

# 1 **Supplementary Text S1:**

## 2 **Importance of feedback and feedforward loops to adaptive** 3 **immune response modeling**

4 Anisur Rahman, Abhinav Tiwari, Jatin Narula and Timothy Hickling

### 5 **Model equations and parameters:**

#### 6 **ODEs for Figure 1(b):**

7 When there is no feedback in the system, it becomes more straightforward and can be described  
8 by the following expressions (1), (2) and (3). X, A and B represent the active fractions of the  
9 corresponding molecules. It is assumed that at initial time points the activation of the molecules  
10 follow 1<sup>st</sup> order kinetics and deactivation follow saturable kinetics throughout.

$$X(t) = \begin{cases} 0, & t < 0 \\ 0.2, & t \geq 0 \end{cases} \quad (1)$$

$$\frac{dA}{dt} = \frac{k_1 X(1-A)}{k_{1M} + (1-A)} - \frac{k_2 A}{k_{2M} + A} \quad (2)$$

$$\frac{dB}{dt} = \frac{k_4 A(1-B)}{k_{4M} + (1-B)} - \frac{k_5 B}{k_{5M} + B} \quad (3)$$

11 In case of positive and negative feedback, equations (1) and (3) remain same and the modified  
12 versions of equation (2) are given respectively:

$$\frac{dA}{dt} = \frac{k_1 X(1-A)}{k_{1M} + (1-A)} - \frac{k_2 A}{k_{2M} + A} + \frac{k_3 AB}{k_{3M} + B} \quad (4^+)$$

$$\frac{dA}{dt} = \frac{k_1 X(1-A)}{k_{1M} + (1-A)} - \frac{k_2 A}{k_{2M} + A} - \frac{k_3 AB}{k_{3M} + B} \quad (4^-)$$

13 The parameter values are given in Table S1.

14 Having observed that the kinetics of the various processes are dynamic on the timescale of hours  
15 and days, and certain rate parameters have units of day<sup>-1</sup>, we have semi-arbitrarily chosen the  
16 parameter values in their respective units. As the objective of our modeling efforts was to  
17 observe the response kinetics qualitatively, we have not explicitly tested the parameters  
18 sensitivity of the models; hence model calibrations may be necessary for more quantitative  
19 output.

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21 **Table S1: Parameter values used for Figure 1(b)** (nu - normalized unit with respect to  $k_1$ )

Parameters	Values (nu)
$k_1$	1
$k_2$	3e-4
$k_3$	10
$k_4$	1e-3
$k_5$	1e-5
$k_{1m}$	0.5
$k_{2m}$	0.01
$k_{3m}$	0.5
$k_{4m}$	0.5
$k_{5m}$	1

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23 **ODEs for Figure 1(d):**

24 Mass-action kinetics was assumed for the feed-forward loops. Equation (5) represents the input  
 25 values used at time  $t > 0$  to plot a dose response curve. The ODEs for the coherent (7c) and  
 26 incoherent (7i) feed-forward loops are given below along with the parameter values (Table S2).

$$X(t) = \begin{cases} 0, & t < 0 \\ 0.01:0.01:2, & t \geq 0 \end{cases} \quad (5)$$

$$\frac{dA}{dt} = k_1X(1 - A) - k_2A \quad (6)$$

$$\frac{dB}{dt} = k_3XA(1 - B) - k_4B \quad (7c)$$

$$\frac{dB}{dt} = \frac{k_5X(1 - B)}{k_{5m} + X} - k_6B \quad (7i)$$

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28 **Table S2: Parameter values used for Figure 1(b)** (nu - normalized unit with respect to  $k_4$ )

Parameters	Values (nu)
$k_1$	0.5
$k_2$	0.1
$k_3$	2
$k_4$	1
$k_5$	2
$k_{5m}$	0.1
$k_6$	1

29

30 **ODEs for Figures 4(a), 4(b) & 4(c):**

31 The kinetic profiles of Figure-4 are qualitative in nature and are used only to illustrate the  
 32 frequent properties of the networks shown. The model assumptions are same as describes before  
 33 [Figure-1(b)]. ODEs without any feedback are given below. Ag, DC, TC, BC and ADA represent  
 34 the active fractions of the corresponding cells or molecules. Parameter values are given in Table  
 35 S3.

$$\frac{d(Ag)}{dt} = -\frac{k_s \cdot Ag}{k_{sm} + Ag} \quad (8)$$

$$\frac{d(DC)}{dt} = \frac{k_1 \cdot Ag \cdot (1 - DC)}{k_{1m} + (1 - DC)} - \frac{k_2 \cdot DC}{k_{2m} + DC} \quad (9)$$

$$\frac{d(TC)}{dt} = \frac{k_4 \cdot DC \cdot (1 - TC)}{k_{4m} + (1 - TC)} - \frac{k_5 \cdot TC}{k_{5m} + TC} \quad (10)$$

$$\frac{d(BC)}{dt} = \frac{k_6 \cdot TC \cdot (1 - BC)}{k_{6m} + (1 - BC)} - \frac{k_7 \cdot BC}{k_{7m} + BC} \quad (11)$$

$$\frac{d(ADA)}{dt} = \frac{k_8 \cdot BC \cdot (1 - ADA)}{k_{8m} + (1 - ADA)} - \frac{k_9 \cdot ADA}{k_{9m} + ADA} \quad (12)$$

36

37 For a negative feedback from ADA to Ag (Figure 4a), equation (8) is changed as follows:

$$\frac{d(Ag)}{dt} = -\frac{k_s \cdot Ag}{k_{sm} + Ag} - \frac{k_3 \cdot ADA \cdot Ag}{k_{3m} + Ag} \quad (13)$$

38 For positive feedback form TC to DC (Figure 4b) and negative feedback from TC to DC (Figure  
 39 4c), equation (9) is modified to (14<sup>+</sup>) and (14<sup>-</sup>) respectively.

$$\frac{d(DC)}{dt} = \frac{k_1 \cdot Ag \cdot (1 - DC)}{k_{1m} + (1 - DC)} - \frac{k_2 \cdot DC}{k_{2m} + DC} + \frac{k_3 \cdot DC \cdot TC}{k_{3m} + DC} \quad (14^+)$$

$$\frac{d(DC)}{dt} = \frac{k_1 \cdot Ag \cdot (1 - DC)}{k_{1m} + (1 - DC)} - \frac{k_2 \cdot DC}{k_{2m} + DC} - \frac{k_3 \cdot DC \cdot TC}{k_{3m} + DC} \quad (14^-)$$

40 As described previously, the parameter values are semi-arbitrary in nature, no sensitivity analysis  
 41 has been done and calibration of the models might be needed for more quantitative results.

42

43

44 **Table S3: Parameter values used for Figure 4(a), 4(b) & 4(c)** (nu - normalized unit with respect to  
 45  $k_1$ )

Parameters	Values (au)	Parameters	Values (au)
$k_s$	1e-4	$k_{sm}$	0.01
$k_1$	1	$k_{1m}$	0.5
$k_2$	3e-4	$k_{2m}$	0.01
$k_3$	10	$k_{3m}$	0.5
$k_4$	1e-3	$k_{4m}$	0.5
$k_5$	1e-5	$k_{5m}$	1
$k_6$	1e-3	$k_{6m}$	0.5
$k_7$	1e-5	$k_{7m}$	1
$k_8$	1e-3	$k_{8m}$	0.5
$k_9$	1e-5	$k_{9m}$	1

46

47 **ODEs for Figures 4(d):**

48 The ODEs used to plot figure 4(d) are given below. A unit step function of Ag is used as the  
 49 input to the system. The parameters are given in Table S4.

$$\frac{d(DC)}{dt} = \frac{k_1 \cdot Ag \cdot (1 - DC)}{k_{1m} + (1 - DC)} - \frac{k_2 \cdot DC}{k_{2m} + DC} \quad (15)$$

$$\frac{d(TC)}{dt} = \frac{k_3 \cdot DC \cdot (1 - TC)}{k_{3m} + (1 - TC)} - \frac{k_4 \cdot TC}{k_{4m} + TC} \quad (16)$$

$$\frac{d(Treg)}{dt} = \frac{k_7 \cdot DC \cdot (1 - Treg)}{k_{7m} + (1 - Treg)} - \frac{k_8 \cdot Treg}{k_{8m} + Treg} \quad (17)$$

$$\frac{d(BC)}{dt} = \frac{k_5 \cdot TC \cdot (1 - BC)}{k_{5m} + (1 - BC)} - \frac{k_6 \cdot BC}{k_{6m} + BC} \quad (18)$$

$$\frac{d(BCi)}{dt} = \frac{k_5 \cdot TC \cdot (1 - BCi)}{k_{5m} + (1 - BCi) + Treg} - \frac{k_6 \cdot BCi}{k_{6m} + BCi} \quad (18i)$$

$$\frac{d(ADA)}{dt} = \frac{k_9 \cdot BC \cdot (1 - ADA)}{k_{9m} + (1 - ADA)} - \frac{k_{10} \cdot ADA}{k_{10m} + ADA} \quad (19)$$

$$\frac{d(ADAI)}{dt} = \frac{k_9 \cdot BCi \cdot (1 - ADAi)}{k_{9m} + (1 - ADAi)} - \frac{k_{10} \cdot ADAi}{k_{10m} + ADAi} \quad (19i)$$

50 Equations (18i) and (19i) are the modified versions of the equations (18) and (19) in case of  
 51 incoherent feed-forward loop.

52

53 **Table S4: Parameter values used for Figure 4(d)**

<b>Parameters</b>	<b>Values (au)</b>	<b>Parameters</b>	<b>Values (au)</b>
$k_1$	0.5	$k_{1m}$	1
$k_2$	0.1	$k_{2m}$	1
$k_3$	2	$k_{3m}$	1
$k_4$	1	$k_{4m}$	1
$k_5$	2	$k_{5m}$	1.1
$k_6$	1	$k_{6m}$	1
$k_7$	0.4	$k_{7m}$	1
$k_8$	1e-3	$k_{8m}$	1
$k_9$	1	$k_{9m}$	1
$k_{10}$	1	$k_{10m}$	1

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## 72 Matlab Codes:

### 73 Figure\_1a:

```
74 tspan = [0:100];
75 y0 = [0 0];
76 global k1 k2 k3 s k4 k5 k1m k2m k3m k4m k5m
77
78 %s->X; y(1)->A; y(2)->B
79
80 s=0.2;
81 k1=1;
82 k2=3e-4;
83 k3=10;
84 k4=1e-3;
85 k5=1e-5;
86 k1m=5e-1;
87 k2m=1e-2;
88 k3m=5e-1;
89 k4m=5e-1;
90 k5m=1;
91
92 [t,y1] = ode15s(@n_fb_paper, tspan, y0);
93 [t,y2] = ode15s(@fbn_paper, tspan, y0);
94 [t,y3] = ode15s(@fbp_paper, tspan, y0);
95
96 y1_100_1 = y1(end,1);
97 y2_100_1 = y2(end,1);
98 y3_100_1 = y3(end,1);
99
100 y1_100_2 = y1(end,2);
101 y2_100_2 = y2(end,2);
102 y3_100_2 = y3(end,2);
103
104 figure(1),plot(t,y1(:,1),'r',t,y2(:,1),'b--',t,y3(:,1),'g','LineWidth',2)
105 legend('no feedback','(-)ve feedback','(+ve feedback')
106 title('concentration')
107
108
109 function dydt = n_fb_paper(t,y)
110 dydt = zeros(2,1);
111 global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m
112
113 dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1));
114 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
115 end
116
117
118 function dydt = fbn_paper(t,y)
119 dydt = zeros(2,1);
120 global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m
121
122 dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-
123 k2*y(1)/(k2m+y(1))+k3*y(1)*y(2)/(k3m+y(2));
124 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
```

```

125 end
126
127
128 function dydt = fbn_paper(t,y)
129 dydt = zeros(2,1);
130 global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m
131
132 dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1))-
133 k3*y(1)*y(2)/(k3m+y(2));
134 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
135 end
136

```

### 137 **Figure\_1b:**

```

138 %%FFL interaction
139 %s->X; y(1)->A; y(2),y(3)->B
140 tspan = [0:0.1:20];
141 y0 = [0 0 0];
142 global k1 k2 k3 s k4 k5 k5m k6 k7 k8
143
144 i=1;
145 for s=0.01:0.01:2;
146
147 % s=1;
148 k1=0.5;
149 k2=0.1;
150 k3=2;
151 k4=1;
152 k5=2;
153 k5m=0.11;
154 k6=1;
155 k7=2;
156 k8=1;
157
158 [t,y1] = ode15s(@fflc_alter_paper, tspan, y0);
159
160 ss(i)=s;
161 coh(i)=y1(end,2);
162 incoh(i)=y1(end,3);
163 i=i+1;
164 end
165
166 figure(2),plot(ss,coh,'g',ss,incoh,'r','LineWidth',2);
167 legend('Coherent FFL','Incoherent FFL')
168 xlabel('Input,X')
169 ylabel('Output,B')
170
171 function dydt = fflc_alter_paper(t,y)
172 dydt = zeros(3,1);
173 global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k7 k7m
174
175 dydt(1) = k1*s*(1-y(1))-k2*y(1);
176 dydt(2) = k3*s*y(1)*(1-y(2))-k4*y(2); %coherent
177 dydt(3) = k5*y(1)*(1-y(3))/(k5m+s)-k6*y(3); %incoherent
178 end

```

179

## 180 **Figure\_4a\_4b\_4c:**

```
181 tspan = [0:500];
182 y0 = [0 0 0 0 0.1];
183 global k1 k2 k3 s k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m ks
184 ksm
185
186 %y(5)->Ag; y(1)->DC; y(2)->TC; y(3)->BC; y(4)->ADA
187
188 s=0.1;
189 k1=1;
190 k2=3e-4;
191 k3=10;
192 k4=1e-3;
193 k5=1e-5;
194 k1m=5e-1;
195 k2m=1e-2;
196 k3m=5e-1;
197 k4m=5e-1;
198 k5m=1;
199 k6=1e-3;
200 k7=1e-5;
201 k8=1e-3;
202 k9=1e-5;
203 k6m=5e-1;
204 k7m=1;
205 k8m=5e-1;
206 k9m=1;
207 ks=1e-4;
208 ksm=0.01;
209
210 [t,y1] = ode15s(@no_feedback, tspan, y0);
211 [t,y2] = ode15s(@neg_fb_ADA2Ag, tspan, y0);
212 [t,y3] = ode15s(@pos_fb_Tc2Dc, tspan, y0);
213 [t,y4] = ode15s(@neg_fb_Tc2Dc, tspan, y0);
214
215 figure, subplot(2,2,1)
216 plot(t,y1(:,5), 'b', t,y2(:,5), 'r', 'LineWidth', 2)
217 legend('no FB', 'neg-fb-ADA2Ag', 'Location', 'best')
218 ylim([0 0.11])
219
220 subplot(2,2,2)
221 plot(t,y1(:,1), 'b', t,y3(:,1), 'g', 'LineWidth', 2)
222 legend('no FB', 'pos-fb-Tc2Dc', 'Location', 'best')
223 ylim([0 1.8])
224
225 subplot(2,2,3)
226 plot(t,y1(:,1), 'b', t,y4(:,1), 'r', 'LineWidth', 2)
227 legend('no FB', 'pos-fb-Tc2Dc', 'Location', 'best')
228 ylim([0 1.2])
229
230 %% function files
231
232 function dydt = no_feedback(t,y)
```

```

233 dydt = zeros(5,1);
234 global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m
235 % y(5) Antigen
236 % y(1) Dendritic cells
237 % y(2) T cells
238 % y(3) B cells
239 % y(4) ADA
240
241 dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %-
242 k3*y(1)*y(2)/(k3m+y(1));
243 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));
244
245 dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
246 dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));
247
248 dydt(5) = -ks*y(5)/(ksm+y(5));
249 end
250
251 function dydt = neg_fb_ADA2Ag(t,y)
252 dydt = zeros(5,1);
253 global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m
254
255 dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %-
256 k3*y(1)*y(2)/(k3m+y(1));
257 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));
258
259 dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
260 dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));
261
262 dydt(5) = -ks*y(5)/(ksm+y(5))-k3*y(4)*y(5)/(k3m+y(5));
263 end
264
265 function dydt = pos_fb_Tc2Dc(t,y)
266 dydt = zeros(5,1);
267 global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m
268
269 dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-
270 k2*y(1)/(k2m+y(1))+k3*y(1)*y(2)/(k3m+y(1)); %-k3*y(1)*y(2)/(k3m+y(1));
271 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));
272
273 dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
274 dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));
275
276 dydt(5) = -ks*y(5)/(ksm+y(5));
277 end
278
279 function dydt = neg_fb_Tc2Dc(t,y)
280 dydt = zeros(5,1);
281 global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m
282
283 dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1))-
284 k3*y(1)*y(2)/(k3m+y(1)); %-k3*y(1)*y(2)/(k3m+y(1));
285 dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));
286
287 dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
288 dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));
289

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```

290 dydt(5) = -ks*y(5)/(ksm+y(5));
291 end
292
293
294 Figure_4d:
295 %%FFL interaction
296 tspan = [0:0.1:20];
297 y0 = [0 0 0 0 0 0 0];
298 global k1 k2 k3 s k4 k5 k6 k7 k8 k9 k10 k1m k2m k3m k4m k5m k6m k7m k8m k9m
299 k10m
300
301 %s->Ag; y(1)->DC; y(2)->TC; y(3)->Treg; y(4)->BC; y(5)->BCi; y(6)->ADA; y(7)-
302 >ADAI
303
304 s=1;
305 k1=0.5;
306 k2=0.1;
307 k3=2;
308 k4=1;
309 k5=2;
310 k6=1;
311 k7=0.4;
312 k8=1e-3;
313 k9=1;
314 k10=1;
315 k1m=1;
316 k2m=1;
317 k3m=1;
318 k4m=1;
319 k5m=1.11;
320 k6m=1;
321 k7m=1;
322 k8m=1;
323 k9m=1;
324 k10m=1;
325
326 [t,y1] = ode15s(@fflc_MM_paper, tspan, y0);
327
328 figure(1),plot(t,y1(:,6), 'k',t,y1(:,7), 'r', 'LineWidth',2);hold on;
329
330 legend('No FFL','(d)')
331 title('concentration of C')
332
333 function dydt = fflc_MM_paper(t,y)
334 dydt = zeros(5,1);
335 global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m k10
336 k10m
337
338 dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %DC
339 dydt(2) = k3*y(1)*(1-y(2))/(k3m+(1-y(2)))-k4*y(2)/(k4m+y(2)); %TC
340 dydt(3) = k7*y(1)*(1-y(3))/(k7m+(1-y(3)))-k8*y(3)/(k8m+y(3)); %Treg
341 dydt(4) = k5*y(2)*(1-y(4))/(k5m+(1-y(4)))-k6*y(4)/(k6m+y(4)); %Bcell no FFL
342 dydt(5) = k5*y(2)*(1-y(5))/(k5m+(1-y(5))+y(3))-k6*y(4)/(k6m+y(4)); %Bcell
343 incoherent FFL
344 dydt(6) = k9*y(4)*(1-y(6))/(k9m+(1-y(6)))-k10*y(6)/(k10m+y(6)); %ADA no FFL

```

```
345 dydt(7) = k9*y(5)*(1-y(7))/(k9m+(1-y(7)))-k10*y(7)/(k10m+y(7)); %ADA
346 incoherent FFL
347 end
348
```