Parameter estimation and sensitivity analysis for dynamic modelling and simulation of beer fermentation

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ABSTRACT

Beer fermentation efficiency improvements have the strongest potential to boost profitability, as its long batch time renders this particular unit operation the throughput bottleneck of this complex, multistage biochemical process which mankind has employed for several millennia. Accurate fermentation models are critical for reliable dynamic simulation and process optimization: empirical trial-and-error approaches are not viable, and incrementally altering proven recipes implies prohibitively expensive campaigns, in terms of equipment use, off-spec production and personnel time for sampling and analysis. This paper considers parameter estimation for a published beer fermentation model, demonstrating that estimating the complete unknown parameter set is an ill-posed problem, which can lead to inconsistent solutions. Systematic sensitivity analysis is pursued, elucidating the relative significance of parametric discrepancy on the validity of key species concentration trajectories. Parameters have been identified and ranked by decreasing importance, and a high-fidelity estimation is performed for a published dataset.

Keywords: Beer fermentation · Parameter estimation · Sensitivity analysis · Morris screening · Elementary effect (EE) coefficients · Multi-start algorithm

1. Introduction

1.1 Background

Beer manufacture is extremely well documented, with suggestions that it is one of the world's oldest prepared beverages (Arnold, 1911). Beer production is a multistage process with a complex chemical system, however its only prerequisite is the use of the four essential ingredients: a starch source, yeast, hops and water (Southby, 1885). Fermentation is the essential brewing stage where yeast is introduced at concentrations of 10 to 20 million cells per mL of wort, as soon as it enters the fermentation vessels (Hudson and Birtwistle, 1966). The primary chemical reaction pathway is the conversion of sugar into ethanol and carbon dioxide, an exothermic reaction coupled with biomass growth. Simultaneously, a wide range of additional organic species are formed at low concentrations, which can have strong bearing on the product flavour (Rodman and Gerogiorgis, 2016b).

Fermentation progression is dependent on many factors including yeast pitching rate, dissolved oxygen content, batch pressure and temperature. The system temperature strongly affects yeast growth and metabolic rate: as long as yeast cells are kept below 30 ºC and not damaged, higher temperatures accelerate fermentation. Beyond this critical temperature, ethanol and volatile flavour compound loss rates are too severe, coupled with increased production of undesirable substances and bacterial growth. Brewers control fermentor temperature within a narrow range

during batch progression, to accelerate fermentation while also ensuring that yeast is not deactivated due to denaturation and that no undesirable flavour compounds are produced. Once fermentable sugar content has been consumed, beer requires further processing prior to bottling and consumption: fresh green beer must be matured, carbonated and finished. Fermentation duration varies by product and flavour sought. Lagers are fermented at temperatures around 10 ºC, thus requiring a fermentation time of about one week (160 hours). Ales are fermented at higher temperatures (~22 ºC) and need less time, between 3 and 4 days (Boulton and Quain, 2008).

Online measurements are cumbersome (Corrieu et al., 2000), so each beer production line has a proprietary temperature manipulation profile, faithfully used for every single batch in order to guarantee product consistency (Trelea et al., 2001). Offline measurements for assessing fermentation progression are often very limited (wort density or specific gravity only). The Plato (specific gravity) scale is used in many breweries as a surrogate for equivalent sucrose concentration, since sugar depletion is a reliable indicator of fermentation extent.

1.2 Fermentation modelling

Computational prediction and performance assessment of a biochemical process toward process optimisation requires a mathematical model representing species consumption and production (Rodman and Gerogiorgis, 2016a, 2016b, 2017). This strategy is frequently used in the context of continuous pharmaceutical manufacturing (Gerogiorgis and Barton, 2009; Jolliffe and Gerogiorgis, 2015a, 2015b), among a wide array of further bioprocesses. Several mathematical models for the beer fermentation process have been proposed (Engasser et al., 1981; Gee and Ramirez, 1988; de Andres-Toro, 1998, Corrieu et al., 2000; Trelea et al., 2001). Models are reduced order, considering only the key species of the several hundred present (Vanderhaegen et al., 2006), due to system complexity rendering exhaustive modelling extremely cumbersome: in fact to date many of the specific chemical interactions in the fermentation process are not understood.

The kinetic model of beer fermentation by Gee and Ramirez (1988) is used in this study: it considers the uptake of three sugars, namely glucose (G), maltose, (M) and maltotriose (N):

$$\frac{dC_G}{dt} = -\mu_G \cdot X(t) \tag{1}$$

$$\frac{dC_M}{dt} = -\mu_M \cdot X(t) \tag{2}$$

$$\frac{dC_N}{dt} = -\mu_N \cdot X(t) \tag{3}$$

The foregoing ordinary differential equations (ODEs) have temperature- and time-dependent consumption rates defined with Monod-type kinetics with inhibition effects on higher sugars:

$$\mu_G(T,t) = \frac{V_G(T) \cdot C_G(t)}{K_G(T) + C_G(t)} \tag{4}$$

$$\mu_M(T,t) = \frac{V_M(T) \cdot C_M(t)}{K_M(T) + C_M(t)} \cdot \frac{K'_G(T)}{K'_G(T) + C_G(t)} \tag{5}$$

$$\mu_N(T,t) = \frac{V_N(T) \cdot C_N(t)}{V_N(T) + C_N(t)} \cdot \frac{K'_G(T)}{K'_G(T) + C_G(t)} \cdot \frac{K'_M(T)}{K'_M(T) + C_M(t)} \tag{6}$$

The rates of biomass and ethanol production are proportionally related to the uptakes of the individual sugars by constant yield coefficients determined from stoichiometry:

$$\frac{dC_E}{dt} = R_{E_G} \cdot \frac{dC_G}{dt} + R_{E_M} \cdot \frac{dC_M}{dt} + R_{E_N} \cdot \frac{dC_N}{dt} \quad (7)$$

$$\frac{dX}{dt} = R_{X_G} \cdot \frac{dC_G}{dt} + R_{X_M} \cdot \frac{dC_M}{dt} + R_{X_N} \cdot \frac{dC_N}{dt} \quad (8)$$

The Gee and Ramirez (1988) model is used directly here; due to their isothermal experimental campaigns for batch fermentation and the corresponding fitting effort, the heat balance has no direct impact on the parameter estimation procedure pursued (dT/dt = 0). The reduced order fermentation model comprises of eight unknown model parameters, summarised in Table 1.

Parameter value variation as a function of progress of beer fermentation has been extensively discussed in the published literature (Engasser et al., 1981; Gee and Ramirez, 1988; de Andres-Toro, 1998, Corrieu et al., 2000; Trelea et al., 2001). Temperature dependence is definite for all parameters analysed, as portrayed in our results (Table 5). Biochemical (essentially biocatalytic) phenomena, i.e. yeast strain activity, are strongly affected by biological factors (yeast strain generation, numbers of prior use/recycling, possible yeast mutations). The premises upon which all published and cited ODE-based brewing models have been developed relies on two key ideas: (1) the feedstock composition variation does not affect model structure or parameter set fidelity, (2) biocatalytic shift (e.g. yeast inactivation or mutation) occurs much slower than fermentation.

The parameter set required for beer fermentation simulation (Table 1) strongly depends on beer type/grade, because the hitherto employed ODE system models include less than a dozen dynamic state variables, thus representing a very coarse approximation of only critical (flavour-relevant) biochemical phenomena. The six (6) Michaelis-Menten parameters (two per sugar for each of glucose, maltose and maltotriose) differ for different yeast strains, though theoretically unchanged for different products from the same yeast. To the best of our knowledge, the two (2) inhibition constant values do not change for a given beer type and yeast strain, as the model (for its fidelity, and to the extent it accurately represents fermentation) encompasses the same three (3) foregoing sugar types which are the only considered (even if their initial values vary by feed composition).

Table 1. Beer fermentation model parameters for determination (Gee and Ramirez, 1988).

Symbol	Description	Units
V_G	Maximum reaction velocity for glucose (G)	h^{-1}
V_M	Maximum reaction velocity for maltose (M)	h^{-1}
V_N	Maximum reaction velocity for maltotriose (N)	h^{-1}
K_G	Michaelis constant for glucose (G)	mol/m^3
K_M	Michaelis constant for maltose (M)	mol/m^3
K_N	Michaelis constant for maltotriose (N)	mol/m^3
K'_G	Inhibition constant for glucose (G)	mol/m^3
K'_M	Inhibition constant for maltose (M)	mol/m^3

2. Global Parameter Estimation (all-at-once)

2.1 Experimental

An experimental campaign has been performed by Gee and Ramirez (1988), where the authors monitored the concentrations of the three sugar species over time during an isothermal batch fermentation by HPLC. This was carried out repeatedly over a range of feasible temperatures for effective fermentation, resulting in four distinct data sets at T = 4, 8, 12, 16 °C. The batches were fermented in 100 L non-agitated conical fermenters using *S. carlsbergensis.* Original experimental data have been provided in the Figures by Gee and Ramirez (1988); therein, there appears to be some confusion due to a labelling discrepancy with respect to the maltose vs.

maltotriose captions of their Fig. 2-3, but one that is easily identified by data value comparisons vs. Fig 7 of the said paper, as well as by referring to the correct data headers and tabulation which is provided in the later PhD Thesis of Gee (1990) at the University of Colorado, USA.

2.2 Multi-start Parameter Estimation

The parameter estimation problem is defined to determine the values of the eight unknown parameters by minimizing the discrepancy between the experimental data set and the model state trajectories. Physical boundaries act as lower parameter non-negativity constraints, and upper limits can be proposed from literature and related fermentation processes, giving a finite span in which the parameter value must lie. Several different objective functions may be used as the minimization criteria. A sum squared error objective is often used, however this will prove bias in favour of matching states of greater absolute magnitude. It can make more sense to divide the discrepancy at each data point by the mean state value, to normalize the significance of matching the individual states. Alternatively, a chi-squared objective may be used given that sufficient data quality exists to determine standard deviations.

For any objective function used the resulting problem optimization problem is nonconvex, being well established that kinetic parameter estimation problems can be extremely challenging to solve to global optimality. A statistics-based objective function uses a branch-and-bound algorithm to guarantee global optimality (Singer et al., 2006). This is particularly useful as if the global solution shows an insufficient fit, one can confidently dismiss the mode structure as inappropriate.

A wide spectrum of deterministic, stochastic and hybrid parameter estimation methodologies have been published in the past two decades, many addressing biochemical and biological engineering problems (Rodrigues-Fernandez et al., 2006a-b; Ferrari et al., 2016; Spann et al., 2017; Anane et al., 2019), with a particular emphasis on global optimization (Moles et al., 2003) as well as on effectively guiding the Design of Experiments/DoE (Banga and Balsa-Canto, 2008). A recent benchmarking study evaluates several optimization methods for parameter estimation in large kinetic models (Villaverde et al., 2018).

Parameter estimation is of paramount importance in dynamic simulation and optimization of beer fermentation, because online sensing and actuation is not frequently encountered in the brewing industry, especially in fermentation processes, which have a timescale of days. Current industrial practice indicates that the most critical state variables that are pivotal to fermentation evolution and thus govern quality are not measurable online (hence are real-time unobservable at large). Online concentration data acquisition for beer quality monitoring is very rare (not widely, if at all performed, and prohibitively expensive, though there are real-sensing R&D efforts under way). Dynamic optimization thus may be more in this context in comparison to e.g. Model-Predictive Control (MPC), which relies on abundance of incoming data. In that case, online parameter estimation methods unleash the potential of real-time process control (Tatiraju & Soroush, 1998).

This paper presents the implementation of a standard local parameter estimation method, with a focus on visualizing the effect of multi-start initialization, which can highlight some properties of this biochemical system (Marti et al., 2016). Given the resolution of the available data set, the sum squared error minimization approach is considered in this work, normalizing the fit at each data point by the mean state value over the time span, where the objective is defined by Eq. 9:

$$min \sum_i \sum_j \left(\frac{(data - model)}{\overline{data_i}}\right)^2 \quad (9)$$

Starting from 1000 points (initial parameter guesses) via Latin- Hypercube sampling (McKay et al., 1979; Stein, 1987) of the input space, the parameter estimation problem has been solved for

each instance using IPOPT (Wächter and Biegler, 2006) via OPTI's MATLAB® implementation (Currie and Wilson, 2017). Taking the parameter set from the 1000 result sets computed which obtains the lowest objective function value of Eq. (9), we can plot the best obtained approximation of the globally optimal fit, shown in Fig. 1 for three of the temperatures considered in the experimental campaign. Visually the model fit appears excellent, however consideration must be given to how appropriate this parameter estimation method is for determining the actual parameter values.

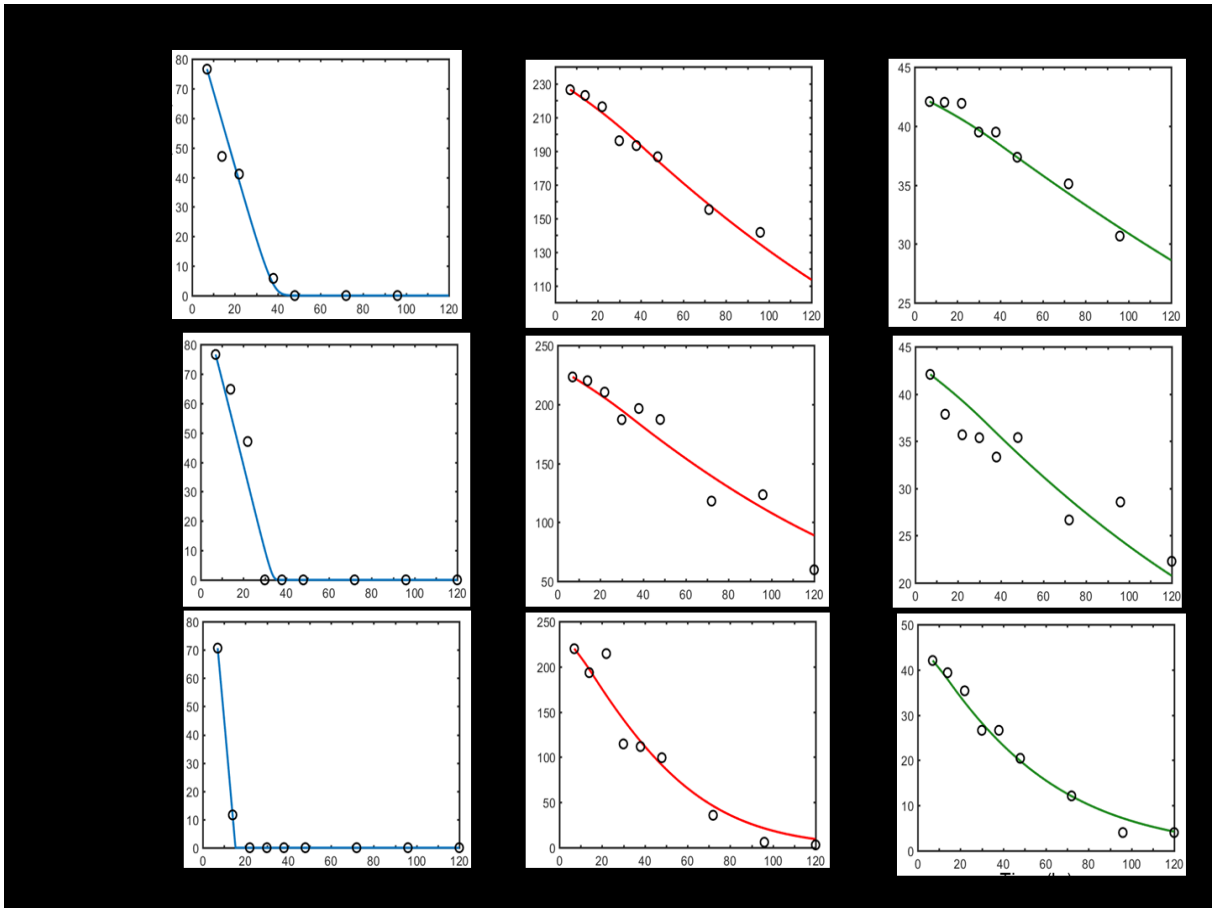

Figure 1. Model fit to experimental data: our novel all-at-once parameter estimation (data: Gee and Ramirez, 1988; Gee, 1990).

Considering the different objective values obtained from the 1000 unique start points, it can be shown how consistently the best solutions are obtained (Fig. 2). Under 10% of cases are realizing the minimum value of the sum squared error objective, with a high number of local solutions being produced.

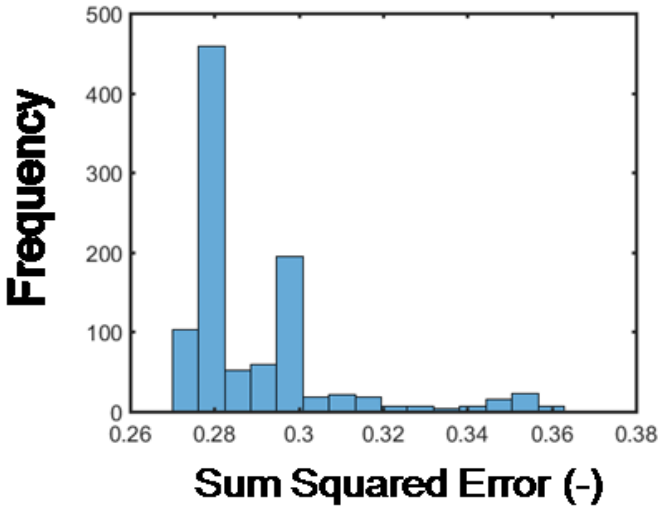

Figure 2. Multi-start objective distribution

The distributions of the parameter values can also be inspected (Fig. 3), showing that very large ranges have been produced for most parameters. This is a result of local solution attainment, as well as cases where approximately the same objective value is produced with significantly different parameter sets. This is a result of an ill conditioned problem where model parameters are highly correlated and thus cannot be uniquely estimated simultaneously.

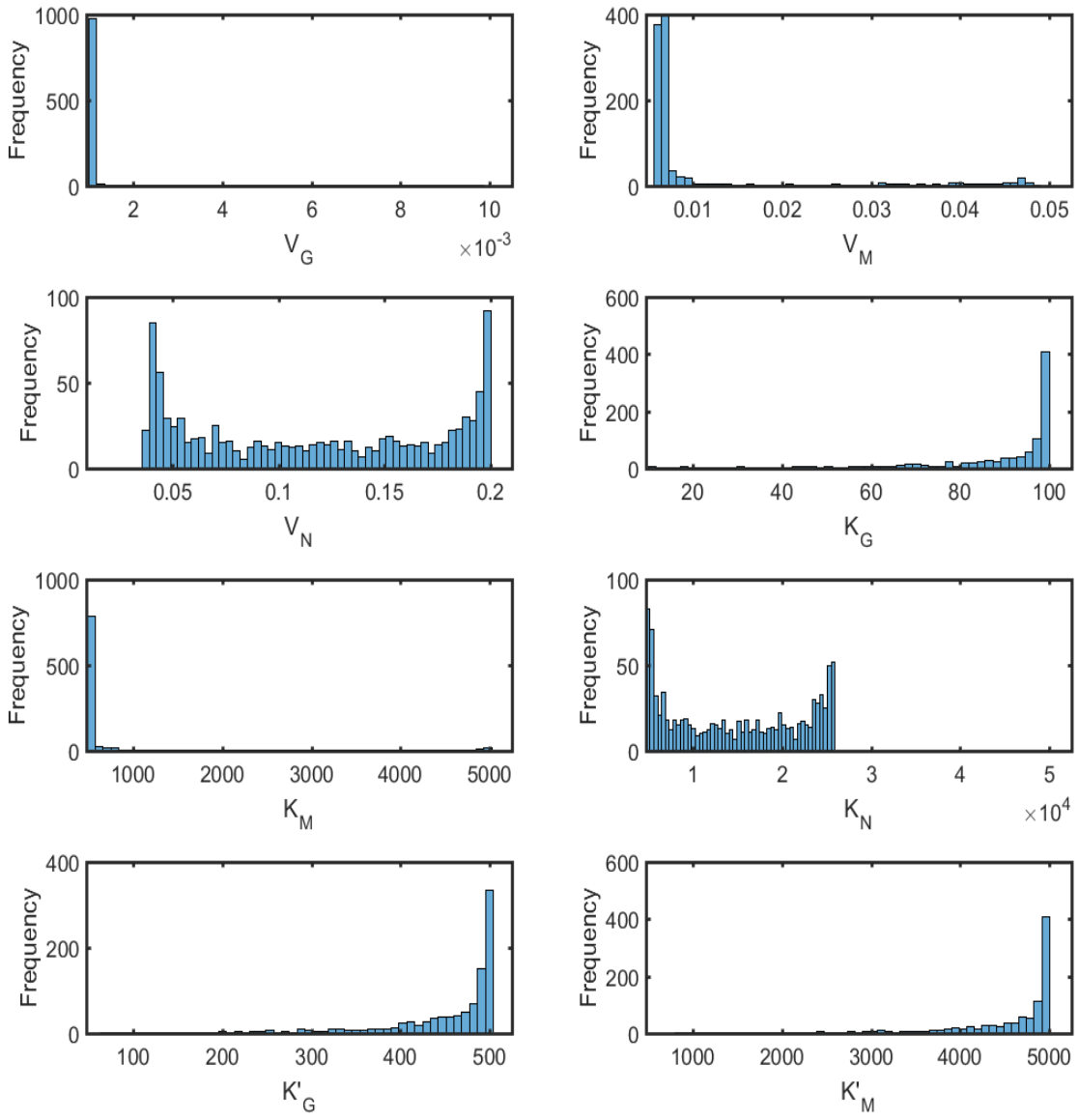

Figure 3. Multi-start parameter value frequency distributions.

This results from the fact that Monod-like models are found to have growth yield parameters which are significantly correlated with the maximum growth rate terms (Sin et al., 2009). It is thus necessary to consider which parameters have the most significant bearing in the model state trajectories, and which less influential ones may be assigned directly from literature to avoid co-dependence issues in the parameter estimation problem. The parameter co-dependence can be confirmed by looking at the covariance matrix (Table 2). It is known that when the absolute value of a correlation for a parameter pair is greater than ~0.95 it may not be possible to estimate the 2 parameters uniquely using the available regression data. Changing the parameter values in a coordinated manner may produce very similar model results in such cases.

Table 2. Parameter covariance matrix

	K_G	K_M	K_N	K'_G	K'_M	V_G	V_M	V_N
K_G	1.000	-0.004	0.185	0.971	-0.004	0.185	-0.001	-0.185
K_M		1.000	-0.124	0.004	1.000	-0.124	-0.942	0.127

K_N	1.000	0.144	-0.123	1.000	0.167	-1.000
K'_G		1.000	0.004	0.144	-0.006	-0.144
K'_M			1.000	-0.123	-0.940	0.125
V_G				1.000	0.167	-1.000
V_M					1.000	-0.170
V_N						1.000

3. Sensitivity Analysis

As it is not effective to directly estimate the entire parameter vector, we wish to inspect how the parameters influence the model states: to perform a rigorous sensitivity analysis. Sensitivity analysis is a valuable tool for a number of reasons, both in and out with parameter estimation (Saltelli et al., 2006). Numerous methods for sensitivity analysis have been developed and published in the engineering literature (e.g. Sin and Gernaey, 2009, 2016; Ruano et al., 2011). These include local methods which consider parameter perturbations around nominal values, and comprehensive but more complex global methods. A useful method is Morris screening (Morris, 1991), which combines favourable properties of both classes for efficient parametric analysis: local sensitivities are computed, but with sampling so as to approximate global parametric effects.

3.1 Morris Screening

Given a generic model (Eq. 10 – 12), the elementary effect of each input parameter is computed by varying a single parameter by a perturbation factor, and integrating the model to observe the effect on the model states. This is repeated over p intervals and as this gives a local elementary effect it is repeated r times around randomly sampled nominal values.

$$\frac{dx}{dt} = f(x, \theta, u, t) \tag{10}$$

$$x(0) = x_0 \tag{11}$$

$$y = g(x, \theta, u, t) \tag{12}$$

$$EE_i^0 = \frac{y(\theta_1^0, \theta_2^0, \ldots, \theta_i^0 + \Delta, \ldots \theta_m^0) - y(\boldsymbol{\theta}^0)}{\Delta} \tag{13}$$

The Morris method inspects model parameter sensitivities in a global context, requiring nominal parameter values to be defined, as well as the associated 'expert uncertainty' in each value such that the algorithm can compute the associated perturbation. Here the nominal parameter values have been taken from the original model publication (Gee and Ramirez, 1988). Uncertainty is considered in three discreet bands: 0.05 = low, 0.25 = moderate and 0.5 = high. In this study three different cases are considered:

- Uniform high uncertainty across the entire parameter set
- Uniform low uncertainty across the entire parameter set
- Arbitrarily assigned uncertainty across the entire parameter set

This is performed for 50 samples with 8 parameter levels in each case, with the range of resultant state trajectories shown in Fig. 4 corresponding to the T = 4 °C case with assigned uncertainty (Table 2).

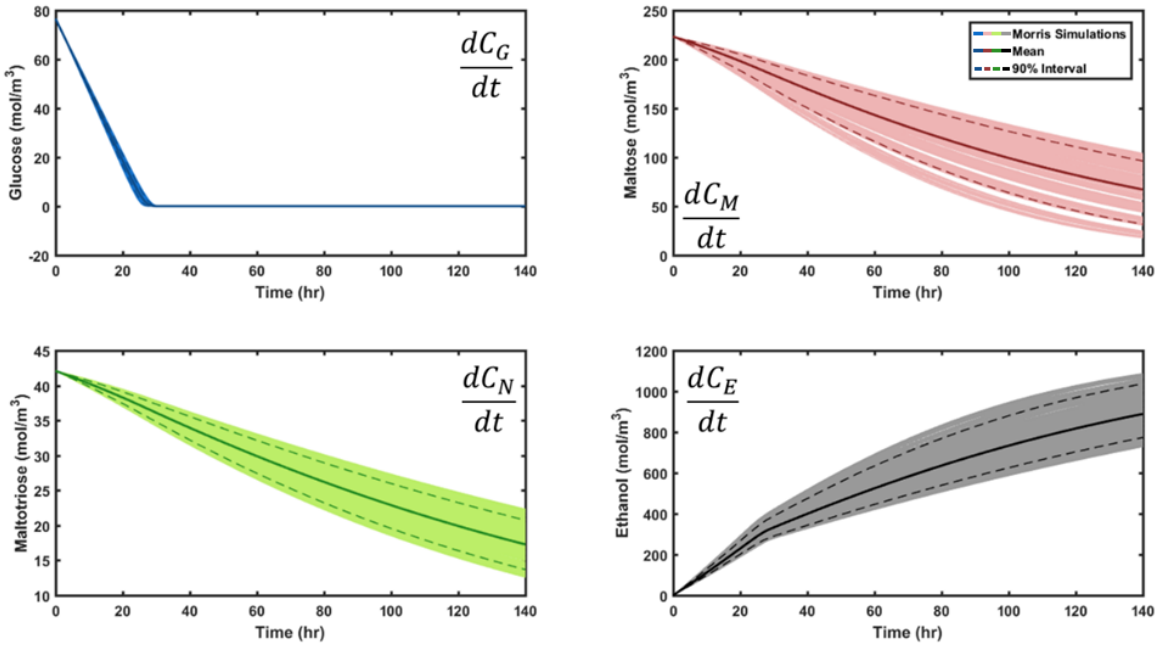

Figure 4. Morris model simulations where samples (r) = 50, parameter bands (p) = 8 and perturbation factor (Δ) = 4/7.

It is demonstrated that glucose shows minimal trajectory variation compared to the other states, as a result of the fewest parameters having influence on this model ODE. Additionally, trajectory banding is clearly observed in the maltose plot due to discrete number of parameter levels considered. It should be noted that ethanol and biomass are affected by all parameters in the same way, as a direct consequence of the ODE model considering both as linear functions of sugar uptake, such that both states are affected in the exact same way by all parameters and the elementary effect is thus always identical.

Table 2. Parameter uncertainty sets considered.

Parameter		V_G	V_M	V_N	K_G	K_M	K_N	K'_G	K'_M
Uncertainty (0 = none, 1 = high)	High	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Low	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Assigned	0.05	0.05	0.25	0.05	0.5	0.05	0.25	0.25

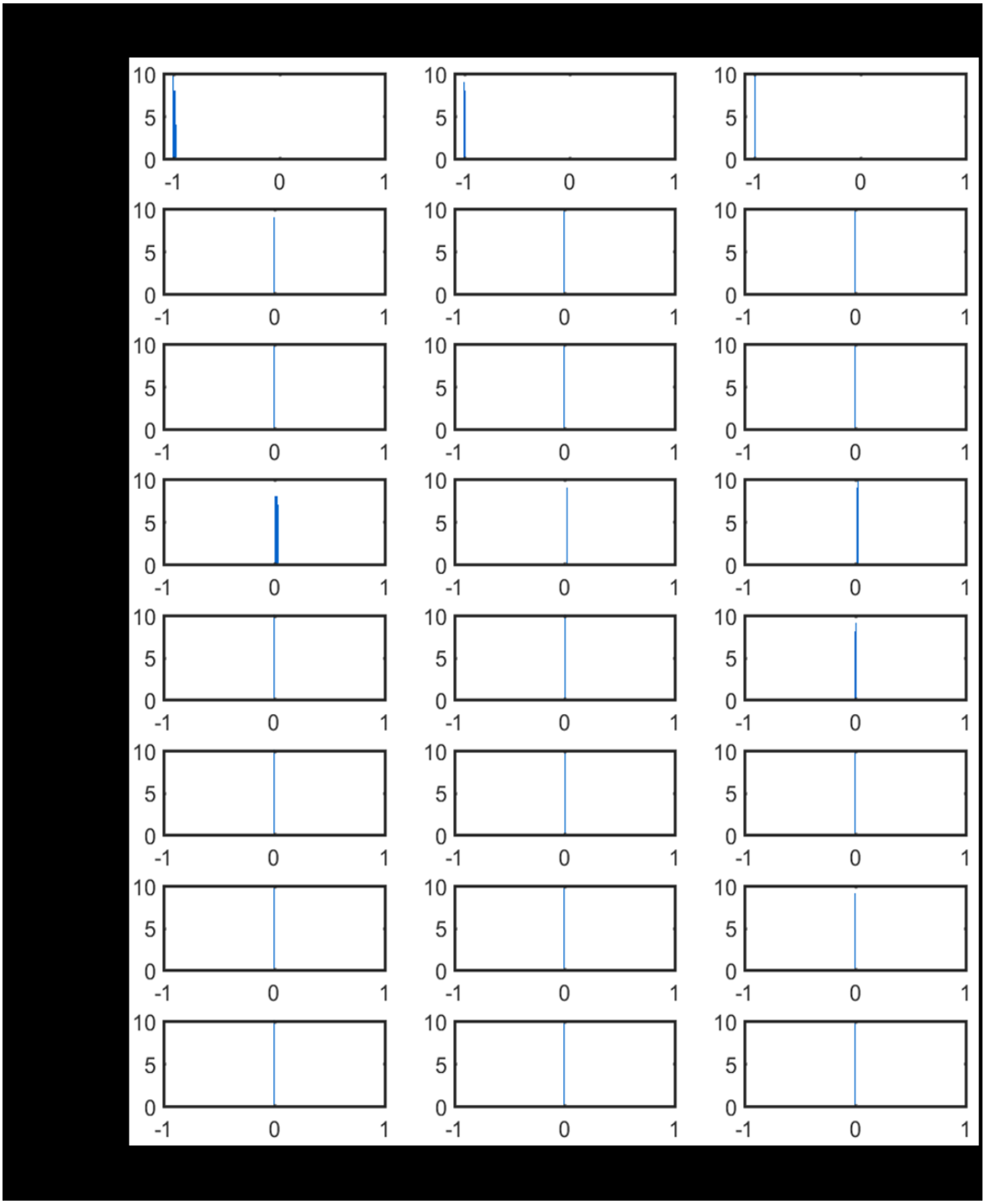

Figure 5. Morris screening elementary effects of each parameter on glucose.

Each histogram in Fig. 5 shows the distribution elementary effects on parameter i, EEi, (Eq. (13)) on glucose (G), with Figs. 6–8 showing the same for maltose (M), maltotriose (N) and ethanol (E), respectively. In all four figures (Fig. 5-8) the 3 columns of plots correspond to the 3 sets of parameter uncertainties defined in Table 2. These histograms allows the mean elementary effect (EE) as well as the standard deviation to be visualised, acting as useful metrics for determining which parameters are most strongly correlated with the state trajectories of interest. The first two columns of histograms represent the elementary effect distributions with the parameter uncertainty considered to be uniformly high and low, respectively. In the final column 3, four

parameters are assigned low uncertainty, three moderate, with only KM defined as having a high uncertainty (Table 2).

The *EE*'s on glucose (Fig. 5) is conclusive, with the maximum reaction velocity for glucose uptake, V_G, shown to be the only significant parameter value to predict this specific model state, regardless of the associated parameter uncertainty being assigned. Here V_G shows a linear negative correlation (*EE* = -1), with all other parameters having essentially no effect (full frequency of *EE* at 0). This could be inferred directly form the model structure where only this single parameter is directly proportional to the model ODE.

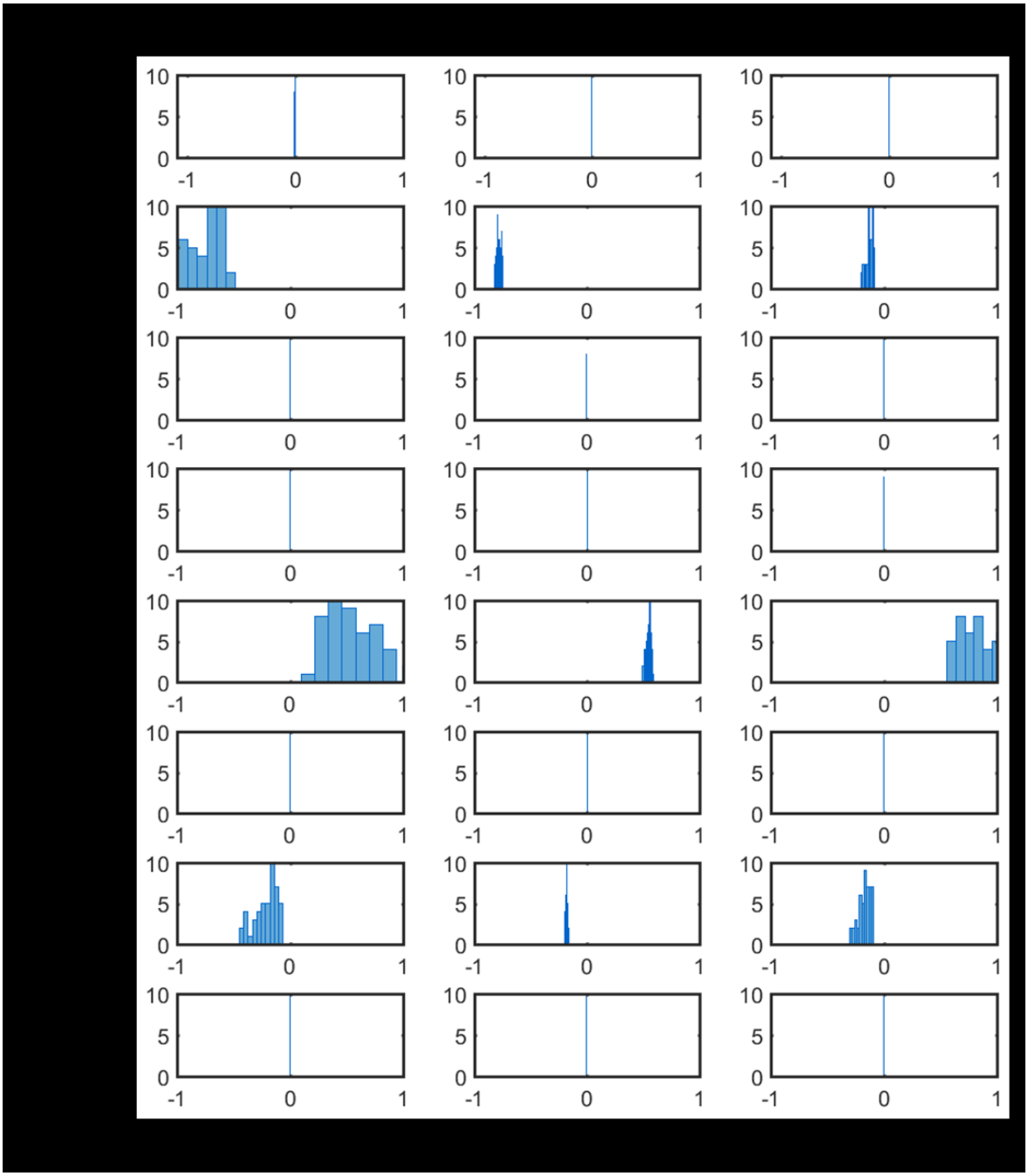

Figure 6. Morris screening elementary effects of each parameter on maltose.

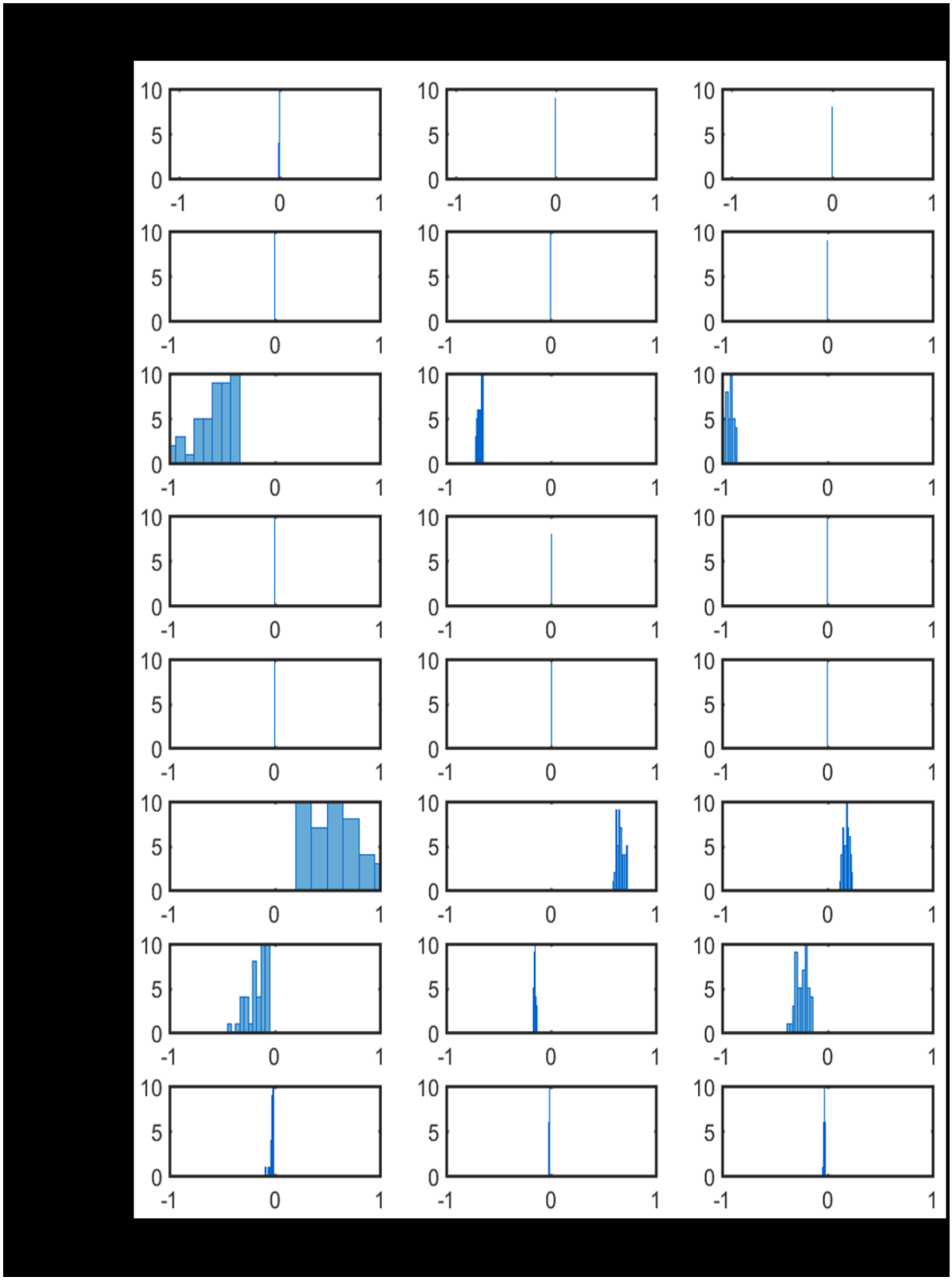

Figure 7. Morris screening elementary effects of each parameter on maltotriose.

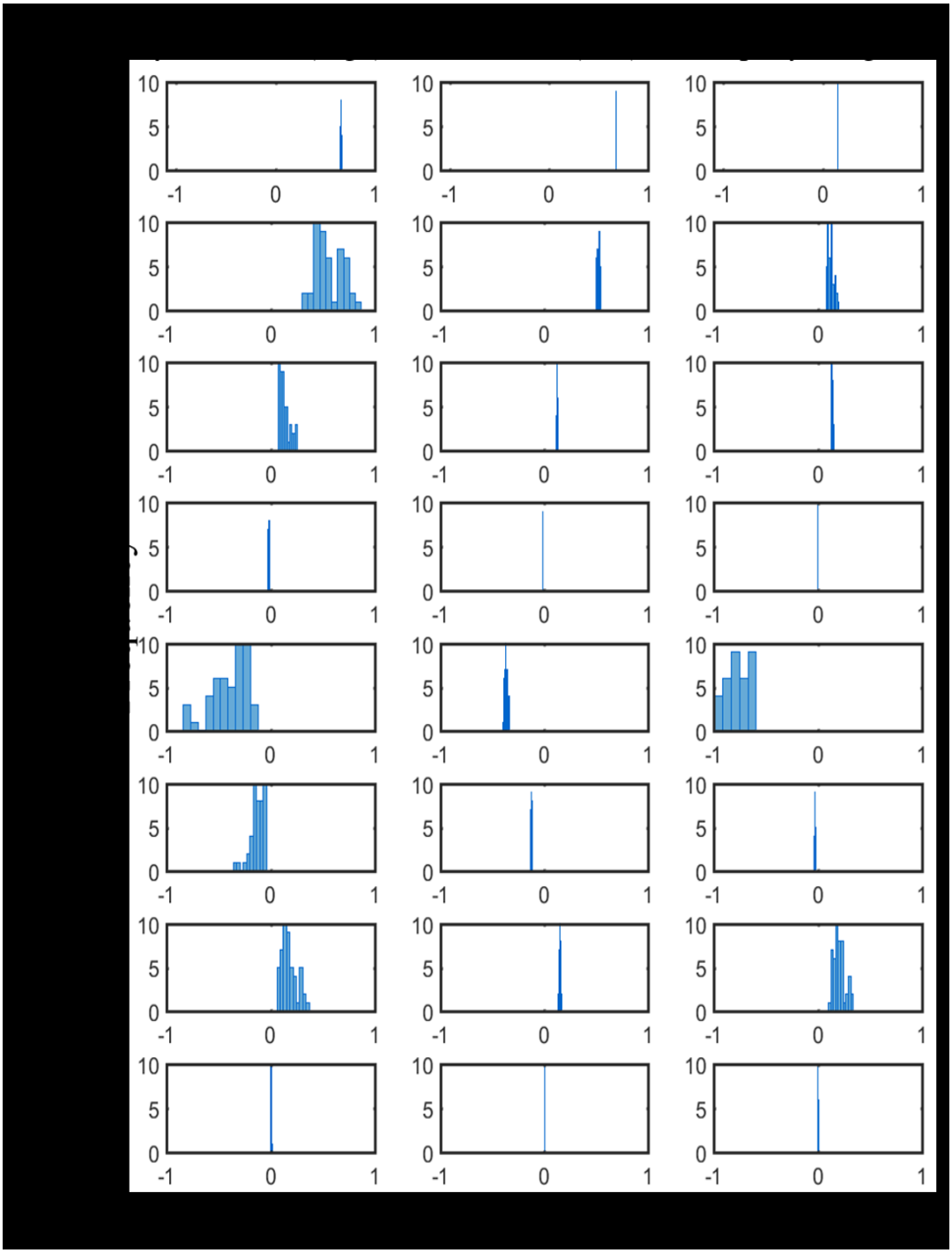

Figure 8. Morris screening elementary effects of each parameter on ethanol.

Comparing the low and high uncertainty parameter set Morris histograms for *EE* on maltose, maltotriose and ethanol shows how the uncertainty magnitudes influence the *EE*s. Between the two cases (column 1 and 2 in these plots) the mean *EE* is not changed significantly when increasing uncertainty fivefold, however, the standard deviation is much greater when uncertainty is high. Both sets of results show V_G, V_M and K_M to have the greatest *EE*. This is in contrast to the final case considered, where K_M significantly outshone the others in terms of mean *EE* and suggested relative importance. This is a result of the greatest concentration of maltose (M) being present, causing the parameters associated with its consumption having the greatest effect on absolute model trajectories. In this scenario it is suggested that V_N, V_M and K'_G have a moderate

effect on these states, with a small positive correlation shown in all three cases. These are all of little significance compared to the very large negative correlation shown for K_M. This would suggest that K_M has considerably stronger bearing in the trajectory of ethanol, however consideration must be given to whether it makes sense to have a priori defined this parameter to have at least twice the uncertainty to all other parameters. This highlights the importance of accurately defining parametric uncertainty before applying the sensitivity analysis method; if expert knowledge is unavailable, a sensible assumption is to treat all uncertainties as equivalent.

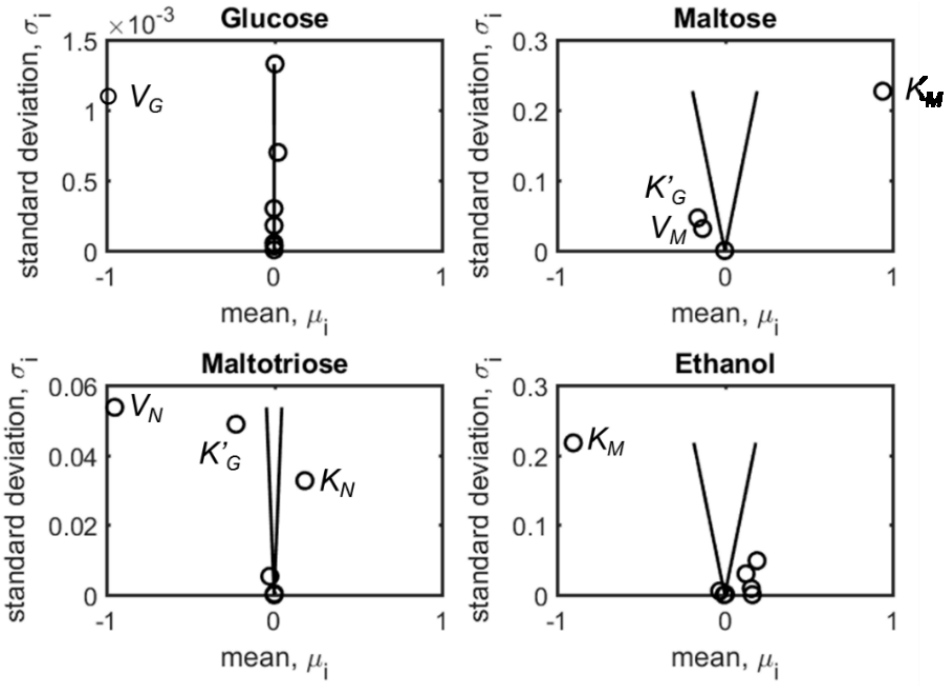

Figure 9. Morris screening mean EEs on ethanol and standard deviation distribution.

The full set of 8 histograms for the effect of any single uncertainty parameter of the considered set on the four key dynamic state variables of the system can be further analysed by means of standard deviation vs. mean (sigma vs. mu) plots (Fig. 9). For example, the 8 histograms from Fig. 8 map into the plot in the bottom right plot of Fig. 9 for ethanol (E), with the other 3 panels showing the equivalent for the sugar states (G, M, N). The solid lines represent the estimated standard error of the mean, such that if the parameter (circle) lies within the bands it is deemed to have a negligible effect on the state. The significance of each parameter on each state according to the absolute mean elementary effect can be ranked, highlighting which are the most influential and this most important for accurate estimation.

Table 2. Elementary effect ranking for all dynamic model parameters.

	Glucose, C_G		**Maltose, C_M**		**Maltotriose, C_N**		**Biomass, X**		**Ethanol, C_E**	
Rank	θ	μ	θ	μ	θ	μ	θ	μ	θ	μ
1	V_G	-1.000	K_M	0.954	V_N	-0.935	K_M	-0.923	K_M	-0.923
2	K_G	0.021	K'_G	-0.144	K'_G	-0.217	K'_G	0.171	K'_G	0.171
3	K_M	0.006	V_M	-0.117	K_N	0.193	V_G	0.150	V_G	0.150
4	K'_G	-0.001	V_G	-0.001	K'_M	-0.027	V_N	0.133	V_N	0.133
5	V_N	-0.001	V_N	0.000	K_M	0.001	V_M	0.114	V_M	0.114
6	V_M	-0.001	K_N	0.000	V_G	-0.001	K_N	-0.028	K_N	-0.028

7	K_N	0.000	K_G	0.000	V_M	0.000	K'_M	0.004	K'_M	0.004
8	K'_M	0.000	K'_M	0.000	K_G	0.000	K_G	-0.003	K_G	-0.003

Table 2 shows that only a single parameter, $V_{G,}$ is significantly influential on glucose, which could be inferred from the model directly (Eq. 1). More insightful is the ranking of the parameter significance on the other states, highlighting that the inhibition constants (K'_i) and maximum reaction velocities (V_i) have much more significance than the Michaelis constants (K_i). It can be noted that because ethanol and biomass are linearly related in the model structure, the dimensionless parameter elementary effects for these two states are identical.

3.2 Differential Sensitivity Analysis

First-order derivative model outputs (states) can be taken with respect to model inputs (parameters) to assess their relative effect (Brun et al., 2002):

$$s_{i,j}(t) = \left. \frac{\partial y_j(t)}{\partial \theta_i} \right|_{\theta_0} \tag{14}$$

Where $s_{i,j}$ is the dynamic sensitivity function of parameter θ_i on model state y_j, where θ_0 signifies the parameter nominal values. This allows visualisation of the time-dependent sensitivities of model states to each parameter, shown in Figure 10. It is shown that the maximum glucose uptake rate, V_G, is initially instrumental on both Glucose and Ethanol, falling to 0 once the glucose is consumed. For maltose and maltotriose it is evident that the maximum reaction velocity has a negative correlation, while the Michaelis constant has a positive correlation of similar magnitude. This is indicative of the highly correlated nature of these 2 parameters with regard to the state trajectory.

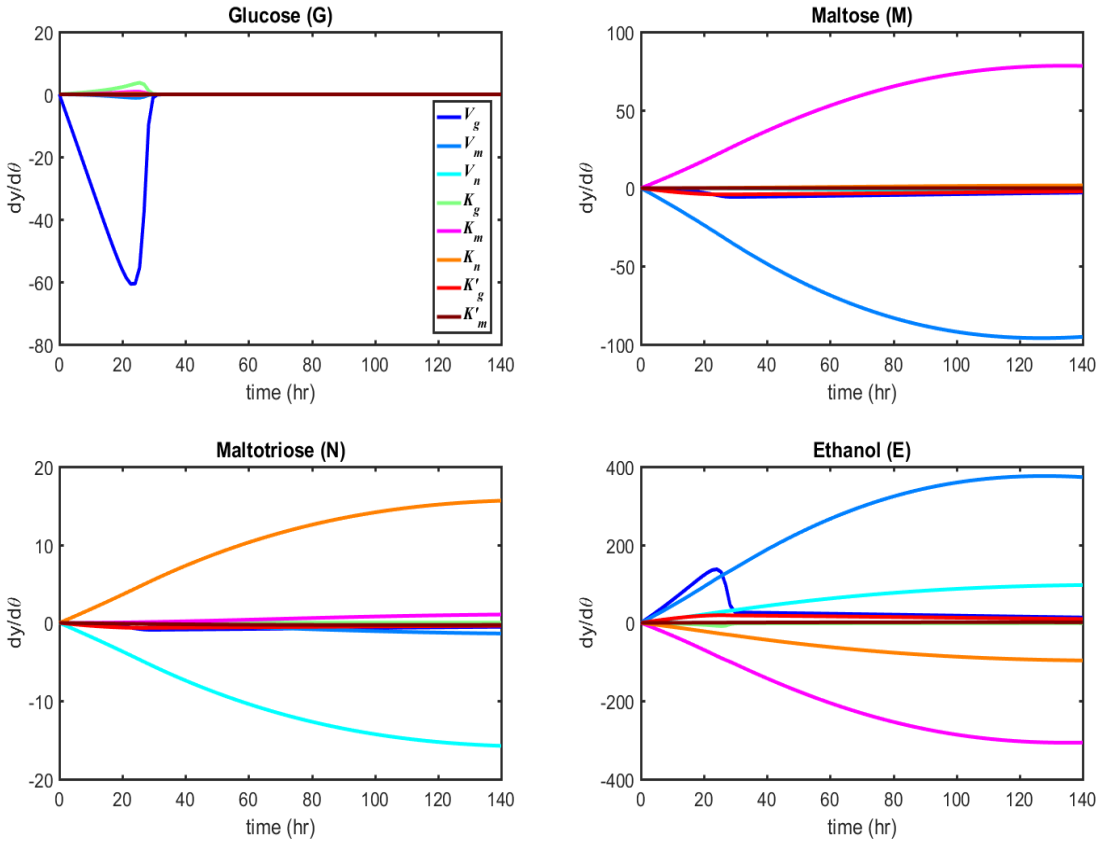

Figure 10. Dimensionless parameter sensitivity profiles.

The mean squared summary of these profiles, $\delta_{i,j}^{msqr}$, can be used as a means to quantitatively compare and rank the effect of each parameter on each model state (Fig. 11), determined by Eq., 15 where the model has been evaluated at n discrete time points. The parameters which dictate the sugars evolution is unsurprising, but interestingly the effect of the inhibition constants are never among the most influential. It is shown how five parameters have significant bearing on Ethanol model predictions. There is a high level of similarity between the results from Morris screening and from differential sensitivity analysis, however a noteworthy difference is that the inhibition constant from glucose is not flagged up here as important here, while it was from Morris screening, highlighting the importance of considering multiple strategies for sensitivity analysis to elucidate the key influential model parameters.

$$\delta_{i,j}^{msqr} = \sqrt{\frac{1}{n}\sum_{t=1}^{n} {s_{i,j}}^2(t)} \tag{15}$$

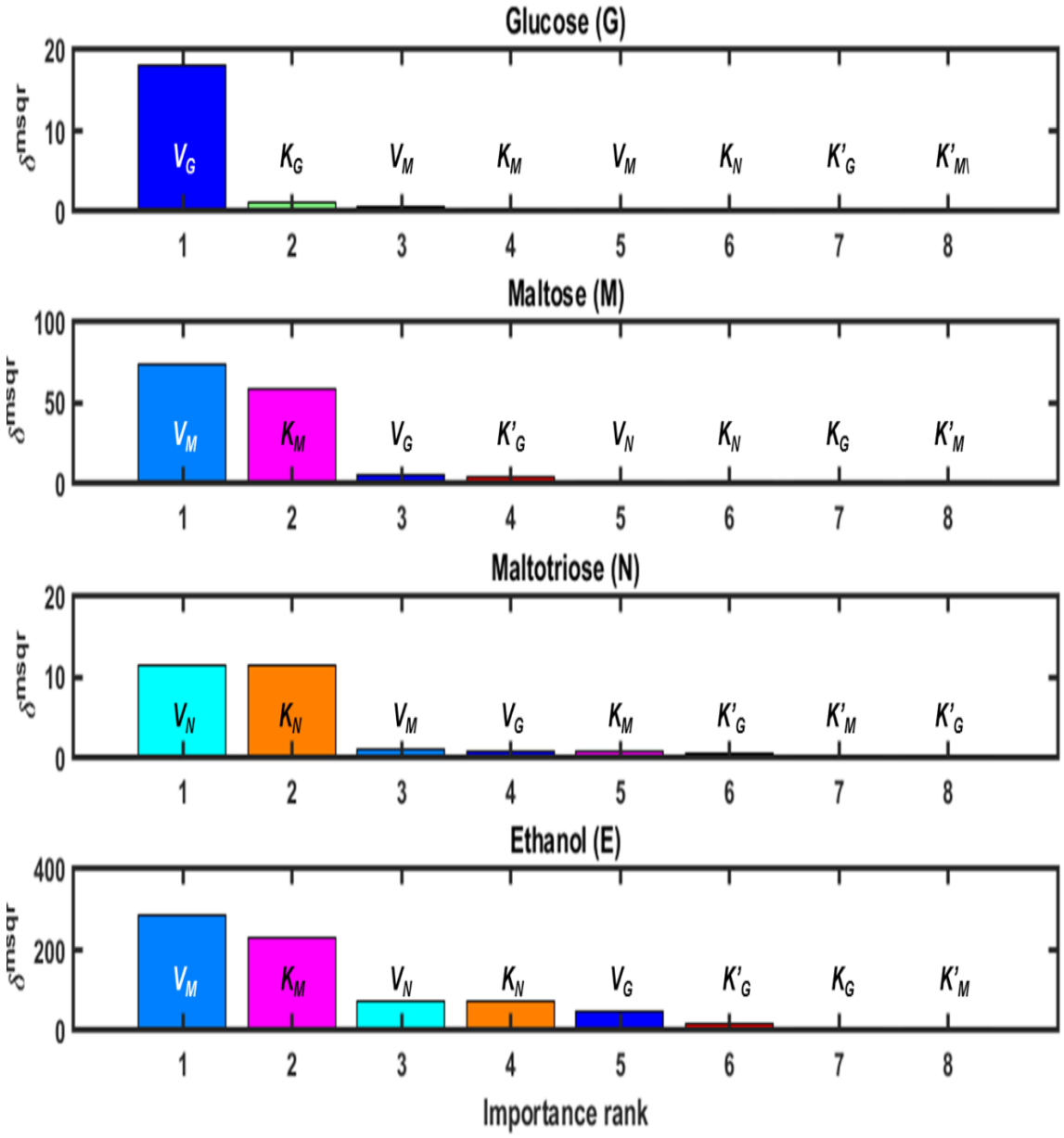

Figure 11. Mean squared summary of time series sensitivity function rankings.

3.3 Estimation of Identifiable Parameter Set

As the most influential model parameters have been identified it is desirable to solve the parameter estimation problem again, focusing specifically on the key parameters while taking those less important from suitable literature sources. To do this we must ensure that the parameter set taken forward for estimation is not ill conditioned, and that linearly correlated parameters are not considered in the problem. A useful way to do this is to consider the collinearity index, γ_K , – a measure of how aligned the sensitivity functions are between pairs of model parameters. With 8 parameters there are 247 sets which could be taken for estimation, ranging from all pairwise combinations, to the final set where all 8 are estimated. This latter case is as performed initially (Fig 2), showing poor solution attainment due to the very large collinearity index. Of the 247 sets, a range of potentially lucrative (low γ_K) cases are presented in Table 4.

Typically the set with the most parameters and lowest index should be taken for estimation. However, it has been identified that neither method found the maltose inhibition parameter, K'_M, to be impactful, so there is little benefit in including this in the estimation. Of those remaining several appear suitable, with 197 taken forward for estimation of the 5 corresponding parameters. This set is incorporating the most influential parameters while ensuring the most heavily correlated pairs are omitted. The values of the three parameters omitted from the estimation have been taken from Gee and Ramirez (1988); the same multi-start parameter estimation problem has been solved again for the remaining five constants, again from 1000 randomly sampled initial guesses. Resulting parameter value distributions are shown in Figure 6, for the T = 4 °C data set.

Table 4. Selected parameter subset with their components and collinearity indexes.

Subset	Components							γ_K
9	V_M	K_G						1.3
79	K_G	K_N	K'_G					2.4
151	V_G	V_M	V_N	K'_G				10.6
154	V_G	V_M	V_N	K_G				7.6
195	V_G	V_M	K_G	K'_G	K'_M			8.7
196	V_G	V_M	K_G	K_N	K'_M			13.5
197	V_G	V_M	K_G	K_N	K'_G			10.7
201	V_G	V_M	V_N	K'_M	K'_N			18.3
205	V_G	V_M	V_N	K_M	K'_G			90.3
207	V_G	V_M	V_N	K_M	K'_M			13.5
208	V_G	V_M	V_N	K_G	K'_G			10.7
225	V_G	V_M	K_G	K_M	K'_G	K'_M		18.2
233	V_G	V_M	V_N	K_G	K'_G	K'_M		18.4
237	V_G	V_M	V_N	K_G	K_M	K'_G		90.4
241	V_G	V_M	V_N	K_G	K_M	K'_G	K'_M	241.0

These results show very consistent parameter values are obtained, regardless of the initialisation, due to ensuring a priori a well-conditioned problem is being solved. It can be seen that there is slight variation in the values of V_M and K'_G, as a result of a local method being used, however this is a vast improvement versus estimating the entire set. Repeating the well-conditioned parameter estimation problem for each of the datasets allows for the temperature dependence of each key parameter to be determined (Table 5). Ensuring temperature-dependent model parameters have been determined consistently is vital for ensuring the model is suitable for fermentor temperature profile dynamic optimisation (Rodman, Fraga and Gerogiorgis, 2018).

Table 5. Estimated parameter values.

Parameter	T (°C): 4	8	12	16
V_G	0.0031701	0.0136754	0.0140371	0.0409614
V_M	0.0095739	0.0115390	0.0118810	0.0270893
K_M	5.8606	4.8347	1.2073	0.6416
K_G	552.845	229.293	135.944	125.503
K'_G	58.289	116.823	119.798	132.425

4. Conclusions

Potential fermentation process improvements can be very lucrative for the beer brewing industry. Recent studies focus on using reduced order fermentation models towards dynamically simulating and optimizing the process. Doing so requires a high-fidelity parameterisation of the model from experimental data, to ensure it accurately represents a real-world process. It is demonstrated that attempting to estimate the complete unknown parameter set results in an ill-conditioned problem and poor solution attainment. Systematic sensitivity analyses using two established methods is performed to assess and elucidate the relative significance of parametric discrepancy on the validity of dynamic simulation of the evolution of certain concentration observables. In doing so the parameters of least importance have been identified, assigning appropriate values to which from literature permits high fidelity estimation of the remaining more significant and influential parameters using an experimental data set. Accurate values for these model parameters are instrumental towards valuable dynamic optimization efforts within the beer fermentation process.

Our key conclusions are summarised below; this contribution to the parameter estimation problem for dynamic simulation and optimization of beer fermentation is process- and product-dependent, but also illustrates the importance of parametric sensitivity analysis studies for industrial datasets.

- Estimation of the full parameter vector for the beer fermentation model presented in this paper is inherently an ill-conditioned problem, typical for Monod kinetic models.
- Maximum reaction velocity parameters show an inverse correlation with Michaelis-type constants, preventing unique identification of either of these values.
- Sensitivity analysis (SA) has been performed using two published and validated methods.
- Morris screening highlights the significance of parameters $^{V}_{G,}$ $^{V}_{M,,}$ $^{V}_{N,,}$ $^{K'}_{G,}$ suggesting Michaelis constants and the maltose inhibition factor are less significant for the dynamic model.
- Mean squared summaries of parameters differential sensitivity profiles have been computed, confirming the importance of maximum reaction velocities, but also highlights significance of higher sugar Michaelis-Menten constants (maltose and maltotriose).
- Parameter subset collinearity indexes used to select a suitable (non-correlated) subset (5 of 8) which can be uniquely estimated, with consistent multi-start solution attainment demonstrated.
- Because our parameter estimation study relies on a published (but modest in size) dataset (and only 4 T-values), temperature-dependent parameter correlations are beyond our scope here. Although parameter values demonstrate consistent monotonic temperature trends (Table 5), Interpolation between given values is the best choice due to variance and dataset limitations. Our key aim is to showcase the methodological implementation, extensible to larger datasets.

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