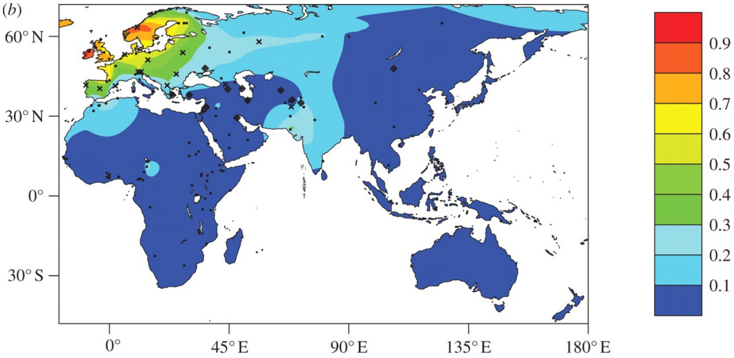
Inférence en génétique des populations IV.

François Rousset & Raphaël Leblois

M2 Biostatistiques 2015–2016

Modeling and analysis of covariances in allele frequencies

Spatial



Intra-family

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Modeling: important parameters in selection processes

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- General formal theory of selection with interactions between relatives

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- Estimate Nm or the *neighborhood size* $4D\pi\sigma^2$
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- Two main spatial models (Wright): island model, and isolation-by-distance
- Estimate *Nm* or the *neighborhood size* $4D\pi\sigma^2$
- A few statistically desirable properties
- Analytical understanding
- Huge literature, often based on very naive ideas

Outline

- An example of the role of spatial structure in evolution
- Modeling of the role of spatial structure
- Formal modelling of covariances: diffusion vs. coalescence
- Genealogical interpretations of covariances and regressions
- An example of statistical inference based on covariances

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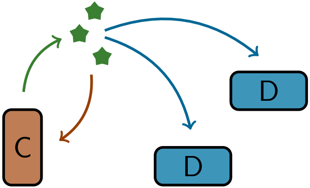
Example: evolution of social behaviour

Siderophore production as "public good"

Pseudomonas aeruginosa



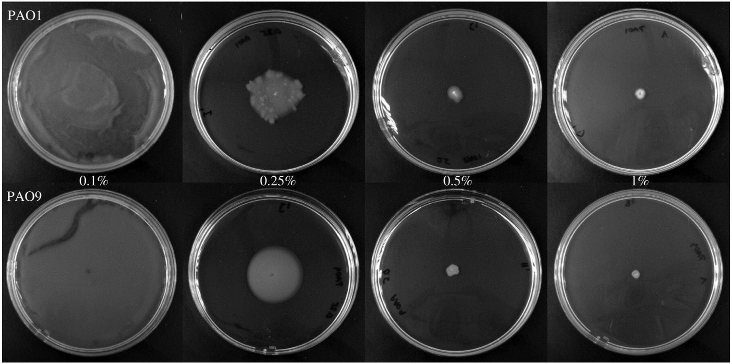
A Defector that does not produce the "public good" still benefits from those produced by the Cooperators.

⇒ Public good production should be counter-selected.

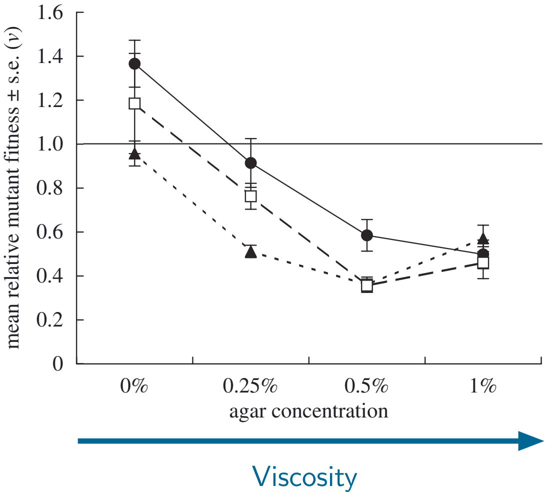
Biologists test theories about the importance of dispersal

Controlling bacterial dispersal

Different agar concentrations:



Public goods production

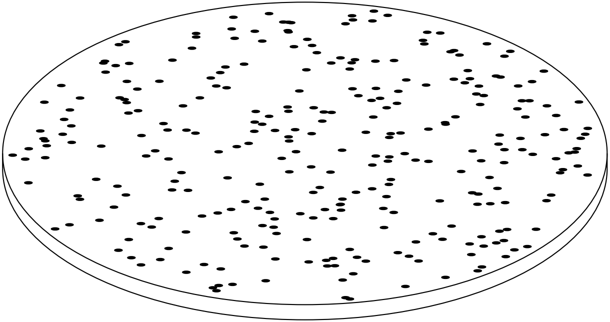


Siderophore-defective strain wins

Siderophore-producing strain wins

Kümmerli et al, PRSB, 2009

The effect of dispersal *almost* explained



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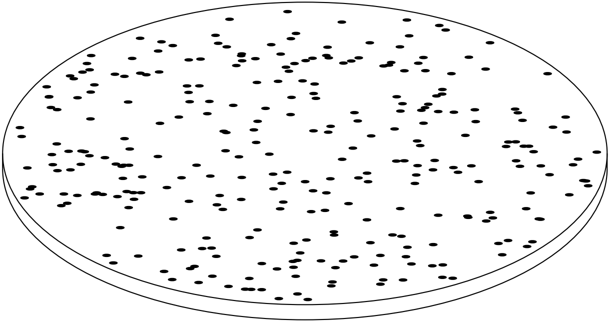

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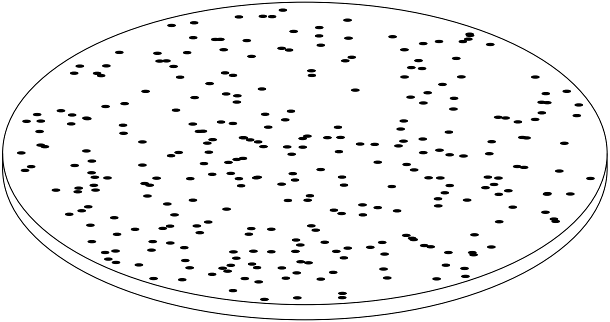

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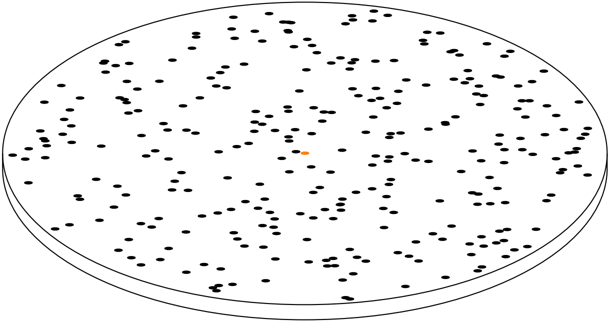

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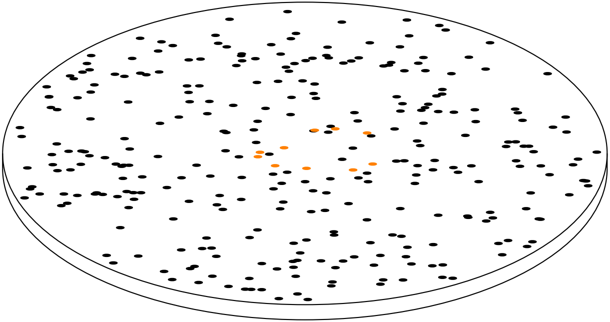

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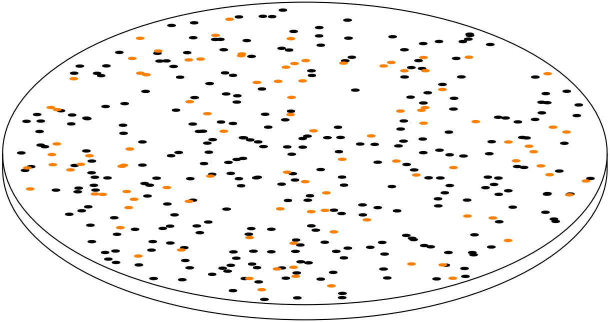

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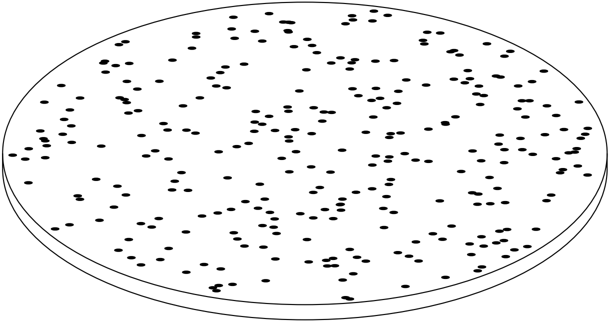

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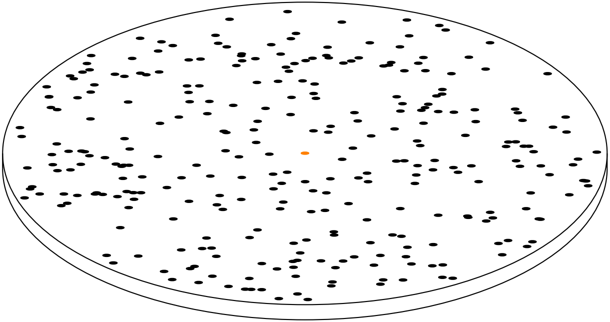

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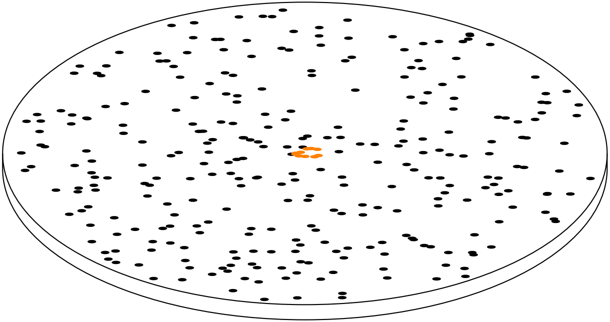

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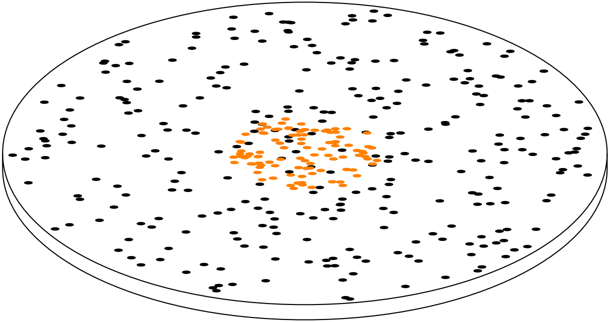

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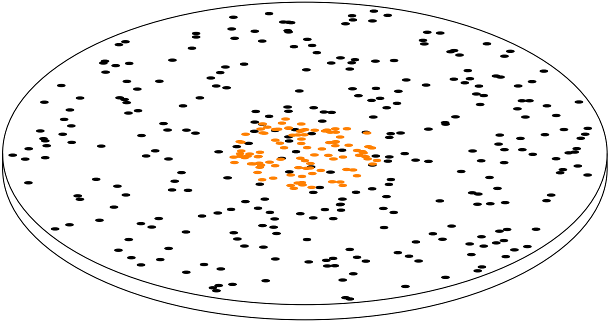

- Same logic important for virtually any trait evolving in a population spatially subdivided in (small) subpopulations.

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Formulation in terms of partial regression

We have seen that (for deterministic models) the change in allele frequency can be written in terms of allelic fitnesses $w_{\textcolor{red}{\bullet}}$ and $w_{\textcolor{blue}{\bullet}}$, as

$$\begin{aligned} p'_{\textcolor{red}{\bullet}} - p_{\textcolor{red}{\bullet}} =& (w_{\textcolor{red}{\bullet}} - w_{\textcolor{blue}{\bullet}}) p_{\textcolor{red}{\bullet}} (1 - p_{\textcolor{red}{\bullet}}) \\ =& \beta_{w,\mathbf{1}_{\textcolor{red}{\bullet}}} \operatorname{Var}(\mathbf{1}_{\textcolor{red}{\bullet}}) = \operatorname{Cov}[w_i, \mathbf{1}_{\textcolor{red}{\bullet}}(i))] \end{aligned}$$

where $\beta_{w,\mathbf{1}_{\textcolor{red}{\bullet}}}$ is the regression coefficient of an individual's allelic fitness w_i on her genotype $\mathbf{1}_{\textcolor{red}{\bullet}}(i)$

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We can apply the standard recursive relationship for regression coefficients between a response variable W and two predictors F and N:

$$\beta_{W,F} = \beta_{W,F.N} + \beta_{N,F} \beta_{W,N.F}.$$

here for $F := \mathbf{1}_{\color{red}\bullet}$, the indicator variable for the (focal) individual's genotype, and $N :=$ the mean value of the indicator variable for a group of social partners

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where $\beta_{w,\mathbf{1}_{\color{red}\bullet}}$ is the regression coefficient of an individual's allelic fitness w_i on her genotype $\mathbf{1}_{\color{red}\bullet}(i)$
This entails the two-predictor regression expression for the change in allele frequency:

$$p'_{\color{red}\bullet} - p_{\color{red}\bullet} = (\beta_{W,F.N} + \beta_{N,F}\beta_{W,N.F}) \operatorname{Var}(\mathbf{1}_{\color{red}\bullet})$$

where $\beta_{N,F}$ is the regression coefficient of the $\color{red}\bullet$ allele frequency among social partners to $\color{red}\bullet$ allele presence in the focal individual.

$\beta_{N,F}$ is (one definition of) relatedness in the genetic literature.

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$$\mathbb{P}(\text{identity}) = \int_0^1 \qquad\qquad f(x)\,\mathrm{d}x$$

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- $$\mathbb{P}(\text{identity}) = \int_0^1 [x^2 + (1-x)^2] f(x)\,\mathrm{d}x = \frac{u + 2Nu^2 + v + 2Nv^2}{(u+v)[1+2N(u+v)]}$$
  $$\approx \frac{1}{1+4Nu} \text{ if } u = v$$

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- Mathematical overkill!

Probability of identity: coalescent argument

- Infinite allele model $\Rightarrow$ identity by descent

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- For c_t the probability that coalescence of a a given pair of genes occurred t generations ago,

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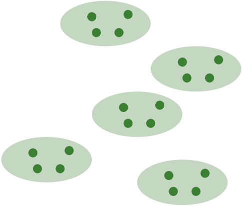
- Generating function
- For Wright-Fisher model:

$$Q = \sum_{1}^{\infty} \frac{1}{N} \left(1 - \frac{1}{N}\right)^{t-1} \gamma^t = \frac{\gamma}{\gamma + N(1-\gamma)}$$

$$\rightarrow \frac{1}{1+2N\mu} \text{ when } N \rightarrow \infty \text{ and } \mu \rightarrow 0$$

Infinite island model; Wright's F_{ST}

A very simple, easily solved model



Immigration m

Frequency of some focal allele ● locally, $p = p_i$ for given "island" i, and globally, $\bar{p}$.

Infinite island model; Wright's F_{ST}

Diffusion approximation for frequency in each "island" *i*:

$$P_i \sim \mathrm{Const} \quad p_i^{2Nm\bar{p}-1}(1-p_i)^{2Nm(1-\bar{p})-1} = \mathrm{Beta}(2Nm\bar{p}, 2Nm(1-\bar{p}))$$

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We have seen that the stationarity distribution satisfies:

$$0 = \frac{\partial f(p,t)}{\partial t} = -\frac{\partial a(p) f(p,t)}{\partial p} + \frac{\partial^2 b(p) f(p,t)}{2\partial p^2}$$

$$f(p) \propto \frac{exp\left(2\int^p a(x)/b(x)\,\mathrm{d}x\right)}{b(p)}$$

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Wright-Fisher model:
$b(p) = p(1-p)$ and
$a(p) = N(-vp + u(1-p)) = -N[(u+v)(p - u/(u+v))]$

Frequency $P \sim \mathrm{Const} \quad p^{2Nu-1}(1-p)^{2Nv-1} = \mathrm{Beta}(\alpha = 2Nu, \beta = 2Nv)$

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Frequency $P \sim \mathrm{Const} \quad p^{2Nu-1}(1-p)^{2Nv-1} = \mathrm{Beta}(\alpha = 2Nu, \beta = 2Nv)$

Island model
$b(p_i) = p_i(1-p_i)$ and $a(p_i) = -N(m(p_i - \bar{p}))$

Frequency $P \sim \mathrm{Beta}[\alpha = 2Nm\bar{p}, \beta = 2Nm(1-\bar{p})]$

Infinite island model; Wright's F_{ST}

Diffusion approximation for frequency in each "island" i:

$$P_i \sim \mathrm{Const} \quad p_i^{2Nm\bar{p}-1}(1-p_i)^{2Nm(1-\bar{p})-1} = \mathrm{Beta}(2Nm\bar{p}, 2Nm(1-\bar{p}))$$

$$F_{\mathrm{ST}} \equiv \frac{\mathrm{Var}\, p_i}{\bar{p}(1-\bar{p})} = \frac{\mathrm{E}(p_i^2) - \bar{p}^2}{\bar{p}(1-\bar{p})} = \frac{1}{1+2Nm}$$

More generally variances and covariances of allele frequencies can be expressed in terms of probabilities of identity of pair of genes. Here locally,

$$\mathbb{P}(\bullet\bullet | p_i; \bar{p}) = F_{\mathrm{ST}} p_i + (1 - F_{\mathrm{ST}})\bar{p}^2$$

(with mutation at a low enough rate: proven in next slides); hence globally

$$\mathbb{P}(\bullet\bullet; \bar{p}) = F_{\mathrm{ST}} \bar{p} + (1 - F_{\mathrm{ST}})\bar{p}^2$$

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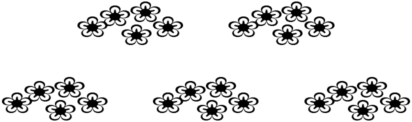
  Infinite island model – F_{ST}, separation of time scales
  Finite island model – coalescence times, separation of time scales
  Isolation by distance – separation of time scales
  $\Rightarrow$ Robustness of regression coefficients
- An example of statistical inference based on covariances

Genealogical interpretation of F_{ST}



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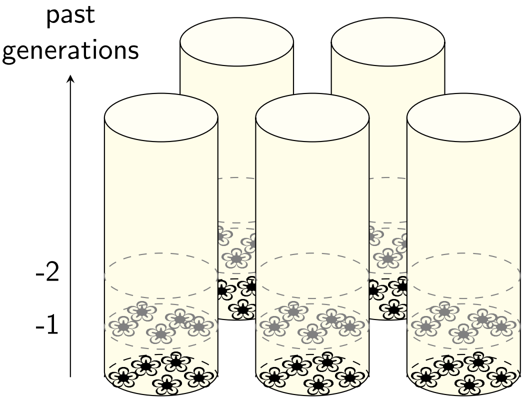

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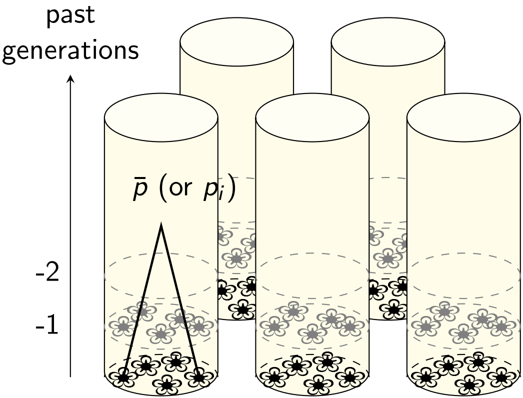

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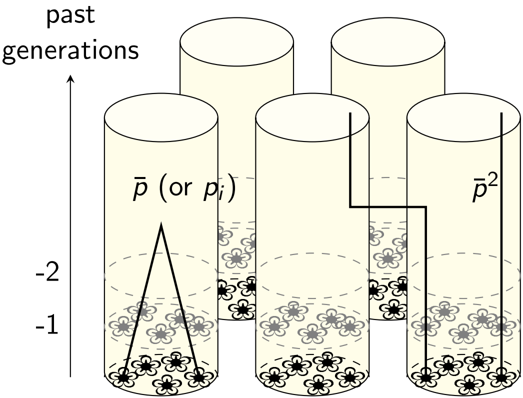

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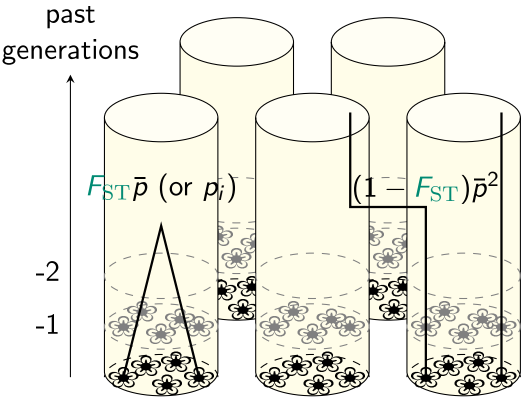

Wright's F_{ST} redefined

(For any genetic marker)

One can describe the correlation of allele types within some given sub-population relative to the allele types of random genes in the total population as

$$F_{\mathrm{ST}} = \frac{Q_{\mathrm{w}} - Q_{\mathrm{b}}}{1 - Q_{\mathrm{b}}}$$

in terms of probabilities of identity Q_{w} and Q_{b} within and between subpopulations.

This leads to relatively simple analysis.

General facts about Wright's *F*-statistics

$$F_{\mathrm{ST}} = \frac{Q_{\mathrm{w}} - Q_{\mathrm{b}}}{1 - Q_{\mathrm{b}}}$$

$$F_{\mathrm{IS}} = \frac{Q_0 - Q_{\mathrm{w}}}{1 - Q_{\mathrm{w}}}$$

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Naive but straightforward estimators

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Relationship with average coalescence times

$$Q = \sum_{t=0}^{\infty} c_t \gamma^t \text{ for } \gamma \equiv (1-\mu)^2 = 1 - 2\mu\, \mathsf{E}(T) + O(\mu^2)$$

$$F_{\mathrm{ST}} \to \frac{\mathsf{E}(T_{\mathrm{b}}) - \mathsf{E}(T_{\mathrm{w}})}{\mathsf{E}(T_{\mathrm{b}})} \text{ when } \mu \to 0.$$

Modelling in terms of probabilities of identity Q

Example: finite island model
Relationship of Q_{w} with Q_{w}, Q_{b} one generation earlier?

where

and

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$$\mathbf{Q}(t+1) = \gamma\mathbf{A}[\mathbf{Q}(t) + \mathbf{c}(t)]$$

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$$\mathbf{Q}(t) = \begin{pmatrix} Q_{\mathrm{w}}(t) \\ Q_{\mathrm{b}}(t) \end{pmatrix} \text{ and } \mathbf{c}(t) = \begin{pmatrix} \frac{1-Q_{\mathrm{w}}(t)}{N} \\ 0 \end{pmatrix}$$

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and

$$\mathbf{A} = \begin{pmatrix} a_{11} = (1-m)^2 + \frac{m^2}{n_{\mathrm{d}}-1} & 1 - a_{11} \\ 1 - \frac{a_{11}}{n_{\mathrm{d}}-1} & \frac{a_{11}}{n_{\mathrm{d}}-1} \end{pmatrix}$$

is the transition matrix for the "random walk" of two gene lineages between the state "within same deme" and the complementary state.

The stationary solution in an informative form

$$\mathbf{Q} = \gamma(\mathbf{I} - \gamma\mathbf{A})^{-1}\mathbf{A}\mathbf{c}$$

Eigensystem of **A**

$\lambda_1 = 1$, $\mathbf{e}_1 = (1, 1)^\top$

$\lambda_2 = \left(1 - m\frac{n_\mathrm{d}}{n_\mathrm{d}-1}\right)^2$, $\mathbf{e}_2 = (n_\mathrm{d} - 1, -1)^\top$

$$\mathbf{c} = \begin{pmatrix} \frac{1-Q_\mathrm{w}}{N} \\ 0 \end{pmatrix} = \frac{1 - Q_\mathrm{w}}{N}\frac{1}{n_\mathrm{d}}(\mathbf{e}_1 + \mathbf{e}_2)$$

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$\lambda_2 = \left(1 - m\frac{n_\mathrm{d}}{n_\mathrm{d}-1}\right)^2$, $\mathbf{e}_2 = (n_\mathrm{d} - 1, -1)^\top$

$$\mathbf{c} = \begin{pmatrix} \frac{1-Q_\mathrm{w}}{N} \\ 0 \end{pmatrix} = \frac{1 - Q_\mathrm{w}}{N}\frac{1}{n_\mathrm{d}}(\mathbf{e}_1 + \mathbf{e}_2)$$

$$\mathbf{Q} = \frac{1 - Q_\mathrm{w}}{N}\frac{1}{n_\mathrm{d}}\left(\frac{\gamma}{1-\gamma}\mathbf{e}_1 + \frac{\gamma\lambda_2}{1-\gamma\lambda_2}\mathbf{e}_2\right)$$

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$$F_\mathrm{ST} \equiv \frac{Q_\mathrm{w} - Q_\mathrm{b}}{1 - Q_\mathrm{b}} = \frac{\gamma\lambda_2}{\gamma\lambda_2 + N(1-\gamma\lambda_2)} \approx \frac{1}{1+2Nm}$$

The stationary solution in another informative form

in terms of eigenvalues of another matrix **G**:

$$\mathbf{Q} = \gamma \mathbf{A}(\mathbf{Q} + \mathbf{c}) = \gamma[\mathbf{G}\mathbf{Q} + (\mathbf{A} - \mathbf{G})\mathbf{1}] = \gamma[\mathbf{G}\mathbf{Q} + (\mathbf{I} - \mathbf{G})\mathbf{1}]$$

where **G** is the matrix whose ijth element is the coefficient of the jth element of **Q** in the ith element of $\mathbf{A}[\mathbf{Q} + \mathbf{c}]$.

Denote ℓ_j and $\mathbf{u}_j$ the eigenvalues and eigenvectors of **G**; and write $(\mathbf{I} - \mathbf{G})\mathbf{1}$ as $\sum_j x_j \mathbf{u}_j$. Then

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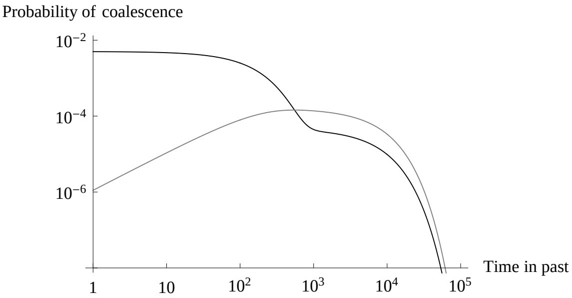
$$\mathbf{Q} = \gamma(\mathbf{I}-\gamma\mathbf{G})^{-1}\sum_j x_j\mathbf{u}_j = \sum_j \frac{\gamma x_j\mathbf{u}_j}{1-\gamma\ell_j} = \sum_t \gamma^t \sum_j \ell_j^{t-1}x_j\mathbf{u}_j$$

i.e. for *i*th element of **Q**, $c_{i,t} = \sum_j \ell_j^{t-1}x_j u_{ji}$.

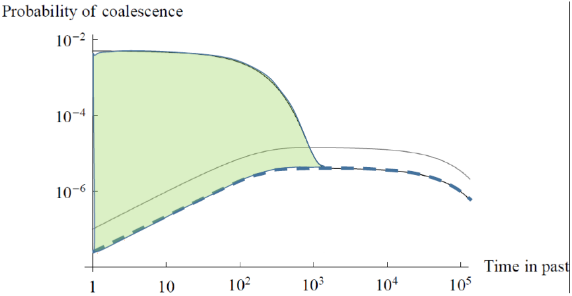
Genealogical interpretation of F-statistics

$(N = 100,\ m = 10^{-3}, \qquad n_{\mathrm{d}} = 10)$



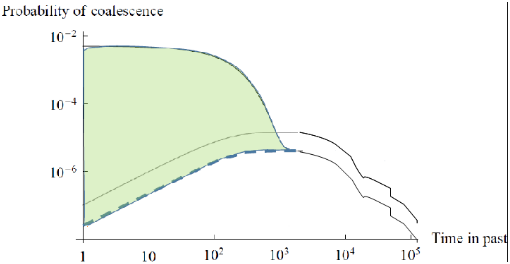
Genealogical interpretation of F-statistics

⇒ Interpretation of F_{ST} from comparison of two distributions of coalescence times



Genealogical interpretation of F-statistics

$\Rightarrow$ robustness: ancient events have no effect on F_{ST}



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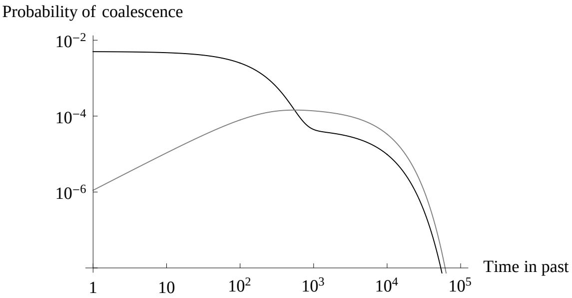

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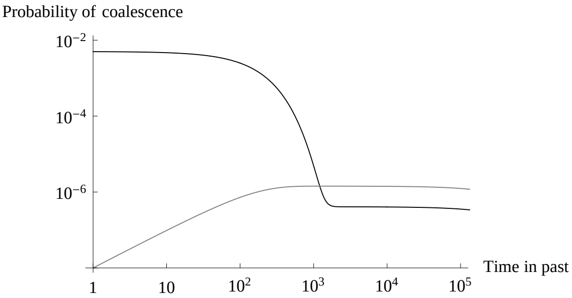

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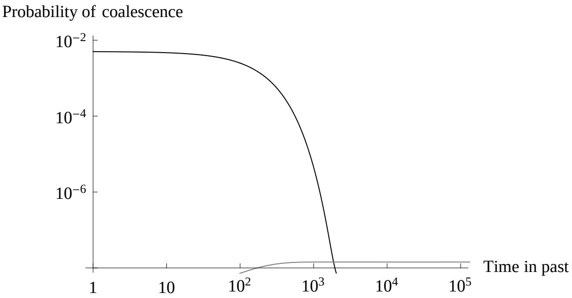
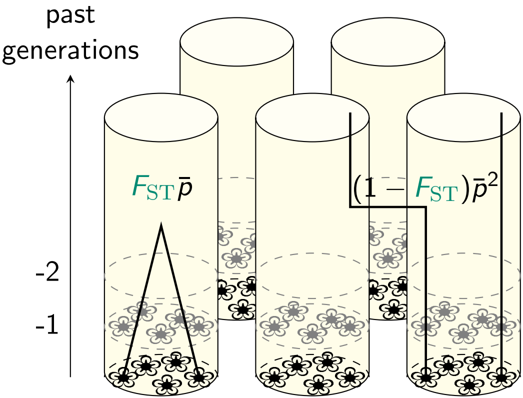
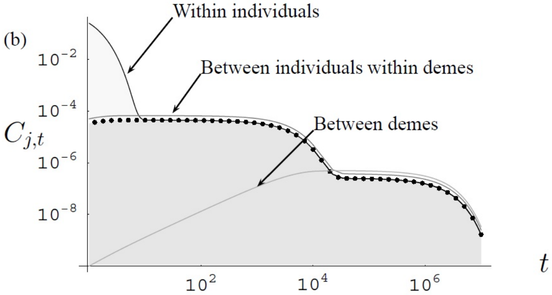


Genealogical interpretation of F_{ST}



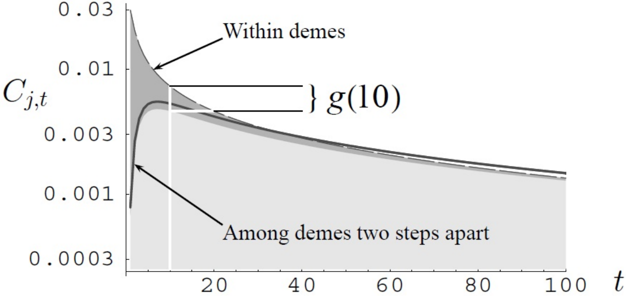
Island model with self-fertilization ("selfing")



Three eigenvalues of $\mathbf{G}$ = different time scales dependent on magnitude of $n_\mathrm{d}N$ vs. N vs selfing rate.

Isolation by distance

Pattern of isolation by distance



Isolation by distance: a quantitative approximation

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- Two dimensional $\lambda_{kl} = \psi^2\left(e^{\imath 2\pi k/n_x}\right)\psi^2\left(e^{\imath 2\pi l/n_y}\right)$;

Isolation by distance: a quantitative approximation

$$
\begin{aligned}
\frac{Q_{\mathrm{w}} - Q_{ij}}{1 - Q_{\mathrm{w}}} &= \frac{1}{N n_{\mathrm{d}}} \sum_k \sum_l \frac{\gamma \lambda_{kl}}{1 - \gamma \lambda_{kl}} (\mathbf{e}_{kl,0} - \mathbf{e}_{kl,ij}) \\
&\approx \frac{1}{N\pi^2} \int_0^\pi \int_0^\pi \frac{\gamma \psi^2(e^{\imath x}) \psi^2(e^{\imath y})}{1 - \gamma \psi^2(e^{\imath x}) \psi^2(e^{\imath y})} [1 - \cos(kx)\cos(ly)] \,\mathrm{d}x \,\mathrm{d}y \\
\frac{Q_{\mathrm{w}} - Q_d}{1 - Q_{\mathrm{w}}} &\approx \frac{\log(d)}{2N\pi\sigma^2} + \mathrm{constant}
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$$

Isolation by distance: a quantitative approximation

$$\frac{Q_\mathrm{w}-Q_{ij}}{1-Q_\mathrm{w}} = \frac{1}{N n_\mathrm{d}} \sum_k \sum_l \frac{\gamma\lambda_{kl}}{1-\gamma\lambda_{kl}}(\mathbf{e}_{kl,0}-\mathbf{e}_{kl,ij})$$

$$\approx \frac{1}{N\pi^2}\int_0^\pi\int_0^\pi \frac{\gamma\psi^2\left(e^{\imath x}\right)\psi^2\left(e^{\imath y}\right)}{1-\gamma\psi^2\left(e^{\imath x}\right)\psi^2\left(e^{\imath y}\right)}\left[1-\cos(kx)\cos(ly)\right]\mathrm{d}x\,\mathrm{d}y$$

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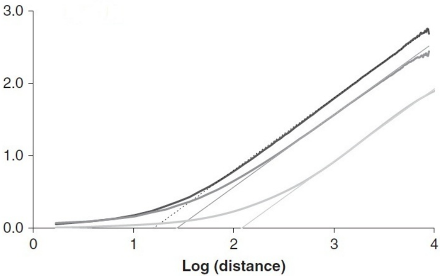
$$2N\pi\sigma^2\frac{Q_\mathrm{w}-Q_d}{1-Q_\mathrm{w}}$$

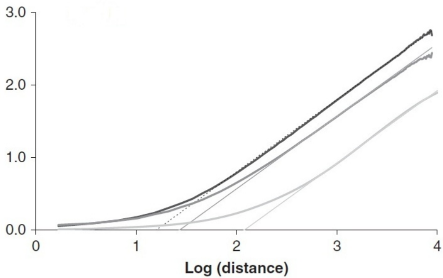


Outline

- An example of the role of spatial structure in evolution
- Modeling of the role of spatial structure
- Formal modelling of covariances: diffusion vs. coalescence
- Genealogical interpretations of covariances and regressions
- An example of statistical inference based on covariances

A simple inference under isolation by distance

$$2N\pi\sigma^2 \frac{Q_{\mathrm{w}} - Q_d}{1 - Q_{\mathrm{w}}}$$



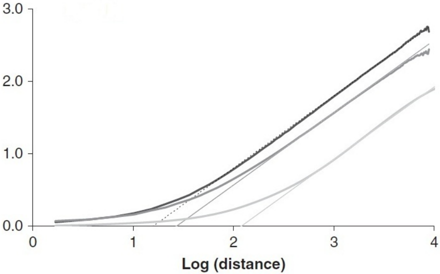
$\Rightarrow$ regress

$$\frac{Q_{\mathrm{w}} - Q_d}{1 - Q_{\mathrm{w}}}$$

against log(distance) to obtain an estimate of $1/2N\pi\sigma^2$.

A simple inference under isolation by distance

$$2N\pi\sigma^2 \frac{Q_{\mathrm{w}} - Q_d}{1 - Q_{\mathrm{w}}}$$



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Statistical inference: an illustration

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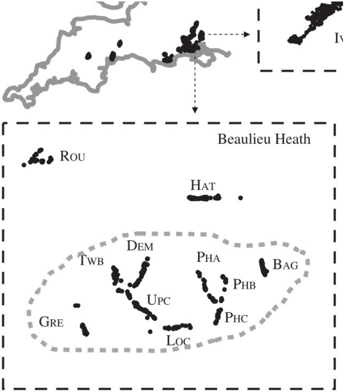

Statistical inference: an illustration

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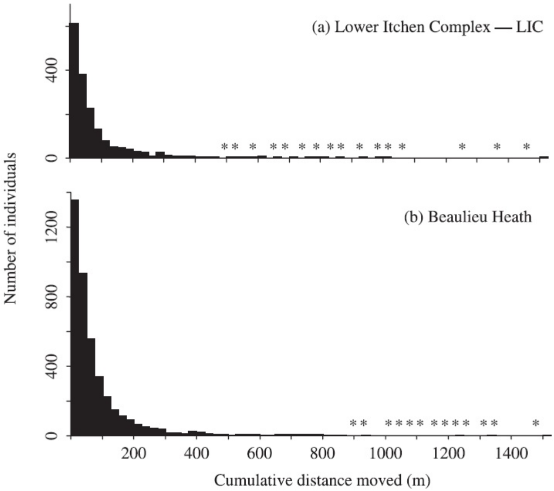

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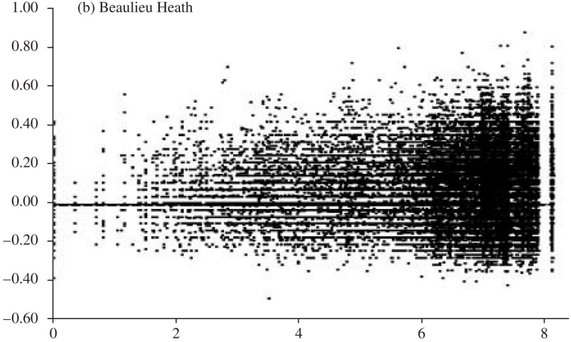
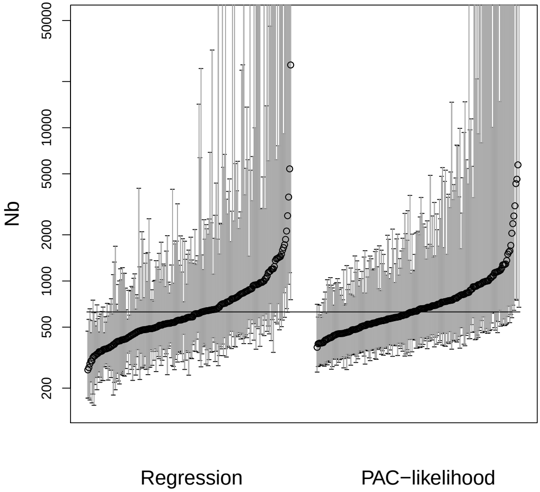


1/regression slope = estimate of “neighborhood size” Nb$\equiv 4D\pi\sigma^2$
Here one finds Nb$\hat{=}$753 with CI 319–3162 obtained by bootstrapping over loci.
(mark-recapture experiments yielded Nb$\hat{=}$555)

Moment vs. likelihood method



Summary

- Various evolutionary processes can be understood in terms of covariances in allele frequencies;
- Formal analysis in terms of probabilities of identity and distributions of coalescence times;
- Wright's F_{ST} and its variants can characterize recent events;
- They can provide some reasonable data analyses, although not the most precise ones.