Models in genomics and biodiversity analysis

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Common mathematical tools in biology

Parameterization

- Stochasticity
  - Discrete: Markov Chain
  - Continuous: Diffusion Process
- Complexity:
  - Confounding factors: Regression

Estimation

- Maximum likelihood
- Bayesian Inference

Markov Chain: A chain of events with Markov property

Random variable X_n

A substitution event can leads to a state of {A,T,C,G}

The probability of the nth substitution event that leads to A: $\mathrm{P}(X_n = A)$

$X_n = [\mathrm{P}(X_n = A), \mathrm{P}(X_n = T), \mathrm{P}(X_n = C), \mathrm{P}(X_n = G)]$

Markov Chain

A sequence of random variables with Markov Property:

$$\mathrm{P}(X_{n+1} = A | X_n = T, X_{n-1} = C, \dots) = \mathrm{P}(X_{n+1} = A | X_n = T)$$

Discrete Time Markov Chain

A sequence of random variables with Markov Property:

$$\mathrm{P}(X_{n+1} = A | X_n = T, X_{n-1} = C, \dots) = \mathrm{P}(X_{n+1} = A | X_n = T)$$

Discrete Time Markov Chain

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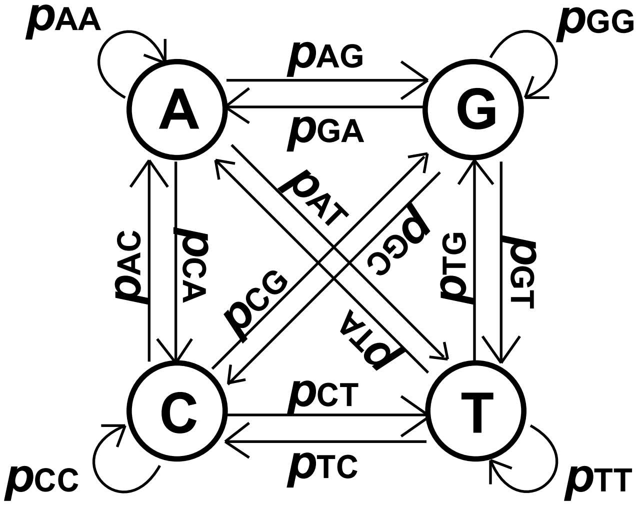
$$\mathrm{P}(X_{n+1} = A | X_n = T, X_{n-1} = C, \dots) = \mathrm{P}(X_{n+1} = A | X_n = T)$$

Transition matrix:

$$P = \begin{bmatrix} p_{AA} & p_{AT} & p_{AC} & p_{AG} \\ p_{TA} & p_{TT} & p_{TC} & p_{AG} \\ p_{CA} & p_{CT} & p_{CC} & p_{CG} \\ p_{GA} & p_{GT} & p_{GC} & p_{GG} \end{bmatrix}$$



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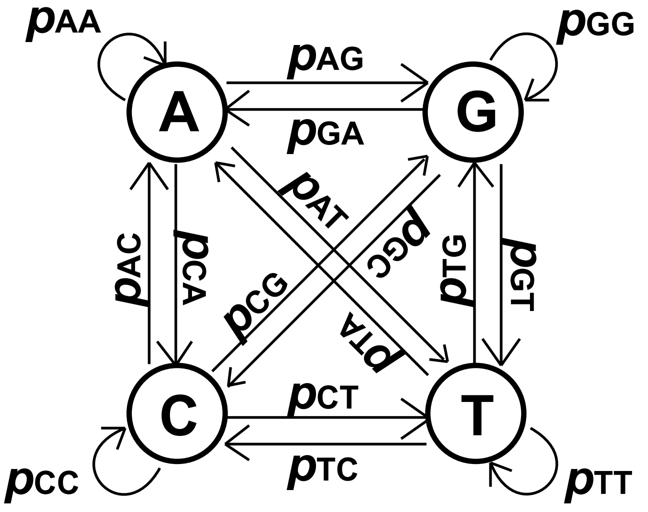
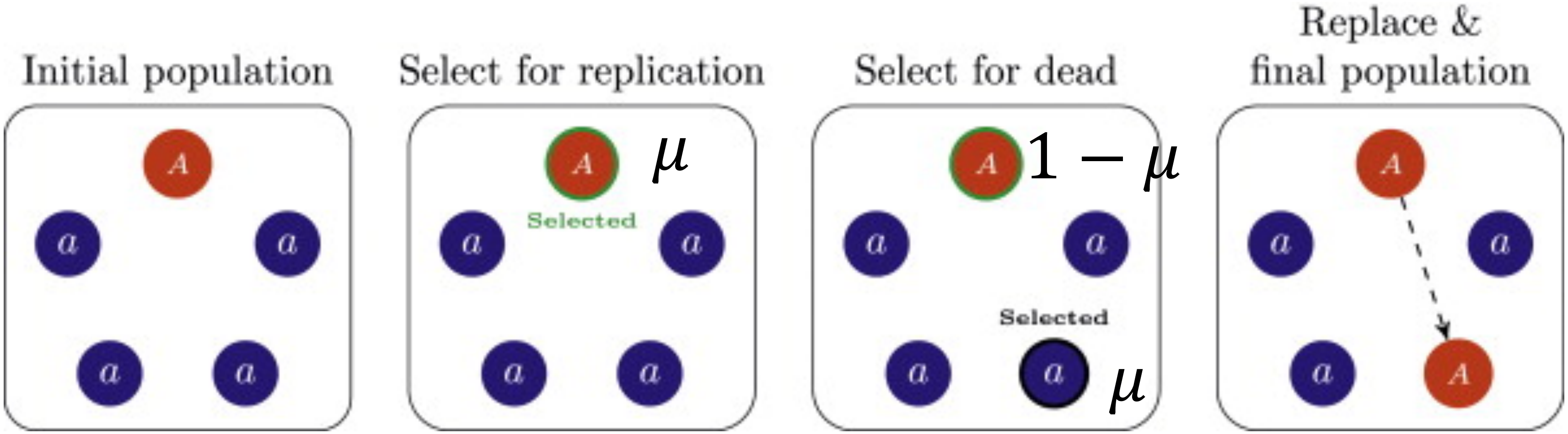


$$\begin{aligned} X_n &= [\mathrm{P}(X_{n-1} = A), \mathrm{P}(X_{n-1} = T), \mathrm{P}(X_{n-1} = C), \mathrm{P}(X_{n-1} = G)]P \\ &= X_{n-1}P = X_{n-2}P^2 = \cdots = X_0P^n \end{aligned}$$

DTMC – Moran Model

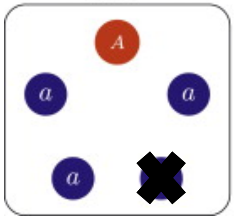


For red individual, states = {1,2,…*N*}, μ=1/*N*

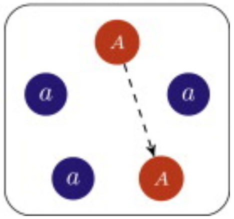
$$P(X_{n+1}=j|X_n=i)=\begin{cases}\mu\,(1-\mu\,) & \text{if } j=i+1\\ (1-\mu\,)\mu & \text{if } j=i-1\\ \mu^2+(1-\mu)^2 & \text{if } j=i\\ 0 & \text{otherwise}\end{cases}$$

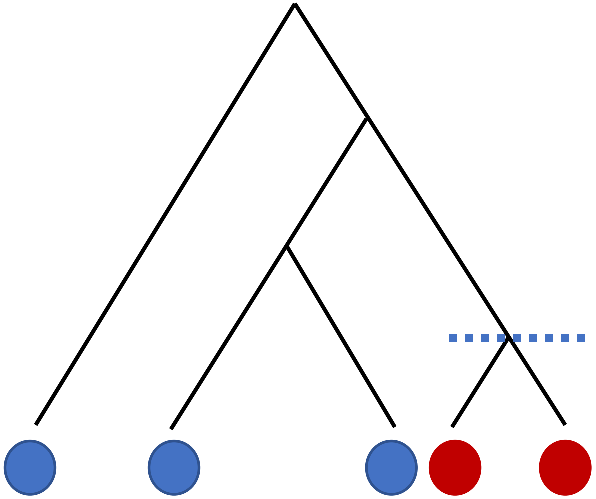
From Moran model to Coalescence

i-1 ancestors



i descendants





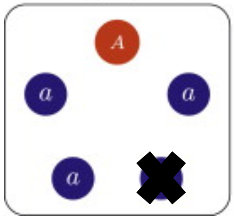
Parent A does not die

$$P(i \text{ lineages from } i-1 \text{ ancestors}) = \left(1-\frac{1}{N}\right)\left(\frac{i}{N}\frac{i-1}{N-1}\right) = \binom{i}{2}\frac{2}{N^2}$$

Both parent and offspring A are in the *i* lineages

From Moran model to Coalescence

i-1 ancestors



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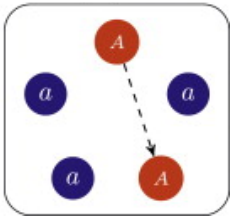

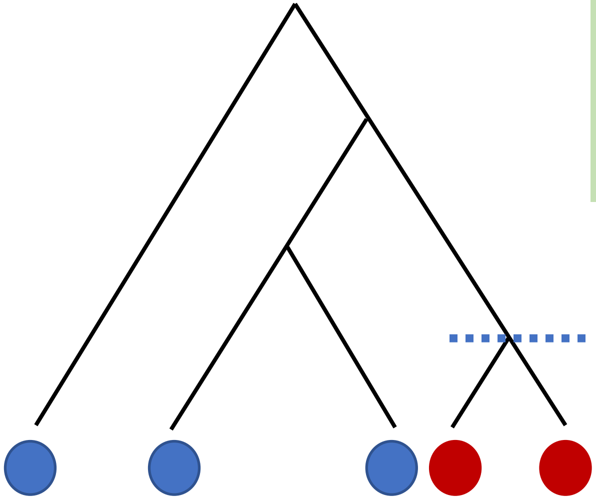

If $t = \frac{2}{N^2}$

as $N \to \infty, t \to 0, P \to \binom{i}{2}$

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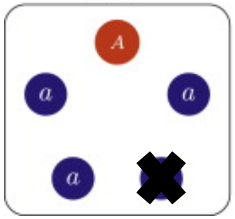

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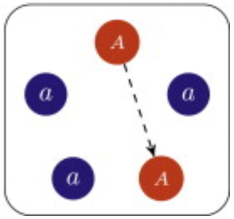
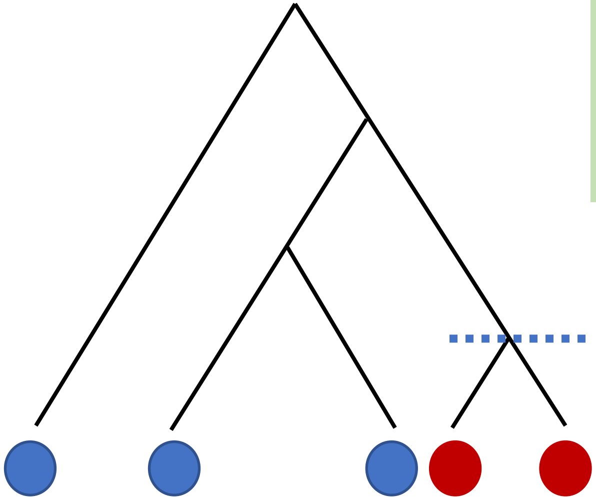




If $t = \frac{2}{N^2}$

as $N \to \infty, t \to 0, P \to \binom{i}{2}$

$$f(T = t) = \binom{i}{2} e^{-\binom{i}{2}t}$$

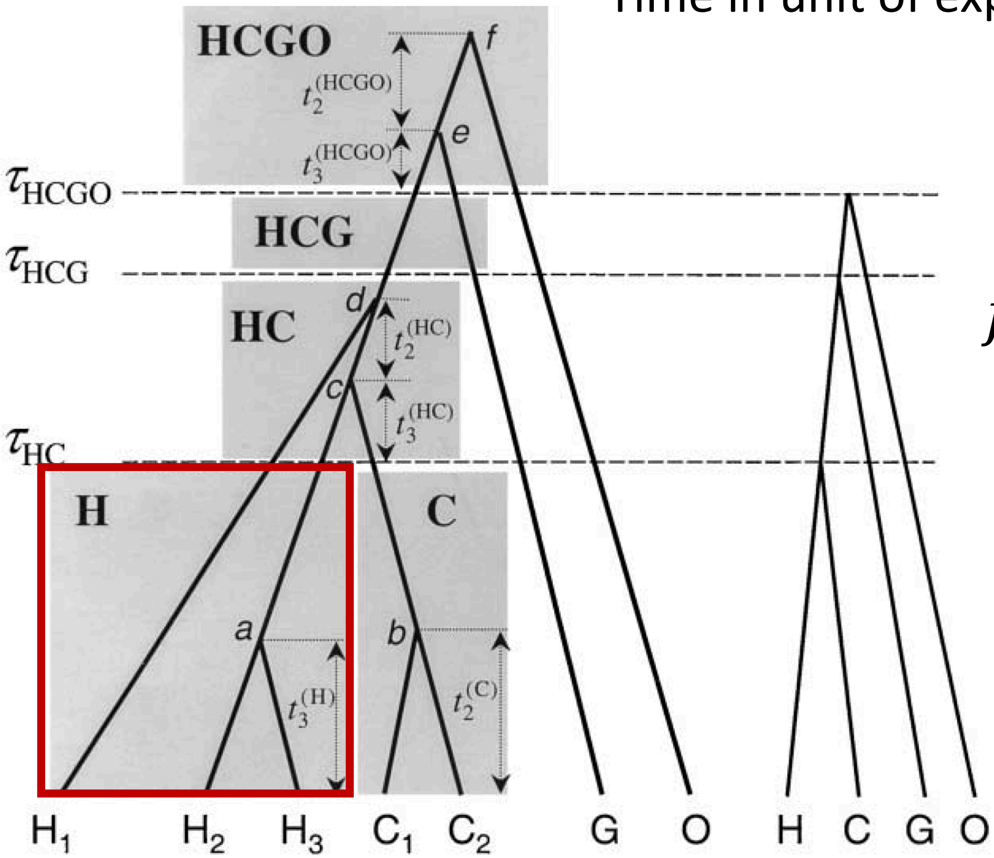
$$p(\text{no coel in } t) = e^{-\binom{i}{2}t}$$

Parent A does not die

$$P(i \text{ lineages from } i-1 \text{ ancestors}) = \left(1 - \frac{1}{N}\right)\left(\frac{i}{N}\frac{i-1}{N-1}\right) = \binom{i}{2}\frac{2}{N^2}$$

Both parent and offspring A are in the *i* lineages

Multi-Species Coalescence



Rannala and Yang 2003 Genetics

Time in unit of expected number of mutations per site

$$f(T=t) = \binom{i}{2}\frac{2}{\theta}e^{-\binom{i}{2}\frac{2}{\theta}t}$$

$$f(H) = \binom{3}{2}^{-1}$$

A coal event happens

$$\times \binom{3}{2}\frac{2}{\theta_H}e^{-\binom{3}{2}\frac{2}{\theta_H}t_3^{(H)}}$$

And the event happens at $t_3^{(H)}$

$$\times e^{-\binom{2}{1}\frac{2}{\theta_H}(\tau_{HC}-t_3^{(H)})}$$

And no coal event between $\tau_{HC}$and $t_3^{(H)}$

Continuous Time Markov Chain

$$\mathrm{P}(X_{n+1} = A | X_n = T) = p_{TA}$$

$$\mathrm{P}(X_{t+\Delta t} = A | X_t = T) = p_{TA}(t; t + \Delta t)$$

Continuous Time Markov Chain

$$\mathrm{P}(X_{n+1} = A | X_n = T) = p_{TA}$$

$$\mathrm{P}(X_{t+\Delta t} = A | X_t = T) = p_{TA}(t; t + \Delta t) \longrightarrow P$$

$$\mathrm{P}(X_{t+dt} = A | X_t = T) = q_{TA} dt, dt \to 0 \longrightarrow Q$$

Transition rate matrix

Continuous Time Markov Chain

$$\mathrm{P}(X_{n+1} = A | X_n = T) = p_{TA}$$

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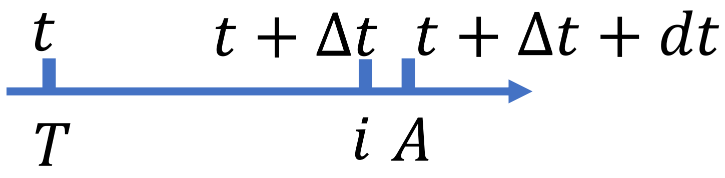
Transition rate matrix

Forward equation:

$$p'_{TA}(t; t + \Delta t) = \sum_{i \in \{A,T,C,G\}} p_{Ti}(t; t + \Delta t) q_{iA}$$



Continuous Time Markov Chain

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Transition rate matrix

Forward equation:

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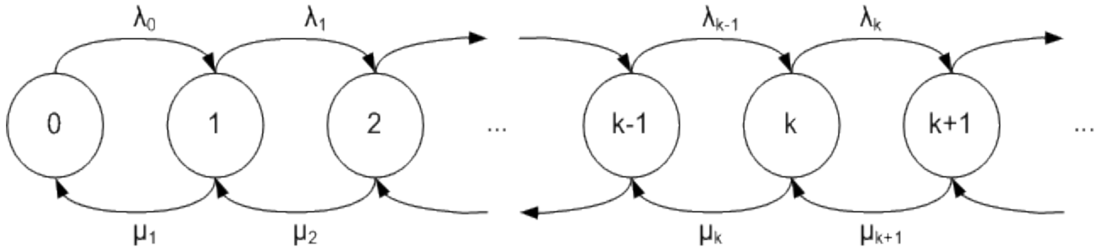
$$P'(t) = P(t)Q, P(0) = I \longrightarrow \boxed{P(\Delta t) = e^{Q\Delta t}}$$

CTMC – Birth-death process

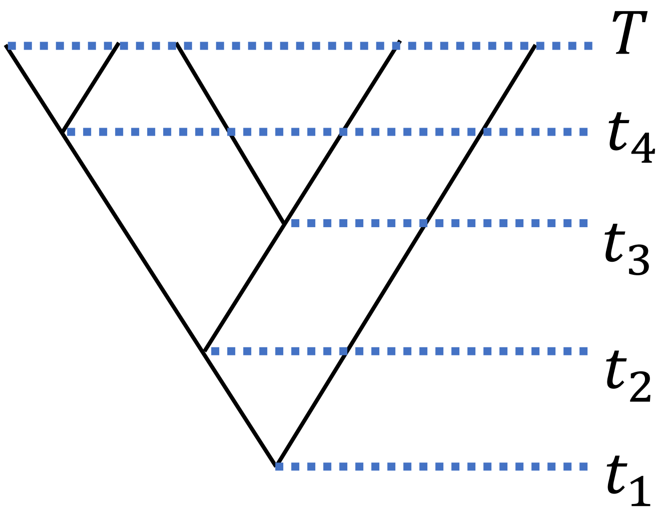


States = {0,1,2,…,N}

$q_{k,k+1} = \lambda$

$q_{k,k-1} = \mu$

$$p'_{kk}(0;t) = p_{k,k-1}\lambda + p_{k,k+1}\mu + p_{k,k}(-\lambda - \mu)$$



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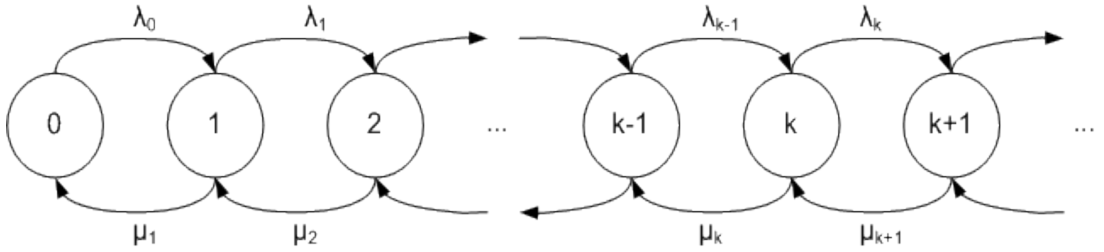

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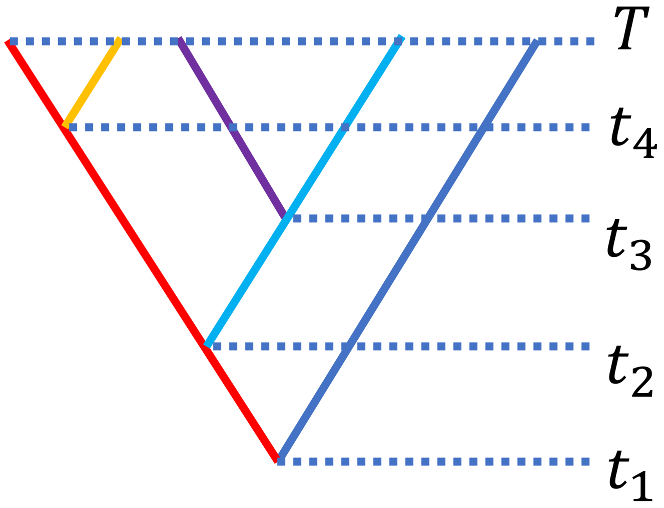

$$f\left(t_{1,\ldots}t_4\right) = \prod_{i=1}^{5} i\times\lambda(t_i)\times p_{11}(\mathrm{T};\mathrm{T} - t_i)$$

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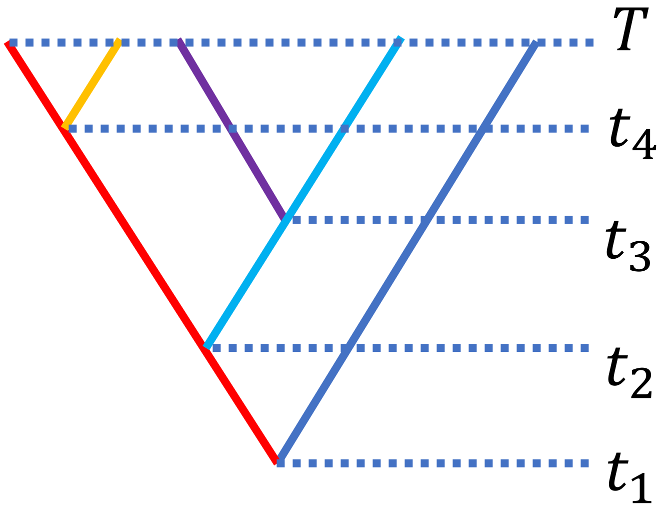

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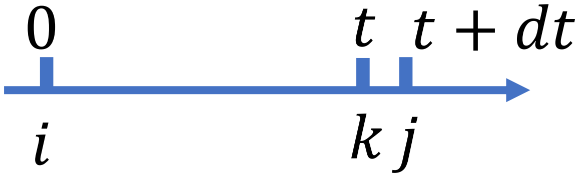

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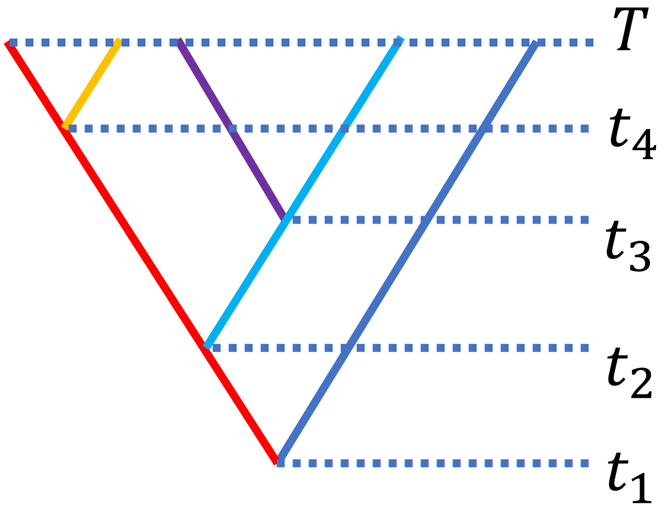

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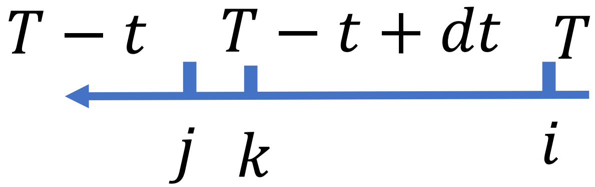

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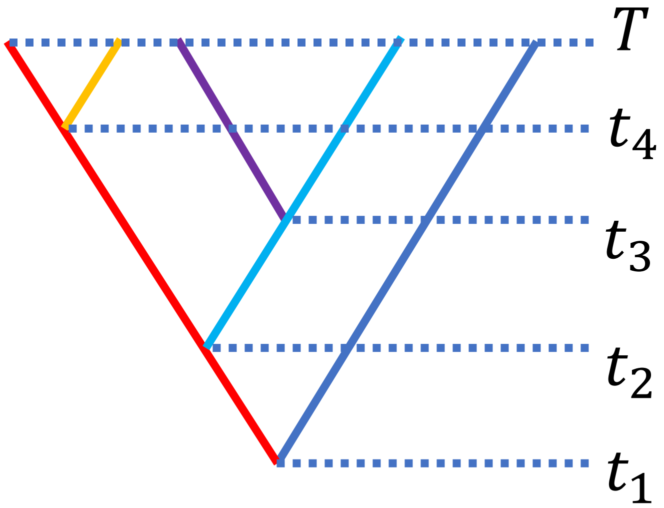

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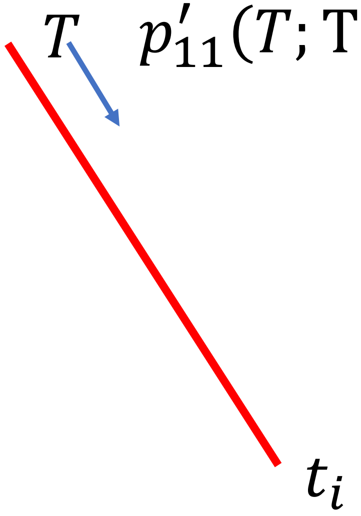
$$p'_{11}(T;\mathrm{T}-t_i) = \mu p_{10} - (\lambda+\mu)p_{11} + \lambda p_{12}, p_{11}(T;T) = 1$$



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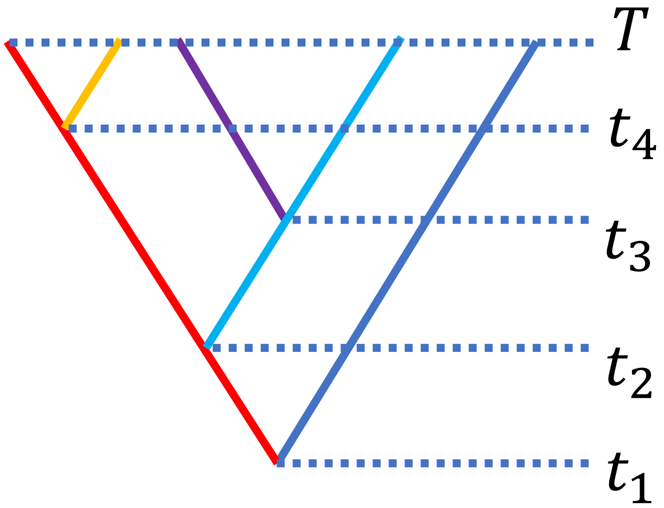

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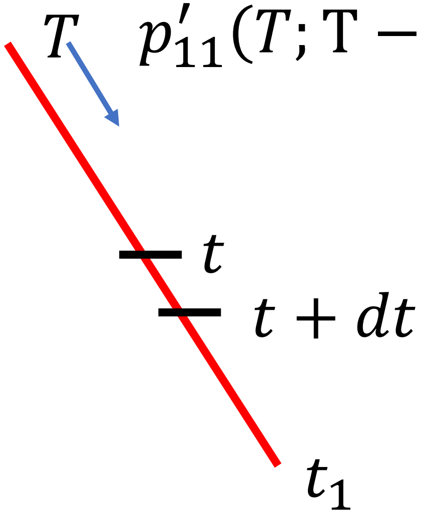

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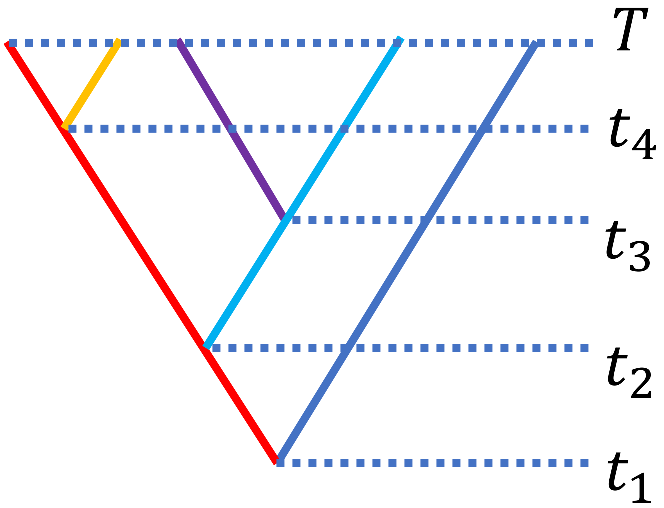

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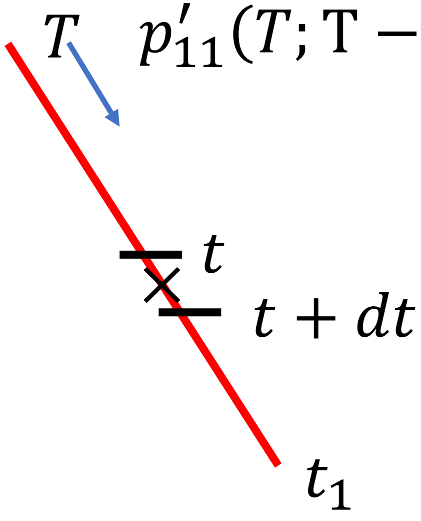

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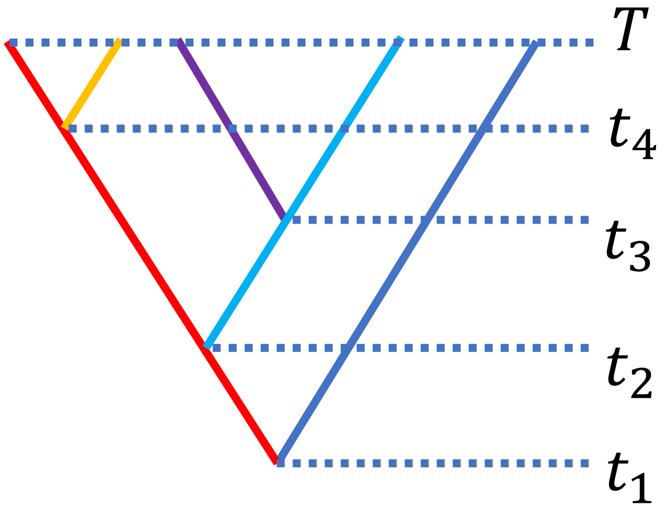

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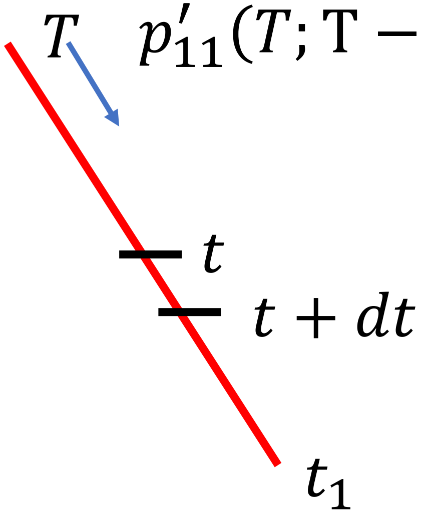

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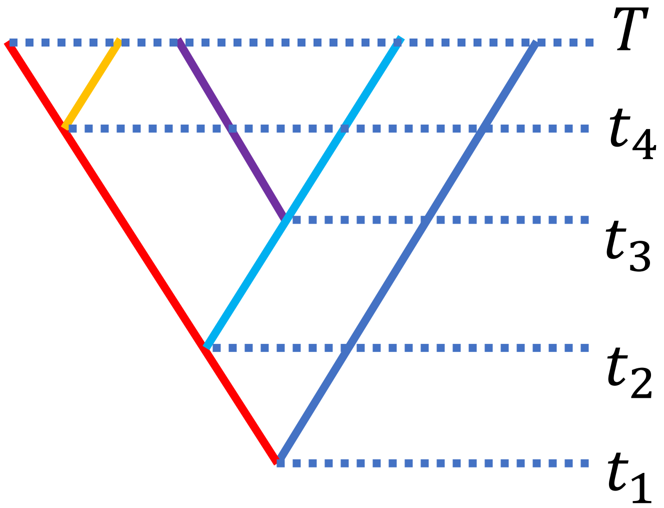

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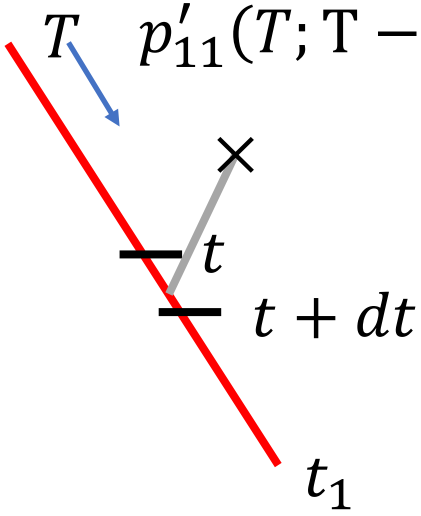

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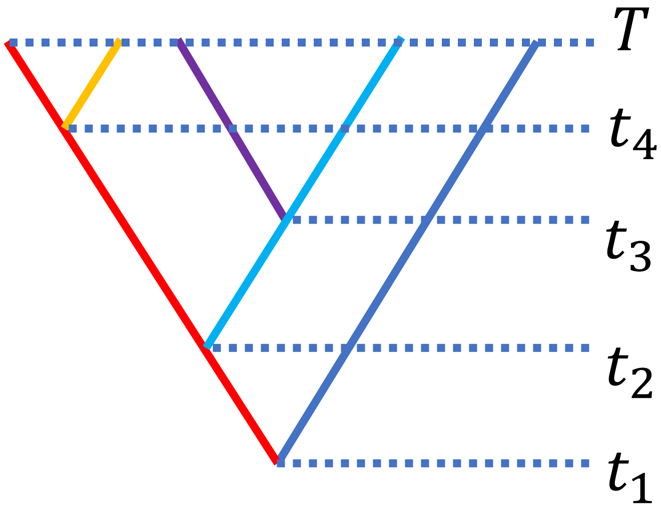

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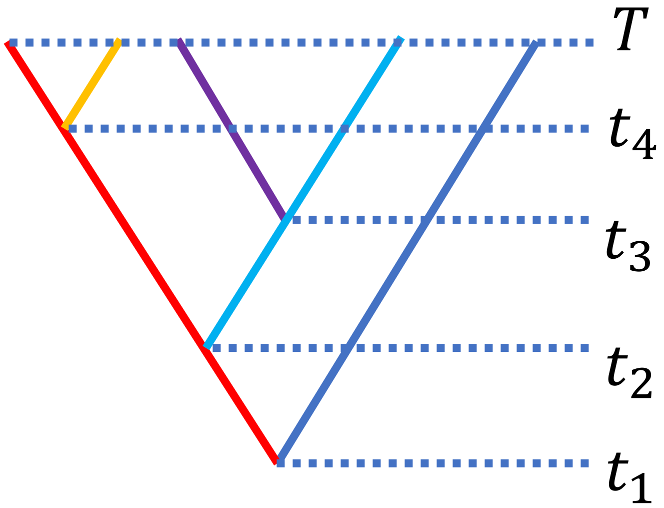

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$$p'_{11}(T;\mathrm{T}-t_i) = -(\lambda+\mu)p_{11} + \lambda 2 p_{11} p_{01},\, p_{11}(T;T) = 1$$

$$p'_{01}(T;\mathrm{T}-t_i) = \mu \underset{\substack{\shortparallel \\ 1}}{p_{00}} - (\lambda+\mu)p_{01} + \lambda \underset{\substack{\shortparallel \\ {p_{01}}^2}}{p_{02}},\, p_{10}(T;T) = 0$$

$$= \mu - (\lambda+\mu)p_{01} + \lambda {p_{01}}^2$$

Diffusion Process

$$\mathrm{P}(X_{t+dt} = A | X_t = T) = q_{TA}dt, dt \to 0$$

$$\mathrm{P}(X_{t+dt} = x + dx | X_t = x) = q_x dt, dt \to 0, dx \to 0$$

Diffusion Process

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$$\mathrm{P}(X_{t+dt} = x + dx | X_t = x) = q_x dt, dt \to 0, dx \to 0$$

$$\mathrm{P}(X_{t+\Delta t} = x + \Delta x | X_t = x) = p\,(x, t)$$

Diffusion Process

$$\mathrm{P}(X_{t+dt} = A | X_t = T) = q_{TA} dt, dt \to 0$$

$$\mathrm{P}(X_{t+dt} = x + dx | X_t = x) = q_x dt, dt \to 0, dx \to 0$$

$$\mathrm{P}(X_{t+\Delta t} = x + \Delta x | X_t = x) = p\,(x, t)$$

Forward equation: $\frac{d}{dt} P = P(t) Q$

$$\frac{\partial}{\partial t} p(x,t) = -\frac{\partial}{\partial x}[p(x,t)\mu(x,t)] + \frac{\partial^2}{\partial x^2}[\frac{1}{2} p(x,t) D(x,t)]$$

Change in mean of x in dt

Change in variance of x in dt

Diffusion Process – Trait evolution

	$\mu(x,t)$	$D(x,t)$
Brownian Motion	0	σ^2
BM with trend	b	σ^2
Ac/Decelerating	0	$\sigma^2 e^{rt}$
Ornstein-Uhlenbeck	$b(\mu - x)$	σ^2
Peak shift	$b(\mu_t - x)$	σ^2

Common mathematical tools in biology

Parameterization

- Stochasticity

  Discrete: Markov Chain

  Continuous: Diffusion Process

- Complexity:

  Confounding factors: Regression

Estimation

- Maximum likelihood
- Bayesian Inference

Regression Models

$$\boxed{Y_i = f(X_i, \beta) + e_i}$$

General Linear Model

$$Y_i = X_i\beta + e_i,\ e_i \sim N(0, \Omega)$$

Autoregressive Model

$$Y_t = X_t\beta + \sum_{j=1}^{p} Y_{t-j} + e_t,\ e_t \sim N(0, \sigma^2)$$

Linear Mixed Model

$$Y_i = X_i\beta + Zu + e_i, u \sim N(0, \Omega), e_i \sim N(0, \sigma^2)$$

Generalized Linear Model

$$g(Y_i) = X_i\beta + e_i,\ e_i \sim N(0, \Omega)$$

Genome-Wide Association Studies

Fisher’s polygenic model:

$$y_i = \mu + \sum_{l=1}^{L} G_{il} + \varepsilon_i$$

Phenotype of individual i

Genotype of locus l of individual i

Kinship Coefficient Matrix

$$Var(y) = 2\sigma_a^2\phi + \sigma_e^2 I$$

Additive genetic variance

Environmental variance

Generalized Linear mixed model:

$$g(y_i) = \mu + \sum_j \beta_j X_j + \beta_k G_{ik} + \sum_{l\neq k}^{L} \beta_l G_{il} + \varepsilon_i$$

Confounding factors

Test SNP

||

$$N(0{,}2\sigma_a^2\phi + \sigma_e^2 I)$$

Accounting for genetic relatedness

Population admixture: $$E(G_{i,j}) = 2\sum_{k=1}^{K} \underset{\uparrow}{\phi_{i,k}}\, P_{k,j}$$

Most restricted: $\sum_{k=1}^{K} \phi_{i,k}=1,\ \phi_{i,k} \geq 0$

Admixture proportion

Principle component analysis: $$E(G_{i,j}) = (\underset{\uparrow}{\phi} F)_{ij}$$

No restriction

loadings factors

Accounting for genetic relatedness

Population admixture: $E(G_{i,j}) = 2\sum_{k=1}^{K} \phi_{i,k} P_{k,j}$

Most restricted: $\sum_{k=1}^{K} \phi_{i,k}$=1, $\phi_{i,k} \geq 0$

Admixture proportion

Sparse factor analysis: $E(G_{i,j}) = (\phi F)_{ij}$

Encouraging sparsity in ϕ
by giving prior $\phi_{i,k} \sim \mathrm{N}(0, \sigma_{i,k}^2)$

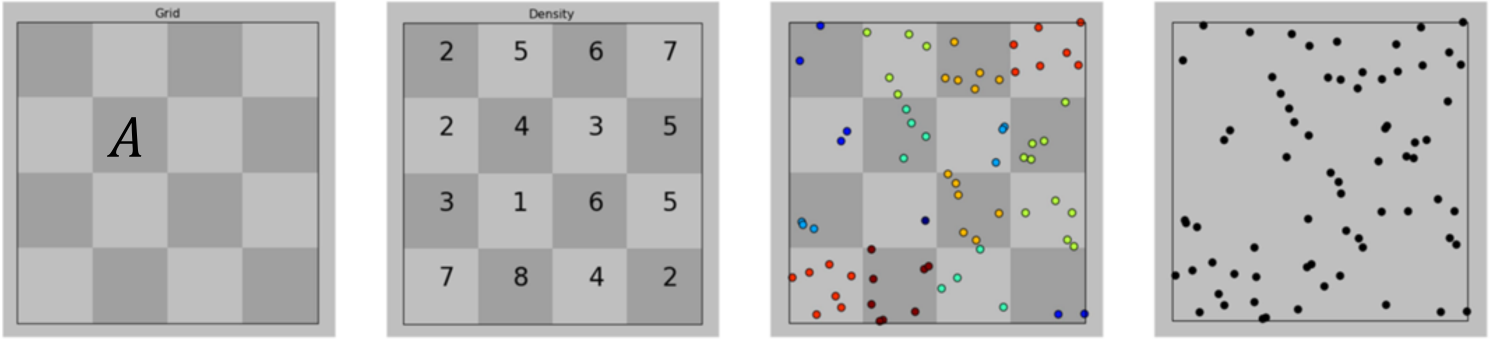
Principle component analysis: $E(G_{i,j}) = (\phi F)_{ij}$

No restriction

loadings factors

Species distribution modeling

$\mathcal{D}$ $\mathrm{Pois}(\int_A \lambda(s)ds)$ $p(s) = \dfrac{\lambda(s)}{\int_{\mathcal{D}} \lambda(s)ds}$ Inhomogeneous Poisson Point Process



2	5	6	7
2	4	3	5
3	1	6	5
7	8	4	2

$$\ln \lambda(s) = \alpha + X(s)\beta$$

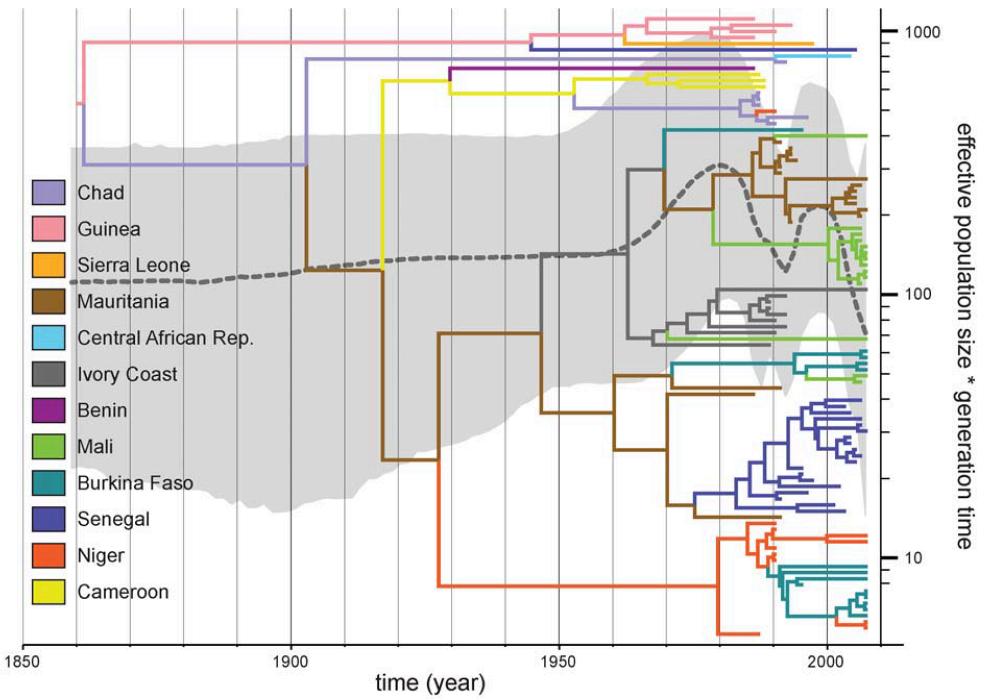
Presence-absence in quadrat A : $N_A \approx \mathrm{Pois}(\lambda(s)A)$

Absence: $\mathrm{P}(N_A = 0) = e^{-Ae^{\alpha+X(s)\beta}}$

Presence: $\mathrm{P}(N_A > 0) = 1 - e^{-Ae^{\alpha+X(s)\beta}} \approx Ae^{\alpha+X(s)\beta}$

Presence-only at s: $\ln p(S) = \alpha + X(s)\beta - \sum_{i \in BG} \dfrac{\mathcal{D}}{n_{BG}} e^{\alpha+X(i)\beta}$

Pathogen Phylodynamics



Lemey et al. 2009 PLoS Computational Biology

States: {Chad, Guinea,…}

$$P(T) = e^{Qt}$$

$$\log Q_{ij} = \sum_{k} \delta_k \beta_k X_{ijk}$$

X_{ijk}: value of predictor *k* between location *i* and *j*

β_k: effective size of predictor *k*

δ_k: (0,1)-indicator of the inclusion of predictor *k*

Common mathematical tools in biology

Parameterization

- Stochasticity
  - Discrete: Markov Chain
  - Continuous: Diffusion Process
- Complexity:
  - Confounding factors: Regression

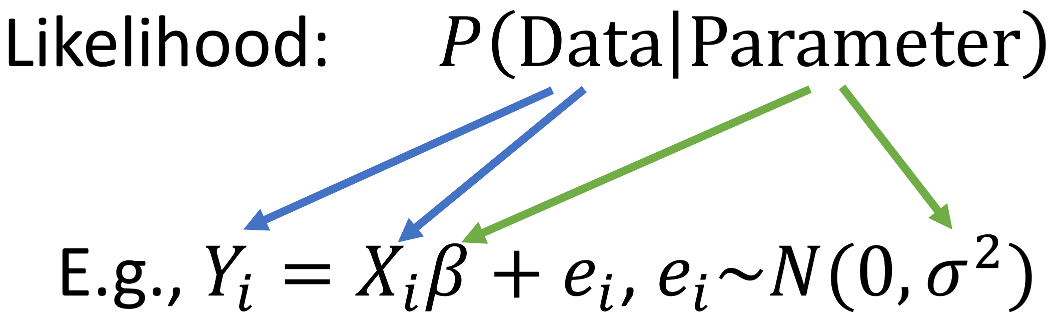
Estimation

- Maximum likelihood
- Bayesian Inference

Maximum Likelihood

Likelihood: $P(\text{Data}|\text{Parameter})$

Maximum Likelihood

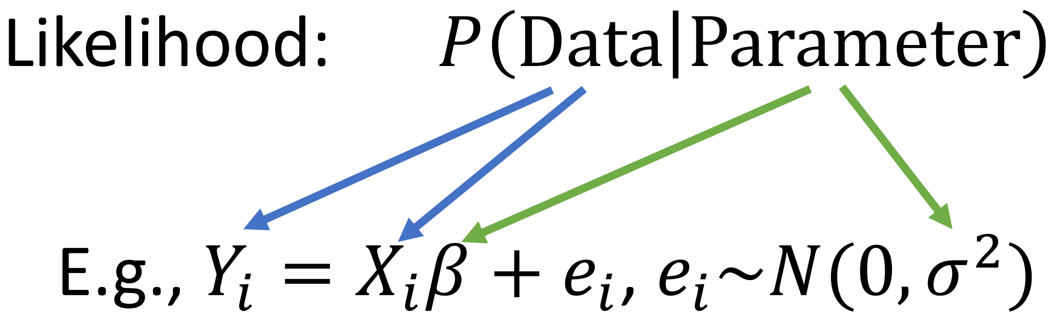


Likelihood: $P(\text{Data}|\text{Parameter})$

E.g., $Y_i = X_i\beta + e_i$, $e_i \sim N(0, \sigma^2)$

$$P(Y|X, \beta, \sigma^2) = \mathrm{N}(X\beta, \sigma^2)$$

Maximum Likelihood



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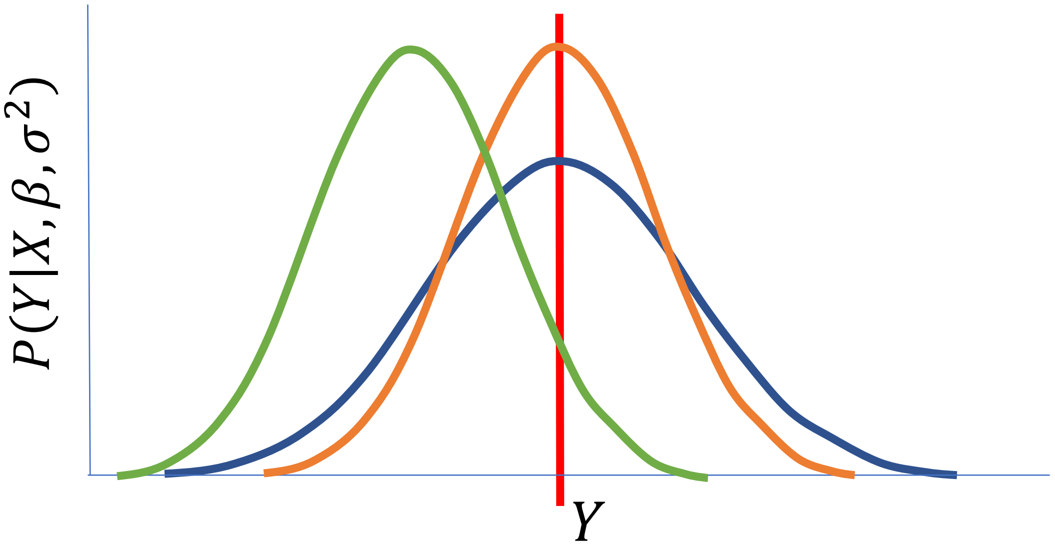


Maximum Likelihood

$$L = \prod_{i=1}^{n} (2\pi\sigma^2)^{-\frac{1}{2}} e^{-\frac{(Y_i - X_i\beta)^2}{2\sigma^2}}$$

$$-lnL = \sum_{i=1}^{n} \frac{1}{2} ln(2\pi\sigma^2) + \frac{(Y_i - X_i\beta)^2}{2\sigma^2}$$

```
f <- function (p, X, Y) {
	beta <- p[1]
	sigma <- exp(p[2])
	n <- length(Y)
	nll <- n/2*log(2*pi*sigma) + sum((Y-X*beta)^2)/2/sigma
	nll
}
mle <- optim(x0=c(0,0),fun=f)
```

Bayesian Inference

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

$$P(\text{Parameter}|\text{Data}) = \frac{P(\text{Data}|\text{Parameter})P(\text{Parameter})}{P(\text{data})}$$

Bayesian Inference

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

$$\underbrace{P(\text{Parameter}|\text{Data})}_{\text{Posterior Probability}} = \frac{\overbrace{P(\text{Data}|\text{Parameter})}^{\text{Likelihood}}\overbrace{P(\text{Parameter})}^{\text{Prior Probability}}}{P(\text{data})}$$

Bayesian Inference

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

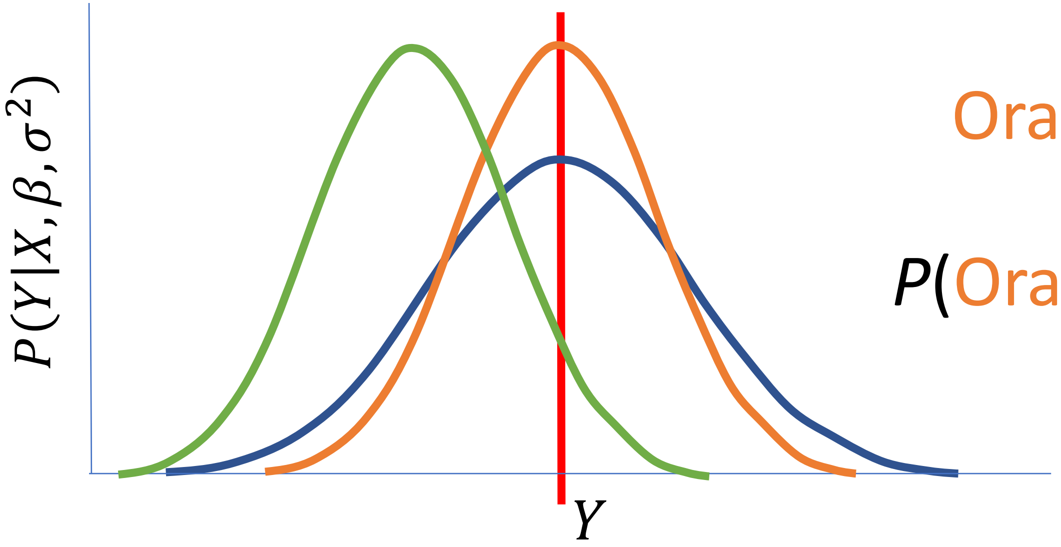
$$\underset{\substack{\uparrow\\ \text{Posterior Probability}}}{P(\text{Parameter}|\text{Data})} = \frac{\overset{\substack{\text{Likelihood}\\ \downarrow}}{P(\text{Data}|\text{Parameter})}\,\overset{\substack{\text{Prior Probability}\\ \downarrow}}{P(\text{Parameter})}}{P(\text{data})}$$

$$\propto P(\text{Data}|\text{Parameter})P(\text{Parameter})$$

Bayesian Inference

Likelihood: $P(Y|X,\beta,\sigma^2) = \mathrm{N}(X\beta,\sigma^2)$

Posterior: $P(\beta,\sigma^2|Y,X) \propto \mathrm{N}(X\beta,\sigma^2)P(\beta,\sigma^2)$

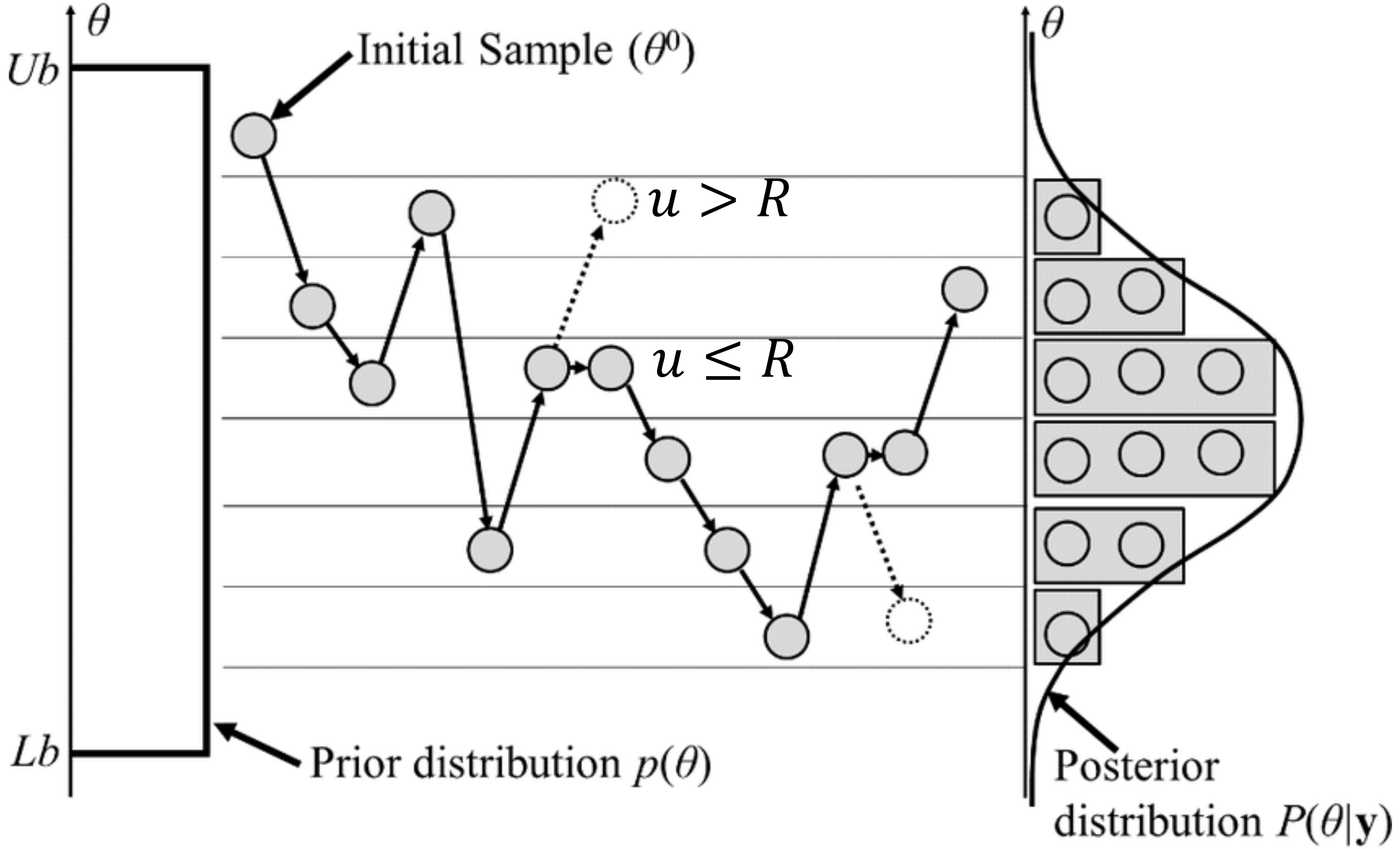


Orange is the ML model

P(Orange)>P(Blue)>P(Green)

MCMC: Metropolis–Hastings algorithm

$$R = \min\left(1, \frac{L(x')\,\mathrm{P}(x')}{L(x)P(x)}\,\frac{g(x|x')}{g(x'|x)}\right)$$



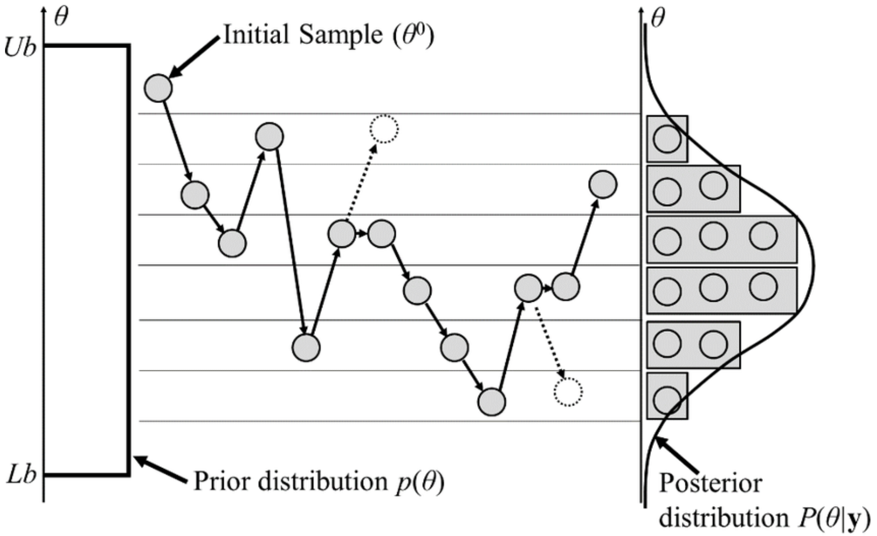
θ
Ub
Lb
Initial Sample (θ^0)
$u > R$
$u \leq R$
Prior distribution $p(\theta)$
θ
Posterior distribution $P(\theta|\mathbf{y})$

Metropolis–Hastings algorithm

$$L = \prod_{i=1}^{n} (2\pi\sigma^2)^{-\frac{1}{2}} e^{-\frac{(Y_i - X_i\beta)^2}{2\sigma^2}}, \quad \beta \sim \mathrm{N}(0{,}10), \quad \sigma^2 \sim \mathrm{Gamma}(0.1{,}0.1)$$

Initialization:

```
pr <- function (beta,sigma) {
      dnorm(beta, 0, sqrt(10), log=T)+dgamma(sigma, 0.1, 0.1, log=T)
}
beta <- rnorm(1, 0, sqrt(10))
sigma <- rgamma(1, 0.1, 0.1)
ll <- -f(c(beta,sigma),X,Y)
lp <- pr(beta,sigma)
beta_up <- 1
sigma_up <- 1
```


θ
Ub
Initial Sample (θ^0)
θ
Lb
Prior distribution $p(\theta)$
Posterior distribution $P(\theta|\mathbf{y})$

Metropolis–Hastings algorithm

Start MCMC:

updating beta:

```
niter <- 5000
for (i in 1:niter) {
    beta_new <- beta+
            runif(1,-beta_up,beta_up)
    ll_new <- -f(c(beta_new,sigma),X,Y)
    lp_new <- pr(beta_new,sigma)
    R <- ll_new + lp_new – ll – lp
    if (R > runif(1,0,1)) {
        beta <- beta_new
        ll <- ll_new
        lp <- lp_new
    }
```

updating sigma:

```
    u <- runif(1, 0, 1)
    sigma_new <- sigma*
            exp(sigma_up*(u-0.5))
    ll_new <- -f(c(beta,sigma_new),X,Y)
    lp_new <- pr(beta,sigma_new)
    R <- ll_new + lp_new – ll – lp
    R <- R*exp(sigma_up*(u-0.5))
    if (R > runif(1,0,1)) {
        sigma <- sigma_new
        ll <- ll_new
        lp <- lp_new
    }
}
```