How much will you become taller?

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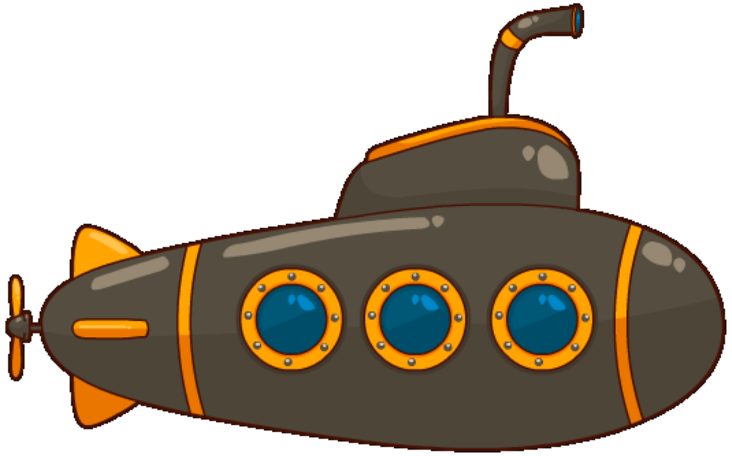
Why it is important?

If you are **very short** you cannot play basketball professionally…

If you are **very tall** you cannot work in a submarine…

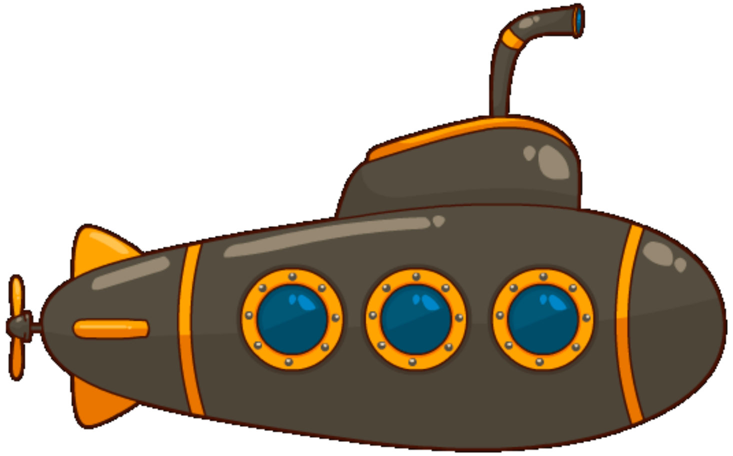


Why it is important?

If you are short y ... ot play
basketball ...

Not really!

If yo ... tall you cannot work
in ... arine…

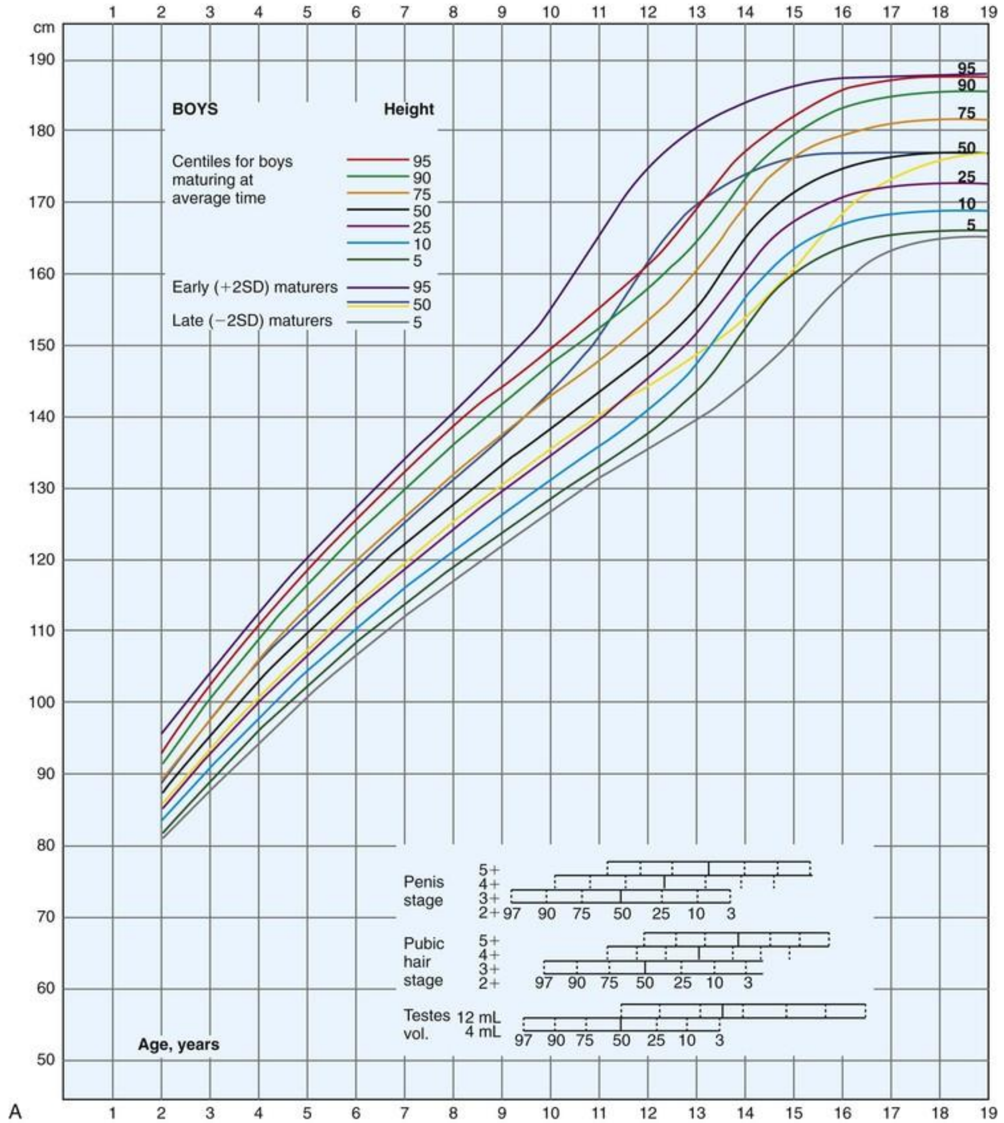


Growth Hormone Deficit (GHD)

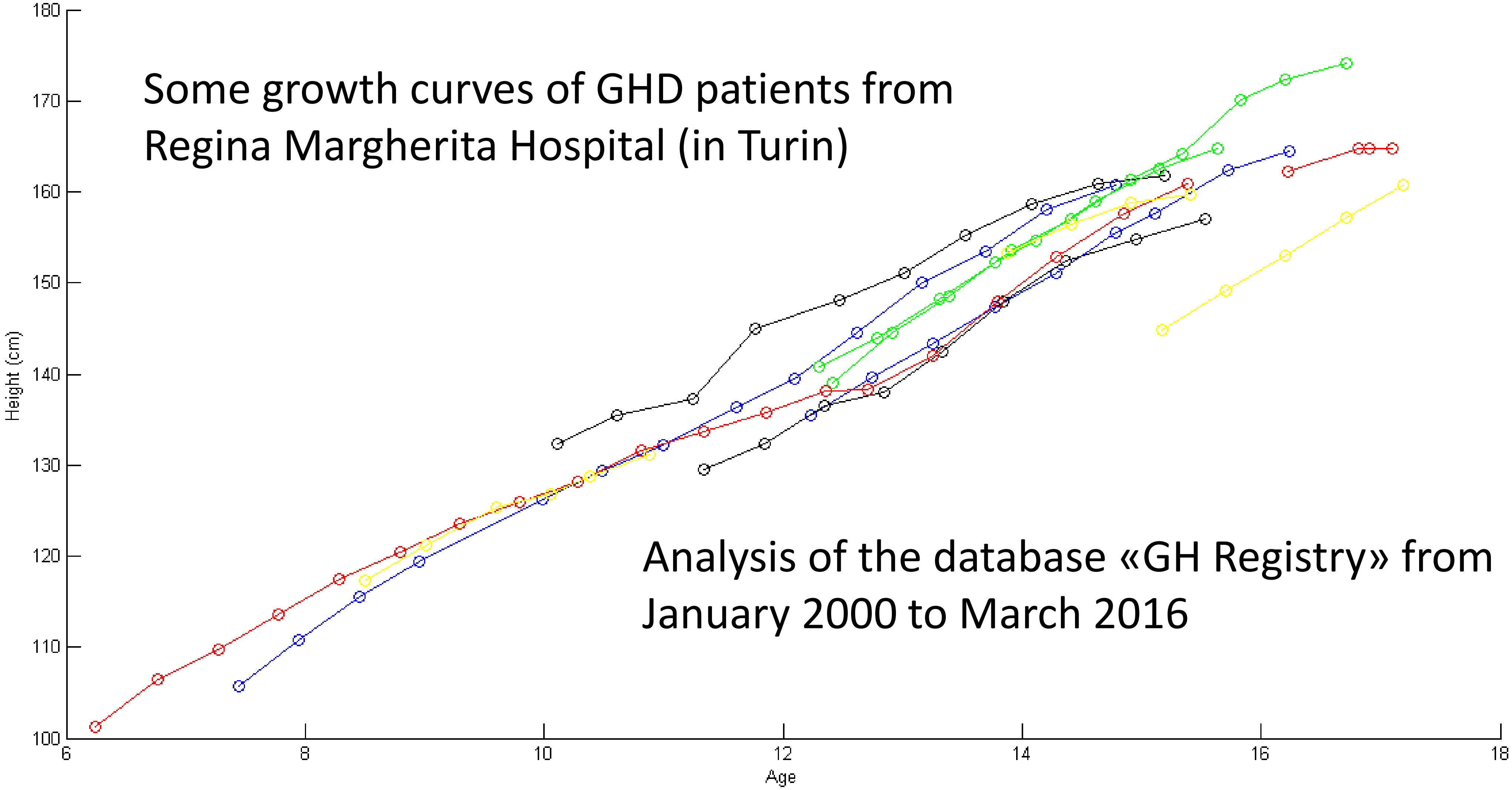
Children do not produce (or do not assimilate) the growth hormone.

They are **short**, but also: slowing of <u>bone production</u>, hypoglycemia, reduction of <u>muscle development</u>, alterations in lipid metabolism, higher risk of <u>cardiovascular disease</u> in adulthood

1986: creation of a synthetic hormone to treat GHD children → extention of the treatment (rhGH)



Real data example

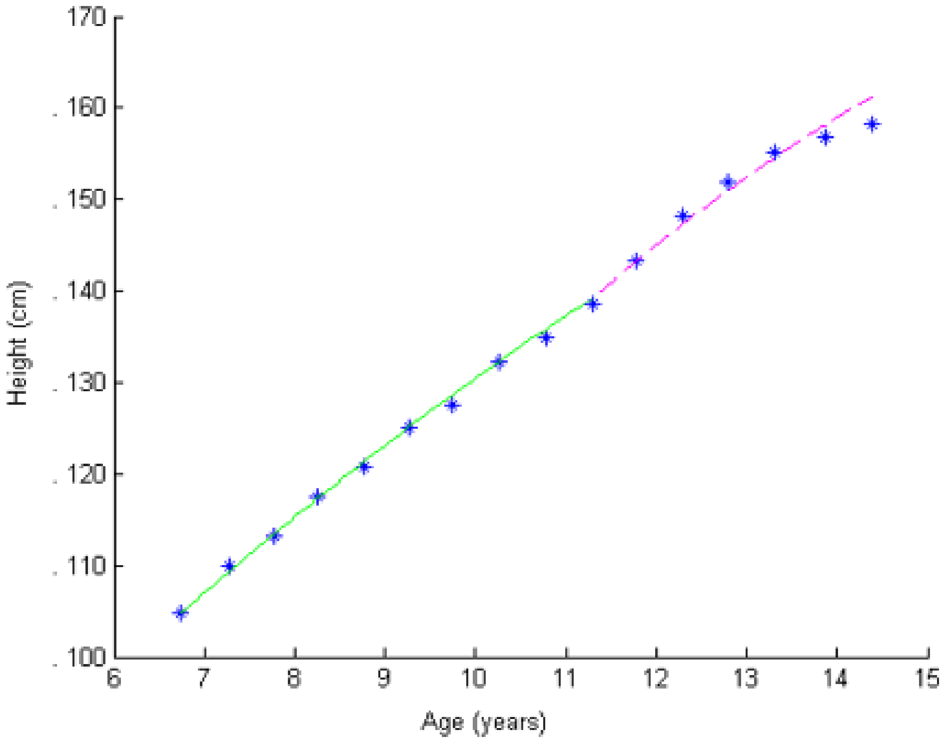


Some growth curves of GHD patients from Regina Margherita Hospital (in Turin)

Analysis of the database «GH Registry» from January 2000 to March 2016

Study questions

- Can I predict the **final height** of the patient?
- Can I predict his/her **growth curve**?
- Can I see the treatment effect **during it**?



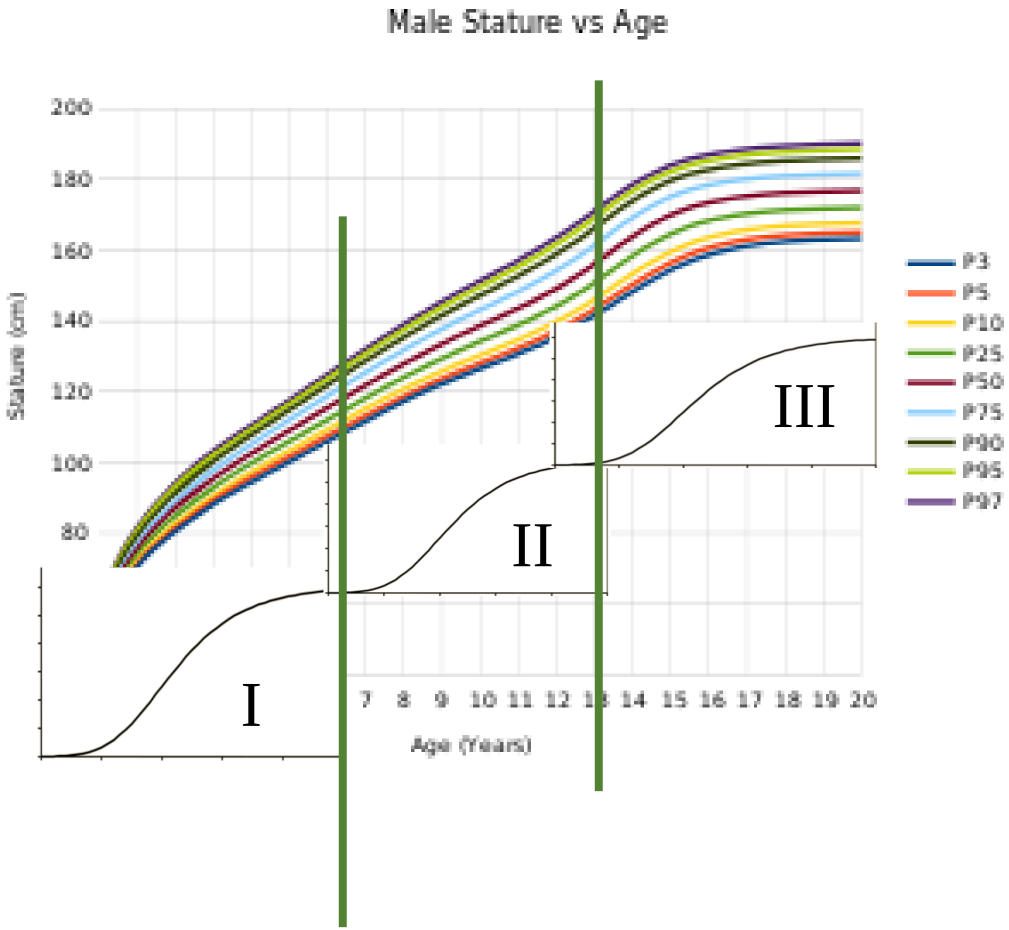
The model

In order to model human growth, we use 3 gompertzian curves*

Carrying capacity

Growth velocity

$$H(t) = H_\infty exp\left\{-log\left(\frac{H_\infty}{H_0}\right) exp[r_i(t - t_0)]\right\}$$



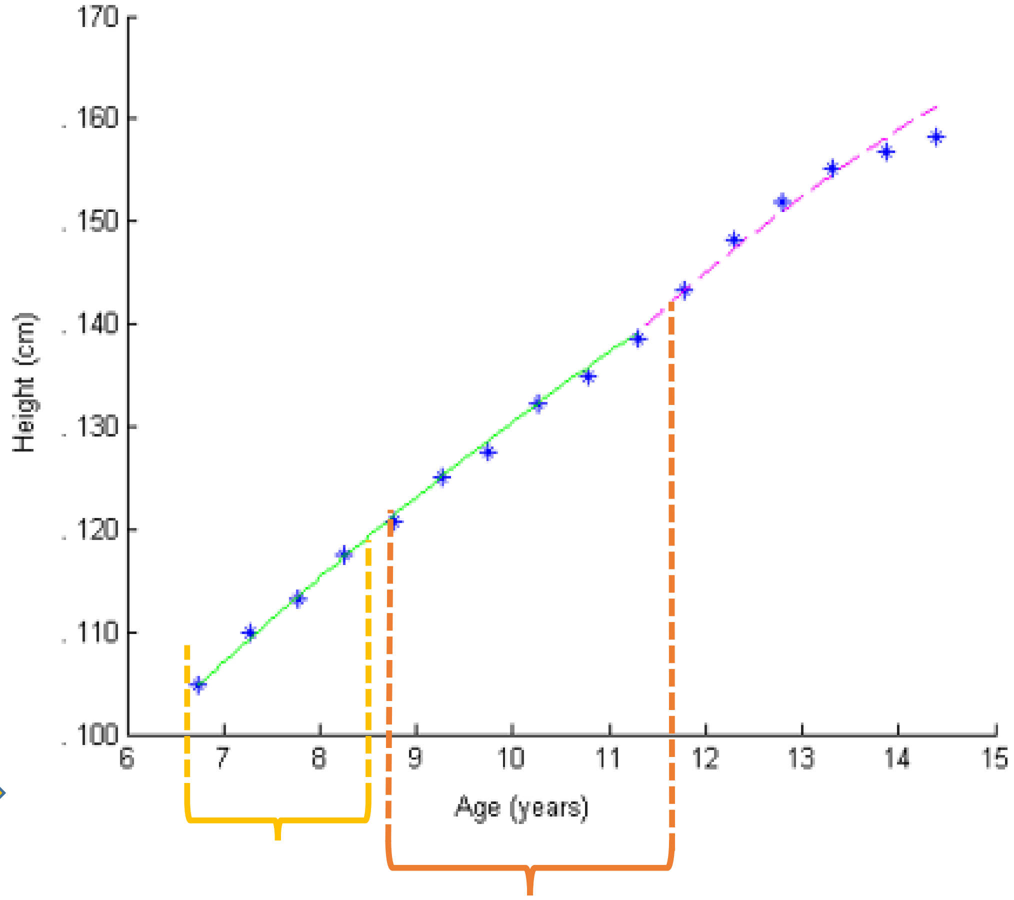
We need to estimate the parameters in each growth period.

*Gliozzi A. S., Guiot C., Delsanto P.P. and D. A. Iordache, A novel approach to the analysis of human growth, Theor. Biol. Med. Model., May 2012; **9**:17

The importance of predicting

- Make predictions as soon as possible
- Few data
- Accuracy

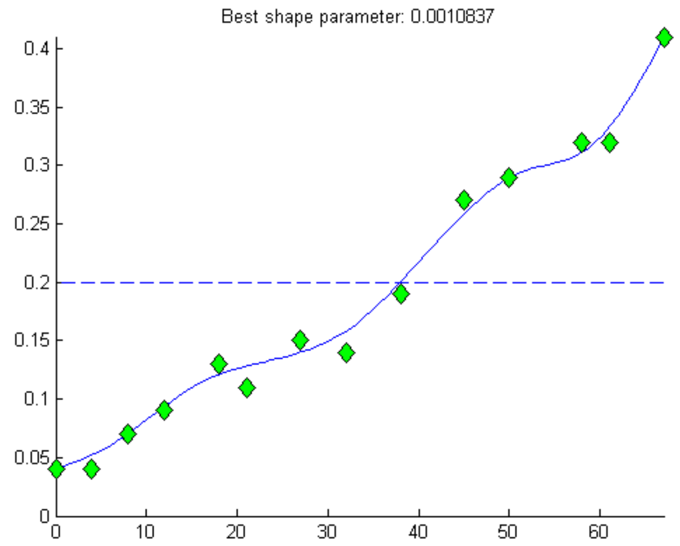
RBF-SOM method



RBF – SOM

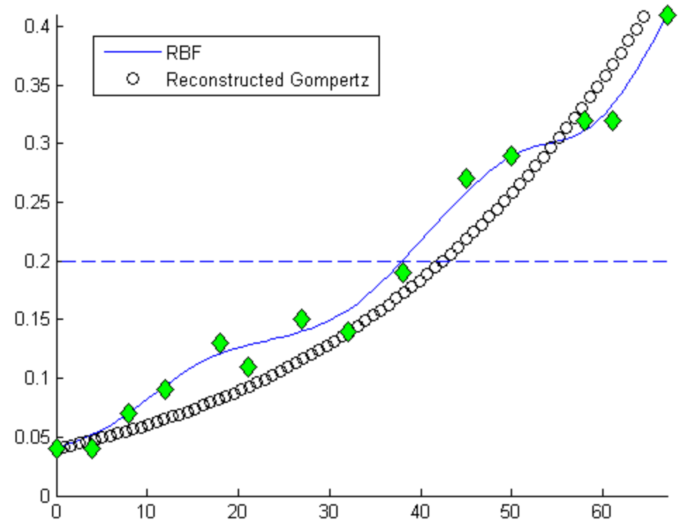
- Radial Basis Functions (RBFs) to have more data

  Robust: OK also in case of non-monotonic and irregularly spaced data!

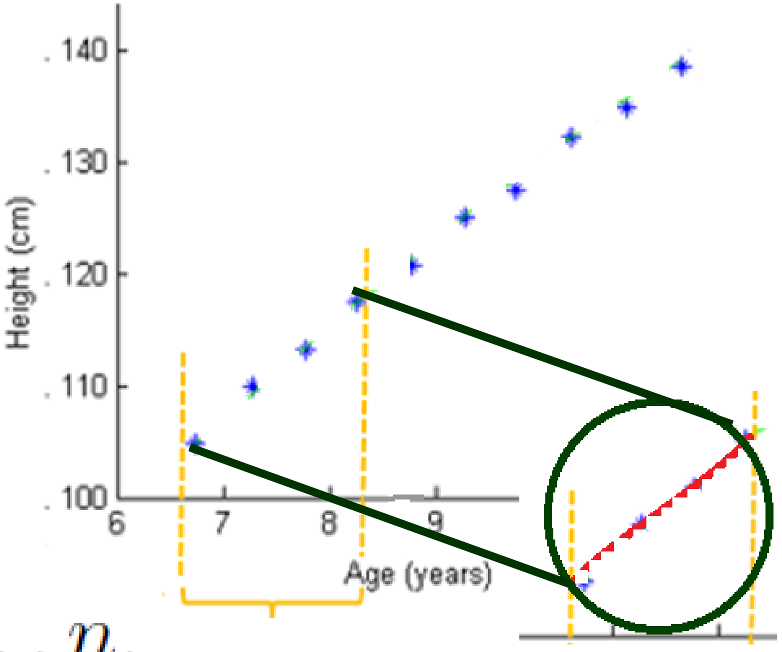


- Stochastic Optimization Methods (SOM) as Particle Swarm Optimization (PSO) or Cuckoo Search (CS) to estimate the parameters

  (Gompertzian) curve reconstruction



RBF



We want to enrich our sample, having s>n data points

$$\mathcal{N}_n = \{N_i, i = 1, \ldots, n\}$$

So, we want to find a function I such that:

$$\mathcal{I} : [t_1, t_N] \longrightarrow \mathbb{R} \qquad \mathcal{I}(t_i) = N_i, \quad i = 1, \ldots, n.$$

We use as RBF the sum of a globally definite function ϕ of the Euclidean distance d:

Globally supported strictly positive definite function (Matérn)

$$\mathcal{I}(t) = \sum_{k=1}^{n} c_k \phi(d(t, t_k)), \quad t \in \Omega = [t_1, t_N] \quad \phi(r) = e^{-\varepsilon r}(1 + \varepsilon r)$$

Where the coefficient c_k are calculated by imposing the interpolation conditions $\Phi c = N$

Parameters estimation

- Now we need to estimate the carrying capacity and the growth velocity:

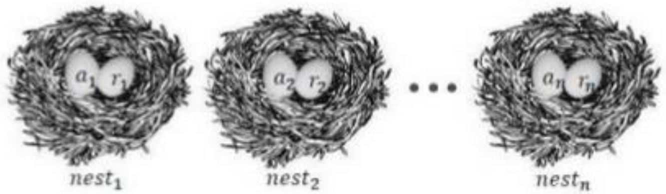
Carrying capacity

Growth velocity

$$H(t) = H_\infty exp\left\{-log\left(\frac{H_\infty}{H_0}\right) exp[r_i(t - t_0)]\right\}$$

- 2 stochastic methods: Cuckoo Search (CS) and Particle Swarm Optimization (PSO)

Cuckoo Search



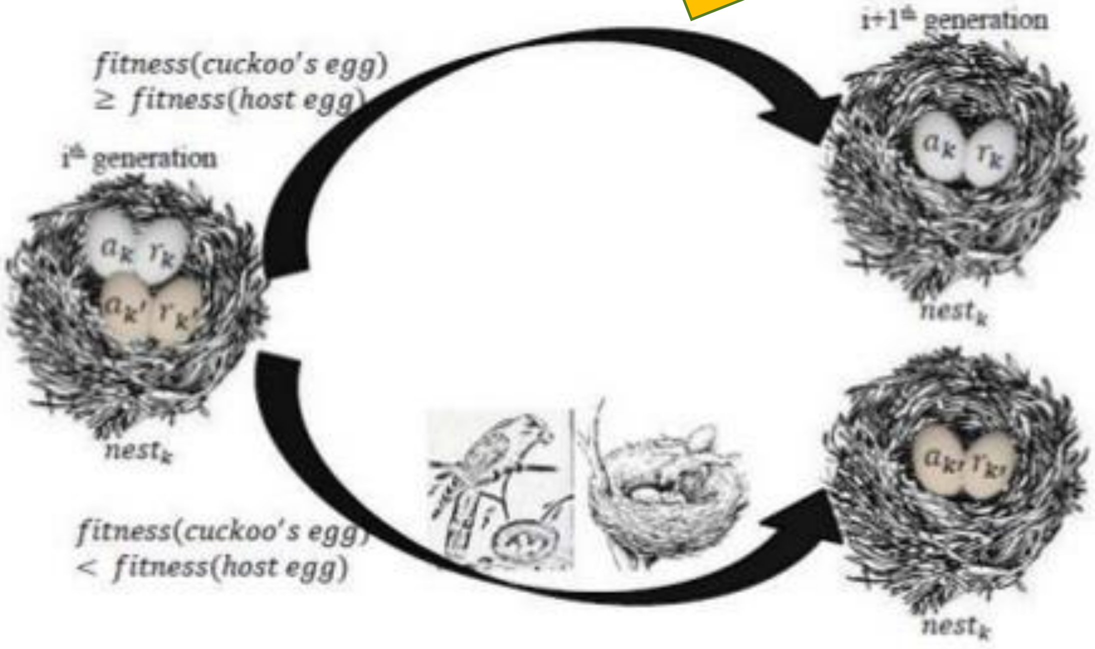
Range of possible solutions

Global minimum

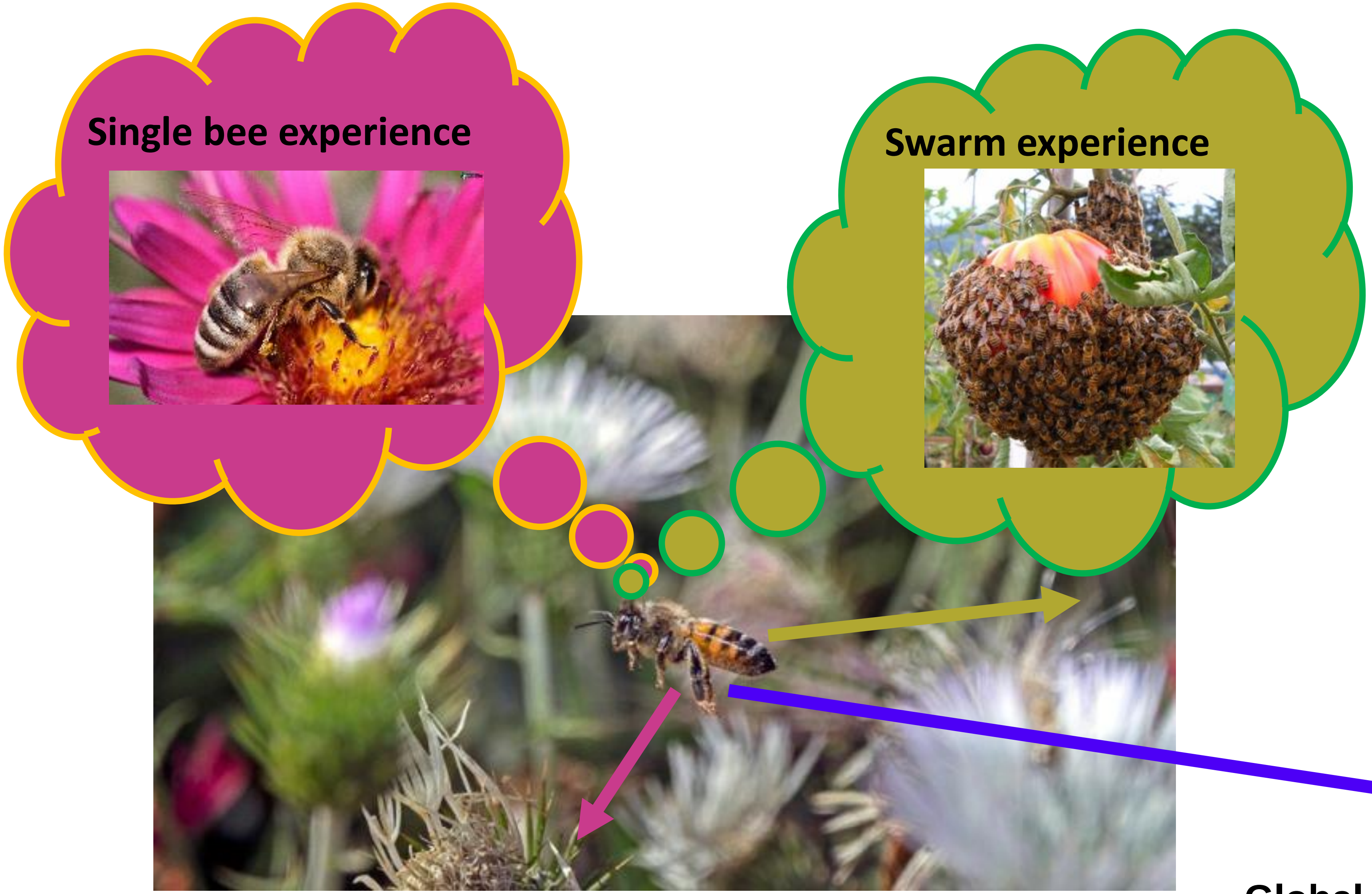
Test of some solutions

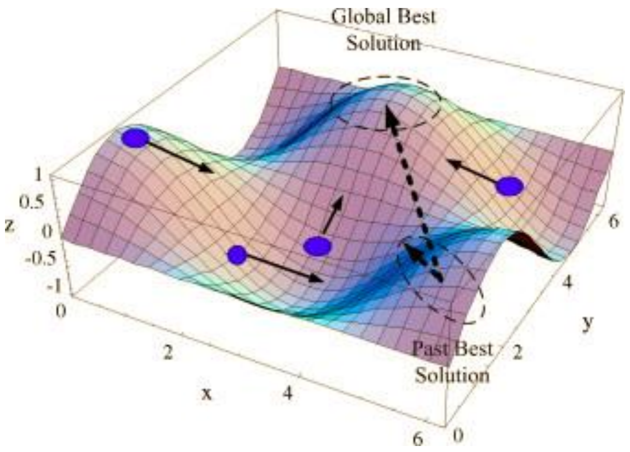
Yang X., S. Deb. Cuckoo search via lévy flights. In 2009 World Congress on Nature and Biologically Inspired Computing, NABIC 2009 - Proceedings

The minimum survives the next iteration



Particle Swarm Optimization





Kennedy, J., and RC. Eberhart. 1995. “Particle Swarm Optimization.” *Proc. of 1995 IEEE Int. Conf. Neural Networks* 1: 1942–48

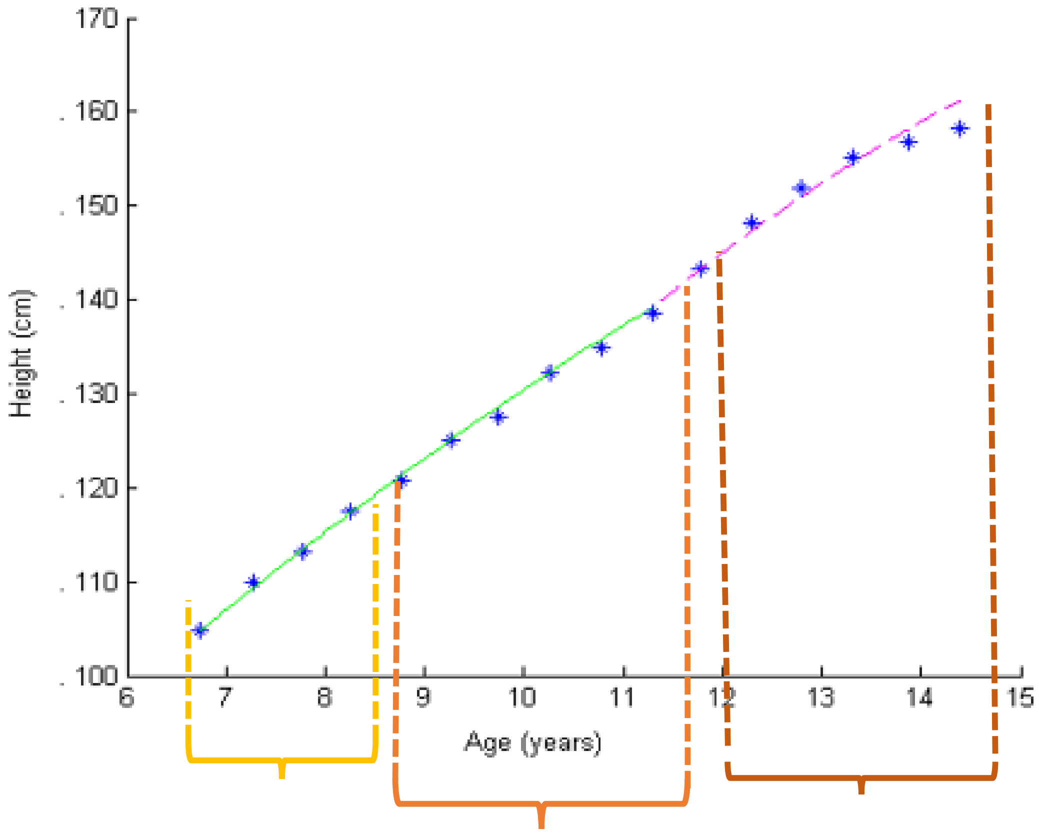
Global minimum

Prevision of final height

Growth velocity in the first period is correlated with the growth velocity in the second and third period!

Knowing r_1, we can estimate r_2 and r_3 without other calculations

After 2 years of follow up, we can estimate the final height (at 18-20 years!)



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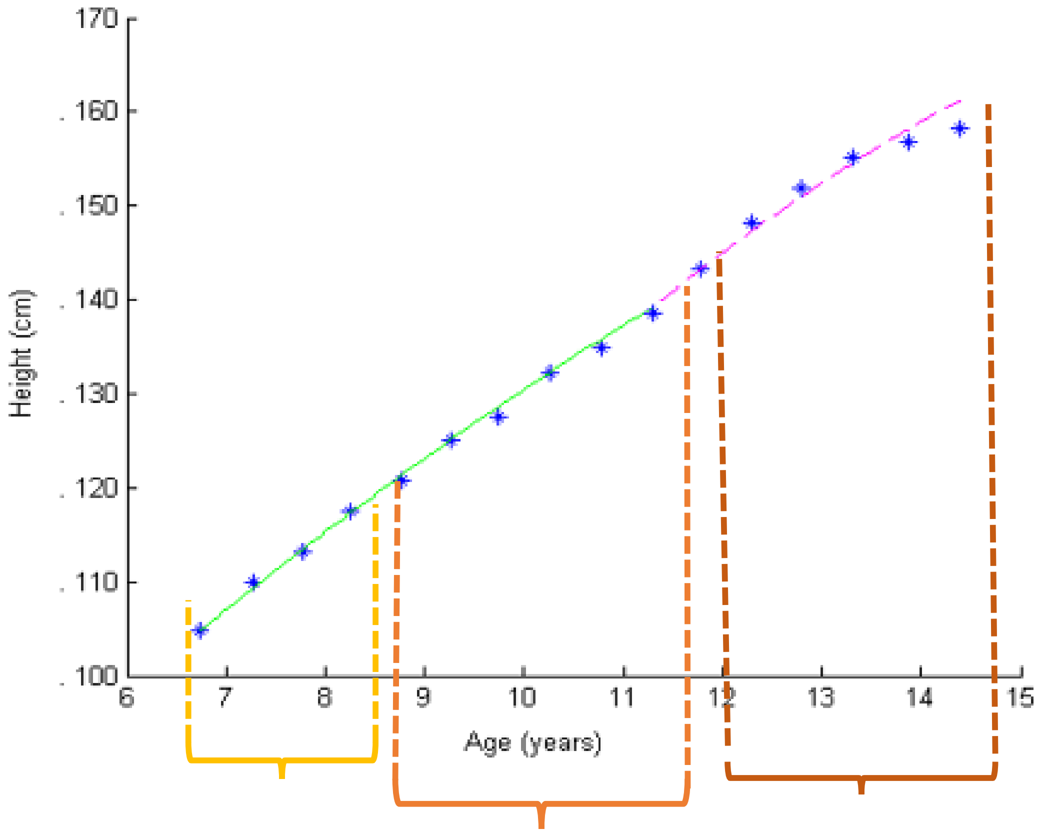


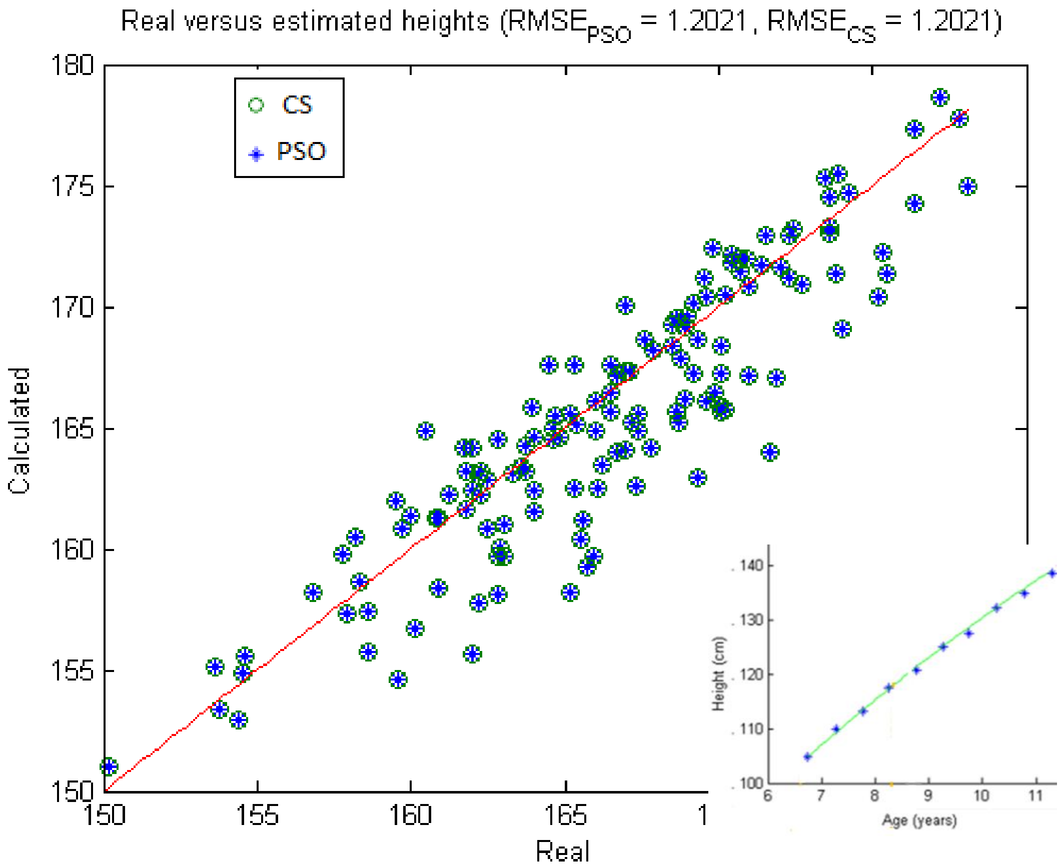
Many errors should be considered: error in reconstruct the RBF, error in estimating the parameters, error in estimating the parameters in the next period

Comparison PSO/CS: 1 parameter

$$\mathrm{RMSE} = \sqrt{\sum \frac{(y_{pred} - y_{ref})^2}{N}}$$

PSO and CS have similar performance estimating 1 parameter (n°patients: 134)

No prevision



True – estimated final height of each period < 2 cm in 80% of cases

Comparison PSO/CS: 1 parameter

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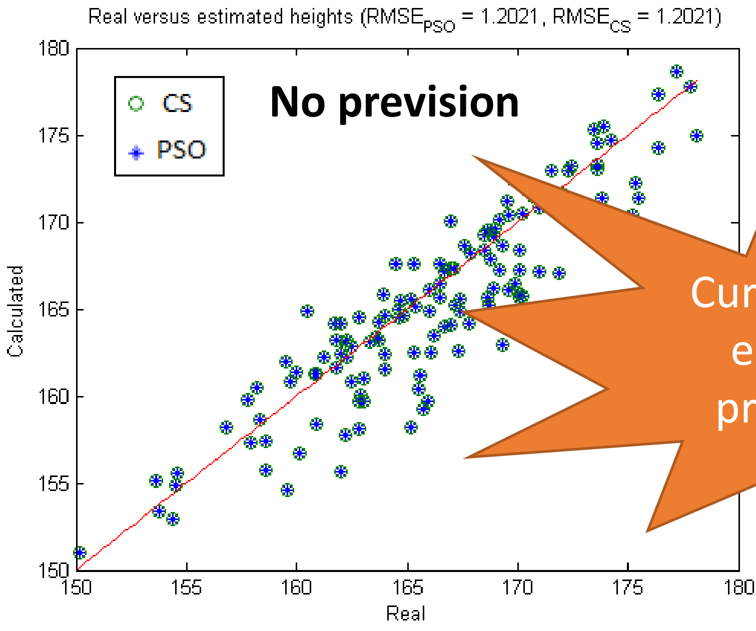
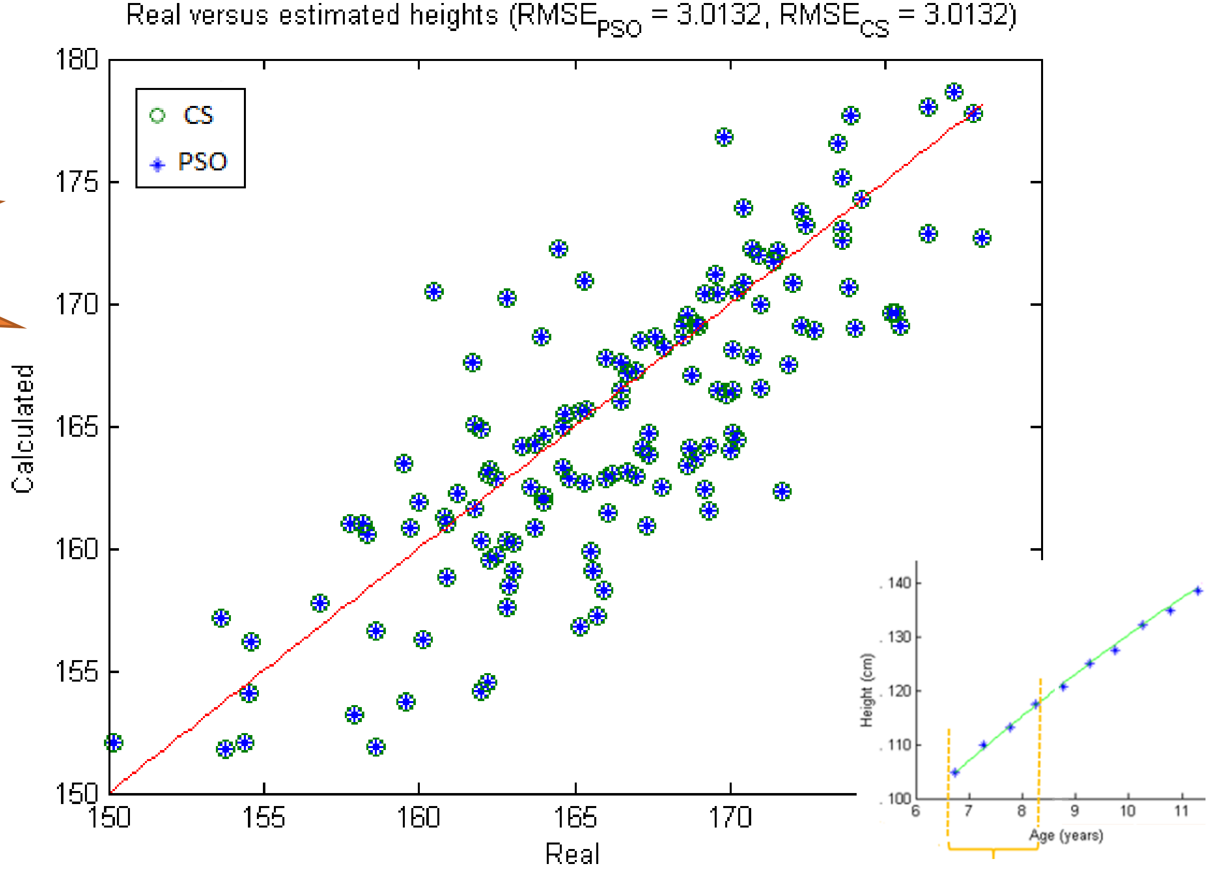


Current acceptable error in clinical practice: 8 cm!!!

True – predicted final height < 5 cm for the 80% of cases

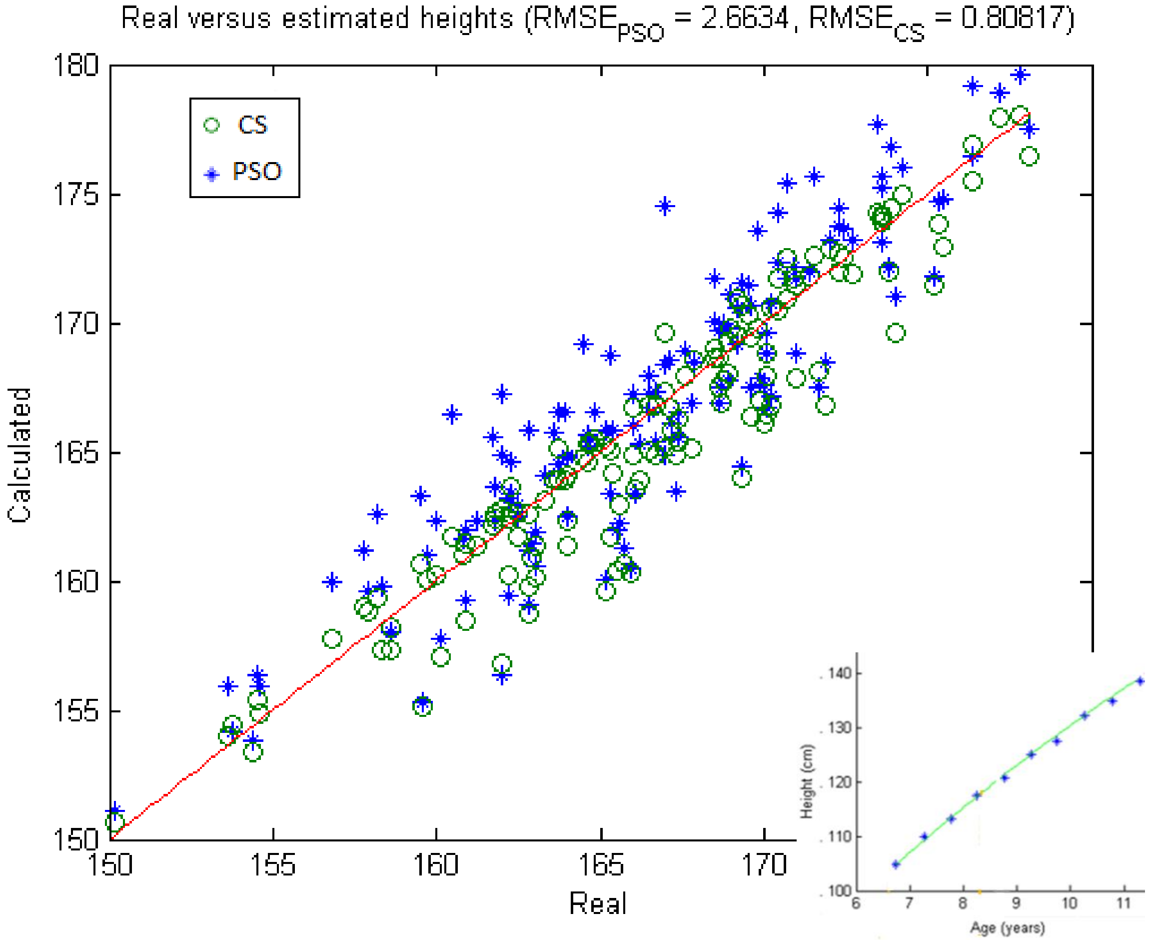
Prevision (by the first 4 data)



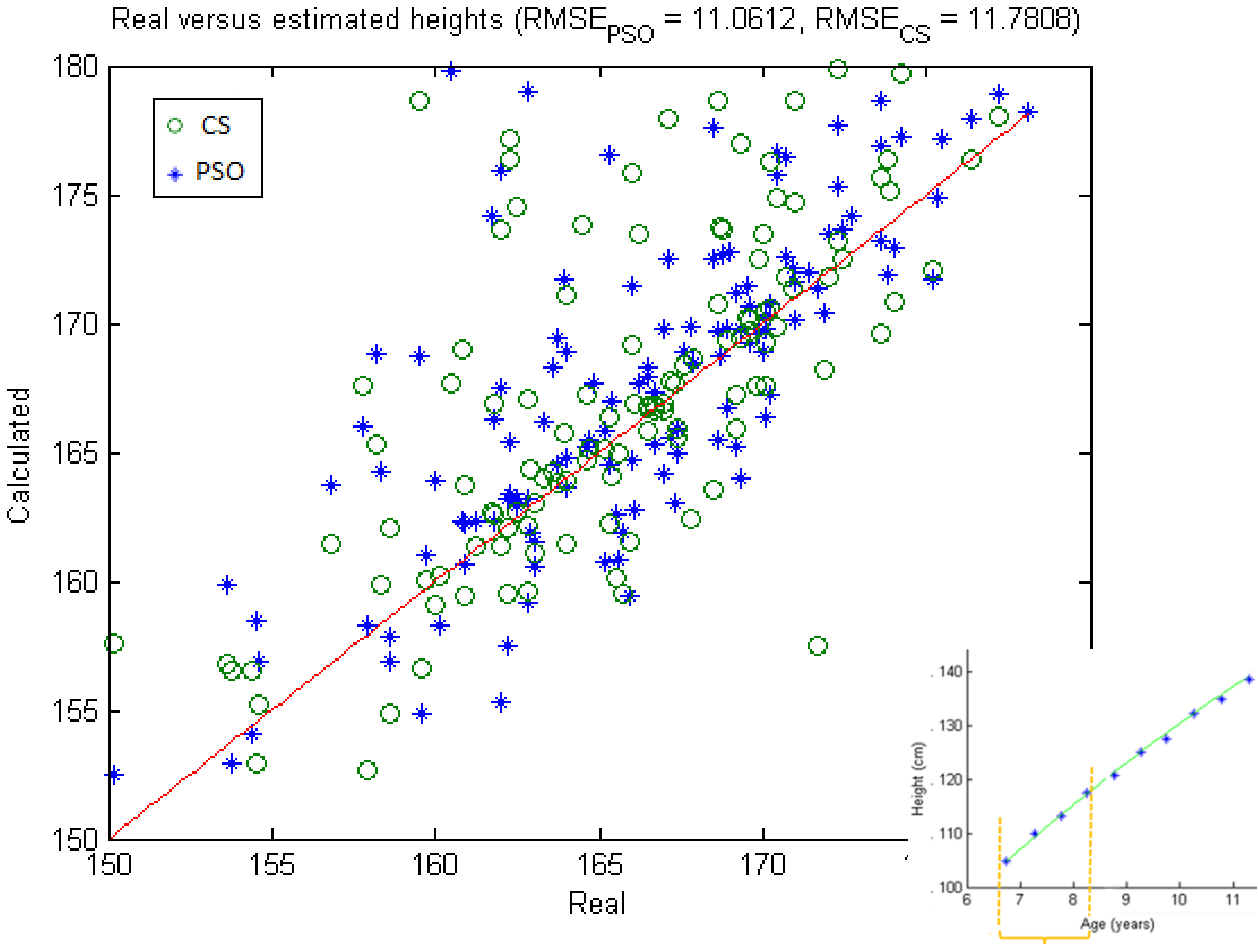
Comparison PSO/CS: 2 parameters

CS is better without previsions, PSO is better with prevision.

No prevision

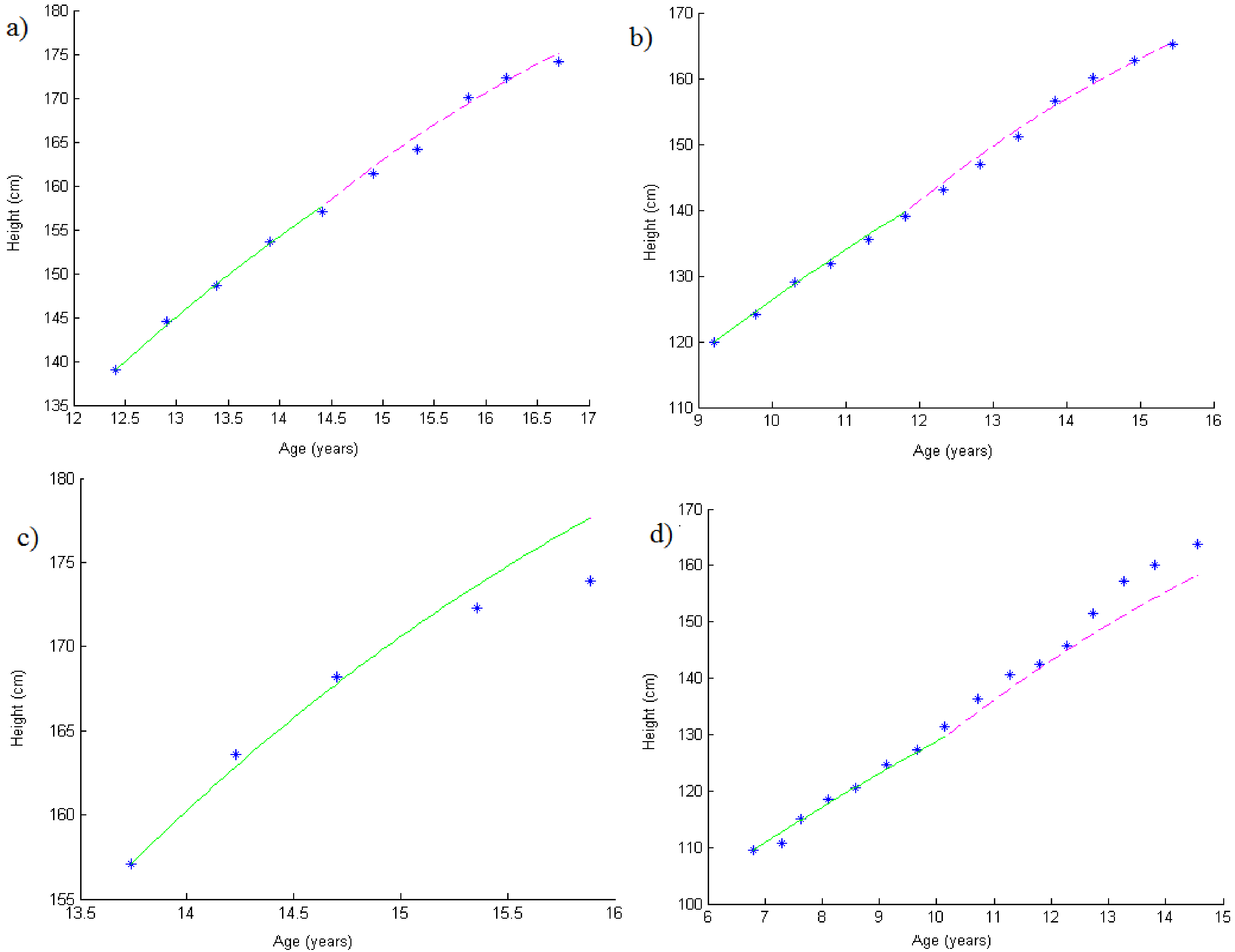


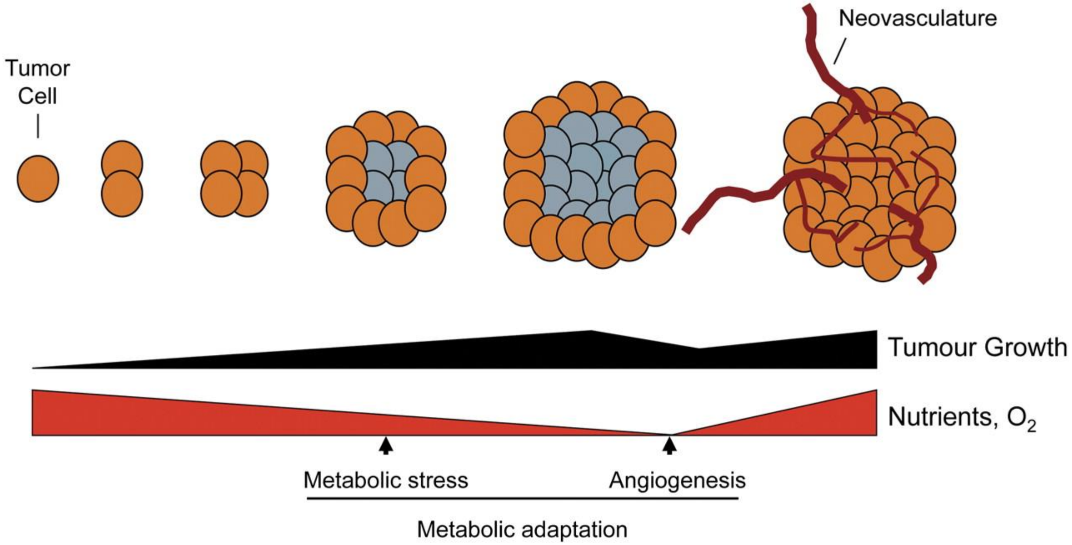
Prevision

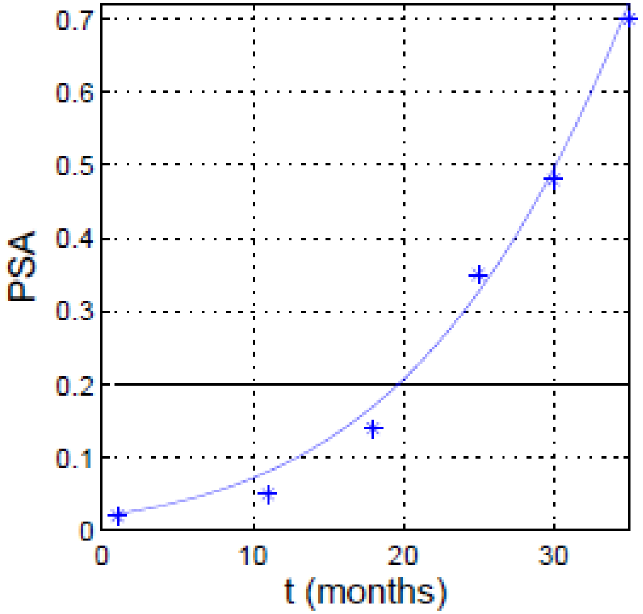


How to use it

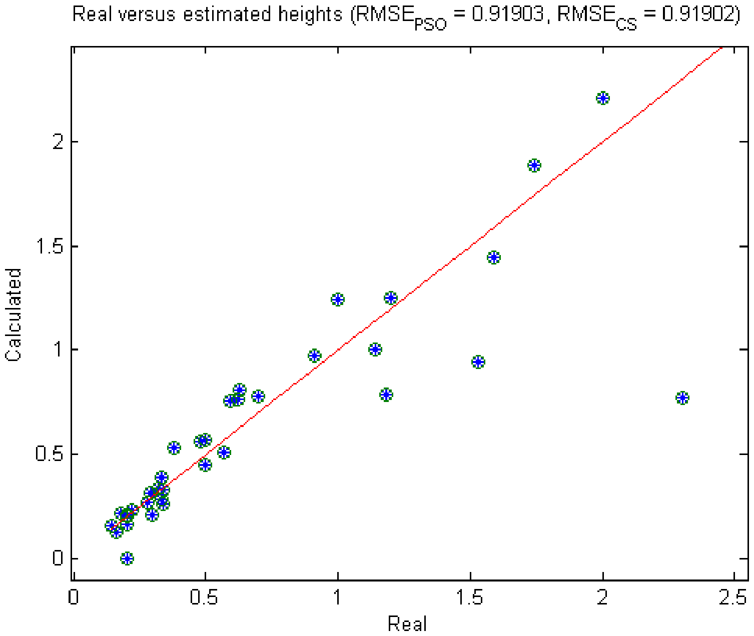
- Control growth regularity
- Comparison with the cohort
- Theoretical growth curve and final height

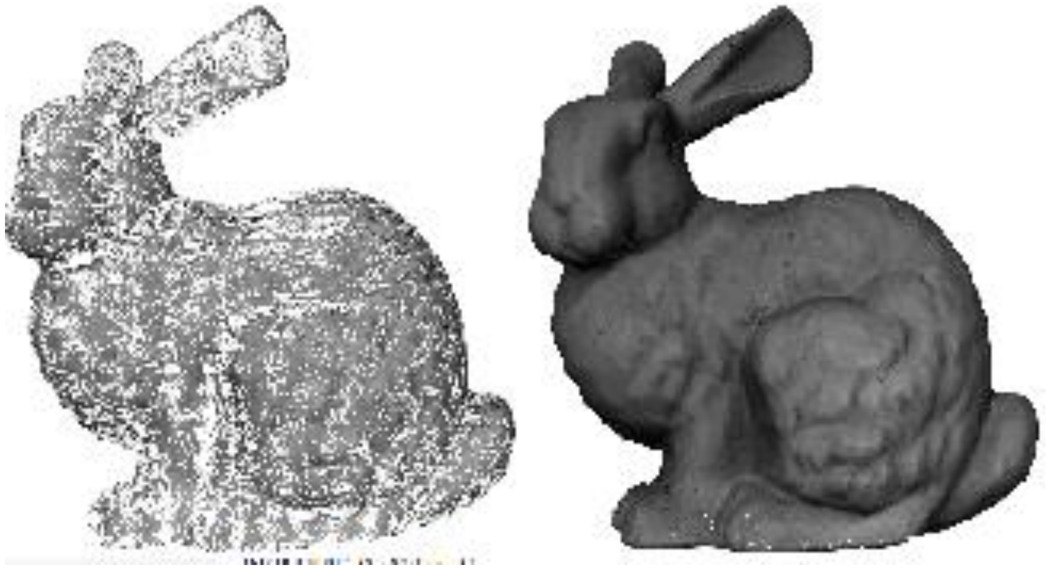






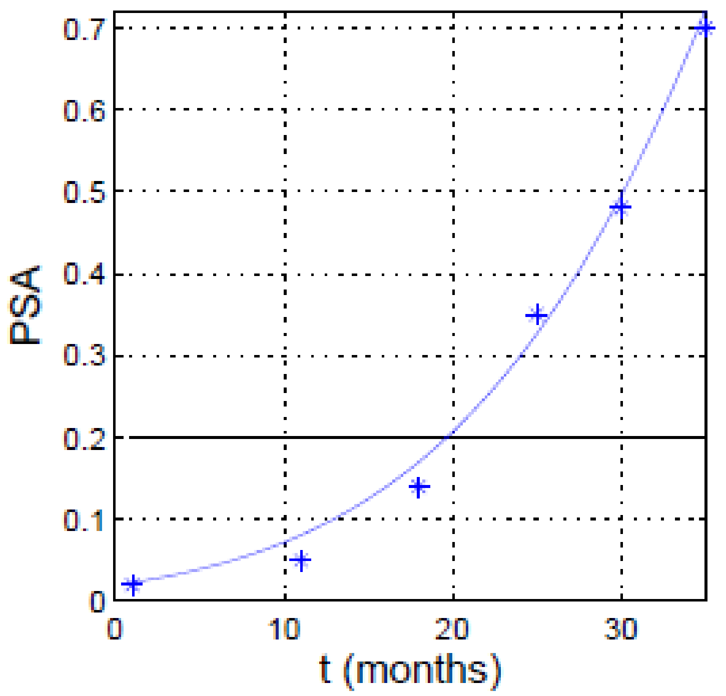
A more general view…

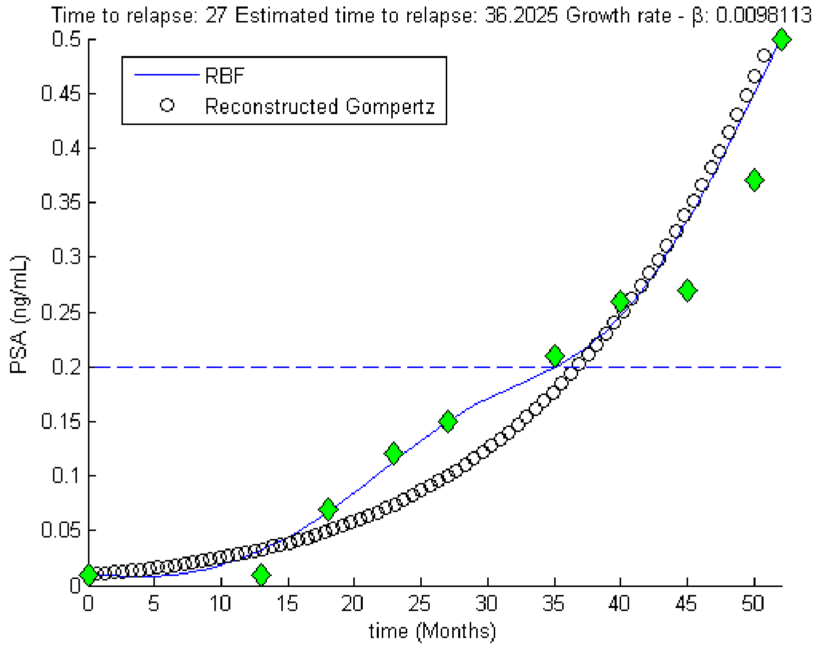




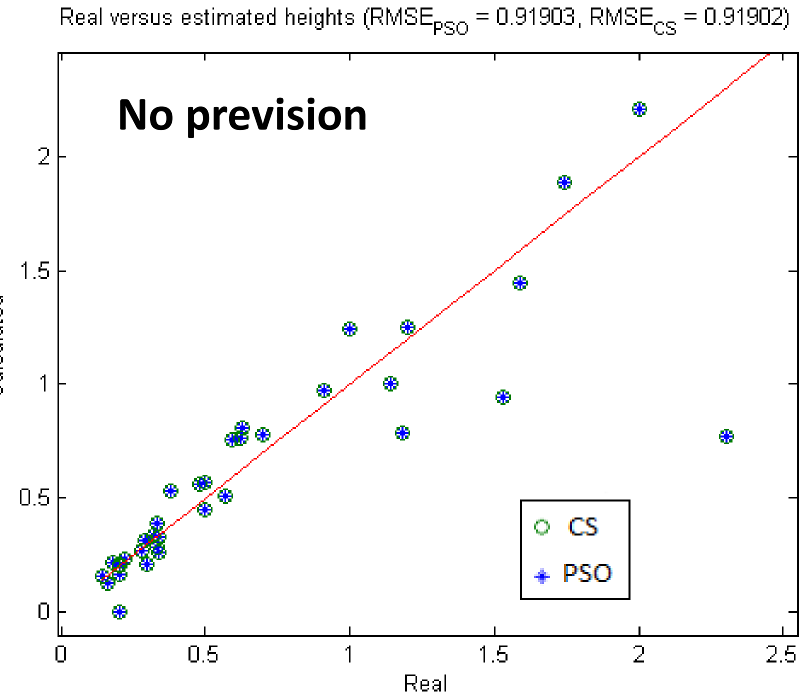
Other (clinical) application

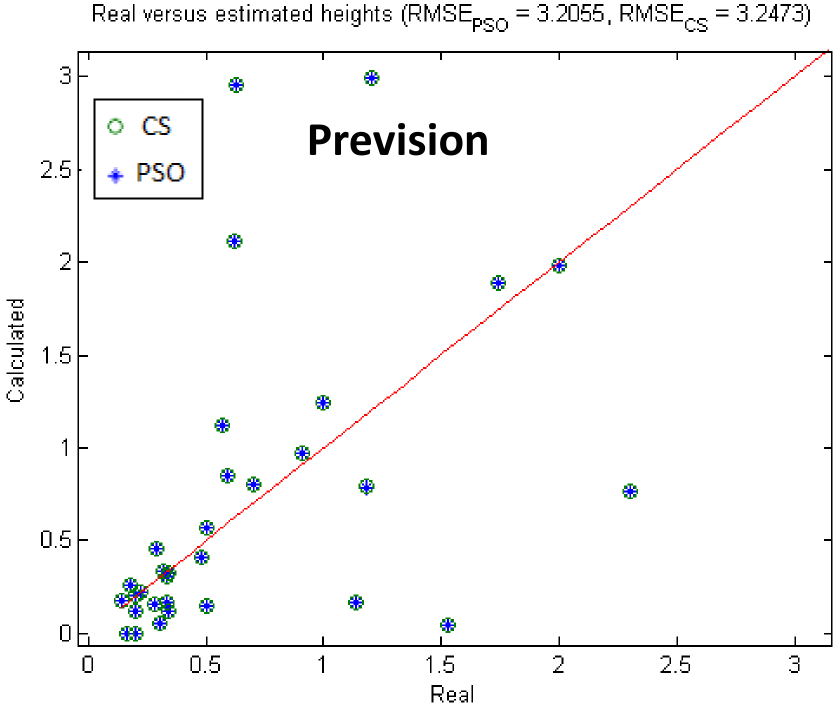
- Prostate cancer grows with a gompertzian law
- After prostatectomy, patients are monitored using a blood biomarker, the Prostate Specific Antigen (PSA)
- PSA values can be used as height measurements in order to estimate the **recurrence velocity** and a possible **time to relapse**



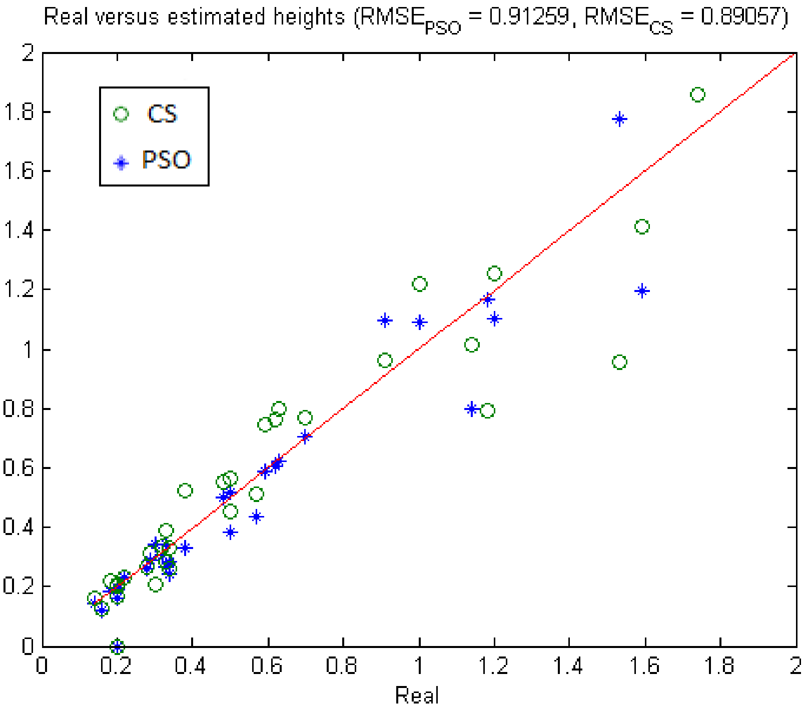


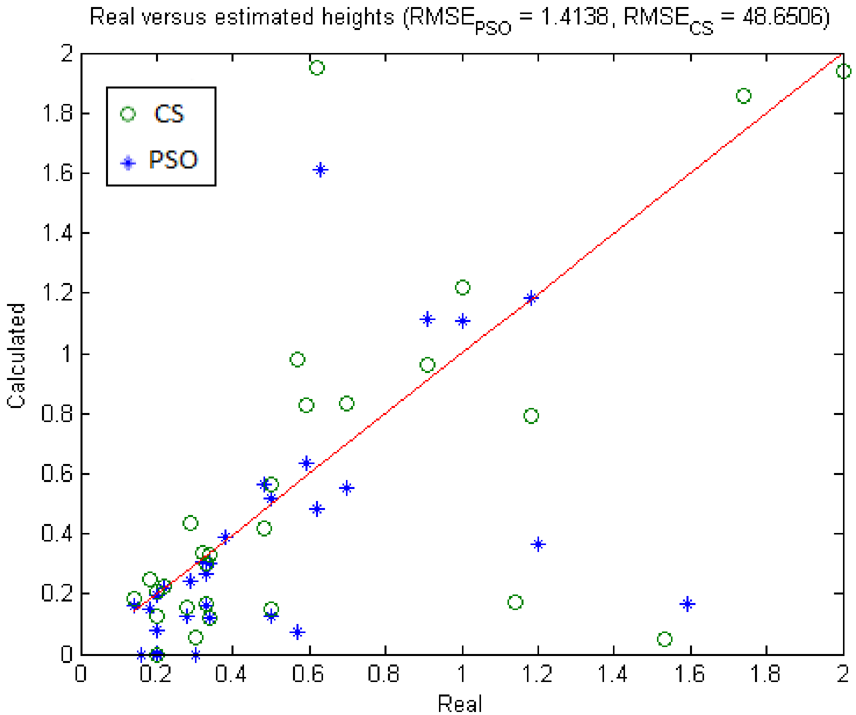
PSA dataset





1 parameter





2 parameters

Conclusions

- RBF-SOM is a general method to estimate growth behaviors
- It requires a growth function
- It is robust in case of few, non-monotonic, irregularly spaced data
- It can be used in clinical practice

Thanks for your attention!

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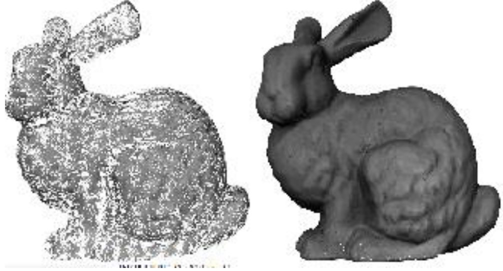
Radial Basis Functions



- Images reconstruction
- $y_j' = R(x_j)$, $j=1,\dots,n$
- **n** as large as you want
- Equispaced data (in output)

RBF

Nodes

Dati di input

$f_i = f(x_i, y_i)$

$$R(\bar{x}) = \sum_{i=1}^{N} c_i \phi(||(\bar{x} - \bar{x}_i)||_2), \qquad x \in \Omega$$

Interpolant

$\{c_i\}_{i=1}^{N}$

Coefficients are estimated imposing:

$R(\bar{x}_i) = f_i,\ i = 1, \dots, N$

E. Perracchione, I. Stura, RBF kernel method and its applications to clinical data, *Dolomites Res. Notes Approx.*, 9:13-18, 2016

Stochastic Optimization Methods

- We search the minimum of:

$$\sum_{i=1}^{n}\Big(\overbrace{y_i}^{\textbf{Dataset}}-\underbrace{H_\infty \exp\left(-\log\left(\frac{H_\infty}{H_0}\right)\exp\big(r(x-x_0)\big)\right)}_{\textbf{Theoretical function}}\Big)^2$$

which is the value of the parameter(s)

- **Cuckoo Search**
- **Particle Swarm Optimization**