Computational Bayesian Tools for Modeling the Aging Process

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Outline

What is Aging?

- **Chronological Age**: A measure of the time elapsed since the birth of an individual.

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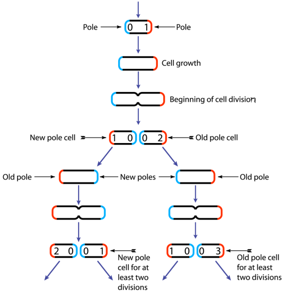
- **Actuarial Age**: A predictor of the occurrence of death.
- **Physiological Age**: The process of accumulation of damages in cells and organisms.

- **Comments**: These three definitions of aging:
  - Can support divergent predictions,
  - Express the focus on the statistical laws,
  - By no means should be understood as a divergence.

Bacteria Do Age

Cell division in the bacterium *E. Coli*



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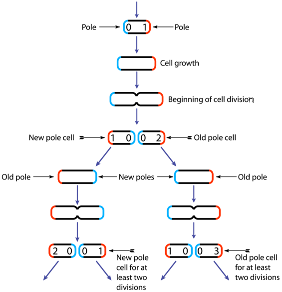
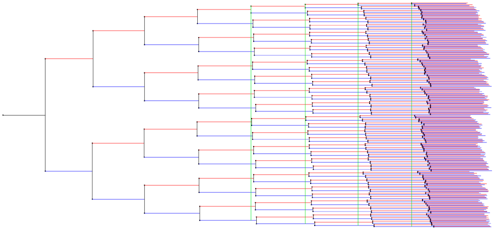


The life cycle of *E. Coli*, E. J. Stewart et al., PLoS Biol. , 2005

- **Replicative Age**: The number of generations since the old pole arose.

Replicative Age Properties

- Increased replicative age known to be associated with defective growth.



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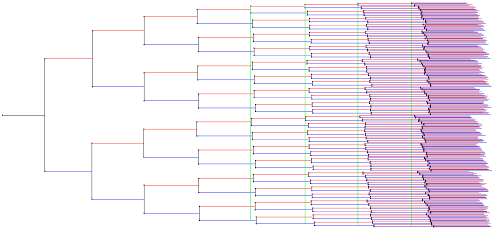

Average lineage showing old pole effect on growth rate, E. J. Stewart et al., PLoS Biol. , 2005

- But accounts for a limited fraction of the observed variance in the physiological characteristics.

Idea Behind Modeling Aging

- **Challenge**: Infer the extent of the asymmetry in the process of the inheritance of damages, using the growth rates as noisy observations of the amount damages.

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Is there a rejuvenation mechanism?

Are damages transmitted evenly to daughter cells?

How can we quantify a potential asymmetry?

Data Description

- **Experiment**: a colony of *E. coli* monitored up to 9 generations.

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- **Data**:
  - A lineage tree reconstructed from a movie by computer vision methods.
  - An estimated growth rate for each cell.
- **Model**: Reconstruct a quantity that explains the physiological variability, as a physical quantity and which grows independently from the cell growth.

Physical variables of the model

- $x_i(t)$: Amount of accumulated damages in cell i at time t, **hidden**,
- γ_i: Growth rate of cell i, seen as a noisy observation of $x_i(t)$ at birth time of cell i,
- t_i: Date of division of cell i,
- T_i: Time elapsed between the formation of the cell i and its division,
- **Indexing convention**: daughters of cell i are indexed $2i+1$ and $2i+2$.

Dynamics of the hidden variable

- x grows according to a drifting Brownian motion:

$$\begin{aligned} \frac{\mathrm{d}x_i(t)}{dt} &= \mu_x + \sigma_x \frac{\mathrm{d}W_t}{dt} \Rightarrow \\ x_i(T_i) &= \mu_x T_i + \mathcal{N}(0, \sigma_x^2 T_i^2) \end{aligned}$$

- x is spread across daughter cells at division, picking a rejuvenated cell randomly ($\delta \sim B(0.5)$):

$$\begin{aligned} x_{2i+1+\delta_i}(t_i) \,|\, \delta_i,\, x_i(t_i) &\sim x_i(t_i) \times Beta(\beta_{rejuvenated}, \beta_{aged}) \\ x_{2i+2}(t_i) + x_{2i+1}(t_i) &= x_i(t_i) \end{aligned}$$

Further specifications

- **Observations**

$$\gamma_{2i+1} \sim Gamma(10, \frac{1}{x_{2i+1}(t_i)})$$

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- **Quantities of interest**
  - The parameter, $\theta = (\mu_x, \sigma_x^2, \beta_{rejuvenated}, \beta_{aged})$.
  - The split ratio, $r = \frac{\beta_{rejuvenated}}{\beta_{rejuvenated} + \beta_{aged}}$.

Background

- **Bayesian Inference**: is focused on the posterior distribution $\pi(\theta \mid y) \propto f(y \mid \theta)\pi(\theta)$ of a parameter vector θ under the prior distribution $\pi(\cdot)$ through the likelihood function $f(\cdot \mid \theta)$ having observed data y.

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- **Approximate Bayesian Computation (ABC) :**
  - Avoids intractable likelihood functions.
  - Draws samples from an approximate posterior distribution
  - Still feasible to simulate data from the model/likelihood.

ABC Methodology

Algorithm 1 Likelihood-free ABC rejection sampler 1

1: Draw parameters $\theta = (\mu_x, \sigma_x, \beta_{rejuvenated}, \beta_{aged}) \sim \pi$.
2: Simulate synthetic data z using these parameter values from the likelihood.
3: If $z = y$ accept the parameters, else reject.
4: Repeat

Outcome:

$f(\theta_i) \propto \sum_z \pi(\theta_i) f(z|\theta_i) \mathbb{I}_y(z) = \pi(\theta_i) f(y|\theta_i) \propto \pi(\theta_i|y)$

ABC Algorithms I

- Extension to the case of the continuous sample spaces.

Algorithm 2 Likelihood-free ABC rejection sampler 2

1: Draw parameters $\theta = (\mu_x, \sigma_x, \beta_{rejuvenated}, \beta_{aged}) \sim \pi$.
2: Simulate synthetic data z using these parameter values from the model $f(\cdot \mid \theta)$.
3: If $d(\eta(z), \eta(y)) < \epsilon$ accept the parameters, else reject.
4: Repeat

- Specifications:
  - η: a function defining a statistic; often not sufficient,
  - d: a distance,
  - ϵ: a tolerance level.

A as Approximate

- $\pi(\theta \mid \eta_{obs}) \approx \pi(\theta \mid y_{obs})$ where $\pi(\theta \mid \eta_{obs}) \propto \pi(\eta_{obs} \mid \theta)\pi(\theta)$.

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- $\pi_\epsilon(\theta|y) = \int \pi_\epsilon(\theta, z|y)\, dz \approx \pi(\theta|y)$

Outcome

- The likelihood-free samples from the marginal in z

$$\pi_\epsilon(\theta, z|y) = \frac{\pi(\theta)f(z|\theta)\mathbb{I}_{A_{\epsilon,y}}(z)}{\int_{A_{\epsilon,y}\times\Theta}\pi(\theta)f(z|\theta)\,dz\,d\theta}$$

where $A_{\epsilon,y} = \{z \in \mathcal{D} | d(\eta(z), \eta(y)) < \epsilon\}$.

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  where $A_{\epsilon,y} = \{z \in \mathcal{D}|d(\eta(z),\eta(y)) < \epsilon\}$.

- The idea behind ABC is that using representative summary statistics with a small tolerance level should produce a good approximation to the posterior.

ABC Algorithms II

- Using simulations from the prior distribution is inefficient.

Algorithm 3 Likelihood-free ABC MCMC sampler

1: Use Algorithm 1 to get a realization (θ_0, z_0) from the ABC target distribution $\pi_\epsilon(\theta, z|y)$.
2: Draw parameters from a Markov truncated-normal kernel $\theta' \sim q(\cdot|\theta_{t-1})$.
3: Simulate synthetic data z' using these parameter values.
4: Draw $u \sim \mathcal{U}_{[0,1]}$.
5: If
$$u \leqslant \frac{\pi(\theta')q(\theta_{t-1}|\theta')}{\pi(\theta_{t-1})q(\theta'|\theta_{t-1})} \quad and \quad d(\eta(z'), \eta(y)) < \epsilon$$
accept the parameters, else reproduce.
6: Repeat from stage 2.

ABC Applied in Aging

- **Motivation**:
  - $\mathbb{P}\left(x \mid \mu_x, \sigma_x, \beta_{rejuvenated}, \beta_{aged}\right)$ is difficult to compute.
  - Avoids the combinatorial explosion when marginalizing δ.

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  - $\mathbb{P}\left(x \,|\, \mu_x, \sigma_x, \beta_{rejuvenated}, \beta_{aged}\right)$ is difficult to compute.
  - Avoids the combinatorial explosion when marginalizing δ.
- **Artificial Dataset**
  - The number of cells is 255; 7 generations.
  - All times to division are set to 1.
  - The values of the parameters are set to $(\mu_x, \sigma_x) = (1, 0.1)$ and $(\beta_r, \beta_a) = \{(10, 15), (15, 15), (2, 3), (3, 3)\}$.

Calibration of ABC in Aging 1

Summary Statistics

- Introduce $\hat{x}_i = \frac{1}{\gamma_i}$
- Reorder $\hat{x}$ so that $\gamma_{2i+2} < \gamma_{2i+1}$
- Define the following statistics

$$
\begin{aligned}
\eta_1 &= mean\left[\frac{\hat{x}_{2i+1} + \hat{x}_{2i+2} - \hat{x}_i}{T_i}\right] \\
\eta_2 &= sd\left[\frac{\hat{x}_{2i+1} + \hat{x}_{2i+2} - \hat{x}_i}{T_i}\right] \\
\eta_3 &= mean\left[\frac{\hat{x}_{2i+1}}{\hat{x}_{2i+1} + \hat{x}_{2i+2}}\right] \\
\eta_4 &= sd\left[\frac{\hat{x}_{2i+1}}{\hat{x}_{2i+1} + \hat{x}_{2i+2}}\right]
\end{aligned}
$$

Calibration of ABC in Aging 2

- The distance d is the euclidean, normalized by the a priori standard deviation of each component.

$$w_1[\eta_1(D_{obs}) - \eta_1(D_{synth})] + \ldots + w_4[\eta_1(D_{obs}) - \eta_4(D_{synth})]$$

where $\sum_{i=1}^{4} w_1[\eta_i(D_{obs}) - \eta_i(D_{synth})] = 1$ under the prior.

In presence of asymmetry

$$(\beta_{rejuvenated}, \beta_{aged}) = (10, 15)$$

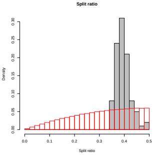

Figura: Split ratio

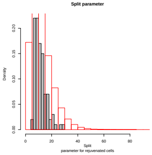

Figura: $\beta_{rejuvenated}$

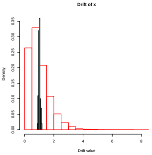

Figura: μ_x

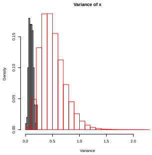

Figura: σ_x

In absence of asymmetry

$$(\beta_{rejuvenated}, \beta_{aged}) = (15, 15)$$

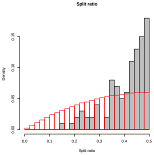

Figura: Split ratio

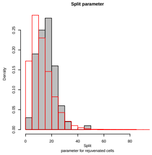

Figura: $\beta_{rejuvenated}$

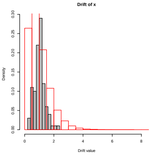

Figura: μ_x

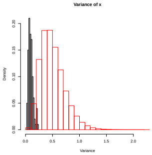

Figura: σ_x

In case of broadly distributed splits

$$(\beta_{rejuvenated}, \beta_{aged}) = \{(2, 3), (3, 3)\}$$

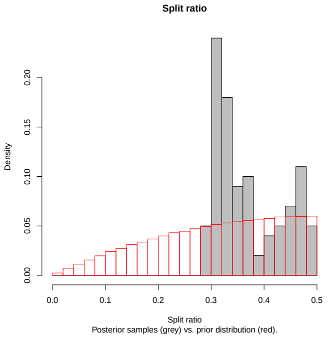

Figura: A

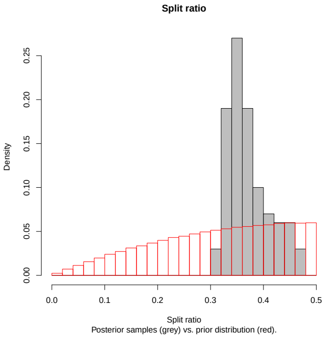

Figura: B

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- Using an MCMC-ABC did not show any improvement.
- **Extensions:**
  - Modeling: Introduction of a hidden *aging-switch* parameter, δ_i.
  - Methodology: Monte Carlo Markov Chain.

Introducing the Aging-Switch Parameter δ_i

$$\begin{aligned}
x_0^b &= 1 && (1)\\
x_i^d &= x_i^b + \mathcal{TN}(\,\mu_x T_i,\ \sigma_x^2 T_i^2\,) && (2)\\
\delta_i &\sim \textit{Bernoulli}(\,0.5\,) && (3)\\
x_{2i+1}^b(t_i)\,|\,\delta_i = 1,\ x_i^d(t_i) &\sim x_i^d(t_i) \times \textit{Beta}(\beta_r,\ \beta_a) && (4)\\
x_{2i+1}^b(t_i)\,|\,\delta_i = 2,\ x_i^d(t_i) &\sim x_i^d(t_i) \times \textit{Beta}(\beta_a,\ \beta_r) && (5)\\
x_{2i+2}^b(t_i) + x_{2i+1}^b(t_i) &= x_i^d(t_i) && (6)\\
\gamma_i^b &\sim \textit{Gamma}(10,\ \frac{1}{x_i^b(t_i)}) && (7)
\end{aligned}$$

Prior Distributions

- Quantities of interest
  - The parameter, $\theta = (\mu_x, \sigma_x^2)$.
  - The split ratio, $r = \frac{\beta_{rejuvenated}}{\beta_{rejuvenated} + \beta_{aged}}$.
- The priors:

$$
\begin{aligned}
\mu_x &\sim Gamma(2,\ 1) \\
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Modeling Specifications

- Aging - Switch parameter δ_i :
  $\mathbb{P}(\delta_i = 1) = 1 - \mathbb{P}(\delta_i = 2) = 0.5$

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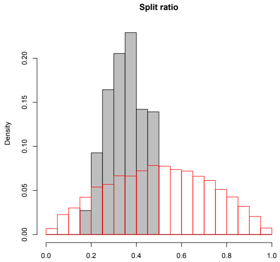
- The exact distribution of $x^b_{2i+1} \,|\, \delta_i = 1,\, x^d_i$:

$$
\begin{aligned}
f_{x^b_{2i+1}}(\, x^b_{2i+1} \,|\, \delta_i = 1,\, x^d_i \,) &= f_{\frac{x^b_{2i+1}}{x^d_i}}\left(\frac{x^b_{2i+1}}{x^d_i}\right)\frac{1}{x^d_i} \\
&= \left(\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_r - 1}\left(1 - \frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_a - 1}\frac{1}{B(\beta_r,\beta_a)x^d_i}
\end{aligned}
$$

Results

- Real dataset
- 24 parallel processes
- 10^8 simulations, 10^{-5} acceptance ratio



Thank you for your attention !

MCMC Background

- Definition
  - A class of methods which generate a Markov Chain whose stationary distribution is the distribution of interest.
  - An approximate sample from the posterior distribution without having to sample from this distribution directly.

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- Practical Techniques for Convergence
  - *Burn-in*: Influence the time of convergence by discarding a number of iterations at the early stage of the sampling process.
  - *Thinning*: Reduce the dependance between the draws of the Markov Chain by building a subchain which keeps only every d-th draw.

Gibbs Sampling

Sampling from a posterior distribution $p(\theta \mid y)$.

Algorithm 4 Gibbs Sampler

1: Choose a vector of starting values $\theta^{(0)}$.
2: Start with any θ. Draw a value $\theta_1^{(1)}$ from the full conditional $p(\theta_1 \mid \theta_2^{(0)}, \ldots, \theta_i^{(0)}, \ldots, \theta_k^{(0)}, y)$.
3: Draw a value $\theta_i^{(0)}$ from $p(\theta_i \mid \theta_1^{(1)}, \ldots, \theta_{i-1}^{(1)}, \theta_{i+1}^{(0)}, \ldots, \theta_k^{(0)}, y)$ by using the most updated values for the other parameters until $i = k$.
4: Draw $\theta^{(2)}$ using $\theta^{(1)}$ and continually using the most updated values.
5: Repeat until we get M draws, with each draw being a vector $\theta^{(i)}$.
6: Optional burn-in and/or thinning.

Full Conditionals Calculation

1. Write out the full posterior distribution ignoring constants of proportionality.
2. Pick a block of parameters and drop everything that doesn't depend on that parameter.
3. Use the knowledge of distributions to determine the distribution of the full conditional.
4. Repeat the previous steps for all parameters.

Metropolis-Hastings Algorithm

If the full conditionals do not look like any known distribution.

Algorithm 5 Metropolis - Hastings Algorithm

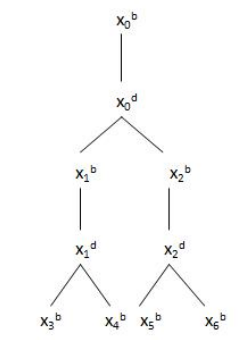
1: Choose a starting value $\theta^{(0)}$.
2: At iteration t, draw a candidate θ^* from a jumping distribution $J_t(\theta^* \mid \theta^{(t-1)})$.
3: Compute an acceptance ratio (probability):

$$r = \frac{\pi(\theta^* \mid y) \,/\, J_t(\theta^* \mid \theta^{(t-1)})}{\pi(\theta^{(t-1)} \mid y) \,/\, J_t(\theta^{(t-1)} \mid \theta^*)}$$

4: Accept θ^* as $\theta^{(t)}$ with probability $min(r, 1)$. If θ^* is not accepted, then $\theta^{(t)} = \theta^{(t-1)}$.
5: Repeat steps 2-4 M times to get M draws from $\pi(\theta \mid y)$, with optional burn-in and/or thinning.

Likelihood Computation - Example

Partial Lineage Tree



Likelihood

$$
\begin{aligned}
L = \; & P(x_0^b) \times P(x_0^d \mid x_0^b) \times \\
& P(x_1^b \mid x_0^d) \times P(x_1^d \mid x_1^b) \times \\
& \delta_{\{x_0^d - x_1^b\}}(x_2^b) \times P(x_2^d \mid x_0^d - x_1^b) \times \\
& P(x_3^b \mid x_1^d) \times \\
& \delta_{\{x_1^d - x_3^b\}}(x_4^b) \times \\
& P(x_5^b \mid x_2^d) \times \\
& \delta_{\{x_2^d - x_5^b\}}(x_6^b)
\end{aligned}
$$

Likelihood - General Form

$$
\begin{aligned}
L = \; & P(x_0^b) \times \prod_{i=0}^{nb_{obs}-1} \mathbb{P}(x_i^d \mid x_i^b) \times \\
& \prod_{\delta_i=1} [\, \mathbb{P}(x_{2i+1}^b \mid x_i^d)\, \delta_{\{x_i^d - x_{2i+1}^b\}}(x_{2i+2}^b) \,] \times \\
& \prod_{\delta_i=2} [\, \mathbb{P}(x_{2i+1}^b \mid x_i^d)\, \delta_{\{x_i^d - x_{2i+1}^b\}}(x_{2i+2}^b) \,] \\
= \; & 1 \times \prod_{i=0}^{nb_{obs}-1} [\, \frac{1}{1-\Phi(0,\mu_X,\sigma_X)} \frac{1}{\sigma_X T_i \sqrt{2\pi}} \exp\{-\frac{[x_i^d - (x_i^b + \mu_X T_i)]^2}{2\sigma_X^2 T_i^2}\} \,] \times \\
& \prod_{\delta_i=1} [\, \frac{(x_{2i+1}^b)^{\beta_r - 1} (x_i^d - x_{2i+1}^b)^{\beta_a - 1}}{(x_i^d)^{\beta_r + \beta_a - 1} B(\beta_r, \beta_a)} \times \delta_{\{x_i^d - x_{2i+1}^b\}}(x_{2i+2}^b) \,] \times \\
& \prod_{\delta_i=2} [\, \frac{(x_{2i+1}^b)^{\beta_a - 1} (x_i^d - x_{2i+1}^b)^{\beta_r - 1}}{(x_i^d)^{\beta_r + \beta_a - 1} B(\beta_a, \beta_r)} \times \delta_{\{x_i^d - x_{2i+1}^b\}}(x_{2i+2}^b) \,]
\end{aligned}
$$

Full Conditional Distributions 1

$$f(\theta\,|\,x) \propto \quad L \times e^{-\frac{(\mu_X-1.25)^2}{2(1.1)^2}} (\frac{1}{\sigma_X^2})^4 e^{-\frac{0.02}{\sigma_X^2}} \beta_r e^{-10\beta_r} \beta_a e^{-10\beta_a} \frac{1}{2}$$

$$\pi(\mu_X|\cdot) \propto \quad (\frac{1}{1-\Phi(0,\mu_X,\sigma_X)})^{nb_{obs}}$$
$$\mathbb{TN}(\frac{\sigma_1^2 \sum_{i=0}^{nb_{obs}-1} \frac{x_i^d - x_i^b}{T_i} + \sigma_X^2 \mu_1}{\sigma_1^2 nb_{obs} + \sigma_X^2} ; (\frac{\sigma_X \sigma_1}{\sqrt{\sigma_1^2 nb_{obs} + \sigma_X^2}})^2) \mathbb{1}_{\mu_X > 0}$$

$$\pi(\sigma_X^2|\cdot) \propto \quad (\frac{1}{1-\Phi(0,\mu_X,\sigma_X)})^{nb_{obs}}$$
$$\mathbb{IG}(\frac{nb_{obs}}{2} + \alpha - 2 ; \frac{1}{2} \sum_{i=0}^{nb_{obs}-1} (\mu_X - \frac{x_i^d - x_i^b}{T_i})^2 + \beta) \mathbb{1}_{\sigma_X > 0}$$

Full Conditional Distributions 2

$$\pi(\beta_r|\cdot) \propto \prod_{\delta_i=1}[(\frac{x^b_{2i+1}}{x^d_i})^{\beta_r}] \times \prod_{\delta_i=2}[(1-\frac{x^b_{2i+1}}{x^d_i})^{\beta_r}] \times$$

$$[\frac{1}{B(\beta_r,\beta_a)}]^{nb_{obs}} \times \beta_r^{\alpha-1} e^{-\beta\beta_r}$$

$$\pi(\beta_a|\cdot) \propto \prod_{\delta_i=1}[(1-\frac{x^b_{2i+1}}{x^d_i})^{\beta_a}] \times \prod_{\delta_i=2}[(\frac{x^b_{2i+1}}{x^d_i})^{\beta_a}] \times$$

$$[\frac{1}{B(\beta_r,\beta_a)}]^{nb_{obs}} \times \beta_a^{\alpha-1} e^{-\beta\beta_a}$$

$$\pi(\delta_i|\cdot) \propto [(x^b_{2i+1})^{\beta_r-1}(x^d_i - x^b_{2i+1})^{\beta_a-1}]^{\delta_1=1}$$

$$[(x^b_{2i+1})^{\beta_a-1}(x^d_i - x^b_{2i+1})^{\beta_r-1}]^{\delta_i=2}$$

Algorithmic Specifications

- Sampling from conditionals of $(\mu_x, \sigma_x^2, \beta_r, \beta_a)$ with a MH step.
- The candidate distributions used on the MH are Truncated Normals.

Algorithmic Specifications

- Sampling from conditionals of $(\mu_x, \sigma_x^2, \beta_r, \beta_a)$ with a MH step.
- The candidate distributions used on the MH are Truncated Normals.
- The artificial dataset is the same as in the ABC application.

Presence of Asymmetry - Sampling Paths

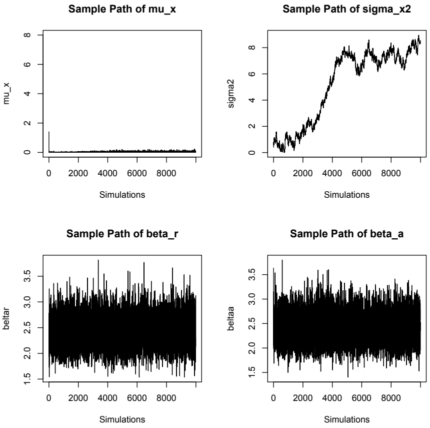


Figura: Number of iterations: 10^6, burn-in $= 10^3$, thin = 100, candidate standard deviations $= (0.1, 0.005, 0.1, 0.1)$,

Absence of Asymmetry - Sampling Paths

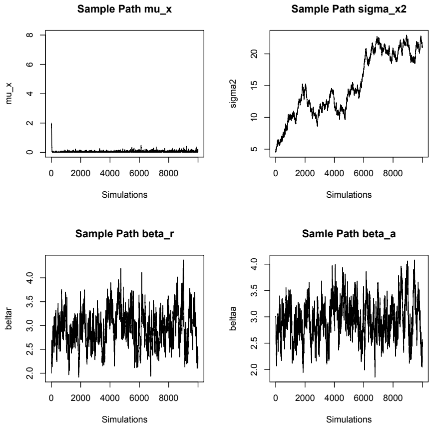


Figura: Number of iterations: 10^4, burn-in $=$ 0, thin = 1, candidate standard deviations $= (0.1, 0.1, 0.1, 0.1)$, $(\beta_r, \beta_a) = (15, 15)$.

Presence of Weak Asymmetry - Sampling Paths

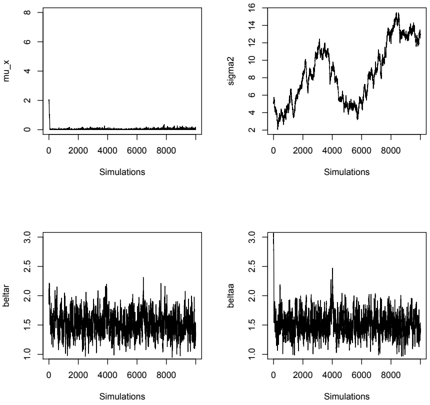


Figura: Number of iterations: 10^4, burn-in $=$ 0, thin = 1, candidate standard deviations $= (0.1, 0.1, 0.1, 0.1)$, $(\beta_r, \beta_a) = (2, 3)$.

Presence of Weak Asymmetry - Sampling Paths

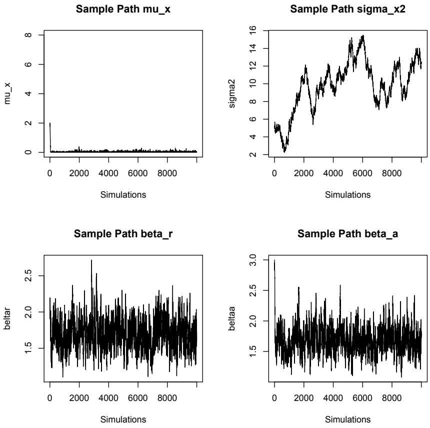


Figura: Number of iterations: 10^4, burn-in $=$ 0, thin = 1, candidate standard deviations $= (0.1, 0.1, 0.1, 0.1)$, $(\beta_r, \beta_a) = (3, 3)$.

Posterior - Prior Histograms

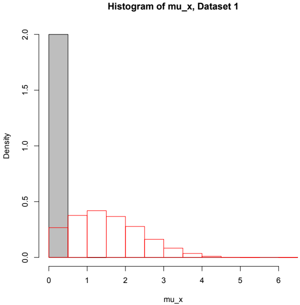


Figura: A

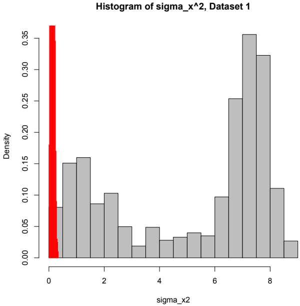


Figura: B

Figura: True values: $(\mu_x, \sigma_x^2) = (1, 0.1)$. Number of iterations: 10^6 .

Fixed σ_x^2

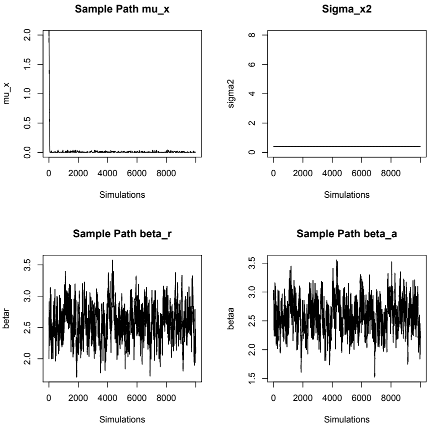


Figura: Number of iterations: 10^4, burn-in $=$ 0, thin = 1, candidate standard deviations $= (0.1, 0.1, 0.1, 0.1)$

Comments

- σ_x^2 does not converge.

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- σ_x^2 does not converge.
- $(\mu_x, \beta_r, \beta_a)$ do not converge to their true value.
- Need for more complex sampling mechanisms.

- Aging Process:

- Aging Process:
  - An ABC for the last model.
  - Selection of explanatory variables.
  - Application to real datasets.

Likelihood

$$L = \left(\frac{1}{1-\Phi(0,\mu_X,\sigma_X)}\right)^{nb_{obs}} \left(\frac{1}{\sigma_X\sqrt{2\pi}}\right)^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right] \times$$

$$\exp\left\{-\sum_{i=0}^{nb_{obs}-1} \frac{[x_i^d-(x_i^b+\mu_X T_i)]^2}{2\sigma_X^2 T_i^2}\right\} \times$$

$$\prod_{\delta_i=1}\left[\left(\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_r}\left(1-\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_a}\right] \times \prod_{\delta_i=2}\left[\left(\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_a}\left(1-\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_r}\right] \times$$

$$\left[\frac{1}{B(\beta_r,\beta_a)}\right]^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{(x_i^d)^2}{x_{2i+1}^b(x_i^d-x_{2i+1}^b)}\right]$$

Likelihood

$$L = \left(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\right)^{nb_{obs}} \left(\frac{1}{\sigma_x\sqrt{2\pi}}\right)^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right] \times$$

$$\exp\left\{-\sum_{i=0}^{nb_{obs}-1} \frac{[\mu_x - \frac{x_i^d - x_i^b}{T_i}]^2}{2\sigma_x^2}\right\} \times$$

$$\prod_{\delta_i=1}\left[\left(\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_r}\left(1-\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_a}\right] \times \prod_{\delta_i=2}\left[\left(\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_a}\left(1-\frac{x_{2i+1}^b}{x_i^d}\right)^{\beta_r}\right] \times$$

$$\left[\frac{1}{B(\beta_r,\beta_a)}\right]^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{(x_i^d)^2}{x_{2i+1}^b(x_i^d - x_{2i+1}^b)}\right]$$

μ_x Full Conditional

$$
\begin{aligned}
\pi(\mu_x|\cdot) = \quad & \prod_{i=0}^{nb_{obs}-1}\Big[\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\frac{1}{\sigma_x T_i\sqrt{2\pi}}\exp\Big\{-\frac{[x_i^d-(x_i^b+\mu_x T_i)]^2}{2\sigma_x^2 T_i^2}\Big\}\Big]\times \\
& \frac{1}{1-\Phi(0,\mu_1,\sigma_1)}\frac{1}{\sigma_1\sqrt{2\pi}}\exp\Big[-\frac{(\mu_x-\mu_1)^2}{2\sigma_1^2}\Big] \\
\propto \quad & \Big(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\Big)^{nb_{obs}}\Big(\frac{1}{\sigma_x\sqrt{2\pi}}\Big)^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\Big[\frac{1}{T_i}\Big]\times \\
& \exp\Big\{-\sum_{i=0}^{nb_{obs}-1}\frac{[x_i^d-(x_i^b+\mu_x T_i)]^2}{2\sigma_x^2 T_i^2}\Big\}\exp\Big[-\frac{(\mu_x-\mu_1)^2}{2\sigma_1^2}\Big] \\
\propto \quad & \Big(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\Big)^{nb_{obs}}\Big(\frac{1}{\sigma_x\sqrt{2\pi}}\Big)^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\Big[\frac{1}{T_i}\Big]\times \\
& \exp\Big\{-\sum_{i=0}^{nb_{obs}-1}\frac{[\mu_x-\frac{x_i^d-x_i^b}{T_i}]^2}{2\sigma_x^2}\Big\}\exp\Big[-\frac{(\mu_x-\mu_1)^2}{2\sigma_1^2}\Big]
\end{aligned}
$$

μ_X Full Conditional

$$
\begin{aligned}
\pi(\mu_X|\cdot) \propto\ & \left(\frac{1}{1-\Phi(0,\mu_X,\sigma_X)}\right)^{nb_{obs}}\left(\frac{1}{\sigma_X\sqrt{2\pi}}\right)^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right]\times \\
& \exp\left\{-\frac{1}{2\sigma_X^2}\left[nb_{obs}\mu_X^2 - 2\mu_X\sum_{i=0}^{nb_{obs}-1}\frac{x_i^d-x_i^b}{T_i} + \right.\right. \\
& \left.\left.\sum_{i=0}^{nb_{obs}-1}\left(\frac{x_i^d-x_i^b}{T_i}\right)^2\right]\right\}\times \\
& \exp\left[-\frac{1}{2\sigma_1^2}(\mu_X^2 - 2\mu_X\mu_1 + \mu_1^2)\right]
\end{aligned}
$$

$$
\begin{aligned}
\propto\ & \left(\frac{1}{1-\Phi(0,\mu_X,\sigma_X)}\right)^{nb_{obs}}\left(\frac{1}{\sigma_X\sqrt{2\pi}}\right)^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right]\times \\
& \exp\left\{-\frac{1}{2\sigma_X^2\sigma_1^2}\left[(\sigma_1^2 nb_{obs} + \sigma_X^2)\mu_X^2 - \right.\right. \\
& \left.\left. 2\left(\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\frac{x_i^d-x_i^b}{T_i} + \sigma_X^2\mu_1\right)\mu_X\right\}\right]\times \\
& \exp\left\{-\frac{1}{2\sigma_X^2\sigma_1^2}\left[\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\left(\frac{x_i^d-x_i^b}{T_i}\right)^2 + \sigma_X^2\mu_1^2\right]\right\}
\end{aligned}
$$

μ_X Full Conditional

$$
\begin{aligned}
\pi(\mu_X|\cdot) \propto \quad & \left(\frac{1}{1-\Phi(0,\mu_X,\sigma_X)}\right)^{nb_{obs}} \left(\frac{1}{\sigma_X\sqrt{2\pi}}\right)^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right] \times \\
& \exp\left\{-\frac{1}{2\left(\frac{\sigma_X\sigma_1}{\sqrt{\sigma_1^2 nb_{obs}+\sigma_X^2}}\right)^2}\left[\left(\mu_X - \frac{\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\frac{x_i^d-x_i^b}{T_i}+\sigma_X^2\mu_1}{\sigma_1^2 nb_{obs}+\sigma_X^2}\right)^2\right]\right\} \times \\
& \exp\left\{-\frac{1}{2\left(\frac{\sigma_X\sigma_1}{\sqrt{\sigma_1^2 nb_{obs}+\sigma_X^2}}\right)^2}\left[\frac{\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\left(\frac{x_i^d-x_i^b}{T_i}\right)^2+\sigma_X^2\mu_1^2}{\sigma_1^2 nb_{obs}+\sigma_X^2} - \right.\right. \\
& \left.\left.\left(\frac{\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\frac{x_i^d-x_i^b}{T_i}+\sigma_X^2\mu_1}{\sigma_1^2 nb_{obs}+\sigma_X^2}\right)^2\right]\right\} \\
\propto \quad & \left(\frac{1}{1-\Phi(0,\mu_X,\sigma_X)}\right)^{nb_{obs}} \\
& \mathbb{TN}\left(\frac{\sigma_1^2\sum_{i=0}^{nb_{obs}-1}\frac{x_i^d-x_i^b}{T_i}+\sigma_X^2\mu_1}{\sigma_1^2 nb_{obs}+\sigma_X^2};\left(\frac{\sigma_X\sigma_1}{\sqrt{\sigma_1^2 nb_{obs}+\sigma_X^2}}\right)^2\right)\mathbb{1}_{\mu_X>0}
\end{aligned}
$$

σ_x^2 Full Conditional

$$\pi(\sigma_x^2|\cdot) = \prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\frac{1}{\sigma_x T_i\sqrt{2\pi}}\exp\left\{-\frac{[x_i^d-(x_i^b+\mu_x T_i)]^2}{2\sigma_x^2 T_i^2}\right\}\right]\times$$

$$\frac{\beta^\alpha}{\Gamma(\alpha)}\left(\frac{1}{\sigma_x^2}\right)^{\alpha-1}\exp\left[-\frac{\beta}{\sigma_x^2}\right]$$

$$\propto \left(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\right)^{nb_{obs}}\left(\frac{1}{\sigma_x\sqrt{2\pi}}\right)^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\left[\frac{1}{T_i}\right]\times$$

$$\exp\left\{-\sum_{i=0}^{nb_{obs}-1}\frac{[\mu_x-\frac{x_i^d-x_i^b}{T_i}]^2}{2\sigma_x^2}\right\}\left(\frac{1}{\sigma_x^2}\right)^{\alpha-1}\exp\left[-\frac{\beta}{\sigma_x^2}\right]$$

σ_x^2 Full Conditional

$$\pi(\sigma_x^2|\cdot) \propto \left(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\right)^{nb_{obs}} \left(\frac{1}{\sigma_x^2}\right)^{(\frac{nb_{obs}}{2}+\alpha-2)+1} \times$$

$$\exp\left\{-\frac{1}{\sigma_x^2}\left[\frac{1}{2}\sum_{i=0}^{nb_{obs}-1}\left(\mu_x - \frac{x_i^d - x_i^b}{T_i}\right)^2 + \beta\right]\right\}$$

$$\propto \left(\frac{1}{1-\Phi(0,\mu_x,\sigma_x)}\right)^{nb_{obs}}$$

$$\mathbb{IG}\left(\frac{nb_{obs}}{2} + \alpha - 2;\ \frac{1}{2}\sum_{i=0}^{nb_{obs}-1}\left(\mu_x - \frac{x_i^d - x_i^b}{T_i}\right)^2 + \beta\right)\mathbb{1}_{\sigma_x > 0}$$

β_r Full Conditional

$$
\begin{aligned}
\pi(\beta_r|\cdot) = \; & \prod_{\delta_i=1}\Big[\frac{(x^b_{2i+1})^{\beta_r-1}(x^d_i - x^b_{2i+1})^{\beta_a-1}}{(x^d_i)^{\beta_r+\beta_a-1}B(\beta_r,\beta_a)}\Big]\times \\
& \prod_{\delta_i=2}\Big[\frac{(x^b_{2i+1})^{\beta_a-1}(x^d_i - x^b_{2i+1})^{\beta_r-1}}{(x^d_i)^{\beta_r+\beta_a-1}B(\beta_a,\beta_r)}\Big]\times \beta_r^{\alpha-1}e^{-\beta\beta_r} \\
\propto \; & \prod_{\delta_i=1}\Big[\Big(\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_r}\Big(1-\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_a}\Big]\times \\
& \prod_{\delta_i=2}\Big[\Big(\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_a}\Big(1-\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_r}\Big]\times \\
& \Big[\frac{1}{B(\beta_r,\beta_a)}\Big]^{nb_{obs}}\prod_{i=0}^{nb_{obs}-1}\Big[\frac{(x^d_i)^2}{x^b_{2i+1}(x^d_i - x^b_{2i+1})}\Big]\times \beta_r^{\alpha-1}e^{-\beta\beta_r} \\
\propto \; & \prod_{\delta_i=1}\Big[\Big(\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_r}\Big]\times \prod_{\delta_i=2}\Big[\Big(1-\frac{x^b_{2i+1}}{x^d_i}\Big)^{\beta_r}\Big]\times \\
& \Big[\frac{1}{B(\beta_r,\beta_a)}\Big]^{nb_{obs}}\times \beta_r^{\alpha-1}e^{-\beta\beta_r}
\end{aligned}
$$

β_a Full Conditional

$$\pi(\beta_a|\cdot) = \prod_{\delta_i=1}\left[\frac{(x^b_{2i+1})^{\beta_r-1}(x^d_i - x^b_{2i+1})^{\beta_a-1}}{(x^d_i)^{\beta_r+\beta_a-1}B(\beta_r,\beta_a)}\right] \times \prod_{\delta_i=2}\left[\frac{(x^b_{2i+1})^{\beta_a-1}(x^d_i - x^b_{2i+1})^{\beta_r-1}}{(x^d_i)^{\beta_r+\beta_a-1}B(\beta_a,\beta_r)}\right] \times \beta_a^{\alpha-1}e^{-\beta\beta_a}$$

$$\propto \prod_{\delta_i=1}\left[\left(\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_r}\left(1-\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_a}\right] \times \prod_{\delta_i=2}\left[\left(\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_a}\left(1-\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_r}\right] \times \left[\frac{1}{B(\beta_r,\beta_a)}\right]^{nb_{obs}} \prod_{i=0}^{nb_{obs}-1}\left[\frac{(x^d_i)^2}{x^b_{2i+1}(x^d_i - x^b_{2i+1})}\right] \times \beta_a^{\alpha-1}e^{-\beta\beta_a}$$

$$\propto \prod_{\delta_i=1}\left[\left(1-\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_a}\right] \times \prod_{\delta_i=2}\left[\left(\frac{x^b_{2i+1}}{x^d_i}\right)^{\beta_a}\right] \times \left[\frac{1}{B(\beta_r,\beta_a)}\right]^{nb_{obs}} \times \beta_a^{\alpha-1}e^{-\beta\beta_a}$$