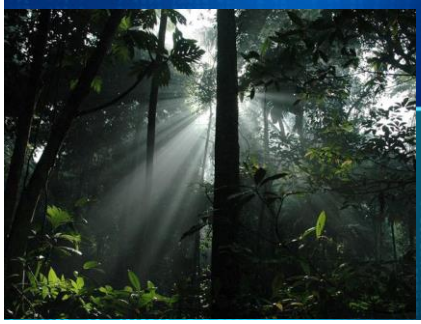
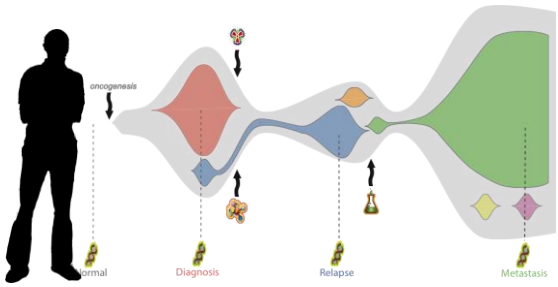
Forestial Problems and the Geometrization of Tumor Evolution



Raúl Rabadán



Comparing evolutionary histories

- Recently mutational trajectories of tumors have been studied in different context. Clinical/Biological questions:
  - Evolutionary questions:
    - how the different phases of tumors are related?
      - Type of evolutionary model:
      - Does it follow clonal replacement of dominant clone? Or only a few cells are responsible (niche, stem cells, etc)?
      - Is the dominant evolutionary factor high mutation rates or clonal heterogeneity?
      - how clones seeding metastasis are related?
  - Clinical questions:
    - » how informative (predictive value) is genomic information of primary tumor on later stages, therapy? Is it linear? Is it branched?
    - » how patients can be stratified using evolutionary genomic profiles?
  - Therapeutic questions:
    - » what are the specific molecular mechanisms driving relapse following certain therapies?

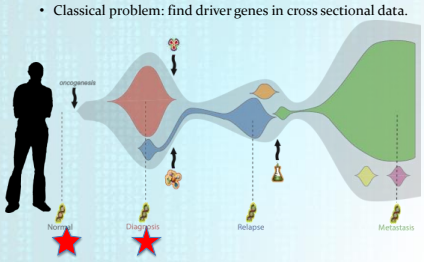
Cartography and landscapes

- Last 5 years have led to development of high throughput genomic technologies, leading to explosion of genomic data and methods to characterize the genomic profile of each tumor.
  - Currently more than 10,000 tumors have been profiled. Every tumor has different mutational spectrum, result of different evolutionary history.
- If every tumor follows a different evolutionary path, how do we go beyond cartography and case reports?
  - Main path: Cross sectional studies.
  - Problem: define the "metric space" where the stories can be compared.
  - Two key ingredients: **metrics** and **statistics**.
  - Most strategies based on convergent evolution, i.e. recurrence: find common alterations, pathways, etc that are altered in statistically significant sets of patients.

HOW CAN WE COMPARE EVOLUTIONARY HISTORIES?

Comparing evolutionary histories

- Previous studies (including large studies TCGA, and our own) characterize single sample per patient. Methods to extract information from cross-sectional studies have been developed and applied in this context.
- Classical problem: find driver genes in cross sectional data.



Frattini et al, *Nature Genetics*
Singh, et al *Science*,
Tiacci et al , NEJM
Pasqualucci et al, *Nature*,
Palomero, *Nature Genetics*,
Wang, *eLife*,
Tzoneva, *Nature Medicine*,

Etc.

Comparing evolutionary histories

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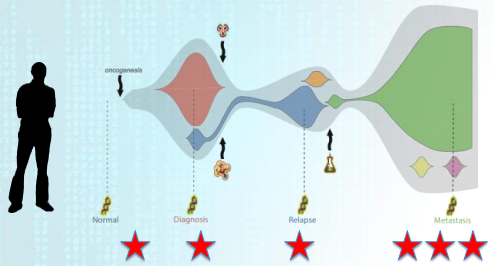
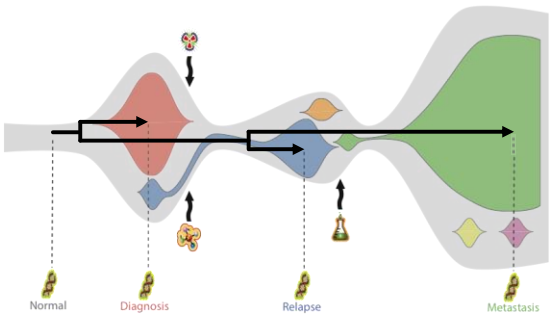


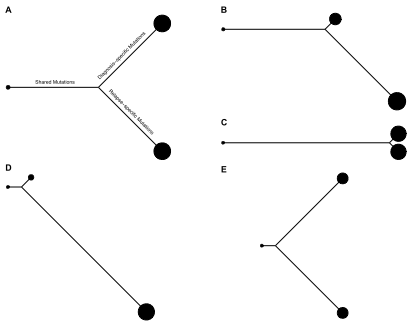
Comparing evolutionary histories

- If every tumor follows a different evolutionary path, how do we extend computational and statistical frameworks to study longitudinal data?
- Aims:
  1) to develop a framework to compare the evolutionary history of different patients -> **metric space** that allow comparison of evolutionary histories.
  2) To develop a **statistical framework** and **machine learning approaches** to longitudinal cohorts.
  3) To develop a statistical/evolutionary framework **to test different evolutionary models** (e.g. multistage due to hard selective sweeps).

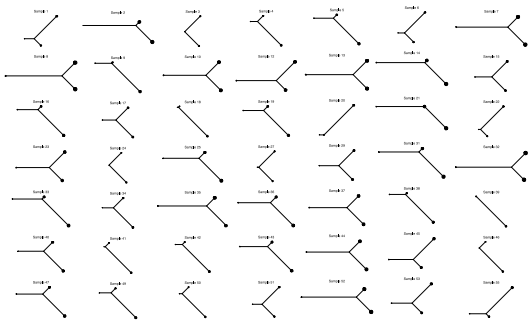
Cancer follows clonal Darwinian evolution



Classifying Evolutionary Behaviors



Patients represent forests of phylogenetic trees



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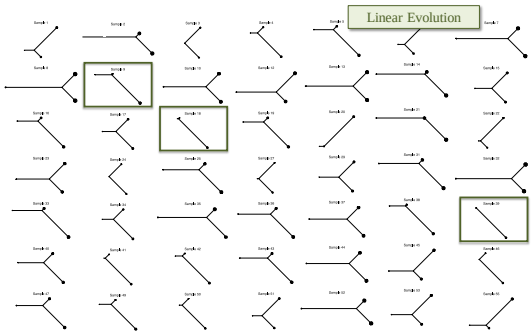

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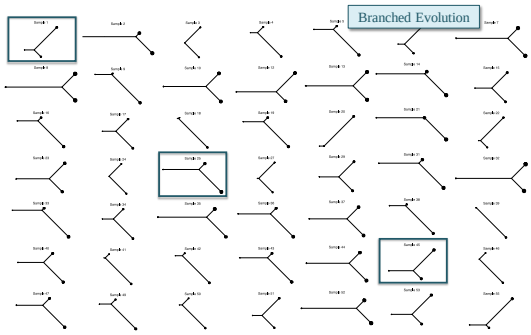

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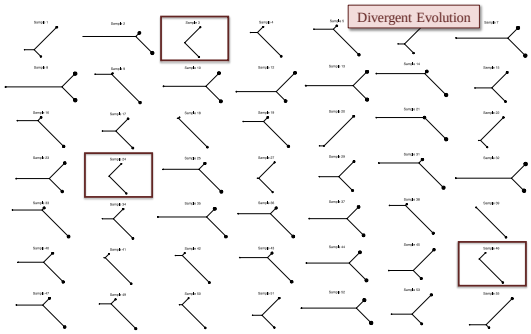

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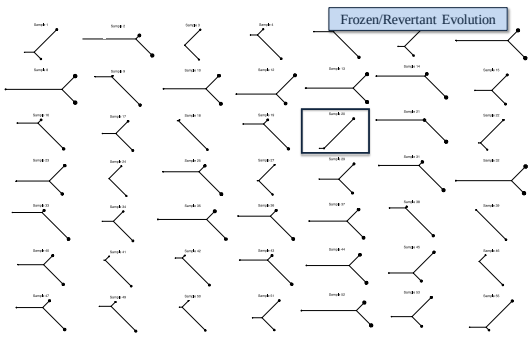


Forestial Questions

Interesting properties I would like to capture:

1) I want to compare trees: how similar are two trees? **Distance**.

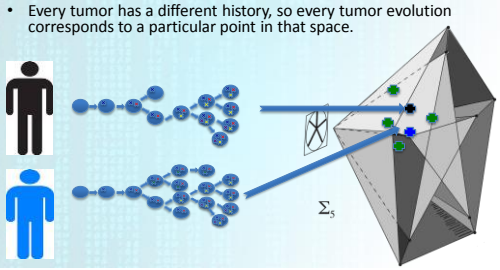
2) I want to do **statistics**: means (average tree), centroids and variances.

- I want to apply **machine learning** techniques to uncover evolutionary patterns.

3) I want to **test different evolutionary models** (e.g. multistage hard selective sweeps).

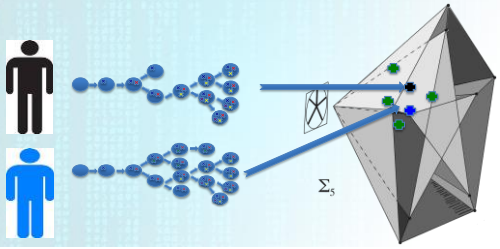
Moduli space of clonal evolution

- To compare two or more histories we would like to find a space that describe all possible evolutionary histories.
  - Moduli space: space whose points correspond to objects of some kind.
- Every tumor has a different history, so every tumor evolution corresponds to a particular point in that space.



Moduli space of clonal evolution

- Instead of talking of:
  - A tumor history -> point in a space
  - All potential histories -> moduli space
  - Cross-sectional data -> distributions of points in moduli space.



Space of trees

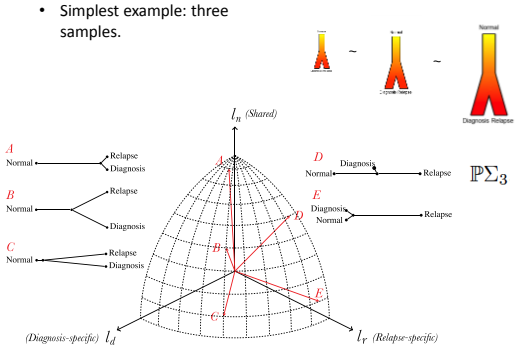
Theorem 1: The space of trees is a Polish space (one can define statistics).

Theorem 2: The space of trees is a CAT(0) space (one can define means and variances in a meaningful way).

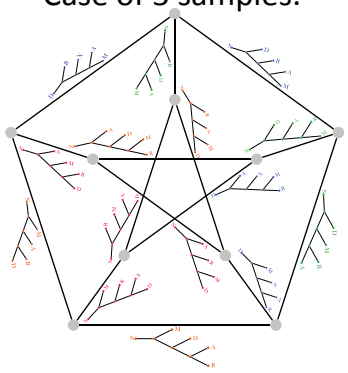
Billera, Holmes, Vogtman (2003)
Zairis, Khiabanian, Blumberg, Rabadan (2014)

Moduli projective space of clonal evolution

- Simplest example: three samples.



Case of 5 samples.

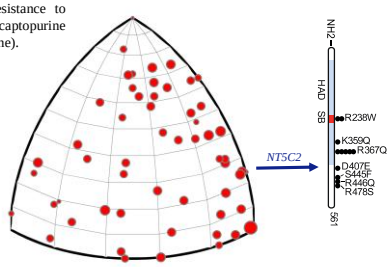


Relapse-specific mutations in ALL

- *NT5C2* mutations in ALL cells induce resistance to therapy (6-mercaptopurine and 6-thioguanine).

Collaboration with T. Palomero and A. Ferrando.

H. Khiabanian



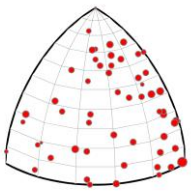
Tzoneva *et al*, Nat. Medicine 2013

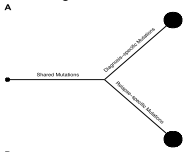
CAN WE RECONSTRUCT THE MAIN ROUTES OF TUMOR EVOLUTION?

Pediatric leukemias (ALL) at relapse: highly branched process

Highly branched process:
- dominant clone at diagnose is erradicated.
- ancestral clone adquires additional mutations that confer resistance to therapy.

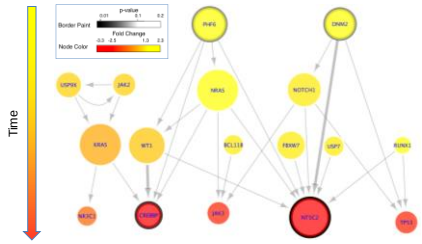
Branched evolution allows to trace back some mutations:
- Reconstruct ancestral clone,
- order the chronological order of mutations.





J. Wang et al, *eLife*

Pediatric leukemias (ALL) at relapse: highly branched process



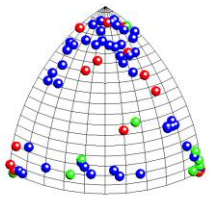
Early events:
- PHF6 (*Nat. Genetics).*

Late events associated to relapse:
- NT5C2 driven relapses (*Nat. Medicine*).

GBM evolution shows distinct evolutionary trajectories associated to specific molecular mechanisms

Collaboration with A. Iavarone and G. Finocchiaro.
J. Wang.

Three data sets:
- ours,
- TCGA triplets,
- Verhaak et al.



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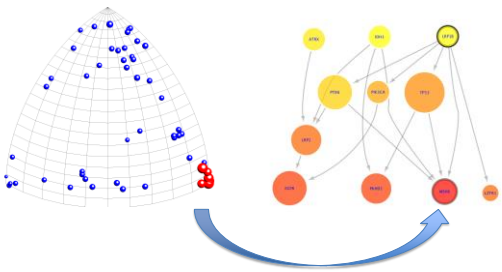
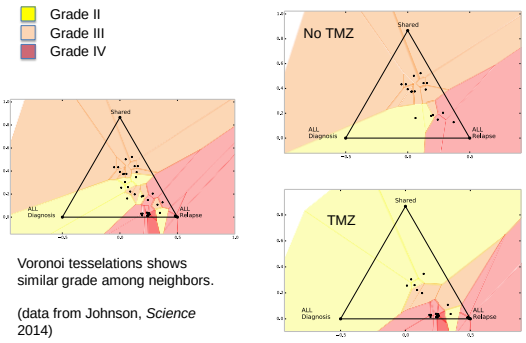


DOES EVOLUTIONARY HISTORY CORRELATES WITH PROGNOSIS?

Clinical Correlates: Grade of Low Grade Glioma at recurrence 's is associated with position in moduli space

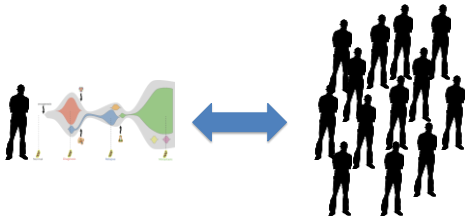


Voronoi tesselations shows similar grade among neighbors.

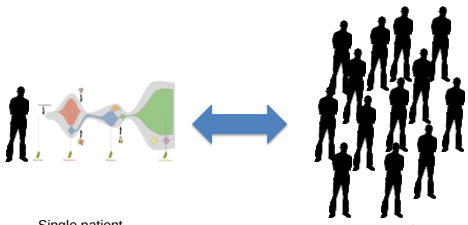
(data from Johnson, *Science* 2014)

ARE THERE PATTERNS IN PROGRESSION OF TUMORS?

Longitudinal vs Cross-sectional



Longitudinal vs Cross-sectional



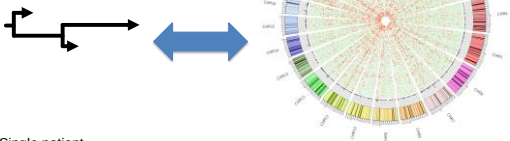
- Single patient
- Evolution (time data)

- Evolutionary language:
  - Fitness
  - phylogenies

- Many patients
- No evolution

- Statistical language:
  - Frequency of alterations

Longitudinal vs Cross-sectional



- Single patient
- Evolution (time data)

- Evolutionary language:
  - Fitness
  - phylogenies

- Many patients
- No evolution

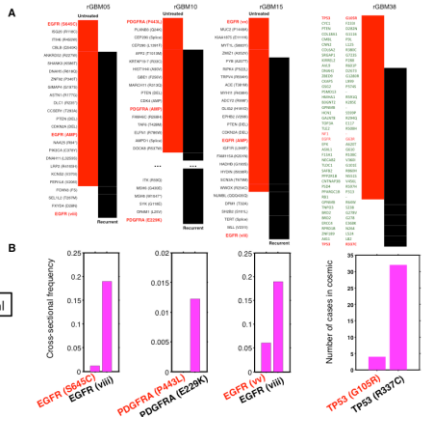
- Statistical language:
  - Frequency of alterations

Principle of common clonal replacement

If in the evolution of a tumor a clone is replaced with another one with different alterations in a particular gene, then the second alteration is more common than the first.

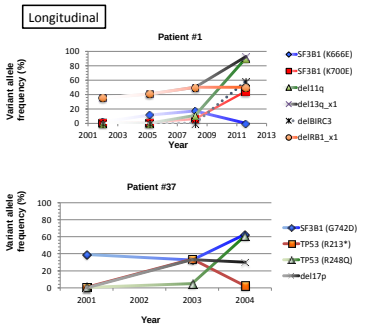
Longitudinal

Cross-sectional

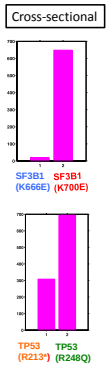


CLL

Longitudinal

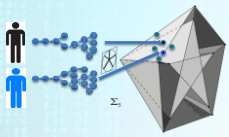


Cross-sectional



Questions

- Can we compare evolutionary cancer histories?
  - CAT(0) spaces: allow define well-behave statistics.
- Can we reconstruct main evolutionary routes?
  - Translate longitudinal data into directed graphs.
- Does evolutionary histories correlate to clinical information?
  - CAT(0) spaces: allow machine learning approaches.
- Are there patterns of progression?
  - Clonal replacement by "cross-sectional" frequent mutations.



Columbia University

Center for Topology of Cancer Evolution and Heterogeneity

A member of the National Cancer Institute's Physical Sciences in Oncology Network

- National Cancer Institute (NCI).
- Leukemia and Lymphoma Society.
- Lymphoma Research Foundation.
- Geneva Foundation.
- Stewart Foundation.

- Columbia University:
  - Departments of Systems Biology and Biomedical Informatics:
    Hossein Khiabanian, Jiguang Wang, Oliver Elliott, Pablo Camara, Rachel Melamed, Albert Lee, Francesco Abate, Sakellarios Zairis, Kevin Emmett, Daniel Rosenbloom, Chioma Madubata.
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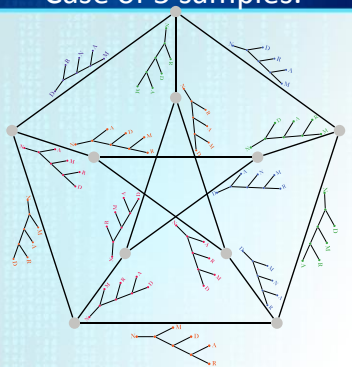
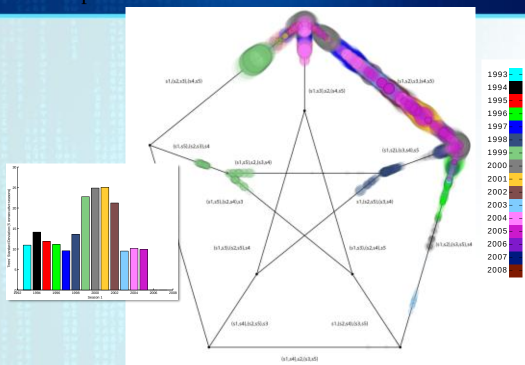
- Texas (Austin), MSRI (Berkeley): **A. Blumberg.**
- Stanford: G. Carlsson.
- Milan: **G. Finnochiaro**

Case of 5 samples.

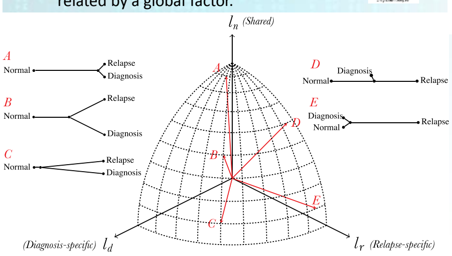


Space of trees with 5 consecutive seasons



Moduli projective space of clonal evolution

- A way of representing and compare the evolution of tumors in different patients is to identify histories that are related by a global factor.



Funding:
- National Cancer Institute (NCI).
- National Institute on Alcohol Abuse and Alcoholism (NIAAA).
- National Library of Medicine (NLM).
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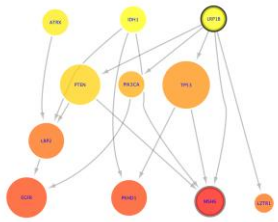
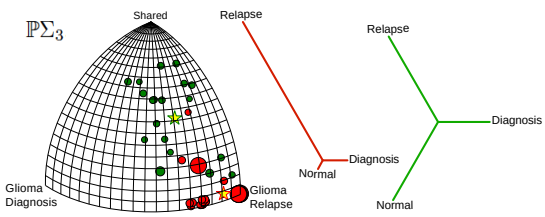
GBM evolution shows distinct evolutionary trajectories associated to specific molecular mechanisms

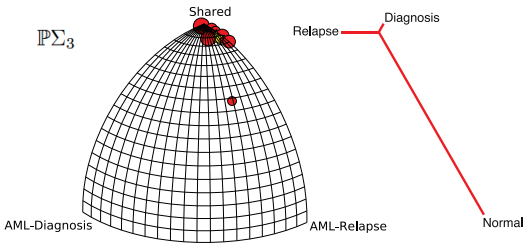


Glioma's therapy-driven highly branched evolution: TMZ drives hypermutation



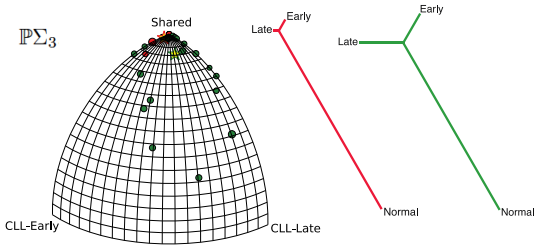
Evolution to low grade to high grade glioma (Johnson, *Science* 2014)

Acute myelogenous leukemia: frozen evolution



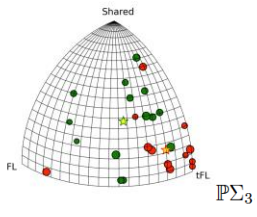
Relapsed AML (Ding et al, Nature 2012): 8 AML patients. Standard induction chemotherapy for AML (anthracycline and cytarabine). Chemotherapy failed to eradicate the founding clone.

Linear vs branched: Chronic lymphocytic leukemia untreated vs. treated: clonal replacement and classic hard selective sweeps



(Landau, *Cell* 2014)

Branched transformation of follicular lymphoma to DLBCL



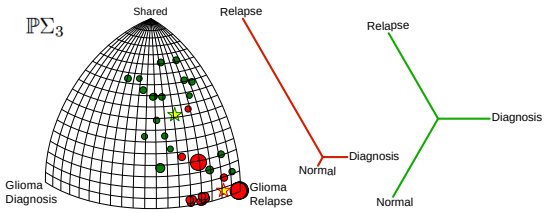
Follicular lymphoma (FL) is an indolent disease, but 30%-40% of cases undergo histologic transformation to an aggressive malignancy

- Red dots: Collaboration with R. dalla Favera and L. Pasqualucci (Cell Reports 2014).
- Okusun (Nat Genetics 2014). 10 triplets.
- Summary:

  - branched transformation: FL is not a direct ancestor of tDLBCL.

  - long branch leading to tFL associated with alterations deregulating cell-cycle progression and DNA damage responses (CDKN2A/B, MYC, and TP53)

Glioma's therapy-driven highly branched evolution: TMZ drives hypermutation



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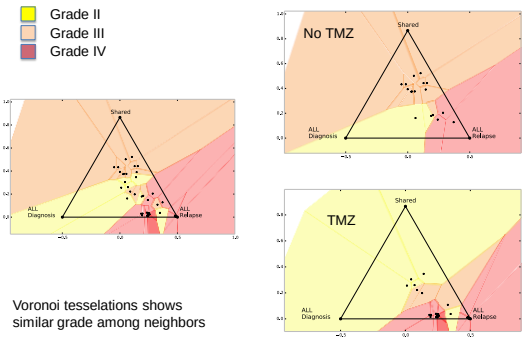

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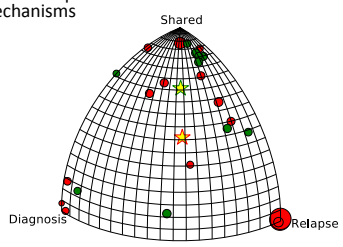

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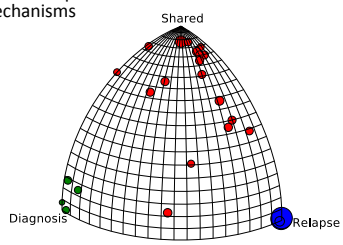
J. Wang.

Three clusters.

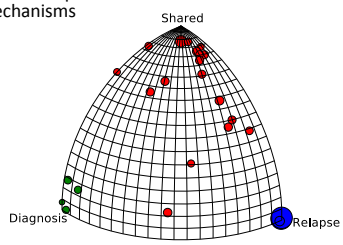


GBM evolution shows distinct evolutionary trajectories associated to specific molecular mechanisms

Collaboration with A. Iavarone and G. Finocchiaro.

J. Wang.

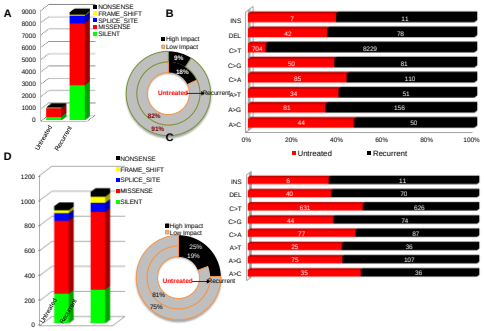
Three clusters.



HMC:

- MSH6 mutations (p-value 0.01)
- Transcription associated hypermutation, C->T.

GBM evolution: hypermutation cluster



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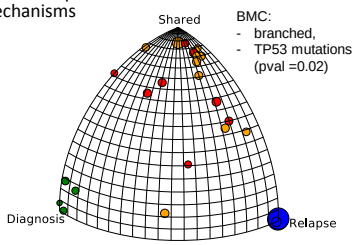


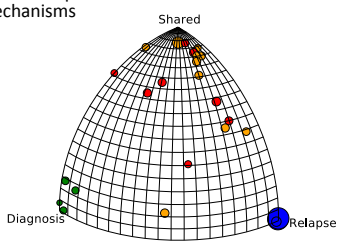
BMC:
- branched,
- TP53 mutations (pval =0.02)

GBM evolution shows distinct evolutionary trajectories associated to specific molecular mechanisms

Collaboration with A. Iavarone and G. Finocchiaro.

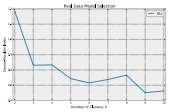
J. Wang.

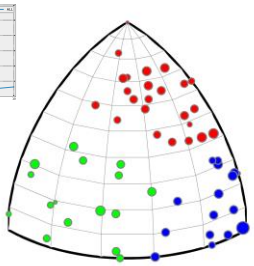
Three clusters.



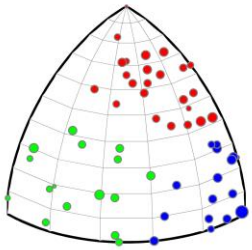
LMC:
- Low mutation cluster at relapse, ???

Pediatric leukemias (ALL): 3 evolutionary trajectories





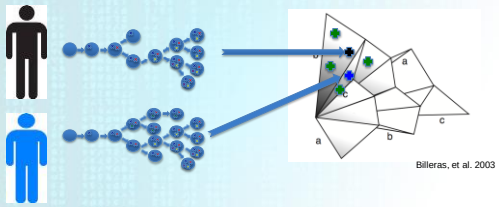
Pediatric leukemias (ALL)



NT5C2 driven relapses
Nat. Medicine

Moduli projective space of clonal evolution

- The extension of the previous examples for cases with more longitudinal data.
- The moduli space with m branches is extremely interesting.
- They have to do with the space of unrooted phylogenetic trees.



Billeras, et al. 2003

Moduli projective space of clonal evolution

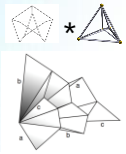
- Moduli space is the Cartesian product of two spaces, providing information on:
  - **Topology**: l_m = Internal branches described by Billeras, Holmes and Voigtmann = BHV_{m-1}
  - **Linearity**: E_m = External branches by positive quadrant in R^m.
  - Important property: **CAT(0)**.
- Projective Moduli space is the join of two spaces (allows to compare different experiments):
  - Internal branches: Boardman space,
  - External branches: Simplex in m-1 dimensions.
  - Important property: exponential branch length distribution translates into uniform distribution in projective coordinates.

$$\Sigma_m = BHV_{m-1} \times \mathbb{R}^{m+}$$

$S_m = l_m \times E_m$
$\dim(l_m) = m - 3$
$\dim(E_m) = m$

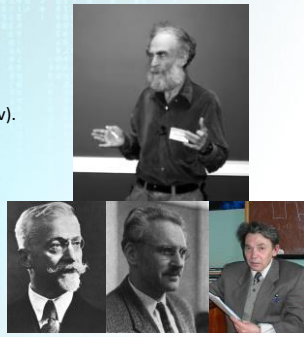
$$\mathbb{P}\Sigma_m = \tau_{m-1} \star T_{m-1}$$

t_{m-4} = Boardman space of dimension m - 4,
T_{m-1} = simplex of dimension m-1.

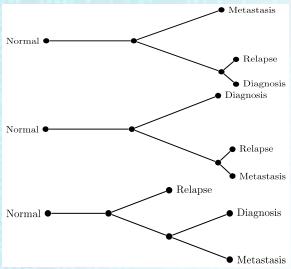


CAT(0) spaces

- *Theorem 1*: The space of trees is CAT(0).
- Coined by Gromov in 1987 (acronym for Cartan, Aleksandrov and Toponogov).
- They are spaces where geodesics can be uniquely defined, one can define centroids, variances, statistics, etc.

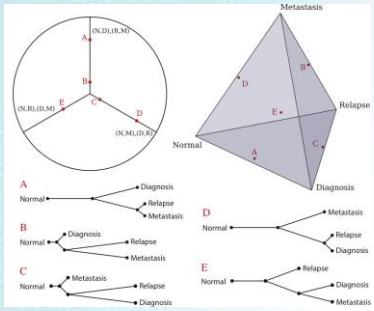


Forestial problem: tree topologies



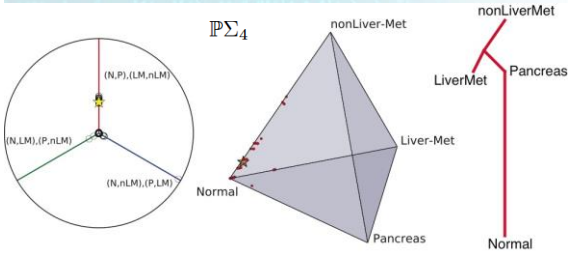
Moduli projective space of clonal evolution

- Four samples: 4 leaves could have 3 topologies.



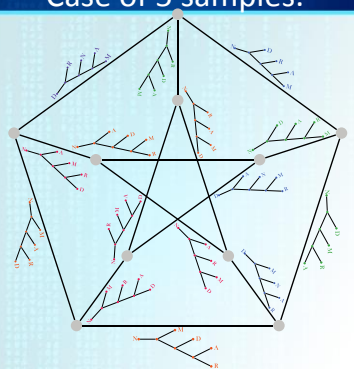
$\mathbb{P}\Sigma_4$

Metastatic Pancreatic Cancer



- Metastasis of pancreatic tumors to the liver and beyond. Question: what is the source of metastasis? (Campbell et al Nature 2010).
- Metastasis derive linearly from primary.

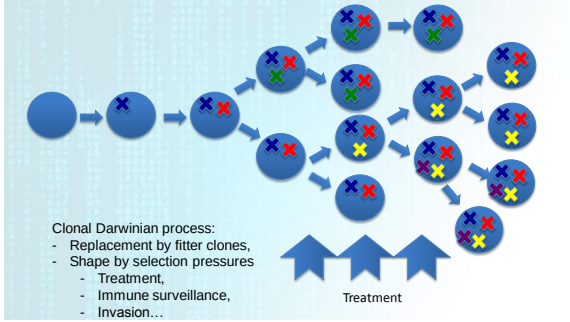
Case of 5 samples.



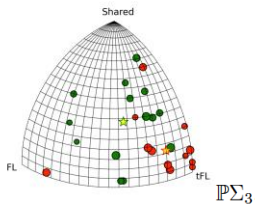
More complex evolutionary behaviors

Underlying evolutionary mechanism	Large N eff	Small Neff: few stems cells, niche, residual cells, etc
No mutation: epigenetic effects?	Frozen evolution	Frozen evolution
Hard selective sweeps: a *de novo* mutation with strong selective advantage.	Linear evolution: **mutation rates** are most dominant effect in relapse.	Branched evolution: **clonal heterogeneity** in small population.
Soft selective sweeps: pre-existing alleles (standing genetic variation) are selected under novel selective pressures.	Branched evolution: **clonal heterogeneity** in large population.	Branched evolution: **clonal heterogeneity** in small population.
Negative selection: elimination of pre-existing clones with alterations that make sensitive to therapy.	Linear evolution: aggressiveness and duration of therapy.	Branched evolution.
Iatrogenic induced relapse.	Divergent evolution.	Divergent evolution.
Polygenic adaptation.	Linear evolution: **mutation rates** are most dominant effect in relapse.	Branched evolution: **clonal heterogeneity** in small population.

Standard model of Cancer Evolution



Branched transformation of follicular lymphoma to DLBCL



Follicular lymphoma (FL) is an indolent disease, but 30%-40% of cases undergo histologic transformation to an aggressive malignancy

- Red dots: Collaboration with R. dalla Favera and L. Pasqualucci (Cell Reports 2014).
- Okusun (Nat Genetics 2014). 10 triplets.
- Summary:

- branched transformation: FL is not a direct ancestor of tDLBCL.

- long branch leading to tFL associated with alterations deregulating cell-cycle progression and DNA damage responses (CDKN2A/B, MYC, and TP53)