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Modeling Anticancer Related Late Effect on Neurocognition (MARLEN study)

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Background:

Paediatric medulloblastoma long-term survivors (MB) present significant impairments in specific cognitive functions. Our major objective was to create retrospectively a mathematical model evaluating **the contribution of key clinical factors** as hydrocephalus (HC), sex, age at diagnosis, socioeconomic status (SES) and cranial irradiation **to impaired neurocognitive performances and their dynamic interactions**.

Methods :

A cohort was created using **a database of children** treated for a brain tumors and subjected to a longitudinal neurocognitive evaluation **from Institute Gustave Roussy (IGR)**. We used pivot tables to select significant factors to be incorporated in complex and dynamic models. We evaluated **neurocognitive patient' dynamic trajectories in terms of Full-Scale Intellectual Quotient (FSIQ)** scores using a discrete-time Markov chains analysis. A simulator integrating a Bayesian approach was created to describe the dynamic interactions between significant co-variates and to create avatars.

Database Risk-N of IGR

Time of evaluation	T0	T1 2-3 years	T2 4-5 years	T3 6-7 years
Nb of children	66	66	47	27

Results :

We selected Medulloblastoma patients treated with radiation therapy (children ≥ 3 years). 46 patients were included with a median age of 6 years. Neurocognition outcome has been evaluated at 4 time points with FSIQ score. Analysis by pivot tables revealed a difference in mean loss of FSIQ **with a loss of 0.7%/year** for children **without hydrocephalus against 3.3%/year** for children **with hydrocephalus**.

Impact of HC and age in terms of %QI loss per year

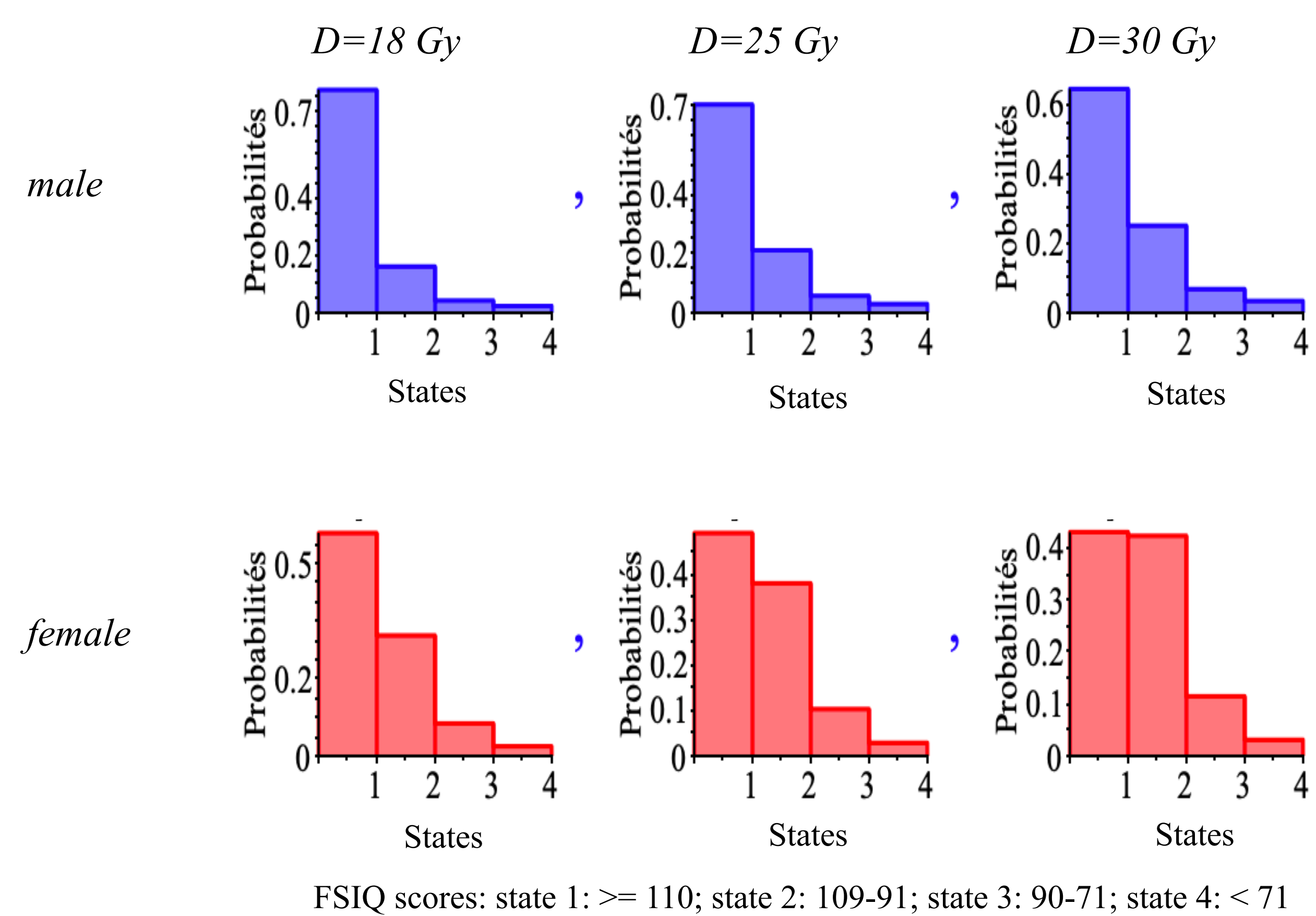
Groups	Without HC		With HC	
Age	3-7 y	8-12 y	3-7 y	8-12 y
mean	-0.8%	-0.7%	-3.4%	-3.0%
nb	6	13	19	8
Ecart-type	3.8%	4.4%	5.3%	9%

Hydrocephalus plays a major role in neurocognitive outcome

The **transition probabilities** estimated for each child by the **Markov chains analysis**. An average weighting factor was calculated for each clinical data: hydrocephalus, age, sex, total radiation dose of sustentorial site, socioeconomic status, **using a Bayesian population approach**.

A **simulator** was generated to estimate the probabilities of being from the best FSIQ (state 1) to the worse FSIQ (state 4) at the end of the assessment and to create **avatars**.

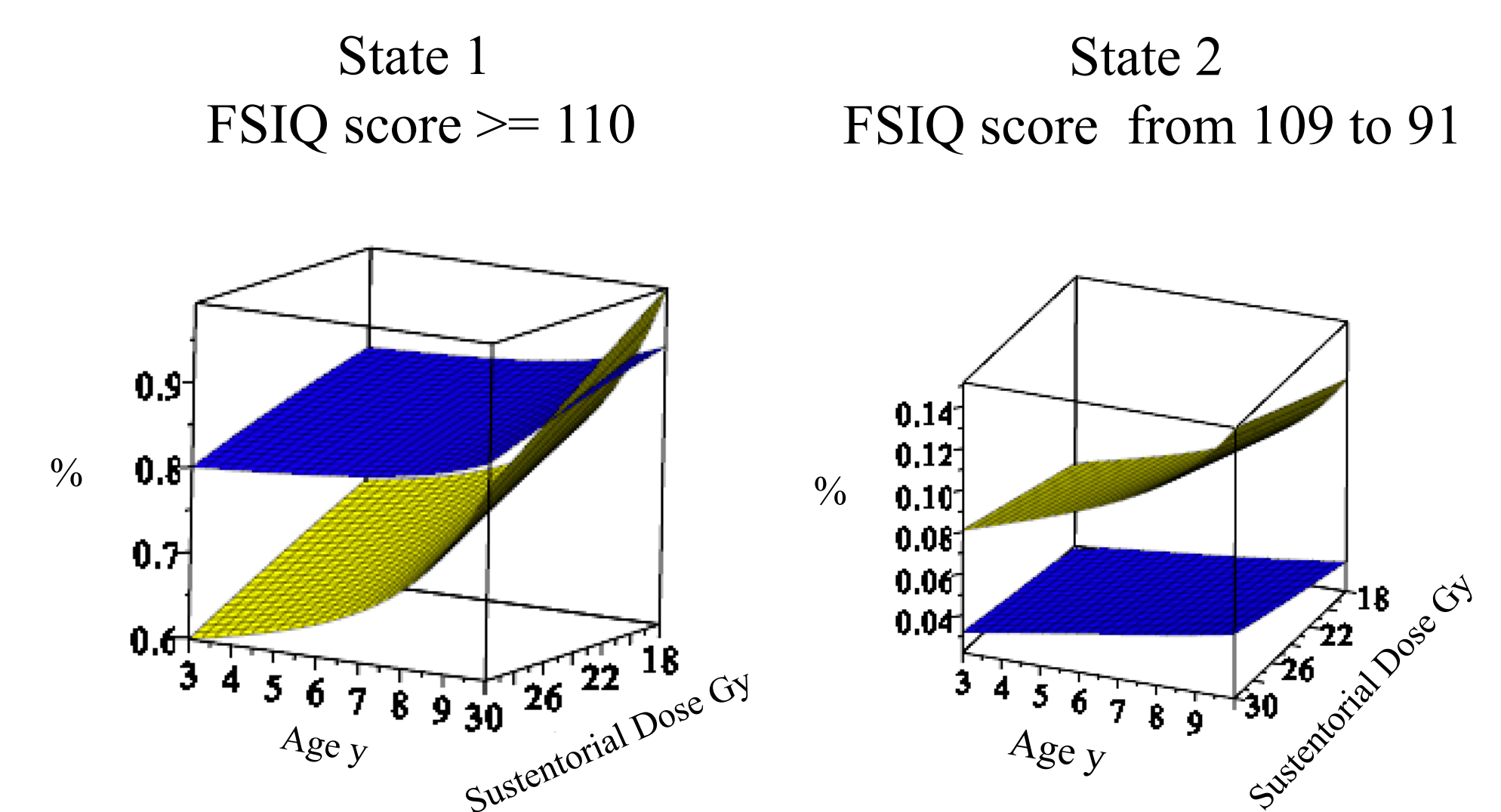
An exemple of avatar : MB 8 years old without hydrocephalus :
neurocognitive outcome according to sex and radiation sustentorial dose



3D Visualisation of Impact of HC, sex and SES according to age and RT sustentorial dose (% of patients in states 1 and 2)

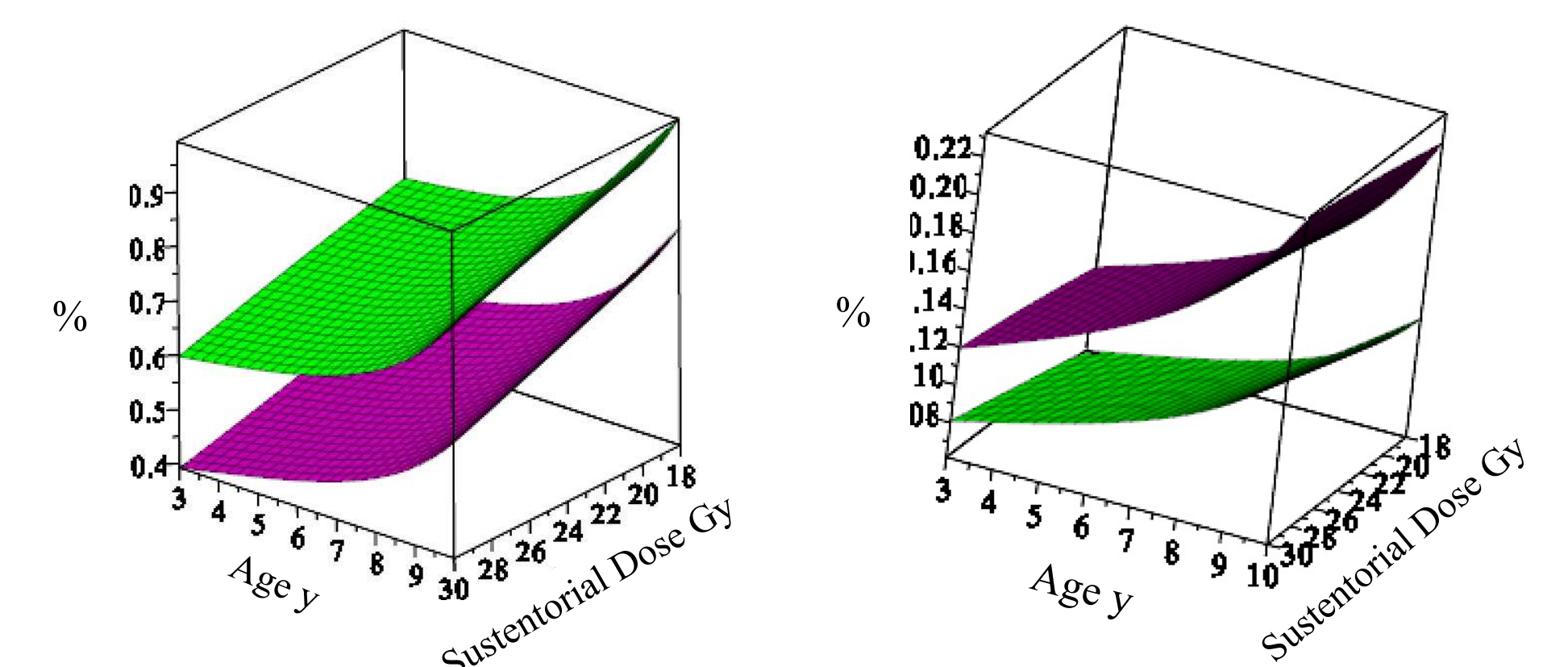
Impact of Hydrocephalus in male:

without HC (blue) vs
with HC (yellow)



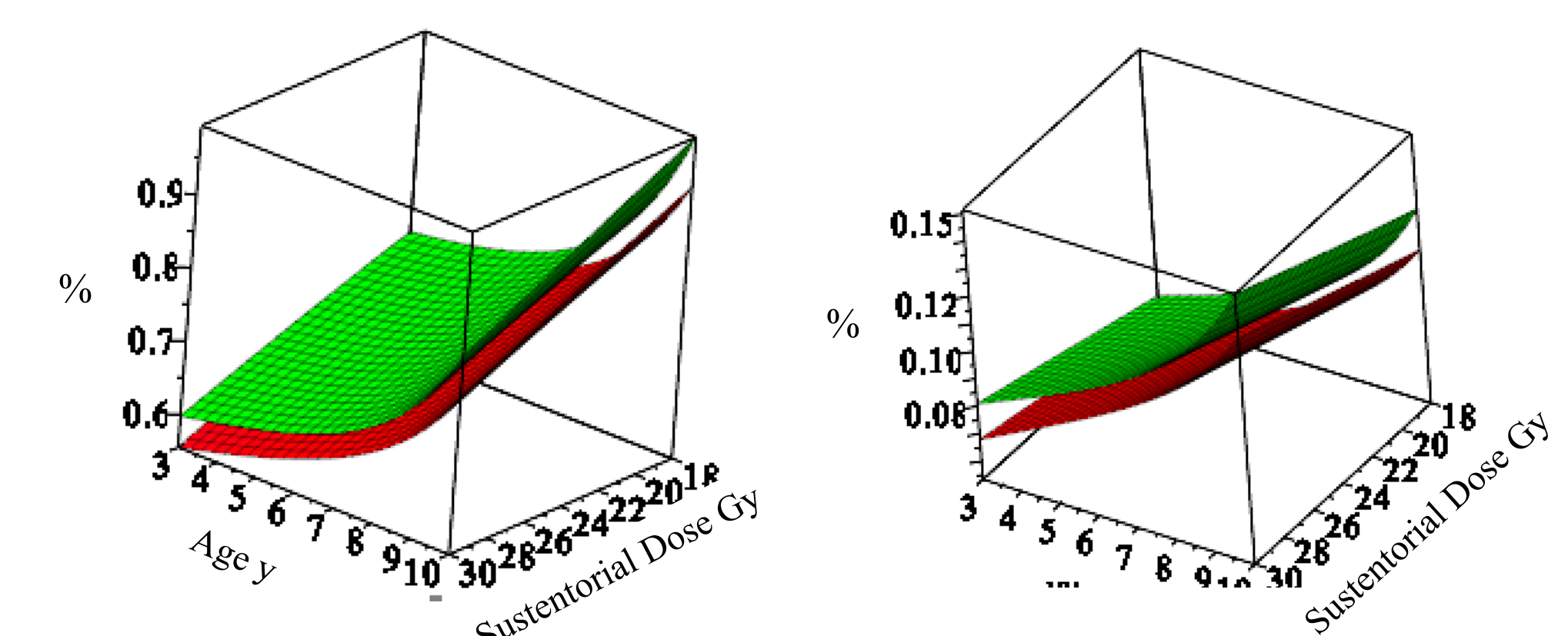
Impact of sex in children with HC :

Male (green) vs
Female (purple)



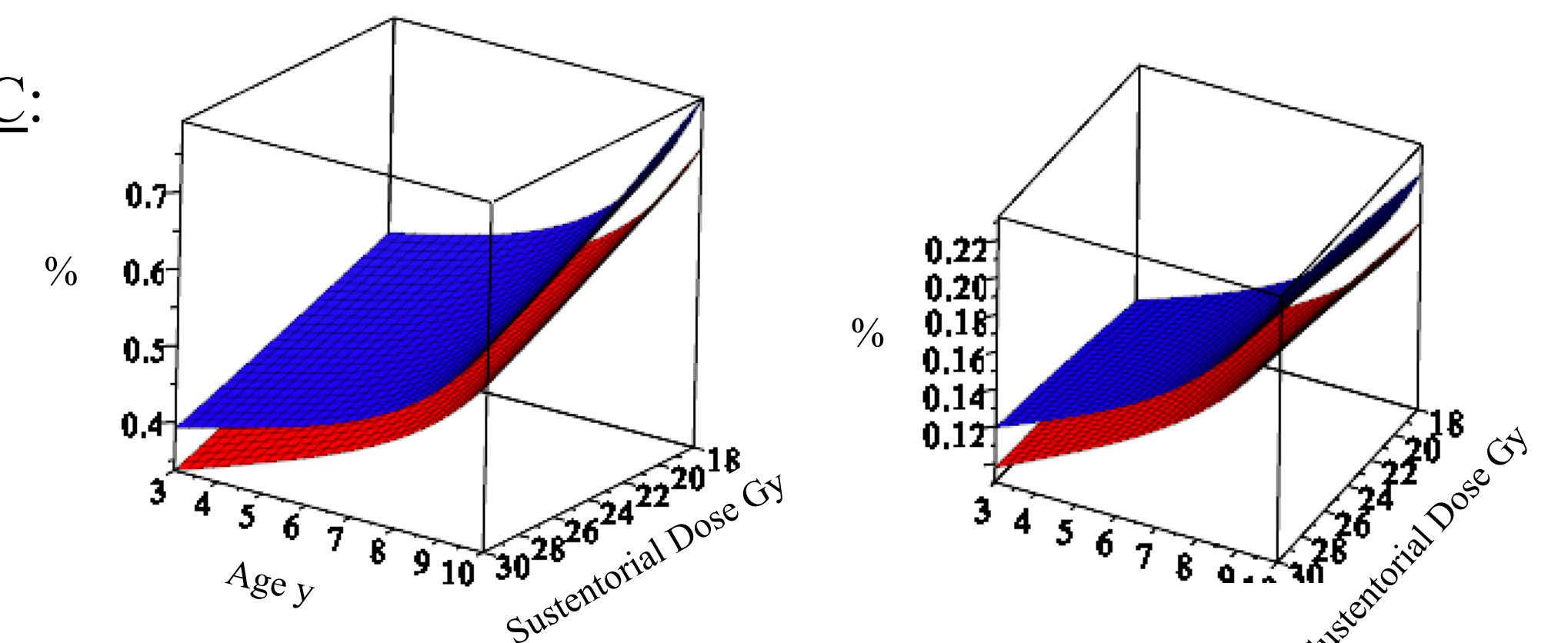
Impact of SES in male with HC:

SES1 as higher (green) vs
SES3 as lower (red)



Impact of SES in female with HC:

SES1 as higher (blue) vs
SES3 as lower (red)



Conclusions :

We elaborated an original **mathematical tool** to analyse the dynamic process of **decline neurocognition** according to main clinical and therapeutic factors. We reported the **major impact of sex** on neurocognitive outcome after treatment for medulloblastoma. This tool will allow **to early assess the potential impact of any preventive or corrective actions or rehabilitation programs** in hope to mitigate the impaired neurocognition.