Modelling Uppsala iGEM 2014

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1 Mathematical construction

1.1 Setting up the basic system

As a first step we thought about a basic sketch of our system. Our system will work inside of the gut where most of the bacterias are stuck to the intestine wall [**?**].We will therefore approximate the system to only the walls of a tube. The real intestine contains a very complex microbialflora which is very complex [**?**]. Because of this complexcity we decided to only concider a system with two bacterial species, our killer, *Lactobacillus*, and our target, *Yersinia entercolitica*(*Yersinia*). This will be a mayor flaw of our system that needs to be included when thinking of the application of the results.

Likewise we will only concider the physics of two molecules, the sensing molecule, 3-oxo-C6-HSL(AHL), and the toxin molecule, colicin Fy-a (cfya).

1.2 The *Yersinia* model

The *Yersinia* is non-motile at 37 degrese celcius [**?**] and therefore the movement will be neglected. During an infection of *Yersinia* it has been found that they reach a maximum density of ?? $cell/mL$ in the intestine [**?**]. Therefore the growth term of *Yersinia* will also be neglected. At last the death rate of *Yersinia* which will be governed by the concentration of cfya(notated as c in formulas), where all *Yersinia* will die once the concentration has reached a limiting value K_c. This will be represented by a heaviside-step-function shown in equation (1).

$$\frac{\partial y}{\partial t} = -\theta(c - K_c)y \tag{1}$$

However letting all bacteria die at the same time once the concentration has been reached might not represent how it will work *in-vivo*. For example, a area with a high *Yersinia* density will likely not die as quickly as a area with low density. To fix this a function for controlling the rate of the killing depending on the *Yersinia* density, $k_d(y)$, can be introduced. Data for the rate of this term would thou need to be determined experimentaly by trying diffrent densities of *Yersinia* exposed to a fixed concentration of cfya that is higher than K_c. The same test could also be carried out, but with fluctuating values of cfya instead, to determine if the death rate, k_d, is dependent on the concentration of cfya. However if the *Yersinia* dies of too quickly this could prove to be difficult to determine.

Assuming the experimental values are possible and dependant on both cfya and *Yersinia* density, we get equation (2), where k_d is a function of the *Yersinia* density and the cfya concentration, $k_d(y, c)$.

$$\frac{\partial y}{\partial t} = -\theta(c - K_c)k_d y \tag{2}$$

1.3 The *Lactobacillus* model

The *Lactobacillus* can be both motile and non-motile in our system depending on the AHL concentration(see project description). When bacteria are motile they move in a random walk fashion[**?**]. When studying a system on population density scale the random walk can be simplified as an diffusion of the bacteria [**?**]. However this creates a problem with the system of a non-mobile and a mobile phase. When the bacterias are in the non-mobile phase we want the mobile bacteria to diffuse towards the non-motile bacteria like there was no bacteria there at all, see figure **??**.

To solve this we decided to make the system give the non-motile *Lactobacillus*(activated *Lactobacillus*, notated l_a in formulas) it's own density and remove that density from the motile *Lactobacillus*(notated l in formulas). The trigger for this change from motile to non-motile will be when the concentration of AHL(notated a) will reach a threshold(notated K_a), this will also be formulated via the heaviside-step-function. The change of *Lactobacillus* density can then be written as in equation (3) and (4) where D_l notates the diffusion constant of a motile *Lactobacillus*.

$$\frac{\partial l}{\partial t} = \nabla \cdot (-D_l \nabla l) - \theta(a - K_a) \cdot l + \theta(K_a - a) \cdot l_a \tag{3}$$

$$\frac{\partial l_a}{\partial t} = \theta(a - K_a) l - \theta(k_a - a) l_a \tag{4}$$

1.4 The AHL model

The change of AHL concentration over time will be dependant on diffusion, production, consumption and degradation. Diffusion of the AHL can be modelled the via the diffusion model [**?**], with a specific diffusion coefficient, D_a. Production will depend on the *Yersinia* density and the amount of AHL [1 cell/mL] *Yersinia* can produce per timestep, β_y. Degradation of AHL can is dependant on pH [**?**] and on degrading cells, like mammalian epitial cells [**?**]. Since theese two values can be concidered constant in the intestine the degradation will be dependant determined by a degradation constant, η_a. The change over time of AHL concentration, with neglected consumption, can be wirtten as equation (5).

$$\frac{\partial a}{\partial t} = \nabla \cdot (-D_a \nabla a) + \beta_a y - \eta_a a \tag{5}$$

Consumption will be dependent on the amount of activated *Lactobacillus* that is present. To give a fair representation of the consumption only the volume of a shell around the *Lactobacillus* will be counted. The thickness of the shell is equal to the maximum traveling distance, d_a, of a molecule of AHL in one second, derived from the diffusionconstant, D_a, as seen in equation (9).

$$V_l = R_l^2 \pi \cdot L_l \tag{6}$$

$$V_{s,l} = (R_l + d_a)^2 \pi \cdot (L_l + 2 \cdot d_a) \tag{7}$$

$$D_a = \frac{d_a^2}{2t} \tag{8}$$

$$d_a = \sqrt{D_a \cdot 2} \tag{9}$$

One activade lactobacillus will then affect the concentration in a volume, $V_{f,l}$.

$$V_{f,l} = V_{s,l} - V_l \tag{10}$$

Assuming that all concentration is lost when *Lactobacillus have activated*, the expression for the consumption can then be written as equation (**??**)

$$consumption = -V_{f,l} l_a K_a \tag{11}$$

Finaly the change of concentration of AHL can be written as:

$$\frac{\partial a}{\partial t} = \nabla \cdot (-D_a \nabla a) + \beta_a y - V_{f,l} l_a K_a - \eta_a a \tag{12}$$

MOVE TO CONSTANTS. Degradation of AHL is dependent on it's enviroment. In the instine the pH is close to 7.4 [] and the AHL is surrounded by bacteria and mammalian cellwall cells. In an alkaline enviroment AHL is degraded by pH-dependant lactonolysis [].

1.5 The colicin fya model

Cfya will resemble the equation of AHL by most parts. The diffusion, degradation and consumption can all be concidered to be formed the same way but with new indicies. Where D_c is the diffusion coefficient, η_c is the degradation and γ_c is the consumption. The production will also be simmular with a production term, β_c, but will be dependant on the activated *Lactobacillus* density, l_a, instead of the *Yersinia* density.

$$\frac{\partial c}{\partial t} = \nabla \cdot (-D_c \nabla c) + \beta_c l_a - V_{f,y} y K_c - \eta_c c \tag{13}$$

1.6 Complete system

The complete system of PDE:s can now be written as:

$$\frac{\partial y}{\partial t} = -\theta(c - K_c) y \tag{14}$$

$$\frac{\partial l}{\partial t} = \nabla \cdot (-D_l \nabla l) - \theta(a - K_a) \cdot l + \theta(K_a - a) \cdot l_a \tag{15}$$

$$\frac{\partial l_a}{\partial t} = \theta(a - K_a) l - \theta(K_a - a) l_a \tag{16}$$

$$\frac{\partial a}{\partial t} = \nabla \cdot (-D_a \nabla a) + \beta_a y - V_{f,l} l_a K_a - \eta_a a \tag{17}$$

$$\frac{\partial c}{\partial t} = \nabla \cdot (-D_c \nabla c) + \beta_c l_a - V_{f,y} y K_c - \eta_c c \tag{18}$$

Initial values will also need to be formed. At the start we will concider n colonies, with their midpoint at x_n and y_n and radius r_y, of *Yersinia* spread out in the

intestine. The density in the colonies will be notated as $y_{0,c}$ as seen in equation (19). At these colonies there will be a steady-state value of AHL concentration, $a_{0,c}$.

$$y_0 = \begin{cases} (x-x_n)^2 + (y-y_n)^2 <= r_y^2 & y_{0,c} \\ otherwise & 0 \end{cases} \tag{19}$$

$$a_0 = \begin{cases} (x-x_n)^2 + (y-y_n)^2 <= r_y^2 & a_{0,c} \\ otherwise & 0 \end{cases} \tag{20}$$

As for *Lactobacillus* we will concider all of the *Lactobacillus* to arrive at the intestine wall at the time zero, evenly distributed with density, l_0. The density of activated *Lactobacillus* can be set to zero since we assume that no AHL was present outside the intestine wall, and therefore the cfya concentration will also be set to zero.

All the molecules and bacteria will be able to flow freely out of the ends of the intestine and therefore the boundaries at the x-limits, 0 and x_{max}. Assuming that the concentration of AHL, cfya, *Lactobacillus* and *Yersinia* is neglectable outside the small intestine, boundary condition, equations (21 - 25), can be written with dirchlet-type.

$$y(0,y,t) = y(x_{max},y,t) = 0 \tag{21}$$

$$l(0,y,t) = l(x_{max},y,t) = 0 \tag{22}$$

$$l_a(0,y,t) = l_a(x_{max},y,t) = 0 \tag{23}$$

$$a(0,y,t) = a(x_{max},y,t) = 0 \tag{24}$$

$$c(0,y,t) = c(x_{max},y,t) = 0 \tag{25}$$

As for y-axis boundaries they should be a connection between eachother, since we have cut the intestine, a tube, along the borders. That can be represented with Newman boundary conditions as seen in equations (**??**-**??**).

1.7 Constants value

Variable	Description	Value	ref
D_l	Diffusionconstant for lactobacillus when motile$[mm^2/s]$	$3 * 10^{-4}$	
D_c	Diffusionconstant for colicin molecules$[mm^2/s]$	$4.2 * 10^{-5}$	[**?**]
D_a	Diffusionconstant for AHL molecules$[mm^2/s]$	$4.9 * 10^{-6}$	
K_c	Concentration of colicin needed Yersina death [titre]	1:4096	
K_a	Concentration of AHL molecule to activate lactobacillus	exp.	
β_c	Ratio of colicin produced per lactobacillus[moles/cell*s]	(937.5 un./min).	
β_a	Ratio of AHL produced per yersinia[moles/cell*s]	exp.	
η_c	Degradationconstant for colicin	exp.	
η_a	Degradationconstant for AHL[1/h]	1.04	
$V_{f,y}$	Volume of impact, Yersinia		
$V_{f,l}$	Volume of impact, Lactobacillus		
$y_{0,c}$	Initial density Yersinia colony		
$a_{0,c}$	Initial concentration AHL at Yersinia colony		
l_0	Initial density Lactobacillus		

2 MATLAB modeling

2.1 Trival test of system

To test our system we constructed a couple of testruns in which a simple input leads to a trival output. A summury can be seen in tabel **??**.

Tested function	Simplification	Figure
Yersinia basic behavior	No AHL and *Lactobacillus*	**??**
Diffusion of AHL	No *Yersinia* and *Lactobacillus*	**??**
Lac		