

Forward-time simulations using simuPOP, a tutorial

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June 15th, 2007

simuPOP workshop

School of Public Health, Department of Biostatistics
University of Alabama Birmingham

outline

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What is
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Various
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- 2 An example
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A forward-time population genetics simulation environment

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A forward-time population genetics **simulation** environment

- A population genetics simulation program

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A **forward-time** population genetics simulation environment

- A population genetics simulation program
- Not coalescent-based

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A forward-time population genetics simulation **environment**

- A population genetics simulation program
- Not coalescent-based
- Based on an object-oriented scripting language (Python)

Forward-time simulation

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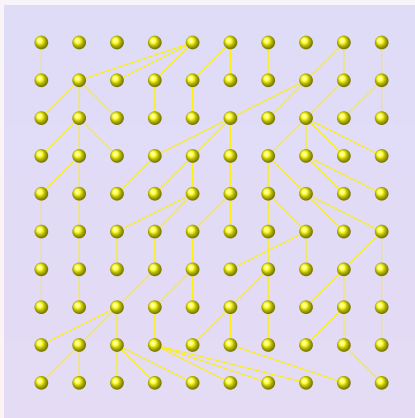
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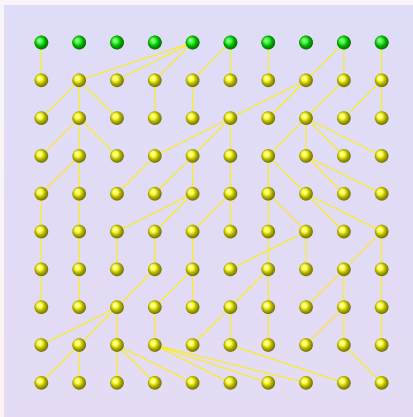
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- Start from an initial population



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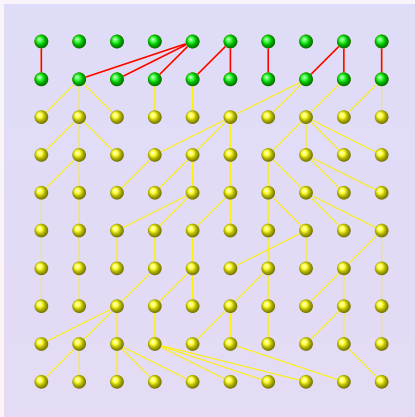
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- Start from an initial population
- Evolve forward in time, generation by generation, subject to certain number of genetic and/or demographic effects

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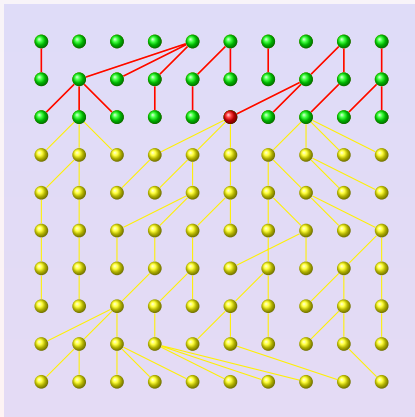
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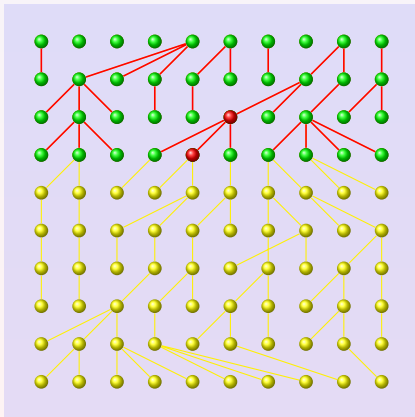
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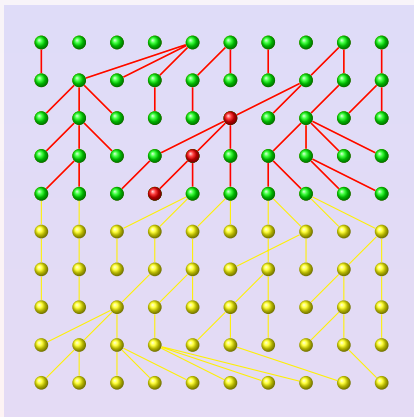
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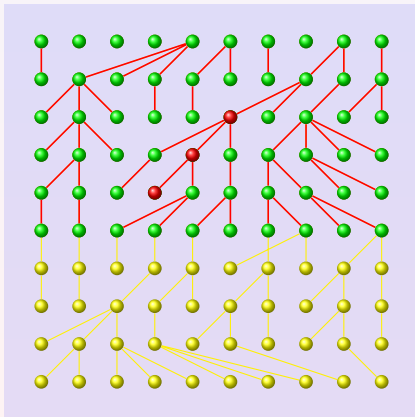
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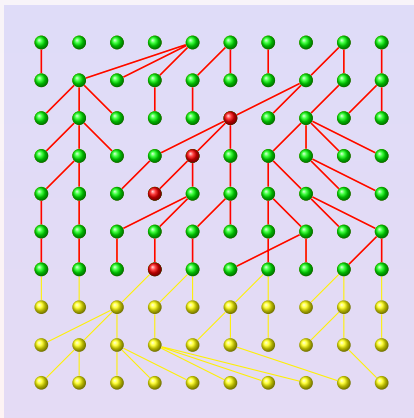
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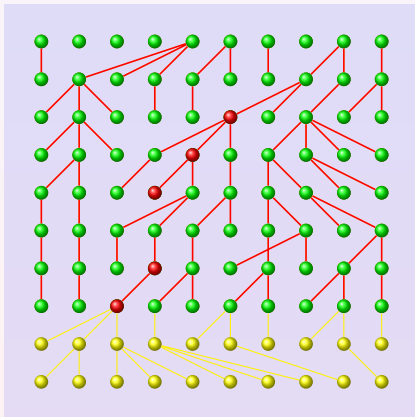
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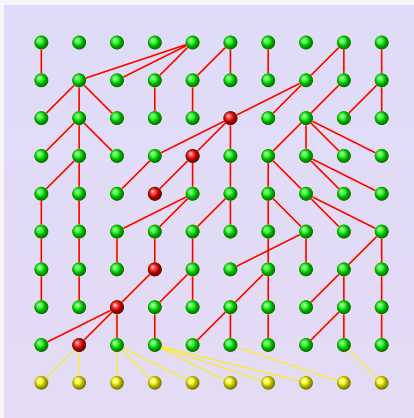
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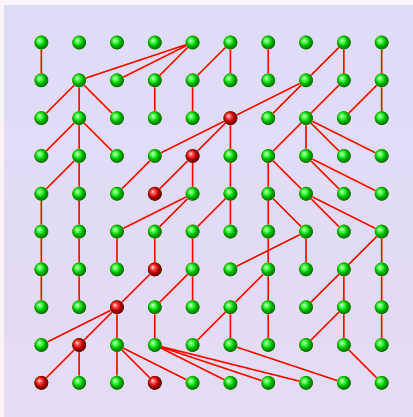
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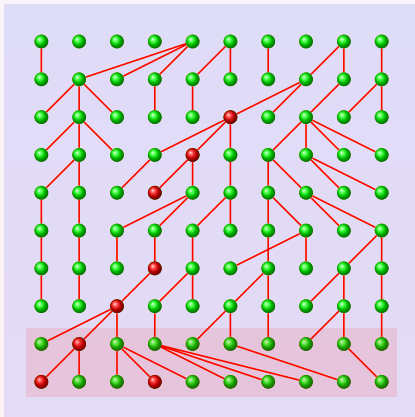
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- Start from an initial population
- Evolve forward in time, generation by generation, subject to certain number of genetic and/or demographic effects
- Samples are collected from the last several generations

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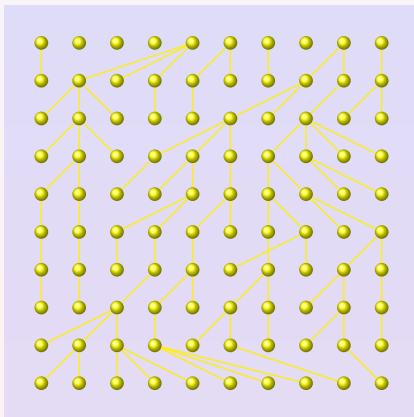
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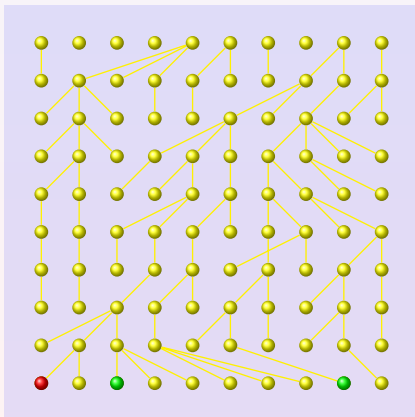
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- Start from a sample with unknown genotype



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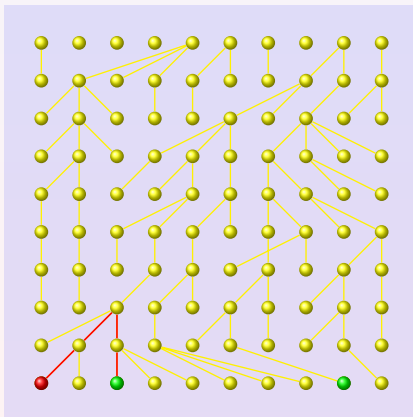
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- Start from a sample with unknown genotype
- Coalesce individuals until the most recent common ancestor of all individuals is found

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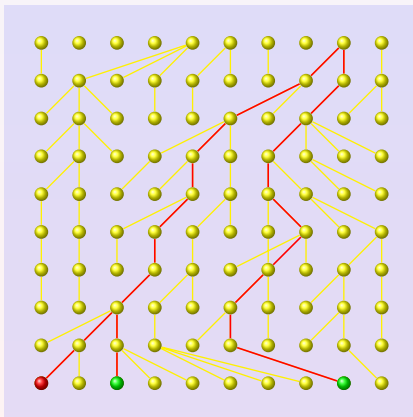
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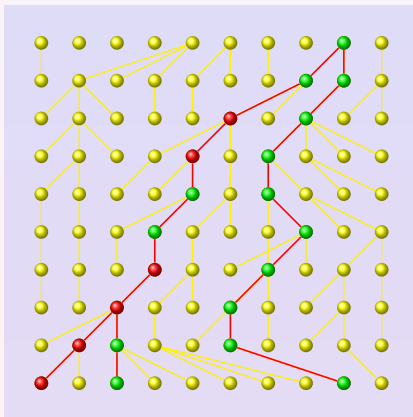
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- Start from a sample with unknown genotype
- Coalesce individuals until the most recent common ancestor of all individuals is found
- Starting from the MRCA, proceed forward in time and fill the genotype of each individual

Forward vs. backward-time simulations

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Backward-time

- Sample based,
efficient

Forward-time

- Population based,
inefficient

Forward vs. backward-time simulations

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Backward-time

- Sample based, efficient
- Limited selection, recombination models and mating schemes

Forward-time

- Population based, inefficient
- Can simulate almost arbitrary evolutionary scenarios

Forward vs. backward-time simulations

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Backward-time

- Sample based, efficient
- Limited selection, recombination models and mating schemes
- Can not study population properties, or properties of ancestral generations

Forward-time

- Population based, inefficient
- Can simulate almost arbitrary evolutionary scenarios
- Can study population properties and ancestral generations

Forward vs. backward-time simulations

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Backward-time

- Sample based, efficient
- Limited selection, recombination models and mating schemes
- Can not study population properties, or properties of ancestral generations
- Used mostly for sample generation

Forward-time

- Population based, inefficient
- Can simulate almost arbitrary evolutionary scenarios
- Can study population properties and ancestral generations
- Not limited to sample generation

Forward-time simulation programs

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For specific applications

- Easy to write simple simulations
- Difficult to write complicated simulations
- A few programs are available (e.g. [EasyPOP](#), [FPG](#), [Nemo](#)), easy to use if they happen to fit your need

Forward-time simulation programs

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Various topics

For specific applications

- Easy to write simple simulations
- Difficult to write complicated simulations
- A few programs are available (e.g. [EasyPOP](#), [FPG](#), [Nemo](#)), easy to use if they happen to fit your need

For general purposes

- Difficult to write
- Easy to set up complicated simulations
- [simuPOP](#) fits in this category

What simuPOP does

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simuPOP provides

- a large number of functions to manipulate populations
copy, split, merge, manipulate individual genotypes,
determine affection status, save to and load from
various formats, generate sample, ...

What simuPOP does

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simuPOP provides

- a large number of functions to manipulate populations copy, split, merge, manipulate individual genotypes, determine affection status, save to and load from various formats, generate sample, ...
- and a mechanism to evolve populations forward in time subject to arbitrary demographic and genetic forces such as population size changes, mutation, migration, recombination, selection, ...

Structure of individuals

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Assume ploidy = 2, maxAllele = 1

0	1	2	3	4	5	6
0	1	1	1	0	0	1
0	0	1	1	1	0	1

0	1	2	3	4	5
0	1	0	0	0	1
1	0	1	1	0	0

Male

● Affected

fitness	father_id	...
---------	-----------	-----

Structure of individuals

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Assume ploidy = 2, maxAllele = 1

0	1	2	3	4	5	6
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Chromosome 0

0	1	2	3	4	5
0	1	0	0	0	1
1	0	1	1	0	0

Male

● Affected

fitness	father_id	...
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0	1	0	0	0	1
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Chromosome 1

Male

● Affected

fitness	father_id	...
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Chromosome 1

Male

Sex

● Affected

fitness | father_id | ...

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Chromosome 1

Male

Sex

● Affected

Affection status

fitness | father_id | ...

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Sex

● Affected

Affection status

fitness | father_id | ...

Information
fields

Structure of populations

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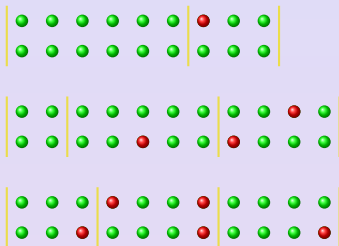
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- Unaffected
- Affected



gen = 2, numAffected = 5, ...

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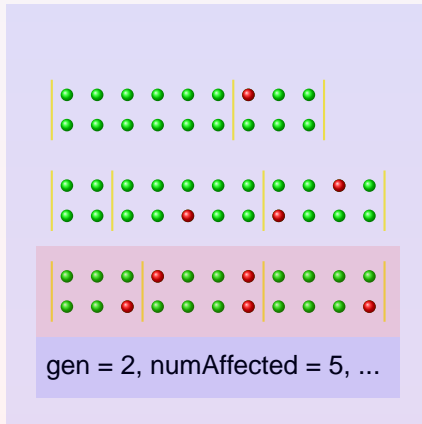
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Current generation

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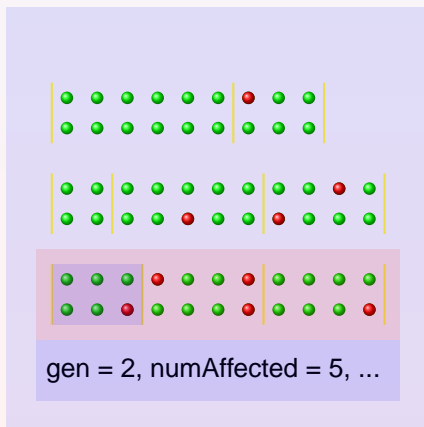
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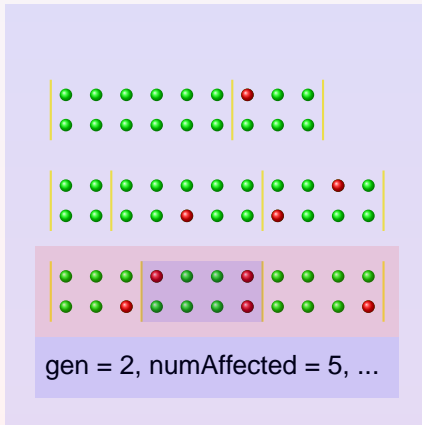
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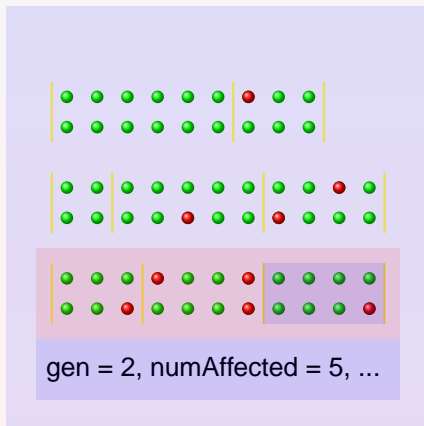
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Current generation

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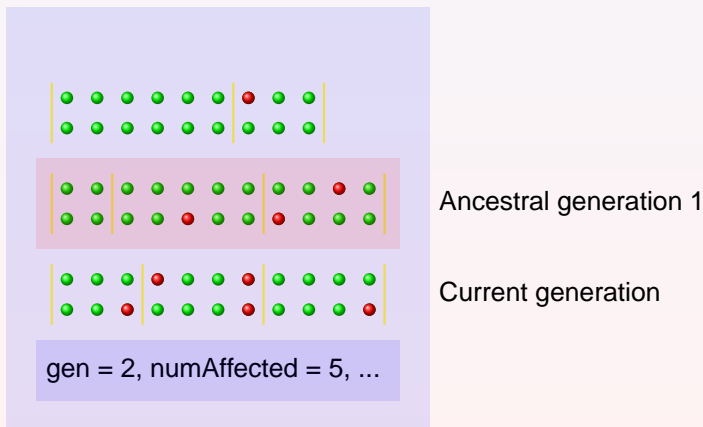
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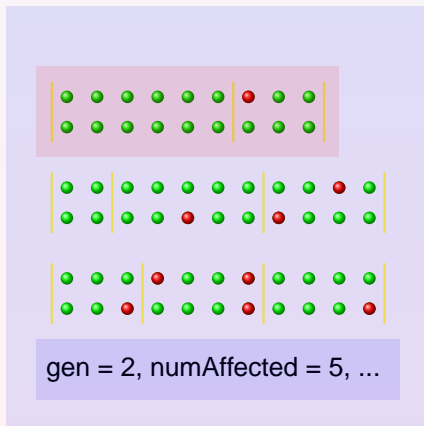
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Ancestral generation 2

Ancestral generation 1

Current generation

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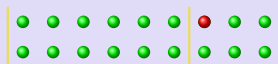
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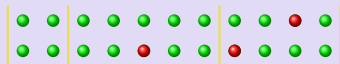
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Ancestral generation 2



Ancestral generation 1



Current generation

gen = 2, numAffected = 5, ...

Population variables

The evolutionary process

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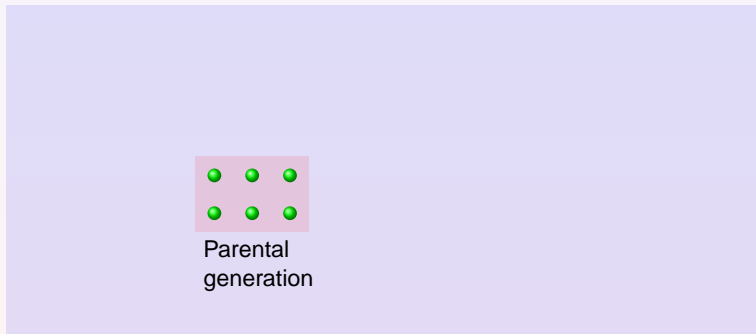
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Involved simuPOP objects: population and individual, operator, mating scheme, simulator

The evolutionary process

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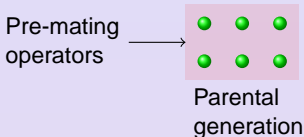
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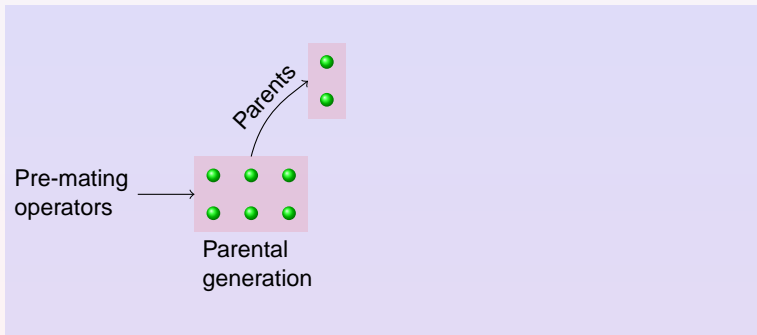
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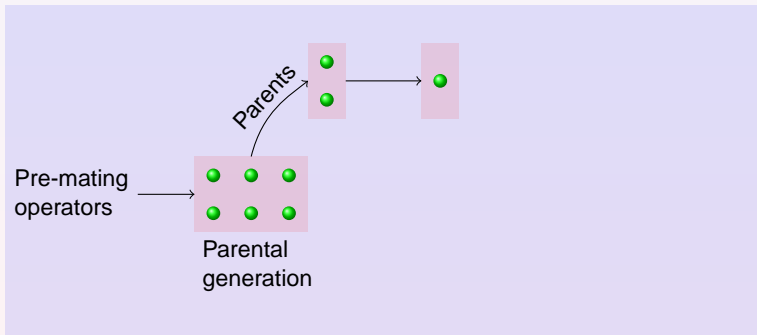
Forward- and
backward-time
simulation

Features of
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An example

Various
topics



Involved simuPOP objects: population and individual, operator, **mating scheme**, simulator

The evolutionary process

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What is simuPOP

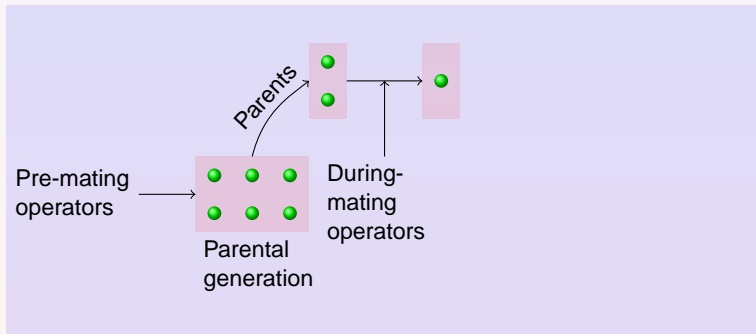
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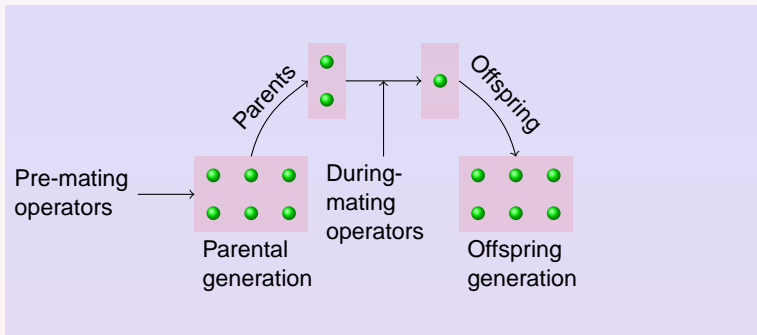
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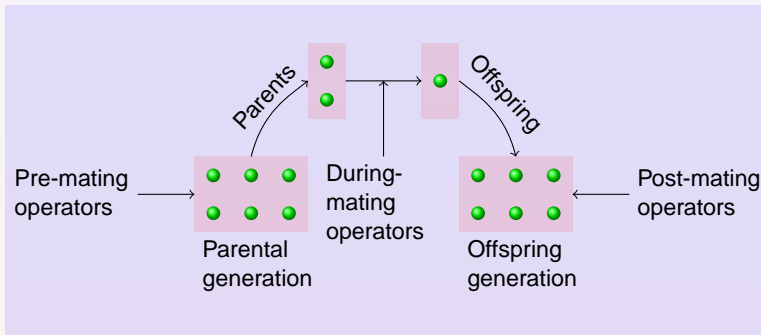
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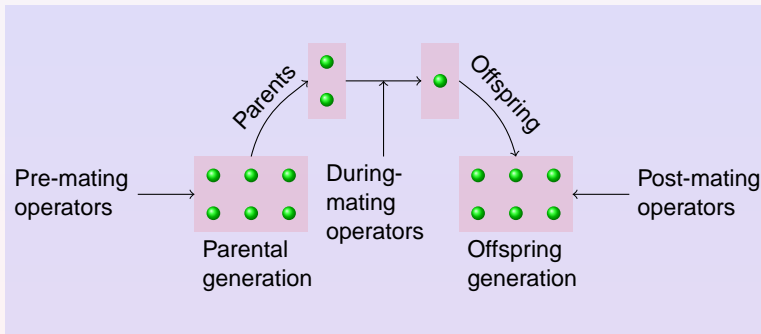
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Involved simuPOP objects: population and individual, operator, mating scheme, **simulator**

What distinguishes simuPOP from others

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scripting simuPOP is provided as a set of Python modules, and is therefore backed by a full-blown object-oriented programming language.

flexibility simuPOP does not impose any limit on the size of genome, population, demographic model, etc. Using a large number of standard and hybrid (Python-assisted) operators, users can simulate almost arbitrarily complex evolutionary processes.

integration Owing to the 'glue language' nature of Python, it is easy to integrate simuPOP with other languages and programs.

I like it, but, oohm, why Python??

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- The core of simuPOP is written in C++ for efficiency
- Python is the glue language, a wrapper of the core
- Python is used to write simuPOP extensions (user interface etc)
- The core sometimes calls Python (Python operators) for maximum flexibility

Do I have to write a script?

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simuPOP can be used in two ways:

- You should learn how to write simuPOP scripts if you
 - need a particular type of simulation for you own research, and
 - know exactly what you want to do
- You can use existing simuPOP scripts without knowing simuPOP if
 - you need to use an existing simulation scenario to simulate samples or populations
 - this scenario is implemented in simuPOP

This is fun, but is it useful?

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simuPOP can simulate the change of the genetic composition of a population in a complicated evolutionary process. It can be used to

- Demonstrate population genetics phenomena

This is fun, but is it useful?

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simuPOP can simulate the change of the genetic composition of a population in a complicated evolutionary process. It can be used to

- Demonstrate population genetics phenomena
- Study the impact of genetic and demographic forces on the evolution of a population

This is fun, but is it useful?

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simuPOP can simulate the change of the genetic composition of a population in a complicated evolutionary process. It can be used to

- Demonstrate population genetics phenomena
- Study the impact of genetic and demographic forces on the evolution of a population
- Study the evolution of (complex) genetic diseases

This is fun, but is it useful?

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simuPOP can simulate the change of the genetic composition of a population in a complicated evolutionary process. It can be used to

- Demonstrate population genetics phenomena
- Study the impact of genetic and demographic forces on the evolution of a population
- Study the evolution of (complex) genetic diseases
- Simulate samples to validate gene-mapping methods

This is fun, but is it useful?

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- Demonstrate population genetics phenomena
- Study the impact of genetic and demographic forces on the evolution of a population
- Study the evolution of (complex) genetic diseases
- Simulate samples to validate gene-mapping methods
- Study ascertainment methods in simulated populations

This is fun, but is it useful?

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simuPOP can simulate the change of the genetic composition of a population in a complicated evolutionary process. It can be used to

- Demonstrate population genetics phenomena
- Study the impact of genetic and demographic forces on the evolution of a population
- Study the evolution of (complex) genetic diseases
- Simulate samples to validate gene-mapping methods
- Study ascertainment methods in simulated populations
- ...

Simulations of complex human diseases

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Backward-time

- Haploid only

Forward-time

- No limit on ploidy

Simulations of complex human diseases

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Backward-time

- Haploid only
- Additive selection and penetrance models

Forward-time

- No limit on ploidy
- Arbitrary selection and penetrance models

Simulations of complex human diseases

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Backward-time

- Haploid only
- Additive selection and penetrance models
- One disease susceptibility locus

Forward-time

- No limit on ploidy
- Arbitrary selection and penetrance models
- Multiple DSL with interaction

Simulations of complex human diseases

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Backward-time

- Haploid only
- Additive selection and penetrance models
- One disease susceptibility locus
- Generate independent samples of fixed format

Forward-time

- No limit on ploidy
- Arbitrary selection and penetrance models
- Multiple DSL with interaction
- Generate multi-generation populations

Availability

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- simuPOP website:
`http://simupop.sourceforge.net`
- Mailing list:
`simupop-list@lists.sourceforge.net`
- License: GPL 2.0
- Platforms: all OS on which Python is available
- Monthly release, currently at 0.7.10
- Documentation: *simuPOP User's Guide* and *simuPOP Reference Manual*

Outline

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- An example
- Visualization with R

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```
>>> from simuPOP import *
>>> simu = simulator(
...     population(size=1000, ploidy=2, loci=[2]),
...     randomMating(),
...     rep = 3)
>>> simu.evolve(
...     preOps = [initByValue([1,2,2,1])],
...     ops = [
...         recombinator(rate=0.1),
...         stat(LD=[0,1]),
...         pyEval(r"'%3d' % gen", rep=0, step=10),
...         pyEval(r"'%f' % LD[0][1]", step=10),
...         pyEval(r"\n", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

Loading simuPOP module

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What is simuPOP

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```
>>> from simuPOP import *
>>> simu = simulator(
...     population(size=1000, ploidy=2, loci=[2]),
...     randomMating(),
...     rep = 3)
```

Import the default simuPOP module

population

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```
>>> from simuPOP import *
>>> simu = simulator(
...     population(size=1000, ploidy=2, loci=[2]),
...     randomMating(),
...     rep = 3)
```

Create a **population** of 1000 **diploid** individuals, each having two **loci** on the first chromosome

simulator and mating scheme

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What is simuPOP

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```
>>> from simuPOP import *
>>> simu = simulator(
...     population(size=1000, ploidy=2, loci=[2]),
...     randomMating(),
...     rep = 3)
```

Create a **simulator** that has one replicate of this population, and a random mating scheme

Operators!

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```
>>> from simuPOP import *
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...         pyEval(r"'%f    ' % LD[0][1]", step=10),
...         pyEval(r"'\\n'", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

`initByValue` is applied before evolution

Operators!

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```
>>> from simuPOP import *
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...         pyEval(r"\n", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

recombinator is applied at every generation when an offspring is produced

Operators!

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```
>>> from simuPOP import *
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...         stat(LD=[0,1]),
...         pyEval(r"%3d    ' % gen", rep=0, step=10),
...         pyEval(r"%f    ' % LD[0][1]", step=10),
...         pyEval(r"' \n'", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

stat is applied to the offspring generation at every generation

Operators!

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```
>>> from simuPOP import *
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...         recombinator(rate=0.1),
...         stat(LD=[0,1]),
...         pyEval(r"'%3d    ' % gen", rep=0, step=10),
...         pyEval(r"'%f    ' % LD[0][1]", step=10),
...         pyEval(r"'\\n'", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

pyEval is applied every 10 generations

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```
>>> from simuPOP import *
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...         stat(LD=[0,1]),
...         pyEval(r"'%3d' % gen", rep=0, step=10),
...         pyEval(r"'%f' % LD[0][1]", step=10),
...         pyEval(r"\n", rep=REP_LAST, step=10)
...     ],
...     end=100
... )
```

Output of the example

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Various topics

0	0.198967	0.197977	0.204966
10	0.055434	0.068286	0.060666
20	0.014920	0.022619	0.007010
30	0.012972	0.029459	0.002545
40	0.000530	0.000840	0.011737
50	0.005701	0.004573	0.030145
60	0.000309	0.009176	0.009877
70	0.005575	0.001398	0.028347
80	0.004875	0.010809	0.006756
90	0.006943	0.001820	0.006256
100	0.001297	0.011626	0.008770

Use R to plot

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Various topics

```
>>> from simuPOP import *
>>> from simuRPy import *
>>> simu = simulator(
...     population(size=1000, ploidy=2, loci=[2]),
...     randomMating(),
...     rep = 3)
>>> simu.evolve(
...     preOps = [initByValue([1,2,2,1])],
...     ops = [
...         recombinator(rate=0.1),
...         stat(LD=[0,1]),
...         varPlotter('LD[0][1]', numRep=3, step=10,
...             saveAs='ld', ylim=[0,.25],
...             lty=range(1, 4), col=range(2, 5),
...             xlab='generation', ylab='D',
...             title='LD Decay'),
...     ],
...     end=100
... )
True
>>>
```


Evolve!

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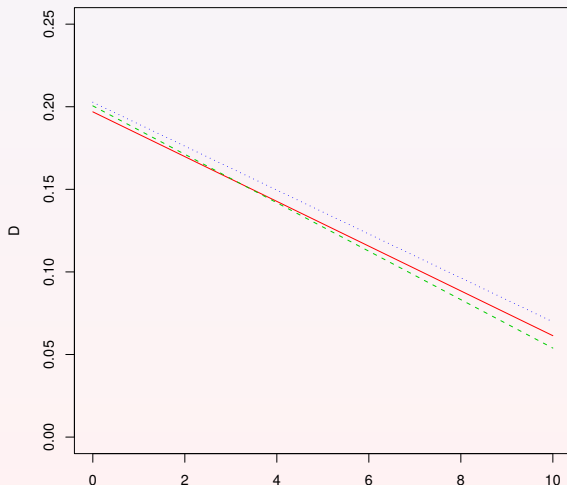
An example

An example

Visualization with R

Various topics

LD Decay



- Update at every 10 generations
- $LD=0.25$ before generation 0
- LD is calculated at the end of each generation

Evolve!

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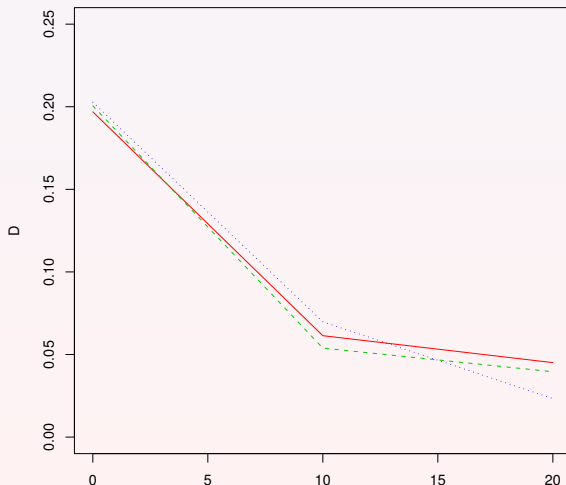
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LD Decay



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Evolve!

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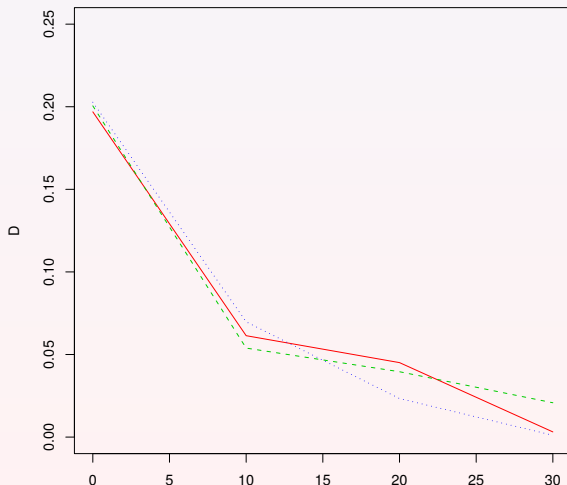
An example

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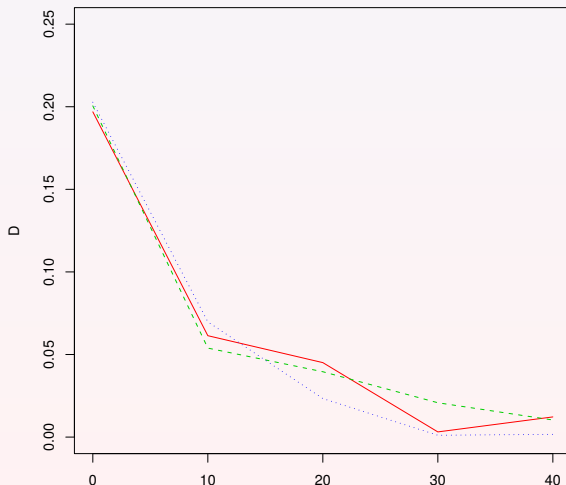
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Evolve!

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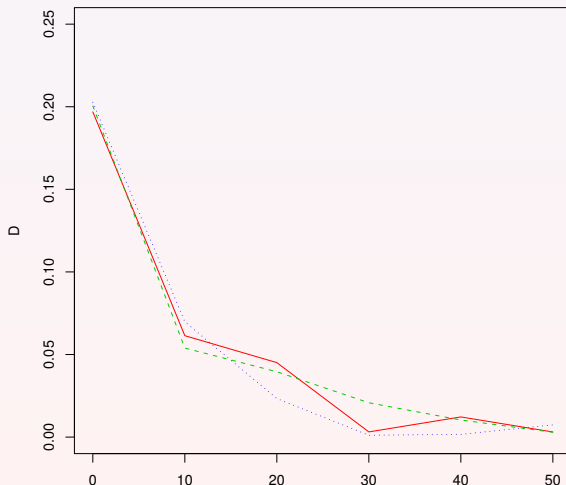
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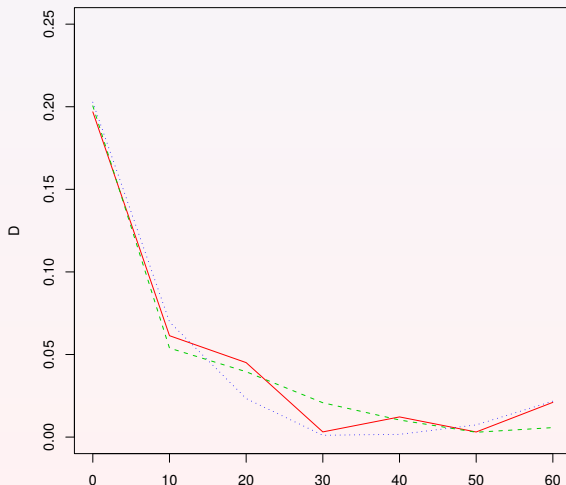
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- Update at every 10 generations
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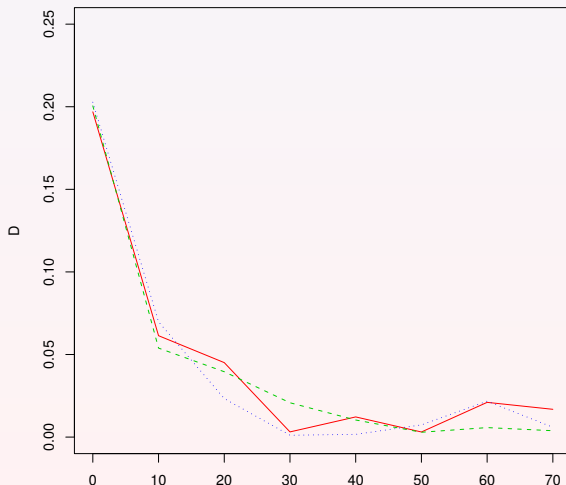
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- Update at every 10 generations
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Evolve!

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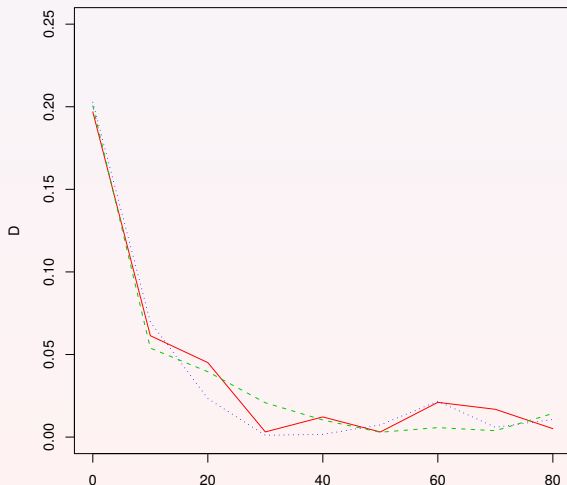
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- Update at every 10 generations
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Evolve!

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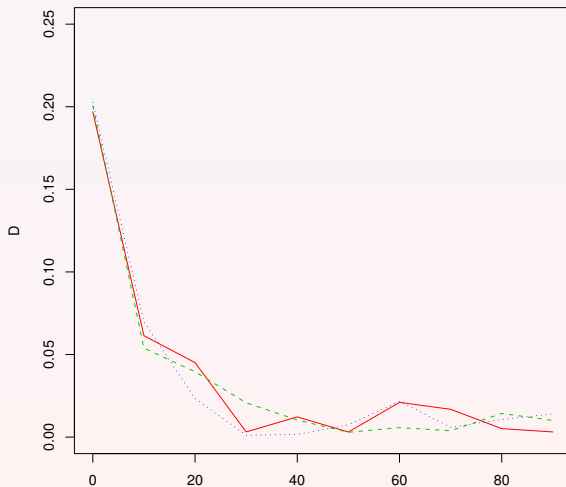
An example

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LD Decay



- Update at every 10 generations
- $LD=0.25$ before generation 0
- LD is calculated at the end of each generation

Evolve!

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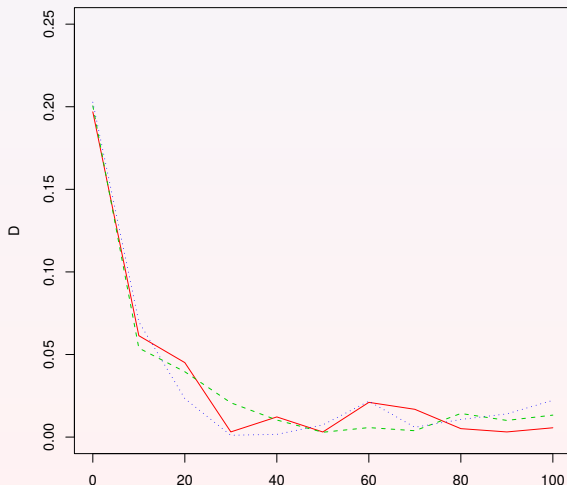
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- Update at every 10 generations
- $LD=0.25$ before generation 0
- LD is calculated at the end of each generation

Exercise time

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- Start python
- Load simuPOP
- Create a population and run

```
pop.ploidyName( )
```

- run tutorial_example1.py

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An example

Various
topics

Dynamic
population size
Calculate statistics
Hybrid Operator
Self-defined
statistics
Read HapMap data
Pick markers from
HapMap data

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Various topics

- Dynamic population size
- Calculate statistics
- Hybrid Operator
- Self-defined statistics
- Read HapMap data
- Pick markers from HapMap data

Dynamic population size

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Dynamic
population size

Calculate statistics

Hybrid Operator

Self-defined
statistics

Read HapMap data

Pick markers from
HapMap data

```
>>> def lin_inc(gen, oldsize=[]):
...     return [10+gen]*5
...
>>> simu = simulator(
...     population(subPop=[5]*5, loci=[1]),
...     randomMating(newSubPopSizeFunc=lin_inc)
... )
>>> simu.evolve(
...     ops = [
...         stat(popSize=True),
...         pyEval(r'"%d %d\n"%(gen, subPop[0]["popSize"])'),
...     ],
...     end=5
... )
0 10
1 11
2 12
3 13
4 14
5 15
True
>>>
```

Calculate statistics

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Dynamic
population size

Calculate statistics

Hybrid Operator

Self-defined
statistics

Read HapMap data

Pick markers from
HapMap data

```
>>> simu = simulator(
...     population(subPop=[10000]*2, loci=[10]),
...     randomMating()
... )
>>> simu.evolve(
...     preOps = [
...         initByFreq([0.2, 0.8], subPop=[0]),
...         initByFreq([0.8, 0.2], subPop=[1]),
...     ],
...     ops = [
...         stat(LD=[[0,1], [5,6]], Fst=range(10), step=100),
...         migrator(rate=[[0, 0.01], [0, 0.02]]),
...         pyEval(r'"Gen: %4d LD: %.3f R2: %.3f Fst: %.3f\n"'
...             ' % (gen, LD[0][1], R2[0][1], AvgFst)',
...             step=100)
...     ],
...     end=1000
... )
```

Calculate statistics (cont.)

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What is simuPOP

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Various topics

Dynamic
population size

Calculate statistics

Hybrid Operator

Self-defined
statistics

Read HapMap data

Pick markers from
HapMap data

```
Gen:    0 LD: 0.091 R2: 0.133 Fst: 0.521
Gen:   100 LD: 0.098 R2: 0.154 Fst: 0.237
Gen:   200 LD: 0.097 R2: 0.152 Fst: 0.203
Gen:   300 LD: 0.066 R2: 0.070 Fst: 0.176
Gen:   400 LD: 0.079 R2: 0.099 Fst: 0.208
Gen:   500 LD: 0.067 R2: 0.072 Fst: 0.245
Gen:   600 LD: 0.068 R2: 0.073 Fst: 0.333
Gen:   700 LD: 0.083 R2: 0.112 Fst: 0.324
Gen:   800 LD: 0.111 R2: 0.198 Fst: 0.311
Gen:   900 LD: 0.116 R2: 0.216 Fst: 0.289
Gen:  1000 LD: 0.105 R2: 0.176 Fst: 0.000
True
>>>
```

A penetrance model

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A penetrance model with two interacting loci

	BB	Bb	bb
AA	0.1	0.1	0.5
Aa	0.1	0.1	0.5
aa	0.5	0.5	0.1

```
>>> def myPene(genotype):
...     'geno is the genotype at the two given loci'
...     loc1 = geno[0] + geno[1]
...     loc2 = geno[2] + geno[3]
...     if (loc1 == 2 and loc2 < 2) or \
...         (loc1 < 2 and loc2 == 2):
...         return 0.1
...     else:
...         return 0.5
```


Calculate effective number of alleles

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Apply this model

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```
>>> pop = population(subPop=[1000], loci=[6])
>>> # initialize the population
>>> InitByFreq(pop, [0.1, 0.9])
>>> # apply penetrance and obtain affection status
>>> PyPenetrance(pop, loci=[3, 5], func=myPene)
>>> # draw case control sample
>>> (sample,) = CaseControlSample(pop, cases=3, controls=3)
>>> # save sample in Merlin QTDT format
>>> from simuUtil import SaveQTDT
>>> SaveQTDT(sample, output='sample', affectionCode=['U', 'A'],
...           fields=['affection'])
>>> # have a look at the sample in Merlin-QTDT Format
>>> print open('sample.map').read()
CHROMOSOME MARKER POSITION
1          loc1-1  1.000000
1          loc1-2  2.000000
1          loc1-3  3.000000
1          loc1-4  4.000000
1          loc1-5  5.000000
1          loc1-6  6.000000
```

Generated sample

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```
>>> print open('sample.dat').read()
```

```
A      affection
```

```
M      loc1-1
```

```
M      loc1-2
```

```
M      loc1-3
```

```
M      loc1-4
```

```
M      loc1-5
```

```
M      loc1-6
```

```
>>> print open('sample.ped').read()
```

```
1 1 0 0 1 A 1 2 2 2 2 2 2 2 1 1 2 2
```

```
2 1 0 0 2 A 2 2 2 2 2 2 2 2 2 2 2 2
```

```
3 1 0 0 2 A 2 2 2 2 2 2 2 2 1 2 2 2
```

```
4 1 0 0 2 U 2 1 2 2 2 2 2 2 2 2 2 2
```

```
5 1 0 0 2 U 2 2 2 2 2 1 2 1 2 1 2 2
```

```
6 1 0 0 2 U 2 2 2 2 2 2 2 2 2 2 2 2
```

```
>>>
```

scripts/loadHapMap.py

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Load genotype from hapmap data file

```
def load_population(pop, ch, type):
    '''Load population from file, with type (subpopulation type)
    subPop = {'CEU':0, 'YRI':1, 'JPT+CHB':2}[type]
    file = genotype_file % (ch, type, rev)
    print 'from %s...' % file
    for line_no, line in enumerate(open(file).readlines()):
        genotype = [int(x) for x in line.split()]
        ind = line_no / 2
        ploidy = line_no % 2
        ind = pop.individual(ind, subPop)
        for i, g in enumerate(genotype):
            # always chromosome 0, because each population has c
            ind.setAllele(g, i, ploidy)
```

Pick markers from HapMap data

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```
>>> genes = [  
...     "rs1042522",  
...     "rs1625895",  
...     "rs1799793",  
... ]  
>>> pops = []  
>>> for i in range(1, 23):  
...     print "Loading hapmap chromosome %d..." % i  
...     pop = LoadPopulation('hapmap_%d.bin' % i)  
...     markers = []  
...     for name in genes:  
...         try:  
...             idx = pop.locusByName(name)  
...             markers.append(idx)  
...         except:  
...             pass  
...     if len(markers) > 0:  
...         markers.sort()  
...         pop.removeLoci(keep=markers)  
...         pops.append(pop)  
>>> all = MergePopulationsByLoci(pops)
```

Acknowledgments

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- W.M. Keck Foundation to the Gulf Coast Consortia through the Keck Center for Computational and Structural Biology
- Rice Terascale Cluster funded by NSF under Grant EIA-0216467, Intel, and HP
- M.D. Anderson Cancer Center High Performance Cluster
- BP was supported in part by a grant CA75432 from NCI
- Yaji Xu helped with all the figures in this talk

For further reading

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That is all

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For more details, please check out

- simuPOP user's guide
- simuPOP reference manual
- Another presentation about the details of each simuPOP components

Under the `doc` directory of your simuPOP distribution.