Usual problems in setting IVIVC

J-M. Cardot

Email: J-michel.cardot@uca.fr

Introduction

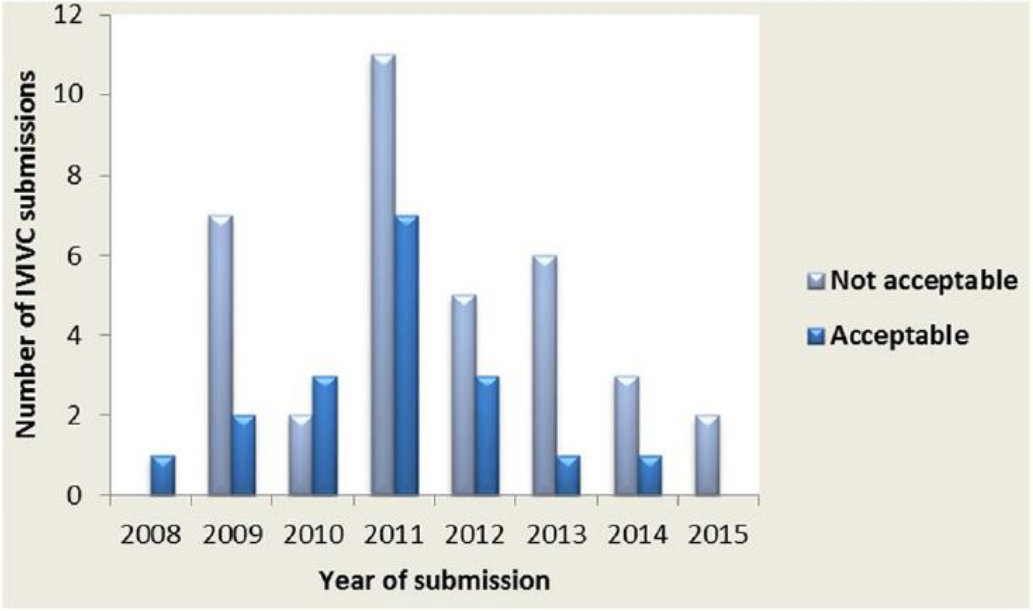
Based on

- My experience
  - CARDOT J-M., DAVIT B., In vitro- in vivo correlations: Tricks and Traps, AAPS Journal 2012, Sep;14(3):491-9
  - ROUDIER B, DAVIT BM, BEYSSAC E, CARDOT JM. In Vitro- In Vivo Correlation's Dissolution Limits Setting. Pharm Res. 2014 Sep;31(9):2529-38

- Some publications last ones:
  - Suarez-Sharp S, Li M, Duan J, Shah H, Seo P. Regulatory Experience with In Vivo In Vitro Correlations (IVIVC) in New Drug ApplicationsAAPS J. 2016 Nov;18(6):1379-1390. Epub 2016 Aug 1.
  - Nguyen MA, et al A survey on IVIVC/IVIVR development in the pharmaceutical industry - Past experience and current perspectivesEur J Pharm Sci. 2017 May 1;102:1-13. doi: 10.1016/j.ejps.2017.02.029. Epub 2017 Feb 21.

Current position

- IVIVC by FDA
  - Two stages 91%
  - One stage 9%
  - Majority level A
- Number fluctuate
- Sucess 42%



Problems for Industry

- Lack of appropriate clinical data
- Regulatory uncertainty
- Deficiency in time and resources
- Inapplicable compound properties
- Complexity of required dissolution method

Failures for industry

- Model does not meet the validation criteria
- Lack of appropriate clinical data
- Deficiency in time and resources
- No difference in the in vitro release characteristics
- Complexity of required dissolution method

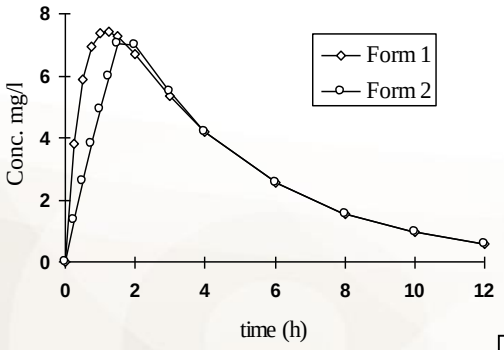
Failures for authorities

In vitro dissolution	Formulation	*In vivo* study design	Modeling	IVIVC application
• May need to be physiologically relevant • Lack of systematic approach in the development of a biopredictive method • Inadequate discriminating power for detecting differences in product performance	• Lack of sufficient number of release rates covering a reasonable range • Formulations used in the model construction are not qualitatively the same • Release rate differences are achieved by adding/deleting the release controlling excipients	• Lack of rank-order correlation • Reference formulation not part of the same *in vivo* study when numerical deconvolution is being applied. • Study conducted under fed conditions for drug products with significant food effect • Lack of *a priori* planning on the design of the study • Exclusion of subjects without justification	• Incorrect used of same scaling factor in the correlation step as indicated by slope value differences among the formulation used in the construction of the IVIVC • Inclusion of non-mechanistic terms without adequate justification • Overparameterization of the model • Inconclusive model predictability with unacceptable validation results • Use of mean PK data in the deconvolution step while deconvolution at individual level is applicable • Lack of justification for the model selected to establish the correlation	• Biowaiver request for lower strengths based on IVIVC models constructed and validated with the highest strength while the strengths are not proportionally similar in composition • Calculation of similarity factor instead of IVIVC predicted PK parameters to support CMC changes • Use of invalid extrapolation to support proposed dissolution acceptance criteria • Comparison of the predicted PK parameters to the target formulation rather than to the opposite proposed bound without appropriate justification

My experience

- Lack of understanding what is IVIVC
- Not understanding limiting factor
- UIR, deconvolution convolution
- Number of formulation, range of formulations, Use outside of range, improvement of F
- Data: Exclusion of data, not exploring data
- Averaging data and wrong setting
- Over parametrization, non linear relationship
- Improper relationship, not know how to use time scaling
- Development of the right dissolution test
- Change of dissolution test between IVIVC and QC
- No external predictability and not use all but exclude one formulation
- A posteriori setting
- Frightened of helping competitors => IVIVC kept within the company

Limiting factor



Drug Dosage Form

Release of API

Dissolution of API

Dissolved API: solution of API

Absorption permeation

Efflux protein: pGp

Absorbed API

First pass

Liver, hepatic first pass effect

Entero hepatic recycling

Excretion ; renal, bile, etc.

Distribution

Elimination

Systemic blood flow ; central compartment

Peripheric compartment if any

Therapeutic response

Metabolisation

Action on targetted receptors

Deconvolution / convolution /UIR

- Need UIR in same subjects … not always the case
  - Use of published data =>quality, population, PK issues
  - Use old data => LOQ, population, PK issues
- Must modelize the UIR and use it
- Problem of large time intervals
- Stability of the algorithm
- If no UIR => Wagner Nelson in case of 1 cp but the prediction => inverse WN => AUC almost always OK

Dissolution and absorption normalization

- Dissolution must be expressed in % of label except in some cases such as TTS
- Dissolution is expected to be complete (100%)
- Absorption must be related to UIR (F) and the even if normalized the F must be reintroduced in the calculations later on.
- Cannot improve the F of new formulation => cannot be predicted

Formulations used: range and improvement of formulations

- Must use a range of formulations:
  - With the same release mechanism
  - Which will be limits of the « space » of usability of the IVIVC
- When IVIVC established
  - Cannot modify the F in case of improvement
  - Cannot use IVIVC outside of the range
  - Must insure same release mechanism

Dissolution test / setting limits

- Often the users do not investigate numerous dissolution tests
- Lack of point to model adequatly the dissolution
- Problem of formulation aging
- Problem in case of accelerated dissolution to keep release mecahnism as per in vivo
- Dissolution used in IVIVC must be the dissolution of QC

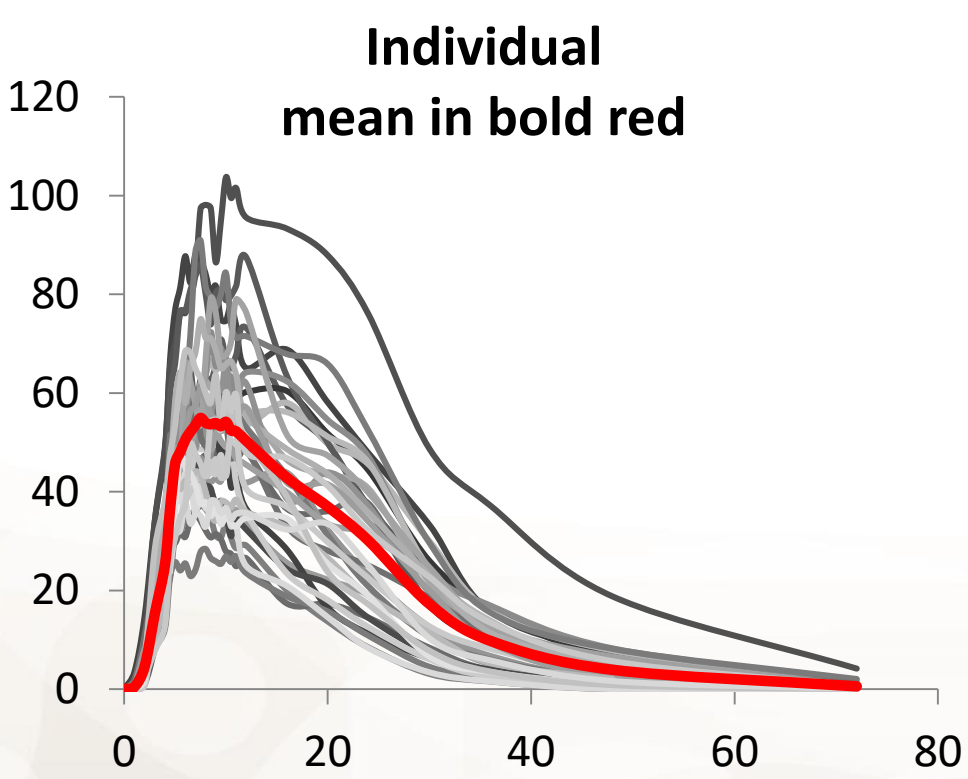
Dissolution test change for QC

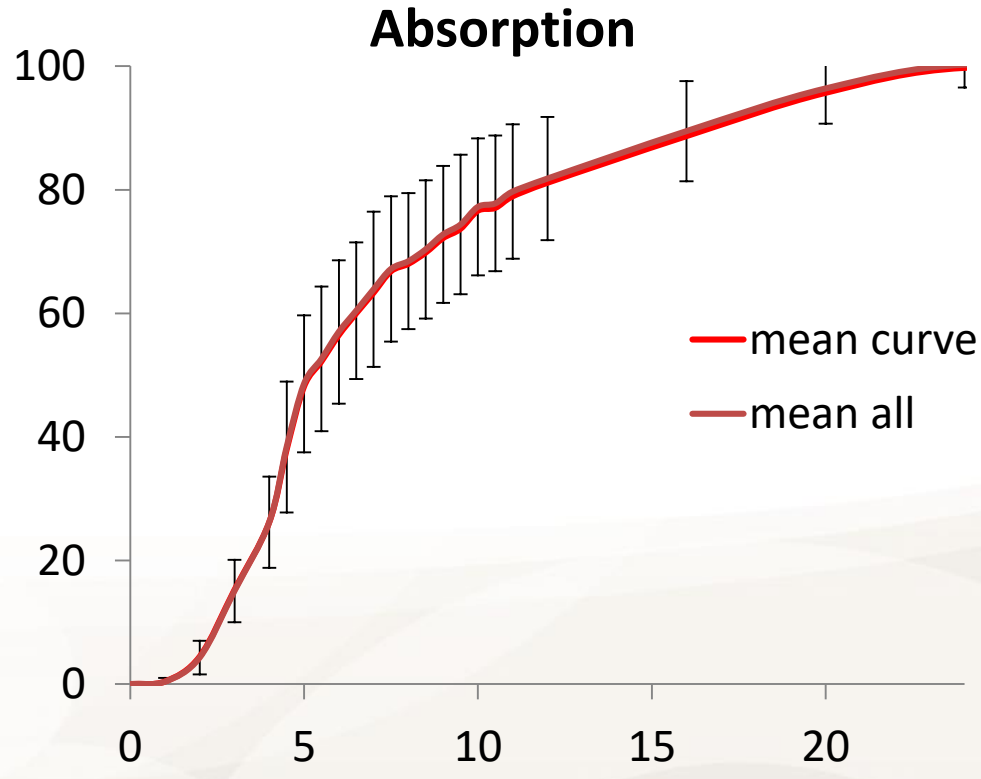
- Dissolution is expected (except in some rare cases) to go up to 100%
- If dissolution too complex for IVIVC cannot use it in QC
- How to link dissolutions IVIVC and QC => time scaling is a possibility
- How to set dissolution limits and to use the variability of in vivo

Averaging

- Often the IVIVC are established on mean curves
  - Mean in vitro dissolution
  - In vivo plasma curve leading to absorption curve which are averaged ….
- Simulations are performed to establish mean profile based on the mean dissolution

Mean curve or mean of indididuals



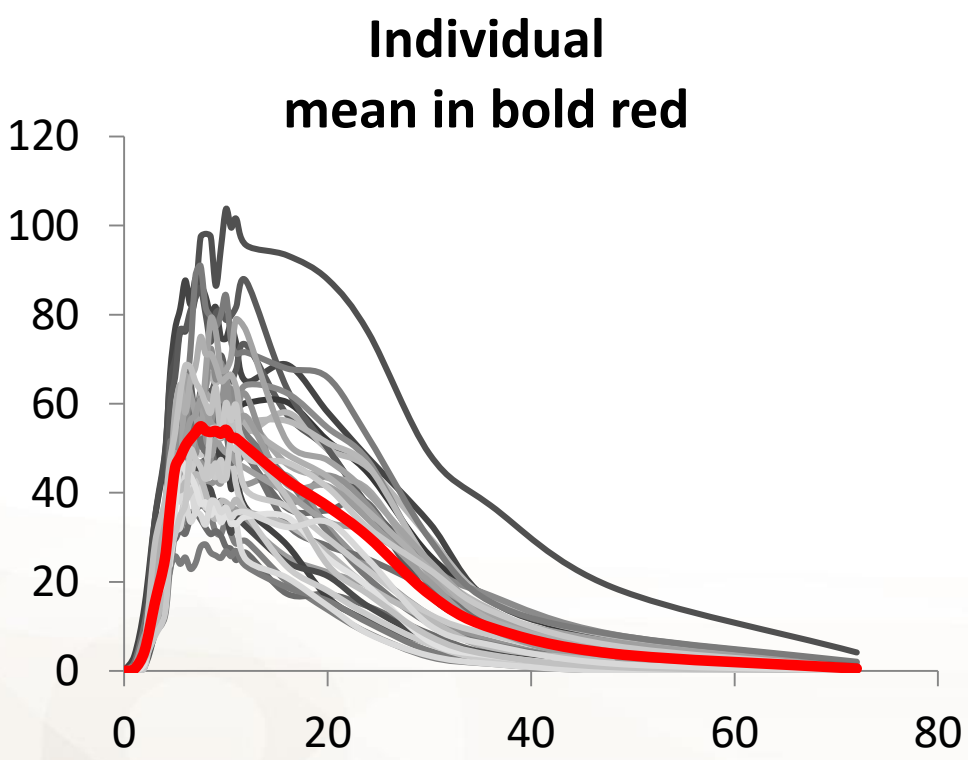


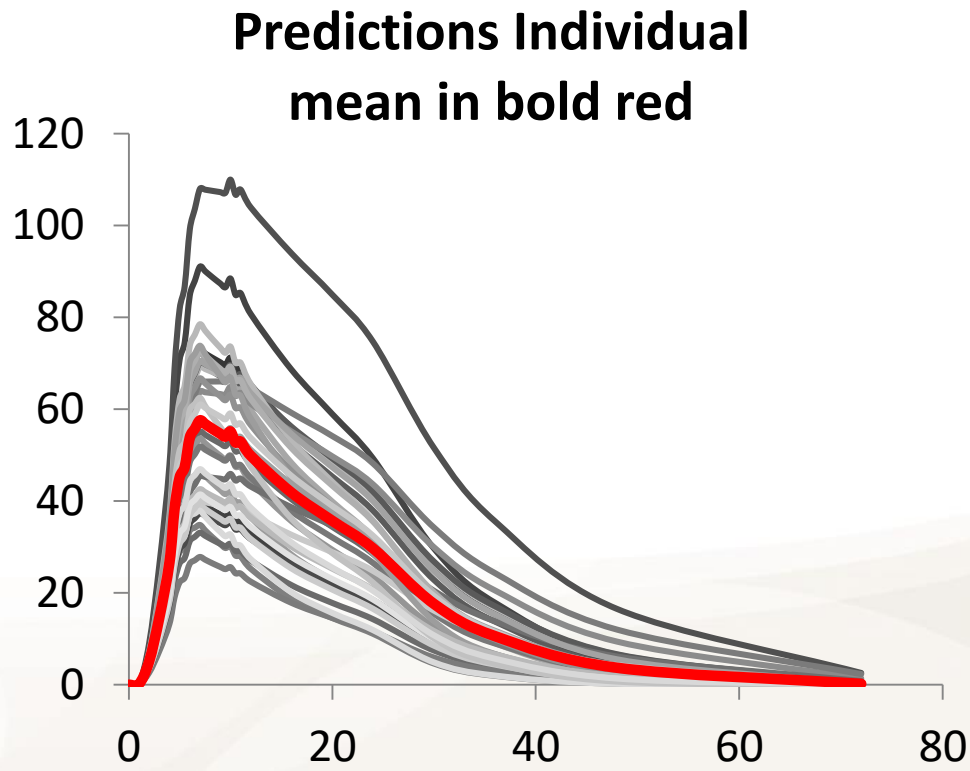
- Only one IVIVC for all subjects … or for the mean
- Variability linked with initial set of subjects
- Some agencies asked to mean only the absoption curve

Mean in vivo curve

- The calculations performed on mean/median curve lead to an sole absorption curve
- Problem if calculations made on individual and then average of mean absorption … prediction are compared to what ? As a sole IVIVC is existing (and not one by subject) in two stage approaches
- Mean of individual Cmax and AUC are difference from Cmax and AUC of mean curves
- arithmetic or geometric means, median ...

and now for prediction…



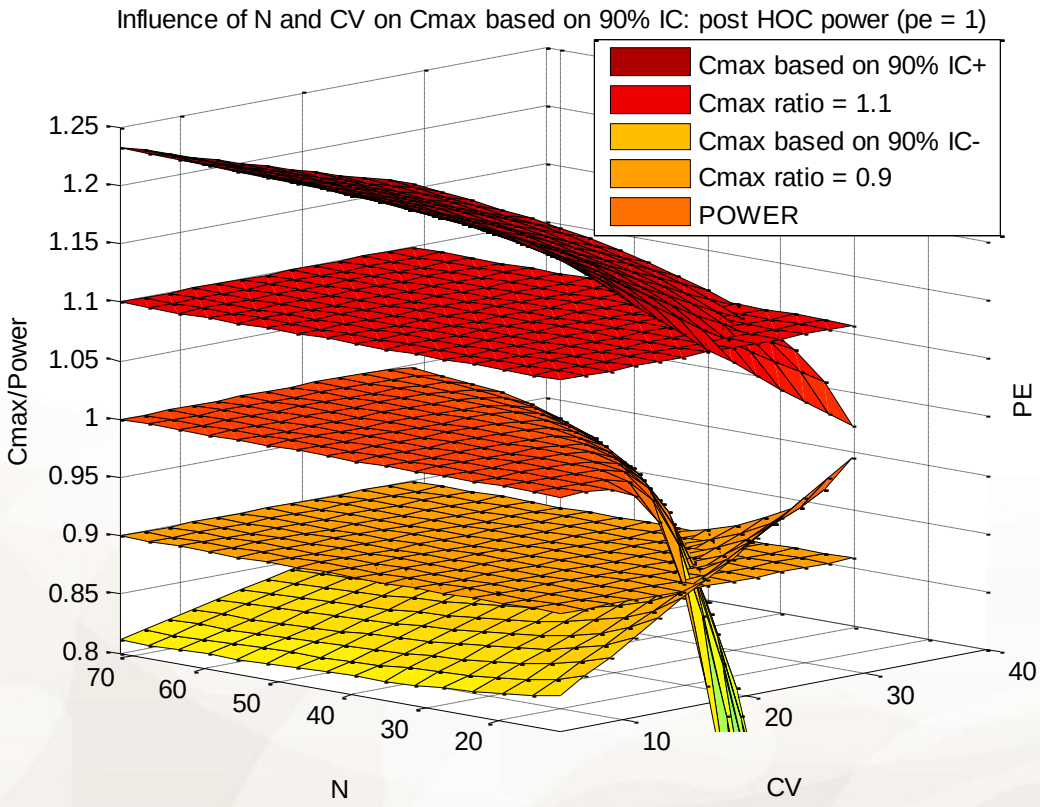


- In case of prediction identical shape as input similar for all subject
- Using means restricted the pool of data to a single set, cannot estimate adequately the variability of response, underestimate the subject effect but IVIVC is usually done when intra subject variability is lower than inter subject … that being not reflected by a a set of data.
- is that a real question?

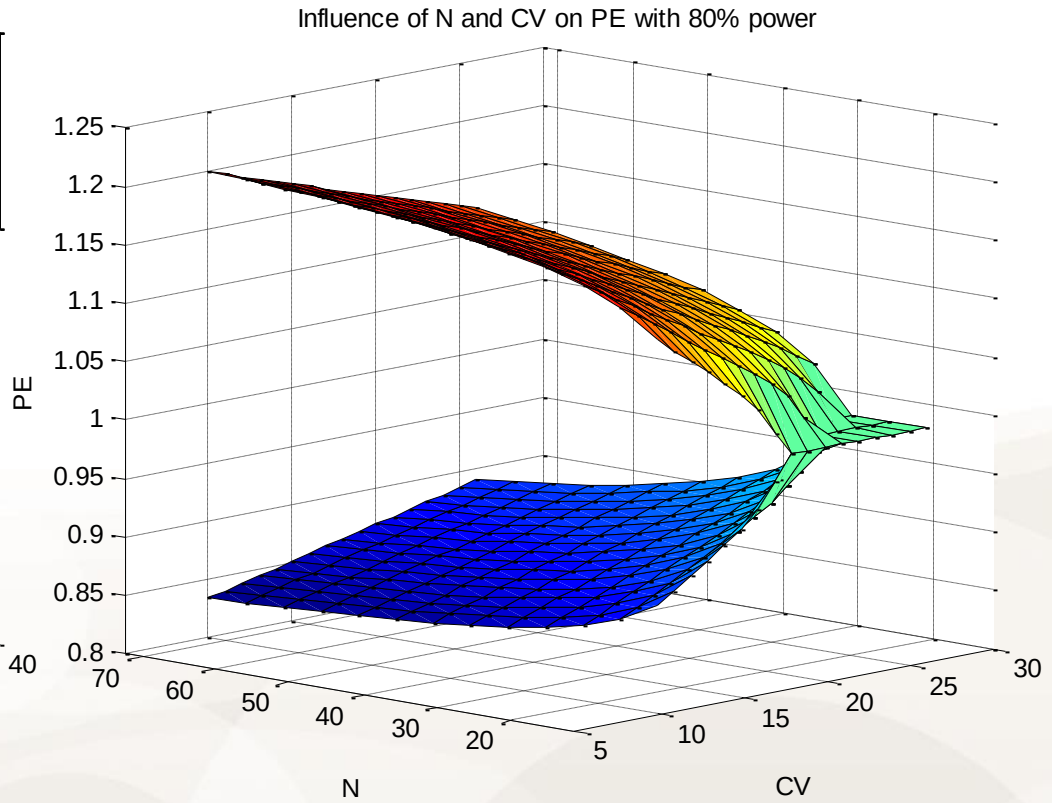
But

- Intra and inter subject variability is known and could be reintroduce in the prediction
- Predictability is an important step see averaging as also one comment…

Comparison of methods based on IVIVC for limits or predictability => introduce intrasubject CV



Not always certain to be BE in vivo….



Always certain to be BE in vivo
Or able to calculate the right number of subjects

A posteriori setting using different data in quality and quantity

- Establish IVIVC after development is discouraged
- If made try « all except one formulation » approach (at least)

Non common/Non linear IVIVC

- IVIVC or time scaling must be common for all formulations
- Non linear IVIVC could exist but avoid Ln or exp or sqrt transformations … as extreme will be underestimated
- Prefer investigate new dissolution of reasonable time scaling and study the shape of it!

Initial IVIVC

- Use a two steps to explore the data
- When initial IVIVC establish and covariates known one stage could be used
- Always have a look on the predictions vs observed curves not only AUC and Cmax but also curve
- Sometime other parameters are of importance such as C(τ)

Thank you

Questions ?

No => perfect !

Yes => Great !!!!!