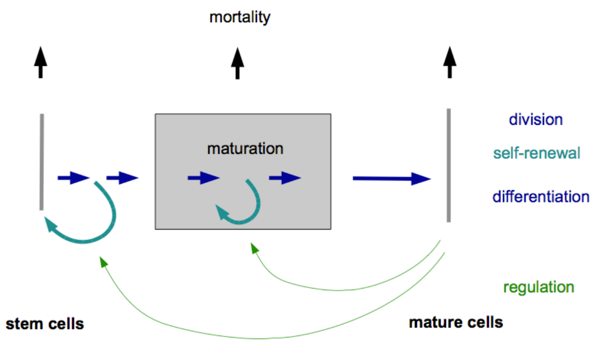
A structured population model for stem cell maturation

Ph. Getto,
BCAM (Basque Center For Applied Mathematics)
www.bcamath.org
work in progress with:
A. Marciniak-Czochra (Heidelberg)
M. Vivanco (CIC Biogune, Bilbao)

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

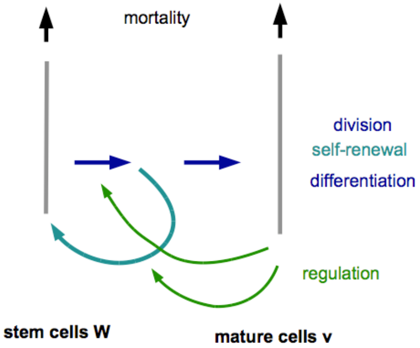
  existence, stability of equilibria (population level)
- investigate

  which quantities at cellular level regulate this?
  how?

Methods:

ODE, infinite dimensional systems

Two-compartment model



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

Existence

$$
\begin{aligned}
(w', v') &= F(w, v) \\
F(w, v) &= \begin{pmatrix} [2s_w(v) - 1]d_w(v))w - \mu_w w \\ 2[1 - s_w(v)]d_w(v)w - \mu_v w \end{pmatrix}
\end{aligned}
$$

- F is locally Lipschitz (not globally)

- solutions are bounded

$\Rightarrow$ global existence

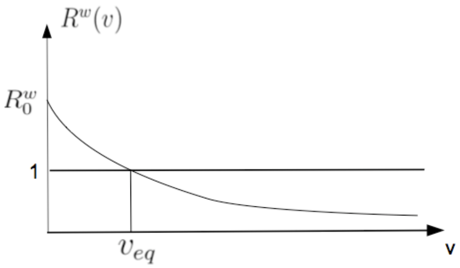
Equilibrium condition $R^w(v) = 1$

$R^w(v) = \frac{[2s_w(v)-1]d_w(v)}{\mu_w}$

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

$:=$ regulated stem cell net reproduction number

Equivalent condition on parameters



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

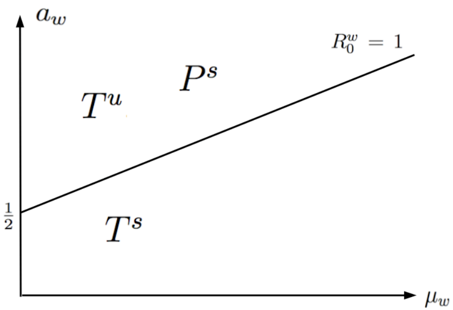
$$R_0^w := \frac{[2a_w - 1]p_w}{\mu_w},$$ *unregulated reproduction number*

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

regulation = reduction $\Rightarrow$

$$R_0^w > 1,$$

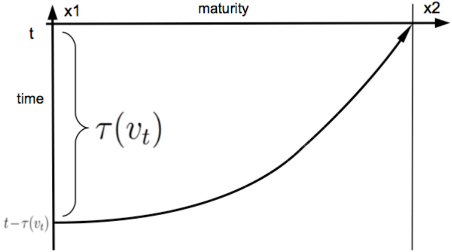
Existence border in $a_w - \mu_w$-space



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

Conclusion of linearized stability:
Exchange of stability

Maturation as a continuous process



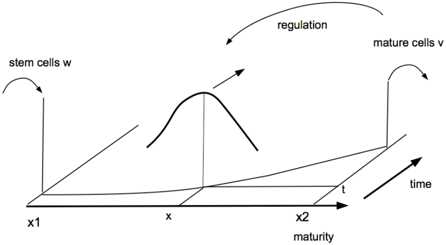
Maturity $x \in [x_1, x_2]$,

$$\begin{aligned} x'(t) &= g(x(t), v(t)) \quad \textit{maturation rate} \rightarrow \textit{regulated by mature cells } v \\ x(0) &= x_1 \end{aligned}$$

ODE well-posed $\rightarrow$ compute time $\tau(v_t)$ to mature from x_1 to x_2

$$\begin{aligned} v_t : [-h, 0] &\rightarrow \mathbb{R} \\ v_t(\theta) &= v(t+\theta),\ \theta < 0, \quad \textit{history of mature cells} \end{aligned}$$

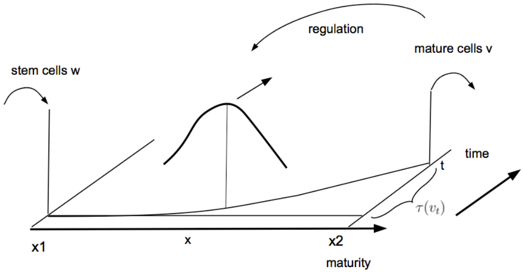
call $\tau(v_t)$ delay $\leftarrow$ state dependent



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

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

$$\begin{aligned} \mathcal{F}'(t) &= [a(x,v) - \mu(x)]\mathcal{F}(t) \\ \mathcal{F}(0) &= 1 \end{aligned}$$

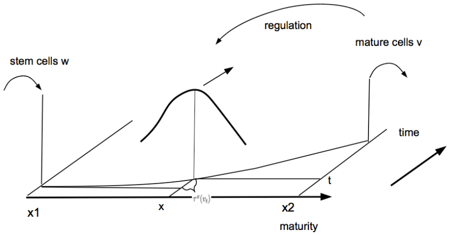


$$w' = [2s_w(v)-1]d_w(v)w - \mu_w w \quad \text{ODE} \leftarrow \textit{as in } 2-\textit{compartment}$$

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

$$\beta(v) = 2[1-s_w(v)]d_w(v), \quad \textit{stem}-\textit{progenitor}-\textit{transition rate}$$

Delay Differential Equation DDE, state dependent delay



compute progenitor cell density via integration along characteristics

$$u(t,x) = \frac{\beta(v(t-\tau^x(v_t)))w(t-\tau^x(v_t))\mathcal{F}(\tau^x(v_t),v_t)}{g(x,v(t))}$$

Different approach:
Formulate transport equation in u coupled to ODE in (v,w)
$\rightarrow$ quasilinear PDE $\rightarrow$ well-posedness open

Define a population state space

$$x'(s) = \frac{\gamma(x(s))}{1 + k^g v(-a+s)}, \; a > s > 0$$

$C \to \mathbb{R}_+; \varphi \mapsto \tau(\varphi)$ not uniformly bounded
$C \supset \overline{B}_R(0) \to \mathbb{R}_+; \varphi \mapsto \tau(\varphi)$ uniformly bounded

$\Rightarrow$ define $h :=$ "longest delay for all from the ball"
$M := \{\varphi \in C([-h,0],\mathbb{R}) : \; 0 \leq \varphi(\theta) \leq R, \; \forall \theta \in [-h,0]\}$

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

well-defined on $C([-h,0],\mathbb{R}_+) \times M$

Use results for finite delay
("Delay Equations", Diekmann et al. Springer 1995)
$\mathcal{O} \subset C([-h,0],\mathbb{R}^n)$, $F : \mathcal{O} \to \mathbb{R}^n$ locally Lipschitz
$\to$ local solution on $I_\varphi := [-h, t_\varphi)$, $t_\varphi > 0$ of

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

- a priori bounds $\to$ global existence, $I_\varphi = [-h, \infty)$
Linearized stability with characteristic equation

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

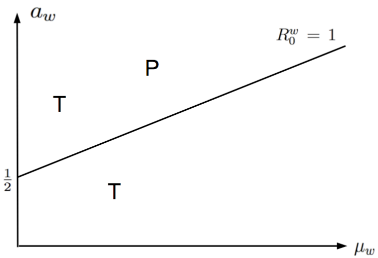
Proofs based on
Perturbation theory of dual semigroups,
see also
(Diekmann, Getto, Gyllenberg SIAM J. Math. Anal. 07)
for $x(t) = F(x_t)$, renewal equations

Alternative approach: $F : C_\sigma(-\infty, 0] \to \mathbb{R}^n$, infinite delay

$$C_\sigma(-\infty,0] := \{\varphi : \ \theta \mapsto e^{\sigma\theta}\varphi(\theta) \ \textit{continuous}, \ \textit{vanishes at} \ -\infty\}$$

exponentially weighted functions
(weight allows steady states)
(Diekmann, Gyllenberg submitted to JDE)

Existence of equilibria in two-parameter space



as in 2 compartment model
we computed $\det(zI - DF(\overline{x})e_z) = 0$, which involved
- differentiation in infinite dimensions
- differentiation of implicitly defined functions: $\tau(\varphi)$

analyze characteristic equation $\longrightarrow$ compute stability boundaries
Stability switch condition: $\omega \geq 0$, take TWO free parameters α, β

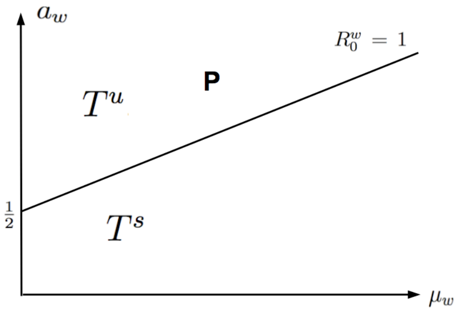
$$\det(i\omega I - DF(\overline{x};\alpha,\beta)e_{i\omega}) = 0,$$
$$F(\overline{x},\alpha,\beta) = 0$$

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

unique equilibrium $\Rightarrow$
$\omega = 0 \longrightarrow$ transcritical bifurcation
$\omega > 0 \longrightarrow$ Hopf-bifurcation

Note: condition necessary for stability switch, not sufficient

Linearized stability for the trivial equilibrium

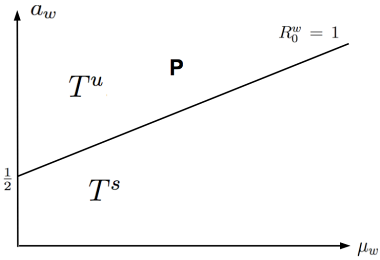


Conclusion: stability switch of trivial as with 2 compartments

Conclusions

- development of structured population model to describe maturation process of stem cells $\leftarrow$ regulation
- formulation as nonlinear *DDE*, state-dependent delay
- global existence and uniqueness
- principle of linearized stability
- computation of characteristic equation
- determination of stability region for trivial equilibrum

Outlook



- stability of positive upon crossing $R_0^w = 1$?
- is there a Hopf-bifurcation curve ?
- specify ingredients for which ODE can be solved by hand
  - $\Rightarrow$ switch condition becomes algebraic equation
- combine curve continuation with integration of ODE
  (de Roos, Diekmann, Getto, Kirkilionis, Bull. Math. Biol. 2010)