



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):

$$Z = \langle L', L'', r, \square \rangle,$$

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

$$L' = \{l'_1, l'_2, \dots, l'_m\}$$

and

$$L'' = \{l''_1, l''_2, \dots, l''_n\};$$

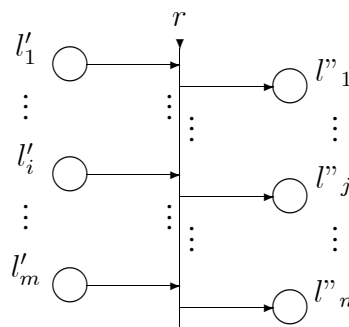


Fig. 1 GN-transition

(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]):

$$r = \begin{array}{c|ccc} & l''_1 & \dots & l''_j & \dots & l''_n \\ \hline l'_1 & & & & & \\ \vdots & & & & & \\ l'_i & & & r_{i,j} & & \\ \vdots & & & & & \\ l'_m & & & & & \end{array} \quad ;$$

($r_{i,j}$ – predicate)
 ($1 \leq i \leq m, 1 \leq j \leq n$)

$r_{i,j}$ 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 \wedge and \vee whose semantics is defined as follows:

$$\begin{aligned} \wedge(l_{i_1}, l_{i_2}, \dots, l_{i_u}) & - \text{ every place } l_{i_1}, l_{i_2}, \dots, l_{i_u} \text{ must contain at least one token,} \\ \vee(l_{i_1}, l_{i_2}, \dots, l_{i_u}) & - \text{ there must be at least one token in all places } l_{i_1}, l_{i_2}, \dots, l_{i_u}, \\ & \text{ where } \{l_{i_1}, l_{i_2}, \dots, l_{i_u}\} \subset L'. \end{aligned}$$

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) Φ 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:



- α -token -- status of BM (in place l_4),
- β -token -- status (quantity and quality) of the trombocytes in maturation process (in place l_5),
- γ -token -- status (quantity and quality) of the RBCs in maturation process (in place l_7),
- δ -token -- status (quantity and quality) of the WBCs in maturation process (in place l_9),
- ε -token -- status of the Cardiovascular System (CS) (in place l_{20}),
- ζ -token -- status of the Respiratory System (RS) (in place l_{22}),
- η -token -- status of the thymus (in place l_{24}),
- θ -token -- status of the spleen (in place l_{26}),
- ι -token -- status of the lymph nodes, tonsils and appendix (in place l_{28}),
- κ -token -- status of the kidneys (in place l_{30}),
- λ -token -- status of the liver (in place l_{33}),
- μ -token -- status of the GIT (in place l_{35}).

There are two other (special) tokens ν and π -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 $\omega \in \{\alpha, \dots, \theta\}$, let us assume that it generate two or more tokens that we shall note by $\omega, \omega_1, \omega_2, \dots$ and the first of them (ω) 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 charactrsistic 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).

$$Z_1 = \langle \{l_{4,19}\}, l_1, l_2, l_3, l_4 \rangle,$$

	l_1	l_2	l_3	l_4	
l_4	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	$>$
l_{19}	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	

Tokens α and ε_7 unite in place l_4 to token α and token α splits to four tokens -- α staying in place l_4 with the above mentioned characteristic, token α_1 in place l_1 , token α_2 in place l_2 and token α_3 in place l_3 . The three later tokens do not obtain any characteristic.

$$Z_2 = \langle \{l_1, l_5\}, \{l_5, l_6\}, \begin{array}{c|cc} & l_5 & l_6 \\ \hline l_1 & \textit{true} & \textit{false} \\ l_5 & \textit{true} & \textit{true} \end{array} \rangle.$$

Tokens β and α_1 unite to token β in place l_5 with the above mentioned characteristic. Token β splits to two tokens - the same token β and to token β_1 that enters place l_6 with characteristic "current status of trombocytes on different maturation stages".



$$Z_3 = \langle \{l_2, l_7\}, \{l_7, l_8\}, \begin{array}{c|cc} & l_7 & l_8 \\ \hline l_2 & true & false \\ l_7 & true & true \end{array} \rangle .$$

Tokens γ and α_2 unite to token γ in place l_7 with the above mentioned characteristic. Token γ splits to two tokens - the same token γ and to token γ_1 that enters place l_8 with characteristic "current status of RBCs on different maturation stages".

$$Z_4 = \langle \{l_3, l_9\}, \{l_9, l_{10}\}, \begin{array}{c|cc} & l_9 & l_{10} \\ \hline l_3 & true & false \\ l_9 & true & true \end{array} \rangle .$$

Tokens δ and α_3 unite to token δ in place l_9 with the above mentioned characteristic. Token δ splits to two tokens - the same token δ and to token δ_1 that enters place l_{10} with characteristic "current status of WBC on different maturation stages".

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

	l_{13}	l_{14}	l_{15}	l_{16}	l_{17}	l_{18}	l_{19}	l_{20}	
l_6	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_7	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_8	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{11}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{12}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{20}	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	<i>true</i>	$> .$
l_{21}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{23}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{25}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{27}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{29}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	
l_{31}	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>false</i>	<i>true</i>	

Tokens $\beta_1, \gamma_1, \delta_1, \varepsilon, \zeta_1, \eta_1, \theta_1, \iota_1, \kappa_1, \lambda_1, \nu$ and π unite to token ε in place l_{20} and token ε splits to eight tokens: token ε staying in place l_{20} with the above mentioned characteristic, token ε_1 in place l_{13} with characteristic "quantity and quality of blood to the RS", token ε_2 in place l_{14} with characteristic "quantity and quality of blood to the thymus", token ε_3 in place l_{15} with the characteristic "quantity and quality of blood to the spleen", token ε_4 in place l_{16} with characteristic "quantity and quality of blood to the lymph nodes, tonsils and appendix",



token ε_5 in place l_{17} with characteristic "quantity and quality of blood to the kidneys",
token ε_6 in place l_{18} with characteristic "quantity and quality of blood to the liver",
and token ε_7 in place l_{19} with characteristic "quantity and quality of blood to the BM".

$$Z_6 = \langle \{l_{13}, l_{22}\}, \{l_{21}, l_{22}\}, \begin{array}{c|cc} & l_{21} & l_{22} \\ \hline l_{13} & true & false \\ l_{21} & true & true \end{array} \rangle .$$

Tokens ε_1 and ζ unite to token ζ in place l_{22} with the above mentioned characteristic. Token ζ splits to two tokens - the same token ζ and to token ζ_1 that enters place l_{21} with characteristic "quantity and quality of blood oxygen received by the RS".

$$Z_7 = \langle \{l_{14}, l_{24}\}, \{l_{23}, l_{24}\}, \begin{array}{c|cc} & l_{23} & l_{24} \\ \hline l_{14} & true & false \\ l_{23} & true & true \end{array} \rangle .$$

Tokens ε_2 and η unite to token η in place l_{24} with the above mentioned characteristic. Token η splits to two tokens - the same token η and to token η_1 that enters place l_{23} with characteristic "quantity and quality of WBCs (lymphocytes) transformed in the thymus".

$$Z_8 = \langle \{l_{15}, l_{26}\}, \{l_{25}, l_{26}\}, \begin{array}{c|cc} & l_{25} & l_{26} \\ \hline l_{15} & true & false \\ l_{25} & true & true \end{array} \rangle .$$

Tokens ε_3 and θ unite to token θ in place l_{26} with the above mentioned characteristic. Token θ splits to two tokens - the same token θ and to token θ_1 that enters place l_{25} with characteristic "quantity and quality of blood stored in the spleen".

$$Z_9 = \langle \{l_{16}, l_{28}\}, \{l_{27}, l_{28}\}, \begin{array}{c|cc} & l_{27} & l_{28} \\ \hline l_{16} & true & false \\ l_{27} & true & true \end{array} \rangle .$$

Tokens ε_4 and ι unite to token ι in place l_{28} with the above mentioned characteristic. Token ι splits to two tokens - the same token ι and to token ι_1 that enters place l_{27} with characteristic "quantity and quality of WBCs (lymphocytes) in the lymph nodes, tonsils and appendix".

$$Z_{10} = \langle \{l_{17}, l_{30}\}, \{l_{29}, l_{30}\}, \begin{array}{c|cc} & l_{29} & l_{30} \\ \hline l_{17} & true & false \\ l_{29} & true & true \end{array} \rangle .$$

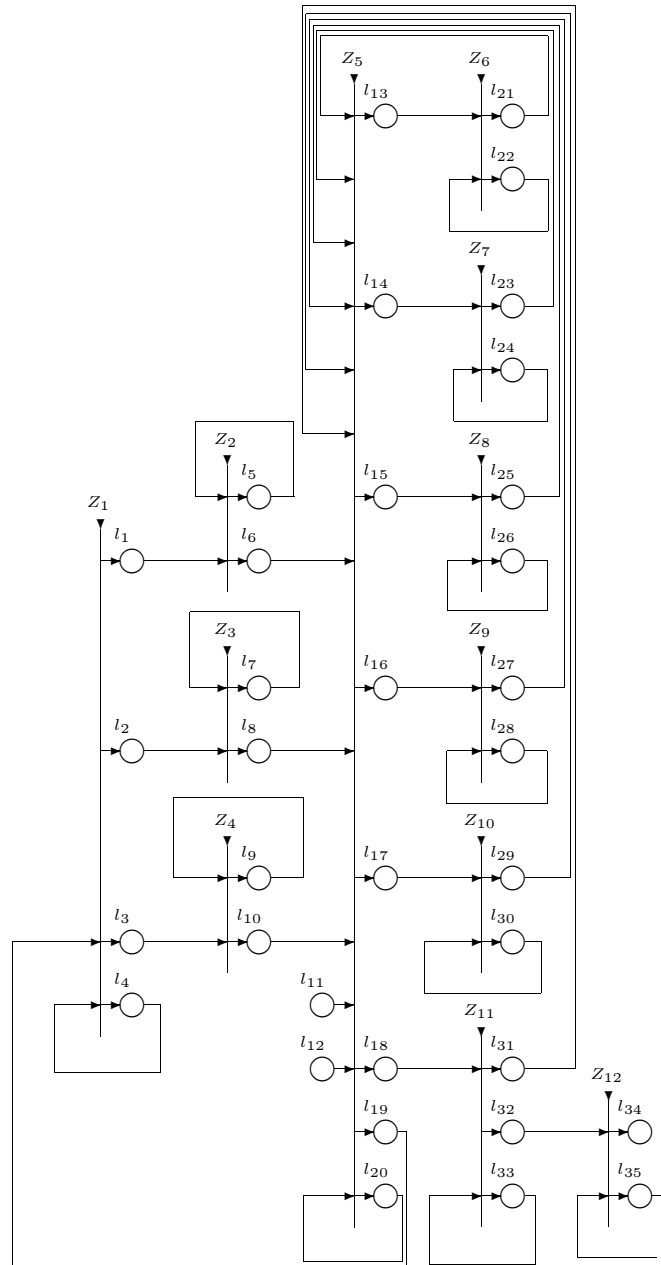


Fig. 2 GN-model of human hematopoietic system

Tokens ε_4 and κ unite to token κ in place l_{30} with the above mentioned characteristic. Token κ splits to two tokens - the same token κ and to token κ_1 that enters place l_{29} with characteristic "quantity and quality of RBC-growth stimulating hormone (erythropoietin) product by the kidney".

$$Z_{11} = \langle \{l_{18}, l_{33}\}, \{l_{31}, l_{32}, l_{33}\}, \begin{array}{c|ccc} & l_{31} & l_{32} & l_{33} \\ \hline l_{18} & false & false & true \\ l_{33} & true & true & true \end{array} \rangle .$$



Tokens λ and ε_7 unite to token λ in place l_{33} with the above mentioned characteristic. Token λ splits to three tokens - the same token λ , token λ_1 that enters place l_{31} with characteristic "quantity and quality of blood cleaned from the liver", and token λ_2 that enters place l_{32} with characteristic "quantity and quality of bile eliminated by GIT".

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

W = "there are excrements to be eliminated".

Tokens μ and λ_2 unite to token μ in place l_{35} with the above mentioned characteristic. Token μ splits to two tokens - the same token μ and to token μ_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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