Abstract

Lyme Disease flare cycles are interpreted as response to the infection of an oscillatory immune system. It is visualized as a system capable of either self-organized oscillations or forced oscillations, the latter imposed on it by the endocrine-menstrual system. One case of neuroborreliosis was analyzed for these two types of oscillations. In line with Burrascano’s treatment guidelines, treatment end was initiated when a switch from the self-organized to the imposed oscillation was observed. The treatment was successful, meaning that the person has remained totally without symptoms after the end of treatment, i.e. for a period of more than 8 years as of 10. February 2008. In conclusion, a rational, model oriented treatment is advocated rather than a “one size fits all” therapy of fixed duration.

Introduction: Treatment Defined By Progress During Therapy

The Mathematical Model

In some infectious diseases other than Lyme it is an established procedure to mathematically model the immune response, in order to

- investigate the processes involved and
- more effectively monitor and adjust therapy

(see Tables of Contents in [Models of immune systems, Models of immune response]).

In particular, researchers have been able to mathematically model and often verify in vivo or in vitro the following possible states of the infection [Dibrov et al. 1976, Dibrov et al.1978, McKenzie and Bossert 1997, Muraill et al. 1996, DeBoer et al. 1993]

1. asymptotic decrease of antigen quantity,
2. approach of its quantity towards constant value (examples: chronic inflammation of the sinus-maxillary floor, persistent lyme arthritis).
3. periodic course of the illness,
4. unlimited growth of the antigen quantity.

There are obvious similarities to Lyme, but current medicine does not yet have a quantitative model that derives Lyme disease clinical dynamics from basic microbiology and immunology. Rather, Lyme disease therapy decisions today, such as Burrascano’s Treatment Guidelines, are based on the medical professional's background in these disciplines, intuitively applied to interpret the clinical dynamics.

In this work a mathematical model accompanies intuition and eventually leads to a rationale for the duration of antibiotic treatment:

Assumption

The detailed microbiologic and immunologic processes (as e.g. reviewed by Rupprecht et al., 2008) work together to produce the overall, observable behavior ("clinical picture").
Method of model formulation

Applying the above mentioned established procedures used in constructing mathematical models of infections, we have reproduced this behavior with

- a non-linear differential equation or
- a set of two non-linear differential equations

that describe(s) a combined microbiological-immunological feedback process or self-organization. Self-organization is the basis of the observed recurrence of Lyme symptoms.

In the next paragraph I will specify my choice of the clinical picture.

The Clinical Picture: The Symptom List and Statistical Analysis

As long as our laboratory diagnostic techniques sometimes produce results that seem to be inconsistent with our clinical findings, the information the ill person is able to provide about the status of his/her disease needs to be discussed.

J.J. Burrascano recommended his patients to "keep a carefully detailed daily diary of their symptoms to help judge the effects of treatment, the presence of the classic four week cycle, and treatment endpoint" [Burrascano 1997].

We took

1. J.J. Burrascano's Symptom Checklist and
2. J.D. Bleiweiss' essay "When to suspect Lyme" [Bleiweiss]

as starting points for our symptom list.

Data processing

To visualize possible cyclical symptoms occurrence,

1. we constructed a spreadsheet (symptom log), where the symptoms are arranged vertically and the time of their occurrence on the horizontal axis. Often, cycles become visible already in this representation. In addition,
2. we employed a frequency analysis to the symptom log, roughly reminiscent of a Fourier analysis. (Results of the analysis)

In the remaining part of this paper I will give a microbiologic and immunologic interpretation of the basic features of the mathematical model of self-organization and how it can help with the therapy. In detail, this interpretation will

1. elucidate the periodic immune response,
2. clarify the driving force behind the periodicity:
   1. niches (e.g. immunologicly privileged body compartments) housing and continuously releasing Bb and driving a self-organized cyclical elimination process of our immune system,
   2. destabilization of the neuro-endocrine system. Finally it will
3. give a rationale for a conservative treatment duration.

(For more details than given below see my summary report ["Evaluation of ...", Gruber 1999a] or my draft ["Compartment Model displaying ...", Gruber 1999b])

1. Borrelia burgdorferi Outer Surface Proteins Stimulate a Periodic Immune Response
Some Outer Surface Proteins (Osp's) of Borrelia burgdorferi (Bb) are thymus-independent antigens of type 1 (TI-1 antigens). This means they do not leave a lasting impression on our immune system. We say "they produce no immunologic memory". Immunologic memory is the attribute of the immune system mediated by memory cells whereby a second encounter with an antigen induces a faster start and a heightened state of immune reactivity [Kuby 1997]. Therefore our immune response to Osp is the same regardless of how many times Osp has already appeared in our system before. Together with a threshold antigen concentration below which our immune system ignores the antigen, this leads to an oscillatory immune system activity ("flare cycles"). The following paragraph will describe microbiologic and immunologic details of the involved mechanism.

### Basics of Flare Cycle Interpretation

Because of the missing memory effect, our immune system gets locked into undamped "feedback oscillations" (also called "self-organized oscillations") in its attempt to eliminate the antigen. As long as Osp's are seen by our immune system, it keeps eliminating them, but it doesn't do so continuously. Here is my interpretation of why it works intermittently.

1. Bb or fragments of Bb reside in niches. Our immune system doesn't see much of the Bb, as long as they are within those niches. So there is no immune system reaction going on (i.e. no symptoms are being felt).
2. The niches leak: Bb (or Bb fragments) enter into compartments that are under immune system surveillance.
3. As soon as the Bb (fragment) concentration exceeds the immune system's tolerance threshold, the immune system responds with inflammation (causing the symptoms) and elimination of the Bb (or Bb fragments).
4. The tolerance threshold is fixed by our immune system depending on various parameters, e.g. our sensitivity given by the endocrine-menstrual system.
5. The immune system stops cleaning up as soon as the Bb (or Bb fragment) level seems low enough to be tolerated (by the immune system).
6. As long as the niches leak, Bb (or Bb fragments) keep contaminating the compartments under immune surveillance. and the immune system keeps cleaning up these compartments.
7. Unlike with many other infectious pathogens that our immune system can remember and thus eventually eliminate completely, our immune system can't remember some of the Osp's of Bb, and thus has to periodically clean out these Osp's to keep their concentrations low. This goes on as long as the Osp's keep coming in from the niches.

When the sizes of the Osp populations in the niches become negligible, our immune system may eventually stop cleaning out the Osp's (in my cleaning crew example: the crew may no longer be needed).

The period of the oscillation -measured as e.g. the average time between any two successive flares- is typical of the mechanism behind the oscillation.

My statistical analysis was marginally accurate enough to reveal that the period of the flare cycles depended on what type of antibiotic we used [Gruber 1999, lengths of cycles].

One reason for this dependence might be that different antibiotics access the niches to a different degree, causing the release of a different amount of Osp's. If there is a larger amount of Osp's within the niche, it may release more of them into compartments under immune surveillance than when there are only few Osp's in the niche. In our cleaning crew analogy, an aggressive antibiotic liberating a large amount of Osp's could be compared with a steady flow of trucks stirring up continuously a lot of dust in the street. To catch up with the larger amount of dust entering our house from the street, the cleaning crew will have to come within shorter periods.

### Cleaning Crew vs. Generation Cycle

Thus, I interpret the periodic flare cycles much like a periodic appearance of a cleaning crew in a building. When only a small amount of dust enters the building every day, the crew doesn't need to come so often. When a long series of trucks stirs up a lot of dust in the street in front of our house, the crew has to come more often to keep the dust level in the house within acceptable limits.

According to this interpretation, symptom cycles -being a self-organized oscillation of the immune system- may be triggered by dead or live Borreliae alike.

Contrary to that, traditional explanations identify the symptom cycle with the Borrelia generation cycle, assuming that a flare is generated because all Borreliae go simultaneously through the cell division phase of their generation cycle [e.g. Kroun M].

This assumption of a synchronized pathogen population is in contradiction to experimental findings: Even if all cells of a bacteria population start out cell-dividing at the same time ("in synchrony with each other"), they lose that synchronization over time. i.e. they get out of step with each other and their cell divisions eventually become statistically distributed over time.

Nevertheless, both interpretations suggest the same timing for an antibiotic pulse treatment "Take antibiotics at the time a flare is experienced."

1. In the model presented here, during a flare the antibiotic helps the "cleaning crew" (our immune system) attack the live fraction of the pathogen when the concentration is above the tolerance threshold. Because only part of the population is in its cell division phase, only that part will be affected by a cell wall antibiotic.
2. In the traditional model the cell wall antibiotic hits the entire bacteria population during a flare, because all bacteria are assumed to be in the cell division phase of their generation cycle.

### 2.1 Niches

Osp on (live or dead) borreliae may reside in niches, leak from these and enter the compartments under immune surveillance. Niches are e.g. compartments poorly accessible to the immune system or antibiotic, but they can be more than that: By definition

- niches protect Bb from
  - the immune system
  - or the antibiotic (Preac-Mursic 1989).
- render (material released from) Bb "invisible" to the immune system, to the effect that the immune system ignores Bb. Example: Glycoprotein S-layer enveloping Bb [Grier].

The protection may wane with time and so will the size of the spirochete or toxin population residing in the niche.

Niches

1. are provided by the host in the form of physical compartments, but they
2. can also be produced by Bb itself in the form of chemical or microbiologic defense mechanisms (see also Fig. 1 in Rupprecht et al. 2008.).

#### Type 1 and Type 2 Niches

**Type 1** niches, the ones provided by the host, are sites within our bodies that are poorly accessible to antibiotics and normal immune surveillance (see e.g. Fallon and Nields 1994 and literature cited therein).

We know such niches very well from other illnesses: When the root of a tooth gets heavily infected, our immune system cannot eliminate the pathogen entirely, and we have to live with an encapsulated infection - which we feel as pain. The infection is being held in check by the immune system. Thus, the sinus-maxillary floor is a compartment under poor immune surveillance. To get rid of the floor's infection we need to access it mechanically, i.e. operate on it from outside.

**Type 2** niches, the one Bb produces itself, are of a chemical and microbiologic nature. Bb

- sheds glycoprotein that forms strong complexes with antibodies [Schutzer et al., 1994], thereby enabling the Bb organism itself to escape immune surveillance [Lawrence et al., 1995].
- or to reduce the attachment of the antibiotic [Chambers et al. 1998 or Sanders 1996].
  - produces beta-lactamases,
  - reduces the permeability of the outer cell membrane or
  - modifies the target of the antibiotic, the "penicillin binding proteins".
- changes its outer surface [Zhang 1997], e.g. developing cell wall deficient (CWD) forms, also called by Mattman L-forms in honor of the Lister Institute [Mursic et al. 1996].
  - Mattman [Mattman 1993] interprets the ubiquitous CWD forms of bacteria and fungi as states of a variable equilibrium between cell wall and outer membrane dissolving and rebuilding processes, the former being driven by lysozymes of the organism itself and external stressors, e.g. antibiotics.
  - According to Phillips et al. [1998] immune system and antibiotics shift this equilibrium in blood of Lyme patients to CWD forms. Together with the blood the CWD forms of Bb may spread throughout the host. Because the penetration of both the immune system and antibiotic into an organ (or compartment) varies from organ to organ, so will the equilibrium form of Bb. In some locations even the parent (spirochetal) form may be able to exist. Thus, the blood compartment may be thought of as a niche releasing Bb into other host compartments.

In my model simulating the flare cycles in the presence of antibiotics, I'm referring to either type 1 or type 2 niches. The basic concept underlying the model is that the niche needs to have the following properties:
1. The immune system or antibiotic needs long periods, possibly several months, to empty a niche.
2. Since the antigen or pathogen within a niche is only "poorly visible" to the immune system, it does not stimulate an inflammatory immune response while in the niche.
3. Depending on the concentration of antigen or pathogen within the niche (and other parameters), a niche releases its content into the compartments under immune system surveillance or where the antibiotic is active.

For short I will characterize the latter compartments as "visible" to the immune system or to antibiotics. These are the compartments in which we feel the Lyme symptoms (flares). There are many types of symptoms as there are many such compartments [Gruber 1999 lengths of cycles]. But saying this, I do not imply a one-to-one relationship between symptom and compartment.

### 2.2 Destabilization of the Neuro-Endocrine System: Oscillations Synchronized with the Menstrual Cycle

In our case, after roughly 1.5 years of treatment with cephalosporins, I observed a transition to an entirely new immune system behavior: The immune system started to oscillate synchronously with the patient's menstrual cycle, which had a rather constant length of 23 days (Gruber 1999 menstrual cycle). The symptoms appeared clustered in the luteal phase (days 12 .. 14 before the next menses) (Gruber 1999 location in menstrual cycle). This was a clearly visible switch from the type of oscillations before, when the period between the flares was more or less 2 weeks. The period of an oscillation is typical of the mechanism driving it, and so apparently now the endocrine-menstrual cycle was driving the immune system as opposed to the self-organized immune system.

It is known that the sensitivity of the immune system changes throughout the menstrual cycle. M. Barkley et al. [1997] found that in women the immune response varies with the clock frequency of the menstrual cycle. I assume that the immune system is more sensitive to the inflammation caused by Osp in the luteal phase. So, the presence of antigen is more "annoying" sometimes than at other times, and this "sometimes" is mostly in the luteal phase. The physician Charlene DiMarco made some comments in an email to me, stating that when her patients' health improved they noticed their symptoms worsening after their menses, whereas at the onset of Lyme they observed the opposite: their symptoms improved during that same period of their menstrual cycle.

### 3. Rationale for a Conservative Treatment Duration

My tentative interpretation of the switch from "self-organized" to "menstrual cycle driven" is that it is the intensity of the infection that causes the switch.

- In the beginning, the load of the pathogen has finally reached such a level that the immune system is locked into that "desperate mode" in which it doesn't stop fighting the pathogen unless it has reduced its concentration to a "harmless" level.
- Later, after a long therapy in which the niches have been cleared form antigen, the immune system has not much left to do: The level of antigen is always rather low, only at times it seems more disturbing to the immune system, and the endocrine-menstrual system allows the immune system periods of indifference, i.e. the follicular phase and the ovulation time.

We have discontinued iv antibiotics after the transition to menstrual cycle driven flares and finished treatment with a sufficient dose of oral doxycycline taken for 4 weeks. We were prepared to monitor this phase comparing the health status with a model of in-vivo Bb population dynamics, but there was no need for restarting therapy. The patient has suffered no relapses thereafter for now 3 years.

### Conclusions

The research described here supports Joseph J. Burrascano's approach to the treatment of Lyme disease caused by Borrelia burgdorferi, in particular his using the severity of the periodically occurring symptoms as an indicator for the necessity of antibiotic treatment.

About 30 medical professionals at the Leiden University Medical Center, Leiden, The Netherlands, who participated in one of my seminars in March 1999, agreed on the following mechanism responsible for the symptom cycles:

"Some cell wall constituents released by B. burgdorferi belong to the class of TI-1 antigens. The immune system does not produce memory cells upon contact with and after successful elimination of TI-1 antigens. Thus, each new encounter with them produces an identical immune response, leading to a chain of periodic immune responses that continues as long as..."
there is a persistent source of antigen in the host."

It has been shown that B. burgdorferi has developed strategies to survive the attack of the immune system and of antibiotics [Brorson 1997, Liegner 1993, Preac Mursic 1996, Zhang 1997].

1. As long as B. burgdorferi persists in a host, it may release TI-1 antigens, thereby locking the host’s immune system into cycles of inflammation and elimination that are felt as disease symptoms cycles.

2. A reservoir of (dead) B. burgdorferi derived TI-1 antigens will perhaps do the same.

To my knowledge, no method has yet been published that can reliably distinguish between alternatives 1 and 2. So, when an individual was carefully diagnosed as having Lyme disease, has received antibiotics and still experiences the same symptoms recurring periodically, we cannot exclude that he or she still harbors a hazardous level of B. burgdorferi.

Research to clarify the background is rapidly progressing.

References


Bleiweiss JD, When to suspect Lyme disease, early 1990's (http://cassia.org/essay.htm).


Tentative Interpretation of Lyme Flare Cycles and a Corresponding Therapy


Gruber J, Evaluation of the long-term inflammation in neuroborreliosis, 1999 ([http://www.lymenet.de/symptoms/cycles/evalsum.htm](http://www.lymenet.de/symptoms/cycles/evalsum.htm)).

Gruber J, Compartment Model Displaying Symptom Cycles, 1999

- Compartment model displaying symptom cycles ([http://www.lymenet.de/symptoms/cycles/statistics.htm#compM](http://www.lymenet.de/symptoms/cycles/statistics.htm#compM))
- lengths of cycles ([http://www.lymenet.de/symptoms/cycles/statistics.htm#summary](http://www.lymenet.de/symptoms/cycles/statistics.htm#summary))
- menstrual cycle ([http://www.lymenet.de/symptoms/cycles/statistics.htm#figviii31](http://www.lymenet.de/symptoms/cycles/statistics.htm#figviii31))
- location of symptoms within menstrual cycle ([http://www.lymenet.de/symptoms/cycles/statistics.htm#figviii32](http://www.lymenet.de/symptoms/cycles/statistics.htm#figviii32))


Kroun M, A pilot study on granulated cellular structures and other abnormal microscopy findings in blood from chronically ill persons, York, June 20, 2003.


McKenzie FE, Bossert WH, The dynamics of Plasmodium falciparum blood-stage infection, 1997 ([http://www.lymenet.de/literatur/immundif.htm#McKenzie FE, Bossert WH, 1997](http://www.lymenet.de/literatur/immundif.htm#McKenzie FE, Bossert WH, 1997)).


Mathematical immune response models, literature survey, April 2000 ([http://www.lymenet.de/literatur/immunsys.htm](http://www.lymenet.de/literatur/immunsys.htm)).

Sanders, CC, Das veränderliche Bild der mikrobiellen Resistenz, Continuing Education 1996, E4-X005: 1-8, Bristol-Myers Squibb Company, Route 206 & Providence Line, Princeton, NJ 08543, USA, Tel.: (001) 609 - 252-5141 ([http://www.lymenet.de/literatur/abstracts.htm#sanders](http://www.lymenet.de/literatur/abstracts.htm#sanders)).


Models of immune systems - The use of differential equations, a literature survey, April 2000 ([http://www.lymenet.de/literatur/immundif.htm](http://www.lymenet.de/literatur/immundif.htm)).