# SENSITIVITY ANALYSIS AND INDIVIDUAL-BASED MODELS IN THE STUDY OF YEAST POPULATIONS

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Sensitivity analysis, ANOVA, Computer experiments, Individual-Based Model, Yeast populations

**ABSTRACT**

Individual-based models (IBMs), the biological agent-based models, are currently being applied to the study of microbial systems. A microbial IBM of yeast populations growing in liquid bath cultures has already been designed and implemented in the simulator called INDISIM-YEAST. In order to improve its predictive capabilities and further its development, a deeper understanding of how the variation of the output of the model can be apportioned, qualitatively or quantitatively, to different sources of variation must be investigated. The aim of this study is to show how insights into the individual cell parameters of INDISIM-YEAST can be obtained combining local and global methods using classic and well-proven methods, and to illustrate how these simple methods provide useful, reliable results with this IBM. This work deals mainly with the use of screening methods, as the main task to perform here is that of identifying the most influential factors for this microbial IBM. This screening exercise has allowed the establishment of significant input factors to this IBM on yeast population growth, and the highlighting of those that require greater attention in the parameterization and calibration processes.

## INTRODUCTION

Microbial modelling deals with complex spatio-temporal systems and involves the building and use of increasingly intricate models. This complexity often makes analytical or mathematical studies very difficult, when not impossible. Individual-based models (IBMs), the biological agent-based models (Grimm and Railsback 2005), are currently being applied to the study of microbial systems. These modelling techniques, in which methodological distinctiveness runs into the complexity of the interactions between the modelled entities, are increasingly present in microbial research (Ferrer et al. 2009, Hellweger and Bucci 2009). The only way to assess the mathematical properties of these microbial models, including sensitivity, uncertainty, stability and error propagation, is through statistical studies of well-designed computer experiments.

Sensitivity analysis is the study of how the variation in the output of a model can be apportioned, qualitatively or quantitatively, to different sources of variation, and of how the given model depends upon the information fed into it (Saltelli et al. 2000). We deal here with the fact that sensitivity analysis can be employed prior to a calibration exercise to investigate the tuning importance of each parameter, i.e. to identify a candidate set of important factors for calibration. The difficulty of calibrating microbial IBMs against laboratory data increases with the number of processes to be modeled, and hence, the number of parameters to be estimated also increases. Sensitivity analysis may allow a dimensionality reduction of the parameter space where the calibration and/or optimization is made; in addition this allows the clarification of the relative importance of one factor to another. The choice of which sensitivity analysis method to adopt is not easy, since each technique has strengths and weaknesses. Such a choice depends on the problem the investigator is trying to address, the characteristics of the model under study, and the computational cost that the investigator can bear. One possible way of grouping sensitivity analysis methods is into three classes: screening methods, local methods and global methods. This distinction is somewhat arbitrary, since screening tests can also be viewed as either local or global. Further, the first class is characterized with respect to its use (screening), while the other two are characterized with respect to how they treat factors. Especially for microbial IBMs, which are non-linear models, the sensitivity of a model output to a given parameter depends on the value of that parameter, the values of the other parameters (interactions), time and the output itself. Hence, sensitivity is highly “local”, and gaining general insight

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into all these aspects is challenging. Although many modellers remain satisfied with local analysis, an increasing number of modellers are favouring global methods, which explore the entire parameter space and allow for quantifying interactions between parameters. Global methods based on variance decomposition are increasingly being used for sensitivity analysis (Saltelli et al. 2000). Of these, analysis of variance (ANOVA) is surprisingly rarely employed. Yet it is a viable alternative to other model-free methods, as it gives comparable results and is readily available in most statistical packages. Furthermore, decomposing the input factors of ANOVA into orthogonal polynomial effects yields additional insights into the impact a parameter has on an IBM output. Some modeling studies in biology systems have used these techniques of sensitivity analysis (i.e. Ginot et al. 2006, Cariboni et al. 2007, Beaudouin et al. 2008; Dancik et al. 2010).

A microbial IBM to deal with yeast populations growing in liquid bath cultures has already been designed and implemented in the simulator called INDISIM-YEAST (Ginovart and Cañadas 2008, Gomez-Mourelo and Ginovart 2009). The mission of modelling the behaviour of a single yeast cell is one of the cores of this approach. Some interesting qualitative results have already been achieved with its use in the study of fermentation profiles, small inocula dynamics and the lag phase, among others (Prats et al. 2010, Ginovart et al. 2011). Nevertheless, in order to improve its predictive capabilities and further its development, a deeper understanding of how the variation of the output of the model can be apportioned, qualitatively or quantitatively, to different sources of variation must be investigated. Furthermore, better understanding of how this model depends on the information input into it is essential. The current version of this simulator contains uncertain input factors that need to be parameterized and calibrated with several types of experimental data.

In this contribution, we suggest combining the use of different sensitivity analysis methods over diverse model outputs in order to gain knowledge about their inherent variability over the time evolution of the virtual system. The aim of this study is to show how insights into the individual cell parameters of INDISIM-YEAST can be obtained combining local and global methods using classic and well-proven methods, and to illustrate how these simple methods provide useful, reliable results with this IBM. A study of the variability observed in the outcomes of this model, the mono-factorial (one-at-a-time) analysis jointly with the ANOVA-based global analyses, will be performed on some of the INDISIM-YEAST output variables in order to show how these simple procedures can yield interesting ideas about the relationships between information flowing in and out of this microbial IBM. This is useful for the advancement of its calibration and further development.

## MATERIAL AND METHODS

### The microbial IBM to deal with yeast populations: INDISIM-YEAST

We used INDISIM-YEAST as the individual-based simulator for this preliminary study which is based on the generic simulator INDISIM (Ginovart et al. 2002). For a wide description of different parts of INDISIM-YEAST the reader can turn to a number of previously published papers (Ginovart and Cañadas 2008, Ginovart et al. 2011). We have recently adopted for this model description the ODD standard protocol established by Grimm and co-authors (2006), and the ODD description for INDISIM-YEAST can be found in the paper written by Ginovart et al. (2011), which deals with a motivating application of this model to the fermentation process. Nevertheless, a very brief presentation of this simulation model is offered in this section only in order to introduce the variables used in the sensitivity analysis performed.

The purpose of this rule-based model was to analyse the dynamics of populations of a generic single-species of yeast growing in a liquid medium, as well as the collective behaviour that emerges from inocula, mainly affected by intra-specific diversity and variability at an individual level. Each yeast cell is defined by a vector that contains its individual characteristics and variables: a) its position in the spatial domain; b) its biomass which is related by the model to spherical geometry in order to evaluate its cellular surface; c) its genealogical age as the number of bud scars on the cellular membrane; d) the reproduction phase in the cellular cycle when it is in the unbudded (Phase 1), preparing to create a bud, and then the budding (Phase 2) phase in which the bud grows until it separates from the parent cell, leaving behind another scar; e) its “start mass”, the mass required to change from the unbudded to budding phase; f) the minimum growth of the biomass for the budding phase; g) the minimum time required to complete the budding phase; and h) its survival time without satisfying its metabolic requirements. The simulated area is a cube, with liquid medium and yeast, divided into spatial cubic cells, each described by a vector that stands for the main nutrient or glucose particles and excreted ethanol particles, as the only end product. The temporal evolution of the population is divided into equal intervals associated with computer or time steps. The sets of rules governing the behaviour of each yeast cell are in the following categories or sub-models: glucose uptake, cellular maintenance, new biomass production, ethanol excretion, budding reproduction and cell viability. The simulation output includes information on temporal evolution of the number of nutrient particles (glucose), the number of metabolites (ethanol particles), the average nutrient consumption, the number of viable yeast cells, the number of non-viable yeast cells, viable yeast biomass,

maintenance energy expended by the yeast population, mean biomass of the cell population, and the budding index (which represents the fraction of budded cells or cells in Phase 2), among other variables. In all the work discussed below we use dimensionless units.

**Sensitivity analyses**

INDISIM-YEAST is intrinsically stochastic, because it includes stochastic processes and some of the main individual yeast parameters are randomly drawn from normal probability distributions (Ginovart and Cañadas 2008, Ginovart et al. 2011). Thus, it is important to have a previous study of the variability observed in the outcomes of this model, and a first set of simulations with INDISIM-YEAST has been used with this purpose. Different simulations with the same set of parameters were carried out with different initial random seeds, which would imply dissimilar values chosen for the random variables that determine actions and characteristics, resulting in a set of replications to be analyzed from the intrinsic variability point of view.

A mono-factorial (one-at-a-time) analysis consists in plotting the model outcome(s) at a given time (often the last one or at certain time steps), versus a fairly wide range of values. When drawing such plots, all other parameters will be fixed to their nominal or referenced values. A "curve" or trend could be obtained for each parameter and for each model outcome, the slope at any point of this curve actually representing the local sensitivity coefficient with respect to that parameter value. A second set of simulations with INDISIM-YEAST was carried out for the one-at-a-time analysis, which is important for assessing how parameters impact on model outputs since global analyses average or integrate these impacts. Nevertheless, with stochastic models like this yeast IBM, simulations are repeated (that is, replications with different random seeds), and the "curve" or trend also displays the variance pattern of the model output.

Another set of sensitivity methods is based on variance decomposition: output variability is decomposed into the main effects of parameters and their interactions. A natural method for variance decomposition is ANOVA combined with a factorial simulation design. After a graphical analysis of the sensitivity profiles that focuses on parameters one-at-a-time, a third set of simulations with INDISIM-YEAST was planned in order to deal with different ANOVAs, to test the contribution of the parameters and of their interactions to the variability of the model outcomes. In ANOVA, an input factor is sampled for a few values, referred to as the "levels", and in standard ANOVA the effect of this input factor is assessed globally, testing only whether at least one of the levels has an effect on the model output, and thus ignoring how this effect specifically occurs. Nevertheless, a few well-chosen levels may account for the general pattern of the model response, and it is possible to gain more insight into the effect of a quantitative level. ANOVA was carried out with the same design for each output, including two levels per factor and the interactions between two factors. Each ANOVA was roughly controlled by the explained variance on each output and by the analysis of residuals. The ANOVA-based sensitivity index (SI) of a factorial effect may be defined as the ratio of the sum of its squares to the total sum of squares. Global sensitivity indices can be calculated for meaningful subsets of the factorial effects. A specific example is the Total Sensitivity Index of a factor (TSI), which is defined as the sum of all SIs associated with the main effect of the factor and the interactions involving it. The ANOVA-based TSI for each parameter (for each output) accounts for the percentage of variance explained by both the main effect of this parameter and the interactions involving that parameter. It can be defined as the ratio of the sum of squares explained by the main effect and the sum of squares explained by the interactions involving that parameter to the total sum of the square of the corresponding output.

**Computer simulations**

Different sets of simulations were carried out with INDISIM-YEAST, which were grouped into three different series (A, B and C). A single yeast cell constitutes the inoculum and a fixed number of glucose particles are distributed uniformly in the spatial domain in the begining.

For Series A, 100 simulations or replications with the reference values of the parameters of the Table 1 were performed to assess the intrinsic variability of the model. Different outcome variables were controlled to analyse the variability that the diverse replications exhibit. In the case of variables with temporal evolutions, specific time steps (100, 200, 300, 400, 500, 600, and 700) were fixed to collect the values for these variables. For Series B, and for a subset of the input parameters of simulation model, the sensitivity of selected outputs was assessed versus the changes of these input parameters. Table 1 presents the parameters chosen to perform the sensitivity analysis. The reference values are those used for the first series of simulations (Series A), and the ranges are those utilized by the second series of simulations (Series B), in which only one parameter will be modified and all the rest of the parameters will be fixed in their reference values. For each of the chosen parameters, a range of values is selected (MinValue, MaxValue), and its discretization is carried out by subdividing this range into 40 different values: Value $i$ = MinValue + ((MaxValue – MinValue) / 40)*$i$ where $i$ = 1, 2, ...,40. For each of these forty values 10 simulations or replications will be performed. This means that for the Series B and for each outcome variable, 3600 simulations have been carried out (10 simulations for each parameter value x 40 parameter values x 9 parameters). For the Series C, to carry out the

ANOVA, two levels were considered sufficient for all parameters in this first stage of the work. Thus the complete simulation design required 5120 runs (nine parameters with two levels, i.e. $2^9$ combinations, and 10 replications). The chosen values for the ANOVA test are presented in Table 1.

Table 1: Parameter values for the INDISIM-YEAST model that are used in this study of sensitivity analysis.

| Parameter (simulation units) | Reference value | Range | ANOVA levels |
|---|---|---|---|
| $U_{max}$: The maximum number of nutrient particles that may be consumed per unit time and per unit of yeast cellular surface | 0.20 | 0.18 - 0.45 | 0.2475 and 0.3150 |
| $K_1$: The constant to represent the effect of the scars on the cellular surface on the uptake | 0.10 | 0.075 - 0.20 | 0.10625 and 0.13750 |
| $E$: The prescribed amount of translocated glucose per unit of biomass that a yeast cell needs to remain viable | 0.001 | 0.00005 – 0.003 | 0.00079 and 0.00153 |
| $Y$: The constant modelling of metabolic efficiency that accounts for the synthesised biomass units per metabolised glucose particle | 0.60 | 0.5 - 1.5 | 0.75 and 1.00 |
| $m_C$: The critical mass, the minimum mass the yeast cell must attain during Phase 1 to move to Phase 2 | 140 | 75 - 225 | 112.5 and 150.0 |
| $\Delta m_{B1}$: The yeast cell has achieved a minimum growth of its biomass to move from Phase 1 to Phase 2 | 50 | 25 - 80 | 38.75 and 52.50 |
| $\Delta m_{B2}$: The minimum growth of biomass required for the initiation of cell division and bud separation, at the end of Phase2 | 70 | 40 - 110 | 57.5 and 75.0 |
| $\Delta T_2$: The minimum number of time steps that the yeast cell must remain in Phase 2 | 4 | 1 - 40 | 10.75 and 20.50 |
| $q$: The proportion that allows determination of the mass that the daughter cell will have | 0.80 | 0.56 - 0.95 | 0.6575 and 0.7550 |

## RESULTS AND DISCUSSION

Figure 1 shows the temporal evolution of the yeast populations growing from the same initial conditions, with a single yeast cell that evolves according to the stochastic rules implemented in the INDISIM-YEAST model, with different initial random seeds.

Two variables were calculated to characterize the outcome of each replication culture growth during the early stages. The first is the classic lag time, defined at the population level of description and calculated through its geometrical definition; it is the graphical intersection between the initial level ($LnN_0$) and the prolongation of the exponential straight line in a semilogarithimic representation ($LnN=\mu t+b$). The maximum growth rate ($\mu$) and b are determined by means of a logarithmic regression of the upper interval of time, once the exponential phase has been achieved. Finally, the lag time evaluation results in $\lambda=(LnN_0-b)/\mu$. The second variable is the first division time, the time when the first microbial division takes place (or time until the first budding reproduction appears).

Table 2 shows the statistical descriptive analyses performed with the data from the 100 replications of the variables related to the growth population. The high variability is apparent in the first stages of the culture growth, before achieving the exponential phase, as revealed in Figure 1, and the statistical descriptive analyses of the lag time and first division time data corroborate. This behaviour differs from the results obtained with the maximum growth rate data (Table 2).

Table 2: Statistical descriptive analyses performed with the data from Series A. SE: Standard Error, CV: Coefficient of variation, (%).

| Variable | Mean | SE | CV | Min | Max |
|---|---|---|---|---|---|
| Lag time | 41.86 | 1.25 | 29.63 | 9 | 69.6 |
| First division time | 47.81 | 1.07 | 22.09 | 22 | 73 |
| Maximum growth rate | 0.01101 | 0.00001 | 0.96 | 0.01079 | 0.01121 |

Data about the number of nutrient particles (glucose), the number of metabolites (ethanol particles), the number of viable yeast cells, the mean biomass of the cell population (defined as the viable biomass in the culture divided by the number of viable cells), and the budding index (which represents the fraction of budded cells or cells that are in Phase 2 of the reproduction) were collected and statistically analysed for different time steps of the evolution of the virtual culture.

Table 3 show the results corresponding to two outputs, the number of viable cells of the yeast population and their budding index. Now we are interested in the assessment of the variability attached to the stochastic components of the model, rather than the uncertainty of the input parameters. For instance, the coefficient of variations for the outcome of the number of viable cells looks very different from the budding index, with different magnitudes and trend. The first one has a non-significant variation along the time steps and the second one shows a rapid decrease over time; the two outcomes do indeed show differing behaviours. This statistical analysis reflects the different nature of these outcome variables.

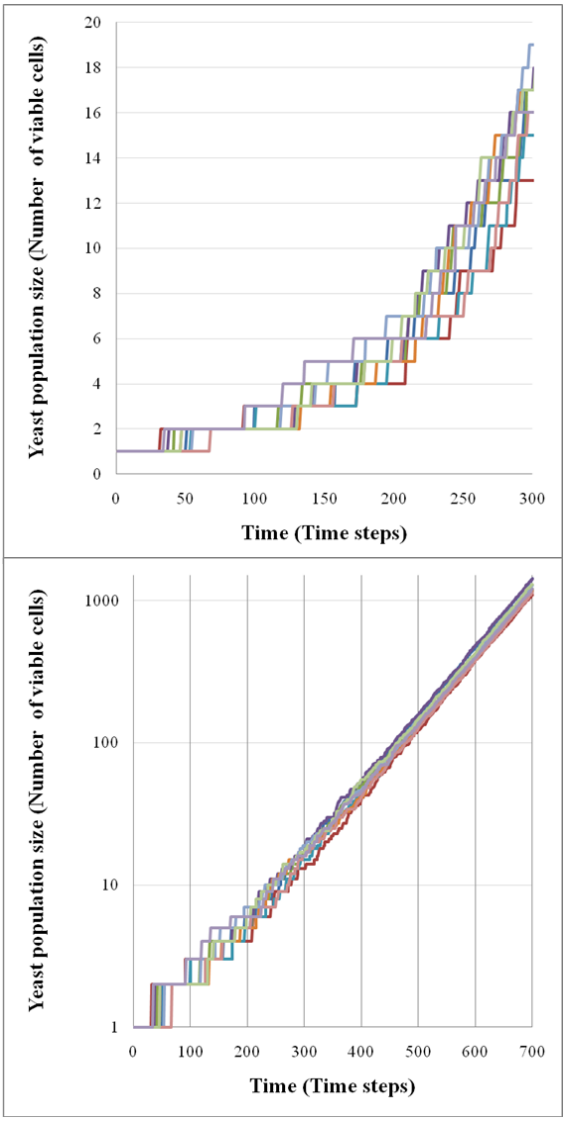


Figure 1: Yeast population growth. Each line represents 1 of 10 replications randomly chosen from Series A. After a time period without reproduction, the exponential growth of the population is manifest.

For Series B, the one-at-a-time (mono-factorial) analyses, consisting in plotting the model responses as a function of each parameter for a wide range of values, were performed. Figures 2 and 3 display the results for the outcomes of the model corresponding to the maximum specific growth rate and budding index at a specific time (300 time steps). The time selected is advanced enough to assure that the yeast cultures had already entered into the exponential phase and that the initial time steps of adaptation (the lag phase) had been surpassed. Both the shape, more or less linear, and the evolution of the variance, more or less constant, may differ from one parameter to another. A specific output variable shows different sensitivities depending on the parameter swept. For instance, the relation between the maximum specific growth rate and the maximum number of nutrient particles that may be consumed per unit of time and unit of yeast cellular surface (or, with the constant modeling, the metabolic efficiency that accounts for the synthesised biomass units per metabolised glucose) shows strong sensitivity, with a linear correlation, but non-apparent sensitivity with other parameters related to the reproduction model (the critical mass, the minimum growth to move from Phase 1 to Phase 2, the minimum growth of biomass required for the bud separation, the minimum number of time steps to remain in Phase 2, or the proportion that allows determination of the daughter bud mass). Furthermore, different output variables show different sensitivities to the same input parameter values. For instance, the response of the budding index to the metabolic efficiency (or to the uptake parameter) compared to the response of the maximum specific growth is very dissimilar; the first shows no relation with decreasing variability to higher values for the parameter, while the second shows a strong positive linear relation. As for the budding index, in the most cases (except in two or three of them, mainly $\Delta m_{B2}$ and $\Delta T_2$) its sensitivity to the controlled parameters is very low and illustrates a much greater dispersion in the output responses.

Table 3: Statistical descriptive analyses performed with the data from Series A. SE: Standard Error, CV: Coefficient of variation, (%).

| Variable | Time steps | Mean | SE | CV | Min | Max |
|---|---|---|---|---|---|---|
| Number of viable cells | 100 | 2.2 | 0.043 | 19.6 | 2 | 4 |
| | 200 | 6.0 | 0.093 | 15.5 | 3 | 8 |
| | 300 | 17.6 | 0.250 | 14.0 | 11 | 25 |
| | 400 | 51.8 | 0.760 | 14.7 | 26 | 75 |
| | 500 | 154.8 | 2.150 | 13.9 | 75 | 228 |
| | 600 | 465.5 | 6.620 | 14.2 | 228 | 688 |
| | 700 | 1400.1 | 19.90 | 14.2 | 684 | 2100 |
| Budding index | 100 | 34.2 | 2.78 | 81.3 | 0 | 100 |
| | 200 | 29.8 | 1.93 | 64.9 | 0 | 80.0 |
| | 300 | 23.3 | 0.94 | 40.5 | 0 | 46.2 |
| | 400 | 24.3 | 0.59 | 24.2 | 11.3 | 39.4 |
| | 500 | 24.1 | 0.37 | 15.2 | 15.8 | 34.9 |
| | 600 | 24.2 | 0.23 | 9.6 | 19.8 | 30.2 |
| | 700 | 24.1 | 0.12 | 5.0 | 21.0 | 26.8 |

If a clear non-linear effect has not been detected in the graphics of the mono-factorial analyses performed, a practical approach when there are many factors is to fix the factors at two levels (as shown in Table 1). In this study, and for the two outcome variables chosen, the ANOVA results were obtained with equireplicate factorial designs with the main effects and first order interaction, indicating a well-balanced design with good statistical properties. This ANOVA was applied to the results of Series C. The explained variance was 99.6% in the case of the maximum specific growth rate and

85.3% for the budding index, very good results for an ANOVA model that included first-order interactions only.

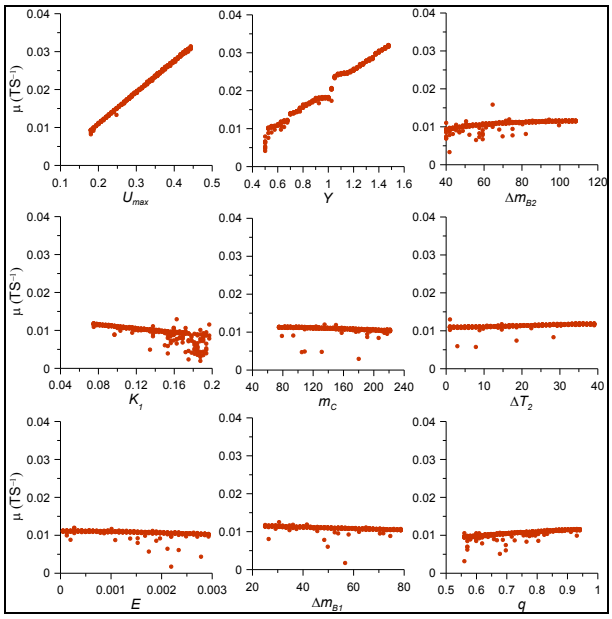


Figure 2: One-at-a-time analysis with the data from Series B. Model response, maximum specific growth rate of the population, for each parameter. All other parameters are fixed to their reference values.

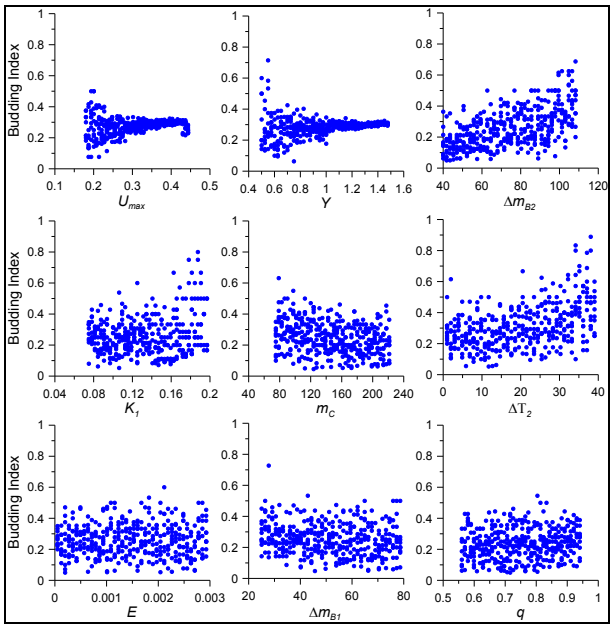


Figure 3: One-at-a-time analysis with the data from Series B. Model response, budding index at time steps 300, for each parameter. All other parameters are fixed to their reference values.

In both cases, the variance explained by the model with low-order interactions remained high, and the residuals (i.e. the differences between observed and predicted values) were not very large; rather, they were small, and regularly hovering around zero. The behaviour of the maximum specific growth rate data versus this analysis is considerably better than the budding index data. Although some of the requirements for carrying out ANOVA, such as the homogeneity of variance, are not completely fulfilled, the results achieved in connection with the decomposition of the different effects on the response variability provide a good basis for discussing the relative importance of the parameters and their main interactions. The significance of the main effects and their interactions are provided by the ANOVA table. Additionally, the information that p-values can give on the importance of the effect on the outcome and the SI calculated for each effect as the ratio of the sum of its square to the total sum of squares can be obtained. The most significant factors differ in the two variables studied and in the concordances and discrepancies in the classification of the most relevant effects for these two outcomes. Some interactions are not always absent, which means that the parameters do not have an independent additive effect on the outputs.

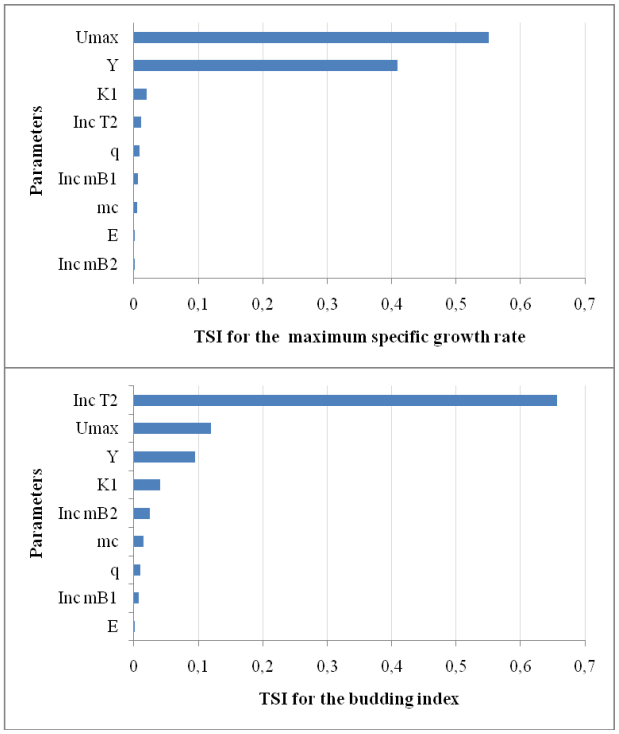


Figure 4: TSIs for two outcome variables with the data from Series C.

The two graphics of Figure 4 display the TSIs for the two variables, maximum specific growth rate and budding index, and identify which parameters have the greatest impact on the corresponding outputs of the model. It is notable that not all the parameters explain a comparable amount of output variability. In the first case, two parameters, $U_{max}$ and $Y$, clearly head the list, indicating that they are the most noteworthy parameters for the maximum specific growth rate of the yeast population in comparison to the others assessed. In the second case, with the budding index, only the parameter

$\Delta T_2$ has greater priority than the others, which are participating at a much lower level.

## CONCLUSIONS

INDISIM-YEAST is an IBM that is already in use to qualitatively investigate different features of yeast populations evolving in liquid batch cultures, such as, among others, fermentation profiles, small inocula dynamics and lag phase. To be able to gain predictive capacities under a particular studying process with this, quantitative results are indispensable. The process to achieve this is not a closed issue, at least in microbial IBMs that require values for parameters not always well known from experimental work. The information acquired with this sensitivity analysis performed is in some places unexpected, requiring deeper reflexion and discussion, so that it must be combined with the information that other outputs of the model can provide. It has been shown that the model is clearly less sensitive to some parameters than others, depending on the output controlled. This allows for focusing energy on the future parameterization and calibration of different outputs and parameters depending on the purpose of the study, and also rethinking and re-examining some of the parts of the sub-models. This preliminary study, as far as we know, is the first to deal with some aspects of a local and global sensitivity analysis performed over a microbial IBM to study yeast populations. This is the beginning of more extensive and exhaustive study that must be followed up in the near future with the simulation model INDISIM-YEAST.

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