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A PARAMETER CONDITION FOR RULING OUT MULTIPLE EQUILIBRIA OF THE PHOTOSYNTHETIC CARBON METABOLISM

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ABSTRACT

In this paper, we propose a reduced molecular network for the photosynthetic carbon metabolism, which can describe the following key characteristics: Calvin cycle, utilization of photosynthate, and photorespiration. Taking the concentrations of the nine major metabolites as variables, we represent the reduced network by deriving a nonlinear differential-algebraic system with 48 parameters, and theoretically study the multi-equilibrium property in the photosynthetic carbon metabolism. Specifically, we equivalently transform the original 9-dimensional system into an independent 2-dimensional subsystem with ten parameters, and show that the original system has no more than one physiologically feasible equilibrium when the ten parameters of the subsystem stay in a certain field around the nominal value of each parameter, no matter what values the other 38 parameters in the original model are taken. Such a theoretical result not only provides profound insights for qualitatively understanding of the dynamic features of the photosynthetic carbon metabolism, but also can be used to make an accurate judgement on a correct strategy for improving the photosynthesis in plants.

Key Words: Metabolic network, multi-equilibrium property, photosynthesis, photosynthetic carbon metabolism.

I. INTRODUCTION

The grain yield of crops has doubled during the past century, but it is still unable to meet the growing demand [1, 2]. Even worse, some studies suggest that there is not much probability of getting any further increase in grain yield by the traditional breeding approaches [3–5]. Instead, scientists have found that improving photosynthesis is an effective way to further dramatically increase crop yield [4–6]. There are two approaches to increase crop yield by improving photosynthesis: one is to increase the total photosynthesis, such as increasing the leaf area and extending the daily duration of photosynthesis; and the other is to improve

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the rate of photosynthesis per unit leaf area (*i.e.* the rate of CO_2 assimilation) [1, 4, 6]. It has also been shown that increasing leaf photosynthesis rate will boost yield potential when other factors are held constant [4, 6].

Photosynthesis is a complex system that includes a large number of biophysical and biochemical reactions, such as absorption of light energy, conversion of light energy to chemical energy, and some other biochemical reactions involved in the photosynthetic carbon metabolism [7, 8]. The carbon in crop yield is mainly from the CO_2 fixed during the photosynthetic carbon metabolism. Much attention has been riveted on photosynthetic carbon metabolism since it is closely related to increasing crop yield.

From a systems viewpoint, the photosynthetic carbon metabolism can be viewed as a molecular network which has many important dynamic characteristics, such as the oscillation driven by variation of external conditions, the sensitivity to each enzyme, stability, and multi-equilibrium property (*i.e.* whether or not the network can admit multiple equilibria). In particular, the multi-equilibrium property in the photosynthetic carbon metabolism is intimately associated with increasing crop yield for the following reason. If the photosynthetic carbon metabolism has two or more equilibria, one of them will correspond to the higher or highest photosynthesis rate, which clearly can be used to increase the grain yields by driving the system into this equilibrium; otherwise, the only thing one can do is to improve the photosynthesis at the existing equilibrium. Thus, it is crucial to accurately judge whether or not this molecular network is able to admit multiple equilibria so that a correct strategy can be adopted. Since there is no current biological experiment available to answer this question [9–12], one has to resort to the systems modeling approach and control theory to gain profound insights on it. Actually, control theory contributes a lot in systems biology [13–21]. Cheng *et al.* proposed a control routh array method to analyze biomolecular networks [13]. Sontag *et al.* used monotone theory to study biological systems [14]. Wellstead *et al.* provided a review of the role of control and system theory in systems biology [16]. Wang *et al.* modeled and analyzed biological oscillations in molecular networks [17]. Chesi proposed a recurive algorithm to compute equilibrium point of genetic regulatory network [18] and analyzed their global asymptotic stability [19].

Up to now, some reasonable and effective models have been proposed for the photosynthetic carbon metabolism to study its multi-equilibrium property [10, 22–27]. Pettersson and Ryde-Pettersson [23] proposed a model for the Calvin cycle (a key part of the photosynthetic carbon metabolism) and found that there are two equilibria when the cytosolic phosphate concentration does not exceed 1.9 mM, but one of them is not stable. Poolman *et al.* [24, 28] showed that the Calvin cycle has two different equilibria in plant leaves at different ages. Zhu *et al.* [12] proposed a simple model of the Calvin cycle which has two key ingredients of the Calvin cycle: Calvin cycle and utilization of photosynthate. For a group of fixed parameter values, Zhu *et al.* found that the model has multiple equilibria by numerical computation, but only one is physiologically feasible.

In the previous works, the model parameters were obtained from different experiments with various conditions. In fact, the parameter values are always different for the photosynthetic carbon metabolism in different mesophyll cells, not to mention different leaves and different plants. Therefore, rather than fixed values, it is more biologically reasonable to let the model parameters vary in an appropriate neighborhood around their experimental values when investigating the multi-equilibrium property in the photosynthetic carbon metabolism, and the results obtained in such a way will have a good suitability for a wide variety of plant species or conditions. However, it is a difficult task to derive such a theoretical result due to the complicated nonlinearity of the model.

In this paper, we develop a reduced molecular network for the photosynthetic carbon metabolism, which describes the following key characteristics: Calvin cycle, utilization of photosynthate, and photorespiration. While we investigate the multi-equilibrium property in the photosynthetic carbon metabolism, nine major metabolites are considered. We propose a nonlinear differential-algebraic model with nine variables and 48 parameters. We first explore the effect of the photorespiration pathway and then study the multi-equilibrium property of the model. Specifically, we equivalently transform the model into an independent 2-dimensional subsystem with ten parameters, and show that the equilibria of the original system can be determined by the 2-dimensional subsystem uniquely. Then, we prove that when the ten parameters in the 2-dimensional subsystem stay in an appropriate neighborhood around their nominal values (*i.e.* the experimental values), the original 9-dimensional system has no more than one equilibrium, no matter what values the other 38 parameters take. Such a result can help us to make an accurate judgement on a correct strategy for improving the photosynthesis in plants.

This paper is organized as follows. In Section II, an introduction of the photosynthetic carbon metabolism is given, and a nonlinear differential-algebraic model

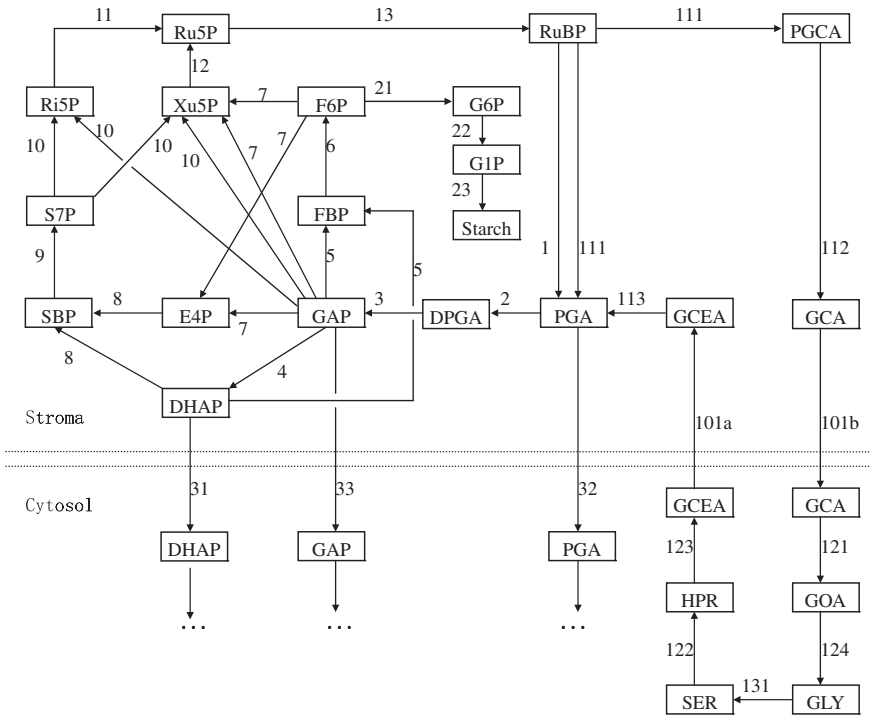

Fig. 1. Complete photosynthetic carbon metabolic network.

is derived. In Section III, a parameter condition is obtained to ensure that the model has no more than one equilibrium, and a certain parameter field meeting such a condition is given by numeric computation. In Section IV, several general remarks and future topics are given to conclude this paper.

II. MODEL OF THE PHOTOSYNTHETIC CARBON METABOLISM

2.1 Photosynthetic carbon metabolism

The photosynthetic carbon metabolism contains a large number of metabolites and biochemical reactions with several major modules: Calvin cycle, photorespiration pathway, starch synthesis, triose-P export and sucrose synthesis, which have been widely studied and mathematically described in detail in [22]. Taking each metabolite as a node and each reaction as an edge, we obtain the photosynthetic carbon metabolic network shown in Fig. 1. The symbols in the boxes are metabolites. An arrow indicates the direction of a reaction. The number on each arrow represents the reaction number. The symbol "$\cdots$" represents a series of reactions that utilize the triose phosphate PGA, GAP and DHAP. The double dotted line represents the chloroplast membrane. Reactions above the line occur in the chloroplast stroma and these below occur in the cytosol.

The abbreviations used for each metabolite in this paper are as follows. RuBP, Ribulose 1,5-bisphosphate; PGA, 3-Phosphoglycerate; DPGA, 1,3-bisphosphoglycerate; GAP, Glyceraldehyde 3-phosphate; Ru5P, Ribulose 5-phosphate; PGCA, 3-Phosphoglycollate; GCA, Glycollate; GCEA, Glycerate; DHAP, Dihydroxyacetone-phosphate; E4P, Erythrose 4-phosphate; SBP, Sedoheptulose 1,7-phosphate; S7P, Sedoheptulose 7-phosphate; FBP, Fructose 1,6-phosphate; F6P, Fructose 6-phosphate; G6P, Glucose 6-phosphate; G1P, Glucose 1-phosphate; Ri5P, Ribose 5-phosphate; Xu5P, Xylulose 5-phosphate; GOA, Glyoxylate; GLY, Glycine; SER, Serine; HPR, Hydroxypyruvate; Rubisco, Ribulose1,5-bisphosphate Carboxylase/Oxygenase.

Our primary interest is whether or not the photosynthetic carbon metabolism can admit multiple equilibria when the model parameters vary in a certain field. Such a theoretical result not only can be used to understand the qualitative dynamics of the photosynthetic carbon metabolism but also may lead a correct decision on the strategy for improving the photosynthesis rate on plants. Although the complete network shown in Fig. 1 provides relatively detailed information on the photosynthetic carbon metabolism, it is difficult to theoretically analyze its asymptotical behaviors even for fixed parameter values due to the nonlinearity of such a complicated system. Hence, we next convert the

complete network shown in Fig. 1 to a reduced one based on some biological principles, which is tractable for theoretical analysis.

GAP is a 3-carbon compound and Ru5P is a 5-carbon compound. The yield of 3 Ru5P molecules will consume 5 GAP molecules. Hence, from such an observation, we simply take reaction $GAP \rightarrow 0.6Ru5P$ to equivalently represent the complicated conversion of GAP into Ru5P. Another part of GAP is converted into starch in the chloroplast stroma by the pathway $GAP \rightarrow FBP \rightarrow F6P \rightarrow G6P \rightarrow G1P \rightarrow Starch$, and we represent this utilization of GAP by $GAP \rightarrow Sink$. Part of the triose phosphate PGA, GAP and DHAP are translocated into the cytosol for different cellular functions, such as sucrose synthesis. We represent this utilization of the triose phosphate GAP, PGA and DHAP by $PGA \rightarrow Sink$ and $GAP \rightarrow Sink$. The transformation of GCA to GCEA occurs in the cytosol. GCA is first translocated from stroma to cytosol, and then goes through a series of reactions to become GCEA. GCEA is finally translocated back to stroma. We reduce this process as $GCA \rightarrow GCEA$. Then we derive a reduced metabolic network of the photosynthetic carbon metabolism, which is shown in Fig. 2. Sink represents the utilization of the photosynthate PGA and GAP. The symbol v_i on each arrow represents the rate of each reaction. The subscript of v_i represents the reaction number. The cycle $RuBP \rightarrow PGA \rightarrow DPGA \rightarrow GAP \rightarrow Ru5P \rightarrow RuBP$ represents the Calvin cycle, and the pathway $RuBP \rightarrow PGCA \rightarrow GCA \rightarrow GCEA \rightarrow PGA$ represents the photorespiration.

The reactions in Fig. 2 are

RN	Reaction
1	$RuBP + CO_2 \longrightarrow 2PGA$
2	$PGA + ATP \longrightarrow DPGA + ADP$
3	$DPGA + NADPH + H^+ \longrightarrow GAP + Pi + NADP$
4	$GAP \longrightarrow 0.6Ru5P$
5	$PGA \longrightarrow Sink$
6	$GAP \longrightarrow Sink$
13	$Ru5P + ATP \longrightarrow RuBP + ADP$
111	$RuBP + O_2 \longrightarrow PGA + PGCA$
112	$PGCA + H_2O \longrightarrow GCA + Pi$
7	$GCA \longrightarrow GCEA$
113	$GCEA + ATP \longrightarrow PGA + ADP$

where RN represents the reaction number. Clearly, such a reduced metabolic network not only simplifies the model but also represents the key processes of the photosynthetic carbon metabolism: Calvin cycle, utilization of photosynthate, and photorespiration. Moreover, *GAP* and *Ru5P* can be viewed as input and output in the conversion of *GAP* to *Ru5P*, respectively. Such a process can be taken as a functional module,

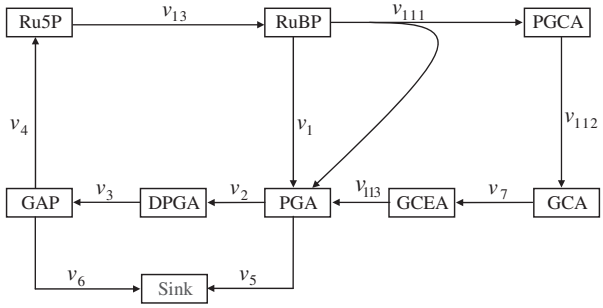

Fig. 2. Reduced photosynthetic carbon metabolic network.

and then reduced as $GAP \rightarrow 0.6Ru5P$. Similarly, $PGA \rightarrow Sink$ and $GAP \rightarrow Sink$. From the view of function, the reduced network (Fig. 2) is equivalent to the complete one (Fig. 1).

2.2 Rate equation of each reaction

Generally, a metabolic network can be modeled by ordinary differential equations (ODE) or stochastic differential equations (SDE). Different models may lead to different results. Lipshtat *et al.* studied the stochastic effects on bistability of genetic switch systems [29]. Since a reasonable and effective ODE model has been proposed and improved [10, 22–27], we model the photosynthetic carbon metabolic systems in a deterministic approach based on the existed works. We now derive some appropriate expressions to describe the rate for each reaction in Fig. 2 in a mathematical manner. We use the symbols of the metabolites to represent their own concentrations.

Badger and Lorimer [30] found that some intermediates of the Calvin cycle, such as PGA, SBP and FBP, can also bind to the Rubisco active sites and competitively inhibit RuBP carboxylation. To model such an inhibition, Badger and Lorimer [30], Pettersson and Ryde-Pettersson [23] took the reaction rate v_1 of RuBP carboxylation as

$$\begin{aligned} v_1 &= V_{\max 1} RuBP/(RuBP + K_{M13}\Psi), \\ \Psi &= 1 + \frac{PGA}{K_{I11}} + \frac{FBP}{K_{I12}} + \frac{SBP}{K_{I13}} \\ &\quad + \frac{Pi}{K_{I14}} + \frac{NADPH}{K_{I15}}, \end{aligned} \tag{1}$$

where $V_{\max 1}$ represents the maximal velocity of the enzymatic reaction, K_{M13} is the Michaelis-Menten constant for RuBP, K_{I11}, K_{I12}, K_{I13}, K_{I14} and K_{I15} are respective constants for PGA, FBP, SBP, Pi and NADPH inhibition of RuBP binding to Rubisco active sites. Moreover, the concentration of Rubisco active sites in the chloroplast stroma can be as high as that

of the substrate RuBP [26, 31–33]. Thus, Farquhar and Caemmerer [10, 25] represented the reaction rate of RuBP carboxylation approximately as

$$v_1 = \frac{V_{\max 1} CO_2 \min\left(1, \frac{RuBP}{E_t}\right)}{CO_2 + K_{M11}\left(1 + \frac{O_2}{K_{M12}}\right)},$$

where $\min(\cdot,\cdot)$ is the function which returns the lowest value in its elements, E_t is the total concentration of Rubisco, K_{M11} and K_{M12} are respective Michaelis-Menten constants for CO_2 and O_2. Based on those previous works, Zhu *et al.* [22] gave

$$v_1 = \frac{RuBP}{RuBP + K_{M13}\Psi} \frac{V_{\max 1} CO_2 \min\left(1, \frac{RuBP}{E_t}\right)}{CO_2 + K_{M11}\left(1 + \frac{O_2}{K_{M12}}\right)}, \quad (2)$$

where Ψ is given in (1).

Since FBP and SBP do not exist in the reduced network (Fig. 2), the inhibition of these two metabolites can be equivalently represented with their upstream metabolite GAP by choosing an appropriate inhibition parameter K_{I16} from mathematical viewpoint. More specifically, the term $\frac{FBP}{K_{I12}} + \frac{SBP}{K_{I13}}$ in the denominator of v_1 in (2) can be replaced by $\frac{GAP}{K_{I16}}$. Hence, we take

$$v_1 = \frac{RuBP}{RuBP + \Phi} \frac{V_{\max 1} CO_2 \min\left(1, \frac{RuBP}{E_t}\right)}{CO_2 + K_{M11}\left(1 + \frac{O_2}{K_{M12}}\right)}, \quad (3)$$

$$\Phi = K_{M13}\left(1 + \frac{PGA}{K_{I11}} + \frac{GAP}{K_{I16}} + \frac{Pi}{K_{I14}} + \frac{NADPH}{K_{I15}}\right).$$

RuBP oxygenation, *i.e.* reaction 111 (see Fig. 2), is also catalyzed by Rubisco. Thus, we take

$$v_{111} = \frac{RuBP}{RuBP + \Phi} \frac{V_{\max 111} O_2 \min\left(1, \frac{RuBP}{E_t}\right)}{O_2 + K_{M12}\left(1 + \frac{CO_2}{K_{M11}}\right)}. \quad (4)$$

The reactions 4, 5, 6 and 7 (see Fig. 2) are all simplifications of a series of biochemical reactions. We assume that all these reactions obey Michaelis-Menten kinetics, and the corresponding reaction rates are

$$v_4 = \frac{V_{\max 4} GAP}{GAP + K_{M4}} \quad (5)$$

$$v_5 = \frac{V_{\max 5} PGA}{PGA + K_{M5}} \quad (6)$$

$$v_6 = \frac{V_{\max 6} GAP}{GAP + K_{M6}} \quad (7)$$

$$v_7 = \frac{V_{\max 7} GCA}{GCA + K_{M7}}. \quad (8)$$

Note that the reverse reaction of the reaction 2 (see Fig. 2) is not considered since it is a very weak process. The rate equations of the reactions 3, 13, 112 and 113 (see Fig. 2) are assumed to be consistent with those developed in [22]. The mathematical expressions are

$$v_2 = \frac{V_{\max 2} PGA \times ATP}{(PGA + K_{M21})(ATP + K_{M22})} \quad (9)$$

$$v_3 = \frac{V_{\max 3} DPGA \times NADPH}{(DPGA + K_{M31})(NADPH + K_{M32})} \quad (10)$$

$$v_{112} = \frac{V_{\max 112} PGCA}{PGCA + K_{M112}\left(1 + \frac{GCA}{K_{I1121}}\right)\left(1 + \frac{Pi}{K_{I1122}}\right)} \quad (11)$$

$$v_{13} = \frac{V_{\max 13}\left(Ru5P \times ATP - \frac{ADP \times RuBP}{K_{E13}}\right)}{\left(Ru5P + K_{M131}\left(1 + \frac{GAP}{K_{I131}} + \frac{RuBP}{K_{I132}} + \frac{Pi}{K_{I133}}\right)\right) ATP\left(1 + \frac{ADP}{K_{I134}}\right) + K_{M132}\left(1 + \frac{ADP}{K_{I135}}\right)} \quad (12)$$

$$v_{113} = \frac{V_{\max 113}\left(GCEA \times ATP - \frac{PGA \times ADP}{K_{E113}}\right)}{\left(ATP + K_{M1131}\left(1 + \frac{PGA}{K_{I113}}\right)\right) GCEA + K_{M1132}}. \quad (13)$$

2.3 Model of the reduced metabolic network

With the above preparation, we take the concentrations of the orthophosphate Pi in the stroma and the eight metabolites *RuBP*, *PGA*, *DPGA*, *GAP*, *Ru5P*, *PGCA*, *GCA* and *GCEA* in Fig. 2 as the variables, and take the concentrations of *ATP*, *ADP*, *NADPH*, CO_2 and O_2 as the parameters. Then, the rate of change of each metabolite concentration is given by the difference between the rates of the reactions that generate the metabolites and the rates of the reactions that consume the metabolites:

$$dRuBP/dt = v_{13} - v_1 - v_{111} \tag{14a}$$

$$dPGA/dt = 2v_1 + v_{111} + v_{113} - v_2 - v_5 \tag{14b}$$

$$dDPGA/dt = v_2 - v_3 \tag{14c}$$

$$dGAP/dt = v_3 - v_4 - v_6 \tag{14d}$$

$$dRu5P/dt = 0.6v_4 - v_{13} \tag{14e}$$

$$dPGCA/dt = v_{111} - v_{112} \tag{14f}$$

$$dGCA/dt = v_{112} - v_7 \tag{14g}$$

$$dGCEA/dt = v_7 - v_{113}, \tag{14h}$$

where the rates v_i are given in (3)–(13). The export of photosynthate PGA, GAP and DHAP from the chloroplast to the cytosol is mediated by the phosphate translocator of chloroplast membrane, and is associated with a counter-import of orthophosphate from the cytosol to the chloroplast. Therefore, the total concentration of phosphate (C_P) in stroma remains constant [22, 23, 34]. We write the conserved quantity of phosphate approximately as

$$C_P = Pi + PGA + 2DPGA + ATP + PGCA + 2RuBP + Ru5P + GAP. \tag{15}$$

Thus, the differential Equations (14) and the algebraic Equation (15) form a coupled nonlinear differential-algebraic system that represents a reduced model of the photosynthetic carbon metabolism with nine variables and 48 parameters.

III. THEORETICAL ANALYSIS

3.1 Effect of the photorespiration

For a dynamic system

$$\frac{dX}{dt} = f(X), \tag{16}$$

where X is a vector-valued function of t and $f(\cdot)$ is a known vector-valued function with appropriate dimension, the equilibrium is defined as the solution of the system of equations obtained by setting the right-hand side of (16) to zero, *i.e.* the solution of $f(X) = 0$.

The difference between the reduced photosynthetic carbon metabolic network (Fig. 2) and that in [12] is that our reduced network includes the photorespiration pathway $RuBP \to PGCA \to GCA \to GCEA \to PGA$, which represents a key biological process in the photosynthetic carbon metabolism. Hence, we will first investigate the effect of the photorespiration pathway on the photosynthetic carbon metabolism. We take the orthophosphate Pi as a parameter and consider the model (14) as the original model here. Without the photorespiration pathway, the model (14) becomes

$$dRuBP/dt = v_{13} - v_1 \tag{17a}$$

$$dPGA/dt = 2v_1 - v_2 - v_5 \tag{17b}$$

$$dDPGA/dt = v_2 - v_3 \tag{17c}$$

$$dGAP/dt = v_3 - v_4 - v_6 \tag{17d}$$

$$dRu5P/dt = 0.6v_4 - v_{13}. \tag{17e}$$

We find that under a mild condition on the reaction rates, the metabolites *PGA*, *DPGA* and *GAP* have the same equilibria regardless of the photorespiration pathway. This property is summarized in the following proposition, which is proven in Appendix 5.1.

Proposition 1. Let $\{RuBP = RuBP_0, PGA = PGA_0, DPGA = DPGA_0, GAP = GAP_0, Ru5P = Ru5P_0\}$ be an equilibrium of the system (17), where $RuBP_0$, PGA_0, $DPGA_0$, GAP_0 and $Ru5P_0$ are fixed positive numbers. Assume that the rate equations v_2, v_3, v_4, v_5 and v_6 do not depend on the variables *RuBP*, *Ru5P*, *PGCA*, *GCA* and *GCEA*. Then, if the system (14) has an equilibrium, it must have the form $\{RuBP = RuBP_1, PGA = PGA_0, DPGA = DPGA_0, GAP = GAP_0, Ru5P = Ru5P_1, PGCA = PGCA_0, GCA = GCA_0, GCEA = GCEA_0\}$, where $RuBP_1$, $Ru5P_1$, $PGCA_0$, GCA_0 and $GCEA_0$ are some positive numbers.

Remark 1. In Proposition 3.1, there is no requirement on the detailed form of the reaction rate v_i. It requires only that the same v_i in system (17) and (14) has the same expression.

Generally, the biochemical reactions 2, 3, 4, 5 and 6 (see Fig. 2) are not affected by the metabolites *RuBP*, *Ru5P*, *PGCA*, *GCA* and *GCEA* [22]. Hence, the condition on the reaction rates in Proposition 1 is always held for the photosynthetic carbon metabolism. Since there

is no requirement on detailed expressions of reaction rates v_2, v_3, v_4, v_5 and v_6, Proposition 1 is suitable for a wide variety of models of the photosynthetic carbon metabolism.

3.2 A parameter condition for ruling out multiple equilibria

For the model composed by the differential equations (14) and the algebraic equation (15), it is still difficult to analyze its multi-equilibrium property when all the 48 parameters vary in certain intervals. Thus, we need to equivalently transform this system into a simplified one.

By setting the right-hand side of (14) to zero and with an equivalent transformation, we get the following algebraic equations,

$$0.6v_4 - v_1 - v_{111} = 0 \tag{18a}$$

$$1.2v_4 - v_2 - v_5 = 0 \tag{18b}$$

$$v_2 - v_3 = 0 \tag{18c}$$

$$v_2 - v_4 - v_6 = 0 \tag{18d}$$

$$0.6v_4 - v_{13} = 0 \tag{18e}$$

$$v_{111} - v_7 = 0 \tag{18f}$$

$$v_{112} - v_7 = 0 \tag{18g}$$

$$v_7 - v_{113} = 0. \tag{18h}$$

With the rate Equations (3)–(13), (18b) and (18d) form an independent subsystem,

$$\frac{1.2V_{\max 4}GAP}{GAP+K_{M4}} - \frac{V_{\max 5}PGA}{PGA+K_{M5}} - \frac{V_{\max 2}PGA\times ATP}{(PGA+K_{M21})(ATP+K_{M22})} = 0 \tag{19a}$$

$$\frac{V_{\max 2}PGA\times ATP}{(PGA+K_{M21})(ATP+K_{M22})} - \frac{V_{\max 4}GAP}{GAP+K_{M4}} - \frac{V_{\max 6}GAP}{GAP+K_{M6}} = 0, \tag{19b}$$

which contains just two variables (*i.e.* *PGA* and *GAP*) and 10 parameters (*i.e.* $V_{\max 2}$, $V_{\max 4}$, $V_{\max 5}$, $V_{\max 6}$, K_{M21}, K_{M22}, K_{M4}, K_{M5}, K_{M6} and ATP).

Lemma 1. If the subsystem (19) has only one positive solution, then the original system (18) has no more than one positive solution.

The proof of this lemma is given in Appendix 5.2.

Based on Lemma 1, we only need to discuss the subsystem (19). Let $x=\frac{1}{PGA}$ and $y=\frac{1}{GAP}$. Then, from (19) we have

$$\frac{1.2V_{\max 4}}{1+K_{M4}y} - \frac{V_{\max 2}ATP}{(1+K_{M21}x)(ATP+K_{M22})} - \frac{V_{\max 5}}{1+K_{M5}x} = 0 \tag{20a}$$

$$\frac{V_{\max 2}ATP}{(1+K_{M21}x)(ATP+K_{M22})} - \frac{V_{\max 4}}{1+K_{M4}y} - \frac{V_{\max 6}}{1+K_{M6}y} = 0. \tag{20b}$$

This transformation only loses the zero root $\{PGA=0, GAP=0\}$ of (19), which has no meaning. Thus, the roots of the systems (19) and (20) are a one-to-one correspondence, and have the same signs.

Eliminating y in (20), we obtain a fractional equation with one variable x that can be written as a polynomial equation of degree 3,

$$ax^3+bx^2+cx+d=0, \tag{21}$$

where a, b, c and d are all polynomials of (K_M, $V_{\max}$, ATP), $K_M=(K_{M21}, K_{M22}, K_{M4}, K_{M5}, K_{M6})$ and $V_{\max}=(V_{\max 2}, V_{\max 4}, V_{\max 5}, V_{\max 6})$.

We take the values of the parameters (K_M, $V_{\max}$, ATP) used in [12, 22, 23] as the nominal values in our work, see Table I. For such nominal values $(K_{M0}, V_{\max 0}, ATP_0)$, the corresponding roots of (21) are

$$x_{10}=-1.385,\ x_{20}=-1.134,\ x_{30}=18.521. \tag{22}$$

That is, (21) has only one positive solution $x_{30}=18.5209$. The corresponding solution of y is $y_{30}=0.562646$. Thus, $\{PGA=0.054, GAP=1.777\}$ is the only positive solution to the subsystem (19), which falls

Table I. Nominal values of the parameters $V_{\max}$, K_M, ATP.

Parameter	Value	Reference
$V_{\max 2}$	10.3	[22, 26, 36]
$V_{\max 4}$	1.5	[22, 37, 38]
$V_{\max 5}$	0.3	[22, 37, 38]
$V_{\max 6}$	0.7	[22, 37, 38]
K_{M21}	0.240	[22, 39]
K_{M22}	0.390	[22, 39]
K_{M4}	0.84	[12]
K_{M5}	0.75	[12]
K_{M6}	5.0	[12]
ATP	0.68	[22, 26]

within the physiologically relevant range $(0.0001-5mM)$ [35].

Next, we discuss the multi-equilibrium property of the original system when the 10 parameters $(K_M, V_{\max}, ATP)$ vary in some field around their nominal values. Before deriving the main result, we give the following lemma about polynomial equation of degree 3, whose proof is given in Appendix 5.3.

Lemma 2. Suppose that the coefficients a, b, c and d of the polynomial equation

$$ax^3+bx^2+cx+d=0 \tag{23}$$

are continuous real functions of $P=(p_1, p_2, \cdots, p_n)\in R^n$ (n is a positive integer), *i.e.* $a=a(P)$, $b=b(P)$, $c=c(P)$ and $d=d(P)$. Let $x_{i0}=x_{i0}(a,b,c,d)=\tilde{x}_{i0}(P_0)$, $i=1,2,3$, be the roots of (23) with respect to the parameter $P_0=(p_{10}, p_{20}, \cdots, p_{n0})$ and $x_{10}<0$, $x_{20}<0, x_{30}>0$. Assume that $\Omega\subset\mathbb{R}^n$ is connected and $P_0\in\Omega$. If $ad(ad-bc)$ has the same sign for all $P\in\Omega$, then the positive root $x_3=\tilde{x}_3(P)$ will keep its sign and the other two roots will stay in the left open half plane when P varies in Ω.

Remark 2. The two roots of (23) that stay in the left half plane could be a pair of conjugate complex numbers, two distinct negative numbers, or two repeated negative numbers.

Theorem 1. Let $\Omega\subset\mathbb{R}^{10}_+=\{(z_1,\cdots,z_{10}): z_i\in\mathbb{R}_+=(0,\infty), i=1,\cdots,10\}$ be connected and contain the nominal values $(K_{M0}, V_{\max 0}, ATP_0)$ listed in Table I, and a, b, c and d be the coefficients of (21). Then, (18) has no more than one equilibrium if $ad(ad-bc)$ does not change its sign whenever $(K_M, V_{\max}, ATP)\in\Omega$.

Proof. The first two roots in (22) are negative and the last one is positive. Noticing that $ad(ad-bc)$ has the same sign for all $(K_M, V_{\max}, ATP)\in\Omega$, we can claim that (21) has one and only one positive root for each $(K_M, V_{\max}, ATP)\in\Omega$ by Lemma 2. This implies that the subsystem (20) has no more than one positive root. By Lemma 1, the original system (18) has no more than one equilibrium for any $(K_M, V_{\max}, ATP)\in\Omega$. □

Remark 3. To get the result in Theorem 3.1, it only needs some condition on the subsystem parameter $(K_M, V_{\max}, ATP)$, which implies the other 38 parameters can vary arbitrarily.

3.3 Numeric results

Based on Theorem 1, we can find a certain parameter field in which the original system (18) has no more than one equilibrium by some numeric computation.

Let $\Omega=\{(K_M, V_{\max}, ATP): LK_{Mi}\le K_{Mi}\le UK_{Mi}, i=21,22,4,5,6, LV_{\max j}\le V_{\max j}\le UV_{\max j}, j=2,4,5,6, LATP\le ATP\le UATP\}$, where LK_{Mi} and UK_{Mi}, $LV_{\max j}$ and $UV_{\max j}$, $LATP$ and $UATP$ are some positive numbers. In other words, Ω is a neighborhood of the nominal values $(K_{M0}, V_{\max 0}, ATP_0)$.

For the nominal values $(K_{M0}, V_{\max 0}, ATP_0)$ listed in Table I, the coefficients of (21) satisfy $a_0d_0-b_0c_0<0, a_0d_0<0$. Thus, we can find some Ω satisfying $ad(ad-bc)>0$ for all $(K_M, V_{\max}, ATP)\in\Omega$. Actually, if the minimal value of the function

$$f(K_M, V_{\max}, ATP)=ad(ad-bc),$$

is positive on Ω, then such an Ω will meet the requirement. It is difficult to obtain the largest Ω. But for a given Ω, it is relatively easy to verify whether or not the condition is satisfied. Varying 25% , 20% and 20% around the nominal values for $V_{\max}$'s, K_M's and ATP, respectively, we can get the following field,

$$\begin{aligned}
&V_{\max 2}\in[7.725, 12.875], \quad K_{M21}\in[0.192, 0.288],\\
&V_{\max 4}\in[1.125, 1.875], \quad K_{M22}\in[0.312, 0.468],\\
&V_{\max 5}\in[0.225, 0.375], \quad K_{M4}\in[0.672, 1.008],\\
&V_{\max 6}\in[0.525, 0.875], \quad K_{M5}\in[0.6, 0.9],\\
&ATP\in[0.544, 0.816], \quad K_{M6}\in[4.0, 6.0].
\end{aligned} \tag{24}$$

Using Mathematica, we find that the function $f(K_M, V_{\max}, ATP)$ takes its minimal value 7.17058×10^6 in Ω at $V_{\max 2}=7.75853$, $V_{\max 4}=1.13436$, $V_{\max 5}=0.373942$, $V_{\max 6}=0.534386$, $K_{M21}=0.192427$, $K_{M22}=0.312$, $K_{M4}=1.00787$, $K_{M5}=0.602485$, $K_{M6}=4.00263$ and $ATP=0.555017$. Therefore, based on Theorem 1, we claim that the model composed by the differential Equations (14) and the algebraic Equation (15) has no more than one equilibrium, when the 10 parameters $V_{\max 2}$, $V_{\max 4}$, $V_{\max 5}$, $V_{\max 6}$, K_{M21}, K_{M22}, K_{M4}, K_{M5}, K_{M6} and ATP stay in the field (24) and the other 38 parameters are arbitrary.

IV. CONCLUSION AND FUTURE WORK

In this paper, we first proposed a reduced molecular network for the photosynthetic carbon metabolism, which describes the key characteristics of the photosynthetic carbon metabolism: Calvin cycle, utilization of photosynthate, and photorespiration. Then a nonlinear differential-algebraic model is derived to represent the reduced network. By investigating the effect of the photorespiration pathway on the multi-equilibrium property in the photosynthetic carbon metabolism, we

found that under a mild condition on the reaction rates v_2, v_3, v_4, v_5 and v_6, the metabolites PGA, DPGA and GAP have robust dynamic behavior and are independent of the dynamics of the photorespiration pathway. Moreover, we studied the multi-equilibrium property of the network allowing the parameters to vary in an appropriate domain. Although there are 48 parameters in our model, we proved that if the 10 parameters in the subsystem stay in a certain field, no matter what values the other 38 parameters take, there exists no more than one equilibrium in the original system. Such a result not only provides profound insights for qualitatively understanding dynamic features of the photosynthetic carbon metabolism but also can be adopted as a quantitative criteria to find a correct strategy to improve the photosynthesis in plants.

From the view of function, the reduced network is equivalent to the entire one. This paper only gives a parameter condition for ruling out multiple equilibria of the reduced network. The parameter condition for the presence of multiple equilibria and the stability of each equilibrium are still worth investigating.

V. APPENDIX

5.1 Proof of Proposition 1

Proof. By setting the right-hand side of the ordinary differential Equations (17) and (14) to zero and with some equivalent transformations, respectively, we get the following algebraic equations,

$$v_{13}-v_1=0 \tag{A1a}$$
$$1.2v_4-v_2-v_5=0 \tag{A1b}$$
$$v_2-v_3=0 \tag{A1c}$$
$$v_3-v_4-v_6=0 \tag{A1d}$$
$$0.6v_4-v_{13}=0, \tag{A1e}$$
$$v_{13}-v_1-v_{111}=0 \tag{A2a}$$
$$1.2v_4-v_2-v_5=0 \tag{A2b}$$
$$v_2-v_3=0 \tag{A2c}$$
$$v_3-v_4-v_6=0 \tag{A2d}$$
$$0.6v_4-v_{13}=0 \tag{A2e}$$
$$v_{111}-v_{112}=0 \tag{A2f}$$
$$v_{112}-v_7=0 \tag{A2g}$$
$$v_7-v_{113}=0. \tag{A2h}$$

Since v_2, v_3, v_4, v_5 and v_6 do not depend on {*RuBP*, *Ru5P*, *PGCA*, *GCA*, *GCEA*}, (A1b)–(A1d) and (A2b)–(A2d) just include the variables *PGA*, *DPGA* and *GAP*, and form two independent subsystems of the systems (A.1) and (A.2), respectively. It is obvious that the subsystems (A1b)–(A1d) and (A2b)–(A2d) are the same. That is, the two systems (A.1) and (A.2) have the same independent subsystem. Thus, the values of *PGA*, *DPGA* and *GAP* in the solutions of systems (A1a) and (A2a) are the same. □

5.2 Proof of Lemma 1

Proof. Since the subsystem (19) (*i.e.* (18b) and (18d)) contains only two variables *PGA* and *GAP*, we can solve *PGA* and *GAP* first. Then, by the following procedure, we can uniquely solve the other seven variables *DPGA*, *GCEA*, *GCA*, Pi, *PGCA*, *RuBP* and *Ru5P*, which means *GAP* and *PGA* can determine the other seven metabolites uniquely. Thus, if the subsystem (19) has only one positive solution, then the original system (18) has no more than one positive solution.

Procedure for solving *DPGA*, *GCEA*, *GCA*, Pi, *PGCA*, *RuBP* and *Ru5P*.

Step 1: Obtaining the value of each reaction rate.

After having obtained the values of $\{PGA, GAP\}$ by the subsystem (19), we can get the values of v_2, v_4, v_5 and v_6 accordingly. By (18c) and (18e), it is obvious that

$$v_3=v_2, \tag{B1}$$
$$v_{13}=0.6v_4. \tag{B2}$$

Denote

$$W_C=\frac{V_{\max 1}CO_2}{CO_2+K_{M11}\left(1+\dfrac{O_2}{K_{M12}}\right)},$$
$$W_O=\frac{V_{\max 111}O_2}{O_2+K_{M12}\left(1+\dfrac{CO_2}{K_{M11}}\right)},$$
$$W=W_C+W_O.$$

Then

$$v_1=\frac{W_C}{W}(v_1+v_{111}),$$
$$v_{111}=\frac{W_O}{W}(v_1+v_{111}).$$

Let

$$\lambda=\frac{0.6}{W}v_4.$$

Then, by (18a) we have (18f), (18g) and (18h),

$$v_1 = W_C \cdot \lambda \tag{B3}$$

$$v_{111} = W_O \cdot \lambda \tag{B4}$$

$$v_7 = W_O \cdot \lambda \tag{B5}$$

$$v_{112} = W_O \cdot \lambda \tag{B6}$$

$$v_{113} = W_O \cdot \lambda. \tag{B7}$$

Step 2: Solving *DPGA*, *GCA* and *GCEA*.

With the rate equations (8), (10) and (13), we can obtain unique *DPGA* , *GCA* and *GCEA* by (B1), (B5) and (B7), respectively.

Step 3: Solving *PGCA*, *RuBP* and *Ru5P* for fixed Pi.

For fixed Pi, *GCA* can determine $PGCA(Pi)$ uniquely by (B6).

For given *PGA* and *GAP*,

$$\varphi(Pi) = K_{M13}\left(1+\frac{PGA}{K_{I11}}+\frac{GAP}{K_{I16}} + \frac{Pi}{K_{I14}}+\frac{NADPH}{K_{I15}}\right)$$

is only a function of Pi. Combining (3) and (B3), we have

$$\frac{RuBP\min\left(1,\dfrac{RuBP}{E_t}\right)}{RuBP+\varphi(Pi)} = \lambda. \tag{B8}$$

If $RuBP \geq E_t$, then (B8) becomes a linear equation

$$\frac{RuBP}{RuBP+\varphi(Pi)} = \lambda. \tag{B9}$$

If $RuBP < E_t$, then (B8) becomes a quadratic equation

$$\frac{RuBP\dfrac{RuBP}{E_t}}{RuBP+\varphi(Pi)} = \lambda, \tag{B10}$$

or equivalently,

$$RuBP^2 - \lambda E_t RuBP - \varphi(Pi)\lambda E_t = 0. \tag{B11}$$

Noting that E_t, $\beta(Pi)$ and λ are all positive, we have $-\varphi(Pi)\cdot\lambda\cdot E_t < 0$. Therefore, one root of the quadratic equation (B11) is positive, and the other is negative.

For fixed Pi, denote the root of (B9) by $RuBP_1(Pi)$, and the positive root of (B11) by $RuBP_2(Pi)$. Then we can show that $RuBP_1(Pi)$ and $RuBP_2(Pi)$ are not positive roots of the original equation (B8) simultaneously, since otherwise, there would be that $RuBP_1(Pi)$ and $RuBP_2(Pi)$ were both positive roots of the original equation (B8) simultaneously. This results in $0 < RuBP_2(Pi) < E_t \leq RuBP_1(Pi)$,

$$\lambda = \frac{RuBP_2(Pi)\dfrac{RuBP_2(Pi)}{E_t}}{RuBP_2(Pi)+\varphi(Pi)} < \frac{RuBP_2(Pi)}{RuBP_2(Pi)+\varphi(Pi)} < \frac{RuBP_1(Pi)}{RuBP_1(Pi)+\varphi(Pi)} = \lambda,$$

which is obviously a contradiction. Therefore, we can obtain an unique positive $RuBP(Pi)$ for fixed Pi. Thus, $RuBP(Pi)$ and *GAP* can determine an unique $Ru5P(Pi)$ for fixed Pi by (B2).

Step 4: Solving Pi, *PGCA*, *RuBP* and *Ru5P*.

We will first show that $PGCA(Pi)$, $RuBP(Pi)$ and $Ru5P(Pi)$ obtained for fixed Pi in Step 3 are all strictly increasing functions of Pi.

Define function $f(\cdot,\cdot)$ as

$$f(RuBP, Pi) = \frac{RuBP\min\left(1,\dfrac{RuBP}{E_t}\right)}{RuBP+\varphi(Pi)}.$$

Then $f(RuBP, Pi)$ is strictly increasing in *RuBP* and decreasing in Pi. Let $Pi_2 > Pi_1 > 0$ be any two fixed values of Pi, and $RuBP(Pi_1)$ and $RuBP(Pi_2)$ be the corresponding roots of (B8). That is, $f(RuBP(Pi_1), Pi_1) = \lambda$ and $f(RuBP(Pi_2), Pi_2) = \lambda$. Noticing the monotonicity of $f(\cdot,\cdot)$, we have

$$f(RuBP(Pi_1), Pi_2) < f(RuBP(Pi_1), Pi_1) = f(RuBP(Pi_2), Pi_2),$$

which implies

$$RuBP(Pi_1) < RuBP(Pi_2).$$

Thus, $RuBP(Pi)$ is strictly increasing in Pi. Similarly, we can show that $PGCA(Pi)$ and $Ru5P(Pi)$ are also strictly increasing in Pi.

Now, we will solve Pi by (15). Define function $g(\cdot)$ as

$$g(Pi) = Pi + PGA + 2DPGA + ATP + GAP + PGCA(Pi) + 2RuBP(Pi) + Ru5P(Pi),$$

where $PGCA(Pi)$, $RuBP(Pi)$ and $Ru5P(Pi)$ are obtained in Step 2. Then (15) becomes

$$g(Pi) = C_P. \tag{B12}$$

By the above argument, $g(Pi)$ is strictly increasing in Pi. Thus, if the solution of (B12) exists for a given parameter C_P, then it must be unique. Suppose that Pi

is the unique solution of (B12). Then we can obtain $PGCA = PGCA(Pi)$, $RuBP = RuBP(Pi)$ and $Ru5P = Ru5P(Pi)$ uniquely. □

5.3 Proof of Lemma 2

Proof. We will first show that "$ad(ad-bc)$ has the same sign for all $P \in \Omega$" is equivalent to "$-\frac{d}{a} > 0$ and $bc > ad$ (or $bc < ad$) for all $P \in \Omega$". Note that $bc > ad$ (or $bc < ad$) for all $P \in \Omega$ means that $ad - bc$ keeps its sign for all $P \in \Omega$, and $-\frac{d}{a} > 0$ is equivalent to $ad < 0$. Thus, $-\frac{d}{a} > 0$ and $bc > ad$ (or $bc < ad$) for all $P \in \Omega$ implies that $ad(ad-bc)$ keeps its sign for all $P \in \Omega$. Conversely, assume that $ad(ad-bc)$ keeps its sign for all $P \in \Omega$. First, $-\frac{d(P_0)}{a(P_0)} = x_{10}x_{20}x_{30} > 0$ implies $a(P_0)d(P_0) < 0$. If there would exist a $P_2 \in \Omega$ such that $a(P_2)d(P_2) > 0$, then there would be a $P_3 \in \Omega$ such that $a(P_3)d(P_3) = 0$ by the connectivity of Ω and the continuity of $a(P)$ and $d(P)$. Then, $a(P_3)d(P_3)(a(P_3)d(P_3) - b(P_3)c(P_3)) = 0$. This contradicts the condition that $ad(ad-bc)$ keeps its sign for all $P \in \Omega$. Thus, $ad < 0$ for all P in Ω, which implies $-\frac{d}{a} > 0$. Similarly, we can show that $bc > ad$ (or $bc < ad$) for all $P \in \Omega$.

Next, we will show that the roots $x_i = \tilde{x}_i(P)$ $(i = 1, 2, 3)$ cannot be on the imaginary axis for all $P \in \Omega$. Noting that $x_1x_2x_3 = -\frac{d}{a}$ and the assumption $-\frac{d}{a} > 0$ for all $P \in \Omega$, we have $x_i \neq 0$ $(i = 1, 2, 3)$. Assume, to arrive at a contradiction, that there existed $P_1 \in \Omega$ such that the corresponding roots $x_{11}(P_1), x_{21}(P_1)$ were a pair of conjugate imaginary roots. Then (23) would have the form

$$a_1(x+p)(x^2+q) = 0, \quad q > 0,$$

or equivalently,

$$a_1x^3 + a_1px^2 + a_1qx + a_1pq = 0, \quad q > 0.$$

That is, $b_1 = a_1p$, $c_1 = a_1q$ and $d_1 = a_1pq$, which implies $b_1c_1 = a_1d_1$. This contradicts the assumption that $bc > ad$ (or $bc < ad$) for all $P \in \Omega$. Hence, there must be no root of (23) on the imaginary axis for any parameter $P \in \Omega$. This means the root set of (23) corresponding to the parameter $P \in \Omega$ is divided into two parts by the imaginary axis.

Since the roots of a polynomial equation of degree 3 depend on the parameters continuously, the roots $x_i = \tilde{x}_i(P)$ $(i = 1, 2, 3)$ cannot cross the imaginary axis when the parameter P varies in Ω continuously. Noticing the connectivity of Ω, we can claim that the roots $x_i = \tilde{x}_i(P)$ $(i = 1, 2, 3)$ will stay in its original field, either the left half plane or the right half plane, no matter how the parameter P varies in Ω.

Finally, we will show that the positive root $x_3 = \tilde{x}_3(P)$ will stay on the positive real axis when P varies in Ω. Otherwise, $x_3 = \tilde{x}_3(P)$ would become into a pair of conjugate complex roots x_{31} and x_{32} since they cannot be two positive roots, and the other two roots (*i.e.* x_1 and x_2) would merge into an negative number, say x_{12}. Thus, the product of the three roots $x_{12}x_{31}x_{32}$ would be negative, that is $-\frac{d}{a} = x_{12}x_{31}x_{32} < 0$. This contradicts the condition $-\frac{d}{a} > 0$ for all $P \in \Omega$. □

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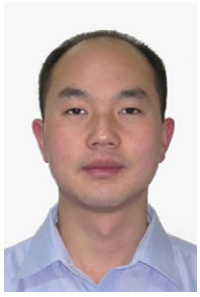

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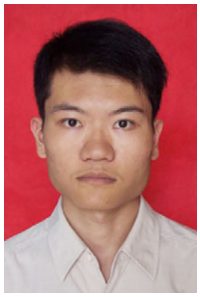

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