Supplementary Information

A Mathematical Model for Enzyme Clustering in Glucose Metabolism

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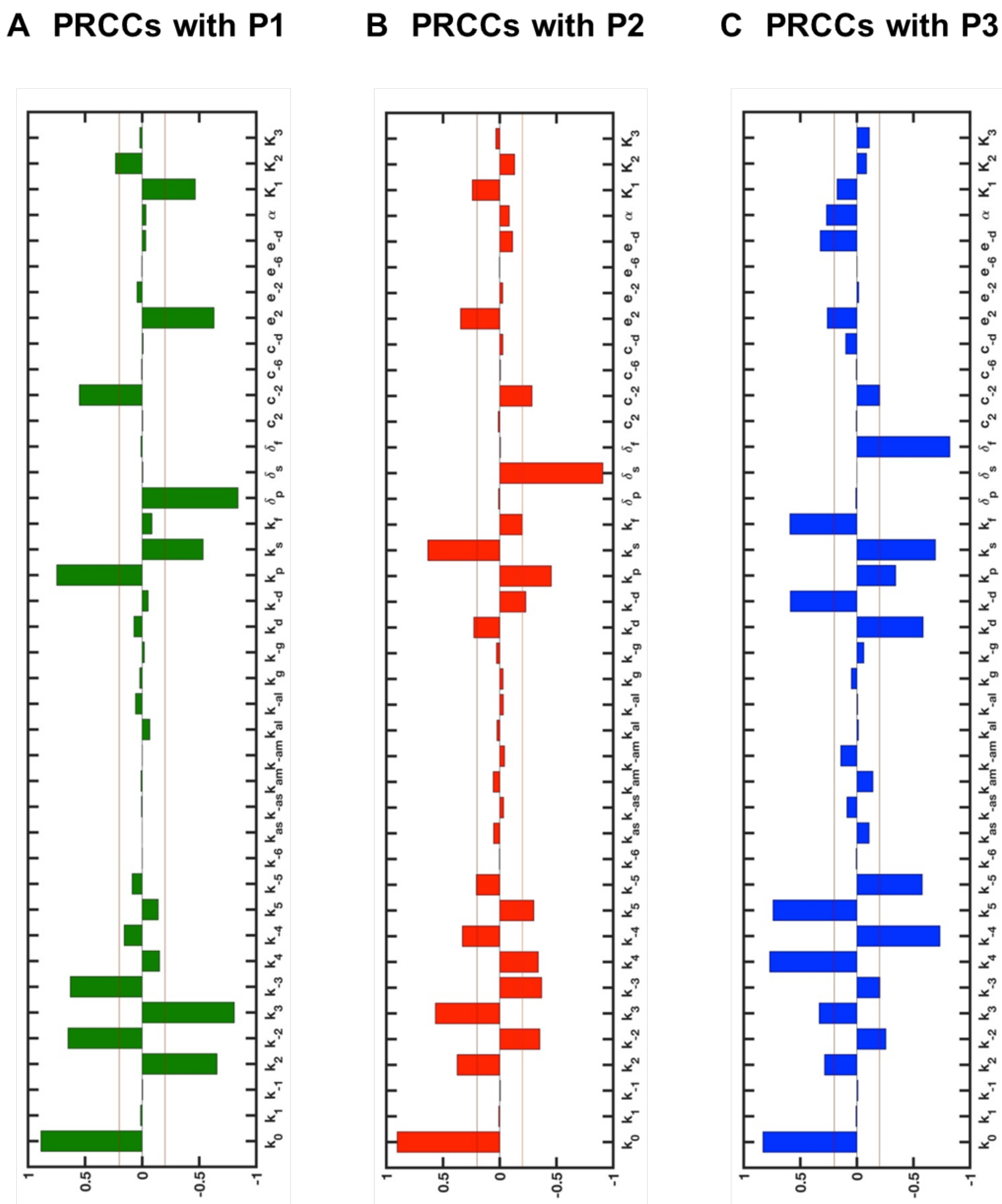

Supplemental Figure S1. The partial rank correlation coefficients (PRCCs) between all the input parameters and the concentrations of metabolic products. The PRCCs with P_1, P_2, and P_3 , respectively, are graphed to provide relative strengths of the correlations between the input parameters and the concentrations of metabolic products. The lines of +0.2 and -0.2 indicate the thresholds we used to distinguish sensitive essential parameters from non-essential parameters. Figure 3 show the PRCC values of sensitive essential parameters for each product. P_1, P_2, and P_3 represent metabolic outcomes of the pentose phosphate pathway, serine biosynthesis and the downstream of glycolysis, respectively.

Supplemental MATLAB code 1: Simulation of Glucose Metabolism

ODEs to simulate glucose metabolism.

```
function dydt = glucosome_ode(t,y,p)

% assign input parameters
k0=p(1); k1=p(2); k_1=p(3); k2=p(4); k_2=p(5);
k3=p(6); k_3=p(7); k4=p(8); k_4=p(9); k5=p(10);
k_5=p(11); k_6=p(12); kas=p(13); k_as=p(14); kam=p(15);
k_am=p(16); kal=p(17); k_al=p(18); kg=p(19); k_g=p(20);
kd=p(21); k_d=p(22); kp=p(23); ks=p(24); kf=p(25);
delta_p=p(26); delta_s=p(27); delta_f=p(28); c2=p(29); c_2=p(30);
c_6=p(31); c_d=p(32); e2=p(33); e_2=p(34); e_6=p(35);
e_d=p(36); alpha=p(37); K1=p(38); K2=p(39); K3=p(40);

% assign variables
S1=y(1); S2=y(2); S3=y(3); S4=y(4); S5=y(5); S6=y(6); S7=y(7);
E1=y(8); E2=y(9); E3=y(10); E4=y(11); ES=y(12); EM=y(13); EL=y(14);
E3i=y(15); E1gly=y(16); P1=y(17); P2=y(18); P3=y(19);

% ode equations
dydt = [k0 - k1*S1 + k_1*S2;...
                %y(1) S1
        k1*S1 - k_1*S2 - k2*(E1+ES+c2*EM+e2*EL)*S2*K1/(K1+S3)...
                + k_2*(E2+c_2*EM+e_2*EL)*S3*K2/(K2+S2) - kp*S2;...
                %y(2) S2
        k2*(E1+ES+c2*EM+e2*EL)*S2*K1/(K1+S3)...
                - k_2*(E2+c_2*EM+e_2*EL)*S3*K2/(K2+S2) - k3*S3...
                + k_3*S4;...
                %y(3) S3
        k3*S3 - k_3*S4 - k4*S4 + k_4*S5 - ks*S4;...
                %y(4) S4
        k4*S4 - k_4*S5 - k5*E3i*S5 + k_6*(E4+c_6*EM+e_6*EL)*S7;...
                %y(5) S5
        k5*E3i*S5 - k_5*S6 - kf*S6;...
                %y(6) S6
        k_5*S6 - k_6*(E4+c_6*EM+e_6*EL)*S7;...
                %y(7) S7
        - kas*E1 + k_as*ES - kg*E1 + k_g*E1gly;...
                %y(8) E1
        - kam*ES*E2*E3*E4 + k_am*EM;...
                %y(9) E2
        - kam*ES*E2*E3*E4 + k_am*EM + kd*E3i...
                - k_d*(E3+c_d*EM+e_d*EL)*(1+alpha*S3/(S3+K3));...
```

```
        %y(10) E3
- kam*ES*E2*E3*E4 + k_am*EM;...
        %y(11) E4
kas*E1 - k_as*ES - kam*ES*E2*E3*E4 + k_am*EM;...
        %y(12) ES
kam*ES*E2*E3*E4 - k_am*EM - 11*kal*EM^(11) + 11*k_al*EL;...
        %y(13) EM
kal*EM^(11) - k_al*EL;...
        %y(14) EL
- kd*E3i + k_d*(E3+c_d*EM+e_d*EL)*(1+alpha*S3/(S3+K3));...
        %y(15) E3* (=E3i)
kg*E1 - k_g*E1gly;...
        %y(16) E1gly
kp*S2 - delta_p*P1;...
        %y(17) P1
ks*S4 - delta_s*P2;...
        %y(18) P2
kf*S6 - delta_f*P3];
        %y(19) P3
```

Supplemental MATLAB code 2: Figures 2, 4 and 5

This code is the code to run 4 subcellular cases with varying parameters.

```
clear all
% parameters
k0=10; k1=10; k_1=10; k2=40; k_2=7; k3=10; k_3=10; k4=14; k_4=7;
k5=1; k_5=10; k_6=10; kg=1; k_g=1; kd=1; k_d=1;
kp=5; ks=5; kf=5; delta_p=0.5; delta_s=0.5; delta_f=0.5;
alpha=1; K1=1; K2=1; K3=1;

% initial conditions (19)
y0 = [0.01; 0.01; 0.01; 0.01; 0.01; 0.01; 0.01;...
    % S1 S2 S3 S4 S5 S6 S7
            99.99; 100; 99.99; 100; 0; 0; 0; 0.01; 0.01;...
        % E1 E2 E3 E4 ES EM EL E3* E1gly
            0.01; 0.01; 0.01];
        % P1 P2 P3

% Parameter changes in Four Subcellular Cases:
% No Cluster, Small Cluster, Medium Cluster, Large Cluster
for n=0:3
    switch n
        case 0
            % No Cluster
            kas=0; k_as=0; kam=0; k_am=0; kal=0; k_al=0;
            c2=0; c_2=0; c_6=0; c_d=0;
            e2=0; e_2=0; e_6=0; e_d=0;
        case 1
            % Small Cluster
            kas=10; k_as=10; kam=0; k_am=0; kal=0; k_al=0;
            c2=0; c_2=0; c_6=0; c_d=0;
            e2=0; e_2=0; e_6=0; e_d=0;
        case 2
            % Medium Cluster
            kas=10; k_as=10; kam=10; k_am=10; kal=0; k_al=0;
            c2=0.2; c_2=10; c_6=10; c_d=0.1;
            e2=0; e_2=0; e_6=0; e_d=0;
        case 3
            % Large Cluster
            kas=10; k_as=10; kam=10; k_am=10; kal=10; k_al=10;
            c2=0.2; c_2=10; c_6=10; c_d=0.1;
            e2=2.5; e_2=0.1; e_6=10; e_d=0.05;

    end
```

```
% parameters (40)
p = [k0,k1,k_1,k2,k_2,k3,k_3,k4,k_4,k5,...
          k_5,k_6,kas,k_as,kam,k_am,kal,k_al,kg,k_g,...
          kd,k_d,kp,ks,kf,delta_p,delta_s,delta_f,c2,c_2,...
          c_6,c_d,e2,e_2,e_6,e_d,alpha,K1,K2,K3];

% times ranges
time_ranges = [0:0.005:10];

% solve ODEs with parameters, initial conditions, time ranges
[T,y] = ode15s(@glucosome_ode,time_ranges,y0,[],p);

P1=y(:,17);
P2=y(:,18);
P3=y(:,19);

pl = [k0,k1,k_1,k2,k_2,k3,k_3,k4,k_4,k5,...
          k_5,k_6,kas,k_as,kam,k_am,kal,k_al,kg,k_g,...
          kd,k_d,kp,ks,kf,delta_p,delta_s,delta_f,c2,1,...
          c_6,c_d,e2,e_2,e_6,e_d,alpha,K1,K2,K3]; % c_2 changed

[Tl,yl] = ode15s(@glucosome_ode,time_ranges,y0,[],pl);

lower_P1=yl(:,17);
lower_P2=yl(:,18);
lower_P3=yl(:,19);

pu = [k0,k1,k_1,k2,k_2,k3,k_3,k4,k_4,k5,...
          k_5,k_6,kas,k_as,kam,k_am,kal,k_al,kg,k_g,...
          kd,k_d,kp,ks,kf,delta_p,delta_s,delta_f,c2,10,...
          c_6,c_d,e2,e_2,e_6,e_d,alpha,K1,K2,K3];

[Tu,yu] = ode15s(@glucosome_ode,time_ranges,y0,[],pu);

upper_P1=yu(:,17);
upper_P2=yu(:,18);
upper_P3=yu(:,19);

% Parameter ranges to change in 'pl' and 'pu'
% k2:10~40, k_2:7~10, k_d:1~10
% c2:0.2~1, c_2:1~10, c_6:1~10, c_d:0.1~1
% e2:1~2.5, e_2:0.1~1, e_6:1~10, e_d:0.05~1

figure (n+1)
hold on
```

```
s1=plot(T,y(:,17),'-','LineWidth',4);
set(s1,'Color',[0,0.5,0])
s2=plot(T,y(:,18),'-r','LineWidth',4);
s3=plot(T,y(:,19),'-b','LineWidth',4);

legend([s1 s2 s3],'P1','P2','P3','Location','northwest')
set(gcf,'color','w');
set(gca,'FontSize',25,'FontName','Times');
xlabel('time','FontSize',30,'FontName','Times');
ylabel('concentration','FontSize',30,'FontName','Times');
axis([0 10 0 18])
box on
hold off

% Save the figures and data
print('-djpeg','-r1000',['subcellular' num2str(n)])
save(['subcellular' num2str(n) '.mat'],'T','y','P1','P2','P3')

close all

figure(n+5)
hold on

T2 = [T; flipud(T)];
inBetween1 = [yl(:,17); flipud(yu(:,17))];
inBetween2 = [yl(:,18); flipud(yu(:,18))];
inBetween3 = [yl(:,19); flipud(yu(:,19))];

h1=fill(T2, inBetween1, [0,0.5,0]);
h2=fill(T2, inBetween2, 'r');
h3=fill(T2, inBetween3, 'b');

set(h1,'EdgeColor','none','facealpha',.2)
set(h2,'EdgeColor','none','facealpha',.2)
set(h3,'EdgeColor','none','facealpha',.2)

x1=plot(T,y(:,17),'-','LineWidth',4);
set(x1,'Color',[0,0.5,0])
x2=plot(T,y(:,18),'-r','LineWidth',4);
x3=plot(T,y(:,19),'-b','LineWidth',4);

legend([x1 x2 x3],'P1','P2','P3','Location','northwest')
set(gcf,'color','w');
set(gca,'FontSize',25,'FontName','Times');
axis([0 10 0 18])
box on
```

```
        hold off

        % Save the figures
        print('-djpeg','-r1000',['c_2_shade' num2str(n)])
        close all

end
```

Supplemental MATLAB code 3: Figures 6 and 7B

This is the code to make predictions at the population level using subcellular simulation data (Figure 2) and experimental data shown in Table 5.

```
clear all
load('subcellular0.mat')
P1_c0=P1;
P2_c0=P2;
P3_c0=P3;
clear P1 P2 P3
load('subcellular1.mat')
P1_c1=P1;
P2_c1=P2;
P3_c1=P3;
clear P1 P2 P3
load('subcellular2.mat')
P1_c2=P1;
P2_c2=P2;
P3_c2=P3;
clear P1 P2 P3
load('subcellular3.mat')
P1_c3=P1;
P2_c3=P2;
P3_c3=P3;
clear P1 P2 P3
save('simul_data.mat')
clear all
load('simul_data.mat')

for k=1:5
        % ratios of cell distribution showing different-sized clusters in the five environments
        Ratio = [1.6 58.3 13.4 26.7;...
                        0.5 43.0 25.7 30.8;...
                        0.0 45.3 29.1 25.6;...
                        0.4 53.1 7.6 38.9;...
                        0 34.7 21.2 44.1];
        Ratio=Ratio/100;

        figure(1)
        hold on
        s1=plot(T,Ratio(k,1)*P1_c0+Ratio(k,2)*P1_c1+Ratio(k,3)*P1_c2...
                +Ratio(k,4)*P1_c3,'-','LineWidth',4);
        set(s1,'Color',[0,0.5,0])
        s2=plot(T,Ratio(k,1)*P2_c0+Ratio(k,2)*P2_c1+Ratio(k,3)*P2_c2...
```

```
            +Ratio(k,4)*P2_c3,'-r','LineWidth',4);
    s3=plot(T,Ratio(k,1)*P3_c0+Ratio(k,2)*P3_c1+Ratio(k,3)*P3_c2...
            +Ratio(k,4)*P3_c3,'-b','LineWidth',4);

    legend('P1','P2','P3','Location','northwest')
    set(gcf,'color','w');
    set(gca,'FontSize',25,'FontName','Times');
    xlabel('time','FontSize',30,'FontName','Times');
    ylabel('concentration','FontSize',30,'FontName','Times');
    axis([0 10 0 10])
    box on
    hold off

    print('-djpeg','-r1000',['population' num2str(k)])
    close all
end
```