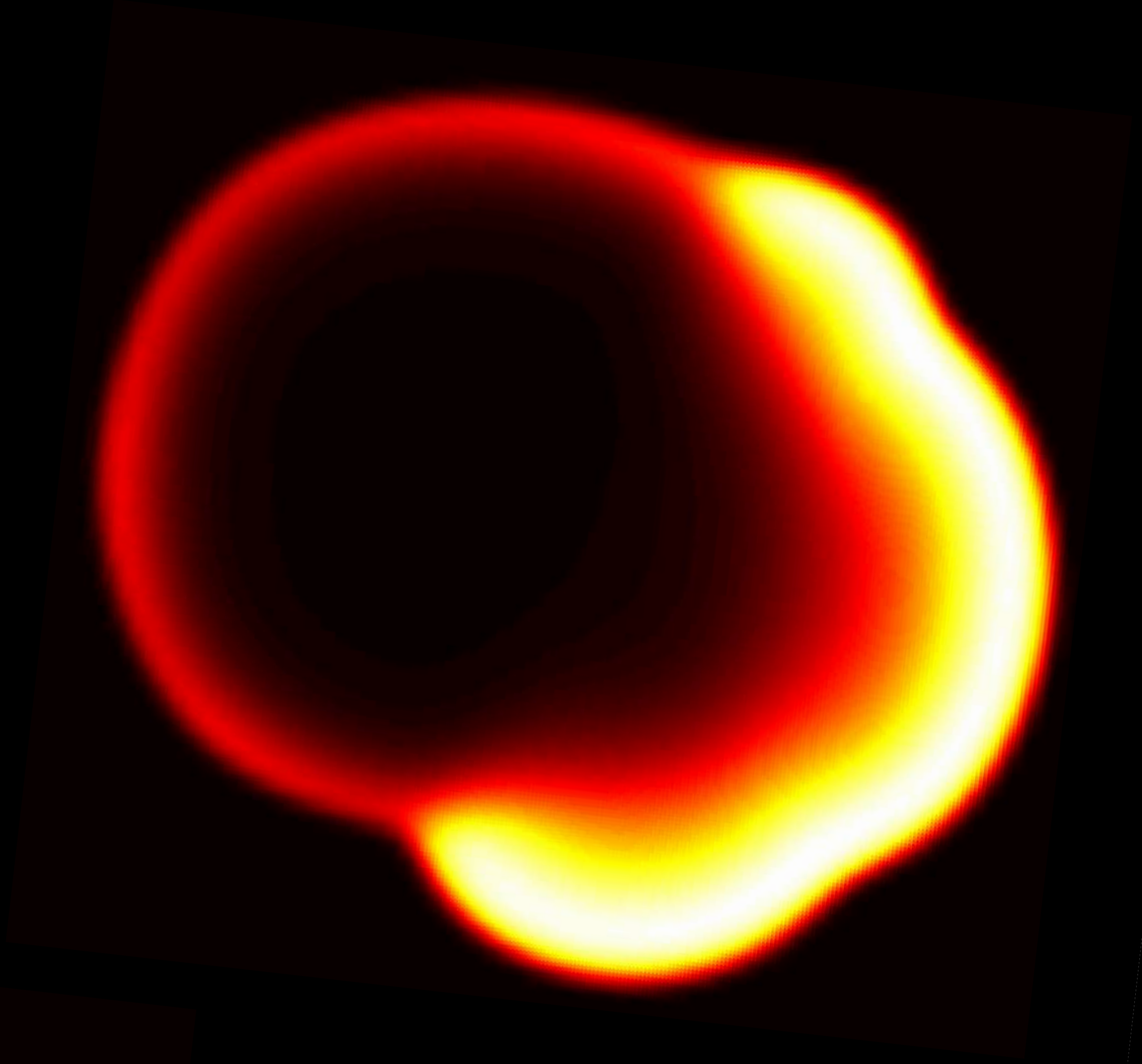
Politecnico di Torino

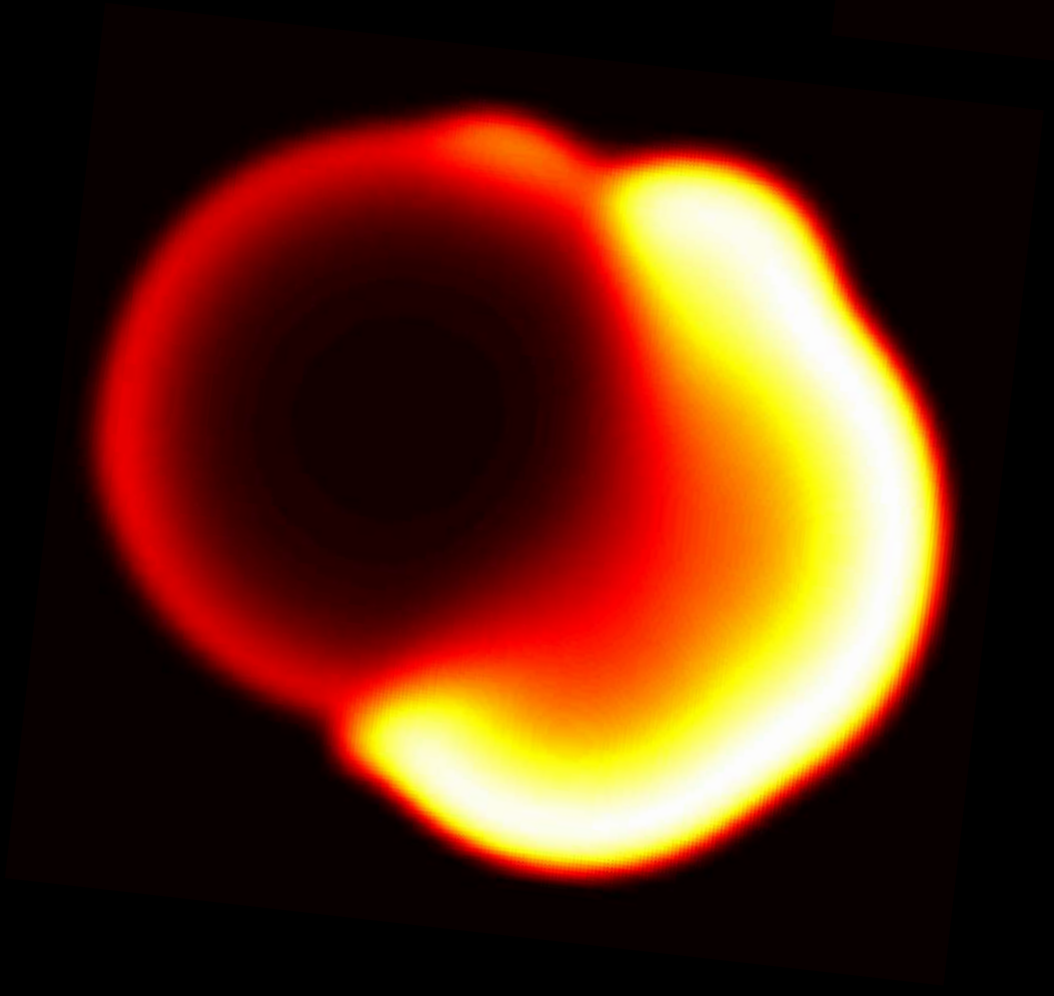
TECHNISCHE UNIVERSITÄT DRESDEN

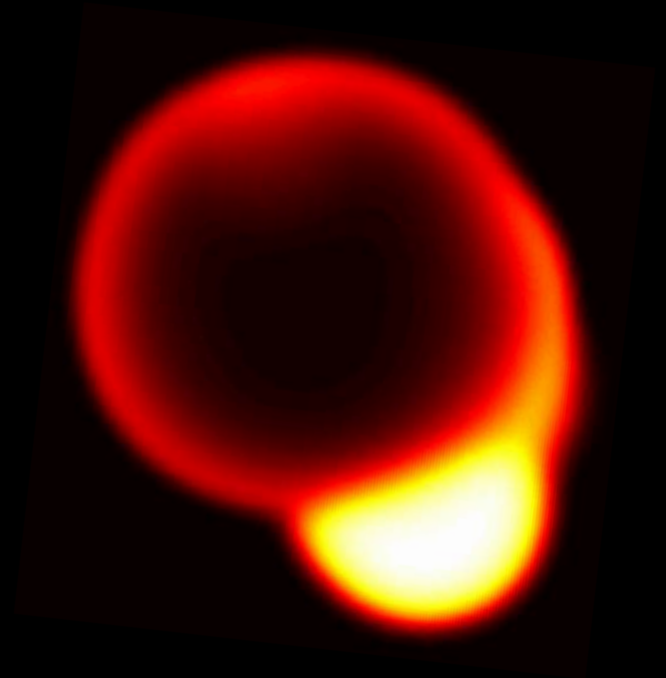
MATHEMATICAL ONCOLOGY LABORATORY

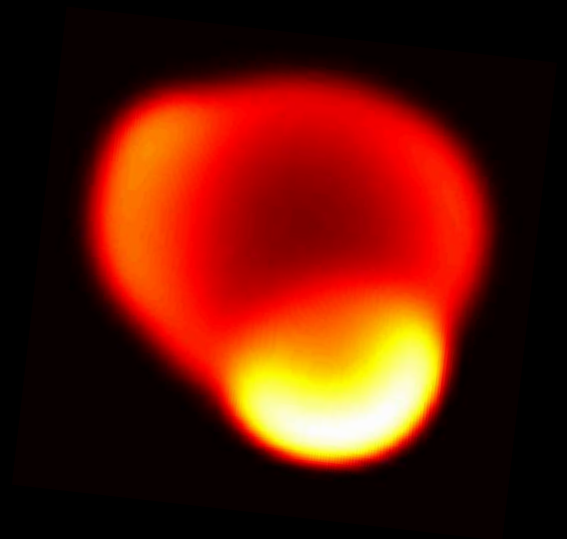
A stochastic discrete mesoscopic simulator of tumor growth

Biomarker discovery and therapy optimization









Juan Jiménez Sánchez

UCLM
Universidad de Castilla~La Mancha


MATHEMATICAL
ONCOLOGY
LABORATORY

1994

BSc in Biotechnology

POLITÉCNICA

UNIVERSIDAD
POLITÉCNICA
DE MADRID

BSc in Biotechnology

POLITÉCNICA

UNIVERSIDAD
POLITÉCNICA
DE MADRID

2012-2016

2016-2017

UAM

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MSc in Biophysics

BSc in Biotechnology

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PhD in Physics and Mathematics

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2016-2017

2018-2022

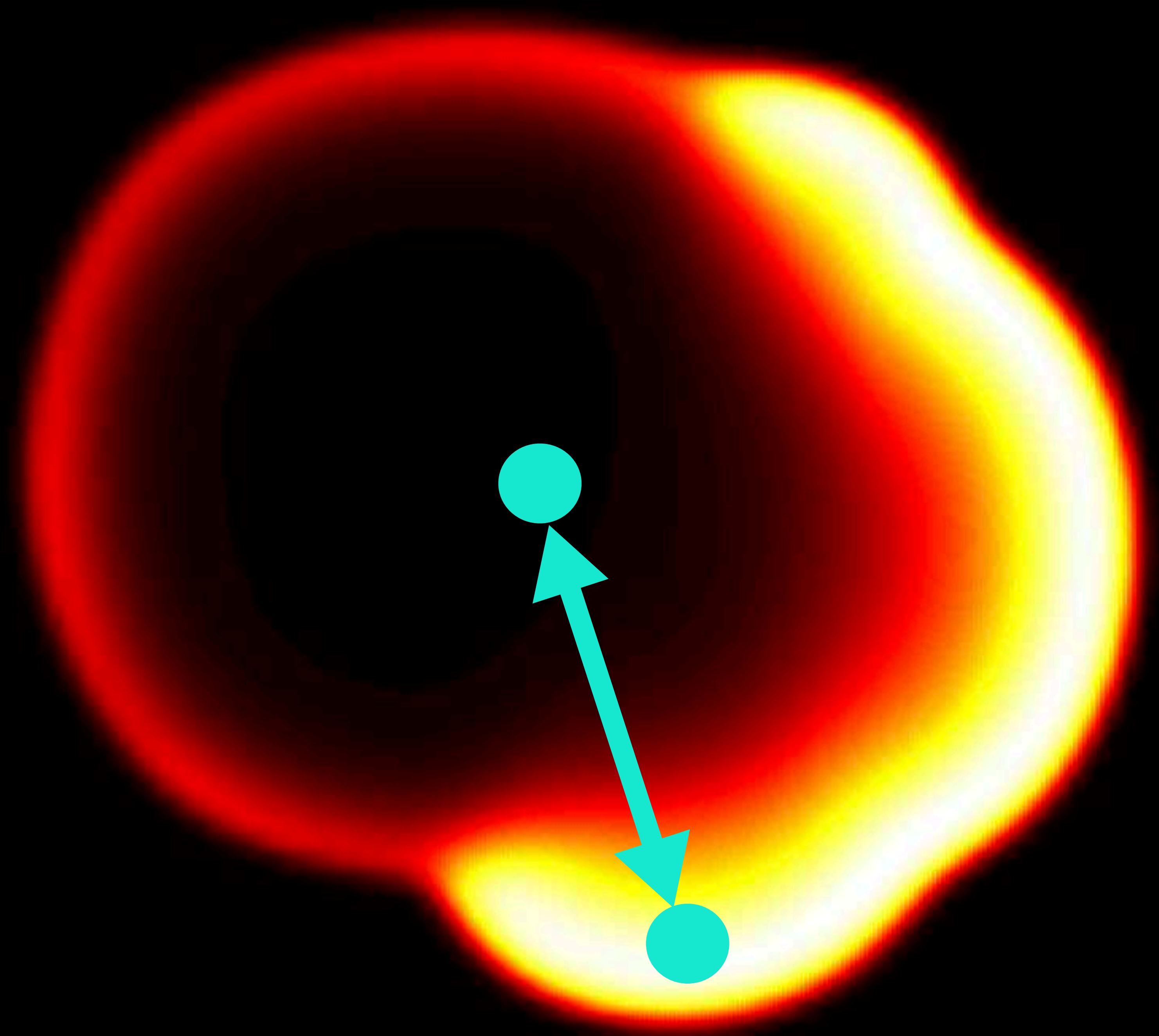
2024

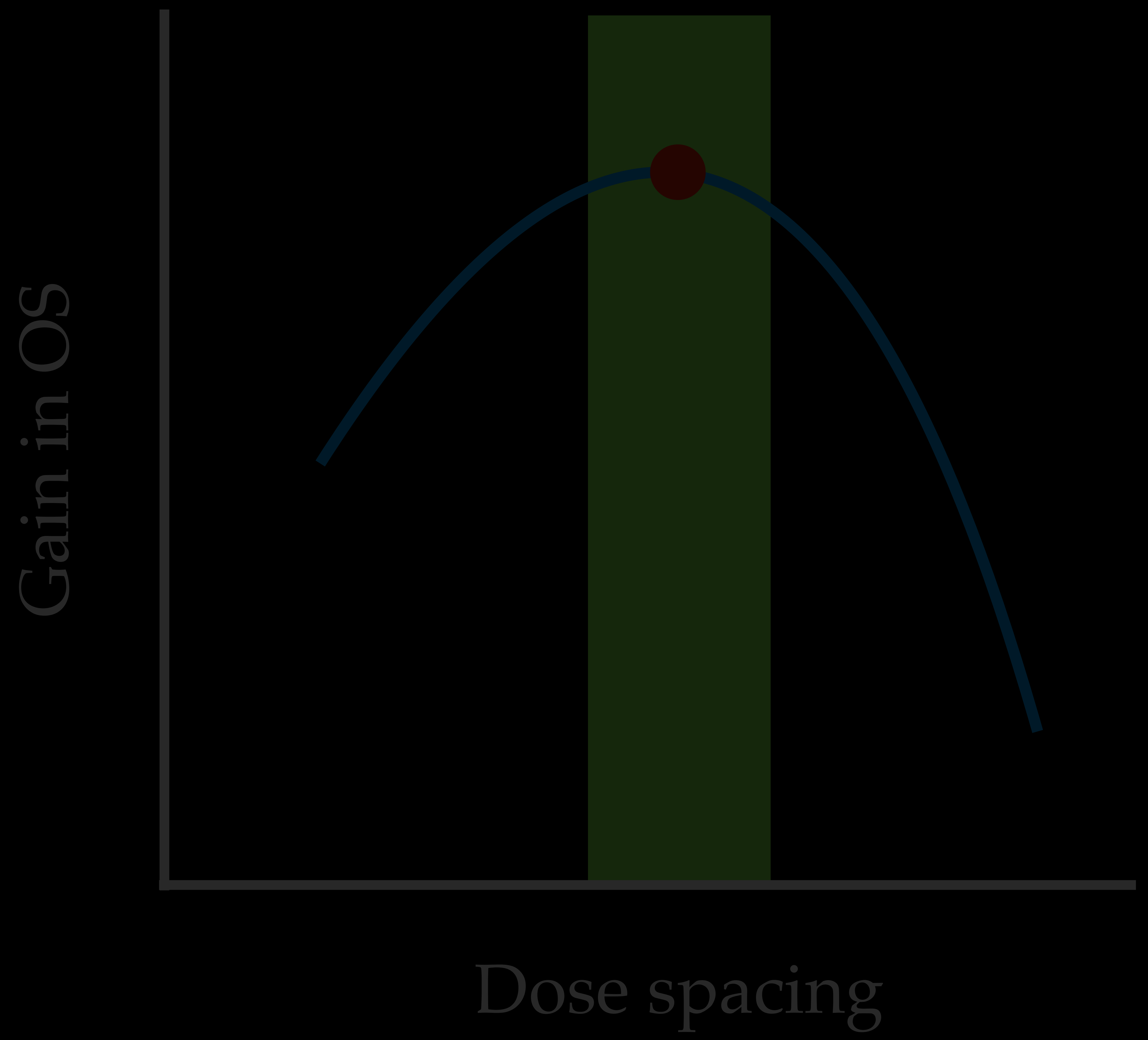
UAM Universidad Autónoma de Madrid

MSc in Biophysics

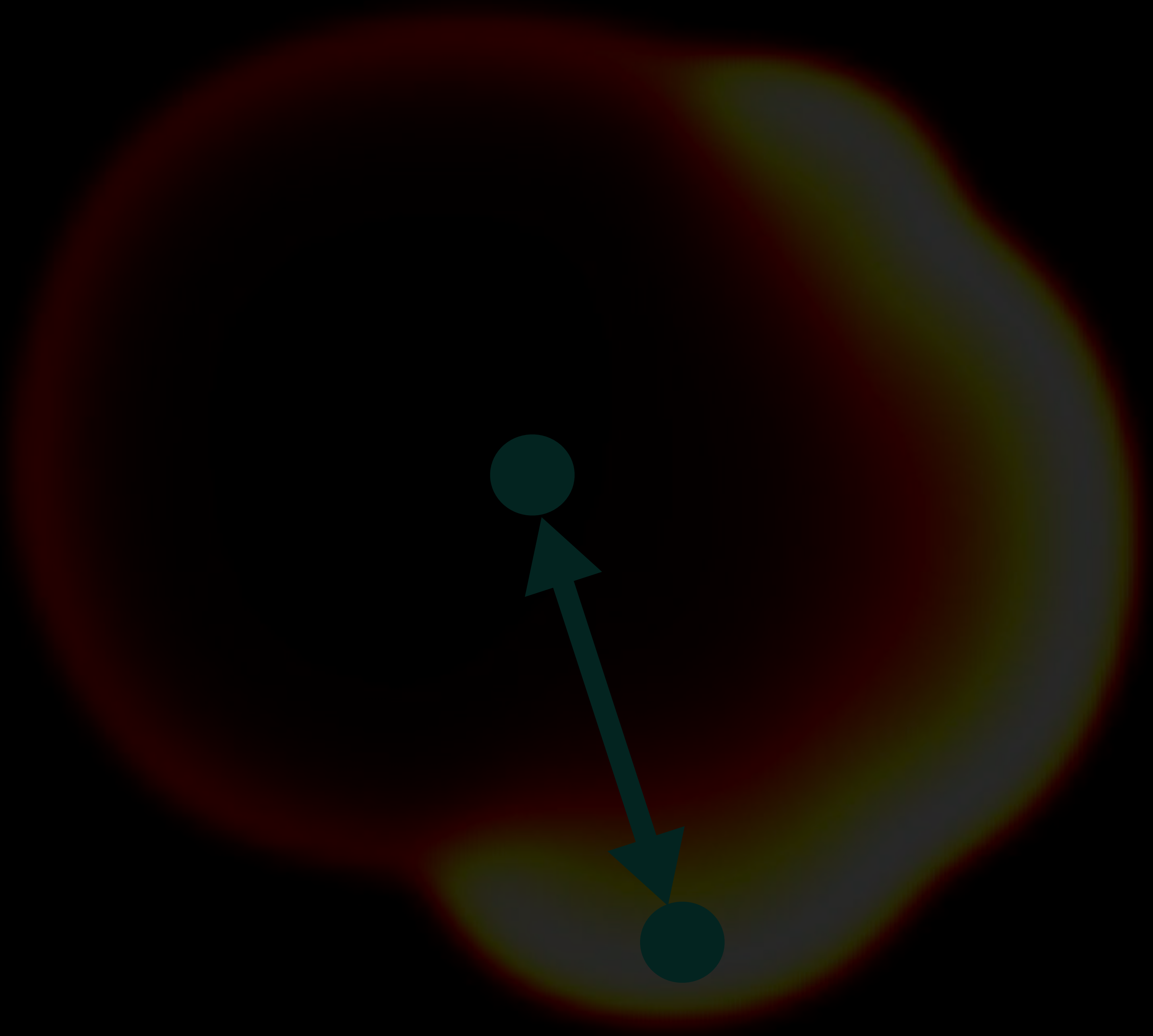
Politecnico di Torino

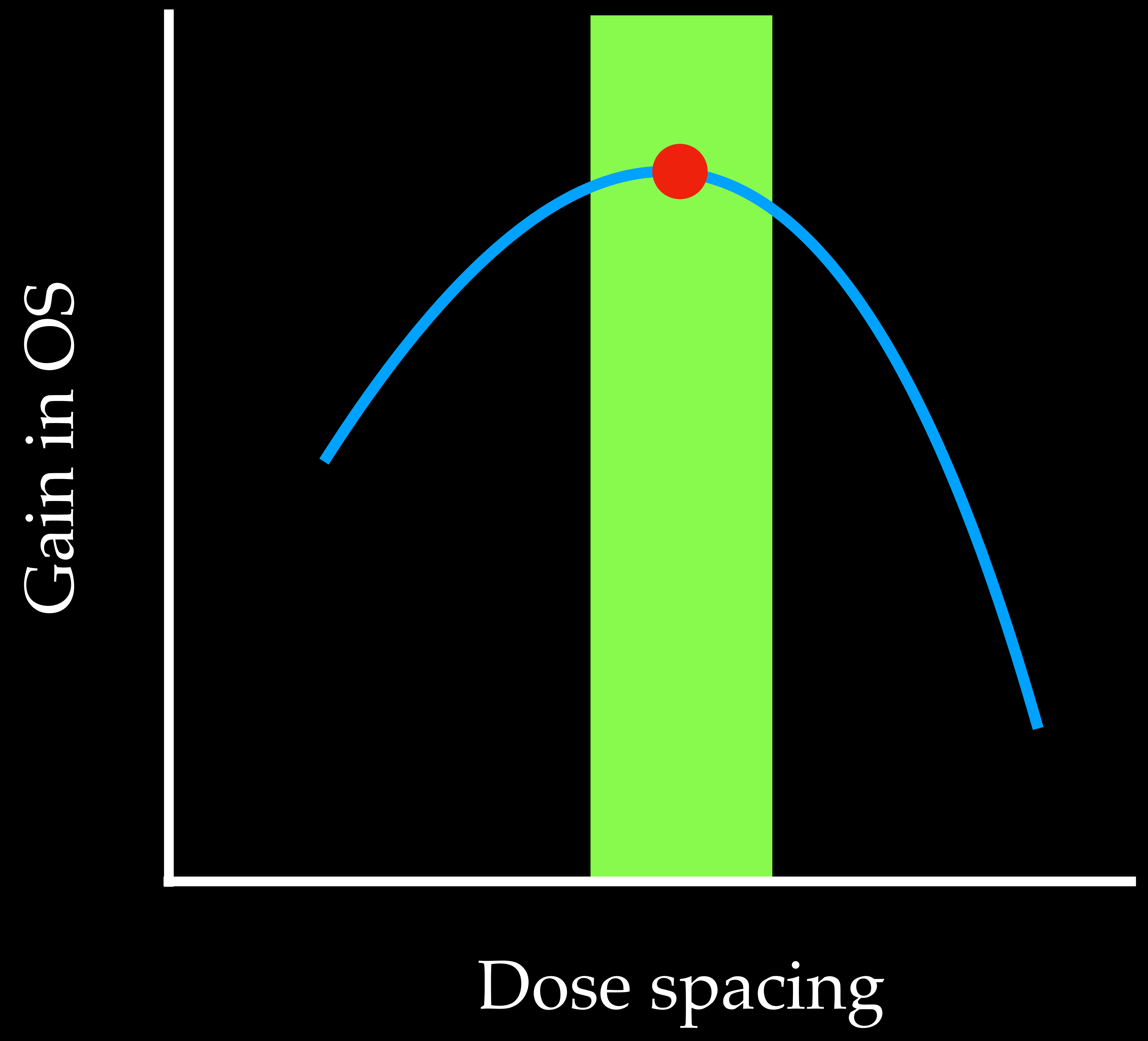
Postdoc





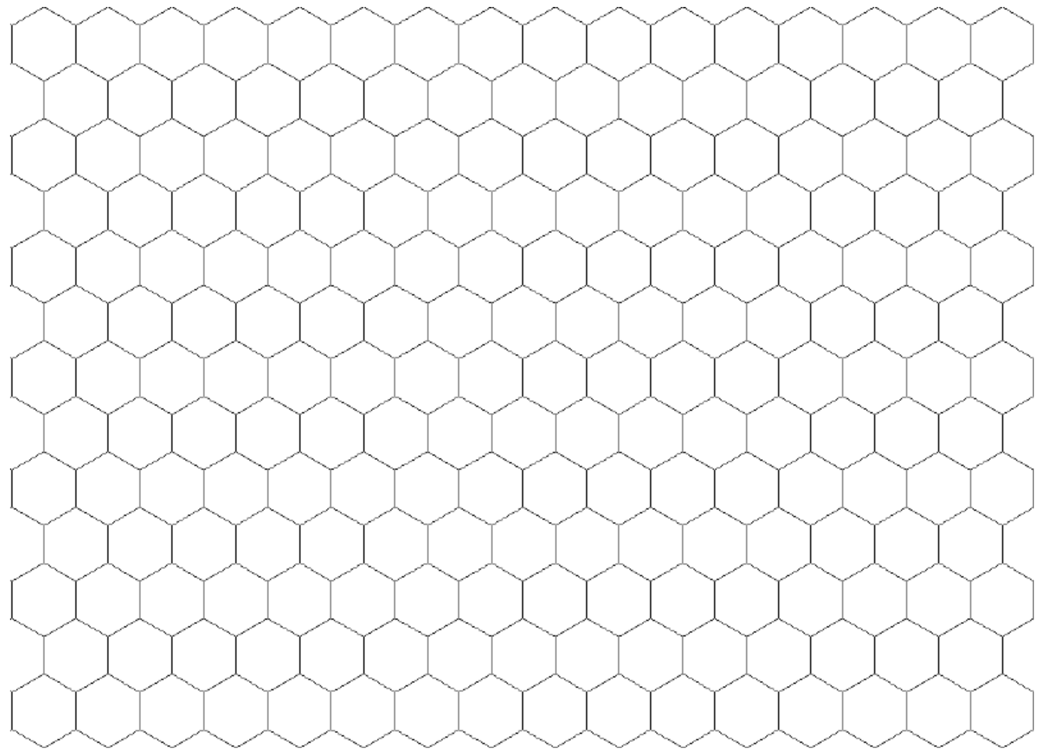
Gain in OS
Dose spacing



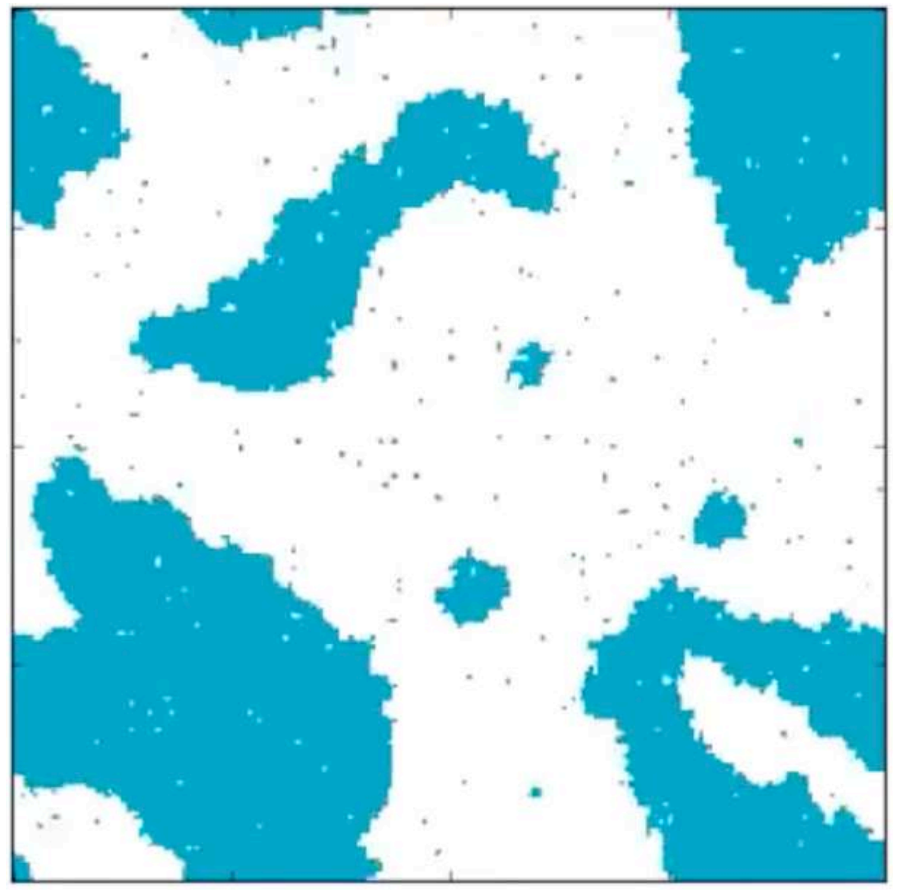

Gain in OS
Dose spacing

Individual-based models

Grid of cells

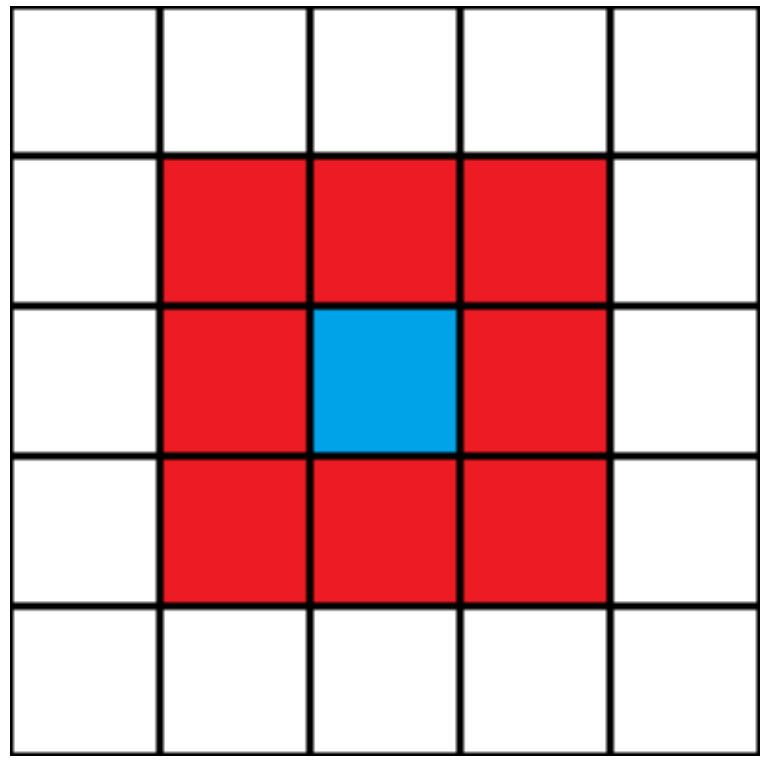


Configuration

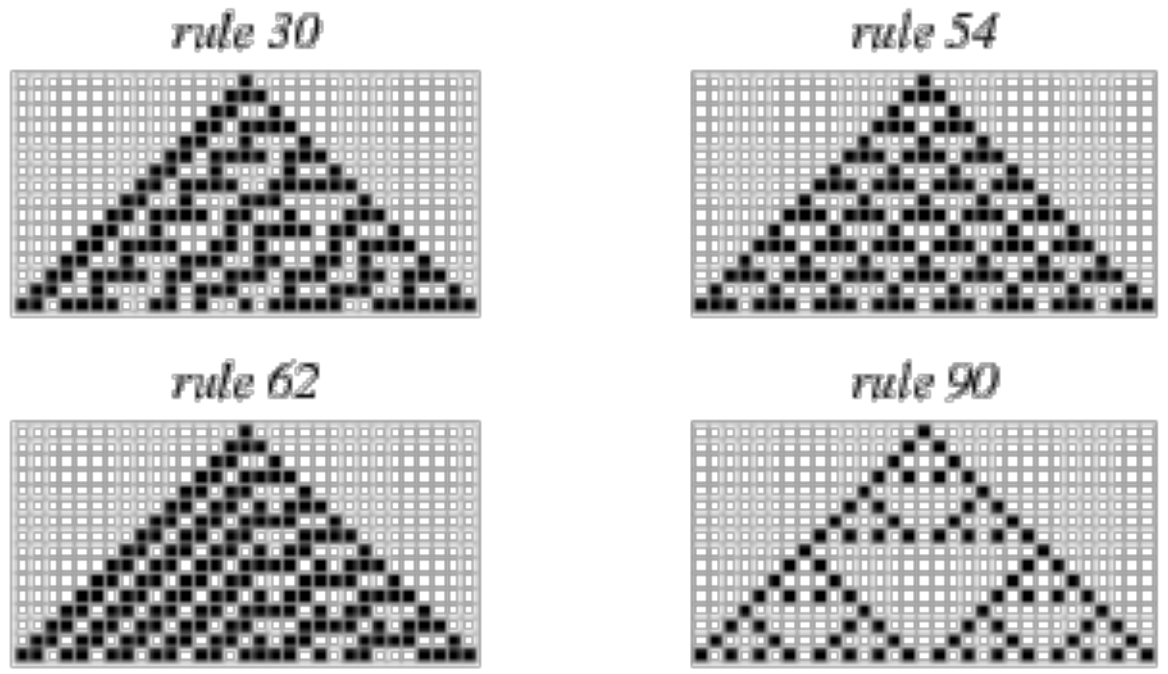


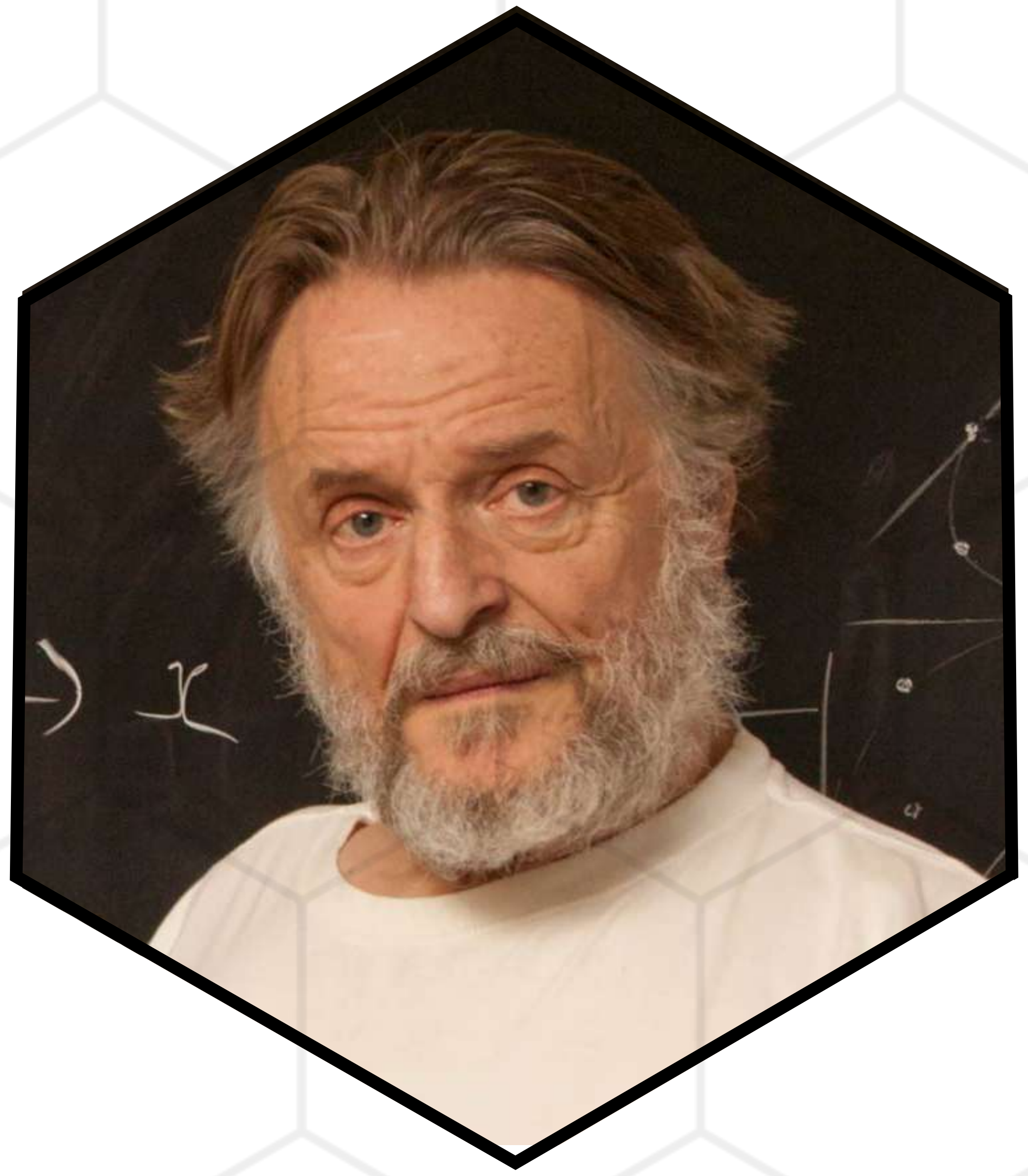
Finite set of states

Neighbourhood

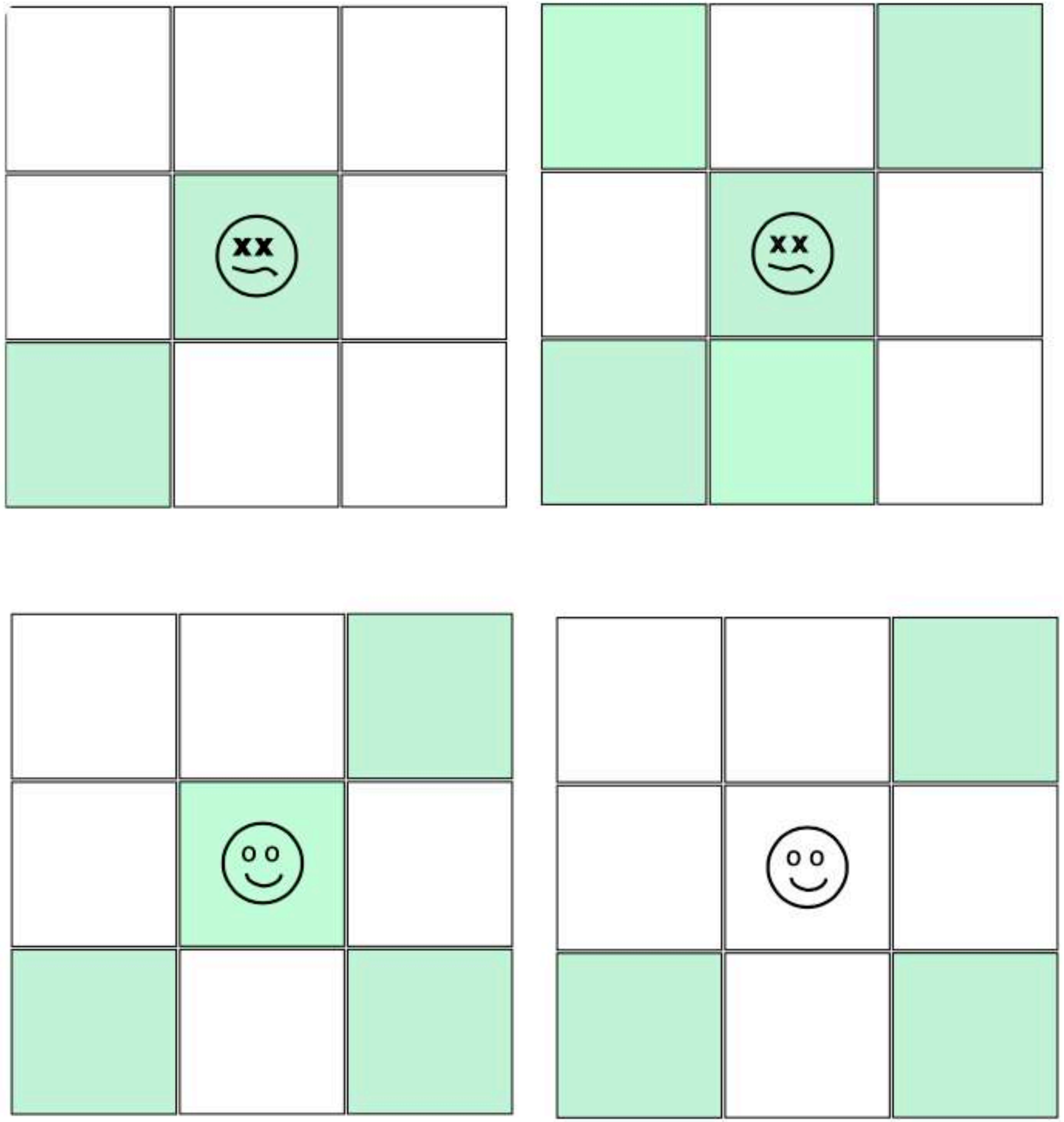


Transition function

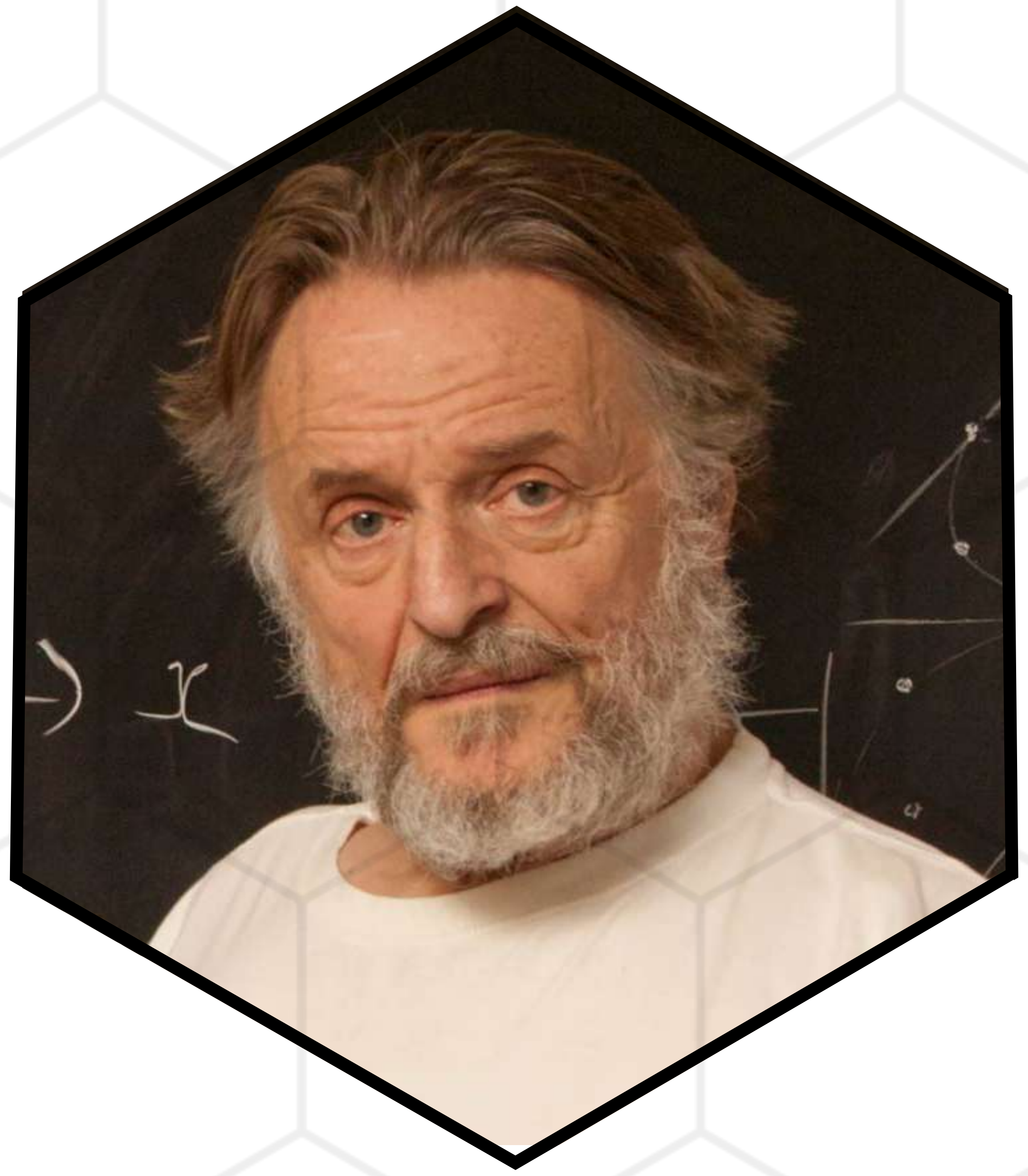




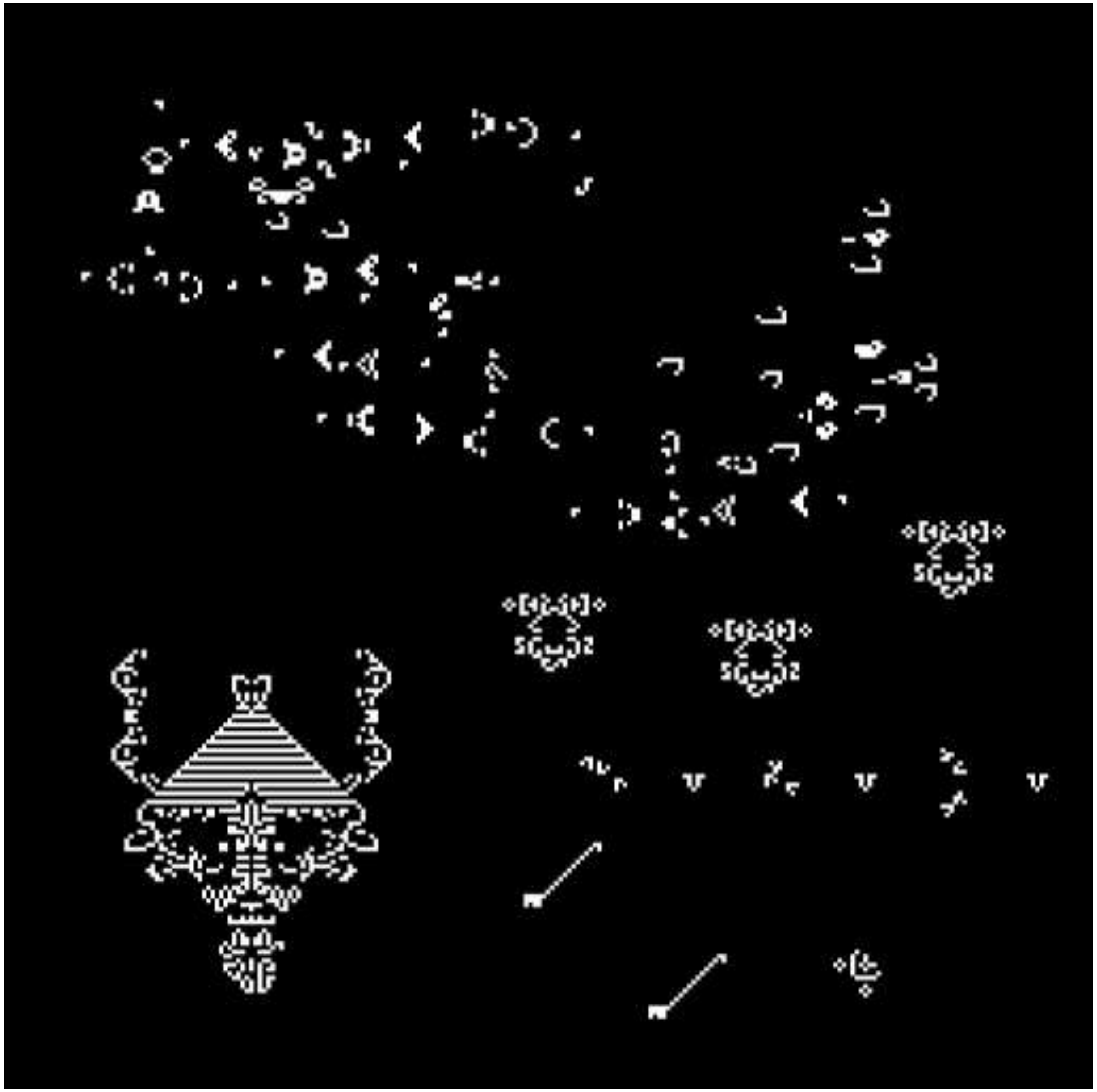
Game of Life



Source: https://beltoforion.de/article.php?a=game_of_life



Game of Life



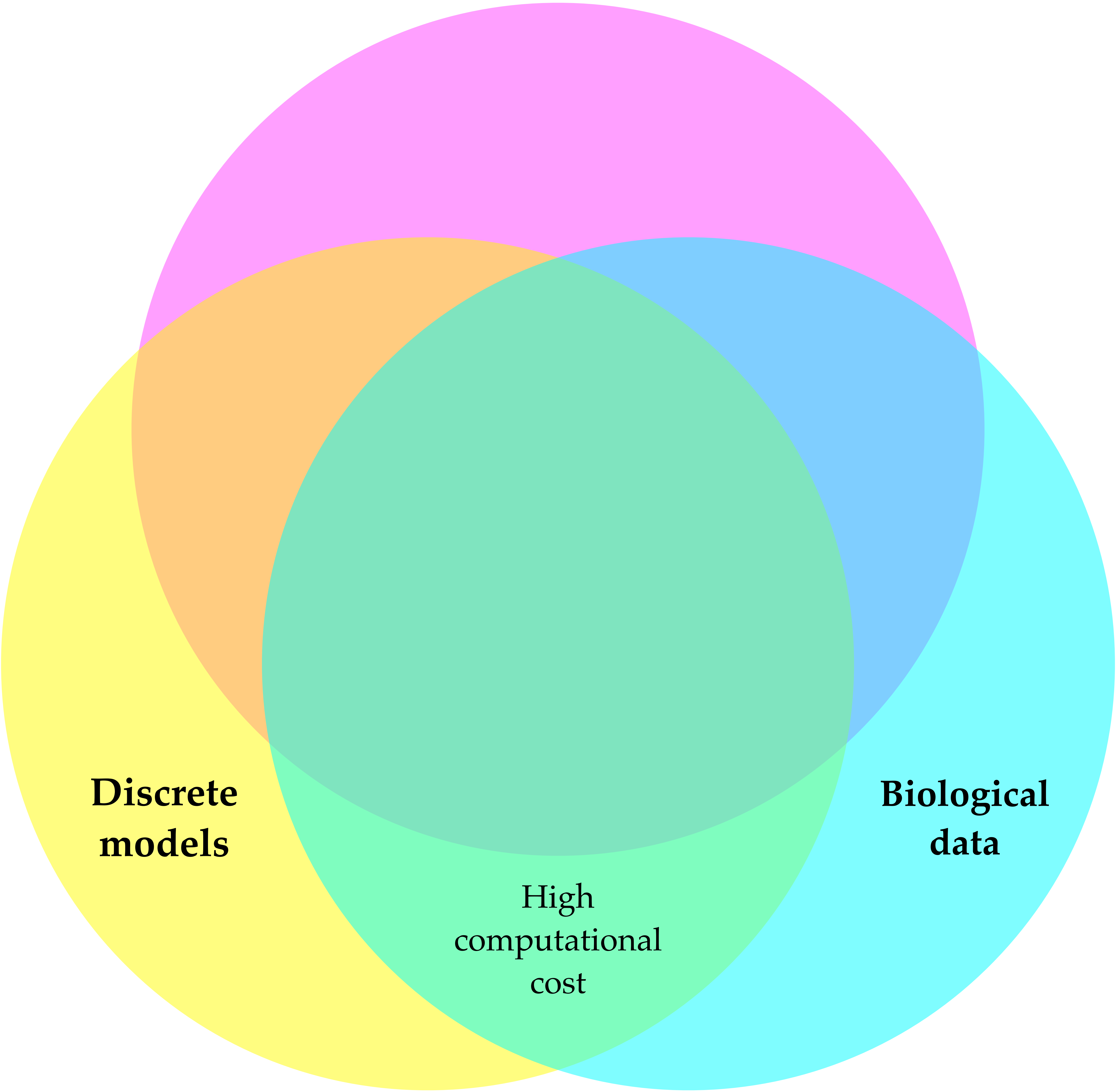
Source: https://experiments.withgoogle.com/conway-game-of-life

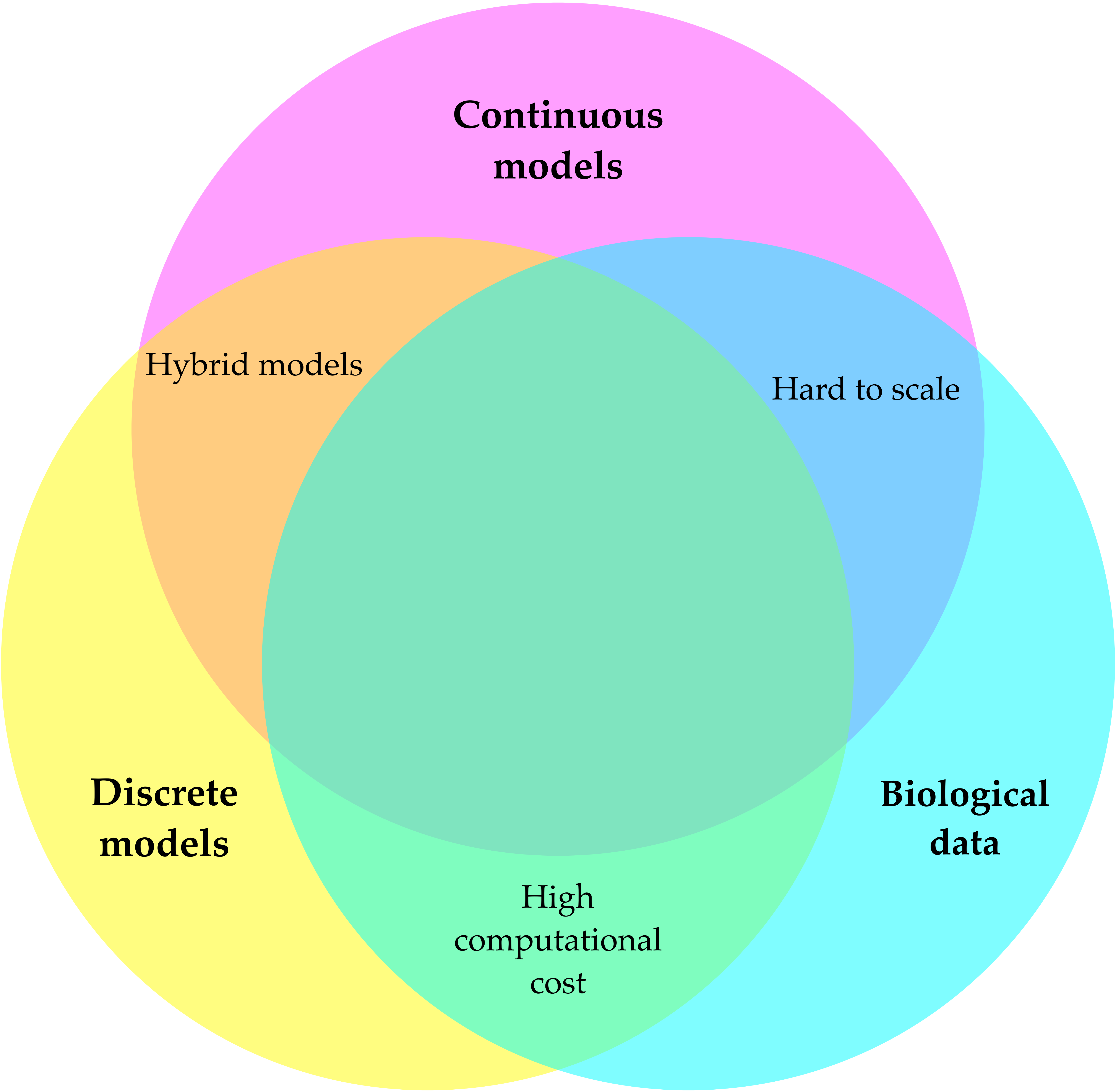
Complexity

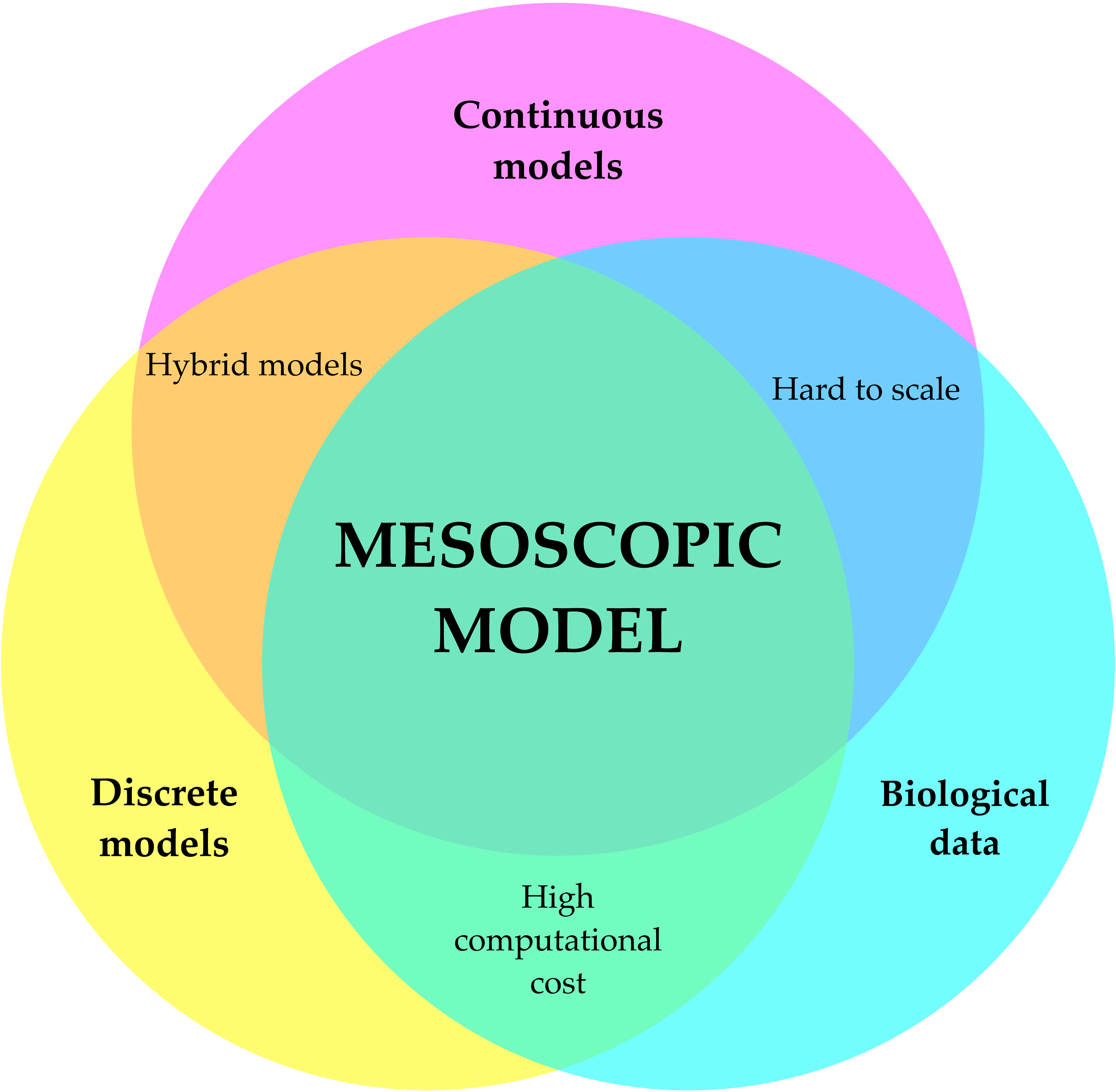
Complexity characterises the behaviour of a system or model whose components interact in multiple ways and follow local rules, leading to nonlinearity, randomness, collective dynamics, hierarchy, and emergence.[1][2]

Emergence

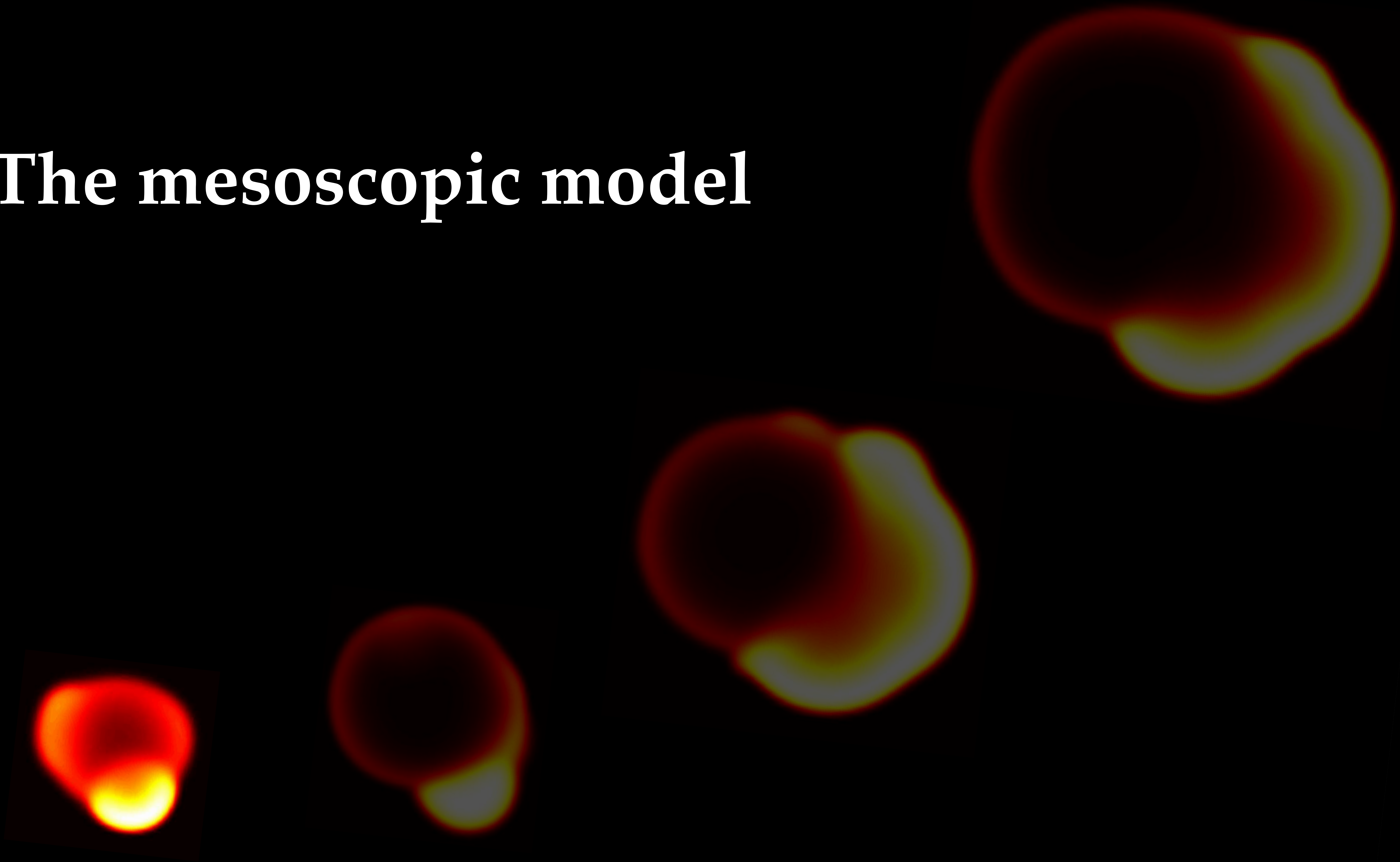
In philosophy, systems theory, science, and art, **emergence** occurs when an entity is observed to have properties its parts do not have on their own, properties or behaviors that emerge only when the parts interact in a wider whole.

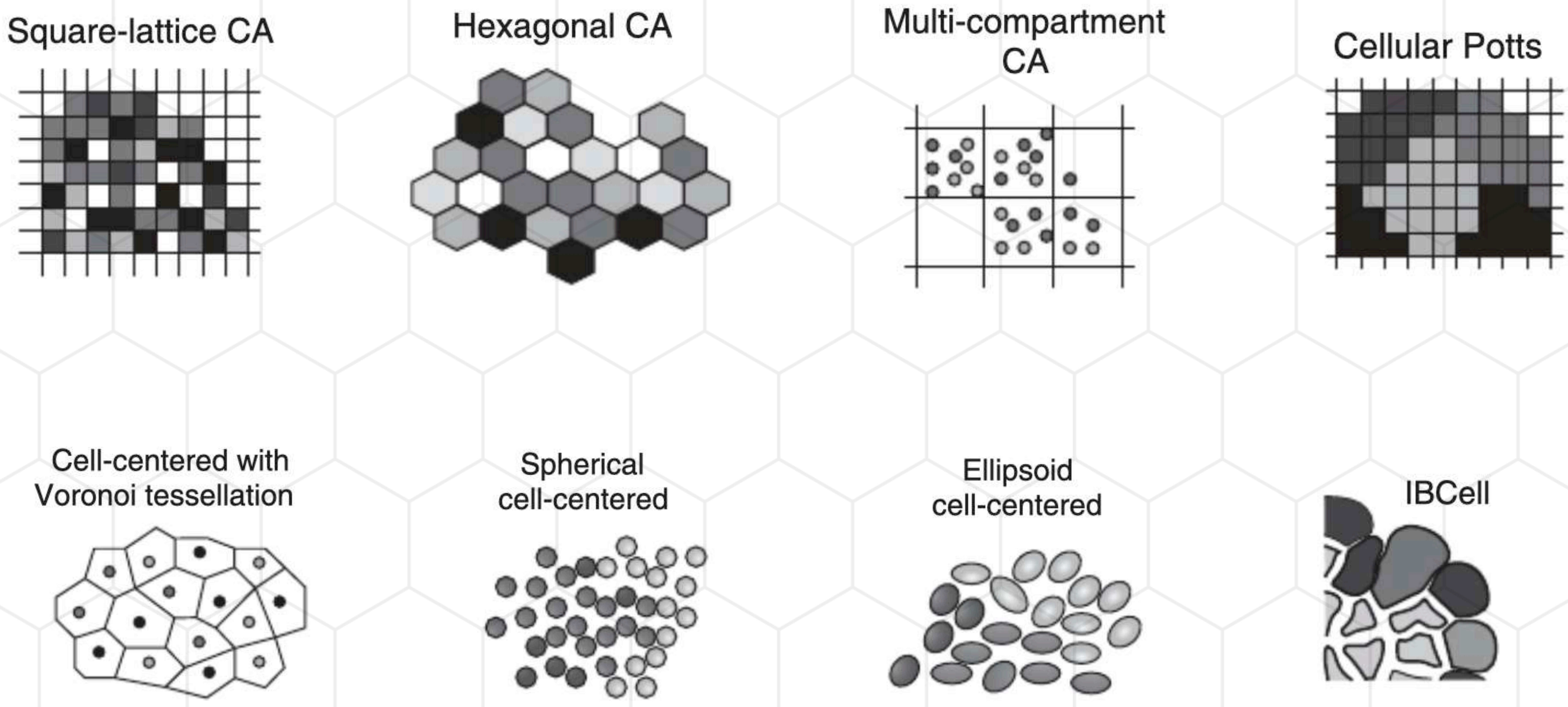

Discrete models
Biological data
High computational cost


Continuous models
Hybrid models
Hard to scale
Discrete models
Biological data
High computational cost

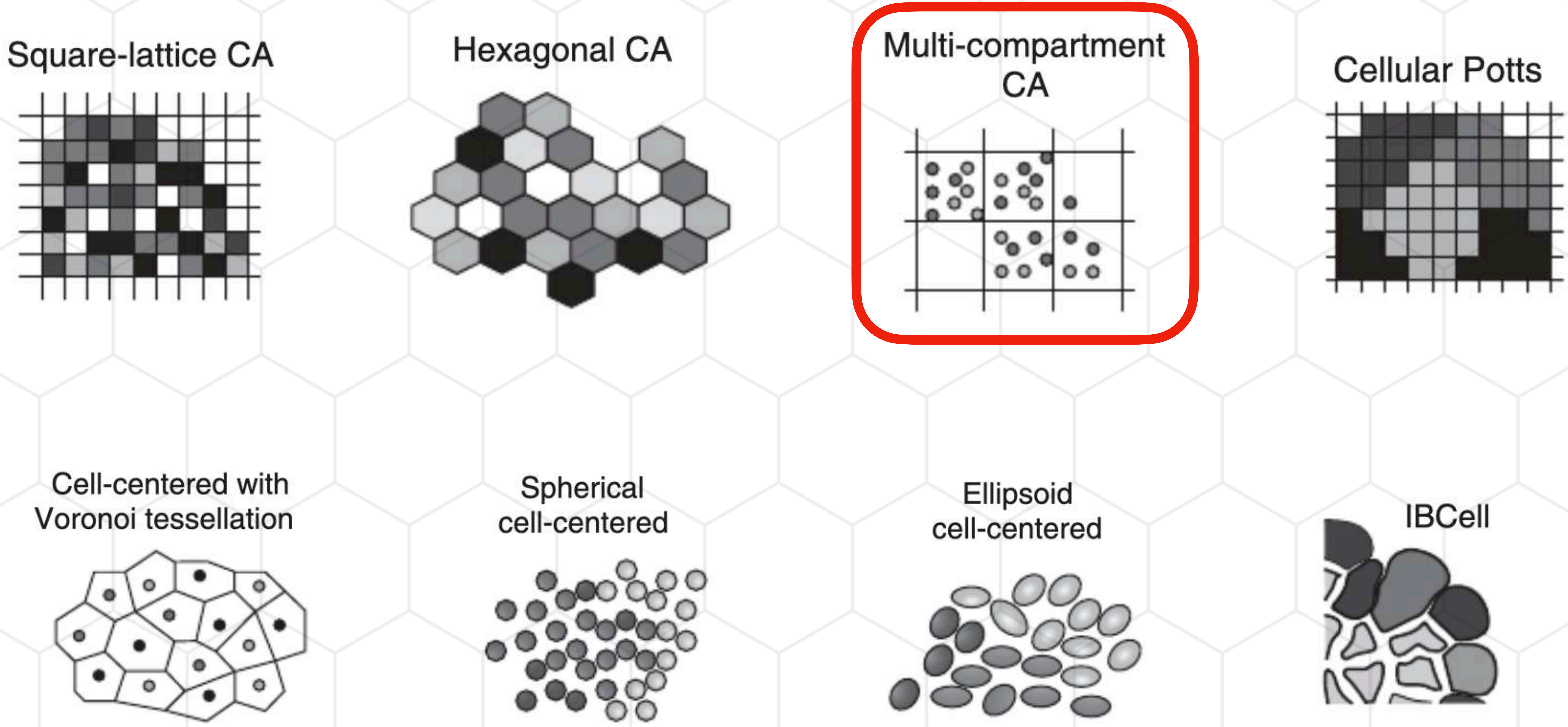

Continuous
models
Hybrid models
Hard to scale
MESOSCOPIC
MODEL
Discrete
models
Biological
data
High
computational
cost

The mesoscopic model



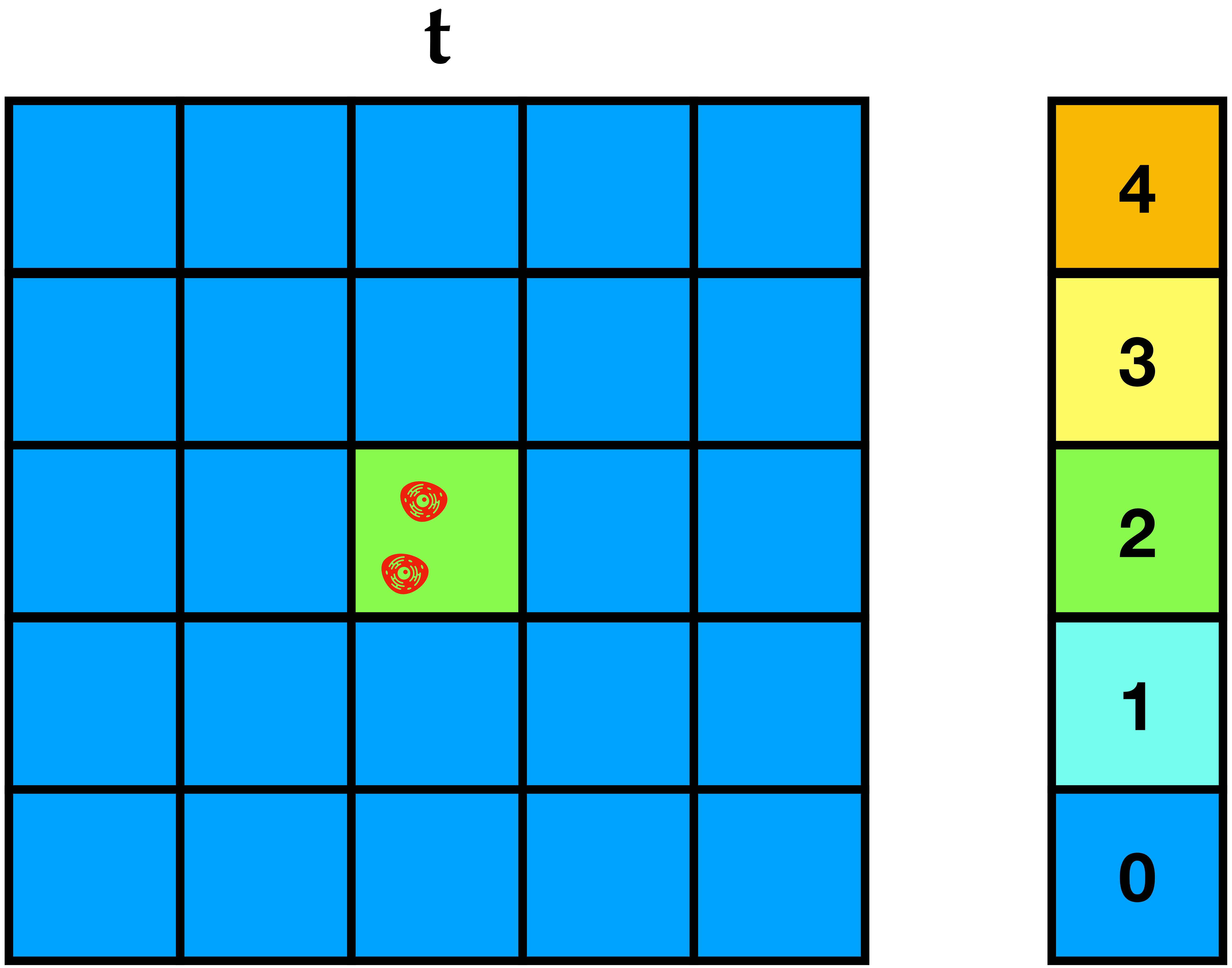


Adapted from: Rejniak, K. A., *Wil.Int.Rev.: Systems Biology and Medicine*, 2011;*3*(1), 115-125



Adapted from: Rejniak, K. A., *Wil.Int.Rev.: Systems Biology and Medicine*, 2011;3(1), 115-125

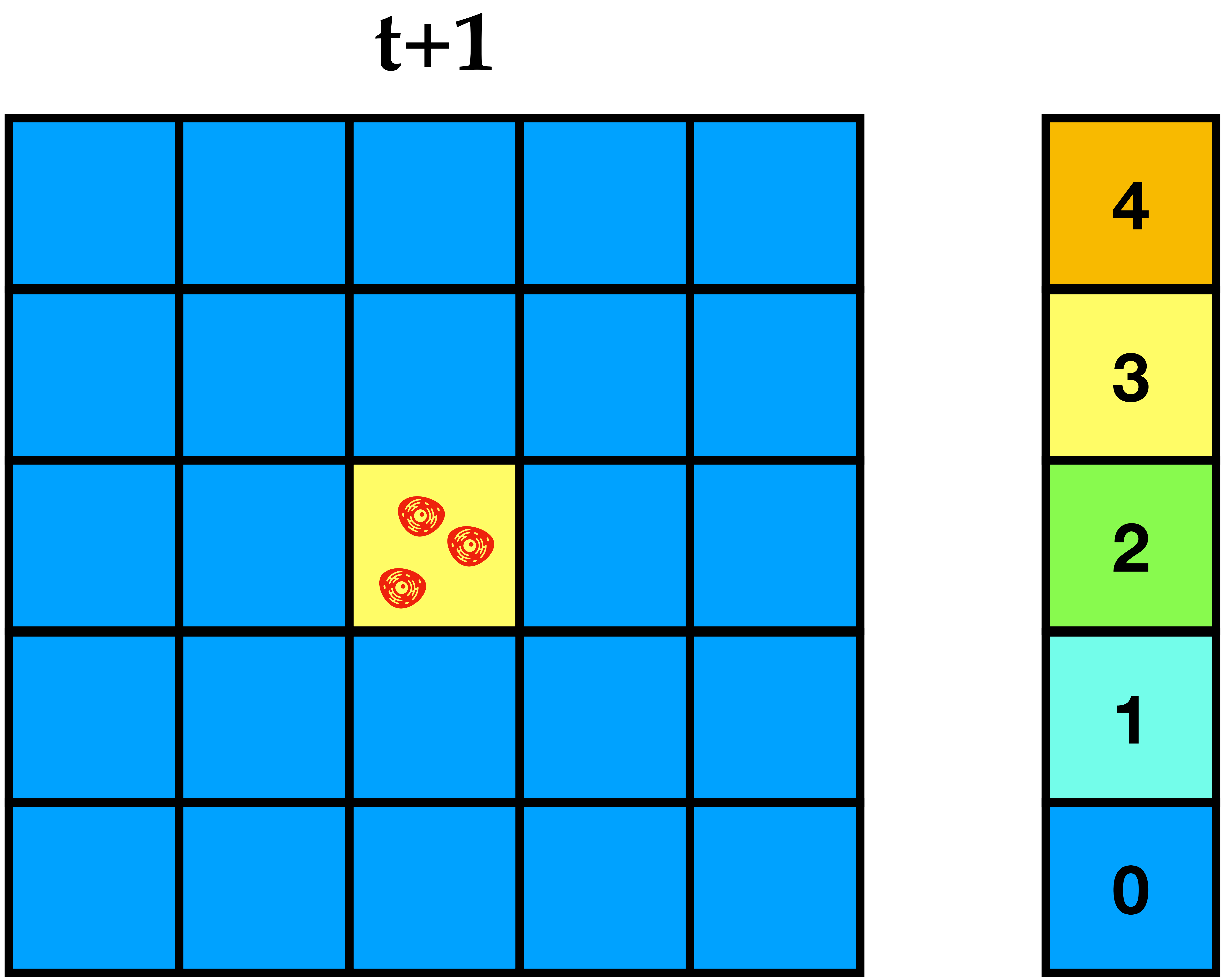
Cell division



Cell division

$$P_{rep} = \frac{\Delta t}{\tau^{rep}}\left(1 - \frac{A + D}{N_{max}}\right)$$

$$X \sim \mathrm{B}(A_i, P_{rep})$$



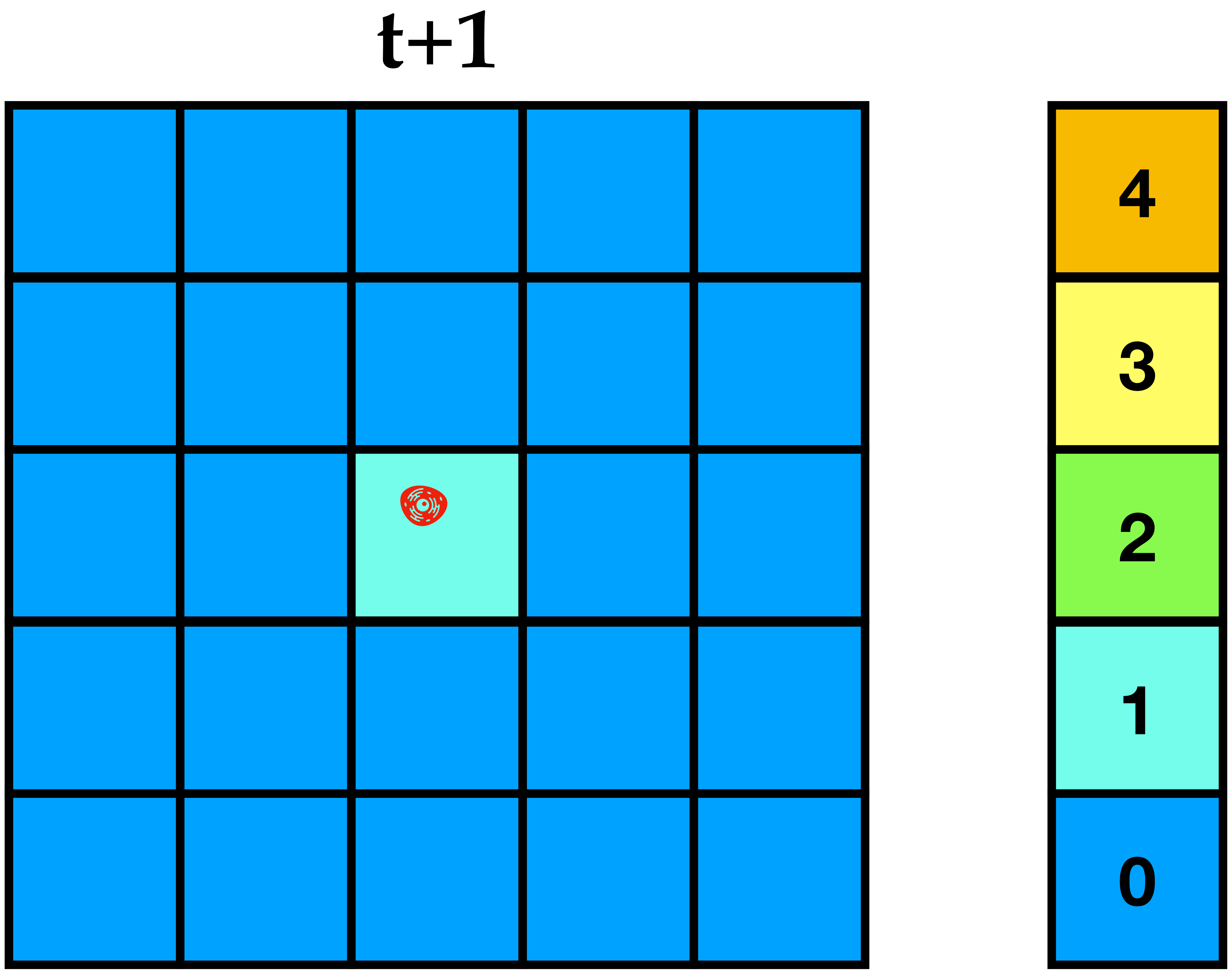
Cell attempts division $\sim$ Bernoulli(P_{div})

N cells attempt division $\sim$ Binomial(N, P_{div})

Cell death

$$P_{death} = \frac{\Delta t}{\tau^{death}} \left(\frac{A + D}{N_{max}} \right)$$

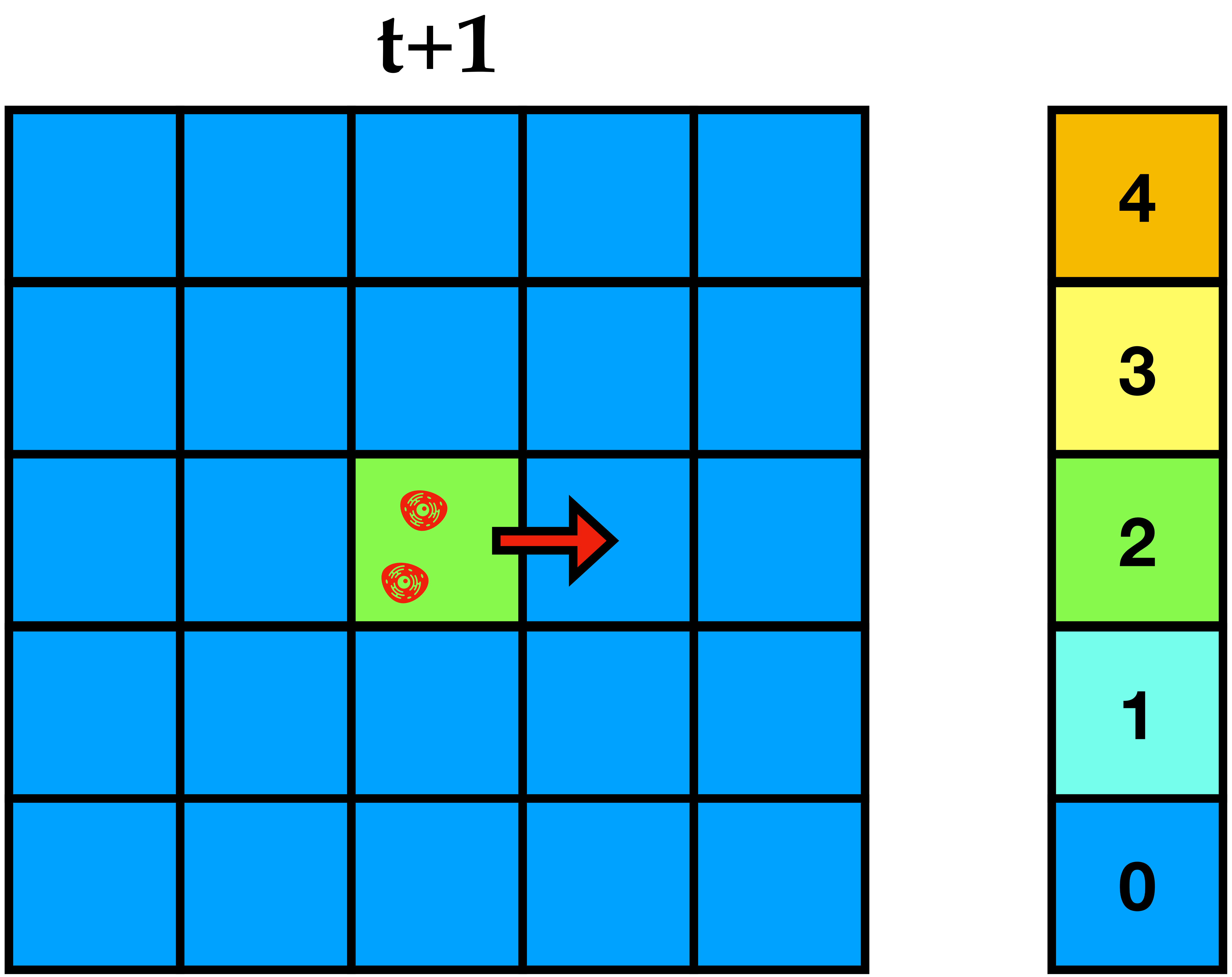
$$X \sim \mathrm{B}(A_i, P_{death})$$

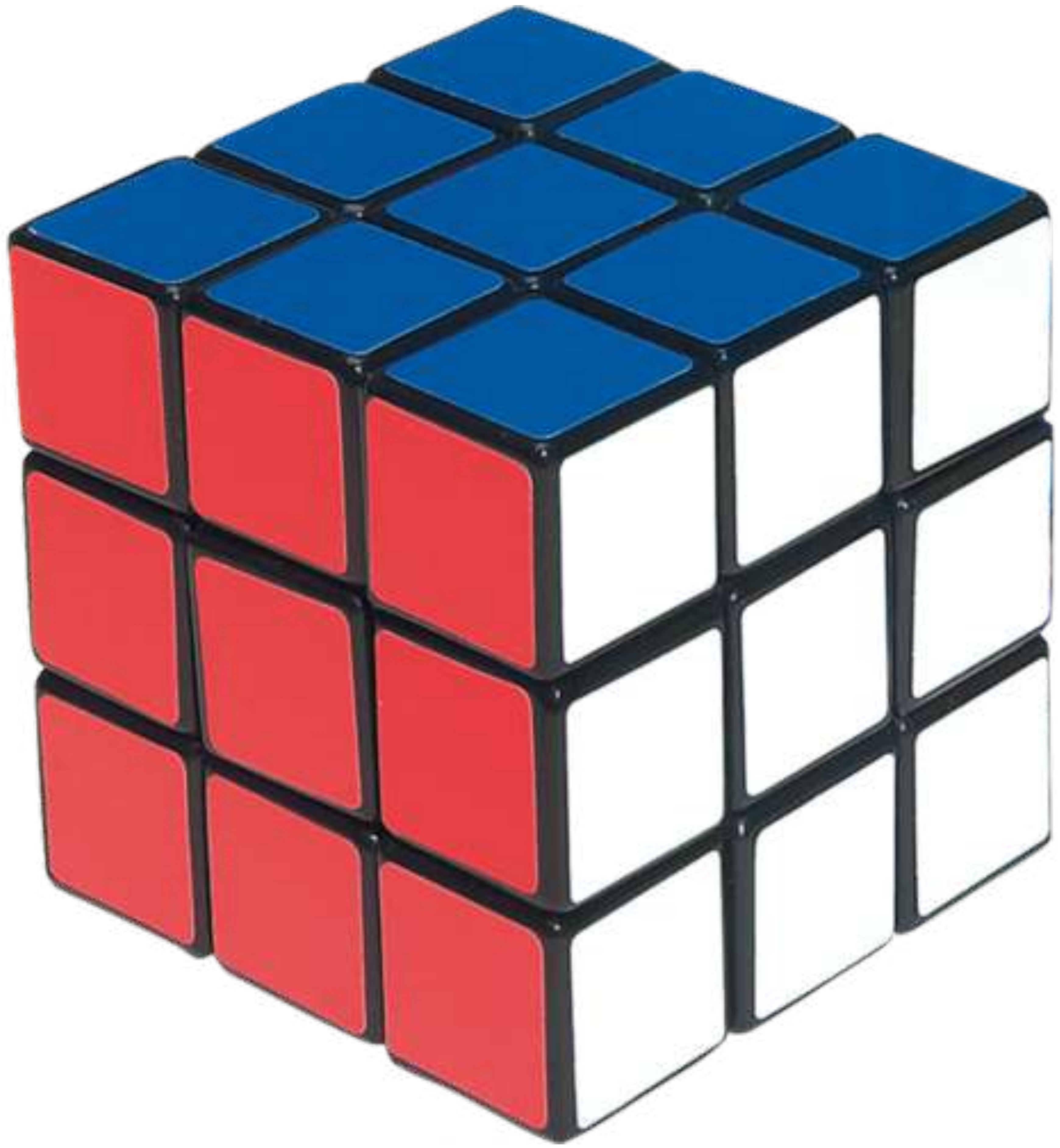


Cell migration

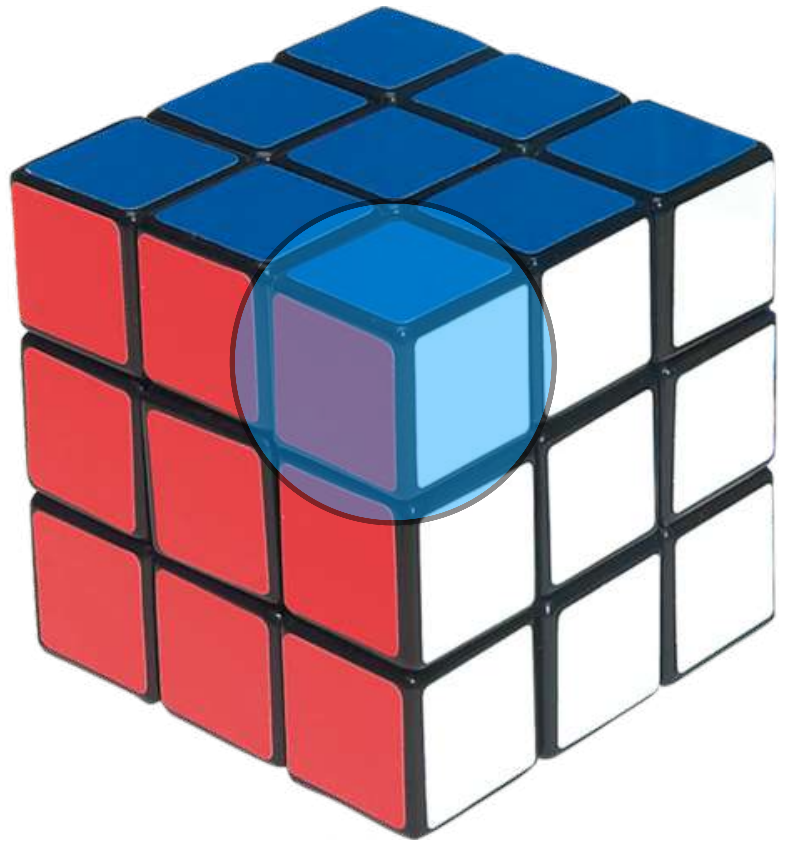
$$P_{mig} = \rho^{mig} \frac{\Delta t}{\Delta x^2} \left(\frac{A + D}{N_{max}} \right)$$

$$X \sim \mathrm{B}(A_i, P_{mig})$$

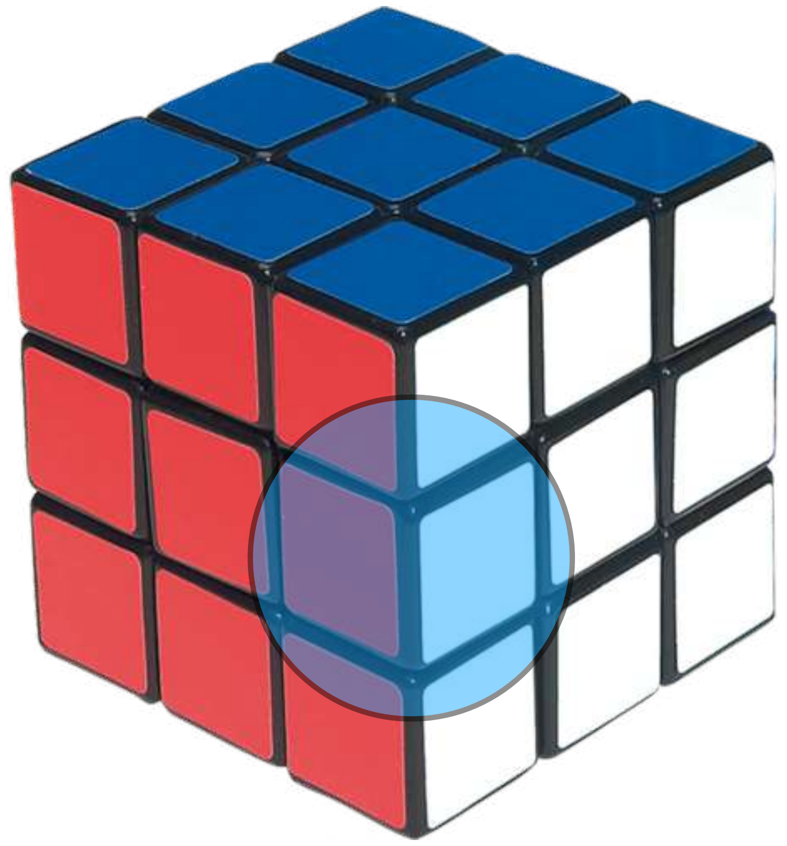


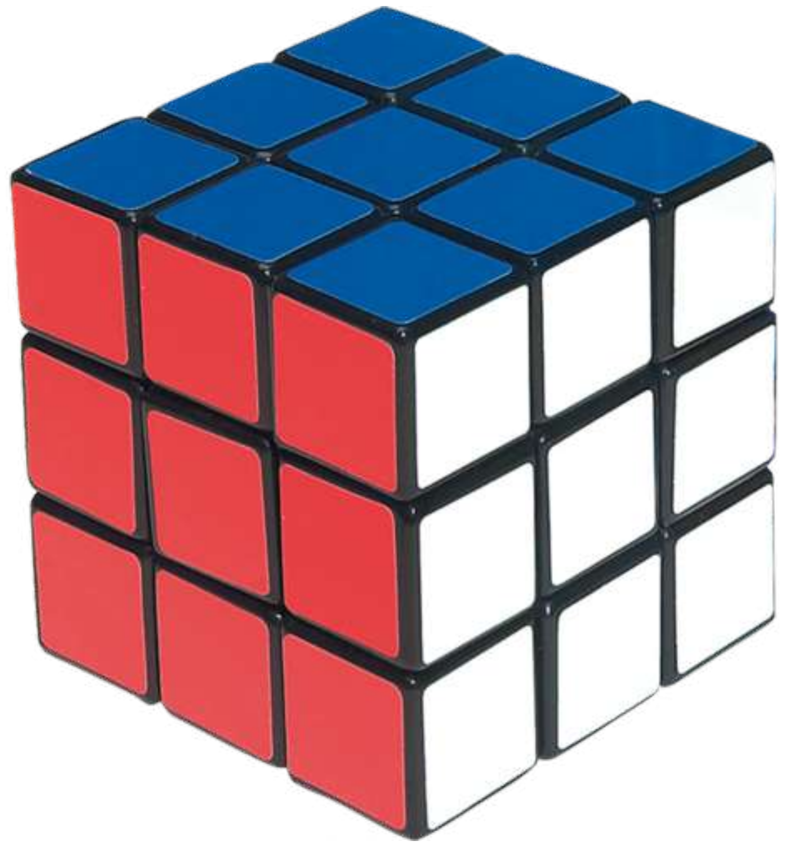


$$P \propto \frac{1}{\sqrt{3}}$$

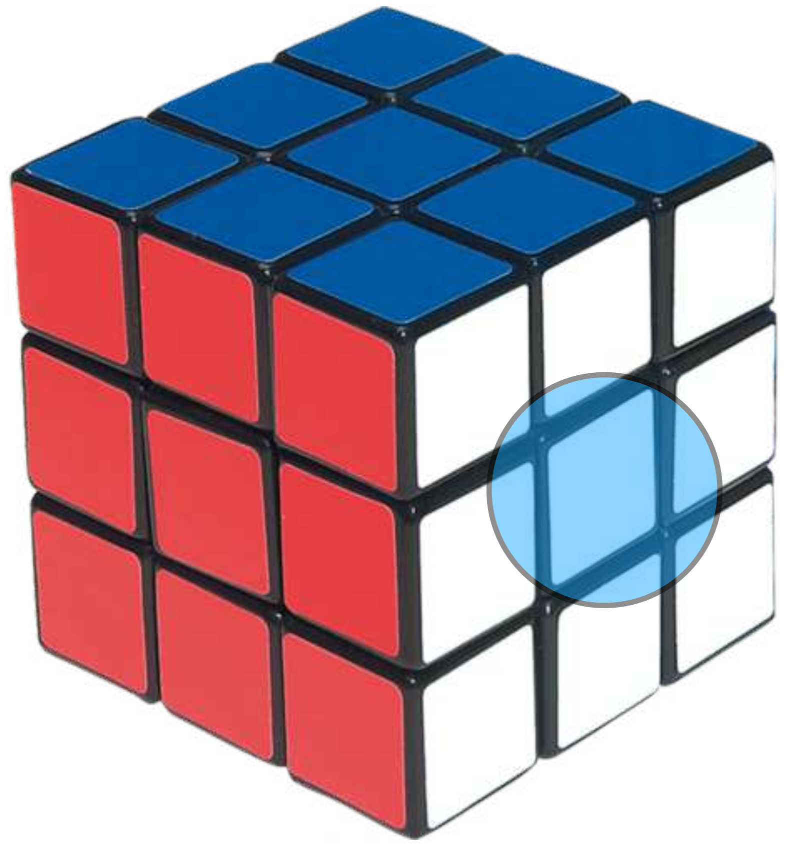


$$P \propto \frac{1}{\sqrt{2}}$$





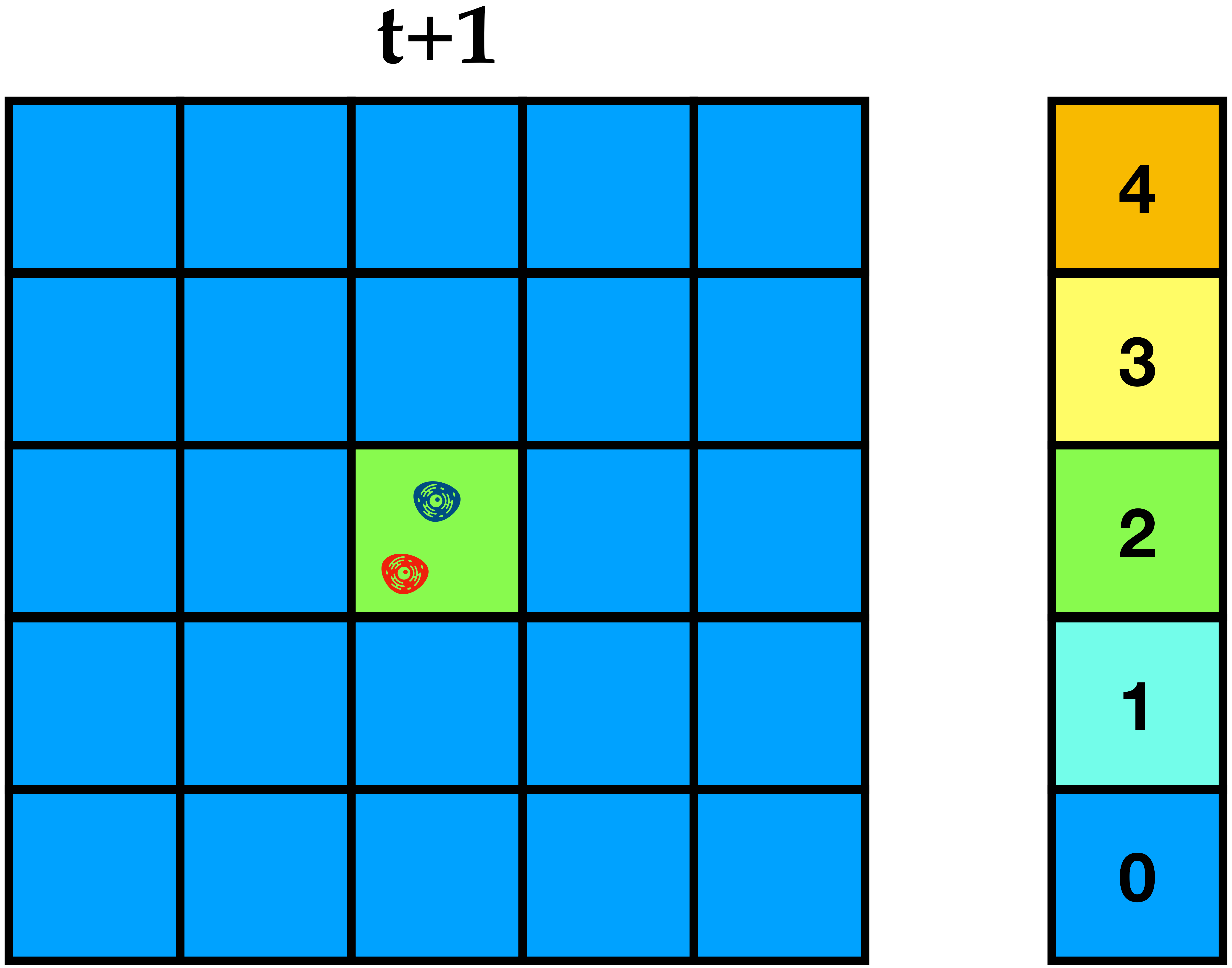
$$P \propto 1$$



Mutation
Phenotypic transition

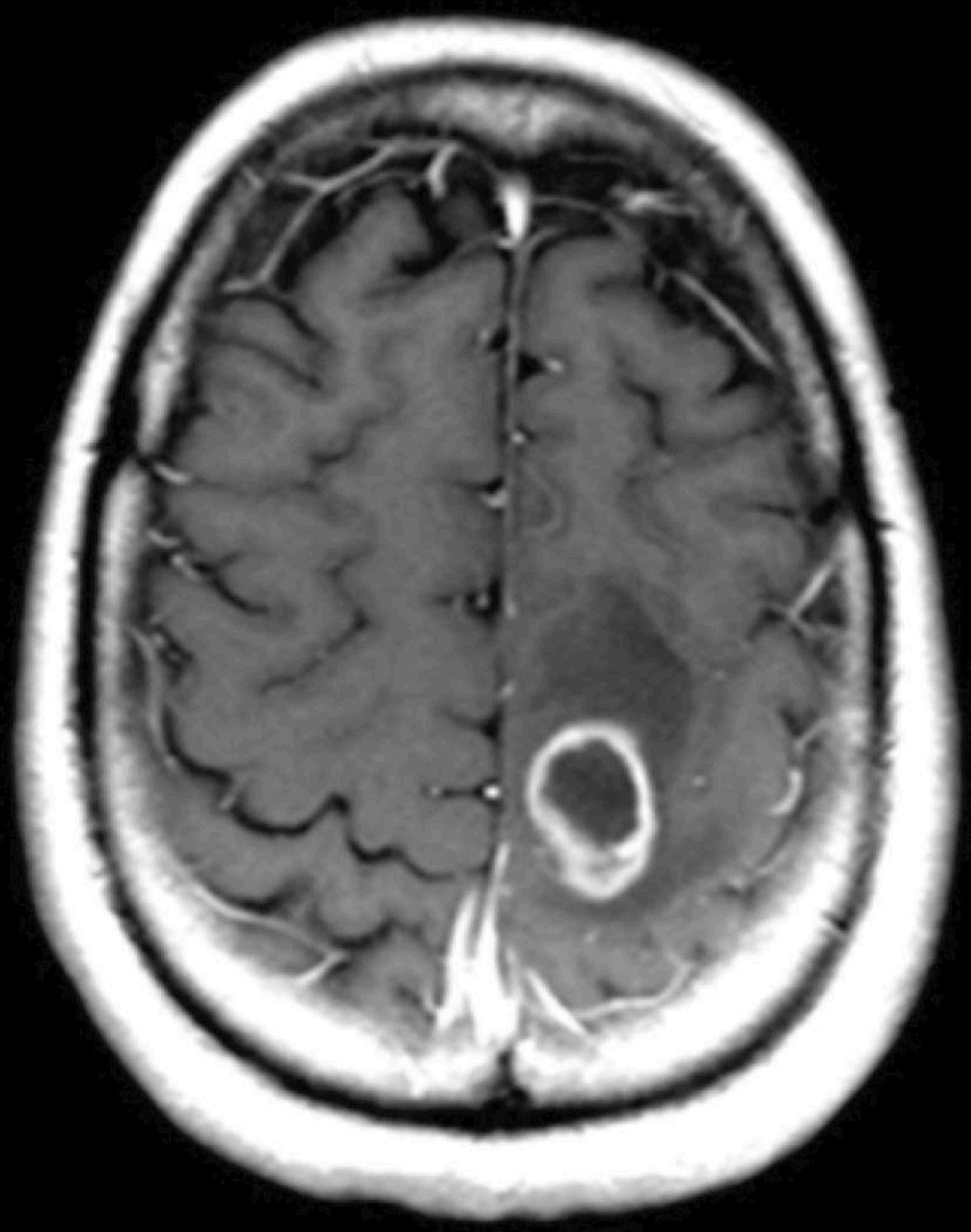
$$P_{mut} = \frac{\Delta t}{\tau^{mut}} \left(\frac{A_i}{N_{max}} \right)$$

$$X \sim \mathrm{Be}(P_{mut})$$

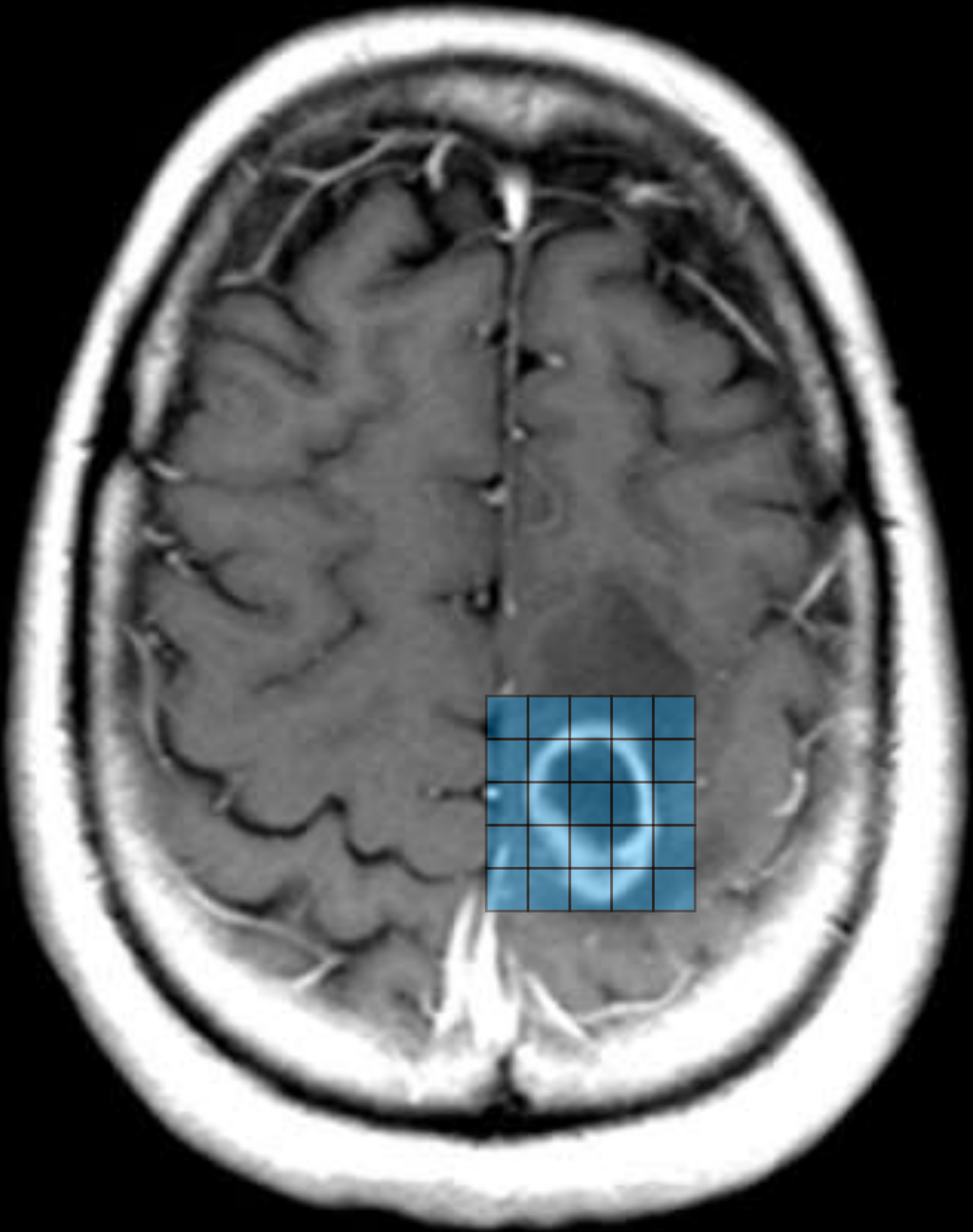


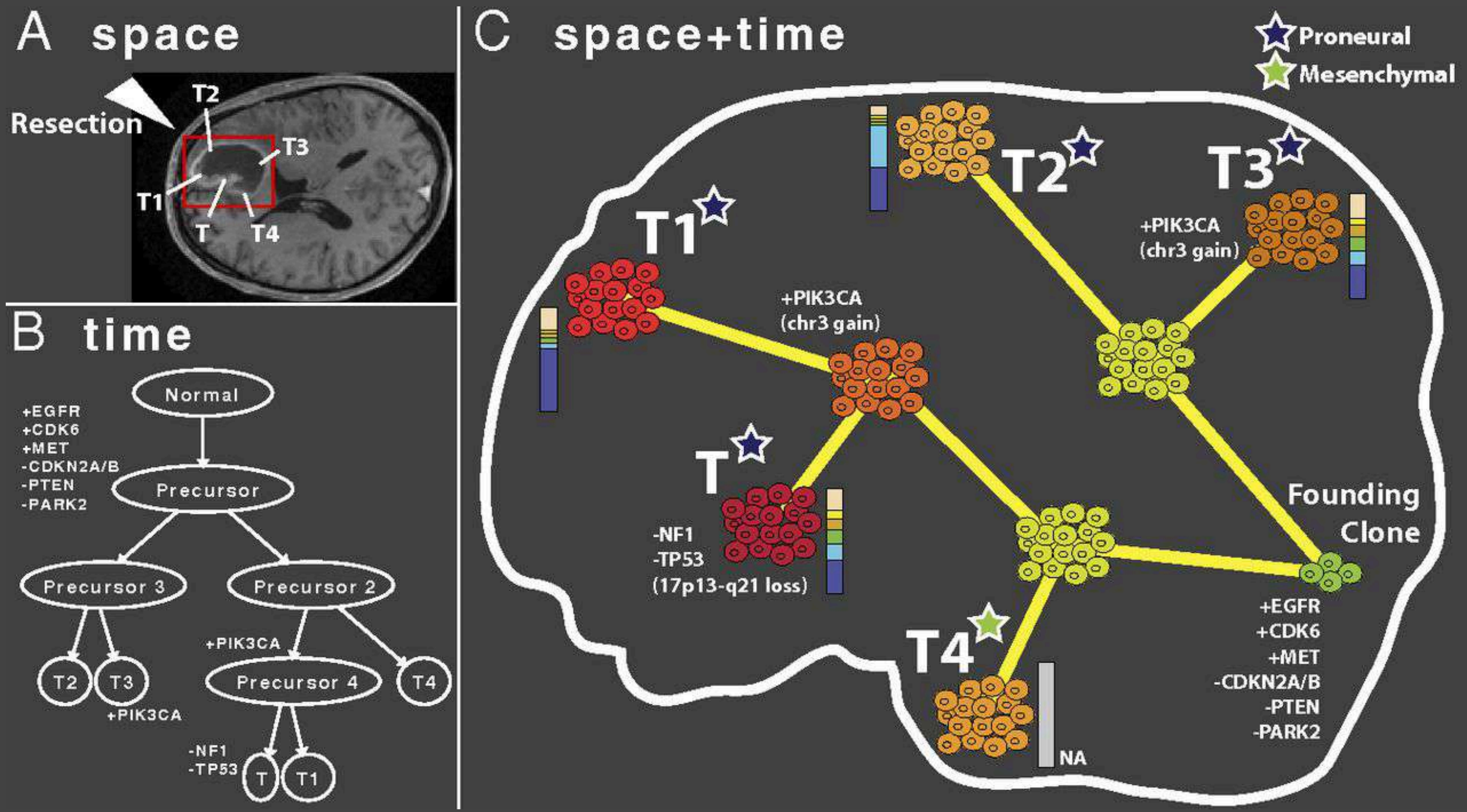
Adapted from: Gaskell H, Sharma P, Colley HE, Murdoch C, Williams DP, Webb SD. Characterization of a functional C3A liver spheroid model. Toxicology research. 2016 Jul 1;5(4):1053-65.

GLIOBLASTOMA:
The most aggressive gliomas

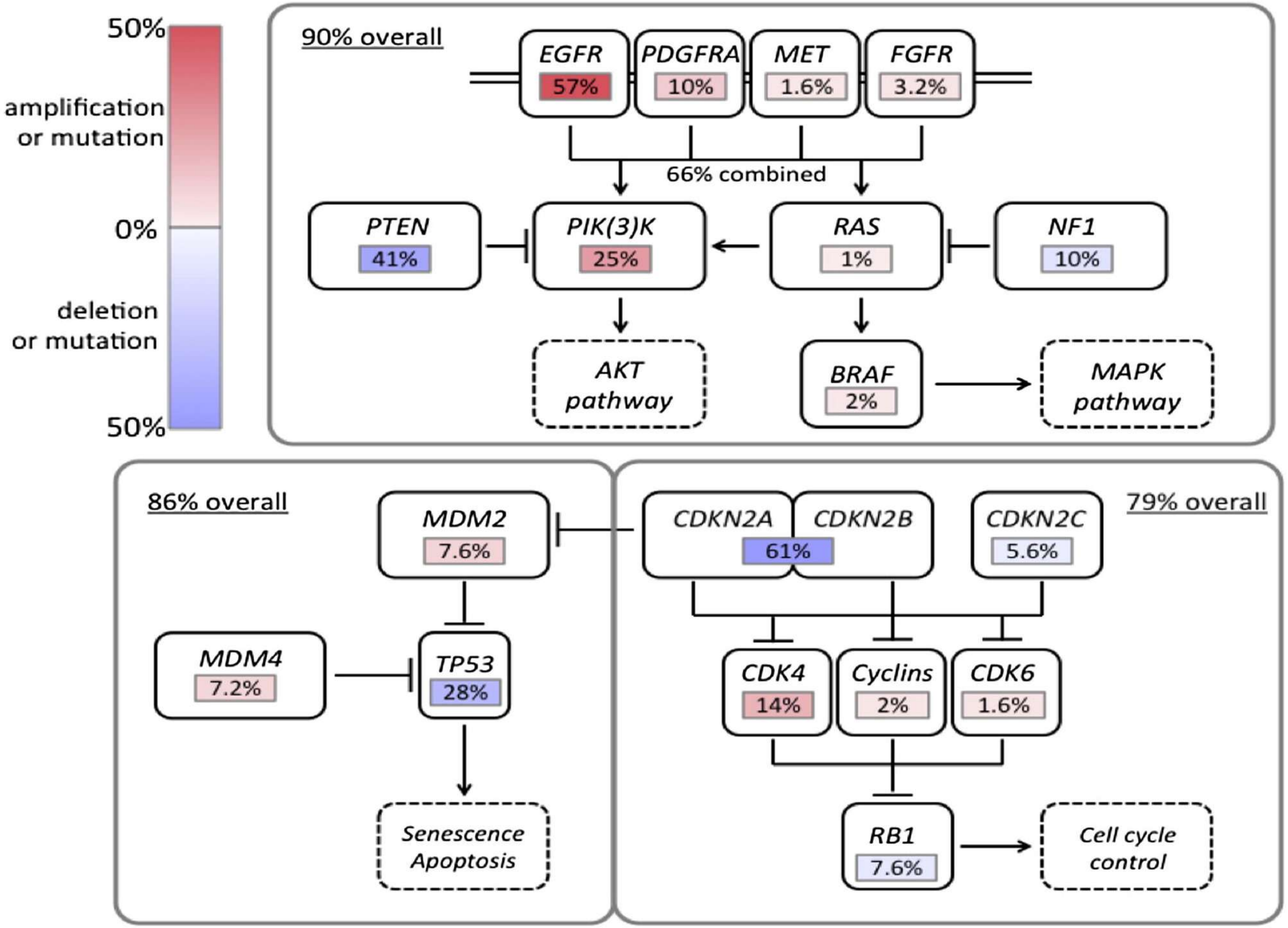


Incurable
Fast progression
Becomes resistant
Reduced survival

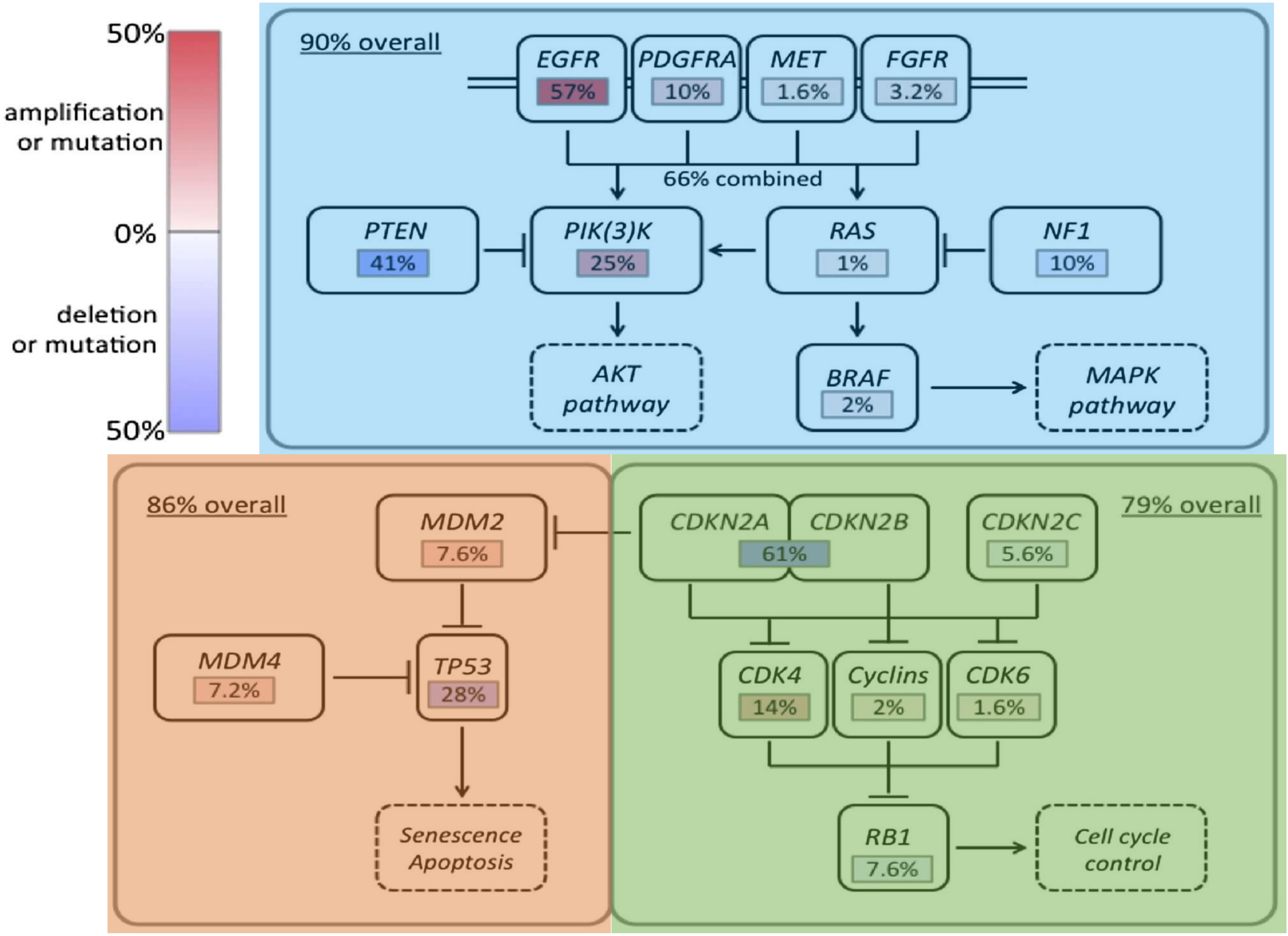




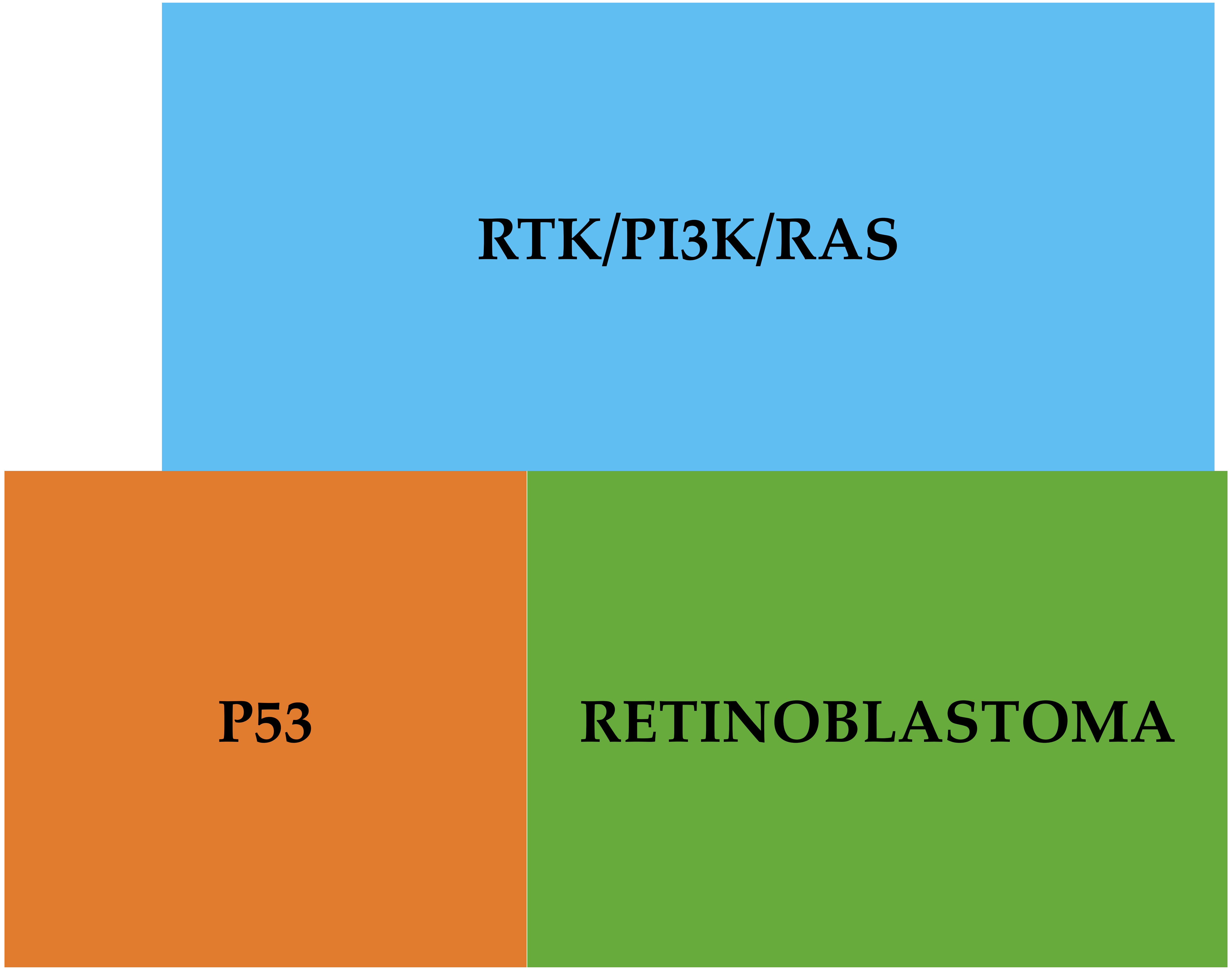
Sottoriva, A. et al. (2013) Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. *Proceedings of the National Academy of Sciences* 110(10), 4009– 4014.

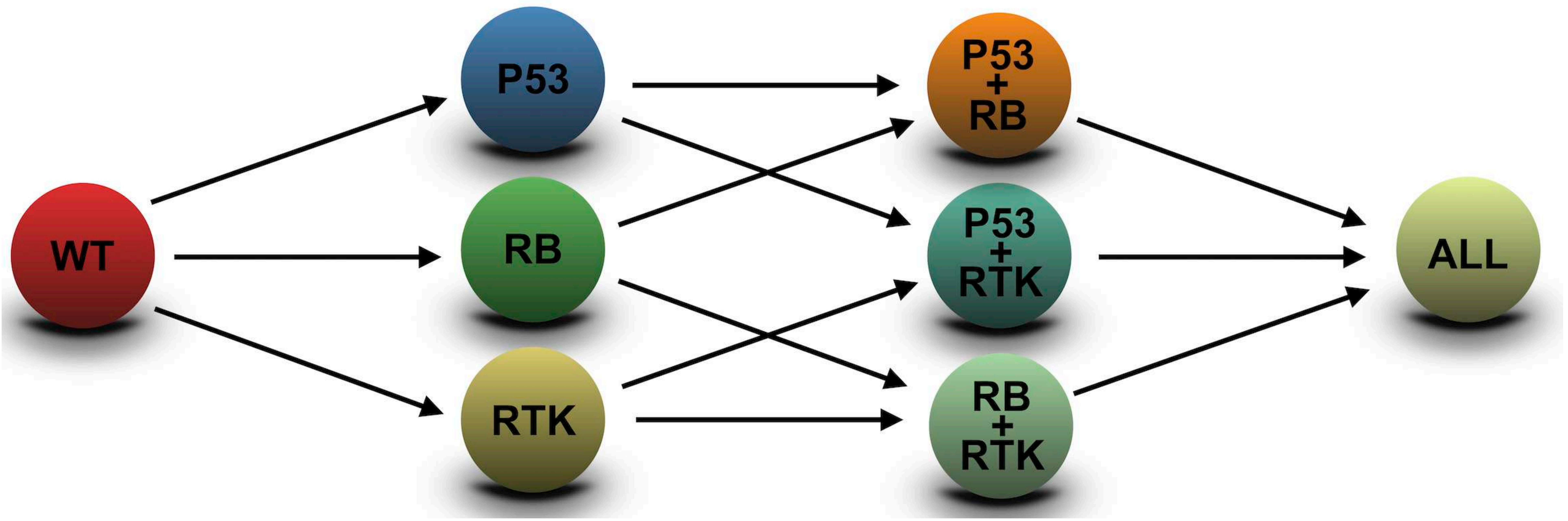


Brennan, C. W. et al. (2013) The somatic genomic landscape of glioblastoma. *Cell* 155(2), 462–477.

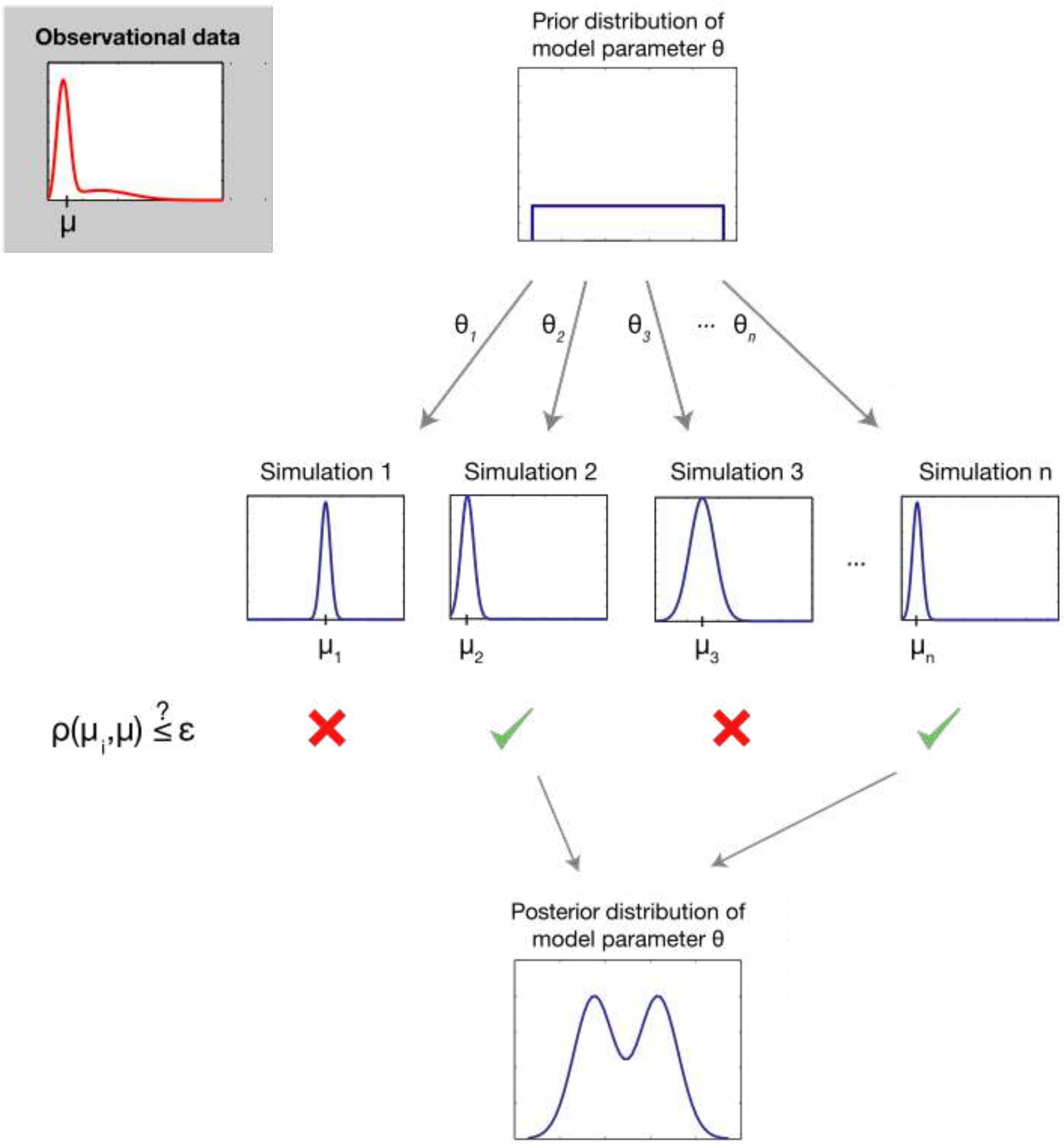


Brennan, C. W. et al. (2013) The somatic genomic landscape of glioblastoma. *Cell* 155(2), 462–477.

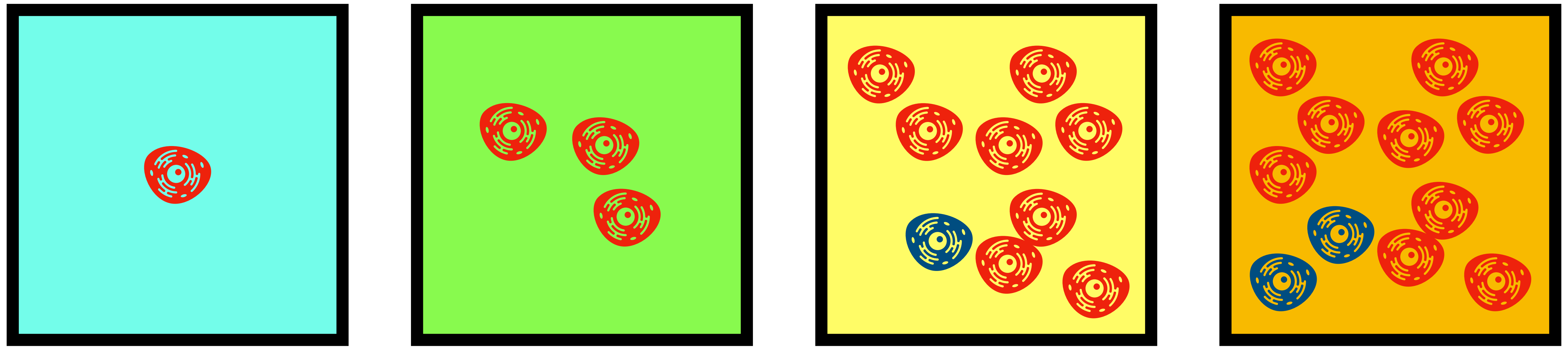

RTK/PI3K/RAS
P53
RETINOBLASTOMA

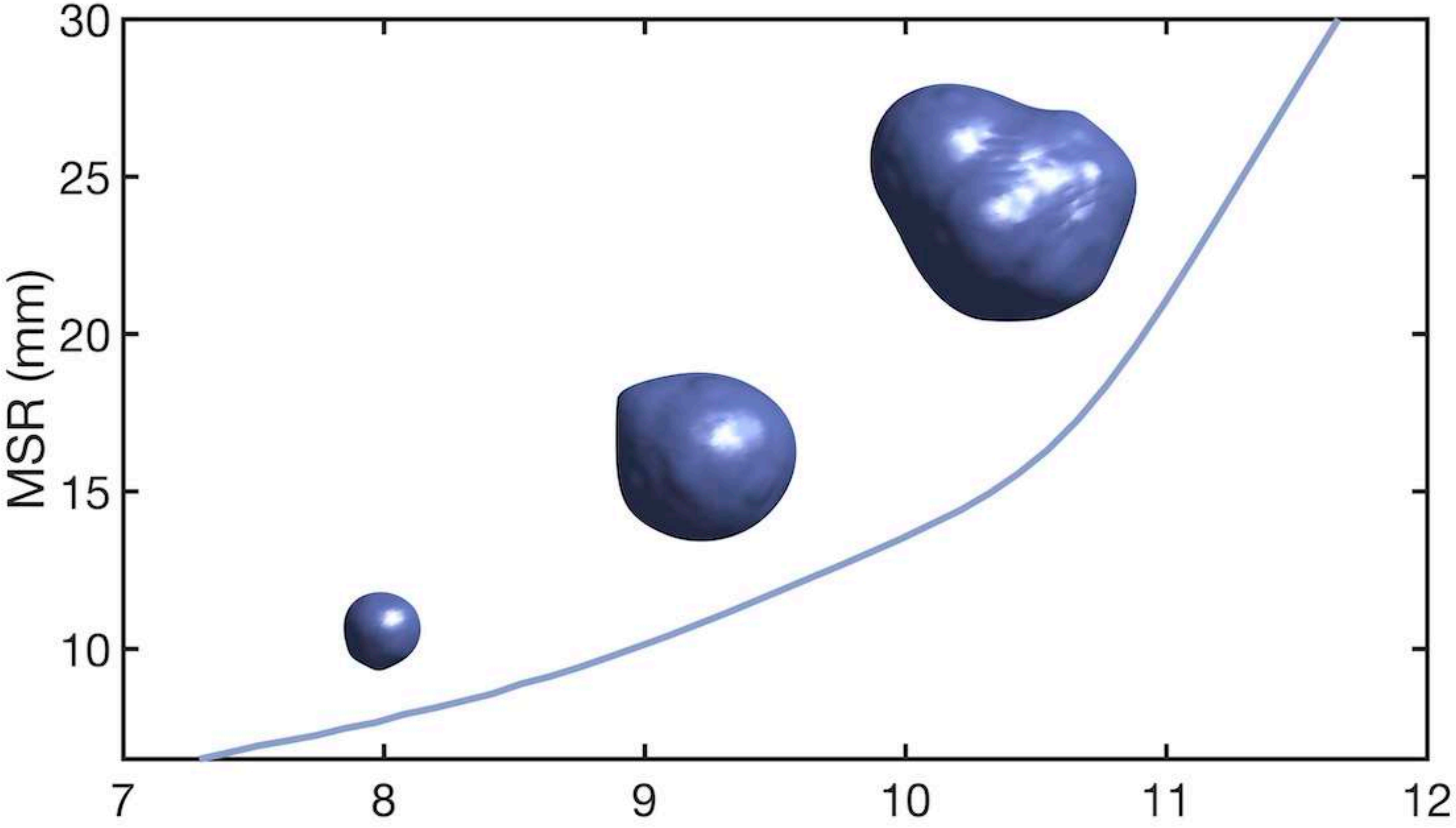

WT
P53
RB
RTK
P53
+
RB
P53
+
RTK
RB
+
RTK
ALL

ABC rejection algorithm

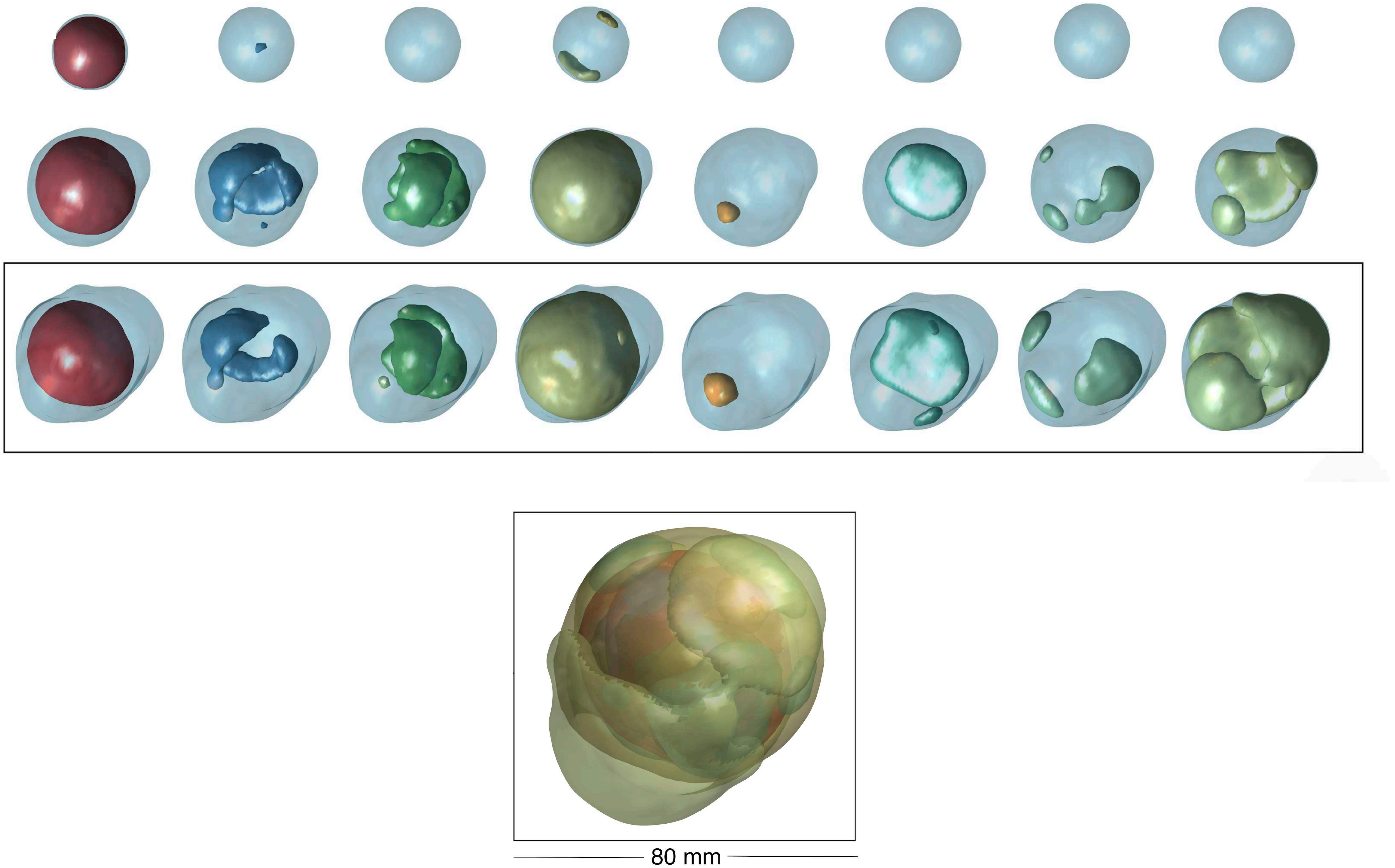


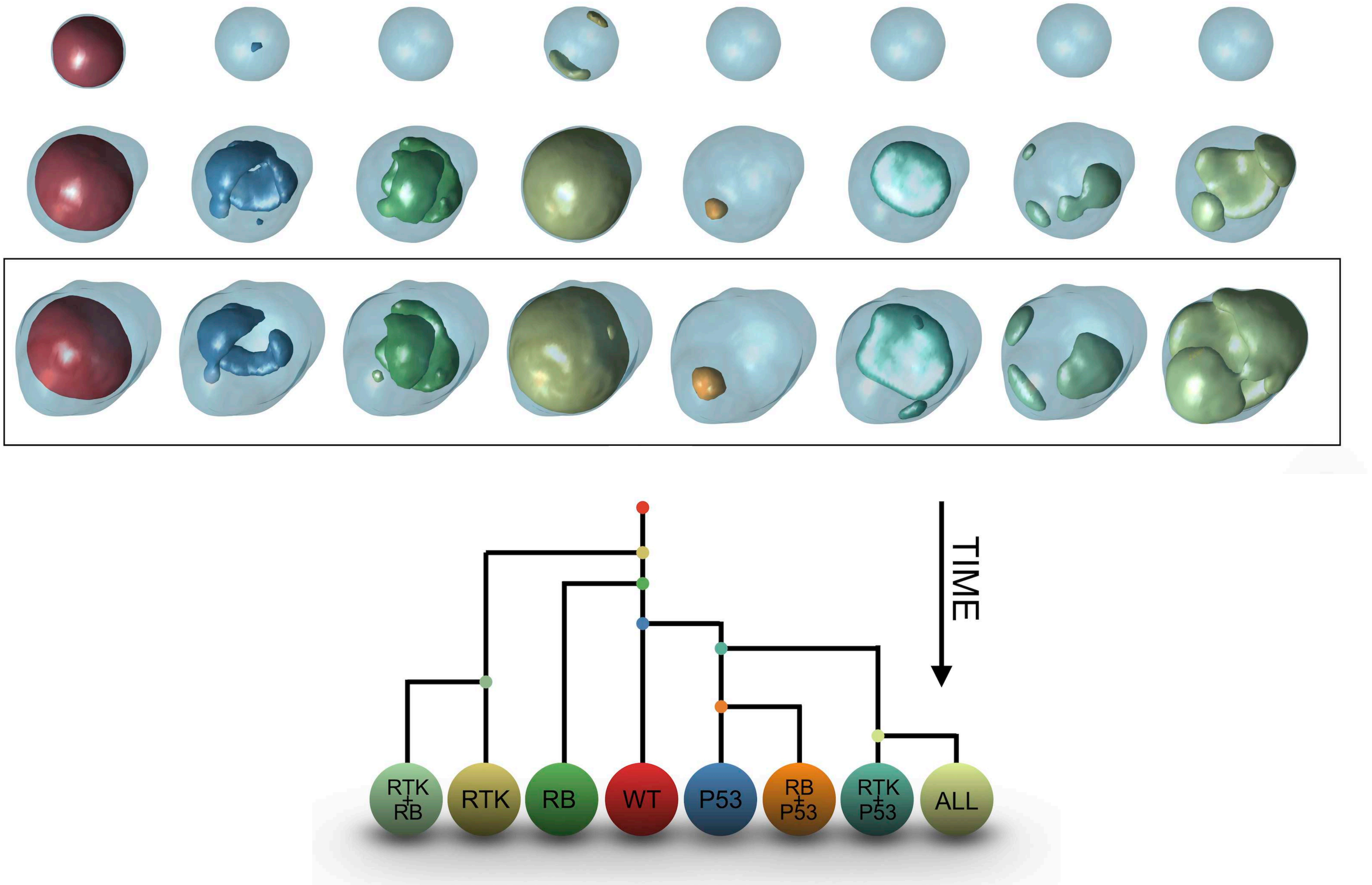

Observational data
μ
% of tumors with altered pathways
100
90
80
70
60
50
40
30
20
10
0
P53
RB
RTK
16
14
12
10
8
6
4
2
0
0
20
40
60
80
100
120
Volumes at diagnosis (cm3)





MSR (mm)
30
25
20
15
10
7
8
9
10
11
12


80 mm

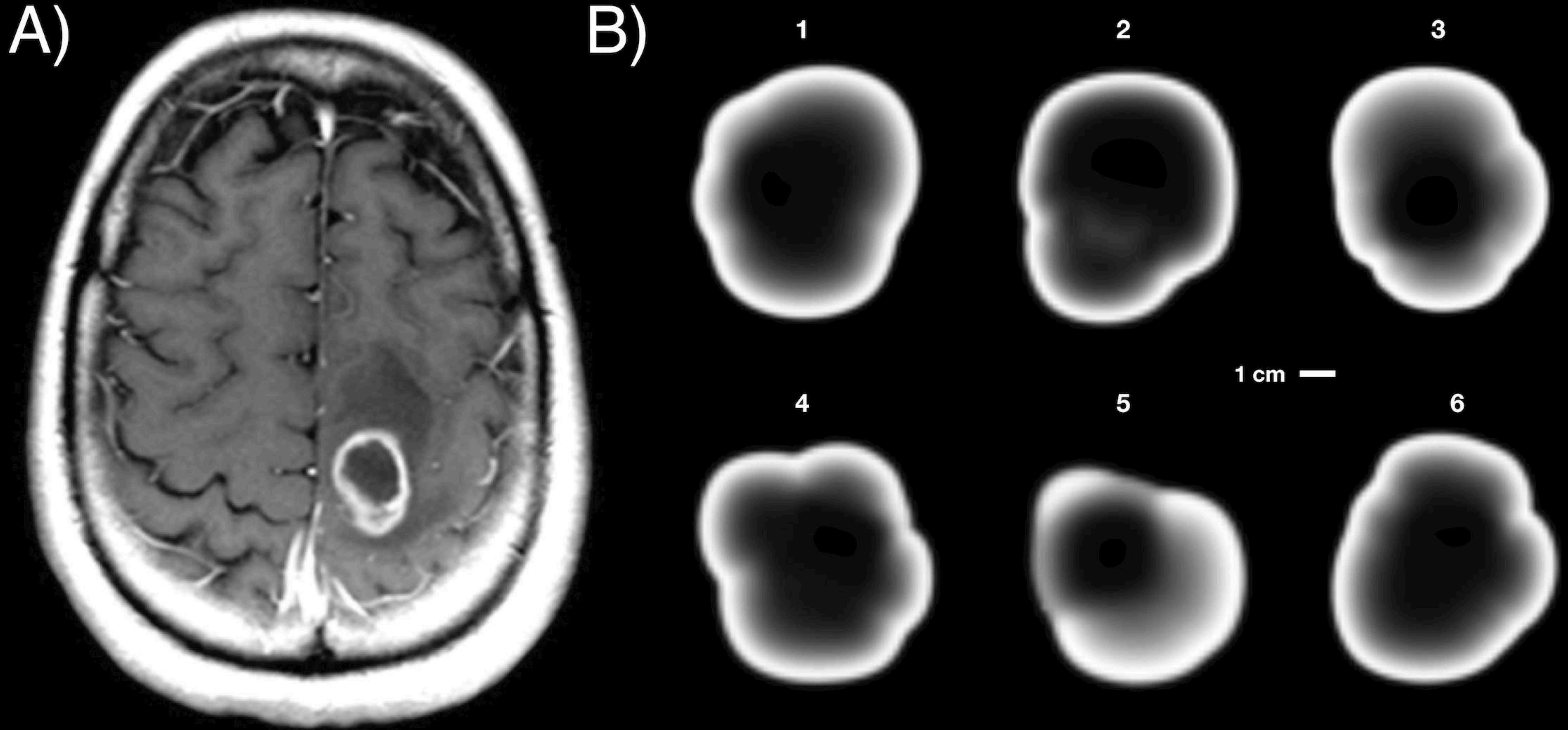

TIME
RTK + RB
RTK
RB
WT
P53
RB + P53
RTK + P53
ALL

PLOS COMPUTATIONAL BIOLOGY

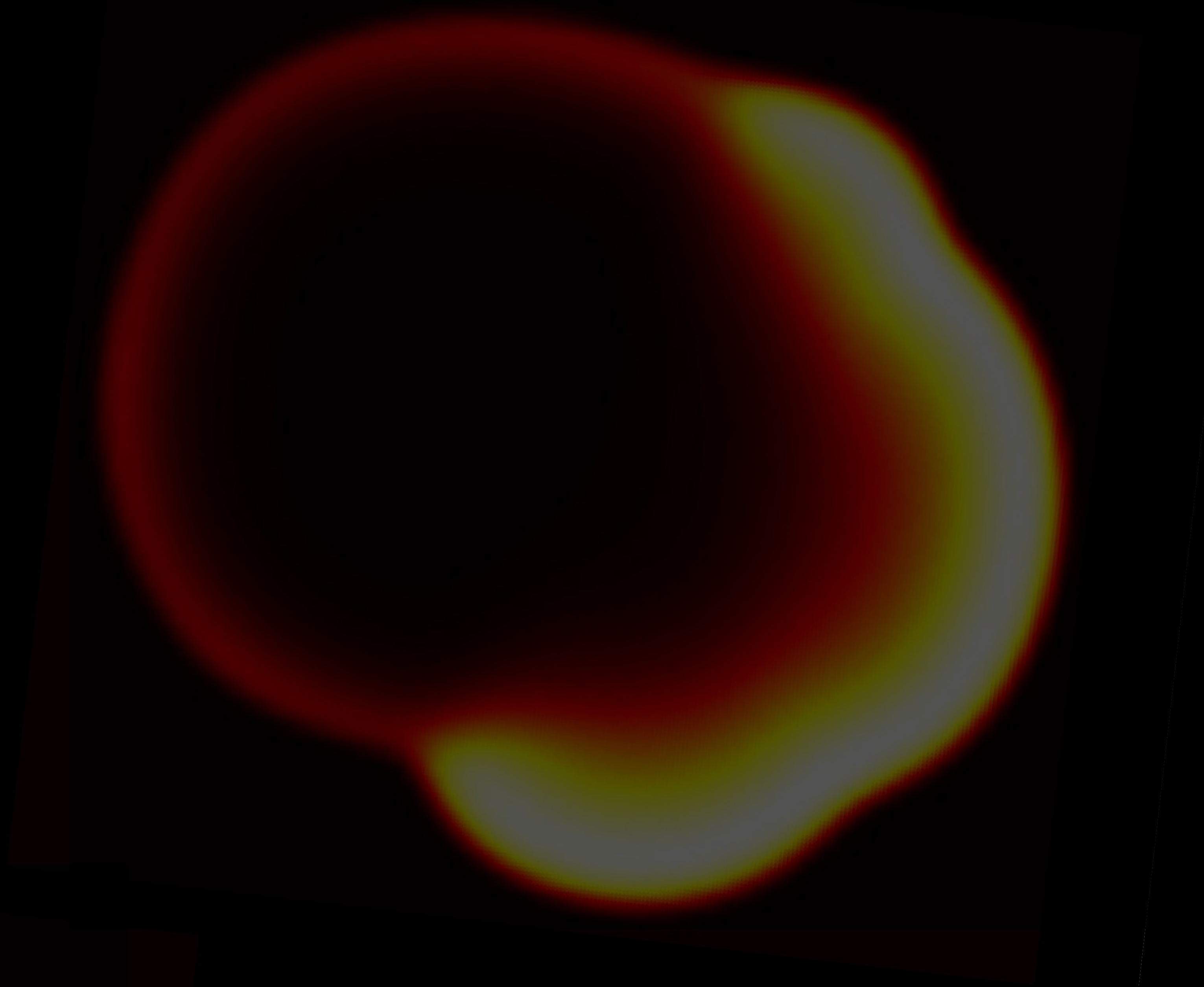
RESEARCH ARTICLE

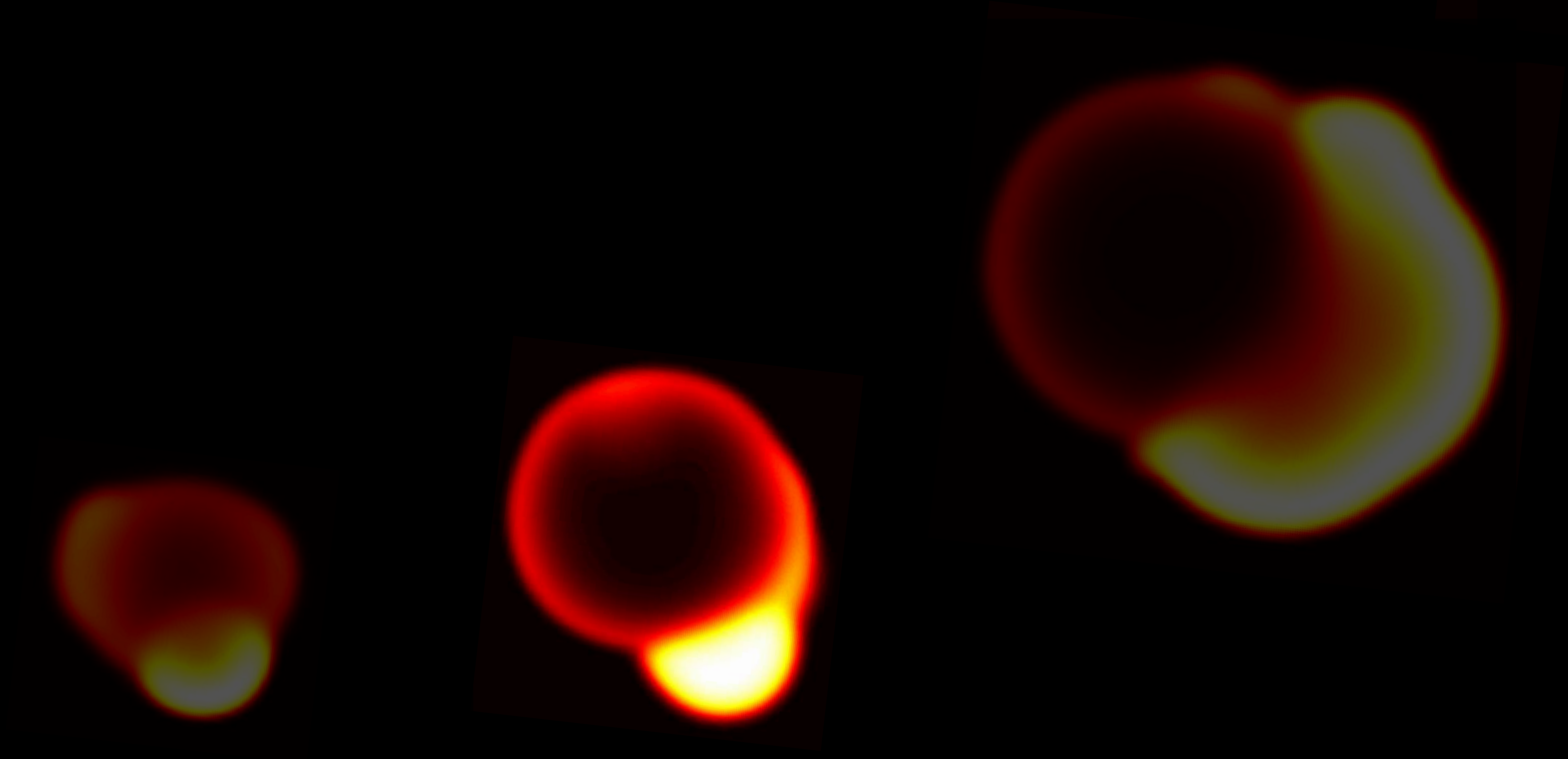
A mesoscopic simulator to uncover heterogeneity and evolutionary dynamics in tumors

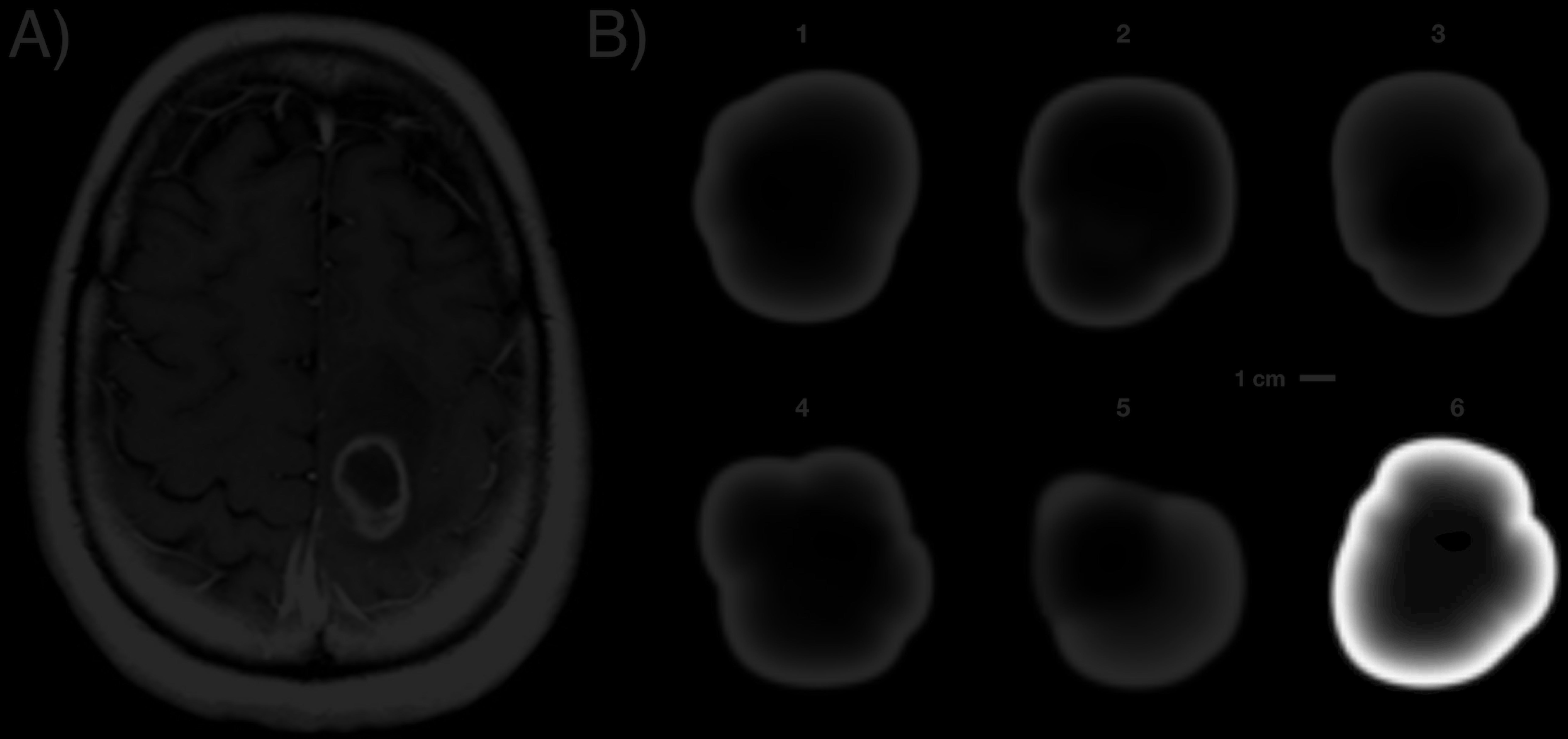
Juan Jiménez-Sánchez[1☯]*, Álvaro Martínez-Rubio[1,2,3☯], Anton Popov[1], Julián Pérez-Beteta[1], Youness Azimzade[4], David Molina-García[1], Juan Belmonte-Beitia[1], Gabriel F. Calvo[1], Víctor M. Pérez-García[1]


A)
B)
1
2
3
1 cm
4
5
6

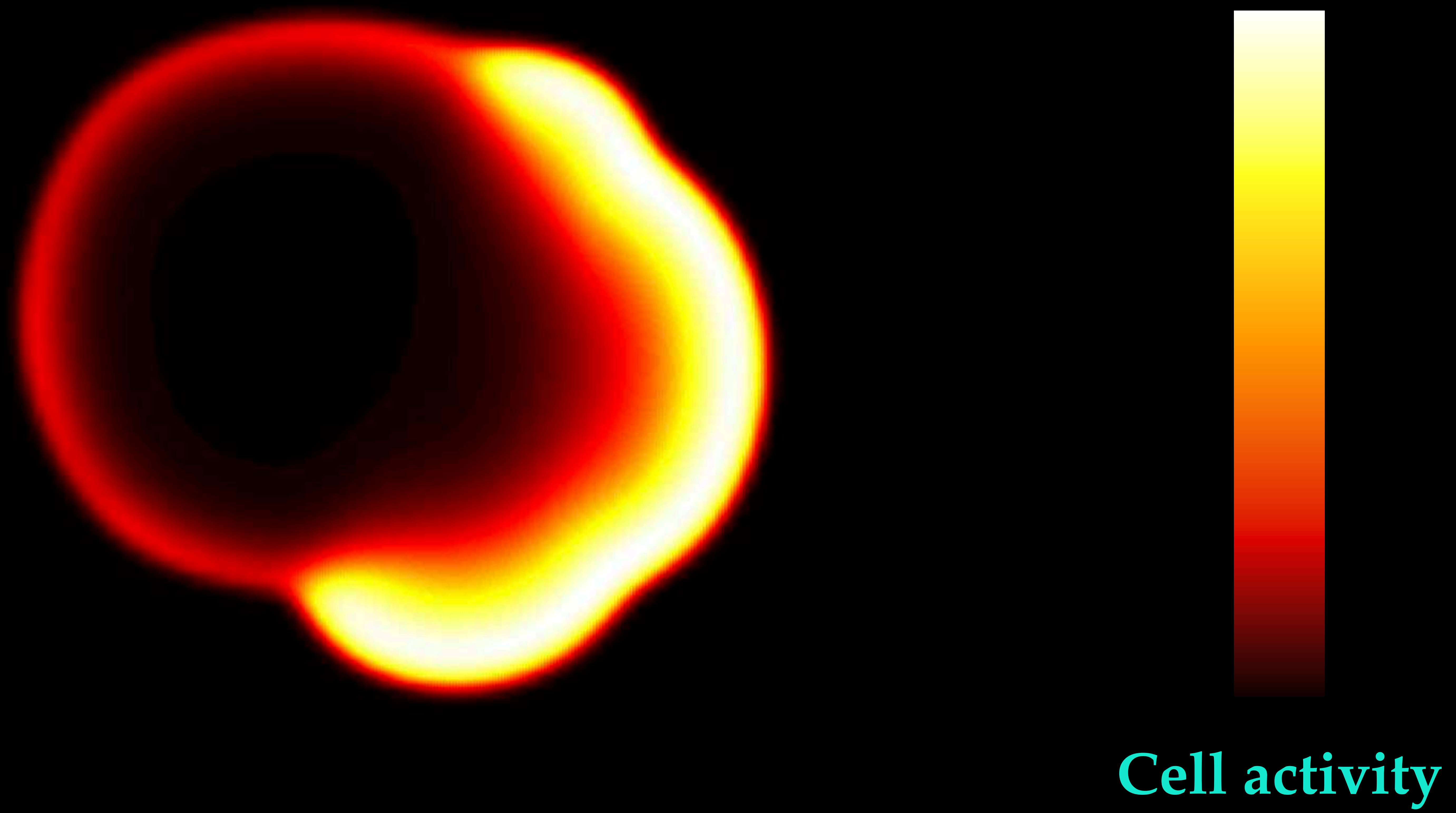
Biomarker discovery

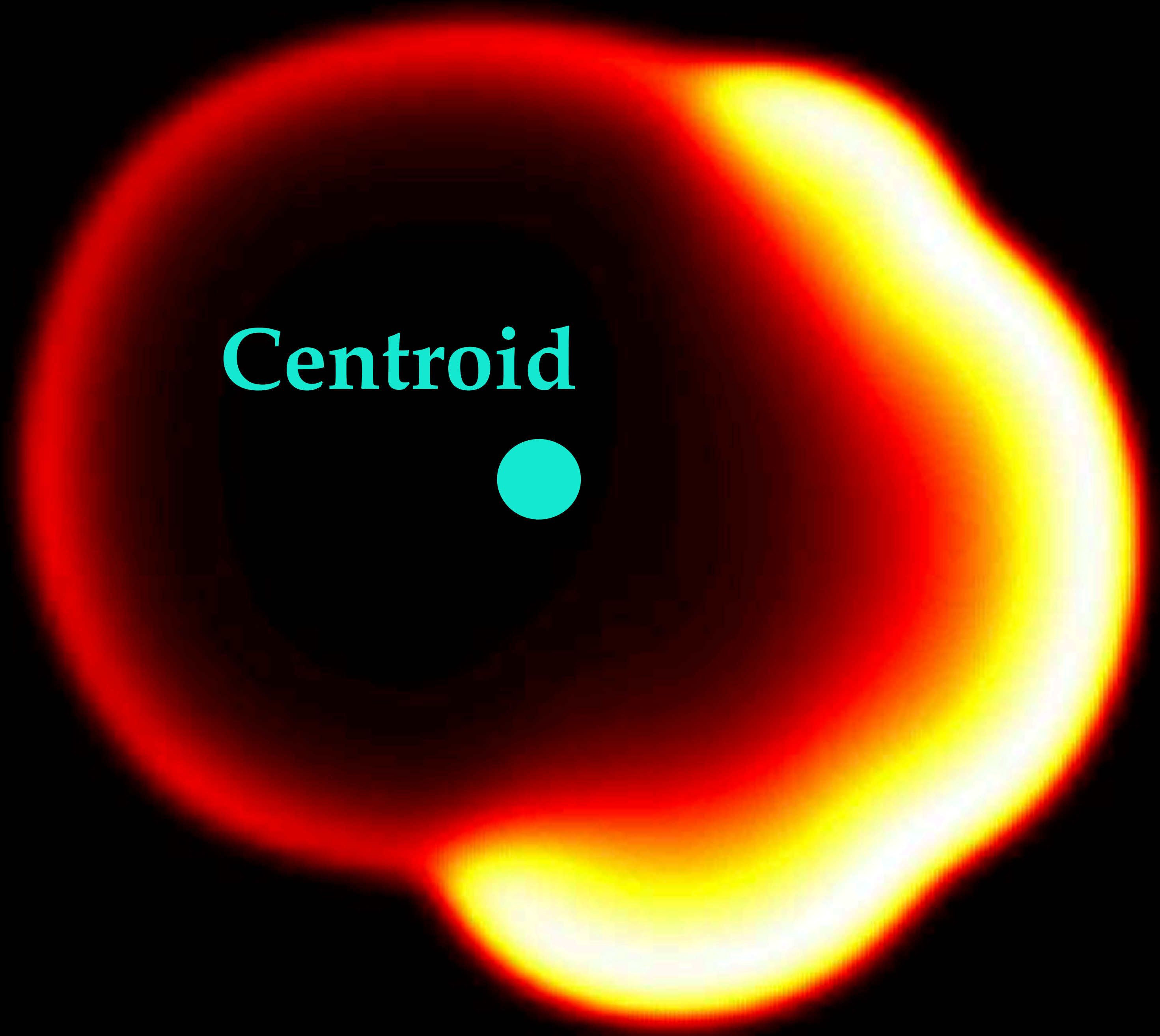


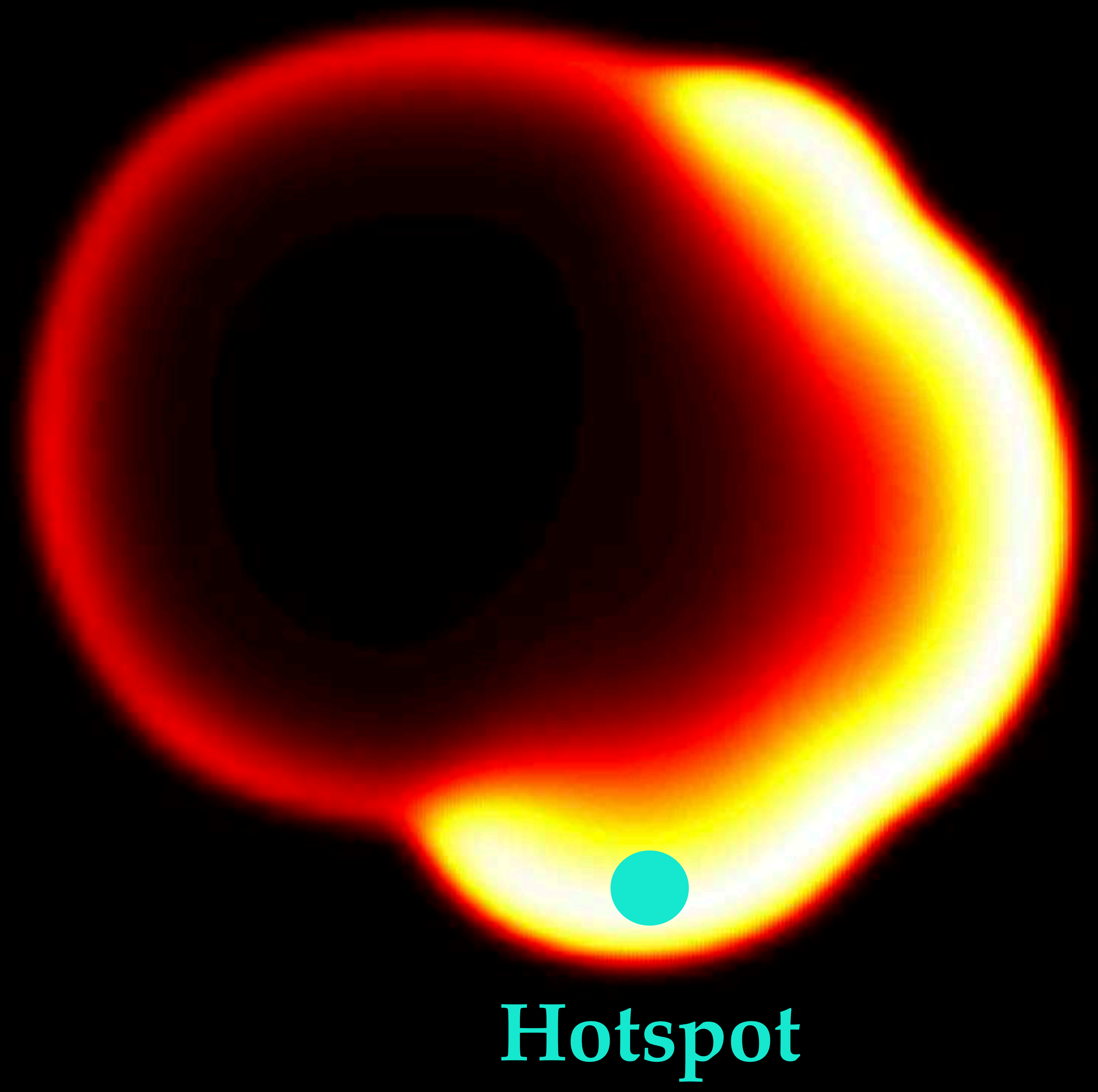


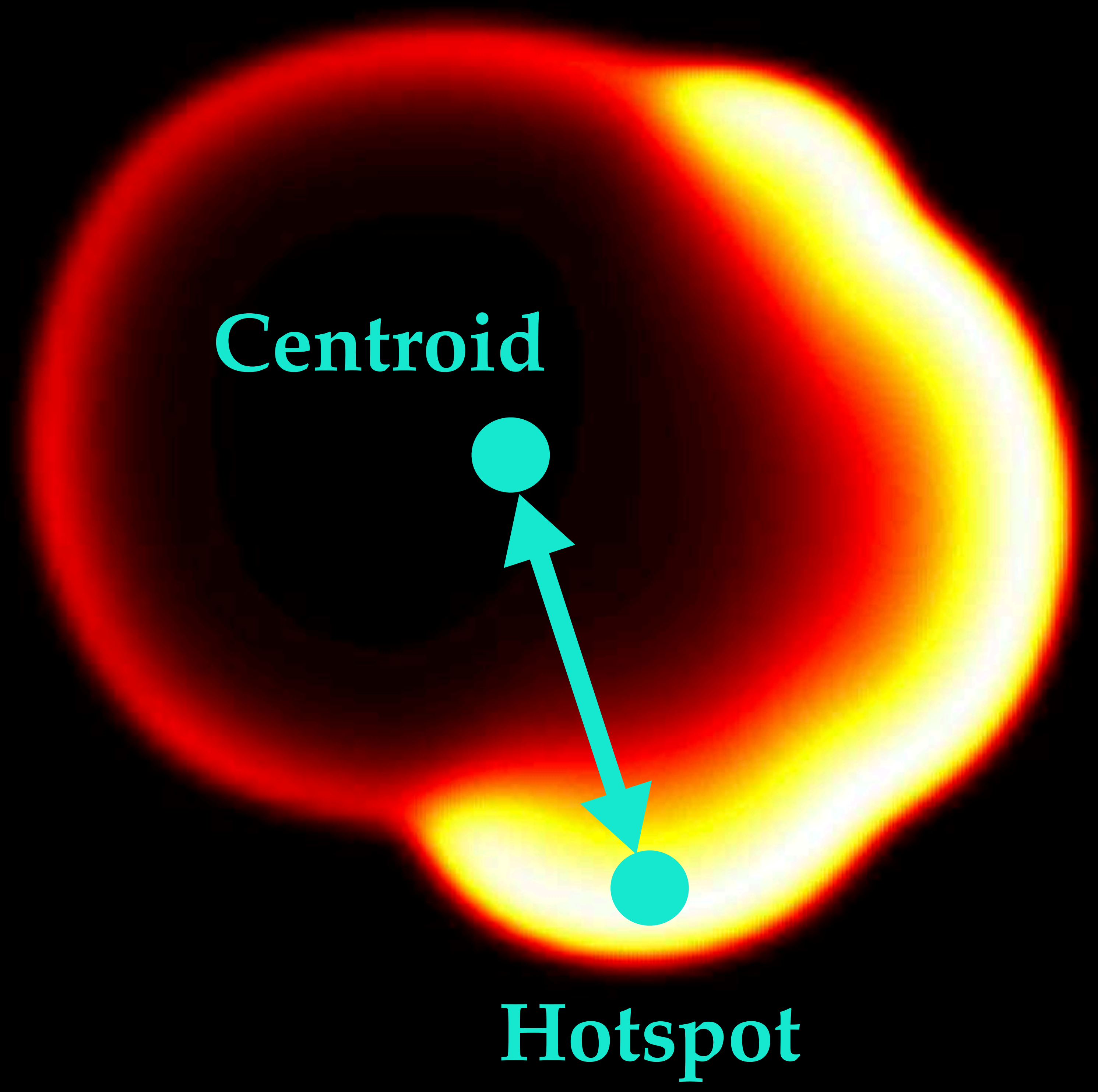


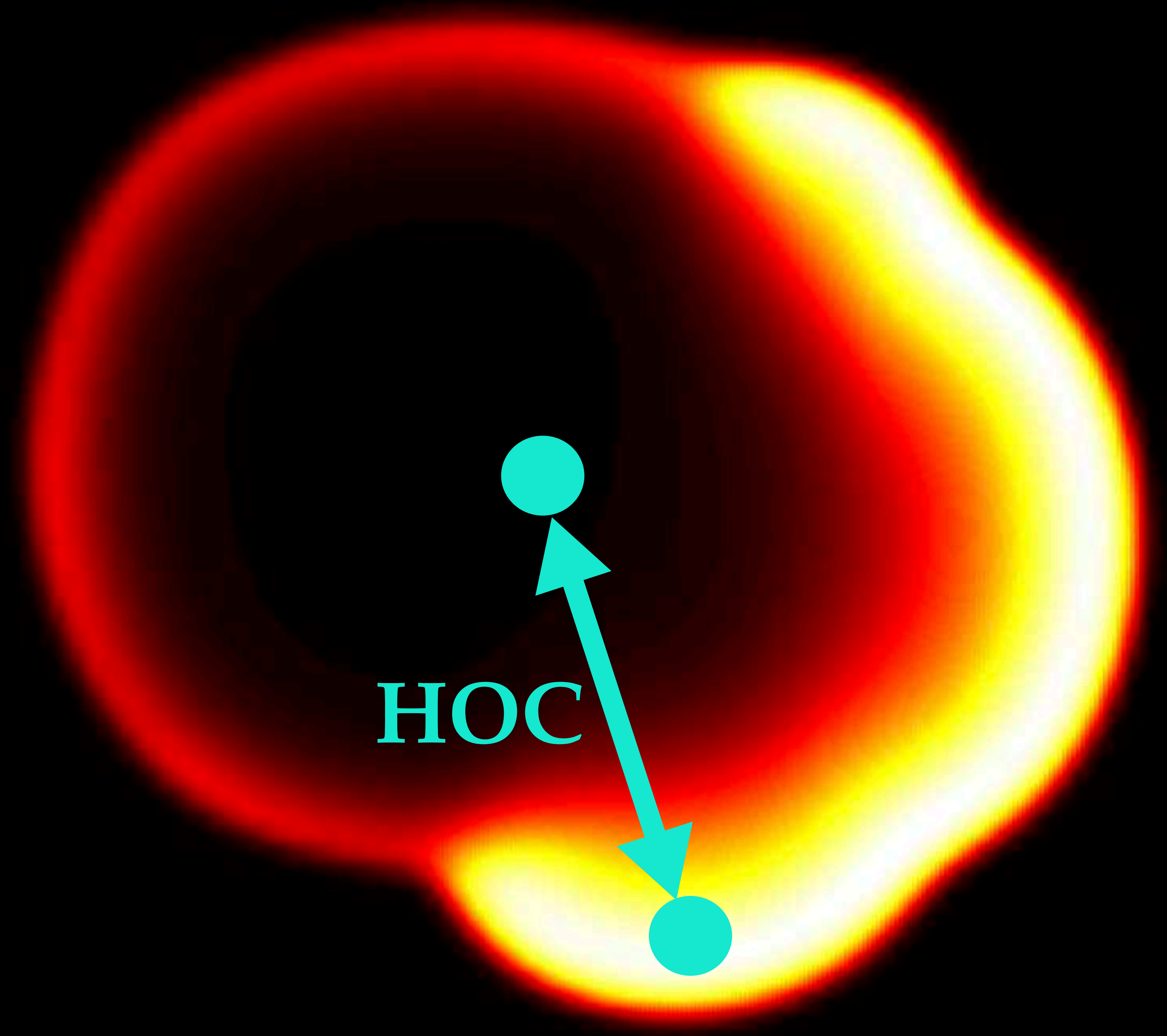
A)
B)
1
2
3
1 cm
4
5
6


Cell activity

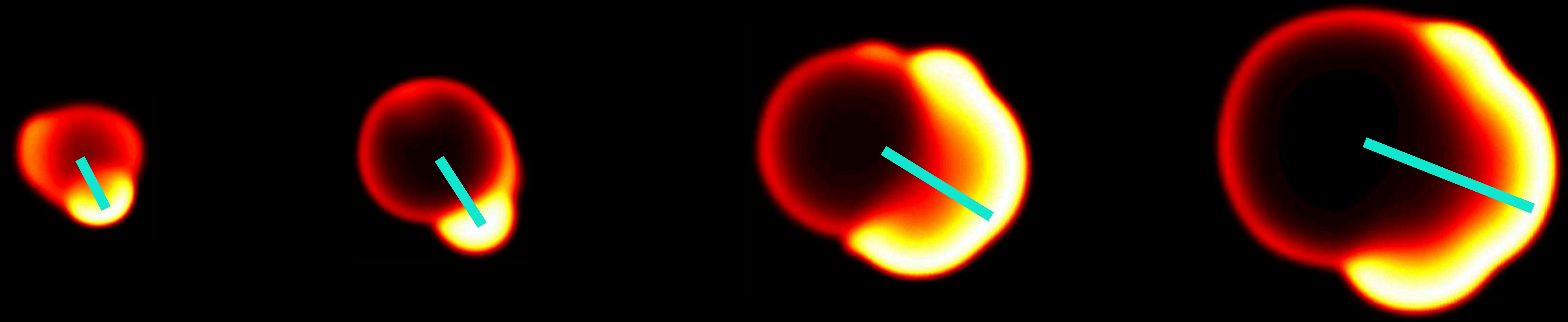

Centroid

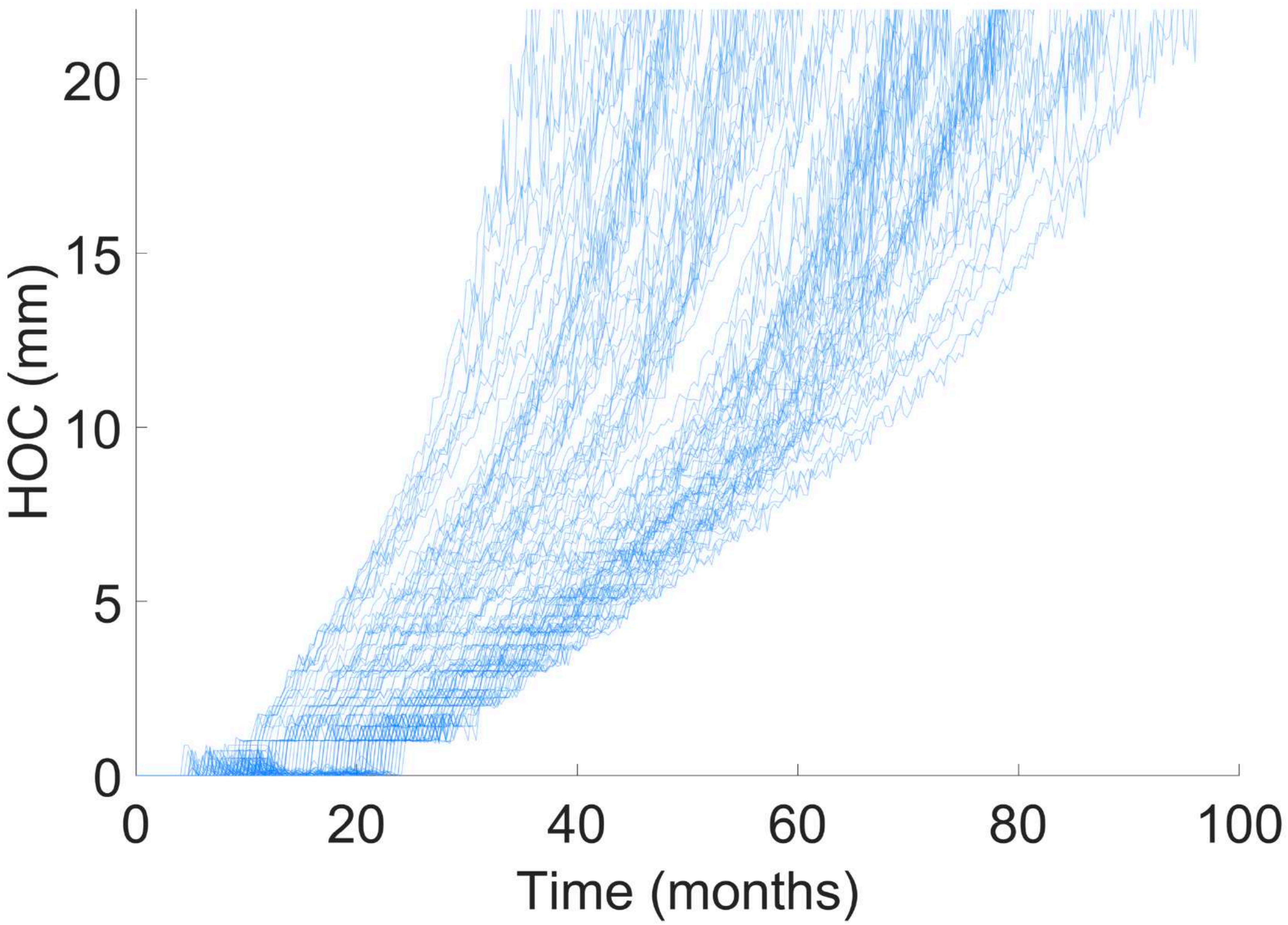

Hotspot


Centroid
Hotspot

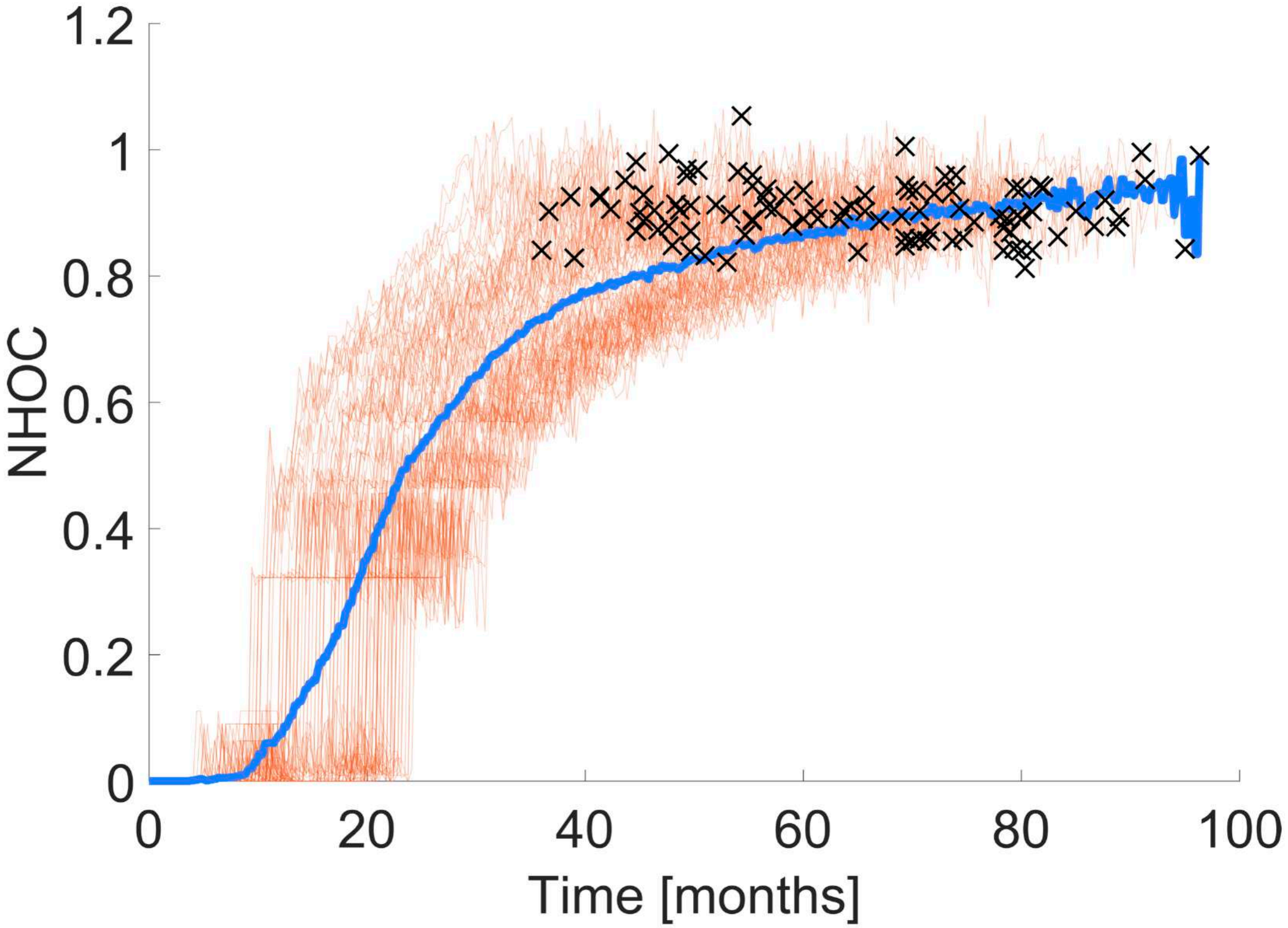


distance from metabolic HOtspot to tumor Centroid

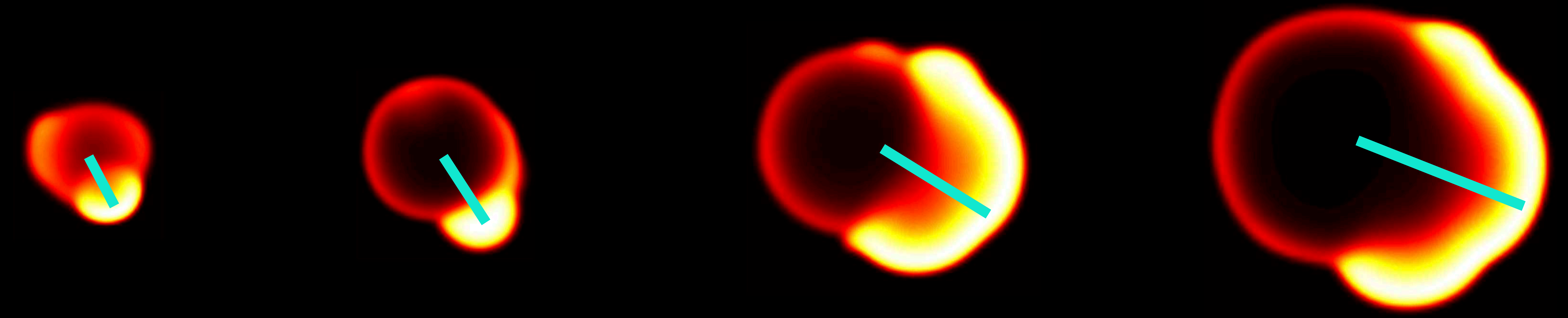


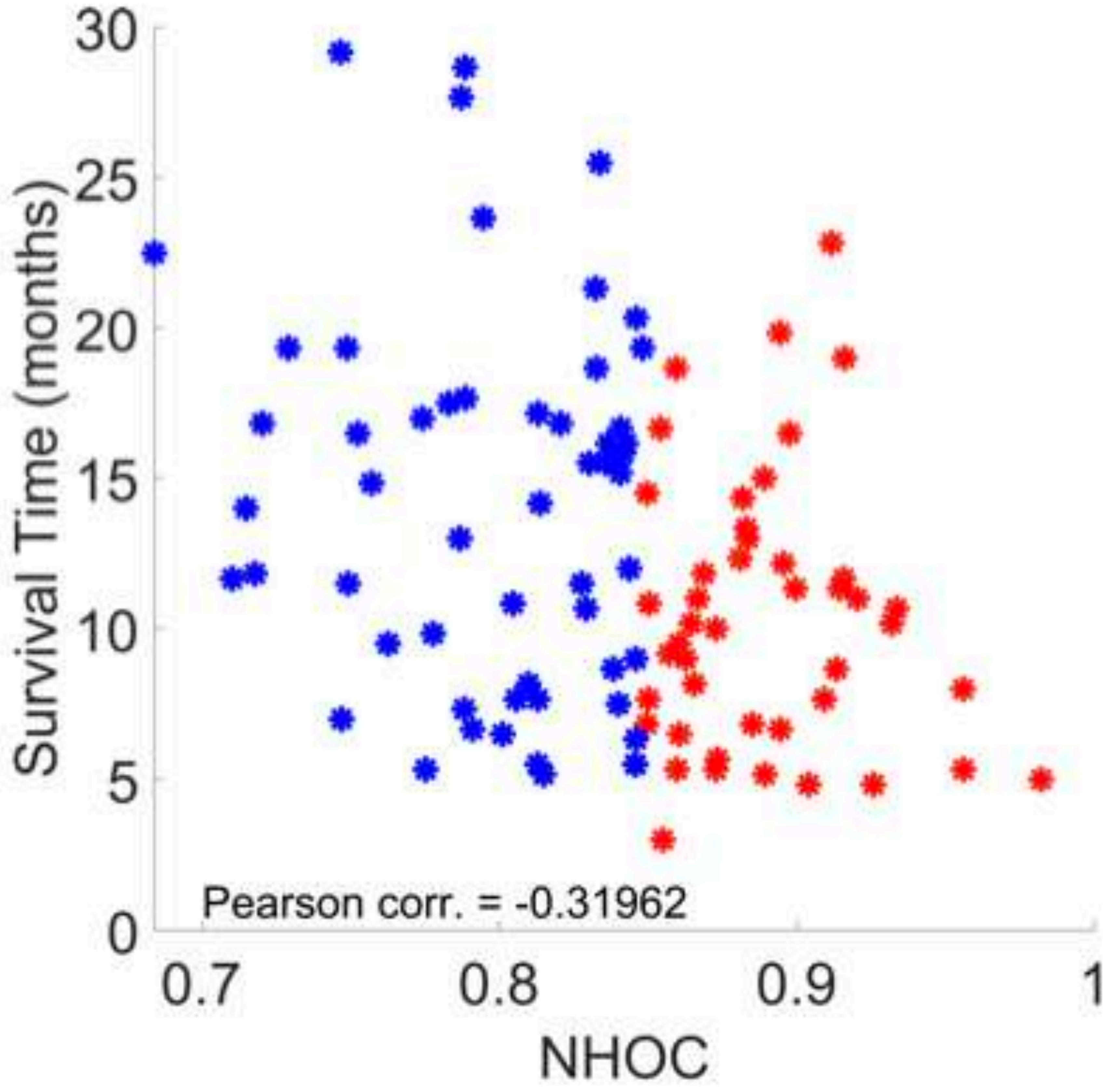


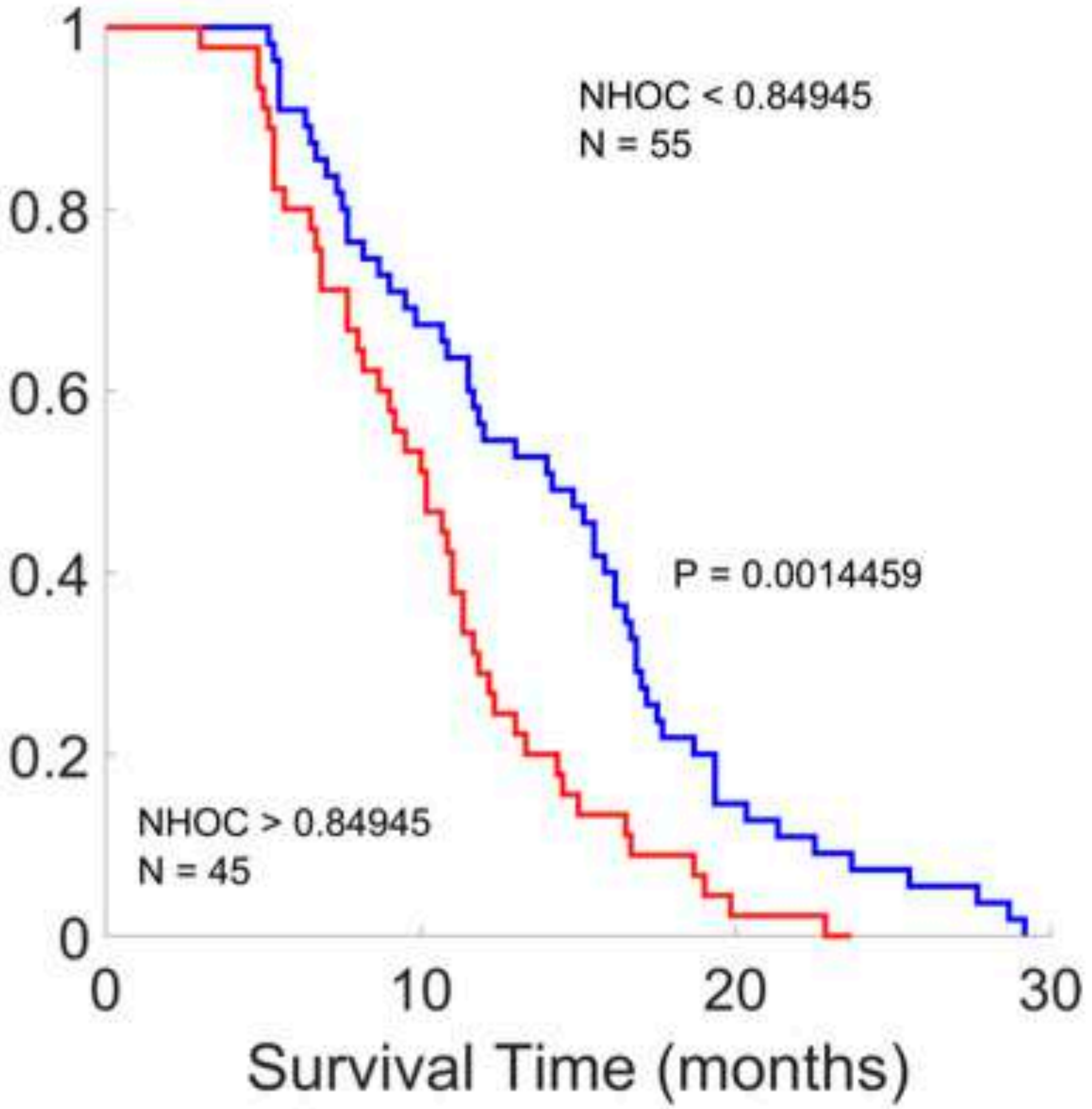
HOC (mm)
0
5
10
15
20
Time (months)
0
20
40
60
80
100

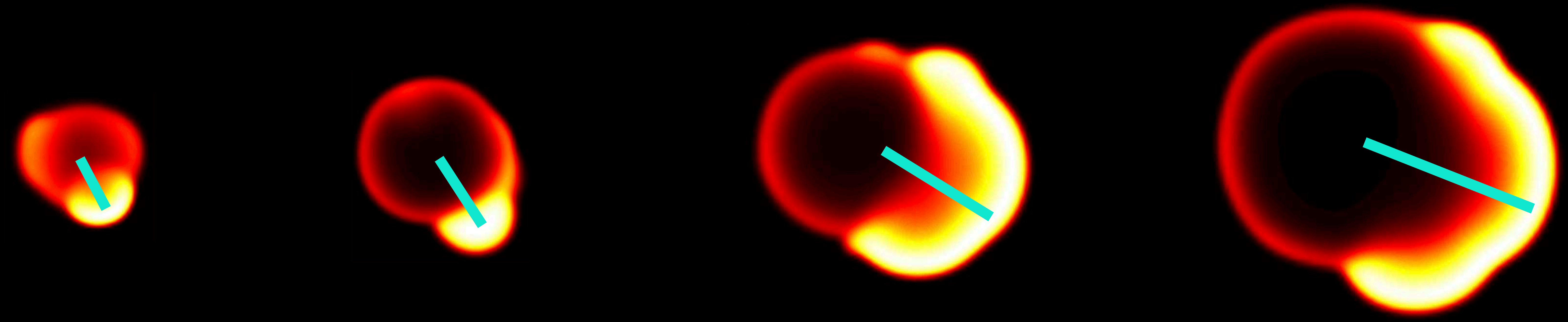


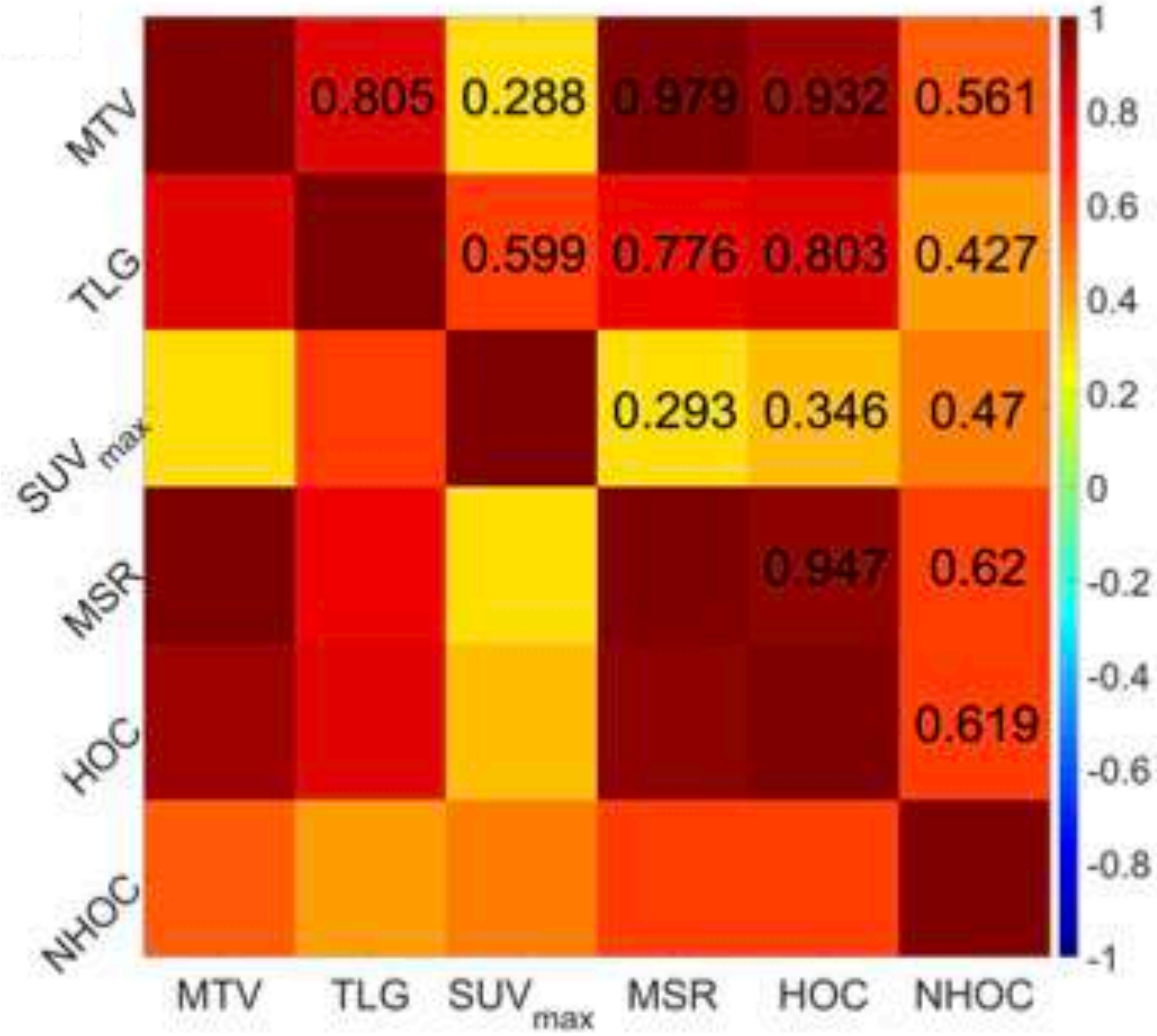
NHOC
0
0.2
0.4
0.6
0.8
1
1.2
Time [months]
0
20
40
60
80
100

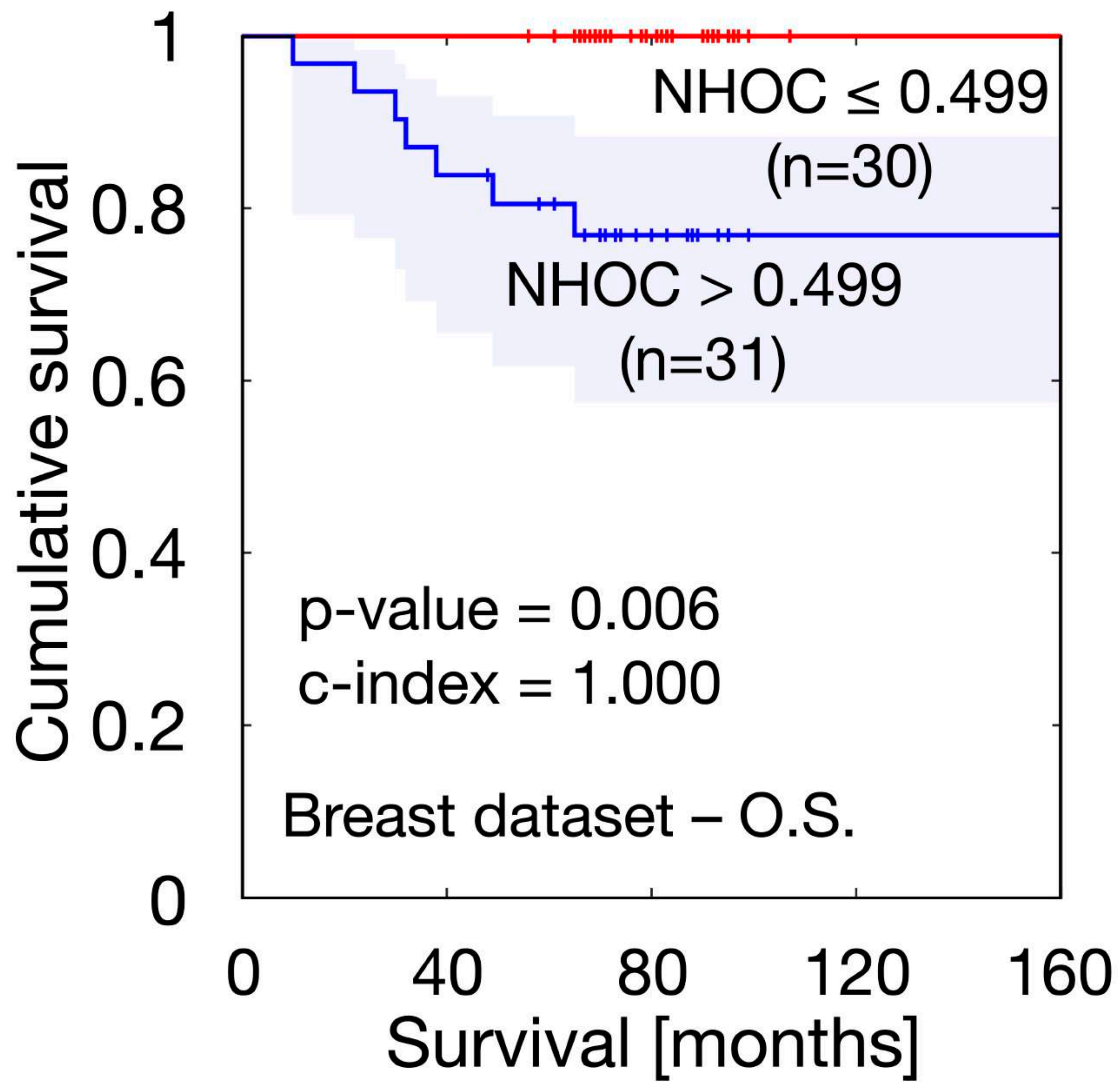



Survival Time (months)
NHOC
Pearson corr. = -0.31962
0
5
10
15
20
25
30
0.7
0.8
0.9
1

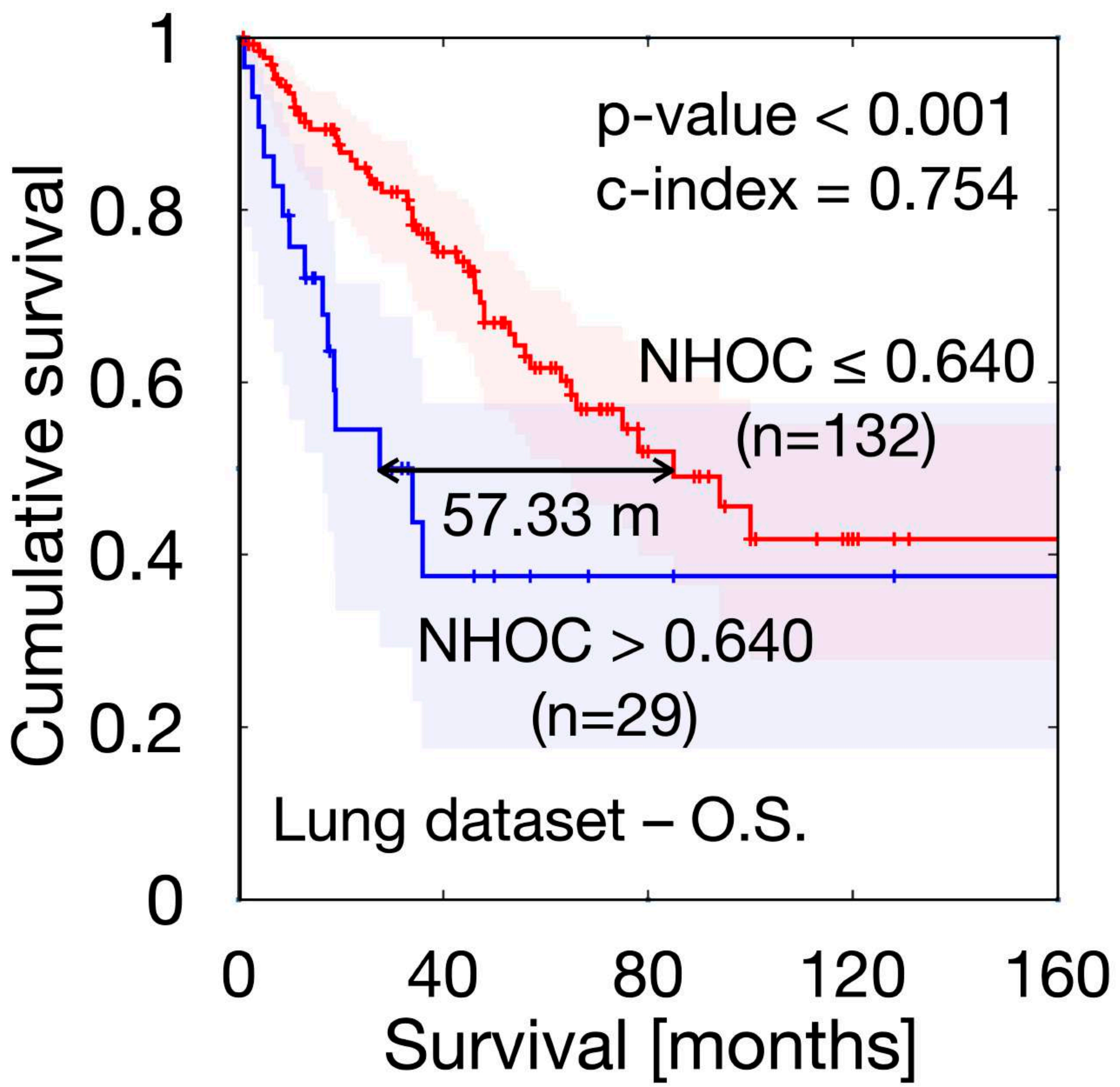

NHOC < 0.84945
N = 55
P = 0.0014459
NHOC > 0.84945
N = 45
Survival Time (months)
0
0.2
0.4
0.6
0.8
1
0
10
20
30



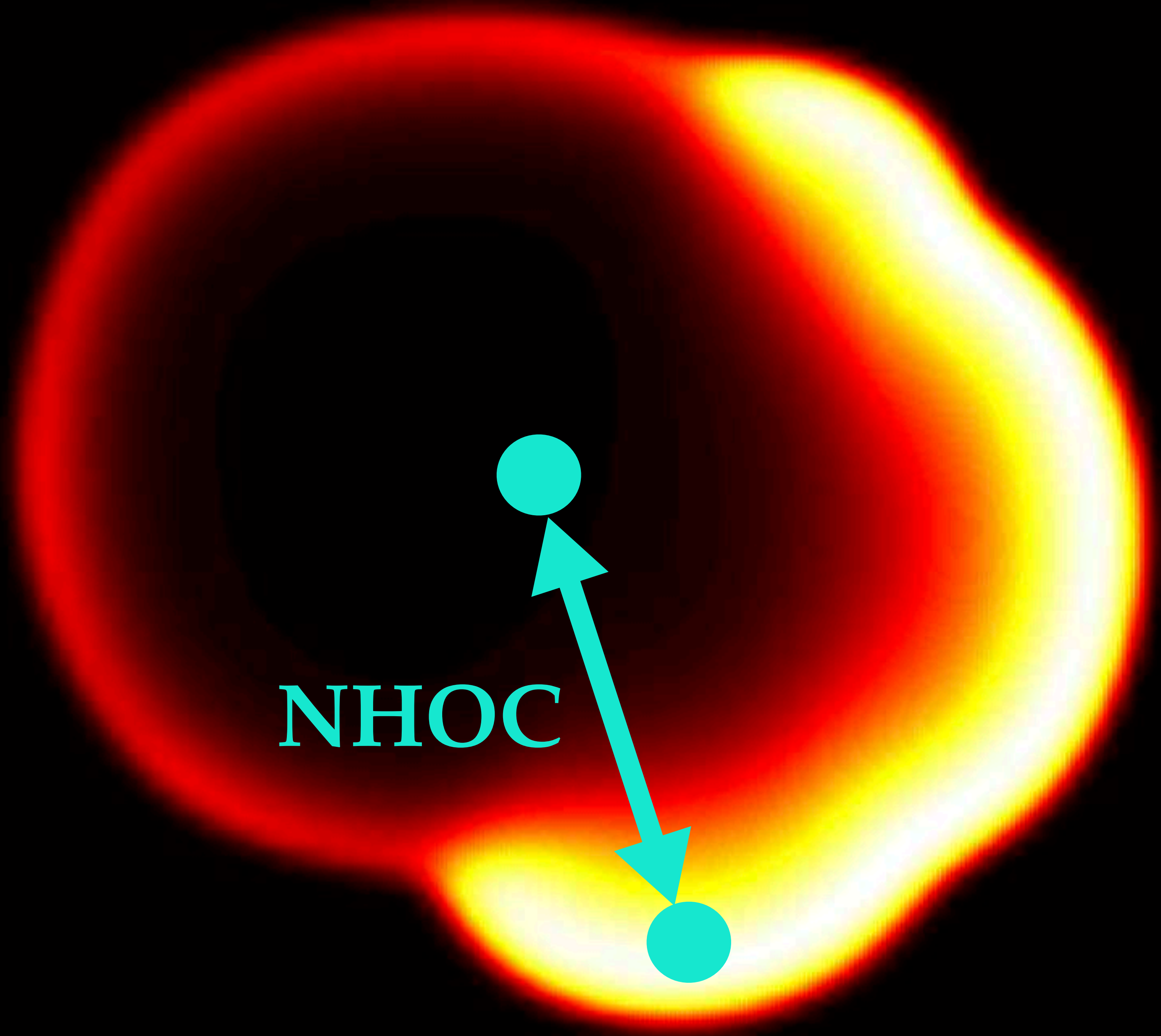

MTV
TLG
SUV max
MSR
HOC
NHOC
0.805 0.288 0.979 0.932 0.561
0.599 0.776 0.803 0.427
0.293 0.346 0.47
0.947 0.62
0.619
MTV TLG SUVmax MSR HOC NHOC
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1



NHOC ≤ 0.499
(n=30)
NHOC > 0.499
(n=31)
p-value = 0.006
c-index = 1.000
Breast dataset – O.S.
Cumulative survival
Survival [months]
0
40
80
120
160
0
0.2
0.4
0.6
0.8
1



p-value < 0.001
c-index = 0.754
NHOC ≤ 0.640
(n=132)
57.33 m
NHOC > 0.640
(n=29)
Lung dataset – O.S.
Cumulative survival
Survival [months]
0
40
80
120
160
0
0.2
0.4
0.6
0.8
1



NHOC carries strong prognostic value

NHOC outcompetes previous biomarkers

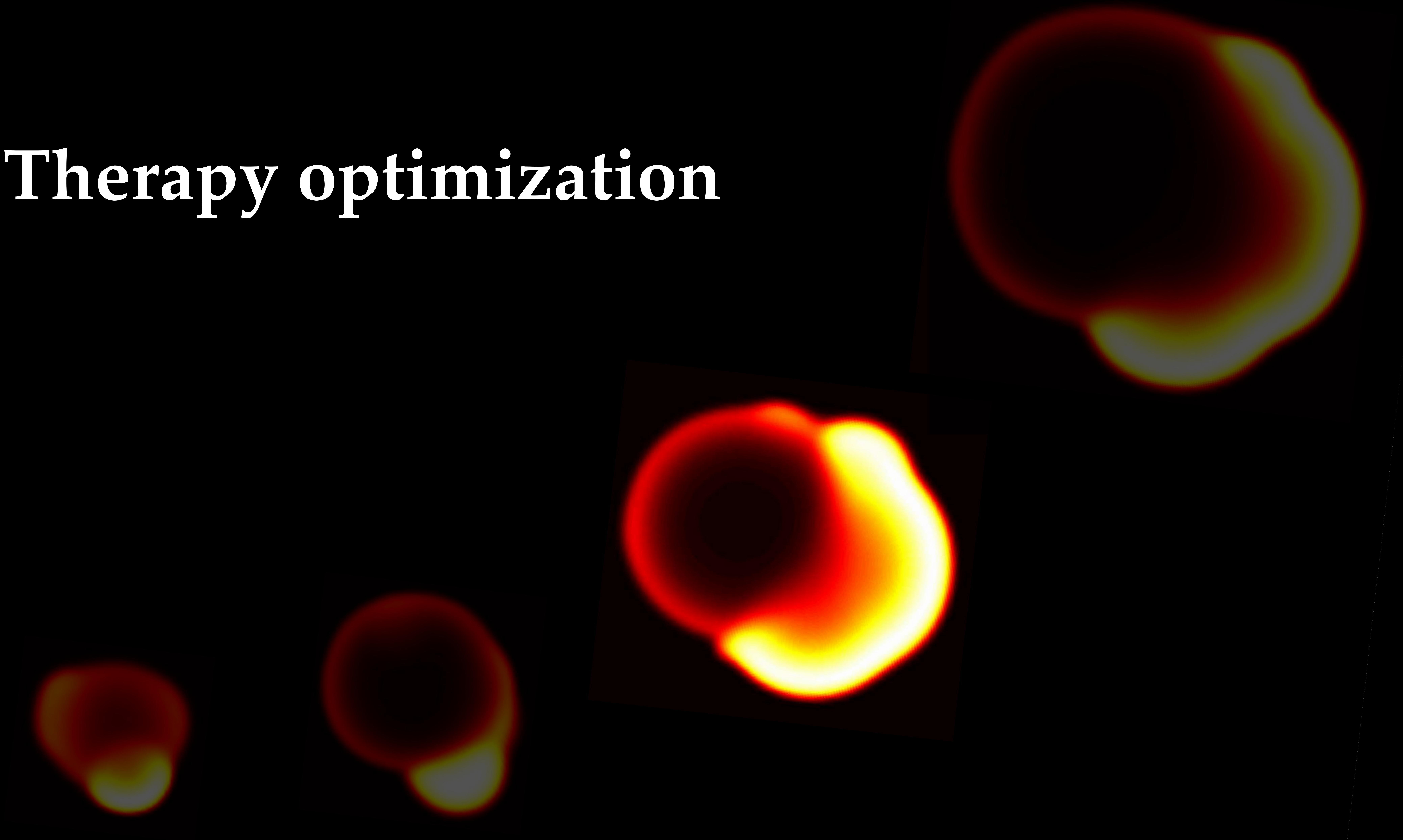
NHOC carries independent information

PNAS

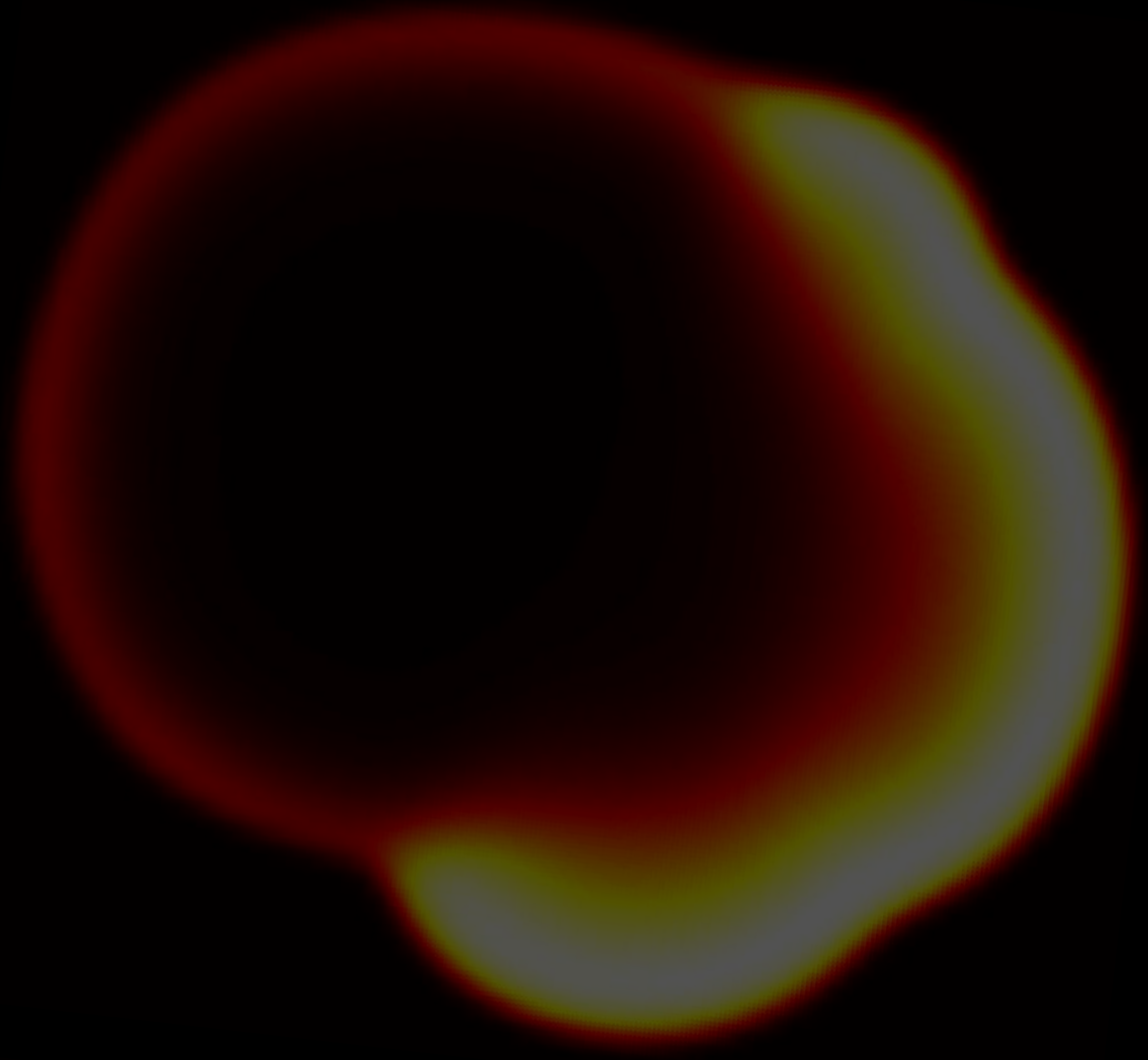
Evolutionary dynamics at the tumor edge reveal metabolic imaging biomarkers

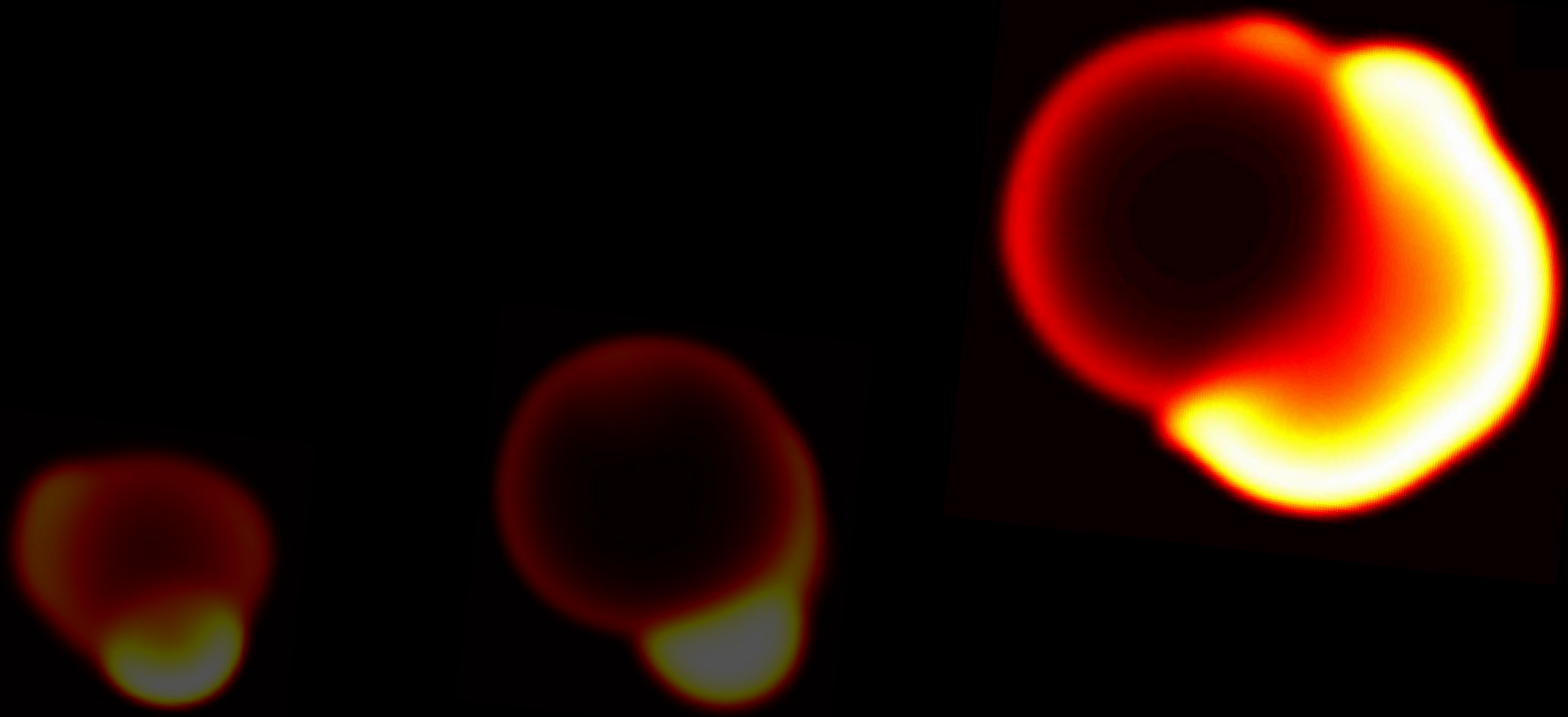
Juan Jiménez-Sánchez[a,1], Jesús J. Bosque[a,1], Germán A. Jiménez Londoño[b], David Molina-García[a], Álvaro Martínez[a,c], Julián Pérez-Beteta[a], Carmen Ortega-Sabater[a], Antonio F. Honguero Martínez[d], Ana M. García Vicente[b], Gabriel F. Calvo[a,2,3], and Víctor M. Pérez-García[a,2,3]

Therapy optimization



GLIOMAS:
The most frequent primary brain tumor



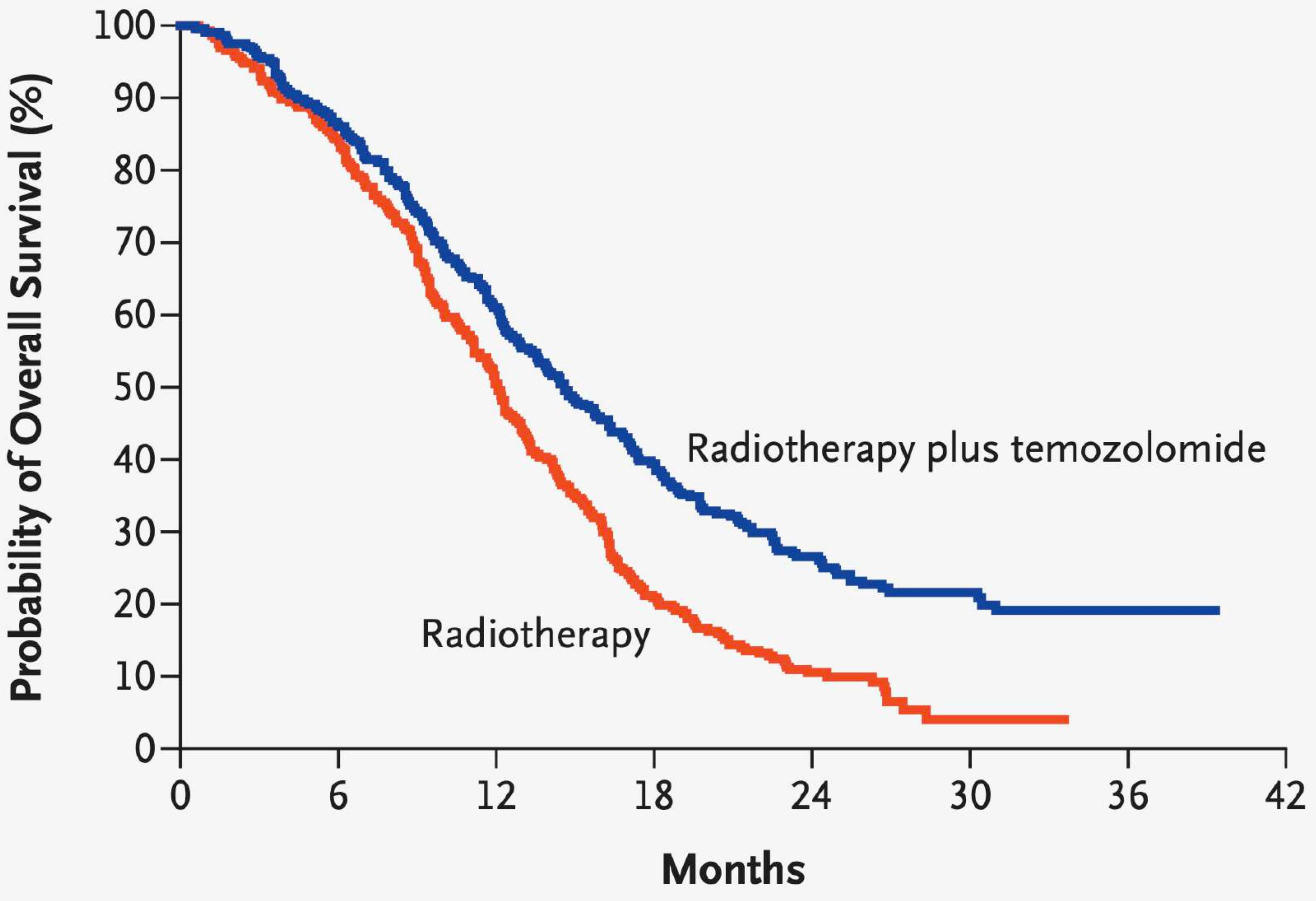


The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

6 weeks RT+TMZ daily

6 cycles of:
1 week TMZ ON-
3 weeks TMZ OFF

APRIL

MON	TUE	WED	THU	FRI	SAT	SUN
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

MAY

MON	TUE	WED	THU	FRI	SAT	SUN
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

JUNE

MON	TUE	WED	THU	FRI	SAT	SUN
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

JULY

MON	TUE	WED	THU	FRI	SAT	SUN
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

AUGUST

MON	TUE	WED	THU	FRI	SAT	SUN
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

SEPTEMBER

MON	TUE	WED	THU	FRI	SAT	SUN
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

OCTOBER

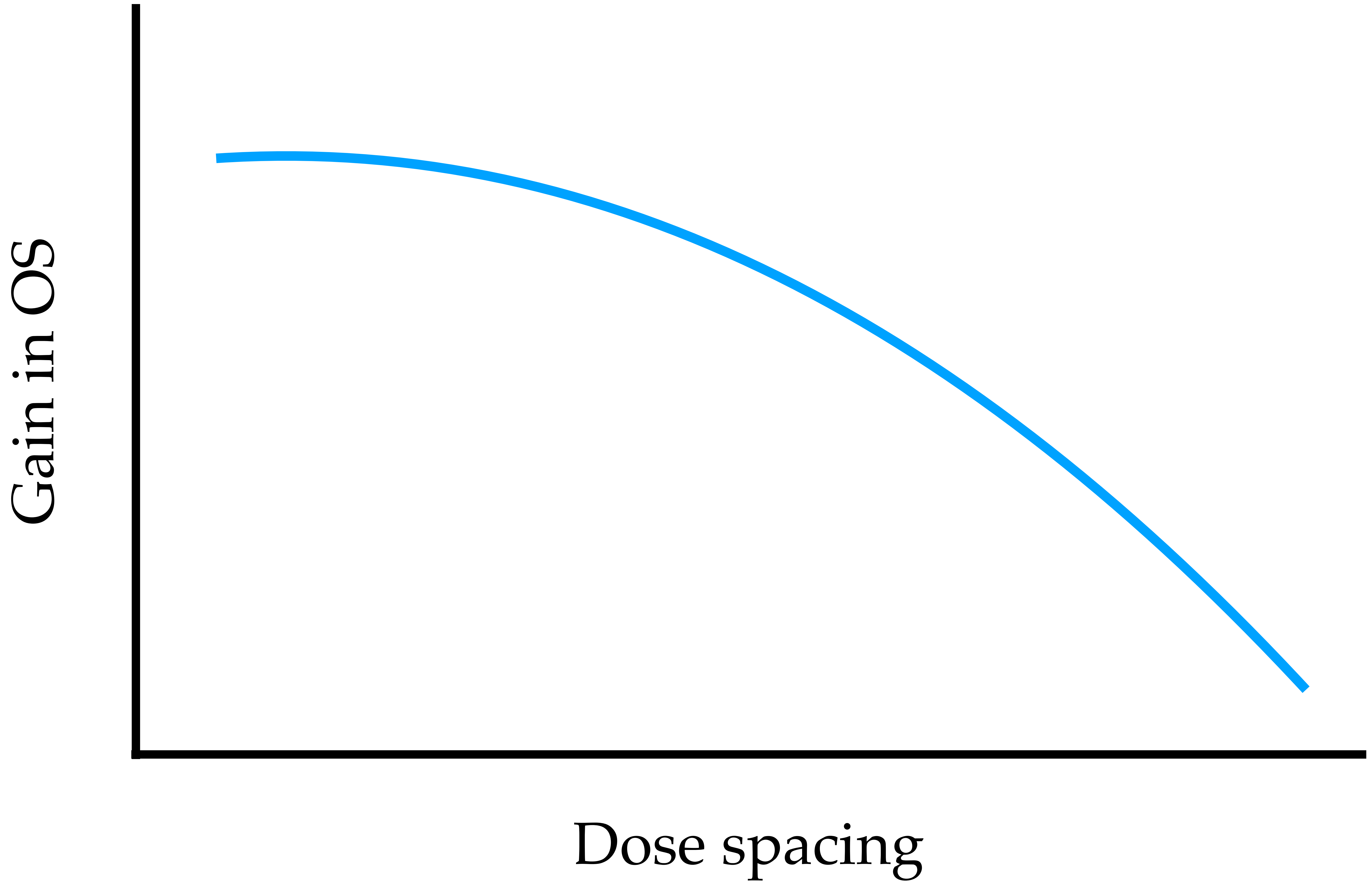
MON	TUE	WED	THU	FRI	SAT	SUN
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

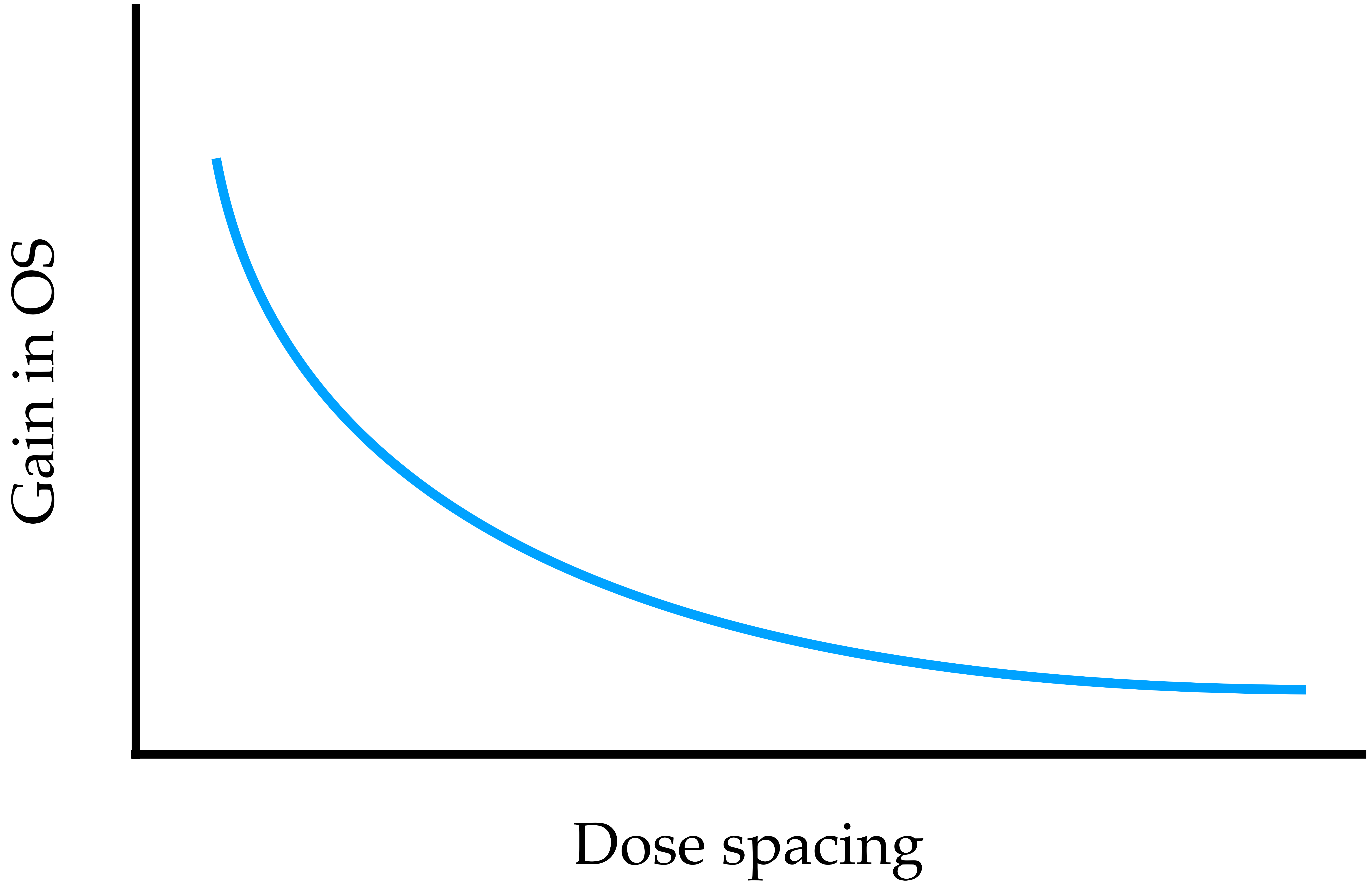
NOVEMBER

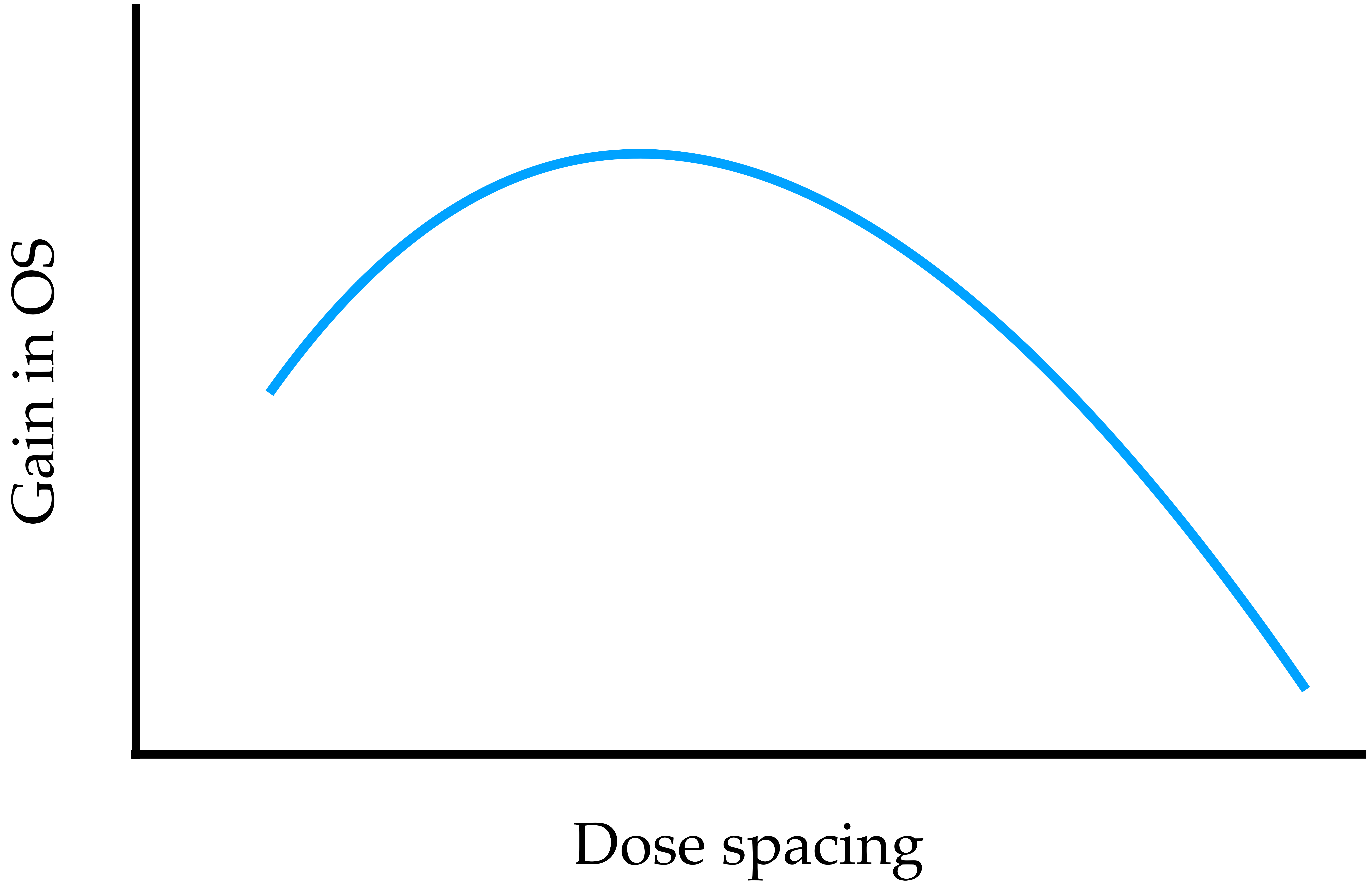
MON	TUE	WED	THU	FRI	SAT	SUN
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

DECEMBER

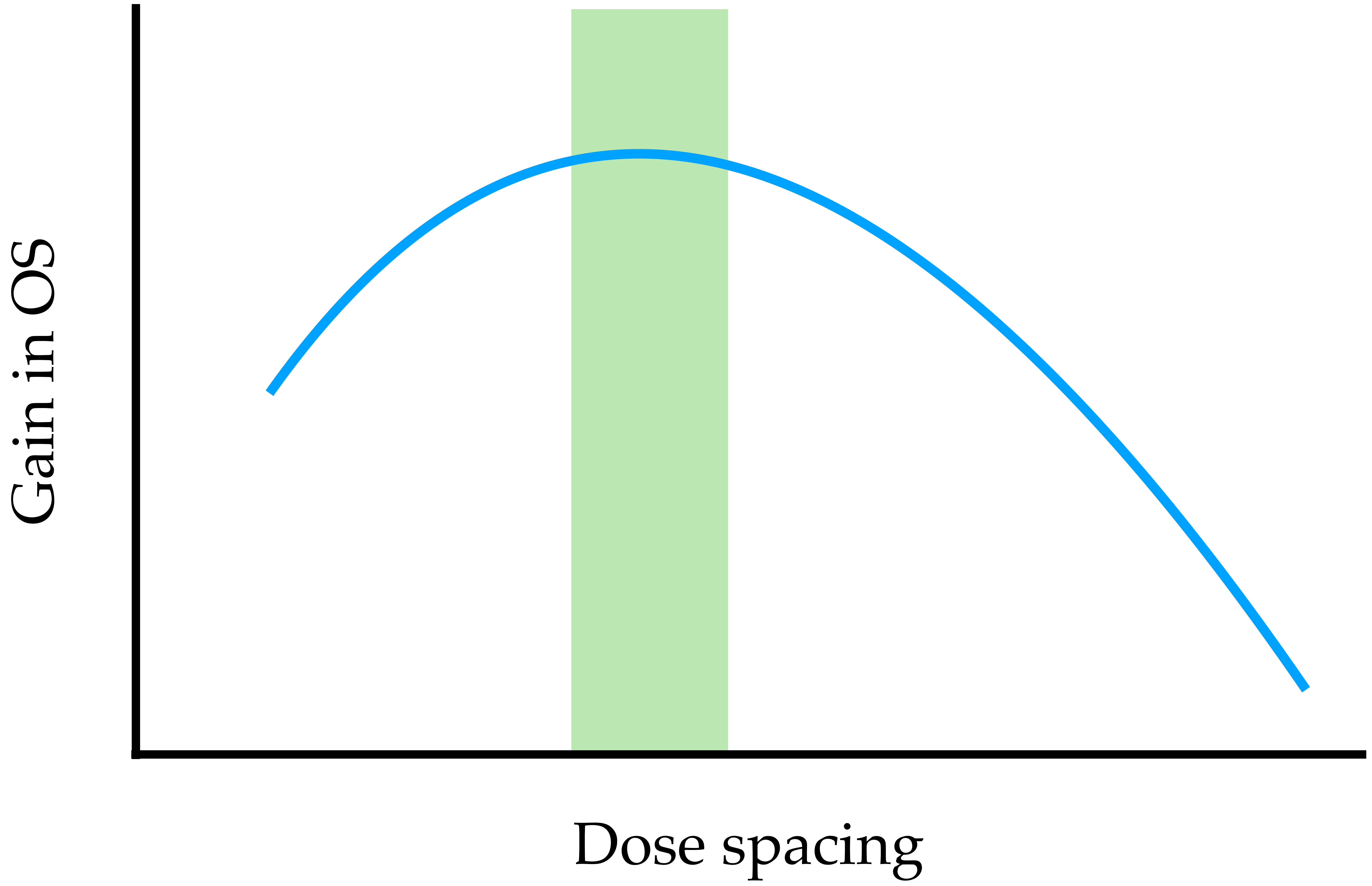
MON	TUE	WED	THU	FRI	SAT	SUN
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

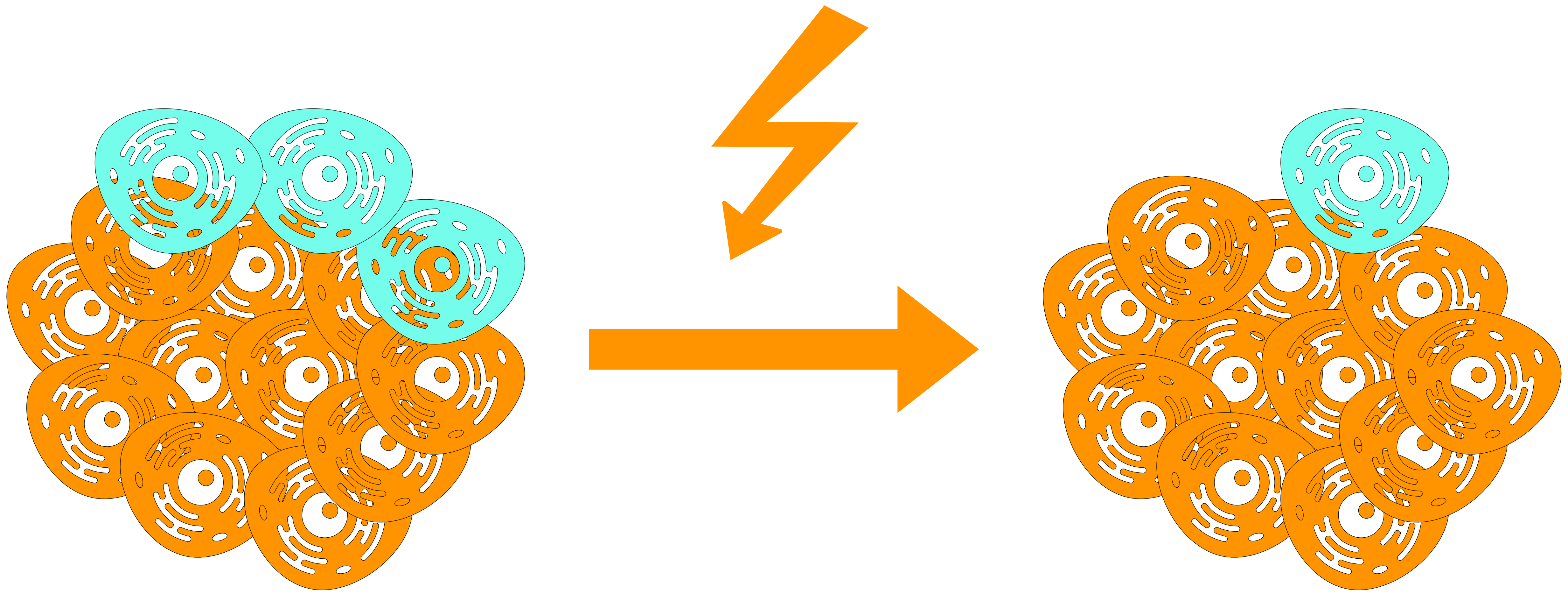

Gain in OS
Dose spacing

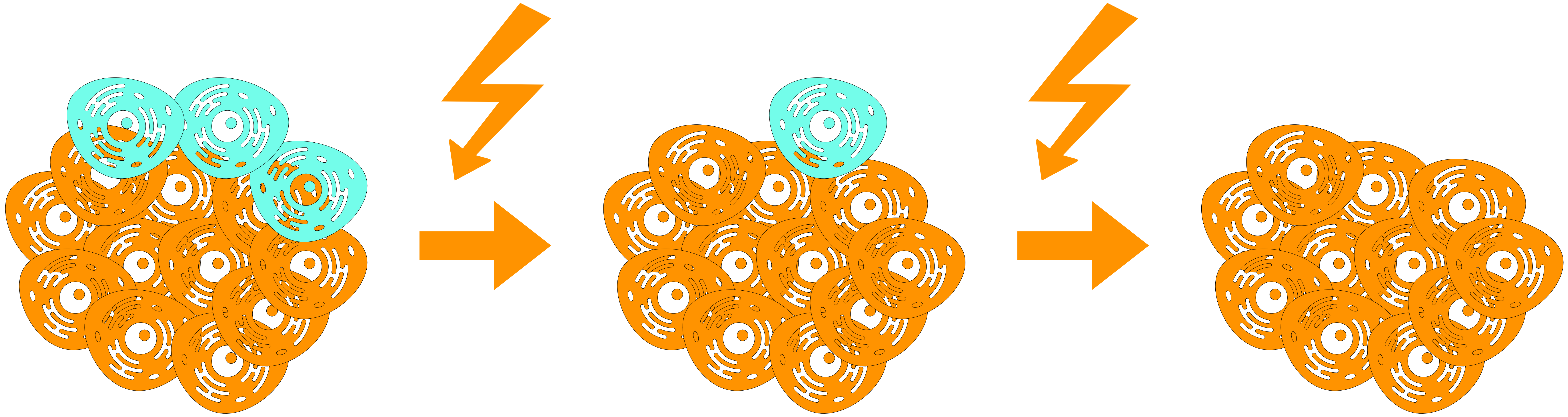

Gain in OS
Dose spacing

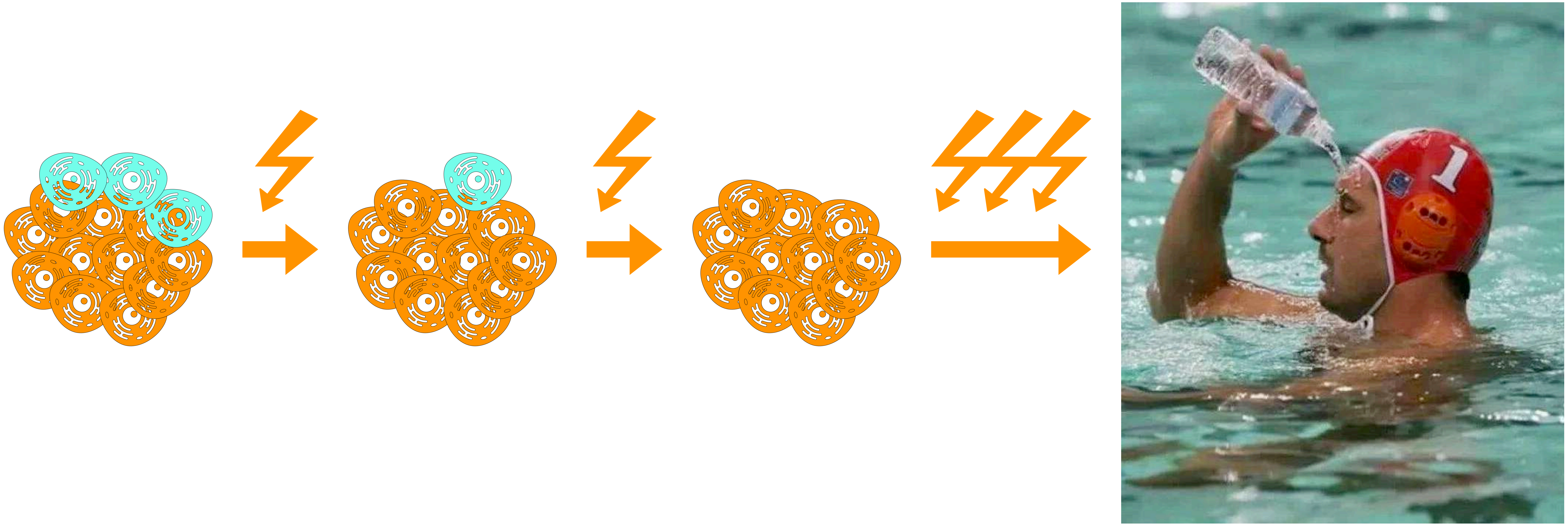

Gain in OS
Dose spacing

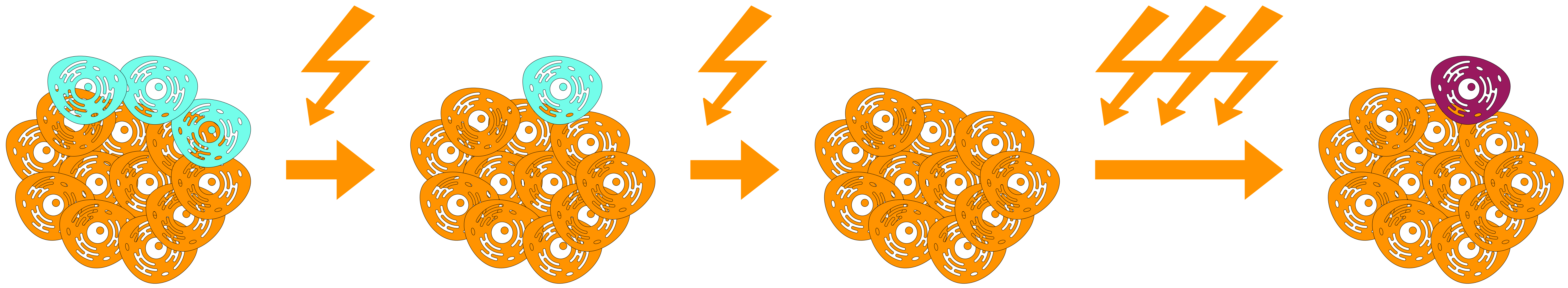
Optimal spacing(s)?

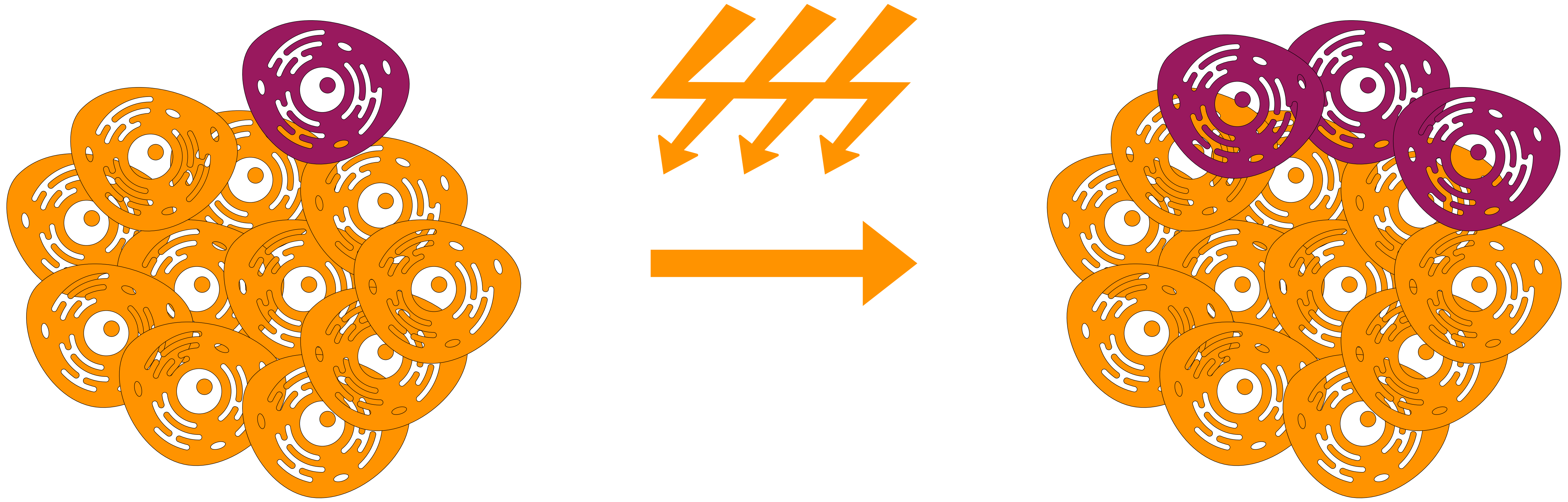




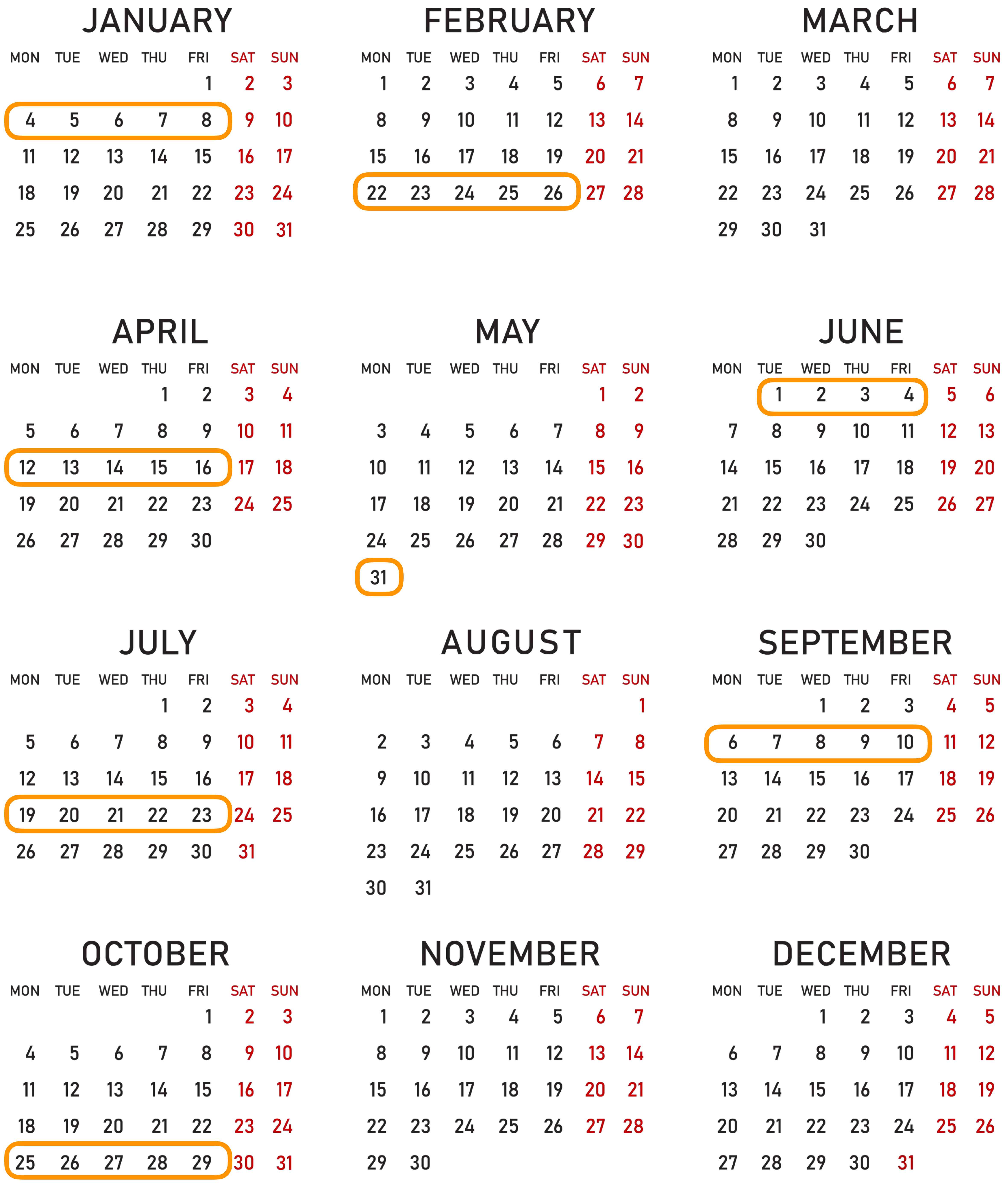








Protracted therapy schemes



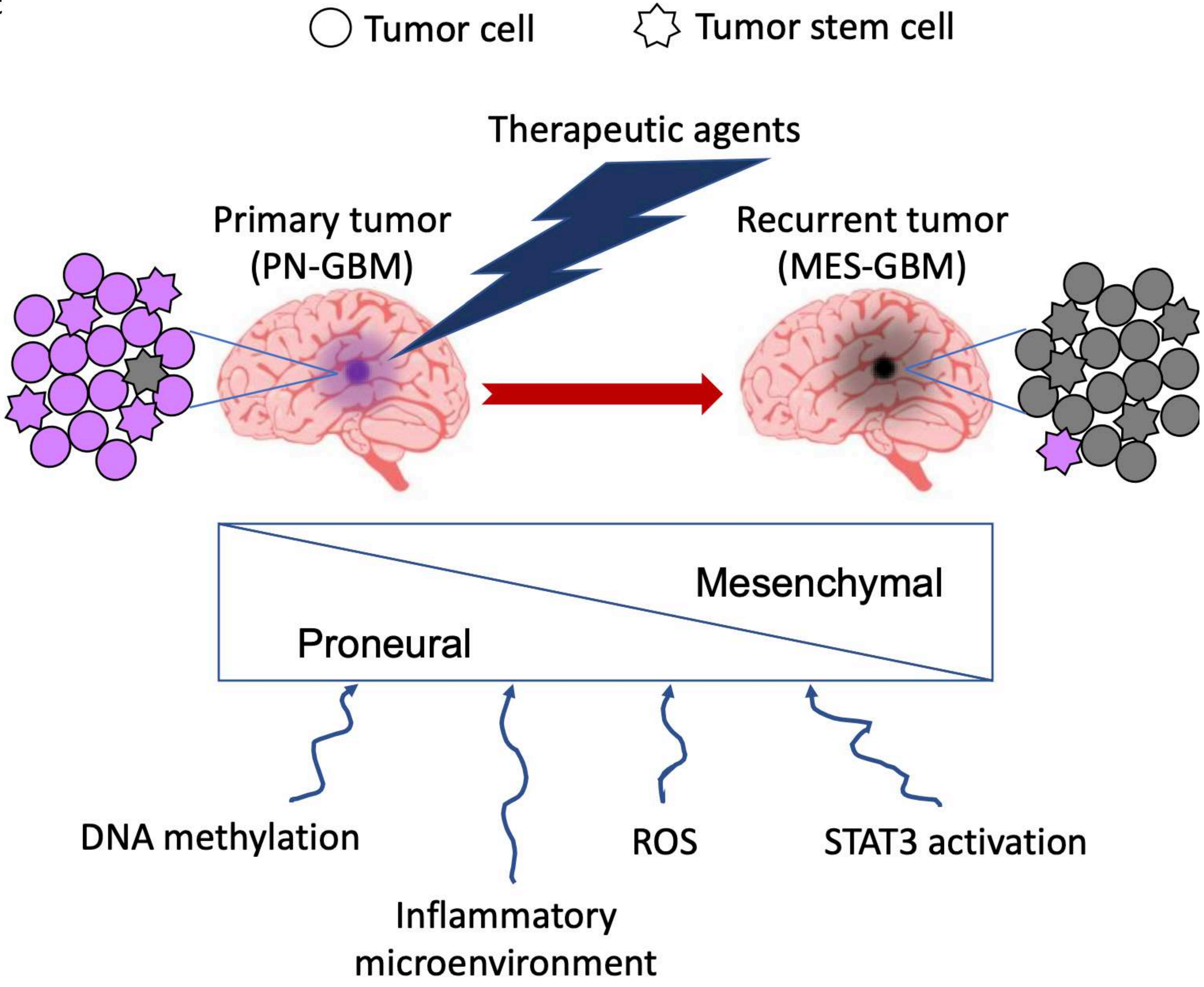
Survival
Resistance
Toxicity

International Journal of *Molecular Sciences*

Review

Proneural-Mesenchymal Transition: Phenotypic Plasticity to Acquire Multitherapy Resistance in Glioblastoma

Monica Fedele [1,*], Laura Cerchia [1], Silvia Pegoraro [2], Riccardo Sgarra [2] and Guidalberto Manfioletti [2,*]



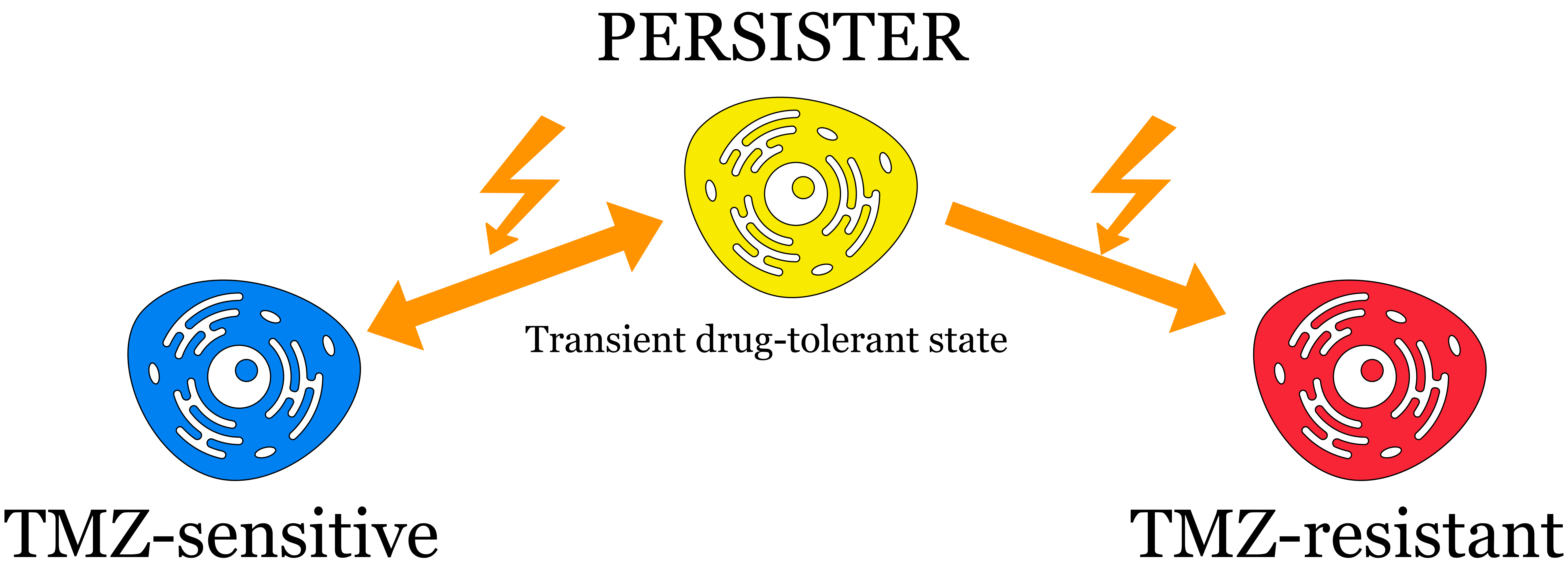
Rabé et al. *Cell Death and Disease* (2020)11:19
https://doi.org/10.1038/s41419-019-2200-2

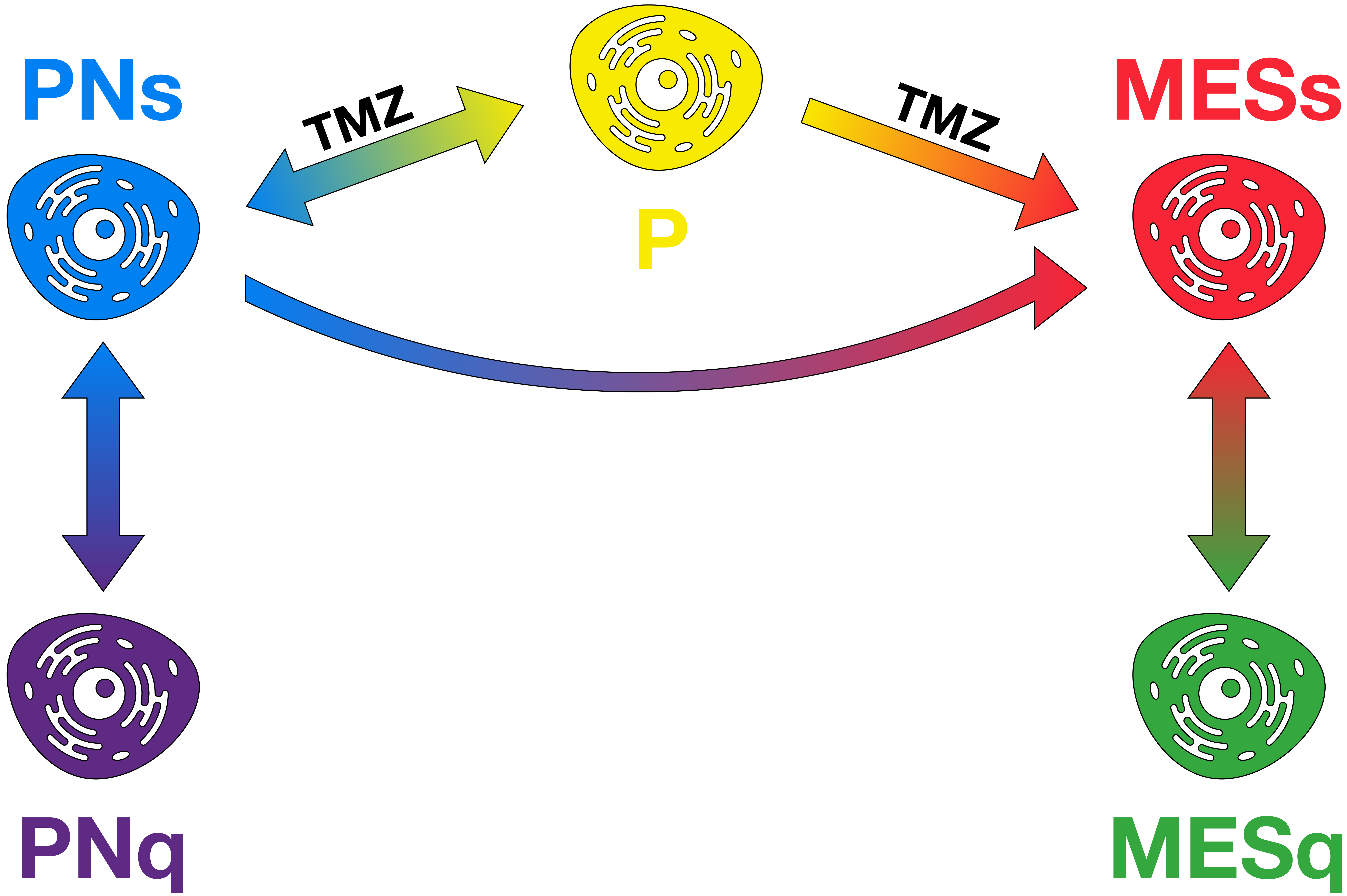
Cell Death & Disease

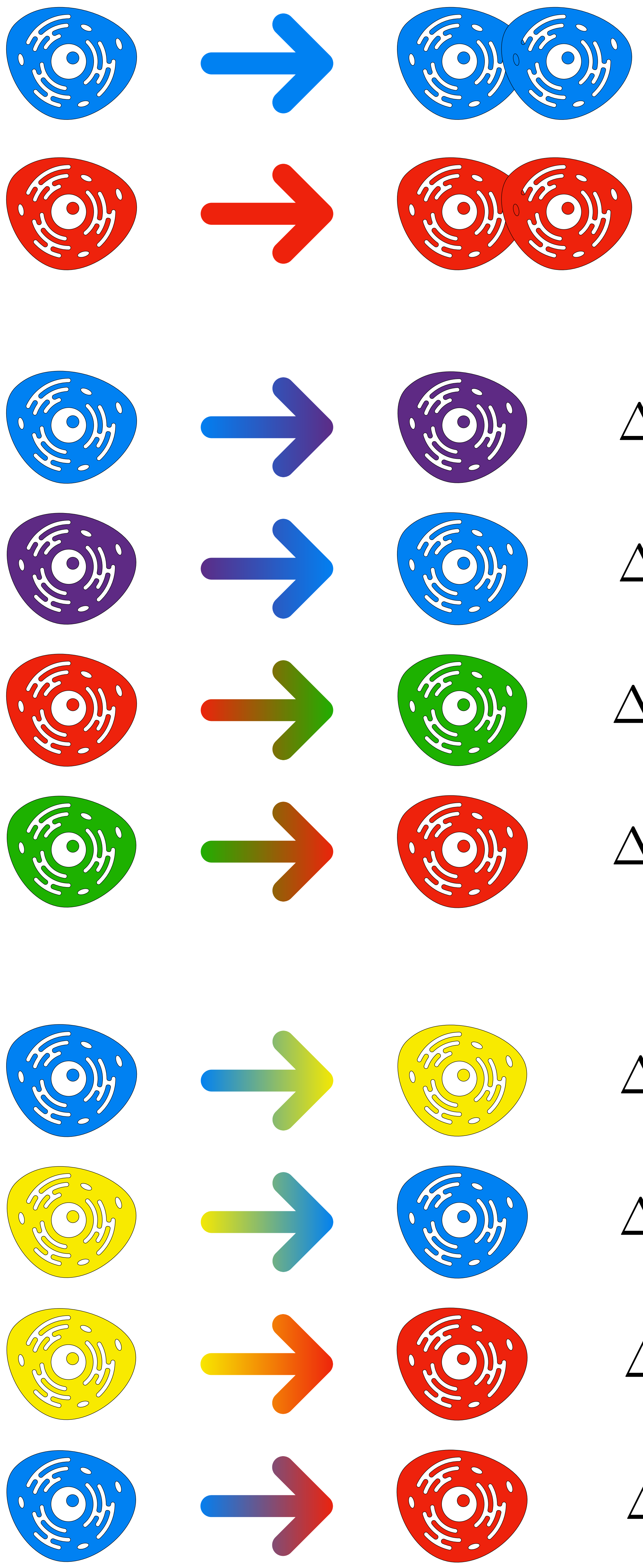
ARTICLE Open Access

Identification of a transient state during the acquisition of temozolomide resistance in glioblastoma

Marion Rabé[1], Solenne Dumont[1,2], Arturo Álvarez-Arenas[3], Hicham Janati[4], Juan Belmonte-Beitia[3], Gabriel F. Calvo[3], Christelle Thibault-Carpentier[5], Quentin Séry[1,6], Cynthia Chauvin[1], Noémie Joalland[1], Floriane Briand[1], Stéphanie Blandin[7], Emmanuel Scotet[1], Claire Pecqueur[1], Jean Clairambault[4], Lisa Oliver[1,8], Victor Perez-Garcia[3], Arulraj Nadaradjane[1,6], Pierre-François Cartron[1,6], Catherine Gratas[1,8] and François M. Vallette[1,6]




PNs
TMZ
P
TMZ
MESs
PNq
MESq



$$\Delta \mathrm{PNs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{PNs}_{i,j,k}^{t}, P_{div}\right)$$

$$\Delta \mathrm{MESs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{MESs}_{i,j,k}^{t}, P_{div}\right)$$

$$P_{div} = \frac{\Delta t}{\tau_{div}}\left(1 - \frac{N_{i,j,k}^{t}}{K}\right)$$

$$\Delta \mathrm{PNq}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{PNs}_{i,j,k}^{t}, P_{sq}\right)$$

$$\Delta \mathrm{PNs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{PNq}_{i,j,k}^{t}, P_{qs}\right)$$

$$P_{sq} = \Delta t \mu_{sq}$$

$$\Delta \mathrm{MESq}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{MESs}_{i,j,k}^{t}, P_{sq}\right)$$

$$\Delta \mathrm{MESs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{MESq}_{i,j,k}^{t}, P_{qs}\right)$$

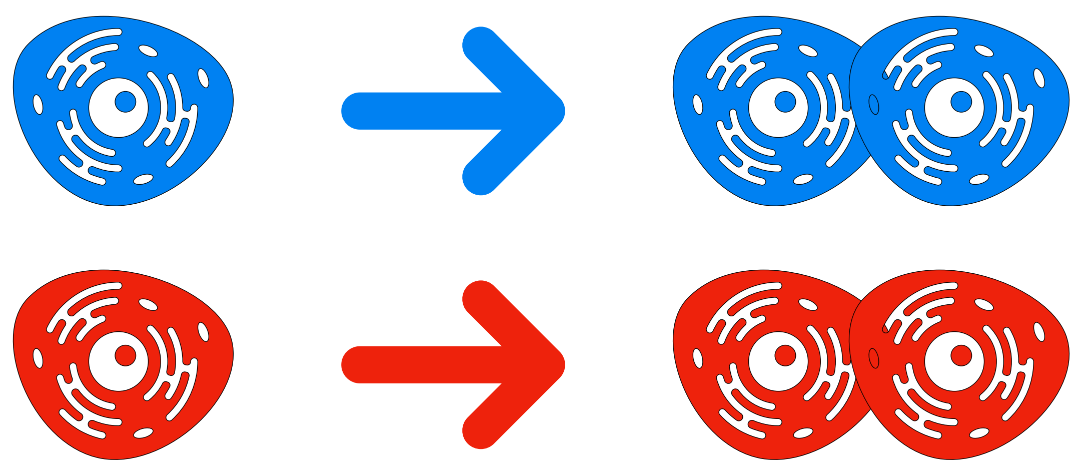
$$P_{qs} = \Delta t \mu_{qs}$$

$$\Delta \mathrm{P}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{PNs}_{i,j,k}^{t}, P_{sp}\right) \qquad P_{sp} = \Delta t \mu_{sp} \mathrm{E}_{\mathrm{TMZ}}$$

$$\Delta \mathrm{PNs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{P}_{i,j,k}^{t}, P_{ps}\right) \qquad P_{ps} = \Delta t \mu_{ps}$$

$$\Delta \mathrm{MESs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{P}_{i,j,k}^{t}, P_{pm}\right) \qquad P_{pm} = \Delta t \mu_{pm} \mathrm{E}_{\mathrm{TMZ}}$$

$$\Delta \mathrm{MESs}_{i,j,k}^{t} \sim \mathcal{B}\left(\mathrm{PNs}_{i,j,k}^{t}, P_{sm}\right) \qquad P_{sm} = \Delta t \mu_{sm}, \quad \text{if} \quad \frac{N_{i,j,k}^{t}}{K} > 0.7$$



$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{div}\right)$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESs}^t_{i,j,k}, P_{div}\right)$$

$$P_{div} = \frac{\Delta t}{\tau_{div}}\left(1 - \frac{N^t_{i,j,k}}{K}\right)$$

Cell division

$$\Delta \mathrm{PN}$$

$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNq}^t_{i,j,k}, P_{qs}\right)$$

$$\Delta \mathrm{MESq}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESs}^t_{i,j,k}, P_{sq}\right)$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESq}^t_{i,j,k}, P_{qs}\right)$$

$$P_{sq} = \Delta t \mu_{sq}$$

$$P_{qs} = \Delta t \mu_{qs}$$

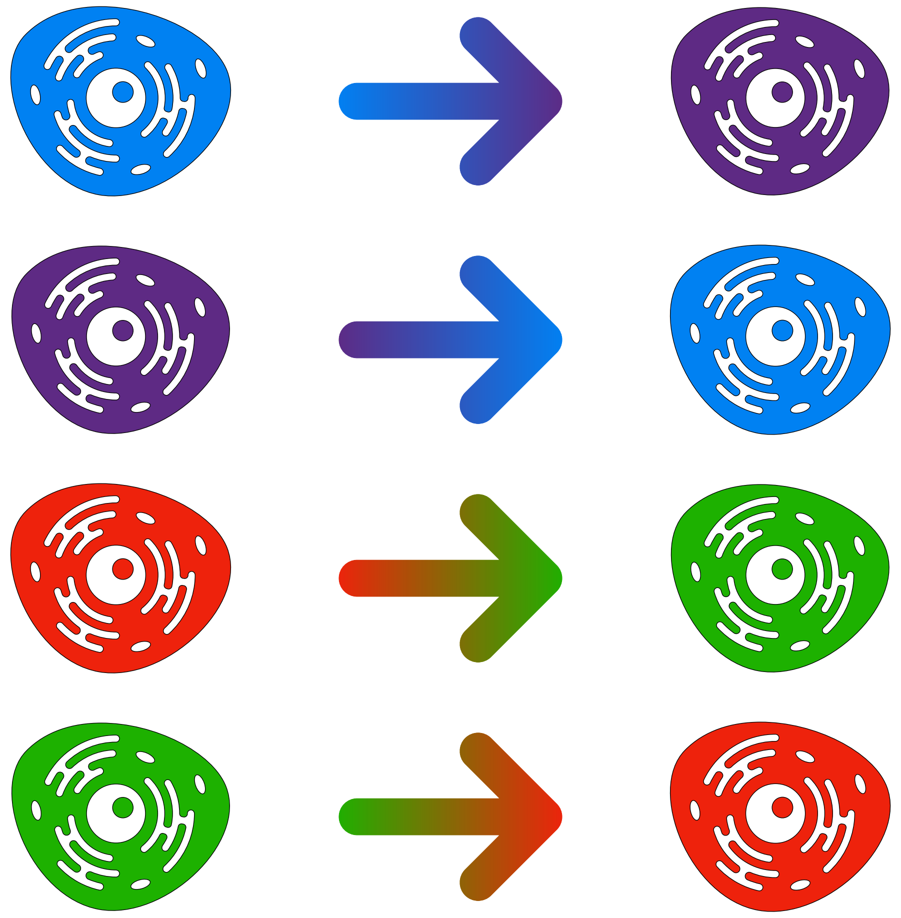
$$\Delta \mathrm{P}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{sp}\right) \qquad P_{sp} = \Delta t \mu_{sp} \mathrm{E_{TMZ}}$$

$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{P}^t_{i,j,k}, P_{ps}\right) \qquad P_{ps} = \Delta t \mu_{ps}$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{P}^t_{i,j,k}, P_{pm}\right) \qquad P_{pm} = \Delta t \mu_{pm} \mathrm{E_{TMZ}}$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{sm}\right) \qquad P_{sm} = \Delta t \mu_{sm}, \quad \text{if} \quad \frac{N^t_{i,j,k}}{K} > 0.7$$

Proliferative-quiescent transitions



$$\Delta \mathrm{PNq}^{t}_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^{t}_{i,j,k}, P_{sq}\right)$$

$$\Delta \mathrm{PNs}^{t}_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNq}^{t}_{i,j,k}, P_{qs}\right)$$

$$\Delta \mathrm{MESq}^{t}_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESs}^{t}_{i,j,k}, P_{sq}\right)$$

$$\Delta \mathrm{MESs}^{t}_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESq}^{t}_{i,j,k}, P_{qs}\right)$$

$$P_{sq} = \Delta t \mu_{sq}$$

$$P_{qs} = \Delta t \mu_{qs}$$

$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{div}\right)$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESs}^t_{i,j,k}, P_{div}\right)$$

$$P_{div} = \frac{\Delta t}{\tau_{div}}\left(1 - \frac{N^t_{i,j,k}}{K}\right)$$

$$\Delta \mathrm{PNq}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{sq}\right)$$

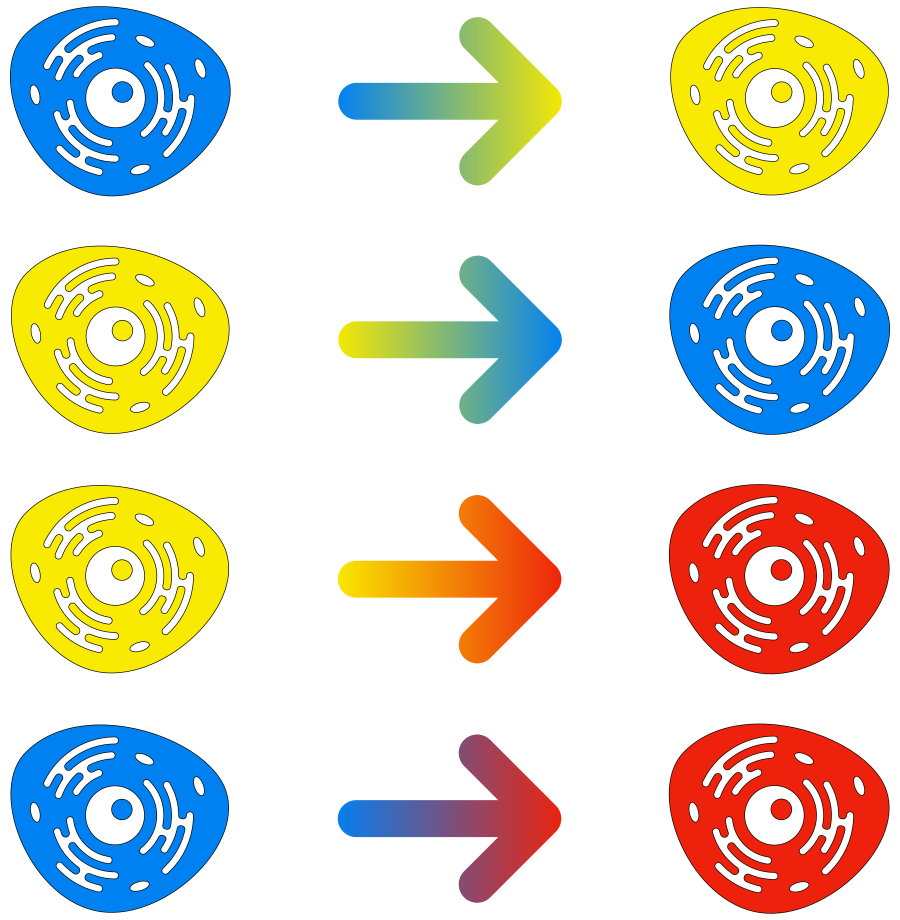
$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNq}^t_{i,j,k}, P_{qs}\right)$$

$$\Delta \mathrm{MESq}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{MESs}^t_{i,j,k}, P_{sq}\right)$$

$$P_{sq} = \Delta t \mu_{sq}$$

$$P_{qs} = \Delta t \mu_{qs}$$

TMZ-dependent transitions

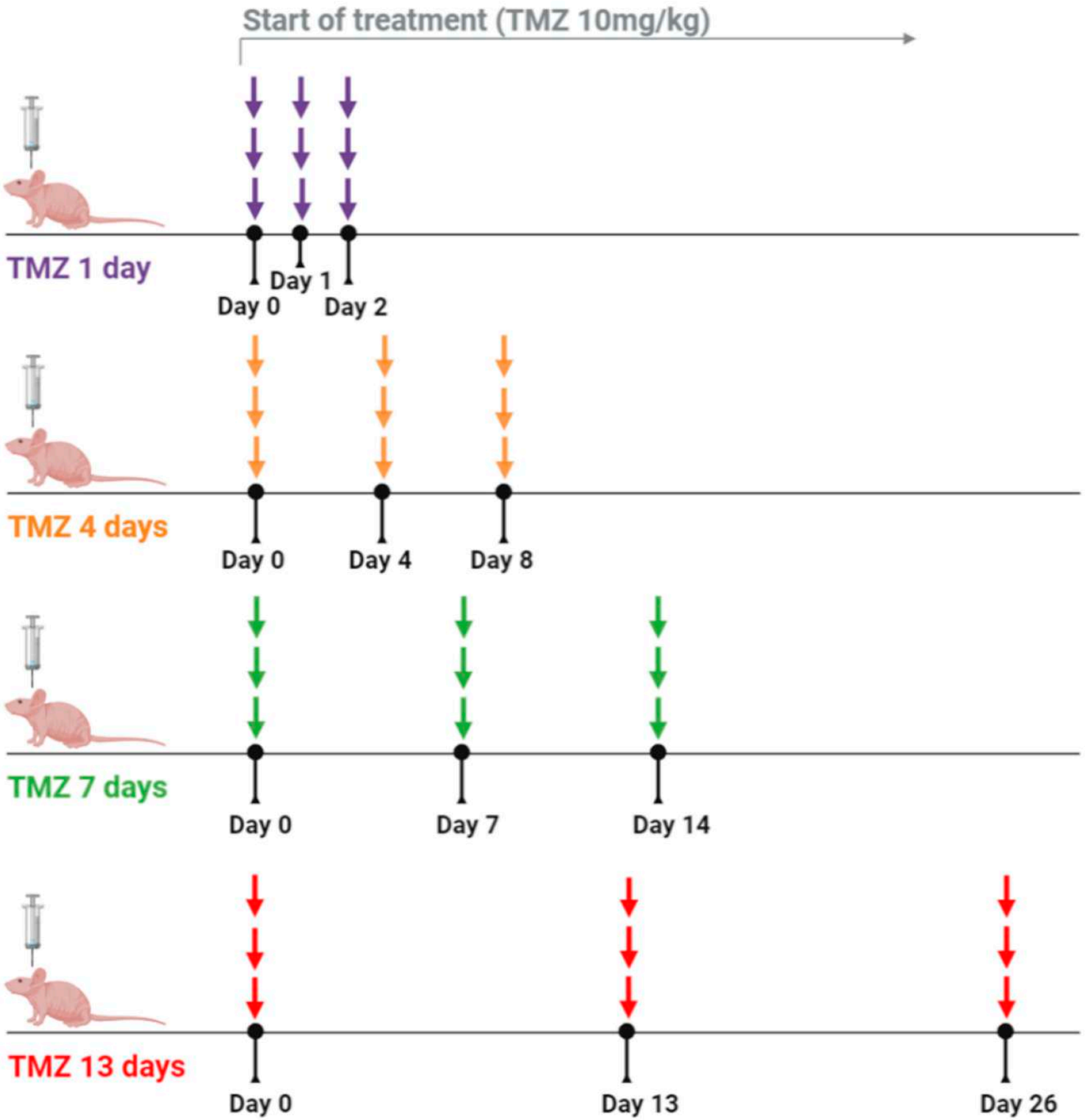


$$\Delta \mathrm{P}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{sp}\right) \qquad P_{sp} = \Delta t \mu_{sp} \mathrm{E}_{\mathrm{TMZ}}$$

$$\Delta \mathrm{PNs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{P}^t_{i,j,k}, P_{ps}\right) \qquad P_{ps} = \Delta t \mu_{ps}$$

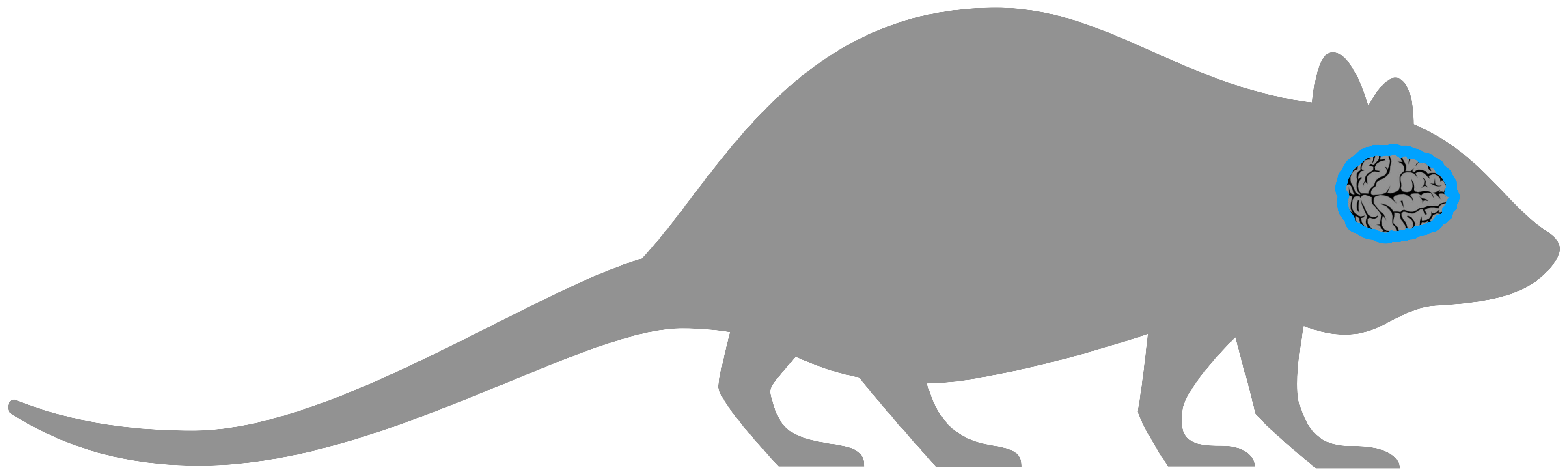
$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{P}^t_{i,j,k}, P_{pm}\right) \qquad P_{pm} = \Delta t \mu_{pm} \mathrm{E}_{\mathrm{TMZ}}$$

$$\Delta \mathrm{MESs}^t_{i,j,k} \sim \mathcal{B}\left(\mathrm{PNs}^t_{i,j,k}, P_{sm}\right) \qquad P_{sm} = \Delta t \mu_{sm}, \quad \text{if} \quad \frac{N^t_{i,j,k}}{K} > 0.7$$



Start of treatment (TMZ 10mg/kg)
TMZ 1 day
Day 0
Day 1
Day 2
TMZ 4 days
Day 0
Day 4
Day 8
TMZ 7 days
Day 0
Day 7
Day 14
TMZ 13 days
Day 0
Day 13
Day 26

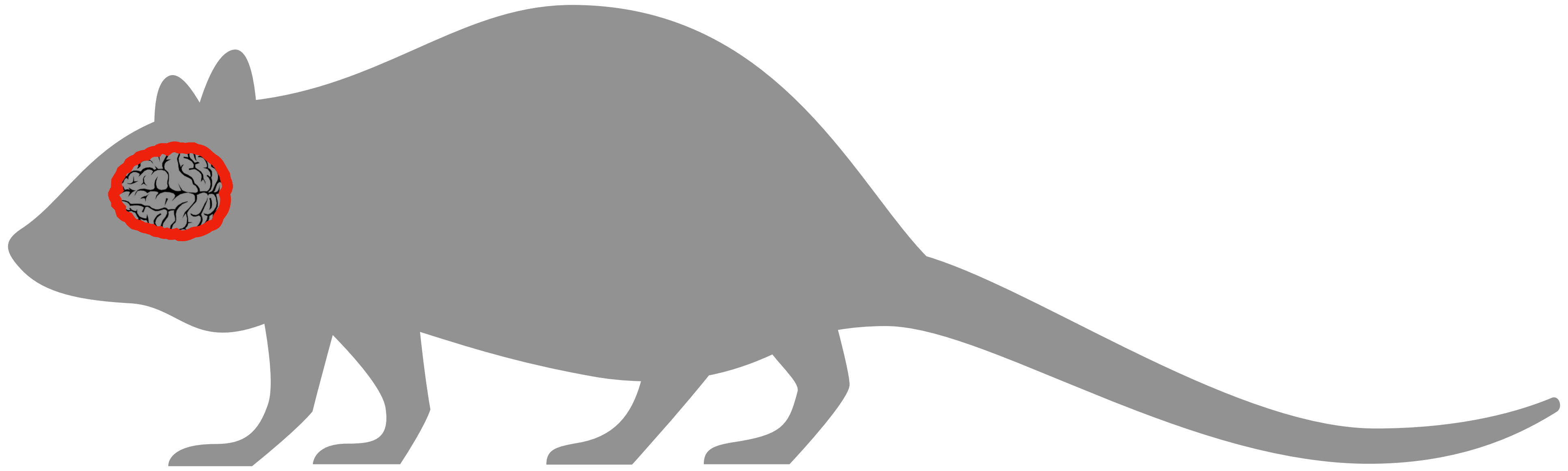
SVZ-EGFRwt



10% S cells

OS: 50-63 days

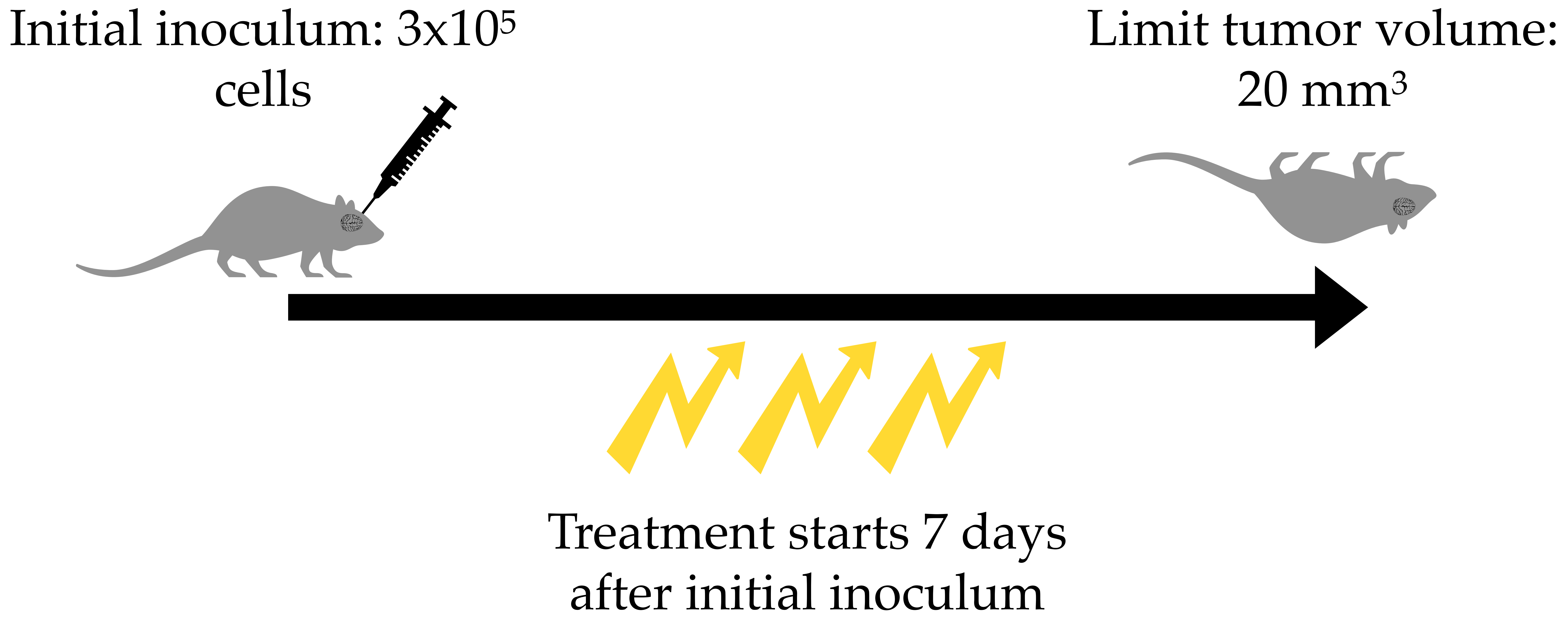
SVZ-EGFRvIII



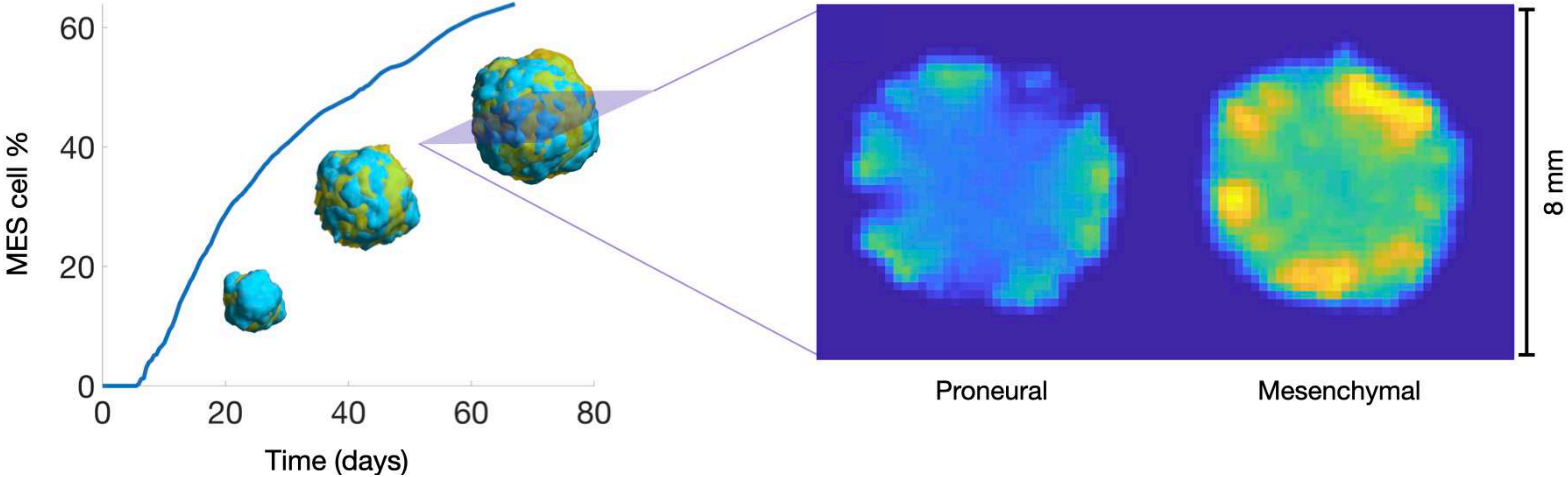
30% S cells

OS: 25-32 days

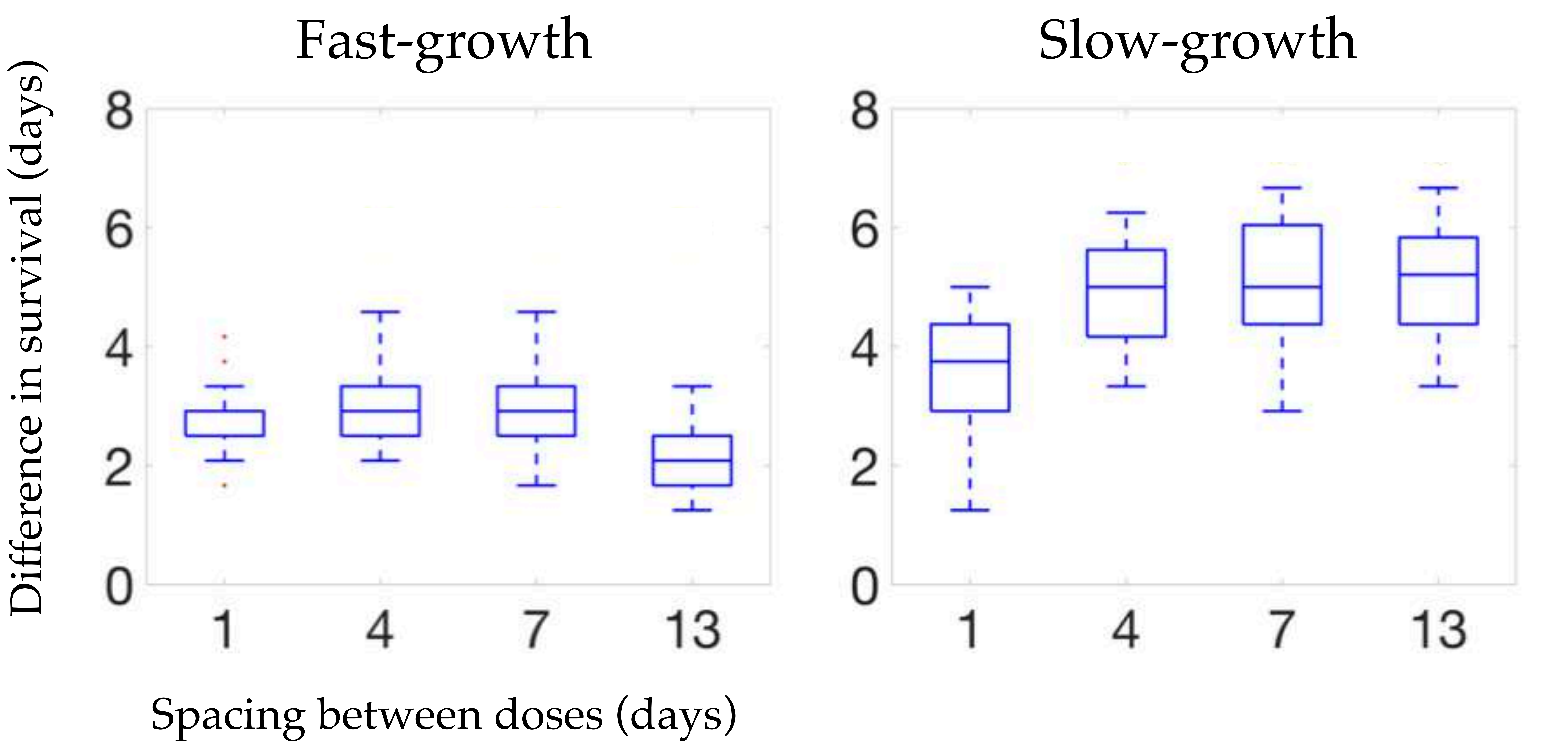
Instituto de Salud Carlos III

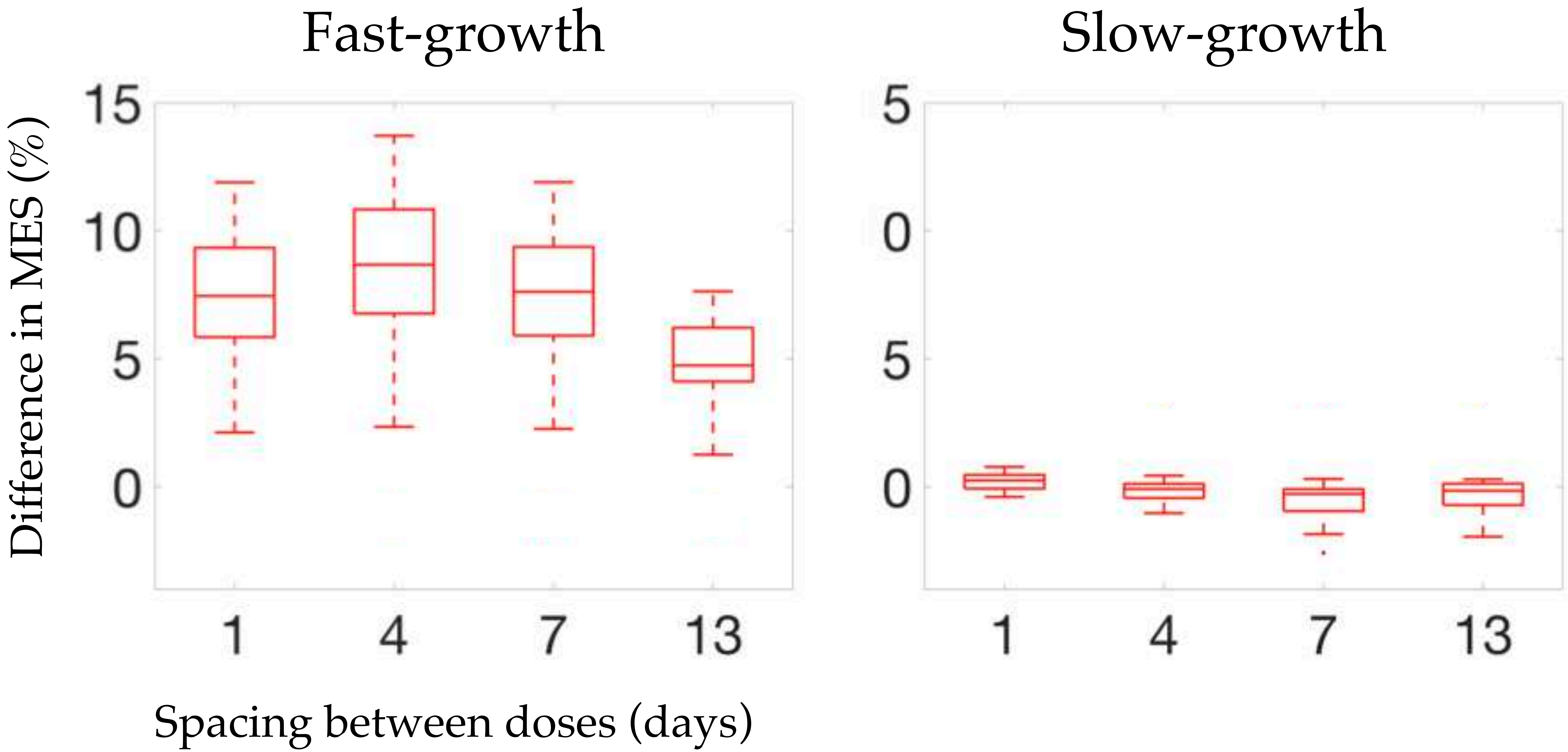


Instituto de Salud Carlos III

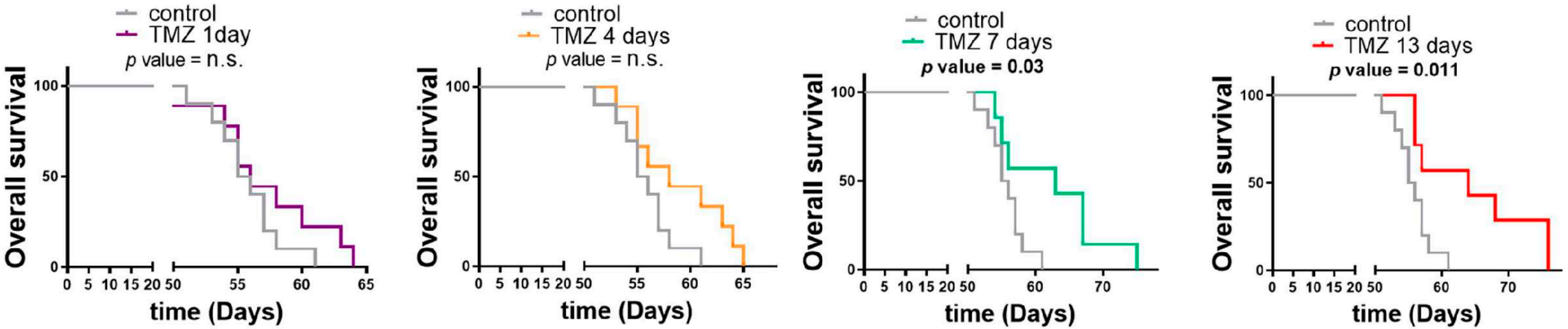


MES cell %
60
40
20
0
0
20
40
60
80
Time (days)
8 mm
Proneural
Mesenchymal

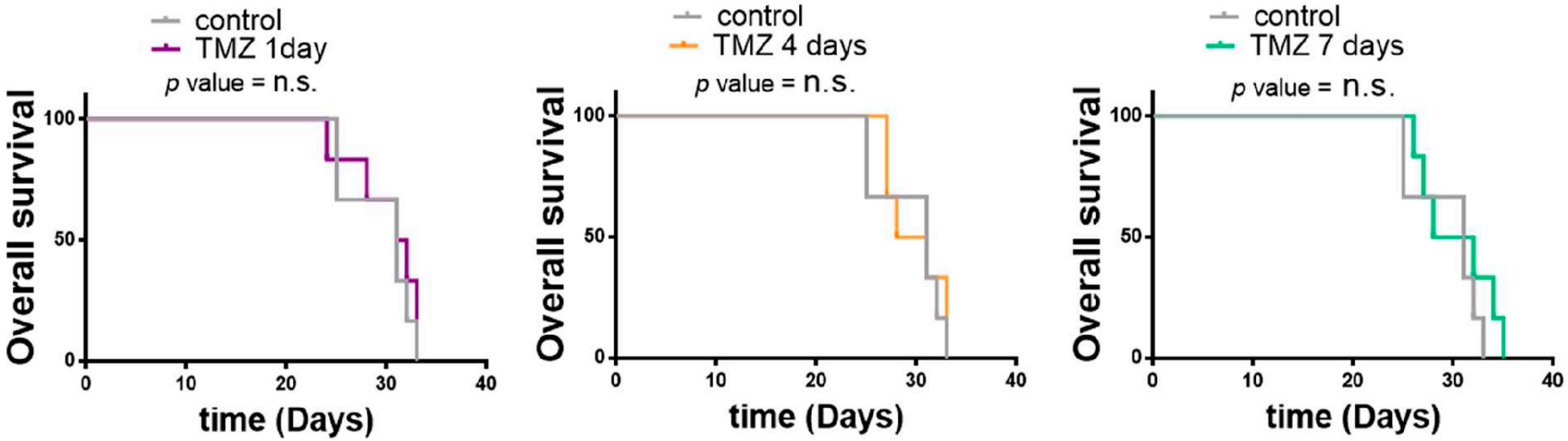

Fast-growth
Slow-growth
Difference in survival (days)
8
6
4
2
0
1
4
7
13
Spacing between doses (days)

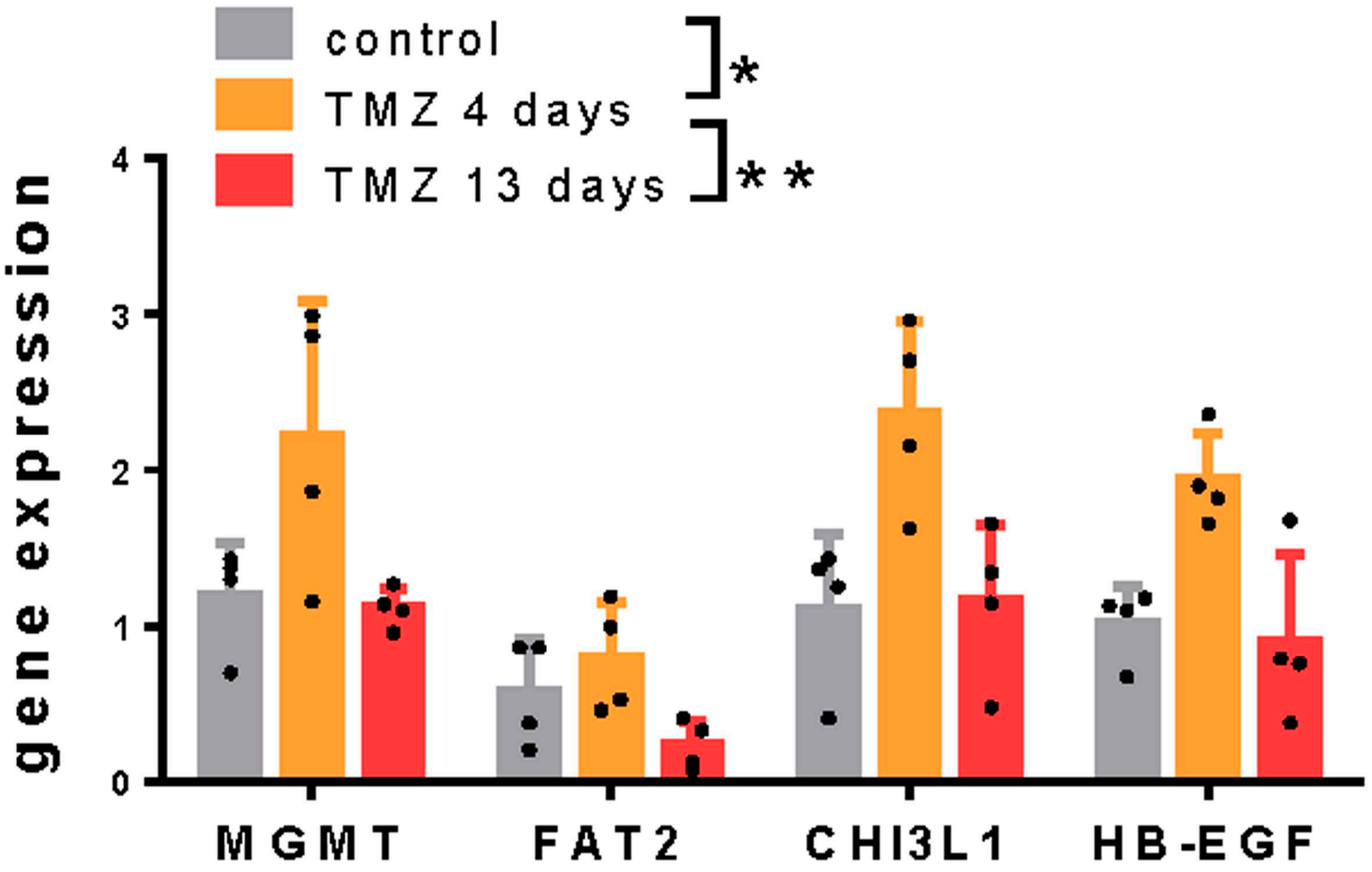

Fast-growth
Slow-growth
Difference in MES (%)
15
10
5
0
5
0
5
0
1
4
7
13
1
4
7
13
Spacing between doses (days)

SVZ EGFR wt/amp

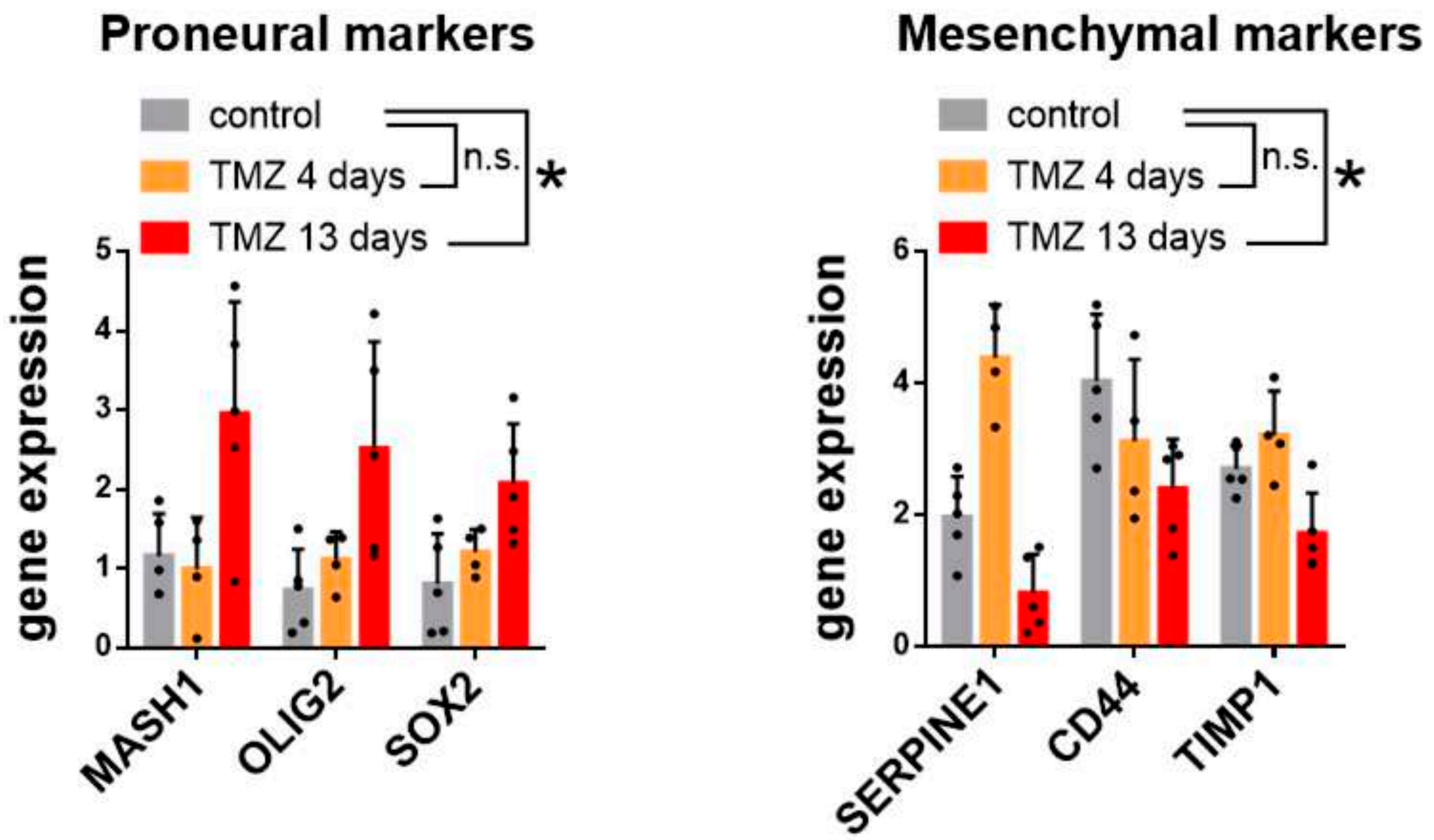


SVZ EGFR vIII





Long-spacings reduce expression of TMZ-resistance markers



Long-spacings reduce expression of MES markers

		TMZ (50mg/kg)		
	Untreated	1 day	7 days	13 days
Hematology				
Leukocytes (x10^9/L)	5,12 ± 2,50	4±3,68	5,1±3,29	5,4±1,59
Neutrophiles (x10^9/L)	3,45± 1,63	2,65±2,26	3,85±2,89	3,57±1,21
Lymphocytes (x10^9/L)	1,03± 0,6	0,78±0,83	0,78±0,38	1,18±0,64
Trombocytes (x10^9/L)	426,75± 172,57	131,25±91,94 (L)	339,5±283,6	349,25±195,22

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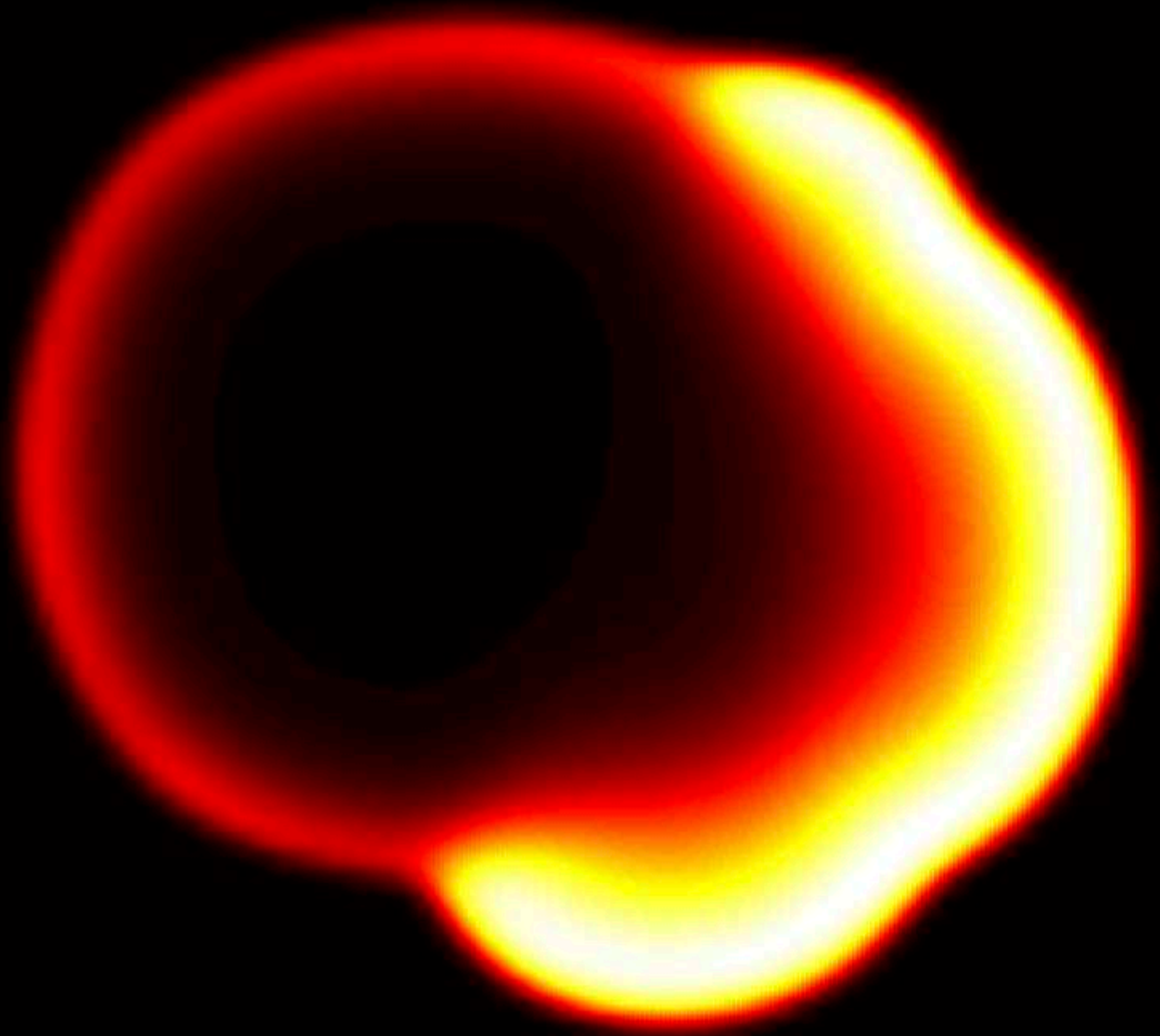
Long-spacings reduce hematologic toxicity

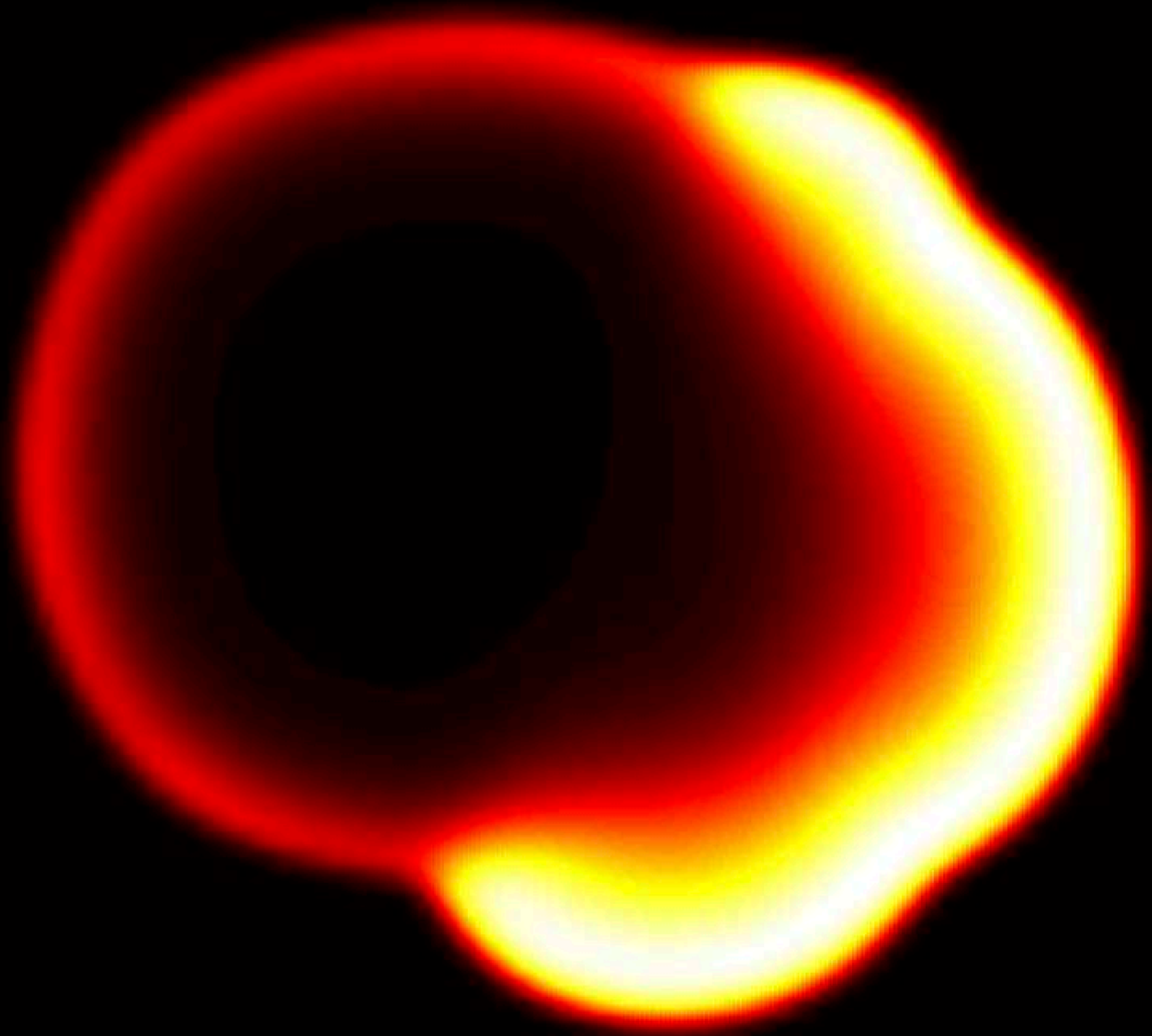


Longer spacings increase survival

Longer spacings delay resistance

Longer spacings reduce toxicity

IN MICE



Longer spacings increase survival

Longer spacings delay resistance

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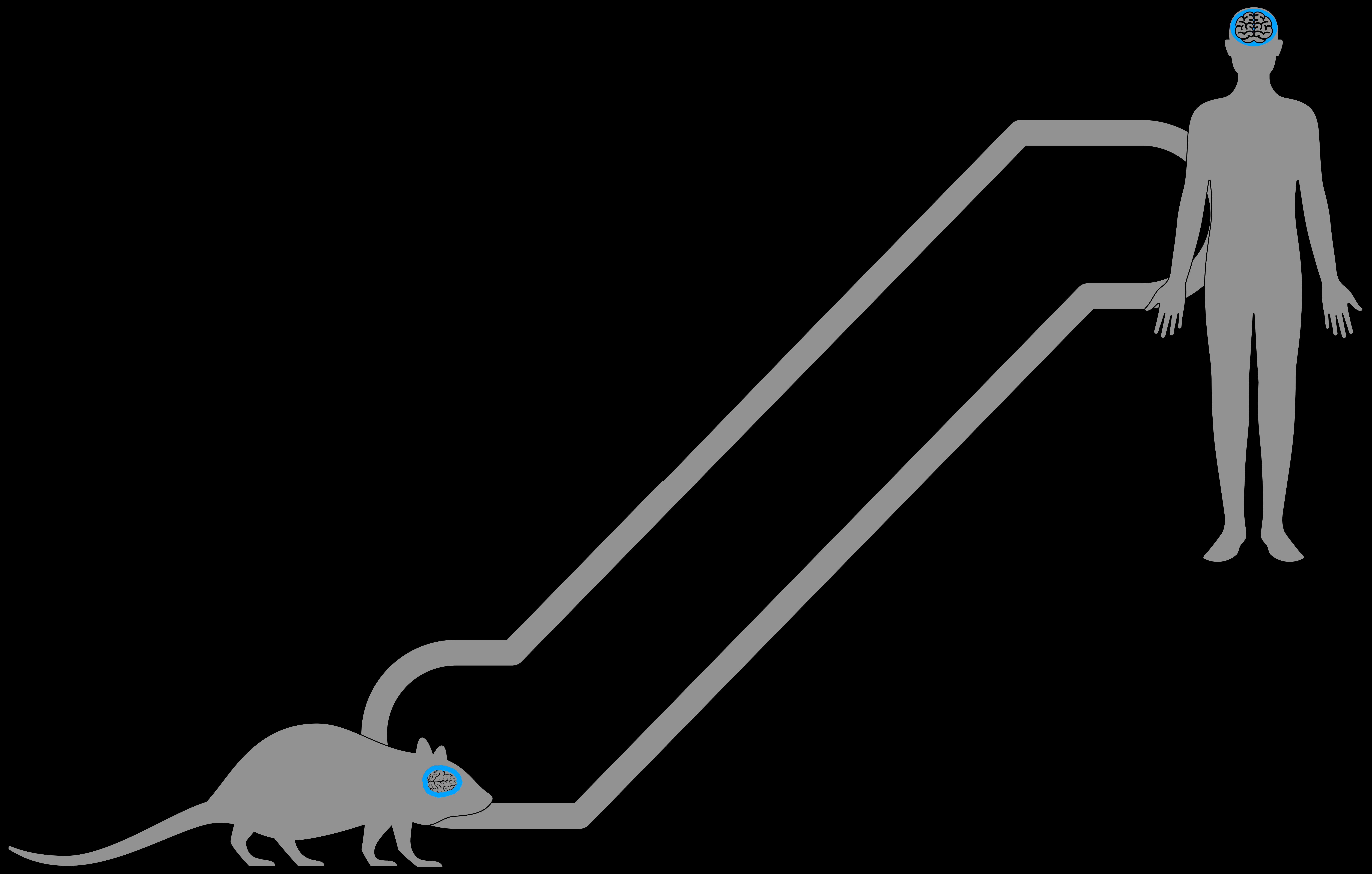
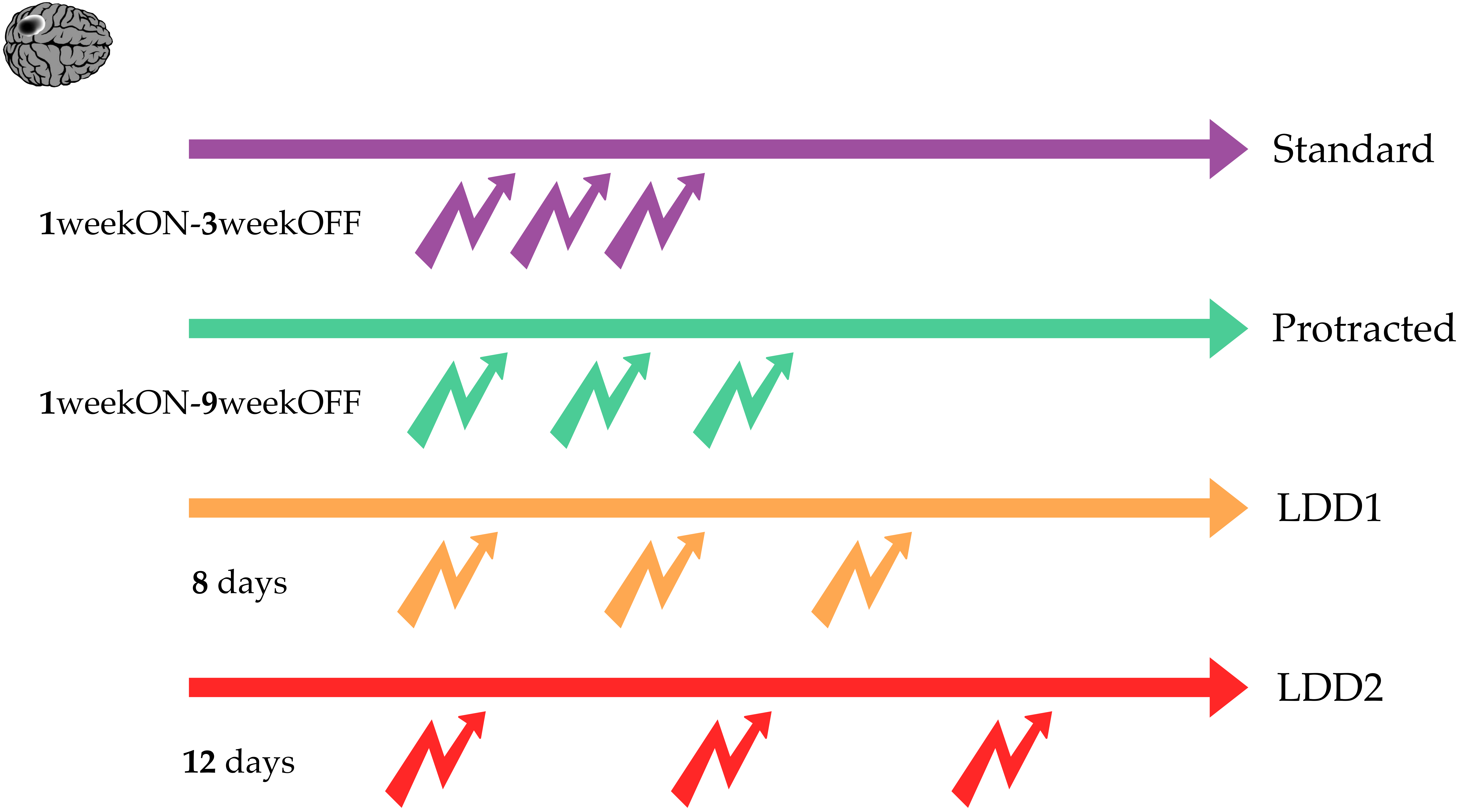
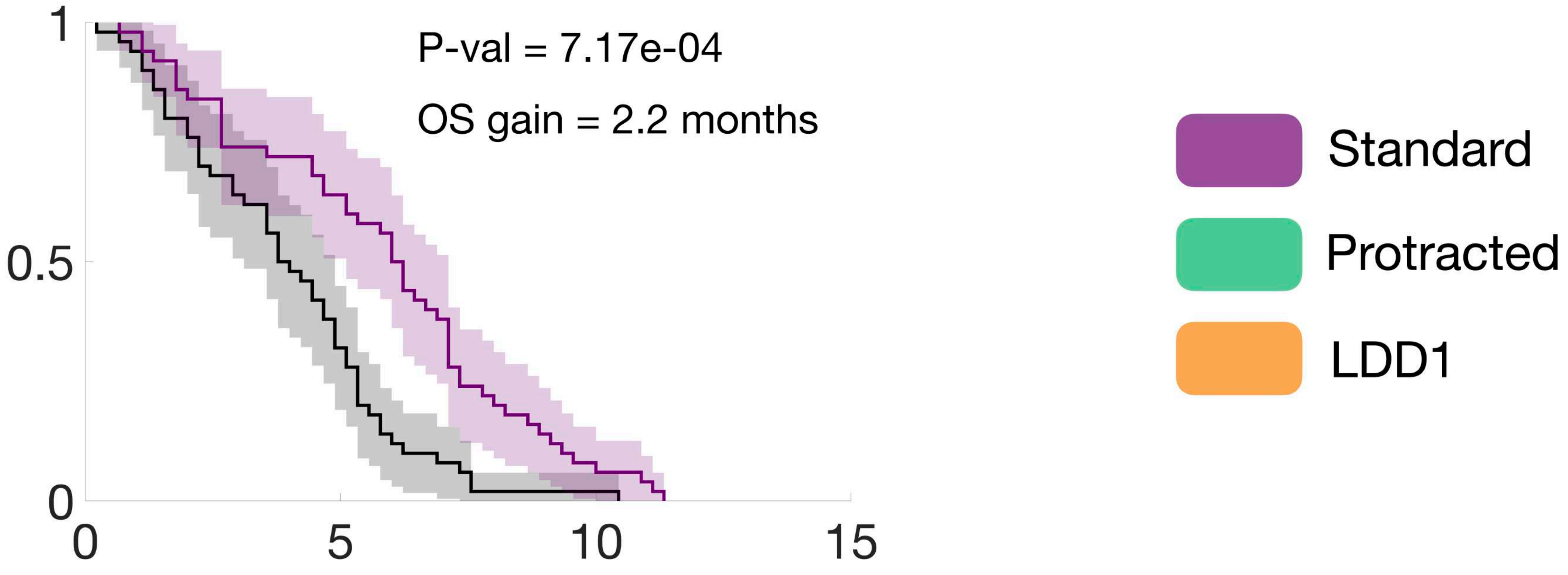
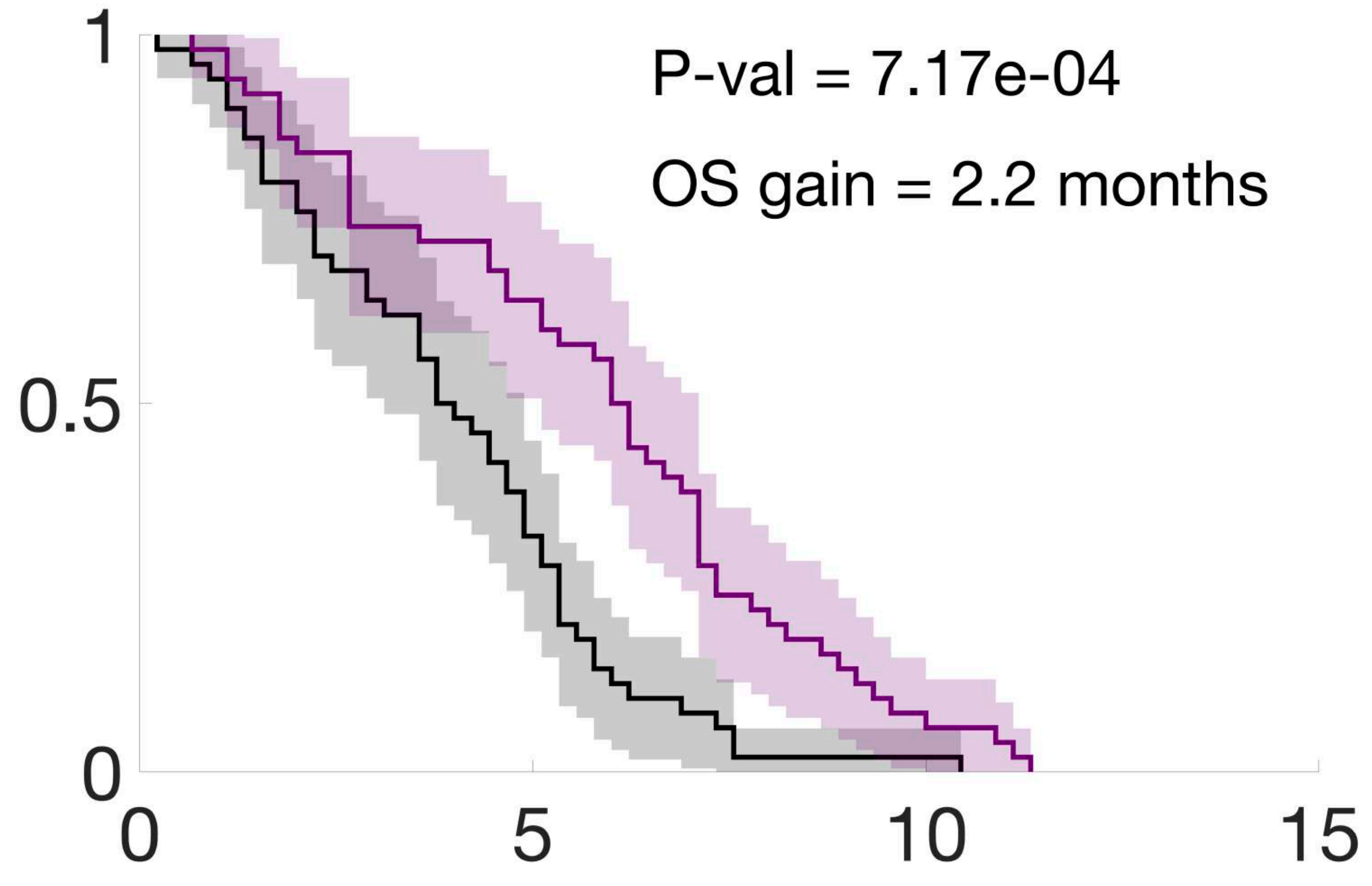


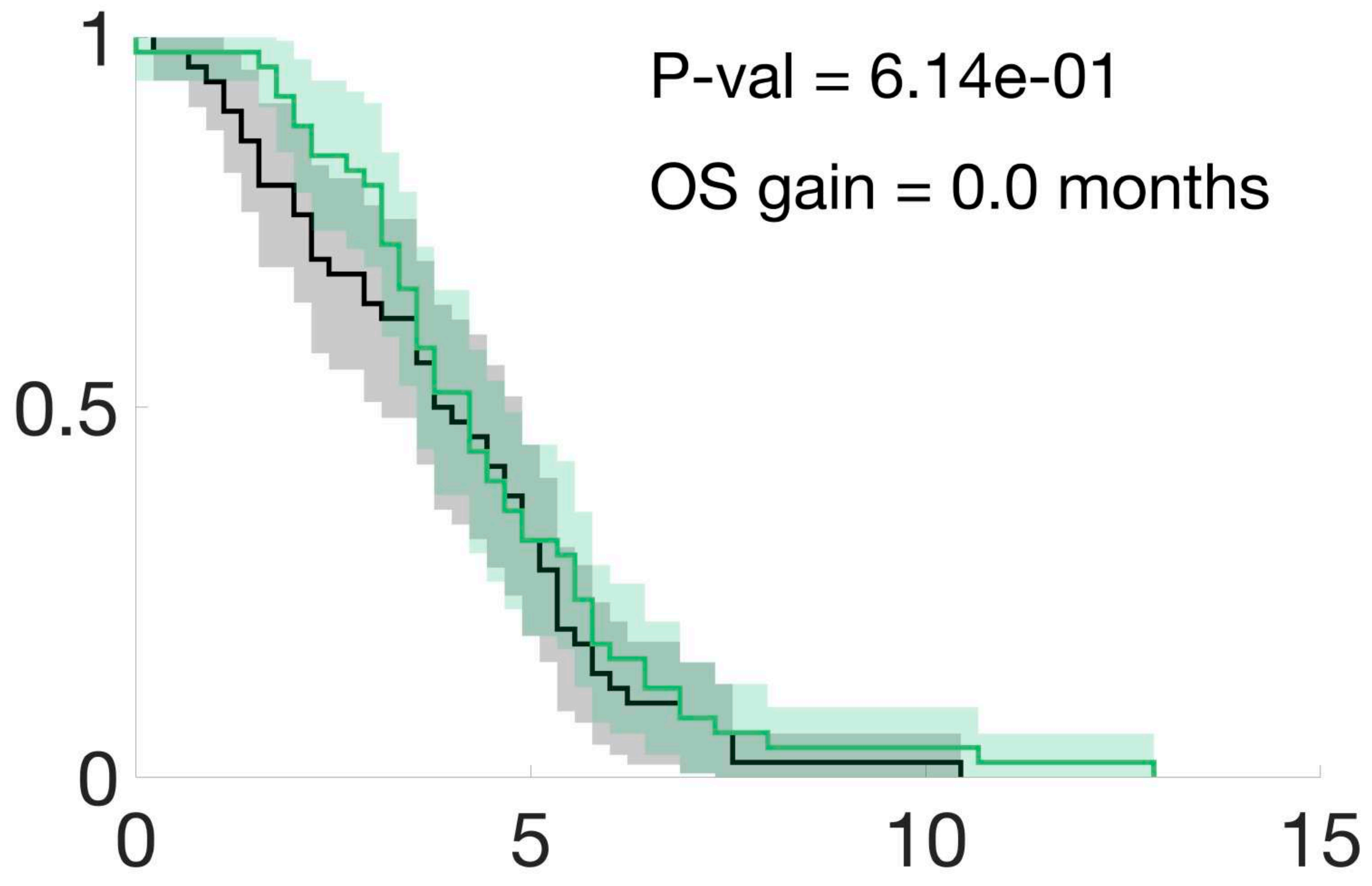

Standard
1weekON-3weekOFF
Protracted
1weekON-9weekOFF
LDD1
8 days
LDD2
12 days

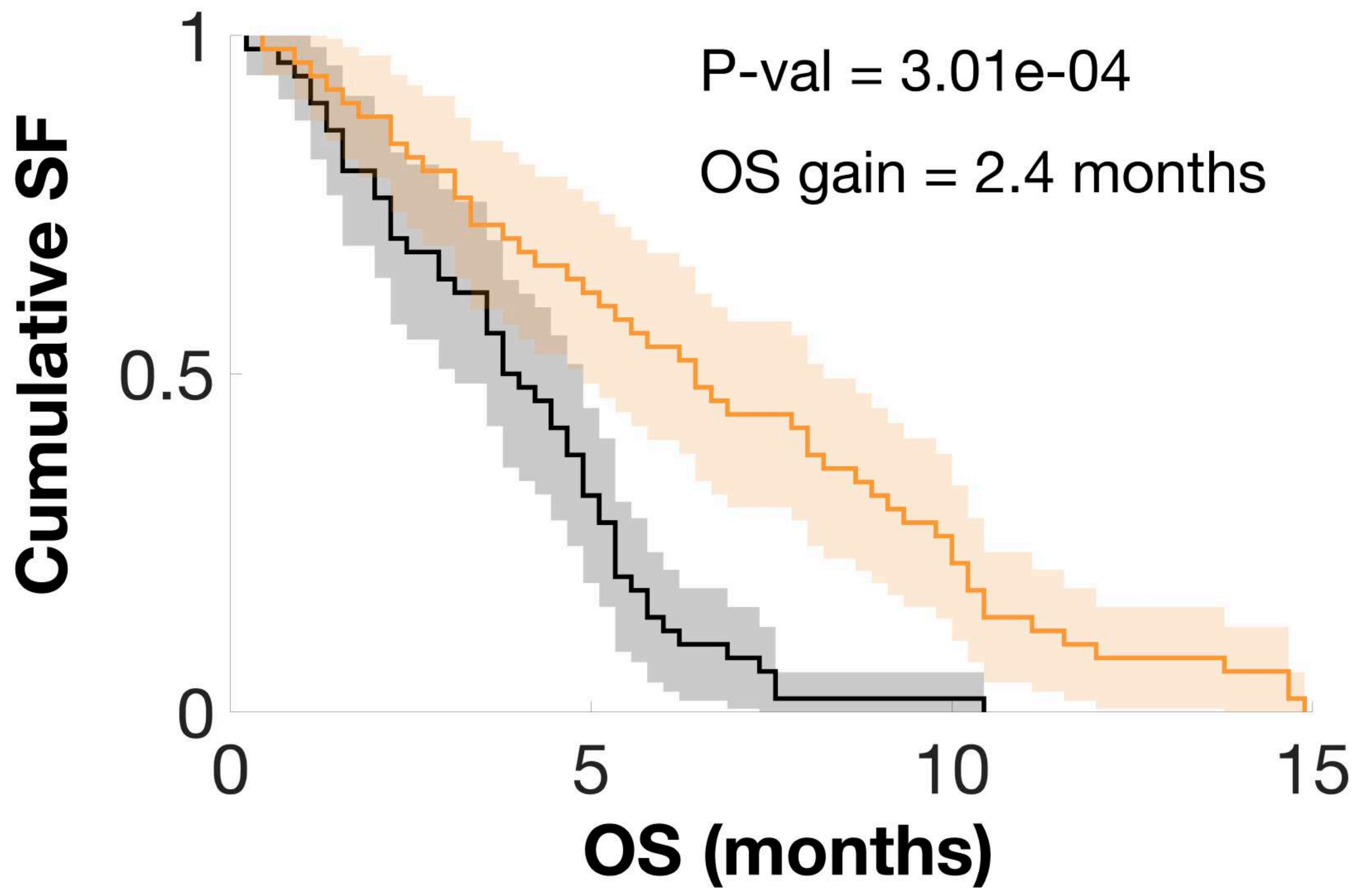


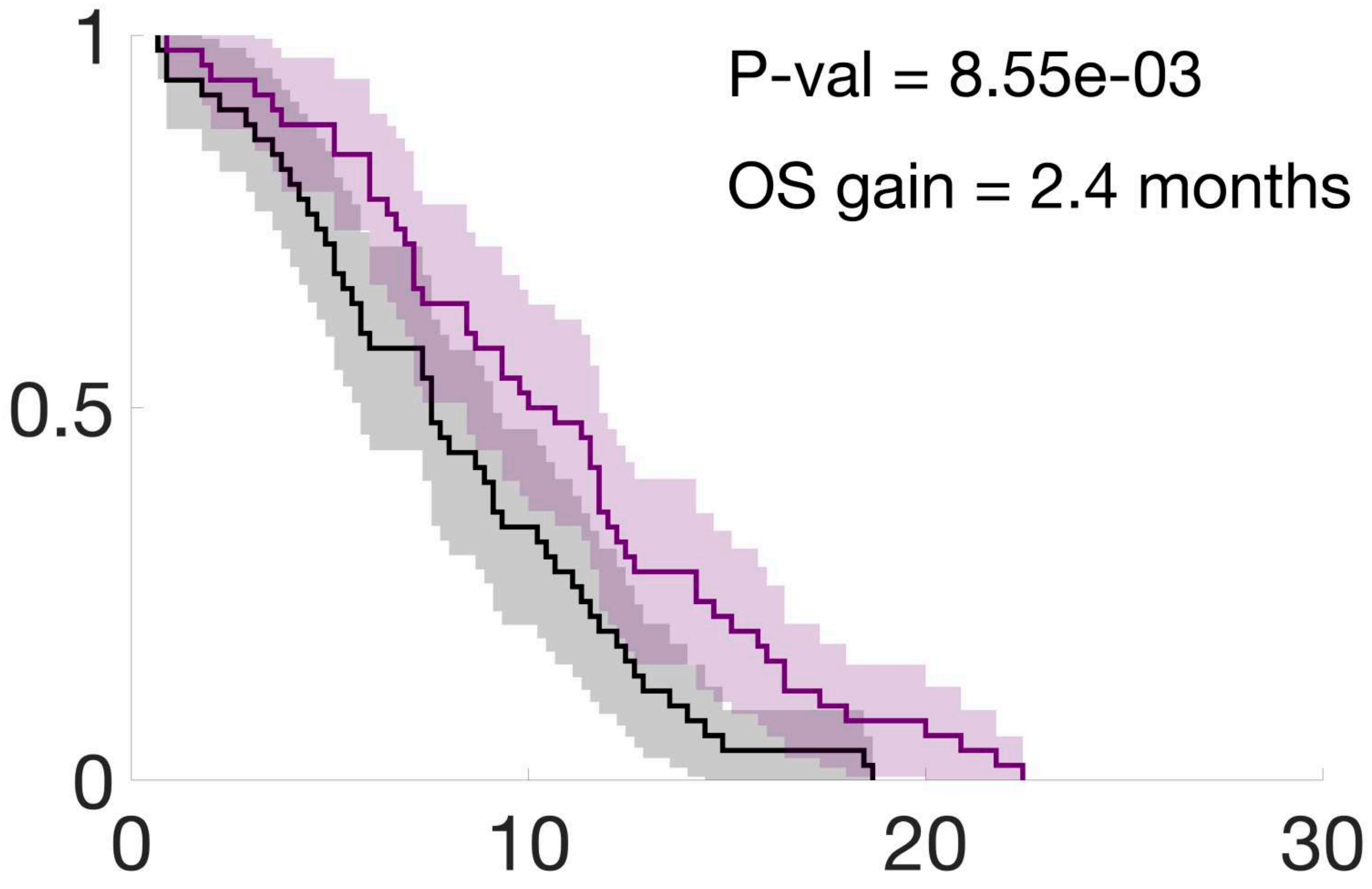
Fast-growing tumors

Fast-growing tumors



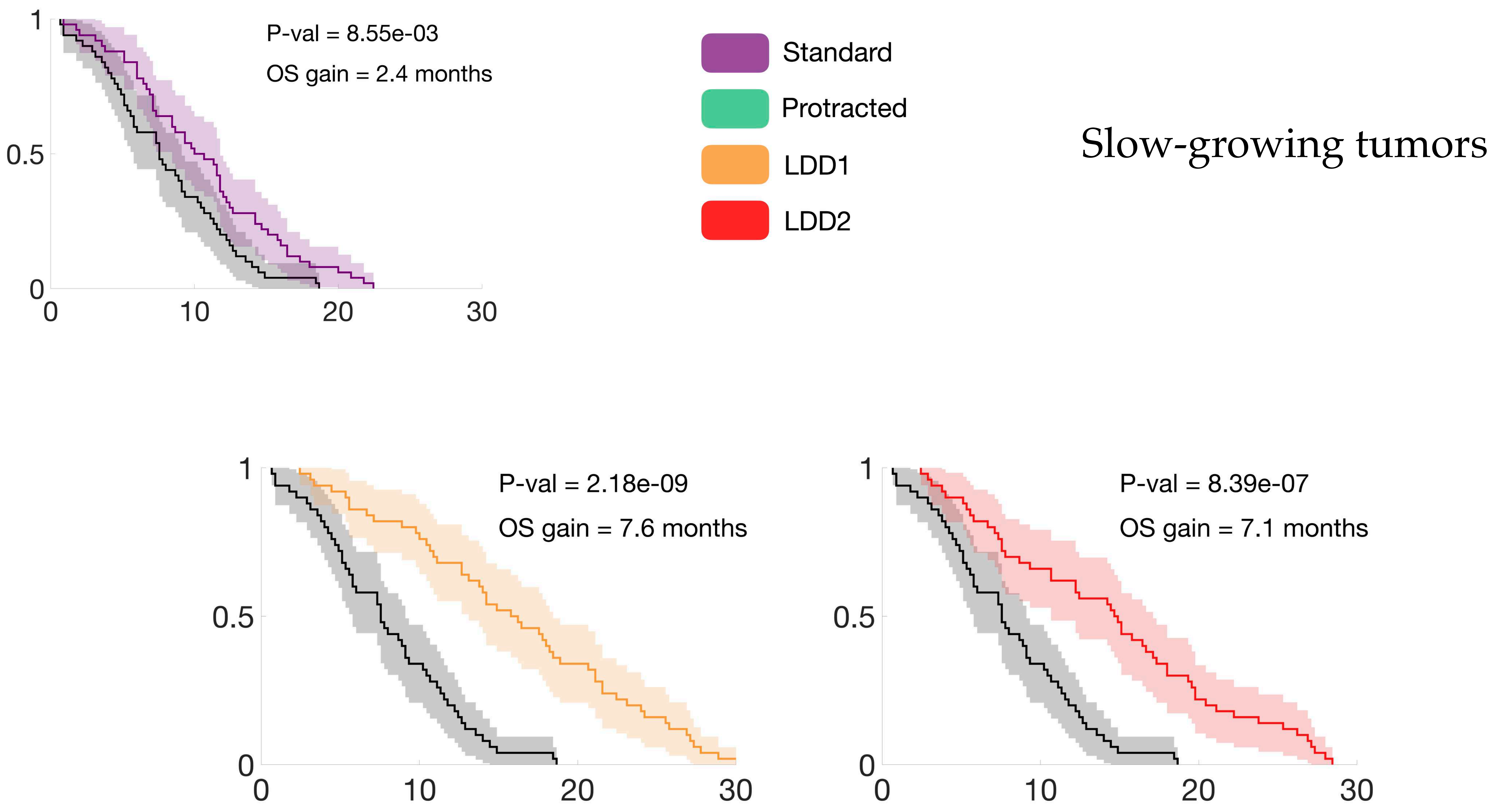


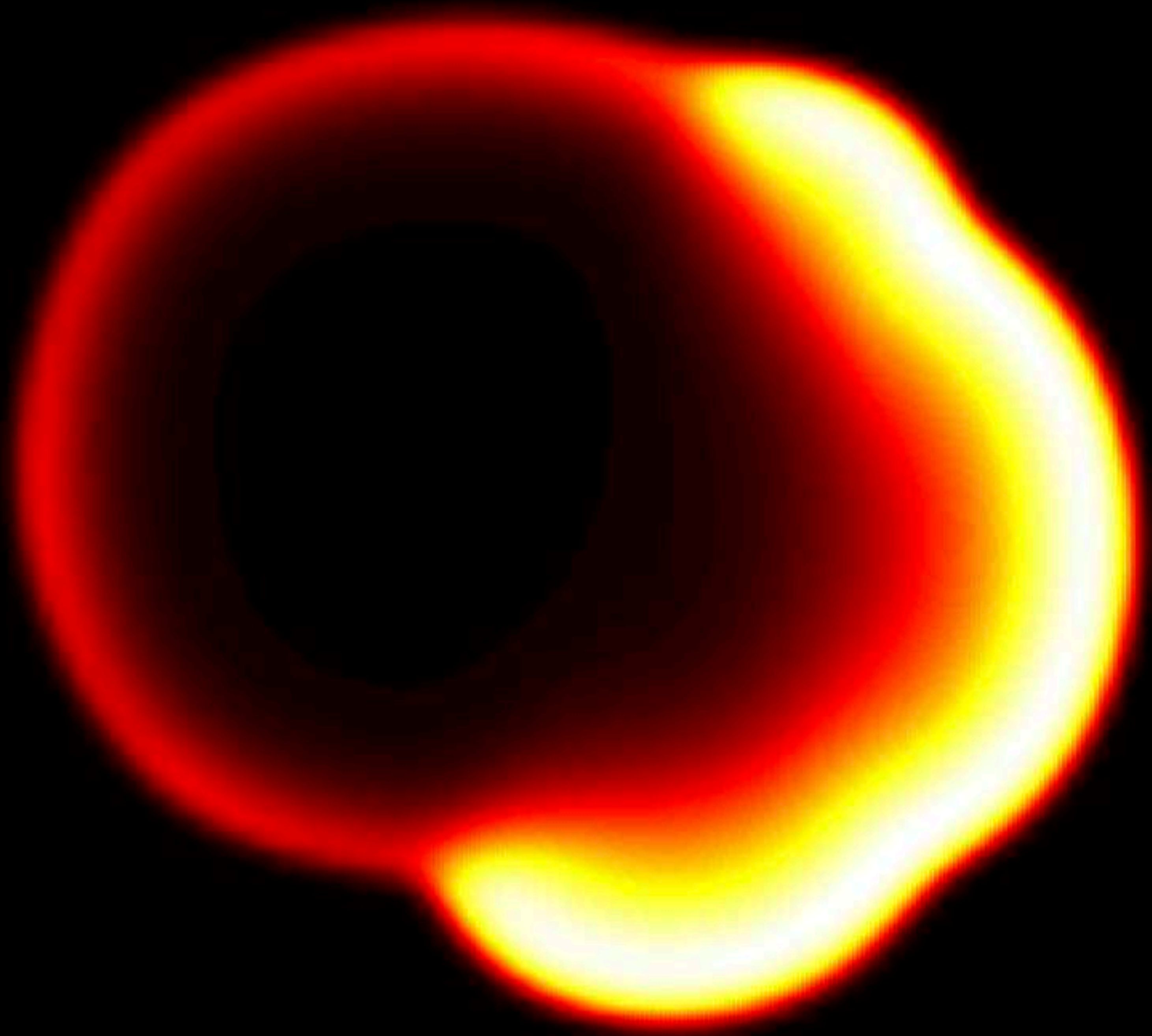




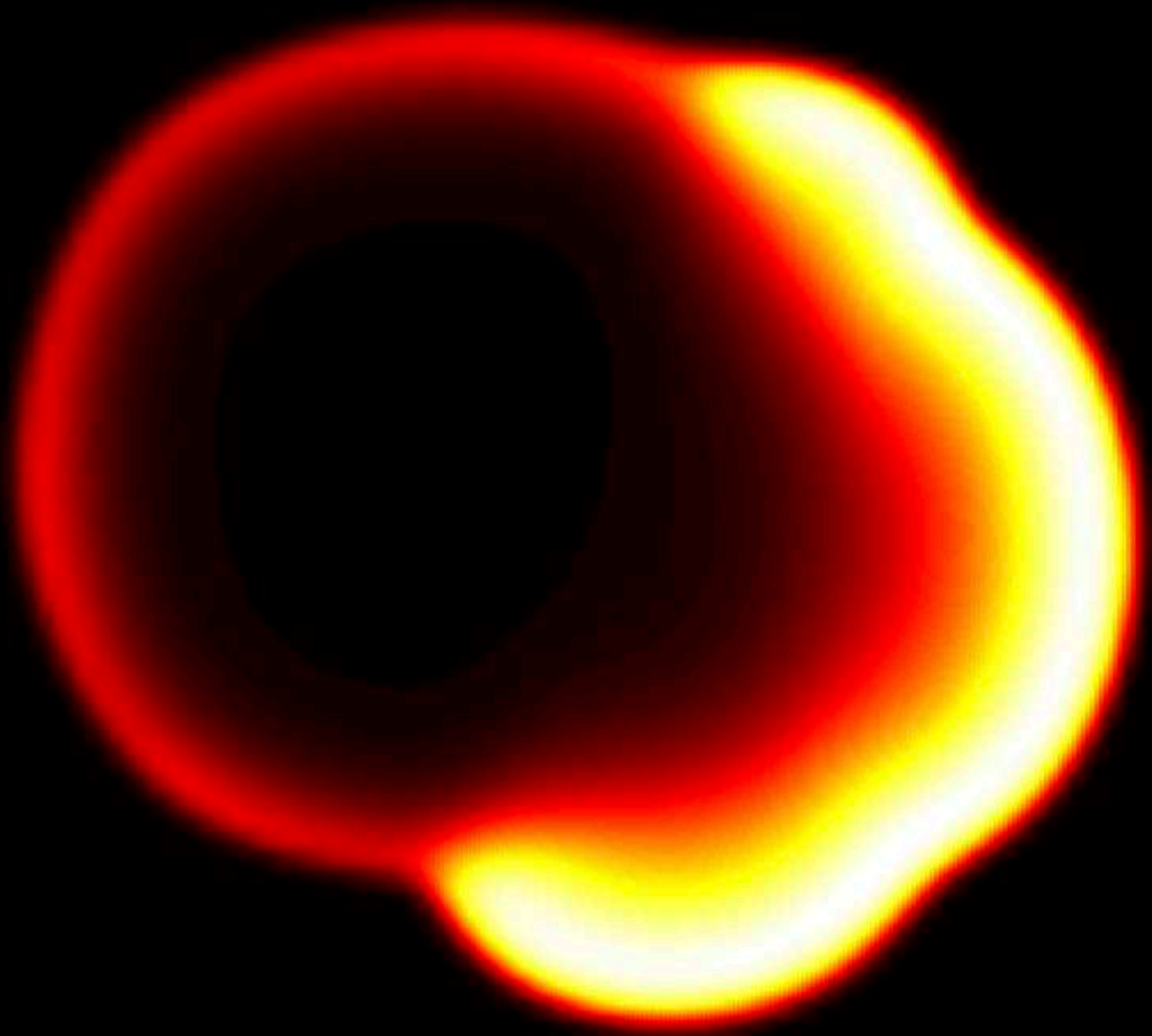
Slow-growing tumors

Standard
Protracted
LDD1
LDD2
Slow-growing tumors
P-val = 8.55e-03
OS gain = 2.4 months
P-val = 7.38e-05
OS gain = 2.7 months
P-val = 5.10e-06
OS gain = 6.7 months
P-val = 6.64e-04
OS gain = 2.4 months


Slow-growing tumors
Standard
Protracted
LDD1
LDD2
P-val = 8.55e-03
OS gain = 2.4 months
P-val = 2.18e-09
OS gain = 7.6 months
P-val = 8.39e-07
OS gain = 7.1 months
1
0.5
0
0
10
20
30



Longer spacings increase survival



Longer spacings increase survival

In Virtual Clinical Trial

Neuro-Oncology Advances

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On optimal temozolomide scheduling for slowly growing glioblastomas

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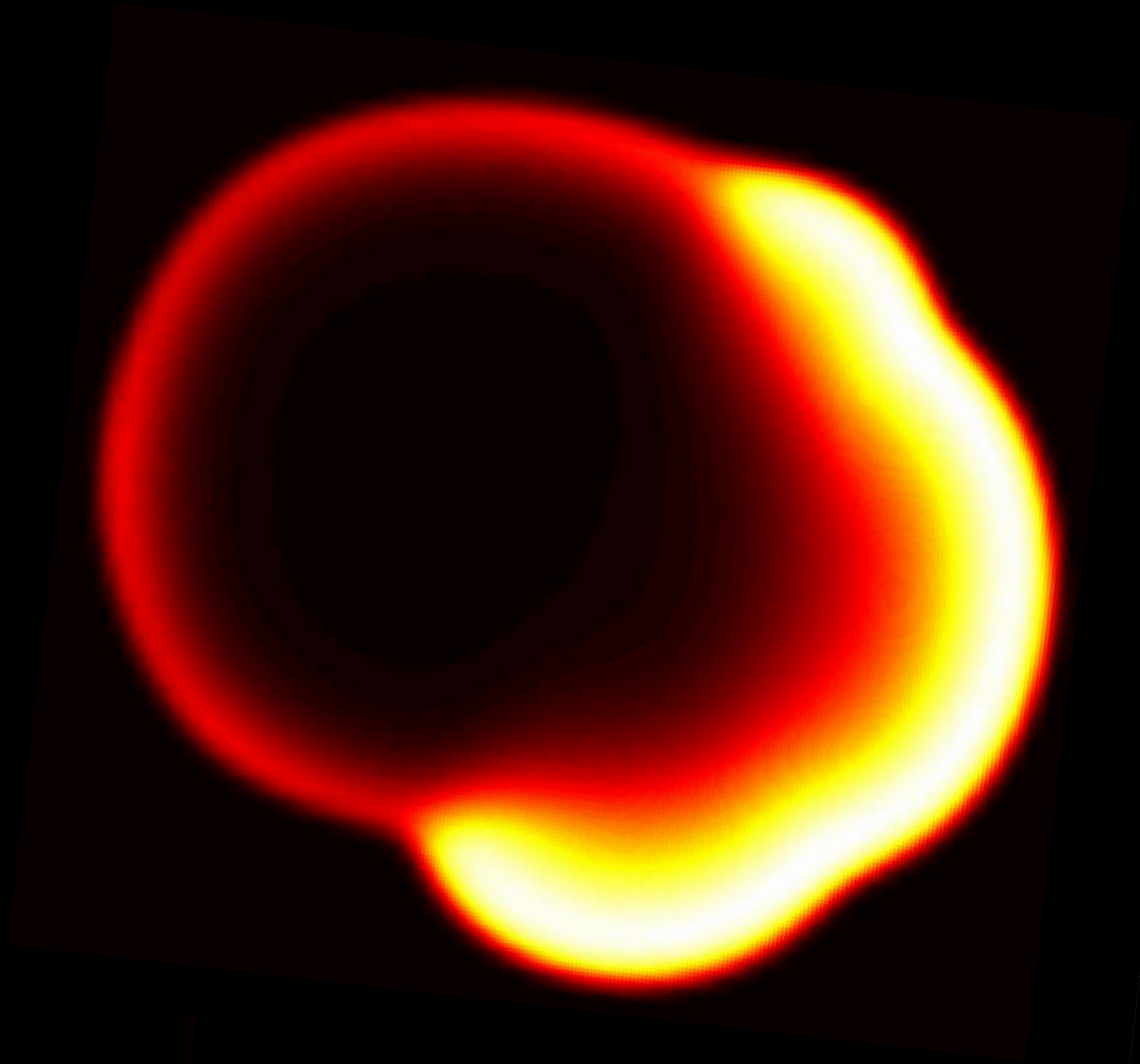
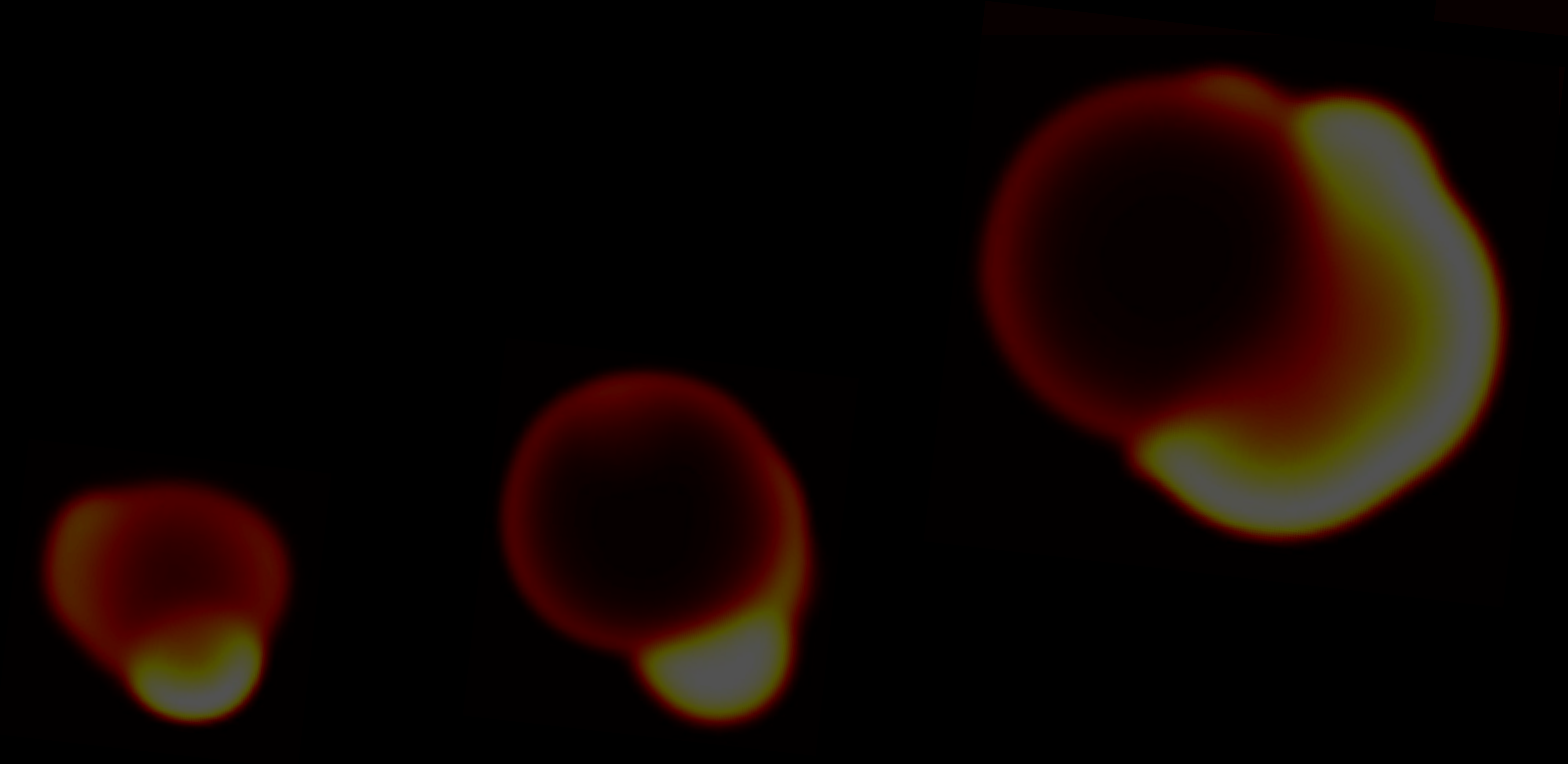
Acknowledgments





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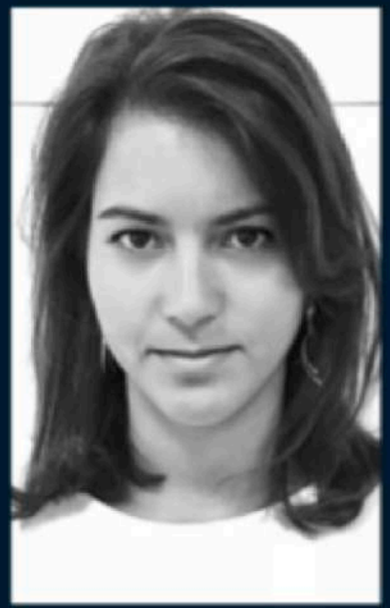
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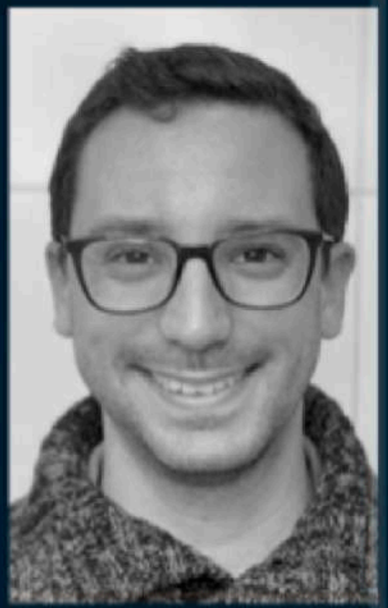
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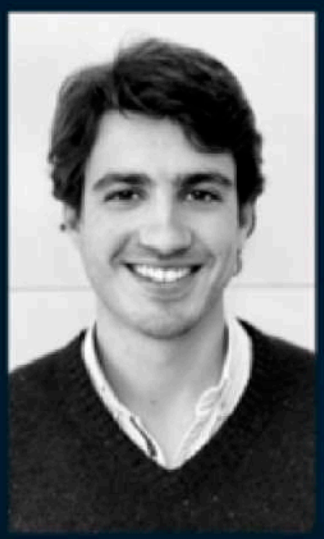
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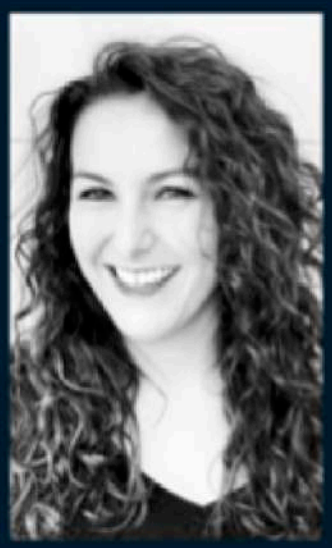
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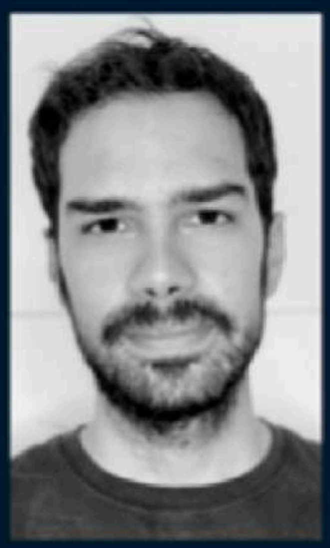
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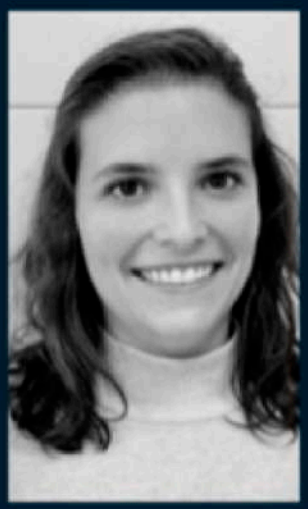
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