MODELING ASPECTS OF THE IMMUNE RESPONSE: DEALING WITH COMPLEXITY

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The Immune Response

- Present in some form in plants, primitive fishes and (through evolution) in humans.
- The evolutionary and co-evolutionary aspects has resulted in a layered, complex, interacting adaptive system. In fact, this system also interacts with the neuro and endocrine (and other) systems in meaningful ways.
- The reductionist approach provides limited information. So, understanding each component may not tell you how the system really works
  - *in vitro* and *in vivo* are different.

Quick Immunology Course

- The systems is divided into several branches:
  - **Innate** – non-specific and ancient (often first line against bacteria)
  - **Humoral** – the antibody side (needed for viral defense)
  - **Cellular** – non-antibody mediated killing of (infected) cells through several methods
- Moreover, each branch plays necessary roles in the operation of the others.

Another way to organize is through lymphoid organs:

- **Thymus and bone marrow**
- **Spleen**
- **Lymph nodes**
- Also **GALT** (gut-associated) and the **Secretory** (mucus membranes)

Important Aspects – not always positive (but probably well-meaning)

- **Autoimmune disease** – RA, Lupus, Hashimoto's, Inflammatory bowel & Crohn's, Behçet's, Sjögren's syndrome, Type I diabetes, …
- **Allergy and hypersensitivity** – Results of the immune response to trigger allergens.
- **Inflammation** – heart disease, tissue damage, fibromyalgia, periodontal disease
- **Tumor surveillance / transplant rejection** – self vs. nonself

Key idea: In many medical situations, it is the control or modulation of the "normal operation" of the system that is the desired effect.

Modeling the Immune Response

- Early efforts in 1970's focused on describing the production of antibody in response to antigenic challenge and theoretical questions.
- By 1980, the first review of this work appeared. In 1988, a two volume "Theoretical Immunology" appeared. Then over the next decades, the work got harder as the researchers tried to relate the models to data and more worked with clinical/laboratory groups.
- Examples:
  - Release of histamine as a result of the binding of IgE to mast cells. This tested the kinetics of binding to and cross-linking of receptors.
  - T cell proliferation in response to IL-2. Make IL-2 the rate-limiting component (everything else in excess) and describe the kinetics.
  - Kinetics of killing of target cells by effector cells (NK, cytotoxic T, ADCC). Understanding an assay system commonly used.

Modern Methods

- "Immunomics" Special issue
- Computational Methods Section

The Examples Presented Here

1) *Early stages of interaction of HIV with the immune response*. Both deterministic model and stochastic models. Little data available (except agreement with endpoint). Goal is to understand critical aspects.
2) *Development of the T-cell repertoire*. A fundamental question is why the system develops as it does, and what happens when this system comes in contact with HIV.
3) *Kinetics of engraftment in hematopoietic stem cell transplants*. Data-driven and then the question as to why it worked.
4) *Modeling the natural history of autoimmune thyroiditis*. Clinically motivated, data-poor.

Point of the Talk

- Each of the examples provides a (well-)motivated question - addressed most directly by models.
- The nature of the questions and aspects of the system under study suggest a modeling/computational approach.
- Complexity of the system is addressed by focusing the question (not trying to do everything) and the nature of the model.
- Care is taken to limit the domain of the model to avoid difficulties with needing to describe the interacting systems.
- Complex situations can have unexpectedly simple results (the converse can also be true) if you look for them.

1. Early stages of interaction of HIV with the immune response

- HIV infects cells displaying the CD4 marker: T cells, and some cells of the macrophage lineage. Early infectious events are met by the cellular, then humoral (neutralizing antibodies) in the acute stage of the disease. HIV infects stimulated T cells.
- The remaining (latently) infected T cells and infected macrophages begin a slow growth phase (determined by the amount of system antigenic stimulation) which slowly kills HIV-specific T cells – then has a more rapid breakout (and tropism change) and more rapid T cell killing.
- The goal is to describe early stages, both to understand the variability in the incubation time, and identify important (patient-dependent) aspects.
- During the period from acute infection to removal of HIV-specific T cells, there is little immune action. In some sense, the evolutionary-learned response was not effective and a chronic infection results.

1a. Modeling approach – incubation time

- A stochastic model in some form is needed to describe the variation in the incubation time.
- Over the time scale here (months to years), viral dynamics are “bursty” and that determines the structure of the stochastic model as a branching process with immigration (Jagers, 1968).
- Count the number of infected T cells over time. Immigration comes from new infected T cells in which the virus came from macrophages.
- Easy to simulate – also, some analytic results are possible. Note that the asymptotic results are not desired, but stopping time information is.

Model specification

- A continuous time branching process involves an exponentially distributed time to the next event (a cell death and a batch of newly infected cells) and a specification of the p.d.f. for the batch size. Declaring the infinitesimal probabilities, $a_0, a_1, \cdots$ specifies the branching process.

$$P(k,h) = \delta_{1k} + a_k h + o(h)$$

is the probability that an infected CD4+ T cell will die in the interval $(t, t+h)$ having given rise to k infected daughters.

- Assuming that the number of new infections is Poisson, there are only 2 parameters (the rate of events and the branching number):

$$a_1 = \alpha(-1 + \lambda e^{-\lambda})$$

The immigration process

- Immigration specified by describing the infinitesimal probabilities of the process.

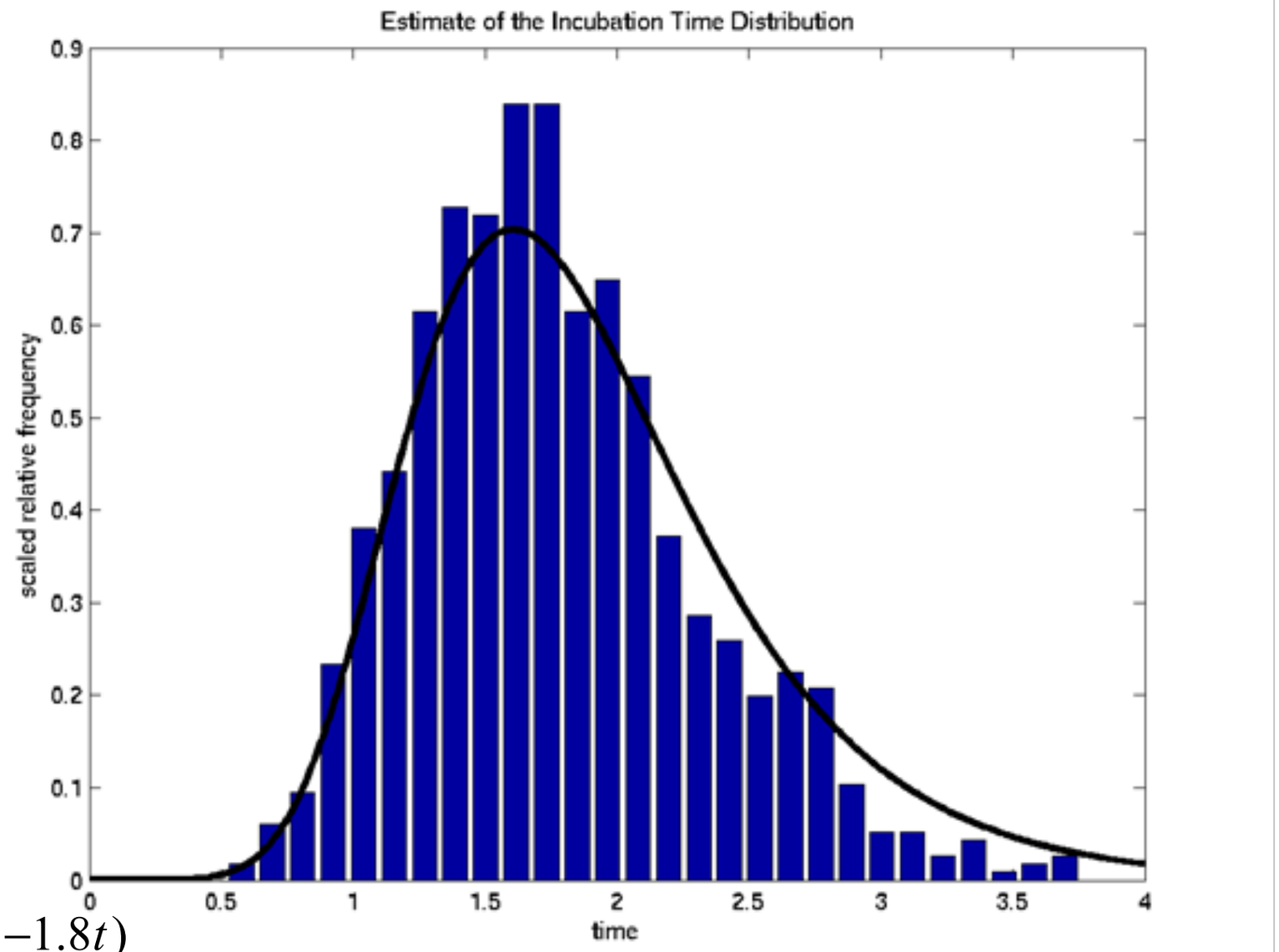
$$R(k,h) = \delta_{0k} + b_k h + o(h),$$

Taking $b_1 = \beta$ and $b_0 = -\beta$ with others = 0 gives a pure birth process as the immigration process.

- The effect of the immigration is to prevent "extinction" in the branching process. This is an important feature of HIV – which makes clear the need for including this aspect.
- The incubation time distribution (time to a fixed point when the immigration aspect is no longer critical) can be shown to be a in the "log gamma" family (includes heavy-tailed with no finite mean).

Simulations

- Figure 4 The result of 1000 simulations of the branching process with immigration. Parameters are $\alpha = 1$, $\lambda = 1.1$, and $\beta = .1$ Solid curve of the form (5) is the pdf



$$g(t) = 53.1e^{-2t-20\exp(-1.8t)}$$

1b. The role of alpha

- Although the shape of the distribution does not depend on alpha, the timing does. What determines alpha?
- The parameter is determined by the overall level of antigenic stimulation in the system (by HIV and other agents). The other agents are called “cofactors.” The question here is what role do cofactors play in establishing the initial infection.
- The important quantity is the non-HIV antigen load, *F(t).* Here, a deterministic model is chosen, as one cannot really describe the stochastic kinetics of all possible stimulation events. Model consisted of 4 ode’s with 10 parameters. *U(t)*, unstimulated unifected T cells, *S(t)*, stimulated uninfected T cells, and infected cells, *I(t)*.

Results

- The uninfected equilibrium is asymptotically stable if

$$\lambda_0 = -c_5 + (c_7 S_0 - c_4^{'}) F_0 < 0$$

and unstable if $\lambda_0 > 0$. Note that if there are enough susceptible cells, then an infection is possible. This is a "threshold condition" often seen in epidemics.

- The equilibrium has at least a 3-d stable manifold. The last arrow either indicates a return to equilibrium after perturbation or escape to a sustained infection.
- Escape would be the starting point of the previous model (branching number greater than 1). The existence of such a clean result, clearly states the importance of the level of cofactor stimulation.

2. Development of the T cell repertoire

- Each clone of T cells has a particular specificity (their range is the repertoire). Each clone also has a size. How is this repertoire & size distribution established and how is it shaped by exposure to antigens over time?
- Each clone has a differential equation (think logistic growth where the maximum growth rate is total pop dependent.

$$\frac{dT_i}{dt} = \gamma_i R f(T_{TOT}) g(T_i) T_i - (1-\gamma_i) d T_i$$

$R -$ maximal growth rate

$\gamma_i -$ fraction of i^{th} clone receiving stimulation

$$T_{TOT} = \sum_i T_i$$

Stochastic version

- With a huge number of clones to monitor, and the linking by total population, this does not seem to be useful.
- Consider, instead, a “bin model” where we look at the clone size as determining the bin number (we will use log of size).
- Growth or reduction of a clone results in changing bins.
- Probabilities of moving to a new bin based on the odes (hard part is the linking of the rates on all of the populations)
- What is desired here is the distribution of clone sizes (how many big ones, small ones, …).
- Relatively more stimulation in a particular clone results in its moving to a higher bin – less stimulation results in a downgrade.

Some details

- Note that $$\frac{dT_i}{dt} = \gamma_i R f(T_{TOT}) g(T_i) T_i - (1-\gamma_i) dT_i$$

Means that for small Δt,

$$\ln T_i(t+\Delta t) - \ln T_i(t) = (\gamma_i [R f(T_{TOT}) g(T_i) + d] - d)\Delta t + o(\Delta t)$$

So, let C_i be the characteristic of the logarithm of the size of the i^{th} clone. Then we can use the above to generate a birth-and-death process for this change of size. Writing down the Kolmogorov forward equations for the fraction of all clones having size j, B_j, we have:

Bin model

- For $j \geq 1$

$$B_j^{'}(t) = \rho f(T_{TOT}) g_{j-1} B_{j-1} + \delta B_{j+1} - (\rho f(T_{TOT}) g_j + \delta) B_j$$

- While for $j = 0$

$$B_0^{'}(t) = \delta B_1 - \rho f(T_{TOT}) g_0 B_0 \quad \text{and} \quad T_{TOT} = \sum_j b^j B_j$$

- All clones start in bin 0 and respond to the environment by changing bins over time.
- Using this structure, it is possible to do quite a lot of analytic work, including showing that there is a proper limit distribution and its structure.

What this looks like in the presence of HIV

- Largest clones correspond to highest stimulation, ubiquitous antigens and any acute infections. The distribution itself is fixed – which clones are where changes over time.
- HIV infects and kills stimulated T cells, which means that the largest clones (highest bin numbers) are eliminated first.
- This results in a sequence of elimination of clones important against likely and always present antigens resulting in the elimination of anti-HIV clones and the susceptibility to diseases normally handled (immune deficiency), the opportunistic infections.

3. Kinetics of Engraftment in hematopoietic stem cell transplants

- Hematopoietic stem cells can be collected from blood (or bone marrow) for later infusion (transplantation) after high-dose chemotherapy.
- In autologous transplants, no rejection is present.
- Interested in monitoring engraftment (return to normal levels) of each cell type – primarily leukocytes (WBC in early counts), lymphocytes, platelets, and red cells.
- Goal is to predict when problems are occurring (and intervention is possible) or when a hospital stay can be ended.

The Question

- From daily blood counts, estimate “time to engraftment” and detect possible problems before they occur.

The Data

- Daily counts from 32 women following transplantation

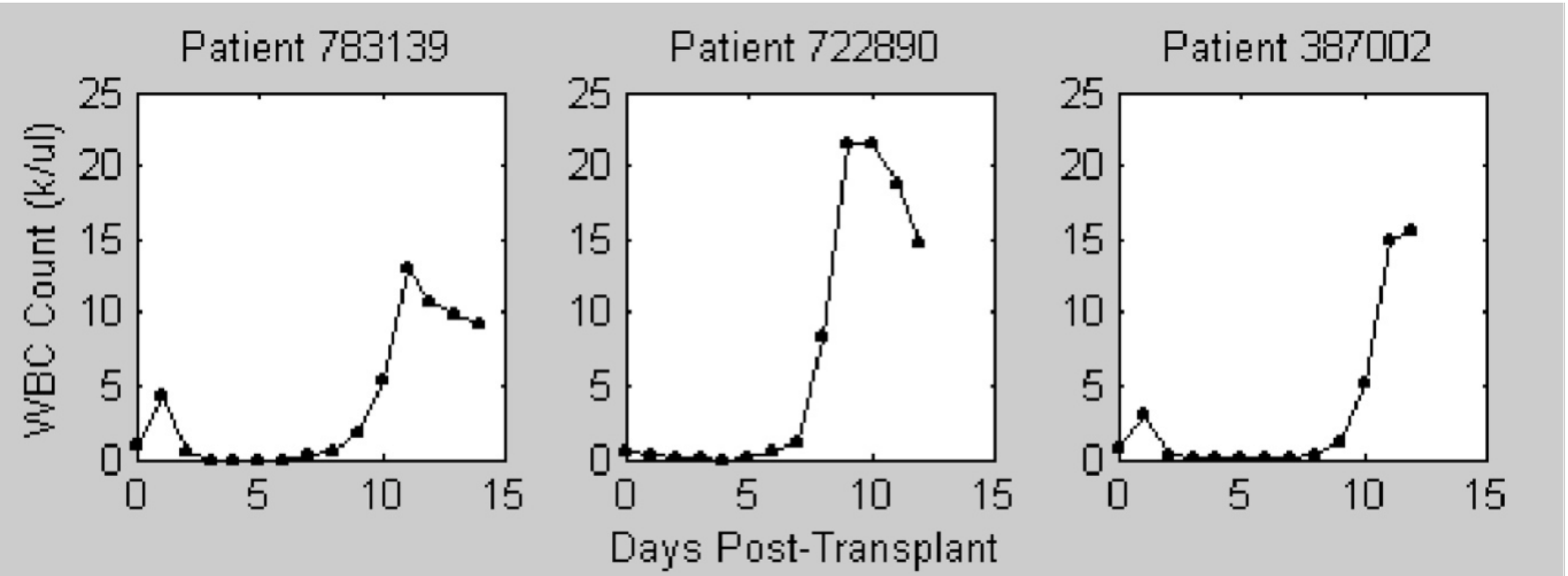
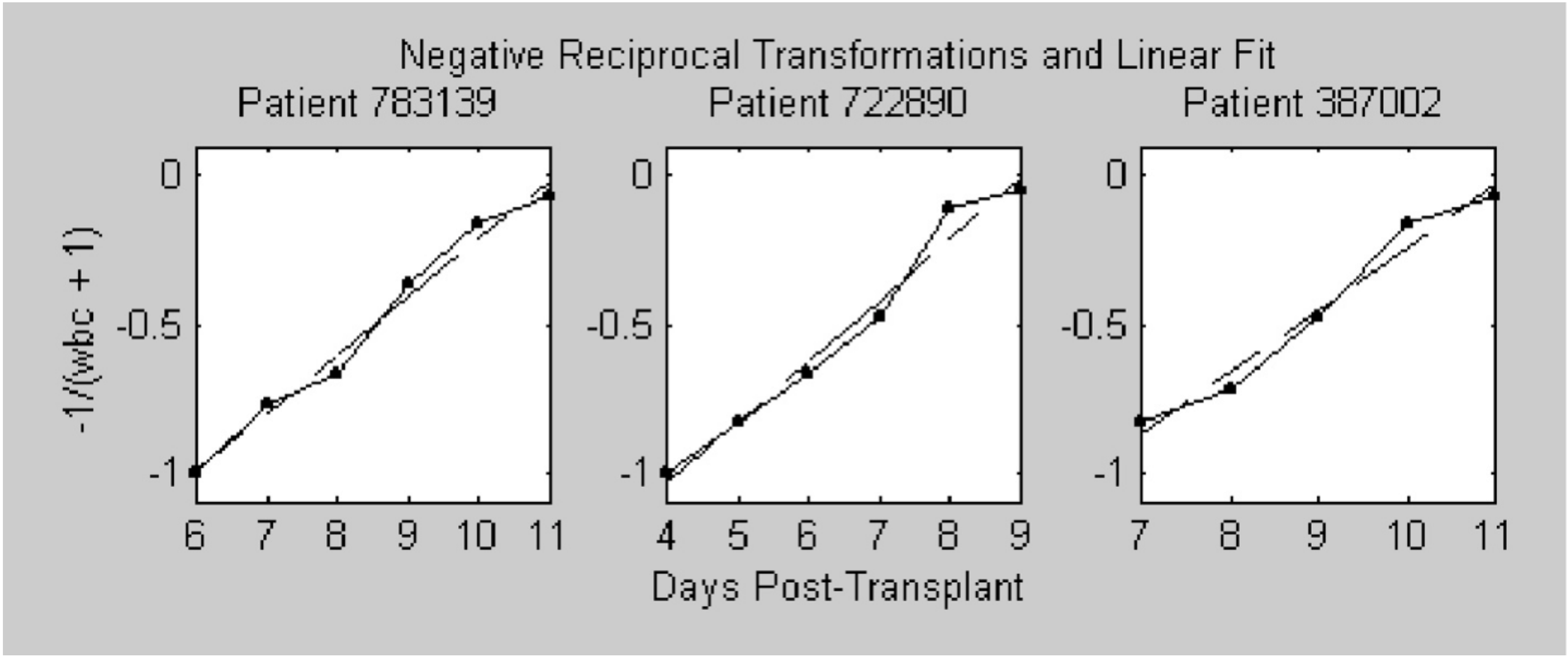


Figure 3.1. Typical WBC plots

The Model

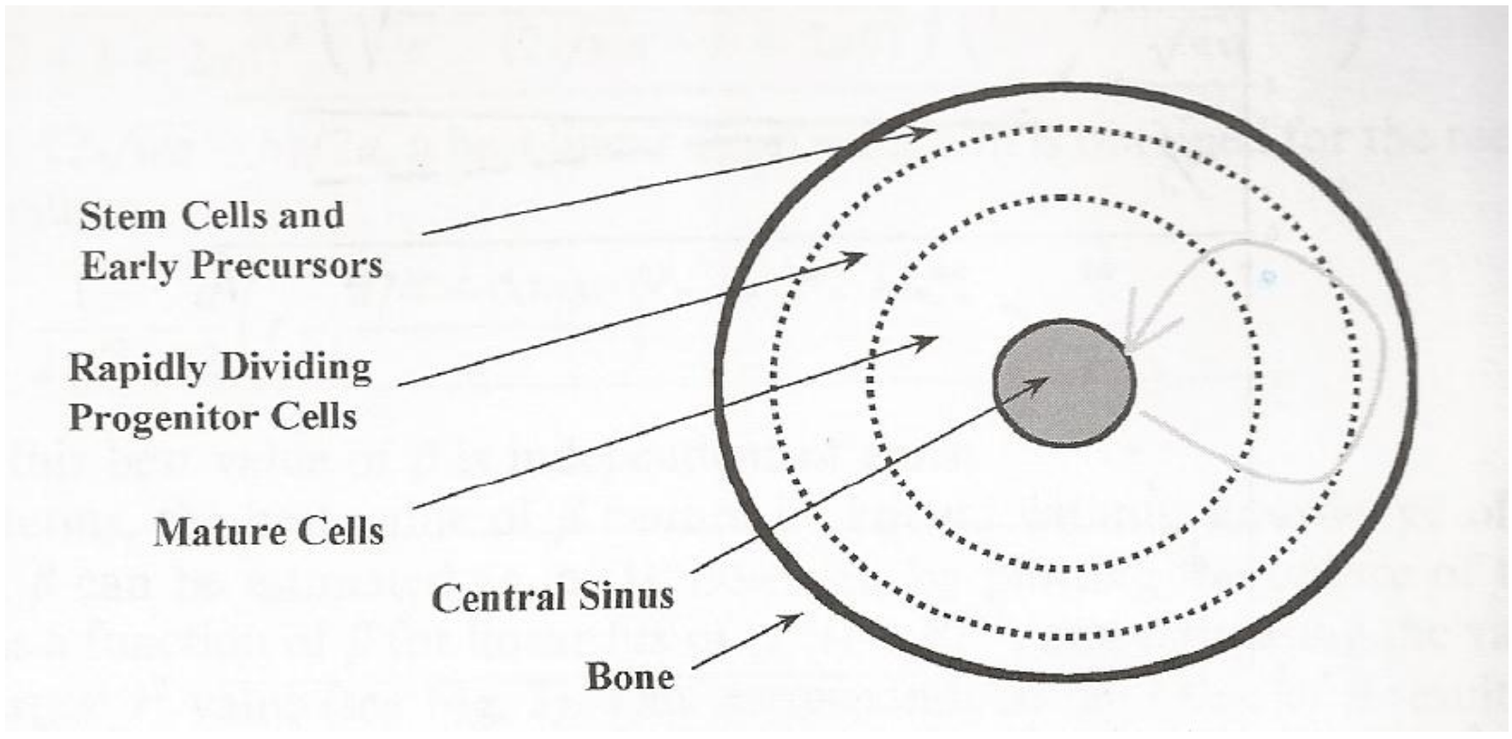
- Reciprocal plot shows hyperbolic growth $r^2 = .94$



Autocatalytic Dynamics

- This kinetic observation (of hyperbolic growth) leads one to a differential equation of the form $x' = c + ax^2 - bx$
- Setting $w = c - b^2/4a$

$$x(t) = \sqrt{\frac{w}{a}} \tan(\sqrt{wa}\ t + const) + \frac{b}{2a}$$



Why were those plots linear?

- Not hard to show that

$$\frac{1}{x(t)+\beta} \approx \frac{1}{2\sqrt{\frac{w}{a}}} - \frac{a}{2}\left(t - \frac{\pi/4 - const}{w}\right)$$

Where $\beta = \frac{2\sqrt{wa} - b}{2a}$.

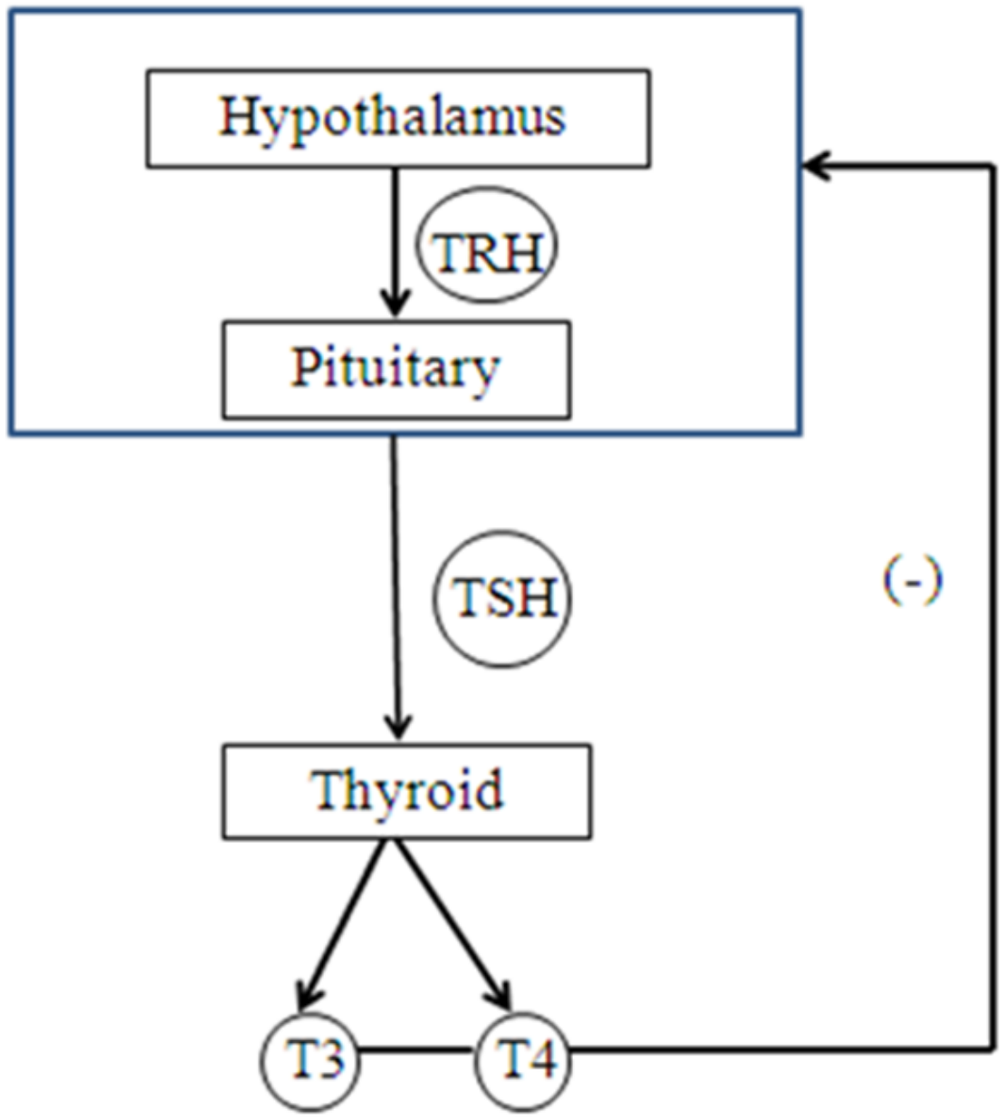
- Best value depends on the parameters – but not *const*.

- In this application, $\beta \approx 1$!

i.e., the parameter chosen to avoid dividing by zero was almost exactly the value needed to get linearity in the reciprocal plot.

4. Modeling the natural history of autoimmune thyroiditis

HPT Axis



The Question

- Can we determine if the patient will eventually develop chronic hypothyroidism?

(If so, when do we start treatment to minimize effects of the disease)

The Data

- 119 patients with autoimmune antibody in Sicily. Each patient has 2-7 measurements of TSH and free T4 at irregular intervals over years.
- Although there are models of the HPT axis, none exist for this situation where the response of the thyroid is disrupted.

Possible Responses

- Impossible – need more data
- Impossible – individual differences reduce the usefulness of even the little data available
- Maybe a simple model can tell us something

$$\frac{dFT4}{dt} = \frac{k_3\, T\, TSH}{k_d + TSH} - k_4 FT4$$

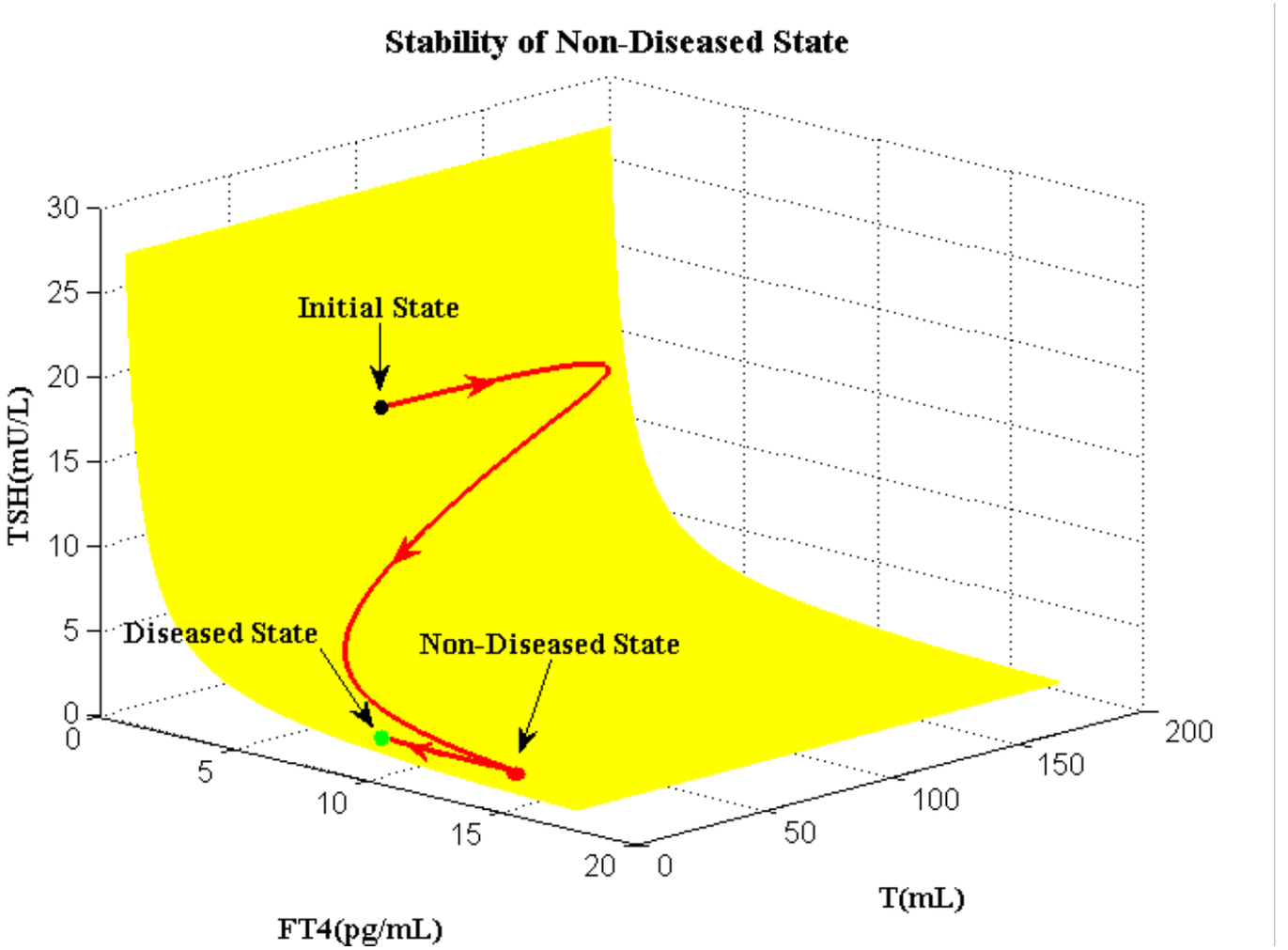
$$\frac{dTSH}{dt} = k_1 - \frac{k_1\, FT4}{k_a + FT4} - k_2\, TSH$$

$$\frac{dT}{dt} = k_5 \left(\frac{TSH}{T} - N \right) - k_6 Ab\, T$$

$$\frac{dAb}{dt} = k_7 Ab\, T - k_8\, Ab$$

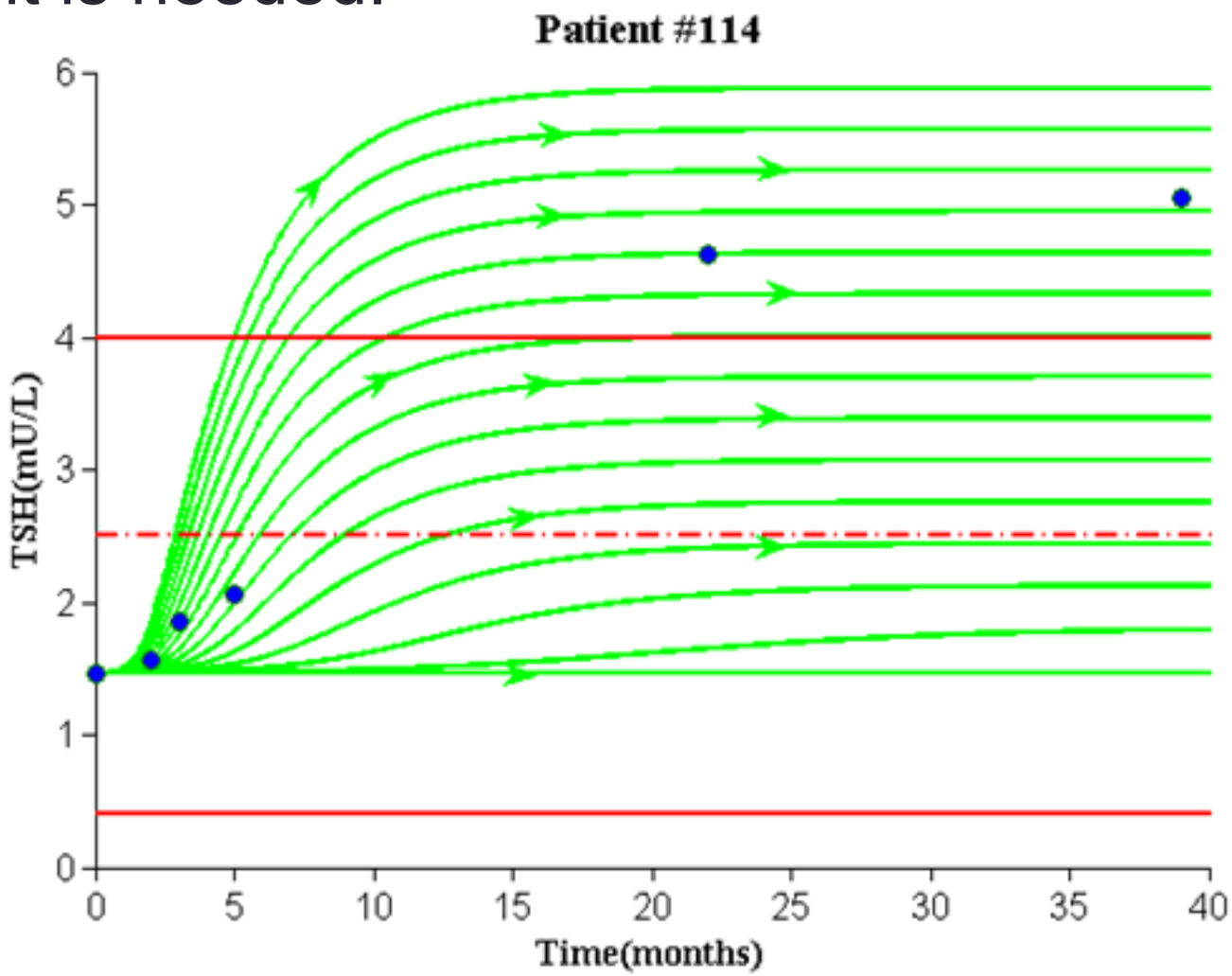
Methods

- Analysis using singular perturbations to get lower dimensional descriptions.
- Validation of the results using simulation and clinical data.



Results

1. Dynamics are simple – depending on only a few parameters
2. For each patient, an approach to the equilibrium can be determined
3. The position of the equilibrium will determine if (and when) treatment is needed.



Conclusions and observations

- This talk emphasized using the nature of the system under study, the question being asked, and the nature of the data to guide modeling.
- It is not unusual to get somewhat simple results from complicated initial stories. It is a good idea to ask “what form could the answer take?” Is it a graph, a table, an equation, … This helps to focus the work.
- Giving talks with so many aspects is difficult to prepare and probably sit through.

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