Measure-valued dynamical systems, with applications to the evolution of aging

- Introduction to the evolutionary problem
- Description of the model
- Feynman-Kac Solution
- Implications of the Solution
- Adding recombination

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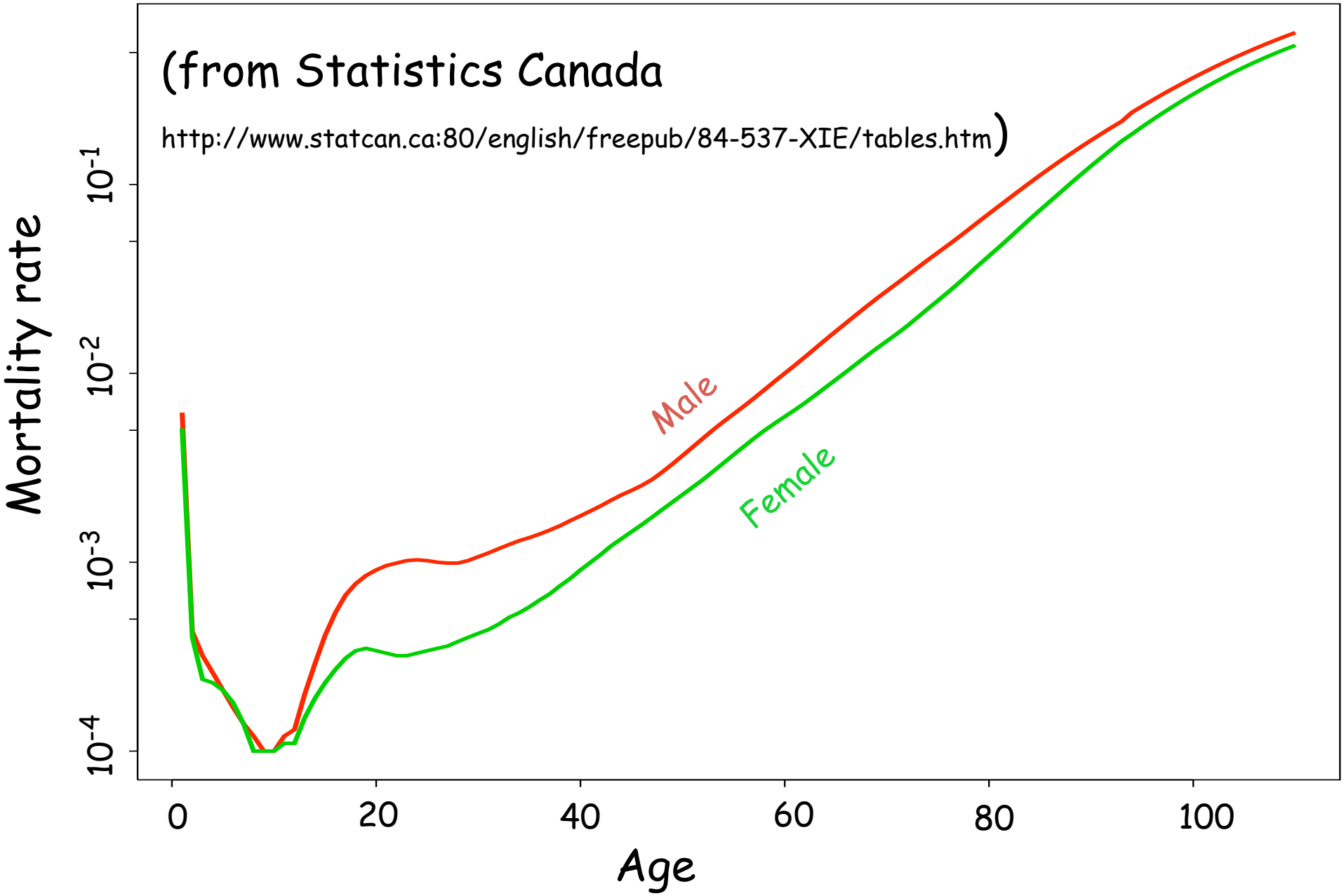
Warning: We have stochastics, and processes, but no stochastic processes!

Canada age-specific mortality 1995-1997



Evolution of Aging

General idea goes back to A. Weismann (late 19th C.), P. Medawar and G. Williams (1950s):

Late-acting deleterious mutations are subject to less stringent selection control

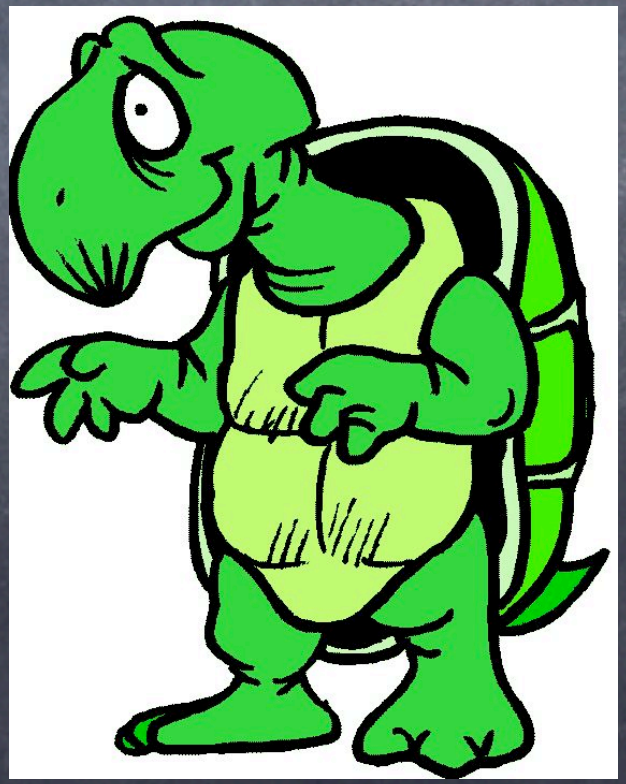
Mayfly

Mayfly

Salmon

Mayfly

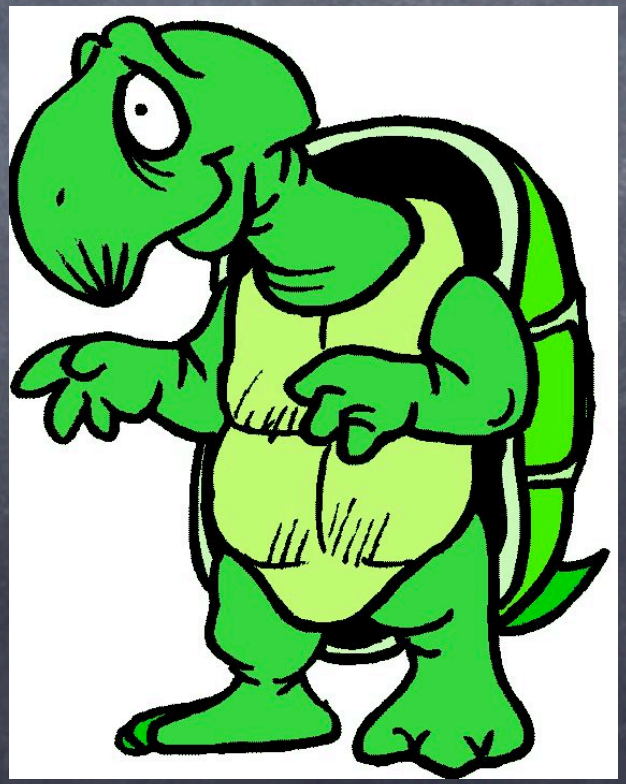
Salmon



Tortoise

Mayfly

Salmon



Tortoise

Mutation-Selection Equilibrium

Intuitive single-locus model: Mutant allele arises at rate ν. Selective cost s. Equilibrium when frequency of mutant is ν/s.

B. Charlesworth (2001):

- constant reproduction rate λ
- high "background mortality" μ
- mutation increases mortality by m at age x
- constant mutation rate ν

cost = $me^{-\mu x}$ of total reproduction

Expect equilibrium frequency $\frac{\nu}{m}e^{\lambda x}$.

Problems:

Mathematical framework for single locus, applied to infinite-locus setting.

Selective cost of multiple mutations non-additive.

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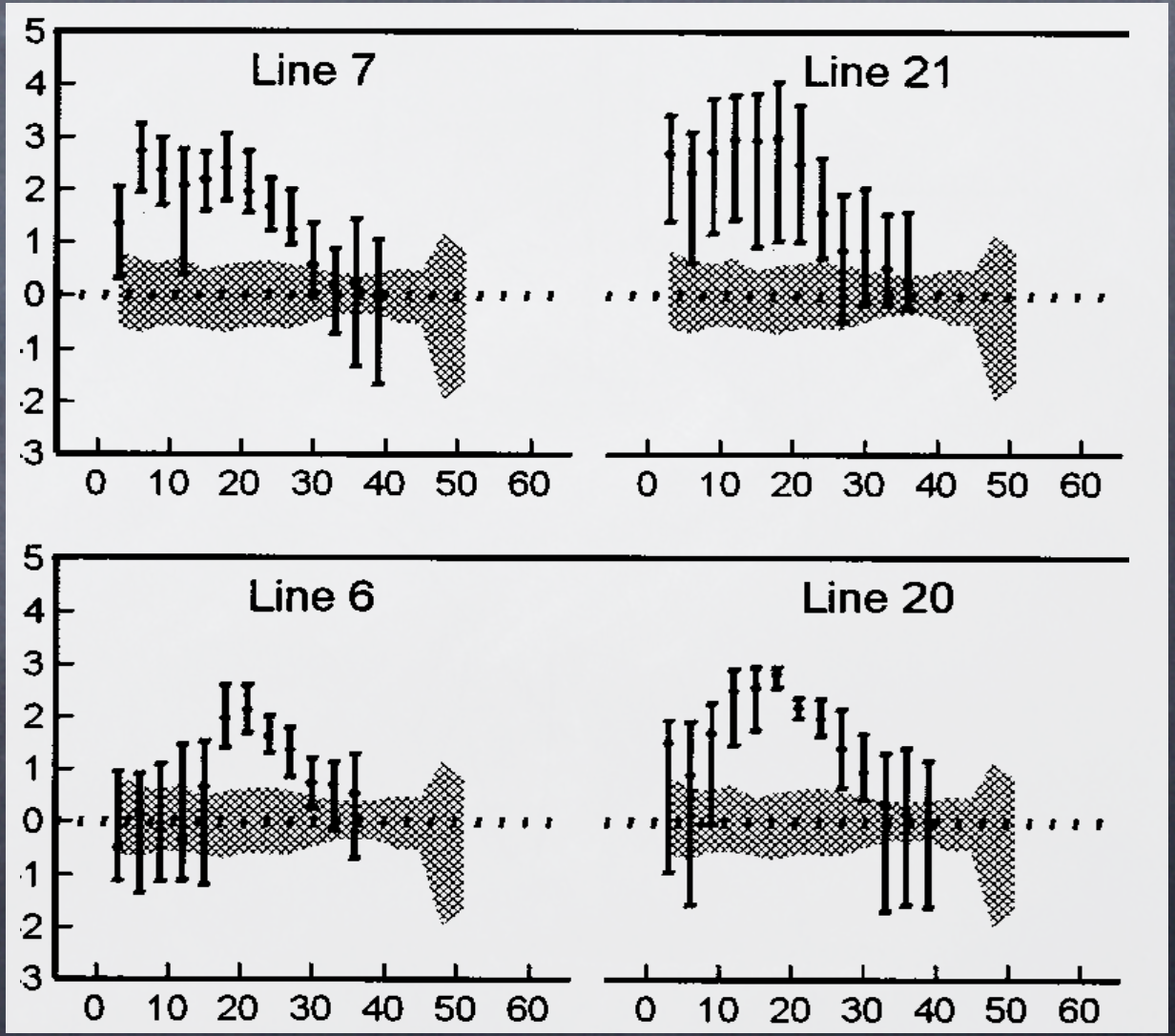
Mathematical framework for single locus, applied to infinite-locus setting.

Selective cost of multiple mutations non-additive.

Mutations which act only at one age are extremely unrealistic.



Improved model (S. Evans, K. Wachter, and DS):

Mutation space M

Mutation rate ν = σ-finite measure on M

Genotype space G =

{countable integer measures on M}

State of system P = probability on G

Selection cost $S : G \to R^+$

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Evolution equation:

$$\frac{d}{dt}P_tF = P_t\left(\int\left[F(\cdot+\delta_m)-F(\cdot)\right]d\nu(m)\right)$$

$$-P_t(FS) + (P_tF)(P_tS)$$

In this case, the solution is unique.

General solution by Feynman-Kac: Let X_t be a Poisson point process with intensity ν. Then

$$P_t F = \frac{\mathbb{E}\left[\exp\left(-\int_0^t S(X_u)\,du\right) F(X_t)\right]}{\mathbb{E}\left[\exp\left(-\int_0^t S(X_u)\,du\right)\right]}.$$

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When S is linear ("non-epistatic"), the solution reduces to a Poisson random measure with intensity

$$\frac{1-e^{-S(m)t}}{S(m)}\,d\nu(m).$$

In this case, the solution is unique.

What does this tell us?

1. Series expansion for P_t and limiting distribution: Let $Y_1, Y_2, \ldots, Y_n$ be an increasing random choice of n mutations (from distribution ν.) Then

$$\lim_{t\to\infty} P_t F = \frac{\sum_{n=0}^{\infty} \nu(\mathcal{M})^n \mathbb{E}\left[\left(S(Y_1)\ldots S(Y_n)\right)^{-1} F(Y_n)\right]}{\sum_{n=0}^{\infty} \nu(\mathcal{M})^n \mathbb{E}\left[\left(S(Y_1)\ldots S(Y_n)\right)^{-1}\right]}.$$

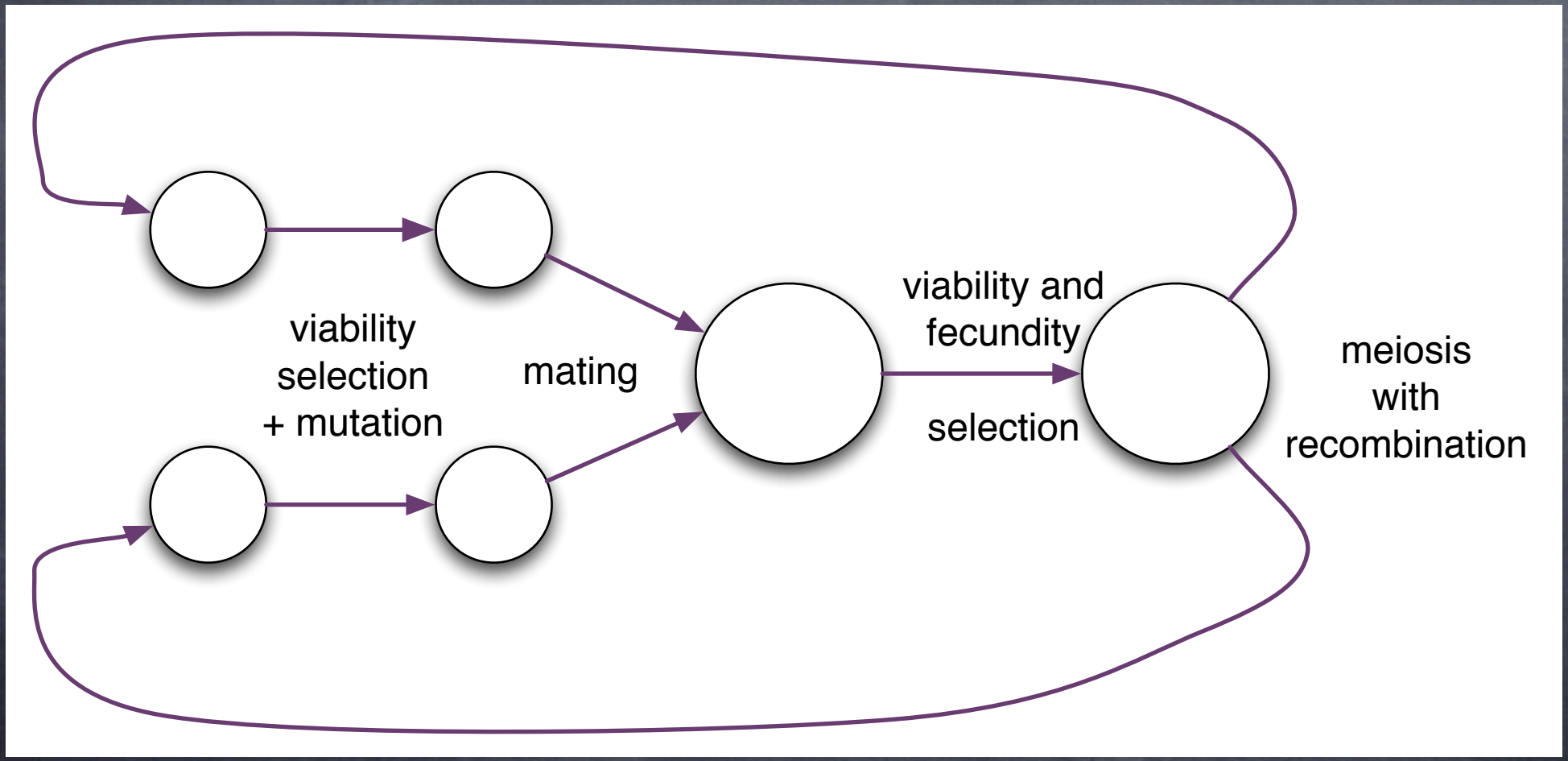
There is a corresponding finite-time formula.

What does this tell us?

2. Explosion: If B is a set s.t. $S(g+b)-S(g)<v(B)$ when $b \in B$, then the number of mutations in B goes to infinity.

Implies "wall of death" rather than Gompertz.

Recombination



Barton-Turelli model

Recombination: Pick a random subset of mutations A from a distribution r. New genotype gets A mutations from one parent, and A^c mutations from the other.

If we iterate this process, the genotypes get completely reshuffled.

End up with a Poisson random measure, with the same marginal intensities as the genotype distribution we start with.

Definition: The <u>recombination measure</u> R is the distribution on subsets of M, defining which sites come from the same parent. R is <u>shattering</u> if there is a positive constant α such that $\mathrm{E}\big[\nu(A \cap R)^2\big] \leq \frac{1}{2}\nu(A)^2 - \alpha\nu(A)^3.$

Definition: A distribution P on genotypes is <u>dispersive</u> if there is a constant β such that for any Borel set A,

$$\int g(A)\mathbf{1}_{\{g(A)\geq 2\}} dP(g) \leq \beta\mu P(A)^2.$$

Recombination Operator

$$\mathfrak{R}P[F] = \int\int\int F(g_1 \,|_R + g_2 \,|_{R^c}) dP(g_1) dP(g_2) d\mathcal{R}(R)$$

Mutation operator; suppose $F(g)=e^{-g[f]}$

$$\mathfrak{M}P[F] = P\left[F \cdot e^{\nu(e^{-f}-1)/n}\right];$$

Selection operator:

$$\mathfrak{S}P[F] = \frac{\int e^{-S(g)/n} F(g) dP(g)}{\int e^{-S(g)/n} dP(g)}.$$

Poissonization operator:

$$\mathfrak{P}P[F] = \exp\left\{\int (e^{-f(m)} - 1) d\mu P(m)\right\}$$

Easy part: Repeated recombination without mutation or selection (or linear selection) converges to Poisson distribution.

Theorem: If P is dispersive and R is shattering, then

$$\|\mathfrak{R}^k P - \mathfrak{P} P\|_{Was} \leq (3\beta + 2)\left(|\nu|^2 \vee 2\alpha|\nu|\right)(k+1)^{-1}.$$

This is a process version of Le Cam's Theorem on convergence to Poisson distribution.

This justifies defining a dynamical system concentrated only on Poisson random measures.

Since mutation and selection are much slower, this converges to a process that is always Poisson.

Let $s_P(m)$ be the average cost of mutations m, averaged over the genotype dist. P.

If P is Poisson, then

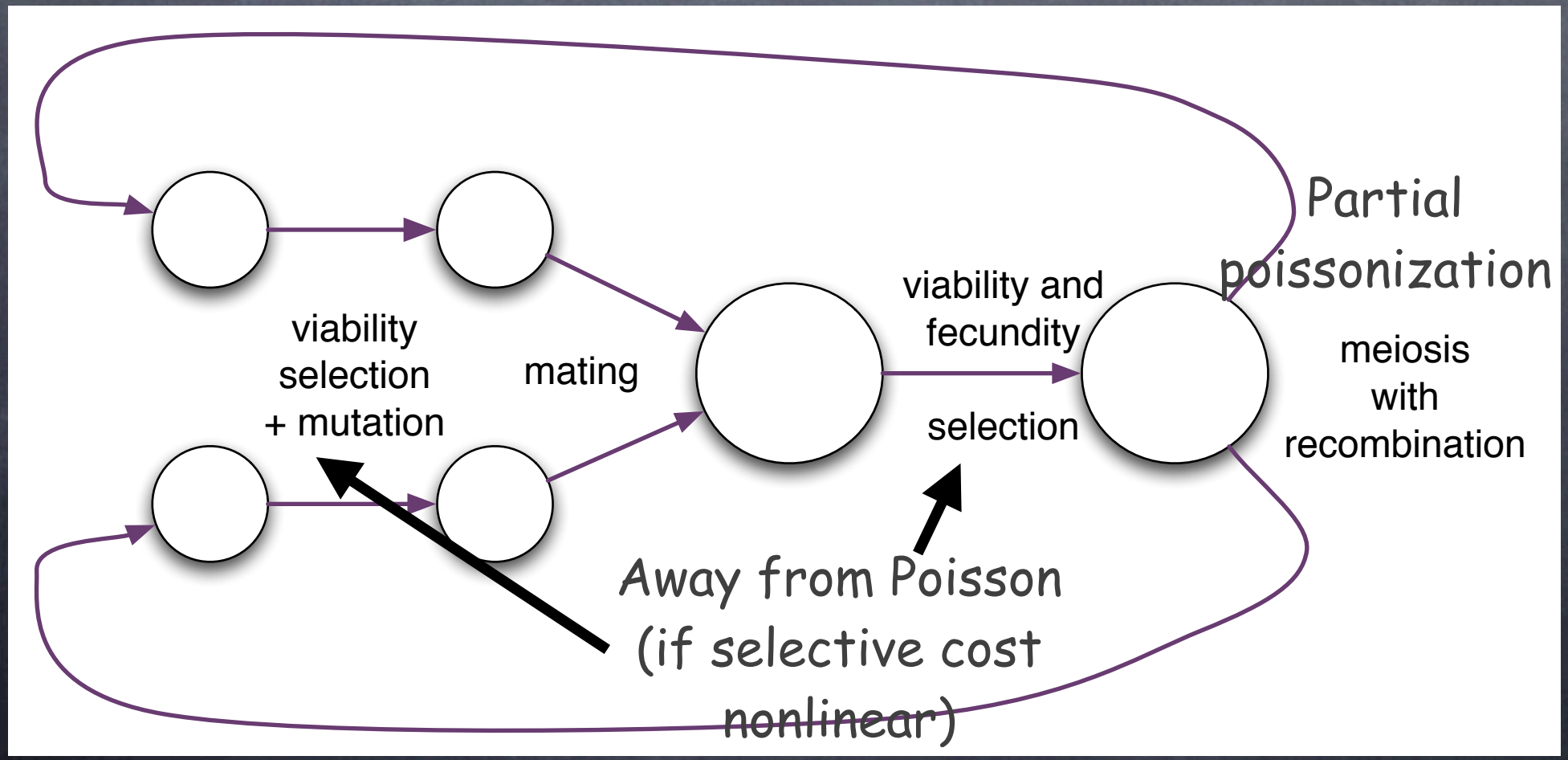
$$s_P(m) := \int \left[S(g + \delta_m) - S(g)\right] dP(g).$$

Let ρ_t be the Poisson intensity at time t.

$$\frac{d\rho_t}{dt} = \nu - s_{P_t}(m)\rho_t.$$

Theorem (Evans, DS, Wachter): If ν is finite, this equation has a unique solution, which remains finite for all t.

Does this poissonization really work?



Main result

Let $Q_k := (\mathfrak{RMS})^k P_0 \qquad Q'_k := (\mathfrak{PMS})^k P_0$

If the initial P_0 is Poisson and R is shattering, then for any positive T,

$$\lim_{n\to\infty} \sup_{t\leq T} \|\Pi_{\rho_t} - Q_{\lfloor tn \rfloor}\|_{Was} = 0.$$

Π_ρ is the Poisson measure with intensity ρ.

Main idea

$$\|Q_k - Q'_k\|_{\mathrm{Was}} \leq \|Q_k - \mathfrak{P}Q_k\|_{\mathrm{Was}} + 4\|\mu Q_k - \mu Q'_k\|_{\mathrm{Was}}$$

$$a_k = \|Q_k - \mathfrak{P}Q_k\|_{\mathrm{Was}}$$

$$b_k = \|\mu Q_k - \mu Q'_k\|_{\mathrm{Was}}$$

$$b_{k+1} \leq e^{\sigma/n}\left(b_k + \frac{2\sigma}{n}a_k + \frac{2\sigma^2}{n^2}\right).$$

Thus, if we can show that a_k stays on order 1/n, the same will be true for b_k.

$$\|Q_k - \mathfrak{P}Q_k\|_{\mathrm{Was}}$$

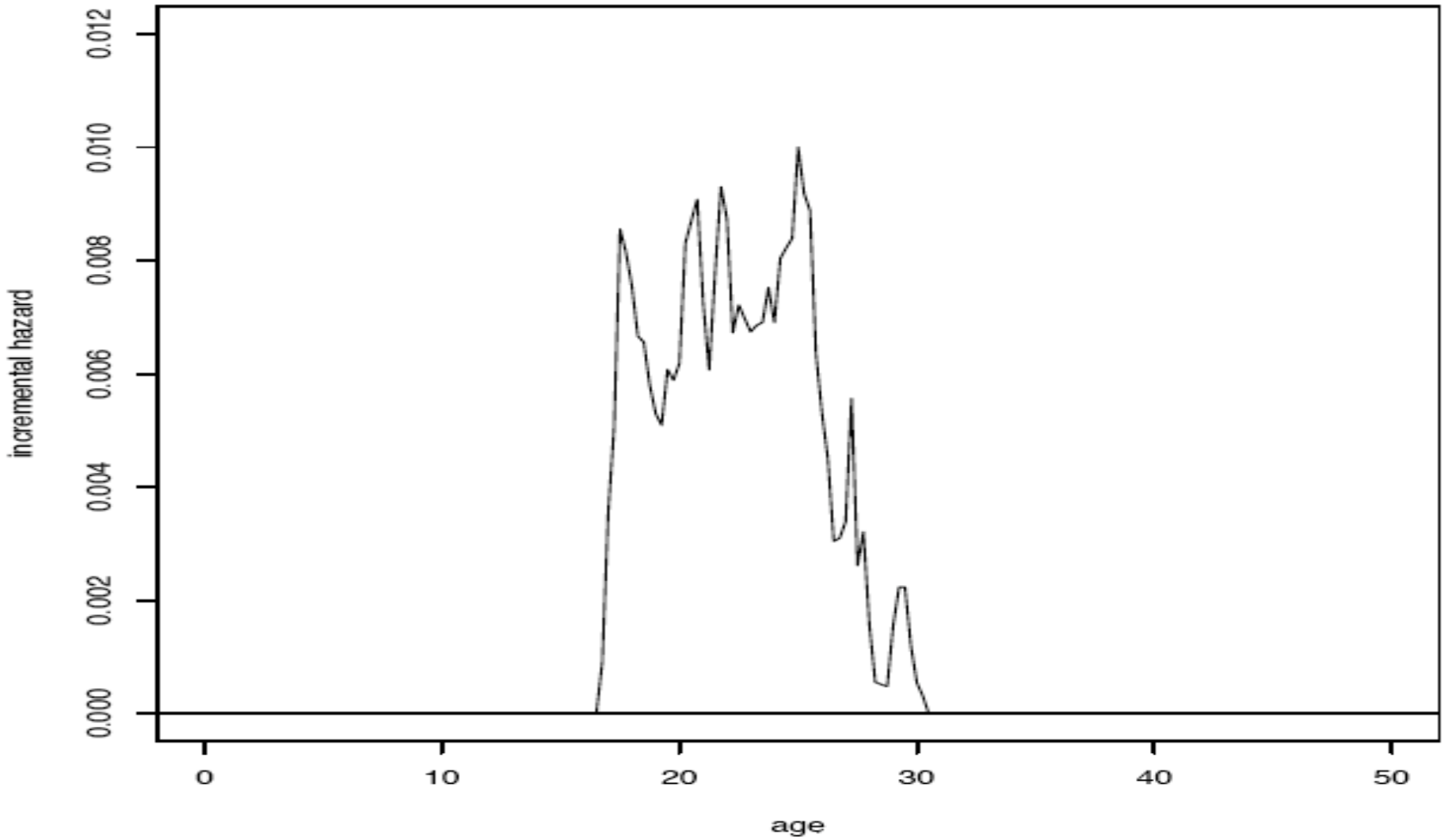
$$\leq \frac{C}{n}\sum_{i=0}^{k-1}\int d\mathcal{R}_k(\mathcal{A})\int\left|\hat{S}'_{Q_i}(g) - \hat{S}_{Q_i^*,\mathcal{A}_{k-i}}(g)\right| dP_i(g)$$

where $\hat{S}_{Q,\mathcal{A}}(g) =$

$$-n\sum_{i=1}^{K}\Big(\log Q\left[e^{-S(X)/n}\,\middle|\,X_{A_i} = g_{A_i}\right] -$$

$$-\log Q\left[e^{-S(X)/n}\right]\Big)$$

Example: Brownian Excursion model



Limit mortality rates