Scale-up of Aerated Industrial Multistage Rushton Impeller Bioreactors with Complex Rheology

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Abstract

The power input and gas-liquid mass transfer rank among the most important industrial fermentation process parameters. The present study analyzes the power input and gas hold-up as a function of the flow regime, impeller diameter, and rheological properties in a pilot scale reactor (160 L) equipped with four Rushton impellers. This leads to four dimensionless numbers for predicting measurements in pilot and industrial bioreactors (110 and 170 m^3) with a standard deviation of 7 % to 29 %. This is unparalleled for the underlying aerated and non-Newtonian fermentation broths. Several existing correlation equations are discussed to be dissatisfying (up to 130 % deviation), and might be sufficiently valid only within scale or for small scaling factors. The introduced approach predicts adequately accurate over three orders of magnitude. Based on these encouraging results, we identified the Galilei number and the power concept as the central elements in combination with the consequent dimensional analysis for an efficient scaling betweeen pilot and industrial scale.

Keywords: non-Newtonian fluid behavior, power input, scale-down, scale-up, viscous media

Introduction

The scaling of the power input and the oxygen mass-transfer of industrial bioreactors is important for the development, process transfer and scale-up of industrial fermentation processes. The power demand for agitation and aeration can be significant, even ranging above a megawatt for a single fermenter. Thus, energy costs may contribute significantly to the manufacturing costs of a desired product. The large power demand might also lead to higher investment costs (agitators, drives, aerators, heat exchangers). However, effective agitation is critically important, since an insufficient oxygen supply is undesired and may strongly influence the specific productivity of the cultivated cells. Therefore, mixing and aeration are well-known targets for process development at all scales (e.g. Garcia-Ochoa & Gomez, 2009; Gogate, Beenackers, & Pandit, 2000; Henzler, 1982; Oldshue, 1966; Paul, Atiemo-Obeng, & Kresta, 2004; Zlokarnik, 1999). For optimizing large-scale operation parameters of industrial bioreactors, it is advisable to scale down and test new conditions before implementing the setup at the production scale. Consequently, a reliable scaling model is of utmost importance.

Many authors described the complex physical processes impacting the oxygen supply in the bioreactor by applying dimensional and/or dimensionless numbers (Garcia-Ochoa, Castro, & Santos, 2000; Garcia-Ochoa & Gomez, 1998; Liepe, Meusel, Möckel, Platzer, & Weißgärber, 1988; Linek, Moucha, & Sinkule, 1996; Loiseau, Midoux, & Charpentier, 1977; Mockel, Wolleschensky, Drewas, & Rahner, 1990; Oldshue, 1966; Petricek et al., 2017; Saravanan, Veerappan, & Kothandaraman, 2009; Van't Riet, Boom, & M. Smith, 1976; Xie et al., 2014b). The most relevant properties proposed in biochemical engineering textbooks are the specific power input (P/V), volumetric mass transfer coefficient ($k_L a$), vessel volume per minute (VVM), gas superficial velocity (u_g), impeller tip speed (u_T) and dissolved oxygen concentration (c_{O2}) (Oldshue, 1966). Keeping one or more of these variables constant represents the standard approach for scaling fermentation processes (Figure S 1). However, it is also evident that the selection of such criteria stems from practical considerations, not strictly following the principles of a similitude model. This might limit the predictive power of those correlation equations. Considerably fewer authors used the Flow number (Fl) and Froude number (Fr) for the prediction of oxygen mass transfer, although these numbers originate from dimensional analysis and were proven to reliably characterize the flow regime induced by the bottom impeller (John M. Smith, Warmoeskerken, & Zeef, 1987).

Several authors applied laboratory-scale (up to 21 L; Garcia-Ochoa et al., 2000; Garcia-Ochoa & Gomez, 1998; Liepe et al., 1988; Linek et al., 1996; Loiseau et al., 1977) and a few pilot-scale experiments (up to 6.43 m3; Hoecker, Langer, & Werner, 1981; Mockel et al., 1990; Petricek et al., 2017; Saravanan et al., 2009; Xie et al., 2014b). The largest scaling step applied in these studies was a factor of 1 : 50 (Petricek et al., 2017). When scaling steps are small, the concepts yield sufficiently accurate predictions. For large steps, scaling effects may occur (cf. Figure S 1) that make predictions inaccurate (Garcia-Ochoa & Gomez, 2009). For application of scaling at a large industrial scale, these concepts are questionable and validation data are lacking.

A further source of inaccurate scaling is that the number of impeller levels is often disregarded. Most studies mentioned above applied stirred tanks equipped with one, two (Garcia-Ochoa & Gomez, 1998; Hoecker et al., 1981; Loiseau et al., 1977; Saravanan et al., 2009), or three impellers (Linek et al., 1996; Mockel et al., 1990; Petricek et al., 2017; J. M. Smith, 1992; Xie et al., 2014a). In contrast, large industrial-scale reactors often exhibit four, five or more levels, depending on the facility. These multi-stage reactors have been shown to behave differently regarding each impellers flow regime (Bombac & Zun, 2006; John M. Smith et al., 1987), power input (Linek et al., 1996; Middleton & Smith, 2004) and gas hold-up (Gogate et al., 2000; Linek et al., 1996) compared to single impeller reactors. Adequate correlation equations are missing important information for understanding and designing the large-scale cultivation of producer cells (Linek et al., 1996; Nocentini, Fajner, Pasquali, & Magelli, 1993; Vrábel, van der Lans, Luyben, Boon, & Nienow, 2000; Zhang, Pan, & Rempel, 2006).

The non-ideal rheological behavior of the fermentation broth is also a known source of inaccuracies of scaling concepts. Many industrial processes show viscous non-Newtonian behavior, e.g., due to mycelial growth or production of metabolic polymers (Wucherpfennig, Kiep, Driouch, Wittmann, & Krull, 2010). The apparent viscosity (Brown, Jones, Middleton, Papadopoulos, & Arik, 2004; Henzler, 2007),

$$\eta_{app} = K\dot{\gamma}_{rep}^{n-1}, \tag{1}$$

of these non-Newtonian fluids depends on the representative shear rate, $\dot{\gamma}_{rep}$ and the fluid-characteristic properties (consistency index K, flow behavior index n). The Power-Law model by Ostwald and de Waele,

$$\tau = K\dot{\gamma}_{rep}^{n}, \tag{2}$$

represents the underlying physical relation between the shear stress, τ, and the representative shear rate independent of scale. Sánchez Pérez, Rodríguez Porcel, Casas López, Fernández Sevilla, and Chisti (2006) summarized the available approaches for describing the dependency of shear rate and impeller speed. Most authors apply the Metzner-Otto concept (Metzner & Otto, 1957) to describe the representative shear rate, assuming a simple proportionality with the impeller speed (Amanullah, Hjorth, & Nienow, 1998; Böhme & Stenger, 1988; Hoecker & Langer, 1977; Jüsten, Paul, Nienow, & Thomas, 1996; Knoch, 1997; Sinevic, Kuboi, & Nienow, 1986).

The Metzner-Otto concept underestimates the representative shear rate for large industrial bioreactors, and overestimates the apparent viscosity for shear thinning fluids (Equation 1)

(Henzler, 2007; Herbst, Schumpe, & Deckwer, 1992). It may be assumed that the Metzner-Otto concept is applicable only for the same scale.

The so-called power concept by Henzler and Kauling (1985) is more advanced in that it is derived from general physical principles (i.e., independent of scale). The representative shear rate is expressed as a function of the specific power input (P):

$$\dot{\gamma}_{rep} = L^{\frac{2}{1+n}} \left(\frac{P/V}{K}\right)^{\frac{1}{1+n}} \tag{3}$$

with the above fluid-characteristic properties (K, n) and a constant parameter (L). Remarkably, the power concept reduces to the Metzner-Otto concept for laminar conditions, as shown by Giese et al. (2014). Henzler (2007) demonstrated that the power concept, unlike the Metzner-Otto concept, is valid over different scales.

The objective of this study is to critically analyze the power input and gas hold-up for aerated bioreactors and to provide novel correlations in a dimensionless form. It seems helpful choosing correlation equations as outlined in Equations 1, 2 and 3 for deriving a new scaling concept for the flow regime and rheology. Instead of impeller-speed-dependent models, we apply an extended power concept considering the shear rate under aerated conditions and choosing corresponding model fluids for scaling rheology. We furthermore extend the concept by a variable impeller diameter, apply the Galilei number and consider pilot- and large-scale gas flow regime by application of multi-impeller reactors with four impeller levels. In this approach we solely use dimensional analysis and scale-independent representations for describing the relevant complex physical processes efficiently and for minimizing scaling effects. In order to validate the novel correlations that cover a large operating and scaling range, we test the prediction quality for two industrial fermentation processes and compare results with existing correlations.

Materials and Methods

Pilot-scale reactor (160 L)

The experiments for the development of the scaling model and its validation were performed in a Plexiglas reactor (PGR) with an inner diameter of T = 0.44 m and a fluid volume of 0.16 m³ (Witz, Treffer, Hardiman, & Khinast, 2016). The vessel was equipped with four longitudinal baffles (thickness = $T/10$) and six blade Rushton impellers (D/T of 0.36, 0.42, 0.46) arranged in four levels with a spacing between the impellers of Z/T = 0.6 and a bottom clearance of C/T = 0.36.

Industrial-scale reactors (data for model verification; > 100 m^3)

Further experiments for validation of the scaling concept were conducted in two large-scale bioreactors. Fermenter 1 exhibits a D/T -ratio of 0.36 and a volume of 170 m^3; fermenter 2 a D/T -ratio of 0.43 and a volume of 110 m^3. Both fermenters were equipped with four Rushton impeller levels with a spacing of Z/T = 0.6. The fermentation broth in fermenter 1 represented a Newtonian behavior with K = 0.02 Pas and n = 1 (invariant over process time). The broth in fermenter 2 displayed a non-Newtonian behavior with a process time variant consistency index ranging from 2.7 to 7.3 and a flow behavior index varying from 0.31 to 0.25.

Model Fluids

All measurements in pilot-scale were conducted applying model fluids. To mimic the fermentation broth's non-coalescent behavior of the air bubbles, Na_2SO_4 was added to deionized water (0.065 mol/L). Non-Newtonian fluids were made using xanthan in four concentrations (0.05, 0.1, 0.3 and 0.4 % [w/w]; Cosphaderm X34, Alexmo Cosmetics, Germany). The density of the solutions was 1005 to 1007 kg m^{-3}. The rheological properties were characterized using a Kinexus pro+ rotational rheometer (Malvern Instruments, UK) and the power-law model (Equation 2).

Experimental range

Impeller speed, aeration rate, impeller diameter and rheological properties of model fluids were varied over a wide range to cover common fermentation conditions in industrial fermentation processes (Table S 1). All experiments were carried out in triplicates, leading to 2889 data points for determining the gas hold-up and 2916 for the power input estimation. For model verification at the pilot-scale, a set of 726 experimentally determined values for the gas hold-up and Newton number were applied.

Measuring methods

The large-scale reactors were equipped with filling level probes for measurement of the gas hold-up. In the plexiglas vessel, the liquid level was measured using a scale. The gas hold-up,

$$\varepsilon = \frac{H_g}{\left(H_g + H_l\right)} \qquad 4$$

was determined by measuring the aerated liquid height relative to the liquid level without aeration. H_g represents the difference of the liquid height in the reactor, when aerated and non-aerated, and H_l the liquid height, when not aerated. Temperature was set to 20 ± 3° C. The influence of the temperature deviation on the air volume was corrected using

$$V_{g,20°C} = \frac{293.15K}{Temperature} V_g(Temperature), \qquad 5$$

where $V_{g,20°C}$ stands for the representative gas volume at 20°C, and $V_g(Temperature)$ for the measured gas hold-up at the observed temperature. A strain gauge with telemetry technique (Trachsler Electronics GmbH, Switzerland) was used for determining the torque on the stirrer shaft of the PGR. The strain gauges were applied above the top impeller and the determined torque represents the sum of the four impellers. The power consumption in the large-scale reactors was determined via the measured engine power input and the experimentally observed energy losses.

Statistical evaluation and parameter identification

The experimental data were subjected to a principal component analysis using the software SIMCA (V14.1, Sartorius Stedim, Germany). The unknown parameters of the correlation equations for the new scaling concept were identified using the Minitab Software (V 17.2, Minitab

Inc. USA), via a non-linear regression and a Gauss-Newton algorithm. The quality of the estimation was assessed by the relative standard deviation (SD) of the experimental ($x_{experimental}$) and predicted values ($x_{predicted}$):

$$SD = \sqrt{\frac{1}{1-N}\sum_{j=1}^{N}\left(\frac{x_{experimental,j}-x_{predicted,j}}{x_{experimental,j}}\right)^2}. \qquad 6$$

Theoretical Aspects

A full dimensional analysis of the power input into an aerated stirred tank reactor by Bieseker (1972) led to a set of 24 dimensionless numbers and was reduced further by Zlokarnik (1973, 1999) to the Froude number ($Fr = \frac{N^2 D}{g}$), Reynolds number ($Re = \frac{ND^2\rho}{\eta_{app}}$), Gas Flow number ($Fl = \frac{Q}{ND^3}$) and the Weber number ($We = \frac{\rho N^2 D^3}{\sigma}$). One shortcoming of selecting a combination of the Reynolds, Froude and Flow numbers is that these depend on the impeller speed. Moreover, the term ND^2 of the Reynolds number is also part of the Flow number. Although the Reynolds number contains information on the rheology of the fluid, a further aspect of its application is that the Newton number is independent of the Reynolds number in the turbulent flow regime (Zlokarnik, 1973). Typically, industrial microbial fermentation processes work in the turbulent regime. The approach proposed by Hoecker et al. (1981) uses the Galilei number (Ga) instead of the Reynolds number:

$$Ga = \frac{Re^2}{Fr} = \frac{D^3 g \rho^2}{\eta_{app}^2} \qquad 7$$

Besides substance properties, such as the dynamic viscosity (η), the Galilei number contains only the impeller diameter, D, as an operating variable, and thus, appears to be a good choice to efficiently scale rheology. Furthermore, the density, ρ, and surface tension, σ, of different fermentation broths were analyzed (data not shown) and the influence was found to be negligible and therefore the We number was excluded. The resulting dimensionless relationship is given by

$$Ne = f(Fr, Fl, Ga). \qquad 8$$

Hoecker et al. (1981) demonstrated that this concept adequately describes the power input in experiments with model fluids of different rheological properties. However, these authors did not include geometric aspects, as experiments were done only at a single scale (50 L), with one Rushton turbine and an untypical H/T ratio. The present work extends this concept through a dimensionless number representing the reactor geometry

$$Ne = A * Fr^{\alpha} Fl^{\beta} \left(\frac{D}{T}\right)^{\gamma} Ga^{\delta}. \qquad 9$$

The variation of the impeller versus tank diameter (D/T) seems to be important, since the impeller diameter is part of all dimensionless numbers, and otherwise the tank diameter would not be represented. A further extension is the aforementioned application of the power concept (Equation 3), considering aerated conditions ($P = P_g$ with P_g, power input under aerated conditions).

In addition to scaling the power input (Ne), the correlation was used for describing the dimensionless gas hold-up (ε, Equation 10)

$$\varepsilon = B * Fr^{\zeta} Fl^{\theta} \left(\frac{D}{T}\right)^{\iota} Ga^{k} \qquad 10$$

For Newtonian fluids with low viscosity the Galilei number depends solely on the impeller diameter. Equations 9 and 10, however, formulate the impeller diameter as separate dimensionless number. Thus, for Newtonian fluids, the Galilei number does not contain additional information on the variation in the data set and was excluded from the Equations 9 and 10. The resulting set of Equations 1, 2, 3 (using $P = P_g$), and Equations 7 to 10 represent the new concept.

Successfully correlating the gas hold-up with the flow regime (Fr, Fl), rheology (Ga) and geometry (D/T) according to this dimensionless concept should support the idea of appropriately characterizing bioreactor conditions with regard to the general oxygen supply as an important biotechnological operations. As a representative control for a dimensional approach, the $k_L a$

(volumetric mass transfer coefficient) value was determined addionally and correlated analogously to Equation 10 (see supplemental material).

Results and Discussion

Derivation of correlation parameters

Initially, the large data set generated in the pilot-scale fermenter was statistically analyzed. A principal component analysis revealed data clusters over two principal components (Figure 1, left). Interestingly, these clusters seem to agree with the bottom-impeller flow regimes (Figure 1, right) flooding, large and vortex cavities, with and without recirculation, as described by Middleton and Smith (2004). These results correspond to our study (Bernauer et al., 2020), which indicates that the bottom impellers flow regime influences the gas-liquid flow of the whole reactor.

Furthermore, the principal component analysis of the experimental dataset indicated that a separation of experiments applying the Newtonian and the non-Newtonian model fluids is beneficial. The data fit after these classifications led to a significant improvement of the "goodness of fit" (Equation 6). We thus conclude that it is beneficial to use this *a priori* knowledge, when facing fundamentally different liquid and gas flow conditions and statistical analysis supports the corresponding classification.

The parameters identified for Equations 9 and 10 are listed in Tables S2 and S3 including the determined SDs, ranging between 1.5 % and 10.6 % and < 7 % for most conditions (70%). The predicted and measured values are available in Figure S 2 of the supplemental material.

Model verification in pilot-scale fermenters

The correlations' accuracies were challenged applying (i) a fluid with rheological properties that were not used for identifying their parameters (0.2 % xanthan test fluid, with the rheological parameters K = 0.46, n = 0.35) and (ii) the full experimental range (i.e., the large cavities, vortex cavities and flooded flow regime). The predicted values of the gas hold-up and Newton number lie close to the experimental values (Figure 2). The SD is 7 % for the Newton number and 8 % for gas hold-up (Table S 2, Table S 3).

Furthermore, a comparison of the experimental values with predictions from literature correlations (listed in Table S 5) was carried out. The prediction of the Newton number (Figure 2 A) by the dimensionless approach of Nienow, Wisdom, and Middleton (1977) shows a very good fit with a SD of 11 %. The approach also includes Froude and Flow number but has no term for describing viscosity. The dimensional correlation of Mockel et al. (1990) shows a large SD of 36 %, which may be due to the application of a dimensional concept and missing viscosity term. The most promising study by Xie et al. (2014a) is a similar approach to ours and based on a dimensionless form including Froude-, Flow- and Reynolds number and was established applying non-Newtonian fluids. However, it exhibits the highest SD of 58% to the experimental data. The large error may be explained by the authors' application of the Metzner-Otto concept for calculation of the shear rate, which leads to inaccurate predictions as expected. Furthermore, their experiments were conducted in the transition range from laminar to turbulent flow, which makes the application of their correlation for turbulent conditions in bioreactors difficult.

The most precise correlation of the gas hold-up (Figure 2 B) with a SD of 21 % is obtained with the correlation by Garcia-Ochoa and Gomez (2004) based on a theoretical approach. Zhang et al. (2006) also shows a good correlation with a SD of 29 %. The study, however, was conducted in a multi-stage reactor with a large d/D ratio of 0.5 and is therefore only comparable to a limited extent with our data. Other studies (Loiseau et al., 1977; J. M. Smith, 1992) exhibit large SDs of 34% and 62%. All predictions show an underprediction of the actual values. It has to be noted that viscosity dependent models of the mentioned gas hold-up studies were obtained in Newtonian liquids.

The $k_L a$ (volumetric mass transfer coefficient) value was determined and correlated analogously to Equation 10 (supplemental material) as a representative control for an established dimensional approach. However, the predictions were not satisfactory with SDs 17 to 34 % (Figure S 3) and in line with dimensional or mixed approaches (39 to 70 % SD) by other authors (Table S 5). This result was expected due to the dimensional form of the $k_L a$ value in Equation 10, and, the application of the Metzner-Otto concept by some authors.

Model verification in industrial-scale fermenters

After verification in the pilot-scale, the predictions of the Newton number and gas hold-up were critically assessed using measured data from two large-scale processes. Figure 3 A and B illustrate the predictions and experimentally measured values for a 170 m^3 scale fermentation process. The fermentation broth had a low-viscosity Newtonian rheology and was invariant over the process time. The flow regime was defined by large cavities without recirculation.

Our model predicts the Newton number extraordinarily well with a SD of 7 %. A comparison to other authors shows that the dimensionless correlation proposed by Nienow et al. (1977) represents the data with a SD of 14 %. The works of Xie et al. (2014a) and Mockel et al. (1990) show a lower prediction capability with 26 % and 29 % SD. Again, the measurements in the transition range between laminar and turbulent flow (Xie et al., 2014a) and the dimensional approach by Mockel et al. (1990) may be the reason for these inaccuracies. Generally, the correlations of all authors do not predict an increase of the Newton number at this large-scale. A possible reason for this underestimation are fluctuations of the large-scale reactors engine power.

The predicted gas hold-up at the large scale exhibits a similar accuracy at the large-scale compared to the prediction of the Newton number (SD 8%). However, other existing correlations display a much lower prediction capability (Liepe et al. (1988): 63 %, Xie et al. (2014b): 85 %, Saravanan et al. (2009): 86 % and Linek et al. (1996): 91 % SD). All cited correlations overpredict the actual gas hold-up. This may be explained by the correlations' dimensional structure of $\varepsilon = {u_g}^x (P/V)^y$. Scaling with such concepts changes the process conditions significantly, as illustrated in Figure S 1. Again, the use of a similitude model is beneficial, as it aims at scaling (keeping) the flow regime of the aerated reactor.

Furthermore, measured data from a reactor scale of 110 m^3 (Figure 3, C and D) were used for validating the proposed correlations for Newton number and gas hold-up. The fermentation broth had a non-Newtonian rheology, the rheological parameters varied over the process time, and the flow regime represented the large-cavities regime without recirculation.

The predicted values of the Newton number by our proposed correlation show a SD of 12%. The relation provided by Nienow et al. (1977) presents a comparable accuracy to our data with a SD of 10%. This can be explained by the similar dimensionless forms of the applied equations with similar exponents for the Froude and Flow number, although Nienow et al. (1977) did not use a viscosity term. Furthermore, in our prediction, the exponent of the Galilei number is small and therefore the influence of viscosity on Newton number was found to be also minor. However, the influence depends on the flow regime and increases, e.g., in the recirculation regime (Table S 2). The correlation proposed by Mockel et al. (1990) shows a better fit for the non-Newtonian process as for the Newtonian process (SD 13%). Xie et al. (2014a) proposed two correlations, one excluding viscosity and one including viscosity by means of the Reynolds number. Interestingly, the equation including the Reynolds number shows a very poor fit with a SD of 65% (as mentioned above, not based on turbulent conditions). The equation without the Reynolds number is a better fit with a SD of 23%.

Our prediction of gas hold-up for non-Newtonian behavior with a SD of 29 % was the closest to the experimental data compared to other studies. The concept of Loiseau et al. (1977) exhibits a

SD of 39 %, but fails at low apparent viscosities. The remaining correlations (Middleton & Smith, 2004; J. M. Smith, 1992; Zhang et al., 2006) show poor predictions of the experimental values (SD of 73%, 80% and 78%). All equations underestimate the gas hold-up of the large-scale bioreactor. A straightforward explanation is the application of the Metzner-Otto concept, which overestimates the viscosity when applying for scale-up. Interestingly, for the data points at the experimentally highest gas hold-up (Figure 3 D) the existing correlations predict a constantly low gas hold-up, whereas the real hold-up increases. A general explanation for this behavior is difficult due to the variety of the dimensional approaches. However, our dimensionless approach and using the Galilei number is capable of describing the high gas hold-up values (Figure 3 D). The large SD of the correlation by Zhang et al. (2006) might be caused by the different system and a large impeller/reactor diameter-ratio. Additionally, Zhang et al. (2006) directly used the impeller speed in the correlation, and therefore, underestimated significantly the gas hold-up in large-scale fermenters, as impeller speed is lower in large-scale reactors for similar volumetric power input. The overall underprediction of gas hold-up by the studied literature correlations may be attributed to an insufficient description of the rheological behavior by applying the viscosity itself or the Reynolds number and paired with the application of the Metzner-Otto concept for non-Newtonian fluids. Our approach still underestimates the hold-up but shows a significantly better prediction of the experimental values.

Furthermore, our study applied four impeller stages and all other refered publications only three or less stages. Since the upper impellers have been shown to yield a larger gas hold-up and power draw (Gogate et al., 2000; Linek et al., 1996; Nocentini, Magelli, Pasquali, & Fajner, 1988; John M. Smith et al., 1987), predominantly due to predispersion of the gas by the bottom impeller (Bernauer et al., 2020), we may expect an underestimation of both values by the correlations of

Table S 5 (derived from data using reactors with less than four impeller levels). However, the results showed variations in the Newton number (Figure 3, A and C) and gas hold-up (Figure 3, B and D) in both directions and to a larger extent than expected from the influence of the number of impeller levels of the reactor. These variations were mainly associated with the previously described influence of the dimensional approaches. Nevertheless, the influence of the number of impellers should be considered for scaling between pilot and large scale and this should be objective of further studies.

Conclusions

Within the scope of the present work, we derived a set of equations constituting a new bioreactor scaling concept for stirring and aeration of Newtonian and non-Newtonian fluids, based on dimensional analysis and scale-independent representations of the relevant physical processes. The scaling of the flow regime by means of the Froude and Flow number leads to significantly better predictions, especially for large scaling steps, as compared with other approaches. The separation of the operating ranges according to the bottom impeller flow regime classification significantly further improves the prediction quality. The underlying fundamentally different overall gas and liquid flow conditions in the reactor impact the power input and gas hold-up strongly, and this might not be adequately described by a single equation. Applying the Galilei number combined with the power concept for aerated conditions enables improved scaling of the shear rate and apparent viscosity, and thus, of both the power input and gas hold-up for non-Newtonian fluids.

The derived correlation equations were tested with pilot-scale data for a non-Newtonian model fluid, and showed good accuracy for the Newton number and gas hold-up (SD < 10 %). Predictions of the gas hold-up and Newton number for production-scale reactors with non-Newtonian and Newtonian fermentation broths (scaling factor 650 and 1000, respectively) demonstrated good agreement with the measured data. Our approach showed no loss in accuracy compared to pilot-scale for Newtonian (SD < 10 %) and only moderate inaccuracies for non-Newtonian broths (SD of 12 % for Ne number and 29 % for gas hold-up).

A wealth of different approaches is available in text books and many important fundamental contributions to the field that yield sufficiently accurate predictions of power input and oxygen supply, when applied for similar scales as they were derived for. This work comprehensively analyzes these scaling concepts for large scaling steps. Remarkable results are generated for predicting the Ne number using Nienow's correlation (SD < 15 %), which is based solely on two dimensionless numbers (Fl, Fr), however, does not consider rheology or prediction of gas hold-up. One reason for the discouraging results for the other approaches (SD > 20 % and up to 130 % for predicting Ne and gas hold-up) may be a change of the flow regimes in the reactors, which is caused by most correlations' dimensional scaling approaches. The presence of an equal number of impeller levels in the reactors might be another important basis for ensuring a comparable flow regime during scale-up/-down. This should be objective for further studies. Another cause of inaccuracy is the common application of the Metzner-Otto concept for scaling the apparent viscosity. Such models yield unsatisfactory predictions due to the assumption of a linear dependence of the shear rate on the stirrer speed. The present work supports the assumption that the application of the Metzner-Otto concept leads to inadequate estimations, during scaling up and potentially even within scale.

The encouraging results of this work for remarkably large scaling factors of three orders of magnitude are a significant progress as underlined by the comprehensive analysis of the correlations available from previous work. This strongly supports the application of the new concept and provides an important step forward in our understanding of industrial fermentation processes.

Nomenclature

A, B	empirical constants [-]
C	reactor bottom clearance [m]
D	impeller diameter [m]
D_L	diffusivity of gas in liquid [m^2 s^{-1}]
Fl	Flow number [-]
Fr	Froude number [-]
g	gravitational constant [$m^3 kg^{-1} s^{-2}$]
Ga	Galilei number [-]
H_g	aerated liquid height [m]
H_L	unaerated liquid height [m]
K	consistency index [Pa s]
K_s	proportionality constant [-]
L	power concept constant [-]
n	flow behavior index [-]
N	impeller frequency [s^{-1}]
Ne	Newton number [-]
P	Power input [W]
PCA	Principal component analysis
P_g	specific power input under aerated condition [W]
P_0	specific power input without aeration [W]
PGR	Plexiglas reactor
Re	Reynolds number [-]
SD	standard deviation
T	tank diameter [m]
u_g	gas superficial velocity [m s^{-1}]
u_T	impeller tip speed [m s^{-1}]
V	volume of the liquid [m^3]

$V_g, 20°C$	gas volume at 20°C
$V_g(Temperature)$	gas volume at the observed temperature
VVM	vessel volume per minute [min^{-1}]
We	Weber number [-]
c_{O2}	dissolved oxygen concentration [%]
Q	aeration rate [$m^3\ h^{-1}$]
Z	spacing between impellers [m]

Greek letters

$\alpha, \beta, \gamma, \delta, \zeta, \theta, \iota, \kappa$	empirical constants [-]
ρ	liquid density [$kg\ m^{-3}$]
ρ_g	density of gas phase [$kg\ m^{-3}$]
σ	surface tension [$kg\ s^{-2}$]
ε	gas hold-up [-]
τ	shear stress [$N\ m^{-2}$]
η_{app}	apparent dynamic viscosity of the liquid [Pa s]
η_w	dynamic viscosity of water [Pa s]
$\dot{\gamma}_{rep}$	representative shear rate [s^{-1}]

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Figure Legends

Figure 1: Principal component analysis (left) of all Newton number and gas hold-up experimental data and the corresponding flow regime map (right). Flooded (green), large cavities (dark blue), large cavities with recirculation (red), vortex cavities (light blue) and vortex cavities with recirculation (orange).

Figure 2: Newton numbers (A) and gas hold-up- (B) observed in pilot-scale in a 0.2% xanthan test fluid with non-Newtonian flow behavior and predictions using correlation equations of other authors (pilot-scale). Graph A: □, Nienow et al. (1977); ◊, Xie et al. (2014a); x, Mockel et al. (1990); Graph B: □, Loiseau et al. (1977); ◊, J. M. Smith (1992); x, Zhang et al. (2006); Δ, Garcia-Ochoa and Gomez (2004). The solid line represents the correlation equation, and dashed lines the ± 20 % error (full data set in Figure S 2).

Figure 3: Newton number and gas hold-up in a 170 m^3 scale fermenter with Newtonian fluid (Graph A and B) and in a 110 m^3 scale fermenter with non-Newtonian fluid (Graph C and D). The measured values are compared to predicted values using various correlations. ○ represents data of ths work. Graph A: □, Nienow et al. (1977); ◊, Xie et al. (2014a); x, Mockel et al. (1990); Graph B: □, Linek et al. (1996); ◊, Xie et al. (2014b); x, Liepe et al. (1988); Graph C: □, Nienow et al. (1977); ◊, Xie et al. (2014a); x, Mockel et al. (1990); Graph D: □, Loiseau et al. (1977); ◊, J. M. Smith (1992); x, Zhang et al. (2006), Δ, Garcia-Ochoa and Gomez (2004). The solid line represents the correlation equation, and dashed lines the respective standard deviation (Tables S2 to S3) of the present work.