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System-level analysis of metabolism in *Yersinia pseudotuberculosis* and the biovars of *Yersinia pestis* using a genome-scale mathematical model.

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The gram-negative bacterium *Yersinia pestis*, the aetiological agent of plague is one of the deadliest and most dangerous pathogens known to man. Here we report the successful coupling of linear optimization and genomic data with the aim of developing system-level models of metabolism in the three biovars of *Yersinia pestis* and its non-lethal ancestor, *Yersinia pseudotuberculosis*. The models were compared with experimental observations to test their accuracy and completeness of our metabolic networks. Finally, we used the models to analyze strain-specific characteristics such as robustness and evolution of metabolic capabilities.

## **System-level analysis of metabolism in *Yersinia pseudotuberculosis* and *Yersinia pestis* using a genome-scale mathematical model.**

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Plague has been one of the deadliest pestilences in history. Although primarily a murine disease, human infection via flea bites leads to a highly contagious disease. The gram negative bacterium *Yersinia pestis* (YP), a direct progeny of the non-lethal enteric bacteria *Yersinia pseudotuberculosis* (YPS), is the aetiological agent of the plague. Despite all of our modern medical advances, plague is still prevalent, and recent reports of antibiotic-resistant strains of YP<sup>1,2</sup> are cause for great alarm. Coupling this ominous development with the potential use of YP as a biological weapon<sup>3</sup> by terrorists or rouge states has increased the interest in the biology of this pathogen.

Based on differences in their metabolic capabilities, genotypes of YP have been classified into three biovars (*antiqua*, *mediaevalis* and *orientalis*). Each of these biovars has been implicated in one of the major pandemic of the past two thousand years<sup>4</sup>. Recently, the genomes of a number of YP strains representing all three biovars as well as that for YPS have been sequenced and are now available to the public<sup>5-8</sup>. Using this data

and other published experimental observations, we have developed several genome-based computational models of cellular metabolism in YP biovars and YPS. Such system-level theoretical models allow us to study the integrated function of an organism's metabolic network and to make important predictions regarding their cellular behavior.

Our models of YP and YPS accurately account for the structural and compositional features of each organism. In each model the metabolic reactions have been appropriately compartmentalized and we have accounted for the inter-compartmental exchange of metabolites, as well as the import of nutrients and export of waste products. Additionally, during its life-cycle, YP has to thrive in two very different environments, i.e. the flea gut and the mammalian blood stream. This environmental change triggers *Y. pestis'* virulence and leads to major changes in the metabolic behavior of the cell. We have ensured that our models account for a majority of these changes.

The model predictions were compared with experimental observations to validate the accuracy of the model and completeness of our metabolic network reconstruction. We have examined the effect of environmental changes on metabolic capabilities and robustness of each biovar. These results have allowed us to determine if the genetic and metabolic changes that exist between the biovars are critical to the survival of each organism in diverse environmental reservoirs. In addition we have begun examining the metabolic differences between YPS and different biovars of YP (see Fig. 1). Such a study could aid in our elucidation of environmental restrictions and evolutionary steps that led to mutation of benign *Yersinia pseudotuberculosis* into the very deadly *Yersinia pestis*.

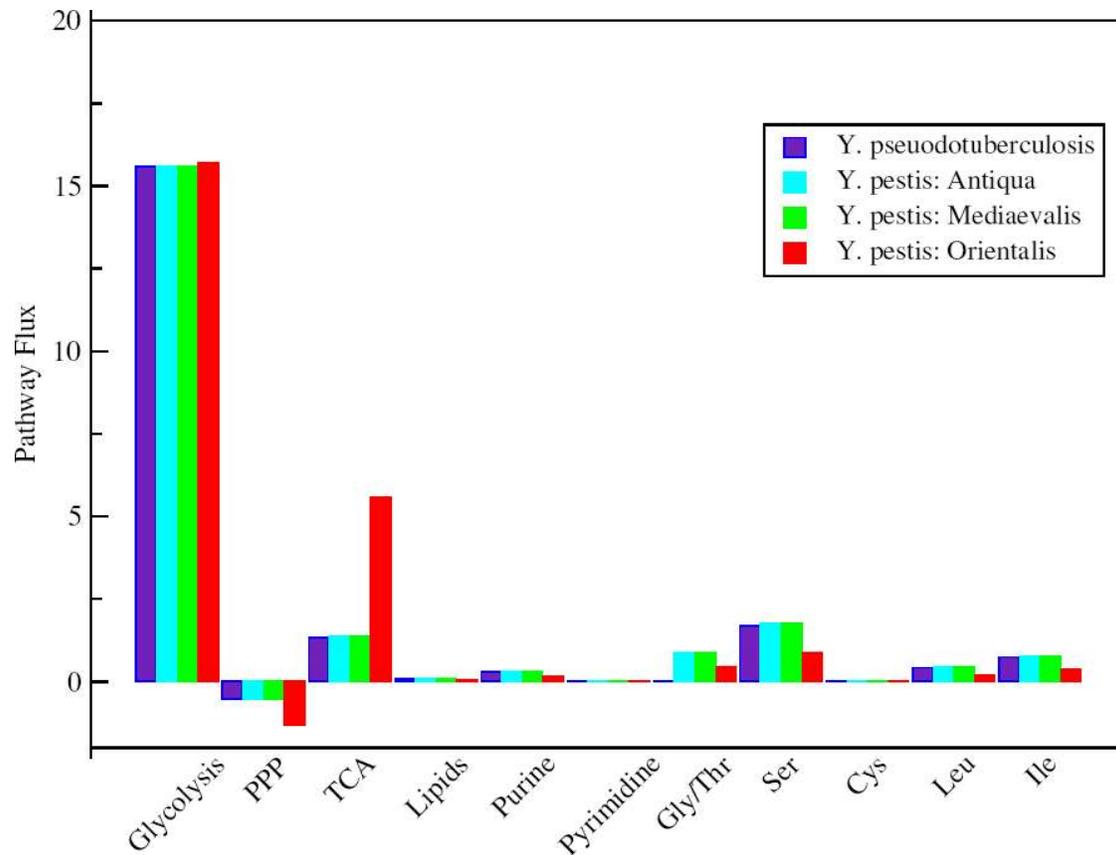


Figure 1. Plot of Fluxes through different metabolic pathways for three biovars of *Yersinia pestis* and *Yersinia pseudotuberculosis*.

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