Modelling and analysis of stem cell differentiation

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Modelling stem cell maturation

Goals:

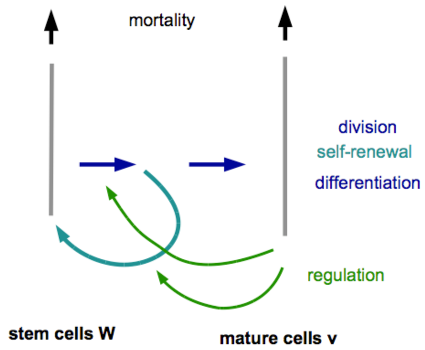
- model stem cell maturation as population dynamical system
- analyse

  existence, stability of equilibria (population level)

Methods:

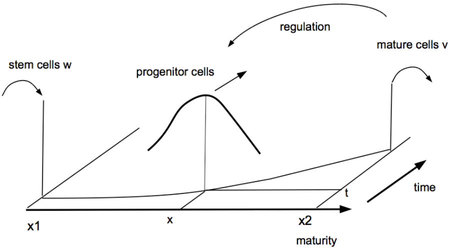
ODE, infinite dimensional systems

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



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

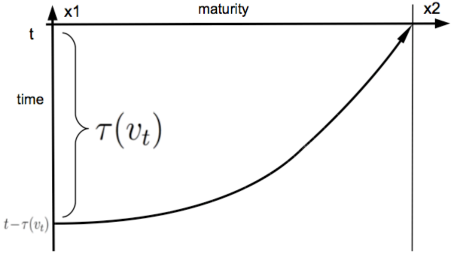
Maturation as a continuous process



Progenitor cells

- inflow of progenitor cells at x_1: $\beta(v)w = 2[1 - s_w(v)]d_w(v)w$
- maturity of progenitor cell $x \in [x_1, x_2]$

$$x' = g(x,v) \quad \textit{maturation speed} \rightarrow \textit{regulated by mature cells } v$$
$$x(0) = x_1$$

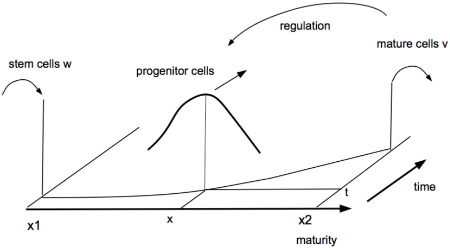


$$\begin{aligned} x' &= g(x, v) \\ x(0) &= x_1 \end{aligned}$$

ODE well-posed $\longrightarrow$ define time τ to mature from x_1 to x_2,
$\tau = \tau(v_t)$, where

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

call $\tau(v_t)$ delay $\leftarrow$ state dependent

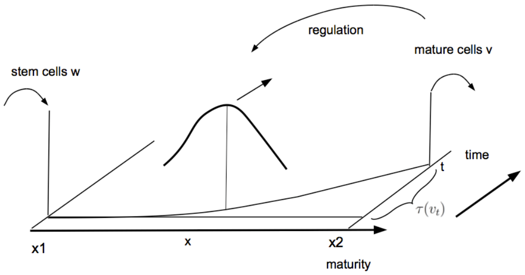


progenitor cells:
self-renewal rate $a(x, v(s)) \leftarrow$ regulated, mortality rate $\mu(x)$

progenitor cell dynamics $\leftarrow$ population (net) growth factor $\mathcal{F}$

$$\begin{aligned} \mathcal{F}' &= [a(x, v) - \mu(x)]\mathcal{F} \\ \mathcal{F}(0) &= 1 \end{aligned}$$

Population equations



$$w' = [2s_w(v) - 1]d_w(v)w - \mu_w w \quad DDE(ODE)$$

$$v'(t) = \beta(v(t - \tau(v_t)))w(t - \tau(v_t))\mathcal{F}(\tau(v_t), v_t) - \mu_v v(t) \quad DDE$$

Two-component Delay Differential Equation DDE, state dependent delay

Use existence result for finite delay

("Delay Equations", Diekmann, Verduyn Lunel, van Gils, Walther. Springer 1995)

$$\begin{aligned} y'(t) &= F(y_t),\ t > 0,\ \ y := (w, v) \\ y(t) &= \varphi(t),\ \ t \in [-h, 0],\ \ \varphi \in \mathcal{O} \end{aligned}$$

$\mathcal{O} \subset C([-h,0],\mathbb{R}^n)$, $F : \mathcal{O} \to \mathbb{R}^n$ locally Lipschitz
$\longrightarrow$ Existence and uniqueness

What is h in $C([-h,0],\mathbb{R}^2)$?

$$x' = \frac{\gamma(x)}{1+k_g v}, \text{ maturation law}$$

$\Rightarrow$ delay $\varphi \mapsto \tau(\varphi)$ not uniformly bounded
way out: restrict initial conditions to $\overline{B}_R(0) \subset C([-h,0],\mathbb{R}^2)$

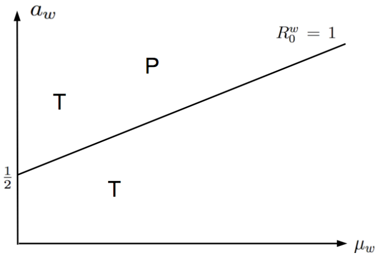
$\Rightarrow$ define $h :=$ "longest delay for all from the ball"
$\Rightarrow$

$$(w,v) \mapsto \begin{pmatrix} [2s_w(v(0))-1]d_w(v(0))w(0) - \mu_w w(0) \\ \beta(v(-\tau(v)))w(-\tau(v))\mathcal{F}(\tau(v),v) - \mu_v v(0) \end{pmatrix}$$

well-defined $\Rightarrow$ Existence and Uniqueness

Equilibria

in two-parameter space



trivial T everwhere, positive P above critical line

in "Delay Equations" book: linearized stability result:
characteristic equation

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

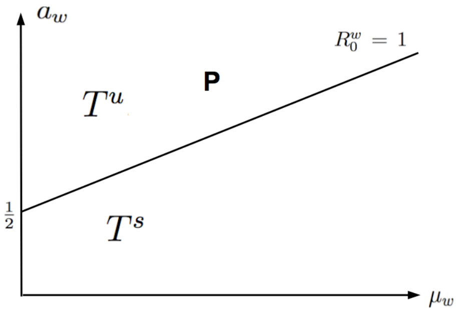
analyze characteristic equation $\longrightarrow$ define stability boundaries

$i\omega$, $\omega \geq 0$, position on imaginary axis
α, β, TWO free parameters
Stability switch condition:

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

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

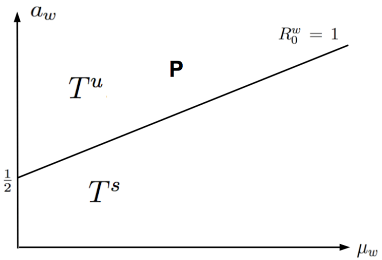
Linearized stability for the trivial equilibrium



T^s trivial stable, T^u, trivial unstable

Conclusion: Positive equilibrium destabilizes trivial

Outlook



- stability of positive upon crossing $R_0^w = 1$?
- is there a Hopf-bifurcation curve ?
  - in general $x' = g(x, v)$ can NOT be solved by hand
  - $\longrightarrow$ combine curve continuation with integration of ODE (de Roos, Diekmann, Getto, Kirkilionis, Bull. Math. Biol. 2010)