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

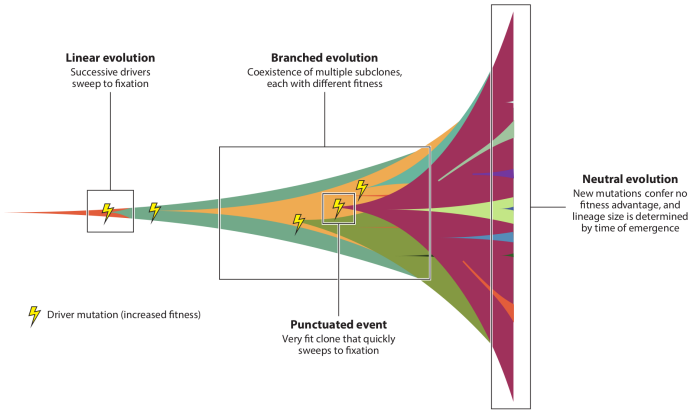
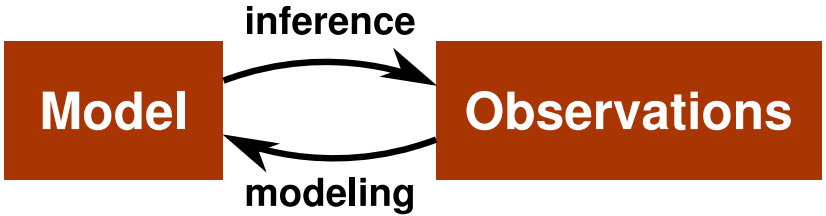


Figure: Schematic view of cancer evolution (Williams *et al.* 2019).

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

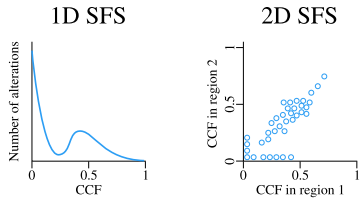
- Spatially implicit or explicit
- Forward-in-time or backward-in-time

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) to cancer cell fraction (CCF)

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

- Easiest when CN=2 and heterozygous alteration: then $\text{VAF} = \frac{1}{2}\text{CCF} \times \phi$, so

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

where $\phi \in [0, 1]$ is the tumor purity. *Example: a heterozygous variant present in $CCF = 100\%$ of tumor cells, given a purity of $\phi = 80\%$, is expected to have a VAF $= \frac{1}{2} \times 1 \times 0.8 = 0.4$.*

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- In region with CN$\neq$ 2: then

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

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

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Note: ideally, inferred simultaneously with evolutionary model

Note 2: although VAFs are informative on tumor evolution, often treated as technical variable!

Approach (i): a simple deterministic forward mathematical model

Williams *et al.* (2016): constant mutation rate + exponential growth (neutral evolution)

Features: mathematical model, spatially implicit, forward-in-time

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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:

$$M(f) = \frac{\mu}{\beta}\left(\frac{1}{f} - \frac{1}{f_{\max}}\right), \qquad \frac{dM(f)}{df} = -\frac{\mu}{\beta}\left(\frac{1}{f^2}\right). \tag{1}$$

Approach (i): a simple deterministic forward 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**

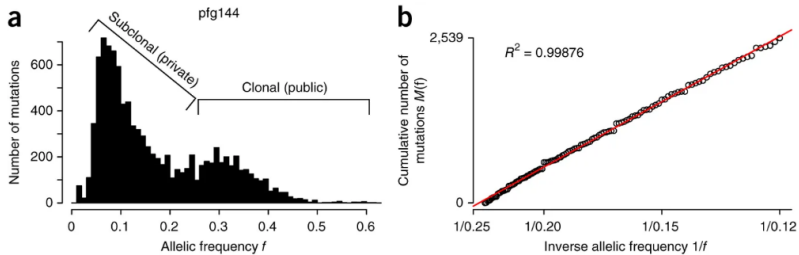


Figure: Gastric cancer whole-genome sequencing data (Williams *et al.* 2016).

Approach (i): a simple deterministic forward 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 forward 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, forward-in-time

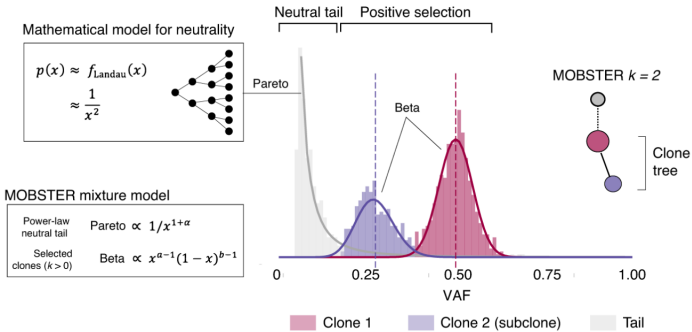


Figure: MOBSTER model (Caravagna *et al.* 2020). The neutral tail is based on the solution to the stochastic Luria–Delbruck model of bacterial growth (Kessler and Levine 2013; Luria and Delbrück 1943).

Approach (ii): a more complicated probabilistic forward 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

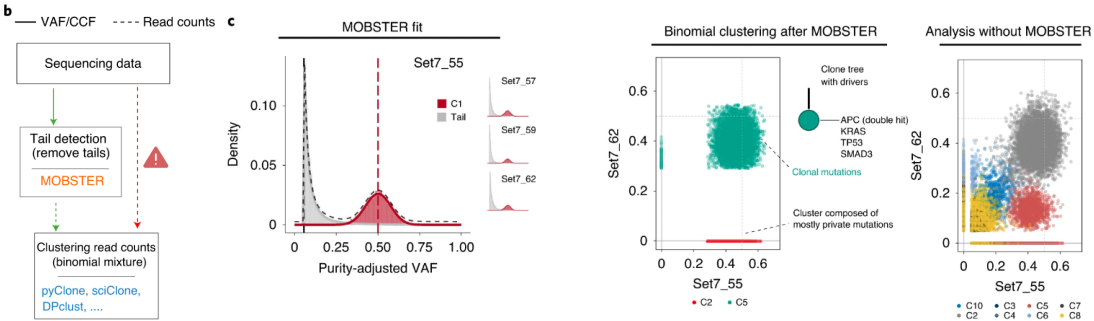


Figure: MOBSTER inference scheme (Caravagna *et al.* 2020).

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

Advantages:

- Encompasses many scenarios
- Allows inference of population parameters

Criticisms:

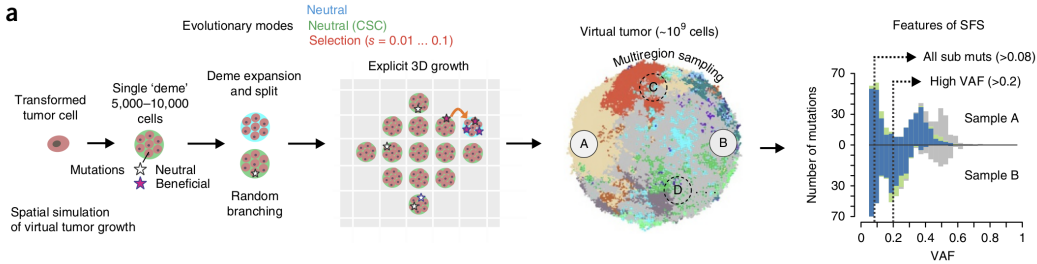
- Spatially implicit ⇒ does not account for spatial heterogeneity
- Only considers exponential growth ⇒ mostly suited for initial progression phase, cannot detect slowing down or tumor regression
- Only considers competition between clones ⇒ not commensalism or cooperation that could help maintain stable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

Approach (iii): a forward computational model

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

Other features: forward-in-time

Model:



Approach (iii): a forward 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

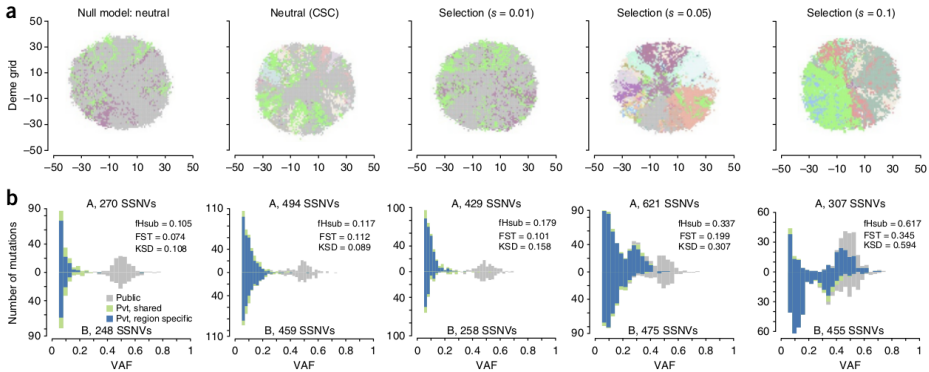


Figure: Predictions under several models (Sun *et al.* 2017).

Approach (iii): a forward 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)

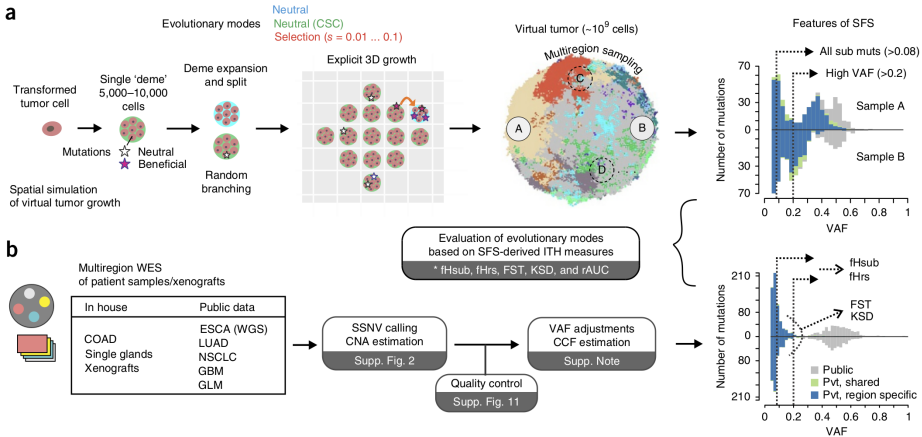


Figure: Model schematic and inference method (Sun *et al.* 2017).

Approach (iii): a forward computational model, inference

In practice, summary statistics enable to separate the 2 qualitative behaviors

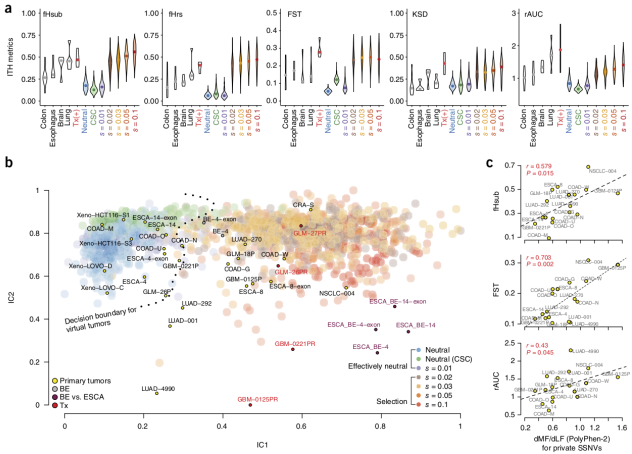


Figure: Application to tumor genomic data (Sun *et al.* 2017).

Approach (iii): a forward computational model, inference

Also extended to study tumor/metastases co-evolution and infer type of seeding (mono- or polyclonal)

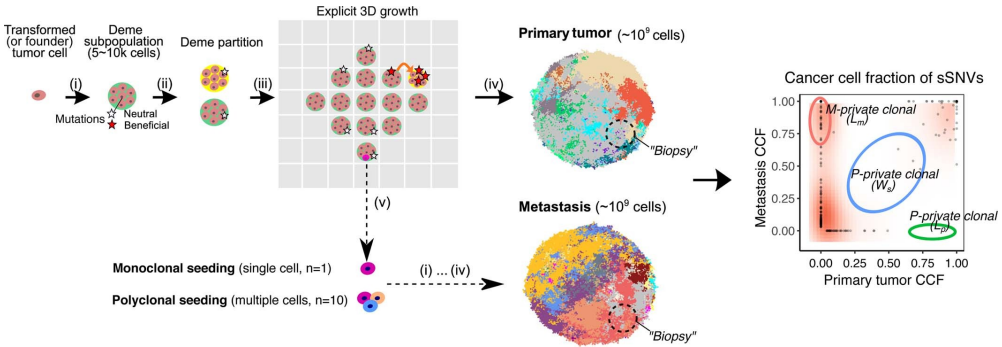


Figure: Model schematic (Hu *et al.* 2020).

Approach (iii): a forward 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)

Approach (iv): a clonal mixture model

Miller *et al.* (2014): clone identification + phylogenetic reconstruction
Other features: no assumption about selection, growth, or mutation rate, backward-in-time
Mixture model: Given N individuals sequenced at M variant positions, the $N \times M$ theoretical CCF matrix **D** is:

$$\mathbf{D} = \mathbf{A}.\mathbf{T}, \tag{2}$$

with **A** a $N \times K$ mixture matrix that gives the proportion of each of K clones in the N samples, and **T** a $K \times M$ genotypes matrix that gives the variants of each clone. The *observed* CCF matrix is $\tilde{\mathbf{D}} \sim Binom(\mathbf{X}, \mathbf{D})$, where **X** is the sequencing coverage matrix.
Tree model: assumes that **A** is tree-like, i.e., it satisfies the sum rule

$$d_{\text{cluster}Y} = d_{\text{clone}Y} + \sum_{X_i \in \text{direct subclones of} Y} d_{\text{cluster}X_i},$$

where d_X is the CCF of X

Approach (iv): a clonal mixture model, inference

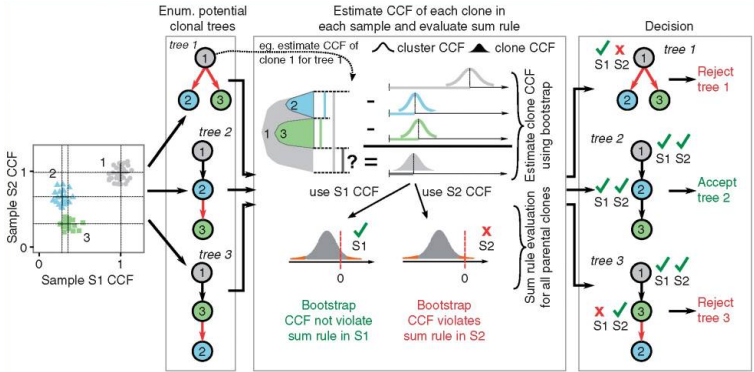


Figure: Example mixture inference (Dang *et al.* 2017)

Approach (iv): a clonal mixture model, inference

Results: Finds peculiar evolutionary patterns (convergent evolution)

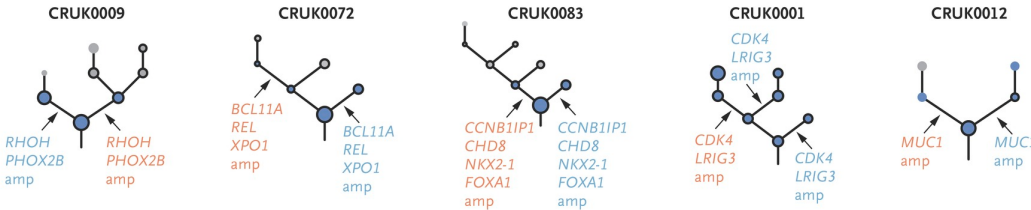


Figure: Phylogenetic tree of non–small–cell lung cancer (Jamal-Hanjani *et al.* 2017).

Approach (iv): a clonal mixture model, inference

Results: Attempts at estimating population size N_e (with phylogenetic software BEAST)

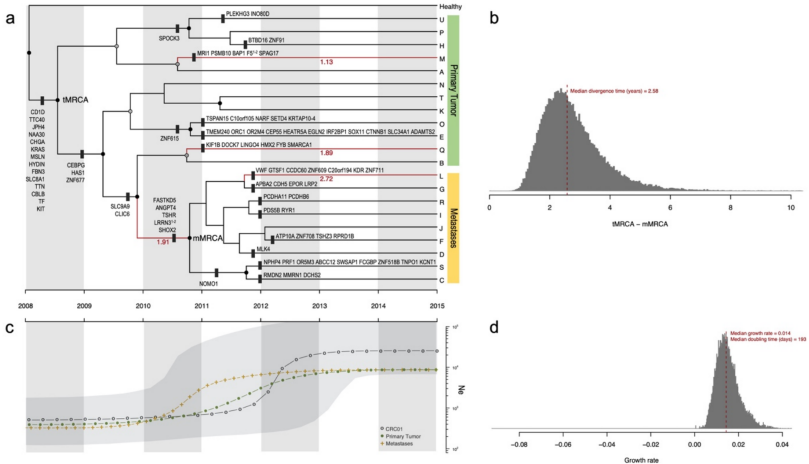


Figure: Phylogenetic tree of non–small–cell lung cancer (Alves *et al.* 2019).

Approach (iv): a clonal mixture model, inference

Advantages

- (relatively) Hypothesis-free
- Infers the history of the tumor–the sequence of alteration events

Criticisms

- Oversimplification of the data (the actual tree has thousands of branches)
- Weakly informative about processes (selection, growth)

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)

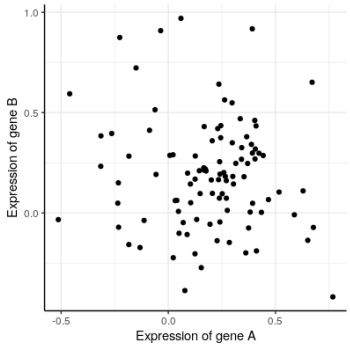
Most traits have **complex genetic architectures**, that are often unknown

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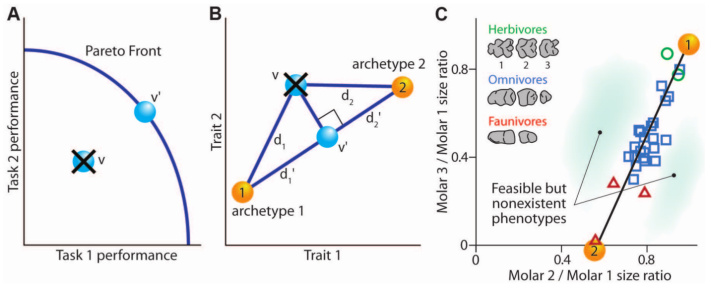
Features: mathematical model, unsupervised, equilibrium model (selection had enough time to act)

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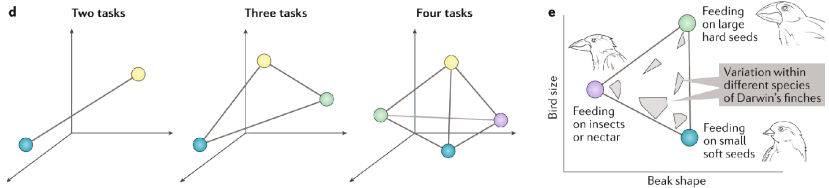
Features: mathematical model, unsupervised, equilibrium model (selection had enough time to act)

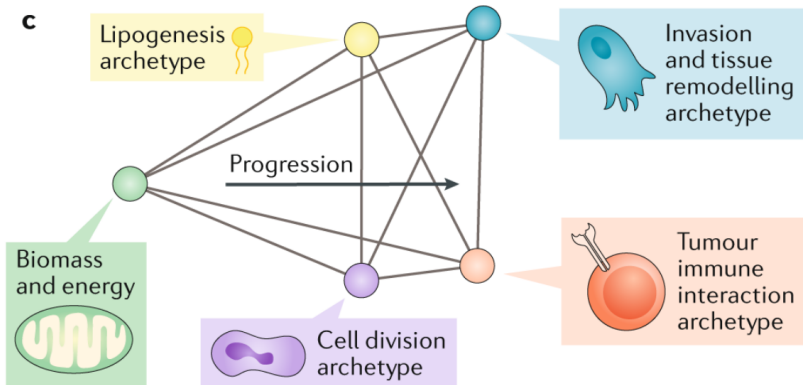
Results:

- 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)



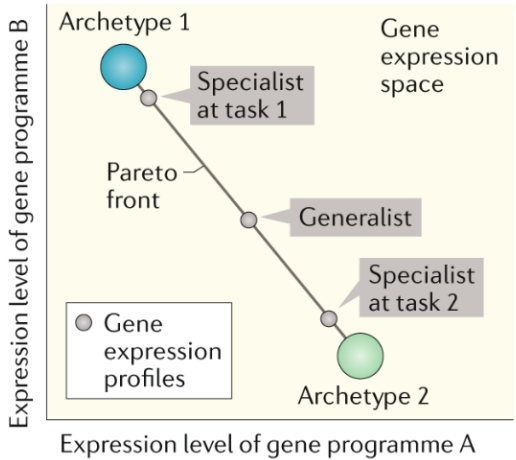
An equilibrium deterministic mathematical model

Hausser *et al.* (2019): most cancer types experience trade-offs between the same 5 tasks



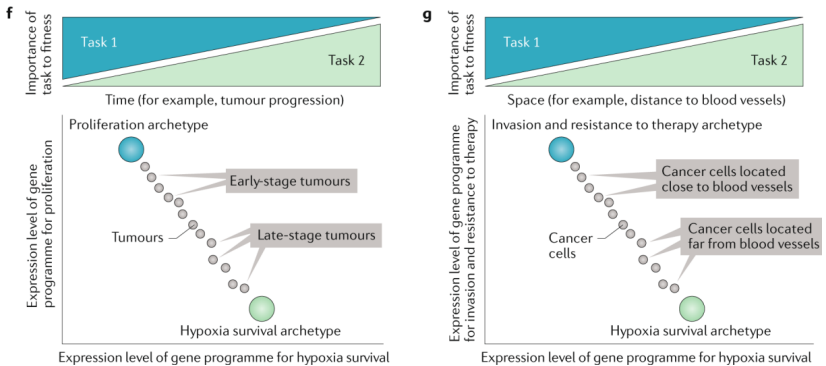
An equilibrium deterministic mathematical model

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

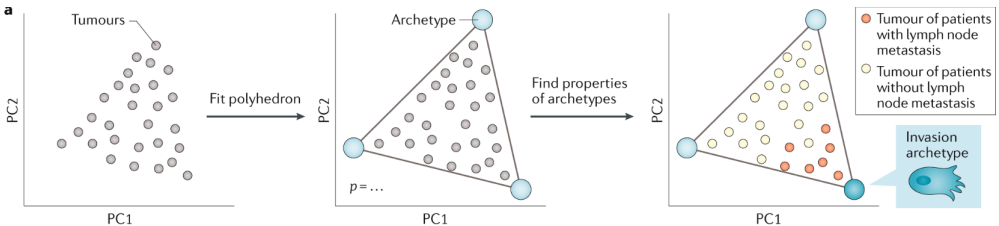
Hausser *et al.* (2019): The optimal position in the Pareto front can vary through time and space



An equilibrium deterministic mathematical model

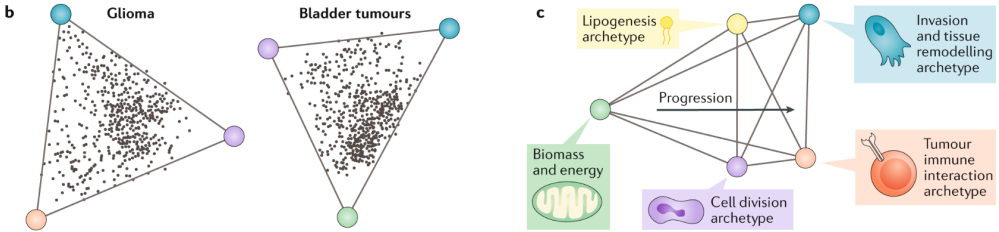
Hausser *et al.* (2019): Method

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



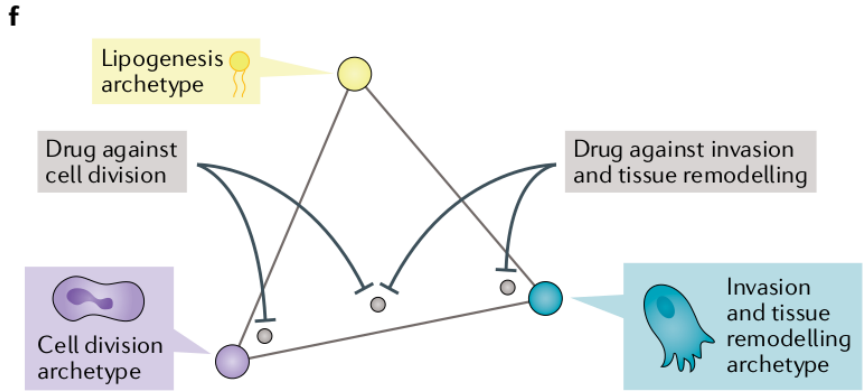
An equilibrium deterministic mathematical model

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?

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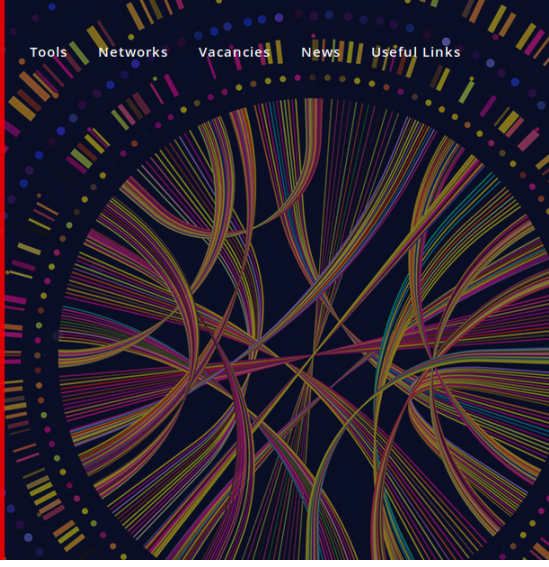

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