A Systems Engineer's Approach to Understanding Waldenstrom's Macroglobulinemia and Idiopathic Thrombocytopenia Purpura

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Abstract

This paper describes the process followed by the author in attempting to understand the body/disease/treatment complex for the diseases he has, Idiopathic Thrombocytopenia Purpura (ITP) and Waldenstrom's Macroglobulinemia (WM) and the development of models and simulations to represent that complex. While little was known by the author about platelets and ITP, and IgM and WM at the time of diagnosis, a tops-down approach was taken to learn the physiology and biology of each. Starting out at the most abstract level, the complete body system, research was performed to understand the processes from an organ/physiological perspective and put it into the context of the separate functional boxes that the author learned during his career as a system engineer working on complex aerospace systems. The models and simulations can become tools to create an interchange vehicle between the modeler and the medical person to further the understanding of this very complicated complex.

Discussion

Background

In my professional career I was a systems engineer primarily involved as the lead integration engineer of complex aerospace systems. In that role I had to have enough understanding of the aspects of the different subsystems that comprised the system and the requirements that the system was to meet. The range of engineering covered, mechanical, electrical, hydraulic, software and radar fields. While a deep understanding of each filed was not required, over my career an understanding of what the pieces were to do to support the object of the entire system was developed.
Over this time I learned to think in terms of sub-systems or boxes and the passing of information and control between them. Another part of the integration task was to develop a process of synthesizing the parts to make the whole system and to establish a process/procedure to accomplish this task.
So my background laid the foundation to carry the experience over to the world of physiology but yet it did not !

Diagnosis

In June of 2004 a blood test, Complete Blood Count (CBC) investigating the possible causes of the frequent occurrence of a bloody nose a platelet count of 1000 / μL was discovered. The typical level for platelet count is between 150,000 and 450,000 / μL. It was also discovered via this CBC that other blood counts were below normal. A bone marrow biopsy (BMB) was then performed and the aspirate was set off to pathology. The pathologist determined that in addition to the ITP I had a form of non-Hodgkins Lymphoma identified as Waldenstrom's Macroglobulinemia (WM). The qualifiers for WM are an elevated level of monoclonal immunoglobulin of isotope M, IgM, and the presence of lymphoplasmacytic cells in the bone marrow.

Prognosis

When I was diagnosed with WM I asked the dreaded question. "How long do I have?". The doctor, in part as my diagnosis was just made and he was uncertain on how I would respond to treatments offered up somewhere between two and twenty years. Well the two was pretty scary and the twenty would get me to eighty, not to bad so I decided to hit the road shortly after that. A later diagnosis was given of between five and thirteen years. So I lost quite a bit on the high end, but the low end urgency number was more optimistic. Further the popular tune was that you are more likely to die with it than from it. Which sounds good, relatively speaking, but now instead of an invisible sliver on the "How am I going to die?" pie chart WM consumes something less than 50%!

Three Phase Effort

Drawn by my eager wish, desirous of seeing the great confusion of the various strange forms created by ingenious nature, I wandered for some time among the shadowed cliffs, and came to the entrance of a great cavern. I remained before it for a while, stupefied, and ignorant of the existence of such a thing, with my back bent and my left hand resting on my knee, and shading my eyes with my right, with lids lowered and closed, and often bending this way and that to see whether I could discern anything within; but that was denied me by the great darkness inside. And after I stayed a while, suddenly there arose in me two things,

fear and desire - fear because of the menacing dark cave, and desire to see whether there were any miraculous things within. ---- Leonardo da Vinci (1452-1519)

The effort was broken down into three phases in order to progressively understand the Complex. The first phase was to see if simple mathematical functions could be fit to the data, in particular the platelet count and the IgM level. With reasonable success and then going forward believing that mathematics to some degree could explain the physiological phenomenon, Phase 2 was initiated to develop models and simulations that would match in a closed loop-treatment-driven manner the results I had achieved. The third phase was to gather information from others with ITP and WM and improved upon the models and simulations.

Phase 1 – Open loop modeling of responses to treatment

"All the effects of nature are only the mathematical consequences of a small number of immutable laws." – P.S. Laplace (1749-1827)

Fitting simple mathematical functions to the data that was measured was a relatively easy first step. Having experience, and a sense of time responses of dynamical systems from my aerospace career, allowed me the ease to produce such functions, right or wrong.
In many cases I received more than one form of treatment concurrently and at this point in time of my effort I was not knowledgeable enough to sort out or separate the individual effects or any synergistic effects that may be happening. So the functions modeled the combined effects. From my systems engineering experiences I guess we were running a bad experiment by introducing more than one variable at a time but we had to keep the patient alive.
The work done in Phase 1 and the later phases as well, that is investigating physiology, biology and medicine in computers, these days is called "in silico", that is in silicon like in computer chips. This manner of scientific effort is an adjunct to the "in vivo", i.e. in the body, and "in vitro", in test tubes and other outside the body testing platforms. While the final answer happens in vivo the other two forms of research and analysis can optimize the road to the solution.
The initial function fitting efforts focused on the ITP and platelet count. The primary reasons were that there was much more data, the platelet count was measured much more frequently than the amount of IgM, and there was a quicker response to the treatments which were focused on reestablishing the platelet count. A secondary reason is that there was much more known about ITP and what was happening seemed somewhat "intuitive" to me so to continue with Phases 2 and 3 the platelet count seemed like the area to focus on first.
Below are a couple of examples of where I was able to fit mathematical functions to my platelet count data.
Having produced reasonable matchups to the data, and with encouragement from Laplace, I then ventured into the world of the body/disease/treatment complex.

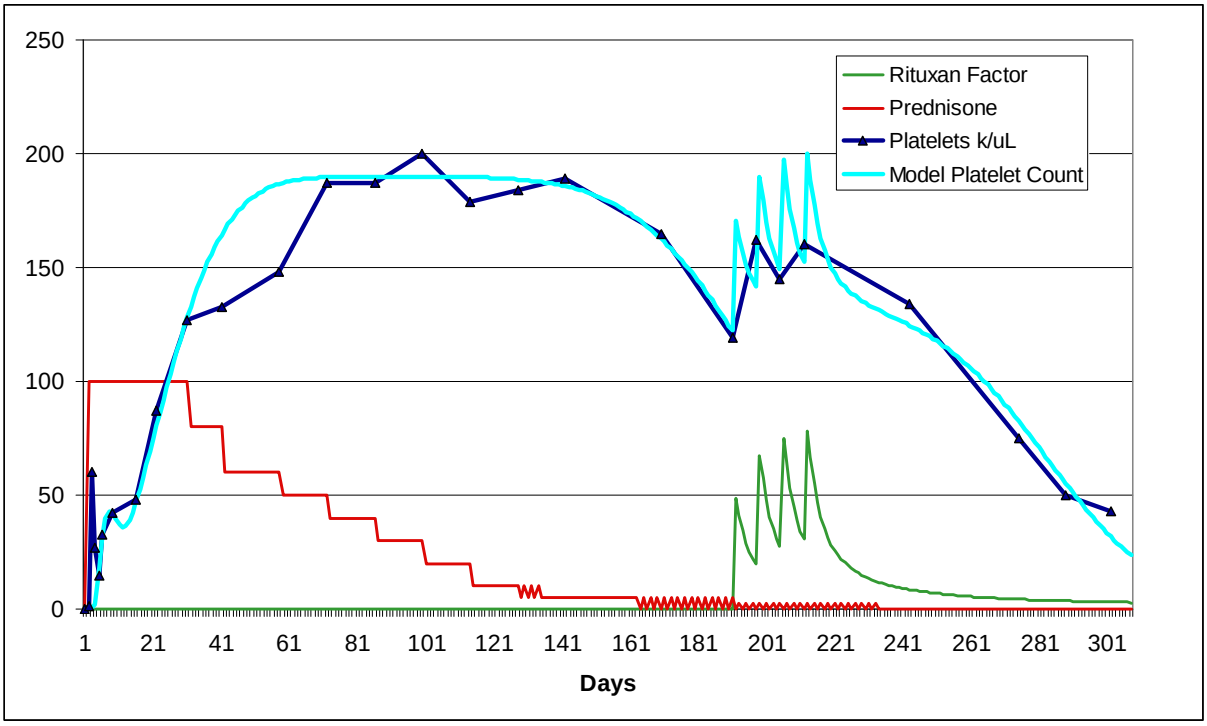

Figure 1 Example of Curve Fitting to Platelet Responses

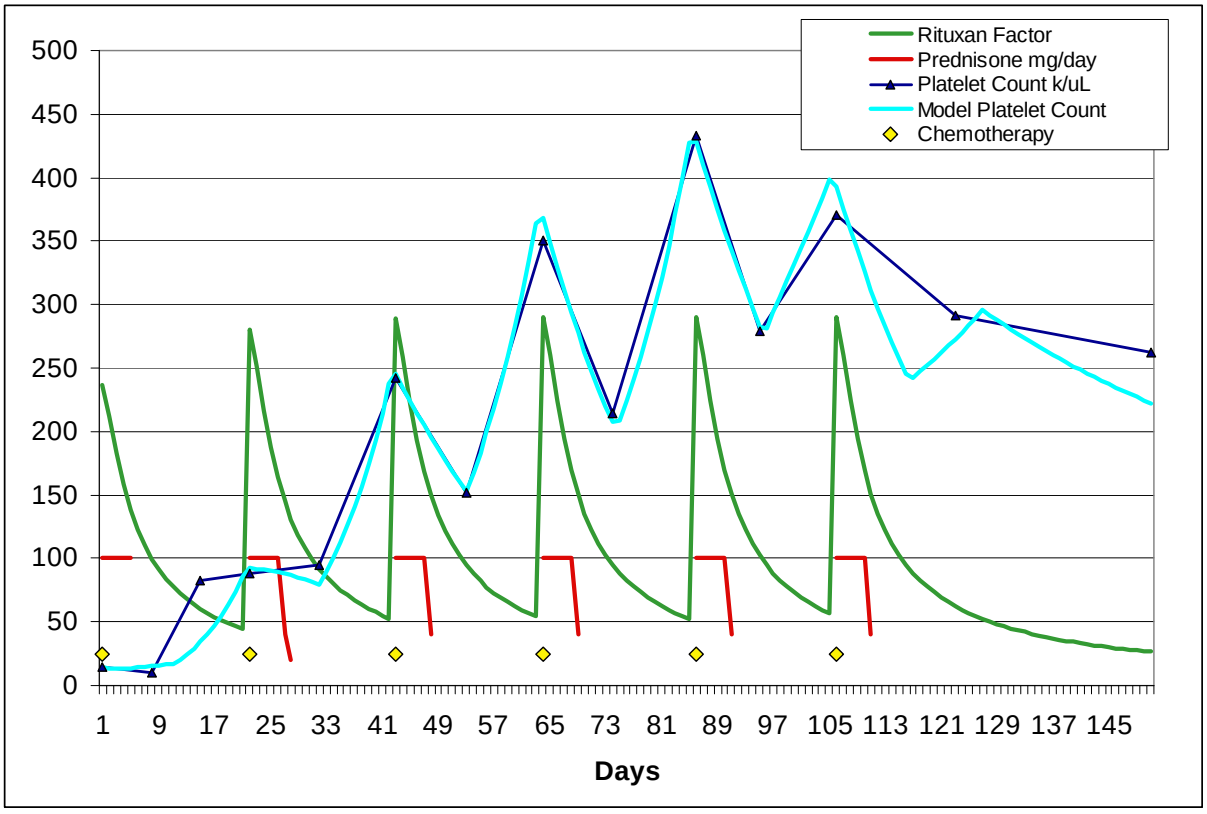

Figure 2 Fitting functions to response to Chemotherapy

Phase 2 – Close-loop models and simulations

Idiopathic Thrombocytopenia (ITP) -- One systems aspect learned from leading the integration of first-of new systems is that when there was a problem, units just are not working together correctly, that everyone was guilty until proven innocent. In other words though the problem may was most likely due to the last step taken, one must be open minded to second order relationships that were not immediately obvious. This way of thinking carried over to the development of models and simulations by incorporating "rheostats", as my oncologist like to describe them, for unknown or un-measurable parameters.

A paradigm that existed in the aerospace systems engineering world was that of modeling and simulation. Like in that world where there were different levels of detail/abstraction that was required at different levels of the systems, from "simple" op-amps up aerodynamic, free-flight models of a complete missile system, the world of biology has a similar hierarchy for modeling and methods. An example of possible methods and tools is shown in Table 1.

My thought is that in aerospace systems engineering there were two general kinds of models, that in fact are a reflective of the two key aspects of the scientific process, which are analysis and synthesis. The analytical models are those used to validate requirements, and establish system and sub system requirements. Analytical models could also be used to understand the "problem" or threat. In my aerospace experience the threat was typically a hostile target, in the world of bio/medicine the threat is the disease. The synthesis of electronic models is those used to put together circuits from components, modules from circuits and subsystems from modules mechanical systems etc.

Table 1 Modeling in the realm of Medicine/Biology

Level of Abstraction	Observation Method	Mathematical Modeling Techniques
Body	**Symptom / Physical Exam / Scan**	**Functional Blocks / Control Theory**
▲	▼▲	▼▲
Organ /Tissue	**Biopsy / Pathology / Blood Counts**	**Partial Differential Equations**
▲	▼▲	▼▲
Cell	**Proliferation / Migration / Clonalgenic Differentiation Arrays**	**Agent Based Cellular Automata**
▲	▼▲	▼▲
Intracellular	**DNA / RNA / Microarray / Western Blot**	**Ordinary Differential Equations**

My initial foray into the platelet process was based on my structuring my thinking of the fundamental parts: platelets are created, they exist and the "die". Below, Figure 3, is my first simplistic "model" of the platelet process.

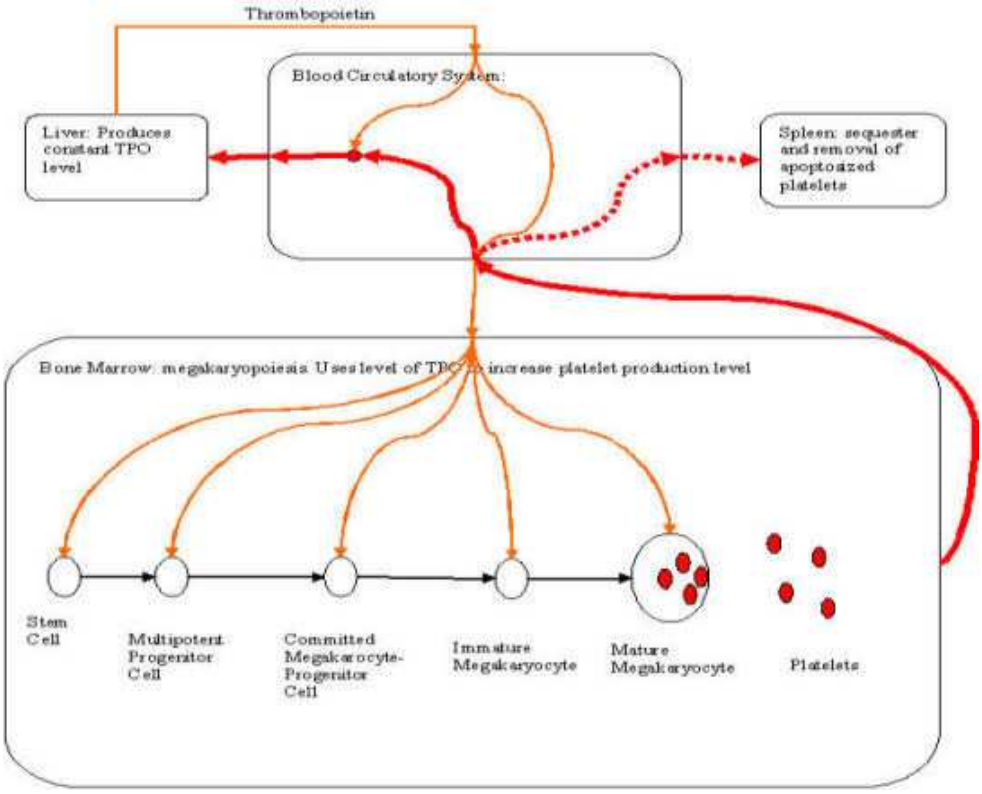

Figure 3 Initial Concept of Platelet Process

Further research on the aspects of the platelet process led to the creation of a simple “closed-loop” mathematical model of that process. While a product like Matlab or simulink could have been used, because of the simple nature of the model it could effectively be modeled in Excel, still as a closed-loop model. The rows of the Excel were day-in-the-life-of and were selected to match to the bandwidth of the platelet process. A block diagram of the Excel implementation is shown in Figure 4. While the details in the figure are not important, the process to compartmentalize the complexity of the physiology of the human body into functional entities and establish networks between them is important point to make. Often times the details within a box are still an area to be discovered, so modeling at this level of abstraction allows a platform to lead to better overall understanding.

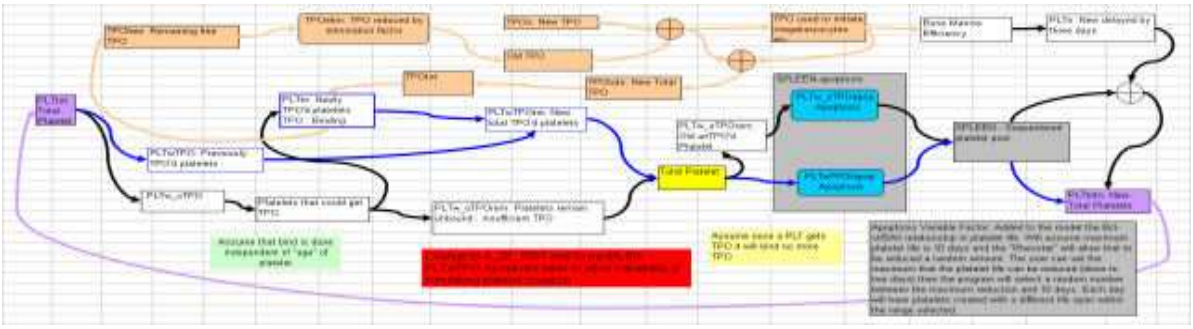

Figure 4 Block Diagram of Platelet Process

An example of the output from this program is shown in Figure 5. The simulation had five parameters that could be adjusted to see the effect on the day-to-day platelet count. This model/simulation could be used as a learning tool or a vehicle for interchange between the modeler and the bio/med platelet expert.

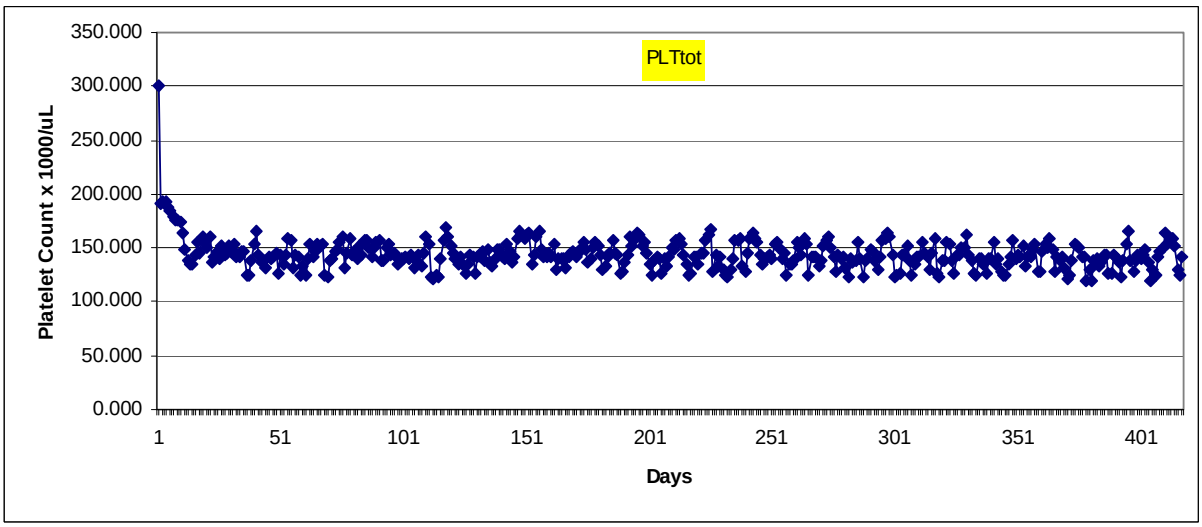

Figure 5 Sample output from Platelet Process Simualtion:
TPO Binding Effic =1 ; TPO Reduction Random Factor = 2 ; Bone Marrow Effic = 0.75 ; Range of Random Reduction in Platelet Life = 4 ; % Seq in Spleen = 40

Once the healthy platelet process model was developed the possible ways that ITP could affect it were considered. A very beneficial diagram in my learning about ITP is shown in Figure 6. In this diagram one can see that there is a close loop process in place, this resonated with my experience with the many closed systems I dealt with in the aerospace domain.

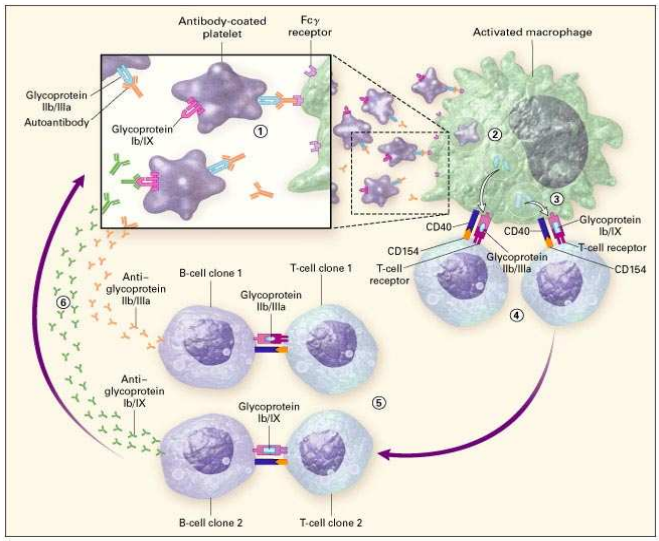

Figure 6 Description of How ITP Works (with permission from NEJM)

At this point in time I had to consider if the loss of platelets was a separate problem from the WM or if WM was in fact the cause of the low platelet count. When I consulted two world leaders in the treatment of WM and ask about the possible link between the ITP and the WM one said no way and the other said that they were related. So interestingly this then pointed to the possible value that creating models and simulations could have, i.e. to help in differentiating diagnoses! The choice was made to consider WM a factor in the low platelet count and the model was extended to reflect this hypothesis. Considering this diagram and the information in the associated article, the model/simulation was updated and the block diagram is shown in Figure 7. Again the details are not important but the ease with which points of influence can be identified for elaborating the model are the power of the figure. Here the effects of WM were model as impacting the creation of platelets in the bone marrow, i.e. the excessive level of WM lymphoplasmacytic cells in the bone crowded out the ability of the bone marrow to make platelets or the excessive amount of IgM was erroneously binding to the platelets and leading to their destruction. The degree of either effect was not known for sure so each possible effect was established as an adjustable parameter.

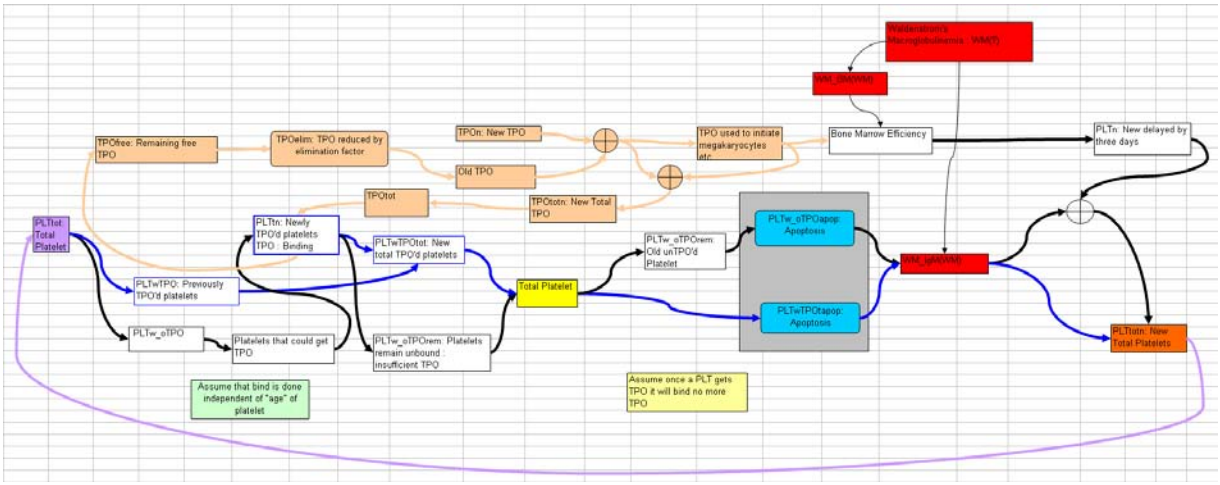

Figure 7 Block Diagram with WM Effect Incorporated

Though there were no measurements to develop the time response of the initiation of the WM effect, a Gompertz type function, often used in biological modeling was implemented, see Figure 8. The parameters were user selectable to aid in the fitting of the effect on the measured response.

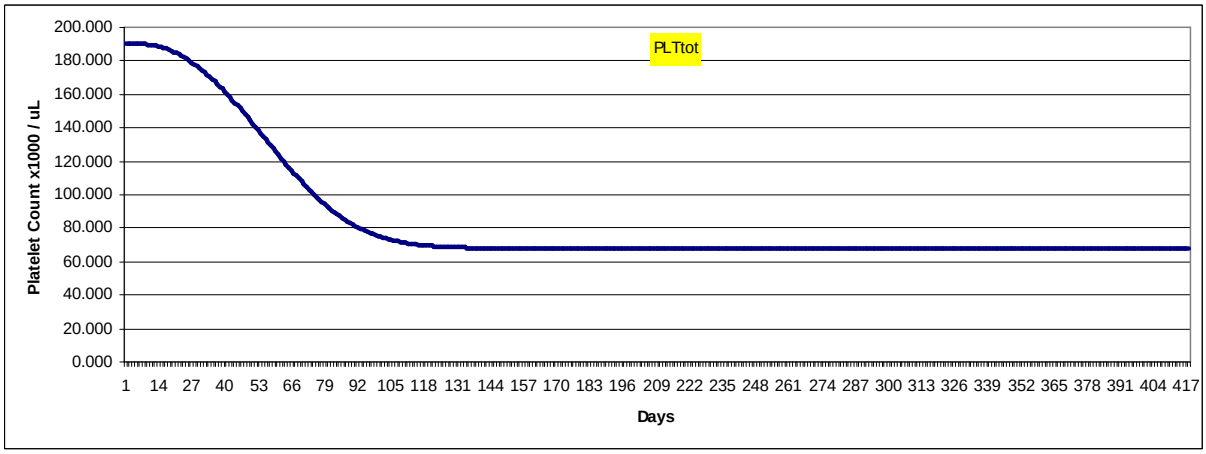

Figure 8 Initiation of Disease on the Platelet Count

In the same paper from which Figure 6 was drawn there was another excellent diagram presenting the possible effects that different forms of treatment could have on this closed-loop, ITP process, see Figure 9.

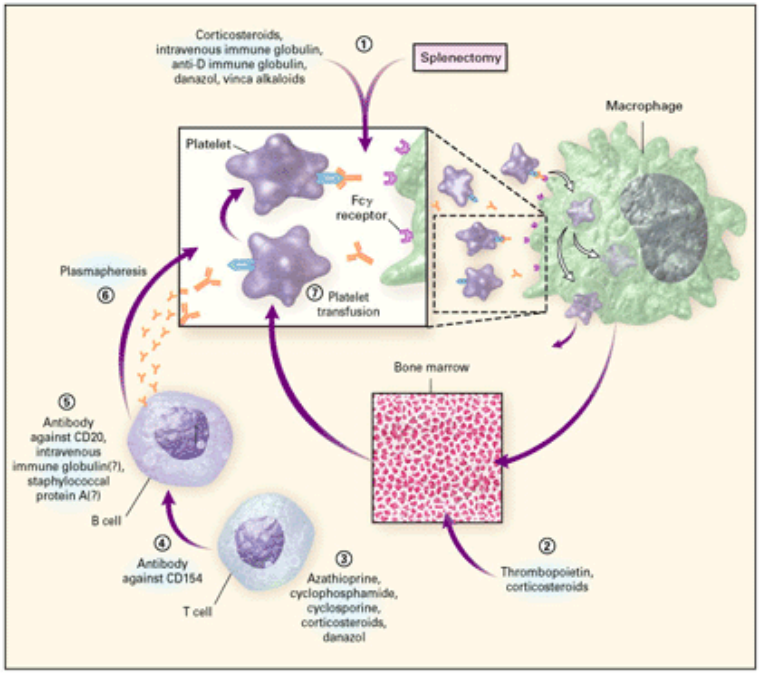

Figure 9 Mechanism of Action of Therapies for ITP (with permission from NEJM)

A third model/simulation was then developed to allow for the effects of the treatments I received to impact the effect of the WM. A block diagram for this model is shown in Figure 10.

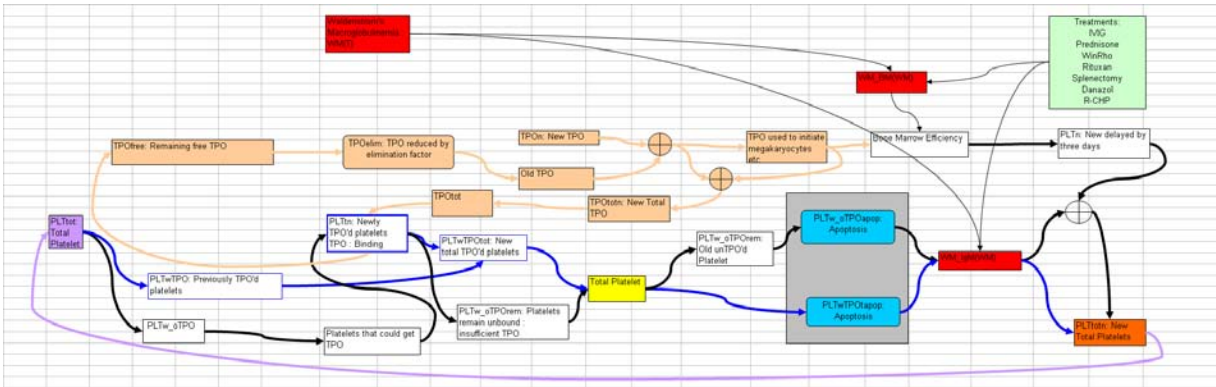

Figure 10 Block Diagram of the Base-Disease-Treatment Model

This model became very complex as the number of adjustable parameters increase to twenty three to be able to deal with all the different forms of treatment. An example of the model for the early series of treatments is shown in Figure 11. As can be seen the model platelet count, in orange, is not accurately modeling the measured platelet count.

Though I would have hoped to have done better than this, it brings the benefit of the process of model-experiment into focus. This also identifies that my systems engineering background and using it to try to understand what the Complex is doing falls short, I lack domain knowledge. I believe that there two main avenues that need to be taken to carry this forward. The first is a need to interface with knowledgeable bio/med folks and have my lack of knowledge and errors in my assumptions to be increased and corrected respectively. This is hard as the acceptance of mathematical modeling in medicine is rare. The discipline of Systems Biology is starting to bridge that gap but even those that practice this form of research are not totally embraced by the medical community. The second way to improve and lead to validation of the model is to run experiments. This road may be even more difficult to travel, let alone get access to the entrance ramp.

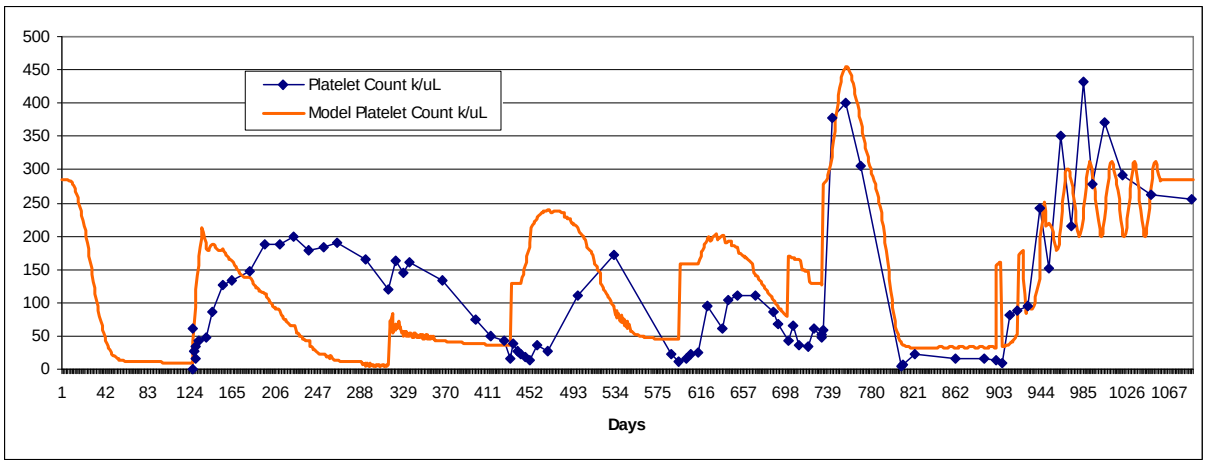

Figure 11 Sample Output From the Base-Disease-Treatment Simulation

Waldenstrom's Macroglobulinemia (WM) -- The development of a model and simulation of the other disease, WM, was also performed. For my degree of understanding, WM fundamentally

differs from ITP in that it is for the most part an open-loop problem. Something has caused a mutation in some B-cells and they reproduce excessively, live longer and thus produce plasma cells that in turn produce a large amount of a monoclonal immunoglobulin of type “M” isotope, i.e. IgM. While we all produce IgM as a part of the immune system response, once a pathogen is under control there is a reduced demand for this unique copy of IgM and production ceases. Consider the closed-loop shown in Figure 6. But for WM there is no target pathogen for its version of IgM so there is no loop.

For the WM problem a hypothesis chart was created, see Figure 12. Like the model and simulation developed for ITP, research was performed once again calling upon Professor Wikipedia, Scholar.Google and others interested in WM. In Figure 12 the yellow line is the closed-loop, treatment driven model of my IgM level. This format was used as a possible way of bridging the modeler-bio/med chasm. Instead of bringing equations down upon the bio/med folks, I felt that a picture and a set of hypotheses may be a better way to establish a dialog. This has been effective in interfacing with my treating oncologist and I have been able to get some feedback on some of my assumptions. As an example, by understanding a bit about the B-cell, plasma cell and IgM typical biological half-lives, I could create multiple choices of what may be happening, see Hypothesis #5.

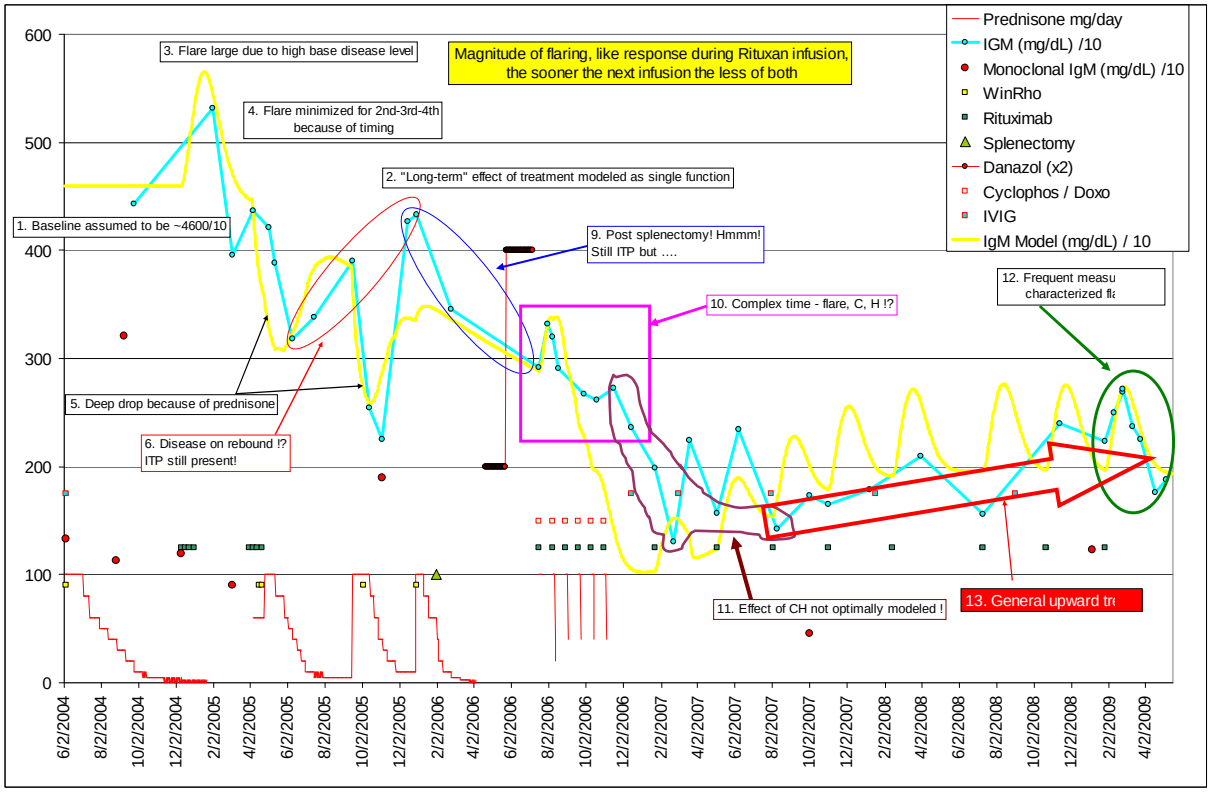

Figure 12 WM Hypothesis Chart

In this case we were able to run somewhat what I would call an experiment. We did not alter the treatment protocols from what is favored these days, all we did is increase the frequency of measuring the IgM, see Hypothesis #12. I had proposed that the varying level of IgM over the 2007-2008 time period was due to a phenomenon called “flaring”. This happens to some WM folks after they receive Rituxan, their IgM level flares up for a period of time. Having taken

measurements of the IgM level more frequently after the January 2009 Rituxan infusion a flare in IgM was seen. Then having that response information in hand the fluctuating levels for the prior two years seem more plausible and the model was closer to what actually happened.
Taking the extra measurements was something that came from my experience in developing the complex aerospace systems. I think that there is much potential in this simple, until the insurance companies get involved, change in the present medical/clinical processes. I knew that the "flare" existed for others with WM who received Rituxan but we did not know for sure if I was a "flarer" until we gathered the extra data. By the way, today the medical community cannot tell you whether or not you will respond to Rituxan let alone if you will have a flare or not.

Phase 3 – Gathering data from others

With the lack of understanding of cellular and molecular biology I decided to grab onto a form of treatment often used in WM, and other diseases, called plasmapheresis (PP) that is more mechanical in nature. Simply, PP is a process where a patients' blood is removed, the various components are separated by filtering or via a centrifuge. The undesired components are discarded and the remainder is returned to the patient with some replacement fluids. In the case of WM the serum, which contains the excessive amounts of IgM, is discarded. This form of treatment does not address the underlying disease problem but can give immediate, but temporary relief by reducing the IgM level.

I was able to gather IgM measurements from several other WMers who had taken the PP treatment. I was then able to develop a simple model to predict the level of the IgM after their PP treatments. Two examples of the modeling results are shown in Figures 13 and 14. In both cases I once again used simple mathematical functions to model the effects of the other forms of treatments that they received. This "fitting" to those responses was done retrospectively. For the modeled response to PP it was in fact predictive. In particular for the model response to the early PP treatments shown in Figure 14 the model did fairly well. Figure 13 was included because that particular patient suffered eye damage because it was not anticipated that he would produce a post-Rituxan IgM flare that was described above. The PP he received was after the very high level of IgM was discovered.

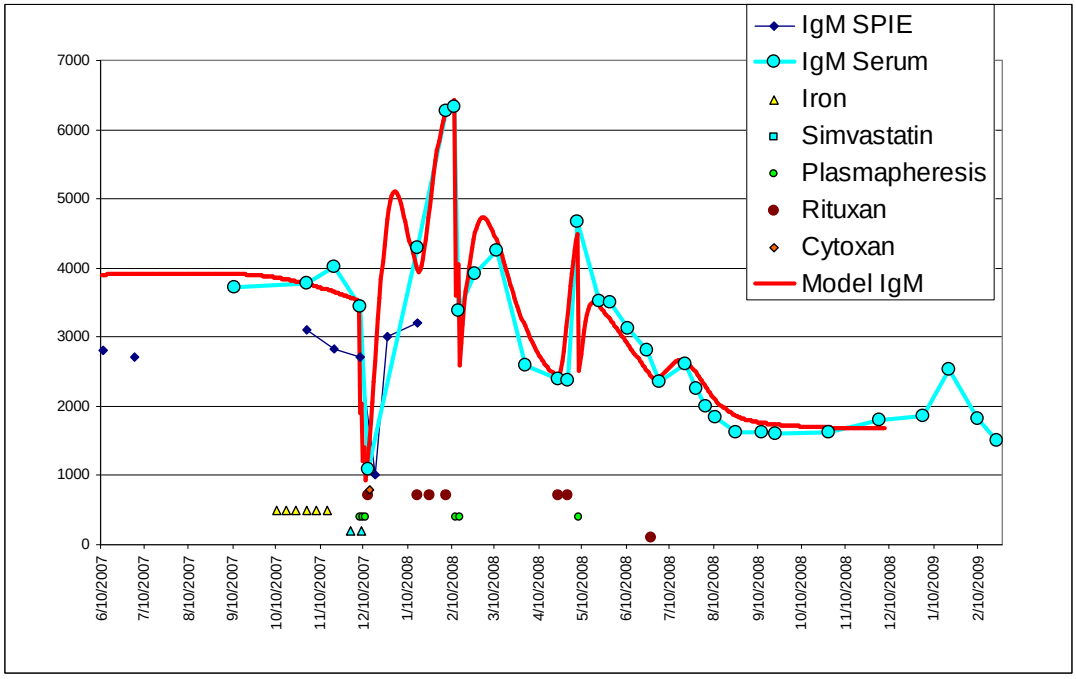

Figure 13 IgM Model of Response to Plasmapheresis

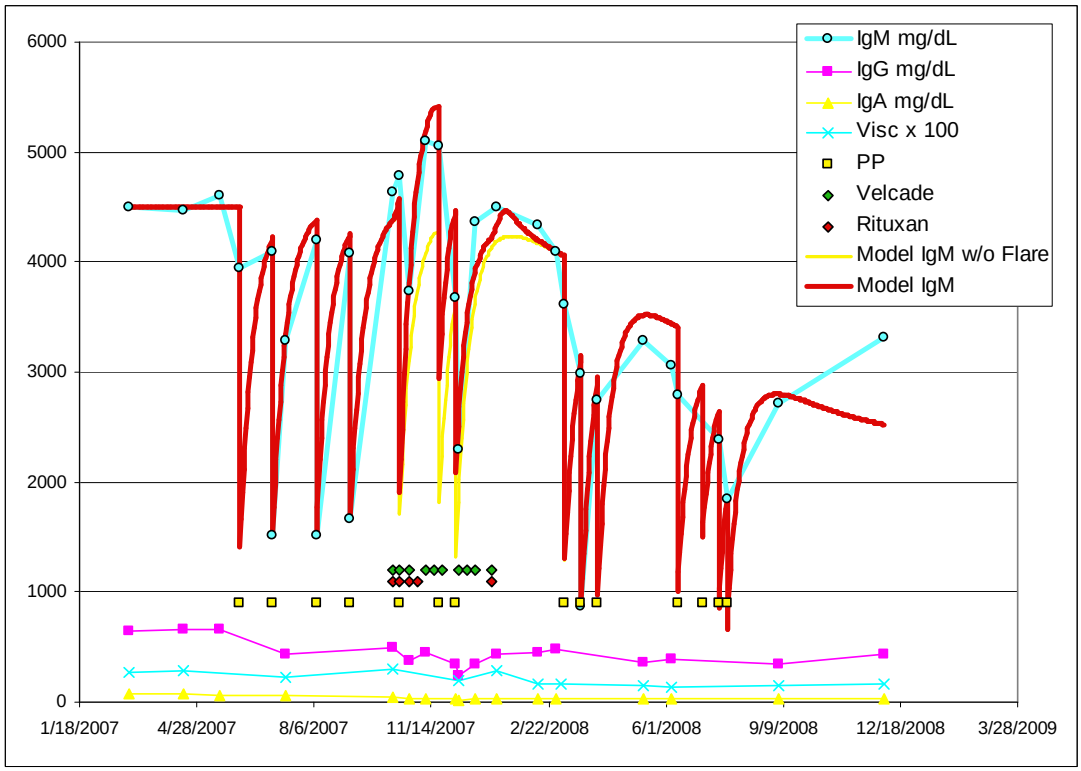

Figure 14 Second Example of Model Post Plasmapheresis

A key point I want to make here is that care for WM patients, from research and clinical trials to choice of treatments available today is a systems problem. As detailed above for the patient from which that data for Figure 13 was acquired, had there been procedures, a method to determine that he was a “flarer” then PP could have been instituted prior to the damage had happened. I think that this is one example where the structure and processes fundamental to systems engineering could help an area where there is a lack of general knowledge.
Using the mathematical model for the patient shown in Figure 13, a hypothetical treatment protocol was proposed and executed using the model. The results can be seen in Figure 15. The protocol was to have the patient receive PP if the IgM “flared” to a level 20% above base line. It is shown in that figure the IgM level was maintained to a level that in all likelihood would not have resulted in the permanent eye damage.

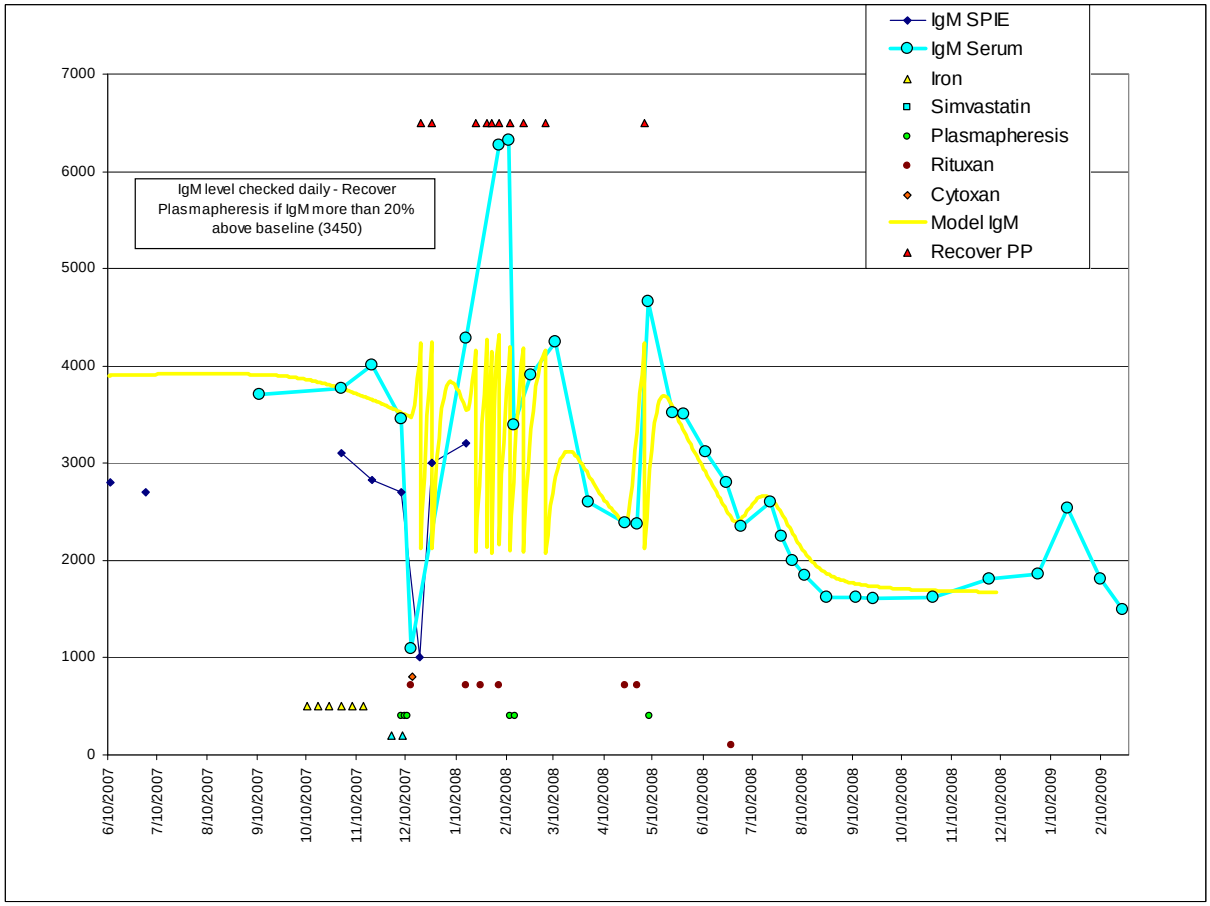

Figure 15 Response using Mathematical Model and Hypothetical Protocol

Conclusions

While a modeling and simulation effort from the tops-down has allowed the development of a representative model in most cases of my history, there has not been much opportunity to use the model and simulations to direct experiments that were a part of my aerospace experience. The elaboration and validation of some models has been done using non-periodic, sparse data. While this parallels the world of clinical trials somewhat, everybody is different; it lacks the consistent sampling intervals. Though each person’s result may be considered anecdotal, it seems to me that a

sufficient number of the anecdotes, properly categorized, can lead to beneficial information that doctors can't necessarily use to select patient treatment protocols but could influence the selection and design of clinical trials.
Also this effort should be considered only one part of the total role that Systems Engineering can play in the overall Healthcare arena. Having been brought into the Healthcare world through the diseases that I have acquired, I have used modeling and simulation to learn about it. I see many areas where the years of experience in developing processes to address complex industrial problems that are a part of Systems Engineering and INCOSE can be brought to bear on Healthcare.
While the complexities within an individual human cell are still being discovered by geneticists and cellular and molecular biologists, putting the pieces together may be another area where Systems Engineering could play a role.

Follow-on Plans

Recently a cross-domain workshop was held between a group of aerospace scientists and engineers and a group form the bio/medical/pharma/Systems Biology community. This workshop was a fallout of my belief in the synergies that can be found if the two domains sit down and share experiences in solving problems in, and with, complex systems. The key element in the success of this type of interchange is Systems Engineering and the processes that embody that discipline. The first workshop was very beneficial as ideas were shared and there were plenty of pro and con dialogs. I hope that further workshops of this type will be held.

I will continue to develop models and simulations of the body-disease-treatment complex that I live within. I think that my Systems Engineering background has not been fully brought to bear on this new problem.

In 2008 the Systems Biology community held a joint workshop with their counterparts in Europe. After the workshop they produced an excellent report on the status of Systems Biology in Cancer. I reviewed that paper and I feel that there were many "needs" they expressed that could be addressed if Systems Engineering was a part of the Systems Biology team. I hope to produce a document and share with them my thoughts on integrating Systems Engineering with Systems Biology.

Biography

The author graduated from the State University of New York at Buffalo in 1967 with a Bachelors of Science in Electrical Engineering. Upon graduating he took up employment with Raytheon Company as a design engineer. He continued with Raytheon through 2004 and advanced his career to become a lead system integration engineer of the first-of many new systems. Along the way he received a Masters of Science in Electrical Engineering at Northeastern University. His last assignment was lead on a novel aerostat radar system. He also was involved with establishing and flowing down requirements from the top-level specification to sub-system specifications on several programs.