Wave equations, evolution on graphs, and carcinogenesis

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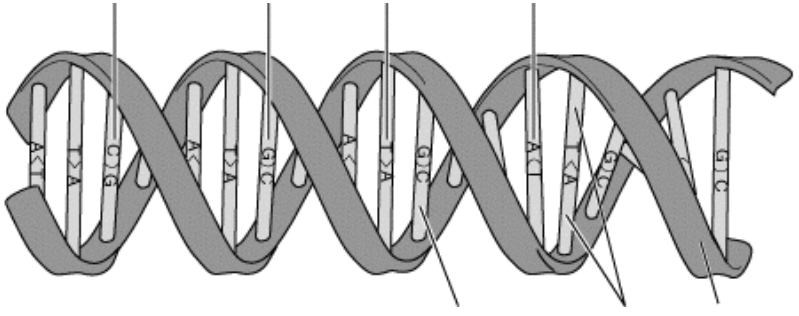
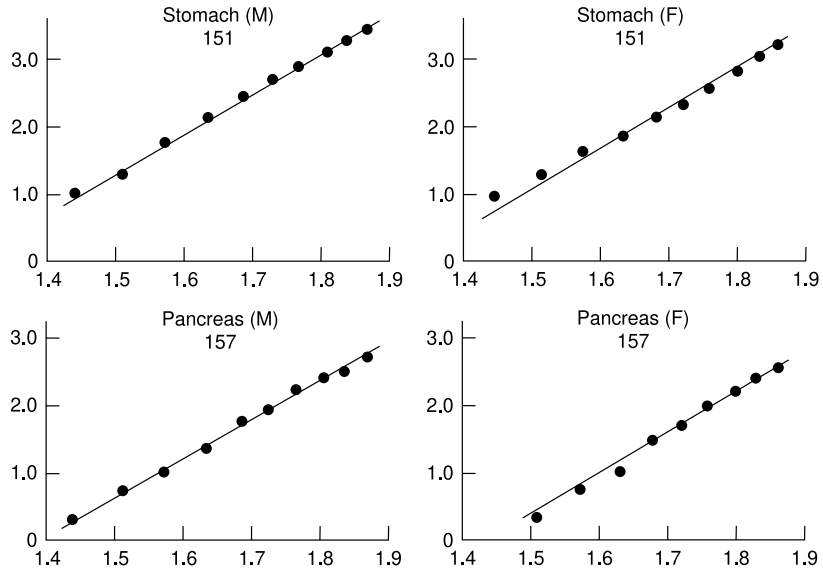
Introduction

Driver mutations



Multi-stage models

P. Armitage and R. Doll[12]



[1] P. Armitage and R. Doll, British Journal of Cancer 1954; 8: 1–12

[2] P. Armitage and R. Doll, British Journal of Cancer 1957; 11(2): 161-169

Multi-stage models

A.G. Knudson[1][2]

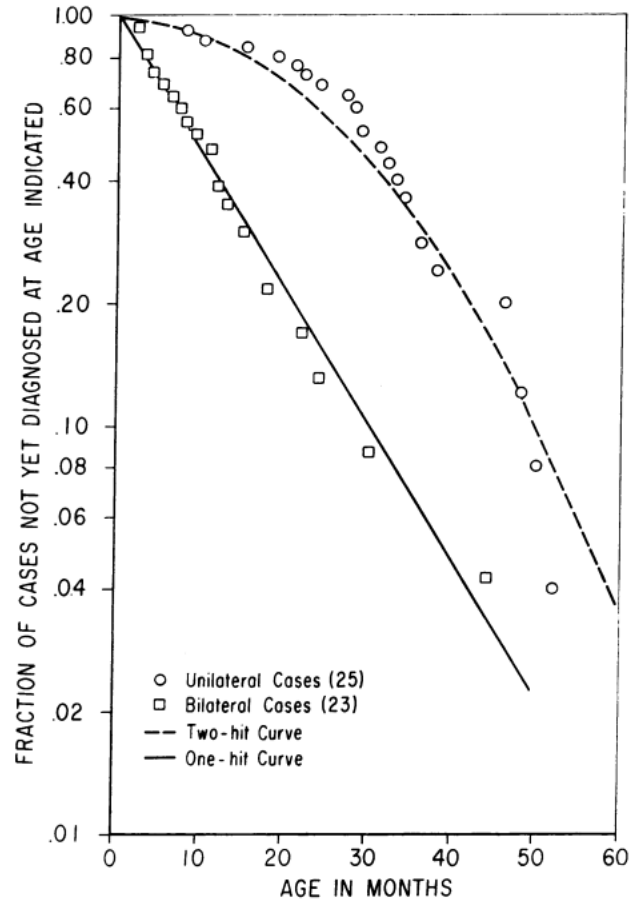


FIG. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -t/30$, the two-hit curve from $\log S = -4 \times 10^{-5} t^2$.

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[1] AG. Knudson, PNAS 68.4 (1971): 820-823.

[2] F. Michor, Y. Iwasa and MA. Nowak, Nature Reviews Cancer 2004; 4: 197-205 doi:10.1038/nrc1295

How do these studies work?

What are the relevant observables in this type of longitudinal study & data analysis?
Track a cohort that initially contains N patients in the study:

- Age-specific incidence $I(a)$: rate at which new cases are recorded in the cohort with ages between a and $a + da$
- Survival function $S(a)$: probability to survive to age a without being diagnosed.

$$I(a) = -N\frac{dS}{da} = -N\ S(a)\frac{d\ln S}{da} \tag{1}$$

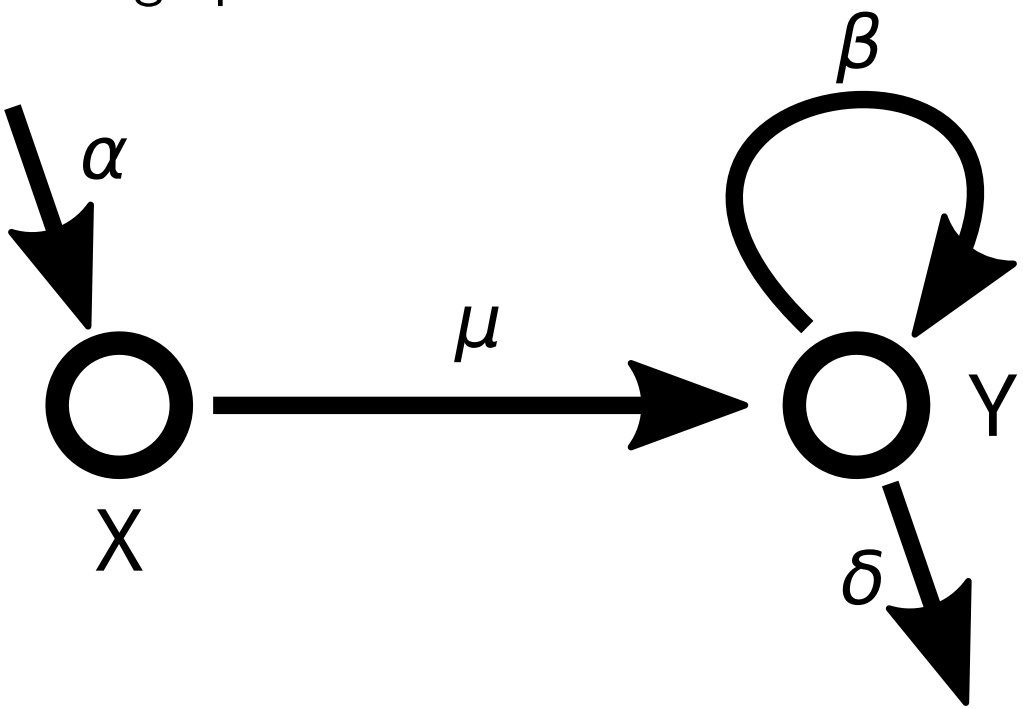
Diagnosis-free survival is the key variable

- The survival curve S(a) determines the incidence curve $I(a)$
- The model determines the survival curve: the probability not to end up at one of the end nodes of the graph. We want to know what model+parameters best agree with data from studies.
- To fit (or "train") the model to longitudinal data, we need to compute $S(a)$!

This is the central mathematical problem in cancer epidemiology. *How do we compute S?*

Multi-stage models as graphs

This graph...



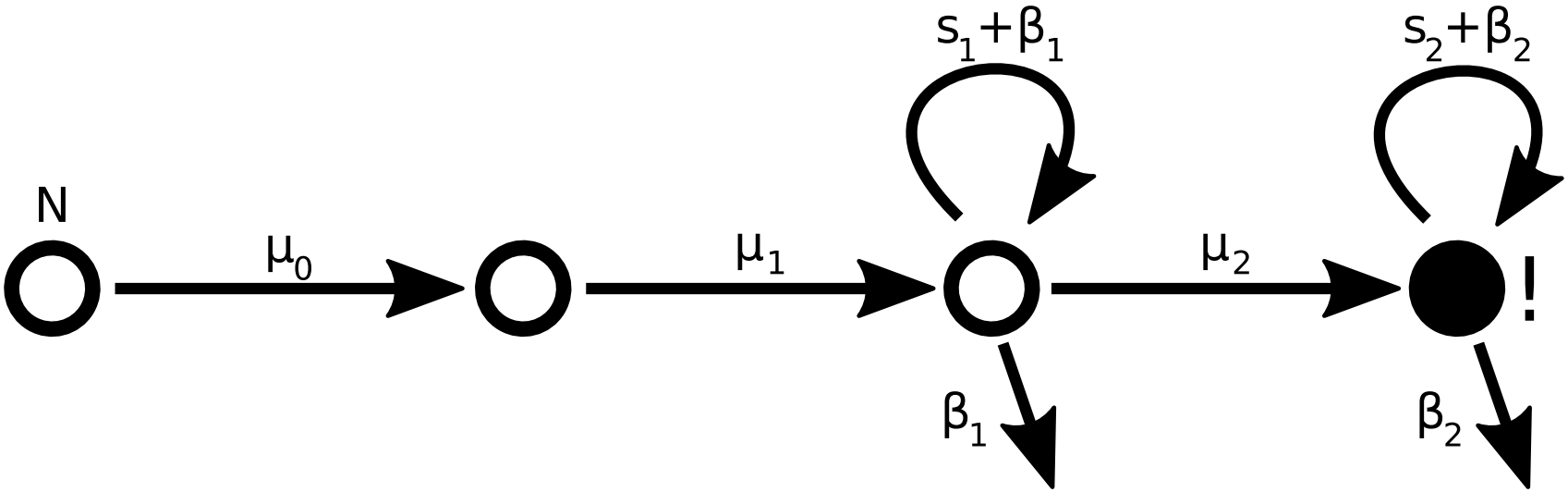
corresponds to this stochastic process:...

$$\begin{aligned} \emptyset &\to X, && \text{rate } \alpha \\ X &\to X + Y, && \text{rate } \mu X \\ Y &\to Y + Y, && \text{rate } \beta Y \\ Y &\to \emptyset, && \text{rate } \delta Y \end{aligned}$$

[1] S. Moolgavkar and G. Luebeck, JNCI 1992; 84(8): 610-618

[2] C. Paterson, I. Bozic, H. Clevers, PNAS 2020; 117(34): 20681-20688

e.g. Armitage & Doll 1957



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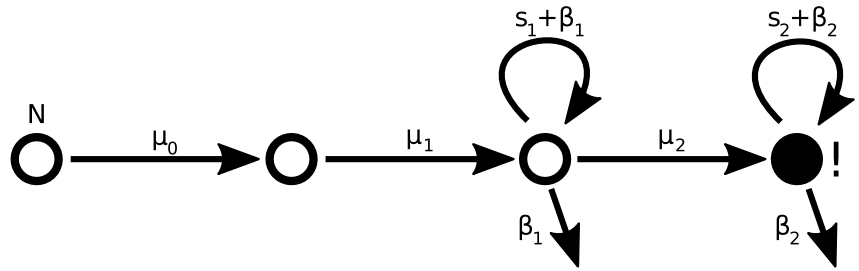
Multi-stage clonal expansion models

2-3 rate limiting steps[123]

Problem: how to compute $S(t)$ for a given model?

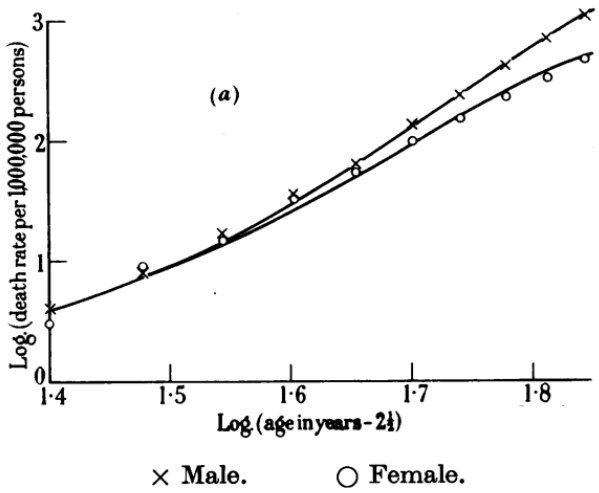


Different methods: Fast:

- Armitage + Doll's approximation[1]
- Moolgavkar + Venzon's quadrature[2]

Very slow:

- Gillespie algorithm + sampling [3]



↓?

[1] P. Armitage and R. Doll, British Journal of Cancer 1957; 11(2): 161-169

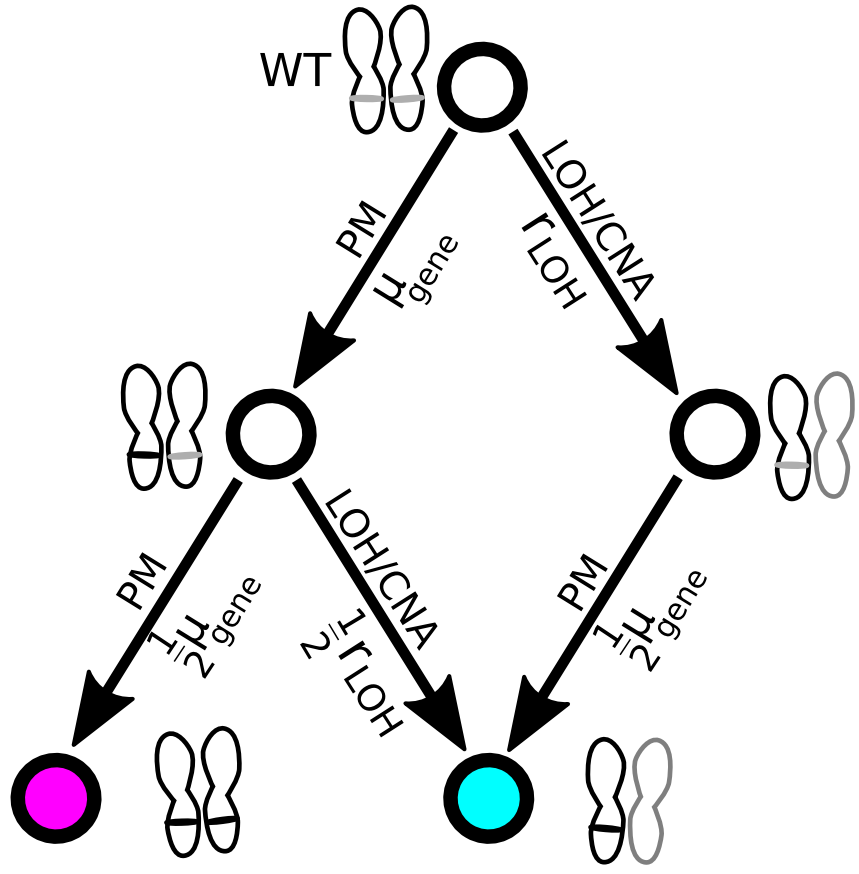
[2] S. Moolgavkar and G. Luebeck, JNCI 1992; 84(8): 610-618

[3] C. Paterson, I. Bozic, H. Clevers, PNAS 2020; 117(34): 20681-20688 (supp. material)

Models on graphs

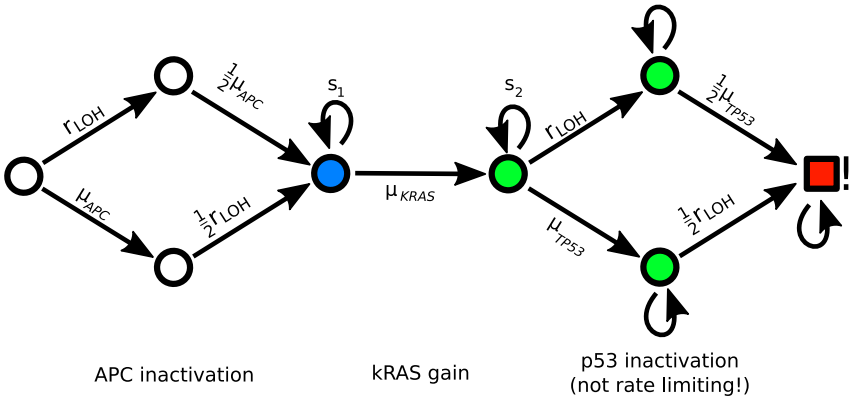
1. Most methods for computing $S(a)$ do not consider graphs with multiple end nodes
2. To study **specific genes** and mechanisms of interest (SNVs, LOH, CNA, etc.), we need to evaluate $S(a)$ for a model defined on a graph (right)
3. What methods do we actually have?

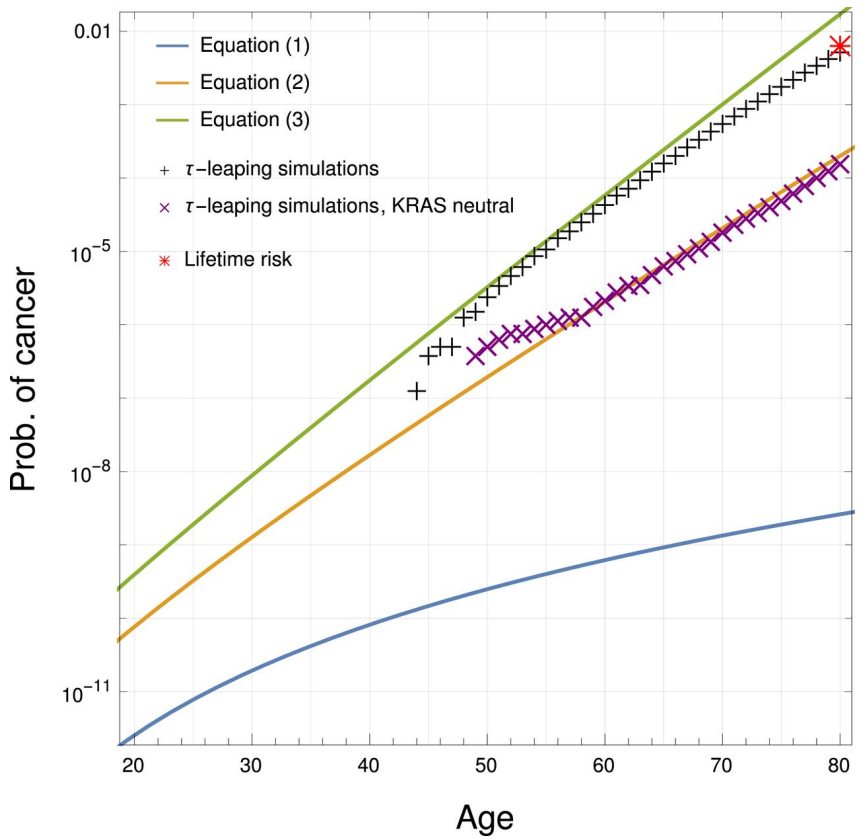
example model



This gets us the incidence of *specific karyotypes*

Colorectal adenocarcinoma model





- Can use A-D type approximation, or stochastic simulations

but:

- Mean-field breaks down at old ages / large probabilities
- Stochastic simulations are *extremely slow*

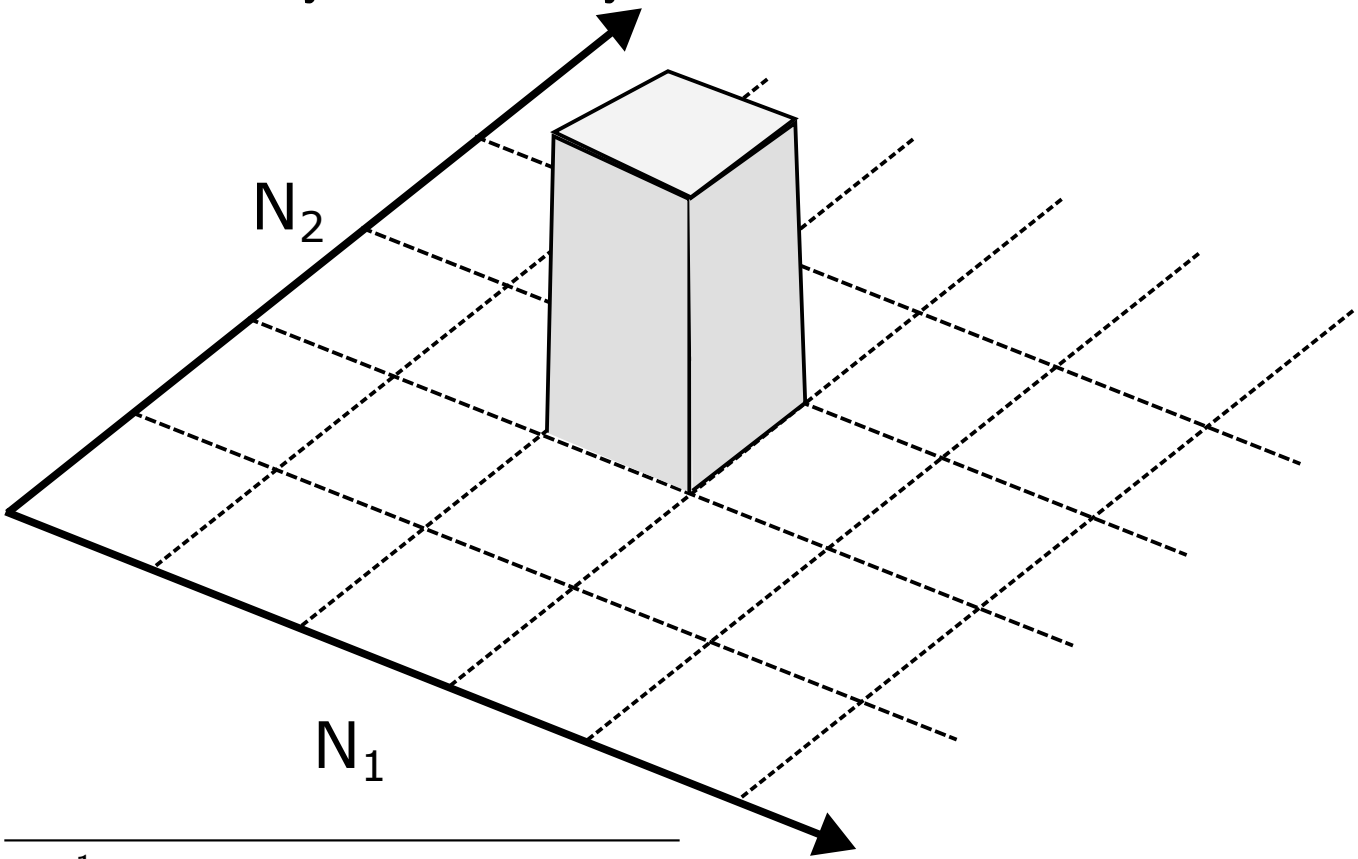
[1] C. Paterson, I. Bozic, H. Clevers, PNAS 2020; 117(34): 20681-20688

Intuition

general form of master equation is[1]

$$\frac{dP(t,\vec{N})}{dt} = \sum_{\vec{N}'} \Big(\omega(\vec{N}' \to \vec{N}) P(t,\vec{N}') - \omega(\vec{N} \to \vec{N}') P(t,\vec{N}) \Big) \quad (2)$$

if $\omega > 0$ only for "nearby" states $\vec{N}'$ then...



[1] Van Kampen, N.G., 1992. Stochastic processes in physics and chemistry (Vol. 1). Elsevier.

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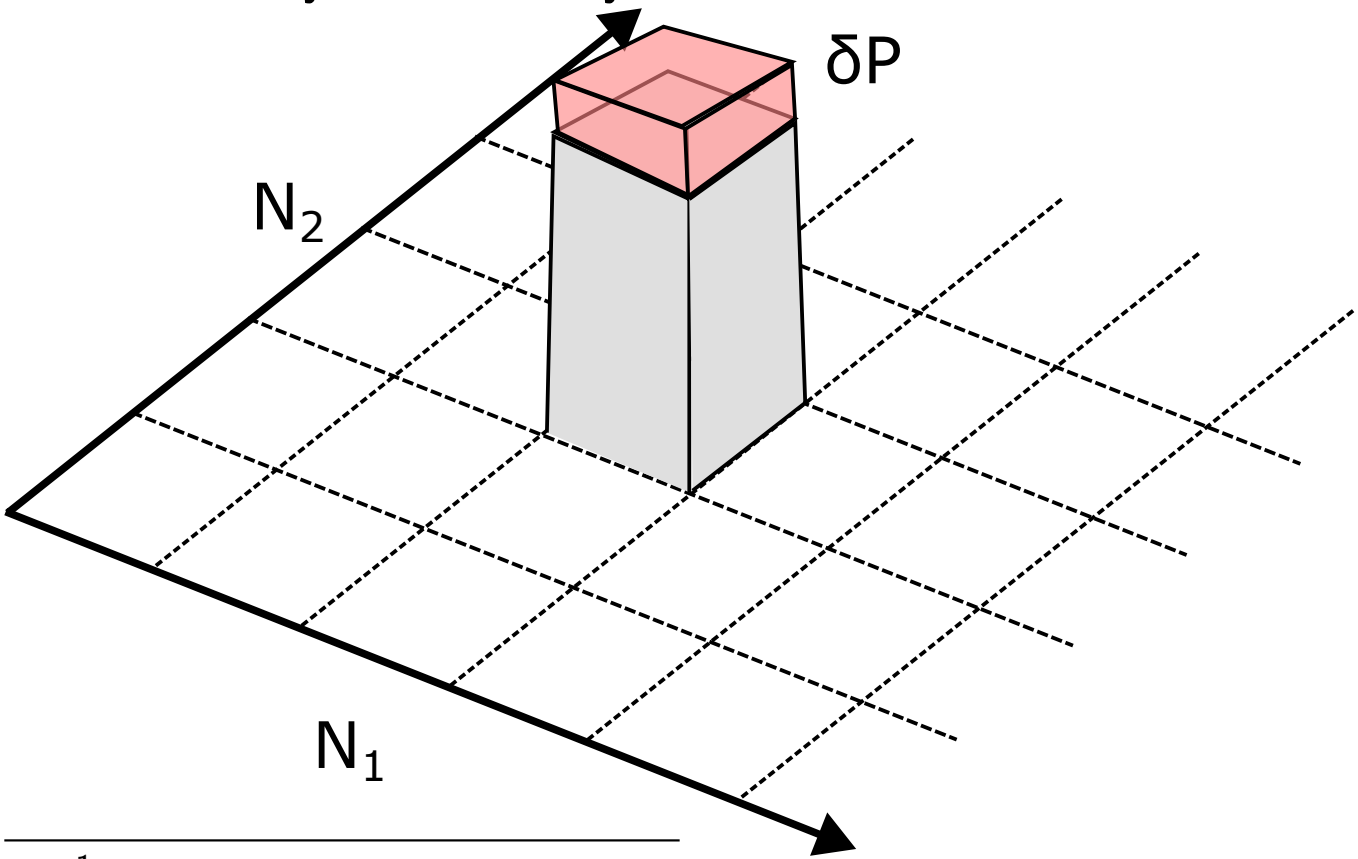

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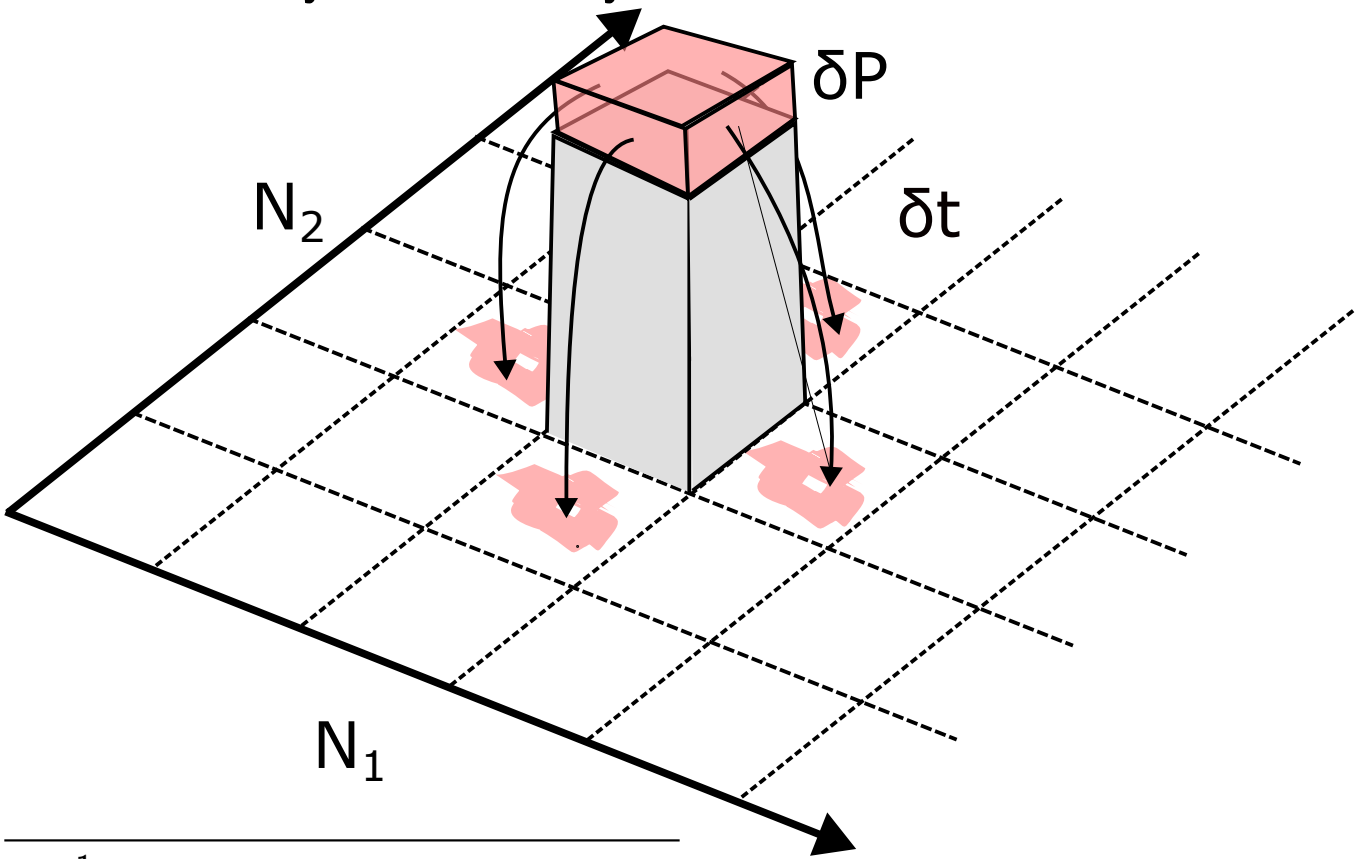

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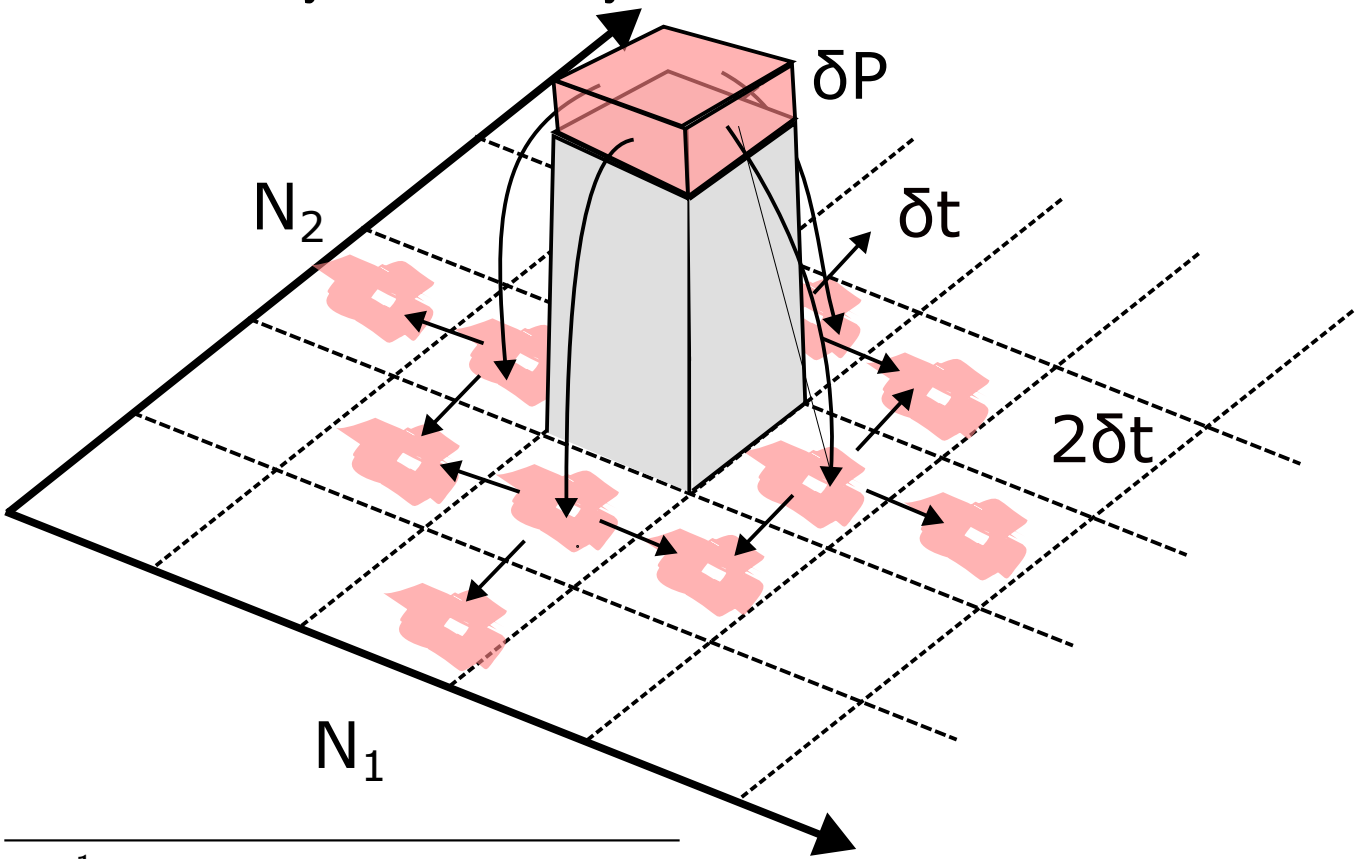

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Intuition

Summary:

- Disturbances *propagate*
- Equation linear: *superposition*

Both hallmarks of wave-like behaviour

Alternative approach: Kolmogorov forward equations

Define a more general generating function Ψ:

$$\Psi(t, \vec{q}) = \mathbb{E}\left[\prod_j q_j^{N_j}\right] = \sum_{\vec{N}} \prod_j q_j^{N_j} P(t, \vec{N}) \tag{6}$$

(the sum is taken over states $\vec{N} := (N_0, \dots)$) and derive Kolmogorov forward equations instead. Then we can numerically integrate these, and get survival curves $S_i(a)$ for different types of cancer i. e.g. tumours with clonal LOH, or no clonal LOH.

$$S_i = \Psi(t, q_j = 1, \dots, q_i = 0) \tag{7}$$

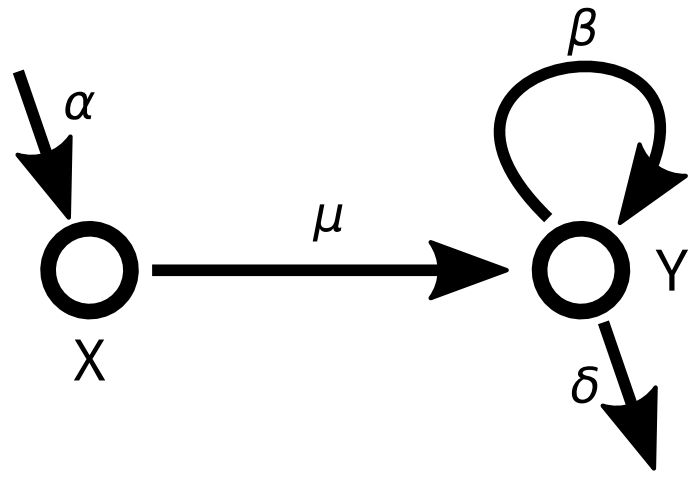
People knew about this approach for a long time (since 1970s) but it was never considered as useful as backward equations.

---

[1] SH Moolgavkar and DJ Venzon, Math. biosc. 1979; 47(1): 55-77

[2] DW Quinn, Risk Analysis 1989; 9(3): 407-13

Kolmogorov forward equations as wave equations



Briefly: the Kolmogorov forward equations in $P(N_0, \dots)$

$$\frac{dP(N_0, N_1, \dots)}{dt} = \sum_{vertices} \alpha(N_j - 1)P(\dots, N_j - 1, \dots) - \alpha N_j P(\dots, N_j, \dots) + \beta(\cdots) + \mu(\cdots) + \delta(\cdots)$$

get transformed with $P \to \Psi$ into...

Kolmogorov forward equations as wave equations

$$\frac{\partial \Psi}{\partial t} = \sum_{\textit{vertices}} \alpha(q_j - 1) q_j \frac{\partial \Psi}{\partial q_j} + \cdots = \mathcal{H}\Psi \tag{8}$$

where $\mathcal{H}$ is a hyperbolic differential operator.
Because this is a hyperbolic wave equation, we can solve for future values of Ψ if we have initial values, by evolving them along *characteristics*.

[1] SH Moolgavkar and DJ Venzon, Math. biosc. 1979; 47(1): 55-77

Kolmogorov forward equations

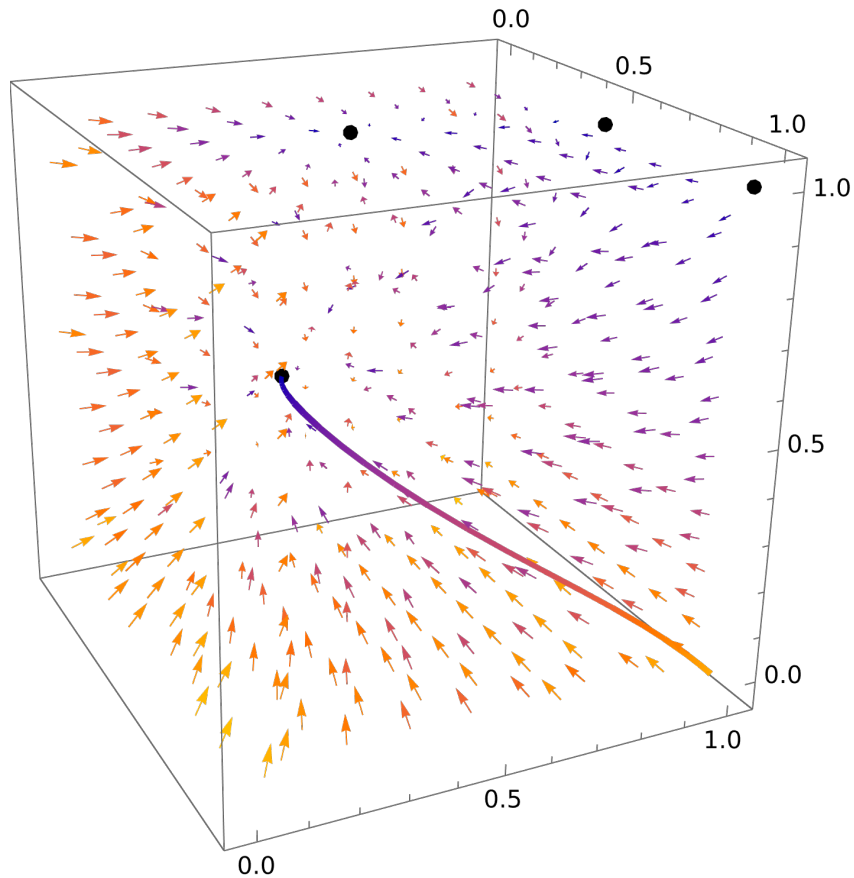
Using the big generating function Ψ, find the corresponding wave equation:

$$\frac{\partial \Psi}{\partial t} = \mathcal{H}\Psi \tag{9}$$

When $\mathcal{H} = \vec{X} \cdot \nabla$ this can be solved using the method of characteristics, so we can instead integrate

$$\frac{d\vec{\gamma}}{dt} = \vec{X} \tag{10}$$

numerically, using an appropriate time stepper.



The vector field $\vec{X}$ and a characteristic $\vec{\gamma}$

[1] SH Moolgavkar and DJ Venzon, Math. biosc. 1979; 47(1): 55-77

Random sampling

Error analysis

To compare methods, ask under what conditions the errors are similar. Stochastic algorithms have

$$\epsilon \sim N^{-1/2} \tag{11}$$

and will thus need

$$N \sim \mathcal{O}(\epsilon^{-2}) \tag{12}$$

runs, so overall runtime $T \propto N$.

Method of characteristics

Error analysis

Why wasn't this method ever used? Wave equation+characteristic methods were studied before, but used Euler integration, which has error

$$\epsilon \sim \Delta t \tag{13}$$

and required two passes, so it ran in

$$T \sim \Delta t^{-2} \sim \mathcal{O}(\epsilon^{-2}) \tag{14}$$

this is asymptotically just as bad as random sampling!

---

[1] SH Moolgavkar and DJ Venzon, Math. biosc. 1979; 47(1): 55-77

[2] DW Quinn, Risk Analysis 1989; 9(3): 407-13

Fast forward method

Error analysis

But what happens if we only need one pass, and replace Euler integration with a Runge-Kutta scheme?

$$\epsilon \sim \Delta t^2 \tag{15}$$

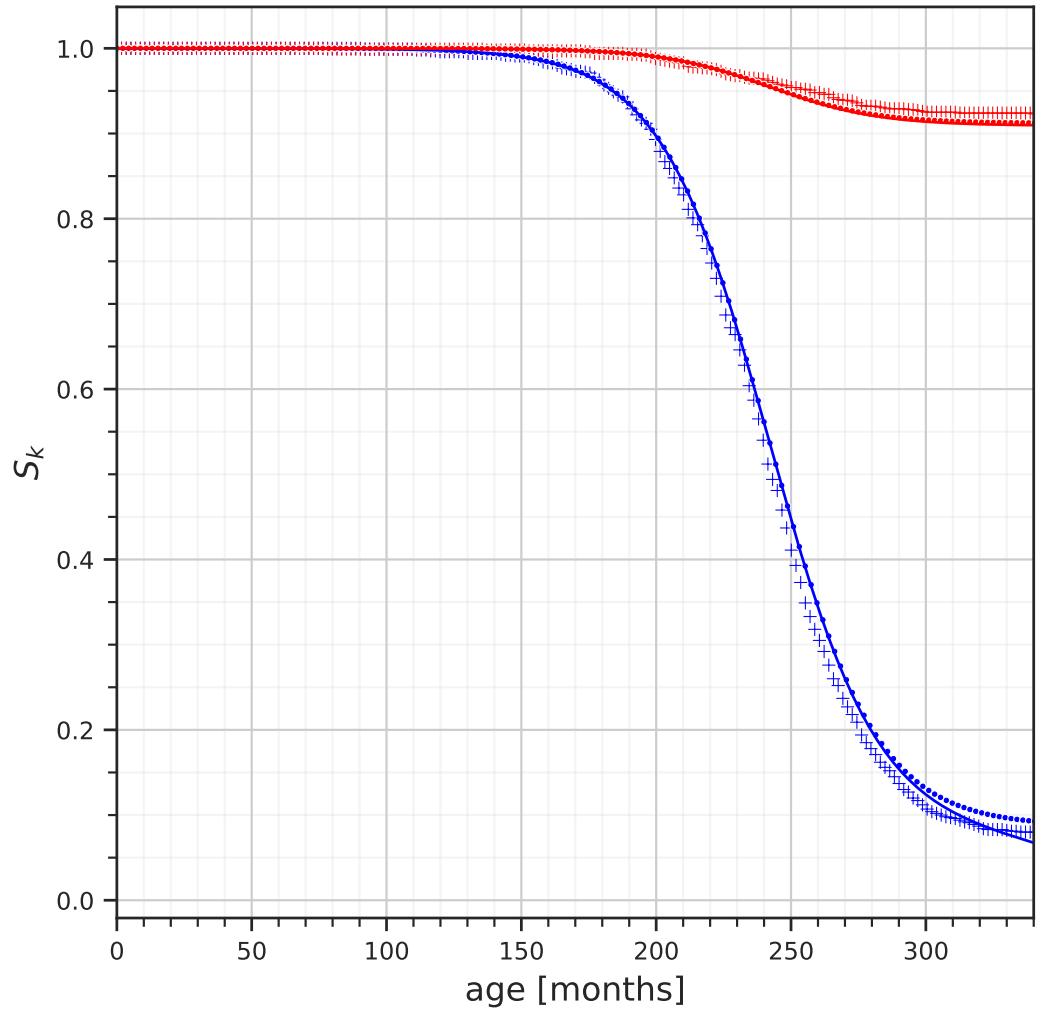
and runs in

$$T \sim \Delta t^{-1} \sim \mathcal{O}(\epsilon^{-1/2}) \tag{16}$$

so new runtime $\sim \mathcal{O}\left(\text{ old runtime }^{1/4}\right)$.

Amazing!

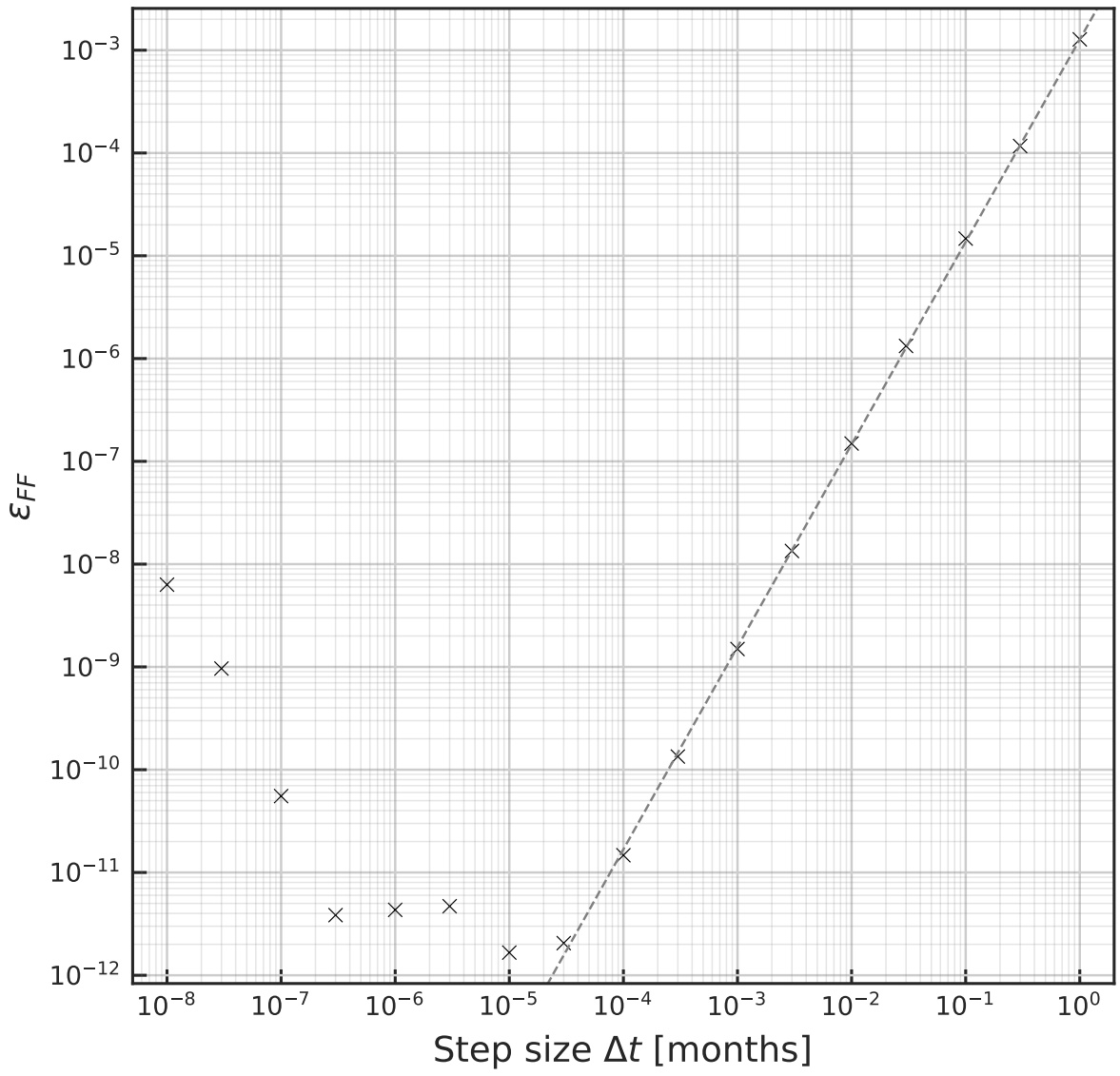
Fast forward method



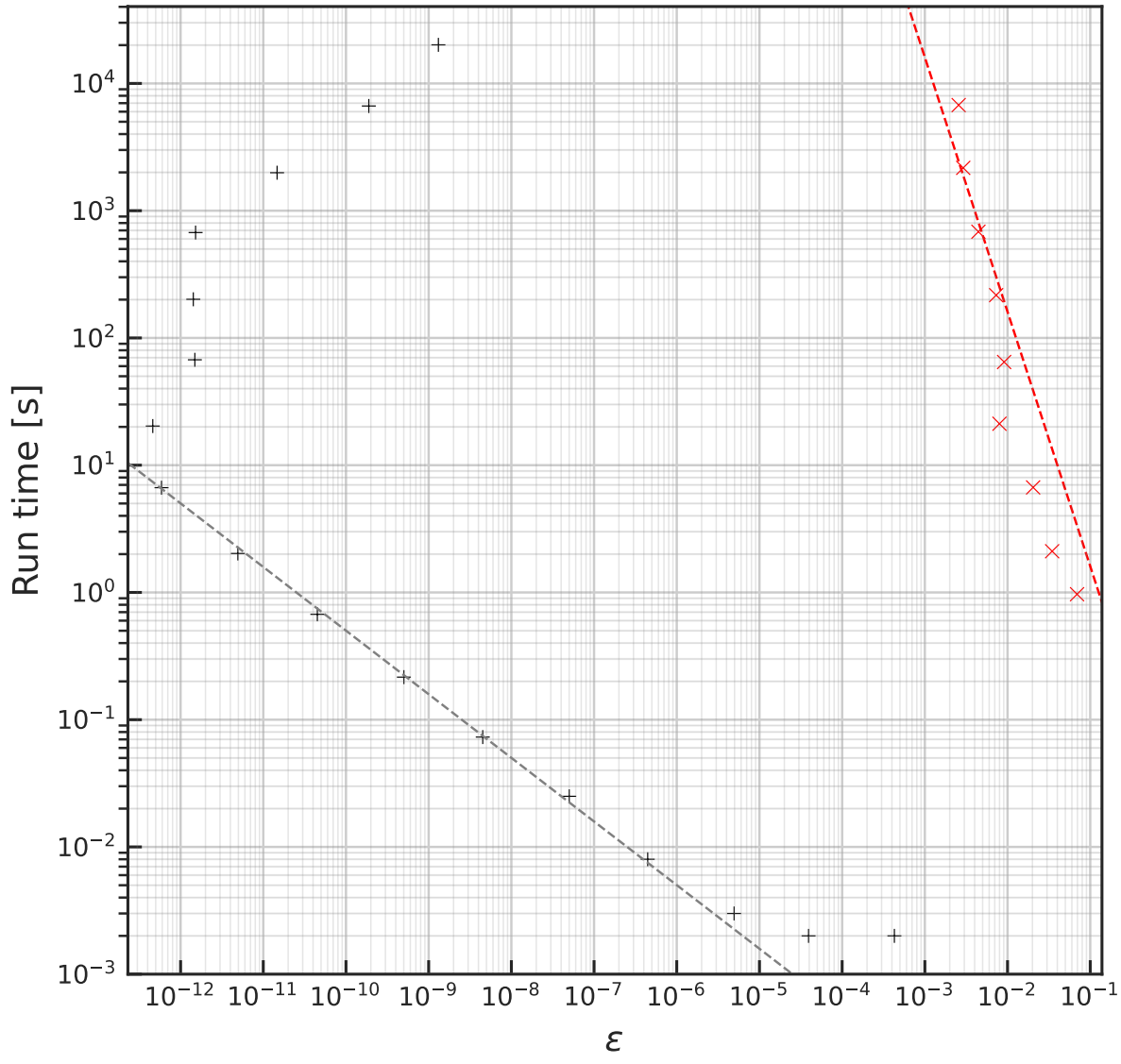
Monte Carlo: $\approx$ 5000s Fast forward: $<$ 4ms

Fast forward method

Error analysis

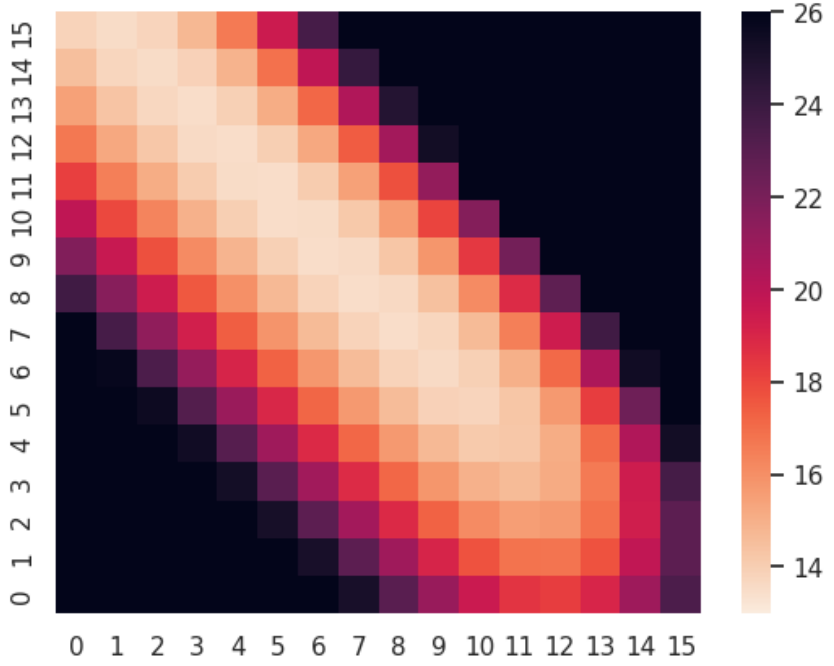


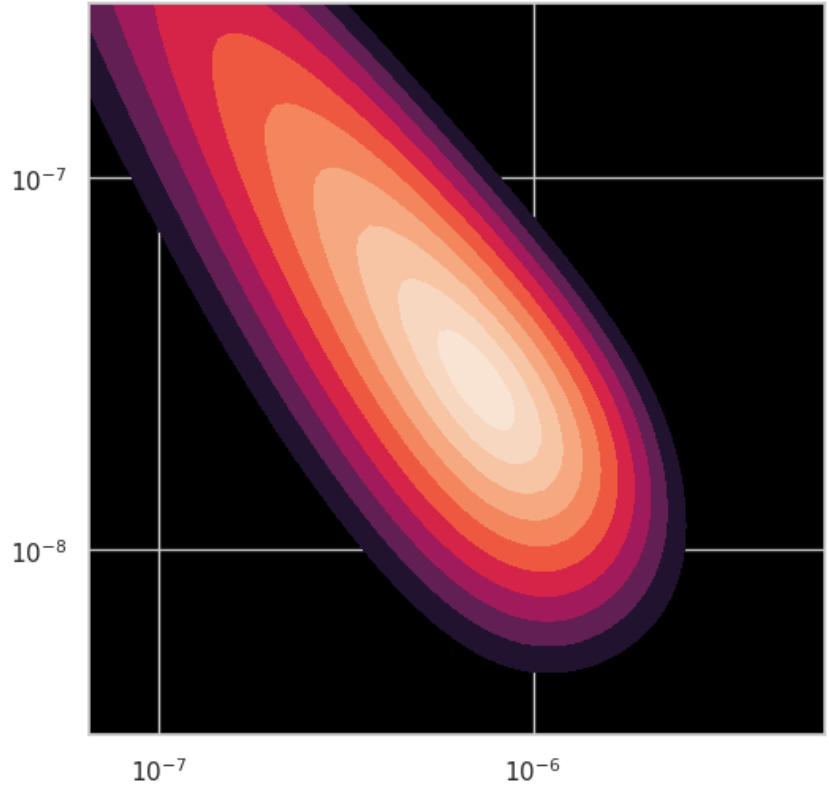
How do they compare?



Fast forward method

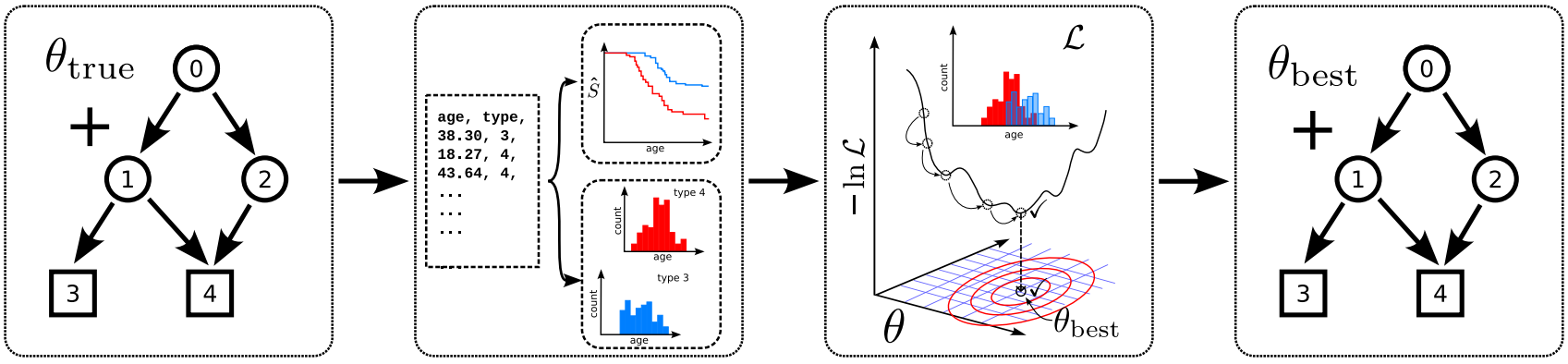
Efficiently computing $S_k(a)$ means we can evaluate likelihood functions directly, just sampling them.....





Fast forward method: really detailed likelihood functions

Parameter inference



Fast forward method

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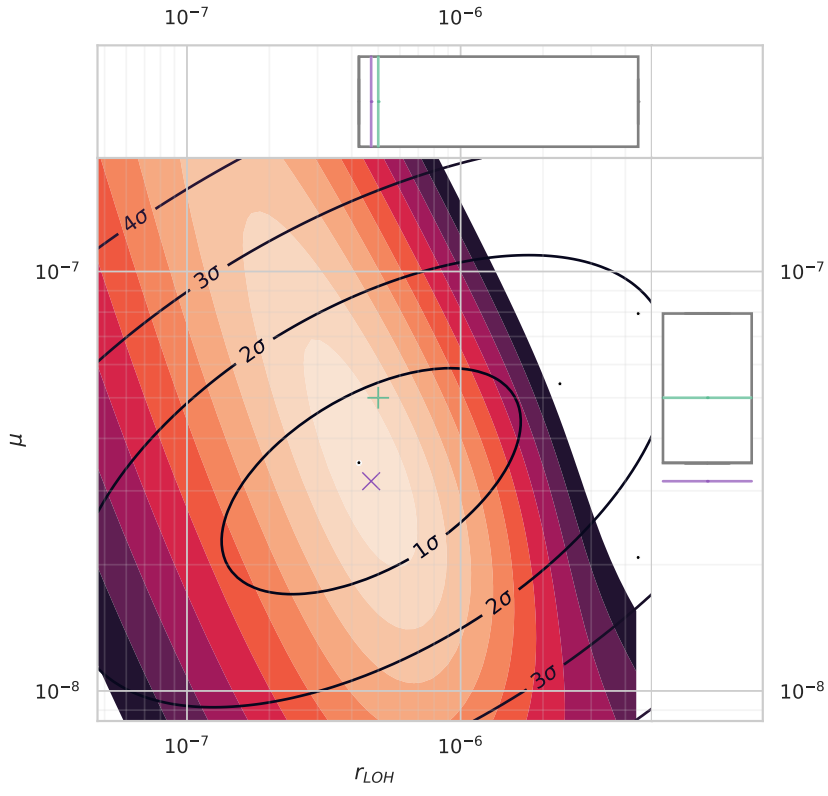
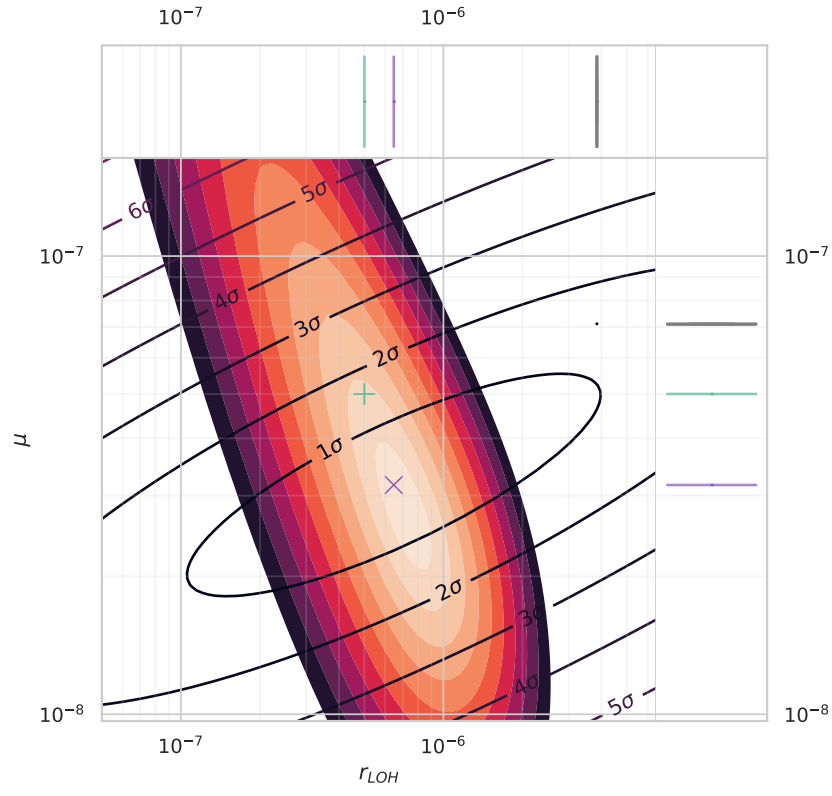
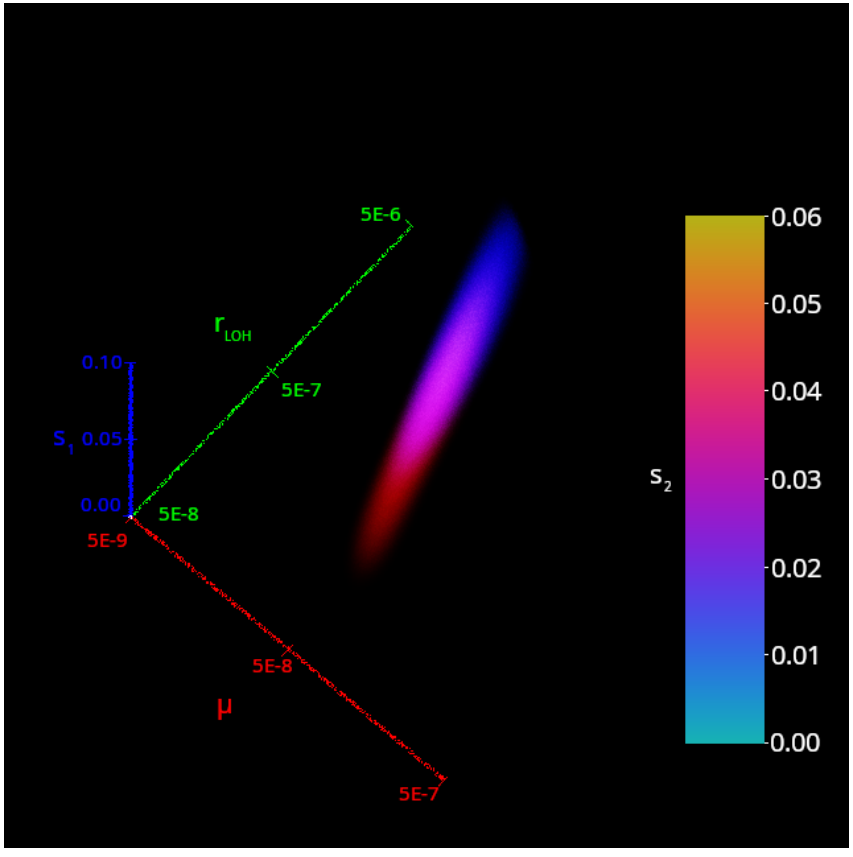
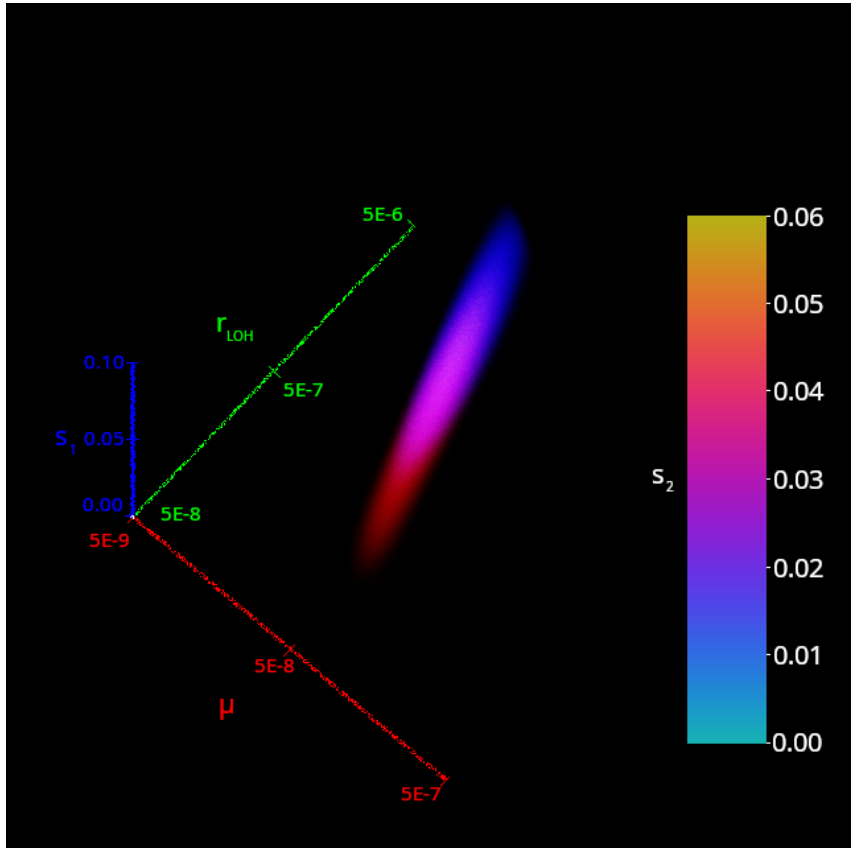




Detailed likelihood functions





Thank you!

What is my message?

- Maths is immediately applicable to RISK STRATIFICATION and SURVIVAL ANALYSIS!
- Age structure is v. important & informative, genes are discrete

What next?
Combine genomic and age data TOGETHER and run these analyses on real studies!

- schwannoma tumours in NF2
- oesophageal cancer in Barrett's cases
- penile adenocarcinoma
- autopsy study

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- Miriam Smith
- Marian Love
- Joshua Hellier
- Vivien Holmes
- Ramishka D. Liyanage