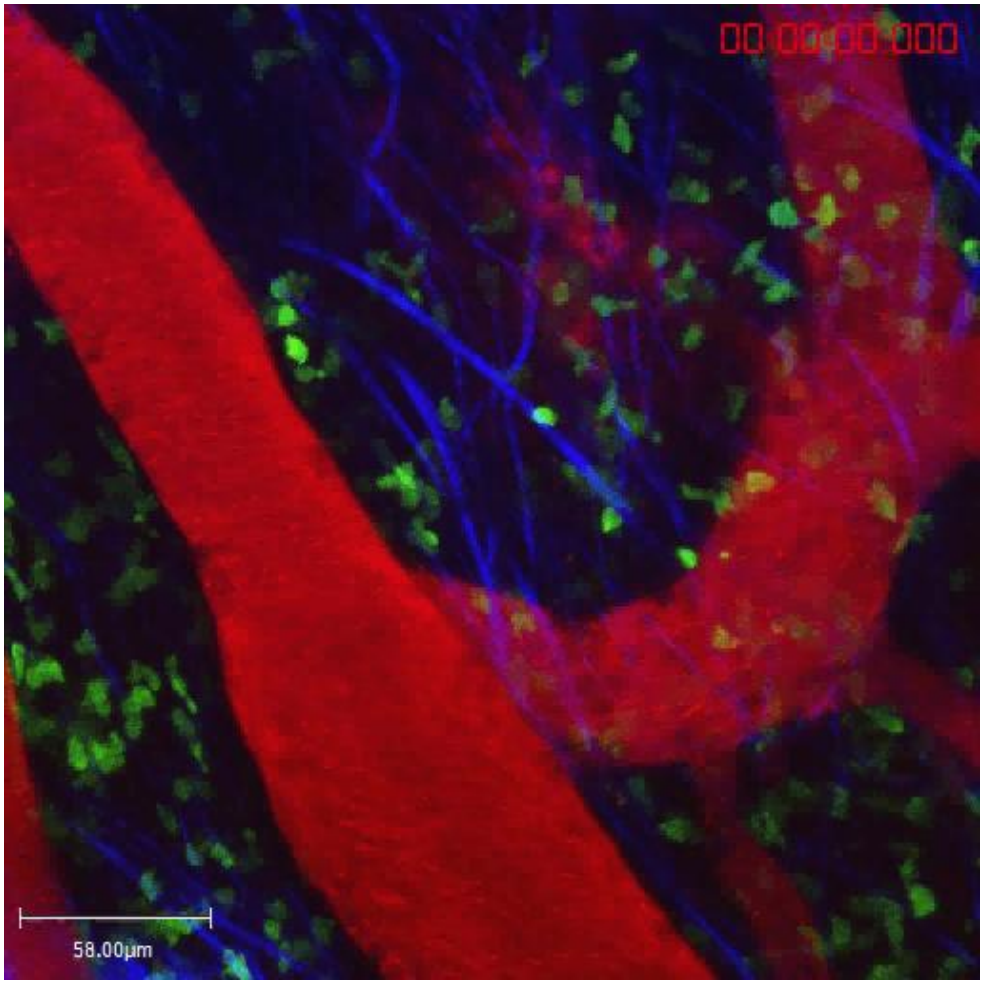
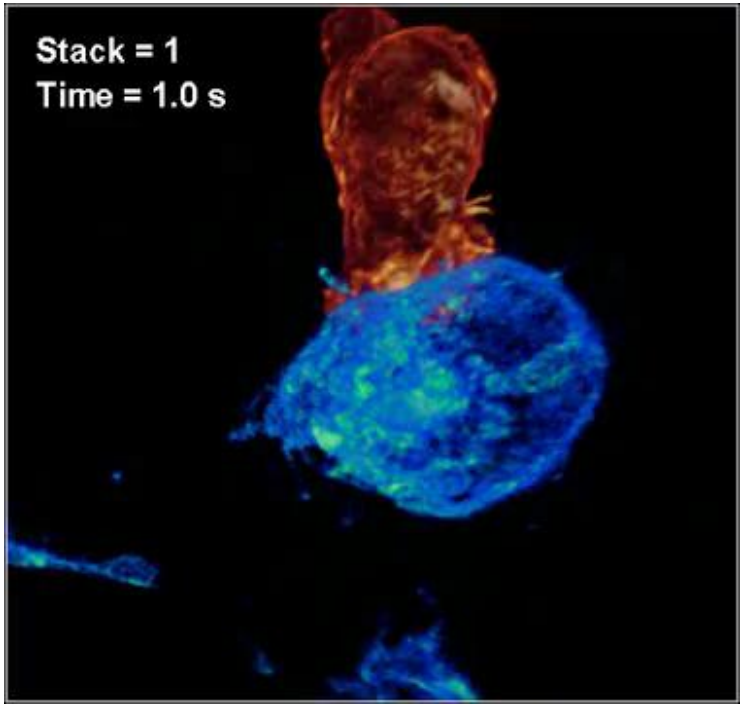
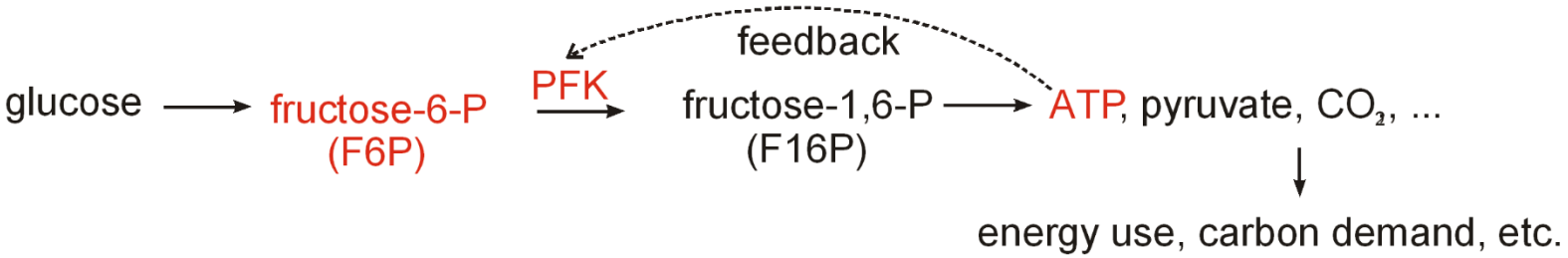
Dynamic systems drive cellular functions





Dynamic systems – HW2Q1 as starting point

In the glycolytic pathway, one point of regulation is the conversion of fructose -6-P to fructose -1,6-P by the enzyme phosphofructokinase (PFK). ATP, a downstream product of the glycolysis pathway, acts to inhibit PFK at high concentrations, slowing down the generation of ATP and regulating the overall level in the cell. Assume ATP acts as an allosteric, non -competitive inhibitor. The components that are central to this question are marked in red.

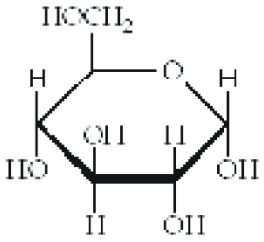


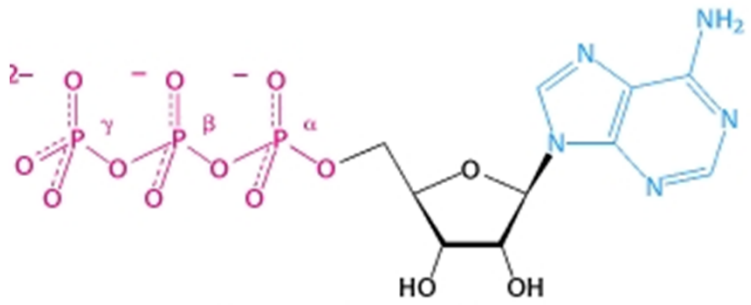
Glycolytic oscillations – Sel'kov model

Glucose → Fructose 6-P → Fructose 1,6-P → Pyruvate

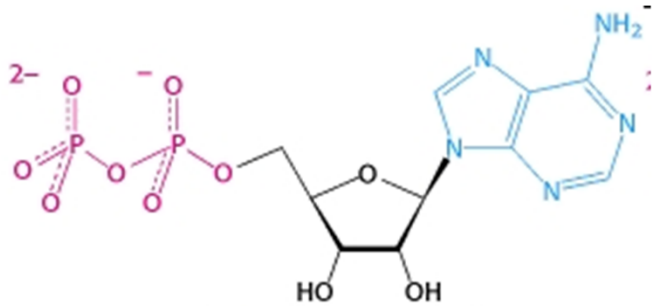
PFK1

ATP ADP

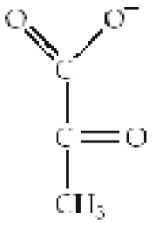




Adenosine triphosphate (ATP)

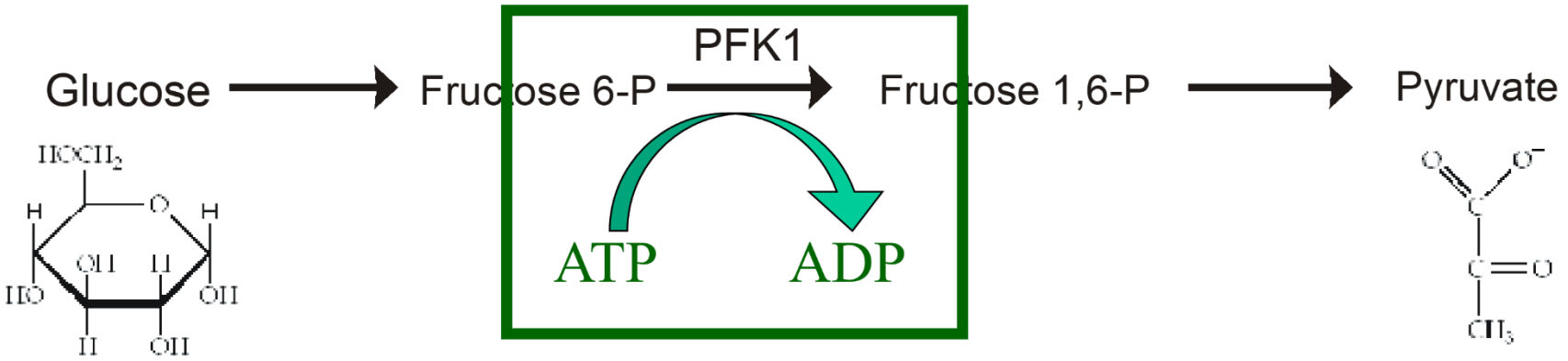


Adenosine diphosphate (ADP)



ATP production

Glycolytic oscillations – Sel'kov model

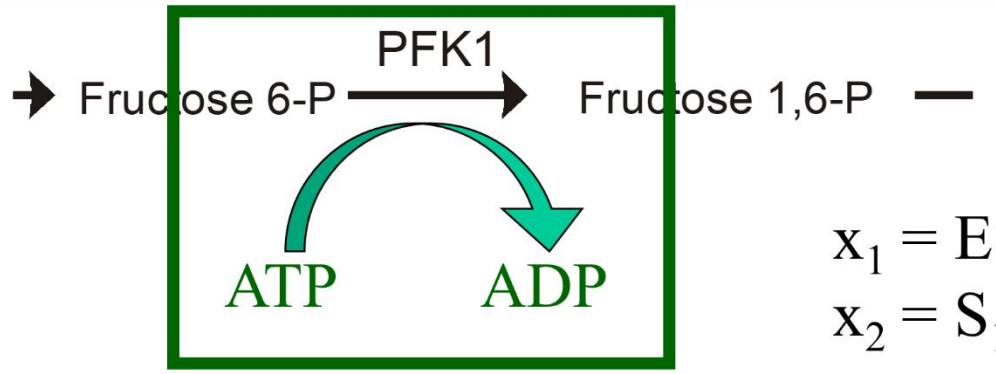


- Steady state doesn't capture full behavior
- Oscillations have been observed in experimental systems
- **Sel'kov** model as a simplified explanation

Competing feedback loops

- ATP is both a substrate and inhibitor of PFK1 (negative feedback)
  - Focus here on ATP as a substrate, to be acted upon by PFK1
- Binding of multiple ADPs activates PFK1 (positive feedback)
  - increasing amounts of ADP enhance reaction rate
  - acts through increasing AMP concentration (won't include that here)
- Goal: find reaction behavior as a function of input ATP

Glycolytic oscillations – Sel'kov model



E = PFK1
S_1=ATP
S_2=ADP

$x_1 = ES_2^\gamma$
$x_2 = S_1 ES_2^\gamma$

Activation of PFK1 by ADP
requires γ ADPs for activation

$$\gamma S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ES_2^\gamma,$$

PFK1 pathways

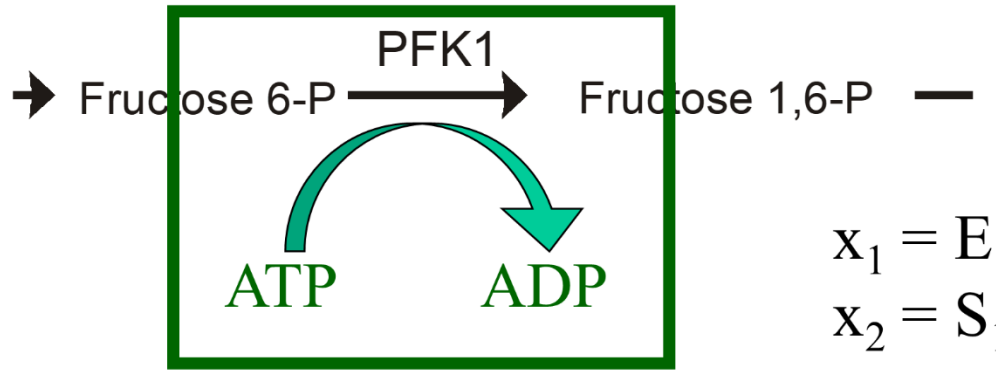
$$\xrightarrow{v_1} S_1,$$

$$S_1 + ES_2^\gamma \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S_1 ES_2^\gamma \xrightarrow{k_2} ES_2^\gamma + S_2$$

$$S_2 \xrightarrow{v_2}.$$

Given input rate v_1, how does this system behave?

Reaction scheme



E = PFK1
S_1=ATP
S_2=ADP

$x_1 = ES_2^{\gamma}$
$x_2 = S_1 ES_2^{\gamma}$

$$\frac{ds_1}{dt} = v_1 - k_1 s_1 x_1 + k_{-1} x_2,$$

$$\frac{ds_2}{dt} = k_2 x_2 - k_3 s_2^{\gamma} e + k_{-3} x_1 - v_2 s_2,$$

$$\frac{dx_1}{dt} = -k_1 s_1 x_1 + (k_{-1} + k_2) x_2 + k_3 s_2^{\gamma} e - k_{-3} x_1,$$

$$\frac{dx_2}{dt} = k_1 s_1 x_1 - (k_{-1} + k_2) x_2.$$

$$e + x_1 + x_2 = e_0$$

$$\sigma_1 = \frac{k_1 s_1}{k_2 + k_{-1}} \qquad u_1 = \frac{x_1}{e_0} \qquad t = \frac{k_2 + k_{-1}}{e_0 k_1 k_2}\tau$$

$$\sigma_2 = \left(\frac{k_3}{k_{-3}}\right)^{1/\gamma} s_2 \qquad u_2 = \frac{x_2}{e_0} \qquad \nu = \frac{v_1}{k_2 e_0}$$

$$\varepsilon = \frac{e_0 k_1 k_2}{(k_2 + k_{-1})^2} \qquad \eta = \frac{v_2 (k_2 + k_{-1})}{k_1 k_2 e_0} \qquad \alpha = \frac{k_2 + k_{-1}}{k_1}\left(\frac{k_3}{k_{-3}}\right)^{1/\gamma}$$

$$\frac{d\sigma_1}{d\tau} = \nu - \frac{k_2 + k_{-1}}{k_2} u_1 \sigma_1 + \frac{k_{-1}}{k_2} u_2,$$

$$\frac{d\sigma_2}{d\tau} = \alpha \left[u_2 - \frac{k_{-3}}{k_2} \sigma_2^{\gamma} (1 - u_1 - u_2) + \frac{k_{-3}}{k_2} u_1 \right] - \eta \sigma_2,$$

$$0 = \epsilon \frac{du_1}{d\tau} = u_2 - \sigma_1 u_1 + \frac{k_{-3}}{k_2 + k_{-1}} \left[\sigma_2^{\gamma} (1 - u_1 - u_2) - u_1 \right],$$

$$0 = \epsilon \frac{du_2}{d\tau} = \sigma_1 u_1 - u_2,$$

time-scaling (quasi-steady state)

$$u_1 = \frac{\sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1},$$

$$u_2 = \frac{\sigma_1 \sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1} = f(\sigma_1, \sigma_2),$$

which allows simplification of the sigma differential equations:

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2),$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta \sigma_2.$$

Give some specific numbers:

Setting: $\gamma=2$; $\nu=0.0285$; $\eta=0.1$; $\alpha=1.0$

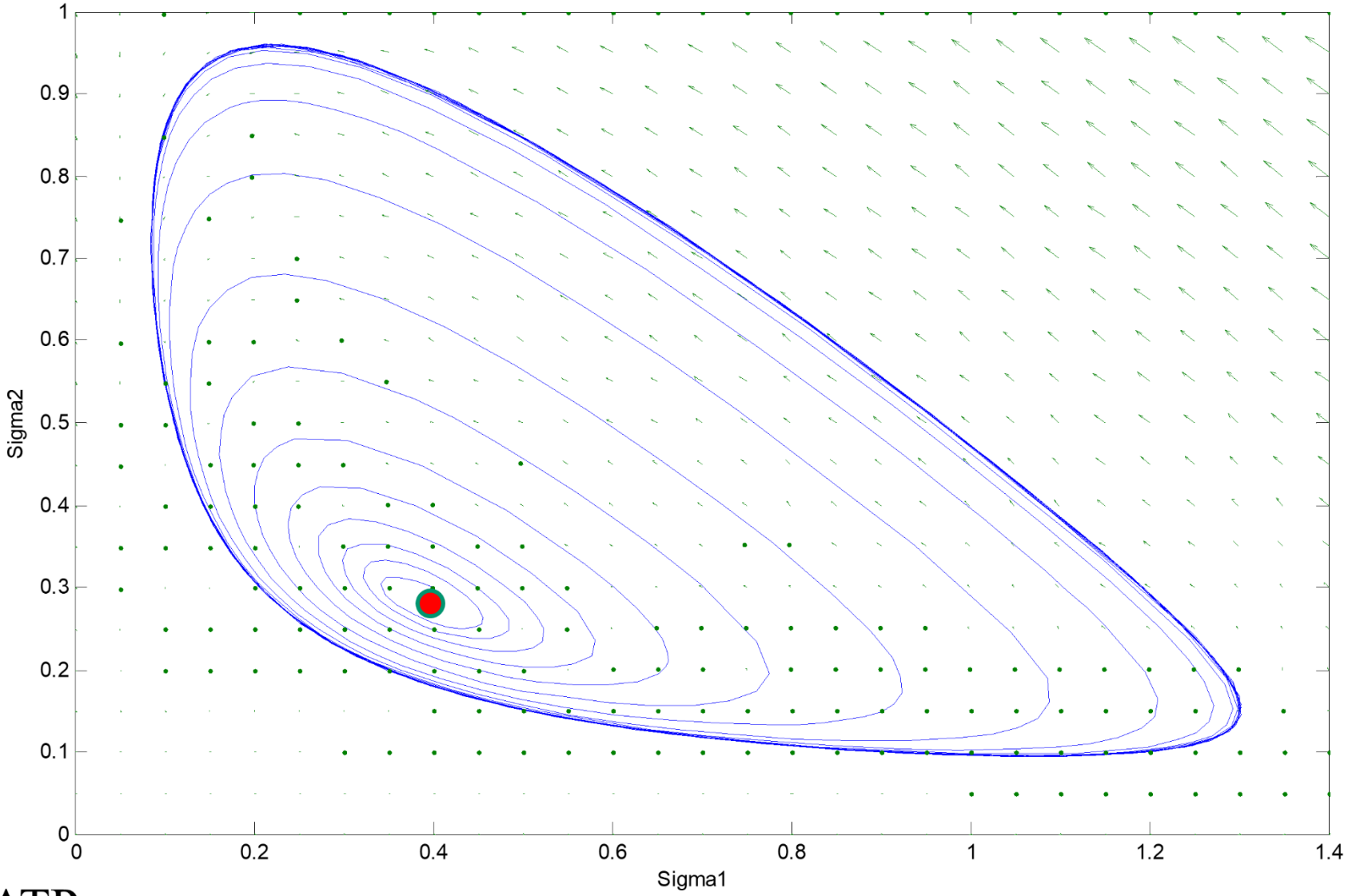
Stable solution $\sigma_1= 0.3905$; $\sigma_2= 0.285$

which allows simplification of the sigma differential equations:

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2),$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2.$$

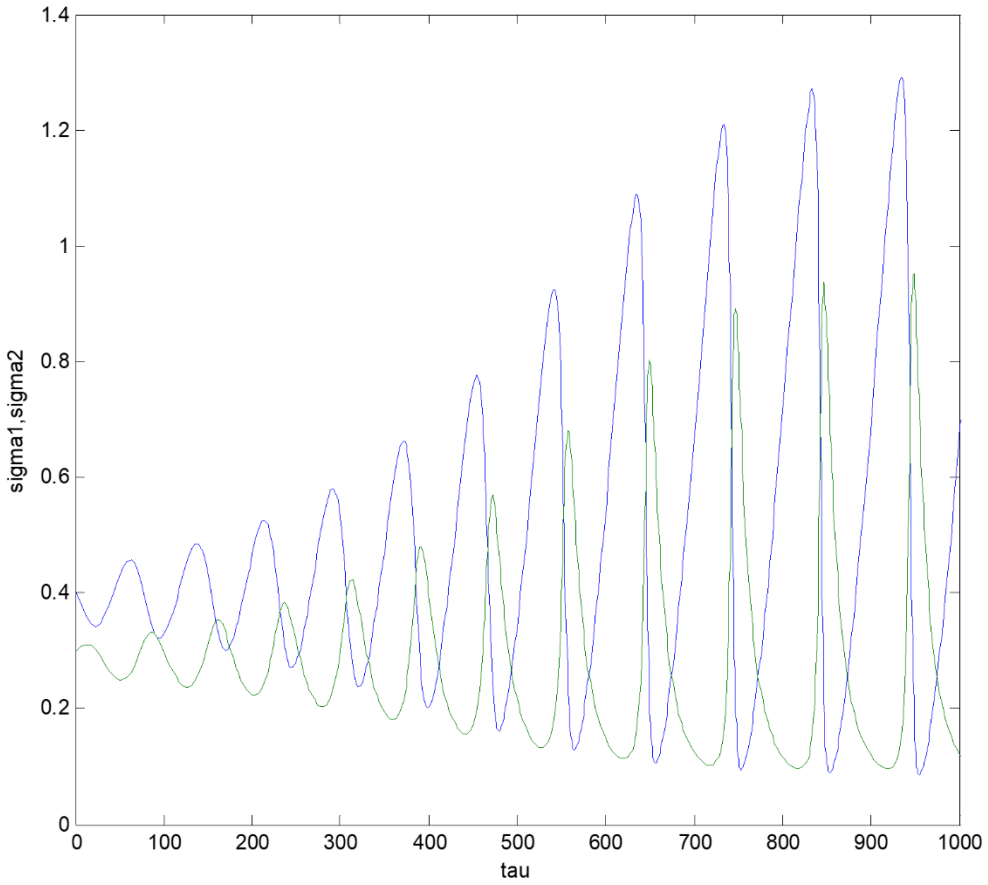
vector map



S_1=ATP
S_2=ADP

γ=2; ν=0.0285; η=0.1; α=1.0

temporal dynamics



S_1=ATP

S_2=ADP

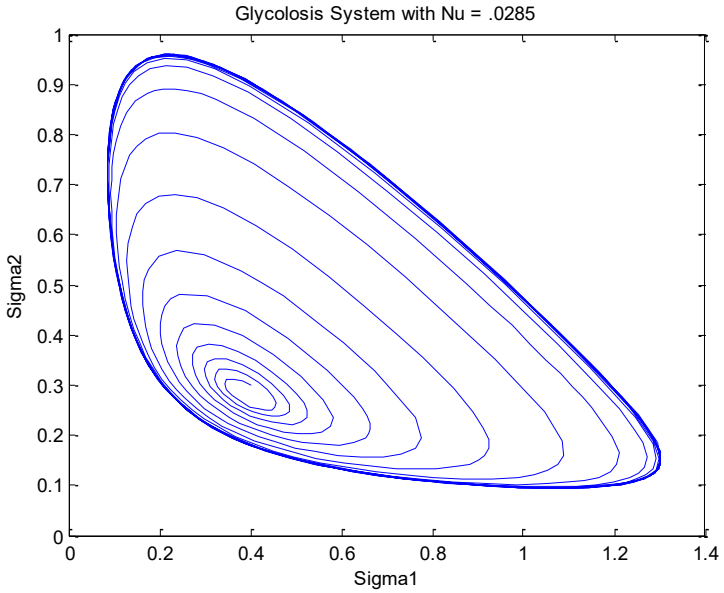
$$\xrightarrow{v_1} S_1,$$

$$\gamma S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ES_2^{\gamma},$$

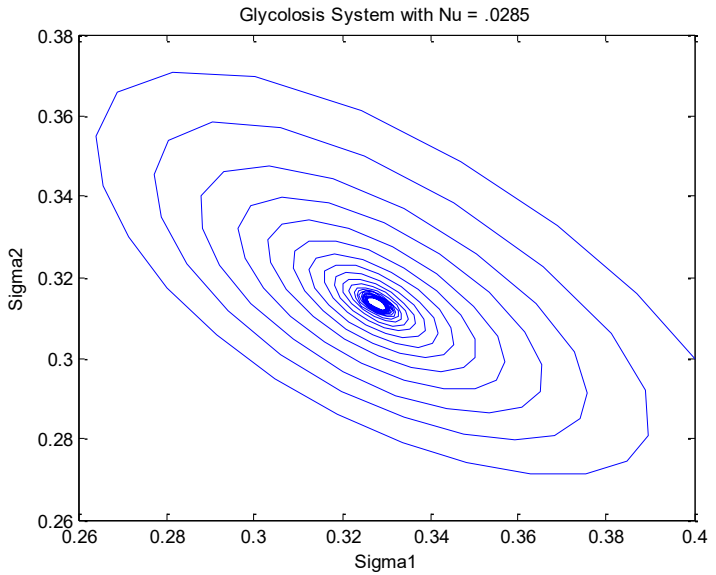
$$S_1 + ES_2^{\gamma} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S_1ES_2^{\gamma} \xrightarrow{k_2} ES_2^{\gamma} + S_2$$

$$S_2 \xrightarrow{v_2}.$$

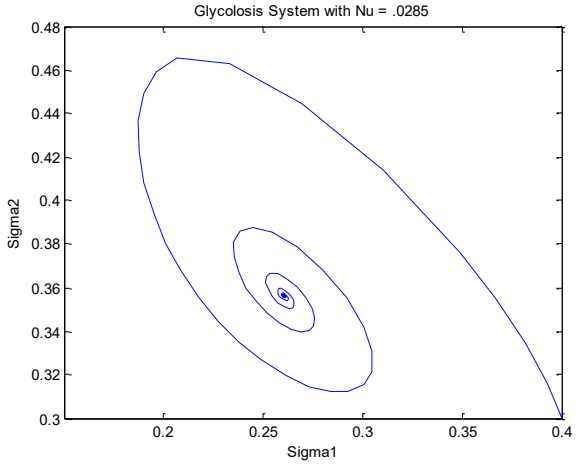
Oscillations don’t occur for all parameters



$\alpha = 1$



$\alpha = 1.1$



$\alpha = 1.25$

MATLAB

- Good, general-purpose mathematics package.
- Great for real data, so-so on symbolic
- Based on the manipulation and processing of matrices / lists (arrays)
- Full programming language
- Good support both from The Mathworks and general users
- Google and the help screens are a great resource

MATLAB vs. Python

MATLAB	Python
• Commercial	• Open source
• Designed for real data	• Adaptable
• Toolboxes for specialization	• Many libraries. For math: NumPy, SciPy
• Core programming capabilities	• “elegant” programming syntax
• Inefficient execution	• Inefficient execution

•https://cuit.columbia.edu/content/matlab

MATLAB

MATLAB is a high-level technical computing language and interactive environment for algorithm development, data visualization, data analysis, and numeric computation.

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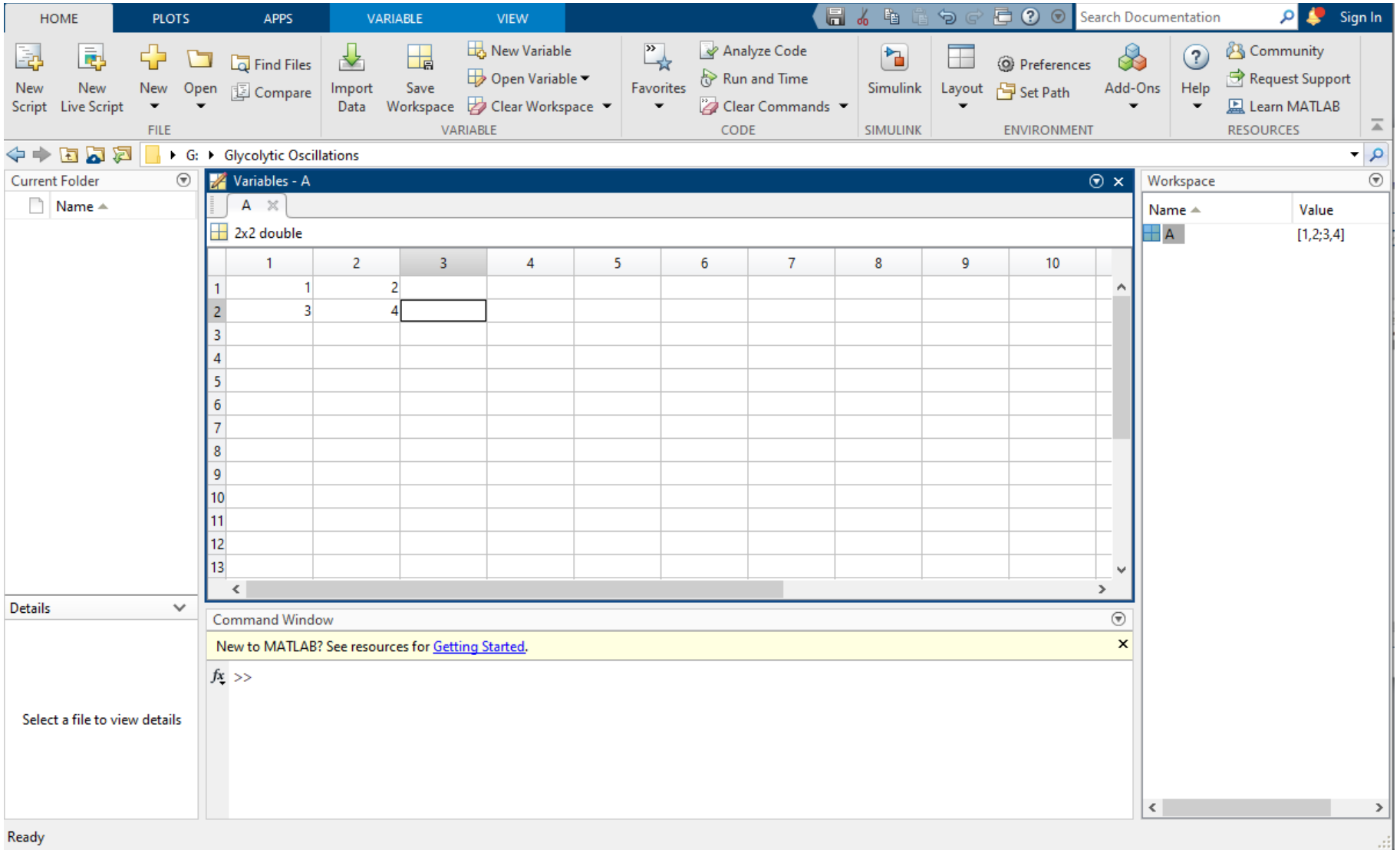
Support Contact

Documentation is available at MathWorks. Technical support is available through Mathworks Support, and online training courses are also available. Guides and other reference materials can also be purchased separately through third parties.

MATLAB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Open Variable
Clear Workspace
VARIABLE
Favorites
Analyze Code
Run and Time
Clear Commands
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Preferences
Set Path
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ENVIRONMENT
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Community
Request Support
Learn MATLAB
RESOURCES
G: ▸ Glycolytic Oscillations
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1 1 2
2 3 4
3 4 5 6 7 8 9 10 11 12 13
Workspace
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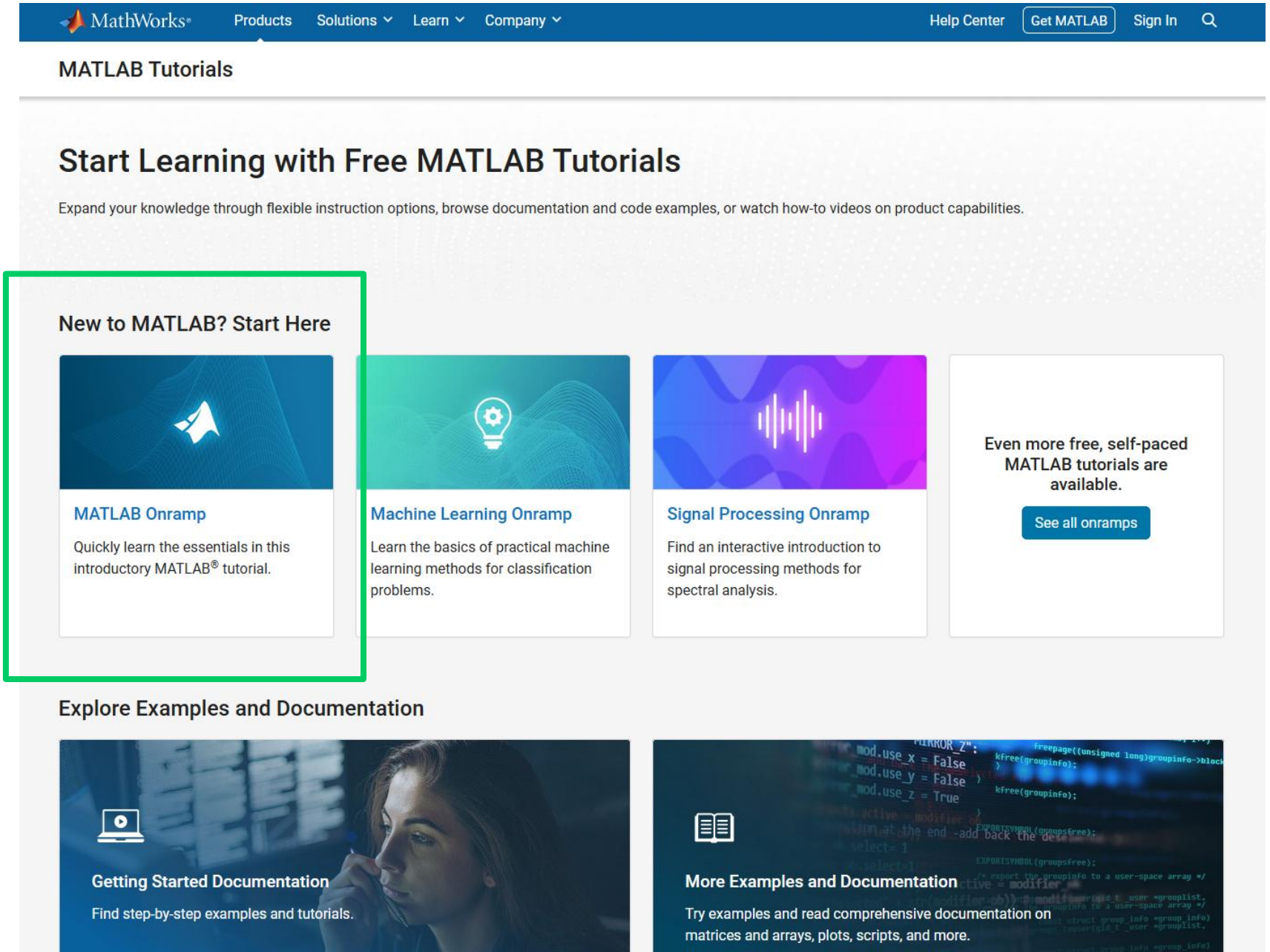
[1,2;3,4]
Details
Select a file to view details
Command Window
New to MATLAB? See resources for Getting Started.
fx >>
Ready

- http://www.mathworks.com/support/learn-with-matlab-tutorials.html



MATLAB in this course will use:

- a basic knowledge of navigating and working in MATLAB.
- ODE solver, ode45
  - requires
    - set of ODEs describing system
    - initial conditions
    - timeframe of solution
  - there are other solvers available, but this is a good starting point

Arrays and Matrices

Matrices: m (rows) x n (column)

Entered as follows:

```
mat1=[1 2 3 ; 4 5 6]
```

generates the 2 x 3 array

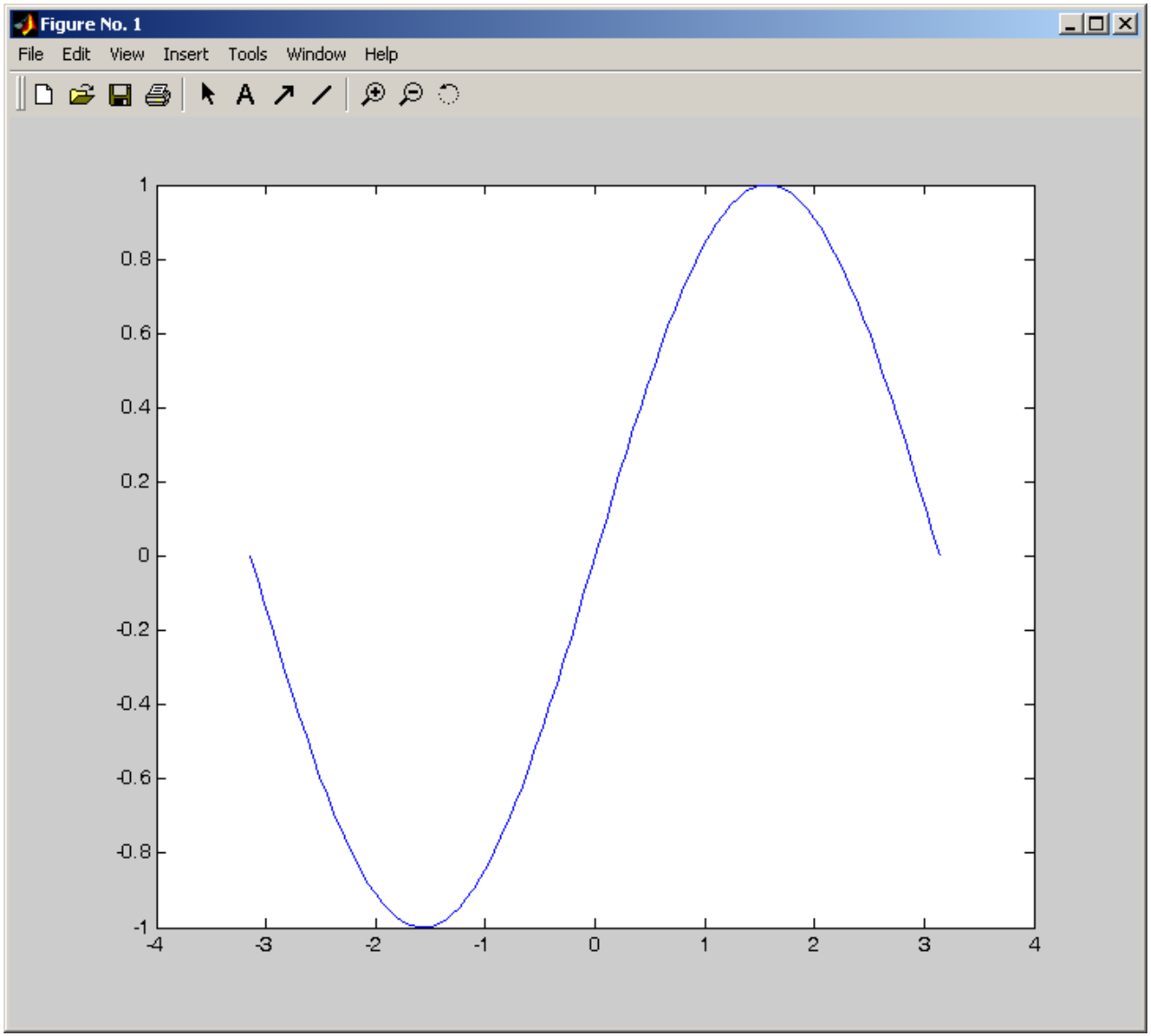
```
mat1=
     [1 2 3]
     [4 5 6]
```

Accessing elements:

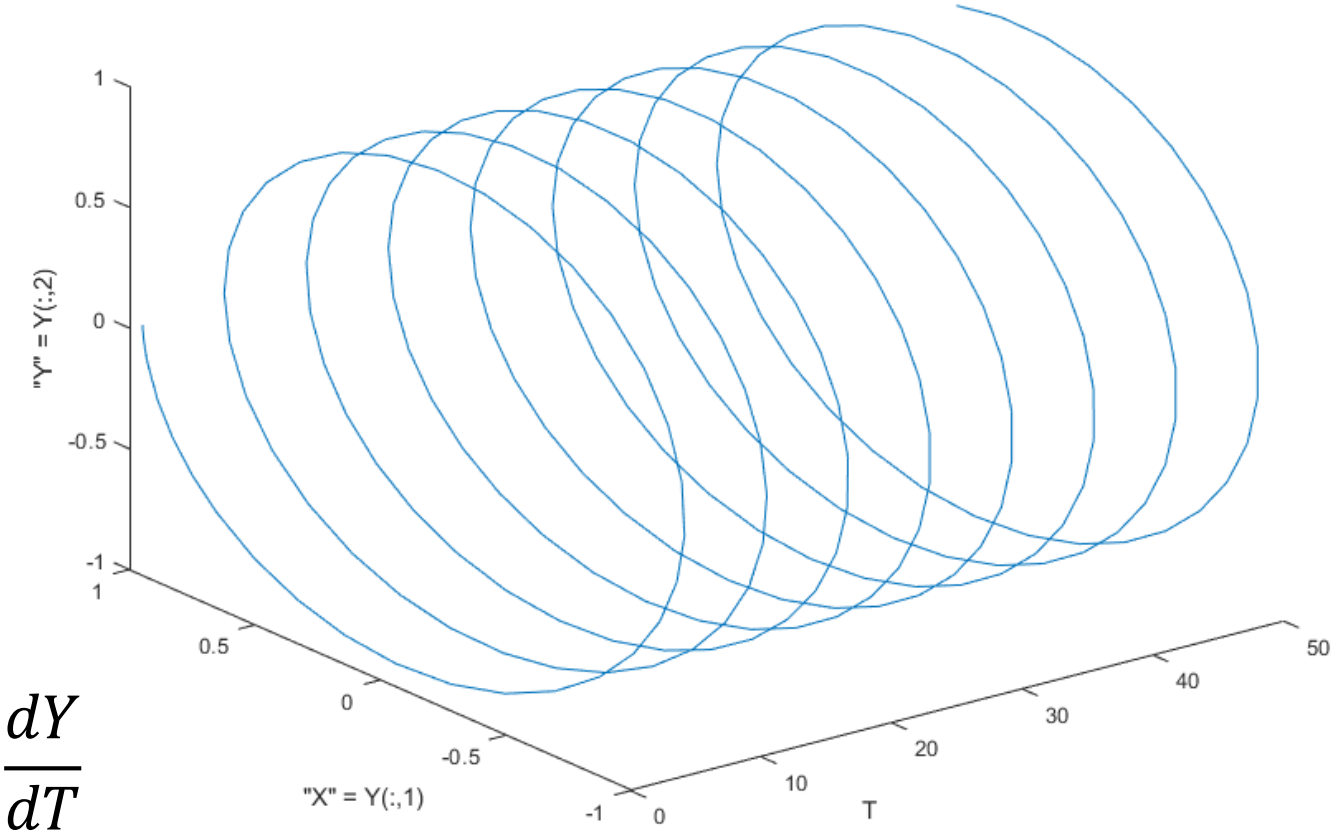
```
mat1(2,1) returns the value 4
mat1(2,:) returns the value [4 5 6]
```

Plotting graphs example

```
x=linspace(-pi,pi,100);
y=sin(x);
plot(x,y);
```



ODE example - spiral



$$\frac{dX}{dT} = \frac{dY}{dT}$$

$$\frac{dY}{dT} = -\frac{dX}{dT}$$

ODE example; sine and cosine

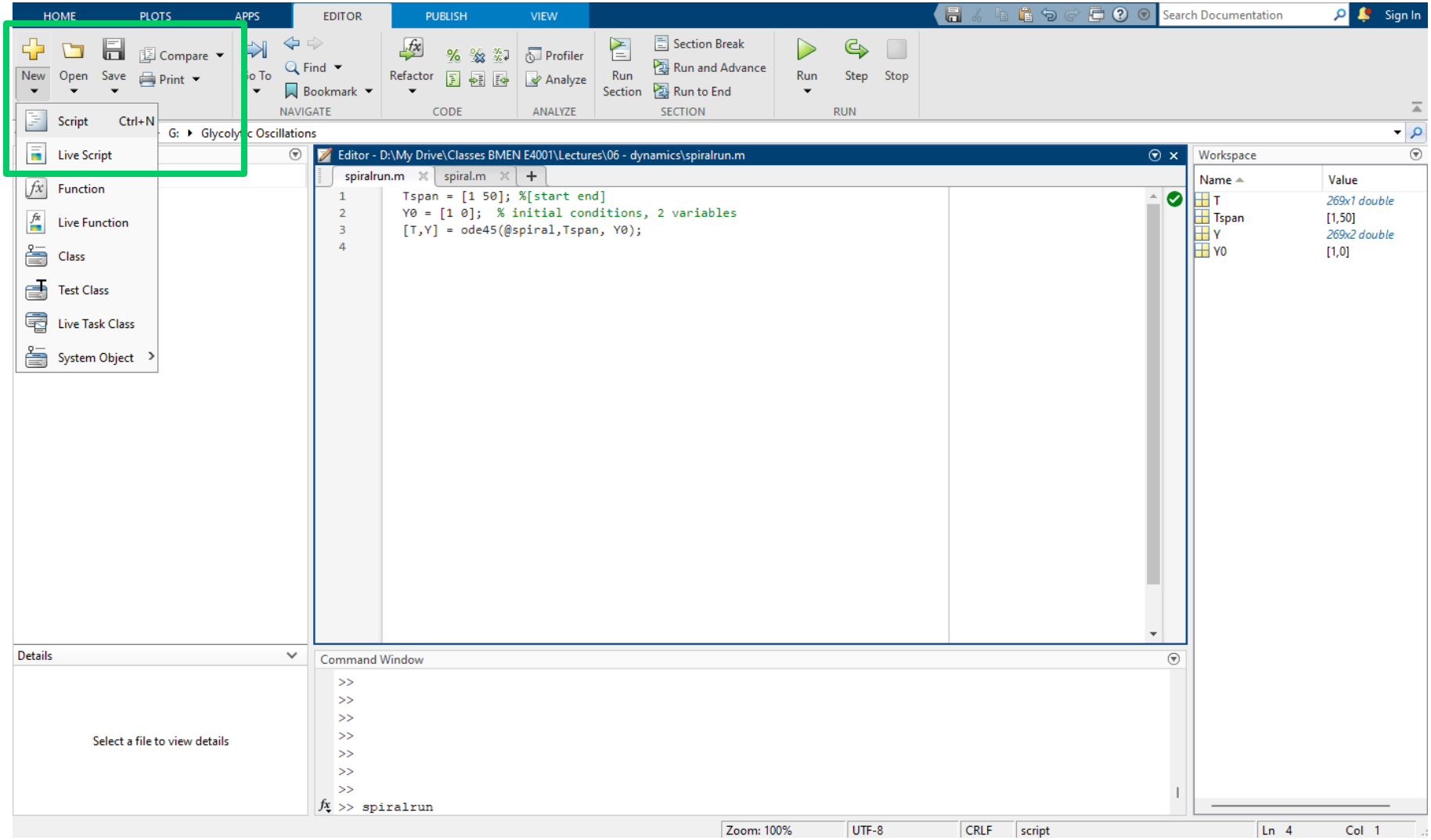
(file "spiralrun.m")

```
Tspan = [1 50]; %[start end]
Y0 = [1 0];  % initial conditions, 2 variables
[T,Y] = ode45(@spiral,Tspan, Y0);
```

(file "spiral.m")

```
function dy = spiral(t,y)
dy=zeros(2,1); % column vector w/ 2 rows
dy(1)=y(2);
dy(2)=-y(1);
```

MATLAB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VIEW
Search Documentation
Sign In
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Open
Save
Compare
Print
Find
Bookmark
NAVIGATE
Refactor
CODE
Profiler
Analyze
ANALYZE
Run Section
Section Break
Run and Advance
Run to End
SECTION
Run
Step
Stop
RUN
Script Ctrl+N
Live Script
Function
Live Function
Class
Test Class
Live Task Class
System Object
Editor - D:\My Drive\Classes BMEN E4001\Lectures\06 - dynamics\spiralrun.m
spiralrun.m
spiral.m
1 Tspan = [1 50]; %[start end]
2 Y0 = [1 0]; % initial conditions, 2 variables
3 [T,Y] = ode45(@spiral,Tspan, Y0);
4
Workspace
Name
Value
T 269x1 double
Tspan [1,50]
Y 269x2 double
Y0 [1,0]
Details
Select a file to view details
Command Window
>> spiralrun
Zoom: 100%
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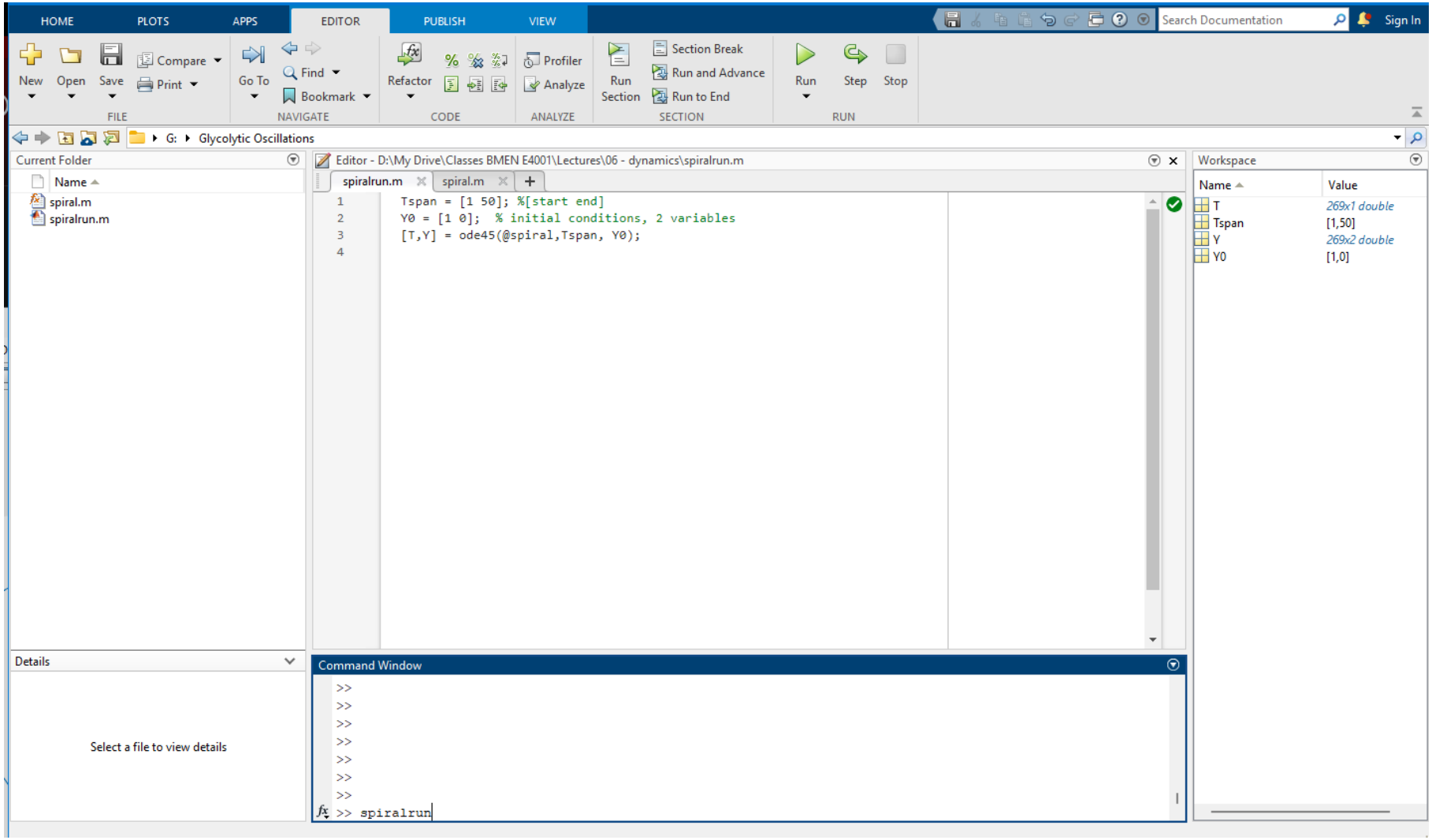
script
Ln 4
Col 1

MATLAB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Compare
Print
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Go To
Find
Bookmark
NAVIGATE
Refactor
CODE
Profiler
Analyze
ANALYZE
Run Section
Section Break
Run and Advance
Run to End
SECTION
Run
Step
Stop
RUN
G: ▸ Glycolytic Oscillations
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spiral.m
spiralrun.m
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spiralrun.m
spiral.m
1 Tspan = [1 50]; %[start end]
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3 [T,Y] = ode45(@spiral,Tspan, Y0);
4
Workspace
Name
Value
T
269x1 double
Tspan
[1,50]
V
269x2 double
Y0
[1,0]
Details
Select a file to view details
Command Window
>>
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>> spiralrun

ODE example; sine and cosine

(file "spiralrun.m")

```
Tspan = [1 50]; %[start end]
Y0 = [1 0];  % initial conditions, 2 variables
[T,Y] = ode45(@spiral,Tspan, Y0);
```

(file "spiral.m")

```
function dy = spiral(t,y)
dy=zeros(2,1); % column vector w/ 2 rows
dy(1)=y(2);
dy(2)=-y(1);
```

ODE solvers (ode45, ode23, ode113, ode15s, ode23s, ode23t, ode23tb)

Basic syntax:

[T,Y] = solver(odefun,tspan,y0)

where:

odefun = handle to user-defined function of form y' = f(t,y)

tspan = 2-element vector specifying beginning and ending tpoints

y0 = initial conditions (scalar or vector)

T = output vector, returns timepoints of solution

Y = output matrix, returns data of solution, 1 row corresponding to one value of associated T.

Structure of a function

function [out1, out2] = myfunc(in1, in2, in3)

1. Takes a number of input variabes (in1, in2, etc.)
2. Returns a set of output variables (out1, out2, etc.)
3. Simplest implementation, save as a local M-file, with name of 'myfunc.m', called from the workspace or another function using myfunc().
4. All variables will be local to the function.

(written to a file in the working directory ,"mysqr.m")

```
function y = mysqr(x)
y=x*x;
```

ODE sample; sine and cosine

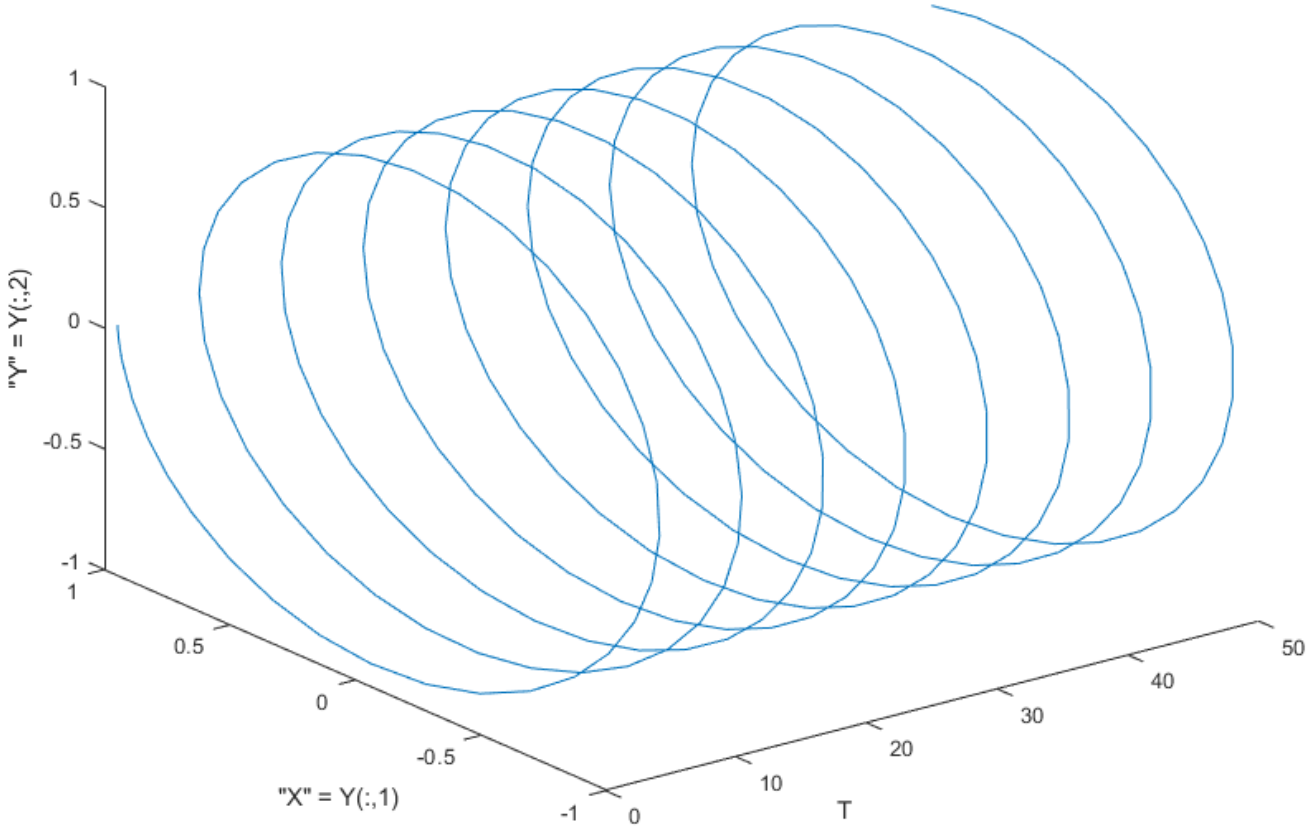
(file "spiralrun.m")

```
Tspan = [1 50]; %[start end]
Y0 = [1 0];  % initial conditions, 2 variables
[T,Y] = ode45(@spiral,Tspan, Y0);
```

(file "spiral.m")

```
function dy = spiral(t,y)
dy=zeros(2,1); % column vector w/ 2 rows
dy(1)=y(2);
dy(2)=-y(1);
```

ODE example - spiral




```
plot3(T,Y(:,1),Y(:,2));
```

Passing variables

*The **global** command can be used to access workspace variables not passed to the function*

(file "spiralrun.m")

```
global mag  %passed parameter
mag = .1;
Tspan = [1 50]; %[start end]
Y0 = [1 0];  % initial conditions, 2 variables
[T,Y] = ode45(@spiral,Tspan, Y0);
```

(file "spiral.m")

```
function dy = spiral(t,y)
global mag
dy=zeros(2,1); % column vector w/ 2 rows
dy(1)=mag*y(2);
dy(2)=-mag*y(1);
```

Numerical stiffness

$$\frac{d\sigma_1}{d\tau} = \nu - \frac{k_2 + k_{-1}}{k_2} u_1 \sigma_1 + \frac{k_{-1}}{k_2} u_2,$$

$$\frac{d\sigma_2}{d\tau} = \alpha \left[u_2 - \frac{k_{-3}}{k_2} \sigma_2^{\gamma} (1 - u_1 - u_2) + \frac{k_{-3}}{k_2} u_1 \right] - \eta \sigma_2,$$

$$0 = \epsilon \frac{du_1}{d\tau} = u_2 - \sigma_1 u_1 + \frac{k_{-3}}{k_2 + k_{-1}} \left[\sigma_2^{\gamma} (1 - u_1 - u_2) - u_1 \right],$$

$$0 = \epsilon \frac{du_2}{d\tau} = \sigma_1 u_1 - u_2,$$

- Disparity of timescales leads to problems in stepsize selection

Runge-Kutta 4,5 method

- Good, general purpose solver.
- Looks at dy/dt at certain points

$$y' = f(t, y), \quad y(t0) = y0.$$

$$y_{n+1} = y_n + (h/6)^* (k_1 + 2k_2 + 2k_3 + k_4); \; t_{n+1} = t_n + h$$

$$k_1 = f(t_n, y_n)$$

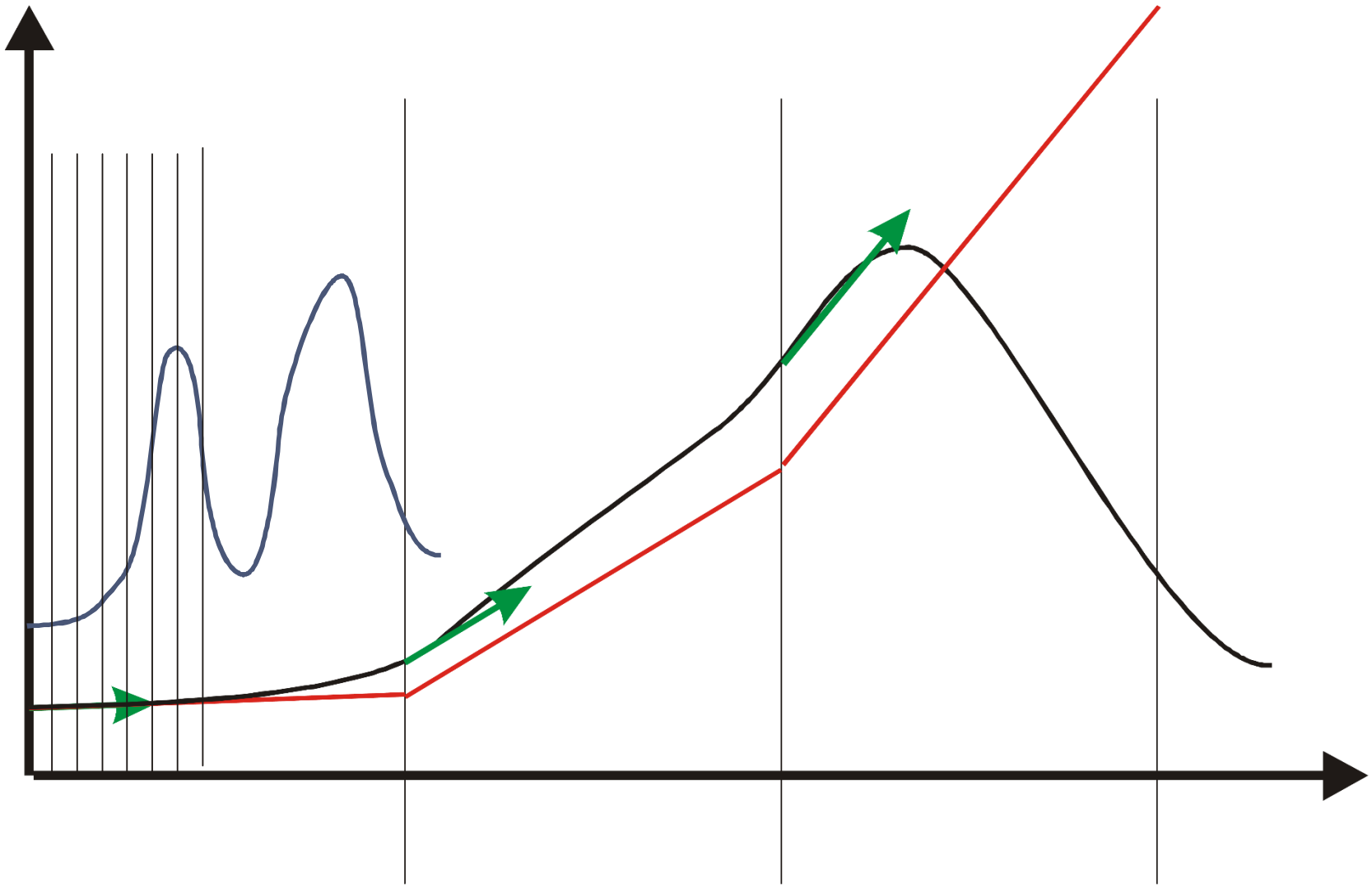
$$k_2 = f(t_n + (h/2), y_n + (h/2)^* k_1)$$

$$k_3 = f(t_n + (h/2), y_n + (h/2)^* k_2)$$

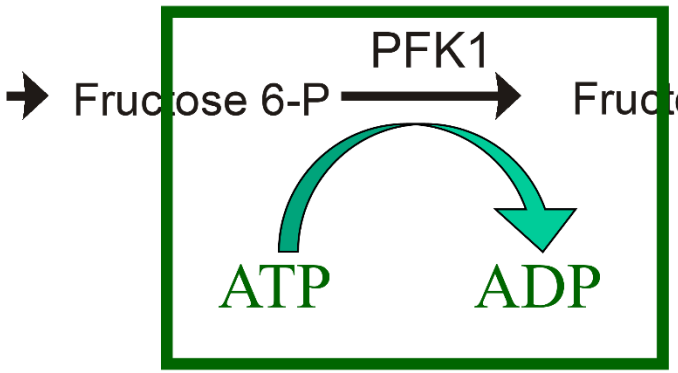
$$k_4 = f(t_n + h, y_n + h^* k_3).$$

- “explicit solution”. “Implicit” variations are around
- selection of timestep is critical, balancing rounding and interpolation/extrapolation errors

Numerical stiffness



Your goal



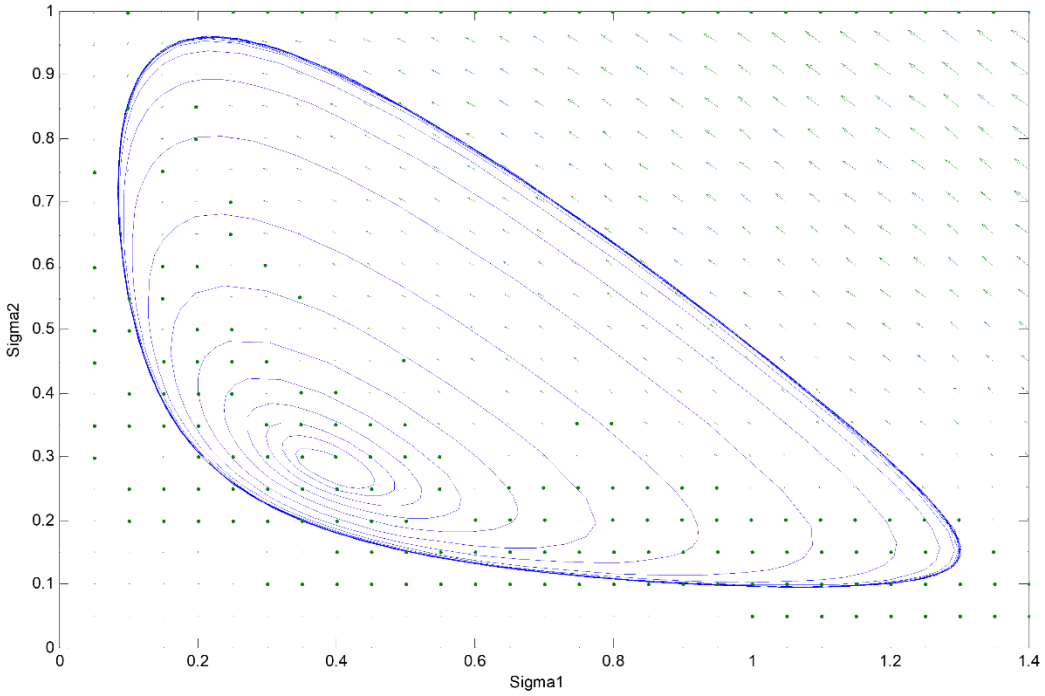
$E = PFK1$

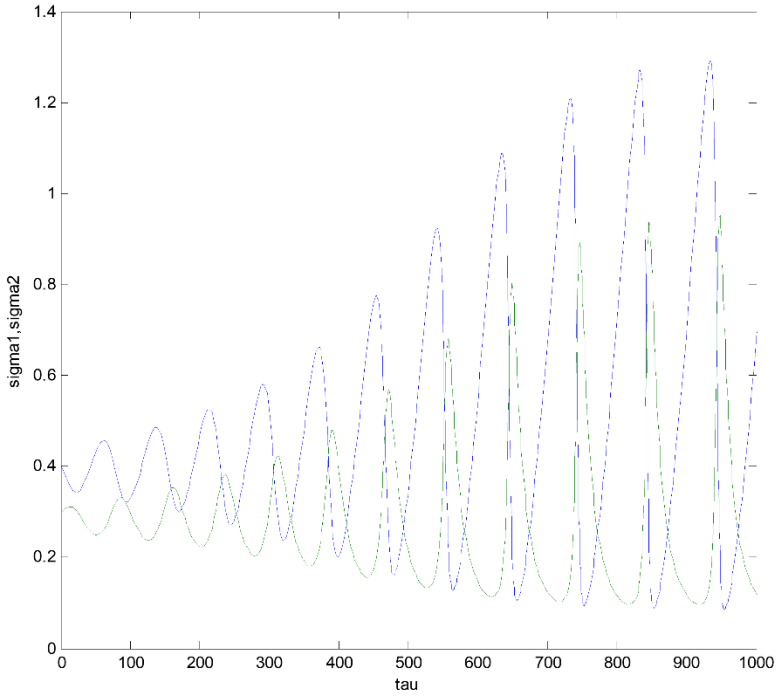
$S_1 = ATP$

$S_2 = ADP$

$x_1 = ES_2^{\gamma}$

$x_2 = S_1 ES_2^{\gamma}$





Your goal: the system

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2),$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2.$$

$$\frac{\sigma_1 \sigma_2^{\gamma}}{\sigma_2^{\gamma}\sigma_1 + \sigma_2^{\gamma} + 1} = f(\sigma_1, \sigma_2)$$

Starting point

(file "spiralrun.m")

```
global mag  %passed parameter
mag = .1;
Tspan = [1 200]; %[start end]
Y0 = [1 2];  % initial conditions, 2 variables
[T,Y] = ode45(@spiral,Tspan, Y0);
```

(file "spiral.m")

```
function dy = spiral(t,y)
global mag
dy=zeros(2,1); % column vector w/ 2 rows
dy(1)=mag*y(2);
dy(2)=-mag*y(1);
```