G7.5

The Map Expansion Obtained with Recombinant Inbred Strains and Intermated Recombinant Inbred Populations for Finite Generation Designs

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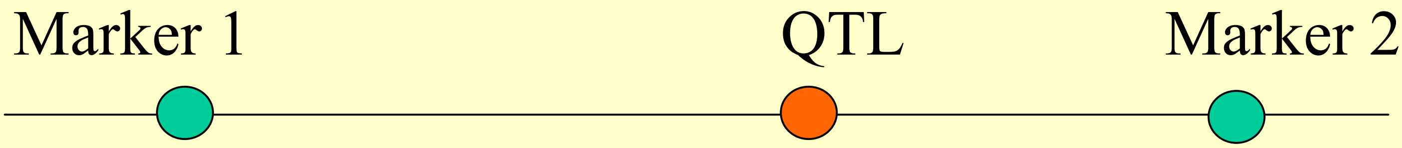
Introduction

Chromosome



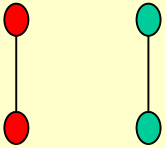
Problem: If markers are close together, few recombinations result in a normal experiment (F_2-intercross). -> no fine mapping

Introduction II

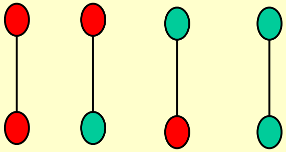
Map (genetic) **distance** ***x***: Expected number of crossovers between two loci during meiosis

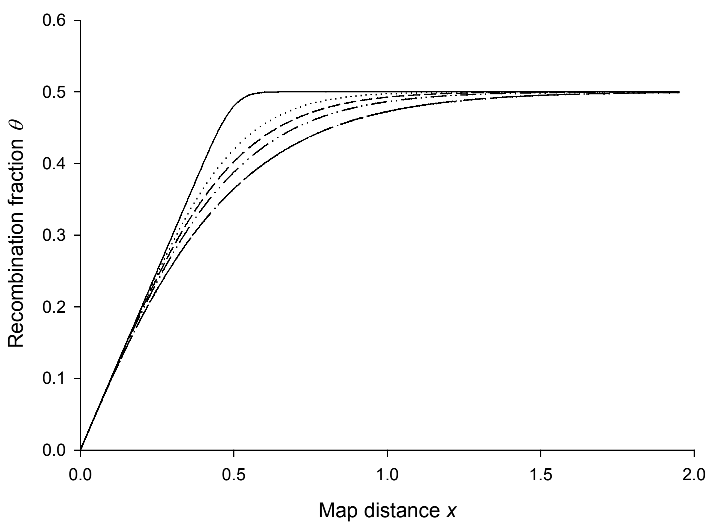
Recombination fraction ***θ***: Fraction of non-parental gametes after meiosis (odd number of crossovers between two loci)

Parental:



Inherited:





Advanced Designs

One way to increase recombination: advanced designs like

recombinant inbred strains (RIS),
advanced intercross lines (AIL), or
intermated recombinant inbred populations (IRIP)

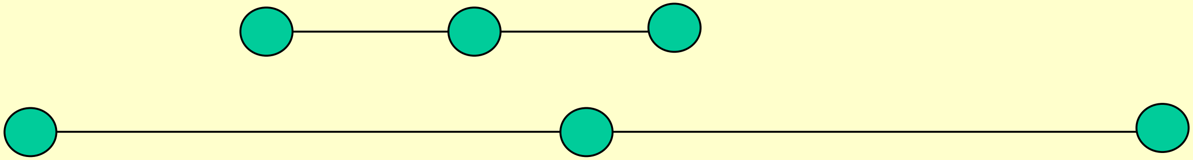
Advanced Designs II

RIS	**AIL**	**IRIP**
$F_1 = L_1 \text{ x } L_2$	$F_1 = L_1 \text{ x } L_2$	$F_1 = L_1 \text{ x } L_2$
$F_2 = F_1 \text{ x } F_1$	$F_2 = F_1 \text{ x } F_1$	$F_2 = F_1 \text{ x } F_1$
RIS(1) =brother x sister	AIL(3)=$F_3 = F_2 \text{ x } F_2$	AIL(3)
....	...	....
RIS(40)	AIL(10)	AIL(10)
		IRIP(10, 1)= RIS(1)
		....
		IRIP(10, 40)=RIS(40)

Map Expansion

Liu et al. (1996): „The degree of map expansion depends on the recombination fraction θ, i.e., the larger the value of θ, the less the expansion.“

Winkler et al. (2003): “We stress however, that the *maximum* map expansion factors apply *only* when the recombination fraction is zero; marker pairs that have larger recombination frequencies will have less map expansion. This point appears to been misunderstood in the literature (Coe et al. 2002; Lee et al. 2002).”



Broman (2005): „In general, one can **define** the map expansion as

$$\mathrm{d}\theta_* / \mathrm{d}\theta \big|_{\theta \to 0} \qquad .$$

Map Expansion II

Let $x_* = g(x)$ be the relation of the genetic scales. Since genetic distances are additive, $g(x_1 + x_2) = g(x_1) + g(x_2)$ holds for two adjacent intervals, i.e., $g(x)$ is a linear function.

Therefore, $x_* = a\,x$ is valid for all x.

The map expansion factor is $a = \mathrm{d}x_* / \mathrm{d}x$.

Map Expansion III

From generation to generation, the map function $\theta = \theta(x)$ is assumed.

For the accumulated meioses, the map function $\theta_* = \theta_*(x_*)$ is assumed.

Known: $\theta_* = \theta_*(\theta)$.

Consider $\theta_*(x_*) = \theta_*\{\theta[x(x_*)]\}$ with $x = x_*/a$.

Then $$\frac{\mathrm{d}\theta_*(x_*)}{\mathrm{d}x_*} = \frac{\mathrm{d}\theta_*(\theta)}{\mathrm{d}\theta}\frac{\mathrm{d}\theta(x)}{\mathrm{d}x}\frac{\mathrm{d}x(x_*)}{\mathrm{d}x_*}$$ holds,

i.e. $$a = \frac{\mathrm{d}\theta_*(\theta)}{\mathrm{d}\theta}\frac{\mathrm{d}\theta(x)}{\mathrm{d}x}\left\{\frac{\mathrm{d}\theta_*(x_*)}{\mathrm{d}x_*}\right\}^{-1} .$$

The map expansion factor *a*

$$a = \frac{\mathrm{d}\theta_*(\theta)}{\mathrm{d}\theta}\frac{\mathrm{d}\theta(x)}{\mathrm{d}x}\left\{\frac{\mathrm{d}\theta_*(x_*)}{\mathrm{d}x_*}\right\}^{-1}$$

If x, x_*, θ, or θ_* is zero, all the others are also zero.

For small map distances, map functions have slope one:

$$a = \left.\frac{\mathrm{d}\theta_*(\theta)}{\mathrm{d}\theta}\right|_{\theta\to 0}$$

$$x_* = x\left.\frac{\mathrm{d}\theta_*(\theta)}{\mathrm{d}\theta}\right|_{\theta\to 0}$$

Advanced genetic distance proportional to genetic distance.
Map expansion factor constant.

Advanced recombination and genetic distance

$$\theta_{\mathrm{AIL}(j)} = \left\{1-(1-\theta)^{j-2}(1-2\theta)\right\}/2$$

Darvasi & Soller (1995),
Liu et al. (1996)

$$x_{\mathrm{AIL}(j)} = j\,x/2$$

$$\theta_{\mathrm{RIS}(\infty)} = \frac{4\,\theta}{1+6\,\theta}$$

Haldane & Waddington (1931

$$x_{\mathrm{RIS}(\infty)} = 4\,x$$

$$\theta_{\mathrm{IRIP}(j,\,\infty)} = \frac{\theta_{\mathrm{AIL}(j)} + 3\,\theta}{1+6\,\theta}$$

Winkler et al. (2003)

$$x_{\mathrm{IRIP}(j,\,\infty)} = \left(j/2+3\right)x$$

Map expansion for finite generations

Finite inbred generations:

$$
\begin{aligned}
\theta_0^* &= \theta_0\,, \\
\theta_1^* &= \theta_0 + (1-2\theta_0)\,\theta/2\,, \\
\theta_2^* &= \theta_0 + (1-2\theta_0)\,\theta\,(1-\theta/2)\,, \\
\theta_3^* &= \theta_0 + (1-2\theta_0)\,\theta\left(1.375-1.5\theta+\theta^2/2\right), \\
&\vdots
\end{aligned}
$$

$$\theta_i^* = \theta_0 + (1-2\,\theta_0)\,\theta\,(\alpha_i + \theta\,\mathrm{P}_i(\theta))$$

For small θ, θ_0:

$$\theta_i^* = \theta_0 + \theta\,\alpha_i$$

$$
\begin{aligned}
x_{\mathrm{RIS}(j,i)} &= (1+\alpha_i)\,x \\
x_{\mathrm{IRIP}(j,i)} &= (j/2+\alpha_i)\,x
\end{aligned}
$$

Map expansion for finite generations II

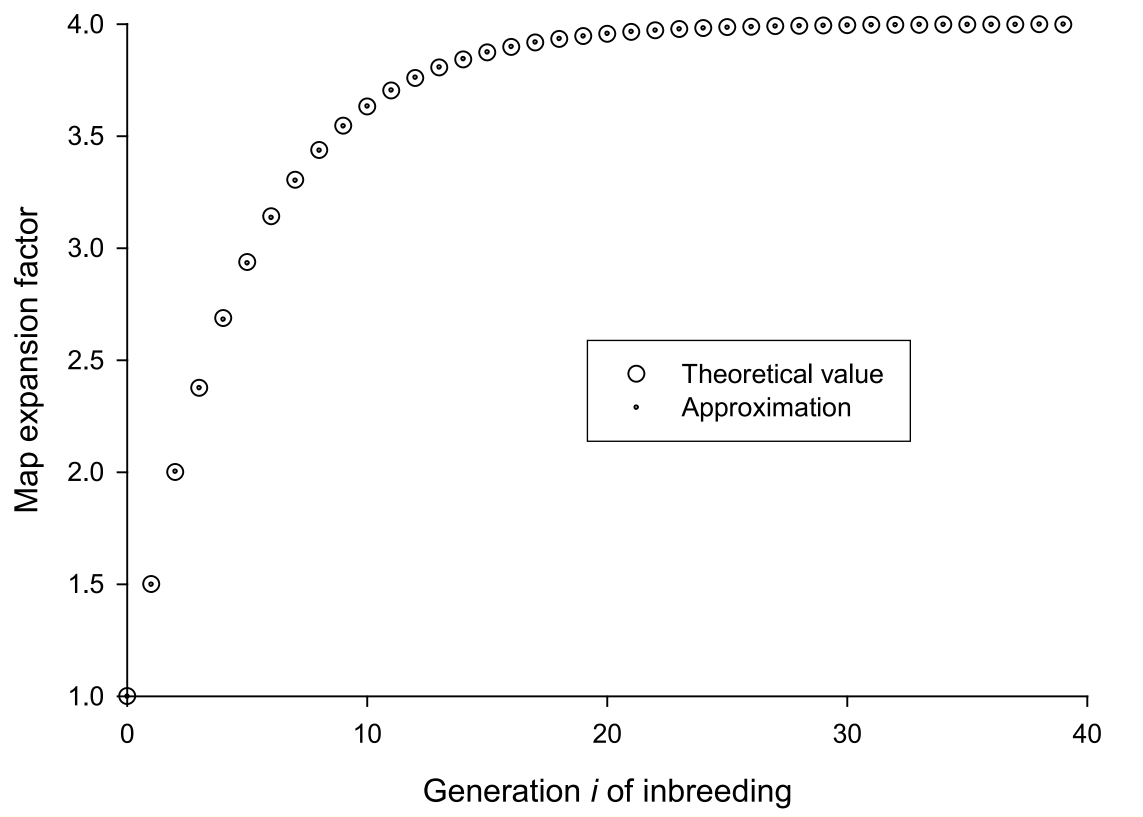
Approximation:

$$\tilde{\alpha}_0 = 0 \quad , \tilde{\alpha}_1 = 0.5$$

$$\tilde{\alpha}_i = -16.208 + 19.208 \tanh\left\{0.10864\,(i + 11.365)\right\} \quad \text{for } i \geq 2$$

Map expansion for finite generations III

RIS(*i*)



Summary

Uncertainties with map expansion clarified.

Finite generation results for RIS and IRIP
(tool for experimental design).

Remark

Take care with mapping. Interference of advanced designs differs from interference acting at meiosis (mostly relaxed).

Thank you!

This contribution based on a manuscript of Teuscher et al. which appears in „Genetics“ June 2005.