Population dynamics analysis for stem cell biology

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Introduction

Yukihiko NAKATA

June	2010 Postdoctoral Fellow at BCAM, Basque country, Spain
March	2010 Doctor of Science (Ph. D.) at Waseda Univ.
April	1983 Out from my mother.

At Paris (2008)

2012 Nobel Prize

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- Stem cell?
- Mathematics?

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- Mathematics?

Eternal youth and immortality

First emperor, China, BC259-BC210

Frieza (Dragon ball Z),
Planet Namek, ?

Alchemy

Eternal youth and immortality

http://www.myspace.com/dragonnpixie

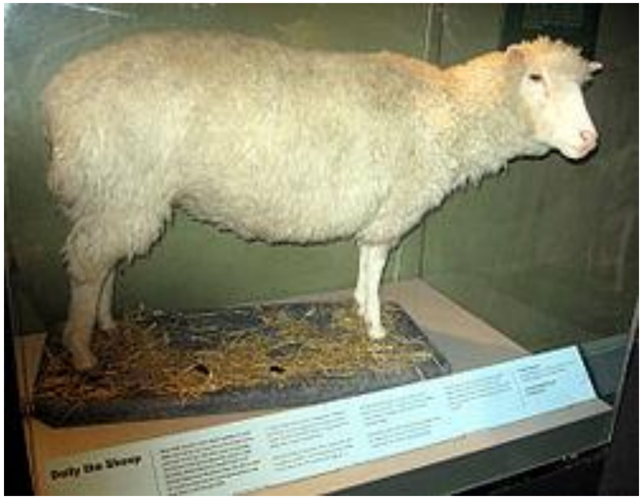
In this 21st century...

Still...we do not overcome the fear of aging.

We want to explain the mechanism.

More precisely,
we want to understand the biological process.

Regeneration (Clone)

Plant	Animal	Human
		Not yet available! (as far as I know) cf. in vitro fertilization >Body organs
Green onion, 2012	Dolly, 1996-2003	

Stem cell as the origin of the body organ.

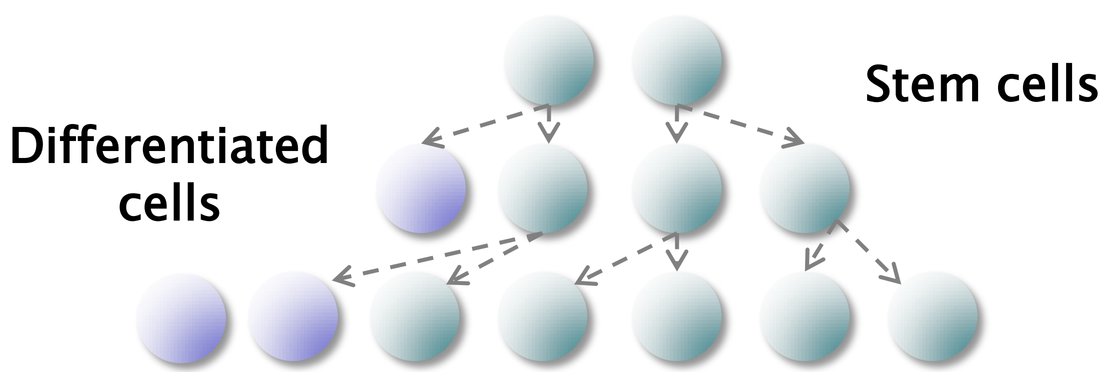
Stem cell is a cell having two abilities:

1. Self-renewal
2. Differentiation

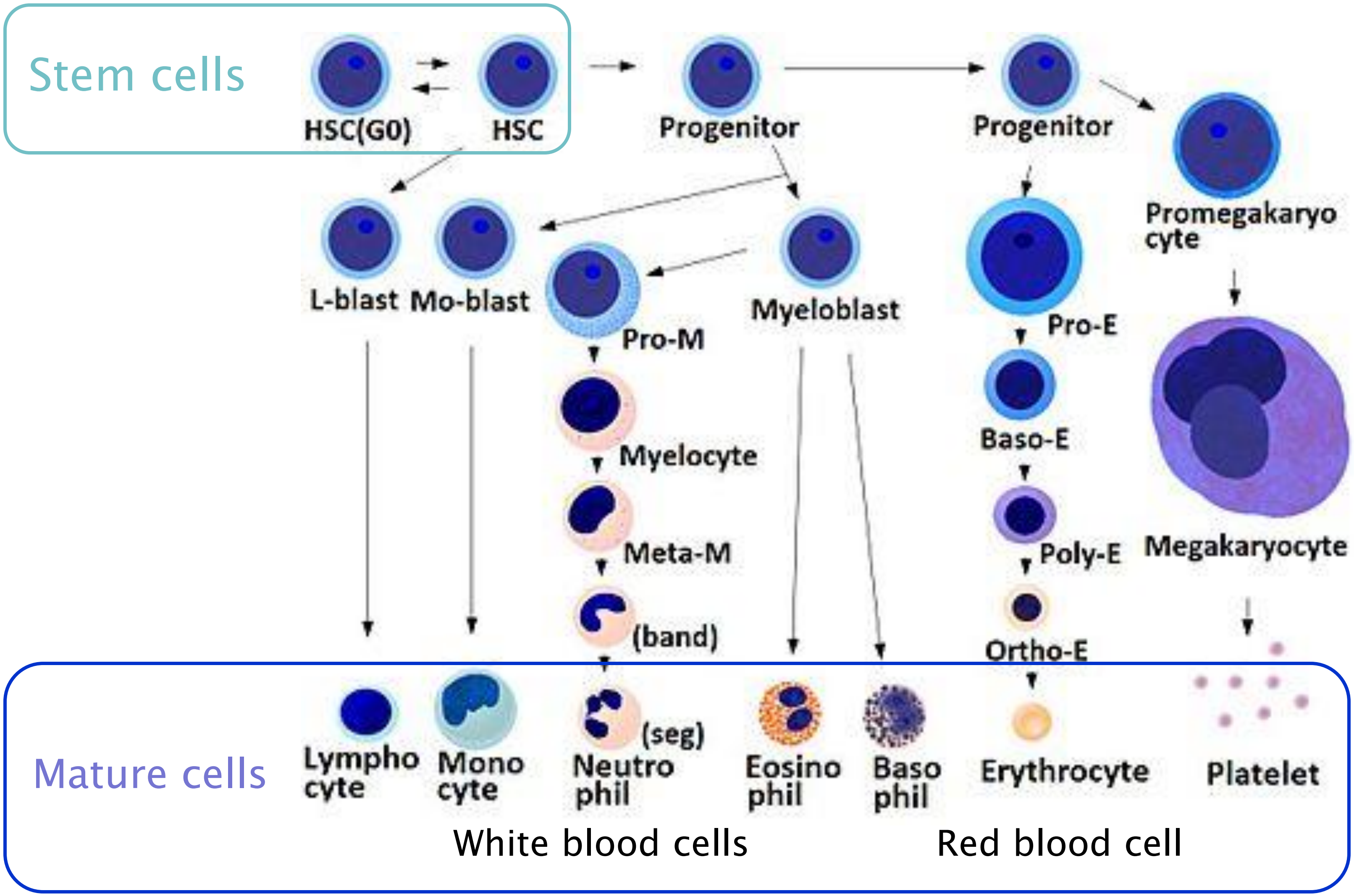
2 stem cells

2x2 daughter cells

3x2 daughter cells

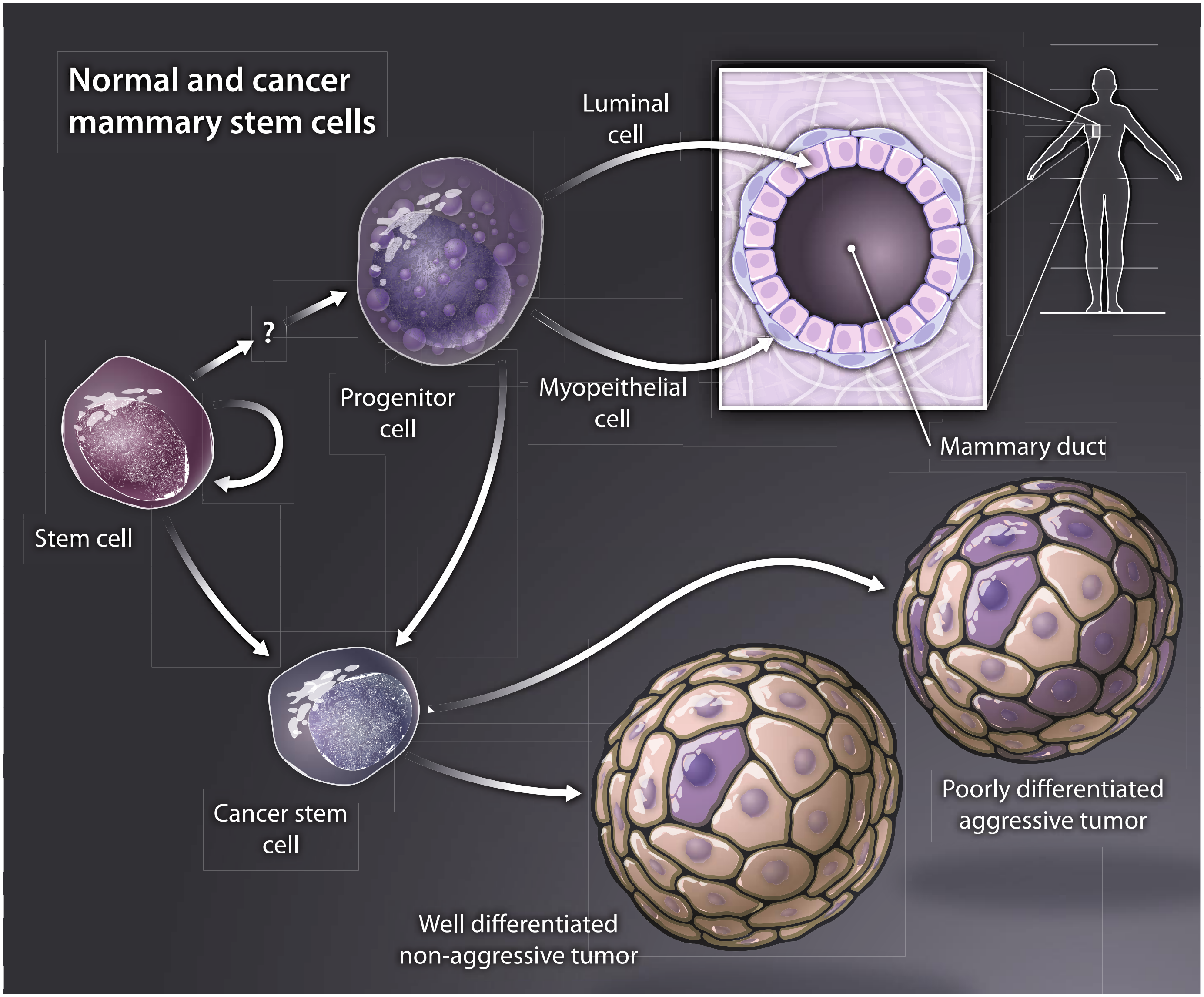


Example: Blood cell production



Hematopoietic stem cell, Wikipedia

Example: mammary gland



M. dM. Vivanco, Function Follows Form: Defining Mammary Stem Cells, (2010)

Regenerative medicine

Beike Biotechnology (China) develops therapies for disorders based on **adult stem cells.**


THIS WEEK

EDITORIALS

GARAGE FLOWERS Why the boom in DIY biology matters to scientists p634

POSTDOCS Please release me, let me go to start my own lab p635

BROUGHT TO BOOK Marine census reveals its results p638

Stem-cell laws in China fall short

The Chinese government's regulations of stem-cell treatments are admirable in principle, but tougher enforcement measures are needed to protect patients.

China does not want to be known as the Wild West of unproven medical technologies. Last year, the government took an important step when it announced regulations requiring, among other things, that anyone who offers stem-cell procedures should present clinical data supporting their efficacy, and secure approval from the health ministry (see *Nature* 459, 146; 2009).

Such regulations are sorely needed. A leading bioethicist in China last year estimated that more than 100 laboratories there offer stem-cell procedures, many of them unproven, although some clinics reportedly stopped offering the treatments after the regulations took effect. But the government needs to do more than simply announce rules; it needs to give companies clear instructions for complying with them.

The regulations have made little difference so far to Beike Biotechnol-

the procedures commercially. He says that Beike "probably should have" taken the same approach in China.

Yet the company has passed muster with the government, says Moffett. Officials have visited Beike's facilities without closing them down, which he interprets as tacit approval for the treatments. He says he knows of no application steps for formal approval from the health ministry — and requested that *Nature* forward him any information about such procedures.

The problem, it seems, is that the regulations do not include enough details for implementation and enforcement. The health ministry is now considering proposed guidelines, created by a group of scientists and ethicists, that set out clear criteria for preclinical and clinical studies, and clinical applications. One of the committee members said

Nature 467 (2010)

1. have been injected into about 9,300 patients
2. as much as USD 26,000 for the procedure
3. Stem cell treatments are NOT READY for those clinical use.

Cancer stem cell hypothesis

S. Sato, Give My Regards to Black Jack, 5

Cancer stem cell hypothesis

Cancer uncontrolled cell growth

Chemotherapy

- ✓ side-effect: feeling sick, loss of hair etc.
- ✓ acquired resistance.
- ✓ (possibly) attacks normal cells

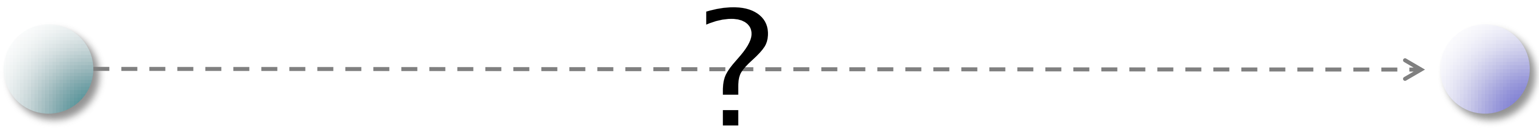
Cancer stem cell hypothesis:
There are also *stem cells* as the origin of cancer?

2012 Nobel Prize

Biological problem

What mechanism makes stem to mature cells?

Signal, regulation, chemical reaction etc..



“It is well known that little is known for stem cell dynamics”

–an anonymous reviewer

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- Stem cell?
- Mathematics?

Mathematics?

ODE Model:

Stem cell maturation model

Problems and strategy

What **regulatory mechanisms** for homeostatic condition?

Mathematical modeling and analysis

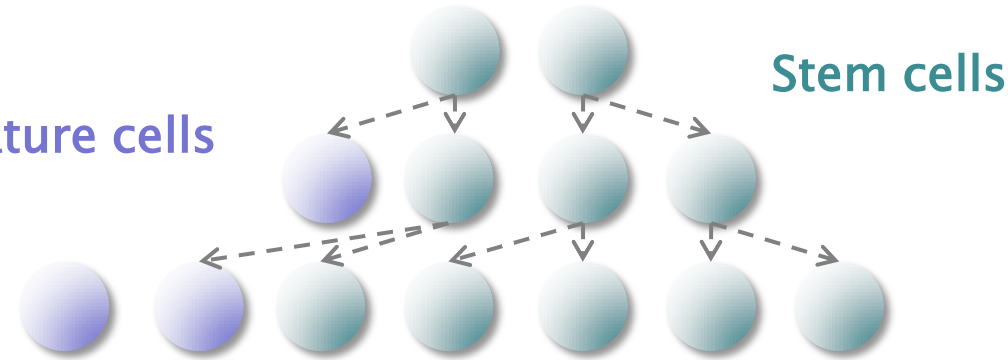
Interpretation in terms of biological parameters

Differentiation and self-renewal

2 stem cells

2x2 daughter cells

3x2 daughter cells



Fraction of self-renewal $s(t) \in (0,1]$

Division rate $d(t)$

	Inflow	Outflow
Stem cells, w(t)	$2s(t)d(t)w(t)$	$d(t)w(t) + \mu_w w(t)$
Mature cells, v(t)	$2(1-s(t))d(t)w(t)$	$\mu_v v(t)$

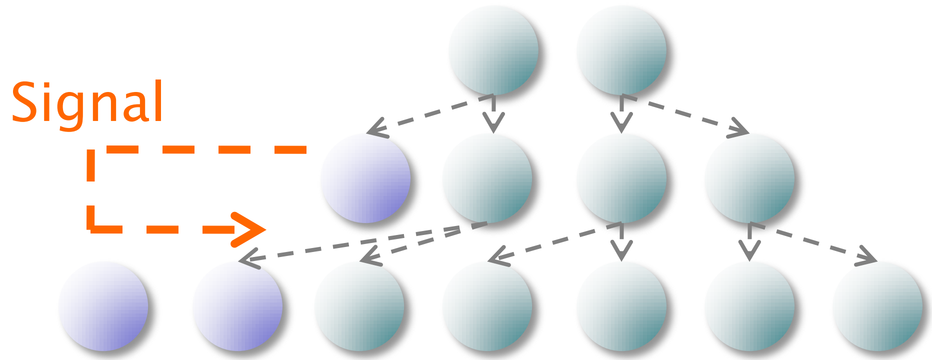
Stem cells / Mature cells

$$\begin{cases} w'(t) &= (2s(t)-1)d(t)w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s(t))d(t)w(t) - \mu_v v(t), \end{cases}$$

A. Marciniak-Czochra et al., (2008), Nakata et al., (2012)

Extracellular signal feedback-Regulatory mechanisms

Assumption:
Signal intensity depends on the amount of mature cells



Regulated fraction of self-renewal $s(t) := s_w(v(t)) := \dfrac{a_w}{1+kv(t)}$

Regulated division rate $d(t) := d_w(v(t)) := \dfrac{p_w}{1+kv(t)}$

$$\begin{cases} w'(t) &= (2s(t)-1)d(t)w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s(t))d(t)w(t) - \mu_v v(t), \end{cases}$$

Stem cells
Mature cells

$$\begin{cases} w'(t) &= (2s_w(v(t))-1)d_w(v(t))w(t) - \mu_w w(t), \\ v'(t) &= 2(1-s_w(v(t)))d_w(v(t))w(t) - \mu_v v(t), \end{cases}$$

Global stability analysis

Scenario 1: The division rate is regulated

Reproduction number

$$S_w := \frac{2a_w p_w}{p_w + \mu_w}$$

	Trivial eq. (0,0)	Positive eq. (w,v)
$S_w < 1$	GAS =Globally Asymptotically Stable	
$S_w > 1$	Exists	GAS

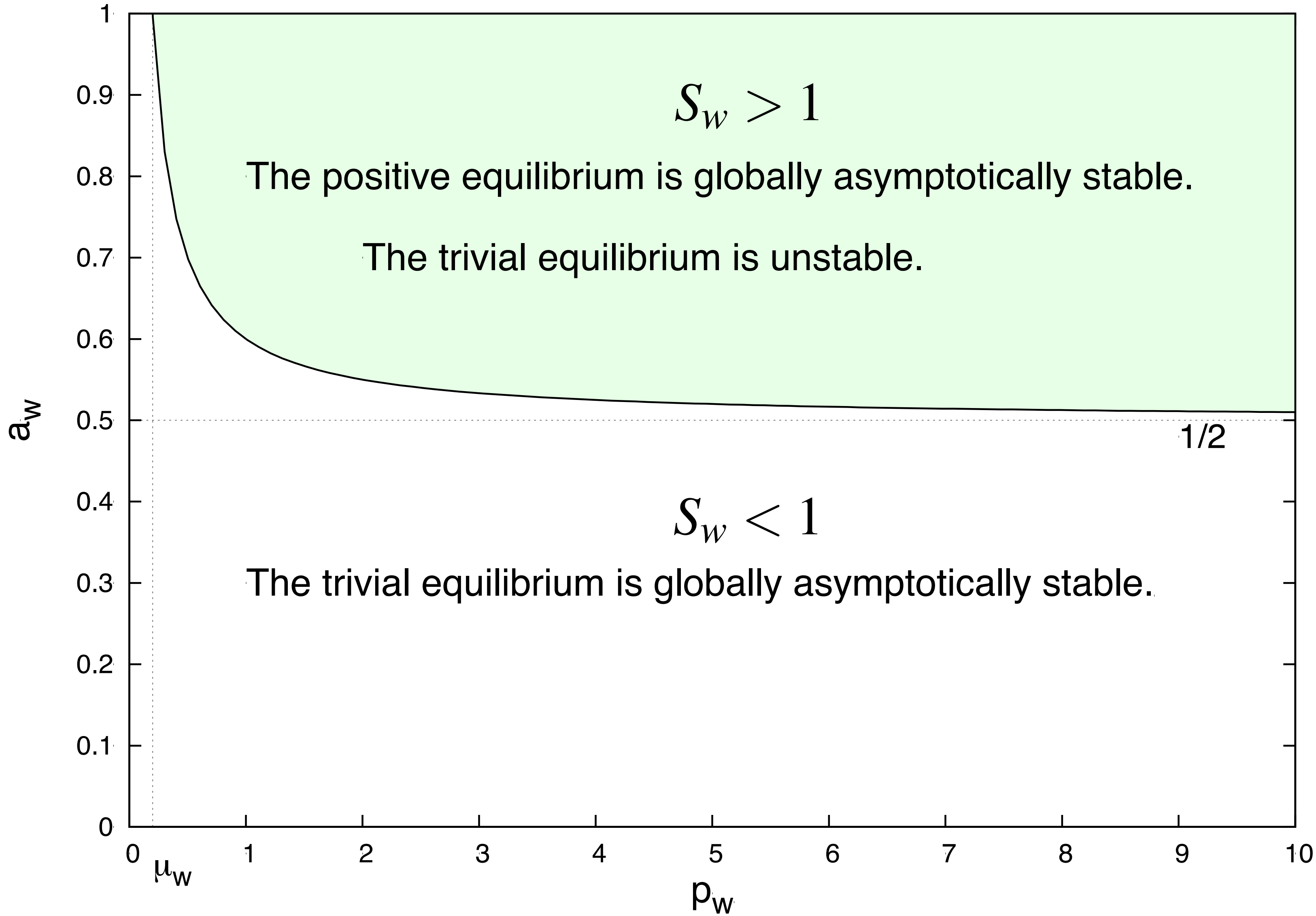
Scenario 2: The fraction of self-renewal is regulated

Reproduction number

$$S_w := \frac{2a_w p_w}{p_w + \mu_w}$$

	Trivial eq. (0,0)	Positive eq. (w,v)
$S_w < 1$	GAS	
$S_w > 1$	Exists	GAS

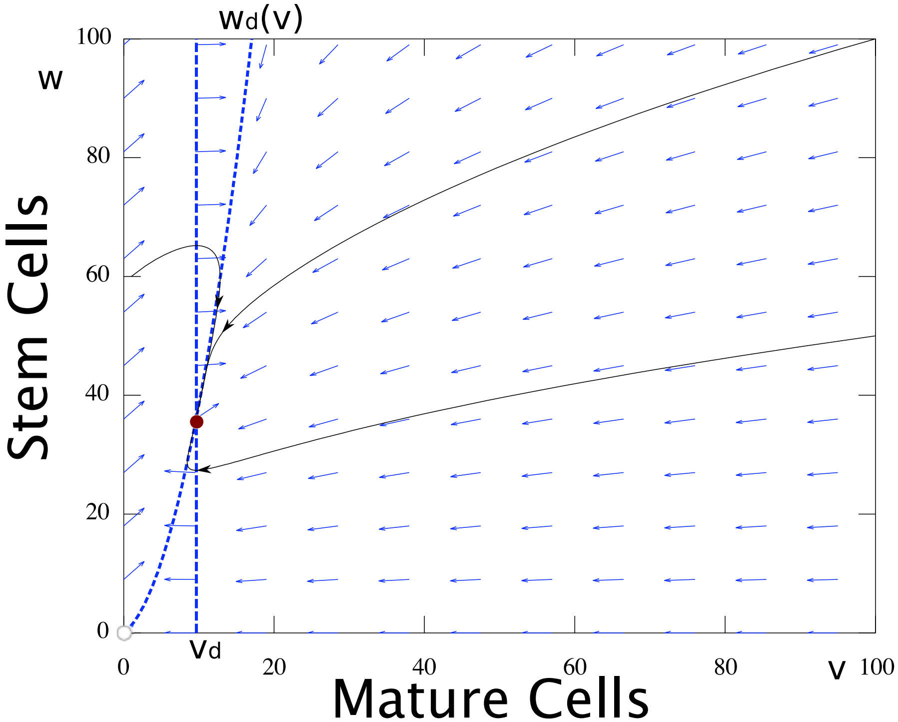
Global stability analysis

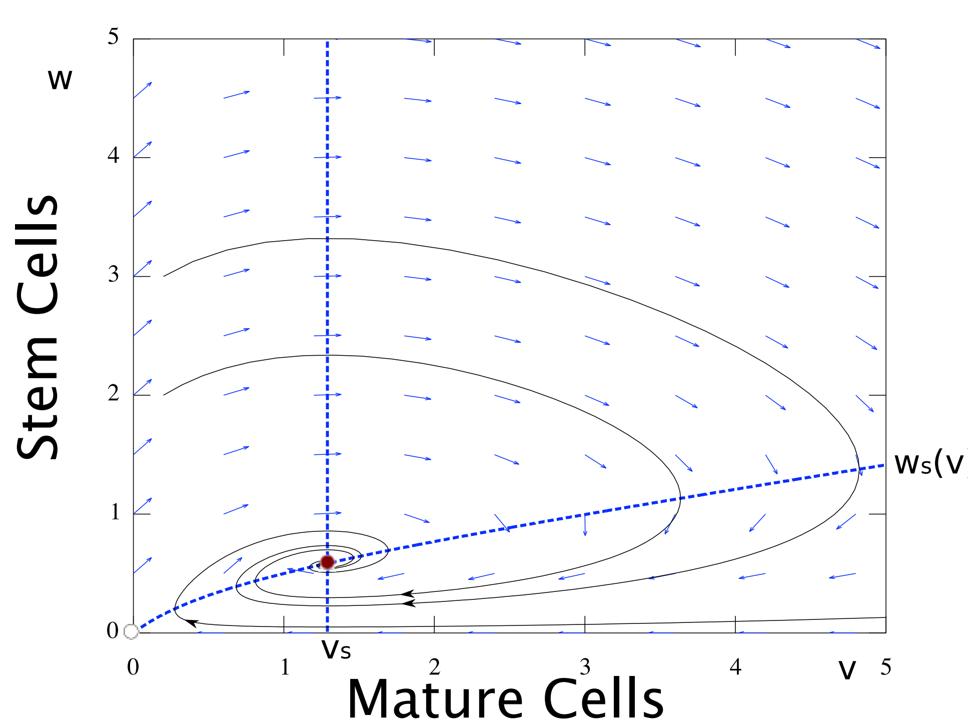


Different types of dynamics

Regulated division rate

Regulated fraction of self-renewal





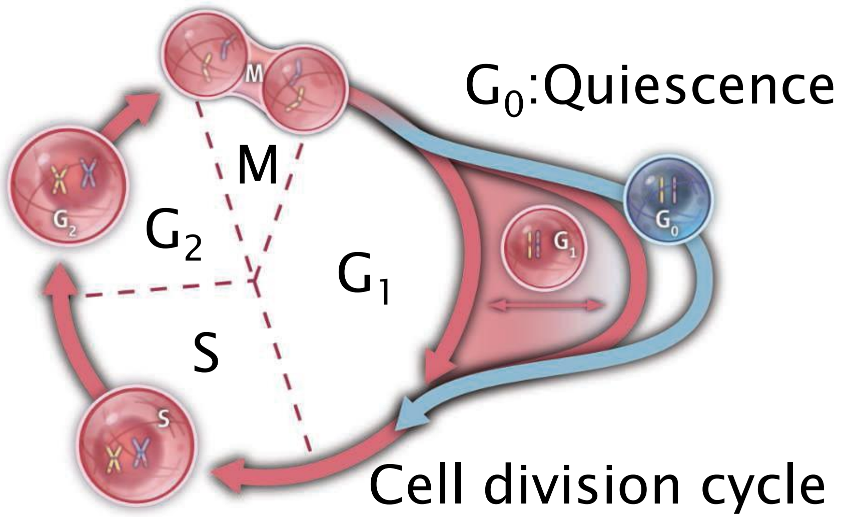
Different required amount of stem cells to keep the population balance of mature cells

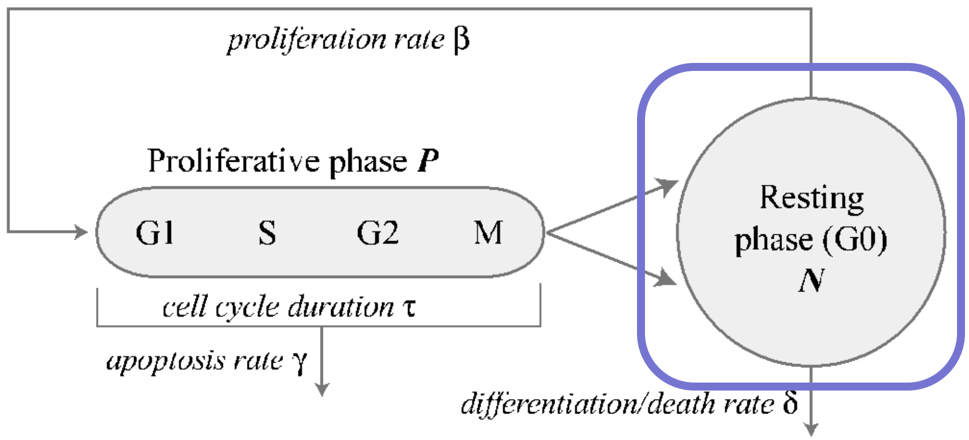
Monotone V.S. oscillatory-like behavior

Renewal Eq. Model:
Quiescence and proliferating

Quiescence?

Example: hematopoietic stem cell





Quiescent cell model, Mackey 1978

$$\frac{d}{dt}P(t) = \beta(N(t))N(t) - e^{-\gamma\tau}\beta(N(t-\tau))N(t-\tau) - \gamma P(t)$$

$$\frac{d}{dt}N(t) = 2e^{-\gamma\tau}\beta(N(t-\tau))N(t-\tau) - (\beta(N(t)) + \delta)N(t)$$

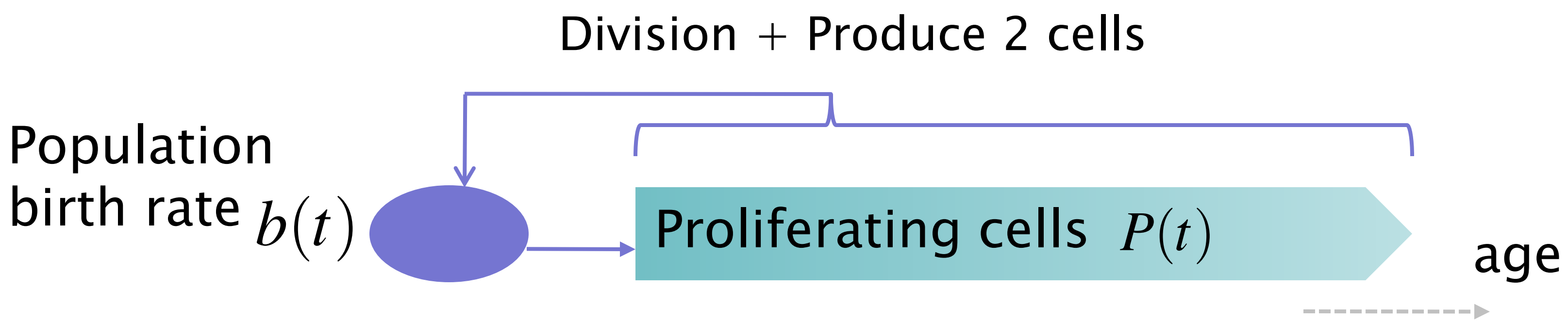
Coller, 2011, Pujo-Menjouet et al. 2005

Our aim

Formulation by Renewal Equations → *Principle of linearized stability* is available

Complete picture of qualitative properties → Stability boundaries in a biological parameter plane

Basic model ingredients–Proliferating cell



The # of proliferating cells

$$P(t) = \int_0^\infty b(t-a)\mathscr{F}(a)e^{-\int_0^a \beta(s)ds}da$$

Probability not to divide up to age a

Survival probability up to age a

Renewal equation $b(t) = 2\int_0^\infty b(t-a)\mathscr{F}(a)\beta(a)e^{-\int_0^a \beta(s)ds}da$

Age-specific division rate

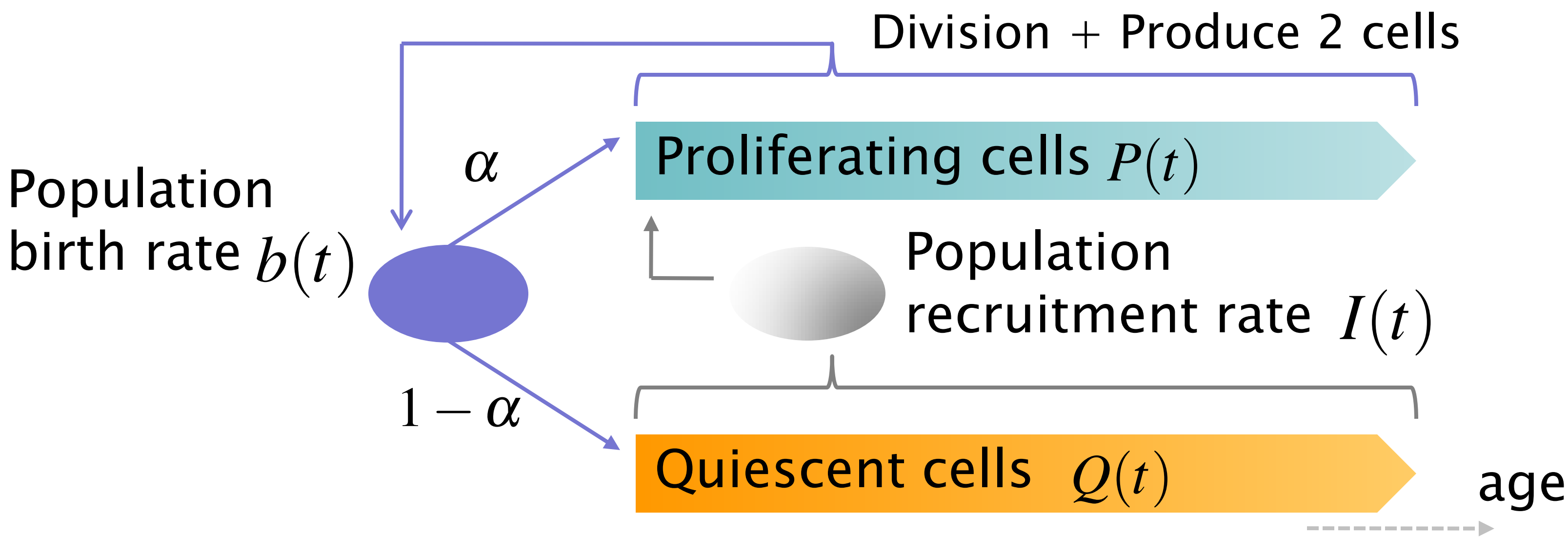
Zilman, Ganusov and Perelson PLoS ONE (2010)

Stability and connection to ODE

Characteristic equation and stability

Connection to Differential Eq.

Quiescent and proliferating cells



The # of proliferating and quiescent cells

$$P(t) = \int_0^\infty (\alpha b(t-a) + I(t-a)Q(t-a))\mathscr{F}(a)e^{-\int_0^a \beta(s)ds}da,$$

$$Q(t) = \int_0^\infty (1-\alpha)b(t-a)\tilde{\mathscr{F}}(a)e^{-\int_0^a I(t-a+s)ds}da$$

Probability not to be recruited

Quiescent and proliferating cells

System of RE

Population birth rate

$$b(t) = 2\int_0^\infty (\alpha b(t-a) + I(t-a)Q(t-a))\mathscr{F}(a)\beta(a)e^{-\int_0^a \beta(s)ds}da$$

Density-dependent recruitment rate

$$I(t) = G((1-q)P(t) + qQ(t))$$

$$q \in [0,1]$$

Gyllenberg et al. 1998 $q = 1/2$

Mackey 1978 $q = 1$

G: decreasing function

How do we analyze stability properties?

Principle of linearized stability

Diekmann, Getto and Gyllenberg, SIAM J. Math. Anal. (2007)

✓Renewal equation

$$x(t) = F(x_t)$$

where $F : L^1([-h,0],\mathbb{R}^n) \to \mathbb{R}^n$

✓Equilibrium: constant sol. s.t.

$$\bar{x} = F(\bar{x})$$

Assume F is Frechet differentiable at the equilibrium.

✓The characteristic equation

$$\det(DF(\bar{x})e_\lambda - E) = 0$$

where $e_\lambda(\theta) = e^{-\lambda\theta}$

Infinite delay: Diekmann and Gyllenberg, J.Diff.Eq. (2011)

Concentrated division

The characteristic equation

$$0 = e^{-\lambda}(\alpha r_0 \lambda + p_1(\mu, c)) - \lambda + p_2(\mu, c)$$

$$\begin{pmatrix} p_1(\mu, c) \\ p_2(\mu, c) \end{pmatrix} := A(q) \begin{pmatrix} \mu \\ c \end{pmatrix}$$

✓A characteristic equation in the literature

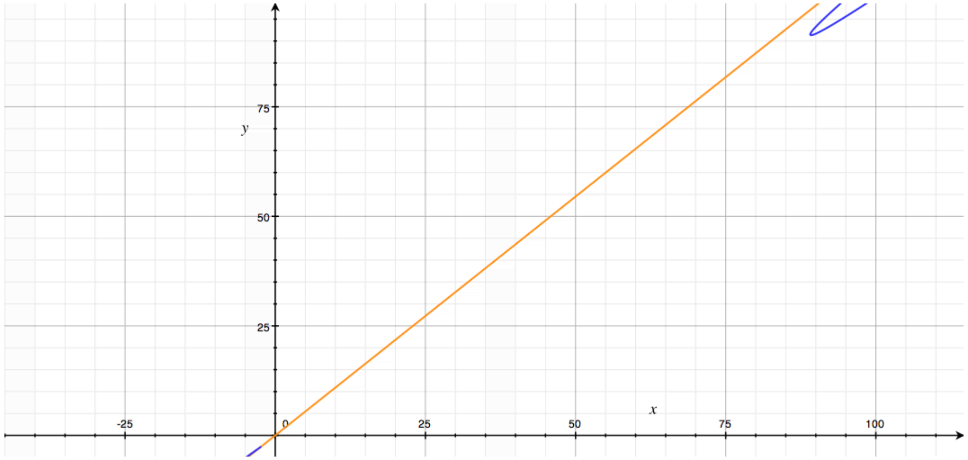
$$0 = e^{-\lambda \tau}(c_1 \lambda + c_2) - \lambda + c_3$$

For $\mathrm{Re}\lambda < 0$

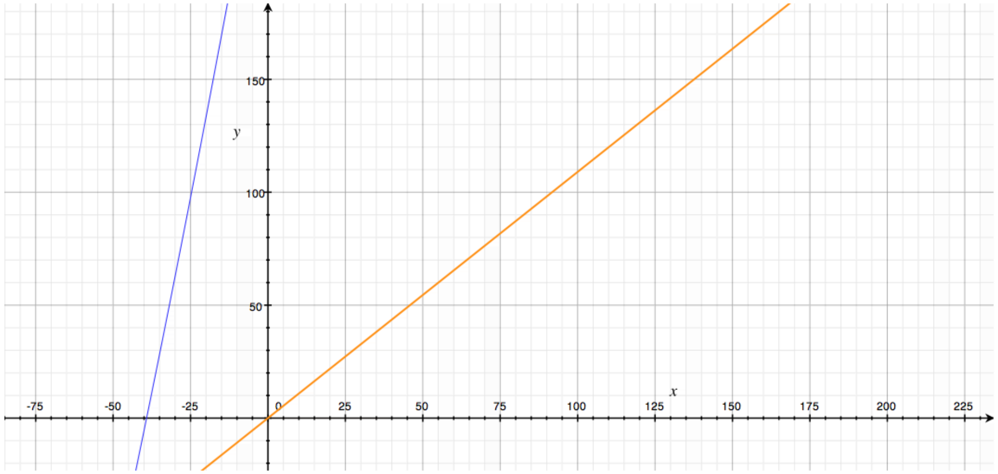
Stepan 1989	A sufficient criteria
Kuang 1993	Exact condition using τ as a free parameter

Development of curves

As increasing q from 0 to 1

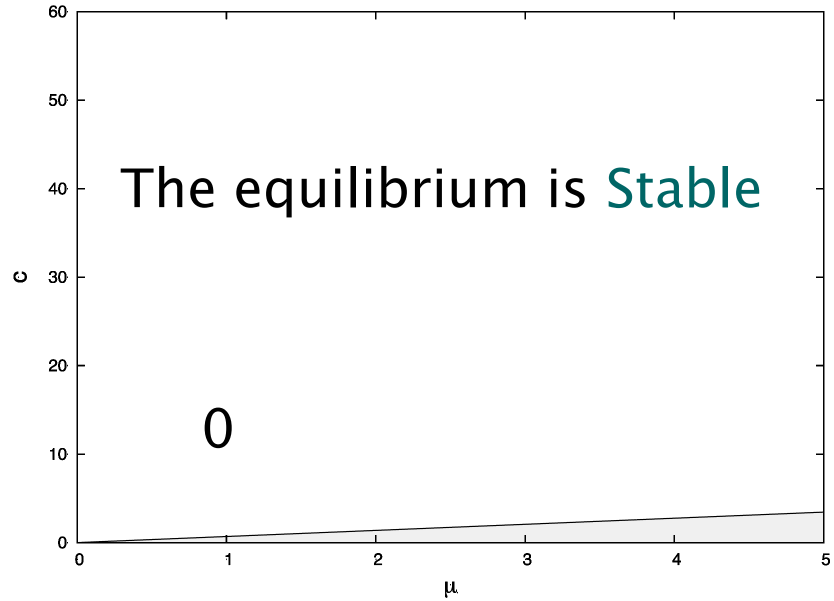


As increasing delay

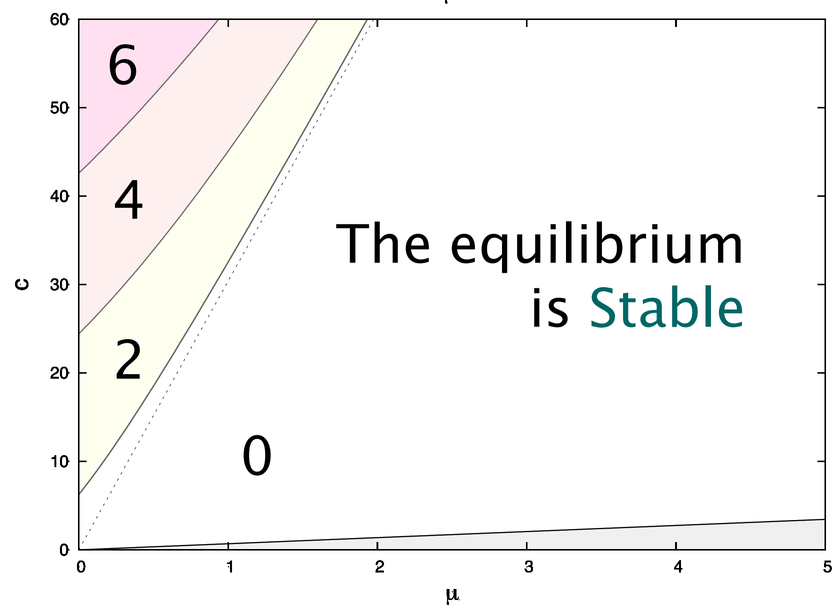


Threshold for existence of instability region

$$q \le \frac{r_0+2}{3r_0+4}$$

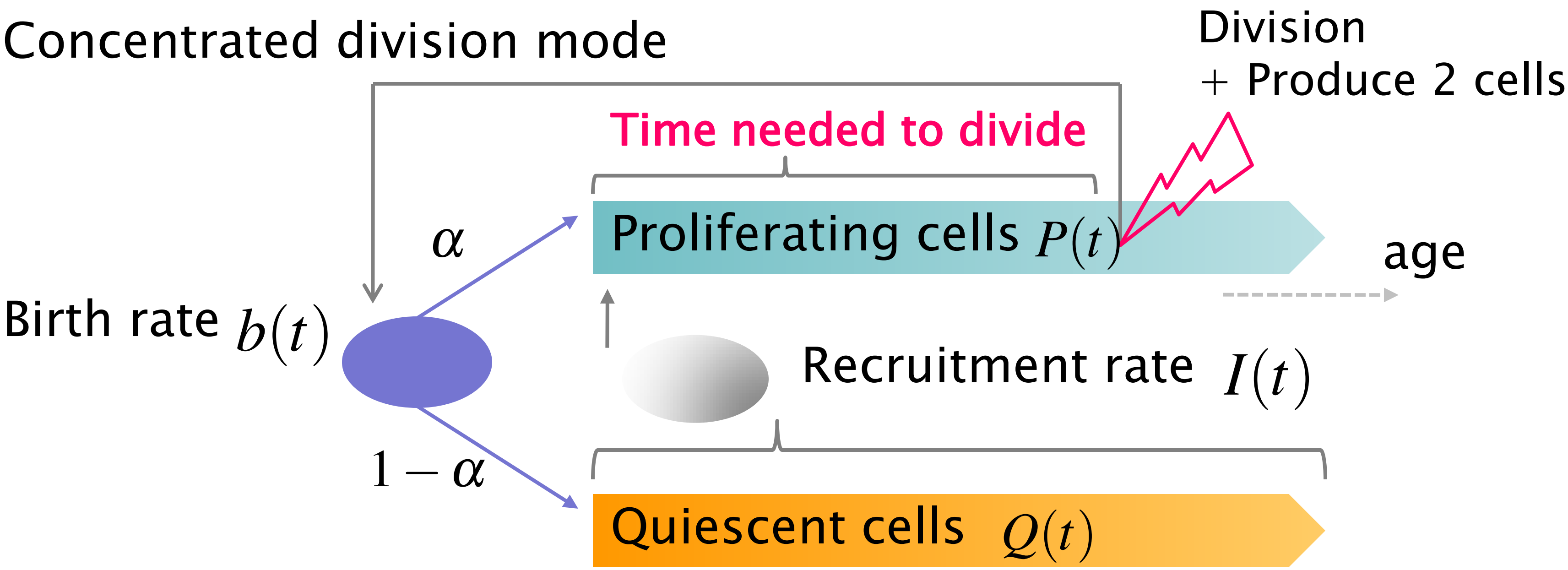


$$q > \frac{r_0+2}{3r_0+4}$$



Mechanism of oscillation

Concentrated division mode



$$b(t) = r_0(\alpha b(t-1) + I(t-1)Q(t-1)) \qquad r_0\alpha < 1$$

Oscillation ← Proliferation due to *recruited quiescent cells*

for your interest

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Research interesting:

Nonlinear dynamical analysis,
Differential / difference equation systems
and its Applications.

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