General Branching Processes and Cell Populations

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Bienaymé–Galton–Watson process, discrete time, synchronized generations
General (Crump–Mode–Jagers) branching process, continuous time, overlapping generations, point process.
Galton–Watson

- Number of children $X$, random variable on $\{0, 1, 2, \ldots\}$
- Size of $n$th generation:
  \[
  Z_n = \sum_{k=1}^{Z_{n-1}} X_k, \ n = 1, 2, \ldots \quad (Z_0 \equiv 1)
  \]

- Growth rate: $m^n$, where $m = E[X]$

- Convergence: $\frac{Z_n}{m^n} \to W$ as $n \to \infty$. 
General

- Reproduction process, $\xi$: point process on $[0, \infty)$

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General

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• Mean reproduction process $\mu(a) = E[\xi(a)], \mu(dt) = E[\xi(dt)]$

• Growth rate: $e^{\alpha t}$, where Malthusian parameter $\alpha$ solves the equation

$$\hat{\mu}(\alpha) = \int_{0}^{\infty} e^{-\alpha t} \mu(dt) = 1$$
Galton–Watson process: $\xi(dt) = X\delta_1(dt)$,

$$\xi(a) = \begin{cases} 0 & \text{if } a < 1 \\ X & \text{if } a \geq 1 \end{cases}$$

In this case,

$$\int_0^\infty e^{-\alpha t} \mu(dt) = me^{-\alpha} = 1$$

gives $\alpha = \log m$ and $e^{\alpha t} = m^n$. 
Random characteristics

- $\chi(a)$: contribution of an individual at age $a$
Random characteristics

• $\chi(a)$: contribution of an individual at age $a$

• $\chi$-counted population

$$Z_t^\chi = \sum_{x \in I} \chi_x (t - \tau_x)$$

where

$I =$ set of all individuals
$\tau_x =$ birth time of individual $x$
Examples:

1. $\chi(a) = I_{R^+}(a)$ – indicator of being born, $Z_t^\chi = \text{number of individuals born before } t$
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1. \( \chi(a) = I_{R_+}(a) \) – indicator of being born, \( Z^\chi_t \) = number of individuals born before \( t \)

2. \( \chi(a) = I_{[0,L)}(a) \) – indicator of being alive, \( Z^\chi_t \) = number of individuals alive at time \( t \)
Convergence result

As \( t \to \infty \),

\[
e^{-\alpha t} Z_t^\chi \to c \, W
\]

where \( W \) is a random variable and

\[
c = \int_0^\infty e^{-\alpha t} E[\chi(dt)]
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Thus:

\[
\frac{Z_t^\chi_1}{Z_t^\chi_2} \to \frac{c_1}{c_2}
\]

Asymptotic stability, for example stable age distribution.
Biological relevance

- Yeast (S. cerevisiae), asymmetric division, finite lifespan.

(Wikipedia)

Prion dynamics (O. and Sindi, Math Pop Studies, 2012)

Telomere dynamics (O. and Bertuch, J Theor Biol, 2010)
Biological relevance

- Yeast (S. cerevisiae), asymmetric division, finite lifespan.
  
(Wikipedia)

Biological relevance

- Yeast (S. cerevisiae), asymmetric division, finite lifespan.


Cell cycle desynchronization

Of interest: Fraction of cells in S phase over time in an initially synchronized population.
Experimental data

(Chiorino, Metz, Tomasoni, Ubezio, *J Theor Biol*, 208, 2001)
Cells forced to start in S phase (synchronization). Fraction of cells in S phase over time:
Previous models


Deterministic model
Previous models


Deterministic model


Heuristic stochastic model
Branching process model

O. and Thomas “Ollie” McDonald (Trinity Univ math major, Rice Univ Ph.D. student)

- Cell cycle time \( L = G_1 + S + G_2 + M \), cdf \( F \)
Branching process model

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- Cell cycle time \( L = G_1 + S + G_2 + M \), cdf \( F \)

- Reproduction by splitting, \( \xi(dt) = 2\delta_L(dt), \mu(dt) = 2F(dt) \)
Branching process model

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• Cell cycle time $L = G_1 + S + G_2 + M, \text{cdf } F$

• Reproduction by splitting, $\xi(dt) = 2\delta_L(dt), \mu(dt) = 2F(dt)$

• Malthusian parameter: $2 \int_0^\infty e^{-\alpha t} F(dt) = 1$
Random characteristic counting cells in S phase:

$$\chi_S(a) = I\{G_1 \leq a \leq G_1 + S\}$$
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Random characteristic counting cells alive:

$$\chi(a) = I\{L > a\}$$
Random characteristic counting cells in S phase:

\[ \chi_S(a) = I\{G_1 \leq a \leq G_1 + S\} \]

Random characteristic counting cells alive:

\[ \chi(a) = I\{L > a\} \]

Fraction of cells in S phase: \( Q(t) := \frac{Z_t \chi_s}{Z_t \chi} \rightarrow \text{constant} \)
Path to the limit?

Initial synchronization?
Expected value:

\[ E[Q(t)] \approx \frac{E[Z_t^s]}{E[Z_t^X]} \]
Expected value:

\[ E[Q(t)] \approx \frac{E[Z_t^{\chi_s}]}{E[Z_t^{\chi}]} \]

Our time zero: time \( \tau = G_1 + T \) in the process, \( T \) on \([0, S]\).
For any characteristic

\[ Z_t^\chi = \chi(t) + Z_{t-L}^\chi(1) + Z_{t-L}^\chi(2) \]

\[ L = \text{lifetime of ancestor} \]
For any characteristic

\[ Z_t^\chi = \chi(t) + Z_{t-L}^\chi(1) + Z_{t-L}^\chi(2) \]

\( L = \) lifetime of ancestor

\[ E[Z_{\tau+t}^\chi] = E[\chi(\tau + t)] + 2E[Z_{\tau+t-L}^\chi] \]

\[ = E[\chi(\tau + t)] + 2E[Z_{t-R}^\chi] \]

\( R = L - \tau \) remaining lifetime of ancestor
\[ E[Z_{\tau+t}^\chi] = E[\chi(\tau + t)] + 2E[Z_{t-R}^\chi] \]
\[ E[Z_{\tau+t}^\chi] = E[\chi(\tau + t)] + 2E[Z_{t-R}^\chi] \]

For \( \chi \):

\[ E[\chi(\tau + t)] = P(R \geq t) \]
\begin{align*}
E[Z^\chi_{\tau+t}] &= E[\chi(\tau+t)] + 2E[Z^\chi_{t-R}] \\
\text{For } \chi: \\
E[\chi(\tau+t)] &= P(R \geq t) \\
\text{For } \chi_S: \\
E[\chi_S(\tau+t)] &= P(S - T \geq t) \\
S - T &= \text{remaining time in S phase}
\end{align*}
\begin{align*}
E[Q(\tau + t)] & \approx \frac{P(S - T \geq t) + 2 \int_{0}^{t} E[Z^\chi_{S}] F_R(dr)}{P(R \geq t) + 2 \int_{0}^{t} E[Z^\chi_{t-r}] F_R(dr)}
\end{align*}

For given phase time distributions, we can find distributions of \( S - T \) and \( R \) using stable population theory.
\[
E[Q(\tau + t)] \approx \frac{P(S - T \geq t) + 2 \int_0^t E[Z^X_{t-r}F_R(dr)]}{P(R \geq t) + 2 \int_0^t E[Z^X_{t-r}F_R(dr)]}
\]

For given phase time distributions, we can find distributions of \( S - T \) and \( R \) using stable population theory.

Phase time distribution parameters from data (Ubezio, personal communication), assume gamma distributions. Run model.
Note: Curve *not fitted* to data!
Article:

O. and McDonald, A stochastic model of cell cycle desynchronization, *Mathematical Biosciences*, 2010

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