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P-Irreducibility of Binding Polynomials

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Abstract—The problem of deciding whether a polynomial of positive coefficients can be factored into polynomials of the same type is important for studying many physiological processes. An efficient method to decide positive irreducibility is highly valuable. The known criteria for positive irreducible polynomials need to know root location first. Here, we present a new criterion for positive polynomials of degree 3 or 4, which can be expressed only by the coefficients of the given polynomials.

Keywords—Binding polynomial, Positive factorization, Positive irreducibility criterion.

1. INTRODUCTION

Protein ligand binding is a process in which the ligand can become bound and interact at a number of sites of a protein macromolecule. It can be described by the binding polynomial introduced by Wyman [1]. If the molecule has n binding sites and x represents ligand activity, then the binding polynomial can be written as $f(x) = 1 + \beta_1 x + \cdots + \beta_n x^n$, $\beta_i \geq 0$, $1 \leq i \leq n-1$, and $\beta_n > 0$. If $f(x)$ can be factored into two polynomials with positive coefficients, then it is natural to interpret each factor as a binding polynomial for a subset of the binding sites. The binding polynomials which are positive irreducible are very important since they imply that all sites are linked. It is of particular interest to determine whether a quartic polynomial be p-irreducible because it covers a large variety of classes of proteins including hemoglobin (see [2]). The problem has been discussed extensively in the literature [1–4], some criteria were established which require the computation of all roots of the polynomial. In this paper, we give a new criterion for polynomials of degree 3 or 4. It only consists of a set of polynomial inequalities defined by the coefficients of $f(x)$.

In the next section, we will present some basic facts about positive polynomials and a criterion for stability. In Section 3, we describe a criterion for positive irreducibility of polynomials with degree 3. Section 4 deals with positive irreducibility of polynomials with degree 4. The algorithm and some examples are included in Section 5.

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2. PRELIMINARY

DEFINITION 1. *A positive polynomial is a real polynomial whose leading and constant coefficients are positive and whose remaining coefficients are nonnegative.*

DEFINITION 2. *A positive factorization of a polynomial is a nontrivial factorization in which each factor is a positive polynomial.*

The positive factorization of a polynomial is not unique. For example:

$$\begin{aligned} f_1 &= x^4 + 4x^3 + 6x^2 + 19x + 30 \\ &= (x+2)\left(x^3 + 2x^2 + 2x + 15\right) \\ &= (x+3)\left(x^3 + x^2 + 3x + 10\right). \end{aligned} \tag{1}$$

DEFINITION 3. *A p-irreducible polynomial is a positive polynomial which does not admit a positive factorization.*

One method determining a polynomial to be p-irreducible is to try all the possible combinations of factors over the real field. For example:

$$\begin{aligned} f_2 &= x^4 + 12x^3 + 34x^2 + 23x + 210 \\ &= (x+7)(x+6)\left(x^2 - x + 5\right) \\ &= (x+7)\left(x^3 + 5x^2 - x + 30\right) \\ &= (x+6)\left(x^3 + 6x^2 - 2x + 35\right), \end{aligned} \tag{2}$$

$$\begin{aligned} f_3 &= x^4 + 8x^3 + 14x^2 + 27x + 90 \\ &= (x+6)(x+3)\left(x^2 - x + 5\right) \\ &= (x+3)\left(x^3 + 5x^2 - x + 30\right) \\ &= (x+6)\left(x^3 + 2x^2 + 2x + 15\right). \end{aligned} \tag{3}$$

f_2 is p-irreducible and f_3 has a positive factorization.

An important class of positive polynomials consists of stable polynomials whose roots all have negative real parts. Binding polynomials which are stable can be factored uniquely into positive linear and p-irreducible quadratic factors of the forms $x+u$, x^2+vx+w ($u>0$, $v>0$, $w>0$) so that the protein will have a number of independent sites corresponding to the linear factors and will have the remaining sites linked in pairs corresponding to the p-irreducible quadratic factors.

Routh in 1875 and Hurwitz in 1895 provided a criterion for stability. Suppose

$$f(x) = c_0x^n + c_1x^{n-1} + \cdots + c_n \tag{4}$$

is a polynomial with real coefficients, and that $c_0 = 1$. Then the Routh-Hurwitz conditions can be written in the form of the inequalities

$$\Delta_1 > 0,\ \Delta_2 > 0, \ldots, \Delta_n > 0, \tag{5}$$

where

$$\Delta_i = \begin{vmatrix} c_1 & c_3 & c_5 & \cdots & & \\ c_0 & c_2 & c_4 & \cdots & & \\ 0 & c_1 & c_3 & \cdots & & \\ 0 & c_0 & c_2 & c_4 & & \\ & & & & \ddots & \\ & & & & & c_i \end{vmatrix} \quad (c_k = 0,\ \forall\, k > n). \tag{6}$$

However, when all the coefficients of $f(x)$ are positive, the inequalities (5) are not independent. For example, for $n=3$, the Routh-Hurwitz conditions reduce to $\Delta_2 > 0$; for $n=4$, reduce to

$\Delta_3 > 0$. This circumstance was investigated by the French mathematicians Liénard and Chipart in 1914 (see [5]).

PROPOSITION 1. STABILITY CRITERION OF LIÉNARD AND CHIPART. *Necessary and sufficient conditions for all the roots of the real polynomial* $f(x) = x^n + c_1 x^{n-1} + \cdots + c_n$ *to have negative real parts can be given in any one of the following four forms:*

1. $c_n > 0, c_{n-2} > 0, c_{n-4} > 0, \ldots;\ \Delta_1 > 0, \Delta_3 > 0, \ldots,$
2. $c_n > 0, c_{n-2} > 0, c_{n-4} > 0, \ldots;\ \Delta_2 > 0, \Delta_4 > 0, \ldots,$
3. $c_n > 0, c_{n-1} > 0, c_{n-3} > 0, \ldots;\ \Delta_1 > 0, \Delta_3 > 0, \ldots,$
4. $c_n > 0, c_{n-1} > 0, c_{n-3} > 0, \ldots;\ \Delta_2 > 0, \Delta_4 > 0, \ldots.$

3. THE CASE $n = 3$

Consider the positive polynomial $f(x) = x^3 + c_1 x^2 + c_2 x + c_3$.

THEOREM 1. *A positive polynomial of degree 3 is p-irreducible if and only if the coefficients satisfy*

$$c_1 c_2 < c_3. \tag{7}$$

PROOF. According to Proposition 1, $f(x)$ will be stable if and only if $c_1 c_2 > c_3$. In this case, $f(x)$ can be factored into linear and quadratic p-irreducible factors. It is obvious that $c_1 c_2 = c_3$ is the sufficient and necessary condition for $f(x) = (x + c_1)(x^2 + c_2)$. Now suppose $c_1 c_2 < c_3$, $f(x)$ is not stable and has no pair of conjugate pure imaginary roots. The roots of $f(x)$ should be in the form $-u, v \pm wI$, $u > 0$, $v > 0$, $w > 0$, that is, $f(x) = (x + u)(x^2 - 2vx + v^2 + w^2)$ is p-irreducible. ∎

4. THE CASE $n = 4$

Consider the positive polynomial $f(x) = x^4 + c_1 x^3 + c_2 x^2 + c_3 x + c_4$.

THEOREM 2. *f is p-irreducible if and only if one of the following seven conditions is satisfied.*

	p_1	p_2	p_3	p_4	p_5	p_6	p_7	p_8	p_9	p_{10}	p_{11}	p_{12}
1	$= 0$										$= 0$	< 0
2	< 0	> 0										
3	< 0	≤ 0		> 0	> 0							
4	< 0	≤ 0	> 0	< 0		< 0						
5	< 0	≤ 0	> 0	> 0		> 0	> 0	≤ 0				
6	< 0	≤ 0	> 0	> 0	≤ 0	> 0	> 0	> 0	≤ 0			
7	< 0	≤ 0	> 0	> 0	≤ 0	> 0	> 0	> 0	> 0	≤ 0		

$p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, p_{10}, p_{11}, p_{12}$ are

$$\begin{aligned}
p_1 &= \Delta_3(f) = c_1 c_2 c_3 - c_1^2 c_4 - c_3^2, \\
p_2 &= \mathrm{Discr}(f) = -192 c_4^2 c_1 c_3 + 256 c_4^3 - 128 c_2^2 c_4^2 - 4 c_1^3 c_3^3 + 16 c_2^4 c_4 \\
&\quad - 4 c_2^3 c_3^2 - 27 c_1^4 c_4^2 - 27 c_3^4 + 144 c_2 c_1^2 c_4^2 + 18 c_1 c_3^3 c_2 + c_2^2 c_1^2 c_3^2 \\
&\quad - 4 c_2^3 c_1^2 c_4 - 6 c_4 c_1^2 c_3^2 + 144 c_4 c_3^2 c_2 - 80 c_1 c_3 c_2^2 c_4 + 18 c_1^3 c_3 c_2 c_4, \\
p_3 &= c_1^2 - 4 c_2, \\
p_4 &= f(-c_1) = c_1^2 c_2 - c_1 c_3 + c_4, \\
p_5 &= f'(-c_1) = -c_1^3 - 2 c_1 c_2 + c_3, \\
p_6 &= f(\alpha_1) f(\alpha_2) = c_2 c_3^2 - c_1 c_3 c_4 + c_4^2, \\
p_7 &= f(\alpha_1) + f(\alpha_2) = -c_1 c_3 + 2 c_4,
\end{aligned}$$

$$
\begin{aligned}
p_8 &= f\left(-\frac{1}{2}c_1\right) = -\frac{1}{16}c_1^4 + \frac{1}{4}c_1^2c_2 - \frac{1}{2}c_1c_3 + c_4,\\
p_9 &= f'(\alpha_1) + f'(\alpha_2) = 2c_3 + 4c_1c_2 - c_1^3,\\
p_{10} &= f'(\alpha_1)\,f'(\alpha_2) = -c_1^2c_2^2 + 4c_2^3 - c_1^3c_3 + 4c_1c_2c_3 + c_3^2,\\
p_{11} &= c_1^2 + c_3^2,\\
p_{12} &= c_2^2 - 4c_4.
\end{aligned}
$$

$\mathrm{Discr}(f)$ is the discriminant of f, α_1, α_2 are the roots of the polynomial $x^2 + c_1x + c_2$.

We will give several lemmas to prove the theorem. Clearly, by Proposition 1, if $\Delta_3(f) > 0$, then f is stable and has a positive factorization.

LEMMA 1. *Suppose $\Delta_3(f) = 0$, then f is p-irreducible if and only if $c_1 = c_3 = 0$ and $c_2^2 - 4c_4 < 0$.*

PROOF. If $\Delta_3(f) = 0$, there are only two possible cases:

(1)
$$c_1c_3 \neq 0, \qquad f(x) = \left(x^2 + \frac{c_3}{c_1}\right)\left(x^2 + c_1x + \frac{c_1c_4}{c_3}\right),$$

(2)
$$c_1 = c_3 = 0, \qquad \text{if } c_2^2 - 4c_4 \geq 0,$$
$$f(x) = \left(x^2 + \frac{c_2 - \sqrt{c_2^2 - 4c_4}}{2}\right)\left(x^2 + \frac{c_2 + \sqrt{c_2^2 - 4c_4}}{2}\right).$$

∎

It is easy to check that $\Delta_3(f) = 0$ is also a necessary condition for f to have a pair of conjugate pure imaginary roots. Now we suppose

$$\Delta_3(f) < 0. \tag{8}$$

PROPOSITION 2. *Let F be a square-free real polynomial with degree n, we have*

$$\mathrm{sign}(\mathrm{Discr}(F)) = (-1)^s, \tag{9}$$

where $2s$ is the number of nonreal roots of F.

PROOF. See [7] for the proof. ∎

LEMMA 2. *If $\Delta_3(f) < 0$ and $\mathrm{Discr}(f) > 0$, then f is p-irreducible.*

PROOF. If $\mathrm{Discr}(f) > 0$, according to Proposition 2, $s = 0, 2$. For $s = 0$, f has four real roots. Since f is a positive polynomial, all roots must be negative. Hence, when $\Delta_3(f) < 0$ and $\mathrm{Discr}(f) > 0$, f must have two pairs of nonreal roots of the forms $a \pm bI$, $-c \pm dI$, $a, b, c, d > 0$, and $f(x) = (x^2 - 2ax + a^2 + b^2)(x^2 + 2cx + c^2 + d^2)$ is p-irreducible. ∎

If $\mathrm{Discr}(f) = 0$, then f has one double real root or one double nonreal root or two double real roots. We have seen the last case is impossible when $\Delta_3(f) < 0$. If f has a double nonreal root, then $f(x) = (x^2 - 2ax + a^2 + b^2)^2$. Since f is a positive polynomial, one must have $a = 0$. It implies $\Delta_3(f) = 0$. Thus, if $\Delta_3(f) < 0$ and $\mathrm{Discr}(f) = 0$, f will have one double negative real zeros and one pair of conjugate nonreal zeros with positive real parts.

If $\mathrm{Discr}(f) < 0$, by Proposition 2, $s = 1$, i.e., f has one pair of conjugate nonreal roots and two negative real zeros.

We suppose in the following:

$$\Delta_3(f) < 0, \qquad \mathrm{Discr}(f) \leq 0. \tag{10}$$

According to the above discussion, f has two negative real roots and a pair of conjugate nonreal roots denoted as $\alpha, \beta < 0$, $a \pm bI, a, b > 0$, respectively, and

$$\begin{aligned} f(x) &= (x-\alpha)(x-\beta)\left(x^2 - 2ax + a^2 + b^2\right) \\ &= (x-\alpha)\left(x^3 + (c_1+\alpha)x^2 + \left(\alpha^2 + c_1\alpha + c_2\right)x - \frac{c_4}{\alpha}\right) \\ &= (x-\beta)\left(x^3 + (c_1+\beta)x^2 + \left(\beta^2 + c_1\beta + c_2\right)x - \frac{c_4}{\beta}\right). \end{aligned} \tag{11}$$

If $c_1 + \alpha = 0$, then $\alpha^2 + c_1\alpha + c_2 = c_2 \geq 0$, f has a positive factorization; else if $c_1 + \alpha < 0$, then $\alpha^2 + c_1\alpha + c_2 > 0$. In addition, if $\alpha^2 + c_1\alpha + c_2 = 0$, then $c_1 + \alpha \geq 0$. The same discussion is suitable to β. Now it is clear that $f(x)$ is p-irreducible if and only if $(c_1+\alpha)(\alpha^2 + c_1\alpha + c_2) < 0$ and $(c_1+\beta)(\beta^2 + c_1\beta + c_2) < 0$. So we have the following proposition.

PROPOSITION 3. *If $c_1^2 - 4c_2 \leq 0$, $f(x)$ is p-irreducible if and only if the real roots $\alpha, \beta \in (-\infty, -c_1)$; otherwise, $f(x)$ is p-irreducible if and only if $\alpha, \beta \in (-\infty, -c_1) \cup (\alpha_1, \alpha_2)$, where α_1, α_2 are defined as in Theorem 2.*

Proposition 3 enables us to determine whether f is p-irreducible by the distribution of the real roots α and β.

PROPOSITION 4. *Given a real polynomial*

$$f(x) = x^n + c_1x^{n-1} + \cdots + c_n = h\left(x^2\right) + xg\left(x^2\right). \tag{12}$$

If $h(x^2)$ does not change sign for $x > 0$ and the last Hurwitz determinant $\Delta_n \neq 0$, $n = 2m$, then the number of roots of $f(x)$ in the right half-plane is determined by the formula

$$k = 2V\left(1, \Delta_1, \Delta_3, \ldots, \Delta_{n-1}\right), \tag{13}$$

where V is the number of sign changes in the sequence $(1, \Delta_1, \Delta_3, \ldots, \Delta_{n-1})$.

The proof can be found in [6]. ∎

PROPOSITION 5. *Suppose $f(-c_1) > 0$. If $f'(-c_1) > 0$, then $\alpha, \beta \in (-\infty, -c_1)$; otherwise, $f'(-c_1) \leq 0$, we have $\alpha, \beta \in (-c_1, 0)$.*

PROOF. Letting $y = x + c_1$, one has

$$\begin{aligned} g(y) &= f\left(y - c_1\right) \\ &= y^4 + \frac{1}{2}f''\left(-c_1\right)y^2 + f\left(-c_1\right) + \frac{1}{6}f^{(3)}\left(-c_1\right)y^3 + f'\left(-c_1\right)y, \\ f\left(-c_1\right) &= c_1^2c_2 - c_1c_3 + c_4, \\ f'\left(-c_1\right) &= -c_1^3 - 2c_1c_2 + c_3, \\ f''\left(-c_1\right) &= 6c_1^2 + 2c_2 \geq 0, \\ f^{(3)}\left(-c_1\right) &= -18c_1 \leq 0, \\ \Delta_1(g) &= \frac{1}{6}f^{(3)}\left(-c_1\right) \leq 0, \\ \Delta_3(g) &= \frac{1}{12}f^{(3)}\left(-c_1\right)f''\left(-c_1\right)f'\left(-c_1\right) - \frac{1}{36}\left(f^{(3)}\left(-c_1\right)\right)^2 f\left(-c_1\right) - \left(f'\left(-c_1\right)\right)^2. \end{aligned}$$

If $f(-c_1) > 0$ and $f'(-c_1) > 0$, then $\Delta_3(g) < 0$. By Proposition 4, $g(y)$ has two zeros in the right half-plane. It implies the two real zeros α, β of $f(x)$ are in $(-\infty, -c_1)$. If $f(-c_1) > 0$ and $f'(-c_1) \leq 0$, it is easy to see from the sign changes of coefficients that g has no negative real zeros, i.e., α and β must be in $(-c_1, 0)$. ∎

LEMMA 3. *If $\Delta_3(f) < 0$, $\mathrm{Discr}(f) \leq 0$, $f(-c_1) > 0$, and $f'(-c_1) > 0$, then $f(x)$ is p-irreducible.*

PROOF. It can be directly deduced from Proposition 3 and Proposition 5. Moreover, if $c_1^2 - 4c_2 \leq 0$, $f(x)$ is p-irreducible if and only if $f(-c_1) > 0$ and $f'(-c_1) > 0$. ∎

PROPOSITION 6. *Let f be a polynomial with real coefficients, a and b be two real numbers, $a < b$, such that the values $f(a)$ and $f(b)$ are nonzero, then the number of roots of f in the open interval (a, b), counted with their multiplicities, is even or odd depending on the product $f(a)f(b)$ being positive or negative.*

The proof can be found in [7]. ∎

REMARK 1. We have assumed $f(x)$ has two real roots. Proposition 6 tells us that there is only one root of $f(x)$ in the open interval (a, b) if $f(a)f(b) < 0$; otherwise, the number of roots of $f(x)$ in (a, b) must be 0 or 2.

LEMMA 4. *If $\Delta_3(f) < 0$, $\mathrm{Discr}(f) \leq 0$, $c_1^2 - 4c_2 > 0$ and $f(-c_1) < 0$, then $f(x)$ is p-irreducible if and only if $f(\alpha_1)f(\alpha_2) < 0$.*

PROOF. If $f(-c_1) < 0$, by Remark 1, there is only one real root in the interval $(-c_1, 0)$, since $f(0) = c_4 > 0$. For this root, it is in (α_1, α_2) if and only if $f(\alpha_1)f(\alpha_2) < 0$. ∎

Now let us suppose $f(-c_1) > 0$. If $f(\alpha_1) \leq 0$, $f(x)$ has a root between $(-c_1, \alpha_1]$; if $f(\alpha_2) \leq 0$, $f(x)$ has a root between $[\alpha_2, 0)$. By Proposition 3, f has a positive factorization. We suppose in the following that

$$f(-c_1) > 0, \qquad f(\alpha_1) > 0, \qquad f(\alpha_2) > 0. \tag{14}$$

REMARK 2. The condition of $f(\alpha_1) > 0$ and $f(\alpha_2) > 0$ is equivalent to $p_6 = f(\alpha_1)f(\alpha_2) = c_4^2 + c_2c_3^2 - c_1c_3c_4 > 0$ and $p_7 = f(\alpha_1) + f(\alpha_2) = -c_1c_3 + 2c_4 > 0$.

LEMMA 5. *If $\Delta_3(f) < 0$, $\mathrm{Discr}(f) \leq 0$, $c_1^2 - 4c_2 > 0$, $f(-c_1) > 0$, $f(\alpha_1) > 0$, $f(\alpha_2) > 0$, and $f(-(1/2)c_1) \leq 0$, then $f(x)$ is p-irreducible.*

PROOF. If $f(\alpha_1) > 0$, $f(\alpha_2) > 0$, and $f(-(1/2)c_1) < 0$, then $\alpha, \beta \in (\alpha_1, -(1/2)c_1) \cup (-(1/2)c_1, \alpha_2)$; otherwise, if $f(-(1/2)c_1) = 0$ and $f(\alpha_1)f(\alpha_2) > 0$, the other real root of $f(x)$ will also belong to the interval (α_1, α_2) according to Remark 1. ∎

PROPOSITION 7. *Suppose $f(\alpha_1) > 0$. If $f'(\alpha_1) > 0$, then $\alpha, \beta \in (-\infty, \alpha_1)$; otherwise, $f'(\alpha_1) \leq 0$, we have $\alpha, \beta \in (\alpha_1, 0)$.*

The proof is similar to the proof of Proposition 5 and we only need to notice that

$$\begin{aligned} f''(\alpha_1) &= -6c_1\alpha_1 - 10c_2 = 3c_1^2 - 10c_2 + 3c_1\sqrt{(c_1^2 - 4c_2)} \geq 0, \\ f^{(3)}(\alpha_1) &= 24\alpha_1 + 6c_1 = -6c_1 - 12\sqrt{(c_1^2 - 4c_2)} \leq 0. \end{aligned} \tag{15}$$

∎

LEMMA 6. *If $\Delta_3(f) < 0$, $\mathrm{Discr}(f) \leq 0$, $c_1^2 - 4c_2 > 0$, $f(-c_1) > 0$, $f(\alpha_1) > 0$, $f(\alpha_2) > 0$, $f(-(1/2)c_1) > 0$, and $f'(-c_1) \leq 0$, then f is p-irreducible if and only if $f'(\alpha_1) \leq 0$.*

PROOF. By Proposition 5, if $f(-c_1) > 0$ and $f'(-c_1) \leq 0$, then $\alpha, \beta \in (-c_1, 0)$. Further, if $f(-(1/2)c_1) > 0$, the number of roots of f in $[-(1/2)c_1, 0]$ must be 0 or 2 since $f(-(1/2)c_1)$ $f(0) > 0$. If $\alpha, \beta > -(1/2)c_1$, then $-c_1 = \alpha + \beta + a + bI + a - bI > -c_1 + 2a$. It is contradictory to the hypothesis $a > 0$. So there are no roots in $[-(1/2)c_1, 0]$, that is $\alpha, \beta \in (-c_1, -(1/2)c_1)$. Moreover, if $f(\alpha_1) > 0$ and $f'(\alpha_1) \leq 0$, then $\alpha, \beta \in (\alpha_1, -(1/2)c_1)$, f is p-irreducible by Proposition 3; otherwise, if $f'(\alpha_1) > 0$, then $\alpha, \beta \in (-c_1, \alpha_1)$ which implies $f(x)$ has a positive factorization. ∎

The condition $f'(\alpha_1) \leq 0$ in Lemma 6 can be replaced by $p_9 = f'(\alpha_1) + f'(\alpha_2) = 2c_3 + 4c_1c_2 - c_1^3 \leq 0$ or $p_9 > 0$ and $p_{10} = f'(\alpha_1)f'(\alpha_2) = -c_1^2c_2^2 + 4c_2^3 - c_1^3c_3 + 4c_1c_2c_3 + c_3^2 \leq 0$.

By now, one can easily prove Theorem 2 and get the following facts.

REMARK 3.

(1) The conditions in Theorem 2 can be checked one by one from left to right and top to bottom.
(2) If $c_1^2 - 4c_2 \leq 0$, then the last two inequalities in Condition 3 are sufficient and necessary.
(3) The last inequality in Condition 4 is sufficient and necessary.
(4) The inequalities $p_6 > 0$, $p_7 > 0$ in Conditions 5–7 are necessary.

5. THE ALGORITHM AND EXAMPLES

The algorithm based on Theorem 2 is constructed so that it gives an efficient decision procedure and avoids unnecessary computations. We choose the computer algebra system MAPLE to implement the algorithm and treats several examples.

```
# Input: Monic polynomial f=x^4+c1*x^3+c2*x^2+c3*x+c4#
# Output: 1, if f is p-irreducible; 0, otherwise #

ispirr:=proc(f)
local c1,c2,c3,c4,p1,p2,p3,p4,p5,p6,p7,p8,p9,p10,p11,
       p12, ispirr0;
ispirr0:=0;
c1:=coeff(f,x,3);
c2:=coeff(f,x,2);
c3:=coeff(f,x,1);
c4:=coeff(f,x,0);
# check for the first condition #
p1:=c1*c2*c3-c1^2*c4-c3^2;
if p1 > 0 then
  RETURN(ispirr0);
elif p1 = 0 then
  if c1 = 0  and c3 = 0 then
    p11:=c2^2-4*c4;
    if p11 < 0 then
      ispirr0:=1;
      RETURN(ispirr0);
    fi
  fi
# check for the second condition #
else
  p2:=-27*c1^4*c4^2-80*c1*c3*c2^2*c4+18*c1^3*c3*c2*c4
      -4*c1^3*c3^3-128*c2^2*c4^2+16*c2^4*c4-4*c2^3*c3^2
      -6*c1^2*c3^2*c4-192*c1*c3*c4^2+18*c1*c3^3*c2
      +144*c2*c1^2*c4^2+c2^2*c1^2*c3^2-4*c2^3*c1^2*c4
      +144*c4*c3^2*c2+256*c4^3-27*c3^4;
  if p2 > 0 then
    ispirr0:=1;
    RETURN(ispirr0);
# check for the third condition #
  else
    p4:=c2*c1^2-c1*c3+c4;
    if p4 =0 then
      RETURN(ispirr0);
```

```
    else
      p5:=-c1^3-2*c1*c2+c3;
      if p4 > 0 and p5 > 0 then
        ispirr0:=1;
        RETURN(ispirr0);
      else
        p3:=c1^2-4*c2;
        if p3 <= 0 then
          RETURN(ispirr0);
# check for the fourth condition #
        else
          p6:=c2*c3^2-c1*c3*c4+c4^2;
          if p4 < 0  then
            if p6 < 0 then
              ispirr0:=1;
              RETURN(ispirr0);
            else
              RETURN(ispirr0);
            fi
# check for the fifth condition #
          elif p6 <= 0 then
            RETURN(ispirr0);
          else
            p7:=-c1*c3+2*c4;
            if p7 <= 0 then
              RETURN(ispirr0);
            else
              p8:=-1/16*c1^4+1/4*c2*c1^2-1/2*c1*c3+c4;
              if p8 <= 0 then
                ispirr0:=1;
                RETURN(ispirr0);
# check for the sixth condition #
              else
                p9:=2*c3+4*c1*c2-c1^3;
                if p9 <= 0 then
                  ispirr0:=1;
                  RETURN(ispirr0);
# check for the seventh condition #
                else
                  p10:=-c1^2*c2^2+4*c2^3-c1^3*c3+4*c1*c2*c3
                       +c3^2;
                  if p10 <= 0 then
                    ispirr0:=1;
                    RETURN(ispirr0);
                  fi
                fi
              fi
            fi
          fi
        fi
      fi
```

```
    fi
  fi
fi;
RETURN(ispirr0);
end:
```

Let us apply the algorithm to experimental data obtained by Imai [8] for stripped native human hemoglobin. The values obtained for overall equilibrium constants are $\beta_1 = 0.456$, $\beta_2 = 0.113$, $\beta_3 = 0.088$, $\beta_4 = 0.089$. It amounts to determining the p-irreducibility of the polynomial: $f(x) = x^4+0.989x^3+1.270x^2+5.124x+11.236$. Compute $p_1 = -30.804 < 0, p_2 = 263842.244 > 0$, so f is p-irreducible according to the inequality Condition 2 in Theorem 2. Thus, all four sites are linked and positive cooperativity occurs everywhere.

We test several more examples and the first three are given in Section 2.

EXAMPLE 1. $f_1 = x^4 + 4x^3 + 6x^2 + 19x + 30$.

$$p_1 = -385 < 0, \qquad p_2 = -6644411 < 0, \qquad p_3 = -8 < 0, \qquad p_4 = 50 > 0, \qquad p_5 = -93 < 0.$$

f_1 is not p-irreducible according to inequality Condition 3 and Remark 3.

EXAMPLE 2. $f_2 = x^4 + 12x^3 + 34x^2 + 23x + 210$.

$$\begin{array}{llll} p_1 = -21385 < 0, & p_2 = -156174091 < 0, & p_3 = 8 > 0, & p_4 = 483 > 0, \\ p_5 = -2521 < 0, & p_6 = 4126 > 0, & p_7 = 144 > 0, & p_8 = 0. \end{array}$$

f_2 is p-irreducible because it satisfies inequality Condition 5.

EXAMPLE 3. $f_3 = x^4 + 8x^3 + 14x^2 + 27x + 90$.

$$\begin{array}{lll} p_1 = -3465 < 0, & p_2 = -109166571 < 0, & p_3 = 8 > 0, \\ p_4 = 770 > 0, & p_6 = -1134 < 0. & \end{array}$$

By Condition 5 and Remark 3, f_3 has a positive factorization.

EXAMPLE 4. $f_4 = x^4 + 0.1134x^2 + 0.00642978$.

$$p_1 = 0, \qquad p_{11} = 0, \qquad p_{12} = -0.0129 < 0.$$

f_4 is p-irreducible according to inequality Condition 1.

EXAMPLE 5. $f_5 = x^4 + 4.111x^3 + 3.212x^2 + 2.001x + 9.123$.

$$\begin{array}{lll} p_1 = -131.763 < 0, & p_2 = -19142.373 < 0, & p_3 = 4.052 > 0, \\ p_4 = 55.181 > 0, & p_5 = -93.885 < 0, & p_6 = 21.043 > 0, \\ p_7 = 10.020 > 0, & p_8 = 0.730 > 0, & p_9 = -12.657 < 0. \end{array}$$

f_5 is p-irreducible since it satisfies inequality Condition 6.

EXAMPLE 6. $f_6 = x^4 + 1.342x^3 + 2.021x^2 + 2.982x + 4.214$.

$$p_1 = -8.383 < 0, \qquad p_2 = 9624.935 > 0.$$

f_6 is p-irreducible according to inequality Condition 2.

EXAMPLE 7. $f_7 = x^4 + 5x^3 + x^2 + 6x + 2$.

$$p_1 = -56 < 0, \qquad p_2 = -175800 < 0, \qquad p_3 = 21 > 0, \qquad p_4 = -3 < 0, \qquad p_6 = -20 < 0.$$

f_7 is p-irreducible according to inequality Condition 4.

EXAMPLE 8. $f_8 = x^4 + 5.1121x^3 + 6.3684x^2 + 3.0871x + 9.1450$.

$$p_1 = -148.018 < 0, \quad p_2 = -6202.283 < 0, \quad p_3 = 0.660 > 0, \quad p_4 = 159.792 > 0,$$
$$p_5 = -195.622 < 0, \quad p_6 = 0.000662 < 0, \quad p_7 = 2.508 > 0, \quad p_8 = 0.176 > 0,$$
$$p_9 = 2.800 > 0, \quad p_{10} = -27.651 < 0.$$

f_8 is p-irreducible according to inequality Condition 7.

EXAMPLE 9. $f_9 = x^4 + 5.1121x^3 + 6.3683x^2 + 3.0871x + 9.1450$.

$$p_1 = -148.020 < 0, \quad p_2 = -6217.067 < 0, \quad p_3 = 0.660 > 0,$$
$$p_4 = 159.790 > 0, \quad p_6 = -0.000291 < 0.$$

By inequality Condition 5 and Remark 3, f_9 has a positive factorization.

By comparing Examples 8 and 9, one can see that small perturbation of the coefficients will affect the p-irreducible property. By the criterion in [2], if the roots all computed to five correct digits, one will find that the roots of f_8 and f_9 all satisfy the set of inequalities that imply they are p-irreducible.

6. CONCLUDING REMARKS

We have given an approach to determine whether positive polynomials of degree 3 or 4 are p-irreducible. The inequality conditions consist of polynomials with the coefficients of the given polynomial. Previous criteria (see [1,2]) need to find all zeros of a polynomial, then check if zeros satisfy a set of inequalities combined by rational functions. It is well known that roots of a polynomial are highly sensitive to even slight variation of coefficients. So it is not stable to check by roots, especially for ill-condition polynomials. Our criterion can be computed without error. It is exact and can easily be checked. Finally, we would like to point out that for the binding polynomials of higher degrees (> 4), the criterion based on coefficients will be more useful because there is no general root-finding formulas. We hope to proceed further by some advance tools in computer algebra such as CAD (see [9]).

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