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A PROBABILISTIC MODEL FOR FITTING MWC POLYNOMIALS IN PROTEIN-LIGAND BINDING

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Given a binding polynomial in Adair form, $A(x) = 1 + \beta_1 x + \ldots + \beta_n x^n$, $\beta_i \geq 0$, a basic problem is to determine (i) a method of fitting a model polynomial to $A(x)$ and (ii) a quantitative measure of the goodness of fit. This paper presents such a method for fitting Monod-Wyman-Changeux (MWC) model polynomials when $A(x)$ is of degree three or four. The method of fitting is based on the property that the zeros of an MWC polynomial of any degree lie on a circle in the complex plane. The parameters in the MWC model are determined so that if possible this circle coincides with the circle on which lie the zeros of $A(x)$. The measure of goodness of fit is provided by a probabilistic model which gives the probability that a binding polynomial has its zeros on a circle on which lie the zeros of an MWC polynomial and if so, the probability that the juxtaposition of the two sets of zeros can occur by chance alone.

1. Introduction

Let $A(x) = 1 + \beta_1 x + \beta_2 x^2 + \ldots + \beta_n x^n$ be a given binding polynomial. A standard method of fitting one of the numerous model binding polynomials to $A(x)$ is by comparison of the coefficients of the two polynomials and to determine the parameters in the model so as to minimize some measure of deviation such as variance. While there is a direct relationship between the coefficients and the zeros of a polynomial, it is also true that small changes in the coefficients can alter the character of the zeros. That is, such changes may change the sign of the discriminant so that the resulting polynomial may have nonreal zeros rather than real zeros or vice versa. The nature and pattern of zeros of a binding polynomial is a useful classification feature of various models. For example, the zeros of MWC model polynomials are all nonreal except for a single real zero when n is odd and several forms of the Koshland-Nemethy-Filmer model have either all real or all nonreal zeros [1]. A basic requirement for the choice of a model to represent $A(x)$ is that the model polynomial be capable of producing the same nature and pattern of zeros that $A(x)$ has. Thus, we will not attempt to use the MWC model unless $A(x)$ has two nonreal zeros for $n = 3$ or four nonreal zeros for $n = 4$. Since a 'good' fit of the polynomials will result in a 'good' fit of the binding curves, we will also require that the median activities of the binding curves agree and the simplest way of insuring this is to transform the polynomials to normalized polynomials having leading coefficients one. Our program, therefore, for normalized Adair polynomials of degrees three and four, is

(i) to determine those circles in the complex plane on which lie the zeros of such polynomials,

(ii) to determine which of these circles are circles on which lie the zeros of a normalized MWC model polynomial and, if so,

(iii) to determine the probability that the juxtaposition of the zeros of the binding polynomial and the MWC polynomial can occur by chance alone.

We assume that the given Adair polynomial is in the form $N(x) = 1 + \alpha_1 x + \alpha_2 x^2 + \ldots + x^n$. The standard form of the three-parameter MWC model is

$$M(x) = \frac{1}{L+1}\left[L(1+K_T x)^n + (1+K_R x)^n\right]. \tag{1}$$

The zeros of $M(x)$ are given by

$$\frac{\omega - t}{-K_R\omega + tK_T} \tag{2}$$

where $t = L^{1/n}$ and $\omega^n = -1$ [1]. $M(x)$ has leading coefficient one if

$$LK_T^n + K_R^n = L + 1. \tag{3}$$

We also observe that $M(x)$ satisfies the functional equation

$$M(x;\ L,\ K_R,\ K_T) = M\left(x;\ \frac{1}{L},\ K_T,\ K_R\right). \tag{4}$$

2. $n = 3$

Assume $N(x) = 1 + ax + bx^2 + x^3$ has a pair of conjugate nonreal zeros, since if $N(x)$ has three real zeros, we reject the use of the MWC model. Let $\mathscr{C}$ be a circle in the complex plane (whose center is on the real axis) on which lie the zeros of an $N(x)$. Let u be the real (negative) zero of $N(x)$ and let v be the other intersection of $\mathscr{C}$ with the real axis. Refer to the appendix for the proof of Theorem 1.

2.1. Theorem 1

$\mathscr{C}$ is a circle on which lie the zeros of a polynomial of the form $N(x)$ if and only if one of the following is satisfied:

$$u < -1 < v \leq 0,\ v^2 < -1/u \tag{I}$$

$$v < -1 < u < 0,\ v^2 > -1/u \tag{II}$$

$$-1 < u,\ 1 < v,\ v \geq \frac{2-u^3}{3u^2} \tag{III}$$

$$u < -1,\ 0 < v < 1,\ v \leq \frac{3u}{2u^3 - 1} \tag{IV}$$

$$u = -1,\ v = 1 \text{ (the unit circle).} \tag{V}$$

These regions are shown in fig. 1.

We must now consider which of these circles are circles on which lie the zeros of a normalized MWC polynomial $M(x)$ of degree three. Let u and v have the same meaning as before. Refer to the appendix for the proof of Theorem 2.

2.2. Theorem 2

$\mathscr{C}$ is a circle on which lie the zeros of a normalized MWC polynomial $M(x)$ if and only if one of the following conditions is satisfied:

$$\sqrt[3]{-4} < u < -1,\ v^2 < -\frac{u^3+4}{3u} \tag{I}$$

$$-1 < u < \sqrt[3]{-1/4},\ v^2 > -\frac{3u^2}{4u^3+1} \tag{II}$$

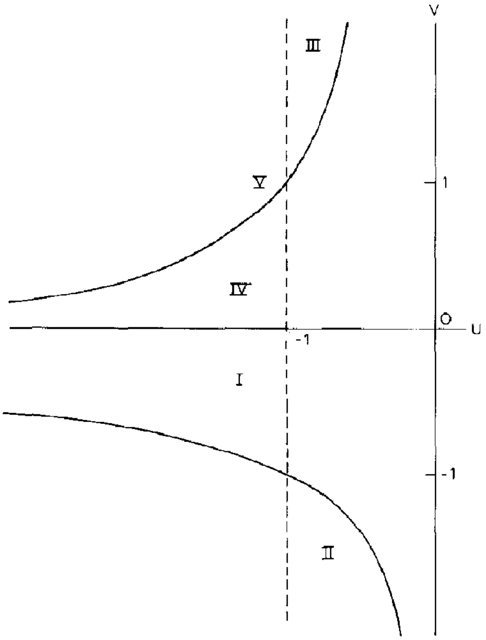

Fig. 1. Circles in the complex plane on which lie the real zero u and two nonreal zeros of $1 + ax + bx^2 + x^3$ and which also intersect the real axis at v.

$u = -1,\ v = 1.$ (III)

[These regions are shown in fig. 2.]

Let us assume for a given $N(x)$ that the circle $\mathscr{C}$ on which lie its zeros satisfies condition I or II of Theorem 2. From the proof of this theorem, it follows that there is a single value of t between zero and one which gives positive values of the parameters K_R and K_T. The reciprocal value of t interchanges the values of K_R and K_T and the same MWC polynomial results by eq. 4. From the proof of Theorem 1 it follows that there is only one location on $\mathscr{C}$ for nonreal zeros which satisfy a normalized cubic so that $N(x) = M(x)$.

Now assume for a given $N(x)$ that the circle $\mathscr{C}$ on which lie its zeros is the unit circle. Thus, $N(x)$ is symmetric so that $a = b$. A simple calculation shows that $M(x)$ is both normal and symmetric if and only if $t = K_R = 1/K_T$ so that eq. 2 becomes $(\omega - t)/(1 - t\omega)$. The real part of this expression when ω is a nonreal cube root of -1 is $(t^2 - 4t + 1)/2(t^2 - t + 1)$. If the real part of the nonreal zeros of $N(x)$ is $\cos\theta$ where $-1 < \cos\theta \leq \frac{1}{2}$, then $t = (2 - \cos\theta \pm \sqrt{3}\sin\theta)/(1 - 2\cos\theta)$, which are reciprocal and non-negative. Again there is a unique MWC polynomial such that $N(x) = M(x)$.

In summary for $n = 3$, if the circle $\mathscr{C}$ for a given $N(x)$ satisfies one of the conditions of Theorem 2, then there is a unique MWC polynomial $M(x)$ such that $N(x) = M(x)$. There is a one-to-one correspondence between ordered pairs (u, v) in the admissible regions in figs. 1 and 2 and the polynomials $N(x)$ and $M(x)$, respectively (except for $(-1,1)$ which is discussed above). Therefore, assuming a uniform distribution of $N(x)$ and $M(x)$ over these regions, the probability that a randomly chosen $N(x)$ can be expressed as an $M(x)$ is the ratio of the areas of the two admissible regions. If a circle of radius r for large r with center at the origin is drawn, then it can be shown that the area of the shaded regions in fig. 1 within the circle is $2r$ plus a term of order $\sqrt{r}$ whereas the corresponding area in fig. 2 is $2(1 - 4^{-1/3})r$ plus a term which is bounded. Therefore, the limit as $r \to \infty$ is $1 - 4^{-1/3} \cong 0.37$ which is the probability that $N(x)$ can be expressed as an $M(x)$.

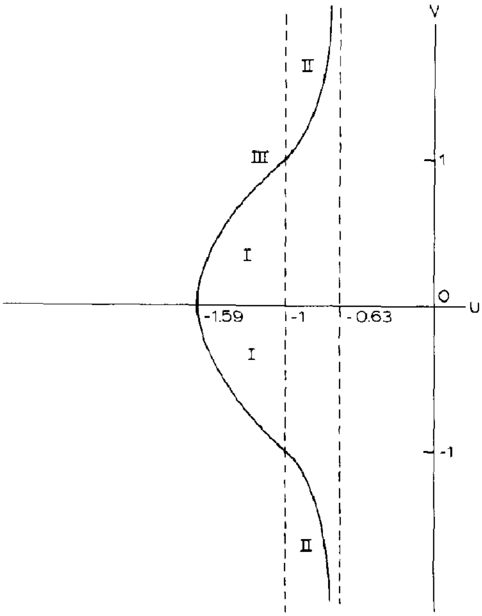

Fig. 2. Circles in the complex plane on which lie the zeros of a normalized MWC polynomial of degree three having real zero u and which also intersect the real axis at v.

3. $n = 4$

Assume $N(x) = 1 + ax + bx^2 + cx^3 + x^4$ has two pairs of conjugate nonreal zeros since, as before, if $N(x)$ has real zeros, we reject the use of the MWC model. The perpendicular bisector of the segment connecting the two zeros in the upper half-plane intersects the real axis at the center of the circle $\mathscr{C}$ on which lie the zeros of $N(x)$. Let the coordinates of the points of intersection of $\mathscr{C}$ and the real axis be u and v where $u < v$. Refer to the appendix for a proof of Theorem 3.

3.1. *Theorem 3*

$\mathscr{C}$ is a circle on which lie the zeros of a polynomial of the form $N(x)$ if and only if one of the following conditions is satisfied.

$u < -1 < v \leq 0$ (I)

$-1 < u < 0,\ v > 1,\ uv + 1 < 0$ (II)

$u < -1,\ 0 < v < 1,\ uv + 1 > 0$ (III)

$u = -1,\ v = 1.$ (IV)

These regions are shown in fig. 3.

We must now determine which of these circles are circles on which lie the zeros of a normalized MWC polynomial $M(x)$ of degree four. Refer to the appendix for the proof of Theorem 4.

3.2. Theorem 4

$\mathscr{C}$ is a circle on which lie the zeros of a normalized MWC polynomial $M(x)$ if and only if one of the following conditions is satisfied:

$u < -1 < v \leq 0$ and (I)

$u^4 + 6u^2v^2 + v^4 < 8$ or (A)

$u^4 + 6u^2v^2 + v^4 < 8u^4v^4$ (B)

$-1 < u < 0,\ v > 1$, and $u^4 + 6u^2v^2 + v^4 < 8u^4v^4$ (II)

$u < -1,\ 0 < v < 1$, and $u^4 + 6u^2v^2 + v^2 < 8$ (III)

$u = -1,\ v = 1.$ (IV).

These regions are shown in fig. 4.

We now define a sample space to be the set of all circles $\mathscr{C}$ which satisfy the conditions of Theorem 3 and let M be the subset of circles $\mathscr{C}$ which satisfy the conditions of Theorem 4. If a circle with large radius r is drawn with center at the origin, then it can be shown that the area of the regions in fig. 3 is $2r$ plus a bounded term and that the area of the regions in fig. 4 is $2(1 - 8^{-1/4})r$ plus a bounded term. Thus assuming a uniform distribution of circles in these regions, the probability that a random circle in the sample space is in the set M is $1 - 8^{-1/4} \cong 0.41$.

From the proofs of Theorems 3 and 4, it is clear that an infinite number of polynomials $N(x)$ have zeros which lie on a circle $\mathscr{C}$ which satisfies the conditions of Theorem 4 whereas, except for the unit circle, there is only one MWC polynomial $\overline{M}(x)$ whose zeros lie on $\mathscr{C}$. If a given polynomial $\overline{N}(x)$ has such a circle, then $\overline{M}(x)$ is taken as the

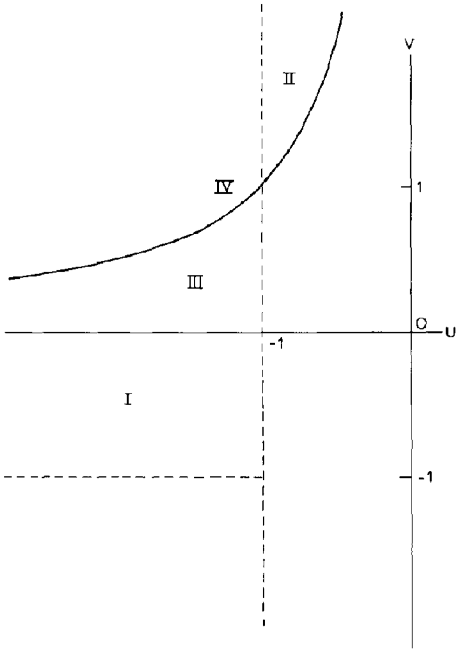

Fig. 3. Circles in the complex plane on which lie four nonreal zeros of $1 + ax + bx^2 + cx^3 + x^4$ and which intersect the real axis at u and v, $u < v$.

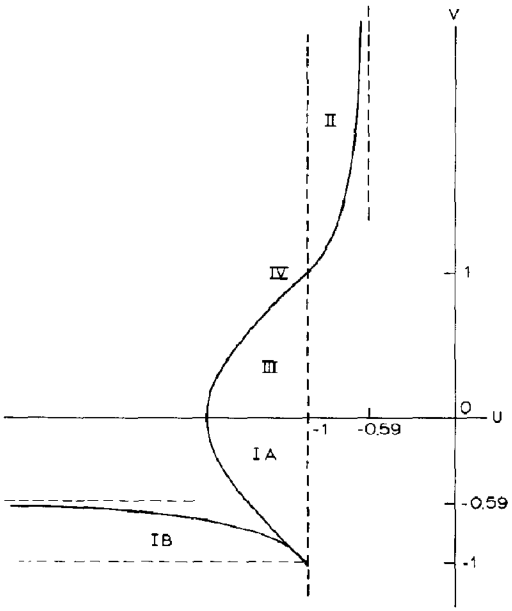

Fig. 4. Circles in the complex plane on which lie the four nonreal zeros of a normalized MWC polynomial of degree four and which intersect the real axis at u and v, $u < v$.

MWC polynomial of best fit. The goodness of this fit is measured by the probability that the juxtaposition of the two sets of zeros on $\mathscr{C}$ can occur by chance alone. A sample space is defined to be the set of all polynomials $N(x)$ whose circles coincide with the circle $\mathscr{C}$ of $\bar{N}(x)$. Each such polynomial can be identified uniquely by an ordered pair of real numbers (θ_1,θ_2), $0 < \theta_2 \le \theta_1 < \pi$ where θ_1 and θ_2 are the radian measures of the angles the two zeros in the upper half-plane form with the center of $\mathscr{C}$ and the positive direction of the real axis. Let $\mathscr{C}$ have center $(d,0)$ and radius r. The zeros of any polynomial $N(x)$ in the sample space can be written as $(r \cos \theta_j + d) \pm ir \sin \theta_j$, $j = 1,2$. From the fact that $N(x)$ must have non-negative coefficients and leading coefficient one we deduce Theorem 5.

3.3. Theorem 5

A polynomial $N(x)$ belongs to the sample space if and only if all the following conditions are satisfied:

$$r(\cos \theta_1 + \cos \theta_2) + 2d \le 0$$

$$2r^2 \cos \theta_1 \cos \theta_2 + 3dr(\cos \theta_1 + \cos \theta_2) + 3d^2 + r^2 \ge 0$$

$$4dr^2 \cos \theta_1 \cos \theta_2 + (r^3 + 2d^2 r)(\cos \theta_1 + \cos \theta_2) + 2d^2 + 2dr^2 \le 0$$

$$\cos \theta_2 = \frac{1 - (d^2 + r^2)^2 - 2dr(d^2 + r^2) \cos \theta_1}{2dr(d^2 + r^2) + 4d^2 r^2 \cos \theta_1}.$$

The first three conditions define a region R in the θ_1,θ_2 plane in which each point corresponds to

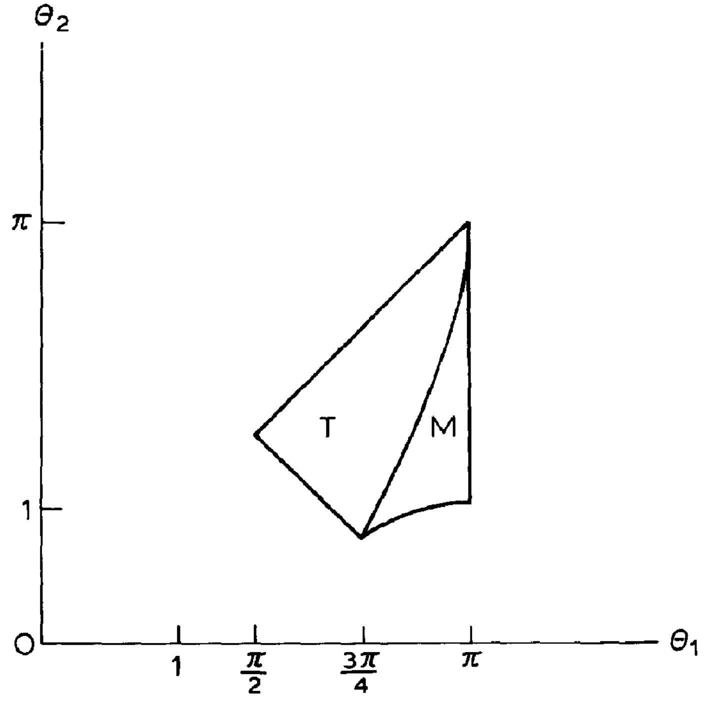

Fig. 5. T represents the region of arguments θ_1 and θ_2, $\theta_2 \le \theta_1$ of zeros of polynomials $1 + ax + bx^2 + cx^3 + x^4$ which lie on the unit circle. The path M represents pairs obtainable from MWC polynomials.

an Adair polynomial whose zeros lie on $\mathscr{C}$ and the last condition defines a path P corresponding to normalized polynomials. We now have two points on the path P, one $\bar{N}$, corresponding to $\bar{N}(x)$ and the other, $\bar{M}$, corresponding to $\bar{M}(x)$. If the length of P in R is l and the length of the path between $\bar{N}$ and $\bar{M}$ is ϵ, then the probability that a random polynomial in the sample space has its corresponding point (θ_1,θ_2) within a path length of ϵ from $\bar{M}$ is $2\epsilon/l$. This probability can be multiplied by 0.41 to give the probability that $\bar{N}(x)$ is represented as well as it is by $\bar{M}(x)$ by chance alone. A small probability can then be taken as evidence that the MWC model is applicable.

A different situation occurs if $\mathscr{C}$ is the unit circle. In this case the conditions of Theorem 5 become $\cos\theta_1 + \cos\theta_2 \le 0$ and $2\cos\theta_1\cos\theta_2 + 1 \ge 0$ which define a region T shown in fig. 5. Any point in T corresponds to a normalized polynomial since the product of its zeros is one. $M(x)$ has its zeros on the unit circle if $K_R = 1/t$ and $K_T = t$ where $t = L^{1/4}$. $\theta_1 = \theta_1(t)$ and $\theta_2 = \theta_2(t)$ can then be obtained from eq. 2 and these parametric equations give a path M in T which is also shown in fig. 5. The probability that a point (θ_1,θ_2) in T is within ϵ of a point on M is the area between curves parallel to M at a distance ϵ divided by the area of T. By numerical integration to the nearest tenth, the length of M is 2.5 and the area of T is 2.0 so that an approximation to this probability is $2.5(2\epsilon)/2 = 2.5\epsilon$.

Appendix

A1. Proof of Theorem 1

Since $N(x)$ is normalized, the product of its zeros is -1. If the absolute value of the nonreal zeros is r, then $r^2u = -1$ or $r^2 = -1/u$ so that the unit circle must intersect $\mathscr{C}$.

(I) If $v^2 < -1/u$, then there is a pair of points on $\mathscr{C}$ having absolute value $1/\sqrt{-u}$.

(II) If $v^2 > -1/u$, then there is a pair of points on $\mathscr{C}$ having absolute value $1/\sqrt{-u}$.

(III) $r > 1$ so $v^2 > -1/u$ is necessary. The nonreal zeros are located at the points of intersection of $\mathscr{C}$ and the circle whose equation is $x^2 + y^2 = -1/u$ and these are

$$x = \frac{u^2v - 1}{u(u+v)},\quad y^2 = -\frac{(u^3+1)(u^2v+1)}{u^2(u+v)^2}.$$

But a cubic polynomial with these zeros has nonnegative coefficients if and only if [2]

$$v \ge \frac{2-u^3}{3u^2} \text{ and } v \ge \frac{3u}{2u^3-1}.$$

But for $-1 < u < 0$, $v \ge (2-u^3)/3u^2$ implies the other two conditions.

(IV) $r < 1$ so $v^2 < -1/u$ is necessary. In addition the inequalities in item III with signs reversed must be satisfied and for $u < -1$, $v \ge 3u/(2u^3 - 1)$ implies the other two conditions.

(V) Nonreal zeros z may appear at any pair of conjugate points on the units circle provided $\pi > |\arg z| \ge \pi/3$.

A2. Proof of Theorem 2

Considering eq. 2 as a bilinear transformation of the complex plane, it follows that $u = -(1+t)/(K_R + tK_T)$ and $v = (1-t)/(-K_R + tK_T)$. We then have for $v \ne 0$

$$K_T = -\frac{(v-u)+(v+u)t}{2uvt},$$

$$K_R = -\frac{(v+u)+(v-u)t}{2uv} \tag{A1}$$

which, when substituted into eq. 3, gives the condition for normality

$$F(t) = [(v-u)+(v+u)t]^3 + [(v+u)+(v-u)]^3 + 8u^3v^3(t^3+1) = 0.$$

$F(t)$ is a symmetric cubic and $1 + ax + ax^2 + x^3 = (1+x)[1 + (a-1)x + x^2]$ has two positive real zeros if and only if $a \le -1$ or $(1+u^3)/(4u^3v^2 + 3u^2 + v^2) \le 0$ in the case of $F(t)$. This is satisfied if $u = -1$ or if

$$u < -1 \text{ and } v^2 < -\frac{3u^2}{4u^3+1} < 1 \text{ or}$$

$$-1 < u \text{ and } v^2 > -\frac{3u^2}{4u^3+1} > 1.$$

If one of these conditions is satisfied, then it is still necessary that eq. A1 gives positive values of K_R and K_T. When this occurs, the values of t are reciprocal and the two sets of values given by eq. A1 are reversed so that by eq. 4 a unique MWC polynomial results.

(I) $u < -1$.

If $-1 < v < 0$, then $v + u < 0$ and $v - u > 0$ and eq. A1 will give positive values provided

$$\frac{u-v}{u+v} < t < \frac{u+v}{u-v}. \tag{A2}$$

$F(t)$ has single zero between 0 and 1 and it will satisfy eq. A2 provided $F(0)$ and $F(u - v/u + v)$ have the same sign. Examination of these expressions shows that this is true provided

$$v^2 < -\frac{u^3+4}{3u}$$

so that $-\sqrt[3]{4} < u < -1$ is necessary. A similar argument can be employed if $0 < v < 1$. If $v = 0$, then $t = 1$ and it can be shown that K_R and K_T are positive in the same interval.

(II) $-1 < u$.

If $v < -1$, then $v - u < 0$ and $v + u < 0$ so that eq. A1 will give positive values. A similar argument holds for $v > 1$.

(III) The zeros of $M(x)$ are on the unit circle if $t = K_R = 1/K_T$.

A3. Proof of Theorem 3

Again the product of the zeros of $N(x)$ is one so that the absolute values of the conjugate pairs must be reciprocal and the unit circle must intersect $\mathscr{C}$.

(I) If $u < -1 < v \le 0$, then $\mathscr{C}$ lies entirely in the left half-plane and intersects the unit circle.

(II) If $-1 < u < 0$ and $v > 1$, then the zeros of an $N(x)$ will lie on $\mathscr{C}$ if its points of intersection with the unit circle have negative abscissae. This value is $(uv + 1)/(u + v)$ which is negative if $uv + 1 < 0$. We must now show that if this value is positive, $\mathscr{C}$ cannot be a circle on which lie the zeros of an $N(x)$. To do this it is necessary to use the following lemma.

Lemma

Let r and s be positive numbers and let R be the region of the plane defined by $|y| < sx/r$ if $0 < x \le r$ and the half-plane $x > r$. If (m,n) is any point in R, then a quartic polynomial having zeros $-r \pm si$, $m \pm ni$ has coefficients of both signs [2].

Assume $uv + 1 > 0$ and let r and s be positive numbers such that $P(-r,s)$ lies on $\mathscr{C}$. We now determine $n > 0$ such that $Q(r,n)$ lies on $\mathscr{C}$. A calculation of the distances shows that $\overline{OP} \cdot \overline{OQ} < 1$. Thus if there is a point Q' on $\mathscr{C}$ such that $\overline{OP} \cdot \overline{OQ'} = 1$, it lies in region R of the lemma so that the corresponding polynomial cannot have non-negative coefficients.

(III) If $u < -1$ and $0 < v < 1$, then, as before, zeros of an $N(x)$ will lie on $\mathscr{C}$ provided $uv + 1 > 0$. Let $P(-r,s)$ lie on $\mathscr{C}$ and let P' be (r,s). Let S be the point of intersection of $\mathscr{C}$ and the ray OP′. Calculation shows that $\overline{OP} \cdot \overline{OS} > 1$ so that if there is a point S' on $\mathscr{C}$ such that $\overline{OP} \cdot \overline{OS'} = 1$, S' must lie in region R.

(IV) Region T in fig. 5 gives polynomials whose zeros lie on the unit circle.

A4. Proof of Theorem 4

The proof follows the same format as that of Theorem 2. The bilinear transformation maps the unit circle onto $\mathscr{C}$ and u and v are the images of ± 1 in some order. Therefore we designate $q = -(1 + t)/(K_R + tK_T)$ and $p = (1 - t)/(-K_R + tK_T)$ which give the equations (A1) in terms of p and q. The polynomial corresponding to $F(t)$ in the condition for normality is $G(t) = a_0 + a_1 t + a_2 t^2 + a_1 t^3 + a_0 t^4$ where $a_0 = p^4 + 6p^2q^2 + q^4 - 8p^4q^4$, $a_1 = 4(p^4 - q^4)$ and $a_2 = 6(p^2 - q^2)^2$. The condition that $G(t)$ have exactly two positive zeros is found in [3] which in this case is that $1 - q^4$ and a_0 have opposite signs. It can be shown that $G(t)$ cannot have four positive zeros so that if an MWC polynomial exists, it is unique. It is convenient to graph this conditions in p^2, q^2 space and we find that $q^2 > 8^{-1/2}$.

(I) $p < 0$, $q < 0$.

(A) If $q < -1 < p < 0$, then K_R and K_T are positive if the zeros of $G(t)$ are greater than $(q - p)/(q + p)$. The sign of $G[(q - p)/(q + p)]$ is the same as that of $8 - p^4 - 6p^2q^2 - q^4$ and since $a_0 > 0$, the conclusion follows.

(B) If $p < -1 < q < 0$, then $p + q < 0$ and $p - q < 0$ so that K_R and K_T are positive.

(II) Since q must be negative, we have $-1 < q < 0$, $p > 1$, $p + q > 0$ and $p - q > 0$ so that K_R and K_T are positive.

(III) If $q < -1$ and $0 < p < 1$, then K_R and K_T will be positive if the zeros of $G(t)$ are greater than $(q+p)/(q-p)$. But $G(t)$ is symmetric so that $t^4 G(1/t) = G(t)$ and the same argument as in item 1A applies.

(IV) The zeros of $M(x)$ are on the unit circle if $t = K_R = 1/K_T$.

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