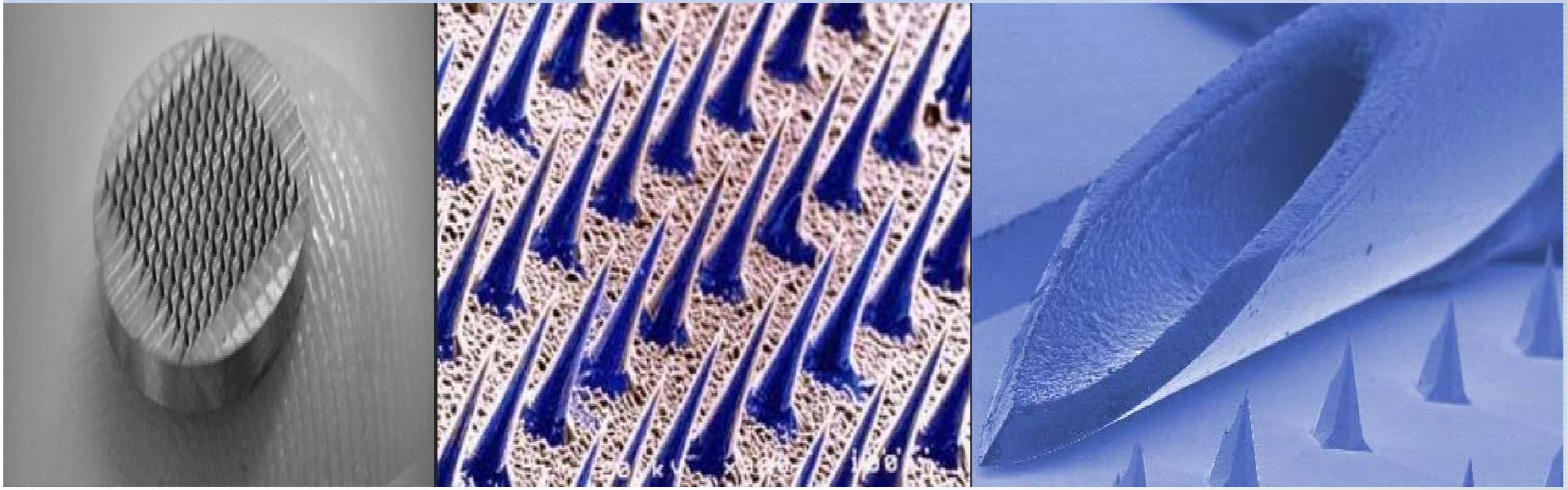
Theoretical And Practical Approach For Transdermal Drug Delivery Using **MICRONEEDLES** For Successful Skin Penetration



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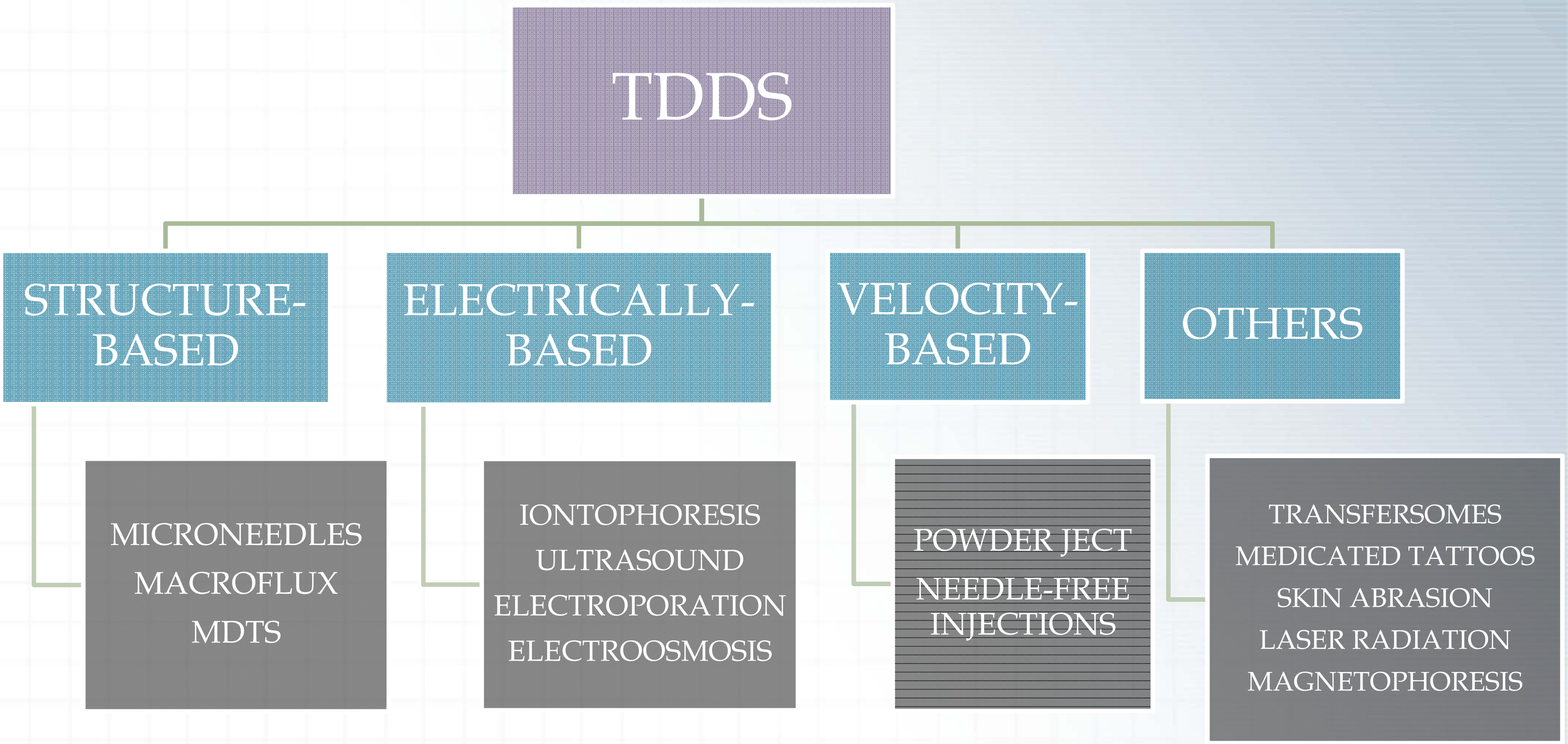
TALK FLOW

- Introduction to TDDS
- Why Microneedles
- Finite Element Method Analysis
- Computational Fluid Dynamics
- Comparison of Microneedle Materials
- Challenges & Future Aspects
- References

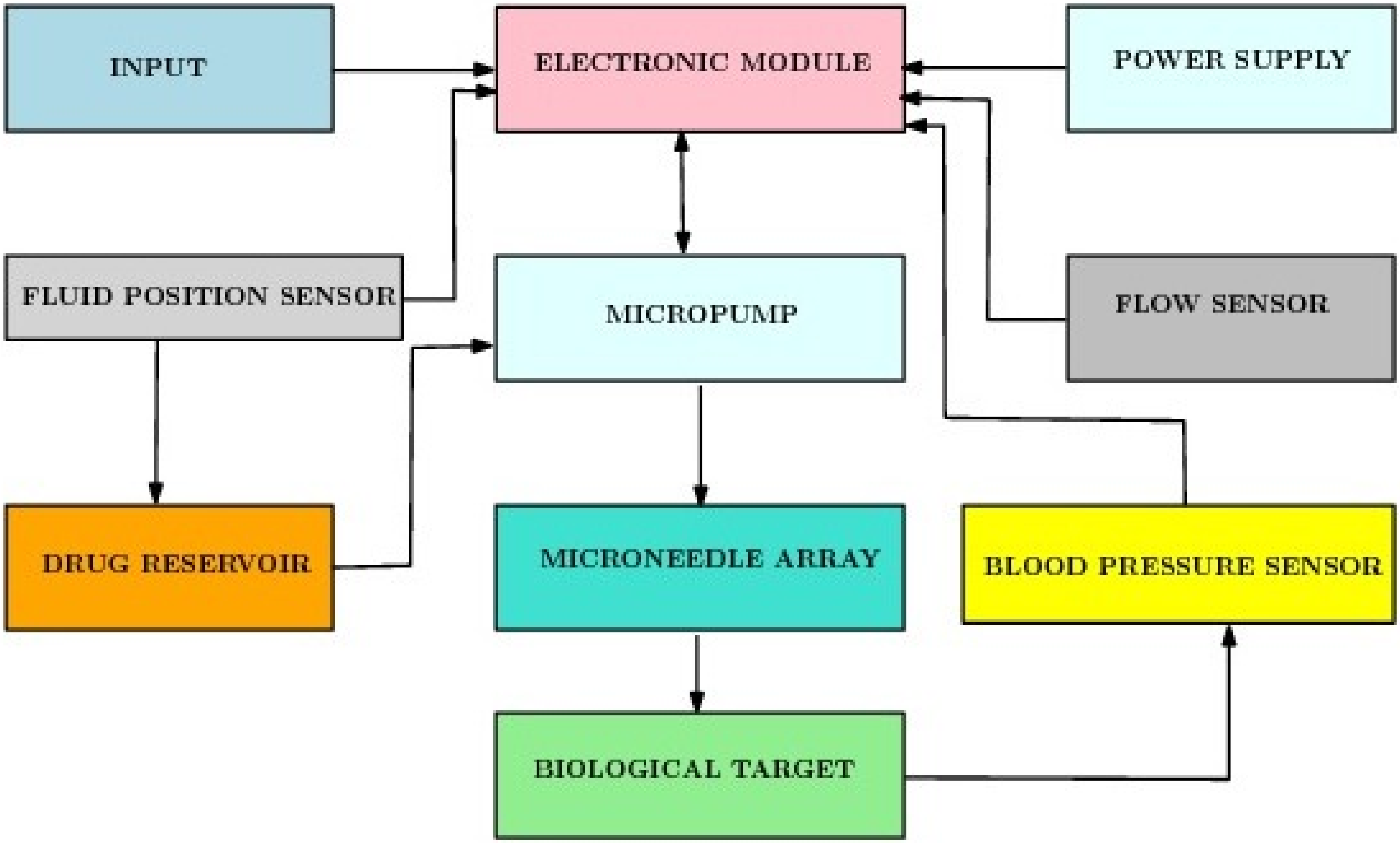
TRANSDERMAL DRUG DELIVERY SYSTEMS



- TDDS
  - STRUCTURE-BASED
    - MICRONEEDLES
    - MACROFLUX
    - MDTS
  - ELECTRICALLY-BASED
    - IONTOPHORESIS
    - ULTRASOUND
    - ELECTROPORATION
    - ELECTROOSMOSIS
  - VELOCITY-BASED
    - POWDER JECT
    - NEEDLE-FREE INJECTIONS
  - OTHERS
    - TRANSFERSOMES
    - MEDICATED TATTOOS
    - SKIN ABRASION
    - LASER RADIATION
    - MAGNETOPHORESIS

Fig(1): Block diagram for TDDS

INTEGRATED BIOCHIP FOR DRUG DELIVERY



Fig(2): Block diagram for integrated biochip

DRAWBACKS OF HYPODERMIC NEEDLES

- Requirement for trained personnel for administration.
- Poor patient compliance.
- Unintended bleeding.
- Hazard of needle-stick injuries to healthcare workers.
- Unreliable and uncontrolled delivery.
- Potentially dangerous biological waste.

NOTE: According to WHO, more than 1.3 million early deaths and cost of US $ 535 million in direct medical cost are attributed annually to unsafe injection practice.

WHY MICRONEEDLES ?

- Micron-scale needles for transdermal vaccination and painless drug delivery.
- Reduces tissue damage and systemic toxicity.
- Reliable and controlled delivery.
- Potential of self-administration.

COMPARISON BETWEEN HYPODERMIC NEEDLES AND MICRONEEDLES

PARAMETERS	HYPODERMIC NEEDLES	MICRONEEDLES
NEEDLE LENGTH	2500-3500 µm	400-600 µm
NEEDLE DIAMETER	550 µm	90-150 µm
NEEDLE DENSITY	<15/cm²	2000/cm²
PAIN	PAIN FELT	PAIN NOT FELT
CHANCE OF INFECTION	Pretty High	Negligible
EASE OF ACCESS	Needs a Trained Professional	Easy to Use
COST	Low Cost	Initially High Cost
APPLICATION	On Overall Areas	Except Stiff Areas

Table(1): Hypodermic needles vs. microneedles

MICRONEEDLE MECHANICS

- Transition slenderness ratio : $(L/r)= \surd(2\pi^2E/S_y)$
- L/r depends only on geometry and Young’s modulus of the material.
- The theoretical pressure required to pierce human skin is 3.183×10^6 Pa.
- Fmaxbuck= $c\pi^2E\,(I_1 + I_2)\,/L^2$ where c=0.25, E= 169GPa for silicon, I(m^4)= $\Pi(d0^4-di^4)/64$ for hollow cylindrical cross-section, $r=\surd(I/A)$
- Fmaxfreebend= $\sigma_y\,(I_1 + I_2)/cL$ where c is the distance of the neutral axis to the outermost edge of the microneedle, c=D/2, σ_y = yield strength

MICRONEEDLE MECHANICS(Continue…)

Skin Force	**$P_{piercing}$**	**A**	**F_{skin}**
Initial state	3.18MPa	53.38 μm^2	1.69mN
After insertion	1.6MPa	100.78 μm^2	0.161mN

Table(2): Calculation of skin force

$F_{maxcompressive} = \sigma_y A$, Where A=Area of Microneedle tip= $\pi\ (RL+rl+R^2-r^2)$

R=Outer radius of the tip
r=Inner radius if the tip
L=Outer slant height of the tip
l=Inner slant height of the tip

$F_{skin} = P_{piercing}A$, where A= Area of insertion

CALCULATION OF MAXIMUM COMPRESSIVE FORCE

Material	**Yield Strength(σ_y)**	$F_{maxcompressive}$
Si	7GPa	373.66mN
SiO_2	8.4GPa	448.39mN
Si_3N_4	360MPa	19.21mN
Glass	3.6GPa	192.17mN
PMMA	120MPa	6.405mN
PLGA	46.1MPa	2.46mN

Table(3): Calculation of compressive force

Assumptions and calculated values:-

R=2 µm, r=1 µm, L=5 µm, l=4 µm, A=53.38 μm^2

CALCULATION OF MAXIMUM BENDING FORCE

Material	**Yield Strength(σ_y)**	**$F_{maxfreebend}$**
Si	7GPa	1.7mN
SiO_2	8.4GPa	2.142mN
Si_3N_4	360MPa	0.918µN
Glass	3.6GPa	91.8 mN
PMMA	120MPa	0.0306 mN
PLGA	46.1MPa	0.117 µN

Table(4): Calculation of bending force

$F_{maxfreebend} = \sigma_y (I_1 + I_2)/cL$

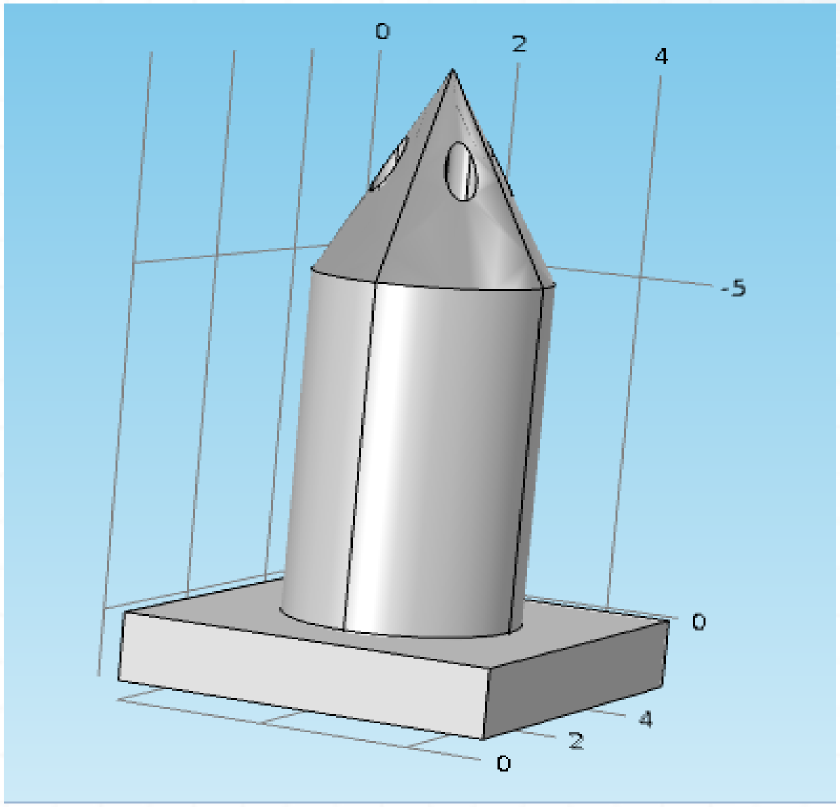
Where;

$I_1 = (\pi/64)(D^4 - d^4)$, $I_2 = Dy^3/396$

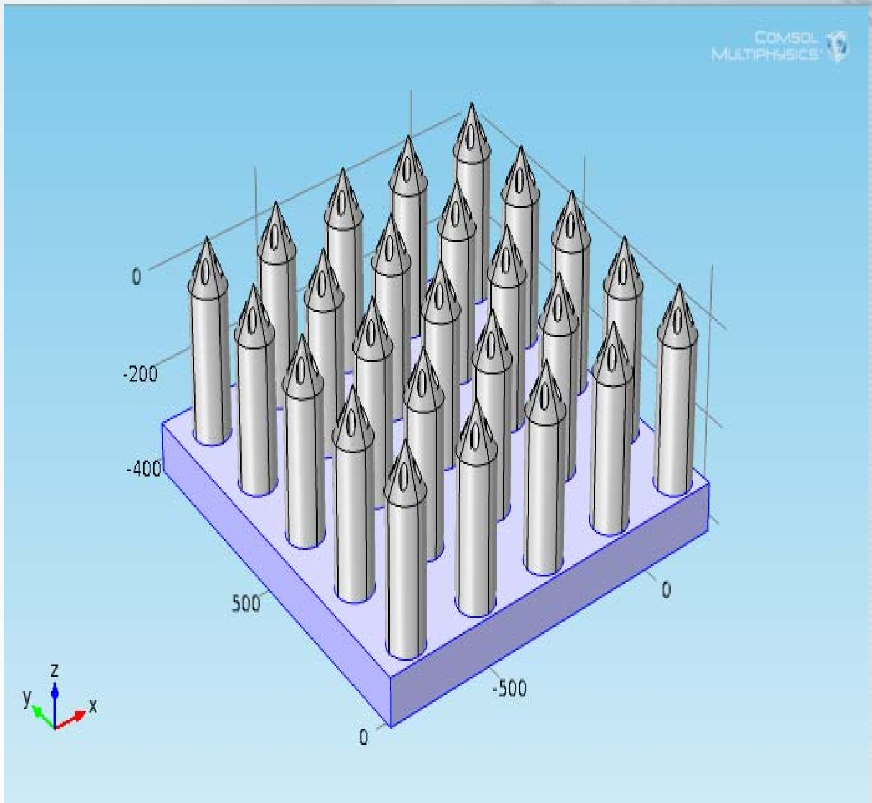
Assumptions and calculated values:-

D=50µm, d=40µm, y=103.07µm, $I_1=1.81\text{x}10^{-19}$m, $I_2=1.38\text{x}10^{-19}$m

STRUCTURAL DESIGN OF MICRONEEDLES

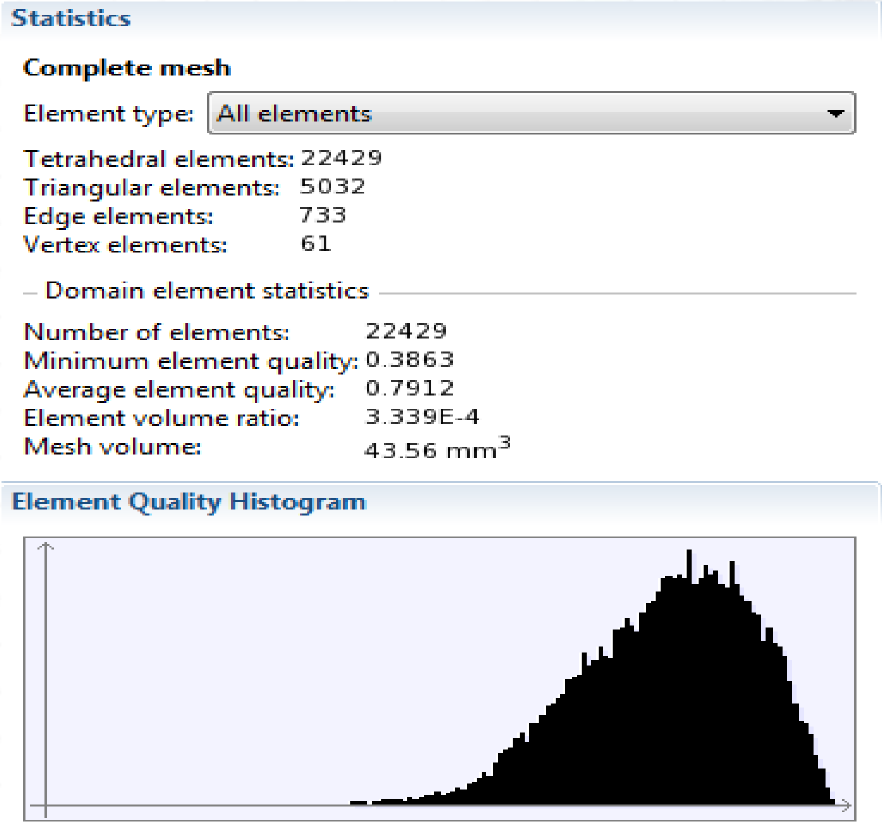


Fig(3): A single microneedle



Fig(4): 5 x 5 microneedle array

STRUCTURE ANALYSIS (FINE MESH)



Statistics

Complete mesh

Element type: All elements

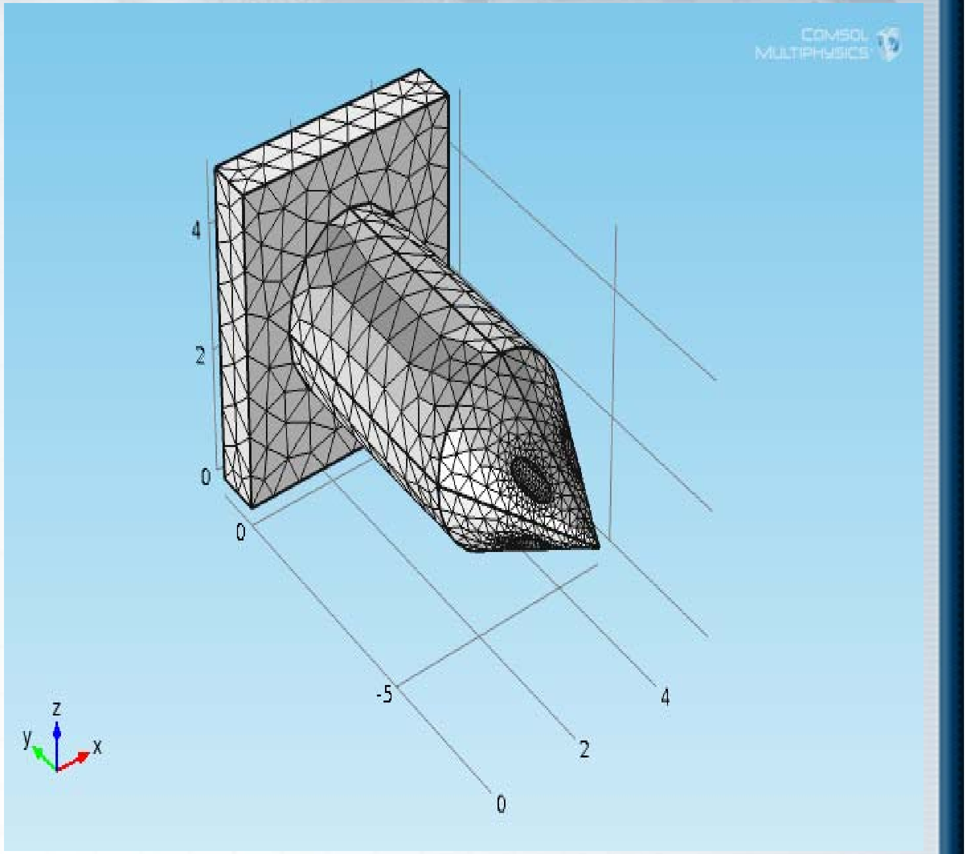
Tetrahedral elements:	22429
Triangular elements:	5032
Edge elements:	733
Vertex elements:	61

Domain element statistics

Number of elements:	22429
Minimum element quality:	0.3863
Average element quality:	0.7912
Element volume ratio:	3.339E-4
Mesh volume:	43.56 mm^3

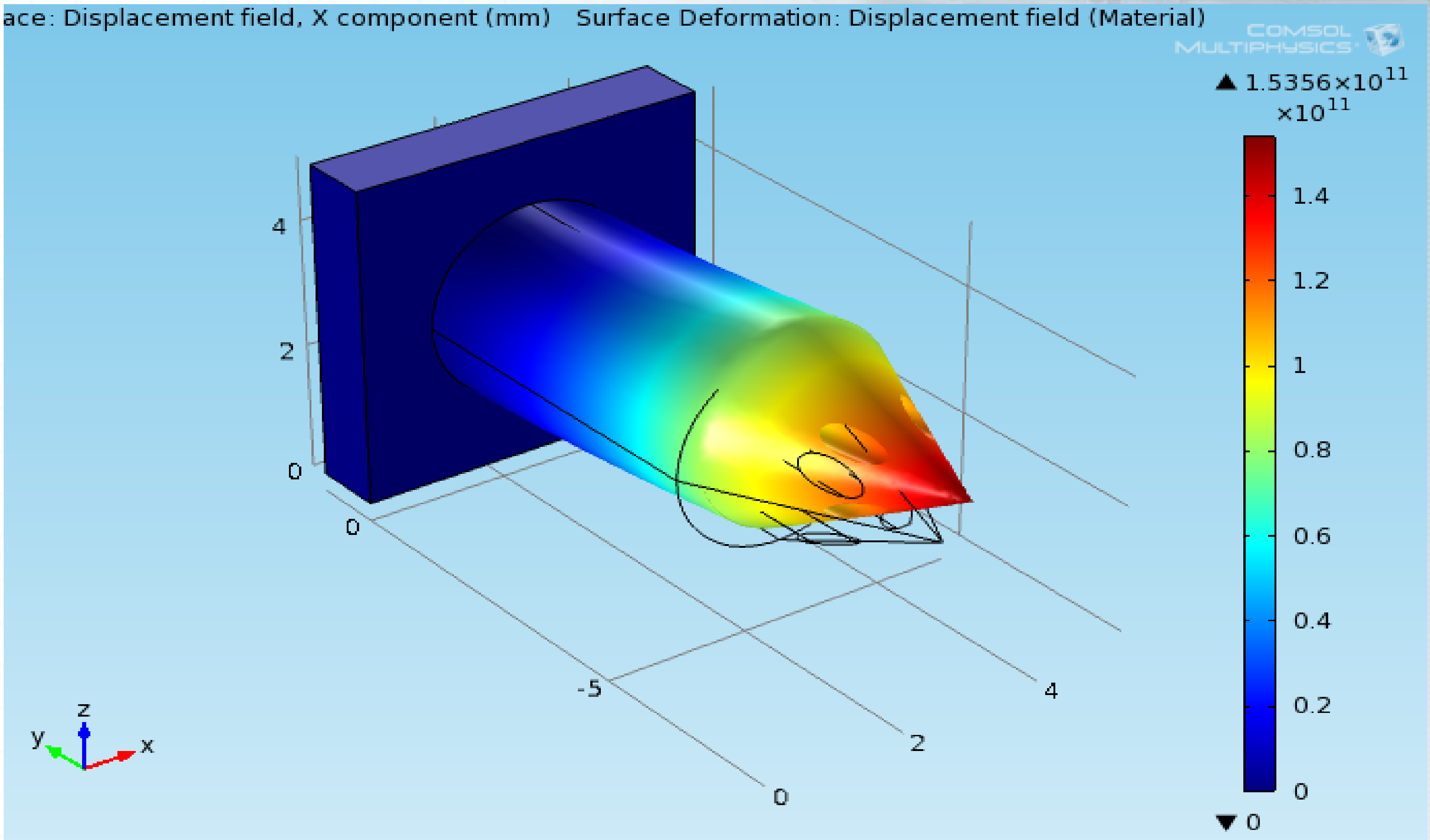
Element Quality Histogram

Fig(5): Mesh analysis



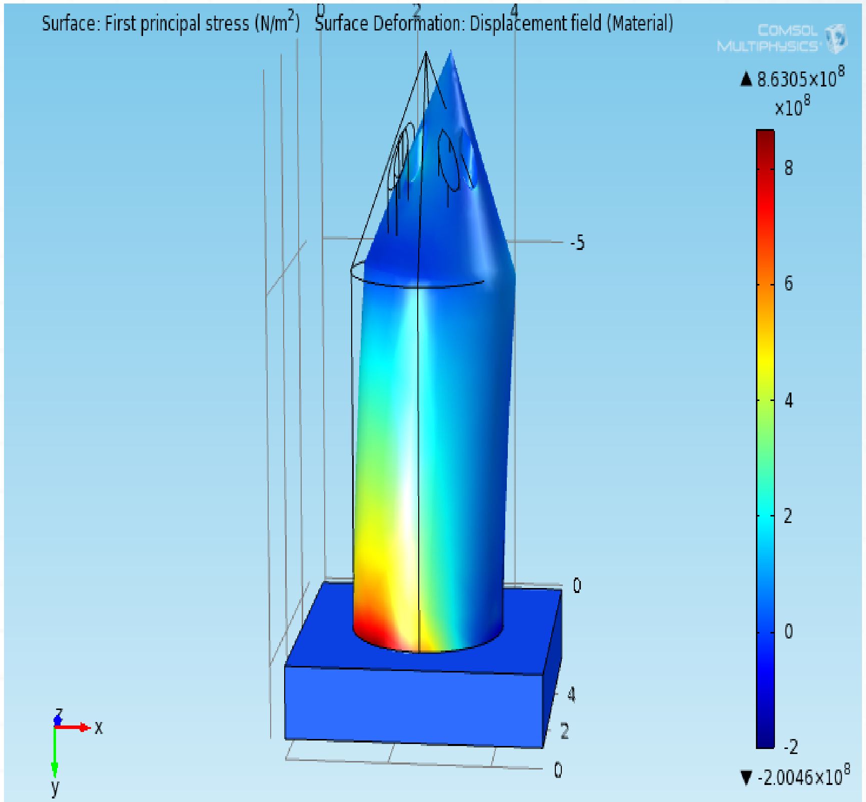
Fig(6): Microneedle mesh structure

STRESS ANALYSIS OF A MICRONEEDLE

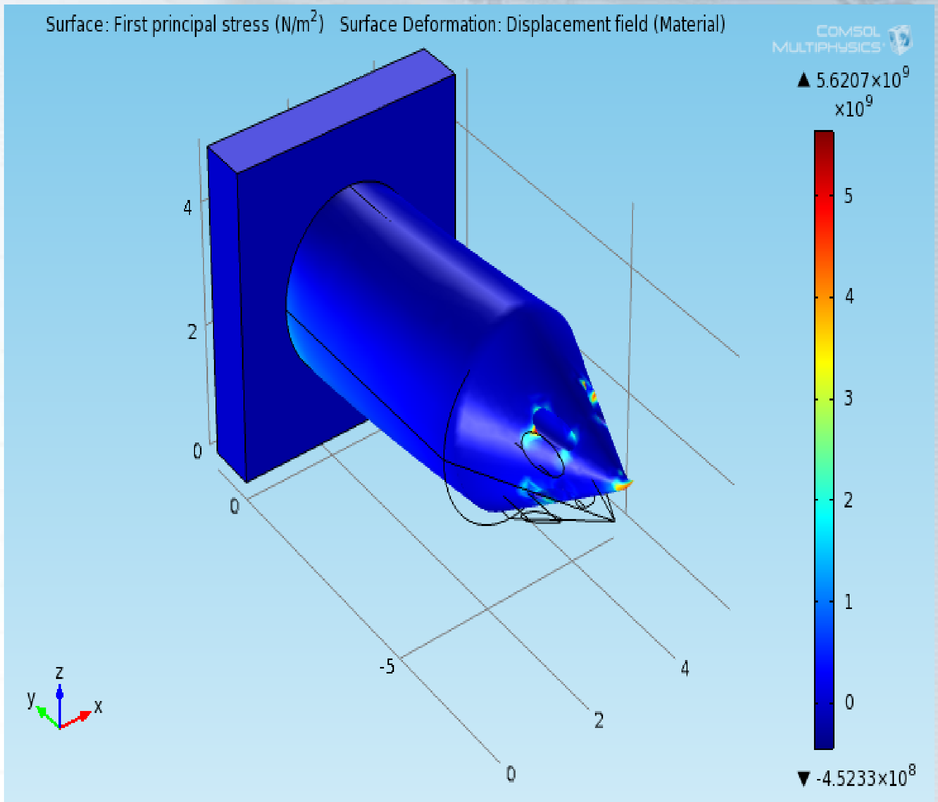


Fig(7): A single microneedle stress analysis

STRESS VS. DISPLACEMENT

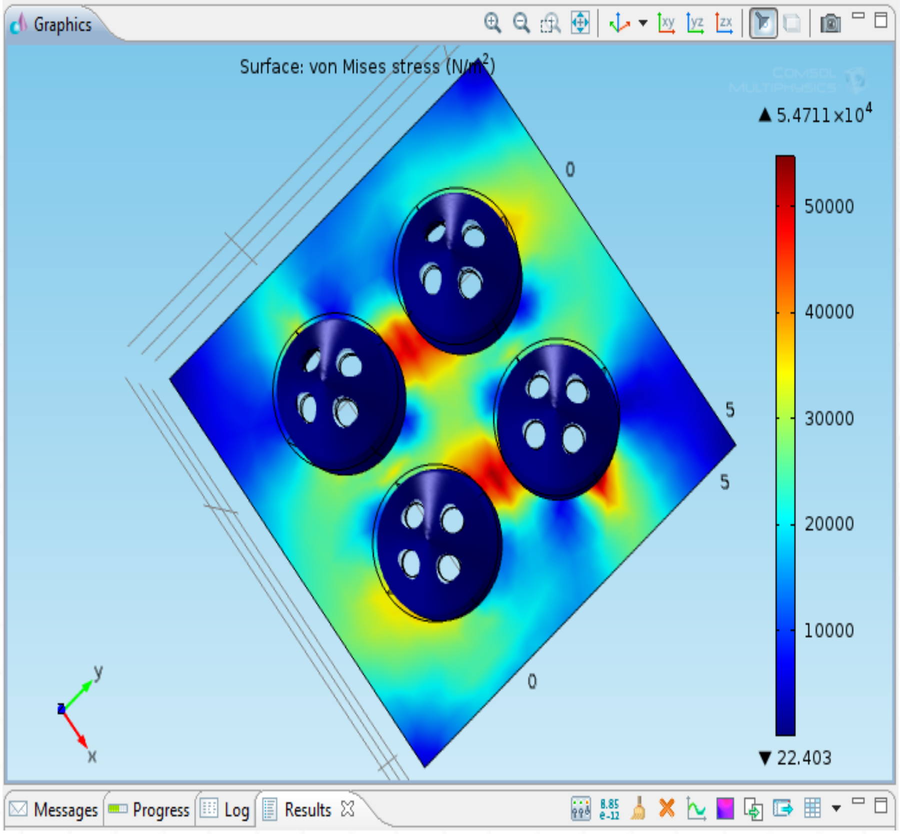


Fig(8): Boundary load : 10 N
No point load.
No body load

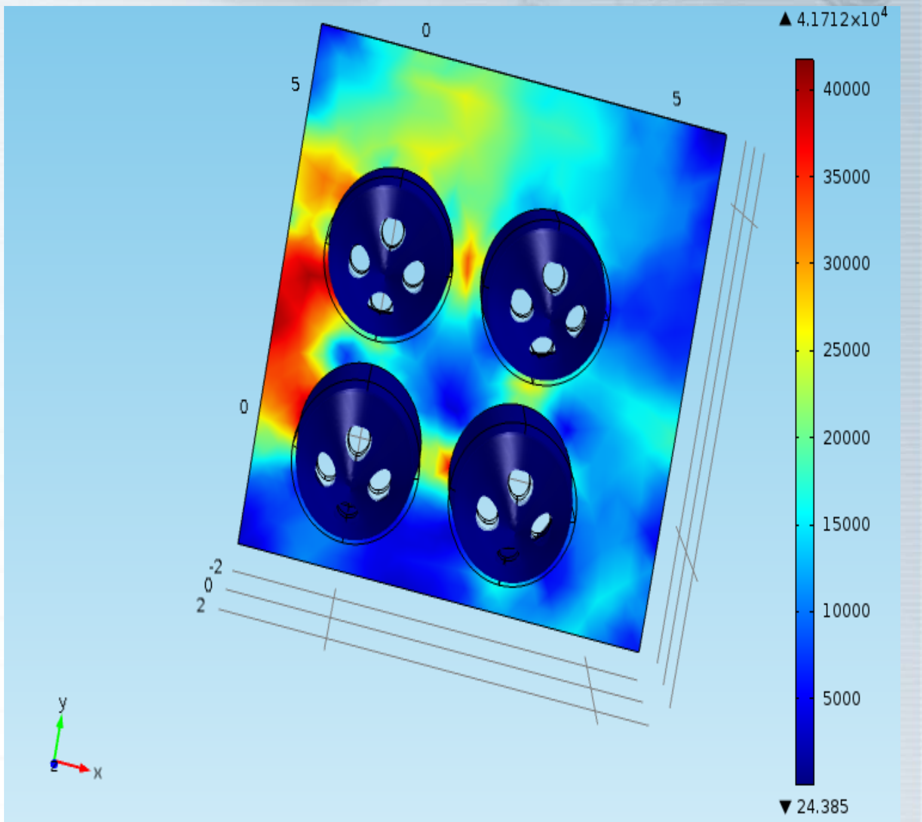


Fig(9): Point load : 10 N
Body load : 10 N/m3
Boundary load : 5 MPa

STRESS ANALYSIS OF ARRAY OF MICRONEEDLE

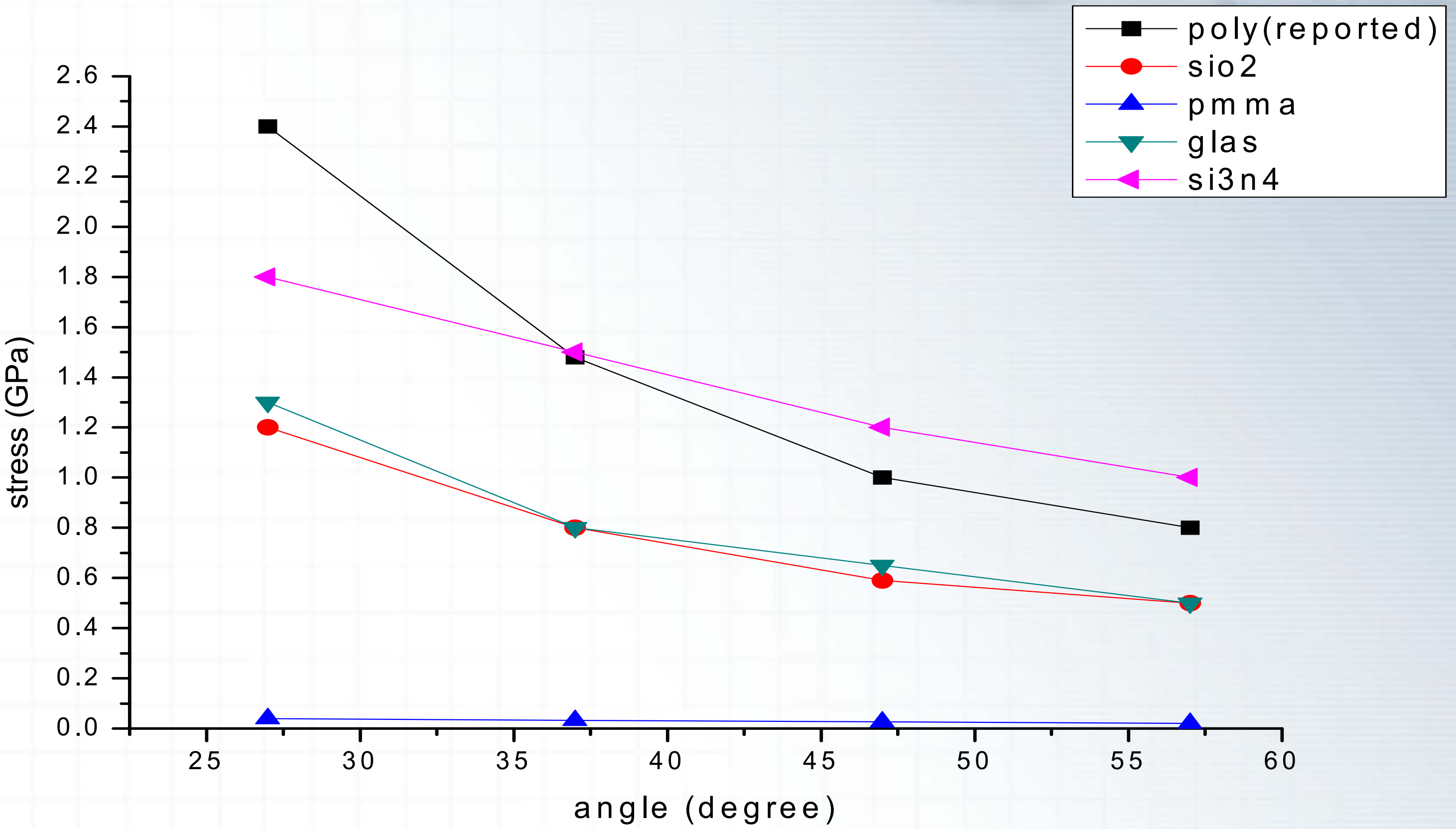


Fig(10): Uniform distribution of microneedle on wafer area



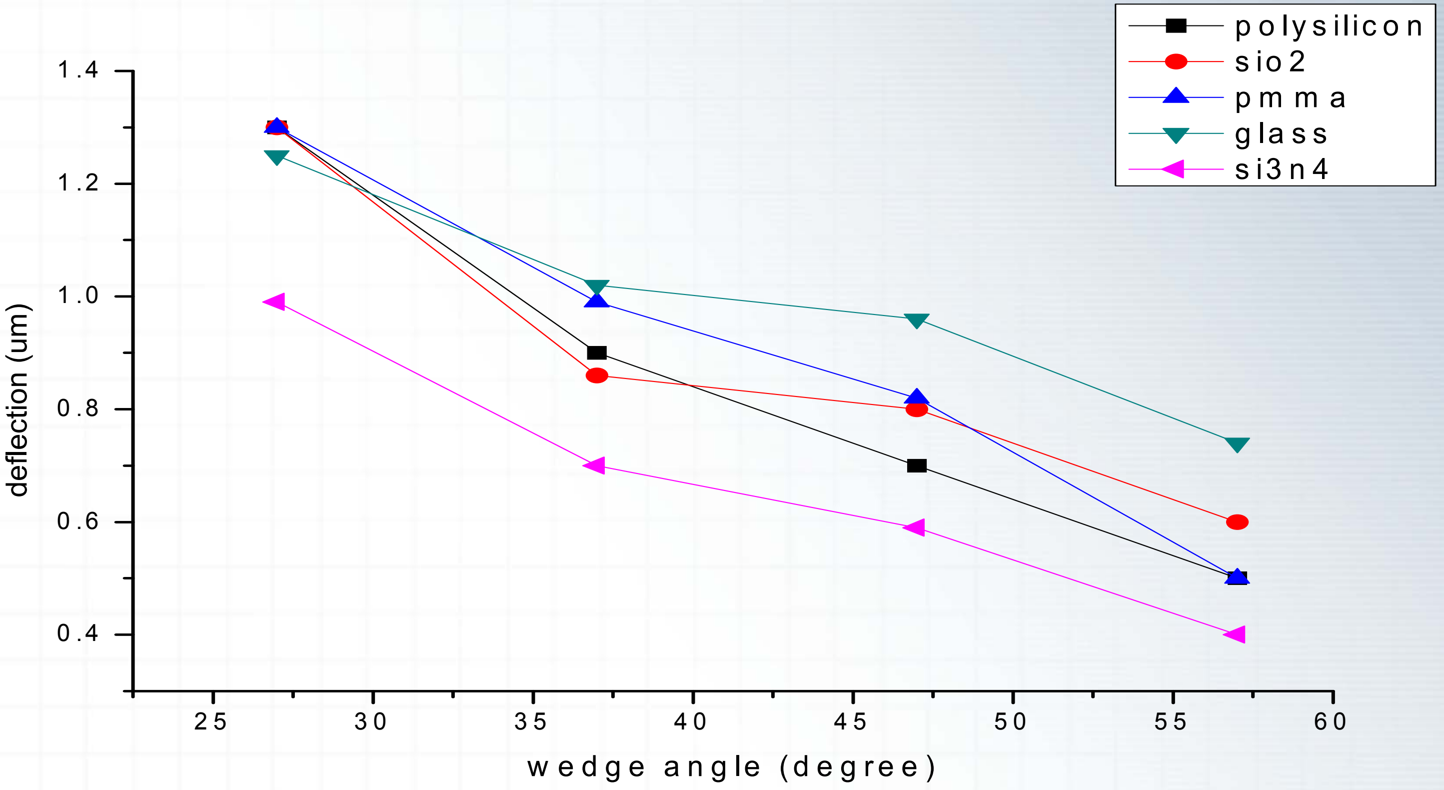
Fig(11): Non uniform distribution of microneedle on wafer area

STRESS VERSUS WEDGE ANGLE



Fig(12): In every material stress decreases with increase in wedge angle. And among all the material stress is minimum in the case of polymer (PMMA).

DEFLECTION VERSUS WEDGE ANGLE



Fig(13): Deflection in all the material decreases with increase in wedge angle.

Minimum deflection is of Silicon Nitrate.

CALCULATION OF FLOW RATE

- Poiseulle's law of fluid flow is considered to determine fluid flow through array of microneedle:

$Q = (\pi * d^4 * p)/ 128\ \mu\ L$

PARAMETERS	EXAMPLE1	EXAMPLE2	EXAMPLE3
Channel diameter(μm)	40	40	50
Channel length(μm)	400	500	400
Flow rate (μL/s)	0.157	0.126	0.385
Pressure drop, Pa	1×10^3	1×10^3	1×10^3
Water density(kg/m^3)	1000	1000	1000
Dynamic viscosity(Pa-s)	0.001	0.001	0.001

Table(6): Calculation of flow rate

FLUID FLOW THROUGH MICRONEEDLES

Reynold’s number is defined as a ratio of inertial to viscous forces, given by:

- $Re = Du\rho/\mu$, laminar flow
- u= magnitude of velocity; (1m/s)
- ρ= fluid density; (1000kg/m^3)
- μ= fluid viscosity; (0.001 N-s/m^2)
- D= diameter of microneedle lumen. (40μm)

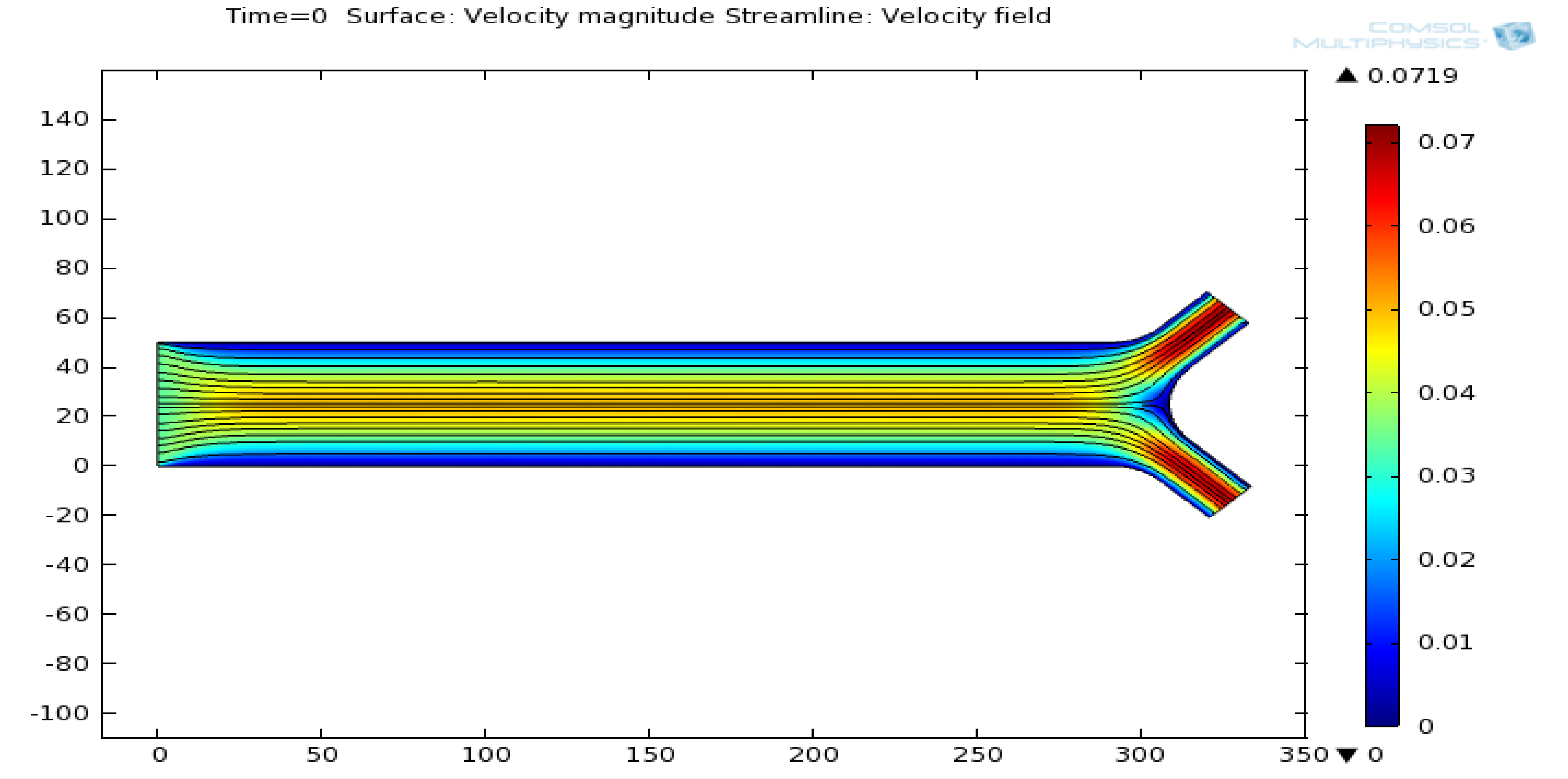
- $Re = \rho DV/\mu$
- $Re = (1000\ kg/m^3 \times 1m/s \times 0.00004m)/\ 0.001\ N\text{-}s/m^2 = 40.0$
- In this example, water is taken as the fluid and the flow is laminar.

COMPUTATIONAL FLUID DYNAMICS

- Incompressible Navier-Stokes equations for the velocity field, $u = (u, v)$, and the pressure p, in the spatial (deformed) moving coordinate system:
- $\rho \partial u/\partial t - \nabla . \eta(\nabla u + (\nabla u^T) + + \rho(u.\nabla)u + \nabla p = F$
- $\nabla . u = 0$,

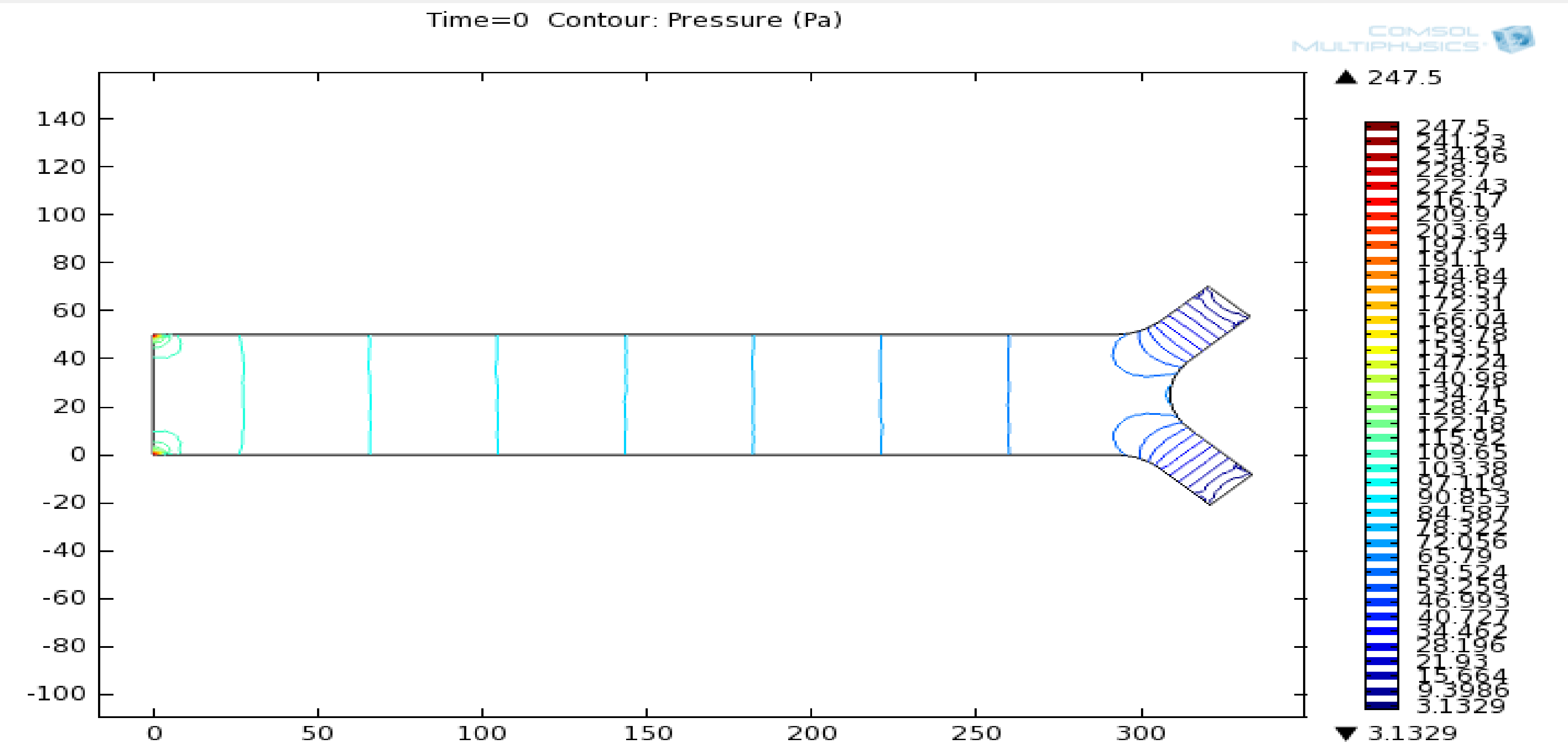
  where ρ is the fluid density, u is the velocity vector field, μ is the fluid viscosity, p is the scalar pressure field, F is the volume force vector field.
- The boundary conditions at the inlet and outlet are set. Pressure, stress and velocity distribution are to be studied.

LAMINAR FLOW AND VELOCITY FIELD



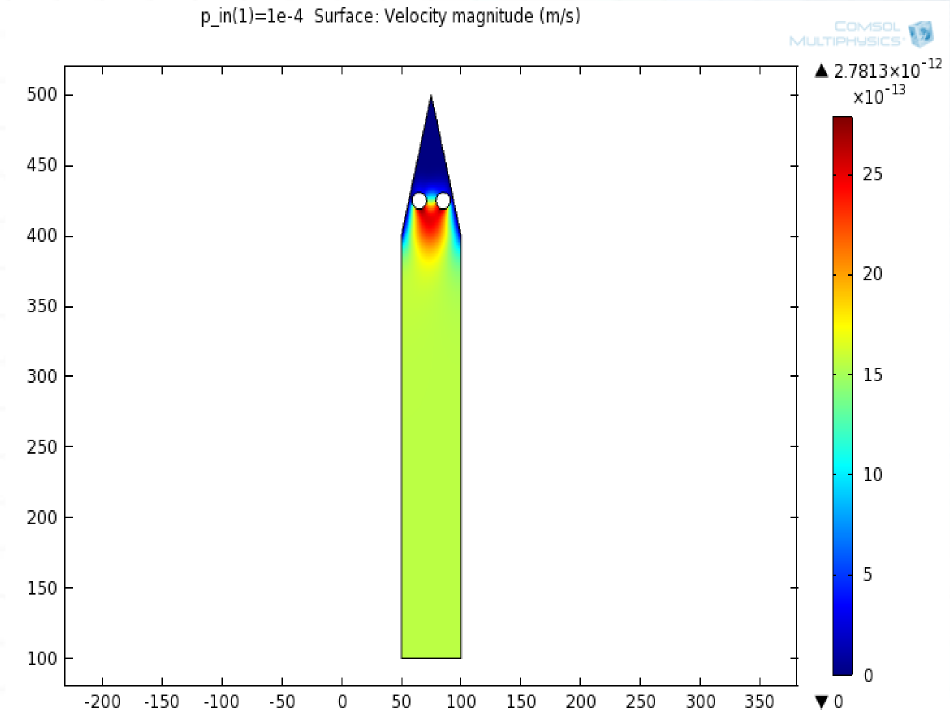
Fig(14): laminar flow (streamline) showing velocity distribution.

PRESSURE DISTRIBUTION FOR A LAMINAR FLOW

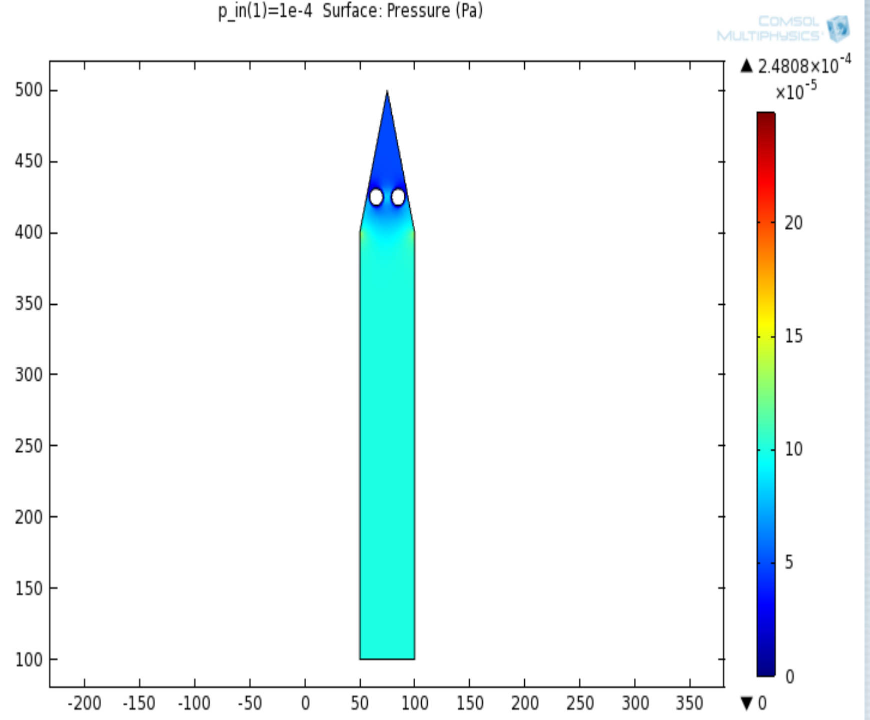


Fig(15): Pressure distribution in a laminar flow in a 2D needle lumen

2D SIMULATION FOR LAMINAR FLOW



Fig(16): Laminar flow showing velocity profile. Velocity: 2.7813 x 10^ -12 m/s



Fig(17): Pressure distribution in a single microneedle fluid flow.

PROPERTIES OF HUMAN SKIN

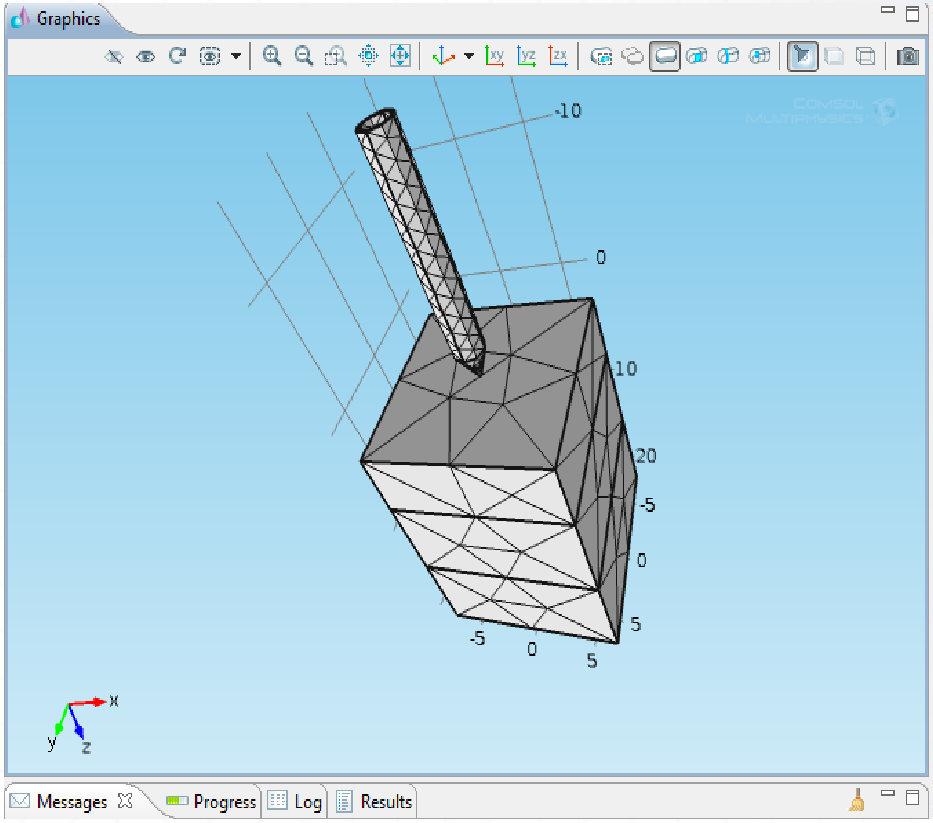
SKIN LAYER	THICKNESS(mm)	DENSITY (kg/m^3)
Stratum Corneum	0.02	1300
Epidermis	0.05	1200
Dermis	0.05	1200

Table(7): Skin properties

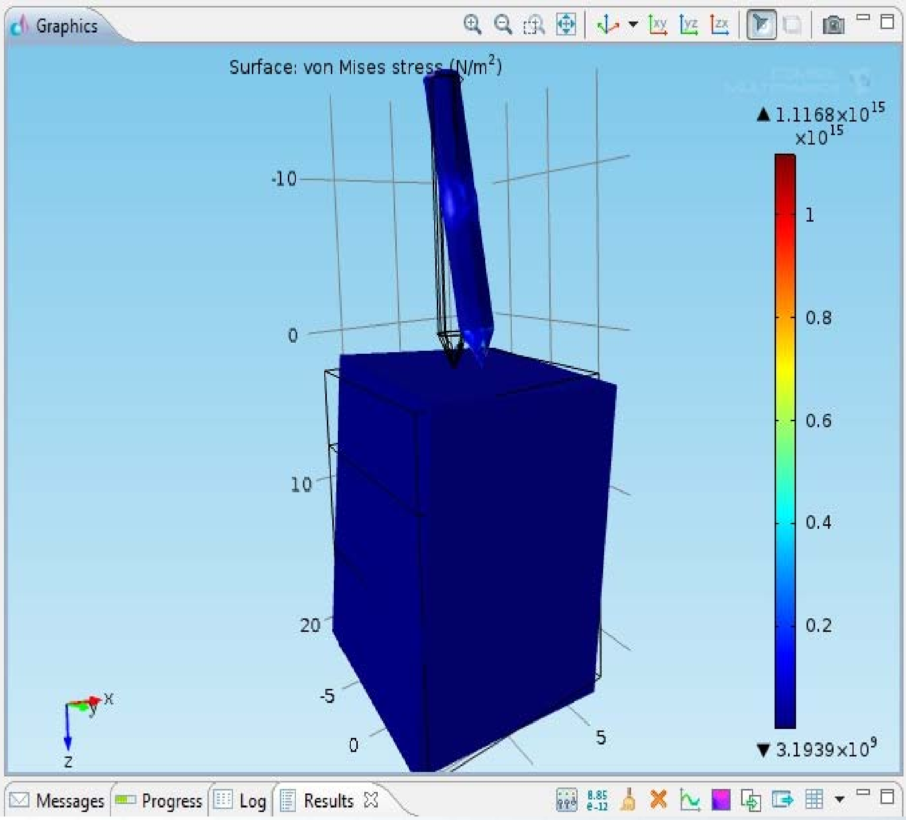
✓Functions:

- Protection
- Thermal regulation
- Sensory reception
- Vitamin D production
- Excretion

MICRONEEDLE INTERACTION WITH SKIN



Fig(18): Tetrahedral structure of microneedle interacting with human skin



Fig(19):Microneedle interaction with skin having Young's modulus 4.2x 10^5 N/m^2

PERFORMANCE COMPARISON BETWEEN MATERIALS

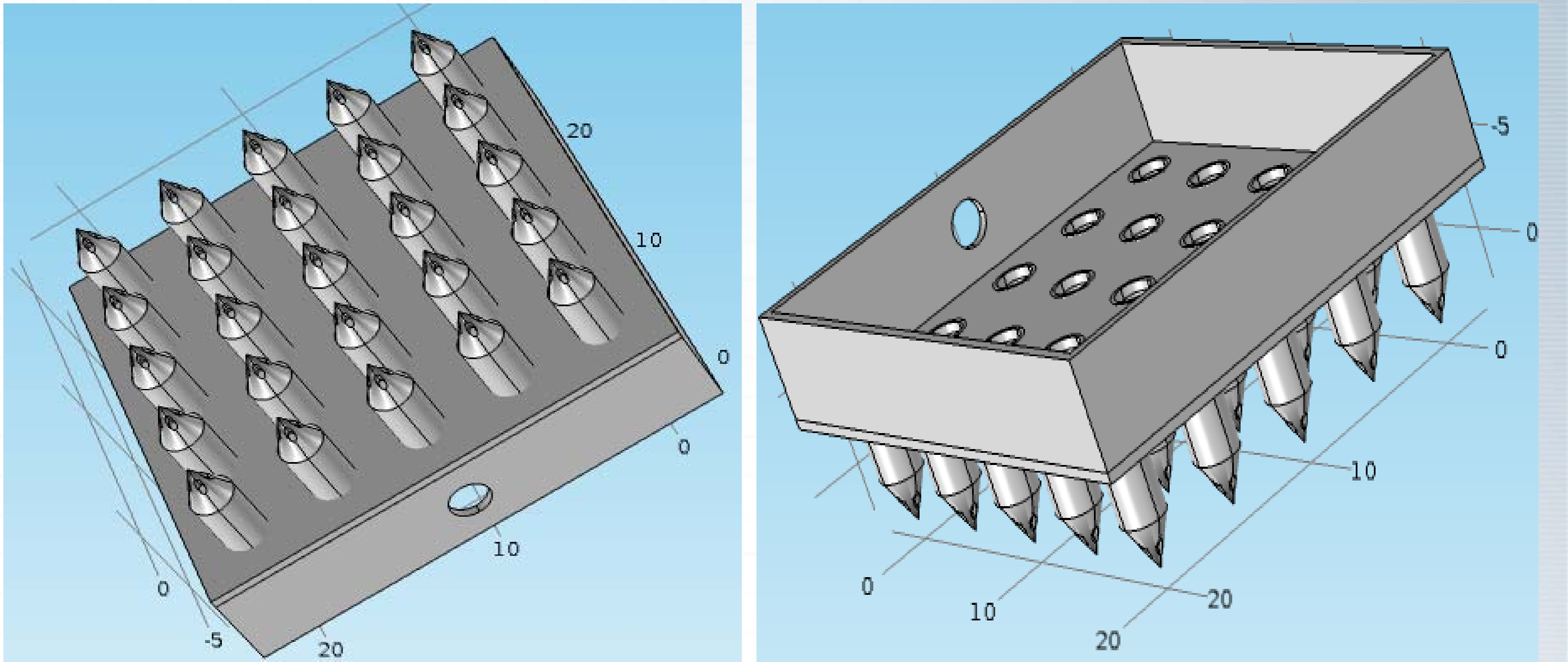
Properties	Silicon	Steel	Polymer
Density	2330 (kg/m^3)	7850 (kg/m^3)	1340(kg/m^3)
Young’s modulus	139e-9 Pa	205e-9 Pa	137e-4 Pa
Poisson’s ratio	0.27	0.28	0.2

Table(8): Comparison of material properties

RESULT INTERPRETATION

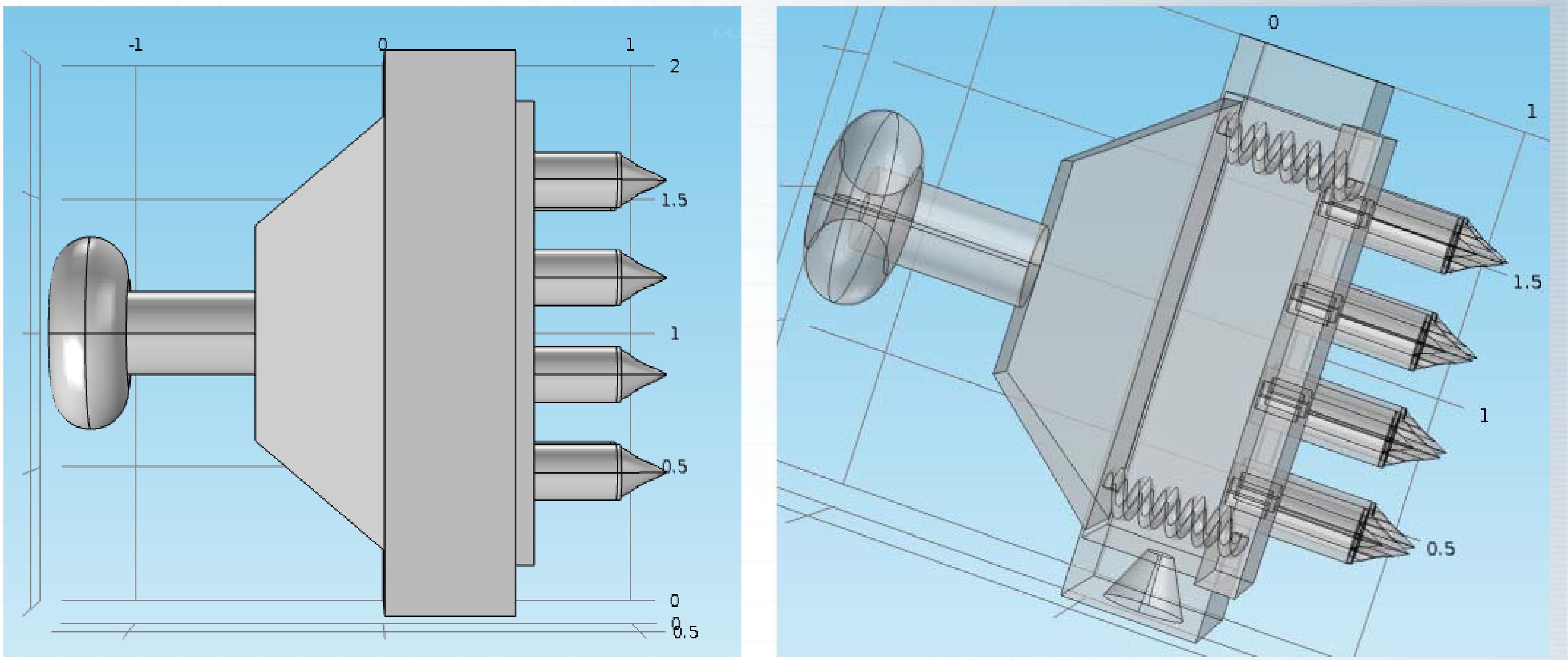
- The proposed hollow cylindrical microneedle with conical tip section gives enough strength to the microneedle to withstand bending and axial forces.
- The pressure is uniform in the main cavity of the needle.
- The velocity field shows the velocity is constant in the needle cavity and is increased in the outlet channel.
- Flow rate is mainly controlled by the applied pressure and the diameter of the hole.
- The strength and deformation of the microneedles have been compared for different materials.

PROPOSED STRUCTURES



Fig(20): Structure of microneedle array with reservoir

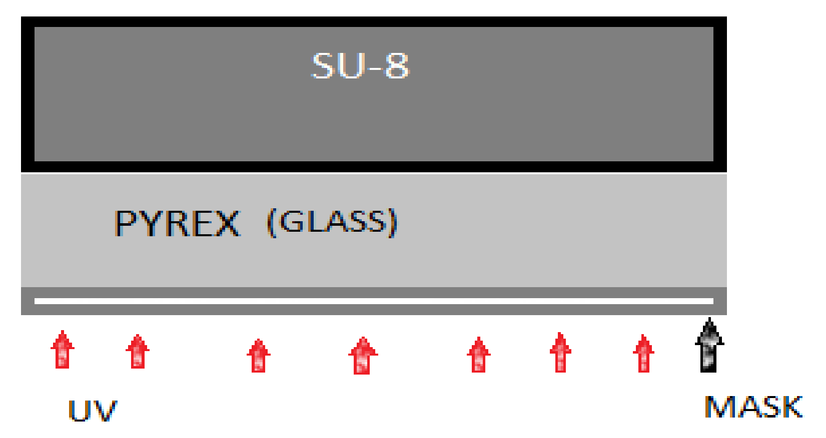
Model of a pyramidal piston micropump coupled to Microneedle having reservoir



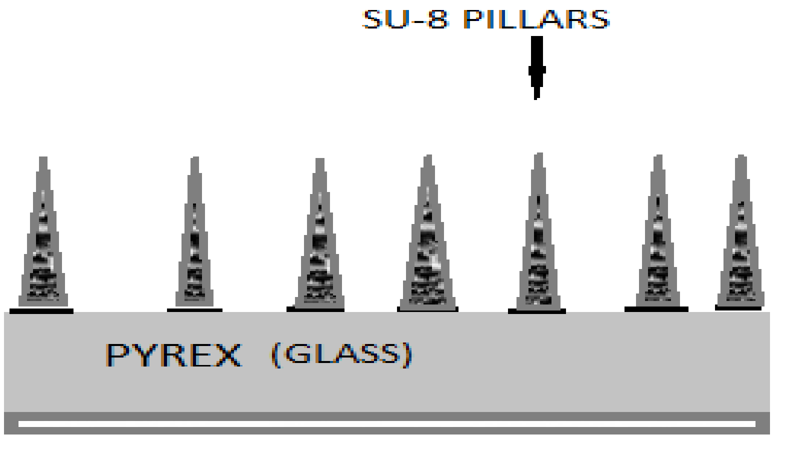
Fig(21): Structure of microneedle array with micropump

FABRICATION PROCESS OF HOLLOW OUT-OF-PLANE POLYMER MICRONEEDLES

STEP 1: SU-8 layer is taken over Pyrex glass substrate of 300 µm thick. And using photolithography, an array of 400µm high cylindrical pillars is fabricated.



STEP 2: The pillars would form the mold structure and will define the needle

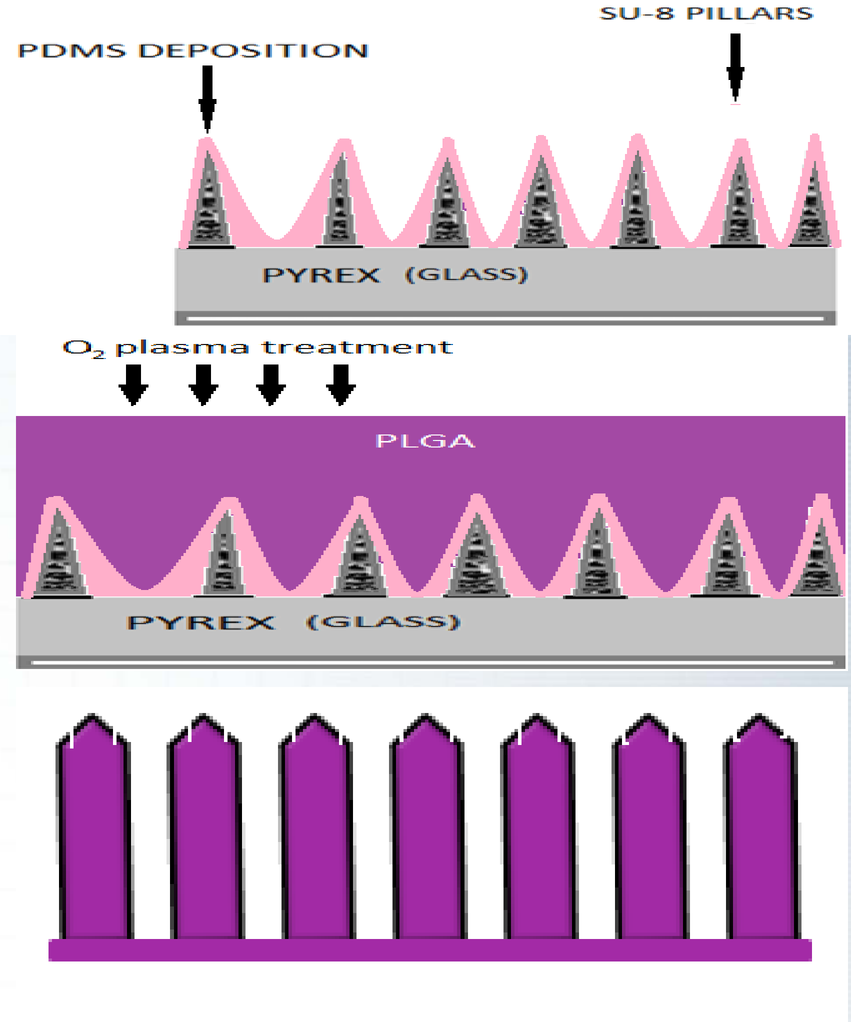


FABRICATION PROCESS continue…….

STEP 3: PDMS is deposited on the mold structure and set at 65°c in an oven.

STEP 4: Poly (d,l-lactide/ glycolide) is deposited onto the pillars by O2 plasma treatment.

STEP 4: Using DRIE method PLGA material is etched to form the microneedle arrays including thin walls around the pillars and is separated from the mold. The needle sides are opened by RIE method to give rise to hollow microneedles.



FUTURE WORKS AND CHALLENGES

- Fabrication of microneedle array design using MEMS fabrication processes.
- Testing and performance analysis using process tools.
- Robustness and strength of the material to resist external stress and sustainability.
- Reliability and biocompatibility issues
- Integration with other microfluidic devices for commercial use and applications in biomedical field.

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