# Cell Replication and Control Chronobiology

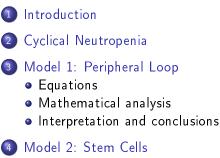
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#### 19 January 2004

Image: Image:

# Outline



- Equations
- Mathematical analysis
- Interpretation and conclusion

### 5) Summary

# Outline

### 1 Introduction

- 2 Cyclical Neutropenia
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- 4 Model 2: Stem Cells
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### Summary



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*<sub>2</sub> in the body.
- Platelets: erythropoietin
- Granulocytes: G-CSF

Also shortens maturation.

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### Periodic diseases

#### Internal origin

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

### Peripheral origin

- Periodic autoimmune hemolytic anemia
- Cyclic thrombopenia

Image: A matrix

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### 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

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### Human

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

#### Grey collie

• Animal model (help for research!)

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# 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

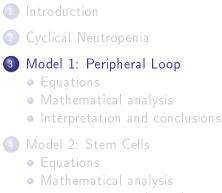
Two classes of models, according to the origin of the destabilization:

- 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.

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Interpretation and conclusion

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# Equations

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

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

where

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

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# Choice for $g(\tau)$

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

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

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

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### Parameter Identification

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

#### Disparition rate

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

#### Density function

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

ightarrow estimation of parameters *a* and *m* 

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Solution of the equation

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

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

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### 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:

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

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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:

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

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Possible sources of destabilization

### Alteration of the characteristics of g( au)

Problems:

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

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### 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.

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# Equations

Coupled differential delay equations:

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

where

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

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# 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  $\gamma$ :

- 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  $\approx 300$ M. Decheme Cell Replication and Control

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# Effect of G-CSF

The main effect of G-CSF is to reduce apoptosis.

In model 2, this correspond to a reduction of  $\gamma,$  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.

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The proposed model succeed to modelize different features:

- apparition of Cyclical Neutropenia
- effect of G-CSF

Thus, it can be conserved for further analysis.

Image: A matrix

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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.