

Supplementary Information

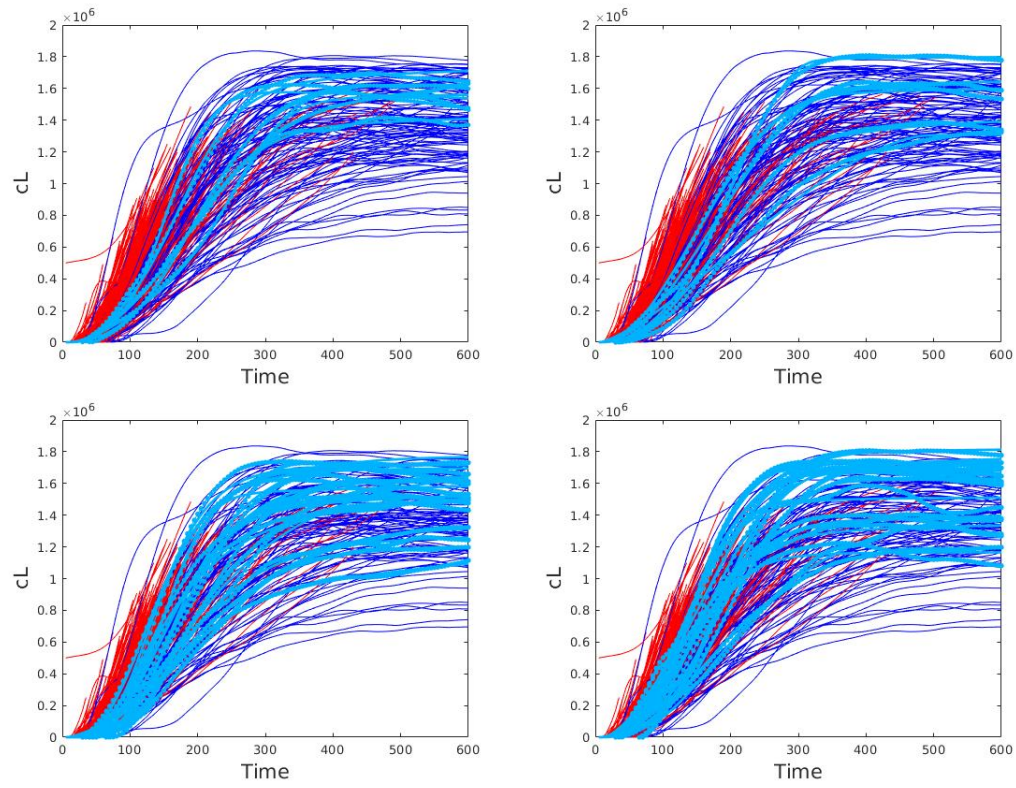
Two-level modeling approach to identify the
regulatory dynamics capturing drug response
heterogeneity in single-cells

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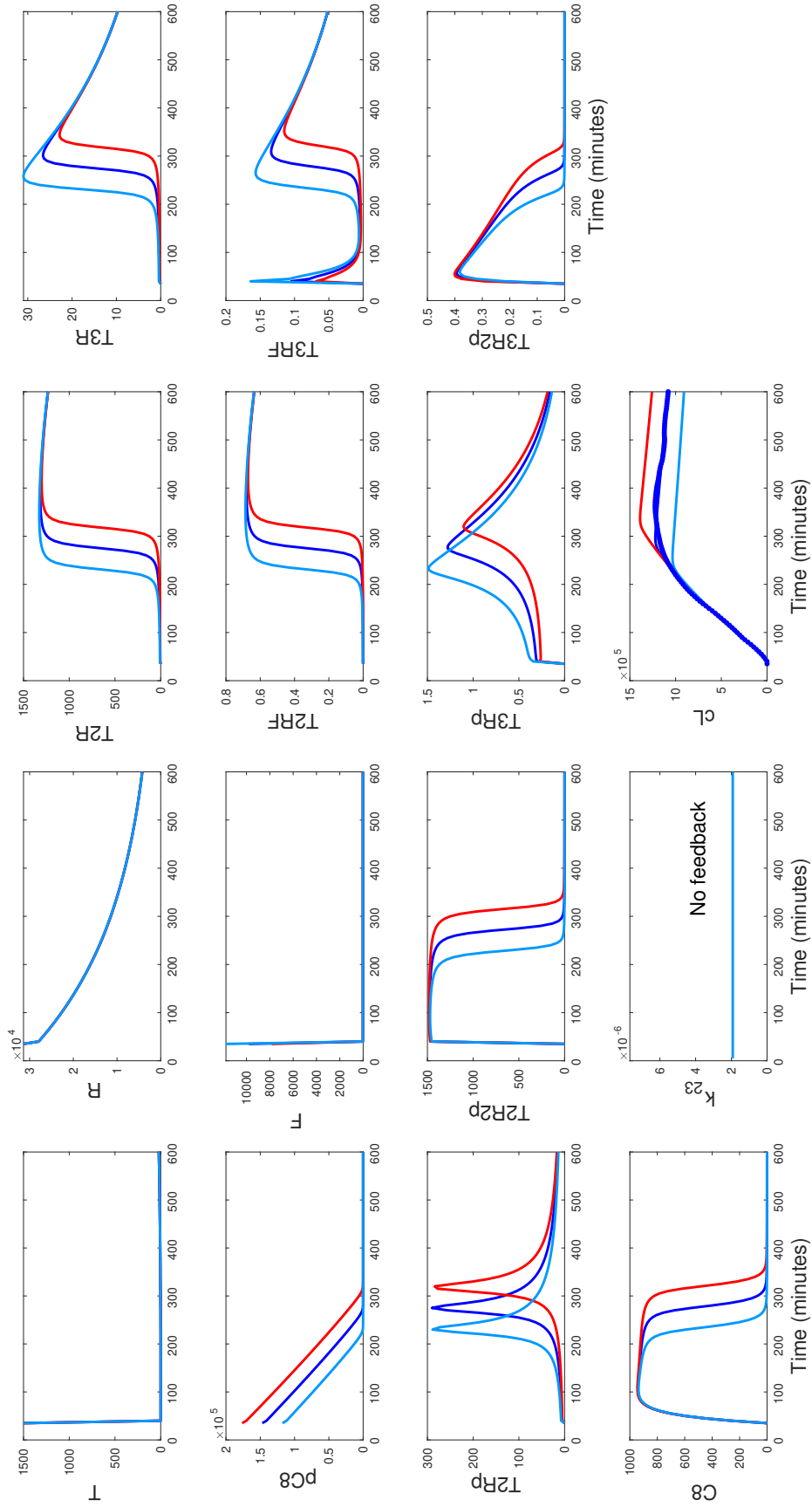
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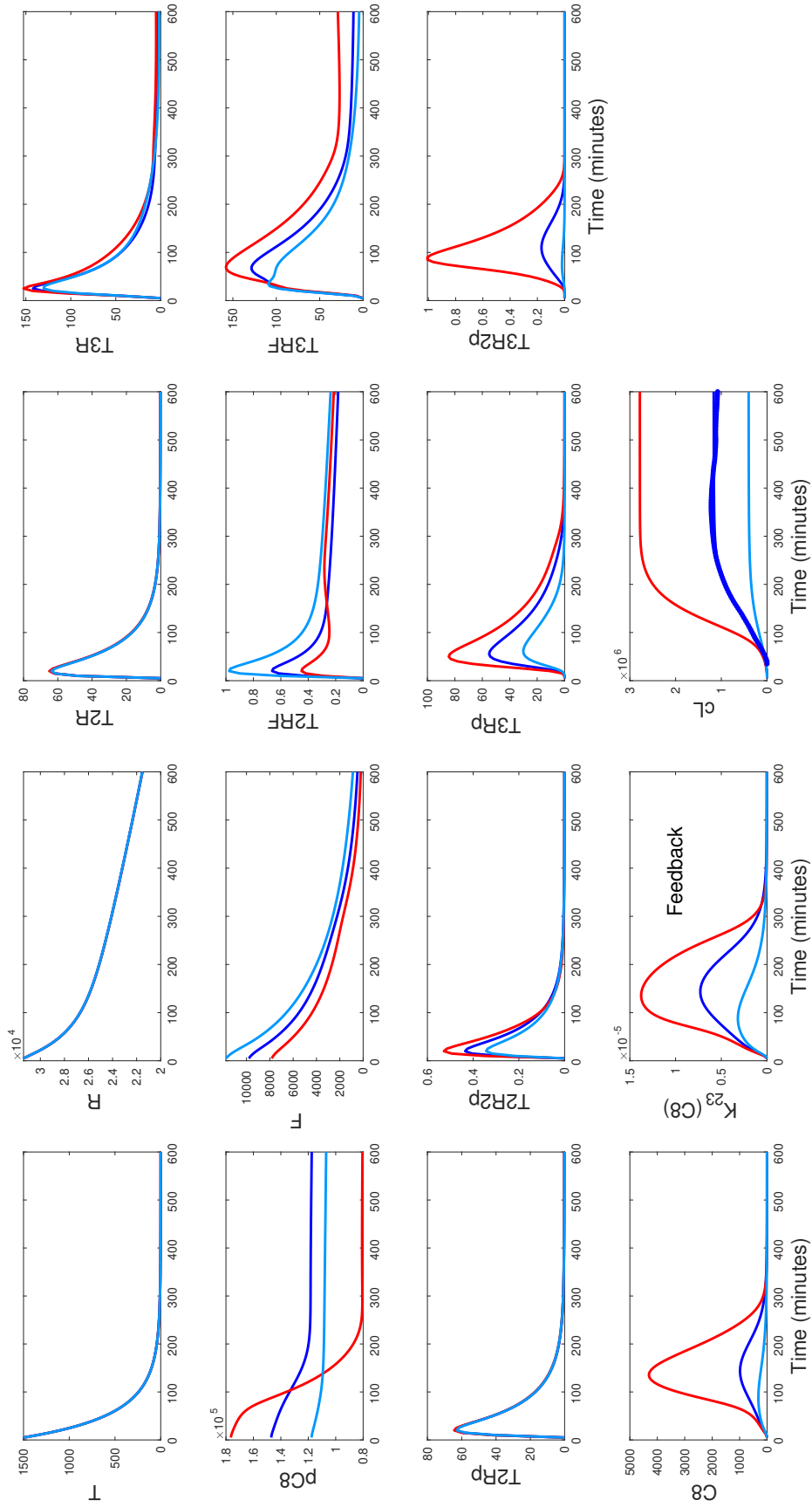
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Supplementary Figure 1: All cells with universal profiles detected for ARRM with feedback from $C8$ into k_5 (top left), k_{72} (top right), k_{35} (bottom left), and k_{23} (bottom right).



Supplementary Figure 2: Dynamics for cell 271, ARRM with no feed-back. Three different initial conditions: nominal ($pC8_0, FLIP_0$) (blue), ($1.2pC8_0, 0.8FLIP_0$) (red), ($0.8pC8_0, 1.2FLIP_0$) (light blue).



Supplementary Figure 3: Dynamics for cell 271, ARRM with $K_{23}(C8)$ feedback. Three different initial conditions: nominal ($pC8_0, FLIP_0$) (blue), $(1.2pC8_0, 0.8FLIP_0)$ (red), $(0.8pC8_0, 1.2FLIP_0)$ (light blue).

Supplementary Table 1: Table of reactions and corresponding parameters, as described by ARRM. The third and fourth columns list the parameter values obtained for cell#271, for ARRM and ARRM+Feedback with $K_{23}(C8)$.

Reaction	Parameter	ARRM	Cell 271 ARRM +Feedback
Ligand-receptor complexes			
T + R → T:R	k1 (# ⁻¹ s ⁻¹)	1.2343 × 10 ⁻⁴	6.6999 × 10 ⁻⁷
T:R → T+R	k2 (s ⁻¹)	0.0754	0.0045
T:R + R → T:2R	k3 (# ⁻¹ s ⁻¹)	0.0142	7.1425 × 10 ⁻⁴
T:2R → T:R+R	k4 (s ⁻¹)	6.9896	0.0560
T:2R + R → T:3R	k5 (# ⁻¹ s ⁻¹)	2.0065 × 10 ⁻⁵	1.1673 × 10 ⁵
T:3R → T:2R+R	k6 (s ⁻¹)	10.7493	0.0080
Ligand-inhibitor complexes			
T:R + F → T:R:F	k9 (# ⁻¹ s ⁻¹)	9.9279 × 10 ⁻⁴	2.8003 × 10 ⁻⁷
T:R:F → T:R+F	k10 (s ⁻¹)	0.0328	0.1442
T:2R + F → T:2R:F	k11 (# ⁻¹ s ⁻¹)	2.5286 × 10 ⁻⁴	8.8298 × 10 ⁻⁷
T:2R:F → T:2R+F	k12 (s ⁻¹)	9.3523	7.8475 × 10 ⁻⁴
T:2R:F + F → T:2R:2F	k11 (# ⁻¹ s ⁻¹)	2.5286 × 10 ⁻⁴	8.8298 × 10 ⁻⁷
T:2R:2F → T:2R:F+F	k12 (s ⁻¹)	9.3523	7.8475 × 10 ⁻⁴
T:3R + F → T:3R:F	k17 (# ⁻¹ s ⁻¹)	6.3154 × 10 ⁻⁵	1.2829 × 10 ⁻⁵
T:3R:F → T:3R+F	k18 (s ⁻¹)	0.2394	1.1047 × 10 ⁻⁴
T:3R:F + F → T:3R:2F	k17 (# ⁻¹ s ⁻¹)	6.3154 × 10 ⁻⁵	1.2829 × 10 ⁻⁵
T:3R:2F → T:3R:F+F	k18 (s ⁻¹)	0.2394	1.1047 × 10 ⁻⁴
T:3R:2F + F → T:3R:3F	k17 (# ⁻¹ s ⁻¹)	6.3154 × 10 ⁻⁵	1.2829 × 10 ⁻⁵
T:3R:3F → T:3R:2F+F	k18 (s ⁻¹)	0.2394	1.1047 × 10 ⁻⁴
Ligand- pro-caspase complexes			
T:2R +pC8 → T:2R:pC8	k35 (# ⁻¹ s ⁻¹)	3.4391 × 10 ⁻⁴	5.6585 × 10 ⁻⁶
T:2R:pC8 → T:2R+pC8	k36 (s ⁻¹)	0.1898	0.0063
T:2R:pC8+pC8 → T:2R:2pC8	k35 (# ⁻¹ s ⁻¹)	3.219 × 10 ⁻⁶	1.113 × 10 ⁻⁶
T:3R+pC8 → T:3R:pC8	k23 (# ⁻¹ s ⁻¹)	1.9205 × 10 ⁻⁶	1.8671 × 10 ⁻⁵
T:3R:pC8 → T:3R+pC8	k24 (s ⁻¹)	0.0064	0.0085
T:3R:pC8 +pC8 → T:3R:2pC8	k23 (# ⁻¹ s ⁻¹)	1.9205 × 10 ⁻⁶	1.8671 × 10 ⁻⁵
Ligand-inhibitor- pro-caspase complexes			
T:2R:F+pC8 → T:2R:F:pC8	k35 (# ⁻¹ s ⁻¹)	3.4391 × 10 ⁻⁴	5.6585 × 10 ⁻⁶
T:2R:F:pC8 → T:2R:F+pC8	k36 (s ⁻¹)	0.1898	0.0063
T:3R:F+pC8 → T:3R:F:pC8	k23 (# ⁻¹ s ⁻¹)	1.9205 × 10 ⁻⁶	1.8671 × 10 ⁻⁵
T:3R:F:pC8 → T:3R:F+pC8	k24 (s ⁻¹)	0.0064	0.0085
T:3R:2F+pC8 → T:3R:F:pC8	k23 (# ⁻¹ s ⁻¹)	1.9205 × 10 ⁻⁶	1.8671 × 10 ⁻⁵
T:3R:2F:pC8 → T:3R:F+pC8	k24 s ⁻¹)	0.0064	0.0085
T:3R:F:pC8+pC8 → T:3R:F:2pC8	k23 (# ⁻¹ s ⁻¹)	1.9205 × 10 ⁻⁶	1.8671 × 10 ⁻⁵

Reaction	Parameter	Cell 271	
		ARRM	ARRM +Feedback
Activation of caspase 8 and fluorescent protein			
T:2R:2pC8 $\rightarrow$ C8 +T:2R	k38 (s^{-1})	0.2012	120.6982
T:3R:2pC8 $\rightarrow$ C8 +T:3R	k38 (s^{-1})	0.2012	120.6982
T:3R:F:2pC8 $\rightarrow$ C8+T:3R:F	k38 (s^{-1})	0.2012	120.6982
C8+Bid $\rightarrow$ C8:Bid	k59 ($\#^{-1}s^{-1}$)	1.8951×10^{-6}	2.1810×10^{-6}
C8:Bid $\rightarrow$ C8+tBid	k60 (s^{-1})	2.9483	3.9524
C8+L $\rightarrow$ C8:L	k59 ($\#^{-1}s^{-1}$)	1.8951×10^{-6}	2.1810×10^{-6}
C8:L $\rightarrow$ C8+L	k60 (s^{-1})	2.9483	3.9524
Synthesis and degradation rates			
$\rightarrow$ R	k64 ($\#s^{-1}$)	0.1451	0.0202
$\rightarrow$ pC8	k65 ($\#s^{-1}$)	0.0136	0.0016
$\rightarrow$ F	k66 ($\#s^{-1}$)	26.9915	0.0061
$\rightarrow$ Bid	k67 ($\#s^{-1}$)	50.1310	2.7465
T $\rightarrow$.	k68 (s^{-1})	1.8043×10^{-4}	7.0599×10^{-5}
R $\rightarrow$.	k69 (s^{-1})	0.0034	3.7205×10^{-4}
F $\rightarrow$.	k70 (s^{-1})	1.4043	0.0031
pC8 $\rightarrow$.	k71 (s^{-1})	5.2947×10^{-4}	3.6925×10^{-5}
C8 $\rightarrow$.	k72 (s^{-1})	0.3264	0.0827
Bid $\rightarrow$.	k73 (s^{-1})	0.0152	7.6013×10^{-4}
tBid $\rightarrow$.	k74 (s^{-1})	0.0167	2.4216×10^{-5}
cL $\rightarrow$.	k75 (s^{-1})	3.9264×10^{-4}	5.4624×10^{-8}
$\rightarrow$ FP	k76 ($\#s^{-1}$)	3.8961	0.1607