Support Information

For The Mathematical Modeling of The Gut Microbiota Regulation By E.coslim

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The proportion of Firmicutes and Bacteriodetes are reported to be linked with human obesity. In the intestines of a man with a bad shape (here it refers to overweight), the ratio of these two bacteria are generally much higher than that inside a healthy person. It seems that by changing this ratio, usually reducing it to a lower value, can we fulfill a beautiful dream—losing weight while enjoying eating.

This ratio relationship can be described by a model considering two species compete for two perfectly substitutable resources since glucose and fatty acid, the most commonly known energy resources, are just exchangeable in our body.

We assume that resources S(sugar) and R(fat) are perfectly substitutable for both populations x_1(Firmicutes) and x_2(Bacteriodetes). Noticing that the real situation is too complicated to be described (the chemical environment in our intestines is not thoroughly understood and the 100 trillion of other bacteria make it even worse), we have to abstract these factors as an exploitative competition in a chemostat. It is at first glance a cursory attempt, but a further look at this idea does make some sense---at least we can give a result on the ratio, which is the key indicator of obesity.

We assume that the volume of suspension in the culture vessel is one cubic unit and that the culture vessel is well-stirred. The ODEs are generally:

$$S'(t) = (S^0 - S(t))D - \sum_{i=1}^{2} \frac{x_i(t)}{\xi_i} \mathcal{S}_i(S(t), R(t)),$$

$$R'(t) = (R^0 - R(t))D - \sum_{i=1}^{2} \frac{x_i(t)}{\eta_i} \mathcal{R}_i(S(t), R(t)),$$

$$x_i'(t) = x_i(t)(-D + \mathcal{G}_i(S(t), R(t))), \quad i = 1, 2,$$

S(t) and R(t) represent the concentrations of the above-mentioned two nutrients.
$x_i(t)$, i = 1,2, denote the biomass of the competing populations of microorganisms in the culture vessel at time t.
$S^0$and R^0 denote the concentrations of resource S and resource R in the feed bottle.
The constant D represents the dilution rate. The specific death rates of the microorganisms are assumed to be insignificant compared to this dilution rate D.
The function $S_i(S,R)$ (respectively, $R_i(S,R)$) represents the rate of conversion of nutrient S (R) to biomass of population x_i. If the conversion of nutrient to biomass is proportional to the amount of nutrient consumed, the consumption rate of resource S (R) per unit of competitor x_i is denoted $S_i(S,R)/\xi_i$ ($R_i(S,R)/\eta_i$) where $\xi_i(\eta_i)$ is the respective growth yield constant.
The function Gi(S,R) represents the rate of conversion of nutrient to biomass of population x_i. Since perfectly substitutable resources are alternate sources of the same essential nutrient, the rate of conversion of nutrient to biomass of population x_i is made up of a contribution from the consumption of resource S as well as R. Therefore $G_i(S,R) = S_i(S,R) + R_i(S,R)$.

It is obvious that there is no particular form of S_i and R_i. Experts are working hard only to tell us what form is reasonable to simulate a competition relationship. Of course, some assumptions are rational and are used to restrict the form.

$$\mathcal{S}_i, \mathcal{R}_i : \mathbf{R}_+^2 \to \mathbf{R}_+,$$

$\mathcal{S}_i, \mathcal{R}_i$ are continuously differentiable.

2. It is natural to expect that if the concentration of resource S in the culture vessel is zero, there will be no consumption or conversion of resource S. A similar statement holds for resource R. Therefore,

$$\mathcal{S}_i(0, R) = 0 \quad \text{for all } R \geq 0 \quad \text{and} \quad \mathcal{R}_i(S, 0) = 0 \quad \text{for all } S \geq 0.$$

3. Assume that the rate of consumption of each resource is a strictly monotone increasing function of the concentration of that resource.

$$\frac{\partial}{\partial S}\mathcal{S}_i(S, R) > 0 \quad \text{and} \quad \frac{\partial}{\partial R}\mathcal{R}_i(S, R) > 0$$
$$\text{for all } (S, R) \in \operatorname{int} \mathbf{R}_+^2.$$

4. It seems natural to assume that increasing the amount of one resource consumed might result in a reduction in the amount of the other resource consumed. This is reflected in the assumption that

$$\frac{\partial}{\partial R}\mathcal{S}_i(S, R) \leq 0 \quad \text{and} \quad \frac{\partial}{\partial S}\mathcal{R}_i(S, R) \leq 0 \quad \text{for all } (S, R) \in \mathbf{R}_+^2.$$

5. Define

$$p_i(S) = \mathcal{S}_i(S, 0) \quad \text{for all } S \geq 0$$

$$q_i(R) = \mathcal{R}_i(0, R) \quad \text{for all } R \geq 0.$$

That is, $p_i(S)/\xi_i$ is the function describing the uptake of nutrient S in the absence of nutrient R.

Let $m_{S_i} = \lim_{S \to \infty} p_i(S), \qquad (m_{R_i} = \lim_{R \to \infty} q_i(R))$ denote the maximal growth rate of population x_i on resource S (R) when none of the other resource is available.

Assume that one of the resources, say S, is superior in the sense that $m_{Si} > m_{Ri}$. It means when both resources are in relatively short supply, increasing the concentration of either resource is beneficial. However, once resource S is plentiful enough that m_{Ri}, the maximal growth rate of population x_i on resource R when there is no resource S available, would be exceeded by consuming only resource S, the presence of resource R would actually become detrimental.

The functions $S_i(S,R)$ and $R_i(S,R)$ are a generalization of the familiar Michaelis-Menten prototype of functional response to a single resource. They are given by

$$\mathcal{S}_i(S,R) = \frac{m_{S_i} S}{K_{S_i}(1 + S/K_{S_i} + R/K_{R_i}))}$$
$$\mathcal{R}_i(S,R) = \frac{m_{R_i} R}{K_{R_i}(1 + S/K_{S_i} + R/K_{R_i})}$$

where m_{Si}, m_{Ri}, K_{Si} and K_{Ri} are positive constants.

$$\mathcal{G}_i(S,R) = \frac{(m_{S_i}/K_{S_i})S + (m_{R_i}/K_{R_i})R}{1 + S/K_{S_i} + R/K_{R_i}}.$$

And

Now recall that $m_{S_i} = \lim_{S\to\infty} p_i(S), \qquad (m_{R_i} = \lim_{R\to\infty} q_i(R))$ denote the maximal growth rate of population x_i on resource S (R) when none of the other resource is available.

These parameters ($m_{Si}\backslash m_{Ri}$) can be assigned values so as to simulate the ability to utilize glucose and fatty acid of Firmicutes and Bacteriodetes. If their ability to use nutrient are given as follow:

	Firmicutes	Bacteriodetes
Glucose	+++ (m_{S1})	++(m_{S2})
Fatty acid	+ (m_{R1})	++(m_{R2})

Then we can set m_{S1}=2.25\m_{R1}=0.5 and m_{S2}=2.1/m_{R2}=2.1
In order to make ODEs simpler, we set $S^0=R^0=D=1$.

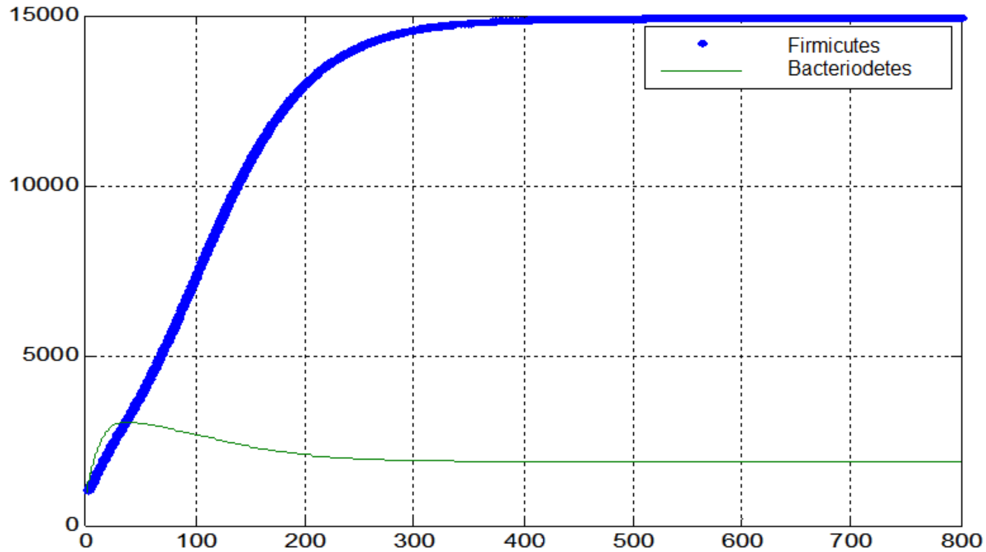
Recall that we have $\xi_i(\eta_i)$ as the respective growth yield constant.
We do not have to consider each of these four parameters, since a certain ratio of ξ_i/η_i can provide enough information and it is this ratio that determines the difference between consuming glucose and fatty acid. Here we take $\xi_i/\eta_i=100$.

The real situation is that inside our body these two bacteria keep a good balance and in the fat this ratio is much higher---approximately 8:1. Fortunately, our SYSTEM has a global asymptotic stationary solution if parameters are set *correct*. For instance, the following initial value (you can set random values) provides a good simulator of our bacteria's ratio.

```
function dy=myfun(~,y)  %y1 to y4 refer to the glucose, fatty acid,
Firmicutes and Bacteriodetes, respectively.
m=[161300,21800];
n=[1613,218];
dy=zeros(4,1);
dy(1)=(1-y(1))-(y(3)/m(1))*(2.25*y(1))/(1+y(1)+y(2))-
(y(4)/m(2))*(2.1*y(1))/(1+y(1)+y(2));
dy(2)=(1-y(2))-(y(3)/n(1))*(0.5*y(2))/(1+y(1)+y(2))-
(y(4)/n(2))*(2.1*y(2))/(1+y(1)+y(2));
dy(3)=y(3)*(-1+(2.25*y(1)+0.5*y(2))/( 1+y(1)+y(2)));
dy(4)=y(4)*(-1+(2.1*y(1)+2.1*y(2))/( 1+y(1)+y(2)));
```

```
end

[t,y]=ode45(@myfun,[0,800],[1,1,1000,1000]);
plot(t,y(:,3),'.',t,y(:,4),'-')
grid
legend('Firmicutes','Bacteriodetes')
```



Now it comes the most important part of our modeling. Based on our initial assumption, if we can change this ratio, mainly reducing it to a lower value, we are able to make this fat person thinner. But the problem is how to manage it?

We try to add a third bacterium, an E.coli with a certain property, into this system. This ideal type of E.coli consumes glucose and fatty acid, thus makes itself a competitor to Firmicutes and Bacteriodetes. While it is reproducing in intestines, the competition among these three types of bacteria makes the number of them change gradually. At last, we hope to achieve a lower ratio of Firmicutes / Bacteriodetes.

As you can see, the key point is to find out how competitive our new E.coli is. In other words, we have to point out its ability to consume glucose and fatty acid---to study new parameters m_{S3} and m_{R3}. For example, if $m_{S3}>m_{S1}$, then we say that our E.coli has a stronger ability to consume glucose than Firmicutes. We try to find out a good pair of m_{S3} and m_{R3}.

However, mathematicians have proved that under this model, adding an equation concerning a new type of bacterium (here refers to x_3) will generally destroy the asymptotic stability of the solution. Yet we find a special case that keeps each of these bacteria alive.
[See *Modeling Population Dynamics, André M. De Roos* for the proof and the following explanations.]

To see this, we consider several situations:

```
function dy=myfun(~,y)%y1 to y5 refer to the glucose, fatty acid,
Firmicutes, Bacteriodetes and the new bacteria, respectively.
```

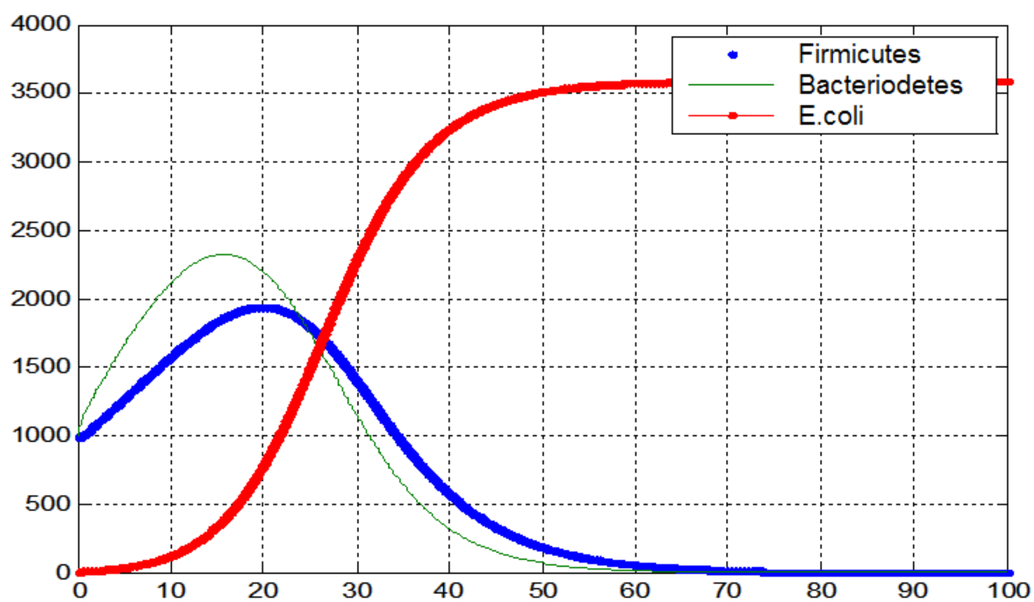
```
m=[161300,21800,10000];
n=[1613,218,100];
dy=zeros(5,1);
a=[*,*];
dy(1)=(1-y(1))-(y(3)/m(1))*(2.25*y(1))/(1+y(1)+y(2))-
(y(4)/m(2))*(2.1*y(1))/(1+y(1)+y(2))-
(y(5)/m(3))*(a(1)*y(1))/(1+y(1)+y(2));
dy(2)=(1-y(2))-(y(3)/n(1))*(0.5*y(2))/(1+y(1)+y(2))-
(y(4)/n(2))*(2.1*y(2))/(1+y(1)+y(2))-
(y(5)/n(3))*(a(2)*y(2))/(1+y(1)+y(2));
dy(3)=y(3)*(-1+(2.25*y(1)+0.5*y(2))/( 1+y(1)+y(2)));
dy(4)=y(4)*(-1+(2.1*y(1)+2.1*y(2))/( 1+y(1)+y(2)));
dy(5)=y(5)*(-1+(a(1)*y(1)+a(2)*y(2))/( 1+y(1)+y(2)));
end
```

We suppose still $\xi_3/\eta_3=100$

Situation 1	Firmicutes	Bacteriodetes	E.coli
Glucose	+++ (m_{S1})	++(m_{S2})	++++(m_{S3})
Fatty acid	+ (m_{R1})	++(m_{R2})	++(m_{R3})

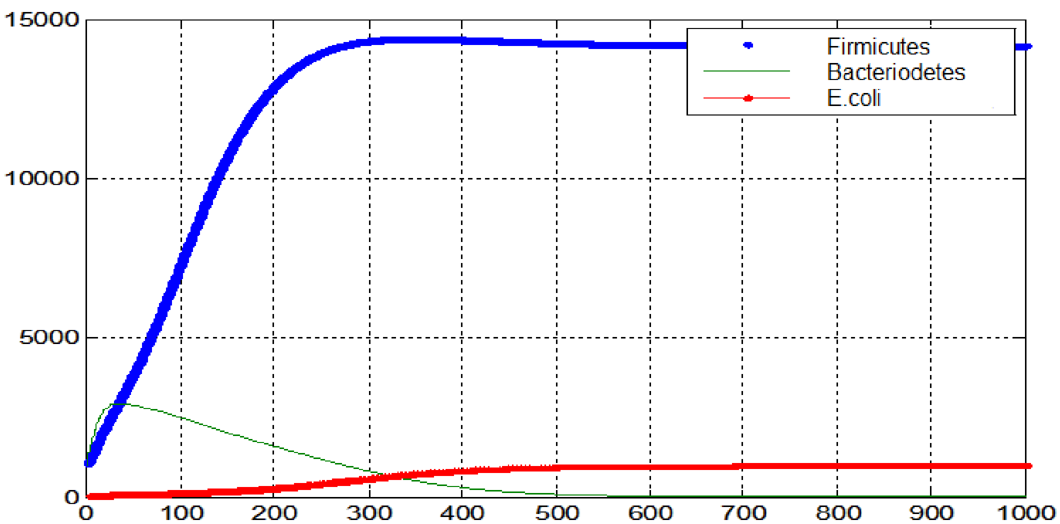
```
a=[2.5,2.1]

[t,y]=ode45(@myfun,[0,100],[1,1,1000,1000,10]);
plot(t,y(:,3),'.',t,y(:,4),'-',t,y(:,5),'.-')
grid
legend('Firmicutes','Bacteriodetes','E.coli')
```



Situation 1'	Firmicutes	Bacteriodetes	E.coli
Glucose	+++ (m_{S1})	++(m_{S2})	++(m_{S3})
Fatty acid	+ (m_{R1})	++(m_{R2})	+++(m_{R3})

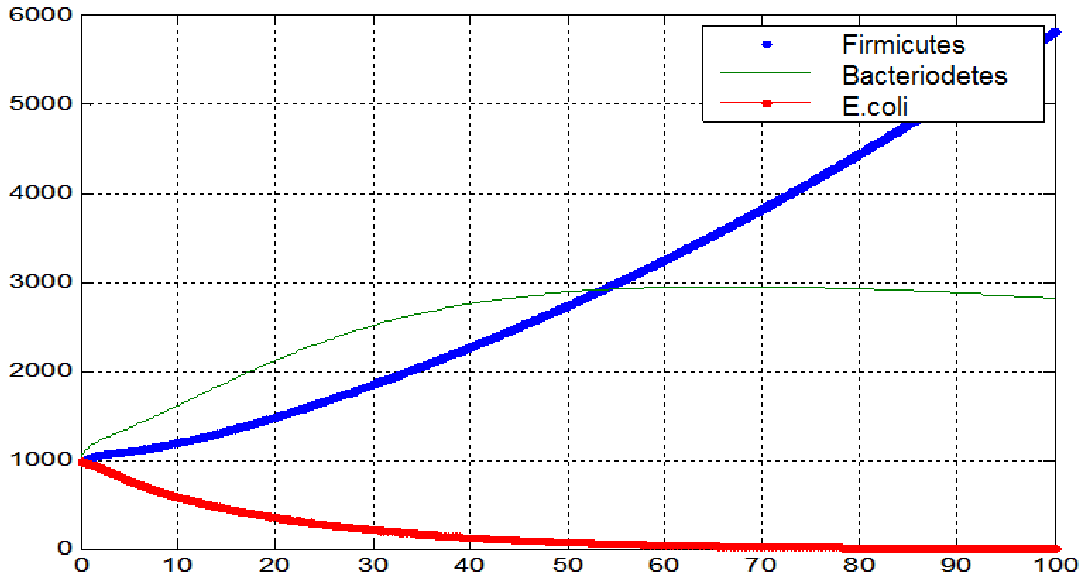
```
a=[2.1,2.5]
[t,y]=ode45(@myfun,[0,1000],[1,1,1000,1000,10]);
plot(t,y(:,3),'.',t,y(:,4),'-',t,y(:,5),'.-')
grid
legend('Firmicutes','Bacteriodetes','E.coli')
```



Situation 1 and *1'* show that the E.coli are so competitive that others die out.

Situation 2	Firmicutes	Bacteriodetes	E.coli
Glucose	+++ (m_{S1})	++(m_{S2})	++(m_{S3})
Fatty acid	+ (m_{R1})	++(m_{R2})	+(m_{R3})

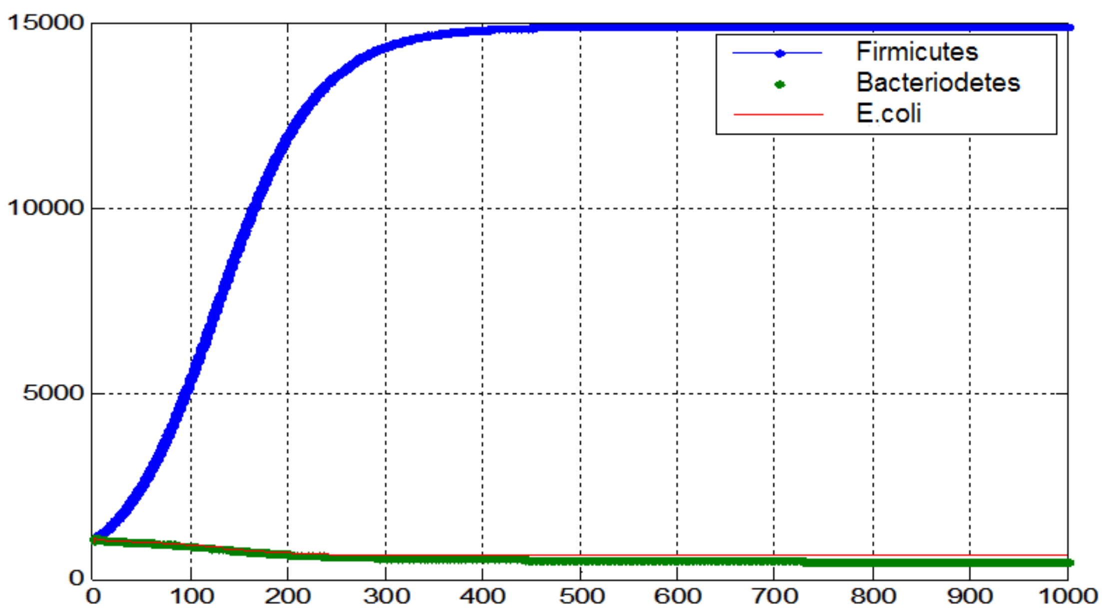
```
a=[2.1,0.4]
[t,y]=ode45(@myfun,[0,100],[1,1,1000,1000,1000]);
plot(t,y(:,3),'.',t,y(:,4),'-',t,y(:,5),'.-')
grid
legend('Firmicutes','Bacteriodetes','E.coli')
```



The E.coli is too weak to survive.

Situation 3	Firmicutes	Bacteriodetes	E.coli
Glucose	+++ (m_{S1})	++(m_{S2})	++(m_{S3})
Fatty acid	+ (m_{R1})	++(m_{R2})	++(m_{R3})

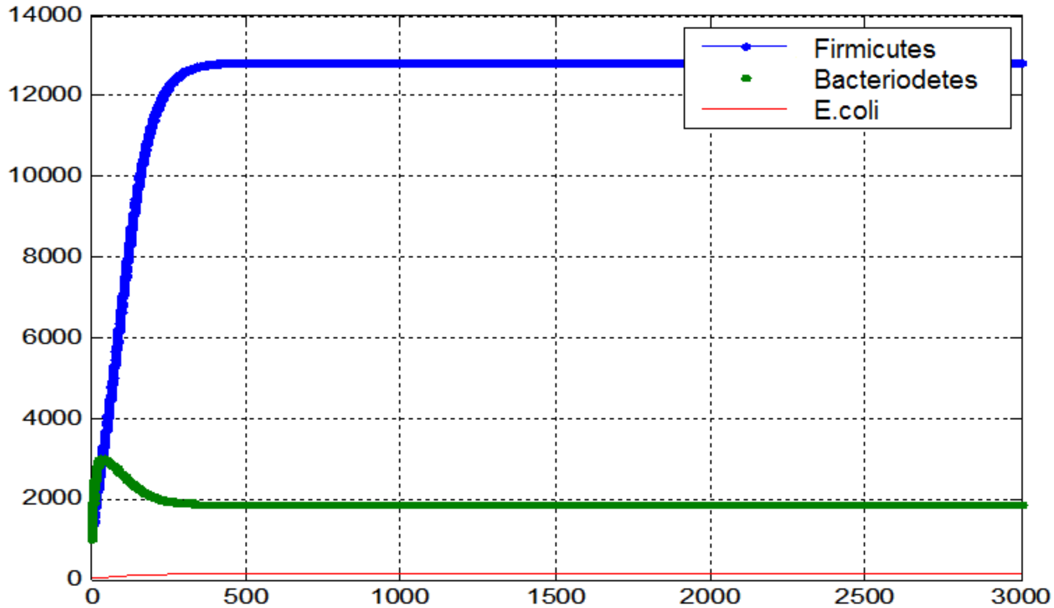
```
a=[2.1,2.11]
[t,y]=ode45(@myfun,[0,1000],[1,1,1000,1000,1000]);
plot(t,y(:,3),'.-',t,y(:,4),'.',t,y(:,5),'-')
grid
legend('Firmicutes','Bacteriodetes','E.coli')
```



The E.coli is so competitive that the ratio of Firmicutes to Bacteriodetes increases.

Situation 4	Firmicutes	Bacteriodetes	E.coli
Glucose	+++ (m_{S1})	++(m_{S2})	+++(m_{S3})
Fatty acid	+ (m_{R1})	++(m_{R2})	+(m_{R3})

```
a=[2.25,0.5]
[t,y]=ode45(@myfun,[0,3000],[1,1,1000,1000,10]);
plot(t,y(:,3),'.-',t,y(:,4),'.',t,y(:,5),'-')
grid
legend('Firmicutes','Bacteriodetes','E.coli')
```




```
y(3000,3)/y(3000,4)
ans =
       4.7920
```

The ratio of Firmicutes to Bacteriodetes has declined from 8.0 to 4.8, just similar to what we have expected. So it is mathematically suggested that the E.coli with a consuming ability described in *Situation 4* will properly regulate the gut microbiota and make people slim. This E.coli is just the one we want --- E.coslim.