Title of the Talk

A Model of Antibiotic Resistance in Biofilm

by

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Outline of the Talk

- Some Biology of Biofilm

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- Some Biology of Biofilm
- Previous Work

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- A chemostat Model

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- Conclusion

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- Biofilm are composed of populations or communities of microorganisms adhering to environmental surfaces. These microorganisms are usually encased in an extracellular polysaccharide that they themselves synthesize.

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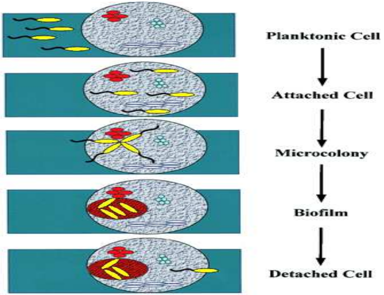
- The EPS may account for 50% to 90% of the total organic carbon of biofilms.

Biofilm:



Planktonic Cell
Attached Cell
Microcolony
Biofilm
Detached Cell

Biofilm:

Advantages and Disadvantages of Biofilm

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  - Water treatment plants, wastewater treatment plants and septic systems.
  - Cycling of elements in nature
  - It can be used to produce a wide variety of biochemical that are purified and use for public good e.g medicines, food additives

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  - Dental plaque

Biofilm:

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- Biofilms associated cells can be differentiated from their suspended counterparts by
  - Generation of an extracellular polymeric substance (EPS).
  - Reduced growth rates.
  - Regulation up and down.
  - Limited supply of nutrients.

Previous Work

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- David Davies, Mark Roberts et al. 1983, N.G Cogan et al. 2004

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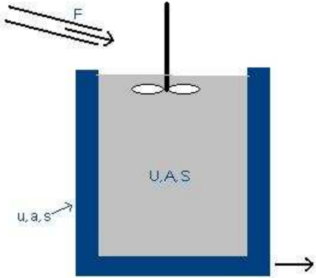
- Very high mixing rate of the fluid compartment to the wall compartment.
- Periodically fluctuating supply of antibiotic.
- Constant nutrient supply.
- The antibiotic kills the bacteria.

The model Figure:



The Model: Constructing

- $VS' =$
- $VA' =$
- $VU' =$
- $vs' =$
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- $VS' =$ input - washout - uptake - flux out
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The Model: Constructing

- $VS' = F(S^0 - S) - \gamma^{-1} VUf(S) - \alpha r_s (S - s)$
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- $VU' =$ growth - washout - killing - attachment
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- $vu' =$

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- $vu' =$ growth - detachment - killing

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- $vu' = (f_u(s) - k_u f_{1u}(s)a)\, u + \alpha r_u(U - u)$

- $f_1(S) = m(S + \alpha)/(a + S)$

Assumptions

Very high mixing rate F, define $\epsilon = V/F$

- $\epsilon S' = (S^0 - S) - \epsilon[\gamma^{-1} VUf(S) - D_s(S - s)]$
- $\epsilon A' = (A_0(t) - A) - \epsilon[VUg(A) - D_a(A - a)]$
- $\epsilon U' = -U + \epsilon[(f(S) - kf_1(S)A)\, VU - D_u(U - u)]$
- $s' = d_s(S - s) - \gamma^{-1} u f_u(s)$
- $a' = d_a(A - a) - u g_u(a)$
- $u' = (f_u(s) - k_u f_{1u}(s)a)\, u + d_u(U - u)$
- where d_s, D_s, are $\frac{\alpha}{v} r_s$ and $\frac{\alpha}{V} r_s$ respectively.

reduced Model

Very high mixing rate F. We have

- $s' = d_s(S_0 - s) - \gamma^{-1} u f_u(s)$
- $a' = d_a(A_0(t) - a) - u g_u(a)$
- $u' = (f_u(s) - d_u - k_u f_{1u}(s) a)\, u$

Periodic Solutions

- Eradication periodic solution $E_0(t) = (S^0, a^*(t), 0)$

Periodic Solutions

- Washout periodic solution
  $E_0(t) = (S^0, a^*(t), 0)$
- Antibiotic failure periodic solution
  $E(t) = (\bar{S}(t), \bar{a}(t), \bar{u}(t))$

Theorem: Stability of Washout Periodic Solution

- The key Floquet exponent for the variational equation $z' = A(t)z$ about $E_0(t) = (S^0, a^*(t), 0)$ is

$$\lambda_1 = f_u(S^0) - k_u f_{1u}(S^0) \int_0^T A_0(s)ds - d_u$$

and so $E_0(t)$ stable if $\lambda_1 < 0$ and unstable if $\lambda_1 > 0$.

Theorem: Persistence for Reduced Model

- If $\lambda_1 > 0$, then biofilm population persist i.e. there exists $\epsilon > 0$, independent of initial data, such that for all solutions satisfying $u(0) > 0$, we have $u(nT) > \epsilon$ for all sufficiently large n.
- In this case, there exists a positive (all components) T periodic solution of above model.

Bifurcation Theorem

There is a family of positive T periodic solutions bifurcating from trivial periodic solution $(S^0, a^*(t), 0)$ of the above reduced system as parameter k_u is varied near $k_{uc} = \frac{f_u(S^0)-1}{[A_0(t)]_m f_{1u}(S^0)}$. To leading order in the small ϵ

$$\begin{aligned}(s(t,\epsilon), a(t,\epsilon), u(t,\epsilon)) &= (S^0, a^*(t), 0) + \\ &\quad \epsilon\zeta(t) + O(\epsilon^2) \\ k_u(\epsilon) &= k_{uc} + \epsilon k_1 + O(\epsilon^2)\end{aligned}$$

where $\zeta(t)$ is the T periodic solution of linearized system $z' = A(t)z$.

Bifurcation Theorem continued..

Moreover, *sign* $u(t,\epsilon) =$ *sign* ϵ for small ϵ and

$$k_1 \;=\; \int_0^T \left[\left(f_u'(S^0) - k_{uc} f_{1u}'(S^0) a^*(s)\right)\zeta_1(s) - k_{uc} f_{1u}(S^0)\zeta_2(s)\right] ds$$

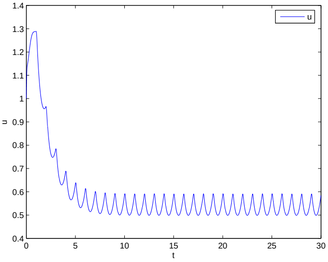
The largest real part of Floquet exponent for bifurcating periodic solution is given as:

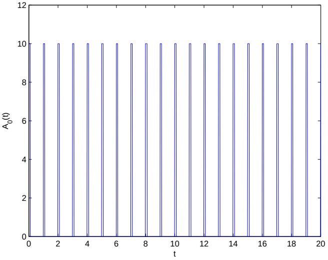
$$\gamma(\epsilon) = \; k_1\epsilon + O(\epsilon^2) \quad \text{for small } \epsilon$$

Global Bifurcation Theorem

There is $K \geq k_{uc}$ such that for each $k_u \in [0, K)$, there exists a nontrivial periodic solution $(s, a, u, k_u) \in B(T) \times R$ of reduced system, satisfying $0 < s(t) + u(t) < \gamma S^0,\ 0 < a(t) < a^*(t)$ for all $t \in R$

Simulation for antibiotic input and bacterial population in biofilms:





killing parameter : $k_u = .4$

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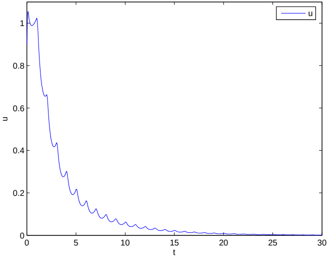

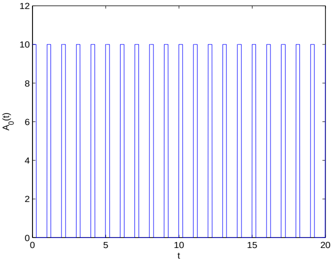

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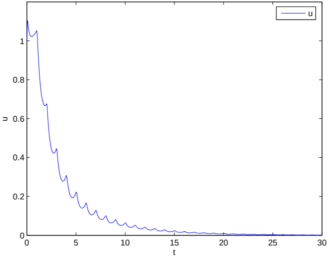

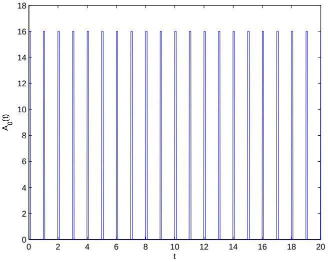

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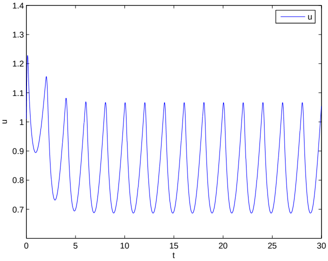

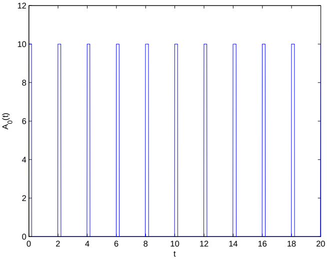

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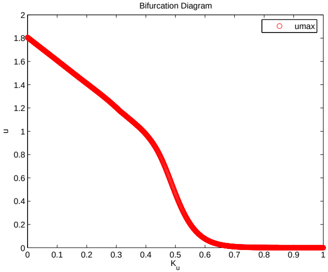

critical value of k_u: $k_{uc} = 0.75$

Conclusion

- Model of antibiotic resistance in biofilm
- We have shown that the existence of threshhold value of killing term.
- Increase the withdrawl time decreases the concentration of bacteria
- Increase the amplitude decreases the concentration of bacteria
- Increase the time period increases the concentration of bacteria

Thank

Special Thanks to Prof. Hal Smith.