多重區間定位法(multiple interval mapping)

- CIM 不能滿足“數量性狀是由所有 QTL 所控制，且受環境影響”的共識。

- CIM 無法立即考慮 QTL 間的交感作用。
  交感作用是一種無所不在的現象(Wright 1980)，必須將交感作用納入模式中考慮。

- 為防止其他QTL對待測QTL之干擾及降低遺傳殘差的最佳方式是直接將其他的 QTL 納入模式中，而非納入（QTL 旁）的標識。

- Kao 等（1999）提出多重區間定位法（MIM）進行 QTL 定位。

  假設共有 m 個 QTL 控制數量性狀，且這 m 個 QTL（$Q_1, Q_2, \ldots, Q_m$）位於 m 個不同的標識區間（$I_1, I_2, \ldots, I_m$）內的 m 個位置（$pos_1, pos_2, \ldots, pos_m$）上，則 MIM 的回交族群統計模式為

$$y_i = \mu + \sum_{j=1}^{m} a_j x_{ij}^* + \sum_{j \neq k}^{m} \delta_{jk}\left(w_{jk} x_{ij}^* x_{ik}^*\right) + \varepsilon_i$$

$$x_{ij}^* = \begin{cases} \frac{1}{2}, \text{如果} Q_j \text{為同質結合體} \left(Q_j Q_j\right) \\ -\frac{1}{2}, \text{如果} Q_j \text{為異質結合體} \left(Q_j q_j\right) \end{cases}$$

$$\varepsilon_i \sim N\left(0, 6^2\right)$$

由於這 m 個 QTL 不正好在標識上，故每一 QTL 之基因型可能有同質或異質兩種情形，當同時考慮 m 個 QTL 時，不同 QTL 基因型的總類共有 2^m 種。

- MIM 模式的概度函數為2^m個常態分布的混合

$$L(\theta|Y,X)=\prod_{i=1}^{n}\left[\sum_{j=1}^{2^m} p_{ij}\mathrm{N}\left(\mu_{ij},\sigma^2\right)\right]$$

p_{ij}和μ_{ij}，$j=1,2,\ldots,2^m$，代表2^m種不同 QTL 基因型的條件機率和基因型值。

- 條件獨立性（conditional independence）

$$\mathrm{P}(\mathrm{Q}_1,\mathrm{Q}_2,\ldots,\mathrm{Q}_m\,|\,\mathrm{I}_1,\mathrm{I}_2,\ldots,\mathrm{I}_m)=\prod_{i=1}^{m}\mathrm{P}(\mathrm{Q}_i\,|\,\mathrm{I}_i)$$

即m個 QTL 基因型的聯合條件機率（joint conditional probability）等於這m個個別基因型邊際條件機率（marginal conditional probability）的乘積。稱此$4^m\times 2^m$的條件機率矩陣為Q矩陣。

- 對 MIM 回交（F_2）族群模式之2^m（或3^m）個常態混合分布進行參數估計的困難所在

	參數個數		常態分布混合數	
m	BC	F_2	BC	F_2
1	1	2	2	3
2	2	4	4	9
⋮	⋮	⋮	⋮	⋮
8	8	16	256	6521
⋮	⋮	⋮	⋮	⋮
12	12	24	4096	531441
⋮	⋮	⋮	⋮	⋮

- MIM 模式之 MLE 和漸近變異和共變異矩陣的推導

Kao & Zeng (1997)推導出一個利用 EM 演算法和 Louis(1982)方法求 MIM 模式中參數的 MLE 和漸近共變異矩陣的一般化公式 (general formulas)。可用此一般化公式解決 MIM 的估計問題。

完全資料可能函數(complete-data likelihood function)為

$$L_c\left(\theta \middle| Y_{obs}, Y_{mis}\right) = \prod_{i=1}^{n}\prod_{j=1}^{2^m}\left[p_{ij}\mathrm{N}\left(\mu_{ij}, 6^2\right)\right]^{I\left[g_i = g_{ij}\right]}$$

E 步驟：算出完全資料對數概度函數的條件期望：

$$Q\left(\theta \middle| \theta^{(t)}\right) = \int \log L_c\left(\theta \middle| Y_{obs}, Y_{mis}\right) f\left(Y_{mis} \middle| Y_{obs}, \theta = \theta^{(t)}\right) dY_{mis}$$

或更新 QTL 基因型的事後條件機率

$$\pi_{ij} = \frac{p_{ij}\mathrm{N}(\mu_{ij}, \sigma^2)}{\sum_{i=1}^{2^m} p_{ij}\mathrm{N}(\mu_{ij}, \sigma^2)};$$

$$i = 1, 2, \cdots, n, \quad j = 1, 2, \cdots 2^m$$

M 步驟：求使 $Q\left(\theta \middle| \theta^{(t)}\right)$最大的$\theta^{(t+1)}$或求$\theta^{(t+1)}$滿足

$$E^{(t+1)} = r^{(t)} - M^{(t)} E^{(t)}$$

$$\mu^{(t+1)} = \frac{1}{n} 1' \left[Y - \Pi^{(t)} D E^{(t+1)} \right]$$

$$\begin{aligned} \sigma^{2^{(t+1)}} = \frac{1}{n} \Big[& \left(Y - 1\mu^{(t+1)}\right)' \left(Y - \mu^{(t+1)}\right) \\ & - 2\left(Y - 1\mu^{(t+1)}\right)' \pi^{(t)} D E^{(t+1)} \\ & + E'^{(t+1)} V^{(t)} E^{(t+1)} \Big] \end{aligned}$$

循環 E 和 M 步驟直到收斂，得收斂值為 MLE θ^*。

共變異矩陣的推導：

Louis(1982)證明$I_{obs}\left(\theta^* \middle| Y_{obs}\right) = I_{oc} - I_{om}$

請參考 Kao & Zeng(1997)有關 MIM 之I_{oc}和I_{om}的詳細公式。

- 簡言之，Kao & Zeng 的一般化公式將對 MIM 的估計規劃成只依賴兩個矩陣$D_{2^m \times k}$和$Q_{4^m \times 2^m}$。D稱為遺傳設計矩陣(genetic design matrix)，包含了 QTL 作用的訊息。Q稱為條件機率矩陣(conditional probability matrix), 包含了 QTL 位置的訊息。

- 統計上之模式選擇(model selection)的技巧可應用於決定 MIM 模式中 QTL 的個數和位置。

- 一個利用 MIM 進行 QTL mapping 的策略

  步驟一：設定臨界值。

  步驟二：模式選擇。

  步驟三：辨別緊密連鎖 QTL。

  步驟四：分析交感作用。

  步驟五：對 QTL 位置和作用的估計進行微調。

  步驟六：建立 QTL 信賴區間。

  步驟七：估計變異成份和遺傳率。

  步驟八：估計個體之基因型值。

- MIM 的優點

(一)滿足“數量性狀是由所有 QTL 與環境共同作用的結果”的共識。

(二)可將已找到的 QTL 納入模式中去找下一個 QTL，QTL 間的交感效應也能一併分析，使得較多的遺傳變異能被模式考慮到。因此，MIM 能有更精確、更強大的 QTL 定位能力。

(三)一些重要的遺傳介量如遺傳率、各個變異成分、數量性狀間的遺傳相關和環境相關可一併估計。

(四)較精確的 MIM 方法可以幫助 QTL 定位，數量性狀遺傳結構（genetic architecture）的估計和標識輔助選拔（marker-assisted selection）三項數量遺傳學的重要研究（Zeng 等 2000）。

● MIM 的一些例子

（一） Kao 等（1999）利用 MIM 對松樹的樹幹腰圍進行 QTL 定位分析，發現有六個 QTL 控制這個性狀，其中有二對 QTL 有交感作用。IM 未發現任何 QTL，而 CIM 只偵測到二個 QTL。

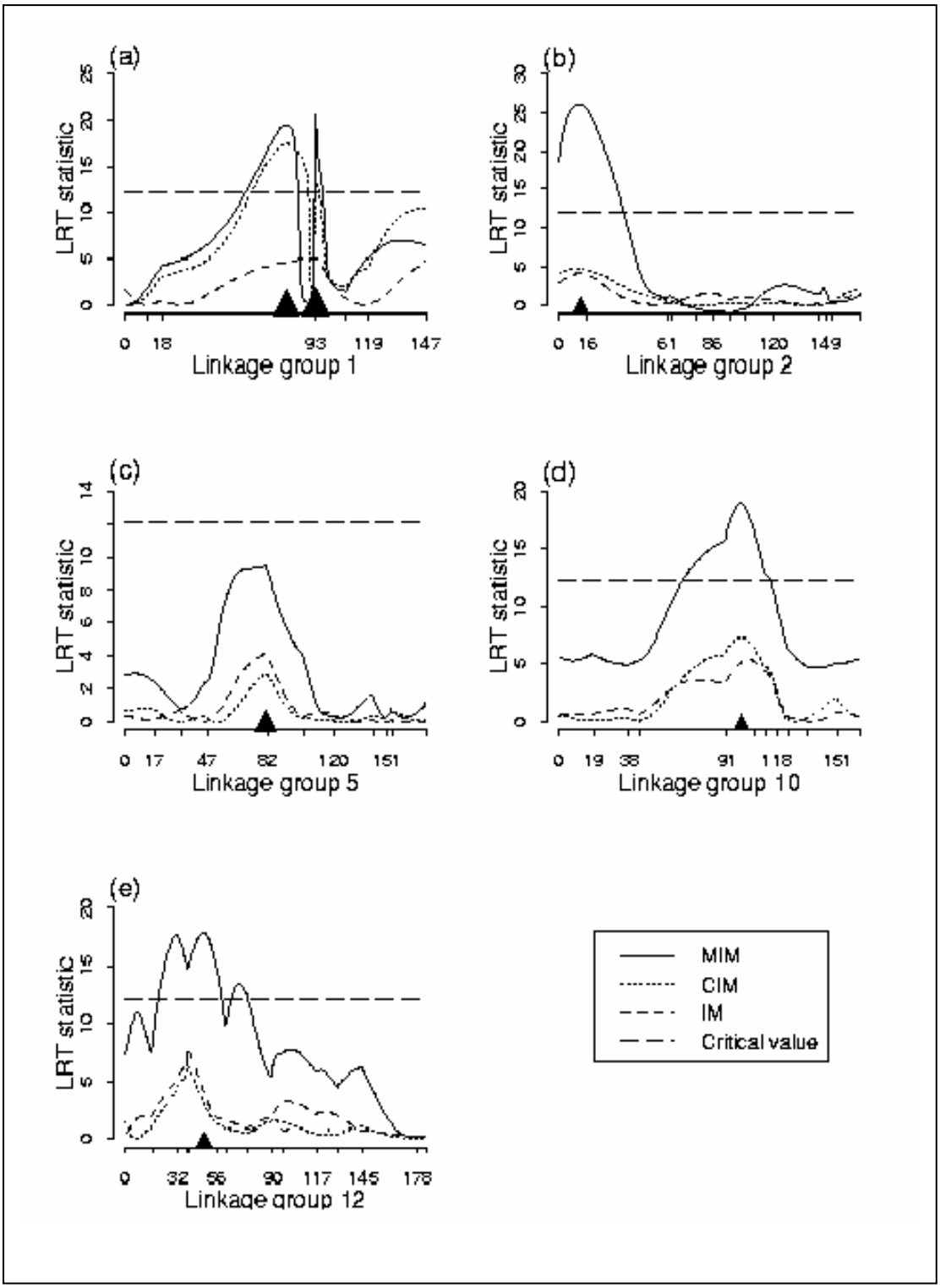
（二） Weber 等(1999)利用 MIM 分析果蠅第三條染色體上影響翅膀形狀的 QTL 時，發現了十一個 QTL，其中有九個有交感作用。CIM 只偵測到其中的十個。

（三） Zeng 等（2000）利用 MIM 對雄果蠅生殖器形狀進行分析，發現了十九個 QTL，其中的六對有交感作用。CIM 偵測到其中的十四個 QTL。

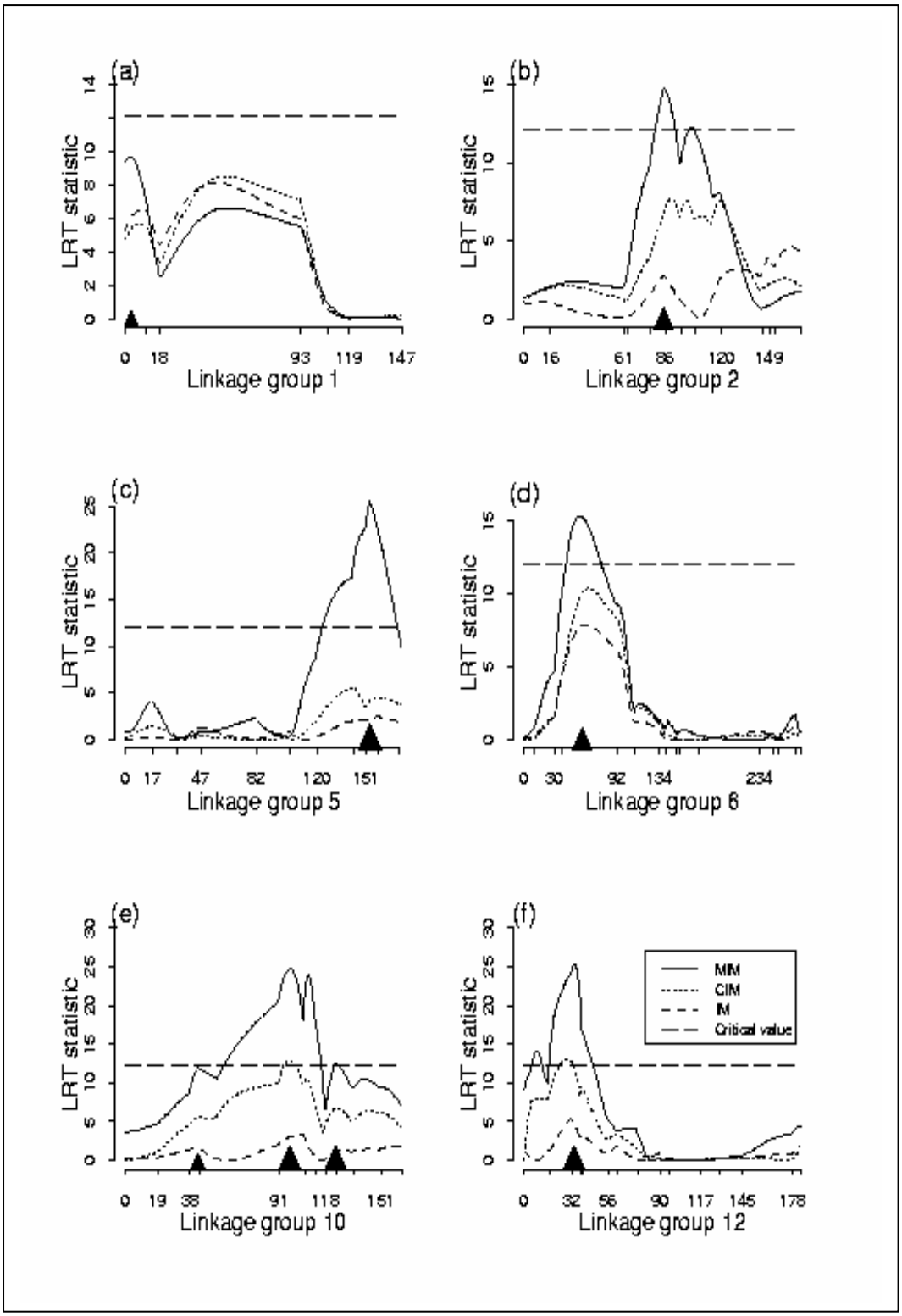
（四） Kao(2000)對松樹毬果數目進行分析，MIM 找到八個，CIM 找到三個，而 IM 沒有找到任何的 QTL。

（五）Tao et al. (2003); Kirst et al. (2004, 2005) .....

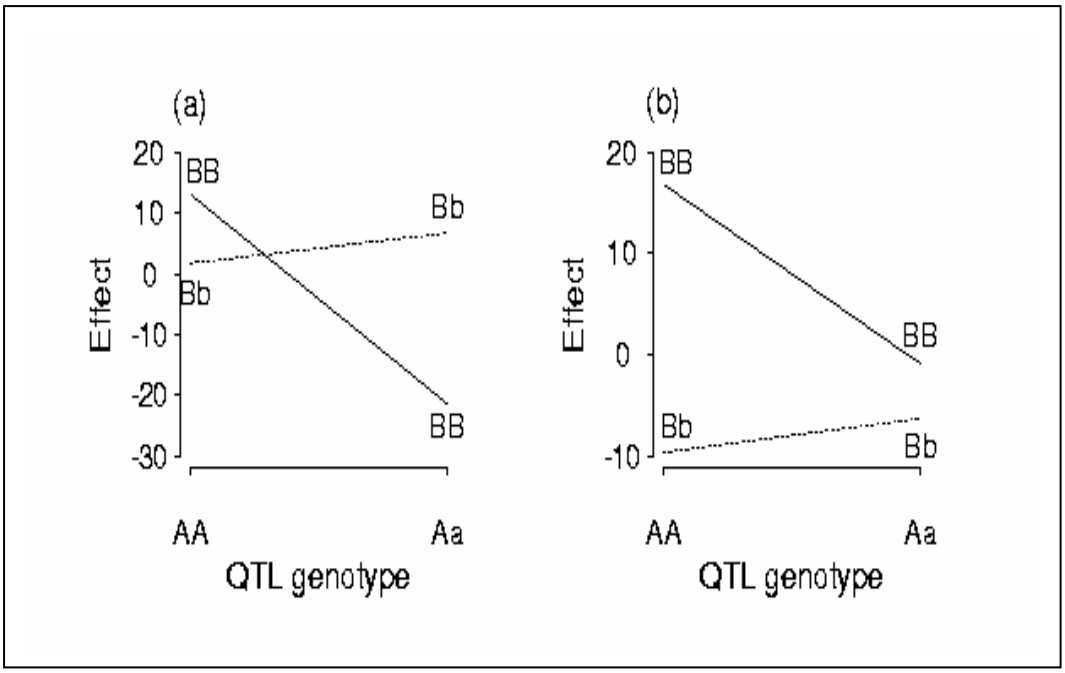
Kao et al. (1999)



Kao（2000）


(a)
LRT statistic
0 2 4 6 8 10 14
0 18 93 119 147
Linkage group 1
(b)
LRT statistic
0 5 10 15
0 16 61 86 120 149
Linkage group 2
(c)
LRT statistic
0 5 10 15 20 25
0 17 47 82 120 151
Linkage group 5
(d)
LRT statistic
0 5 10 15
0 30 92 134 234
Linkage group 6
(e)
LRT statistic
0 5 10 15 20 25 30
0 19 38 91 118 151
Linkage group 10
(f)
LRT statistic
0 5 10 15 20 25 30
0 32 56 90 117 145 178
Linkage group 12
MIM
CIM
IM
Critical value

交感作用（Kao et al. 1999）



預測與觀測值的比較

	No. of QTL		Subpopulation					
			Select decrease		Select increase		Unselected popu.	
Trait	detected	Applied	observed	predicted	observed	predicted	observed	predicted
CN[a]	7	4[b]	0.83	0.90	13.61	17.03	9.93	7.83
			(0.43)		(.)		(8.29)	
DBH[e]	6	5[d]	163.05	160.06*	232.38	233.84*	197.75	197.68
			(35.64)		(20.00)		(34.49)	
BS[e]	5	3[f]	1.24	2.20	5.01	5.13	3.70	3.36
			(.)		(0.82)		(1.07)	

CN, DBH and BS denote cone number, diameter and branch score, respectively. a: Numbers of individual trees are 3, 1 and 113 in the three subpopulations. b: Select cone QTLs at [2,6,0], [5,10,0], [10,5,7] and [10,9,0]. c: Numbers of individuals are 2, 3 and 129 in the three populations. d: Select diameter QTLs at [1,4,0], [2,2,0], [5,5,0], [10,5,9] and [12,5,9]. e: Numbers of individual are 1, 5 and 128 in the three populations. f: Select branch score QTLs at [11,4,21], [11,5,16] and [12,5,0]. *: Assume that the QTLs at [1,3,61] and [1,4,0] have coupling phase. Numbers in brackets are standard deviations.

QTL 間若有交感，但被忽略時，對 QTL 定位有何影響(Kao & Zeng 2002)？

假設數量性狀 y 只受到 Q_A（x_1）和 Q_B（x_2）兩個 QTL 的影響。當 y 對 x_1 做回歸分析時，在回交族群可得回歸係數

$$b_{yx_1} = a_1 + (1-2r)a_2.$$

當 y 對 x_1 和 x_2 做回歸分析時，x_1 的淨回歸係數為

$$b_{yx_1.x_2} = \frac{\sigma_{yx_1.x_2}}{\sigma^2_{x_2}} = \sigma_{yx_1} - \frac{\sigma_{yx_2}\sigma_{x_1x_2}}{\sigma^2_{x_2}}$$

$$= \frac{(1-(1-2r)^2)/4a_1}{(1-(1-2r)^2)/4} = a_1.$$

所以…….

在 F_2 族群，當 y 對任意一個標識 M 做回歸分析時，M 的累加作用回歸係數為

$$a_M = (1-2r_{AM})a_1 + (1-2r_{BM})a_2$$
$$-\frac{1}{2}(1-2r_{AB})(1-2r_{BM})i_{ad}$$
$$-\frac{1}{2}(1-2r_{AB})(1-2r_{AM})i_{da}.$$

M的顯性作用回歸係數為

$$d_M = (1-2r_{AM})^2 d_1 + (1-2r_{BM})^2 d_2 - (1-2r_{AM})(1-2r_{BM}) i_{aa}.$$

當y對x_1和x_2做回歸分析時，x_1的累加作用和顯性作用的淨回歸係數分別為

$$a_{A.B_a} = a_1 - \frac{1}{2}(1-2r_{AB}) i_{da}$$

和

$$d_{A.B_d} = d_1 - \frac{(1-2r_{AB})}{1+(1-2r_{AB})^2} i_{aa}.$$

在F_∞模式下，以上四個式子分別為

$$a_M = (1-2r_{AM}) a_1 + (1-2r_{BM}) a_2 + \frac{1}{2}(1-2r_{AM})[1-(1-2r_{BM})^2] i_{ad} + \frac{1}{2}(1-2r_{BM})[1-(1-2r_{AM})^2] i_{da}$$

$$d_M = (1-2r_{AM})^2 d_1 + (1-2r_{BM})^2 d_2 - (1-2r_{AM})(1-2r_{BM}) i_{aa} + \frac{1}{2}[(1-2r_{AM})^2 + (1-2r_{BM})^2] i_{dd}$$

$$a_{A.B_a} = a_1 + \frac{1}{2} i_{ad} - \frac{1}{2}(1 - 2r_{AB}) i_{da}$$

$$d_{A.B_d} = d_1 - \frac{(1 - 2r_{AB})}{1 + (1 - 2r_{AB})^2} i_{aa} + \frac{1}{2} i_{dd}$$

所以…….

定位控制胚乳性狀(endosperm traits)的 QTL

目前的方法：

Variance component analysis: Gale 1975; Bogyo et al. 1988; Mo 1987; Zhu & Weir 1994; ....

二倍體的方法: Tan et al. 1999; Wang & Larkins 2001; Wang et al. 2001; ....

三倍體的方法: Wu et al. (2002a,b) and Xu et al. (2003) 考慮胚乳三倍體的特性提出以 IM 為基礎的方法。

Kao(2004)提出以 MIM 為基礎的方法：

$$
\begin{aligned}
y_i = \mu &+ \sum_{j=1}^{m} a_j x_{ij}^* + \sum_{j=1}^{m} d_{j1} z_{ij1}^* + \sum_{j=1}^{m} d_{j2} z_{ij2}^* + \sum_{j<k}^{m} i_{a_j a_k} (x_{ij}^* x_{ik}^*) \\
&+ \sum_{j \neq k}^{m} i_{a_j d_{k1}} (x_{ij}^* z_{ik1}^*) + \sum_{j \neq k}^{m} i_{a_j d_{k2}} (x_{ij}^* z_{ik2}^*) \\
&+ \sum_{j<k}^{m} i_{d_{j1} d_{k1}} (z_{ij1}^* z_{ik1}^*) + \sum_{j<k}^{m} i_{d_{j1} d_{k2}} (z_{ij1}^* z_{ik2}^*) \\
&+ \sum_{j<k}^{m} i_{d_{j2} d_{k1}} (z_{ij2}^* z_{ik1}^*) + \sum_{j<k}^{m} i_{d_{j2} d_{k2}} (z_{ij2}^* z_{ik2}^*) \\
&+ \varepsilon_i \ , \quad i = 1, 2, \ldots, n,
\end{aligned}
$$

MIM 現況：

MT-MIM (multiple trait multiple interval mapping):

CT-MIM (categorical trait multiple interval mapping):

Tao et al. (2003)

ET-MIM (endosperm trait multiple interval mapping):

Kao (2004)

Software: QTL Cartographer (Basten, Zeng & Weir 2003)

Application of MIM to QTL mapping experiments: Kao et al. (1999); Weber et al. (1999); Zeng et al. (2000); Tao et al. (2003); Kirst et al. (2004; 2005);……

分離緊密連鎖 QTL 的效率（Efficiency of separating closely linked QTL）

- 假設 QTL 正好都位在標識上，則 MIM 模式便簡化成一迴歸模式，$n\left(\underline{\hat{a}}-\underline{a}\right)$的漸近分布為一多元常態分布

$$n\left(\underline{\hat{a}}-\underline{a}\right)\xrightarrow{D}\mathrm{N}\left(\underline{0},\ A_0^{-1}\sigma^2\right)$$

上式之

$$A_0=\lim_{n\to\infty}\frac{X'X}{n}=\frac{1}{4}\begin{bmatrix}1 & \lambda_{12} & \lambda_{13} & \cdots & \lambda_{1m}\\ \lambda_{12} & 1 & \lambda_{23} & \cdots & \lambda_{2m}\\ \lambda_{13} & \lambda_{32} & 1 & \cdots & \lambda_{3m}\\ \vdots & \vdots & \vdots & & \vdots\\ \lambda_{1m} & \lambda_{2m} & \lambda_{3m} & \cdots & 1\end{bmatrix}$$

$$\sigma^2=V_G\times\frac{h^2}{1-h^2}$$

$\lambda=1-2r$稱為連鎖參數(linkage parameter)。連鎖 QTL 的效率在各種條件(樣本數，作用大小、遺傳率和遺傳距離）下，大於某特定臨界值的機率（即成功辨別緊密連鎖 QTL 的能力）可被算出。

- 在實際情況下，QTL 不會都正好位在標識上，故實際之分辨能力會低於由多元常態分布所預測之分辨能力。

- 實際上，研究人員傾向於增加緊密連鎖 QTL 區域附近之標識密度(即減少 QTL 之 missing information）以便操作 QTL。隨著 QTL 附近標識密度的增加，實際之辨別能力會逐漸接近所預測的辨別能力。

QTL 定位分析的軟體

可於http://www.stat.wisc.edu/~yandell/qtl/software/

找到許多有關 QTL mapping 的軟體，但皆缺

MIM 方法。MIM Fortran 程式可從網址

http://www.stat.sinica.edu/～chkao/下載。

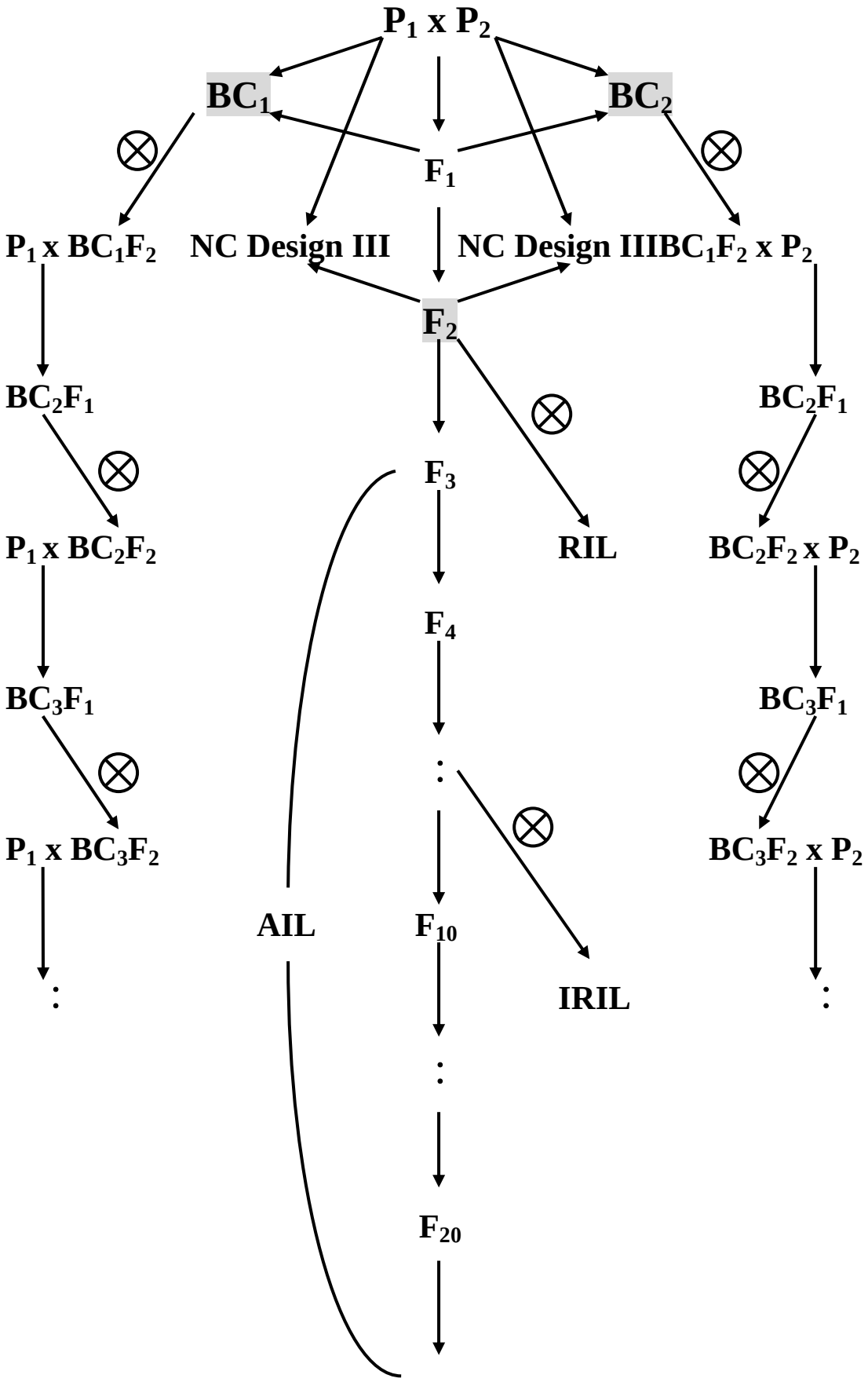
實際應用 QTL 定位於生物研究的例子

- 水稻:Tang 等(2000)。Hittalmani 等(2000)。Wu 等(2000)。Li 等(2000);Lu 等(1996，1997)；Li 等(1997); Xiao 等(1998)。Yamamoto 等(2000)；Xiao 等(1998) 。Yan 等(1998)；Lu 等(1996)；Zhuang 等(1997); Xiao 等(1998)。Pessoir 等(1998); Albar 等(1998)。Cai & Morishima(2000)。Zou 等（2000）
- 玉米、蕃茄、松樹、尤加利、高梁：Grattapaglia 等(1996)；Aitken 等(1997)；Emebiri 等(1998)；Doebley 等 1995; Weller 等(1988)；Lin 等(1995)；Kumar 等(2000)。TUBEROSA 等(2002); Kirst et al. (2004; 2005)
- 老鼠：Harvat & Medrano(1995)；Brockmann 等(1998)；Dragani 等(1995)。Hilbert 等(1991)；Jacob 等

(1991)。Lee等(1995); Lyons et al. (2003); Lionikas et al. (2003)

- 雞：Marek's Disease Virus；Vallejo 等 1998);Carlborg et. al. (2003)
- 豬： Andersson 等(1994);Marklun (1999)。
- 果蠅： Zimmerman 等(2000)。Vieira 等(2000)。Liu 等(1996)；Zeng 等(2000)。Tao 等(2003)

Populations Derived from Inbred Lines



參考文獻

劉清、陳英勇（1992）利用遺傳標識定位數量性狀基因座。中華農藝，2，1-21

戴政（1995）人類遺傳疾病研究統計方法評介。數學傳播第 29 卷第二期，8-13

歐尚靈（1999）定位二元資料與順序資料的數量性狀基因座。國立台灣大學博士論文

高振宏 （2000）對試驗族群進行數量性狀基因座定位的統計方法評介。中國統計學報第 38 卷第一期，1-36

Aitken K. S., G. Small, J. Drenth, Y. LI, C.-H. Kao and R. D. Teasdale, 1997 Detection of quantitative trait loci (QTL) for cone production in Pinus radiata. In Burdon, R.D. and J. M. Moore. (Eds) "IUFRO '97 genetics of Radiata pine". Proceedings of NZFRI-IUFRO Conference, 1-4 December, and Workshop, 5 December, Rotorua, New Zealand, Pp 337-341. FRI Bulletin. No. 203.

Albar, L., M. Lorieux, N. Ahmadi, I. Rimbault, A. Pinel, A. A. Sy, D. Fargette and A. Ghesquiere (1998), Genetic basis and mapping of the resistance to rice yellow mottle virus. I. QTLs identification and relationship between resistance and plant morpholoty. Theor Appl Genet 97:1145-1154.

Andersson, L., C. S. Haley, H. Ellegren, S A. Knott, M. Johansson, K. Andersson, L. Andersson-Eklund, I. Edfors-Lilja, M. Fredholm, I. Hansson, J. Hakansson, K. Lundstrom (1994), Genetic Mapping of Quantitative Trait Loci for Growth and Fatness in Pigs. Science 263:1771-1774.

Brockmann, G. A., C. S. Haley, U. Renne, S. A. Knott and M. Schwerin (1998), Quantitative Trait Loci Affecting Body Weight and Fatness From a Mouse Line Selected for Extreme High Growth. Genetics 142:369-381.

Cai, H.-W. and H. Morishima (2000), Genomic regions affecting seed shattering and seed dormancy in rice. Theor Appl Genet 100:840-846.

Carlborg O., S. Kerje, K. Schutz, L. Jacobsson, P. Jensen, and L. Andersson A Global Search Reveals Epistatic Interaction Between QTL for Early Growth in the Chicken Genome Res., March 1, 2003; 13(3): 413 - 421.

Dempster, A. P., N. M. Laird and D. B. Rubin (1977), Maximum likelihood from incomplete data via the EM algorithm. Journal of the Royal Statistical Society 39: 1-38.

Dragani, T.A., Zeng, Z.-B., Canzian, F., Gariboldi, M. Ghilarducci, M.T., Manenti, G. and Pierotti, M.A. (1995), Mapping of body weight loci on mouse Chromosome X. Mammalian Genome 6, 778-781.

Emebiri, L. C., M. E. Devey, A. C. Matheson and M. U. Slee (1998), Interval mapping of quantitative trait loci affecting NESTUR, a stem growth efficiency index of radiata pine seedings. Theor Appl Genet 97:1062-1068.

Grattapaglia, D., F. L. G. Bertolucci, R. Penchel and R. R. Sederoff

(1996), Genetic mapping of quantitative trait loci controlling growth and wood quality traits in Eucalyptus grandis using a maternal half-sib family and RAPD markers. Genetics 144: 1205-1214.

Hilbert, P., K. Lindpaintner, J. S. Beckmann, T. Serikawa, F. Soubrier, C. Dubay, P. Cartwright, B. De Gouyon, C. Julier, S. Takahasi, M. Vincent, D. Ganten, M. Georges and G. M. Lathrop (1991), Chromosomal mapping of two genetic loci associated with blood-pressure regulation in hereditary hypertensive rats. Nature 353:521-529

Hittalmani, S., A. Parco, T. V. Mew and R.S. Xeigler (2000), Fine mapping and DNA marker-assisted pyramiding of the three major genes for blast resistance in rice. Theor. Appl. Genet. 100:1121-1128.

Horvat, S., and J. F. Medrano (1995), Interval Mapping of high growth (hg), a Major Locus That Increases Weight Gain in Mice. Genetics 139:1737-1748.

Jacob, H. J., K. Lindpaintner, S. E. Lincoln, K. Kusumi, R. K. Bunker, Y. P. Mao, D. Ganten and V. J. Dzau (1991), Genetic Mapping of a Gene Causing Hypertension in the Stroke-Prone Spontaneously Hypertensive Rat. Cell 57:213-224.

Kao, C.-H. and Z.-B Zeng (1997), General formulas for obtaining the MLEs and the asymptotic variance-covariance matrix in mapping quantitative trait loci when using the EM algorithm. Biometrics 53: 359-371.

Kao, C.-H., Z.-B Zeng and R. D. Teasdale (1999), Multiple interval mapping for quantitative trait loci. Genetics 152.

Kao, C.-H. (2000), Efficiency of Separating Closely Linked Genes Affecting Quantitative traits (manuscript).

Kirst M, A. A. Myburg, J. P.G. De Leon, M. E. Kirst, J. Scott, and R. Sederoff Coordinated Genetic Regulation of Growth and Lignin Revealed by Quantitative Trait Locus Analysis of cDNA Microarray Data in an Interspecific Backcross of Eucalyptus Plant Physiology, August 1, 2004; 135(4): 2368 - 2378.

Kirst M., C. J. Basten, A. A. Myburg, Z.-B. Zeng, and R. R. Sederoff Genetic Architecture of Transcript-Level Variation in Differentiating Xylem of a Eucalyptus Hybrid Genetics, April 1, 2005; 169(4): 2295 - 2303.

Kumar, S., R. J. Spelman , D. J. Garric, T. E. Richardson, M. Lausberg and P. L. Wilcox (2000), Multiple-marker mapping of wood density loci in an outbred pedigree of radiata pine. Theor Appl Genet 100:926-933.

Lee, G. H., L. M. Bennett, R. A. Carabeo and N. R. Drinkwater (1995), Identification of Hepatocarcinogen-Resistance Genes in DBA/2 Mice. Genetics 139:387-395.

Lexer C., D. M. Rosenthal, O. Raymond, L. A. Donovan, and L. H. Rieseberg Genetics of Species Differences in the Wild Annual Sunflowers, Helianthus annuus and H. petiolaris Genetics, April 1, 2005; 169(4): 2225 - 2239.

Li, Z., S. R. M. Pinson, W. D. Park, A. H. Paterson and J. W. Stansel (1997), Epistasis for three grain yield components in rice (Oryza sativa L.). Genetics 145: 453-465.

Li, J. X., S. B. Yu, C. G. Xu, Y. F. Tan and Y. J. Gao (2000), Analyzing quantitative trait loci for yield using a vegetatively replicated F_2 population from a cross between the parents of an elite rice hybrid. Theor Appl Genet (2000), 101:248-254.

Li, Z., S. R. M. Pinson, W. D. Park, A. H. Paterson and J. W. Stansel (1997), Epistasis for Three Grain Yield Components in Rice (Oryza sativa L.). Genetics 145: 453-465

Lin, Y. R., K. F. Schertz and A. H. Paterson (1995), Comparative Analysis of QTLs Affecting Plant Height and Maturity Across the Poaceae, in Regerence to and Interspecific Sorghum Population. Genetics 141:391-411.

Lionikas A., D. A. Blizard, D. J. Vandenbergh, M. G. Glover, J. T. Stout, G. P. Vogler, G. E. McClearn, and L. Larsson Genetic architecture of fast- and slow-twitch skeletal muscle weight in 200-day-old mice of the C57BL/6J and DBA/2J lineage Physiol Genomics, December 16, 2003; 16(1): 141 - 152.

Liu, J., Mercer, J.M., Stem, L.F., Gibson, G.C., Zeng, Z.-B. and Laurie, C.C. (1996), Genetic analysis of a morphilogical shape difference in the male genitalia of Drosophite simulans and D. mauritiana. Genetics 142 1129-1145.

Louis, T. A. (1982), Finding the observed information matrix when using the EM algorithm. Journal of Royal Statistical Society, Series B 44: 226-233.

Lu, C., L. Shen, Z. Tan, Y. Xu, P. He, Y. Chen and L. Zhu (1996), Comparative mapping of QTLs for agronomic traits of rice across environments using a doubled haploid population. Theor Appl Genet. 93:1211-1217.

Lu, C., L. Shen, Z. Tan, Y. Xu, P. He, Y. Chen and L. Zhu (1997), Comparative mapping of QTLs for agronomic traits of rice across environments by using a doubled-haploid population. Theor Appl Genet. 94:145-150.

Lyons M. A., H. Wittenburg, R. Li, K. A. Walsh, M. R. Leonard, G. A. Churchill, M. C. Carey, and B. Paigen New quantitative trait loci that contribute to cholesterol gallstone formation detected in an intercross of CAST/Ei and 129S1/SvImJ inbred mice Physiol Genomics, August 15, 2003; 14(3): 225 - 239.

Marklund, L., P. E. Nystrom, S. Stern, L. Andersson-Eklund and L. Andersson (1999), Confirmed quantitative trait loci for fatness and growth on pig chromosome 4. Heredity 82:134-141.

Pressoir, G., L. Albar, N. Ahmadi, I. Rimbault, M. Lorieux, D. Fargette and A. Ghesquiere (1998), Genetic basis and mapping of the resistance to rice yellow mottle virus. II. Evidence of a complementary epistasis between two QTLs. Theor Appl Genet 97:1155-1161.

M. Slotman, A. della Torre, and J. R. Powell The Genetics of Inviability and Male Sterility in Hybrids Between Anopheles gambiae and An. Arabiensis Genetics, May 1, 2004; 167(1): 275 - 287.

Tang, D., W. Wu, W. Li, H. Lu and A. J. Worland (2000), Mapping of QTLs conferring resistance to bacterial leaf streak in rice. Theor Appl Genet, 101:286-291.

Tao Y., Z.-B. Zeng, J. Li, D. L. Hartl, and C. C. Laurie Genetic Dissection of Hybrid Incompatibilities Between Drosophila simulans and D. mauritiana. II. Mapping Hybrid Male Sterility Loci on the Third Chromosome
Genetics, August 1, 2003; 164(4): 1399 - 1418.

TUBEROSA R. SALVI, M. C. SANGUINETI, P. LANDI, M. MACCAFERRI, and S. CONTI Mapping QTLs Regulating Morpho-physiological Traits and Yield: Case Studies, Shortcomings and Perspectives in Drought-stressed Maize Ann. Bot., June 15, 2002; 89(7): 941 - 963.

Vallejo, R. L., L. D. Bacon, H. C. Liu, R. L. Witter, M. A. H. Groenen, J. Hillel and H. H. Cheng (1998), Genetic Mapping of Quantitative Trait Loci Affecting Susceptibility to Marek's Disease Virus Induced Tumors in F_2 Intercross Chickens. Genetics 148:349-360.

Vieira, C., E. G. Pasyukova, Z. B. Zeng, J. B. Hackett, R. F. Lyman and T. F. C. Mackay (2000), Genotype-Environment Interaction for Quantitative Trait Loci Affecting Life Span in Drosophila melanogaster. Genetics 154:213-227.

Viitala S. M.. Schulman, D. J. de Koning, K. Elo, R. Kinos, A. Virta, J. Virta, A. Maki-Tanila, and J. H. Vilkki Quantitative Trait Loci Affecting Milk Production Traits in Finnish Ayrshire Dairy Cattle J Dairy Sci, May 1, 2003; 86(5): 1828 - 1836.

Weber, K. R. Eisman, L. Morey, A. Patty, J. Sparks, M. Tausek and Z.-B. Zeng (1999), An analysis of polygenes affecting wing shape on Chromosome 3 in Drosophila melanogaster. Genetics 153:773-786.

Weller, J. I., M. Soller and T. Brody (1988), Linkage Analysis of Quantitative Traits in an Interspecific Cross of Tomato (Lycopersicon esculentum X Lycopersicon pimpinellifolium) by Means of Genetic Markers. Genetics 118:329-339.

Wright, S. (1980), Genic and organismic selection. Evolution 34: 825-843.

Wu, P., C. Y. Liao, B. Hu, K. K. Yi and W. Z. Jin (2000), QTLs and epistasis for aluminum tolerance in rice (Oryza sativa L.) at different seedling stages. Theor Appl Genet 100:1295-1303

Xiao, J., J. Li, S. Grandillo, S. N. Ahn, L. yuan, S. D. Tanksley and S. R. McCouch (1998), Identification of Trait -Improving Quantitative Trait Loci Alleles From a Wild Rice Relative, Oryza rufipogon. Genetics 150:899-909.

Yamamoto, T., H. Lin, T. Sasaki and M. Yano (2000), Identification of Heading Date

Quantitative Trait Locus Hd6 and Characterizatoin of Its Epistatic Interactions With Hd2 in Rice Using Advanced Backcross Progeny. Genetics 154:885-891.

Yan, J., J. Zhu, C. He, M. Benmoussa and P. Wu (1998), Molecular Dissection of Developmental Behavior of Plant Height in Rice (Oryza sativa L.). Genetics 150:1257-1265

Zeng, Z.-B., C.-H. Kao and C. J. Basten (1999) Estimating the genetic architecture of quantitative traits. Genet. Res. 74: 279-289.

Zeng, Z.-B., J. Liu, L. F. Stam, C.-H. Kao, J. M. Mercer and C. C. Laurie (2000), Genetic architecture of a morphological shape difference between two Drosophila species. Genetics 154:299-310.

Zhuang, J.-Y., H.-X. Lin, J. Lu, H.-R. Qian, S. Hittalmani, N. Huang and K.-L. Zheng (1997), Analysis of QTLXenvironment interaction for yield components and plant height in rice. Theor Appl Genet 95:799-808.

Zimmerman, E., A. Palsson and G. Gibson (2000), Quantitative Trait Loci Affecting Components of Wing Shape in Drosophila melanogaster. Genetics 155:671-683.