MCEB 2022

Château d'Oex, Suisse
June 26-30, 2022

MATHEMATICAL AND COMPUTATIONAL EVOLUTIONARY BIOLOGY

Program

LIRMM
cnrs
UNIVERSITÉ DE MONTPELLIER
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Swiss National Science Foundation
GdR BiM
GdR EcoStat
INRAE
LabEx NUMEV
SIB Swiss Institute of Bioinformatics
Département de Biologie Computationnelle

INFORMATION

Meeting Point

Directly at the Hotel Roc & Neige on Sunday, May 26th.

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=> inside France use 0 to start (06 48...), outside france use +33 without the 0 (336 48...)

Location

The conference will be held in the village of **Chateau d’Oex**, The municipality is located in the Vaud part of the Sarine valley between the Saanenland in the canton of Bern (in French: Gessenay) upstream and the Intyamon in the canton of Fribourg downstream, at an altitude of approximately 1,000 m. Château-d’Œx is the largest municipality in the canton of Vaud, with an area of 11,374 ha5 , of which 2% is residential and infrastructure land, 44.6% is agricultural land, 35.9% is woodland and 16.6% is unproductive land.

The minimum altitude of the municipality is 870 m at the level of the Sarine, the average altitude is 1,489 m and the highest point is at 2,548 m on the summit of Tarent on the Pic Chaussy - Cape au Moine ridge.
The municipality comprises several villages and hamlets. Apart from Château-d’Œx, the main town, the most important are Les Moulins and Les Granges, at the bottom of the valley, as well as L’Étivaz and La Lécherette, on the road to the Col des Mosses.

Practical INFORMATION

Hotel
ROC & NEIGE
CHATEAU-D'OEX · SWITZERLAND

Hôtel Roc et Neige

Route des Monnaires 46, 1660 Château-d’Oex
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info@rocetneige.ch
https://www.roc-et-neige.ch/contact

Train :

To get there by train, you have to go through Geneva, then Lausanne, Montreux and finally Chateau d’Oex. It takes 2h30 from Geneva.
To reach the hotel from the station, you have to walk a distance of 800m.
The map below explains the itinerary.

Tickets and information

Montreux-Oberland Bernois -Buy tickets - 00 41 21 989 81 90
SNCF - 01 84 94 36 35
Chemins de fer fédéraux suisses - Buy tickets - 00 41 900 300 300

Program

Sunday, June 26th

19h00 Welcome drink

20h00 Dinner

Monday, June 27th

09h00 **Keynote – Niko Beerenwinkel**
Inferring tumor evolution from single-cell data

10h00 Coffee break

10h40 **Scholz Guillaume**
Fast detection of recombinant sequences in viruses using phylo-k-mers

11h00 **Latrille Thibault**
Empirical evidence for positive selection that is not adaptive evolution

11h20 Break

11h40 **Mashayekhi Somayeh**
Fractional coalescent

12h00 **Otto Moritz**
Recombination, selection and the evolution of tandem gene arrays

12h30 Lunch
Afternoon: social activities and discussions

17h30 **De Sousa Mota Bárbara**
Imputation of ancient genomes

17h50 **Anchieri Lucas**
Benchmarking methods using time-series data to infer selection

18h10 Break

18h40 **Nesterenko Luca**
Phyloformer: Fast and accurate phylogeny estimation with self-attention networks

19h00 **De Vienne Damien M.**
The overlooked effect of ghost lineages for the study of gene flow

19h30 Dinner

Program

Tuesday, June 28th

09h00 **Keynote** – **Denise Kühnert**
Archaeogenetics meets phylodynamics: tracking the evolution of pathogens over millennia

10h00 Coffee break

10h40 **Cornuault Josselin**
Do genes' coalescence times carry information on demography?

11h00 **Catanzaro Daniele**
Balanced Minimum Evolution: Theoretical and Computational Advances

11h20 Break

11h40 **Bollen Nena**
Exploiting genomic surveillance to map the spatio-temporal dispersal of SARS-CoV-2 spike mutations in Belgium across 2020

12h00 **Huson Daniel**
SplitsTree6 - integrating phylogenetic trees and networks

12h30 Lunch
Afternoon: social activities and discussions

17h **Keynote** - **Carolin Kosiol**
Polymorphism-aware phylogenetics models

18h **Poster session (1 to 12) + aperitif**

19h30 Dinner

Wednesday, June 29th

09h00 **Keynote** – **David Bryant**
The Concatenation Question

10h00 Coffee break

10h40 **Szollosi Gergely**
Trade-off between reducing mutational accumulation and increasing commitment to differentiation determines tissue organization

Program

11h00 **Featherstone Leo**
Assessing the effects of date and sequence data in phylodynamics

11h20: Break

11h40 **Zhukova Anna**
Fast and Accurate Resolution of the Birth-Death Exposed-Infectious (BDEI) Model

12h00 **Bastide Paul**
A Cauchy process to model trait evolution on a phylogeny

12h30 Lunch
Afternoon: social activities and discussions

17h **Keynote – Maria Anisimova**
Phylogenetics with indels

18h **Poster session (13 to 23) + aperitif**

19h30 Dinner

Thursday June 30th

09h00 **Keynote – Cécile Ané**
Estimating species networks to model reticulate evolution: challenges and identifiability

10h00 Coffee break

10h40 **Dalla Riva Giulio Valentino**
Phylogenetics and ecological networks: old challenges and new opportunities

11h00 **Urban Lara**
The ghost of past selection in the critically endangered kākāpō

11h20 Break

11h40 **Layan Maylis**
Impact and mitigation of sampling bias to determine viral spread: evaluating discrete phylogeography through CTMC models and structured coalescent model approximations

12h00 **Vaughan Timothy** - *Bayesian phylodynamic inference of multi-type population trajectories using genomic data*

12h30 Lunch
14h00 **Departure**

Keynote speakers

> Cecile ANE
Professor of Botany and Statistics
University of Wisconsin–Madison

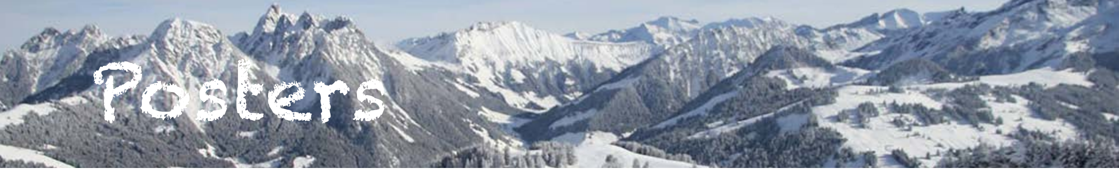
> Maria ANISIMOVA
Head of Applied Computational Genomics and Lecturer, SIB group leader
ZHAW School of Life Sciences and Facility Management
Fachstelle Computational Genomics

> Niko BEERENWINKEL
Professor Dep. of Biosystems Science and Eng
ETH Zürich Computational Biology Group

> David BRYANT
Professor University of Otago
University of Otago, New Zealand

> Carolin KOSIOL
Lecturer in Bioinformatics
University of St Andrews

> Denise KÜHNERT
Transmission, Infection, Diversification & Evolution Group - Research Group Leader
Max Planck Institute for the Science of Human History



Posters

1 - Jowkar Gholamhossein
ARPIP: Ancestral sequence Reconstruction with insertions and deletions under the Poisson Indel Process
2 - Gamblin Jasmine
Beyond one-gain models for pangenome evolution
3 - Rocu Pauline
Sampling consistency of diffusion statistics in bayesian phylogeography
4 - Talibart Hugo
PPalign: Optimal alignment of Potts models representing proteins with direct coupling information
5 - Linard Benjamin
Improving gene classification into gene families via phylo-k-mers
6 - Romashchenko Nikolai
Mutual Information-based Feature Selection of Informative Phylo-k-mers
7 - Li Yimin
Preprocessing Strategies for Bayesian Phylogeographic Analysis Using Large-Scale Genomic Sequence Data
8 - Wirtz Johannes
Combinatorics of multiple-merger coalescent genealogies
9 - Potter Barney
Leveraging tools from Nextstrain for bespoke phylogenetic analysis of viral pathogen epidemics
10 - Tuffet Rémi
Modeling the dynamics of antibiotic resistance genes: towards an ecology of the bacterial pangenome
11 - Zarebski Alexander
Estimation of reproductive number and prevalence using genomic and time series data
12 - Bastian Mélodie
Bridging the gap between population genomic and phylogenetic approaches
13 - Moi David
Convolutional graph networks for Coevolution detection in COVID19
14 - Nahata Kanika
Bayesian model comparison of molecular clock models - a phylogenetic simulation study
15 - Carpentier Mathilde
P*rotein folds as synapomorphies of the tree of life*
16 - Boussau Bastien
Evaluation of methods to detect shifts in directional selection at the genome scale

Posters

17 - Verbiest Max

Uncovering the Diverse Roles of Short Tandem Repeat Variation in Colorectal Cancer

18 - Genestier Alice

The influence of genetic dosage on PRDM9-dependent evolutionary dynamics of meiotic recombination

19 - Pourhasanzade Fateme

An Individual-based model to study the importance of trade-offs in the evolution and diversification of traits in host-phage population dynamics

20 - Hong Samuel

GPU-accelerated online phylodynamic inference using BEAST

21 - Koubinova Darina

Intergeneric relationships within Ophioglossaceae untangled with organelle phylogenomics

22 - Paul Zaharias

The robustness of bootstrap branch supports with respect to taxon sampling

23 - David Swofford

Likelihood Via Decomposition : A fast, highly parallelizable alternative to Felsenstein pruning for computing likelihoods of phylogenetic trees

Talks

Fast detection of recombinant sequences in viruses using phylo-k-mers

Guillaume Scholz * 1 , Benjamin Linard 2,3 , Eric Rivals 2 , and Fabio Pardi 2

1 - Institut für Bioinformatik, Leipzig Universität, Germany – Germany
2 - LIRMM, Université de Montpellier, CNRS, Montpellier, France – LIRMM – France
3 - Spygen, Le-Bourget-du-Lac, France – SPYGEN [Le Bourget-du-Lac] – France

Novel recombinant viruses may have important medical and evolutionary significance, as they sometimes display new traits not present in the parental strains. This is particularly concerning when the new viruses combine fragments coming from phylogenetically distinct viral types (or variants). Here, we consider the task of screening large collections of sequences for such novel recombinants. A number of methods already exist for this task. However, these methods rely on complex models and heavy computations that are not always practical for a quick scan of a large number of sequences. We have developed SHERPAS (1), a new program to detect novel recombinants and provide a first estimate of their parental composition. Our approach is based on the precomputation of a large database of 'phylogenetically-informed k-mers' (or 'phylo-k-mers' for short), an idea recently introduced in the context of phylogenetic placement in metagenomics. Our experiments show that SHERPAS is hundreds to thousands of times faster than existing software, and enables the analysis of thousands of whole genomes, or long-sequencing reads, within minutes or seconds, and with limited loss of accuracy. In this talk, I will present SHERPAS-K2 (2), the new version of SHERPAS. While the general approach, based on phylo-k-mers, remains the same, we have reworked the inner-working of the algorithm. Experiments show that SHERPAS-K2 is even faster than SHERPAS. In addition, we observe an significant improvement in the accuracy of the results.

References:

(1) G. E. Scholz, B. Linard, N. Romashchenko, E. Rivals and F. Pardi. Rapid screening and detection of inter-type viral recombinants using phylo-k-mers, Bioinformatics (2020) 36(22-23): 5351-5360.
(2) G. E. Scholz, B. Linard, E. Rivals and F. Pardi. SHERPAS-K2, higher performances in the screening and detection of inter-type viral recombinants using phylo-k-mers. Manuscript in preparation.

Empirical evidence for positive selection that is not adaptive evolution

Thibault Latrille * 1 , Nicolas Salamin 3,2 , and Julien Joseph

1 - Laboratoire de Biométrie et Biologie Evolutive - UMR 5558 – Université Claude Bernard Lyon 1, Centre National de la Recherche Scientifique – France
3 - Swiss Institute of Bioinformatics (SIB) – Quartier Sorge - Batiment Genopode 1015 Lausanne Switzerland, Switzerland
2 - Department of Computational Biology, University of Lausanne – Rue du Bugnon 27 1011, Lausanne Switzerland, Switzerland

Evidence for positive selection occurring in protein-coding DNA sequence is widespread across different taxa. Positive selection can be a result of adaptive evolution, meaning that individuals have had to adapt to a change in environment or selective pressure. However, current positive selection can also be the result of mutations compensating for deleterious substitutions that have accumulated along lineages, in which case positive selection is nonadaptive and predictable. To evaluate the extent of non-adaptive positive selection, we have combined population-genetics and phylogenetics datasets. We first leveraged phylogenetic codon models which are based on a population-genetics formalism, assuming a non-adaptive fitness landscape. These models estimate the fitness of each of the 20 amino acids for each protein site, given mammalian protein-coding DNA alignments and gene tree topologies. Second, we integrated mammalian divergence data with polymorphic variants found in 29 populations across 7 mammalian genera. For each non-synonymous variant observed at the population level, we predicted its change in fitness from amino-acid fitnesses estimated at the mammalian scale. We found that a large proportion of observed non-synonymous changes are predicted to be positively selected, meaning that the ancestral allele is sub-optimal. These supposedly advantageous variants are indeed showing signs of recent positive selection in all populations. Our work confirms that deleterious substitutions have accumulated across the phylogeny and are currently being compensated for, resulting in widespread positive selection that is not adaptive evolution. This study also shows the leverage obtained by integrating phylogenetic and population genetics on a common formalism.

Fractional coalescent

Somayeh Mashayekhi * 1 and Peter Beerli 2

1 - Kennesaw State University – United States
2 - Florida State University – United States

The fractional coalescent is a generalization of Kingman's n-coalescent. It facilitates the development of the theory of population genetic processes that deviate from Poisson-distributed waiting times. It also marks the first use of methods developed in fractional calculus in population genetics. The fractional coalescent extends Canning's model, where the variance of the number of offspring per parent is a random variable. The distribution of the number of offspring depends on an additional parameter which is a potential measure of the environmental heterogeneity commonly ignored in current inferences. The fractional coalescent has been implemented in the population genetic model inference software MIGRATE. Bayes factor comparisons of simulated and real data (H1N1 influenza, Malaria parasites) showed an improved model fit of the fractional coalescent over the n-coalescent. The development of the fractional coalescent and its inclusion into the inference program MIGRATE facilitates testing for deviations from the n-coalescent.

Recombination, selection and the evolution of tandem gene arrays

Moritz Otto * 1 , Yichen Zheng 1 , and Thomas Wiehe 1

1 - University of Cologne – Germany

Multi-gene families – immunity genes or sensory receptors, for instance – are often subject to diversifying selection. Allelic diversity may be favoured not only through balancing or frequency dependent selection at individual loci, but also by associating different alleles in multi copy gene families. Using a combination of analytical calculations and simulations, we explored a population genetic model of epistatic selection and unequal recombination, where a trade-off exists between the benefit of allelic diversity and the cost of copy abundance. Starting from the neutral case, where we showed that gene copy number is Gamma-distributed at equilibrium, we derived also mean and shape of the limiting distribution under selection. Considering a more general model which includes variable population size and population substructure, we explored by simulations mean fitness and some summary statistics of the copy number distribution. We determined the relative effects of selection, recombination and demographic parameters in maintaining allelic diversity and shaping mean fitness of a population. One way to control the variance of copy number is by lowering the rate of unequal recombination. Indeed, when encoding recombination by a rate modifier locus, we observe exactly this prediction. Finally, we analyzed the empirical copy number distribution of three genes in human and estimated recombination and selection parameters of our model.

Imputation of ancient genomes

Bárbara De Sousa Mota * 1,2 , Simone Rubinacci 1,2 , Diana Ivette Cruz Dávalos 1,2 , Carlos Eduardo G. Amorim 3 , Martin Sikora 4 , Eske Willerslev 4 , Anna-Sapfo Malaspinas 1,2 , and Olivier Delaneau 1,2

1 - Department of Computational Biology – University of Lausanne, Switzerland
2 - Swiss Institute of Bioinformatics – Switzerland
3 - Department of Biology, California State University – United States
4 - Centre for GeoGenetics, Natural History Museum of Denmark and Department of Biology, University of Copenhagen – Denmark

The number of sequenced ancient genomes has been rapidly increasing over the last two decades. Ancient DNA (aDNA) studies have unraveled significant aspects of our past as a species that contribute to a deeper understanding of the genetic variation we observe today. aDNA is affected by extensive damage, including fragmentation and C-to-T substitutions. As a result, ancient genomes often have low sequencing depth, which is an impediment to confident genotype calling. Imputation has been proposed as a solution to this problem. However, it is unclear whether low-coverage ancient genomes can be accurately imputed and how imperfect imputation affects downstream analyses. To address these questions, we downsampled 42 high-coverage ancient human genomes (> 10x) to low coverage and subsequently imputed them with GLIMPSE, an imputation and phasing tool, using 1000 Genomes as a reference panel. For most individuals, we recovered original high-coverage genotypes with low error rates (< 5% for genotypes with at least one copy of the alternative allele). Error rates were higher for African genomes, likely due to underrepresentation in the reference panel. There were no measurable differences between imputation accuracy of transversion and transition sites, where the latter are known to be affected by postmortem damage (C-to-T substitutions). Finally, we analyzed high-coverage and imputed genomes with principal component analysis (PCA), genetic clustering to estimate ancestry contributions in the case of the European individuals, and runs of homozygosity (ROH), an inbreeding measure typically requiring diploid data. For these applications, we obtained similar results with high-coverage and imputed genomes when depth of coverage was at least 0.5x. Al together, we show that, depending on the ancestry and coverage of the ancient genomes, imputation can be reliably applied to expand aDNA studies.

Benchmarking methods using time-series data to infer selection

Lucas Anchieri ∗ 1 , C. Eduardo Guerra Amorim 2 , Samuel Neuenschwander 1,3 , and Anna-Sapfo Malaspinas 1

1 - UNIL, Department of Computational Biology – Switzerland
2 - California State University Northridge, Department of Biology – United States
3 - Swiss Institute of Bioinformatics – Switzerland

With the increasing availability of genomic data from ancient human individuals it has become possible to obtain allele trajectories over time (time-series data). These allele trajectories can be used to estimate selection at specific loci. Several methods have been developed to that effect and have been validated with simulations by assuming large datasets. However, in reality, genomic data of ancient humans are low in numbers of individuals over time and typically of low genomic coverage making estimations challenging. Here, we assessed the performance of the proposed methods through simulations miming characteristics of realistic ancient human studies, in particular the reduced sample size. We used SLiM to simulate allele trajectories under realistic parameters for human populations and tested the methods using time-series data sampled from the simulations. We considered several sampling schemes as well as different population dynamics to determine how specific methods perform under different conditions. We show that the performance of the methods is quite variable depending on the data generated, and that they do not always recover the true value when the samples are realistic in size.

Phyloformer: Fast and accurate phylogeny estimation with self-attention networks.

Luca Nesterenko ∗ 1, Johanna Trost 1 , Bastien Boussau 1 and Laurent Jacob 1

1 - Univ Lyon, Université Claude Bernard Lyon 1, CNRS UMR 5558, LBBE, F-69100, Villeurbanne, France

An important problem in molecular evolution is that of phylogenetic reconstruction, that is, given a set of sequences descending from a common ancestor, the reconstruction of the binary tree describing their evolution from the latter. State of the art methods for the task, namely Maximum likelihood and Bayesian inference, have limited applicability due to their high computational cost. Recently researchers have begun investigating deep learning based approaches to the problem but so far these attempts have been mostly limited to the reconstruction of quartet tree topologies, addressing phylogenetic reconstruction as a classification problem. We present here a radically different approach with Phyloformer, a transformer based network architecture that, given a multiple sequence alignment, predicts all the pairwise evolutionary distances between the sequences, which in turn allow us to accurately reconstruct the tree topology with a classical distance-based algorithm. The architecture and its high degree of parameter sharing allow us to apply the same network to alignments of arbitrary size, both in the number of sequences and in their length. Our proposed network uses self-attention to progressively update, via learnable functions, the representation of each pair of sequences in the input alignment, alternatively focusing on different pairs and on different sites and thus getting, through several layers, an increasingly predictive estimate of all the pairwise evolutionary distances. The interactions across different sequence pairs enable the network to build context aware representations allowing to exploit all the information contained in the input MSA overcoming, with this joint prediction, the drawback of classical distance-based methods which usually take in input independently computed distance estimates.

Phyloformer's network architecture allows exploiting all the symmetries of the problem, namely the predicted tree topology is invariant to sequence permutations in the input MSA and to permutations of sites in the sequences, taking advantage of the common assumption that evolution is an independent and identically distributed process at each site. Nevertheless this doesn't limit the applicability of the proposed network to scenarios in which a more sophisticated model of evolution, which models interactions between sites, is considered, as in that case it would suffice to add a positional encoding, as in classical transformers, to the network's input. In this work we test our network trained on two different sequence simulators. The first simulator is based on the commonly used PAM exchangeability matrix. We show the applicability of our model for reconstructing phylogenies with different numbers of sequences and sequence lengths. Phyloformer performs better than a pairwise distance method, and

approaches the performance of a state of the art maximum likelihood method, in a fraction of the time. Furthermore we prove the robustness of our method to model misspecification testing it on a different model of sequence evolution from the one it has been trained on. The second set of simulations is based on a mixture model which combines 9 different amino acid replacement matrices and further simulates heterogeneity in the rate of sequence evolution both across sites and across branches. This allows us to show the applicability of our method to a fairly complex model and to directly compare our results to those obtained by previously published neural networks. We show not only that we consistently outperform the latter but also that for most configurations of simulation parameters we get the best results among all considered predictive methods, with a network trained only on a little subset of such parameter configurations. Overall, our results show that Phyloformer can already be used as an alternative to maximum likelihood and pairwise distance methods. Looking forwards, we present planned improvements that could install deep learning approaches among the phylogeneticist's standard toolbox.

The overlooked effect of ghost lineages for the study of gene flow

Damien de Vienne ∗ 1 , Eric Tannier 2,3 , and Théo Tricou 4

1 - Laboratoire de Biométrie et Biologie Évolutive (LBBE) – CNRS : UMR5558, Université de Lyon, Université Lyon 1 – France
2 - INRIA Rhône-Alpes (INRIA Grenoble Rhône-Alpes) – INRIA – ZIRST 655 Avenue de l'Europe Montbonnot 38334 Saint Ismier cedex, France
3 - Laboratoire de Biométrie et Biologie Evolutive (LBBE) – CNRS : UMR5558, Université Claude Bernard - Lyon I (UCBL), INRIA – 43 Bld du 11 Novembre 1918 69622 VILLEURBANNE CEDEX, France
4 - Laboratoire de Biométrie et Biologie Evolutive (LBBE) – CNRS : UMR5558, Université Claude Bernard - Lyon I (UCBL) – France

Introgression, endosymbiosis and gene transfer, i.e. Horizontal Gene Flow (HGF), are primordial sources of innovation in all domains of life. Our knowledge on HGF relies on detection methods that exploit some of its signatures left on extant genomes, such as the effect of HGF on branch lengths and on topologies of constructed phylogenies. These signature have been formalized in statistical tests for HGF detection, and used in various contexts, for example to detect massive adaptive gene flows in malaria vectors or to order evolutionary events involved in eukaryogenesis. However these studies rely on the assumption that ghost lineages (all unsampled extant and extinct taxa) have little influence. We demonstrate here with simulations and data re-analysis, that when considering the more realistic condition that unsampled taxa are legion compared to sampled ones, the conclusion of these studies become unfounded or even reversed. This illustrates the necessity to recognize the existence of ghosts in evolutionary studies. It also suggests that the detection of gene flow may be an indirect way of identifying and characterizing ghost lineages. Preliminary results on this new topic will also be presented.

Do genes' coalescence times carry information on demography?

Josselin Cornuault ∗ 1 , Fabio Pardi 2 , and Céline Scornavacca 1

1 - ISEM - Montpellier – UMR ISEM – France
2 - LIRMM - Montpellier – LIRMM – France

The coalescent theory predicts that past variations of population size should leave an imprint on genes' coalescence times. As a result, genetic data have been widely used to infer the demographic history of populations and species. The coalescent model is a continuous-time, large-population, approximation of a body of discrete-time population models, such as the Wright-Fisher and Moran models, which all make the assumption that population size varies deterministically. In this paper we investigate the robustness of demographic inference from genealogical data to relaxing this assumption of determinism. To do so, we study the predictions, in terms of generated genealogies, of population models with a random population size: the Galton-Watson (GW) models. We show analytically that GW models can be grouped into equivalence classes within which different models generate genealogies identically and are thus observationally, and statistically, indistinguishable. Importantly we show that any GW model, characterized by some arbitrary curve of the expected population size through time, belongs to an equivalence class that comprises a myriad of models with all possible population curves. In other words, the curve of population size through time cannot be identified from genealogical information. This suggests a profound lack of robustness of the coalescent to deviations from its assumption that population size changes deterministically, which we illustrate by doing demographic inference with the coalescent on GW-generated data, without success.

Balanced Minimum Evolution: Theoretical and Computational Advances

Daniele Catanzaro

We discuss here some recent theoretical and computational advances on Balanced Minimum Evolution (BME). We start by showing that BME is an information entropy minimization problem and that its minimum BME-length phylogeny encodes the minimum crossentropy between the probability distributions associated to the n the evolutionary processes (rooted binary trees) having the n taxa under study as sources (roots). This new perspective both extends the previous interpretations of the BME length function described in the literature and enables the identification of an efficiently computable family of lower bounds on the value of its optimal solution. We also address a long standing open question concerning the characterization of the necessary and sufficient conditions that a nxn symmetric integer matrix must satisfy to encode the Path-Length Matrix (PLM) of an Unrooted Binary Tree (UBT) with n leaves and we present a new state of the art massively parallel branch-and-cut algorithm to exactly solve instances of the BMEP. Finally, we discuss some fundamental limits of BME that involve and relate numerical stability with statistical consistency issues.

Exploiting genomic surveillance to map the spatio-temporal dispersal of SARS-CoV-2 spike mutations in Belgium across 2020

Nena Bollen * 1 , Simon Dellicour , and Guy Baele

1 - KULeuven – Belgium

Since the start of the COVID-19 pandemic, an unprecedented number of genomic sequences of SARS-CoV-2 have been generated and shared with the scientific community. The unparalleled volume of available genetic data presents a unique opportunity to gain real-time insights into the virus transmission during the pandemic, especially since the emergence of variants of concern. At the same time, it presents a daunting computational hurdle if analyzed with gold-standard phylogeographic approaches. To tackle this practical limitation, we have developed a proof-of-concept for a rapid analytical pipeline to analyze the spatiotemporal dispersal history and dynamics of SARS-CoV-2 lineages, by combining maximum likelihood phylogenetic inference with Bayesian phylogeographic inference. We focus on different resolutions (country-wide versus province-specific) in applying this methodology. We pay specific attention to the Belgian province of Liège that has been consistently sampled throughout 2020, but was also one of the main epicenters of the second European epidemic wave. Specifically, we infer the regional dispersal history of viral lineages associated with three specific mutations on the spike protein (S98F, A222V and S477N) and quantify their relative importance through time. This analytical pipeline enables analysing large data sets and has the potential to be quickly applied and updated to track target mutations in space and time throughout the course of an epidemic.

SplitsTree6 - integrating phylogenetic trees and networks

Daniel Huson * 1 and David Bryant * 2

1 - University of Tuebingen – Germany
2 - University of Otago – New Zealand

Phylogenetic trees are the main work-horses of evolutionary analysis. Phylogenetic networks are much less widely used. With SplitsTree6, we hope to provide a platform that makes it easy to explore the use of phylogenetic networks in evolutionary studies. SplitsTree6 provides methods for calculating and visualizing unrooted and rooted phylogenetic trees and networks, including split networks, phylogenetic outlines, hybridization networks, haplotype networks, densi-trees and tanglegrams. The program is based on the concept of a workflow, which explicitly represents the data and algorithms in use. This is joint work with David Bryant.

Trade-off between reducing mutational accumulation and increasing commitment to differentiation determines tissue organization

Gergely Szöllősi ∗[1]

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Species-specific differences control cancer risk across orders of magnitude variation in body size and lifespan, e.g., by varying the copy numbers of tumor suppressor genes. It is unclear, however, how different tissues within an organism can control somatic evolution despite being subject to markedly different constraints, but sharing the same genome. Hierarchical differentiation, characteristic of self-renewing tissues, can restrain somatic evolution both by limiting divisional load, thereby reducing mutation accumulation, and by increasing cells' commitment to differentiation, which can "wash out" mutants. I describe our recent results exploring the organization of hierarchical tissues that have evolved to limit their lifetime incidence of cancer. Estimating the likelihood of cancer in the presence of mutations that enhance self-proliferation, we demonstrate that a trade-off exists between mutation accumulation and the strength of washing out. Our results explain differences in the organization of widely different hierarchical tissues, such as colon and blood.

Assessing the effects of date and sequence data in phylodynamics

Leo Featherstone ∗[1,2], Sebastian Duchene [1,2], and Timothy Vaughan [3,4]

1 - Department of Microbiology and Immunology, The University of Melbourne – Australia
2 - Peter Doherty Institute for Infection and Immunity – Australia
3 - Department of Biosystems Science and Engineering, ETH Zurich – Australia
4 - Swiss Institute of Bioinformatics – Australia

There has been a longstanding need in phylodynamics to quantify the relative effects of genetic sequence data and sampling time data when inferring epidemiological parameters. It has previously been shown that sequence sampling times, rather than the actual genome data, can drive phylodynamic inference. This raises the question of the utility of genome data for estimating epidemiological parameters with each new analysis. We introduce a formal method to quantify the effects of date and sequence data under the birth-death model to address this question. We show that either data source can drive inference of the basic reproductive number (R_0), but our method is applicable to any parameter. This framework enables phylodynamics to draw conclusions about which data drive inference, which is crucial for a deeper understanding of commonly used phylodynamic models and to better direct sequencing efforts during future outbreaks.

Fast and Accurate Resolution of the Birth-Death Exposed-Infectious (BDEI) Model

Anna Zhukova ∗[1,2,3,4], Frederic Hecht [5], Yvon Maday [6,5], and Olivier Gascuel [1,7]

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The birth-death exposed-infectious (BDEI) model describes the transmission of pathogens that feature an incubation period (when the host is already infected but not yet infectious), like for example Ebola and SARS-CoV-2. In a phylodynamics framework, BDEI model allows us to infer such epidemiological parameters as the basic reproduction number R0, the incubation period and the infectious time from a phylogenetic tree (a genealogy of pathogen sequences). With constantly growing sequencing data, the BDEI model should be extremely useful for unravelling information on pathogen epidemics. However, the existing implementations of this model in a phylodynamics framework have not yet caught up with the sequencing speed. While the accuracy of the estimations should increase with the data set size, the existing BDEI implementations are limited to medium data sets of up to 500 samples, for both computing time and numerical instability reasons. We improve the accuracy and drastically reduce the computing time for the BDEI model by rewriting its differential equations in a highly parallelizable way, and by using numerical analysis methods for their efficient resolution. Our implementation takes less than 1 minute on a phylogenetic tree of 10,000 samples. We compare on simulated data our parameter estimator to the existing implementations, such as the golden standard Bayesian tool BEAST2 ; results show that we are not only much faster, but also more accurate. The application of our method to the 2014 Ebola epidemic in Sierra-Leone is also very convincing, with more accurate estimates of the incubation period.

A Cauchy process to model trait evolution on a phylogeny

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Phylogenetic comparative methods correct for the shared evolutionary history among a set of non-independent organisms by modeling the sampled continuous trait as arising from a diffusion process along the branches of a phylogenetic tree (1). Beyond the Brownian motion, several processes have been proposed in the literature, either Gaussian, in which case efficient algorithms relying on the Kalman filter are available (2,3), or based on more general Lévy processes, that can model a realistic evolution with jumps, but that are computationally intensive (4-7). Here, we propose to use a Cauchy process, for which we derive a recursive algorithm to compute the likelihood in a polynomial time. The Cauchy process is a pure jump process, that can also be seen as a Brownian motion with an inverse gamma relaxed variance parameter (8). It is already widely used to model virus spatial diffusion in phylodynamics approaches, as it can capture both small scale and large scale diffusion events, that are common in an epidemics. It can also be used in ecology to account for the heterogeneous evolution of functional traits of related organisms on long time scales.

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Phylogenetics and ecological networks: old challenges and new opportunities

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Can we predict the structure of an ecological network from the phylogeny of the species present in that network? In this talk I will tell the story of how we went from a ``sadly no” to a promising ``probably yes”. Moreover, I will present some of the open challenges and novel opportunities for large scale systems.

The evolutionary nature of ecological network structures is at the same time obvious and elusive: despite some high-level ecological roles have deep phylogenetic identities (such as the plants vs. animals, erbivora vs. carnivora, ...) Blomberg’s et al. notice that ``behavioral traits exhibit lower signal”. In other words, the fine position of species in the ecological networks tends to be less evolutionary conserved and more strongly determined by enviromental factors and filtering effects. The preponderance of enviromental mechanism may explain a certain scepticism toward phylogenetic methods in network ecology. At the same time, most of the research in the time development and growth of ecological networks has focused on models where events are discrete changes, such as the appearence or disappearence of a node (a species), the addition or removal of an edge (an ecological relation). The discreteness and the resulting combinatorial complexity prevented the full deployment of phylogenetic comparative methods.

Our approach to cut the Gordian Knot is the outcome of a different representation of ecological network. Instead of focusing on them as discrete objects, we consider their (reversible) embedding as cloud of points in a low-dimensional metric space(1). This, in turns, allows us to model continuous, probabilistic objects and consider their time development as a (evolutionary) dynamical system. In a recent paper(2) we showed that we can accurately exploit this representation and the knowledge of ecological relationship in other networks to predict a target network solely from the phylogeny of the species in it.

Yet, much more can be done. Namely, we can use this approach to attemp the ancestral state reconstruction of ecological networks, or even predict their evolution under diverse speciation and extinction models. Finally, we can pose questions such as: what genes, or groups of genes, are more closely aligned to the position of species in ecological networks, and what do they mean for the evolutionary processes?

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The ghost of past selection in the critically endangered kākāpō

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The combination of genomic and phenotypic data in wildlife conservation enables the application of quantitative genomic approaches that link genomic regions with important traits and directly assess the adaptive potential of populations. We leveraged cutting-edge quantitative genomic approaches to explore genomic, phenotypic, and environmental factors that affect the persistence of the critically endangered kākāpō (Strigops habroptilus). An extraordinarily detailed phenotypic catalogue allowed us to assess heritability and polygenicity, identify underlying genes and gene pathways, and evaluate genomic predictability of various traits of the species. Here, we will focus on the genomic architecture of kākāpō plumage morphology to showcase the power of such quantitative genomic approaches and their potential to elucidate past and on-going selection pressures on an endangered species: Through phenotypic and genomic analyses, we were able to fully explain kākāpō plumage based on two epistatic single-nucleotide polymorphisms. We followed up with in-depth evolutionary genomic analyses and simulations to understand how and why these genomic polymorphims were maintained, where our genetic forward simulations found a remarkably stable valley of the two epistatic polymorphisms in the evolutionary load landscape. We will present genomic, phenotypic and simulation results which point towards that this genomic architecture is the footprint of past selection on plumage through a now extinct predator.

Impact and mitigation of sampling bias to determine viral spread: evaluating discrete phylogeography through CTMC models and structured coalescent model approximations

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Over the past decade, Bayesian phylogeographic inference has greatly benefited viral epidemiological studies in unraveling the origin and subsequent spread of viral epidemics, the spatial processes driving viral spread, and environmental and human-related factors associated with viral spread. These approaches are complementary to mathematical modeling and epidemiological studies, and particularly informative when epidemiological data are scarce. However, genetic samples potentially constitute a biased snapshot of the underlying viral spread, especially when isolated through passive surveillance systems. The impact of such sampling bias is insufficiently characterized. Here, we investigated the impact of sampling bias on the spatiotemporal reconstruction of viral epidemics using Bayesian phylogeographic models and explored different operational strategies to mitigate this impact. We considered a popular computationally efficient discrete phylogeographic inference approach that makes use of continuous-time Markov chain (CTMC) modeling as well as two structured coalescent approximations (BASTA and MASCOT). We first simulated viral epidemics across three and seven discrete locations using a stochastic metapopulation model, based on rabies virus epidemics in dogs in Morocco. We subsequently simulated and subsampled whole-genome viral sequences associated with each infection in a biased or unbiased way before comparing the estimated spatiotemporal history to the simulated one. We were able to estimate the true underlying genetic processes (e.g., evolutionary rate, tree topology) in a robust manner but found that the expected number of migration events was dramatically impacted by sampling bias under a CTMC model. BASTA and MASCOT did not capture as well as CTMC the number of migration events in the absence of sampling bias, but their estimates were little impacted by sampling bias. Increasing the number of analyzed genomes led to more robust estimates at low sampling bias for all algorithms. Alternative sampling strategies that maximize the spatiotemporal coverage greatly improved the inference at intermediate sampling bias, especially for CTMC and to a lesser extent for MASCOT and BASTA. We applied these phylogeographic models on two empirical data sets: a rabies virus data set from the Philippines covering the 2004-2010 period, and a SARS-CoV-2 data set from the first wave of infections in early 2020 across the world. In conclusion, sampling biases are ubiquitous in phylogeographic analysis but may be accommodated by increasing sample size, balancing spatial and temporal composition in the data, and informing phylogeographic models with additional data, notably case count data. In the context of resource-limited settings, careful sequencing strategies could improve the applicability of phylogeographic inference in a cost-effective manner.

Bayesian phylodynamic inference of multi-type population trajectories using genomic data

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Phylodynamic methods provide a coherent framework for the inference of ancestral population-level parameters directly from genetic data. They are a important tool for understanding both the behaviour of epidemics as well as long-term macroevolutionary trends in speciation and extinction. In particular, phylodynamic methods based on multi-type birth-death models have been used to model the evolution of discrete traits, the movement of individuals or pathogens between geographic locations or host types, or the transition of infected individuals between disease stages. Typically, methods which allow inference of parameters and ancestral trait values under multi-type birth-death models integrate out the possible birth-death trajectories to reduce the computational demands of the inference. As a result, it has not been possible to use these methods to directly infer the dynamics of trait-specific population sizes, infected host counts or other such demographic quantities. In this paper we present a straight-forward method which recovers these multi-type trajectories almost no additional computational cost. We demonstrate the practicality of our approach by applying it to a previously-published set of MERS-CoV genomes, allowing us to directly infer the numbers of human and camel cases through time, together with the timing of spillovers from the camel reservoir.

Posters

ARPIP: Ancestral sequence Reconstruction with insertions and deletions under the Poisson Indel Process

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Phylogenetics is a wide research field with a variety of applications ranging from reconstructing the tree of life to investigating ongoing epidemics. Given a phylogeny and a multiple sequence alignment from surviving species, we can infer the ancestral sequences. This insight into the evolutionary history of ancient molecules helps us understand gene function and investigate gene adaptation and convergent evolution. Here we propose a dynamic programming algorithm for joint reconstruction of ancestral sequences under the Poisson Indel Process. This modelling approach provides an explicit biological interpretation of indel events and linear time complexity for the likelihood computation with respect to the number of sequences. Our method, which we call ARPIP, consists of two steps, namely finding the most probable indel points and reconstructing ancestral sequences. First, we find the most likely indel points and prune the phylogeny to reflect the insertion and deletion events per site. Second, we infer the ancestral states on the pruned subtree in a manner similar to FastML. We applied ARPIP on a simulated dataset and on real data from the Betacoronavirus genus. We show that ARPIP reconstructs both the indel events and substitutions with a high degree of accuracy, and that our method fares well when compared to established state-of-the-art methods such as FastML and PAML. Moreover, the method can be extended to allow us to explore both optimal and suboptimal reconstructions, include rate heterogeneity through time and more. We believe it will expand the range of novel applications of ancestral sequence reconstruction.

Beyond one-gain models for pangenome evolution

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A species pangenome is the set of all genes carried by at least one representant of the species. In bacteriae, pangenomes can be much larger than the set of genes carried by one individual. Many questions remain unanswered regarding the evolutive forces shaping these bacterial pangenomes. One of them is to explain the U-shape of the gene frequency spectrum: there are more genes present in very few or almost all genomes than at intermediate frequencies. Two papers from 2012 (Baumdicker et al. and Heageman and Weitz) explained this distribution with stochastic models allowing genes to be gained only once in the species phylogeny. However the importance of intra-specific horizontal gene transfer (HGT) in many bacterial species calls for more complex models. Using a dataset of 436 commensal E.coli genomes, we show that a model with only one gain per gene is not able to reproduce the patterns of presence/absence of genes at the leaves of the phylogeny. We thus introduce a new model of pangenome evolution including a category of genes that can be gained and lost in the phylogeny multiple times, interpreted as genes undergoing frequent HGT. Both the gene frequency spectrum and the presence/absence patterns are reproduced more accurately.

Sampling consistency of diffusion statistics in Bayesian phylogeography

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Bayesian phylogeography provides insight into the past evolution and spread of an organism using genetic and geographic data. The inference of the spatial diffusion of this organism is based on the evolution of a continuous multivariate trait: location, expressed as latitude and longitude coordinates. Common models for this continuous trait include the Brownian process (strict or relaxed (1)) and the Cauchy process (allowing jumps in the diffusion (2)).
In order to analyze and characterize the evolution, we can rely on diffusion statistics, mainly the diffusion rate (3) and the diffusion coefficient (4,5) which aim at estimating the pace at which lineages spread throughout their habitat.

However, we found that for both location models, the diffusion rate is impacted by the number of samples we are studying. More precisely, if we have N samples, the diffusion rate evolves in sqrt(N) for a Brownian process, and in log(N) for a Cauchy process. This result implies that the statistics studied would be sensitive to sampling, and that their analysis would require special consideration. Practical analyses on BEAST (6) with sequences from the West Nile Virus also showed a sampling bias on the diffusion rate value, but not in the same way as the theory predicted. Simulations were therefore carried out to test the sampling consistency of the statistics.

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PPalign: Optimal alignment of Potts models representing proteins with direct coupling information

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To assign structural and functional annotations to the ever increasing amount of sequenced proteins, the main approach relies on sequence-based homology search methods, e.g. BLAST or the current state-of-the-art methods based on profile Hidden Markov Models (pHMM), which rely on significant alignments of query sequences to annotated proteins or protein families. While powerful, these approaches do not take coevolution between residues into account. Taking advantage of recent advances in the field of contact prediction, we propose here to represent proteins by Potts models, which model direct couplings between positions in addition to positional composition, and to compare proteins by aligning these models. Due to non-local dependencies, the problem of aligning Potts models is hard and remains the main computational bottleneck for their use. We introduced an Integer Linear Programming formulation of the problem and PPalign, a program based on this formulation, to compute the optimal pairwise alignment of Potts models representing proteins in tractable time. The approach was assessed with respect to a non-redundant set of reference pairwise sequence alignments from SISYPHUS benchmark which have lowest sequence identity (between 3% and 20%) and enable to build reliable Potts models for each sequence to be aligned. This experimentation confirmed that Potts models can be aligned in reasonable time (1'37” in average on these alignments). The contribution of couplings was evaluated in comparison with HHalign and independent-site PPalign. Although Potts models were not fully optimized for alignment purposes and simple gap scores were used, PPalign yielded a better mean F1 score and found significantly better alignments than HHalign and PPalign without couplings in some cases. These results, published in BMC Bioinformatics last year, show that pairwise couplings from protein Potts models can be used to improve the alignment of remotely related protein sequences in tractable time. Our experimentation suggested yet that new research on the inference of Potts models is now needed to make them more comparable and suitable for homology search. We are currently investigating in this direction, with the challenge of inferring more sensitive models with relevant coupling information.

Improving gene classification into gene families via phylo-k-mers

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The functional annotation of a proteome or a transcriptome is a task generally based on the classification of each of their sequence into gene families, e.g. a sets of genes that are co-orthologs from a fixed taxonomic perspective. Commonly, this task is based on similarities derived from local alignments (Blast-like approaches) Markov Model based alignments. Profiles and alignments can be built for each family independently. However, to improve the quality of the classification, one must however consider the evolutionary relationships that link the different gene families, in particular when varying evolutionary rates are characterising them. Some authors attempted to resolve this issue by computing nested profiles for different tree levels and refining the classification via phylogenetic placement tools (Tang et al, 2019, Emms et al, 2022). An alternative approach was designed by Rossier et al, with a 2-step algorithm based on k-mer indexation and tree contextualization based on ``ancestral" k-mer shared by all members of a subtree (Rossier et al, 2020). Taking into account the evolutionary relationships between families improved the classification. Such contextualization can also be performed via phylo-k-mers, a probabilistic photogenically-aware extension of the notion of k-mers that we recently developed (Linard et al, 2019, Scholz et al, 2020). From alignments and phylogenetic trees describing each gene family, phylo-k-mers can be computed. They are not necessarily observed in the input data, they are indexed when they show a high probability to have diverged from a specific branch of the family tree. I will present a new algorithm of gene classification based on phylo-k-mers. This new approach aims to reunite the power of k-mers (scalability) and phylogeny (accuracy). In particular, i) it aims to reduce the taxonomic biases encountered when profiles or alignments of strong taxonomic composition biais are used, ii) it aims to be agnostic to frame-shifts, iii) its 2-step design allows very fast classifications, and iv) optionally, it allows immediate phylogenetic placement into the family tree. We recently reinforced the scalability of this approach with the help of new algorithmic development dedicated to the production of fast and efficient phylo-k-mer computations. I will briefly discuss these developments.

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Mutual Information-based Feature Selection of Informative Phylo-k-mers

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Phylo-k-mers is a probabilistic phylogenetically-aware extension of the notion of k-mers. For a reference alignment of sequences of a genomic region and a phylogenetic model of sequence evolution, they describe what k-mers can be observed at different locations of a fixed phylogeny and with what probability. Computation of phylo-k-mers is a prerequisite for the recently proposed methods of alignment-free phylogenetic placement and detection of novel viral recombinants. Many k-mers - potentially 4ˆk for DNA and 20ˆk for protein sequences - need to be considered at each tree node, making the resulting collections of phylo-k-mers large in size.

We proposed an information-based method of selecting phylo-k-mers that are informative for phylogenetic placement. The method adapts an existing feature selection approach for text classification, computing Mutual Information between the tree branch variable and the variable indicating the presence of a k-mer in hypothetical sequences originating from this branch. Experiments on phylogenetic placement using filtered sets of phylo-k-mers showed that accurate phylogenetic placement can be performed using only small fractions of the most informative phylo-k-mers: 6% of their total number for placing rbcL gene sequences and 12% for 16S rRNA gene sequences.

Preprocessing Strategies for Bayesian Phylogeographic Analysis Using Large-Scale Genomic Sequence Data

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The ongoing SARS-CoV-2 pandemic has been posing a huge threat to public health, economic development and social interactions since the end of 2019. Different SARS-CoV-2 variants keep emerging throughout this pandemic and are important to study in terms of their evolution, local and/or global dispersal, impact on transmissibility, severity, and immunity. First detected in December 2020, SARS-CoV-2 lineage B.1.525 contains several mutations of biological significance. The E484K mutation and ΔY144 deletion tend to drive immune escape, while the D614G mutation and ΔH69/V70 deletion can increase transmissibility and infectivity. With nearly ten thousand genomes from this lineage being available, conducting a detailed Bayesian phylogeographic analysis on the complete data is not feasible. We explore different strategies for reducing this data set to a representative set of genomic sequences that enable us to reconstruct the origin and dispersal history of this lineage. Initial data exploration strategies such as provided in TempEst have yielded different results depending on data set size, with the complete data set seemingly evolving at half the evolutionary rate as a data set that consists only of high-quality genomes. We first explore various maximum-likelihood and Bayesian inference methodologies - paying special attention to different molecular clock and tree prior specifications - on this core high-quality data set to establish a consensus for both TMRCA and mean evolutionary rate, which we compare to estimates from other SARS-CoV-2 lineages. We subsequently evaluate the temporal signal in the remaining genomes, grouping by time, sequencing lab and country, to determine which genomes bias the temporal signal in the core data set and warrant further investigation. To this end, we use several popular inference packages, such as BEAST, TreeTime and Chronumental. When the final data set has been constructed, we employ several subsampling procedures to avoid sampling bias, as this might impact estimation of important phylogenetic and phylogeographic parameters. Targeted at analysing thousands of viral sequences, our work aims to provide a reproducible genomic data (pre-)processing pipeline for (SARS-CoV-2) phylogeographic inference analyses.

Combinatorics of multiple-merger coalescent genealogies

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Sample genealogies generated according to Kingman’s Coalescent are always binary. More precisely, they are elements of the class of binary time-labelled trees of finite size. The combinatorial aspects of this class are well-understood, and it is also well-known what probability distribution is imposed on them by the process. However, under a lot of other population models, such as the Lambda-Coalescents, of which Kingman’s Coalescent is a special case, or various spatial models (e.g. the spatial Lambda-Fleming-Viot, Branching Brownian Motions etc), internal nodes of sample genealogies do not need to be binary. The combinatorial class of general time-labelled trees is not as well-understood as their binary counterpart, and there are also few results regarding what probability distribution is induced on them by the differend models. We make use of techniques borrowed from the field of analytic combinatorics to study the asymptotics of the number of trees of any size, and point out some relations between the Lambda-Coalescents (particularly, the so-called Psi-Coalescents) and their respective tree probability distributions.

Leveraging tools from Nextstrain for bespoke phylogenetic analysis of viral pathogen epidemics

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Timely, actionable analysis of emergent viral outbreaks is vital to inform effective public health intervention. Phylogenetic and phylogeographic techniques represent powerful, flexible tools for inference of epidemiological factors of a viral outbreak that are of public health import: reproductive number, evolutionary rate, effective viral population size, and the timing of geographic migrations can all be inferred using phylogenetic techniques. Today, a key challenge to using these methods for the analysis of viruses of great threat to human health-particularly SARS-CoV-2, the causative agent of COVID-19-is the vast quantity of genomic sequence data and associated metadata that are generated every day. Due to the computational complexity of phylogenetic modeling techniques, it is necessary for researchers to employ principled methods of data selection and analysis to strike a balance between ensuring analytical timeliness through subsampling, thereby preserving key trends that may inform public health interventions. Nextstrain, a phylogenetics toolkit that facilitates analysis from database-to-visualization, sits at the forefront of real-time phylogenetic and genomic epidemiological analysis. Here, we describe a methodology by which Nextstrain tools can be used in conjunction with other existing phylogenetic analysis software and custom scripts to create bespoke analyses of SARS-CoV-2 genomic sequence data. Our novel methodology supplements existing pipelines in three major ways. First, we show how high-resolution geographic metadata may be incorporated into existing Nextstrain workflows to facilitate the identification and characterization of local viral transmission chains within the context of a single country's SARS-CoV-2 landscape. Second, we enable and showcase the use of custom phylogenetic inference approaches within Nextstrain for tree building, and ancestral state reconstruction. Finally, we demonstrate how Nextstrain tools used in conjunction with the novel methodologies we describe can be used to inform further analyses that account for phylogenetic and phylogeographic uncertainty.

Modeling the dynamics of antibiotic resistance genes: towards an ecology of the bacterial pangenome

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One of the major challenges for human and animal health in the coming decades is to control the emergence and spread of antibiotic resistance (AR) in bacteria. Mobile genetic elements (MGEs) are the main vehicles of AR genes and their evolutionary trajectories are partly independent of those of their bacterial hosts. Understanding the dynamics of AR requires understanding the co-evolution of bacterial and MGE strategies, and identifying the forms of evolutionary cooperation and conflict between these entities. Here, we focus on the evolution of MGE strategies in the bacterium Acinetobacter baumannii (Ab). Ab represents a growing public health problem due to its level of resistance to antibiotics. In Ab, as in many other bacteria, natural transformation (acquisition of extracellular DNA controlled by bacteria) is a way to cope with environmental stochasticity by ensuring both the acquisition of new genes (e.g. from MGEs carrying AR genes) and their elimination. While MGEs carrying AR genes could insert themselves randomly into the genome, we showed that in more than 96% of the cases, they integrate into a specific gene (comM) which results in a drastic (but not total) reduction of the transformation rate of bacteria. This suggests that MGEs cooperate with bacteria (by carrying AR genes) but also have a form of conflict with them (by partially inhibiting natural transformation). To test this hypothesis, we propose a model to quantify the success of competing MGEs while inserting into sites that partially, not at all or completely inhibit transformation. From this model parameterized with experimental data, we observed that the insertion of MGEs into the site that partially inhibits natural transformation confers a selective advantage to MGEs when the host bacteria are exposed to a stochastic environment. This strategy allows MGEs to minimize the risk of being eliminated from genomes by natural transformation, while ensuring that their host cells maintain a basal transformation activity that allows them to acquire other adaptive genetic determinants, thus favoring the propagation of these MGEs. This work shows that the probability of persistence of AR genes depends strongly on the strategies of the MGEs that carry them. It is therefore necessary to develop new approaches to better understand the eco-evolutionary dynamics of MGEs and bacteria (alternating conflicts and evolutionary cooperation) to understand the dynamics of the AR and more broadly the dynamics of bacterial pangenomes. We propose to develop new models inspired by theories and tools of ecology to understand this complexity, going beyond the classical approaches of genomics.

Estimation of reproductive number and prevalence using genomic and time series data

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In genetic epidemiology, current methods can struggle with the size of pathogen genome datasets. While the methodology for processing increasingly large datasets receives substantial attention, less progress has been made in integrating additional types of data into analyses. For example, utilising both pathogen genomes and time series of confirmed cases to inform estimates. Mechanistic models of transmission and observation (e.g. the birth-death-sampling model) provide a natural approach to include additional streams of data but can be challenging to apply in practice. To utilise both genomic and case data on a large scale, we developed an efficient and accurate approximation scheme, called TimTam, capable of estimating both the reproductive number and the prevalence of infection. This method (with piecewise constant rate parameters) will soon be available as a BEAST2 package.

Bridging the gap between population genomic and phylogenetic approaches

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The availability of an increasing amount of genetic data has resulted in a boom in molecular evolution studies in recent years and a better elucidation of evolutionary mechanisms such as genetic drift. The intensity of the genetic drift is inversely proportional to the number of breeders in the population, i.e. the effective size (Ne). It can impact both short and long term evolutionary processes (estimated respectively from polymorphism and divergence data). The aim of my work is to contrast intraspecific and interspecific data in order to bridge the gap between population genomic and phylogenetic analyses.

In this study, I estimate variations in Ne between species based on genome-wide heterozygosity, correcting for variations in mutation rate (μ), along the mammalian phylogeny in order to study correlations between Ne, ecological traits and molecular traits such as selection intensity (both long term, based on dN/dS, and short-term, based on piN/piS). For this purpose, I devised a pipeline from the recovery of orthologous gene sequences, ecological and heterozygosity data to Bayesian integrative analysis aiming at reconstructing Ne by a multivariate process (1). I observe that the Ne of very massive animals is much smaller than the Ne of small mammals. I obtain positive corelations between dN/dS and life history traits, consistent with previous analyses (2) and suggestive of a role of Ne. The more direct correlation of traits with heterozygosity and Ne is still under investigation.

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Convolutional graph networks for Coevolution detection in COVID19

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Since the start of the COVID19 pandemic we have had access to an unprecedented volume of data available to inform epidemiological and healthcare policy decisions, but making sense of this deluge of genomic data has been difficult using current bioinformatics methods. One technique which may provide insight into COVID's evolutionary trajectory in response to the shifting fitness landscape is to study coevolutionary patterns in the genome or protein sequences. Finding these evolutionary associations could point to shared constraints in the viral replication cycle between multiple sites and provide valuable targets for treatment and prevention. Unfortunately, finding coevolutionary signals between sites of the viral genome or the viral proteome has so far been prohibitively computationally expensive due to quadratic

time complexity associated with comparing all 30K sites combined with the sheer number of sequences (over 3.5 million and rapidly increasing). This presentation showcases tools built around distributed computing, probabilistic data structures and machine learning to deal with these problems and extract pairs of coevolving sites from the GISAID database containing all available COVID sequences. While the COVID19 pandemic is currently unique in its density of sampling, we may see similar datasets emerge in coming years in the context of continuous metagenomic monitoring, in the unfortunate event of further pandemics or in other heavily sequenced species such as humans. We hope that the ideas presented in this work will also see adoption in these emerging areas.

Bayesian model comparison of molecular clock models - a phylogenetic simulation study

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In the 1960s, several groups of scientists - including Emile Zuckerkandl, Linus Pauling and Allan Wilson - had noted that proteins experience amino acid replacements at a surprisingly consistent rate across very different species. Since the proposal of such a (strict) clock model, a wide range of different clock model parameterizations have emerged which now take up a prominent place in the field of phylogenetic inference as well as in many other areas of evolutionary biology. In studying pathogen evolution, molecular clocks allow combining the genetic differences between samples and their collection times to estimate time-calibrated phylogenies. Along with the development of increasingly complex clock models comes the need to accurately determine which model is best suited to analyse a particular data set. For this purpose, different marginal likelihood estimators have been developed in recent years to compare relative model fit in a Bayesian framework. These estimators have shown considerable improvements in accuracy, but often at the expense of an increased computational cost. In our simulation study, we examine the performance of these estimators in identifying the correct underlying molecular clock model.

Protein folds as synapomorphies of the tree of life

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Structural domains of proteins are defined by the connectivity and organisation in three dimensions of their secondary structures: the ``fold". The total number of folds is quite stable, about 1200 which is surprisingly low. It is possible that folds are extremely reliable characters, thus reliable phylogenetic entities, complementary to traditional phylogenetic signals. Moreover, their slower dynamic of change could allow to highlight deep evolution of organisms. We have explored the repartition of folds within the tree of Life to evaluate their potential as phylogenetic markers and trying to answer the question of structural convergence by measuring the consistency of their repartition within a reference phylogeny. We mapped folds onto a tree of life and measure the consistency of each fold character. We have developed and explored a methodology which allows us to analyze the repartition of folds relying on a seriated heatmap and several clusterings.

Our results show that 20% of the folds are present in all superkingdoms, and 53.9% are potential synapomorphies. We find fold characters consistently supporting several nested eukaryotic clades with divergence times spanning from 1,100 mya to 380 mya. As for the earliest branches of the tree of life, the three superkingdoms are discriminated by eukaryotic specific folds (181) as well as shared folds between Eukaryota and one of the two other superkingdoms. Many folds shared by parts of eukaryotes and some eubacteria should result from past horizontal transfers (e.g. cyanobacteria to photosynthetic eukaryotes) witnessing significant fold flow to eukaryotes. Among eukaryotes, some folds therefore appear as synapomorphies of the species phylogeny, while others are markers of transfers to Eukaryota.

We have highlighted that folds are reliable synapomorphies. They are witnesses of ancient events like primary and secondary endosymbiosis, but they can be specific of more recent clades like metazoan or vertebrates. We have also analyzed functions of folds inherited from archaea and bacteria which reveal in both cases an over-representation of informational function. For specific eukaryote folds, we observe an overrepresentation of regulation functions linked to extra-cellular mechanism matching with multicellularity appearance.

Folds provide information for reconstructing the history of life as witnesses of major evolutionary events or as witnesses of the appearance of new functions during evolution. They can also provide valuable insights into the evolution and design of protein folds: how do they arise, evolve and adapt to specific functions? However, our work highlights the complex history of folds and the need to untangle the evolutionary events of lateral transfers to understand the divergence and apparition of new protein structure. Here we would like to discuss with the community the best approaches to address these questions.

Evaluation of methods to detect shifts in directional selection at the genome scale

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Identifying the footprints of selection in coding sequences can inform about the importance and function of individual sites. Analyses of the ratio of non-synonymous to synonymous substitutions (dN /dS) have been widely used to pinpoint changes in the intensity of selection, but cannot distinguish them from changes in the direction of selection, i.e., changes in the fitness of specific amino acids at a given position. A few methods that rely on amino acid profiles to detect changes in directional selection have been designed, but their performance have not been well characterized. In this paper, we investigate the performance of 6 of these methods. We evaluate them on simulations along empirical phylogenies in which transition events have been annotated, and compare their ability to detect sites that have undergone changes in the direction or intensity of selection to that of a widely used dN /dS approach, codeml's branch-site model A. We show that all methods have reduced performance in the presence of biased gene conversion but not CpG hypermutability. The best profile method, Pelican, a new implementation of (Tamuri et al., 2009), performs as well as codeml in a range of conditions except for detecting relaxations of selection, and performs better when tree length increases, or in the presence of persistent positive selection. It is fast, enabling genome-scale searches for site-wise changes in the direction of selection associated with phenotypic changes.

Uncovering the Diverse Roles of Short Tandem Repeat Variation in Colorectal Cancer

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Short tandem repeats (STRs, also known as microsatellites) are highly variable, back-to-back repetitions of small DNA motifs. Insertions and deletions of repeat motifs are common in STR loci and can affect gene expression levels and protein structures. Their high mutability can result in tumor-specific neoantigens, making them promising targets for cancer vaccines and immune therapies. Although recently developed computational approaches allow for accurate genotyping of STRs from sequencing data, many investigations of STR variation in cancer predate these methods. We therefore suspect that the contribution STRs have to the molecular picture of cancer is currently underestimated. To investigate this, we used repeat-specific methods to generate and genotype a panel of over 1.8 million STR loci in colorectal cancer (CRC) patients from The Cancer Genome Atlas. We stored both the panel of STR loci and their variability in CRC patients in a PostgreSQL database, which will be made available to the scientific community through a web interface for easy access. We detected tumor STR variants by comparing repeat lengths between patient-matched healthy and diseased tissue. We then estimated the contribution of these tumor STR variants to gene expression changes in CRC using existing catalogues of STRs known to affect expression. For STR variants in coding regions, we determined the expected changes in protein structure and monitored the potential generation of targetable neoantigens. While a lot of this is still work in progress, we expect our results will provide a better understanding of the diverse roles of STR variation in CRC. Using computational methods specifically designed to analyse STRs, we will demonstrate the importance of this abundant but often bypassed source of variation in cancer. Furthermore, by making our panel of STR loci and their variation in CRC patients available to the community, we hope to stimulate future investigations into this important topic.

The influence of genetic dosage on PRDM9-dependent evolutionary dynamics of meiotic recombination

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Meiosis is an important step in the eukaryotic life cycle during which recombination and proper chromosome segregation takes place. In mammals, recombination is regulated by the Prdm9 gene. This gene, which possesses a double function (recruitment of the double strand break machinery and facilitation of the pairing of homologous chromosomes), induces an intra-genomic Red Queen resulting from the opposition of two antagonistic forces : erosion of the recombination landscape by biased gene conversion and positive selection on PRDM9. This Red Queen was previously modeled, but without taking into account the role of PRDM9 as a pairing facilitator. Accordingly, I developed a mechanistic model taking into account the dual role of PRDM9. This modeling work gives important insights into the Red Queen mechanism, thus completing previous studies. In particular, it reveals that positive selection of new PRDM9 alleles is due to the reduced symmetrical binding caused by the loss of high affinity binding sites and, on the other hand, it demonstrate the influence of the genetic dosage of PRDM9 on the dynamics of the Red Queen, which can result in negative selection on new PRDM9 alleles entering the population.

An Individual-based model to study the importance of trade-offs in the evolution and diversification of traits in host phage population dynamics and long-term co-existence

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It has revealed over the last few decades that viruses play an important role in the evolution of all species, shaping populations and biodiversity in marine ecosystems. Mathematical and agent-based models are useful tools in studying/predicting the surprising patterns in virus-host dynamics, especially when we consider the fact that monitoring viral population parameters are challenging in the field and laboratory. We have developed an individual-based model to explore the dynamics of host and virus populations. Host dynamics are validated with lab results for different initial multiplicities of infection (MOI). We have studied the impact of coevolution and showed the importance of trade-offs between competitive and defensive host traits that can shape biological interactions and diversity in the host-phage dynamics. We have also investigated the effect of several organismal and environmental parameters such as the burst size of viruses on the dynamics of host and virus populations. Our model serves as a powerful tool to study bacteria phage interactions in different environmental settings.

GPU-accelerated online phylodynamic inference using BEAST

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The COVID-19 pandemic has put genomic epidemiology at the forefront of the pandemic response, with genome sequencing as an essential tool for tracking the emergence and spread of novel SARS-CoV-2 variants. Within this context, Bayesian phylodynamics provides a powerful framework to jointly reconstruct the evolution and spread of new variants while incorporating non-genomic data such as travel history and mobility information. A limitation of Bayesian phylodynamic analyses is that they take considerable time to run, due to the fact that sampling trees through Markov chain Monte Carlo (MCMC) is a very time-consuming process. This is specially cumbersome during an ongoing epidemic as continuous data generation requires frequently updated analyses. To account for this, a data augmentation procedure had previously been implemented in BEAST, allowing for phylodynamic inference in an online fashion. This approach has been shown to significantly reduce the burn-in time required for MCMC to converge. In addition, BEAST - in conjunction with the BEAGLE library - allows for GPU acceleration to further reduce the required computation time. In this study, we aim to assess the performance gains that can be obtained by parallelizing BEAST runs using multiple GPUs when performing online inference. For this purpose, we considered an early epidemic scenario by constructing an initial alignment of 502 SARS-CoV-2 genomes sampled during the beginning of the pandemic, which we updated 10 times at equally spaced time intervals using the online inference implementation in BEAST. At each time point, we ran 8 parallel GPU accelerated analyses and calculated the time required to obtain an effective sample size (ESS) of 200 when combining results using 1 to 8 GPUs. Our results show that using multiple GPUs significantly reduces the runtime required to obtain ESS > 200, with up to a 7.4-fold reduction in runtime across all dataset sizes (n=502 to 2,108) using 8 GPUs. Additionally, we observe that the marginal reduction in runtime decreases as more GPUs are included in the analysis, with 6 GPUs being the threshold after which we start observing diminishing returns.

Intergeneric relationships within Ophioglossaceae untangled with organelle phylogenomics

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Ophioglossaceae is one of fern families comprising of several ancient-diverged lineages, and some ancient lineages in this family contain only few living remnants, such as the monotypic subfamilies Helminthostachyoideae and Mankyuoideae. The four earliest diverged lineages among extant Ophioglossaceae are now recognized as different subfamilies, but their relationships remain unresolved seemingly due to insufficient phylogenetic efforts in previous studies. Former attempts to infer phylogenetic tree structures included only limited plastid regions, and some of them even contained a great portion of missing data. In two one phylogenomic analyses, the plastome dataset was used but scarce representatives with only one or two for each subfamily (or only three of them) sampled. Besides, a rather simplified substitution model applied in these phylogenomic datasets might introduce systematic errors. To tackle the deepest and also difficult nodes in Ophioglossaceae, we adopted a phylogenomic approach with adding more subfamily representatives (9 out of total of 12 currently recognized genera) and analyzed datasets from not only plastome but also mitogenome. We used genome skimming data to assemble these organelle genomes and from the resulting assemblies, we extracted the coding sequences (CDS) for the phylogenomic inferences. We tested different partition and substitution models for these phylogenomic datasets, including finer ones in order to better account for rate heterogeneity among loci and codon positions. Our phylogemonic results overall supported a novel, previously uncovered topology which presented the most solid infra-family backbone for Ophioglossaceae. Finally, based on this infra-family backbone, we traced phylogenetic origins of the hypothesized horizontal gene transfer (HGT) in organellar genomes, ancient whole genome duplication (WGD) events, and key morphological innovations in Ophioglossaceae.

The robustness of bootstrap branch supports with respect to taxon sampling

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The bootstrap method is based on resampling alignments and reestimating trees. Felsenstein's bootstrap proportions (FBP; Felsenstein 1985) is the most common approach to assess the reliability and robustness of sequence-based phylogenies. However, when increasing taxon-sampling (i.e., the number of sequences) to hundreds or thousands of taxa, FBP will tend to return low supports for deep branches. The Transfer Bootstrap Expectation (TBE; Lemoine et al. 2018) has been recently suggested as an alternative to FBP. TBE is measured using a continuous transfer index in [0,1] for each bootstrap tree, instead of the {0,1} index used in FBP to measure the presence/absence of the branch of interest. TBE has been shown to yield higher and more informative supports, without inducing falsely supported branches. Nonetheless, it has been argued that TBE must be used with care due to sampling issues, especially in datasets with high number of closely related taxa. In this study, we conduct multiple experiments by varying taxon sampling and comparing FBP and TBE support values on different phylogenetic depth, using both simulated and empirical datasets. Our results show that the main critic of TBE stands in extreme cases, but that TBE is still very robust to taxon sampling in most simulated and empirical cases, while FBP is inescapably negatively impacted by high taxon sampling. We suggest guidelines and good practices in TBE computing and interpretation.

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