1. Measure metabolite concentration time series.

2. Calculate metabolite concentration slopes. Calculate reaction rates of system boundary enzymes with known kinetics.

3. Estimate internal enzyme reaction rate time series.

4. Divide enzymes with assumed dynamic/static module determination. All system boundary enzymes are regarded as dynamic enzymes.

5. Estimate static enzyme reaction rate time series by HDS method with assumed dynamic/static combination.

6. Calculate metabolite concentration time series by numerical integration of enzyme reaction rate time series.

7. Compare estimated metabolite concentration time series with measured data. Calculate the fitness function.

8. Modify the assumed dynamic/static combination until the fitness function is minimized.