Using selective pressure to improve protein tridimensional structure prediction

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MIEP

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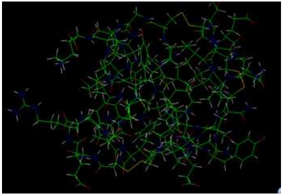
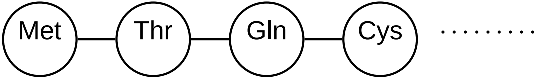
1. Context
2. Markov random fields
3. Parameter posterior distribution
4. Model choice
5. Simulations
6. Conclusion

Aim

Predict the tridimensional structure of the protein



Knowning amino acid sequence



Existing methods

- **Experimental methods :**
  - X-ray cristallography
  - Nuclear magnetic resonance spectroscopy
  - Cryomicroscopy

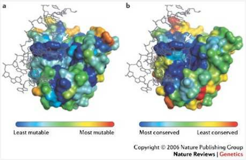
↬ Expensive and slow, but provide the exact 3D structure

- **Computational methods :**
  - Based on homologies with proteins of known structure : methods based on sequence similarity, protein threading
  - *De novo* prediction

↬ Gives several possible 3D structures, with no criterion of choice

Purpose : build a ranking method based on a phylogenetic stability criterion

- In a 3D structure, amino acids in contact frequently have similar modification tolerances



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- **Criterion :** selective pressure sequence

Data

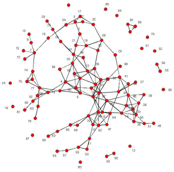
- **First step :** Estimate the selective pressure sequence $\omega_1, \ldots \omega_n$ on a multiple aligment of homologs

Seq :	caa	agg	tgc	tta
H1 :	cat	agg	tgc	gta
H2 :	cat	tgg	tgc	cta
H3 :	aat	tgg	tgc	ctg

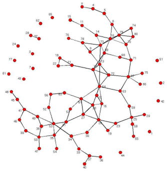
$$\downarrow$$

$$\omega_1 \quad \omega_2 \quad \omega_3 \quad \omega_4$$

- *m* folding candidates



or



Statistical tools

- Markov random fields
- ABC (Approximate Bayesian Computation)
- Bayesian model choice

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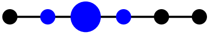
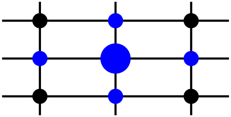
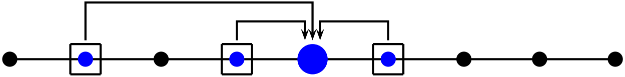
Definition

- Markov chain :



- Markov random field : Markov chain generalisation





Definition (2)

- State at a point i only depends on the state of its neighbours $n(i)$:

$$\pi(x_i = j | x_{-i}) = \pi(x_i = j | z_{n(i)})$$

- Hammersley-Clifford theorem :

$$P(X = x) = \frac{1}{Z} exp(-U(x))$$

with

- $U(x)$: potential

$$U(x) = \sum_{c \in C} V_c(x)$$

$$U(x) = -\theta \sum_{(i,j):i \overset{S}{\sim} j} \mathbf{1}_{\{x_i = x_j\}}$$

- Z : normalizing constant

$$Z = \sum_{x} exp(-U(x))$$

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Bayesian modelisation

- Prior distribution :
  - $(\theta) \sim \pi(\theta)$
- Likelihood :

$(X|\theta) \sim MRF(\theta)$

$$f(x|\theta) = \frac{1}{Z_\theta} exp(\theta \sum_{(i,j):i\sim j} \mathbf{1}_{\{x_i=x_j\}})$$

↬ **Target :** Posterior distribution of θ

Parameter posterior distribution

MCMC methods :

Hastings-Metropolis algorithm :

- Proposal : $\theta' \sim p(\theta'|\theta^{(t)})$
- $\theta^{(t+1)} = \theta'$ with probability

$$min\{1, \frac{\frac{1}{Z_{\theta'}} q_{\theta'}(X)}{\frac{1}{Z_{\theta^{(t)}}} q_{\theta^{(t)}}(X)} \frac{p(\theta^{(t)}|\theta')}{p(\theta'|\theta^{(t)})} \frac{\pi(\theta')}{\pi(\theta^{(t)})}\}$$

$\looparrowright$ Ratio involves intractable normalizing constants $Z_{\theta'}$ and $Z_{\theta^{(t)}}$

ABC : Approximate Bayesian Computation

- Bayesian inference without using likelihood
- **Idea :** Data sufficiently close provide similar parameter posterior distribution
- What we need :
    - **Simulate** data given parameter values
    - **Summary statistics** (sufficient)
    - Calculate closeness between our data (X^0) and simulated data (X^{i^*}) : **distance** between summary statistics

ABC Algorithm

- **Sufficient statistic :** $S(X) = \sum_{(i,j):i\sim j} \mathbf{1}_{\{x_i = x_j\}}$
- **Distance :** $d(S(X^0), S(X^{i*})) = (S(X^0) - S(X^{i*}))^2$
- **Algorithm :**
  - Generate $\theta^{i*} \sim \pi(\theta^{i*})$
  - Generate $(X|\theta^{i*}) \sim MRF(\theta^{i*})$
  - Calculate $d_i = d(S(X^0), S(X^{i*}))$
  - Accept θ^{i*} if $d_i < \varepsilon$
- **Result :** sample of independent draws from $f(\theta|d < \varepsilon)$
  $\looparrowright$ Good approximation of $f(\theta|X^0)$
- In practice, ε is a 1% quantile of d

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Bayesian hierarchical modelisation

1 model $\longleftrightarrow$ 1 neighborhood / 3D structure

- Prior distributions :
  - $s \sim \pi(s)$
  - $(\theta_s | s) \sim \pi_s(\theta_s)$
- Likelihood :

  $(X | \theta_s, s) \sim MRF(\theta_s, s)$

$$f_s(x|\theta_s) = \frac{1}{Z_{\theta_s,s}} exp(\theta_s \sum_{(i,j):i \overset{s}{\sim} j} \mathbf{1}_{\{x_i = x_j\}})$$

Bayes factor definition

-

$$BF_{0/1} = \frac{\frac{P(s=0|X)}{P(s=1|X)}}{\frac{P(s=0)}{P(s=1)}} = \frac{\int f_0(X|\theta_0)\pi_0(\theta_0)d\theta_0}{\int f_1(X|\theta_1)\pi_1(\theta_1)d\theta_1}$$

- **Interpretation :**
  - $BF > 1$: Model 0
  - $BF < 1$: Model 1
  - Jeffreys scale :

$< 10^{-2}$ $> 10^{2}$	$[10^{-2}, 10^{-3/2}]$ $[10^{3/2}, 10^{2}]$	$[10^{-3/2}, 10^{-1}]$ $[10^{1}, 10^{3/2}]$	$[10^{-1}, 10^{-1/2}]$ $[10^{1/2}, 10^{1}]$
decisive	very hard	hard	substantial

Another way to write the Bayes factor

$$
\begin{aligned}
P(S_i(X) = s|\theta_i) &= \sum_{X : S_i(X) = s} f_i(X|\theta_i) \\
&= \frac{1}{Z_{\theta_i, i}} exp(\theta_i \; s) \; card\{X : S_i(X) = s\}
\end{aligned}
$$

$$
BF_{0/1} = \frac{card\{X : S_1(X) = s_1\}}{card\{X : S_0(X) = s_0\}} \frac{\int P(S_0(X) = s_0|\theta_0)\pi_0(\theta_0)d\theta_0}{\int P(S_1(X) = s_1|\theta_1)\pi_1(\theta_1)d\theta_1}
$$

ABC algorithm

- **Vector of summary statistics :** $S(X) = S_1(X), ..S_m(X)$ avec $S_s(X) = \sum_{(i,j):i\overset{s}{\sim}j} \mathbf{1}_{\{x_i=x_j\}}$
- **Distance :** $d(S(X^0), S(X^{i*})) = \sum_s (S_s(X^0) - S_s(X^{i*}))^2$
- **Algorithm :**
  - Generate $s^{i*} \sim \pi(s)$
  - Generate $(\theta_{s^{i*}} | s^{i*}) \sim \pi_{s^{i*}}(\theta^*_{s^{i*}})$
  - Generate $(X | \theta^*_{s^{i*},i*}) \sim MRF(\theta^*_{s^{i*},i*})$
  - Calculate $d_i = d(S(X^0), S(X^{i*}))$
  - Accept $(s_{i*}, \theta^*_{s_{i*}})$ if $d_i < \varepsilon$

- Result : $((s_{i*}, \theta^*_{s_{i*}})_i)$

$$\looparrowright \frac{card(s_{i*} = 0)}{card(s_{i*} = 1)} \text{ estimate of } \frac{\int P(S_0(X) = s_0|\theta_0)\pi_0(\theta_0)d\theta_0}{\int P(S_1(X) = s_1|\theta_1)\pi_1(\theta_1)d\theta_1}$$

- Calculate $\dfrac{card\{X : S_1(X) = s_1\}}{card\{X : S_0(X) = s_0\}}$ to obtain $\widehat{BF}$

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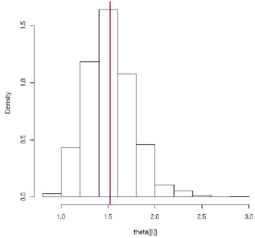
Models

- **M0 : iid case,** $Bernouilli(p)$
  - $f_0(X|\theta, m=0) = \frac{1}{Z_{\theta,0}} exp(\theta \sum_i \mathbf{1}_{\{x_i=1\}})$
  - $p = \frac{exp(\theta)}{1+exp(\theta)}$
- **M1 : Markov chain with transition matrix** P
  - $f(X|\theta,1) = \frac{exp(2\theta \; \sum_{i=1}^{n-1} \mathbf{1}_{\{x_i=x_{i+1}\}})}{2(1+exp(2\theta))^{n-1}}$
  - $P = \begin{pmatrix} \frac{exp(2\theta)}{1+exp(2\theta)} & \frac{1}{1+exp(2\theta)} \\ \frac{1}{1+exp(2\theta)} & \frac{exp(2\theta)}{1+exp(2\theta)} \end{pmatrix}$

Parameter estimation

- 

- Comparison ML/ABC estimates : $|\widehat{\theta}_{abc} - \widehat{\theta}_{mv}|$

$1stQu.$	$Median$	$Mean$	$3rdQu.$	Var
$1.68e-03$	$3.28e-03$	$3.27e-03$	$5.001e-03$	$3.89e-06$

Model choice

- $$\widehat{BF} = \frac{C_{n-1}^{s_1}}{C_n^{s_0}} \frac{card(s_{i*}=0)}{card(s_{i*}=1)}$$
- $$BF = \frac{\int \frac{exp(\theta_0 S_0(X))}{(1+exp(\theta_0))^n}\pi_0(\theta_0)d\theta_0}{\int \frac{exp(2\theta_1 S_1(X))}{(1+exp(2\theta_1))^{n-1}}\pi_1(\theta_1)d\theta_1}$$
- Comparison on 10.000 simulated data :

		BF		
		$M0$	?	$M1$
$\widehat{BF}$	$M0$	4684	2	30
	?	158	339	53
	$M1$	5	261	4464

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Conclusion

- **Conclusion**
  - Parameter estimation in MRF is not too expensive using ABC
  - BF is a good way to choose between some neighborhoods
- **Perspectives :**
  - Estimate / calculate the number of configurations given a value of S
  - Apply on biological data

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