Markov Chain Monte Carlo

Metropolis-Hastings and related algorithms

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Outline

Motivation

- $P(\theta|x)$ and $P(\theta)$ are conjugate if the posterior $P(\theta|x)$ is of the same family as the prior $P(\theta)$

$$P(\theta|x) = \frac{P(x|\theta)P(\theta)}{P(x)} = \frac{P(x|\theta)P(\theta)}{\int P(x,\theta')d\theta'}$$

- The denominator is $P(x)$, the Bayesian evidence, which does not depend on θ.
- The dependence of $P(\theta|x)$ on θ is same as that of $P(x|\theta)P(\theta)$, but to get a normalized form for $P(\theta|x)$, we need to integrate out θ to find the evidence $P(x)$.
- The parameters of the conjugate prior distribution are called hyperparameters.

Motivation

$$
\begin{aligned}
L(\theta) = \quad & P(\text{data } D|\text{params } \theta) && = \text{likelihood} \\
F(\theta, \alpha) = \quad & P(\theta|\text{hyperparams } \alpha) && = \text{prior} \\
G(\theta) = \quad & P(\theta|\alpha, D) && = \text{posterior}
\end{aligned}
$$

L and F are conjugate if $G(\theta) = F(\theta, \alpha')$ where $\alpha' \equiv \alpha'(\alpha, D)$

Common conjugacies

Likelihood	Prior
Exponential	Gamma
Binomial	Beta
Multinomial	Dirichlet
Gaussian (fixed precision)	Gaussian
Gaussian (varying precision)	Gaussian + Gamma

Outline

Gamma distribution

- Exponential, Poisson, Gamma distributions
  - Exponential distribution: pdf for time to first event, T, given that mean event rate is μ

$$P(T|\mu) = \mu \exp(-\mu T)$$

  - Poisson: probability distribution of number of events, n, in time T, given that mean event rate is μ

$$P(n|\mu) = \frac{(\mu T)^n \exp(-\mu T)}{n!}$$

(NB exponential distribution can be obtained by setting $n = 0$ and differentiating w.r.t. T)

Gamma distribution

- Poisson

$$P(n|\mu) = \frac{(\mu T)^n \exp(-\mu T)}{n!}$$

- Gamma, conjugate to Poisson.
  Shape parameter α, rate parameter β.

$$P(\mu|\alpha,\beta) = \frac{\mu^{\alpha-1}\beta^{\alpha}\exp(-\mu\beta)}{\Gamma(\alpha)}$$

where Γ is the gamma function

$$\Gamma(\alpha) = \int_0^{\infty} (\mu\beta)^{\alpha-1} \exp(-\mu\beta) d(\mu\beta)$$

Gamma function

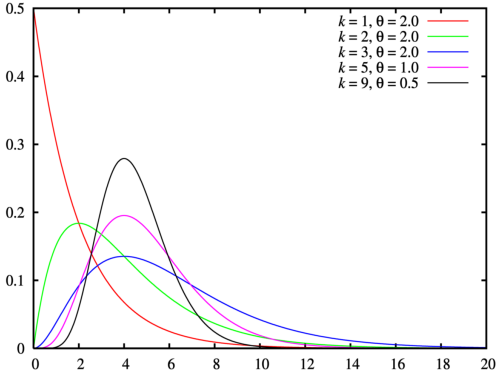
Changing variables in the gamma function integral

$$\Gamma(z) = \int_{u=0}^{\infty} u^{z-1} \exp(-u) du$$

Clearly $\Gamma(1) = 1$. Integrating by parts for positive integer z,

$$\begin{aligned}\Gamma(z+1) &= \int_{u=0}^{\infty} u^{z} \exp(-u) du \\ &= [-u^{z} \exp(-u)]_{u=0}^{\infty} + z\Gamma(z) \\ &= z!\end{aligned}$$

Gamma distribution



$k = \alpha$, $\theta = 1/\beta$

θ is called the scale parameter.

Gamma distribution

- Properties of gamma distribution:
  mean of μ is α/β and variance is α/β^2.
- Conjugacy:

$$P(n) = \frac{\Gamma(\alpha')}{\Gamma(n+1)\Gamma(\alpha)} \frac{T^n \beta^\alpha}{(\beta')^{(\alpha')}}$$

$$P(\mu|n) = \frac{\mu^{\alpha'-1} (\beta')^{\alpha'} \exp(-\mu\beta')}{\Gamma(\alpha')}$$

  i.e. posterior for μ is a gamma distribution with shape $\alpha' = \alpha + n$ and rate $\beta' = \beta + t$.
- α and β are like a *pseudocount* and *pseudotime*.

Gamma distribution

- Lengthier derivation:

$$
\begin{aligned}
P(n) &= \int_{\mu=0}^{\infty} P(n|\mu)P(\mu)d\mu \\
&= \int_{\mu=0}^{\infty} \frac{(\mu T)^n \exp(-\mu T)}{\Gamma(n+1)} \frac{\mu^{\alpha-1}\beta^{\alpha}\exp(-\mu\beta)}{\Gamma(\alpha)} d\mu \\
&= \frac{T^n \beta^\alpha}{\Gamma(n+1)\Gamma(\alpha)} \int_{\mu=0}^{\infty} \mu^{n+\alpha-1}\exp(-\mu(T+\beta))d\mu \\
&= \frac{T^n \beta^\alpha}{\Gamma(n+1)\Gamma(\alpha)} \frac{1}{(T+\beta)^{n+\alpha}} \int_{u=0}^{\infty} u^{n+\alpha-1}\exp(-u)du \\
&= \frac{\Gamma(\alpha')}{\Gamma(n+1)\Gamma(\alpha)} \frac{T^n \beta^\alpha}{(\beta')^{(\alpha')}}
\end{aligned}
$$

Outline

Dirichlet distribution

- Multinomial, Dirichlet distributions
  - Multinomial: K possible outcomes, outcome probabilities $\mathbf{p}$, outcome frequencies $\mathbf{n}$ in $N = \sum_k n_k$ trials

$$P(\mathbf{n}|\mathbf{p}) = \frac{N!}{\prod_k n_k!} \prod_k p_k^{n_k}$$

  - Conjugate prior: let $\mathbf{a}$ be a vector of pseudocounts, $a_1 \ldots a_k$. The Dirichlet distribution for $\mathbf{p}$ is

$$P(\mathbf{p}|\mathbf{a}) = \frac{\prod_i p_i^{a_i - 1}}{\mathcal{B}(\mathbf{a})} \delta\left(\sum_i p_i - 1\right)$$

where $\mathcal{B}()$ is the type one Dirichlet integral or the multinomial beta function

$$\mathcal{B}(\mathbf{a}) = \int \left(\prod_i p_i^{a_i - 1}\right) \delta\left(\sum_i p_i - 1\right) d\mathbf{p} = \frac{\prod_k \Gamma(a_k)}{\Gamma(\sum_k a_k)}$$

Dirichlet distribution

- Properties: mean value of p_k is $a_k / \sum_j a_j$. Modal value is $p_k = (a_k - 1)/(\sum_j a_j - 1)$.
- Note the relationship between the multinomial coefficient and $\mathcal{B}$

$$\frac{N!}{\prod_k n_k!} = \frac{1}{\mathcal{B}(\mathbf{n}+\mathbf{1})} \times \frac{\Gamma(N+1)}{\Gamma(N+K)}$$

- Conjugacy:

$$\begin{aligned} P(\mathbf{n}|\mathbf{a}) &= \frac{\mathcal{B}(\mathbf{a}')}{\mathcal{B}(\mathbf{a})} \frac{N!}{\prod_k n_k!} \\ P(\mathbf{p}|\mathbf{n},\mathbf{a}) &= \frac{\prod_i p_i^{a'_i - 1}}{\mathcal{B}(\mathbf{a}')} \delta \left(\sum_i p_i - 1 \right) \end{aligned}$$

where $\mathbf{a}' = \mathbf{a} + \mathbf{n}$ (hence the name "pseudocount").

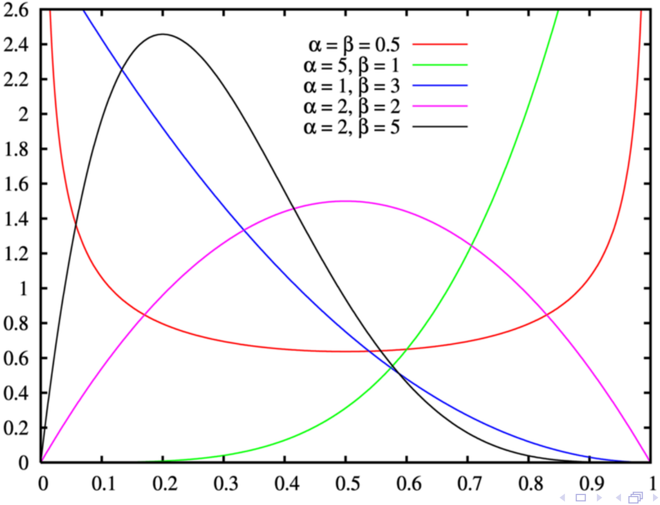
Dirichlet distribution

- Special case of {Multinomial,Dirichlet} when $K = 2$ is {Binomial,Beta}, and $\mathcal{B}$ is the beta function.
- The following snippets from Mathworld point to a more rigorous solution of the type one Dirichlet integral
  - The beta integral may be obtained by writing $m!n!$ as a product of gamma functions with integrands u, v, transforming to $(x, y) = (\sqrt{u}, \sqrt{v})$ and then to polar co-ordinates $(x, y) = r(\cos\theta, \sin\theta)$. This yields

$$\mathcal{B}(m+1, n+1) = 2\int_0^{\pi/2} \cos^{2m+1}\theta \sin^{2n+1}\theta d\theta = \frac{m!n!}{(m+n+1)!}$$

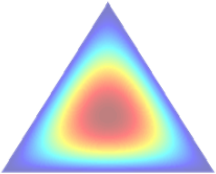
    See `mathworld.wolfram.com/BetaFunction.html` for details.
  - More info on Dirichlet type one integral at `mathworld.wolfram.com/DirichletIntegrals.html`

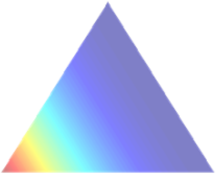
Beta distribution

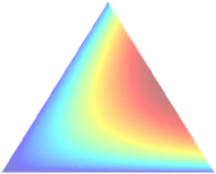


Dirichlet distribution

- For $K = 3$, the probabilities (p_x, p_y, p_z) satisfy $p_x + p_y + p_z = 1$
- Like 3D points lying on the 2D triangle with corners at $(0, 0, 1)$, $(0, 1, 0)$ and $(1, 0, 0)$







Outline

Normal-gamma distribution

- Normal (Gaussian) and Normal-gamma distributions
  - Mean μ, precision τ (precision is reciprocal of variance). Data $\{x_i\}$ with moments $m_k = \sum_i x_i^k$

$$
\begin{aligned}
P(\mathbf{x}|\mu,\tau) &= \prod_i \sqrt{\frac{\tau}{2\pi}} \exp\left(-\frac{\tau}{2}(x_i-\mu)^2\right) \\
&= \left(\frac{\tau}{2\pi}\right)^{m_0/2} \exp\left(-\frac{\tau}{2}(m_2 - 2\mu m_1 + \mu^2 m_0)\right)
\end{aligned}
$$

Normal-gamma distribution

- Normal

$$P(\mathbf{x}|\mu,\tau) = \left(\frac{\tau}{2\pi}\right)^{m_0/2} \exp\left(-\frac{\tau}{2}(m_2 - 2\mu m_1 + \mu^2 m_0)\right)$$

- Conjugate prior

$$\begin{aligned} P(\mu,\tau) &= P(\tau)P(\mu|\tau) \\ P(\tau) &= \frac{e^{-\beta\tau}\tau^{\alpha-1}\beta^{\alpha}}{\Gamma(\alpha)} \\ P(\mu|\tau) &= \sqrt{\frac{\lambda\tau}{2\pi}} \exp\left(-\frac{\lambda\tau}{2}(\mu-\epsilon)^2\right) \end{aligned}$$

- $P(\tau)$ is gamma (shape α, rate β)
- $P(\mu|\tau)$ is Normal (mean ϵ, precision $\lambda\tau$)
- Full set of hyperparameters is $\{\alpha, \beta, \epsilon, \lambda\}$

Normal-gamma distribution

- Conjugacy:

$$P(\mathbf{x}) = (2\pi)^{-m_0/2} \frac{\Gamma(\alpha')}{\Gamma(\alpha)} \frac{\beta^\alpha}{\beta'^{\alpha'}} \sqrt{\frac{\lambda}{\lambda'}}$$

$$P(\mu,\tau|\mathbf{x}) = \frac{e^{-\beta'\tau}\tau^{\alpha'-1}\beta'^{\alpha'}}{\Gamma(\alpha')} \times \sqrt{\frac{\lambda'\tau}{2\pi}} \exp\left(-\frac{\lambda'\tau}{2}(\mu-\epsilon')^2\right)$$

where $\epsilon' = \frac{\lambda\epsilon+m_1}{\lambda+m_0}$, $\lambda' = \lambda + m_0$, $\alpha' = \alpha + \frac{m_0}{2}$ and $\beta' = \beta + \frac{1}{2}\left(\epsilon^2 + m_2 - \frac{(\lambda\epsilon+m_1)^2}{\lambda+m_0}\right)$.

- NB if we regard τ as fixed, then Gaussian is auto-conjugate.

χ^2 distribution

$$P(\mu, \tau | \mathbf{x}) = \frac{e^{-\beta'\tau} \tau^{\alpha'-1} \beta'^{\alpha'}}{\Gamma(\alpha')} \times \sqrt{\frac{\lambda'\tau}{2\pi}} \exp\left(-\frac{\lambda'\tau}{2}(\mu - \epsilon')^2\right)$$

- Rescale the posterior distribution for τ: divide by $(m_2/m_0 - m_1^2/m_0)^{-1}$ (the posterior mean estimate for τ)
- Resulting gamma distribution with shape $m_0/2$ and scale $1/2$ is the "χ^2 distribution".
- Canonical definition of the quantity χ^2 is in the special case where $\mu = 0$ and $\tau = 1$, in which case $\chi^2 = m_2$

Outline

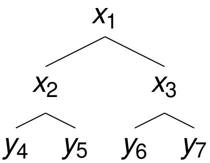
1. Conjugate prior distributions
   - Gamma distribution
   - Dirichlet distribution
   - Normal-gamma distribution
   - Summary
2. MCMC in theory
   - Motivation
   - Metropolis-Hastings
   - Gibbs sampling
   - Jacobians
   - MCMC on continuous parameters
3. MCMC in bioinformatics
   - Alignments
   - Trees
   - Structures

Common conjugacies

- Exponential/Poisson $\leftrightarrow$ Gamma
- Binomial $\leftrightarrow$ Beta
- Multinomial $\leftrightarrow$ Dirichlet
- Normal $\leftrightarrow$ Normal-gamma

Outline

Motivation



$$P(X|Y) = \frac{P(X,Y)}{P(Y)} = \frac{P(X,Y)}{\sum_{X'} P(X',Y)}$$

- Let A = alphabet size
- Felsenstein's pruning algorithm for $P(Y)$
  - Time $\mathcal{O}(NA^2)$
  - Memory $\mathcal{O}(NA)$
- Exponentiating an $A \times A$ matrix N times
  - Time $\mathcal{O}(NA^3)$
- OK: bases ($A = 4$), amino acids ($A = 20$), codons ($A = 64$)
  - Painful: Gene Ontology ($A = 33,587$), GO-Slim ($A = 127$)

MCMC: general idea

- Want to sample from some pdf $P(X) = \frac{f(X)}{Z}$ where $X \in \mathcal{X}$
- Problem: set $\mathcal{X}$ is large; computing $Z = \sum_{X \in \mathcal{X}} f(X)$ is hard
- Construct a stochastic process $X_1, X_2, X_3, X_4, \ldots$ such that the equilibrium distribution is $P(X)$
- If the process is ergodic, then $X_t \sim P(X)$ for "large" t
    - How large must t be? The burn-in time or mixing time

MCMC: construction

- Want a Markov process $X_1, X_2, \ldots$ w/equilibrium $P(X)$
- Let $Q(i,j) = P(X_{t+1} = j | X_t = i)$ be the transition matrix
- One way to make $P(X)$ the equilibrium distribution is to force Q to satisfy detailed balance

$$P(i)Q(i,j) = P(j)Q(j,i) \qquad \forall i, j \in \mathcal{X}$$

- If $P(X) = \frac{f(X)}{Z}$ we can drop the Z

$$f(i)Q(i,j) = f(j)Q(j,i)$$

- Note this process is reversible (MCMC doesn't have to be, but usually is)

Outline

Metropolis-Hastings algorithm: the proposal

- One way to construct a Q that satisfies detailed balance

$$f(i)Q(i,j) = f(j)Q(j,i)$$

- Start with a proposal distribution $U(i,j) = P(X_{t+1} = j | X_t = i)$
  - Metropolis/Teller (1953): symmetric proposal, $U(i,j) = U(j,i)$
  - Hastings (1970) generalized to reversible proposal

$$g(i)U(i,j) = g(j)U(j,i)$$

  - Note $g \neq f$: proposal does **not** have to converge on f
- Now we adapt this U to construct Q

Metropolis-Hastings algorithm: accept/reject

- We have a proposal density, U, satisfying (for some g)

$$g(i)U(i,j) = g(j)U(j,i)$$

- Process:
  - Given X_n, propose a move by sampling X' from

$$P(X' = j | X_n = i) = U(i,j)$$

  - Calculate the Hastings ratio

$$h(X, X') = \frac{f(X')}{f(X)} \frac{g(X)}{g(X')} = \frac{f(X')}{f(X)} \frac{U(X', X)}{U(X, X')}$$

  - If $h(X, X') \geq 1$, then accept the move: set $X_{n+1} \leftarrow X'$
  - If $h(X, X') < 1$, then
    - Sample an r.v. α from $U(0,1)$ (uniform distribution)
    - If $\alpha < h(X, X')$, then accept the move
    - If $\alpha \geq h(X, X')$, then reject the move: set $X_{n+1} \leftarrow X_n$

Metropolis-Hastings: proof of detailed balance

$$\begin{aligned} h(i,j) &= \frac{f(j)}{f(i)}\frac{U(j,i)}{U(i,j)} \\ Q(i,j) &= U(i,j) \times \min\left(1, h(i,j)\right) \end{aligned}$$

- Suppose (with no loss of generality) that $h(i,j) \leq 1$

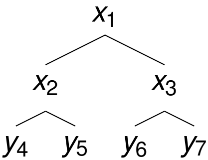
$$\begin{aligned} Q(i,j) &= U(i,j)h(i,j) \\ &= U(i,j)\frac{f(j)}{f(i)}\frac{U(j,i)}{U(i,j)} \\ &= \frac{f(j)}{f(i)}U(j,i) \end{aligned}$$

- Since $h(j,i) \geq 1$, we must have $Q(j,i) = U(j,i)$, and so

$$f(i)Q(i,j) = f(j)Q(j,i)$$

Outline

Gibbs sampling



- The X in $P(X)$ is N-dimensional, $X = (x_1, x_2 \ldots x_N)$
- Gibbs Sampling proposal distribution is as follows
  - Pick a dimension m, where $1 \leq m \leq N$
  - Conceptually, fix all of the $\{x_n\}$ except for x_m; sample x_m from its marginal distribution conditional on all the others
  - Proposal distribution is

$$\begin{aligned} U(X, X') &= U(\{x_n\}, \{x'_n\}) \\ &= P(x'_m | \{x_n : n \neq m\}) \times \prod_{n \neq m} \delta(x'_n = x_m) \end{aligned}$$

- All proposals accepted; Hastings ratio always 1 (prove it!)

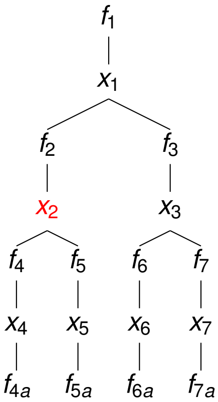
Gibbs sampling: the marginal distribution

Let $X_{\text{other}} = \{x_n : n \neq m\}$

$$
\begin{aligned}
P(x'_m | X_{\text{other}}) &= \frac{P(x'_m, X_{\text{other}})}{P(X_{\text{other}})} \\
&= \frac{P(x'_m, X_{\text{other}})}{\sum_k P(x'_m = k, X_{\text{other}})}
\end{aligned}
$$

If $P(X)$ is a product of functions of sparse subsets of X (c.f. factor graphs), then many of these functions will cancel in numerator and denominator

Gibbs sampling: factor graph example



$$P(x_2'|X_{\text{other}}) = \frac{f_2(x_1, x_2') f_4(x_2', x_4) f_5(x_2', x_5)}{\sum_k f_2(x_1, k) f_4(k, x_4) f_5(k, x_5)}$$

Outline

The Jacobian matrix and its determinant

- Function $F : \Re^n \rightarrow \Re^m$
- Let $(y_1 \ldots y_m) = F(x_1 \ldots x_n)$
- The Jacobian matrix of F is

$$J_F(x_1, \ldots, x_n) = \begin{bmatrix} \frac{\partial y_1}{\partial x_1} & \cdots & \frac{\partial y_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_m}{\partial x_1} & \cdots & \frac{\partial y_m}{\partial x_n} \end{bmatrix}$$

- For square matrices ($m = n$), the magnitude of the Jacobian determinant, $|\det(J_F)|$, gives the factor by which the function F expands or shrinks volumes in $\mathbf{x}$

Multidimensional change of variables

- If $p(x)$ is pdf of x, and $y = F(x)$, what is pdf $q(y)$ of y?
    - Now with multidimensional $x = (x_1 \ldots x_n)$ and $y = (y_1 \ldots y_n)$
- Derivation:

$$
\begin{aligned}
dy_1 dy_2 \ldots dy_n &= \left|\det\left(J_F\right)\right| dx_1 dx_2 \ldots dx_n \\
q(y) dy_1 dy_2 \ldots dy_n &= p(x) dx_1 dx_2 \ldots dx_n \\
q(y) &= p(x) / \left|\det\left(J_F\right)\right| \\
&= p(F^{-1}(y)) \left|\det\left(J_{F^{-1}}\right)\right|
\end{aligned}
$$

where the last line uses the inverse function theorem,

$J_{F^{-1}} = (J_F)^{-1}$ ... c.f. chain rule: $J_{F \circ G}(x) = J_F(G(x)) J_G(x)$

Outline

MCMC on continuous variables

- Let x be a continuous state
- Suppose the proposal generates x' by sampling some parameter u from a p.d.f. $g(u)$, so $x' = x'(x, u)$
  - Let $u' = u'(x, u)$ be the inverse parameter that takes us back from $x' \to x$
  - For convenience, define the function $F(x, u) = (x', u')$
- The Hastings ratio then depends on the Jacobian J_F

$$h(x, x') = \frac{P(x')}{P(x)} \frac{g(u')}{g(u)} \left|\det\left(J_F\right)\right|$$

- Interpretation: we are moving through (x, u)-space rather than just x-space
- Green (1995, 2003)

There's much more

- Summarizing results of an MCMC run
- Diagnosing MCMC convergence
  - Replicates
  - Intra- and inter-chain variance

Not covered in depth here.

Outline

Sampling ungapped sequence alignments

- Example: ungapped sequence alignments (Lawrence *et al*)
  - Suppose you have K sequences, $\{S^{(1)} \ldots S^{(K)}\}$, and that $S_i^{(k)}$ is the i'th residue of the k'th sequence.
  - Let x_k be the indentation of the k'th sequence. The motif (of length M) runs from x_k to $x_k + M - 1$.

Sampling ungapped alignments

- Let $\mathcal{U}$ denote the null hypothesis that the sequences are unrelated. Then

$$\frac{P(\mathbf{x})}{P(\mathcal{U})} = \prod_{m=0}^{M-1} \frac{f(\mathbf{n}(m))}{\prod_{\omega} q(\omega)^{n_{\omega}(m)}}$$

where $q(\omega)$ is a background distribution over alphabet symbols ω, and $n_{\omega}(m)$ is the number of times symbol ω appears in column m of the motif

$$n_{\omega}(m) = \sum_{k=1}^{K} \delta(S_{x_k+m} = \omega)$$

Sampling ungapped alignments

- The $f(\mathbf{n})$ function should reward conserved columns. Lawrence *et al* use an entropy-like measure

$$f(\mathbf{n}) = \prod_{\omega} p_{\omega}^{n_{\omega}} = \exp(-KS[p])$$

where $p_k = n_k/K$. Note that this is the distribution $\mathbf{p}$ that maximizes $\prod_{\omega} p_{\omega}^{n_{\omega}}$ for a given $\mathbf{n}$. Due to this implicit maximization, the above $f(\mathbf{n})$ is not strictly a probability distribution for $\mathbf{n}$.

- Typically a vector of pseudocounts $\mathbf{a}$ is added to $\mathbf{n}$. This suggests the Dirichlet evidence as an alternative form for f that does not involve any implicit maximization:

$$f(\mathbf{n}) = \frac{\mathcal{B}(\mathbf{n}+\mathbf{a})}{\mathcal{B}(\mathbf{a})\mathcal{B}(\mathbf{n})}$$

Sampling ungapped alignments

- Another way to formulate this problem is as a chain over $(\mathbf{x}, \{\mathbf{p}(m)\})$ with Gibbs-sampling steps that alternate between resampling one of the x_k's and resampling all the $\mathbf{p}$'s.
- For good mixing it's also useful to allow moves that slide the entire motif window, i.e. $\mathbf{x} \leftarrow \mathbf{x} \pm \mathbf{1}$

Outline

Sampling trees

- Priors: coalescent
- Moves:
  - Topology: prune-and-graft operations, swapping nodes & branches
  - Branch lengths: rescaling, sliding
- Equivalent ML moves:
  - quartet-puzzling (Strimmer & von Haeseler)
  - pplacer's “pendant branch length” (Matsen)

Extensions

- Co-sampling alignment and tree (and secondary/3D structure, ...)
- Models and approximations that sum out alignment, ancestral sequence, tree

Outline

Molecular dynamics

- Folding
- Docking
- Transport
- Kinetics
- etc.