Models of the IKK-IκB-NFκB module (single NFκB 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$^{-/-}$, ikba$^{-/-}$b$^{-/-}$
- uses an assumed IKK curve as input
- includes regulated IkBb 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 NFκB Model version 1:
BIOMD0000000140 (WT cells); BIOMD0000000139 (IkBb$^{-/-}$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 ikba$^{-/-}$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 IkBb transport regulation used in version 1.0.
- parameters fitted to actual mRNA profiles of IkBa, IkBb, 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$^{-/-}\beta^{-/-}$ 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 IκBδ
- Shows that IkBd 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)

4.1. Caldwell et al 2012 Genes Dev., 28, pp.2120-33 (Cheng)

- 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 NFkB 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 IkBa and IkBe negative feedback
- shows that IkBe 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 NFkB 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