Predicting the impact of combined therapies on myeloma cell growth using a hybrid multi-scale agent-based model

Supplementary Materials

Model development

In this study, we defined five types of agents in the HABM model to represent BMSC, MIC, MM, CD8+, and Treg. We initialized the tumor extracellular matrix (ECM) as a 100*100*100 3D matrix. BMSC cells were simulated as edges of 3D rectangular framework embedded into the ECM. At the beginning, the mixed population of MIC, MM, CD8+, and Treg, were initialized in the center of the 3D ECM as a sphere. The numbers of each type of cell are 100 (MIC), 100 (MM), 20 (CD8+), and 5 (Treg). The proposed multi-scale modeling consisted of three scales: intracellular, intercellular and tissue scales, which were illustrated in the section of “Materials and Methods”, and described in details in the following sections.

Stochastic simulation of cell behaviors

The Markov Chain Monte Carlo approach was used to simulate cell behaviors of each individual cell. As shown in Figure 10, cell behaviors were simulated by probability-based rule implementation. A cell sensed the hints of its neighborhood such as stiffness, SDF-1 and TGFβ level, and drug doses, processed them with signaling pathways (via OED systems or Hill functions), and outputted the changes of probabilities of corresponding cell behaviors including cell proliferation rate, survival (apoptosis) rate, differentiation ratio, migration rate, and cytokine secretion rate. Cell decision was then determined by rolling a dice and compared with the probability of a given cell behavior. Cell behaviors in turn updated the properties of its niches. Details of each cell behavior for each type of cell agent as well as the corresponding rule was introduced in the following sections.

Intracellular scale

Each BMSC agent determines its biomechanical phenotype via the ODE system of SDF-1/CXCR4 signaling pathway (see Materials and Methods). Each grid point of the BMSC represented a section of the BMSC reticular. Each BMSC agent senses the local concentration of SDF-1, then activates the SDF-1/CXCR4 pathways, and finally output the stiffness.

Similarly, the oncogenic effect of the niche stiffness on the proliferation rates of myeloma initiating cells (MIC) and mature multiple myeloma (MM) were described with a Hill function (Eq.1).

\[ P_{\text{prot}} = \frac{P_0 + P_{\text{pathway}}}{1 + \left(\frac{E - E_0}{K_E}\right)^2} \]  

(1)

Where \( P_{\text{prot}} \), \( l = 1, 2 \) were the proliferation rates of MIC, and MM, respectively. \( P_0 \) denotes the initial proliferation rate, \( P_{\text{pathway}} \) is the maximal proliferation rate of the embedded signaling pathway in BMSC cells. \( K_E, E \), and \( E_0 \) were the maximal stiffness, local stiffness, and base stiffness value. We assumed that the contraction of a BMSC section altered the stiffness of its local extracellular matrix, and thus defined the stiffness a myeloma cell sensed \( E \), as the maximal stiffness of its neighbor BMSC sections within 3 grid distance.

The proliferation rate of CD8+ T cell was not only regulated by local concentration of TGFβ and the dose of Lenalidomide, but also was affected by the population of Tregs (Eq. 2).

\[
\text{Prod}_{\text{CD8+}} = \text{Prod}_{\text{CD8+}, \text{base}} + \text{Prod}_{\text{CD8+}, \text{norm}} \left\{ 1 + \left(\frac{PL}{K_L}\right)^2 \right\} \left\{ 1 + \left(\frac{TGF}{K_T}\right)^2 \right\} \left\{ 1 + \left(\frac{\text{Treg}}{K_{\text{Treg}}}\right)^2 \right\} 
\]

(2)

Where \( \text{Prod}_{\text{CD8+}} \) is the base proliferation rate of CD8+ T cells. \( PL \) denotes the relative LEN dose and \( K_L \) the sensitivity of the CD8+ T cells to LEN. \( TGF \) denotes the relative TGFβ concentration at the grid point \((i, j, k)\); and \( K_T \) denotes the threshold TGF level to suppress CD8+ T cells. The effect of Tregs on CD8+ was described with \( R \), which determined by the population ratio of Treg against CD8+. Based on the Haart’s experimental data [1], we inferred the formulation of function R according to different ratios of Treg to CD8+ (Eq. 3).

\[ R = 0.82 - 3.03 \times \frac{\text{ratio} - 0.0659}{3.5609 + (\text{ratio} - 0.0659)} \]  

(3)

\[ \text{ratio} = \frac{\text{Treg}}{\text{CD8+}} \]  

(4)
According to formula (3–4), we can clearly know that increase of Treg population will suppress the proliferation of CD8+.

Finally, the proliferation rate of Treg cell was defined as Eq. 5.

$$Prol_{Treg} = Prol_{Treg}^0 + Prol_{Treg} = \left(1 + \frac{T_{ec}}{K_{ec}}\right) \left(1 + \frac{T_{es}}{K_{es}}\right) \frac{1}{1 + \frac{PL}{K_{f}}}$$

Where $Prol_{Treg}^0$ is the base proliferation rate of regulatory T cells (Treg). Formula (5) indicates that the production of Tregs can be promoted by TGFβ and suppressed by IMiD drug (such as, LEN).

Cell decision-making process was defined by agent rules, and the stochastic feature of the decision of an individual cell was realized by die casting simulation. Here, we used the cell decision-making of entering cell cycle as an example to elaborate the algorithm. Cell proliferation rules were defined according to proliferation rates as probabilities of two cell decisions with a die $C_{rand} \in [0,1]$.

$$\begin{cases} C_{rand} \in [0,P_{pre}] \\ \text{cell cycle ON} \\ C_{rand} \in [P_{pre},1] \\ \text{cell cycle OFF} \end{cases}$$

If the die fell into the interval $[0, P_{pre}]$, the cell entered cell cycle and started to proliferate; otherwise, stayed quiescent. Four cell cycle phases (G0/G1, S, G2, and M) were defined. Cells kept migrating during the first three phases, while tried to find a location to divide after entering the M phase, which was defined in the following sections. The duration of stage G0/G1 was determined by the Monte Carlo simulation (die casting) process, the S phase lasted for 20 hours (10 time steps), and the G2 phase would not exceed 10 hours (5 time steps).

### Stem cell fate determination

Once a MIC decided to enter cell cycle, its fates were further determined according to its microenvironment. A MIC either generates two MIC daughter cells, known as self-renewal, or to two MM cells, known as differentiation. The probability of each fate was denoted as $r_f$. Rules for MIC fate determination were represented in Eq.7:

$$\begin{cases} C_{rand} \in [0, r_f] \\ \text{self renewal} \\ C_{rand} \in [r_f,1] \\ \text{differentiation} \end{cases}$$

Where $r_f = r_{f,0} + \Delta r$. $\Delta r$ describes the effects of stiffness-triggered MIC signaling pathway on cell fates, and was determined by Eq.8:

$$\Delta r = r_{pathway} \frac{(E - E_0)^2}{K_{GG}} \frac{1}{1 + \left(\frac{E - E_0}{K_{GG}}\right)^2}$$

Where denotes the signaling pathway activation threshold.

Proliferation fate of MM agents. The fates of MM cell agents were determined by their passage age (Eq. 9).

$$MM \rightarrow \begin{cases} 2\text{MM} \\ \text{Dead} \end{cases} \begin{cases} \text{generation number} \leq \text{LGN} \\ \text{generation number} > \text{LGN} \end{cases}$$

### Intercellular scale

Each type of cells would proliferate, migrate, being quiescent, or undergo death, which were described in the intercellular scale.

### Migration

A non-M-phase cell at position $p$ would migrate if it would find free space nearby. Except BMSC agents, other four types of cell agents can migrate from one place to another free space. MICs and MMs prefer to migrate towards the stiffer BMSCs. Once they attached on BMSC sections, they prefer to stay there rather than move to non-BMSC position (Supplementary Figure S2). For the CD8+ T cells, they tried to migrate towards Myeloma cells (MICs and MMs) and to induce the lysis of tumor cells. As to Tregs, they prefer to migrate to CD8+ T cell population, and to induce the cell cycle arrest or apoptosis of the effector cells.

Now, we firstly introduce the migration of MIC. In this study, if a MIC cell will migrate depends on what’s its current position. If a MIC cell is not attaching on BMSC, it will definitely implement the procedure of migration; otherwise, we firstly calculate the adhesion rate ($P_{adh}$) of MIC with local stiffness via ODE system, then make dice rolling to generate a random value $md$ and to determine if it will migrate to another place ($P_{adh} < md$). According to Supplementary Figure S2, we can find that MIC prefers to continuously stay on BMSC rather than move to non-BMSC position. The migration was defined in the following rules. All the unoccupied positions within a radius $r_{max}$ (Eq. 10)

$$r_{max} = \frac{2(1 + 4D\Delta t)}{10} + 1$$

We were listed as candidates, where $D$ was the basic migration speed index, $\Delta t$ is the time step (2hours). All candidate locations were ranked as Eq. 11.

$$R_i = p(r_i) \cdot \max(C_{cell}^r \cdot C_{CTL} \cdot V_i)$$

$R_i$ was the ranking score of each candidate position $P_{ijl}$. Variable $r_i$ is the distance from the candidate location to the original position $P_{i0l}$, and the subscript $ijl$ is the coordinates of the candidate locations, $P_{i0l}$ is the visiting chance of $P_{ijl}$ (Eq. 12).

$$p(r_i) = \frac{1}{4\pi D\Delta t} \exp \left( -\frac{r_i^2}{4\pi D\Delta t} \right)$$
\( C_i^n, n = 1, \ldots, 6 \) were the preference of neighbor at \( P_{ijk} \). The position \( P_{ijk} \) had six immediate neighbors. The value of \( C_i^n \) was defined by Eq. 13.

\[
C_i^n \rightarrow \begin{cases} 
F_E \left( E^{\text{spr}}_i \right) & \text{if the n-th neighbour is BMSC} \\
\frac{1}{4} & \text{otherwise}
\end{cases}
\] (13)

Where

\[
F_E \left( E^{\text{spr}}_i \right) = F_{E,0} + F_{E,\text{max}} \left( \frac{E^{\text{spr}}_i - E_0}{K_{FE}} \right)^2 \left( 1 + \left( \frac{E^{\text{spr}}_i - E_0}{K_{FE}} \right)^2 \right)^{-1}
\] (14)

The coefficients \( F_{E,0} \) and \( F_{E,\text{max}} \) were the weights of Eq. 14 which described the degree of preference of an MIC attaching to an unprimed BMSC and the increase of such preference to a primed MBMSC. \( E^{\text{spr}}_i \) was the stiffness at \( P_{ijk} \) 's n-th neighbor with the exact coordinate \((x,y,z)\). \( E_0 \) was the minimal sensed stiffness and \( E_{\text{max}} \) the maximal. \( K_{FE} = \frac{E_{\text{max}} - E_0}{2} \). Variable \( C_{i,\text{CTL}} \) denotes if \( P_{ijk} \) exists a neighbor as CD8\(^+\) T cell. If yes, the value of \( C_{i,\text{CTL}} \) is small to decrease the chances of MICs migration to CD8\(^+\); otherwise, \( C_{i,\text{CTL}} \) is large (Eq. 15).

\[
C_{i,\text{CTL}} \rightarrow \begin{cases} 
\frac{1}{4} & \text{at least a neighbor is CD8} \\
1 & \text{otherwise}
\end{cases}
\] (15)

Variable \( V_i \) was defined as Eq. 16.

\[
V_i = \begin{cases} 
0.125 & P_{ijk} \text{ has 5–6 neighbor cells} \\
0.25 & P_{ijk} \text{ has 3–4 neighbor cells} \\
0.5 & P_{ijk} \text{ has 1–2 neighbor cells} \\
1 & P_{ijk} \text{ has no neighbor cells}
\end{cases}
\] (16)

Eq. 16 represents that myeloma cells try to avoid loneliness as well as crowdedness, though they are not as sensitive as solid tumor cells are. Ranks of all candidates were normalized so that the sum of all normalized ranks is 1 (Eq. 17).

\[
\hat{R}_i = \frac{R_i}{\sum R_i}
\] (17)

To facilitate die-casting, all normalized ranks were incorporated to form a scale \( S \), in which each candidate is corresponding to a range.

\[
S = \{ S_i : S_i = \sum w_i \hat{R}_i, \sum w_i \hat{R}_i \}
\] (18)

The dice casting generates a random value \( d \in [0,1) \). If \( d \) falls in \( S_i \), the position \( P_{ijk} \) is chosen as the next migration stop.

For the MM, its migration rules were very similar as MIC except the definition of variable \( C_i^n \). Here, \( C_i^n \) was set to 1 if the n-th neighbor of \( P_{ijk} \) was BMSC (Eq. 19).

\[
C_i^n \rightarrow \begin{cases} 
1 & \text{if the n-th neighbor is BMSC} \\
\frac{1}{4} & \text{otherwise}
\end{cases}
\] (19)

For the CD8\(^+\) T cell, it will migrate towards MIC or MM rather than empty position and BMSC. The CD8-mediated lysis of myeloma cell might probably occur the positions where are not BMSC. In other word, myeloma cell adhere to BMSC will reduce the probability of apoptosis and escape from immune system [1]. The candidate rank was calculated with Eq. 20.

\[
R_i = p(r_i) \cdot \max \left( C_i^n \right) \cdot V_i
\] (20)

In Eq. 20, the values of \( p(r_i) \) and \( V_i \) are calculated by Eq. 12 and Eq. 16. The value of \( C_i^n \) for CD8\(^+\) T cell was defined by Eq. 21.

\[
C_i^n \rightarrow \begin{cases} 
1 & \text{if the n-th neighbor is MIC/MM} \\
\frac{1}{2} & \text{otherwise}
\end{cases}
\] (21)

As to the regulatory T cell (Treg), it will migrate towards CD8\(^+\) T cell and try to suppress the proliferation of CTL. The candidate rank was also calculated with Eq. 20. In Eq. 20, the values of \( p(r_i) \) and \( V_i \) are also calculated by Eq. 12 and Eq. 16. The value of \( C_i^n \) for Treg was defined by Eq. 22.

\[
C_i^n \rightarrow \begin{cases} 
1 & \text{if the n-th neighbor is CD8+} \\
\frac{1}{2} & \text{otherwise}
\end{cases}
\] (22)

\section*{CD8\(^+\) mediated Lysis of myeloma cells}

During the migration of CD8\(^+\) T cells, they moved towards to target cells (MICs or MMMs) and tried to kill them. When a CD8\(^+\) T cell located at a position where there was a myeloma cell, the target cell was labeled with a status variable and will put into apoptosis list in the next time step.

\section*{Suppression effect of Tregs on CD8\(^+\)}

When regulatory T cells were activated, they would sharply colon themselves. Tregs would move towards CD8\(^+\) T cells and tried to suppress the generation of CD8\(^+\) T cells by inducing cell cycle arrest or direct apoptosis.

\section*{Apoptosis}

At each time step, if the apoptosis rate of the cell (MIC, MM, CD8\(^+\), and Treg) was lesser than the threshold; all four types of cells in this system would start apoptosis. Cell took 10 time steps to finish apoptosis and was then absorbed. As we discussed in this study, cytotoxic drug BTZ increased the apoptosis rate of cancer cell as Eq. 23 (for MIC) and Eq. 24 (for MM).
\[ Apop_{\text{mic}} = Apop_{\text{mic}}^b + Apop_{\text{mic}}^t \ast (1 - Sur_{\text{mic}}^{\text{BTZ}} \ast Sur_{\text{cin}}) \]  

(23)

According to Eq.23, we can see that the apoptosis of MIC cell are regulated by two factors: (1) BTZ treatment; (2) CD8+ mediated lysis. They were defined with Eq. 24–25.

\[ Sur_{\text{mic}}^{\text{BTZ}} = \left( \frac{S_a}{K_a} \right)^3 + \frac{S_b}{K_b} \]  

(24)

\[ Sur_{\text{cin}} = \left( \frac{S_a}{K_a} \right)^4 + \frac{S_b}{K_b} \]  

(25)

Where \( S_a \) is the ODE-inferred survival rate based on the local stiffness and relative concentration of BTZ. \( S_b \) is the CD8-induced survival ratio of myeloma cell [1]. As to MM cell, its apoptosis rate was defined as Eq. 26.

\[ Apop_{\text{mm}} = Apop_{\text{mm}}^b + Apop_{\text{mm}}^t \ast \left(1 - Sur_{\text{mm}}^{\text{BTZ}} \ast Sur_{\text{cin}}\right) \]  

(26)

\[ Sur_{\text{mm}}^{\text{BTZ}} = \left( \frac{S_a}{K_a} \right)^4 + \frac{S_b}{K_b} \]  

(27)

Where \( S_b \) is the BTZ-induced survival ratio inferred from literature [4]. At last, the apoptosis rates of CD8+ and Treg were defined as Eq.28–29.

\[ Apop_{\text{cd8}} = Apop_{\text{cd8}}^b + Apop_{\text{cd8}}^t \ast \left[ \frac{T_{ij}}{K_T} \right] \]  

(28)

\[ Apop_{\text{treg}} = Apop_{\text{treg}}^b + Apop_{\text{treg}}^t \ast \left[ \frac{LEN}{K_T} \right] \]  

(29)

**Tissue scale**

In the tissue scale of this HABM model, the secretion of SDF-1 (from MIC) and TGFβ (from both MM and BMSC) and the diffusion of them in the 3D ECM defined the dynamic 3D distribution of SDF-1 and TGFβ, which were both described as Eq.30.

\[ S_{ij}(t+1) = (1 - \text{deg}) \left[ S_{ij}(t) \ast (1 - \mu) + \frac{\mu}{6} \sum S_{kl}(t) \right] \]  

(30)

\[ S_{ij}(t+1) \] was the concentration of the factor on the location \( P_{ij} \) in the time step \( t+1 \), and \( \mu \) was the diffusion constant. \( S_{ij}(t), i=1,2,...,6 \) were the factor’s values of \( P_{ij} \)’s six immediate neighbors in the current time step \( t \). The constant \( \text{deg} \) represented the degrading rate.

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Supplementary Figure S1: Significant expressed proteins in the RPPA dataset of BMSCs.

Supplementary Figure S2: Manually developed signaling pathway map of MIC based on RPPA data.
Supplementary Figure S3: Growth and Drug resistance of SP U266 Cells on Hydrogel and Collagen Gels and model prediction. 

(A) the cell viability of MIC cells on Collagen gels. 
(B) growth of MIC cells on hydrogel treated 6 days by Bortezomib. 
(C–D) The predicted cell viabilities of MIC cells with or without BTZ treatment.
Supplementary Figure S4: The adhesion of MIC cells. (A) the difference of adhesion ability between Normal BMSC and Myeloma BMSC. (B) stiffness-induced effect on the adhesion of MICs. (C) The predicted adhesion ability of MICs on hydrogel with different stiffness levels.
Supplementary Figure S5: The growth of myeloma in bone marrow with or without immune system.

Supplementary Figure S6: Synergy effects of BTZ, LEN, and Thal on total myeloma growth in BMSC niches. Blue points indicate synergistic and red points represent antagonistic.
Supplementary Figure S7: The fitting curves of the ODE model of myeloma BMSC.
Supplementary Figure S8: The results of uncertainty analysis for the output variable stiffness in the ODE system in BMSC. The line with green color corresponds to the output of the baseline model (BMSC).

Supplementary Figure S9: The results of uncertainty analysis for the output variables (survival rate and adhesion rate) in the ODE system in MIC. Two lines with green color correspond to survival rate and adhesion rate of the baseline model (MIC).
### Supplementary Table S1: The significant expressed proteins in MIC under condition of 400 pa to 100 pa

| Antibody Name                  | 400 Pa VS 100 Pa |
|--------------------------------|------------------|
| HER2_pY1248                    | 2.67403          |
| IRS-1(V)                       | 2.21406          |
| HSP70(c)                       | 2.209577         |
| Pras40_pT246(V)                | 2.099551         |
| BCL-2(V)(Mouse)                | 2.099497         |
| P90RSK_pT359_S363(C)           | 2.085224         |
| Shc                            | 1.993025         |
| IGFBP2(V)                      | 1.757789         |
| PARP cleaved                   | 1.754373         |
| ACC1(c)                        | 1.634121         |

### Supplementary Table S2: The estimated parameters in the ODE system of SDF1-triggered BMSC stiffness

|  | K<sub>1</sub> | H<sub>1</sub> | d<sub>1</sub> | H<sub>1</sub> | d<sub>1</sub> |
|---|--------------|---------------|---------------|---------------|---------------|
|  | 0.5609       | 0.2244        | 0.2246        | 0.3456        | 0.6791        |
|  | 0.5004       | 0.5020        | 0.1284        | 0.8460        | 0.524         |
|  | 0.98         | 0.1           | 0.9893        | 0.6183        | 0.1347        |
|  | 0.8905       | 0.1902        | 0.8363        | 0.2110        | 0.6820        |
|  | 0.0910       | 0.3744        | 0.0447        | 0.2110        | 0.6820        |
|  | 0.7677       | 0.9960        | 0.4953        | 0.6820        | 0.5872        |
|  | 0.7731       | 0.9231        | 0.1271        | 0.5872        | 0.3591        |
|  | 0.6381       | 0.6379        | 0.1182        | 0.8035        | 0.3076        |
|  | 0.1729       | 0.1232        | 0.0447        | 0.2110        | 0.6820        |
|  | 0.9854       | 0.6788        | 0.4953        | 0.6820        | 0.1023        |

### Supplementary Table S3: The estimated parameters in the ODE system of MICs

|  | K<sub>1</sub> | H<sub>1</sub> | d<sub>1</sub> | H<sub>1</sub> | d<sub>1</sub> |
|---|--------------|---------------|---------------|---------------|---------------|
|  | 0.5932       | 0.2164        | 0.1284        | 0.5872        | 0.3591        |
|  | 0.3480       | 0.8460        | 0.524         | 0.8035        | 0.3076        |
|  | 0.0310       | 0.9893        | 0.6820        | 0.1023        | 0.1023        |
|  | 0.8107       | 0.8363        | 0.524         | 0.8035        | 0.3076        |
|  | 0.3256       | 0.0447        | 0.6820        | 0.1023        | 0.1023        |
|  | 0.4187       | 0.4953        | 0.524         | 0.8035        | 0.3076        |
|  | 0.6662       | 0.1271        | 0.6820        | 0.1023        | 0.1023        |
|  | 0.7570       | 0.3366        | 0.524         | 0.8035        | 0.3076        |
|  | 0.5238       | 0.1182        | 0.6820        | 0.1023        | 0.1023        |
|  | 0.3867       | 0.5586        | 0.524         | 0.8035        | 0.3076        |
|  | 0.8945       | 0.3076        | 0.6820        | 0.1023        | 0.1023        |
|  | 0.7326       | 0.1023        | 0.524         | 0.8035        | 0.3076        |

|  | K<sub>BZM</sub> | H<sub>BZM</sub> |
|---|-----------------|-----------------|
|  | 0.7326          | 0.1023          |
## Supplementary Table S4: The parameters were used in ABM

| Symbol | Variable                                                                 | Initial value      | Reference |
|--------|--------------------------------------------------------------------------|--------------------|-----------|
| $E_0$  | Base stiffness of BMSC                                                  | 250pa              | [5]       |
| $K_E$  | Coefficient of Hill Function                                            | $\frac{530 \sim 250}{2}$ pa | [5]       |
| $P_u$  | Initial proliferation rate of MIC cells                                 | 0.01               | [6–8]     |
| $P_u^2$| Initial proliferation rate of MM cells                                  | 0.065              |           |
| $P\_pathway$\* | Effects of MIC stiffness pathway on proliferation               | 0.058              |           |
| $P\_pathway^2$* | Effects of MM stiffness pathway on proliferation                     | 0                   | [8]       |
| $\text{Pro}l_{\text{CD8+}}^0$ | Initial proliferation rate of CD8+ T cells                          | 0.01               |           |
| $\text{Pro}l_{\text{CD8+}}^1$* | Effects of LEN dose, TGFβ concentration, and Treg population on proliferation of CD8+ | 0.02               |           |
| $K_L^*$ | Coefficient of Hill Function                                           | 0.47               | [9]       |
| $K^*$  | Coefficient of Hill Function                                            | 0.5                | [10]      |
| $K_T^*$ | Coefficient of Hill Function                                           | 0.5                |           |
| $\text{Pro}l_{\text{Treg}}^0$* | Initial proliferation rate of Treg                                  | 0.01               |           |
| $\text{Pro}l_{\text{Treg}}^1$* | Effects of LEN dose and TGFβ concentration on proliferation of CD8+  | 0.023              |           |
| $r\_pathway$ | Effects of MIC stiffness pathway on MIC self-renewal                   | 0.15               | [8]       |
| $D$    | Migration speed index                                                  | 2 $\mu$m           | [8]       |
| $E_{E,0}^*$ | Myeloma base preference to attached to MBSMC                          | 0.5                | [6, 7]    |
| $E_{E,max}^*$ | Myeloma increased preference to attached to MBMSC                      | 0.5                | [6]       |
| $\text{Apop}_{\text{MIC}}^0$ | Initial apoptosis rate of MIC                                         | 0.005              | [6–8, 11] |
| $\text{Apop}_{\text{MIC}}^1$ | Effects of BTZ dose and CD8+ population on apoptosis of MIC           | 0.03               | [1, 7, 8, 11] |
| $\text{Apop}_{\text{MM}}^0$ | Initial apoptosis rate of MM                                           | 0.01               | [6, 7, 11] |
| $\text{Apop}_{\text{MM}}^1$ | Effects of BTZ dose and CD8+ population on apoptosis of MM            | 0.055              | [1, 4]    |
| $K_a^*$ | Coefficient of Hill Function                                           | 0.4                | [6]       |
| $K_b^*$ | Coefficient of Hill Function                                           | 0.5                | [1]       |
| $K_c^*$ | Coefficient of Hill Function                                           | 0.6                | [4]       |
| $\text{Apop}_{\text{Treg}}^0$* | Initial apoptosis rate of CD8+ T cells                               | 0.01               |           |
| $\text{Apop}_{\text{Treg}}^1$* | Effects of TGFB concentration on apoptosis of CD8+ T cells            | 0.01               |           |
| $\text{Apop}_{\text{Treg}}^0$* | Initial apoptosis rate of Tregs                                       | 0.01               |           |
| $\text{Apop}_{\text{Treg}}^1$* | Effects of LEN dose and TGFβ concentration on apoptosis of Tregs      | 0.02               |           |
| Lamada SDF1 | Diffusion constant of SDF-1                                             | 0.612              | [6, 7]    |
| Lamada TGFβ | Diffusion constant of TGFβ                                              | 0.44               | [6, 7]    |

*: Indirectly inferred.