**Supplementary Figure S1: GR-PXR signal regulatory network:** GR-PXR signal regulatory network was constructed in using CellDesigner (v4.0.1; Systems Biology Institute, http://celldesigner.org/index.html), a graphical front-end for creating process diagrams of biochemical networks in Systems Biology Markup Language (SBML) and utilising Systems Biology Graphical Notation (SBGN). Each individual chemical or protein is identified as a species (Gene = gene; mRNA = mRNA; Protein or NR = protein; chemical = chemical). Interactions between species are identified as reactions (re1....ren) , and correspond to reaction identifiers (v1…vn) in Supplementary table S1.
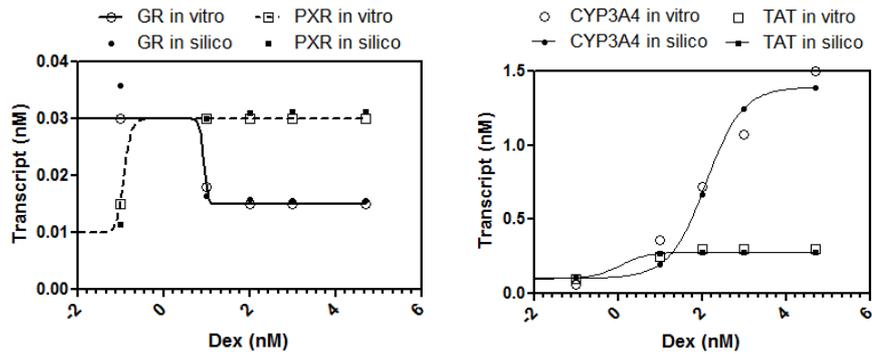
Supplementary Figure S2: In silico model for the response to the artificial glucocorticoid Dexamethasone: Primary human hepatocytes were exposed to vehicle or (0.1-50000 nM) dexamethasone as indicated for 48 hours, RNA extracted and transcript levels of PXR, GR, CYP3A4 and TAT quantified by TaqMan Q-PCR. Average transcript levels (±SEM) from triplicate cultures are indicated by open symbols, and the concentration-response curve shown by the full line was fitted to these data. Transcript levels of PXR, GR, CYP3A4 and TAT following 48 hours exposure to indicated concentrations of cortisol were also simulated by the model, and are presented as closed symbols.
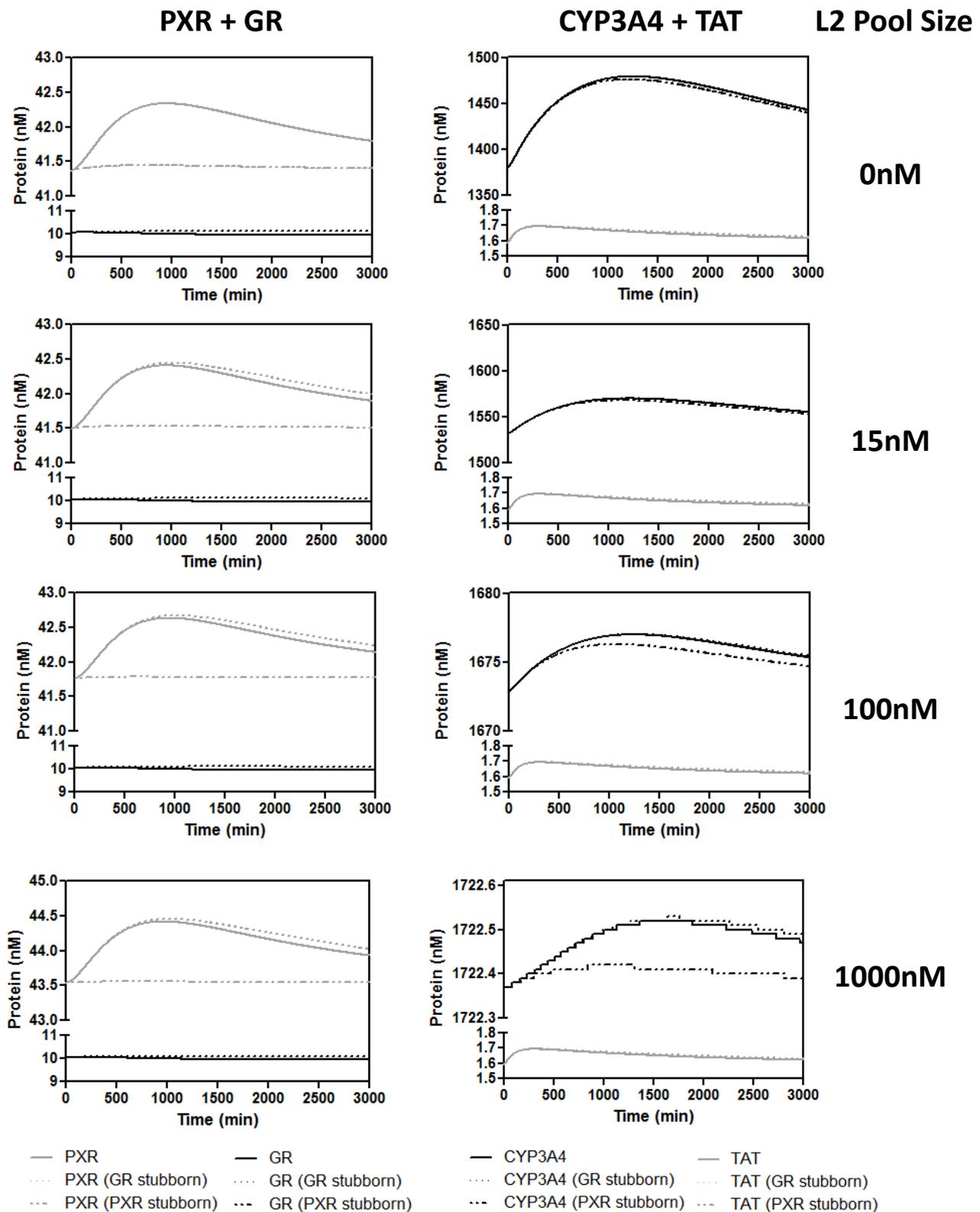
Supplementary Figure S3: Impact of L2 pool size on response of the gene regulatory network to an acute stress episode: Protein levels for GR, PXR, CYP3A4 and TAT were simulated over 3000 minutes following addition of a single spike of cortisol, doubling free cortisol concentration from 15-30nM. Simulations were undertaken in the presence of a second PXR ligand pool (L2), at the indicated concentration. Solid lines represent levels under the complete single-ligand model, whereas dashed lines represent levels GRstubborn and PXRstubborn scenarios as indicated.
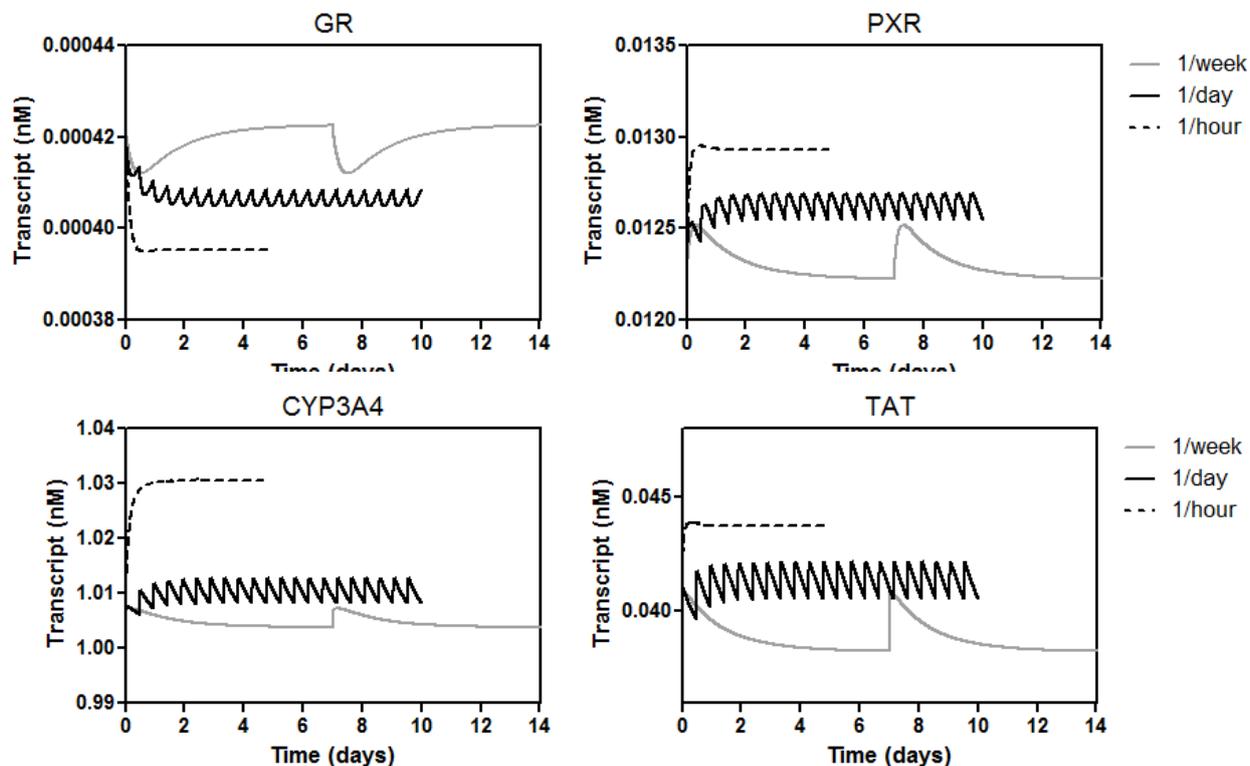
Supplementary Figure S4: Response of the gene regulatory network to repeat stress episodes: Transcript levels for GR, PXR, CYP3A4 and TAT were simulated over 21 days following addition of repeat spikes of cortisol, such that each spike doubled the free blood cortisol concentration. Frequency of cortisol spikes were 1/week (grey line), 1/day (black line) or 1/hour (dashed line).
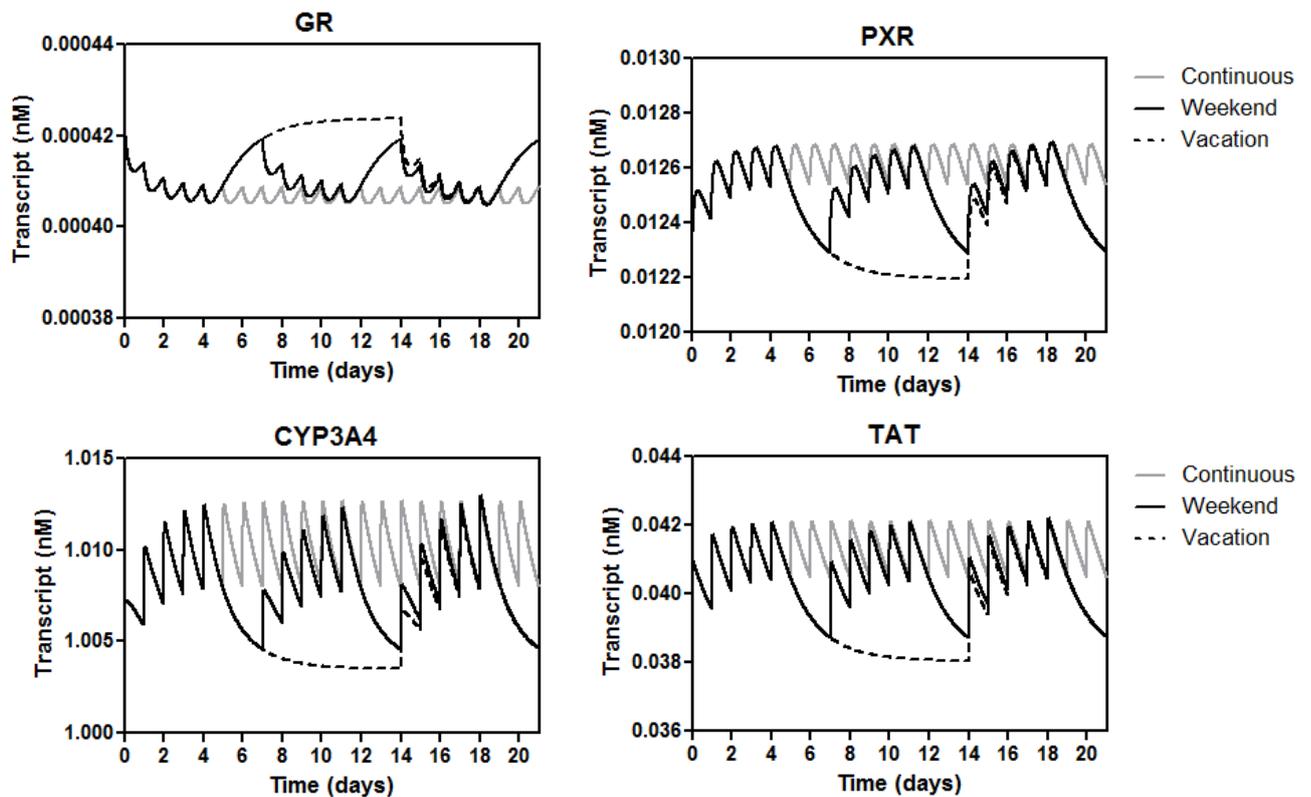
Supplementary Figure S5: A low stress vacation required to allow adaptation to a stressful week: Transcript levels for GR, PXR, CYP3A4 and TAT, as well as free blood cortisol, were simulated over 21 days following addition of repeat spikes of cortisol, such that each spike doubled the free blood cortisol concentration. Cortisol spikes were applied 1/day for either continuous throughout the period (grey line), with a weekend break (black line) or a 9-day vacation (dashed line).

Supplementary Table S1: Model Parameters for cortisol (L1) model

Reactions		Parameters
v_1	CYPmRNA synthesis: $k_1 \cdot CYPgene(t)$ [nM/min]	* $k_1 = 0.00321$ min^{-1}
v_2	CYPmRNA degradation: $k_2 \cdot CYPmRNA(t)$ [nM/min]	$k_2 = 0.04$ min^{-1} [41,42]
v_3	CYPprotein synthesis: $k_3 \cdot CYPmRNA(t)$ [nM/min]	$k_3 = 2.5$ min^{-1} [41]
v_4	CYPprotein degradation: $k_4 \cdot CYPptotein(t)$ [nM/min]	$k_4 = 0.0005$ min^{-1} [43,44]
v_5	PXRmRNA synthesis on inactive PXRgene: $k_5 \cdot PXRgene(t)$ [nM/min]	* $k_5 = 5.52\text{e-}05$ min^{-1}
v_6	PXRmRNA degradation: $k_6 \cdot PXRmRNA(t)$ [nM/min]	** $k_6 = 0.006$ min^{-1} [45]
v_7	PXRprotein synthesis: $k_7 \cdot PXRmRNA(t)$ [nM/min]	$k_7 = 10$ min^{-1} [46]
v_8	PXRprotein degradation: $k_8 \cdot PXRptotein(t)$ [nM/min]	$k_8 = 0.003$ min^{-1} [47]
v_9	GRmRNA synthesis on inactive GRgene: $k_9 \cdot GRgene(t)$ [nM/min]	* $k_9 = 3.2\text{e-}06$ min^{-1}
v_{10}	GRmRNA degradation: $k_{10} \cdot GRmRNA(t)$ [nM/min]	** $k_{10} = 0.003$ min^{-1} [45]
v_{11}	GRprotein synthesis: $k_{11} \cdot GRmRNA(t)$ [nM/min]	$k_{11} = 19.98$ min^{-1} [48]
v_{12}	GRprotein degradation: $k_{12} \cdot GRptotein(t)$ [nM/min]	$k_{12} = 0.001$ min^{-1} [48,49]
v_{13}	TATmRNA synthesis on inactive TATgene: $k_{13} \cdot TATgene(t)$ [nM/min]	* $k_{13} = 0.000855$ min^{-1}
v_{14}	TATmRNA degradation: $k_{14} \cdot TATmRNA(t)$ [nM/min]	$k_{14} = 0.064$ min^{-1} [50]
v_{15}	Cortisol binding GRprotein: $k_{15f} \cdot Cort(t) \cdot GRprotein - k_{15b} \cdot GRproteinCort(t)$ [nM/min]	$k_{15f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{15b} = 600$ min^{-1} (Kd = 10 nM [51])
v_{16}	GRproteinCort degradation: $k_{16} \cdot GRptoteinCort(t)$ [nmoles/min]	$k_{16} = 0.001$ min^{-1} [48,49]

v_{17}	Cortisol binding PXRprotein: $k_{17f} \cdot Cort(t) \cdot PXRprotein - k_{17b} \cdot PXRproteinCort(t)$ [nM/min]	$k_{17f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{17b} = 600000$ min^{-1} [52]
v_{18}	PXRproteinCort degradation: $k_{18} \cdot PXRptotein\,Cort(t)$ [nM/min]	$k_{18} = 0.0015$ min^{-1} [47]
v_{19}	Cort degradation: $$CYPptotein \cdot \frac{V_{mC} \cdot \frac{Cort(t)}{K_{MC}}}{1 + \frac{Cort(t)}{K_{MC}} + \frac{L2(t)}{K_{ML2}}}$$ [nM/min]	$V_{mC} = 10$ min^{-1} ($k_{cat}=V_{mC}/1200$(nM max CYP protein conc in cell) nM $=0.083$); $K_{MC} = 15000$ nM Since L2=0, Competition between cortisol and L2 for CYP is neglected [53,54]
v_{20}	PXRpoteinCortisol binding CYPgene: $k_{20f} \cdot PXRproteinCort(t) \cdot CYPgene(t)$ $- k_{20b} \cdot PXRprotein\,CortCYPgen\,e(t)$ [nM/min]	$k_{20f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{20b} = 1$ min^{-1}
v_{21}	CYPmRNA synthesis on active PXRproteinCortCYPgene: $k_{21} \cdot PXRproteinCortCYPgene(t)$ [nM/min]	* $k_{21b} = 0.05$ min^{-1}
v_{22}	GRpoteinCortisol binding PXRgene: $k_{22f} \cdot GRproteinCort(t) \cdot PXRgene(t)$ $- k_{22b} \cdot GRproteinCortPXRgene(t)$ [nM/min]	$k_{22f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{22b} = 200$ min^{-1}
v_{23}	PXRmRNA synthesis on active GRproteinCortPXRgene: $k_{23} \cdot GRproteinCortPXRgene(t)$ [nM/min]	* $k_{23} = 0.00011$ min^{-1}
v_{24}	GRpoteinCortisol binding GRgene: $k_{24f} \cdot GRproteinCort(t) \cdot GRgene(t)$ $- k_{24b} \cdot GRproteinCortGRgene(t)$ [nM/min]	$k_{24f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{24b} = 60$ min^{-1}
v_{25}	GRmRNA synthesis on active GRproteinCortGRgene: $k_{25} \cdot GRproteinCortGRgene(t)$ [nM/min]	* $k_{25} = 1.2\text{e-}06$ min^{-1}
v_{26}	GRpoteinCortisol binding TATgene: $k_{26f} \cdot GRproteinCort(t) \cdot TATgene(t)$ $- k_{26b} \cdot GRproteinCortTATgene(t)$ [nM/min]	$k_{26f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{26b} = 300$ min^{-1}

v_{27}	TATmRNA synthesis on active GRproteinCortTATgene: $k_{27} \cdot GRproteinC\,ortTATgene\,(t)$ [nM/min]	* $k_{27} = 0.005$ min^{-1}
v_{28}	DEX binding GRprotein: $k_{28f} \cdot DEX\,(t) \cdot GRprotein - k_{28b} \cdot GRproteinDEX\,(t)$ [nM/min]	$k_{28f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{28b} = 60$ min^{-1} (calculated from Kd that is in the order of magnitude of 1 nM [55])
v_{29}	GRproteinDEX degradation: $k_{29} \cdot GRptoteinD\,EX\,(t)$ [nmoles/min]	$k_{29} = 0.001$ min^{-1} [48,49]
v_{30}	DEX binding PXRprotein: $k_{30f} \cdot DEX\,(t) \cdot PXRprotein - k_{30b} \cdot PXRproteinDEX\,(t)$ [nM/min]	$k_{30f} = 60$ nM^{-1}min^{-1} (diffusion limited);; $k_{30b} = 60000$ min^{-1} (calculated from Kd that is in the order of magnitude of 1000 nM [56])
v_{31}	PXRproteinDEX degradation: $k_{31} \cdot PXRptotein\,DEX\,(t)$ [nmoles/min]	** $k_{31} = 0.0015$ min^{-1} [47]
v_{32}	DEX degradation: $$CYPptotein \cdot \frac{V_{mDEX} \cdot \dfrac{DEX(t)}{K_{MDEX}}}{1 + \dfrac{DEX(t)}{K_{MDEX}} + \dfrac{Cort(t)}{K_{MC}} + \dfrac{L2(t)}{K_{M:2}}}$$ [nM/min]	$V_{mDEX} = 5.1$ min^{-1}; (($k_{cat} = V_{mC}/$ 1200 (max CYP protein conc in cell) nM $=$ 0.00425$^)$;) $K_{MDEX} = 23000$ nM [57]
v_{33}	PXRpoteinDEX binding CYPgene: $k_{33f} \cdot PXRproteinDEX\,(t) \cdot CYPgene\,(t)$ $- k_{33b} \cdot PXRprotein\,DEXCYPgene\,(t)$ [nM/min]	$k_{33f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{33b} = 1$ min^{-1}
v_{34}	CYPmRNA synthesis on active PXRproteinDEXCYPgene: $k_{34} \cdot PXRprotein\,DEXCYPgene\,(t)$ [nM/min]	* $k_{34} = 0.05$ min^{-1}
v_{35}	GRpoteinDEX binding PXRgene:	$k_{35f} = 60$ nM^{-1}min^{-1}

	$k_{35f} \cdot GRproteinDEX(t) \cdot PXRgene(t)$ $- k_{35b} \cdot GRproteinD\ EXPXRgene(t)$ [nM/min]	(diffusion limited); * $k_{35b} = 200$ min^{-1}
v_{36}	PXRmRNA synthesis on active GRproteinDEXPXRgene: $k_{36} \cdot GRproteinD\ EXPXRgene(t)$ [nM/min]	* $k_{36} = 0.00011$ min^{-1}
v_{37}	GRpoteinDEX binding GRgene: $k_{37f} \cdot GRproteinDEX(t) \cdot GRgene(t)$ $- k_{37b} \cdot GRproteinD\ EXGRgene(t)$ [nM/min]	$k_{37f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{37b} = 60$ min^{-1}
v_{38}	GRmRNA synthesis on active GRproteinDEXGRgene: $k_{38} \cdot GRproteinD\ EXGRgene(t)$ [nM/min]	* $k_{38} = 1.2e\text{-}06$ min^{-1}
v_{39}	GRpoteinDEX binding TATgene: $k_{39f} \cdot GRproteinDEX(t) \cdot TATgene(t)$ $- k_{39b} \cdot GRproteinD\ EXTATgene(t)$ [nM/min]	$k_{39f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{39b} = 300$ min^{-1}
v_{40}	TATmRNA synthesis on active GRproteinDEXTATgene: $k_{40} \cdot GRproteinD\ EXTATgene(t)$ [nM/min]	* $k_{40} = 0.005$ min^{-1}
v_{41}	DEX transport through cellular membrane: $k_{41f} \cdot DEXout(t) - k_{41b} \cdot DEXin(t)$ [nM/min]	$k_{41f} = 100$ min^{-1}; $k_{41b} = 100$ min^{-1} (taken at high value not to limit DEX uptake)
v_{42}	Endogenous cortisol synthesis: $k_{42f} \cdot Cortisone(t) - k_{42b} \cdot Cort(t)$ [nM/min]	$k_{42f} = 0.016$ min^{-1}; $k_{42b} = 0.016$ min^{-1} (fitted to have realistic cortisol concentration)
V_{43}	TATprotein synthesis: $k_{43} \cdot TATmRNA(t)$ [nM/min]	* $k_{43} = 0.5$ min^{-1}
v_{44}	TATprotein degradation: $k_{44} \cdot TATptotein(t)$ [nM/min]	$k_{44} = 0.012$ min^{-1} [50]
$V_{cortisolTransport}$	Transport of cortisol through cellular membrane: $k_{ctf} \cdot CortOUT(t) - k_{ctb} \cdot Cort(t)$ [nM/min]	$k_{ctf} = 1000$ min^{-1}; $k_{ctb} = 1000$ min^{-1}
$V_{L2\_PXR\_binding}$	Ligand2 binding PXRprotein: $k_{l2pxrf} \cdot L2(t) \cdot PXRprotein - k_{l2pxrb} \cdot PXRproteinLigand2(t)$ [nM/min]	$k_{l2pxrf} = 0$ nM^{-1}min^{-1} (diffusion limited); $k_{l2pxrb} = 0$ min^{-1} [52]

$V_{L2\_PXR\_deg}$	PXRproteinLigand2 degradation: $k_{l2\_pxr} \cdot PXRptotein\,Ligand\,2(t)$ [nM/min]	$k_{l2\_pxr} = 0$ min^{-1} [47]
$V_{CYPmRNA\_synt\_PXR\_L2}$	CYPmRNA synthesis on active PXRproteinLigand2CYPgene: $k_{synt\_cyp\_b} \cdot PXRprotein\,Ligand\,2CYPgene(t)$ [nM/min]	* $k_{synt\_cyp\_b} = 0$min^{-1}
$V_{CYPmRNA\_PXR\_L2\_binding}$	PXRproteinLigand2 binding CYPgene: $k_{bind\_cyp\_f} \cdot PXRproteinLigand\,2(t) \cdot CYPgene(t)$ $- k_{bind\_cyp\_b} \cdot PXRproteinLigand\,2CYPgene(t)$ [nM/min]	$k_{bind\_cyp\_f} = 0$ nM^{-1}min^{-1} (diffusion limited); * $k_{bind\_cyp\_b} = 0$ min^{-1}
$V_{cort\_distribution}$	Cortisol through the blood $k_{distribution} \cdot CortOUT(t)$ [nM/min]	$k_{distribution} = 1000$ min^{-1}
V_{cort_CBG}	Transport of cortisol through cellular membrane: $k_{cortCBG\_1} \cdot CortOUT(t) - k_{cortCBG\_2} \cdot CBG\_CortOUT(t)$ [nM/min]	$k_{cortCBG\_1} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{cortCBG\_2} = 270$ min^{-1}
$V_{cort\_albumin}$	$k_{cortALB\_1} \cdot CortOUT(t) - k_{cortALB\_2} \cdot Alb\_CortOUT(t)$	$k_{cortALB\_1} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{cortALB\_2} = 900000$ min^{-1}

Supplementary Table S2: Balance Equations for cortisol (L1) model

Balance equations	
dCort(t)/dt	$-v_{15}+v_{16} -v_{17}+v_{18}-v_{19}+v_{42}+ V_{cortisolTransport}$ [nM/min]
dCortAdded(t)/dt	$- V_{cort\_distribution}$[nM/min]
dCortOUT(t)/dt	$V_{cort\_distribution}$ $-V_{cort\_albumin} - V_{cort\_CBG} - V_{cortisolTransport}$ [nM/min]
dCBG_CortOUT(t)/dt	V_{cort_CBG}[nM/min]
dAlb_CortOUT(t)/dt	$V_{cort\_albumin}$ [nM/min]
dCBG(t)/dt	$-V_{cort\_CBG}$[nM/min]
dAlb(t)/dt	$-V_{cort\_albumin}$ [nM/min]
dCortisone(t)/dt	0 (considered an infinite reservoir)
dCYPgene(t)/dt	$-v_{20}-v_{33}$ [nM/min]
dCYPprotein(t)/dt	$+v_3-v_4$ [nM/min]
dCYPmRNA(t) /dt	$+v_1-v_2 +v_{21}+v_{34}+V_{CYPmRNA\_PXR\_L2\_binding}$ [nM/min]

dPXRproteinCortCYPgene(t) /dt	$+v_{20}$ [nM/min]
dPXRproteinLigand2CYPgene(t) /dt	$+ \mathbf{V}_{CYPmRNA\_PXR\_L2\_binding} - \mathbf{V}_{CYPmRNA\_synt\_PXR\_L2}$ [nM/min]
dPXRproteinDEXCYPgene(t) /dt	$+v_{33}$ [nM/min]
dDEX(t)/dt	$-v_{28}+v_{29} -v_{30}+v_{31}-v_{32}+v_{41}$ [nM/min]
dLigand2(t)/dt	$- \mathbf{V}_{L2\_PXR\_binding}+ \mathbf{V}_{L2\_PXR\_deg}$ [nM/min]
dDEXdeg(t)/dt	$+v_{32}$ [nM/min]
dDEXout(t)/dt	$-v_{41}$ [nM/min]
dGRgene(t)/dt	$-v_{24} -v_{37}$ [nM/min]
dGRprotein(t)/dt	$+v_{11}-v_{12}-v_{15}-v_{12}-v_{28}$ [nM/min]
dGRmRNA(t)/dt	$+v_{9}-v_{10}+v_{25}+v_{38}$ [nM/min]
dGRproteinCortGRgene(t)/dt	$+v_{24}$ [nM/min]
dGRproteinDEXGRgene(t)/dt	$+v_{37}$ [nM/min]
dGRproteinCort(t)/dt	$+v_{15}-v_{16}-v_{22}-v_{24}-v_{26}$ [nM/min]
dGRproteinDEX(t)/dt	$+v_{28}-v_{29}-v_{35}-v_{37}-v_{39}$ [nM/min]
dPXRgene(t)/dt	$-v_{35} -v_{22}$ [nM/min]
dPXRprotein(t)/dt	$+v_{7}-v_{8}-v_{17}-v_{30}$ [nM/min]
dPXRmRNA(t)/dt	$+v_{5}-v_{6}+v_{23}+v_{36}$ [nM/min]
dGRproteinCortPXRgene(t)/dt	$+v_{22}$ [nM/min]
dGRproteinDEXPXRgene(t)/dt	$+v_{35}$ [nM/min]
dPXRproteinCort(t)/dt	$+v_{17}-v_{18}-v_{20}$ [nM/min]
dPXRproteinLigand2(t)/dt	$+\mathbf{V}_{L2\_PXR\_binding}-\mathbf{V}_{L2\_PXR\_deg}-\mathbf{V}_{CYPmRNA\_PXR\_L2\_binding}$ [nM/min]
dPXRproteinDEX(t)/dt	$+v_{30}-v_{31}-v_{33}$ [nM/min]
dTATgene(t)/dt	$-v_{26}-v_{39}$ [nM/min]
dTATmRNA(t)/dt	$+v_{13}-v_{14}+v_{27}+v_{40}$ [nM/min]
dGRproteinCortTATgene(t)/dt	$+v_{26}$ [nM/min]
dGRproteinDEXTATgene(t)/dt	$+v_{39}$ [nM/min]
dTATprotein(t)/dt	$+v_{43}-v_{44}$ [nM/min]

Supplementary Table S3: Conserved Moieties for cortisol (L1) model

Conserved Moieties		
GRgene$_{total}$	GRgene(t) + GRproteinCortGRgene(t) + GRproteinDEXGRgene(t)	****0.83 [nM]
PXRgene$_{total}$	PXRgene(t) + GRproteinCortPXRgene(t) + GRproteinDEXPXRgene(t)	****0.83 [nM]
CYPgene$_{total}$	CYPgene(t) + PXRproteinCortCYPgene(t) + PXRproteinLigand2CYPgene(t)+ PXRproteinDEXCYPgene(t)	****0.83 [nM]
DEX$_{total}$	DEX(t) + DEXdeg(t) + DEXout(t) +	1000 [nM]

| | GRproteinDEXGRgene(t) + GRproteinDEX(t) + GRproteinDEXPXRgene(t) + PXRproteinDEX(t) + GRproteinDEXTATgene(t) + PXRproteinDEXCYPgene(t) | |

Supplementary Table S4: Initial Conditions for cortisol (L1) model

Initial conditions	
Cort(0)	1.14 [nM]
Cortisone(0)	23 [nM]
CortOUT(0)	0[nM]
CortAdded(0)	0[nM] at t=0 for the initial state, then ~130 [nM] added into the blood as an exposure of cortisol.
CBG_CortOUT(0)	0[nM]
Alb_CortOUT(0)	0[nM]
CBG(0)	550[nM]
Alb(0)	60000[nM]
Ligand2(0)	0[nM]
CYPgene(0)	0.82976 [nM]
CYPprotein(0)	104 [nM]
CYPmRNA(0)	75e-3 [nM] 94x levels of GR mRNA. Experimentally derived and consistent with [58,59]
PXRproteinCortCYPgene(0)	0.00024 [nM]
PXRproteinLigand2CYPgene(0)	0 [nM]
PXRproteinDEXCYPgene(0)	0 [nM]
DEX(0)	0 [nM]
DEXdeg(0)	0 [nM]
DEXout(0)	1000 [nM]
GRgene(0)	0.5 [nM]
GRprotein(0)	GRtotal=80.0 nM =GR (47.24) +GRprotCort(32.36) + GRprotCortGRgene (0.33) + GRproteinCortTATgene(0.02) + GRproteinCortPXRgene(0.05) [60,61]
GRmRNA/dt	0.0008 [nM] Experimentally derived and consistent with [58,62]
GRproteinCortGRgene(0)	0.33 [nM]
GRproteinDEXGRgene(0)	0 [nM]

GRproteinCort(0)	32.36 [nM]
GRproteinDEX(0)	0 [nM]
PXRgene(0)	0.78 [nM]
PXRprotein(0)	*****99.9 [nM]
PXRmRNA(0)	0.007 [nM]
	9x levels of GR mRNA. Experimentally derived and consistent with [58,59]
GRproteinCortPXRgene(0)	0.05 [nM]
GRproteinDEXPXRgene(0)	0 [nM]
PXRproteinCort(0)	0.01 [nM]
PXRproteinLigand2(0)	0 [nM]
PXRproteinDEX(0)	0 [nM]
TATgene(0)	0.81 [nM]
TATmRNA(0)	0.4[nM]
	Experimentally derived and consistent with http://www.genecards.org/
TATprotein(0)	0.462028 [nM]
GRproteinCortTATgene(0)	0.02 [nM]
GRproteinDEXTATgene(0)	0 [nM]

Supplementary Table S5: Model Parameters for cortisol (L1) and second ligand (L2) model

Reactions		Parameters
v_1	CYPmRNA synthesis: $k_1 \cdot CYPgene(t)$ [nM/min]	* k_1 = 0.00321 min^{-1}
v_2	CYPmRNA degradation: $k_2 \cdot CYPmRNA(t)$ [nM/min]	k_2 = 0.04 min^{-1} [41,42]
v_3	CYPprotein synthesis: $k_3 \cdot CYPmRNA(t)$ [nM/min]	k_3 = 2.5 min^{-1} [41]
v_4	CYPprotein degradation: $k_4 \cdot CYPptotein(t)$ [nM/min]	k_4 = 0.0005 min^{-1} [43,44]
v_5	PXRmRNA synthesis on inactive PXRgene: $k_5 \cdot PXRgene(t)$ [nM/min]	* k_5 = 5.52e-05 min^{-1}
v_6	PXRmRNA degradation: $k_6 \cdot PXRmRNA(t)$ [nM/min]	** k_6 = 0.006 min^{-1} [45]
v_7	PXRprotein synthesis: $k_7 \cdot PXRmRNA(t)$ [nM/min]	k_7 = 10 min^{-1} [46]
v_8	PXRprotein degradation: $k_8 \cdot PXRptotein(t)$ [nM/min]	k_8 = 0.003 min^{-1} [47]

v_9	GRmRNA synthesis on inactive GRgene: $k_9 \cdot GRgene\,(t)$ [nM/min]	$* k_9 = 3.2e\text{-}06$ min^{-1}
v_{10}	GRmRNA degradation: $k_{10} \cdot GRmRNA\,(t)$ [nM/min]	$** k_{10} = 0.003$ min^{-1} [45]
v_{11}	GRprotein synthesis: $k_{11} \cdot GRmRNA(t)$ [nM/min]	$k_{11} = 19.98$ min^{-1} [48]
v_{12}	GRprotein degradation: $k_{12} \cdot GRptotein(t)$ [nM/min]	$k_{12} = 0.001$ min^{-1} [48,49]
v_{13}	TATmRNA synthesis on inactive TATgene: $k_{13} \cdot TATgene\,(t)$ [nM/min]	$* k_{13} = 0.000855$ min^{-1}
v_{14}	TATmRNA degradation: $k_{14} \cdot TATmRNA(t)$ [nM/min]	$k_{14} = 0.064$ min^{-1} [50]
v_{15}	Cortisol binding GRprotein: $k_{15f} \cdot Cort(t) \cdot GRprotein - k_{15b} \cdot GRproteinCort(t)$ [nM/min]	$k_{15f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{15b} = 600$ min^{-1} (Kd = 10 nM [51])
v_{16}	GRproteinCort degradation: $k_{16} \cdot GRptoteinCort(t)$ [nmoles/min]	$k_{16} = 0.001$ min^{-1} [48,49]
v_{17}	Cortisol binding PXRprotein: $k_{17f} \cdot Cort(t) \cdot PXRprotein - k_{17b} \cdot PXRproteinCort(t)$ [nM/min]	$k_{17f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{17b} = 600000$ min^{-1} [52]
v_{18}	PXRproteinCort degradation: $k_{18} \cdot PXRptotein\,Cort\,(t)$ [nM/min]	$k_{18} = 0.0015$ min^{-1} [47]
v_{19}	Cort degradation: $$CYPptotein \cdot \dfrac{V_{mC} \cdot \dfrac{Cort(t)}{K_{MC}}}{1 + \dfrac{Cort(t)}{K_{MC}} + \dfrac{L2(t)}{K_{ML2}}}$$ [nM/min]	$V_{mC} = 10$ min^{-1} ($k_{cat} = V_{mC} / 1200$(nM max CYP protein conc in cell) nM $= 0.083$); $K_{MC} = 15000$ nM. Since L2=0, Competition between cortisol and L2 for CYP is neglected [53,54]
v_{20}	PXRpoteinCortisol binding CYPgene:	$k_{20f} = 60$ nM^{-1}min^{-1}

	$k_{20f} \cdot PXRproteinCort(t) \cdot CYPgene(t)$ $- k_{20b} \cdot PXRprotein CortCYPgen e(t)$ [nM/min]	(diffusion limited); * $k_{20b} = 1$ min^{-1}
v_{21}	CYPmRNA synthesis on active PXRproteinCortCYPgene: $k_{21} \cdot PXRproteinCortCYPgene(t)$ [nM/min]	* $k_{21b} = 0.05$ min^{-1}
v_{22}	GRpoteinCortisol binding PXRgene: $k_{22f} \cdot GRproteinCort(t) \cdot PXRgene(t)$ $- k_{22b} \cdot GRproteinC ortPXRgene(t)$ [nM/min]	$k_{22f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{22b} = 200$ min^{-1}
v_{23}	PXRmRNA synthesis on active GRproteinCortPXRgene: $k_{23} \cdot GRproteinC ortPXRgene(t)$ [nM/min]	* $k_{23} = 0.00011$ min^{-1}
v_{24}	GRpoteinCortisol binding GRgene: $k_{24f} \cdot GRproteinCort(t) \cdot GRgene(t)$ $- k_{24b} \cdot GRproteinC ortGRgene(t)$ [nM/min]	$k_{24f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{24b} = 60$ min^{-1}
v_{25}	GRmRNA synthesis on active GRproteinCortGRgene: $k_{25} \cdot GRproteinC ortGRgene(t)$ [nM/min]	* $k_{25} = 1.2\text{e-}06$ min^{-1}
v_{26}	GRpoteinCortisol binding TATgene: $k_{26f} \cdot GRproteinCort(t) \cdot TATgene(t)$ $- k_{26b} \cdot GRproteinC ortTATgene(t)$ [nM/min]	$k_{26f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{26b} = 300$ min^{-1}
v_{27}	TATmRNA synthesis on active GRproteinCortTATgene: $k_{27} \cdot GRproteinC ortTATgene(t)$ [nM/min]	* $k_{27} = 0.005$ min^{-1}
v_{28}	DEX binding GRprotein: $k_{28f} \cdot DEX(t) \cdot GRprotein - k_{28b} \cdot GRproteinDEX(t)$ [nM/min]	$k_{28f} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{28b} = 60$ min^{-1} (calculated from Kd that is in the order of magnitude of 1 nM [55])
v_{29}	GRproteinDEX degradation: $k_{29} \cdot GRptoteinD EX(t)$ [nmoles/min]	$k_{29} = 0.001$ min^{-1} [48,49]
v_{30}	DEX binding PXRprotein: $k_{30f} \cdot DEX(t) \cdot PXRprotein - k_{30b} \cdot PXRproteinDEX(t)$ [nM/min]	$k_{30f} = 60$ nM^{-1}min^{-1} (diffusion limited);; $k_{30b} = 60000$ min^{-1} (calculated from Kd that is in the order of magnitude of 1000 nM [56])

v₃₁	PXRproteinDEX degradation: $$k_{31} \cdot PXRptotein\,DEX(t) \;[\text{nmoles/min}]$$	** $k_{31} = 0.0015$ min^{-1}[47]
v₃₂	DEX degradation: $$CYPptotein \cdot \frac{V_{mDEX} \cdot \dfrac{DEX(t)}{K_{MDEX}}}{1 + \dfrac{DEX(t)}{K_{MDEX}} + \dfrac{Cort(t)}{K_{MC}} + \dfrac{L2(t)}{K_{M:2}}} \;[\text{nM/min}]$$	$V_{mDEX} = 5.1$ min^{-1}; ($^{(}$k$_{cat}$=V_{mC} / 1200 (max CYP protein conc in cell) nM $=$ 0.00425$^{)}$;) $K_{MDEX} = 23000$ nM [57]
v₃₃	PXRpoteinDEX binding CYPgene: $$k_{33f} \cdot PXRprotein\,DEX(t) \cdot CYPgene(t)$$ $$- k_{33b} \cdot PXRprotein\,DEXCYPgene(t) \;[\text{nM/min}]$$	$k_{33f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{33b} = 1$ min^{-1}
v₃₄	CYPmRNA synthesis on active PXRproteinDEXCYPgene: $$k_{34} \cdot PXRprotein\,DEXCYPgene(t) \;[\text{nM/min}]$$	* $k_{34} = 0.05$ min^{-1}
v₃₅	GRpoteinDEX binding PXRgene: $$k_{35f} \cdot GRprotein\,DEX(t) \cdot PXRgene(t)$$ $$- k_{35b} \cdot GRprotein\,DEXPXRgene(t) \;[\text{nM/min}]$$	$k_{35f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{35b} = 200$ min^{-1}
v₃₆	PXRmRNA synthesis on active GRproteinDEXPXRgene: $$k_{36} \cdot GRprotein\,DEXPXRgene(t) \;[\text{nM/min}]$$	* $k_{36} = 0.00011$ min^{-1}
v₃₇	GRpoteinDEX binding GRgene: $$k_{37f} \cdot GRprotein\,DEX(t) \cdot GRgene(t)$$ $$- k_{37b} \cdot GRprotein\,DEXGRgene(t) \;[\text{nM/min}]$$	$k_{37f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{37b} = 60$ min^{-1}
v₃₈	GRmRNA synthesis on active GRproteinDEXGRgene: $$k_{38} \cdot GRprotein\,DEXGRgene(t) \;[\text{nM/min}]$$	* $k_{38} = 1.2e-06$ min^{-1}
v₃₉	GRpoteinDEX binding TATgene: $$k_{39f} \cdot GRprotein\,DEX(t) \cdot TATgene(t)$$ $$- k_{39b} \cdot GRprotein\,DEXTATgene(t) \;[\text{nM/min}]$$	$k_{39f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{39b} = 300$ min^{-1}
v₄₀	TATmRNA synthesis on active GRproteinDEXTATgene: $$k_{40} \cdot GRprotein\,DEXTATgene(t) \;[\text{nM/min}]$$	* $k_{40} = 0.005$ min^{-1}
v₄₁	DEX transport through cellular membrane: $$k_{41f} \cdot DEXout(t) - k_{41b} \cdot DEXin(t) \;[\text{nM/min}]$$	$k_{41f} = 100$ min^{-1}; $k_{41b} = 100$ min^{-1} (taken at high value not to limit DEX uptake)
v₄₂	Endogenous cortisol synthesis:	$k_{42f} = 0.016$ min^{-1};

	$k_{42f} \cdot Cortisone(t) - k_{42b} \cdot Cort(t)$ [nM/min]	$k_{42b} = 0.016$ min^{-1} (fitted to have realistic cortisol concentration)
V_{43}	TATprotein synthesis: $k_{43} \cdot TATmRNA(t)$ [nM/min]	* $k_{43} = 0.5$ min^{-1}
v_{44}	TATprotein degradation: $k_{44} \cdot TATptotein(t)$ [nM/min]	$k_{44} = 0.012$ min$^{-1\ 50}$
$V_{cortisolTransport}$	Transport of cortisol through cellular membrane: $k_{ctf} \cdot CortOUT(t) - k_{ctb} \cdot Cort(t)$ [nM/min]	$k_{ctf} = 1000$ min^{-1}; $k_{ctb} = 1000$ min^{-1}
$V_{L2\_PXR\_binding}$	Ligand2 binding PXRprotein: $k_{l2pxrf} \cdot L2(t) \cdot PXRprotein - k_{l2pxrb} \cdot PXRproteinLigand2(t)$ [nM/min]	$k_{l2pxrf} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{l2pxrb} = 600000$ min$^{-1\ 52}$
$V_{L2\_PXR\_deg}$	PXRproteinLigand2 degradation: $k_{l2\_pxr} \cdot PXRptotein\,Ligand2(t)$ [nM/min]	$k_{l2\_pxr} = 0.0015$ min$^{-1\ 47}$
$V_{CYPmRNA\_synt\_PXR\_L2}$	CYPmRNA synthesis on active PXRproteinLigand2CYPgene: $k_{synt\_cyp\_b} \cdot PXRproteinLigand2CYPgene(t)$ [nM/min]	* $k_{synt\_cyp\_b} = 0.05$ min^{-1}
$V_{CYPmRNA\_PXR\_L2\_binding}$	PXRproteinLigand2 binding CYPgene: $k_{bind\_cyp\_f} \cdot PXRproteinLigand2(t) \cdot CYPgene(t)$ $- k_{bind\_cyp\_b} \cdot PXRproteinLigand2CYPgene(t)$ [nM/min]	$k_{bind\_cyp\_f} = 60$ nM^{-1}min^{-1} (diffusion limited); * $k_{bind\_cyp\_b} = 1$ min^{-1}
$V_{cort\_distribution}$	Cortisol through the blood $k_{distribution} \cdot CortOUT(t)$ [nM/min]	$k_{distribution} = 1000$ min^{-1}
V_{cort_CBG}	Transport of cortisol through cellular membrane: $k_{cortCBG\_1} \cdot CortOUT(t) - k_{cortCBG\_2} \cdot CBG\_CortOUT(t)$ [nM/min]	$k_{cortCBG\_1} = 60$ nM^{-1}min^{-1} (diffusion limited); $k_{cortCBG\_2} = 270$ min^{-1}
$V_{cort\_albumin}$	$k_{cortALB\_1} \cdot CortOUT(t) - k_{cortALB\_2} \cdot Alb\_CortOUT(t)$	$k_{cortALB\_1} = 60$ nM^{-1}min^{-1} (diffusion limited);

		$k_{cortALB\_2} = 900000$ min^{-1}

Supplementary Table S6: Balance Equations for cortisol (L1) and second ligand (L2) model

Balance equations	
dCort(t)/dt	$-v_{15}+v_{16}-v_{17}+v_{18}-v_{19}+v_{42}+ \mathbf{V}_{cortisolTransport}$ [nM/min]
dCortAdded(t)/dt	$- \mathbf{V}_{cort\_distribution}$[nM/min]
dCortOUT(t)/dt	$\mathbf{V}_{cort\_distribution} - \mathbf{V}_{cort\_albumin} - \mathbf{V}_{cort\_CBG} - \mathbf{V}_{cortisolTransport}$ [nM/min]
dCBG_CortOUT(t)/dt	$\mathbf{V}_{cort\_CBG}$[nM/min]
dAlb_CortOUT(t)/dt	$\mathbf{V}_{cort\_albumin}$ [nM/min]
dCBG(t)/dt	$-\mathbf{V}_{cort\_CBG}$[nM/min]
dAlb(t)/dt	$-\mathbf{V}_{cort\_albumin}$ [nM/min]
dCortisone(t)/dt	0 (considered an infinite reservoir)
dCYPgene(t)/dt	$-v_{20}-v_{33}$ [nM/min]
dCYPprotein(t)/dt	$+v_3-v_4$ [nM/min]
dCYPmRNA(t) /dt	$+v_1-v_2+v_{21}+v_{34}+\mathbf{V}_{CYPmRNA\_PXR\_L2\_binding}$ [nM/min]
dPXRproteinCortCYPgene(t) /dt	$+v_{20}$ [nM/min]
dPXRproteinLigand2CYPgene(t) /dt	$+ \mathbf{V}_{CYPmRNA\_PXR\_L2\_binding}- \mathbf{V}_{CYPmRNA\_synt\_PXR\_L2}$ [nM/min]
dPXRproteinDEXCYPgene(t) /dt	$+v_{33}$ [nM/min]
dDEX(t)/dt	$-v_{28}+v_{29}-v_{30}+v_{31}-v_{32}+v_{41}$ [nM/min]
dLigand2(t)/dt	$- \mathbf{V}_{L2\_PXR\_binding}+ \mathbf{V}_{L2\_PXR\_deg}$ [nM/min]
dDEXdeg(t)/dt	$+v_{32}$ [nM/min]
dDEXout(t)/dt	$-v_{41}$ [nM/min]
dGRgene(t)/dt	$-v_{24}-v_{37}$ [nM/min]
dGRprotein(t)/dt	$+v_{11}-v_{12}-v_{15}-v_{12}-v_{28}$ [nM/min]
dGRmRNA(t)/dt	$+v_9-v_{10}+v_{25}+v_{38}$ [nM/min]
dGRproteinCortGRgene(t)/dt	$+v_{24}$ [nM/min]
dGRproteinDEXGRgene(t)/dt	$+v_{37}$ [nM/min]
dGRproteinCort(t)/dt	$+v_{15}-v_{16}-v_{22}-v_{24}-v_{26}$ [nM/min]
dGRproteinDEX(t)/dt	$+v_{28}-v_{29}-v_{35}-v_{37}-v_{39}$ [nM/min]
dPXRgene(t)/dt	$-v_{35}-v_{22}$ [nM/min]
dPXRprotein(t)/dt	$+v_7-v_8-v_{17}-v_{30}$ [nM/min]
dPXRmRNA(t)/dt	$+v_5-v_6+v_{23}+v_{36}$ [nM/min]
dGRproteinCortPXRgene(t)/dt	$+v_{22}$ [nM/min]
dGRproteinDEXPXRgene(t)/dt	$+v_{35}$ [nM/min]
dPXRproteinCort(t)/dt	$+v_{17}-v_{18}-v_{20}$ [nM/min]
dPXRproteinLigand2(t)/dt	$+\mathbf{V}_{L2\_PXR\_binding}-\mathbf{V}_{L2\_PXR\_deg}-\mathbf{V}_{CYPmRNA\_PXR\_L2\_binding}$ [nM/min]

dPXRproteinDEX(t)/dt	$+v_{30}-v_{31}-v_{33}$ [nM/min]
dTATgene(t)/dt	$-v_{26}-v_{39}$ [nM/min]
dTATmRNA(t)/dt	$+v_{13}-v_{14}+v_{27}+v_{40}$ [nM/min]
dGRproteinCortTATgene(t)/dt	$+v_{26}$ [nM/min]
dGRproteinDEXTATgene(t)/dt	$+v_{39}$ [nM/min]
dTATprotein(t)/dt	$+v_{43}-v_{44}$ [nM/min]

Supplementary Table S7: Conserved Moieties for cortisol (L1) and second ligand (L2) model

Conserved Moieties		
GRgene$_{total}$	GRgene(t) + GRproteinCortGRgene(t) + GRproteinDEXGRgene(t)	****0.83 [nM]
PXRgene$_{total}$	PXRgene(t) + GRproteinCortPXRgene(t) + GRproteinDEXPXRgene(t)	****0.83 [nM]
CYPgene$_{total}$	CYPgene(t) + PXRproteinCortCYPgene(t) + PXRproteinLigand2CYPgene(t)+ PXRproteinDEXCYPgene(t)	****0.83 [nM]
DEX$_{total}$	DEX(t) + DEXdeg(t) + DEXout(t) + GRproteinDEXGRgene(t) + GRproteinDEX(t) + GRproteinDEXPXRgene(t) + PXRproteinDEX(t) + GRproteinDEXTATgene(t) + PXRproteinDEXCYPgene(t)	1000 [nM]

Supplementary Table S8: Initial Conditions for cortisol (L1) and second ligand (L2) model

Initial conditions	
Cort(0)	1.14 [nM]
Cortisone(0)	23 [nM]
CortOUT(0)	0[nM]
CortAdded(0)	0[nM] at t=0 for the initial state, then ~130 [nM] added into the blood as an exposure of cortisol.
CBG_CortOUT(0)	0[nM]
Alb_CortOUT(0)	0[nM]
CBG(0)	550[nM]
Alb(0)	60000[nM]
Ligand2(0)	100[nM]
CYPgene(0)	0.82976 [nM]
CYPprotein(0)	104 [nM]
CYPmRNA(0)	75e-3 [nM] 94x levels of GR mRNA. Experimentally derived and

	consistent with [58,59]
PXRproteinCortCYPgene(0)	0.00024 [nM]
PXRproteinLigand2CYPgene(0)	0 [nM]
PXRproteinDEXCYPgene(0)	0 [nM]
DEX(0)	0 [nM]
DEXdeg(0)	0 [nM]
DEXout(0)	1000 [nM]
GRgene(0)	0.5 [nM]
GRprotein(0)	GRtotal=80.0 nM =GR (47.24) +GRprotCort(32.36) + GRprotCortGRgene (0.33) + GRproteinCortTATgene(0.02) + GRproteinCortPXRgene(0.05) [60,61]
GRmRNA/dt	0.0008 [nM] Experimentally derived and consistent with [58,62]
GRproteinCortGRgene(0)	0.33 [nM]
GRproteinDEXGRgene(0)	0 [nM]
GRproteinCort(0)	32.36 [nM]
GRproteinDEX(0)	0 [nM]
PXRgene(0)	0.78 [nM]
PXRprotein(0)	*****99.9 [nM]
PXRmRNA(0)	0.007 [nM] 9x level of GR mRNA. Experimentally derived and consistent with [58,59]
GRproteinCortPXRgene(0)	0.05 [nM]
GRproteinDEXPXRgene(0)	0 [nM]
PXRproteinCort(0)	0.01 [nM]
PXRproteinLigand2(0)	0 [nM]
PXRproteinDEX(0)	0 [nM]
TATgene(0)	0.81 [nM]
TATmRNA(0)	0.4[nM] Experimentally derived and consistent with http://www.genecards.org/
TATprotein(0)	0.462028 [nM]
GRproteinCortTATgene(0)	0.02 [nM]
GRproteinDEXTATgene(0)	0 [nM]

*mRNA and protein synthesis rates are fitted according to the experimental data obtained.

**mRNA and protein degradation are fitted to concur with [63]

***Kd of binding of liganded NRs to REs is fitted in the realistic order of magnitude [64]

**** Taken in the realistic order of magnitude that is calculated from (~1.7×10^{-12} nmoles of REs (1,000 molecules) per cell (de Kloet et al, 2000), consequently per volume of nucleus. Volume of nucleus is ~0.45×10^{-12} L [61])

*****Taken in the realistic order of magnitude that is calculated from (NR total=NR + NRDEX +NRCortisol is 1.7×10^{-9} nmoles (100,000 molecules) per cell [60,65]; volume of cell is ~2×10^{-12} L [61]

## Supplementary Table S9: Sensitivity analysis of main conclusions for Figure 2
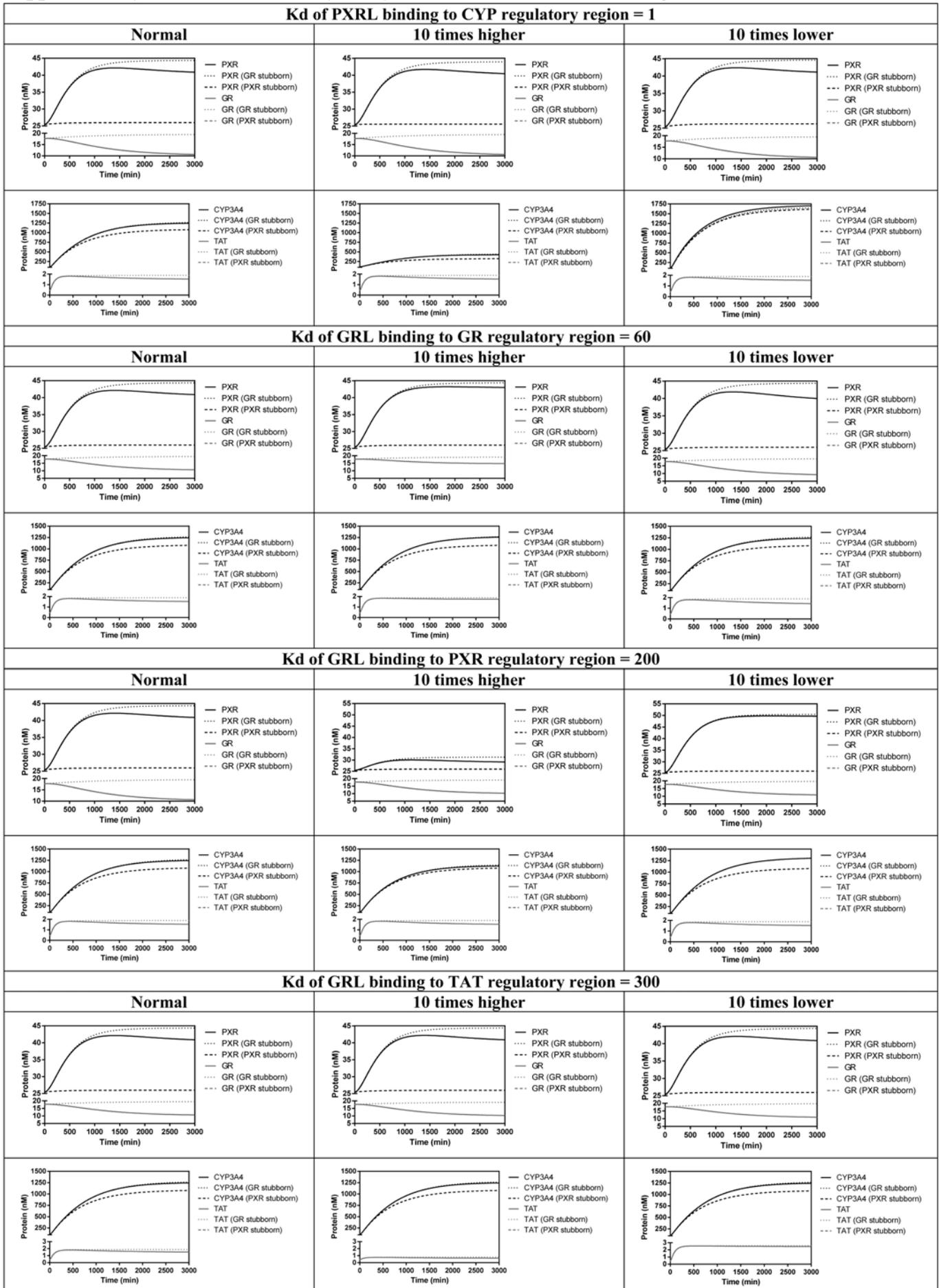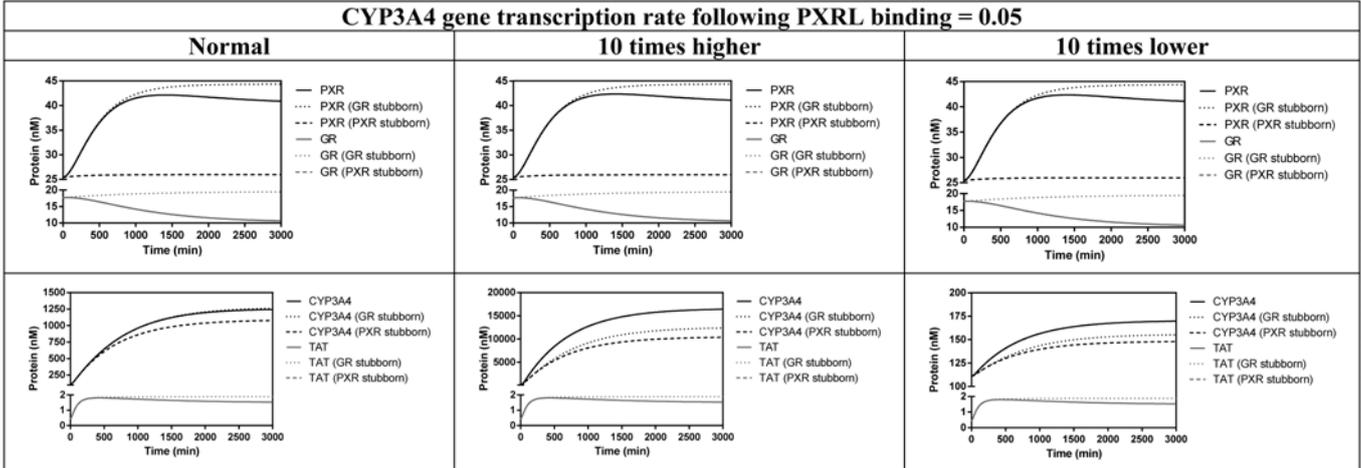
	Kd of PXRL binding to CYP regulatory region = 1	
Normal	**10 times higher**	**10 times lower**

	Kd of GRL binding to GR regulatory region = 60	
Normal	**10 times higher**	**10 times lower**

	Kd of GRL binding to PXR regulatory region = 200	
Normal	**10 times higher**	**10 times lower**

	Kd of GRL binding to TAT regulatory region = 300	
Normal	**10 times higher**	**10 times lower**

CYP3A4 gene transcription rate following PXRL binding = 0.05

Normal	10 times higher	10 times lower

GR gene transcription rate following GRL binding = 1.2e-6

Normal	10 times higher	10 times lower

PXR gene transcription rate following GRL binding = 0.00011

Normal	10 times higher	10 times lower

TAT gene transcription rate following GRL binding = 0.005

Normal	10 times higher	10 times lower
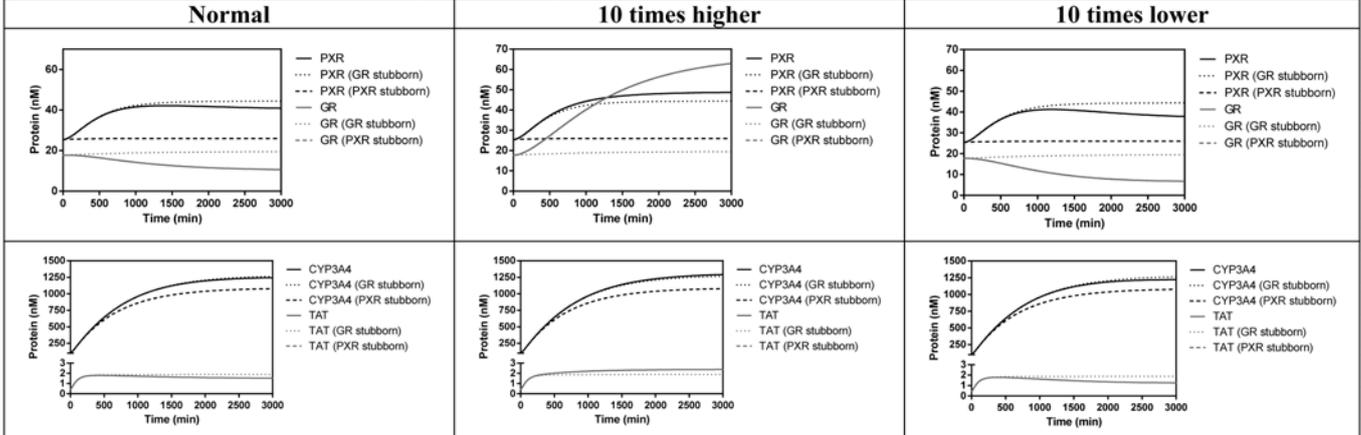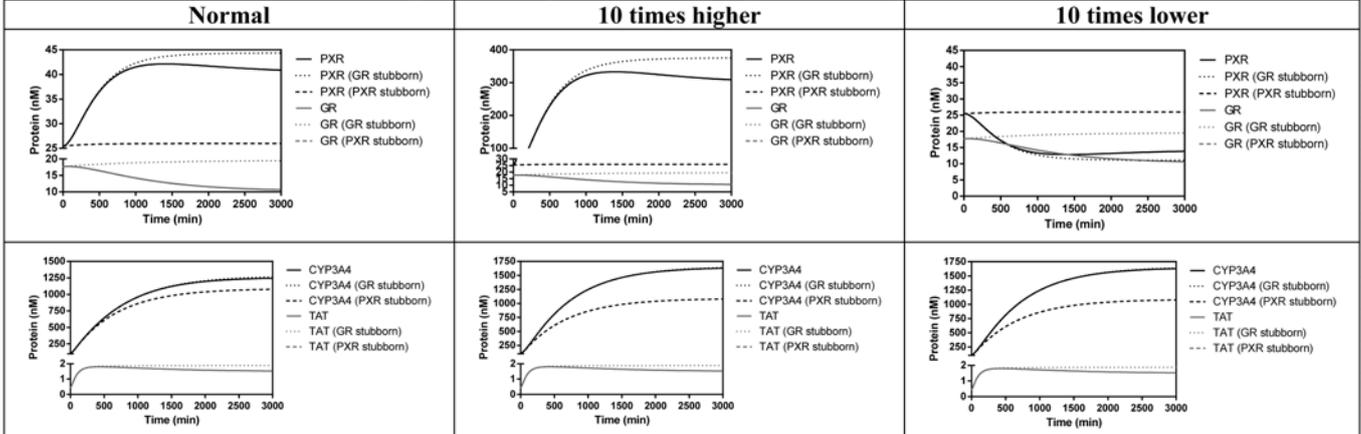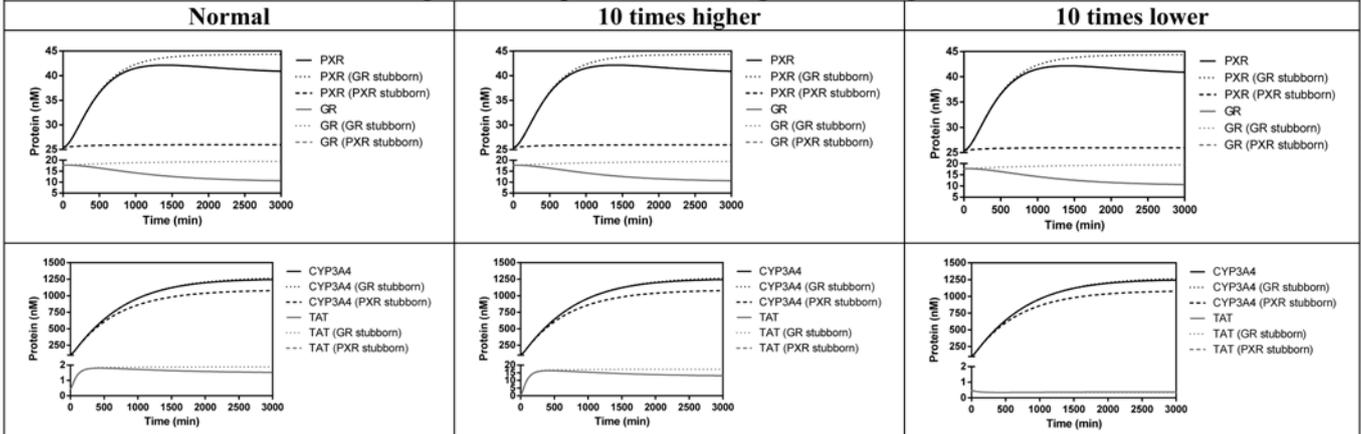
Supplementary Table S10: Sensitivity analysis of main conclusions for Figure 3
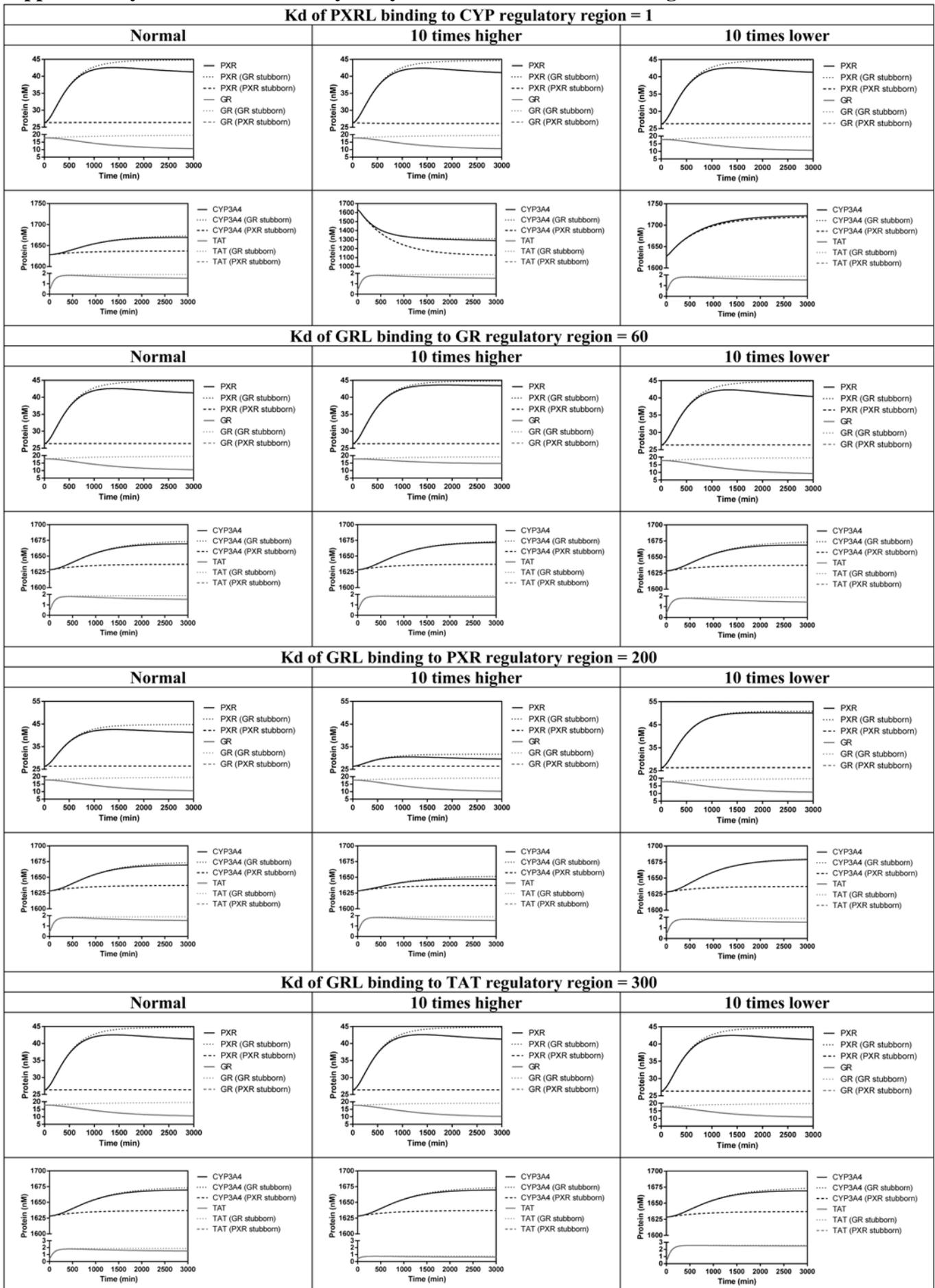
**CYP3A4 gene transcription rate following PXRL binding = 0.05**
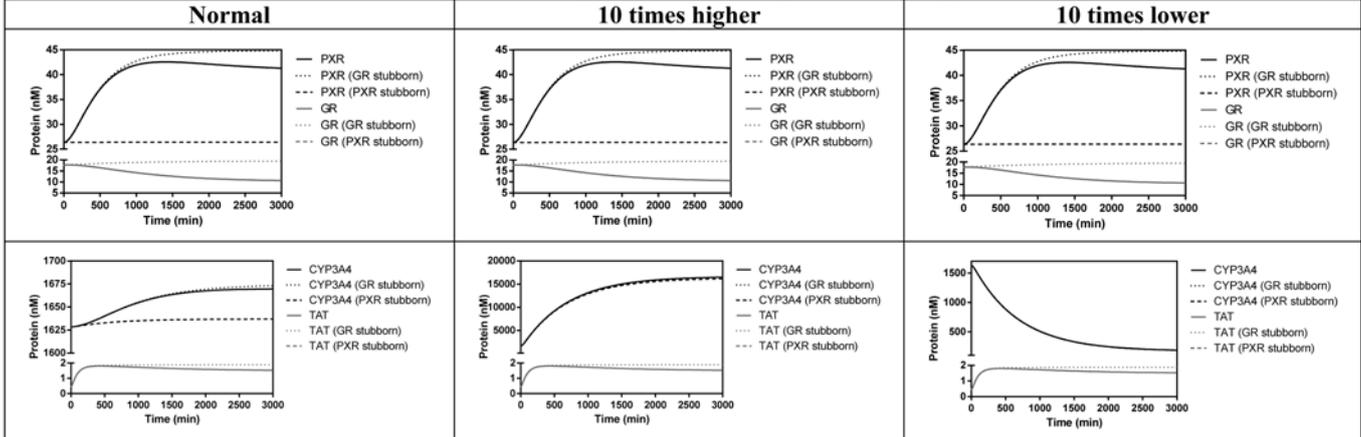
| Normal | 10 times higher | 10 times lower |

GR gene transcription rate following GRL binding = 1.2e-6

| Normal | 10 times higher | 10 times lower |

PXR gene transcription rate following GRL binding = 0.00011

| Normal | 10 times higher | 10 times lower |

TAT gene transcription rate following GRL binding = 0.005

| Normal | 10 times higher | 10 times lower |
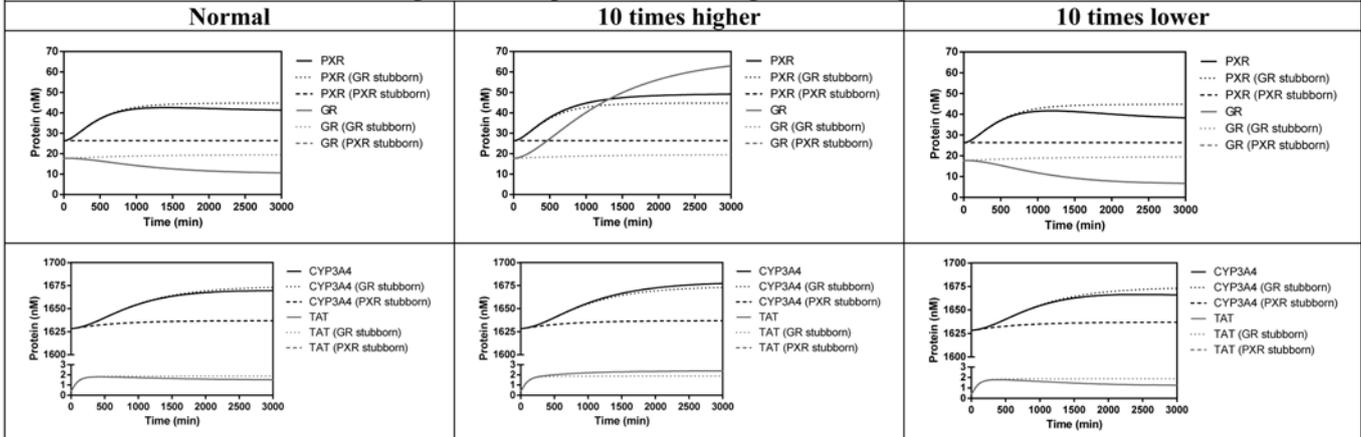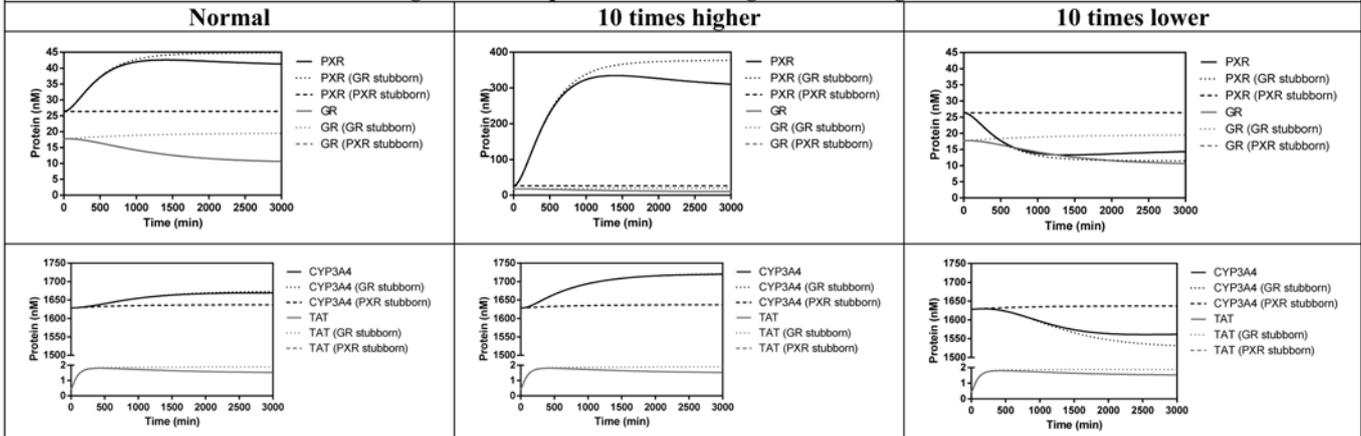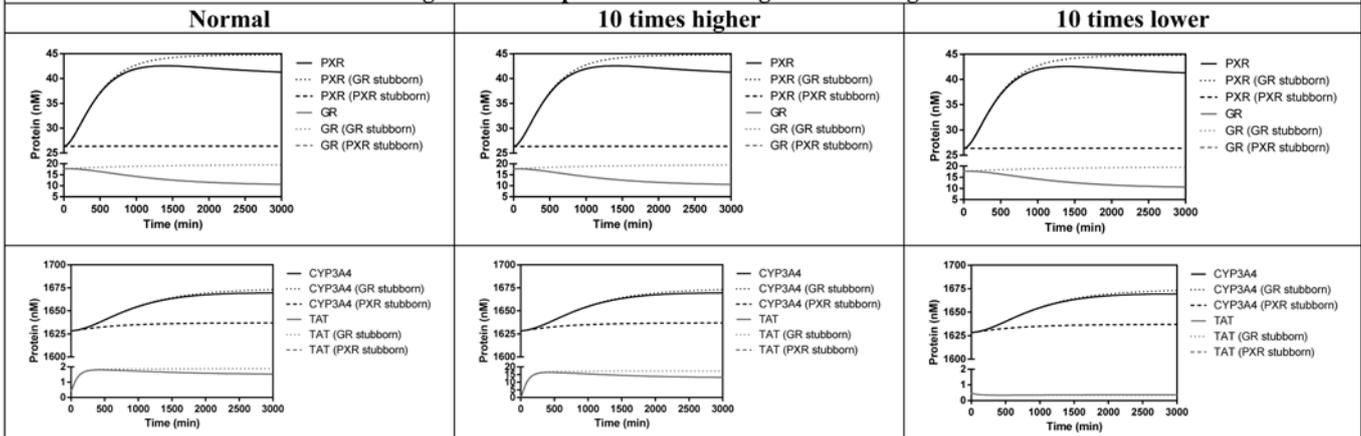
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