Meaning	KCs	Value Adopted	Evidence
Association rate for BK and B2R Disassociation rate for BK:B2R	k_{α}^{+} k_{α}^{-}	$3.4 \times 10^{8}\ M^{-1}s^{-1}$ $1\ s^{-1}$	BK can bind to B2R with a high affinity (k_d = 2.9× 10^{-9}) [1]. k^{-} is unknown; we assume a small value for k^{-}= 1 s^{-1}. Using the formula $k_d = \frac{k^{-}}{k^{+}}$, determined the association rate k^{+} for BK and B2R.
Generation of BK by P-KAL:HK	k_{α}	0.1 s^{-1}	The product of P-KAL and HK can release BK [2]. The generation rate is unknown; we estimated a small value for it.
Inhibation of BK by TAFIa	$k_{\beta 1}^{+}$	2.8× $10^{5} M^{-1}s^{-1}$	As for BK and TAFIa binding, k_{cat} = 19.7 s^{-1} , k_m = 70.6 μM [3]. Assume a small value for k^{-} = 0.1. Using the formula $k^{+} = \frac{k^{-}+k_{cat}}{k_m}$ determined the association rate k^{+} for BK and TAFIa.
Association rate for P-KAL and HK Disassociation rate for P-KAL:HK	k_{τ}^{+} k_{τ}^{-}	8.3× $10^{7}\ M^{-1}s^{-1}$ $1s^{-1}$	BK can binds to B2R with high specificity and affinity (disassociation constant k_d= 1.2× 10^{-8}) [4]. The association rate for P-KAL and HK k^{+} can be computed from the formula $k_d = \frac{k^{-}}{k^{+}}$. Assumed a small value for k^{-}.
Activation of HK by KAL	k_{σ}^{+}	8.3× $10^{7}\ M^{-1}s^{-1}$	Estimated based on the association rate of P-KAL and HK.
Activation of KAL by P-KAL	k_{γ}^{+}	2.7× $10^{4}\ M^{-1}s^{-1}$	KAL auto-activation [5], [6].
Production of IL-6 by BK:B2R	$k_{\omega 1}$	$0.1s^{-1}$	BK, via B2R, can stimulate the production of IL-6 [7]. Estimation of the production rate of IL-6 by the BK and B2R complex.
Degradation rate of IL-6	k_{φ}^{-}	0.1 s^{-1}	Assumption.
Cleavage rate of BK by Icatibant	k_{c1} k_{m1}	0.1 s^{-1} 1 M	Assumption.
Cleavage rate of BK:B2R by Icatibant	k_{c2} k_{m2}	0.1 s^{-1} 1 M	Assumption.
Cleavage of C5 by KAL	k_{c3} k_{m3}	0.01 s^{-1}	Kallikrein can cleaves C5 as reported by Conway [8]. Assumed small values for the

		$1.0 \times 10^{-12}\ M$	catalytic rate constant and Michaelis constant
Cleavage rate of C5a:C5aR1 by IFX1	k_{c4} k_{m4}	0.1 s^{-1} 1 M	Assumption.
Inhibation of C5a by TAFIa	$k_{\beta 2}^{+}$	1.35× $10^{5} M^{-1} s^{-1}$	TAFIa can inhibit C5a. $\mathrm{k_{cat}} = 29.5\ \mathrm{s}^{-1}$, k_m= 219.0 μM [3], [9]. Assume a small value for $k^{-} = 0.1\mathrm{s}^{-1}$. Using the formula $k^{+} = \frac{k^{-} + \mathrm{k_{cat}}}{k_m}$, determined the association rate k^{+} for C5a and TAFIa.
Inhibition of B2R by Icatibant	$k_{\gamma 1}^{+}$	1.0× $10^{2} M^{-1} s^{-1}$	A drug Icatibant specifically targets the B2R, it has a strong binding affinity (with a K_i value of 0.064nM) for the B2R [8]. The association rate for Icatibant and B2R is assumed. (See https://go.drugbank.com/drugs/DB06196). It can be used against COVID-19 [11].
Inhibition of C5 and C5a by IFX-1	$k_{\gamma 2}^{+}$	1.0× $10^{2} M^{-1} s^{-1}$	The association rate for IFX1 (Vilobelimab) and C5 is assumed.
Inhibition of C5a by IFX1	$k_{\gamma 3}^{+}$	1.0× $10^{3} M^{-1} s^{-1}$	Vilobelimab (IFX1) is a chimeric monoclonal immunoglobulin G4 (IgG4) antibody that binds to the soluble form of human C5a with high affinity. The dissociation constant is 9.6pM (See https://go.drugbank.com/drugs/DB16416). The Anti-C5a antibody, IFX1 showed an effective treatment vs. severe COVID-19 treatment [12]. The association rate for IFX1 and C5a is estimated.
Association rate for C5a and C5aR1 Disassociation rate for C5a:C5aR1	k_{λ}^{+} k_{λ}^{-}	$2.2 \times 10^{8}\ \mathrm{M}^{-1}\mathrm{s}^{-1}$ $0.1\ \mathrm{s}^{-1}$	$\mathrm{k_d}$ for the product C5a:C5aR1 is $\approx 4.5 \times 10^{-9}$M and free energy of association ($\Delta \mathrm{G_{bind}}$) is -13.6 ± 4.1 kcalmol^{-1}[13]. Assumed k^{-} = 0.1 s^{-1}, estimated for k^{+} by formula $\mathrm{k_d} = \frac{\mathrm{k}^{-}}{\mathrm{k}^{+}} = \mathrm{e}^{\frac{\Delta \mathrm{G_{bind}}}{\mathrm{RT}}}$.
Production of IL-6 by C5a:C5aR1	$k_{\omega 2}$	$0.1\ s^{-1}$	C5a via C5aR1 can induce IL-6 as reported by Vlaar et al. [14]. Estimation for production rate of IL-6 by C5a and C5aR complex.

Table S1. The kinetic constants for the entities interactions in the biochemical network as model.

References

[1] J. Feierler, M. Wirth, B. Welte, S. Schüssler, M. Jochum, and A. Faussner, “Helix 8 plays a crucial role in bradykinin B 2 receptor trafficking and signaling,” J. Biol. Chem., vol. 286, no. 50, pp. 43282–43293, 2011, doi: 10.1074/jbc.M111.256909.

[2] M. L. Merchant et al., “Plasma kininogen and kininogen fragments are biomarkers of progressive renal decline in type 1 diabetes,” Kidney Int., vol. 83, no. 6, pp. 1177–1184, Jun. 2013, doi: 10.1038/ki.2013.8.

[3] T. Myles et al., “Thrombin Activatable Fibrinolysis Inhibitor, a Potential Regulator of Vascular Inflammation,” J. Biol. Chem., vol. 278, no. 51, pp. 51059–51067, 2003, doi: 10.1074/jbc.M306977200.

[4] T. Renné, J. Dedio, J. C. M. Meijers, D. Chung, and W. Müller-Esterl, “Mapping of the discontinuous H-kininogen binding site of plasma prekallikrein. Evidence for a critical role of apple domain-2,” J. Biol. Chem., vol. 274, no. 36, pp. 25777–25784, 1999, doi: 10.1074/jbc.274.36.25777.

[5] M. S. Chatterjee, W. S. Denney, H. Jing, and S. L. Diamond, “Systems Biology of Coagulation Initiation: Kinetics of Thrombin Generation in Resting and Activated Human Blood,” PLoS Comput. Biol., vol. 6, no. 9, p. e1000950, Sep. 2010, doi: 10.1371/journal.pcbi.1000950.

[6] R. Méndez Rojano et al., “Kinetics of the coagulation cascade including the contact activation system: sensitivity analysis and model reduction,” Biomech. Model. Mechanobiol., vol. 18, no. 4, pp. 1139–1153, 2019, doi: 10.1007/s10237-019-01134-4.

[7] G. WANG, Y. YE, X. ZHANG, and J. SONG, “Bradykinin stimulates IL-6 production and cell invasion in colorectal cancer cells,” Oncol. Rep., vol. 32, no. 4, pp. 1709–1714, Oct. 2014, doi: 10.3892/or.2014.3366.

[8] E. M. Conway, “Reincarnation of ancient links between coagulation and complement,” J. Thromb. Haemost., vol. 13, no. S1, pp. S121–S132, 2015, doi: 10.1111/jth.12950.

[9] J. H. Foley, P. F. Cook, and M. E. Nesheim, “Kinetics of activated thrombin-activatable fibrinolysis inhibitor (TAFIa)-catalyzed cleavage of C-terminal lysine residues of fibrin degradation products and removal of plasminogen-binding sites,” J. Biol. Chem., vol. 286, no. 22, pp. 19280–19286, 2011, doi: 10.1074/jbc.M110.215061.

[10] J. Shen and H. Zhang, “Function and structure of bradykinin receptor 2 for drug discovery,” Acta Pharmacol. Sin., vol. 44, no. 3, pp. 489–498, Mar. 2023, doi: 10.1038/s41401-022-00982-8.

[11] J. A. Roche and R. Roche, “A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications,” FASEB J., vol. 34, no. 6, pp. 7265–7269, 2020, doi: 10.1096/fj.202000967.

[12] A. P. J. Vlaar et al., “Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial,” Lancet Rheumatol., vol. 2, no. 12, pp. e764–e773, Dec. 2020, doi: 10.1016/S2665-9913(20)30341-6.

[13] A. C. Dumitru et al., “Submolecular probing of the complement C5a receptor–ligand binding reveals a cooperative two-site binding mechanism,” Commun. Biol., vol. 3, no. 1, pp. 1–13, 2020, doi: 10.1038/s42003-020-01518-8.

[14] P. Conigliaro, P. Triggianese, C. Perricone, M. S. Chimenti, and R. Perricone, “COVID-19: disCOVering the role of complement system,” Clin Exp Rheumatol, vol. 38, pp. 587–591, 2020.