Supplementary Text S1:

Importance of feedback and feedforward loops to adaptive immune response modeling

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Model equations and parameters:

ODEs for Figure 1(b):

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

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

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

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

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

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

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

The parameter values are given in Table S1.

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

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

ODEs for Figure 1(d):

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

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

$$\frac{dA}{dt} = k_1 X(1 - A) - k_2 A \qquad (6)$$

$$\frac{dB}{dt} = k_3 XA(1 - B) - k_4 B \qquad (7c)$$

$$\frac{dB}{dt} = \frac{k_5 X(1 - B)}{k_{5m} + X} - k_6 B \qquad (7i)$$

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

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

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

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

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

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

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

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

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

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

For positive feedback form TC to DC (Figure 4b) and negative feedback from TC to DC (Figure 4c), equation (9) is modified to (14^+) and (14^-) respectively.

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

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

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

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

ODEs for Figures 4(d):

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

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

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

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

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

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

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

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

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

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

Parameters	Values (au)	Parameters	Values (au)
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

Matlab Codes:

Figure_1a:

```
tspan = [0:100];
y0 = [0 0];
global k1 k2 k3 s k4 k5 k1m k2m k3m k4m k5m

%s->X; y(1)->A; y(2)->B

s=0.2;
k1=1;
k2=3e-4;
k3=10;
k4=1e-3;
k5=1e-5;
k1m=5e-1;
k2m=1e-2;
k3m=5e-1;
k4m=5e-1;
k5m=1;

[t,y1] = ode15s(@n_fb_paper, tspan, y0);
[t,y2] = ode15s(@fbn_paper, tspan, y0);
[t,y3] = ode15s(@fbp_paper, tspan, y0);

y1_100_1 = y1(end,1);
y2_100_1 = y2(end,1);
y3_100_1 = y3(end,1);

y1_100_2 = y1(end,2);
y2_100_2 = y2(end,2);
y3_100_2 = y3(end,2);

figure(1),plot(t,y1(:,1),'r',t,y2(:,1),'b--',t,y3(:,1),'g:','LineWidth',2)
legend('no feedback','(-)ve feedback','(+)ve feedback')
title('concentration')


function dydt = n_fb_paper(t,y)
dydt = zeros(2,1);
global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m

dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
end


function dydt = fbp_paper(t,y)
dydt = zeros(2,1);
global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m

dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-
k2*y(1)/(k2m+y(1))+k3*y(1)*y(2)/(k3m+y(2));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
```

```
end


function dydt = fbn_paper(t,y)
dydt = zeros(2,1);
global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m

dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1))-
k3*y(1)*y(2)/(k3m+y(2));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));;
end
```

Figure_1b:

```
%%FFL interaction
%s->X; y(1)->A; y(2),y(3)->B
tspan = [0:0.1:20];
y0 = [0 0 0];
global k1 k2 k3 s k4 k5 k5m k6 k7 k8

i=1;
for s=0.01:0.01:2;

% s=1;
k1=0.5;
k2=0.1;
k3=2;
k4=1;
k5=2;
k5m=0.11;
k6=1;
k7=2;
k8=1;

[t,y1] = ode15s(@fflc_alter_paper, tspan, y0);

ss(i)=s;
coh(i)=y1(end,2);
incoh(i)=y1(end,3);
i=i+1;
end

figure(2),plot(ss,coh,'g',ss,incoh,'r','LineWidth',2);
legend('Coherent FFL','Incoherent FFL')
xlabel('Input,X')
ylabel('Output,B')

function dydt = fflc_alter_paper(t,y)
dydt = zeros(3,1);
global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k7 k7m

dydt(1) = k1*s*(1-y(1))-k2*y(1);
dydt(2) = k3*s*y(1)*(1-y(2))-k4*y(2); %coherent
dydt(3) = k5*y(1)*(1-y(3))/(k5m+s)-k6*y(3); %incoherent
end
```

Figure_4a_4b_4c:

```
tspan = [0:500];
y0 = [0 0 0 0 0.1];
global k1 k2 k3 s k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m ks
ksm

%y(5)->Ag; y(1)->DC; y(2)->TC; y(3)->BC; y(4)->ADA

s=0.1;
k1=1;
k2=3e-4;
k3=10;
k4=1e-3;
k5=1e-5;
k1m=5e-1;
k2m=1e-2;
k3m=5e-1;
k4m=5e-1;
k5m=1;
k6=1e-3;
k7=1e-5;
k8=1e-3;
k9=1e-5;
k6m=5e-1;
k7m=1;
k8m=5e-1;
k9m=1;
ks=1e-4;
ksm=0.01;

[t,y1] = ode15s(@no_feedback, tspan, y0);
[t,y2] = ode15s(@neg_fb_ADA2Ag, tspan, y0);
[t,y3] = ode15s(@pos_fb_Tc2Dc, tspan, y0);
[t,y4] = ode15s(@neg_fb_Tc2Dc, tspan, y0);

figure, subplot(2,2,1)
plot(t,y1(:,5),'b',t,y2(:,5),'r','LineWidth',2)
legend('no FB','neg-fb-ADA2Ag','Location','best')
ylim([0 0.11])

subplot(2,2,2)
plot(t,y1(:,1),'b',t,y3(:,1),'g','LineWidth',2)
legend('no FB','pos-fb-Tc2Dc','Location','best')
ylim([0 1.8])

subplot(2,2,3)
plot(t,y1(:,1),'b',t,y4(:,1),'r','LineWidth',2)
legend('no FB','pos-fb-Tc2Dc','Location','best')
ylim([0 1.2])

%% function files

function dydt = no_feedback(t,y)
```

```
dydt = zeros(5,1);
global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m
% y(5) Antigen
% y(1) Dendritic cells
% y(2) T cells
% y(3) B cells
% y(4) ADA

dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %-
k3*y(1)*y(2)/(k3m+y(1));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));

dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));

dydt(5) = -ks*y(5)/(ksm+y(5));
end

function dydt = neg_fb_ADA2Ag(t,y)
dydt = zeros(5,1);
global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m

dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %-
k3*y(1)*y(2)/(k3m+y(1));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));

dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));

dydt(5) = -ks*y(5)/(ksm+y(5))-k3*y(4)*y(5)/(k3m+y(5));
end

function dydt = pos_fb_Tc2Dc(t,y)
dydt = zeros(5,1);
global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m

dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-
k2*y(1)/(k2m+y(1))+k3*y(1)*y(2)/(k3m+y(1)); %-k3*y(1)*y(2)/(k3m+y(1));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));

dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));

dydt(5) = -ks*y(5)/(ksm+y(5));
end

function dydt = neg_fb_Tc2Dc(t,y)
dydt = zeros(5,1);
global ks ksm k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m

dydt(1) = k1*y(5)*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1))-
k3*y(1)*y(2)/(k3m+y(1)); %-k3*y(1)*y(2)/(k3m+y(1));
dydt(2) = k4*y(1)*(1-y(2))/(k4m+(1-y(2)))-k5*y(2)/(k5m+y(2));

dydt(3) = k6*y(2)*(1-y(3))/(k6m+(1-y(3)))-k7*y(3)/(k7m+y(3));
dydt(4) = k8*y(3)*(1-y(4))/(k8m+(1-y(4)))-k9*y(4)/(k9m+y(4));
```

```
dydt(5) = -ks*y(5)/(ksm+y(5));
end
```

Figure_4d:

```
%%FFL interaction
tspan = [0:0.1:20];
y0 = [0 0 0 0 0 0 0];
global k1 k2 k3 s k4 k5 k6 k7 k8 k9 k10 k1m k2m k3m k4m k5m k6m k7m k8m k9m
k10m

%s->Ag; y(1)->DC; y(2)->TC; y(3)->Treg; y(4)->BC; y(5)->BCi; y(6)->ADA; y(7)-
>ADAi

s=1;
k1=0.5;
k2=0.1;
k3=2;
k4=1;
k5=2;
k6=1;
k7=0.4;
k8=1e-3;
k9=1;
k10=1;
k1m=1;
k2m=1;
k3m=1;
k4m=1;
k5m=1.11;
k6m=1;
k7m=1;
k8m=1;
k9m=1;
k10m=1;

[t,y1] = ode15s(@fflc_MM_paper, tspan, y0);

figure(1),plot(t,y1(:,6),'k',t,y1(:,7),'r','LineWidth',2);hold on;

legend('No FFL','(d)')
title('concentration of C')

function dydt = fflc_MM_paper(t,y)
dydt = zeros(5,1);
global s k1 k2 k3 k4 k5 k1m k2m k3m k4m k5m k6 k6m k7 k7m k8 k8m k9 k9m k10
k10m

dydt(1) = k1*s*(1-y(1))/(k1m+(1-y(1)))-k2*y(1)/(k2m+y(1)); %DC
dydt(2) = k3*y(1)*(1-y(2))/(k3m+(1-y(2)))-k4*y(2)/(k4m+y(2)); %TC
dydt(3) = k7*y(1)*(1-y(3))/(k7m+(1-y(3)))-k8*y(3)/(k8m+y(3)); %Treg
dydt(4) = k5*y(2)*(1-y(4))/(k5m+(1-y(4)))-k6*y(4)/(k6m+y(4)); %Bcell no FFL
dydt(5) = k5*y(2)*(1-y(5))/(k5m+(1-y(5))+y(3))-k6*y(4)/(k6m+y(4)); %Bcell
incoherent FFL
dydt(6) = k9*y(4)*(1-y(6))/(k9m+(1-y(6)))-k10*y(6)/(k10m+y(6)); %ADA no FFL
```

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