Generalized Net Model of Human Hematopoietic System

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Abstract. Generalized Nets (GNs) are extensions of Petri nets and other their modifications. GNs are suitable tool for modelling of parallel processes. In a series of papers the authors describe the ways of functioning of the separate systems in the human body. In the present one a GN-model of the human hematopoietic system is described and its applications are discussed.

Keywords: Generalized net, Hematopoietic system, Human body

Introduction

The blood consists of liquid (plasma) and blood cells produced by the human HematoPoietic System (HPS). The blood cells in the circulation belong to three main lines. The first line are the Red Blood Cells (RBCs) which provide the gas exchange of oxygen and carbon dioxide in the tissues. The second line are the White Blood Cells (WBCs) responsible for the immunity of the body both against foreign agents (viruses, bacteria, parasites, alien substances) and internal changes (modified own body cells and the macromolecules produced by them). The WBC line consists of lymphocytes (T and B), granulocytes (neutrophils, eosinophils, basophils) and monocytes. The third cell line are the thrombocytes (platelets) which play an important role in the complex process of blood clotting thus preventing excessive bleeding and filling in defects of the blood vessel walls, in this way preserving the integrity of the body.

The Bone Marrow (BP) is the main hematopoietic organ. Maturation of all three lines of blood cells takes place in it. They all originate from one primary stem cell named Colony Forming Unit (CFU), differentiating with each successive division until reaching end stage maturity. After leaving the bone marrow some lymphocytes are finally differentiated on passing through the thymus. The following proliferation of an activated lymphocyte line takes place in the lymph nodes, tonsils and appendix.

Only mature, completely differentiated cells are normally found in the circulating blood. Their count is within certain range depending on age, sex and specific conditions. For example, during an infectious disease a higher number of immune cells necessary for destruction of the
pathogenic agent are produced, so the WBC count is increased. On climbing to a higher altitude the excessive RBC, whose normal life span in circulation is about 120 days, are destroyed in the spleen, the hemoglobin released is broken down to bile pigments which are eliminated via the GastroIntestinal Tract (GIT). The spleen has also reservoir function, retaining certain amount of blood out of the circulation and ready to release it when necessary, during increased physical activity for example.

In the present model we will present the hematopoietic system as a whole, not giving details on the maturation stages of the different cells in the bone marrow. All WBC's will be presented unified; the detail mechanisms of immune reactions will not be discussed.

Remarks on the generalized nets
The concept of a Generalized Net (GN) is described in [1]. Some GNs may not have some of the components, thus giving rise to special classes of GNs called "reduced GNs". For the needs of the present research we shall use (and describe) one of the reduced types of GNs.

This information is Copyright© 1998 Personal TeX, Inc. All Rights Reserved. Formally, every transition of this reduced class of GNs is described by (Fig. 1):

\[ Z = (L', L'', r, \square), \]

where:

(a) \(L'\) and \(L''\) are finite, non-empty sets of places (the transition's input and output places, respectively). For the transition in Fig. 1 these are

\[ L' = \{l'_1, l'_2, \ldots, l'_m\} \]

and

\[ L'' = \{l''_1, l''_2, \ldots, l''_n\}; \]

(b) \(r\) is the transition's condition determining which tokens will pass (or transfer) from the transition's inputs to its outputs; it has the form of an Index Matrix (IM; see [1]):

Fig. 1 GN-transition
\[ r = \begin{array}{c|c}
\cdots & \cdots \\
\vdots & \vdots \\
\cdots & \cdots \\
{l_i} & (r_{i,j} \text{ - predicate }) \\
x_i & (1 \leq i \leq m, 1 \leq j \leq n)
\end{array} \]

\( r_{i,j} \) is the predicate which corresponds to the \( i \)-th input and \( j \)-th output places. When its truth value is "true", a token from the \( i \)-th input place can be transferred to the \( j \)-th output place; otherwise, this is not possible.

(c) \( \square \) is a Boolean expression. It may contain as variables the symbols which serve as labels for transition's input places, and it is an expression built up from variables and the Boolean connectives \( \land \) and \( \lor \) whose semantics is defined as follows:

\[ \land \left( l_{i_1}, l_{i_2}, \ldots, l_{i_u} \right) \triangleq \text{every place } l_{i_1}, l_{i_2}, \ldots, l_{i_u} \text{ must contain at least one token}, \]

\[ \lor \left( l_{i_1}, l_{i_2}, \ldots, l_{i_u} \right) \triangleq \text{there must be at least one token in all places } l_{i_1}, l_{i_2}, \ldots, l_{i_u}, \text{ where } \{l_{i_1}, l_{i_2}, \ldots, l_{i_u}\} \subset L'. \]

When the value of a type (calculated as a Boolean expression) is "true", the transition can become active, otherwise it cannot.

The ordered four-tuple

\[ E = \langle A, K, X, \Phi \rangle \]

is called simplest reduced Generalized Net (briefly, we shall use again "GN") if:

(a) \( A \) is a set of transitions;

(b) \( K \) is the set of the GN's tokens.

(c) \( X \) is the set of all initial characteristics the tokens can receive when they enter the net;

(d) \( \Phi \) is a characteristic function which assigns new characteristics to every token when it transfers from an input to an output place of a given transition.

Over the GNs a lot of types of operators are defined. One of these types is the set of hierarchical operators. One of them changes a given GN-place with a whole subnet (see [1]). Below, having in mind this operator, we shall use three places that will represent three separate GNs, constructed by the authors early.

**A generalized net model**

Here we shall construct a GN-model of human hematopoetic system. The GN contains 12 transitions and 12 types of tokens (in special places of the separate transitions), that represent respectively:
There are two other (special) tokens $\nu$ and $\pi$-tokens that represent respectively foreign agents and modified own body cells and their products activating the immunity (in places $l_{11}$ and $l_{12}$).

When some of these tokens splits, e.g., token $\omega \in \{\alpha, ..., \theta\}$, let us assume that it generate two or more tokens that we shall note by $\omega, \omega_1, \omega_2, ...$ and the first of them ($\omega$) will continue to stay in its place, while the other ones will go somewhere in the net. Each one of the above mentioned tokens will have as initial and current characteristics the status of the respective system, organ or process and all necessity for the model parameters of this system, organ or process.

The GN contains eight transitions that have the following descriptions (see Fig. 2).

\[
Z_1 = \left\{ \{l_{19}\}, l_1, l_2, l_3, l_4 \right\},
\begin{array}{cccc}
l_4 & l_1 & l_2 & l_3 & l_4 \\
l_{19} & true & true & true & true \\
\end{array}
\]

Tokens $\alpha$ and $\varepsilon_7$ unite in place $l_4$ to token $\alpha$ and token $\alpha$ splits to four tokens -- $\alpha$ staying in place $l_4$ with the above mentioned characteristic, token $\alpha_1$ in place $l_1$, token $\alpha_2$ in place $l_2$ and token $\alpha_3$ in place $l_3$. The three later tokens do not obtain any characteristic.

\[
Z_2 = \left\{ \{l_5\}, \{l_5, l_6\} \right\},
\begin{array}{cc}
l_5 & l_6 \\
l_5 & true & false \\
\end{array}
\]

Tokens $\beta$ and $\alpha_1$ unite to token $\beta$ in place $l_5$ with the above mentioned characteristic. Token $\beta$ splits to two tokens - the same token $\beta$ and to token $\beta_1$ that enters place $l_6$ with characteristic "current status of thrombocytes on different maturation stages".
\[ Z_3 = < \{ l_2, l_7 \}, \{ l_7, l_8 \}, \begin{array}{c|cc} l_7 & l_8 \\ \hline \text{true} & \text{false} \end{array} >. \]

Tokens \( \gamma \) and \( \alpha_2 \) unite to token \( \gamma \) in place \( l_7 \) with the above mentioned characteristic. Token \( \gamma \) splits to two tokens - the same token \( \gamma \) and to token \( \gamma_1 \) that enters place \( l_8 \) with characteristic "current status of RBCs on different maturation stages".

\[ Z_4 = < \{ l_3, l_9 \}, \{ l_9, l_{10} \}, \begin{array}{c|cc} l_9 & l_{10} \\ \hline \text{true} & \text{true} \end{array} >. \]

Tokens \( \delta \) and \( \alpha_3 \) unite to token \( \delta \) in place \( l_9 \) with the above mentioned characteristic. Token \( \delta \) splits to two tokens - the same token \( \delta \) and to token \( \delta_1 \) that enters place \( l_{10} \) with characteristic "current status of WBC on different maturation stages".

\[ Z_5 = < \{ l_6, l_7, l_8, l_{11}, l_{12}, l_{20}, l_{21}, l_{23}, l_{25}, l_{27}, l_{29}, l_{31} \}, l_{13}, l_{14}, l_{15}, l_{16}, l_{17}, l_{18}, l_{19}, l_{20} \}, \]

\[
\begin{array}{cccccccc}
\text{l}_6 & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_7 & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_8 & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{11} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{12} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{20} & \text{true} & \text{true} & \text{true} & \text{true} & \text{true} & \text{true} & \text{true} & \text{true} >. \\
\text{l}_{21} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{23} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{25} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{27} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{29} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\text{l}_{31} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{false} & \text{true} \\
\end{array}
\]

Tokens \( \beta_1, \gamma_1, \delta_1, \varepsilon, \zeta_1, \eta_1, \theta_1, \iota_1, \kappa_1, \lambda_1, \nu \) and \( \pi \) unite to token \( \varepsilon \) in place \( l_{20} \) and token \( \varepsilon \) splits to eight tokens: token \( \varepsilon \) staying in place \( l_{20} \) with the above mentioned characteristic, token \( \varepsilon_1 \) in place \( l_{13} \) with characteristic "quantity and quality of blood to the RS", token \( \varepsilon_2 \) in place \( l_{14} \) with characteristic "quantity and quality of blood to the thymus", token \( \varepsilon_3 \) in place \( l_{15} \) with the characteristic "quantity and quality of blood to the spleen", token \( \varepsilon_4 \) in place \( l_{16} \) with characteristic "quantity and quality of blood to the lymph nodes, tonsils and appendix".
token $\varepsilon_5$ in place $l_{17}$ with characteristic "quantity and quality of blood to the kidneys",
token $\varepsilon_6$ in place $l_{18}$ with characteristic "quantity and quality of blood to the liver",
and token $\varepsilon_7$ in place $l_{19}$ with characteristic "quantity and quality of blood to the BM".

\[
Z_6 = \langle \{l_{13}, l_{22}\}, \{l_{21}, l_{22}\}, \frac{l_{21}}{l_{22}} \mid \frac{true}{false} \rangle.
\]

Tokens $\varepsilon_1$ and $\zeta$ unite to token $\zeta$ in place $l_{22}$ with the above mentioned characteristic. Token $\zeta$ splits to two tokens - the same token $\zeta$ and to token $\zeta_1$ that enters place $l_{21}$ with characteristic "quantity and quality of blood oxygen received by the RS".

\[
Z_7 = \langle \{l_{14}, l_{24}\}, \{l_{23}, l_{24}\}, \frac{l_{23}}{l_{24}} \mid \frac{true}{false} \rangle.
\]

Tokens $\varepsilon_2$ and $\eta$ unite to token $\eta$ in place $l_{24}$ with the above mentioned characteristic. Token $\eta$ splits to two tokens - the same token $\eta$ and to token $\eta_1$ that enters place $l_{23}$ with characteristic "quantity and quality of WBCs (lymphocytes) transformed in the thymus".

\[
Z_8 = \langle \{l_{15}, l_{26}\}, \{l_{25}, l_{26}\}, \frac{l_{25}}{l_{26}} \mid \frac{true}{false} \rangle.
\]

Tokens $\varepsilon_3$ and $\theta$ unite to token $\theta$ in place $l_{26}$ with the above mentioned characteristic. Token $\theta$ splits to two tokens - the same token $\theta$ and to token $\theta_1$ that enters place $l_{25}$ with characteristic "quantity and quality of blood stored in the spleen".

\[
Z_9 = \langle \{l_{16}, l_{28}\}, \{l_{27}, l_{28}\}, \frac{l_{27}}{l_{28}} \mid \frac{true}{false} \rangle.
\]

Tokens $\varepsilon_4$ and $\iota$ unite to token $\iota$ in place $l_{28}$ with the above mentioned characteristic. Token $\iota$ splits to two tokens - the same token $\iota$ and to token $\iota_1$ that enters place $l_{27}$ with characteristic "quantity and quality of WBCs (lymphocytes) in the lymph nodes, tonsils and appendix".

\[
Z_{10} = \langle \{l_{17}, l_{30}\}, \{l_{29}, l_{30}\}, \frac{l_{29}}{l_{30}} \mid \frac{true}{false} \rangle.
\]
Fig. 2 GN-model of human hematopoietic system

Tokens $\varepsilon_4$ and $\kappa$ unite to token $\kappa$ in place $l_{30}$ with the above mentioned characteristic. Token $\kappa$ splits to two tokens - the same token $\kappa$ and to token $\kappa_1$ that enters place $l_{29}$ with characteristic "quantity and quality of RBC-growth stimulating hormone (erythropoetin) product by the kidney".

$$Z_{11} = \{ l_{18}, l_{33} \}, \{ l_{31}, l_{32}, l_{33} \}, \begin{array}{lll} l_{18} & l_{31} & l_{32} & l_{33} \\ false & false & true & . \\ l_{33} & true & true & true \end{array}$$
Tokens λ and ε₁ unite to token λ in place \( l_{33} \) with the above mentioned characteristic. Token \( \lambda \) splits to three tokens - the same token \( \lambda \), token \( \lambda_1 \) that enters place \( l_{31} \) with characteristic "quantity and quality of blood cleaned from the liver", and token \( \lambda_2 \) that enters place \( l_{32} \) with characteristic "quantity and quality of bile eliminated by GIT".

\[
Z_{12} = \langle \{l_{32}, l_{35}\}, \{l_{34}, l_{35}\}, \begin{array}{c|c}
\lambda_{32} & \lambda_{35} \\
false & true \\
l_{35} & W \\
true & \end{array} \rangle.
\]

\( W = \) "there are excrements to be eliminated".

Tokens \( \mu \) and \( \lambda_2 \) unite to token \( \mu \) in place \( l_{35} \) with the above mentioned characteristic. Token \( \mu \) splits to two tokens - the same token \( \mu \) and to token \( \mu_1 \) that enters place \( l_{34} \) with characteristic "quantity and quality of the excrements".

**Conclusion**

The present study is an attempt to model the specific activity of a concrete system and its relationships with the other human body systems by means of the GN theory.

The developed GN model can be used for simulation of processes in the HPS, such as prediction of the reactions of the system to changes in the environment (toxic agents, changes in concentration or lack of substances, dysfunction of other body systems etc.). This model can also assist investigations of the effect of new drugs on the HPS. The current research is the first step in this direction. In the future, the basic logical conditions that determine the way of functioning of the HPS will be described in substantial detail. The theoretical results of analytical approaches to modelling processes in the HPS will be represented within our model - prepared in a system-theoretical way, these will be implemented through initial, current and final tokens characteristics of the extended GN-model. The modelled processes will be estimated by intuitionistic fuzzy values (see, [2]).

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**References**