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Feed-forward and Feedback Mechanisms in a Dynamic Model of Human T Cell Development and Regulation

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Abstract. *We describe a computational model of human T cell regulatory dynamics. We used this model to simulate changes in T cell pool numbers and for studying feedback and feed-forward responses in and among these pools. The pools identified were the bone marrow stem cell compartment, early and late thymocyte compartments and the peripheral compartment of mature T lymphocytes. Simulated data showed variable intercompartmental strengths indicative of a range of sensitivities to feedback regulation and respective variable feed-forward responses. The results compare well to known clinical and experimental data, rendering the computational model a good basis for further research in T cell development and regulation.*

Feedback control constitutes one of the most important mechanisms that allow the hematopietic and lymphatic systems to adapt the body's defense reactions to changes in the environment; alterations in peripheral cell pool numbers influence proliferative or inhibitory responses in (the less mature) thymic and stem cell pools. This phenomenon causes the clinically diagnostic leukocytosis and "*shift to the left*" with less mature neutrophils as commonly noted in the peripheral blood in severe bacterial infections, or lymphocytosis with less mature lymphocytes in viral infections (1). Metcalf once suggested that a disturbed feedback mechanism may be contributory to neoplastic cell proliferation (2). We collected and quantified T cell data arising from different acute and chronic viral infections to further substantiate this phenomenon (3-5).

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In order to study such cell pool changes in infectious and neoplastic diseases, we designed and validated a computational model for simulating T cell pool dynamic changes (6-8). The model is based upon cells shifting from immature to mature cell pools under the influence of various factors, as well as of feedback and feed-forward mechanisms according to current concepts of the T cell immune system and using standard textbook data (9-11). The proposed model has also proven useful for simulating cellular changes in chronic viral infections as in cases of pseudolymphomatous lymphoproliferation, *i.e.* the Canale-Smith syndrome (8). The present study reports data of stability testing of this model by alterations of virtual feed-forward and feedback parameter values and discusses their possible biological implications.

Materials and Methods

The basic conceptual model (for technical details see (6-8)) is presented in Figures 1 and 2 with its full mathematical representation as:

$$\dot{w}=\mu_w+w\left(\sum_{h=1}^{H}P_{w_h}-\sum_{j=1}^{J}D_{w_j}-\sum_{k=1}^{K}I_{w_k}+\alpha x-by+cz\right),$$

$$\dot{x}=\mu_x+x\left(\sum_{l=1}^{L}P_{x_l}-\sum_{m=1}^{M}D_{x_m}-\sum_{n=1}^{N}I_{x_n}-dy+ez\right)+fw,$$

$$\dot{y}=\mu_y+y\left(\sum_{q=1}^{Q}P_{y_q}-\sum_{r=1}^{R}D_{y_r}-\sum_{s=1}^{S}I_{y_s}+gz\right)+ux,$$

$$\dot{z}=\mu_z+z\left(\sum_{\theta=1}^{\Theta}P_{z_\theta}-\sum_{\omega=1}^{\Omega}D_{z_\omega}-\sum_{\gamma=1}^{\Gamma}I_{z_\gamma}\right)+\delta\gamma. \quad (1)$$

Detailed stability and validity testing using data from our human patients (3-5,9) confirmed the practicality of our approach through numerous model simulation studies (7). The model functions in a circular ring-type network configuration with feed-forward and feedback connections expressed as a system of four interrelated ordinary differential equations (ODEs) as shown schematically in Figure 2. Notations used are as follows:

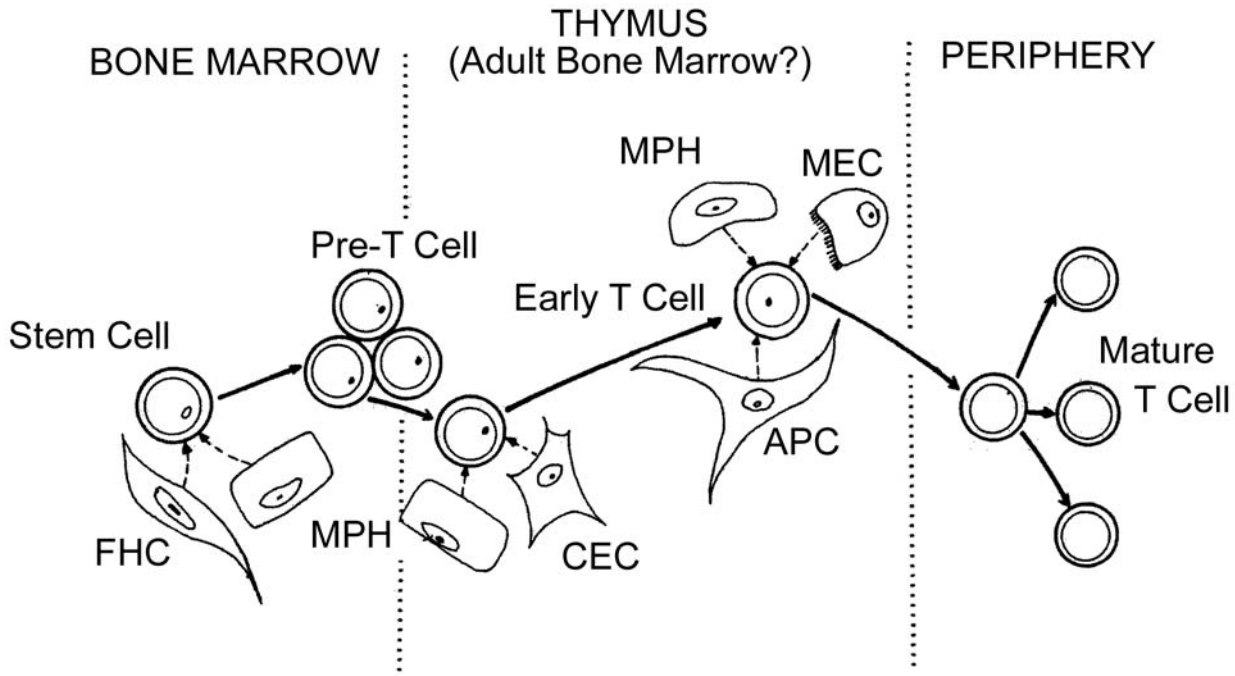

Figure 1. *Basic steps in T cell maturation and microenvironmental influences: stem cells from the bone marrow enter and move through the thymus, where they expand and undergo maturation and selection under the influence of factors from epithelial cells, macrophages and antigen presenting cells. They leave the thymus into the periphery (blood and lymphoid tissues) as mature virgin lymphocytes (FHC: fibrohistiocyte; MPH: macrophage; CEC: cortical epithelial cell; MEC: medullary epithelial cell; APC: antigen presenting cell).*

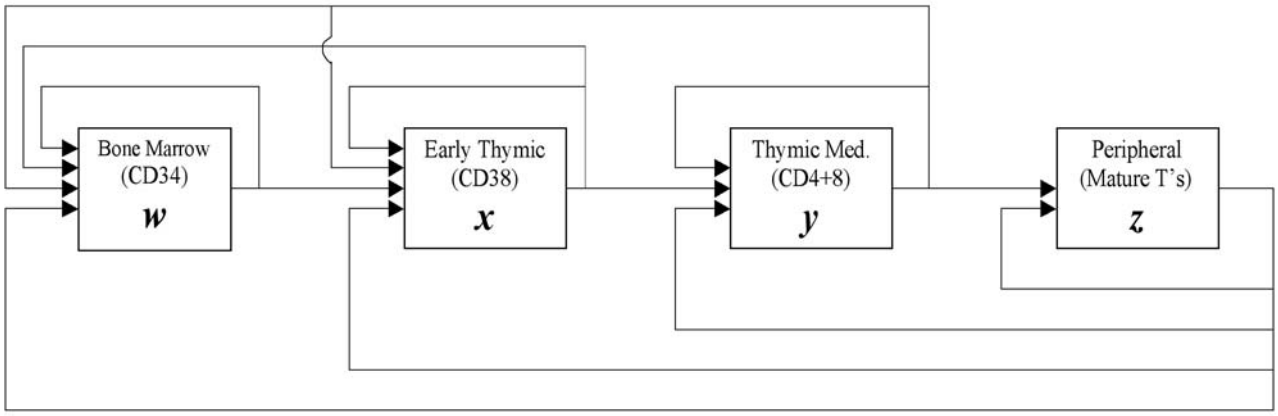

Figure 2. *Simplified block diagram of computer model with individual maturation steps of T lymphocytes under feed-forward and feedback control. Selective cell markers identified in the individual cell pools are used in a way that they can also be determined in the peripheral blood, where these cells are indicative of their activities in individual pools. (Note: in the practical approach, additional markers are applied for differential diagnosis of cells).*

- *w, x, y, z*: Number of T cells in the bone marrow (stem cells), thymic cortex, thymic medulla (immature stages) and periphery (mature cells), respectively at any given time *t*.
- The dot notation indicates time rate of change of cell numbers in each pool (*e.g.* $\dot{w} = dw/dt$)
- $\{P, D, I\}_{[w\text{-}z]}$: set of factors regulating proliferation, differentiation and inhibition respectively, in cell pools *w, x, y* and *z*. Each individual *P, D,* or *I* factor is represented by a real number in the model. For the stem cell pool (*w*), for example, there would be a total of *H* proliferation factors, *J* differentiation factors and *K* inhibition factors in a full-blown model, and so on for the other three pools. At this time we do not have data on all such factors in the model. Here we have estimated them by "pre-summating" each pool's factor set so as to simplify both the model (by reducing the overall number of parameters) and increasing the speed of simulations. Lumping factors in this way reduces the overall validity of the model somewhat and is thus a trade-off between speed/efficiency and accuracy.

Table I. *Base model parameters for simulating normal T cell pools across the lifespan of a typical normal individual used in* **(2)** *and Figure 3.*

$w(t_0)=100.0$	$x(t_0)=1.0 \times 10^4$	$y(t_0)=1.0 \times 10^7$	$z(t_0)=1.0 \times 10^5$
$\mu_w=50.0$	$\mu_x=25.0$	$\mu_y=2.5 \times 10^6$	$\mu_z=1.0 \times 10^4$
$\Sigma\ (P_w - D_w - I_w)=-0.531$	$\alpha=5.0 \times 10^{-7}$	$b=2.0 \times 10^{-7}$	$c=5.0 \times 10^{-7}$
$\Sigma\ (P_x - D_x - I_x)=-0.04$	$d=-5.5 \times 10^{-8}$	$e=3.6 \times 10^{-7}$	$f=5.0 \times 10^{-7}$
$\Sigma\ (P_y - D_y - I_y)=-0.7$	$g=1.0 \times 10^{-7}$	$u=0.05$	$\delta=0.001$
$\Sigma\ (P_z - D_z - I_z)=-0.023$			

Pool values were downsized exponentially while maintaining the inter-pool relationships in order to keep computational working times within realistic limits; for the same reason initial pool values at t_0 were adjusted from the textbook values of $w=1 \times 10^5$; $x=2.0 \times 10^7$; $y=4.5 \times 10^{11}$ and $z=8.0 \times 10^9$.

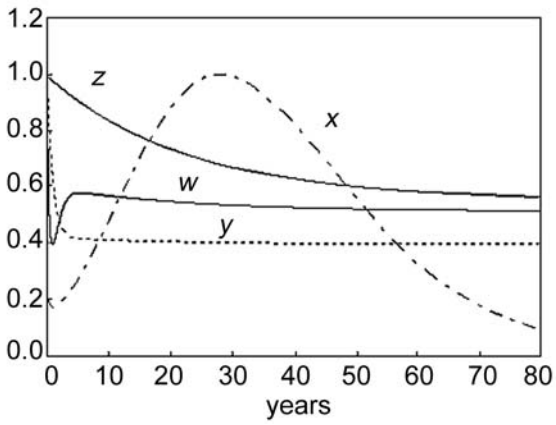

Figure 3. *Computer simulation of normative data over a typical normal person's lifespan (birth to 80 years). Shown are relative cell counts vs. time for cell pools in bone marrow (w: stem cells), thymic cortex and medulla (x, y) and peripheral total T cells (z). Absolute cell counts are normalized so as to fit all four curves into a single plot.*

- $\mu_{[w\text{-}z]}$: average regeneratory potential of each cell pool.
- $a - g$, u, δ: scalar gains (strengths) of the feed-forward and feedback connections within and between cell pools.

The model's feedback terms are implemented as a multiplication of the state variable of the pool itself, the inflow from the forward pool and a compartmental cross-renewal rate implemented as a scalar gain term (*e.g.*, axw). In this sense, $\alpha - g$, u and δ represent virtual values for the "strength of connections" between pools, thus of feedback and feed-forward mechanisms. Their actual values under normal conditions (*i.e.* in the healthy individual) were determined by use of both manual and semi-automated search procedures (serial parameter search algorithm) during the model validation phase. These procedures were described in detail in previous publications (6-8).

The model operates with textbook data for normal pool sizes (9-11). Simulations were carried out using Matlab software developed by us. The ODEs were solved using fourth-order Runge-Kutta integration. Each computer run was simulated continuously over a given timeframe, *e.g.*, for establishing the lifetime values from birth ($t_0 = 0$) to the age of 80 years. The respective initial cell pool conditions and parameter values that we used for simulating a clinically normal human adult are listed in Table I.

In order to further study the sensitivity of the cell pools w - z to feedback and feed-forward control, we varied the factorial parameters $\alpha - g$, u and δ (*i.e.* the virtual values for the strength of connections between pools) in a stepwise manner (one at a time with all other gains fixed) and monitored the resulting shifts in cell pools. Cut-off points for the present study were changes in cell numbers, which – according to clinical experience – are usually incompatible with an average healthy human individual (*i.e.* more than 30% deviation from normal average).

Results

When substituting parameters from Table I into **(1)**, one obtains the following set of ordinary differential equations:

$$\dot{w} = 50.0 - 0.531w + (5.0\text{x}10^{-7})wx - (2.0\text{x}10^{-7})wy + (5.0\text{x}10^{-7})\,wz,$$
$$\dot{x} = 25.0 - 0.04x - (5.5\text{x}10^{-8})xy + (3.6\text{x}10^{-7})xz + (5.0\text{x}10^{-7})\,w,$$
$$\dot{y} = (2.5\text{x}10^{6}) - 0.7y + 0.05x + (1.0\text{x}10^{-7})\,yz,$$
$$\dot{z} = (1.0\text{x}10^{4}) - 0.023z + 0.001y. \qquad \textbf{(2)}$$

Note that the summated proliferation, differentiation and inhibition factors reduce to a single negative self-feedback gain factor in each compartment (cell pool). From these equations, the following pool interactions are observed: 1) there is negative self-feedback for each compartment; 2) there is a positive feed-forward from compartments $w \rightarrow x \rightarrow y \rightarrow z$; 3) compartment z is in a positive feedback relationship with its previous compartments y, x and w; and 4) compartment y is in a negative feedback relationship with its previous compartments x and w. This seems to be in good agreement with known human T cell system developmental dynamics (9, 11). Figure 3 shows a simulation run of normative developmental data across the lifespan using **(2)**. The main feature we observe is the slowly exponentially decreasing number of peripheral T lymphocytes across the lifespan, which compares well with actual human lymphocyte counts decreasing from 6,320±3,000/mL blood at age 1 month to 1,890±830/mL blood at 80 years (9). T cells decrease, respectively, during this period from 78%±10% to 61%±13% of total lymphocyte counts. The stem cell pool *(w)* remains fairly stable during the 80-year period, while early and late thymic cells (x and y) reflect the physiological involution of the organ. This is most prominent in the rapidly proliferating pool of early thymic cells *(x)*.

Table II lists the ranges of values for the feedback and feed-forward parameters for the individual cell pools $w - z$ (bone marrow to peripheral lymphatic cells) permitting an overall "healthy" state. The relative sensitivity of each parameter was determined in an arbitrary manner by dividing this range by its midrange value (similar to the measure of coefficient of

Table II. *Ranges and sensitivities of virtual values for the "connection strengths" among pools, i.e. for combined feedback and feed-forward mechanisms.*

Parameter	Function	Low Range Value	High Range Value	Relative Sensitivity
a	feedback $x \rightarrow w$	-2.0×10^{-6}	3.0×10^{-6}	Low
b	feedback $y \rightarrow w$	2.0×10^{-7}	4.0×10^{-7}	Med
c	feedback $z \rightarrow w$	-6.0×10^{-7}	5.0×10^{-7}	Low
d	feedback $y \rightarrow x$	0.55×10^{-7}	0.65×10^{-7}	High
e	feedback $z \rightarrow x$	3.4×10^{-7}	3.8×10^{-7}	High
f	feed-forward $w \rightarrow x$	-2.0×10^{-6}	2.0×10^{-6}	Low
g	feedback $z \rightarrow y$	0.7×10^{-7}	1.8×10^{-7}	Med
u	feed-forward $x \rightarrow y$	-2.0	10.0	Low
d	feed-forward $y \rightarrow z$	0.0005	0.0012	Med
$\mu(w)$	regeneratory potential *(w)*	40.0	80.0	Med
$\mu(x)$	regeneratory potential *(x)*	-10.0	5.0×10^{4}	Low
$\mu(y)$	regeneratory potential *(y)*	2.3×10^{6}	2.7×10^{6}	High
$\mu(z)$	regeneratory potential *(z)*	0.7×10^{4}	1.1×10^{4}	High
$P_w - D_w - I_w$	self-feedback *(w)*	-1.0	-0.3	Low
$P_x - D_x - I_x$	self-feedback *(x)*	-0.07	-0.03	Med
$P_y - D_y - I_y$	self-feedback *(y)*	-0.75	-0.65	High
$P_z - D_z - I_z$	self-feedback *(z)*	-0.025	-0.022	High

variation): if the ratio was less than 0.5 we labeled it "high" sensitivity in Table II, if the ratio was between 0.5 and 1 we called it "med", and if greater than 1 we classified it as "low." Of the seventeen parameters listed in Table II, eleven were classified as medium to low sensitivity. A wide range of values for a given parameter indicates that a cell pool is fairly insensitive to extraneous influences and therefore has a significant amount of inherent stability. Representative graphs are shown in Figures 4 and 5.

Several reaction patterns are suggested by applying our computational model:

A) Bone marrow and early thymic cell pools *(w, x)* appear to be relatively insensitive to feedback influences allowing for a wide range of factorial values without showing pathological changes. This indicates that these cell compartments possess a sturdy internal stability and that any external stimuli must be quite strong in order to cause abnormal cell pool numbers and therefore disease resulting from this. In addition, the bone marrow stem cells apparently also possess a high regeneratory potential *(μ_w)*.

B) On the contrary, intrathymic feedback control *($y \rightarrow x$)* appears quite sensitive, as does the feedback from the periphery to the thymus *($z \rightarrow y$, $z \rightarrow x$)*. Thus low-level stimuli will be responded to sensitively, but exceeding such low levels may lead to system imbalance, hence possible disease. Inherent stability thus appears quite low. The regeneratory potentials *(μ_x* and *μ_y)* however, are quite high as well.

C) The intensity of a feedback stimulus from early thymus back to the bone marrow stem cell pool appears to be quite high compared with the other pools. Thus there may be an intense request for stem cell influx in cases of decreasing thymic cortical cell pools.

D) The compartmental negative self-feedback sensitivity varies from low *(w),* to medium *(x),* to high for both y and z. It is known from system theory that negative self-feedback helps to maintain a stable system behavior. Therefore we see that w and x allow for a more relaxed or flexible self-control as compared with compartments y and z, that exert a firmer, tighter self-control (by virtue of their narrow normative ranges). This tighter self-control regime in and of itself would be indicative of a less flexible and/or adaptive response to external stimuli in general, whereas a broader self-control regime would lead to a more flexible response to such stimuli.

E) Feed-forward values, *i.e.* the stimulus for cell progression (or differentiation) from one pool to the next mature one, show a broad range of control (*i.e.* insensitive response to stimulus) for cell influx into the thymus and cell movement within the thymus, yet a narrower range (*i.e.* higher sensitivity to stimulus) for outflow of cells from thymus into peripheral compartments.

Discussion

The computational model we have presented here originated from a number of experimental and clinical studies into the pathogenesis of malignant lymphomas (7, 12), and was designed exclusively by us to simulate changes in cell pool numbers in order to serve investigations of atypical cell proliferation and malignancy, or cell loss and aplasia. It does not focus on functional activities of mature peripheral T cells as a number of other computational models currently in use do (13-19). Available cell numbers, however, such as in hyperplastic, aplastic and neoplastic responses, do influence functional activities and our model may well supplement others in this regard.

Since Rudolph Virchow's first description of leukemoid reactions (1, 2, 20, 21), it has been presumed that a certain feedback mechanism exists between peripheral blood cell numbers and cell production sites. One major source for the regeneration of mature peripheral lymphocytes, and thus a potential target for feedback control, is the stem cell pool (23-25). An essential intermediate for the production of fully immunocompetent lymphocytes is the thymus or respective extrathymic sites (26-28). A thymic cell pool thus could constitute another focus for feedback regulation. It was intriguing, therefore, to use our computational model for studying the cell population dynamics along with their feedback and feed-forward mechanisms.

Our simulations showed that the essential source for stem cells (bone marrow and early thymocytes) display a striking internal regeneratory stability, which may render them fairly insensitive to extraneous (toxic and other) stimuli. This appears reasonable, since otherwise we would probably expect more frequent aplastic and immune deficient responses. The strength of the connection between the bone marrow pool *(w)* and the thymic cortical pool *(x)* appears in a way that both may be considered a single unit. Once cells have entered the thymic compartments, their shifting to further developmental stages appears quite sensitive even to minor stimuli, reflecting the importance of "*thymic imprinting*" for the production of functioning T lymphocyte populations. Also, feedback mechanisms exerted by peripheral cell pools to the thymus appear quite sensitive, guaranteeing a response even to minor stimuli. This appears of practical importance, since it is only a minor percentage of peripheral T lymphocytes that may exert such stimuli, *i.e.* the pool of virgin (naive) T lymphocytes. Overall changes in the entire peripheral T cell pool do not apparently affect the thymic outflow of mature naive T cells (29-32). Although small, this pool of peripheral naive T cells is responsible for maintaining T cell diversity (33).

Feed-forward values, *i.e.* the transition of cells from one pool into the next maturation stage, relate well to the variable intensity of feedback stimulation and its interpretation and thus confirm the validity of our simulations. Again, the moderately high sensitivity of feed-forward from thymus to the periphery guarantees the effective replacement of naive mature T lymphocytes. With respect to compartmental self-feedback control, we found that the capacity for "*elastic homeostasis*" resides predominantly in the bone marrow and early thymic compartments, in comparison to the thymic medullary and peripheral blood compartments. This may suggest the latter two as targets for developed future therapies that may increase their flexibility (decrease sensitivity), hence reducing possible susceptibility to disease.

The computational model we have presented for simulating cell pool changes in the T cell system appears capable of calculating cell pool changes and respective alterations in feedback and feed-forward controls. It thus can mimic disorders arising from changes in selective cell numbers or their unresponsiveness and hyper-responsiveness. Future studies should focus on qualitative aspects of feedback and feed-forward controls so that an even closer correlation of computer simulations with the pathogenesis of human diseases becomes possible.

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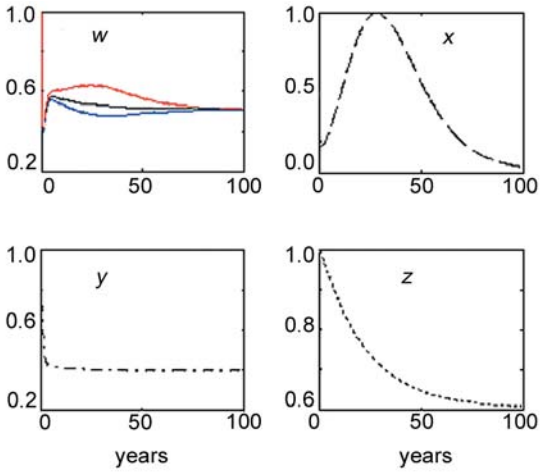

Figure 4. *Exemplary computational simulation of the ranges of virtual values of feedback responses from thymic cortex to bone marrow (see Table II, factor a). Shown are the cell changes in compartments bone marrow (top left), thymic cortex (top right), thymic medulla (bottom left) and periphery (bottom right). Black are normal medium values, shaded are upper and lower ranges. Physiological deviations in the bone marrow under these conditions do not cause alterations in the other cell pools (only one cell curve indicates overlapping of values for upper and lower ranges).*

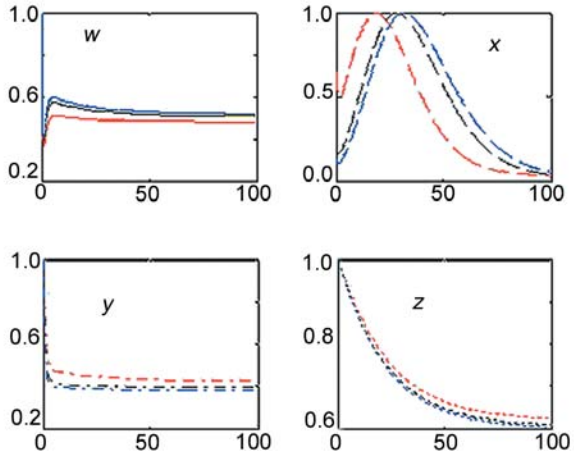

Figure 5. *Exemplary computational simulations of the ranges of virtual values of feedback responses from the periphery to the thymic medullary pool (see Table II, factor g). Cell pools are the same as shown in Figure 4.*

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