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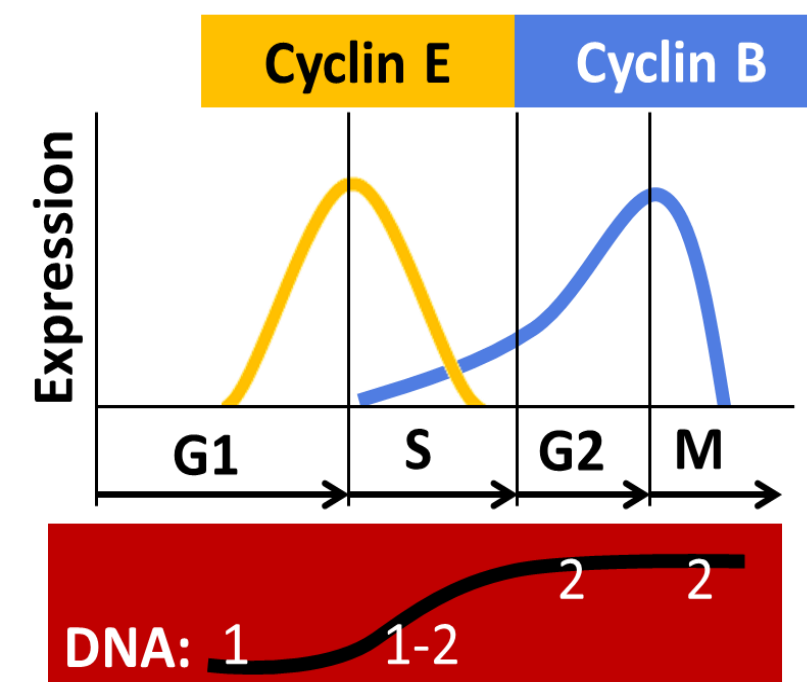
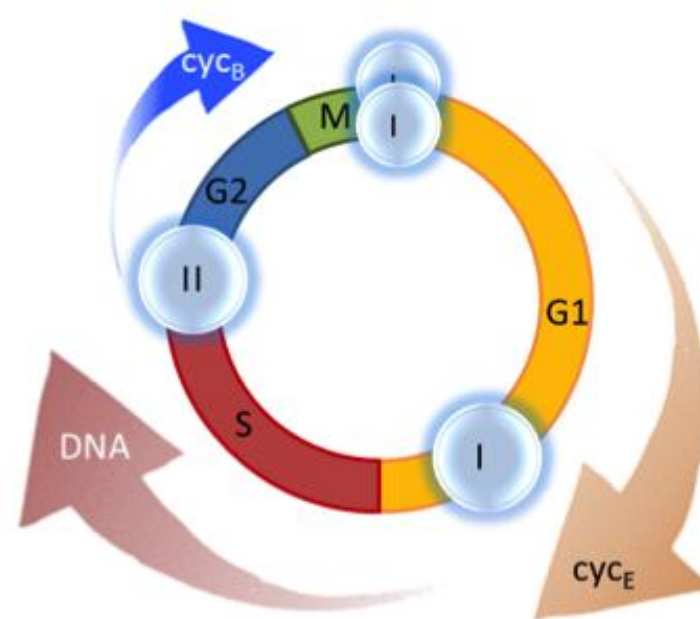
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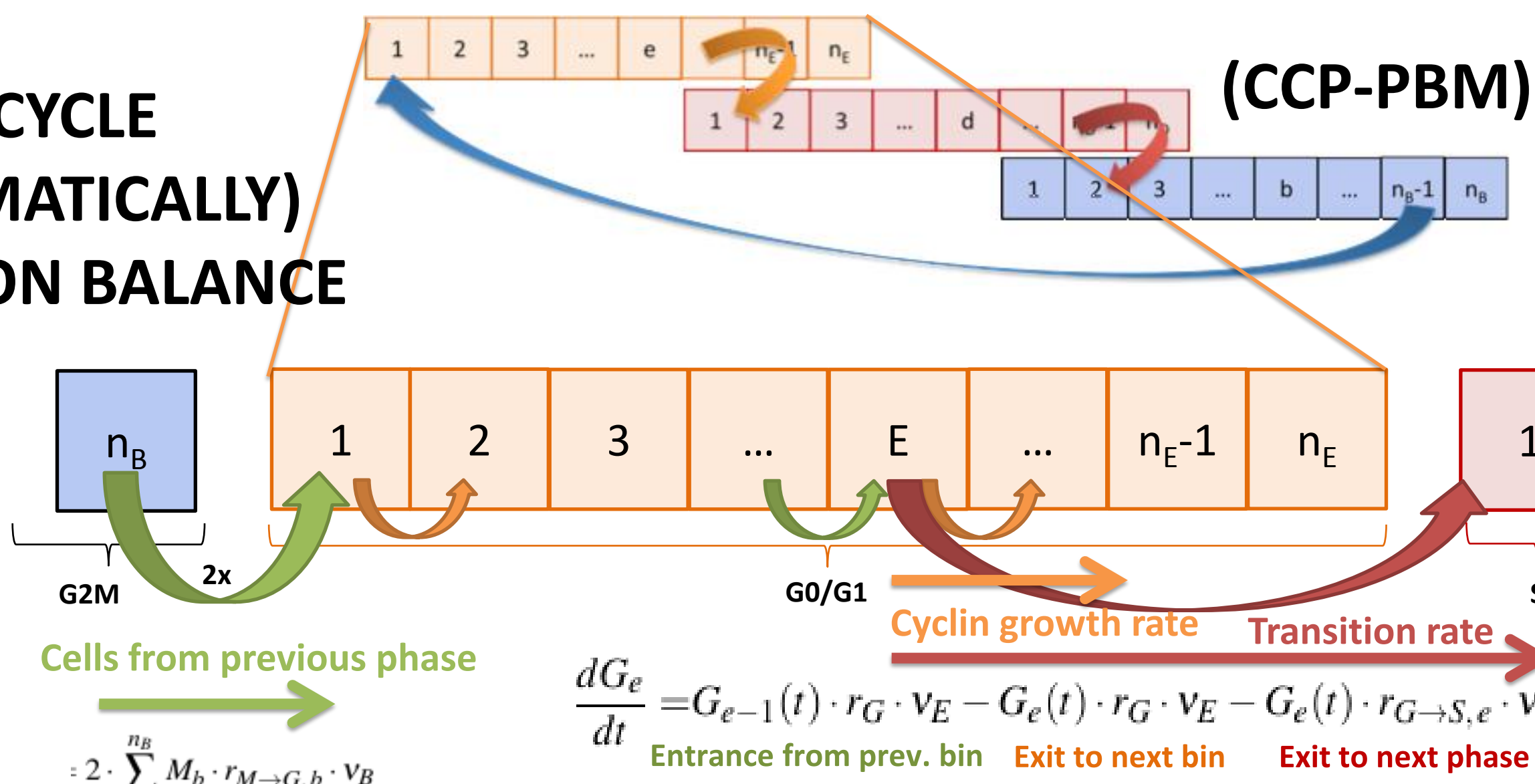
**Keywords:** pharmacokinetics, pharmacodynamics, chemotherapy optimisation, mathematical models of the cell cycle, cyclin, leukaemia heterogeneity

## AML

### CELL CYCLE (BIOLOGICALLY)



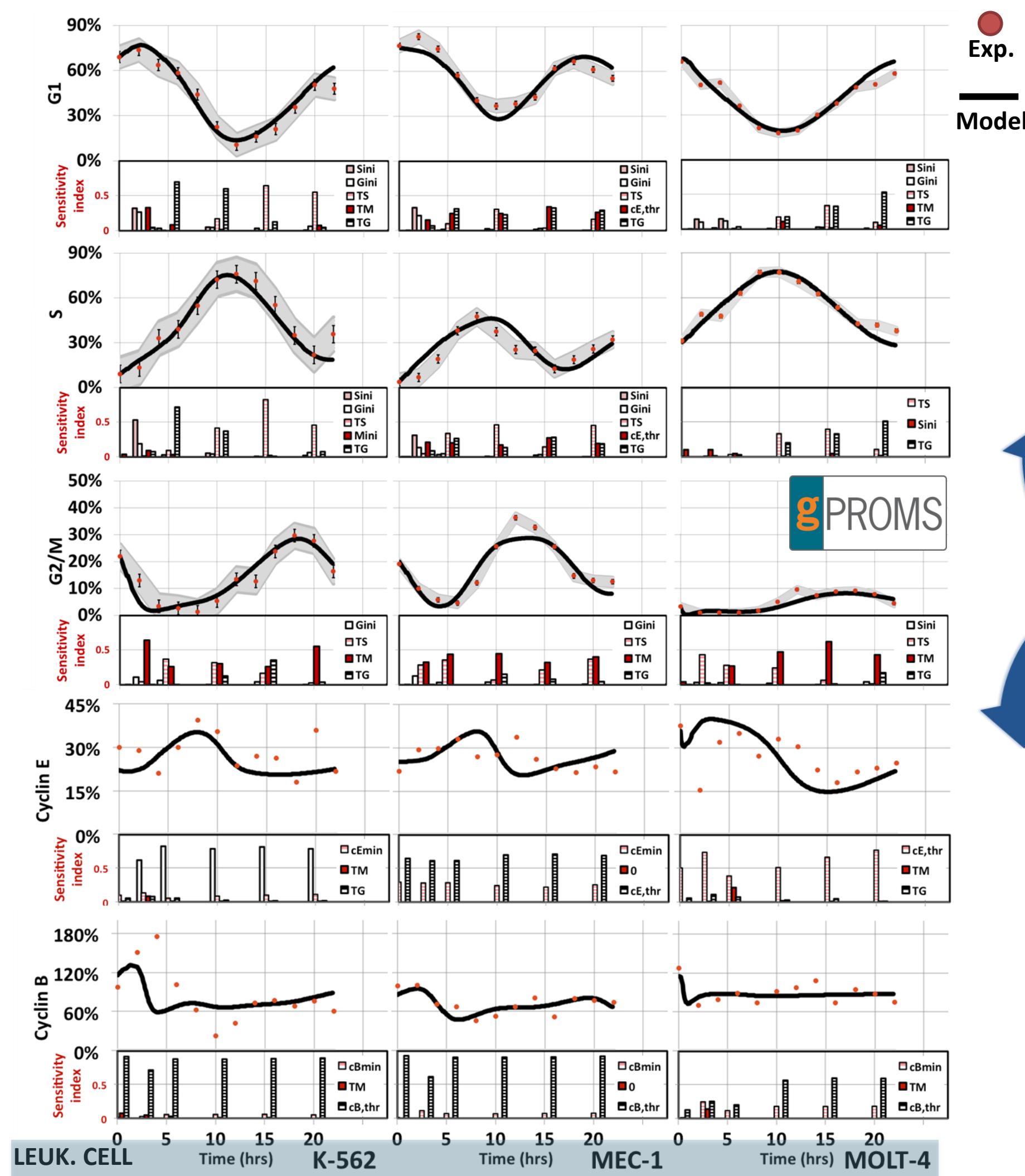
### CELL CYCLE (MATHEMATICALLY) POPULATION BALANCE



$$\frac{dG_e}{dt} = G_{e-1}(t) \cdot r_G \cdot V_E - G_e(t) \cdot r_G \cdot V_E - G_e(t) \cdot r_{G \rightarrow S} \cdot V_E$$

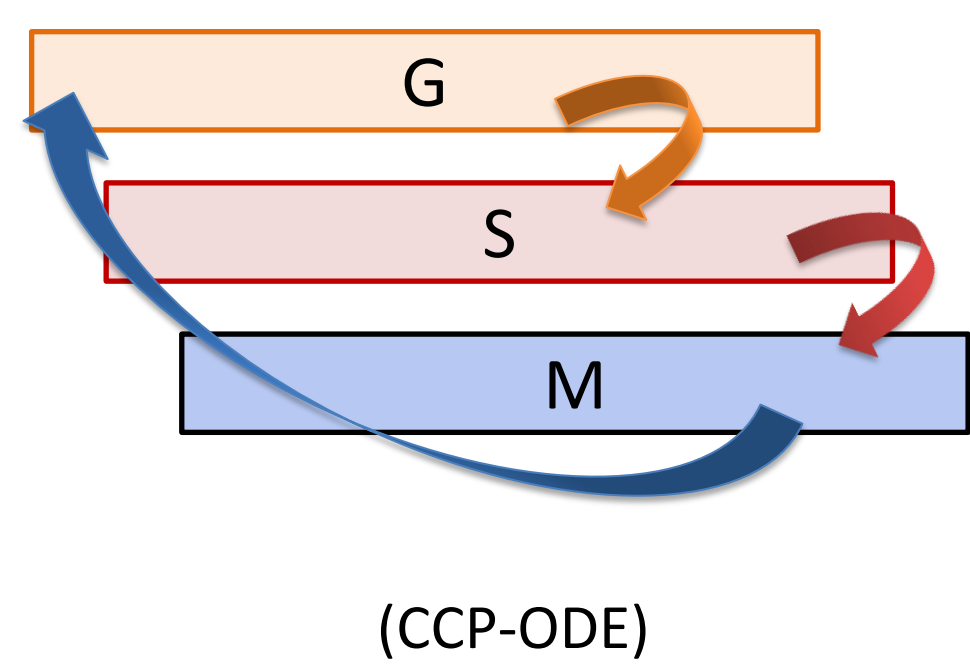
Entrance from prev. bin    Exit to next bin    Exit to next phase

## EXP. VALIDATION: 3 CELL LINES

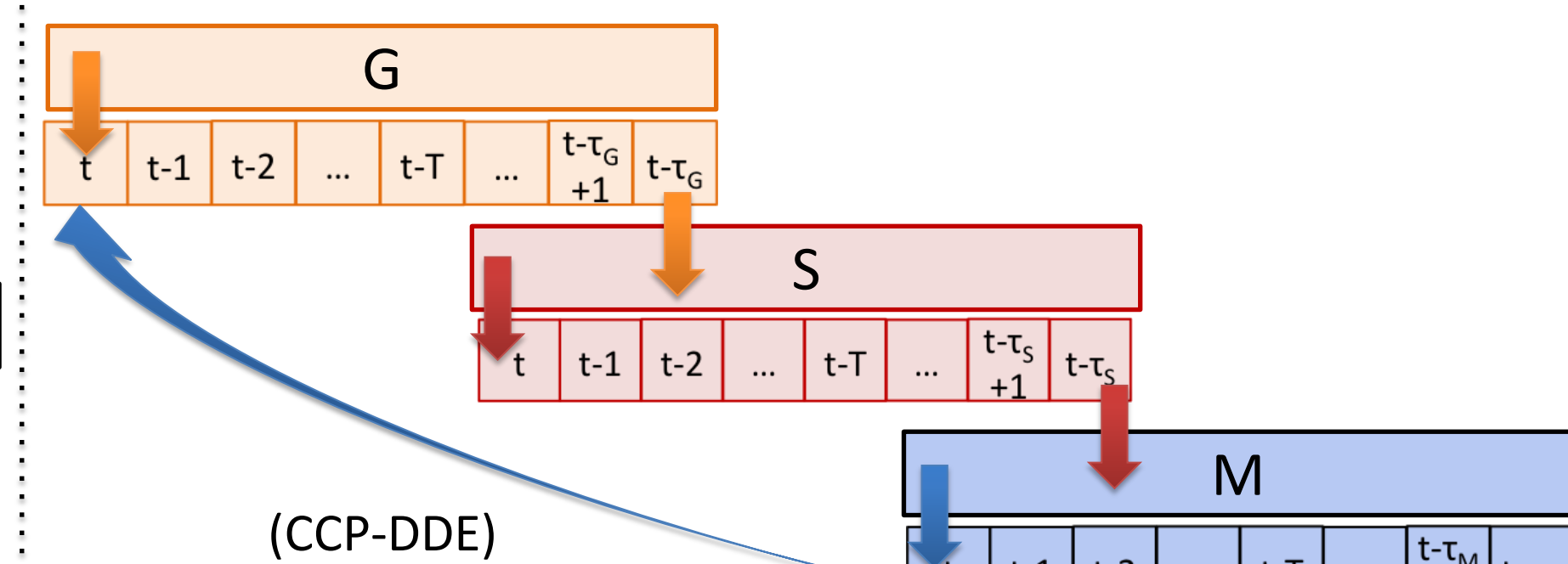


## COMPARISON WITH...

### Mass balance

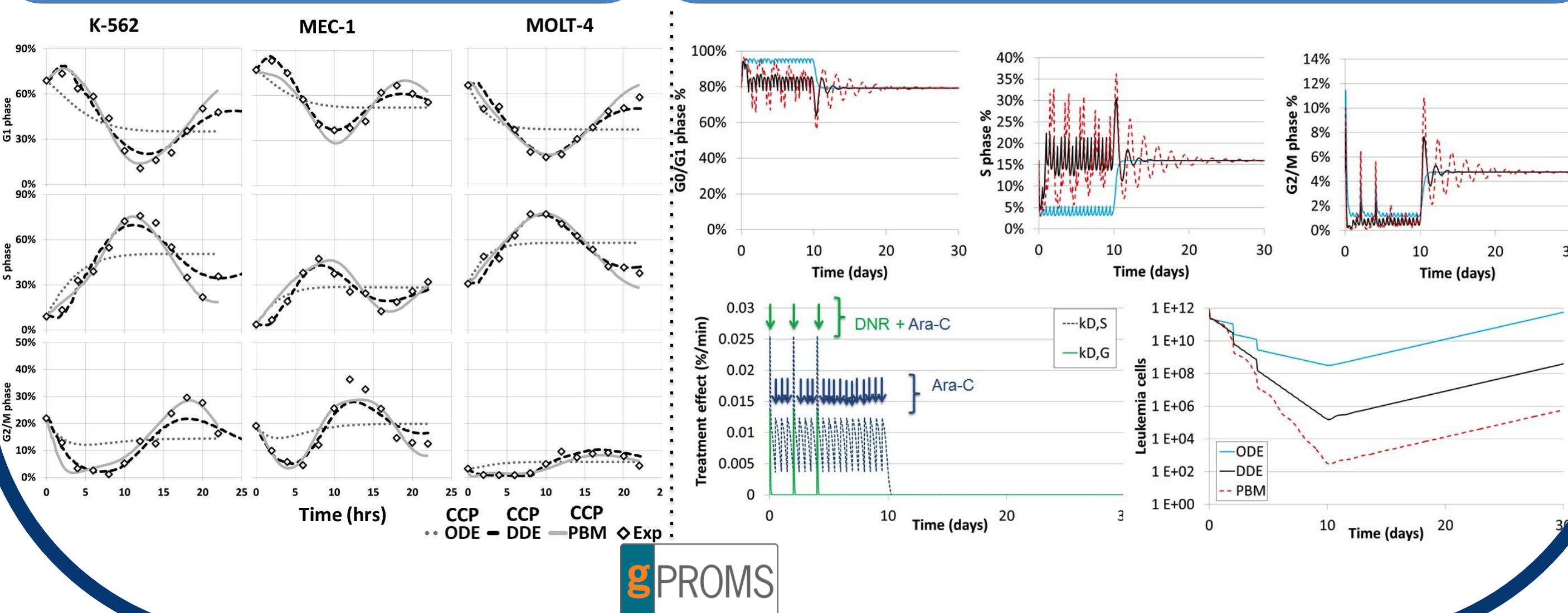


### Delay differential equations



## FITTING EXP. DATA

## SENSITIVITY TO TREATMENT



## B-CLL

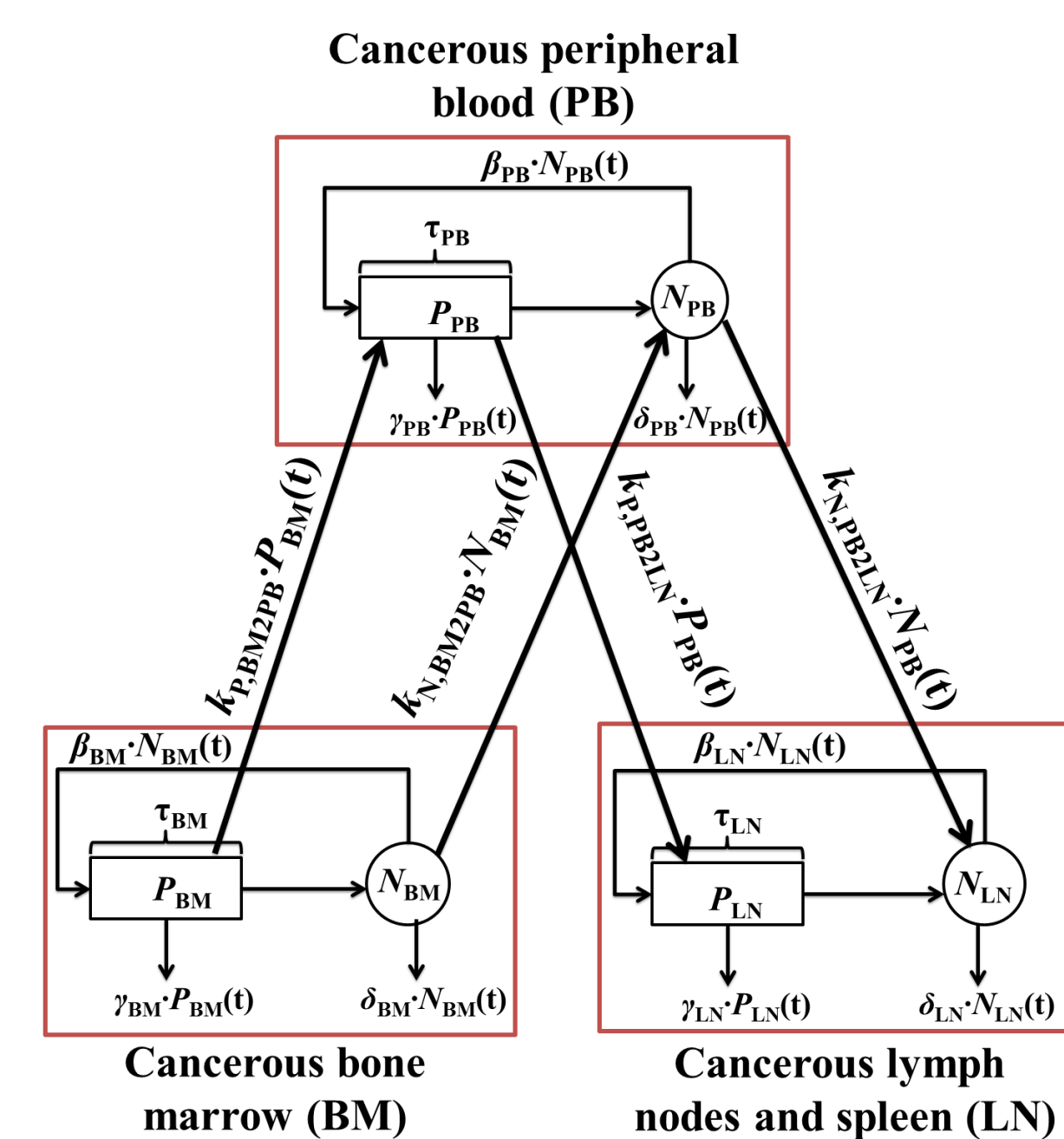
### RESEARCH MOTIVATION

- B-CLL is the most common form of leukaemia of the elderly in the western world
- Accumulation of cancerous B cells in bone marrow, peripheral blood, lymph nodes and spleen<sup>[1]</sup>
- Treatment of CLL is especially challenging as it is a heterogeneous disease<sup>[1]</sup>
- Slow progressive disease and example for par excellence for personalized treatment

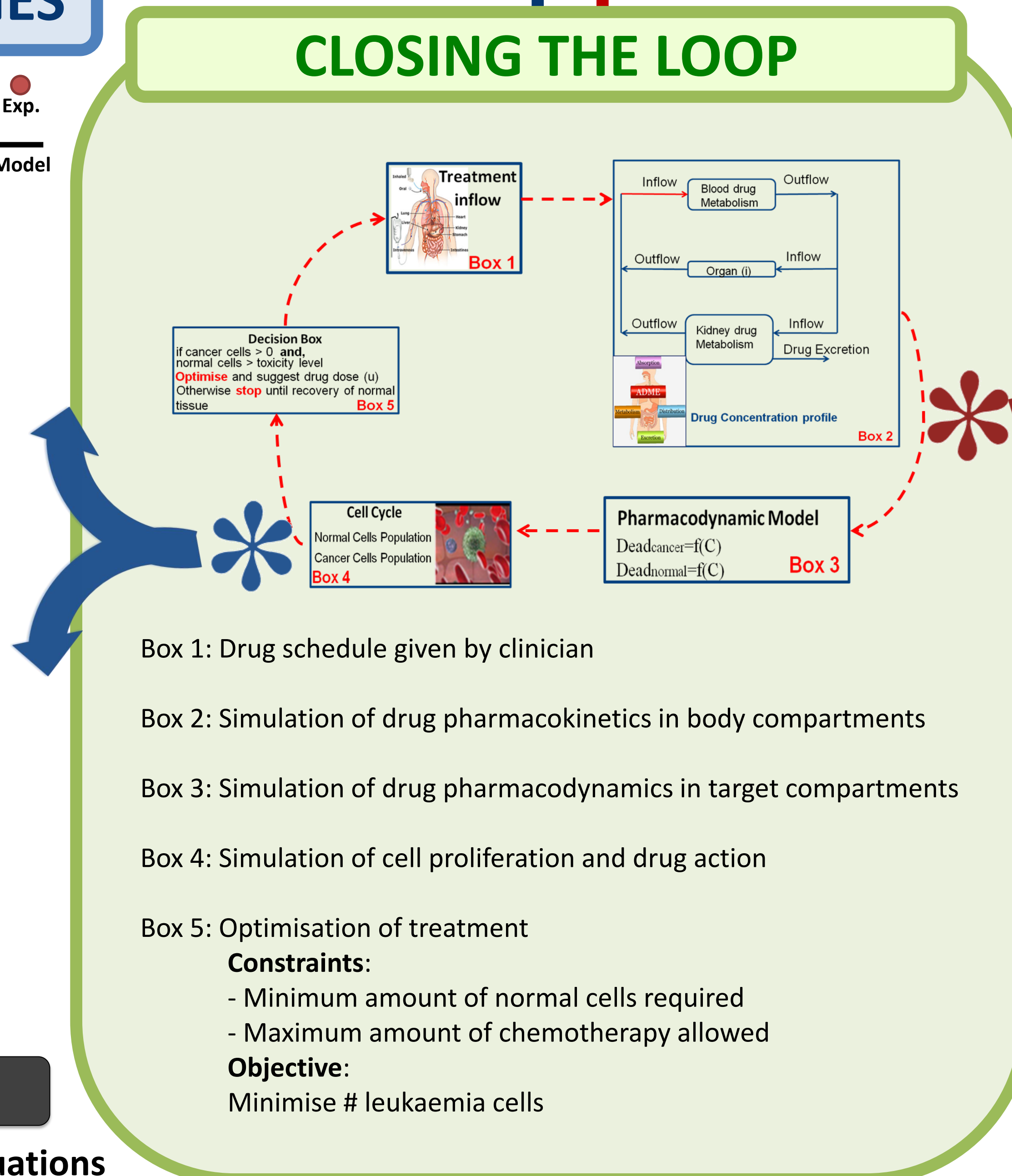
### INTRODUCTION

Objective: the development of the first physiologically-relevant dynamic mathematical model of B-CLL which:

- takes into account body compartments
- uses as input measurable parameters (e.g. bone marrow biopsy, lymphocytosis in peripheral blood)
- predicts the symptoms



## CLOSING THE LOOP



Box 1: Drug schedule given by clinician

Box 2: Simulation of drug pharmacokinetics in body compartments

Box 3: Simulation of drug pharmacodynamics in target compartments

Box 4: Simulation of cell proliferation and drug action

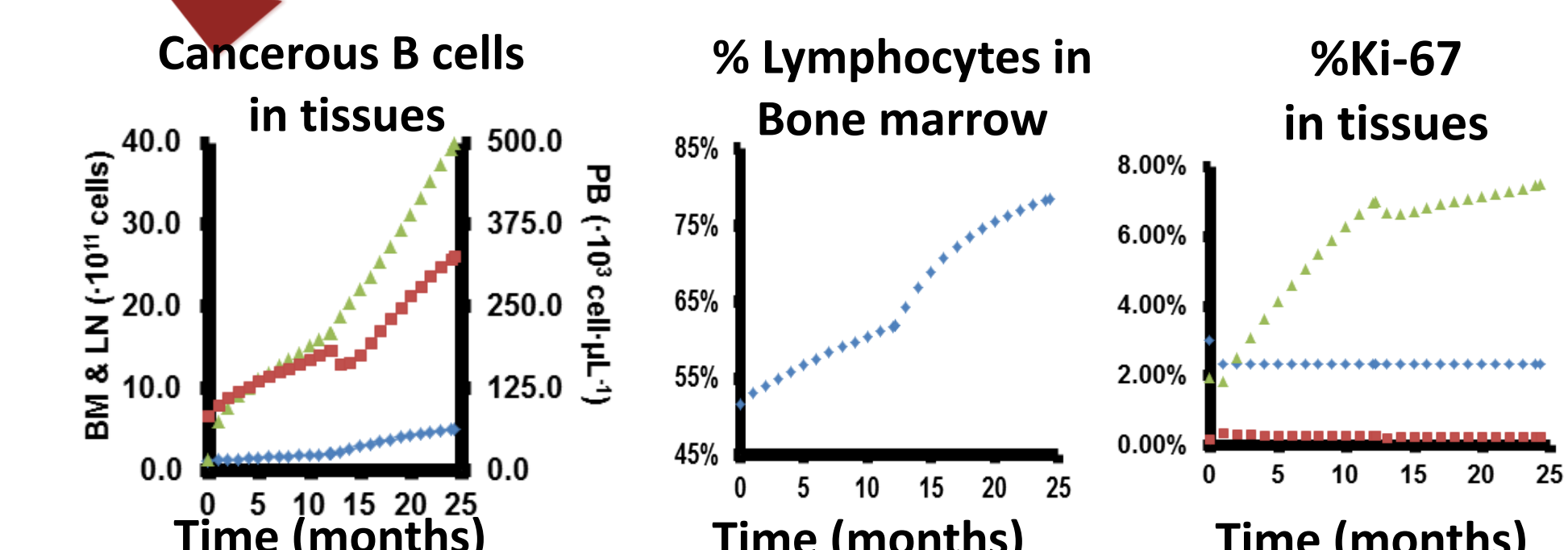
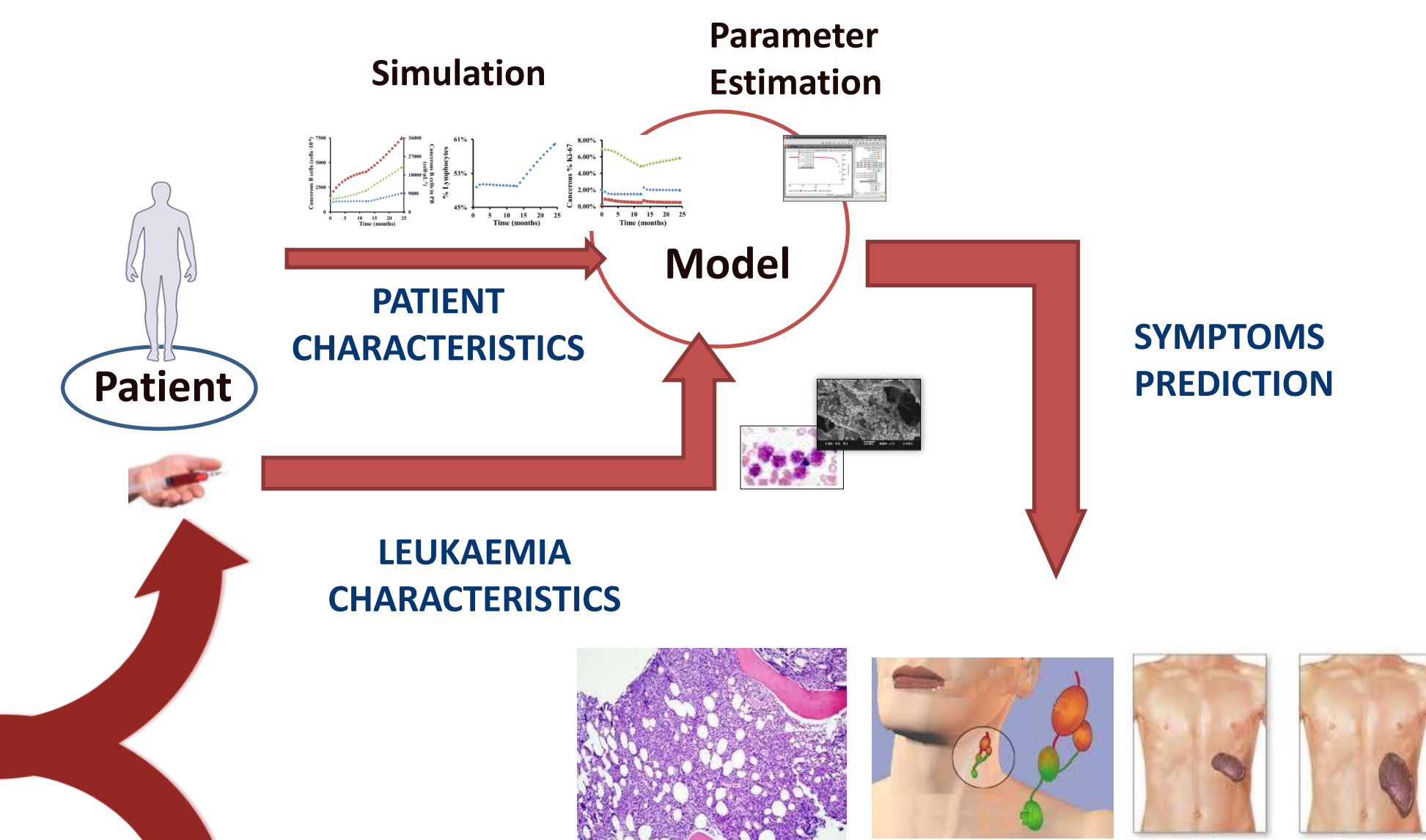
Box 5: Optimisation of treatment

#### Constraints:

- Minimum amount of normal cells required
- Maximum amount of chemotherapy allowed

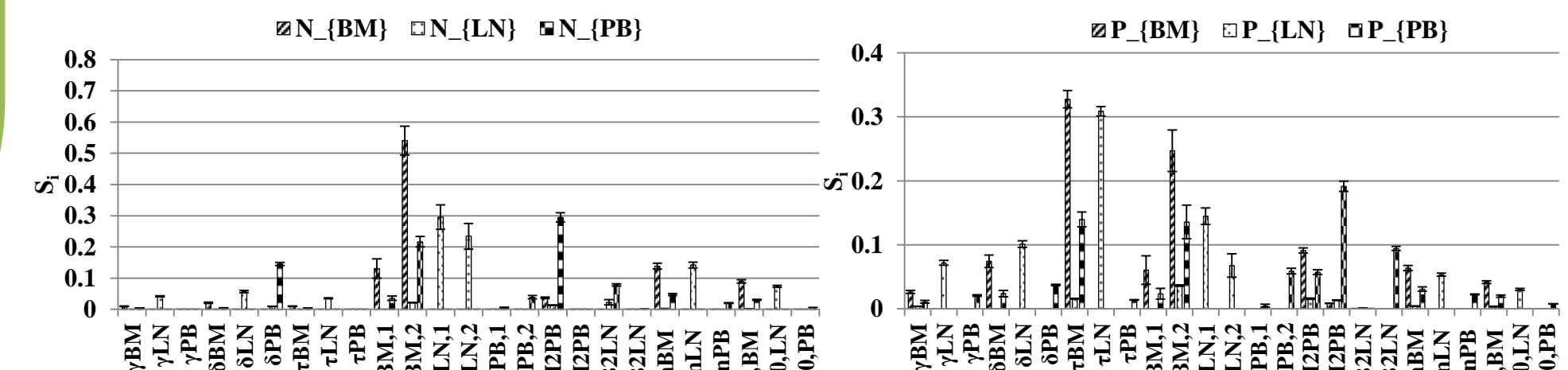
#### Objective:

Minimise # leukaemia cells



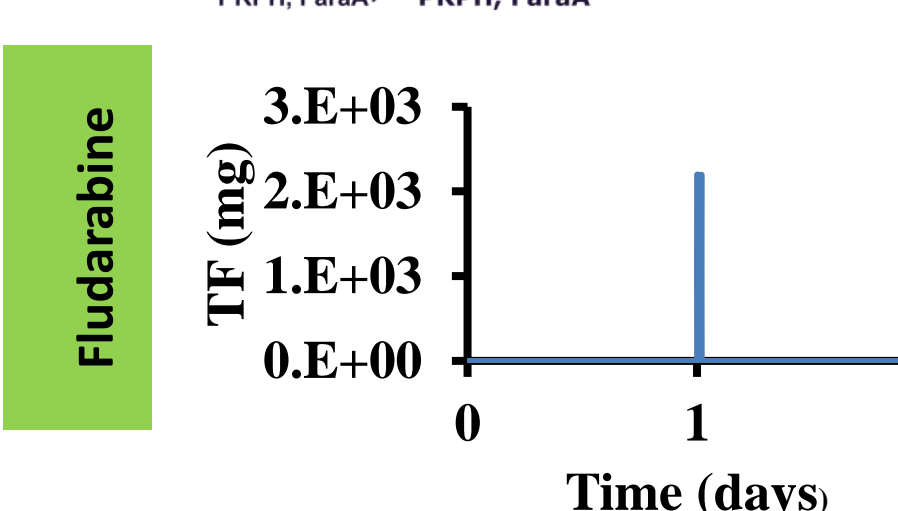
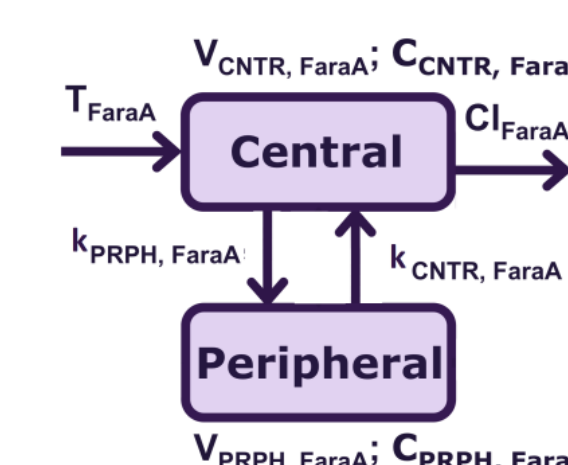
Case	Symptoms	Initially	Finally
Binet Stage B to C	Bone marrow pattern Enlarged lymph nodes Splenomegaly	Mixed Yes No	Diffuse [Diameter (cm), #] [4, 12], [5, 6], [6, 4] Mixed (7 cm x 14 cm)

### GLOBAL SENSITIVITY ANALYSIS (varying 25 parameters ± 50%)

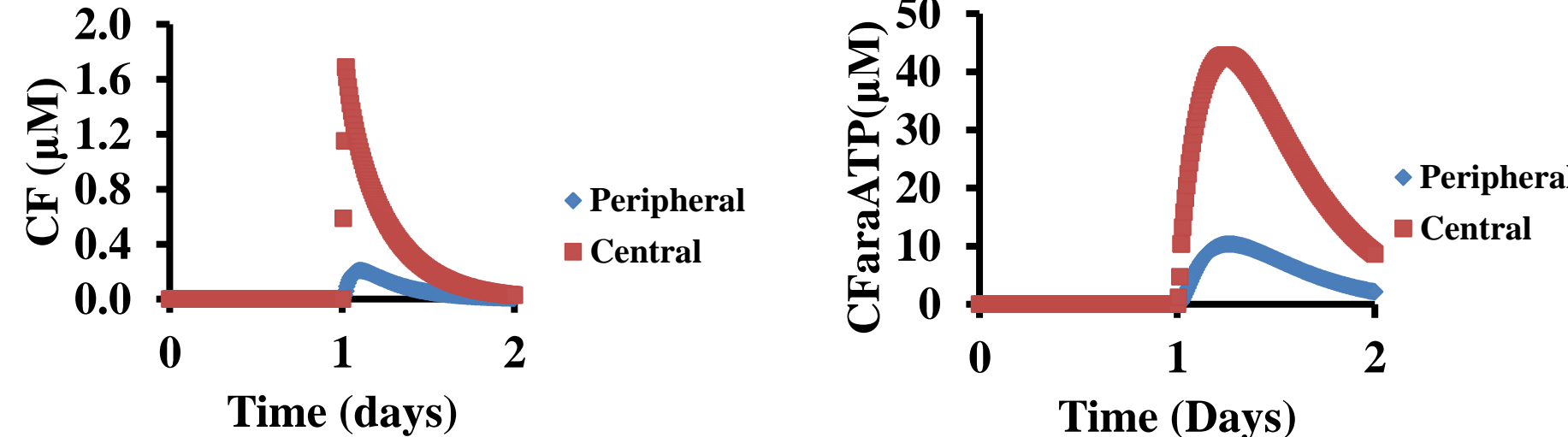
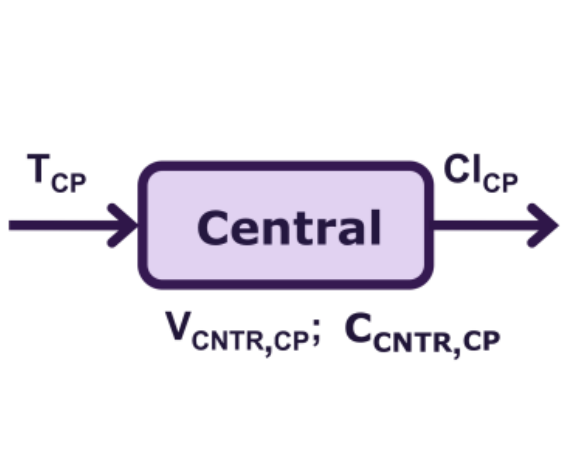


## PHARMACOKINETICS

### Fludarabine



### Cyclophosphamide



### Rituximab

