Cost of failure to treat autoimmune thyroiditis in thyroid cancer initiation and growth

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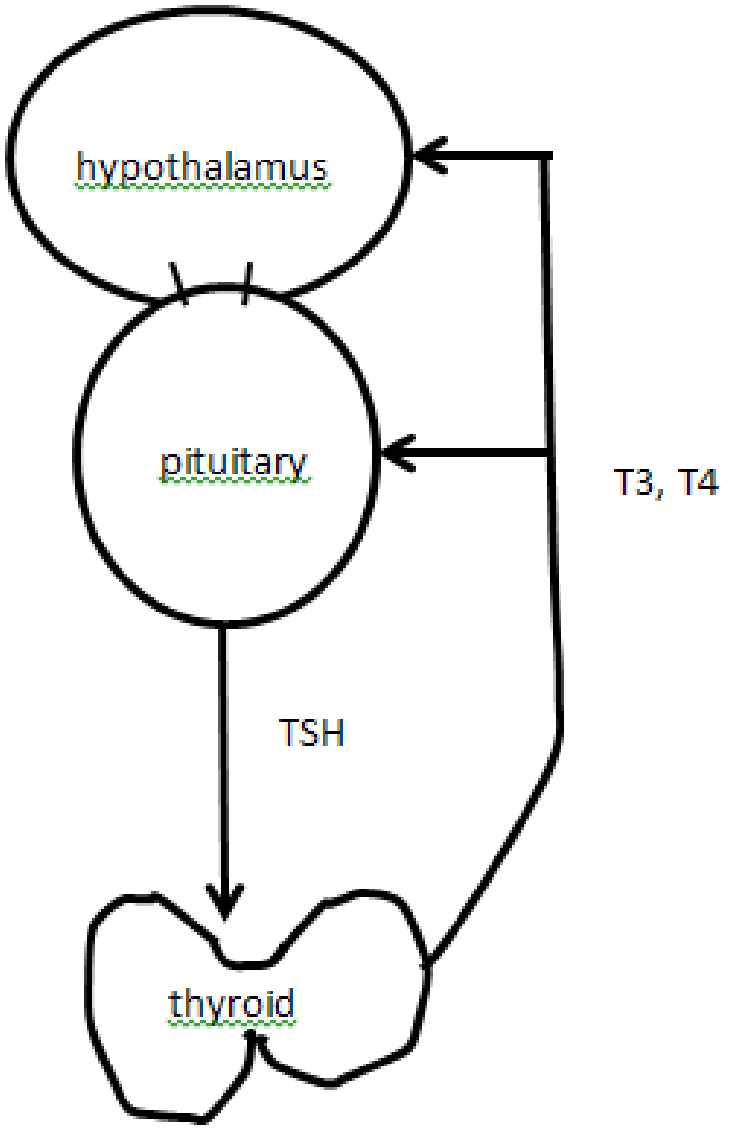
Thyroid Gland

- One of the largest endocrine gland, controlling metabolism in the body
- Also controls how the body should react to other hormones (such as products of the adrenal gland)
- Produces two hormones, T3, which has 3 atoms of iodine and T4, which has 4.
- T3 is the active form, produced from T4 by one of two deiodination enzymes.
- Hypothyroidism (low T4) is most commonly caused by an autoimmune condition. Incidence is increasing world-wide
- Hypothyroidism is usually treated by hormone replacement with synthetic T4, Levothyroxine.

Basic Idea

- **Basic feedback control -- the HPT axis.**
- **This control is disrupted in autoimmune (Hashimoto's) thyroiditis**
- **As the thyroid is slowly destroyed, the thyroid is unable to respond to the TSH signal**
- **As T4 falls -- TSH increases.**



Consequences of increasing TSH

- **Areas of the thyroid are stimulated to grow, forming "nodules" of follicular cells (the T4-producing cells).**
- **The overall size of the thyroid can grow dramatically, forming a temporary thyroid goiter.**
- **In the face of autoimmune thyroiditis, there is a large inflammatory response and sometimes a large short-term release of T4, Hashitoxicosis.**
- **For any cancers that form in a nodule, TSH acts as a hormonal growth factor.**

Thyroid Nodules

- **Found in 20-70% of the population**
- **About 5% (and to up to 15% in thyroiditis) are malignant**
- **Main type of thyroid cancer is carcinoma, papillary (75%), follicular (10%), other types (15%).**
- **Treatment options: thyroidectomy sometimes followed by radioactive iodine or TSH suppression by levothyroxin (T4)**

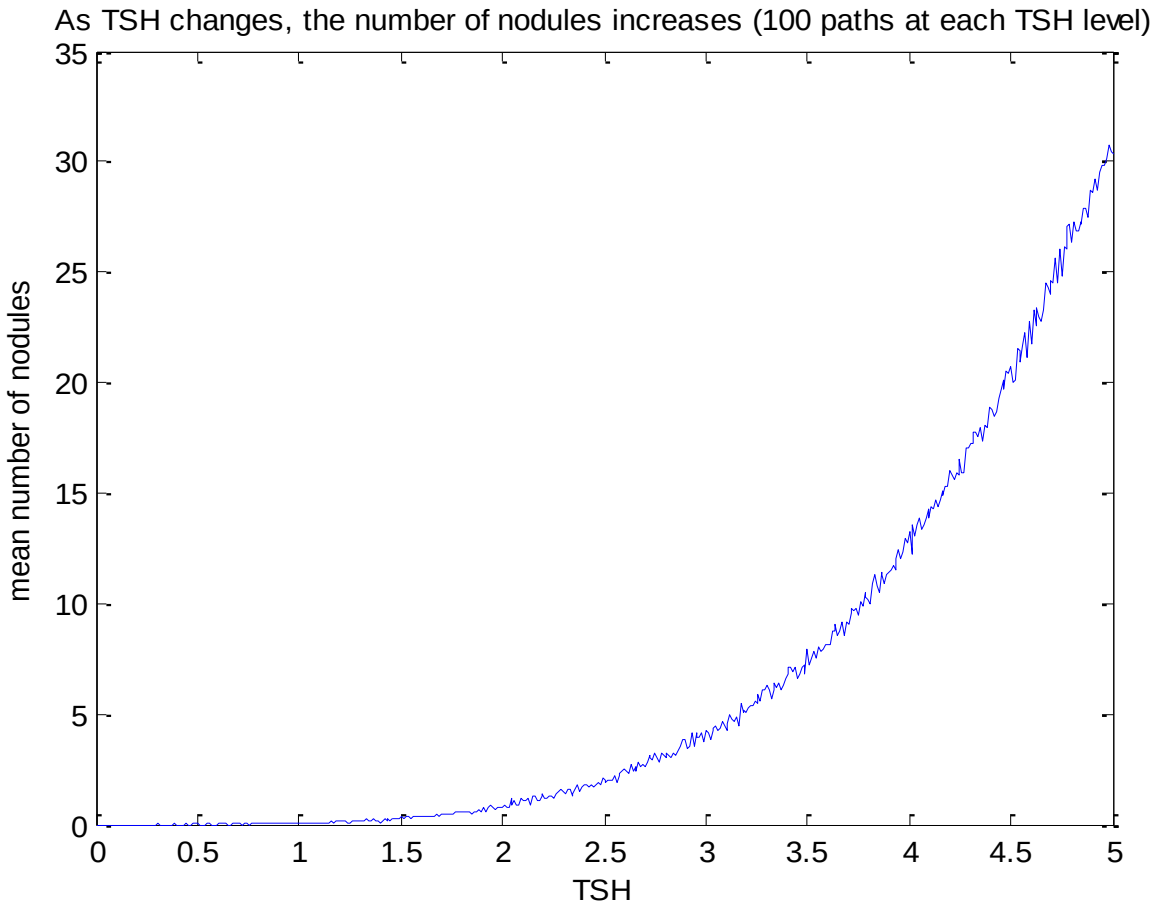
Outline of the model

1. Due to the nature of the process, a stochastic model (with a continuous input) is chosen.
2. In any Δt of time, a region in the thyroid may be stimulated to begin a nodule. This rate is determined by TSH.
3. Growth of an existing nodule is determined by TSH.
4. Cancer development rate is determined by the nodule growth rate. Once started, growth rate of a cancerous nodule is greater than the growth rate of other nodules.

How many areas get a nodule initiation signal?

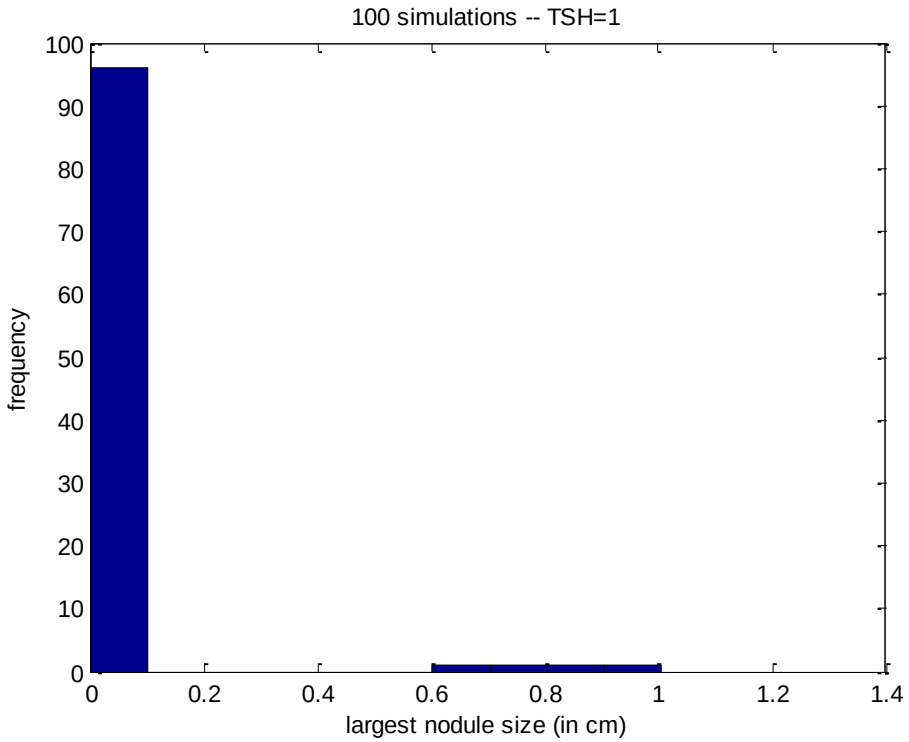
- **Assuming N potential growth sites, consider the distribution of M TSH molecules distributed to the N sites (assuming a large signal would mean a nodule initiation).**
- **Number of molecules per site follows a binomial distribution. Counting the number of sites that exceed a threshold given M molecules in this case can be approximated by** $\frac{TSH^4}{K + TSH^4}$ **for some** K.

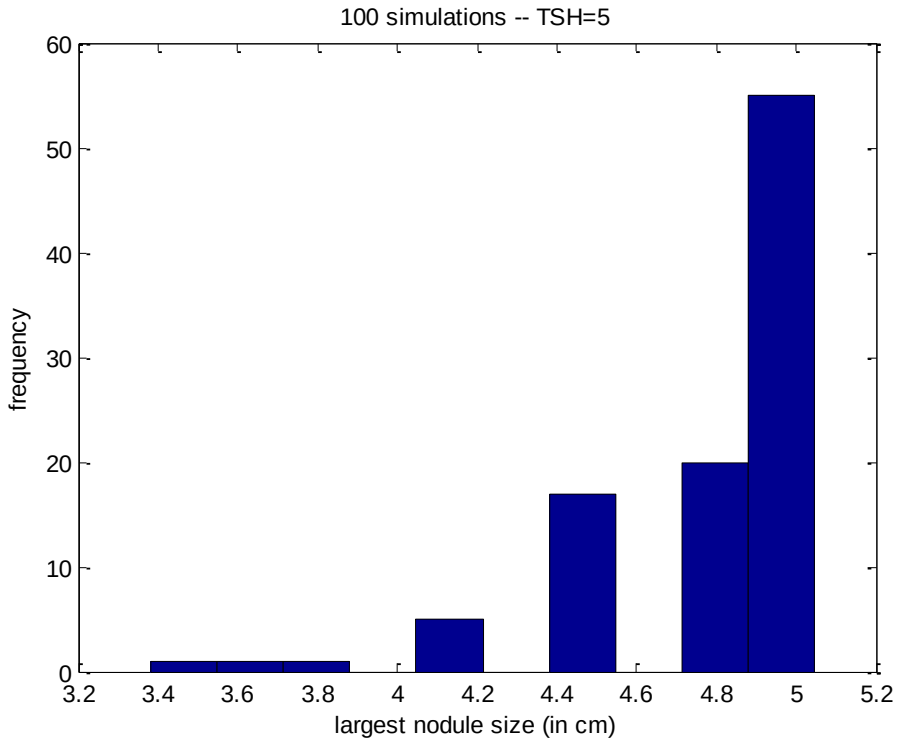
Number of Nodules



Over 30 years, effect of elevated TSH.

Largest Nodule increases with TSH





Frequency of large, 4 cm nodules increases if TSH increases. Half of these may be cancerous in autoimmune thyroiditis.

The connection to autoimmune thyroiditis

- There can be a long period of asymptomatic hypothyroidism (T4 normal or low, TSH increasing).
- Treatment (with levothyroxin) is often started when TSH is beyond normal reference (4-5 μU/mL) .
- This can result in a long (several year) period where TSH is high and nodule formation is encouraged.
- In undiagnosed conditions, TSH can reach very high levels, raising the risk of cancer.

Question of Interest

- **What is the cost (in terms of increased thyroid cancer) for late treatment of hypothyroidism?**
- **Approach is to compare the untreated and treated simulated populations and to compare cancer incidence.**
- **Need to find a way to mimic the natural changes in TSH in this disease.**

Model of Autoimmune Thyroiditis

- **The work of a doctoral student, Bala Pandiyan, along with Dr. Salvatore Benvenga, University of Messina in Sicily and an undergraduate McNair Fellow, Mike Castillo (Marian University)**
- **Based on data from Benvenga's clinic of hundreds of thyroiditis patients.**
- **Describes the disruption of the feedback system's ability to keep TSH and T4 at set levels as a result of the disease.**
- **Takes the form of a nonlinear system of differential equations.**

Pandiyan's Model

- T is the functional (active) size of the thyroid
- Ab is the level of antithyroid antibodies (TPOAb) and TgAb

$$\frac{d(TSH)}{dt} = k_1 - \frac{k_1 T4}{k_a + T4} - k_2 TSH$$

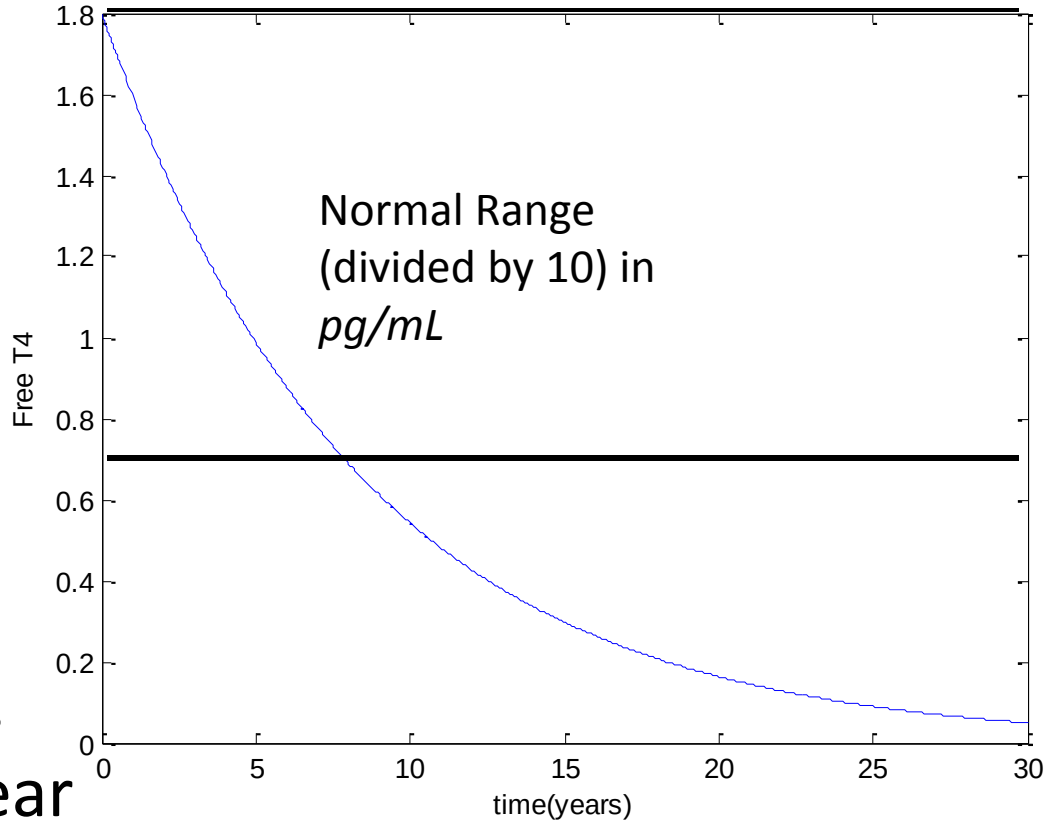
$$\frac{d(T4)}{dt} = \frac{k_3 T(TSH)}{k_d + TSH} - k_4 T4$$

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

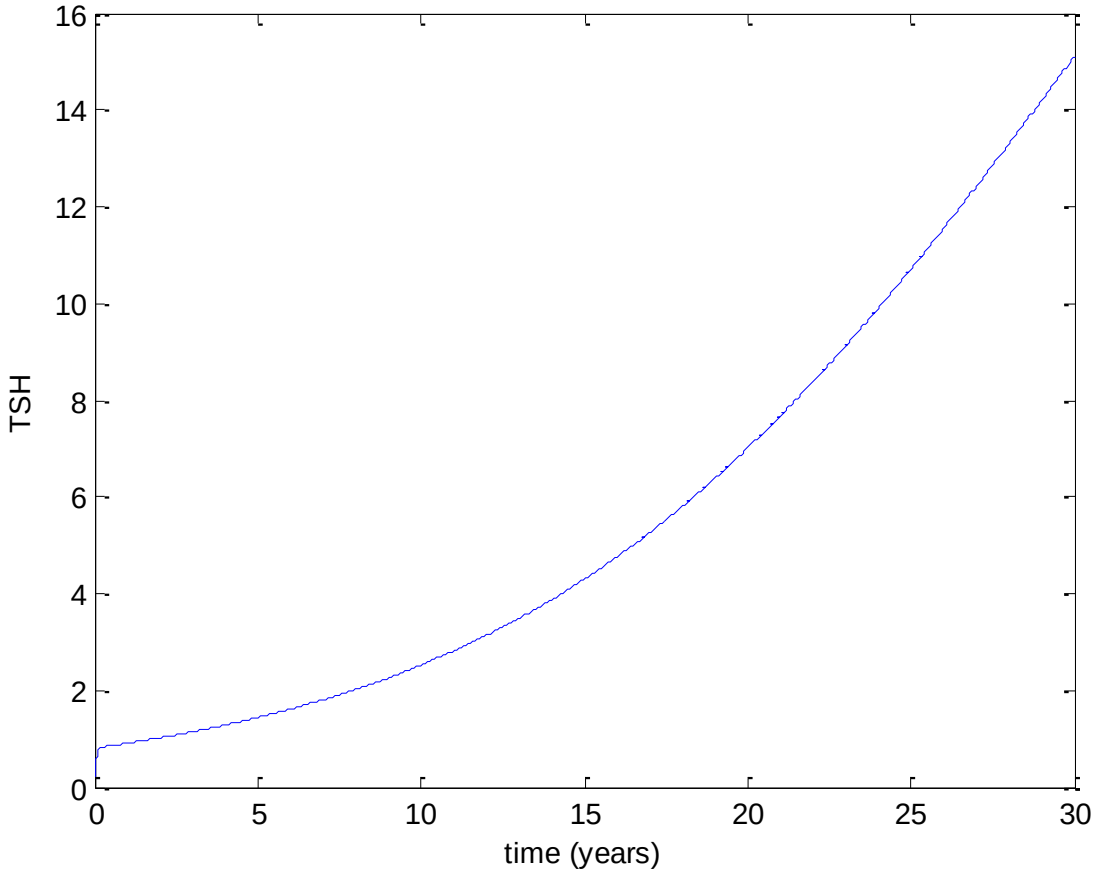
$$\frac{d(Ab)}{dt} = k_7 (Ab) T - k_8 Ab$$

Parameters

- Determined by the literature, data, equilibrium arguments, and simulation.
- Typical drop in T4 which results in a corresponding large increase in TSH. log(TSH) is nearly linear in T4.



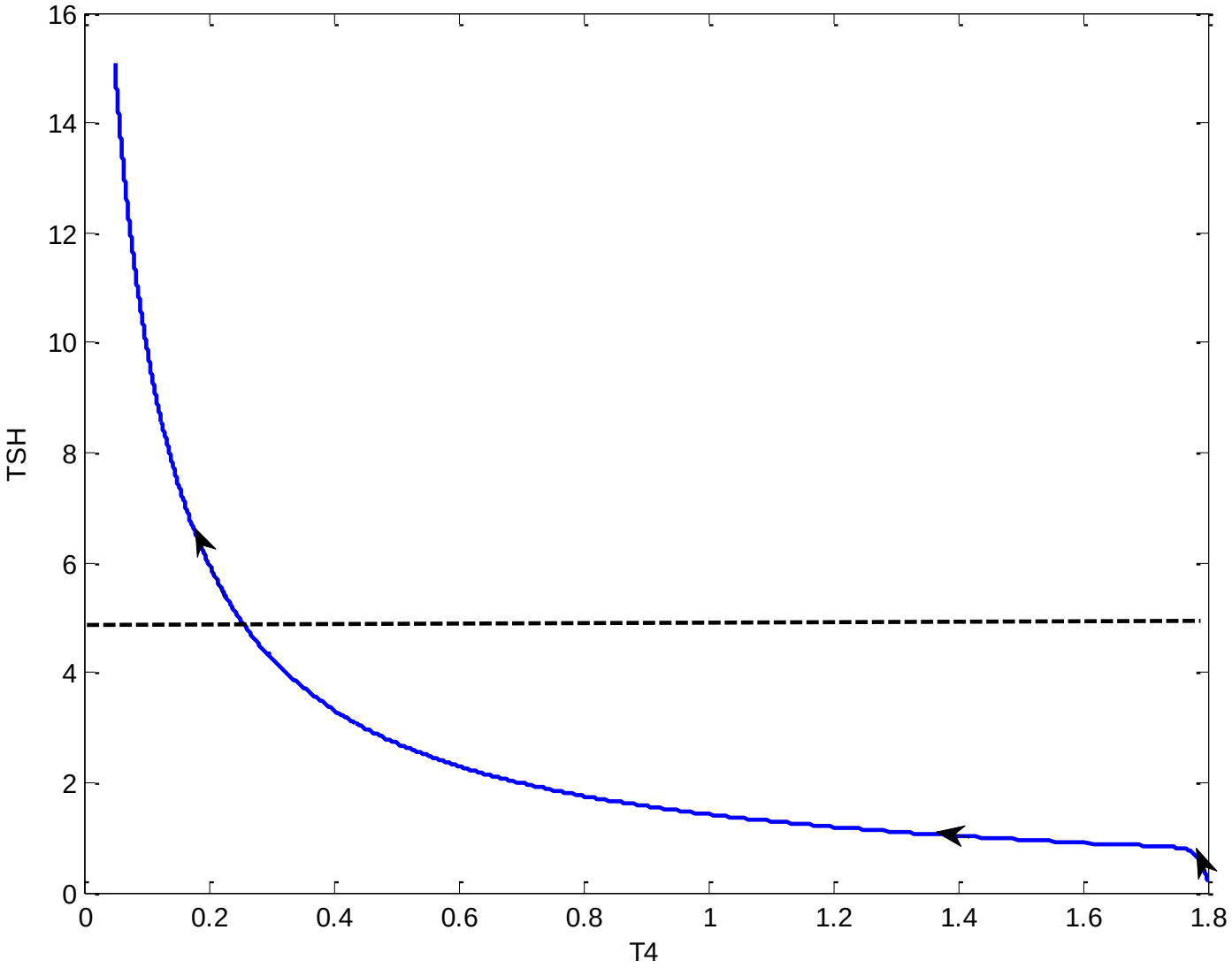
TSH increases over time



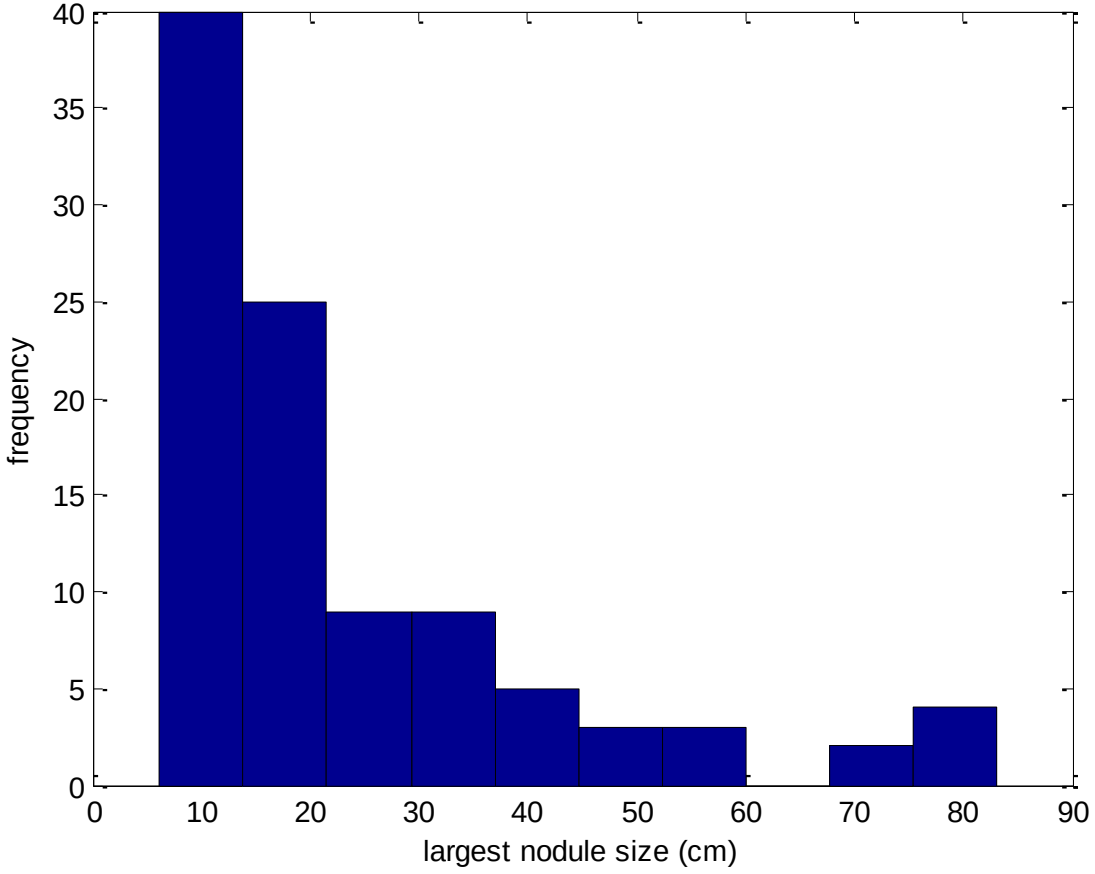
Behavior of the model

- Depends on parameter k_7 . If that parameter is small, the normal “euthyroid” state is globally stable, attracting all solutions (that is, the system maintains itself). If that parameter is large, there is a new stable equilibrium and the system works its way toward that new equilibrium over a period of years.

Disease Progression



Untreated

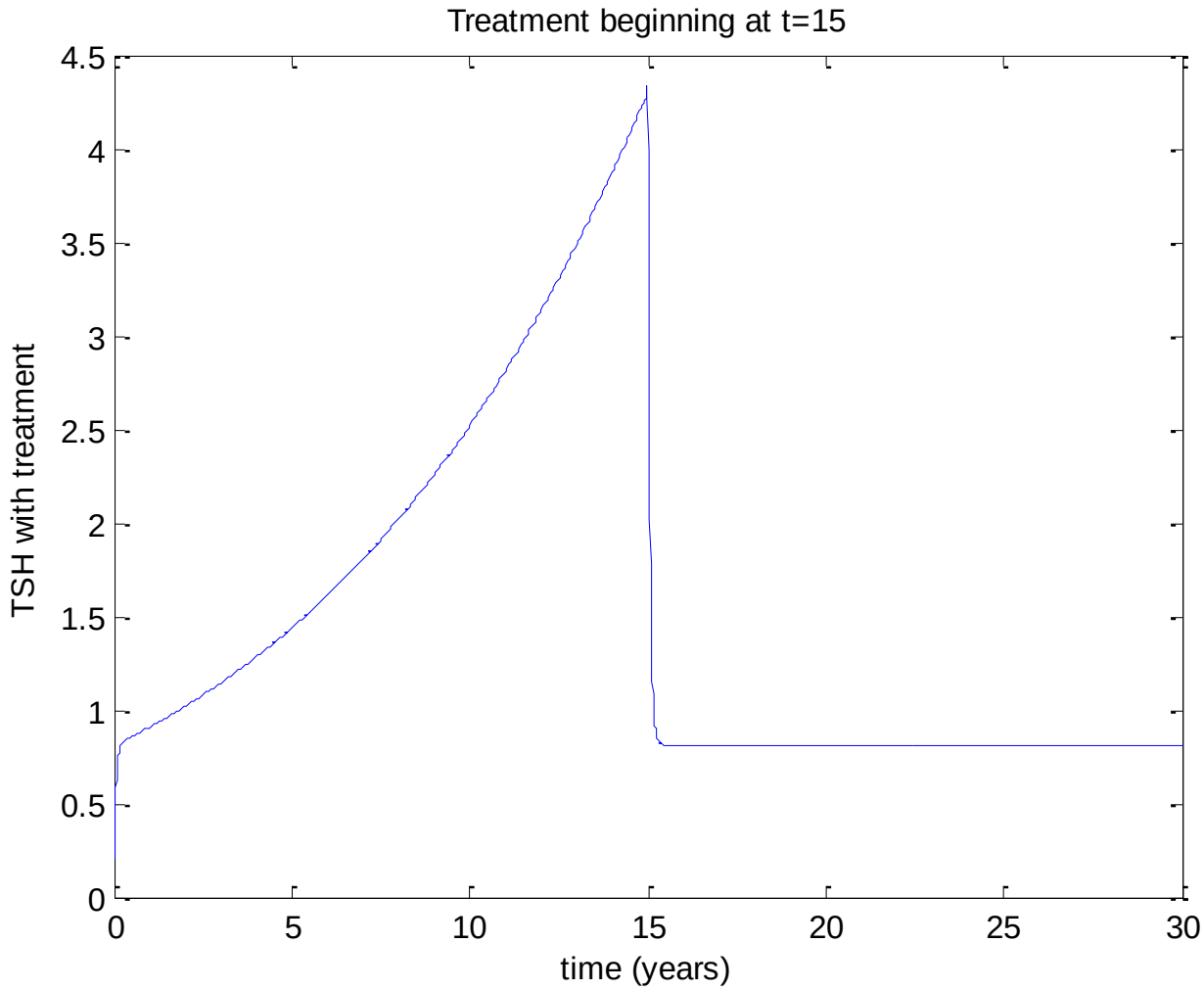

frequency
largest nodule size (cm)
0
5
10
15
20
25
30
35
40
0
10
20
30
40
50
60
70
80
90

With Treatment

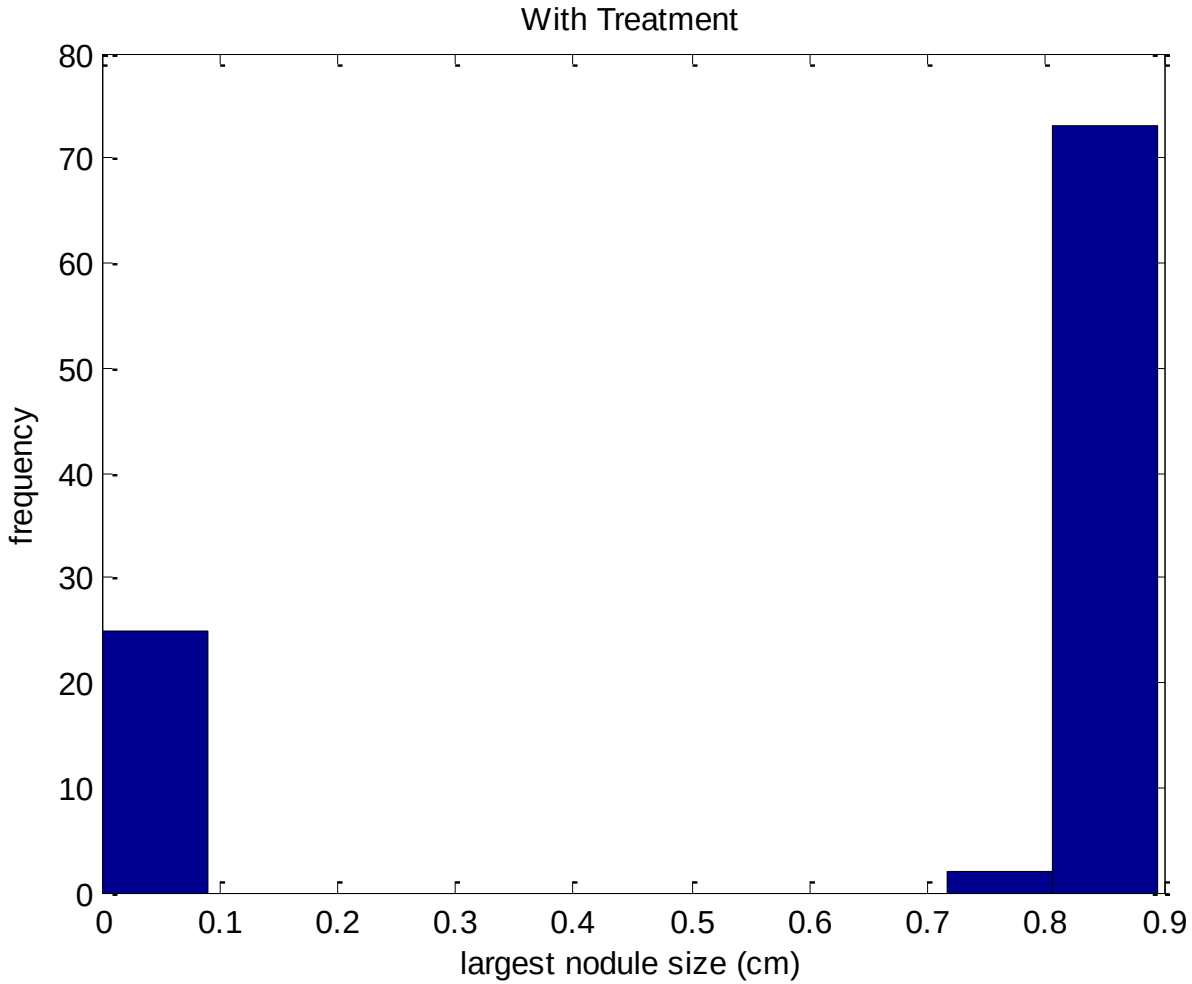
TSH returns

To normal

levels



Nodule sizes – with Treatment



Summary

- **A dynamic model of autoimmune thyroiditis enables one to study consequences of the disease, such as initiation and growth of thyroid cancer.**
- **Similar studies could be done to study other treatment effects, such as side effects or even patient satisfaction.**
- **Patient-specific parameters can be identified.**

Thank You!

Much of this presented work was joint with Mike Castillo (no picture available)