Mathematical model for pilocytic astrocytoma growth and progression provides clinical decision support

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Sino-German Workshop on Multiscale spatial computational systems biology

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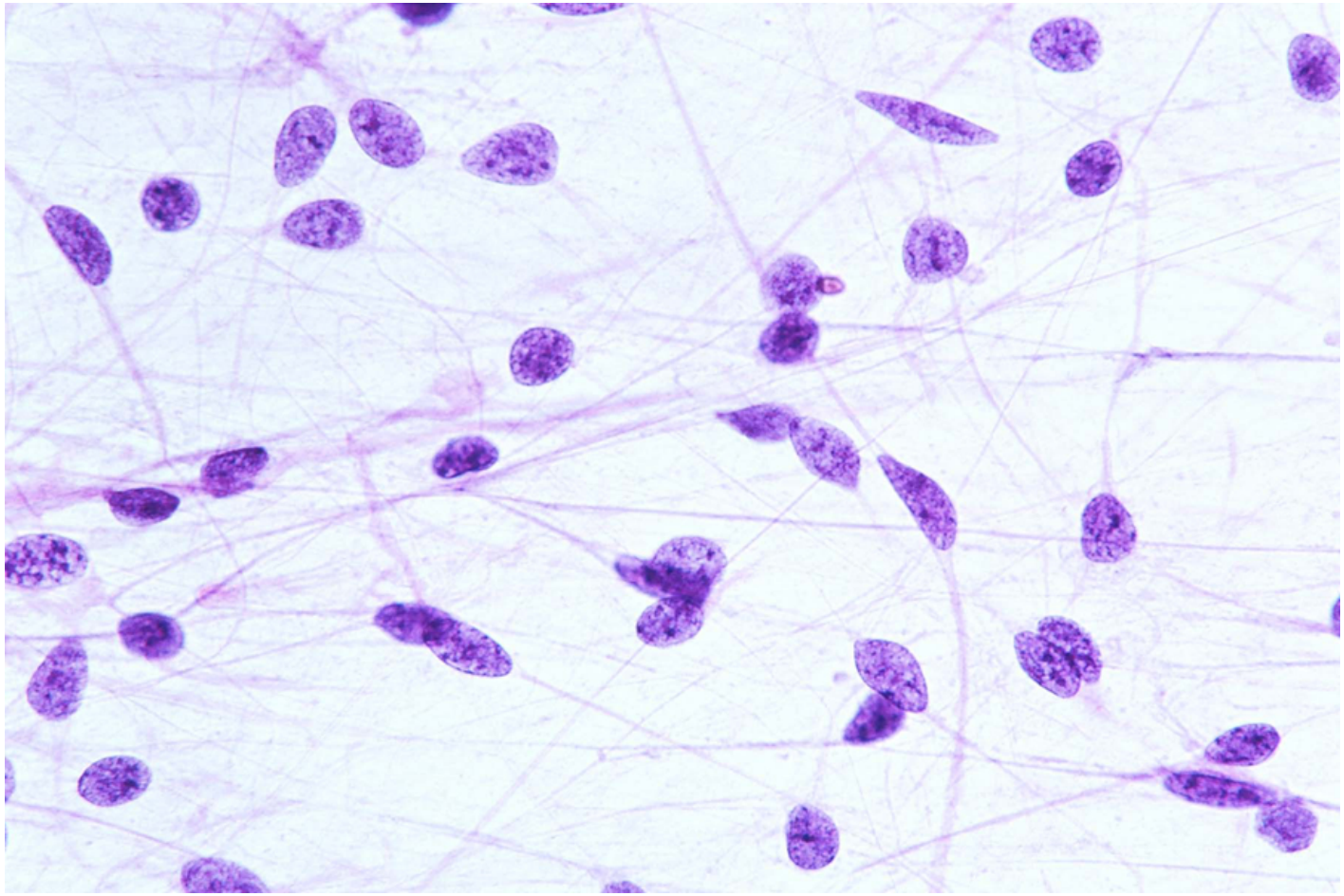
Contents

Pilocytic Astrocytoma (PA)



Johns Hopkins, Department of Pathology

Characteristics

- classified as WHO grade I
- epidemiology
  - 75 % occurring in the first two decades of life
  - highest age incidence: 5 - 15 years
- location
  - *frequently:* cerebellum (60 %)
  - *also:* cerebellar hemisphere, optic chiasm, hypothalamus, brainstem, spinal cord

Characteristics

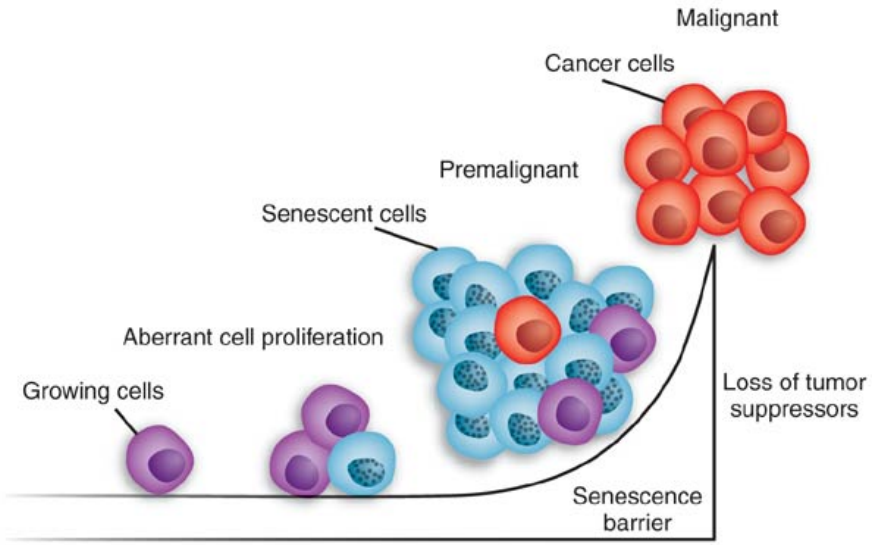
- tumors
  - grow as solid masses
  - well-circumscribed tumors
  - non-invasive
- *subtypes*
  - determined on molecular level
  - differ in their aggressiveness

Subtypes

PA I

- indolent behavior
- slowly growing
- considered as benign
- genetic level
  - activation of *MAPK* pathway sufficient
  - BRAF, KRAS, NF1
  - *single-pathway disease*
- *MAPK* activation
  - initially promotes cell proliferation
  - *but also* induces senescence by increased activity of TSG (e.g. CDKN2A)
  - **oncogene-induced senescence**

Subtypes



Narita, M. et al. 2011

PA II

- aggressive behavior
- malignant transformation
- senescence is overcome by additional *genetic alterations*, e.g. *CDKN2A*
- enables fast tumor growth

Therapy

gross total resection

- treatment of choice
- *favorable prognosis:* 90 % cured without additional therapy
- *problem:* location determines extent of resection
  - cerebellum, superficial cerebrum
  - optic pathway, brain stem tumors

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$\Rightarrow$ **Only partial resection possible in many cases**

Therapy

partial resection

- *lower survival rates* than patients with total resection
- prognosis is *highly unpredictable*
  - tumor regrowth
  - tumor growth arrest
  - tumor regression
- controversy about *further therapy*
  - *wait and see* approach?
  - *radiation therapy*?
  - extent of *follow-up observation*?

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How could clinicians be supported?

Decision support

Insights into regression chance in dependency of residual tumor size could

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Decision support

Insights into regression chance in dependency of residual tumor size could

- **justify** *wait and see* approach if there is a high chance for regression
- **justify** *side effects of additional therapy*, e.g. radiation, if there is a low chance for regression
- **justify** *extent of resection*
  - *avoid risks* if only *small effect on regression chance*
  - *justify risks* if *high effect on regression chance*

Decision support

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- **justify** *wait and see* approach if there is a high chance for regression
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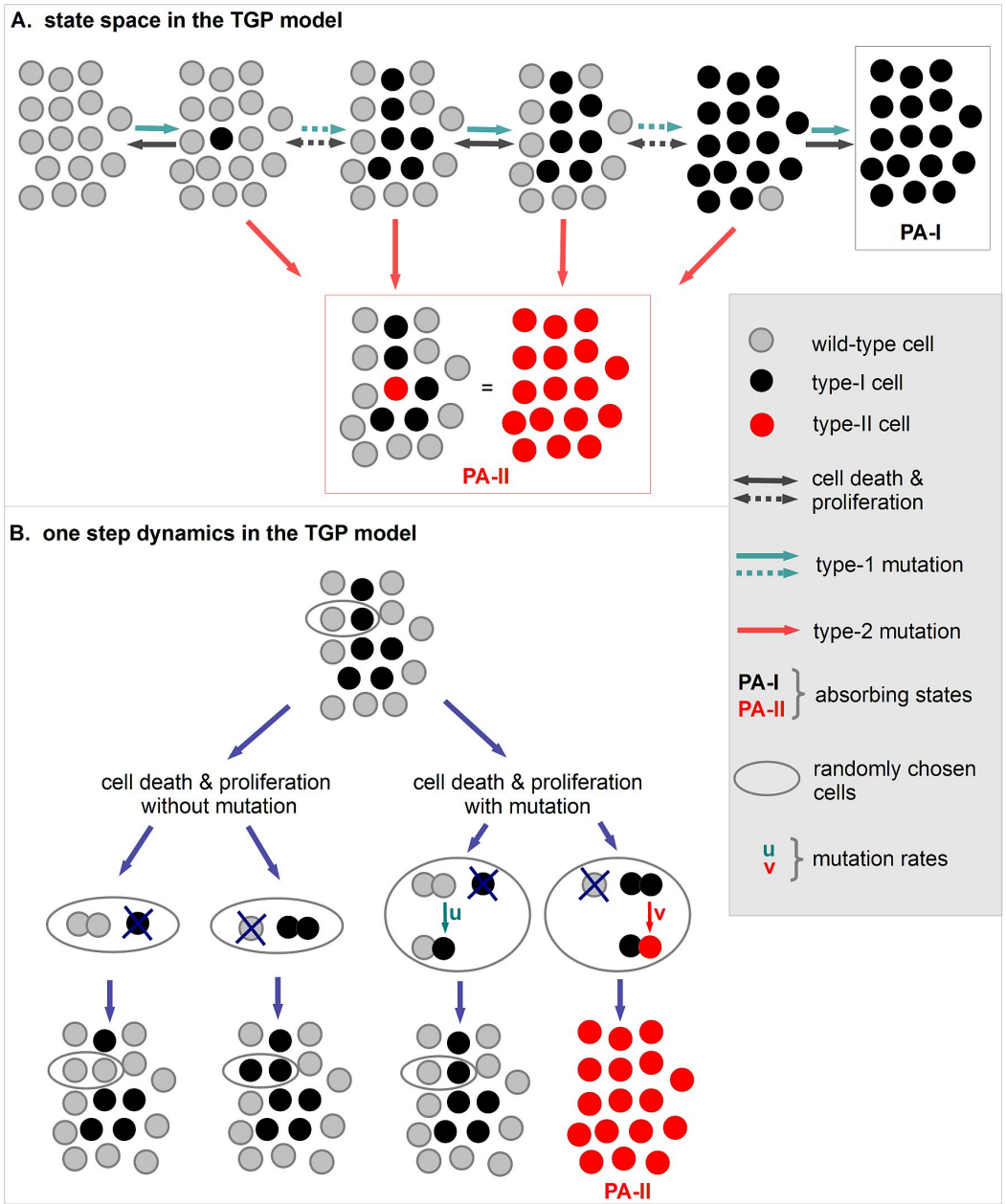
Mathematical model in order to balance between **risk of operation and side effects of further therapies** and **risk of regrowth or progression**.



Tumor growth and progression model

Parameters

- critical tumor size N
  - no regression possible anymore
- mutation parameters u, v

Dynamics

- cell death, proliferation, mutations

Assumptions

- no spatial aspects
- one type-II cell $\equiv$ diagnosis

Mathematical Model

- *TGP process* X_t
- state space $S = \{0, 1, 2, ..., N, E\}$
  - $0 \equiv$ all cells wild-type
  - $k \equiv k$ type-I cells, no type-II cell, $\quad 1 \leqslant k \leqslant N$
  - $E \equiv$ at least one type-II cell
- no modeling beyond critical size N
- two absorbing states N and E representing *PA I* and *PA II*

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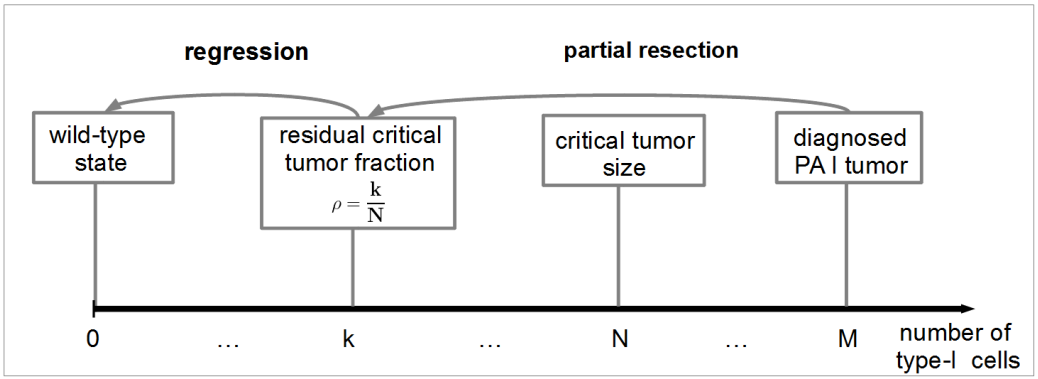

- regression function

$$\beta_\gamma(\varrho) := \mathbb{P}(X_t = 0 \text{ for some t} | X_0 = N\varrho), \varrho \in [0, 1].$$

Parameter regime

$Nu \ll 1$

- each mutant lineage can be investigated independently
- *biological implication:* tumor develops from a single mutated cell

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risk coefficient $\gamma := (N\sqrt{v})^2 > 0$

- positive probability of absorption in both states N and E
- *biological implication: PA I* and *PA II* are possible outcomes of the model
- γ determines the *absorption probability* and therefore the fractions of PA I and PA II in the model

Fraction of PA I cases in the model

Derivation sketch

- assume occurence of single *successful* mutant and set $u = 0$
- *First Step Analysis*

$$\alpha^N(i) = \sum_{j \in S} \alpha^N(j) p(i,j).$$

- *Linear system of equations*

$$P' \alpha^N = b$$

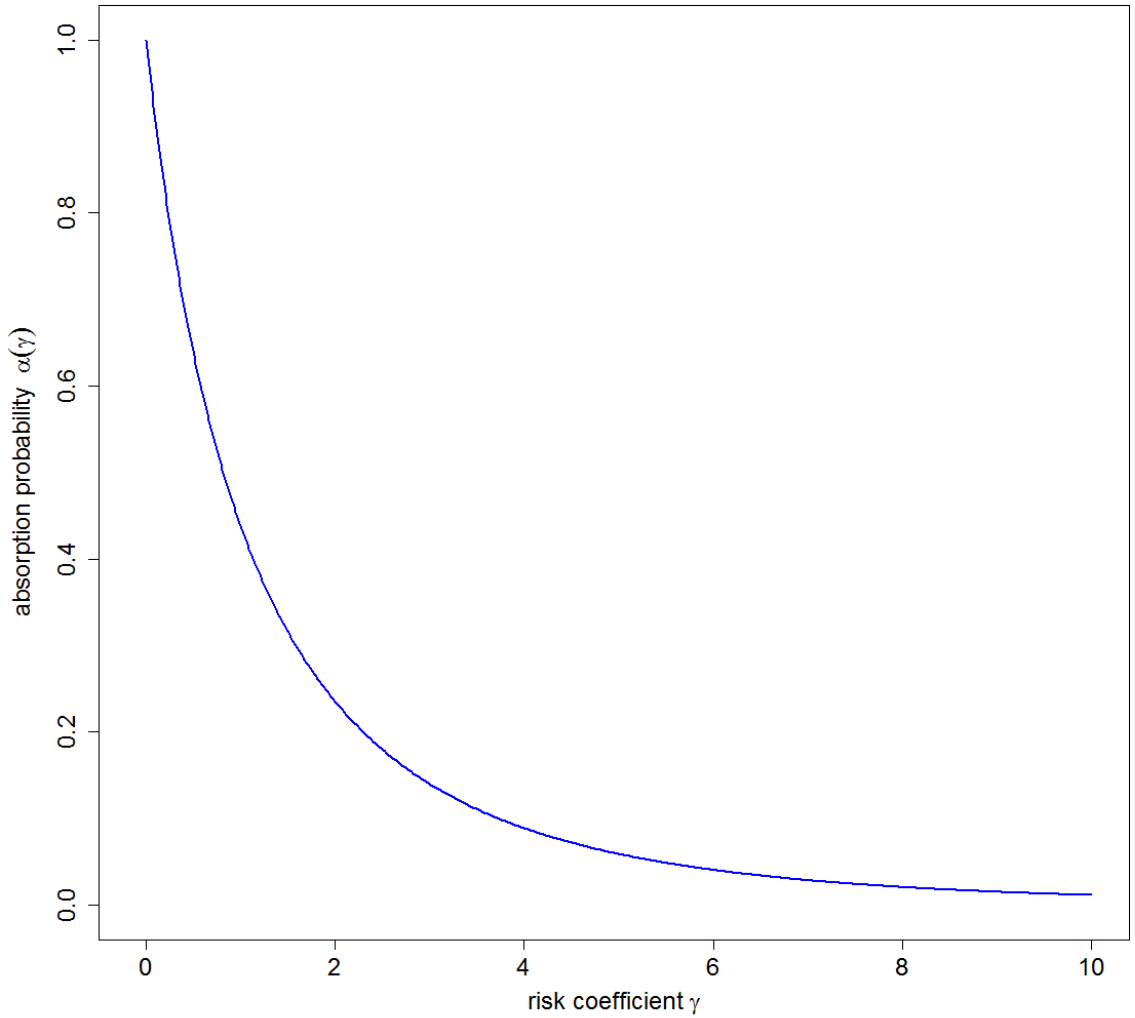
- *Cramer's rule*

$$\alpha^N(1) = \frac{detP_1'}{detP'} = \frac{1}{P_{N-1}\left(\frac{v+1}{1-v}\right)}$$

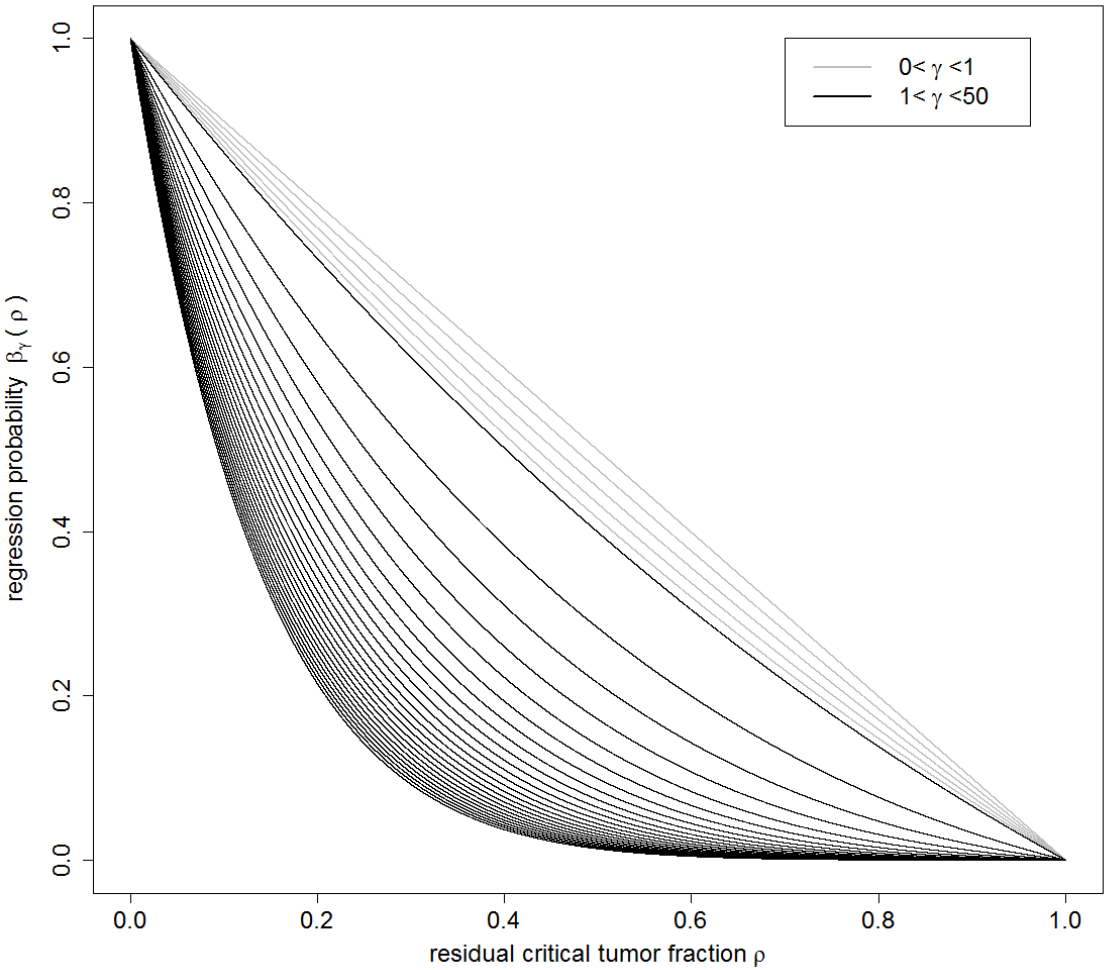
- asymptotic result for $N \to \infty$

$$\alpha(\gamma) := \lim_{N \to \infty} \alpha^N(1) = \frac{1}{I_0(2\sqrt{\gamma}).}$$

Fraction of PA I cases in the model



Tumor regression function



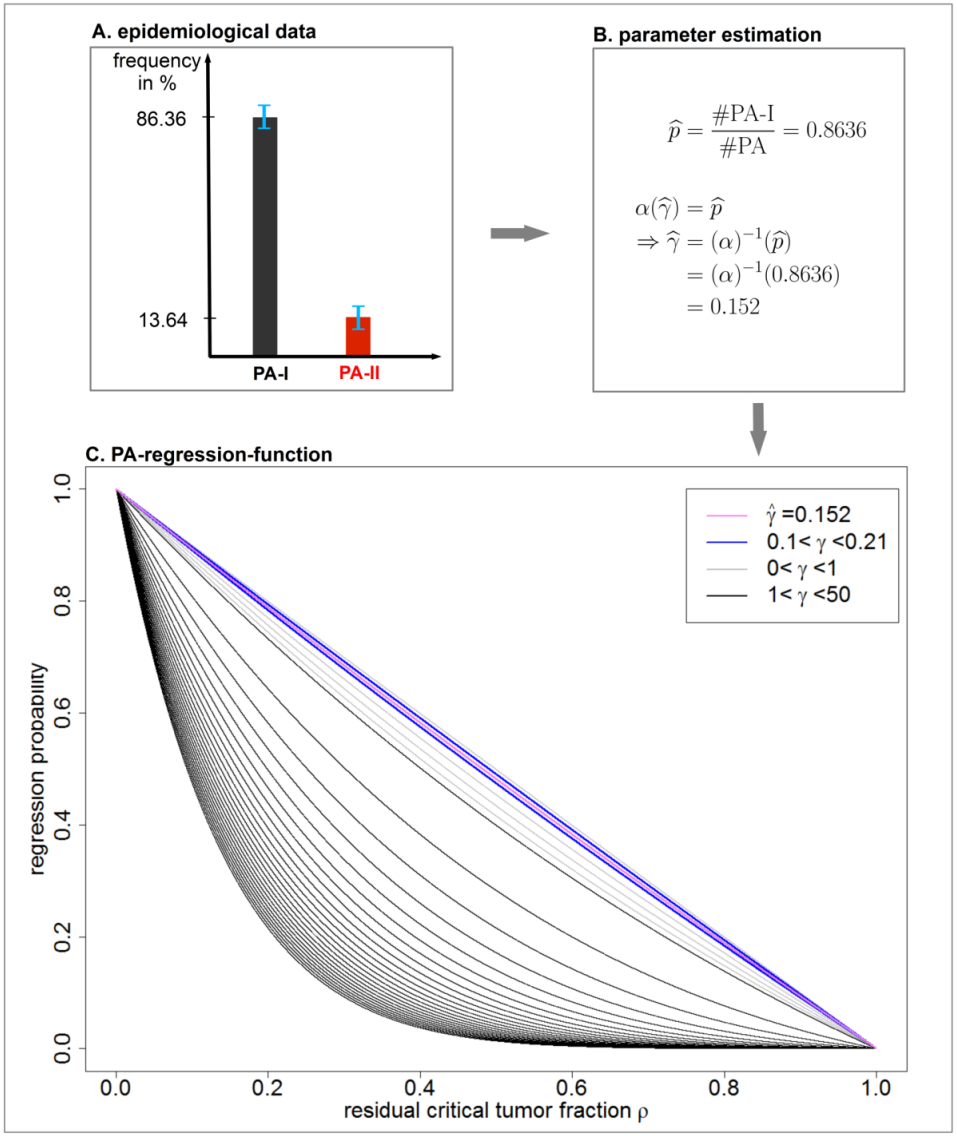
- tumor regression function
  - diffusion approximation
  - $\varrho = \frac{k}{N}$

$$\beta_\gamma(\varrho) = \frac{\sqrt{1-\varrho} I_1\left(2\sqrt{\gamma(1-\varrho)}\right)}{I_1(2\sqrt{\gamma})}$$

- risk parameter γ has crucial impact on regression function

Goal: estimate risk coefficient γ

Estimating the risk coefficient γ



Clinical implications

Linear dependency between residual tumor fraction and regression.

- PA-regression-function approximately

$$T_1(\varrho) = 0.9817 - \varrho$$

- very good approximation

$$|R_1(\varrho)| \leqslant \frac{\gamma}{8} = 0.0185$$

- every resected percentage point contributes equally to regression probability
  - *avoid risks* by resecting small fractions
  - resections *always contribute* to the regression probability

Clinical implications

Quantitative prediction of the regression probability.

- literature research: critical tumor size N equals 9 cm^3

Residual tumor size (cm^3)	Tumor regression probability (in %)
0.1	98.91
0.5	94.06
1	88.16
2	76.50
3	65.03
4	53.75
5	42.64
6	31.71
7	20.47
8	10.39

Clinical implications

Non-existence of an extent of resection (EOR) threshold.

- malignant brain tumors: EOR threshold of 78 %
- our results suggest non-existence of such a threshold in PA
- important: TGP model able to reproduce EOR threshold

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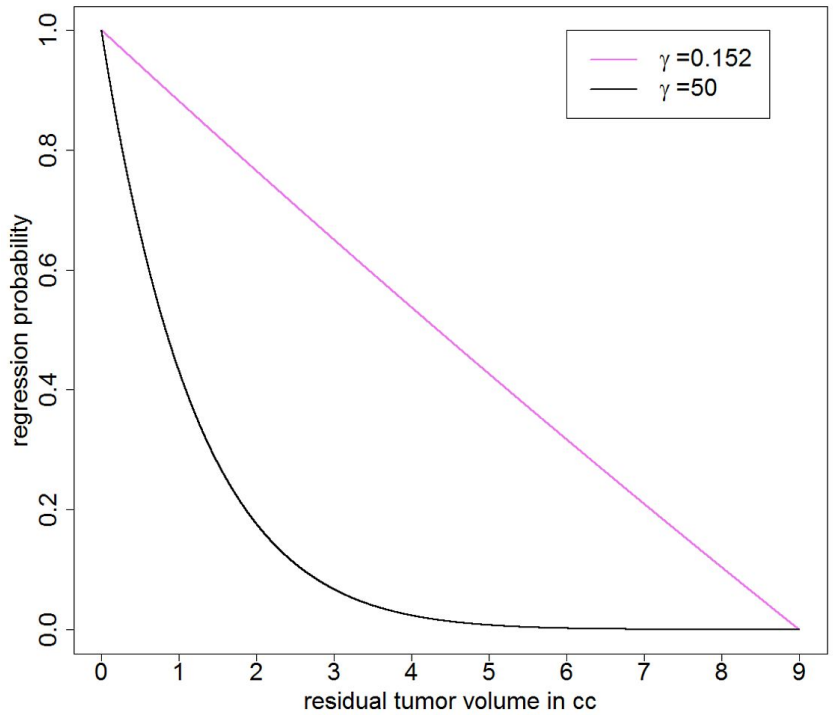
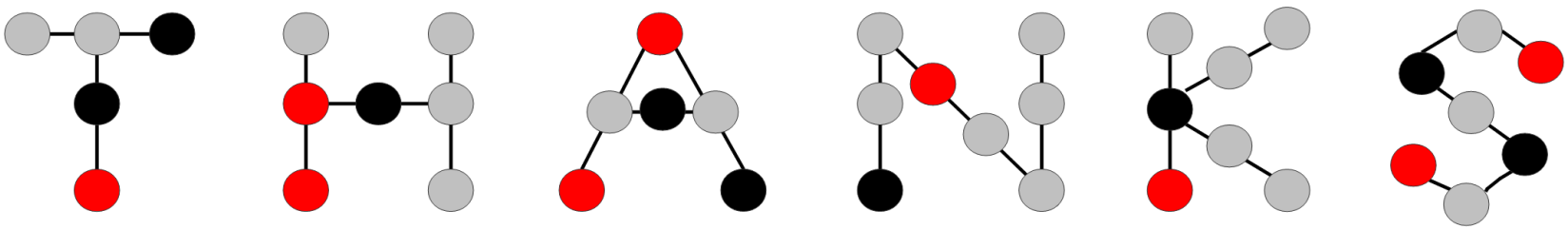


Discussion

- first theoretical model of PA based on population dynamics of tumor and wild-type cells
  - only one parameter: risk parameter γ
  - results robust to changes of γ
- limited long-term follow-up data
  - no clinical studies of influence of residual tumor volume
  - results suggest: residual tumor volume is important prognostic marker
  - lack of data could be reason for different results in clinical studies on additional treatment in PA



for your attention!

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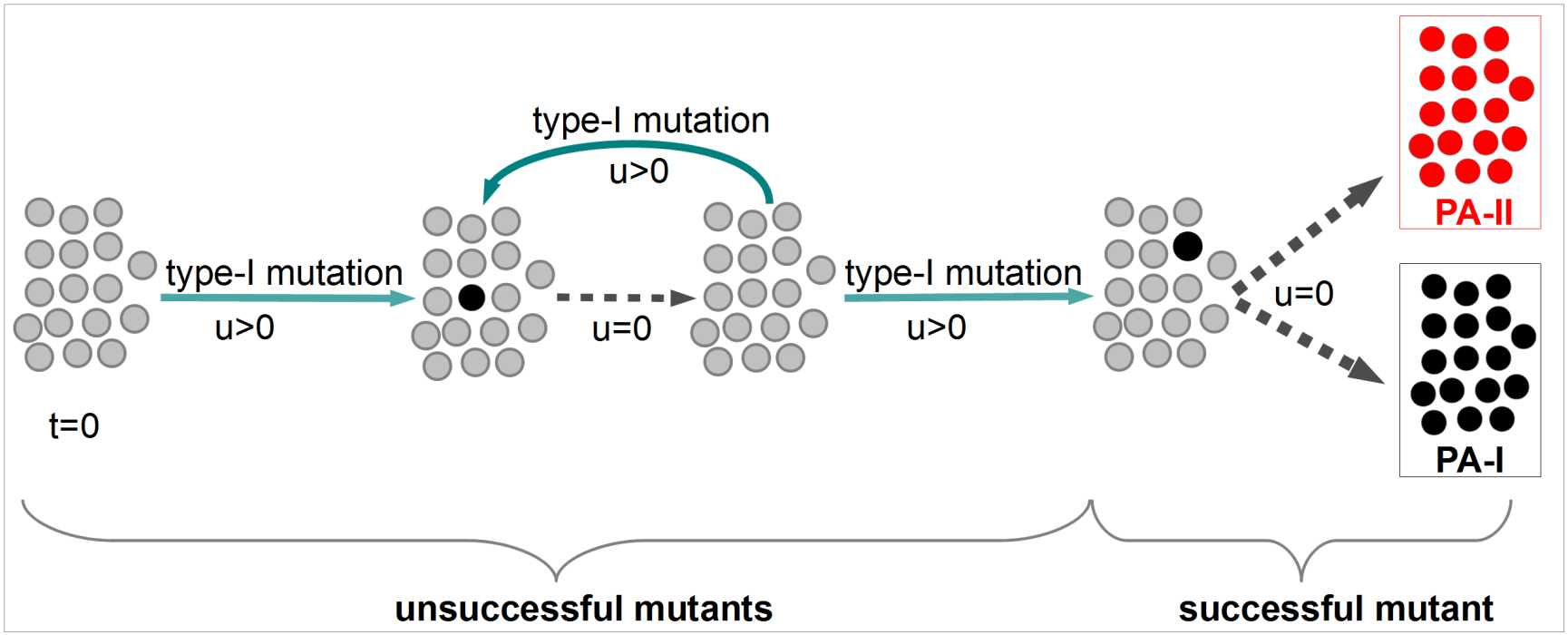
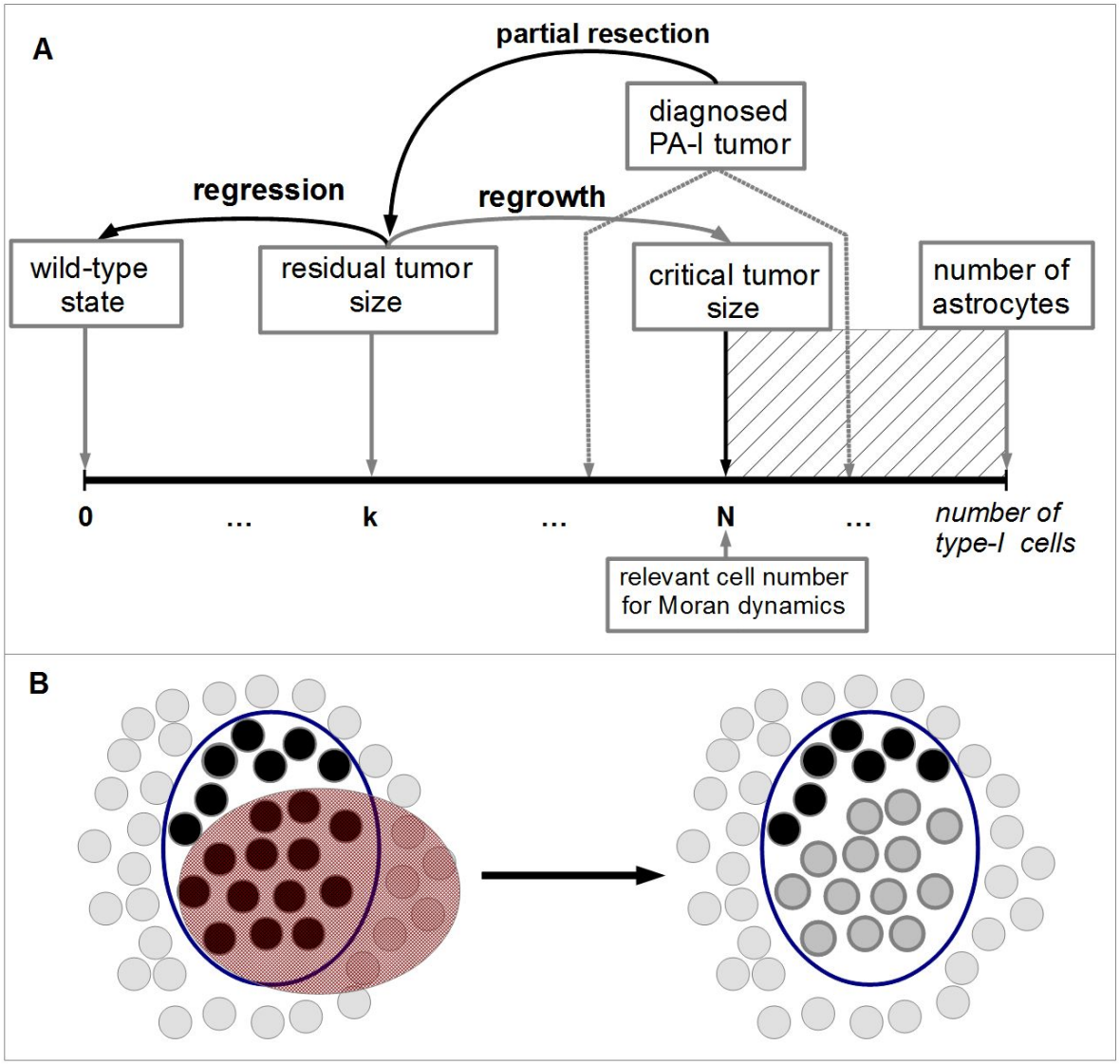
Decomposition into two sub-processes



Regression in the TGP model



Absorption probabilities

$$P_1' = \begin{pmatrix} 0 & (N-1)(1-v) & 0 & \cdots & \cdots & 0 \\ 0 & -2(N-2)-2v & (N-2)(1-v) & 0 & \ddots & 0 \\ 0 & (N-3) & -2(N-3)-3v & (N-3)(1-v) & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & \ddots & 2(1-v) \\ -(1-v) & 0 & \cdots & \cdots & 1 & -2-(N-1)v \end{pmatrix}$$

Absorption probabilities

$$|detP_1^{'}| = (1-v)\begin{vmatrix} (N-1)(1-v) & 0 & \cdots & \cdots & \cdots & 0 \\ -2(N-2)-2v & (N-2)(1-v) & 0 & \ddots & \ddots & 0 \\ (N-3) & 2(N-3)-3v & (N-3)(1-v) & \ddots & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & \ddots & \ddots & \ddots & 2(1-v) \end{vmatrix}$$

$$= (1-v)(N-1)(1-v)\begin{vmatrix} (N-2)(1-v) & 0 & \cdots & \cdots & 0 \\ 2(N-3)-3v & (N-3)(1-v) & \ddots & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & \ddots & \ddots & 2(1-v) \end{vmatrix}$$

$$= \ldots$$

$$= (1-v)(N-1)(1-v)(N-2)(1-v)(N-3)(1-v)\ldots 2(1-v)$$

$$= (N-1)!(1-v)^{N-1}.$$

Absorption probabilities

$$detP^{'} = \begin{vmatrix} -(3+v) & 2 & 0 \\ 3(1-v) & -(4+2v) & 1 \\ 0 & 2(1-v) & -(2+3v) \end{vmatrix} = 6(v^3 + 9v^2 + 9v + 1)$$

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$$detP^{'} = 120(v^5 + 25v^4 + 100v^3 + 100v^2 + 25v + 1)$$

$$= 5!(v^5 + 5^2v^4 + 10^2v^3 + 10^2v^2 + 5^2v + 1) \text{ for } N = 6$$

Absorption probabilities

$$detP' = \begin{vmatrix} -(3+v) & 2 & 0 \\ 3(1-v) & -(4+2v) & 1 \\ 0 & 2(1-v) & -(2+3v) \end{vmatrix} = 6(v^3+9v^2+9v+1)$$

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$$= 5!(v^5+5^2v^4+10^2v^3+10^2v^2+5^2v+1) \text{ for } N=6$$

$$detP' = (N-1)!\left(\binom{N-1}{N-1}^2 v^{N-1} + \binom{N-1}{N-2}^2 v^{N-2} + \ldots + \binom{N-1}{2}^2 v^2 + \binom{N-1}{1}^2 v^1 + \binom{N-1}{0}^2 v^0\right)$$

$$= (N-1)!\sum_{i=0}^{N-1}\binom{N-1}{i}^2 v^i.$$

Absorption probabilities

$$\alpha^N(1,v) = \frac{detP_1'}{detP'} = \frac{(N-1)!(1-v)^{N-1}}{(N-1)!\sum_{i=0}^{N-1}\binom{N-1}{i}^2 v^i.} = \frac{(1-v)^{N-1}}{\sum_{i=0}^{N-1}\binom{N-1}{i}^2 v^i.} = \frac{1}{P_{N-1}\left(\frac{v+1}{1-v}\right)},$$

where $P_N(x)$ denotes the *Legendre polynomials* which are the particular solutions to the Legendre differential equation

$$\left(1-x^2\right) f''(x) - 2x\, f'(x) + N(N+1)\, f(x) = 0, \quad N \in \mathbb{N}_0.$$

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N	u	v	$\gamma = (N\sqrt{v})^2$	$\alpha^N(1)$	simulated fraction of fixation
10	10^{-4}	10000^{-1}	0.1^2	0.99106	0.9913
10	10^{-4}	2500^{-1}	0.2^2	0.96494	0.96536
100	10^{-4}	10000^{-1}	1	0.44174	0.44162
100	10^{-4}	2500^{-1}	2^2	0.08999	0.08973

The influence of γ

$(N\sqrt{v})^2 = \gamma$, hence $v = \frac{\gamma}{N^2}$ and therefore

$$\alpha^N(1,\gamma) = \frac{1}{P_{N-1}\left(\frac{v+1}{1-v}\right)} = \frac{1}{P_{N-1}\left(\frac{\frac{\gamma}{N^2}+1}{1-\frac{\gamma}{N^2}}\right)} = \frac{1}{P_{N-1}\left(\frac{N^2+\gamma}{N^2-\gamma}\right)}.$$

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It holds that

$$P_N(x) = \frac{1}{\pi}\int_0^\pi \left[x + \sqrt{x^2-1}\cos\varphi\right]^N \mathrm{d}\varphi, \quad x \in \mathbb{R}\backslash\{-1,1\},$$

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hence

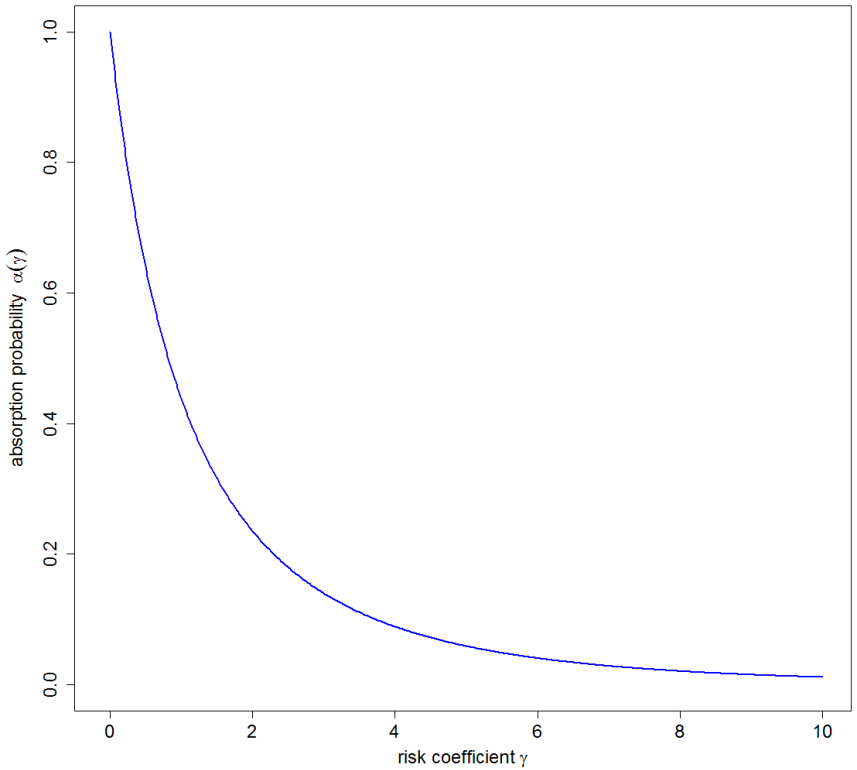
$$\lim_{N\to\infty} P_{N-1}\left(\frac{N^2+\gamma}{N^2-\gamma}\right) = \lim_{N\to\infty} \frac{1}{\pi}\int_0^\pi \left[\frac{N^2+\gamma+2N\sqrt{\gamma}\cos\varphi}{N^2-\gamma}\right]^{N-1} \mathrm{d}\varphi$$

$$= \frac{1}{\pi}\int_0^\pi \lim_{N\to\infty}\left[\frac{N^2+\gamma+2N\sqrt{\gamma}\cos\varphi}{N^2-\gamma}\right]^{N-1} \mathrm{d}\varphi$$

$$= \frac{1}{\pi}\int_0^\pi e^{2\sqrt{\gamma}\cos\varphi}\,\mathrm{d}\varphi = I_0(2\sqrt{\gamma}).$$

Fraction of PA I cases in the model

$$\alpha(\gamma) := \lim_{N\to\infty} \alpha^N(1,\gamma) = \frac{1}{I_0(2\sqrt{\gamma}).}$$



I_0 denotes the *modified Bessel function of the first kind*.