Cell Replication and Control

Chronobiology

M. Dechesne

Department of Electrical Engineering and Computer Science
Montefiore Institute
University of Liège

19 January 2004

Outline

Outline

Blood Cells

Variety of blodd cells. Amon those:

- Erythrocytes (RBC)
- Megakaryocytes (evolve to platelets)
- Leukocytes (WBC):
  - Granocytes (neutophils, basophils, eosinophils)
  - Monocytes
  - Lymphocytes (B and T)

All derived from the hematopoietic stem cell (morphollogically undifferentiated).

Blood Cells Regulation

Stem cells

Balance between self-renewal and differentiation.
Local regulatory mecanism not well characterized.

Blood cells

Negative feedbacks:
a mediator regulates CFU apoptosis

- *RBC*: erythropoietin
  Related to the demand for O_2 in the body.
- *Platelets*: erythropoietin
- *Granulocytes*: G-CSF
  Also shortens maturation.

Periodic diseases

Internal origin

- Cyclical Neutropenia
- Periodic Chronic Myelogenous Leukemia
- Polycythemia Vera
- Aplastic Anemia

Peripheral origin

- Periodic autoimmune hemolytic anemia
- Cyclic thrombopenia

Outline

Clinical data

Description

Periodic fall in the circulating *neutrophils* numbers from normal values to very low values, but also oscillations from normal to high, in the levels of *platelets*, *monocytes*, *eosinophils*, and occasionnally *reticulocytes* and *lymphocytes*.

Fluctuations in putative regulators

- G-CSF: out-of-phase of neutrophil and in-phase with monocyte
- Erythropoietin: in phase with reticulocyte

Question: related to the causes of Cyclical Neutropenia **or** only secondary effects

Clinical data

Description

Periodic fall in the circulating *neutrophils* numbers from normal values to very low values, but also oscillations from normal to high, in the levels of *platelets*, *monocytes*, *eosinophils*, and occasionnally *reticulocytes* and *lymphocytes*.

Fluctuations in putative regulators

- G-CSF: out-of-phase of neutrophil and in-phase with monocyte
- Erythropoietin: in phase with reticulocyte

Question: related to the causes of Cyclical Neutropenia **or** only secondary effects

Subjects

Human

- Sporadically or inherited
- $\tau \sim$ 19-21 days

Grey collie

- Animal model (help for research!)
- $\tau \sim$ 11-15 days

Subjects

Human

- Sporadically or inherited
- $\tau \sim$ 19-21 days

Grey collie

- Animal model (help for research!)
- $\tau \sim$ 11-15 days

Control

Phlebotomy

No effects.

Hypertransfusion

- Eliminates reticulocytes cycling
  BUT reappear with *same phase* as hematocrit falls back
- No effect on neutrophile cycling

Conclusion: robustness to perturbation in peripheral control

Cytokine therapy (=injection of G-CSF)

- Increase in mean numbers of neutrophil (10-20)
- In human: increase in the amplitude and decrease in the period (21-24 days)

Origin

Loss of stability

Two classes of models, according to the origin of the destabilization:

- *peripheral control loop* (negative feedback with delay)
- *control of stem cells* (abnormally large death rate)

Though they are clinical evidences in favor of the second class of models, the first one has been widely used to study this system.

Outline

Equations

Rate of change of the peripheral (circulating) withe blood cell density:

$$\frac{dx}{dt} = -\alpha x + \mathcal{M}_0(\tilde{x})$$

where

$$\tilde{x} = \int_{\tau_m}^{\infty} x(t-u)g(u)du = \int_{-\infty}^{t-\tau_m} x(u)g(t-u)du$$

Choice for $g(\tau)$

Density of the *gamma distribution* $(a, m \geq 0)$:

$$g(\tau) = \begin{cases} 0, & \tau \leq \tau_m \\ \frac{a^{m+1}}{\Gamma(m+1)}(\tau - \tau_m)^m e^{-a(\tau-\tau_m)} & \tau_m < \tau \end{cases}$$

- Good fit on the existing data
- Used intensively to fit distributions of cell cycles times

Parameter Identification

Experimental data: $t_{1/2}$ and $N(t)$

Disparition rate

$$\alpha = \frac{\ln 2}{t_{1/2}} \in [1.7, 2.4](days^{-1})$$

Density function

$$g(t) = \alpha N(t) + N'(t)$$

$\longrightarrow$ estimation of parameters a and m

Steady State

Solution of the equation

$$\alpha x^* = \mathcal{M}_0(x^*)$$

- Unique as $\mathcal{M}_0$ is monotone decreasing
- Independent of $g(\tau)$
  BUT stability depends on $g(\tau)$

Stability analysis
Transcendental equation

Linearization $z = x - x^*$:

$$\frac{dz}{dt} \approx -\alpha z + \mathcal{M}'_{0*}\tilde{z}$$

If $z(t)$ has the form $e^{\lambda t}$, we get:

$$\lambda + \alpha = \mathcal{M}'_{0*}\left(\frac{a}{\lambda + a}\right)^{m+1} e^{-\lambda\tau_m} \qquad (1)$$

which has an infinity of solutions

Stability analysis
Bifurcations

Locus of the (supercritical) Hopf bifurcation of (1) in the $(\alpha, \mathcal{M}'_{0*})$ parameter space:

$$\begin{aligned}
\alpha(\omega) &= -\frac{\omega}{\tan[\omega\tau_m + (m+1)\tan^{-1}(\omega/a)]} \\
\mathcal{M}'_{0*}(\omega) &= -\frac{\omega}{\cos^{m+1}[\tan^{-1}(\omega/a)]\sin[\omega\tau_m + (m+1)\tan^{-1}(\omega/a)]} \\
\left.\frac{d\lambda}{d\mathcal{M}'_{0*}}\right|_{\lambda=i\omega} &< 0
\end{aligned}$$

Possible sources of destabilization

Alteration of the characteristics of $g(\tau)$

Problems:

- Experimental data: lowering of the curve (in the stability zone)
- x^*independent of $g(\tau)$

$\longrightarrow$ incapable of singlehandedly inducing an instability

Decrease of $\mathcal{M}'_{0*}$ (and $\mathcal{M}_{0*}$ so that x^* decreases)

Problem: the calculated period at bifurcation are shorter than all the period observed

Conclusion

The proposed model has to be rejected
Thus, the oscillations are probably due to a destabilization on the control process of stem cells. This solution is explored in model 2.

Outline

Equations

Coupled differential delay equations:

$$\begin{aligned} \frac{dP}{dt} &= -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau \\ \frac{dN}{dt} &= -[\beta(N) + \delta]N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau \end{aligned}$$

where

$$\beta(N) = \frac{\beta_0\theta^n}{\theta^n + N^n}$$

Steady States and Stability Analysis

$(P_1^*, N_1^*) = (0, 0)$

- *Stable* if it is the only steady state.
- *Unstable* otherwise.

$(P_2^*, N_2^*) > (0, 0)$

Stability depends on γ:

- *Unstable* if $0 < \gamma_{crit,1} < \gamma < \gamma_{crit,2}$ with supercritical Hopf bifurcation at $\gamma = \gamma_{crit,1}$.
- *Stable* otherwise

Result in good agreement with the experimental data:
$\gamma_{max}^{CN} \approx 7\gamma_{max}^{norm}$
Although the model predicts other types of bifurcations (and even chaos), those are obtained only for non-physiological values

Effect of G-CSF

The main effect of G-CSF is to reduce apoptosis.
In model 2, this correspond to a reduction of γ, thus favorizing a return in the stable zone.
This suggest possible injection of G-CSF in patients, to reduce Cyclical Neutropenia symptoms.
Note that the situation is a bit more complicated in reality, as they are also effects linked with GM-CSF, but those are not yet well-understood.

Conclusion

The proposed model succeed to modelize different features:

- apparition of Cyclical Neutropenia
- effect of G-CSF

Thus, it can be conserved for further analysis.

Outline

Summary

To modelize WBC regulation, and especially the apparition of Cyclical Neutropenia, we examined 2 models:

- The first one was based on a *destabilization in the peripheral loop, due to variations of* $\mathcal{M}'_{0*}$ *or of parameters of* $g(\tau)$. As it failed to modelize Cyclical Neutropenia, and to fit with clinical data, it had to be rejected.
- The second one was based on a *destabilization in the control loop of the stem cell population, due to delay and increse in apoptosis*. This model has been validated for Cyclical Neutropenia and effect of G-CSF.