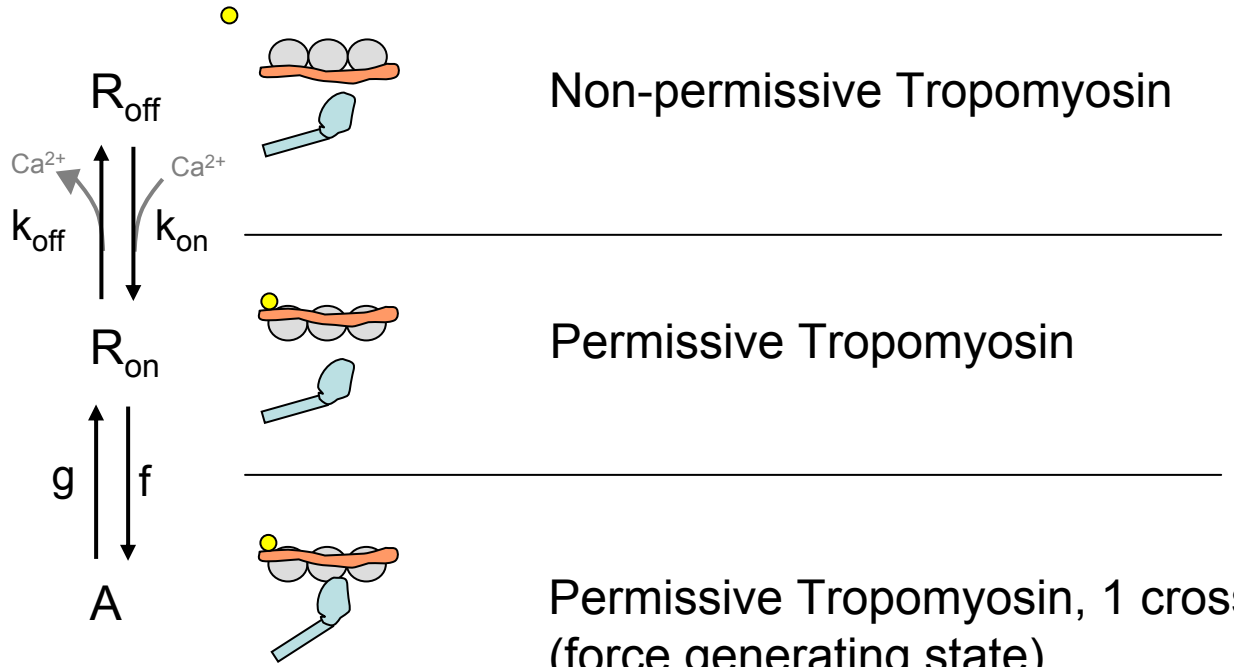
State Transition Model: Myofilament Force Production



Assuming an isometric contraction, force produced is simply proportional to the amount of attached crossbridges (A).

Model Equations

- Governing ordinary differential equations (ODEs) come from mass conservation:

$$\frac{dR_{off}}{dt} = k_{off} R_{on} - k_{on}[Ca^{2+}]R_{off}$$

$$\frac{dR_{on}}{dt} = k_{on}[Ca^{2+}]R_{off} + gA - \left(k_{off} + f\right)R_{on}$$

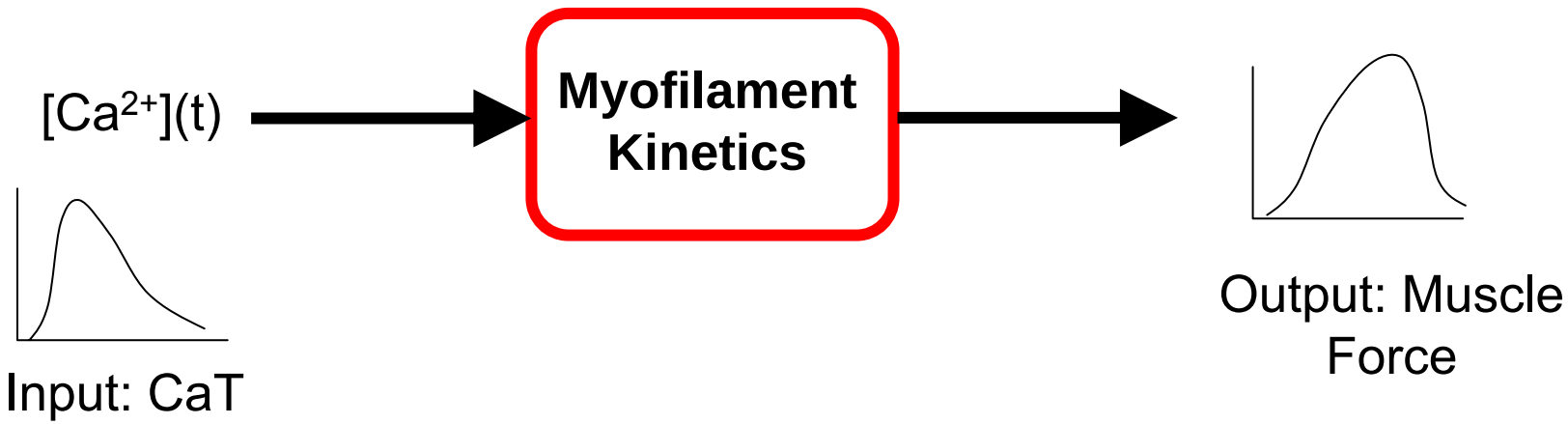
$$\frac{dA}{dt} = fR_{on} - gA$$

Because mass is conserved, one of the above equations can be replaced by the following algebraic expression:

$$U_t = R_{off} + R_{on} + A \longrightarrow R_{on} = U_t - R_{off} - A$$

Using MATLAB to examine Ca^{2+}-Contraction Dynamics

- We will use MATLAB to examine the response of the 3-state contraction model to a transient calcium release event
  - Define initial conditions
  - Integrate the system of coupled ODEs over a time interval of our choosing to find the response of the system



Solving ODE's Using Runge-Kutta Methods

Given equations of the form $\frac{dp}{dt} = f(t, p)$ and initial conditions $p(t_0) = p_0$

For each time step, we approximate the solution:

$$p_{t+\Delta t} = p_t + \frac{\Delta t}{6}\left(k_1 + 2k_2 + 2k_3 + k_4\right)$$

Where

$$k_1 = f(t, p_t)$$

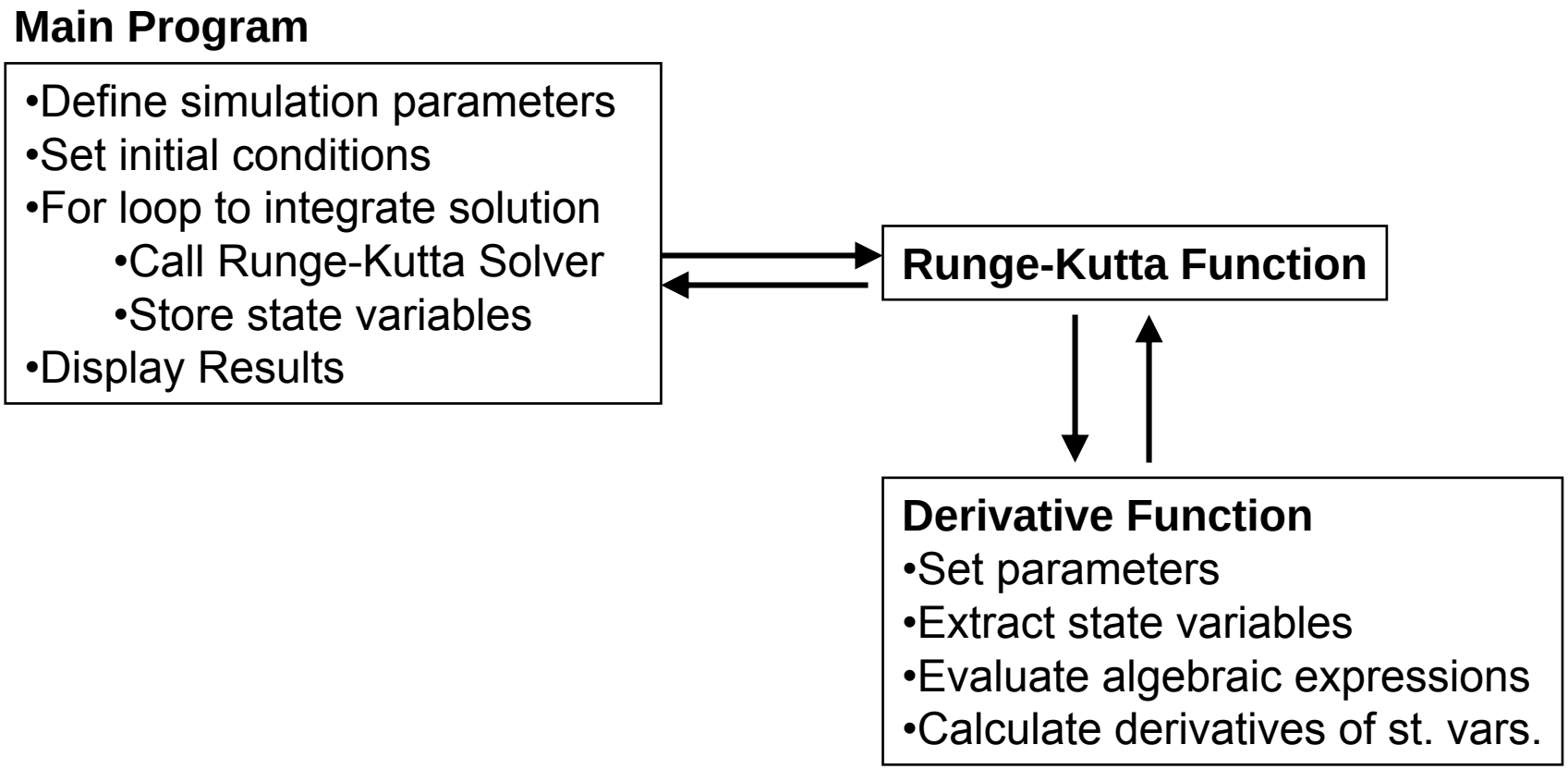
$$k_2 = f\left(t + \frac{1}{2}\Delta t, p_t + k_1\frac{1}{2}\Delta t\right)$$

$$k_3 = f\left(t + \frac{1}{2}\Delta t, p_t + k_2\frac{1}{2}\Delta t\right)$$

$$k_4 = f\left(t + \Delta t, p_t + k_3\Delta t\right)$$

The first time through, set $p_t = p_0$. In each successive time step, set $p_t = p_{t+\Delta t}$.

General Program Structure



The Derivative Function

For a given value of time, *t*, and vector of state variables, p_t, what is the slope of the state variable functions, $\frac{dp_t}{dt}$?

$$\frac{dR_{off}^t}{dt} = k_{off} R_{on}^t - k_{on}[Ca^{2+}](t) R_{off}^t$$

$$\frac{dA^t}{dt} = fR_{on}^t - gA^t$$

Return these values

Task 1

- Download XB_model.m from the website, open MATLAB, and open XB_model.m in the editor
- Read through and understand the code
- Complete the derivative function by entering model parameters (table below) and governing equations
- Estimate some initial conditions for the state variables
- Run the model and examine the output

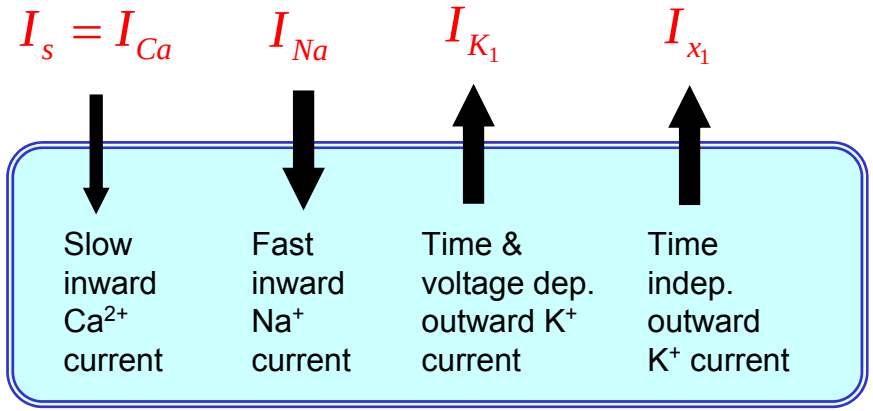
Model Parameters		Units
k_off	40	1/s
k_on	20	1/s
f	15	1/s
g	20	1/s

Task 2

- Determine steady state initial conditions for the model
  - Do this by setting the Ca^{2+} concentration to be constant at 0.01 μM and running the model until steady state is reached.
  - Replace your estimated IC's with ones determined from steady state

Beeler-Reuter Action Potential Model (1)

- First application of Hudgkin-Huxley theory to cardiac cells
- Beeler, G.W. and H. Reuter, *Reconstruction of the action potential of ventricular myocardial fibres.* J Physiol, 1977. **268**(1): p. 177-210.
- 4 ionic membrane currents plus a stimulus current are included
- Currents are functions of the independent variables of the ODE set:
  - 6 gating variables
  - Calcium concentration
  - Membrane potential



$$\frac{dV_m}{dt} = -\left(\frac{1}{C_m}\right)\left(I_{K_1} + I_{x_1} + I_{Na} + I_s - I_{stim}\right)$$

$$I_{ion} = f\,(V_m, [Ca]_i, x1, m, h, j, d, f)$$

Beeler-Reuter Action Potential Model (2)

- Action potentials are modeled as a system of time dependent ODE's
- Beeler-Reuter model uses 8 ODE's found by curve fitting experimental patch-clamp data

- 6 ODE's describe the state of gated ion channels
  - (y represents 6 gating conductance variables x_1, m, h, j, d, and f)
  - the gating parameters α_y and β_y are calculated with various sets of constants c_i from curve fits

$$\frac{dy}{dt} = \frac{(y_\infty - y)}{\tau_y}$$

$$with \quad y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y} \quad and \quad \tau_y = \frac{1}{\alpha_y + \beta_y}$$

$$\alpha_y \ or \ \beta_y = \frac{c_1 e^{c_2 (V_m + c_3)} + c_4 (V_m + c_5)}{e^{c_6 (V_m + c_3)} + c_7}$$

Beeler-Reuter Action Potential Model (3)

- 1 ODE describes intracellular Ca^{2+} concentration

$$\frac{d[\mathrm{Ca}]_i}{dt} = \left(-10^{-7}\right) I_s + 0.07\left(10^{-7} - [\mathrm{Ca}]_i\right)$$

- 1 ODE describes membrane voltage – Statement of Charge Conservation

$$\frac{dV_m}{dt} = -\left(\frac{1}{C_m}\right)\left(I_{K_1} + I_{x_1} + I_{Na} + I_s - I_{stim}\right)$$

- The ODE set is integrated over time
  - Given an initial condition, each time step calculated from previous solution
  - Rapid rise of AP with fast Na^+ kinetics => this is a stiff system
  - Need numerical solvers that can handle this situation
    - Common choice is implicit Runge-Kutta with adaptive time stepping
  - Currents I_{ion} are calculated at each time step from the solution of the independent variables at the current time

Task 3

- Download BR.m from the website and open it in the MATLAB editor
- Read through and understand BR.m, RK4.m, and BR_deriv_std.m
- Run BR.m with the standard RK4 solver
- Create an output section at the end of BR.m to plot different model results (i.e. membrane voltage, channel currents, etc.)
- Gradually increase the time step and note what happens.

Task 4

- Run BR.m using the MATLAB RK solver, which uses variable time steps.
- Compare the execution times of the two different solvers.
- Compare transmembrane voltage produced by the two solvers.

Advanced Task

- Merge the Beeler-Reuter AP model with the crossbridge kinetics model to generate a complete EC coupling event.
  - Merge state variable vectors
  - Merge derivative functions into one
- Make a plot showing the time relationships between stimulus, AP, Ca^{2+} and force.