

June 24th Meeting

Different Models

The Main Model V1

Loop until $T(t) < K$

For a given clone compute:

$$[X_{Dy_i}, X_{NB_i}, X_{NT_i}] \sim Multinom(CS_i, [p_{DR_i}, p_{NB_i}, 1 - (p_{DR_i} + p_{NB_i})])$$
$$X_{NB_i} \sim Binom(CS_i, PR_i - \lambda)$$

$$\lambda = (PR_0 - DR_0) \frac{T(t)}{K}$$

If $X_{ND_i} > 0$,

$$PR_j \sim Normal(Parent_{PR_i}, 0.001)$$
$$MR_j \sim Normal(Parent_{MR_i}, MR_0)$$

Bozic

Init. cond.

Then update the clone as,

$$CS_i = (CS_i + X_{NB_i}) - (X_{Dy_i} + X_{ND_i})$$

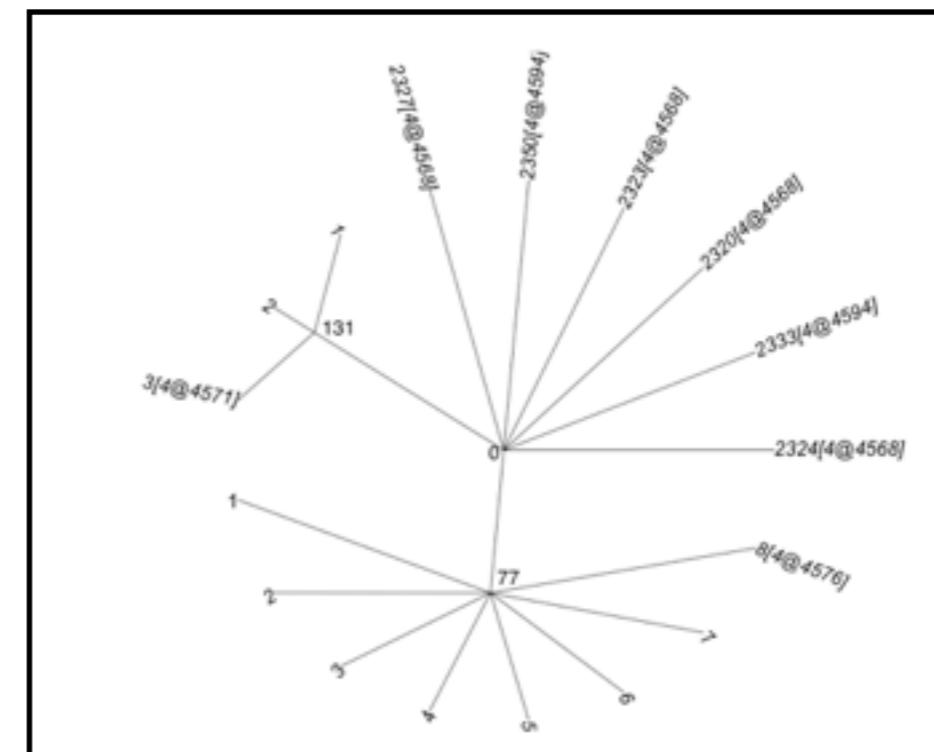
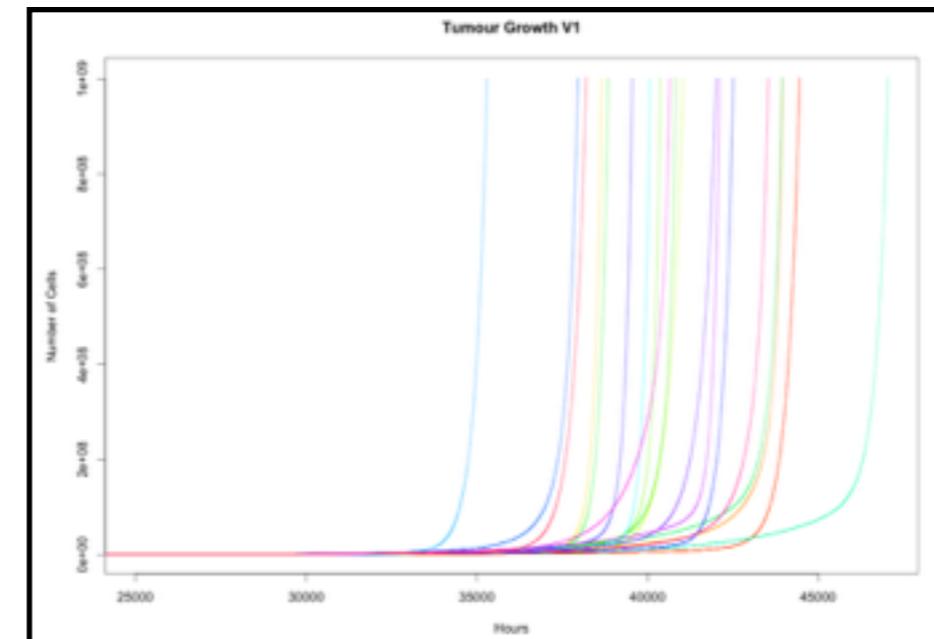
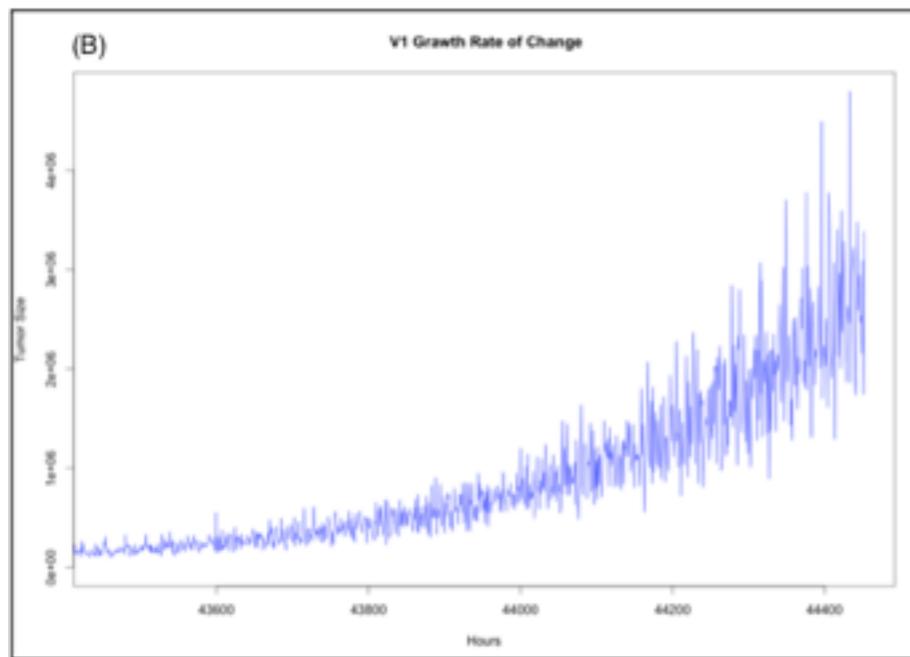
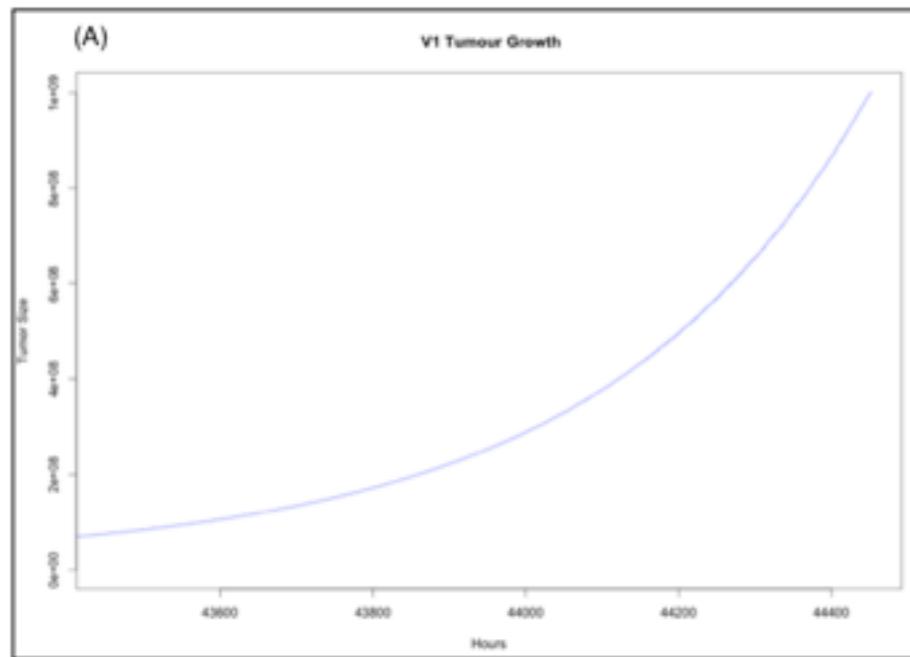
Therefore, the active tumour burden is,

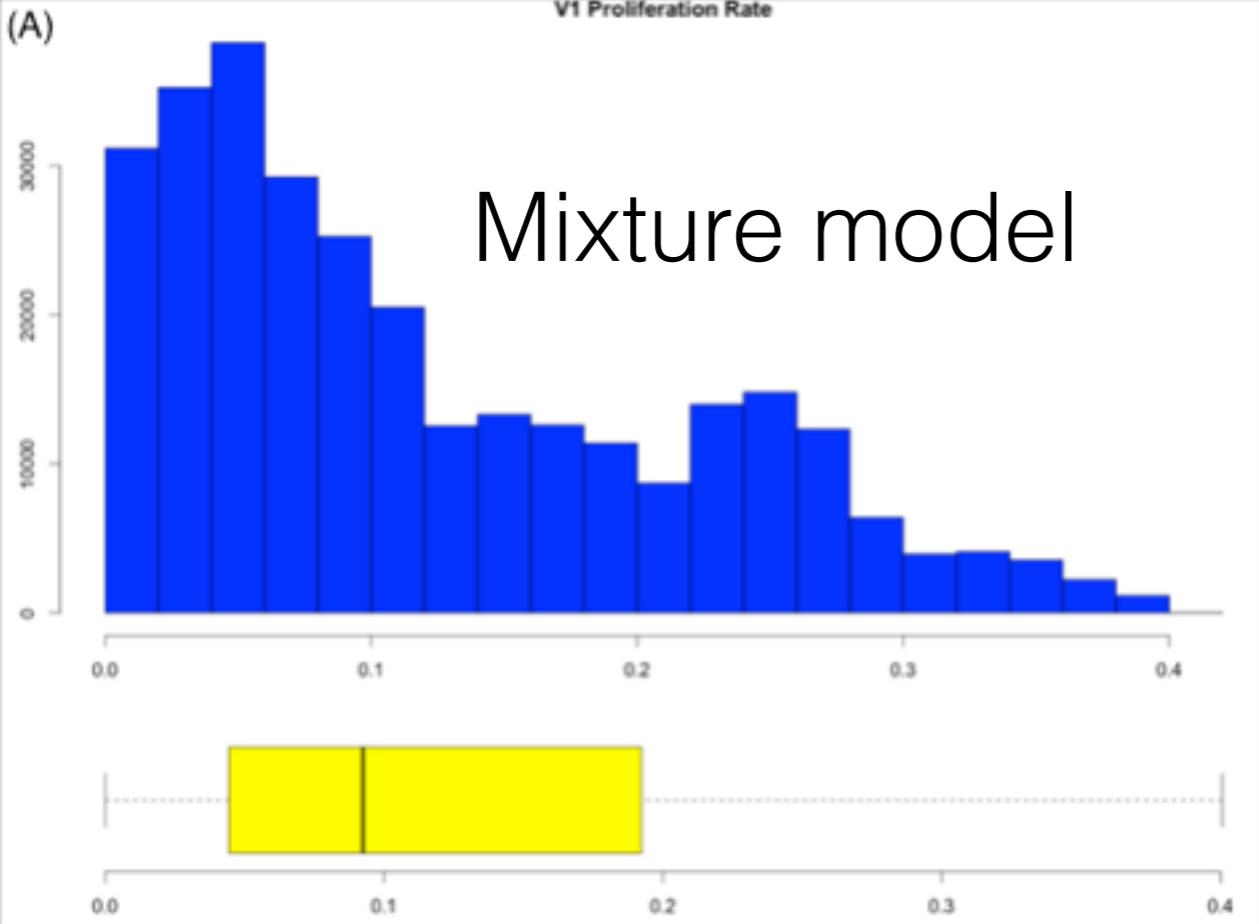
$$T(t) = \sum_{i=1}^N CS_i$$

Output V1

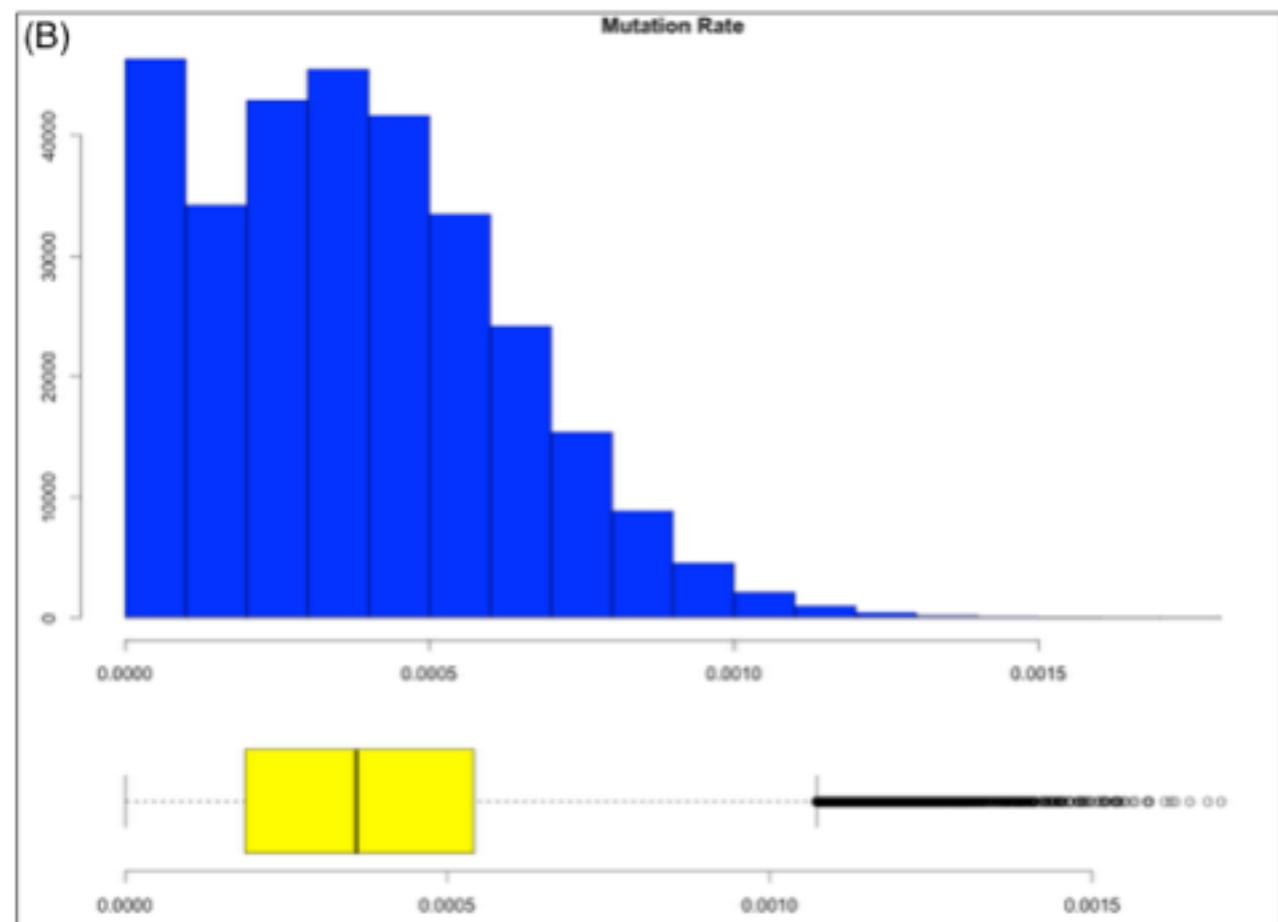
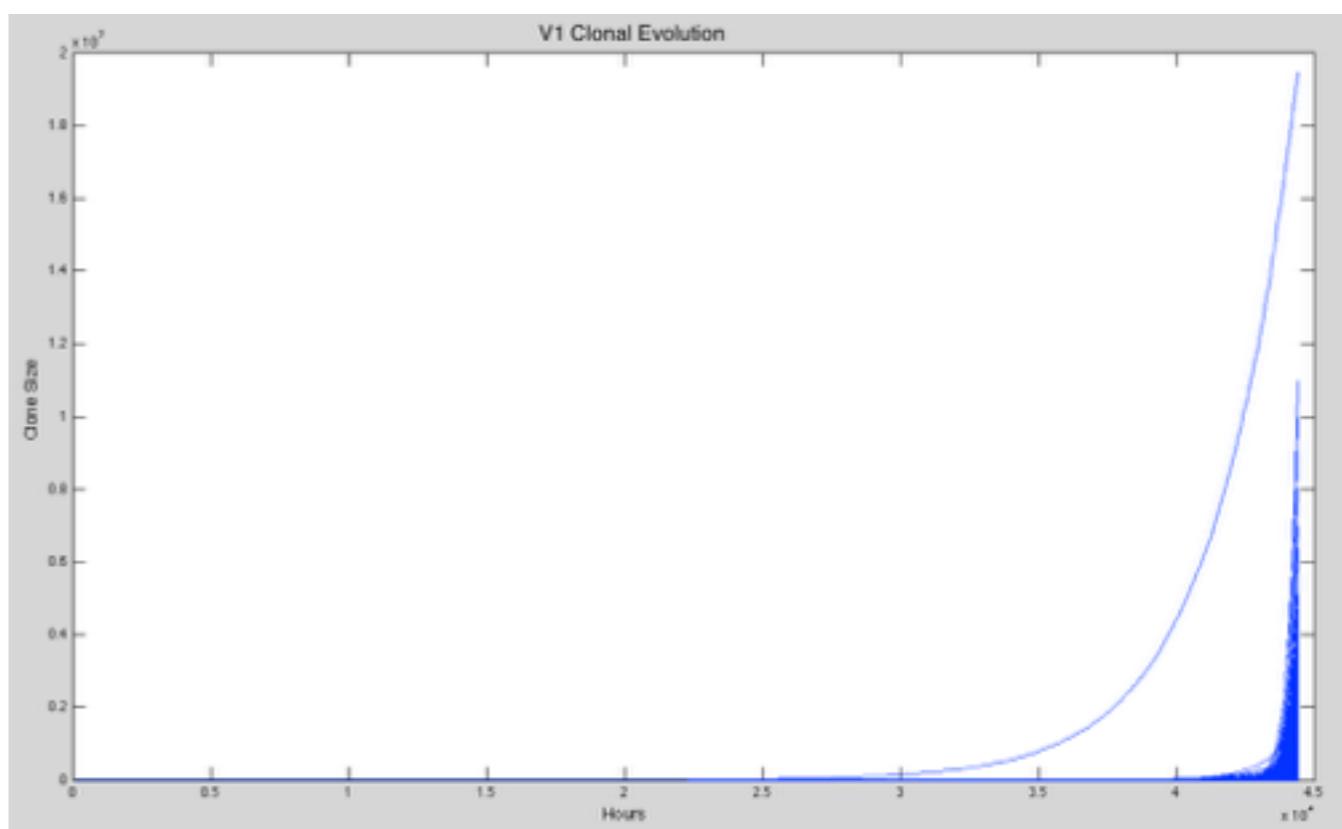
Increasing Stochastic

More variance
than previous models

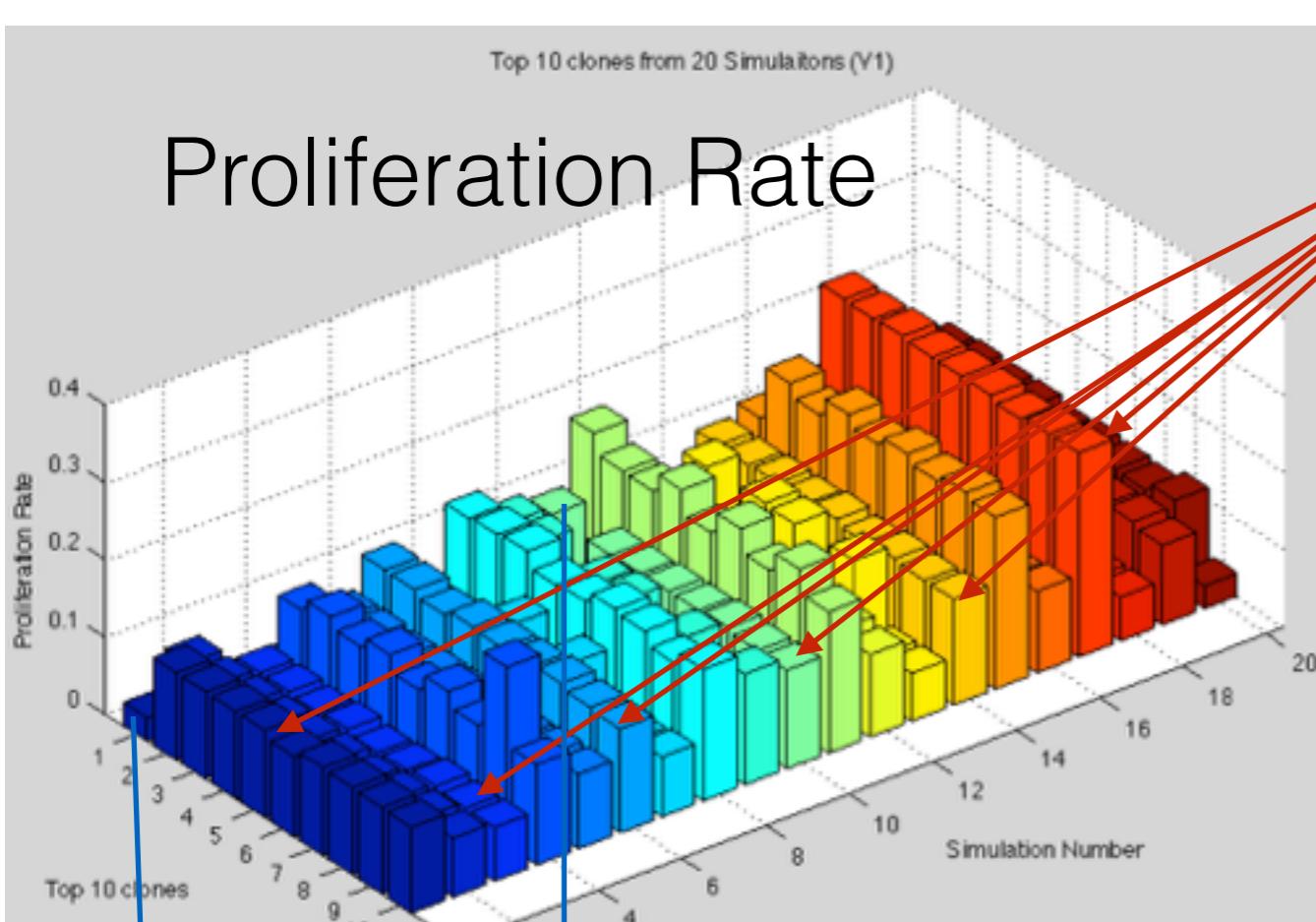




Clonal Evolution:
Always progenitor dominates

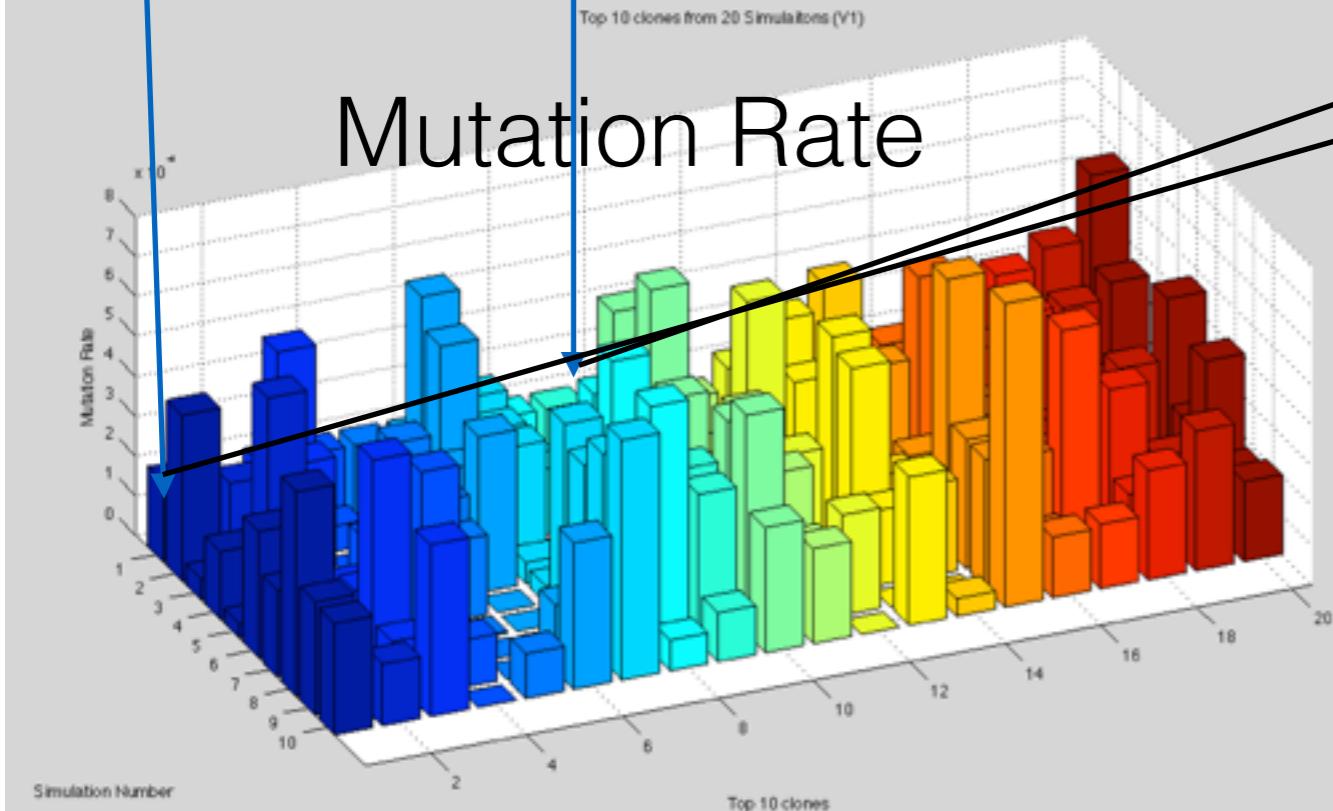


Proliferation Rate



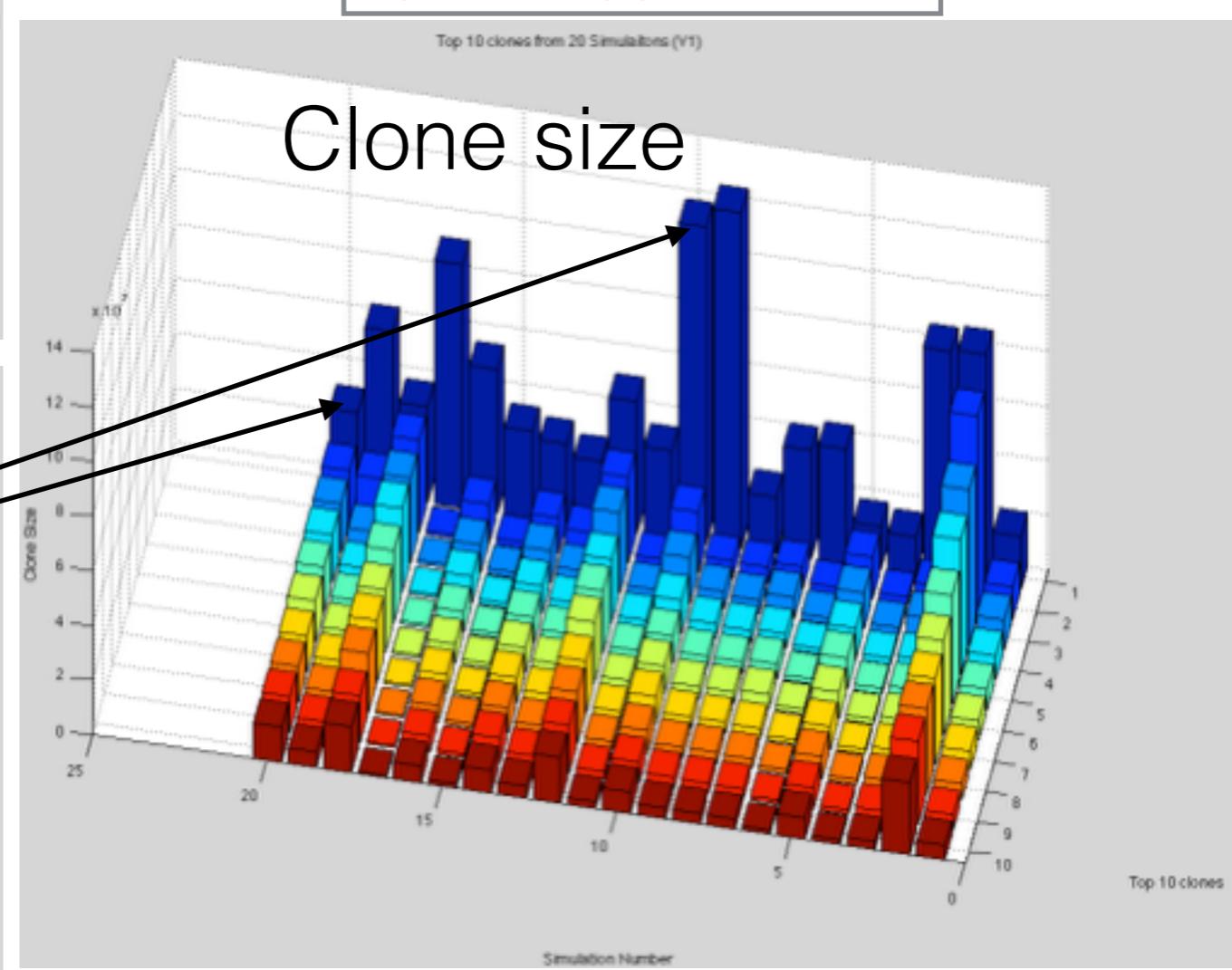
Sweet spot
Proliferation rate

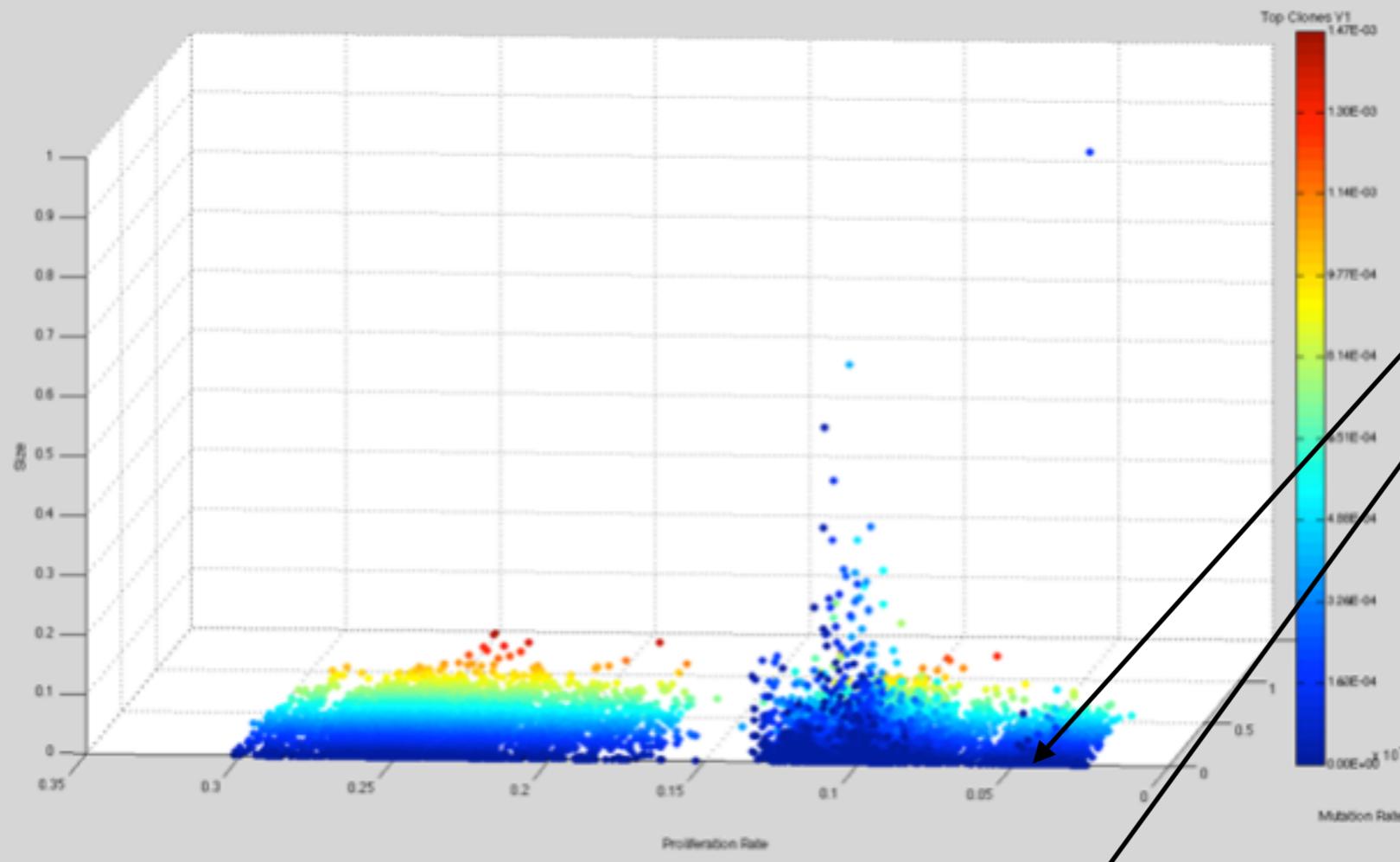
Mutation Rate



Low MR and High PR
gives bigger clones

Clone size





Low MR and High PR gives bigger clones

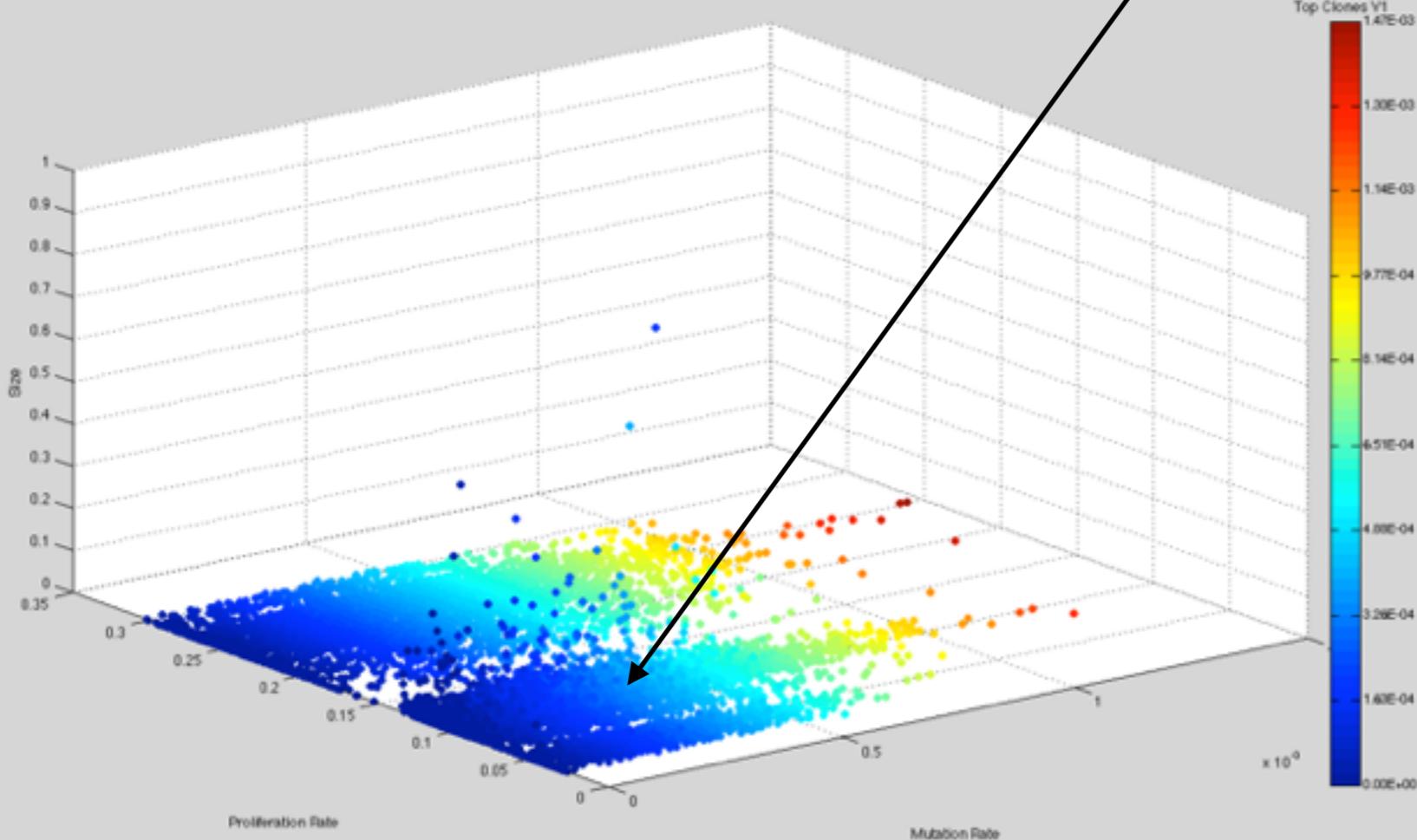
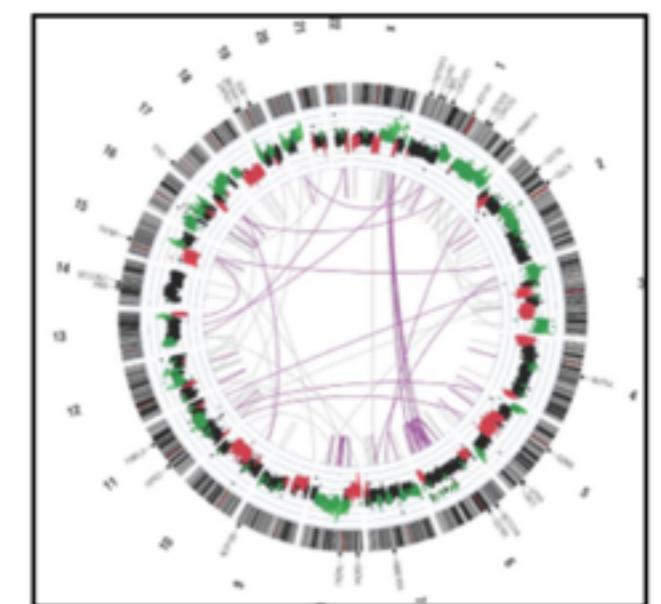
The reason,

$$\textcolor{green}{\uparrow} CS_i = (\textcolor{green}{\uparrow} CS_i + X_{NB_i}) - (X_{Dy_i} + \textcolor{red}{X_{ND_i}})$$

This clone does NOT induce diversity, just expands

Good Driver and/or oncogen addiction

Hypothesis:



But, too much heterogeneity?

- (1) Huge files.
- (2) Difficult to open in R/Matlab.

Motivation for Version 2.

Generate a mutational driver quantile.

Version 2

Loop until $T(t) < K$

For a given clone compute:

$$[X_{Dy_i}, X_{NB_i}, X_{NT_i}] \sim Multinom(CS_i, [p_{DR_i}, p_{NB_i}, 1 - (p_{DR_i} + p_{NB_i})])$$

$$X_{NB_i} \sim Binom(CS_i, PR_i - \lambda)$$



If $X_{ND_i} > 0$,

$$x \forall X_{ND_i} : K(x) \quad (16)$$

Where $K(x)$ is,

$$K(x) = \begin{cases} PR_j \sim Normal(Parent_{PR_i}, 0.001); MR_j \sim Normal(Parent_{MR_i}, MR_0) & \text{if } Z \geq X_{Dr} \\ CS_i = CS_i - 1 & \text{if } Z \leq X_{Ki} \\ PR_i = PR_i + CS_i^{-1} & \text{if } X_{Ben} \geq Z \leq X_{Dr} \\ PR_i = PR_i - CS_i^{-1} & \text{if } X_{Ki} \geq Z \leq X_{Del} \\ PR_i = PR_i - I_{\{NP_i=c\}}\beta & \text{Otherwise} \end{cases}$$

$$\lambda = (PR_0 - DR_0) \frac{T(t)}{K}$$

Mutational effect
sampled from
Normal distribution



Then update the clone as,

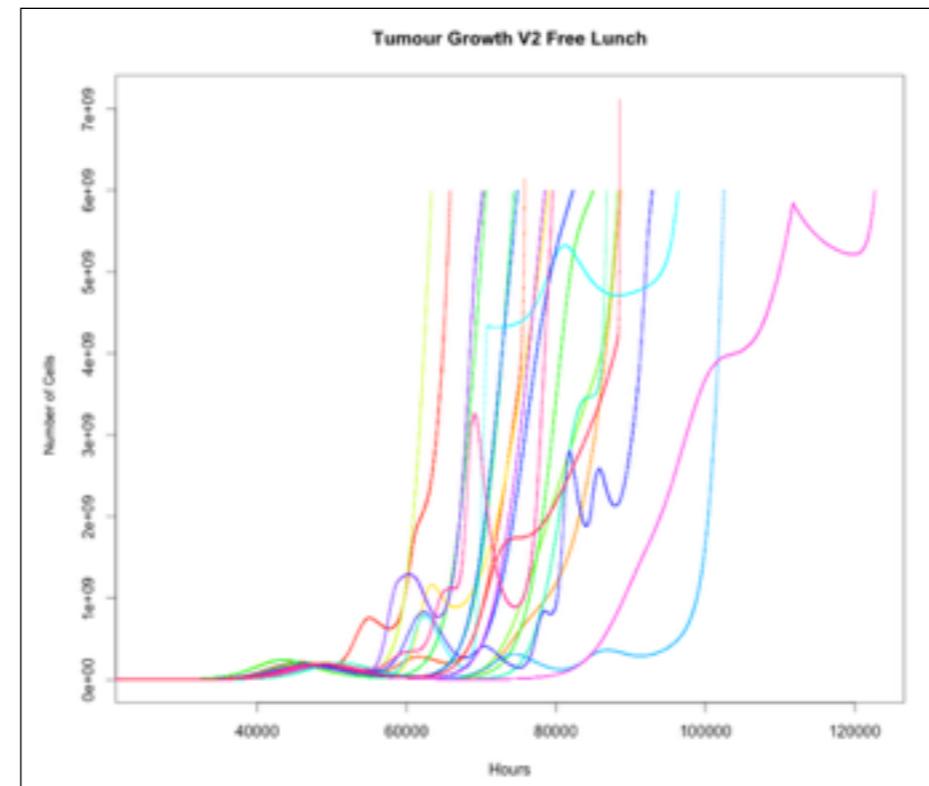
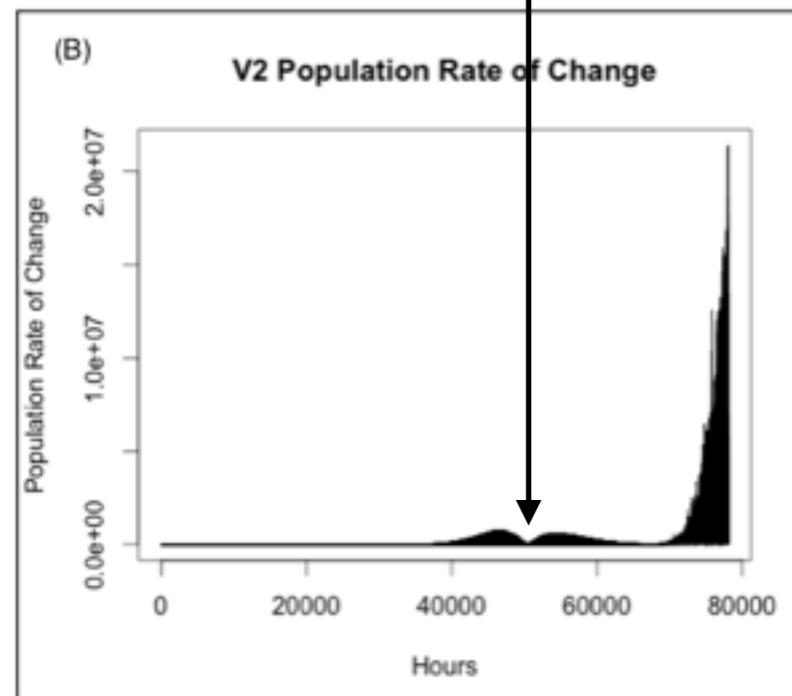
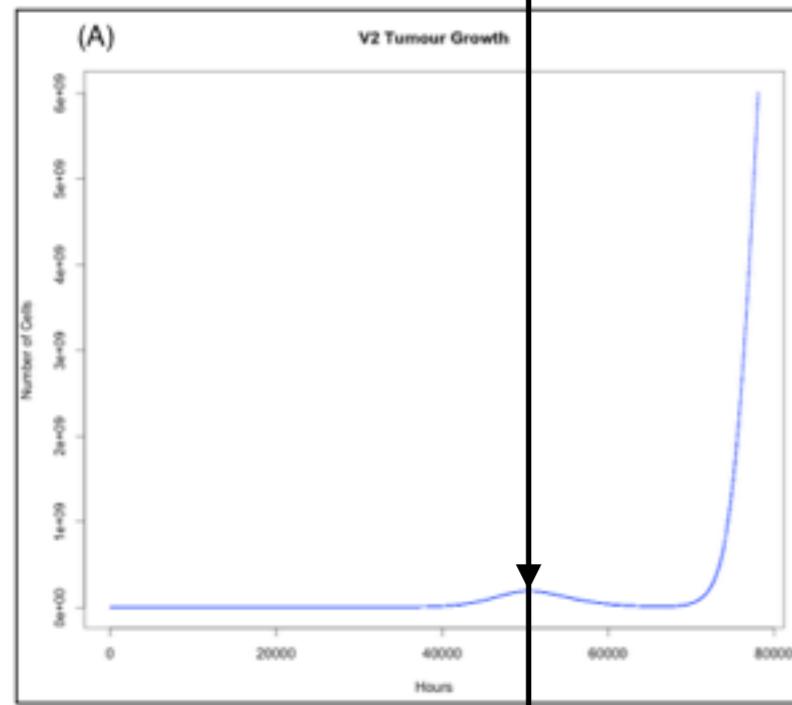
$$CS_i = (CS_i + X_{NB_i}) - (X_{Dy_i} + X_{ND_i})$$

Therefore, the active tumour burden is,

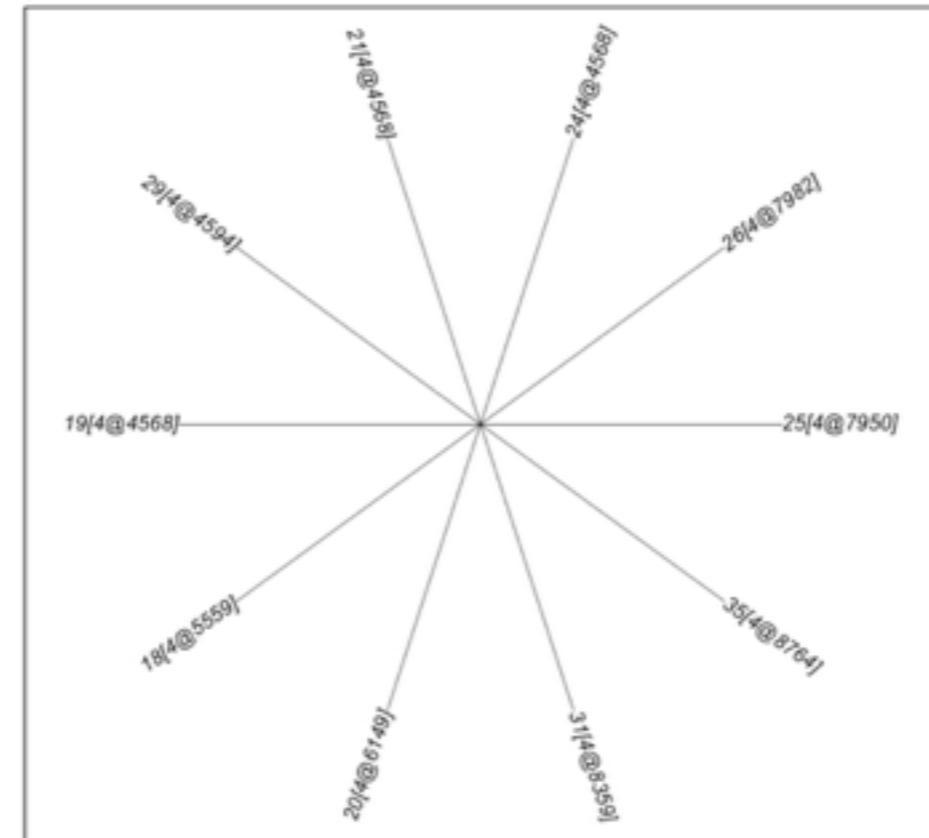
$$T(t) = \sum_{i=1}^N CS_i$$

Output

Initial Extinction



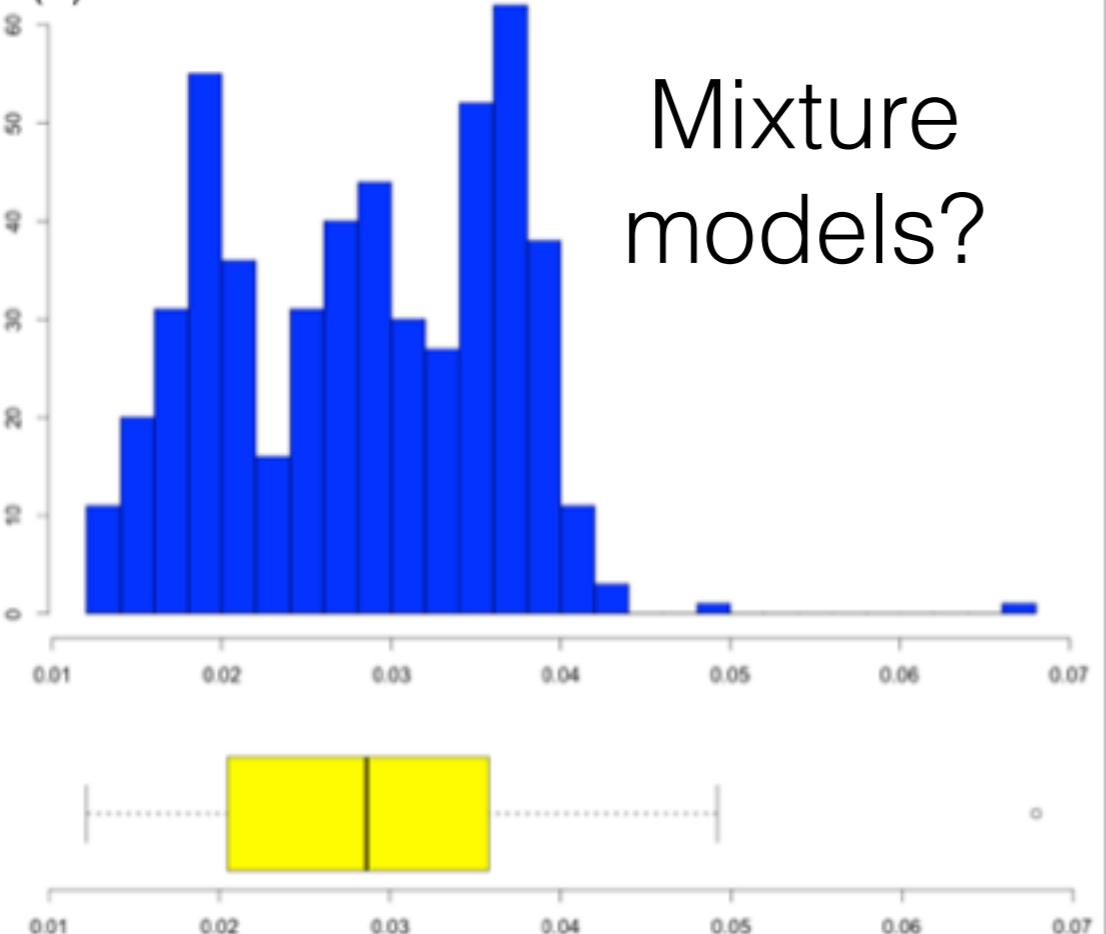
Wavy evolutionary dynamics.
How to select the best growth function?



(A)

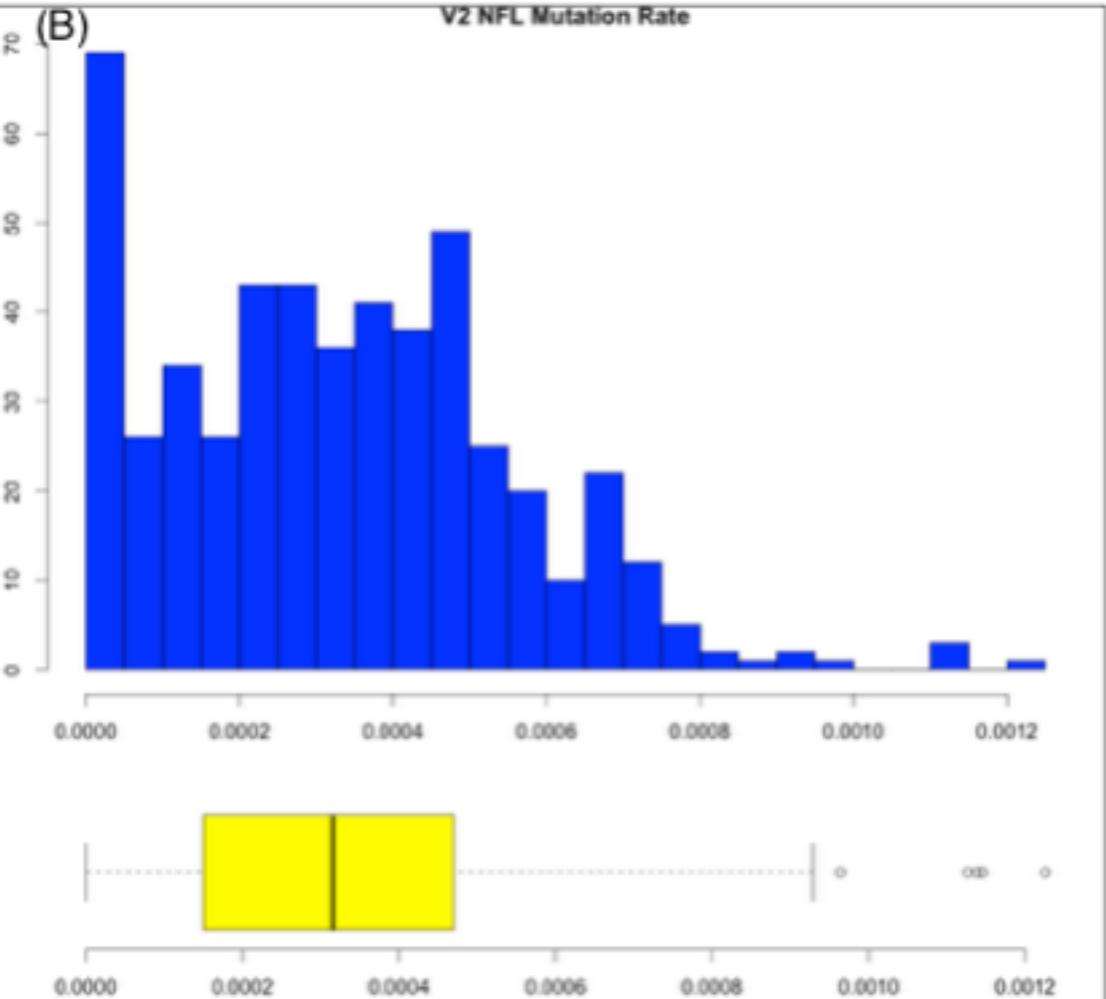
V2 NFL Proliferation Rate

Mixture
models?

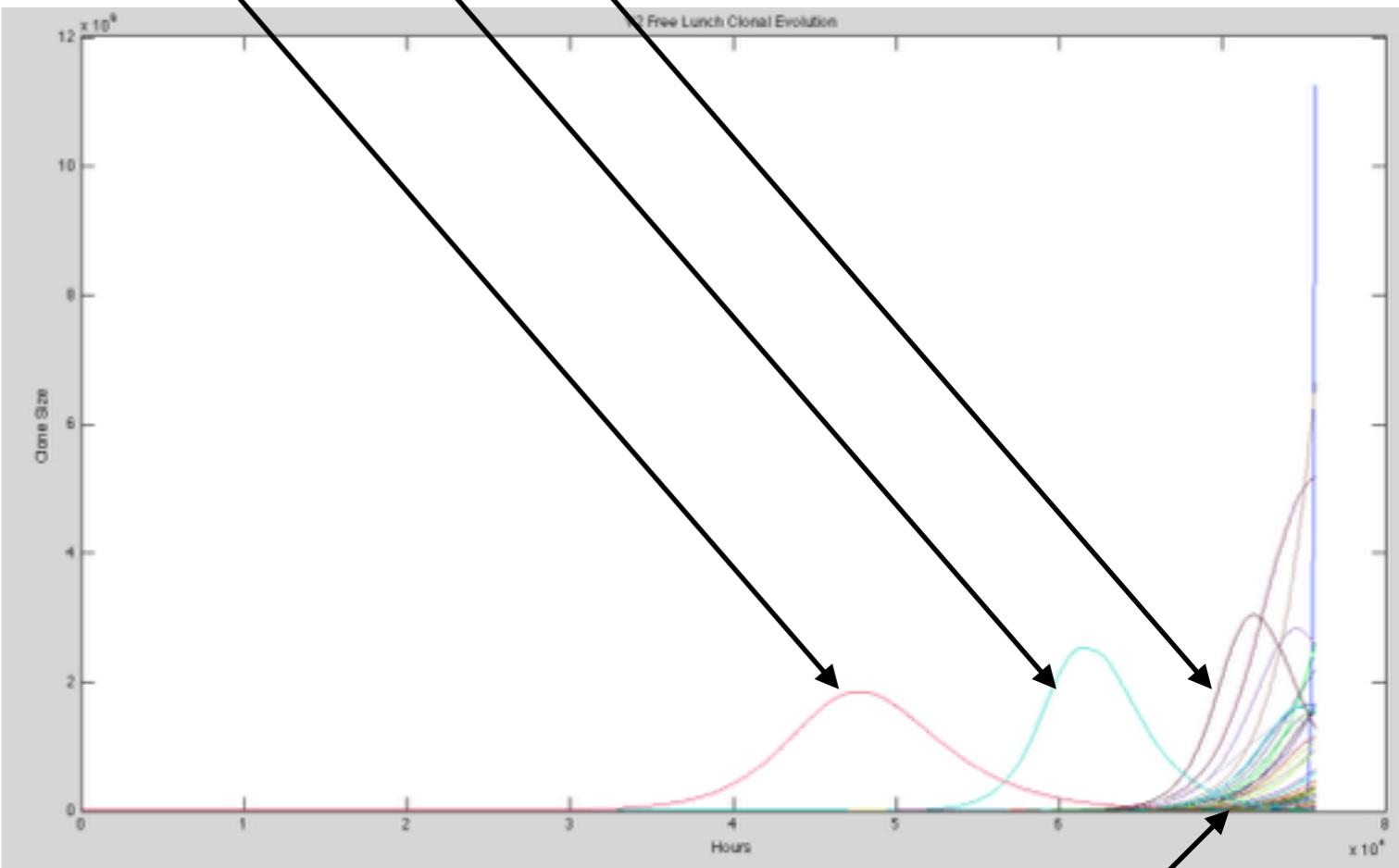


(B)

V2 NFL Mutation Rate

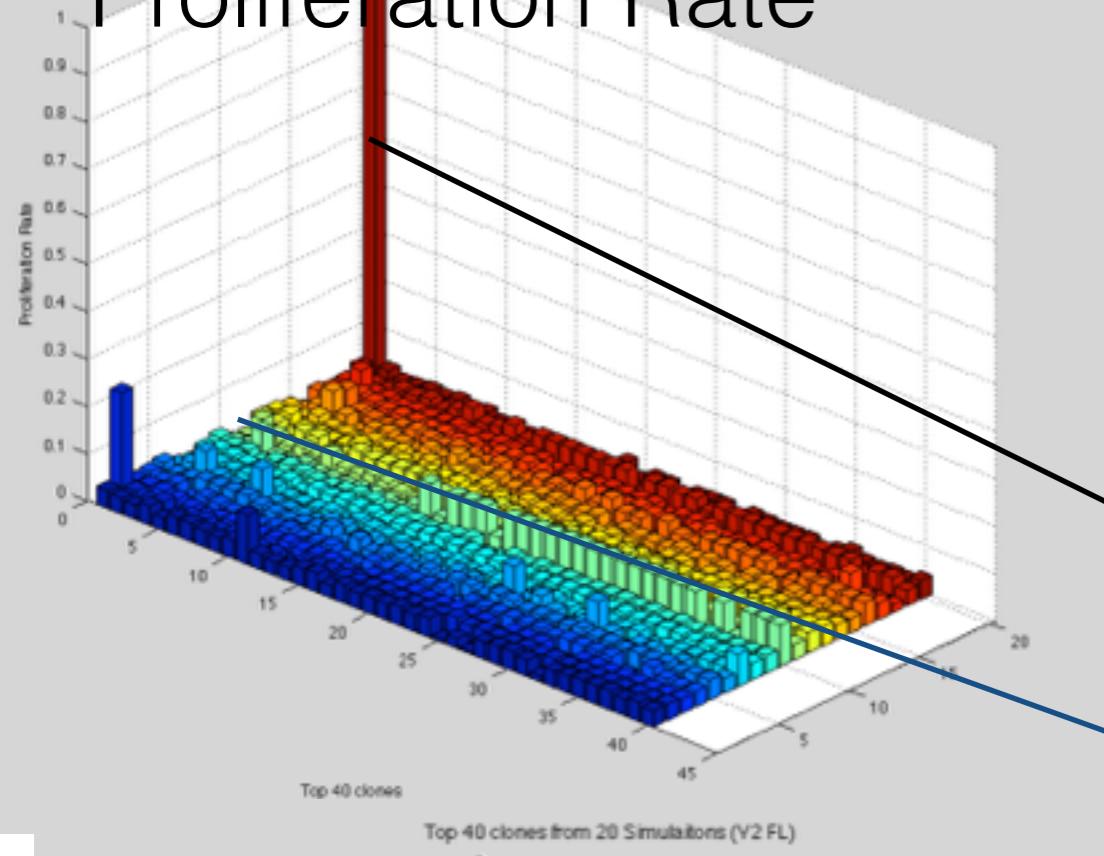


Clonal extinction rounds

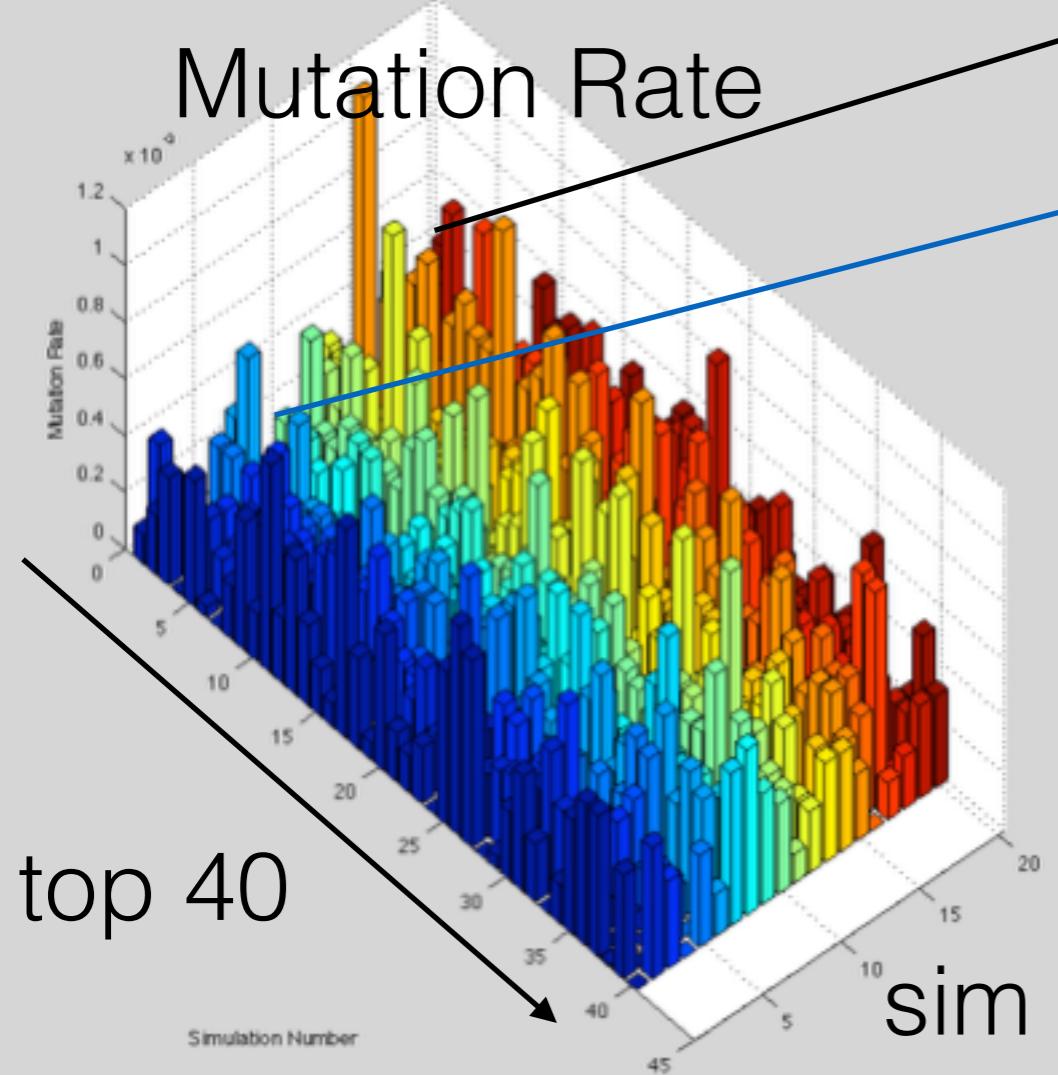


However, dominant
clones arose here

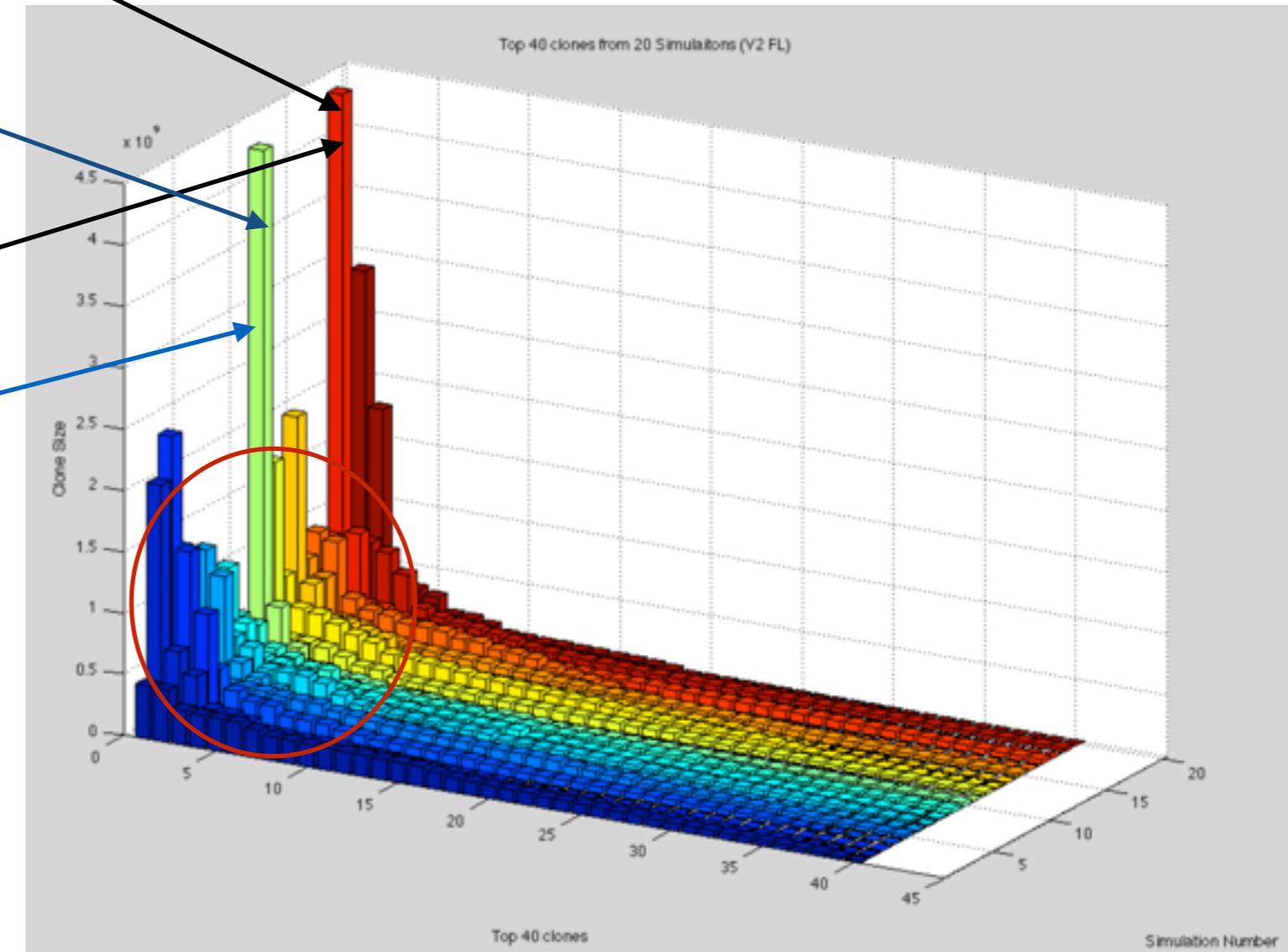
Proliferation Rate

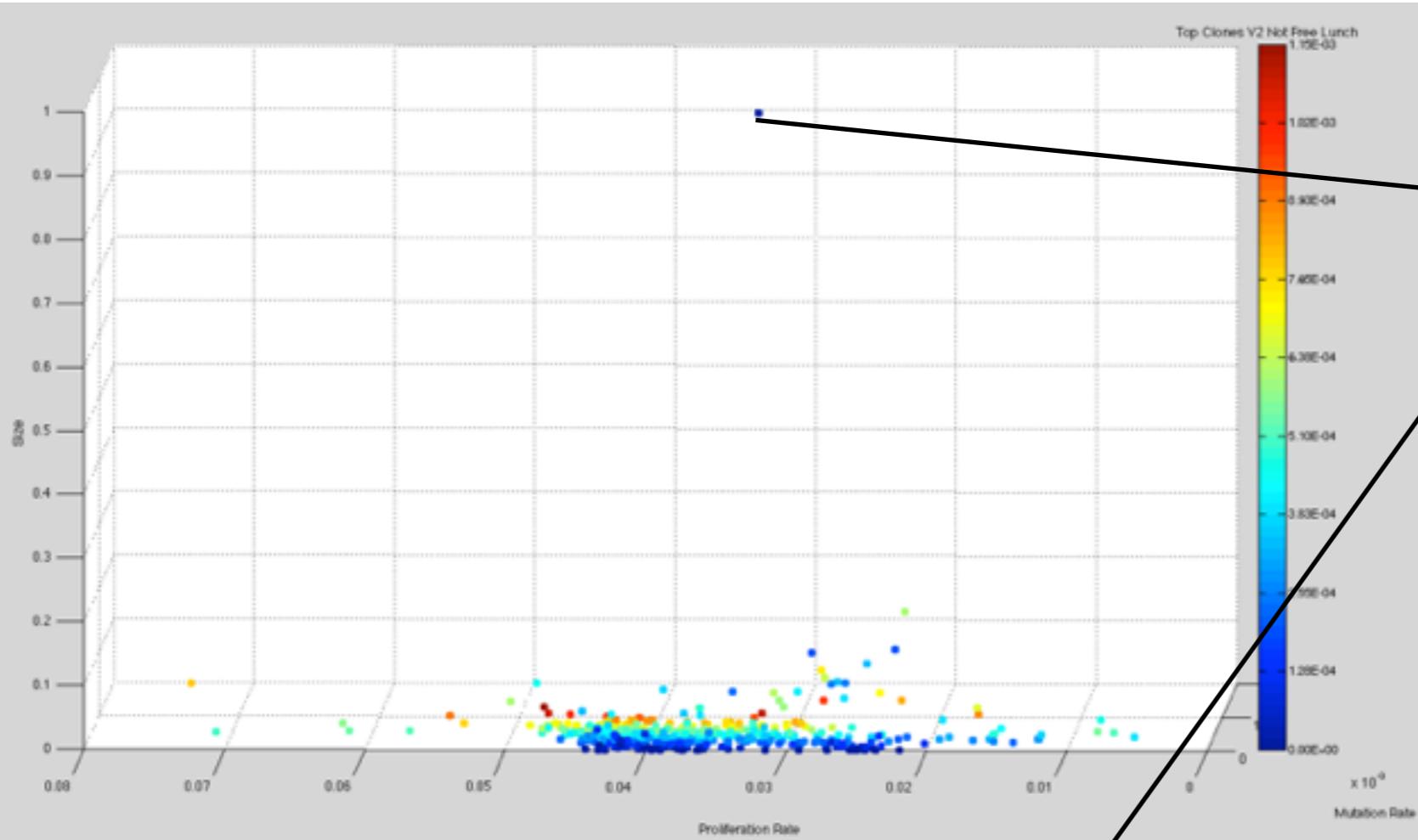


Mutation Rate



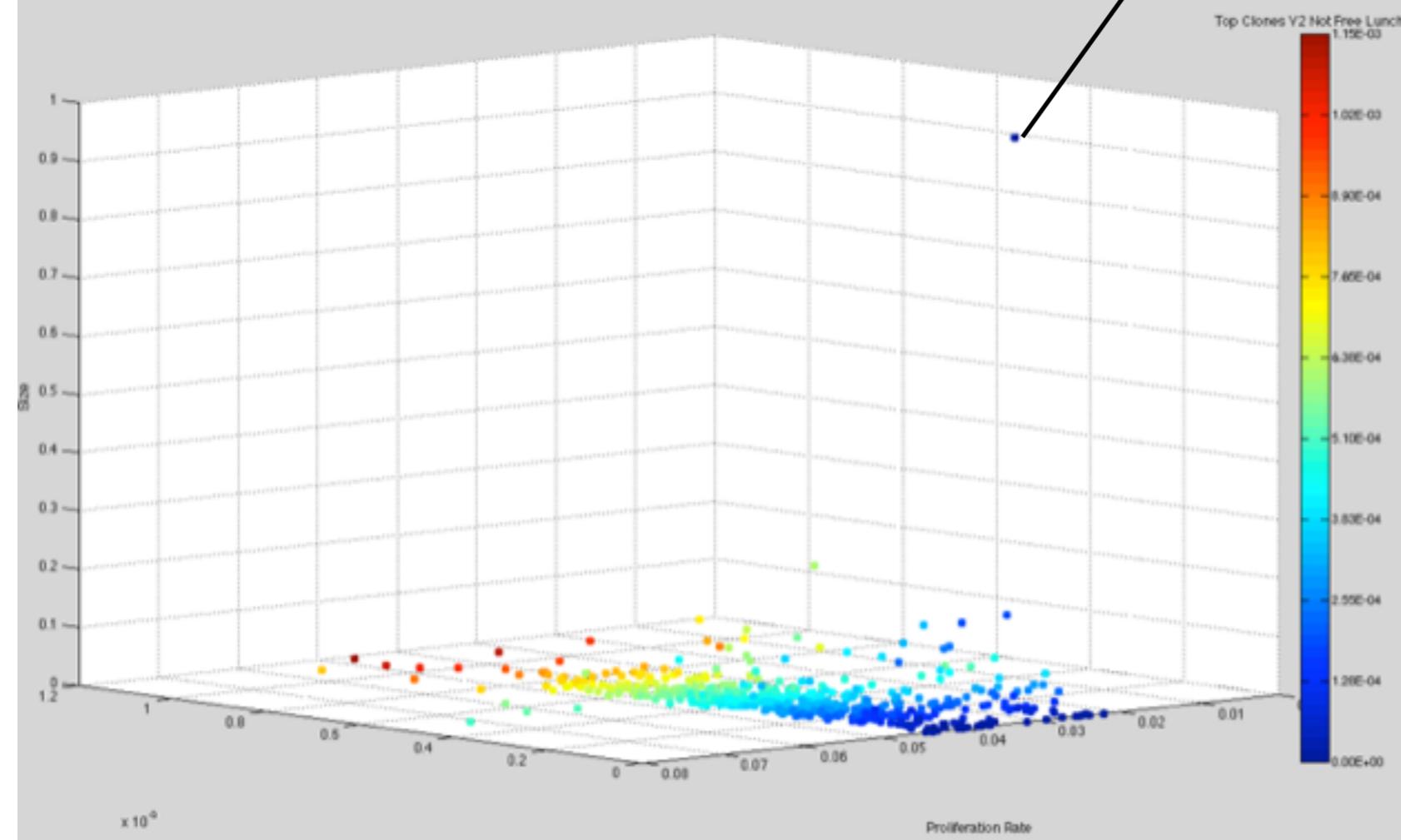
Same effect here,
but it requires different
times to attain the size





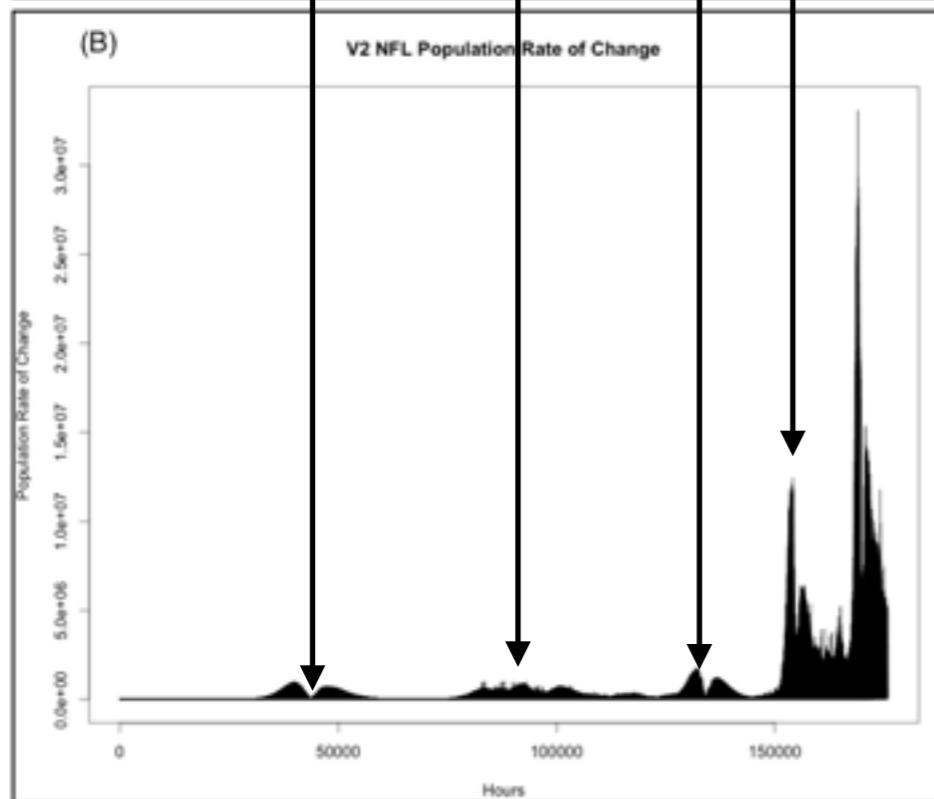
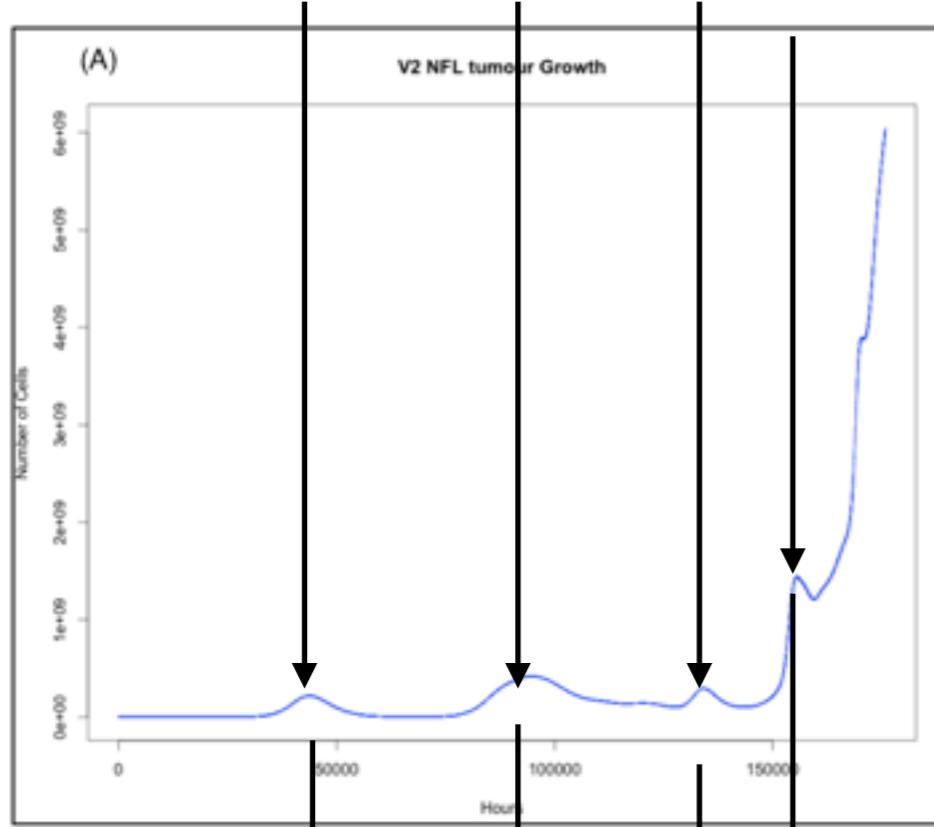
One dominant clone

But can vary
depending on
the simulation

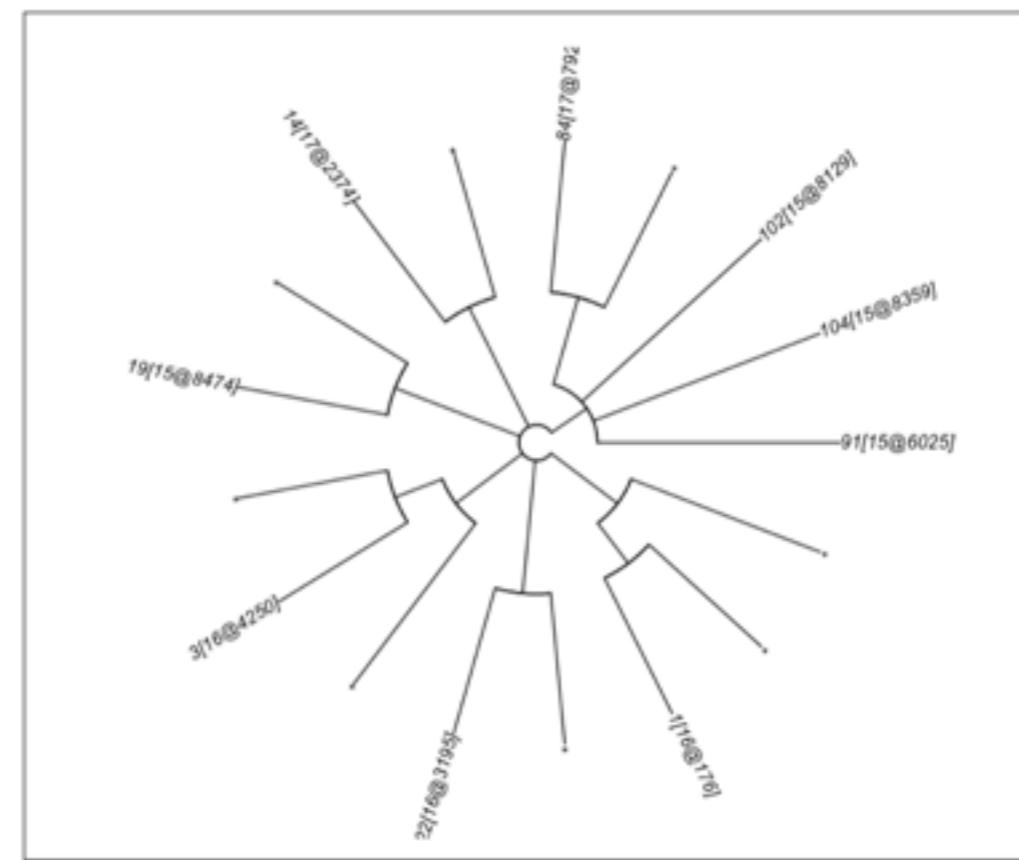
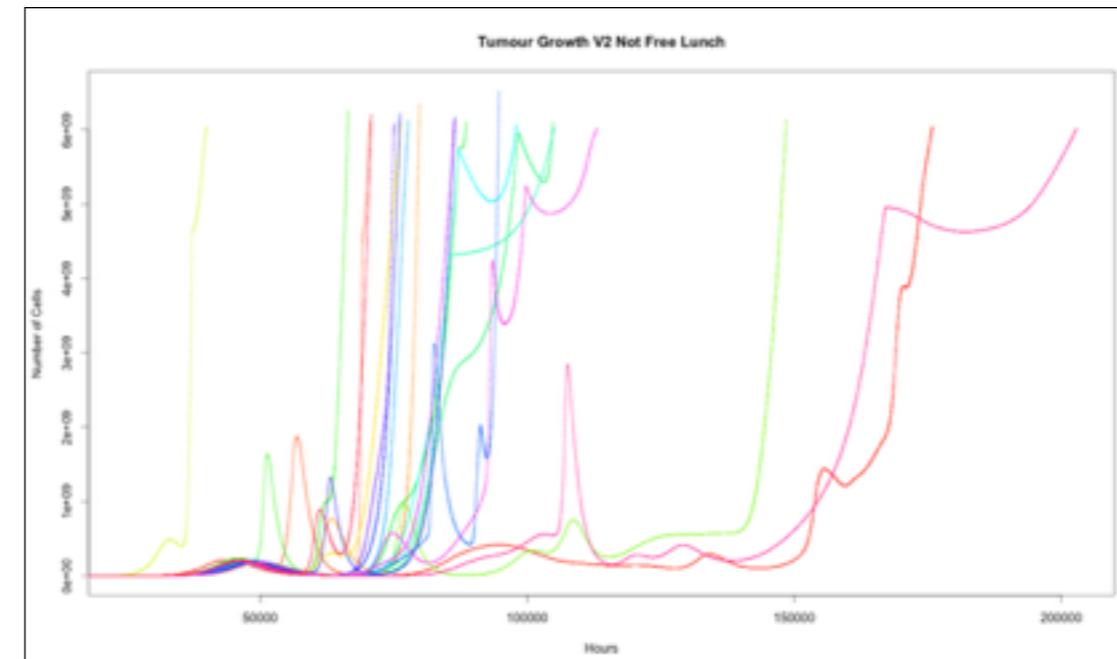


Output V2 NFL

Constant extinction

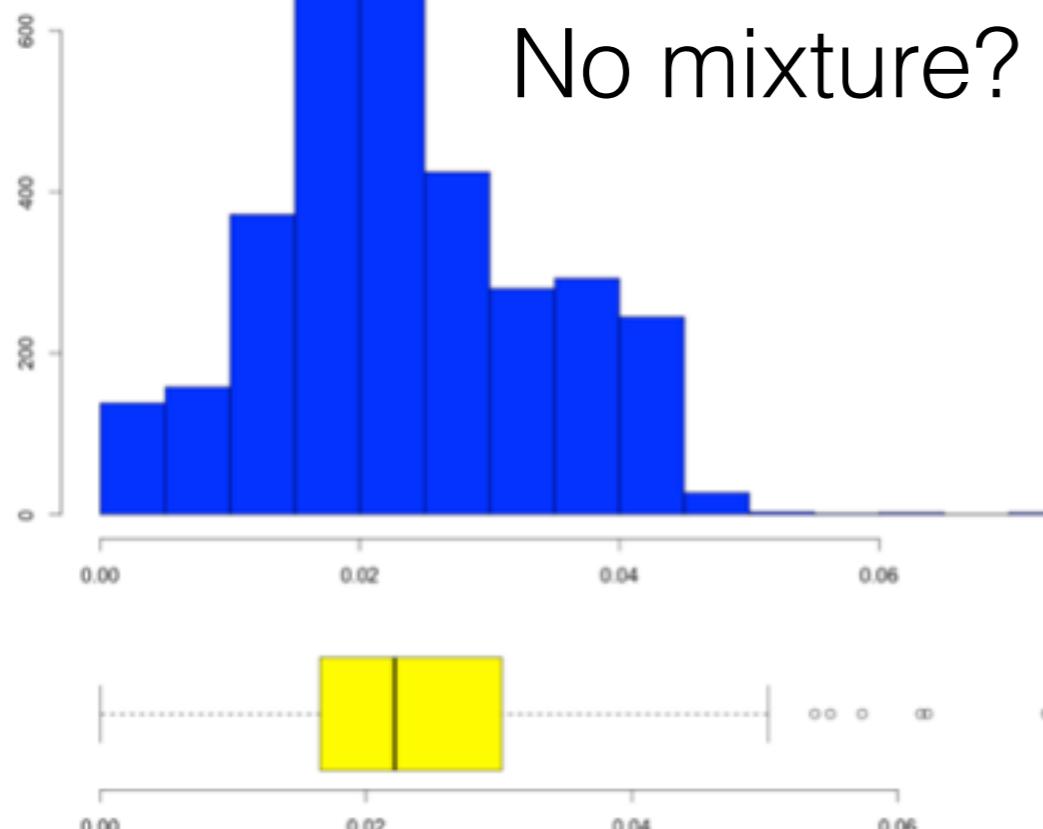


NFL may take more clonal rounds to attain K

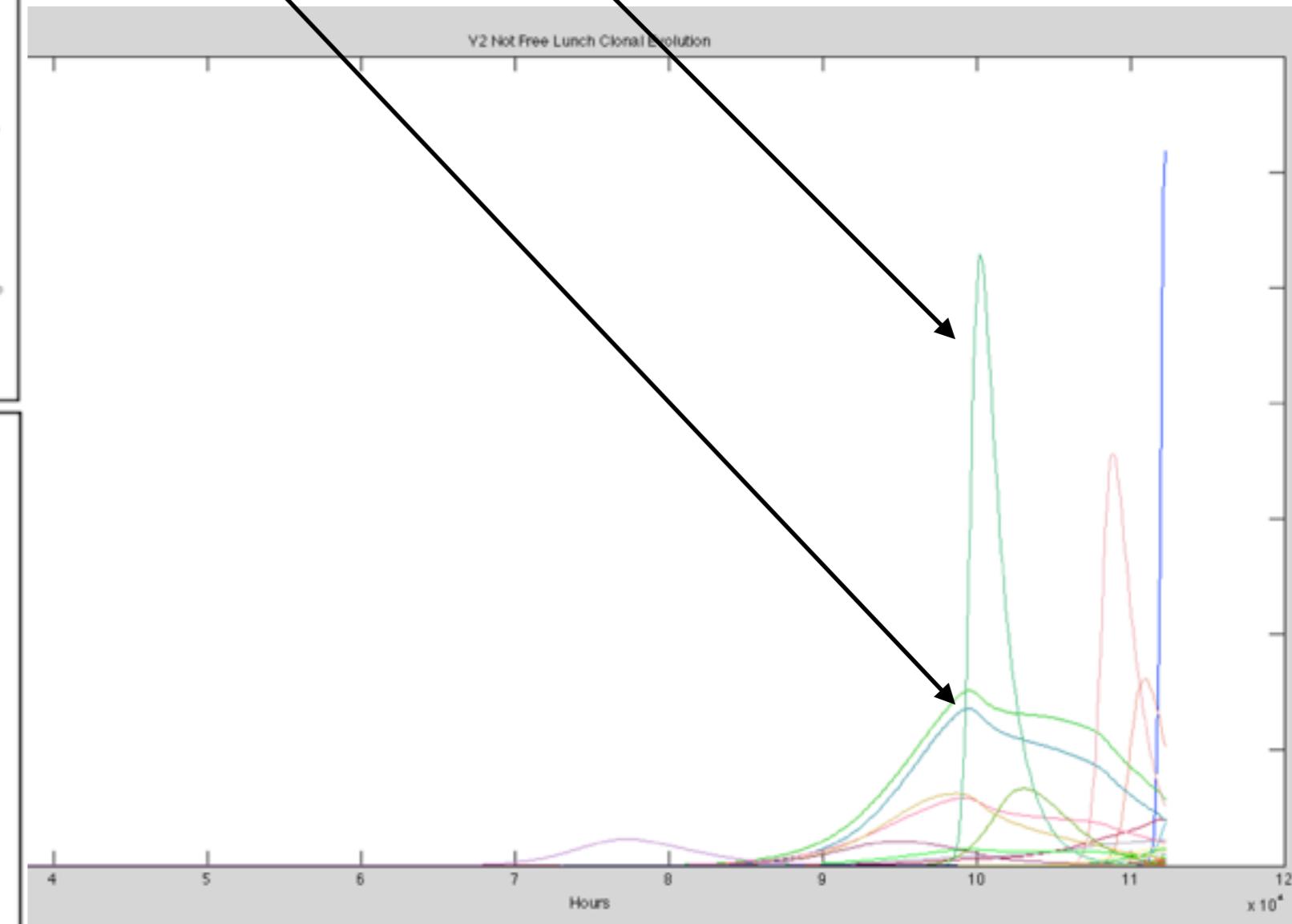


(A)

No mixture?

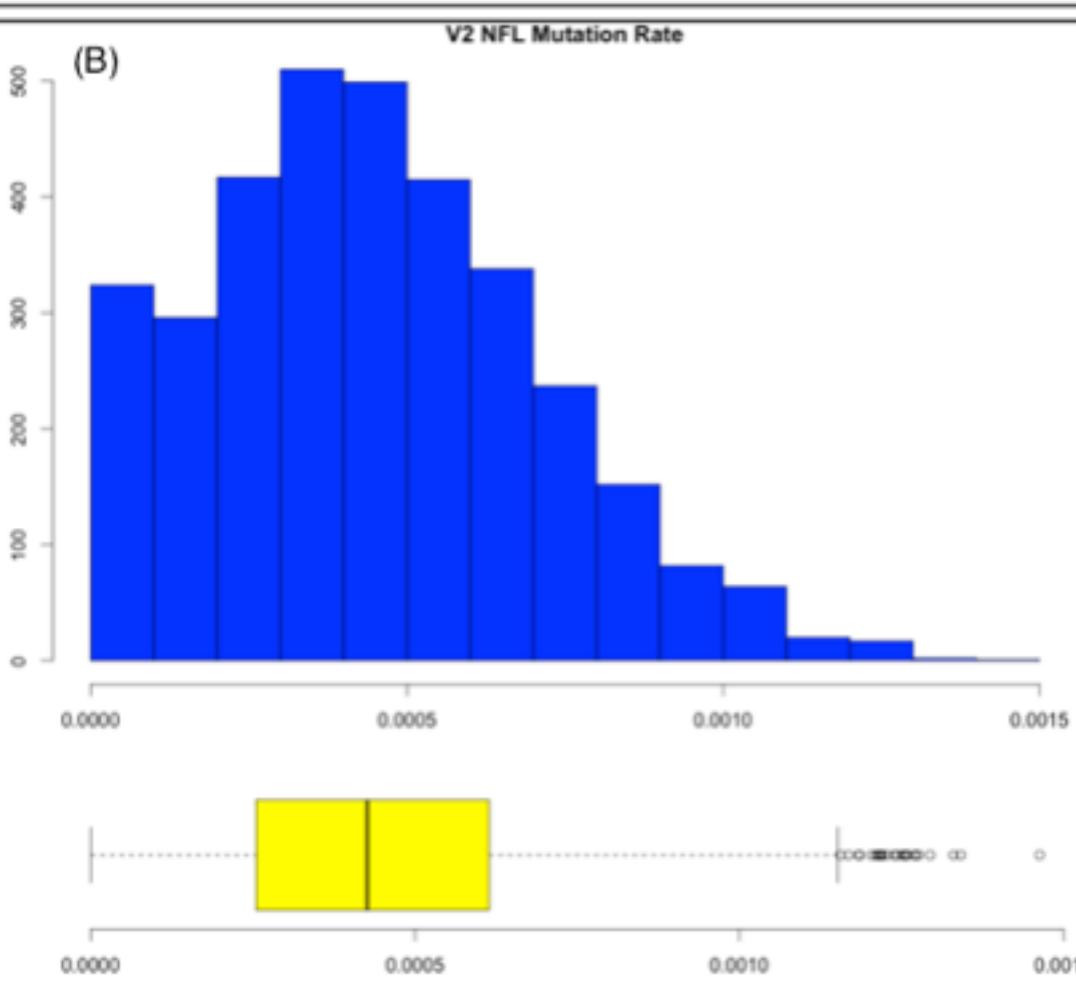


Some clonal expansions lead
to eventual dead ends



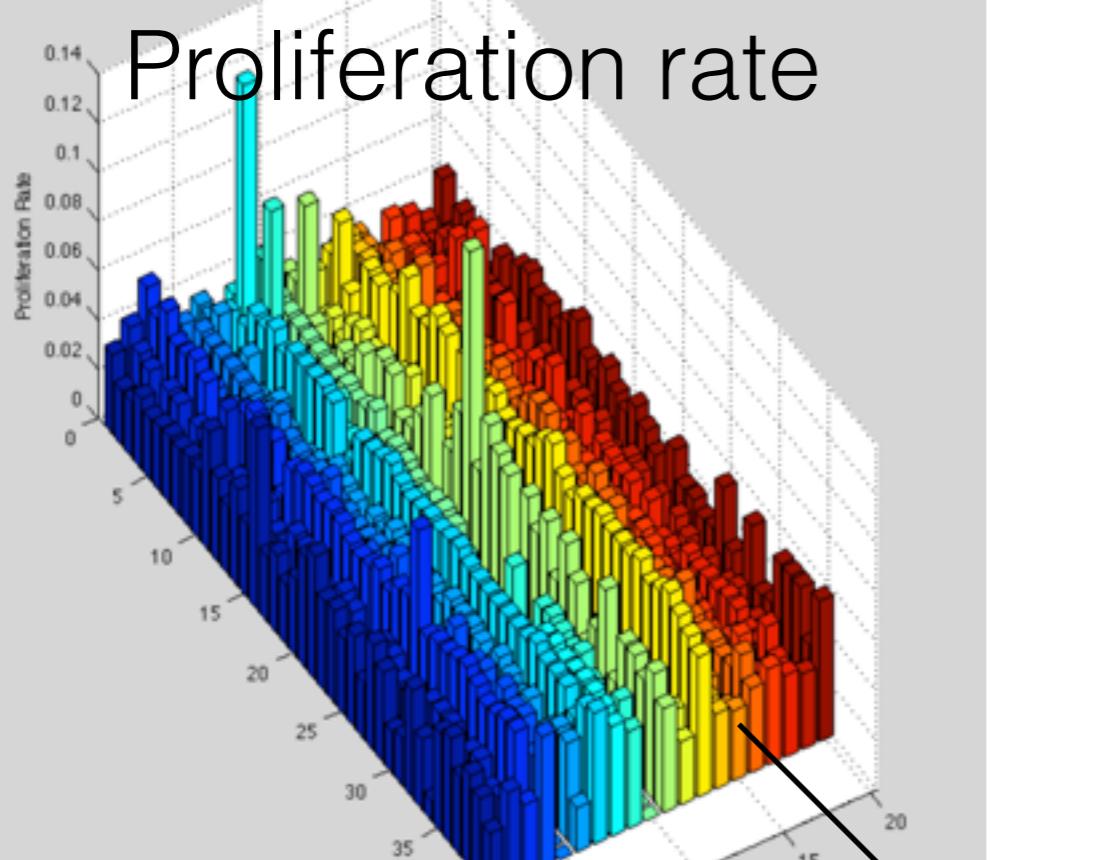
(B)

V2 NFL Mutation Rate

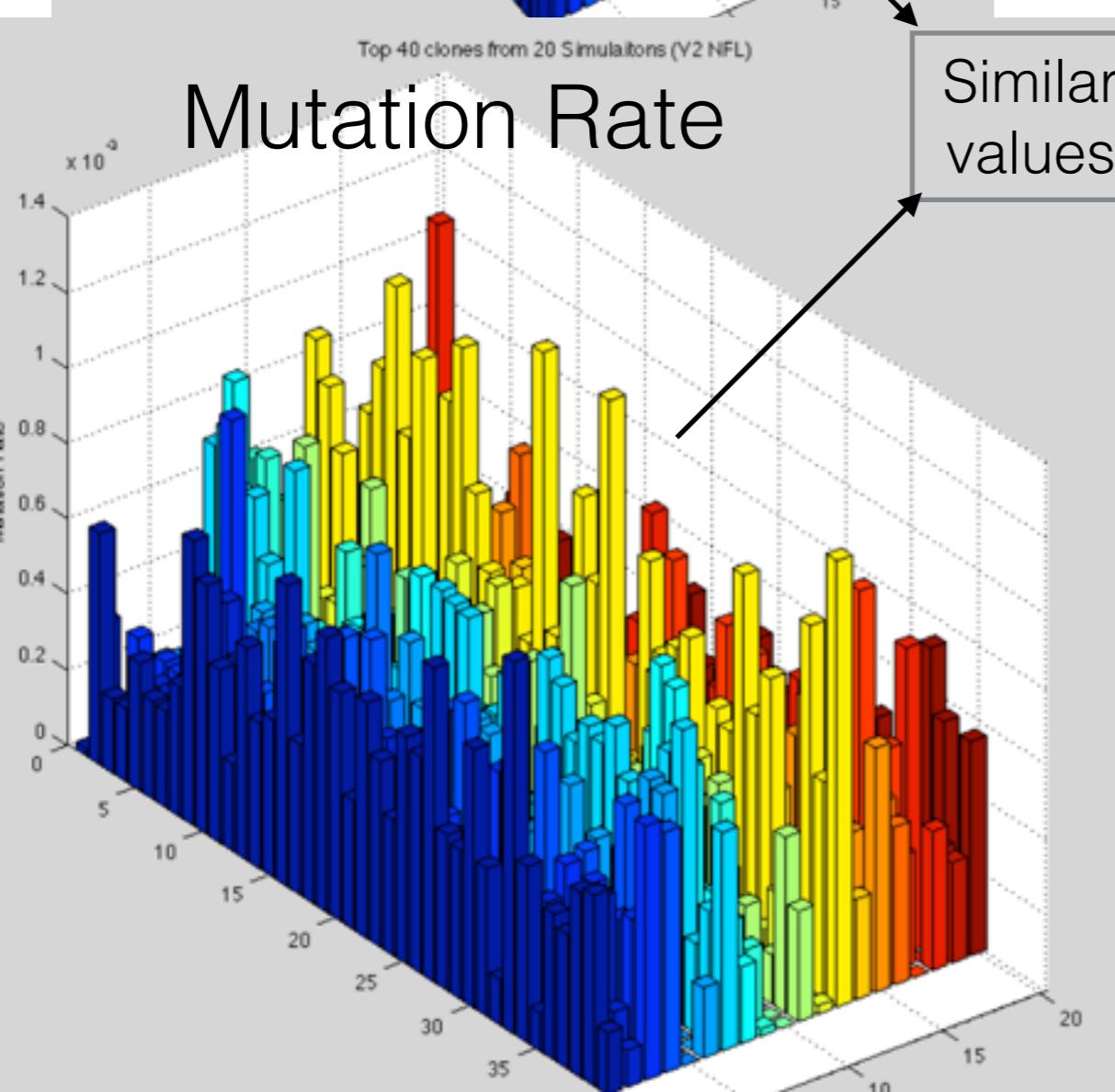


It seems like a more competitive
dynamic

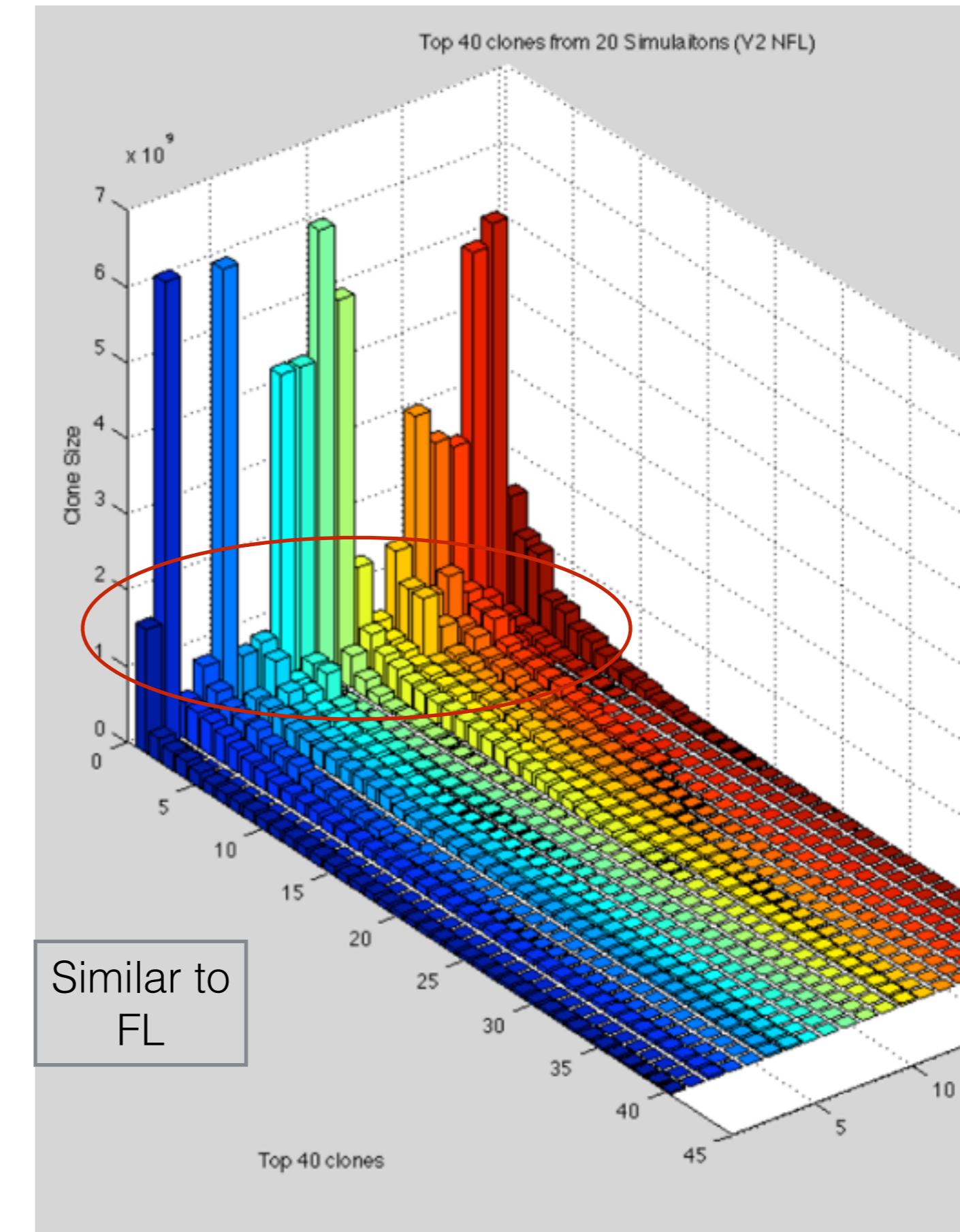
Proliferation rate



Mutation Rate



Top 40 clones from 20 Simulations (Y2 NFL)



Version 3

Loop until $T(t) < K$

For a given clone compute:

$$[X_{Dy_i}, X_{Qu_i}, X_{NB_i}, X_{NT_i}] \sim Multinom(CS_i, [p_{DR_i}, p_{Qu_i}, p_{NB_i}, 1 - (p_{DR_i} + p_{Qu_i} + p_{NB_i})])$$

$$X_{NB_i} \sim Binom(CS_i, PR_i - \lambda)$$



If $X_{ND_i} > 0$,

$$x \forall X_{ND_i} : K(x) \quad (16)$$

Where $K(x)$ is,

$$K(x) = \begin{cases} PR_j \sim Normal(Parent_{PR_i}, 0.001); MR_j \sim Normal(Parent_{MR_i}, MR_0) & \text{if } Z \geq X_{Dr} \\ CS_i = CS_i - 1 & \text{if } Z \leq X_{Ki} \\ PR_i = PR_i + CS_i^{-1} & \text{if } X_{Ben} \geq Z \leq X_{Dr} \\ PR_i = PR_i - CS_i^{-1} & \text{if } X_{Ki} \geq Z \leq X_{Del} \\ PR_i = PR_i - I_{\{Np_i=c\}}\beta & \text{Otherwise} \end{cases}$$

$$\lambda = (PR_0 - DR_0) \frac{T(t)}{K}$$

Mutational effect
sampled from
Normal distribution

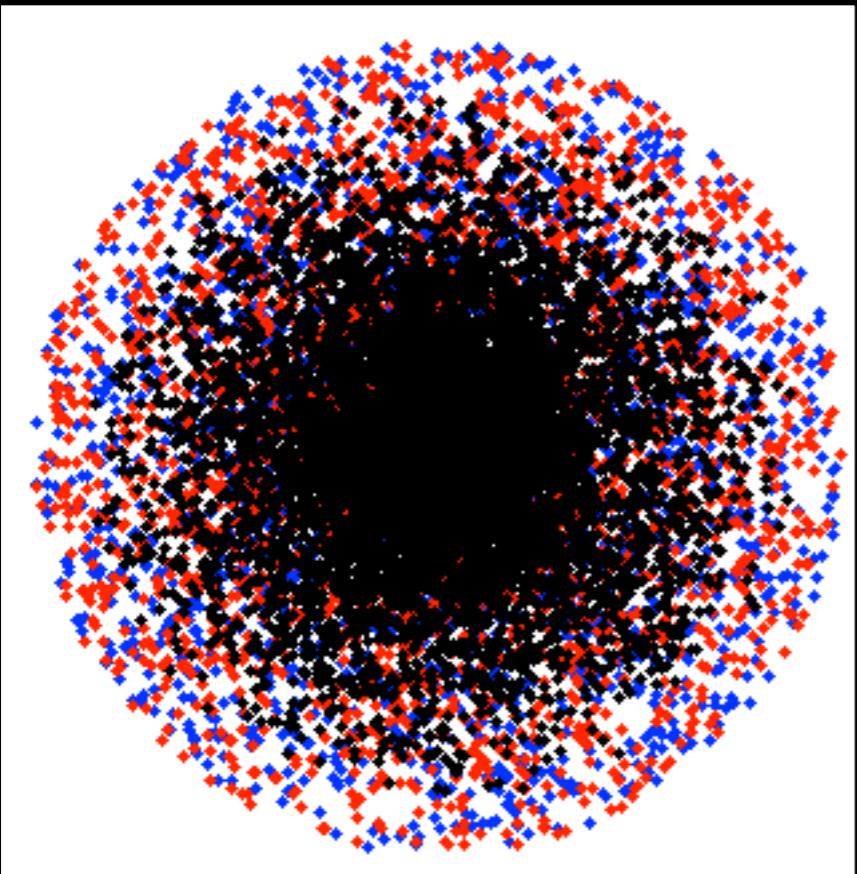


Then update the clone as,

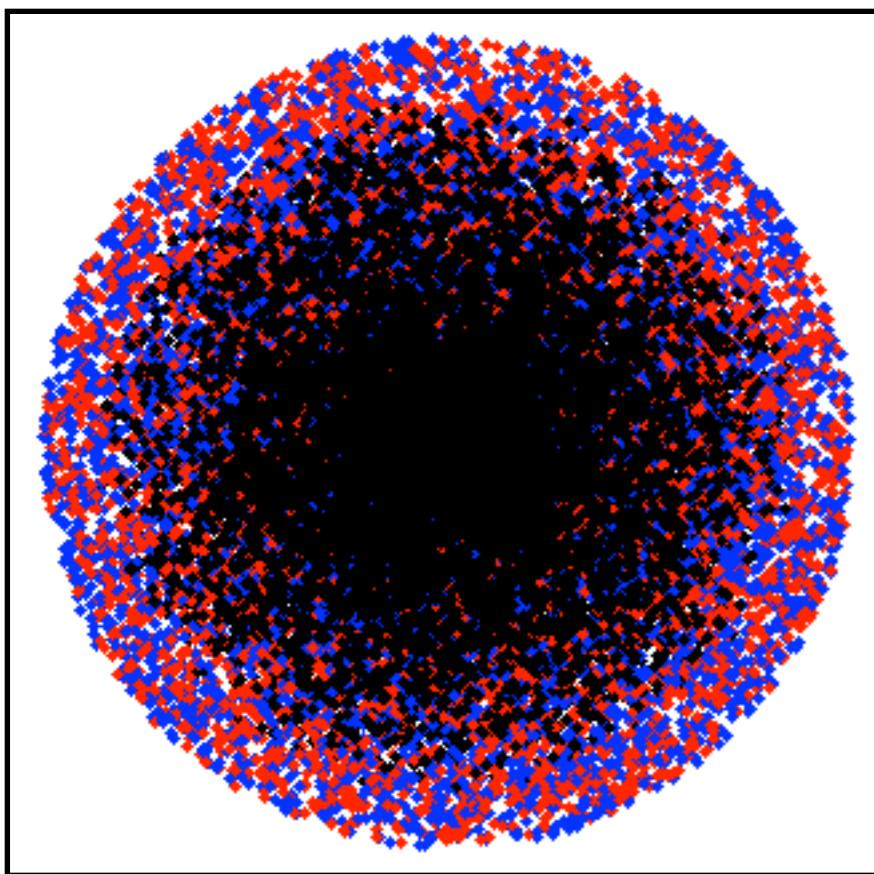
$$CS_i = (CS_i + X_{NB_i}) - (X_{Dy_i} + X_{ND_i}) + X_{Qui}$$

Therefore, the active tumour burden is,

$$T(t) = \sum_{i=1}^N CS_i$$



The Basic Model of Solid
Tumours with different
parameters.



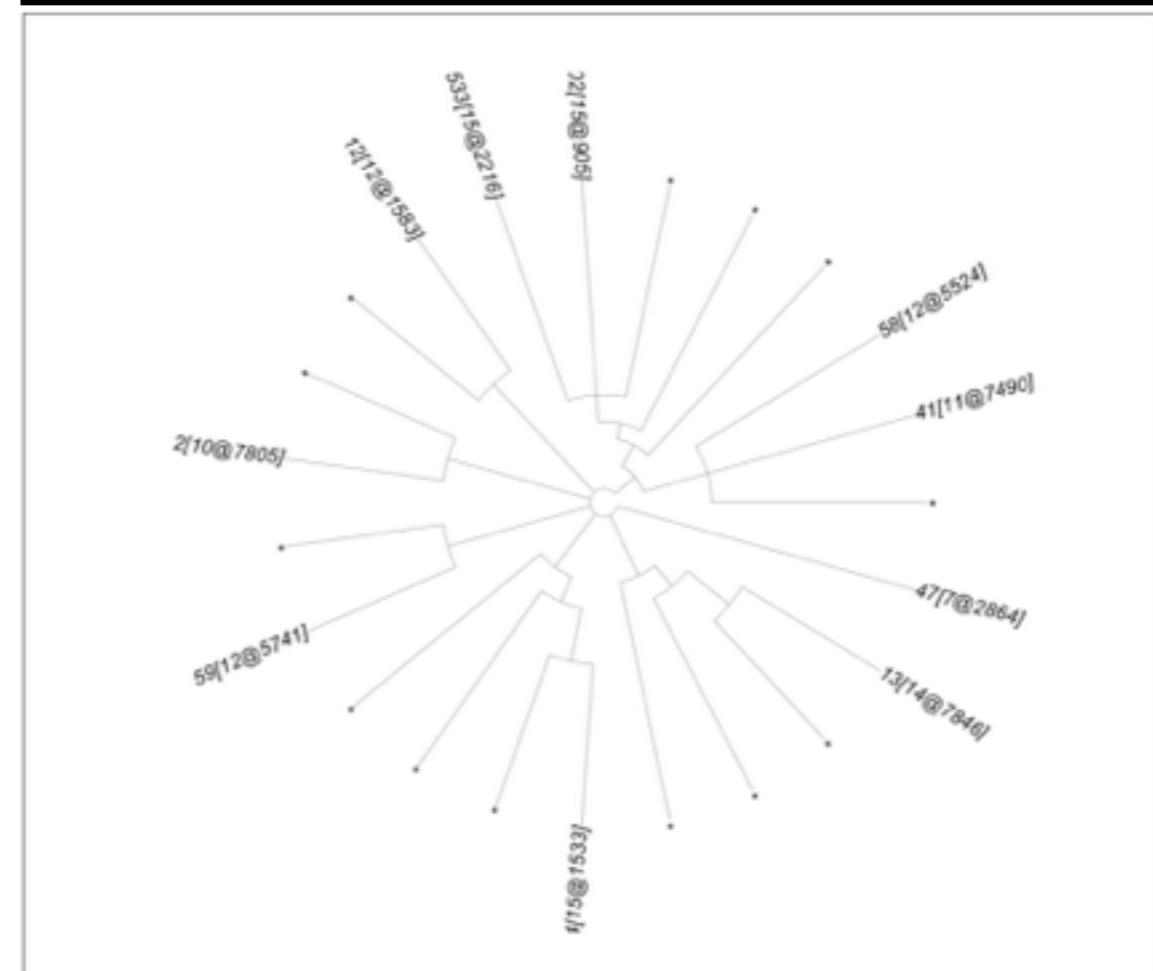
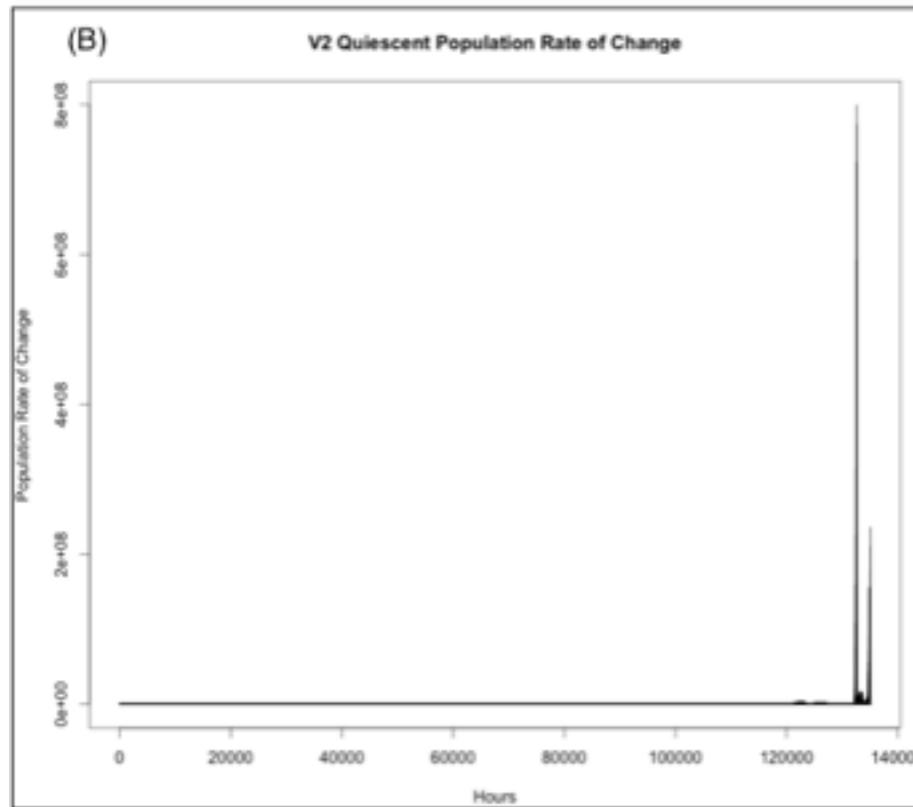
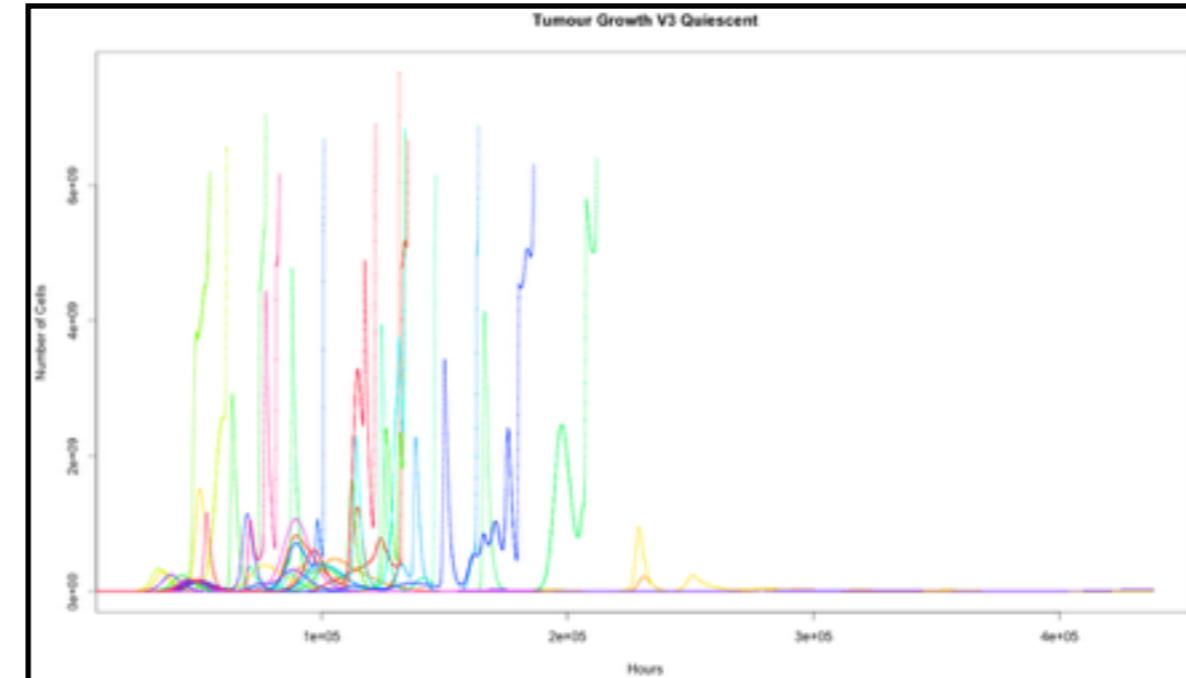
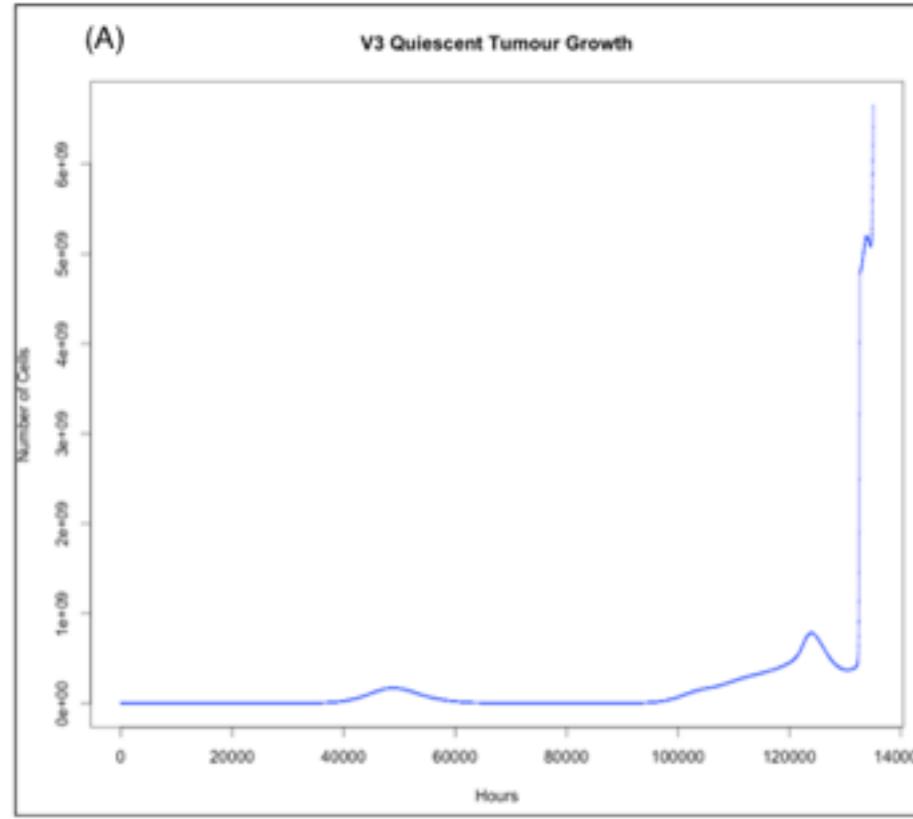
$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} \left[\frac{p}{p+q} \frac{\partial}{\partial x} (p + q) \right] + g(c)p(1 - p - q - n) - f(c)p$$

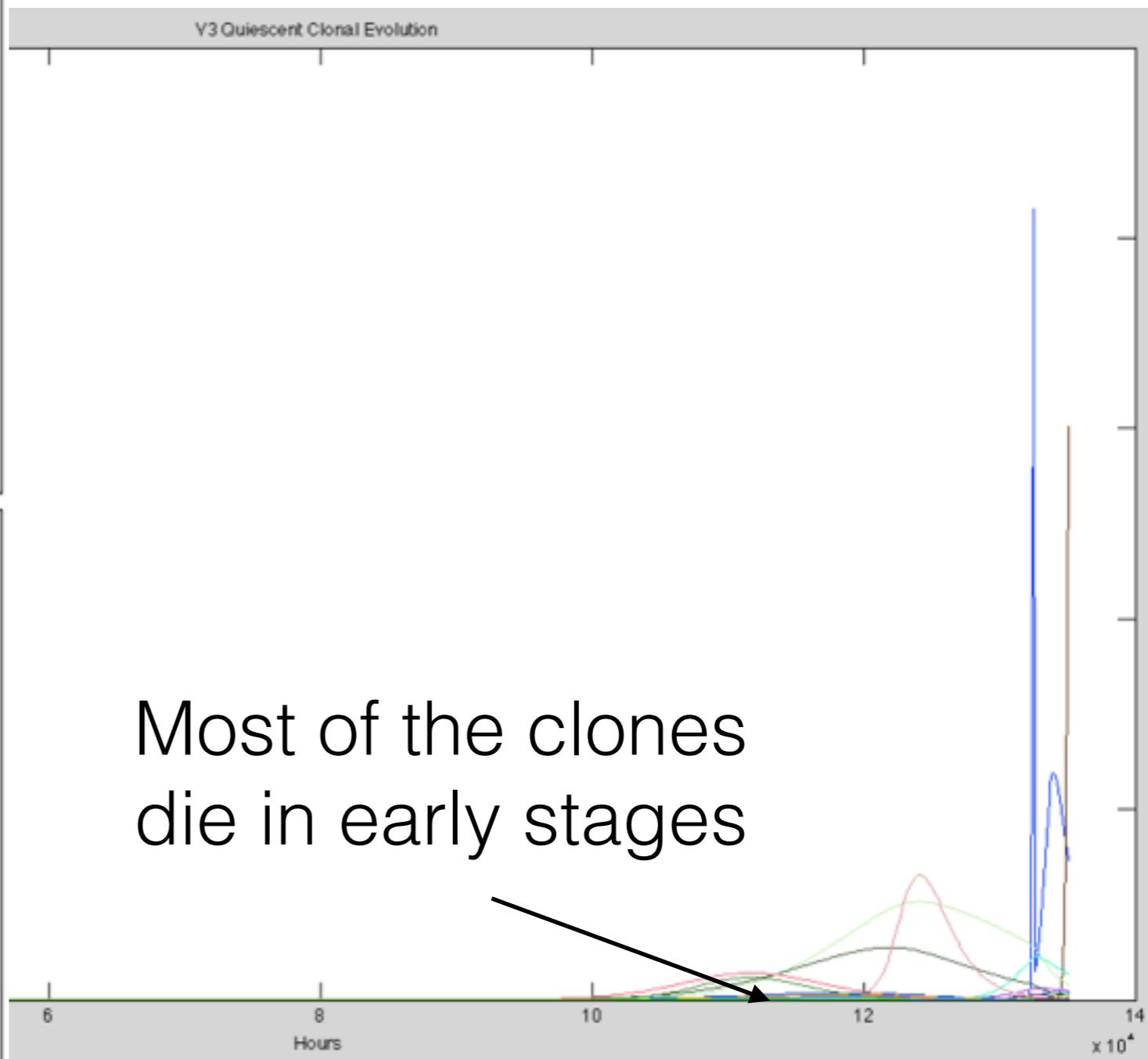
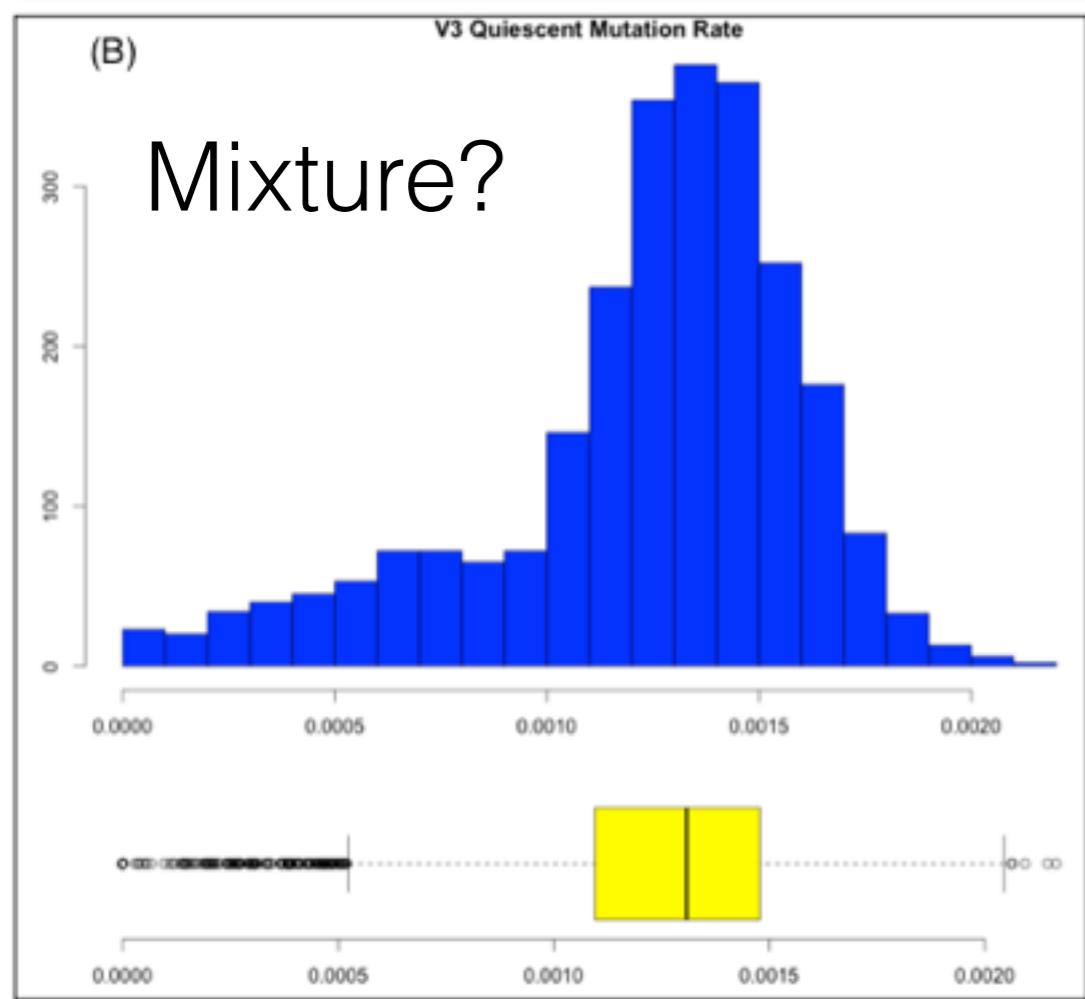
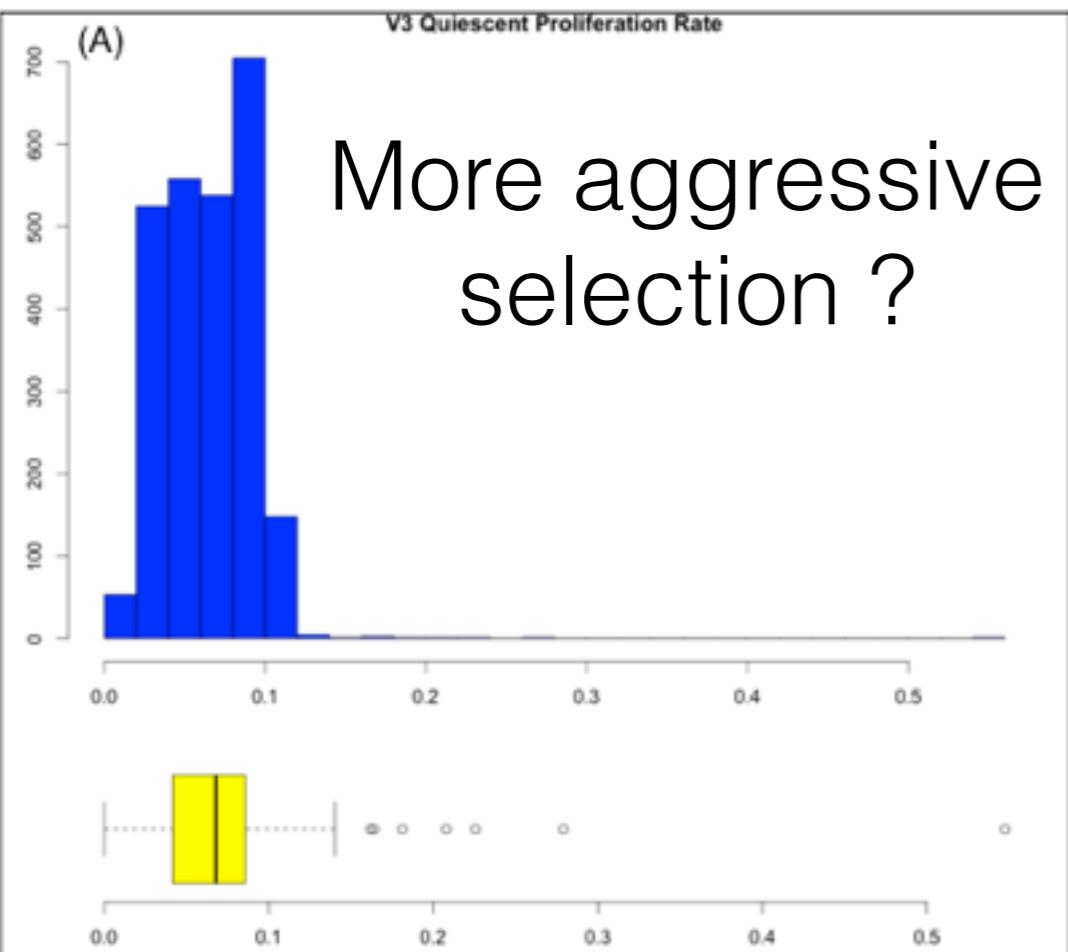
$$\frac{\partial q}{\partial t} = \frac{\partial}{\partial x} \left[\frac{q}{p+q} \frac{\partial}{\partial x} (p + q) \right] + f(c)p - h(c)q$$

$$\frac{\partial n}{\partial t} = h(c)q$$

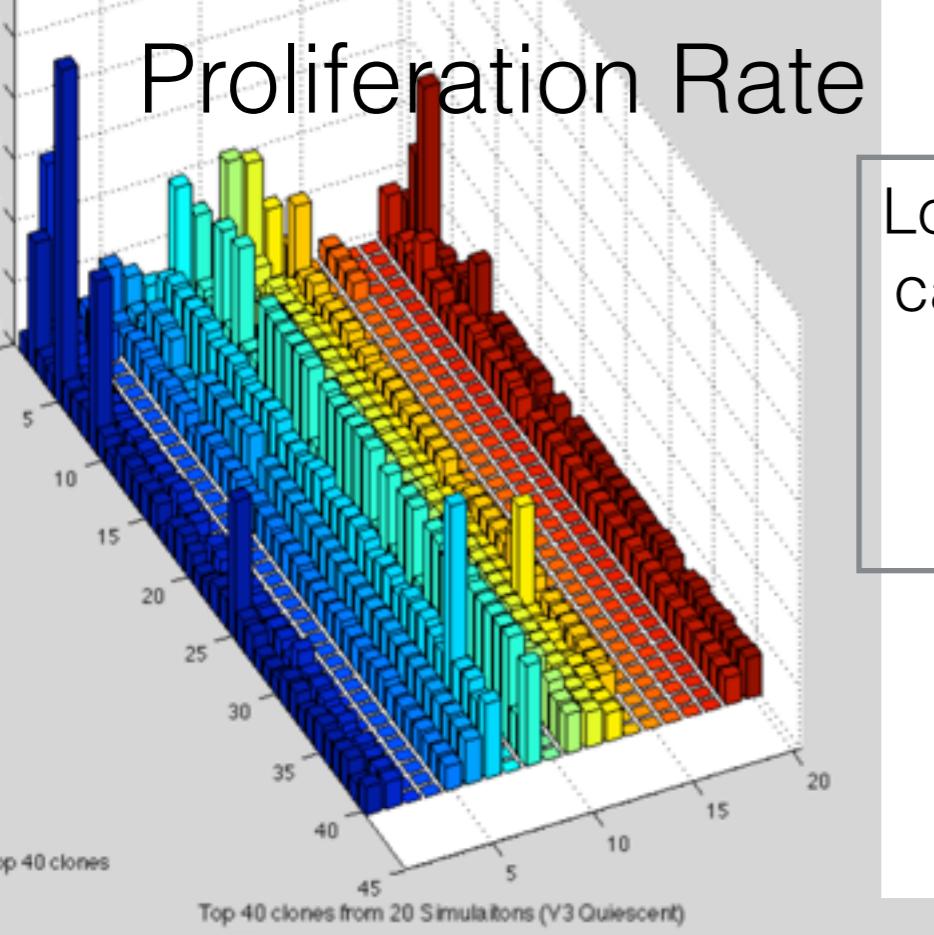
Output

Simulations can grow or not
or stay quiescent



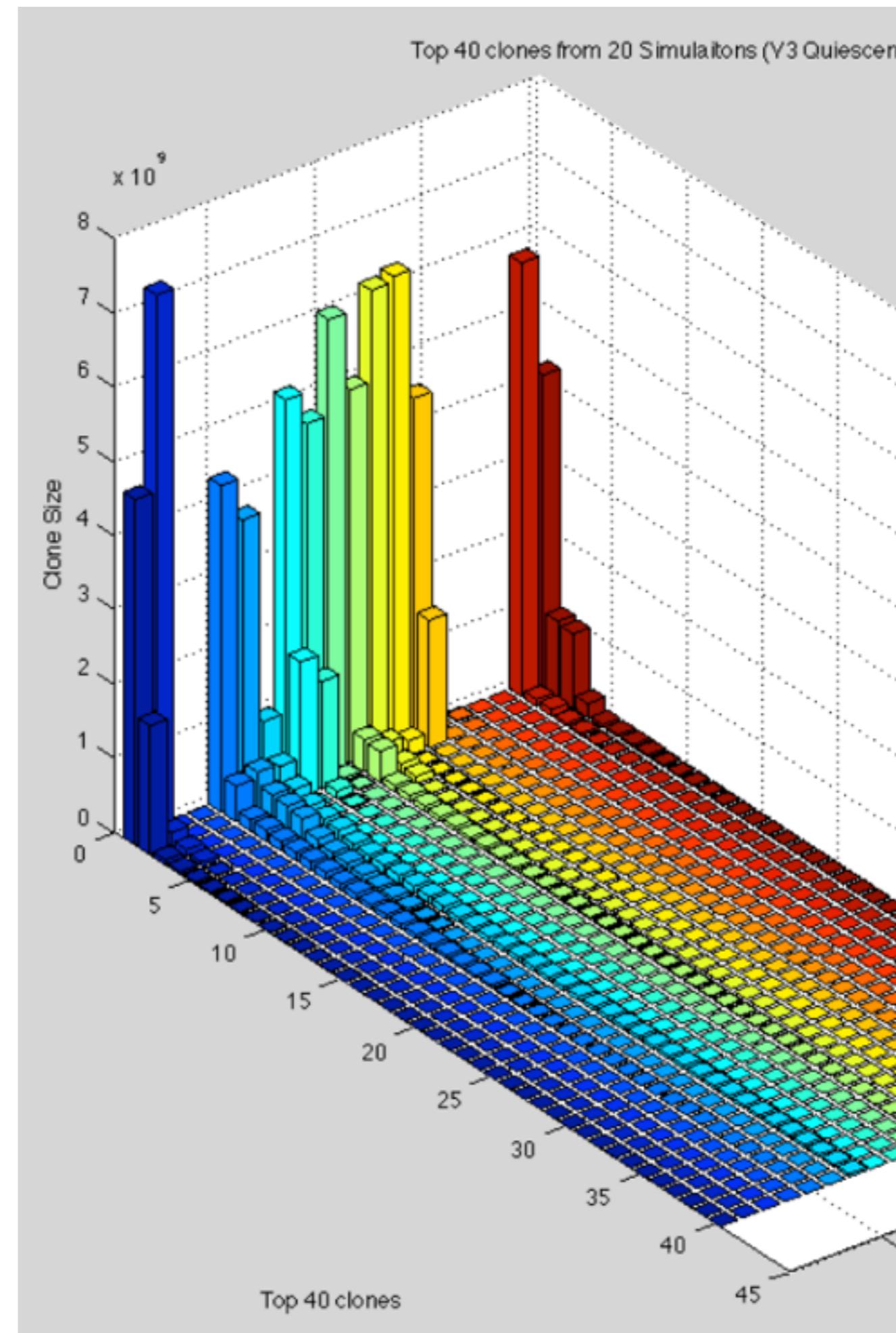
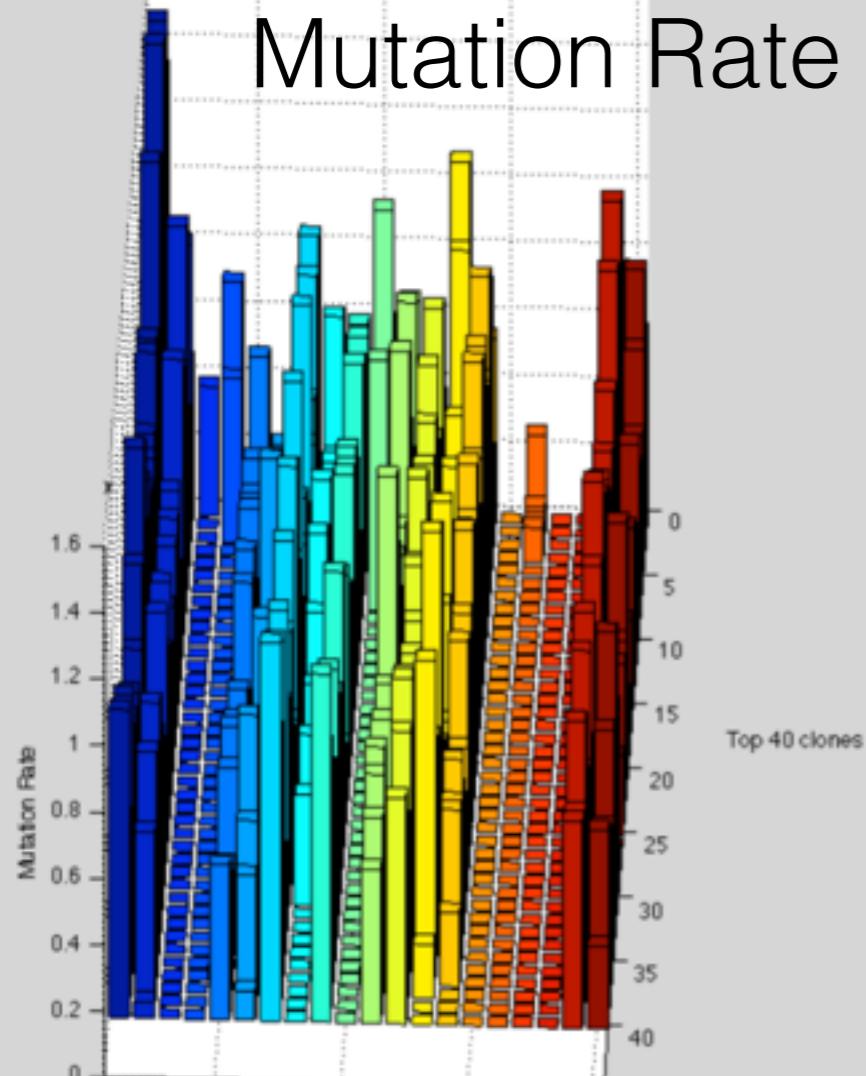


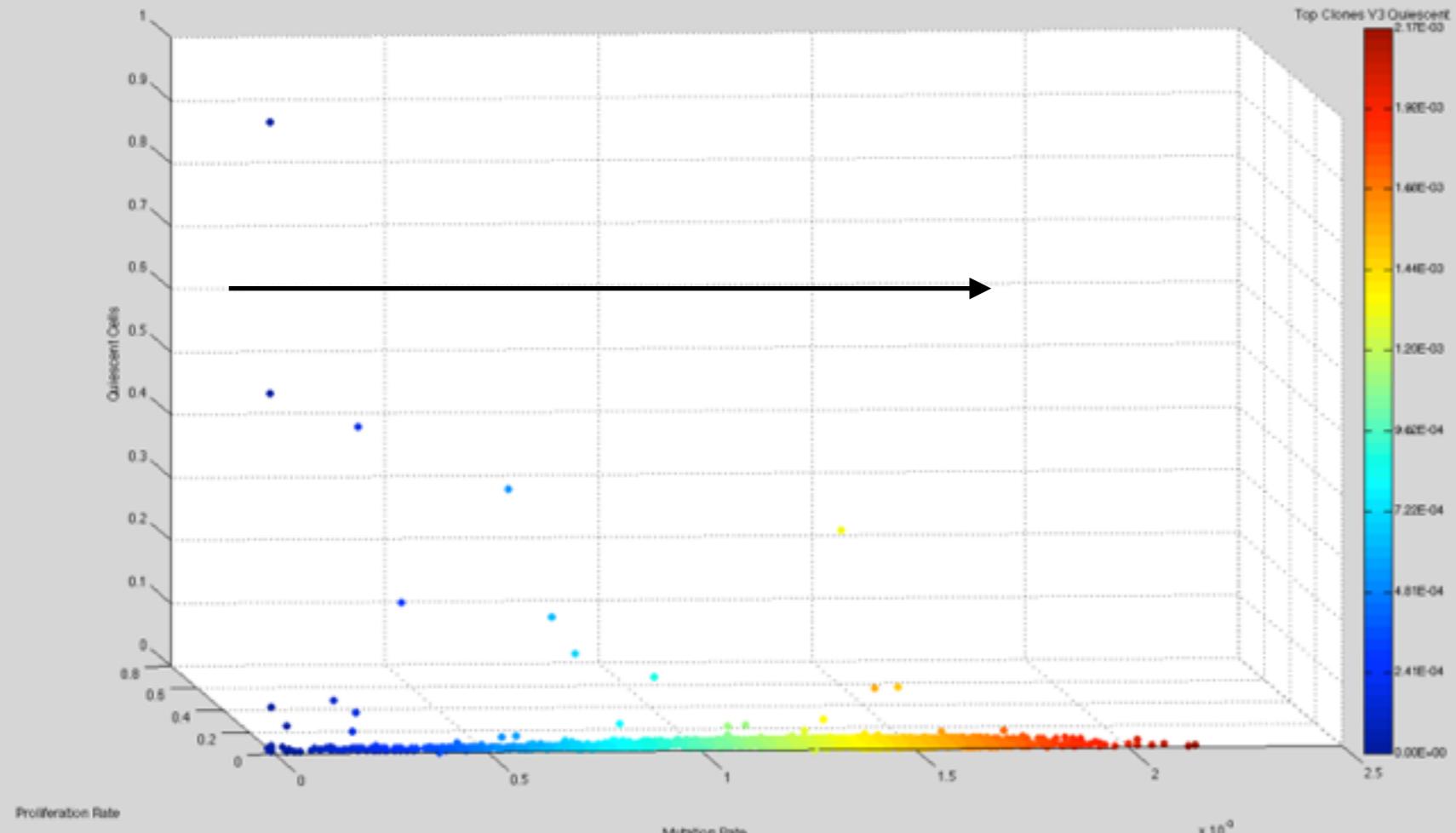
Proliferation Rate



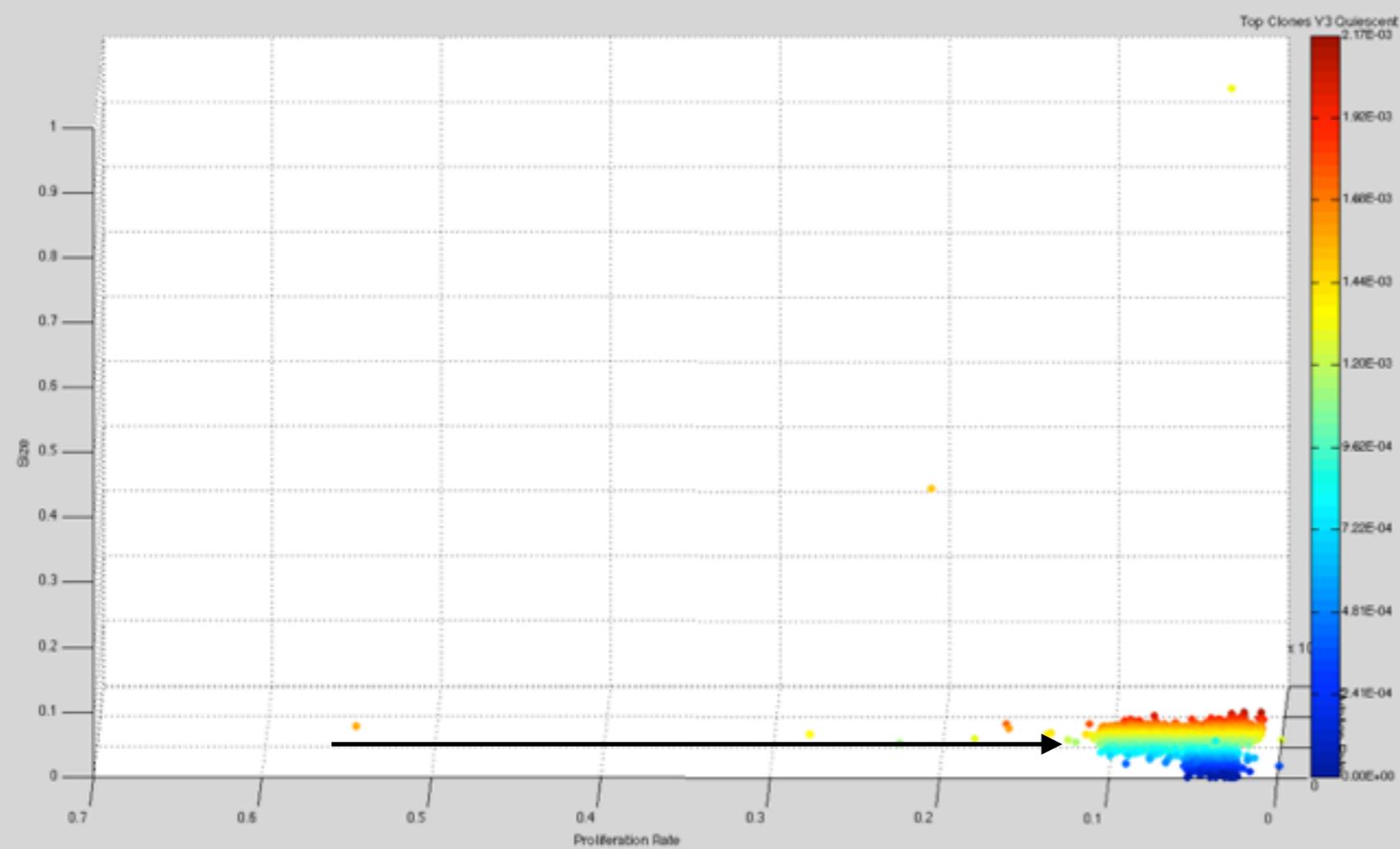
Low proliferation
can change the
odds of
survival by
quiescence

Mutation Rate





Is more difficult
to grow tumours
with this scheme



Next Steps

Loop until $T(t) < K$

For a given clone compute:

$$[G0_i, G1_i, S_i, G2_i, M_{N_i}, M_{M_i}] \sim Multinom(CS_i, [p_{Qu_i}, p_{G1_i} - \alpha_1, p_{S_i} - \alpha_2, p_{G2_i} - \alpha_3, p_{Div_i} - \alpha_3, p_{Mut_i} - \alpha_3^*] - \alpha_4)$$

$$X_{NB_i} \sim Binom(CS_i, PR_i - \lambda)$$



If $X_{ND_i} > 0$,

$$x \forall X_{ND_i} : K(x) \quad (16)$$

Where $K(x)$ is,

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$$\lambda = (PR_0 - DR_0) \frac{T(t)}{K}$$

Mutational effect
sampled from
Normal distribution



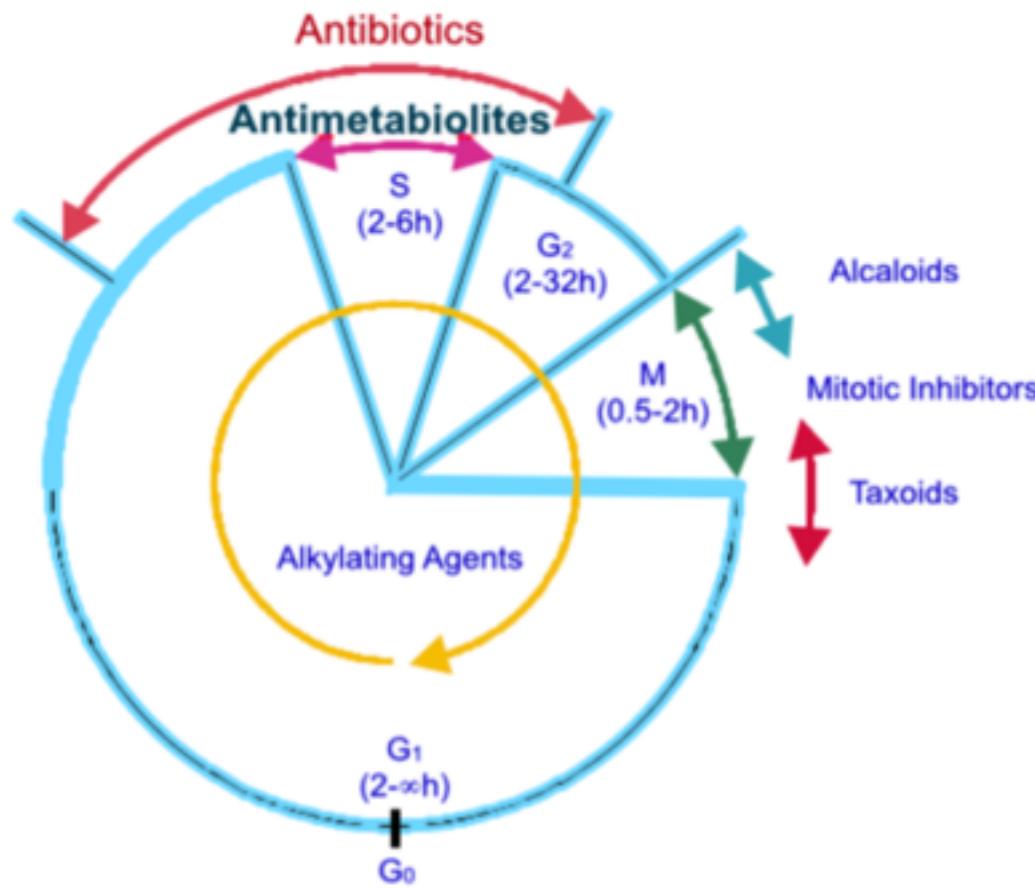
Then update the clone as,

$$CS_i = (CS_i + X_{NB_i}) - (X_{Dy_i} + X_{ND_i}) + X_{Qui}$$

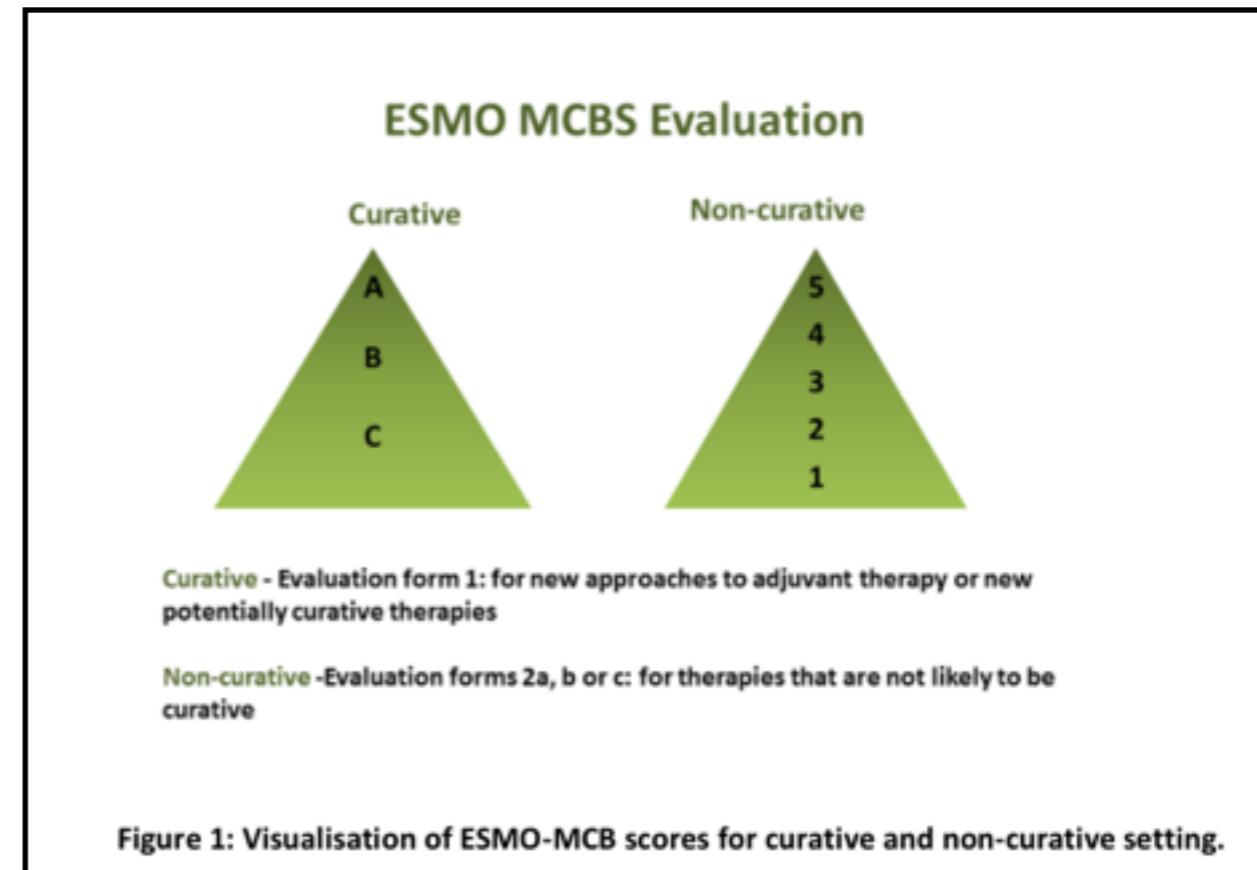
Therefore, the active tumour burden is,

$$T(t) = \sum_{i=1}^N CS_i$$

Assessing clinical trials is an URGENT matter.



alphas introduce stage specific selective pressure.



LUNG CANCER

Medication (New vs control)	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO - MCBS	ref
Erlotinib vs carboplatin/gemcitabine	OPTIMAL, CTONG-0802	1st line stage IIIb or IV non-squamous, with EGFR mutation	PFS	4.6 mth	8.5 mth	0.16 (0.10-0.26)					12% less serious adverse events	4	[75]
Erlotinib vs platinum-based chemotherapy doublet	EURTAC	1st line stage IIIb or IV non-squamous, with EGFR mutation	PFS (crossover allowed)	5.2 mth	4.5 mth	0.37 (0.25-0.54)	19.5 mth		NS		15% less severe adverse reactions	4	[76]
Gefitinib vs carboplatin + paclitaxel	IPASS	1st line stage IIIb or IV adenocarcinoma, with EGFR mutation	PFS (crossover allowed)	6.3 mth	3.3 mth	0.48 (0.34-0.67)				Improved	Reduced toxicity	4	[77, 78]
Afatinib vs Cisplatin + pemetrexed	LUX - Lung 3	1st line stage IIIb or IV adenocarcinoma with EGFR mutation (Del19/L858R)	PFS (crossover allowed)	6.9 mth	4.2 mth	0.58 (0.43-0.78)				Improved		4	[79, 80]
				6.9 mth	6.7 mth	0.47 (0.34-0.65)				Improved			
Crizotinib vs chemotherapy		1st line stage IIIb or IV non-squamous, with ALK mutation	PFS (crossover allowed)	3.0 mth	4.7 mth	0.49 (0.37-0.64)				Improved	1% increased toxic death	4	[81]
Crizotinib vs cisplatin + pemetrexed		1st line stage IIIb or IV non-squamous, with ALK mutation	PFS	7.0 mth	3.9 mth	0.45 (0.35-0.60)				Improved		4	[82]
Pemetrexed vs placebo		Stage IIIb or IV disease maintenance after responding to 4 cycles platinum doublet	PFS stratified for histology (non-squamous)	2.6 mth	1.9 mth	0.47 (0.37-0.60)	10.3 mth	5.2 mth	0.20 (0.56-0.88)			4	[83]
Cisplatin pemetrexed vs cisplatin/gemcitabine		1st line stage IIIb or IV (non-squamous)	OS (non-inferiority)				10.4 mth	1.4 mth	0.81 (0.70-0.94)		Less grade 3+ toxicity neutropenia anaemia thrombocytopenia	4	[84]
Chemotherapy +/- palliative care		Stage IV non-small cell ECOG<2	QoL				8.9 mth	2.7 mth	HR for death in control arm 1.7 (1.14-2.54)	Improved		4	[85]
Paclitaxel/carboplatin +/- bevacizumab		1st line stage IIIb or IV, non-squamous	OS				10.3 mth	2.0 mth	0.79 (0.67-0.92)			2	[86]
Erlotinib vs placebo	SATURN	Stage IIIb or IV disease maintenance after responding to 4-6 cycles platinum doublet	PFS	11.1 wk	1.2 wk	0.71 (0.62-0.82)	11.0 mth	1.0 mth	0.81 (0.70-95)			1	[87]

Can these be improved?

BREAST CANCER											from http://camnco.oxfordjournals.org/	QoL	Toxicity	ESMO-MCBS	ref
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR						
Chemotherapy +/- trastuzumab	HERA	(Neo)adjuvant HER-2 positive tumours	DFS	2 years DFS 77.4%	8.40%	0.54 (0.43-0.67)								A	[88]
T-DM1 vs lapatinib + capecitabine	EMILIA	2nd line metastatic after trastuzumab failure	PFS and OS	6.4 mth	3.2 mth	0.65 (0.55-0.77)	25 mth	6.8 mth	0.58 (0.55-0.68)		Delayed deterioration			5	[89, 90]
Trastuzumab + chemotherapy +/- pertuzumab	CLEOPATRA	1st line metastatic	PFS	12.4 mth	6 mth	0.62 (0.52-0.84)	40.8 mth	15.7 mth	0.68 (0.56-0.84)		No improvement			4	[91-94]
Lapatinib +/- trastuzumab	EGF104900	3rd line metastatic	PFS	2 mth	1 mth	0.73 (0.57-0.93)	9.5 mth	4.5 mth	0.24 (0.57-0.97)					4	[95, 96]
Capecitabine +/- lapatinib		2nd line metastatic after trastuzumab failure	PFS	4.4 mth	4 mth	0.49 (0.34-0.71)				NCT00616669 of Melbourne Library				3	[97]
Eribulin vs other chemotherapy	EMBRACE	3rd line metastatic after anthracycline and taxane	OS				10.6 mth	2.5 mth	0.81 (0.66-0.99)					2	[98]
Paclitaxel +/- bevacizumab		1st line metastatic	PFS	5.9 mth	5.8 mth	0.60 (0.51-0.70)				NCT01256205 June 11, 2015		No improvement		2	[24]
Exemestane +/- everolimus	BOLERO-2	Metastatic after failure of aromatase inhibitor (with PFS>6 mth)	PFS	4.1 mth	6.5 mth	0.43 (0.35-0.54)			NS		No improvement			2	[99]

Can we test these under different schemes?

PROSTATE CANCER

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS	ref
Best standard non chemotherapy or radiotherapy treatment +/- radium-223	ALSYMPCA	Castration refractory and bone pain	OS				11.3 mth	3.6 mth	0.70 (0.55-0.88)	Improved		5	[100]
Prednisone +/- abiraterone		Castration refractory after docetaxel	OS				10.9 mth	3.9mth	0.65 (0.54-0.77)			4	[49]
Enzalutamide vs placebo	AFFIRM	Castration refractory after docetaxel	OS				13.6 mth	4.8 mth	0.63 (0.53-0.75)	Improved		4	[50]
Enzalutamide vs placebo	PREVAIL	Castration refractory pre docetaxel	PFS and OS	3.2 mth	>12 mth	0.19 (0.15-0.23)	30.2 mth	2.2 mth	0.71 (0.60-0.84)	Improved		3	[101]
Docetaxel(Q7 or Q21) prednisone vs mitoxantrone + prednisone		Castration refractory	OS				16.5 mth	2.4 mth (Q21) 0.9 mth (Q.7)	0.76 (0.62-0.94) 0.83 (0.70- 0.99)	Improved Improved		3	[102]
Cabazitaxel+ prednisone vs mitoxantrone + prednisone	TROPIC	Castration refractory after docetaxel	OS				12.7 mth	2.4 mth	0.70 (0.59-0.83)			2	[47]

on http://asconc.oxfordjournals.org at University of Melbourne Library on June 11, 2015

COLORECTAL CANCER

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS	ref
FOLFOX4 +/- panitumumab	PRIME	1st line metastatic (Post hoc KRAS, NRAS BRAF WT)	PFS	7.9 mth	2.3 mth	0.72 (0.58-0.90)	20.2 mth	5.8 mth	0.48 (0.62-0.99)			4	[62]
Panitumumab + mFOLFOX6 vs bevacizumab +mFOLFOX6	PEAK	1st line metastatic (KRAS-WT)	PFS			NS	24.3 mth	9.9 mth	0.62 (0.44-0.89)			4*	[103]
FOLFIRI +/- cetuximab	CRYSTAL	1st line metastatic stratified for KRAS-WT (Post hoc KRAS, NRAS WT)	PFS	8.4 mth	3.0 mth	0.56 (0.41-0.76)	20.2 mth	8.2 mth	0.69 (0.54-0.88)			4	[65]
Cetuximab vs best supportive care		Refractory metastatic KRAS-WT	OS	1.9 mth	1.8 mth	0.4 (0.30-0.54)	4.8 mth	4.7 mth	0.65 (0.41-0.740			4	[104]
FOLFOX4 +/- panitumumab	PRIME	1st line metastatic KRAS-WT	PFS	8 mth	1.6 mth	0.80 (0.66-0.97)	19.4 mth	4.4 mth	0.68 (0.70-0.98)			3	[60, 61]
FOLFIRI +/- cetuximab	CRYSTAL	1st line metastatic stratified for KRAS-WT	PFS	8.4 mth	1.5 mth	0.70 (0.56-0.87)	20 mth	3.5 mth	0.60 (0.67-0.95)			3	[63, 64]
ILF +/- bevacizumab		1st line metastatic	OS				15.6 mth	4.7 mth	0.56 (0.54-0.81)			3	[105]
FOLFIRI +/- panitumumab		2nd line metastatic KRAS-WT	PFS	3.9 mth	2 mth	0.73 (0.59-0.90)						3	[106]
FOLFOX+/- bevacizumab vs bevacizumab alone	E3200	2nd line metastatic after FOLFIRI	OS				10.8 mth	2.1 mth	0.61 (0.63-0.89)			2	[107]
Panitumumab, vs best supportive care		3rd line metastatic stratified for KRAS	PFS	7.3 wk	5 wk	0.45 (0.34-0.59)						2	[108]
FOLFIRI bevacizumab vs FOLFOXIRI bevacizumab		1st line metastatic	PFS	9.7 mth	2.4 mth	0.75 (0.62-0.90)						2	[109]
TAS-102 vs placebo	CONCOURSE	3rd line or beyond metastatic	OS				5.3 mth	1.8 mth	0.68 (.058-0.81)			2	[110]
Regorafenib vs placebo	CORRECT	3rd line metastatic	OS				5 mth	1.4 mth	0.77 (0.64-0.94)			1	[111]
2nd line chemotherapy +/- bevacizumab	ML18147	2nd line beyond progression on bevacizumab	OS				9.6 mth	1.5 mth	0.81 (0.69-0.94)			1	[112]
FOLFIRI+/- afibbercept	VELOUR	2nd line after oxaliplatin based treatment	OS	4.7 mth	2.2 mth	0.76 (0.66-0.87)	12 .1 mth	1.5 mth	0.82 (0.71-0.94)			1	[113]
FOLFIRI +/- Ramucirumab	RAISE	2 nd line metastatic after bevacizumab, oxaliplatin, fluoropyrimidine	OS				11.7 mth	1.6 mth	0.84 (0.73-0.97)			1	[114]
*unbalanced crossover													

http://annonc.oxfordjournals.org/

Issue 11, 2015

OVARIAN CANCER													http://annonc.oxfordjournals.org/ at University of Melbourne Library on June 11, 2015	QoL	Toxicity	ESMO-MCBS	ref
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR								
Paclitaxel or topotecan or liposomal doxorubicin +/- bevacizumab	AURELIA	Recurrent platinum resistant	PFS (crossover allowed)	3.4 mth	3.3 mth	0.48 (0.38-0.60)				Improved					4	[115, 116]	
Paclitaxel and carboplatin (5 or 6 cycles) +/- bevacizumab till 18 cycles or progression	ICON7	High risk, early stage post resection or advanced ovarian or primary peritoneal	PFS stratified for stage and risk of progression	(All) 22.4 mth (high risk) 14.5 mth	1.7 mth 3.6 mth	0.81 (0.70-0.94) 0.73 (0.60-0.90)	28.8 mth	7.8 mth	0.64 (0.48-0.85)						1	[117]	
Gemcitabine and carboplatin +/- bevacizumab	OCEANS	Recurrent platinum sensitive	PFS (crossover allowed)	8.4 mth	4 mth	0.48 (0.39-0.61)									3	[118]	
Paclitaxel and carboplatin (6 cycles) +/- bevacizumab continual till 10 months or progression	GOG 218	Incompletely resected stage III and stage IV	PFS (crossover allowed)	10.3 mth	Bevacizumab continual 3.9 mth	0.72 (0.63-0.82)			NS						3	[119]	
Liposomal doxorubicin +/- trabectedin	OVA-301	2nd line metastatic	PFS stratified for platinum sensitivity/ resistance	(sensitive) 7.5 mth (resistant) 5.8 mth	1.7 mth 1.5 mth	0.73 (0.56-0.95) 0.79 (0.65-0.96)									2	[120]	
Olaparib vs placebo		BRCA ovarian cancer in remission	PFS	4.3 mth	6.9 mth	0.18 (0.10-0.31)			NS	Not improved					2	[121]	

SARCOMA

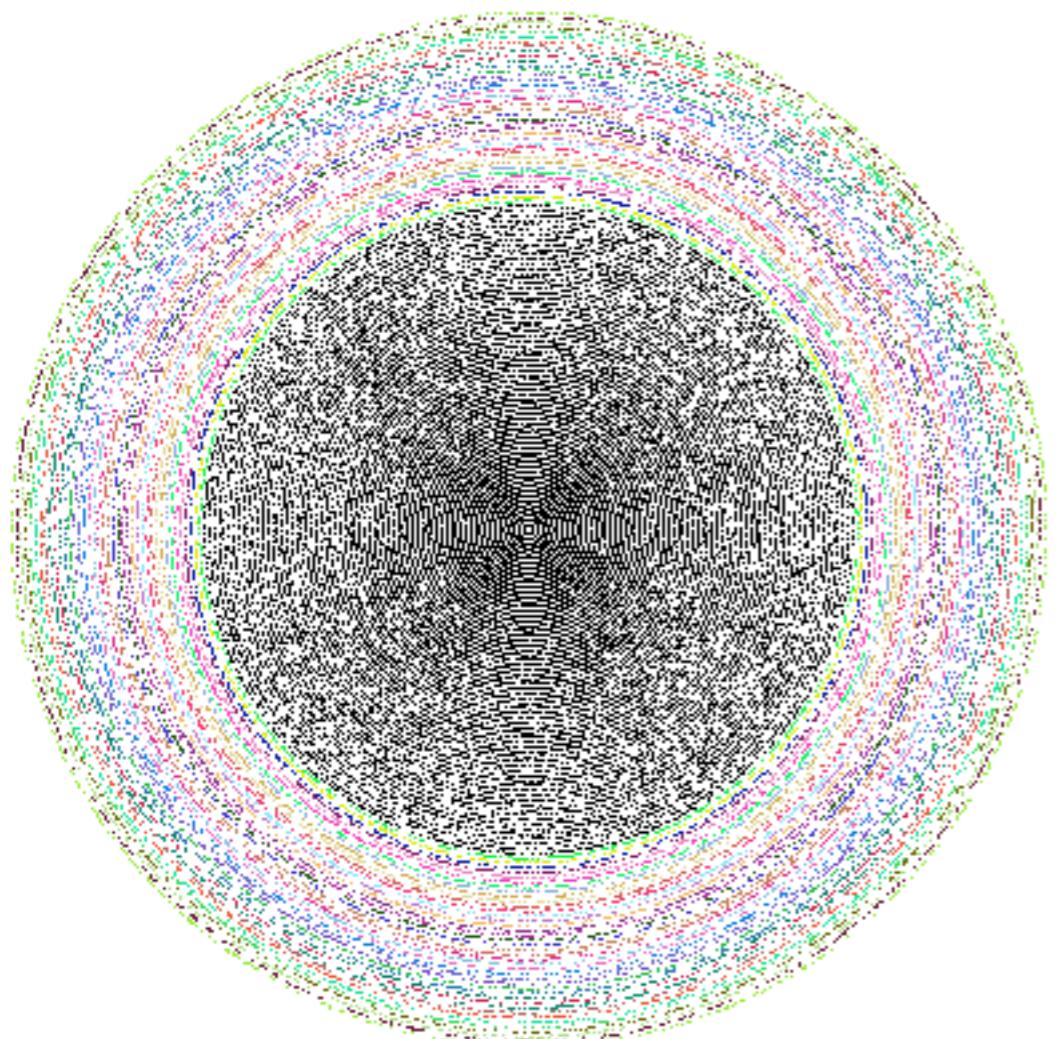
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MELANOMA

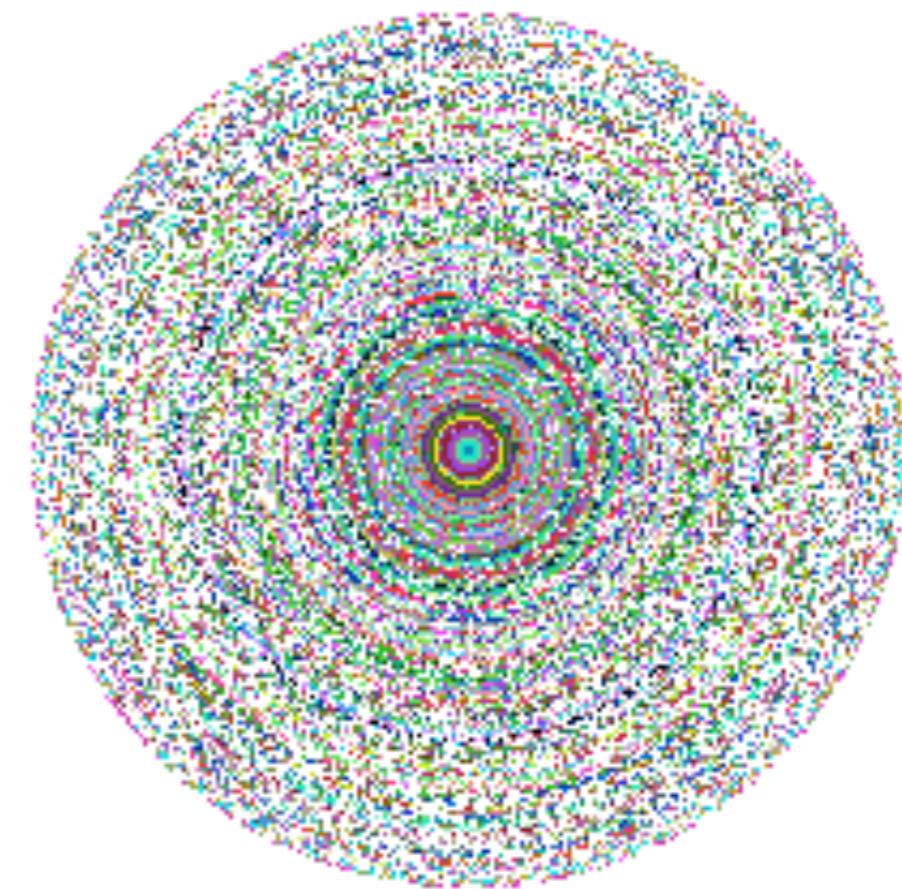
Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	QoL	Toxicity	ESMO-MCBS	ref
Ipilimumab +/- glycoprotein 100 vaccine vs vaccine alone		Previously treated metastatic	OS				6.4 mth	3.7 mth	0.69 (0.56-0.85)			4	[138]
Vemurafenib vs dacarbazine	BRIM-3	1st line or 2nd line after IL-2 metastatic with BRAF V600E mutation	PFS and OS	1.6 mth	4.7 mth	0.26 (0.20-0.33)	9.7 mth	3.9 mth	0.70 (0.57-0.87)			4	[66, 67]
Trametinib vs dacarbazine or paclitaxel	METRIC	Unresectable or metastatic with BRAF V600E mutation	PFS (crossover allowed)	1.5 mth	3.3 mth	0.45 (0.33-0.63)	6 mth: 67%	14.00%		Improved		4*	[139, 140]
Dabrafenib +/- trametinib		1st line unresectable or metastatic with BRAF V600E mutation	Toxicity, PFS	5.8 mth	3.6 mth	0.30 (0.25-0.62)					12% reduction skin cancer	4	[141]
Dabrafenib vs dacarbazine		1st line unresectable or metastatic with BRAF V600E mutation	PFS (crossover allowed)	2.7 mth	2.1 mth	0.30 (0.18-0.51)				Improved		4	[142, 143]
Dabrafenib + trametinib vs vemurafenib		1st line unresectable or metastatic with BRAF V600E mutation	OS	7.3 mth	4.1 mth	0.69 (0.53-0.89)	1 year: 65%	7%	0.69 (0.53-0.89)		17% reduction skin cancer	4*	[144]
Vemurafenib +/- cobimetinib		1st line unresectable or metastatic with BRAF V600E mutation	PFS	6.2 mth	3.7 mth	0.51 (0.39-0.68)	9mth: 73%	8%			9% reduction skin cancer	4*	[145]
Dacarbazine +/- nivolumab		1st line unresectable or metastatic BRAF-V600-WT	OS	2.2 mth	2.9 mth	0.43 (0.34-0.56)	10.8 mth	6+ mth	0.42 (0.25-0.73)			4*	[146]
Dacarbazine +/- ipilimumab		1st line metastatic	OS (crossover allowed)				3 years survival 12.2%	8.60%				3	[51, 147]

* immature survival data

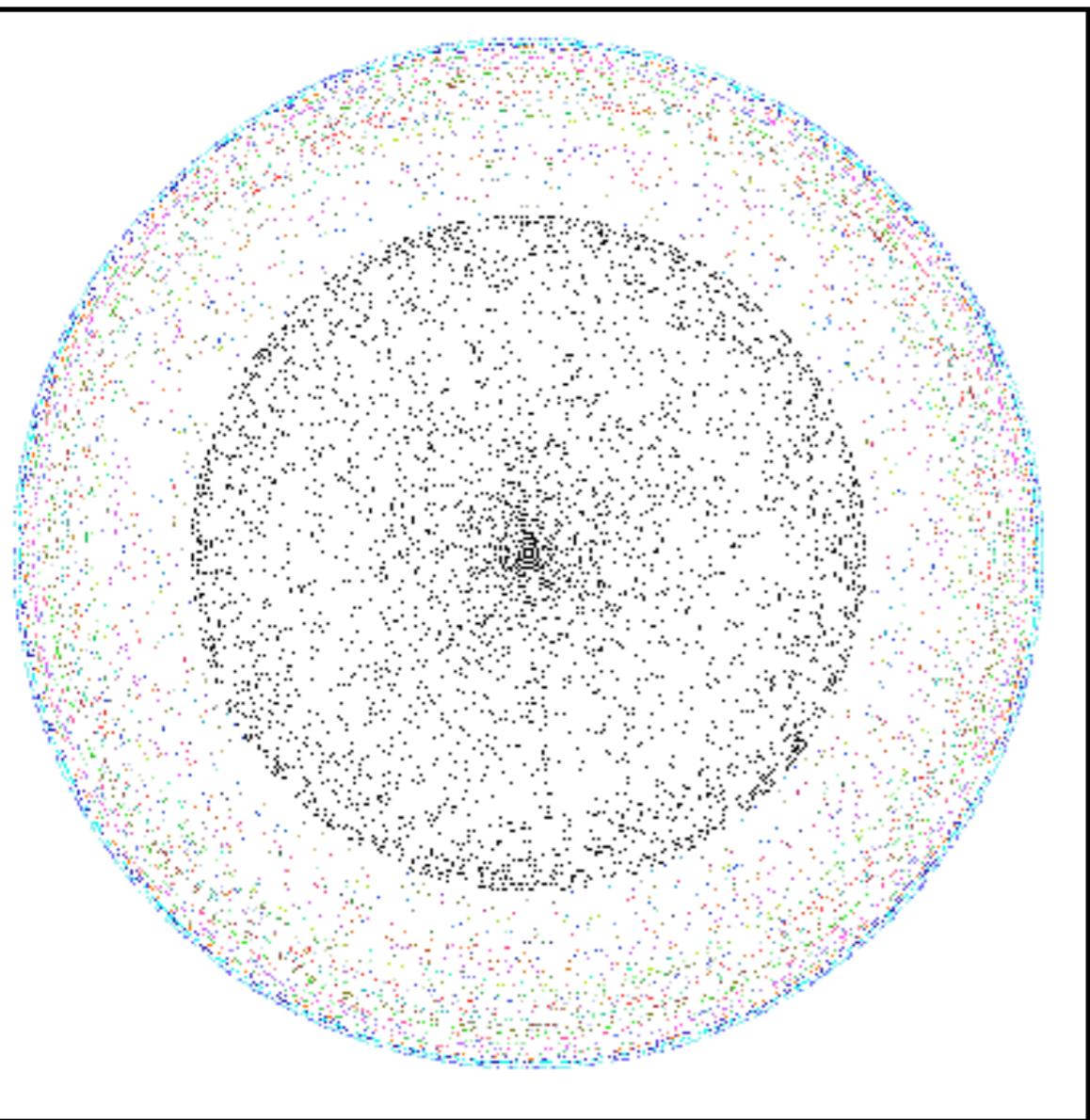
Heterogeneity Plots



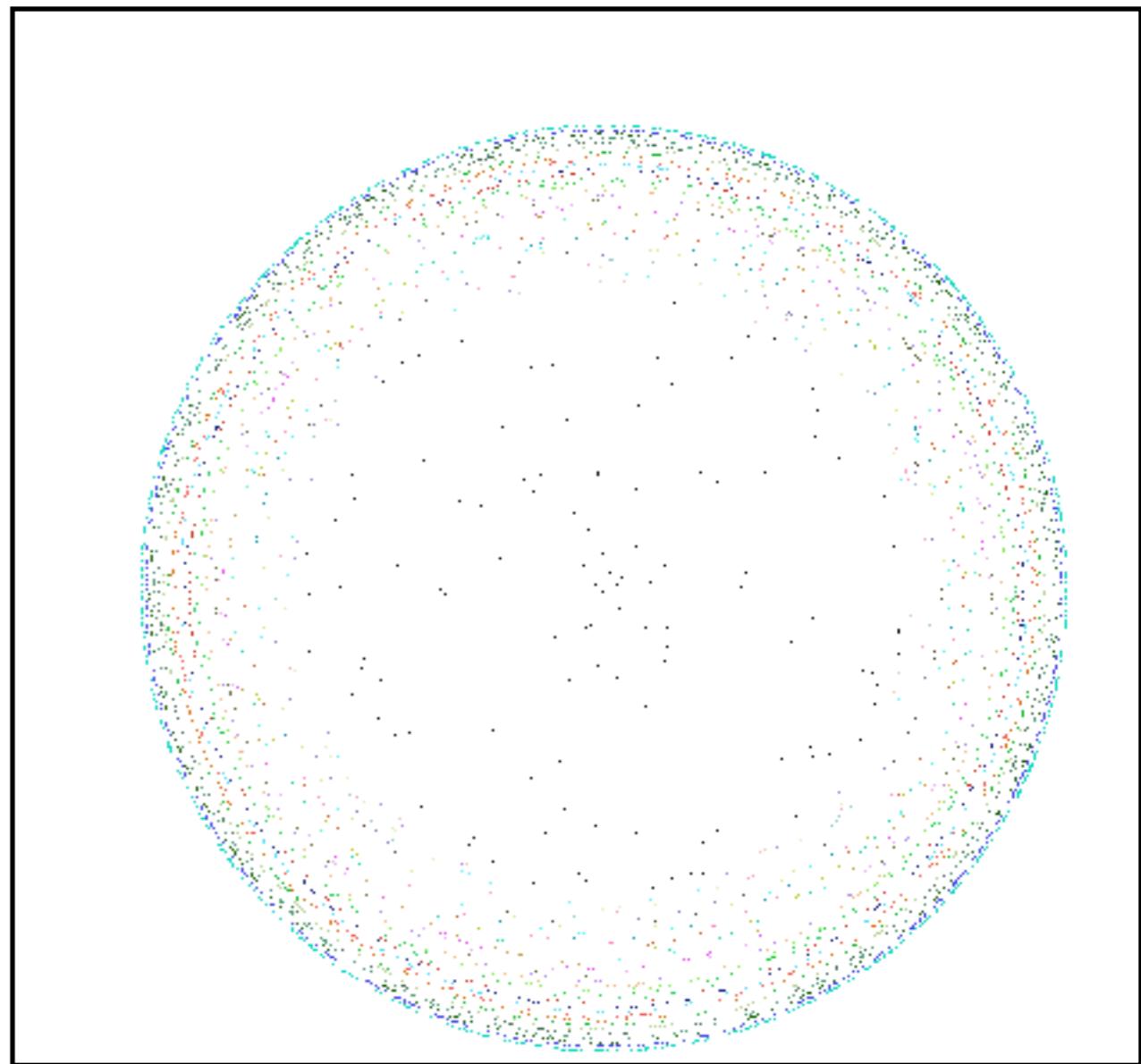
Necrotic core



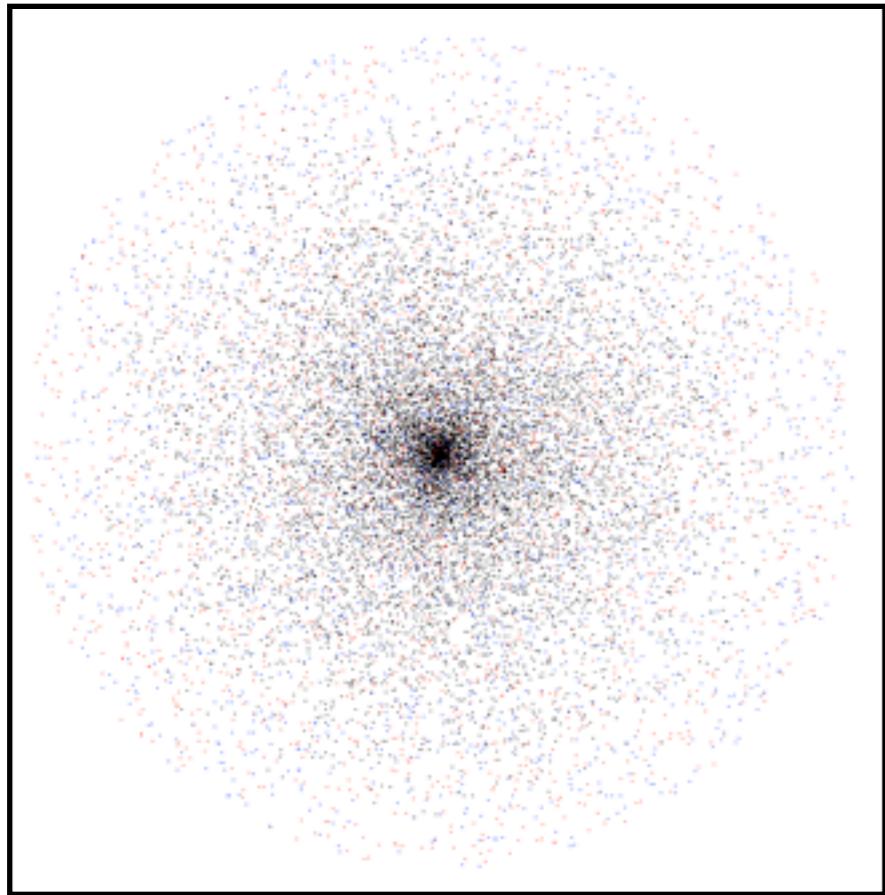
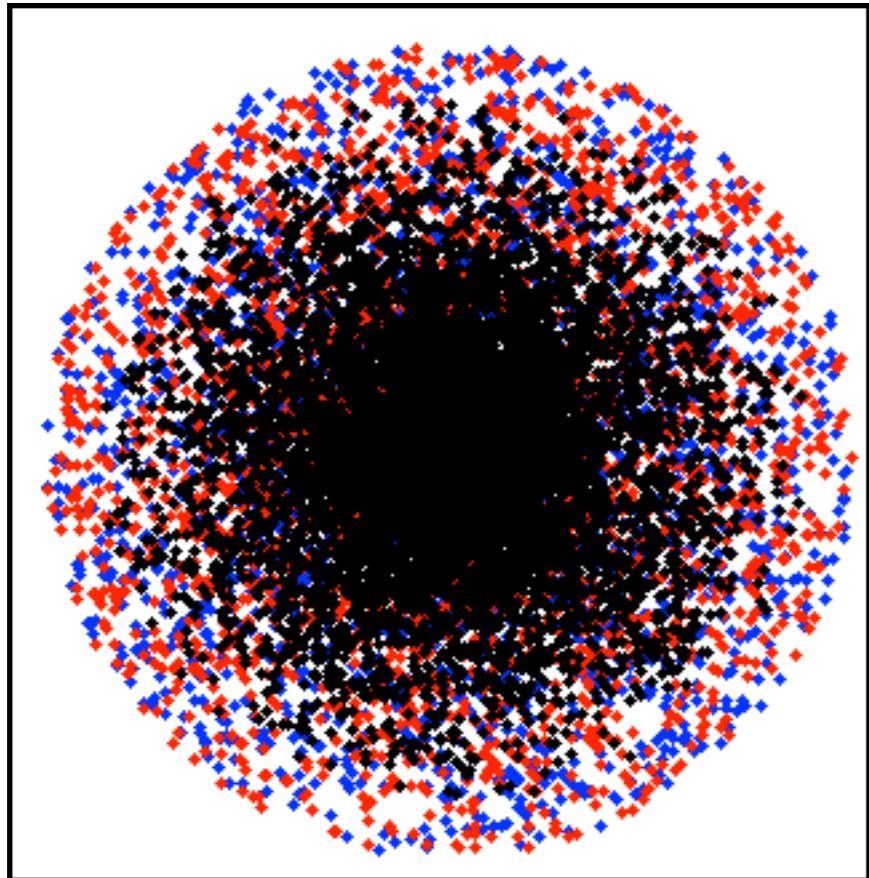
Without the CORE



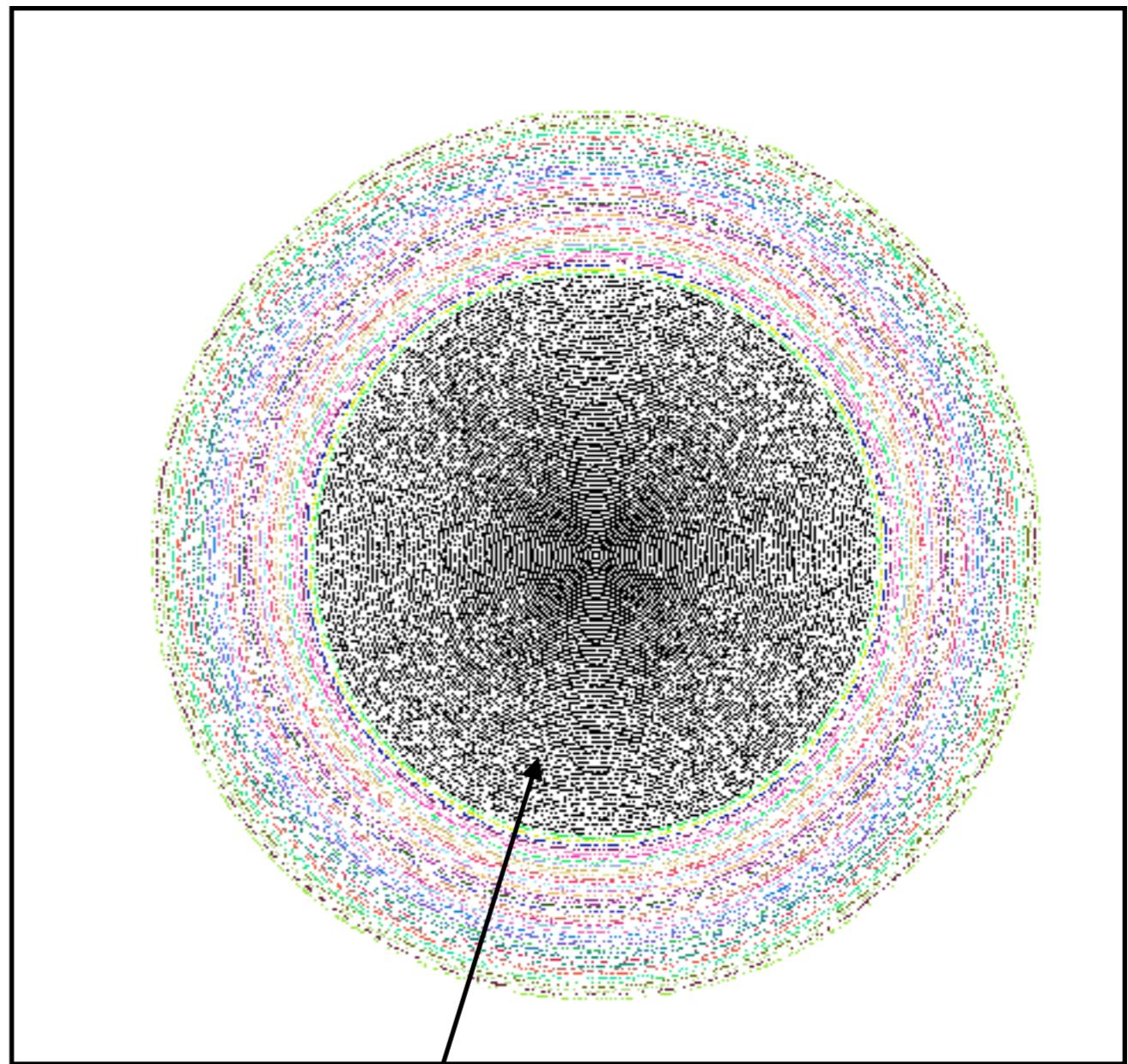
Necrotic Core



Without the core



Our model is up to 4 billion



Necrotic Core

Future Work

- Adjust/compare models.
- Code the drug component.
- Code for differential landscapes.
- Data analysis code.