On Multi-type Decomposable Branching Processes in Continuous Time and Time to Escape Extinction

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Background

- M. C. Serra: *On the waiting time to escape*, Journal of Applied Probability (2006)
- M. C. Serra, P. Haccou: *Dynamics of escape mutants*, Theoretical Population Biology (2007)
- Iwasa, Y., Michor, F., Nowak, M.A. *Evolutionary dynamics of escape from biomedical intervention*, Proc. R. Soc. London (2003)
- Iwasa, Y., Michor, F., Nowak, M.A. *Evolutionary dynamics of invasion and escape*, J. Theor. Biol. (2004)
- P. Haccou, P. Jagers and V. A. Vatutin (2005): *Branching Processes: Variation, Growth, and Extinction of Populations, Cambridge University Press, Cambridge*;

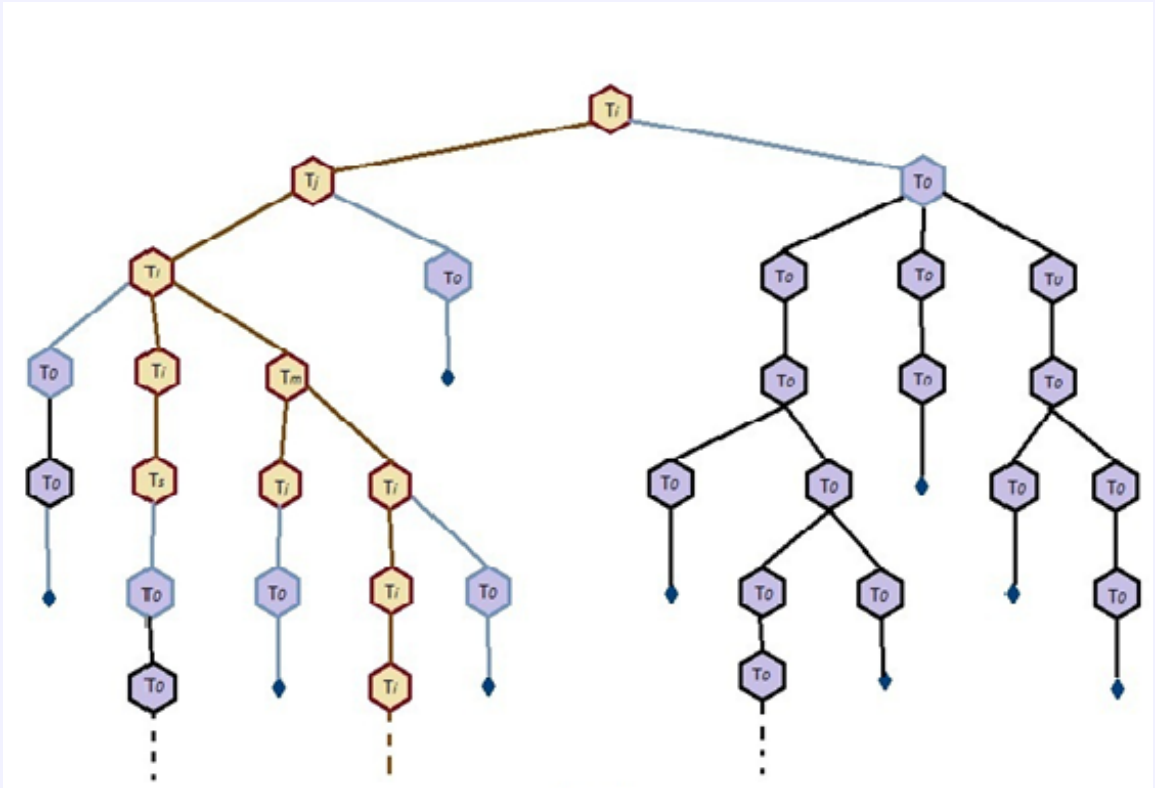
Motivation

- consider multi-type branching processes with **continuous time** to model the dynamics of different types of cells, which due to a small reproductive ratio of cells are fated to become extinct
- **mutations** occurring during the reproduction process, may lead to the appearance of new type of cells that may escape extinction
- a typical real world situation with the emergence of scatters after local eradication of a certain type of cancer during the chemotherapy
- a cell of the ”mutation” type which leads to the beginning of a lineage, that will never extinct is called ”successful mutant”
- “escape extinction”

$k+1-$type Bellman-Harris branching process (BHBP)

- Multi-type BHBP with $k+1$ types $\mathbf{Z}(t) = (Z^0(t), Z^1(t), \ldots, Z^k(t)), t \geq 0,$
- $Z^k(t)$ - number of cells of type k at time t
- all cells of type l, $l \neq 0$ are **subcritical**, i.e. have reproduction mean m_l, $0 < m_l < 1$ and each of their daughter cells can mutate, independently of the others, to type 0 with probability u_{l0}, $0 < u_{l0} < 1$
- only cells of type 0, are **supercritical**, i.e. have reproduction mean m_0, $1 < m_0 < \infty$
- u_{ij} are the probabilities that a cell of type i can produce a cell of type j, $i \neq j$, $i, j \neq 0$
- $u_{0i} = 0$, $i \neq 0$

Sample tree



Mean matrix - different schemes

- $f_0(s) = E(s^{Z^0}|Z^0(0) = 1)$

  $f_i(s) = E(s^{Z^i}|Z^i(0) = 1), i = 1, \ldots, k$

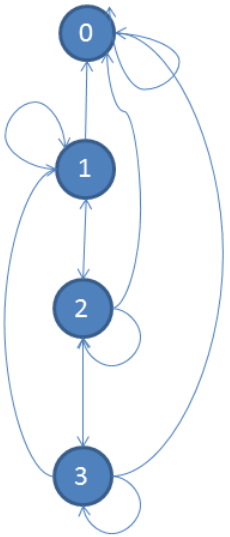
  $F_i(t; s_0, s_1, \ldots, s_k) = E(s_0^{Z^0(t)} s_1^{Z^1(t)} \ldots s_k^{Z^k(t)} | Z^i(0) = 1, i \neq 0, Z^j(0) = 0, j \neq i)$

  $\mathbf{F}(t; \mathbf{s}) = (F_0(t; \mathbf{s}), F_1(t; \mathbf{s}), \ldots, F_k(t; \mathbf{s})),$
  $\mathbf{s} = (s_0, s_1, \ldots, s_k)$

- $$m_{ij}(t) = \frac{\partial F_i(t; s_0, s_1, \ldots, s_k)}{\partial s_j}|_{\mathbf{s}=\mathbf{1}} = m_j(t) u_{ij}$$

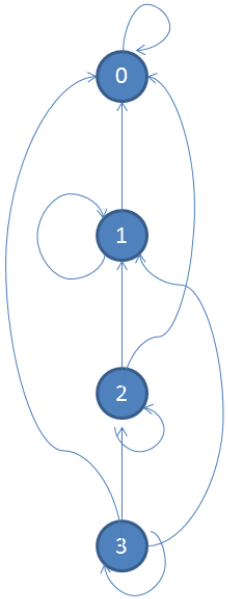
Mean matrix - different schemes

- $$A = \begin{bmatrix} m_{00}(t) & 0 & \dots & 0 \\ m_{10}(t) & m_{11}(t) & \dots & m_{1k}(t) \\ \vdots & \vdots & \ddots & \vdots \\ m_{k0}(t) & m_{k1}(t) & \dots & m_{kk}(t) \end{bmatrix}$$
- a scheme allowing mutations: $i \to j$, $i \neq j$



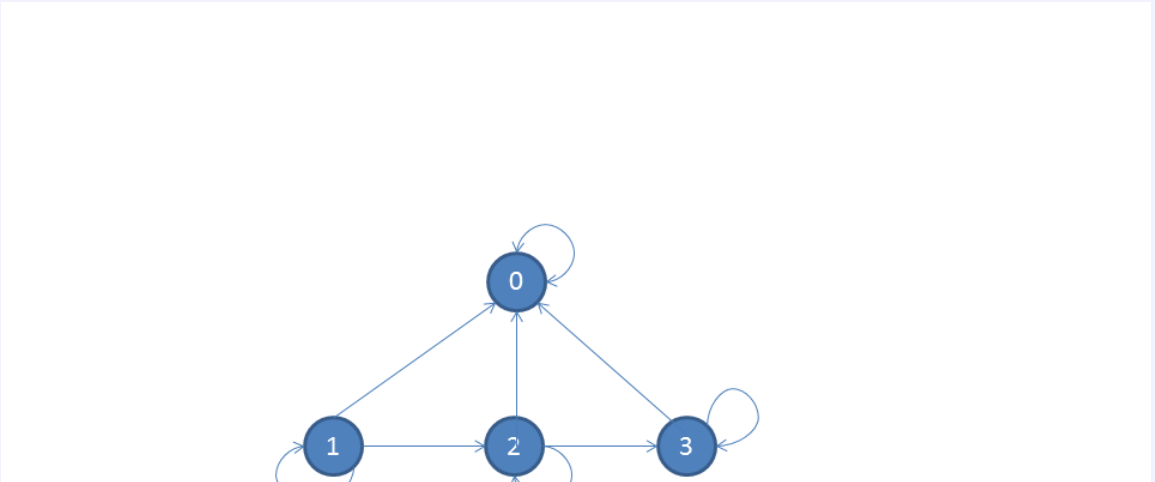
Mean matrix - allowing for backward mutations

- $$\tilde{A} = \begin{bmatrix} m_{00}(t) & 0 & 0 & \dots & 0 & 0 \\ m_{10}(t) & m_{11}(t) & \dots & 0 & 0 & 0 \\ m_{20}(t) & m_{21}(t) & m_{22}(t) \dots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ m_{k0}(t) & 0 & 0 & \dots & m_{kk-1}(t) & m_{kk}(t) \end{bmatrix}$$
- a scheme allowing only for backward mutations: $i \to j$, $i > j$



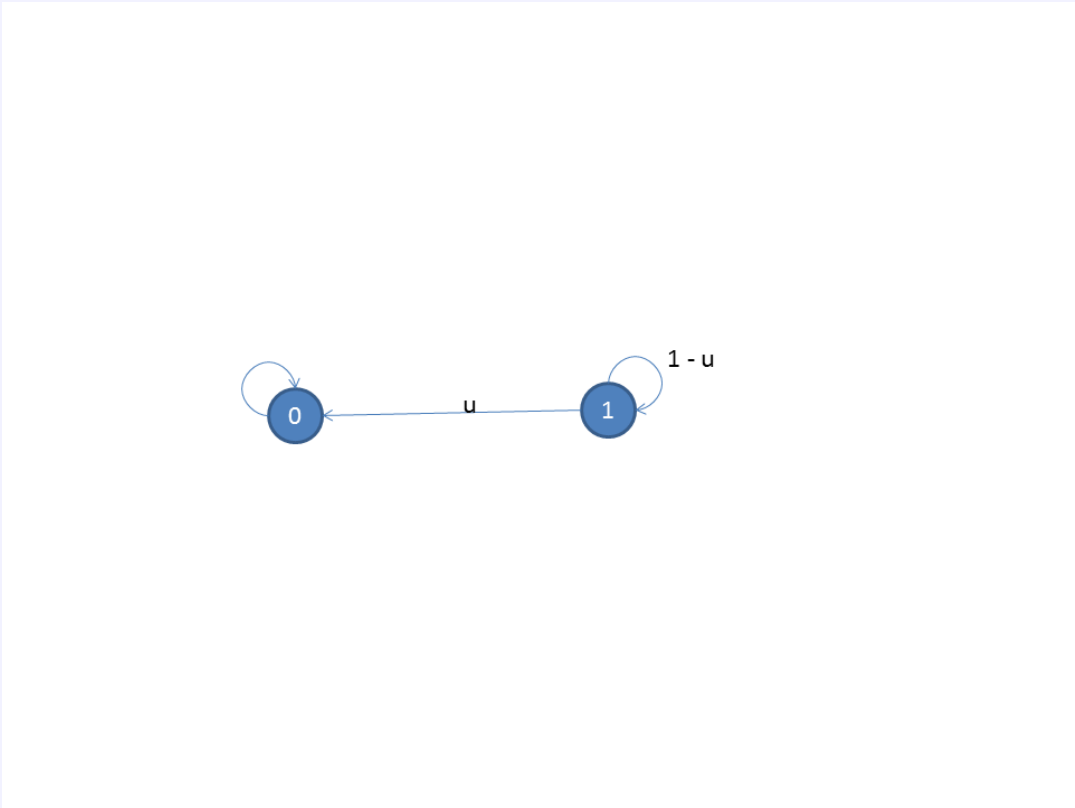
Mean matrix - not allowing for backward mutations

- $$\tilde{A} = \begin{bmatrix} m_{00}(t) & 0 & 0 & \dots & 0 & 0 \\ m_{10}(t) & m_{11}(t) & m_{12}(t) & 0 & 0 & 0 \\ m_{20}(t) & 0 & m_{22}(t) \dots & m_{23}(t) & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ m_{k-10}(t) & 0 & \ddots & \ddots & m_{k-1k-1}(t) & m_{k-1k}(t) \\ m_{k0}(t) & 0 & 0 & \dots & 0 & m_{kk}(t) \end{bmatrix}$$
- a scheme not allowing for backward mutations: $i \to j$, $i > j$



Functional equations for two-type Bellman-Harris branching processes

- Let us denote $G_i(t)$ d.f. of the life-time distribution of the cells of type $i = 0, 1$
- u = mutation probability or the probability a particle of type 1 to produce 0-type particle



Functional equations for the p.g.f. of two-type Bellman-Harris branching processes

- **Theorem 1.** The p.g.f. $F(t, s_0, s_1) = E(s_0^{Z^0(t)} s_1^{Z^1(t)})$ satisfies the functional equation

$$F_1(t, s_0, s_1) = s_1(1 - G_1(t)) + \int_0^t f_1(uF_0(t - v, s_0) + (1 - u)F_1(t - v, s_0, s_1)))dG_1(v), \tag{1}$$

- where

$$F_0(t, s_0, s_1) \equiv F_0(t, s_0) = s_0(1 - G_0)(t)) + \int_0^t f_0(F_0(t - v, s_0))dG_0(v), \tag{2}$$

$$F_0(0, s_0) = s_0.$$

P.G.F. of the number of mutations

- r.v. I(t) - number of mutations up to time t (including)
- r.v. I - total number of mutations in the whole process
- **Theorem 2.** The p.g.f. $h_{I(t)}(s) = E\{s^{I(t)}\}$ and $h_I(s) = E\{s^I\}$ satisfy the functional equations

$$h_{I(t)}(s) = 1 - G_1(t) + \int_0^t f_1(us + (1-u)h_{I(t-v)}(s))G_1(v),$$

- $$h_I(s) = f_1(t - v, us + (1-u)h_I(s)), \qquad (3)$$

for all $s \in [0,1]$.

Probability of extinction in two-type BHBP

- $q_0 = P(Z^0(t) = Z^1(t) = 0, t \geq 0 | Z^0(0) = 1, Z^1(0) = 0)$
- $q_1 = P(Z^0(t) = Z^1(t) = 0, t \geq 0 | Z^0(0) = 0, Z^1(0) = 1)$
- q_0 is just the extinction probability of a single-type supercritical BHBP
- $q_0 : f_0(s) = s$

Probability of escape in two-type BHBP

- To determine q_1 we need only to remember that the process is extinct if and only if the lineage of cells that mutated from type 1 to type 0 is also extinct. Since the number of such cells is given by the r.v. I, we have $q_1 = E[q_0^I] = h_I(q_0)$ where $h_I(.)$ is given by (3).
- $r_0 = P(Z^0(t) \to \infty | Z^0(0) = 1, Z^1(0) = 0)$
- $r_1 = P(Z^0(t) \to \infty | Z^0(0) = 0, Z^1(0) = 1)$
- $r_0 = 1 - q_0, r_1 = 1 - q_1 = 1 - h_I(q_0)$.

Probability of escape in $k+1-$ type BGWBP (Serra and Haccou (2007))

- $r_j = P(Z^0(t) \to \infty | Z^j(0) = 1, j \neq 0, Z^i(0) = 0, \forall i \neq j)$
- $r_j \approx \frac{m_j}{1-m_j} \sum_{i=0, i \neq j} u_{ji} r_i.$
- $\mathbf{r} = (r_1, r_2, \ldots, r_k)$

T – time to escape extinction

- $T = \infty$ if no successful mutant is produced
- **Theorem 3.** The distribution of the r. v. T has the following properties:
- $P(T > t) = h_{I(t)}(q_0) = Q_t, t \geq 0,$
- $P(T = \infty) = q_1,$
- $E(T|T < \infty) = \frac{1}{1-q_1} \int_0^\infty \{h_{I(t)}(q_0) - q_1\} dt.$

The immediate risk to escape – hazard function

- $g(t)dt = P(T \in (t, t+dt) | T > t, Z^1(t) > 0)$
- probability to produce a successful mutant at time t given that it has not been produced yet and the subcritical population is not extinct at time t
- $$g(t)dt = \frac{-Q_t' dt}{Q_t - \mathbb{P}(T > t, Z^1(t) = 0)}, t \geq 0.$$

Time to attain level x

- r.v. L_x - the first moment when the single-type Bellman-Harris BP process $Y(t)$ crosses level x,
- $L_x = \inf_t : \{Y(t) \geq x\}$
- Conditioned on non-extinction L_x will be finite for all x, since then $Y(t) \to \infty$, as $t \to \infty$.
- $\{Z^0(t), Z^1(t), t \geq 0\}$ - the two-type Bellman-Harris BP
- r. v. $T_x = \inf_t : \{Z^0(t) \geq x\}$ - the time for the number of escape type cells to cross level x,
- **Goal:** For small values of u: the distribution of r.v. $(T_x|T < \infty)$ can be approximated by the sum of two independent r.v. $(T|T < \infty)$ and $(L_x|Y(t) \to \infty)$.
- Nagaev (1971), Roesler (2000)

Conclusion

- Viruses, bacteria, eukaryotic parasites, cancer cells and agricultural pests have an unfortunate tendency to escape from selection pressures that are meant to control them. Chemotherapy, anti-viral drugs or antibiotics fail because their targets do not hold still, but evolve resistance. A major problem in developing vaccines is that microbes evolve and escape from immune responses.
- The fundamental question is the following: if a genetically diverse population of replicating organisms is challenged with a selection pressure that has the potential to eradicate it, what is the probability that this population will produce escape mutants?
- We propose multi-type branching processes in continuous time to describe the accumulation of mutants in independent lineages. We show how to estimate the probability of success or failure of biomedical intervention, such as drug treatment and vaccination, against rapidly evolving organisms.

Open questions

- approximations of the random quantities for binomial, geometric and double fission reproduction,
- different schemes of mutations,
- limit theorems.

Thank you for your attention !