

## COMPUTATIONAL BIOLOGY TOOLS IN DESIGN OF AN AGROCHEMICAL AGAINST *Xylella fastidiosa*

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### Abstract

*Xylella fastidiosa* is a Gram-negative, non-flagellated bacterium that causes CVC in citrus and Pierce's disease in grapevines. The CVC affects 40% of the 200 million orange trees in São Paulo state. It colonizes the xylem vessels of the plants, blocking the water and nutrient flows. PiIT protein is a part of the motility system and very important for *Xylella* pathogenicity and our protein target for drug design. Computational biology tools were used to design the compound able to inhibit the formation of the PiIT hexamer, leading to loss of *Xylella* pathogenicity. This approach could be employed in the development of new inhibitors against different targets belonging to the same protein family of PiIT.

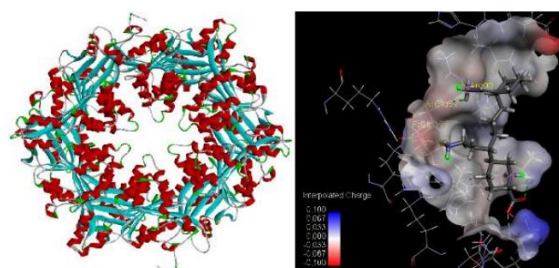
*Key words: Xylella fastidiosa, PiIT, computational biology tools.*

### Introduction

Type IV pili has an important role in the pathogenicity of almost all Gram-negative bacteria, as it is responsible for the motility and bacterial dispersion at surfaces, auto aggregation and biofilm formation. Commonly, the energy required for this movement is provided by ATP hydrolysis which is obtained by PilB and/or PiIT protein activities. The inhibition of PiIT protein leads to the loss of pathogenicity in some bacteria strains.

### Results and Discussion

Computational biology tools were used to design a homology model for the *Xylella fastidiosa* PiIT protein using the PiIT from *Pseudomonas aeruginosa* and *Aquifex aeolicus* (PDB entries: 3JVU and 2GSZ). Model refinement and molecular dynamics simulations were used in the model validation procedure. Different pockets in the protein PiIT hexamer were identified and used for ligand docking and virtual high throughput screening (vHTS) with commercial compounds. The best inhibitor structures were then improved using de novo compound design techniques aimed to find the best proteinligand pair for posterior in vitro tests.



**Figure 1.** PiIT hexamer modeled using *P. aeruginosa* (PDB entry 3JVU) and one pocket with the proposed inhibitor.

### Conclusions

The design of new drugs and agrochemicals could be improved using in silico approach, allowing the discovery of the best sites in the target protein and enabling the design of appropriate inhibitors, providing the best host-inhibitor interaction.

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<sup>1</sup> Hopkins, D.L.; Purcell, A.H., *Plant Dis.* **2002**, 86, 1056.

<sup>2</sup> Hopkins, D.L., *Annu. Rev. Phytopathol.*, **27**, 271-290, 1989.

<sup>3</sup> Neshich, I. A. P.; Nishimura, L.; Moraes, F. R.; Salim, J. A.; Villalta-Romero, F.; Borro, L.; Yano, I. H.; Mazoni, I.; Tasic, L.; Jardine, J. G.; Neshich, G., *Curr. Protein Pept. Sci.* **2015**, 16, 1.

<sup>4</sup> EMBRAPA Informática Agropecuária. Neshich, I. A. P.; Nishimura, L.; Salim, J. A.; Mazoni, I.; Jardine, J. G.; Neshich, G. PI1089068 out 2010, Brasil.