Genome wide association studies of human complex diseases with EGEE

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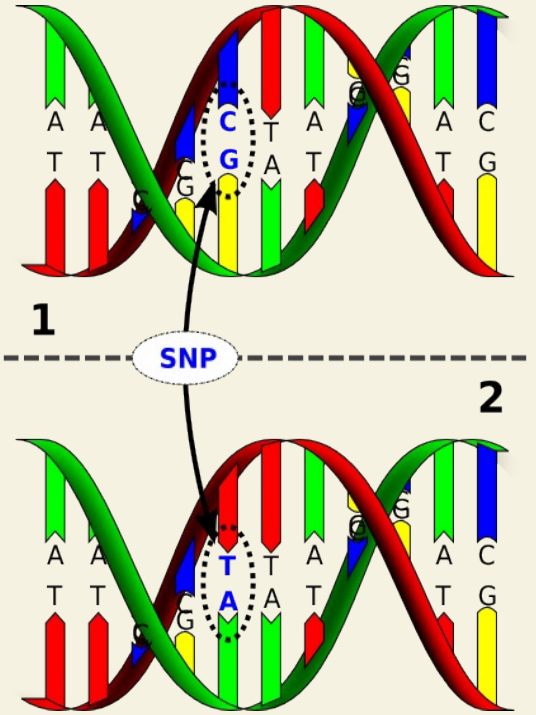
Association studies

- Single Nucleotide Polymorphism (SNP)
  - a single genetic variation at a specific location on the genome

- Find genetic factors responsible for a disease :
  - compare frequency of SNPs between cases and controls
    - most commonly : each SNP is analysed at a time



source: wikipedia

Haplotype associations

~Haplotype :

- combination of SNPs on a chromosome
- more powerful approach than looking at each SNP separately

~Why ?

- several SNPs taken together could be responsible for the disease
- haplotypes better characterize the variable structure of the genome

THESIAS program

Testing Haplotype Effects In Association Studies

~Difficulty

- haplotypes must be inferred from the genotype
  - ~for individuals who are double heterozygotes (AC|GT) haplotypes cannot be deduced
    - example with the combination of SNPs A/C and G/T

	GG	GT	TT
AA	(AG,AG)	(AG,AT)	(AT,AT)
AC	(AG,CG)	(AG,CT) ***or*** (AT,CG)	(AT,CT)
CC	(CG,CG)	(CG,CT)	(CT,CT)

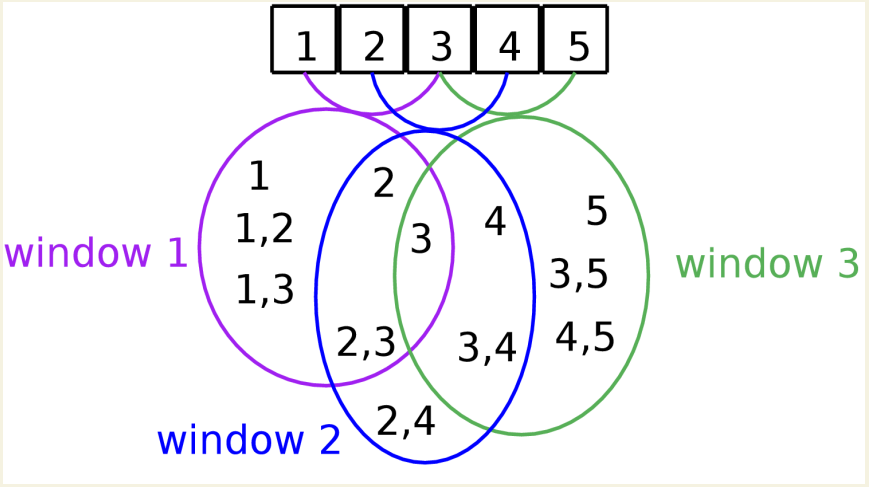
    - with more than 2 SNPs, the difficulty increases

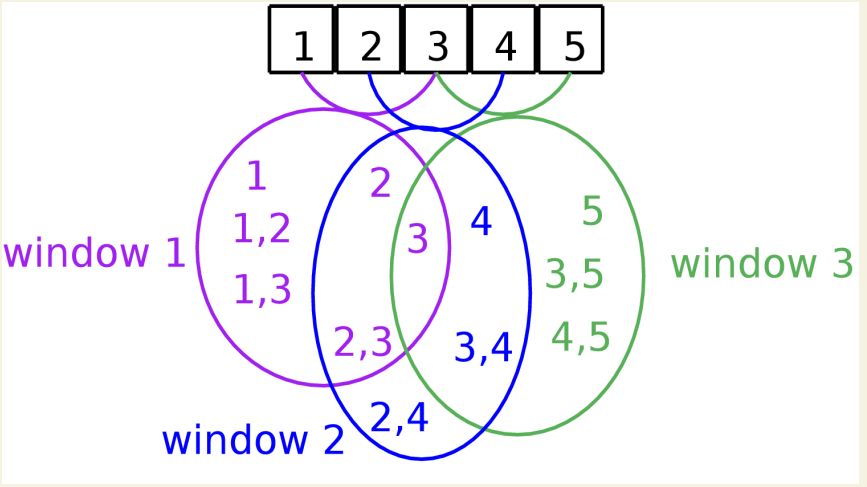
Complexity

- DNA chips
  - allow to genotype hundreds of thousands of SNPs across the genome
- Example with 8500 SNPs :
  - SNP only study
    - 8500 computations
  - haplotypes study
    - $C_{8500}^{1}+C_{8500}^{2}+\ldots+C_{8500}^{8499}+C_{8500}^{8500}=2^{8500}-1$ computations

Reducing complexity in THESIAS

- The sliding-window approach
  - haplotypes composed of SNPs located close to each other are expected to be more biologically meaningful





- The chosen combinations approach
  - keep only relevant combinations, by eliminating SNPs providing the same information

THESIAS job definition

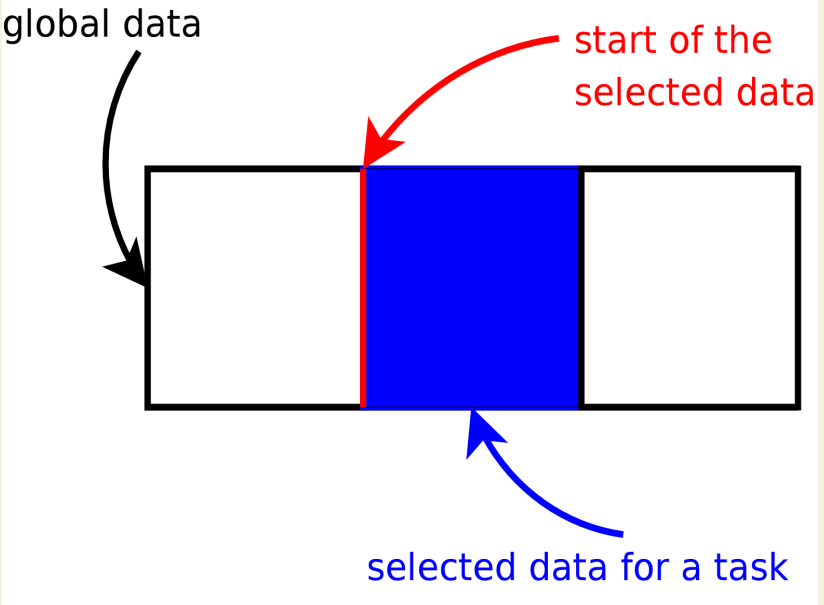
- A process on the grid
  - computes one block of SNPs combinations
  - defined by two arguments of THESIAS
    - start_id , end_id

1 job = one block of combinations

ID	Combination
1	(1,8)
2	(2,8)
3	(3,8)
4	(4,8)
5	(5,8)

THESIAS task definition

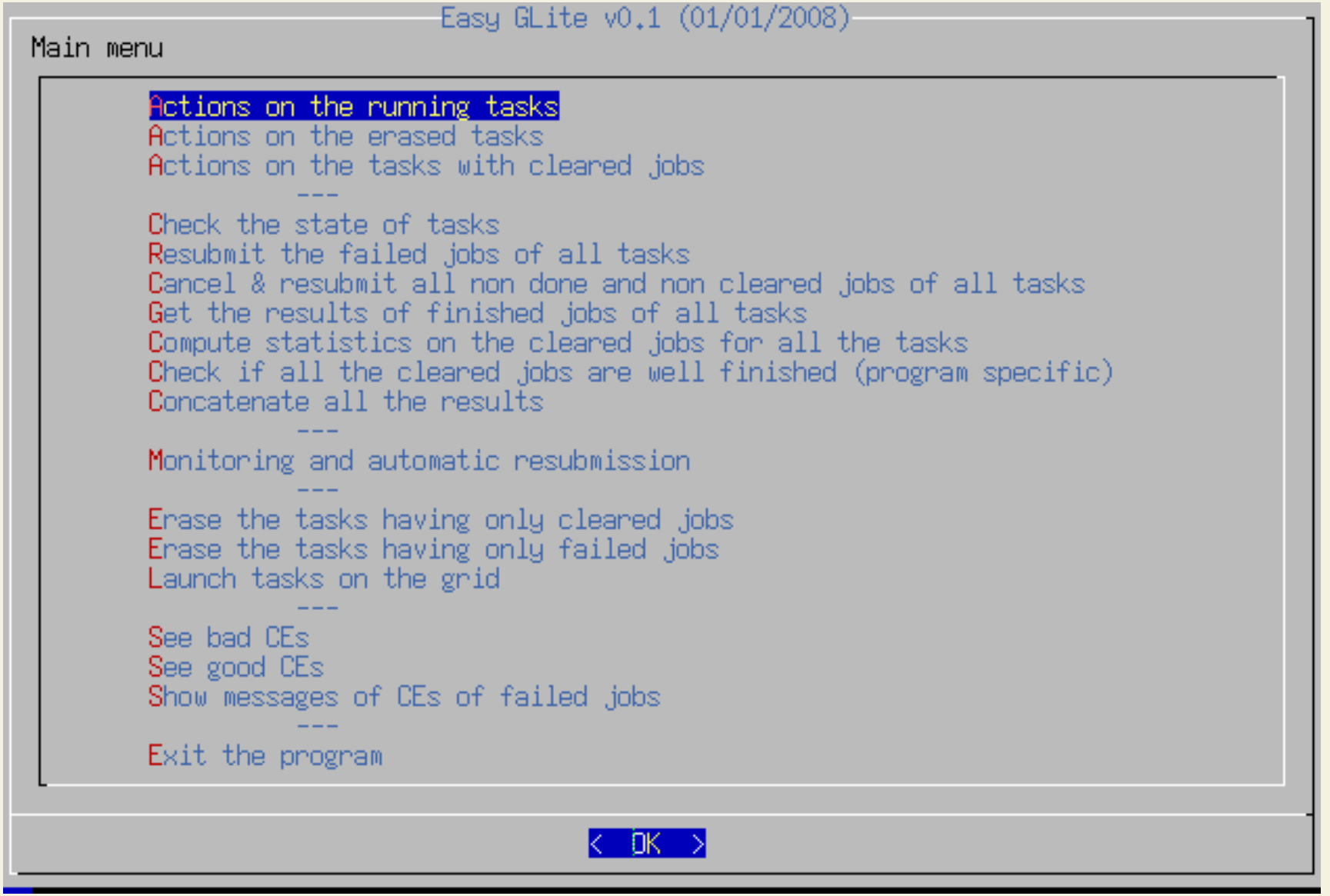
- Original set of SNPs splitted into regions
- Only the region containing the data needed for specific computations is sent on the grid
- Task definition
  - a set of blocks of SNPs combinations (a set of jobs) in a given region to be investigated



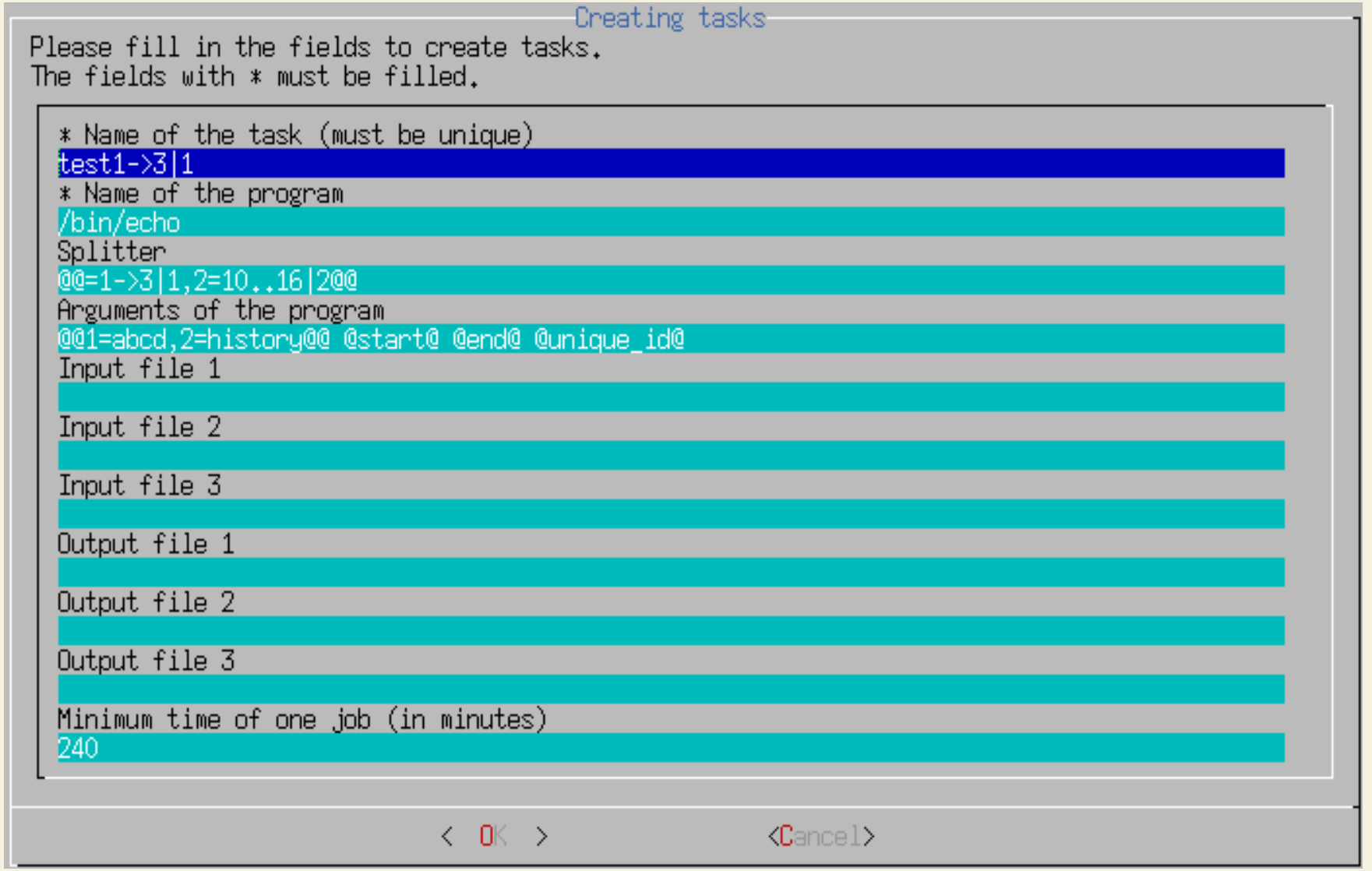
Easy-gLite

- General purpose and easy to use interface on top of the gLite UI (User Interface)
  - created to simplify batch jobs submissions
- Features
  - creating sets of tasks by filling only one form
  - manage jobs, tasks and all the tasks
  - automatic resubmission (“timeout” or failed jobs)
  - output retrieval of all (or some) completed jobs

Easy-gLite main menu



Easy-gLite submission form



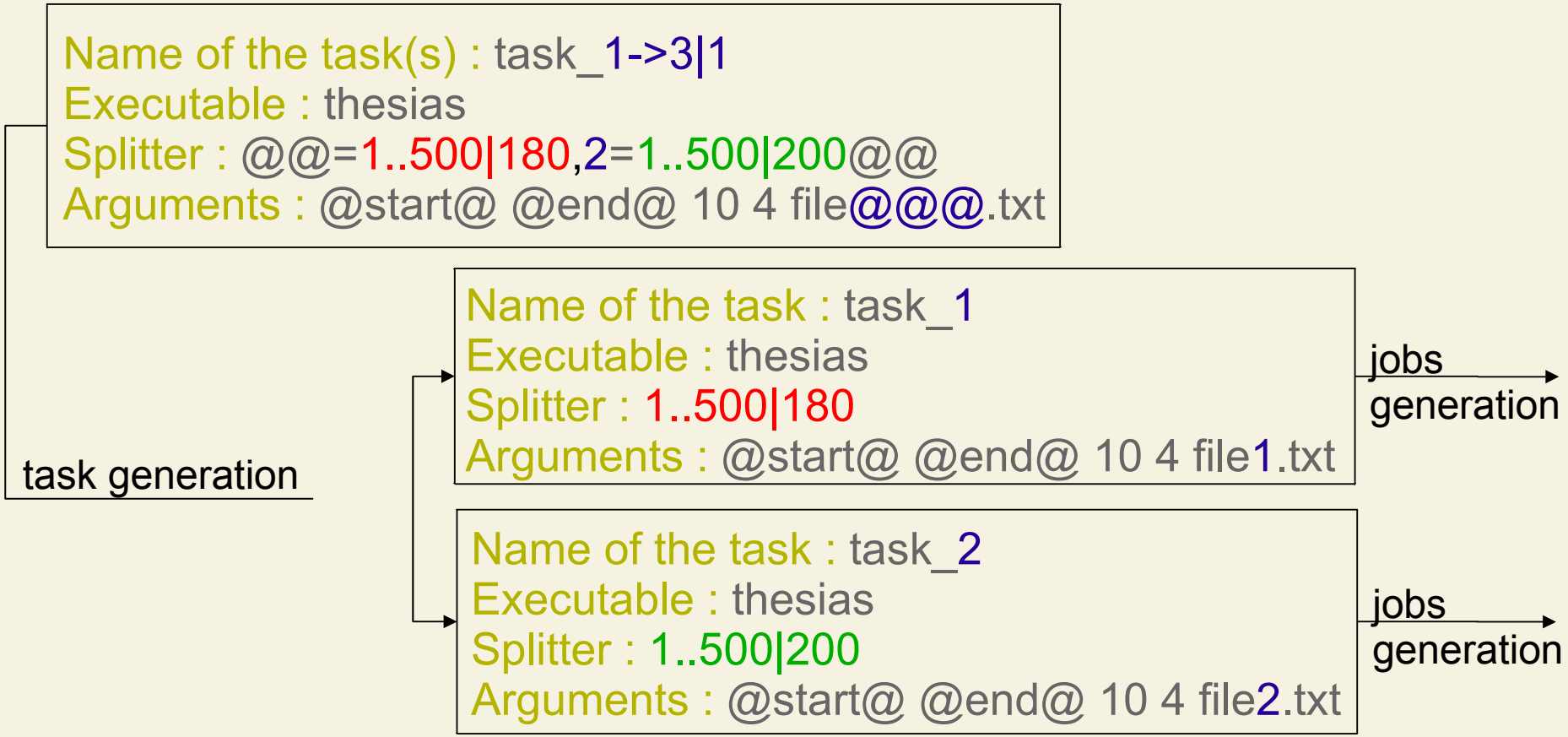
Easy-gLite submission form syntax

- Example of task creation with generation of arguments
  - the syntax “x..y|z” in the Splitter field

    - 3 jobs are generated with different parameters
- The syntax can eventually be improved by changing a small part of the code

Easy-gLite submission form syntax

- Example of a set of tasks creation
  - the “x->y|z” syntax in the “Name of the task” field



Other Easy-gLite features

- Logs of the jobs can be viewed or saved
- Reasons of failed jobs are stored
  - to analyse failures on different sites
- Consistency verification of the output files
  - with submission of jobs having bad output files
- Maintain a blacklist for Computing Elements (CE) where many jobs failed
  - in order to avoid unreliable CE for our jobs

Remarks

- Documentation
  - finished for both THESIAS and easy-gLite
- Release
  - the programs will soon be released

Results

- Proof of concept
  - over 1 million SNPs combinations of 8456 SNPs from a chromosome were analysed
  - several regions where haplotypes are associated with the disease have been identified
- EGEE performance
  - 3 days on EGEE while 2 years and a half on a single computer

Work in progress

- Genome wide analysis
  - ~5000 cases and controls with ~500000 SNPs

Credits

- François Cambien
- David Trégouët

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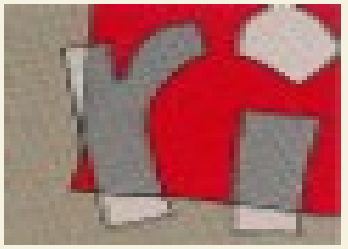

Thank you

Questions ?