

# contrast enhancing lesions in relapsing-remitting multiple sclerosis

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## Abstract

**Background:** Multiple sclerosis (MS) is a chronic autoimmune disease that may affect both white matter and gray matter (1-3). The acute focal inflammatory events in the white matter are evident on magnetic resonance imaging (MRI) as contrast enhancing lesions (CELs). A negative binomial distribution model was recently used to best describe the CEL generation and resolution in the absence of treatment (4). Interferon beta-1b (IFN-beta-1b) is widely used for the treatment of relapsing-remitting (RR) MS. Despite being first-line treatment, IFN-beta-1b is considered only partially effective in reducing CEL activity (2).

**Objectives:** The aims of this work are (1) to characterize the effect of IFN-beta-1b in preventing CEL formation and (2) to investigate its ability in promoting CEL resolution.

**Methods:** Nine patients with RRMS, not receiving any immunomodulatory treatment but steroids to treat clinical exacerbations, underwent monthly MRIs for 48 months (5). The number of CELs was monthly recorded. Monthly CELs were also available from 6-months pre-therapy and 36-months therapy phases from another group of 15 RRMS patients (6). Therapy consisted of subcutaneous administration of 250 µg IFN-beta-1b every other day for 36 months as well as steroids to treat clinical exacerbations. Using the previously published negative binomial distribution model (4) as the baseline model, effect of IFN-beta-1b was evaluated on all the model parameters using different time functions. The analyses were performed using NONMEM version 7.2 (7).

**Results:** IFN-beta-1b produced an expected decrease in the predicted numbers of CELs ( $\lambda$ ) by  $\lambda_0$  inhibition. No effect was identified on the Markovian elements that also define  $\lambda$ . The findings imply that the IFN-beta-1b might prevent the formation of new CELs but does not affect their resolution.

**Conclusions:** A previous study by our group (4) indicated that the use of steroids contributes to the resolution of existing CELs, but does not reduce the development of new CELs. Interestingly, the analyses performed in this study complement these findings, indicating that the use of IFN-beta-1b reduces the formation of new CELs but does not promote disappearance of already-formed CELs. These results suggest that the design of optimal therapies combining IFN-beta-1b and steroids might affect the occurrence and resolution of inflammation more effectively.

## Background

- Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS). It attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees.
- It is diagnosed based on supporting evidence from tests like the magnetic resonance imaging (MRI) of the brain. Contrast enhancing lesions (CELs) are visible on the MRI and represent the acute focal inflammatory events in the white matter.
- The most common form of the disease is the relapsing-remitting (RR) type that affects about 85% of MS patients. It is marked by relapses or exacerbations of symptoms followed by periods of remission, when symptoms improve or disappear.
- CEL generation and resolution in the absence of any treatment were recently described using a negative binomial distribution model (4).
- Interferon beta-1b (IFN  $\beta$ -1b) is widely used for the treatment of relapsing-remitting MS. Despite being the first-line treatment, IFN  $\beta$ -1b is considered only partially effective in reducing CEL activity (2).

## Aims

- To characterize the effect of IFN  $\beta$ -1b in preventing CEL formation.
- To investigate its ability in promoting CEL resolution.

## Methods

- Data available for this study:
  - Numbers of CELs monthly recorded for 48 months in 9 RRMS patients (5). Patients received no treatment except steroids to treat clinical exacerbations. See Figure 1A.
  - Numbers of CELs monthly recorded for 6-months pre-therapy and 36-months therapy phases in 15 RRMS patients (6). See Figure 1B. Therapy consisted of subcutaneous administration of 250 µg IFN  $\beta$ -1b every other day for 36 months as well as steroids to treat clinical exacerbations.
- The data shown in Figures 1A and 1B were combined for this analysis. See Figure 1C.
- Using the previously published negative binomial distribution model (4) as the baseline model, effect of IFN  $\beta$ -1b was evaluated on all the model parameters using different time functions.
- Using the final model, simulations were carried out to optimize combined IFN  $\beta$ -1b-steroid therapy. Simulations were carried out in MATLAB R2013a.

## Results

### 1. Data:

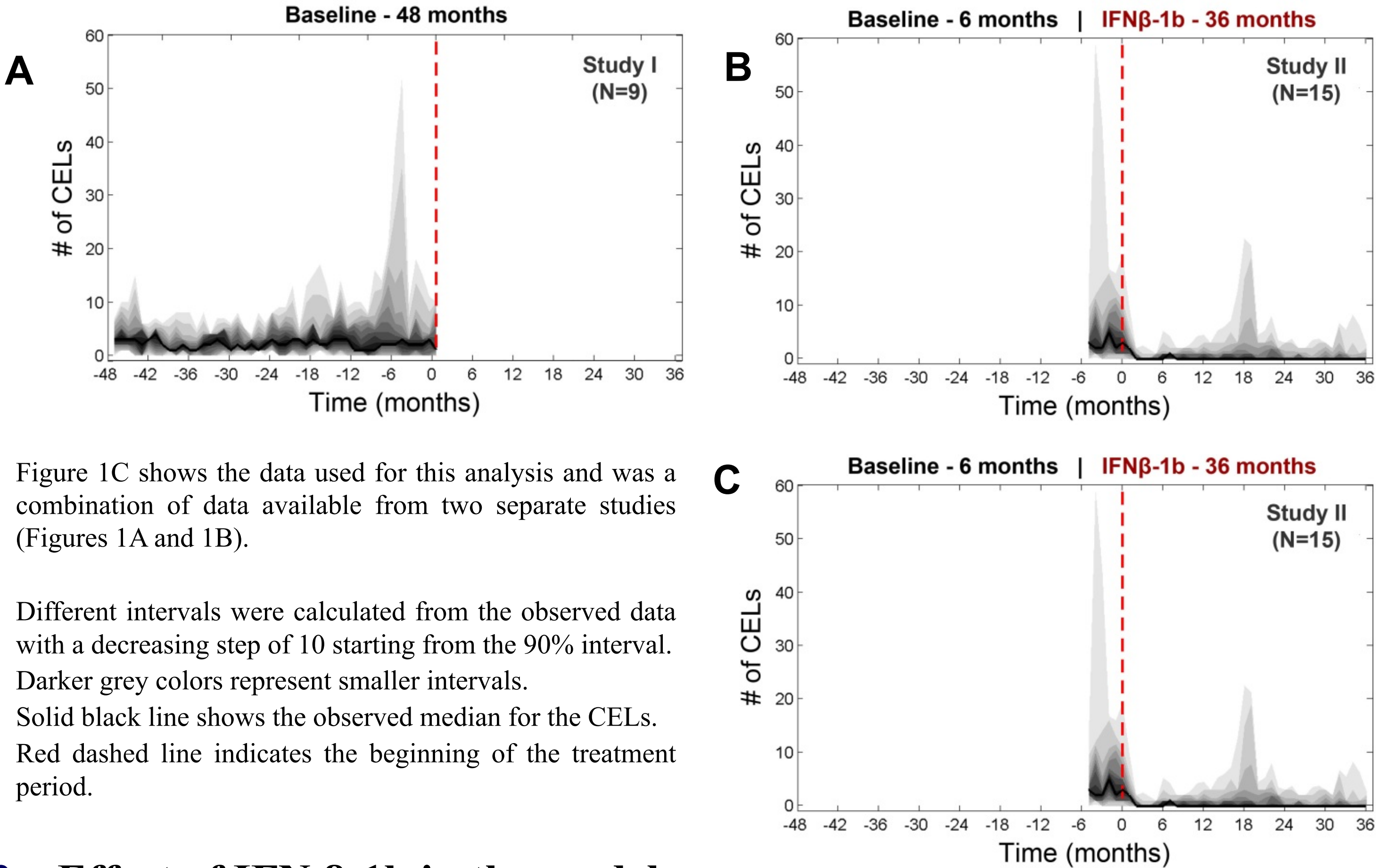
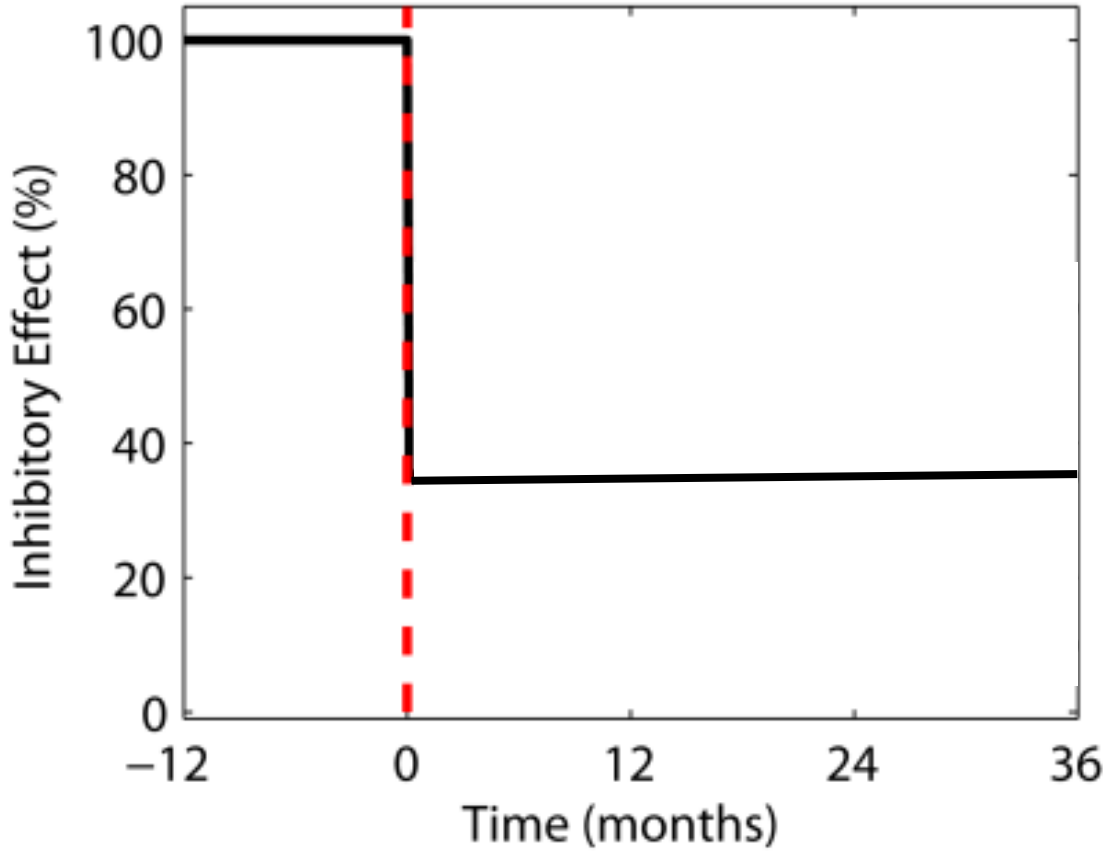
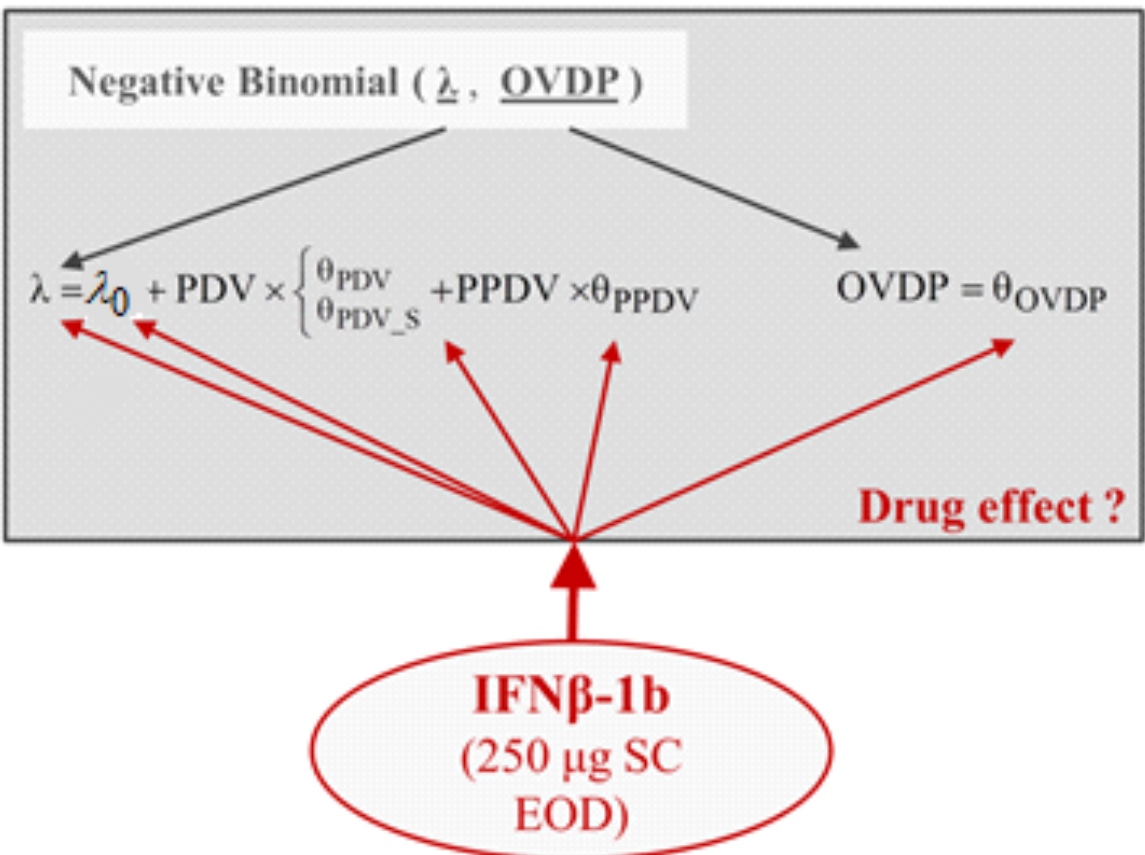


Figure 1C shows the data used for this analysis and was a combination of data available from two separate studies (Figures 1A and 1B).

Different intervals were calculated from the observed data with a decreasing step of 10 starting from the 90% interval. Darker grey colors represent smaller intervals. Solid black line shows the observed median for the CELs. Red dashed line indicates the beginning of the treatment period.

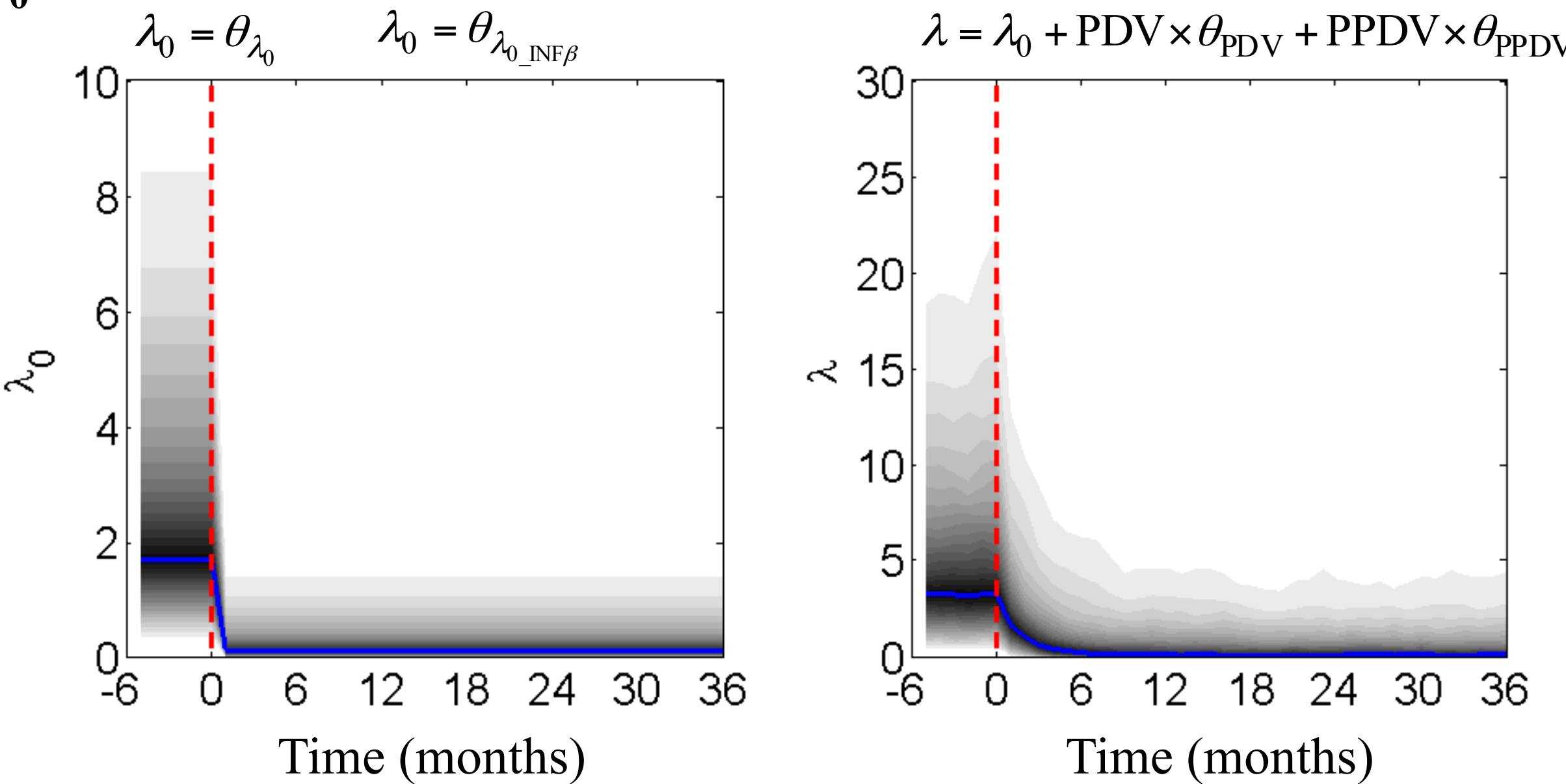
### 2. Effect of IFN $\beta$ -1b in the model:



$$\lambda_0 = \begin{cases} \theta_{\lambda_0} & \text{if no IFN } \beta\text{-1b treatment} \\ \theta_{\lambda_0\text{-IFN}\beta} & \text{otherwise} \end{cases}$$

### 3. Estimated $\lambda_0$ and $\lambda$ :

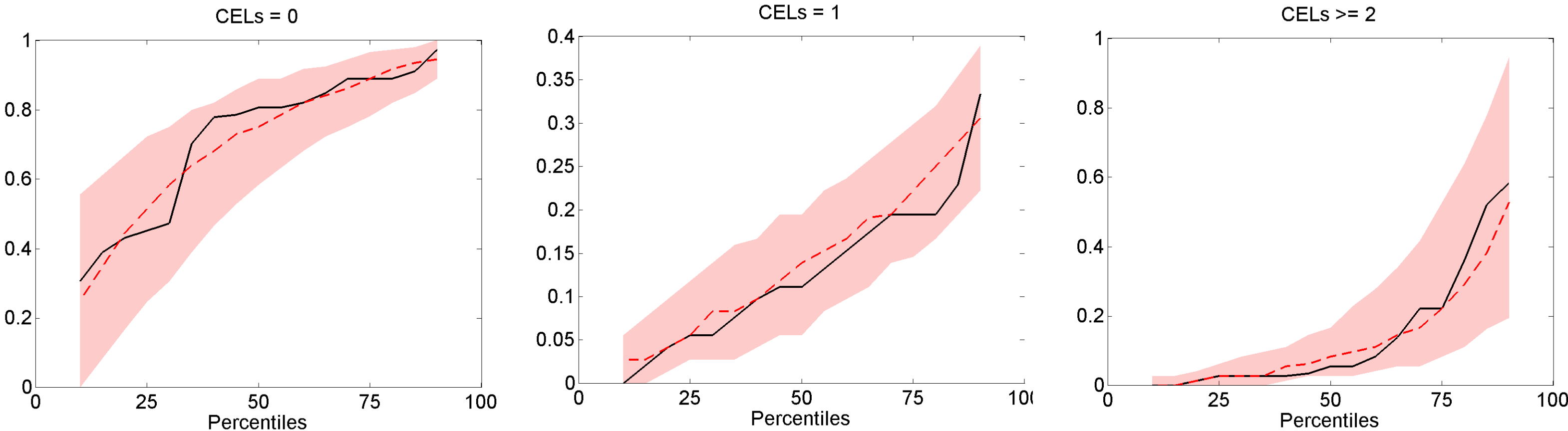
Different intervals were calculated using the estimated parameters and the final model with a decreasing step of 10 starting from the 90% interval. Darker grey colors represent smaller intervals. Solid blue line shows the median of  $\lambda_0$  (left) and  $\lambda$  (right). Red dashed line indicates the beginning of the treatment period.



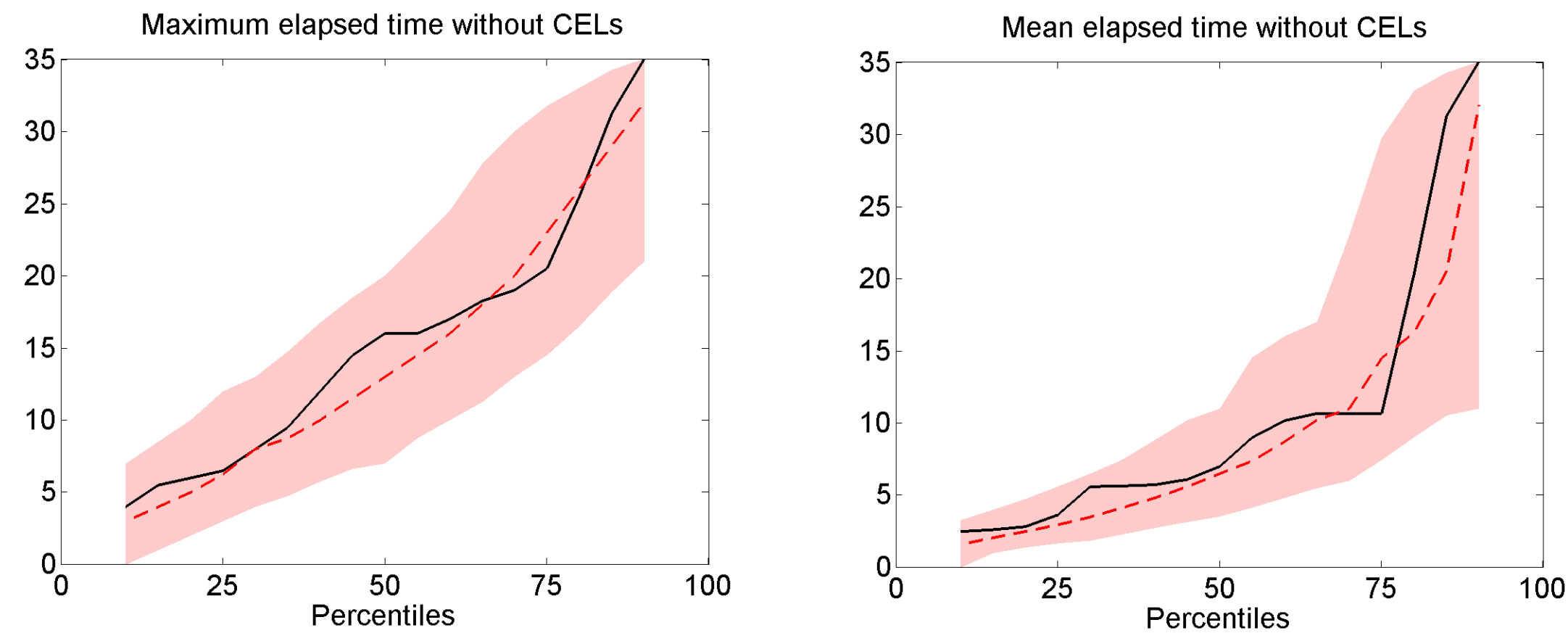
### 4. Predicted interval of Visual Numerical Predictive Check:

Different dynamic descriptors were compared for the observed and simulated data based on the selected model. For each of the descriptors, 10<sup>th</sup> to 90<sup>th</sup> percentiles were calculated with an increasing step size of 5. Solid black line shows the observed median. The 95% predicted interval is represented by the red area and the simulated median is represented by the dashed red line.

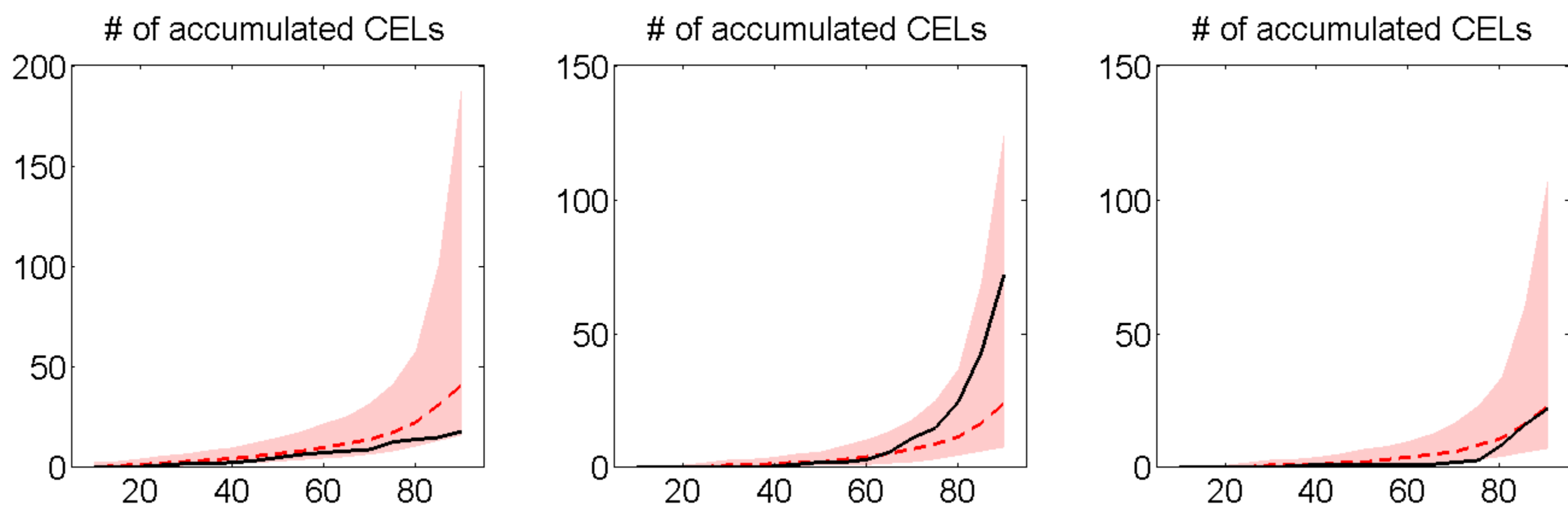
#### A. Probability of having 0, 1 or $\geq 2$ CELs:



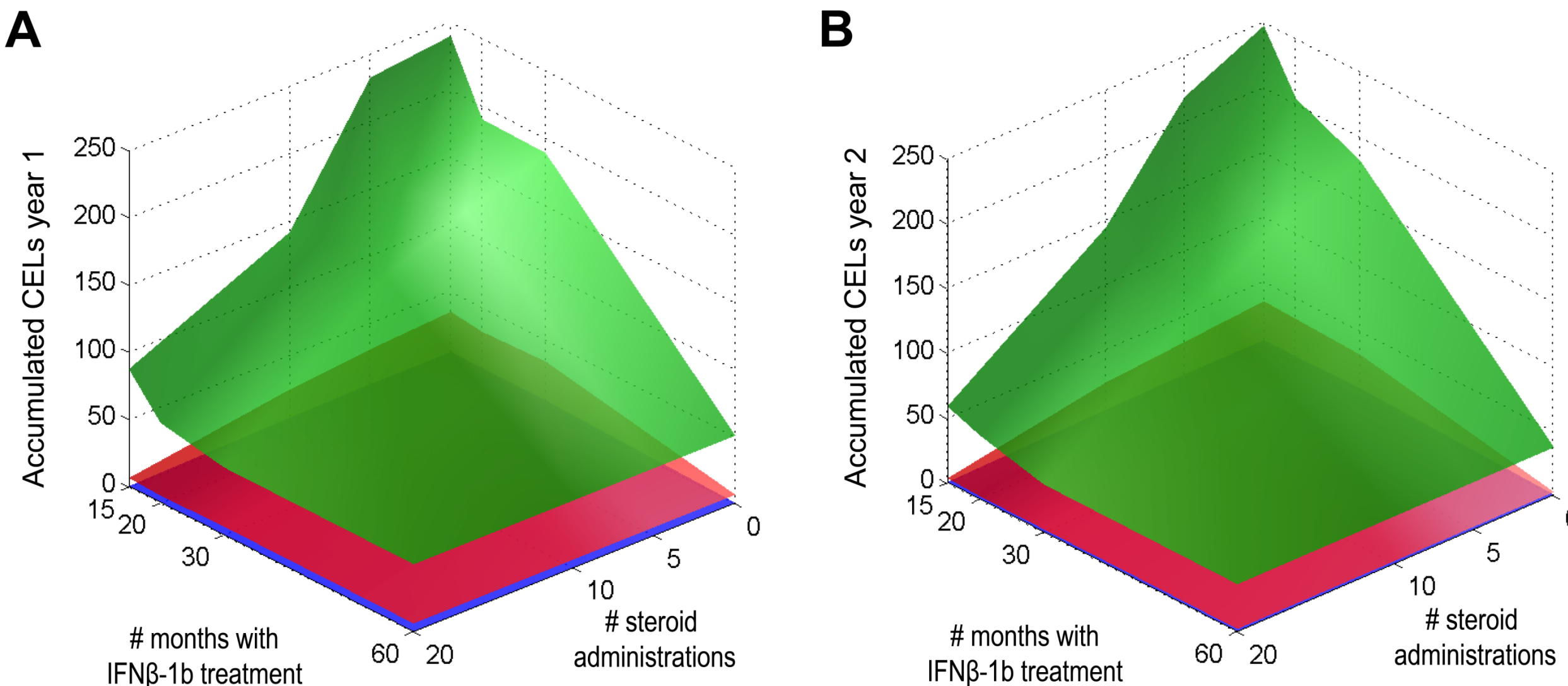
#### B. Elapsed time (in months) without CELs:



#### C. Accumulated CELs in the 1<sup>st</sup> year, 2<sup>nd</sup> year or 3<sup>rd</sup> year:



### 5. Simulated accumulated CELs using combinations of varying number of doses of IFN $\beta$ -1b and steroids



Based on the selected model, accumulated CELs were simulated for a 5 year (60 months) therapy period for several treatment combinations of IFN  $\beta$ -1b and steroids:

**IFN  $\beta$ -1b treatments:** subcutaneous administration of 250 µg IFN  $\beta$ -1b every other day for the treated months: (a) every month (60 months with IFN  $\beta$ -1b); (b) every 2 months (30 months with IFN  $\beta$ -1b); (c) every 3 months (20 months with IFN  $\beta$ -1b); (d) every 4 months (15 months with IFN  $\beta$ -1b).

**Steroid administration:** A single dose every: (a) 0 months (0 dose administrations); (b) 3 months (20 dose administrations); (c) 6 months (10 dose administrations); (d) 12 months (5 dose administrations).

Simulated accumulated CELs for the 1<sup>st</sup> (Figure 5A), 2<sup>nd</sup> (Figure 5B) and 3<sup>rd</sup> years (Figure 5C) are shown as surface plots. The blue, red and green surfaces represent the 5<sup>th</sup>, 50<sup>th</sup> and 95<sup>th</sup> percentiles, respectively.

## Discussion

- The analyses performed in this study indicates that the use of IFN  $\beta$ -1b reduces the formation of new CELs but does not promote disappearance of already-formed CELs.
  - A previous study (4) indicated that the use of steroids contributes to the resolution of existing CELs, but does not reduce the development of new CELs.
- These results suggest that the design of optimal therapies combining IFN  $\beta$ -1b and steroids might affect the occurrence and resolution of inflammation more effectively.

## References

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