Tracing genealogy within an invasion wave

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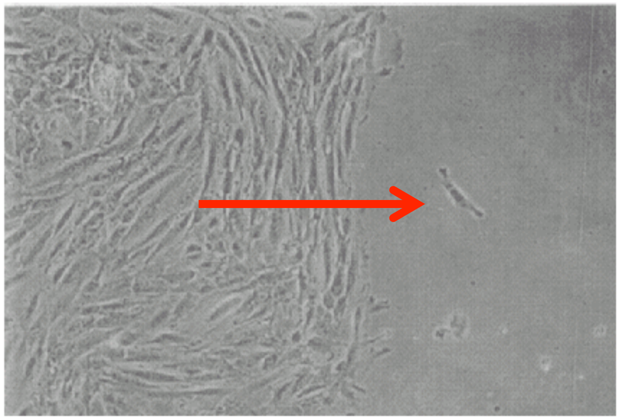
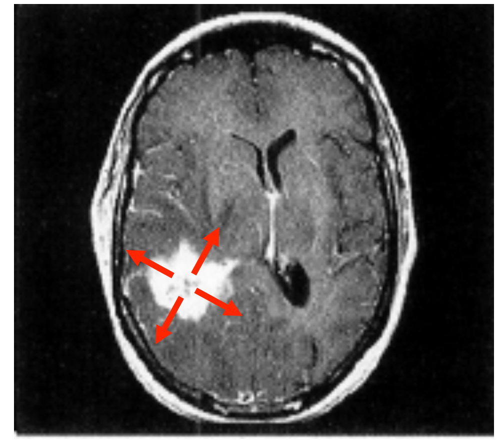
SIAM – PD15

Cell and species invasion

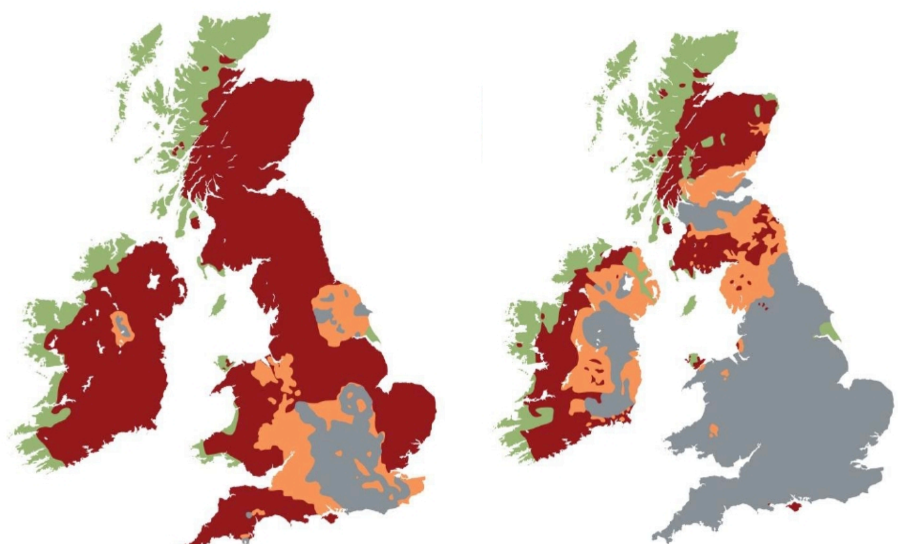


Maini et al, Tissue Eng (2004)



Spence et al, J Nuclear Med 45 (2004)

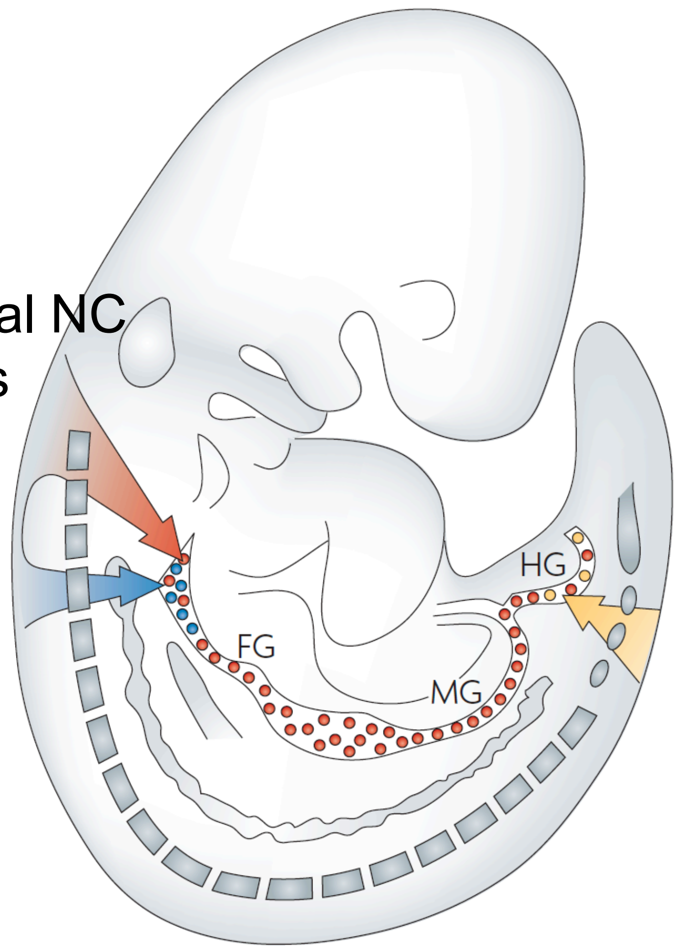
1945 2000

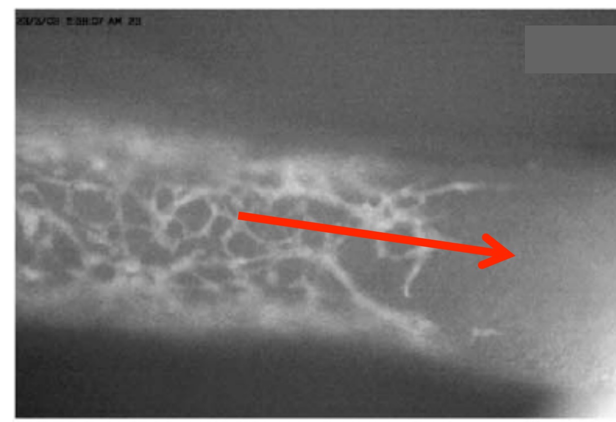


Squirrel populations

The brain in your gut: enteric nervous system (ENS)

ENS development in vertebrates: Neural crest cell invasion



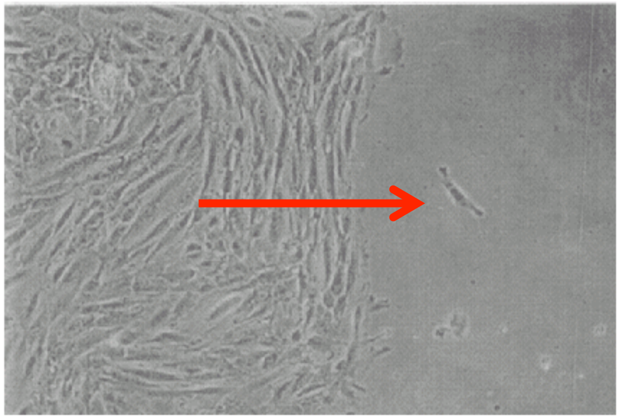


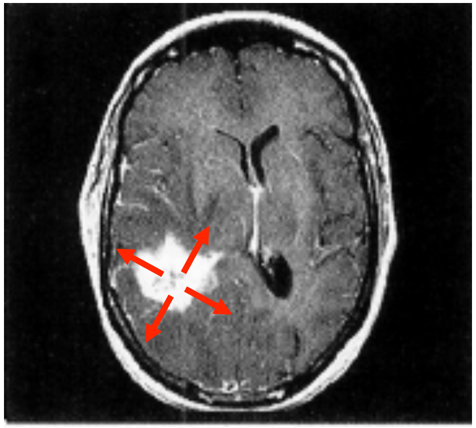
Young et al. Dev Biol 270 (2004)

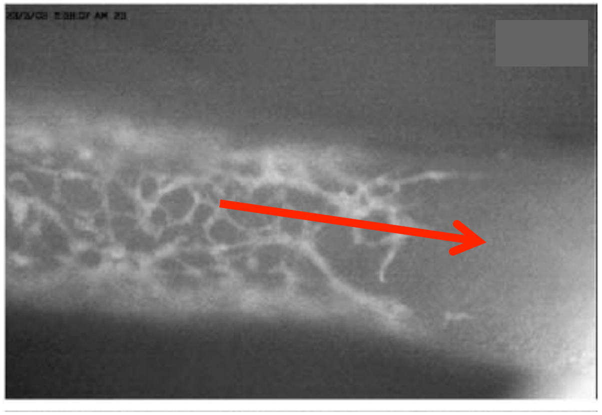
cells move and undergo cell division

Heanue & Pachnis, Nature Reviews 8 (2007)

Cell and species invasion: travelling waves

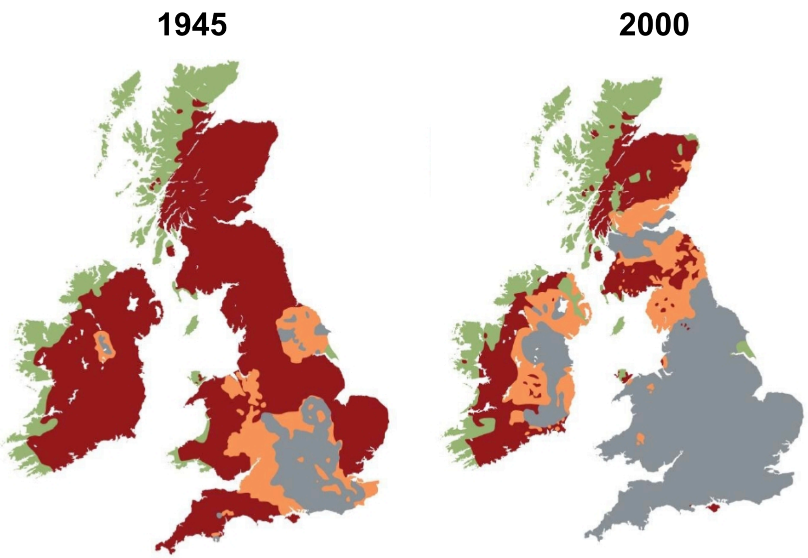






$$\frac{\partial u}{\partial t} = \underbrace{D\frac{\partial^2 u}{\partial x^2}}_{\text{Motility}} + \underbrace{\lambda u\left(1 - \frac{u}{K}\right)}_{\text{Proliferation}}$$

Fisher's equation (1937)



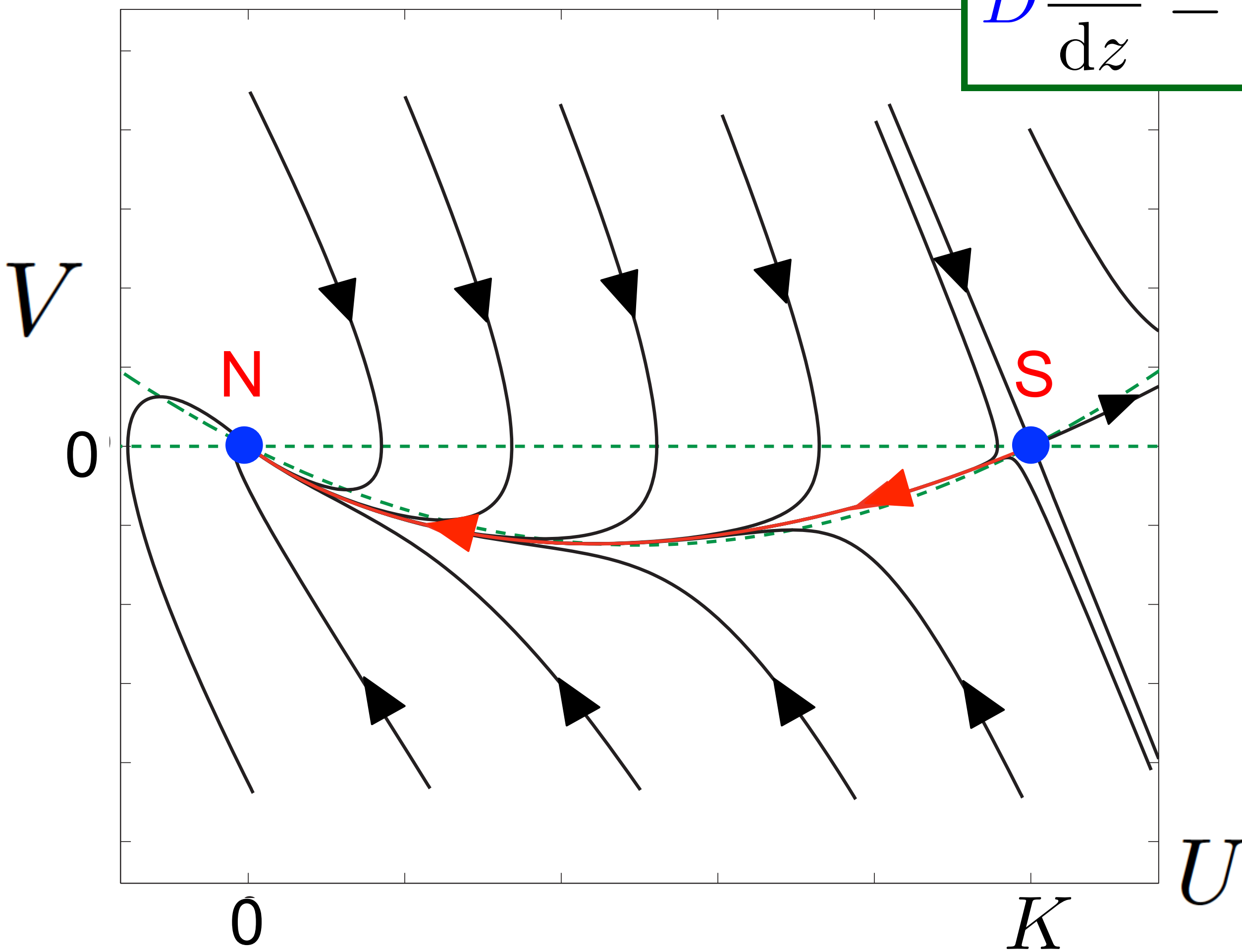
Fisher's travelling wave

$$z = x - c\,t$$

$$u(x,t) = U(z)$$

$$\frac{\mathrm{d}U}{\mathrm{d}z} = V$$

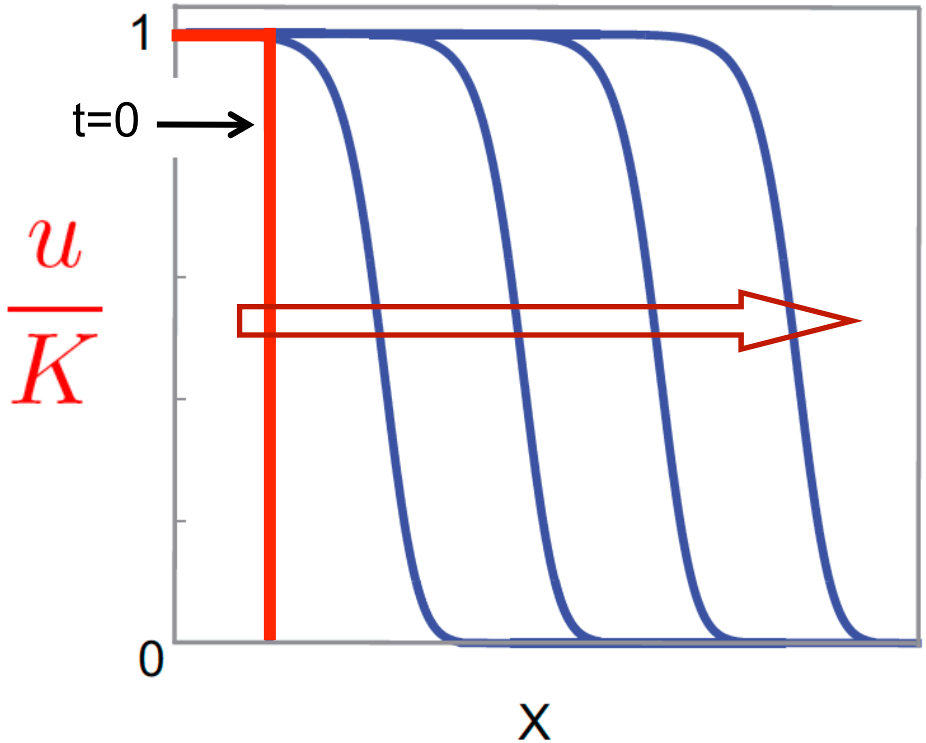
$$D\frac{\mathrm{d}V}{\mathrm{d}z} = -cV - \lambda U(1 - \frac{U}{K})$$



At (0,0), stable node, not focus

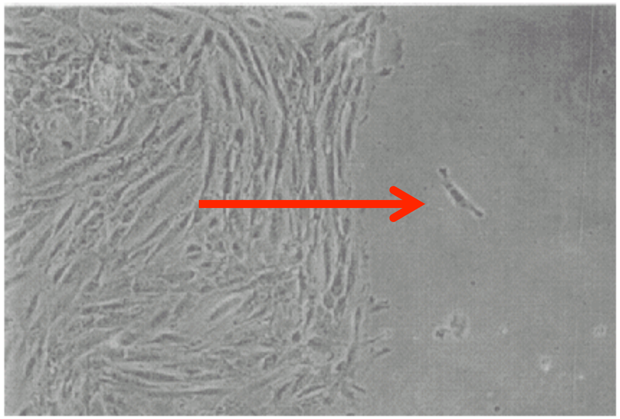
$$c \geq 2\sqrt{D\lambda}$$

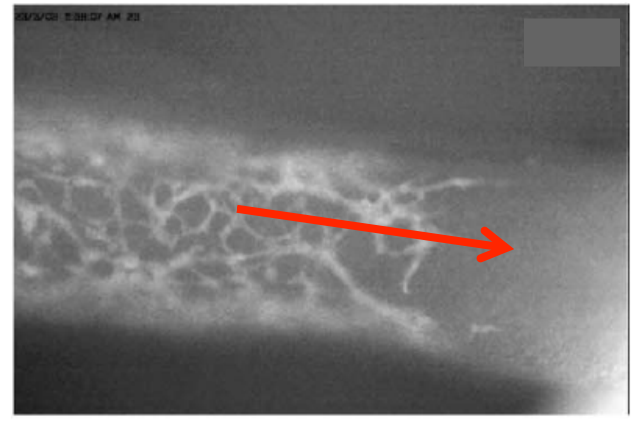
Fisher's travelling wave



Wave speed: $$c = 2\sqrt{D\lambda}$$

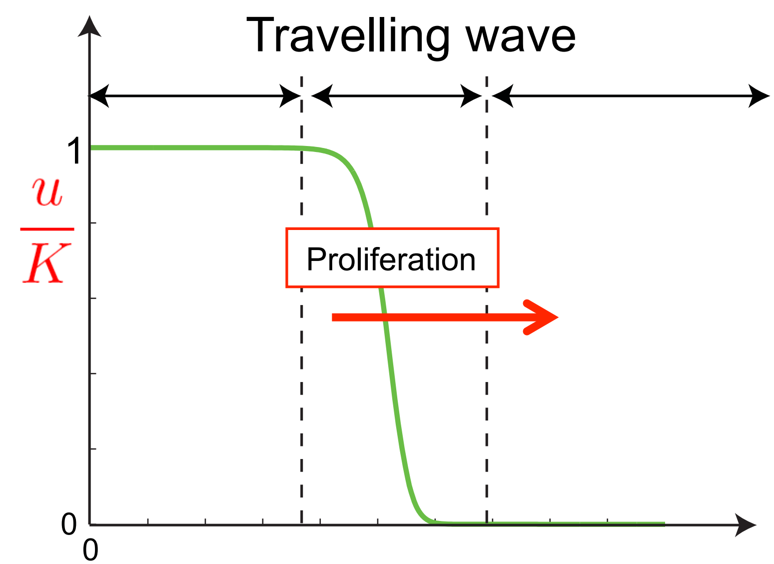
Invasion models: Fisher's travelling wave



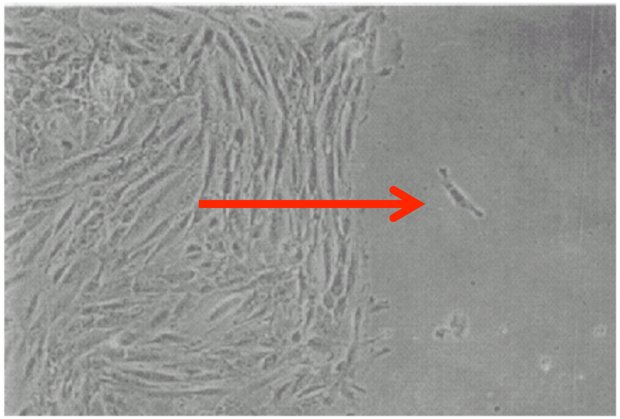


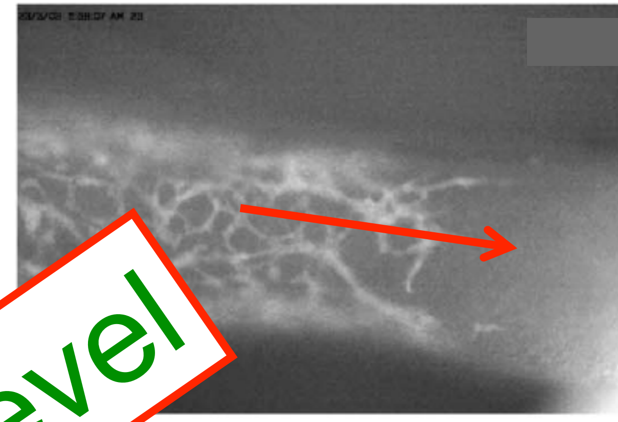
$$\frac{\partial u}{\partial t} = \underbrace{D\frac{\partial^2 u}{\partial x^2}}_{\text{Motility}} + \underbrace{\lambda u\left(1 - \frac{u}{K}\right)}_{\text{Proliferation}}$$

$$c = 2\sqrt{D\lambda}$$ parameter estimation



Invasion models: Fisher's travelling wave



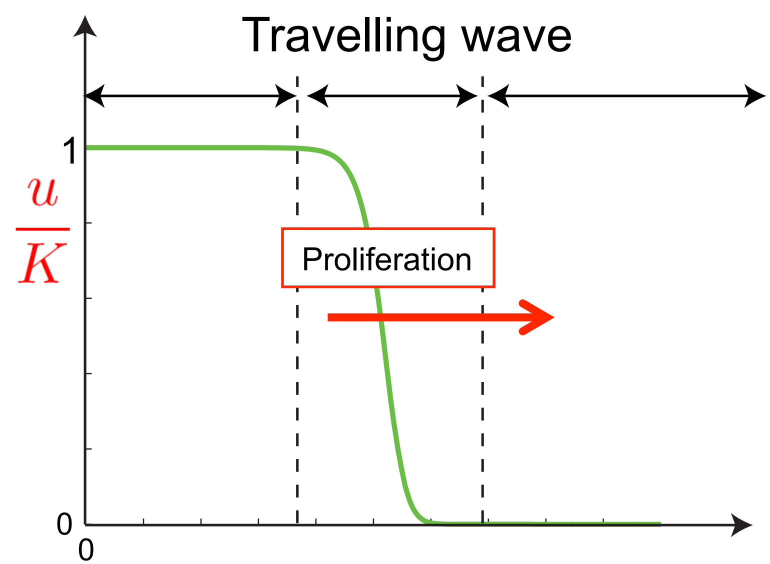


Population-level

$$\frac{\partial u}{\partial t} = \underbrace{D\frac{\partial^2 u}{\partial x^2}}_{\text{Motility}} \; \ldots \; - \frac{u}{K})$$

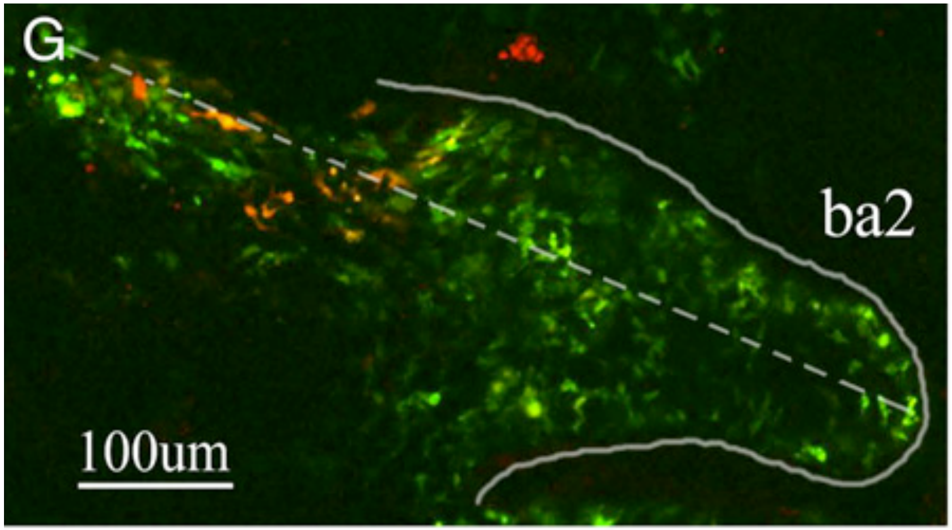
Motility

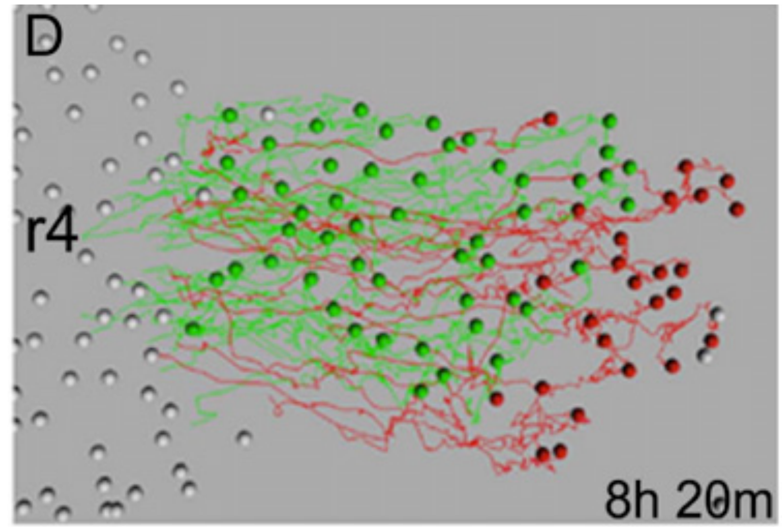
Proliferation



$c = 2\sqrt{D\lambda}$ parameter estimation

Cell labelling, tracking paths and progeny





Kulesa et al. Development, 316 (2008)

Develop. Growth Differ. (2013) **55**, 563–578

Review Article

The Japanese Society of Developmental Biologists

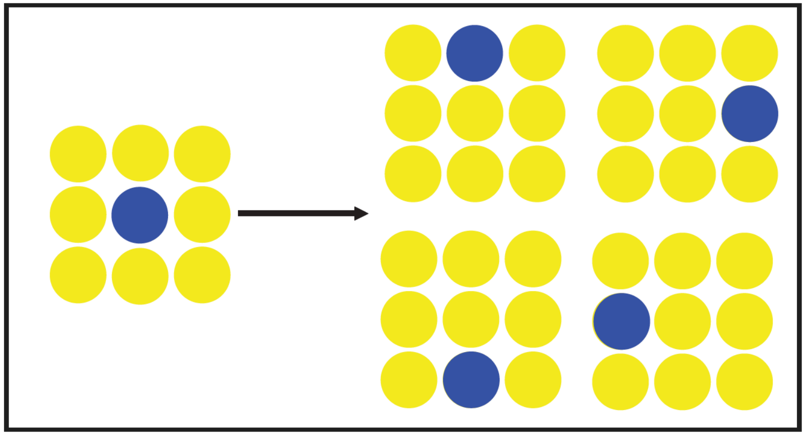
Towards comprehensive cell lineage reconstructions in complex organisms using light-sheet microscopy

Fernando Amat* and Philipp J. Keller*

Agent-based models

Lattice-based, stochastic, exclusion process

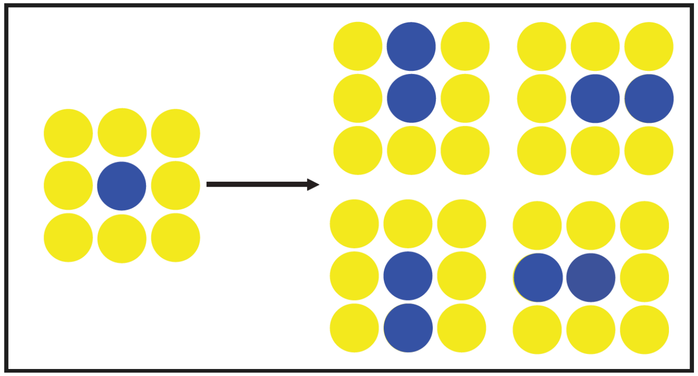
Motility P_m



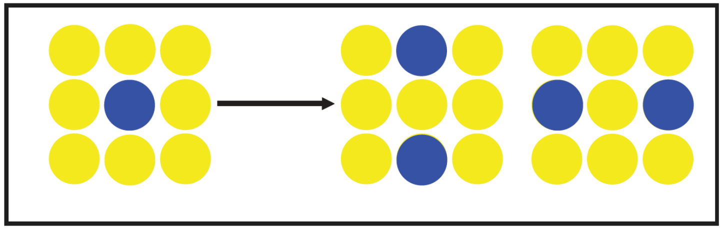
Blue agents, yellow lattice sites

No death

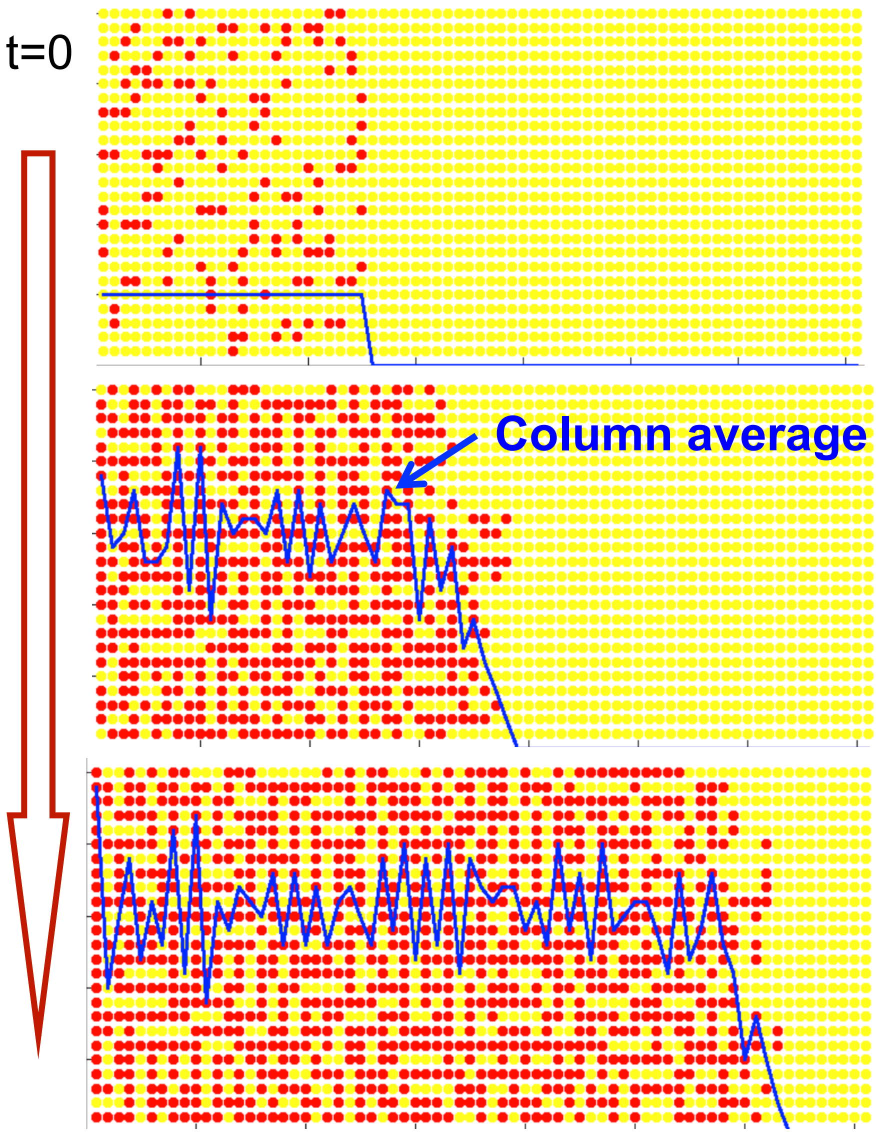
Proliferation P_p



or

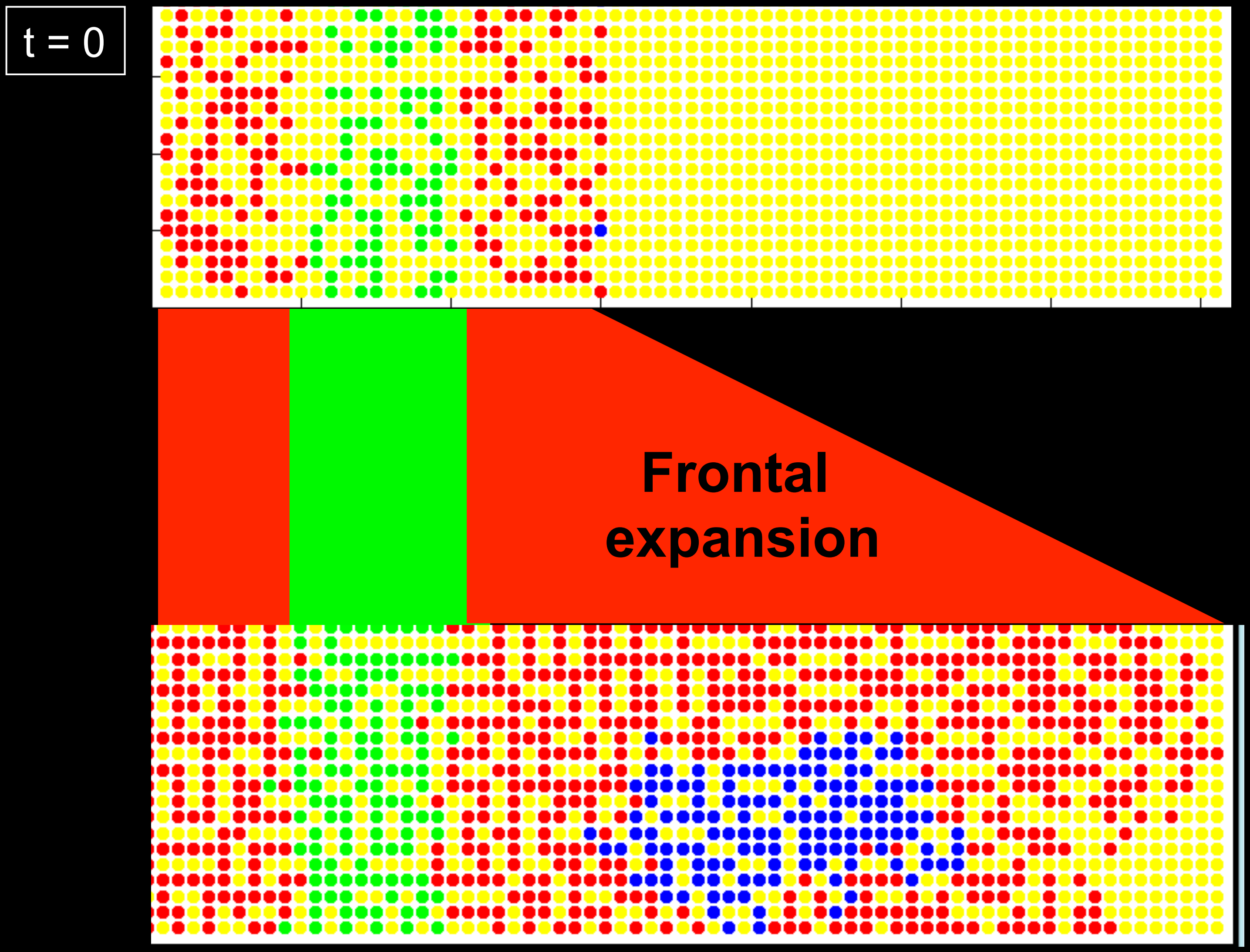


Reproduces Fisher's travelling wave

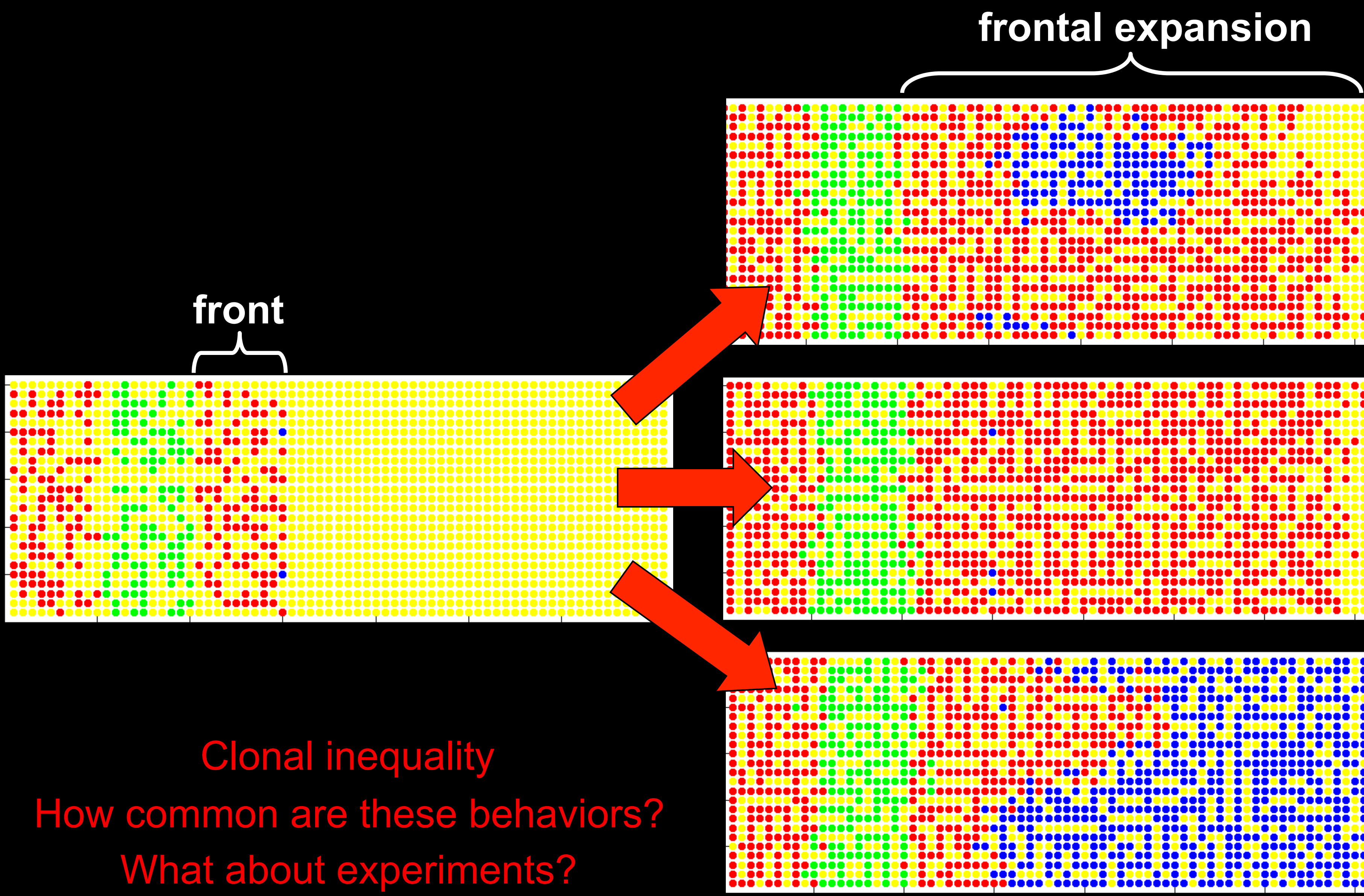


predictable

Frontal expansion



Variability in individual contributions



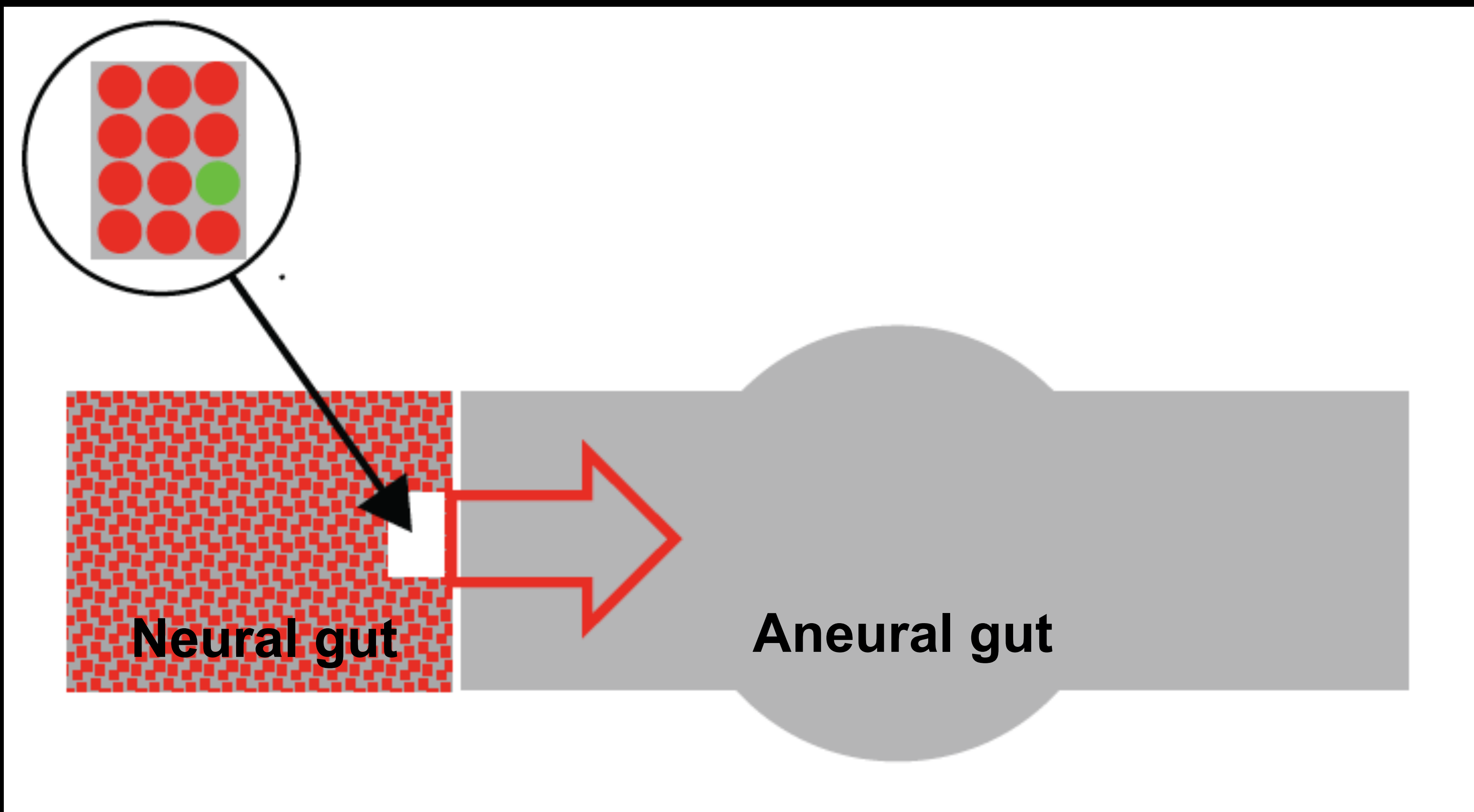
Clonal inequality

How common are these behaviors?

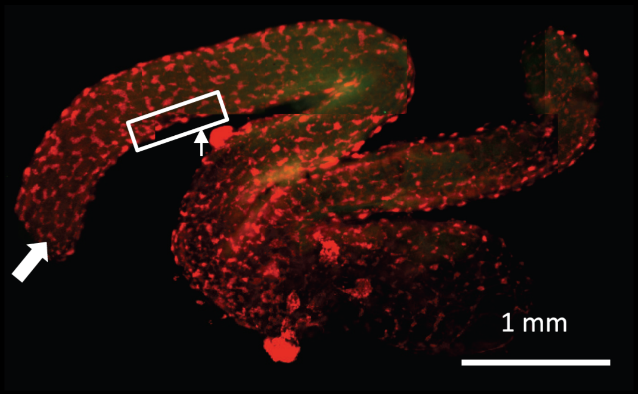
What about experiments?

Cloning in a crowd experiments: lineage tracing

One labeled cell…passes label to progeny

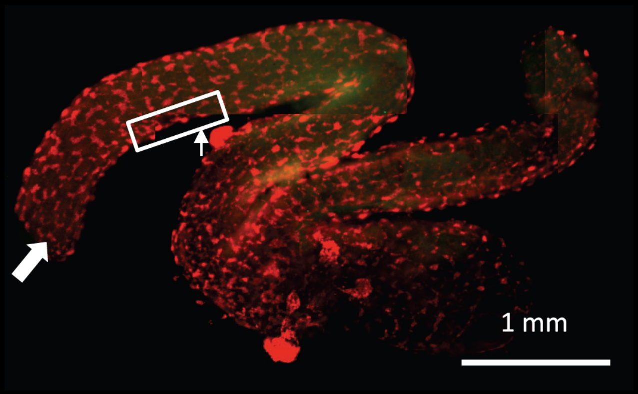


Cloning in a crowd results



Cell count	Frequency
1-99	42
100-199	1
200-299	0
300-399	0
400-499	1
500-599	2
600-699	1
700-799	2
800-899	2

Cloning in a crowd results



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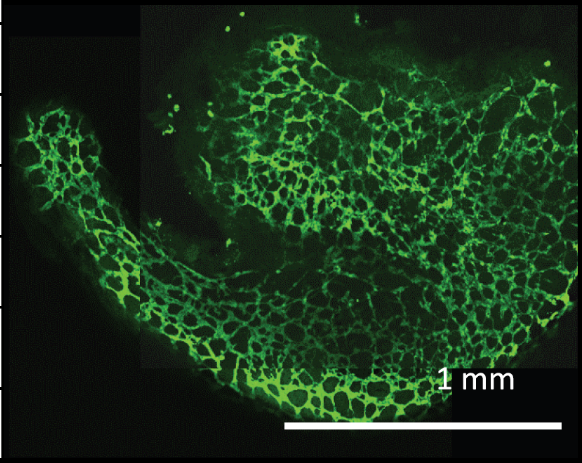
700-799	2
800-899	2
900-999	1
1000-1999	4
2000-2999	4
3000-3999	0
4000-4999	1
5000-20000	0
> 20000	1



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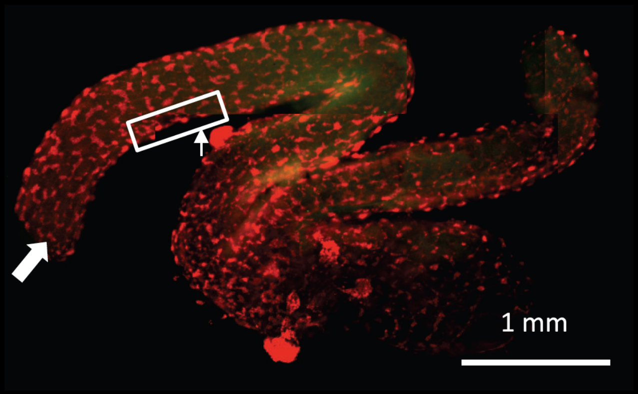

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4000-4999	1
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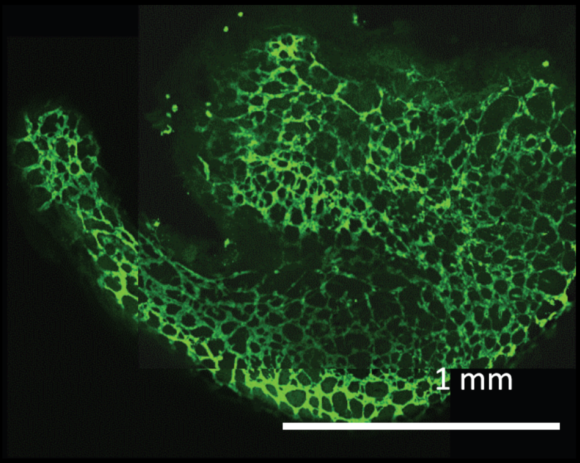
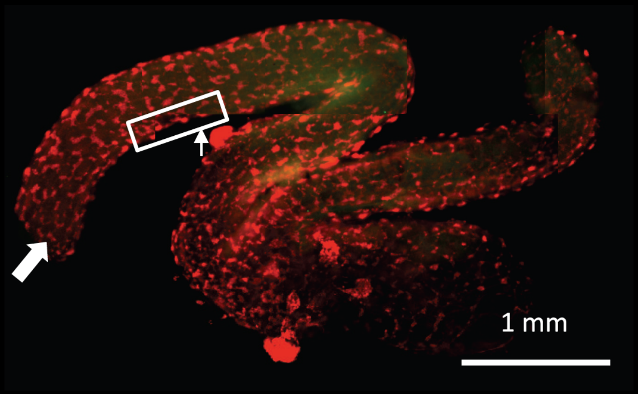
> 20000	1

Superstar



Cloning in a crowd results



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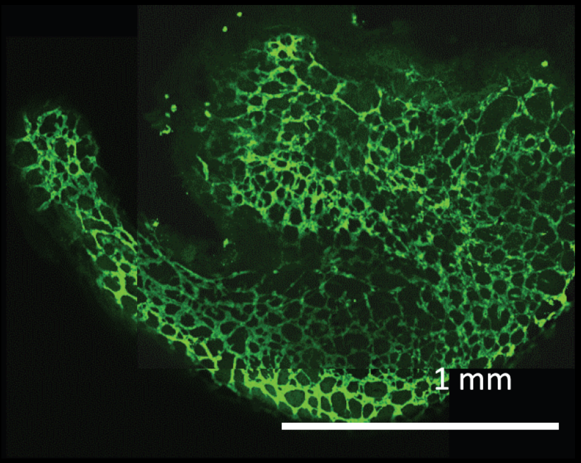
900-999	1
1000-1999	4
2000-2999	4
3000-3999	0
4000-4999	1
5000-20000	0
> 20000	1

Clonal inequality is real

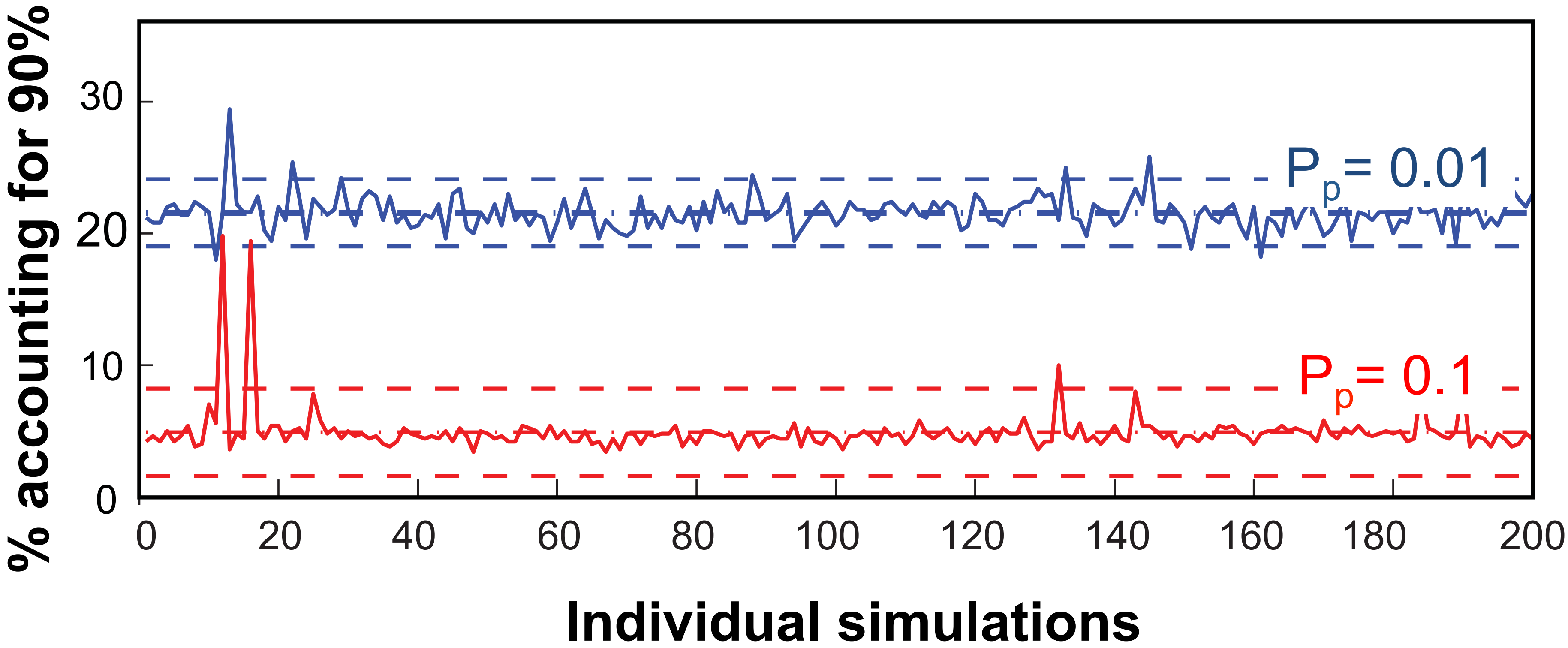
A few 'superstars' have a disproportionate contribution to the final population

Superstar



Superstars are always present

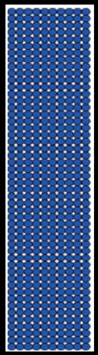
P_p= probability of proliferation



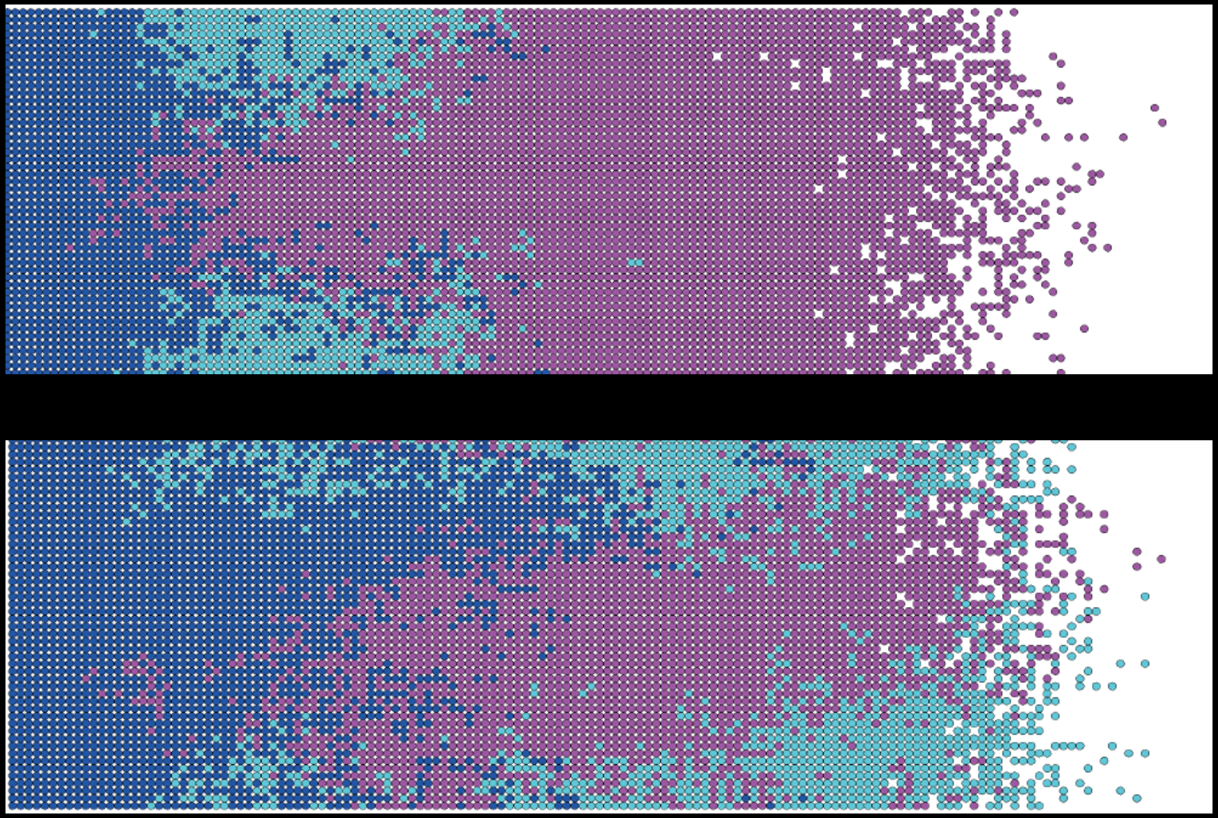
Superstars are not freaks – EVERY colonizing population, EVERY time, has a few superstars!

Agent lineage tracing

t = 0

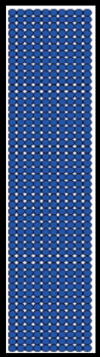


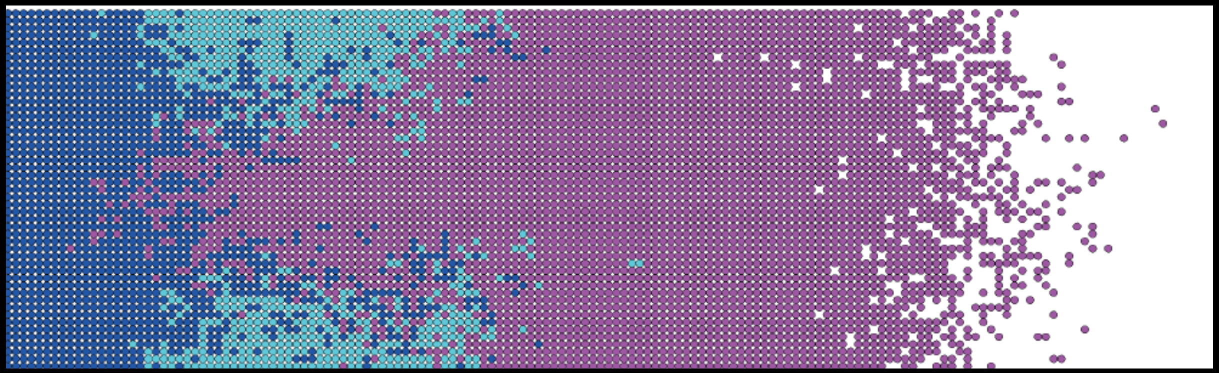
2 simulations: largest and 2nd largest tracings



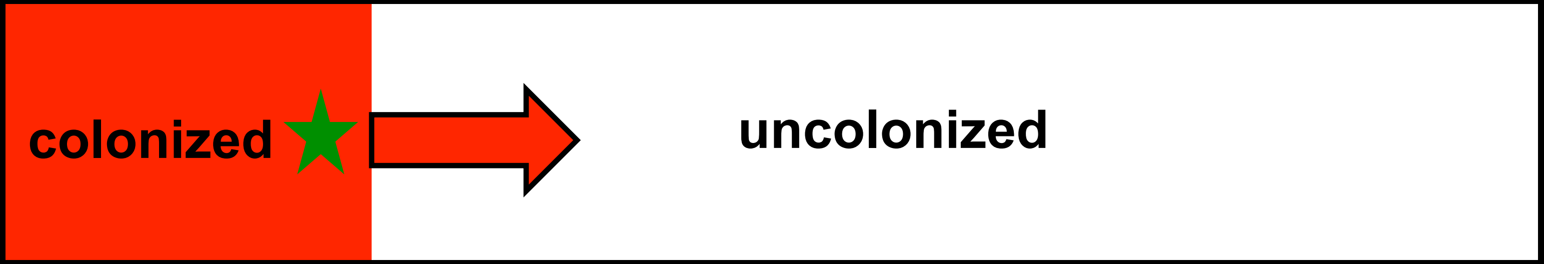
Analogy to a lottery

Differences





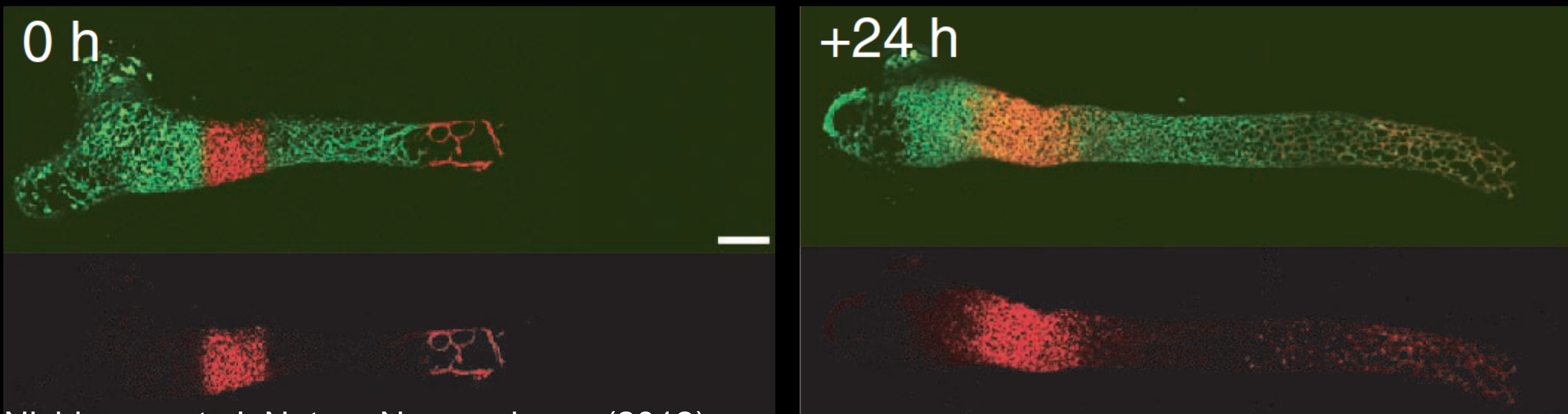
Every clone/lineage



Single clone/lineage

If tracing every cell lineage is not possible

- Track generations: Kikume GR

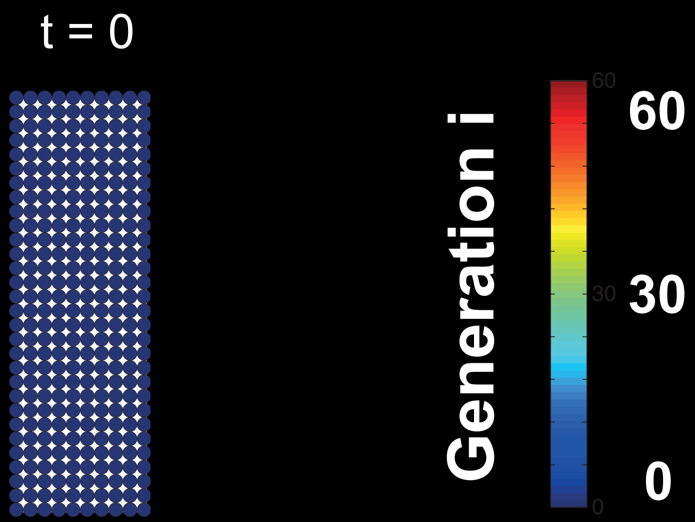


Nishiyama et al. Nature Neuroscience (2012)

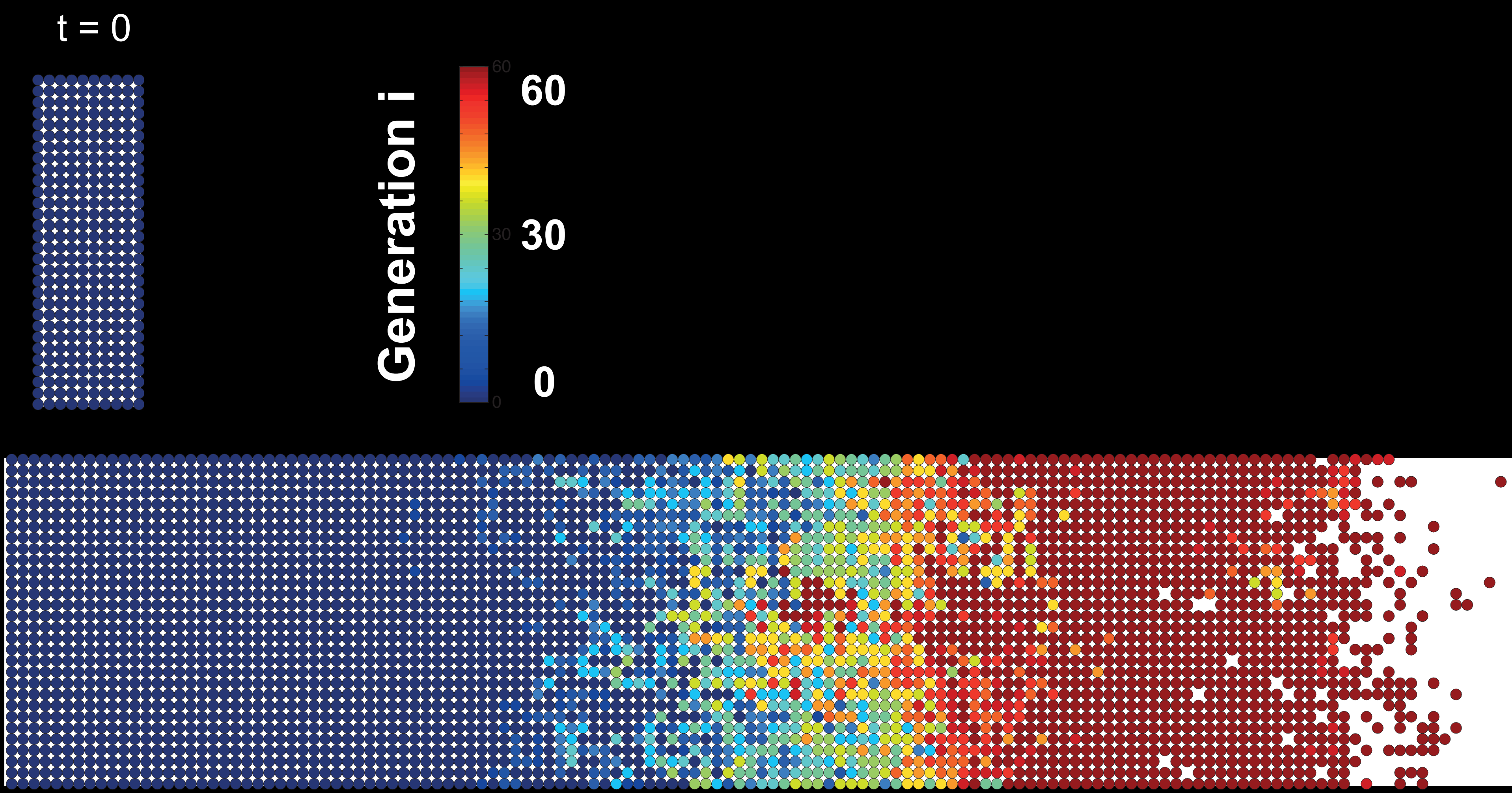
- From cell generation data, can we estimate cell lineages?

- Propose new technique

Spatial distribution of generation number



Spatial distribution of generation number



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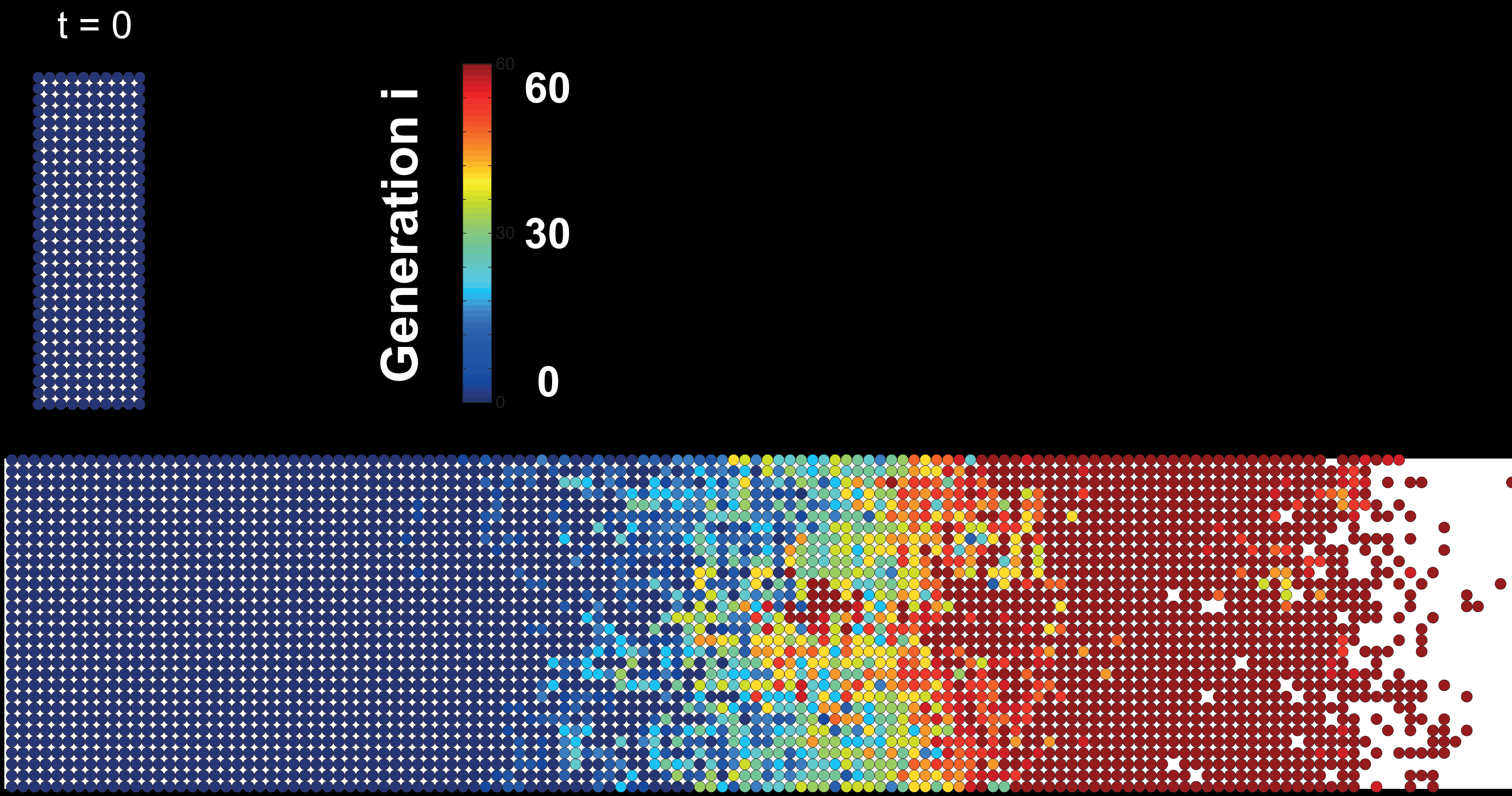

Can we describe with PDEs?

Multi-species model of cell generations

Multi-species model of cell generations

Generation i and time step k

$$n_i^k(\mathbf{v})$$

$$c^k(\mathbf{v}) = \sum_{i=0}^{\infty} n_i^k(\mathbf{v})$$

Multi-species model of cell generations

Generation i and time step k

$$n_i^k(\mathbf{v})$$

$$c^k(\mathbf{v}) = \sum_{i=0}^{\infty} n_i^k(\mathbf{v})$$

Master equation for motility part

$$n_i^{k+1}(\mathbf{v}) - n_i^k(\mathbf{v}) \ =$$

Multi-species model of cell generations

Generation i and time step k

$$n_i^k(\mathbf{v}) \qquad\qquad c^k(\mathbf{v}) = \sum_{i=0}^{\infty} n_i^k(\mathbf{v})$$

Master equation for motility part

$$n_i^{k+1}(\mathbf{v}) - n_i^k(\mathbf{v}) = -\frac{P_m}{4}\, n_i^k(\mathbf{v}) \sum_{\mathbf{v}'\in\mathcal{N}(\mathbf{v})} \underbrace{\left[1 - c^k(\mathbf{v}')\right]}_{\text{exclusion}}$$

Mean-field approximation

Multi-species model of cell generations

Generation i and time step k

$$n_i^k(\mathbf{v}) \qquad\qquad c^k(\mathbf{v}) = \sum_{i=0}^{\infty} n_i^k(\mathbf{v})$$

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Mean-field approximation

$$+\frac{P_m}{4} \underbrace{\left[1 - c^k(\mathbf{v})\right]}_{\text{exclusion}} \sum_{\mathbf{v}' \in \mathcal{N}(\mathbf{v})} n_i^k(\mathbf{v}')$$

Multi-species model of cell generations

Generation i and time step k

$$n_i^k(\mathbf{v}) \qquad\qquad c^k(\mathbf{v}) = \sum_{i=0}^{\infty} n_i^k(\mathbf{v})$$

Master equation for motility part

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Mean-field approximation

$$+\frac{P_m}{4} \underbrace{\left[1 - c^k(\mathbf{v})\right]}_{\text{exclusion}} \sum_{\mathbf{v}' \in \mathcal{N}(\mathbf{v})} n_i^k(\mathbf{v}')$$

Continuum limit

$$x = \Delta \mathbf{v}\ ,\ t = k\tau$$

$$n_i^k(\mathbf{v}) = n_i(\mathbf{x}, t)\ ,\ c^k(\mathbf{v}) = C(\mathbf{x}, t)$$

$$D = \frac{P_m}{4} \lim_{\Delta, \tau \to 0} \frac{\Delta^2}{\tau}$$

Multi-species model of cell generations

Total density $$C(x,t) = \sum_{i=0}^{\infty} n_i(x,t)$$ density of generation i

$$\frac{\partial n_i}{\partial t} = D\frac{\partial}{\partial x}\left((1-C)\frac{\partial n_i}{\partial x} + n_i\frac{\partial C}{\partial x}\right)$$

$$+$$

Multi-species model of cell generations

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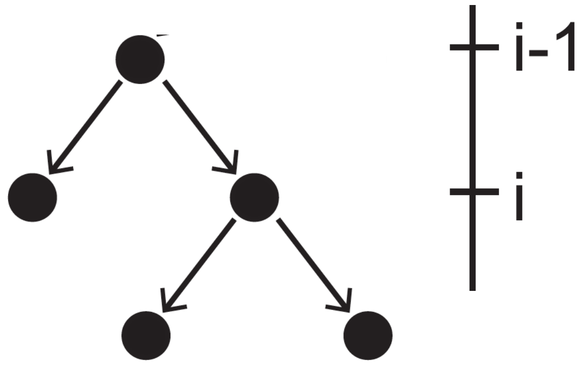
$i = 1, 2, \ldots$



$$\lambda = \lim_{\tau \to 0} \frac{P_p}{\tau}$$

Multi-species model of cell generations

Total density $$C(x,t) = \sum_{i=0}^{\infty} n_i(x,t)$$ density of generation i

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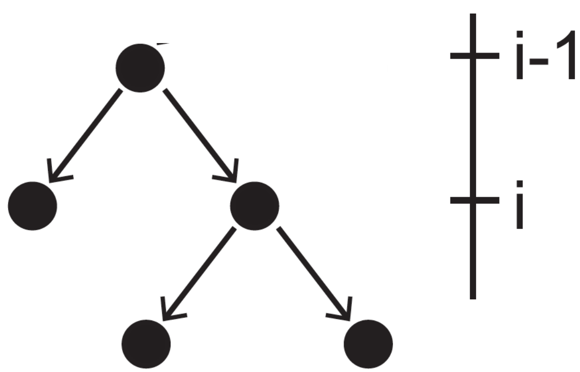
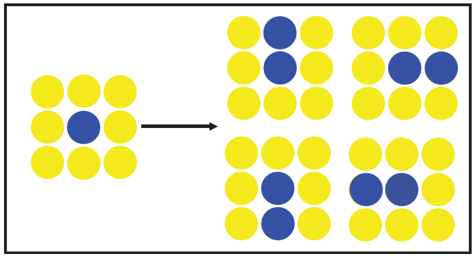


exclusion



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$i = 1, 2, \ldots$

$$\frac{\partial n_0}{\partial t} = D\frac{\partial}{\partial x}\left((1-C)\frac{\partial n_0}{\partial x} + n_0\frac{\partial C}{\partial x}\right) - \lambda n_0(1-C)$$

Multi-species model of cell generations

Total density $$C(x,t) = \sum_{i=0}^{\infty} n_i(x,t)$$ density of generation i

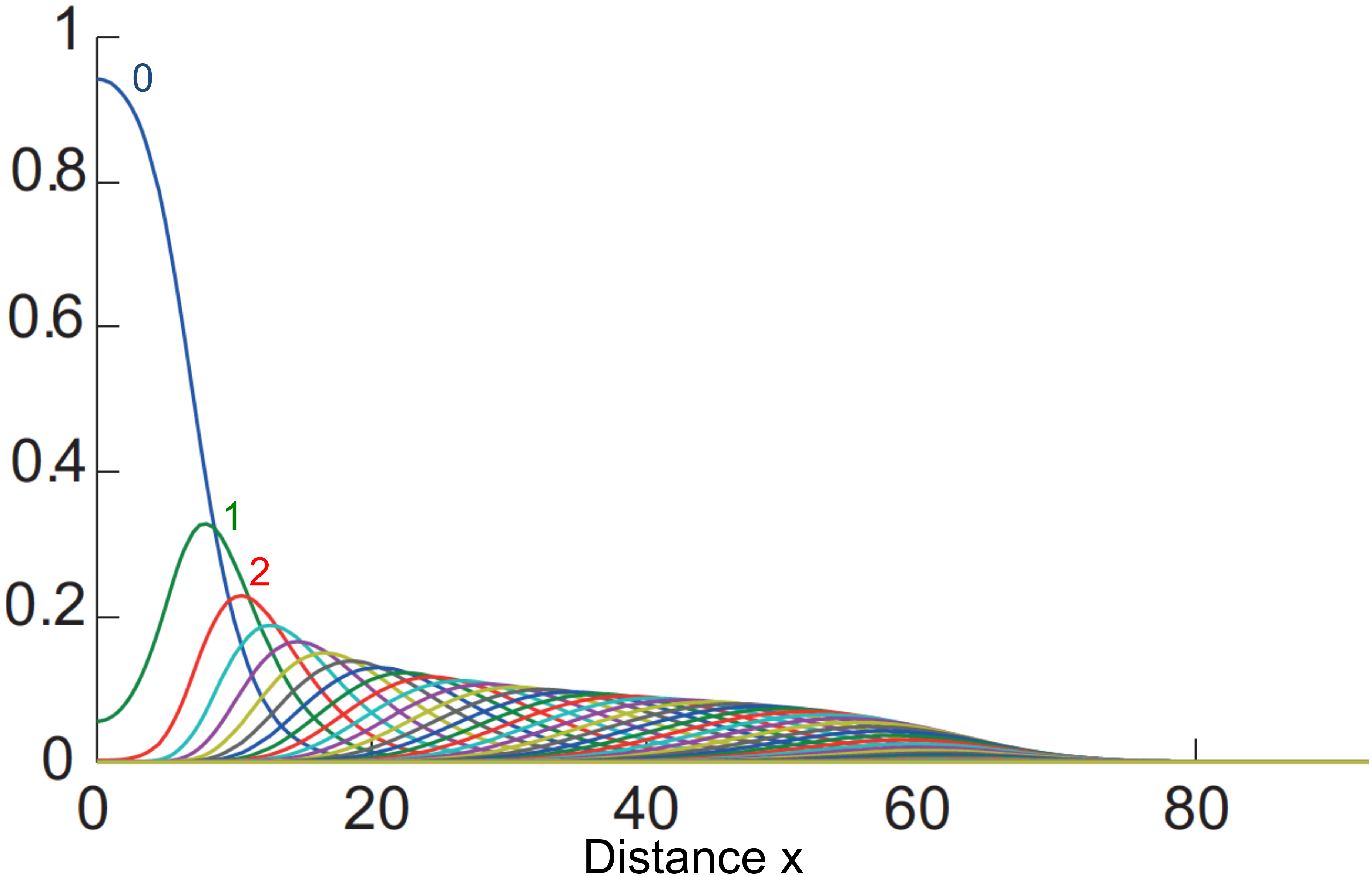
$$\frac{\partial n_i}{\partial t} = D\frac{\partial}{\partial x}\left((1-C)\frac{\partial n_i}{\partial x} + n_i\frac{\partial C}{\partial x}\right) + \lambda(2n_{i-1} - n_i)(1-C)$$

$i = 1, 2, \ldots$

$$\frac{\partial n_0}{\partial t} = D\frac{\partial}{\partial x}\left((1-C)\frac{\partial n_0}{\partial x} + n_0\frac{\partial C}{\partial x}\right) - \lambda n_0(1-C)$$

SUM all = Fisher eqn for C

Spatial distributions of generation density



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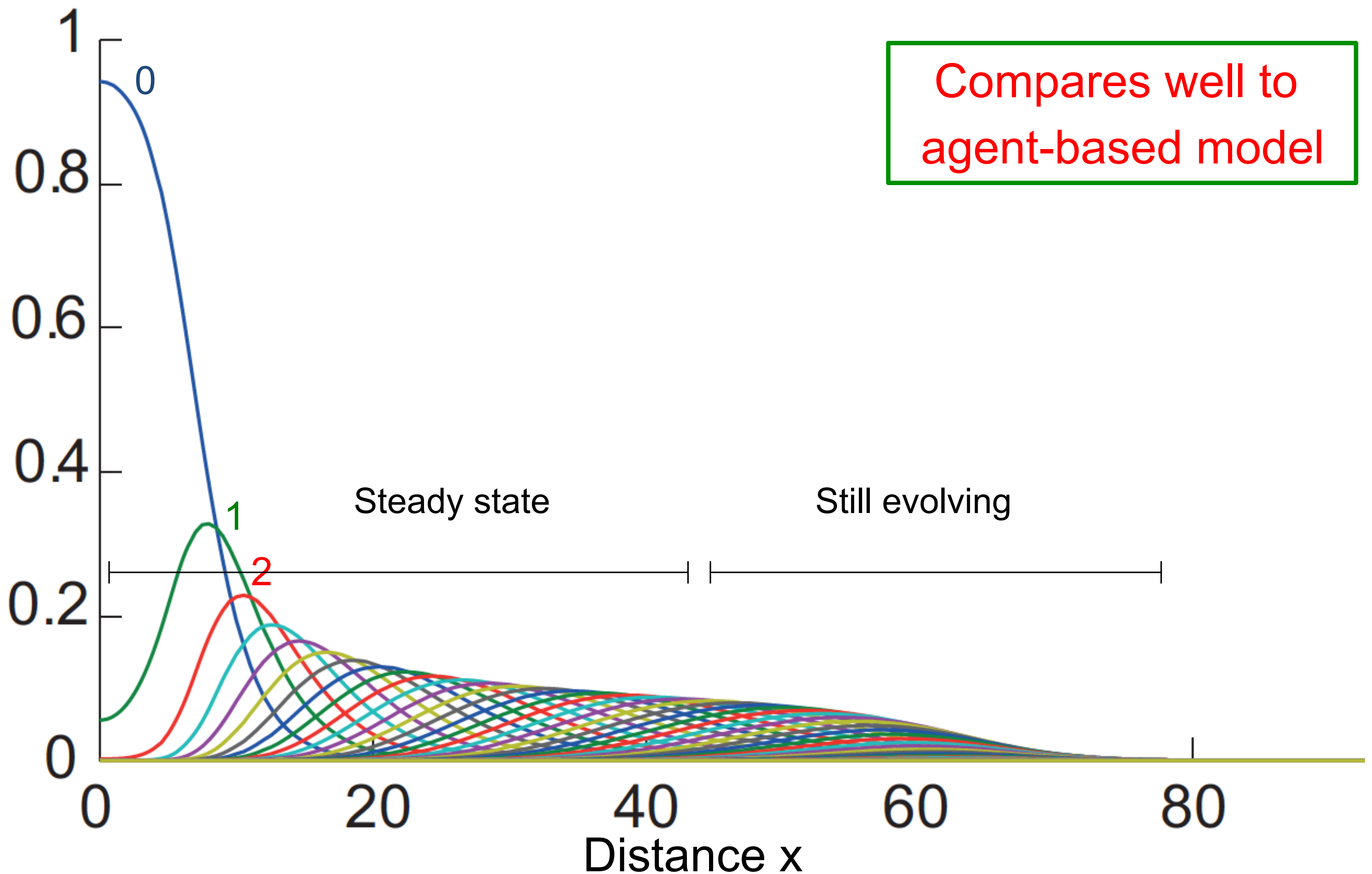

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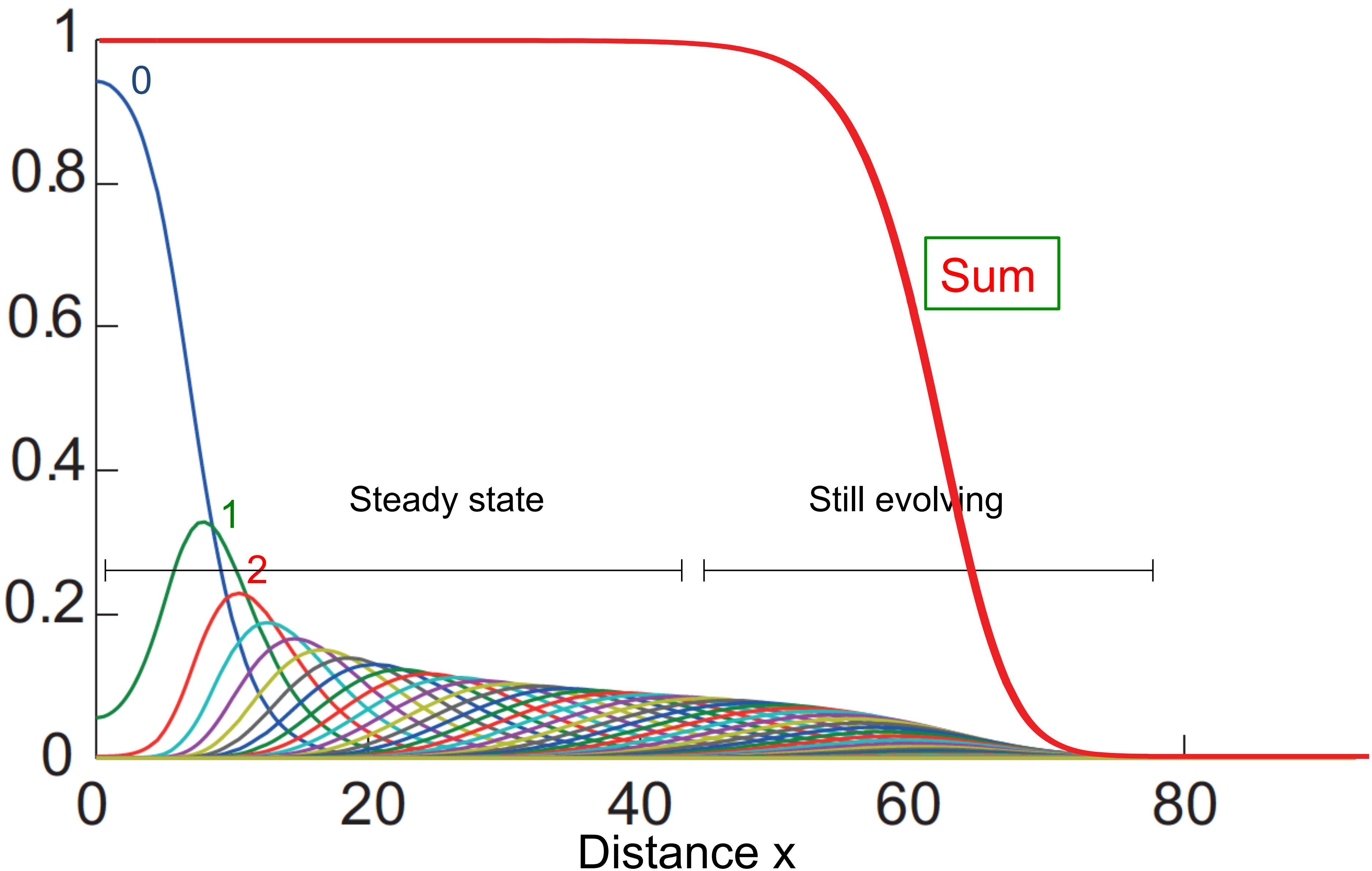

From regular generation profiles, can we predict lineage variability and superstars?

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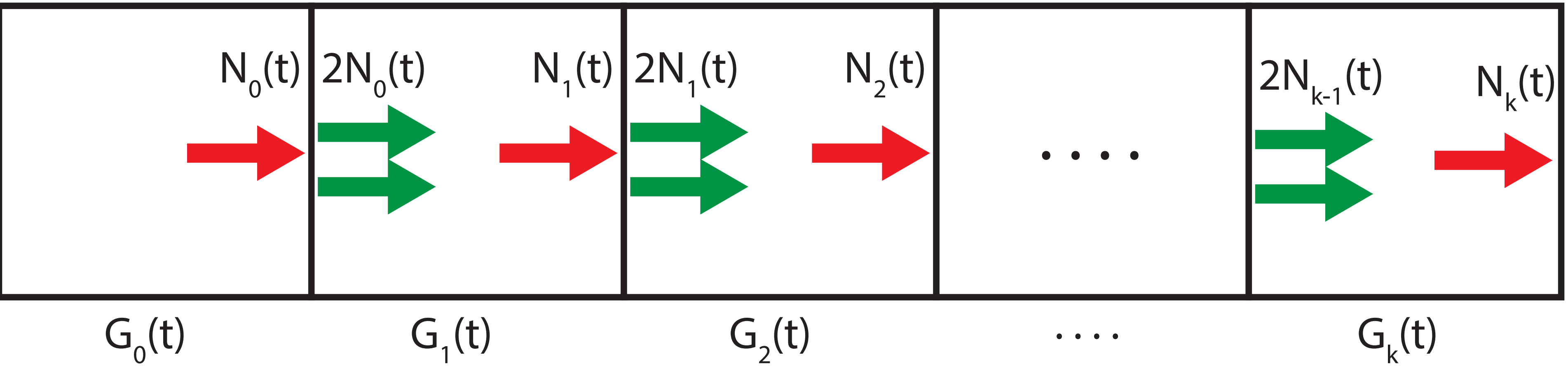
Flow between generations at time t:



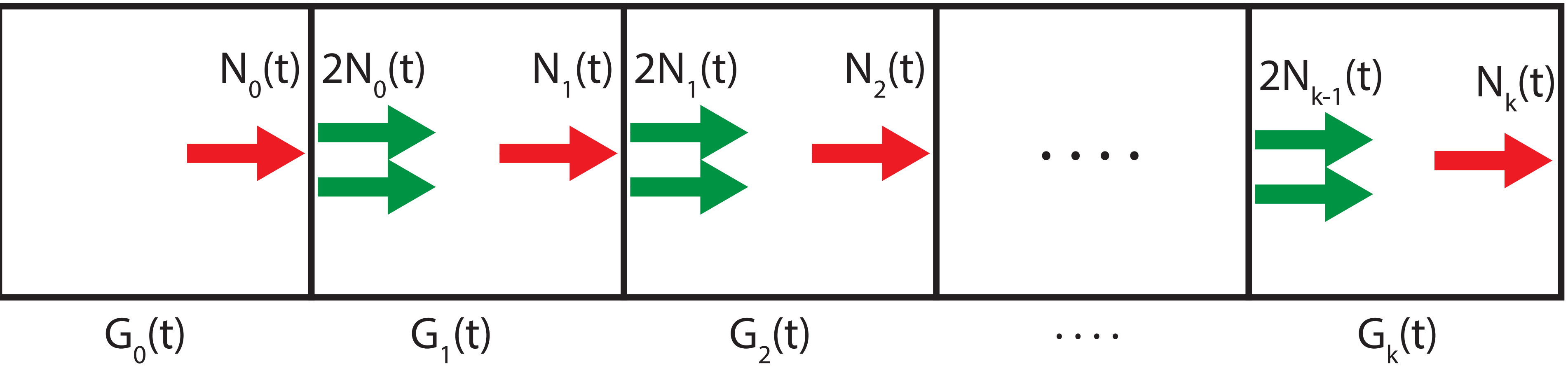
$$G_i(t) = \int_0^\infty n_i(x,t)\,dx$$ # cells in i^{th} generation at time t

(known)

$$N_i(t)$$ # cells that have undergone cell division in i^{th} generation by time t

From regular generation profiles, can we predict lineage variability and superstars?

Flow between generations at time t:



$$G_i(t) = \int_0^\infty n_i(x,t)dx$$

cells in i^th generation at time t

(known)

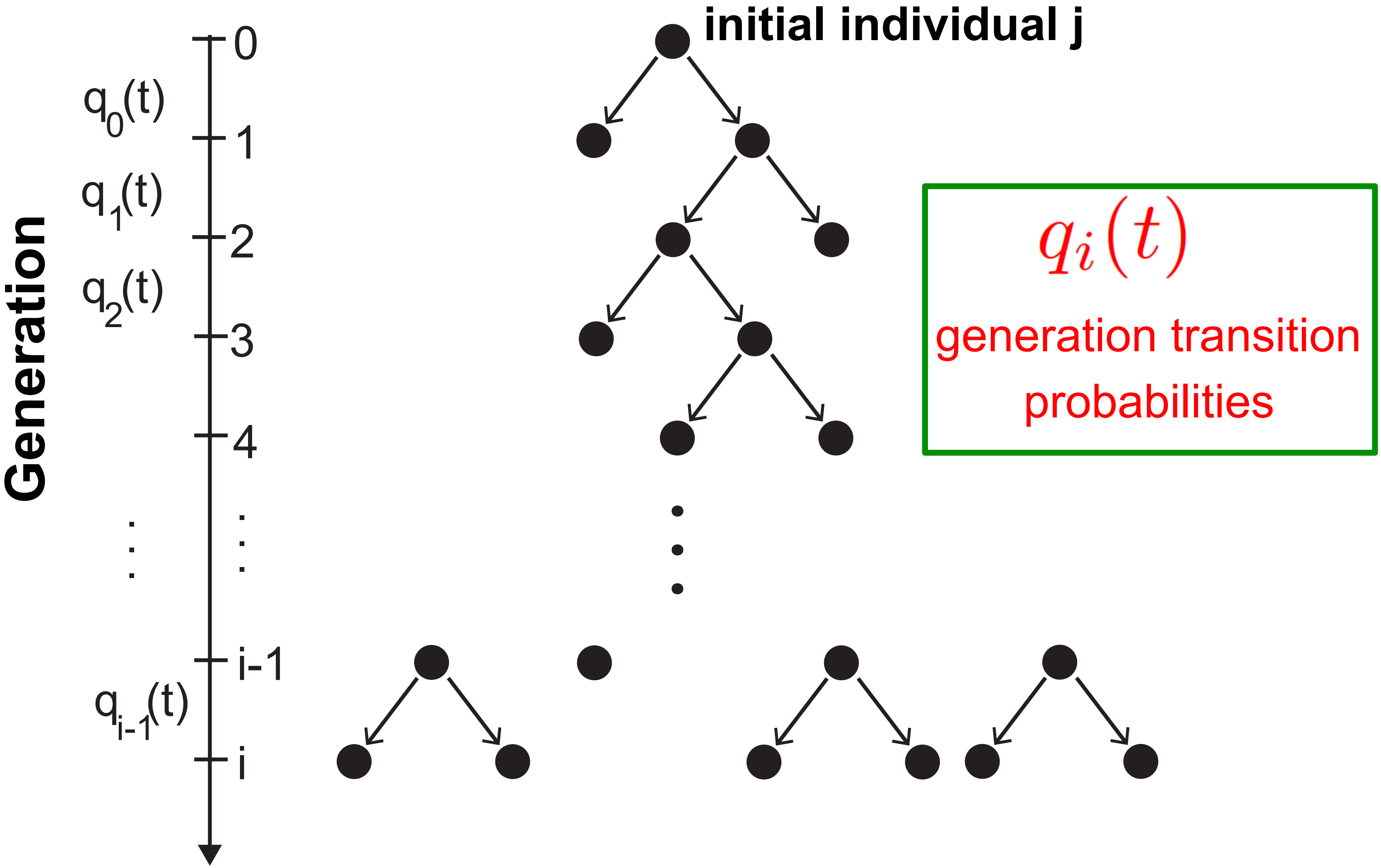
$$N_i(t)$$

cells that have undergone cell division in i^th generation by time t

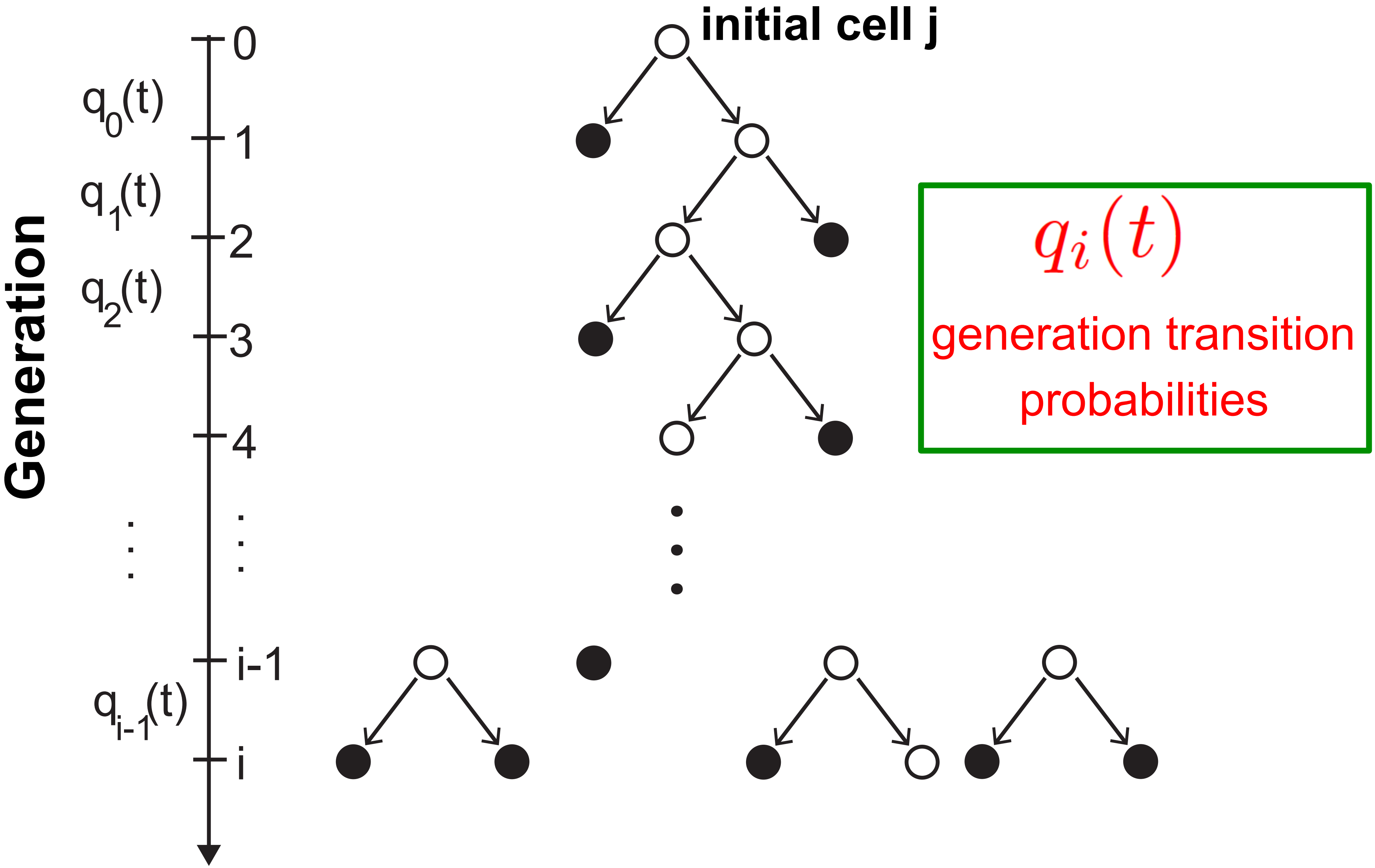
generation transition probabilities

$$N_i(t) = q_i(t)\ 2N_{i-1}(t)$$

Galton-Watson process: offspring



Galton-Watson process: cell division



Generation transition probabilities

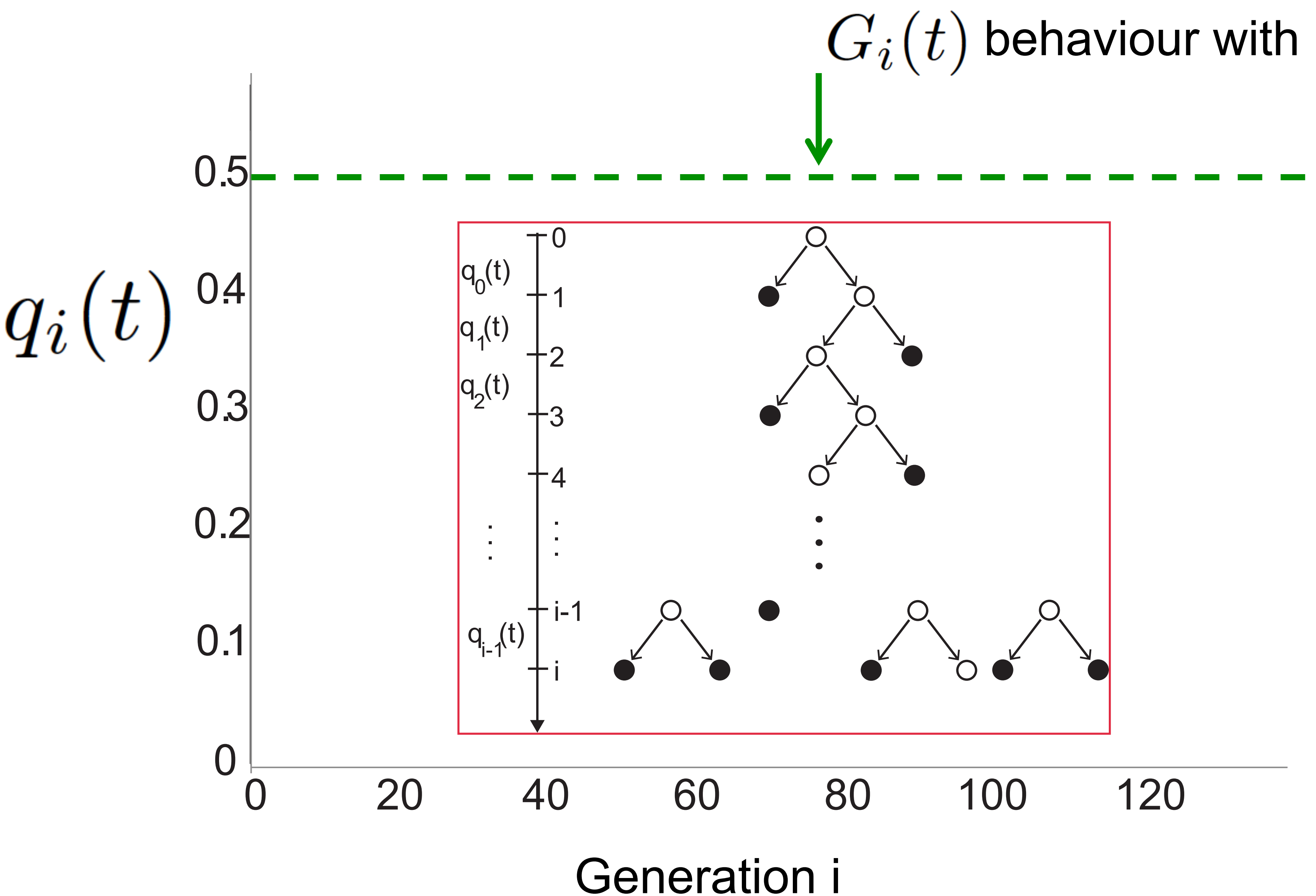
$$q_i(t) = F\Big(G_0(t), G_1(t), G_2(t), \ldots G_i(t)\Big)$$

$$i = 1, 2, 3 \ldots$$

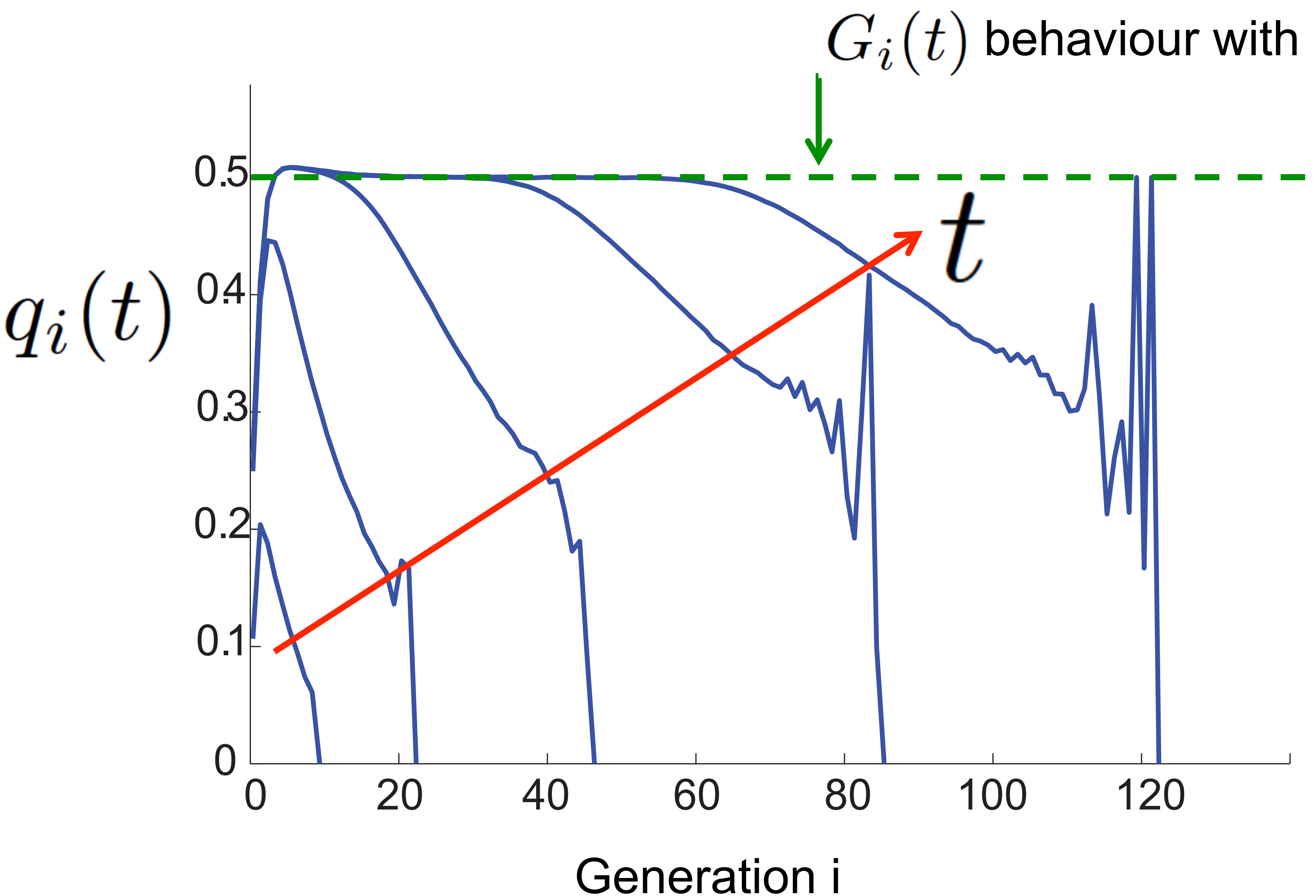
$$q_0(t) = 1 - \frac{G_0(t)}{G_0(0)}$$

$G_i(t)$ determined from PDE model

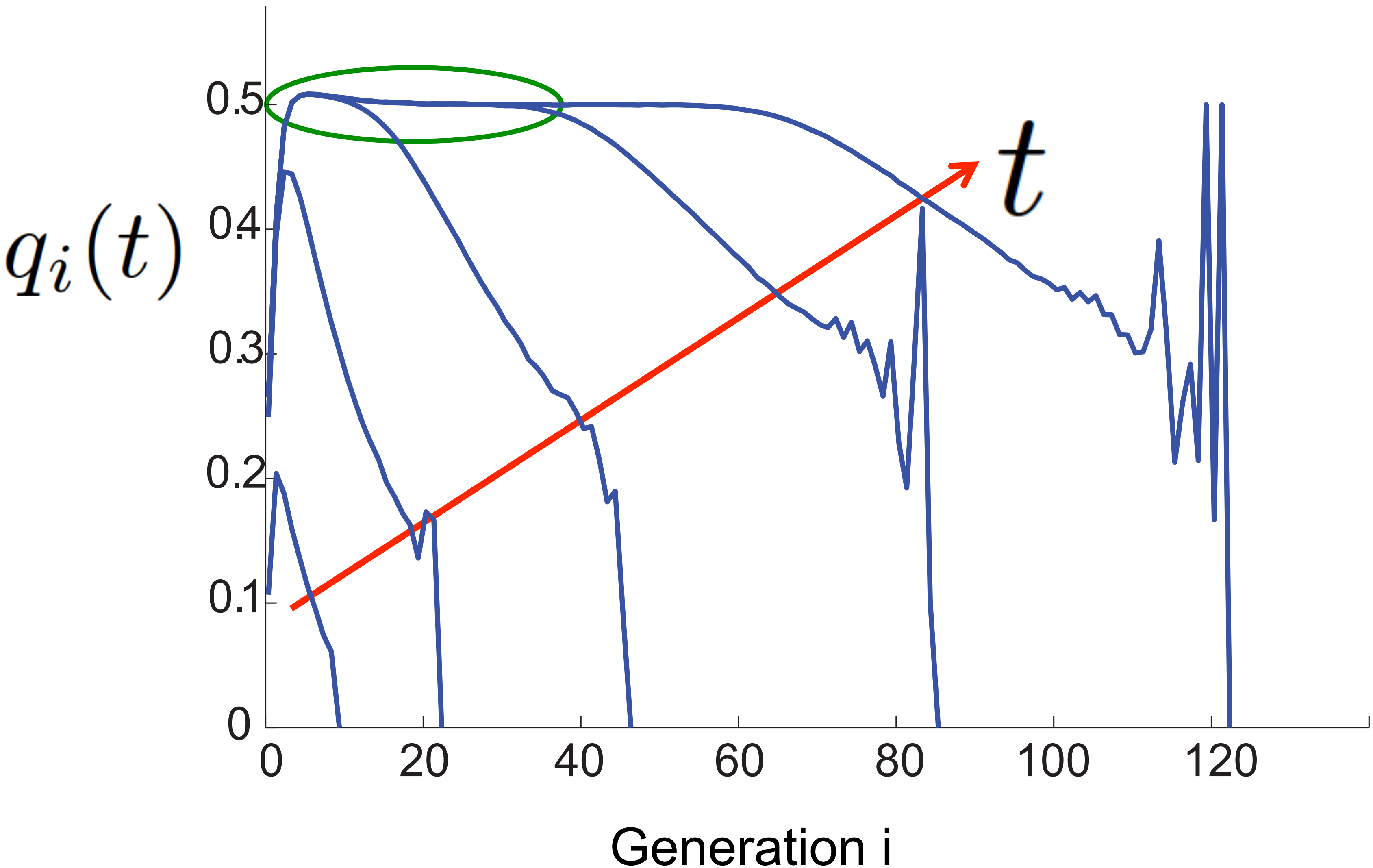
Generation transition probabilities



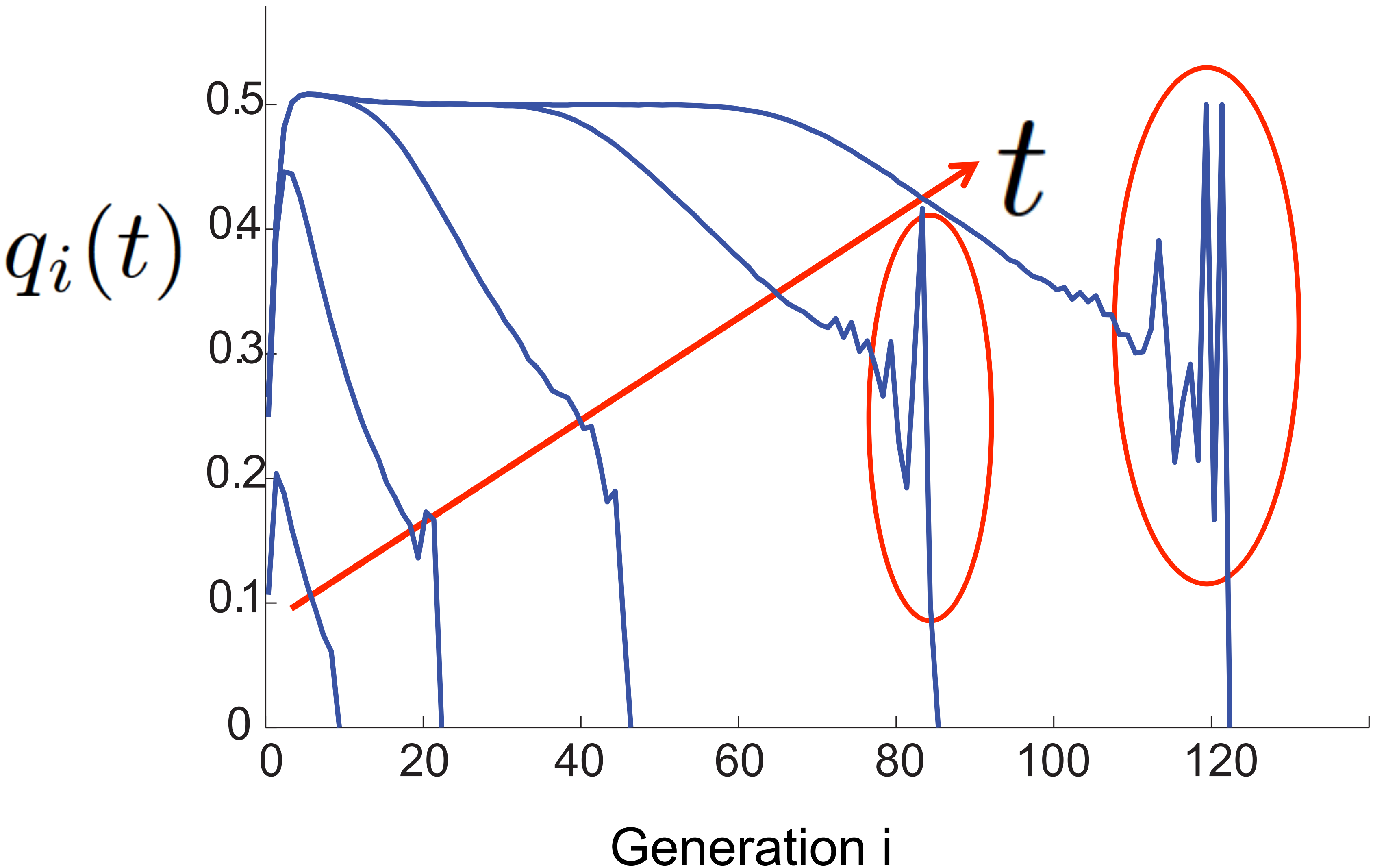
Generation transition probabilities



Generation transition probabilities



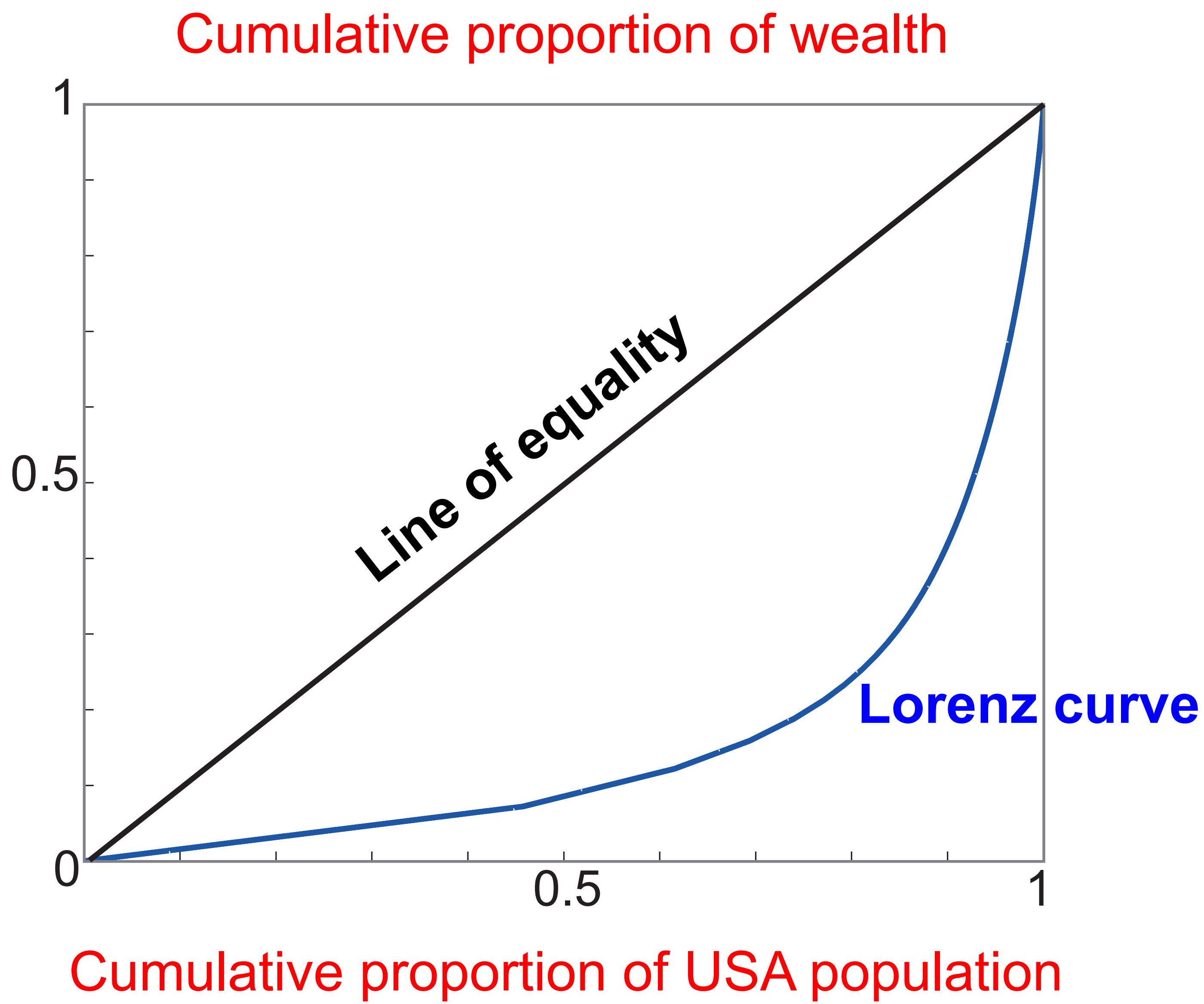
Generation transition probabilities



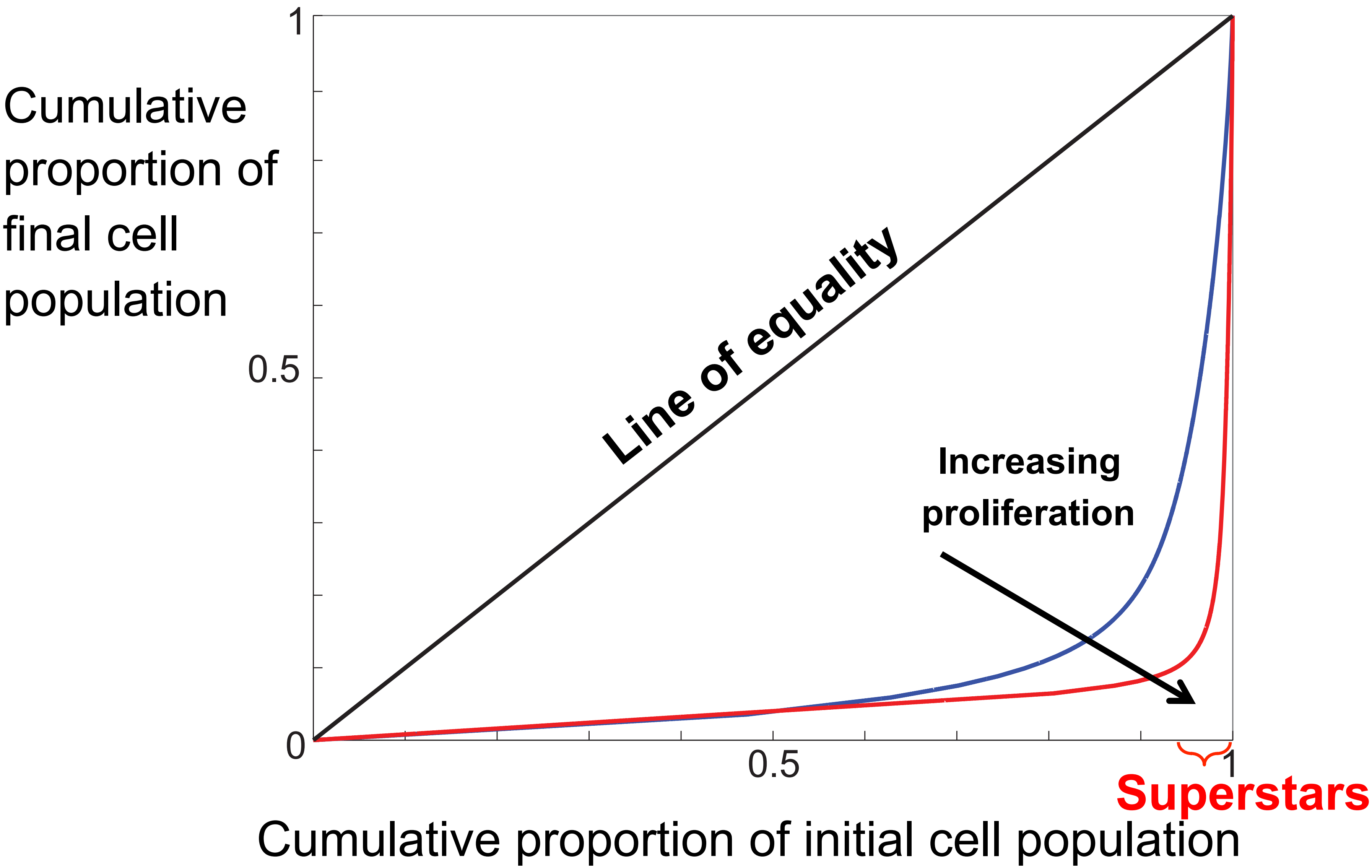
Generating cell lineage from generation info

- Simulate G-W process j = 1, 2. …n
- Run until all branching trees terminate
- Require a measure of inequality

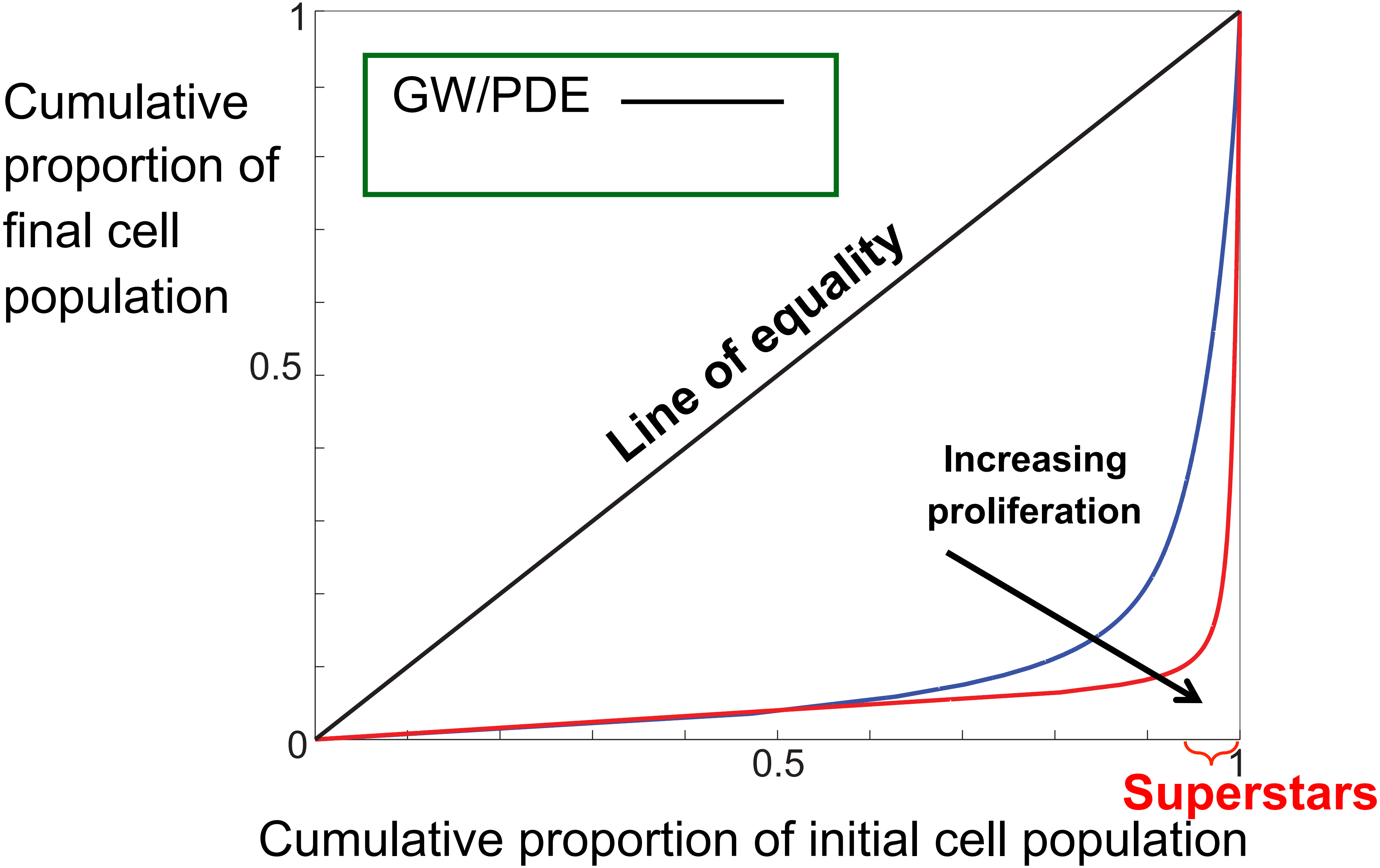
Measure of inequality



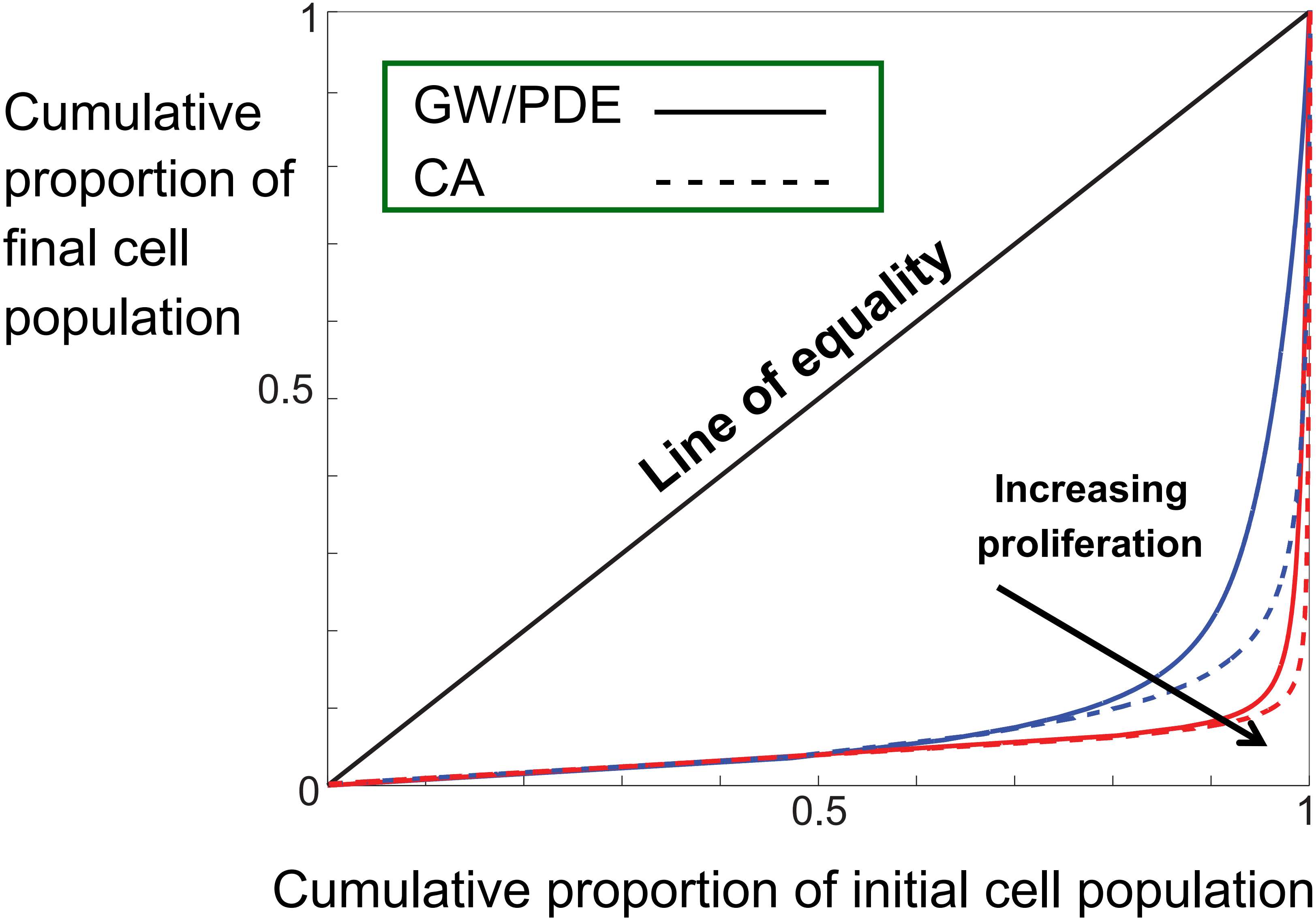
Measure of inequality



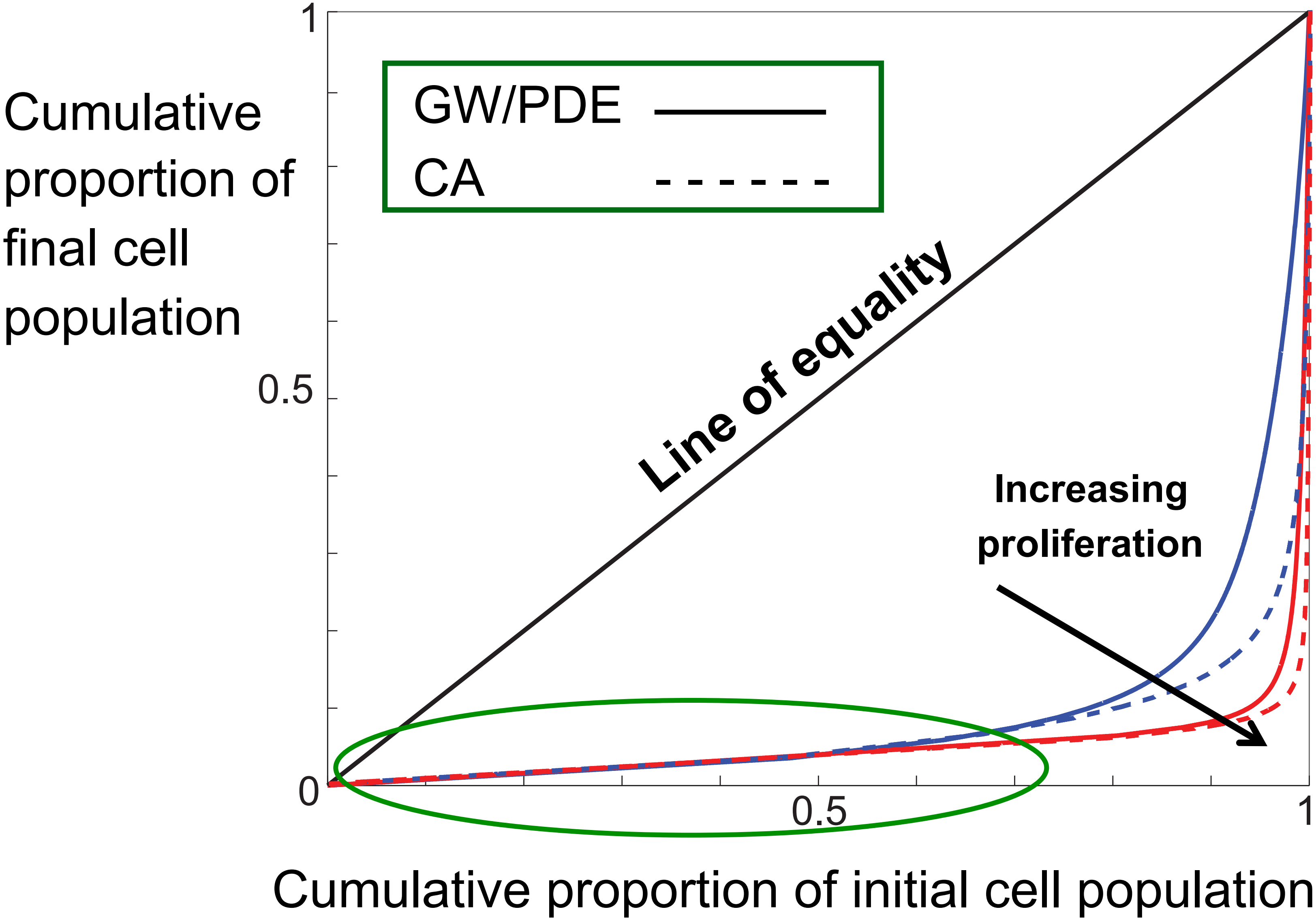
Measure of inequality



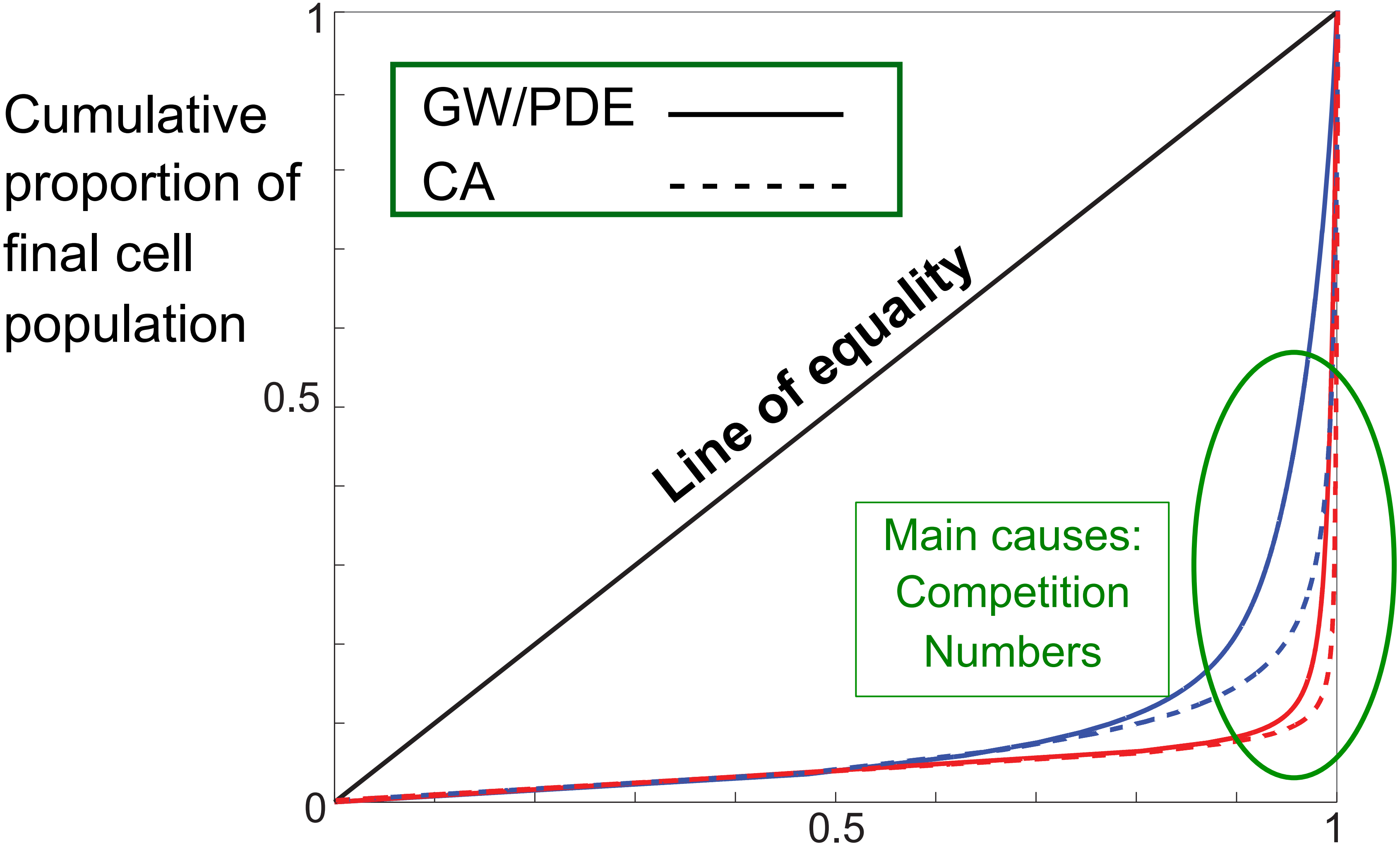
Measure of inequality



Measure of inequality



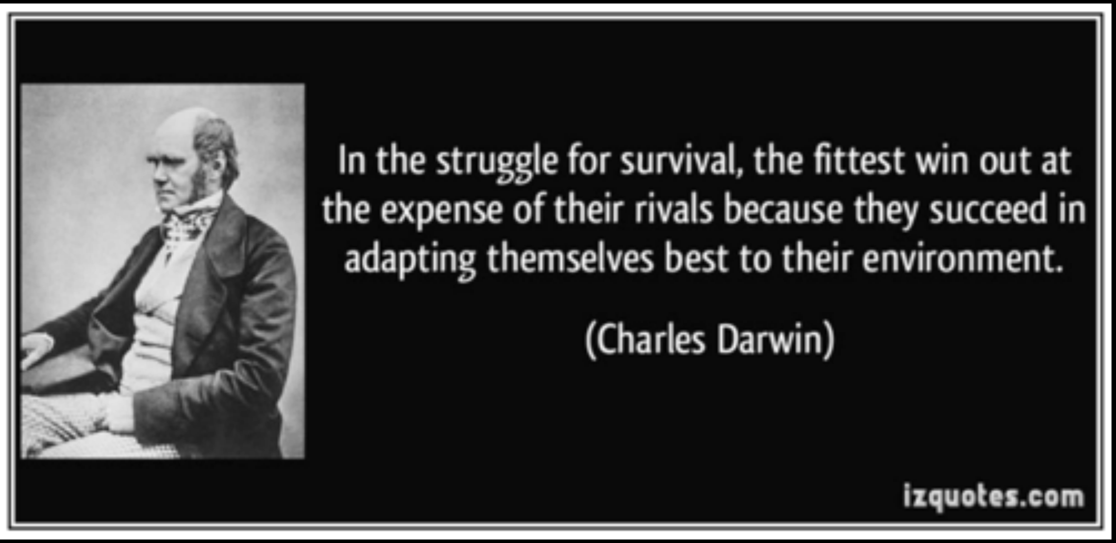
Measure of inequality

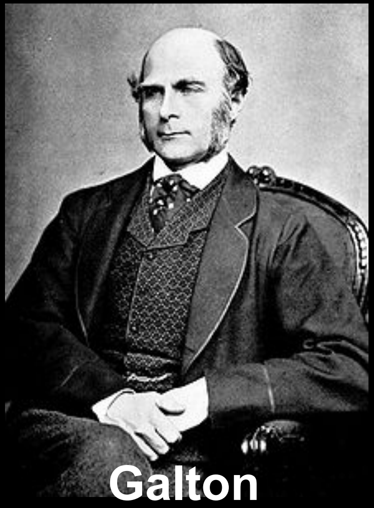


Generation PDEs & GW constructed lineages

- Growing tissues and domain growth
- Other PDEs
- Potential technique for deducing lineage data

Tracing genealogy within an invasion wave





1. Cheeseman, Zhang, Binder, Newgreen, Landman, J Royal Soc Interface (2014)
2. Cheeseman, Newgreen, Landman, J Theoretical Biol (2014)

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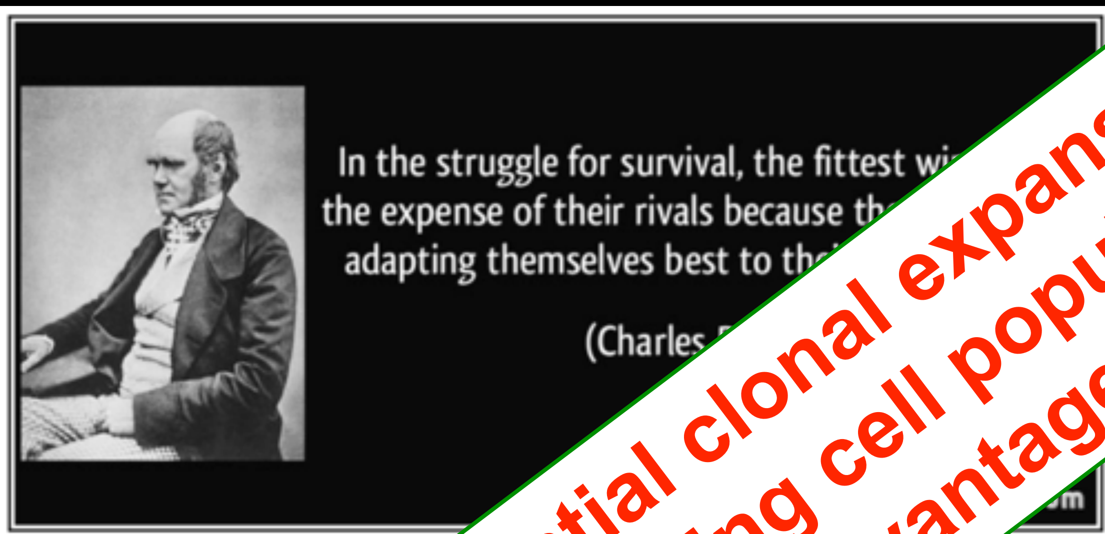

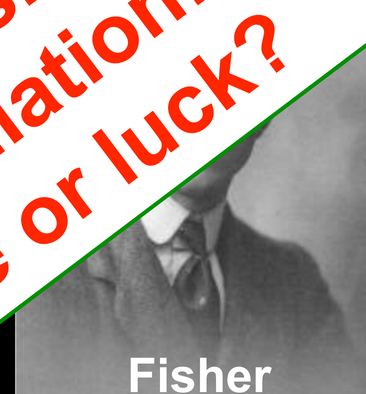

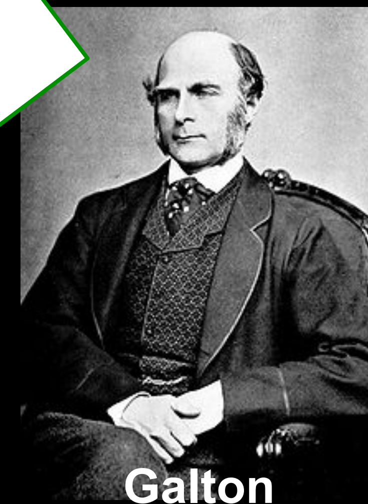

Differential clonal expansion in an invading cell population: clonal advantage or luck?

1. Cheesem , Newgreen, Landman, J Royal Soc Interface (2014)

2. Cheeseman, en, Landman, J Theoretical Biol (2014)

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