

Maximum likelihood phylogenetic inference and GARLI

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Outline

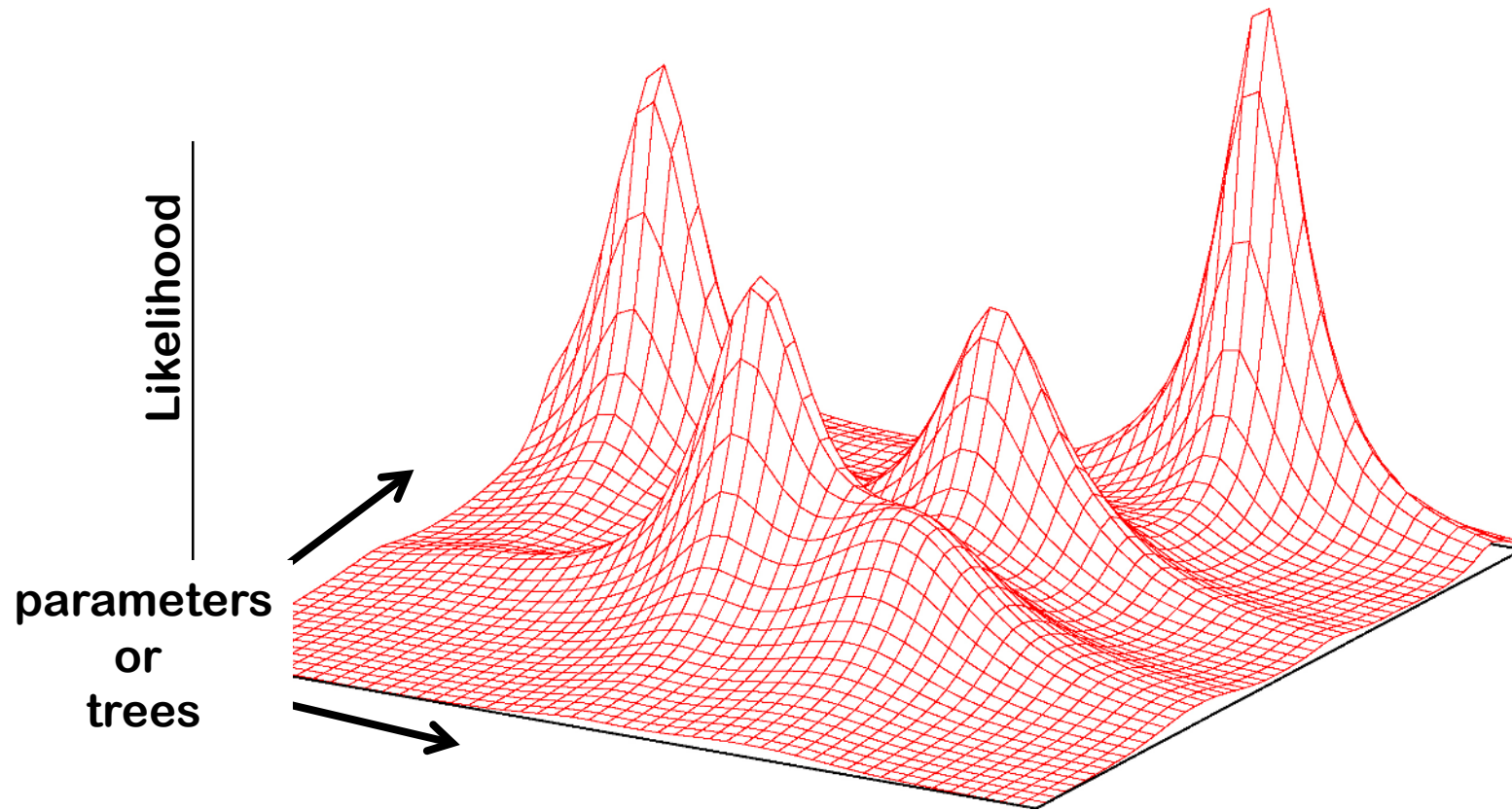
- Heuristic methods
- ML tree inference, parameter estimation and GARLI
- Model odds and ends
- Using GARLI in practice
- Computer exercises

Heuristic methods

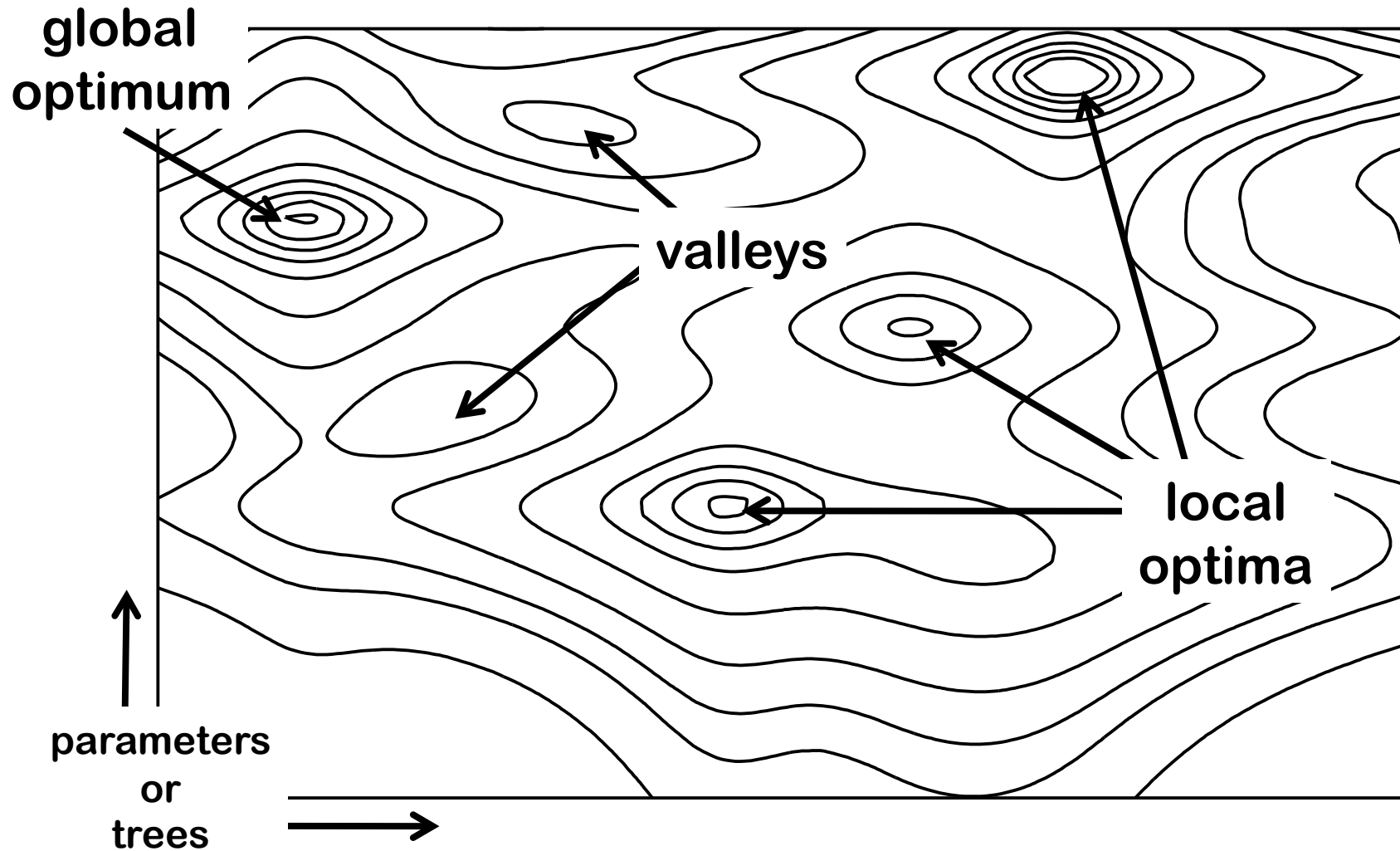
Heuristics

- Aim to optimize or solve some problem
- Results never guaranteed
- Deterministic and/or stochastic
- Many, many types

The likelihood landscape



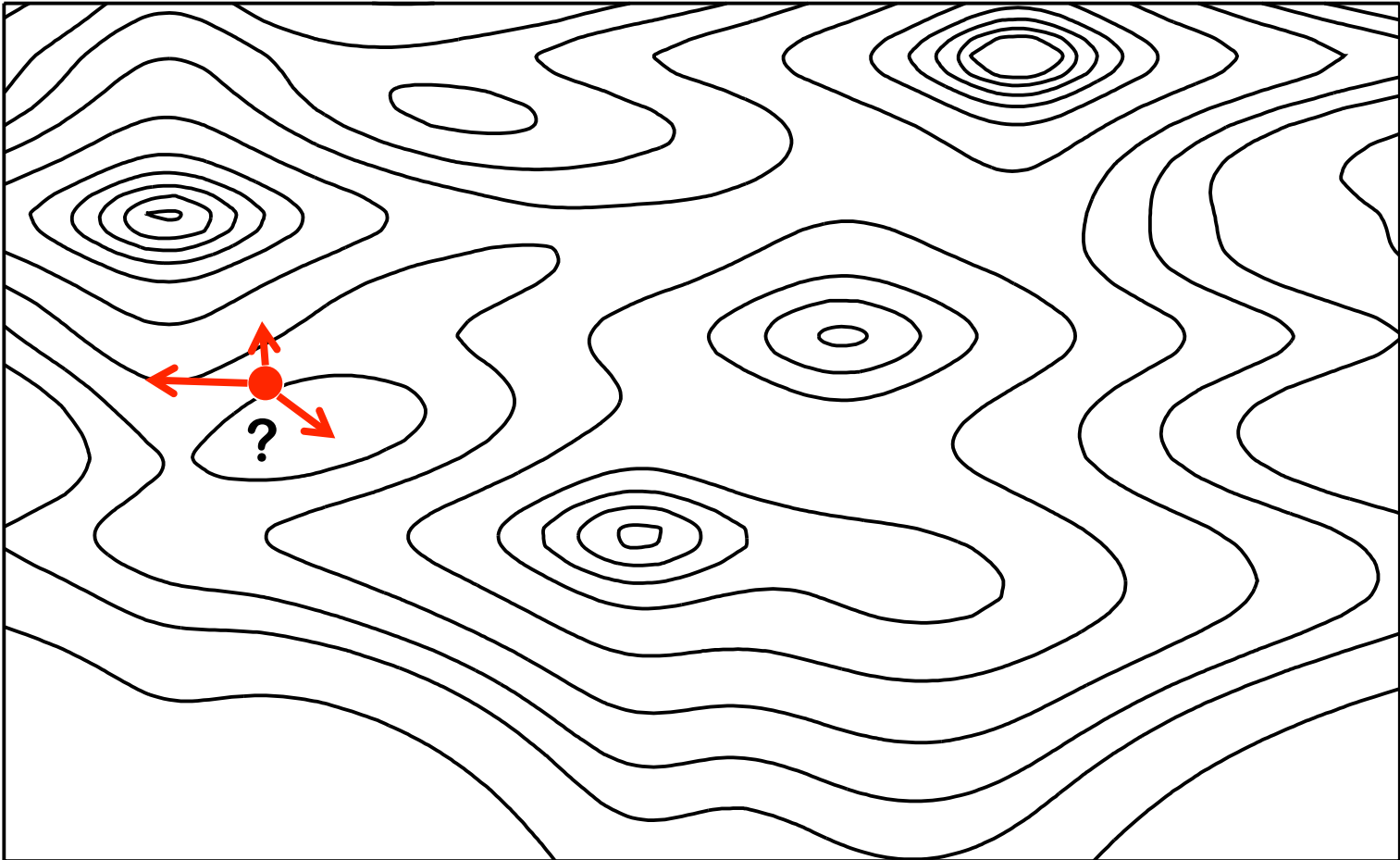
The likelihood landscape (from above)



Heuristic features

- **Main differences (simplified):**
 - How are new points proposed?

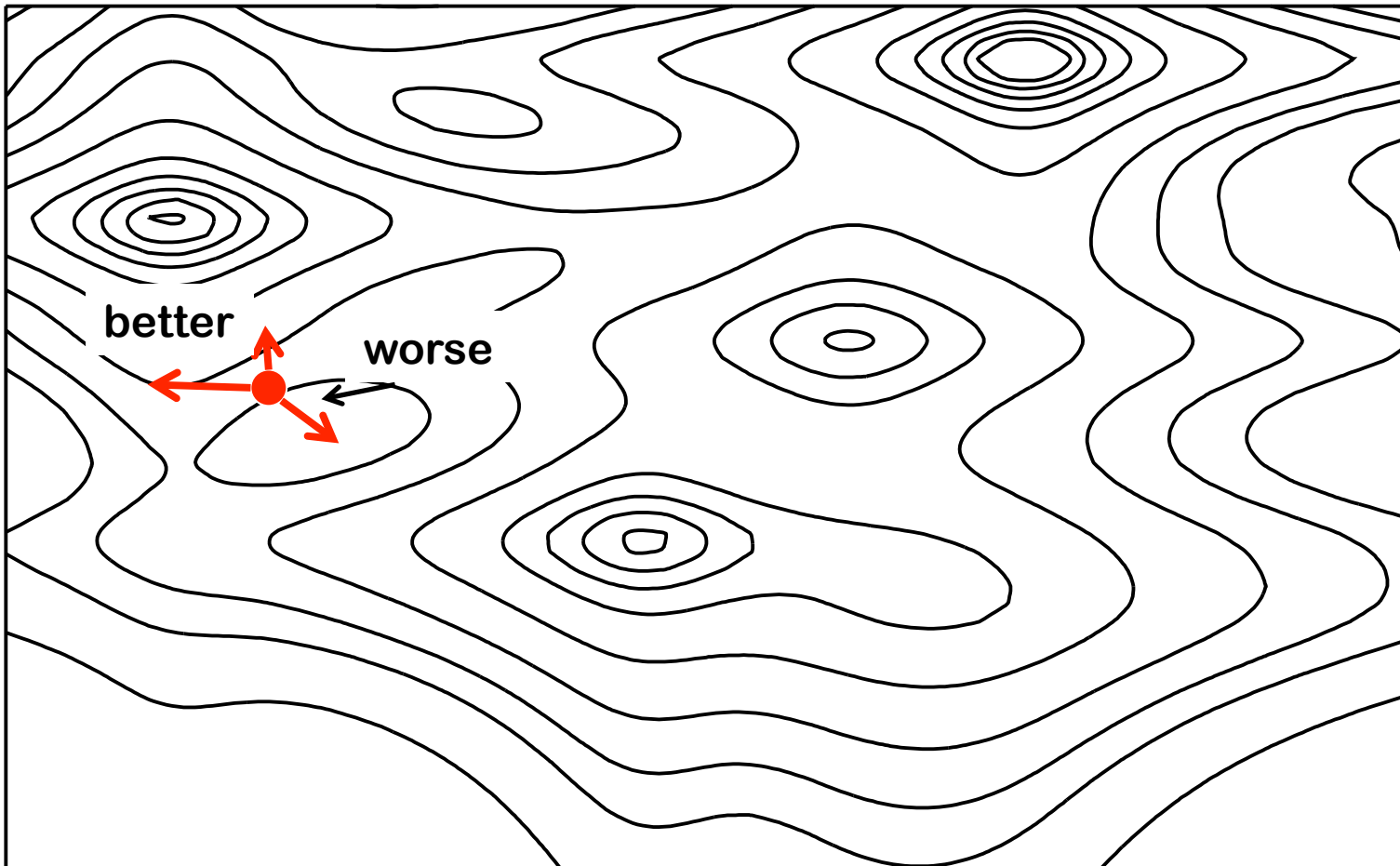
Proposing new points



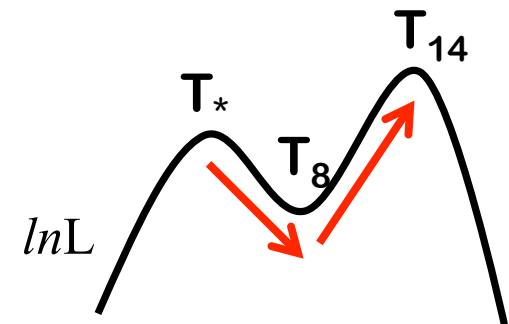
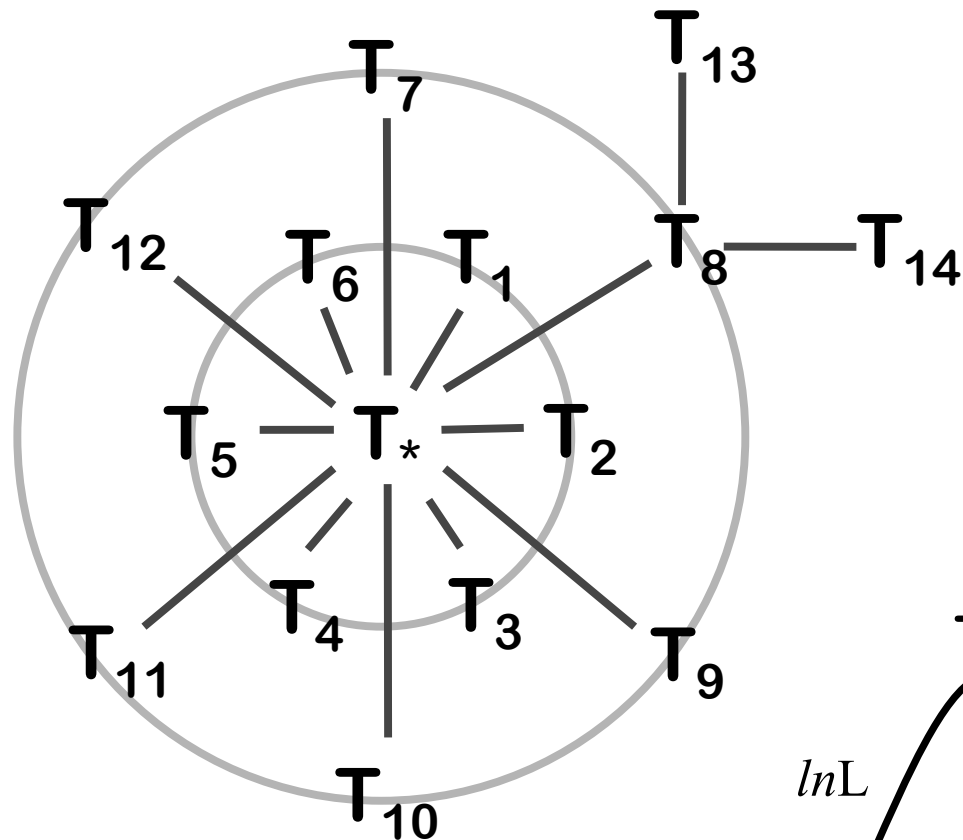
Heuristic features

- **Main (simplified) differences:**
 - How are new points proposed?
 - How does the method move between proposed points?

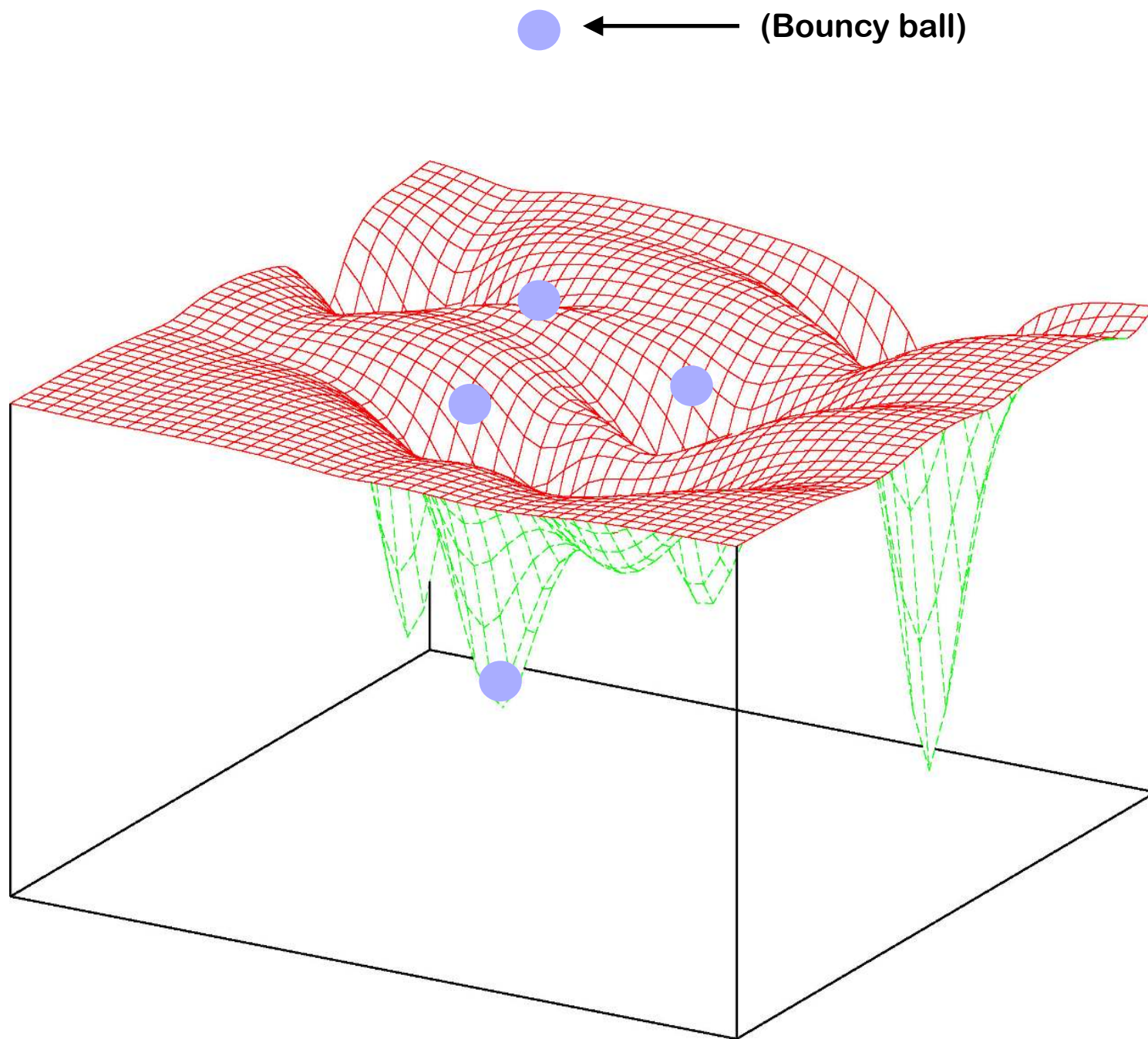
Moving between points

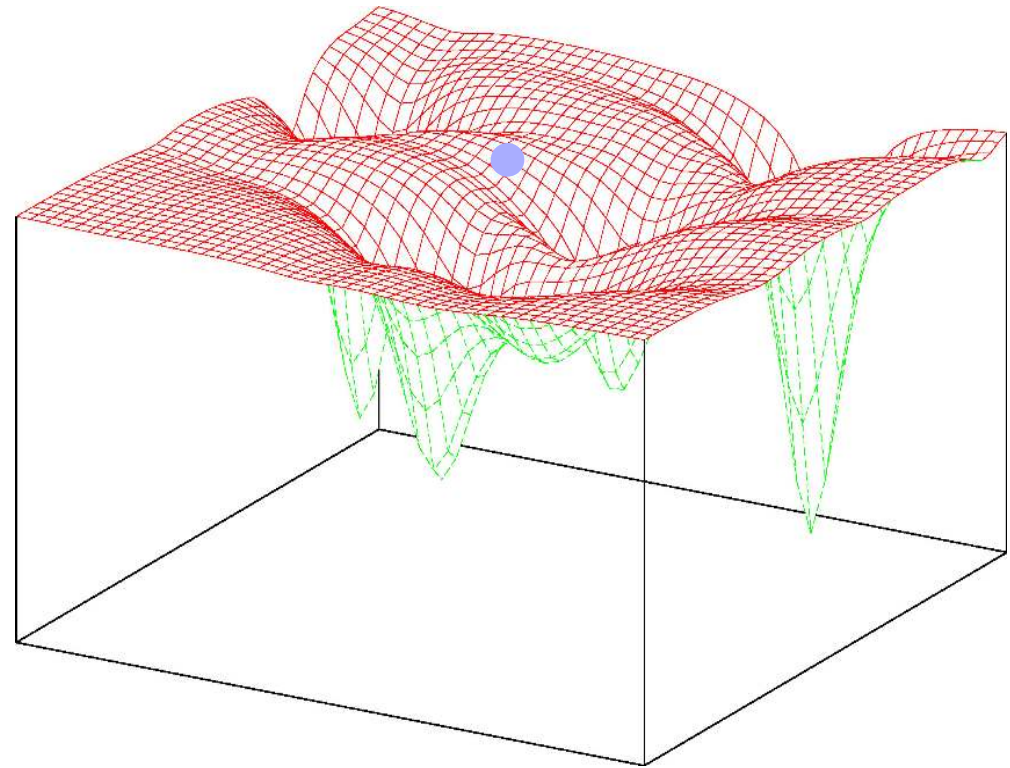
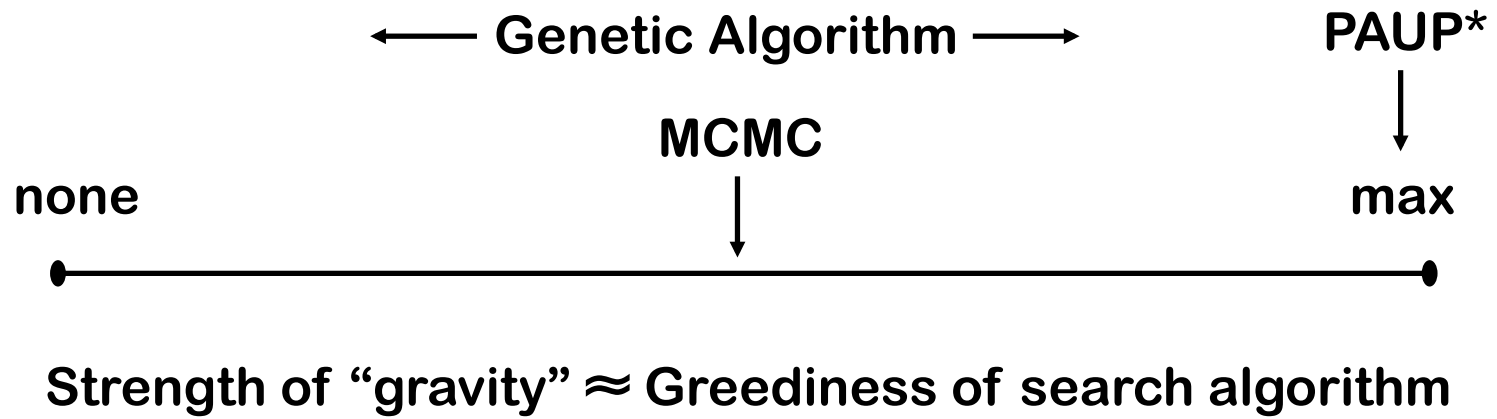


Moving through treespace



Higher likelihood
↓





Heuristic features

- **Few restrictions on how a heuristic can work**
- **The best choice may be problem specific**

A specific heuristic: The Genetic Algorithm

- **Computational analogue of evolution by natural selection**
- **A few simple requirements:**
 - **Measure of fitness**
 - **Method of selection**
 - **Mutation operators**
 - **Recombination operators**

Is GARLI a GA?

- **Well, no**
- **Serial algorithm does not use recombination between individuals, which technically disqualifies it**
- **Also atypical of GA's in other aspects (small population sizes, very strong selection pressure)**

Other possible names...

GARLI*

***not actually a genetic algorithm
or**

SHuRLI

**(Stochastic Heuristic ...)
or**

EARLI

(Evolutionary Algorithm ...)

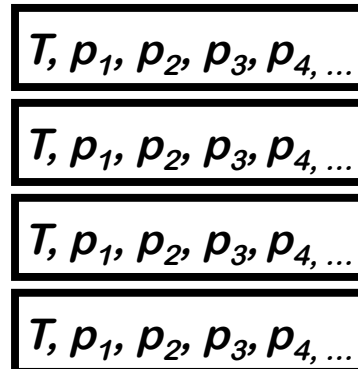
(I think that I'm stuck with the current name...)

GA terminology

- Individual (set of parameter values)
- Population
- Fitness (log-likelihood)
- Selection function (fitness proportional)
- Generation

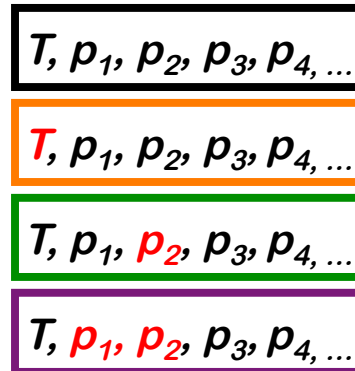
One generation

Create initial
population
of individuals



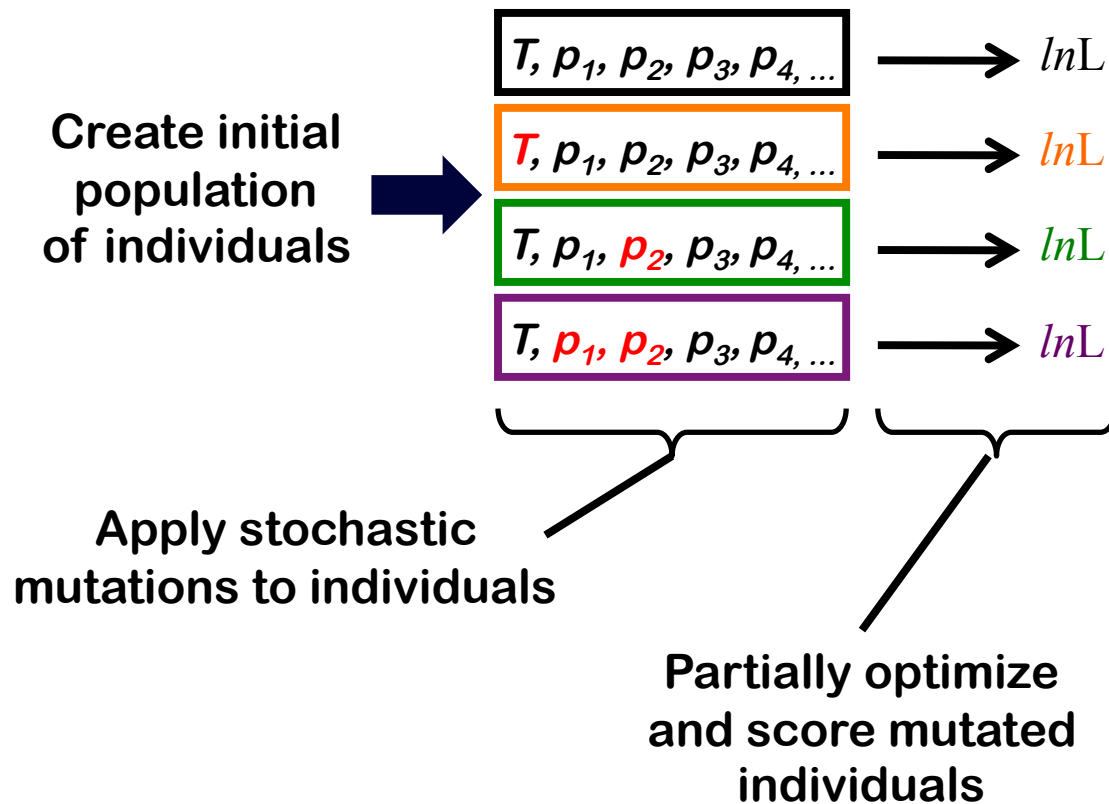
One generation

Create initial
population
of individuals

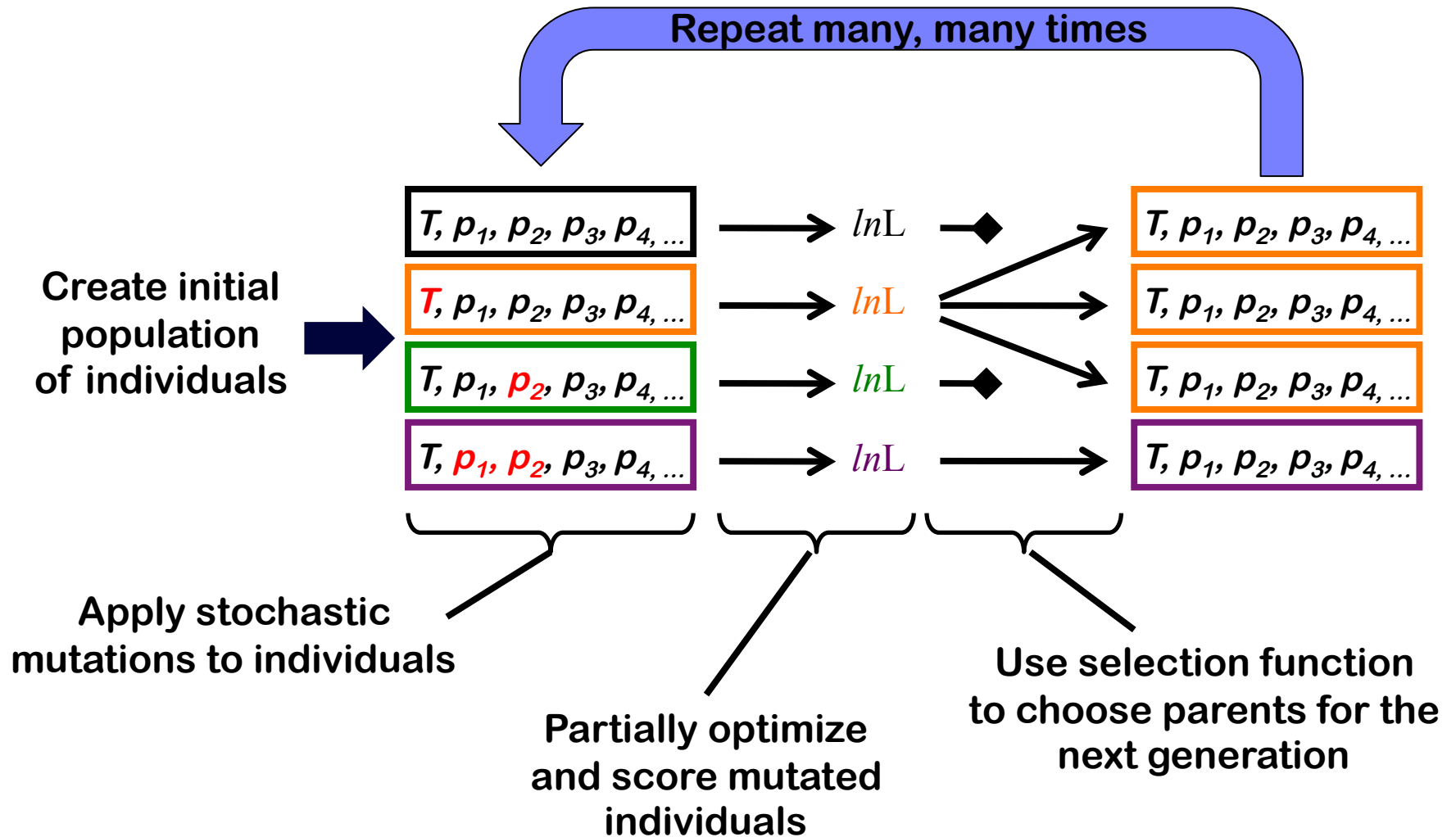


Apply stochastic
mutations to individuals

One generation



One generation



GA mutations

- Similar to proposals in Bayesian MCMC phylogenetic methods (but with a bit more freedom)
- Random component, but need not be but truly random
- GARLI uses independent (mutually exclusive) types:
 - Topology (NNI, local SPR, full SPR)
 - Model parameters
 - Branch lengths

GARLI

- **Genetic Algorithm for Rapid Likelihood Inference**
- **Descendent of GAML (Lewis, 1998)**
- **Development goal: make ML phylogenetic searches feasible for large datasets**

How is GARLI different?

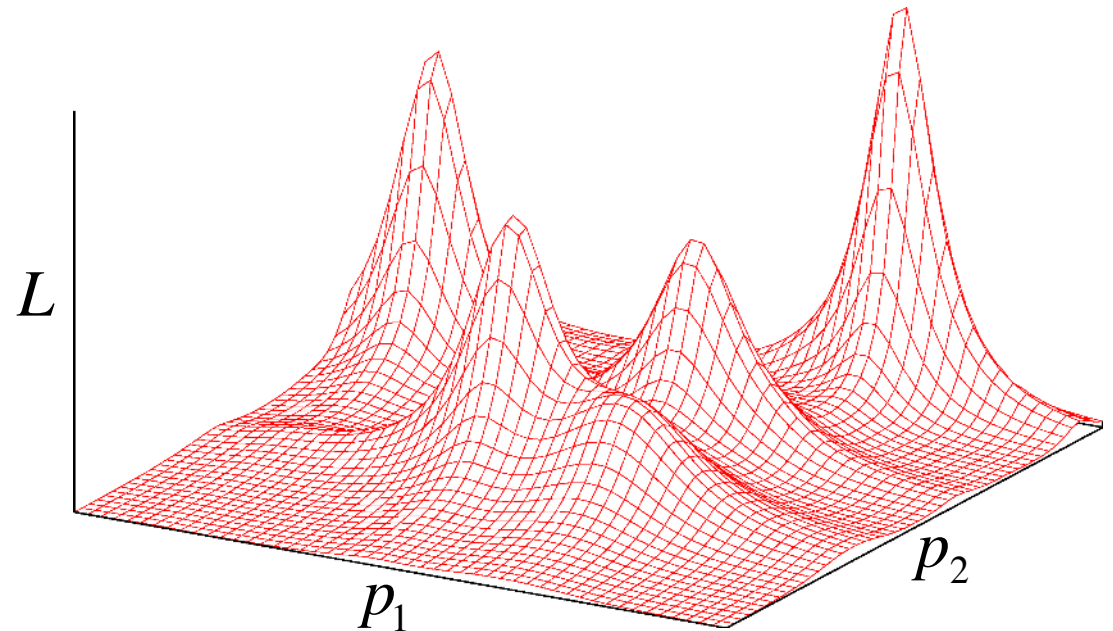
- Stochastic, genetic algorithm-like approach instead of deterministic hill climbing
- Gradually optimizes tree topology, branch lengths and model parameters
- Allows accurate ML tree inference on large datasets (hundreds of sequences) in hours

ML inference

Maximize

$$\Pr(Data \mid Model) = f(p_1, p_2, p_3 \dots)$$

Set of parameter values
maximizing this function
is the maximum likelihood
estimate $\{\hat{p}_1, \hat{p}_2, \hat{p}_3 \dots\}$



The ML estimate

- Point estimate of the best supported parameter values
- Assessing confidence requires other techniques, e.g. bootstrapping or measuring the curvature of the likelihood surface

ML phylogenetic inference

- Objective: find highest likelihood point in treespace
- Difficulties:
 - Enormous number of trees to consider
 - Lots of computation needed to score each tree (optimize parameters)

ML vs. Bayesian inference

- **ML inference: find the likelihood peak**
- **Bayesian inference: summarize the entire posterior distribution**
- **Differ in practicality and appropriateness for particular problems**
- **Bayesian methods are particularly appropriate when:**
 - **Low signal to parameter ratio (complex models or little signal)**
 - **Strong prior knowledge can be incorporated**

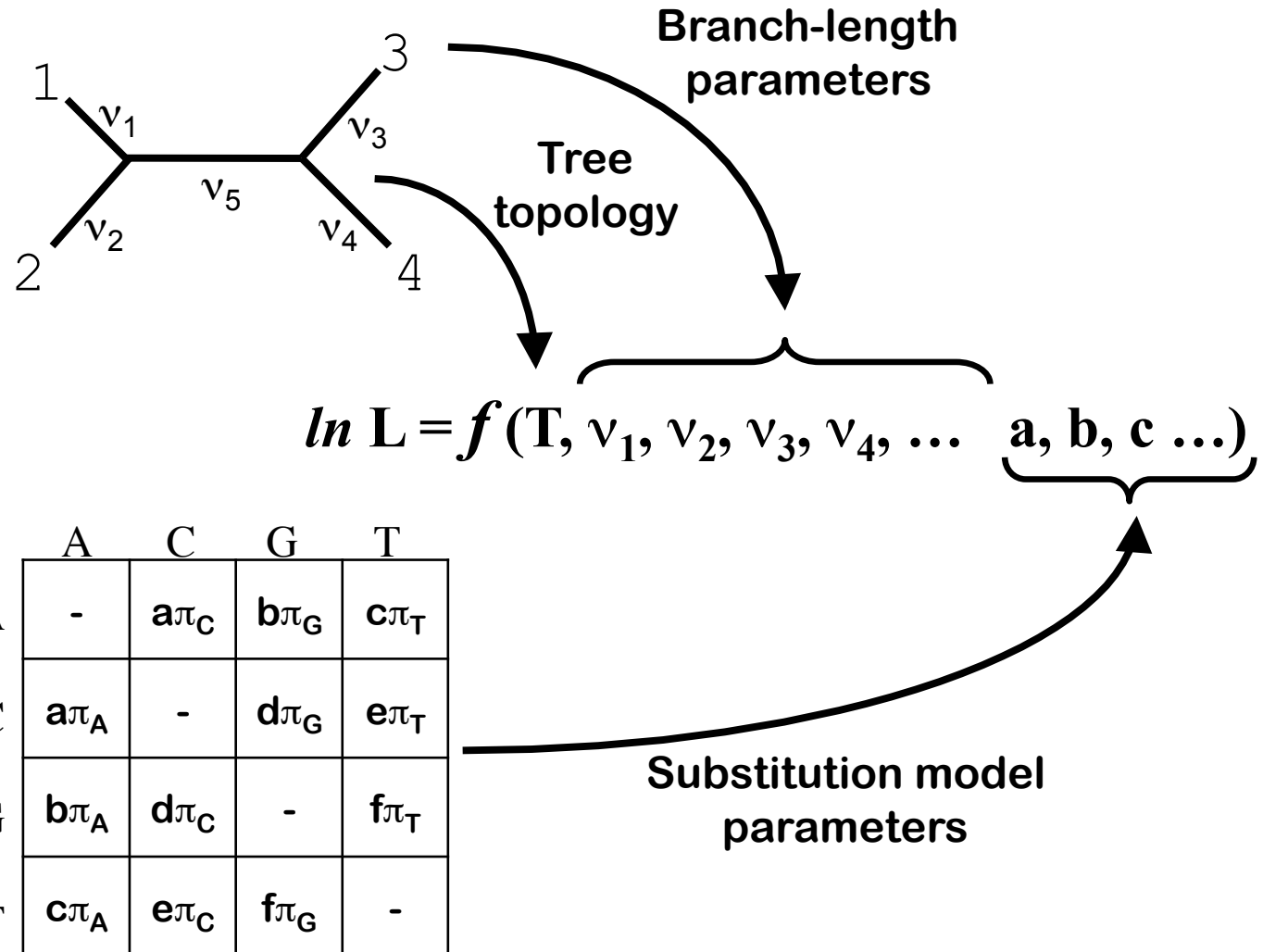
ML vs. Bayesian inference

- ML methods are appropriate when
 - Inferential signal is fairly strong
 - Datasets are very large (practicality)
- Choice often comes down to personal preference, and the results of inference will be similar
- Often the results of both methods are shown

ML phylogenetics

Input data

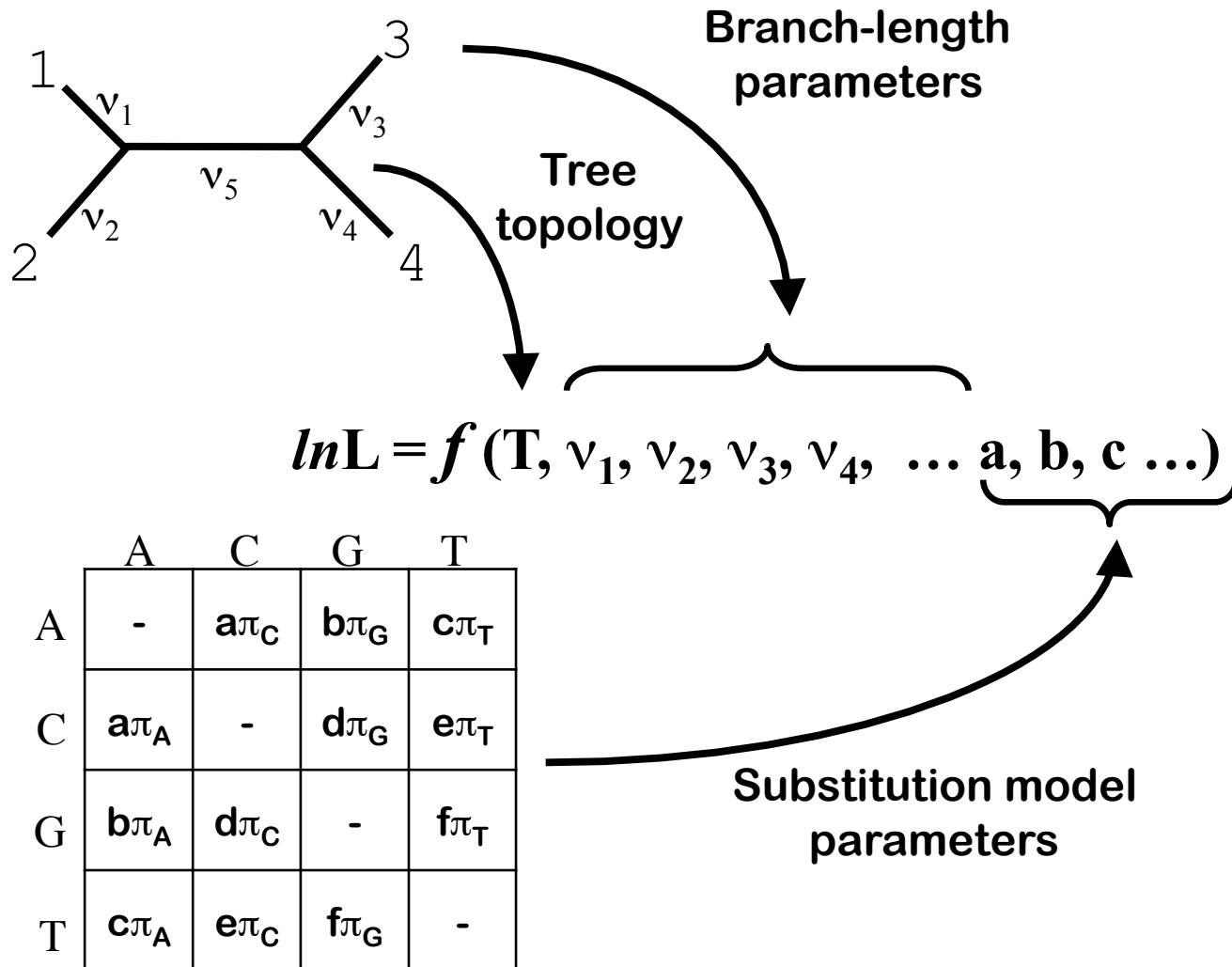
1 ACGC...
2 AATC...
3 AACC...
4 GATC...



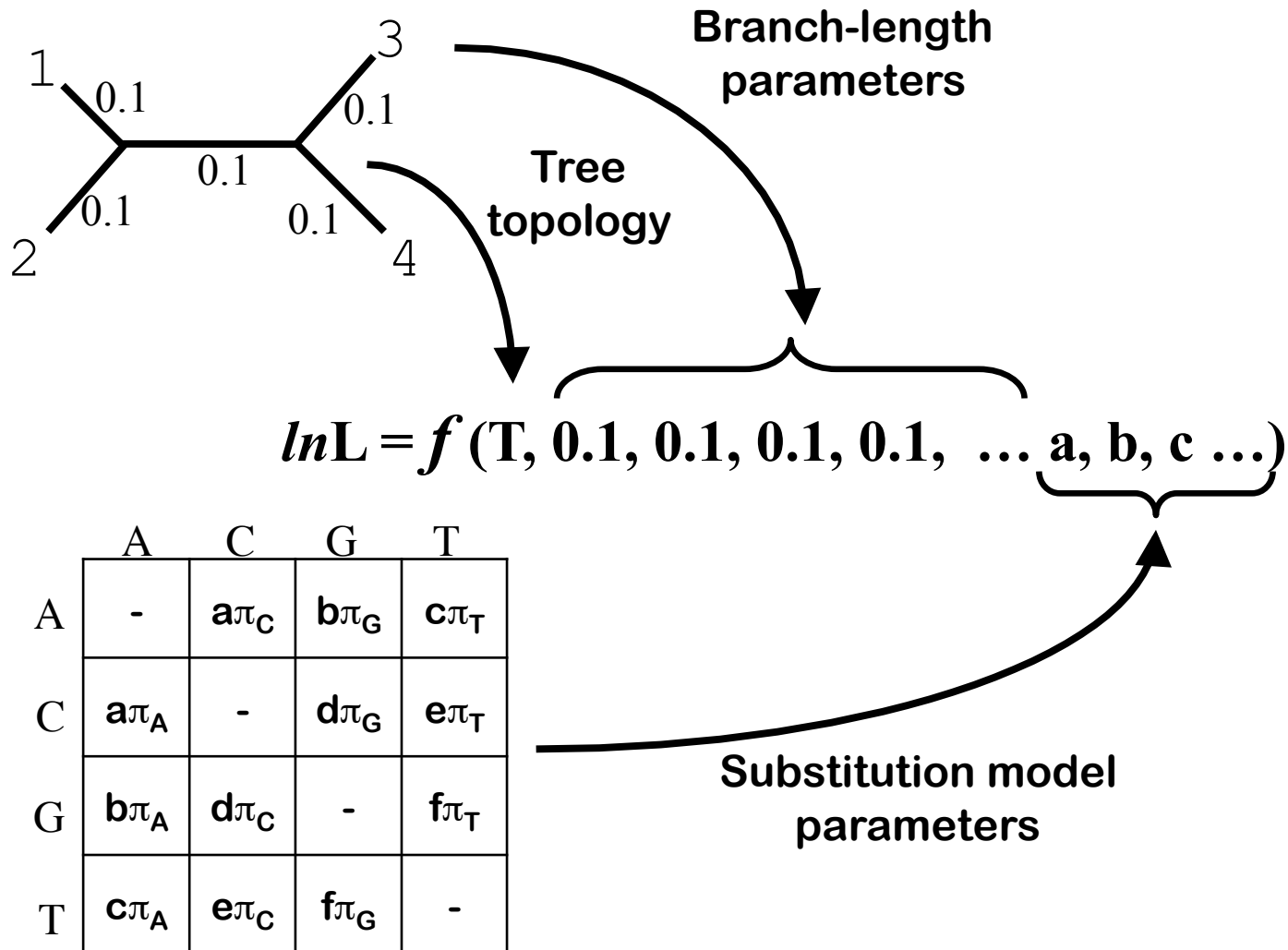
ML phylogenetics

- Likelihood is still just a function to be optimized
- But, with some unique aspects
 - Tree topology is a strange discrete parameter
 - Branch-length parameters aren't equivalent on different trees
 - Optimal parameter values are strongly correlated

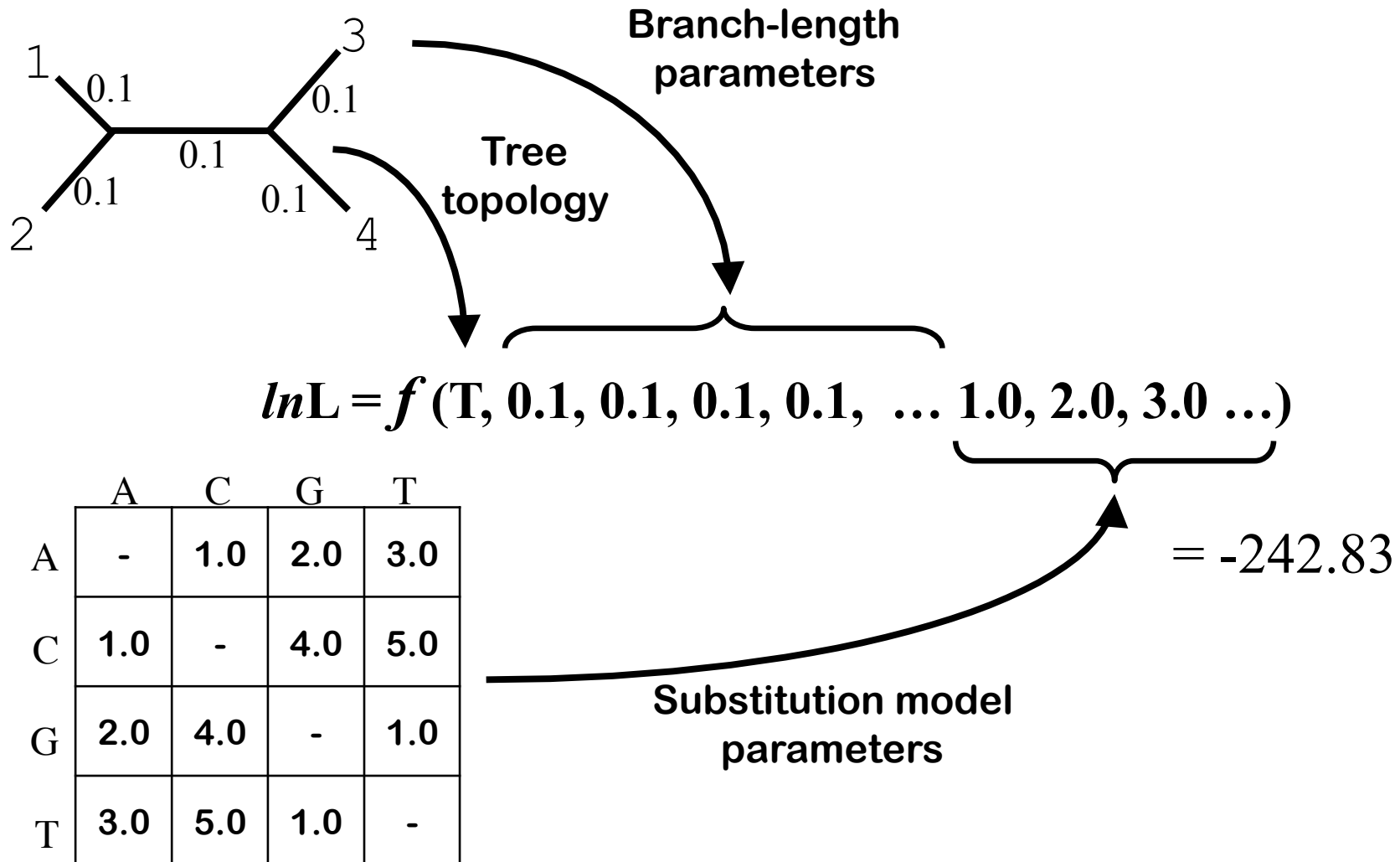
Scoring a topology



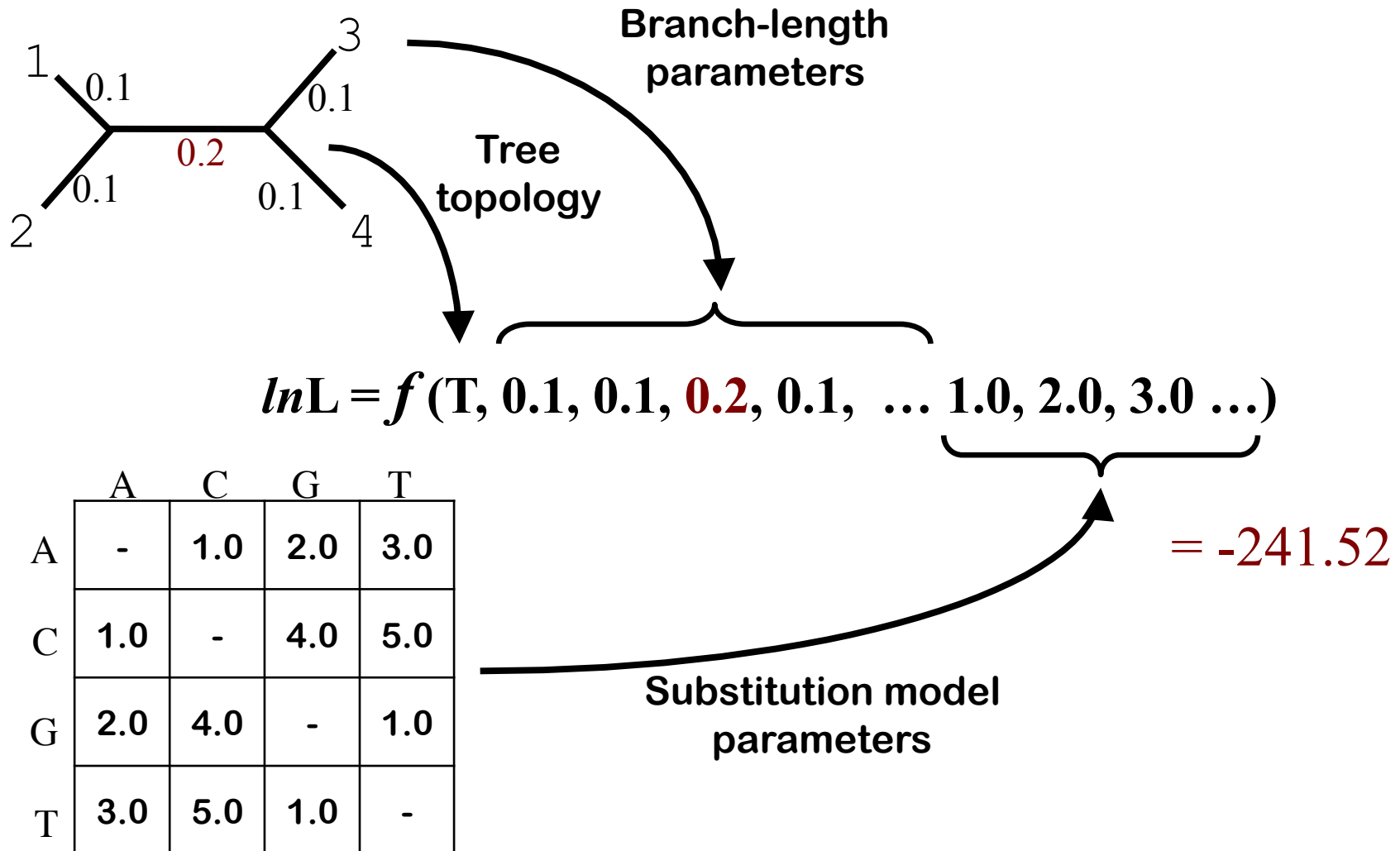
Scoring a topology



Scoring a topology



Scoring a topology



The likelihood of a topology

- **Single topology essentially represents range of likelihood scores, depending on parameter values**
- **Likelihood of a given tree and specific parameter values can be calculated quickly**

The maximized likelihood of a topology

- **The “likelihood of a tree”: the likelihood with other parameters at their optimal values (“maximized likelihood”)**
- **I’ll talk mainly about the optimization of branch-length parameters**

Obtaining the maximized likelihood

$$\text{Y} \quad \ln L = f(T, 0.1, 0.1, 0.2, 0.1 \dots 1.0, 2.0, 3.0 \dots) = -242.83$$

$$\text{Y} \quad \ln L = f(T, 0.1, 0.1, \mathbf{0.08}, 0.1 \dots 1.0, 2.0, 3.0 \dots) = \mathbf{-241.52}$$

$$\text{Y} \quad \ln L = f(T, \mathbf{0.05}, 0.1, 0.08, 0.1 \dots 1.0, 2.0, 3.0 \dots) = \mathbf{-241.23}$$

$$\text{Y} \quad \ln L = f(T, 0.05, 0.1, 0.08, \mathbf{0.16} \dots 1.0, 2.0, 3.0 \dots) = \mathbf{-241.11}$$

·
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$$\text{Y} \quad \ln L = f(T, 0.05, 0.23, 0.08, 0.16 \dots 1.2, 4.6, 1.7 \dots) = \mathbf{-239.31}$$

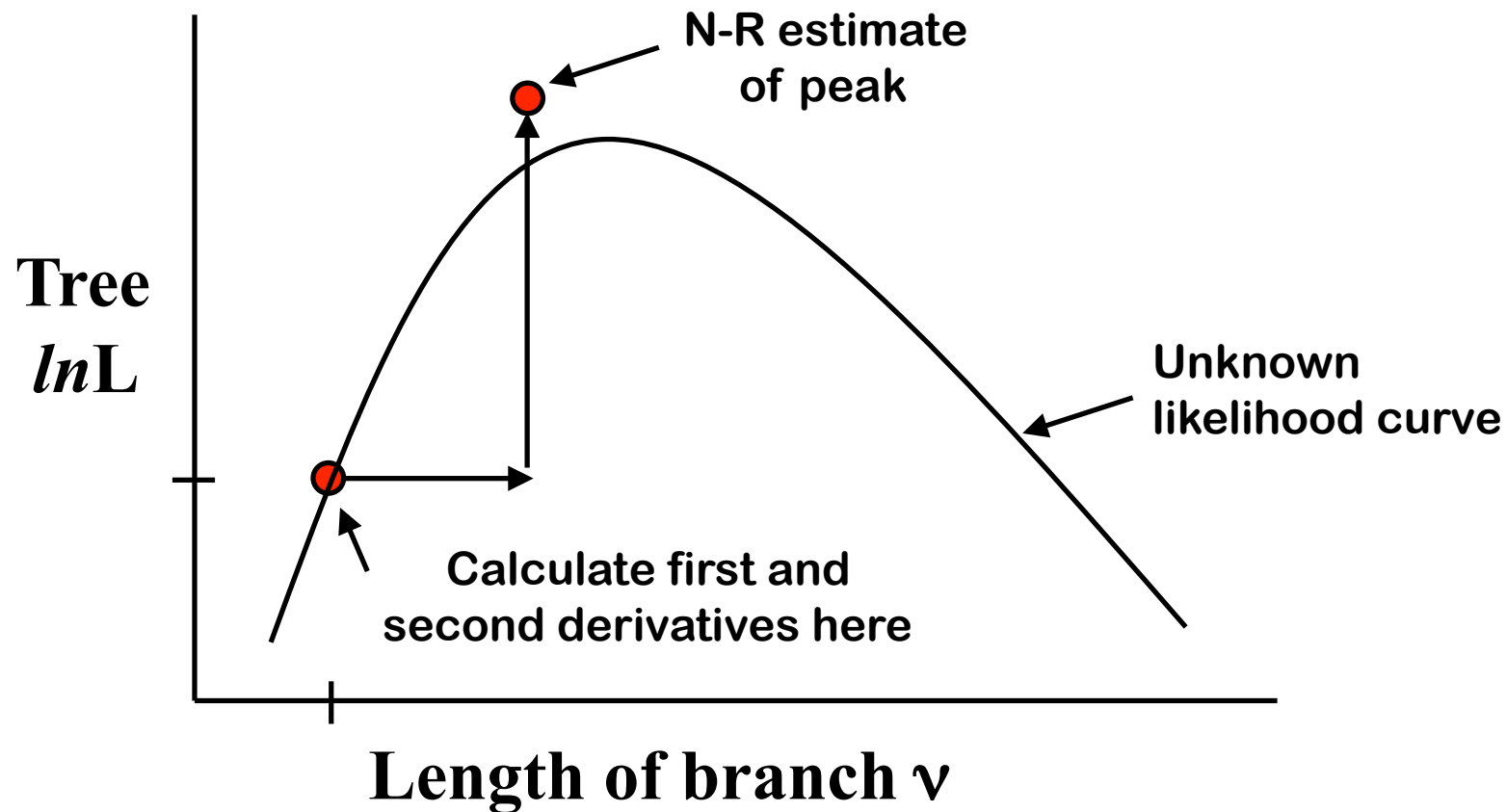
$$\text{Y} \quad \ln L = f(T, 0.05, 0.23, \mathbf{0.12}, 0.16 \dots 1.2, 4.6, 1.7 \dots) = \mathbf{-239.29}$$

Etc.

Parameter optimization

- Many methods, generally based on slope of likelihood surface or bracketing of maximum
- Often done sequentially, but not required

Branch-length optimization (Newton-Raphson method)



Maximized likelihood: pros

- **By definition, our goal is to find the topology with the highest maximized likelihood**
- **If we calculate it for every tree we examine, we'll always know which tree is the best**

Maximized likelihood: cons

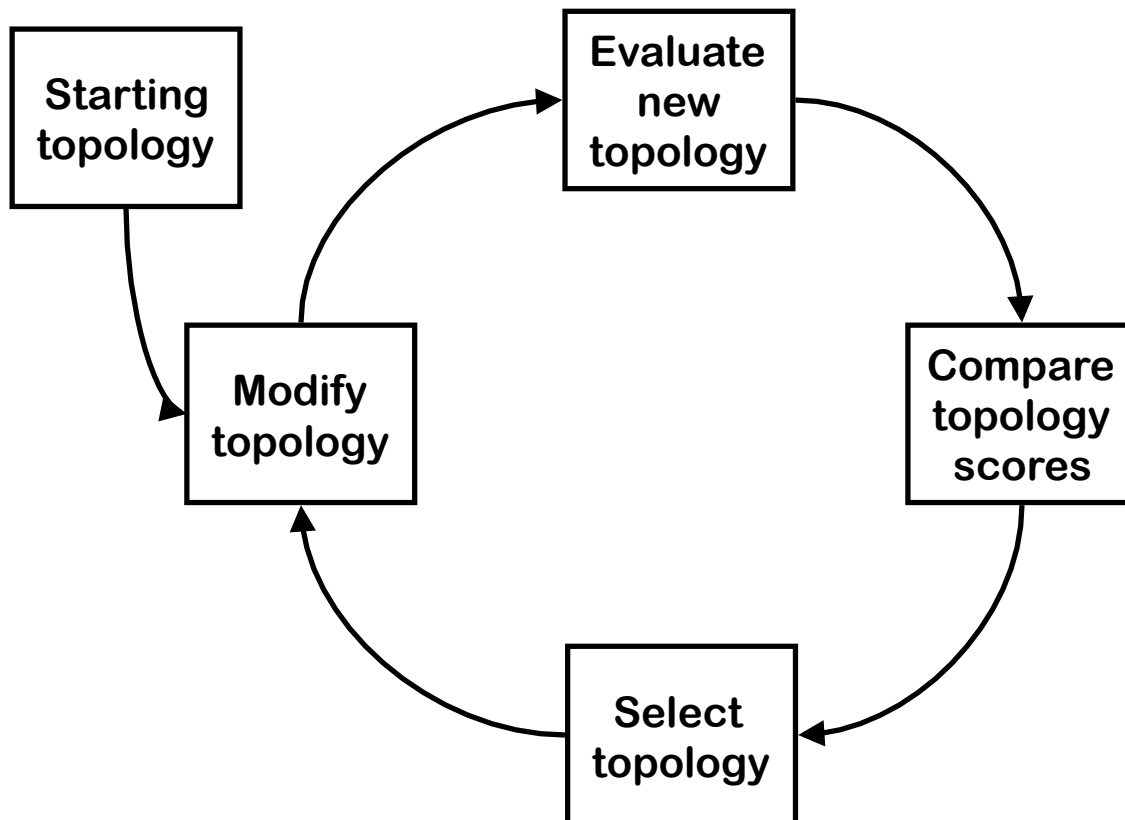
- Fully optimizing even a single branch length can take a lot of computation
- When one parameter changes, optimal values of all others also change

Maximized likelihood: cons

- **As optimization is applied (and applied, and applied, ...), maximized likelihood approached asymptotically**
- **This is the majority of the computation required in ML inference, and it grows quickly as the number of sequences increases**

Heuristic runtimes

$$\text{Inference time} = \text{\# of topologies to evaluate} \times \text{time to evaluate each}$$



Both are strongly a function of the # of sequences when calculating maximized likelihood

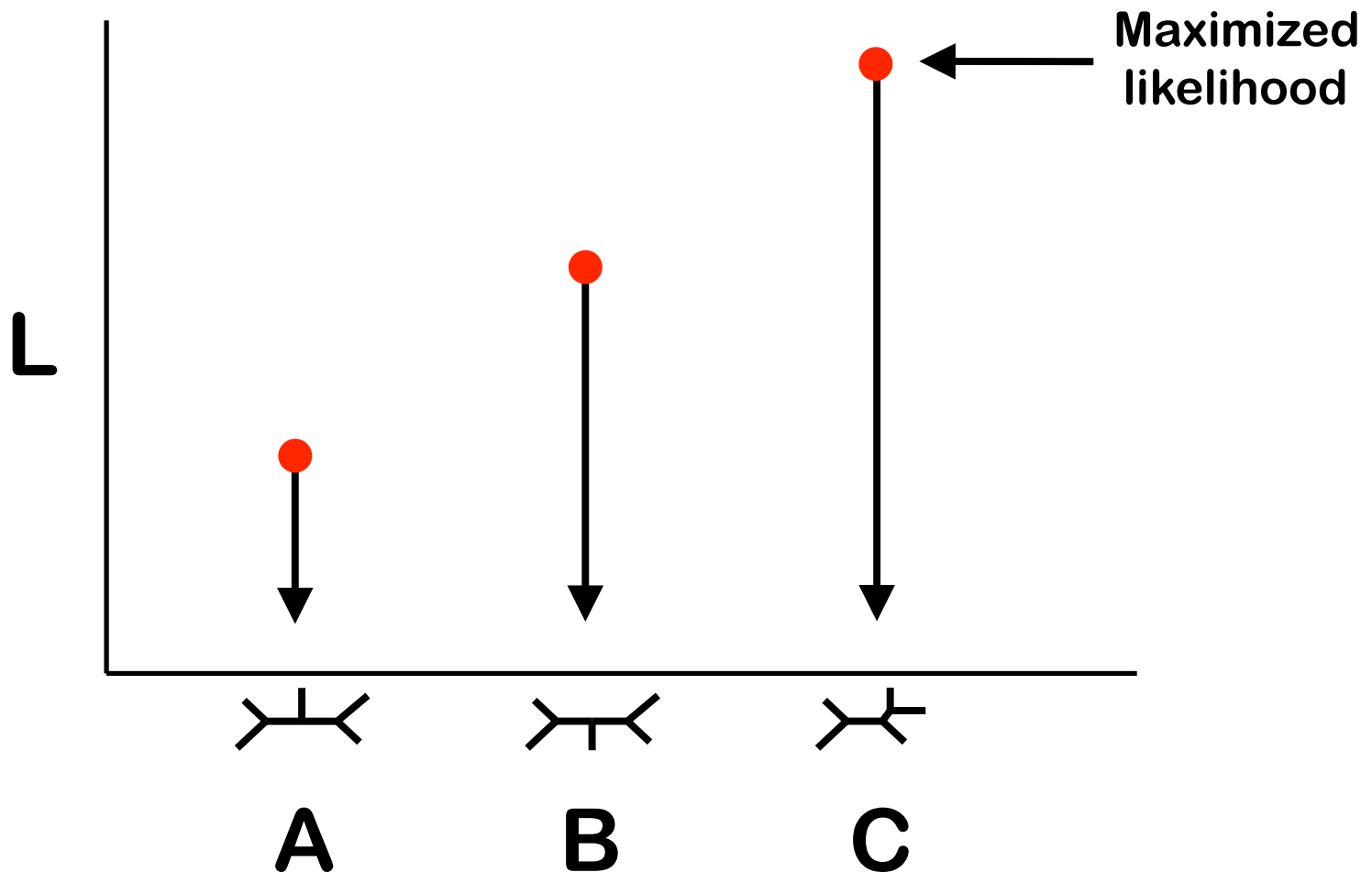
What other options do we have?

- We want to accurately judge the merits of topologies, *as if* we had the maximized likelihood

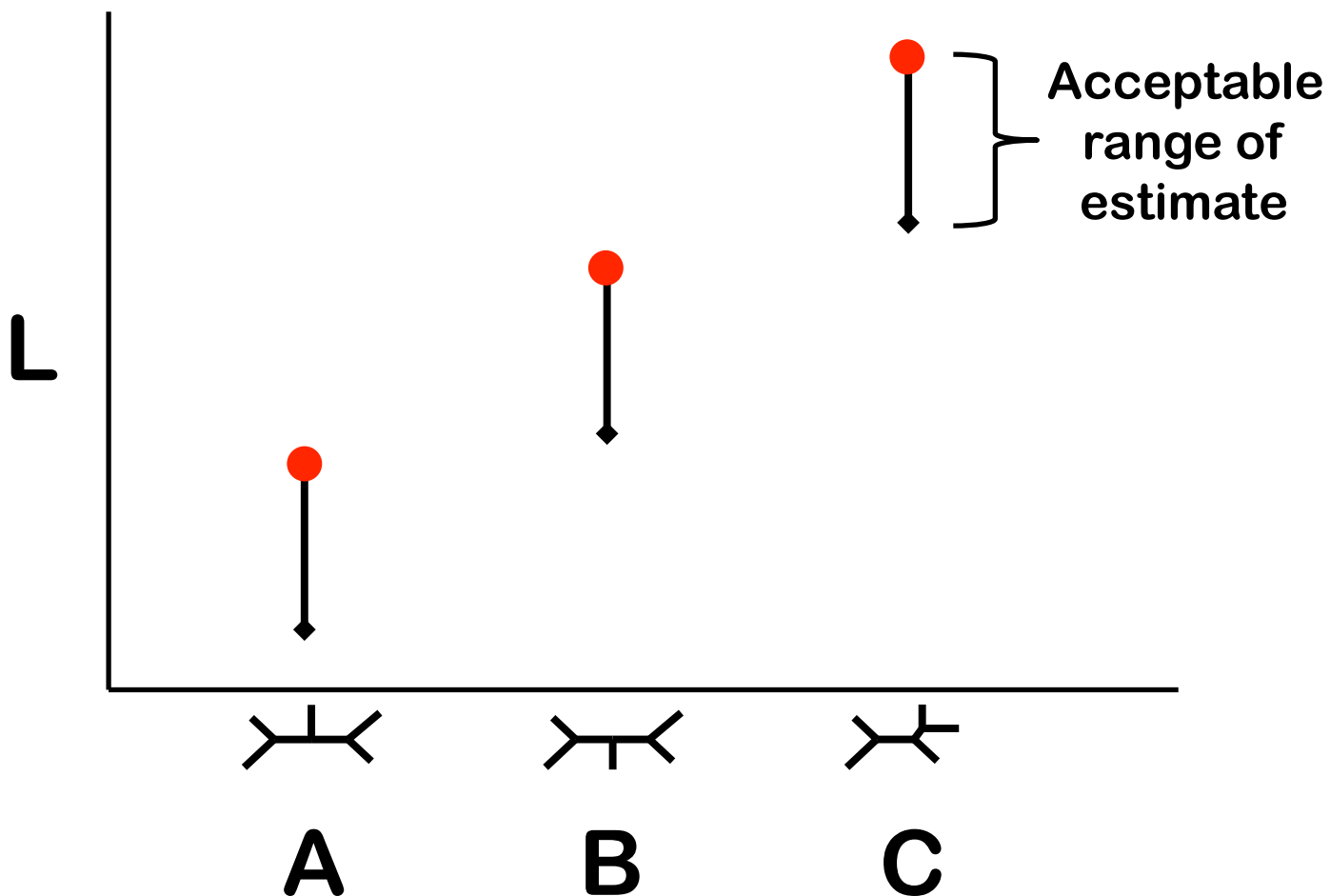
... but without actually calculating it

- We'll explore the idea of an approximate likelihood score for topologies

How accurate does a tree likelihood estimate need to be?

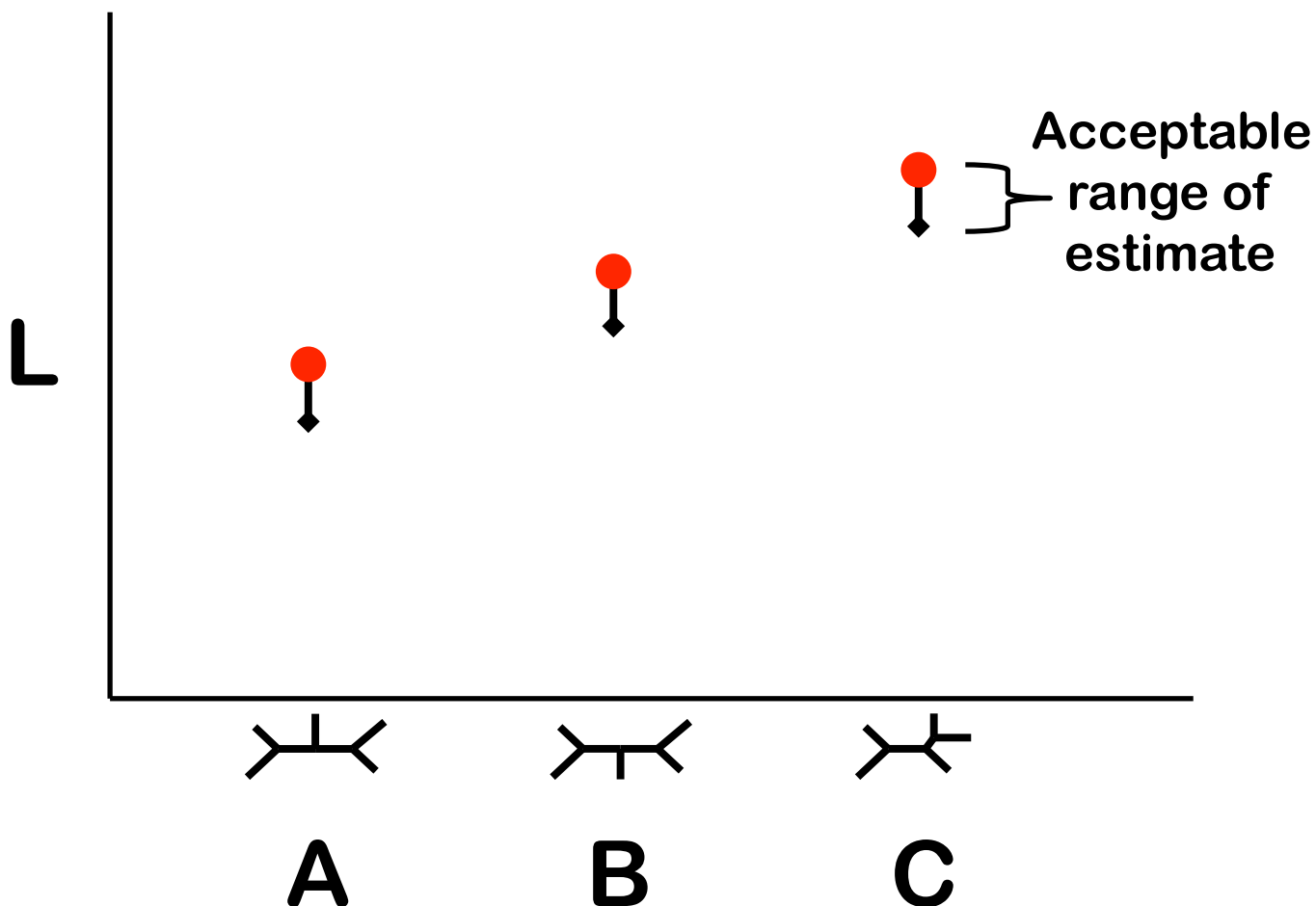


How accurate does a tree likelihood estimate need to be?

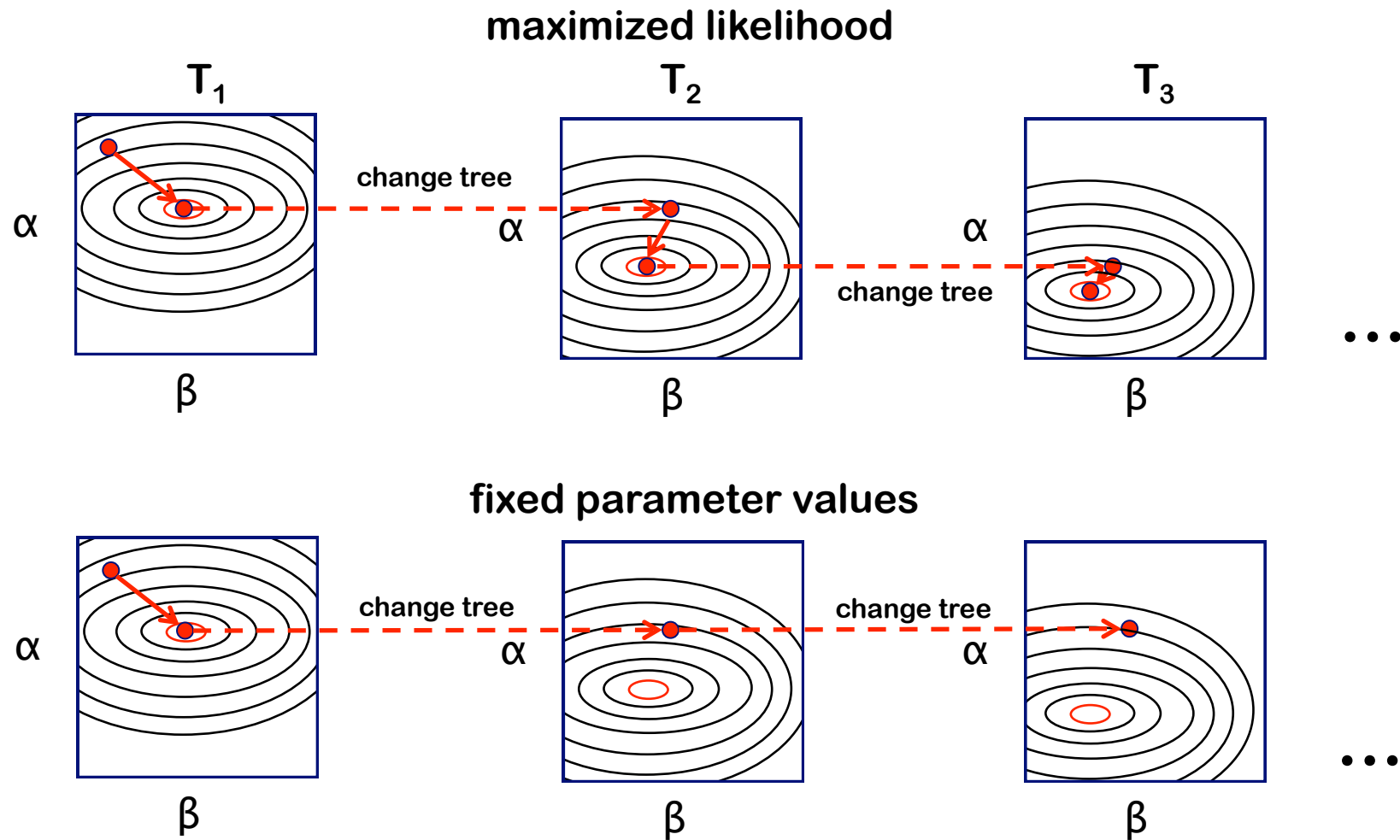


How accurate does a tree likelihood estimate need to be?

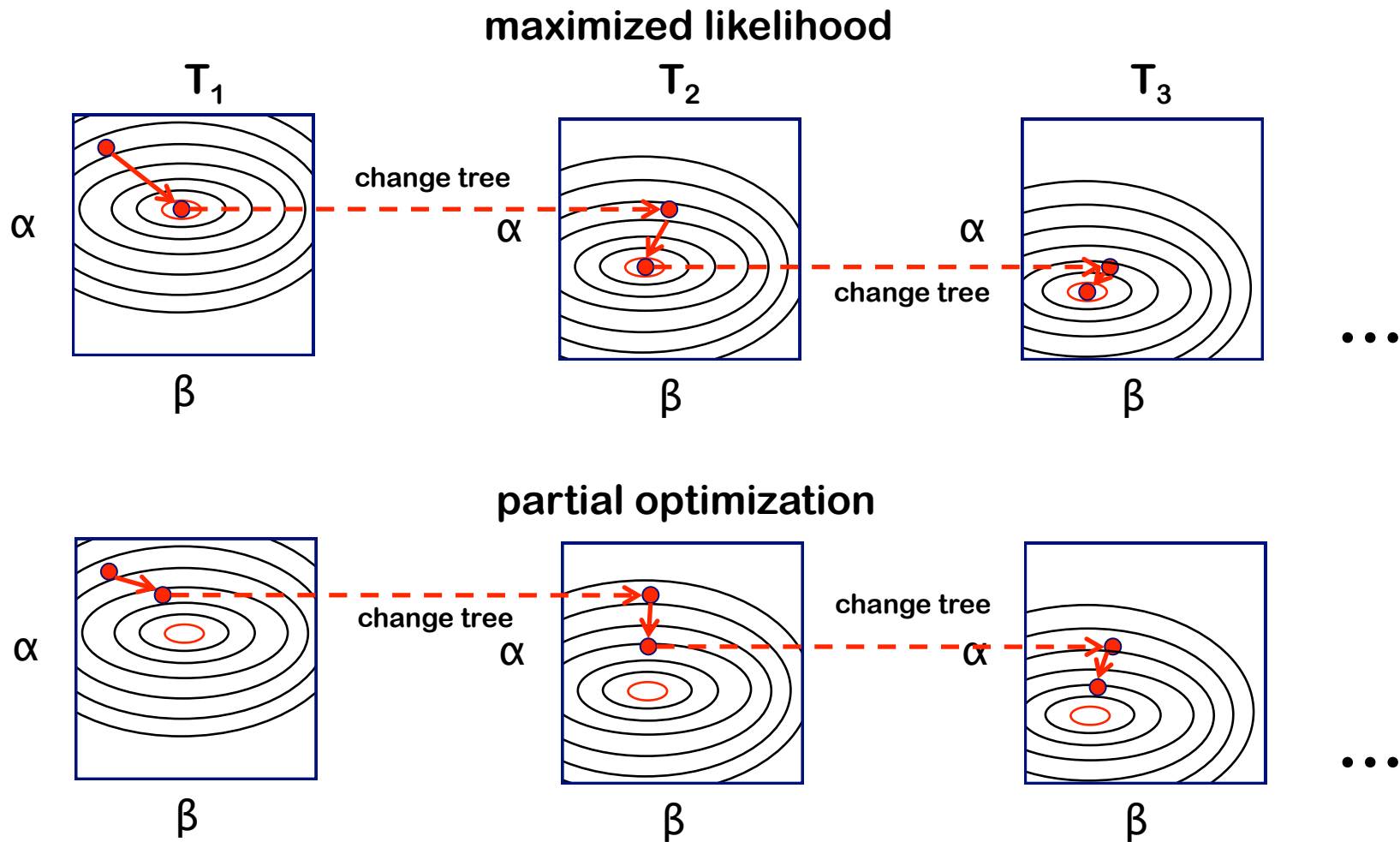
(when tree scores are more similar)



Parameter optima and tree changes

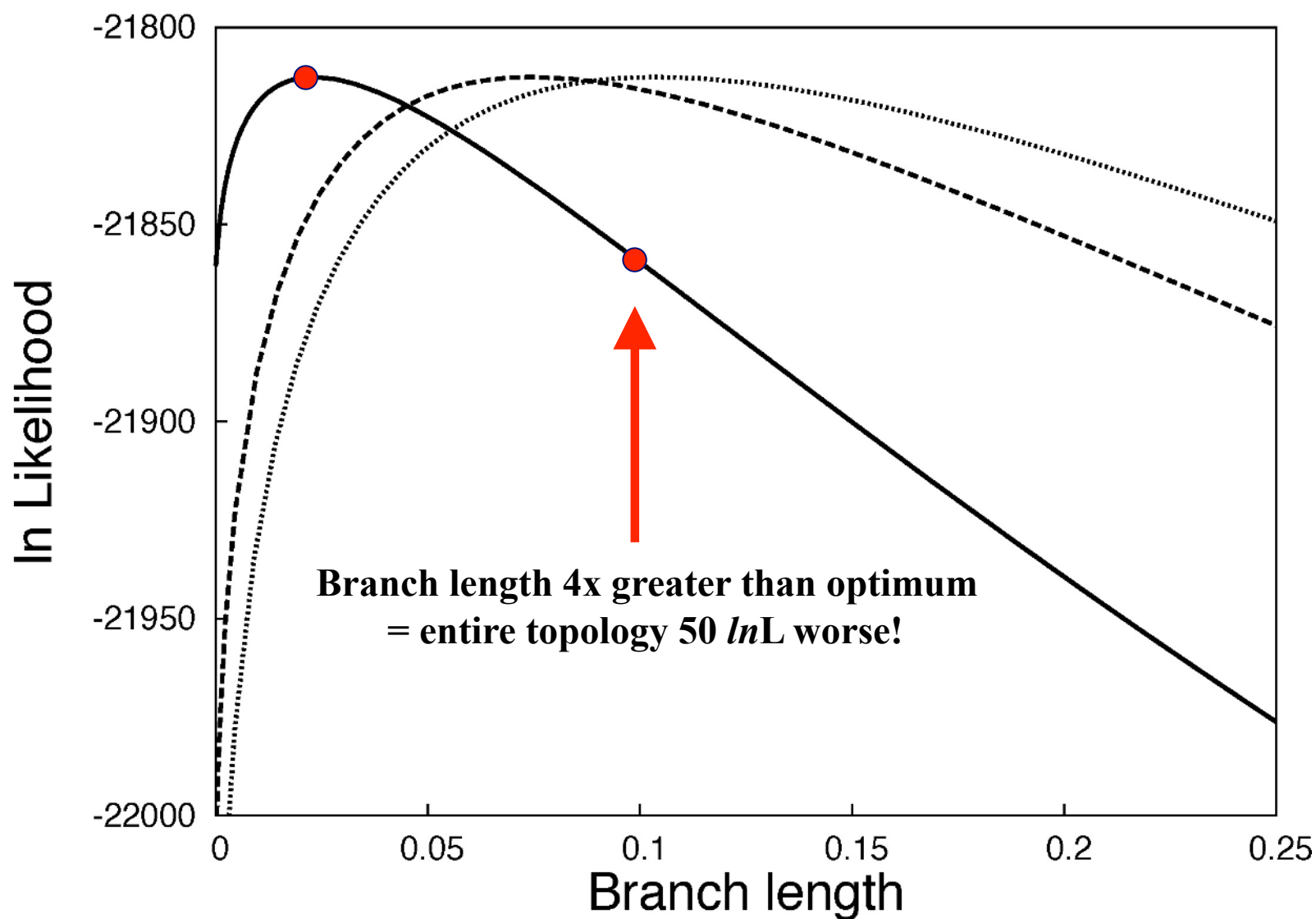


Parameter optima and tree changes



How important are branch-length values?

(three example branches in a specific 64-taxon tree)



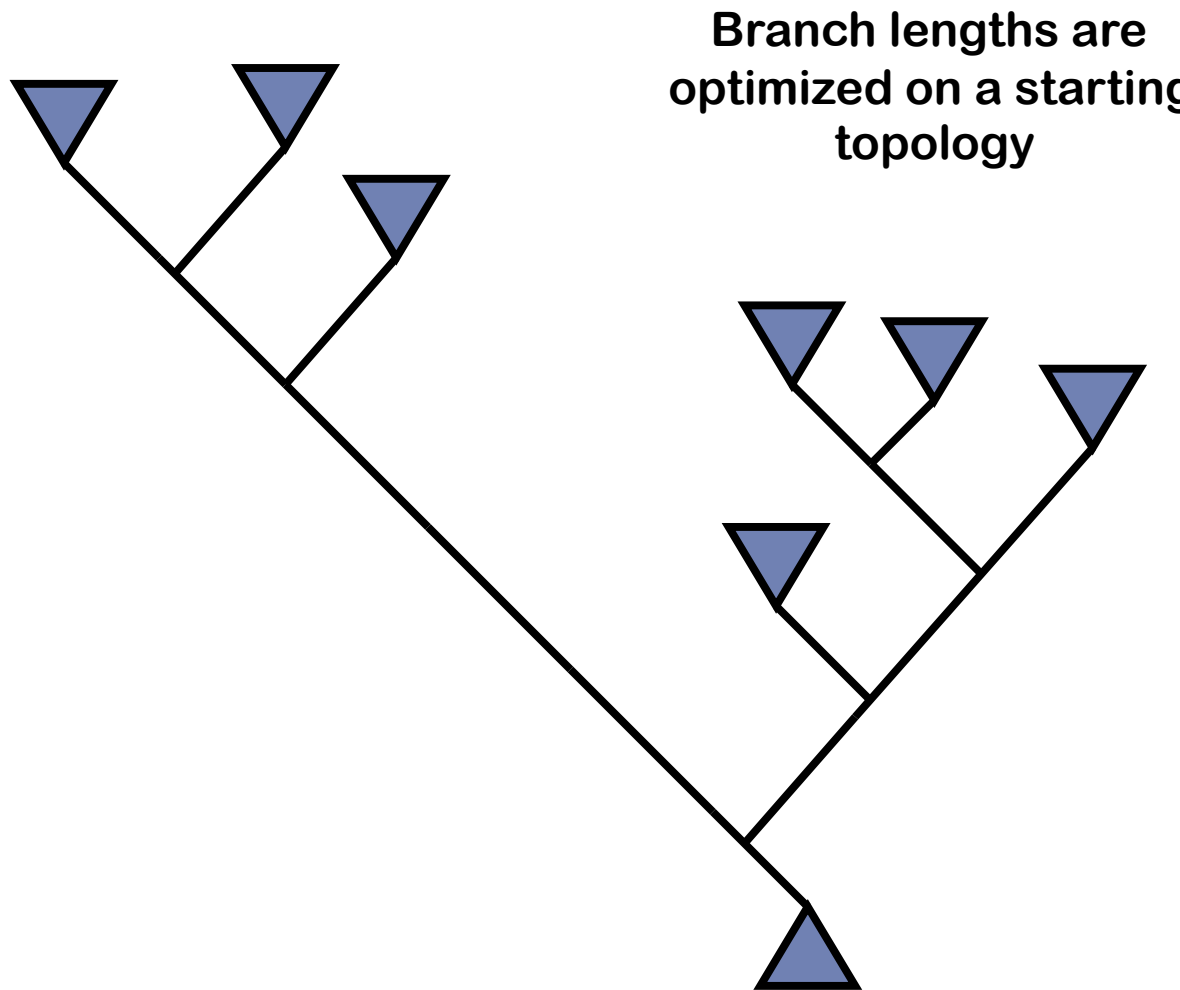
Branch length importance

- **If even one branch length is far from optimal, the estimated likelihood will not be useful**
- **How can we get around optimizing every branch length on every tree?**

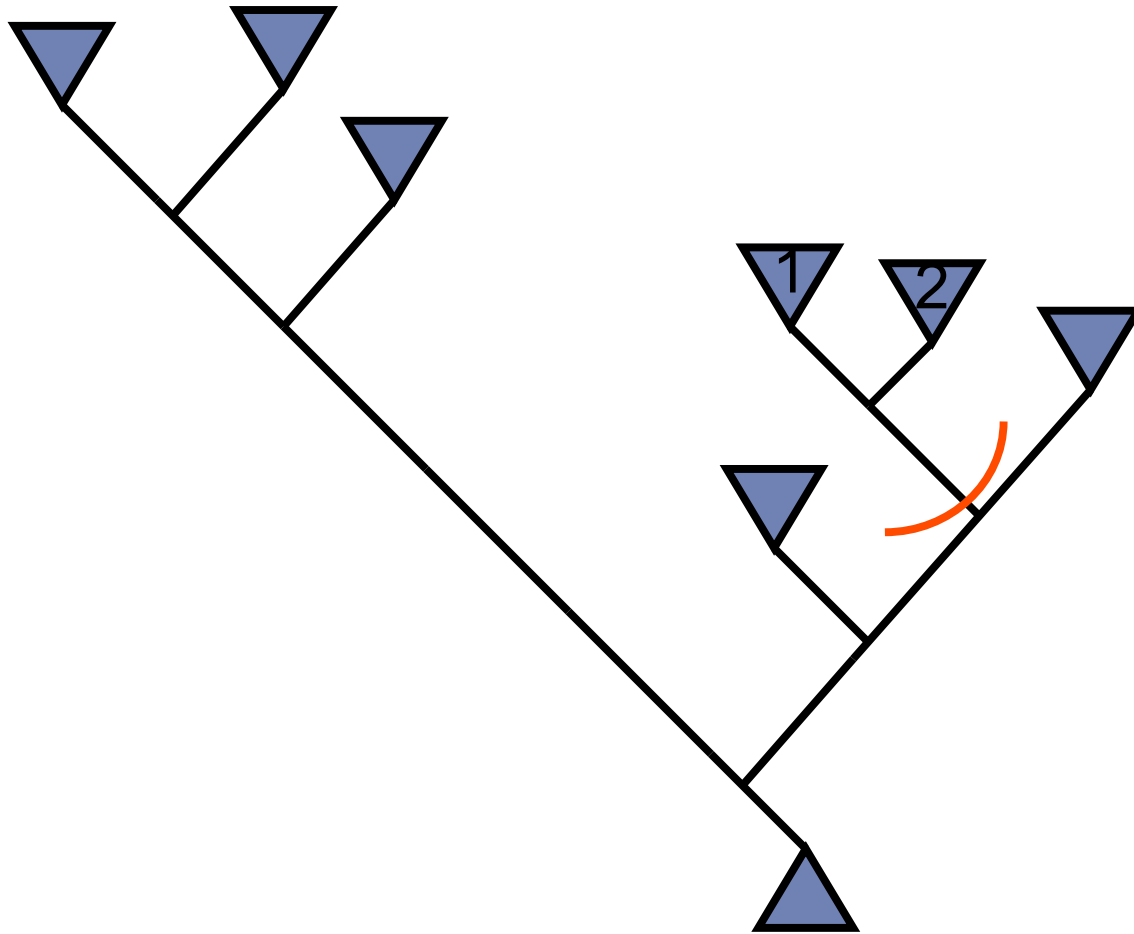
Using topological similarity

- During a tree search we don't compare trees drawn at random
- Trees compared are usually very similar – in fact they are created by slightly modifying an existing tree
- We can capitalize on this when dealing with branch-length parameters

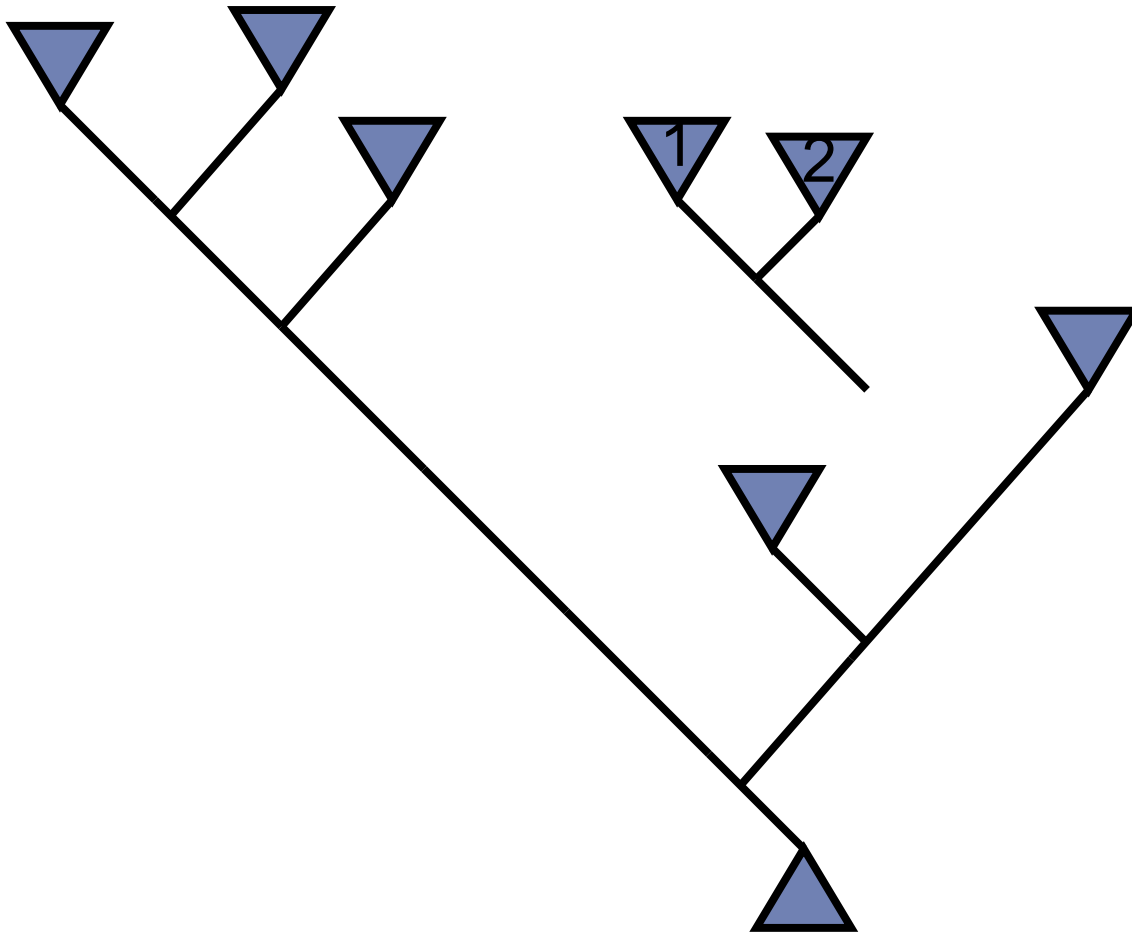
Searching with approximate likelihoods



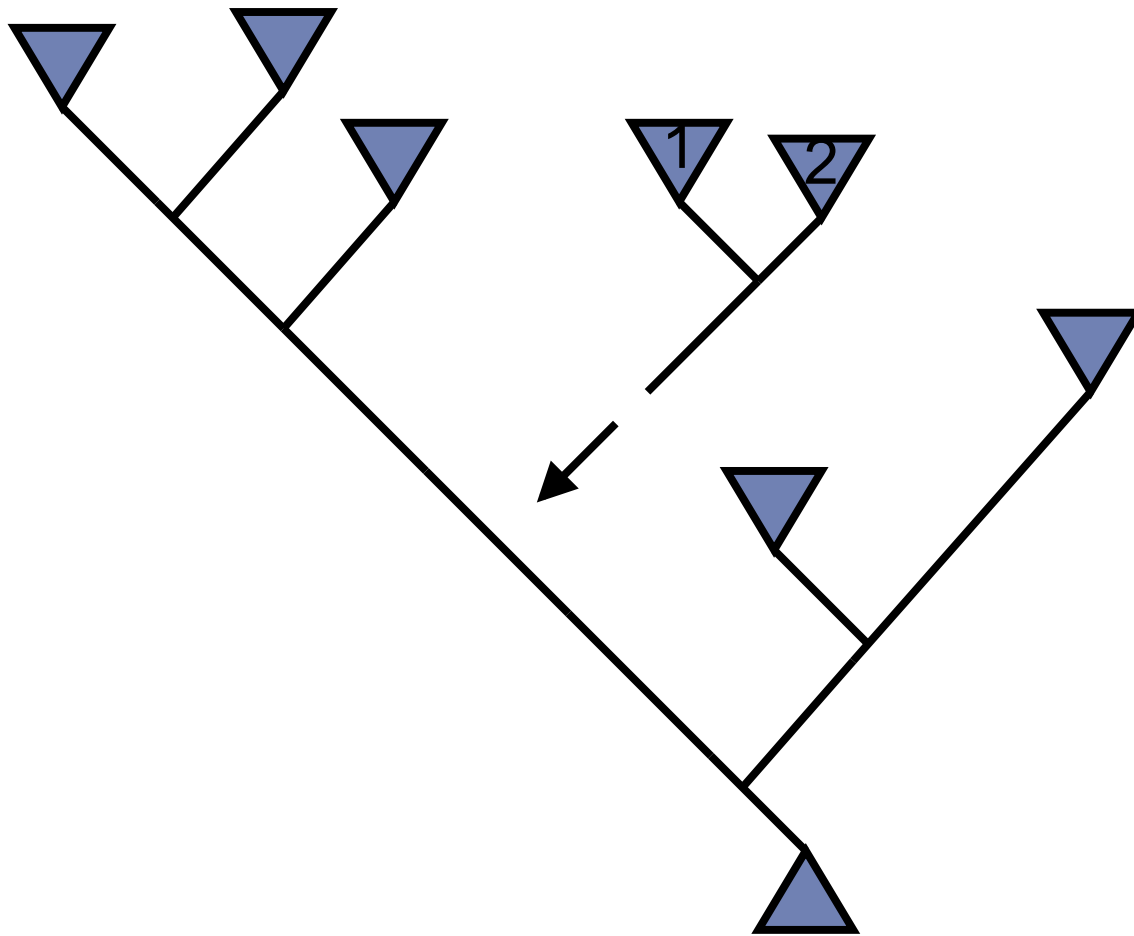
Altering the tree – subtree pruning-regrafting (SPR)



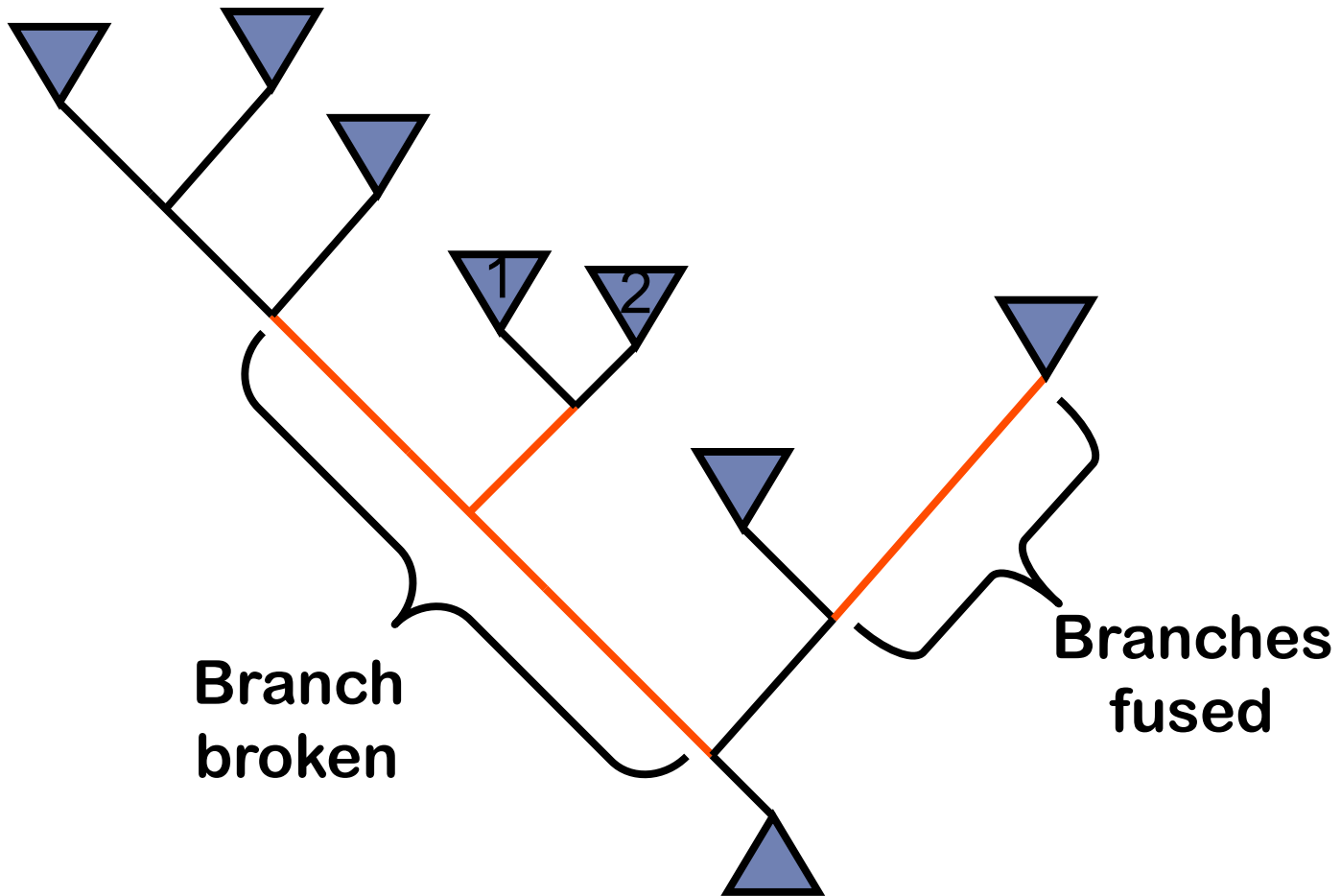
Altering the tree – subtree pruning-regrafting (SPR)



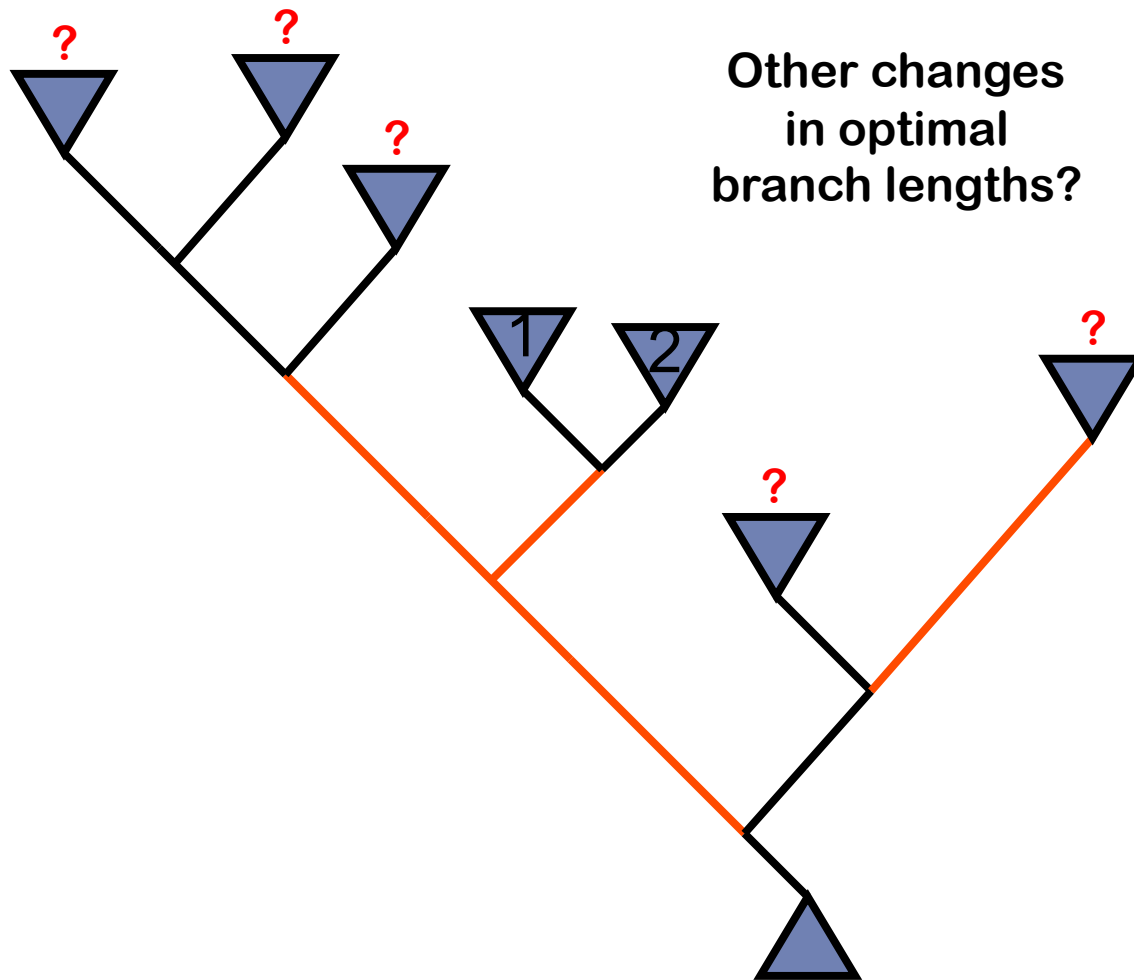
Altering the tree – subtree pruning-regrafting (SPR)



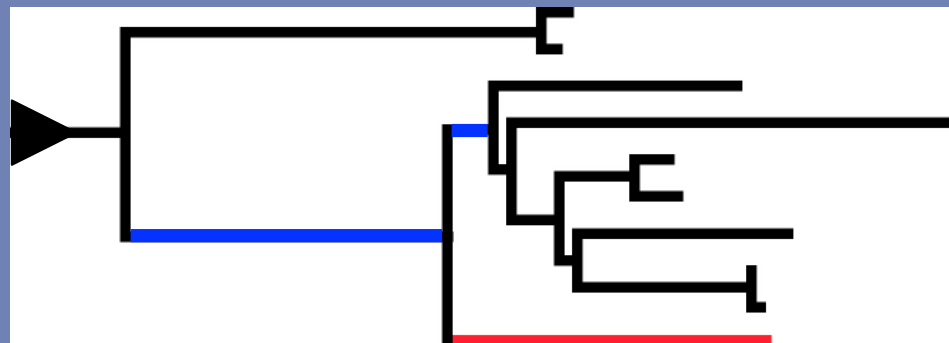
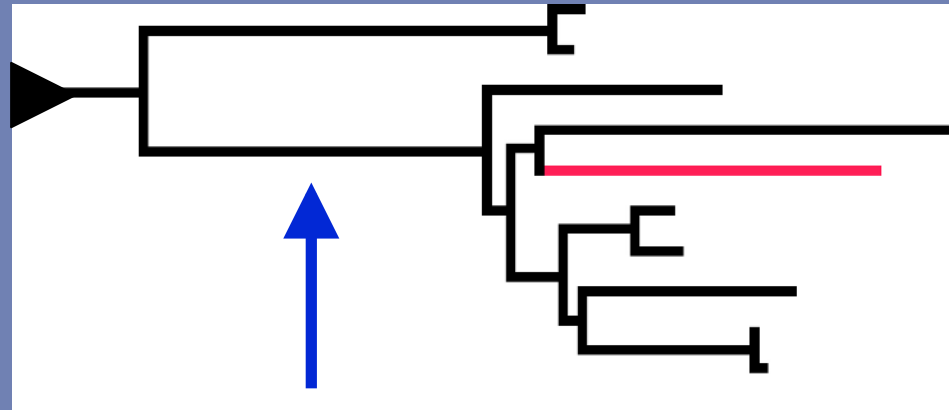
Scoring and optimizing the new topology



Scoring and optimizing the new topology



Where do optimal branch lengths change?



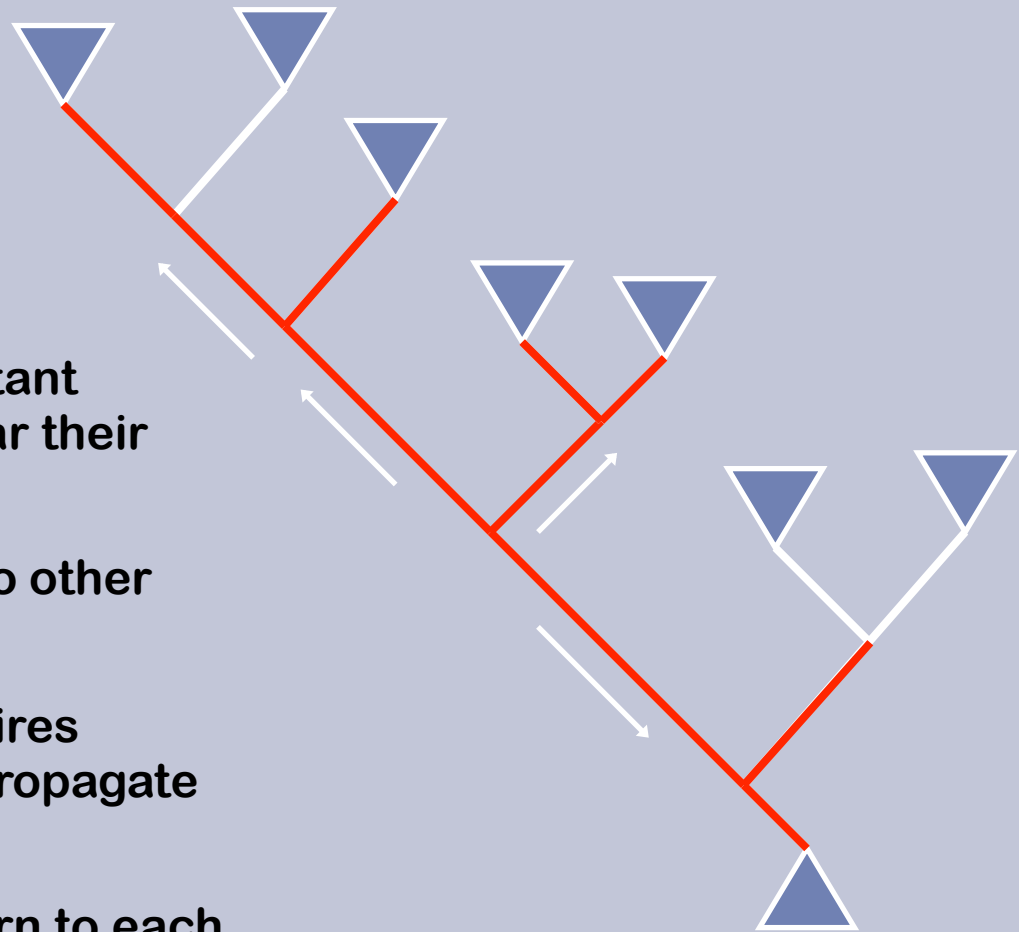




GARLI's post-swap optimization

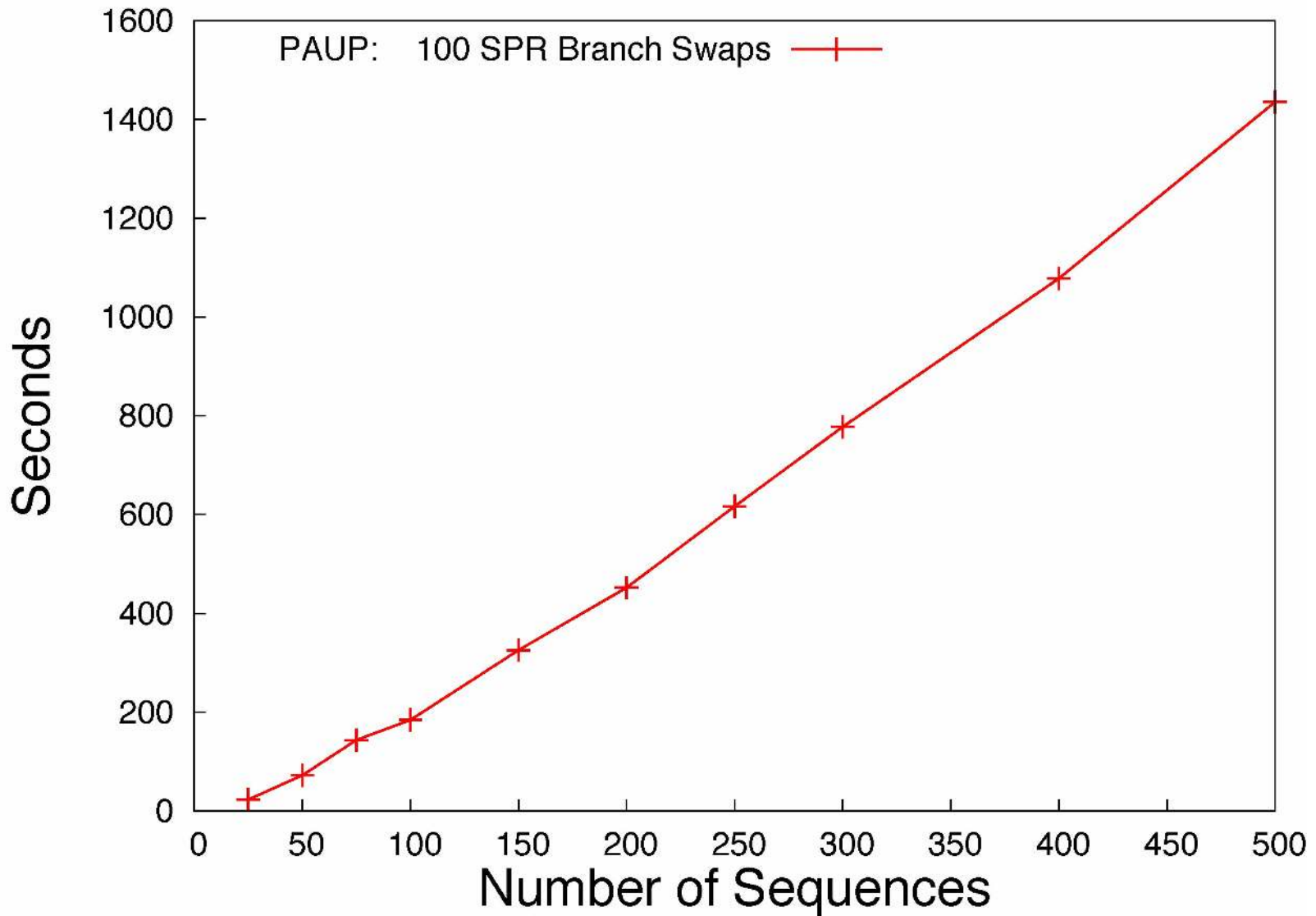
Optimization rules:

1. Optimize the 3 most important branches until they are near their optimal values
2. "Propagate" optimization to other branches outward
3. If a particular branch requires optimization, continue to propagate outward
4. After full propagation, return to each branch that was changed for another optimization pass



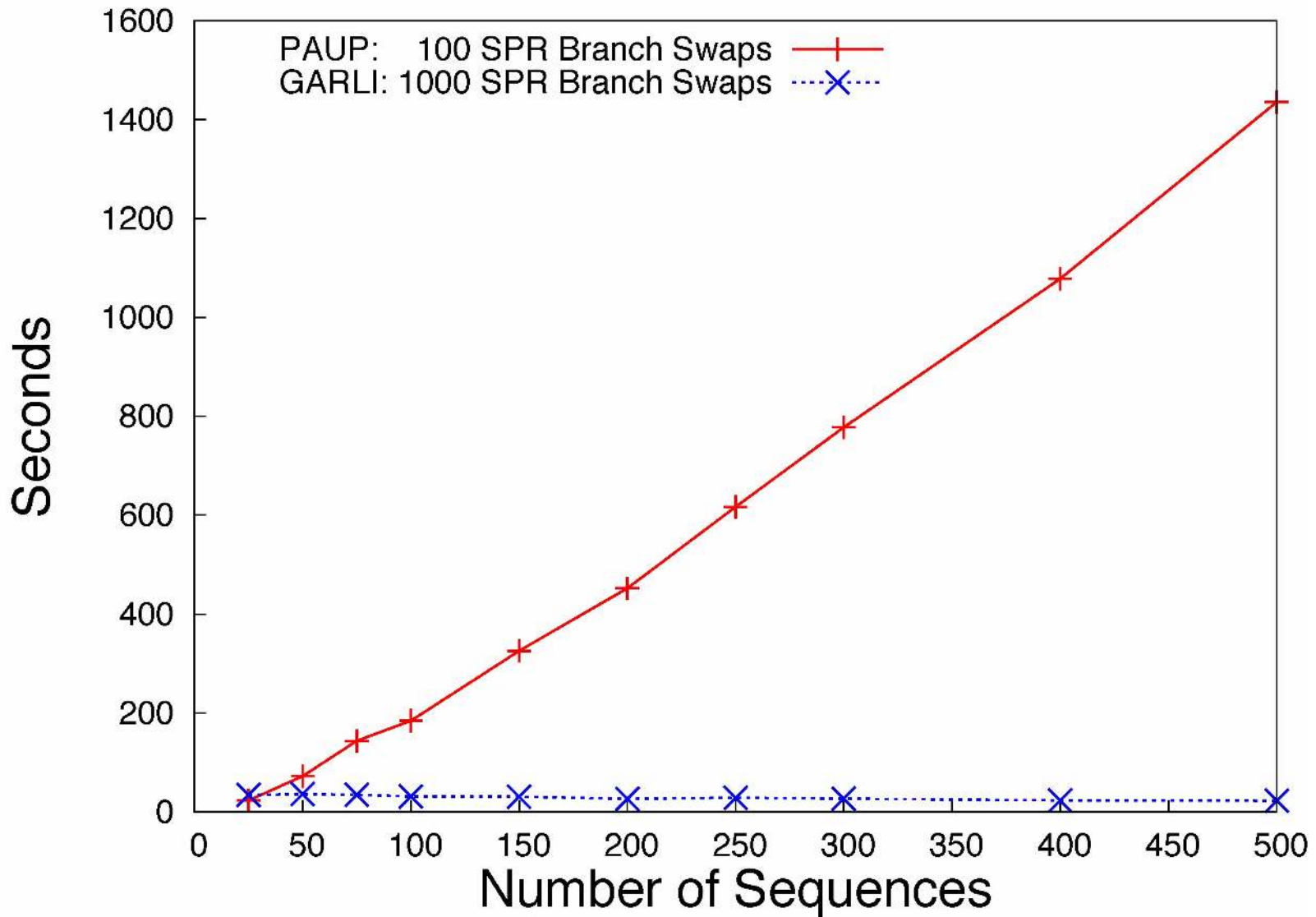
Topology evaluation times

(normalized with respect to # of site patterns)



Topology evaluation times

(normalized with respect to # of site patterns)



Conclusions

- **GARLI's localized method makes branch-length optimization largely independent of the number of sequences**
- **Several other fast ML heuristics also owe part of their speed to localized optimization (PHYML, RAxML)**

What about model parameters?

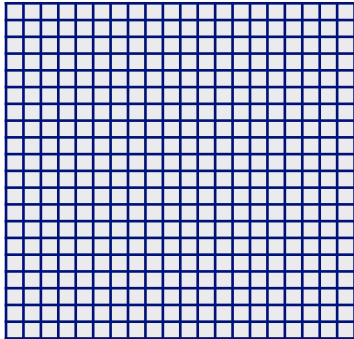
- Also have different optimal values depending on the topology, branch lengths and other parameter values
- Fortunately, strong correlations between optimal model parameter values and topologies are not common
- GARLI also avoids optimizing of the model parameters on each tree

Tree inference at different model levels

Models of sequence evolution



Nucleotide: 4 states

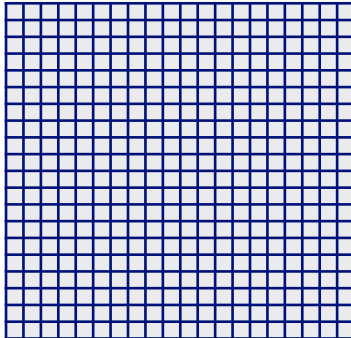


Amino acid (20 states)

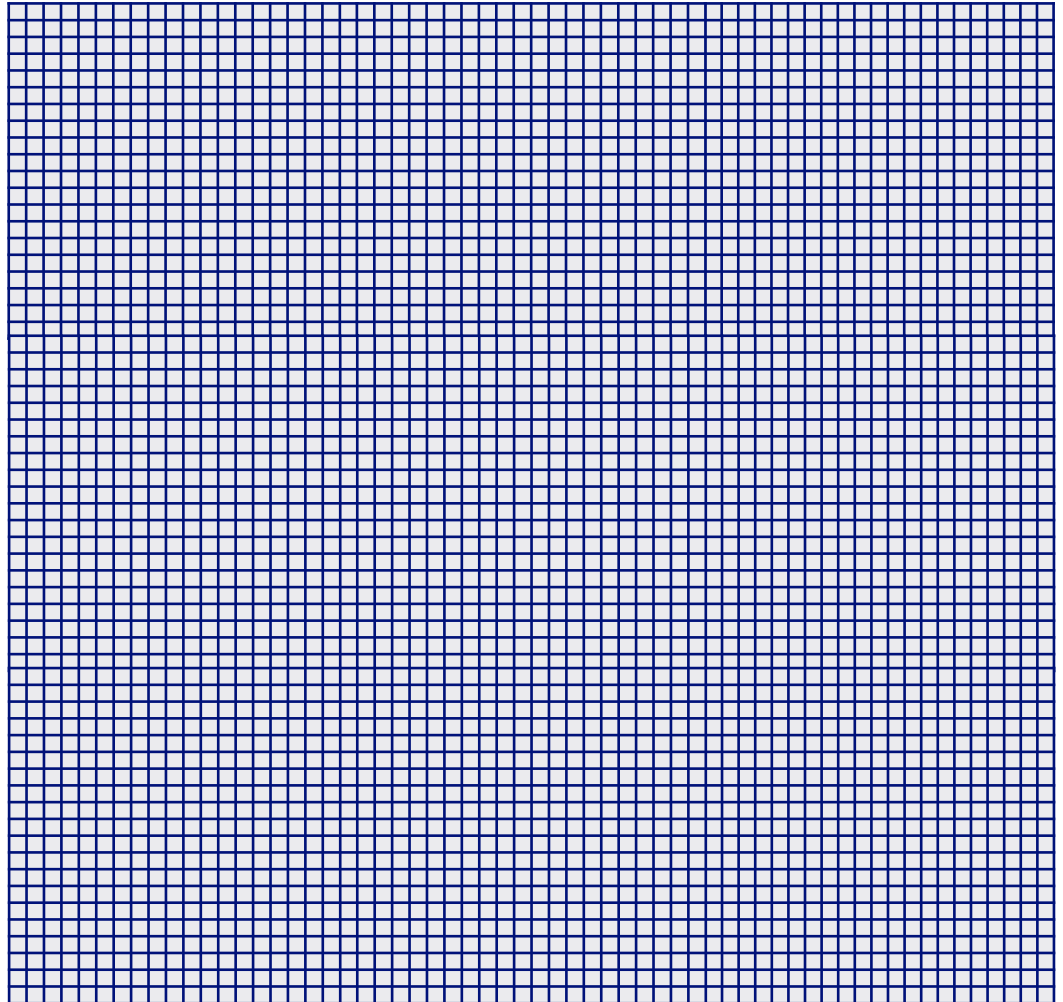
Models of sequence evolution



Nucleotide: 4 states



Amino acid (20 states)



Codon (60-62 states)

Model level pros and cons

- **Nucleotide models**
 - fast and simple
 - use all substitutions
- **Amino acid models**
 - use information from observed AA exchange frequencies
 - ignore synonymous substitutions
- **Codon models (simple ones):**
 - use information from the genetic code
 - deal with non-independence of codon positions
 - computationally difficult

Parameter numbers

- **Note: non-nucleotide models have larger state spaces, but often fewer free parameters**

When can we use codon models for tree inference?

- **Protein coding genes**
- **Aligned on codon boundaries**
- **Known and constant genetic code**
- **Don't need a tree in the next hour**

When should we use codon models for tree inference?

- Mixture of divergent and closely related sequences
- ...?

Example search statistics:

(very divergent 72 taxon x 6288 column alignment)

Average runtimes:

States	Model	Approx Time / Search
Nucleotide	GTR+I+G	23 min
Amino acid	WAG+F+I+G	2 hr 34 min
Codon	GY-1 ω rate	6 hr 32 min
	GY-2 ω rates	12 hr 25 min
	GY-3 ω rates	19 hr 28 min

Example search statistics:

(very divergent 72 taxon x 6288 base alignment)

Average runtimes:

States	Model	Approx Time / Search	Ratio (exp)
Nucleotide	GTR+I+G	23 min	1
Amino acid	WAG+F+I+G	2 hr 34 min	6.8 (8.3)
Codon	GY-1 ω rate	6 hr 32 min	17.2 (19.4)
	GY-2 ω rates	12 hr 25 min	32.7 (38.8)
	GY-3 ω rates	19 hr 28 min	51.7 (58.1)

Example search statistics:

(very divergent 72 taxon x 6288 base alignment)

Average runtimes:

States	Model	Approx Time / Search	Ratio (exp)	Time for 512 bootstraps
Nucleotide	GTR+I+G	23 min	1	8 days
Amino acid	WAG+F+I+G	2 hr 34 min	6.8 (8.3)	1.4 mo.
Codon	GY-1 ω rate	6 hr 32 min	17.2 (19.4)	3.2 mo.
	GY-2 ω rates	12 hr 25 min	32.7 (38.8)	6.6 mo.
	GY-3 ω rates	19 hr 28 min	51.7 (58.1)	12.7 mo.

Example search statistics:

(very divergent 72 taxon x 6288 base alignment)

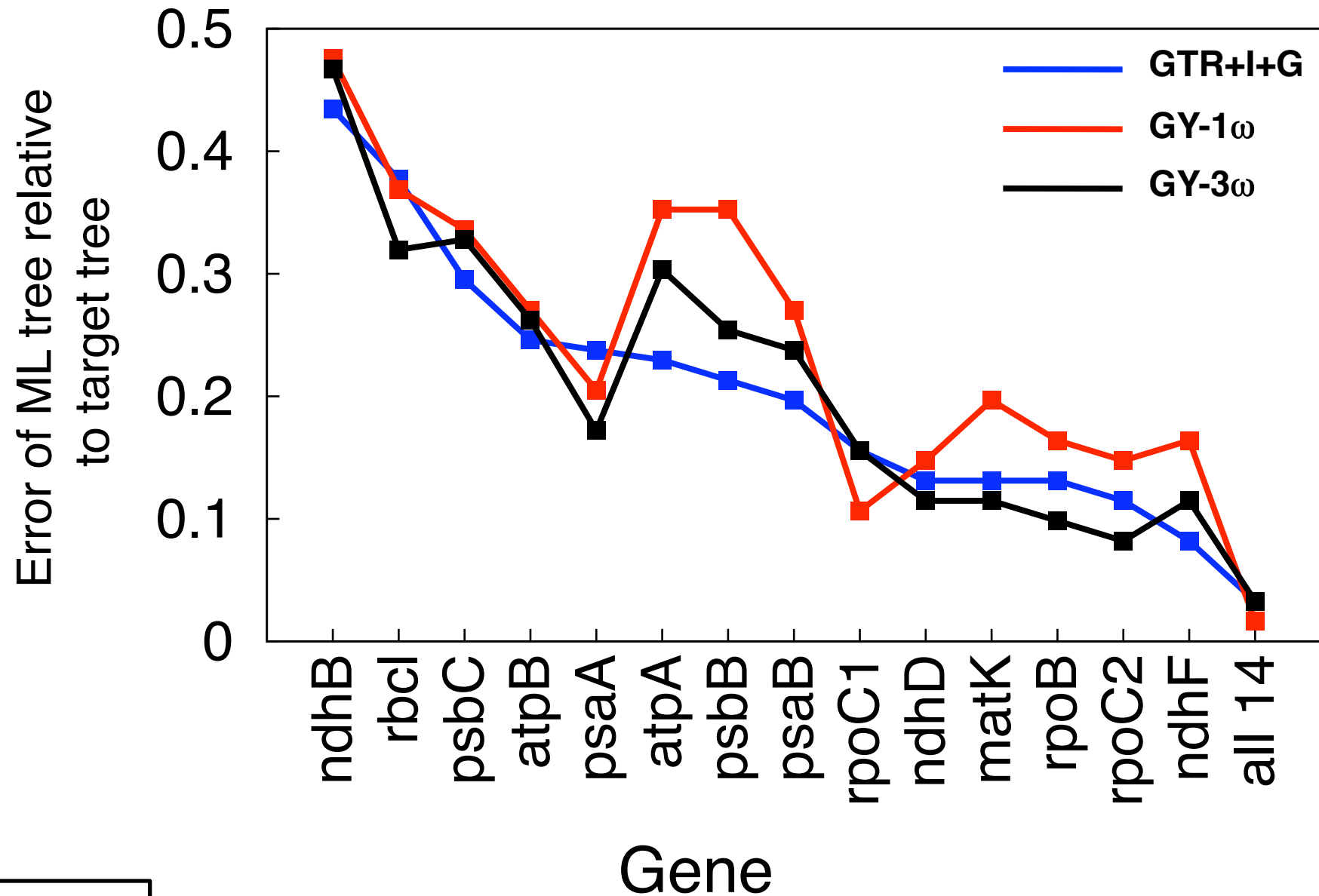
Average runtimes:

States	Model	Approx Time / Search	Ratio (exp)	Time for 512 bootstraps	Minimum memory
Nucleotide	GTR+I+G	23 min	1	8 days	92 MB
Amino acid	WAG+F+I+G	2 hr 34 min	6.8 (8.3)	1.4 mo.	165 MB
Codon	GY-1 ω rate	6 hr 32 min	17.2 (19.4)	3.2 mo.	136 MB
	GY-2 ω rates	12 hr 25 min	32.7 (38.8)	6.6 mo.	271 MB
	GY-3 ω rates	19 hr 28 min	51.7 (58.1)	12.7 mo.	405 MB

Experiment

1. Infer trees at multiple model levels using full mitochondrial or chloroplast genomes
2. Infer trees for individual genes at each model level
3. Compare gene trees to genome trees as some proxy for inferential power, accuracy or repeatability

Individual gene analyses (shallow divergence)



Conclusions

- My (limited) empirical results don't suggest a large accuracy advantage to using codon models (simulations may disagree)
- Ignoring ω rate variation across codons can be detrimental to phylogenetic accuracy (inappropriate codon models can do *worse* than nucleotide)

Conclusions

- Although nucleotide and amino acid models each perform well at certain levels of divergence, codon models do fairly well across the board
- Many improvements to codon models are possible, and are likely to increase their utility for tree inference

Using gap characters

- GARLI implements two models appropriate for use on gaps (not fully available yet)
- DIMM model based on Rivas and Eddy (2008)
 - Real model of insertion-deletion process
 - Non-reversible, dollo (one insert, multiple delete)
- Variant of Mk_v (Lewis, 2001) model (no full gap columns)
 - Allows many gap-base transitions

Fixed alignment analysis options

gapped alignment

Taxon \ Character	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000
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[illegible]

**ignore gaps, e.g. GTR
(the usual)**

Fixed alignment analysis options

gapped alignment

Taxon \ Character	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000
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5-state approach (e.g., Rivas and Eddy)

[illegible]

**ignore gaps, e.g. GTR
(the usual)**

Fixed alignment analysis options

gapped alignment

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5-state approach (e.g., Rivas and Eddy)

[illegible]

**ignore gaps, e.g. GTR
(the usual)**



**“gapcode”
matrix
&
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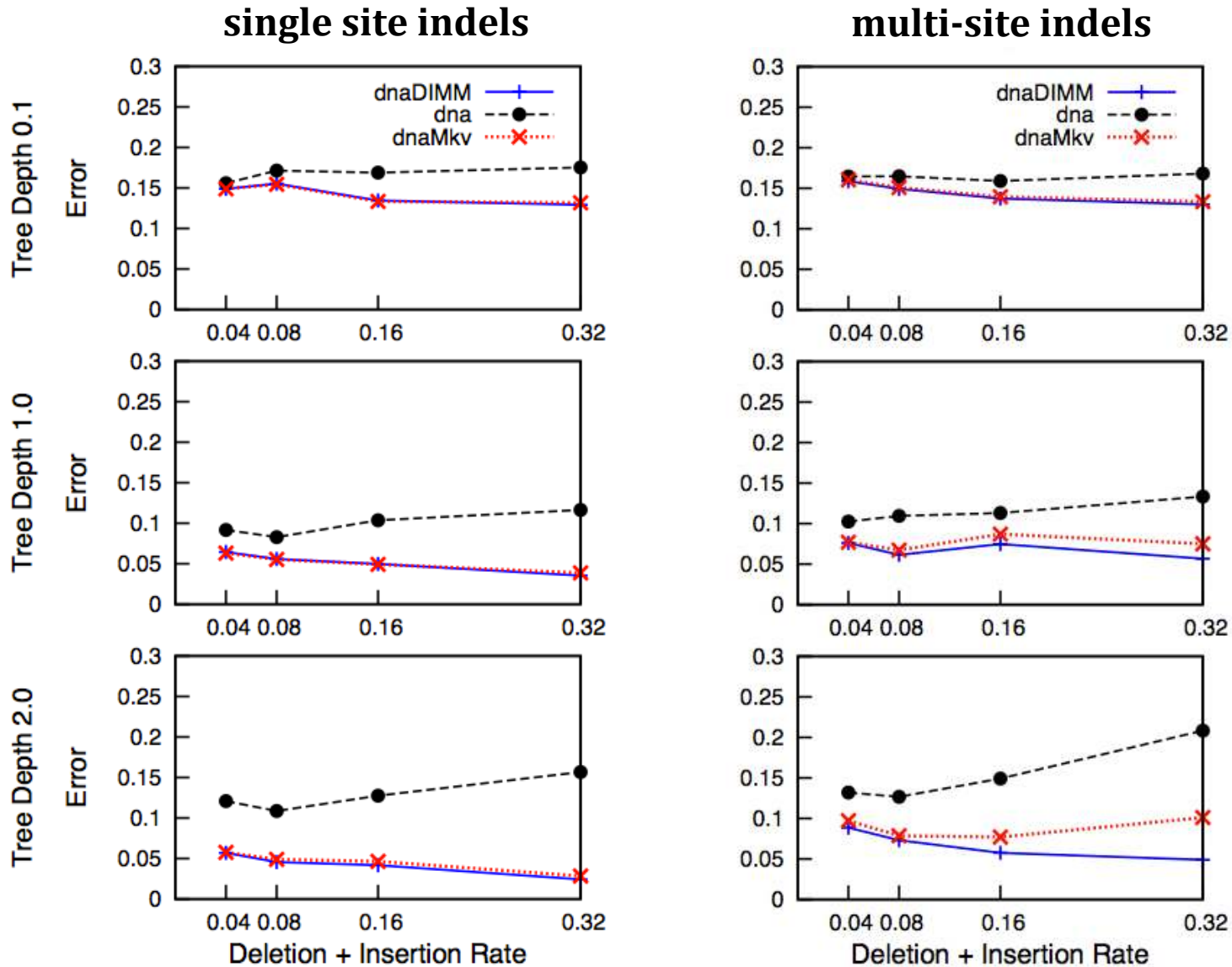
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Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Accession	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62																																						

[illegible]

DIMM
(or Mk_v)

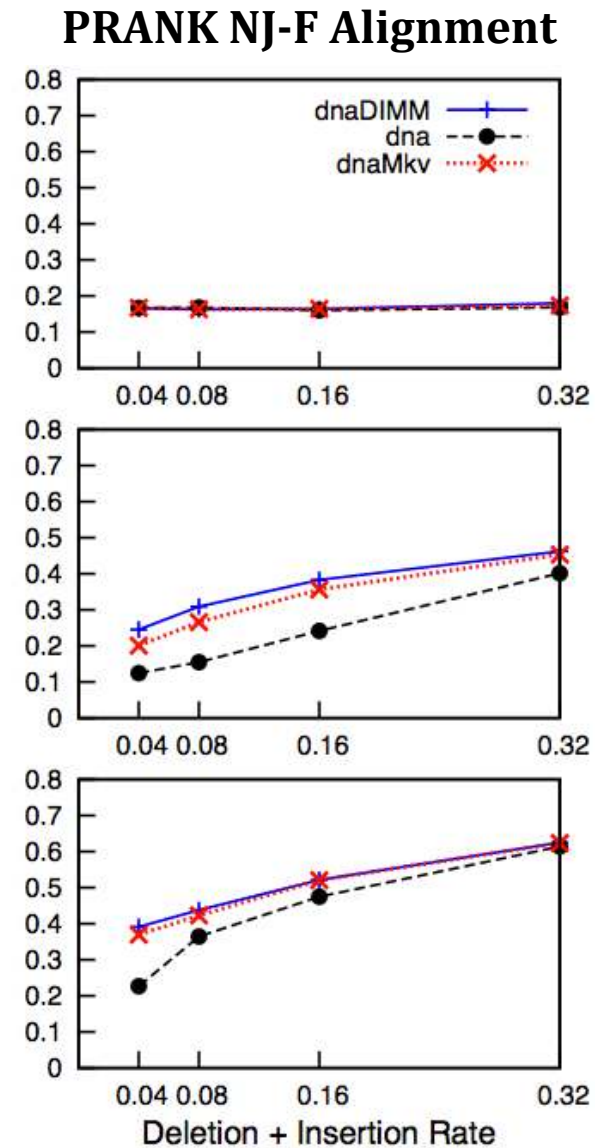
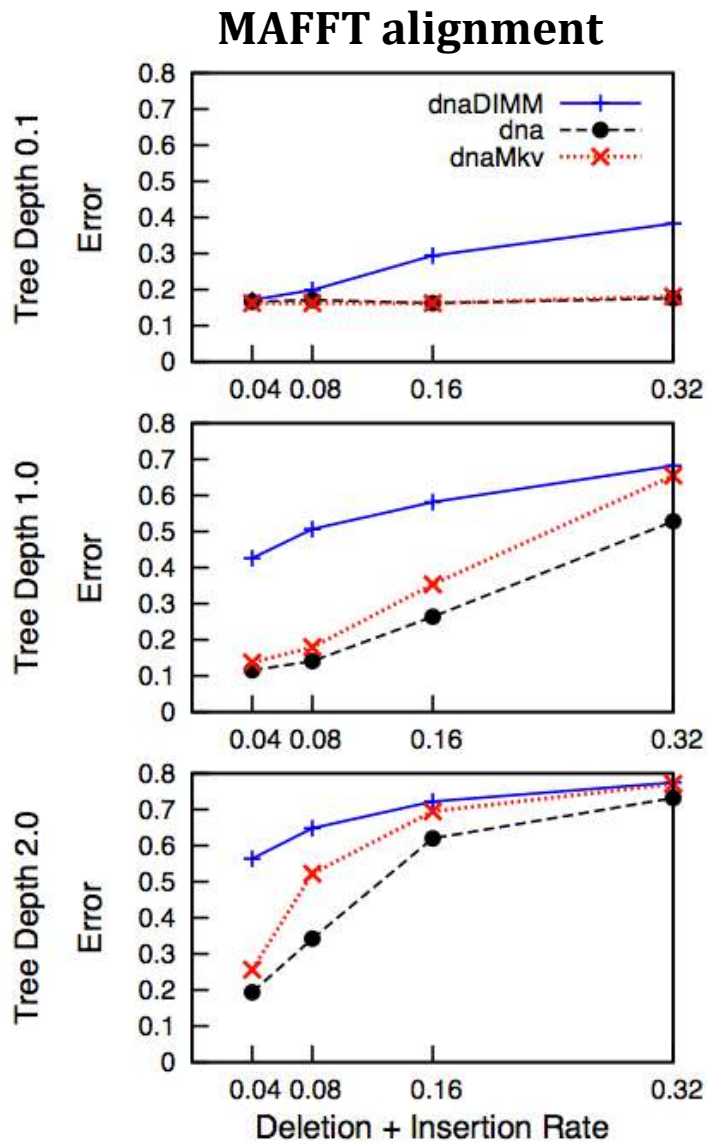
Gap model accuracy – 64 taxa, true alignments

deeper trees
↓



higher indel rates
→

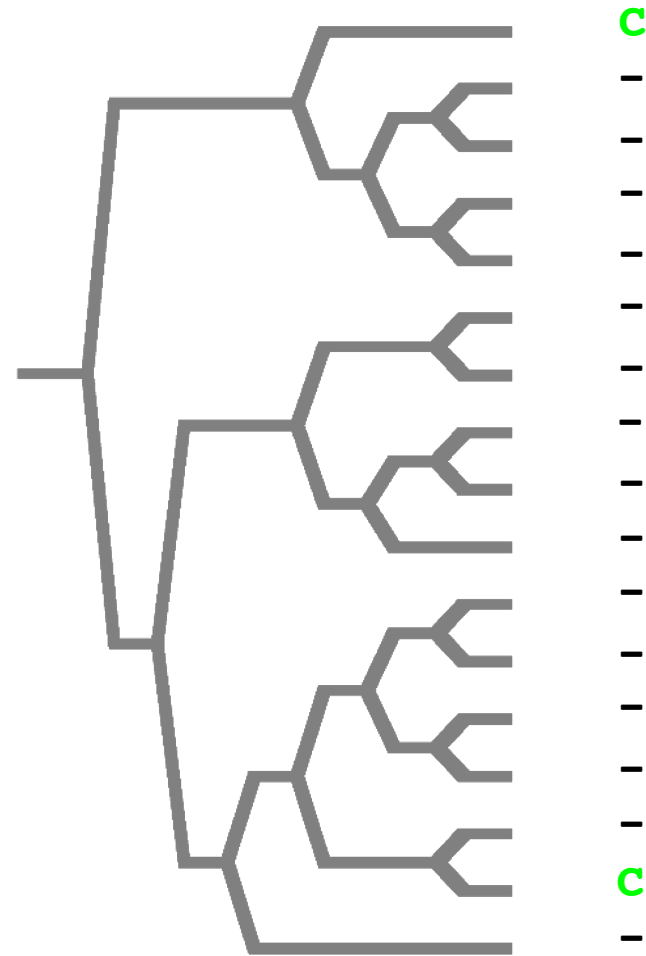
Gap model accuracy – 64 taxa, estimated alignments



Part of the problem: innocuous alignment errors

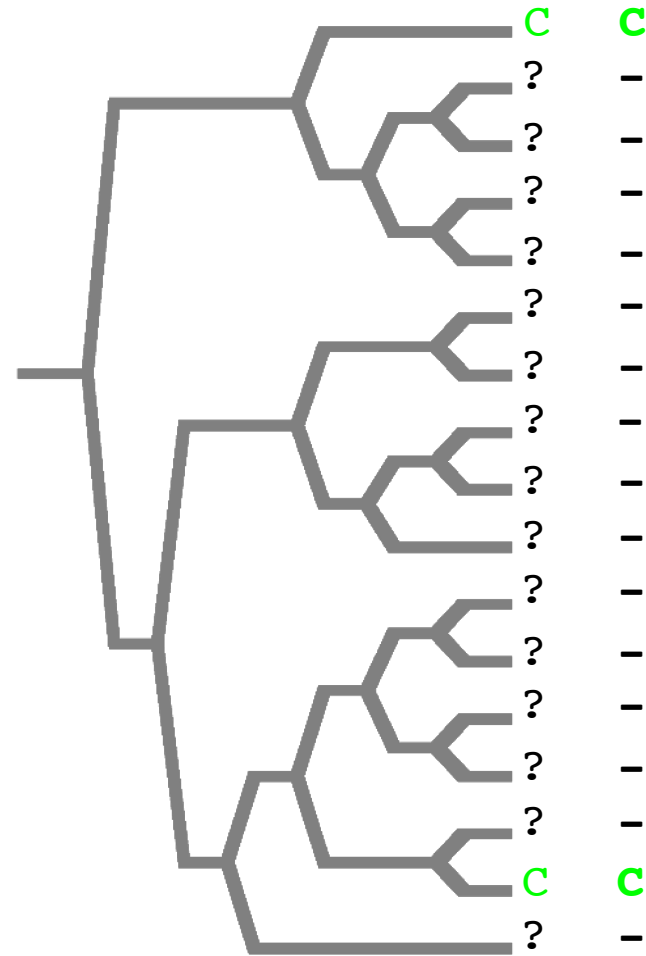
[illegible]

Innocuous alignment errors?



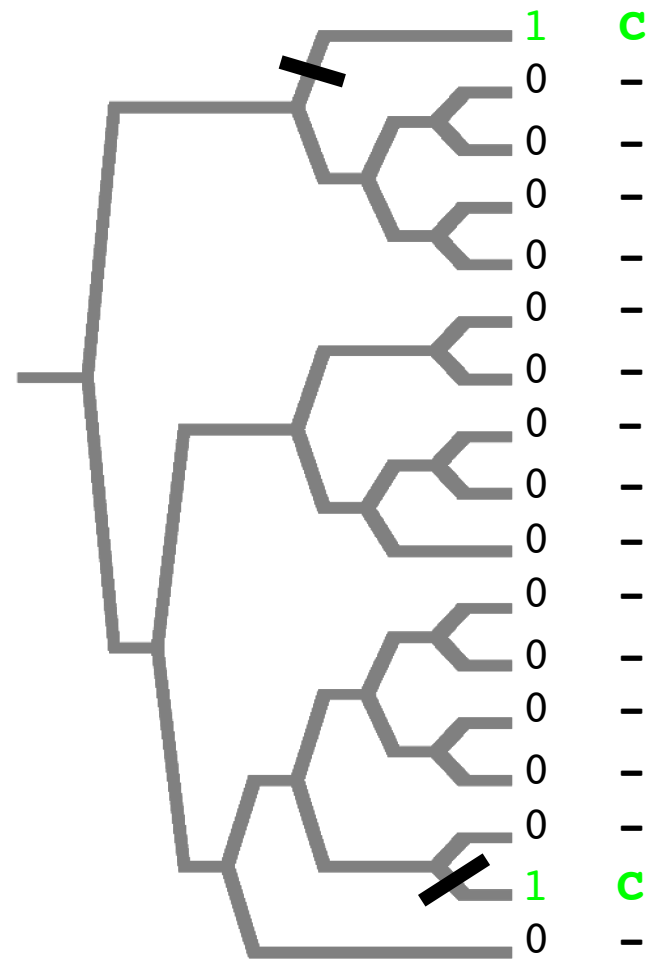
Innocuous alignment errors?

- GTR – no events, little effect



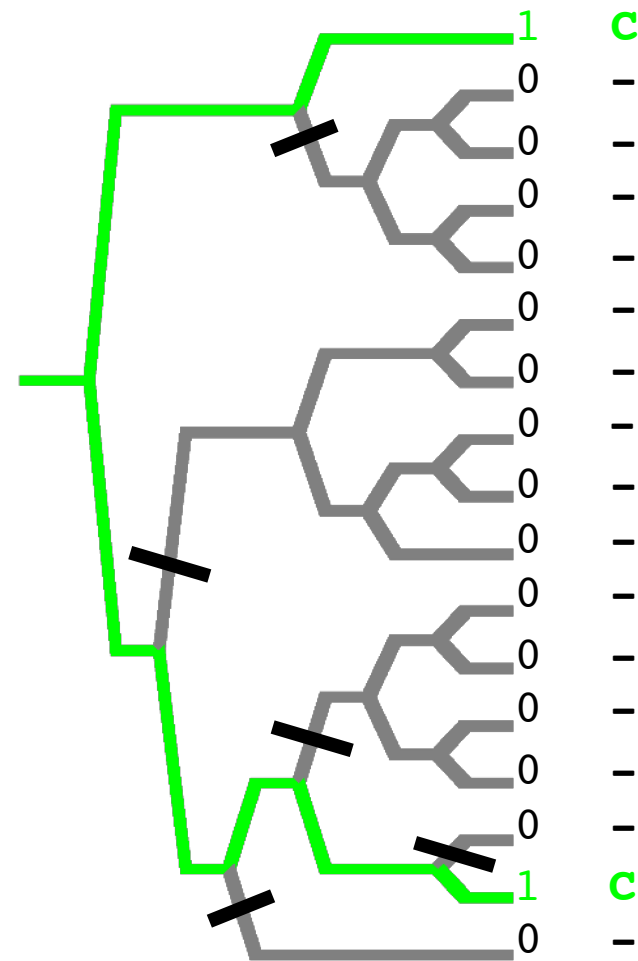
Innocuous alignment errors?

- GTR – no events, little effect
- Mk_v – 2 events, moderate effect



Innocuous alignment errors?

- GTR – no events, little effect
- Mk_v – 2 events, moderate effect
- DIMM – 5 deletions! strong effect (Dependent on tree size!!)



Conclusions

- Insertion deletion events can provide useful phylogenetic signal if properly modeled
- BUT, without correct column homology they can do more evil than good

Using GARLI in practice

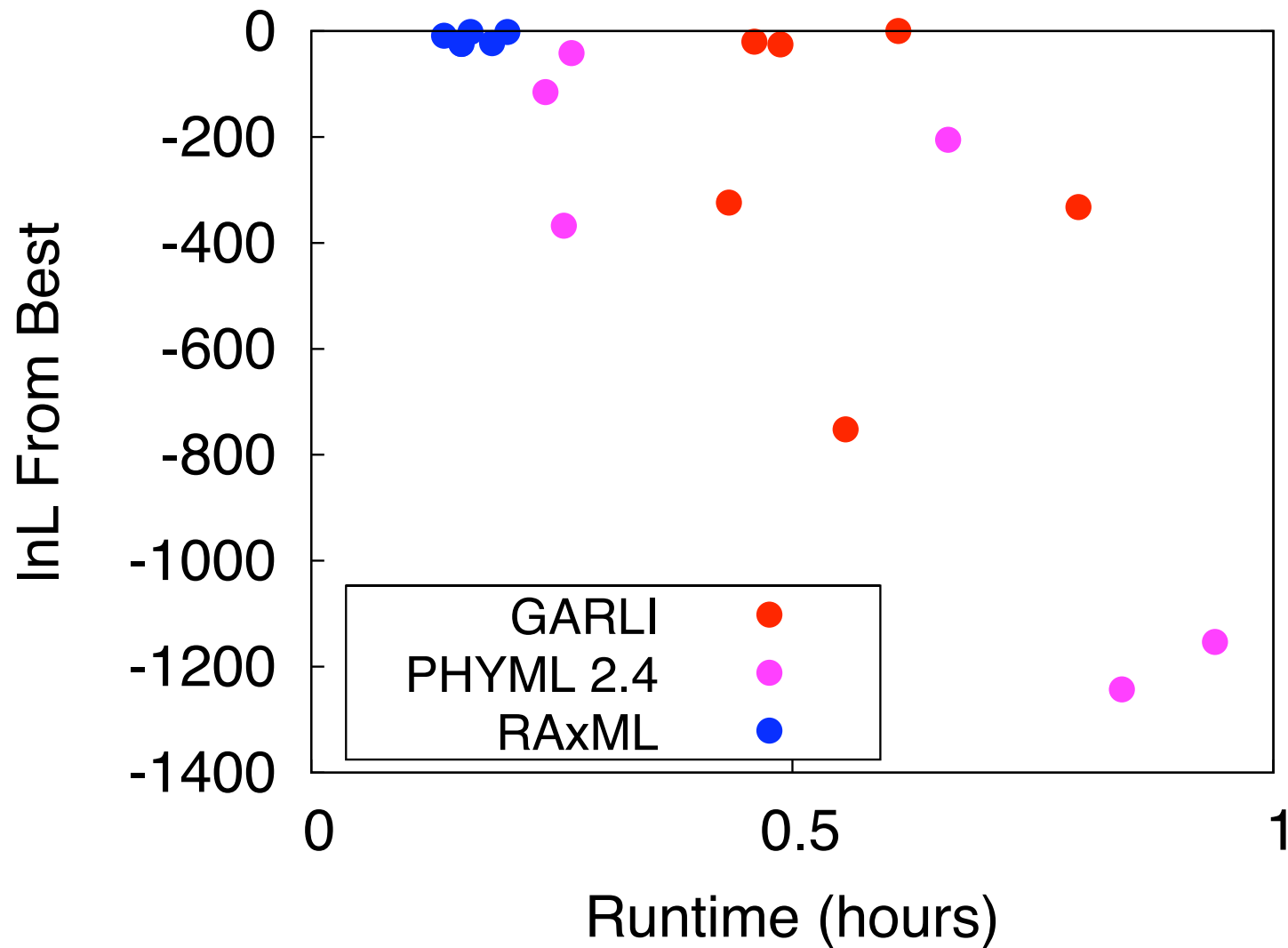
Using GARLI in practice

- Performance comparisons
- Allowed models
- Search strategies

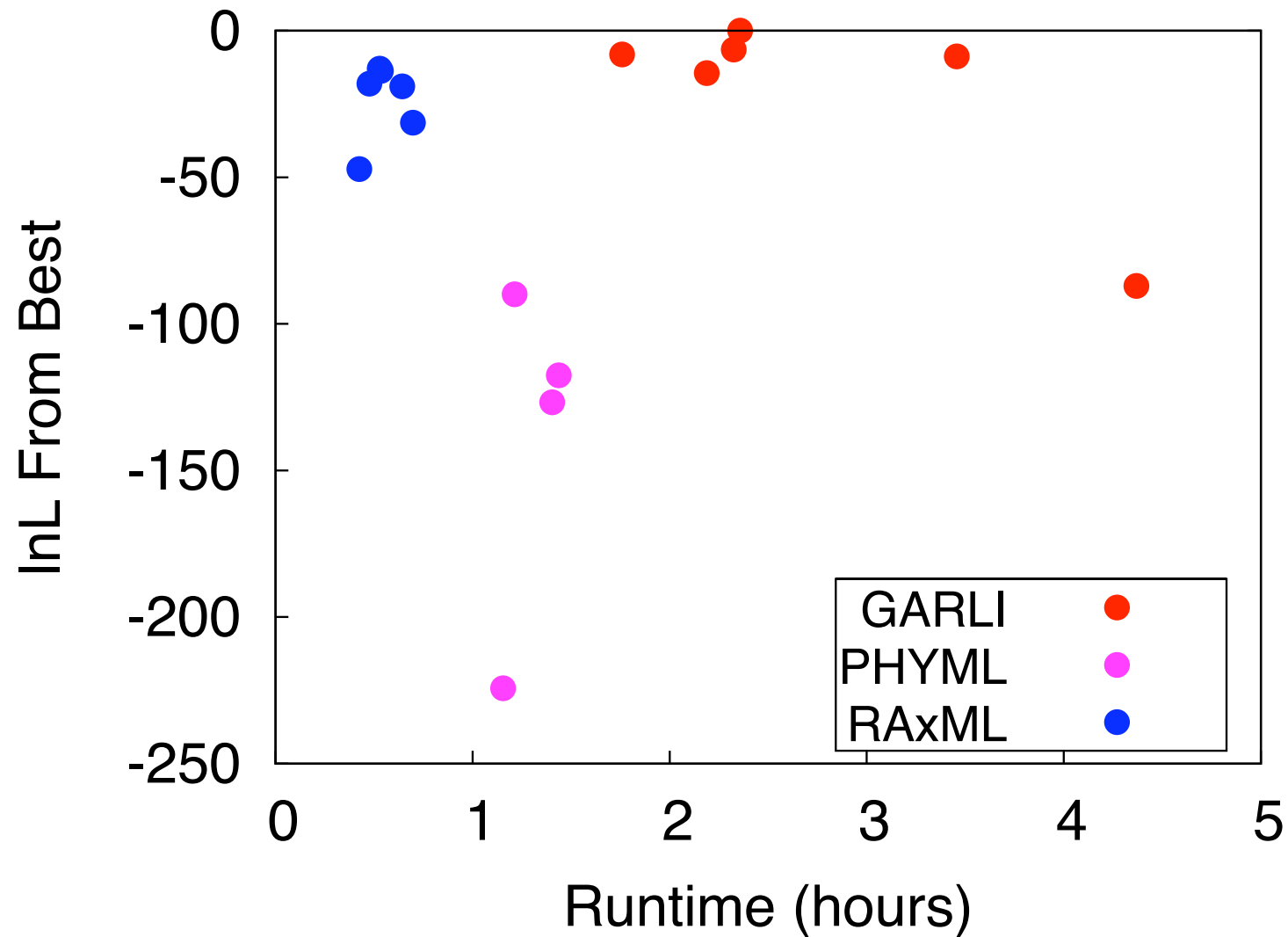
Performance comparisons against other software

- **More subjective than one would like:**
 - **What constitutes comparable analyses?**
 - **What criteria should be used to compare methods?**
 - **Models and likelihood values often not exactly comparable**
 - **Most software can be “tuned” to perform better on any particular dataset**
 - **Simulated datasets are far too easy to analyze**

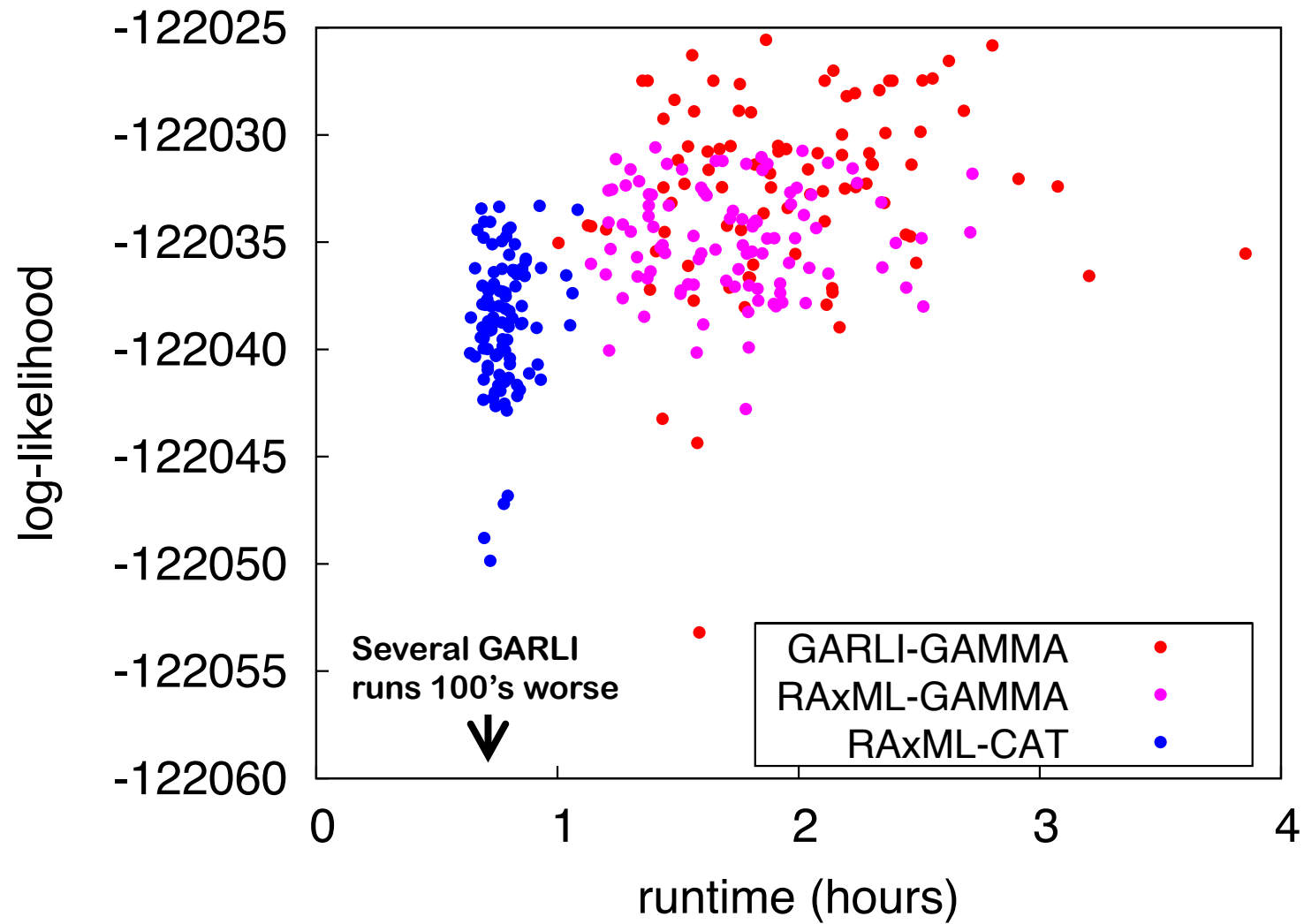
**Performance comparison:
132 taxon x 1880 nucleotide dataset**



Performance comparison: “Treezilla” 500 taxon x 1398 nucleotide dataset



Performance comparison: 228 taxon x 4811 nucleotide dataset



Performance generalizations

- For small datasets, all of the programs perform well
- For large datasets (hundreds of sequences):
 - Optimality of the results of RAxML and GARLI overlap broadly
 - PHYML v2.4 is often somewhat less optimal
 - GARLI often has a slight edge in optimality (although often more variability)
 - Runtimes vary, with RAxML generally the fastest
- RAxML is very efficient for huge datasets (thousands of sequences)

Performance generalizations

- There can be substantial differences in which program performs best depending on the specific dataset

Available evolutionary models

- Model availability is another criterion for choosing among software
 - GARLI, RAxML and PHYML all allow nucleotide and amino acid analyses, GARLI (and now PHYML) allow codon
 - GARLI and RAxML implement models for non-sequence data (Mk and Mk_v)
 - GARLI offers a greater variety of nucleotide models (any submodel of GTR)
 - GARLI and RAxML implement partitioned models, with GARLI allowing more flexibility
 - GARLI will soon have publicly available gap models

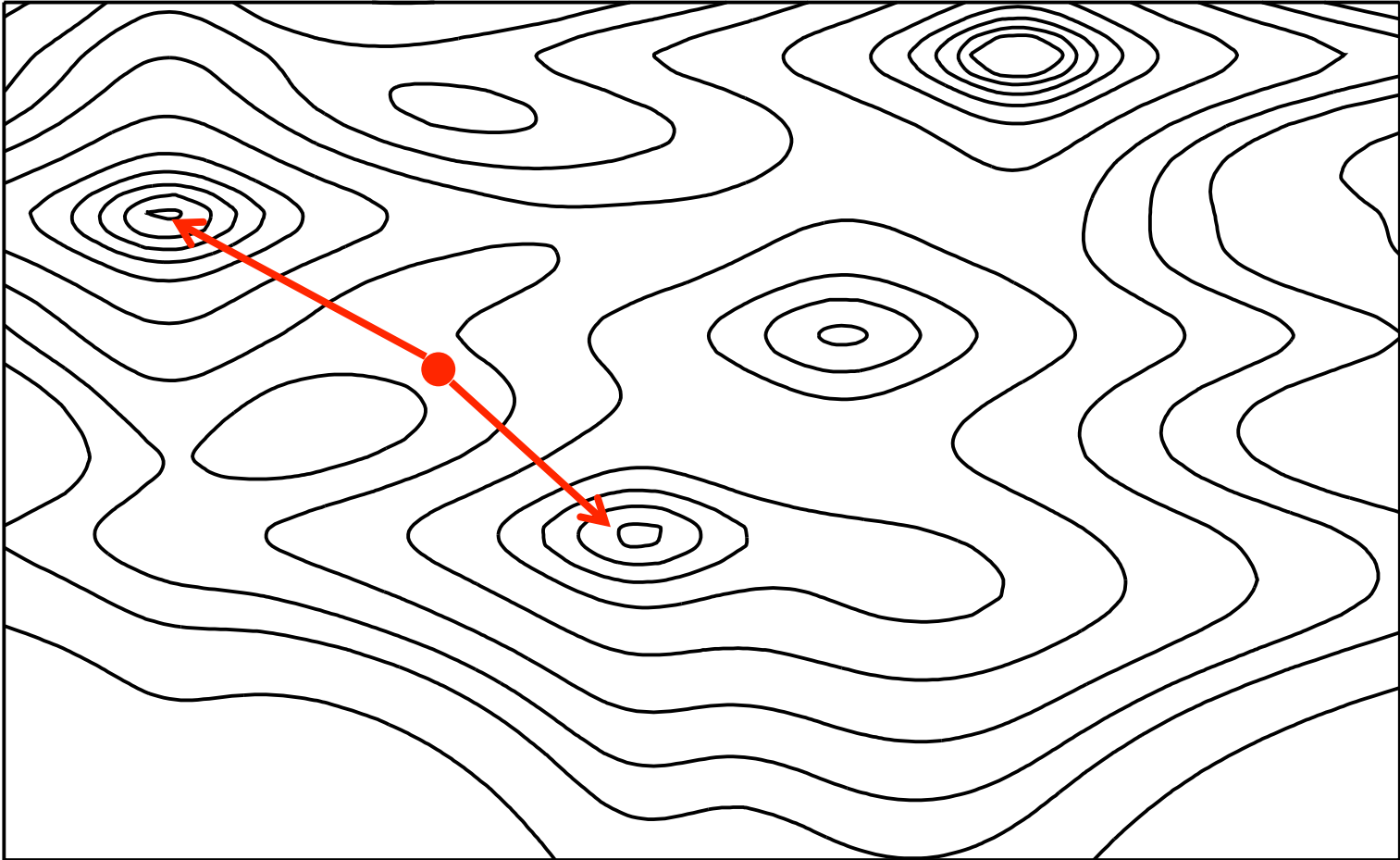
Evolutionary models

- GARLI is geared toward model flexibility and rigorous parameter estimation

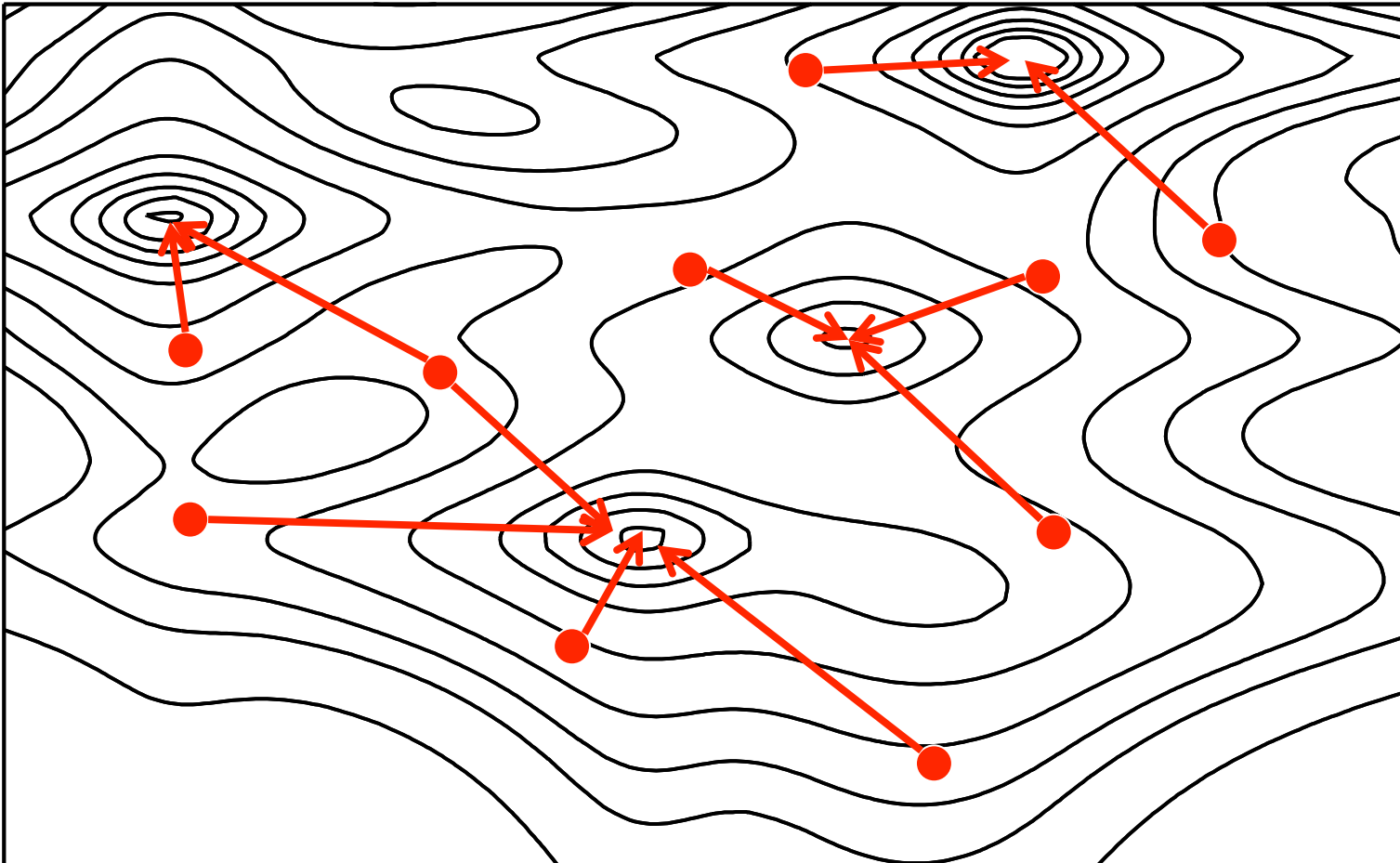
Search strategies in GARLI

- **Multiple search replicates must ALWAYS be done**
- **If variable results across search replicates seen:**
 - **Make changes to improve the search**
 - **and/or do more search replicates**

Search repeatability and multiple replicates



Search repeatability and multiple replicates



Search difficulty

- On average:
 - More sequences = worse
 - More characters (signal) = better
- # parsimony informative sites better indicator of signal than total # of sites

Tuning search intensity

- Tradeoff between search intensity and runtimes
- Not always a direct relationship between search intensity and solution optimality
- Given a certain amount of time, how can we best use it?

Balancing search intensity and runtimes



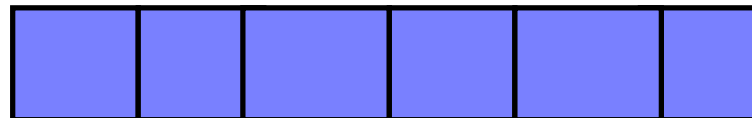
H hours

Per run, more likely
to find global
optimum



3 thorough searches

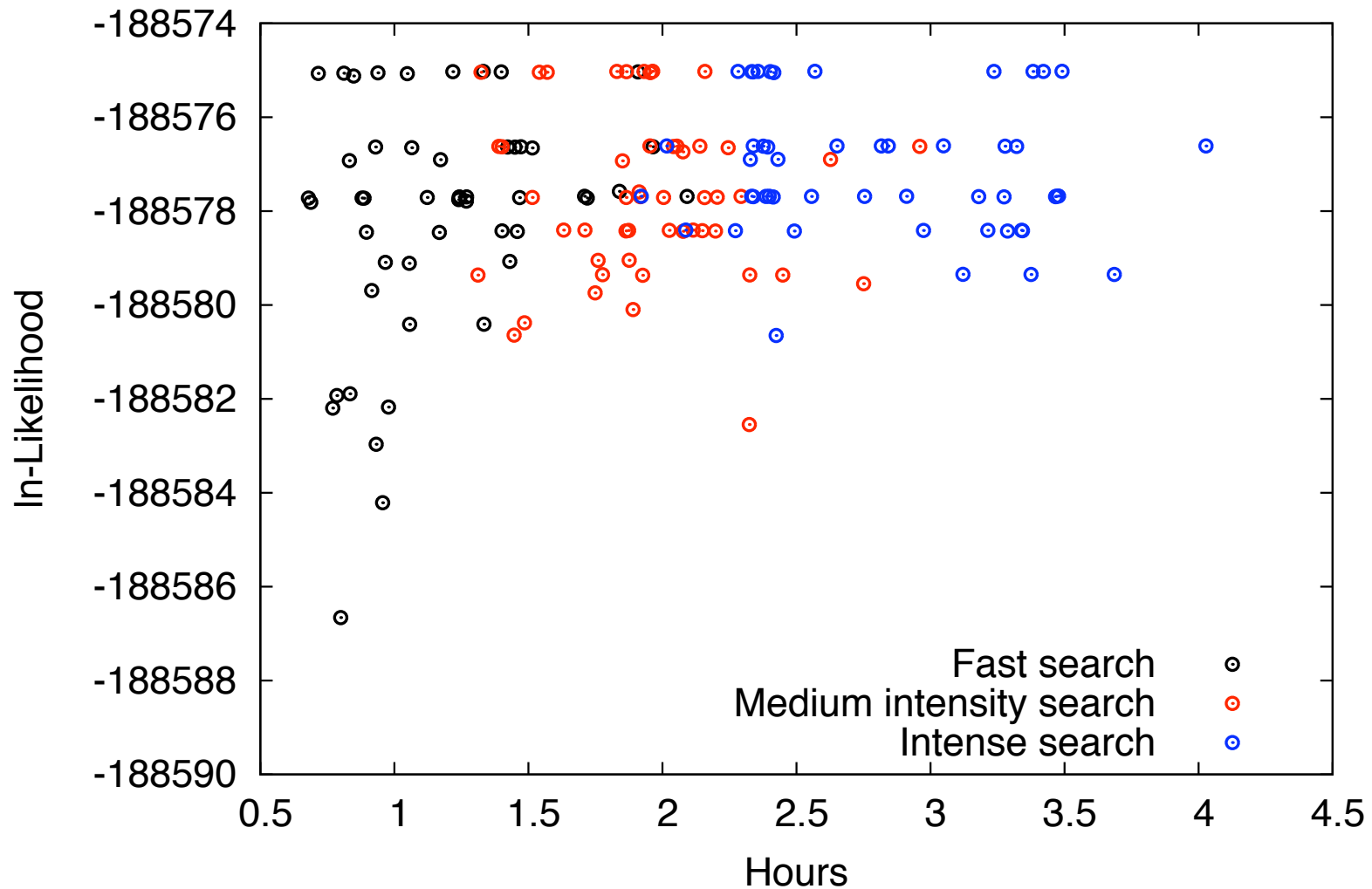
May be more likely
to find global
optimum
within H hours



6 fast searches

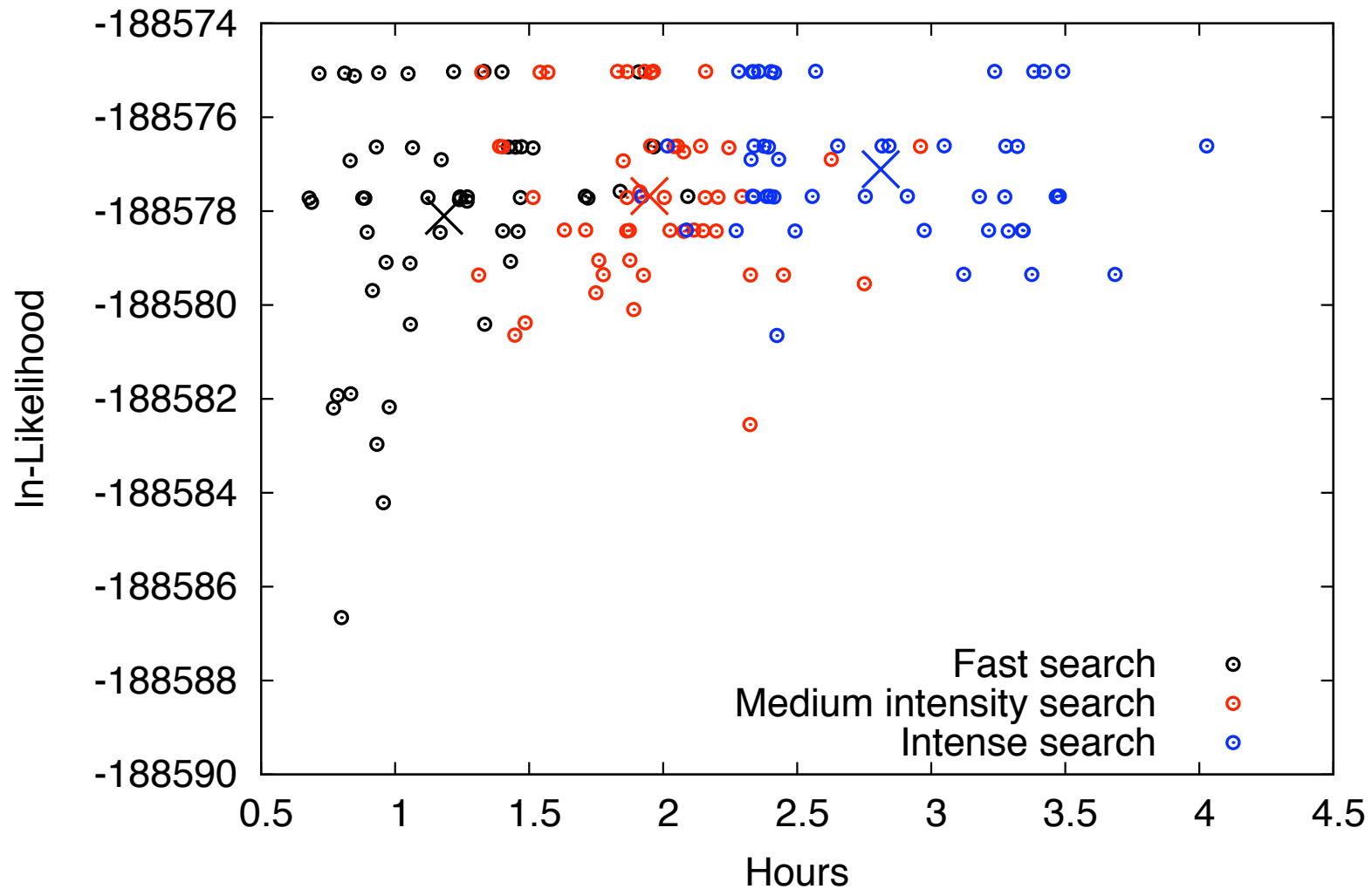
An empirical example (50 search replicates each)

142 taxa x 6804 nucleotides



An empirical example (50 search replicates each)

142 taxa x 6804 nucleotides



An empirical example

142 taxa x 6804 nucleotides

search strategy	average lnL	average search runtime (hrs.)
fast	-188578.10	1.18
medium	-188577.68	1.95
intense	-188577.11	2.81

An empirical example

142 taxa x 6804 nucleotides

search strategy	average lnL	average search runtime (hrs.)	proportion of searches finding the best tree
fast	-188578.10	1.18	0.16
medium	-188577.68	1.95	0.18
intense	-188577.11	2.81	0.22

An empirical example

142 taxa x 6804 nucleotides

search strategy	average lnL	average search runtime (hrs.)	proportion of searches finding the best tree	searches possible in 100 hrs.
fast	-188578.10	1.18	0.16	84.56
medium	-188577.68	1.95	0.18	51.30
intense	-188577.11	2.81	0.22	35.57

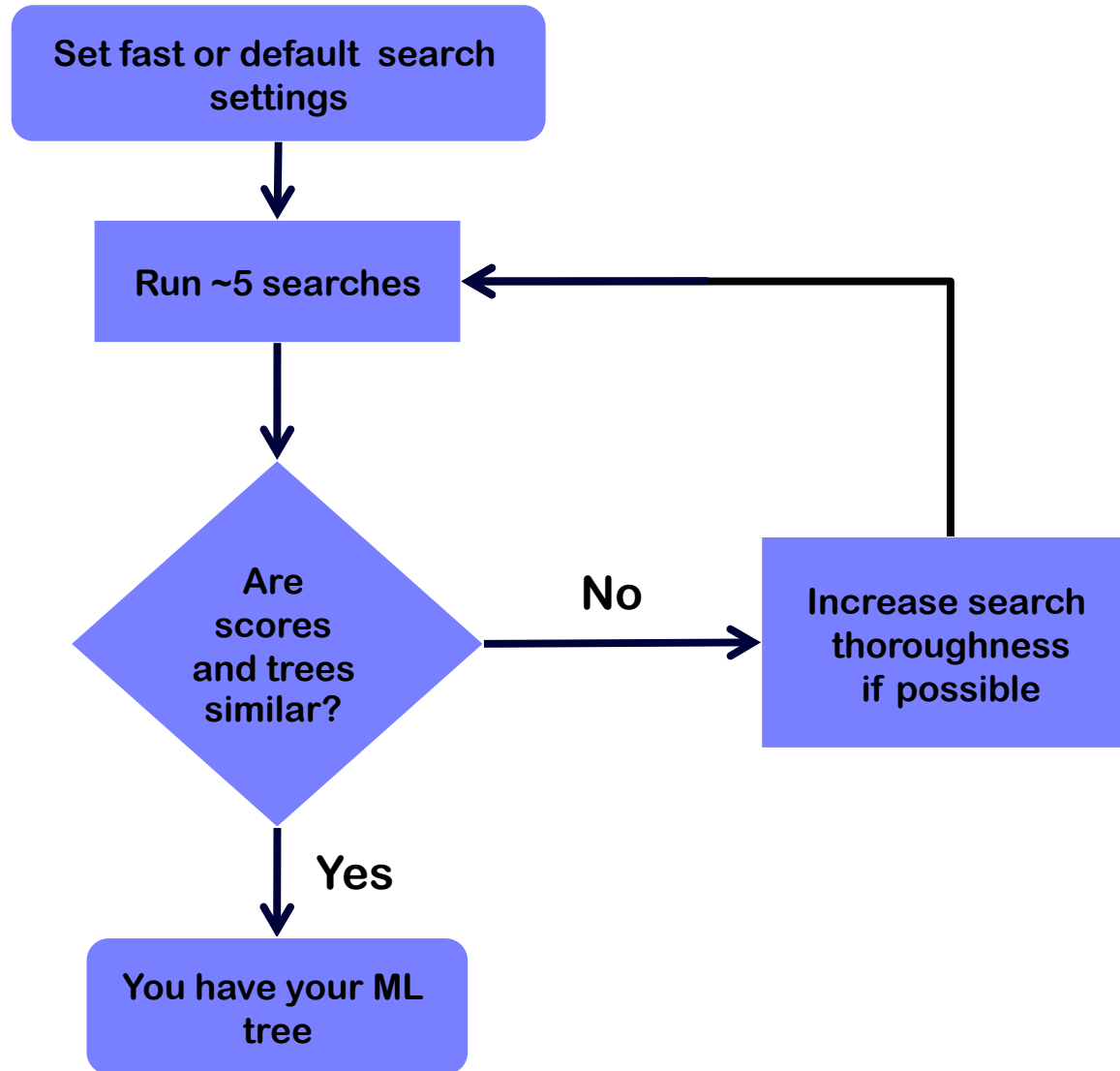
An empirical example

142 taxa x 6804 nucleotides

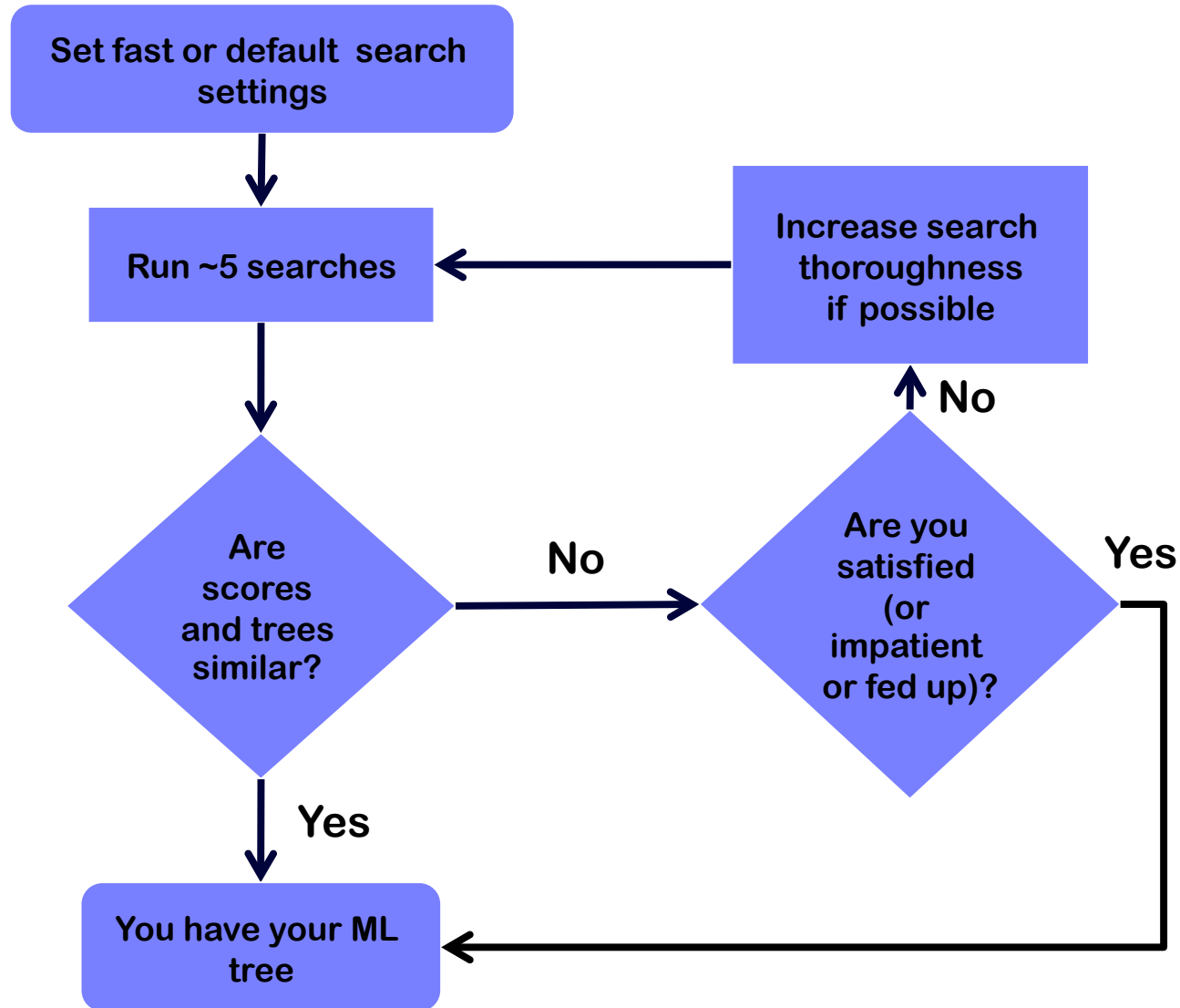
search strategy	average lnL	average search runtime (hrs.)	proportion of searches finding the best tree	searches possible in 100 hrs.	expected # best trees found in 100 hrs.
fast	-188578.10	1.18	0.16	84.56	13.53
medium	-188577.68	1.95	0.18	51.30	9.23
intense	-188577.11	2.81	0.22	35.57	7.82

Despite the more intense searches having better average scores and being more likely to find the best tree *per search*, they are less likely to find the best tree *per unit time*

Practical search recommendations



Practical search recommendations



Practical search recommendations

- Search repeatability is good indicator of how analyses are going (much like convergence of independent MCMC runs)
- In general, saturating the search space (lots of searches) may be better than very long searches
- On some large datasets you are unlikely to get the same tree twice

How else can I speed up/improve searches?

- **Eliminate identical sequences!**
- **Constrained tree searches won't necessarily help**
- **Starting tree**
 - **Providing a decent (potentially unresolved) starting tree can help on large datasets**

What about bootstrapping?

- **GARLI can run multiple search replicates per bootstrap reweighting, with the best scoring tree saved**
- **More intense searches add up quickly when bootstrapping**
- **Best to find the fastest settings that give consistent results on the real data and use those for bootstrapping**

Partitioning

- **GARLI 2.0 allows partitioned models**
- **Allows use of any GTR submodel for each nucleotide subset**
- **Allows combination of DNA, AA, codon and morphology models**

How/when to partition

- Little work done in an ML framework
- Many, many combinations of possible models
- In principle the AIC method should allow choice between model assignments and partitioning schemes
- Smaller subsets increase sampling error, lead to parameter estimation difficulties and model breakdown
- Over-partitioning may have serious consequences in ML inference, probably less in Bayesian

Assorted GARLI features

- A single data file may be analyzed at the nucleotide, amino acid and codon levels without making any changes to it
- Multithreaded version for multiple CPU cores
- MPI version simplifies bootstrapping on clusters
- Full checkpointing functionality
- Searching with topological constraints (positive, negative, backbone)

Other assorted GARLI features

- Specification and fixation of model parameter values
- Site-likelihood output for all models including partitioned, for input into CONSEL, etc.
- Ancestral state reconstruction for all models
- Eventually: Beagle GPU version

Computer exercises