ABSTRACT
IMA-638 and IMA-026 are humanized IgG1 monoclonal antibodies (mAbs) that target non-overlapping epitopes of IL-13. Separate first-in-human single ascending dose studies were conducted for each mAb. These studies had similar study designs, but mild to moderate asthmatics were recruited for the IMA-638 study and healthy subjects were recruited for the IMA-026 study. IMA-638 and IMA-026 showed similar pharmacokinetic (PK) profiles, but very different total IL-13 (free and drug bound IL-13) profiles; free IL-13 was not measured. IMA-026 treatment induced a dose-dependent accumulation of total IL-13, while IMA-638 treatment led to a much smaller accumulation without any clear dose-response. To understand the differences between the two total IL-13 profiles and to predict the free IL-13 profiles for each mAb treatment, a mechanistic PK/pharmacodynamic model was developed. PK-related parameters were first fit to the mean PK profiles of each mAb separately; thereafter, the target-related parameters were fit to both total IL-13 profiles simultaneously. The IL-13 degradation rate was assumed to be the same for asthma patients and healthy subjects. The model suggests that an approximately 100-fold faster elimination of IL-13-IMA-638 complex than IL-13-IMA-026 complex could be responsible for the differences observed in total IL-13 profiles for the two mAbs. Furthermore, the model predicts that IMA-638 administration results in greater and more prolonged free IL-13 inhibition than equivalent dosing of IMA-026 despite similar binding Kd and PK profile. In conclusion, joint modeling of two similar molecules provided mechanistic insight that the elimination rate of mAb-target complex can regulate the degree of free target inhibition.

Introduction
Interleukin-13 (IL-13) is a pleiotropic cytokine of type 2 helper T cells (Th2) that triggers signaling by binding to the heterodimeric receptor complex consisting of IL-13Rα1 and IL-4Rα.1 In addition, IL-13 can also bind to IL-13Rα2, which has a very short cytoplasmic domain (17 kDa) that does not interact with any known signaling molecules.2 IL-13Rα2 acts primarily as a decoy receptor, binding to IL-13 with higher affinity than IL-13Rα1, and sequestering IL-13 from the signaling complex.3,4 IL-13Rα2 also mediates the internalization and clearance of bound IL-13, and thereby functions as a sink. IL-13 is involved in inflammatory responses, mucus production, fibrosis, and contributes to IgE production by B cells.5,6 Neutralization of IL-13 has the potential for treating several diseases, including asthma and inflammatory bowel diseases.7,9

Two humanized IgG1 monoclonal antibodies (mAbs) against IL-13, IMA-026 and IMA-638 (also called anrakinzu-mab) were developed to block the responses through the IL-13Rα1/IL4Rα complex (Fig. 1A). IMA-026 and IMA-638 bind to non-overlapping epitopes on IL-13. As a result, IMA-026 inhibits the interaction between IL-13 and IL-13Rα1, while IMA-638 inhibits the recruitment of IL-4Rα after IL-13 binds to IL-13Rα1. Moreover, IMA-026 also interferes with IL13 binding to IL-13Rα2, subsequently blocking IL-13Rα2-mediated internalization and clearance of both free IL-13 and antibody bound IL-13. In contrast, IL-13 binding to IMA-638 has no effect on IL-13Rα2-mediated internalization and clearance of both free and antibody bound IL-13.

Both IMA-026 and IMA-638 were evaluated in separate Phase 1 single dose escalation studies that had very similar designs (same dose levels and route of administration), but different study populations (IMA-026: healthy subjects; IMA-638: mild to moderate asthmatics).10 As a result of differences in the populations, the IMA-638 study had higher mean baseline IL-13 levels. While the pharmacokinetic (PK) profiles were similar for both mAbs, the total IL-13 (free and drug-bound) profiles were quite different. IMA-026 treatment induced a dose-dependent accumulation of total IL-13 with maximum increase (765-fold at 4 mg/kg subcutaneous [SC] administration) observed around day 14 post-dose, while IMA-638 treatment resulted in a much smaller accumulation (10-fold at 4 mg/kg SC administration) with no clear dose-response.

Accumulation of total IL-13 suggests that the mAb binds to the target; however, the efficacy of treatment is most likely associated with the inhibition of free IL-13, the signaling trigger. Since the baseline levels of IL-13 are low, it is difficult to directly

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measure the additional decrease in free IL-13 in the presence of an anti-IL13 mAb. As reported here, we developed a mechanistic PK and pharmacodynamic (PK/PD) model to leverage the available data on mAb PK and total IL-13 for both mAbs. The model was then used to mechanistically understand the differences in total IL-13 profiles in the case of the two mAbs and to predict the free IL-13 profiles for each mAb treatment.

Results

Model fitting of pharmacokinetics data for IMA-026 and IMA-638

Fig. 1B schematically shows the model structure. First, the PK parameters in the model were fit to mean serum concentration-time data from each treatment group for IMA-026 and IMA-638 separately. Fig. 2 shows a comparison between clinical data\textsuperscript{10} and simulation results for the mean serum concentration-time profiles of IMA-026 and IMA-638 after parameter optimization. The proposed 2-compartment model well captures the PK data for both IMA-026 and IMA-638 at all dose levels. The estimated PK parameters ($V_c$, $k_{12}$, $k_{21}$, $k_s$, $k_a$ and $f_{bio}$) are summarized in Table 1. Most parameter estimates were comparable for IMA-026 and IMA-638 with the exception of volume of central compartment ($V_c$) and mAb distribution rates ($k_{12}$, $k_{21}$). Volume of central compartment ($V_c$) for IMA-026 was about 2-fold of $V_c$ for IMA-638; whereas the rate of mAb distribution from central to peripheral ($k_{12}$) and from peripheral to central ($k_{21}$) for IMA-638 was about 10- and 4-fold of those for IMA-026, respectively. The overall exposures of the two molecules are similar, with IMA-638 exposure being slightly higher (but $< 2\times$) than that of IMA-026 at the same dose levels based on $C_{max}$ and $AUC_{inf}$ calculated from non-compartmental analysis (data not shown).

Model fitting of total IL-13 data for IMA-026 and IMA-638

Next, target-related parameters were fit to the mean total IL-13 data from each treatment group for IMA-026 and IMA-638 simultaneously while the PK parameters were fixed to the values obtained above. These data were fit simultaneously and the IL-13 degradation rate ($k_{deg}$) was set to be same between the two studies. This setup allows identification of an optimal IL-13 degradation rate that is independent of mAb treatment and best describes total IL-13 data for both studies. Fig. 3 shows a comparison between clinical data\textsuperscript{10} and fitting results for mean concentration-time profiles of total IL-13 for IMA-026 (Fig. 3A) and IMA-638 (Fig. 3B) in central compartment after...
Note that the rate of binding of mAb to IL-13 (\(k_{\text{on}}\)) was fixed to the diffusion-limited maximum value because usually it is impossible to estimate this parameter from limited early time-course data. Also, the IL-13 degradation rate (\(k_{\text{deg}}\)) was assumed to be the same for mild asthmatic subjects and healthy individuals, and as a result we get a single estimate of 82 day\(^{-1}\) \((t_{1/2} = 12\) mins\). This estimate is comparable to the half-lives reported for other cytokines such as granulocyte-macrophage colony-stimulating factor, tumor necrosis factor and interferon \(\gamma\). Of the remaining two target-related parameters, equilibrium dissociation constant for binding of mAb to IL-13 \((K_D)\) and elimination rate of IL-13-mAb complex \((k_{\text{deg}})\), the former was found to be comparable for the two mAbs whereas the latter was 100x faster for IMA-638. In addition to being comparable to each other, the \(K_D\) estimate for IMA-638 was within 3-fold of the \(K_D\) measured using Biacore. By comparing the fitted parameters, the model suggests that a 100x difference in the elimination rate of complex could be responsible for the differences in total IL-13 profiles for the two mAbs.

**Model predictions for free IL-13 profiles with IMA-026 and IMA-638 treatment**

The optimized model was then used to predict free IL-13 suppression after treatment with IMA-026 and IMA-638. Fig. 4 shows the predicted percent free IL-13 concentrations relative to baseline IL-13 concentration in the central compartment. The model predicts that IMA-638 is more potent at suppressing free IL-13 concentration both with regards to maximum inhibition and the duration of inhibition (Fig. 4) despite a smaller accumulation of total IL-13 (Fig. 3).

**Effect of varying target-related parameters on free and total IL-13 predictions for IMA-026 and IMA-638**

To understand how target-related parameters (baseline IL-13, binding \(K_D\) to IL-13, turnover rate of IL-13, turnover rate of the IL-13-mAb complex) affect the magnitude of target parameter optimization. The baseline IL-13 concentrations were slightly different for the two studies potentially because of the differences in the clinical populations that were recruited: the mild-moderate asthmatic subjects included in the IMA-638 study had mean IL-13 = 1.55x10\(^{-5}\) nM = 2.48x10\(^{-4}\) ng/mL, while the healthy subjects included in the IMA-026 study had mean IL-13 = 5.94x10\(^{-6}\) nM = 9.5x10\(^{-5}\) ng/mL. Model fitting captured the baseline IL-13 concentrations for both studies very well \((T_0 = 1.68x10^{-5} \text{ nM} = 2.69x10^{-4} \text{ ng/mL for IMA-638 and } T_0 = 6.72x10^{-6} \text{ nM} = 1.07x10^{-4} \text{ ng/mL for IMA-026). Despite the lower baseline IL-13 for the study with IMA-026, the model was able to capture the much higher total IL-13 increase with a clear dose-response for IMA-026 treatment. The model simulation after fitting shows that IMA-638 treatment resulted in a saturated response at doses higher than 0.3 mg/kg where increasing dose did not have a significant effect on the maximum increase of total IL-13. Additionally, the model predicts that the duration of total IL-13 increases slightly with an increase in the dose of IMA-638, but not with IMA-026 (Fig. 3). Overall, our model captures the total IL-13 profiles for both mAbs reasonably well.

![Figure 3](image_url)

**Figure 3.** Time course of total IL-13 serum concentrations for IMA-026 (A) and IMA-638 (B) in humans after single dose IV or SC administration. The symbols represent mean clinical data, whereas lines are model-estimated profiles.
suppression and the total IL-13 profile, we systematically evaluated the effect of varying various target-related parameters on free IL-13 (Fig. 5) and total IL-13 (Fig. 6) profiles. In this analysis, each parameter was varied one at a time by 10-fold lower or higher (0.1 x and 10 x) than the nominal value listed in Table 1 and a single 4 mg/kg SC dose of either IMA-026 or IMA-638 was simulated. We find that, for both IMA-026 and IMA-638, varying baseline IL-13 concentration does not affect percent free IL-13 profile (note the three curves are overlapping in Figs. 5A and 5E) nor percent total IL-13 profiles (note the three curves are overlapping in Figs. 6A and 6E) because in the plots they are expressed relative to the baseline IL-13, which negates the effect of any change. As shown in Fig. 5, lower $K_D$ results in greater suppression of IL-13 for both IMA-026 and IMA-638 (Figs. 5B and 5F). However, the effect of $K_D$ on total IL-13 increase is much smaller for IMA-638 compared with IMA-026 (Figs. 6B and 6F). Interestingly, the effects of varying IL-13 and complex turnover rates were opposite, whereby a slower IL-13 degradation rate or a faster complex elimination rate resulted in greater suppression of free IL-13 with IMA-026 and IMA-638 (Figs. 5C-D and 5G-H). Finally, depending on the parameter being varied, the increased suppression of free IL-13 is associated with either increased (when varying $K_D$) or decreased (when varying $k_{deg}$ and $k_{elC}$) total IL-13 relative to the nominal values (compare corresponding panels in Figs. 5 and 6).

Discussion

In this work, we developed a mechanistic PK/PD model to describe the PK and total IL-13 profiles for two anti-IL-13 mAbs, IMA-026 and IMA-638. After fitting to the clinical data from two separate Phase 1 studies conducted for IMA-026 and IMA-638, the model predicted that the difference in the total IL-13 profiles observed with the two molecules was mainly due to the ~100 x difference in the elimination rate of the IL-13-mAb complex ($k_{elC}$). The model further predicted that IMA-638 is a more potent inhibitor of free IL-13 despite the similar binding affinities to the target ($K_D$) and PK properties of the two molecules.

We used a 2-compartment model, which is commonly used for mAbs,16,17 to describe PK, and target-related mechanisms,
including binding of mAbs to the target, target degradation rate and target-mAb elimination rate. The model allows the mAb-related parameters to be different for the two molecules, but IL-13 degradation rate \((k_{deg})\) was assumed to be same (Table 1) because it is independent of the therapeutic. The mAb distribution parameters, \(k_{12}\) and \(k_{21}\), are 10- and 4-fold higher, respectively, for IMA-638 than IMA-026. These differences are mainly due to the difference in available PK data at early time points (≤24 hour post dose) where more frequent data were collected in the IMA-638 study, thereby allowing a better characterization of the distribution phase. Since \(k_{12}\) and \(k_{21}\) mostly affect the mAb exposure during first day while total IL-13 increases over a much longer period of time, these differences in \(k_{12}\) and \(k_{21}\) had a minimal effect on overall mAb exposure, and a minimal effect on the prediction of total IL-13.

IL-13 levels have been reported to be slightly higher in mild asthmatics than in healthy subjects.\(^{16}\) Consistent with the previous report, the mean baseline IL-13 levels measured in the current studies were also slightly higher (2-fold) in mild asthmatic patients. The model assumed that the difference in baseline IL-13 levels was due to the increased synthesis and not decreased degradation. This is because glomerular filtration is probably the main clearance pathway for IL-13 in blood due to its low molecular weight,\(^{16}\) and asthma is not known to modulate this clearance. If the target-related parameters were separately fit to IMA-026 and IMA-638 data, then the IL-13 degradation rate will be poorly defined in the case of IMA-638, since the total IL-13 data are quite noisy and without any clear observable dose-response. In such a scenario, fitting will yield a wide range for \(k_{deg}\) with an overall similar fitting result for total IL-13. Therefore, by simultaneously fitting the two sets of data, the model parameters, particularly \(k_{deg}\), became better confined.

The model predicted that the differences in total IL-13 profile between the two mAbs is mainly due to the difference in the elimination rate of the IL-13-mAb complex, which is supported by the understanding of the biology.\(^{10}\) IMA-638 and IMA-026 bind to IL-13 at different epitopes such that the former does not inhibit the binding of IL-13 to its decoy receptor, IL-13Ro2, while the latter does. Consequently, IL-13-IMA-638 complex can still bind to IL-13Ro2, get internalized and cleared; while IL-13-IMA-026 cannot be cleared through IL-13Ro2, which in turn leads to a larger accumulation of total IL-13. The IL-13-IMA-026 complex is probably cleared through endocytosis similar to mAbs,\(^{20}\) so that the complex elimination rate \((k_{elC} = 0.091 \text{ day}^{-1})\) is similar to the mAb elimination rate \((k_{el} = 0.042 \text{ day}^{-1})\).

The total IL-13 assays for both the mAbs used Singulex platform for sensitive detection of low level of IL-13,\(^{21}\) however, they are slightly different due to the difference in binding epitopes. In these assays, different mAbs were used as the capture mAb, whereas the detection mAb was same. Both assays were validated following the company’s standard operating procedures and performed in the same lab. Therefore, it is unlikely that the differences observed in total IL-13 profiles are assay-related.

Despite the higher increase in total IL-13 for IMA-026 than IMA-638, the model predicted that IMA-638 is a more potent inhibitor of free IL-13 (Fig. 4). At the same non-saturating dose, IMA-638 led to a larger decrease in free IL-13 and more importantly, a much more prolonged inhibition of IL-13 than IMA-026. This prediction is consistent with the better efficacy observed clinically in allergen challenge study with IMA-638.\(^{22}\) Since the PK profile and \(K_D\) for the two mAbs are similar, the model suggested that (like total IL-13 accumulation) the difference in free IL-13 inhibition is a consequence of the differences in elimination rates of IL-13-mAb complexes. IL-13 binding to mAb to form IL-13-mAb is a reversible reaction, thus higher IL-13-mAb concentration for IMA-026 requires higher mAb concentration to maintain inhibition of IL-13. We demonstrated through simulations that if we only increase \(k_{elC}\) by 100× and keep all other parameters unchanged for IMA-026, then the total IL-13 and free IL-13 profiles becomes similar to IMA-638 (data not shown). Due to the lack of appropriate functional assays in early drug discovery, researchers tend to use \(K_D\) as a surrogate of potency to select lead candidates during the compound selection stage.\(^{23,25}\)

![Figure 6. Effects of varying model parameter values on predicted fold of total IL-13 concentrations (relative to baseline IL-13) with 4 mg/kg SC dose of IMA-026 (top row) and IMA-638 (bottom row). Same parameters were varied as in Fig. 5. Colors and symbols have the same meaning as in Fig. 5.](image-url)
However, this work highlights that $K_D$ is only one variable of many that should be considered. Other information, especially the underlying mechanism (e.g., binding epitope), could also be important. This study also points to a new mechanism for increasing potency, which takes advantage of the elimination rate of target-drug complex. However, this strategy can be applied only if the target biology allows the faster clearance of target-mAb complex, which may be the case, for example, if there is a target clearance pathway that is separate from the signaling pathway such that a mAb can be designed to block the signaling pathway and not the clearance pathway.

It is often challenging to measure the decrease in free target concentration in clinical studies if the baseline level in circulation is already low, as is the case for IL-13. On the other hand, the increase in total target concentration is often observed post-dose due to the stabilization of the target-mAb complex, and it is then easier to measure. Since efficacy is associated with a decrease in free target concentration, it is desirable to establish a relationship between the increase in total target concentration and the decrease in free target concentration. Our simulations suggest that this relationship is not always straightforward. In some cases, the increase in total target concentration is associated with better suppression of free target (e.g., varying $K_D$) (Fig. 5 B&F, Fig. 6 B&F). In other cases, the increase in total target concentration is associated with less suppression of free target (e.g., varying complex turnover rate) (Fig. 5 C&G, Fig. 6 C&G). This work suggests that we should be cautious when trying to use an increase in total target concentration to infer target coverage, especially while comparing the degree of free target inhibition between two different molecules. For within molecule comparison, dose-dependent increases in total target concentration do show a correlation with increased inhibition of free target. In summary, the mechanistic PK/PD model developed and tested in this study can be used to better describe the inhibitory activity and therapeutic potential of the various agents targeting the IL-13 pathway.

**Materials and Methods**

**Clinical studies and PK and total IL-13 data**

Two separate single dose escalation studies were conducted to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of IMA-026 (NCT00517348) and IMA-638 (NCT00339872). Both studies included escalating single SC doses of 0.3, 1, 2 and 4 mg/kg and a single intravenous (IV) dose of 3 mg/kg. In both studies, each cohort included 7 or 8 subjects receiving active treatment and 2 subjects receiving placebo treatment. The study with IMA-026 was conducted in healthy subjects whereas the study with IMA-638 was conducted in subjects with mild to moderate asthma. Blood samples for assessment of PK and PD were collected. Serum concentrations of IMA-026 and IMA-638 were measured using validated ELISA assays of similar format where recombinant human IL-13 (internal source) was used as the capturing reagent and either a goat (IMA-026) or mouse (IMA-638) anti-human IgG (Fc)-HRP (both from Southern Biotech, Birmingham, AL) was used as the detection reagent. The PK assays for both molecules detected free drug and drug bound to a single IL-13 molecule. The lower limit of quantification for the assay was 50.0 ng/mL and 46.8 ng/mL for IMA-638 and IMA-026, respectively. Serum total IL-13 was measured at Wyeth Biomarker Laboratory (Collegeville, PA) using validated immunoassay with Singulex platform. Mean PK and total IL-13 data for each treatment group were used for model fitting. Both protocols and consent forms were reviewed and approved by the institutional review boards for each of the study sites, and all subjects provided signed informed consent. All studies were conducted in accordance with the ethical standards of the Declaration of Helsinki.

**Mathematical model**

For this analysis, we developed a two-compartment model with central (blood) and peripheral (tissue) compartments (Fig. 1). A depot compartment was included to model subcutaneous dosing. The set of ODEs that describe the system are as follows:

$$\frac{dD}{dt} = f_{bio} k_a \frac{AD}{V_c} + k_{21} \frac{AT}{V_c} - k_{12} D + k_{off} C - k_{syn} DT - k_{deg} D$$  \(1\)

$$\frac{dT}{dt} = k_{syn} - k_{deg} T - k_{off} C + k_{off} C$$  \(2\)

$$\frac{dC}{dt} = k_{syn} DT - k_{off} C - k_{cic} C$$  \(3\)

$$\frac{dA_T}{dt} = k_{12} DV_c - k_{31} A_T$$  \(4\)

$$\frac{dA_D}{dt} = - k_a A_D$$  \(5\)

where $D$, $T$ and $C$ represent the concentrations of free drug, free target and drug-target complex in the central compartment, respectively. $A_T$ and $A_D$ are the amounts of free drug in peripheral and depot compartments.

IV Administration of mAb is modeled as a bolus in the central compartment ($V_c$), whereas SC administration is modeled using a depot compartment with two parameters, depot to central absorption rate ($k_a$) and bioavailability ($f_{bio}$). mAb distributes into the peripheral tissues ($k_{12}$, $k_{31}$) and binds reversibly ($k_{syn}$, $k_{off}$) to the target (IL-13) to form mAb-target complex only in central compartment. $K_D$ (=$k_{off}/k_{syn}$) is the equilibrium dissociation constant for the binding of mAb to IL-13. Both mAb ($k_a$) and mAb-target complex ($k_{cic}$) are eliminated systemically from the central compartment with a first order elimination. Target is assumed to be synthesized ($k_{syn}$) and degraded ($k_{deg}$) in the central compartment, and to allow for homeostasis in the absence of mAb, synthesis rate is calculated as the product of degradation rate and baseline target concentration ($k_{syn} = k_{deg} T_0$).

**Optimization**

All optimizations were performed using the particle swarm function (particleswarm) in MATLAB 2015a (The Mathworks Inc., Natick, MA) and were repeated at least 15 times. For each run the algorithm randomly selects an initial condition within the specified parameter bounds (Table 2) and proceeds to minimize the given objective function. Due to the stochastic nature of the algorithm, each run traverses a different trajectory to
minimize the objective function, and can thus give rise to degenerate parameter sets that all describe the data equally well.

First, the reduced model without target and mAb-target complex (equations (1), (4) and (5)) was fitted separately to serum concentration vs. time data for IMA-026 and IMA-638 to estimate the PK parameters \( (V_c, k_{12}, k_{21}, k_{el}, k_{on}, f_{bio}) \). The objective function \( (O_1) \) for this minimization was:

\[
O_1 = \sqrt{\sum_{i} \left( \frac{D - D_{data}}{D} \right)^2}
\]

where \( t \) represents the time points for which PK samples \( (D_{data}) \) were collected and \( D \) represents the model estimate.

Next, the full model with target and mAb-target complex (equations (1)- (5)) was fitted simultaneously to total IL-13 data for IMA-026 and IMA-638 to estimate the various target-related parameters \( (T_0, k_{deg}, k_{elC}, k_{DF}) \). Note that \( k_{on} \) was fixed to the diffusion-limited maximum value\(^1\) because usually it is impossible to estimate this parameter from limited early time-course data. A single \( k_{deg} \) value was used for both IMA-026 and IMA-638, while \( T_0, k_{elC} \) and \( k_{DF} \) were different for IMA-026 and IMA-638. During this fitting, the PK parameters for each mAb were fixed to the best fit values obtained from the previous fitting step. The objective function \( (O_2) \) for this minimization was:

\[
O_2 = \sqrt{\sum_{i} \left( \frac{T + C_{IMA026}^{data} - [T + C]_{IMA026}}{T + C_{IMA026}} \right)^2 + \sum_{i} \left( \frac{T + C_{IMA638}^{data} - [T + C]_{IMA638}}{T + C_{IMA638}} \right)^2}
\]

samples \( ([T + C]_{IMA026}^{data}) \) were collected for IMA-026 and IMA-638, respectively. \( [T + C]_{IMA026} \) and \( [T + C]_{IMA638} \) represent the model estimates of total IL-13 for IMA-026 and IMA-638, respectively.

**Local sensitivity analysis**

For both mAbs each target-related parameter was varied one at a time by 10-folder lower or higher (0.1 \times and 10 \times) than the nominal value (listed in Table 1) estimated from fitting.

**Disclosure of potential conflicts of interest**

All authors on the manuscript were employed by Pfizer, Inc., at the time when research was conducted. The research work was funded solely by Pfizer Inc.

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**Table 2. Parameter bounds for optimization.**

| Parameter          | Lower bound | Upper bound |
|--------------------|-------------|-------------|
| \( V_c \) \((L)\)  | 0.3         | 30          |
| \( k_{12} \) \((day^{-1})\) | 0.02        | 2           |
| \( k_{21} \) \((day^{-1})\) | 0.02        | 2           |
| \( k_{el} \) \((day^{-1})\) | 0.01        | 1           |
| \( k_{on} \) \((day^{-1})\) | 0.25        | 2.5         |
| \( f_{bio} \)     | 0.5         | 1           |
| \( T_0 \) \((nm)\) | 3\times10^{-6} | 3\times10^{-5} |
| \( K_D \) \((nm)\) | 0.05        | 0.5         |
| \( k_{deg} \) \((day^{-1})\) | 0.69        | 165         |
| \( k_{elC} \) \((day^{-1})\) | 0.01        | 33          |
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