Cancer Evolution: from processes to genomic patterns and back again

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Lyon, France

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Reminder: cancer evolution shapes observed heterogeneity

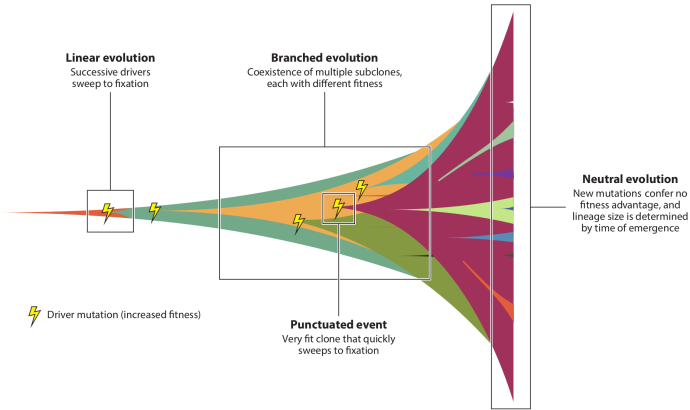
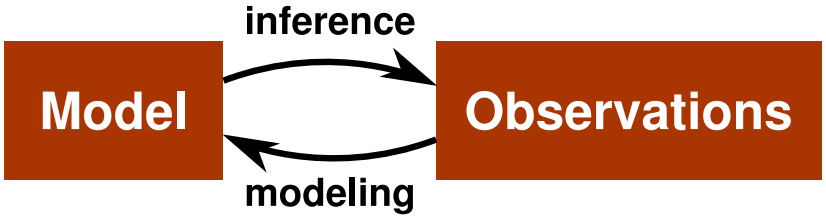


Figure: Schematic view of cancer evolution (Williams *et al.* 2019).

Why do we need models?

Models enable quantitative predictions about genomic patterns that can be tested using statistical inference methods



What are the important parameters?

Evolutionary parameters

- **Cancer cell population size**: gives an idea of tumor progression
- **Cell generation time**: rate of division of self-renewing cells
- **Mutation rate**: how often do alterations appear?
- **Selection coefficients**: do different tumor cells have different growth rates?

Ecological parameters

- **Ecological strategy**: what is the phenotype of the cancer cells? how does it provide an advantage?
- **Carrying capacity/Habitat quality**: what is the extent of vasculature and hypoxic niches? what it the nutrient concentration (e.g., glucose)?
- **Migration rate**: how often do cells migrate/metastasize to other locations?
- **Predation**: how much do immune cells (e.g., tumor-infiltrating lymphocytes) pressure the tumor?

Part I: evolution of the cancer genome

Modeling approaches

Theoretical frameworks are based on **population genetics** (the study of mutations in populations–at micro-evolutionary time-scales) and **molecular phylogenetics** (the study of mutations in species–at macro-evolutionary time-scales)

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Frameworks

- **Mathematical models**: *equations* describing the relationships between processes and observable quantities; allow precise description of the impact of evolutionary processes on genomic patterns
- **Computational models**: *algorithm* describing the effect of processes on observable quantities; allows complex models (e.g., model each cell)

Features

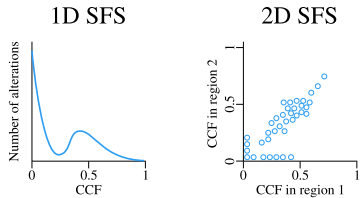
- e.g., spatially implicit or explicit

What is the main quantity of interest?

The cancer cell fraction (CCF)

Definition: proportion of tumor cells that harbor a given somatic alteration (e.g., mutation, indel, structural variant)

Typical representation: the Site Frequency Spectrum (SFS)



How to get the CCF?

Goal: go from variant allelic fraction (VAF, proportion of reads carrying the alteration) to cancer cell fraction (CCF)

Method: call single nucleotide variants (SNVs) and copy number variants (CNVs), and correct VAFs for CN state

- Easiest in diploid regions: then $\text{VAF} = \frac{1}{2}\text{CCF} \times \phi$, so

$$\text{CCF} = \frac{2}{\phi}\text{VAF},$$

where ϕ is the tumor purity. *Example: a heterozygous variant present in* $CCF = 100\%$ *of tumor cells in a tumor with purity* $\phi = 80\%$ *has VAF* $= \frac{1}{2} \times 1 \times 0.8 = 0.4$.

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- In non-diploid regions:

$$\text{CCF} = \frac{2(1-\phi) + C_{\text{total}}\phi}{C_{\text{mut}}\phi}\text{VAF},$$

where C_{total} is the total CN in the tumor and C_{mut} is the allele-specific CN.

Approach (i): a simple deterministic mathematical model

Williams *et al.* (2016): constant mutation rate + exponential growth (neutral evolution)
Features: mathematical model, spatially implicit

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Model:

- Number of mutations M: $\frac{dM}{dt} = \phi\mu\lambda N(t)$ (i), where μ is the mutation rate and λ the growth rate
- Population size: $N(t) = e^{\lambda\beta t}$ (ii), where β is proportion of surviving cells per division
- Frequency of a mutation (under infinite sites model): $f = \frac{1}{\phi N(t)}$ (iii)

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Observable values: $M(f)$, the cumulative number of mutations at frequency f, $dM(f)/df$, the number of mutations at frequency f
Solving (i)-(iii) for $M(f)$ gives:

$$M(f) = \frac{\mu}{\beta}\left(\frac{1}{f} - \frac{1}{f_{\max}}\right) \quad (1)$$

Approach (i): a simple deterministic mathematical model, inference

Eq. 1 is equivalent to a simple linear model

$$M(x) = ax + b,$$

with $x = 1/f$, $a = \frac{\mu}{\beta}$, and $b = -\frac{\mu}{\beta f_{\max}}$.
Thus, we can estimate a scaled mutation rate μ/β, and a general model fit using **linear regression**

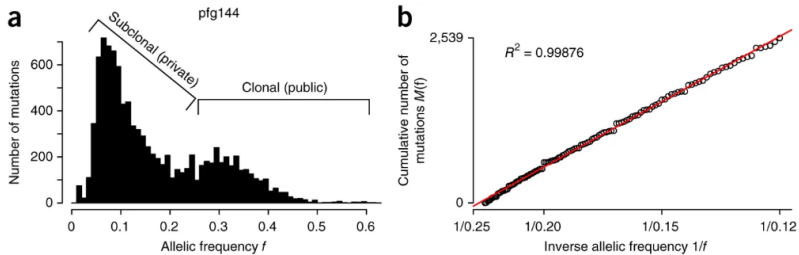


Figure: Gastric cancer whole-genome sequencing data (Williams *et al.* 2016).

Approach (i): a simple deterministic mathematical model, inference

Advantages:

- Mathematically tractable
- Simple, general predictions

Criticisms:

- Other processes can produce similar predictions (Tarabichi *et al.* 2018)
- Deterministic nature does not capture variability of evolutionary processes and does not allow classical hypothesis testing
- Is neutral evolution the null in cancer evolution?

Approach (ii): a more complicated probabilistic mathematical model

Caravagna *et al.* (2020): mixture of neutrally evolving (constant mutation rate + exponential growth) and selected clones (exponential growth at rate higher than the neutral growth)

Features: mathematical model, spatially implicit

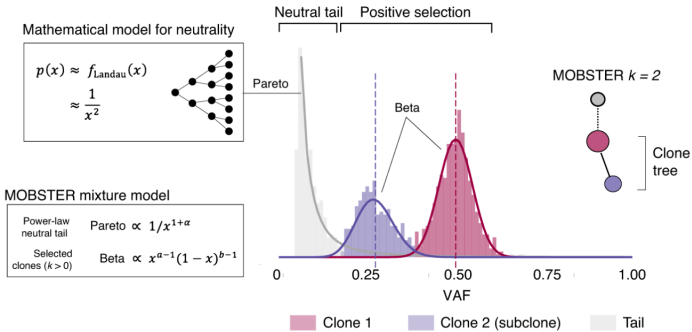


Figure: MOBSTER model (Caravagna *et al.* 2020). The neutral tail is based on the solution to the stochastic Luria–Delbruck model of bacterial growth (Kessler and Levine 2013; Luria and Delbrück 1943).

Approach (ii): a more complicated probabilistic mathematical model, inference

Fit a $k+1$ component mixture model, where each alterations comes either from the neutral tail or from one of k selected clones

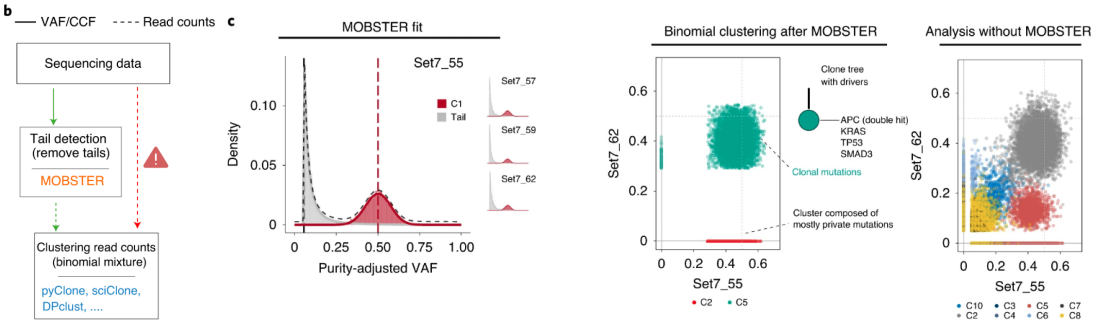


Figure: MOBSTER inference scheme (Caravagna *et al.* 2020).

Approach (ii): a more complicated probabilistic mathematical model, inference

Advantages:

- Encompasses many scenarios
- Allows inference of population parameters

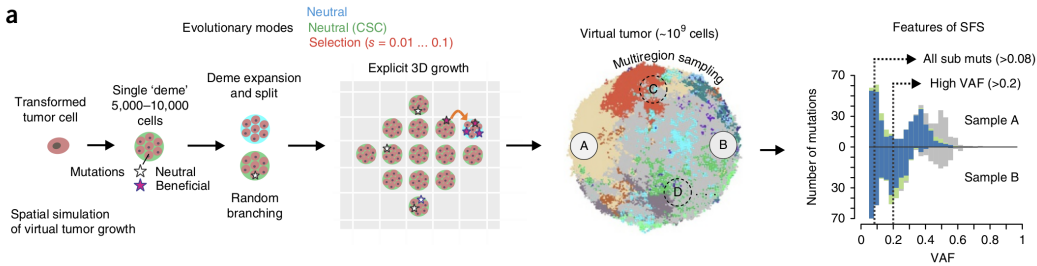
Criticisms:

- Spatially implicit ⇒ does not account for spatial heterogeneity
- Only considers exponential growth ⇒ mostly suited for initial progression phase, cannot detect slowing down or tumor regression
- Only considers competition between clones ⇒ not commensalism or cooperation that could help maintain stable proportions of different clones through time

Approach (iii): a computational model

Sun *et al.* (2017): constant mutation rate + spatially explicit 3-D growth + selection

Model:



Approach (iii): a computational model

The model allows to make **quantitative predictions** in different scenarii, and distinguish **qualitative behaviors**:

- neutral or effectively neutral models lead to weak spatial correlation, little differentiation between regions, and no private "bumps" in the SFS

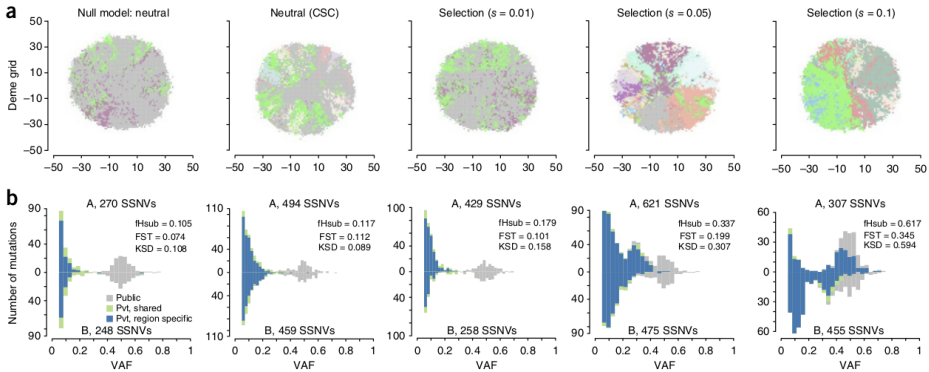


Figure: Predictions under several models (Sun *et al.* 2017).

Approach (iii): a computational model, inference

Compute summary statistics, compare their values with that of many simulations ($\sim 10^6$); Retain the parameters of simulations with stats closest to the observations (Approximate Bayesian Computation)

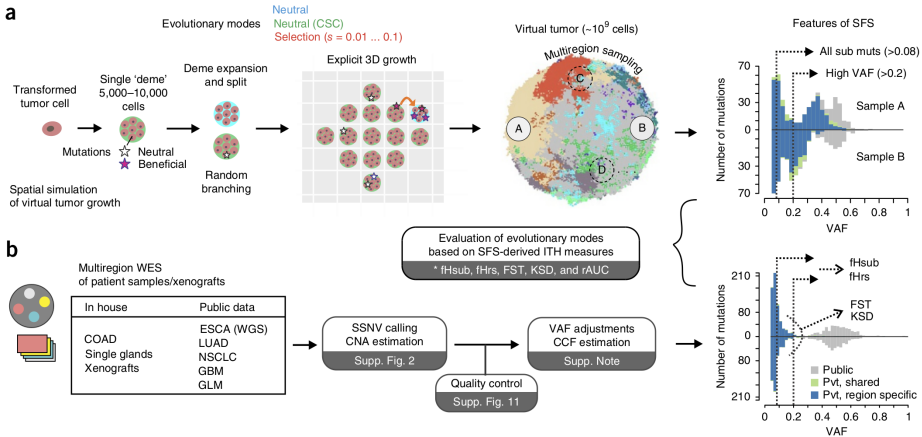


Figure: Model schematic and inference method (Sun *et al.* 2017).

Approach (iii): a computational model, inference

Advantages:

- Allows arbitrarily complex scenarios that fit the biology

Criticisms:

- Computationally intensive (large parameter space to explore)
- Identifiability is unknown (worked in this case but might not for other applications)

Part II: evolution of the cancer transcriptome

Modeling approaches

Theoretical frameworks are based on **quantitative genetics** (the study of the evolution of phenotypes in populations) and **phylogenetics of traits** (the study of the evolution of phenotypes in species)

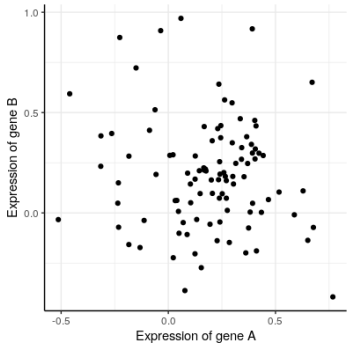
Most traits have **complex genetic architectures**, that are often unknown

What is the main quantity of interest?

Molecular traits

Definition: quantitative molecular variables (e.g., gene expression) that have an important role in cancer initiation and progression

Typical representation: a scatterplot, where each dimension represents a trait of interest



How to get the right molecular traits?

Goal: identify molecular the variables that are important for cancer evolution

Methods:

- (Supervised) use biological knowledge of a cancer type to choose relevant pathways
- (Unsupervised) leverage the between-patient molecular variation within a cohort to identify major sources of variation

An equilibrium deterministic mathematical model

Hausser and Alon (2020): directional selection + constraints (trade-off)

Features: mathematical model, unsupervised, equilibrium model (selection had enough time to act)

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Model:

- cancer cells have to perform **multiple tasks** (e.g., cell division, energy production, interaction with immune system, invasion and tissue remodeling)
- cells **cannot excel at everything** (e.g., the optimal phenotype for cell division will not be optimal in terms of interaction with immune system) $\Rightarrow$ **trade-offs**

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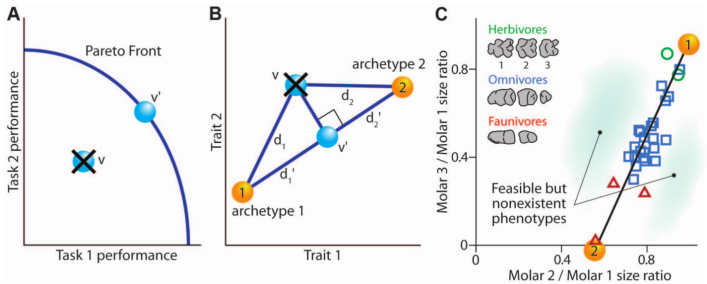
Features: mathematical model, unsupervised, equilibrium model (selection had enough time to act)

- **Pareto front**: set of phenotypes that cannot be improved at all tasks at once (increasing some performances requires reducing performance at other tasks)
- **Archetype**: optimal phenotype for a task



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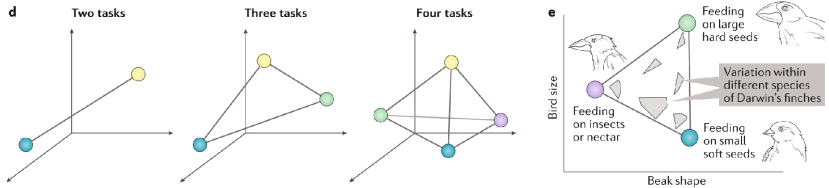
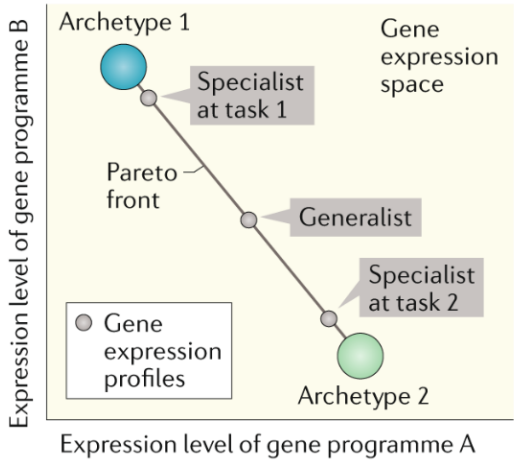
Results:

- the Pareto front has a **simple geometric shape** that only depends on the number of tasks (2 tasks: line, 3 tasks: triangle, four tasks: tetrahedron, etc)
- position within the front depends on the strength of selection for each task (strong selection for a tasks: specialist, equal selection for each task: generalist)



An equilibrium deterministic mathematical model

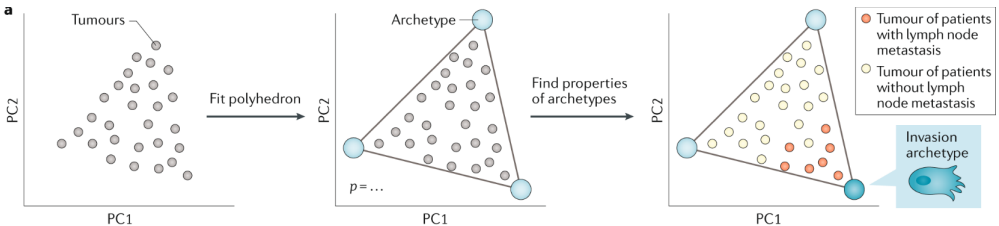
Hausser *et al.* (2019): we expect cancer transcriptomes to be a proxy for the molecular phenotypes facing trade-offs between tasks



An equilibrium deterministic mathematical model

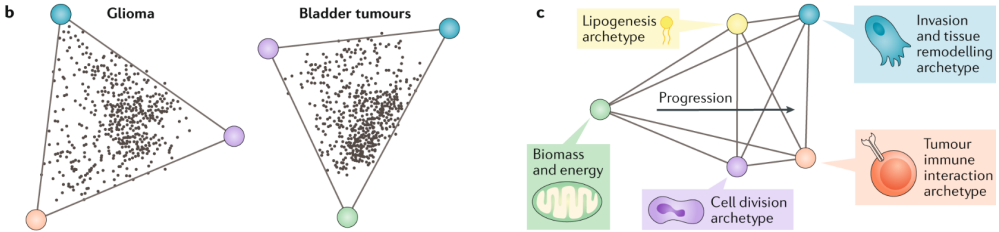
Hausser *et al.* (2019): Method

- Create a low-dimensional representation of the data (PCA)
- Fit a simplex and identifying vertices (archetypes)
- Interpret archetypes through gene-set enrichment analyses



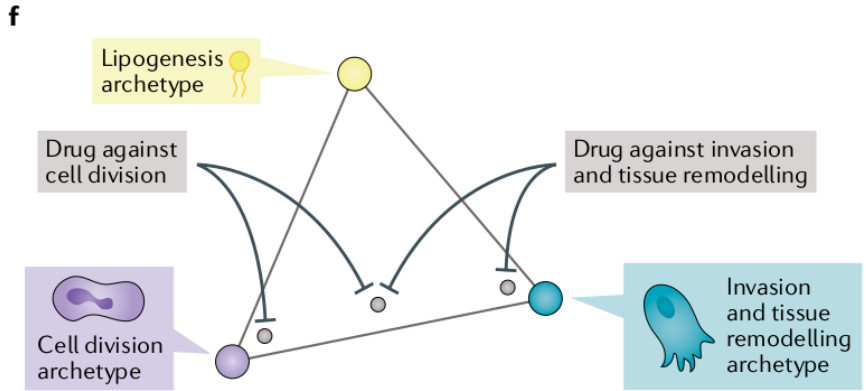
An equilibrium deterministic mathematical model

Hausser *et al.* (2019): Results



An equilibrium deterministic mathematical model

Hausser *et al.* (2019): Clinical implications



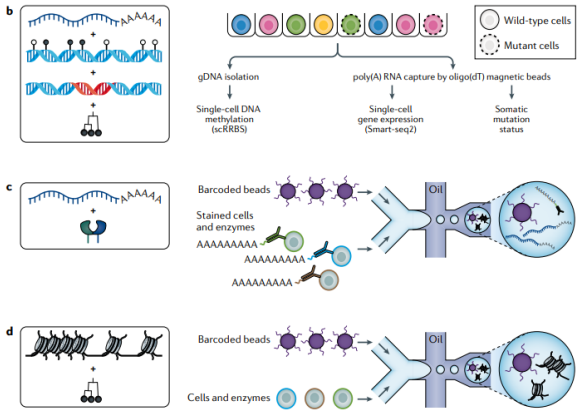
Take-home message

Interpret the geometry of the data

1. **Look at the molecular variation** (preferably after applying some linear dimensionality reduction)
2. Think about the **constraints in the data**: which genes are never overexpressed simultaneously? what does it say about the trade-offs between biological functions?
3. **Interpret the vertices and edges** of the distribution: do they have clear molecular phenotypes corresponding to pure tumoral strategies?

Part III: cancer evolution at the single cell resolution

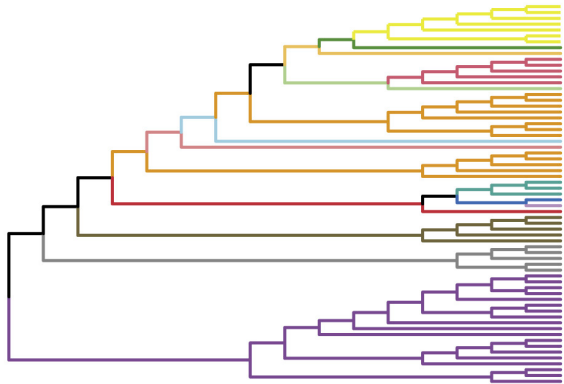
- Evolutionary theory describes how individuals (here cells) compete and cooperate within populations (here tumor)
- Most evolutionary theory methods require individual-level genetic information, which is finally available for cell populations



What is the main quantity of interest?

The cancer cell genealogy

Definition: ancestral relationships between tumor cells
Typical representation: genealogical tree



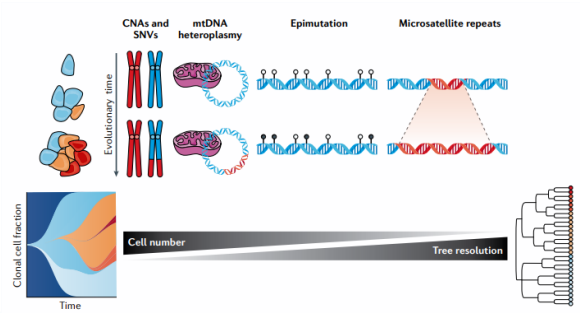
How to reconstruct cell genealogies?

Using genetic markers as natural barcodes (Nam *et al.* 2021)

scWGS: use somatic CNVs, indels in microsatellite repeats, and a finite sites mutation model to resolve phylogeny (SNVs not reliable enough due to sparsity and sequencing artefacts)

scRNA-seq/ATAC-seq: use somatic mtDNA SNVs to resolve phylogeny

scDNAme: use DNA methylation as molecular clock to infer phylogeny



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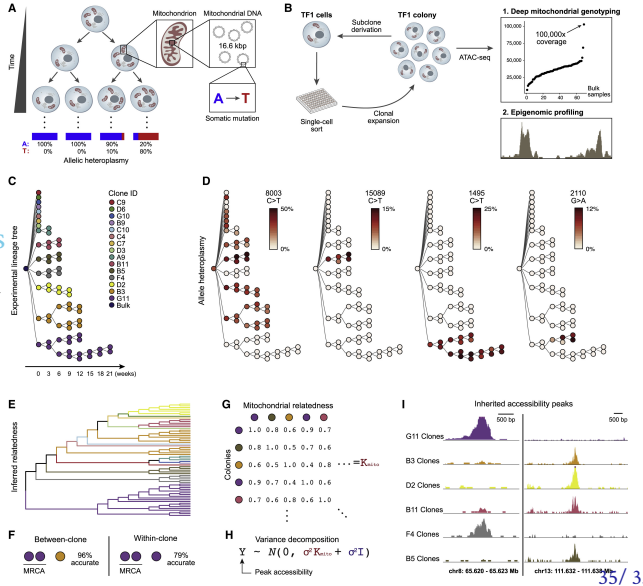

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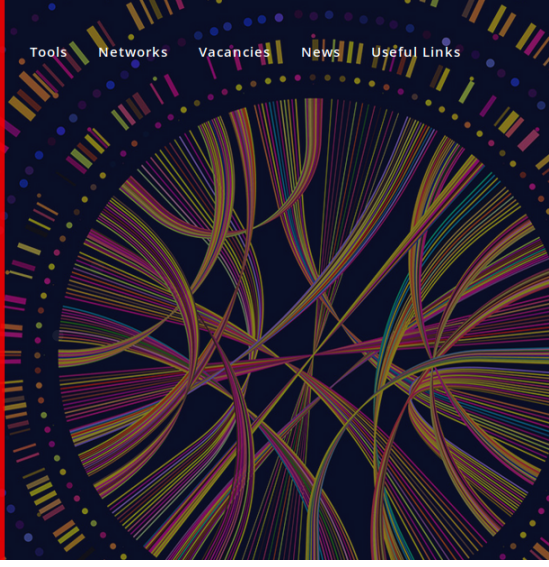

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