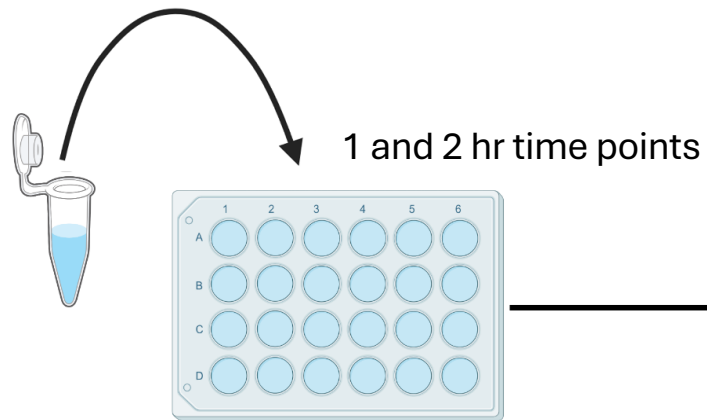
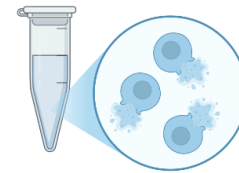


Add LPS to induce IL6 expression



Differentiated THP-1 macrophages



Collect cell lysate



ELISA to measure cAMP levels

Figure S1. *Experimental validation with LPS-induced IL-6 . Use of LPS to induce an elevated IL-6 environment predicted to produce persistently elevated cAMP levels in THP-1 macrophages.*

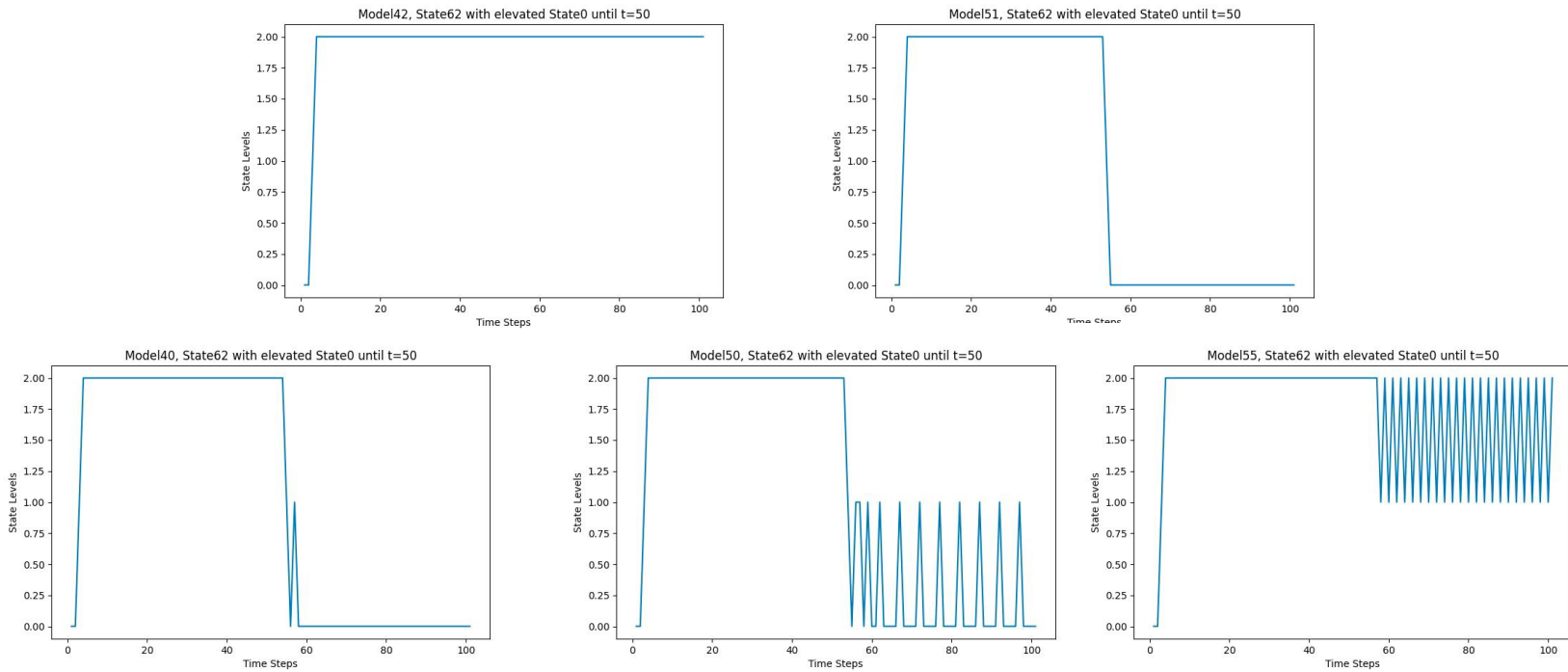
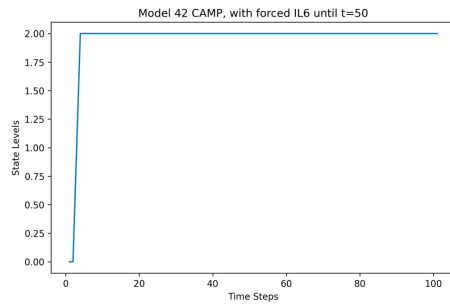
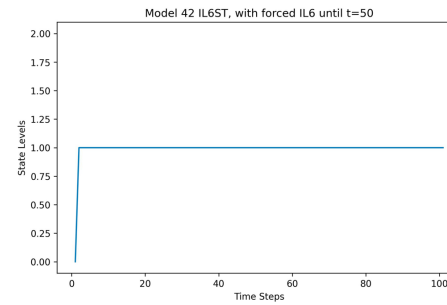


Figure S2. *Characteristic cAMP responses to simulated perturbation experiments.* Simulations (synchronous update) based on 48 models that support persistent stable activation of cAMP show 5 characteristic predicted responses, (a) stable and persistent upregulation, (b) transient upregulation only, (c) transient with single oscillation, (d) transient with sustained slow low-medium oscillation and (e) transient with sustained medium-high rapid oscillation



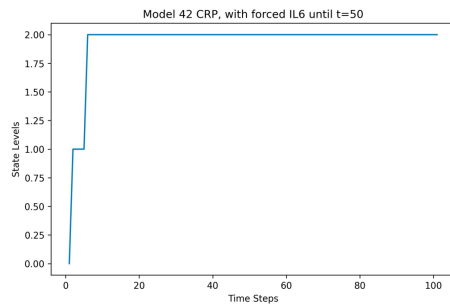
Type A (k=16)

IL6, EGFR, IL17A, POU2F1, POMC, SERPINA3, IL1B, AKT, ADIPOQ, PI3K, MAPK14, MAPK3, STAT1, NOS3, ERBB2, CAMP



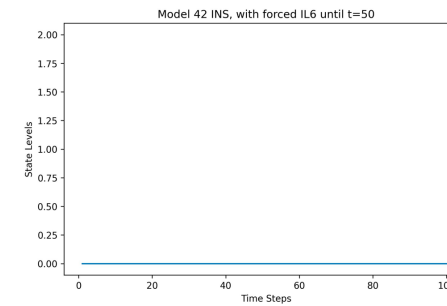
Type B (k=8)

IL6ST, STAT3, RORA, ERK, HCK, CCL2, CD14, IFNG,



Type C (k=1)

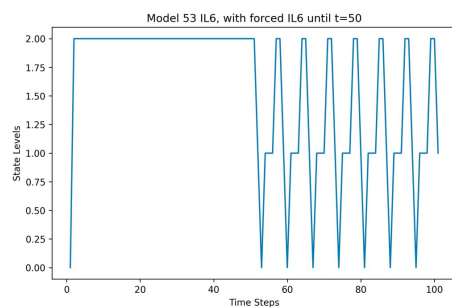
CRP



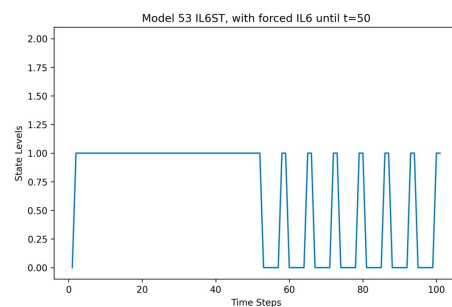
Type D (k=38)

INS, TNF, MAPK1, IKBKB, PTGS2, IKBKG, RIPK1, IL18, CXCL12, CD40LG, AGT, TRAF2, TLR2, TGFA, PTEN, CD40, TIMP3, MAP3K1, TNFRSF1A, RIPK2, CHUK, AKT2, XDH, TNFRSF1B, NFKBIA, IFNA1, MYD88, IFI16, EP300, IRAK1, IRF5, TLR9, CXCL8, IRF7, IRF3, IFNB1, TLR3, TBK1

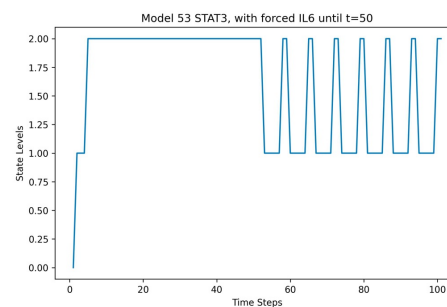
Figure S3. Simulated response for all 63 nodes to IL6 pulse perturbation experiment using Model 42. State transition trajectories for all network nodes resulting from a transient IL6 pulse under synchronous update only.



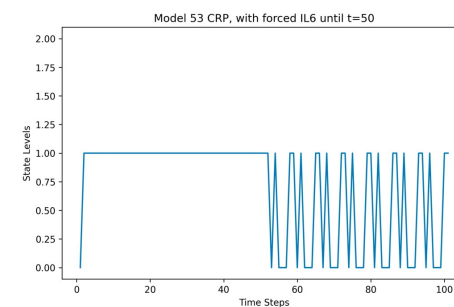
Type A (k=7)
IL6, EGFR, SERPINA3, AKT, PI3K,
MAPK14, MAPK3



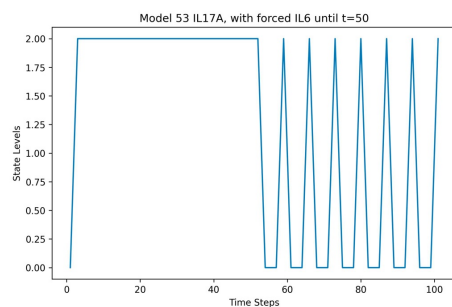
Type B (k=6)
IL6ST, RORA, ERK, HCK, CD14, IFI16



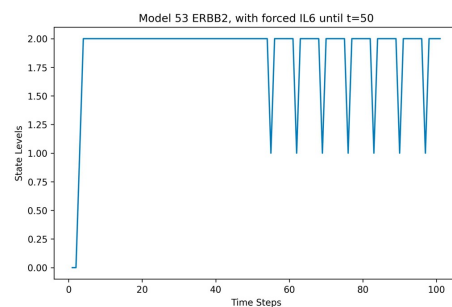
Type C (k=1)
STAT3



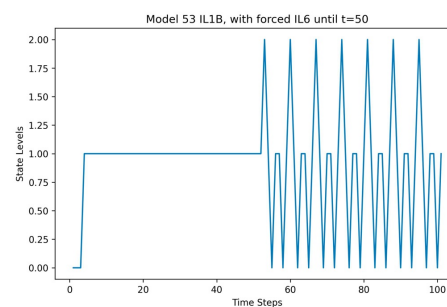
Type D (k=1)
CRP



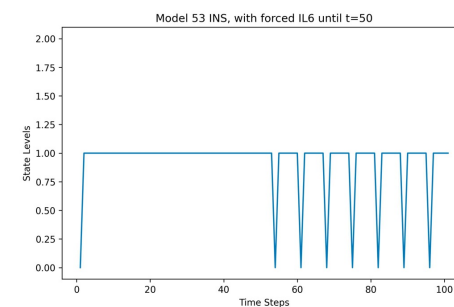
Type E (k=3)
IL17A, POMC, STAT1



Type F (k=2)
POU2F1, ERBB2

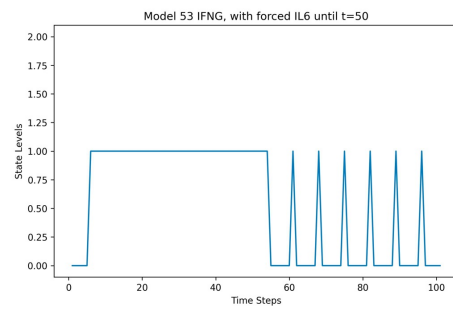


Type G (k=1)
IL1B

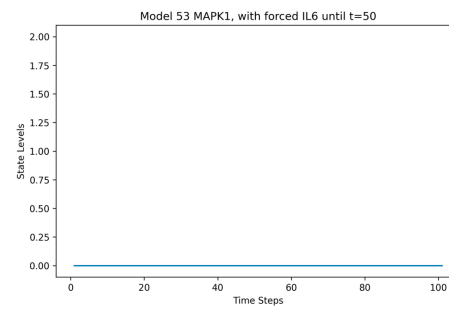


Type H (k=1)
INS

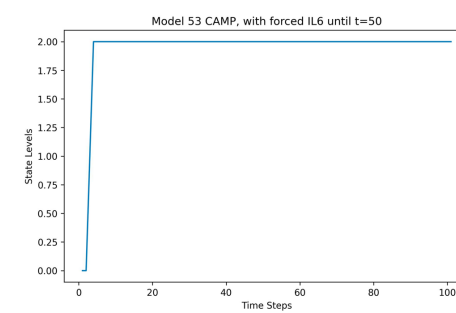
Figure S4(a). Simulated response for all 63 nodes to IL6 pulse perturbation experiment using [Model 53](#). State transition trajectories for all network nodes resulting from a transient IL6 pulse under synchronous update only.



Type I (k=1)
IFNG



Type J (k=37)
TNF, MAPK1, IKBKB, PTGS2, IKBKG, RIPK1, IL18, CXCL12, CCL2, CD40LG, AGT, TRAF2, TLR2, TGFA, PTEN, CD40, TIMP3, MAP3K1, TNFRSF1A, RIPK2, CHUK, AKT2, XDH, TNFRSF1B, NFKBIA, IFNA1, MYD88, EP300, IRAK1, IRF5, TLR6, CXCL8, IRF7, IRF3, IFNB1, TLR3, TBK1



Type K (k=3)
ADIPOQ, NOS3, CAMP

Figure S4(b). Simulated response for all 63 nodes to IL6 pulse perturbation experiment using Model 53. State transition trajectories for all network nodes (cont'd) resulting from a transient IL6 pulse under synchronous update only.