

MAGIC

Multiparent

Advanced

Generation

Inter-

Cross

Multiparent populations for fine mapping complex traits in crop species.

The Advanced Intercross

Introduced by Darvasi & Soller 1995:

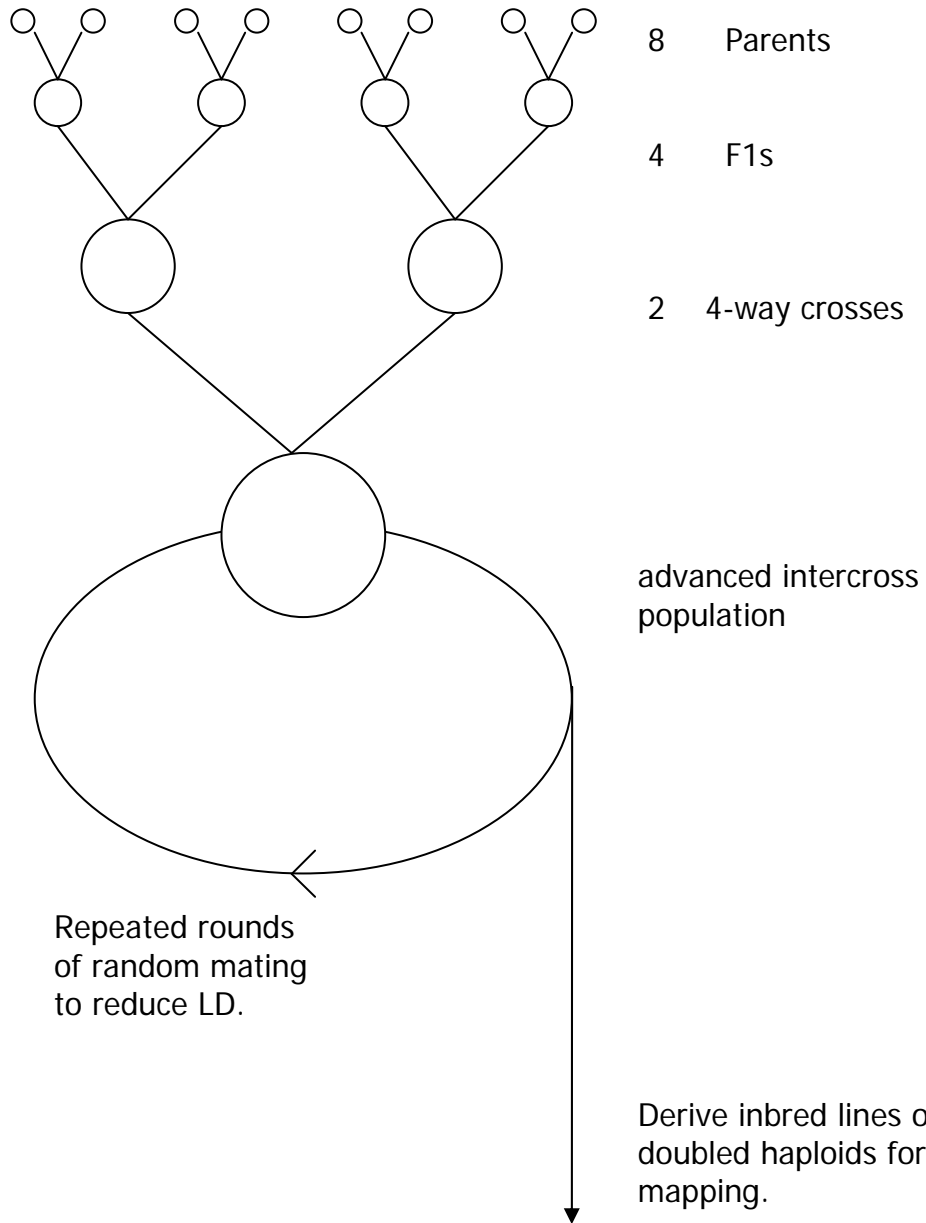
instead of linkage analysis on F_2 derived lines

first intermate the F_2 for several generations:

linkage analysis on F_n derived lines

precision is improved

but power of detection is worse.



MAGIC

Diverse: good for multiple interacting traits and loci.

QTL detection in early generations

Fine mapping in later generations

Success in mouse

97 traits

843 QTLs, average 95% confidence interval of 2.8 Mb.

The QTLs contribute to variation in 97 traits, including models of human disease (asthma, type 2 diabetes mellitus, obesity and anxiety) as well as immunological, biochemical and hematological phenotype

- 4.8 Mb region with QTL for anxiety

- Select conserved regions and compare sequence distribution pattern among founders with that of the QTN

- 14 SNPs identified as functional candidates out of 15,000

The Collaborative Cross

Mouse genetics and mouse models of human disease are extremely important in medical and pharmaceutical research.

\$3.5m p.a. for 8 years + \$3m for genotyping.

<http://www.complextait.org/>

“Ideal resource for systems biology as it will provide a reproducible, highly varied yet controlled set of genetic backgrounds for functional genomic studies.”

Success in maize

Illinois long-term selection experiment. (b 1896)

Gen 70 – high and low selections crossed

Hybrid population intermated for 10 generations

50 QTL accounting for 50% Vg identified by LD mapping

Laurie et al Genetics 2004, **168**:2141-2155

NIAB programme in wheat

2 new populations

1 diverse	16 founders	selected on markers
1 elite	8 founders	selected on phenotype

2 lines in common

5 parents of existing bi-parental mapping populations

2 existing populations

1 INRA	60 founders	12 gens gms facilitated outcrossing
1 UK	22 founder	4 gens gms facilitated outcrossing

Plan to generate 1000 inbred lines from each population

NIAB aspirations

Had hoped to get UK funding (failed) for:

Sorghum (ICRISAT)

Rice (IRRI)

Faba bean (ICARDA)

Phaseolus (CIAT)

Cowpea (IITA)

MAGIC: design

P1 x P2

P3 x P4

generation 1

12

x

34

generation 2

1234

AABB x aabb

AABB x aabb

or

AABB x AABB

aabb x aabb

AaBb x

AaBb

AABB x

aabb

+ recombination

- recombination

With more lines and more alleles it is impossible to cover all bases

Eight parent MAGIC population: make all possible crosses

G1: $n(n-1)/2 = 28$ F1 combinations

G2: $n(n-1)(n-2)(n-3)/8 = 210$ crosses among unrelated F1s

G3: $210 \times 3 / 2 = 315$ ways to make the final generation
(ABCD can be crossed with EFGH or EGFH or EHFG)

NB G3 is segregating, so maybe need replicate crosses

With 8 founders everything is just about possible. >8 cause problems

Intelligent design of crossing schemes

Search for balanced schemes in which the expected contribution of recombinant and non-recombinant haplotypes is as uniform as possible.

Borrow methods of construction from balanced incomplete block designs constructed from Latin Squares.

Four crossing schemes for 16 founder MAGIC

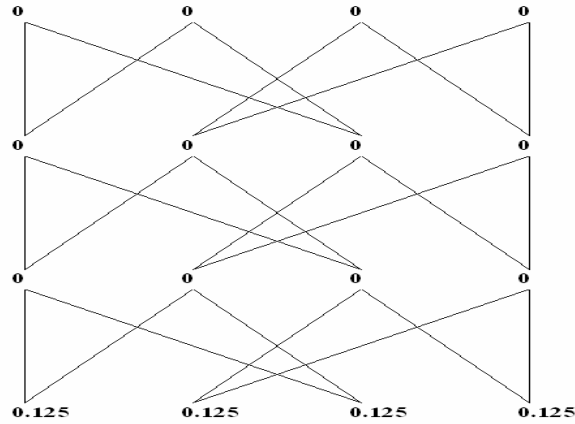
No. of crosses in each generation

Gen	simple	sparse	balanced	full
0	8	40	120	120
1	4	20	60	5860
2	2	10	30	forget it
3	1	5	15	

Computer simulation – provided you don't use a simple funnel scheme, it doesn't seem to make much difference.

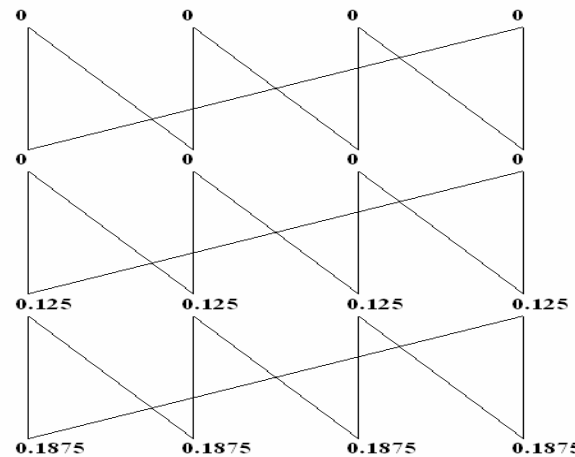
Methods of population maintenance

Double first cousin mating:



$$f_3 = 0.125$$

Half sib or circular mating



$$f_3 = 0.1875$$

Random mating (no selfing)

$$f_3 = 0.3047$$

Methods of analysis

Single marker analysis

Multipoint analysis – HAPPY (www.well.ox.ac.uk) tests for differences in effects of progenitor haplotypes

Linkage analysis – keep track of the pedigree

Related methods

Buckler group, Nested Association Mapping:

5000 RILs total from 25 inbreds x B73 crosses
sequence parents
genotype progeny ~ 2500 SNPs per line

Illinois long-term selection experiment:

500 S2 lines derived and tested per-se and in test-crosses
2 reps, 3 locations, 2 years
genotyped at 488 SNPs which discriminate between high and low
(*plus some SNPs selected from candidate oil genes*)

These (and MAGIC) are large scale studies because:

- 1) Precision goes up but power falls.
- 2) Why dick about?

Conclusions

Lower costs and higher densities of markers offer new opportunities for mapping.

Biology of the crop, availability of markers and phenotypes will be major determinants in choice of mapping population, but:

MAGIC promises improved methods for fine mapping in many crops in breeder relevant germplasm and provides a common platform for multiple researchers.

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