AN ATYPICAL JOINT MODEL OF PSA AND CTC COUNT KINETICS DURING TREATMENT IN PROSTATE CANCER

Mélanie Wilbaux, Michel Tod, Johann De Bono, David Lorente, Joaquin Mateo, Gilles Freyer, Benoit You, Emilie Hénin

TherapeutiC Targeting in Oncology - EMR 3738
Faculty of medicine Lyon-Sud, France
University Claude Bernard Lyon 1

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BACKGROUND

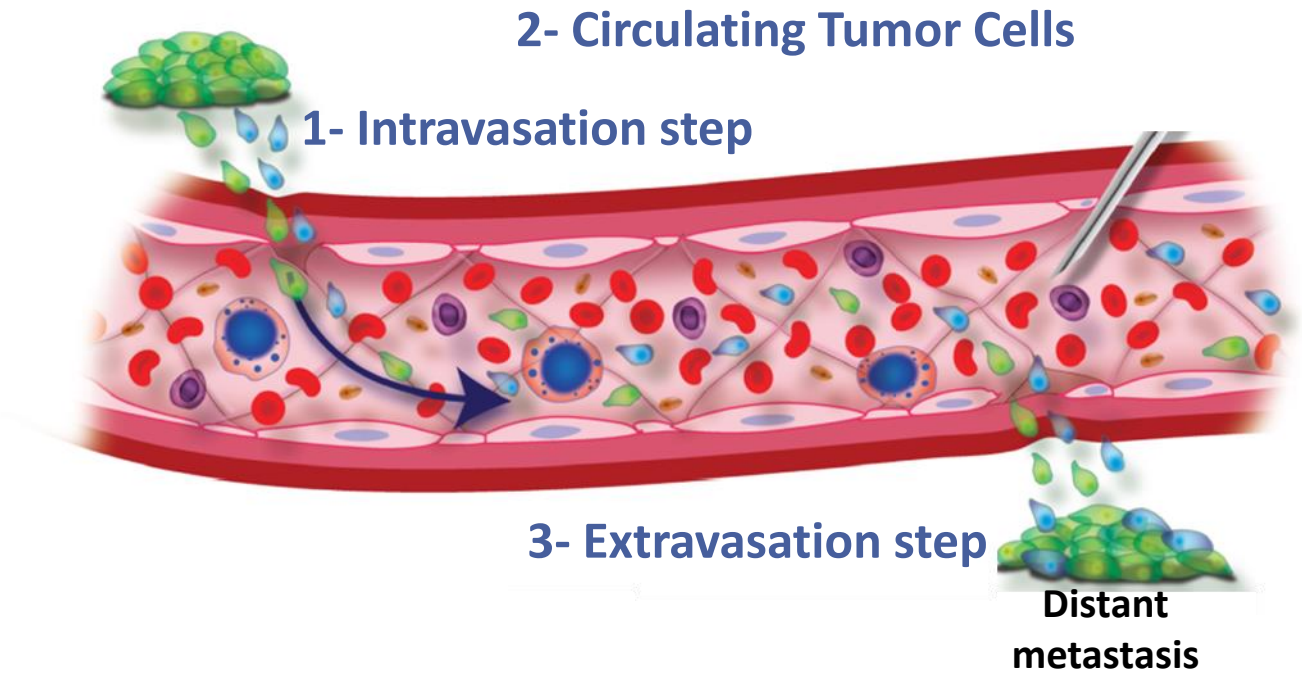
Background – Prostate cancer & PSA

- **Prostate cancer (PC):**
  - The most common cancer
  - The 3rd leading cause of cancer deaths
  - Bone: the most common site of metastasis → non-measurable tumor burden / disease evolution to evaluate treatment efficacy
- **PSA (Prostate-Specific Antigen):**
  - The most widely used serum tumor marker to evaluate treatment effect in PC
  - Controversial validity of its use as a surrogate marker

→ Need of strong surrogate markers for disease outcome and clinical benefit in metastatic PC

Background – CTCs: Definition

- Circulating Tumor Cells [1]: new emergent serum tumor marker
- Tumor cells released into blood which potentially lead to the development of metastases [2] :



[1] Ashworth et al. A case of cancer in which cells similar to those in the tumours were seen in the blood after death. The Medical Journal of Australia. 1869. [2] Danila et al. Circulating tumor cells as biomarkers. *Cancer J.* 2011.

Background – CTCs: Definition

- Circulating Tumor Cells [1]: new emergent serum tumor marker
- Tumor cells released into blood which potentially lead to the development of metastases [2] :

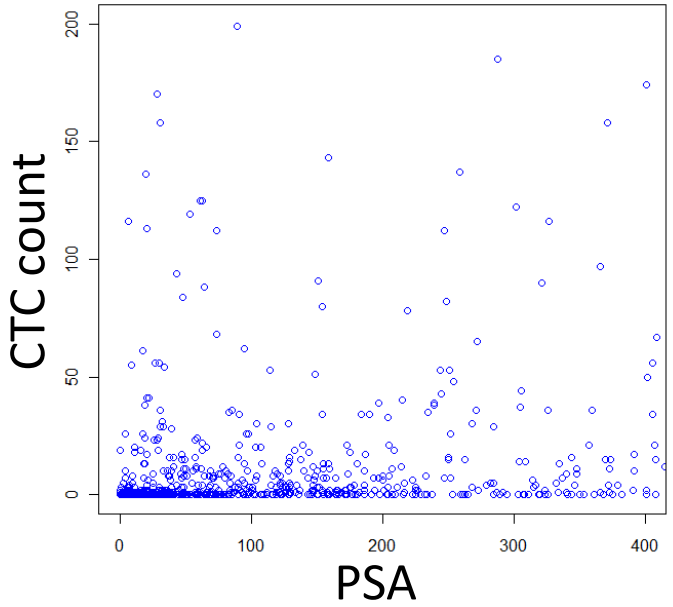
- Potential application as a **biomarker** in oncology
- In PC: CTC count (<5 vs >=5) associated with **overall survival** [3]
- CTC count **better predictor** of survival than PSA decrease [3]

[3] De Bono et al. Circulating tumor cells prdict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2008.

Background – CTC count kinetics

- Could be a useful tool to evaluate treatment response
- Could provide information about the evolution of the total tumor burden = primary tumor + metastases

→**Kinetics of CTC counts, along with their relationships with other markers, need to be addressed**



→ No clear direct relationship

→ Different kinetics

Objectives

- To quantify the **dynamic relationships** between the kinetics of PSA and CTC count in metastatic prostate cancer patients under treatments

- To build a semi-mechanistic model combining several **advanced features** in pharmacometrics

PATIENTS & METHODS

Patients & Data

- **223** metastatic castration-resistant prostate cancer (mCRPC) patients [3]
- Treated by chemotherapy + / - hormonotherapy
- For each patient:
  - No drug concentration data
  - **Number of CTCs / 7.5 mL aliquot** of blood : Med = 2 [0 – 6 437] (CellSearch method)
  - **PSA concentration** ($ng.mL^{-1}$) : Med = 116 [LOQ – 17 800]
  - Median of **4** PSA and **4** CTCs values per patient

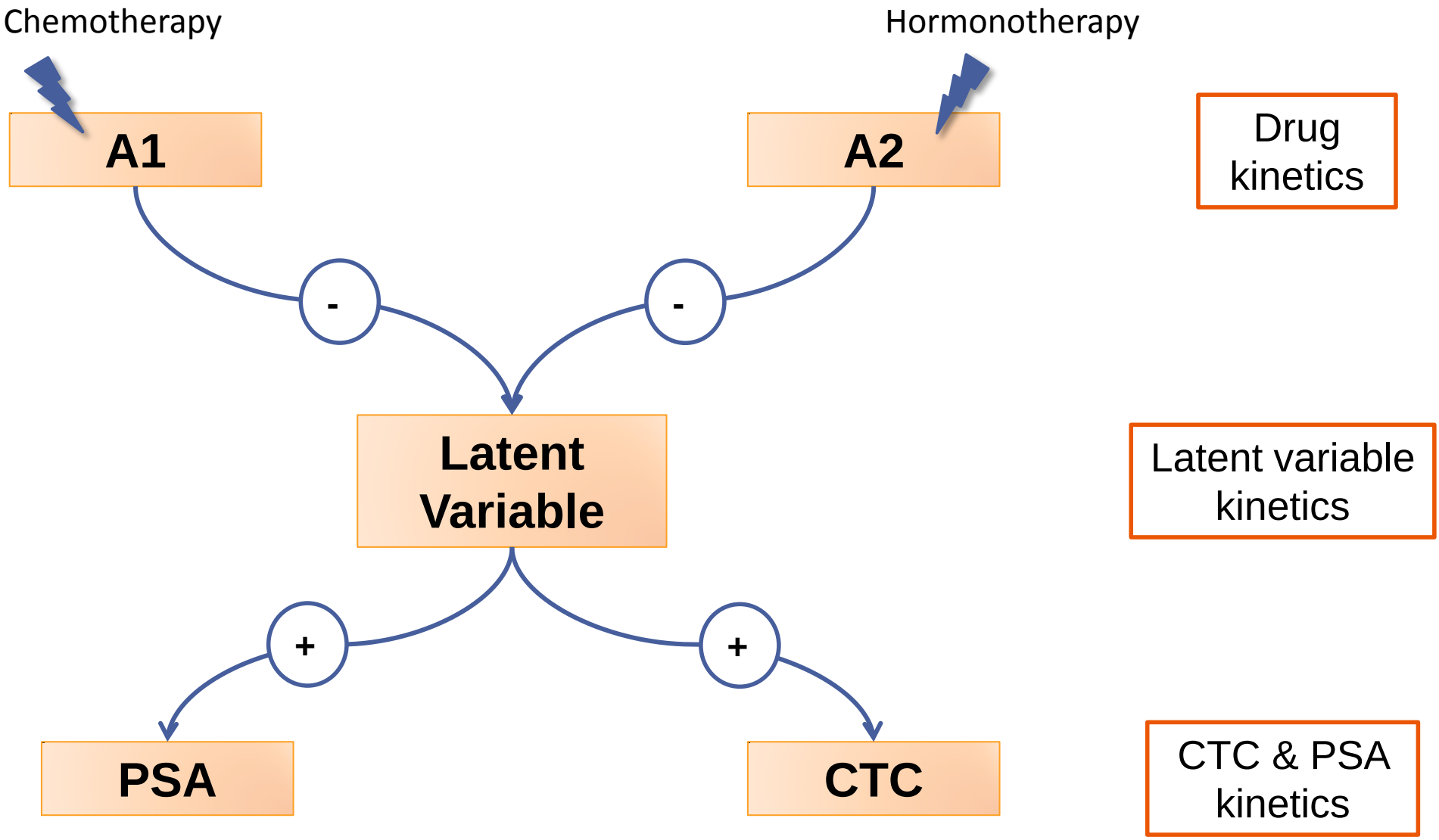
[3] De Bono et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res.* 2008.

Modeling Methods

- Model-building process:
  - Model for PSA kinetics
  - Model for CTC count kinetics
  - → Combined and linked with a **common unobserved variable**

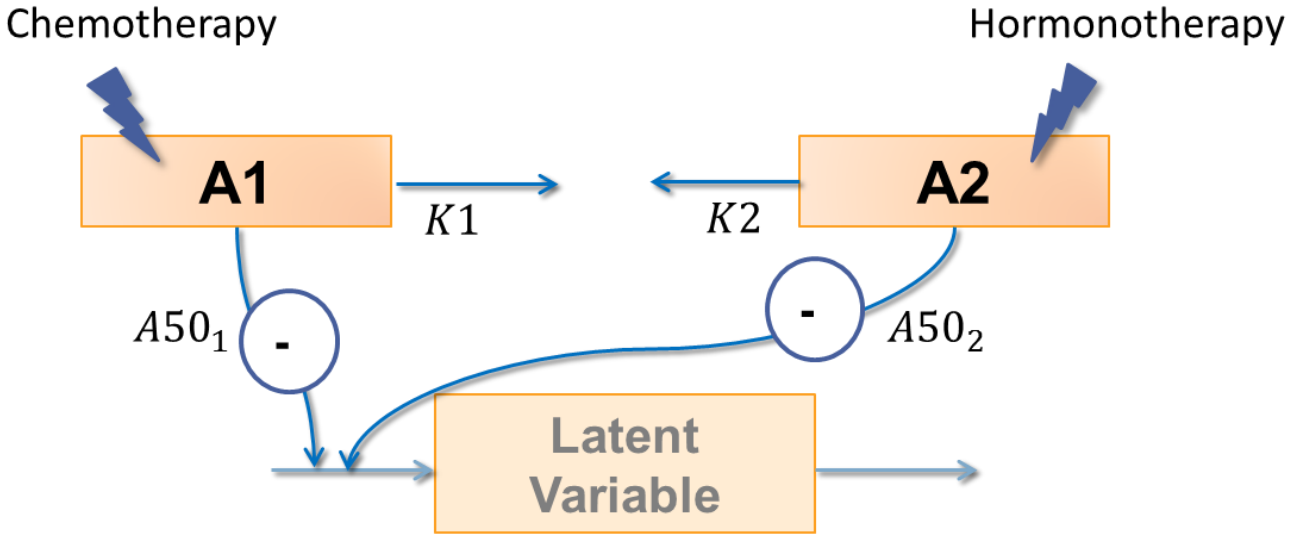
- **Non-linear mixed effects** modeling:
  - NONMEM 7.3 (SAEM algorithm)
  - Model selection & evaluation:
    - Likelihood
    - Standard error (SE) and Shrinkage values
    - Goodness-of fit (GOF) plots
    - Simulation-based diagnostics (Visual predictive Check: VPC)

MODEL STRUCTURE


Chemotherapy
Hormonotherapy
A1
A2
-
-
Latent Variable
+
+
PSA
CTC
Drug kinetics
Latent variable kinetics
CTC & PSA kinetics

Drug effect kinetics

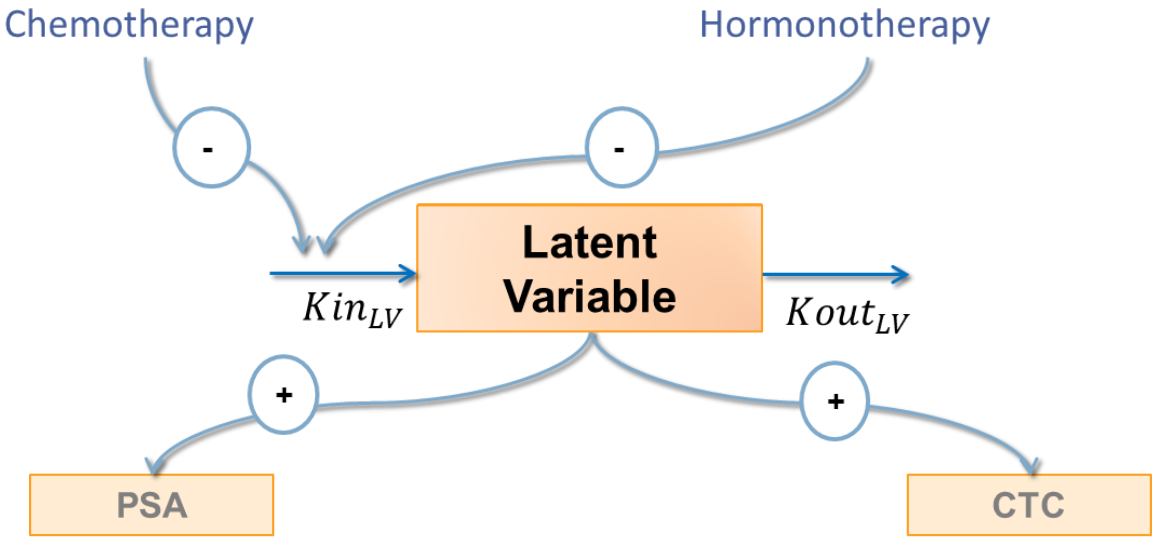
- No PK data → **K-PD** approach [4]
- 2 K-PD compartments for chemotherapy and hormonotherapy
- Estimation of different kinetics and efficacy parameters



[4] Jacqmin et al. Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. *J Pharmacokinet Pharmacodyn.* 2007.

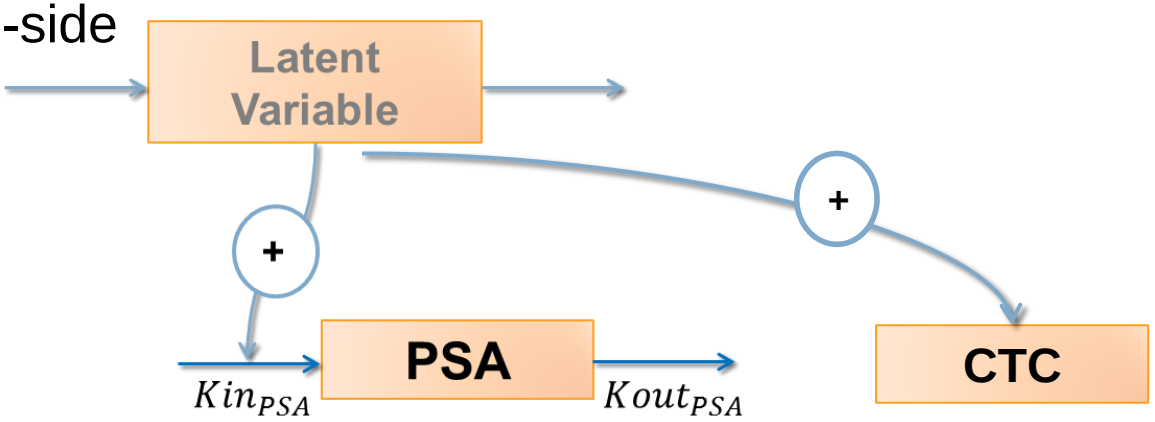
Dynamic links between PSA and CTC

- No clear direct relationship, but triggered by a common variable
- Use of a **latent variable**: underlying, non-observed variable
  - Non-steady-state model
  - 0-order production and 1st order elimination rates



Joint modeling of PSA and CTC kinetics

- **PSA:**
  - **Continuous** data
  - Non-steady-state model
  - 0-order production and 1st order elimination rates
  - Log-transformed both-side



- **CTC count:**
  - **Discrete** data
  - Produced by a discrete process
  - **Cell Life Span model** [5]

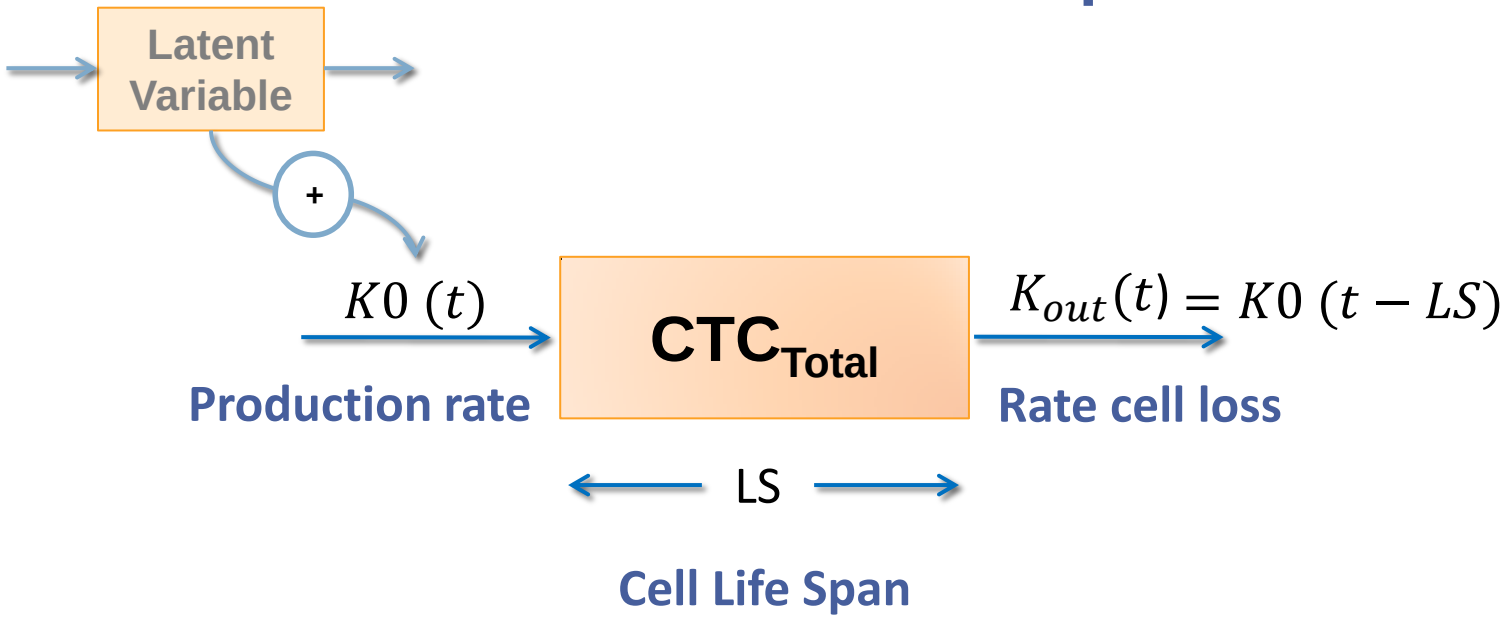
[5] Krzyzanski et al. Lifespan based indirect response models. *J Pharmacokinet Pharmacodyn.* 2012.

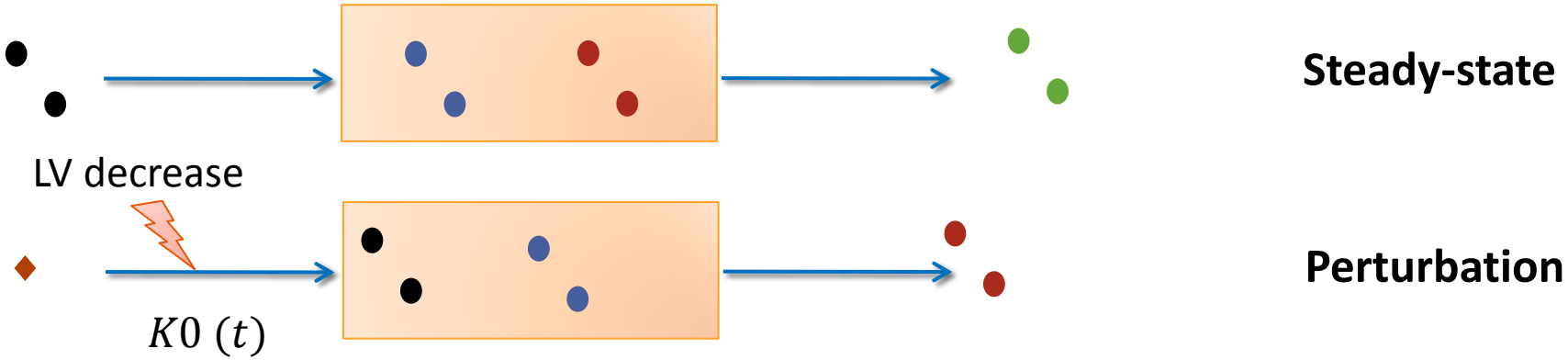
CTC kinetics: Cell Life Span model

- Commonly used for the modeling of blood cells maturation [5]

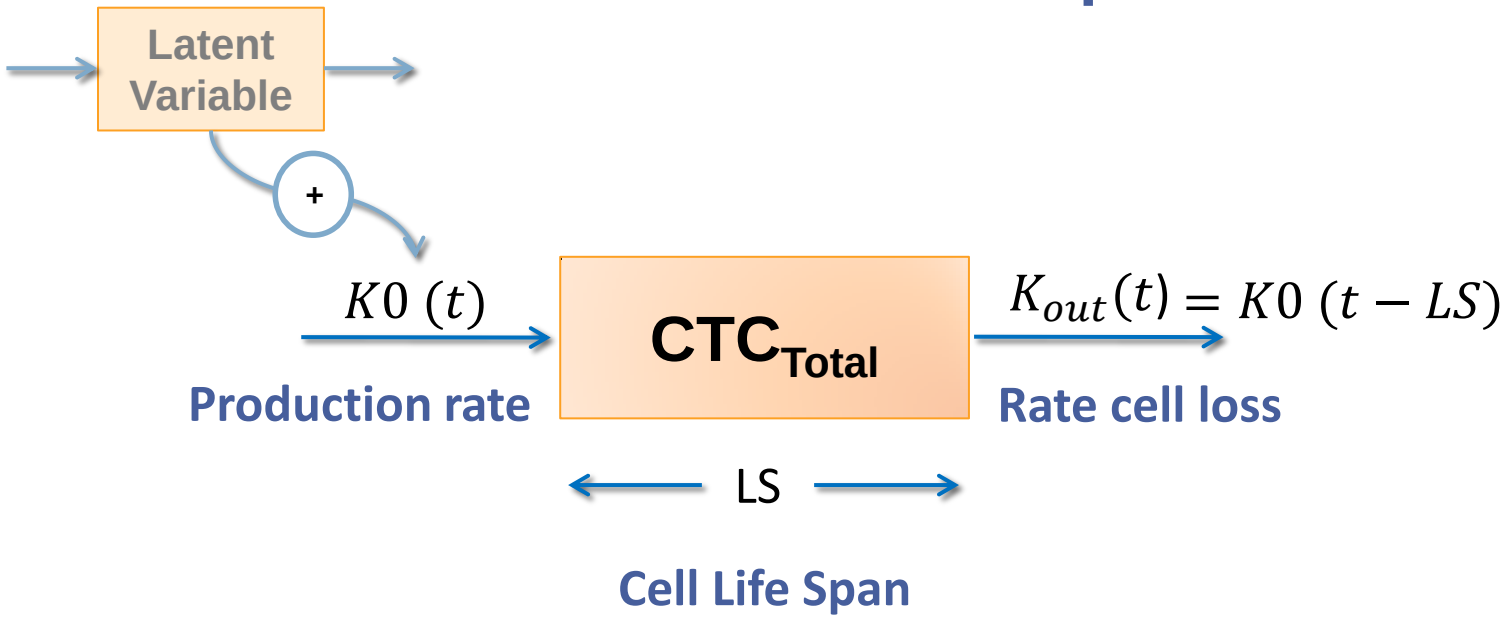
[5] Krzyzanski et al. Lifespan based indirect response models. *J Pharmacokinet Pharmacodyn.* 2012.

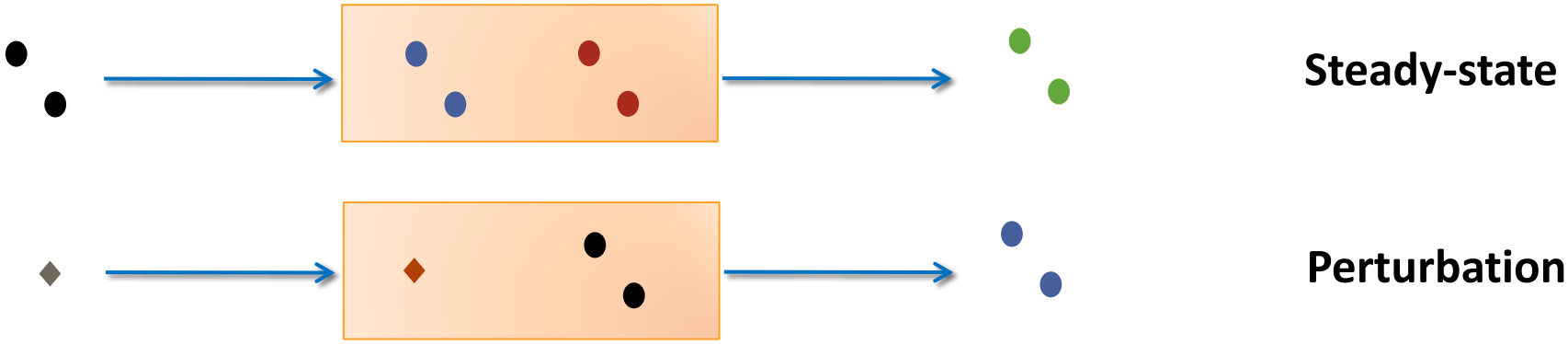
CTC kinetics: Cell Life Span model



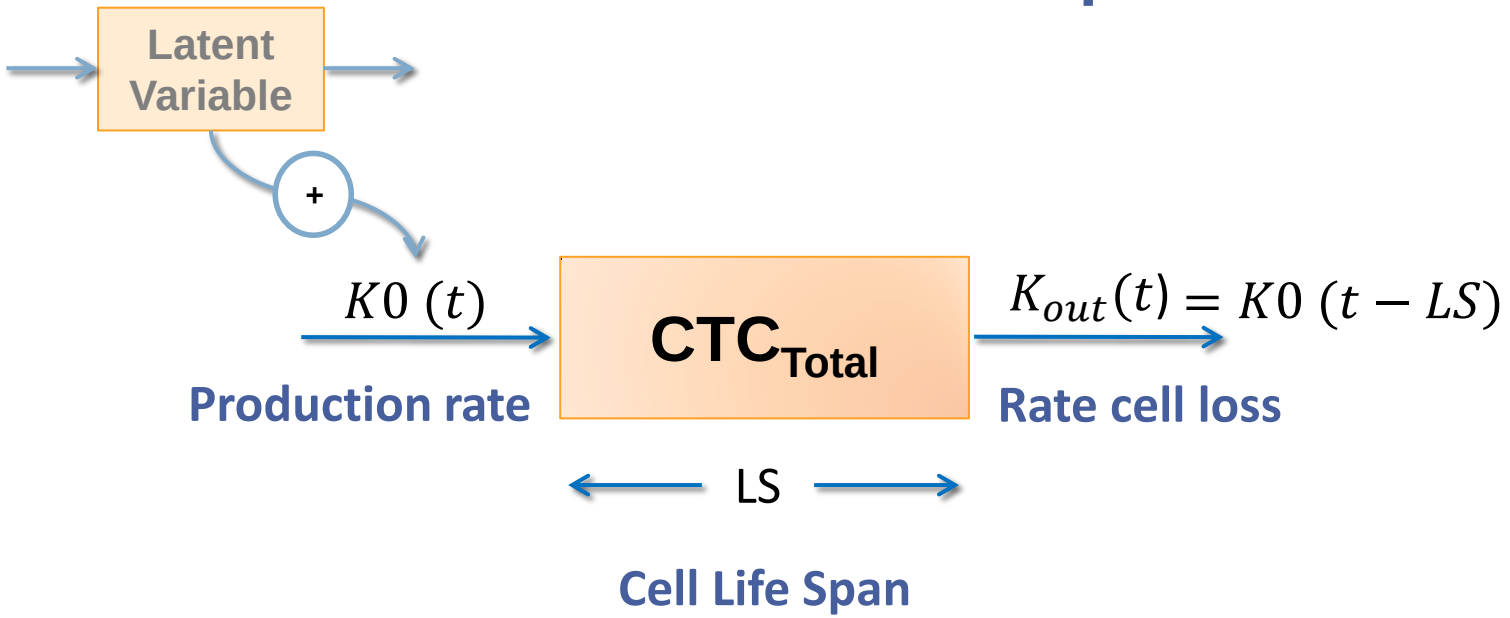


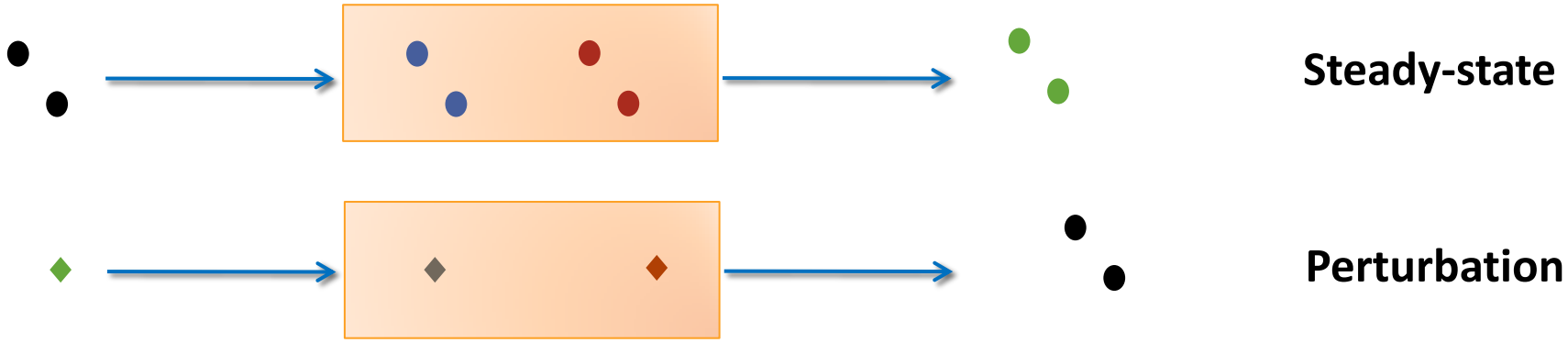
CTC kinetics: Cell Life Span model



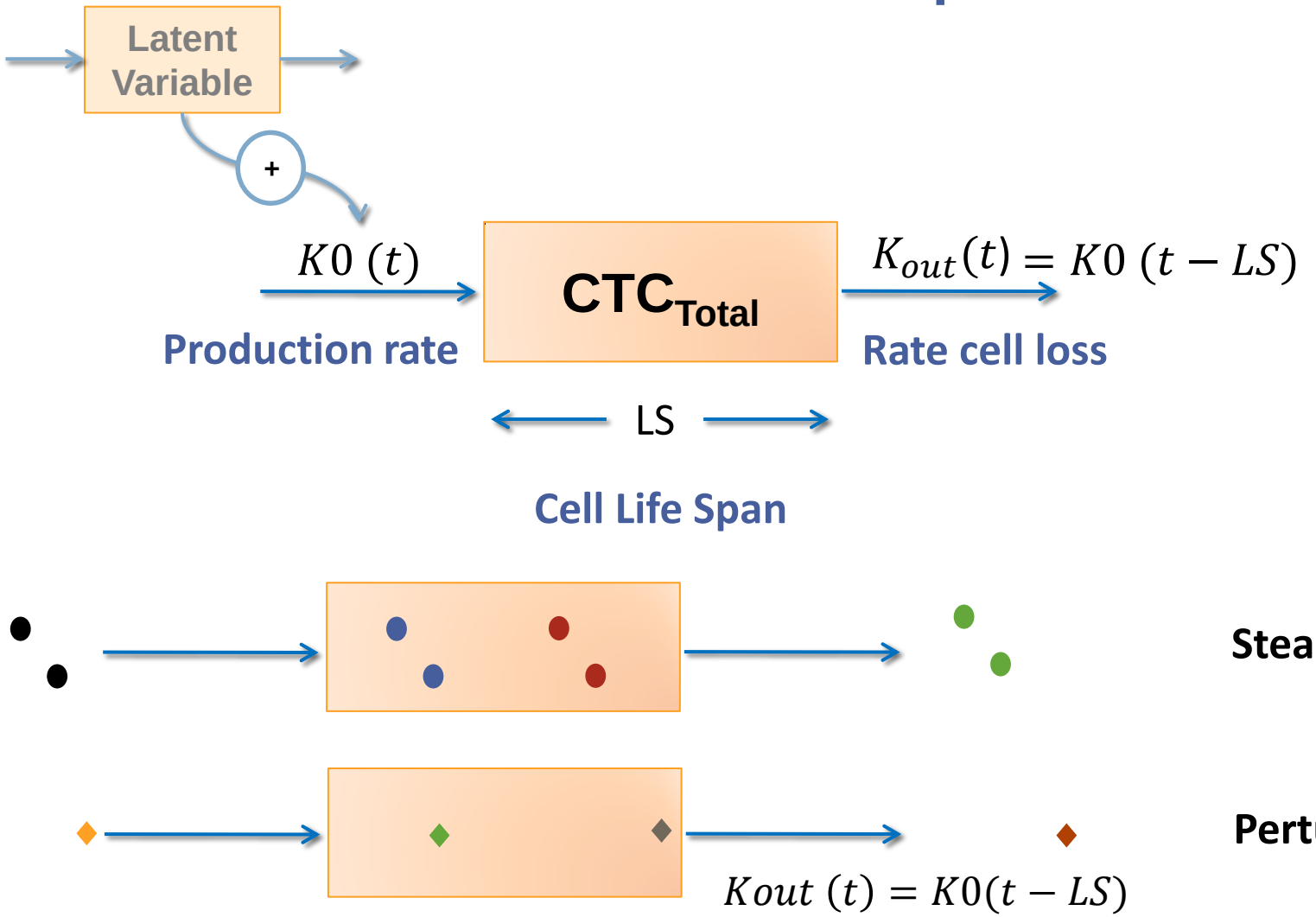


CTC kinetics: Cell Life Span model



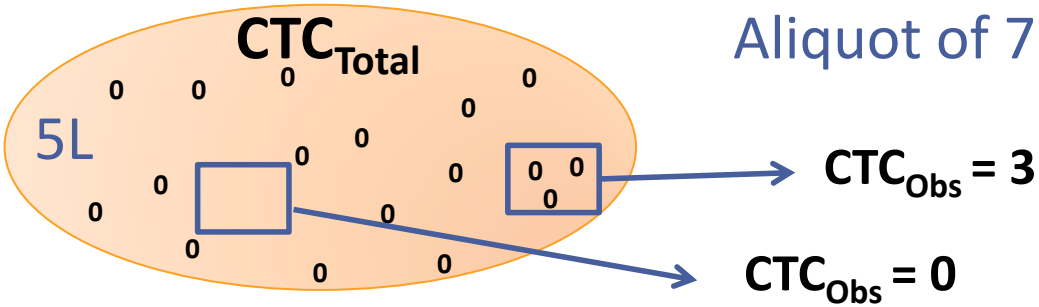


CTC kinetics: Cell Life Span model



Random sampling of CTCs

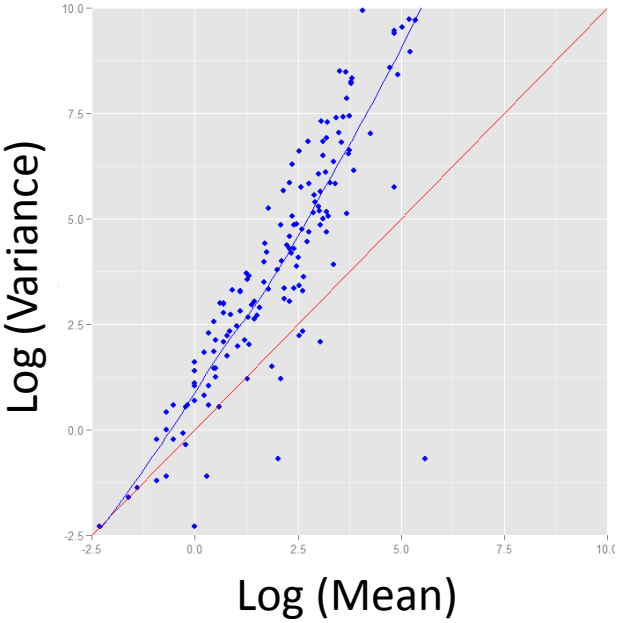
- The observed CTC count is a sample of a true CTC count:



→ **Random process**

- Expected CTC count per aliquot:
  - Homogeneous repartition of CTCs
  - $\hat{\lambda} = \widehat{CTC_{Total}} \times \alpha \qquad \alpha = {}^{7.5}/_{5\,000}$

- $CTC_{Obs} \sim Poisson\ (\lambda)$:
  - **Negative Binomial distribution**
  - Overdispersion: variance > mean

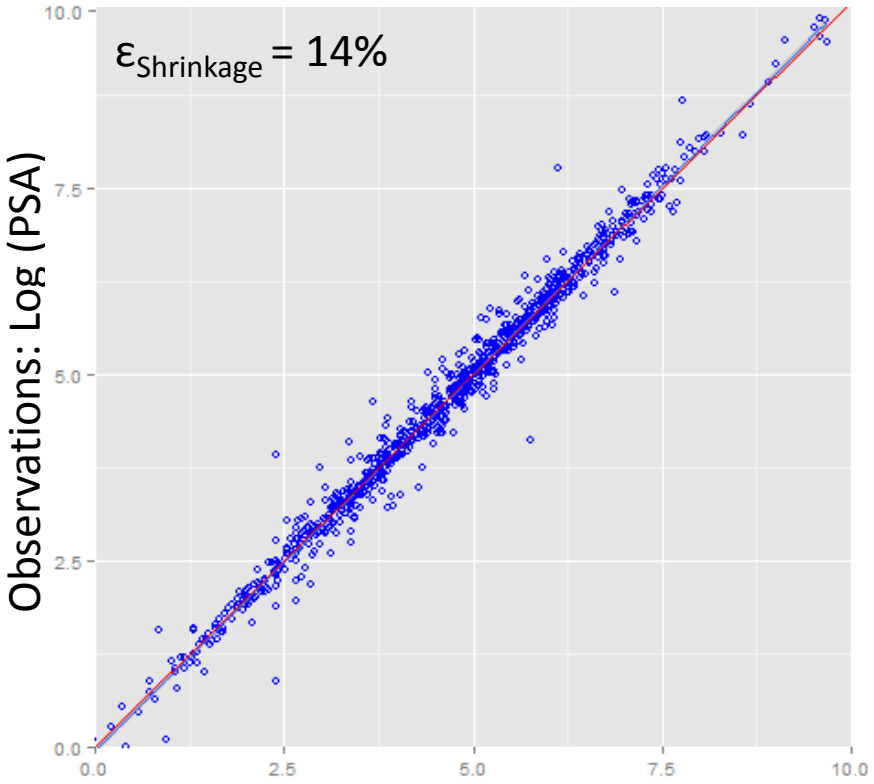


RESULTS

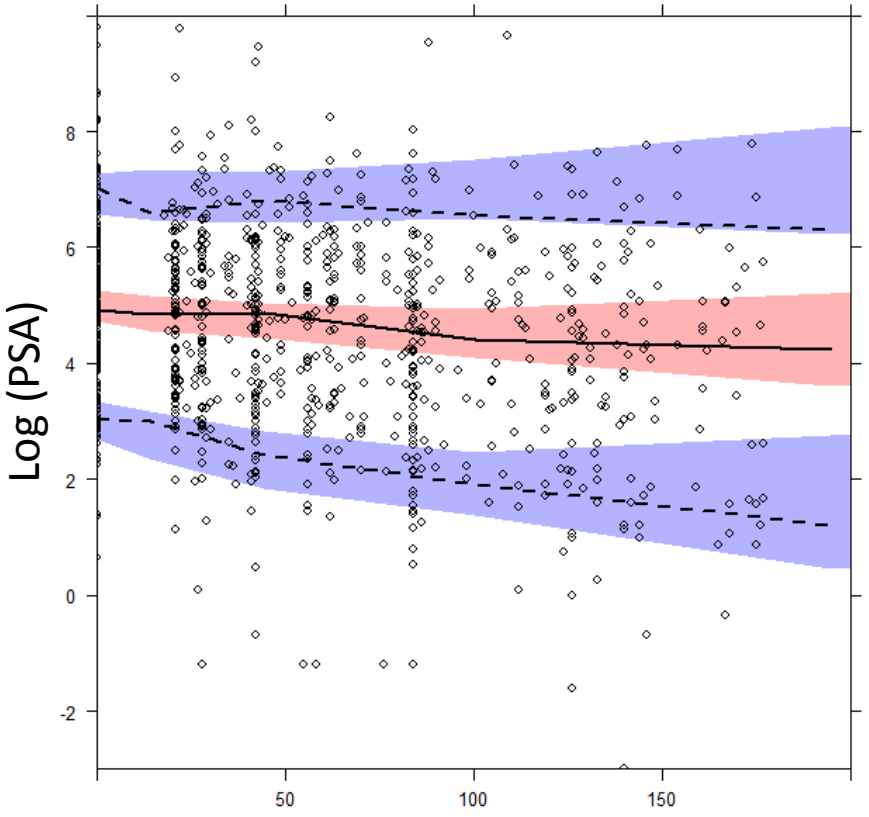
PSA Evaluation

Observations
Observed percentiles
Simulated 95% c.i of 10th & 90th percentiles
Simulated 95% c.i of the median

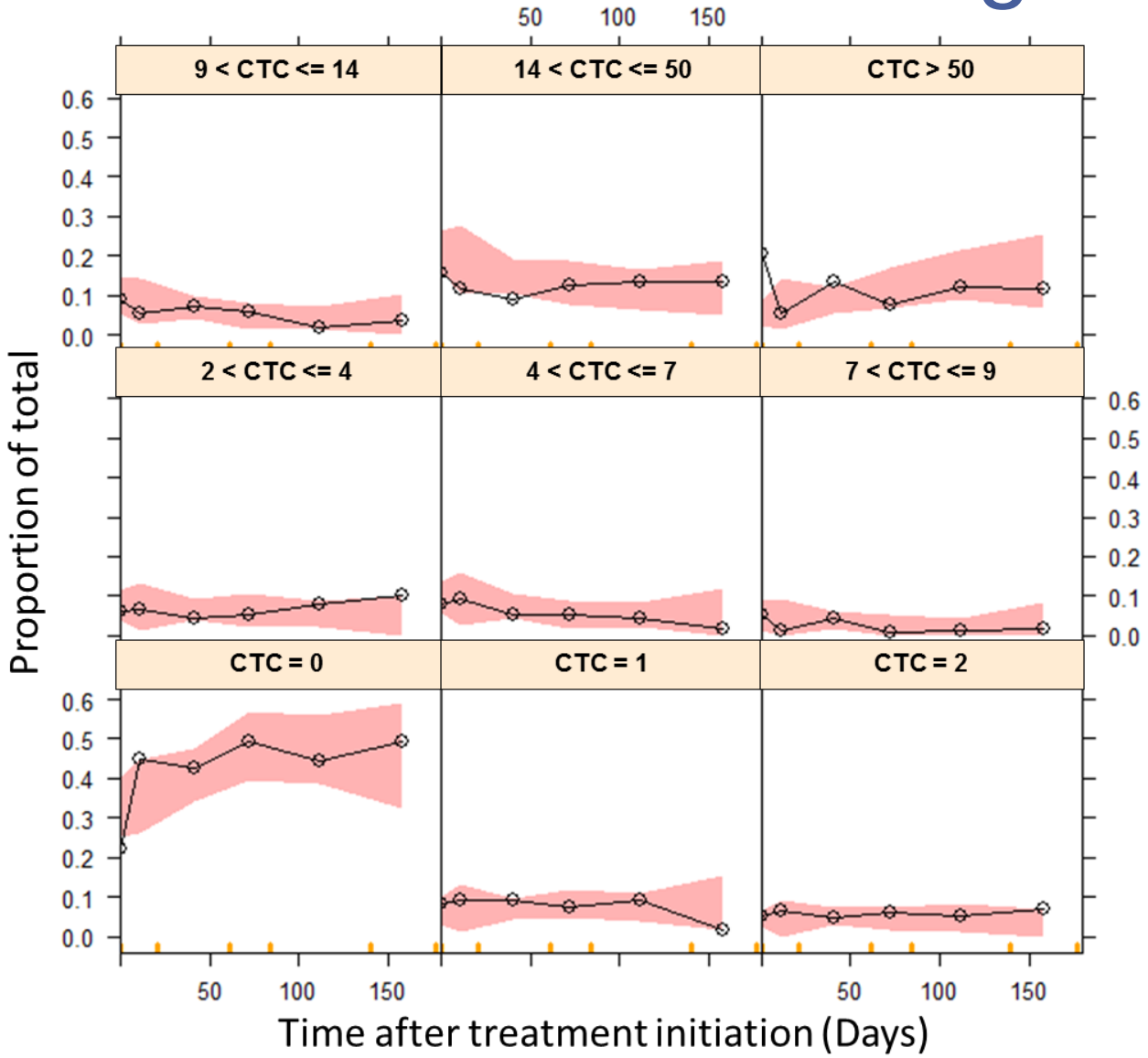
Individual predictions VS Observations



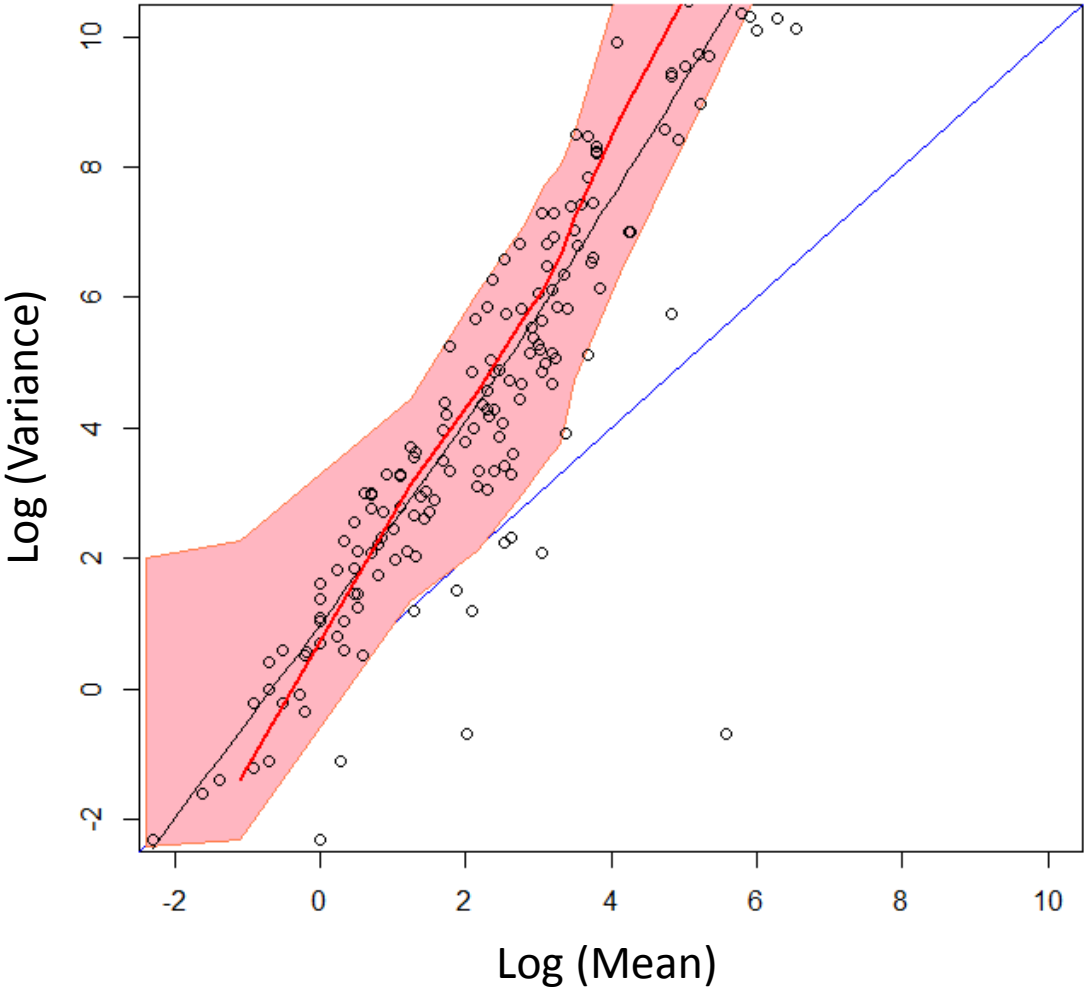
Visual Predictive Check (VPC)



CTC Evaluation: Categorical VPCs

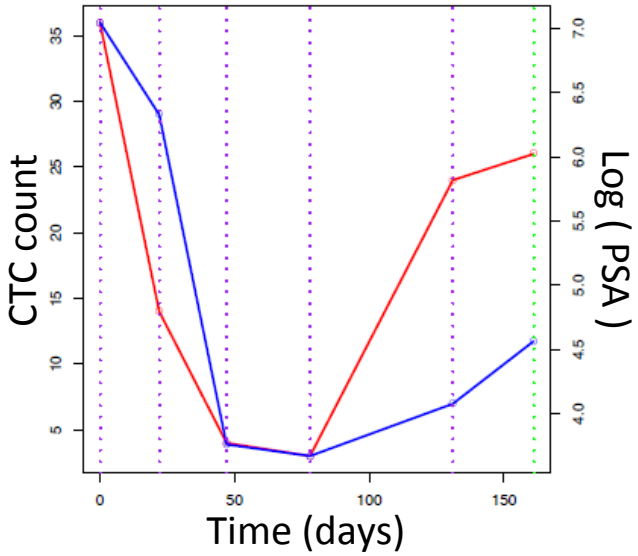


CTC Evaluation: Overdispersion VPC



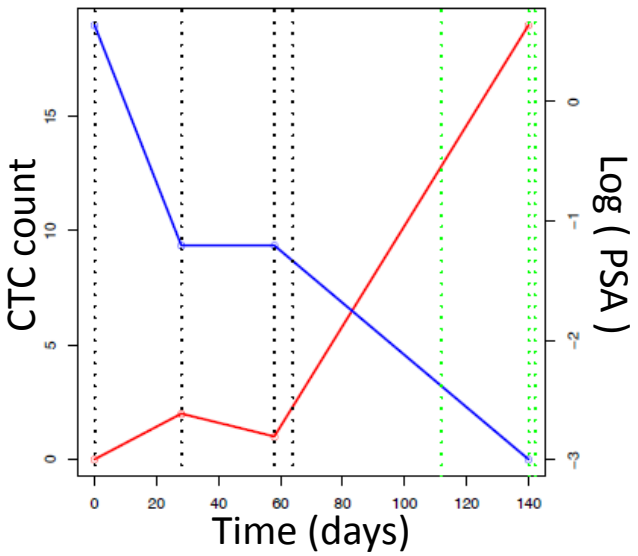
Identity line
Simulated median
Simulated 95% predicted interval
Observations

Observed individual kinetic profile #1



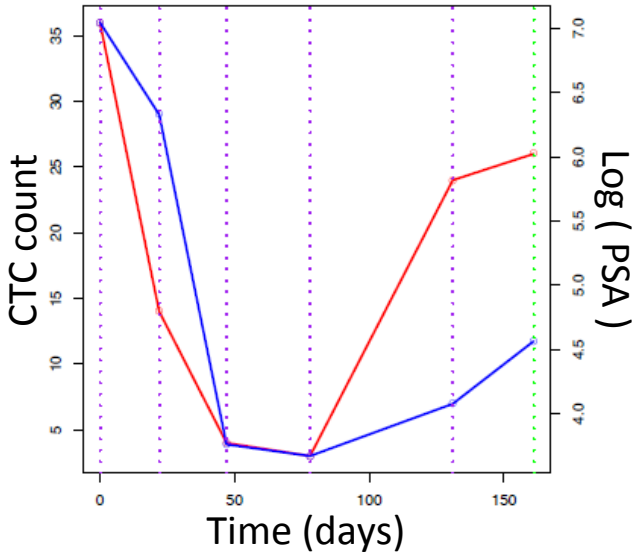
PSA kinetics
CTC count kinetics
Chemotherapy
Hormonotherapy
Both treatment
Latent variable kinetics

Observed individual kinetic profile #2



→ **Large heterogeneity in the types of observed individual kinetics profiles**

Observed individual kinetic profile #1



PSA kinetics
CTC count kinetics
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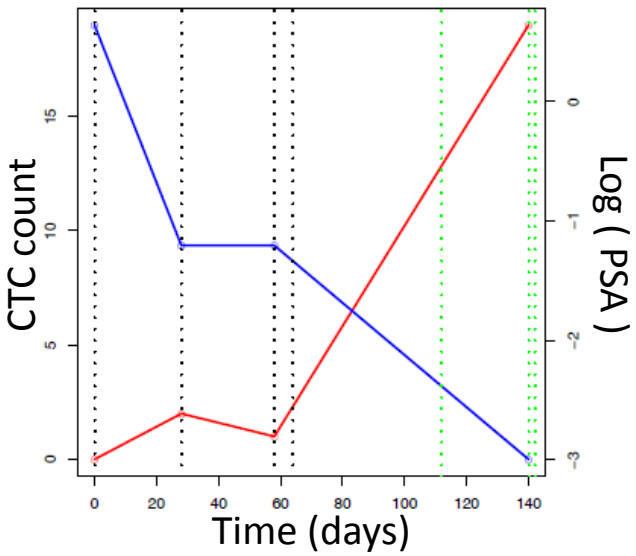
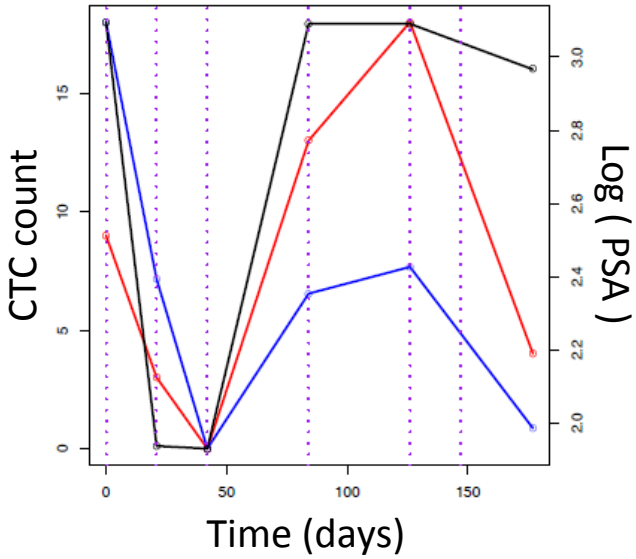
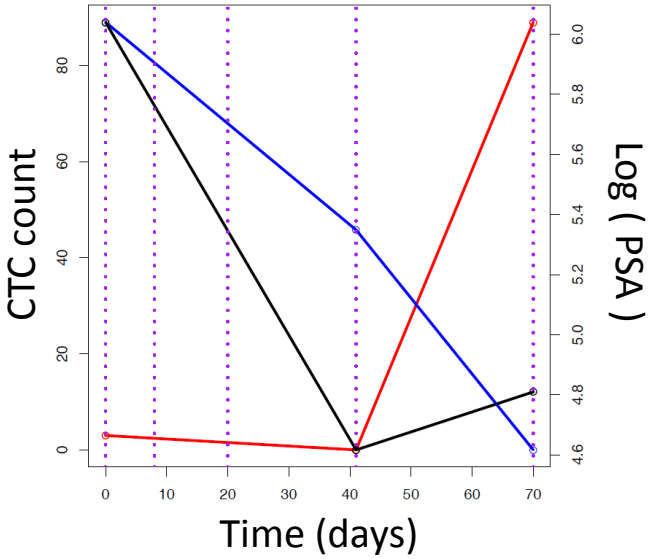
Observed individual kinetic profile #2



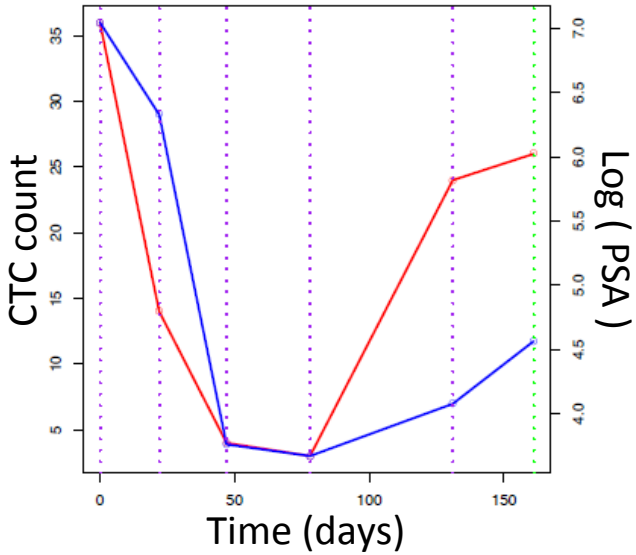
Simulated individual kinetic profile #3



Simulated individual kinetic profile #4

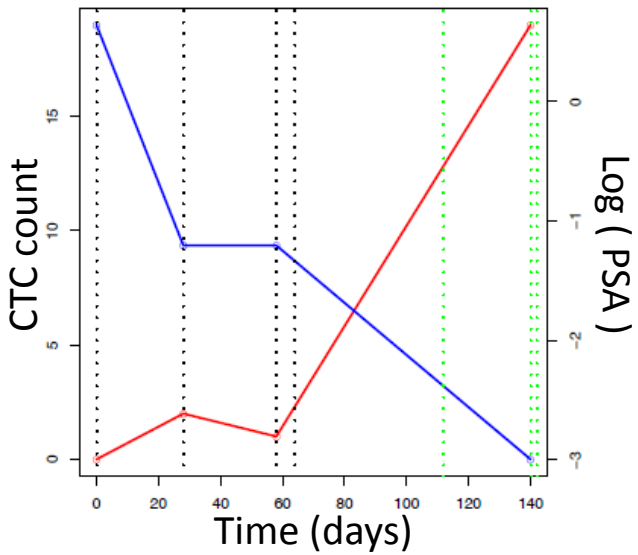


Observed individual kinetic profile #1

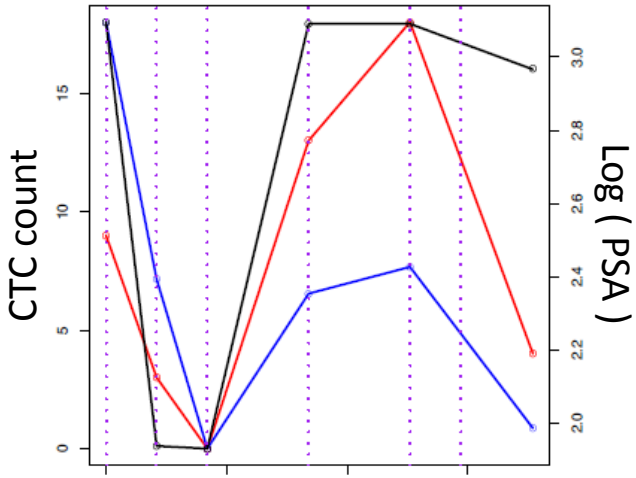


PSA kinetics
CTC count kinetics
Chemotherapy
Hormonotherapy
Both treatment
Latent variable kinetics

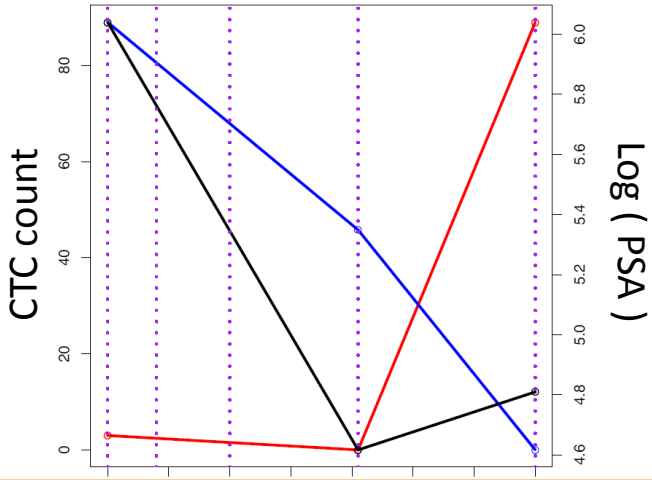
Observed individual kinetic profile #2



Simulated individual kinetic profile #3



Simulated individual kinetic profile #4



→ **Simulations of different types of individual kinetic profiles similarly to those observed**

Parameter estimates

- Relative standard errors all less than 13 %

→ **Satisfactory precision** in the estimations

- **Large inter individual variability** (IIV)

→ Supported by the data. No available covariates.

- $Q50_{Chemo} = 0.0006 < Q50_{Hormo} = 0.04$

→ Chemotherapy had a **greater inhibiting potency**

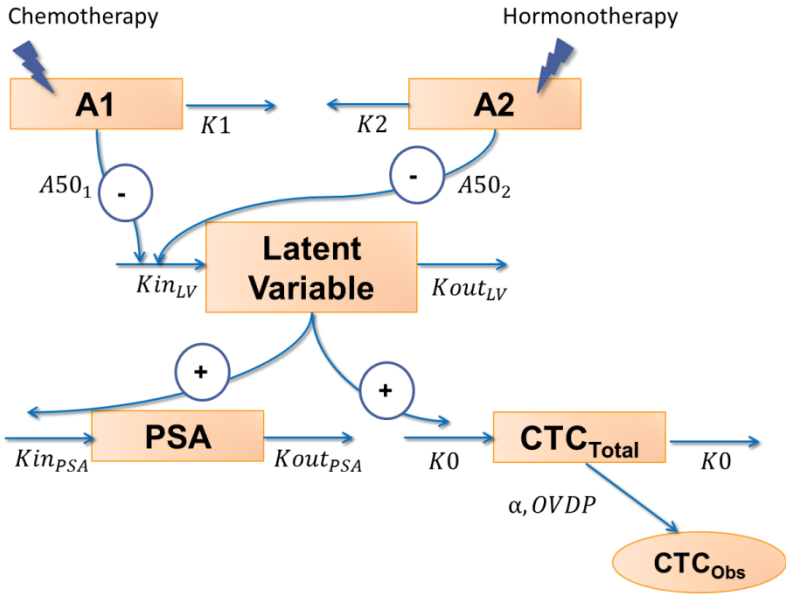
- PSA half-life = 98 days

- CTC lifespan = 114 days (CV=15%)

DISCUSSION & CONCLUSIONS

Discussion

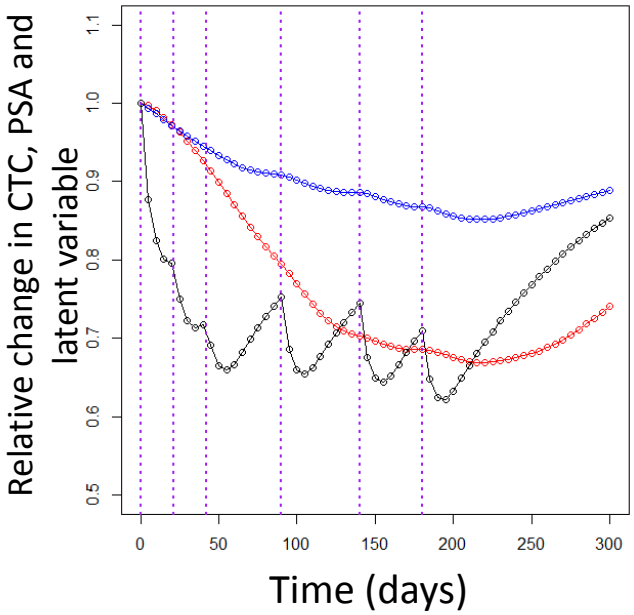
- An **atypical model** combining several advanced features in pharmacometrics:
  - K-PD modeling for each treatment type
  - Latent variable: tumor burden producing PSA and CTC
  - Joint modeling of count and continuous data
  - Cell life span model
  - Negative binomial distribution for the CTC random sampling process



- First model quantifying the **dynamic relationships** between the kinetics of PSA and CTC count in treated mCRPC patients

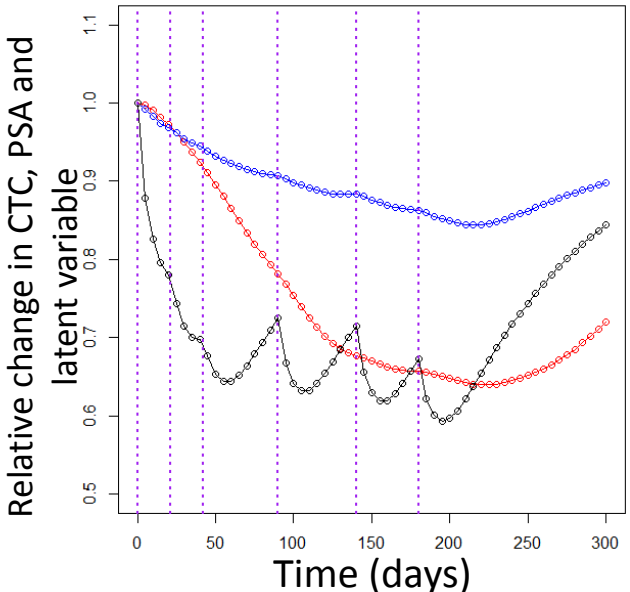
Typical simulated kinetic profiles

Typical patient receiving chemotherapy

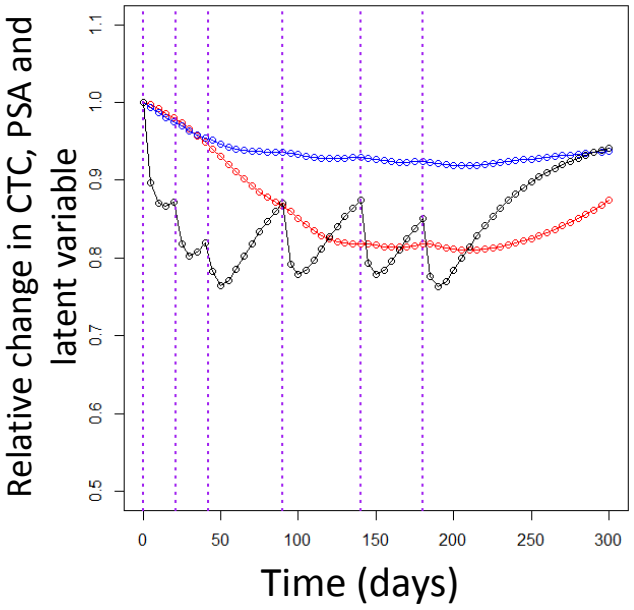


PSA kinetics
CTC count kinetics
Latent variable kinetics
Treatment cycle

Typical patient receiving both

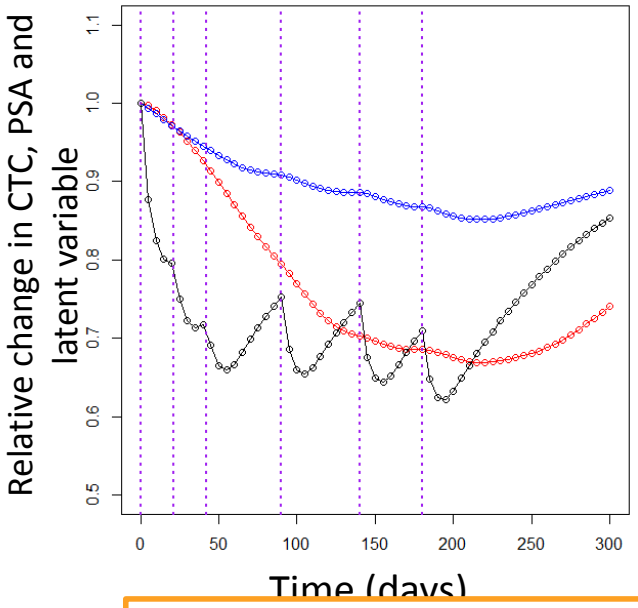


Typical patient receiving hormonotherapy



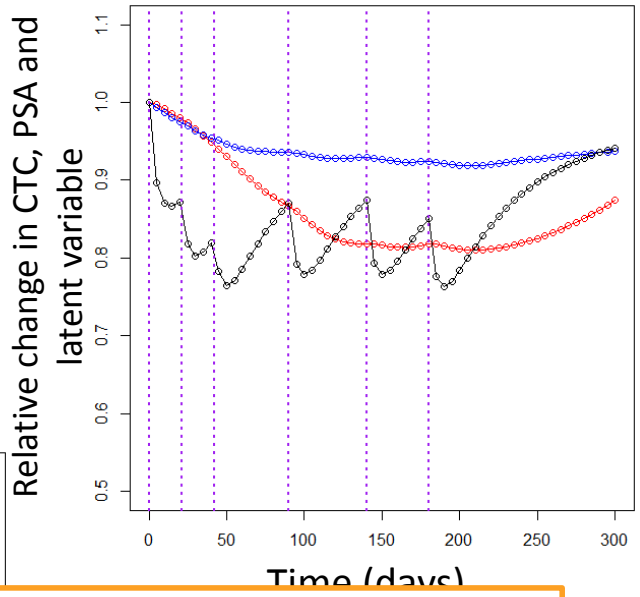
Typical simulated kinetic profiles

Typical patient receiving chemotherapy

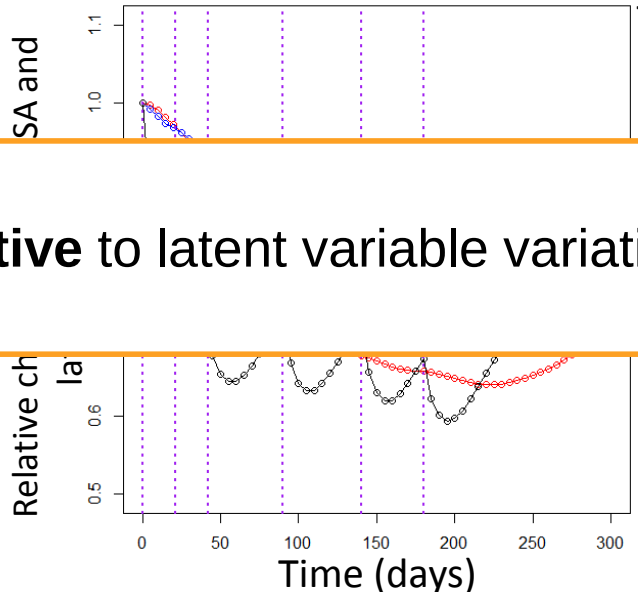


PSA kinetics
CTC count kinetics
Latent variable kinetics
Treatment cycle

Typical patient receiving hormonotherapy

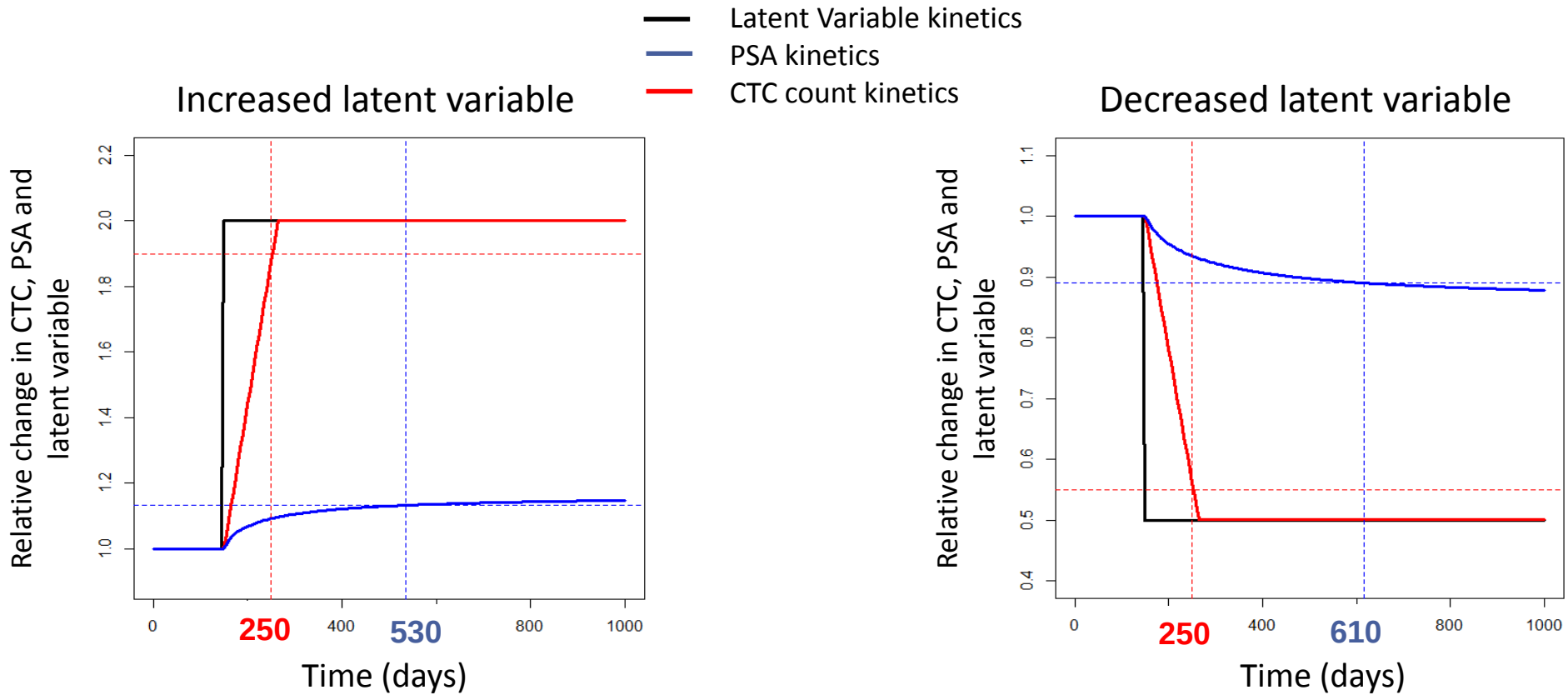


Typical patient receiving both



→ **CTC more sensitive** to latent variable variations compared to PSA

PSA & CTC kinetics sensitivity



→ **CTC more sensitive** to latent variable variations compared to PSA

→ **CTC kinetics faster** than PSA kinetics

Perspectives and Applications

- **To establish** a link between a CTC kinetic parameter and survival (OS or PFS)
- **To compare** the sensitivity and specificity of PSA and CTC count for predicting treatment efficacy
- **To identify** some covariates explaining the variability

→ To predict treatment efficacy during drug development or for therapeutic adjustment in treated mCRPC patients

Thank you !


PAGE
Population Approach
Group Europe


UCBL
Lyon 1


CTO
EMR 3738
UNIV. LYON I

BACKSLIDES

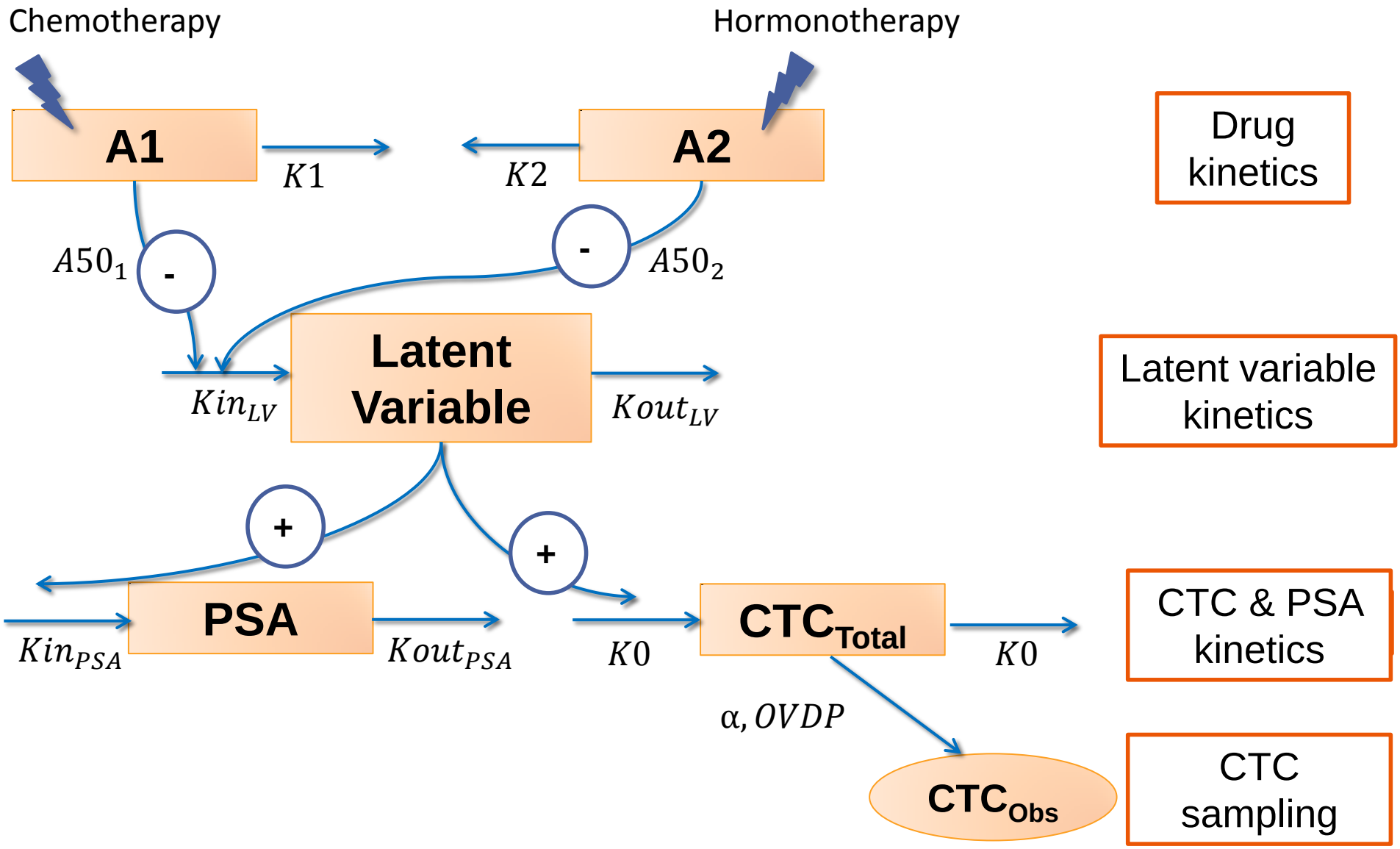
Patient characteristics (1)

Patient characteristics	Data
Number of patients	223
Total Number of CTC observations	919
CTC count value	2 [0 – 6 437]
Baseline CTC count	7 [0 – 5 925]
Number of CTC count = 0	365 (40%)
Number of CTC observations per patient	4 [2 - 6]
Total Number of PSA observations	928
PSA concentration ($ng.mL^{-1}$)	116 [LOQ – 17 800]
Baseline PSA concentration ($ng.mL^{-1}$)	130 [2 – 17 800]
Number of BLQ values of PSA	1 (0.11%)
Number of PSA observation per patient	4 [1 - 6]
Follow-up time (days)	124 [21 - 177]
Number of treatment cycles	5 [2 - 10]

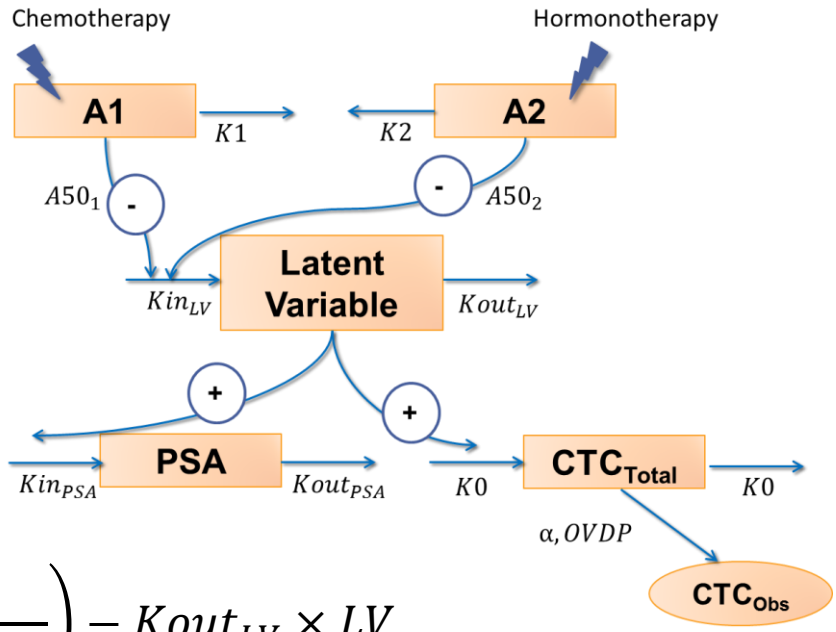
Patient characteristics (2)

Patient characteristics	Data
XRT before T0: Yes No	142 (63%) 82 (37%)
Radical Prostatectomy before T0: Yes No	63 (28%) 161 (72%)
Bisphosphonates before T0: Yes No	15 (7%) 209 (93%)
Corticotherapy before T0: Yes No	48 (21%) 176 (79%)
Ketocenazole before T0: Yes No	44 (20%) 180 (80%)
Type of chemotherapy at T0: Taxanes Other	164 (73%) 60 (27%)
Type of hormonotherapy at T0: 0 An GnRH An GnRH + Anti andro An GnRH + Oestro Anti andro Oestro	45 (20.1%) 170 (75.9%) 1 (0.4%) 6 (2.8%) 1 (0.4%) 1 (0.4%)
Line of chemotherapy at T0: 1 2 >2	148 (66%) 39 (17%) 37 (17%)
Line of hormonotherapy: 1 2 3 >3	53 (24%) 101 (45%) 42 (19%) 28 (12%)

Model


Chemotherapy
Hormonotherapy
A1
A2
K1
K2
A50₁
A50₂
-
-
Latent Variable
Kin_LV
Kout_LV
+
+
PSA
Kin_PSA
Kout_PSA
K0
CTC_Total
K0
α, OVDP
CTC_Obs
Drug kinetics
Latent variable kinetics
CTC & PSA kinetics
CTC sampling

Model Equations



$$\begin{cases} \dfrac{dA1}{dt} = -K1 \times A1 \\ \dfrac{dA2}{dt} = -K2 \times A2 \\ \dfrac{dLV}{dt} = Kin_{LV} \times \left(1 - \dfrac{A1}{Q50_1 + A1}\right) \times \left(1 - \dfrac{A2}{Q50_2 + A2}\right) - Kout_{LV} \times LV \\ \dfrac{dPSA}{dt} = Kin_{PSA} \times LV - Kout_{PSA} \times PSA \\ \dfrac{dCTC_{Total}}{dt} = K0 \times LV - K0 \times LVD \end{cases}$$

$$\begin{cases} A1(0) = 0 \\ A2(0) = 0 \\ LV(0) = LV_0 = 1 \; FIX \;\; with \; LV_0 < \dfrac{Kin_{LV}}{Kout_{LV}} \\ PSA(0) = PSA_0 \\ CTC_{Total}(0) = K0 \times LS \times LV_0 \end{cases}$$

Latent Variable Condition

$$LV(0) = LV_0 \;\; with \; LV_0 < \frac{Kin_{LV}}{Kout_{LV}}$$

→ To allow the latent variable to increase

→ Use of the Logit function:

$$LV_0 = \frac{Kin_{LV}}{Kout_{LV}} \times \frac{exp(THETA + ETA)}{1 + \exp(THETA + ETA)}$$

→ Applying on KinLV:

$$Kin_{LV} = \frac{LV_0 \times Kout_{LV}}{\frac{exp(THETA + ETA)}{1 + \exp(THETA + ETA)}}$$

Negative Binomial Distribution

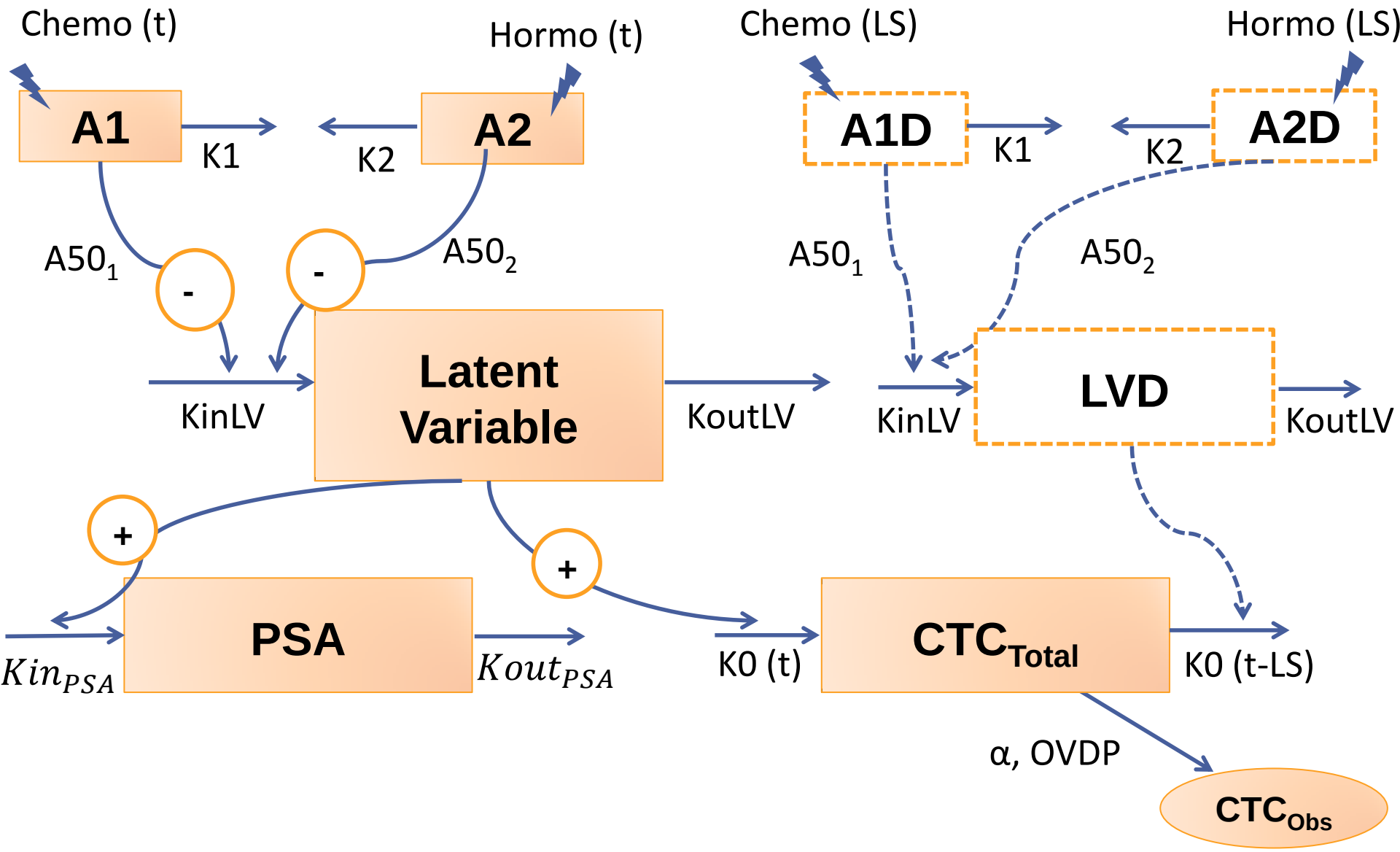
Equation:

$$P(CTC_{Obs} = n) = \left[\frac{\Gamma(n + \frac{1}{OVDP})}{n! \times \Gamma(\frac{1}{OVDP})}\right] \times \left(\frac{1}{1 + OVDP \times \lambda}\right)^{\frac{1}{OVDP}} \times \left(\frac{\lambda}{\frac{1}{OVDP} + \lambda}\right)^{n}$$

Γ and n! are the Gamma and Factorial functions. OVDP is the overdispersion parameter, allowing to estimate a variance greater than the mean.
The variance of the negative binomial model is equal to:

$$Var = \lambda \times (1 + OVDP \times \lambda)$$

Model with delayed compartments



Model equations with delayed compartments

$$
\begin{cases}
\dfrac{dA1}{dt} = -K1 \times A1 \\
\dfrac{dA2}{dt} = -K2 \times A2 \\
\dfrac{dLV}{dt} = Kin_{LV} \times \left(1 - \dfrac{A1}{Q50_1 + A1}\right) \times \left(1 - \dfrac{A2}{Q50_2 + A2}\right) - Kout_{LV} \times LV \\
\dfrac{dA1D}{dt} = -K1 \times A1D \\
\dfrac{dA2D}{dt} = -K2 \times A2D \\
\dfrac{dLVD}{dt} = Kin_{LV} \times \left(1 - \dfrac{A1D}{Q50_1 + A1D}\right) \times \left(1 - \dfrac{A2D}{Q50_2 + A2D}\right) - Kout_{LV} \times LVD \\
\dfrac{dCTC}{dt} = K0 \times LV - K0 \times LVD \\
\dfrac{dPSA}{dt} = Kin_{PSA} \times LV - Kout_{PSA} \times PSA
\end{cases}
$$

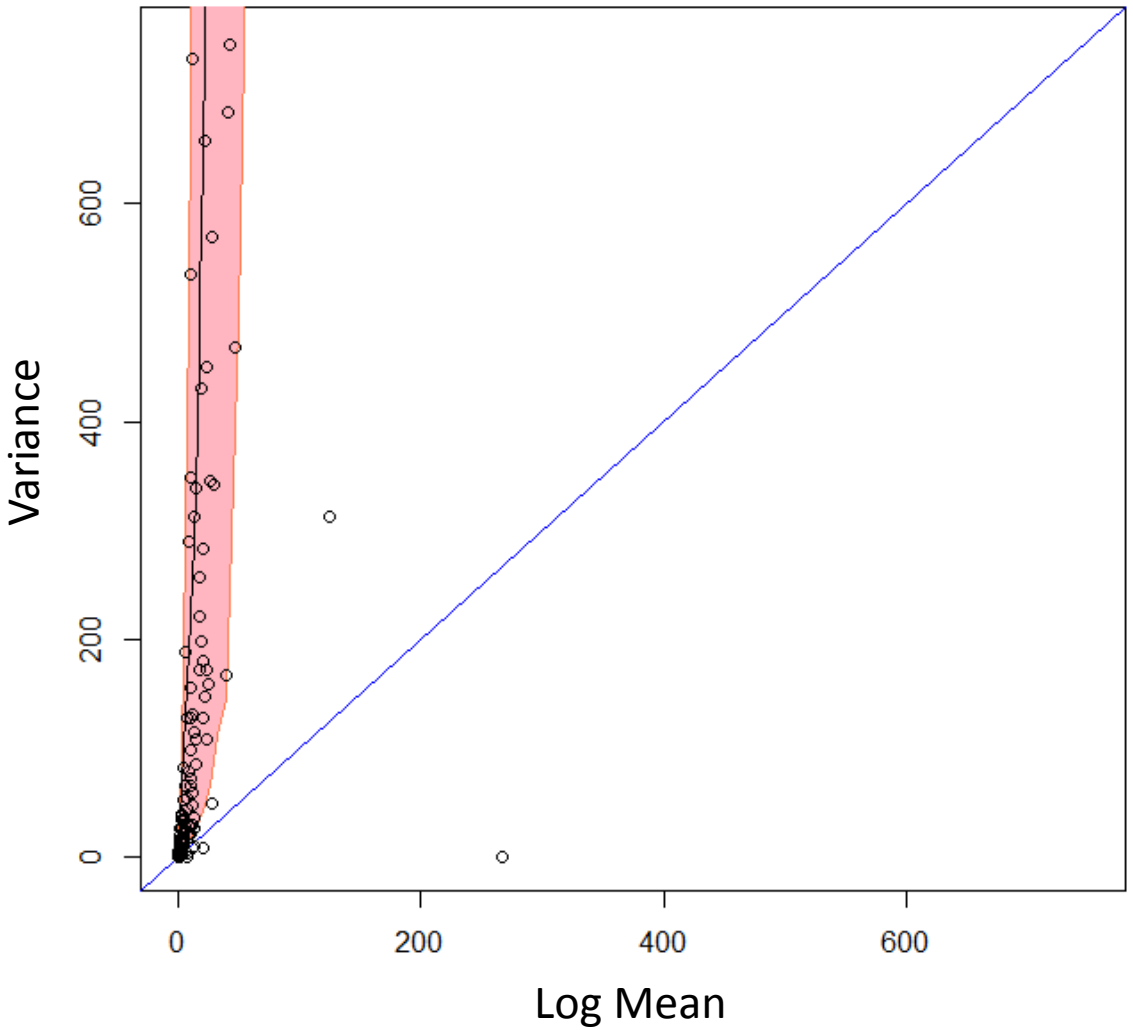
Conditions initiales:

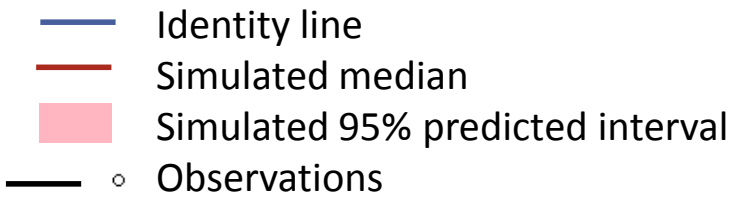
$$
\begin{aligned}
A1(0) &= 0 \\
A2(0) &= 0 \\
\text{LV}(0) &= LV0 = 1 \text{ FIX} \\
F4 &= K0 \times LS5 \\
LS6 &= LS5 \\
LS7 &= LS5
\end{aligned}
\qquad
\begin{aligned}
A1D(0) &= 0 \\
A2D(0) &= 0 \\
LVD(0) &= LV0 \\
PSA(0) &= PSA0
\end{aligned}
$$

Parameter Estimates

Part of the model	Parameter (unit)	Estimate	RSE Estim. (%)	IIV CV (%)	RSE IIV
Drug kinetics 1: chemotherapy 2: hormonotherapy	K1 (Day^{-1})	0.595	10	126	3
	K2 (Day^{-1})	0.456	8	114	3
	$Q50_1$ (AU)	0.0006	6	114	8
	$Q50_2$ (AU)	0.0433	11	105	1
Latent variable kinetics	LV0 (AU)	1 FIX	/	0 FIX	/
	$Kout_{LV}$ (Day^{-1})	0.00734	13	204	13
	Kin_{LV} ($AU.day^{-1}$)	8.88	1	126	6
PSA kinetics	Kin_{PSA} ($ng.mL^{-1}.day^{-1}.AU^{-1}$)	1.04	5	155	5
	$Kout_{PSA}$ (Day^{-1})	0.0071	7	145	4
	PSA0 ($ng.mL^{-1}$)	150	5	152	2
CTC kinetics	K0 ($CTC.day^{-1}.AU^{-1}$)	153	0.9	11	2
	LS (Day)	114	1	15	2
CTC sampling	OVDP (AU)	5.7	4	141	1
Residual Variab	PSA Residual error	0.3		/	/

VPC Overdispersion (normal scale)





Categorical VPCs : <= 5 CTCs vs >5 CTCs