Modelling and analysis of stem cell maturation

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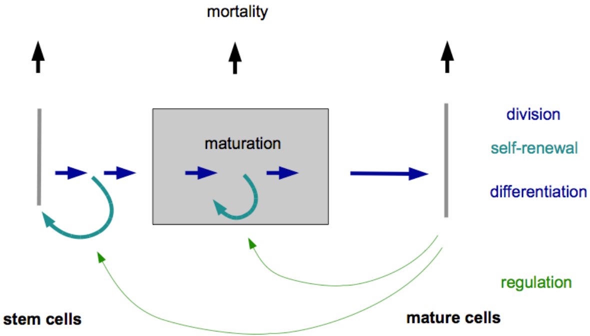
Modelling stem cell maturation



Multi-compartment models in

(A. Marciniak-Czochra et al. *Stem Cells and Development* 2008)

see also (Lander, *Journal of Biology* 2009)

- biological relevance of population dynamical modelling
- exact nature of maturation, regulation process unknown

Goals:

- model process as population dynamical system
- analyse

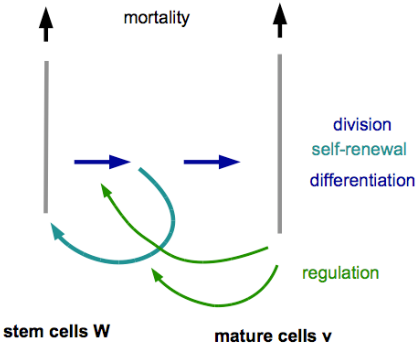
  existence, stability of equilibria (population level)
- investigate

  which quantities at cellular level regulate this?
  how?

Methods:

ODE, infinite dimensional systems

Two-compartment model



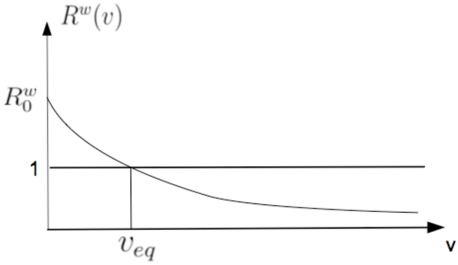
$$
\begin{aligned}
w' &= [2s_w(v) - 1]d_w(v)w - \mu_w w \\
v' &= 2[1 - s_w(v)]d_w(v)w - \mu_v v \\
d_w(v) &= \frac{p_w}{1 + k_p v}, \quad s_w(v) = \frac{a_w}{1 + k_a v}
\end{aligned}
$$

Equilibrium condition $R^w(v) = 1$

$R^w(v) = \frac{[2s_w(v)-1]d_w(v)}{\mu_w}$
$=$ regulated stem cell net reproduction number

$= \langle\sharp\rangle$ stem cells coming in minus going out via division
in time a cell would live if it would not divide

Equivalent condition on parameters



$$a_w := s_w(0), \; p_w := d_w(0)$$

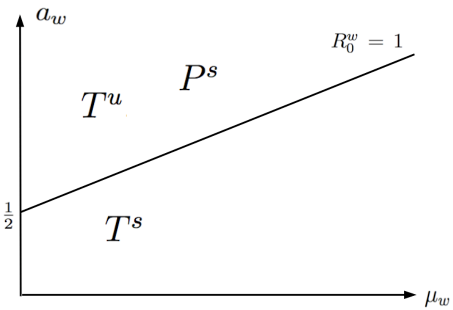
$$R_0^w := \frac{[2a_w - 1]p_w}{\mu_w}, \text{ \textit{unregulated reproduction number}}$$

$$\Rightarrow R_0^w := R^w(0)$$

regulation = reduction $\Rightarrow$

$$R_0^w > 1,$$

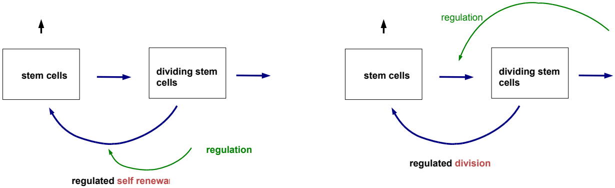
Existence border in $a_w - \mu_w$-space



T =trivial, P = positive, ^{s} = stable, ^{u} = unstable

Conclusion of linearized stability:
Exchange of stability for both regulation modes

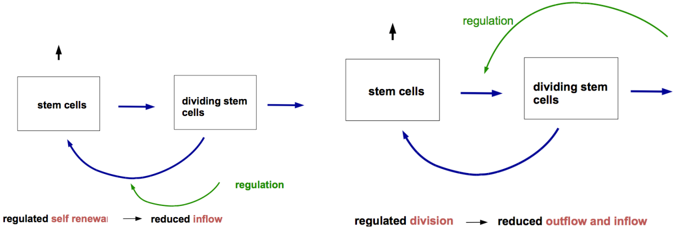
Compare two regulation modes



regulated self-renewal: denote $R^{w}(v)$ as $R^{w,s}(v)$

regulated division: denote $R^{w}(v)$ as $R^{w,d}(v)$

Then: $R^{w,d}(v) > R^{w,s}(v)$



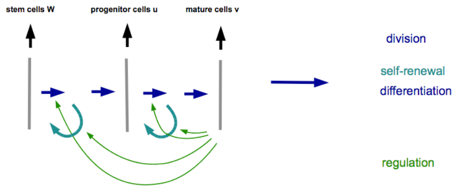
Explanation:

- regulation =reduction
- regulated self-renewal $\Rightarrow$ reduced inflow
- regulated division$\Rightarrow$ reduced inflow plus reduced outflow

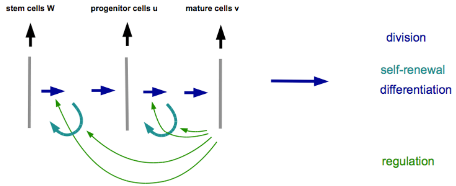
$\Rightarrow$ latter better for stem cells $\Rightarrow R^{w,d}(v) > R^{w,s}(v)$
Now, in equilibrium $R^{w}(v) = 1$ in both models $\Rightarrow v_{eq}^{d} > v_{eq}^{s}$

CONCLUSION:
More output of mature cells when regulating division

Three compartment model



$$
\begin{aligned}
w' &= [2s_w(v) - 1]d_w(v)w - \mu_w w \\
u' &= 2[1 - s_w(v)]d_w(v)w + [2s_u(v) - 1]d_u(v)u - \mu_u u \\
v' &= 2[1 - s_u(v)]d_u(v)u - \mu_v v
\end{aligned}
$$



Exactly 3 types of equilibria

$(0,0,0)$ trivial, $(0,u,v)$ no stem cell, $(\overline{w},\overline{u},\overline{v})$ positive

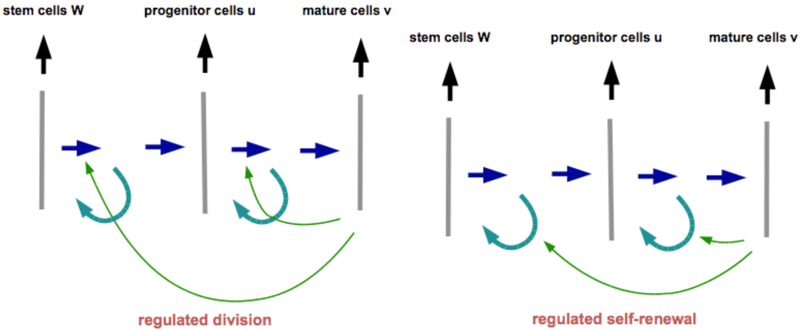
no regulation $\Rightarrow$ only trivial, some regulation $\Rightarrow$ all combinations

for any regulation mode

1) no stem cell equilibrium exists $\Leftrightarrow R_0^u > 1$
($\longrightarrow$ 2 compartment model)

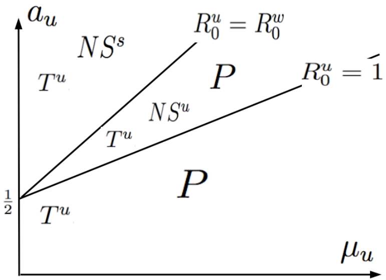
2) positive equilibrium exists $\Rightarrow R_0^w > 1$
(otherwise stem cells would decline)

Comparison of two cases of regulation



regulated division vs. regulated self-renewal

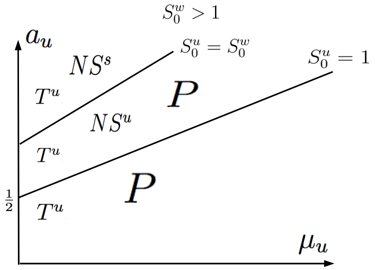
simultaneous regulation



Assume $R_0^w > 1$, regulated division

trivial (T) everywhere,
no stem cell (NS) above $R_0^u = 1$, $\rightarrow$ two compartment model
positive (P) below $R_0^u = R_0^w$

P destabilizes NS

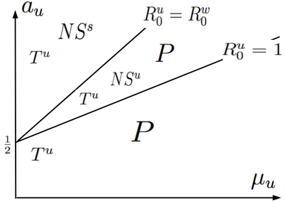


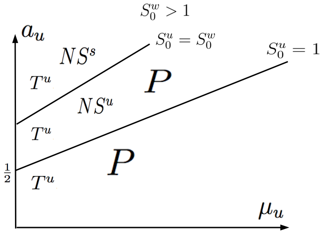
regulated self-renewal

introduce new reproduction number $S_0^u = \frac{2a_u p_u}{p_u + \mu_u}$
$= \langle \sharp \rangle$ cells coming in by self-renewal during cell's lifetime

- recall that $R_0^u = \frac{(2a_u - 1)p_u}{\mu_u}$,
$\Rightarrow R_0^u > 1$ equivalent to $S_0^u > 1$, $\Rightarrow$ lower line as before

upper border for P now: $S_0^u = S_0^w$
not equivalent to $R_0^u = R_0^w \Rightarrow$ upper line different



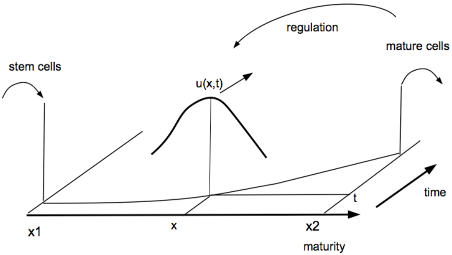


Conclusions: different modes of simultaneous regulation $\Rightarrow$

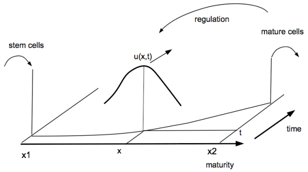
1) two concepts of reproduction numbers

2) For low μ_u
regulated self-renewal $\longrightarrow$
no stable no stem cell equilibrium upon crossing $1/2$
$\longrightarrow$ regulated self-renewal more realistic model?

Maturation as a continuous process



$$
\begin{aligned}
x'(t) &= g(x(t), v(t)), \quad \textit{regulated maturation speed} \\
x(0) &= x_1 \\
u(x,t) &= \textit{maturity density at time } t
\end{aligned}
$$



$$
\begin{aligned}
w' &= [2s_w(v) - 1]d_w(v)w - \mu_w w \\
g(x_1, v)u(\cdot, x_1) &= 2[1 - s_w(v)]d_w(v)w \\
\partial_t u(t,x) + \partial_x g(x, v(t))u(t,x) &= [a(x, v(t)) - \mu_u(x)]u(t,x) \ \textit{transport of progenitor cells} \\
v' &= g(x_2, v)u(x_2, \cdot) - \mu_v v
\end{aligned}
$$

continuous maturation $\Rightarrow a(x, v) =$ rate of inflow at any $x \in [x_1, x_2]$
BEFORE: $s_u(v) =$ probability to pass to another compartment

$\Rightarrow$ continuous model more deterministic

1) $u(t, x_2) \neq \sharp$ mature cells
2) quasi-linear model, well-posedness open $\Rightarrow$ reformulate as *DDE*

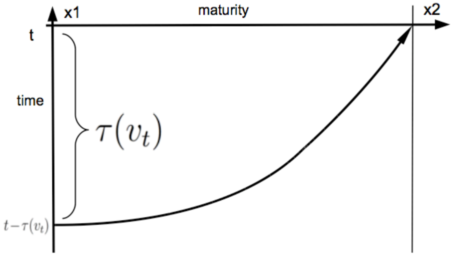
Reformulation as Delay Differential Equation

Idea:

- compute progenitor cell density $u(t,x)$ as function of v and w
  $\leftarrow$ integration along characteristics
- plug u into equations for v and w
- mature cells appear with delay
  $\tau(v_t) =$ time to mature from x_1 to x_2

$$
\begin{aligned}
w' &= [2s_w(v)-1]d_w(v)w - \mu_w w, \quad \mathit{ODE} \\
v'(t) &= \beta(v(t-\tau(v_t)))w(t-\tau(v_t))\mathcal{F}(\tau(v_t), v_t) - \mu_v v(t), \quad \mathit{DDE} \\
\beta(v) &= 2[1-s_w(v)]d_w(v), \ \mathit{stem-progenitor-transition\ rate} \\
\mathcal{F}(\tau, v) &= \mathit{survival\ probability}
\end{aligned}
$$

How to compute delay?



$$v_t(\theta) \quad = \quad v(t+\theta), \quad \theta < 0 \textit{ history of mature cells}$$

$$\textit{mature regulate maturation} \;\; x'(t) = g(x, v(t)) \qquad (1)$$

length of delay depends on maturation speed
⇒ delay depends on history of mature cells (integrated ODE)
⇒ state dependent delay $\tau = \tau(v_t)$, compute via
$X(t, v_t) = x_2$, where X solution of (1)

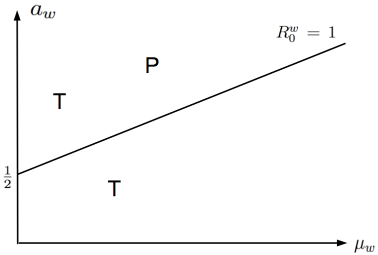
we obtain Delay Differential Equation

$$\begin{aligned} x'(t) &= F(x_t),\ t > 0 \\ x(t) &= \varphi(t),\ \ t \in [-h, 0] \end{aligned} \qquad (2)$$

- show F is C^1, then
  - contractivity $\rightarrow$ well-posedness
    $\rightarrow$ approximate solutions through convergent iteration
  - principle of linearized stability holds

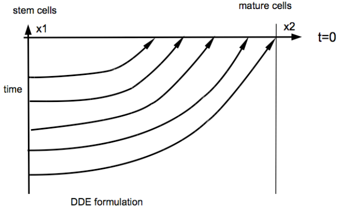
Note: - For quasi-linear models in PDE formulation this is open
- for (2) can be applied results obtained via perturbation theory for adjoint semigroups
(Delay Equations, Diekmann et al. Springer 1995)

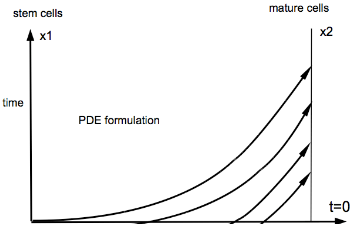
Existence of equilibria in two-parameter space



as in 2 compartment

No no stem cell equilibrium in either formulation





Stability analysis via characteristic equation

$$\det(zI - DF(\overline{x})e_z) = 0, \ \ e_z(\theta) = e^{z\theta}, \ \theta \in [-h, 0], \qquad (3)$$

We computed (3). This involved

- differentiation in infinite dimensions
- differentation of implicitly defined functions (maturity $X(t, v_t)$)

Analyse (3) by computing stability boundaries

$$\det(i\omega I - DF(\overline{x}; \alpha, \beta)e_{i\omega}) = 0, \ \ \alpha, \beta \textit{ free parameters}$$
$$F(\overline{x}, \alpha, \beta) = 0$$

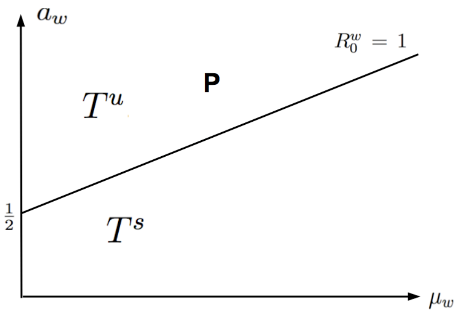
4 equations, 5 unknowns $\overline{x}, \alpha, \beta, \omega \rightarrow$ curve in (α, β)-space,

Two methods to compute stability boundary:

(a) specify ingredients for which ODE can be solved by hand $\rightarrow$ algebraic equation

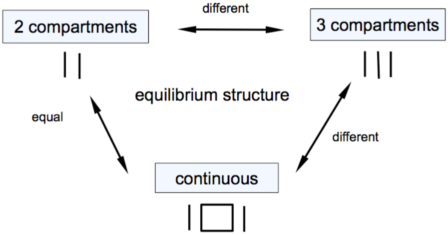
(b) combine curve continuation with integration of ODE (de Roos, Diekmann, Getto and Kirkilionis, *Bull. Math. Biol.* 2010)

Linearized stability for the trivial equilibrium



Conclusion: stability switch of trivial as with 2 compartments

Conclusions



For two compartments

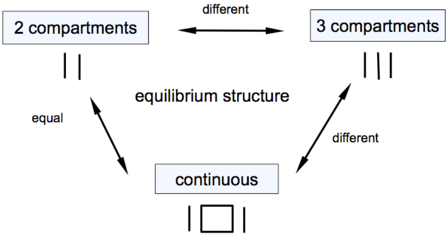
regulating division preferable ← more mature cells

For three compartments

regulating self-renewal preferable ← more realistic

← no stable no stem cell equilibrium

Outlook



Comparison between 2-compartment and continuous model: consider low transition of stem cells

- 2-compartments: negative effect on mature cells
- continuous model: compensation by progenitor cells' self-renewal?

Estimation of parameters in low compartment models!

in discussion with experimental biologists (CIC Biogune,...)