

Mathematical Model of Infection Mechanism of Bordetella



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Abstract

In this work, the infection strategy of Bordetella has been modelled. Four classes of genes, called virulence factors, need to perform specific dynamic response in Bordetella to infect its host. These genes are the products of a two-component signal transduction system known as BvgAS. The proteins that are modelled in this paper are namely, BvgA, BvgS, class 1, class 2, class 3 and class 4. BvgA can exist in three possible states which depends on the phosphorylation of specific domain of protein, these states are namely BvgA-P1, BvgA-P2, BvgA-P3. Also BvgA protein can also exist in two active and inactive states. Active BvgA is responsible for auto-transcription and transcription of class1 to class 4 genes. We used stochastic simulation to solve the 20 model equations as given in the paper. Gillespie algorithm will be used to solve the system of equations. In Gillespie algorithm we define the probability of each reaction happening and then this probability will decide which reaction will happen more frequently. We assume that at any instance only one reaction will be occurring (proportional to its probability). The number of molecules of certain species will then be changed according to these defined probabilities. We reproduced all the different results given in the paper by reproducing the dynamic plots of class 1-class 4 gene expressions.

Introduction

In this work we mathematically modelled the signal transduction and central dogma process of a bacteria called bordetella. Virulence factors are the proteins which are responsible for the infection in the host. In Bordetella there are four virulence proteins which are regulated by a protein system inside a cell called BvgAS. In its life time bordetella faces various types of environment and in response to that it changes the dynamics of virulence factors production so that it can effectively infect its host. Three types of environmental changes were considered in our model namely Bvg⁻, Bvgⁱ and Bvg⁺, changes in these environment were modelled by changing the signal strength (S). Bvg⁻ represents absence of signal, Bvg⁺ represents the signal strength is very high and Bvgⁱ represents that the concentration of signal is intermediate. In the presence of signal, the trans-membrane protein (BvgS) activates itself by attaching a phosphate group (PO⁴²⁻). This phosphate group is then travels through three domains of BvgS to ultimately activate another protein called BvgA (Figure 1). Once BvgA is activated to BvgA-P, it then acts as a transcription factor which regulates the protein production of all the virulence genes (Class 1 to Class 4) and also responsible for production of BvgAS system proteins (Positive feedback).

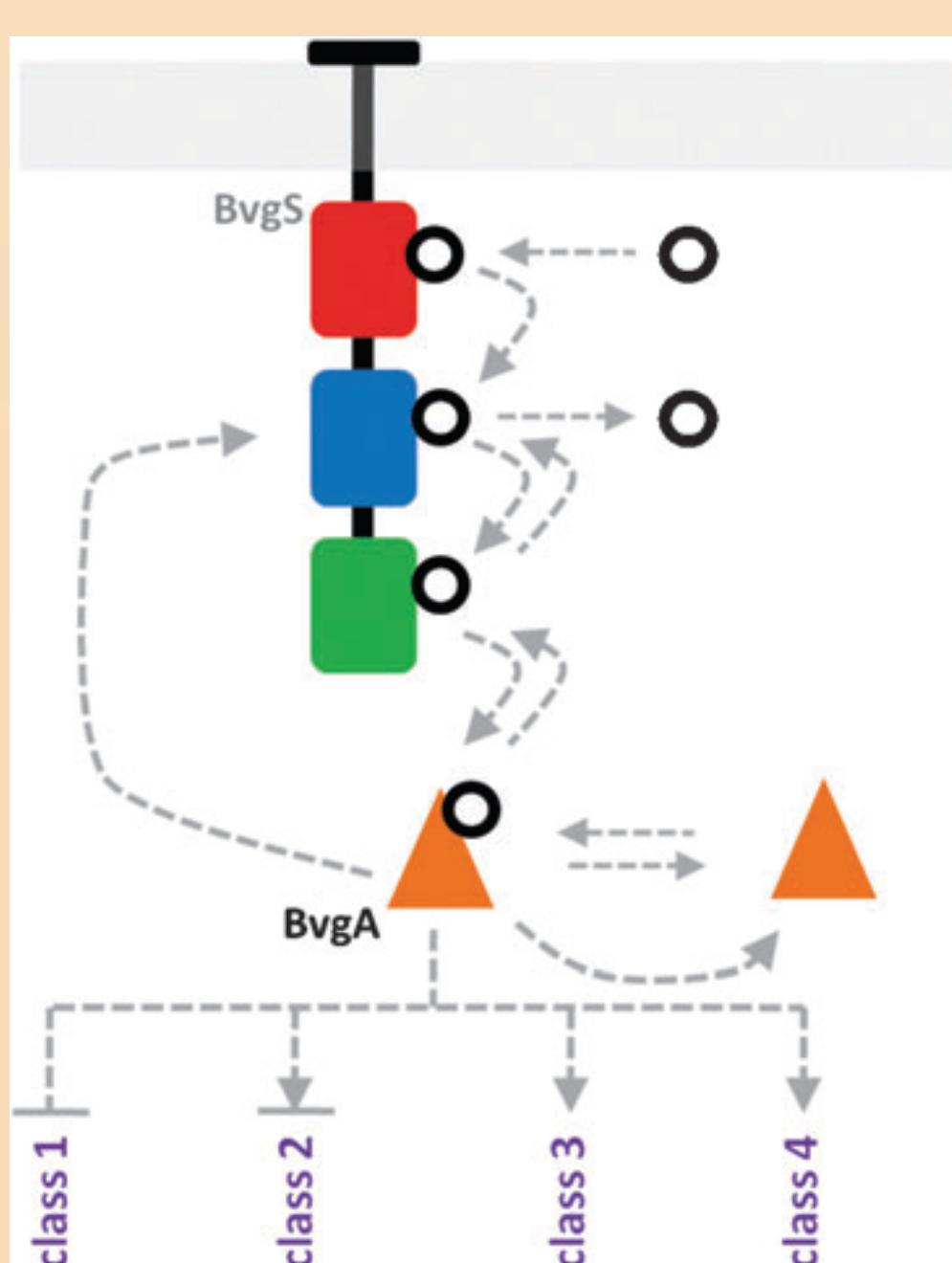


Fig.1 Cartoon representation of the BvgAS regulatory network. In presence of signal, BvgS autophosphorylates itself, and passes the phosphate group (black circles) to BvgA (triangle) in three steps. Phosphorylated BvgA then controls expression of class 1, 2, 3, and 4 genes. In addition, BvgA-P also controls expression of BvgA and BvgS.

Model construction

In the paper, there are 20 “chemical reaction” equations. The rate constants in above reactions are listed in Table 1. Since the model is stochastic in nature, Gillespie Algorithm were used to solve the system of equations.

The rate laws for different interactions are listed below.

(1) Auto-phosphorylation of BvgS into BvgS-P1 (activation of BvgS)

$$r_1 = \frac{k_1 \times BvgS \times S / k_{1a}}{\left(1 + \frac{S}{k_{1a}}\right) \times (k_{1b} + BvgS)}$$

(3) Transfer from BvgS-P2 to null (Dephosphorylation)

$$r_3 = k_3 \times BvgS - P2$$

(4) Transfer from BvgS-P2 to BvgS-P3

$$r_4 = k_4 \times BvgS - P2$$

(5) Transfer from BvgS-P3 to BvgS-P2 (reverse transfer of phosphate group)

$$r_5 = k_5 \times BvgS - P3$$

(6) Transfer from BvgS-P3 to BvgA (activation of BvgA protein)

$$r_6 = \frac{k_6 \times BvgS - P3 \times BvgA}{(k_{6p} + BvgS - P3) \times (k_{6q} + BvgA)}$$

(7) Transfer from BvgA to BvgS-P3

$$r_7 = \frac{k_7 \times BvgA - P \times BvgS}{(k_{7r} + BvgS) \times (k_{7s} + BvgA - P)}$$

(8) Degradation of BvgS

$$r_8 = k_8 \times BvgS$$

(9) Degradation of BvgA

$$r_9 = k_9 \times BvgA$$

(10) Degradation of BvgA-P

$$r_{10} = k_{10} \times BvgA - P$$

(11) Production of BvgA and BvgS proteins

$$r_{11} = \frac{k_{11} \times (BvgA - P)^2}{(k_{11a})^2 + (BvgA - P)^2}$$

(12) Production of Class 1 proteins

$$r_{12} = \frac{k_{12}}{1 + (BvgA - P / k_{12r})^2}$$

(13) Production of Class 2 proteins

$$r_{13} = \frac{k_{13} \times (BvgA - P)^2}{[(k_{13a})^2 + (BvgA - P)^2] \times [1 + (BvgA - P / k_{13r})^2]}$$

(14) Production of Class 3 proteins

$$r_{14} = \frac{k_{14} \times (BvgA - P)^2}{(k_{14a})^2 + (BvgA - P)^2}$$

(15) Production of Class 4 proteins

$$r_{15} = \frac{k_{15} \times (BvgA - P)^4}{(k_{15a})^4 + (BvgA - P)^4}$$

(16) Degradation of class 1

$$r_{16} = k_{16} \times \text{class 1}$$

(17) Degradation of class 2

$$r_{17} = k_{17} \times \text{class 2}$$

(18) Degradation of class 3

$$r_{18} = k_{18} \times \text{class 3}$$

(19) Degradation of class 4

$$r_{19} = k_{19} \times \text{class 4}$$

(20) BvgA-independent (basal) production of BvgAS

$$r_{20} = k_{20}$$

Results and discussion

The dynamics of virulence protein production in wild type Bordetella

The picture below is our simulation results for the virulence protein dynamics for wild type bordetella. (Fig. 2).

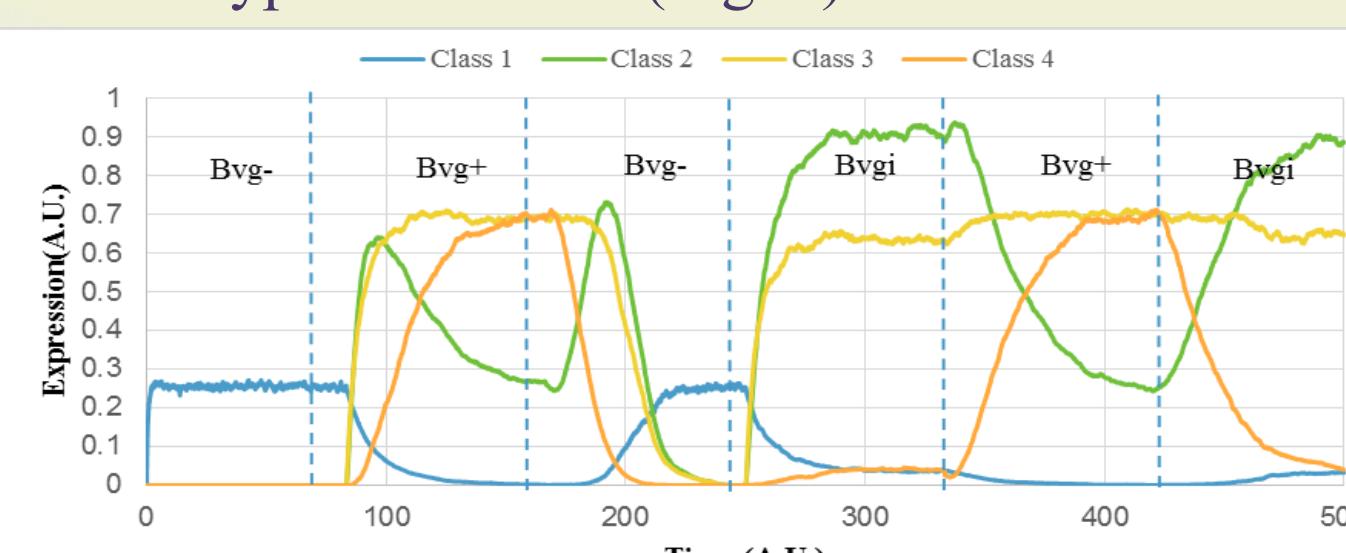


Fig. 2 Normalized gene expression dynamics of class 1, class 2, class 3, and class 4 under various environmental conditions. The graph captures dynamics in Bordetella in the six possible transitions between Bvg⁻, Bvgⁱ, and Bvg⁺ conditions. The transitions were studied by varying the environmental signal strength, S.

Comparing the dynamics of mutant protein with wild type when only one domain of BvgS is present instead of three

To investigate the significance of the presence of three domains, we performed simulations for systems where BvgS possessed only one phosphotransfer domain, and compared against the wild-type BvgS. Simulations were performed with a different BvgS mutant. We changed k₂, k₃ and k₄ to 1500, 0 and 1500, respectively. All other biochemical parameters of the system were kept identical as the wild type. The simulation results are indicated in the below figure (Fig. 3).



Fig. 3 Dynamics of expression of class 1 (A), class 2 (B), class 3 (C), and class 4 (D) genes in wild-type Bordetella (green line), BvgS with a single component (BvgS1C) (blue line) in the six transitions between Bvg⁻, Bvgⁱ, and Bvg⁺ environments.

Comparing the dynamics of mutant protein with wild type when Dephosphorylation is not allowed

We compared the dynamics of the four classes of genes in wild-type Bordetella and a BvgS-mutant (BvgS-DP), where the dephosphorylation step is not permitted. In the simulations, we set k₃=0, which means the rate constant for dephosphorylation equal to zero. Results are showed in Fig. 4.

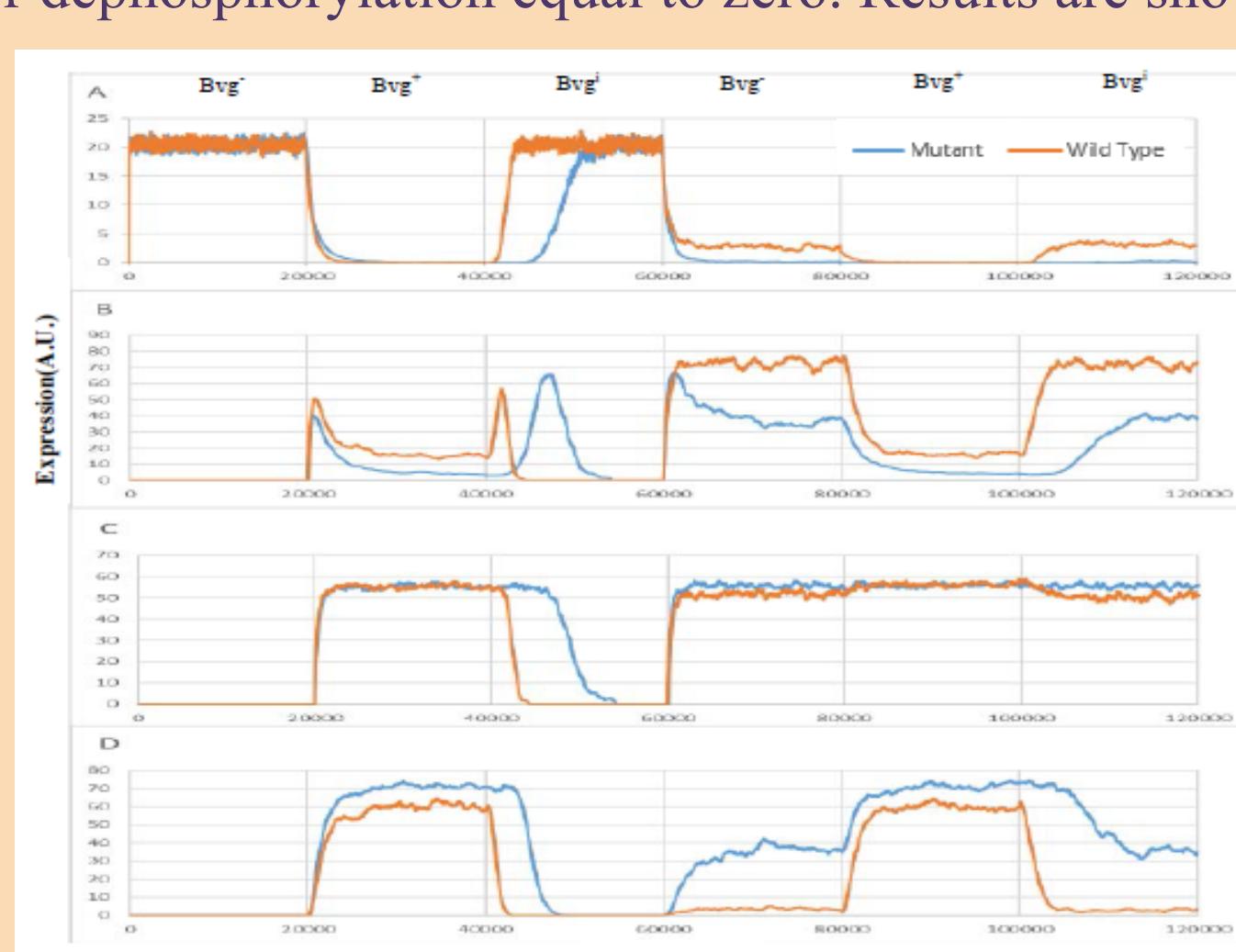


Fig.4 Comparison of dynamics of class 1 (A), class 2 (B), class 3 (C), and class 4 (D) genes in wild type (orange) and BvgS-DP (BvgS mutant where dephosphorylation is not allowed) (blue) in transitions between Bvg⁻, Bvgⁱ, and Bvg⁺ conditions.

Comparing the dynamics of mutant protein when BvgA is not allowed to produce itself

To test the importance of positive feedback in the system, we let k₁₁=0 and make other terms in the model were kept the same. The results areas shown in Fig.5.

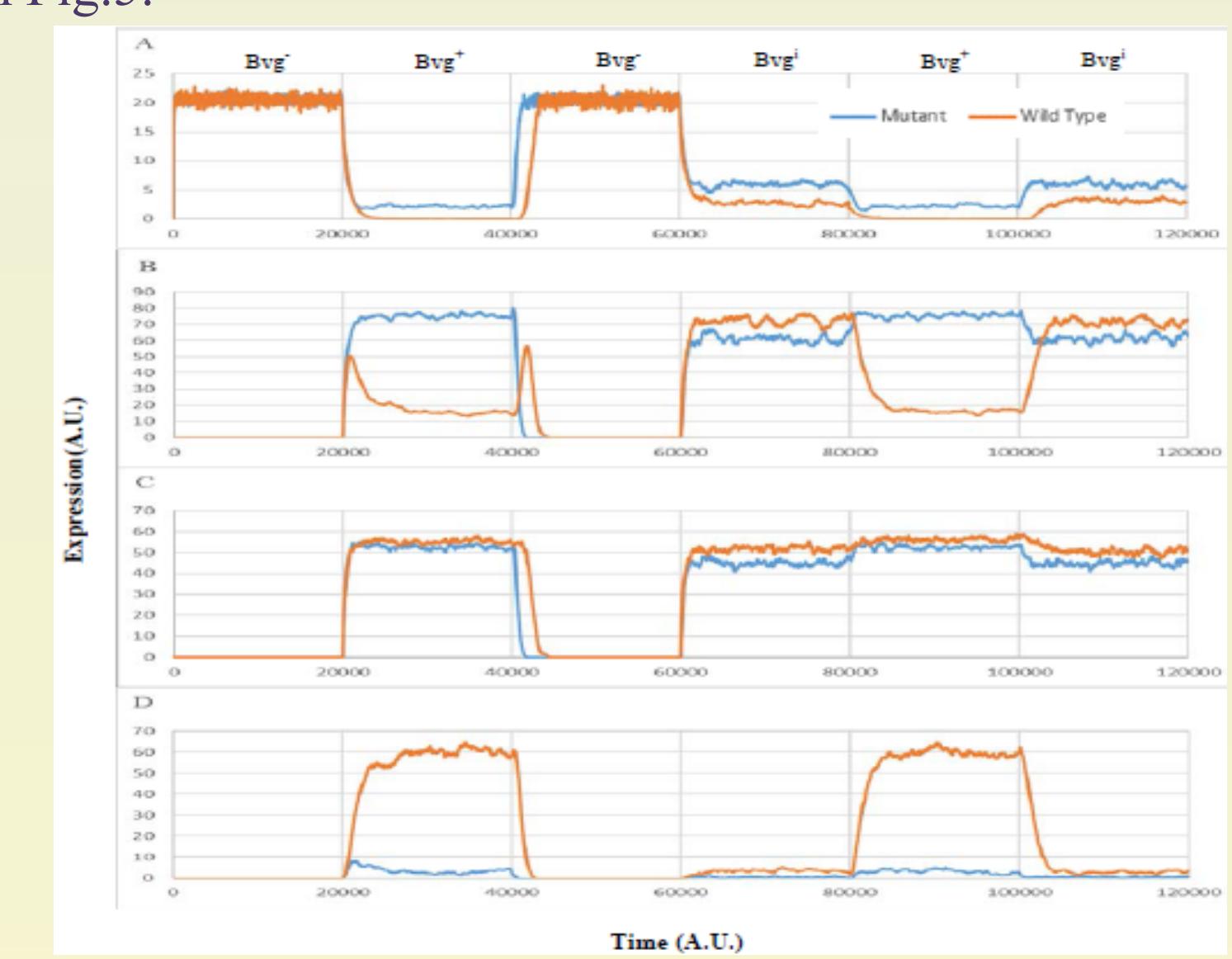


Fig.5 Comparison of dynamics of class 1 (A), class 2 (B), class 3 (C), and class 4 (D) genes in wild type (orange) and WT-FB (BvgS mutant where positive feedback is not allowed) (blue) in transitions between Bvg⁻, Bvgⁱ, and Bvg⁺ conditions.

Comparing the dynamics of mutant protein when reverse flow of phosphate group is not allowed

To test the role of reversible steps in phosphate transfer, we let k₅, k₇=0 and kept the other parameter value same as wild type. We tested the dynamics of class 1, 2, 3, and 4 genes in wild type and in mutants where the reversibility of the phosphate flow was not allowed (Fig. 6).

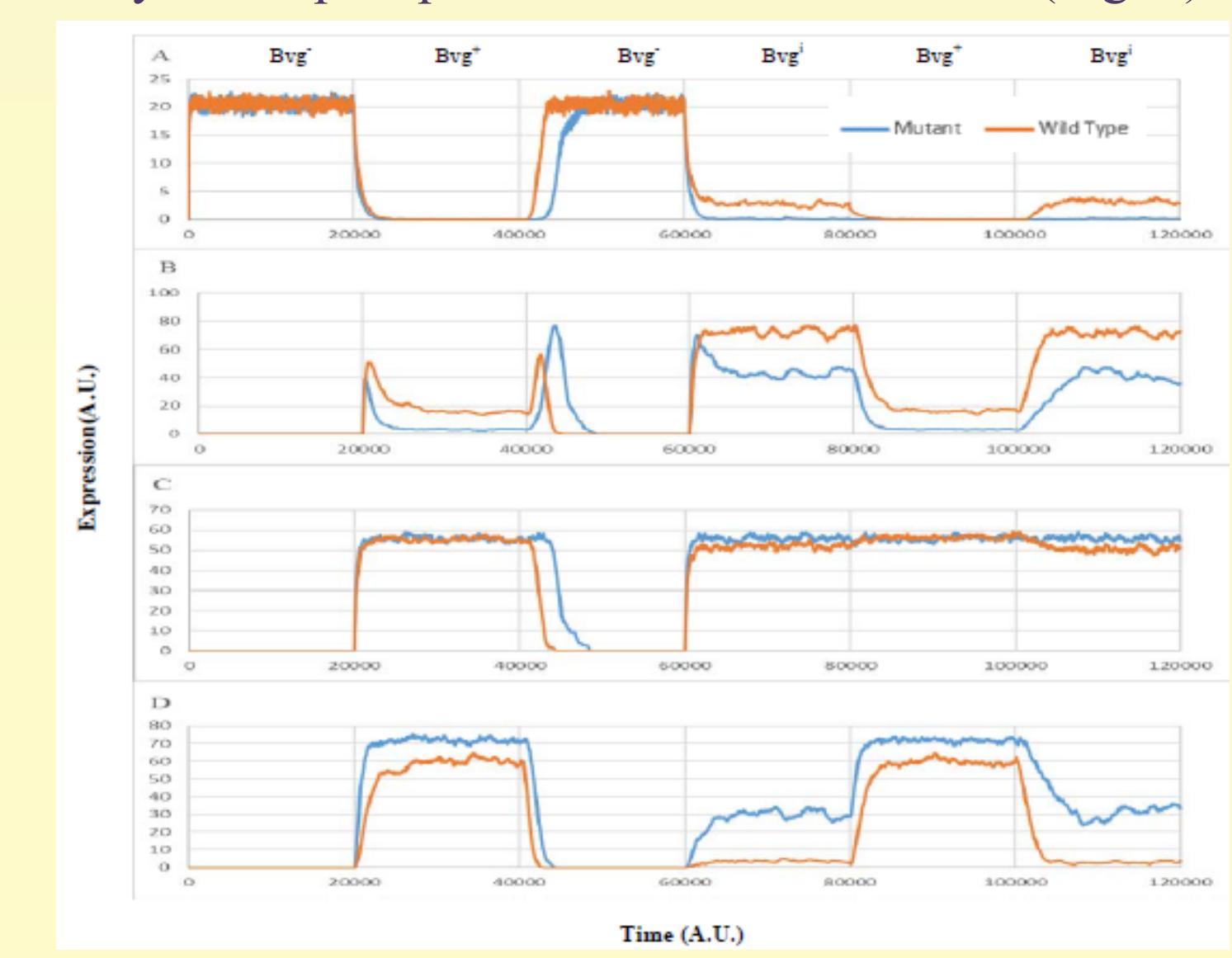


Fig.6 Comparison of dynamics of class 1 (A), class 2 (B), class 3 (C), and class 4 (D) genes in wild type (orange) and a mutant where reversible phosphorylation is not allowed (BvgS-R) (blue) in transitions between Bvg⁻, Bvgⁱ, and Bvg⁺ conditions.

Conclusion

The signal transduction system of bordetella were mathematically modelled. The modelled was then solved using a stochastic simulation method called Gillespie algorithm. We plotted the dynamics of virulence protein of wild type in order to compare the results with experimental data in literature. Later different types of mutant were developed by changing the parameter values to appropriate values and the dynamics of virulence protein were compared with mutant. We discovered that there is quite a difference in the dynamics of virulence protein between wild type and mutants. The results found by our simulation matches with the results produced in the paper.

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