Metastasis formation models

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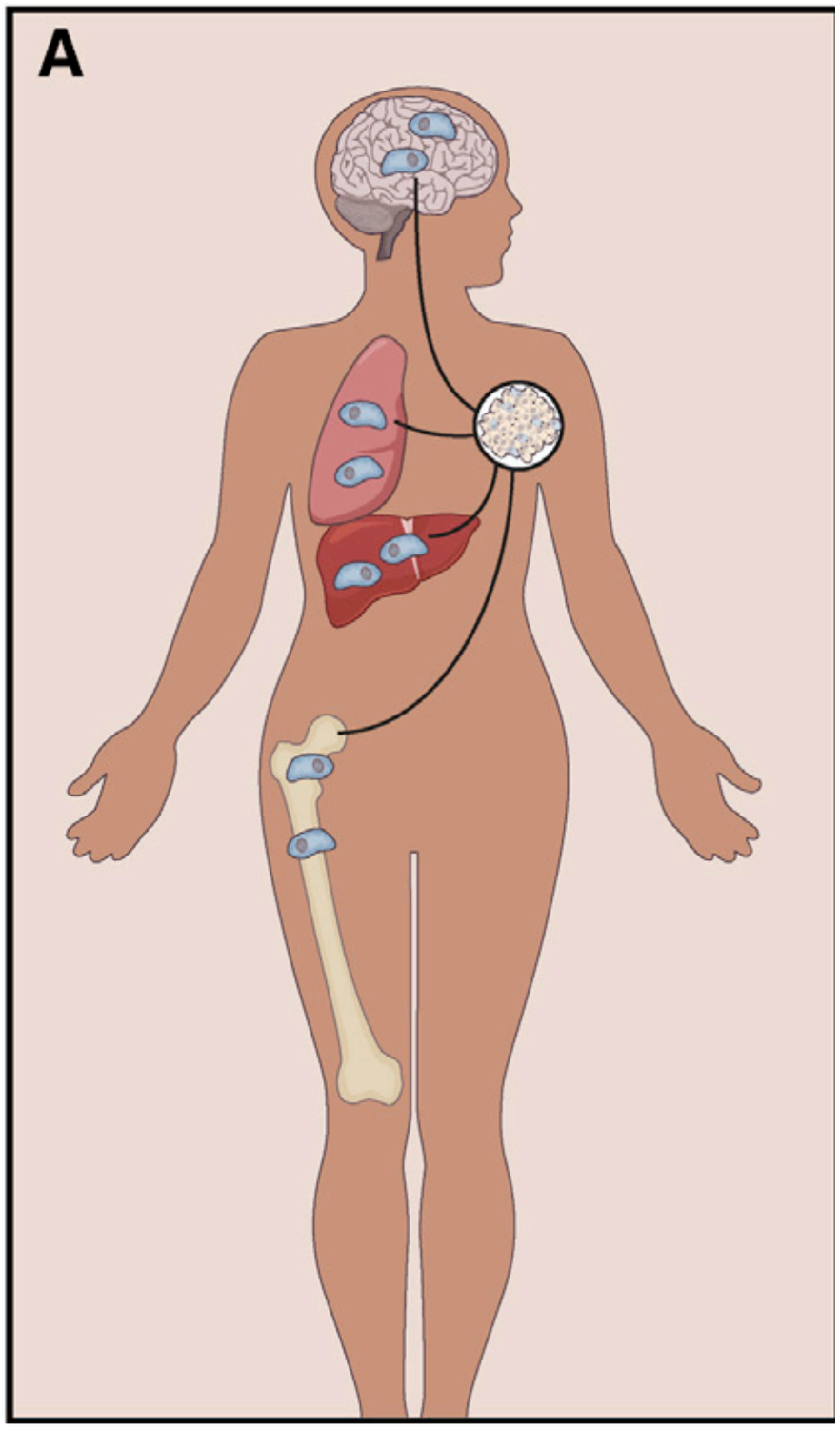
S. Avanzini, T. A: Cancer recurrence times from a branching process model
PLoS Comput Biol 15(11): e1007423.

X. Brunet Guasch, M. Nicholson + Lab of K. Naxerova, D. Cheek, D. Andel:
in preparation

3 approaches



I: backward in time: phylogenetic

II: forward in time: evolutionary model

III: combination

I: backward in time: phylogenetic

LETTER

doi:10.1038/nature09515

Distant metastasis occurs late during the genetic evolution of pancreatic cancer

Shinichi Yachida, ..., Christine A. Iacobuzio-Donahue[1]

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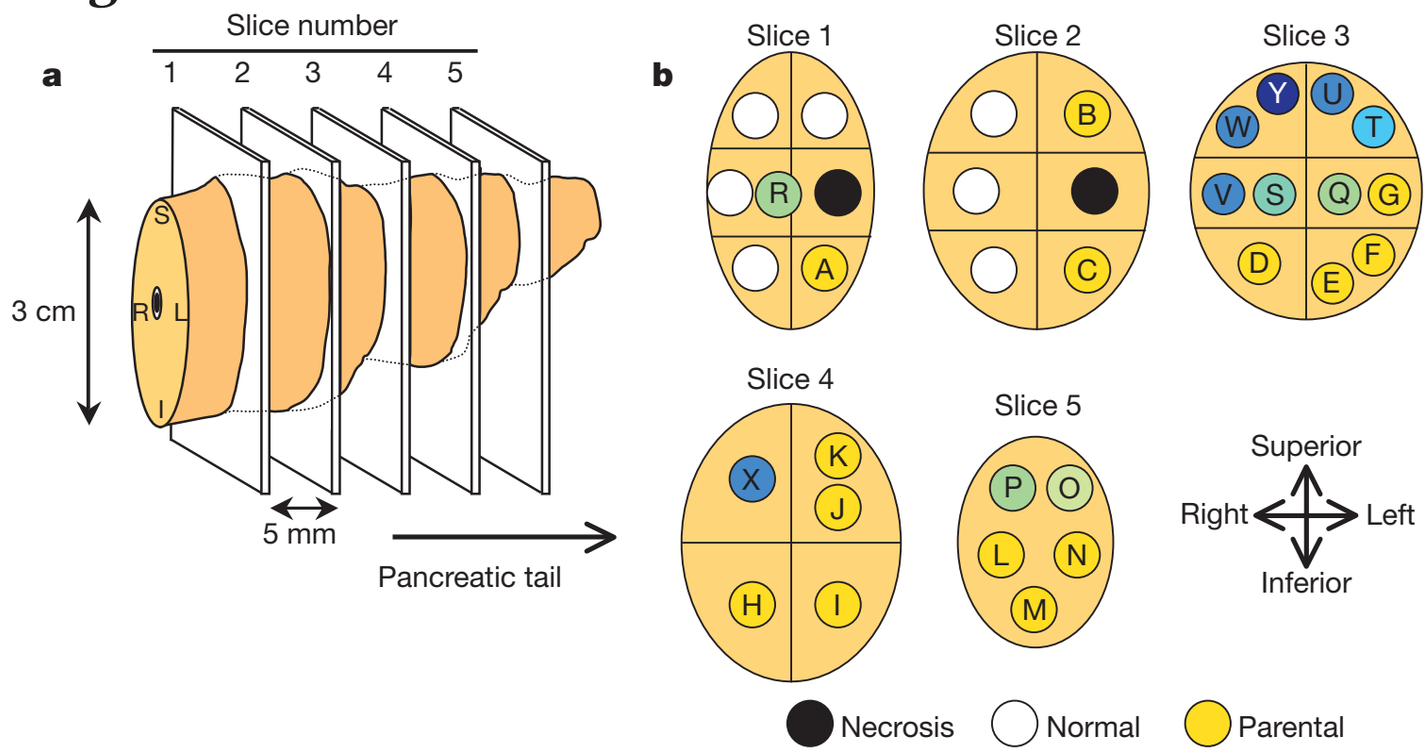
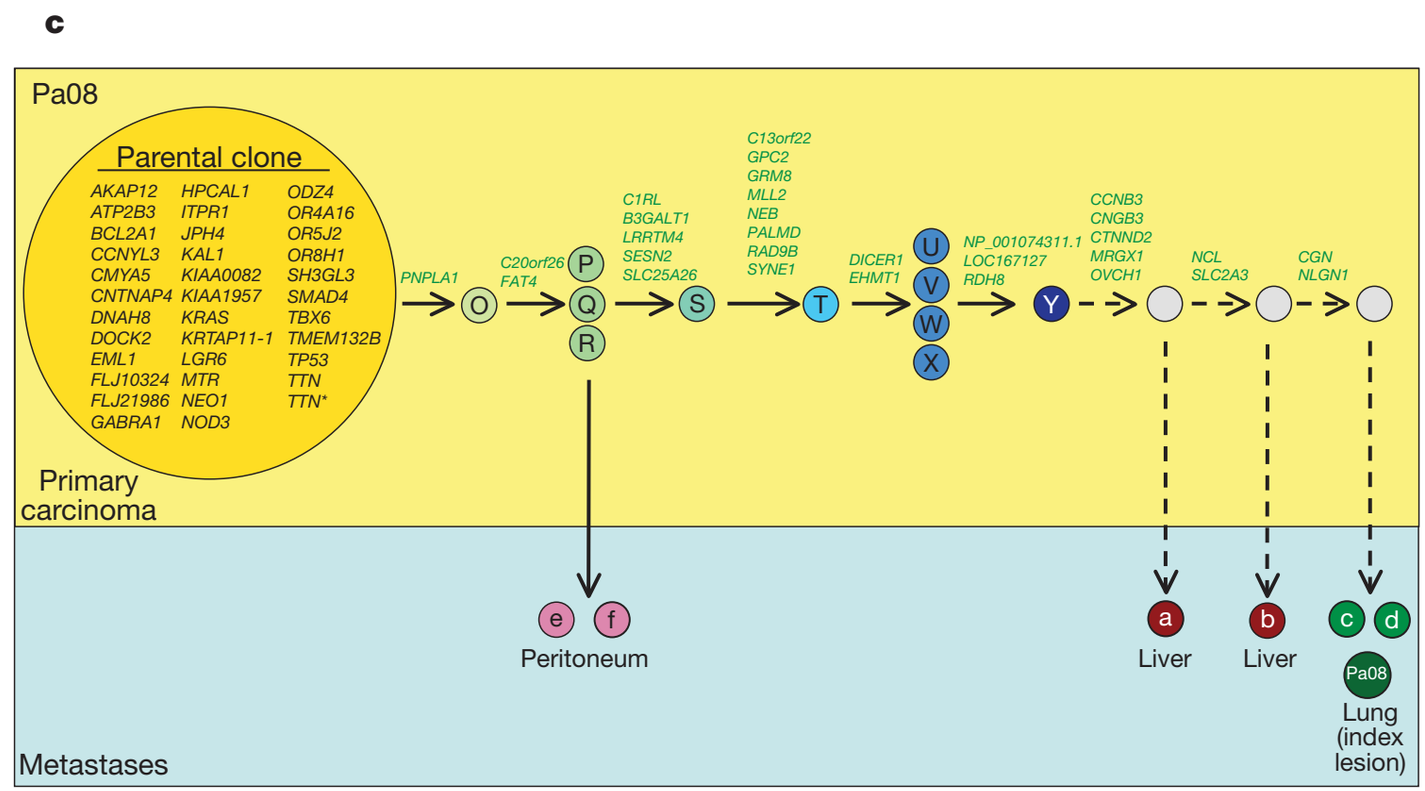
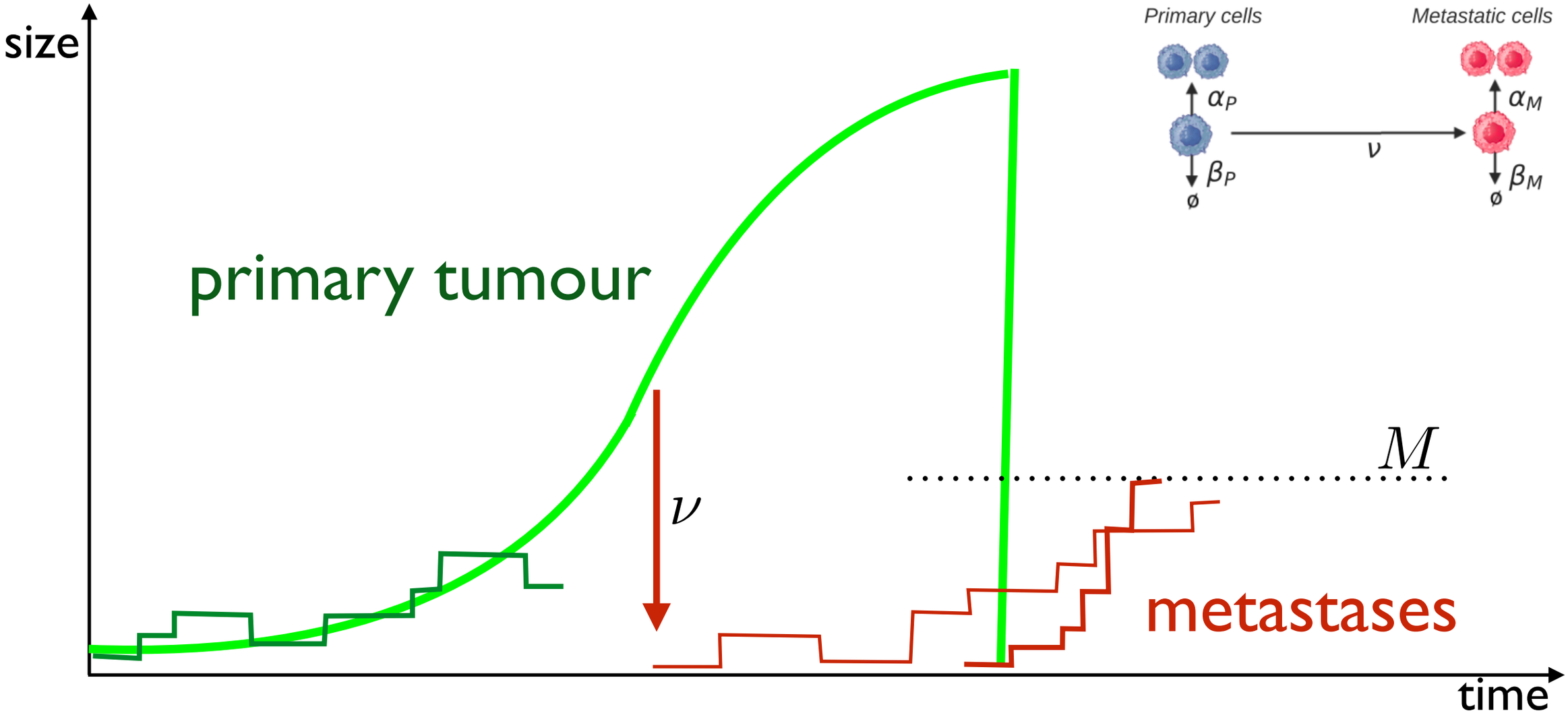




Avanzini, A, PLoS C B 15(11): e1007423

II: forward in time: evolutionary model

when do metastases become detectable?



Luria SE, Delbruck M. Mutations of bacteria from virus sensitivity to virus resistance. Genetics. 1943; 48(6):491–511

LEA, D. E. and COULSON, C. A. (1949). The distribution of the numbers of mutants in bacterial populations. J. Genet. 49 264–285.

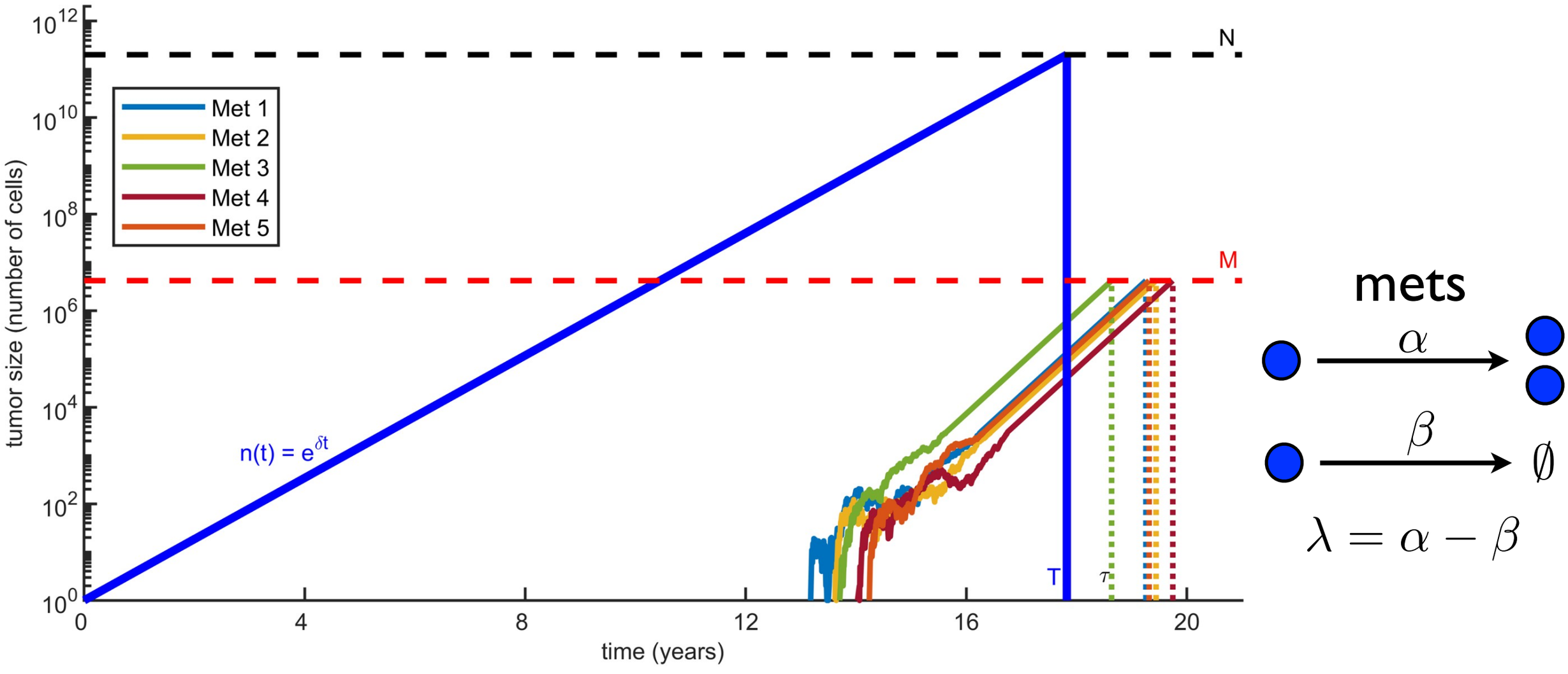
KENDALL, D. G. (1960). Birth-and-death processes, and the theory of carcinogenesis. Biometrika 47 13–21. MR0112761

Haeno H, Michor F. The evolution of tumor metastases during clonal expansion. Journal of Theoretical Biology. 2010; 263(1):30–44.

TA, PL Krapivsky, Journal of Statistical Mechanics: Theory and Experiment 2011 (08), P08018

D Cheek, TA, Stochastic Processes and their Applications 130 (11), 6580-6624

e.g. exponential primary



$$K_t = S_t + M_t$$

parameter estimates

Table 1. Typical ranges of volume doubling times for the primary tumor (DT_{pt}) and metastasis (DT_m), tumor potential doubling time (T_{pot}) and tumor diameter at resection (d_{pt}) for breast, colorectal, headneck, lung and prostate cancer.

Cancer type	Parameter	Typical range	Estimate	References
Breast	DT_{pt} (days)	103 – 353	210	[47–52]
	DT_m (days)	85 – 199	105	[53, 54]
	T_{pot} (days)	8 – 35	15	[44, 55]
	d_{pt} (cm)	1.4 – 3	2.5	[56–58]
Colorectal	DT_{pt} (days)	130 – 438	175	[59–61]
	DT_m (days)	45 – 155	105	[54, 62–64]
	T_{pot} (days)	3 – 4	4	[55, 65]
	d_{pt} (cm)	3.5 – 5.1	4.5	[59, 61, 66, 67]
Headneck	DT_{pt} (days)	15 – 256	84	[68, 69]
	DT_m (days)	9.5 – 320	56	[70, 71]
	T_{pot} (days)	1 – 14	4	[65, 72]
	d_{pt} (cm)	1.3 – 4	2.8	[73, 74]
Lung	DT_{pt} (days)	22 – 269	168	[54, 75–78]
	DT_m (days)	32 – 98	56	[42, 79]
	T_{pot} (days)	2 – 17.5	2.5	[75, 80]
	d_{pt} (cm)	1.7 – 4.1	2	[77, 81, 82]
Prostate	DT_{pt} (days)	36 – 1080	392	[83–85]
	DT_m (days)	29 – 213	98	[85, 86]
	T_{pot} (days)	15.2 – 97.8	34	[84, 87]
	d_{pt} (cm)	0.1 – 2.9	1.2	[88, 89]

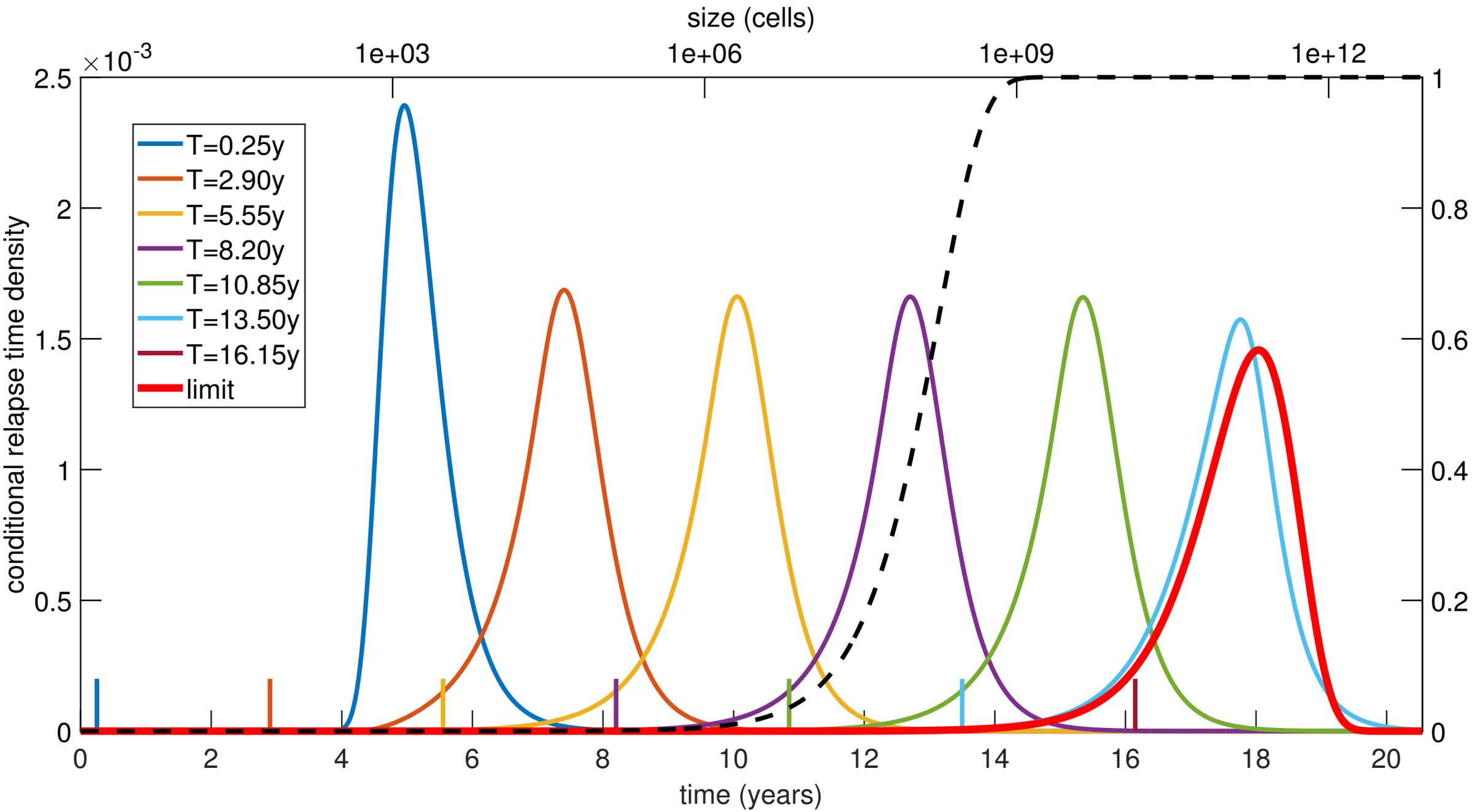
Table 2. Parameter estimates for the primary net growth rate δ, the metastatic net growth rate λ, the initiation rate ν, the extinction probability q, the primary tumor size at resection N and the minimal detectable size M.

	Breast	Colorectal	Headneck	Lung	Prostate
δ (cells/day)	0.0033	0.0040	0.0083	0.0041	0.0018
λ (cells/day)	0.0066	0.0066	0.0124	0.0124	0.0071
ν (cells/day)	1.87×10^{-10}	8.42×10^{-10}	9.36×10^{-10}	7.49×10^{-10}	4.13×10^{-11}
q	0.9010	0.9736	0.9505	0.9691	0.7595
N (cells)	8.18×10^{9}	4.77×10^{10}	1.15×10^{10}	4.19×10^{9}	9.05×10^{8}
M (cells)	4.19×10^{6}	4.19×10^{6}	4.19×10^{6}	4.19×10^{6}	4.19×10^{6}

(init rate from first met expected at diam 0.5cm)

relapse times for different resection times

(conditioned on at least one met by resection)



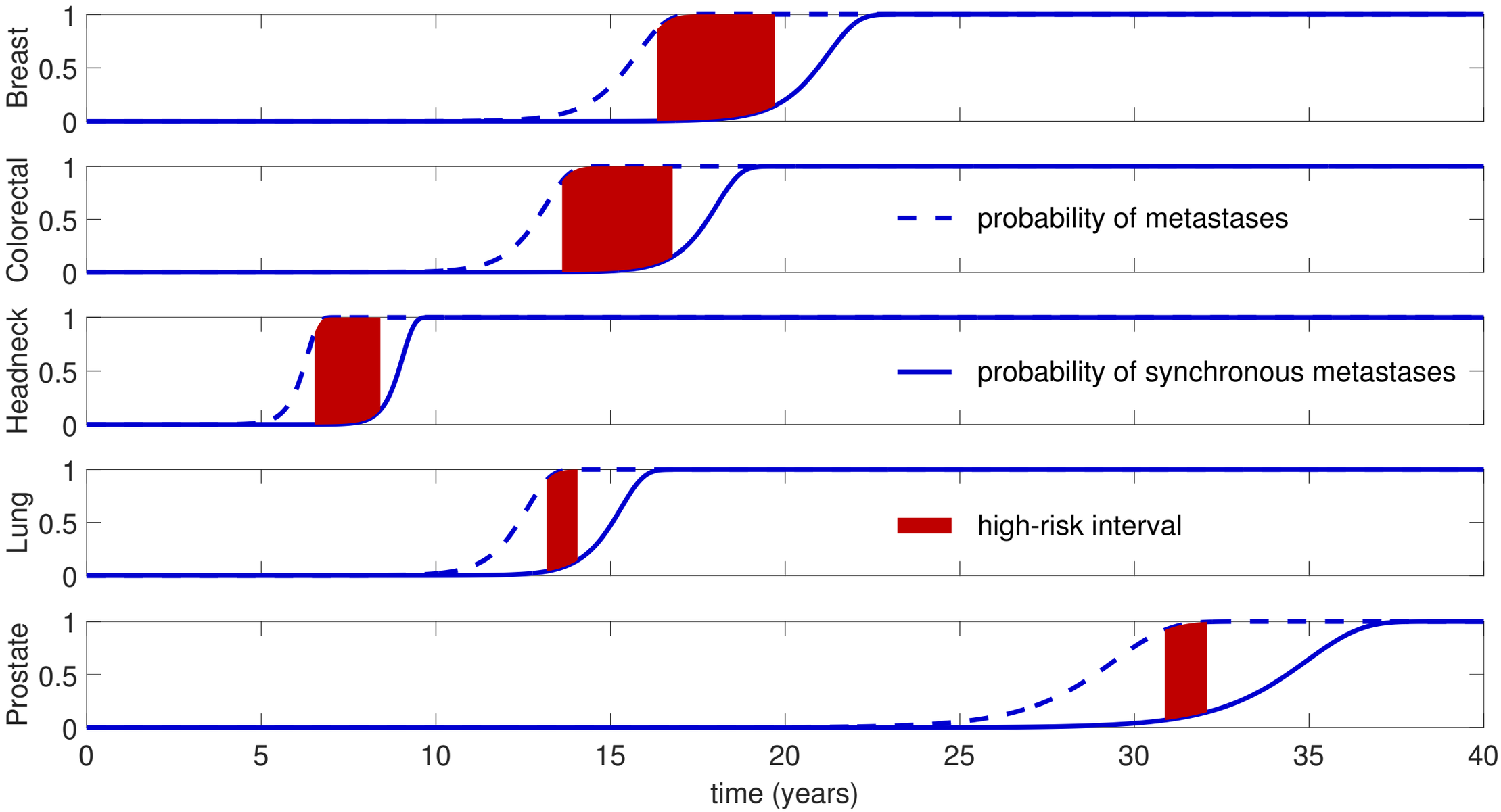
Gumbel of max at beginning; Gumbel of mins at end

results

Cancer type	**Output**	**Range from clinical data**	**Theoretical prediction**	**Reference**
Breast	$P(S_T \geq 1)$ (%)	$5 - 10$	6.13	[5, 15, 124]
	$\mathrm{E}[\tau - T \mid U_T]$ (days)	$590 - 1022$	725	[67, 36, 87]
Colorectal	$P(S_T \geq 1)$ (%)	$15 - 25$	20.17	[63, 89, 79, 32, 53, 124]
	$\mathrm{E}[\tau - T \mid U_T]$ (days)	$353 - 760$	356	[52, 86, 32, 103, 53]
Headneck	$P(S_T \geq 1)$ (%)	$1 - 16.8$	1.65	[34, 57]
	$\mathrm{E}[\tau - T \mid U_T]$ (days)	$219 - 623$	435	[77, 31, 118]
Lung	$P(S_T \geq 1)$ (%)	$30 - 55.39$	33.96	[124, 111]
	$\mathrm{E}[\tau - T \mid U_T]$ (days)	$210 - 602$	249	[2, 54, 33]
Prostate	$P(S_T \geq 1)$ (%)	$10 - 34$	13.53	[70, 61, 4]
	$\mathrm{E}[\tau - T \mid U_T]$ (days)	$730 - 1131$	969	[14, 108]

$$U_T = \{M_T \geq 1, S_T = 0\}$$

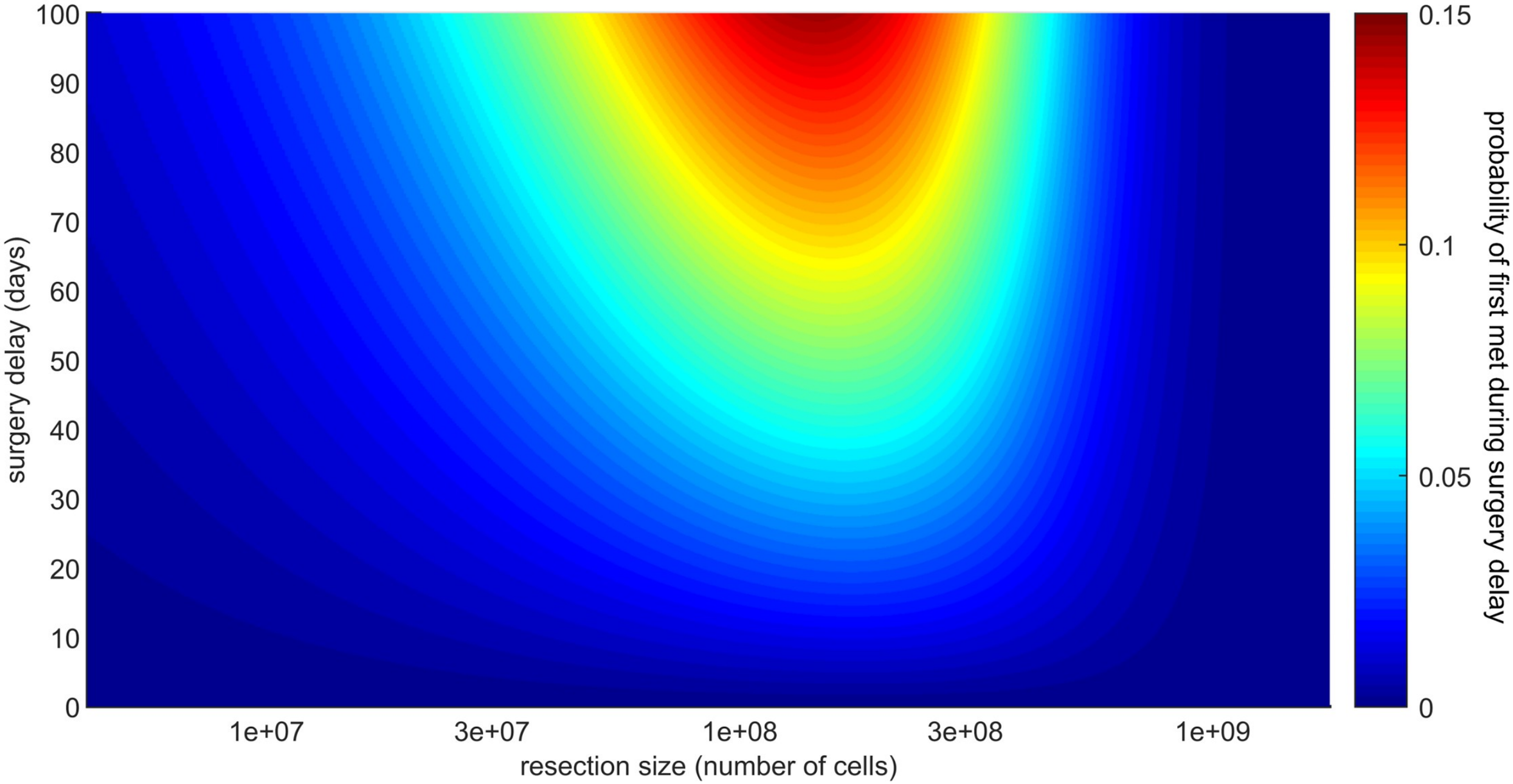
undetectable metastasis window (exponential growth)



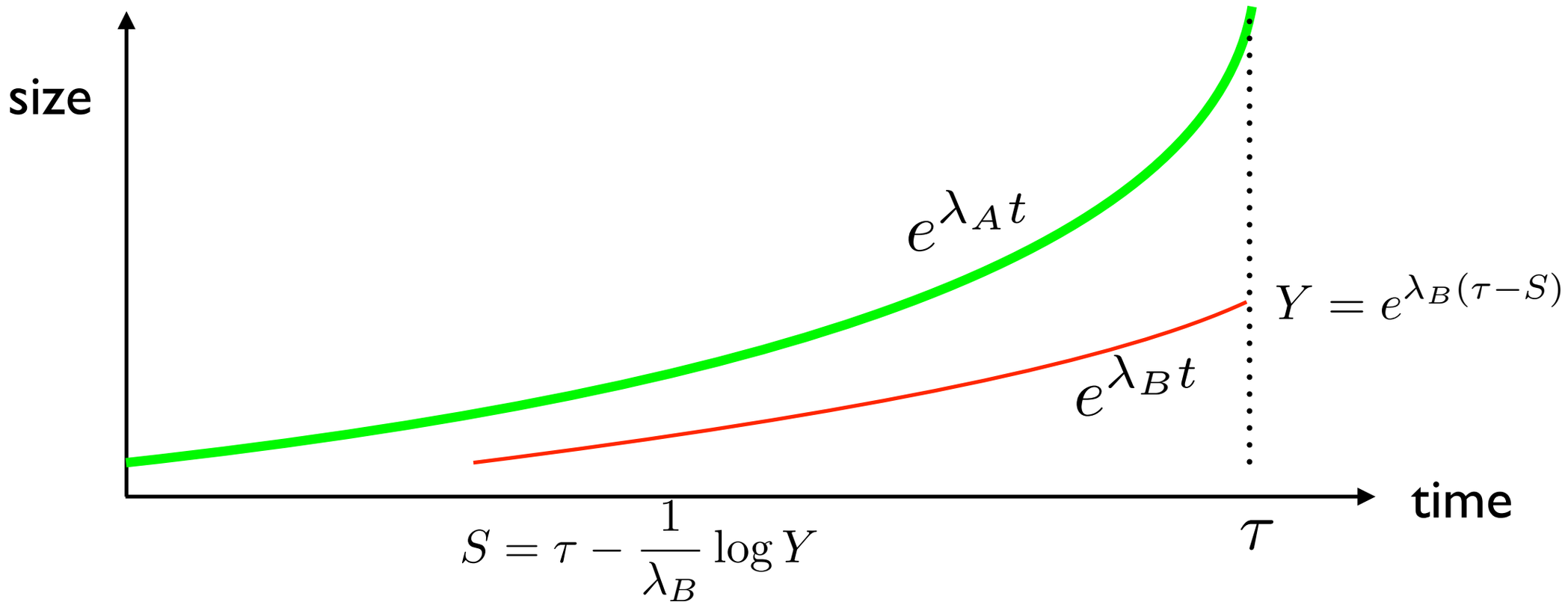
$$\mathrm{P}(U_T) \;=\; \mathrm{P}(M_T \geq 1, S_T = 0) = \;\mathrm{P}(M_T \geq 1)\,\mathrm{P}(S_T = 0)$$

$$= e^{-b_T} - e^{-a_T} = \;\mathrm{P}(K_T \geq 1) - \;\mathrm{P}(S_T \geq 1)$$

effect of delay in treatment



heuristic for met size



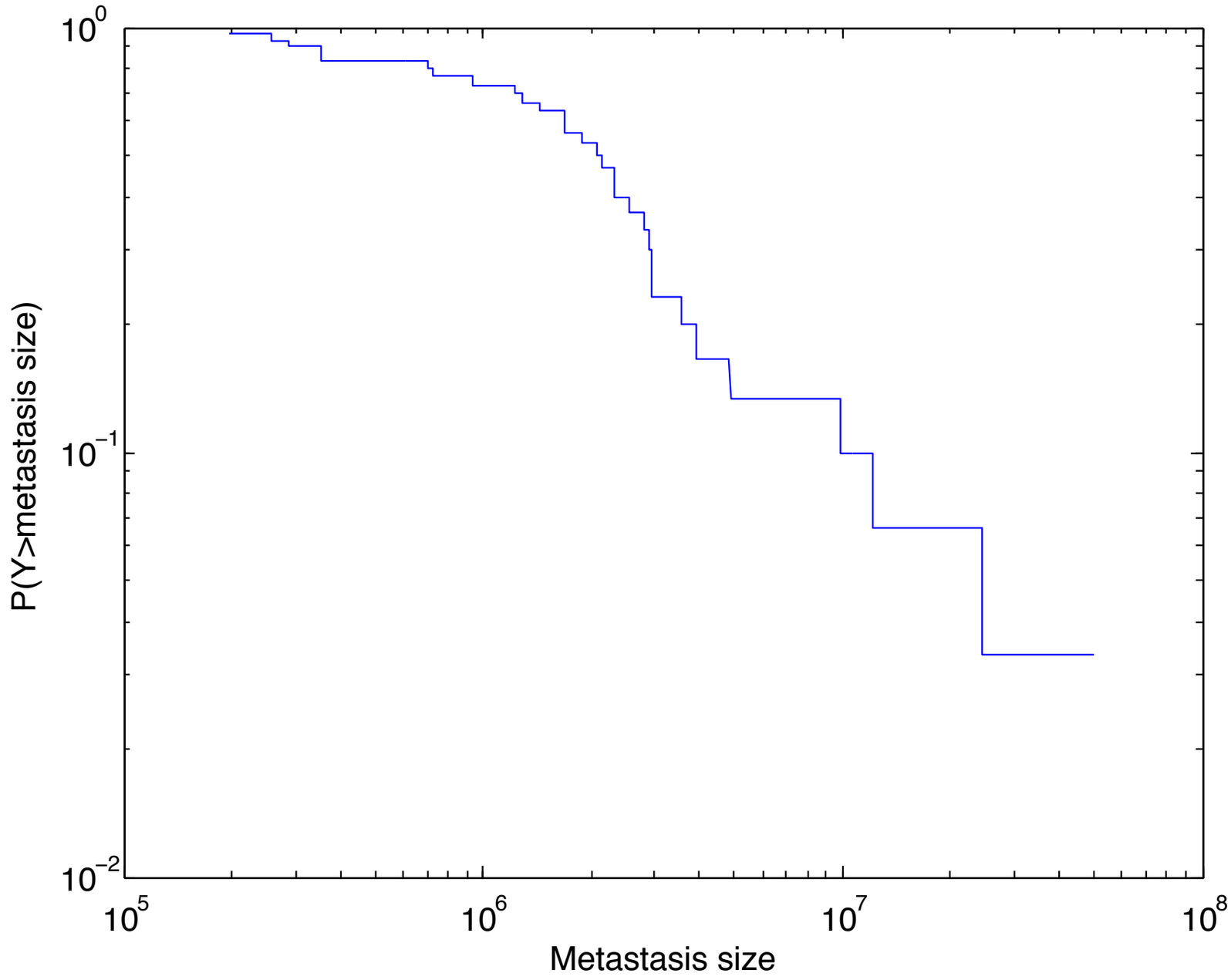
$$P(S < s) = \frac{\int_0^s \nu e^{\lambda_A t} dt}{\int_0^\tau \nu e^{\lambda_A t} dt} = e^{-\lambda_A(\tau - s)}$$

$$P(Y > y) = P(S < \tau - \frac{1}{\lambda_B}\log y) = e^{-\lambda_A(\tau - \tau + \frac{1}{\lambda_B}\log y)} = y^{-\lambda_A/\lambda_B}, \quad y \geq 1$$

neutral mets $\quad P(Y > y) = y^{-1}, \quad f_Y(y) = y^{-2}, \quad EY = \infty$

heuristic for met size

one patient with 30 mets, data from Bozic '13, Nicholson, A '15



III: combine evolutionary model + phylogenetic

two problems:

do cancer cells need ability to metastasise?

why mets are more diverse for certain cancer types?

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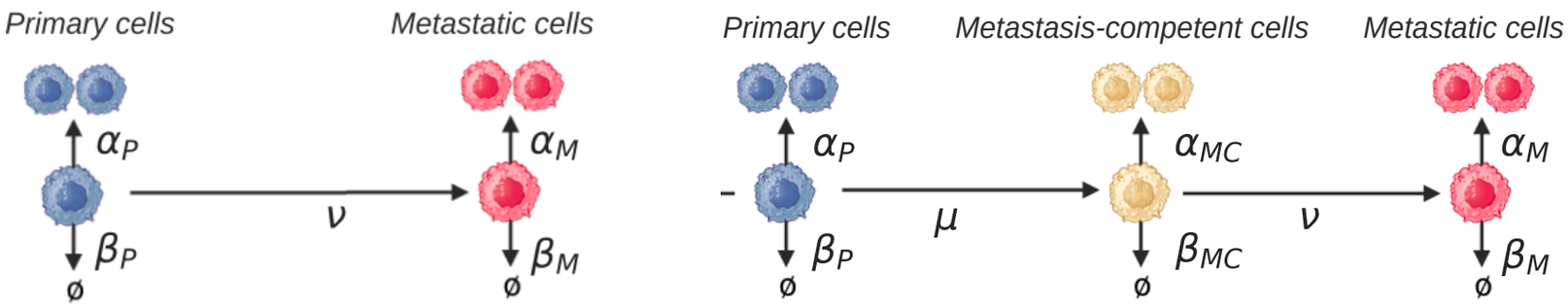
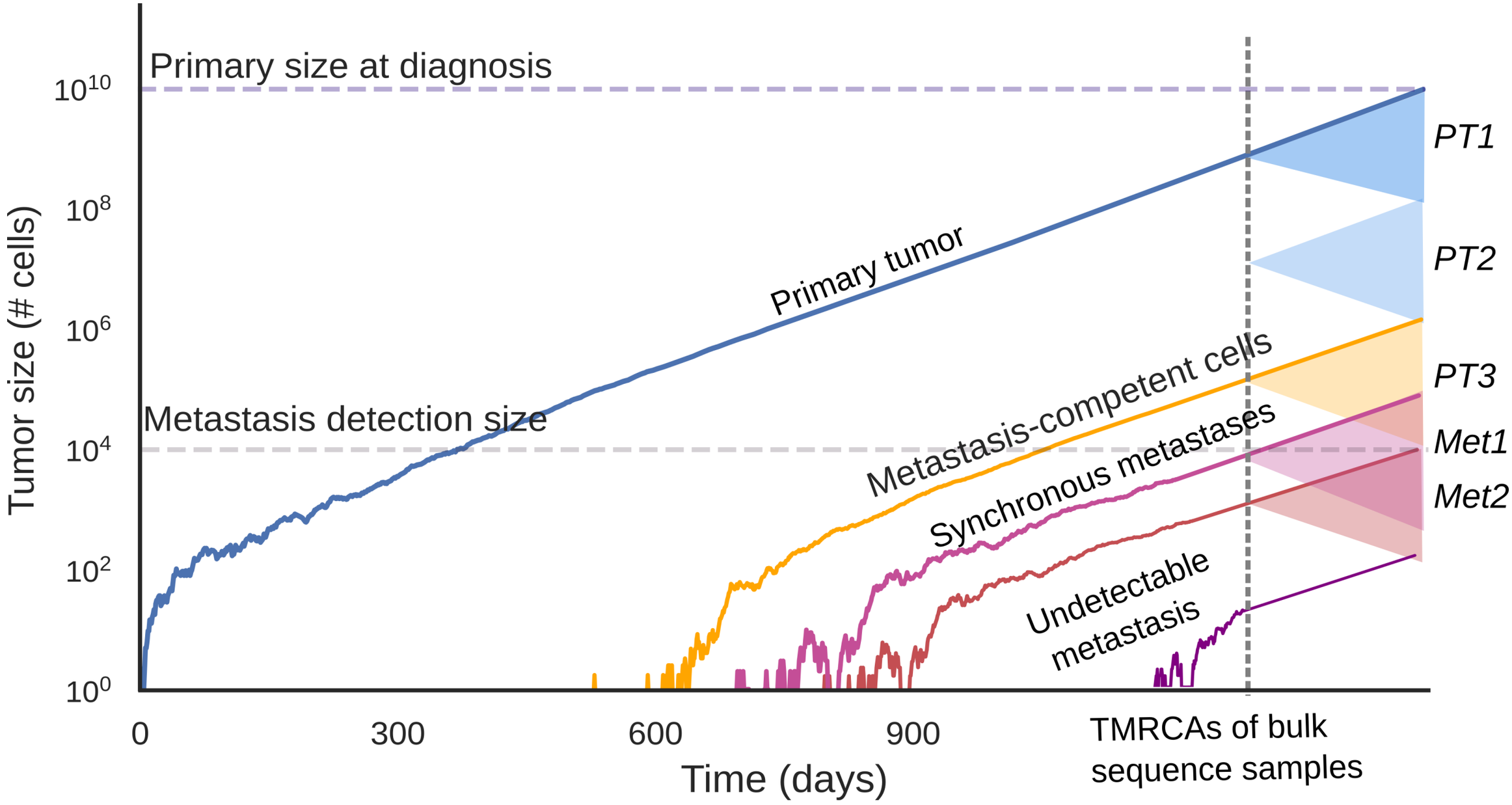
add "competence"



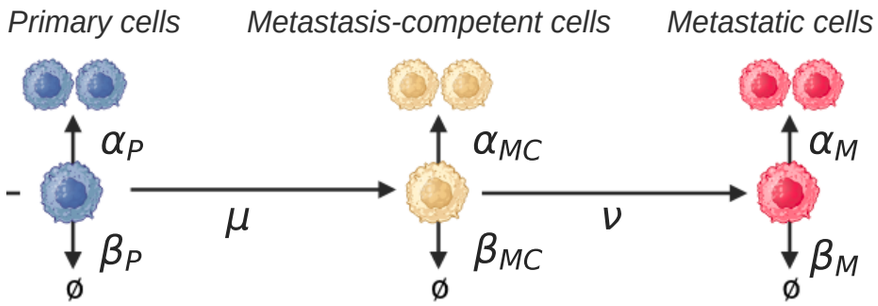
Haeno H, Michor F. The evolution of tumor metastases during clonal expansion. Journal of Theoretical Biology. 2010; 263(1):30–44.

simulation of populations, + sampling



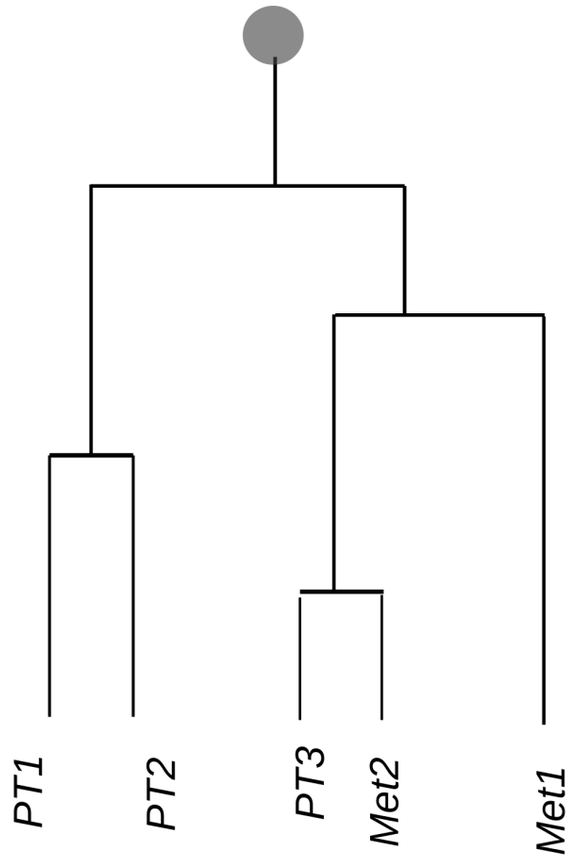
2 and 3 type models give the same result for sizes and timing.

but 3-type model can explain met diversity



Quartet Diversity Score = 0

Quartet Diversity Score



MMPP quartets: *M1M2P1P3 , M1M2P3P2 , M1M2P1P2*

Evidence
met diversty:

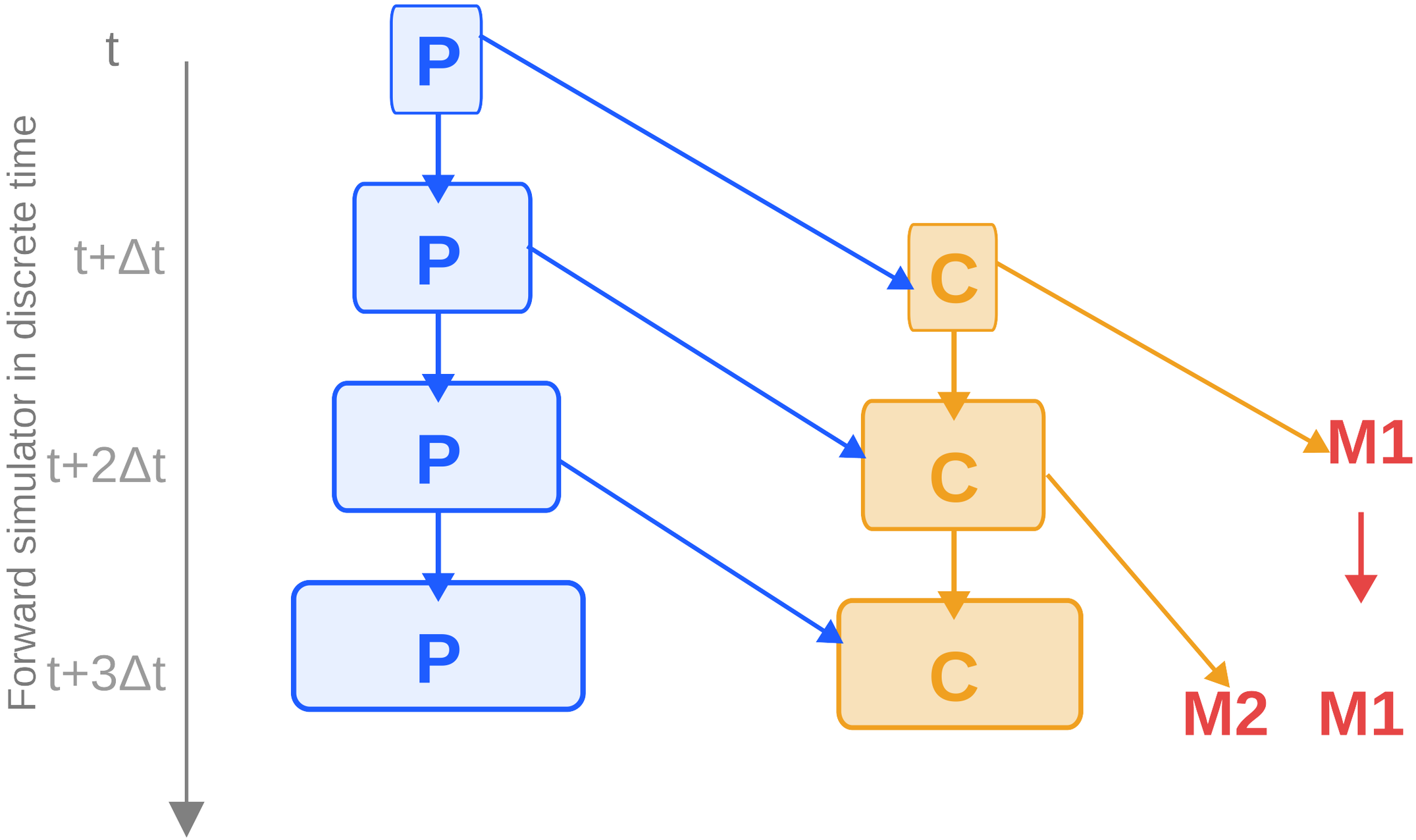


Quartet Diversity Score = 2/3

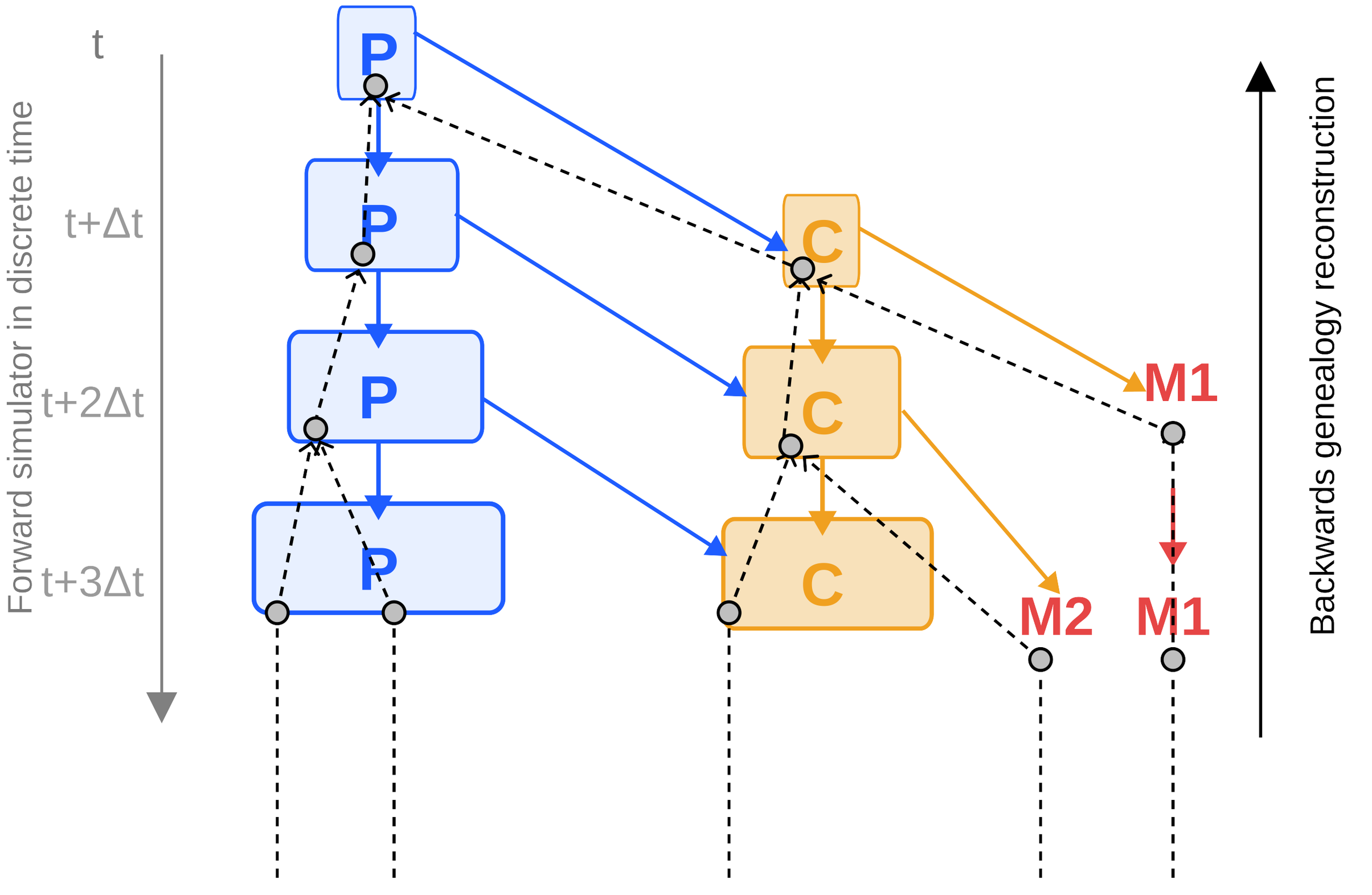
for random coalescent of
PT1, PT2, Met1, Met2

$$\mathbb{E}(QDS) = 1 - \left(\frac{1}{6} + \frac{1}{6}\frac{1}{3}\right) = \frac{7}{9}$$

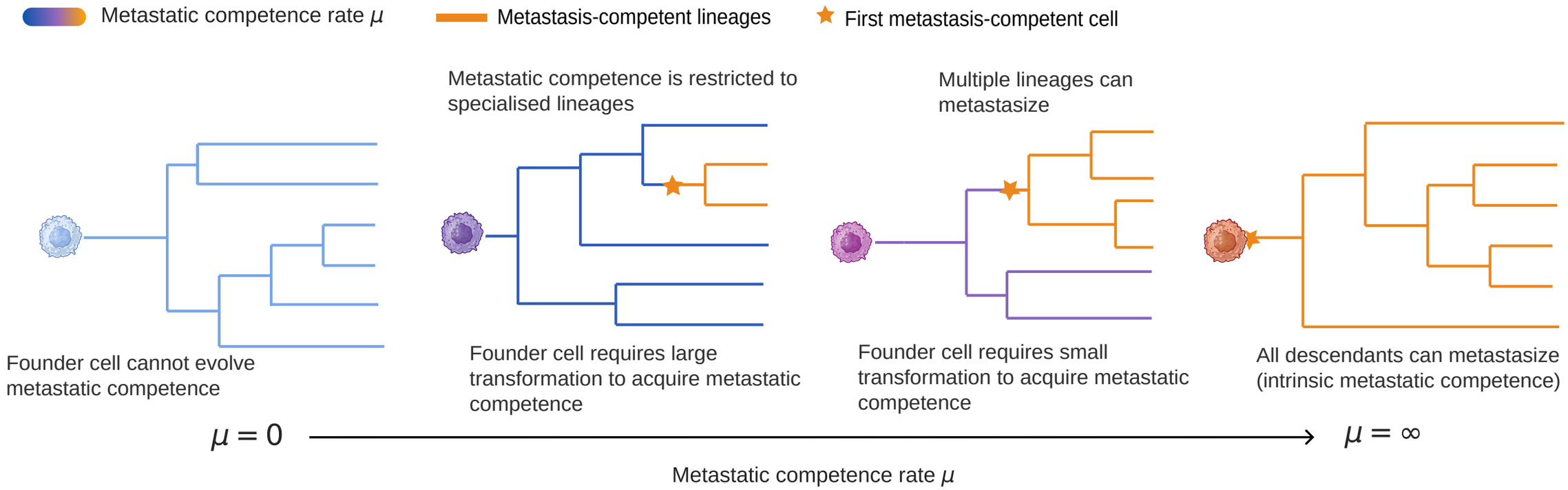
how to simulate efficiently?



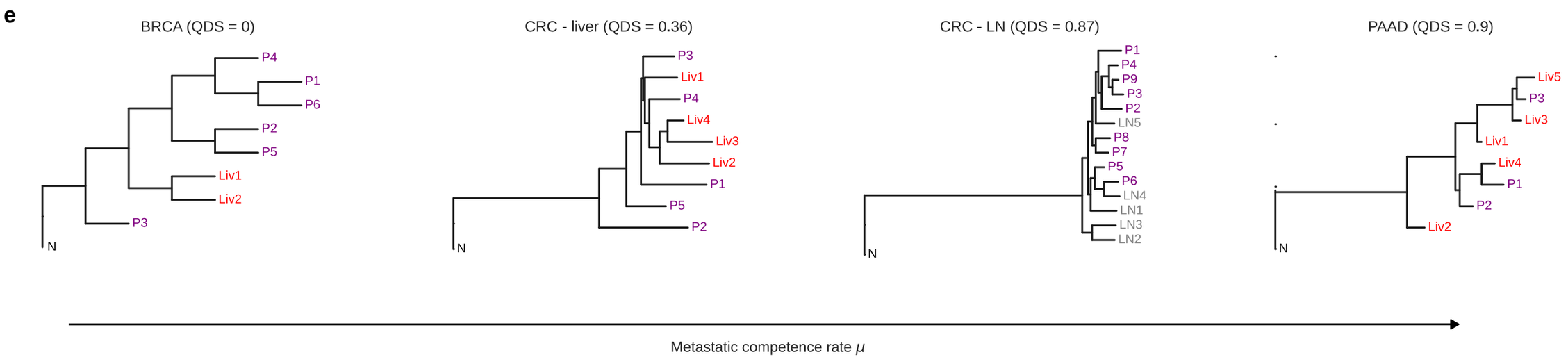
how to simulate efficiently?



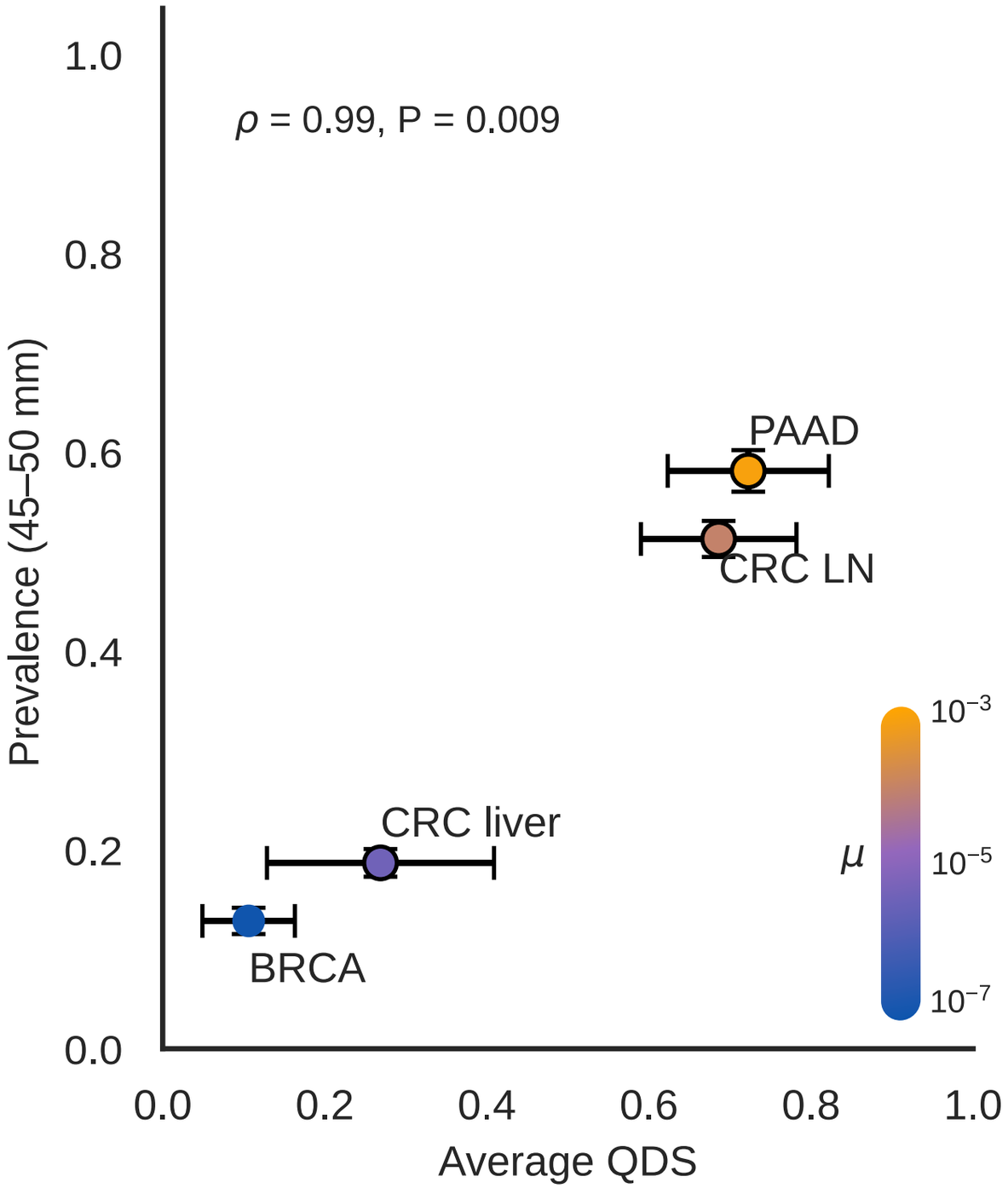
prediction

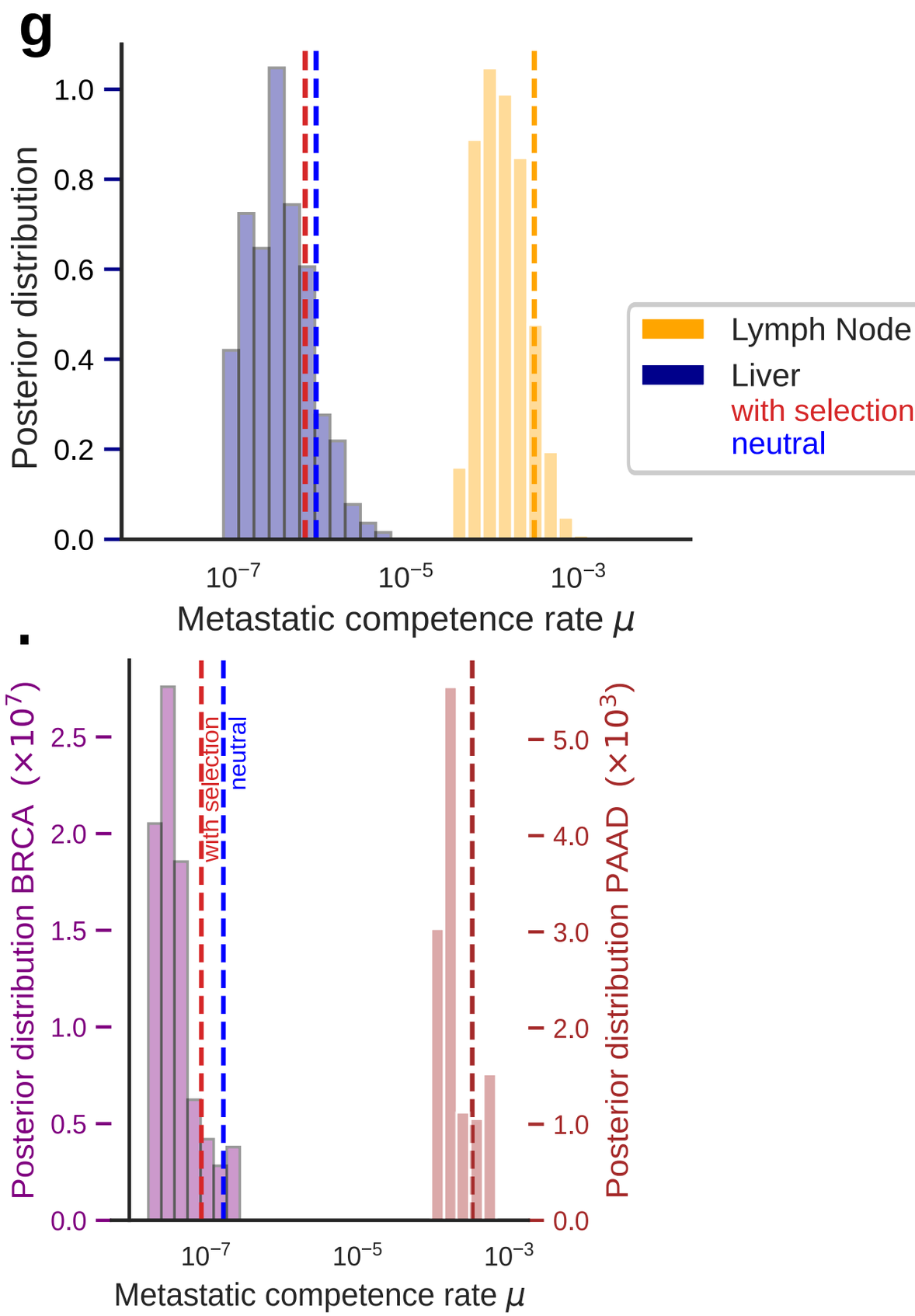


data

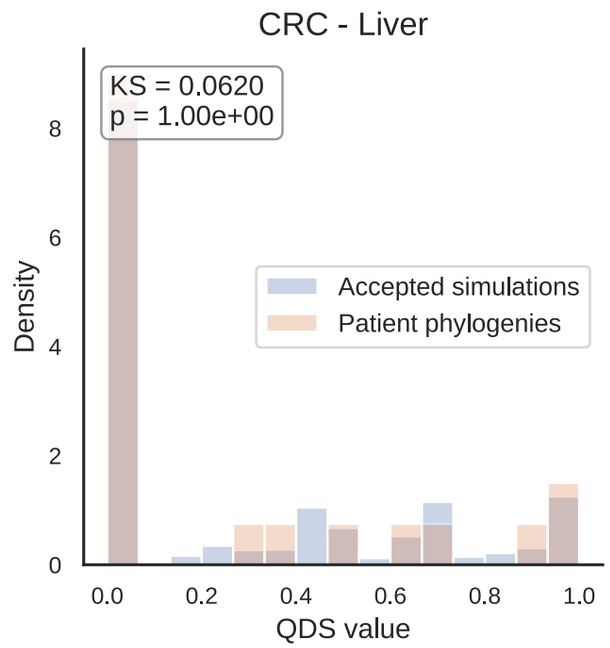


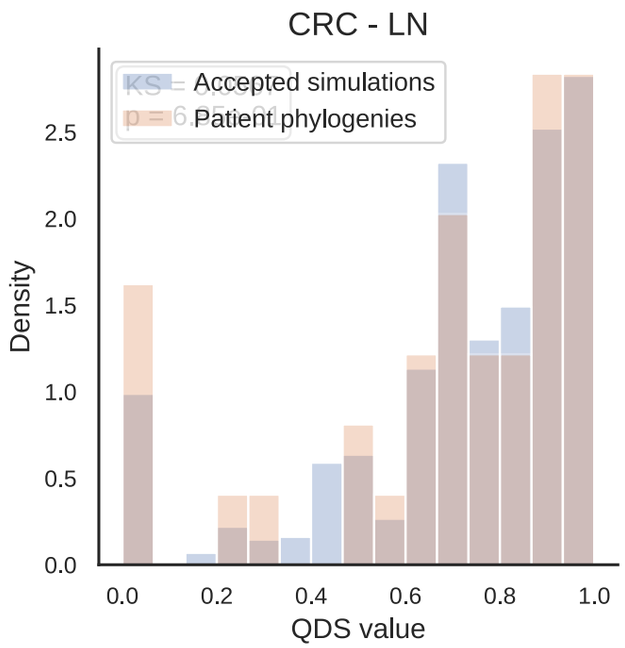
fitting to cohort mean QDS and prevalence with ABC

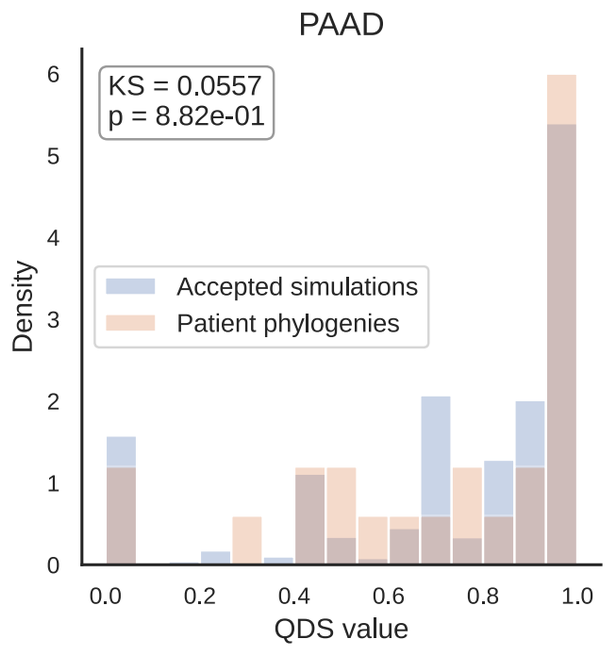


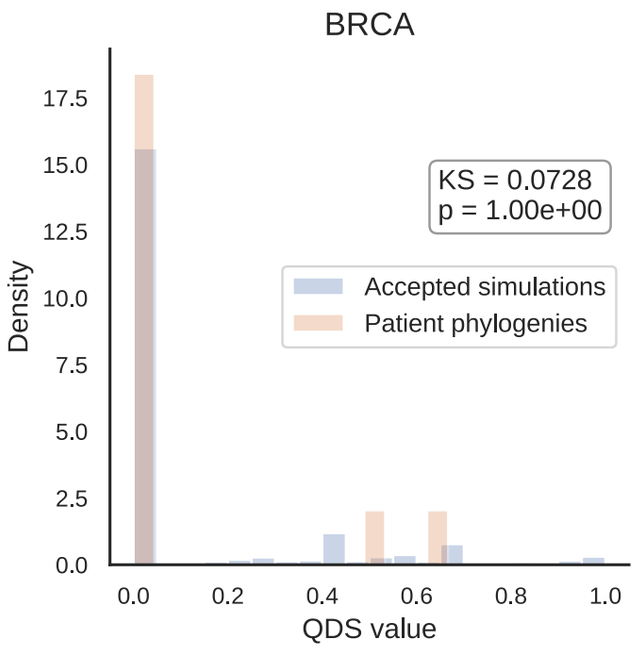


QDS distribution: model vs data



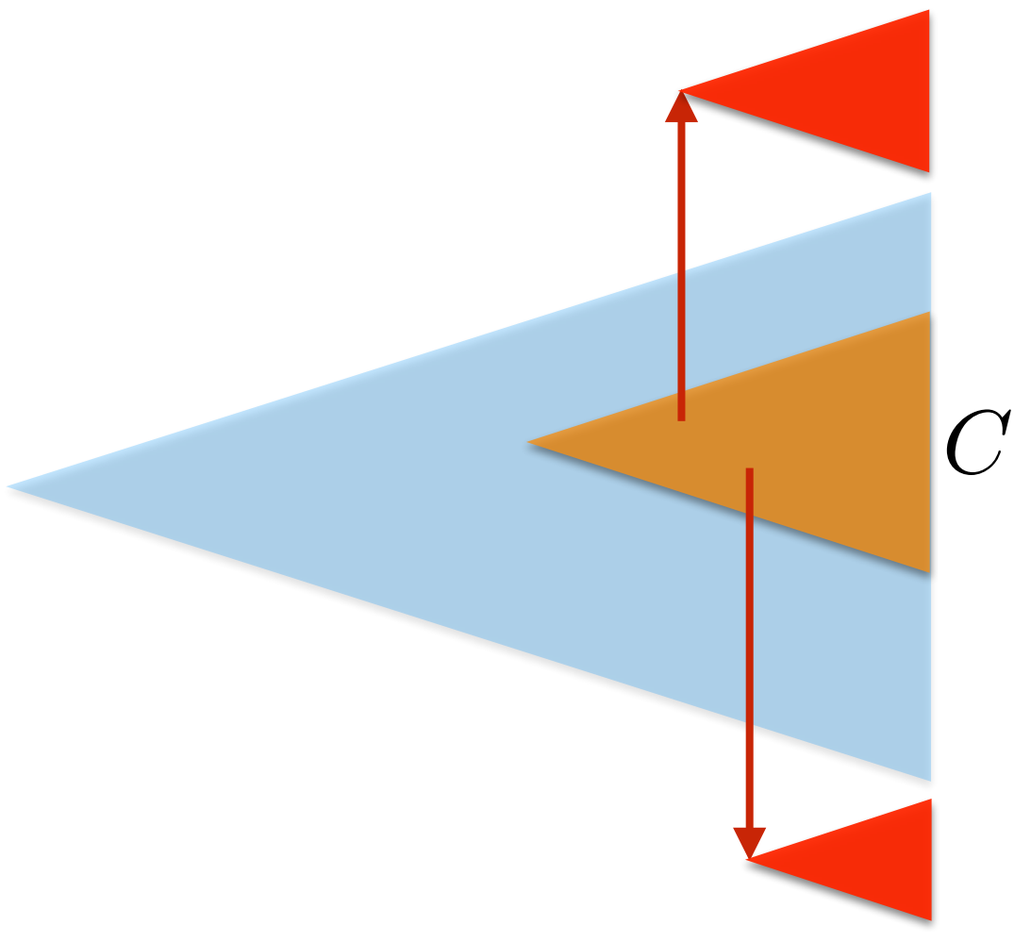






heuristic for QDS (called D)

one competent clone only $\quad \mathbb{E}[K_C] = \dfrac{\mu N}{\lambda_P} \ll 1$



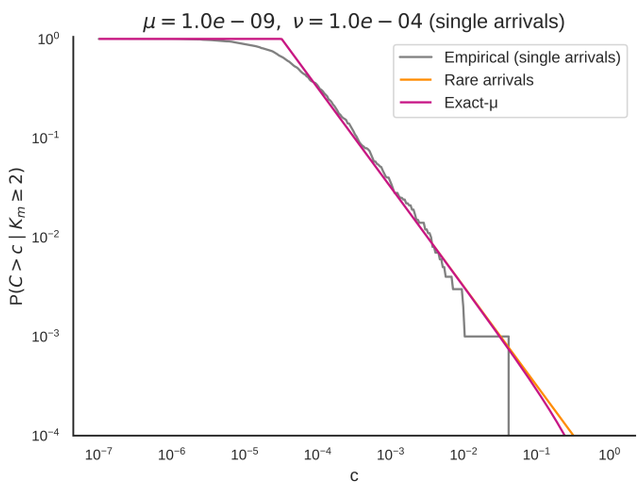
$$\mathbb{E}(D|C) = (1-C)^2 0 + 2C(1-C)\frac{2}{3} + C^2\frac{7}{9}$$

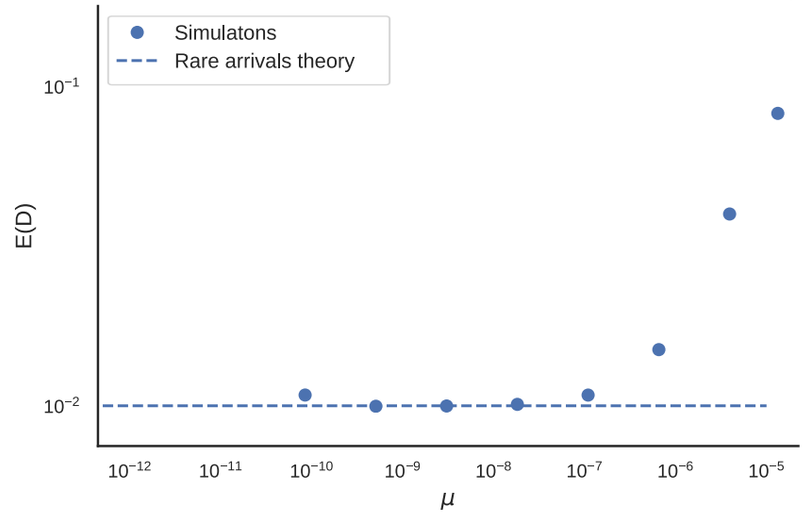
$$\mathbb{E}D = \frac{4}{3}\mathbb{E}C - \frac{5}{9}\mathbb{E}C^2$$

$$\mathbb{P}(C > c \mid k_M \geq 2) = \begin{cases} 1, & c < c_0, \\ c_0/c, & c_0 \leq c \leq 1. \end{cases}$$

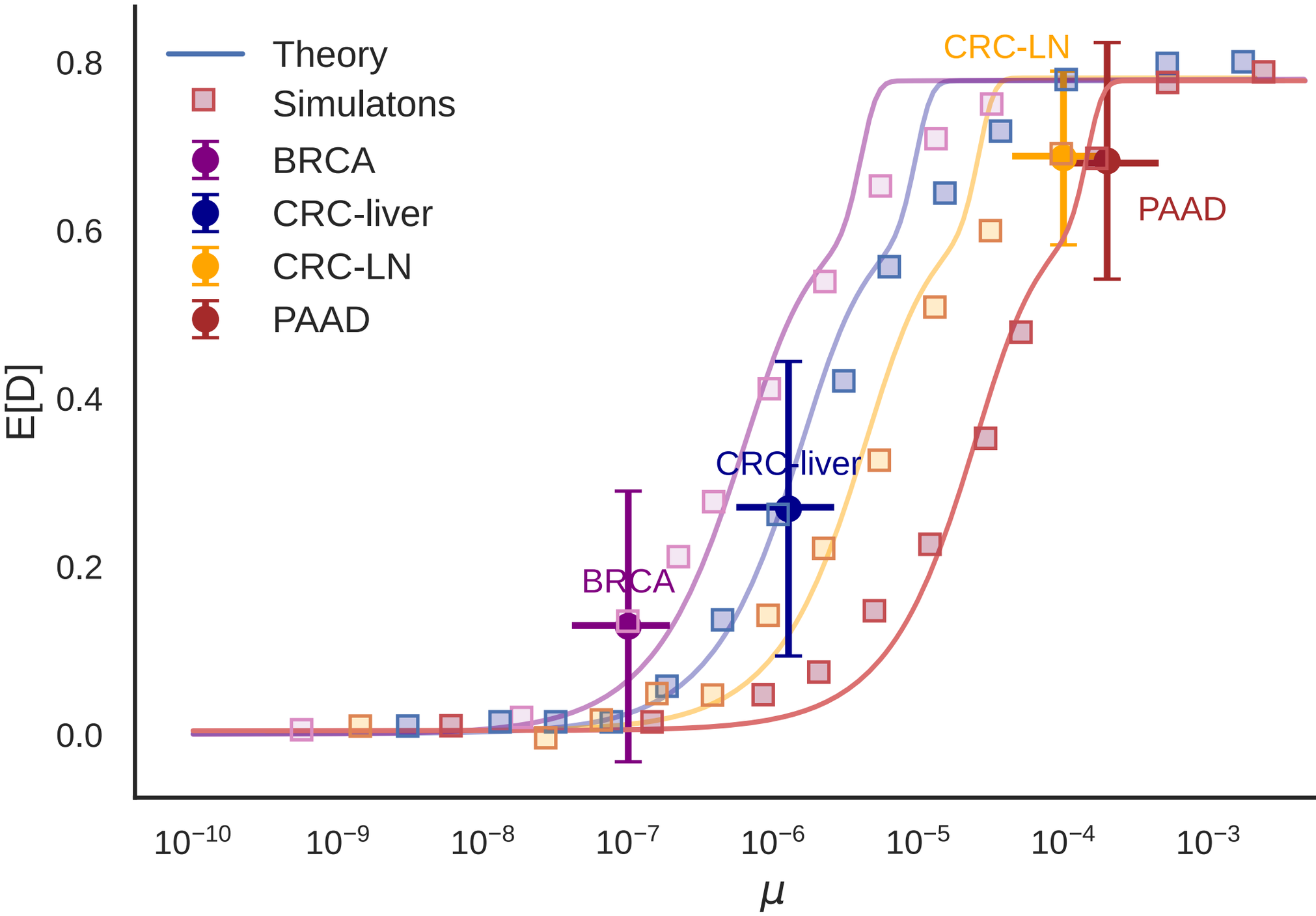
$$c_0 = \frac{\lambda m}{\nu N}, \quad \lambda_P = \lambda_C = \lambda_M =: \lambda$$

$$\mathbb{E}D = \frac{c_0}{9}\left(2 + 5c_0 + 12\log\frac{1}{c_0}\right)$$





heuristic for QDS with more than one clone



summary

simple evolutionary models can be fitted to data

- two types are enough for sizes and times
- three types are needed for met diversity
- they provide intuition and insight

simple models are the best

~ Bobby McFerrin.