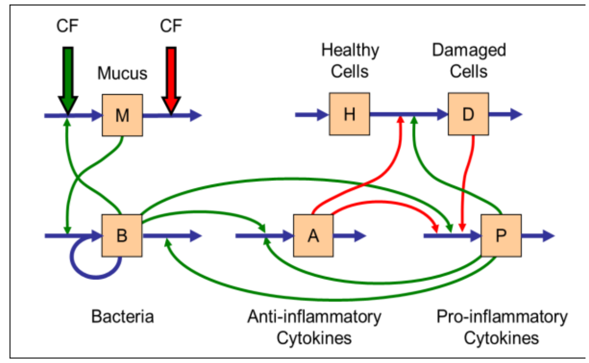
Systems Analysis of Cystic Fibrosis

In the first project of the semester, you explored the key features of CF as a systemic disease. In this last project, you will explore some aspects of the disease with a mathematical model. The diagram of the model is shown in the figure. It shows interactions between healthy and diseased cells (H and D), mucus (M), bacteria (B), and pro- and anti-inflammatory cytokines (P and A). Blue arrows represent the flow of material, red arrows are inhibition signals, and green arrows are activation signals. For example, mucus helps bacteria grow, while pro-inflammatory cytokines hasten their death.



Model Diagram

A very simplistic, dynamic model (see box) of the system is set up by defining an ordinary differential equation for each variable, in the following manner. The derivative of a variable, denoted with an apostrophe, represents the changes in the variable over time. Each change is equal to all processes that increase the variable minus all processes that decrease this variable. Each process is represented with a rate constant that reflects the turn-over speed of the process, multiplied to a product of all directly contributing variables. Each variable in each process has an exponent, called a kinetic order, whose sign and magnitude reflect its impact: a positive kinetic order means a positive (increasing) influence on the process; a negative kinetic order means an inhibiting influence; a value of zero (variable does not show at all in the process term) means no influence. The larger the magnitude of a kinetic order is the stronger is the positive or negative effect.

Model Equations:

$M' = 0.0002B^{0.24}2^{CF} - 0.00015M^{2-CF}$	$M(0) = 1.4$
$B' = 0.02B^{0.8}M^{1.4} - 0.016B^{1.2}P^{0.1}$	$B(0) = 4.5$
$P' = 125B^{0.2}D^{-0.4}A^{-0.1} - 50P^{0.5}$	$P(0) = 2$
$A' = 1.5B^{0.1}P^{0.1} - 1.2A^{0.5}$	$A(0) = 2.0$
$H' = 650 - 15H^{0.5}P^{0.3}A^{-0.1}$	$H(0) = 1500$
$D' = 15H^{0.5}P^{0.3}A^{-0.1} - 450D^{0.2}$	$D(0) = 6$

CF = 0: healthy; *CF* = 1: cystic fibrosis

Your task is to implement the equations in some software. The most convenient is probably PLAS*, but you are welcome to use another program, such as Matlab, instead. Once you have implemented the model, compute solutions (time courses from $t = 0$ to $t = 2000$) of all variables for healthy individuals and CF sufferers in order to make sure your code runs; this particular test result is rather boring. But now, explore repeated bacterial infections and different intervention strategies, such as mucus removal or treatment with antibiotics or anti-inflammatory cytokines. For instance, reduce the bacterial population with an antibiotic to a very small number, which however is still greater than 0. Summarize your findings in a report, make recommendations for treatments, and discuss the limitations of the model.

Presentation: December 4
Report: December 6

* URL for PLAS: http://enzymology.fc.ul.pt/software. A free PowerPoint tutorial for PLAS will be posted on t-square. PLAS only runs directly on PCs. To use a Mac, it is possible to run PLAS within Wine bottler (http://winebottler.kronenberg.org/) or some other PC-emulation software.