A Computational Time Machine
with possible applications to phylogenetic tree reconstruction

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5th of November, 2009
Overview of Talk
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Part 1  A Systematic Method for Retrodictive Inference
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- Motivation and theoretical context
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- ‘Retrodictive’ Master Equations
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- Stochastic solution of RMEs (Retrodictive SSA)
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Part 1  A Systematic Method for Retrodictive Inference
- Motivation and theoretical context
- ‘Retrodictive’ Master Equations
- Stochastic solution of RMEs (Retrodictive SSA)

Part 2  Application of the RSSA to Phylogenetic Tree Reconstruction
Part I

Systematic methods for Retrodictive Inference
Continuous-time birth/death processes

- Govern the markovian stochastic dynamics of systems which undergo discrete state changes at random times.
Continuous-time birth/death processes

- Govern the markovian stochastic dynamics of systems which undergo discrete state changes at random times.
- Employed to describe a vast array of physical processes in
  - physics (statistical and quantum mechanics),
  - chemistry (chemical reactions) and
  - biology (stochastic population dynamics, sequence evolution models, etc. etc.).
Continuous-time birth/death processes

A single-variable example:
Continuous-time birth/death processes

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A single-variable example:

\[ n \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \]
Continuous-time birth/death processes

A single-variable example:

$$P(n,t|n_0,t_0)$$
Continuous-time birth/death processes

A single-variable example:

In general, probability distributions of continuous-time birth/death processes satisfy the

Master Equation

$$\frac{d}{dt} P(\tilde{n}, t|\tilde{n}_0, t_0) = \sum_k \left[ T_k(\tilde{n}'_k) P(\tilde{n}'_k, t) - T_k(\tilde{n}) P(\tilde{n}, t) \right]$$
Looking into the past: retrodictive inference
As solution of the ME yields conditional probabilities of later states given earlier states, it is naturally suited to predictive inference.
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- To use $P(\vec{n}_f, t_f | \vec{n}_i, t_i)$ to infer earlier states from later states (i.e. retrodiction), employ Bayes’ theorem:
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$$P(\vec{n}_i, t_i | \vec{n}_f, t_f) = \frac{P(\vec{n}_f, t_f | \vec{n}_i, t_i)P_0(\vec{n}_i, t_i)}{\sum_{\vec{m}} P(\vec{n}_f, t_f | \vec{m}, t_i)P_0(\vec{m}, t_i)}$$
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Is there a more direct approach?
A completely equivalent description of the stochastic dynamics is provided by the ...
Looking into the past: retrodictive inference

A completely equivalent description of the stochastic dynamics is provided by the . . .

**Backward Master Equation**

\[
\frac{d}{dt_0} P(\vec{n}, t|\vec{n}_0, t_0) = \sum_k T_k(\vec{n}_0) \left[ P(\vec{n}, t|\vec{n}_0', t_0) - P(\vec{n}, t|\vec{n}_0, t_0) \right]
\]
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Backward Master Equation

\[
\frac{d}{dt_0} P(\vec{n}, t|\vec{n}_0, t_0) = \sum_k T_k(\vec{n}_0) \left[ P(\vec{n}, t|\vec{n}''_0, t_0) - P(\vec{n}, t|\vec{n}_0, t_0) \right]
\]

(Can be derived from the regular ME by noting that \(d/ds \sum_{\vec{m}} P(\vec{n}, t|\vec{m}, s)P(\vec{m}, s|\vec{n}_0, t_0) = 0\) for \(t > s > t_0\).)
Looking into the past: retrodictive inference

For convenience, define

\[ R(\vec{n}, \tau | \vec{n}_f) = \frac{P(\vec{n}_f, t_f | \vec{n}, t_f - \tau)}{\sum_{\vec{m}} P(\vec{n}_f, t_f | \vec{m}, t_f - \tau)} \]

which is equivalent to the posterior distribution over states at the earlier time \( t_f - \tau \), given a uniform prior.
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which is equivalent to the posterior distribution over states at the earlier time $t_f - \tau$, given a uniform prior.

Via the BME one finds $R(\vec{n}, \tau | \vec{n}_f)$ evolves due to the . . .

**Retrodictive Master Equation**

$$\frac{d}{d\tau} R(\vec{n}, \tau | \vec{n}_f) = \sum_k T_k(\vec{n}) \left[ R(\vec{n}'_k, \tau | \vec{n}_f) - R(\vec{n}, \tau | \vec{n}_f) \right]$$

$$-\dot{\Omega}(\tau) R(\vec{n}, \tau | \vec{n}_f)$$

where $\dot{\Omega}(\tau)$ preserves global normalisation.

Example: pure death process

Consider process governed by the reaction:

\[ \text{X} \rightarrow 0 \]
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Figures show \( P(n, t) \) and \( R(n, \tau) \) at \( t = \tau = 0 \)
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Figures show \( P(n, t) \) and \( R(n, \tau) \) at 

t = \( \tau \) = 0.2
Example: pure death process

- Consider process governed by the reaction:
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  \[ t = \tau = 0.5 \]
Example: pure death process

Consider process governed by the reaction:

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Figures show \( P(n, t) \) and \( R(n, \tau) \) at \( t = \tau = 1.0 \).
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- Figures show \( P(n, t) \) and \( R(n, \tau) \) at \( t = \tau = 1.0 \)

Note: \( R(\bar{n}, \tau) \) is not simply time-reversed \( P(\bar{n}, t) \)!
The problem of complexity
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Direct integration of master equations (either predictive or retrodictive) is usually impossible in practice. This is due to the vast state space available to the dynamics of even simple systems. For example, a population composed of 30 types of organism, with each subpopulation having $< 100$ members can exist in any one of over $\left(\frac{100^2}{2}\right)^{30} \sim 10^{110}$ distinct states.
There are approximately $10^{80}$ atoms in the visible universe.
Solution: Stochastic Simulation Algorithms (SSAs)
Central Idea

Sacrifice *precision* for *computability*.
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- For forward-time MEs, involve literally simulating the birth/death process.

![Diagram showing a step-by-step decrease in n(t) with time intervals δt₁, δt₂, and δt₃.](attachment:image.png)
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- For forward-time MEs, involve literally simulating the birth/death process.

- The simulated trajectories can be considered picks from the solution to the associated ME.
An equivalent expression the dynamics described by ME is given by the following “reaction probability density function”:

\[
p(k, \delta t | \vec{n}, t) = T_k(\vec{n}) \exp[-\delta t \sum_k T_k(\vec{n})]
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Algorithm

1. Initialize trajectory state to \( \vec{n}_0 \) or \( P(\vec{n}_0) \),
2. Draw \( \delta t \) and reaction type \( k \) from RPDF,
3. Update trajectory state and time,
4. If trajectory time \( < \) finishing time, GOTO 2
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The relative frequency of trajectories posessing state \( \vec{n} \) at time \( t \) converges to \( P(\vec{n}, t| \vec{n}_0, t_0) \).
A Stochastic Interpretation of RMEs
There are intrinsic difficulties in finding stochastic solutions to retrodictive master equations:
A Stochastic Interpretation of RMEs

There are intrinsic difficulties in finding stochastic solutions to retrodictive master equations:

- Equation of motion is nonlinear due to the normalisation term.

\[
\frac{\partial}{\partial \tau} R(\vec{n}, \tau|\vec{n}_f) = \sum_k T_k(\vec{n}) \left[ R(\vec{n}_k, \tau|\vec{n}_f) - R(\vec{n}, \tau|\vec{n}_f) \right] - \dot{\Omega}(\tau) R(\vec{n}, \tau|\vec{n}_f)
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\]

- Remaining linear component does not preserve normalization, meaning that there is no description in terms of relative frequencies of single unweighted trajectory states.

These difficulties are related to the fact that \( R(\vec{n}, \tau | \vec{n}_f) \) describes incomplete information – not the relative frequencies of outcomes of a random experiment.
A Stochastic Interpretation of RMEs

Predictive master equation transition rate

\[ T_k(\vec{n}) \]
A Stochastic Interpretation of RMEs

Retrodictive master equation (un-normalised) transition rates
A Stochastic Interpretation of RMEs

Equivalent rate configuration
Here we have defined a composite reaction which occurs at rate:

$$\mathcal{I}_k(\vec{n}) = \max[T_k(\vec{n}), T_k(\vec{n}'_k)]$$

and involves either a standard jump, the creation of a new trajectory, or the deletion of the current trajectory with the respective probabilities:

$$\pi_k^{(j)}(\vec{n}) = \min[T_k(\vec{n}), T_k(\vec{n}'_k)],$$

$$\pi_k^{(c)}(\vec{n}) = \max[T_k(\vec{n}'_k) - T_k(\vec{n}'_k), 0] \text{ and}$$

$$\pi_k^{(d)}(\vec{n}) = \max[T_k(\vec{n}) - T_k(\vec{n}'_k), 0].$$
A Stochastic Interpretation of RMEs

Can write the RME explicitly in terms of these non-conservative reactions:

\[
\frac{\partial}{\partial \tau} R(\vec{n}, \tau | \vec{n}_f) = \sum_k \left\{ T_k(\vec{n}'') \left[ \pi_k^{(j)}(\vec{n}'') + \pi_k^{(c)}(\vec{n}'') \right] R(\vec{n}'', \tau | \vec{n}_f) - T_k(\vec{n}) \left[ \pi_k^{(j)}(\vec{n}) + \pi_k^{(d)}(\vec{n}) \right] R(\vec{n}, \tau | \vec{n}_f) \right\} - \dot{\Omega}(\tau) R(\vec{n}, \tau | \vec{n}_f)
\]
Thus, just as for the predictive master equation, an equivalent expression of the dynamics described by the RME is given by the modified reaction probability density function:

\[ p(k, \delta \tau | \vec{n}) = \mathcal{I}_k(\vec{n}) \exp[-\delta \tau \sum_k \mathcal{I}_k(\vec{n})] \]
A Stochastic Interpretation of RMEs

Thus, just as for the predictive master equation, an equivalent expression of the dynamics described by the RME is given by the modified reaction probability density function:

\[ p(k, \delta \tau | \vec{n}) = \mathcal{T}_k(\vec{n}) \exp[-\delta \tau \sum_k \mathcal{T}_k(\vec{n})] \]

**General Retrodictive SSA**

1. Initialise trajectory state to \( \vec{n}_f \) or \( P(\vec{n}_f) \),
2. draw \( \delta \tau \) and \( k \) from modified RPDF,
3. Select a jump, creation or deletion with probabilities \( \pi_k^{(j)}, \pi_k^{(c)} \) and \( \pi_k^{(d)} \), respectively.
4. Update trajectory state and time according to chosen reaction.
5. Fork process to follow created trajectory, terminate process of deleted trajectory.
6. If trajectory time < finishing time, GOTO 2.
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Solution

Explicitly or implicitly resample the trajectory ensemble.
Resampling will eventually cause the trajectories in the ensemble to become artificially correlated, leading to systematic errors. The magnitude of these errors will vary inversely with the size of the ensemble.
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**Solution**

Repeat each calculation with progressively larger trajectory ensembles, until the result converges to a fixed value.
Realistic models of population genetics can involve a large number of reaction types $M$, and the computational complexity of naive implementations of the reaction-selection scale as $O(M)$. 
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**Solution**

Just as for the Gibson-Bruck modification to the predictive SSA, use binary search trees to change the scaling to $O(\log(M))$. 
Simple example: The Moran model
Consider a fixed population of 2 alleles (a and A) evolving under a neutral continuous-time Moran model:

\[ a + A \rightarrow 2A \]
\[ a + A \rightarrow 2a \]
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\[
\begin{align*}
& a + A \longrightarrow 2A \\
& a + A \longrightarrow 2a
\end{align*}
\]

The RME for this system is

\[
\frac{\partial}{\partial \tau} R(n, \tau \mid n_f) = n(N - n) \left[ R(n + 1, \tau \mid n_f) + R(n - 1, \tau \mid n_f) \right] - 2R(n, \tau \mid n_f) - \dot{\Omega}(\tau) R(n, \tau \mid n_f)
\]

where \( n \) is the number of individuals carrying the \( a \) allele and \( N \) is the total population size.
Simple example: The Moran model

Allele ‘a’ Extinct (‘A’ Fixed)

$R(n, \tau = 0.1, l, n_l = 0)$

$n_a$

RSSA

Exact
Simple example: The Moran model
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Allele ‘a’ NOT Extinct

\[ R(n, \tau=0.1, l, n_l=1) \]

- RSSA
- Exact

\( n_a \)
Simple example: The Moran model

Allele ‘a’ NOT Extinct

\[ R(n, \tau=1, l, n_t=1) \]

- RSSA
- Exact

\( n_a \)
Possible Enhancements
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- Investigate whether phase-space methods can be used to dramatically improve the scalability of these calculations to large populations.
Possible Enhancements
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slow horse
Possible Enhancements

slow horse

wonky wheel
Part II

Applications to Phylogenetic Tree Reconstruction
Possible uses for RSSAs in Phylogenetics
1. Full retrodictive inference of the past system history given a realistic stochastic model of evolutionary dynamics.
Possible uses for RSSAs in Phylogenetics

1. Full retrodictive inference of the past system history given a realistic stochastic model of evolutionary dynamics.

2. A systematic means of combining forwards-time mutation/migration dynamics with the Kingman $n$-coalescent process.
Full retrodictive inference
Full retrodictive inference

Bad News

This is computationally intractable using SSA-style algorithms for most systems of realistic size.
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Potentially tractable problems include:

- Exponential growth stage of within-host viral infection.
- Spatially constricted populations with small carrying capacities.
Good News

Coalescent formalism allows us to avoid explicit consideration of the bulk of a population by focusing on sampled individuals.
Combining forward processes with the Coalescent

Start with basic coalescent:

Coalescence rate $T_C(k) \simeq \frac{1}{2N} k(\tau)(k(\tau) - 1)$
Combining forward processes with the Coalescent

Start with basic coalescent:

\[ T_C(k) \simeq \frac{1}{2N} k(\tau)(k(\tau) - 1) \]

Coalescence rate

Look closer:

\[ T_{C,a}(\vec{k}) \simeq \frac{1}{2n_a(\tau)} k_a(k_a - 1) \]
Combining forward processes with the Coalescent

Mutation occurs as a Poisson process along lineages:
Combining forward processes with the Coalescent

Mutation occurs as a Poisson process along lineages:

\[
\frac{d}{d\tau} R(\vec{k}, \tau | \vec{k}_s) = \mu_{aA} k_a \left[ R(\vec{k}_{-a+A}, \tau | \vec{k}_s) - R(\vec{k}, \tau | \vec{k}_s) \right]
+ \mu_{Aa} k_A \left[ R(\vec{k}_{-A+a}, \tau | \vec{k}_s) - R(\vec{k}, \tau | \vec{k}_s) \right]
- \dot{\Omega}(\tau) R(\vec{k}, \tau | \vec{k}_s)
\]
RME for combined coalescent/mutation process

\[
\frac{d}{d\tau} R(\vec{k}, \tau | \vec{k}_s) = T_{C,a}(\vec{k}_{+a}) R(\vec{k}_{+a}, \tau | \vec{k}_s) - T_{C,a}(\vec{k}) R(\vec{k}, \tau | \vec{k}_s) \\
+ T_{C,A}(\vec{k}_{+A}) R(\vec{k}_{+A}, \tau | \vec{k}_s) - T_{C,A}(\vec{k}) R(\vec{k}, \tau | \vec{k}_s) \\
+ \mu_a A_k a \left[ R(\vec{k}_{-a+A}, \tau | \vec{k}_s) - R(\vec{k}, \tau | \vec{k}_s) \right] \\
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Combining forward processes with the Coalescent

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1. the presence of the background population sizes of each allele in the RME, and
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There are two *unholy* stumbling blocks stopping us from using this approach to directly generate samples from the posterior distribution of trees:

1. the presence of the background population sizes of each allele in the RME, and
2. the difficulty of simulating coalescence events when sequence space is large.
Conclusions
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Thank-you!