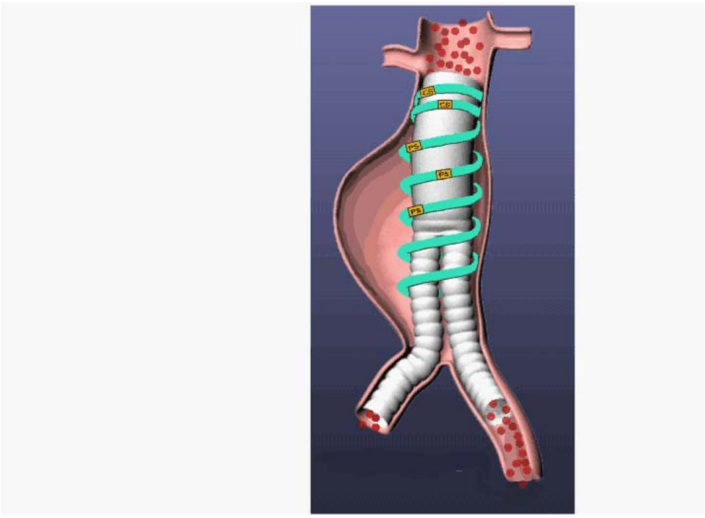
Mamea Imaging AB

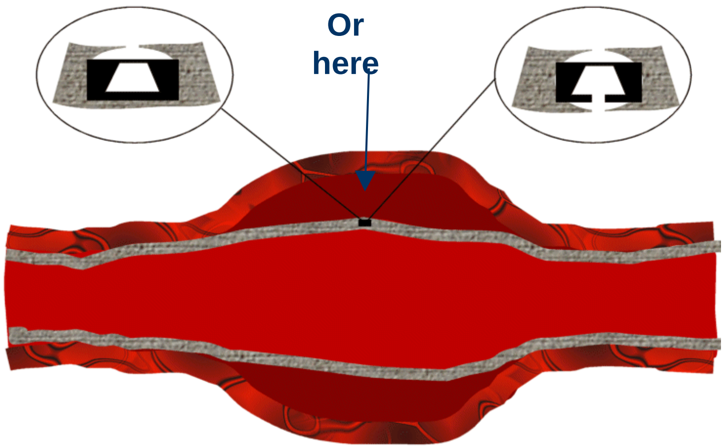


Stent graft sensing

- AAA: Abdominal Aortic Aneurism
- Mission - improving the long term reliability of AAA stent grafts
- The Product - introducing an add-on to the AAA stent grafts to enable a real time monitoring device to alert for possible sudden rupture and endo-leaks.

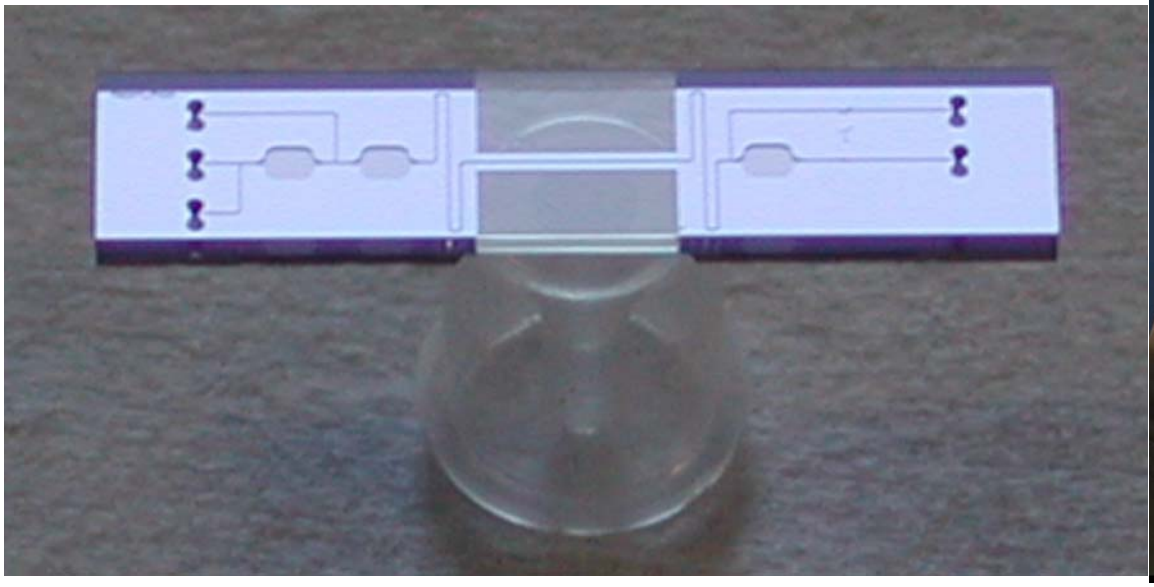


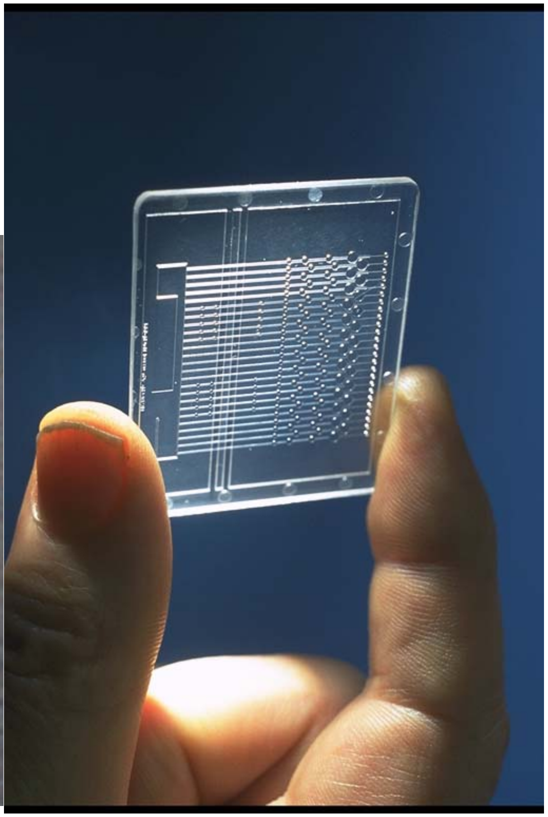




Lab-on-a-chip for diagnostics based on mRNA anaylsis

- Microfluidic handling
- Real-time RNA amplification
- Fluorescent read-out.

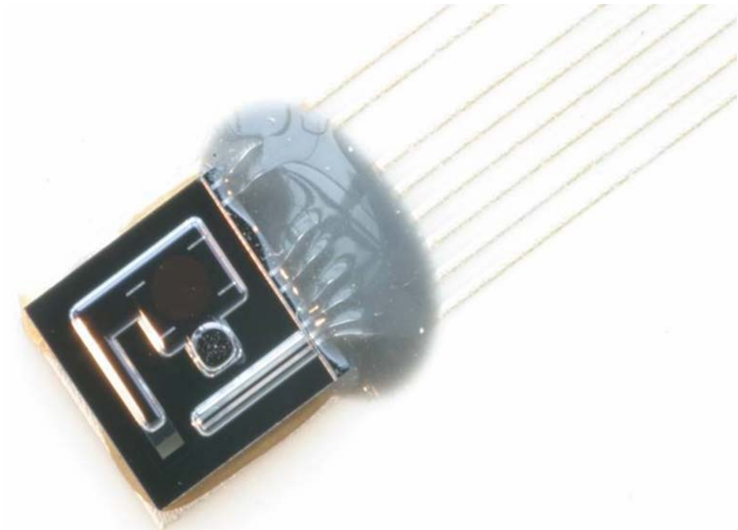


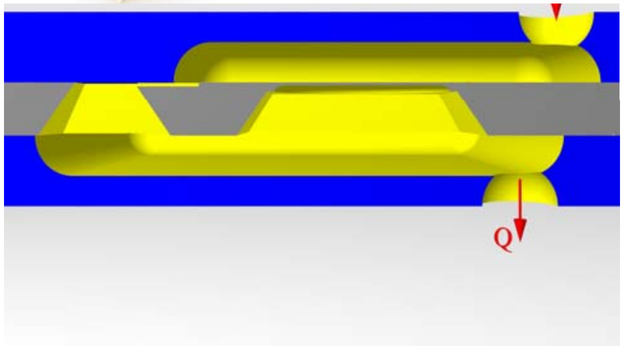


Flow sensor

- Application: Reagents flow measurements, dosing of drugs
- Fluid flow through chip
- Differential pressure sensor
- Protected conductors/resistors

- Typical flow rate 5 μl/min
- Laminar flow, low Re numbers
- Narrow channel, Pouseille flow





$$\Delta p = \frac{12 \cdot \eta \cdot l \cdot Q}{w \cdot h^3}$$

- Channel: 800x1500x10 μm
- Pressure drop ~ 100 -200 Pa

- Integrated temperature sensor

Conclusion

- Medical sensors and BioMEMS is a rapidly growing field.
- Many novel sensors products are under development or already on the market
- Future medical sensors will require
  - Small low cost, low power sensors
  - Remote power generation
  - Wireless communication
  - Nanotechnology and advanced functional and bio compatibel materials
- The field is highly inter disiplinary
  - Requires arenas and projects http://biox.stanford.edu/
  - Education
- The MiNaLab facility at SINTEF enables Norwegian industry and scientists to utilize new technology for new products and reserach tools.