Intelligent Modelling of a Fluidised Bed Granulator used in Production of Pharmaceuticals

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The aim of dynamic modelling and simulation is to improve the control of the fluidised bed granulator. Modelling and simulation was done on the basis of data collected from several test campaigns. Several modelling methodologies have been compared in Matlab-Simulink environment. A solution based on dynamic linguistic equation models was chosen. The main input variables are humidity difference between incoming and outgoing air, temperature difference between inflowing air and granule and the rate of inflowing air. The final output is the estimated granule size but the overall models contains also dynamic models for temperature and humidity. The simulator combines several models which are specific to the operating conditions. According to the results, the spraying and drying processes included short-duration periods. Extension to fuzzy LE models provides useful information about uncertainties of the forecasted granulation results. The complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis.

Introduction

Powder particles are agglomerated though granulation processes due to interparticle bonds caused by the addition of a granulation liquid. The handling of the starting materials is facilitated and further processing (e.g. tabletting) becomes more secure [1]. Granulation usually refers to processes whereby aggregates with sizes ranging from approximately 0.1 to 2.0 mm are produced by agitation of moistened powder. Compression characteristics are improved, and handling of powders become easier because of less dust, less adhesion with hydroscopic materials. [2]

During the granulation process a three-phase system of solid, liquid and gas is established. The system will reduce its free energy by formation of liquid bridges between the particles. By the liquid bridges cohesive forces are established which may cause agglomeration and consolidation of the agglomerates in so far as they can resist the disruptive forces. The outcome depends on the interactions between apparatus, process and compositional variables and the properties of the powder. [3, 4, 5]

Airflow rate, temperature and humidity of the inlet air and the addition rate and droplet size of the granulating liquid are critical input variables. Temperature and humidity measurements of the process air are the most important parameters for monitoring heat and mass transfer. However, the inlet air humidity cannot usually be specified accurately because the seasonal variations in the process air humidity are difficult to control entirely.

The actual effect of different humidity levels of the inlet air on the various fluid bed process parameters have been studied in [6]. Properties of the particles are also important. Effects of primary particle surface wettability by a binder solution on the rate of agglomeration were investigated in [7].

A physically-based mathematical model for the description of particle wetting and of temperature and concentration distribution in fluidized bed spraygranulation is presented in [8]. The bed mass and particle diameter growth in discontinuous granulation are taken into account and the two-dimensional calculation of the temperature and concentration distributions were carried out for the steady, continuous fluidized bed spray-granulation.

The physical changes in the beginning of spraying process are fast, because the weight of granules increases rapidly, which requires also that the amount of the inlet air has to be increased significantly so that fluidising would continue. This part of the process was the most difficult part to model. Correspondingly during the first few minutes of drying, the surface drying proceeds quickly until the balance is found. According to samples, the size of granules continued to grow for a while even the drying phase was started.

The aim of dynamic modelling and simulation is to improve the control of the fluidised bed granulator. Modelling is based on linguistic equation (LE) approach introduced in [9]. LE approach has been used in various applications [10, 11].

Dynamic LE models have provided accurate prediction and good performance in continuous processes, e.g. a lime kiln and a solar collector field [10]. A set of interactive intelligent systems can be combined with other modelling and simulation methodologies to build practical simulators for industrial processes [12].

For granulation process, dynamic modelling and simulation is necessary. Dynamic LE modelling was started in 2000 in cooperation with Helsinki University and Orion [13]. Dynamic models are well suited for forecasting the granulation result [13, 14]. The research equipment used in this project was a bench-scale fluidized bed granulator (Glatt WSG 5) shown in Figure 1. Modelling and simulation was done on the basis of data collected from test campaigns based on experimental design.

This paper presents more details of the solution and extends the models to uncertain environment.

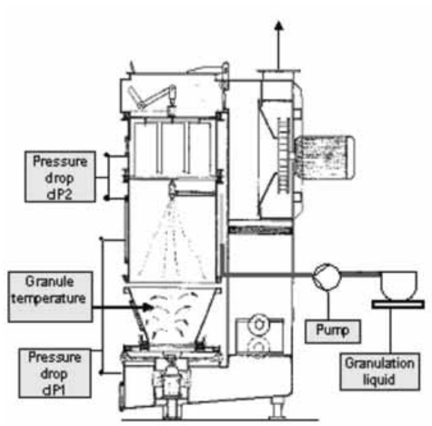

Figure 1. A bench-scale fluidised bed granulator.

1 Measurements

The granulation process shown in Figure 1 has three main phases:

- mixing to get granules homogeneous,
- spraying with PVP granulation liquid, and
- drying with warm air.

The model formulation (batch size 3500 g) consisting of verapamil hydrochloride, microcrystalline cellulose and lactose monohydrate was applied. Polyvinylpyrrolidone was used as a binder. The temperature of the drying air was 60 $°C$.

To eliminate the granules escape from granulator, filters were needed to shake every 100 seconds. The shaking takes 10 seconds, and meanwhile the process flows are off. For proper modelling it was essential to eliminate the effect of shaking as well as possible. More stable data and better modelling was achieved by median and moving average method.

Testing data was collected from 38 batches, 27 batches were used to training and the rest of the 11 to testing. The design of experiments for the test batches R1-11 presented in Table 1 includes three levels (high, normal and low) for the feed rate and the pressure of the granulation liquid. To confirm the functionality there were three repeated batches in the normal conditions.

Table 1. The design of experiments for the batches.

Test	Feed rate of granulation liquid [l/min]	Feed pressure of granulation liquid [bar]
R1	100	1.5
R2	125	1.5
R3	100	2
R4	125	2.5
R5	100	2
R6	125	2
R7	112.5	1.5
R8	112.5	2.5
R9	112.5	2
R10	112.5	2
R11	112.5	2

Numerous variables are known to affect the fluid bed process and the final granules. During the test campaigns, on-line measurements of more than 40 variables were collected with sampling time of one second. Air flow rate, temperature and humidity of the inlet air and the addition rate of the granulation are important variables. The instrumentation is described in [15].

Particle size analyses of intermediate and product granules and bulk factor were done off-line. Particle size analysis introduces two challenges: (1) it is based on samples, and there cannot be too many of them, and (2) particle size has always a distribution. The data driven modelling was based on the average particle size, and interpolation based on nonlinear regression was used to obtain additional points required for the dynamic modelling.

Seasonal variation in humidity is considerable and that will cause the changes in the water amount of the incoming air. The incoming air humidity should be included to the input variables or another possibility is to make a pre-moistening to a constant moisture value in the beginning of granulation.

2 Nonlinear modelling

Nonlinear models are needed in modelling of the granulation process. Various statistical and intelligent methodologies have been compared in this project.

2.1 Statistical modelling

Response surface methodology combines linear terms with interaction and quadratic terms to calculate one output variable y from multiple input variables x_j:

$$
\begin{aligned}
y = b_0 + b_1 x_1 + b_2 x_2 + b_3 x_3 + .. + b_{12} x_1 x_2 \\
+ b_{13} x_1 x_3 \\
+ b_{23} x_2 x_3 + .. + b_{11} x_1^2 \\
+ b_{22} x_2^2 + b_{33} x_3^2 + ..
\end{aligned} \tag{1}
$$

The number of parameters increases very fast with the number of variables.

Statistical models have been used for interpolating the granule size to obtain data for dynamic modelling. There are considerable differences between the batches (Figure 6).

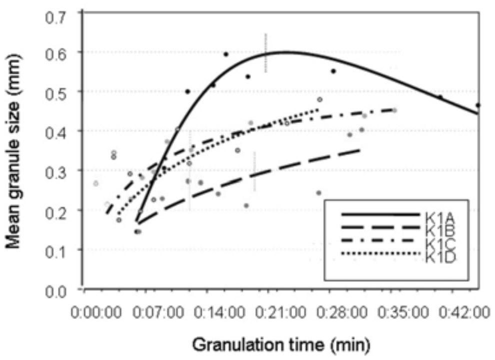

Figure 2. Interpolation of the granule size from 8 samples, starting point presumed to been 0.05 mm.

Dynamic statistical modelling is widely used in system identification. For parametric models, the output at time t is computed as a linear combination of past inputs and past outputs in such a way that the output at time t can depend on the signals at many previous time instants chosen according to appropriate time delays [16]. The number of delayed inputs and outputs is usually referred as the model order(s). The simplest model, ARX model, is usually written

$$
y(t) + A_1 y(t-1) = A_2 u(t - n_k) + e(t) \tag{2}
$$

where A_1 and A_2 are model coefficients, $y(t)$ and $y(t-1)$ state variables and $u(t-n_k)$ input variable delayed with n_k time steps. State-space models are widely used for combining effects of several input variables.

Various structures based on ARMAX, output error and Box Jenkins with different orders of the respective polynomials have been compared. Nonlinear models are needed, i.e. higher orders were needed in the parametric models, and the state-space models were insufficient.

2.2 Fuzzy modelling

Fuzzy set theory was first presented by Zadeh [17] to form a conceptual framework for linguistically represented knowledge. Extension principle is the basis generalisation of the arithmetic operations if the inductive mapping $F(x)$ is a monotonously increasing function, e.g. $F(x) = x_2$ in Figure 3. These results can be combined by applying fuzzy interval analysis in fuzzy arithmetic [18].

Linguistic fuzzy models [19], where both the antecedent and consequent are fuzzy propositions, suit very well to qualitative description of the process as they can be interpreted by using natural language, heuristics and common sense knowledge. The key idea is to use membership functions for both the inputs x and the outputs y. These functions can be defined by expert knowledge or by experimentation. The input-output mapping is realized by the fuzzy inference mechanism equipped with conversion interfaces, fuzzification and defuzzification. The approximate reasoning is based on T-norms and T-conorms [19].

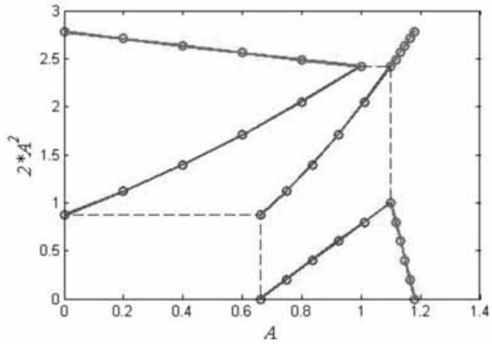

Figure 3. Fuzzy extension of a power function.

The Takagi-Sugeno (TS) fuzzy modelling method was proposed by Takagi and Sugeno as a framework for generating fuzzy if–then rules from numerical data [20]. A TS fuzzy model consists of a set of fuzzy rules, each describing a local linear input–output relationship:

$$
\begin{aligned}
If\ x_1\ is\ A_{i1}\ and\ \dots and\ x_n\ is\ A_{in}\ then\ y_i \\
= a_i x + b_i, i = 1,2, \dots, K
\end{aligned} \tag{3}
$$

where $A_{i1}, \ldots, A_{in}$ are fuzzy sets defined in the antecedent space and y_i is the rule output of the model. K denotes the number of rules. The results of the rules are usually combined as a weighted average where the weights are obtained from the fulfilment of the rules.

Fuzzy relational models [21], which allow one particular antecedent proposition to be associated with several different consequent propositions, can be regarded asgeneralizations of the linguistic fuzzy models. Each element of the relation represents the degree of association between the individual reference fuzzy sets defined in the input and output domains, i.e. all the antecedents are tied to all the consequents with different weights.

Dynamic fuzzy models can be constructed on the basis of state-space models, input-output models or semimechanistic models [22]. In the state-space models, fuzzy antecedent propositions are combined with a deterministic mathematical presentation of the consequent. The most common structure for the input-output models is the NARX (Nonlinear AutoRegressive with eXogenous input) model, in which the input and output values are chosen as in the ARX model according to appropriate system orders. The regressor vector consists of a finite number of past inputs and outputs [23]. This structure is directly used for multiple input, single output (MISO) systems. Multiple input, multiple output (MIMO) systems can be built as a set of coupled MISO models.

2.3 Neural modelling

Artificial neural networks consist of neurons

$$y_i = F(\sum_{j=1}^{m} w_{ij} p_j + B_i) \qquad (4)$$

where w_{ij} is the weight factor of the element p_j in the input vector of the neuron i, and B_i a scalar bias. For the input layer, the elements are usually normalized values of the variables $x_j, j = 1,2, \ldots, m$.

Neurofuzzy systems use fuzzy neurons to combine the weight factors and the inputs. The activation function is handles as a function in the extension principle.

Dynamic ANN models are based on similar structures as the dynamic fuzzy models: simple structures, e.g. NARX structures, can constructed by taking delays into account in the input vector p in (2). A dynamic ANN model can be realised by a static feedforward network and an external feedback connection [23].

Another possibility is to use recurrent networks, e.g. Elman networks} are two-layer feedforward networks, with the addition of a feedback connection from the output of the hidden layer to its input [24]. This feedback path allows Elman networks to learn to recognize and generate temporal patterns, as well as spatial patterns. The weight factors w_{ij} can also depend on time.

3 LE modelling

Data-driven steady state modelling is normally used in linguistic equation (LE) modelling [11]. Dynamic structures extend the models to dynamic simulation, and in this paper uncertainty of the results is handled with fuzzy arithmetics.

3.1 Steady state LE modelling

Linguistic equation models consist of two parts: interactions are handled with linear equations, and nonlinearities are taken into account by (membership definitions) [10]. The output is obtained by

$$x_{out} = f_{out}(-\frac{\sum_{j=1, j\neq out}^{m} A_{ij} f_j^{-1}(x_j) + B_i}{A_{iout}}) \qquad (5)$$

Where parameters $A_{ij}, j = 1, \ldots, m,$ and B_i are the interaction coefficients of the linguistic equation i. Nonlinear scaling is based on membership definitions f_j and corresponding inverse functions f_j^{-1}. This model corresponds to the neural model (4) if the normalization is replaced by the nonlinear scaling.

In the LE models, the nonlinear scaling is performed twice: first scaling from real values to the interval $[-2, 2]$ before applying linguistic equations and then scaling from the interval $[-2, 2]$ to real values after applying linguistic equations (Figure 4). The linguistic level of the input variable j is calculated the inverse functions of the polynomials [11].

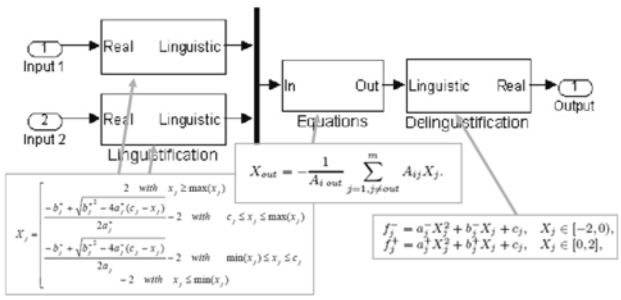

Figure 4. A steady state LE model for two inputs and one output.

3.2 Dynamic LE modelling

The basic form of the linguistic equation (LE) model is a static mapping in the same way as fuzzy set systems and neural networks, and therefore dynamic models will include several inputs and outputs originating from a single variable. External dynamic models provide the dynamic behaviour. The models are developed for a defined sampling interval in the same way as in various identification approaches [16]. However, the LE simulators normally use variable time step integrators.

Rather simple input-output LE models, where the old value of the simulated variable and the current value of the control variable as inputs and the new value of the simulated variable as an output, can be used since nonlinearities are taken into account by membership definitions. To use integration methods available in the simulation software, a difference of the output is calculated (Figure 5).

Nonlinear scaling reduces the order of the model, i.e.the number of input and output signals needed for modelling of nonlinear systems. Need for higher order models can be tested by applying classical identification with different polynomial degrees to the data after scaling with membership definitions. For the default LE model, all the degrees of the polynomials in parametric models become very low, i.e. all the parametric models become the same, ARX model shown in (2).

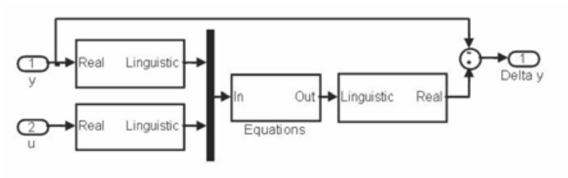

Figure 5. Dynamic LE model of Δy.

Several artificial neural networks have been compared for expanding the linear models, but these more complex model structures do not provide any considerable improvement to the results obtained by the basic LE models, i.e. a linear activation function can be chosen in (4) if the nonlinear scaling described above is used for the input variables.

Changing operating conditions can be taken into account by modifying membership defintions and/or interaction coefficients of the LE models. Linguistic fuzzy models can be used for selecting submodels. This approach is used for selecting the appropriate submodels for spraying and drying.

Also structures used Takagi-Sugeno type fuzzy models can be used if the interaction coefficients depend clearly on the input variables.

3.3 Fuzzy LE modelling

Universal approximators for fuzzy functions can be constructed as extension principle extensions of continuous real-valued functions which continuously map fuzzy numbers into fuzzy numbers [18, 25]. LE models can extended to fuzzy inputs with this approach if the membership definitions and the corresponding inverse functions, are replaced by corresponding extension principle extensions of these functions presented in Figure 4.

The argument of the function f_{out} in (1) is obtained by fuzzy arithmetics. Here the calculations are based on interval analysis which has been widely used in physics for handling measurement errors. In this methodology, measurement values are assumed to be on intervals whose lengths depend on the accuracy of the measurements. The interval analysis is used for estimating the intervals of calculated variables [26]:

$$\begin{aligned}
[a,b] + [c,d] &= [a+c, b+d],\\
[a,b] - [c,d] &= [a-c, b-d],\\
[a,b] \cdot [c,d] &\\
= [\min(ac,ad,bc,bd)\,,\max(ac,ad,bc,bd)],&\\
{[a,b]}\Big/{[c,d]} &= [a,b] \cdot \left[\frac{1}{d}, \frac{1}{c}\right]\ if\ 0 \notin [c,d]
\end{aligned} \qquad (6)$$

where intervals $[a,b]$ and $[c,d]$ are arbitrary real intervals.

The original interval analysis does not include any gradual approach, but the methodology can be generalized to horizontal membership functions (Figures 3 and 6) by applying interval analysis on each α-cut separately. The number of α levels should be increased when the fuzziness of the input increases.

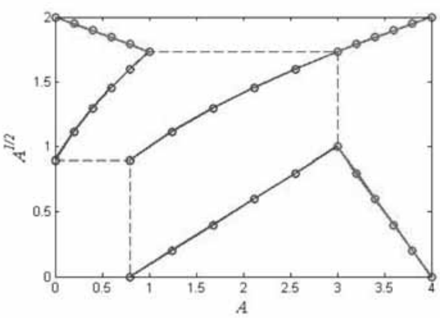

Figure 6. Fuzzy extension for a square root function.

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Only addition and subtraction are needed if the interactioncoefficients are crisp. The only fuzzy part in the linguistification function is the term which includes the input x_j (Figure 4). The extension principle is used to obtain a square root of the fuzzy number (Figure 6). The width and location of the input fuzzy number are modified by the parameters of the scaling functions. The output fuzzy numbers of these blocks are limited to the range $[-2, 2]$.

In the equation block presented by (2), the state variable $y(t-1)$ and the input variable $u(t-n_k)$, which are both fuzzy numbers, are multiplied by crisp numbers – A_1 and A_2, respectively, if the model is crisp. The sum of the resulting fuzzy numbers is the new state variable $y(t)$ in the range $[-2, 2]$.

In the delinguistification block, the terms X_j^2 can be obtained by the extension principle (Figure 3) or by multiplication $X_j \cdot X_j$ with fuzzy interval analysis. The resulting fuzzy number and the original fuzzy number X_j multiplied by crisp numbers shown in Figure 4 are then added to the crisp number c_j to obtain the fuzzy output.

Fuzzy LE models with fuzzy inputs can be constructed by using fuzzy multiplication and division as well since the parameters $a_j^-, b_j^-, a_j^+, b_j^+$ and $c_j$are all fuzzy numbers. Fuzzy extension of the classical interval analysis suits very well also to these calculations. However, the result becomes naturally more uncertain when fuzzy models are used.

Results of the fuzzy interval analysis have always maximal uncertainty as it takes the worst case. A negative associations between the input variables reduces the uncertainty considerably. In the calculations, this can be taken into account by using own membership functions for the upper and lower parts of the value range.

4 Dynamic simulator

Data was separated to three main processes: mixing, spraying and drying. Modelling for mixing area has not done so far because of insignificant changes in the humidity and the airflow. Thus physical knowledge of mixing process is not well known. The aim of mixing step is to make a homogeneous batch.

In the beginning of spraying the physical changes were very rapid and that part of process has been the most difficult area to model. The weight of granules increase rapidly, i.e. the inlet air has to be increased significantly to maintain fluidising. Correspondingly during the first few minutes of the drying, the surface drying proceeds quickly until the balance is founded. The granule growth may still continue for some time in the beginning of the drying phase.

The overall model for the spraying and drying phases consists of three models:

- temperature,
- humidity, and
- granule size.

Output variables were the temporary value of the granule temperature, the new value of humidity difference and the new estimated value of the granule size, correspondingly. The dynamic submodels have similar structures as shown in Figure 5 and model specific variables:

- The new granule size depends on the current granule size and two other variables, temperature difference and humidity difference.
- The granule temperature depends on airflow (F_{in}), humidity difference between inlet and outlet air (U_{diff}) and temperature between granule and inlet air (T_{diff}).
- The humidity depends on T_{diff}, U_{diff} and granule temperature.

The distribution of the particle size is based on the fuzzy extension principle, i.e. the membership function of the particle size is computed in each time step from the uncertain input values by using the dynamic LE model as a function. In this way the uncertainty of the model is not forgotten in the analysis. The system is able to select automatically the best submodel during the granulation process and move gradually from one submodel to another when the process proceeds by fuzzy methods.

The LE models have been developed and tuned in the FuzzEqu Toolbox: the LE model in Figure 7 is a model of the granule size. Membership definitions have been developed from the data: a batch specific example is shown in Figure 8.

5 Results and discussion

Testing data was collected from 38 batches, 27 batches were used to training and the rest of the 11 to testing. Stable data for modelling was obtained by filtering. The modelled and simulated results were compared with experimental data.

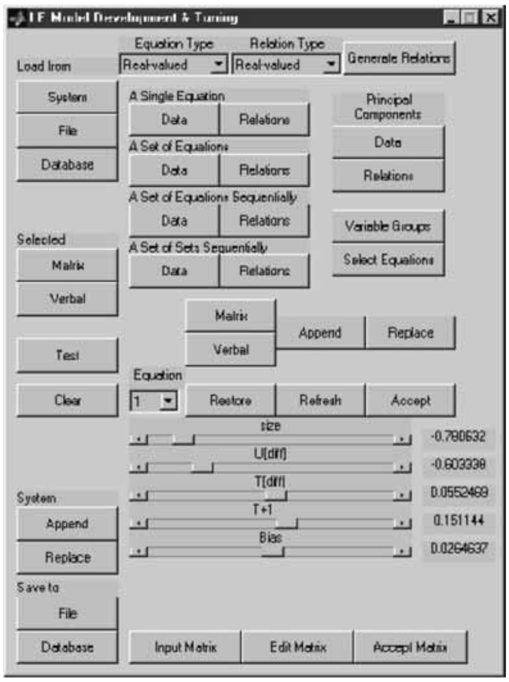

Figure 7. Model development and tuning in FuzzEquToolbox.

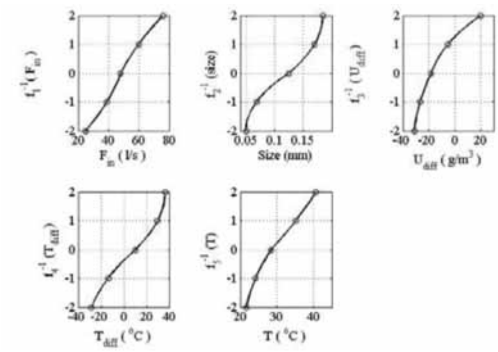

Figure 8. Membership definitions.

According to the modeling and simulation results, the most representative input variables were airflow in(F_{in}), humidity difference between inlet and outlet air (U_{diff}) and temperature between granule and inlet air (T_{diff}). In Simulink model, also other input variables were used but the interaction coefficients of these variables are rather small.

Modelling is aimed to help in estimating the granule size while processing since the analysis result of samples is not available on line. The granulation goes through considerably different routes depending on the operating conditions. By controlling the interaction coefficients of the variables the model worked well also in rapidly changing areas.

The temperature of granules varied mainly from 20 to 60 °C. The data of the batches were shared to several subperiods, and the membership definitions were made for every area. In the linguistic equation model, the variables are scaled between -2 and $+2$. The value range of the variables must be wide enough to guarantee the applicability to the modelling.

Fuzzy modelling is a reasonable extension as also the granule size has always a distribution rather than a single value. This distribution changes with time, and the result becomes more and more uncertain when the prediction horizon increases. Negative associations between T_{diff} and U_{diff} alleviate this problem slightly.

The first results show that the complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis. This study will be extended to the complete data set as it provides a lot of useful additional information about the granulation process. In future, the results will be compared to the measured distributions of the granule size. The goal is to develop more general models, i.e. the membership definitions will be developed from the complete data set related to the batches of the verapamil granulations.

Partly the uncertainty is caused by uncontrolled process conditions, e.g. seasonal variation in humidity is considerable and that will cause the changes in the water amount of the incoming air. The incoming air humidity should be included to the input variables or another possibility is to make a pre-moistening to a constant moisture value in the beginning of granulation. Later a humidifying system has been included, and this enables high and fluctuating humidity of the process air.

6 Conclusions

The data based modelling succeeded well after the main process stages were divided into sub stages corresponding to shorter time periods. The interaction of the main variables was improved by using fuzzy modelling. Extension to fuzzy LE models provides useful information about uncertainties of the forecasted granulating results. The complexity of the models is increased only slightly with the new system based on the extension principle and fuzzy interval analysis. Associations between input variables were useful in reducing the uncertainty of the final result.

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