

# **SUSTAINED RELEASE DRUG DELIVERY SYSTEMS AS A PHARMACOLOGICAL TOOL AGAINST BIOFILMS**

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**ANNUAL ISRAELI CF SOCIETY**

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# WHAT IS A BIOFILM???

**Bio + Film = ?**

# **BIOFILMS**

**COLLECTION OF CELL - FREE ORGANELLES,  
MICROBES, CELLS and THEIR PRODUCTS  
ATTACHED TO**

**A BIOLOGICAL (HARD / SOFT)**

**or**

**NON-BIOLOGICAL SUBSTRATUM**



# Biofilms Impact ...



Teeth

Cooling Water



Food Processing



Oil Recovery

Ship Hulls



Drinking Water

Paper Manufacturing



Medical Implants

**80% of bacteria are  
immobilized in biofilms**

**Diseases: Cystic fibrosis,  
Urinary track infections,  
ear infections...**

**AND ELSE WHERE**

# BIOFILMS

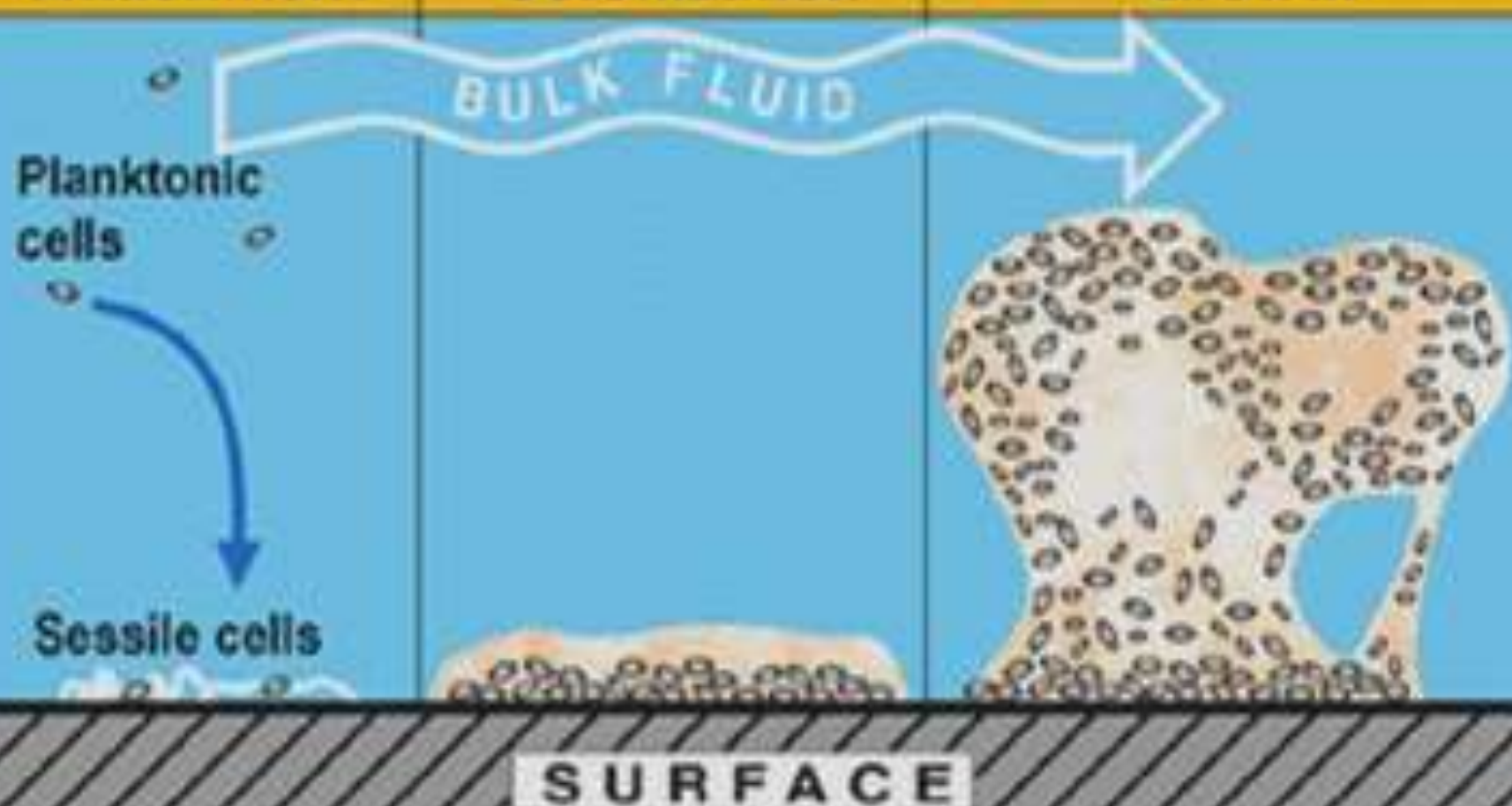
## GENERAL INTRODUCTION

# Biofilm formation:

Attachment

Colonization

Growth



# Biofilm formation:

Attachment

Colonization

Growth

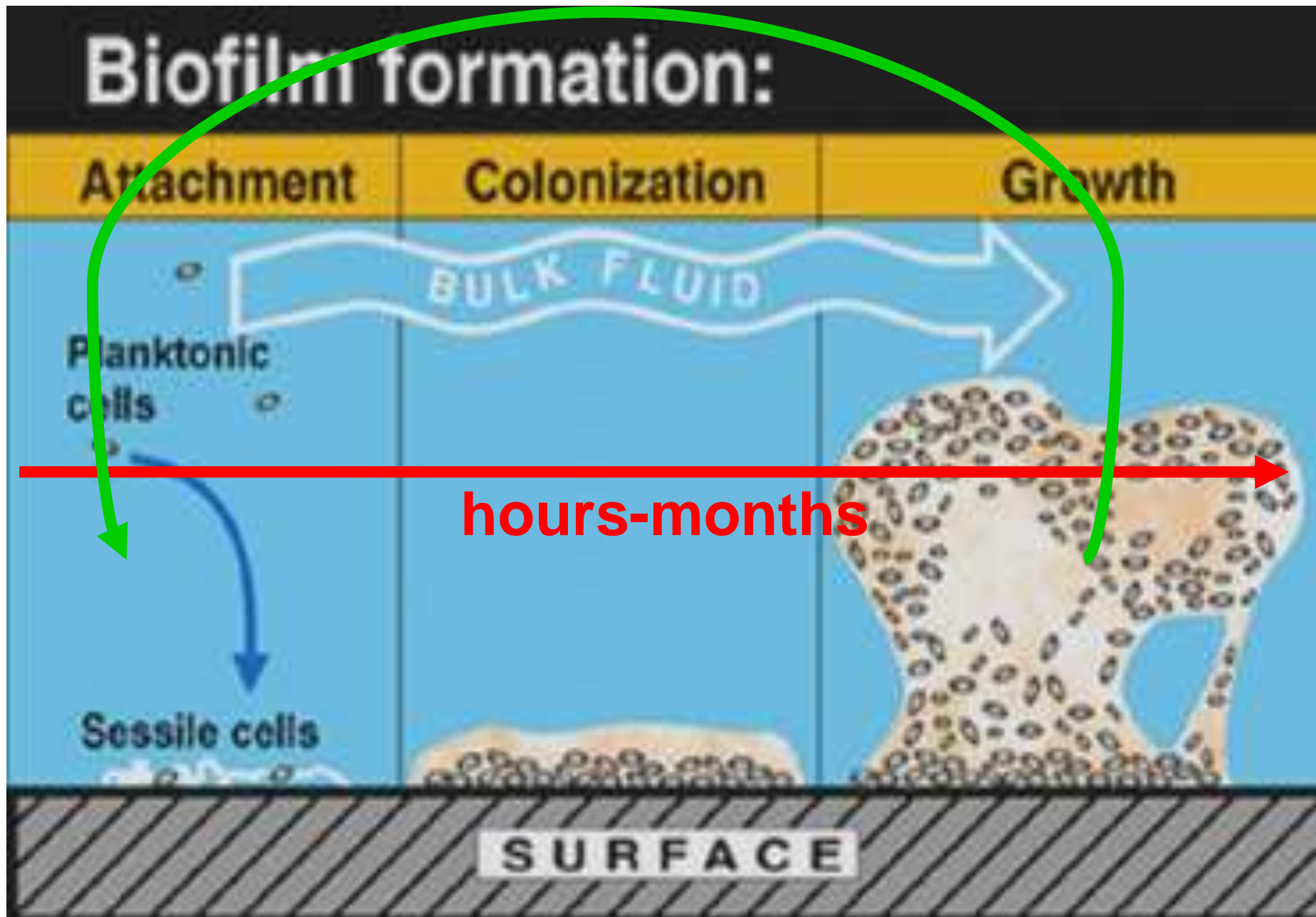
BULK FLUID

Planktonic cells

Sessile cells

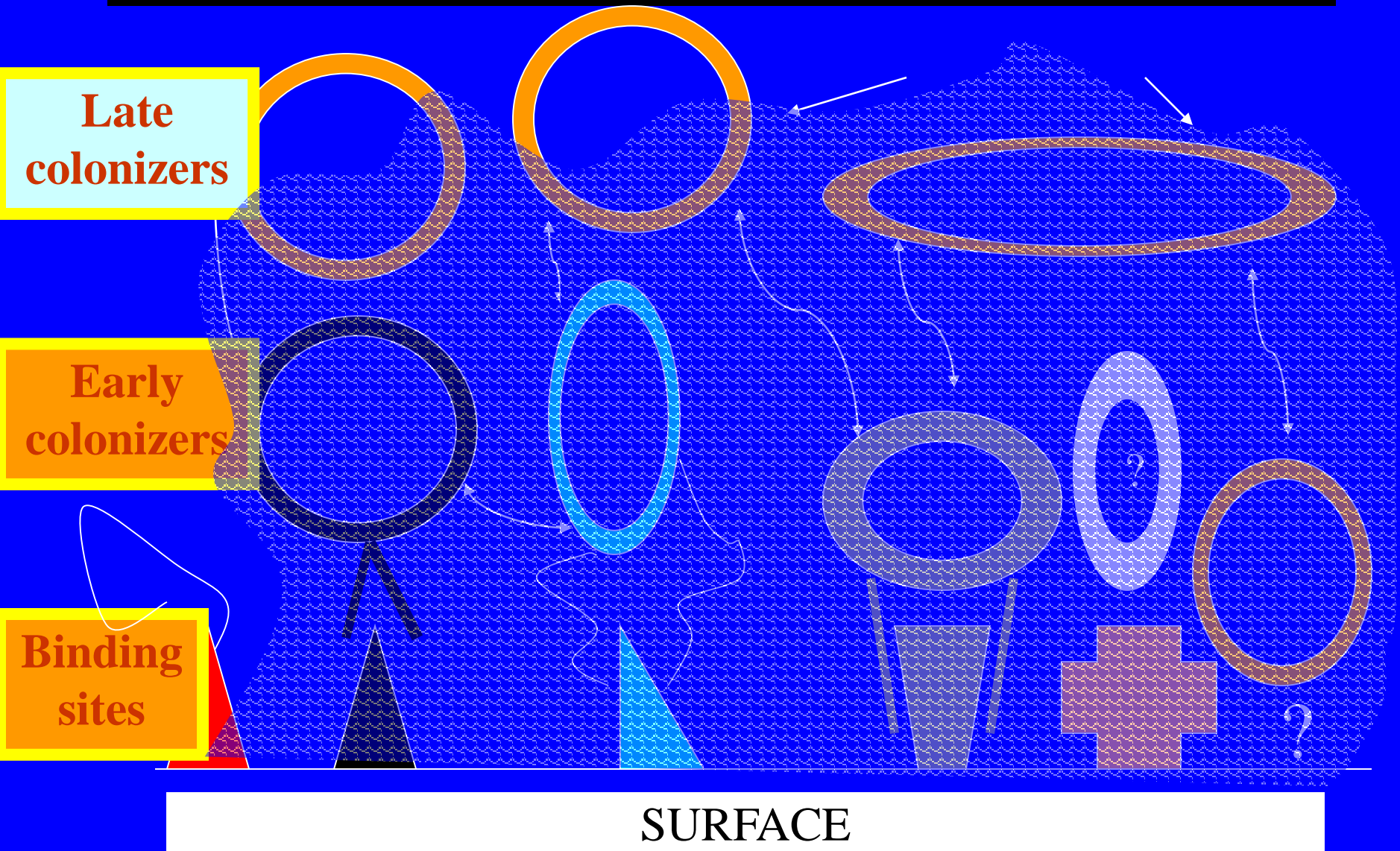
SURFACE

hours-months





# BIOFILM STRUCTURE



SO WHAT ????????????

# Bacteria in Biofilms

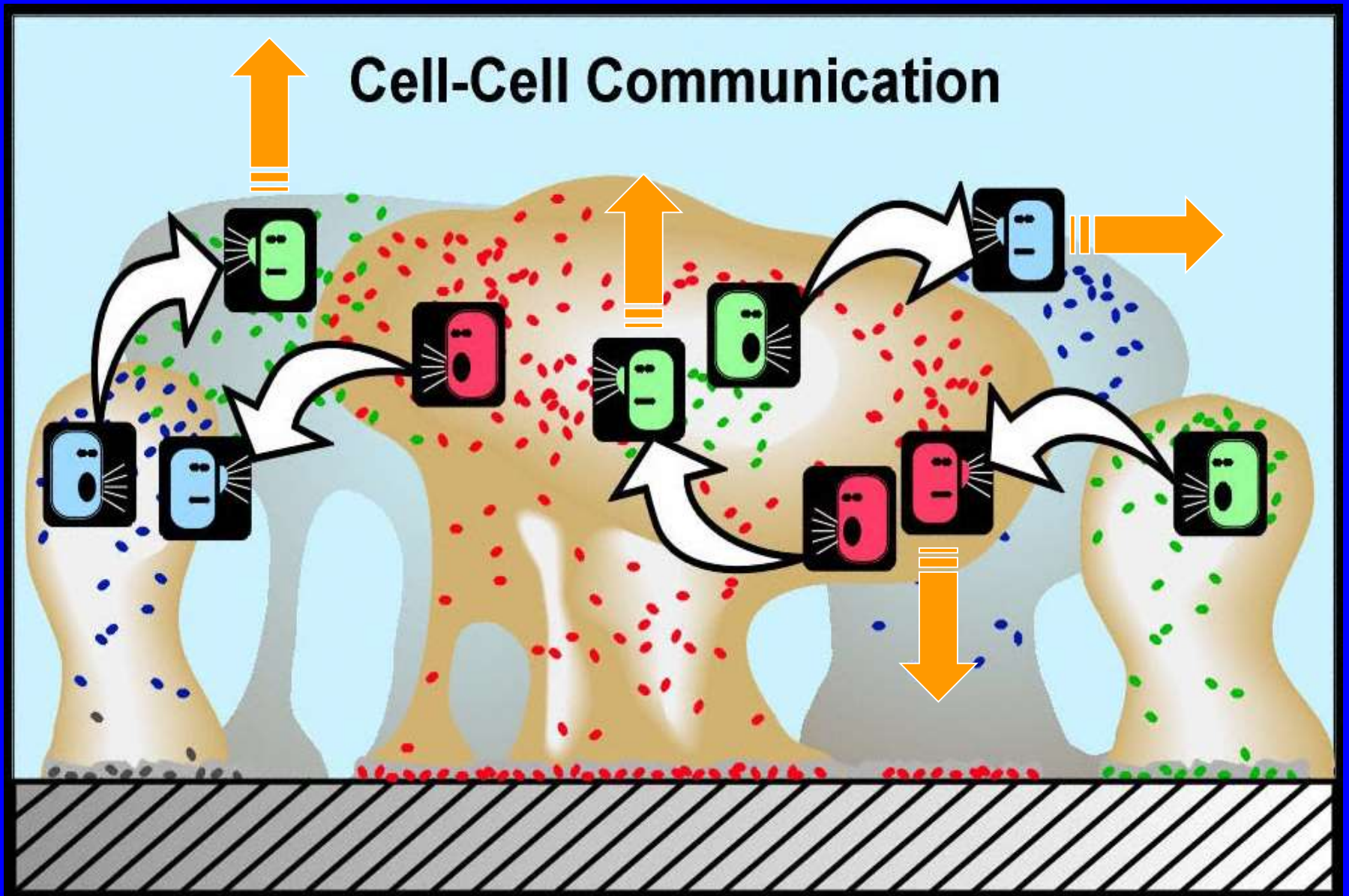
Different than Planktonic bacteria!!!!!!

Pathogenicity  
Antibiotic sensitivity  
Antibiotic resistance  
Growth rate  
Acid tolerance  
Metabolism  
Gene expression  
Genetic competence  
etc.

# CELL-CELL COMMUNICATION

**QUORUM SENSING**

# Cell-Cell Communication



# QUORUM SENSING

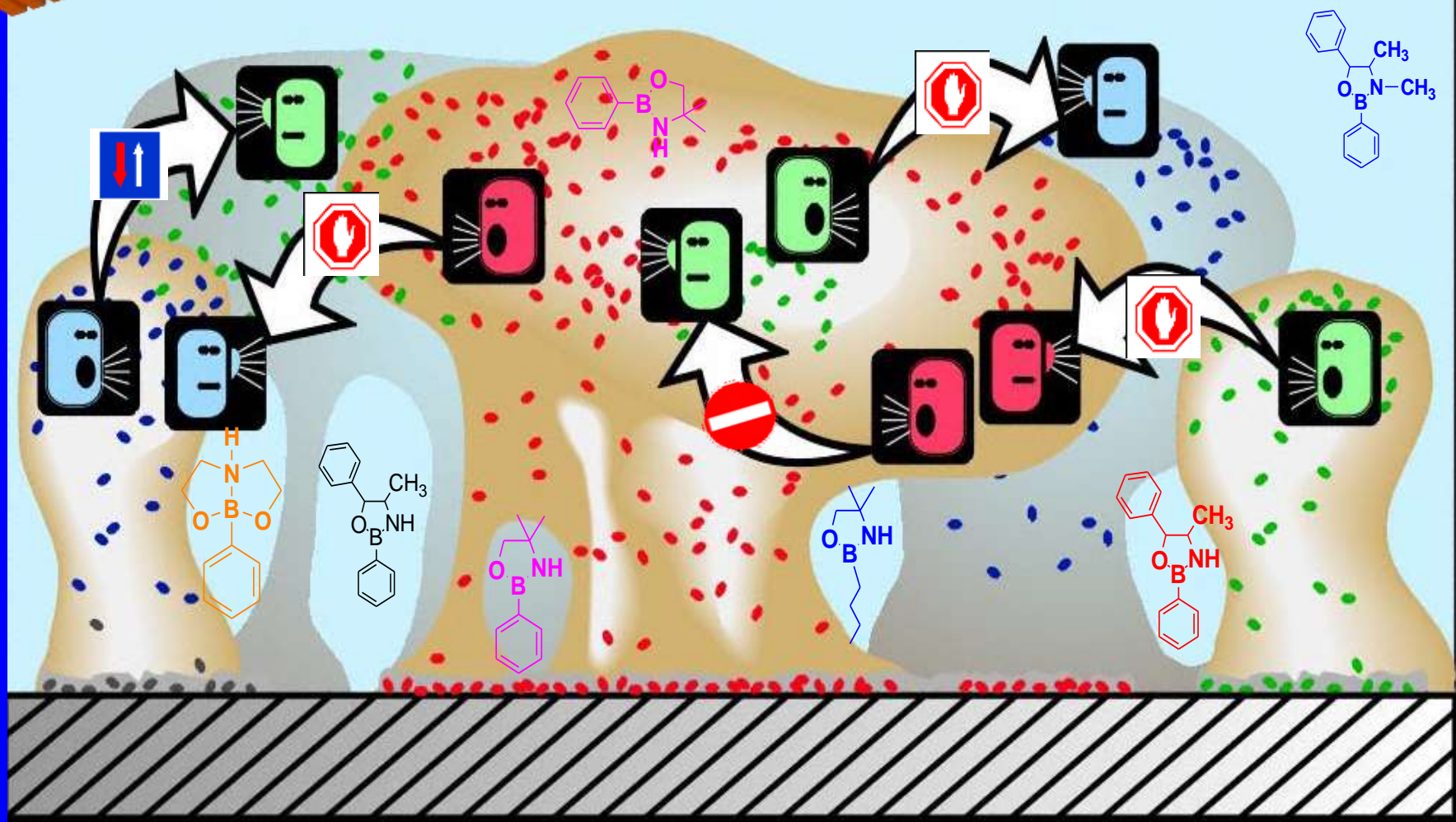
## bacteria-bacteria communication

- PATHOGENICITY
- BIOFILM FORMATION
- “RESISTANCE” TO ANTIBACTERIAL AGENTS
- GENETIC COMPETENCE
- ACID PRODUCTION
- MORE.....

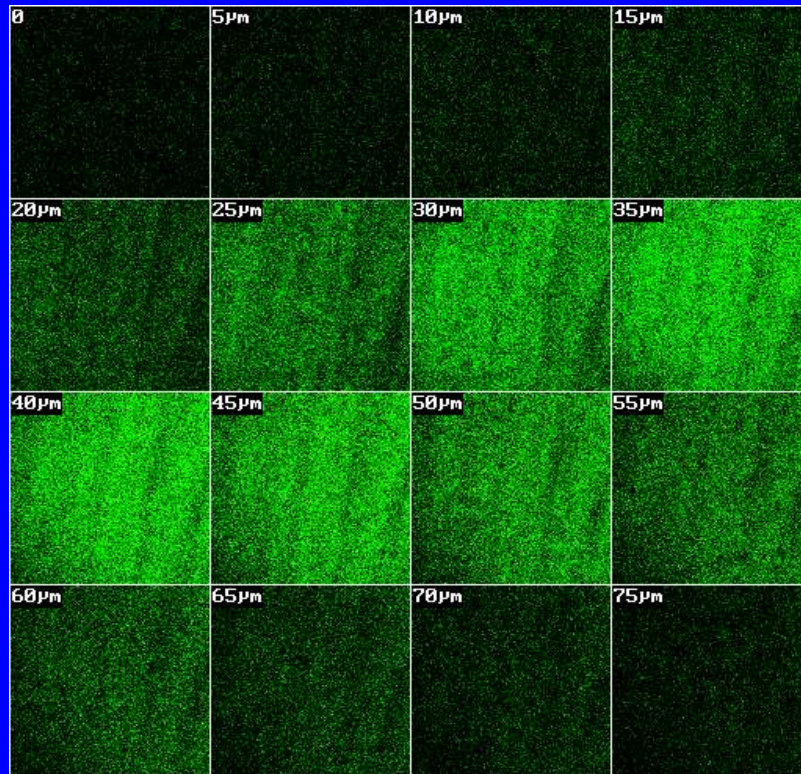


# INHIBITORS

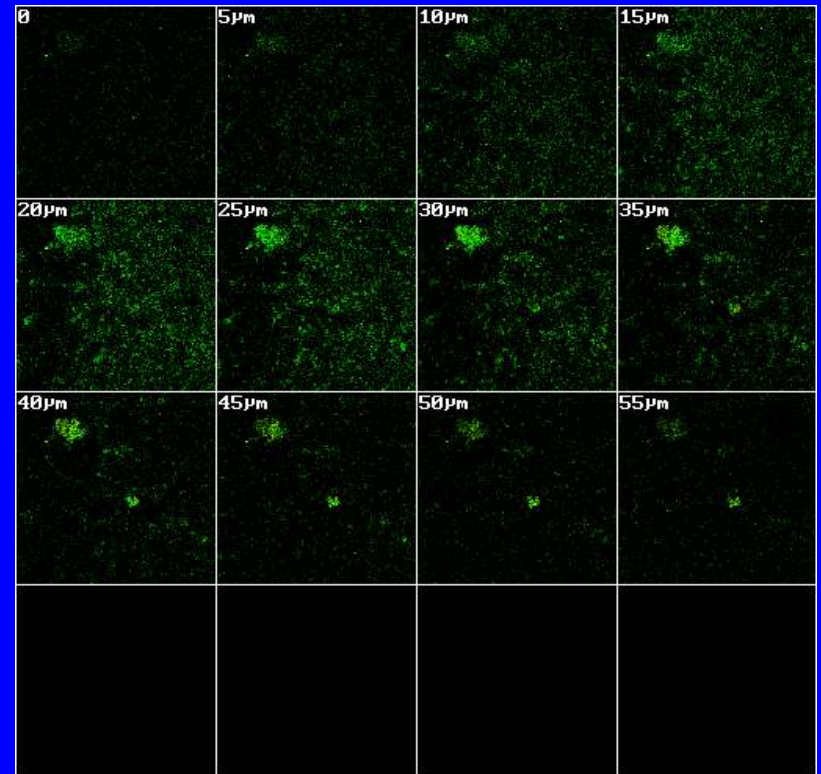
## Cell-Cell Communication



# DISINTEGRATION OF PREFORMED BIOFILM (*Vibrio harveyi* 0/N)



Control



S10 [0.20mM]

BELOW THE MIC



# EFFECT OF TZD ON SWARMING OF PSEUDOMONAS



control



TZD-C8  
(0.2 mM)

# In silico modeling in Pseudomonas

- Blind docking-

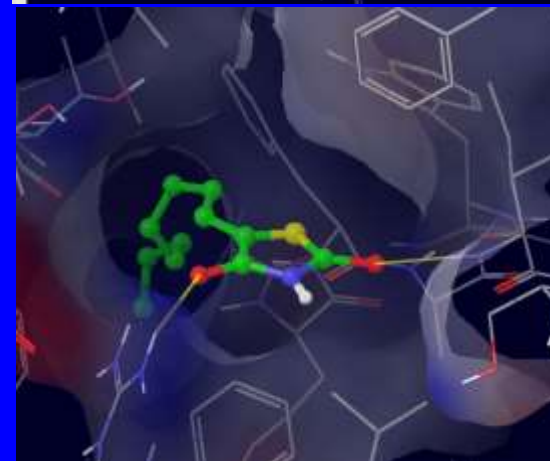
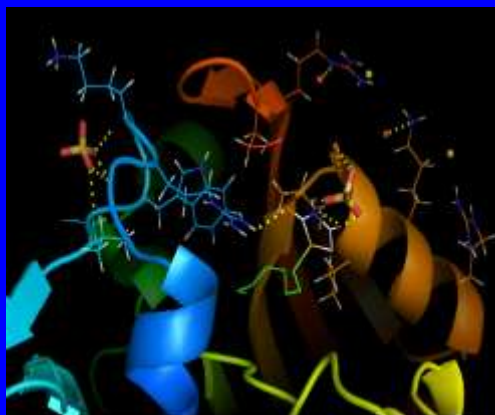
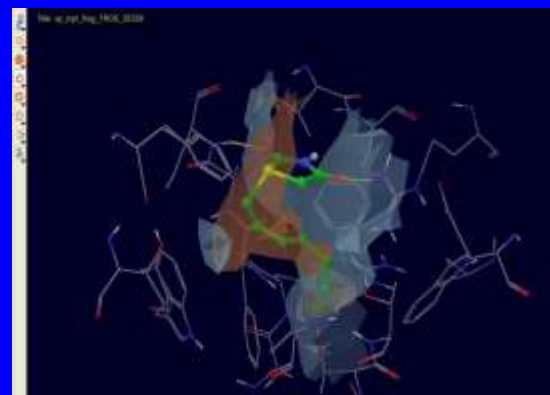
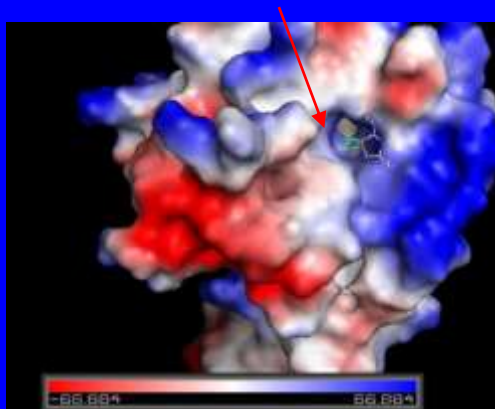
affinity calculations  
between small molecule  
(QS inhibitor) and protein  
(lasI).

Calculations:

Docking into protein active  
site...

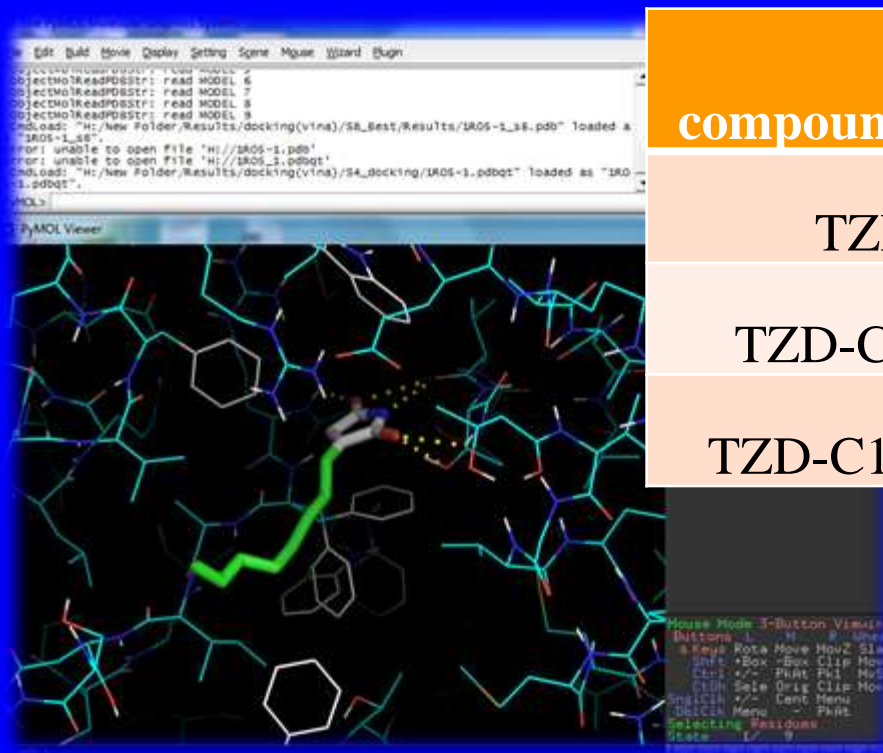
Precursor : -4 kcal/mol

Compound: -11 kcal/mol



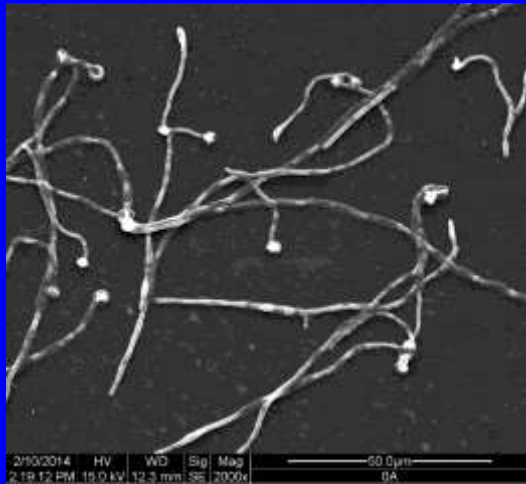
### 3. *In silico* analysis

Computational prediction analysis aims to predict • molecular interaction between a molecule and a protein: such as LasI and TZD derivatives...

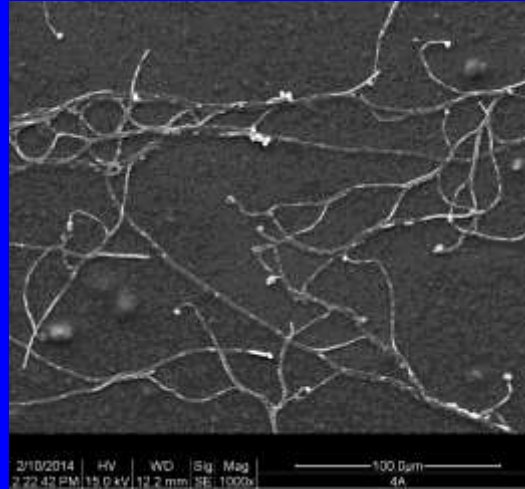


compound	QscR	LasR	PqsR	LasI
TZD	-4.5	-4.3	-4.3	-4.2
TZD-C8	-5.3	-7	-4.8	-8.1
TZD-C10	-6.5	-5	-5.7	-6.2

# EFFECT OF ANTI QUORUM SENSING (TZD $\mu\text{g}/\text{m}$ ) ON CANDIDA-PHENOTYPE



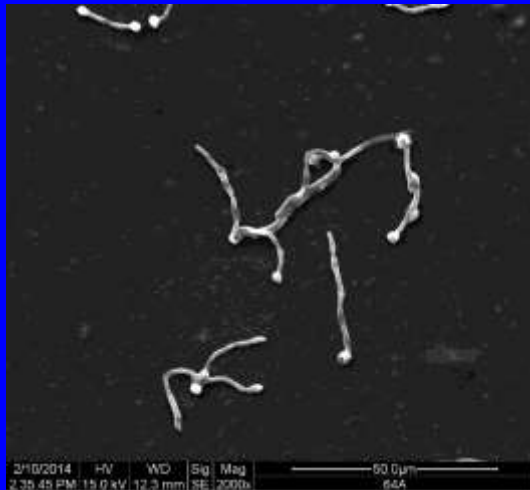
O- CONTROL



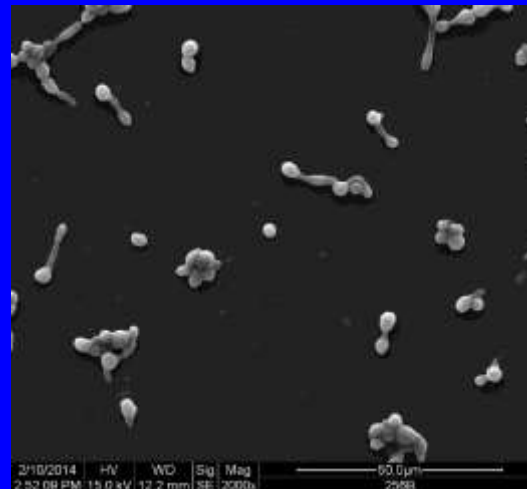
4



16



64

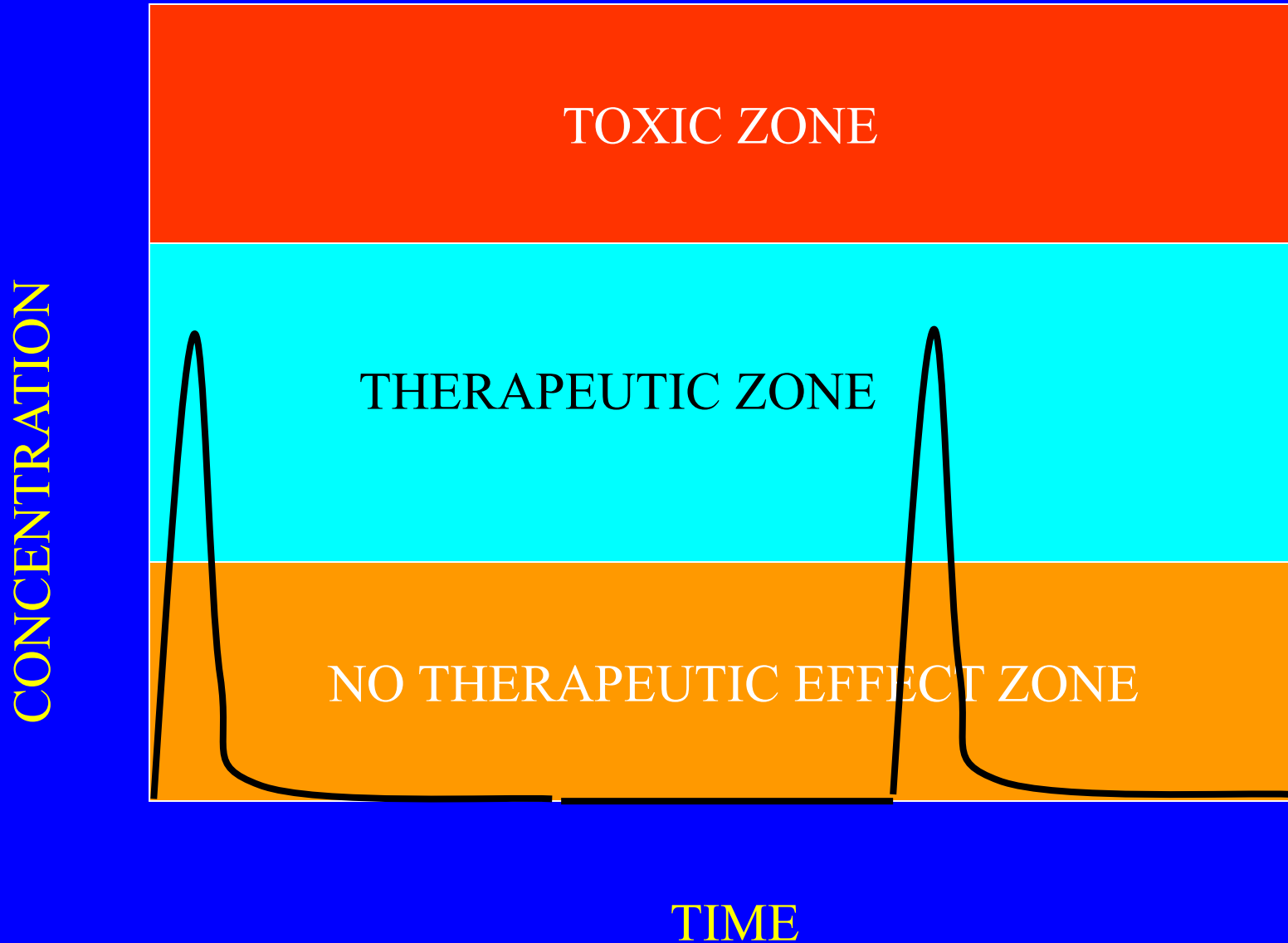


256

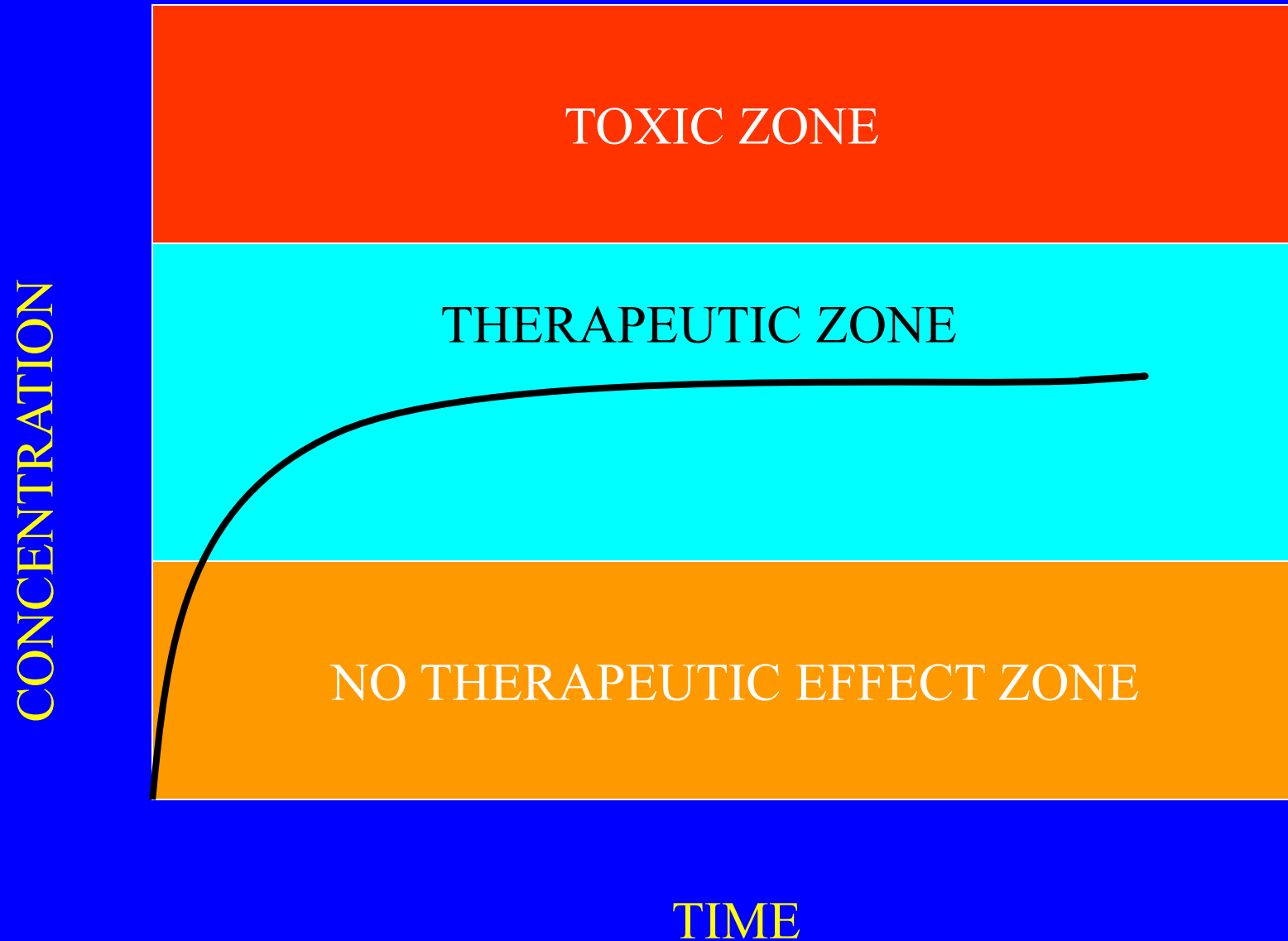
x2000

Is that good enough??

# PHARMACOKINETICS



# PHARMACOLOGICAL ASPECTS OF SRD

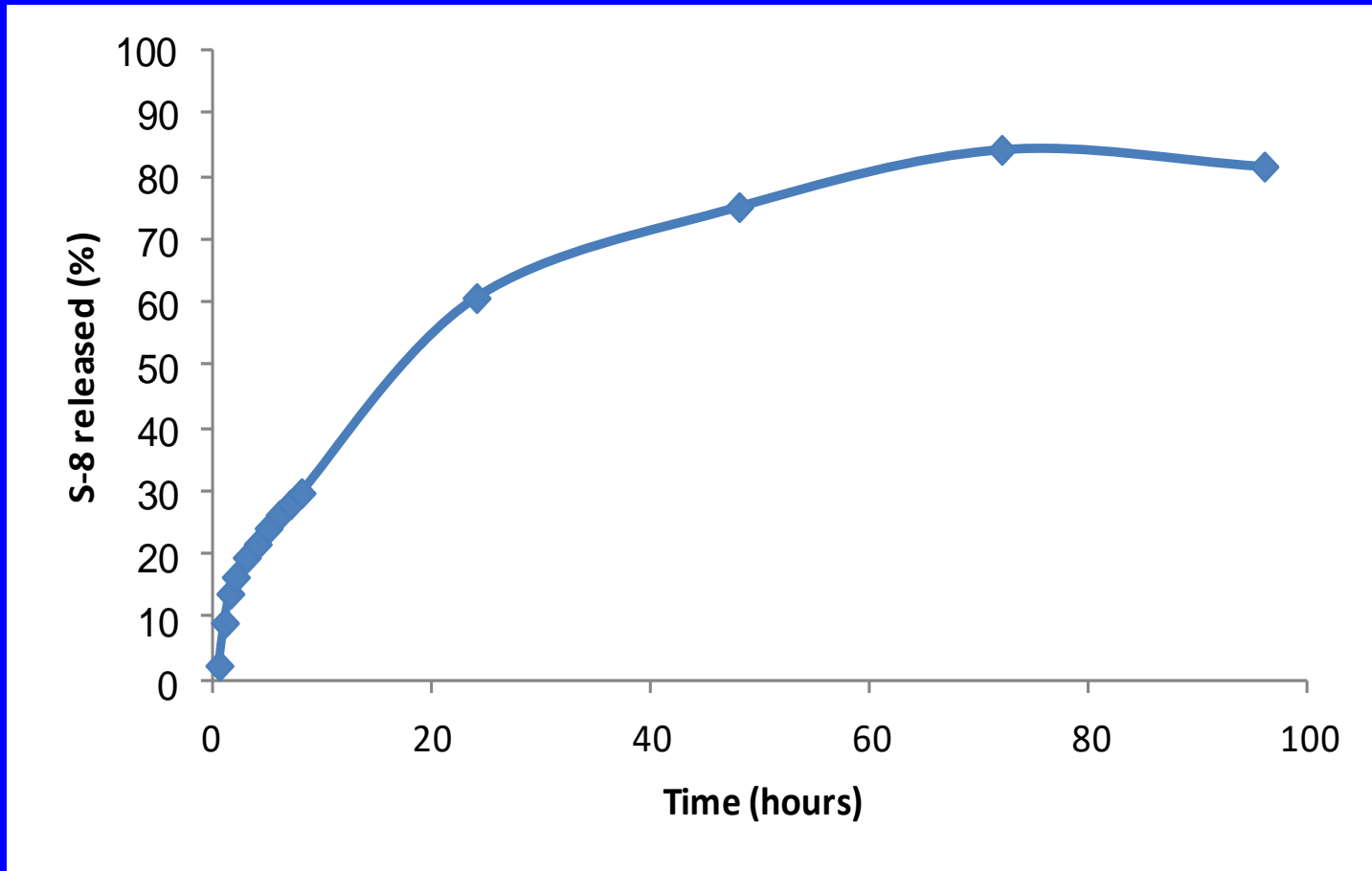


# SUSTAINED RELEASE DEVICES



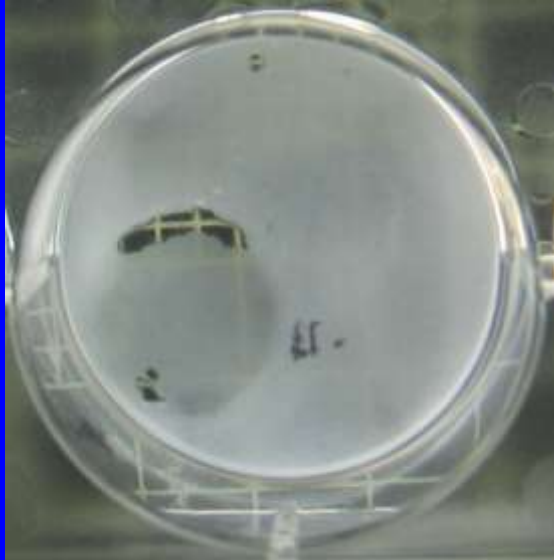
# SUSTAINED RELEASE DELIVERY SYSTEM

# KINETICS OF RELEASE OF ANTI QUORUM SENSING (TZD-8) FROM SUSTAINED RELEASE SYSTEM

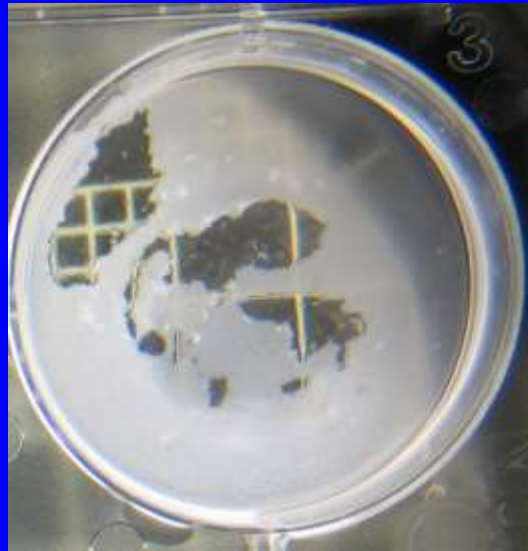


# EFFECT OF SRV-TZD ON BIOFILM OF CANDIDA

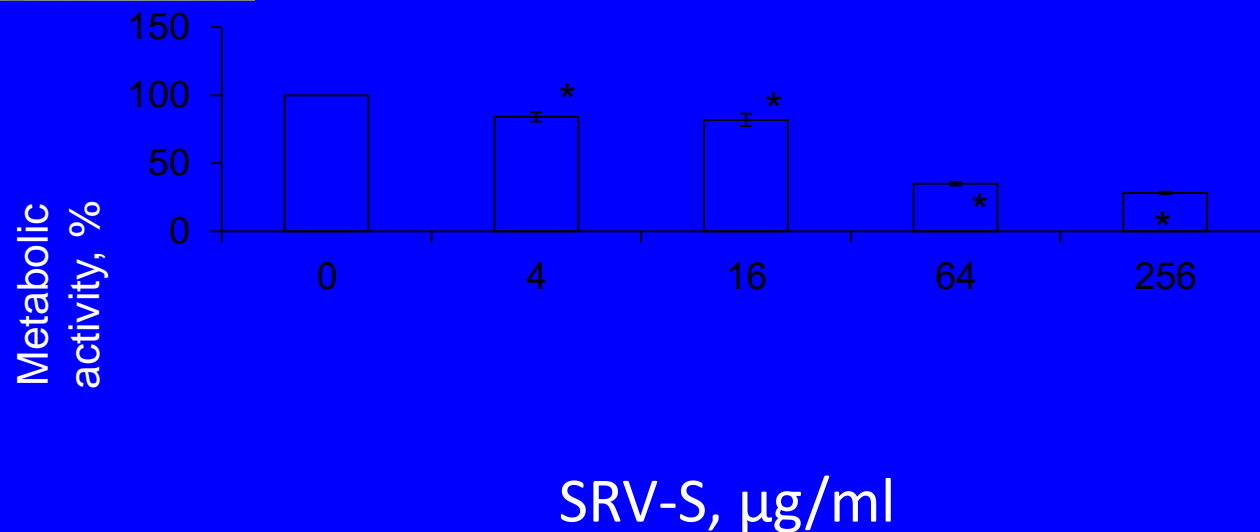
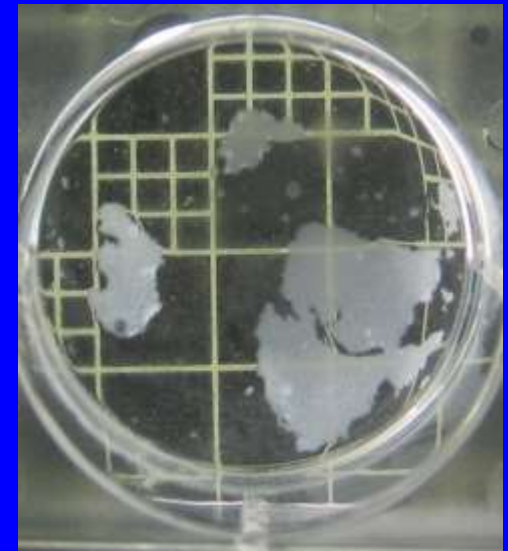
CONTROL



TZD 16



TZD 256



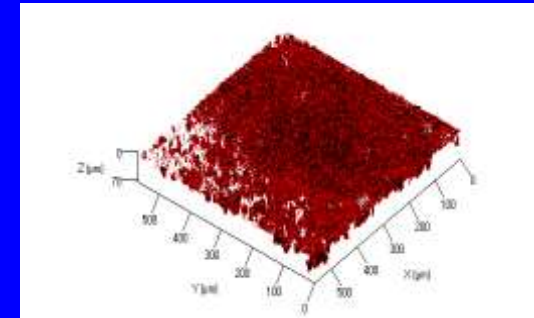
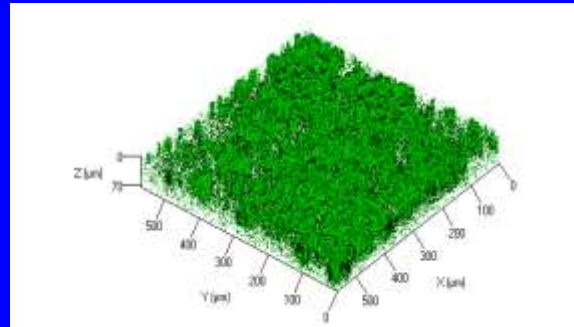
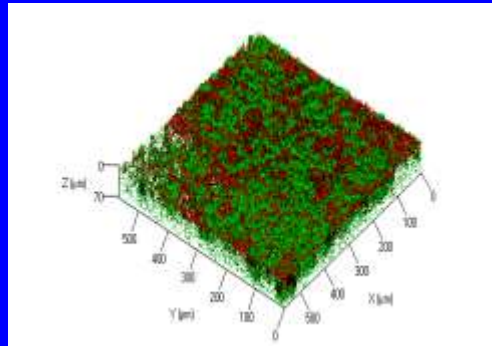
SRV-S-I,  $\mu\text{g/ml}$

EPS/Cell

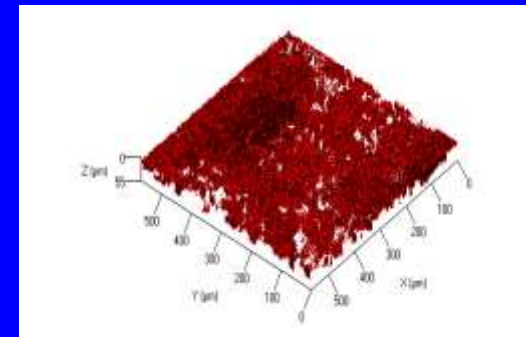
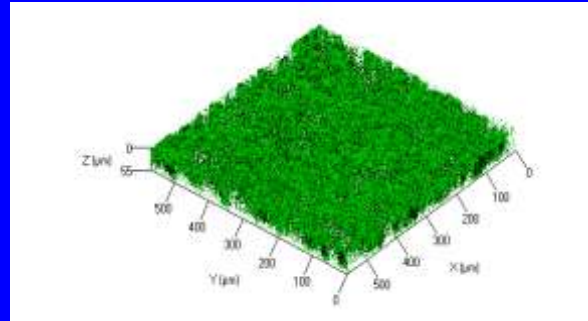
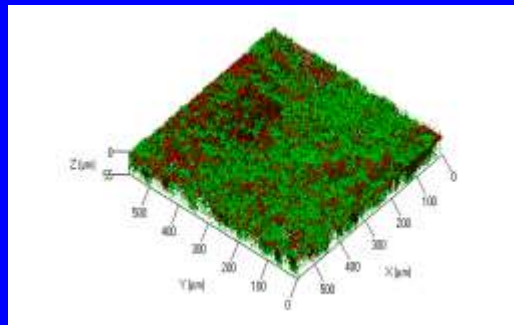
Cells

EPS

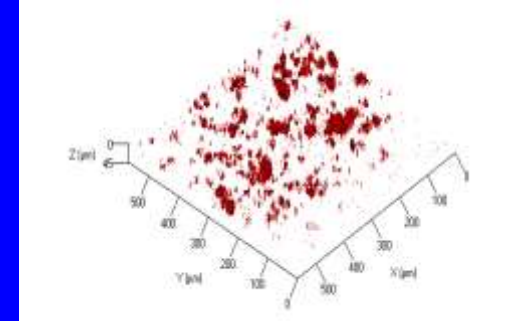
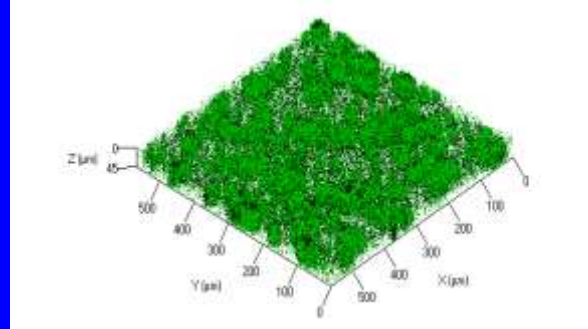
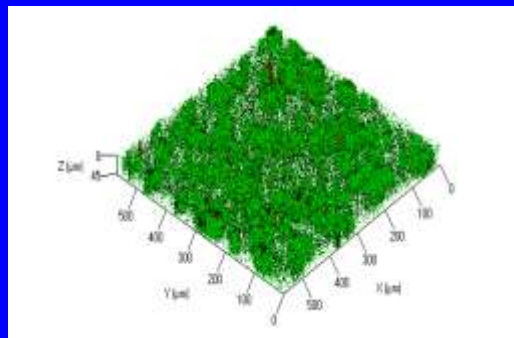
0



4



16



# **SUMMARY**

**MICROBES IMMOBILIZE IN BIOFILM  
ARE MORE PATHOGENIC**

**ANTI QUORUM SENSING AGENTS:  
NEW ERA IN COMBATING MICROBES**

**SUSTAINED RELEASE DELIVERY SYSTEM:  
PHARMACOLOGICAL/CLINICAL  
ADVANTAGES**

# FUTURE PROSPECTIVE

APPLICATION OF THE TECHNOLOGY  
TO CF PATIENT'S????.....

**Thank you!**