

# Experimental design for parameter estimation of two time-scale model of photosynthesis and photoinhibition in microalgae<sup>☆</sup>

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## Abstract

A method for parameter estimation of two time-scale model of photosynthesis and photoinhibition is presented.

The model structure coincides with the earlier mechanistic concept of photosynthetic factory by Eilers and Peeters, however, our formulation respects the decomposition of the phase-space into the fast phase  $x_A$ , and the slow one,  $x_B$ . The experimental design for model parameters estimation is based on three complementary measurements. In addition to the standard measurement of microbial kinetics, identifying three of five model parameters, two time dependent experiments are proposed. The first one resides in photoinhibition measurement under constant irradiance (identifying the slow system dynamics), and the second one is based on periodic piecewise constant input. It is shown how to set up the input signal in order to maximize the sensitivity to the fast dynamics parameter.

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## 1. Introduction

The identification of model structure and parameters from experimental data remains a bottleneck for a major breakthrough of the computational analysis of biological systems.

In this paper, we show the modelling and experimental design for parameter estimation of a dynamical system of photosynthesis and photoinhibition evolving on widely separated time-scales.

The photosynthetic microorganisms growth modelling has long been regarded as a well-defined discipline in algal biotechnology, consisting of the coupling between photosynthesis and irradiance, resulting in the light response curve, which represents the microbial kinetics, see e.g. so-called *Monod* or *Haldane* type kinetics [2,12]. The main difficulty in considering the dynamic behavior of the photosynthetic processes (i.e. light and dark reactions and photoinhibition)

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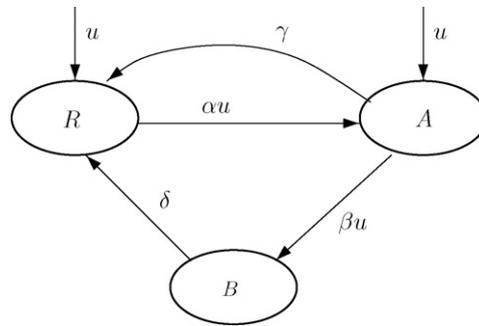


Fig. 1. States and transition rates of the photosynthetic factory – Eilers and Peeters’s PSF model.

consists in their different time scales. While the characteristic time of microalgal growth (e.g. doubling time) is in order of hours, light and dark reactions occur in milliseconds and photoinhibition in minutes.

Since we possess some experiment based knowledge of relevant processes, we can formulate the basic model behavior and further determine the model structure and the number of model parameters. These are our most important qualitative experimental results: (i) the steady state kinetics is of *Haldane* type, and (ii) the microalgal culture in suspension has so-called *light integration* property, i.e. as the so-called light/dark cycle frequency is going to infinity, the value of resulting production rate goes to a certain limit value, which depends on average irradiance only [8].

The widely cited phenomenological model of photosynthetic factory **PSF model** proposed by Eilers and Peeters in 1988 [3] inherently fulfills the above requirements.

Nevertheless, there is only one work where **all** PSF model parameter estimation is broadly studied [14].<sup>1</sup>

For that reason we aim to describe in this contribution our optimal experimental design based methodology to estimate PSF model parameters.

## 2. Model of photosynthesis and photoinhibition in microalgae

The so-called model of photosynthetic factory, see Fig. 1, has been recently studied in the biotechnological literature [3,4,6,14]. It has the following form

$$\dot{x} = [\mathcal{A} + u(t)\mathcal{B}]x, \tag{1}$$

$$\mathcal{A} = \begin{bmatrix} 0 & \gamma & \delta \\ 0 & -\gamma & 0 \\ 0 & 0 & -\delta \end{bmatrix}, \mathcal{B} = \begin{bmatrix} -\alpha & 0 & 0 \\ \alpha & -\beta & 0 \\ 0 & \beta & 0 \end{bmatrix}. \tag{2}$$

The state vector  $x$  is three dimensional, namely,  $x = (x_R, x_A, x_B)^\top$ , where  $x_R$  represents the probability that PSF is in the resting state  $R$ ,  $x_A$  the probability that PSF is in the activated state  $A$ , and  $x_B$  the probability that PSF is in the inhibited state  $B$ . The transition rates are:  $\alpha u, \beta u, \gamma, \delta$  (unit:  $s^{-1}$ ).

The single scalar input  $u(t)$  represents the irradiance (unit:  $\mu E m^{-2} s^{-1}$ ) in the culture (it is assumed that  $u(t)$  is at least piecewise continuous, see e.g. Fig. 2).

The PSF can only be in one of these states, so:

$$x_R + x_A + x_B = 1. \tag{3}$$

Taking into account the above normalization condition and preferring the states  $x_A, x_B$  (due to their measurability), we further analyze only two differential equations (for more detail see our paper [11] where this formulation of PSF

<sup>1</sup> However, either the “dynamic” and “static” model parameters were treated together, which resulted in large 95 % confidence interval; see Table 2 in [14].

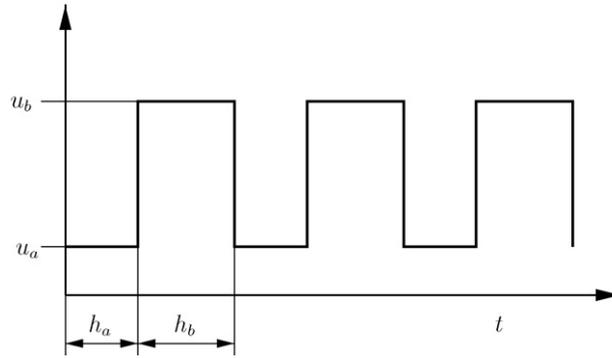


Fig. 2. Schematic presentation of the periodic intermittent input signal  $u(t)$ , total cycle period is  $h = h_a + h_b$ .

model was firstly used) in the form:

$$\begin{bmatrix} \dot{x}_A \\ \dot{x}_B \end{bmatrix} = \begin{bmatrix} -\gamma & 0 \\ 0 & -\delta \end{bmatrix} \begin{bmatrix} x_A \\ x_B \end{bmatrix} + u(t) \begin{bmatrix} -(\alpha + \beta) & -\alpha \\ \beta & 0 \end{bmatrix} \begin{bmatrix} x_A \\ x_B \end{bmatrix} + u(t) \begin{bmatrix} \alpha \\ 0 \end{bmatrix}, \tag{4}$$

where  $\alpha, \beta, \gamma, \delta$  are four rate constants of PSF model and  $u(t)$  is the known scalar function. In other words, PSF model is the so-called bilinear controlled system, cf. [1] and references within there.

The PSF model has to be completed by an equation connecting the hypothetical states of PSF model with some quantity related to the cell growth.

This quantity is the specific growth rate  $\mu$ .<sup>2</sup> According to [3,14], the rate of photosynthetic production (specific growth rate) is proportional to the number of transitions from the activated to the resting state, i.e.  $\gamma x_A(t)$ . Finally, for the average specific growth rate we have the relation:

$$\mu = \frac{\kappa\gamma}{t_f - t_0} \int_{t_0}^{t_f} x_A(t) dt, \tag{5}$$

where  $\kappa$  is a new dimensionless constant – the fifth PSF model parameter.

Eq. (5) reveals the reason why PSF model can successfully model the microalgae growth in high-frequency intermittent light: the growth is described through the “fast” state  $x_A$ , hence the sensitivity to high-frequency input fluctuations (e.g. flashing light experiments [8]) is reached.

The normalized (by its maximum) rate of photosynthetic production (i.e the normalized average value of  $x_A$ ) will be further used in Section 3.3.

Having the constant input signal  $u$ , there are three eigenvalues of system matrix of (1), i.e.  $\mathcal{A} + u\mathcal{B}$ . Two eigenvalues are negative and the third is zero (its corresponding eigenvector is the steady state solution of (1)). Two non-zero eigenvalues can be determined also from (4). Let  $|\lambda_F| \geq |\lambda_S|$ , then the next formulas hold (for details see [9]):

$$\lambda_F = -\frac{1}{2} \left[ (\alpha + \beta)u + \gamma + \delta + \sqrt{[(\alpha - \beta)u + \gamma - \delta]^2 + 4\beta u(\gamma - \delta)} \right], \tag{6}$$

$$\lambda_S = -\frac{1}{2} \left[ (\alpha + \beta)u + \gamma + \delta - \sqrt{[(\alpha - \beta)u + \gamma - \delta]^2 + 4\beta u(\gamma - \delta)} \right]. \tag{7}$$

Let us realize that the system (4) is a stiff system, moreover, according to [3,14],  $\alpha \gg \beta$  and  $\gamma \gg \delta$  then the following approximation of the above formulas ((6) and (7)) can be derived (for details see [10]):  $\lambda_F \cong -[(\alpha + \beta)u + \gamma]$ ,  $\lambda_S \cong -[\alpha\beta u^2 / (\alpha + \beta)u + \gamma + \delta]$ . The steady state values of states  $x_A$  and  $x_B$ , for a constant  $u \geq 0$ , are then

$$x_{A_{ss}} = \frac{\delta \cdot \alpha u}{\lambda_F \lambda_S}, \quad x_{B_{ss}} = \frac{\alpha \beta u^2}{\lambda_F \lambda_S}. \tag{8}$$

We note that this steady-state solution of (4) is stable, because the eigenvalues are negative for every  $u \geq 0$ .

<sup>2</sup>  $\mu := \dot{c}_x / c_x$ , where  $c_x$  is the cell density. The notation used is the most usual in biotechnological literature, cf. [2].

Moreover, there exists a value of irradiance to maximize growth rate in steady-state condition. Let be denoted the input which maximize  $x_{A_{ss}}$  with respect to  $u$  as  $u_{opt_{ss}}$ . Then holds:

$$u_{opt_{ss}} := \sqrt{\frac{\gamma\delta}{\alpha\beta}}. \tag{9}$$

**Remark 1.** Notice that both in the Introduction mentioned requirements for a process model are accomplished:

(1) the PSF model steady state behavior corresponds to *Haldane* type kinetics: Let put  $x_{A_{ss}}$  from (8) into (5), then the next relation is received:  $\mu = \kappa\gamma\delta\alpha u/\alpha\beta u^2 + \delta(\alpha + \beta)u + \gamma\delta$ .

The governing relation of the steady-state production curve of *Haldane* type (or so-called *Substrate inhibition kinetics*) is:  $\mu = \mu^*S/K_S + S + S^2/K_I$ , where  $S$  is a limiting substrate and  $\mu^*$ ,  $K_S$ ,  $K_I$  are model constants. Maximum occurs at  $S = \sqrt{K_S K_I}$ , when  $\mu_{max} = \mu^*/2\sqrt{K_S/K_I} + 1$ . Note that for  $K_I \rightarrow \infty$ , the production curve changes to *Monod* kinetics. The connection between PSF model and *Haldane kinetics* could be described as follows:  $\mu^* = \kappa\gamma\alpha/\alpha + \beta$ ,  $K_S = \gamma/\alpha + \beta$ , and  $K_I = \delta(\alpha + \beta)/\alpha\beta$ .

(2) the light integration capacity is the inherent property of bilinear system due to the *Lipschitz dependence of trajectories on control* [1].

### 2.1. PSF model re-parametrization

In the sequel, we define the dimensionless input as  $u^* := u/u_{opt_{ss}}$ , and we further rewrite the ODE system (4) and one algebraic-integral Eq. (5) by introducing new parameters  $\theta_i$ ,  $i = 1, \dots, 5$ :

$$\theta_1 := \sqrt{\frac{\gamma\delta}{\alpha\beta}}, \theta_2 := \sqrt{\frac{\alpha\beta\gamma}{\delta}} \frac{1}{\alpha + \beta}, \theta_3 := \kappa\gamma\sqrt{\frac{\alpha\delta}{\beta\gamma}}, \tag{10}$$

$$\theta_4 := \alpha\theta_1, \theta_5 := \frac{\beta}{\alpha}. \tag{11}$$

Notice that  $\theta_1$  units are those of irradiance ( $\mu\text{E m}^{-2} \text{s}^{-1}$ ),  $\theta_2, \theta_5$  are dimensionless,  $\theta_3, \theta_4$  are in  $\text{s}^{-1}$ . The reasoning for such a choices arises either from the steady state PSF model behaviour (parameters  $\theta_1, \theta_2, \theta_3$ ) and from the PSF model dynamics (the *fast* rate  $\theta_4 := \alpha u_{opt_{ss}}$  and the *slow* rate  $\theta_4\theta_5 := \beta u_{opt_{ss}}$ ), for more details see [11]. The parameter  $\theta_5$  quantifies the separation between the fast and slow dynamic;  $\theta_5 \approx 10^{-4}$ , based on [14].<sup>3</sup>

Hence, introducing new parameters  $\theta_i$ ,  $i = 1, \dots, 5$  and the dimensionless irradiance  $u^*$ , the resulting ODE is:

$$\frac{1}{\theta_4} \begin{bmatrix} \dot{x}_A \\ \dot{x}_B \end{bmatrix} = \begin{bmatrix} -\theta_2(1 + \theta_5) & 0 \\ 0 & -\frac{\theta_5}{\theta_2(1 + \theta_5)} \end{bmatrix} \begin{bmatrix} x_A \\ x_B \end{bmatrix} + u^* \begin{bmatrix} -(1 + \theta_5) & -1 \\ \theta_5 & 0 \end{bmatrix} \begin{bmatrix} x_A \\ x_B \end{bmatrix} + u^* \begin{bmatrix} 1 \\ 0 \end{bmatrix}. \tag{12}$$

The relation for the specific growth rate is:

$$\mu = \theta_2\theta_3(1 + \theta_5) \frac{1}{t_f - t_0} \int_{t_0}^{t_f} x_A(t) dt. \tag{13}$$

<sup>3</sup> For the microalga *Porphyridium* sp. the following values of PSF model parameters  $\theta_1, \dots, \theta_5$  (on basis of Wu and Merchuk's parameters  $\alpha, \beta, \gamma, \delta, \kappa$ ) were calculated:  $\theta_1 = 250.106 \mu\text{E m}^{-2}$ ,  $\theta_2 = 0.301591$ ,  $\theta_3 = 0.176498e - 3 \text{s}^{-1}$ ,  $\theta_4 = 0.483955 \text{s}^{-1}$ ,  $\theta_5 = 0.298966e - 3$ .

The purpose of such a re-parametrization was twice:

- To underline the two-time scale system nature.
  - To prepare the three-step PSF model parameter estimation (i.e. three different experiments):
- (1) the “sufficiently long” growth measurements under constant input signal leading to the steady state, and consequent estimation of parameters  $\theta_1, \theta_2, \theta_3$ ;
  - (2) the determination of the step input response of the “slow” state  $x_B$ , leading to the estimation of the photoinhibition rate (e.g. *via* measuring the chlorophyll fluorescence quantum yield), and consequently to estimate the product  $(\theta_4 \cdot \theta_5)$ ;
  - (3) the dynamic measurements of a time-varying asymptotic steady state regime (e.g. *via* measuring the photosynthetic oxygen evolution rate) forced by the periodic piecewise constant signal  $u$ , in order to determine the fast dynamic parameter  $\theta_4$ .

### 3. Experimental design

As stated in the preceding section, to estimate the first three PSF model parameters  $(\theta_1, \theta_2, \theta_3)$  is equivalent to determine the steady state photosynthetic production, see e.g. [3]. Neither the determination of the step input response in order to determine the slow dynamics  $(\theta_4 \cdot \theta_5)$  represents serious problems. Conversely, the reliable estimation of the remaining “fast rate” parameter  $\theta_4$  represents a scientific challenge. It was shown in our paper [11] that due to the presence of the fast and the slow dynamics, the step response is able to determine slow dynamics time constant only.

While in [11] the harmonic forcing was studied, here we develop the optimal experimental design based on the periodic intermittent piecewise constant input response. This is the main contribution of the paper.

#### 3.1. Modelling of flashing light experiments

It was proved in [9] that the solution of ODE system (1), i.e. the state trajectories of PSF model, for the intermittent piece-wise constant input (see Fig. 2:  $u \in \{u_a, u_b\}$ , cycle period  $h = h_a + h_b$ , where  $h_a$  is “dark” period and  $h_b$  is light period) has after a “sufficiently large” time of transition to this so-called *quasi steady-state* the same periodic pattern as the input variable  $u(t)$ . This can be formulated as

$$x(t_0) = x(t_0 + h). \quad (14)$$

Because we are able to measure the average photosynthetic rate only, it is the average value of state  $x_A$  which is proportional to the photosynthetic rate, see (5), we are interested in. This value  $x_{A_{av}}$  can be evaluated by the integration of  $x_A$  over one cycle period  $h$ :

$$x_{A_{av}} = \frac{1}{h} \int_0^h x_A(t) dt = \frac{1}{h} \left( \int_0^{h_a} x_A(t) dt + \int_{h_a}^h x_A(t) dt \right). \quad (15)$$

A somewhat tedious but straightforward evaluation of (15) was performed in detail in [9] for the case of so-called *flashing light experiments* (i.e. for  $u_a = 0$ ).<sup>4</sup>

#### 3.2. Order reduction of the ODE system (2)

The resulting expression for  $x_{A_{av}}$  published in [9] is too complicated for our purposes of experimental design. Nevertheless, when the period  $h$  of light/dark cycles is “small”, we can further simplify the ODE system (12) by reducing the PSF model dynamics to the one dimensional one using the singular perturbation approach with respect to the small parameter  $q_5 \approx 10^{-4}$  [13]. The system (12) thanks to the properties of its right hand side clearly satisfies

<sup>4</sup> See [5,8] for more details about these so-called flashing light experiments.

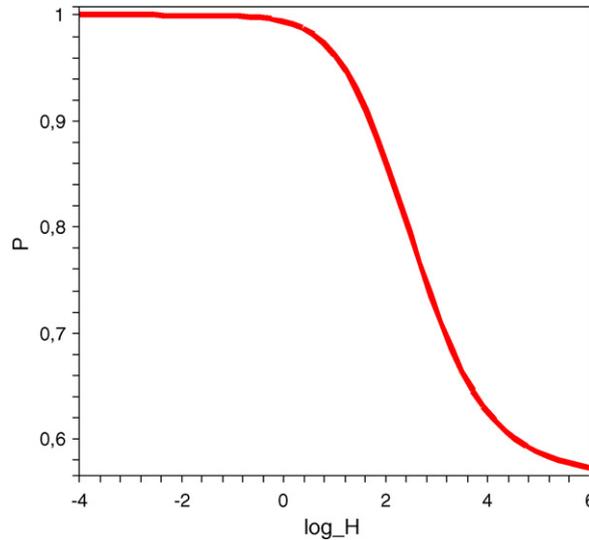


Fig. 3. Dependence of the photosynthetic production  $P := x_{Aav}/x_{A_{ss}}(u_{av}^*)$  on cycle period.

the sufficient condition for the convergence of the singular perturbation.<sup>5</sup> One can therefore take the limit  $q_5 \rightarrow 0$  in (12) to obtain  $\dot{x}_B = 0$ , i.e.  $x_B = x_{B_{ss}}(u_{av}^*)$ ,  $u_{av}^* := h_b u_b^*$ . Consequently, only one ODE for the fast dynamics of  $x_A$  state is received:

$$\dot{x}_A = -\theta_4(u^* + \theta_2)x_A + \theta_4 u^* [1 - x_{B_{ss}}(u_{av})]. \tag{16}$$

### 3.3. Photosynthetic productivity under high frequency light/dark cycles

The time averaged value of state  $x_A$  under high frequency light/dark cycles is calculated similarly as in [9]. When we set up  $h_b/h_a = 1$ , then holds:

$$x_{Aav} = x_{A_{ss}}(u_{av}^*) \frac{1 + \theta_2}{2 + \theta_2} \left[ 1 + \frac{\sinh(\theta_2 \theta_4 h)}{\theta_2 \theta_4 h (1 + \theta_2/2)} \frac{\sinh((2 + \theta_2)\theta_4 h)}{\sinh(2(1 + \theta_2)\theta_4 h)} \right]. \tag{17}$$

Notice that  $\lim_{h \rightarrow 0} x_{Aav} = x_{A_{ss}}(u_{av}^*)$ , i.e. once more is demonstrated the light integration property of the PSF model. Eq. (17), which connects the average value of state vector  $x_A$  with the fast dynamic model parameters  $\theta_4$  and the period of intermittent input  $h$  actually represents our mathematical tool to simulate flashing light experiments. Moreover, in order to define the dimensionless normalized photosynthetic production rate (normalized specific growth rate), we divide (17) by  $x_{A_{ss}}(u_{av}^*)$  and define  $P$ :

$$P = \frac{1 + \theta_2}{2 + \theta_2} \left[ 1 + \frac{\sinh(\theta_2 \theta_4 h)}{\theta_2 \theta_4 h (1 + \theta_2/2)} \frac{\sinh((2 + \theta_2)\theta_4 h)}{\sinh(2(1 + \theta_2)\theta_4 h)} \right]. \tag{18}$$

We see that the unknown parameter  $\theta_4$  arises in the above equation always in product with the cycle period  $h$ , i.e. with the independent variable. In order to study the sensitivity of  $P$  with respect to  $\theta_4$  it is convenient to substitute in (17) the product  $\theta_4 h$  by  $H$ :

$$P = \frac{1 + \theta_2}{2 + \theta_2} \left[ 1 + \frac{\sinh(\theta_2 H)}{\theta_2 H (1 + \theta_2/2)} \frac{\sinh((2 + \theta_2)H)}{\sinh(2(1 + \theta_2)H)} \right]. \tag{19}$$

Fig. 3 shows the dependence of  $P$  on  $H$  (for  $\theta_2 = 0.3$ ). In the following subsection we will study the sensitivity of  $P$  with respect to  $\theta_4$ , aiming to derive an analytical condition to maximize the sensitivity with respect to the period  $h$ .

<sup>5</sup> Roughly speaking we can also apply the theorem of Lipschitz dependence of trajectories on control [1,9] when we suppose that the period  $h$  is “sufficiently small” for “averaging” of  $x_B$  but not so small for averaging  $x_A$ .

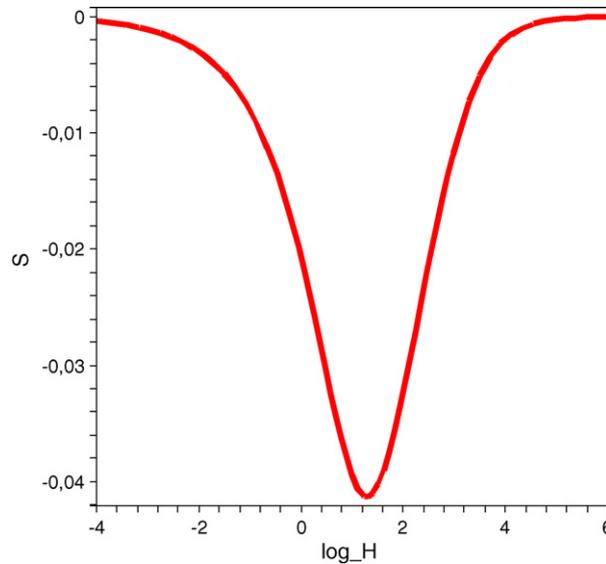


Fig. 4. Dependence of the sensitivity  $S := \partial P / \partial H$  on  $\log H$  ( $H := h\theta_4$ ).

#### 3.4. Sensitivity analysis of the relation (19)

As a matter of fact, while maximizing the sensitivity of  $P$  with respect to  $\theta_4$ , we have to consider the following equation:

$$\frac{\partial(\partial P / \partial \theta_4)}{\partial h} = 0. \quad (20)$$

Because  $P$  depends on  $H := \theta_4 h$  only ( $\theta_2$  is supposed to be known from previous steady state experiments), Eq. (20) can be evaluated as follows (applying theorem for derivative of composed function):

$$\frac{\partial^2 P}{\partial H^2} H + \frac{\partial P}{\partial H} = 0. \quad (21)$$

Fig. 4 shows the dependence of  $\partial P / \partial H$  on  $H$  (for  $\theta_2 = 0.3$ ) and encourages us to look for a solution of (21). After the straightforward calculation, the Eq. (21) is solved for  $H$  in a closed form. Computer Algebra System helps us in this process and for the known value of  $\theta_2$  we finally find the value  $H^* \cong 12$  ( $\log H^* \cong 2.48$ ), and consequently from (19) the corresponding value  $P^* \cong 0.79$ . The value of  $P^*$  helps us to find  $h^*$ , and the subsequent experiments performed for this “optimal cycle period” will be used to estimate the value of parameter  $\theta_4$ , see the next subsection.

#### 3.5. Algorithm of experimental design for $\theta_4$ parameter estimation

Having the condition for an optimal value  $H^*$  (maximizing the sensitivity of  $P$  with respect to the period  $h$ ), we can propose an algorithm which design the experiment leading to  $h^*$ . The idea is to perform as much experiments as possible for this value  $h^*$ . The corresponding experimental results of normalized productivity let be denoted as  $P_i^*$ ,  $i = 1, \dots, N^*$ , where  $N^*$  is the number of measurements performed for period  $h^*$ .

- (1) set up  $h_0, h_{step}, \delta$
- (2) loop until convergence:

— perform the experiment for the  $h_0$ :

- measure  $P(h_0)$
- evaluate  $\Delta := P(h_0) - P^*$

- if  $|\Delta| < \delta$  then  $h^* := h_0$  continue to (3)
  - if  $\Delta > 0$  then  $h := h_0 + h_{step}$
  - if  $\Delta < 0$  then: new value of  $h_{step} := h_{step}/2$  and  $h := h_0 - h_{step}$
- return the new value of period  $h_0 = h$
- (3) return the identified  $h^*$

Having performed  $N^*$  experiments for just identified period  $h^*$  we further can evaluate the mean value and variance of  $P(h^*)$ , in order to finally solve (17) with respect to  $\theta_4$ . By this way the variance of the  $\theta_4$  parameter estimate is minimized.

#### 4. Conclusions

In this paper, an experimental design for parameter estimation of two time-scale model of photosynthesis and photoinhibition was presented. Its main purpose was to propose the reliable methodology of the PSF model parameter  $\theta_4$  (corresponding to the fast dynamics phenomena) estimation. This nonlinear parameter estimation was based on the prediction of the response to periodic piecewise constant forcing. Important lesson here is that using singular perturbation approach the order reduction of the ODE system (4) permits the analytical study of the sensitivity of photosynthetic production on its factors. Consequently, the algorithm searching the optimal period of flashing light experiments has been established. Once having the reliable methodology of PSF model parameters estimation, the PSF model may further serve for optimizing photosynthetic production of real biotechnological plants [7].

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