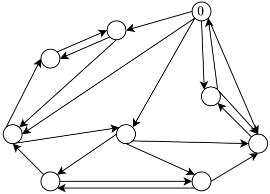
Genetic Composition of Supercritical Branching Populations under Rare Mutation Rates

Vianney Brouard

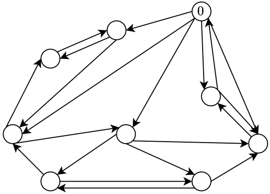
UMPA, ENS de Lyon
ICJ Université Lyon 1

June 12, 2023

- **Biological motivation:**
  Capturing the genetic composition of a population of cells during carcinogenesis.
- **Trait space:**
  a finite oriented graph (V, E), $0 \in V$: 0 represents *wild-type cell*, $v \in V \backslash \{0\}$ represents *mutant cells*,



- **Biological motivation:**
  Capturing the genetic composition of a population of cells during carcinogenesis.
- **Trait space:**
  a finite oriented graph (V, E), $0 \in V$: 0 represents *wild-type cell*, $v \in V \backslash \{0\}$ represents *mutant cells*,

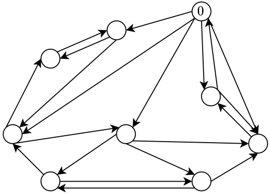


- **Birth and death dynamics:**
  $(Z_v(t))_{t\geq 0}$: Continuous time multitype branching process.
  Division and death at rate α_v and β_v for individuals of trait v.
  The growth rates are

$$\lambda_v := \alpha_v - \beta_v.$$

  Assumption: $\lambda_0 > 0$.

- **Biological motivation:**
  Capturing the genetic composition of a population of cells during carcinogenesis.
- **Trait space:**
  a finite oriented graph (V, E), $0 \in V$: 0 represents *wild-type cell*, $v \in V \backslash \{0\}$ represents *mutant cells*,



- **Birth and death dynamics:**
  $(Z_v(t))_{t \geq 0}$: Continuous time multitype branching process.
  Division and death at rate α_v and β_v for individuals of trait v.
  The growth rates are

$$\lambda_v := \alpha_v - \beta_v.$$

  Assumption: $\lambda_0 > 0$.
- **Mutations:**
  Division event of a cell of trait v: independent mutation to trait u over the two daughter cells with probability $1_{\{(v,u) \in E\}} \mu(v, u)$.
- **Initial condition:** $Z_v(0) = 1_{\{v=0\}}$.

Large Population Rare Mutation Limit

- **Biological context:**
  - tumour size $\sim 10^9$ cells,
  - mutation rate per base pair per cell division $\sim [10^{-10}, 10^{-8}]$,

$\Longrightarrow$ tumor size $\times$ mutation rate $\approx$ constant!

- **Biological context:**
  - tumour size $\sim 10^9$ cells,
  - mutation rate per base pair per cell division $\sim [10^{-10}, 10^{-8}]$,

$\Longrightarrow$ tumor size $\times$ mutation rate $\approx$ constant!

- **Rare mutation regime:**

$$\forall (v,u) \in E, \mu^{(n)}(v,u) \approx \frac{\mu(v,u)}{n}. \qquad (1)$$

$\Longrightarrow$ a sequence of $\left(Z_v^{(n)}\right)_{n\in\mathbb{N}}$ with $\left(\mu^{(n)}(v,u)\right)_{n\in\mathbb{N}}$.

- **Biological context:**
  - tumour size $\sim 10^9$ cells,
  - mutation rate per base pair per cell division $\sim [10^{-10}, 10^{-8}]$,

$\Longrightarrow$ tumor size $\times$ mutation rate $\approx$ constant!

- **Rare mutation regime:**

$$\forall (v,u) \in E, \mu^{(n)}(v,u) \approx \frac{\mu(v,u)}{n}. \tag{1}$$

$\Longrightarrow$ a sequence of $\left(Z_v^{(n)}\right)_{n\in\mathbb{N}}$ with $\left(\mu^{(n)}(v,u)\right)_{n\in\mathbb{N}}$.

- **Biological relevant times:**

$$\begin{cases} \sigma_t^{(n)} := \inf\left\{ s \geq 0 : \sum_{v\in V} Z_v^{(n)}(s) \geq n^t \right\}, \\ \eta_t^{(n)} := \inf\left\{ s \geq 0 : Z_0^{(n)}(s) \geq n^t \right\}. \end{cases} \tag{2}$$

Theorem $\left(\text{Number of mutants at time } \rho^{(n)}\right)$

Let $v \in V$ such that $(0, v) \in E$. Conditioning on $\rho_1^{(n)} = \sigma_1^{(n)}$ or $\eta_1^{(n)} < \infty$,

$$Z_v^{(n)}\left(\rho_1^{(n)}\right) \approx \sum_{i=1}^{K^*} Y_i(\xi_i),$$

K^* is Poisson distributed, Y_i are i.i.d. birth and death processes, ξ_i are i.i.d. exponential distribution.

D.Cheek and T.Antal (2018) and (2020)

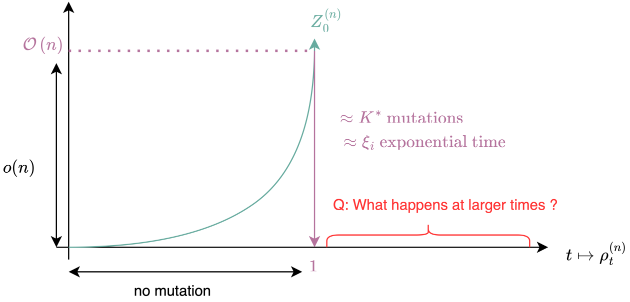
Theorem $\left(\text{Number of mutants at time } \rho^{(n)} \right)$

Let $v \in V$ such that $(0, v) \in E$. Conditioning on $\rho_1^{(n)} = \sigma_1^{(n)}$ or $\eta_1^{(n)} < \infty$,

$$Z_v^{(n)} \left(\rho_1^{(n)} \right) \approx \sum_{i=1}^{K^*} Y_i(\xi_i),$$

K^* is Poisson distributed, Y_i are i.i.d. birth and death processes, ξ_i are i.i.d. exponential distribution.

D.Cheek and T.Antal (2018) and (2020)



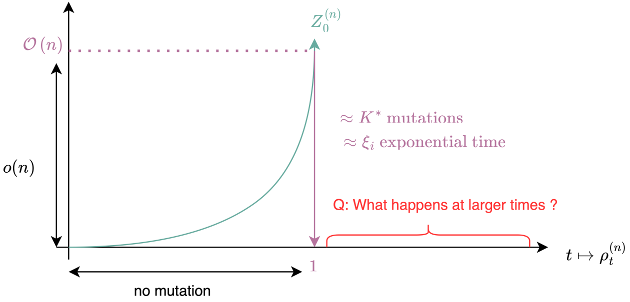
Theorem $\left(\text{Number of mutants at time } \rho^{(n)} \right)$

Let $v \in V$ such that $(0, v) \in E$. Conditioning on $\rho_1^{(n)} = \sigma_1^{(n)}$ or $\eta_1^{(n)} < \infty$,

$$Z_v^{(n)}\left(\rho_1^{(n)}\right) \approx \sum_{i=1}^{K^*} Y_i(\xi_i),$$

K^* is Poisson distributed, Y_i are i.i.d. birth and death processes, ξ_i are i.i.d. exponential distribution.

D.Cheek and T.Antal (2018) and (2020)



$\Longrightarrow$ understand the dynamics of $Z_v^{(n)}\left(\rho_t^{(n)}\right)$, $\forall t > 1$? And for non neighbouring vertices ?

Approximating Deterministic Time-scale

Lemma (Control Wild-Type Population)

For all $0 < T_1 < T_2$,

$$\forall s \in \left[T_1 \frac{\log(n)}{\lambda(0)}, T_2 \frac{\log(n)}{\lambda(0)} \right], \; Z_0^{(n)}(s) \approx W e^{\lambda_0 s},$$

where $W :\stackrel{law}{=} Ber\left(\frac{\lambda_0}{\alpha_0}\right) \otimes Exp\left(\frac{\lambda_0}{\alpha_0}\right)$.

Lemma (Control Wild-Type Population)

For all $0 < T_1 < T_2$,

$$\forall s \in \left[T_1 \frac{\log(n)}{\lambda(0)}, T_2 \frac{\log(n)}{\lambda(0)} \right], \; Z_0^{(n)}(s) \approx W e^{\lambda_0 s},$$

where $W \overset{law}{:=} Ber\left(\frac{\lambda_0}{\alpha_0}\right) \otimes Exp\left(\frac{\lambda_0}{\alpha_0}\right)$.

$$W e^{\lambda_0 s} = n^t \iff s = \frac{t \log(n)}{\lambda_0} - \frac{\log(W)}{\lambda_0}.$$

Lemma (Control Wild-Type Population)

For all $0 < T_1 < T_2$,

$$\forall s \in \left[T_1 \frac{\log(n)}{\lambda(0)}, T_2 \frac{\log(n)}{\lambda(0)}\right],\ Z_0^{(n)}(s) \approx We^{\lambda_0 s},$$

where $W \overset{law}{:=} Ber\left(\frac{\lambda_0}{\alpha_0}\right) \otimes Exp\left(\frac{\lambda_0}{\alpha_0}\right)$.

$$We^{\lambda_0 s} = n^t \iff s = \frac{t\log(n)}{\lambda_0} - \frac{\log(W)}{\lambda_0}.$$

Proposition $\left(\text{Deterministic Approximation of } \eta_t^{(n)}\right)$

Conditioning on $W > 0$, $\forall 0 < T_1 < T_2$

$$\forall t \in [T_1, T_2],\ \eta_t^{(n)} \approx t\frac{\log(n)}{\lambda_0} - \frac{\log(W)}{\lambda_0}.$$

Lemma (Control Wild-Type Population)

For all $0 < T_1 < T_2$,

$$\forall s \in \left[T_1 \frac{\log(n)}{\lambda(0)}, T_2 \frac{\log(n)}{\lambda(0)}\right], \; Z_0^{(n)}(s) \approx We^{\lambda_0 s},$$

where $W \overset{law}{:=} Ber\left(\frac{\lambda_0}{\alpha_0}\right) \otimes Exp\left(\frac{\lambda_0}{\alpha_0}\right)$.

$$We^{\lambda_0 s} = n^t \iff s = \frac{t \log(n)}{\lambda_0} - \frac{\log(W)}{\lambda_0}.$$

Proposition $\left(\text{Deterministic Approximation of } \eta_t^{(n)}\right)$

Conditioning on $W > 0$, $\forall 0 < T_1 < T_2$

$$\forall t \in [T_1, T_2], \; \eta_t^{(n)} \approx t\frac{\log(n)}{\lambda_0} - \frac{\log(W)}{\lambda_0}.$$

$\Rightarrow$ **First Step:**
understand the growth dynamics of $Z_v^{(n)}$ in the time scale $\left(t\frac{\log(n)}{\lambda_0}\right)_{t\in\mathbb{R}^+}$.

- **Bibliography:**

R.Durrett, J.Mayberry (2011)
A. Bovier, L. Coquille, C. Smadi (2019)
J. Blath, A. Tóbiás (2020)
N. Champagnat, S. Méléard, V.C. Tran (2021)
L. Coquille, A. Kraut, C. Smadi (2021)
M. Esser, A. Kraut (preprint, 2021)

- **Bibliography:**
  R.Durrett, J.Mayberry (2011)
  A. Bovier, L. Coquille, C. Smadi (2019)
  J. Blath, A. Tóbiás (2020)
  N. Champagnat, S. Méléard, V.C. Tran (2021)
  L. Coquille, A. Kraut, C. Smadi (2021)
  M. Esser, A. Kraut (preprint, 2021)
- **Stochastic Exponent:**

$$\beta_v^{(n)}(t) := \frac{\log\left(1 + Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right)\right)}{\log(n)} \iff Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right) = n^{\beta_v^{(n)}(t)} - 1.$$

- **Bibliography:**
  R.Durrett, J.Mayberry (2011)
  A. Bovier, L. Coquille, C. Smadi (2019)
  J. Blath, A. Tóbiás (2020)
  N. Champagnat, S. Méléard, V.C. Tran (2021)
  L. Coquille, A. Kraut, C. Smadi (2021)
  M. Esser, A. Kraut (preprint, 2021)
- **Stochastic Exponent:**

$$\beta_v^{(n)}(t) := \frac{\log\left(1 + Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right)\right)}{\log(n)} \iff Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right) = n^{\beta_v^{(n)}(t)} - 1.$$

- **Convergence result:**

$\beta_v^{(n)}(t) \approx$ positive deterministic non-decreasing piecewise linear continuous function.

Result on Stochastic Exponent

- **First occurrence time:**
  For a path γ, define $t(\gamma) := \#$ of edges on γ.
  For $v \in V\backslash\{0\}$, define $t(v) := \min\{t(\gamma), \gamma : 0 \to v\}$.

$$\implies \forall t \leq t(v), \beta_v^{(n)}(t) = 0, \forall t > t(v), \beta_v^{(n)}(t) > 0.$$

- **First occurrence time:**
  For a path γ, define $t(\gamma) := \#$ of edges on γ.
  For $v \in V \backslash \{0\}$, define $t(v) := \min\{t(\gamma), \gamma : 0 \to v\}$.

$$\implies \forall t \leq t(v), \beta_v^{(n)}(t) = 0, \forall t > t(v), \beta_v^{(n)}(t) > 0.$$

- **But what about:**
  (i) Stochasticity ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t n^{\beta_v^{(n)}(t(v)+t)}.$$

- **First occurrence time:**
  For a path γ, define $t(\gamma) := \#$ of edges on γ.
  For $v \in V \backslash \{0\}$, define $t(v) := \min\{t(\gamma), \gamma : 0 \to v\}$.

$$\Longrightarrow \forall t \leq t(v), \beta_v^{(n)}(t) = 0, \forall t > t(v), \beta_v^{(n)}(t) > 0.$$

- **But what about:**
  (i) Stochasticity ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t n^{\beta_v^{(n)}(t(v)+t)}.$$

  (ii) Factor depending on n but not as power of n ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t \varphi_t(n) n^{\beta_v^{(n)}(t(v)+t)}.$$

- **First occurrence time:**
  For a path γ, define $t(\gamma) := \#$ of edges on γ.
  For $v \in V\backslash\{0\}$, define $t(v) := \min\{t(\gamma), \gamma : 0 \to v\}$.

$$\Longrightarrow \forall t \leq t(v), \beta_v^{(n)}(t) = 0, \forall t > t(v), \beta_v^{(n)}(t) > 0.$$

- **But what about:**
  (i) Stochasticity ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t n^{\beta_v^{(n)}(t(v)+t)}.$$

  (ii) Factor depending on n but not as power of n ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t \varphi_t(n) n^{\beta_v^{(n)}(t(v)+t)}.$$

  (iii) Characterisation of pathes contributing to the size of the trait v ?

$\Longrightarrow$ getting results directly on the first asymptotic order of $Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right)$.

- **First occurrence time:**
  For a path γ, define $t(\gamma) := \#$ of edges on γ.
  For $v \in V \backslash \{0\}$, define $t(v) := \min\{t(\gamma), \gamma : 0 \to v\}$.

$$\Longrightarrow \forall t \leq t(v), \beta_v^{(n)}(t) = 0, \forall t > t(v), \beta_v^{(n)}(t) > 0.$$

- **But what about:**
  (i) Stochasticity ?

$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t n^{\beta_v^{(n)}(t(v)+t)}.$$

  (ii) Factor depending on n but not as power of n ?

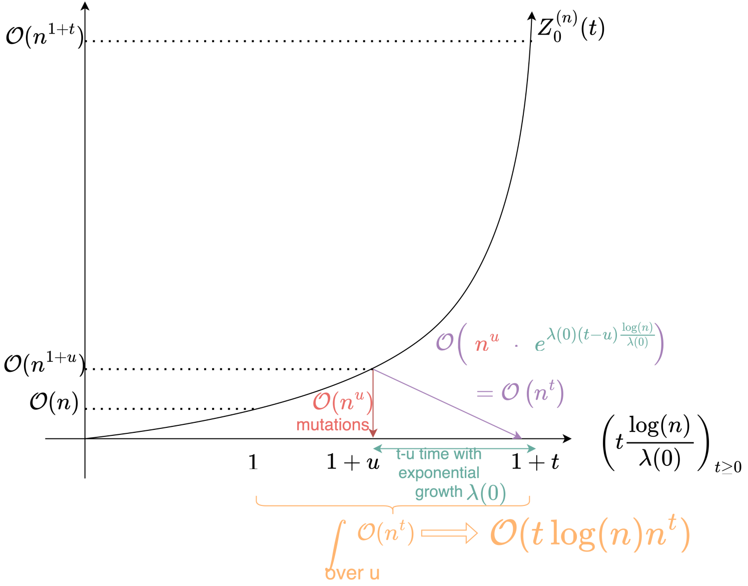
$$Z_v^{(n)}\left((t(v)+t)\frac{\log(n)}{\lambda_0}\right) \approx X_t \varphi_t(n) n^{\beta_v^{(n)}(t(v)+t)}.$$

  (iii) Characterisation of pathes contributing to the size of the trait v ?
  $\Longrightarrow$ getting results directly on the first asymptotic order of $Z_v^{(n)}\left(t\frac{\log(n)}{\lambda_0}\right)$.
  Disclaimer: needs the non-increasing growth rate condition

$$\forall v \in V, \lambda_v \leq \lambda_0.$$

Heuristic for a Neutral Mutation

Assumption: $\lambda_1 = \lambda_0$.



- For γ a path on the graph,

$$\theta(\gamma) := \# \text{ of edges pointing to a neutral vertex.}$$

- For $v \in V \backslash \{0\}$,

$$\theta(v) := \max\{\theta(\gamma) : \gamma : 0 \to v, t(\gamma) = t(v)\},$$
$$A(v) := \{\gamma : 0 \to v, t(\gamma) = t(v) \text{ and } \theta(\gamma) = \theta(v)\}.$$

- For γ a path on the graph,

$$\theta(\gamma) := \# \text{ of edges pointing to a neutral vertex.}$$

- For $v \in V \backslash \{0\}$,

$$\theta(v) := \max\{\theta(\gamma) : \gamma : 0 \to v, t(\gamma) = t(v)\},$$
$$A(v) := \{\gamma : 0 \to v, t(\gamma) = t(v) \text{ and } \theta(\gamma) = \theta(v)\}.$$

Theorem (First Asymptotic Order of Mutants)

Assume $\forall v \in V, \lambda_v \leq \lambda_0$. For all $t > 0$

$$Z_v^{(n)}\left((t(v) + t)\frac{\log(n)}{\lambda_0}\right) \approx n^t W \log^{\theta(v)}(n) \sum_{\gamma \in A(v)} w(\gamma) I_\gamma(t),$$

and

$$Z_v^{(n)}\left(\rho_{t(v)+t}^{(n)}\right) \approx n^t 1_{\{W>0\}} \log^{\theta(v)}(n) \sum_{\gamma \in A(v)} w(\gamma) I_\gamma(t).$$

Stochastic time-scale: J. Foo, K. Leder (2013)

(i) Without any condition on the growth rate function λ, is it possible to get asymptotic results directly on $Z_v^{(n)}\left(t\frac{\log(n)}{\lambda(0)}\right)$?

(i) Without any condition on the growth rate function λ, is it possible to get asymptotic results directly on $Z_v^{(n)}\left(t\frac{\log(n)}{\lambda(0)}\right)$?

(ii) What would happen if the number of traits in the population is growing with n ? $(V^{(n)}, E^{(n)})$ of finite oriented labeled graph such that

- $|V^{(n)}|$ is non-decreasing,
- $E^{(n)} \subset E^{(n+1)} \underset{n\to\infty}{\longrightarrow} E \subset \{(i,j), \forall i \neq j \in \mathbb{N}_0\}$,

Assume that

$$|V^{(n)}| \approx \ell(V) n^{\ell} \text{ or } \ell(V)\log^{\ell}(n),$$

$$\forall (v,u) \in E, \mu^{(n)}(v,u) \approx \frac{\mu(v,u)}{n}.$$