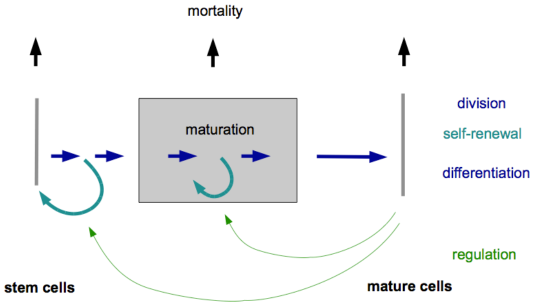
A differential equation with state dependent delay from cell population dynamics

Ph. Getto,
BCAM (Basque Center For Applied Mathematics)
joint work with:
T. Alarcon (CRM)
A. Marciniak-Czochra (Heidelberg)
M. Vivanco (CIC Biogune, Bilbao)

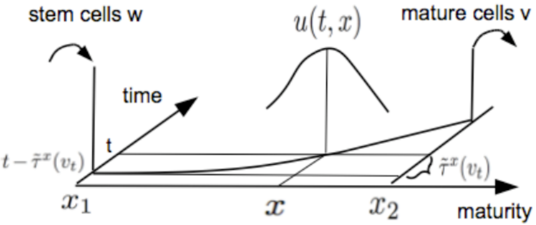
Stem cell population dynamics



understand mechanisms:
stability of population equilibrium $\leftrightarrow$ intercellular regulation

multi-compartment models by A. Marciniak-Czochra et al.

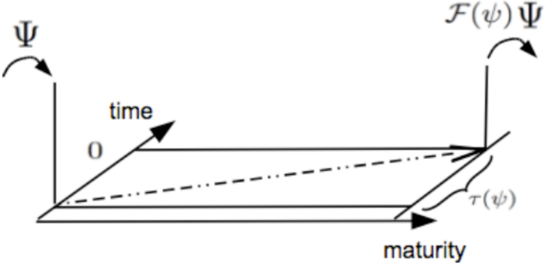
Population dynamics as transport equation



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

quasilinear PDE $\rightarrow$ no theory: well-posedness, linearized stability

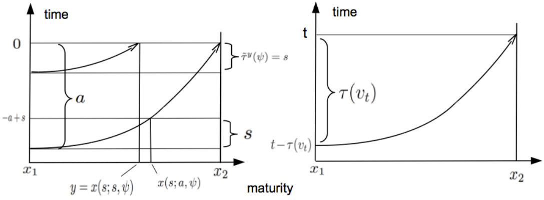
Population dynamics as Delay Equation



$$
\begin{aligned}
w' &= [2s_w(v)-1]d_w(v)w - \mu_w w \\
v' &= \beta(v(t-\tau(v_t)))w(t-\tau(v_t))\mathcal{F}(v_t) - \mu_v v
\end{aligned}
$$

$\beta(v)w$ = flow Ψ (stem cells $\to$ progenitors),
$\tau(v_t)$ = length of progenitor phase,
$\mathcal{F}(v_t)$ = progenitor net population growth factor,
if maturation at time t
$v_t(\theta) := v(t+\theta)$, $\theta < 0$ history of mature cell population

Dependence of delay on state



$x(s; a, \psi)$ solution of maturation law

$$x'(s) = g(x(s), \psi(-a+s)), \quad x(0) = x_1$$

define delay $\tau(\psi) := s$, where s solution of

$$x(s; s, \psi) = x_2$$

state dependence of delay only implicitly defined

Well-posedness for DDE with state-dependent delay

general DDE

$$f : U \to R^n$$
$$x'(t) = f(x_t), \quad t > 0, \quad x_0 = \varphi \in X_f \subset U$$

$U := C[-h, 0]$, f Lipschitz $\Rightarrow$ well-posedness

However: $f(\varphi) := \varphi(-\tau(\varphi)) \to$ not Lipschitz

Hence suppose $U \subset C^1$. Then necessarily $\varphi'(0) = f(\varphi)$

This is also sufficient:

Theorem

(Walther, Krisztin, Walther, Wu) Suppose $U \subset C^1$ open,
$f : U \to R^n$ sufficiently smooth,
$X_f := \{\varphi \in C^1[-h, 0] : \; \varphi'(0) = f(\varphi)\}$ nonempty, then
(i) X_f C^1-submanifold of U of codimension n
(ii) $\forall \; \varphi \in X_f \; \exists!$ maximal solution x^φ

Well-posedness for the stem cell maturation model

$$f(w,v) = \begin{pmatrix} q(v(0))w(0) \\ \beta(v(-\tau(v)))w(-\tau(v))\mathcal{F}(v) - \mu_v v(0) \end{pmatrix}$$

$$X_f := \{(v,w) \in C^1 : (v,w)'(0) = f(v,w)\}$$

We have shown (to appear in *Discr. Cont. Dyn. Sys. b*):

existence of maximal solution by theorem:

- $(0,0) \in X_f$. Hence X_f nonempty
  nontrivial equilibria also lie in X_f (if they exist)
- $v \mapsto \mathcal{F}(v)$, $v \mapsto \tau(v)$ smooth
- $v \mapsto \mathcal{F}(v)$, $v \mapsto \tau(v)$ smooth $\Rightarrow$ f smooth

nonnegativity

global existence

Nontrivial equilibrium

rate of self-renewal $s_w(v) = \frac{a_w}{1+k_s v}$
division rate $d_w(v) = \frac{p_w}{1+k_d v}$

$k_s = k_d = 0$ (no regulation) $\Rightarrow$ only trivial equilibrium

$k_s > 0$ or $k_d > 0$ (any regulation) $\Rightarrow$
non-trivial equilibrium exists $\Leftrightarrow \frac{2a_w}{p_w+\mu_w} > 1$

$\frac{2a_w}{p_w+\mu_w}$ stem cell individual reproduction number

$\langle\sharp\rangle$ stem cells coming in via self renewal per stem cell during its lifetime

Outlook: stability of equilibrium?

For 2 compartments equilibrium globally stable (where it exists)
work in preparation with Yukihiko Nakata

For maturation delay we conject destabilization:
goal: apply linearized stability result
(Diekmann, van Gils, Verduyn-Lunel, Walther)

characteristic equation:

$$\det\left(DF(\overline{x})e_{\lambda} - \lambda Id\right) = 0, \quad e_{\lambda}(\theta) := e^{\lambda\theta} \tag{1}$$

- all roots λ of (1) in the left half plane of $C \Rightarrow \overline{x}$ stable
- (1) λ has root in right halfplane $\Rightarrow \overline{x}$ unstable

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