

PIMENTO: a Physics and biology-informed Neural network for dynamic inference of gene regulatory networks to model plant response to biotic stresses

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In a scenario of climate change, plants are exposed to an increasing variety of pathogens, accompanied by additional hostile conditions. Comprehensive understanding of plant immunity is essential to ensure food production and security. Gene regulatory networks (GRNs) provide a powerful representation of these intricate regulatory systems. However, most inference methods measure only static properties and face the trade-off between scalability and mechanistic interpretability.

Here, we propose PIMENTO, a novel hybrid model based on physics-informed neural-networks to infer fully interpretable GRNs from time-series omics data. This approach exploits the ability of neural-networks to approximate high-dimensional systems in combination with explicit ODEs and prior biological knowledge.

PIMENTO showed robustness on synthetic data compared to random predictors when inaccurate prior is provided, when trained on as few as 4 timepoints and noise. PIMENTO on 21 time-series (3-7 timepoints, 2- 8 replicates) of tomato (*Solanum lycopersicum*) plants upon infection by diverse economically important pathogens, with prior network composed of 11822 genes, 277 transcription factors (TFs) and 66343 edges, yielded several TFs with pivotal role in plant defense. Among the top 10, *Solyc12g009240-ERF16* and *Solyc06g070900-TCP17* were functionally validated using the virus-induced gene-silencing system in tomato, demonstrating their key role in the response to *Botrytis cinerea* infection, as silencing of either TF resulted in increased susceptibility.

Overall, PIMENTO showed good performances regarding scalability, interpretability, predictivity and suitability to model time-series with few timepoints, which will fulfil a gap in the literature. PIMENTO can be used beyond plants, since the model is agnostic of the biological system.