Clinical Application of a Math Model of the HPT Axis for Personalized Euthyroid Targets

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Is there a need to personalise thyroid hormone targets for hypothyroid patients on L-thyroxine replacement?

Clinical Unmet Need

- An estimated 200 million people worldwide who suffer from some form of thyroid disease – major endocrine metabolic epidemic after diabetes (Lancet Diabetes Endocrinol 2013)
- Up to 40% of all adults may have some degree of hypothyroidism
- A sizeable fraction of those defined as euthyroid continues to feel subnormal
- Suboptimal thyroid replacement may account for depression, hypertension, hypercholesterolemia, obesity, etc.
- Current approach is thus far from perfect

Discordance between Pre-disease State & Euthyroidism on Treatment

- Clinicians round the world recognize a common phenomenon of patients who persistently experience residual symptoms of hypothyroidism or thyroid excess despite having achieved circulating levels of [FT4] and [TSH] within the normal ranges

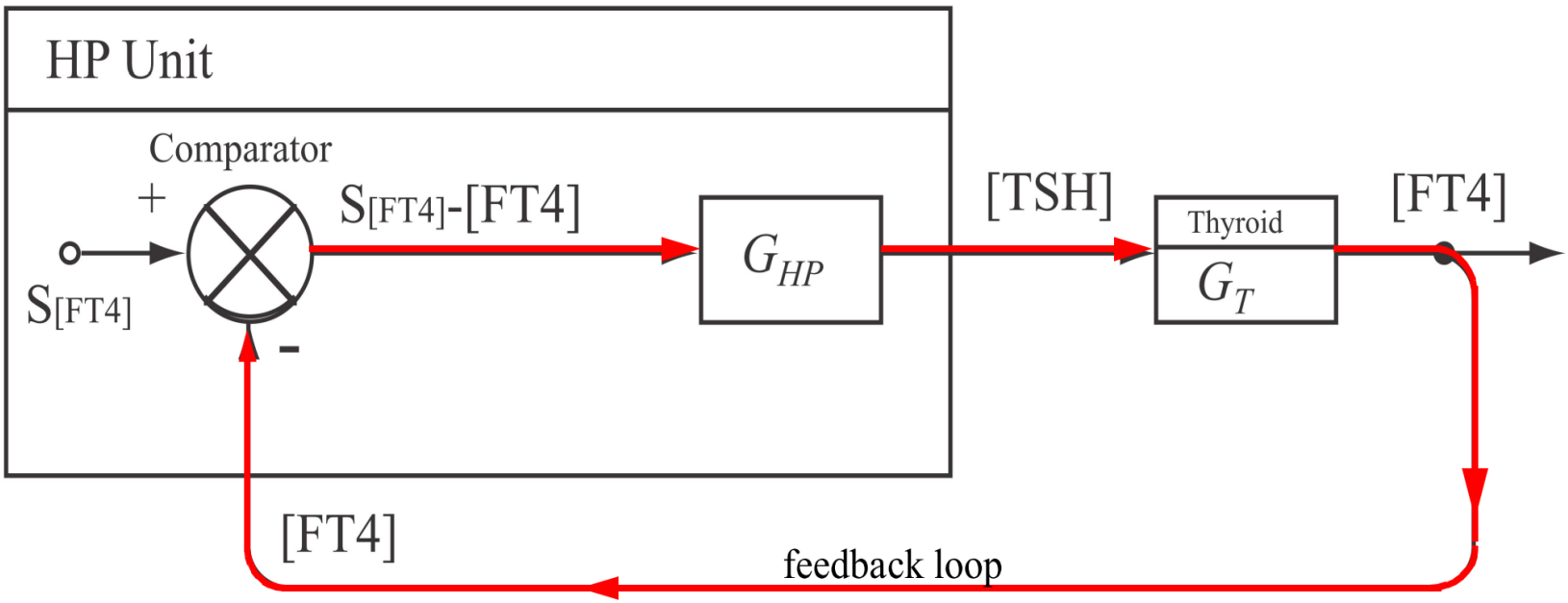
  – Tigas et al., *Thyroid* 2000
  – Saravanan et al., *Clin Endocrinol* 2002
  – Gullo et al., *PLoS One* 2011

Present Definition of Euthyroidism Not Necessarily Appropriate for Everyone

- General application of the lab-quoted [TSH] reference range is not always optimal for everyone in clinical practice

  - Taylor *et al*., *JCEM* 2013
  - Asvold *et al*., *Eur J Endocrinol* 2013
  - Wartofsky & Dickey, *JCEM* 2005
  - Hamilton *et al*., *JCEM* 2008

Closed Feedback Loop of the HPT Axis Implies the Existence of a Set Point



$$G_L = \left| G_{HP} \cdot G_T \right| > 1$$

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A mathematical model of pituitary–thyroid interaction to provide an insight into the nature of the thyrotropin–thyroid hormone relationship

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A novel minimal mathematical model of the hypothalamus–pituitary–thyroid axis validated for individualized clinical applications

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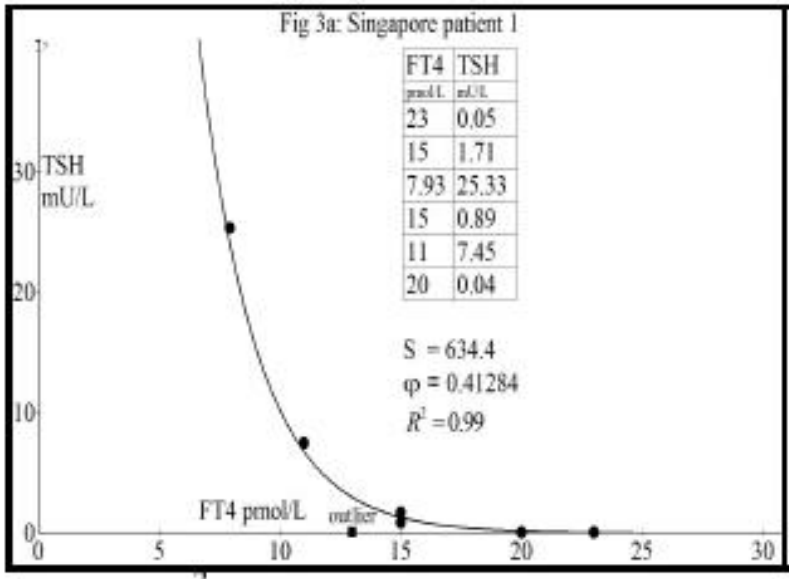
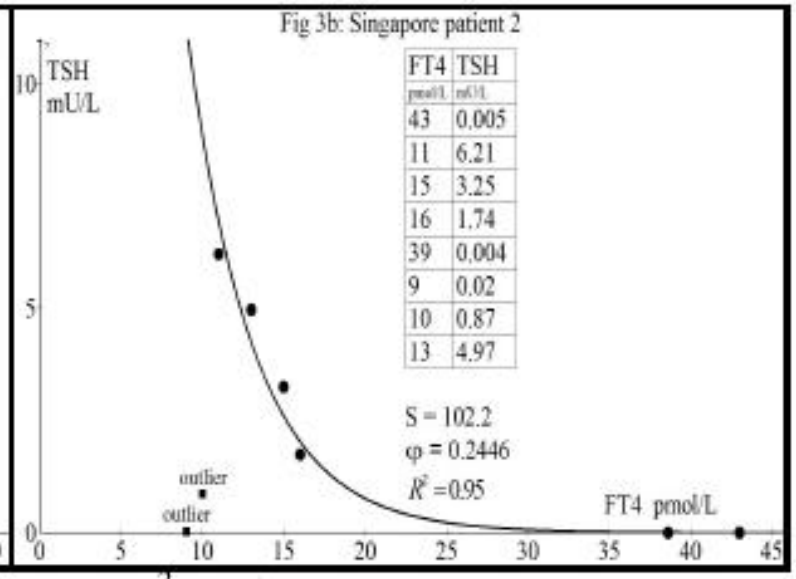


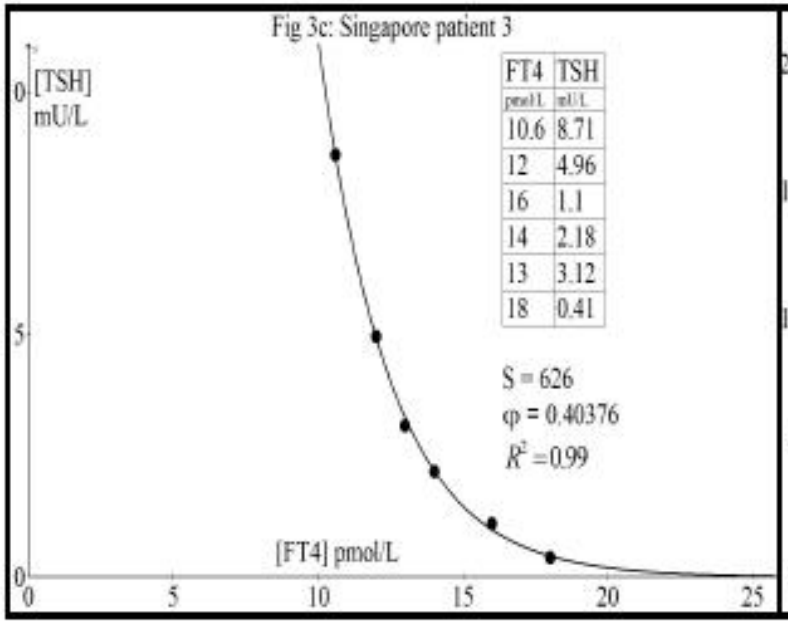
FT4 pmol/L	TSH mU/L
23	0.05
15	1.71
7.93	25.33
15	0.89
11	7.45
20	0.04

Fig 3a R^2 = 99%



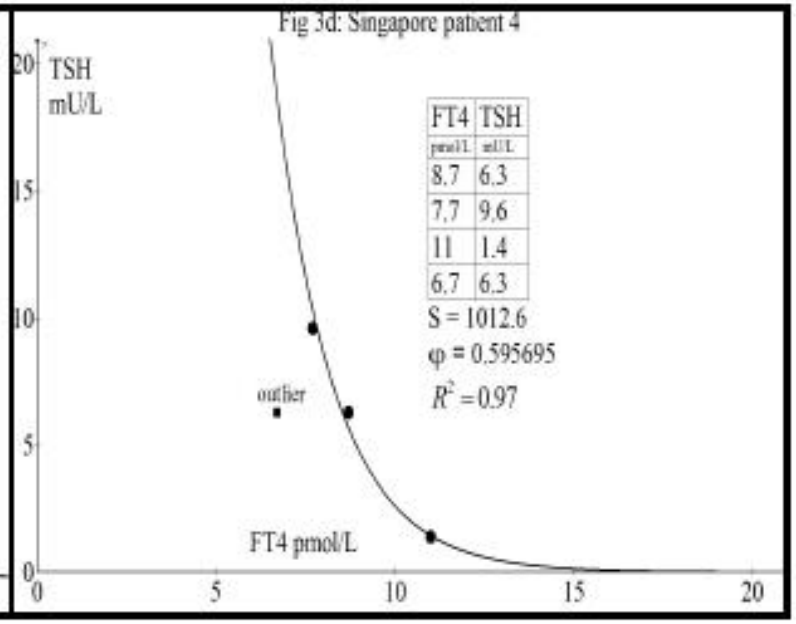
FT4 pmol/L	TSH mU/L
43	0.005
11	6.21
15	3.25
16	1.74
39	0.004
9	0.02
10	0.87
13	4.97

Fig 3b R^2 = 95%



FT4 pmol/L	TSH mU/L
10.6	8.71
12	4.96
16	1.1
14	2.18
13	3.12
18	0.41

Fig 3c R^2 = 99%



FT4 pmol/L	TSH mU/L
8.7	6.3
7.7	9.6
11	1.4
6.7	6.3

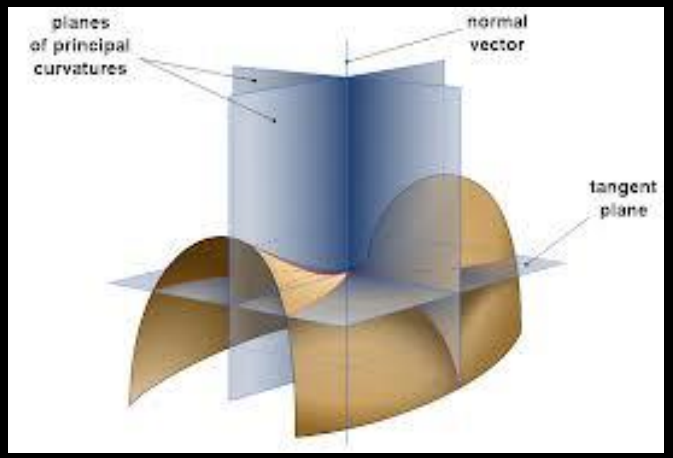
Fig 3d R^2 = 97 %

Theory of Greatest Curvature

$$f2 = K = \frac{d^2y/dx^2}{\left(1+\left(dy/dx\right)^2\right)^{3/2}}$$

$$y = S\exp(-\varphi x)$$

$$K = \frac{\varphi^2 S\exp(-\varphi x)}{(1+\varphi^2 S^2\exp(-2\varphi x))^{3/2}}$$



$$f3 = \frac{dK}{dx} = \frac{\varphi^3 S\exp(-\varphi x)\{1+\varphi^2 S^2\exp(-2\varphi x)\}^{0.5}[2\varphi^2 S^2\exp(-2\varphi x)-1]}{\{1+\varphi^2 S^2\exp(-2\varphi x)\}^3}$$

$$2\varphi^2 S^2\exp(-2\varphi x)-1=0$$

Euthyroid Set Point Equations

$$[FT4] = \frac{\ln(\varphi S\sqrt{2})}{\varphi}$$

$$[TSH] = \frac{1}{\varphi\sqrt{2}}$$

Leow and Goede *Theoretical Biology and Medical Modelling* 2014, 11:35
http://www.tbiomed.com/content/11/1/35

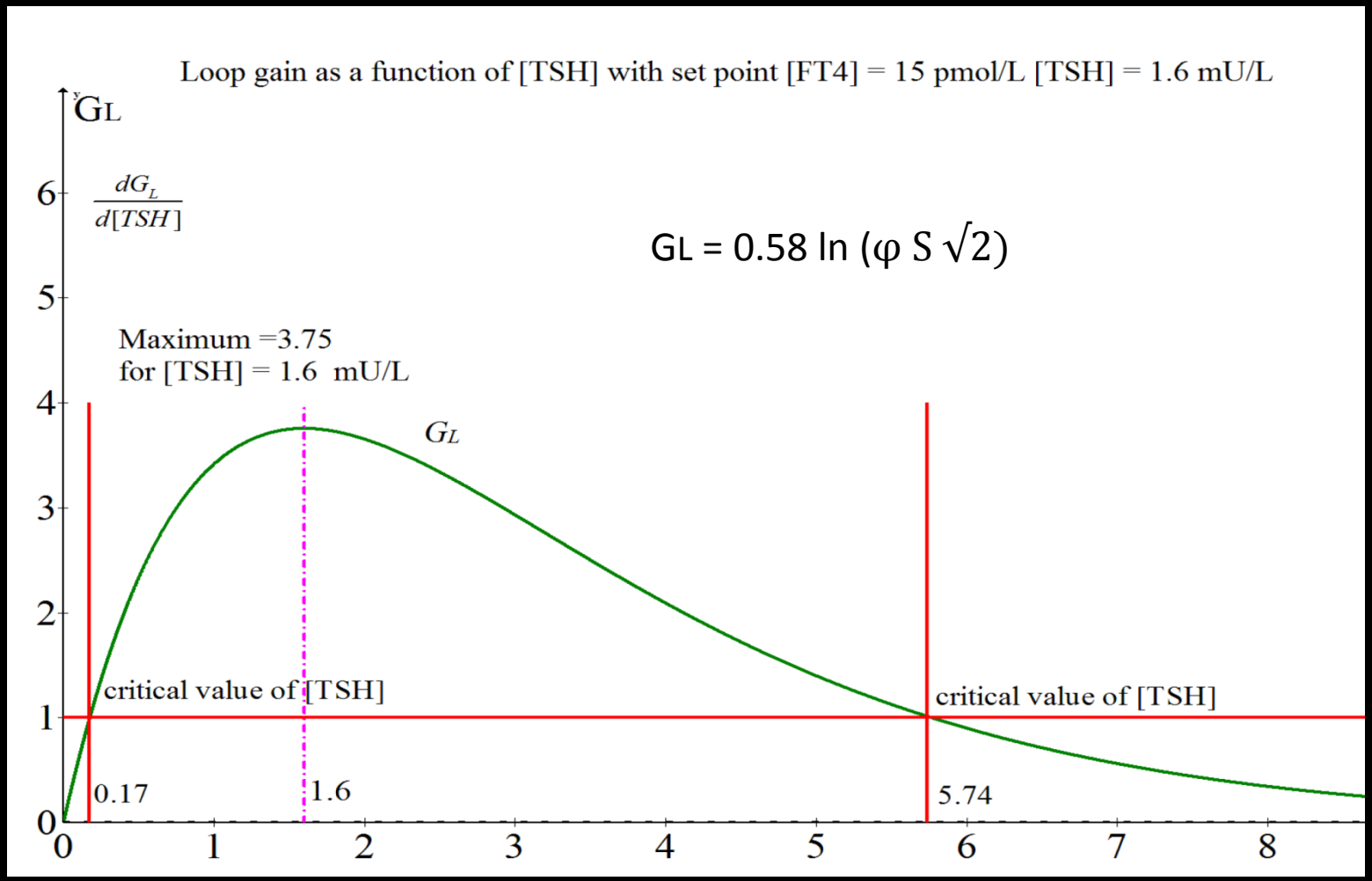
THEORETICAL BIOLOGY AND MEDICAL MODELLING

RESEARCH Open Access

The homeostatic set point of the hypothalamus-pituitary-thyroid axis – maximum curvature theory for personalized euthyroid targets

Melvin Khee-Shing Leow[1,2,3,4,5,6,7*] and Simon L Goede[8]

Maximum Loop Gain and Stability at the Euthyroid Set Point



We Are All Uniquely “Euthyroid”

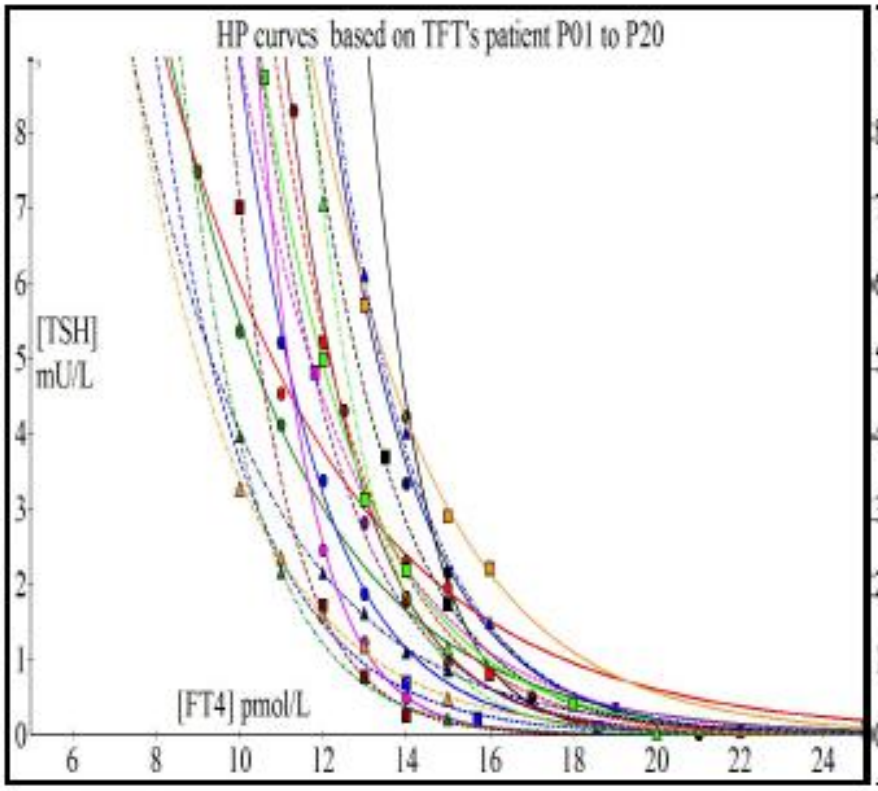


Fig. 6C. HP curves fitted with TFTs (N=20)

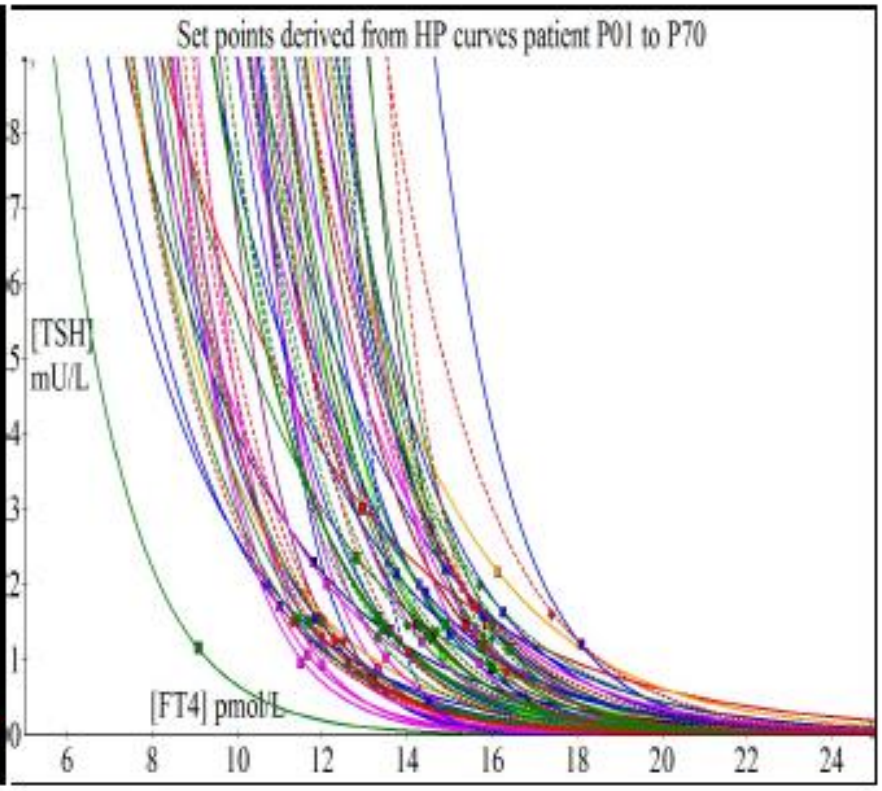
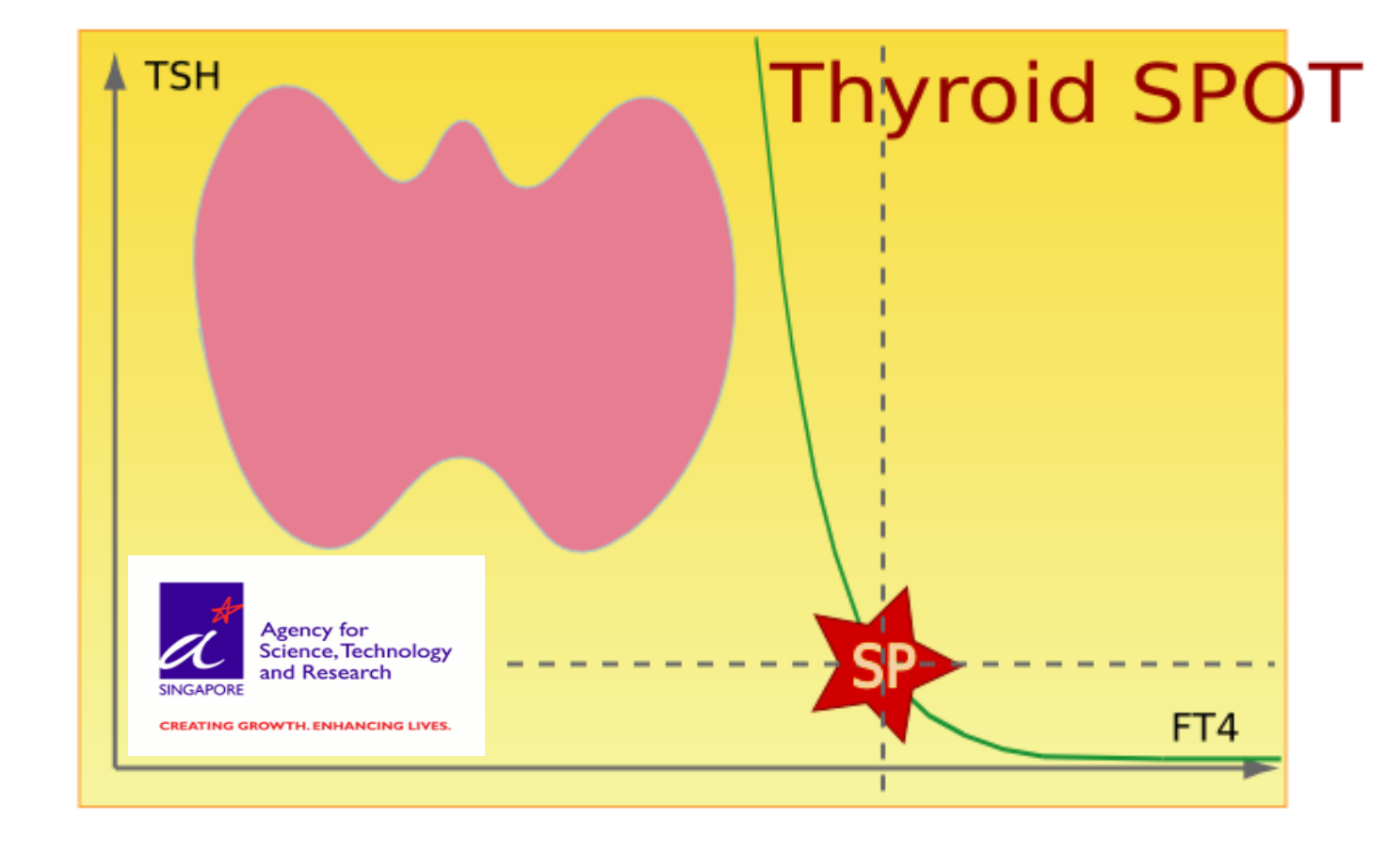


Fig. 6D. HP curves with set points (N=70)



Patented Software: Thyroid Set Point Optimization and Targeting (Thyroid-SPOT)

Co-inventors: Melvin Leow, Sam Goede, Johannes Dietrich

Thyroid SPOT - version 0.3.0.9

Singapore Institute for Clinical Sciences
A*STAR

Patient Info

Singapore p03

Description	Singapore p03
Birthday	1/1/1900 12:00:00 AM
Gender	Female
Race	Chinese

New Patient | Edit Patient

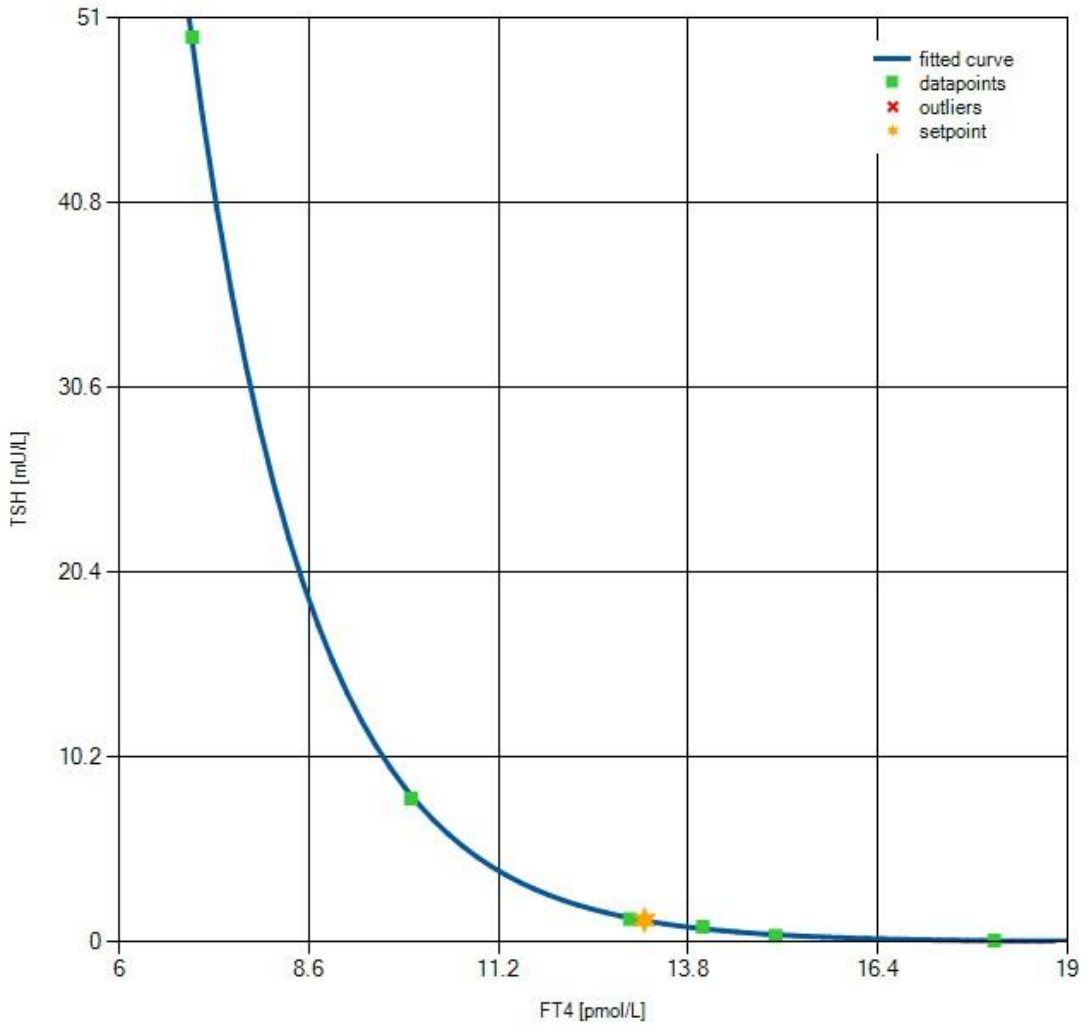
Data

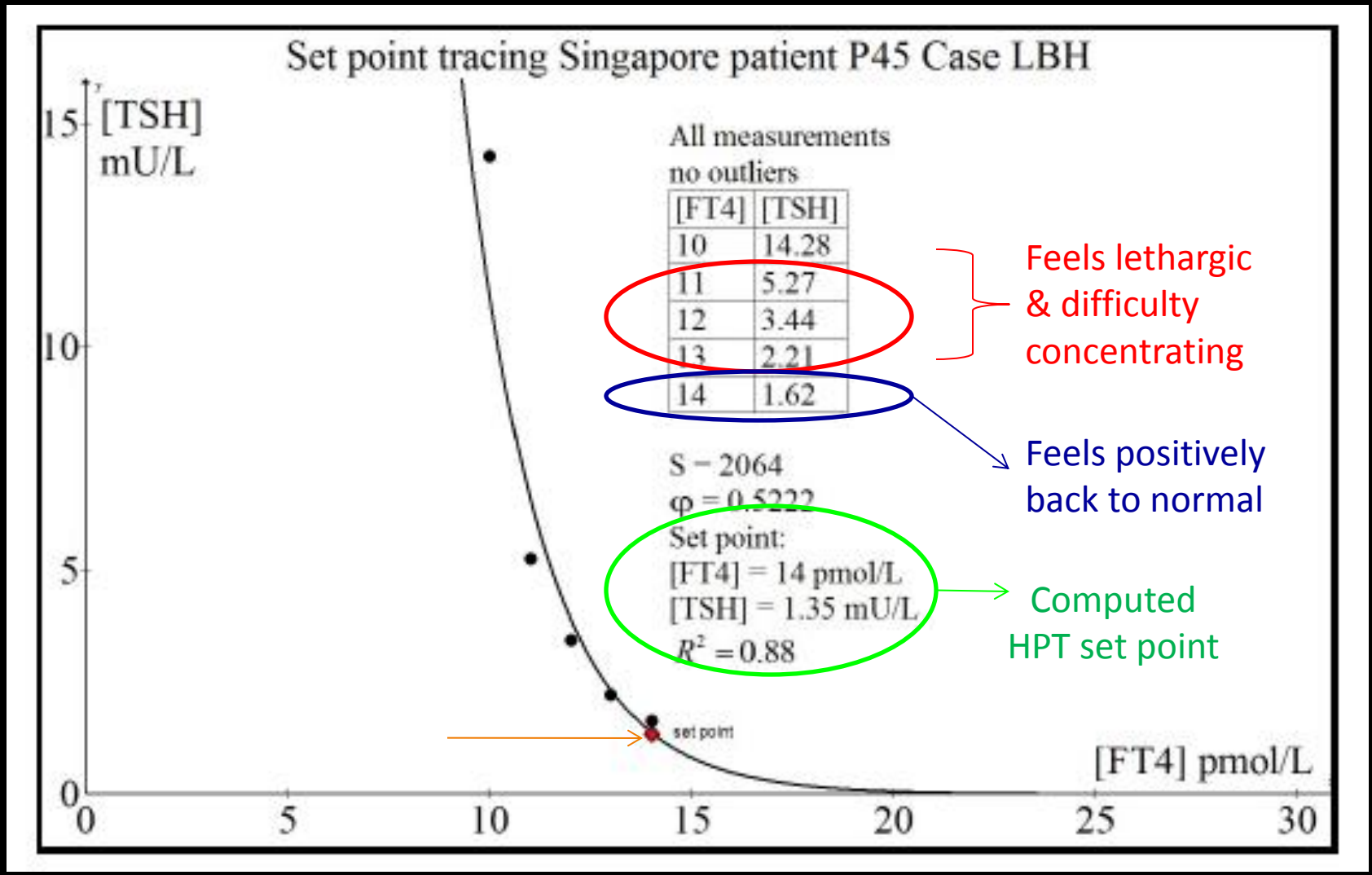
	FT4	TSH
▶	7	49.96
	18	0.07
	10	7.90
	14	0.83
	13	1.26
	15	0.34
*		

Setpoint

S	3403.1
Phi	0.60427
FT4	13.2 pmol/L
TSH	1.20 mU/L

Recalculate





Her original pre-op euthyroid TFT: FT4 = 13, TSH = 1.35

GL = 0.58 ln (φ S $\sqrt{2}$) = 4.3 (>1) $\Longrightarrow$ feedback loop optimal

Stabilized at FT4 13-15, TSH = 1.2-1.6; "felt back to normal"

EQUILEBRATE Clinical Trial

- A Prospective Randomized, Double-blind, Parallel Arm, Multi-centre Clinical Trial to **E**valuate the **Qu**ality of **L**ife and **E**uthyroid **B**alance using Conventional Thyroid Hormone Repl**a**cement versus Se**t** Point Strat**e**gy

Thank you for your kind attention!