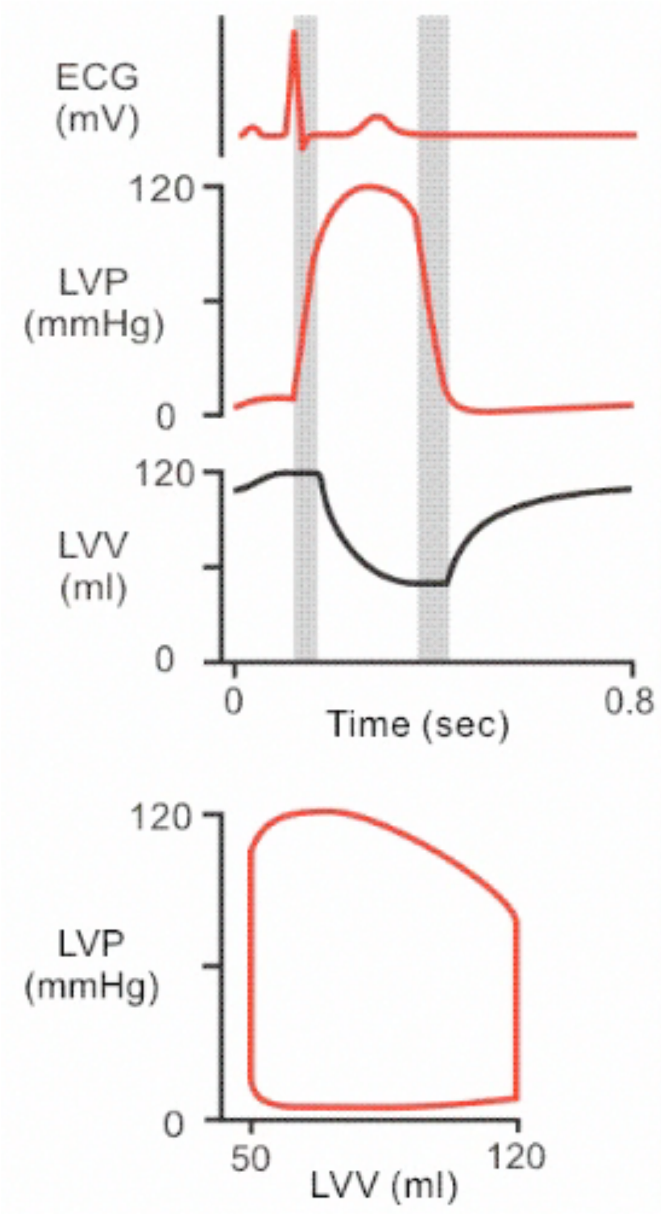
CV BSc Module 1
Molecular and Cellular Cardiology

Steven Marston, Cesare Teracciano, Ralph Knöll

Introduction: mechanisms of contractility in the heart

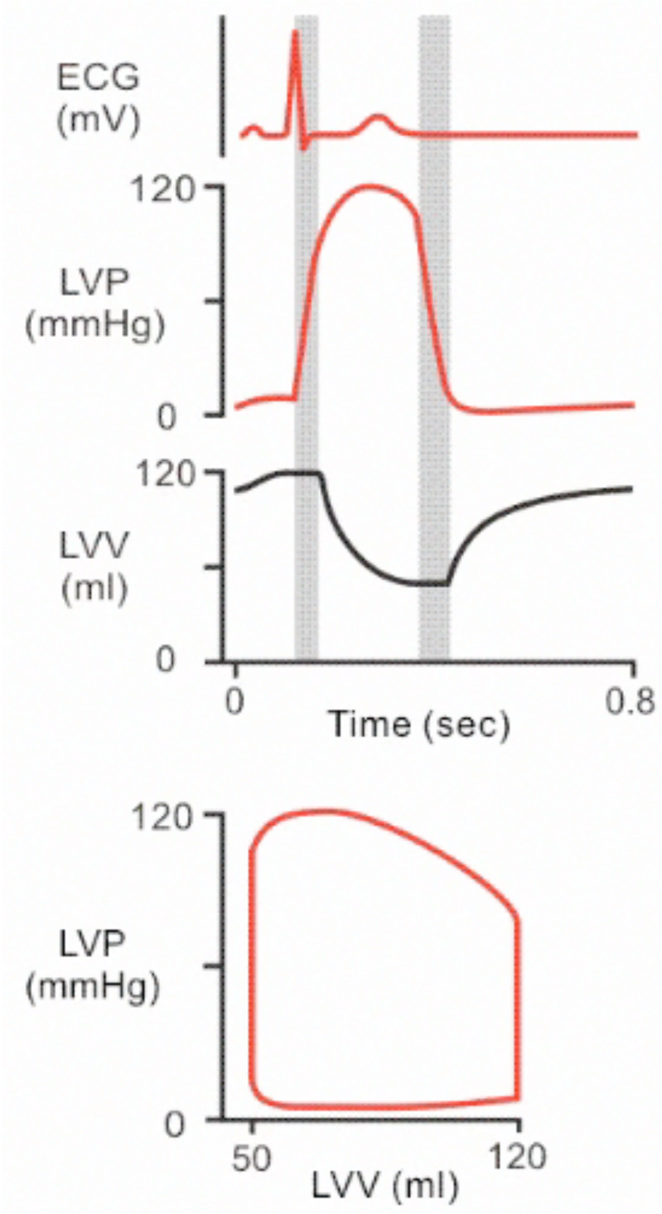
Basic equations for rates and equilbria



Basic mechanics of the heart

Work= force x distance
= pressure x volume
= area of PV loop
= about 1 Joule per beat

Power= work/time
= 1 to 5 Watts



Energy conversion

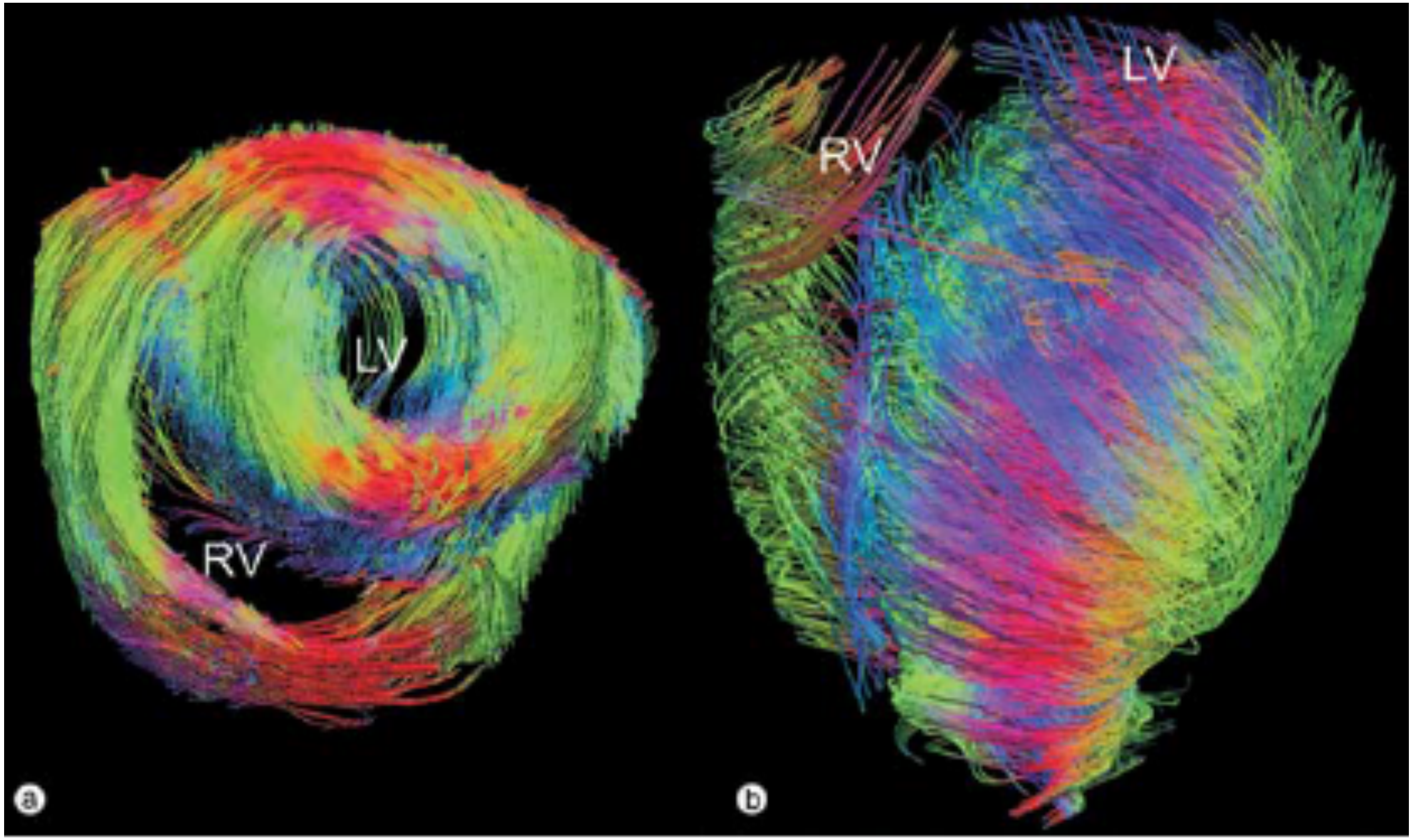
Chemical energy in the form of high-energy phosphate bonds of ATP is converted into mechanical work by motor proteins

ATP > ADP + Pi + work+heat

ΔG= 60 kJ per mole of ATP

Muscle is a linear motor

Linear motion is converted to changes in heart chamber volume by the spiral arrangement of muscle fibres (wringer-like action)



Schmid et al., Eur J Cardiol 2005
doi:10.1016/j.ejcts.2004.11.036

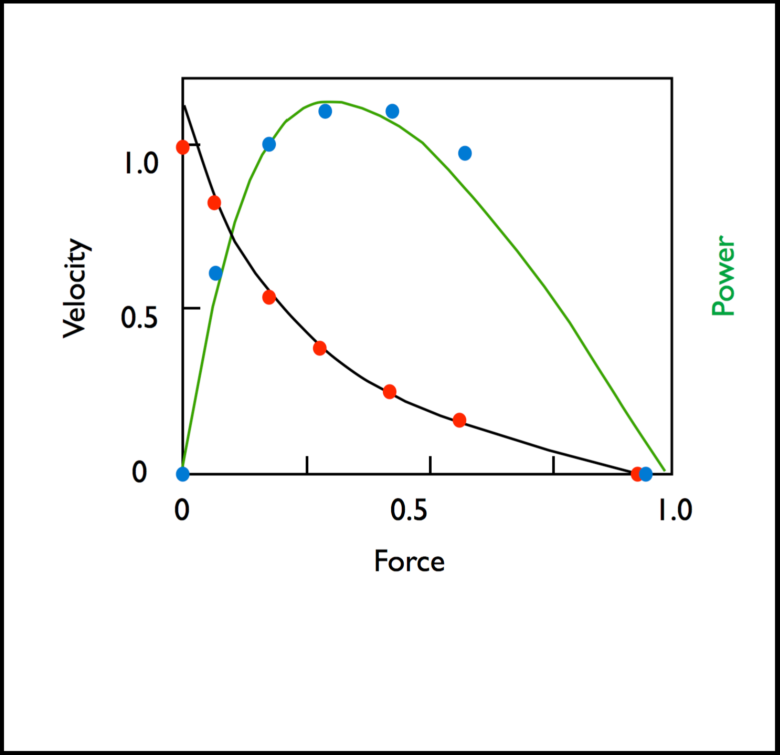
Contraction of a single human cardiac myocyte stimulated at 0.5 Hz

mechanics of contractility

switching on and off

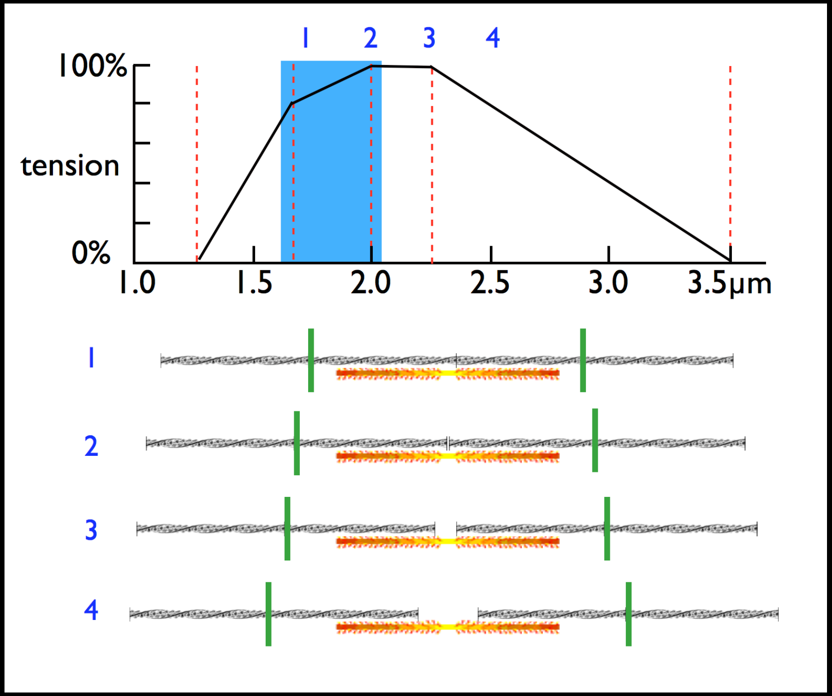
fuel supply

Force-velocity relationship



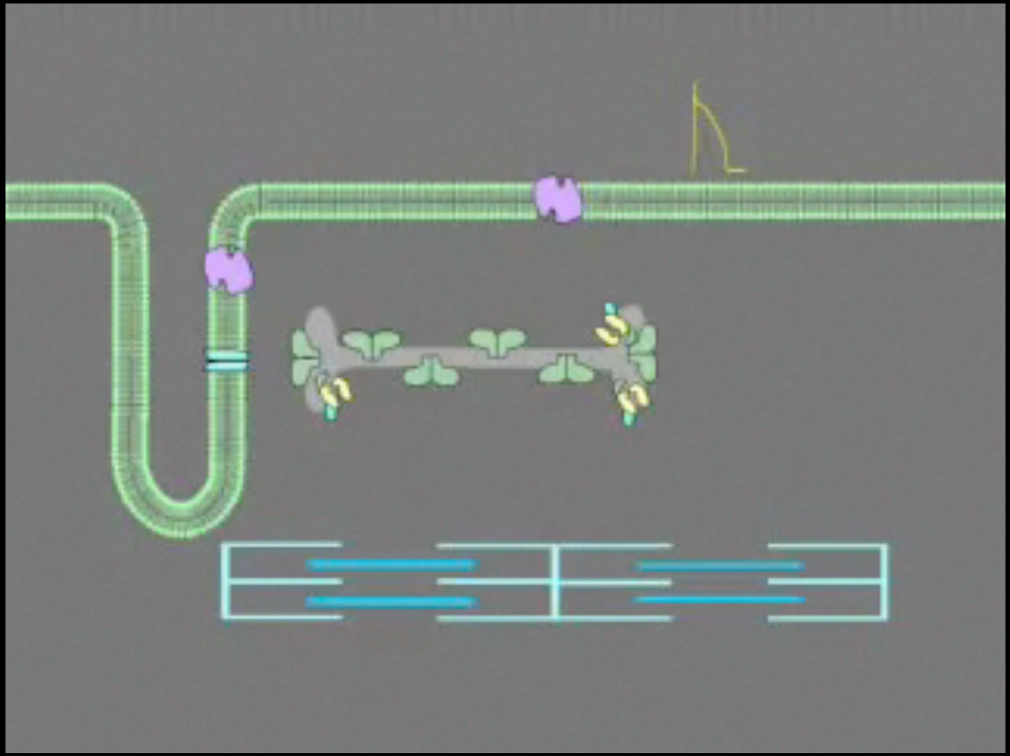
Maximum force is isometric
maximum speed is unloaded
maximum power is at an intermediate speed

Length-tension relationship



This relationship is due to the sliding filament mechanism of muscle contraction
Heart muscle contracts in the length range below optimum
The length-tension and force-velocity relationships are net result of the action of a large number of independent force generating molecules

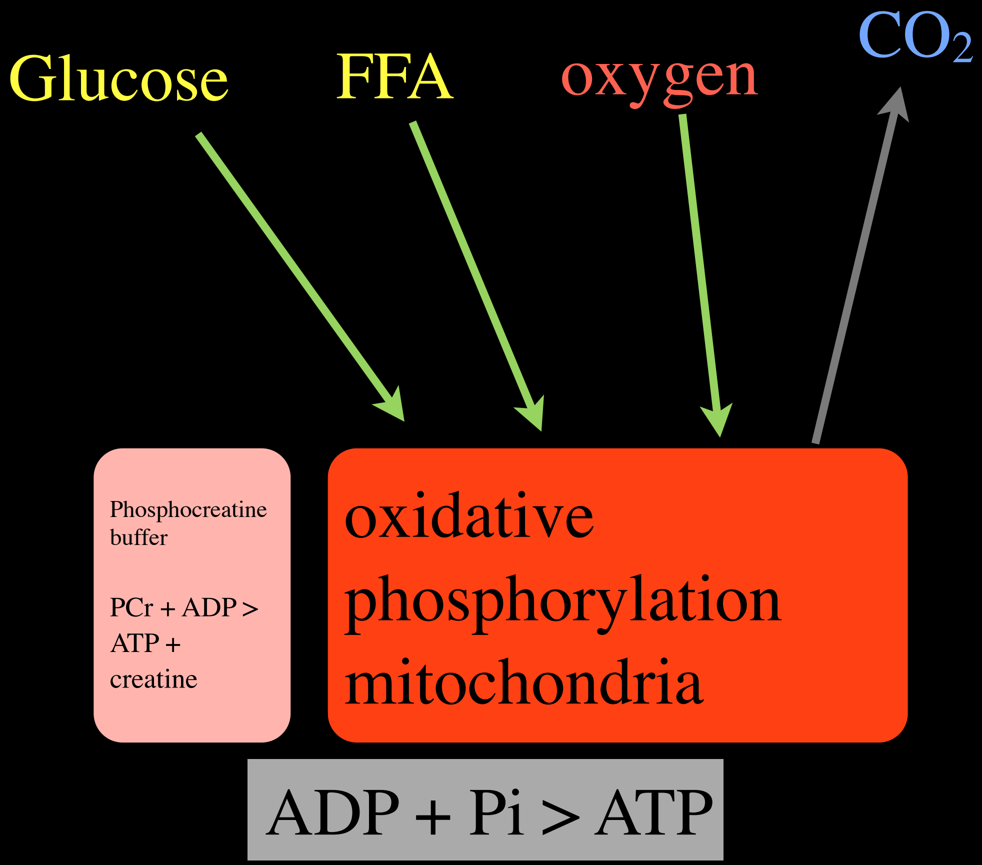
Excitation-contraction coupling



animation by Cesare Teracciano

The action potential switches on contraction via release of Ca^{2+} into the cytoplasm which then activates the contractile proteins.
Relaxation is due to pumping Ca^{2+} out of the cytoplasm into the sarcoplasmic reticulum

Energy for contraction is generated by oxidative phosphorylation



Glucose

FFA

oxygen

CO_2

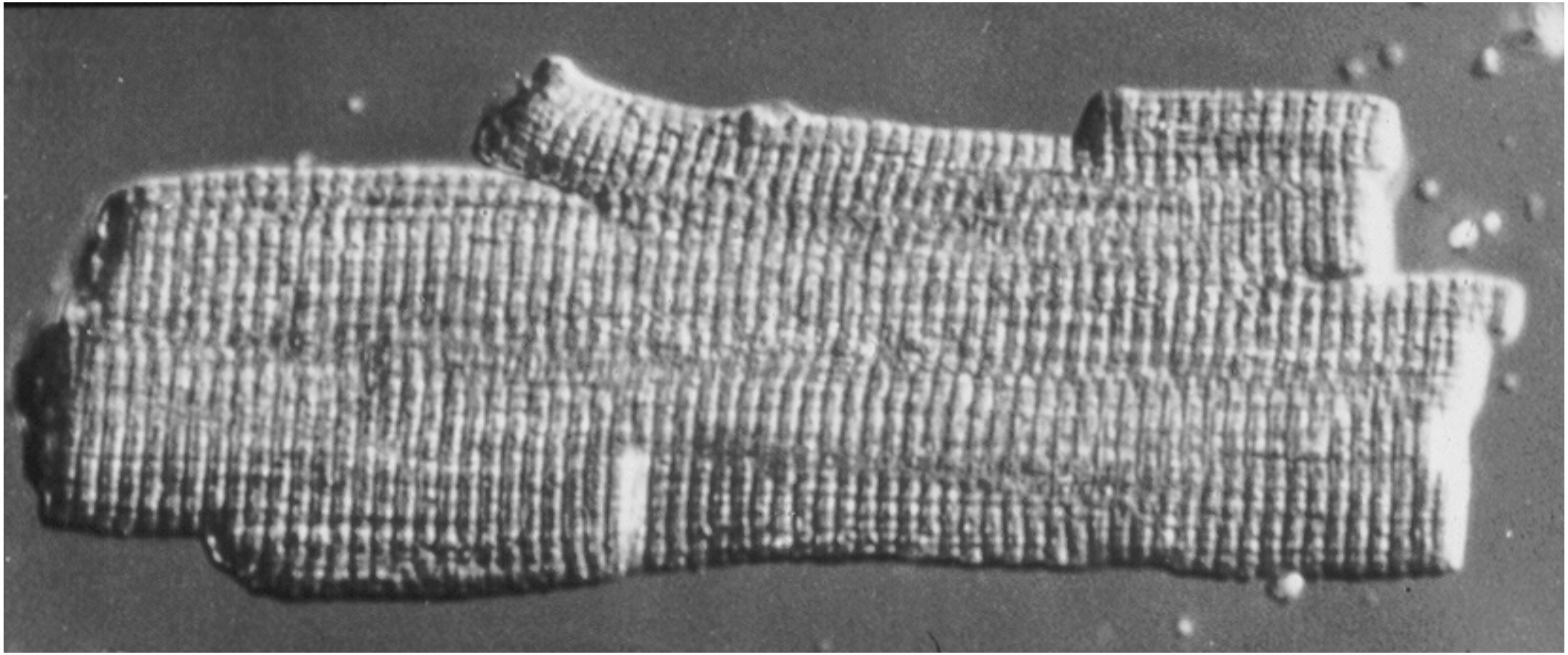
Phosphocreatine buffer

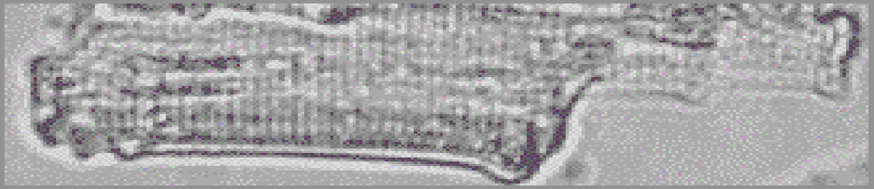
PCr + ADP > ATP + creatine

oxidative phosphorylation mitochondria

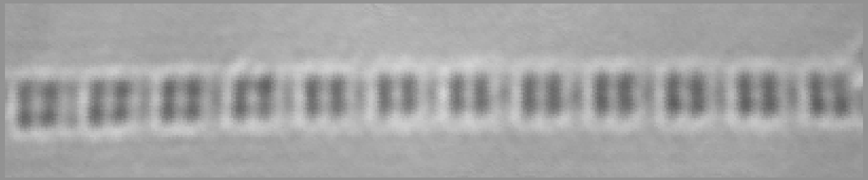
ADP + Pi > ATP

Mechanism of cardiac muscle contractility





Myocyte



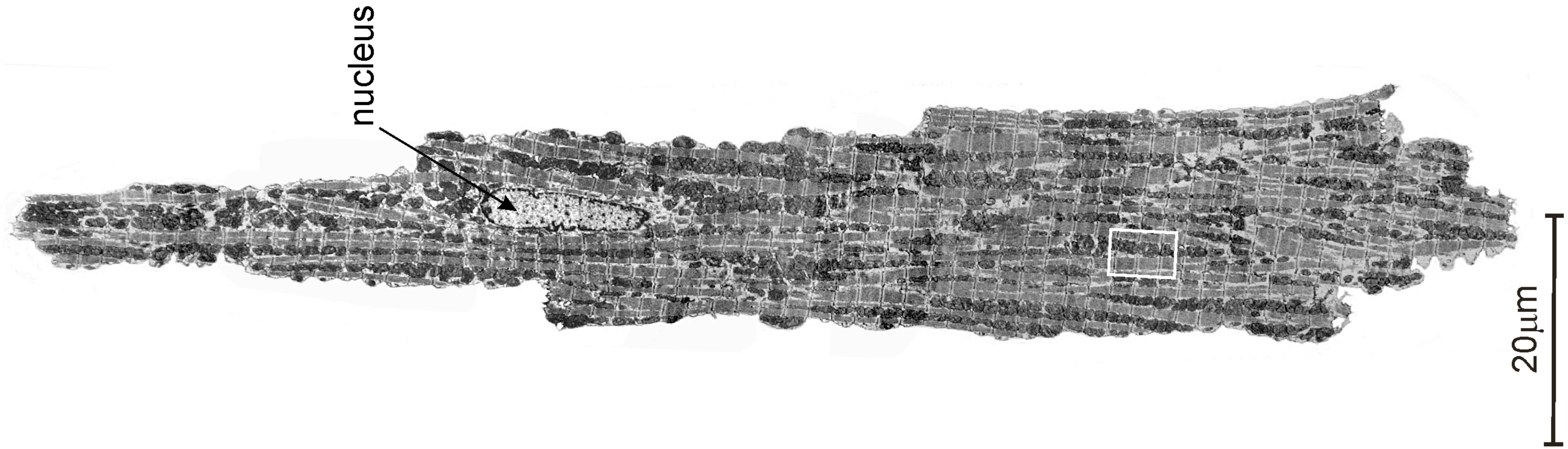
Myofibril

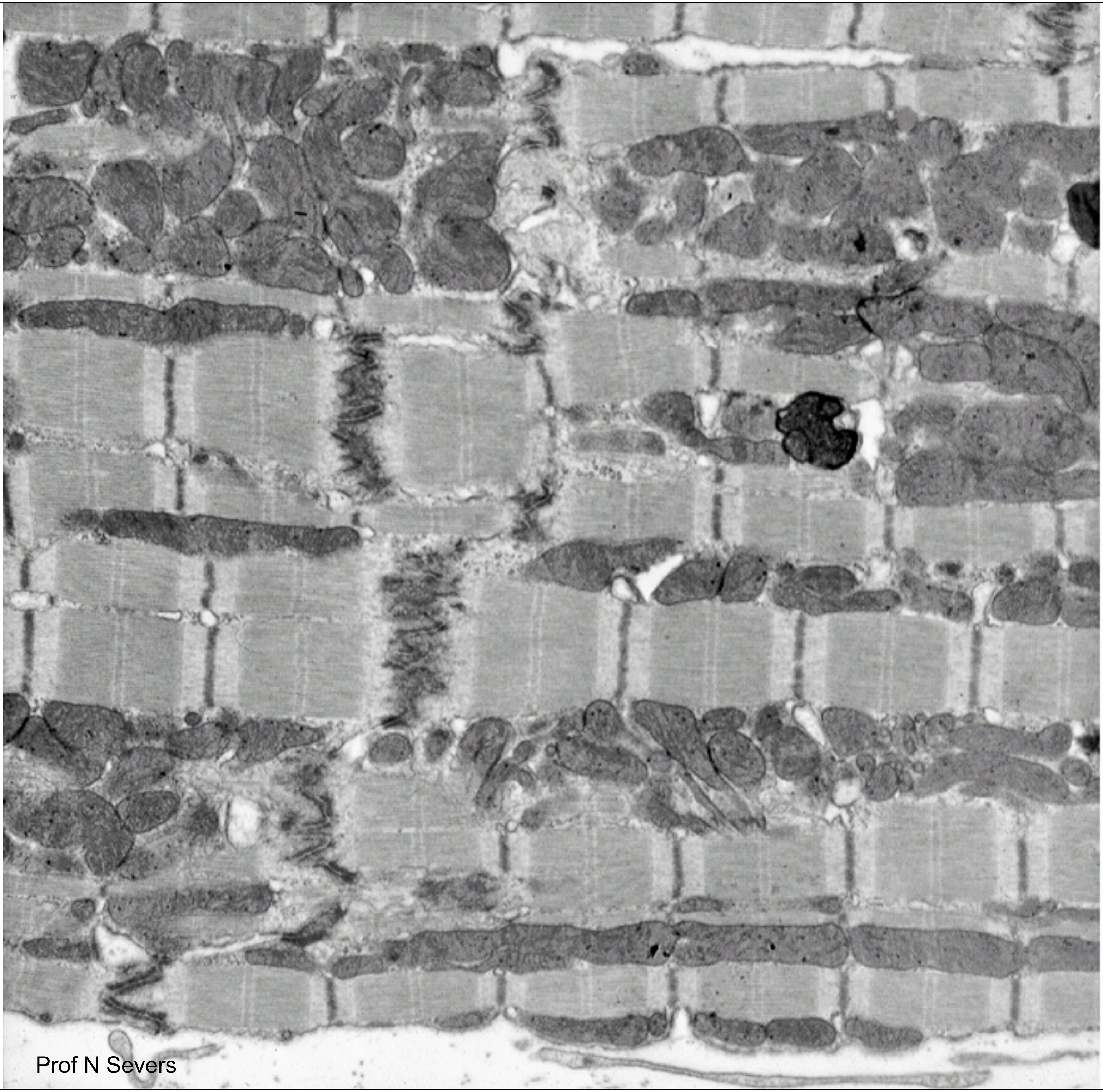
Sarcomere

Actomyosin

Isolated cardiomyocytes

Prof N Severs





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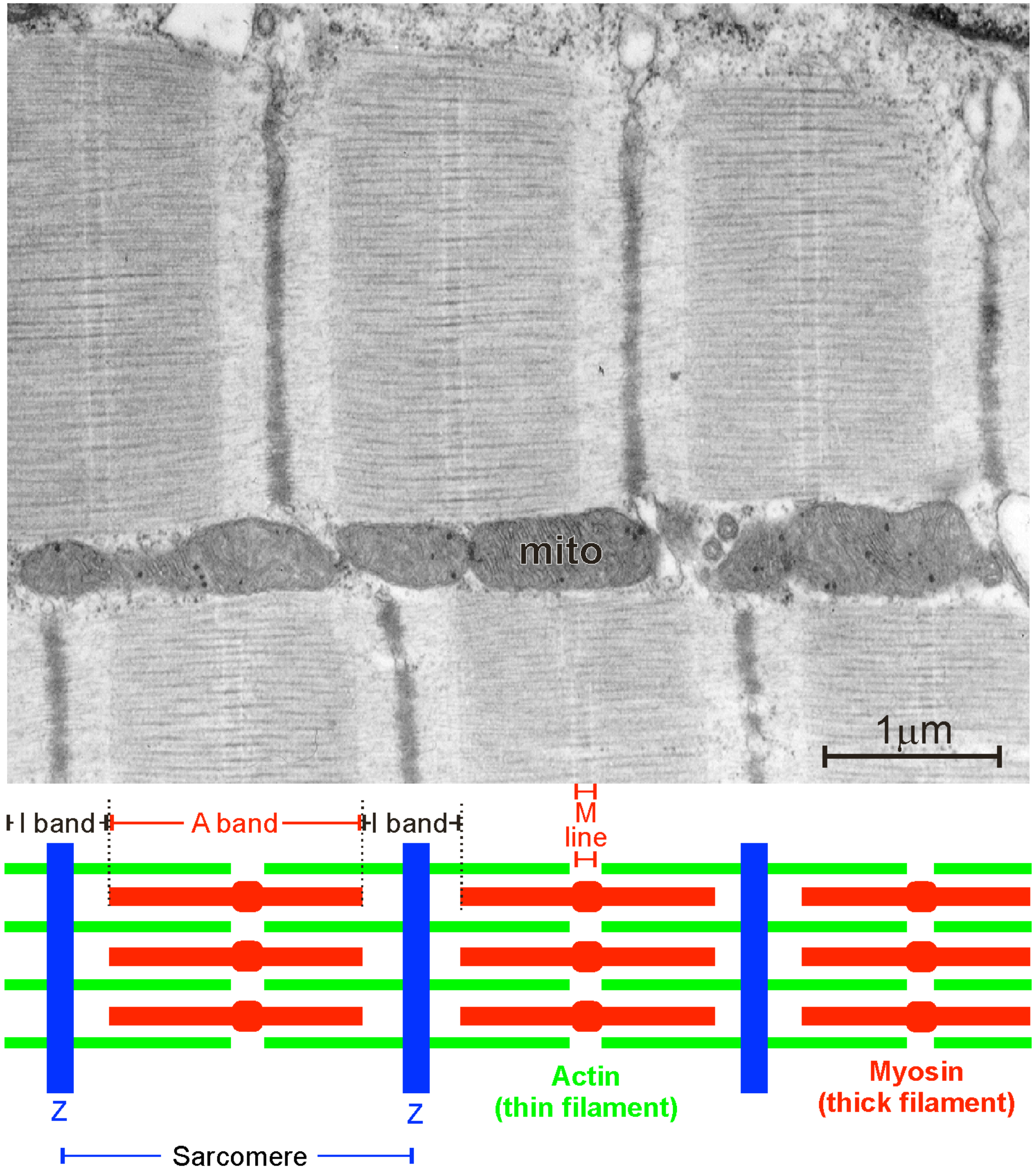
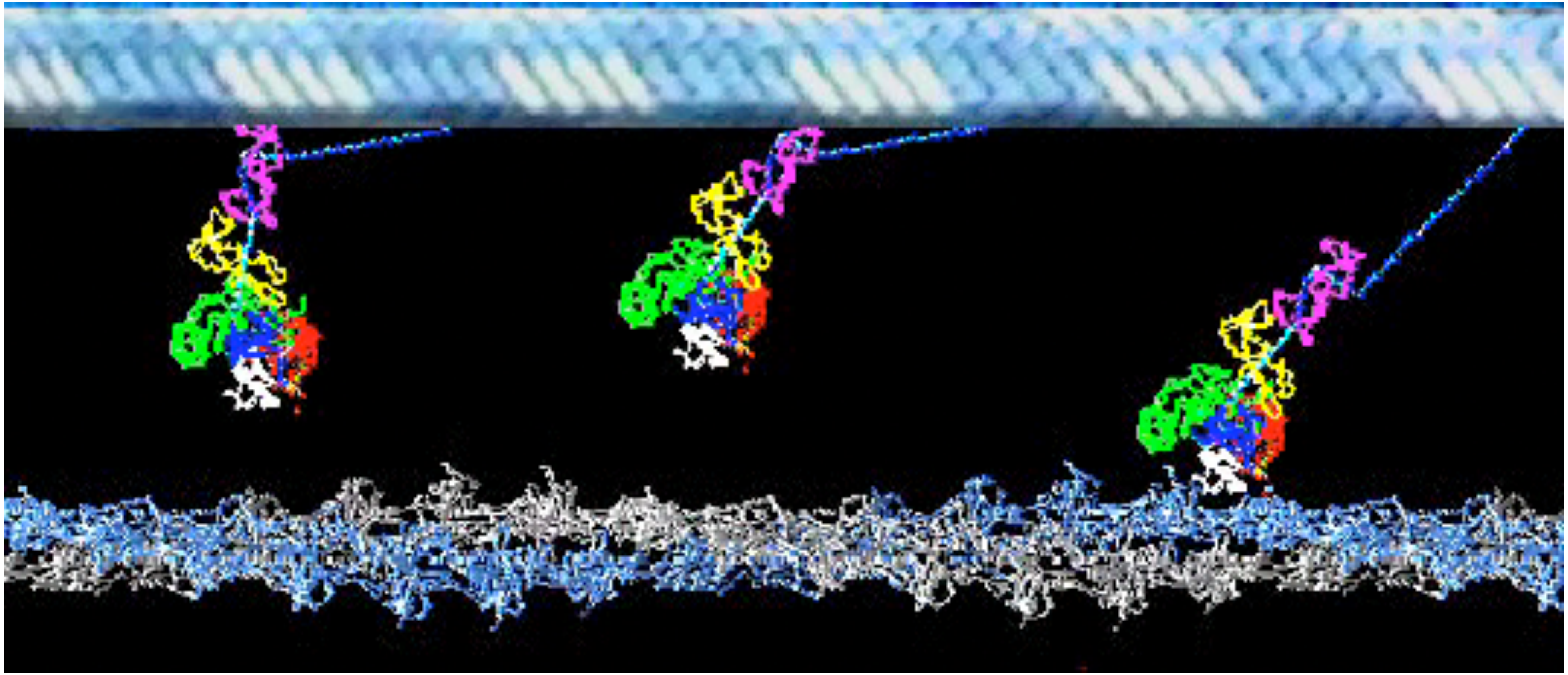
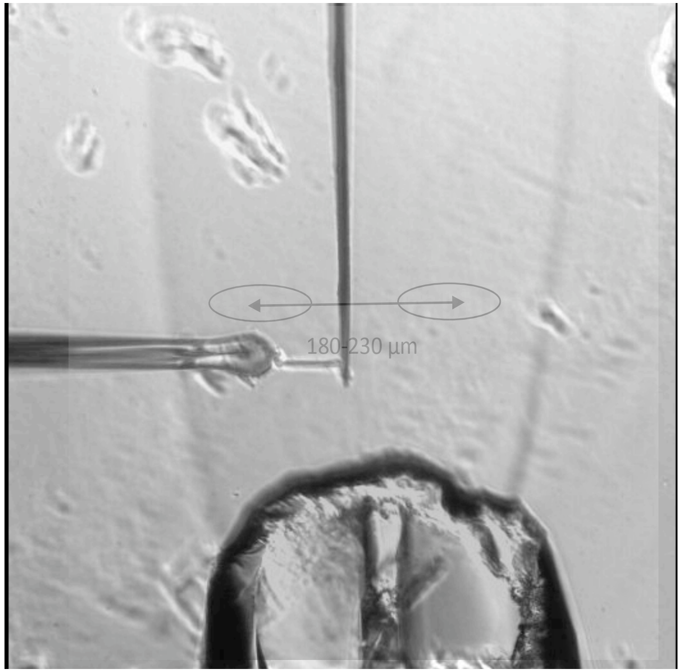
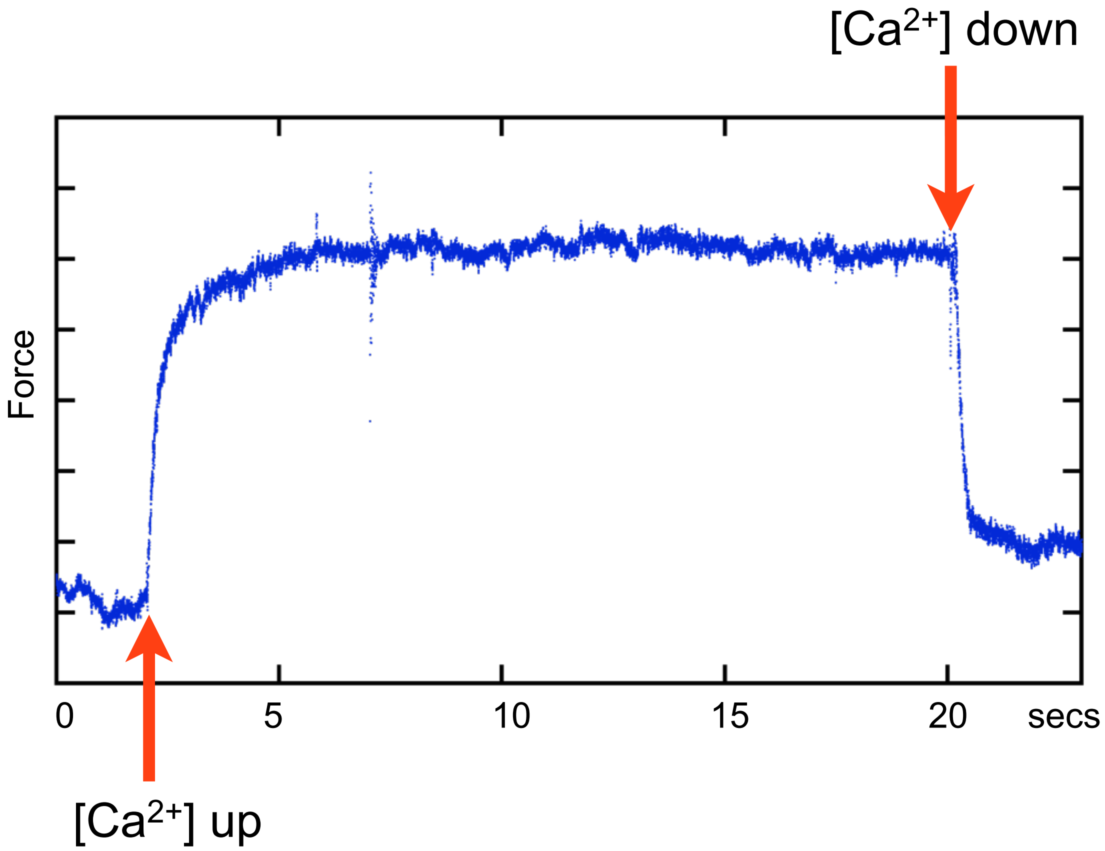

mito
1μm
I band
A band
I band
M line
Z
Z
Actin (thin filament)
Myosin (thick filament)
Sarcomere



Rates and equilibrium: Ca^{2+} activation of contraction and relaxation





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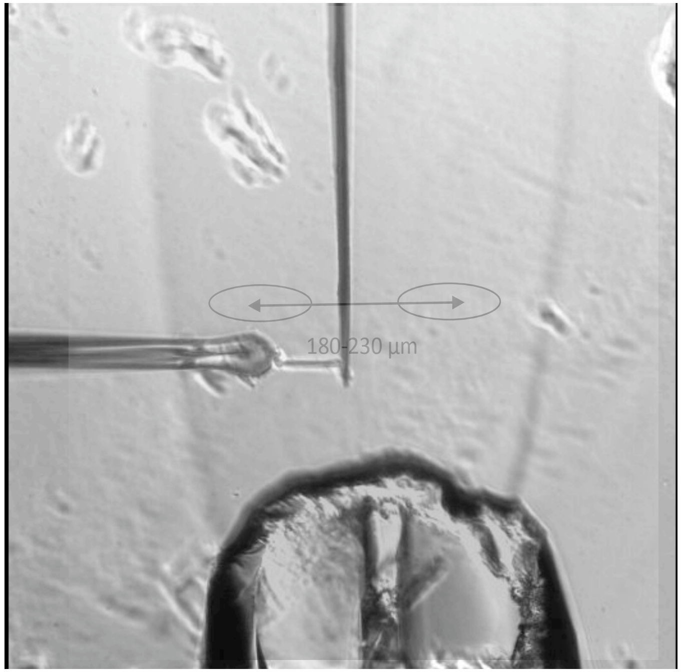
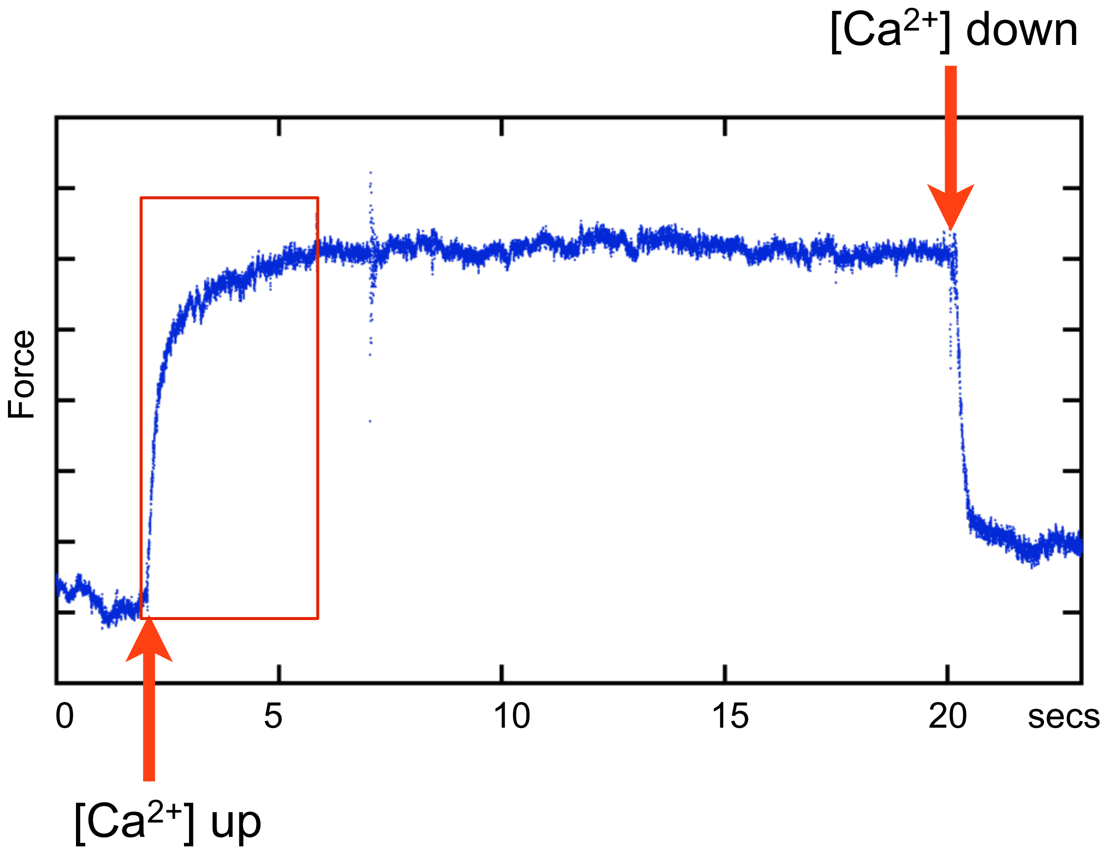
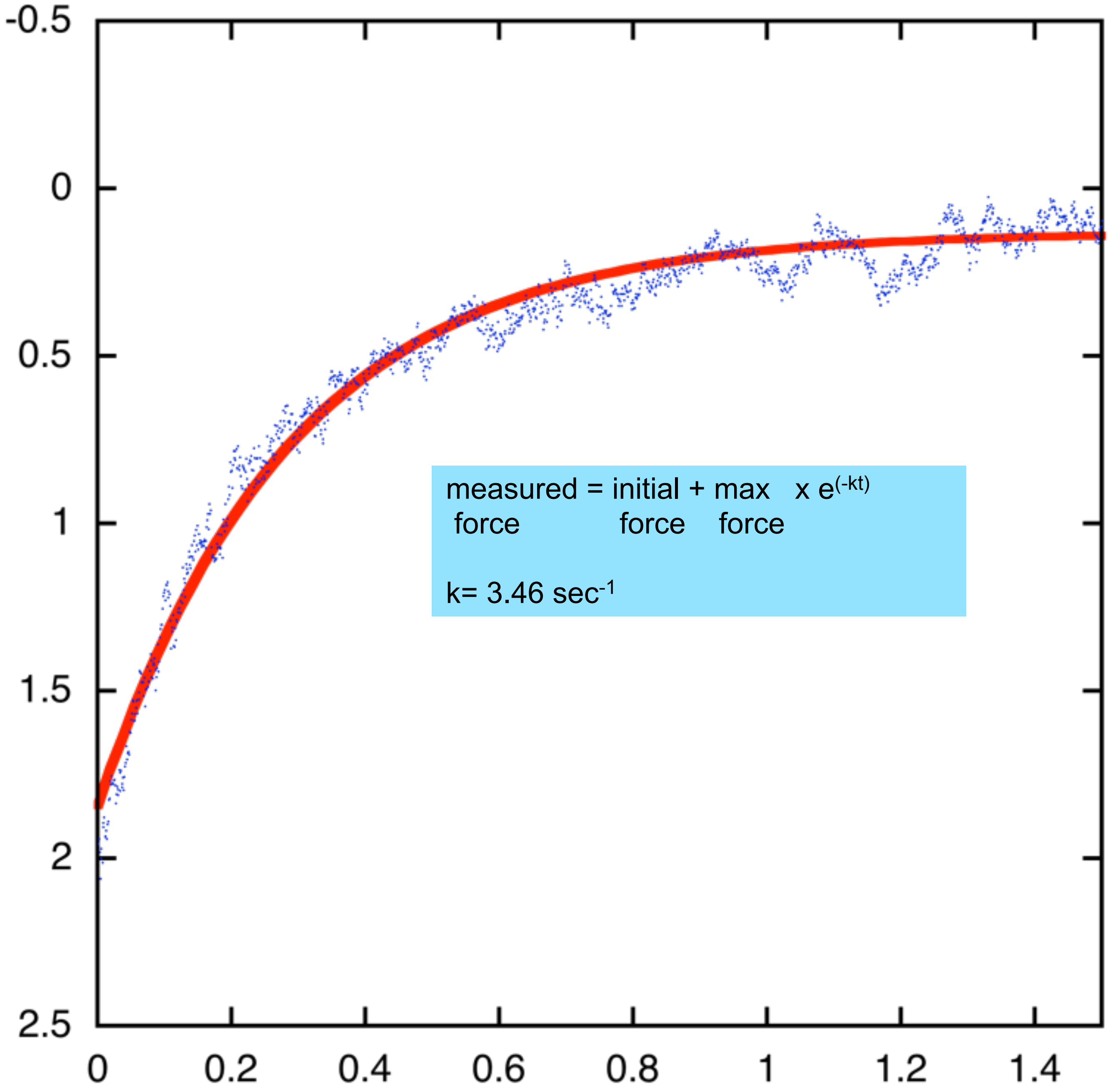




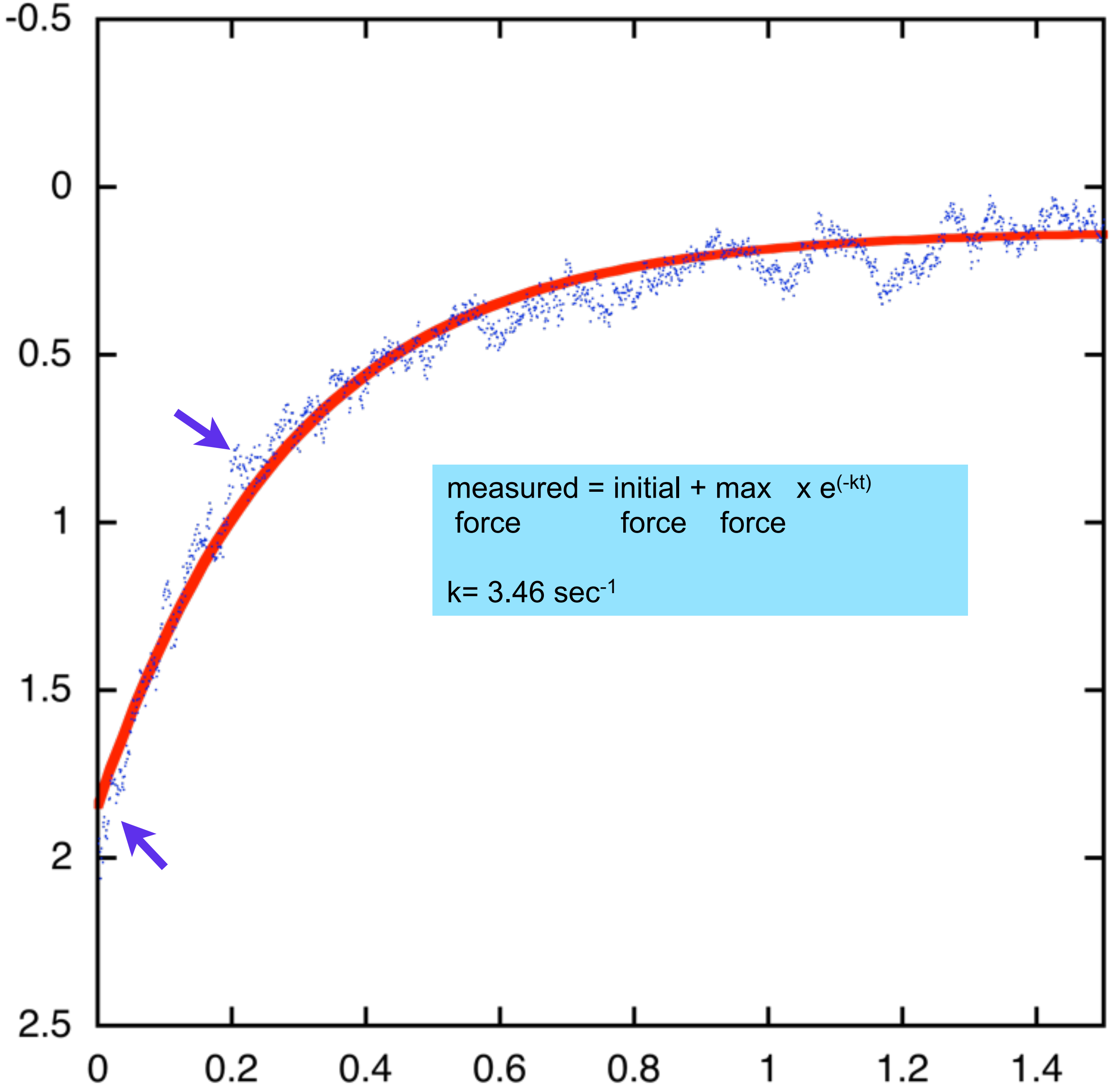
measurement of rate of a process



measured = initial + max x $e^{(-kt)}$
force force force

k= 3.46 sec^{-1}

measurement of rate of a process: single exponential

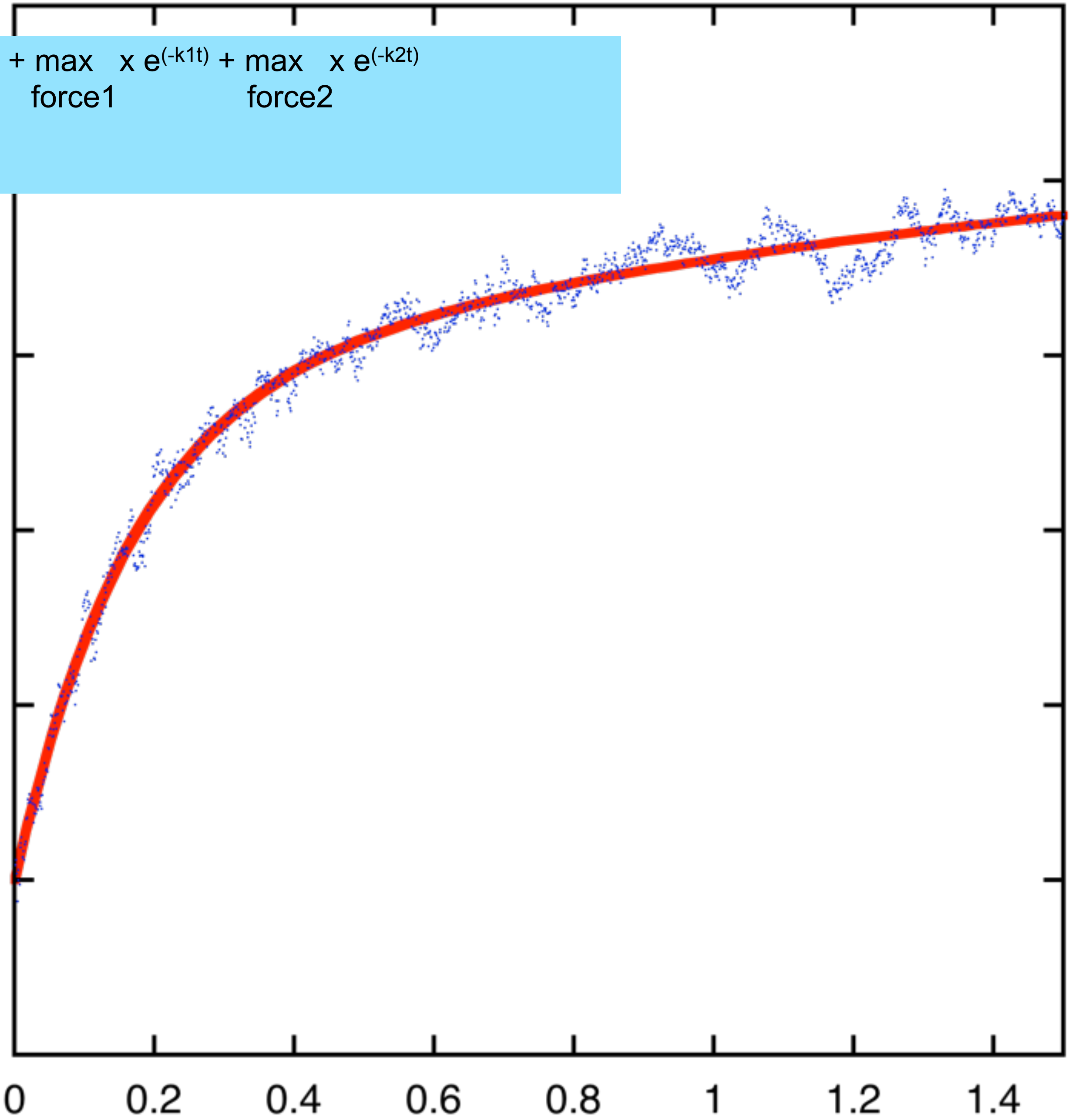


measured = initial + max x $e^{(-kt)}$
force force force

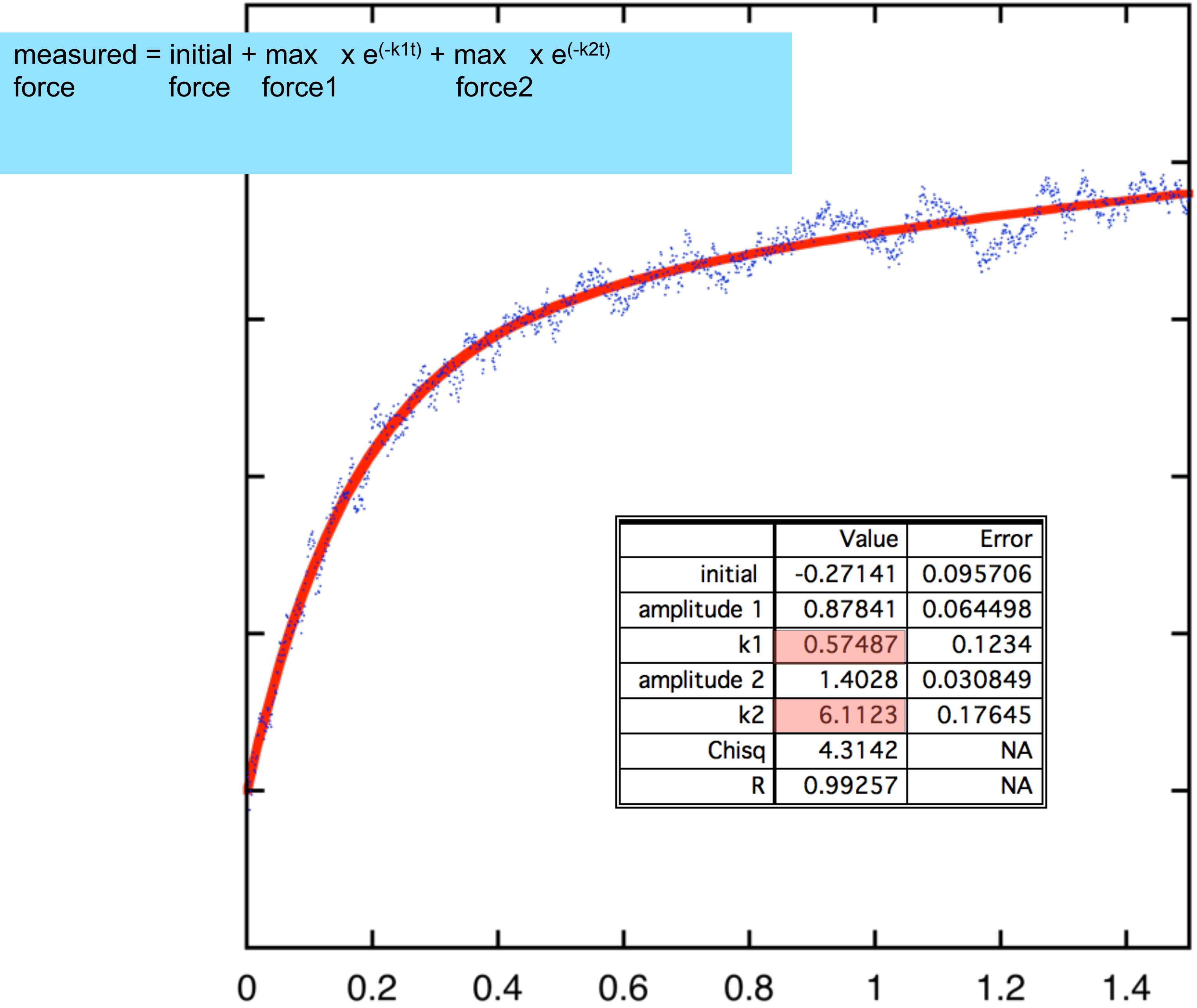
k= 3.46 sec^{-1}

measurement of rate of a process: single exponential

measured = initial + max x $e^{(-k1t)}$ + max x $e^{(-k2t)}$
force force force1 force2



measurement of rate of a process: double exponential fit

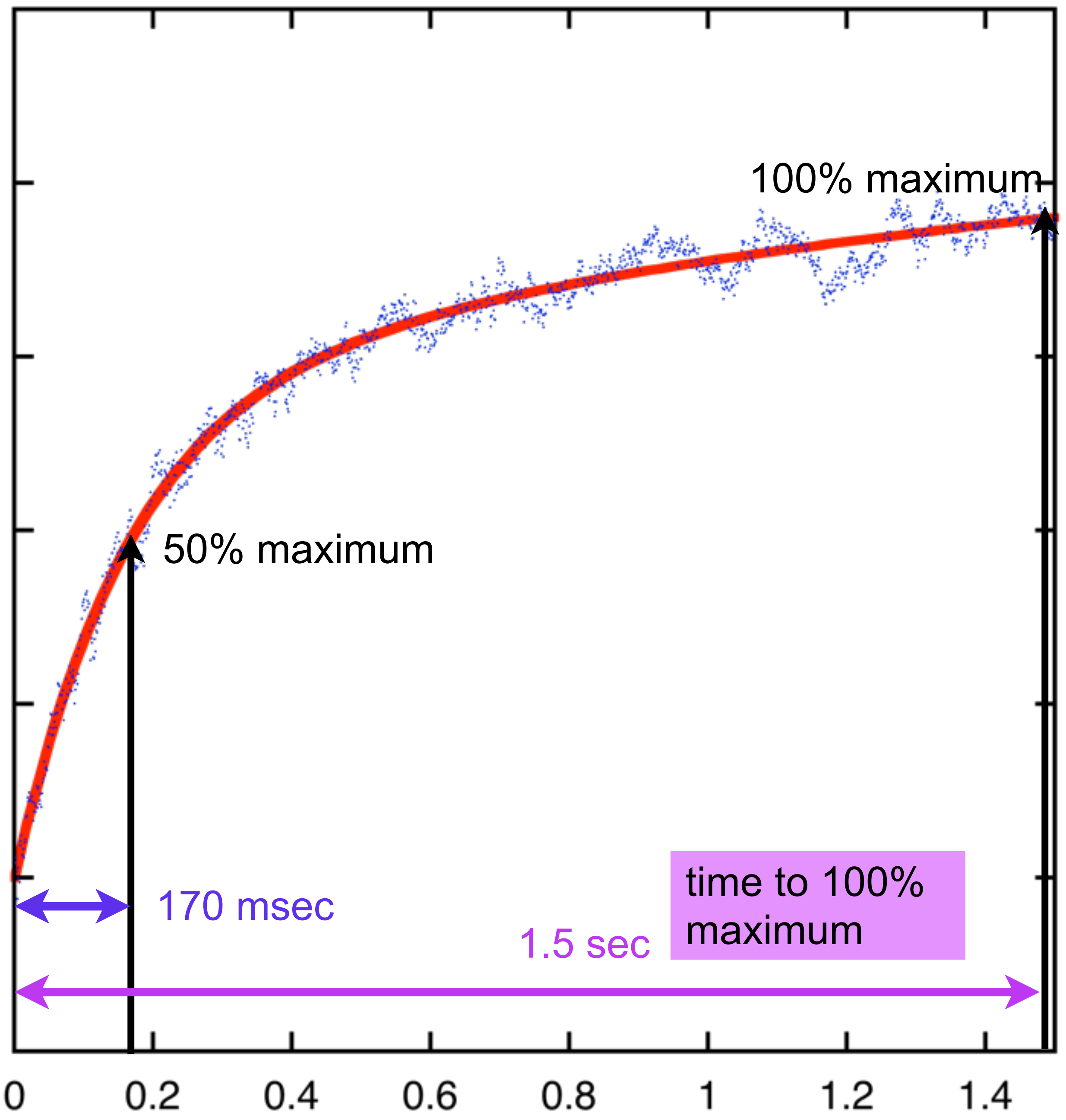


measured = initial + max x $e^{(-k1t)}$ + max x $e^{(-k2t)}$
force force force1 force2

	Value	Error
initial	-0.27141	0.095706
amplitude 1	0.87841	0.064498
k1	0.57487	0.1234
amplitude 2	1.4028	0.030849
k2	6.1123	0.17645
Chisq	4.3142	NA
R	0.99257	NA

measurement of rate of a process: double exponential fit

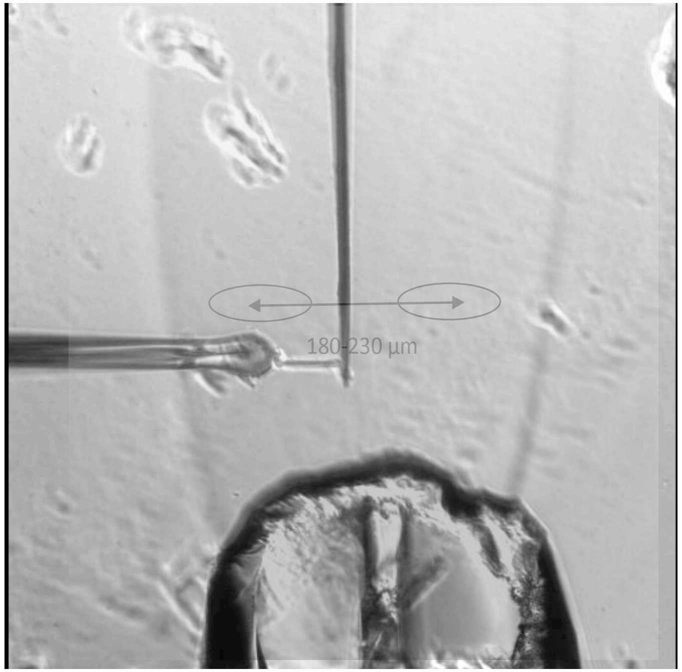
time to 50% maximum or half-life
=ln2/k if a single exponential process

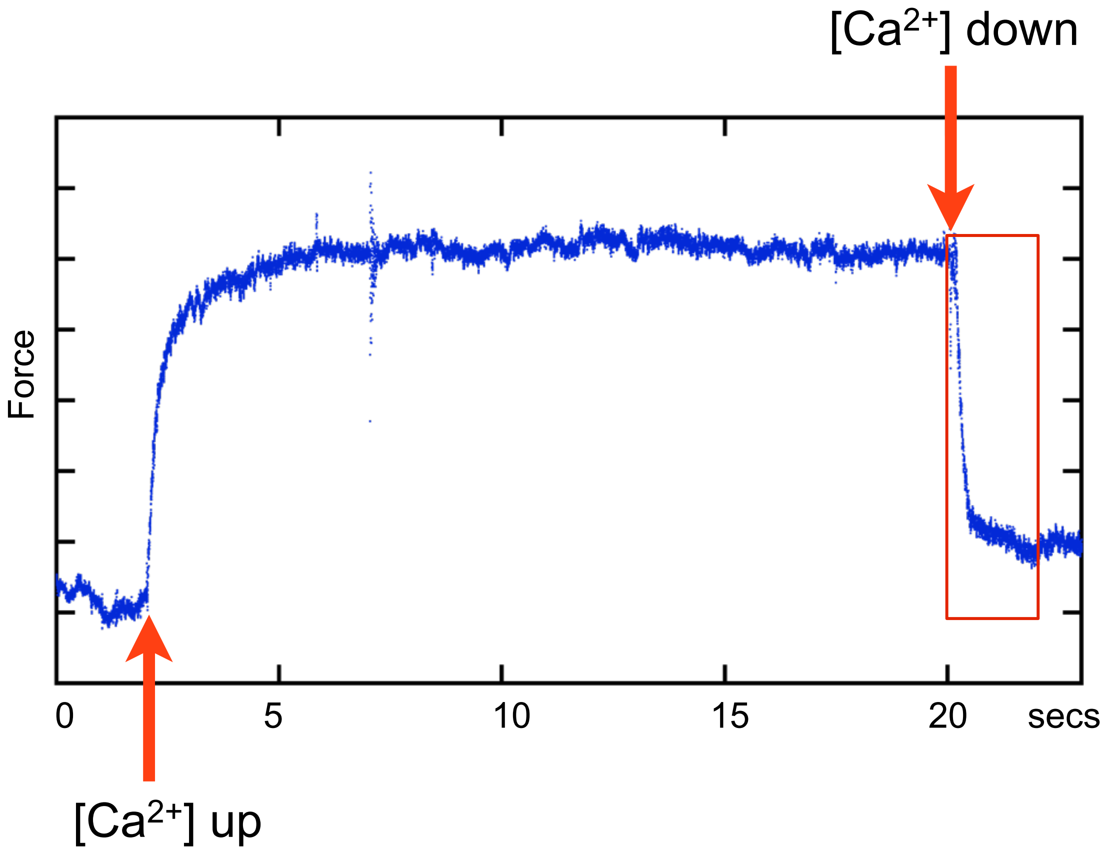


time to 100% maximum

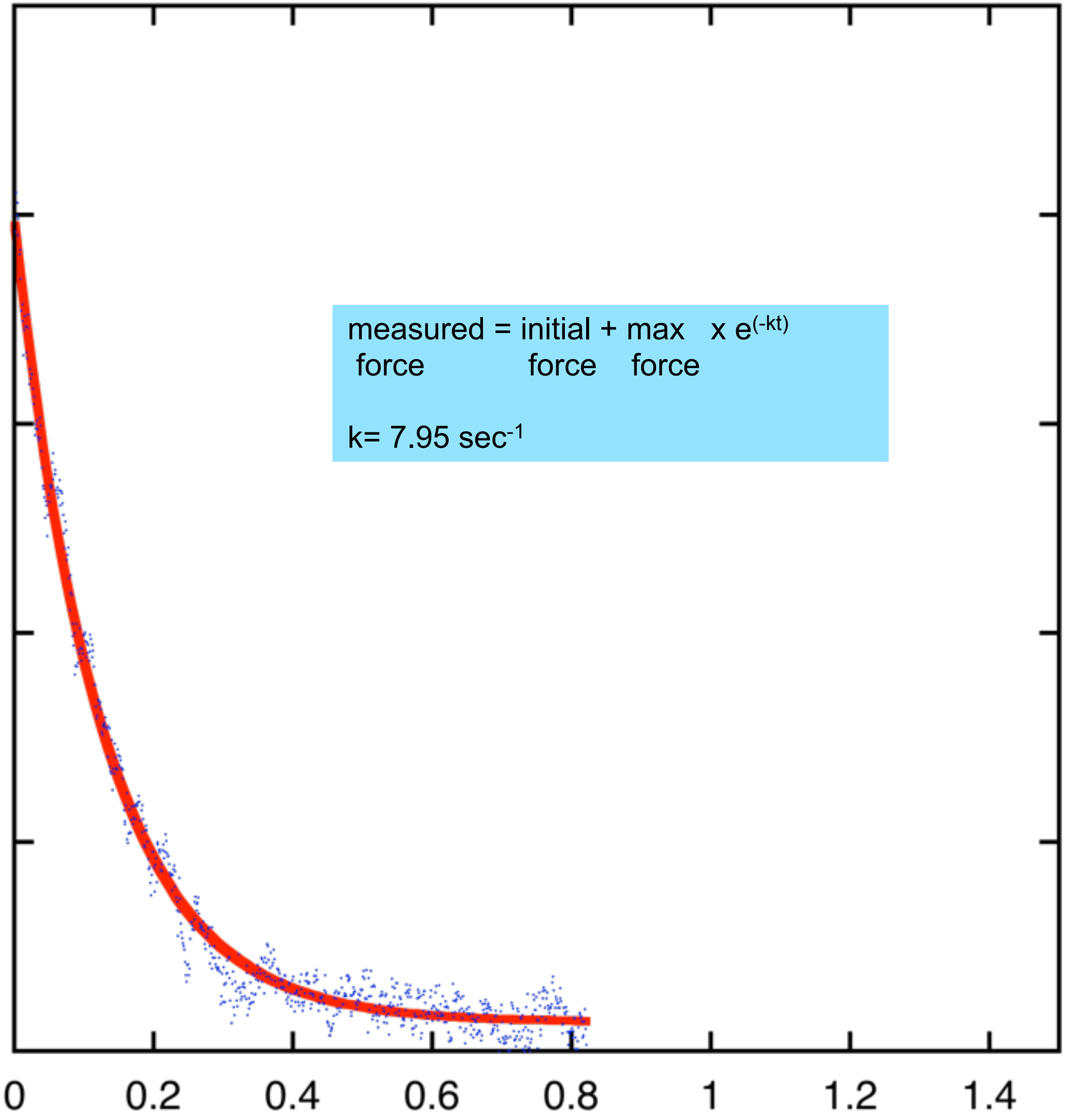
measurement of rate of a process: half life, time to maximum

Rates and equilibrium: Ca^{2+} activation of contraction and relaxation





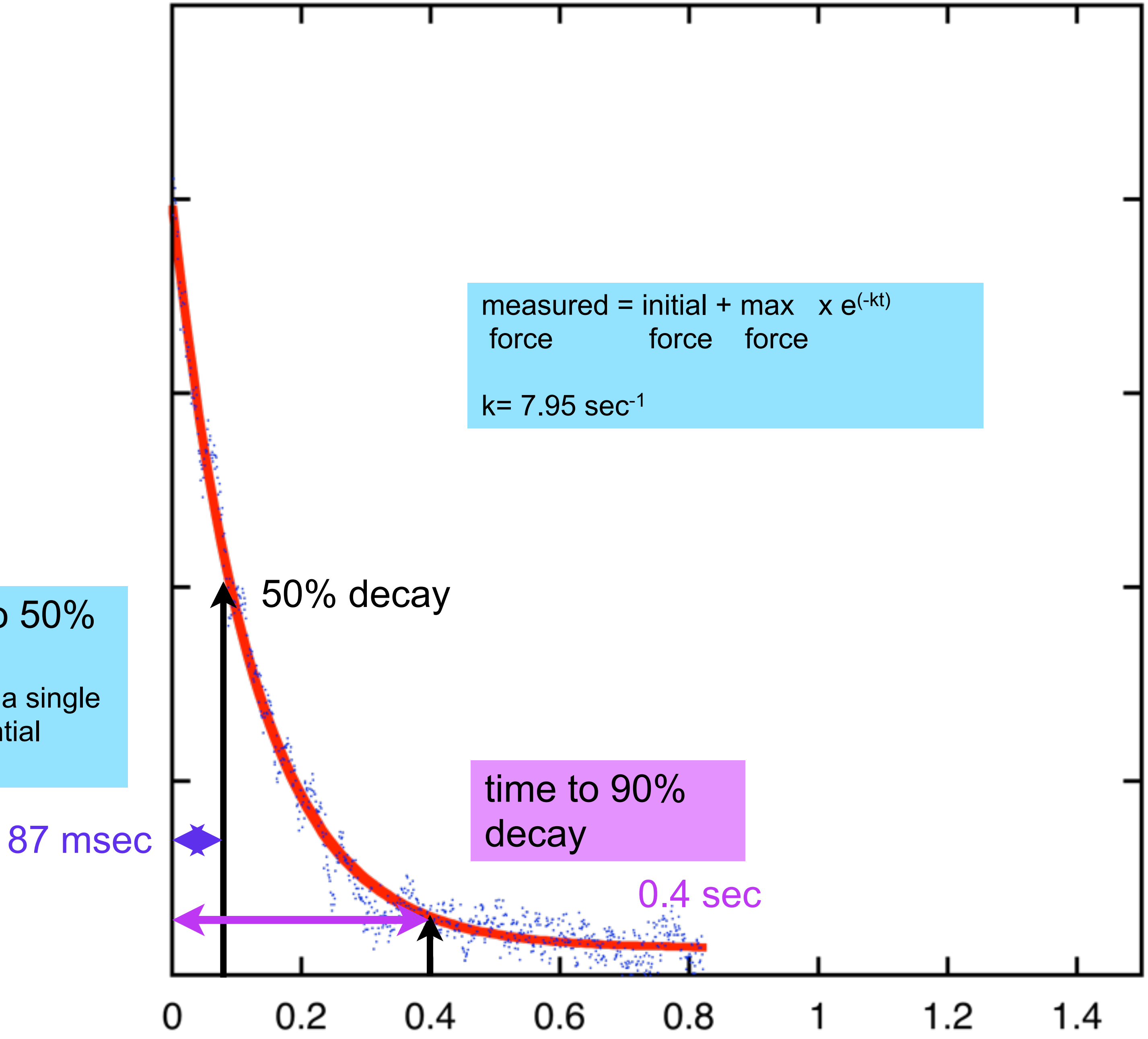
measurement of rate of a process



measured = initial + max x $e^{(-kt)}$
force force force

k= 7.95 sec^{-1}

measurement of rate of a process: single exponential



measured = initial + max x $e^{(-kt)}$
force force force

k= 7.95 sec^{-1}

50% decay

time to 50% decay
=ln2/k if a single exponential process

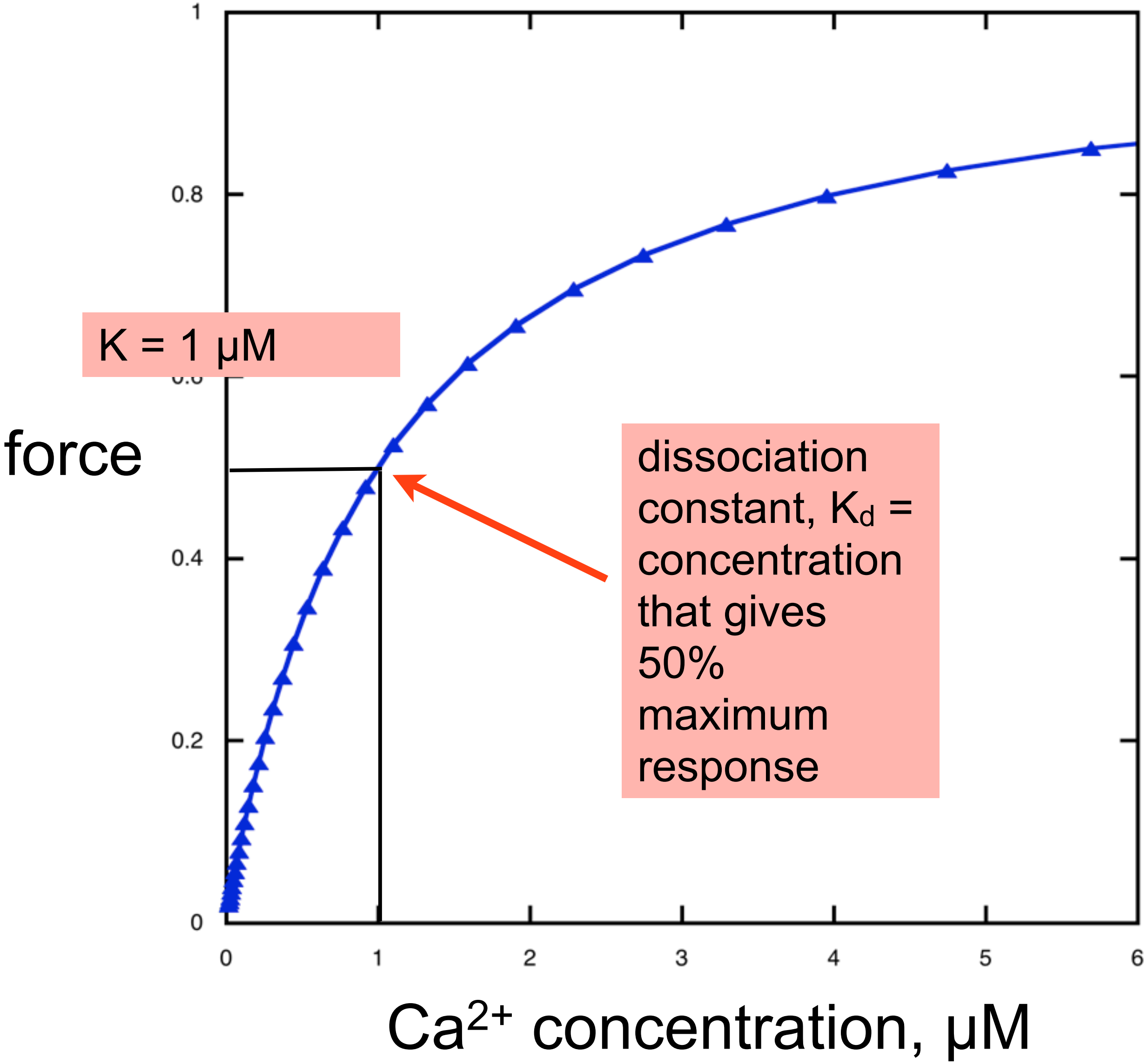
87 msec

time to 90% decay

0.4 sec

measurement of rate of a process: time to 50% and 90% decay simple dose-response curve e.g Ca^{2+} dependence of force is defined by equation

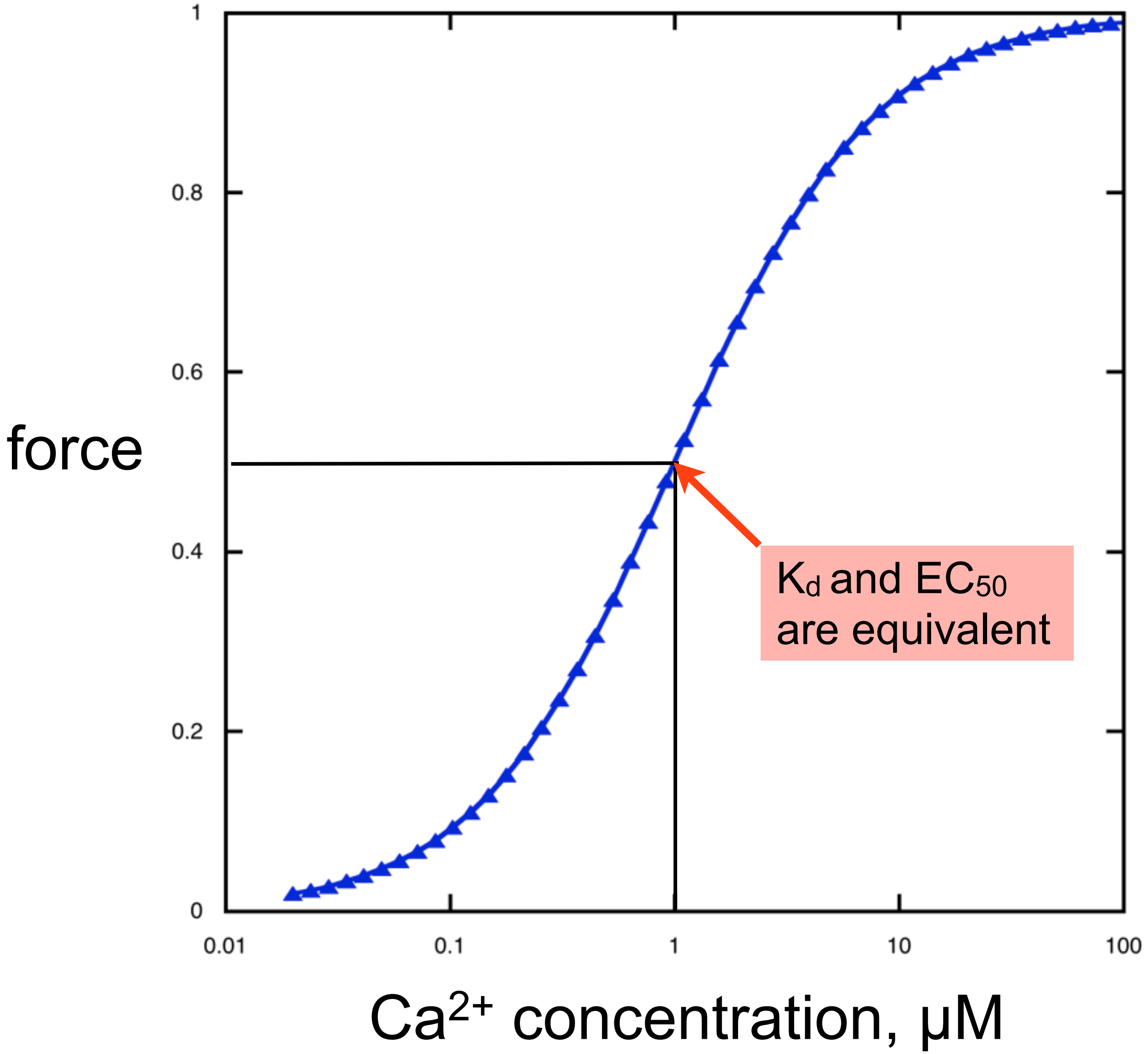
$$y = \frac{\text{Max response x dose}}{\text{constant+dose}}$$



K = 1 µM

dissociation constant, K_d = concentration that gives 50% maximum response

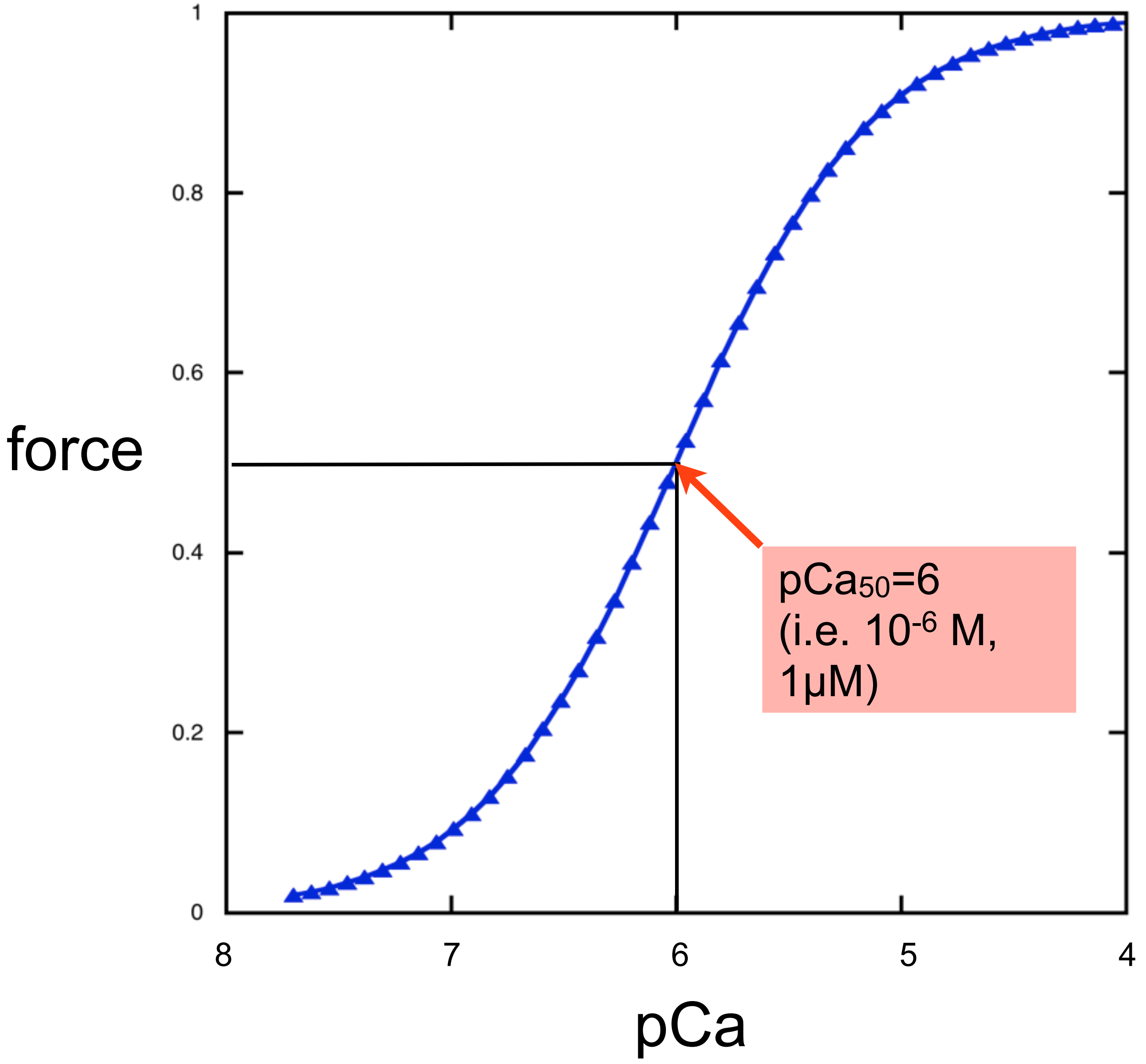
simple dose-response curve is often plotted on a log scale
The curve then appears sigmoid



K_d and EC_{50} are equivalent

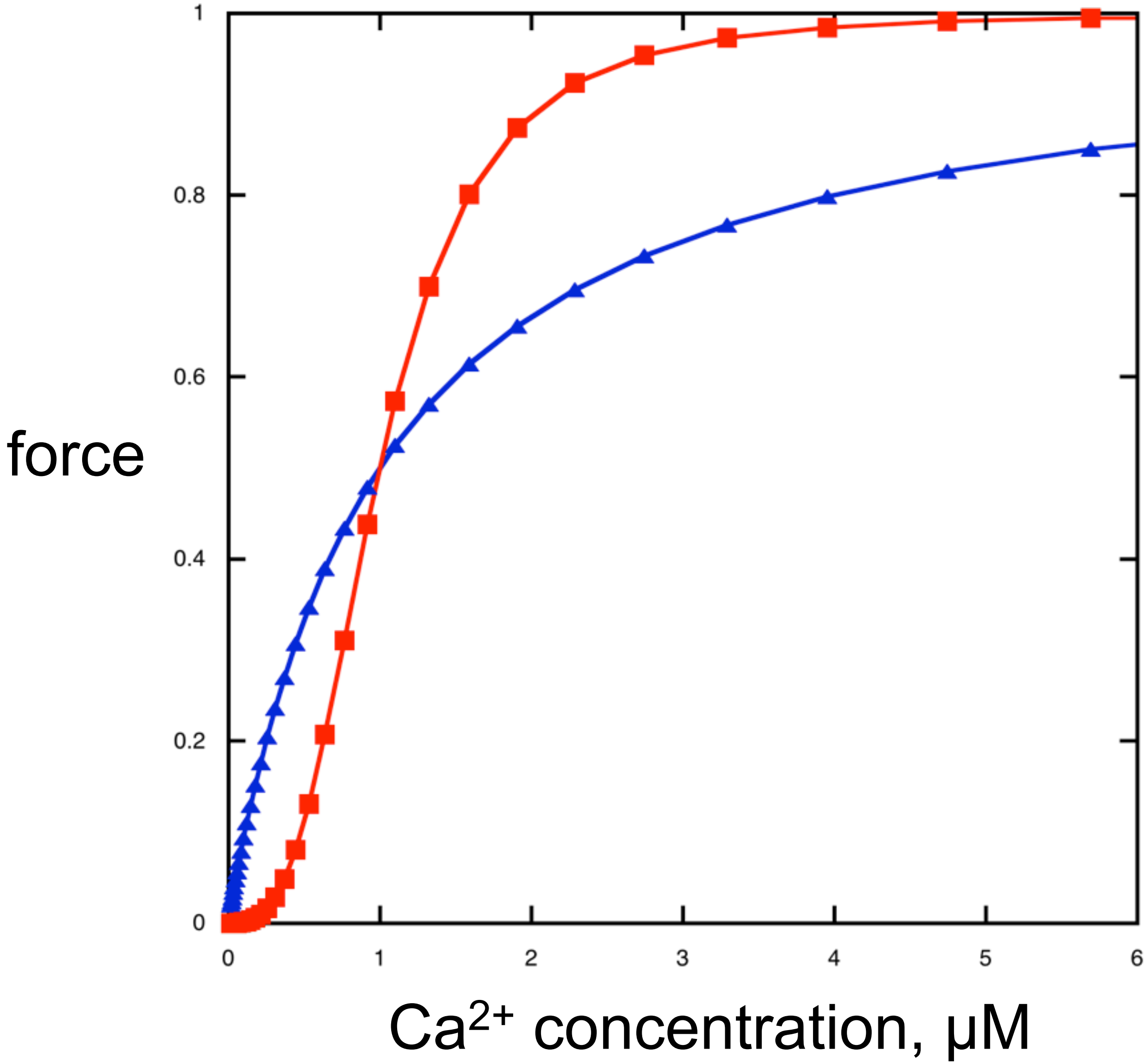
simple dose-response curve is often plotted on a log scale
Ca^{2+} concentration is often shown as pCa

pCa = - log Ca^{2+} concentration



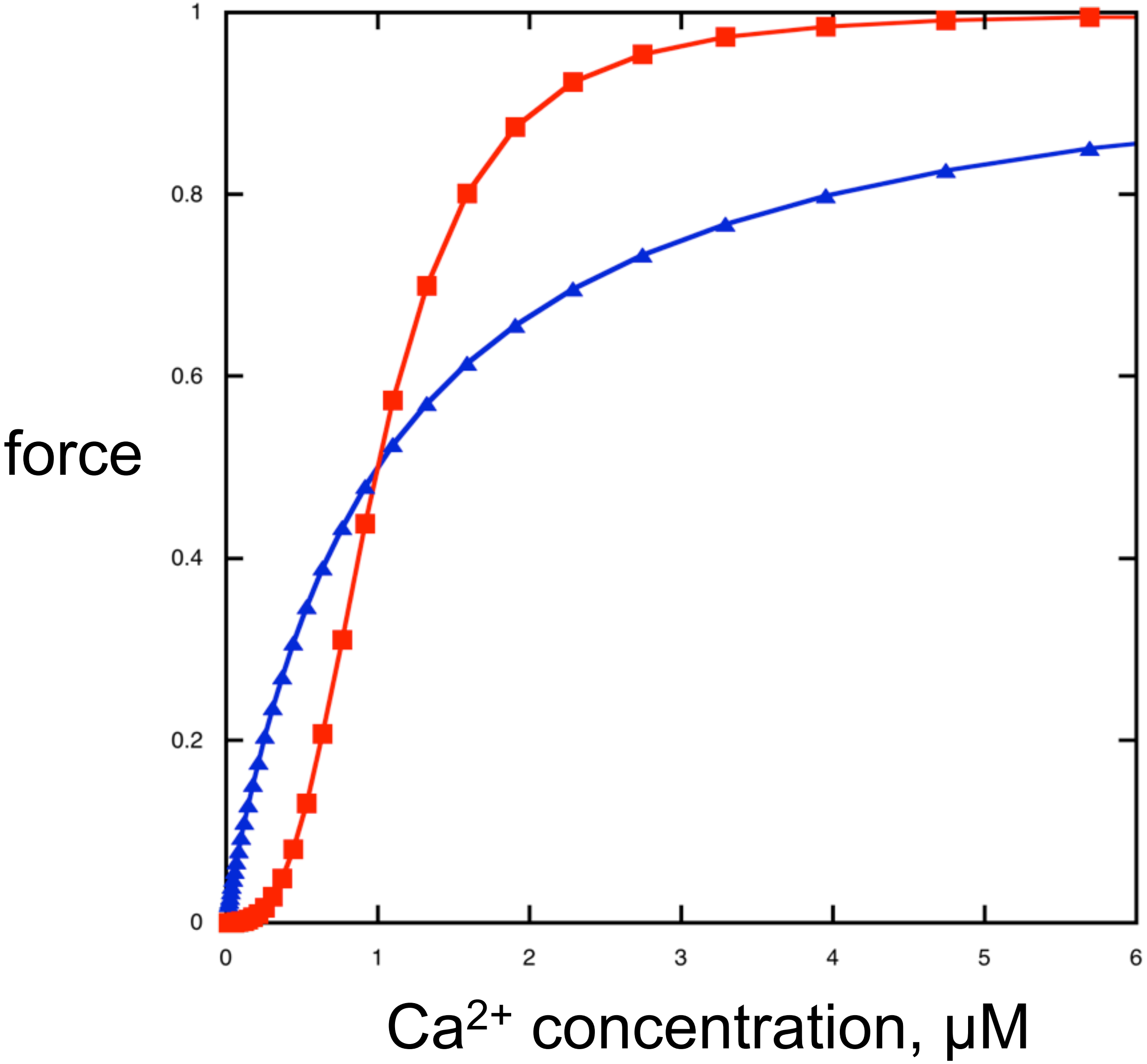
pCa_{50}=6
(i.e. 10^{-6} M,
1μM)

Often the dose-response curve cannot be described by a single constant. Most dose-response curves can be described by the **Hill equation** which introduces an extra constant, nH to account for cooperative interactions

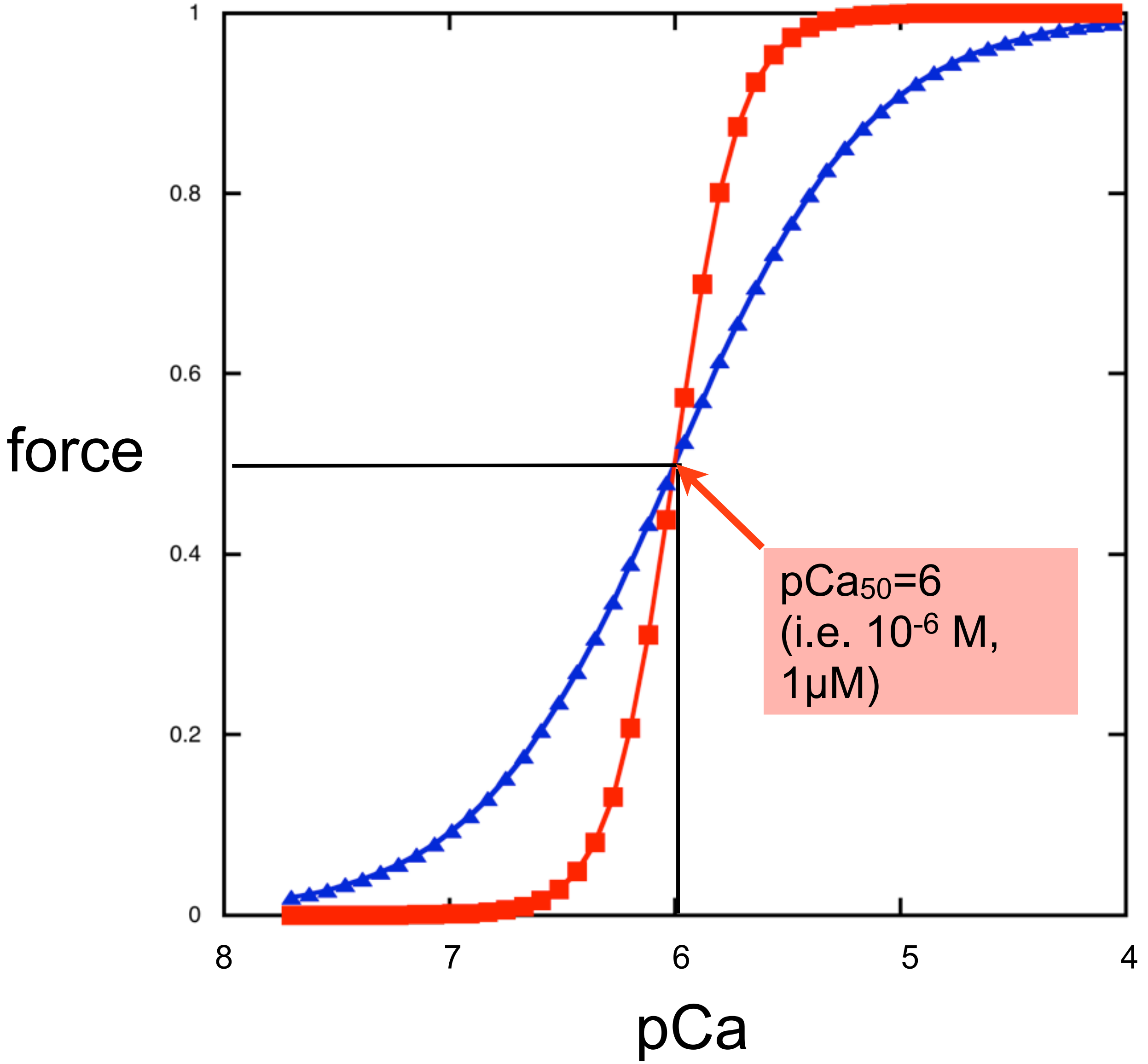


Hill equation: $$y = \frac{\text{Max response x dose}^{nH}}{\text{constant}^{nH} + \text{dose}^{nH}}$$

In this simulation nH= 3

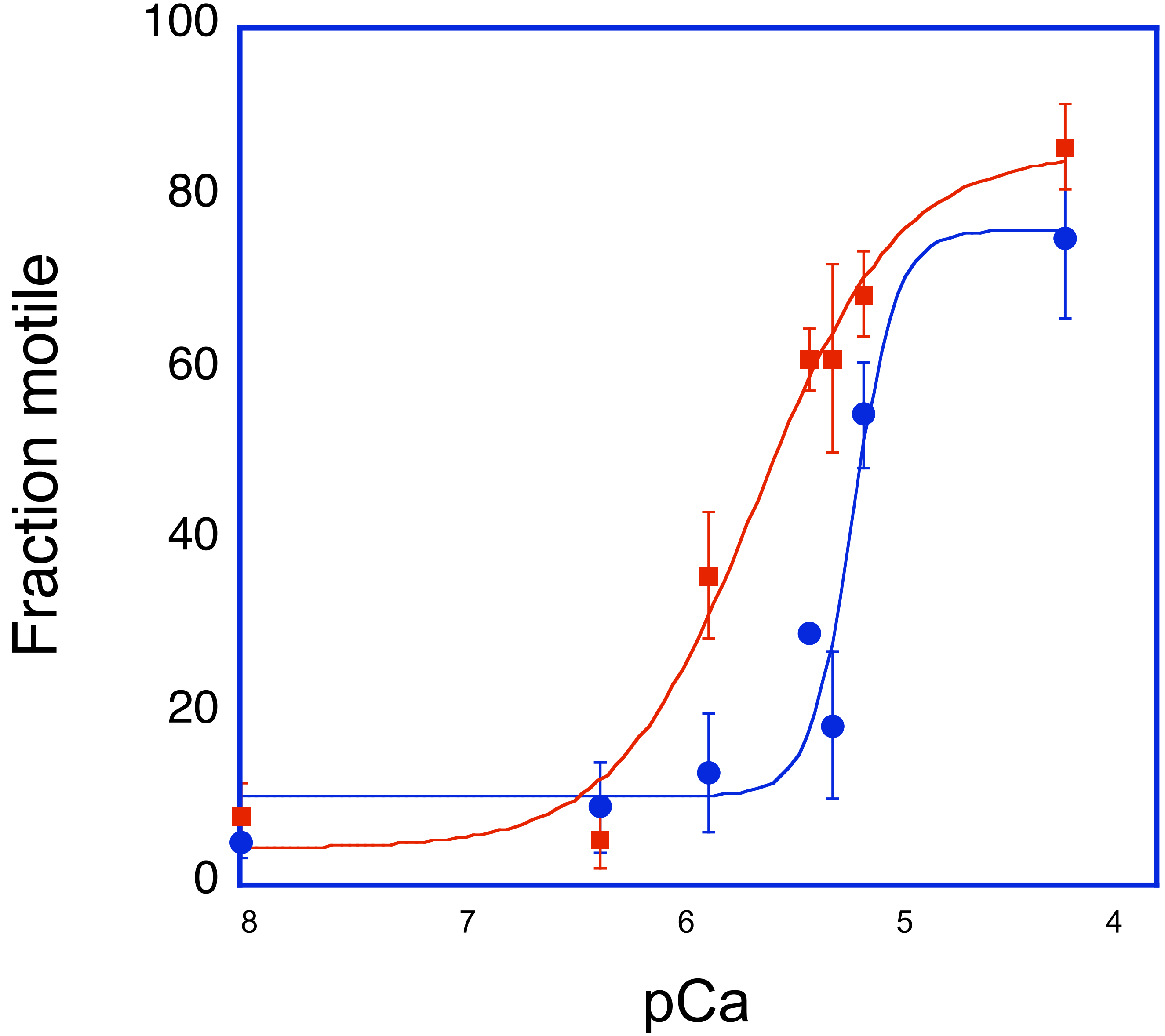


On a log scale the curve is still sigmoid but steeper. The gradient of the line at pCa_{50} equals n^H



$pCa_{50}=6$
(i.e. 10^{-6} M,
1μM)

A practical example- The Ca^{2+} activation of a reconstituted actomyosin in the in vitro motility assay. Wild-type is compared with a mutant troponin T (red) that causes hypertrophic cardiomyopathy: pCa_{50} is higher (i.e. EC_{50} is lower, Ca^{2+}-sensitivity is higher)



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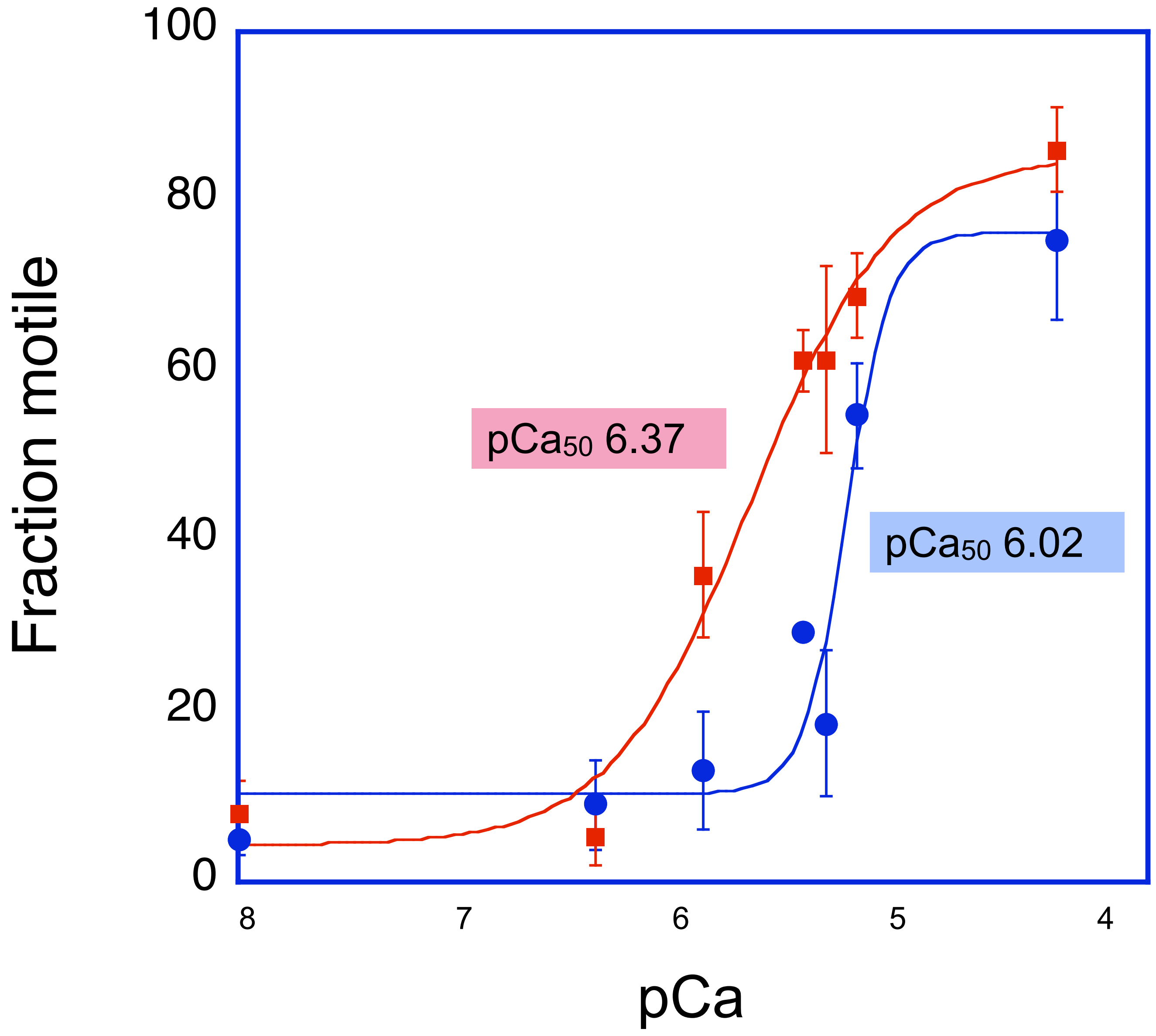

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