

<https://doi.org/10.15255/KUI.2021.040>

KUI-14/2022

Original scientific paper

Received June 5, 2021

Accepted August 14, 2021

Regional Sensitivity Analysis of a Chelating Process Model Applied to Siderophore (Pyoverdine) Production

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Abstract

Regional sensitivity analysis is a part of global sensitivity analysis methods. In this study, a multivariate sensitivity analysis was conducted on a qualitative-phenomenological model. Study results allowed us to pinpoint the most influential parameters. Moreover, important measures or ranking gave more insight into factors ordering according to their relative influence and permitted them to follow parameter sensitivities over time. Lastly, a confirmatory procedure using extensive parameter randomisation that covered a broad range of the parameters space allowed more insight into and certainty of each input parameters' relative importance.

Keywords

Dynamic modelling, regional sensitivity analysis, time-varying sensitivities, rank sensitivities, siderophore, pyoverdine, iron deficient media

1 Introduction

Nowadays, the increase in computing power allows analysts to create complex mathematical models of increasing sophistication. Based on sole intuition, it is virtually impossible to directly understand the relationship between the endogenous and exogenous variables that constitute these models. Thus, mathematical modelling provides a systematic framework to describe, explain, and quantify function in biological systems known to be multi-dimensional search problems where assumptions represent uncertain information that cannot be collected from real-life observations.¹

Given that complexity, different techniques of sensitivity analysis (SA) have been developed to determine how models' output uncertainty (e.g., a statistic of the simulated time series such as the average simulated stream flow, or an objective function like the root mean squared error) can be apportioned, qualitatively or quantitatively, to different sources of uncertainty in the model input (e.g., subjective assumptions on parameters, initial states, input data, time or spatial resolution grid, etc.).^{2,3}

In addition, SA is applied to explore the importance of input parameters, and is considered an essential element of the model development process (experimental plan setting). SA assists with explaining the effect of various model

constructions, guide parameter estimation, and preparation for model calibration.^{3,4}

In the present study, a univariate along with a multivariate sensitivity analysis was carried out on a phenomenological lag phase model that involved several state variables and parameters related to growth activity substrate availability and secondary metabolites production (pyoverdine).

Finally, the choice of *Pseudomonas fluorescens* Pf-5 was motivated by the fact that *Pseudomonas* strains are known to be efficient biocontrol agents of plant pathogens, because of their catabolic versatility that releases a great diversity of exoproducts with antimicrobials, metal chelating, lytic, and phytohormonal activity.⁵⁻⁸

2 Material and methods

2.1 Measurement of growth and siderophore assay

P. fluorescens Pf-5 is remarkable as a bio-control agent, for its rhizosphere competence and large spectrum of secondary metabolites that it produces.^{9,10}

Cultures were grown with continuous shaking at 200 rpm for 40 h at 25 °C in an Erlenmeyer flask containing 250 ml of King's-B medium; the pH was adjusted to 7. Growth and pyoverdine production were measured by taking 2 ml media each hour for 2 days.

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Both the growth and siderophore production were determined by the method of Meyer and Abdallah.¹¹ Bacterial biomass was turbidimetrically calculated at 600 nm. The produced siderophore was determined by measuring the supernatant's absorbance at 400 nm (optical density (OD)). Siderophore concentration (g l^{-1}) was calculated by the following expression:

$$(\text{OD})_{400 \text{ nm}} \cdot M_w / \varepsilon$$

where $\varepsilon = 16.500 \text{ M}^{-1} \text{ cm}^{-1}$ is an extinction constant and $M_w = 1500 \text{ Da}$ represents the molecular weight of pyoverdine.^{12,13}

2.2 Numerical experiments

2.2.1 Presentation of the numerical model

The studied model is a lag phase type model which was derived from the well-known Baranyi's model; the latter being constituted by 05 non-linear ordinary differential equations (ODE) that form a non-autonomous system.^{14,15}

This model expects that a small portion α of the entire bacterial population (N) adds to the development cycle, while the leftover cells adjust their new physiological state. The pyoverdine content is given by its optical density (P), iron bioavailability is represented by (S), and chelated iron is denoted by (Q).

The model that was applied to growth and secondary metabolite measurements of *Pseudomonas fluorescens* Pf-5 strain is given below:

$$\begin{cases} \frac{dN}{dt} = \alpha(t)Nf_1(S) + \alpha(t)Nf_2(Q) & (1) \\ \frac{dS}{dt} = -\frac{1}{Y_n}\alpha(t)Nf_1(S) - f_3(S)P & (2) \\ \frac{dP}{dt} = \alpha(t)Nf_4(S)\frac{dN}{dt} & (3) \\ \frac{dQ}{dt} = f_3(S)P - \frac{1}{Y_n}\alpha(t)Nf_2(Q) & (4) \end{cases}$$

With,

$$\frac{d\alpha}{dt} = v\alpha(1-\alpha) \quad (5)$$

For the assessment of pyoverdine production, used were the standard inhibition kinetics equations. Thus, we obtained:

$$\begin{cases} f_1(S) = \frac{\mu S}{k+S} & (6) \\ f_2(Q) = \sigma Q & (7) \\ f_3(S) = \beta S & (8) \\ f_4(S) = \frac{\delta}{S^\infty + S} & (9) \end{cases}$$

where, Y_n ($\mu\text{g } \mu\text{l}^{-1}$) represents a growth yield constant; μ

(h^{-1}) is the specific growth rate as a function of substrate concentration; k (μM) is the nutrients concentration where the specific growth rate μS has half its maximum value; S^∞ (μM) is the iron concentration triggering pyoverdine synthesis; σ ($\text{h}^{-1}/\mu\text{M}$) represents the rate of iron chelation; v (unitless) is the population recovery rate; δ (μM) and β (h^{-1}/OD) are both coefficients of linear functions which are functions of the amount of freely available iron in the media, and finally, $\alpha(t)$ represents the physiological adaptation state of the studied population. All coefficients: μ , k , σ , β , δ , Y_n , S^∞ , v are positive values.¹⁵

2.2.2 Regional Sensitivity Analysis (RSA)

RSA, is a global sensitivity analysis method, widely used because of its ease of implementation in factor mapping procedures.^{16,17} In this study, we firstly performed a univariate rank sensitivity analysis consisting in determining the sensitivity indexes defined by partial derivatives given by Eq. (10).

$$S_i = \left(\frac{\theta_i^*}{y^*} \frac{\partial y}{\partial \theta_i} \Big|_{\theta = \theta^*} \right) \quad (10)$$

Sensitivities were then ordered by their respective absolute values in ascending direction. Here, y^* is the output value of the model obtained for the vector (optimal, reference vector), which is initially fed as input.

The values of this reference vector were obtained by calibration of the present Lag-Log phase model (Eqs. 1–9) to laboratory-based experimental data (biomass and pyoverdine content).¹⁸ In a second study, the same vector had been used to test model response to small variation following two cross fold deviations (in both directions) from the optimal default vector, along with an extensive parameter randomisation analysis that, conversely to the present work focused on state variables sensitivity, was centred on parameters sensitivities.¹⁹

In a second step, a multivariate sensitivity analysis was carried out by determining the sensitivity indexes defined by partial derivatives. Here we calculated the standardised sensitivity index that gave relative sensitivities by the mean of the terms (11) that consider time-varying sensitivities.

$$S_{\text{rel}} = \frac{\partial y}{\partial \theta} \frac{\theta}{y^*}, y \neq 0 \text{ or } S_{\text{rel},\theta} = \frac{dy}{d\theta} \frac{\theta}{y}, y \neq 0 \quad (11)$$

where, y is the output value of the model obtained for the input vector θ^* .

At each time moment t , sensitivities were evaluated at specific parameters value, and were only valid in the environs of the default parameter set. For a non-linear model, sensitivities were computed at parameter values close to optimal param values. It is usually considered that the higher the value of the sensitivity index, the more the input parameter influences the model's output.

Lastly, an extensive parameter randomisation analysis was performed by using a uniform Latin hypercube sampling

procedure (LHS) that sampled 10.000 vectors in the stratified 8-dimensional hypercube space instead of studying the response of a unique input vector θ^* (baseline vector). Time-varying sensitivities were calculated at each time moment t . For the sake of conciseness, plots are drawn for the top three most frequent parameters at (8, 24, and 40 h).^{18,20}

All computations were performed in *MATLAB 2012a* (*MathWorks, Natick, MA*) and each simulation covered a 40-hour time interval simulation.

3 Results and discussion

3.1 Multivariate sensitivity analysis

3.1.1 Rank sensitivity analysis

In complex models, one-variate sensitivity analysis is insufficient for a comprehensive study of any model. Hence, simultaneous changes in more than one parameter's values would result in an unexpected output change because of uncertainty and non-linear relationships among different model components.^{21,22} Therefore, one-variate sensitivity analysis should be followed by a multivariate sensitivity analysis that uses dimensionless sensitivities of model output to parameters and collapses them into summary values. In this case, the highest sensitivity value was associated with the most critical parameter. Therefore, the magnitudes of the sensitivity summary values could be used to compare or classify input parameters, and help users to select the most influential parameters that can be subsequently optimised.^{23,24}

In this section, a plot of each S_i is given in Fig. 1 for the variable biomass (A) and pyoverdine content (B).

From Fig. 1 (A), inputs can be roughly classified into three groups: Y_n , M_u , v , and k that constitute the 1st group (in order of decreasing effect magnitude) with both the highest to medium overall and interaction (non-linear) effect. Secondly, Sigma, Delta, and Beta's parameters hold the following position with a relatively low effect group; and finally, S_{inf} which represents the least important parameter in the model.

For the pyoverdine content variable (P), sensitivity indexes can be classified into four groups that are distributed among three classes of effects: Y_n and Beta represent the 1st group, immediately followed by S_{inf} , v , and M_u (in order of decreasing effect magnitude); both groups hold the highest overall and interaction effect class. In the intermediate and lowest class, we respectively find the parameter Delta alone, followed by k and Sigma that exert the least important effects.

Summary values of sensitivity index S_i for the state variables biomass and pyoverdine clearly show that Y_n exerted the highest effect, where S_{inf} and the two parameters (k & Sigma) exerted the least important effects on biomass and pyoverdine content variables.

According to Fig. 1, we can investigate the effect of any input parameter. For example, the parameter Y_n has the highest value of sensitivities (3.9 & 3.8), which means that, given a slight increase in Y_n (+/-10%), the biomass and pyoverdine output will change by $\cong 4$ times on average. Therefore, if the dynamic model is to be fine-tuned, the most minor influential parameters should be kept at their default value or fixed to any constant within their feasible range, as it makes no sense to fine-tune parameters that have no or negligible effects.

Alternatively, we can add, substitute or delete insensitive parameters by others that have a more significant impact on the description of the phenomenon of interest. However, it must be kept in mind that this approach could alter the overall structural integrity as it increases the need for more experimental data that are rarely readily available.

The increase in the model's number parameters leads to a mechanical rise in model complexity. On the other hand, the model's oversimplification (high aggregation level) induces a system openness that renders biological model testing virtually impossible critically and objectively. Thus, a trade-off between the two earlier cases should be found by simulation experiments. In both situations, the system should be maintained in a tractable and manageable numerical form that guarantees reliable and effective predictions.^{4,25}

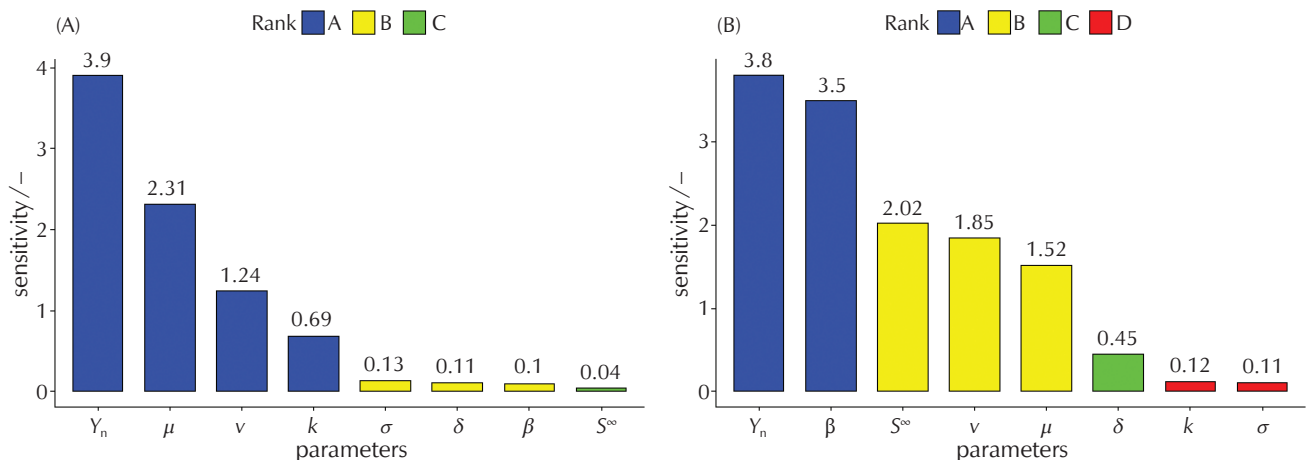


Fig. 1 – Model's rank sensitivities for biomass (A) and pyoverdine content (B)

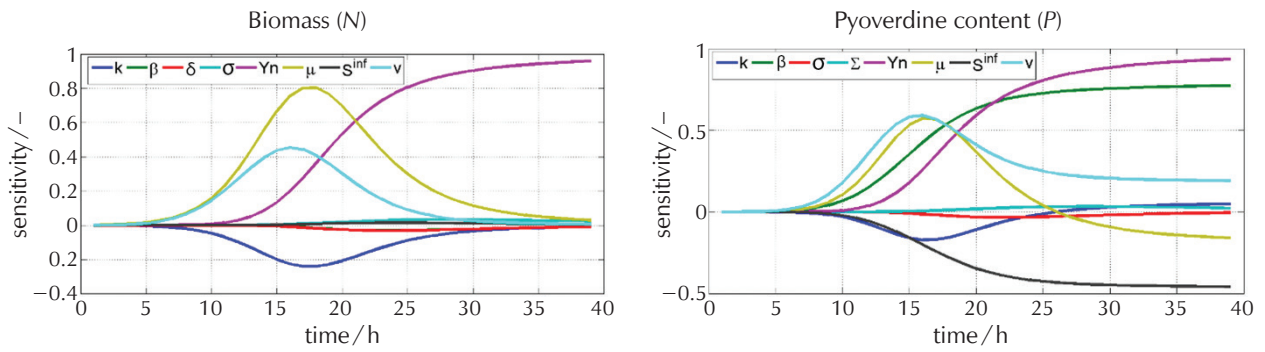


Fig. 2 – Dynamic parameters' sensitivity for biomass (N) and pyoverdine content (P)

3.2 Time-varying sensitivity analysis

Since we are dealing with a dynamic model, sensitivities of the modelled variables biomass and pyoverdine content to the parameters' values may change over time. Thus, it makes sense to visualise the sensitivity functions as they fluctuate.

The following plot provides information about the parameters models dynamic importance during simulation (see Fig. 2).

The parameters Y_n , M_u , and v have a consistently positive effect on the number of bacterial cells, as their corresponding sensitivity functions are always positive. However, higher values of k consistently decrease the biomass of the bacterial population.

Several sensitivity functions exhibit strong similarities for the output variable biomass (N). For instance, M_u and v share the same curve tendency, which indicates that these parameters have a comparable effect on this output variable. If too similar, like in the case of the parameters Beta, Delta, Sigma, and S_{inf} , where the sensitivity functions are highly correlated, the joint estimation of these parameter combinations may not be possible on these sets of experimental data alone. Thus, the increase in the value of any of these parameters will generate approximately the same output response if the value of the other parameters is decreased by the corresponding appropriate amount.²⁶

For the output variable pyoverdine content (P), the similarities between Delta and Sigma; v and M_u ; Beta and Y_n are relatively strong. However, some parameters

had equivalent cumulative effect while having opposite dynamic behaviour implying negative relationships (i.e., v and M_u regarding k ; Beta regarding S_{inf}) (Fig. 2).

3.3 Extensive parameter randomisation sensitivity analysis

Classification of input parameter effects is given in Fig. 3. Presented are the three most important parameters based on the occurrence percentages of the total 10,000 random parameter sets for which different model's parameters demonstrated the largest (solid bars), 2nd largest (striped bars), and 3rd-largest (stippled bars) relative change, in response to the modulation of model parameters.

Model predictions are shown for three representative time point simulations that respectively correspond to the Lag, Log, and stationary growth phase (8, 24, and 40 h).

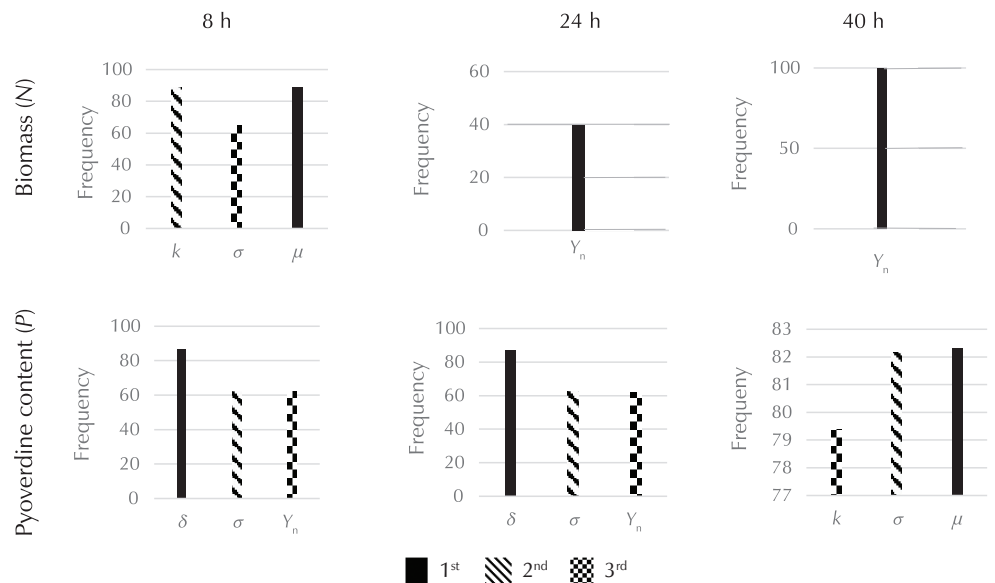


Fig. 3 – Distribution of the three top-ranked input parameters based on the count of events. Shown are the percentages of the total 10,000 randomised parameter sets for which different parameters in the model demonstrated the 1st (solid bars), 2nd most significant (striped bars), and 3rd-largest (stippled bars) relative change at three representative time point simulation.

The present modelling analysis confirmed that for a wide range of scenarios, the two-state variables (biomass and pyoverdine content) may demonstrate consistently significant relative changes in their local concentrations induced by independent variations of the parameters: substrate-to-biomass yield factor (Y_n) or bacterial specific growth rate (M_u).

Overall, parameter importance varied from point to point. For example, at time 8 h, 88.8 %, 88.79 %, and 64.56 % of the 10,000 events ranked the parameters: M_u at 1st place, k at 2nd, and Sigma as the 3rd most influential parameter, while at the time 40 h of virtual growth, the ranking was entirely and exclusively in favour of parameter Y_n .

This constation is relatively accurate for the variable pyoverdine content. We observed a shift in parameters ranking sensitivities over time, ending up with M_u as the top-ranking parameter, followed by Sigma, then k with an occurrence frequency of respectively 82.31 %, 82.17 %, and 79.4 % of the 10,000 random vectors. For the remaining occurrence frequencies, these were widely distributed among the rest of the input parameters, and depended greatly on the combination of input values.

Globally, these results confirm that, for a complex model in which the input parameters interact with each other, the sensitivity for input parameters may vary significantly from point to point in the parameter space.²⁷

4 Conclusion

Current efforts to isolate, characterise, and select the most efficient bacterial antagonists to control phytopathogens worldwide are continuously reported in the literature. However, there has been limited success in the development of commercial products containing viable cells of *Pseudomonas*. For instance, only two highly competent strains are approved in Europe for plant protection because of expensive field sampling and fastidious laboratory analysis procedures.

In the present study, we have quantitatively validated a lag-phase growth model that describes the bacterial dynamic and pyoverdine production against population size count and pyoverdine content measurements of a *Pseudomonas fluorescens* pf-5 strain grown in an iron-deficient media. In addition, regional sensitivity analysis allowed us to successfully pinpoint which parameters needed to be measured more precisely and/or optimised to obtain better predictions and better yields. Namely, the parameters Y_n and M_u (2.04^{-2} and 1.35^{-2} g l⁻¹ of pyoverdine for *Pseudomonas fluorescens* Pf-5 strain). Finally, the extensive parameter randomisation that covered a large range of the parameters space enabled confirmation of rank sensitivity analysis results, which allowed us to gain more insight into the relative importance of input parameters over time.

Globally, the studied system of the differential equation-based model can be used as an indirect experimental tool for PGPR strains selections (strains with high Y_n and M_u values) and real-time monitoring of iron depletion over time, although the small number of repetitions and limited

growth conditions emphasise the need of additional experiments on other *Pseudomonas* strain.

Finally, no absolute sensitivity analysis method is suitable for all types of biological problems. Thus, one should be cautious about the precision of sensitivity analysis results, especially when the model parameters are not identifiable (parameters that cannot be directly measured experimentally) or if one focuses on a single parameter variation and does not take into account possible linear or non-linear interactions amongst parameters. Therefore, further investigation should focus on using an efficient global optimisation approach to confirm the present findings and bring evidence that we did not converge to the localised solutions of the output space parameter that enhances the risk of having inappropriate or nonsensical responses.

ACKNOWLEDGEMENTS

The authors are grateful to Chetouani Fatma El Zohra and Hamza Al Mushet (The Hashemite University) for their numerous valuable suggestions and help on *MATLAB* programming, and Mrs Derouag Mounira for her helpful comments on the final version of this manuscript.

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SAŽETAK

Analiza regionalne osjetljivosti modela nastanka kelata primijenjenog u proizvodnji siderofora

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Regionalna analiza osjetljivosti dio je metoda globalne analize osjetljivosti. U ovom je istraživanju provedena multivarijantna analiza osjetljivosti na kvalitativno-fenomenološkom modelu. Rezultati istraživanja omogućili su određivanje najutjecajnijih parametara. Dan je poredak čimbenika prema njihovu relativnom utjecaju na parametre i omogućeno praćenje osjetljivosti parametara tijekom vremena. Konačna potvrda važnosti ulaznih parametara modela dobivena je nasumičnim odabirom u širokom rasponu njihovih vrijednosti.

Ključne riječi

Dinamičko modeliranje, regionalna analiza osjetljivosti, vremenski promjenjive osjetljivosti, rang osjetljivosti, siderofor, pioverdin, mediji s nedostatkom željeza

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Izvorni znanstveni rad
Prispjelo 5. lipnja 2021.
Prihvaćeno 14. kolovoza 2021.