Table S1: **Summary of the computational model**

Proteins and protein complexes	Model component	Initial Concentration	Location
		μM	
IKK	IKK	0.001, 0.8 [a]	Cytoplasm
NF-κB	NFkB	0	Cytoplasm
NF-κB	NFkBn	0	Nucleus
IκBα	IkBa	0	Cytoplasm
IκBα	IkBan	0	Nucleus
IκBβ	IkBb	0	Cytoplasm
IκBβ	IkBbn	0	Nucleus
IκBε	IkBe	0	Cytoplasm
IκBε	IkBen	0	Nucleus
IκBα mRNA	IkBat	0	Cytoplasm
IκBβ mRNA	IkBbt	0	Cytoplasm
IκBε mRNA	IkBet	0	Cytoplasm
IKK-IκBα	IKKIkBa	0	Cytoplasm
IKK-IκBβ	IKKIkBb	0	Cytoplasm
IKK-IκBε	IKKIkBe	0	Cytoplasm
IκBα-NF-κB	IkBaNFkB	0.0875	Cytoplasm
IκBα-NF-κB	IkBaNFkBn	0	Nucleus
IκBβ-NF-κB	IkBbNFkB	0.025	Cytoplasm
IκBβ-NF-κB	IkBbNFkBn	0	Nucleus
IκBε-NF-κB	IkBeNFkB	0.0125	Cytoplasm
IκBε-NF-κB	IkbeNFkBn	0	Nucleus
IKK-IκBα-NF-κB	IKKIkBaNFkB	0	Cytoplasm
IKK-IκBβ-NF-κB	IKKIkBbNFkB	0	Cytoplasm
IKK-IκBε-NF-κB	IKKIkBeNFkB	0	Cytoplasm
Reaction	**Parameter:Value**	**Category**	**Location**
IkBa + IKK → IKKIkBa	a_c_ai: 1.35 μM^{-1} min^{-1}	Association	Cytoplasm
IkBa + NFkB → IkBaNFkB	a_c_an: 30.0 μM^{-1} min^{-1}	Association	Cytoplasm
IkBb + IKK→ IKKIkBb	a_c_bi: 0.36 μM^{-1} min^{-1}	Association	Cytoplasm
IkBb + NFkB → IkBbNFkB	a_c_bn: 30.0 μM^{-1} min^{-1}	Association	Cytoplasm
IkBe + IKK→ IKKIkBe	a_c_ei: 0.54 μM^{-1} min^{-1}	Association	Cytoplasm
IkBe + NFkB → IkBeNFkB	a_c_en: 30.0 μM^{-1} min^{-1}	Association	Cytoplasm
IKKIkBa + NFkB →	a_c_2ain: 30.0 μM^{-1}	Association	Cytoplasm

IKKIkBaNFkB	min^{-1}		
IkBaNFkB + IKK → IKKIkBaNFkB	a_c_2ani: 11.1 μM^{-1} min^{-1}	Association	Cytoplasm
IKKIkBb + NFkB → IKKIkBbNFkB	a_c_2bin: 30.0 μM^{-1} min^{-1}	Association	Cytoplasm
IkBbNFkB + IKK → IKKIkBbNFkB	a_c_2bni: 2.88 μM^{-1} min^{-1}	Association	Cytoplasm
IKKIkBe + NFkB → IKKIkBeNFkB	a_c_2ein: 30.0 μM^{-1} min^{-1}	Association	Cytoplasm
IkBeNFkB + IKK → IKKIkBeNFkB	a_c_2eni: 4.2 μM^{-1} min^{-1}	Association	Cytoplasm
IkBan + NFkBn → IkBaNFkBn	a_n_an: 30.0 μM^{-1} min^{-1}	Association	Nucleus
IkBbn + NFkBn → IkBbNFkBn	a_n_bn: 30.0 μM^{-1} min^{-1}	Association	Nucleus
IkBen + NFkBn → IkBeNFkBn	a_n_en: 30.0 μM^{-1} min^{-1}	Association	Nucleus
IKKIkBa → IkBa + IKK	d_c_ai: 0.075 min^{-1}	Dissociation	Cytoplasm
IkBaNFkB → IkBa + NFkB	d_c_an: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBb → IkBb + IKK	d_c_bi: 0.105 min^{-1}	Dissociation	Cytoplasm
IkBbNFkB → IkBb + NFkB	d_c_bn: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBe → IkBe + IKK	d_c_ei: 0.105 min^{-1}	Dissociation	Cytoplasm
IkBeNFkB → IkBe + NFkB	d_c_en: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBaNFkB → IKKIkBa + NFkB	d_c_2ain: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBaNFkB → IkBaNFkB + IKK	d_c_2ani: 0.075 min^{-1}	Dissociation	Cytoplasm
IKKIkBbNFkB → IKKIkBb + NFkB	d_c_2bin: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBbNFkB → IkBbNFkB + IKK	d_c_2bni: 0.105 min^{-1}	Dissociation	Cytoplasm
IKKIkBeNFkB → IKKIkBe + NFkB	d_c_2ein: 6E-5 min^{-1}	Dissociation	Cytoplasm
IKKIkBeNFkB → IkBeNFkB + IKK	d_c_2eni: 0.105 min^{-1}	Dissociation	Cytoplasm
IkBaNFkBn → IkBan + NFkBn	d_n_an: 6E-5 min^{-1}	Dissociation	Nucleus
IkBbNFkBn → IkBbn	d_n_bn: 6E-5 min^{-1}	Dissociation	Nucleus

+ NFkBn			
IkBeNFkBn → IkBen + NFkBn	d_n_en: 6E-5 min^{-1}	Dissociation	Nucleus
IkBan → IkBa	ex_a: 0.012 min^{-1}	Export	-
IkBbn → IkBb	ex_b: 0.012 min^{-1}	Export	-
IkBen → IkBe	ex_e: 0.012 min^{-1}	Export	-
NFkBn → NFkB	ex_n: 0.0048 min^{-1}	Export	-
IkBaNFkBn → IkBaNFkB	ex_2an: 0.828 min^{-1}	Export	-
IkBbNFkBn → IkBbNFkB	ex_2bn: 0.414 min^{-1}	Export	-
IkBeNFkBn → IkBeNFkB	ex_2en: 0.414 min^{-1}	Export	-
IkBa → IkBan	in_a: 0.018 min^{-1}	Import	-
IkBb → IkBbn	in_b: 0.018 min^{-1}	Import	-
IkBe → IkBen	in_e: 0.018 min^{-1}	Import	-
NFkB → NFkBn	in_n: 5.4 min^{-1}	Import	-
IkBa →	pd_c_a: 0.12 min^{-1}	Prot. deg.	Cytoplasm
IkBb →	pd_c_b: 0.18 min^{-1}	Prot. deg.	Cytoplasm
IkBe →	pd_c_e: 0.18 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBa → IKK	pd_c_2ai: 1.8E-3 min^{-1}	Prot. deg.	Cytoplasm
IkBaNFkB → NFkB	pd_c_2an: 6E-5 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBb → IKK	pd_c_2bi: 1.8E-3 min^{-1}	Prot. deg.	Cytoplasm
IkBbNFkB → NFkB	pd_c_2bn: 6E-5 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBe → IKK	pd_c_2ei: 1.8E-3 min^{-1}	Prot. deg.	Cytoplasm
IkBeNFkB → NFkB	pd_c_2en: 6E-5 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBaNFkB → IKK + NFkB	pd_c_3ain: 0.36 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBbNFkB → IKK + NFkB	pd_c_3bin: 0.12 min^{-1}	Prot. deg.	Cytoplasm
IKKIkBeNFkB → IKK + NFkB	pd_c_3ein: 0.18 min^{-1}	Prot. deg.	Cytoplasm
IkBaNFkBn → NFkBn	pd_n_2an: 6E-5 min^{-1}	Prot. deg.	Nucleus
IkBbNFkBn → NFkBn	pd_n_2bn: 6E-5 min^{-1}	Prot. deg.	Nucleus
IkBeNFkBn → NFkBn	pd_n_2en: 6E-5 min^{-1}	Prot. deg.	Nucleus
IkBan →	pd_n_a: 0.12 min^{-1}	Prot. deg.	Nucleus
IkBbn →	pd_n_b: 0.18 min^{-1}	Prot. deg.	Nucleus

IkBen →	pd_n_e: 0.18 min^{-1}	Prot. deg.	Nucleus
→ IkBa	ps_c_a: 0.2448 min^{-1}	Prot. synth.	Cytoplasm
→ IkBb	ps_c_b: 0.2448 min^{-1}	Prot. synth.	Cytoplasm
→ IkBe	ps_c_e: 0.2448 min^{-1}	Prot. synth.	Cytoplasm
IkBat →	rd_a: 0.0336 min^{-1}	RNA deg.	-
IkBbt →	rd_b: 0.0168 min^{-1}	RNA deg.	-
IkBet →	rd_e: 0.0118 min^{-1}	RNA deg.	-
→ IkBat (induced by NF-κB)	rsr_an: 1.386 μM^{-1} min^{-1} h_an: 2.0	RNA synth.	-
→ IkBbt (induced by NF-κB)	rsr_bn: 0.01 μM^{-1} min^{-1} rsr_delay: 45 min h_bn: 2.0	RNA synth.	-
→ IkBet (induced by NF-κB)	rsr_en: 0.18 μM^{-1} min^{-1} rsr_delay: 45 min h_en: 2.0	RNA synth.	-
→ IkBat (constitutive)	rsu_a: 1.848E-4 min^{-1}	RNA synth.	-
→ IkBbt (constitutive)	rsu_b: 4.272E-5 min^{-1}	RNA synth.	-
→ IkBet (constitutive)	rsu_e: 4.572E-6 min^{-1}	RNA synth.	-
IKK →	pd_c_i: 0.0 min^{-1} pd_c_i_2: 7.2E-3 min^{-1} pd_c_i_3: 1.0 min^{-1}	Prot. deg.	Cytoplasm

The model contains 24 components with distinct nuclear and cytoplasmic localizations and is comprised of 72 reactions. NF-κB–inducible IκB transcription reactions (IkBat, IkBbt, and IkBet; all induced by NF-κB) use a Hill coefficient with a value of 2.0. NF-κB–inducible IκBε and -β transcription reactions (IkBbt and IkBet) utilize previous values of nuclear NF-κB to affect the poststimulation transcriptional delay observed by RPA. Degradation of the IKK input signal follows different kinetics for equilibrium, poststimulation, and recovery simulation phases.

[a]The initial concentration of IKK is 0.001 μM during the equilibration phase and steps to 0.8 at the start of the stimulation phase.