Mathematical models of invasion and evolution in adenocarcinomas

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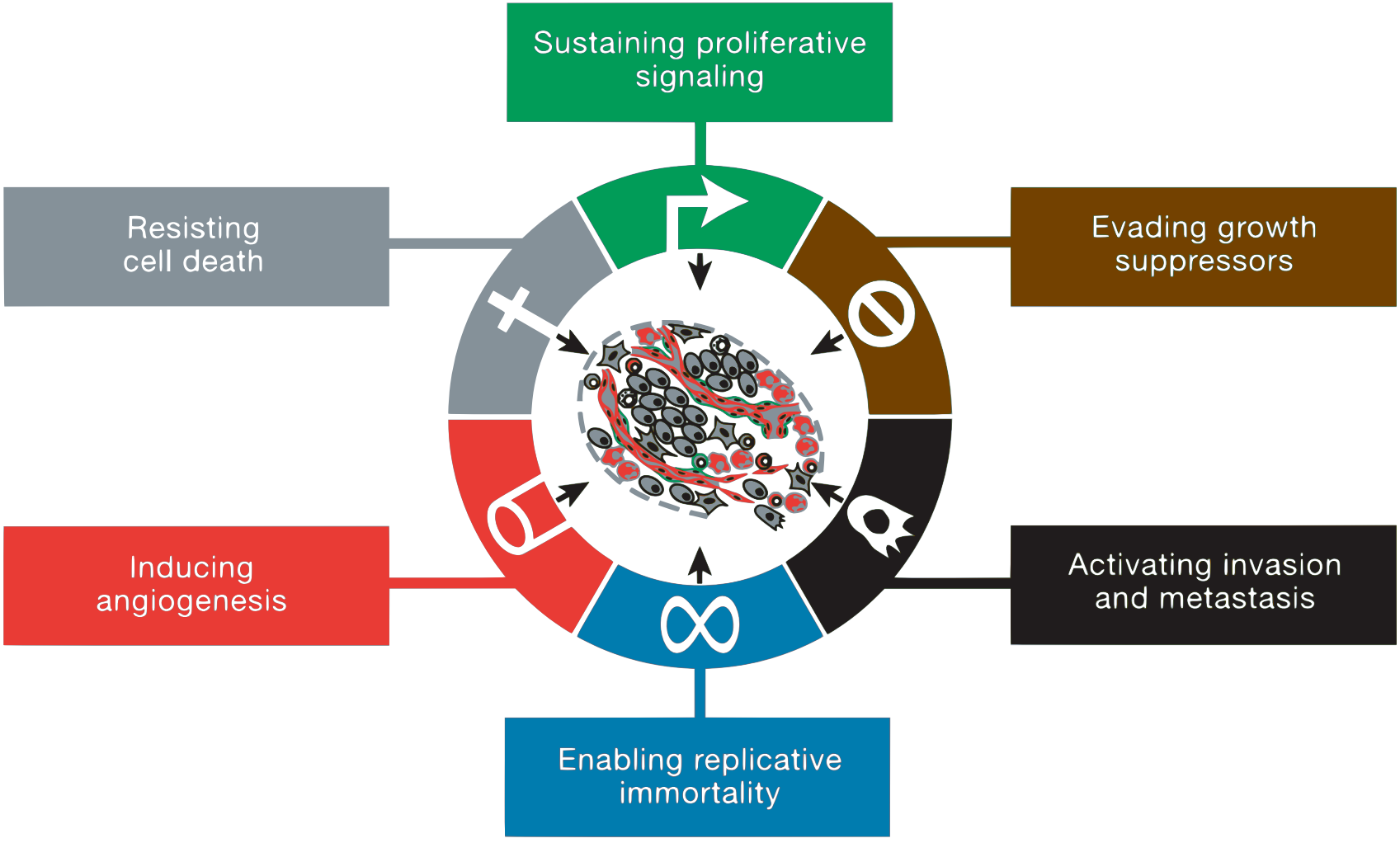
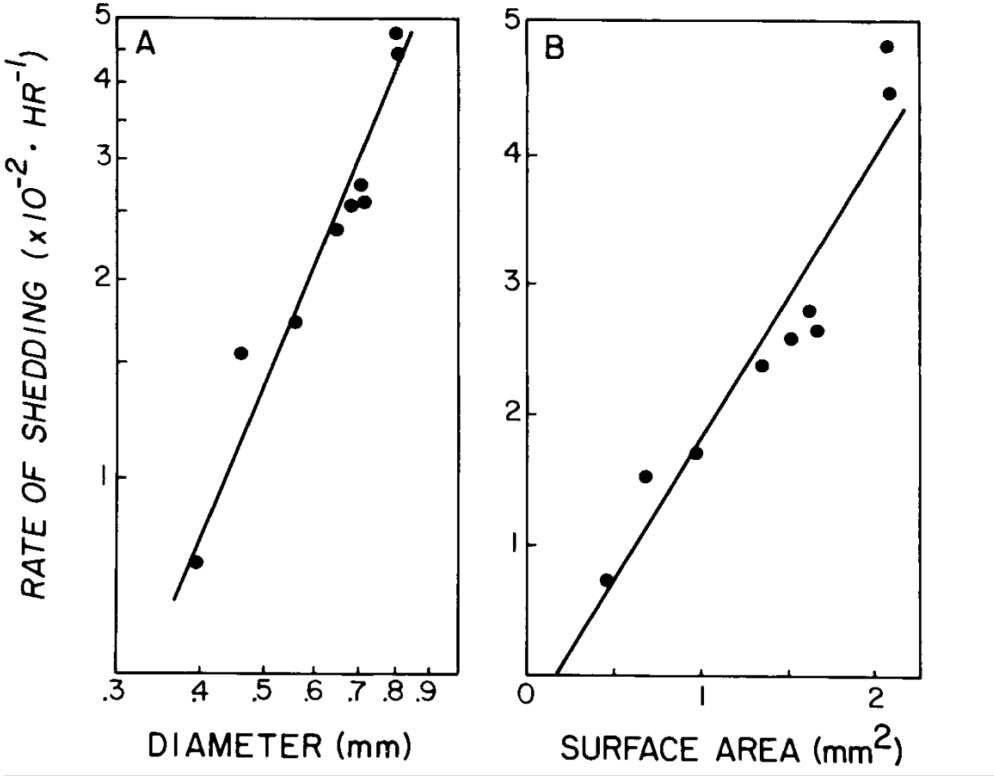
What is cancer?



D. Hanahan, and R. A. Weinberg. "The hallmarks of cancer: The Next Generation." *Cell* 144.5 (2011): 646-674

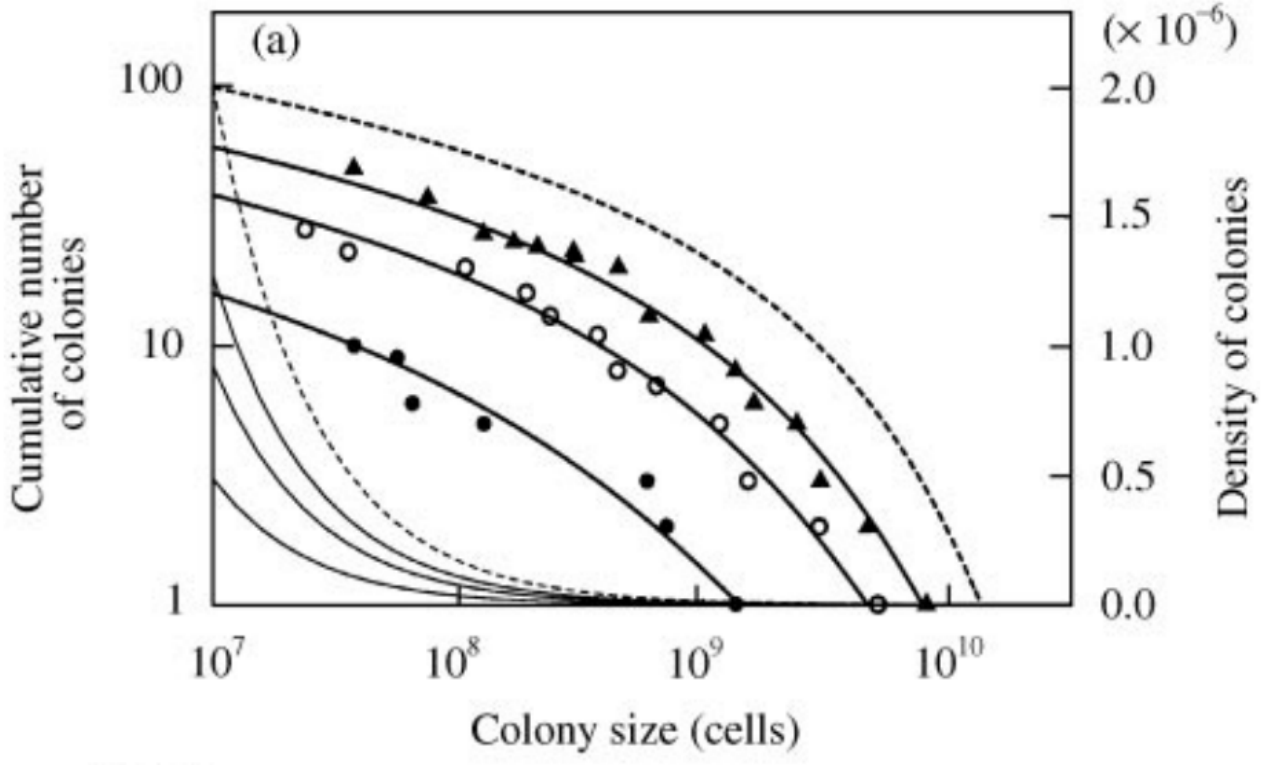
In vitro experiments

1. Lesions are spheroidal
2. Expanded with steady speed 0.03 $\mathrm{mm/hr}$
3. Shed cells at rate $\propto 0.05\ \mathrm{hr}^{-1}\mathrm{mm}^{-2}\times$ surface area



J. Landry *et al.*, "Shedding of mitotic cells from the surface of multicell spheroids during growth", *Journal of cellular physiology* 106.1 (1981): 23-32

In vivo experiments

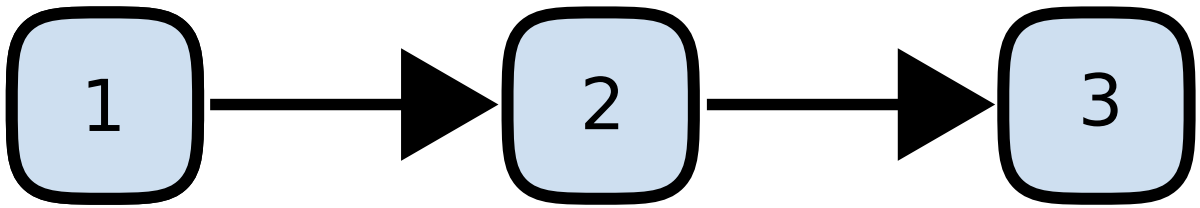


Explains entire size distribution *and* growth rate with *two equations*!

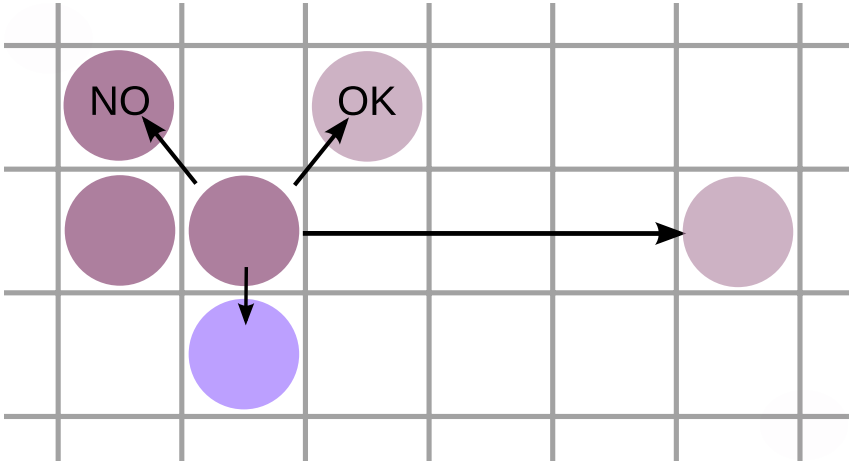
K. Iwata, K. Kawasaki, and N. Shigesada, "A dynamical model for the growth and size distribution of multiple metastatic tumors." *Journal of theoretical biology* 203.2 (2000): 177-186

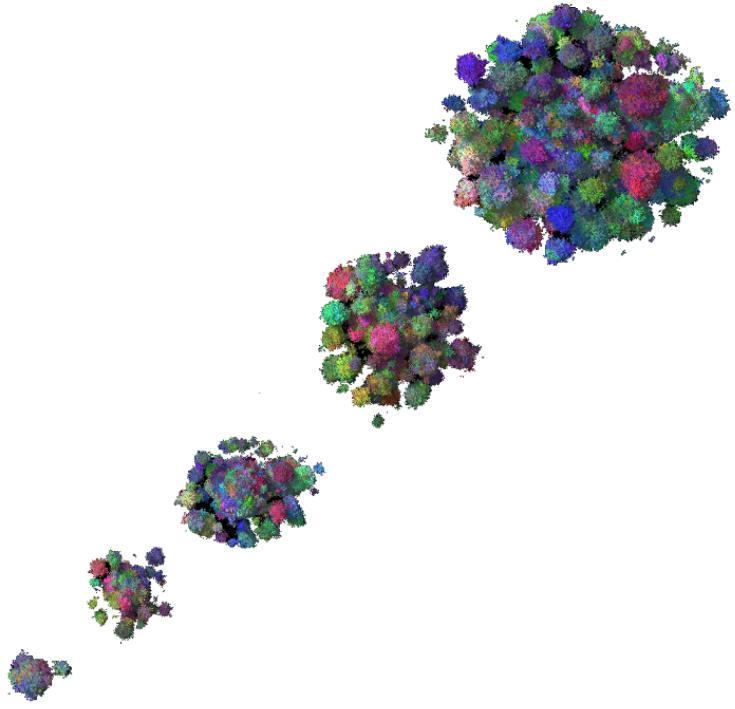
Evolutionary dynamics

Initially, assume a completely linear space of possible genotypes:



Lattice simulations

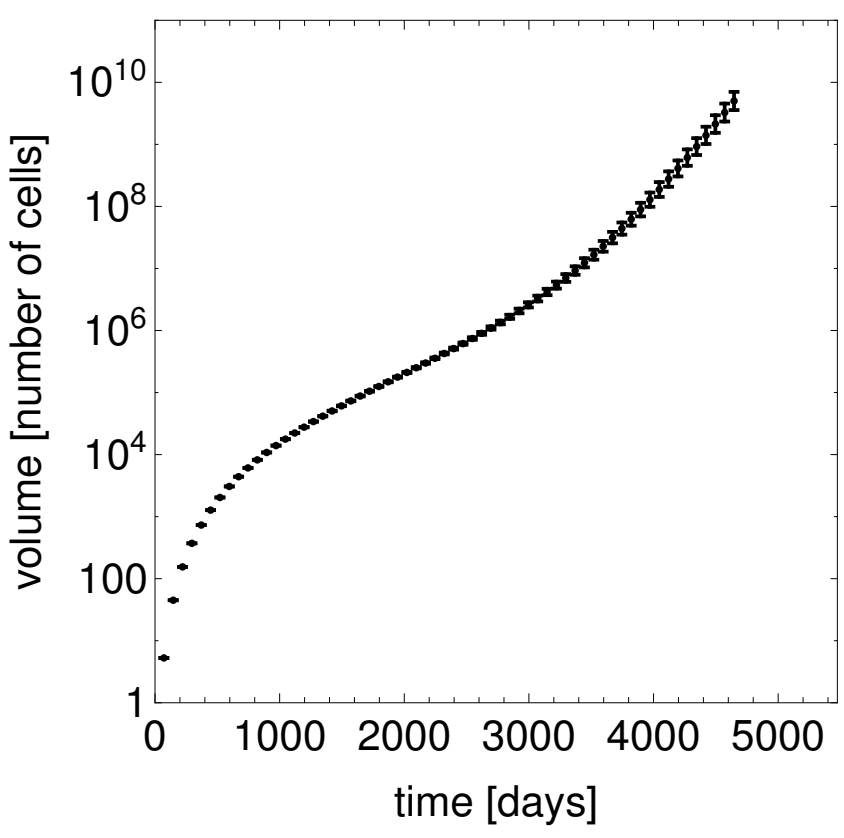


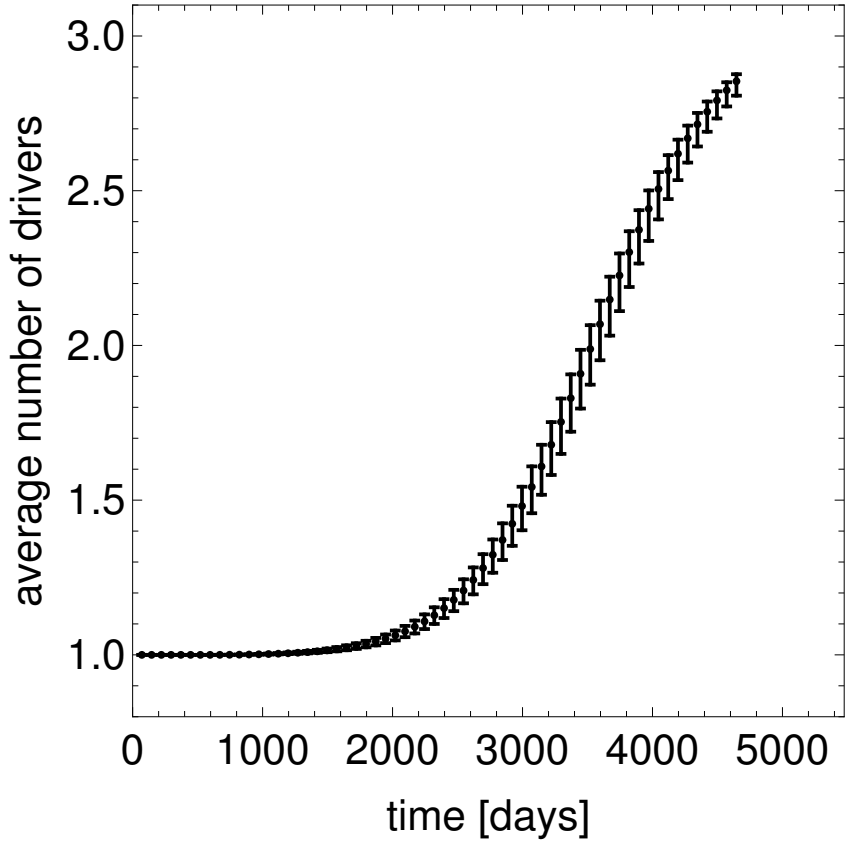


Controlled by:

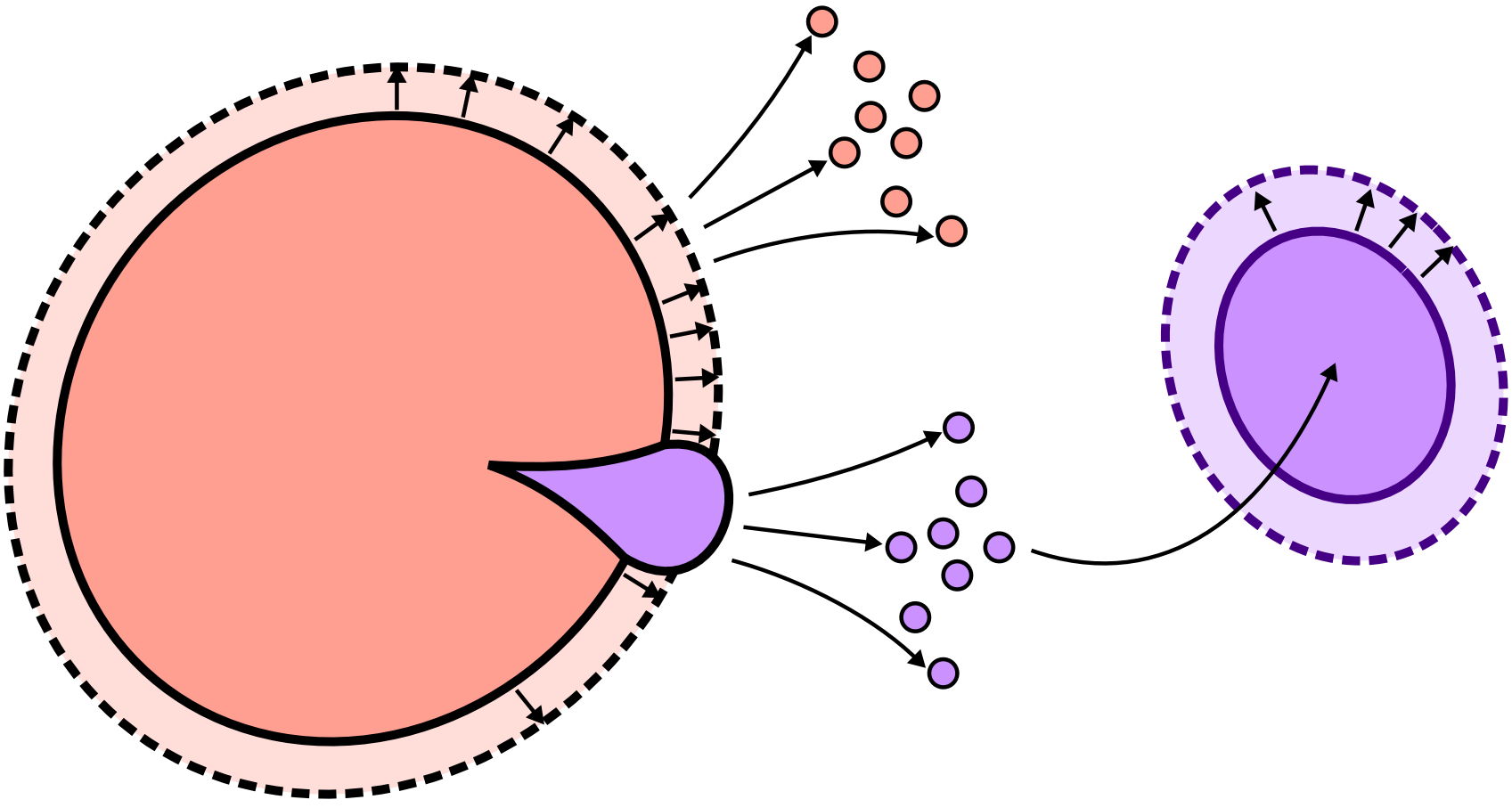
- Birth/death rates b_n, d_n
- Migration probability M
- Mutation probability p_μ

Lattice simulations





Analytical model



Analytical model

Two equations:

1. growth
2. invasion+mutation

$$\partial_t f_n(a,t) + \partial_a f_n(a,t) = 0 \tag{1}$$

$$f_n(0,t) = \int_0^\infty r_n(a)\phi_n(a)f_n(a,t)da + \int_0^\infty (1 - r_{n-1}(a))\phi_{n-1}(a)f_{n-1}(a,t)da \tag{2}$$

Chay Paterson, Martin A. Nowak, Bartlomiej Waclaw, "An exactly solvable, spatial model of mutation accumulation in cancer", *Scientific Reports* 2016

Exact solution!

1. Total number and total mass of lesions of sub-type n grows exponentially with growth rate G_n satisfying

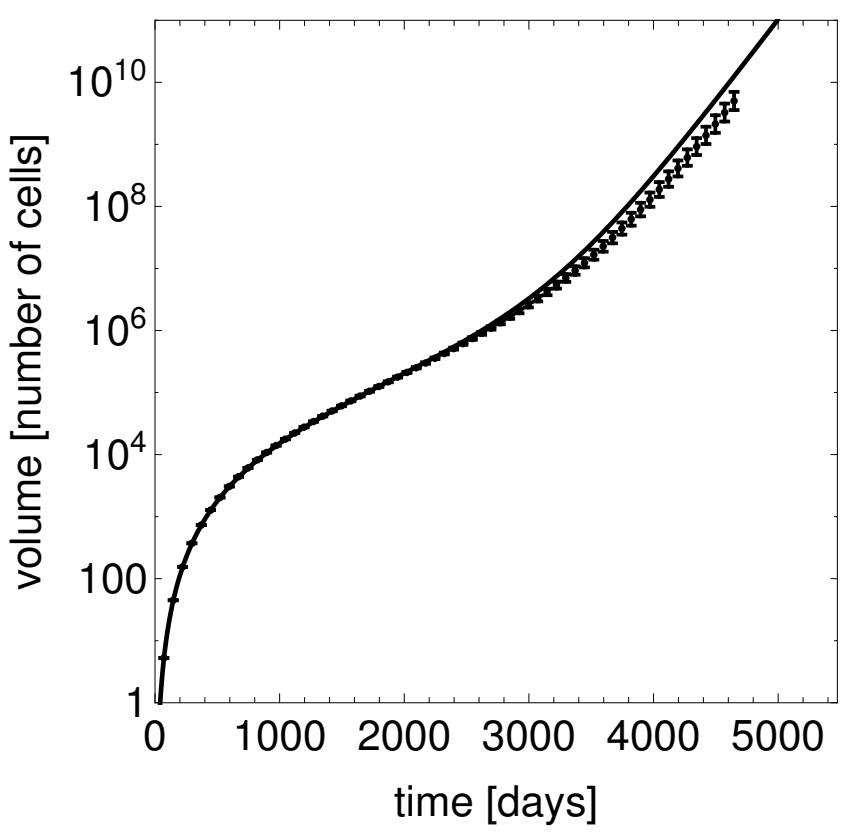
$$\int_0^\infty \phi_n(a) \mathrm{e}^{-G_n a} da = 1$$

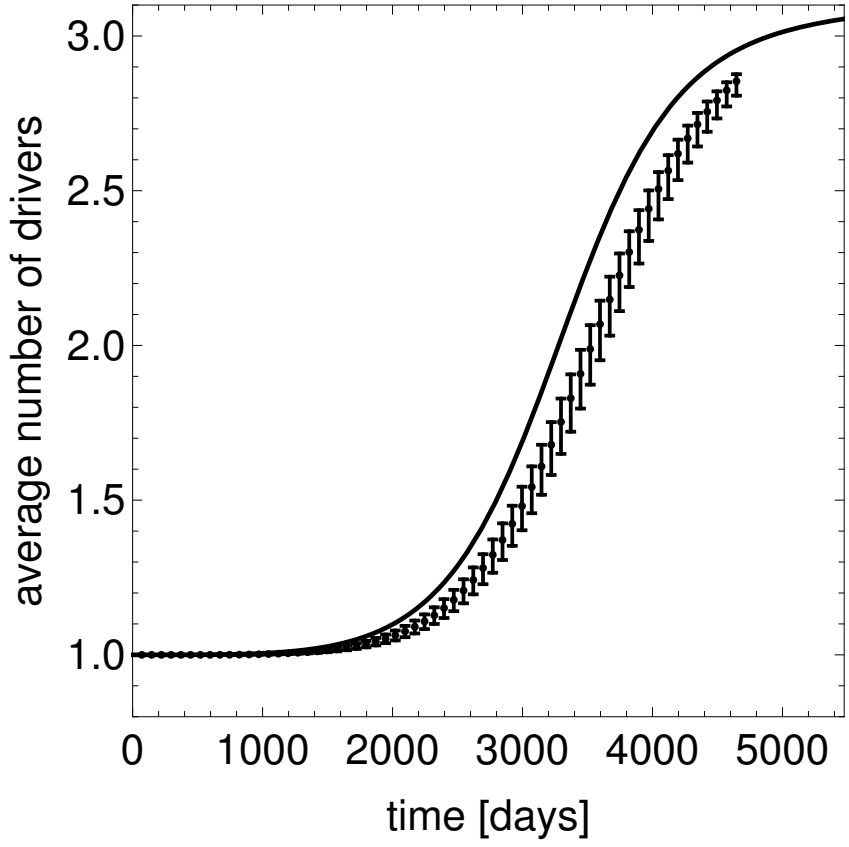
2. E.G. for $\phi_n = 4\pi M v_n^3 a^2$ and $r_n = \exp(-\mu a)$,

$$G_n = 2\pi^{1/3}\ M^{1/3} v_n$$

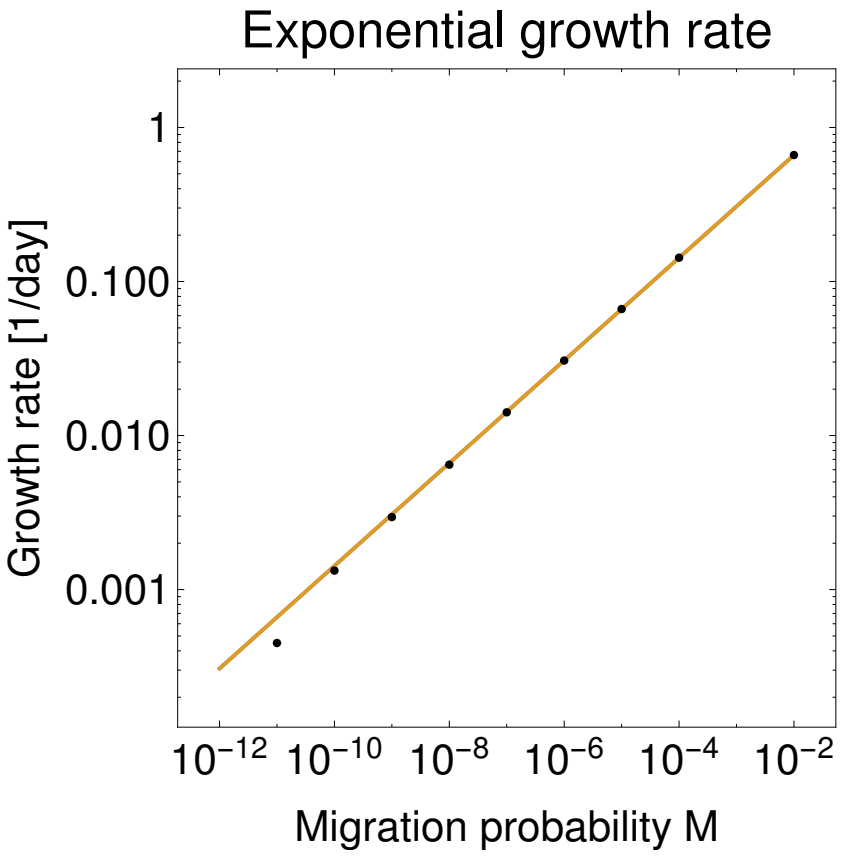
Chay Paterson, Martin A. Nowak, Bartlomiej Waclaw, "An exactly solvable, spatial model of mutation accumulation in cancer", *Scientific Reports* 2016

Comparison of models



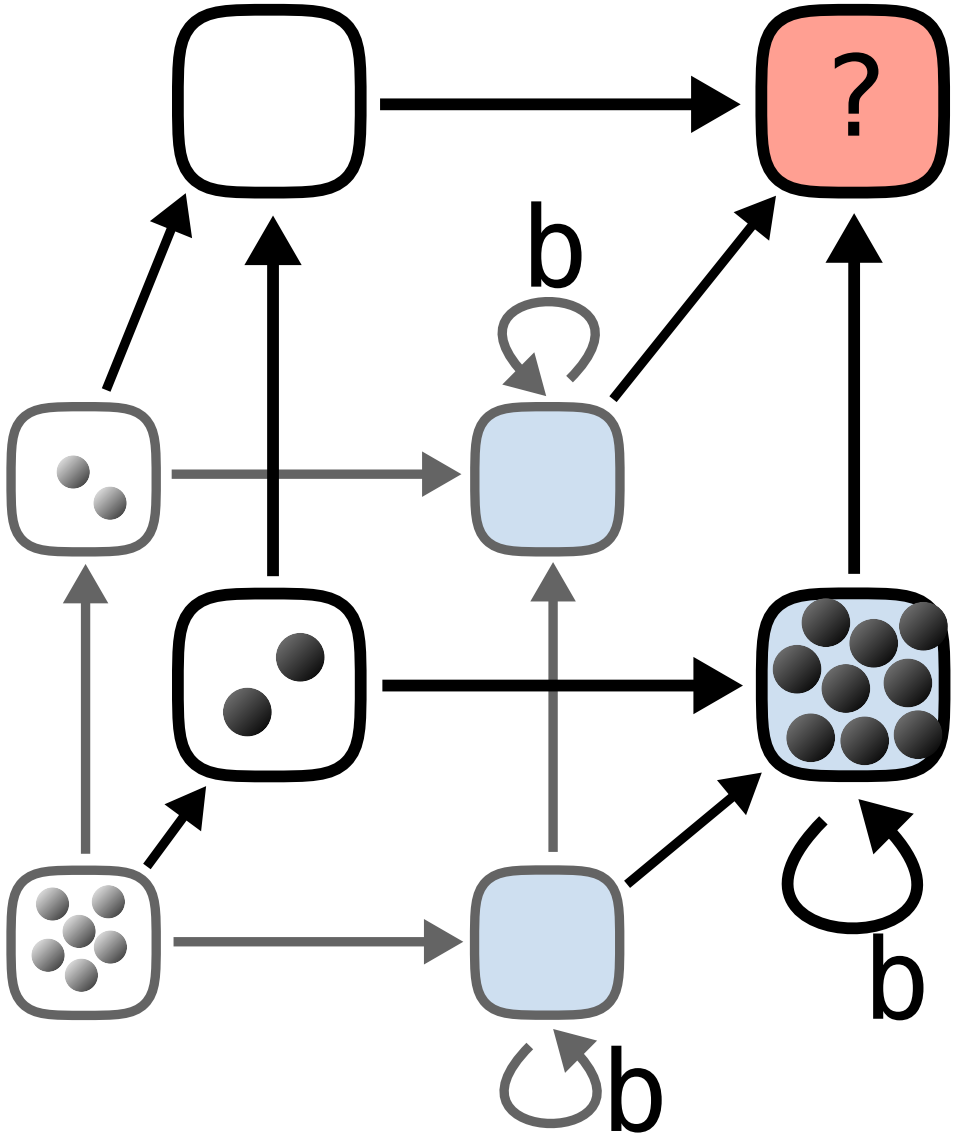


How could invasion affect evolution?

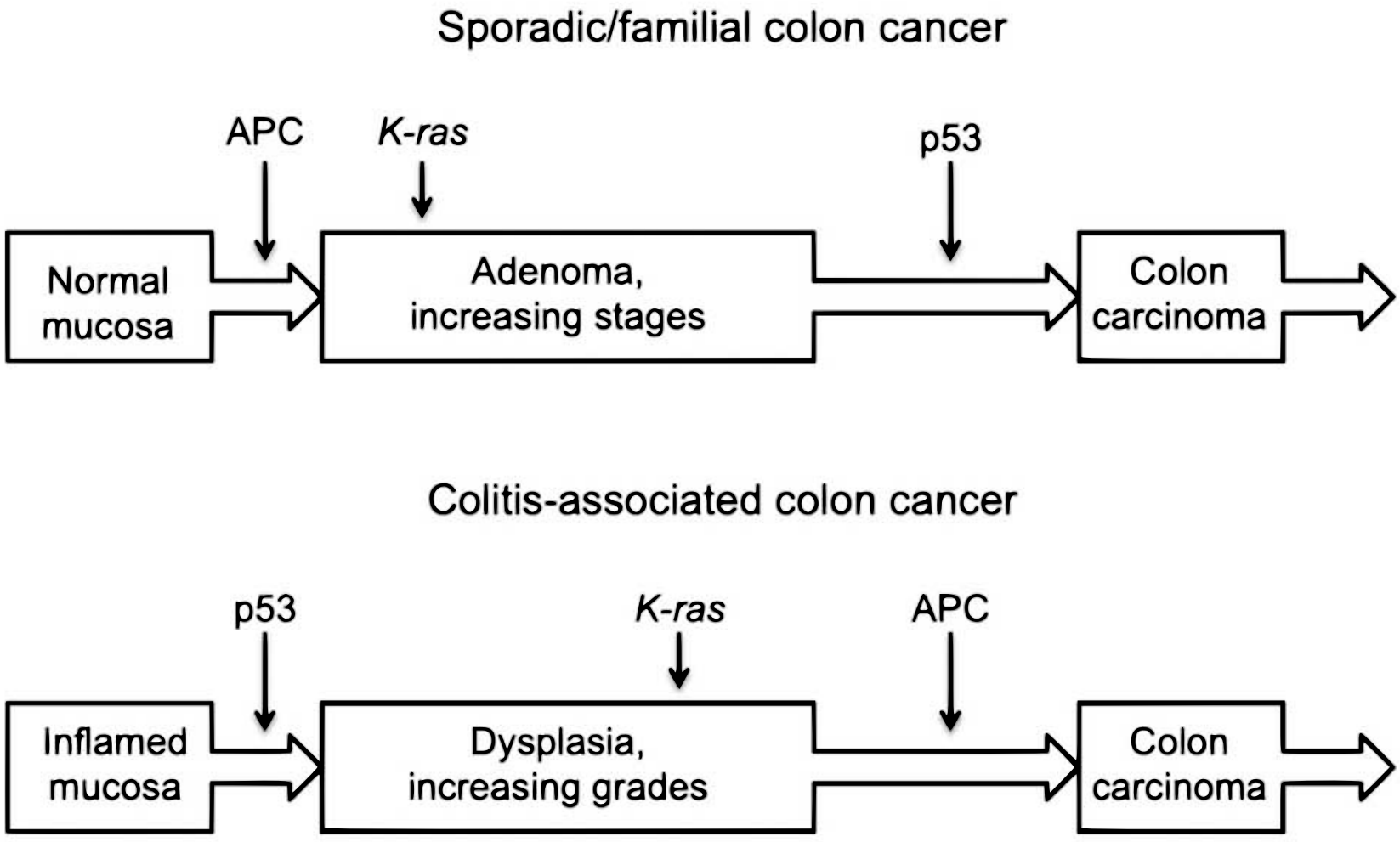


- Growth *exponential*
- Consistent with clinical doubling times
- PREDICTION: higher motility $\rightarrow$ higher *fitness*

What about branching/complex pathways?

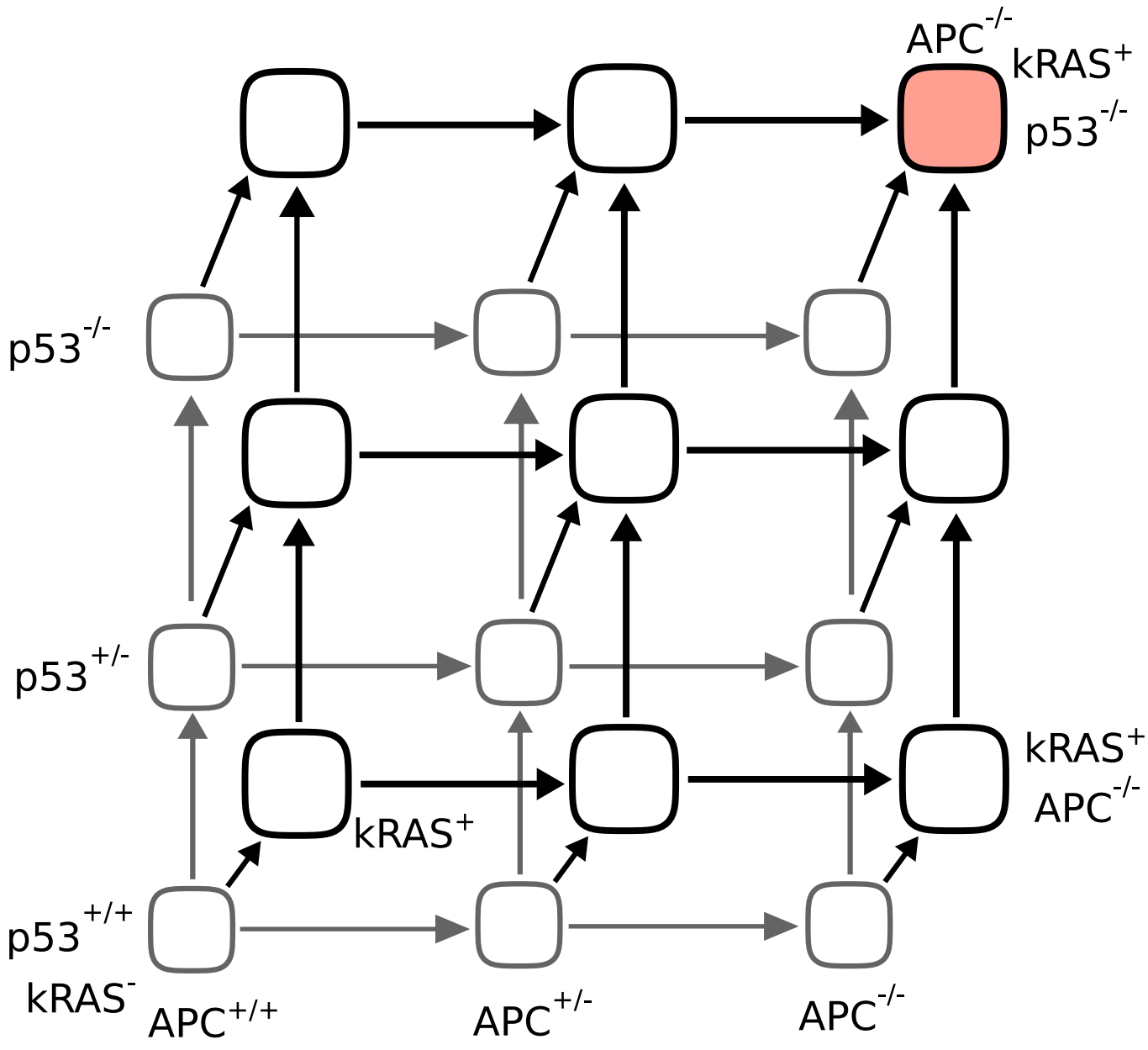


Colorectal adenocarcinoma



A. De Lerma Barbaro *et al.*, "Inflammatory cues acting on the adult intestinal stem cells and the early onset of cancer", International Journal of Oncology, 45(3) 2014.

Colorectal adenocarcinoma



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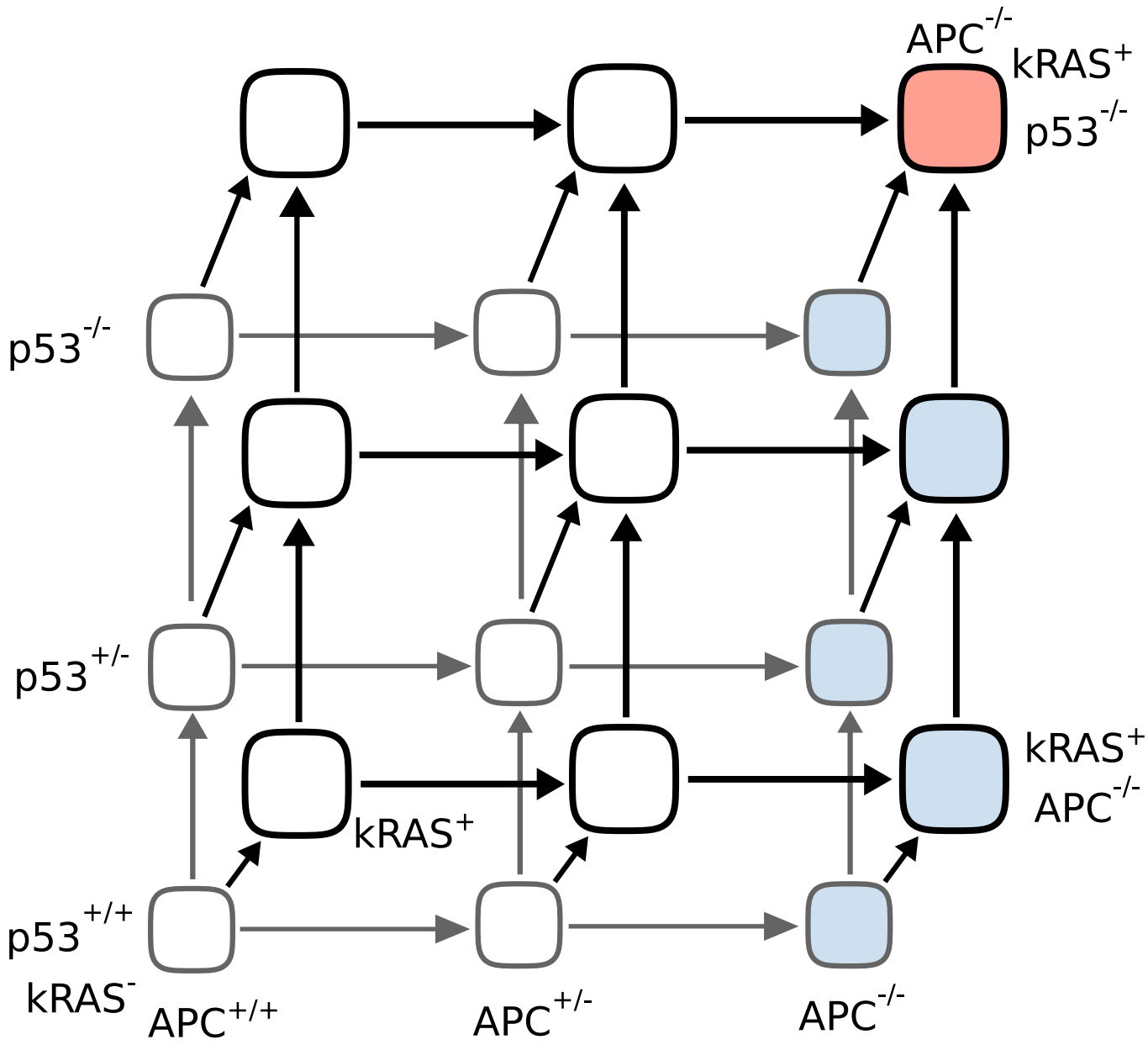

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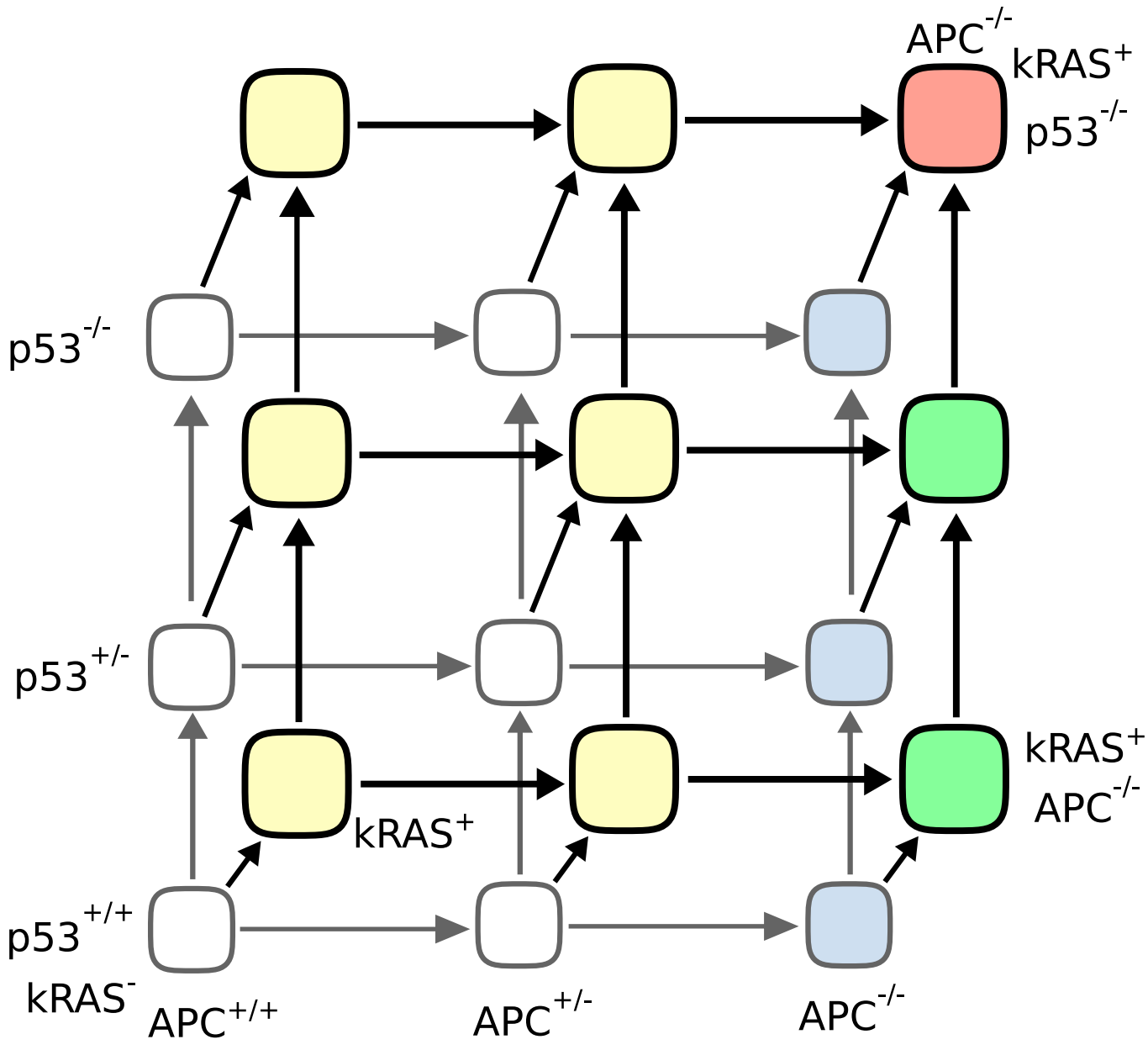


The speed of cancer evolution

In the limit that mutation is rare compared to growth, these are:

$$Pr(\text{cancer}) \approx \frac{1}{4} N r_{APC} r_{tp53} r_{kRAS} r_{LOH}^2 \cdot t^5 \tag{3}$$

$$Pr(\text{cancer}) \approx \frac{3}{2} N \frac{r_{APC} r_{tp53} r_{kRAS} r_{LOH}^2}{b_1^3} \cdot t^2 e^{b_1 t} \tag{4}$$

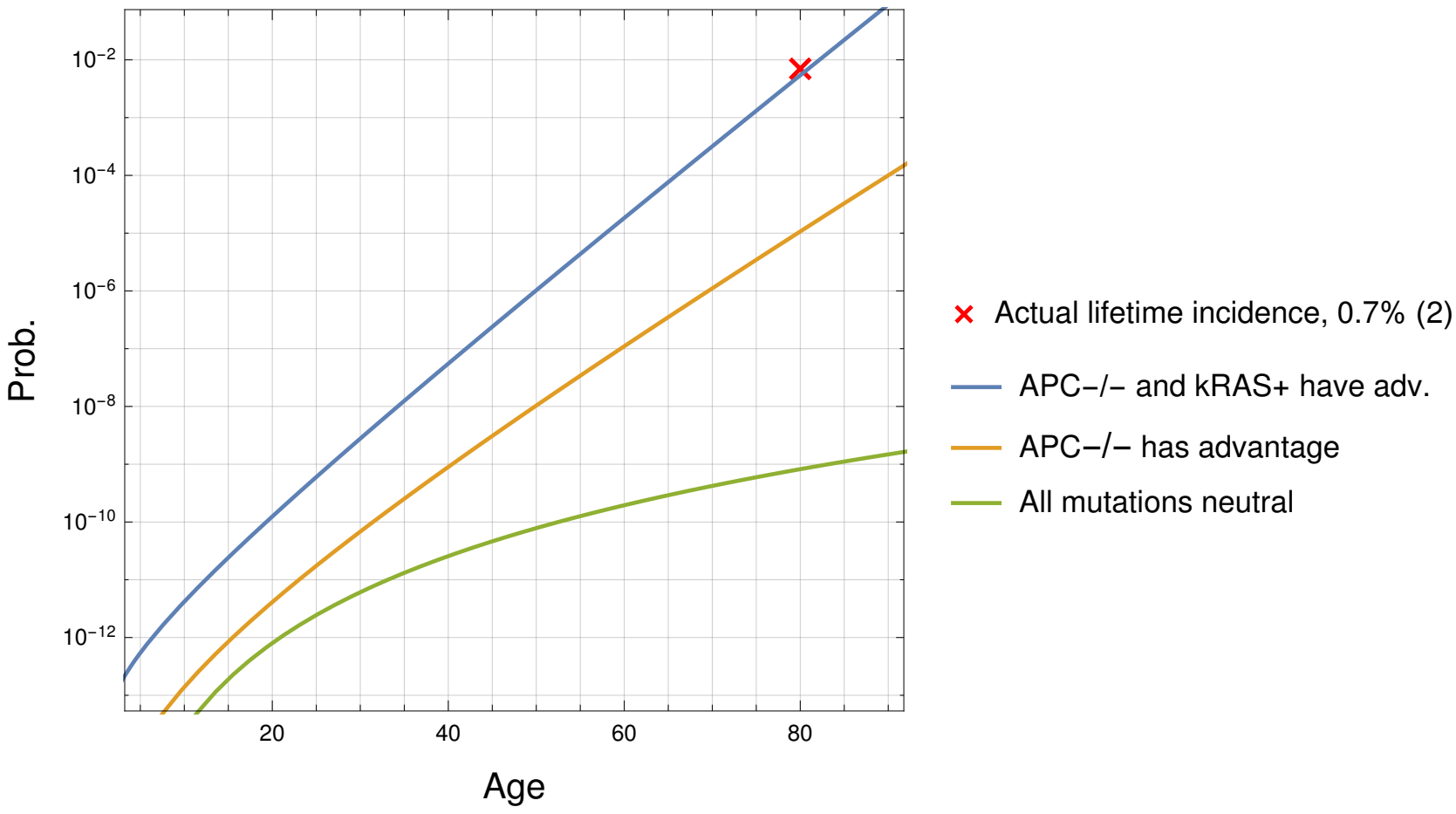
$$Pr(\text{cancer}) \approx c N r_{APC} r_{tp53} r_{kRAS} r_{LOH}^2 \tau^4 \cdot t\ e^{b_{12} t} \tag{5}$$

(compare Armitage & Doll 1954), where

$$\tau^4 = \frac{1}{b_{12}^3 (b_{12} - b_1)} + \frac{1}{b_{12}^3 (b_{12} - b_2)} + \frac{1}{b_{12}^2 (b_{12} - b_2)^2}$$

Ivana Bozic, Chay Paterson, Hans Clevers, "Mathematical model of colorectal cancer initiation", (pending submission), 2019

How does evolution affect lifetime risk?



Ivana Bozic, Chay Paterson, Hans Clevers, "Mathematical model of colorectal cancer initiation", (pending submission), 2019

(2) C. Tomasetti, B. Vogelstein, "Variation in cancer risk among tissues can be explained by the number of stem cell divisions", *Science* 347(78-81) (2015).

Conclusions

- Motility can "boost" fitness.
- Fitness differentials accelerate cancer evolution.
- Current experimental knowledge *can* explain incidence.
- All of our inputs are empirically measurable.
- The main output, incidence against age, is also measurable.

Open questions

Application to other cancers/disorders?

- Familial adenomatous polyposis?
- Bloom syndrome?

"Inverse problem": can different molecular subtypes be deduced from incidence data?