

# Asking & Answering Questions with Bayesian Phylogenetics

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National  
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CENTRE FOR BIODIVERSITY ANALYSIS

- Model averaging
- Model selection
- Model comparison

# What does a model look like

Model = tree prior + site model + clock model + *priors* + *hyper priors*

startpage

phylogenetic models

go

≡

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**Classification models**

- Cladistics – sprout or branch
- Studies traits to understand phylogeny
- Cladogram – model of the phylogeny of a species based on shared traits

**Phylogeny**

Ch. 7 & 8

17.2 The Six Kingdoms

EK 1B2

DNA, Proteins and Cell Wall Components

Parts of a phylogenetic tree

Modern Phylogenetic Comparative Methods and Their Application in Evolutionary Biology

The Six Kingdoms of Organisms

Overview

- Evolution and sequence variation
- Phylogenetic trees
- The meaning of distance
- Constructing phylogenetic trees
- Constructing trees
- Sequence alignment

Difference between Phylogenetic Trees and Cladistics

- Phylogenetic tree
- Cladogram

Evolution and Sequence Variation

Generating new models for detecting phylogenetic signals of antibiotic and dispersal effects of

# What does a model look like

Model Comparison: Which one is better?

Model Selection: Which one to pick?

Model Averaging: What if you don't want to choose?

Model = tree prior + site model + clock model + *priors* + *hyper priors*

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# Model averaging

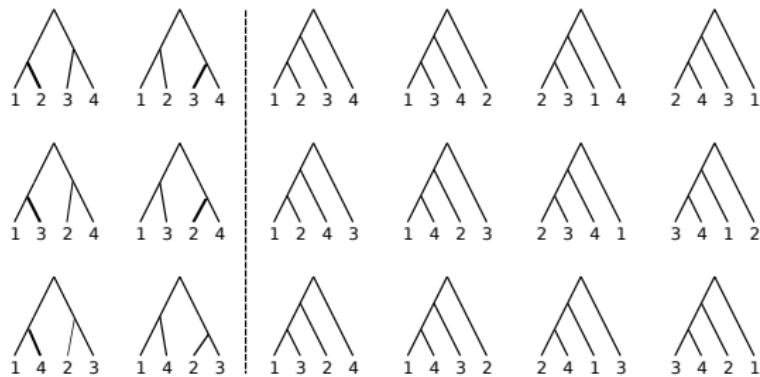
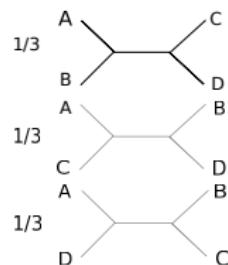
- Posterior:

$$p(\theta|D) = \sum_k \overbrace{P(M_k)}^{\text{model prior}} \underbrace{\pi(\theta|M_k)L(D|M_k, \theta)}_{\text{posterior}}$$

- Models can be substitution models, clock models, tree topologies, etc.
- Accounts for model uncertainty
- Requires specifying another prior  $P(M_k)$

# Model averaging

Already been doing that this all week: each tree topology is a model



18 ranked rooted trees –  $1/3$  probability of being balanced

## Model averaging: stochastic variable selection

Use indicator variable to select model

- Example: ancestral state reconstruction using mask matrix  $I$  and rate matrix  $R$

$$I = \begin{pmatrix} - & i_{12} & i_{13} & i_{14} \\ i_{21} & - & i_{23} & i_{24} \\ i_{31} & i_{32} & - & i_{34} \\ i_{41} & i_{42} & i_{43} & - \end{pmatrix} \quad R = \begin{pmatrix} - & r_{12} & r_{13} & r_{14} \\ r_{21} & - & r_{23} & r_{24} \\ r_{31} & r_{32} & - & r_{34} \\ r_{41} & r_{42} & r_{43} & - \end{pmatrix}$$

- Use  $r_{ij}$  if  $i_{ij}$  is true, but use rate 0 if  $i_{ij}$  is false
- Sample  $I$  and all rates in  $R$  throughout MCMC run.
- Use strong prior on number of  $i_{ij} = \text{true}$  to reduce number of non-zero rates

Lemey et al, PLoS Comput Biol, 2009

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Stochastic variable selection:

- Simple to implement
- Potentially inefficient in sampling unused parameters

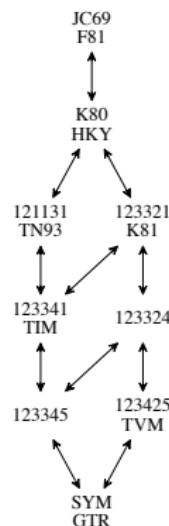
# Model averaging: reversible jump

The probability of acceptance of a (possibly trans-dimensional) proposal is

$$\min\{1, \text{posterior ratio} \times \text{proposal ratio} \times \text{Jacobian}\}$$

- **posterior ratio** is the posterior of the proposed state  $S'$  divided by that of the current state  $S$ ,
- **proposal ratio** the probability of moving from  $S$  to  $S'$  divided by the probability of moving back from  $S'$  to  $S$
- **Jacobian** is the determinant of the matrix of partial derivatives of the parameters in the proposed state with respect to that of the current state

Green, Biometrika, 1995



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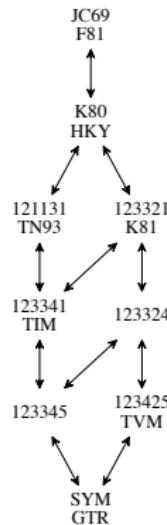
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Reversible jump:

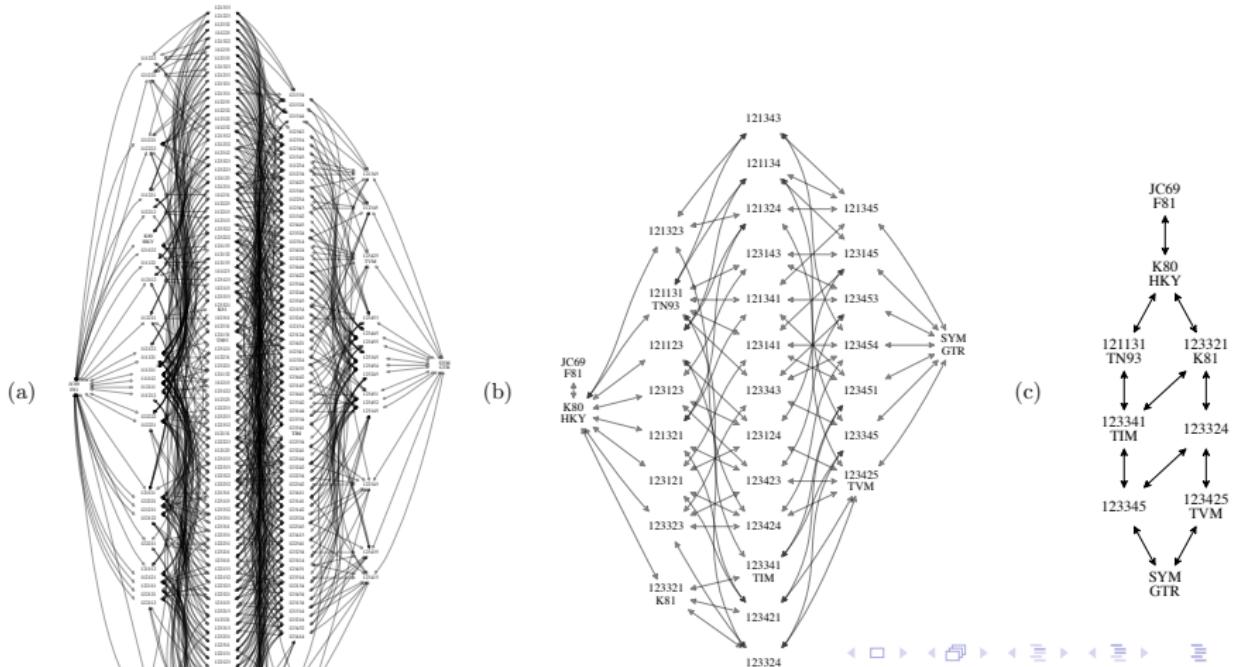
- Hard to implement correctly
- Efficient sampling



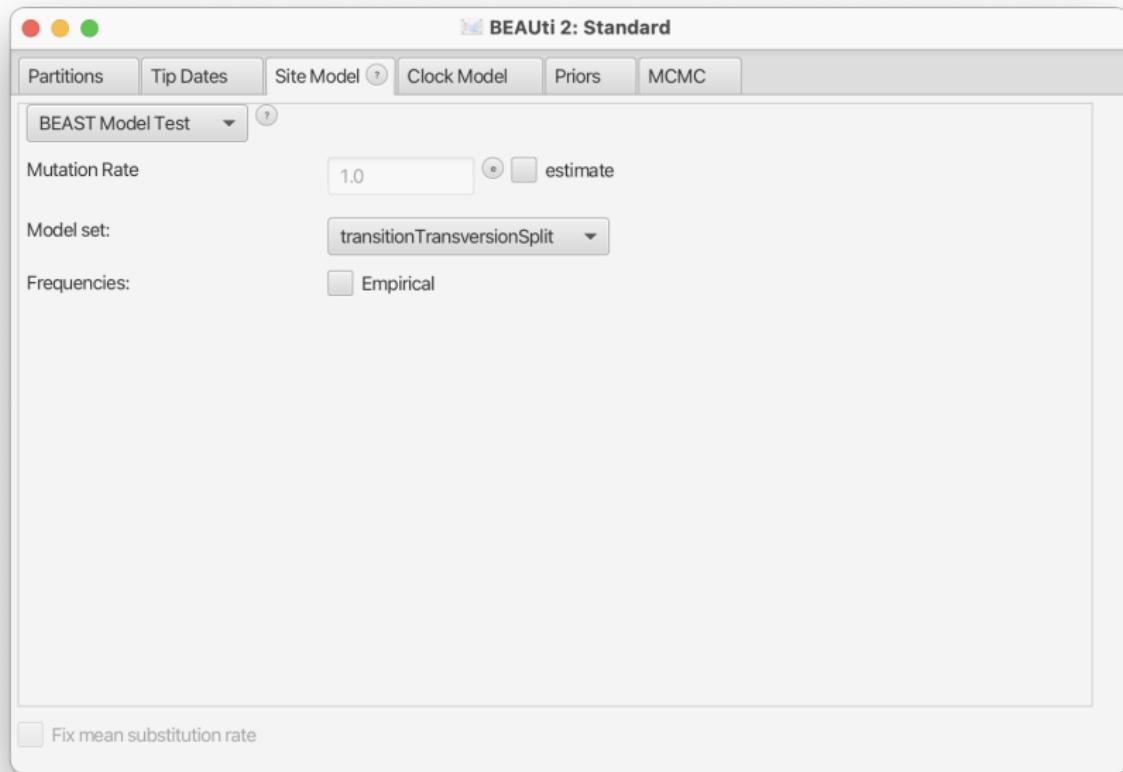
## Model averaging: bModelTest

Bouckaert & Drummond, BMC Evo Bio, 6 Feb 2017

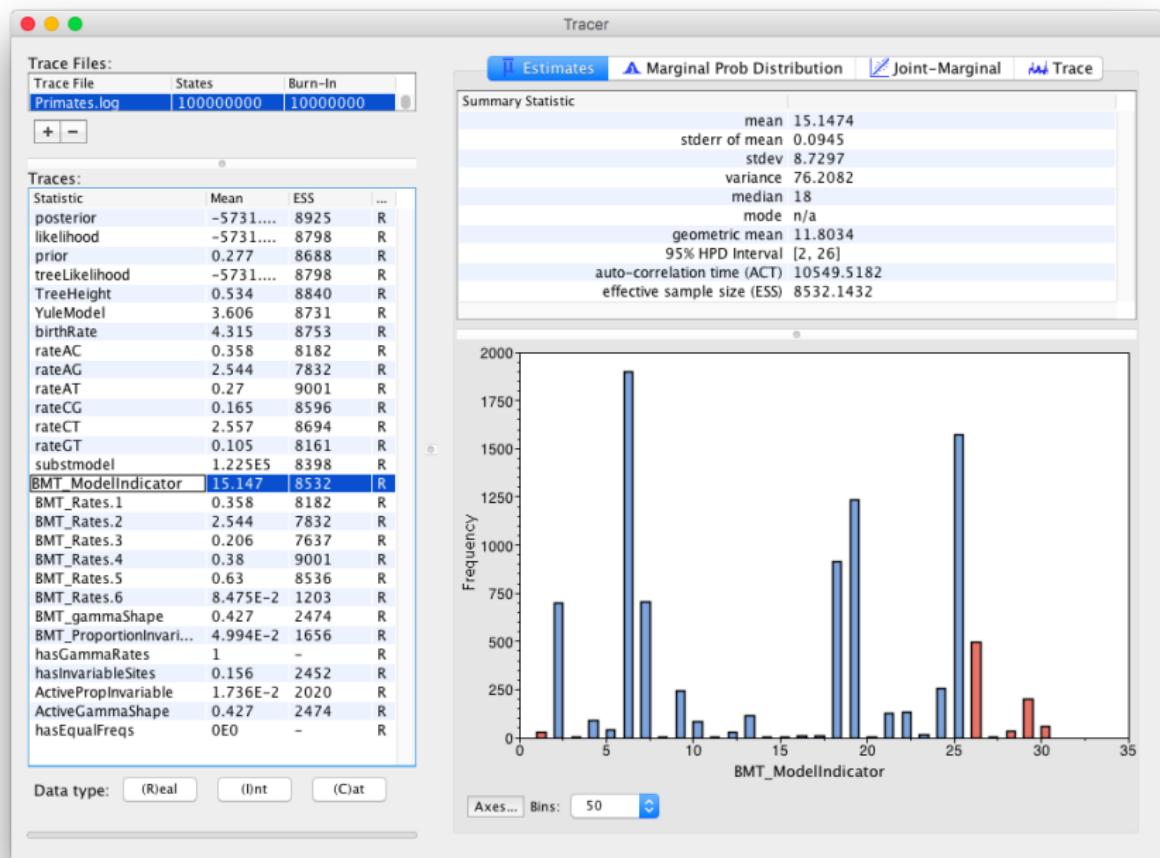
- Averages over substitution models
  - Estimated/fixed frequencies
  - With/without gamma rate heterogeneity
  - With/without gamma proportion invariable sites



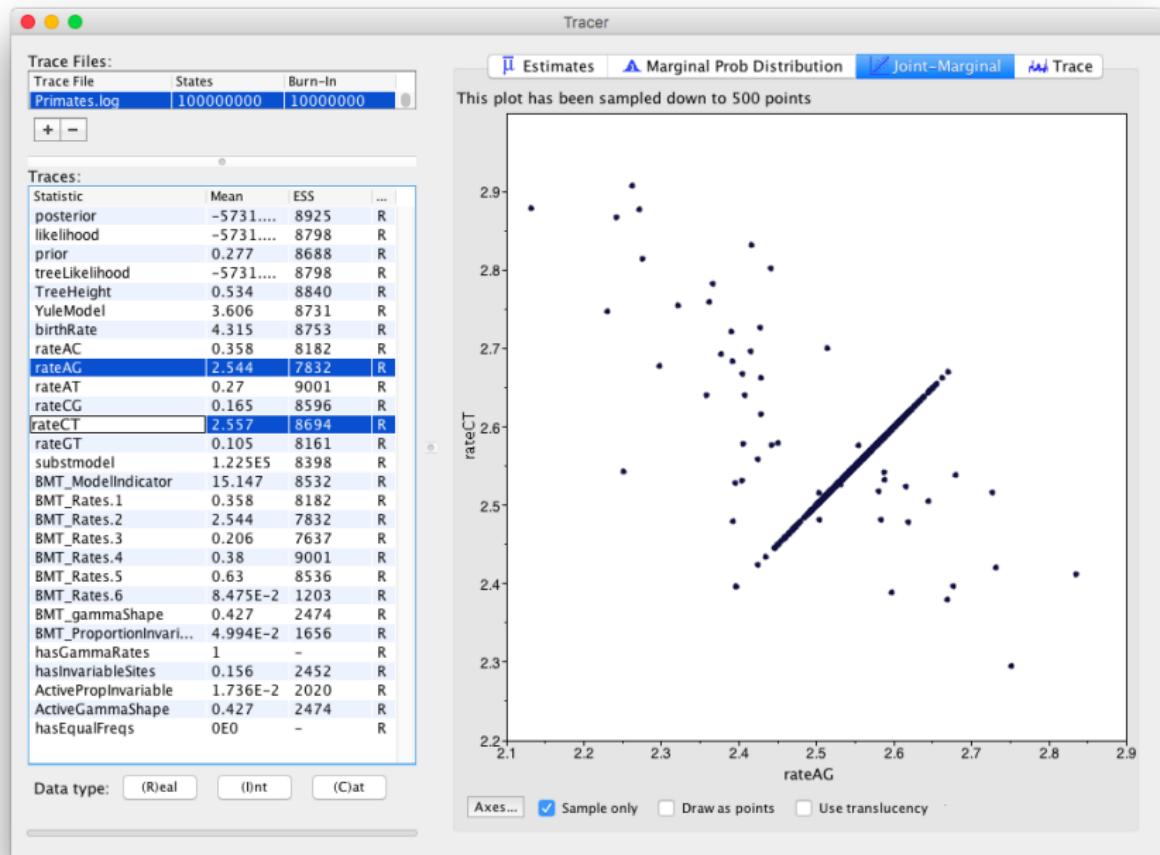
# Model averaging: install bModelTest package



# Model averaging: bModelTest



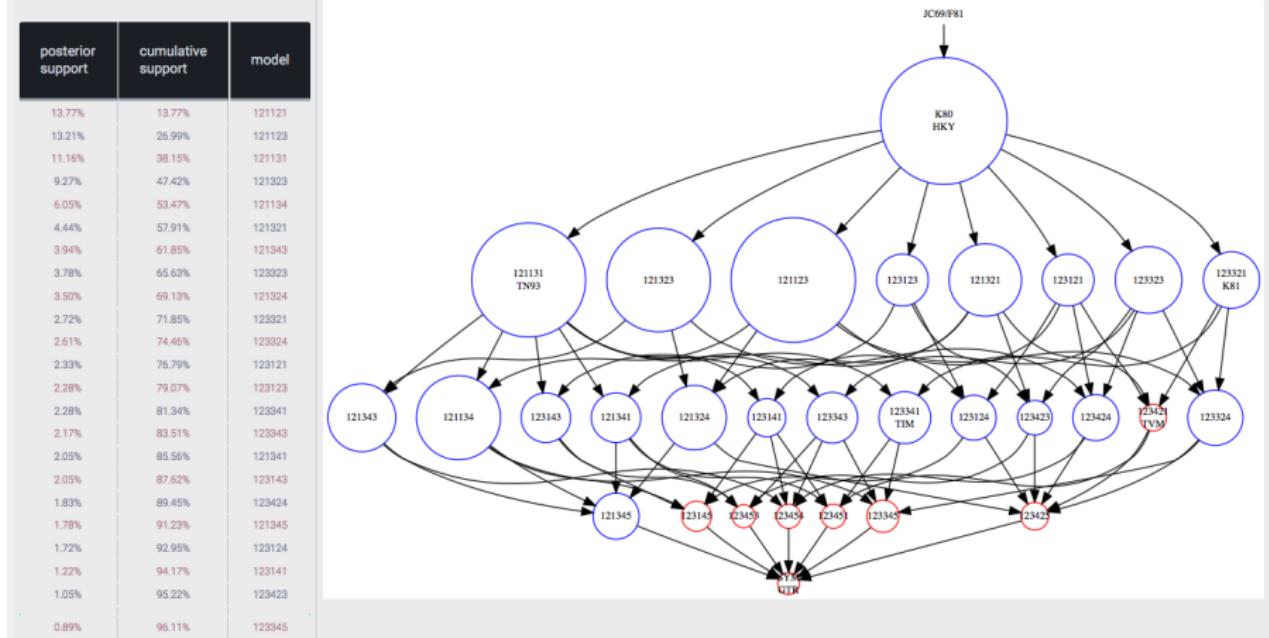
# Model averaging: bModelTest



# Model averaging: bModelTest BModelAnalyser app

File: Primates.log item: substmodel

Models with blue circles are inside 95%HPD, red outside, and without circles have 0.00% support.

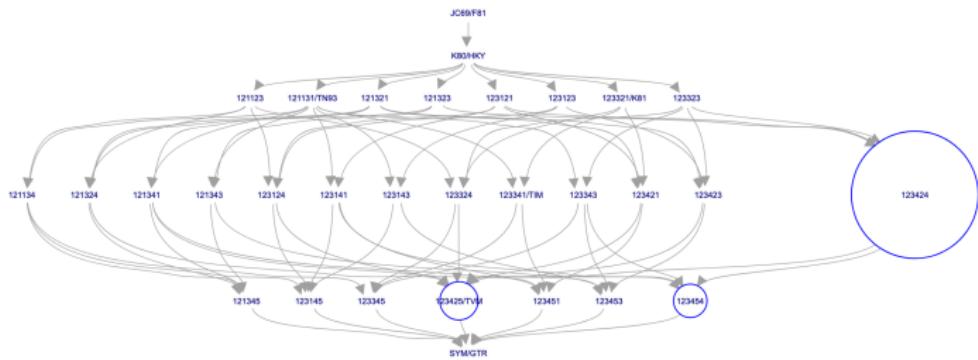


# Model averaging: bModelTest BModelAnalyser app

File: hbvz-bmt-cexp.log item: substmodel

Models with blue circles are inside 95%HPD, red outside, and without circles have at most 0.34% support.

posterior support	cumulative support	model
85.91%	85.91%	123424
7.79%	93.70%	123425
5.96%	99.66%	123454
0.34%	100.00%	123456



## Model averaging: bModelTest model priors

Posterior:

$$p(\theta|D) = \sum_k P(M_k) \pi(\theta|M_k) L(D|M_k, \theta)$$

$P(M_k)$  model prior:

- uniform over substitution models in model set
  - ▶ For 31 model set:  $P(JC) = P(HKY) = P(TN) = P(GTR) = \frac{1}{31}$
- uniform over number of parameters in substitution models
  - ▶ For 31 model set:  $P(JC) = P(HKY) = P(GTR) = \frac{1}{6}$  but  
 $P(TN) = \frac{1}{6} \cdot \frac{1}{8} = \frac{1}{48}$

# Model selection

When to do model selection:

- answers of interest are not robust for different models
- to test hypotheses (encoded by prior)
- not because the reviewers demand it

Evade it if you can

# Model selection

Measures of fit:

- Super naive: compare posteriors
  - ▶ priors are not normalised, so posteriors cannot be compared
  - ▶ **Never do this!**

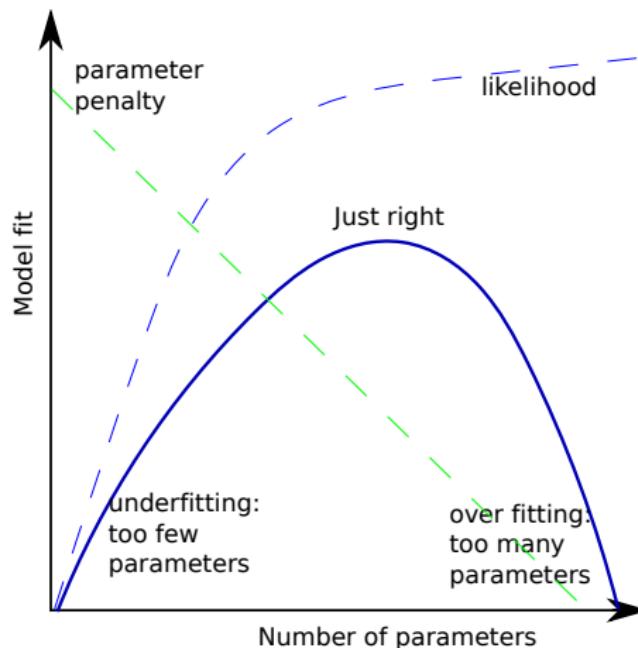
# Model selection

Measures of fit:

- Super naive: compare posteriors
  - ▶ priors are not normalised, so posteriors cannot be compared
  - ▶ **Never do this!**
- Super naive: compare likelihoods
  - ▶ overparameterisation/overfitting cannot be detected
  - ▶ **Never do this!**

# Model selection: select model with best "fit"

Desirable model fit property 1: likelihood - parameter penalty



Desirable model fit property 2: replicability/low variance

Desirable model fit property 3: easy & cheap to calculate

(this list is not exhaustive)

# Bayesian model selection: marginal likelihood

Posterior:

$$p(\theta|D, M) = \frac{\overbrace{\pi(\theta|M)}^{\text{prior}} \overbrace{L(D|M, \theta)}^{\text{likelihood}}}{\underbrace{p(D|M)}_{\text{marginal likelihood}}}$$

Marginal likelihood:

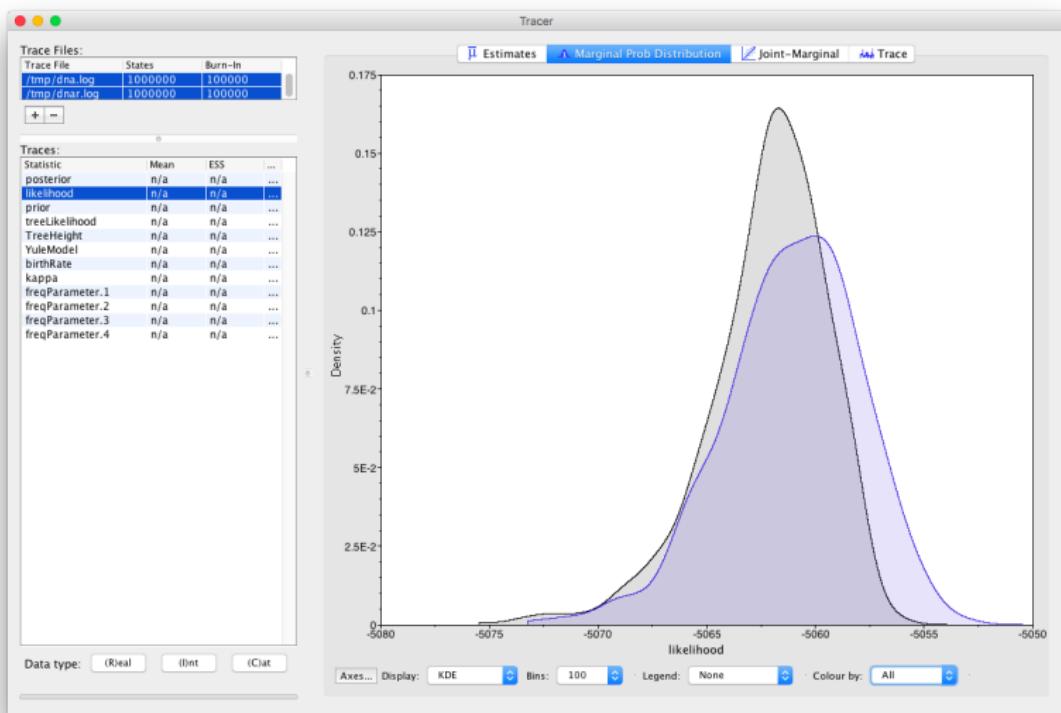
$$p(D|M) = \int_{\theta \in \Theta} \pi(\theta|M) L(D|M, \theta) d\theta$$

integrate/marginalise out  $\theta$

Bayes factor:

$$\frac{p(D|M_1)}{p(D|M_2)}$$

# Model selection: “marginal likelihood” in Tracer



This is the likelihood averaged over samples from the posterior, not prior.

## Model selection: marginal likelihood

Naive: Harmonic mean estimator (HME) of marginal likelihood

$$HME = \left( \frac{1}{n} \sum_{i=1}^n \frac{1}{L(D|\theta_i)} \right)^{-1}$$

where  $\theta_1, \dots, \theta_n$  a sample from the posterior

- Only requires a sample from the posterior
- Conveniently & quickly calculated in Tracer
- High variance estimator  $\Rightarrow$  unreliable

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- A post on Dr. Radford Neal's blog <http://radfordneal.wordpress.com/2008/08/17/the-harmonic-mean-of-the-likelihood-worst-monte-carlo-method-ever>

“The total unsuitability of the harmonic mean estimator should have been apparent within an hour of its discovery.”

- **Never do this!**

## Path sampling/Stepping stone theory

- Marginal likelihood:

$$p(D) = \int_{\theta} \pi(\theta) L(D|\theta) d\theta$$

hard to estimate directly.

- Define *power posterior* for some tractable reference distribution  $p_w(\theta)$

$$P_{\beta}(\theta|D) = \frac{[L(D|\theta)\pi(\theta)]^{\beta} p_w(\theta)^{1-\beta}}{c_{\beta}}$$

$P_1(\theta|D)$  is the posterior,  $c_1$  the marginal likelihood.

$P_0(\theta|D)$  is the reference distribution,  $c_0 = 1$

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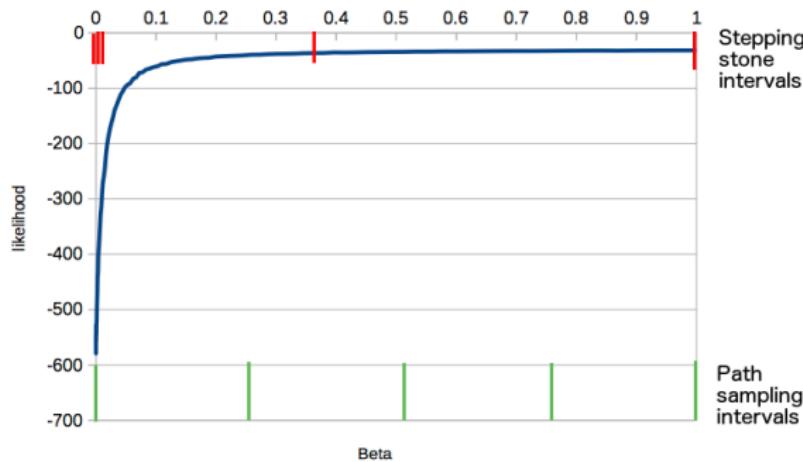
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- $$\frac{c_{\beta_k}}{c_{\beta_{k-1}}} \approx \frac{1}{n} \sum_{i=1}^n p(D|\theta_{k-1,i})^{\beta_k - \beta_{k-1}}$$

- $$P(D|M) = \frac{c_1}{c_0} = \frac{c_1}{c_{0.3}} \frac{c_{0.3}}{c_{0.1}} \frac{c_{0.1}}{c_{0.01}} \frac{c_{0.01}}{c_0} = \frac{c_1}{\cancel{c_{0.3}}} \frac{\cancel{c_{0.3}}}{\cancel{c_{0.1}}} \frac{\cancel{c_{0.1}}}{\cancel{c_{0.01}}} \frac{\cancel{c_{0.01}}}{c_0}$$

## Model selection: *Stepping stone vs path sampling*

Both use prior as reference distribution ( $p_w(\theta) = \pi(\theta)$ )



Stepping stone uses different intervals (set of  $\beta$  values) from path sampling, but otherwise the same

# Generalised Stepping Stone

Use 'working distribution' for  $p_w(\theta)$  based on posterior sample

- For parameters, use empirical distribution based on kernel estimators
- For trees, we need a distribution on topology and branch lengths
- Promises lower variance estimates
- Currently tedious to set up, since working distribution needs to be specified

Holder et al, Bayesian phylogenetics, 2014, Beale et al, Sys Bio, 2016

# Pairwise Stepping Stone

Use posterior of  $M_2$  for  $p_w(\theta)$ .

- Calculates Bayes factor between  $M_1$  and  $M_2$  directly
- + requires fewer steps for accurate estimate
- - does not result in marginal likelihoods directly

Baele et al, BMC Bioinformatics, 2013

# Path sampling/Stepping stone in practice

Number of steps:

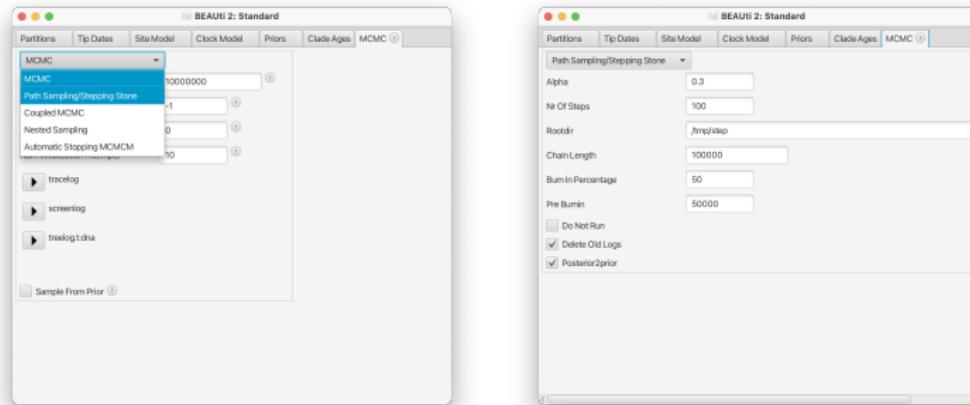
- Start with small nr of steps, say 16 and estimate ML
- increase nr of steps, estimate ML
- continue till ML estimate does not decrease any more

Chain length per step/ESS:

- total chain length at least as long as for posterior
- not all ESSs have to be 200 (errors cancel out)
- run different runs to get impression of variance of estimate
- use logcombiner to combine logs, for final estimate

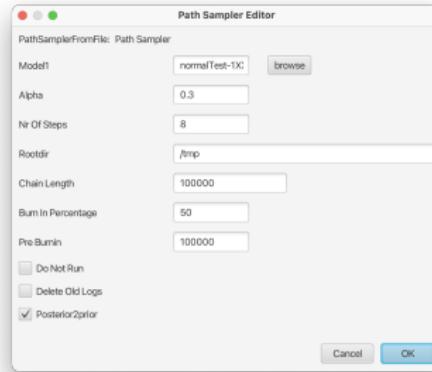
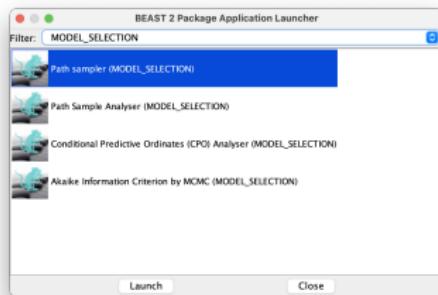
# Path sampling/Stepping stone in practice

Requires MODEL\_SELECTION package



# Path sampling/Stepping stone in practice

Set up through XML or GUI



Set up through CLI:

- to list BEAST apps:

```
/path/to/appauncher -list
```

- To show PathSampler options:

```
/path/to/appauncher PathSampler -help
```

- To set up PathSampler analysis:

```
/path/to/appauncher PathSampler -nrOfSteps 64 -rootdir  
dir/withs/steps -burnInPercentage 50 -model beast.xml
```

# Path sampling/Stepping stone in practice

To set up on a HPC cluster

- Set up locally, using 'doNotRun' flag = true
- Move steps to cluster, and run steps in parallel there
- Estimate ML using PathSampleAnalyser

```
/path/to/appauncher PathSampleAnalyser -nrOfSteps 64  
-rootdir dir/withs/steps -burnInPercentage 50
```

# Path sampling/Stepping stone in practice

## Trouble shooting

- ESS too small for a step: resume runs for that step
- Infinite likelihoods caused by numeric instability: improper priors – use proper priors instead
- -Infinite likelihoods: priors too wide – narrow priors
- Inspect log files in step directory to see which parameter escapes, so which prior to adjust

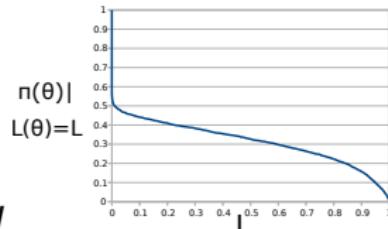
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$$= \int_{L=0}^{\infty} L \left( \int_{\theta, L(\theta)=L} \pi(\theta) d\theta \right) dL$$

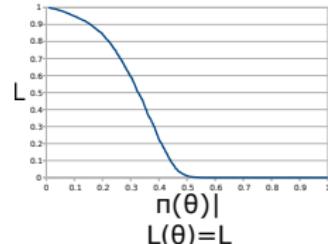
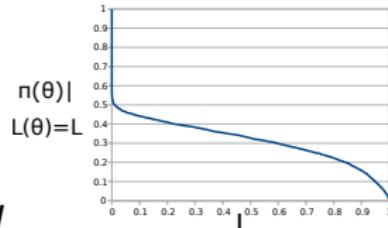


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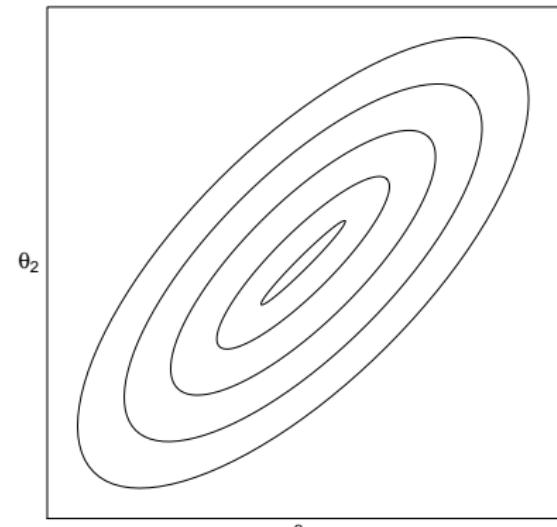
$$= \int_{L=0}^{\infty} L \left( \int_{\theta, L(\theta)=L} \pi(\theta) d\theta \right) dL$$

$$= \int_{X=0}^1 \mathcal{L}(X) dX$$

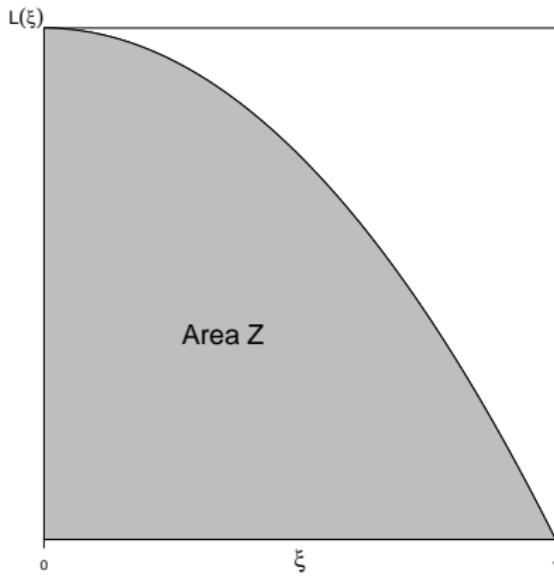


where  $\mathcal{L}(X)$  inverse likelihood

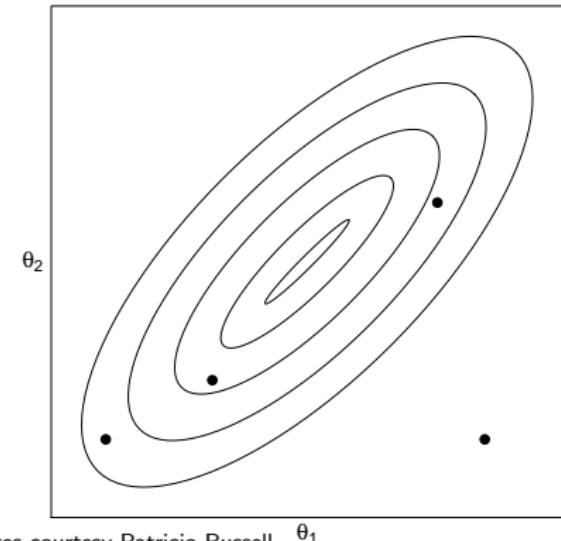
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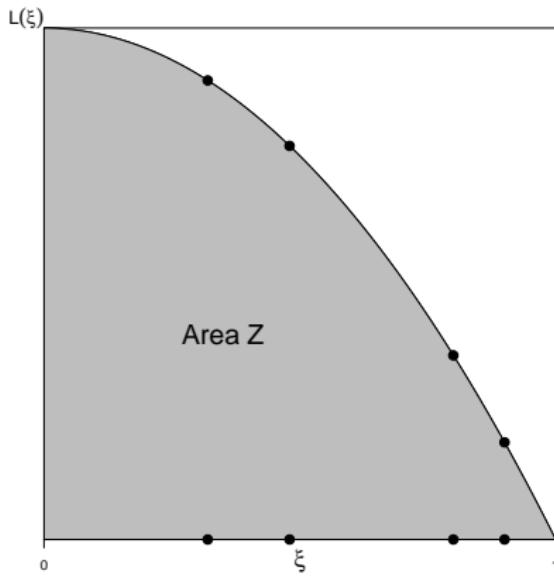
images courtesy Patricio Russell



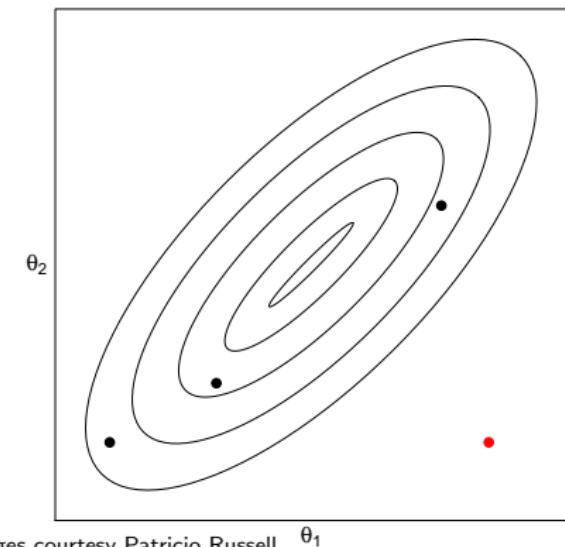
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images courtesy Patricio Russell

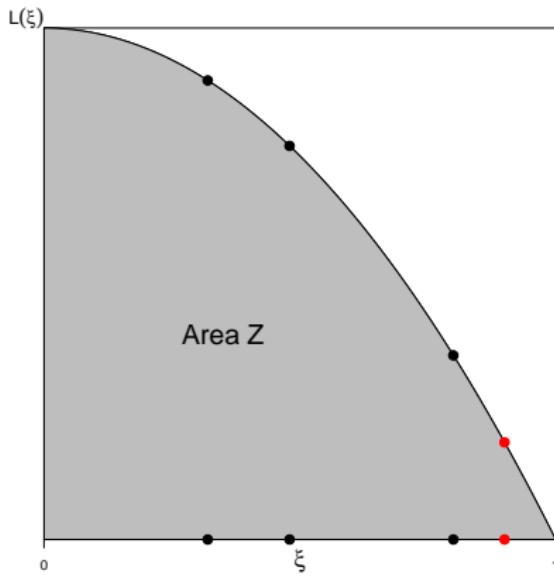


# Nested sampling



images courtesy Patricio Russell

$\theta_1$

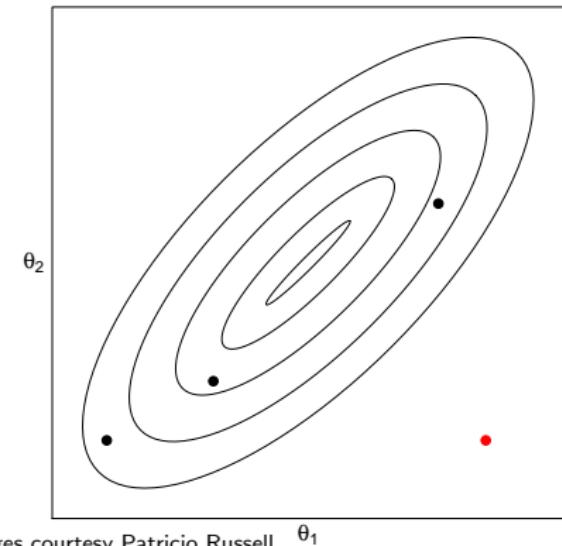


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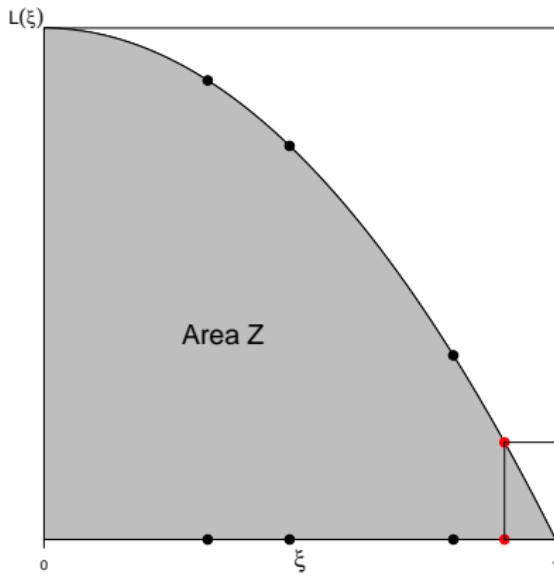
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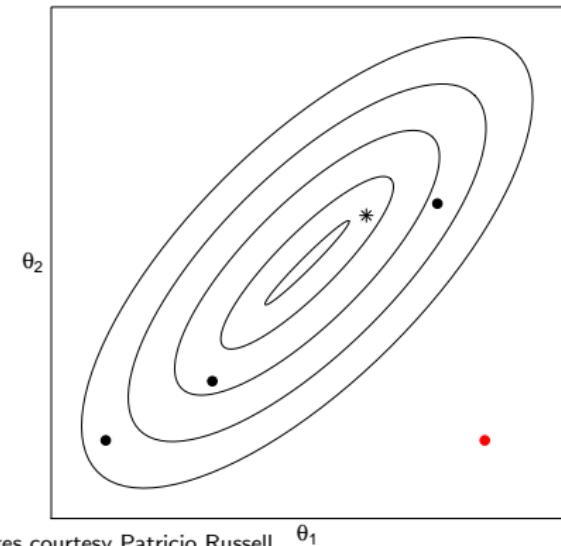
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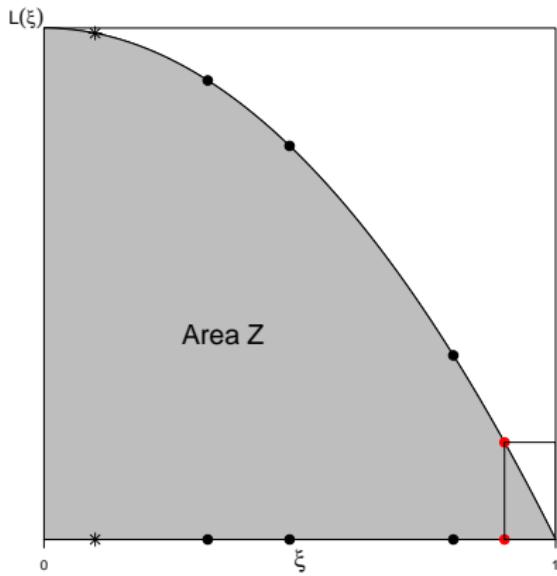
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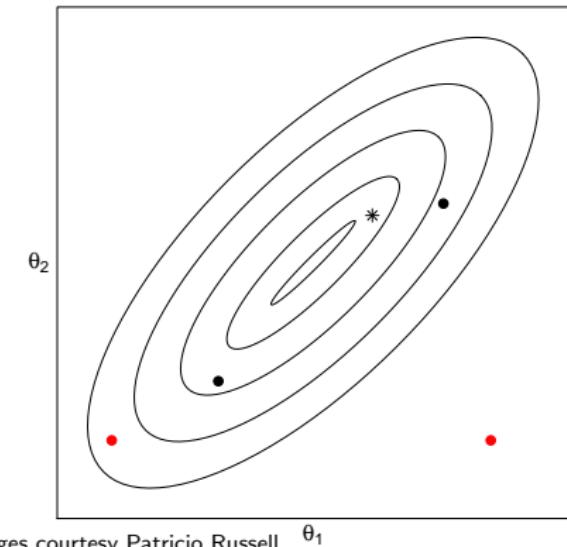
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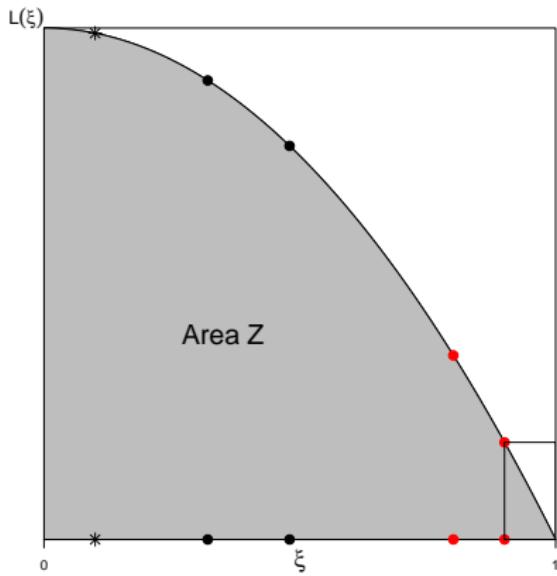
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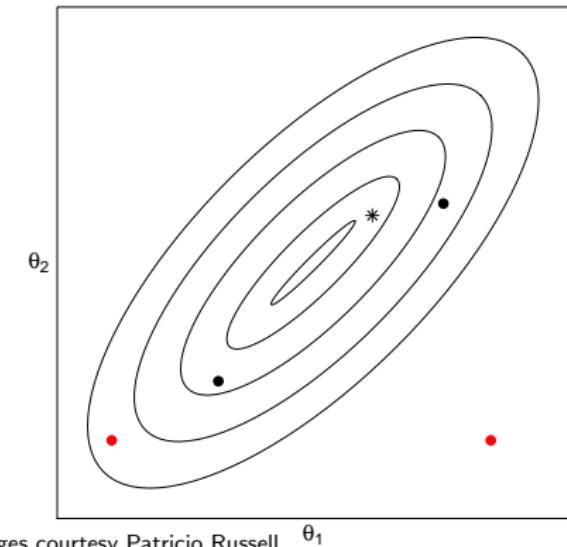
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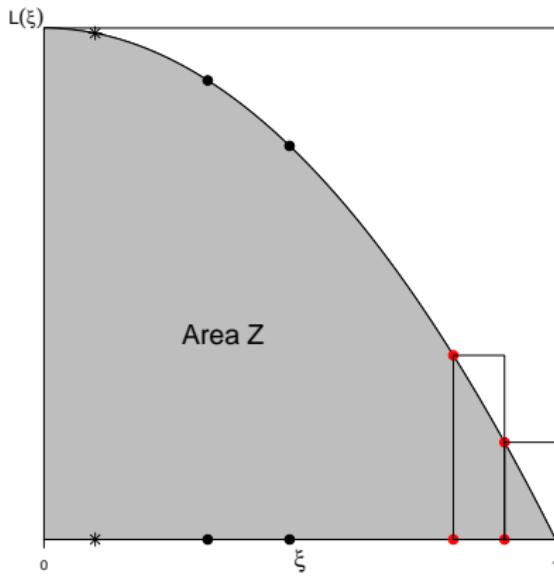
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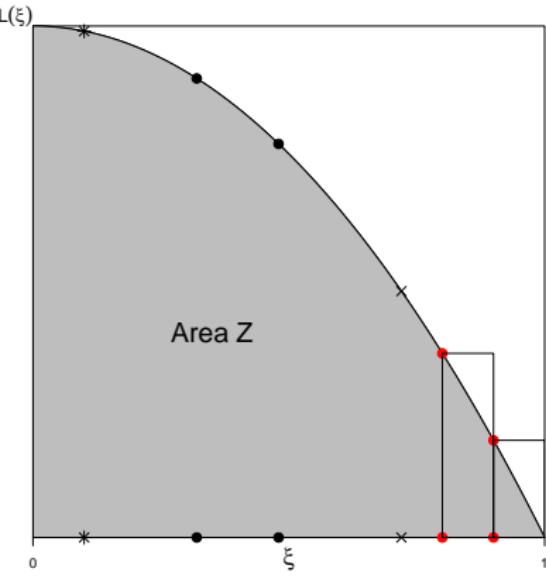
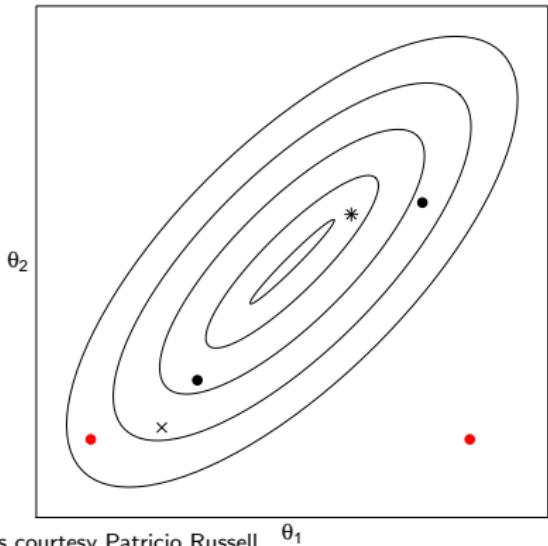
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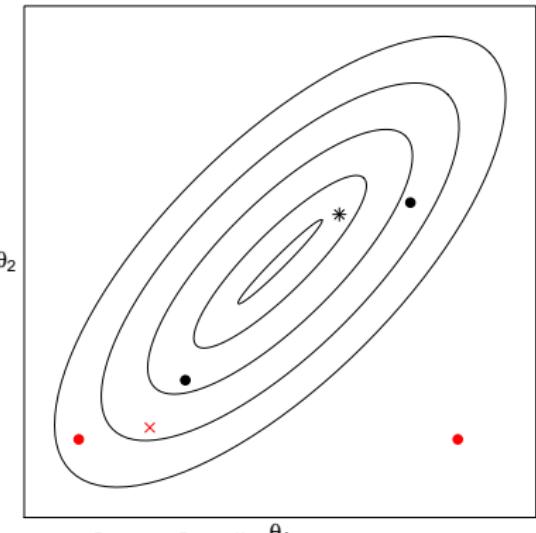


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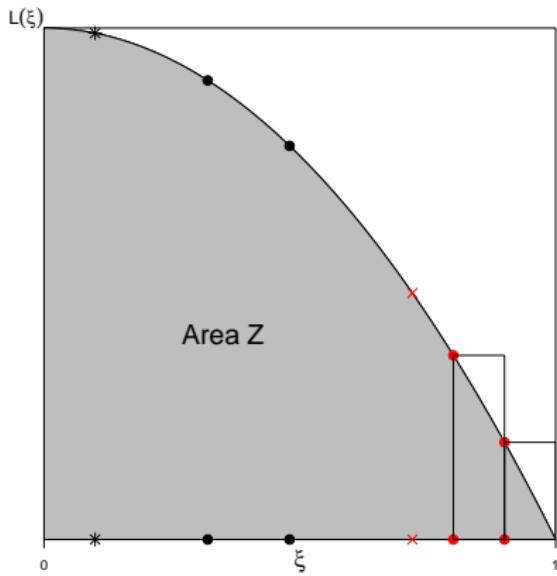


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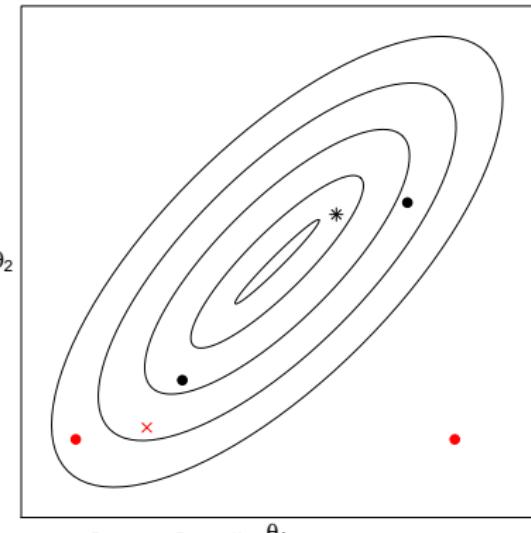
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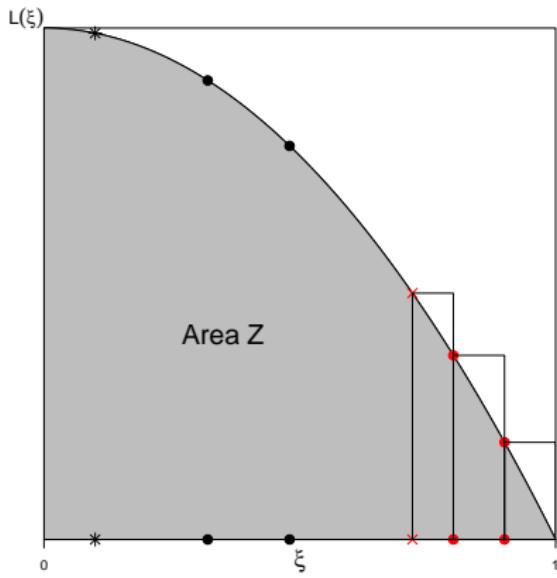
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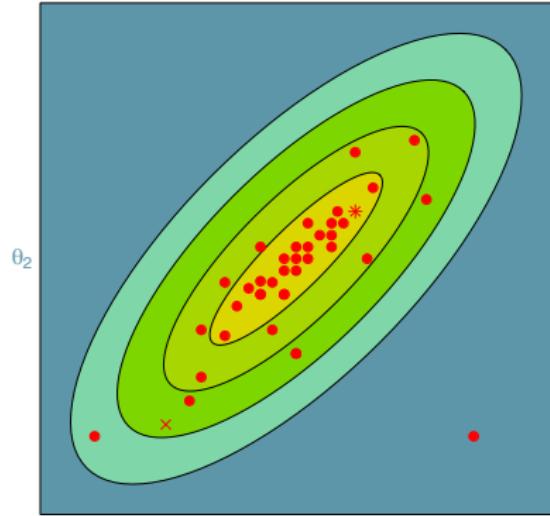
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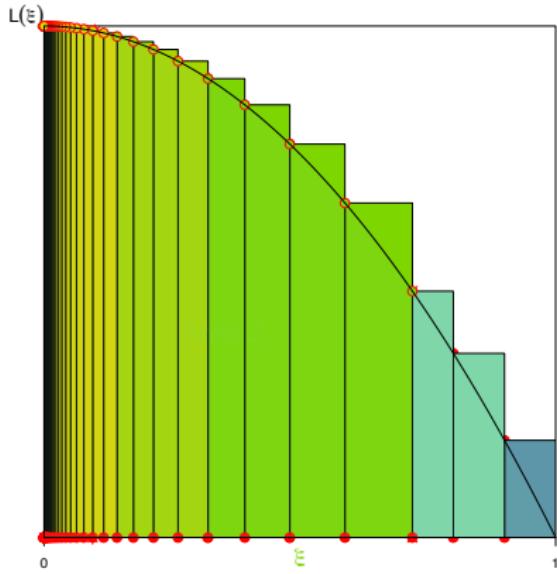
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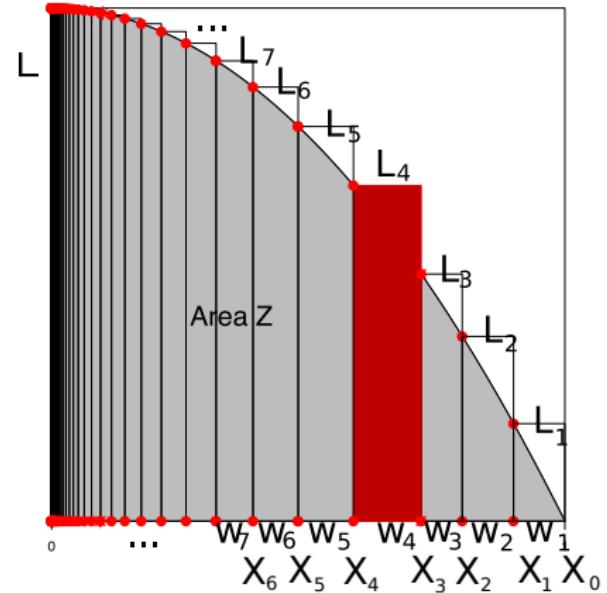
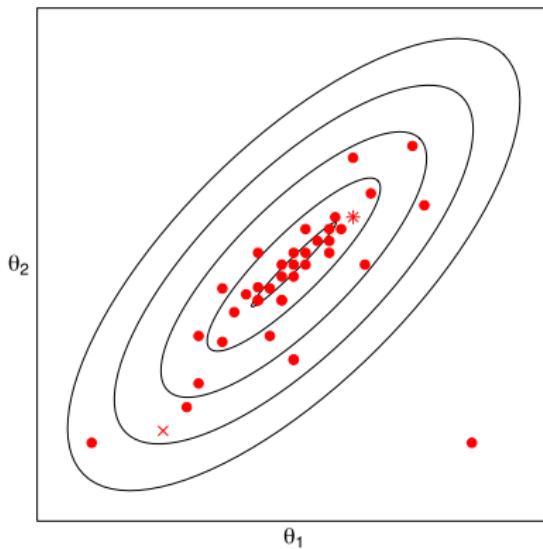
# Nested sampling



images courtesy Patricio Russell



Area under curve is  $ML = \mathcal{Z}$ , with  $N$  active points



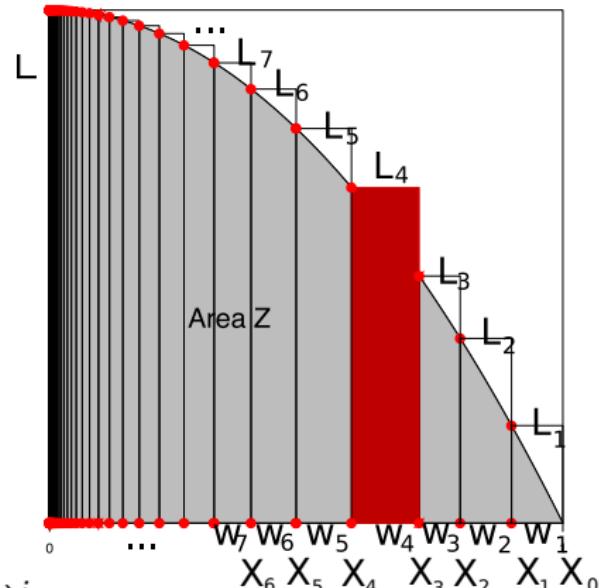
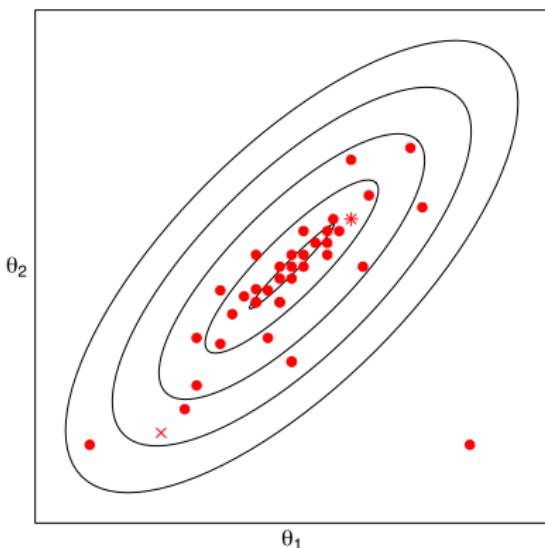
$$X_0 = 1$$

$X_i$  = proportion of prior mass with likelihood at least  $L_i$

$$w_i = X_i - X_{i-1}$$

$$\mathcal{Z} \approx \sum_i w_i L_i$$

## Defining $X_i$ with $N$ active points

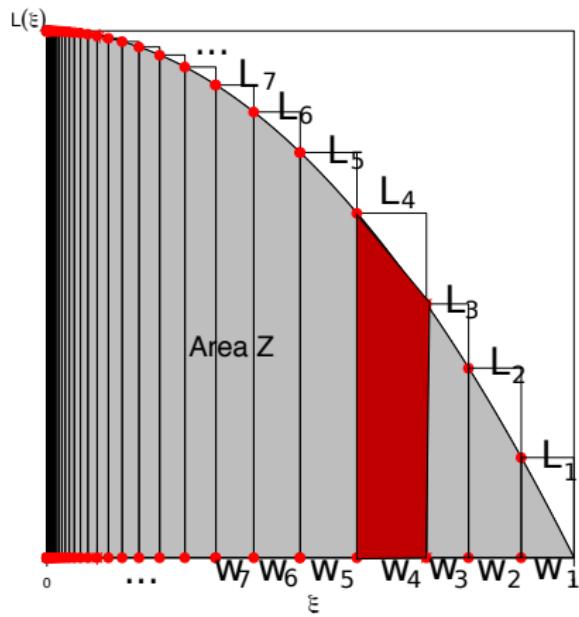
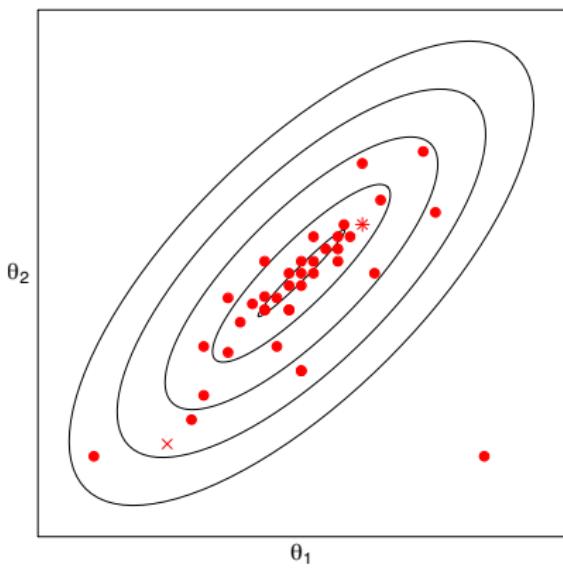


1. Arithmetic mean:  $X_i = (\frac{N}{N+1})^i$
2. Geometric mean:  $X_i = e^{-\frac{i}{N}} <=$  fast, most popular
3. Stochastic:  $X_i = \beta(1, N)X_{i-1}, X_0 = 1 <=$  allows SD estimate

$$w_i = X_i - X_{i-1}$$

$$\mathcal{Z} \approx \sum_i w_i L_i$$

## Use trapezium rule for more accurate ML estimate



$$\mathcal{Z} = \sum \dots$$

## Nested sampling with $N$ active points

Assign weights to 'saved points'

$$E\{w_i\} = e^{-(i-1)/N} - e^{-i/N}$$

Estimate of marginal likelihood

$$\mathcal{Z} = \sum_i w_i L_i$$

## Nested sampling with $N$ active points

Assign weights to 'saved points'

$$E\{w_i\} = e^{-(i-1)/N} - e^{-i/N}$$

Estimate of marginal likelihood

$$\mathcal{Z} = \sum_i w_i L_i$$

Estimate of standard deviation of marginal likelihood

$$sd(\log \mathcal{Z}) = \sqrt{\frac{H}{N}}$$

where the information  $H \approx \sum_i w_i \frac{L_i}{\mathcal{Z}} \log \frac{L_i}{\mathcal{Z}}$

## Nested sampling with $N$ active points

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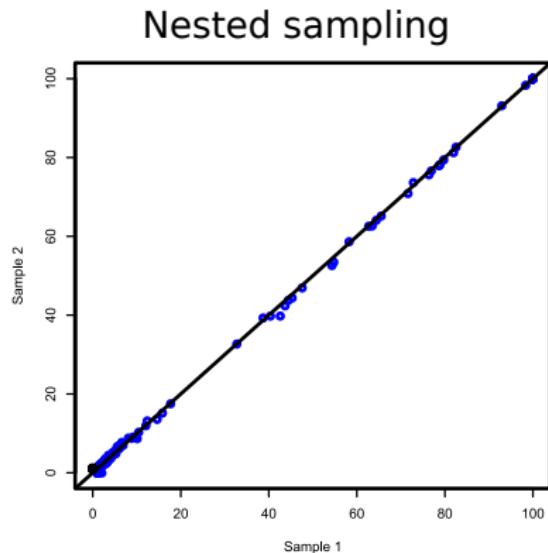
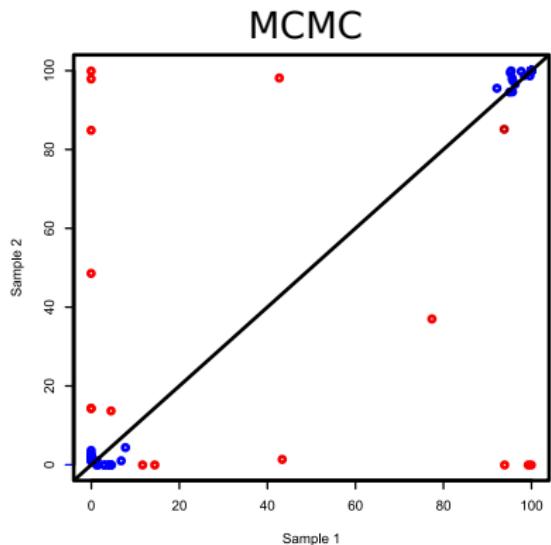
$$sd(\log \mathcal{Z}) = \sqrt{\frac{H}{N}}$$

where the information  $H \approx \sum_i w_i \frac{L_i}{\mathcal{Z}} \log \frac{L_i}{\mathcal{Z}}$

Sample from posterior by sampling saved points according to weights  $\frac{w_i L_i}{\mathcal{Z}}$

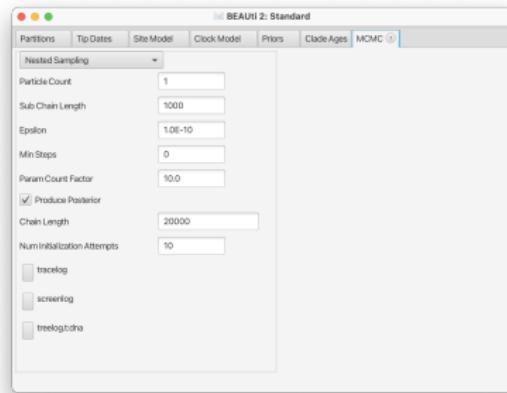
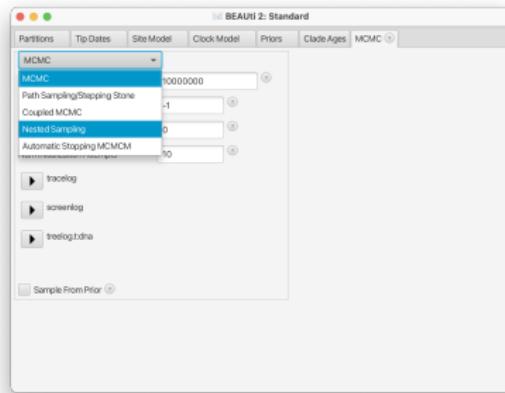
# DS1: where MCMC fails

- DS1 data set with tree islands
- MCMC has trouble moving between islands
- Consequently MCMC/stepping stone/path sampling fails



# NS in practice: Setting up an analysis

Requires NS package



## NS in practice: Setting up an analysis

Set up analysis in BEAUti, then edit XML and replace

```
<run id="mcmc" spec="MCMC" chainLength="100000000">
```

with

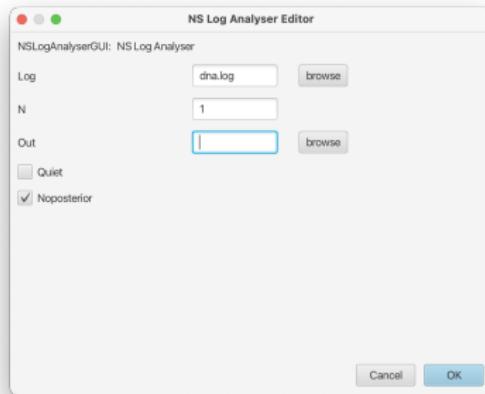
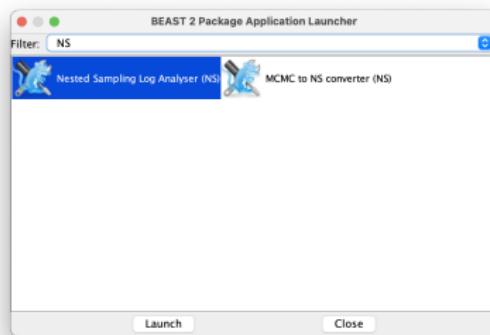
```
<run id="mcmc" spec="beast.gss.NS" chainLength="20000"  
    particleCount="1" subChainLength="5000" epsilon="1e-12">
```

More info:

<https://github.com/BEAST2-Dev/nested-sampling/wiki/How-to-use-NS>

# NS in practice: NSLogAnalyser

1. Launch via BEAUTi menu 'File => Launch apps' or BEAST AppLauncher
2. Provide log file, whether to generate posterior, number of points in NS analysis...



# NS in practice: NSLogAnalyser output

```
Loading /Users/remco/workspace/nested-sampling/dna.log, burnin 0%, skipping 0 log lines
|-----|-----|-----|-----|-----|-----|-----|
*****  
Marginal likelihood: -5536.566149988712 sqrt(H/N)=(10.69286805851783)=?SD=(11.303193986907344) Information: 114.33742731687087
Max ESS: 1.0018687743866186

Calculating statistics
|-----|-----|-----|-----|-----|-----|-----|
*****  
#Particles = 1
item      mean      stddev
posterior -5406.83 0.195683
likelihood -5410.40 0.184464
prior      3.570151 0.021772
treeLikelihood -5410.40 0.184464
TreeHeight   0.241741 0.000902
YuleModel    5.872736 0.021772
birthRate    7.939643 0.042047
Done!
Done invoking nestedsampling.util.NSLogAnalyser
```

Can also launch from terminal

## NS in practice: Are we there yet?

- Run multiple times (like MCMC).
- Check  $\mathcal{Z}$  estimates are compatible

$$|\log \mathcal{Z}_1 - \log \mathcal{Z}_2| \leq 2\sqrt{(SD_1^2 + SD_2^2)}$$

- If not, run with longer sub chain length
- Check  $\mathcal{Z}$  estimates are compatible with shorter runs/not systematically biased in multiple runs

Note, nested sampling under estimates  $\mathcal{Z}$ . Longer sub chain length results in lower  $\mathcal{Z}$  if not converged yet.

## NS in practice: Model selection with Nested sampling

Given  $M_1$  and  $M_2$ : say HKY vs GTR

- ① estimate log marginal likelihoods  $\mathcal{Z}_1$  for  $M_1$  and  $\mathcal{Z}_2$  for  $M_2$ 
  - NS provides standard deviations  $SD_1$  and  $SD_2$  for **log** marginal likelihoods
- ② if  $|\log \mathcal{Z}_1 - \log \mathcal{Z}_2| \geq 2\sqrt{SD_1^2 + SD_2^2}$  calculate Bayes factor  
 $BF = \log \mathcal{Z}_1 - \log \mathcal{Z}_2$ . Done!
- ③ else if  $\sqrt{SD_1^2 + SD_2^2} < 3(?)$  then  $M_1$  and  $M_2$  cannot be distinguished.  
Done!
- ④ else, run NS with more particles. How many? Use  $SD = \sqrt{\frac{H}{N}}$  so  
 $N = SD^2/H$  for desired  $SD$  ( $H$  from NS run) and goto (2)

## NS in practice: Pitfalls

- Subchain length too short – run with different length, compare whether estimates differ
- Epsilon too large, causing early stopping, underestimate of  $\mathcal{Z}$
- ...

## NS in practice: Parallel implementation

- Maintaining shared pool to selected starting point => behaves like single thread  $N$  particle
- Runtime scales linear with nr or particles  $N$
- $N$  single particle runs can be combined => embarrassingly parallel
- Little communication required, so can be forked out over different CPUs

# Stepping Stone and Nested Sampling work on any model

provided the prior is proper

## Model selection summary

Stepping Stone and Nested Sampling work on any model

**provided the prior is proper**

Improper priors do not integrate to one, e.g.,  $1/X$ , uniform( $0, \infty$ )

# Model selection summary

- Compare posterior or likelihoods: **this is forbidden**
- Naive: Harmonic mean estimator (HME) of marginal likelihood
  - ▶ High variance estimator  $\Rightarrow$  unreliable
  - ▶ **Also forbidden**
- Path sampling/Stepping stone:
  - ▶ computationally expensive
  - ▶ most stable marginal likelihood estimation we got (so far)
  - ▶ use this if you can
- Nested sampling:
  - ▶ Provides estimate of ML + its variance
  - ▶ Computation (inverse) proportional to accuracy of estimate
  - ▶ Can choose accuracy as desired

# Model comparison/Bayesian hypothesis testing

- Through model selection:
  - ▶ compare Bayes factors based on ML estimates
- Through model averaging: post-hoc analysis
  - ▶ compare Bayes factors based on empirical estimates from prior and posterior samples

Bayes factor:

$$\frac{p(D|M_1)}{p(D|M_2)} \text{ estimated by } \frac{\frac{\text{empirical posterior}(M_1)}{\text{empirical prior}(M_1)}}{\frac{\text{empirical posterior}(M_2)}{\text{empirical prior}(M_2)}}$$

Obtain sample from prior for  $M_1$  and  $M_2$ .

Obtain sample from posterior for  $M_1$  and  $M_2$ .

# Bayes Factors

$BF$ range	$\ln(BF)$ range			$\log_{10}(BF)$ range			Interpretation
1 – 3	0	–	1.1	0	–	0.5	hardly worth mentioning
3 – 20	1.1	–	3	0.5	–	1.3	positive support
20 – 150	3	–	5	1.3	–	2.2	strong support
> 150	>	5		>	2.2		overwhelming support

Kass & Raftery, JASA, 1995

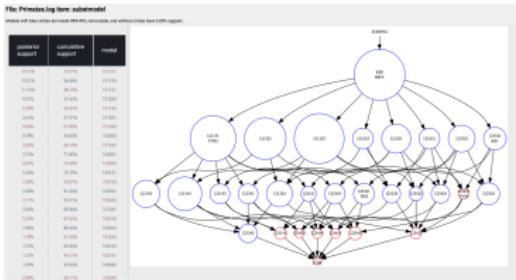
## Model comparison of topologies

- Clade support for two alternative clades –  $M_1$ : clade  $A$  is present  $M_2$ : clade  $B$  is present
- From sample from prior:  $P(M_1) = 0.3$   $P(M_2) = 0.4$
- From sample from posterior:  $P(D|M_1) = 0.6$   $P(D|M_2) = 0.1$
- Bayes factor

$$\frac{p(D|M_1)}{p(D|M_2)} = \frac{\frac{posterior(M_1)}{prior(M_1)}}{\frac{posterior(M_2)}{prior(M_2)}} = \frac{\frac{0.6}{0.3}}{\frac{0.1}{0.4}} = 8$$

- Positive support for  $M_1$  for clade  $A$  vs clade  $B$

# Model comparison of substitution models



- bModelTest –  $M_1$ : HKY vs  $M_2$ : GTR
  - From sample from prior:  $P(M_1) = \frac{1}{31}$   $P(M_2) = \frac{1}{31}$
  - From sample from posterior:  $P(D|M_1) = 0.1377$   $P(D|M_2) = 0.006$
  - Bayes factor

$$\frac{p(D|M_1)}{p(D|M_2)} = \frac{\frac{posterior(M_1)}{prior(M_1)}}{\frac{posterior(M_2)}{prior(M_2)}} = \frac{0.1377/\frac{1}{31}}{0.006/\frac{1}{31}} = 22.95$$

- Strong support for  $M_1$ : HKY

# Model comparison of root age

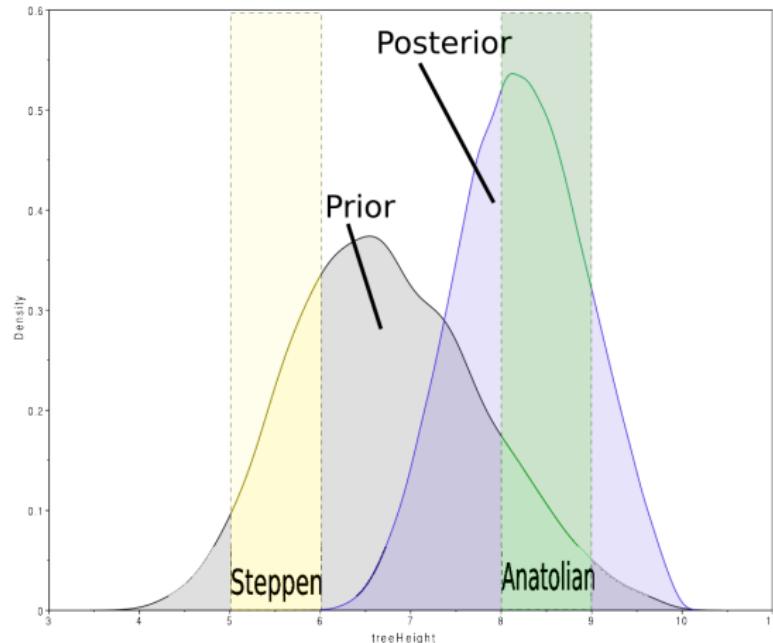
Origin of Indo-European: Two competing theories



Steppen 5000 – 6000BP, Anatolian 8000 – 9000BP

# Model comparison of root age

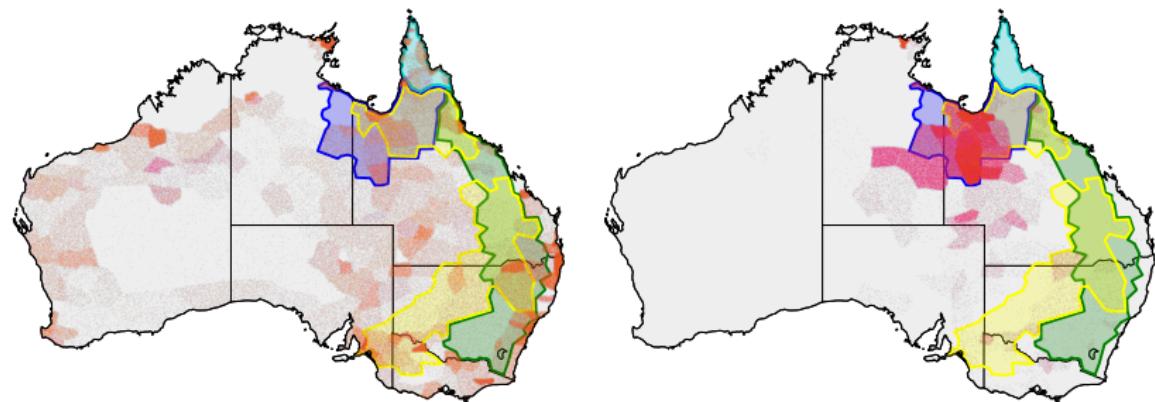
Origin of Indo-European: Two competing theories



Root height Prior = 6.8 [4.9, 8.8] Posterior 8.2 [6.9, 9.6]  
Bayes Factor  $\gg 100$  in favour of Anatolian hypothesis

# Model comparison of root location

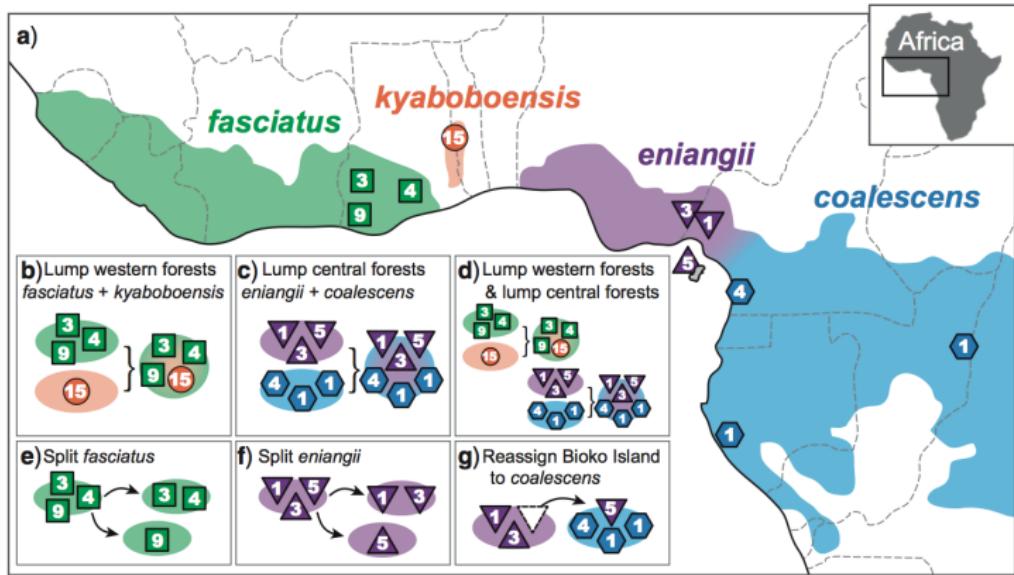
Root location: Pama Nyungang  $M_1$   $M_2$   $M_3$   $M_4$



Bayes Factors:

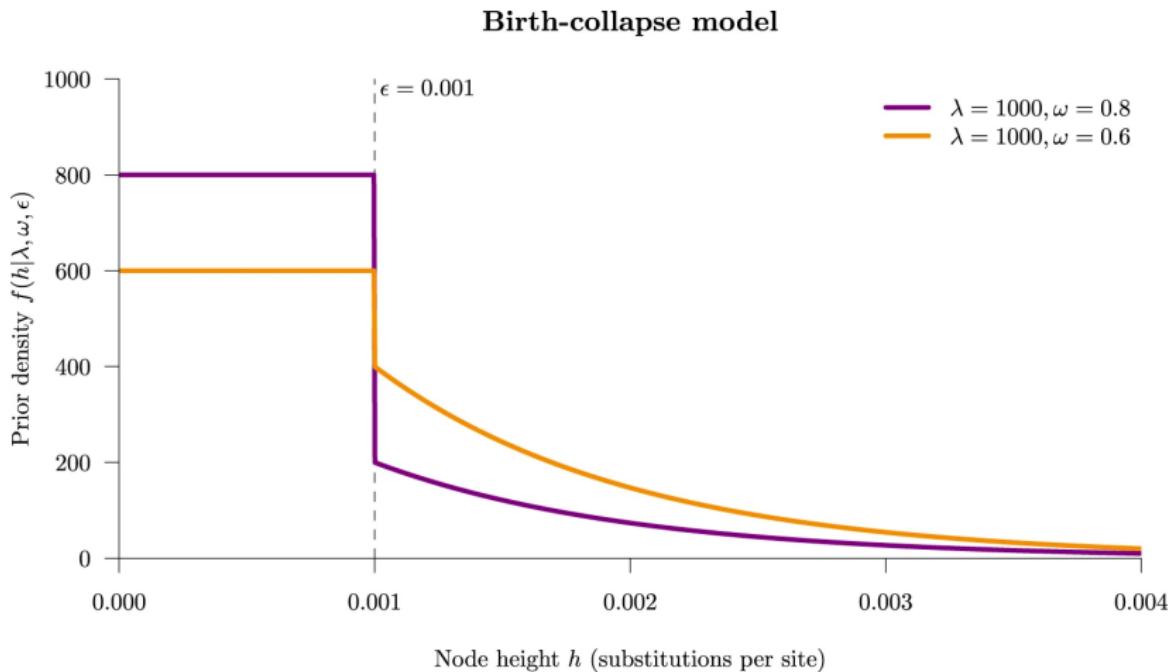
	$M_1$	$M_2$	$M_3$	$M_4$
$M_1$	—	6.22	76.66	486.34
$M_2$	0.16	—	12.33	78.23
$M_3$	0.01	0.08	—	6.34
$M_4$	0.00	0.01	0.16	—

# Species delimitation – BFD = Bayes Factor Delimitation



Model	#Species ML	Rank BF
a. Current taxonomy	4	-12890.3
b. Lump western forests	3	-15024.5
c. Lump central forests	3	-14094.0
d. Lump western & central forests	2	-16190.4
e. Split <i>fasciatus</i>	5	-13088.0
f. Split <i>eniangii</i>	5	-12615.3
g. Reassign Bioko Island to <i>coalescens</i>	4	-13434.4

# Species delimitation – SpeeDemon



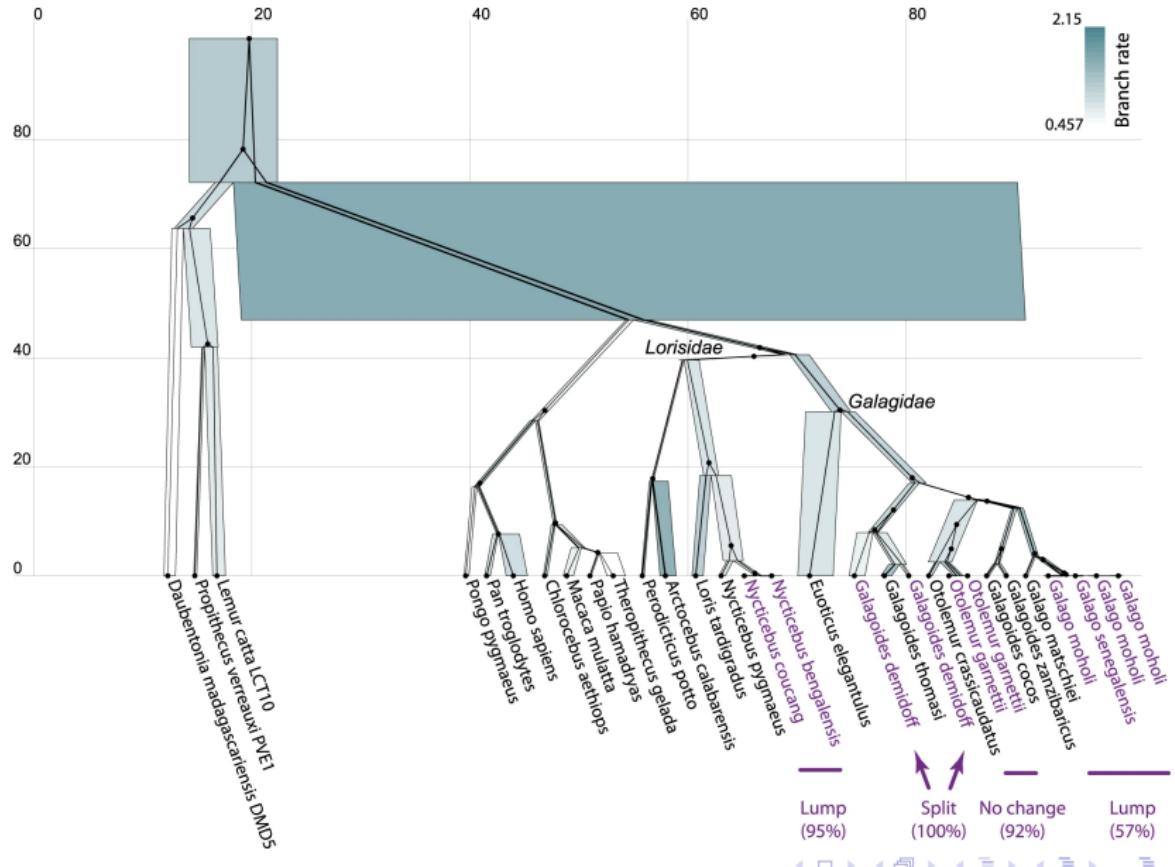
## Tree prior: Yule skyline collapse

Douglas & Bouckaert, 2022

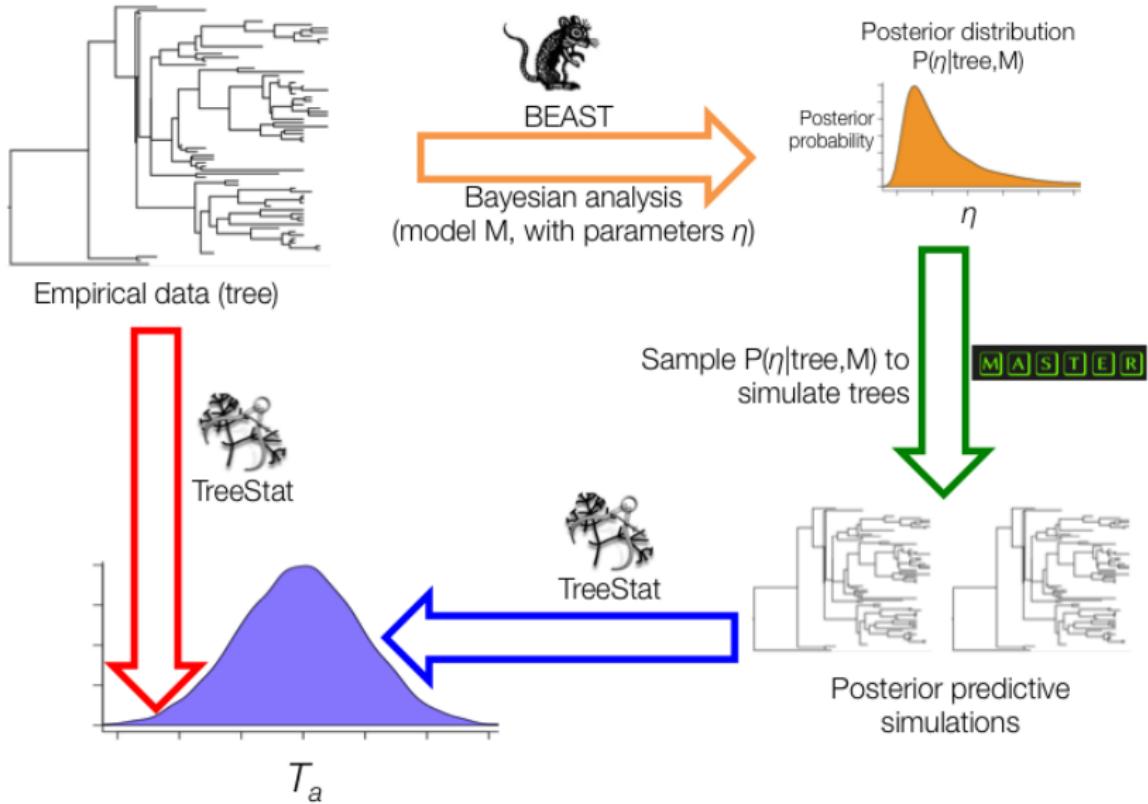
# Species delimitation – SpeeDemon



## Species delimitation – SpeeDemon



# Model adequacy: Is this model adequate for my data?



# Model adequacy: Is this model adequate for my data?

Posterior predictive simulation:

- Sample from posterior
- Generate data for each posterior sample
- Calculate summary statistics on generated data and actual data
  - ▶ frequency of nucleotides (for different substitution models)
- Use loss function to compare statistics
  - ▶ Deviance loss function  $L: \sum_{x \in \{A, C, G, T\}} \log\left(\frac{\pi_x}{\hat{\pi}_x}\right)$
  - ▶ Criterion  $E\{L\} + L$
- Automates goldilocks zone:
  - ▶ If model is too simple, goodness of fit of mean statistic will be low
  - ▶ If model is too complex, variability of statistic will be high

# Summary model comparison, selection & averaging

Questions?

Thanks: Patricio Russell for slides