Models of the IKK-\( \kappa \)B-NF\( \kappa \)B module (single NF\( \kappa \)B dimer)

1.0. Hoffmann et al. 2002  Science 298 pp.1241 (Levchenko)
   - reproduces activation and attenuation of NF-kB in response to TNF pulse (> 5min) and persistent stimulation in wt, ikbe\(^{+/}b^{-}\), ikbe\(^{+/}a^{+/}\), ikbe\(^{+/}b^{+/}\)
   - uses an assumed IKK curve as input
   - includes regulated IkB\( \beta \) transport to mimic nuclear accumulation of a hypo-phosphorylated form reported by S Ghosh lab
   - unable to reproduce the steady state NF-kB control of “resting cells” in knockouts
   - was also used in Barken et al. 2005  Science 308, pp.52a: amplitude and period of oscillatory response is regulated by the NF-kB expression level

SBML NF\( \kappa \)B Model version 1:
BIOMD0000000140 (WT cells); BIOMD0000000139 (IkB\( \beta \)-e\(^{-}\) cells)

1.1. O’Dea et al. 2007, MSB 3:111 (Barken/Kearns)
   - this model is about the steady state: use it only for equilibration phase simulations
   - reproduces steady state control of NF-kB in “resting” wild-type and knockout cells (except for ik\( \beta ^{a^{-}b^{-}} \)) and the experimentally determined ratios of free and bound IkB protein pools
   - includes newly measured degradation rate constants including nuclear degradation of free and bound IkB protein pools
   - includes basal IKK activity in resting cells

BIOMD0000000147 (WT cells)

1.2. Kearns et al. 2006  JCB 173, pp.659 (Kearns)
   - includes newly described negative feedback for IkBe, provides mechanism for steadying NF-kB activity at late times of the TNF timecourse
   - also recapitulates NF-kB activity of “resting” cells in all knockouts
   - removed Ik\( B \)\( \beta \) transport regulation used in version 1.0.
   - parameters fitted to actual mRNA profiles of IkBa, IkB\( \beta \), IkBe

2.0. Werner et al 2005  Science 309 pp.1857 (Barken)
   - utilizes numerically defined IKK activity profiles as inputs for simulations
   - recapitulates both TNF and LPS-induced NF-kB signaling up to 2 hrs
   - does not contain delay in IkBe negative feedback

MODEL1008110000 (not yet curated)

2.1. Behar et al 2013 Cell, 155, pp.448-461 (Barken)
   - contains delay in IkBe negative feedback
   - improved transport parameters
   - comprehensive parameter sensitivity analysis for TNFc, TNFp and LPSp signaling
   - reproduces NF-kB signaling up to 2hrs in response to all inflammatory stimuli
   - no sustained oscillations in ikbe\(^{+/}b^{-}\) cells

2.2. O’Dea et al 2008 Mol Cell, 30, pp.632 (Kearns)
   - reproduces UV-induction of NF-kB activity via translational inhibition
   - otherwise same as 2.1.

2.3. Mathes et al 2008 EMBO J 27, pp.1357 (O’Dea)
• IKK has no preference for bound IkB over free IkB (based on new experimental results): same IKK-IkB interaction and reaction rates for bound and free IkBs

SBML NFκB Model version 2

3.0 Basak et al. 2007 Cell 128, pp.369 (Kearns)
• includes a newly characterized 4th IkB activity (multimeric complex of p100) whose degradation is unresponsive to TNF but responsive to LTbR
• allows for numerically defined (experimentally measured) inputs for IKK1 and IKK2
• reproduces RelA NF-kB activation in response to stimulation of LTbR, TNFR, and TLR4, although TNF timecourse profile is suboptimal
• reproduces experimentally observed crosstalk between TNFR and LTbR signaling in the control of RelA NF-kB

MODEL8478881246 (not yet curated)

3.1. Shih et al. 2009 PNAS 106, pp.9619 (Kearns)
• Refined synthesis and degradation params for IkBδ
• Shows that IkBδ attenuates NFkB in response to TLR but not cytokine stimuli
• Not used for LTbR signaling (see models in v.5 series)

Models of Receptor-proximal Signaling modules linked to the IKK-IκB-NFκB module (single NFκB dimer)

4.0. Werner et al 2008 Genes Dev, 22. pp.2093 (Kearns)
• uses TNF concentration as an input to calculate NFkB activity in MEFs
• includes TNFR activation steps to complex 1 and IKK and A20
• includes a 3-step IKK cycle including IKKi
• reproduces TNF dose responses: concentration (0.001 ng/ml to 100 ng/ml) and temporal (1 min pulse and up)

• focuses on TNF production by BMDMs in response to TLR stimulation, parameterized by bulk measurements
• TNF production is a function of NFkB-driven mRNA synthesis and p38/ERK-dependent mRNA processing, halflife stabilization, and protein processing
• Then links to 4.0 so that autocrine TNF signaling functions can be explored

4.2. Cheng et al 2015 Science Signaling 8, ra69 (Cheng)
• focuses LPS/TLR4 responsive NFkB activation in Raw264.7 cells
• explores distinction between TRIF and Myd88 pathways
• utilizes single cell datasets: captures the cell-to-cell variability and locates extrinsic noise sources

4.3. Taylor et al in prep
• recapitulates single cell data in BMDMs responding to TNF and various TLR ligands in a dose response
• shows that IkBa feedback mediates both oscillatory and non-oscillatory NFkB
• does not include IkBb, IkBe, IkBd, or A20
• Indicates a role for IkBsome
Models of Multi-Dimer NFκB control modules

5.0. Tsui et al 2015 Nature Communications, 6, 7068. (Tsui)
- develops a model for the NFκB dimer generation module
- to model of p50:p65 (HET) and p65:p65 (HOM) generation and activation
- allows for exploration of the chaperone role of IκBβ in generating p65:p65
- recapitulates canonical activation of p50:p65 and p65:p65

5.1 Shih et al 2012 Nature Immunology, 13(12):1162-70. (Davis-Turak)
- model of RelA:p50, RelB:p50 and RelB:p52 activation
- recapitulates activation of these 3 dimers in MEFs and DCs in response to canonical and non-canonical stimuli

5.2 Alves et al 2014 J. Immunology, 192, pp.3121-32 (Tsui)
- model of RelA:p50, cRel:p50 activation in follicular B-cells long or short term canonical IKK (IgM and LPS)
- explores the dimer specificities of IκBa and IκBe negative feedback
- shows that IκBe is critical for cRel attenuation in a wide variety of conditions

5.3. Almaden et al 2014 Cell Reports, 9, pp.2098-111 (Tsui)
- model of RelA:p50, RelA:52, RelB:p52, cRel:p50, cRel:52, p50:p50, p52:p52 activation in follicular B-cells stimulated with canonical (IgM, LPS) or non-canonical (BAFF) stimuli
- shows that non-canonical stimulation may activate cRel-containing dimers in conditions of canonical stimulation (proliferating cells)
- employs repeated single cell simulations to relate to averaged population biochemical data.

5.4. Mitchell/Tsui et al in prep
- multi-dimer model to investigate RelA:p50 and RelB:p52 activation
- allows exploration of crosstalk between canonical and non-canonical signaling to recapitulate NFκB activation in different cell states

5.5. Mitchell et al in prep
- investigates the role of RelA-mediated synthesis of RelB and p100 in the production/activation of RelB:p52
- shows that a balance of signaling crosstalk and substrate cross-competition allows for licensing and insulation between the two pathways

Models of multi-dimer NFκB modules linked to effector circuits

6.0 Shokhirev et al 2015 Molecular Systems Biology, 11, pp.783-96
Mitchell et al 2018 PNAS 459, pp.428
- links a version of 5.3 to models of apoptosis (Sorger lab) and cell cycle (Tyson lab) effector modules, to allow for simulating B-cell population dynamics as a function of input IKK activities.
- using distributed parameter values, ensemble simulations generate cell-to-cell variable responses as observed by FACS