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**Review Article**

# A Review of Application of Experimental Design Techniques Related to Dark Fermentative Hydrogen Production

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*ABSTRACT*

The current review purpose is to present a general overview of different experimental design methods that are applied to investigate the effect of key factors on dark fermentation and are efficient in predicting the experimental data for biological hydrogen production. The methods of two levels full and fractional factorials, Plackett–Burman, and Taguchi were employed for screening the most important factors in dark fermentation. The techniques of central composite, Box–Behnken, Taguchi, and one factor at a time for optimization of the dark fermentation were extensively used. Papers on the three levels full and fractional factorials, artificial neural network coupled with genetic algorithm, simplex, and D-optimal for the optimization of the dark fermentation are limited, and no paper on the Dohlert design has been reported to date. The artificial neural network coupled with genetic algorithm is a more suitable method than the RSM technique for the optimization of dark fermentation. Literature shows that the optimization of critical factors plays a significant role in dark fermentation and is useful to improve the hydrogen production rate and hydrogen yield.

## 1. INTRODUCTION

In recent years, hydrogen has received global recognition as a clean energy carrier with a potential to substitute liquid fossil fuels. Hydrogen can be useful for solving the problem of growing global warming and greenhouse gas emissions. Hydrogen is produced from fossil fuel, water, and biomass through physicochemical and biological methods [1]. One of hydrogen production methods is dark fermentation that occurs under facultative or strictly anaerobic conditions in the absence of light [2,3]. Dark fermentation as a complicated multiproduct process is affected by many variables such as temperature, pH, bioreactor configuration, hydrogen partial pressure, substrate type and concentration, nutrients, inhibitors, hydraulic retention time (HRT), and so on [4,5]. Thus, its production depends largely on the optimization of various controlling factors.

Experiments are described as tests that make purposeful changes in the factors (input variables) of a system or process, and effect of these changes in the responses (output variables) are noticed [6]. It is evident that if experiments are carried out randomly, the observed results will also be random and are affected by noise. Therefore, it is beneficial to fit the data with appropriate statistical methods [7]. Design of experiments (DOE) is a technique for systematically employing statistical methods to carry out experiments, that was proposed by Fisher in 1920 [8]. An appropriate DOE must avoid systematic error, be accurate, allow the estimation of the size of the random error, and have extensive validity [9]. Randomization, replication, and blocking are the three basic principles of DOE [10]. Design of experiments is employed for three experimental objectives including screening, optimization, and robustness testing. The screening stage is applied to recognize the key factors that affect the results [11]. The two levels full factorial design (2-FFD), two levels fractional factorial design (2-PFD), and Plackett–Burman design (PBD) methods are mainly used for the screening stage [12]. Frequently, the initial estimate of the factor levels is far from the actual optimum values [6,13]. Thus, the approximate level of key factors generating optimal conditions can be estimated using approaches such as steepest ascent and descent. The optimization is a critical step to obtain appropriate levels of key factors to find the best possible response. The optimization represents increasing the efficiency of a product, a system, a procedure, or a process to receive the maximum benefit out of it [14] and is more implicated than the screening stage and requires more experiments to be performed [11]. The models of one factor at a time (OFAT), Taguchi design (TD), three levels full factorial design (3-FFD), three levels fractional factorial design (3-PFD), Box-Behnken design (BBD), central composite design (CCD), D-optimal (DO), Dohlert design (DD), simplex method (SM), and artificial neural network (AAN) design are mainly used for the optimization stage. DOE methods are shown in Fig. 1. The choice of a suitable DOE method is a very intricate issue and depends on a set of criteria including type of problem, degree of optimization, time and cost constraints, number of factors under investigation and their interactions, the possible presence of identifiable and non-identifiable extraneous factors, ease of understanding and implementation, complexity of using each design, required training, statistical validity and robustness of approach, etc. [15,16]. Designing experiments presents more advantages such as reducing time, cost, resources, and effort than the univariate procedures that facilitate collecting large quantities of information while minimizing tedious experimental work [15].

Since DFHP is affected by many factors and depends largely on the optimization of controlling factors, there is a need to

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have at hand a reliable technique of DOE for optimization of various controlling factors that can help facilitate a better understanding of individual and interactive effects of each factor on hydrogen production. The present study covers the conventional experimental design methods related to DFHP that are currently employed to study the effect of key factors on dark fermentation. An appropriate DOE method can be used to find optimum conditions for maximizing hydrogen yield (HY) and hydrogen production rate (HPR).

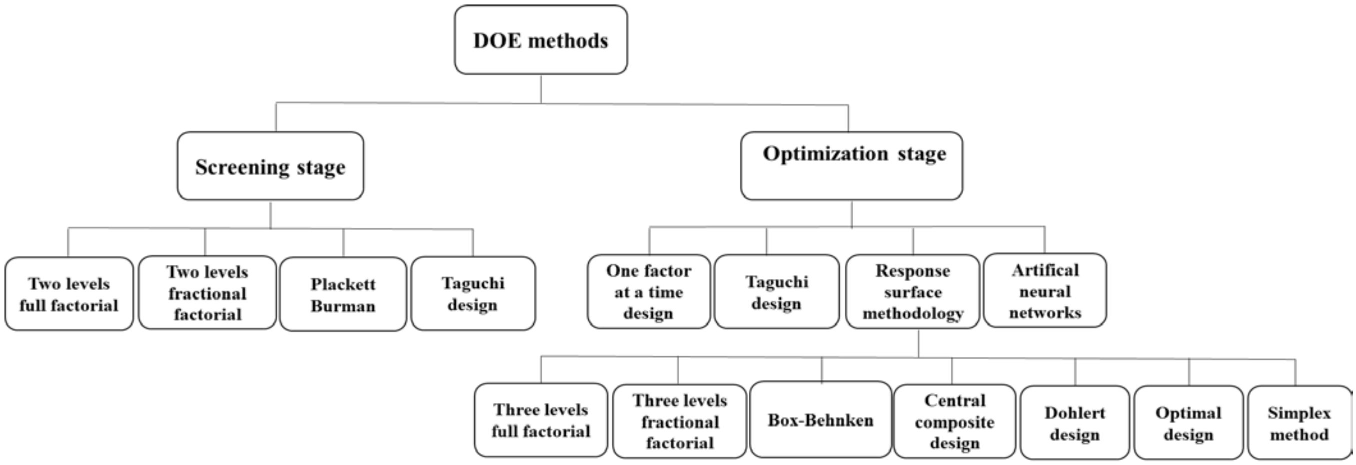


**Figure 1.** DOE methods.

## 2. DOE METHODS

### 2.1. Screening stage

#### 2.1.1. Two levels full or fractional factorials

A factorial approach is classified into full and fractional factorial design. A full factorial design (FFD) consists of all possible combinations of factor levels to investigate the effect of the factors on a response simultaneously. In this approach, the total number of experiments for studying k factors, each at L levels, is $L^k$ and for various levels ($L_1, L_2, \ldots, L_n$) is obtained by multiplication of levels ($L_1 \times L_2 \times \ldots \times L_n$). All interactions between factors are investigated in the FFD [17]. Frequently, experimenters do not have adequate time, cost, and resources to perform full factorial experiments [10]. The partial (fractional) factorial design (PFD) is used when the number of experiments of FFD is too large, which was first presented by Finney in 1945 [18]. PFD investigates the effect of factors on a response under an economical condition. A PFD is generally represented in the form of $L^{k-p}$, where k, L, and $1/L^p$ are the number of factors, levels, and the fraction of the full factorial $L^k$, respectively. The two levels full and fractional factorials are mainly used for screening the key factors, where the total number of experiments for k factors is $2^k$ and $2^{k-p}$, respectively [19]. The number of experiments of $2^k$ and $2^{k-p}$ is given in Table 1. PFD does not enable the estimation of all major and interaction effects separately because some of them are estimated together [15].

Some of the studies on screening stage for dark fermentative hydrogen production are summarized in Table 2. Rasdi et al. [20] employed two-level FFD for the initial screening of the most influential variables, namely substrate concentration, pH, inoculum size, and heat treatment for hydrogen production from palm oil mill effluent. They illustrated that according to the $2^4$ design, chemical oxygen demand (COD) of POME and pH significantly influenced hydrogen production. The factors with p-values less than 0.05 are considered significant, whereas values greater than 0.05 are insignificant. A CCD was applied after a two-level FFD to optimize selected variables. The preliminary screening of temperature, initial pH, inoculum size, and COD by two-level FFD was carried out by Ismail et al. [21] and, later, CCD optimization for hydrogen production from food wastes was used. The results of $2^4$ design showed that initial pH and temperature were selected as the most critical variables on hydrogen production individually and interactively.

**Table 1.** Comparison of the numbers of experiments of $2^k$ and $2^{k-p}$ (2 levels, k factors**)** design.

| Factors | Reduced fraction ($1/2^p$) | Numbers of experiments in $2^k$ | Numbers of experiments in $2^{k-p}$ |
|---|---|---|---|
| 6 | 1/2 | $2^6$=64 | $2^{6-1}$=32 |
| 6 | 1/4 | $2^6$=64 | $2^{6-2}$=16 |
| 6 | 1/8 | $2^6$=64 | $2^{6-3}$=8 |
| 6 | 1/16 | $2^6$=64 | $2^{6-4}$=4 |
| 5 | 1/2 | $2^5$=32 | $2^{5-1}$=16 |
| 5 | 1/4 | $2^5$=32 | $2^{5-2}$=8 |

#### 2.1.2. Plackett-Burman design

Plackett-Burman design, which is a two levels design, is a useful alternative to a $2^{k-p}$ design and was introduced by Plackett and Burman in 1946 [22]. Method of BPD has been extensively used to screen a large number of factors for further investigations [23]. Generally, a first-order polynomial model as observed in Eq. (1) is applied to study experimental results of PBD, where $y$, $\beta_0$, $\beta_i$, and Xi are the response, constant, linear coefficient, and coded factor, respectively [24]. The number of runs (N) of PBD for studying k factors is N = (k + 1), which is equal to a multiple of 4 for a PBD [25]. The design have runs of 12, 20, 24, 28, etc. PBD method has one major drawback, that is to say, the interactions between factors are ignored [26].

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i \, x_i \quad (1)$$

Costa et al. [27] used PBD for the screening of eleven variables of glycerol, peptone, yeast extract, temperature, initial pH, $K_2HPO_4$, $KH_2PO_4$, $NH_4Cl$, $(NH4)_2SO_4$, $FeSO_4.7H_2O$, and $MgSO_4.7H_2O$ for hydrogen production by

*Klebsiella pnemoniae* BLb01 from residual glycerol from biodiesel plant. According to the PBD, nine variables present the most significant effect on hydrogen production. The factors having the important effect on hydrogen production (p-value < 0.05) were then detected through a 2-level FFD. Six factors of initial pH, temperature, glycerol, $KH_2PO_4$, $K_2HPO_4$, and yeast extract were investigated by 2-level FFD and the other three factors were fixed in their optimal values. According to the $2^{6-2}$ FFD, three factors of $KH_2PO_4$, $K_2HPO_4$, and temperature were considered as key factors. Then, the level of three factors was optimized by CCD. Jiang et al. [28] studied hydrogen production from glucose by *Clostridium butyrium.* The variables include concentration of glucose, $K_2HPO_4$, $KH_2PO_4$, yeast extract, tryptone, L-cysteine, $MgSO_4{\cdot}7H_2O$, and $FeSO_4{\cdot}7H_2O$ were investigated in 12 experimental runs by PBD. The results of PBD screening indicated that yeast extract and glucose concentration were statistically significant in the hydrogen production. After PBD, the CCD method was carried out to identify optimal values of the level of two factors. Varrone et al. [29] investigated the effect of five factors of temperature, tryptone, glycerol concentration, initial pH, and yeast extract on the dark fermentation by PBD. Based on PBD, temperature, glycerol concentration, and initial pH were considered as important factors. The temperature and initial pH indicated a positive effect on HY, while the concentration of glycerol showed a negative effect. BBD was then carried out for the optimization of level of key factors. The techniques of PBD and BBD were used to screen important factors and identify the optimal condition of hydrogen production by *Ethanoligenens harbinense* B49. Initial screening of factors of $K_2HPO_4$, $ZnSO_4.\ 7H_2O$, NaCl, $MgCl_2$, $FeSO_4.7H_2O$, and $CaCl_2.2H_2O$ by PBD for hydrogen production was performed by Guo et al. [30]. The results of 12 experimental runs of PBD showed that $MgCl_2$ and $FeSO_4.7H_2O$ significantly affected hydrogen production. Then, BBD was used to identify optimal values that promoted maximum hydrogen production. The methods of PBD followed by CCD were employed to screen the key factors and optimize their levels by Boonsayompoo et al. [31]. Six factors of $FeSO_4$, $CaCl_2$, peptone, $MgCl_2$, $NiCl_2$, and $NaHCO_3$ were screened by PBD in 12 experimental runs. The results indicated that hydrogen production from the sweet sorghum bagasse by *thermoanaerobacterium thermosaccharolyticum* KKU19 was affected by key factors of $FeSO_4$, $CaCl_2$, $MgCl_2$, and $NaHCO_3$. Pan et al. [32] studied the effects of eight factors of glucose, yeast extract, initial pH, peptone, $FeSO_4$, phosphate buffer, mineral salt solution, and vitamin solution, on DFHP by PBD in 12 experimental runs. The screening results showed that glucose, phosphate buffer, and vitamin solution had individual significant effect on DFHP. The optimal key factor level and effect of their interactions on production of hydrogen were further investigated by BBD. The application of PBD for screening the most important factors of DFHP by some researchers is reported in Table 2.

**Table 2.** Studies of screening stage on DFHP.

| Inoculum | Substrate | Design | Studied factors | Ref. |
|---|---|---|---|---|
| Heat-treated palm oil mill sludge | Palm oil mill effluent | 2-FFD ($2^4$) | Substrate concentration, pH, inoculum size, heat treatment | [20] |
| Heat-treated palm oil mill sludge | Food wastes | 2-FFD ($2^4$) | Initial pH, temperature, inoculum size, COD | [21] |
| *Klebsiella pneumoniae* BLb01 | Residual glycerol from biodiesel plant | 2-PFD ($2^{6-2}$) | Glycerol, initial pH, temperature, yeast extract, $KH_2PO_4$, $K_2HPO_4$ | [27] |
| *Klebsiella pneumoniae* BLb01 | Residual glycerol from biodiesel plant | PBD | Glycerol, initial pH, temperature, $K_2HPO_4$, $KH_2PO_4$, $(NH_4)_2SO_4$, peptone, $MgSO_4{\cdot}7H_2O$, $NH_4Cl$, yeast extract, $FeSO_4{\cdot}7H_2O$ | [27] |
| *Clostridium butyrium* | Glucose | PBD | Glucose, yeast extract, tryptone, $K_2HPO_4$, $KH_2PO_4$, L-cysteine, $MgSO_4{\cdot}7H_2O$, $FeSO_4{\cdot}7H_2O$ | [28] |
| Mixed culture | Glycerol | PBD | Temperature, glycerol concentration, initial pH, tryptone, yeast extract | [29] |
| *Ethanoligenens harbinense* B49 | Glucose | PBD | $K_2HPO_4$, Mg $Cl_2$, $FeSO_4{\cdot}7H_2O$, NaCl, $ZnSO_4.7H_2O$ $CaCl_2.2H_2O$ | [30] |
| *Clostridium sp. Fanp2* | Glucose | PBD | Glucose, yeast extract, initial pH, peptone, $FeSO_4$, phosphate buffer, mineral salt solution, vitamin solution | [32] |
| *Enterobacter aerogenes* MTCC 111 | Glucose | PBD | Yeast extract, tryptone, initial pH, glucose, ferric chloride, inoculum size | [33] |
| *Enterobacter* MTCC 7104 | Glucose, sucrose and xylose | PBD | Yeast extract, sucrose, initial pH, peptone, tryptone, xylose and glucose | [34] |
| Heat-treated sludge | Sweet sorghum syrup | PBD | Peptone, initial pH, sodium bicarbonate, total sugar, nutrient solution, iron (II) sulphate ($FeSO_4$) | [35] |
| *Enterobacter aerogenes* | Glucose and glycerol | PBD | Temperature, initial pH, yeast extract, tryptone, glycerol, glucose, agitation rate, inoculum size | [36] |
| *Thermoanaerobacterium thermosaccharolyticum* KKU19 | Sweet sorghum bagasse | PBD | Peptone, $FeSO_4$, $CaCl_2$, $NaHCO_3$, $NiCl_2$, $MgCl_2$ | [31] |
| *E. coli* | Formate | PBD | Formate, cell density, yeast extract, NaCl, tryptone, stirring speed | [37] |
| Mixed culture | Pineapple waste extract | PBD | Substrate concentration, initial pH $FeSO_4$, $NaHCO_3$, endo–nutrient | [38] |
| Mixed culture | Cow manure slurry | Taguchi | Temperature, pH, substrate concentration, agitation, ultrasound, $KH_2PO_4$ | [39] |

## 2.2. After screening: Method of steepest ascent/descent

The technique of steepest ascent/descent is applied to identify the region that contains the optimum operating conditions [40]. The variables screened by the screening methods can be further studied using steepest ascent/descent method. This approach is a simple and efficient method [24].

As presented in Table 3, the steepest ascent technique was applied by researchers after screening the most important factors of DFHP. Varrone et al. [29] employed the steepest ascent method after PBD to determine the design center of key factors of initial pH, glycerol concentration, and temperature for dark fermentation. The path of steepest ascent was used to find the best starting point of two critical factors of HRT and pH by Lay et al. [41]. After screening of key factors by PBD, Boonsayompoo and Reungsang [31] determined the proper direction of changing the concentration of key factors, $CaCl_2$, $MgCl_2$, $FeSO_4$, and $NaHCO_3$, by the path of steepest ascent for DFHP. Experimental results showed that the steepest ascent technique was an effective method to determine region of optimal levels. However, the optimal values of factors need to be determined by the following optimization methods.

**Table 3.** Studies after screening stage (before optimization) by steepest ascent method in dark fermentation.

| Inoculum | Substrate | Studied factors | Ref. |
|---|---|---|---|
| *Clostridium sp. Fanp2* | Glucose | Glucose, vitamin solution, phosphate buffer | [32] |
| *Clostridium butyrium* | Glucose | Glucose, yeast extract | [28] |
| Mixed culture | Glycerol | Glycerol concentration, initial pH, temperature | [29] |
| Heat-treated sludge | Sweet sorghum syrup | Initial pH, $FeSO_4$, total sugar | [35] |
| *Enterobacter* MTCC 7104 | Xylose | Xylose, initial pH, and peptone | [34] |
| *Enterobacter* sp. CN1 | Xylose | Xylose, $FeSO_4$, peptone | [42] |
| *Thermoanaerobacterium thermosaccharolyticum* KKU19 | Sweet sorghum bagasse | $FeSO_4$, $MgCl_2$, $CaCl_2$, $NaHCO_3$ | [31] |
| Anaerobic digested sludge | Starch | pH and HRT | [41] |

## 2.3. Optimization stage

### 2.3.1. One factor at a time design

The one factor at a time approach studies just one factor at a time while keeping the levels of the other factors constant [13]. The OFAT approach consists of selecting a baseline set of levels of each factor and changing each factor over its favorable range, while keeping the other factors constant at the baseline level [43]. The OFAT design is simple and easy. The technique has some major drawbacks, that is to say (a) interactions between factors are ignored, (b) the optimum can be missed, especially when the interactions among factors are significant, and (c) it presents a relatively large number of runs, is susceptible to high cost, and takes long time to perform especially when the number of factors is large [25,44].

There are a large number of studies available in the literature on OFAT method for dark fermentation, a few of which are reported in Table 4. Satar et al. [45] studied the effect of glucose concentration, feed flow rate, and fermentation time with around 20 runs on DFHP by *Enterobacter aerogenes* ATCC 13048 using OFAT design. Each time, only the effect of one factor on HY was studied and the levels of other factors were kept constant. Results showed that the optimal glucose concentration, feed flow rate and retention time were 8 g/L, 0.5 mL/min, and 24 h, respectively. In optimal conditions, hydrogen yield was 9.44 mmol/g glucose. The method of OFAT design was performed to study the effect of four factors of initial pH, starch, nitrogen, and iron concentration on DFHP from starch. The optimum pH, concentration of iron, nitrogen, and starch were calculated as 7–8, 10 mg/L, 5.64 g/L, and 15 g/L, respectively. Hydrogen yield in optimum conditions was reported as 178 mL/g starch [46].

**Table 4.** Studies in optimization stage on DFHP.

| Inoculum | Substrate | Design | Studied factors | Ref. |
|---|---|---|---|---|
| Wasted activated sludge | Sucrose | Taguchi | Three phosphate sources, three carbonate sources, and a nutrient formulation | [92] |
| Wasted activated sludge | Sucrose | Taguchi | Concentration of 13 nutrients | [93] |
| *Pseudoalteromonas* sp. BH11 | Glucose | Taguchi | Glucose, yeast extract, sea water, tryptone | [94] |
| *Thermoanaerobacterium thermosaccharolyticum* IIT BTST1 | Glucose | Taguchi | Temperature, pH, glucose, $FeSO_4$, yeast extract | [49] |
| Cow dung | Glucose | Taguchi | C/N ratio, pH, temperature, yeast extract | [50] |
| Wastewater | Potato starch | Taguchi | Ultrasonic frequency, energy, exposure time, starch concentration | [95] |
| Mixed consortia | Glucose and xylose | Taguchi | Glucose: xylose ratio, pH, inoculum size, and inoculum age | [96] |
| Mixed culture | Cane molasses | Taguchi | pH, recycle ratio, dilution rate | [97] |
| Mixed culture | Wastewater | Taguchi | Inoculums, pre-treatment, inlet pH and feed composition | [98] |
| Municipal wastewater | Xylose | 3-PFD ($3^{k-p}$) | pH, oleic acid concentration, biomass concentration | [55] |
| Brewery wastewater | Steam exploded corn stalk liquor | 3-PFD ($3^{k-p}$) | Temperature, pH, HRT | [54] |

| | | | | |
|---|---|---|---|---|
| *Thermoanaerobacterium aotearoense* SCUT27/Δldh | Sugarcane bagasse | 3-FFD ($3^k$) | Sulfuric acid concentration, treatment time | [99] |
| *E. coli* (DJT 135) | Formate | 3-FFD ($3^k$) | Substrate concentration, pH | [56] |
| Anaerobic sludge | Renewable waste | Simplex | Corn stalk, Bean husk, organic fraction of solid municipal waste | [80] |
| Buffalo dung compost | Renewable agri-waste | Simplex | Corn husk, ground nut shell, rice husk | [79] |
| Mixed culture | Co-digestion Mixture | Simplex | Cheese whey, crude glycerol, buffalo slurry | [81] |
| Mixed culture | Agricultural wastes | Simplex | Food waste, potato pulp, cattle manure, and pig manure | [100] |
| Mixed culture | Glucose | D-optimal | Substrate concentration, compost leachate concentration | [73] |
| *E. coli* (XL1-BLUE) | Formate | OFAT | Formate concentration | [37] |
| *Clostridium acetobutylicum* X9 and *Ethanoigenens harbinense* B2 | Cellulose | OFAT | Substrate concentration, initial pH, C/N ratio, L-cysteine concentration, incubation time | [101] |
| Wastewater sludge | Sucrose | OFAT | Gas reflux, liquid reflux | [102] |
| Fermentative bacteria B49 | Glucose | OFAT | Magnesium concentration, iron concentration, sparging gas type | [103] |
| Mixed culture | Starch | OFAT | Nitrogen concentration, iron concentration, initial pH, substrate concentration | [46] |
| *Escherichia coli* MC13-4 | Glucose | OFAT | Immobilized gel bead size | [104] |
| *Enterobacter aerogenes* ATCC 13048 | Glucose | OFAT | Glucose, feed flow rate, fermentation time | [45] |
| *Clostridium thermolacticum* | Lactose | OFAT | Dilution rate and pH | [105] |
| Mixed culture | Citric acid wastewater | OFAT | Organic loading rate | [106] |
| *Clostridium* sp. Fanp2 | Glucose | BBD | Glucose, phosphate buffer, vitamin concentrations | [32] |
| Mixed culture | Glycerol | BBD | Glycerol concentration, initial pH, temperature | [29] |
| *Enterobacter aerogenes* MTCC 111 | Glucose | BBD | Substrate concentration, initial pH, ferric chloride | |
| Heat-treated sludge | Sweet sorghum syrup | BBD | Initial pH, $FeSO_4$, total sugar | [35] |
| *Thermoanaero bacterium thermosaccharolyticum* IIT BTST1 | Glucose | BBD | Temperature, pH, glucose, $FeSO_4$, yeast extract | [49] |
| Anaerobic sludge | Bean husk, corn stalk, solid municipal waste | BBD | Substrate concentration, HRT, pH, temperature | [80] |
| Mixed culture | Synthetic food waste | BBD | Initial pH, linoleic acid concentration, initial COD concentration | [60] |
| *Ethanoligenens harbinense* B49 | Glucose | BBD | Glucose concentration, $FeSO_4$. $7H_2O$, $MgCl_2$ | [30] |
| *Enterobacter aerogenes* | Glucose | BBD | Glucose concentration, pH, temperature | [107] |
| *Clostridium tyrobutyricum* JM1 | Glucose | BBD | Glucose concentration, pH, temperature | [108] |
| *Escherichia coli DJT135* | Glucose | BBD | Glucose concentration, pH, temperature | [109] |
| Mixed culture | Glucose | BBD | Linoleic acid concentration, initial pH, number of glucose injections | [110] |
| *Klebsiella. pneumoniae* ECU-15 | Glucose | BBD | Substrate concentration, ammonium sulfate concentration, trace elements concentration | [111] |
| Anaerobic sludge | Dairy wastewater | BBD | Substrate concentration, pH, COD/N ratio, COD/P ratio | [112] |
| Anaerobic sludge | Glucose | BBD | pH, microwave treatment duration, microwave intensity | [113] |
| Gamma irradiated sludge | Glucose | BBD | Temperature, initial pH, substrate concentration | [114] |
| Brewery wastewater | Steam exploded switchgrass liquor | BBD | pH, HRT, linoleic acid concentration | [74] |
| *Enterobacter* sp. CN1 | Xylose | BBD | Xylose, $FeSO_4$ , peptone | [42] |
| Anaerobic sludge | Brewery wastewater | BBD | Temperature, pH, brewery wastewater concentration | [115] |
| Heat-treated anaerobic sludge | *Laminaria japonica* | BBD | HCl concentration, heating temperature, reaction time | [116] |
| *Klebsiella pneumoniae* BLb01 | Residual glycerol from biodiesel plant | CCD | Temperature, $KH_2PO_4$, $K_2HPO_4$ | [27] |
| *Thermoanaerobacterium thermosaccharolyticum* KKU19 | Sweet sorghum bagasse | CCD | $FeSO_4$, $MgCl_2$, $CaCl_2$, $NaHCO_3$ | [31] |
| Mixed culture | Pineapple waste extract | CCD | Substrate concentration, initial pH, $FeSO_4$ | [38] |
| Heat-treated anaerobic granular sludge | Lactose, glucose, and cheese whey powder | CCD | Substrate concentration, initial pH | [117] |
| *Clostridium acidisoli* and *Rhodobacter Sphaeroides* | Sucrose | CCD | Sucrose concentration, initial pH, inoculum ratio | [64] |
| Mixed culture | Sucrose | CCD | Substrate concentration, initial pH | [118] |
| Seed sludge | Sucrose | CCD | Ultrasonic time, density | [119] |
| Anaerobic sludge | Wheat powder | CCD | C/N ratio and C/P ratio | [120] |

| | | | | |
|---|---|---|---|---|
| Mixed culture | Food residues and manure | CCD | Temperature, HRT, $N_2$-flow rate | [121] |
| *Clostridium butyricum* EB6 | Palm oil mill effluent | CCD | Temperature, pH, COD of POME | [122] |
| *Clostridium butyricum* EB6 | Glucose | CCD | Glucose concentration, pH, iron concentration | [123] |
| Anaerobic digester sludge | Food waste with residual blood | CCD | HRT, total solids feed (% TS), proportion of residues (% Blood) | [124] |
| Anaerobic grass compost | Food wastes | CCD | $PO_4^{3-}$, $Fe^{2+}$, $NH_4^+$ concentrations | [125] |
| Mixed culture | Organic municipal solid waste | CCD | Organic municipal solid waste, pretreated anaerobic digestion sludge, amount of hydrogen-producing bacteria | [126] |
| Anaerobic digested sludge | Starch | CCD | HRT, pH | [127] |
| *Clostridium* sp. | Beer brewing industry wastewater | CCD | Glucose addition concentration, pH, temperature | [128] |
| Anaerobic sludge | Sucrose | CCD | Substrate concentration, HRT | [65] |
| Cow dung compost | Sucrose | CCD | Substrate concentration, initial pH | [118] |
| Anaerobic sludge | Palm oil mill effluent | CCD | C/N ratio, C/P ratio, $Fe^{+2}$ concentration | [129] |
| Anaerobic sludge | Glucose | CCD | Substrate concentration, pH, temperature | [130] |
| Anaerobic sludge | Glucose | CCD | Substrate concentration, pH, temperature | [131] |
| Anaerobic sludge | Sucrose | CCD | Substrate concentration, pH, temperature | [132] |
| Mixed culture | Swine manure, fruit, and vegetable market waste | CCD | HRT, substrates ratio | [133] |
| Lesser panda manure | Corn stalk | CCD | Temperature, time, solid state compound enzyme | [134] |
| Anaerobic sludge | Glycerin (standard or residual) | CCD | pH, glycerin concentration, volatile suspended solids | [135] |
| Mixed culture | Cow manure slurry | CCD | pH, temperature | [39] |
| Anaerobic sludge | Sugarcane bagasse hydrolysate | CCD | Substrate concentration, substrate: buffer ratio, inoculum: substrate ratio | [136] |
| *Escherichia coli* WDHL | Wheat straw hydrolysate | CCD | Temperature, pH, total reducing sugars | [137] |
| *Clostridium butyrium* | Glucose | CCD | Glucose, yeast extract | [28] |
| Anaerobic sludge | Glucose | CCD | pH and autoclave | [138] |
| Anaerobic hydrogen producing bacteria | Starch | CCD | Starch concentration , ferrous iron concentration, L-cysteine concentration | [139] |
| *Clostridium pasteurianum* | Crude glycerol | CCD | Temperature, initial pH, glycerol concentration | [140] |
| Granular sludge | Cassava's stillage | CCD | Initial pH, $MoO_4^{-2}$ concentration | [141] |
| Digested anaerobic granular sludge | Glucose | CCD | Glucose concentration, initial pH, nickel nanoparticles concentration | [142] |
| Heat-treated POME sludge | Palm oil mill effluent | CCD | Substrate concentration, pH | [20] |
| *Enterobacter* MTCC 7104 | Xylose | CCD | Xylose concentration, initial pH, peptone concentration | [34] |
| Mixed culture | Waste glycerol and sludge | CCD | Waste glycerol concentration, sludge concentration, and amount of Endo-nutrient addition | [143] |
| Mixed culture | Sugar refinery wastewater | CCD | pH, HRT, organic loading rate | [63] |
| Anaerobic seed sludge | Food waste | CCD | Inoculums concentration, substrate concentration, citrate buffer concentration | [144] |
| Anaerobic sludge | Starch | CCD | Starch concentration, Fe, Ni | [145] |
| Anaerobic seed sludge | Palm oil mill effluent | CCD | Substrate concentration, initial pH, temperature, inoculum volume | [146] |
| Anaerobic activated sludge | Sugar refinery wastewater | ANN | VLR, ORP, pH, alkalinity | [147] |
| Sewage sludge | Sucrose | ANN | HRT, sucrose concentration, sucrose degradation, biomass concentrations, ethanol, acetate, propionate and butyrate concentrations. ORP, pH, recycle ratio, alkalinity | [148] |
| *Enterobacter* MTCC 7104 | Xylose | ANN | Xylose concentration, initial pH, peptone concentration | [34] |
| *E. coli* | Cheese Whey | ANN | ORP, pH, dissolved $CO_2$ | [149] |
| Thermal preheated sludge | Starch | ANN | Organic loading rate, pH, VSS yield | [150] |
| Mixed culture | Thin stillage, glucose, sucrose | ANN | Initial pH, substrate concentration, temperature, maximum fermentation time, biomass concentration | [87] |
| Buffalo dung compost | Glucose and xylose | ANN-GA | Inoculum age, inoculum size, pH, glucose: xylose ratio | [91] |
| Anaerobic digested sludge | Glucose | ANN-GA | Temperature, pH, substrate concentration | [151] |
| Anaerobic digested sludge | Sucrose | ANN-GA | Organic loading rate, HRT, influent alkalinity | [152] |

### 2.3.2. Taguchi design

The Taguchi design was applied in screening and optimization stages, which was introduced by Genechi Taguchi in the 1950s [16]. In this approach, the application of orthogonal array reduces the number of runs [23]. The Taguchi approach can recognize key factors and best level of a factor from a pre-determined number of levels. However, the actual optimal value of the level of a factor cannot be determined using this approach. This problem can be modified using techniques such as neural network [16]. The technique can help reduce the number of experiments significantly and minimize the operational time and cost [47]. Naturally, it is susceptible to several limitations, that is, it is only effective when employed in the early design of process or product. If the design variables and their nominal values are determined, Taguchi method may not be cost effective. This approach may not be a proper choice for a continuous variable. Also, the method is not always accurate and actual optimal factor levels may not be guaranteed [48]. The number of experiments covered by Taguchi techniqe is reported in Table 5.

Wang et al. [39] carried out screening of factors with Taguchi method followed by CCD optimization. They used the Taguchi design $L_{18}$ orthogonal array to screen variables of temperature, pH, substrate concentration, agitation, ultrasound, and $KH_2PO_4$ at three levels.The results indicated that temperature and pH were selected as key factors. Roy et al. [49] studied the effect of glucose concentration, temperature, pH, yeast extract concentration, and $FeSO_4$ at three levels by the Taguchi technique. A $L_{27}$ orthogonal array with three degrees of freedom was applied to evaluate the effect of factors on DFHP by *Thermoanaerobacterium thermosaccharolyticum* IIT BT-ST1. According to Taguchi method, temperature was found as the most important variable followed by pH and glucose concentration. The effect of factors of temperature, yeast extract concentration, substrate concentration, pH, and carbon to nitrogen (C/N) ratio on hydrogen production using cow dung was investigated with Taguchi design by Kumari and Das [50]. Statistical analysis indicated that the C/N ratio was the essential factor in hydrogen production. The similar studies are reported in Table 4.

**Table 5.** Number of experiments of Taguchi techniqe.

| Number of factors | Number of levels | | | |
|---|---|---|---|---|
| | 2 | 3 | 4 | 5 |
| 2 | L4 | L9 | L16 | L25 |
| 3 | L4 | L9 | L16 | L25 |
| 4 | L8 | L9 | L16 | L25 |
| 5 | L8 | L18 | L16 | L25 |
| 6 | L8 | L18 | L32 | L25 |
| 7 | L8 | L18 | L32 | L50 |
| 8 | L12 | L18 | L32 | L50 |
| 9 | L12 | L18 | L32 | L50 |
| 10 | L12 | L27 | L32 | L50 |

### 2.3.3. Response surface methodology

The response surface methodology (RSM) is a collection of the mathematical and statistical methods that are useful for the optimization of an interest response, which is affected by several factors [51]. The RSM techniques of three levels full or fractional factorial, central composite design, Box-Behnken design, Doehlert design, simplex design, and optimal design are widely used in the optimization stage. Finding a suitable relation between the response and the factors for the RSM methods is necessary. Generally, a linear polynomial model (first-order: Eq. (1)) or quadratic polynomial model (second-order: Eq. (2)) is used to explain the effect of key variables on a response [52].

**Table 6.**Comparison of the efficiency of 3- FFD, CCD, BBD, and DD [53].

| Factors (K) | Number of coefficients | Number of experiments | | | | Efficiency | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 3- FFD | CCD | BBD | DD | 3- FFD | CCD | BBD | DD |
| 2 | 6 | 9 | 9 | - | 7 | 0.67 | 0.67 | - | 0.86 |
| 3 | 10 | 27 | 15 | 13 | 13 | 0.37 | 0.67 | 0.77 | 0.77 |
| 4 | 15 | 81 | 25 | 25 | 21 | 0.18 | 0.60 | 0.60 | 0.71 |
| 5 | 21 | 243 | 43 | 41 | 31 | 0.09 | 0.49 | 0.61 | 0.68 |
| 6 | 28 | 729 | 77 | 61 | 43 | 0.04 | 0.36 | 0.46 | 0.65 |
| 7 | 36 | 2187 | 143 | 85 | 57 | 0.02 | 0.25 | 0.42 | 0.63 |
| 8 | 45 | 6561 | 273 | 113 | 73 | 0.0069 | 0.16 | 0.4 | 0.62 |

The efficiency of an experimental design is defined as the number of coefficients in the estimated model divided by the number of runs. It is concluded from Table 6 that the efficiency DD> BBD> CCD> 3-FFD [53]. However, it is seen that CCD is extensively applied to optimization.

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<j}^{k} \sum \beta_{ij} x_i x_j + \varepsilon \qquad (2)$$

#### 2.3.3.1. Three levels full or fractional factorial design

The full and fractional factorial designs with three levels (−1, 0, +1) are used to study quadratic effects and are mainly applied in the optimization stage. The total number of experiments for k factors is $3^k$ and $3^{k-p}$ in the 3-FFD and 3-PFD, respectively. A $3^k$ or $3^{k-p}$ design might need too many runs, depending on the values of k and p [18]. Since the factorial design for more than two factors requires a considerable number of experiments, designs those offer a smaller number of runs such as the BBD, CCD, and DD are applied more often.

After screening key factors (pH, HRT, and temperature), a 3-PFD was employed by Shanmugam et al. [54] to optimize hydrogen production from lignocellulosic biomass. A $3^{3-1}$ analysis indicated that the hydrogen yield was affected by all the experimental variables. However, the effect of temperature was greater than HRT and pH. Chaganti et al. [55] investigated the effect of pH, concentration of oleic acid (OA), and biomass on DFHP from xylose by a 3-PFD. According to a $3^{3-1}$ design, the terms of linear and quadratic OA and pH were significant, and the concentration of biomass was insignificant. A 3-FFD ($3^2$) was applied by Bakonyi et al. [56] to determine the optimum conditions of two operational variables (pH and substrate concentration) to obtain maximum hydrogen yield from formate by both strains of *E. coli* (XL1-BLUE) and *E. coli* (DJT 135). The total number of 12 experimental runs (including 3 replications in the center point) were performed for both strains of wild-type and metabolic engineering. The results showed that pH and formate concentration were statistically important. However, the effect of formate concentration was much higher than pH.

#### 2.3.3.2. Box-Behnken design

The Box-Behnken approach is a class rotatable (or nearly rotatable) second-order design [57], introduced by Box and Behnken in 1960 [58]. The BBD is based on three levels (-1, 0, +1) fractional factorial design and can be applied to problems having three or more factors. The number of required experiments in this design is $2k\ (k-1) + n_c$, where k and $n_c$ are the number of factors and central points, respectively [57]. The technique is more efficient and economical in terms of the number of required experiments and is a spherical design with all points lying on a sphere of radius 2. The BBD does not require any run where all factors are simultaneously at their highest or lowest levels. Therefore, this design can be considered appropriate when unsatisfactory results occur at the extreme points of the experimental region [59].

As presented in Table 4, many research studies have employed BBD to optimize DFHP from various substrates. Having performed initial screening by PBD, Long et al. [42] applied BBD in 15 runs of experiment to optimize the most important operational variables of concentration of substrate, $FeSO_4$, and peptone on hydrogen production from xylose using *Enterobacter* sp. CN1. The results show the initial concentration of xylose and $FeSO_4$ and their substantial effect on hydrogen production, while peptone remains unaffected. Under the optimal medium condition, hydrogen yield of 2 mol $H_2$/mol xylose was obtained. The effects of individual and interaction of three key factors, namely concentration of linoleic acid (LA), initial pH, and chemical oxygen demand (COD), on DFHP using a BBD in 13 runs of experiments were studied by Pendyala et al. [60]. The results indicated that pH, concentration of LA, COD, and their interactions affected hydrogen production. A PBD followed by BBD was performed to screen important parameters and identify the optimal value of key factors, glucose concentration, $Mg^{2+}$, and $Fe^{2+}$, in dark fermentation by *E. harbinense* B49. According to 17 runs of experiment of BBD, optimal concentrations were obtained and, under the optimal condition, HY was 2.2 mol/mol glucose. Among the studied factors, $Mg^{2+}$ and $Fe^{2+}$ had significant individual effect, while their interactions were no significance [30].

#### 2.3.3.3. Central composite design

The central composite design is a favorite class of experimental design and is employed for fitting the second-order model that was introduced by Box and Wilson in 1951 [40]. The CCD investigates each factor at five levels ($-\alpha$, $-1$, 0, +1, + $\alpha$), where $\alpha$ is the distance of the axial runs from the design center. The number of experiments in this design is $2^k+2k+n_c$, where k and $n_c$ are the number of factors and central points, respectively [61]. Two variables of $\alpha$ and $n_c$ in this design must be determined [53]. Generally, three to five center runs are suggested. $\alpha$ value depends on the number of factors and can be calculated by $\alpha = 2^{0.25k}$ ,where for two, three, and four factors is 1.41, 1.68, and 2, respectively [62].

Hydrogen production in an anaerobic sequencing batch bioreactor was optimized using CCD by Won et al. [63]. Three operational variables (pH, HRT, and OLR) were studied in 18 experimental runs. Results showed that HRT had lower significant effect on hydrogen production than pH and OLR, whereas OLR had much effect on hydrogen production rate. A CCD after PBD screening was used to evaluate the effects of the most important variables, namely sucrose concentration, inoculum ratio, and initial pH, on hydrogen production by co-culture of *Clostridium acidisoli* and *Rhodobacter sphaeroides*. According to 15 experimental runs, all of the key factors individually affected hydrogen yield, and pH and sucrose concentration interacted interdependently [64]. Zao et al. [65] employed CCD to evaluate both interactive and individual effects of HRT and sucrose concentration on DFHP from sucrose. The results indicated that under optimum conditions, HY of 1.62 mol $H_2$/mol hexose was obtained. Both HRT and sucrose concentration present a significant individual effect on hydrogen yield. However, their interactions have no significant effect on the hydrogen yield. There are many reports available in the literature on the application of CCD to optimize hydrogen production from various substrates, as depicted in Table 4.

#### 2.3.3.4. Dohlert design

An advantage of experimental design for second-order models is the uniform shell design, introduced by Doehlert in 1970. Dohlert design is polyhedron based on hyper triangles with a hexagonal structure in the simplest case [66]. The number of experiments in this design is $k^2 + k + n_c$, where k and $n_c$ are the number of factors and central points, respectively. Unlike CCD and BBD, Dohlert design is neither orthogonal nor rotatable [67] and has more advantages than CCD and BBD such as DD requires less number of experiments [12]. As shown in Table 7, a DD presents different number of levels for all factors, which is an interesting property. Thus, the factors that are considered more important can be measured at more levels [67]. Another attractive feature of DD is the possibility of introducing new factors during an experimental design without losing the runs already performed [53]. As seen in Figure 2, it is also feasible to displace the experimental region to another place. To the best of our present knowledge, Dohlert design has not been used to meet the objective of dark fermentation to date.

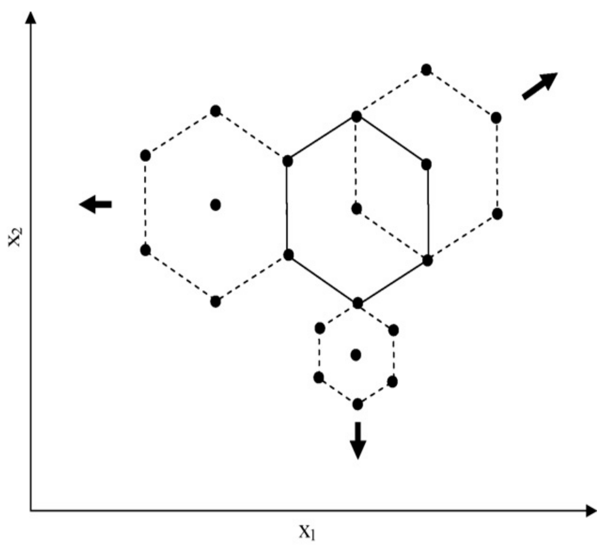


**Figure 2.** Displacement ability of Dohlert design [14].

**Table 7.** Number of levels of DD generated for two to six factors [53].

| Factors | Number of levels of factors |
|---|---|
| 2 | 3,5 |
| 3 | 3,7,5 |
| 4 | 3,7,7,5 |
| 5 | 3,7,7,7,5 |
| 6 | 3,7,7,7,7,5 |

### 2.3.3.5. Optimal design

Typically, there is a standard response surface design such as CCD and BBD, provided that the experimental region is a cube or a sphere. However, sometimes, an experimenter encounters a situation where a standard response surface design may not be the best choice [6]. A certain approach to handling the irregular experimental region is using creation of computer-aided optimal design. The optimal designs represent a class of DOE, which is optimal with respect to some statistical criteria. The designs are particularly useful when the factor space is not uniformly accessible, qualitative factors have more than two levels, and so on. In optimal designs, the best sets of experiments are chosen based on some criteria. There are several popular designs related to optimality criteria such as A-optimality, G-optimality, E-optimality, D-optimality, and so on, where the D-optimality is the criterion that receives the most attention in the literature among them [68,69]. A design is expressed as D-optimal if $|(X\ X^T)^{-1}|$ is minimized, where X is the matrix of design points and T denotes the transpose [70]. The D-optimal designs are used for multi-factor experiments with both quantitative and qualitative factors, while the factors can be studied at a mixed number of levels [71]. The number of experiments of D-optimal is lower than FFD and PFD. The design can be considered very efficient if its efficiency is 0.8, 0.9 or higher [72].

Liu et al. [73] used D-optimal method to find optimal operating conditions for DFHP from the co-fermentation of glucose and leachate by anaerobic sludge. The results showed that the HY was affected by the glucose concentration and organic loading of leachate. According to a two-factor D-optimal design, the cubic model was suggested and a hydrogen yield of 1.6 mol $H_2$/ mol glucose was predicted at 6174.93 mg/L glucose and 3383.20 mg COD/L leachate. D-optimal design is also applicable to the validation stage. A validation study was carried out for variables of temperature, pH, and HRT by the D-optimality procedure after a 3-PFD design. The index of D-optimality is between 0 and 1, where a value closer to 1 shows a completely favorable solution. In the validation study, the value of D-optimality of 1 was obtained with a HY of 100 mL/g TVS at 9.5 h HRT, pH 4.5, and 53 ºC [54]. Veeravalli et al. [74] employed D-optimality analysis to perform the validation of optimal level for the three factors of HRT, pH, and LA after BBD. Results of D-optimality showed that maximum hydrogen yield was 99.86 mL $H_2$/g TVS at HRT 10 h, pH 5, and LA concentration of 1.75 g/L.

### 2.3.3.6. Simplex method (mixture designs)

The Nelder-Med simplex design proposed by John Nelder and Roger Mead (1965) is used for performing nonlinear unconstrained optimization [75] and is different from the simplex of Dantzig for linear programming [76]. A Nelder-Mead simplex has a geometric shape with k+1 corners, where k is the number of factors. As illustrated in Figure 3- (a) and (b), a simplex is an equilateral triangle and tetrahedron in two and three dimensions, respectively [26]. The simplex is a stepwise technique by which the runs are carried out one by one. The direction for improvement is obtained by moving away from the vertex with the smallest value [77]. The principles for a simplex optimization with two factors are illustrated in Figure 3-(c). Further application of the simplex optimization is employed to investigate the effects of mixture components on the variable of response. The total amount of components is kept constant (100 %) in the mixture designs. There are several different types of mixture designs where simplex lattice and centroid are the most common ones [78]. The contour plot of simplex lattice design is depicted in Figure 3-(d).

Prakasham et al. [79] studied hydrogen production from buffalo dung compost with untreated mixed renewable agro-residues. Corn husk (CH), ground nut shell (GNS), and rice husk (RH) were used as the substrate sources of agri-residues. A mixture design demonstrated that a partial supplementation of rice husk or ground nut shell to corn husk enhanced hydrogen yield. Maximum hydrogen production of 65.78 mL $H_2$/ g TVS with a 70:16:12 (CH: RH: GNS) without any material treatment was determined. A simplex design was applied by Sekoai et al. [80] to obtain the optimum proportions of agro-municipal waste (corn stalk (CS), bean husk (BH), and organic fraction of solid municipal waste (OFSMW)). The results indicated that the optimum hydrogen production was observed at a ratio of 30: 0: 0 (OFSMW: BH: CS) without any material treatment or at a ratio of 15: 15: 0 (OFSMW: BH: CS) in optimum conditions of the process. Marone et al. [81] reported hydrogen production from different substrate mixtures, namely cheese whey (CW), buffalo slurry (BS), and crude glycerol (CG). Mixture design was employed to determine the optimal three-substrate composition and distinguish the effect of the mixing ratio on the hydrogen yield. The optimum hydrogen production was obtained at a ratio of 66:33:0 (BS: CW: CG).

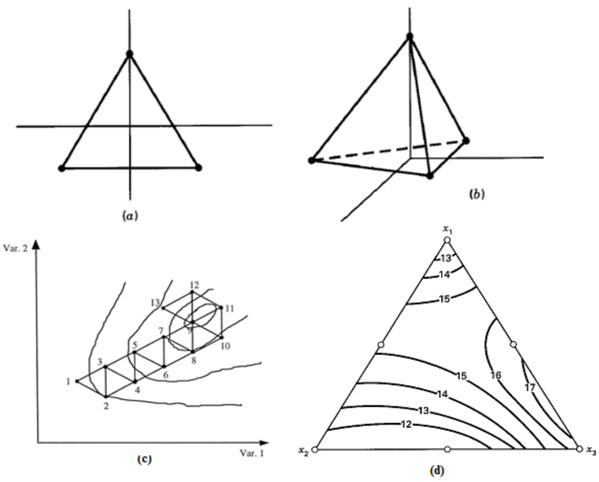


**Figure 3.** Simplex designs in two dimensions (a) and three dimensions (b), illustration of a simplex optimization with two factors (c), contour plot of simplex lattice design (d) [52, 77].

### 2.3.4. Artifical neural networks

An artifical neural network (ANN), introduced by Rosenblatt (1959) and Widrow and Hoff (1960) [82], simulates the brain's learning process by mathematically modeling the network structure of interconnected nerve cells. As depicted in Figure 4, the configuration of an ANN consists of an input layer, one or more hidden layers, and an output layer. The essential processing elements of ANN are called artificial neurons or nodes. The neurons in the hidden layer are connected to the neurons in the input and output layers by adjustable weights that enable the network to compute complicated associations between the factors and response. The input of each neuron in the hidden and output layers is summed up, and the activation function is applied to process the resulting summation. Initially, the weights are randomly chosen and, then, an iterative algorithm is employed to obtain the weights that minimize the differences between the network calculated and actual outputs. The application of conventional optimization methods including gradient-based technique to optimize an ANN model is complex because it is difficult to calculate the derivatives of the model [25,83–85]. The genetic algorithm (GA) as a strong optimization method was introduced by Holland (1975) [86], which mimics the process of natural evolution. The neural network coupled with genetic algorithm optimization model (ANN-GA) has been successfully employed to optimize complex processes [83].

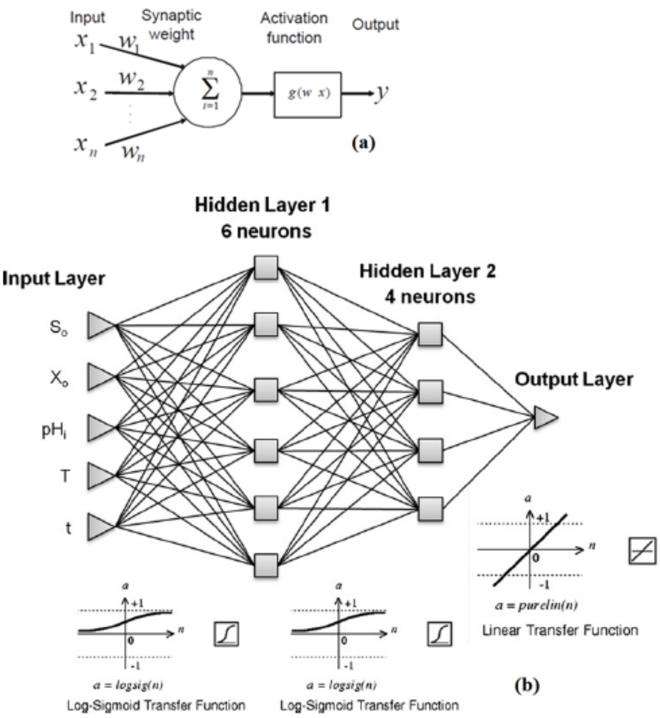


**Figure 4.** Artificial neural network configuration, (a) operation of a single neuron (b) operation of a three layers (input, hidden, output) network [87].

Nasr et al. [87] used a feed-forward network with back propagation algorithm (configuration of 5-6-4-1 layers) to model the profile of hydrogen production in batch experiments. The input and output layers consisted of five neurons (biomass concentrations, substrate, initial pH, temperature, and time) and one neuron (hydrogen production with time), respectively. 60, 20, and 20 % of the data sets were used for training, testing, and validation, respectively. $R^2$ of training, testing, and validating data was observed as 0.988, 0.996, and 0.987, respectively. Results depicted that a correlation coefficient of 0.976 was obtained for predicting the profile of hydrogen production with time. Karthic et al. [34] employed ANN (configuration of 3-8-1 layers) to model the hydrogen yield in batch experiments. The input and output layers were three neurons (peptone concentration, xylose concentration, and initial pH), and one neuron (hydrogen yield), respectively. Method of CCD was also applied to investigate the effect of the aforementioned variables. The modeling ability of RSM and ANN was investigated in predicting the HY at the estimated values of root mean square error (RMSE), standard error of prediction (SEP), and correlation coefficients ($R^2$). The reported values of RMSE, SEP, and $R^2$ of RSM and ANN showed that the accuracy of fitness and prediction of ANN were higher than that of RSM design. An ANN method can approximate all kinds of non-linear functions including quadratic functions, whereas RSM is useful only for quadratic approximations [88]. It is reported that the ANN is a suitable method compared to the RSM technique in terms of the modeling and optimization of fermentation processes [89,90]. Prakasham et al. [91] employed an ANN-GA (configuration of 4-10-1 layers) to predict hydrogen production by mixed anaerobic consortia. The age and size of the inoculum, pH, and glucose to xylose ratio as four input parameters and HY as one output parameter were considered. 80 and 20 % of the data sets were applied to training and verification, respectively. The optimum conditions were obtained after performing GA evaluation of 300 generations. After optimization, HY increased from 325.35 to 378.29 mL/g substrate, showing an increase of approximately 16 %. More studies are reported in Table 4.

## 3. DISCUSSION

The experimental design approaches have been successfully employed for the optimization of dark fermentation. The dark fermentative hydrogen production is a complicated multi-product process that depends on different variables. The optimization purpose of the DFHP process is to improve data analysis, design, and operation and ultimately to enhance the hydrogen production rate and yield. In order to optimize DFHP, the selection of factors and levels is more important and, then, choosing an appropriate experimental design method is necessary to fit with a mathematical function. The quality and accuracy of the fitted model to predict the experimental data is investigated by regression coefficients and interpreted in a response contour plot. Analysis of variance (ANOVA) is a collection of statistical techniques used to analyze the differences between group means and their associated procedures. ANOVA is essential to investigate the significance and adequacy of the model. Screening methods are employed for a large number of process or design variables to identify the most important variables that have significant effect on the process performance. In the case of the DFHP, methods such as Plackett–Burman, two levels full or fractional factorial, and Taguchi design are used for screening the key factors. The methods of Plackett–Burman and two levels full or fractional factorial at two levels for each factor are economical and efficient. When there are few factors, the two levels FFD can be employed for screening key factors. When the number of factors increases, two levels fractional factorial or Plackett–Burman can be used for screening. Further, the DFHP is followed by the steepest ascent/descent technique to approach the neighborhood of the optimal conditions. Subsequently, the optimization methods are applied. As illustrated in Table 8, each experimental design method is characterized by certain advantages and limitations. The OFAT was widely employed to evaluate the effect of various factors on DFHP. However, the technique has some major disadvantages: (a) disregard for interactions between factors and (b) requiring a rather large number of experiments, being expensive, taking long time, and highly consuming materials. The OFAT design is always less efficient than other DOE methods. The literatures indicate that, among the RSM methods, CCD and BBD are more applicable than DD, simplex, D-optimal, and three levels full or fractional factorial for DFHP optimization. The CCD as a very effective method for fitting the second-order model for the optimization of DFHP is widely used. The application of BBD is often recommended owing to its economic advantages. The BBD and DD approaches are slightly more useful than CCD. However, they are more effective than the 3-FFD and 3-PFD. The three levels factorial designs have limited application in DFHP when the number of factors is larger than two, because the number of required experiments for more than two factors is very large. Generally, the FFD for more than two factors requires a large number of experiments, which is not economically and practically feasible. Therefore, an FFD method is useful when there are few factors and levels involved. The reviewed papers show that there has been no report on the DD to date for the optimization of the DFHP. The DD has two attractive features (different number of levels for each factor and displacement ability) that provides a specific advantage in some studies. Thus, the DD method of optimization is suggested for DFHP. Some studies have reported on the optimization of substrate mixture with simplex method of optimization. In the mixture designs, the total amount of components is constant. The D-optimal for optimization and model validation has been used. An irregular experimental region can be handled with the D-optimal design. The D-optimality as a favorable index varies between zero (worst case) and one (ideal case). The Taguchi design for the screening and optimization of the DFHP has been applied. Taguchi approach is able to identify the key factors and the best level of factors from a pre-determined number of levels. However, the approach cannot guarantee determining the optimal condition. This problem can be modified using methods such as ANN. The ANN as a well-known technique to solve the complex non-linear optimization problems is an effective method to optimize several responses simultaneously and also optimize DFHP. It appears that ANN and ANN-GA are more suitable methods than the RSM technique for DFHP optimization. Although the studies of the ANN-GA, simplex, and D-optimal for the optimization of the DFHP are limited. Therefore, more studies covering these aspects are suggested.

**Table 8.** Advantages and disadvantages of experimental design methods.

| Design method | Advantages | Disadvantages | Application |
|---|---|---|---|
| 2-FFD | ➢ Identification of main effect and the interaction of factors | ✓ Large number of runs, time, cost, and consumed materials<br>✓ Only two levels | Screening |
| 2-PFD | ➢ Smaller number of runs compare to 2-FFD for the equal number of factors | ✓ Only two levels<br>✓ Effect of interaction of factors is limited and may be unobserved | Screening |
| PBD | ➢ Good screening tool<br>➢ Minimum number of required runs for large number of factors | ✓ Ignoring interactions between factors<br>✓ Only two levels | Screening |
| OFAT | ➢ Simple and easy | ✓ Ignoring interactions between factors<br>✓ Large number of experiments, time, cost, and consumed materials<br>✓ Less efficient than other methods of DOE<br>✓ Optimum can be missed | Optimization |
| TD | ➢ Using orthogonal array<br>➢ Reducing number of runs significantly<br>➢ Minimizing the operational time and cost<br>➢ Applicable to industrial process | ✓ Cannot guarantee the determination of optimal conditions | Optimization and Screening |
| CCD | ➢ Rotatable<br>➢ Estimate curvature | ✓ Moderate number of runs | Optimization |
| BBD | ➢ Rotatable (or nearly rotatable)<br>➢ Small number of runs in relation to CCD<br>➢ Estimate curvature | ✓ Less coverage than central composite | Optimization |
| DD | ➢ Smaller number of experiments in relation to CCD and BBD<br>➢ Different number of levels for each factor<br>➢ Displacement ability | ✓ Neither orthogonal nor rotatable | Optimization |
| 3-FFD | ➢ Identification of main effect and the interaction of factors | ✓ Large number of runs, time, cost, and consumed material<br>✓ Is not rotatable | Optimization |
| 3-PFD | ➢ Smaller number of runs than 3-FFD for the equal number of factors | ✓ Is not rotatable<br>✓ Effect of interaction of factors is limited | Optimization |
| DO | ➢ Applicable to any experimental region (such as irregular experimental region)<br>➢ Applicable to combination of quantitative and qualitative factors<br>➢ Number of experiments is lower than FFD and PFD | ✓ It does not always lead to a good design | Optimization |
| SM | ➢ The variables are not independent (total amount of the factors must be 1)<br>➢ Applicable to quantitative factors | ✓ Not very efficient for problems having multiple responses that need to be simultaneously optimized | Optimization |

| | | | |
|---|---|---|---|
| ANN | ➢ Handling large amounts of data easily<br>➢ Optimize several responses simultaneously<br>➢ Suitable to optimize complex processes and all kinds of non-linear functions | ✓ Can be overtrained<br>✓ Training process can be time consuming<br>✓ It usually requires a lot of data<br>✓ Selection of layers, neurons, activation function may be mistaken | Optimization |

## 4. CONCLUSIONS

The present review highlights the recent studies on experimental design approaches to hydrogen production by dark fermentation. The CCD, BBD, OFAT techniques for the optimization of the DFHP were extensively used. The 3-FFD and 3-PFD are not applied frequently, the application of which has been limited to the optimization of two factors. The papers on the ANN-GA, simplex, and D-optimal for the optimization of the DFHP are limited and no paper on the DD has been reported so far. Therefore, more studies covering these aspects are required. The ANN coupled with GA is a more suitable method than the RSM technique for the optimization of dark fermentation. The RMSE and the SEP for the ANN method were much smaller than those for the RSM, indicating that the ANN had a much higher modeling ability and accuracy than the RSM approach. Therefore, more research studies covering these aspects are required. Further comparative studies of these techniques are suggested. Most of the optimization studies presented here were carried out in the batch mode of operation. Thus, the DOE methods used to investigate the effect of the key factors on DFHP in both batch and continuous operations are recommended.

## 5. ACKNOWLEDGEMENT

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