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Computational Challenges in Analyzing Complex Traits

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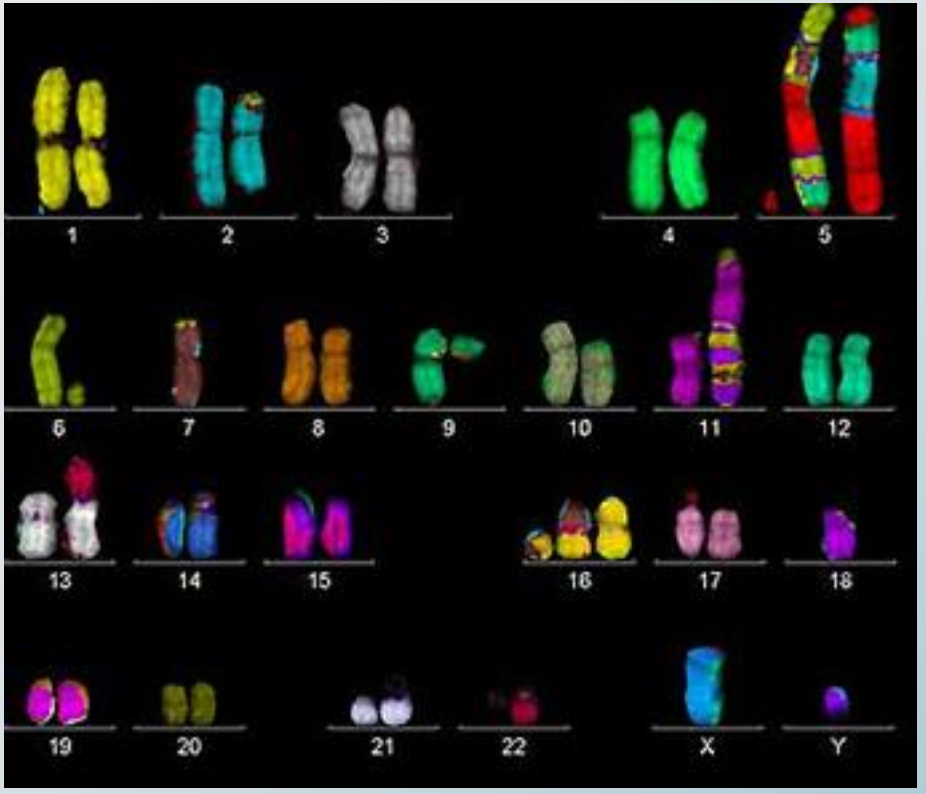
Mendelian Traits

- Phenotypes controlled by singular genes
- No epistasis
- No GE interaction

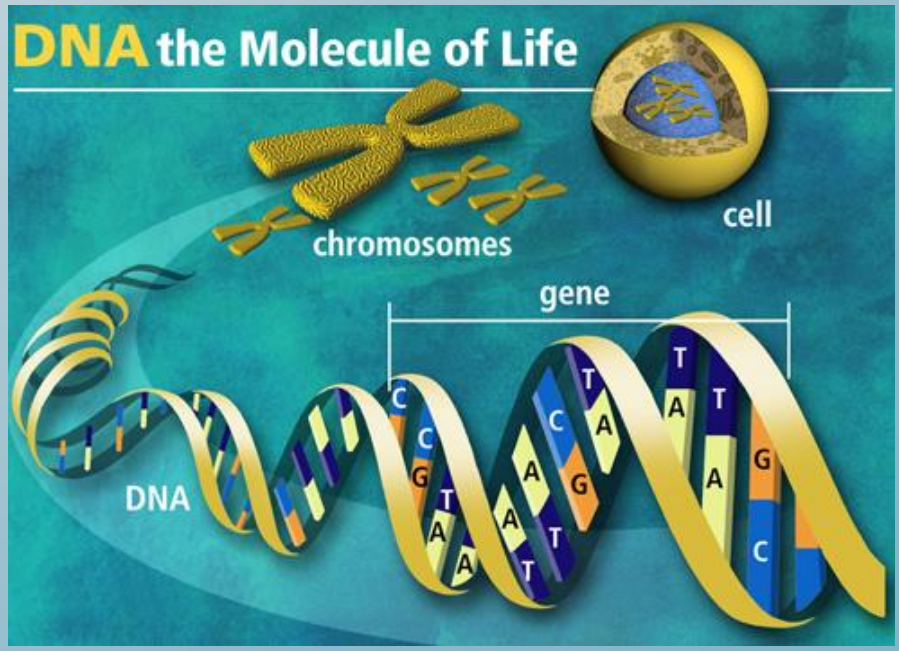
Complex Traits

- Phenotypes controlled by multiple genes
- Epistasis (gene-gene interaction)
- Gene-environment interaction
- Genetic pleiotropy and heterogeneity
- Low heritability
- Limited statistical power

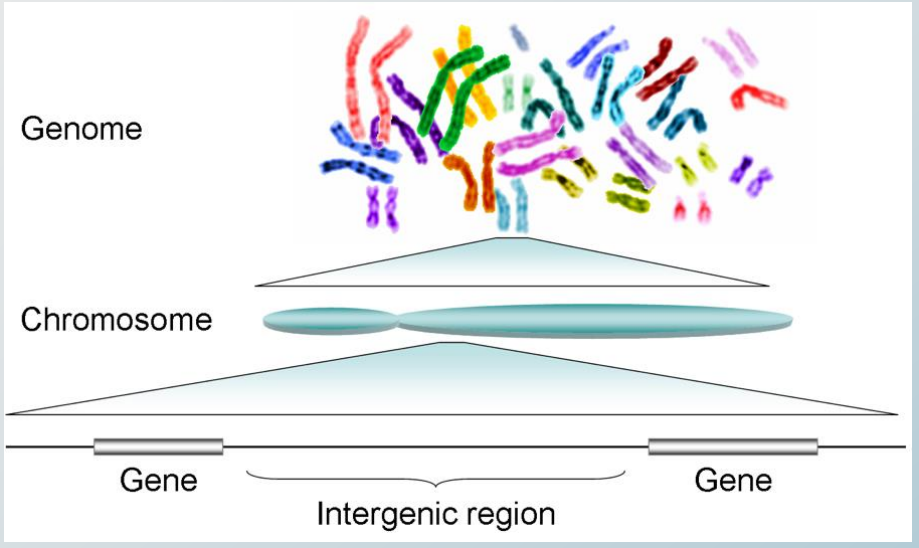
- **Human Chromosomes**



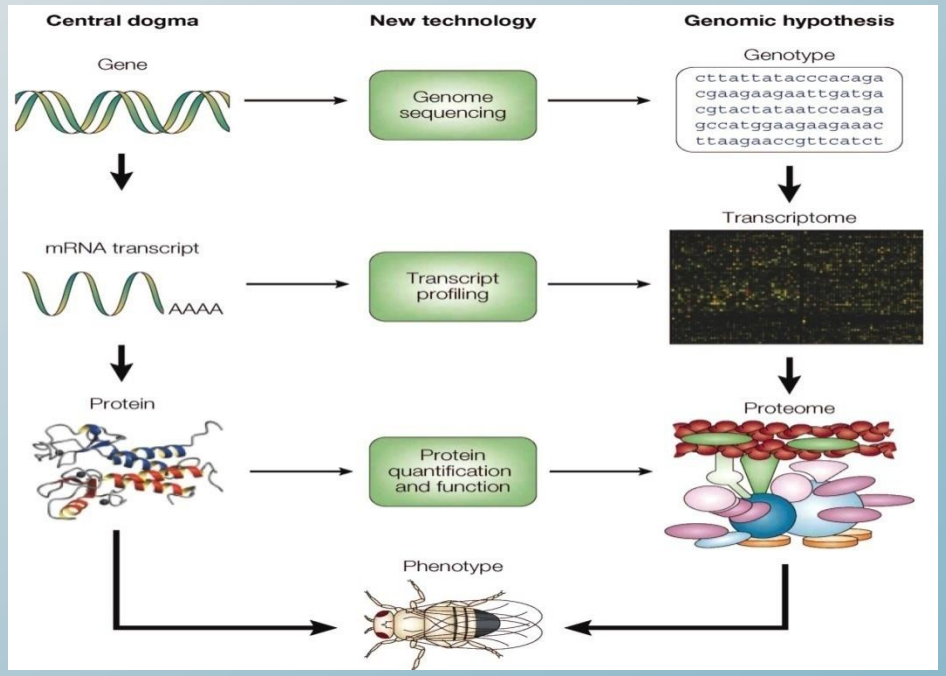
- **Chromosome to DNS**



- **From Genome to Genes**

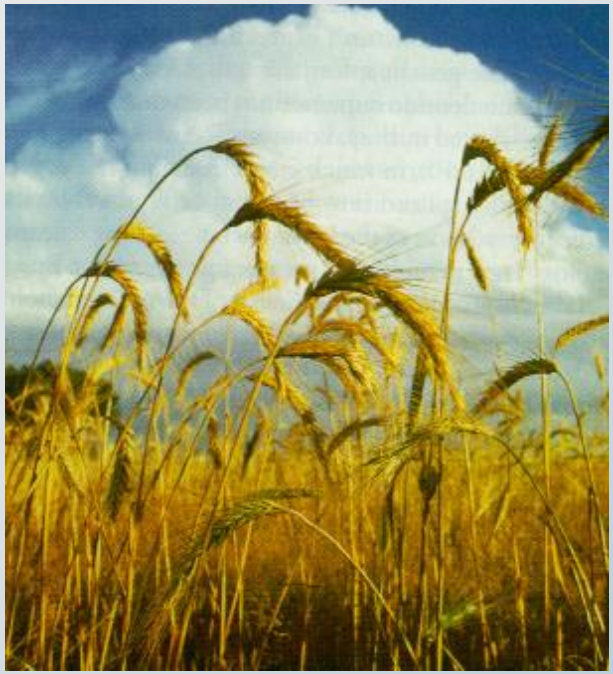


- **From Gene to Phenotype**



Partition of Phenotypic Variation

Phenotype $y = \mu + E + G + GE + e$



G

GE

E

Genetic Effect: A, D, I

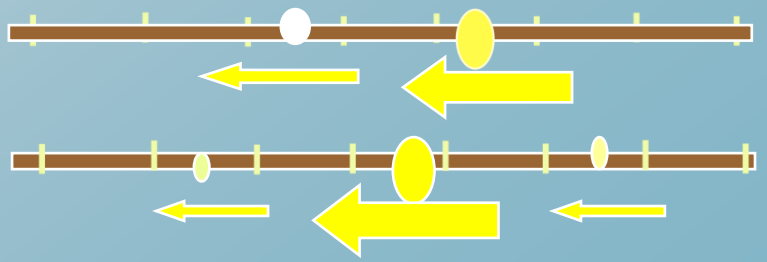
GE: AE, DE, IE

Macro Env, Micro Env

Genetic Effects

QTL Position & Effects

Genome



Partitioning of Phenotypic Variation

$$y = \mu + E + G + GE + e$$

- **Gene Effects (G):**
  Addtive (A), Dominance (D)
  Gene-Gene Interaction (AA, AD, DD)
- **Environment Effects (E):**
  Location, Weather, Treatment
- **Gene-Environment Interaction (GE)**
  AE, DE, AAE, ADE, DDE
- **Random Error (*e*)**

Partitioning of Phenotypic Variation

$$y = \mu + E + G + GE + e$$

- **Classical quantitative genetics**

$$G = A + D + (AA + AD + DD)$$

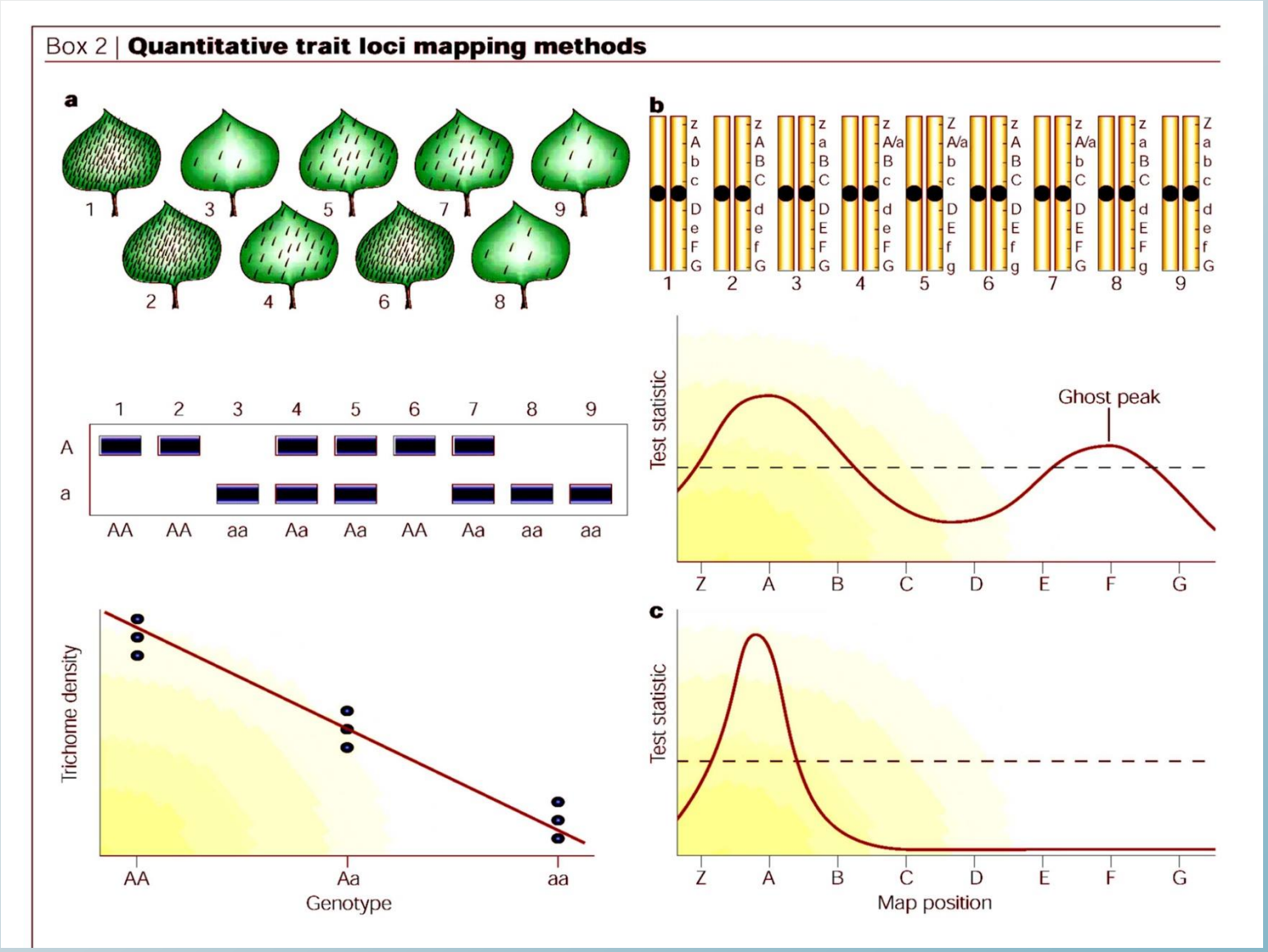
$$GE = AE + DE + (AAE + ADE + DDE)$$

- **Molecule quantitative genetics**

$$G = \sum a + \sum d + (\sum\sum aa + \sum\sum ad + + \sum\sum dd)$$

$$GE = \sum ae + \sum de + (\sum\sum aae + \sum\sum ade + + \sum\sum dde)$$

Method of Mapping QTL



NATURE REVIEWS 2001

Presentation of QTL

Multiple QTL

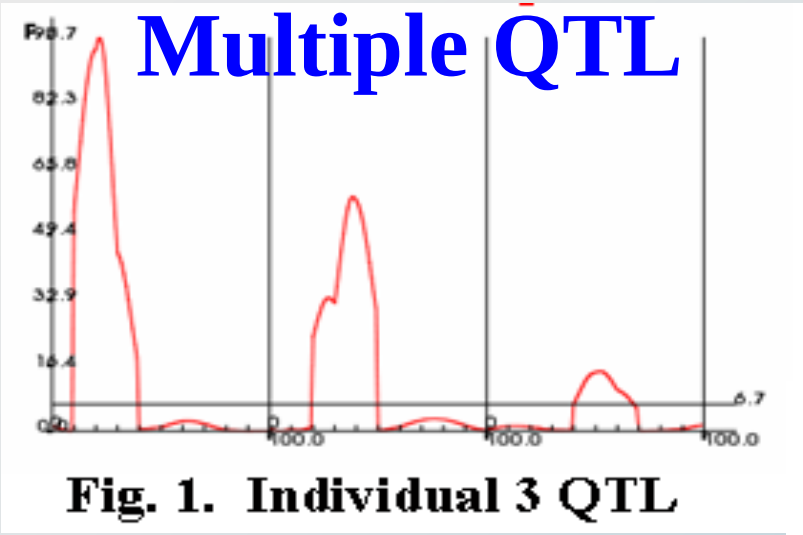


Fig. 1. Individual 3 QTL

QTL × Env

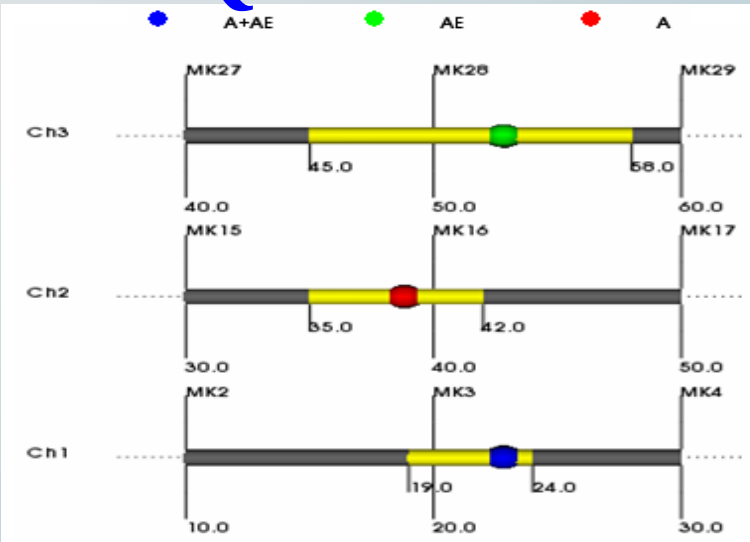


Fig. 2. Differential expression of 3 QTL

QTL Network

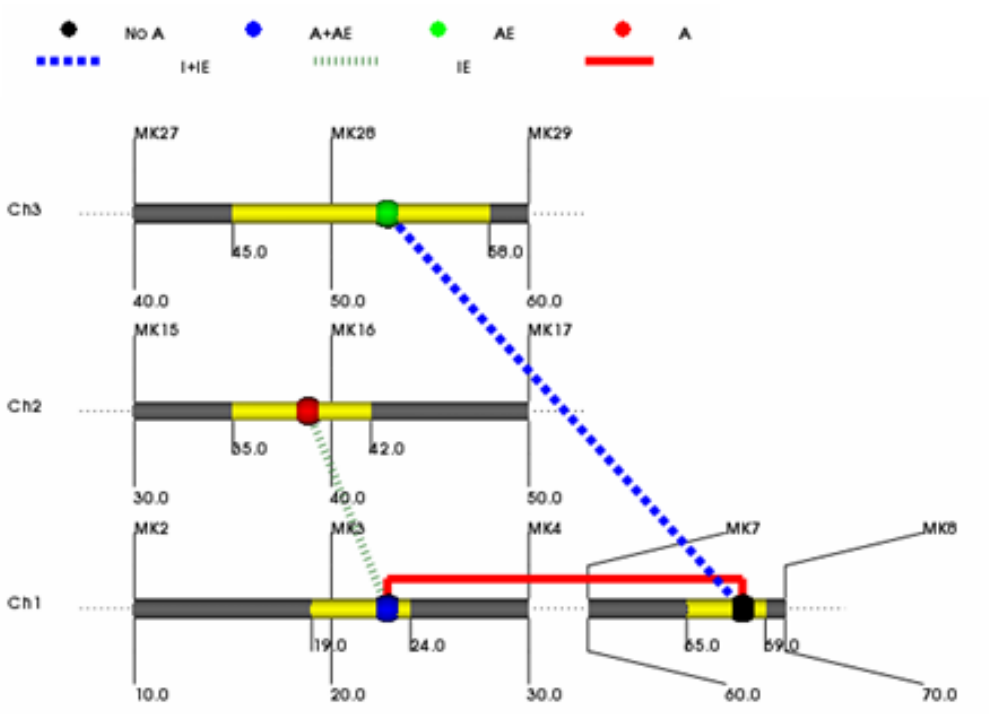
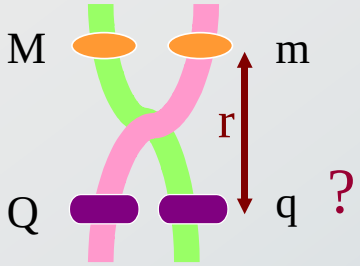


Fig. 3. Differential expression of QTL network

Populations for Mapping QTL



$(\frac{MQ}{MQ})$ $P_1 \times P_2$ $(\frac{mq}{mq})$

$\left(\begin{array}{cccc} \frac{MQ}{MQ} & \frac{Mq}{Mq} & \frac{mQ}{mQ} & \frac{mq}{mq} \\ \frac{1-r}{2} & \frac{r}{2} & \frac{r}{2} & \frac{1-r}{2} \end{array}\right)$

$(\frac{MQ}{mq})$ F_1 → Haploid → DH

$P_1 \times F_1$ $P_2 \times F_1$

$\left(\begin{array}{cccc} MQ & Mq & mQ & mq \\ \frac{1-r}{2} & \frac{r}{2} & \frac{r}{2} & \frac{1-r}{2} \end{array}\right)$

BC_1

$\left(\begin{array}{cccc} \frac{MQ}{MQ} & \frac{MQ}{Mq} & \frac{MQ}{mQ} & \frac{MQ}{mq} \\ \frac{1-r}{2} & \frac{r}{2} & \frac{r}{2} & \frac{1-r}{2} \end{array}\right)$ ⊗

F_2

BC_2

$\left(\begin{array}{cccc} \frac{mq}{MQ} & \frac{mq}{Mq} & \frac{mq}{mQ} & \frac{mq}{mq} \\ \frac{1-r}{2} & \frac{r}{2} & \frac{r}{2} & \frac{1-r}{2} \end{array}\right)$ ⊗

$\left(\begin{array}{ccccccccc} \frac{MQ}{MQ} & \frac{MQ}{Mq} & \frac{Mq}{Mq} & \frac{MQ}{mQ} & \frac{MQ}{mq}/\frac{Mq}{mQ} & \frac{Mq}{mq} & \frac{mQ}{mQ} & \frac{mQ}{mq} & \frac{mq}{mq} \\ \frac{(1-r)^2}{4} & \frac{r(1-r)}{2} & \frac{r^2}{2} & \frac{r(1-r)}{2} & \frac{r^2+(1-r)^2}{2} & \frac{r(1-r)}{2} & \frac{r^2}{2} & \frac{r(1-r)}{2} & \frac{(1-r)^2}{4} \end{array}\right)$

Experimental Design
(Observations n = 250×12×3=9,000)

- **Mapping Population**

  250 DH lines
- **Environments**

  4 Location, 3 Years
- **Replications**

  3 Blocks

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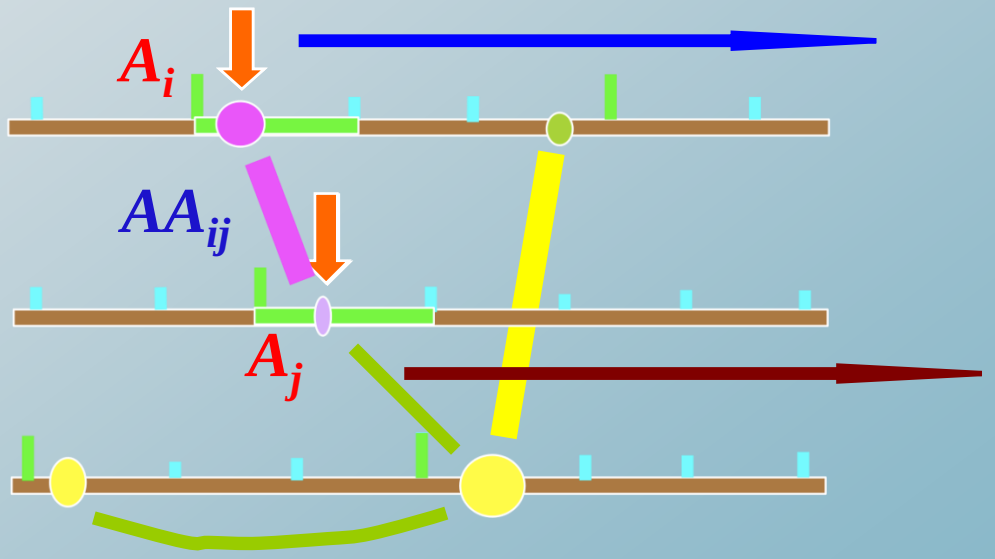
Mixed-model-based Composite Interval Mapping

(Wang & Zhu et al. 1999, TAG, V99)

Mapping QTL with A+AA and QE Interaction (DH, RIL)

$$y = \mu + A_i + A_j + AA_{ij} + E + A_iE + A_jE + AA_{ij}E + G_M + G_{MM} + G_ME + G_{MM}E + \varepsilon$$



Mixed-Linear Model Approaches

$$\mathbf{y} = \mathbf{Xb} + \mathbf{U}_E\mathbf{e}_E + \mathbf{U}_{QE}\mathbf{e}_{QE}$$
$$+\mathbf{U}_M\mathbf{e}_M + \mathbf{U}_{MM}\mathbf{e}_{MM} + \mathbf{U}_{ME}\mathbf{e}_{ME} + \mathbf{U}_{MME}\mathbf{e}_{MME} + \mathbf{e}_\varepsilon$$
$$= \mathbf{Xb} + \sum \mathbf{U}_u\mathbf{e}_u$$
$$\sim N(\mathbf{Xb}, \underset{(n\times n)}{\mathbf{V}} = \sum_{u=1}^{m}\sigma_u^2\mathbf{U}_u\mathbf{R}_u\mathbf{U}_u^T)$$

The Likelihood Function for QTL Mapping Model

$$L(\mathbf{b},\mathbf{V}) = (2\pi)^{-\frac{n}{2}}\left|\mathbf{V}\right|^{-\frac{1}{2}}\exp[-\tfrac{1}{2}(\mathbf{y}-\mathbf{Xb})^T\mathbf{V}^{-1}(\mathbf{y}-\mathbf{Xb})]$$

Estimation of QTL Main Effects

$$\ddot{\mathbf{b}} = (\mathbf{X}^T\mathbf{V}^{-1}\mathbf{X})^{-1}\mathbf{X}^T\mathbf{V}^{-1}\mathbf{y}$$

Prediction of QTL-Environment Interaction Effects

$$\ddot{\mathbf{e}}_u = \sigma_u^2\mathbf{U}_u^T[\mathbf{V}^{-1} - \mathbf{V}^{-1}\mathbf{X}(\mathbf{X}^T\mathbf{V}^{-1}\mathbf{X})^+\mathbf{X}^T\mathbf{V}^{-1}]\mathbf{y}$$

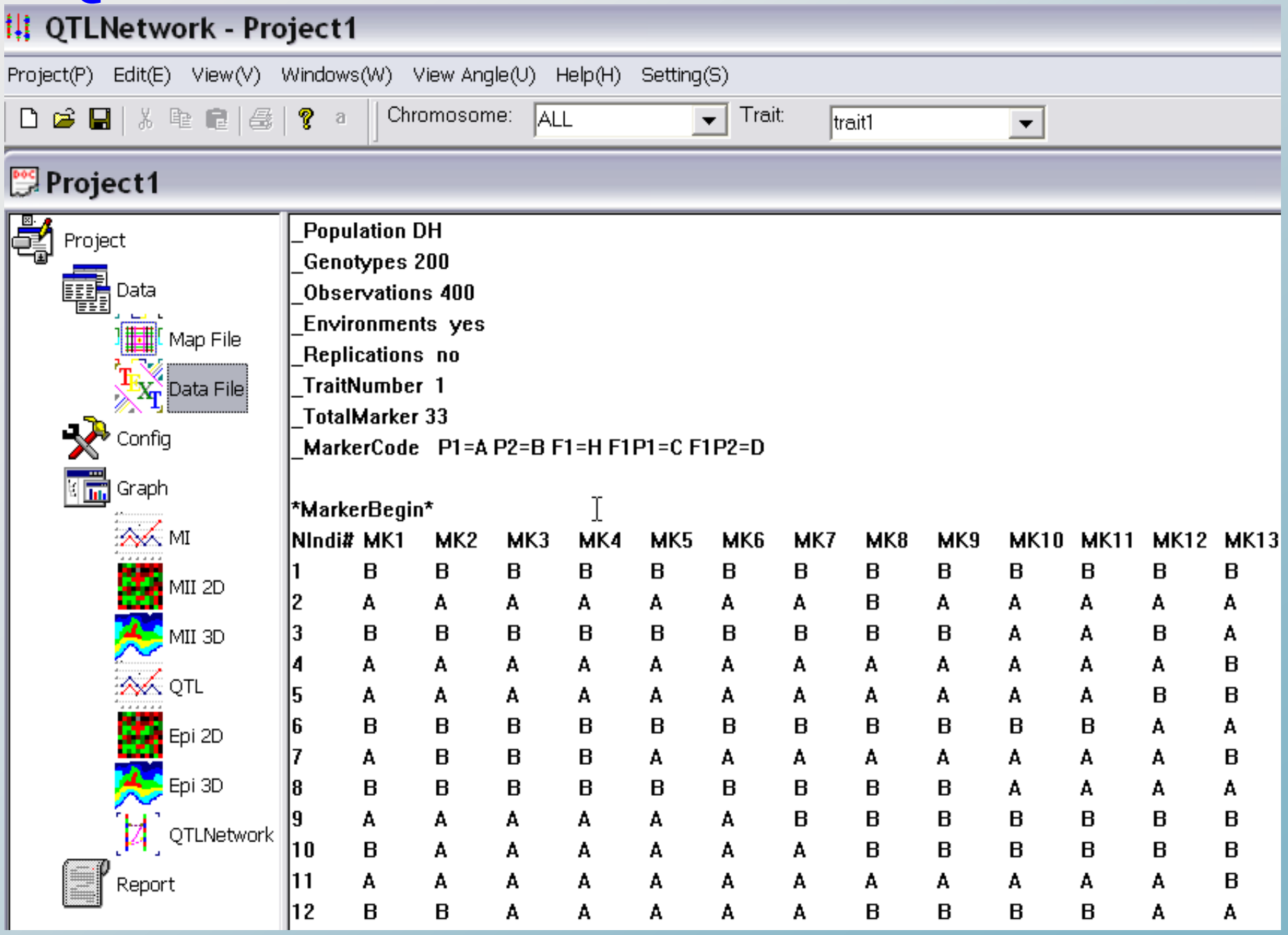
Challenges in Computation for Inverses of Big Matrix $\mathbf{V}_{(9000\times 9000)}$

- Rice Map Distance = 2031 cM
- Step of QTL Searching= 1 cM
- Steps of Two-dimession Search

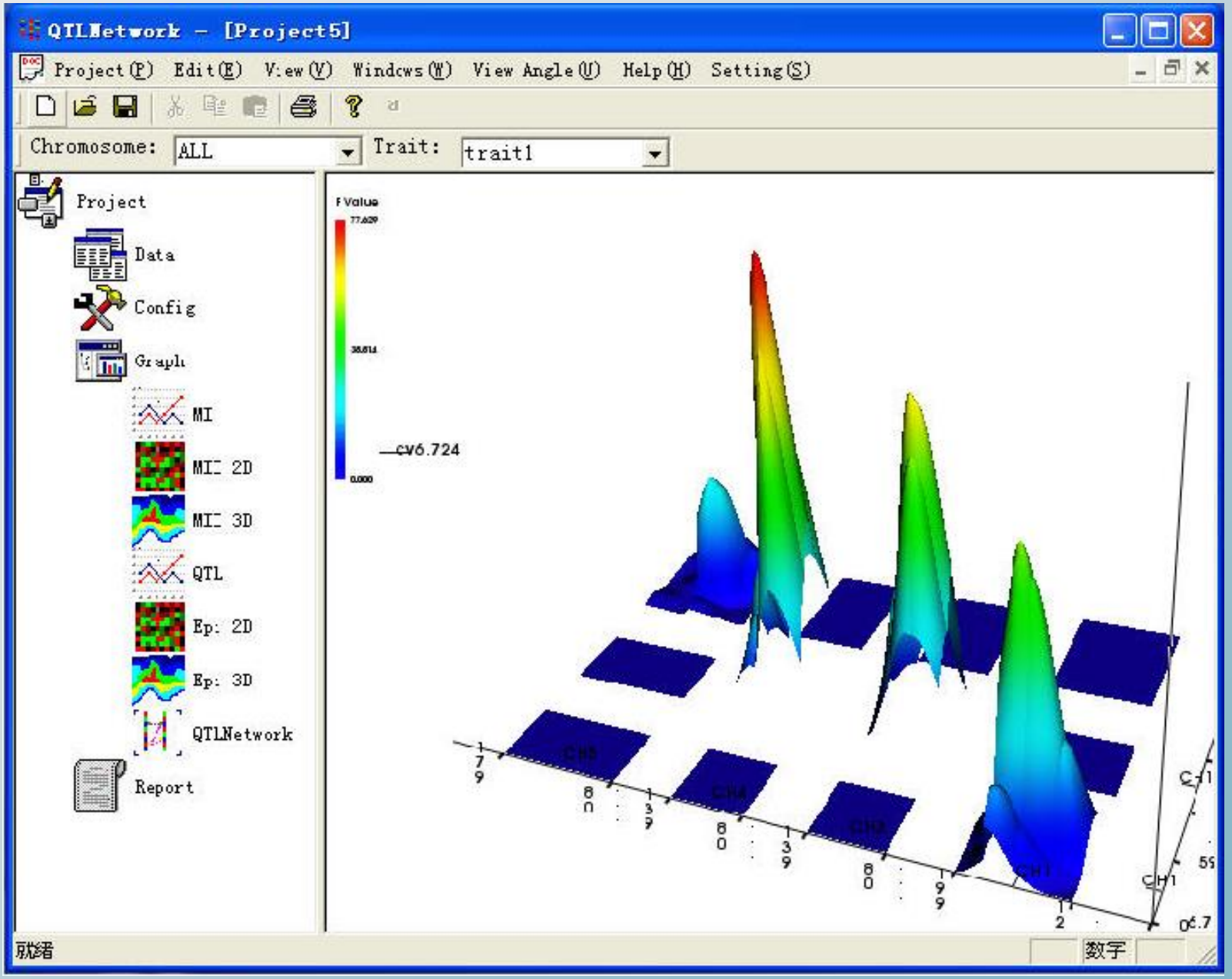
  = 2031× 2030/2 = 2.06 Millions

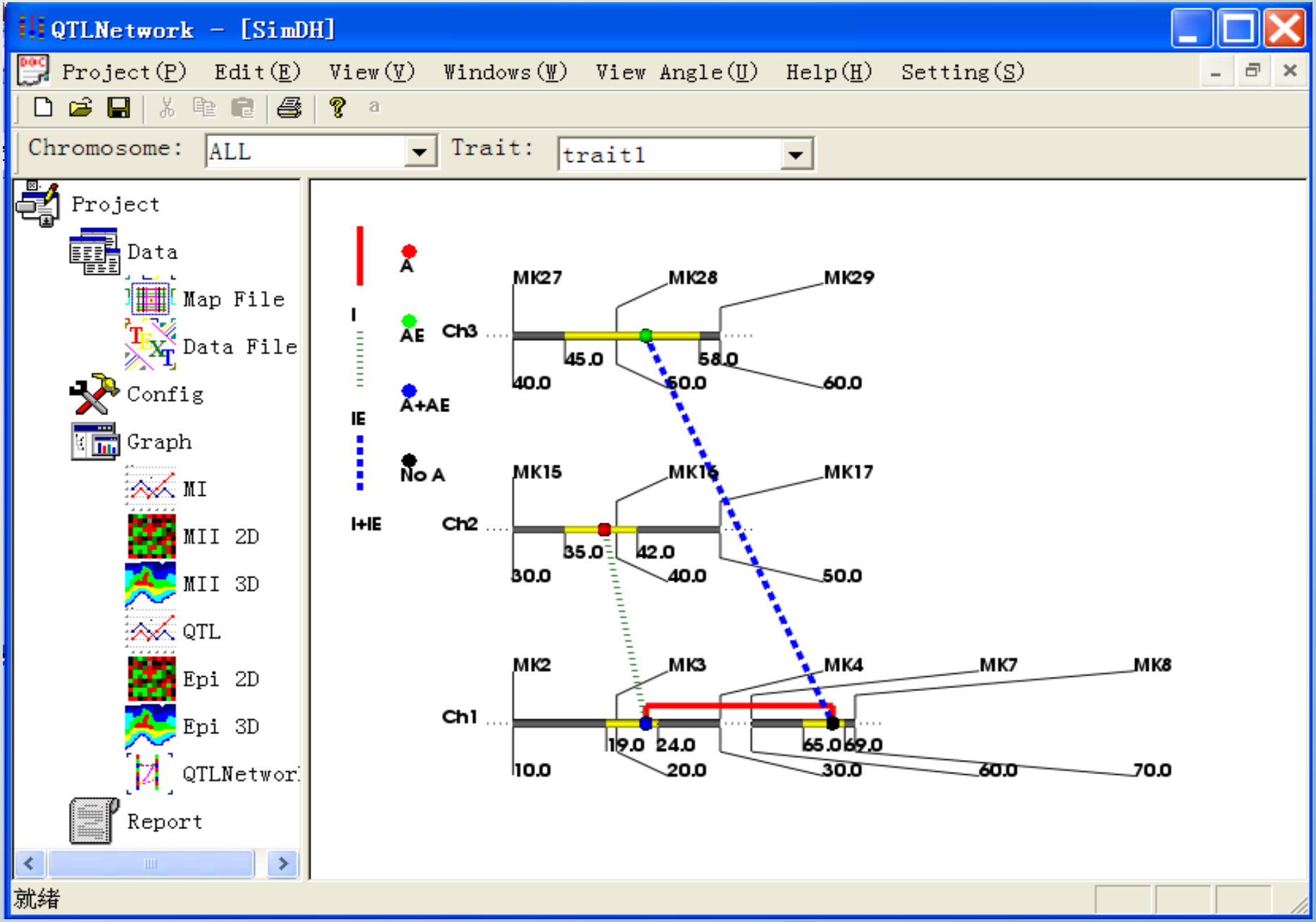
- Detecting QTLs for 10 Traits Needs to Calculate 20.6 Millions Inverses of V

QTLNetwork version 2.0



QTLNetwork 2.0




QTLNetwork - [SimDH]
Project(P) Edit(E) View(V) Windows(W) View Angle(U) Help(H) Setting(S)
Chromosome: ALL
Trait: trait1
Project
Data
Map File
Data File
Config
Graph
MI
MII 2D
MII 3D
QTL
Epi 2D
Epi 3D
QTLNetwor
Report
A
AE
A+AE
No A
I
IE
I+IE
Ch3
MK27
MK28
MK29
40.0
45.0
50.0
58.0
60.0
Ch2
MK15
MK16
MK17
30.0
35.0
40.0
42.0
50.0
Ch1
MK2
MK3
MK4
MK7
MK8
10.0
19.0
20.0
24.0
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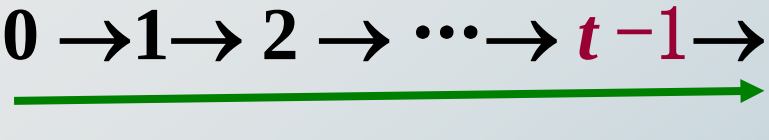
65.0
69.0
60.0
70.0
就绪

Mapping Developmental QTL for Complex Traits



Unconditional Model for Phenotypic Value at Time t

$$y(t) = \mu(t) + G_Q(t) + E(t) + G_QE(t)$$

$$+ G_M(t) + G_ME(t) + \varepsilon(t)$$

Analyzing Q & QE Effects from Time 0→t

Conditional Model for Phenotypic Value at Time t

$$y(t|t\text{-}1) = \mu(t|t\text{-}1) + G_Q(t|t\text{-}1) + E(t|t\text{-}1)$$

$$+ G_QE(t|t\text{-}1) + G_M(t|t\text{-}1) + G_ME(t|t\text{-}1) + \varepsilon(t|t\text{-}1)$$

Analyzing Net Q & QE Effects From Time t -1 → t

Table 2. Chromosomal regions and estimated genetic effects of QTLs for plant height (cm) at different stages in two environments. (Yan, *et al.* 1998, Genetics, V150)

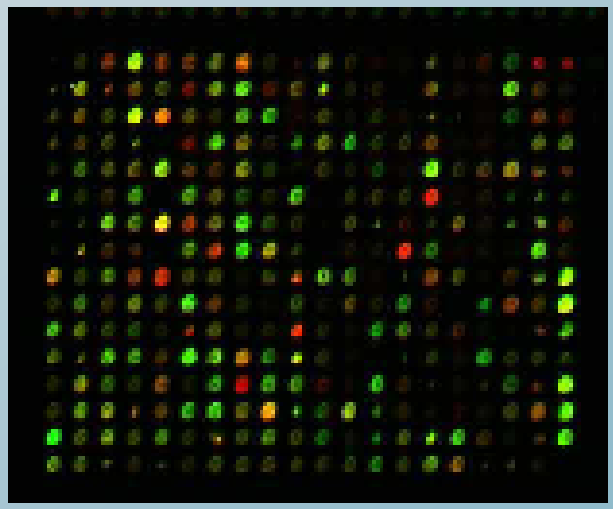
QTL	Maker Interval	Dist-ance (cM)	Days	Main effect		GE in Hangzhou		GE in Hainan	
				t	$t\|t-1$	t	$t\|t-1$	t	$t\|t-1$
Ph1	RZ730-RZ801	33.1	10	-2.14	-2.14			-1.08	-1.08
			20	-2.47				-0.95	
			30	-3.6				-1.45	-0.52
			40	-4.6				-3	-0.52
			50	-5.06			-1.68	-3.12	1.05
			60	-9.54	-0.55	-3.09	-1.7	-2.64	1.1
			70	-12.57		-4.39		-3.51	
			80	-15.01		-4.47		-4.35	
			90	-16.98		-4.07		-4.36	
Ph2	Amy1A/C-RG95	12.8	10	1.03	1.03			0.63	0.63
			20	1.51				0.76	
			30	1.93				0.93	
			40	2.91		0.99		1.25	
			50	2.77	0.92		-0.74	1.05	-0.74
			60	4.74		2.55			
			70	6.07		2.67			
			80	7.73		2.42		1.93	
			90	7		1.62		1.69	

Challenges in Presentation of G-G and G-E During Developmental Stages

- For G-G interaction presentation, there needs two-dimension display
- When Genes express differently across times and spaces, there needs four-dimension display or three-dimension dynamic display

Experimental Design for Microarray Testing

- **Array Design：**
  - **14112 Genes (84 x 68)/Array**
- **Treatment Design（3 Way Factors）：**
  - **Factor G: 14112 Genes**
  - **Factor C：8 Cancer Cells**
  - **Factor M：7 Medicine**
- **Replicates: 3**



Combining Analysis

$$y_{ijkl} = G_l + A_i + C_j + M_k + GA_{li} + GC_{lj} + GM_{lk} + \varepsilon_{ijkl}$$

Challenges in Mixed-Model Approaches for Array Analysis

$$\mathbf{y} = \mathbf{X}\mathbf{b}_G + \mathbf{U}_A\mathbf{e}_A + \mathbf{U}_C\mathbf{e}_C + \mathbf{U}_M\mathbf{e}_M$$
$$+\mathbf{U}_{GA}\mathbf{e}_{GA} + \mathbf{U}_{GC}\mathbf{e}_{GC} + \mathbf{U}_{GM}\mathbf{e}_{GM} + \mathbf{e}_\varepsilon$$
$$= \mathbf{X}\mathbf{b}_G + \sum_{u=1}^{7}\mathbf{U}_u\mathbf{e}_u \sim N(\mathbf{X}\mathbf{b}_G, \underset{(n\times n)}{\mathbf{V}} = \sum_{u=1}^{7}\sigma_u^2\mathbf{U}_u\mathbf{U}_u^T)$$

Prediction of Random Effects

$$\hat{\mathbf{e}}_{u(1)} = \mathbf{U}_u^T\mathbf{V}_{(1)}^{-1}(\mathbf{y} - \mathbf{X}\hat{\mathbf{b}})$$
$$= \mathbf{U}_u^T[\mathbf{V}_{(1)}^{-1} - \mathbf{V}_{(1)}^{-1}\mathbf{X}(\mathbf{X}^T\mathbf{V}_{(1)}^{-1}\mathbf{X})^+\mathbf{X}^T\mathbf{V}_{(1)}^{-1}]\mathbf{Q}_{(1)}\mathbf{y}$$

Experiment Size

n = 14112 ×8×7×3 = 2.37 Millions

A Two-step Strategy for Detecting Differential Gene Expression of cDNA Microarray Data

(Lu, Zhu, &, Liu, 2005, Current Genetics. 47: 121–131)

Choosing a subset of potential genes with differential expression

$$y_{ijk(l)} = \mu_{(l)} + A_{i(l)} + V_{j(l)} + D_{k(l)} + \gamma_{ijk(l)}$$

Combining analysis of multiple genes

$$y_{ijkl} = G_l + A_i + C_j + M_k + GA_{li} + GC_{lj} + GM_{lk} + \varepsilon_{ijkl}$$

Experiment Size Reduced to ≈ 300

n = 300×8×7×3 ≈ 50,400

Thank You!