Mechanistic networks for cancer genomics

Cancer, copy number alterations, and age

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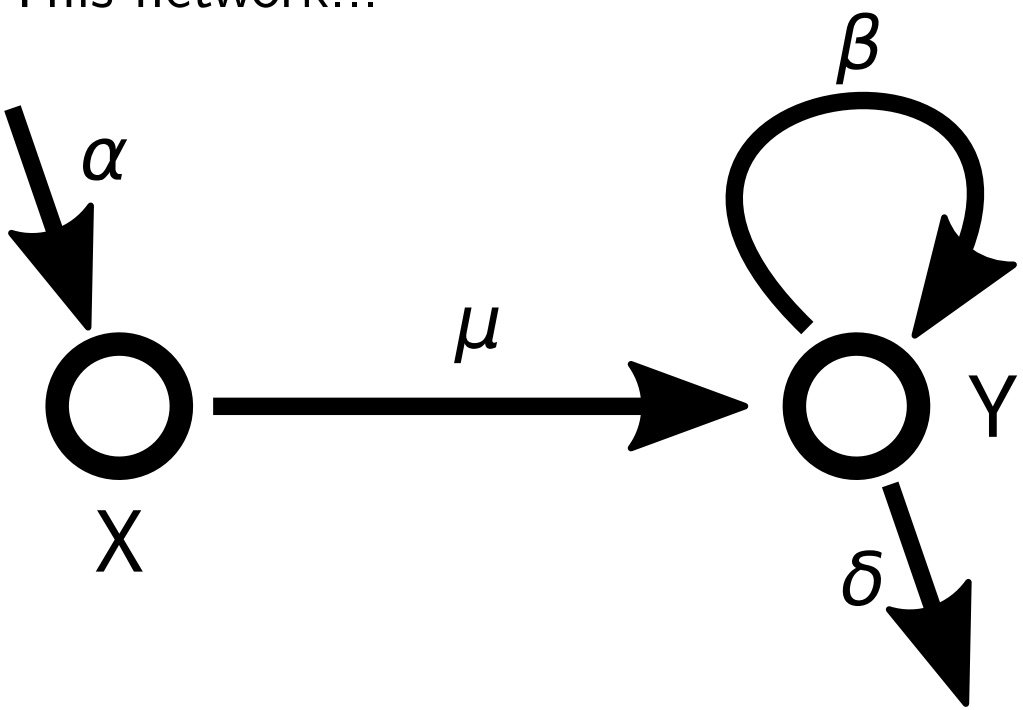
Warning

There will be very few equations in this talk!

This network...



corresponds to this stochastic process:...

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

and approximately this linear system...

$$\frac{d}{dt}\begin{pmatrix} E[X] \\ E[Y] \end{pmatrix} = \begin{bmatrix} 0 & 0 \\ \mu & \beta - \delta \end{bmatrix} \cdot \begin{pmatrix} E[X] \\ E[Y] \end{pmatrix} + \begin{pmatrix} \alpha \\ 0 \end{pmatrix}$$

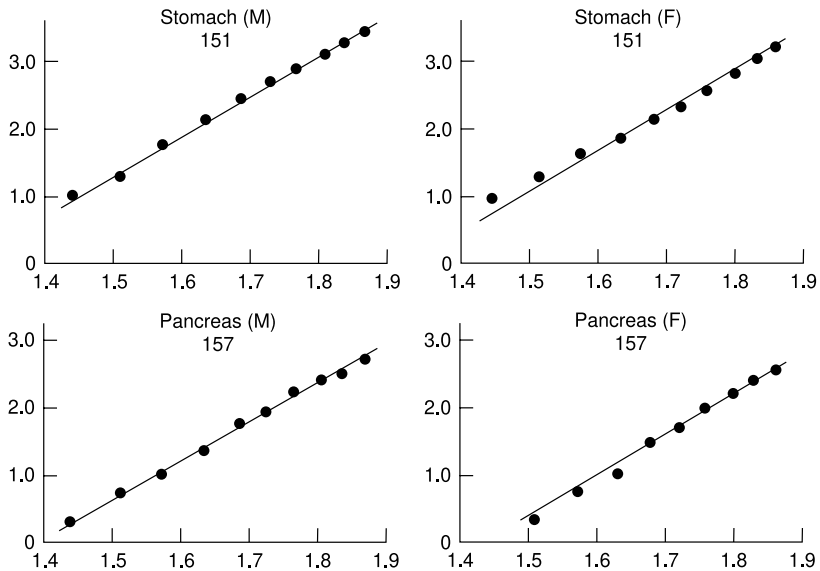
Most of our models are linear, high-dimensional and sparse[1]

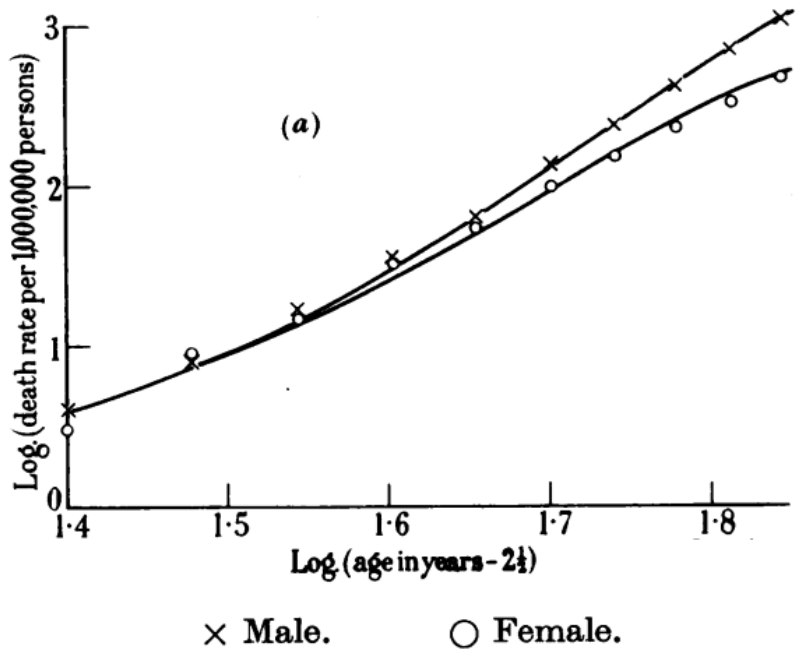
[1] C. Paterson, I. Bozic, H. Clevers, PNAS 2020; 117(34): 20681-20688

Age and cancer

P. Armitage and R. Doll[12]

Risk of cancer increases with age:





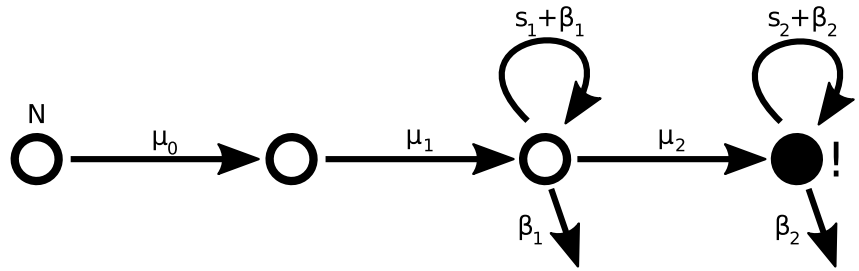
[1]P. Armitage and R. Doll, British Journal of Cancer 1954; 8: 1–12

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

Multi-stage clonal expansion models

2-3 rate limiting steps[123]

Problem: how to compute $P(cancer, t)$ for a given model?



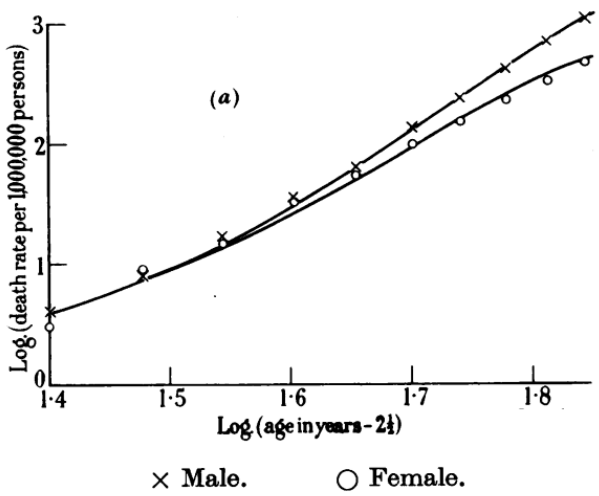
Different methods: Fast:

- Mean-field approximation[1]
- Numerical quadrature[2]

Slow:

- Gillespie algorithm + sampling [3]
- tau leaping + sampling [3]

↓?



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

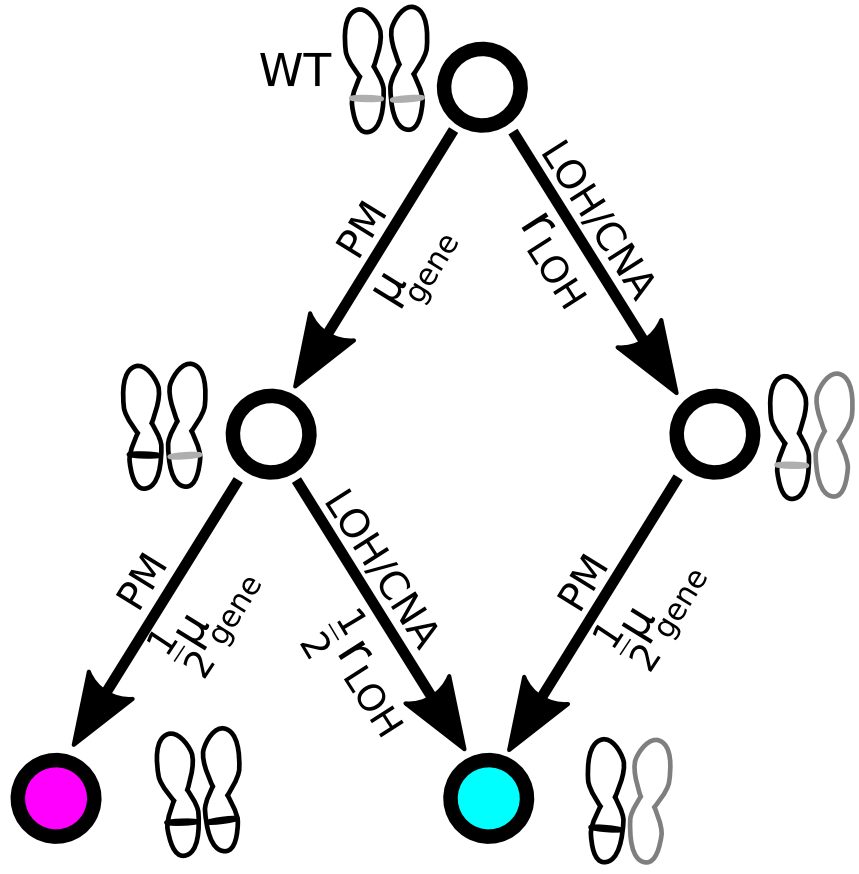
[2] S. Moolgavkar and G. Luebeck, JNCI 1992; 84(8): 610-618

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

Network models

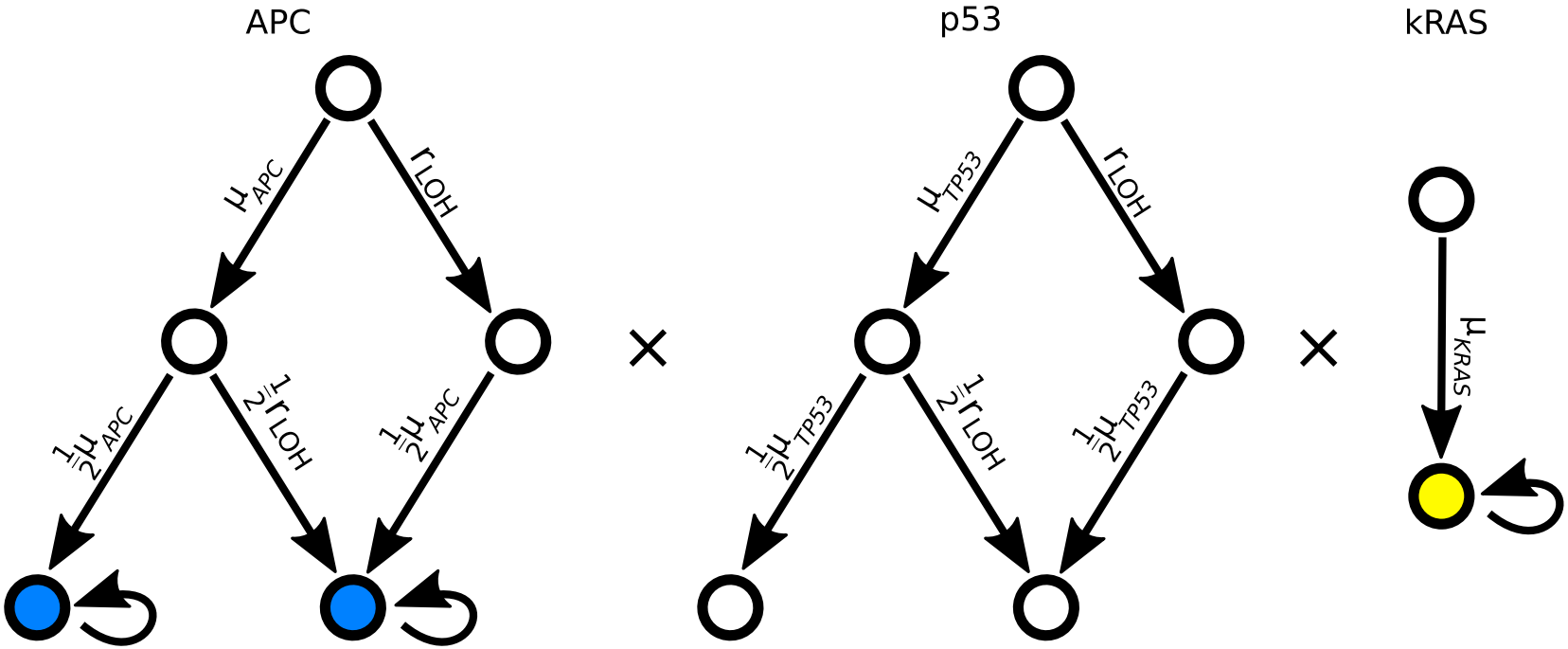
1. Study **specific genes** and mechanisms of interest (SNVs, LOH, CNA, etc.)
2. Fix parameters from sequences and experiments
3. Distinguish different orders of events

example model



This gets us the incidence of *specific karyotypes*

Colorectal adenocarcinoma model



- *APC-p53-kRAS* combo accounts for about 15% of incidence
- 5-year survival about 60% (any stage)

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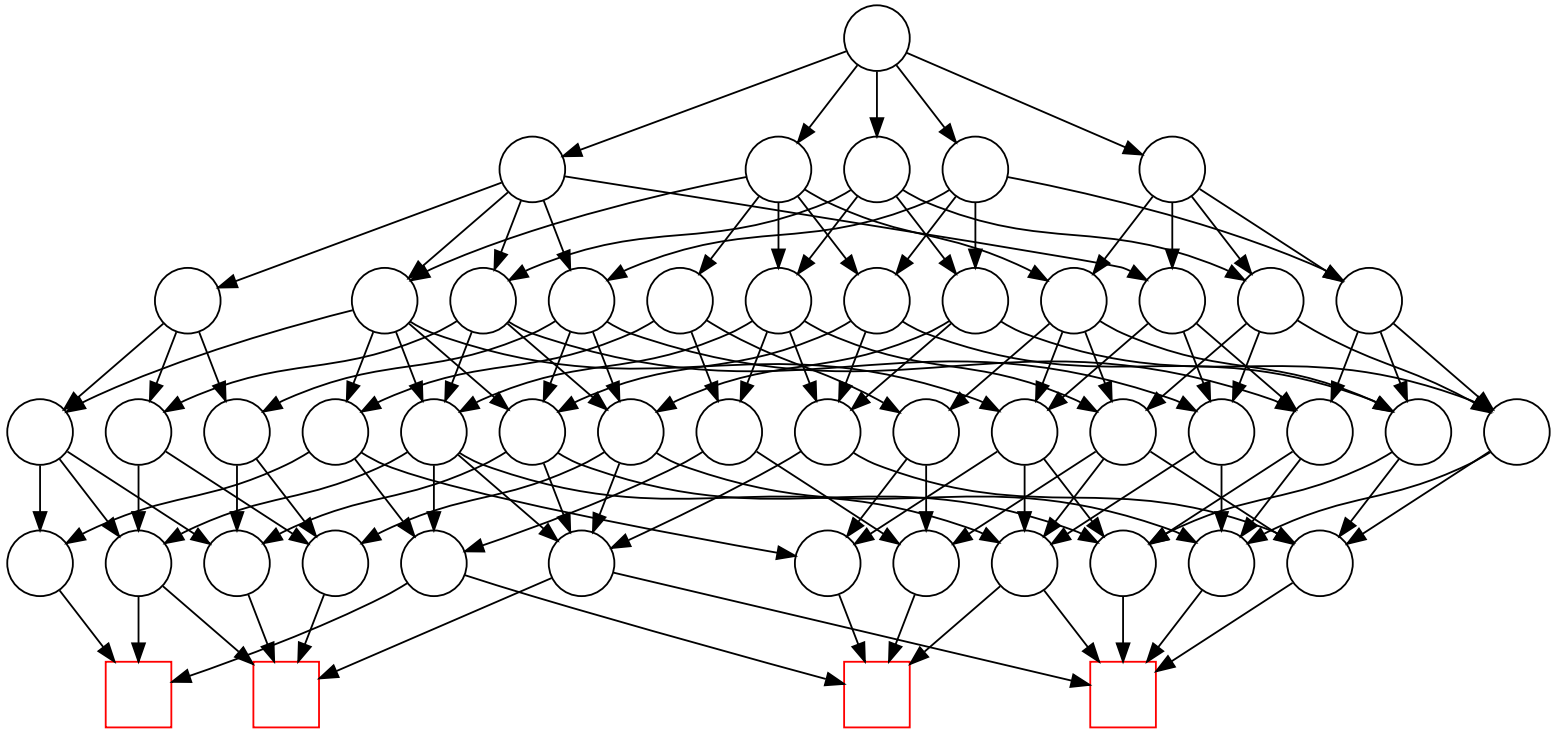
[1] Fearon et al. TODO

[1] M. S. Lawrence et al., Nature 2014; 505: 495–501

[2] Office for National Statistics, England 2019

Colorectal adenocarcinoma model

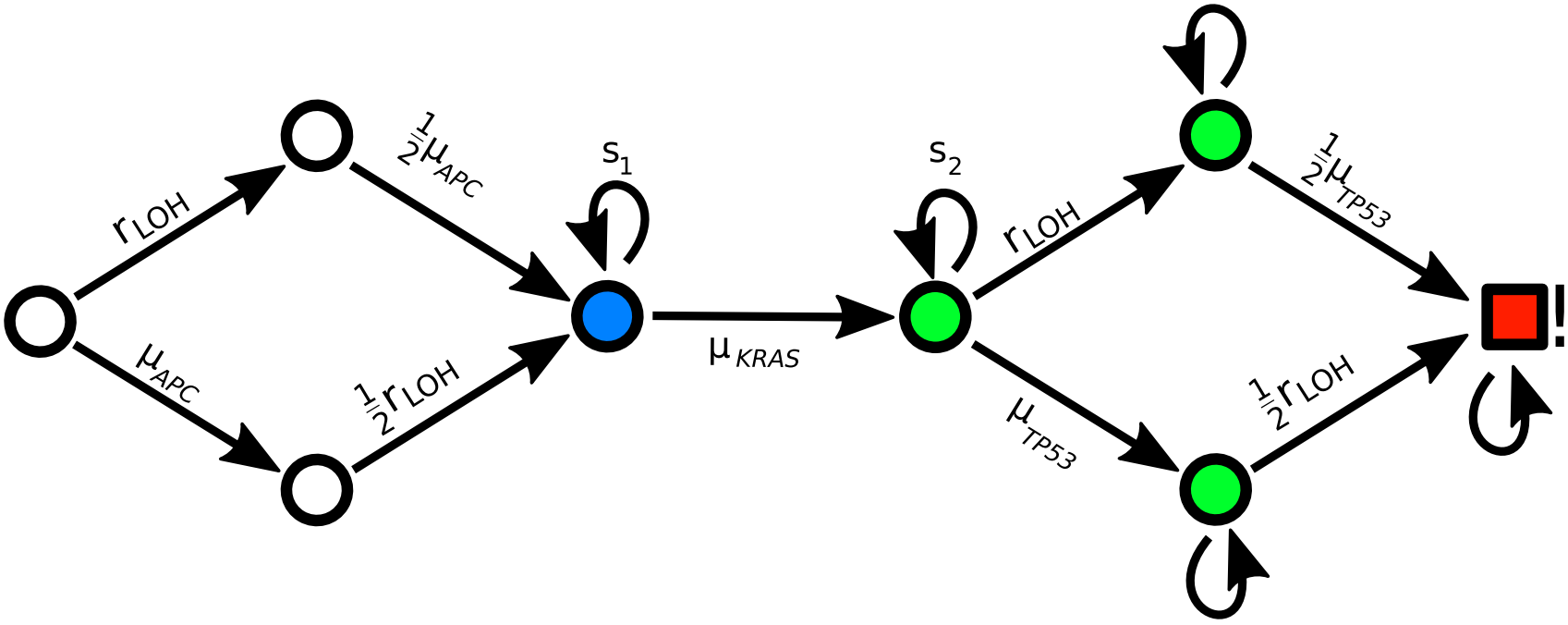


each end node is a different copy number profile

e.g. $(-17p, -5q)$, etc

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

Colorectal adenocarcinoma model



$$P(t) \sim te^{s_2 t}$$

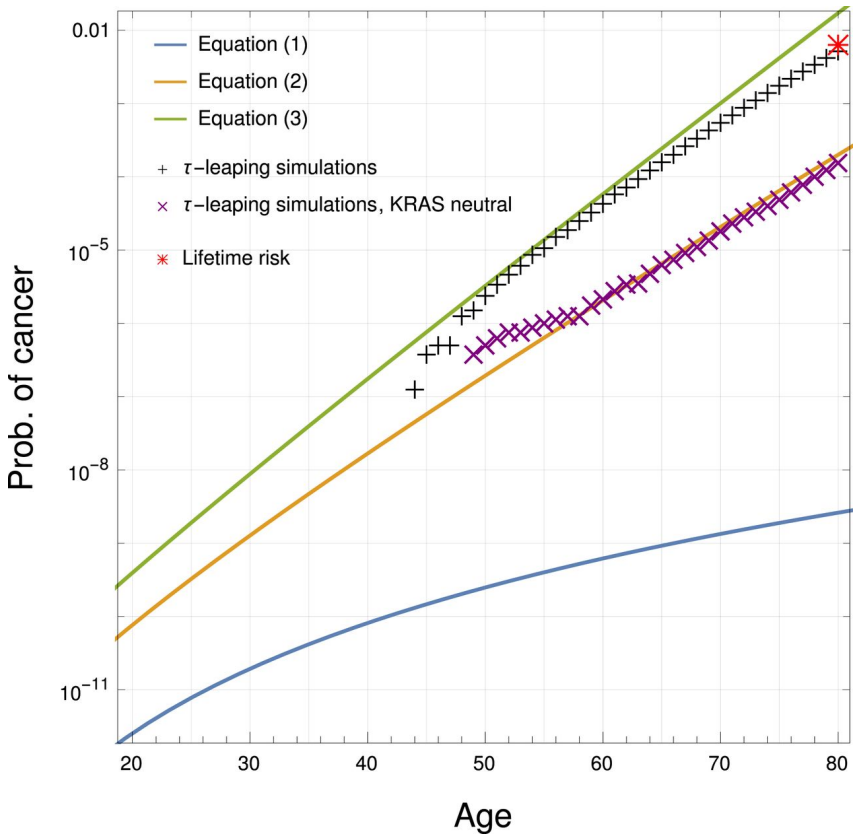
- The 4 most likely paths account for 50% of the risk
- Consistent with classic model[2]

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

[2] Kinzler and Vogelstein 1990

Colorectal adenocarcinoma model

Successful *ab initio* model



- Can constrain *APC/KRAS* epistasis ($s_2 < 0.31$/yr)
- Timing of *p53* inactivation: must be *late*
- *Compatible with* 3-hit models, similar curve: *p53 not rate limiting*

but:

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

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

[2] (relative to the others)

Why study vestibular schwannoma?

Sometimes rare events make more interesting science possible

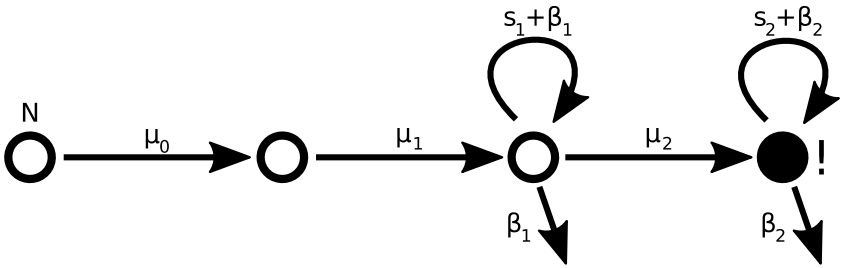
1. genomic subtypes better characterised: *NF2/Merlin* altered in $85 - 100\%$ of cases[1,2], *TP53* in $\approx 0\%$
2. usually benign = **easier to study timing!** (of drivers, malignant transformation...)
3. only 3 hits, weak selection (almost neutral)
4. probabilities low: approximations v. accurate **because it's rare**

[1] ML Carlson et al., Otology & Neurotology: 2018;39(9):860 – 871

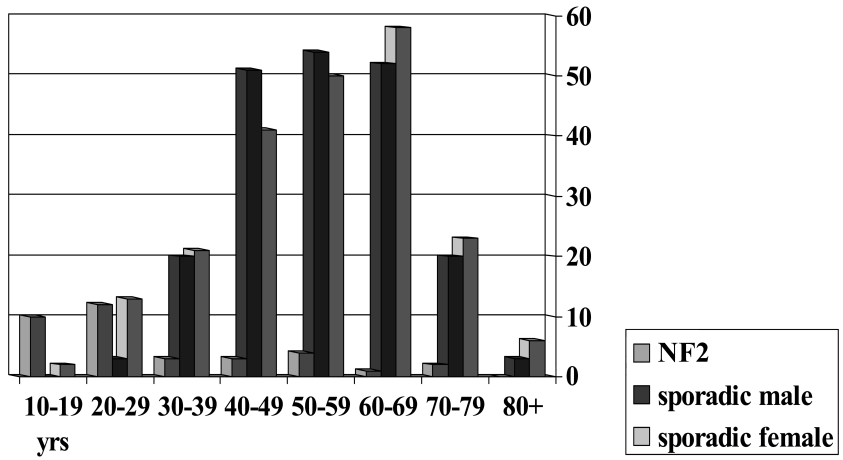
[2] AL Håvik et al., Journal of Neurosurgery JNS. 2017;128(3):911 – 922.

Vestibular schwannoma

3-*event* model



- Fitness suspiciously low, $s \approx 0.005/\text{yr}$ [1]
- Suggests nearly-neutral 3-hit model [3]



Gareth Evans 2005[2]

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[1] R. Woods *et al.* Genetic Epidemiology (2003)24: 265–272

[2] DGR. Evans *et al.* Otology & Neurotology (2005)26:93–97

[3] C Paterson, I Bozic, MJ Smith, X Hoad, DGR Evans, https://doi.org/10.1101/2021.10.03.457528

Vestibular schwannoma incidence

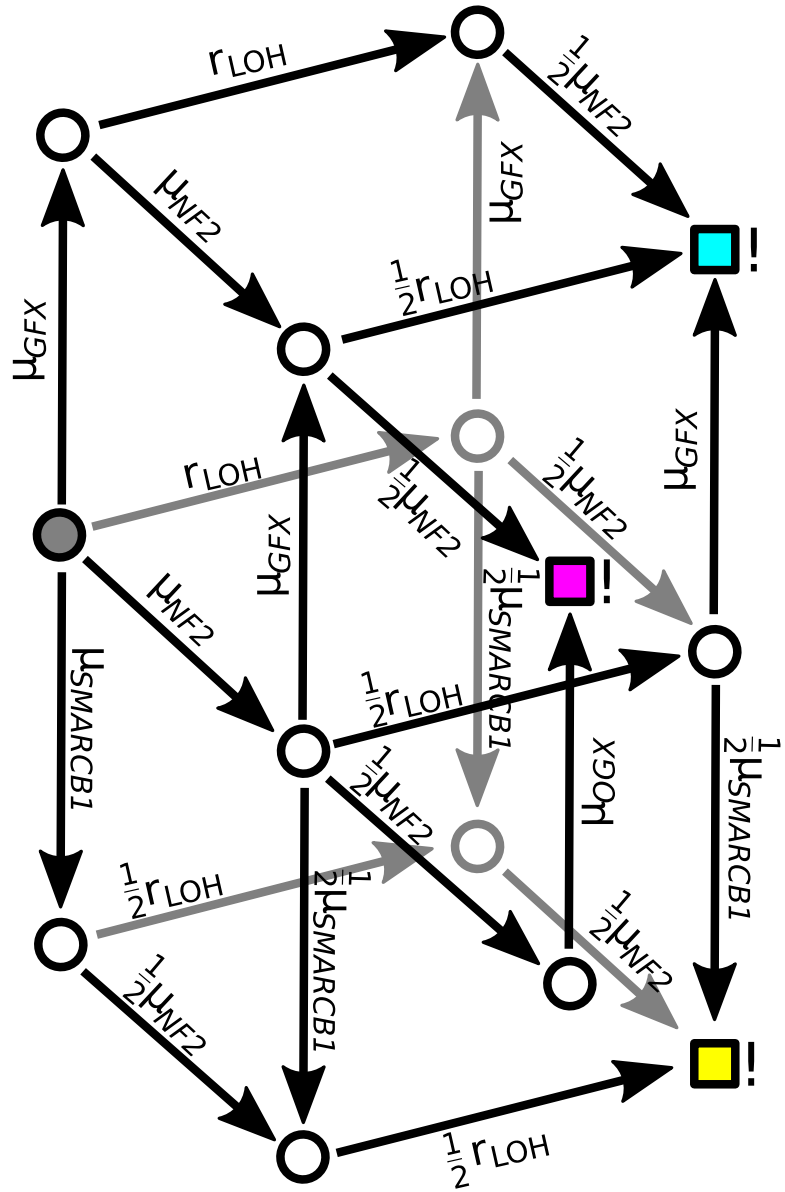
Our model for sporadic VS

- Include *NF2*, *SMARCB1* and (simplified) linkage
- Add hypothetical oncogene *GFX*

Risk of each subtype looks like

$$P(\blacksquare) \propto \frac{t^3}{3!}$$

$$P(\blacksquare) \approx N_{WT}\mu_{GFX} r_{LOH} \frac{1}{2}\mu_{NF2} \frac{t^3}{3!} \times 6$$

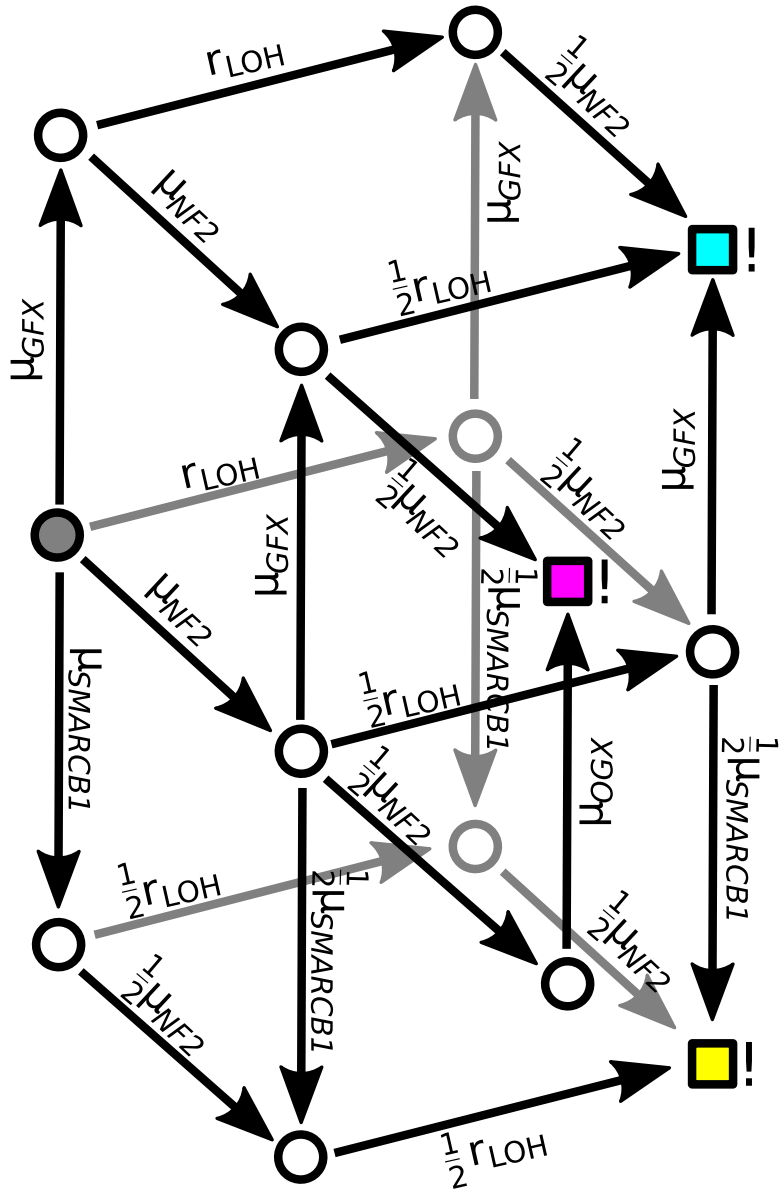


[1] C Paterson, I Bozic, MJ Smith, X Hoad, DGR Evans, https://doi.org/10.1101/2021.10.03.457528

Vestibular schwannoma incidence

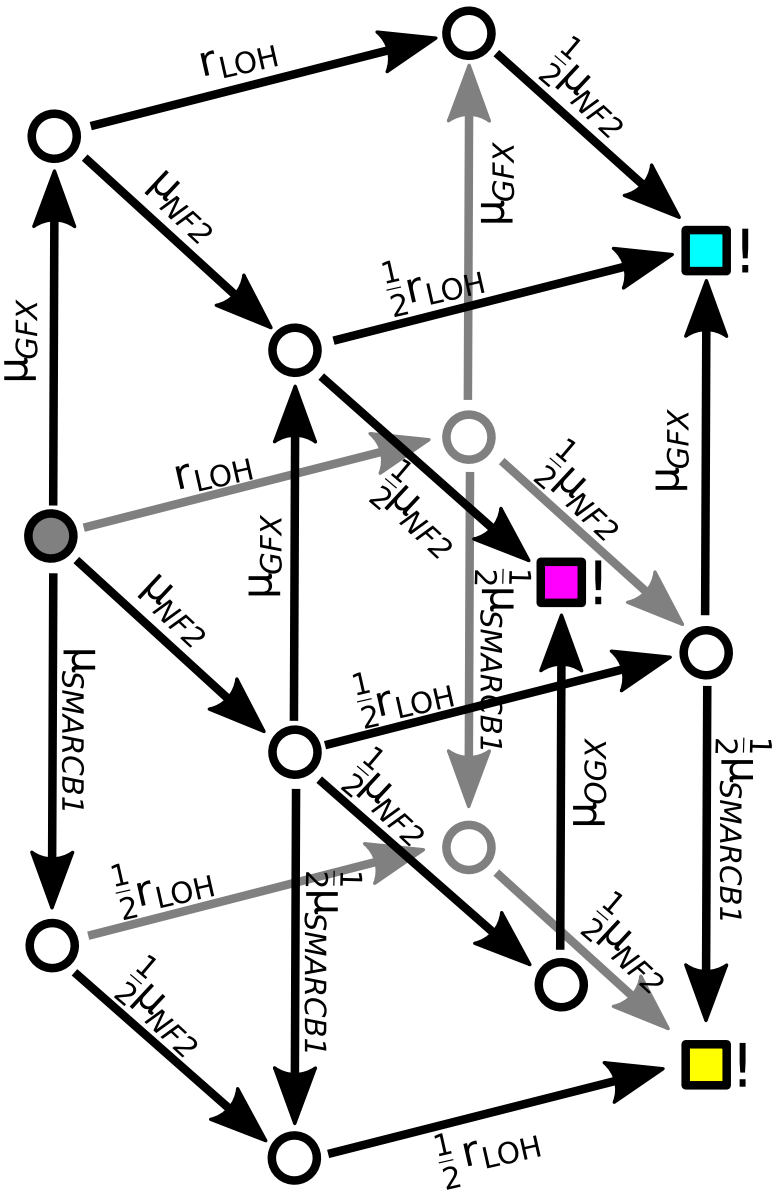
Our model for sporadic VS

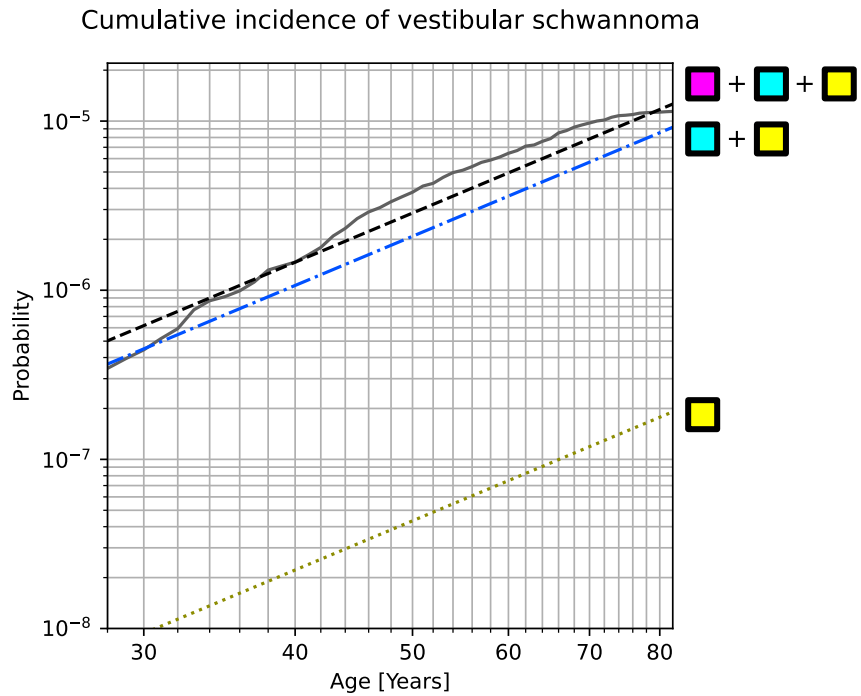
- *Don't* use *ab initio* point estimates for u, r_{LOH}, n_{GFX} this time...
- Instead use $P(t) = \square + \square + \square$, $f_{LOH} = \frac{\square + \square}{\square + \square + \square}$, and $f_{SMARCB1} = \frac{\square}{\square + \square + \square}$ to fix the parameters!



Vestibular schwannoma incidence

Our model for sporadic VS

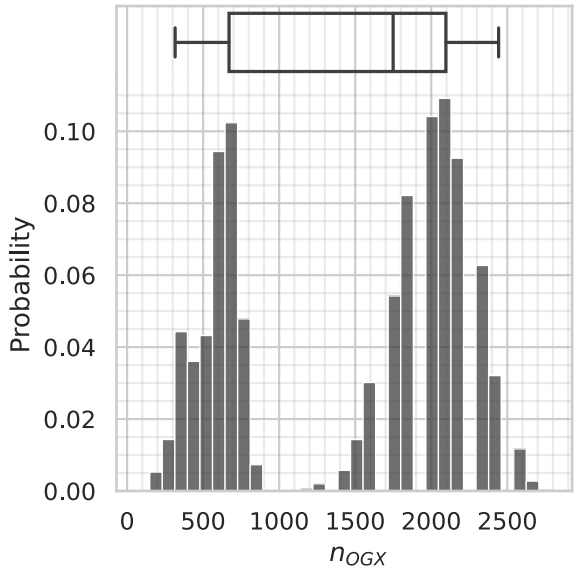


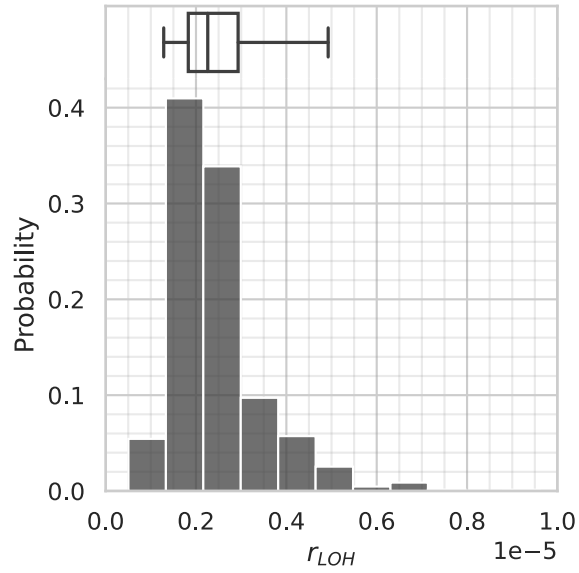


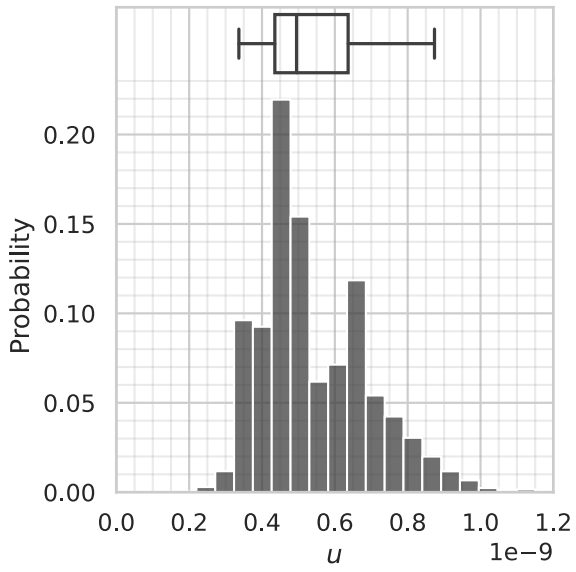
[1] C Paterson, I Bozic, MJ Smith, X Hoad, DGR Evans, https://doi.org/10.1101/2021.10.03.457528

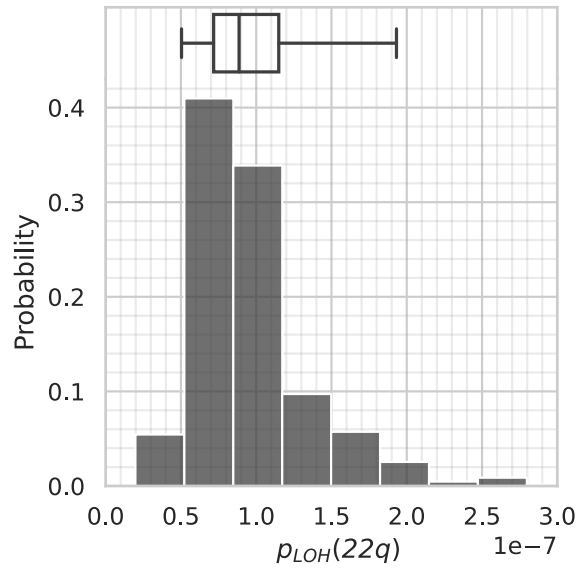
Vestibular schwannoma incidence

New parameter estimates









Main outputs

1. Better estimates of event rates in Schwann cells
2. Can constrain timing of "*TSX*" (resp. for malignancy)
3. Can constrain size of *GFX* and *TSX*

To do list

Experiments:

- Sporadic VS to constrain $f_{SMARCB1}$: $n > 300$
- Empirical CNA/NGS in MPNST (**rare!**)?: $n > 30$

Theory:

- Convert n_{GFX} and n_{TSX} to estimates for multiple genes using *integer partitions*
- Implement new efficient algorithm in parameter inference with max. likelihood

Acknowledgements

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In order of appearance...

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