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An extension of Chou's graphic rules for deriving enzyme kinetic equations to systems involving parallel reaction pathways

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An extension has been made to the Chou's graphic rules in order to cover those enzyme-catalysed reaction systems in which there are two or more parallel reaction routes between any two enzyme species.

Graphical methods have been used more and more widely in modern biology [e.g. see King & Altman (1956), Wong & Hanes (1962), Volkenstein & Goldstein (1966), Cha (1968), Fromm (1970), Orsi (1972), Seshagiri (1972), Ainsworth (1974), Wong (1975), Indge & Childs (1976), Volkenstein (1977), Hill (1977), Cornish-Bowden (1977), Chou *et al.* (1979), Whitehead (1979), Chou & Liu (1981), Jackson *et al.*, (1981), Goldstein (1983) and others]. The advantage of doing so lies not only in the visual intuitive aid provided to qualitative analysis and discussion, but also in the mathematical efficacy, i.e. in greatly simplifying calculations and hence helping to obtain the desired quantitative results. In particular, certain comparatively recent advances in this field due to Chou (1980, 1981*b*) made possible the analytic solutions for some very complicated enzyme-catalysed mechanisms (Chou *et al.*, 1981; Chou, 1981*a*) that had previously been found formidable (Ainsworth, 1977) when the general derivation procedures were followed. An additional particular merit of Chou's (1980, 1983) rules is that, compared with the other graphical methods in enzyme kinetics, a set of self-checking formulae are included by which any omissions in subgraphs and terms during calculations can be avoided. This is very useful when one is dealing with complex systems (Chou *et al.*, 1981; Chou, 1981*a*; Jackson *et al.*, 1981).

However, in enzyme kinetics we are often confronted with mechanisms in which two or more parallel reactions (Cornish-Bowden, 1976) exist between the same pair of enzyme species (see Examples 1 and 2 below). For such a system with parallel reactions interconverting any two enzyme species, Volkenstein & Goldstein (1966) put forward the condensation principle to simplify calculation, which can be stated as follows. If there are two or more steps interconverting the same pair of enzyme species, these steps can be condensed into one by adding the rate constants for the parallel reactions when the King & Altman (1956) graphical method is used. Can such a condensation principle also be incorporated into the Chou's (1983) rules, and, if so, how? The present paper is devoted to a solution of this problem.

Extension of Chou's Rules

In enzyme kinetics the concentrations of enzyme species and the rate of formation for product P are two kinds of basic quantities that often need to be calculated; they can be formulated as follows (Chou, 1983):

$$[E_m] = \frac{N_m}{\sum_{i=1}^{n} N_i} e_0 \quad (m = 1, 2, \ldots, n) \qquad (1)$$

$$v = \frac{d[P]}{dt} = \frac{\vec{P} - \overleftarrow{P}}{\sum_{i=1}^{n} N_i} e_0 \qquad (2)$$

where $[E_m]$ is the concentration of the mth enzyme species E_m, e_0 is the total enzyme concentration, v is the rate of formation for product P, and N_i ($i = 1, 2, \ldots, n$) and $\vec{P}$ and $\overleftarrow{P}$ are explicitly defined below. On the basis of a series of previous papers (Chou *et al.*, 1979, 1980, 1981; Chou & Forsén, 1980, 1981; Chou, 1980, 1981*a*,*b*), two elegant rules were summarized by Chou (1983) for the calculation of the quantities in eqns. (1) and (2) respectively. Below, let us see how these two rules (Chou, 1983) should be extended in order to be able to cover the enzyme-catalysed systems in which there are two

or more parallel reaction routes between any two enzyme species.

Before going ahead, let us recall that in all graphical calculation methods the first thing is always to draw a reaction graph by which to represent the enzyme system concerned. In such a graph, various enzyme species are represented by different points, and the interconversion between any two enzyme species by an arc that is with an arrow and weighted by a rate constant to indicate the conversion direction and rate respectively (see, e.g., Figs. 1 and 5). The reaction graph thus depicted is symbolized as $\mathscr{D}$, and on the basis of this Chou's (1983) Rule 1 and Rule 2 can be reformulated as follows (in order to make it clear what modifications have been made here, below Chou's original rules are printed in normal type with our alterations being given in *italics*).

Chou's Rule 1 (for calculating N_i)

(1) *In the reaction graph $\mathscr{D}$, if there are two or more arcs linking a same pair of enzyme species and having the same conversion direction, these arcs can be condensed into one by adding their rate constants together. The graph obtained by such a condensation step is denoted by $\mathscr{D}_c$ (e.g. see Fig. 2).*

(2) To each point in $\mathscr{D}_c$ add a loop with a weight equal to the sum of the weights of the arcs departing from that point. The graph thus obtained is denoted by $\mathscr{D}^\dagger$. For instance, the $\mathscr{D}_c$ in Fig. 2 is accordingly transformed into $\mathscr{D}^\dagger$ of Fig. 3.

(3) Select any point in $\mathscr{D}^\dagger$, e.g. E_s, as a starting reference point. Then for any specified point E_m, find all subgraphs each of which possesses a path from E_s to E_m, and all cycles and loops that intersect with neither each other nor the path. Then for each such subgraph, take the product of all its weights and multiply with a sign factor given by

$$(-1)^{C_y} \tag{3}$$

where C_y is the number of the cycles (not including loops) in the corresponding subgraph. Taking a sum of all these results, we immediately obtain N_m of eqn. (1). Note that the result thus obtained for N_m is always the same irrespective of which point is chosen as the starting reference point. *But when the starting point is chosen as the specified point itself, i.e. $E_s = E_m$, the path from E_s to E_m will degenerate into a point, whose weight in this case should be assigned as 1 for calculation (e.g. see eqns. 10 and 11).* By following such a method, all N_i ($i = 1, 2, \ldots, n$) in eqn. (1) can easily be obtained, so that the concentrations of all the enzyme species can be found as well.

(4) In order to avoid losing any subgraph during calculations, the following method can serve to make a check. According to the transformed graph $\mathscr{D}^\dagger$, construct a matrix $\mathbf{A} = [a_{ij}]$, in which:

$$a_{ij} = \begin{cases} 1, \text{ if there is an arc from } E_i \text{ to } E_j \text{ in } \mathscr{D}^\dagger \\ 0, \text{ if there is no arc from } E_i \text{ to } E_j \text{ in } \mathscr{D}^\dagger \end{cases} \tag{4}$$

Then, when E_s is taken as the starting point to calculate N_m, the number of subgraphs to be counted must be:

$$n^{s\to m} = \text{per } \mathbf{A}_{m,s} \tag{5}$$

where $\mathbf{A}_{m,s}$ is the submatrix obtained by removing the mth row and sth column from the matrix $\mathbf{A}$. And per $\mathbf{A}_{m,s}$ denotes the sum of all terms obtained by expanding the determinant of $\mathbf{A}_{m,s}$ but taking all the signs of expansion as plus (e.g. see eqn. 21). Since the elements of $\mathbf{A}$ are either 1 or 0 (see eqn. 4), the value of per $\mathbf{A}_{m,s}$ as defined above is very easy to calculate.

Furthermore, we can also predict the number of terms in N_m by the following method. *According to the reaction graph $\mathscr{D}$, construct a matrix $\boldsymbol{B} = [b_{ij}]$, in which:*

$$b_{ij} = \textit{the number of arcs from } E_i \textit{ to } E_j \textit{ in } \mathscr{D} \tag{6}$$

On the basis of $\mathbf{B}$, reconstruct a matrix $\mathbf{C} = [c_{ij}]$, in which:

$$c_{ij} = \begin{cases} \sum_{t=1}^{n} b_{ij}, & \text{if } i = j \\ \\ -b_{ij}, & \text{if } i \neq j \end{cases} \tag{7}$$

Then the number of terms in N_m must be equal to:

$$P_m = \det \mathbf{C}_{m,m} \tag{8}$$

where $\mathbf{C}_{m,m}$ is the submatrix obtained by removing the mth row and mth column from $\mathbf{C}$, and the symbol det means taking the determinant value for the matrix next to it.

The theoretical justification of the above extension for Chou's Rule 1 will become obviously after combining Appendix B of the previous paper by Chou *et al.* (1979) and Appendix 4 by Chou & Forsén (1981).

Chou's Rule 2 (for calculating $\vec{P}$ and $\overleftarrow{P}$)

(1) Define two types of cycles as follows: (*a*) product-releasing cycle, when a circuit is made along it the net number of the released P is greater than zero; (*b*) product-combining cycle, when a circuit is made along it, the net number of the combined P is greater than zero.

Both these two types of cycles play a key role in calculating the rate of formation for the product P,

and hence may be termed as the master cycle. *However, during calculation all the master cycles should be found directly from the original reaction graph $\mathscr{D}$ rather than from the condensed graph $\mathscr{D}_c$ or its transformed graph $\mathscr{D}^\dagger$, except when $\mathscr{D}$ and $\mathscr{D}_c$ are identical (i.e. there is no parallel reaction between any pair of enzyme species; only in this case can both graph $\mathscr{D}$ and graph $\mathscr{D}^\dagger$ be used to find the master cycles).*

(2) Find all subgraphs each of which possesses one product-releasing cycle (or product-combining cycle), and all the other cycles and loops. *The latter, however, are found from the transformed graph $\mathscr{D}^\dagger$, but they must not intersect with each other nor with the master cycle even when the graphs $\mathscr{D}$ and $\mathscr{D}^\dagger$ are overlapped.* Then for each of these subgraphs take the product of all its weights and multiply with a factor given by:

$$(-1)^{C_y^*}g \tag{9}$$

where C_y^* is the number of the cycles (not including the master cycle and loops) in the respective subgraph, and g is the number of P released (or combined) when a circuit of the product-releasing cycle (or the product-combining cycle) is made. Taking a sum of these results, we immediately obtain $\overrightarrow{P}$ (or $\overleftarrow{P}$).

The above extension for Chou's Rule 2 can be easily derived from the Appendix in the previous paper by Chou (1981*b*).

Examples

Michaelis–Menten (1913) mechanism

Although the advantage of applying Chou's rules to a simple mechanism such as this might be not very remarkable, yet it is very easy to see how the extended Chou's rules work through such an illustration. The reaction graph $\mathscr{D}$ for the following Michaelis–Menten mechanism:

$$E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} E + P$$

is depicted in Fig. 1. The corresponding condensed graph $\mathscr{D}_c$ and transformed graph $\mathscr{D}^\dagger$ are shown in Figs. 2 and 3 respectively [cf. steps (1) and (2) of the extended Chou's Rule 1]. Then, in accordance with step (3) of that rule, we immediately have:

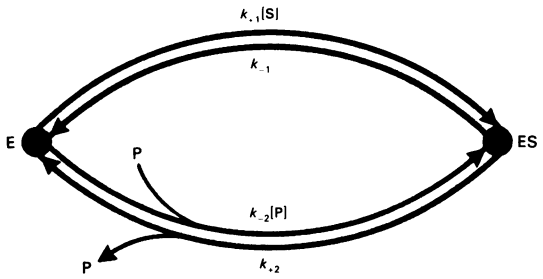


Fig. 1. *Reaction graph $\mathscr{D}$ for the Michaelis–Menten mechanism*

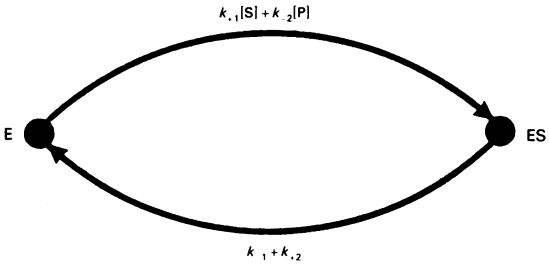


Fig. 2. *Condensed graph $\mathscr{D}_c$ obtained from Fig. 1 in accordance with step (1) of the extended Chou's Rule 1*

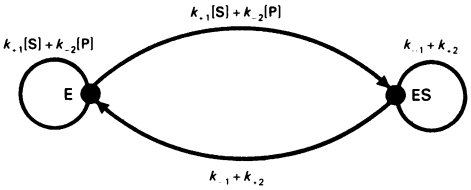
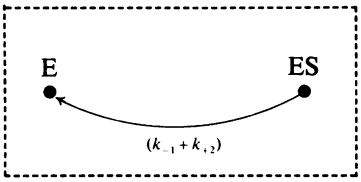
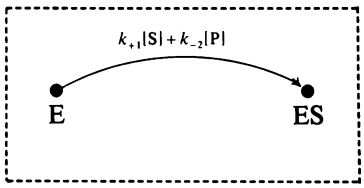


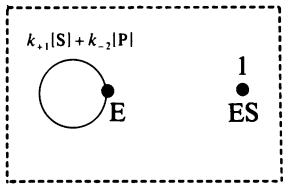
Fig. 3. *Transformed graph $\mathscr{D}^\dagger$ obtained from Fig. 2 in accordance with step (2) of the extended Chou's Rule 1*

From the above we see that the results of N_E and N_{ES} are independent of the choice of the starting reference point. However, generally there will be fewer subgraphs to count if the starting point is chosen farther from the specified point, the one corresponding to the enzyme species of interest.

$$N_E = (-1)^0$$  $$= (-1)^0$$  $$= k_{-1} + k_{+2}$$

(if taking ES as the starting reference point) (if taking E itself as the starting reference point) (10)

$N_{ES} = (-1)^0$ 

$= (-1)^0$ 

$= k_{+1}[S]+k_{-2}[P]$

(if taking E as the starting reference point) (if taking ES itself as the starting reference point) (11)

Substitution of eqns. (10) and (11) into eqn. (1) will give:

$$[E] = \frac{(k_{-1}+k_{+2})}{k_{-1}+k_{+2}+k_{+1}[S]+k_{-2}[P]}\, e_0 \quad (12)$$

$$[ES] = \frac{k_{+1}[S]+k_{-2}[P]}{k_{-1}+k_{+2}+k_{+1}[S]+k_{-2}[P]}\, e_0 \quad (13)$$

Now let us use step (4) of the extended Chou's Rule 1 to make a check. For $\mathscr{D}^{\dagger}$ in Fig. 3, in accordance with eqn. (4) we have:

$$\mathbf{A} = \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}$$

Then it follows from eqn. (5) that:

$$n^{E\to ES} = n^{E\to E} = n^{ES\to E} = n^{ES\to ES} = \text{per}\,[1] = 1$$

which indicates no subgraph was missed during calculating N_E and N_{ES}. Furthermore, for $\mathscr{D}$ of Fig. 1, in accordance with eqns. (6) and (7) we have:

$$\mathbf{B} = \begin{bmatrix} 0 & 2 \\ 2 & 0 \end{bmatrix} \quad \text{and} \quad \mathbf{C} = \begin{bmatrix} 2 & -2 \\ -2 & 2 \end{bmatrix}$$

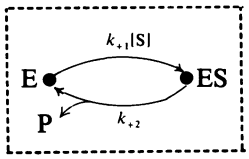
respectively. Thus it follows from eqn. (8) that:

$$P_E = P_{ES} = \det\,[2] = 2$$

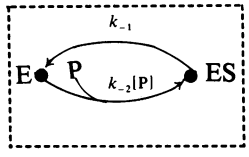
which means no term was lost in eqns. (10) and (11).

The above checking procedures becomes very useful when the mechanism considered becomes complicated (Chou *et al.*, 1981; Jackson *et al.*, 1981).

On the other hand, according to the extended Chou's Rule 2, it follows that:

$\vec{P} = (-1)^0 \cdot 1$ 

$= k_{+1}k_{+2}[S]$ (14)

$\overleftarrow{P} = (-1)^0 \cdot 1$ 

$= k_{-1}k_{-2}[P]$ (15)

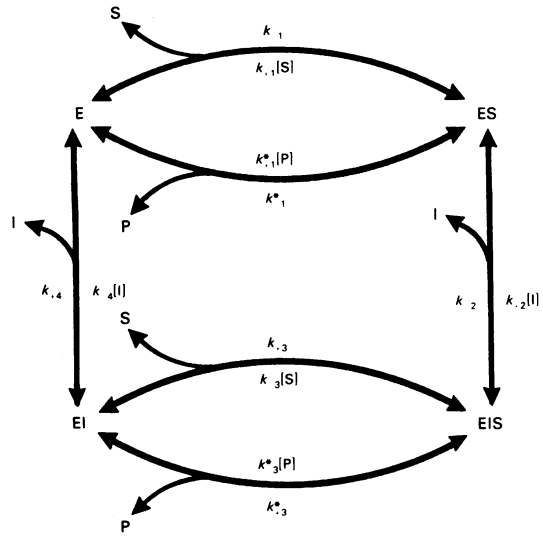


Fig. 4. *Botts–Morales mechanism.*

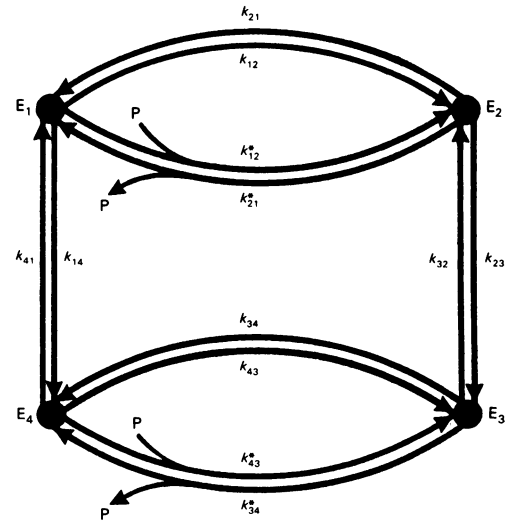


Fig. 5. *Reaction graph $\mathscr{D}$ for the Botts–Morales mechanism*

(Note that in this example all the loops and cycles found in $\mathscr{D}^{\dagger}$ of Fig. 3 must intersect with the above two master cycles when Fig. 3 and Fig. 1 are overlapped, and therefore make no contribution to $\vec{P}$ and $\overleftarrow{P}$.) Substituting eqns. (14) and (15) as well as eqns. (10) and (11) into eqn. (2), we immediately obtain:

$$v = \frac{k_{+1}k_{+2}[S] - k_{-1}k_{-2}[P]}{k_{-1} + k_{+2} + k_{+1}[S] + k_{-2}[P]} e_0 \qquad (16)$$

which is none other than the rate of formation for the product P in the Michaelis–Menten enzyme-catalysed system.

Botts–Morales (1953) mechanism

A schematic expression for the Botts–Morales mechanism is shown in Fig. 4. For simplicity, let $E_1 = E$, $E_2 = ES$, $E_3 = EIS$ and $E_4 = EI$, and $k_{12} = k_{+1}[S]$, $k_{21} = k_{-1}$, $k^*_{12} = k^*_{+1}[P]$, $k^*_{21} = k^*_{-1}$, $k_{23} = k_{+2}[I]$, $k_{32} = k_{-2}$, $k_{34} = k_{+3}$, $k_{43} = k_{-3}[S]$, $k^*_{34} = k^*_{+3}$, $k^*_{43} = k_{-3}[P]$, $k_{41} = k_{+4}$ and $k_{14} = k_{-4}[I]$; then the reaction graph for the Botts–Morales mechanism can be depicted as in Fig. 5. By following steps (1) and (2) of the extended Chou's Rule 1, Fig. 5 can be transformed into $\mathscr{D}^{\dagger}$ of Fig. 6. Thus, in accordance with step (3) of that rule, we obtain:

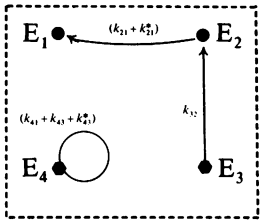
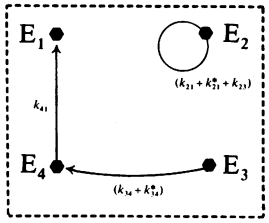
Substituting eqns. (17)–(20) into eqn. (1), we immediately obtain the concentrations for the enzyme species $E = E_1$, $ES = E_2$, $EIS = E_3$ and $EI = E_4$.

In addition, by following the same checking procedures as illustrated in the last example, it follows [cf. eqns. (4), (6) and (7) and Figs. 5 and 6] that:

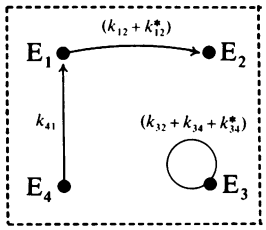
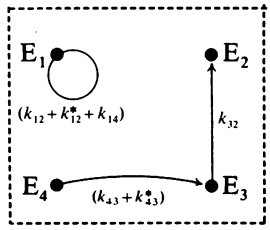
$$\mathbf{A} = \begin{bmatrix} 1 & 1 & 0 & 1 \\ 1 & 1 & 1 & 0 \\ 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 1 \end{bmatrix}$$

$$\mathbf{B} = \begin{bmatrix} 0 & 2 & 0 & 1 \\ 2 & 0 & 1 & 0 \\ 0 & 1 & 0 & 2 \\ 1 & 0 & 2 & 0 \end{bmatrix}$$

$$\mathbf{C} = \begin{bmatrix} 3 & -2 & 0 & -1 \\ -2 & 3 & -1 & 0 \\ 0 & -1 & 3 & -2 \\ -1 & 0 & -2 & 3 \end{bmatrix}$$

$N_1 = (-1)^0$  $+ (-1)^0$  $= k_{32}(k_{21} + k^*_{21})(k_{41} + k_{43} + k^*_{43}) + k_{41}(k_{34} + k^*_{34})(k_{21} + k^*_{21} + k_{23})$

(taking E_3 as the starting reference point) (17)

$N_2 = (-1)^0$  $+ (-1)^0$  $= k_{41}(k_{12} + k^*_{12})(k_{32} + k_{34} + k^*_{34}) + k_{32}(k_{43} + k^*_{43})(k_{12} + k^*_{12} + k_{14})$

(taking E_4 as the starting reference point) (18)

Similarly:

$$N_3 = k_{23}(k_{12} + k^*_{12})(k_{41} + k_{43} + k^*_{43}) + k_{14}(k_{43} + k^*_{43})(k_{21} + k^*_{21} + k_{23}) \qquad (19)$$

$$N_4 = k_{23}(k_{34} + k^*_{34})(k_{12} + k^*_{12} + k_{14}) + k_{14}(k_{21} + k^*_{21})(k_{32} + k_{34} + k^*_{34}) \qquad (20)$$

Then in accordance with eqns. (5) and (8) we have:

$$n^{3\to 1} = \text{per } \mathbf{A}_{1,3} = \text{per}\begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 1 & 0 & 1 \end{bmatrix} = 2 \Bigg\} \quad (21)$$
$$n^{1\to 2} = n^{1\to 3} = n^{2\to 4} = 2$$

and

$$P_1 = \det \mathbf{C}_{1,1} = \begin{vmatrix} 3 & -1 & 0 \\ -1 & 3 & -2 \\ 0 & -2 & 3 \end{vmatrix} = 12 \Bigg\} \quad (22)$$
$$P_2 = P_3 = P_4 = 12$$

respectively. Eqns. (21) and (22) indicate that neither subgraphs nor terms were lost during calculating N_m (see eqns. 17–20).

For the rate of formation of the product P in this example, according to the extended Chou's Rule 2 we have (remember that in the following subgraphs the master cycle should be found from $\mathscr{D}$ of Fig. 5, and the other part from $\mathscr{D}^\dagger$ of Fig. 6):

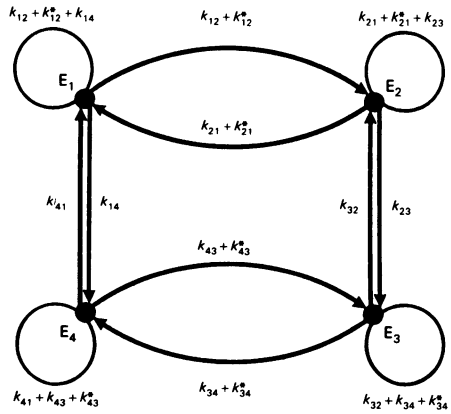
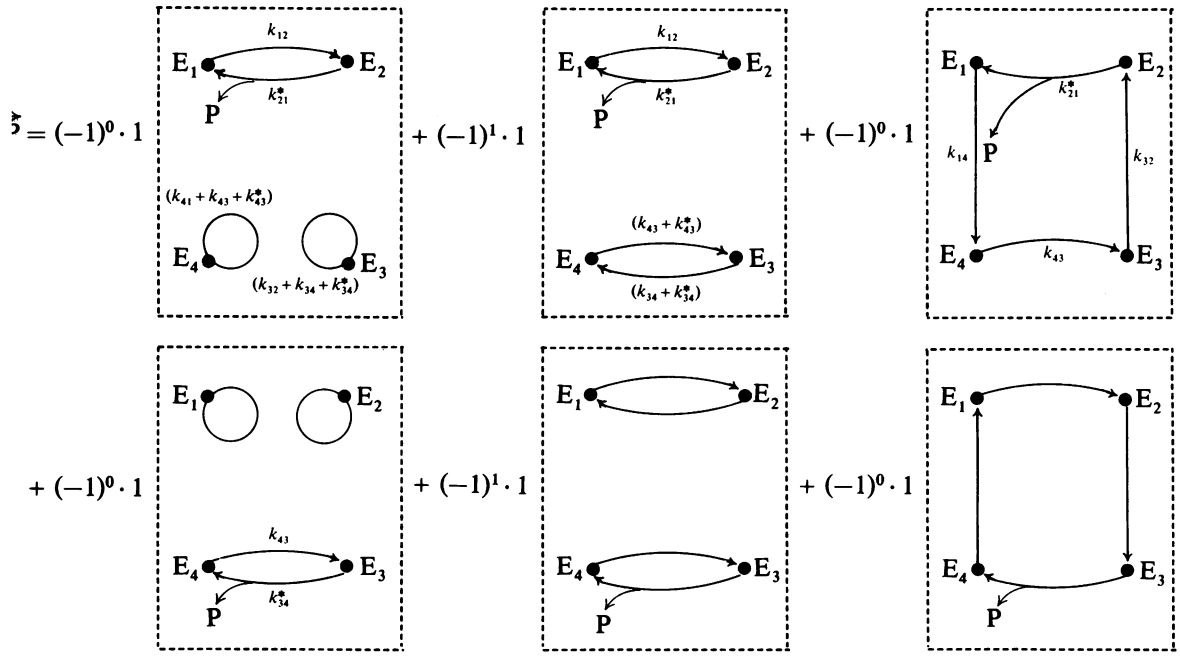
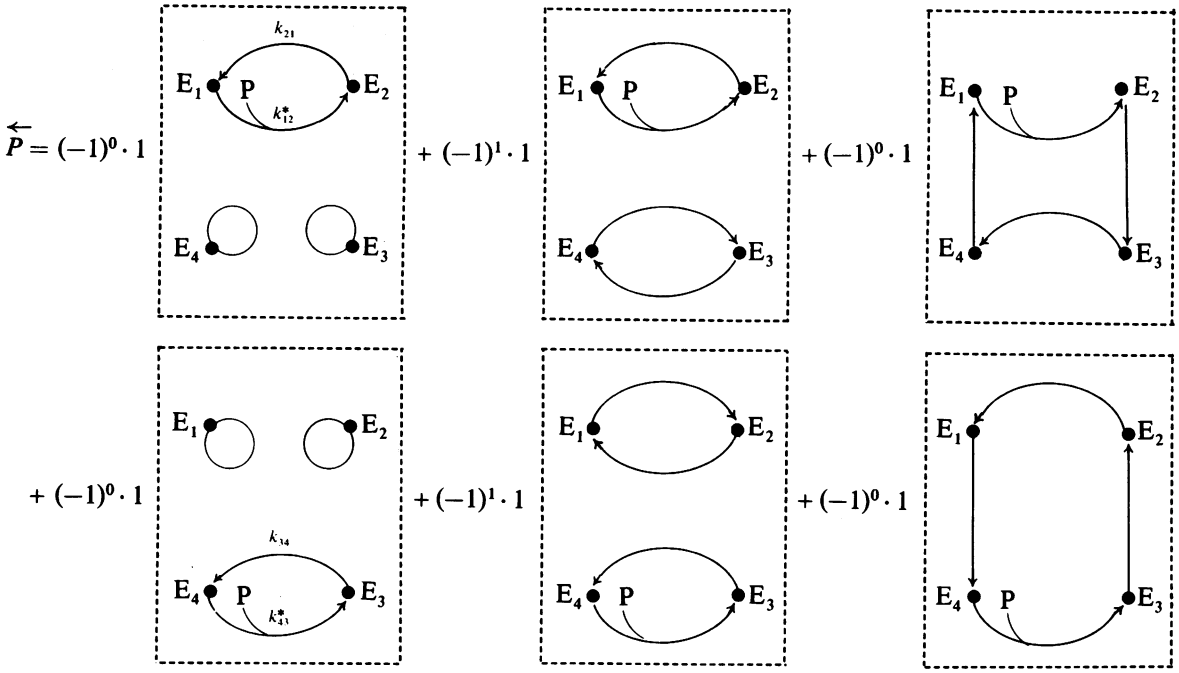


Fig. 6. *Transformed graph $\mathscr{D}^\dagger$ obtained from Fig. 5 by following steps (1) and (2) of the extended Chou's Rule 1*

Substituting eqns. (23) and (24) into eqn. (2), we immediately obtain $v = \mathrm{d[P]}/\mathrm{d}t$, the rate of formation for product (note the denominator is the same as the expression for the concentration of enzyme species, and hence has already been obtained in the preceding calculation).



$$= k_{12}k_{21}^*(k_{32}+k_{34}+k_{34}^*)(k_{41}+k_{43}+k_{43}^*) - k_{12}k_{21}^*(k_{34}+k_{34}^*)(k_{43}+k_{43}^*) + k_{14}k_{43}k_{32}k_{21}^* + k_{43}k_{34}^*(k_{14}+k_{12}+k_{12}^*)(k_{21}+k_{21}^*+k_{23}) - k_{43}k_{34}^*(k_{12}+k_{12}^*)(k_{21}+k_{21}^*) + k_{41}k_{12}k_{23}k_{34}^*$$
$$= k_{21}^*k_{12}(k_{32}k_{41}+k_{32}k_{43}+k_{43}^*k_{32}+k_{34}k_{41}+k_{34}^*k_{41}) + k_{21}^*k_{14}k_{43}k_{32} + k_{34}^*k_{43}(k_{21}k_{14}+k_{21}^*k_{14}+k_{14}k_{23}+k_{12}k_{23}+k_{12}^*k_{23}) + k_{34}^*k_{41}k_{12}k_{23} \quad (23)$$



$$= k_{12}^* k_{21}(k_{32}k_{41} + k_{32}k_{43} + k_{43}^* k_{32} + k_{34}k_{41} + k_{34}^* k_{41}) + k_{12}^* k_{23}k_{34}k_{41} + k_{43}^* k_{34}(k_{21}k_{14} + k_{21}^* k_{14} + k_{14}k_{23} + k_{12}k_{23} + k_{12}^* k_{23}) + k_{43}^* k_{32}k_{21}k_{14} \quad (24)$$

However, it is very easy to make errors if the King–Altman method is applied to the above example, since one has to find 12 subgraphs (only two subgraphs, however, are enough when using the extended Chou's Rule 1) for calculating each N_m ($m = 1, 2, 3, 4$). Besides, in the King–Altman method the rate of formation for product is calculated through the following equation:

$$v = \frac{\mathrm{d[P]}}{\mathrm{d}t} = k_{21}^*[\mathrm{E_2}] + k_{34}^*[\mathrm{E_3}] - k_{12}^*[\mathrm{E_1}] - k_{43}^*[\mathrm{E_4}]$$

$$= [k_{21}^* N_2 + k_{34}^* N_3 - k_{12}^* N_1 - k_{43}^* N_4]e_0 / \sum_{i=1}^{4} N_i \quad (25)$$

Therefore, even though all N_i are obtained, when substituting them into eqn. (25) one still must be very careful to find out all reciprocally cancelled terms (there are in all 24 reciprocally cancelled terms in the present example) in order to obtain the final result. This kind of cancellation operation is clearly both wasted labour and prone to errors. But, in the extended Chou's Rule 2, there is not any cancelled term between $\vec{P}$ and $\overleftarrow{P}$, because this kind of terms has already been automatically ruled out by the rule itself in calculating $\vec{P}$ and $\overleftarrow{P}$.

Through the above comparison, the merits of the extended Chou's rules are very clear. Actually, the more complicated the mechanism considered, the more striking will the advantage of these rules be manifest, as shown in Chou *et al.* (1981) and Chou (1981*a*). Especially, after becoming familiar with these two rules, one need not depict the decomposed subgraphs one by one as demonstrated above; the desired results can be directly written down according to the graphs $\mathscr{D}$ and $\mathscr{D}^\dagger$ even for very complicated mechanisms.

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