NMDA RECEPTORS AND THE COMPUTATIONAL PRIMITIVES OF NEURONS

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NMDA RECEPTORS AND THE COMPUTATIONAL PRIMITIVES OF NEURONS

- **VIEWPOINT: 'Electrical Engineering' (reflecting my background)**
- **MOTIVATION: Interest in computational neuroscience and *neuromorphic systems***
- **TOPIC: Characteristics of neural behavior with implications for signal processing capabilities**
  - **The characteristics I describe (e.g., *bistability*) may arise from network interactions, but I focus on the primitives associated with *individual neurons)***

Other people who have looked at this:

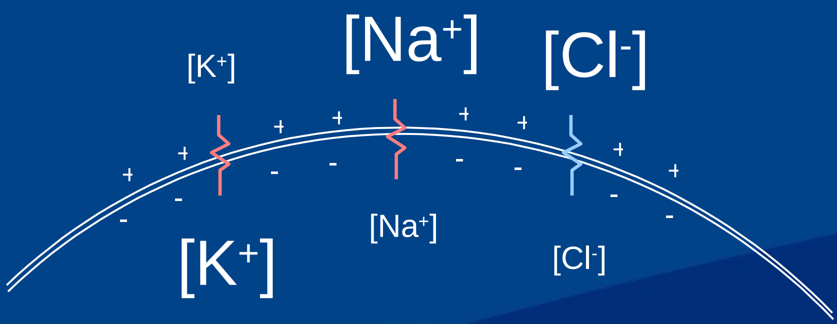
M. Lazarewicz (U. Penn.) *et al*. (-> *Neurocomputing* 69: 1025-1029, 2006)

- **Preliminary analysis of NMDA-dependent voltage bistability in dendritic compartments**

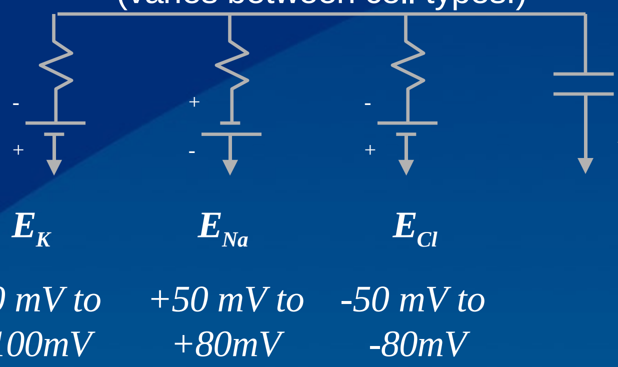
J. Schiller (Technion) *et al*.

- **Experimental evaluation of bistability in mammalian cortical neurons**

ELECTRICAL SIGNALS IN NEURONS



Typical V_m at rest: -50 to -80 mV
(varies between cell types!)



Weighted sum approximation to Goldman-Huxley-Katz Equation:

Potential of inside of neuron with respect to outside:

$$V_m = \frac{G_K E_K + G_{Na} E_{Na} + G_{Cl} E_{Cl}}{G_K + G_{Na} + G_{Cl}}$$

G => membrane conductance

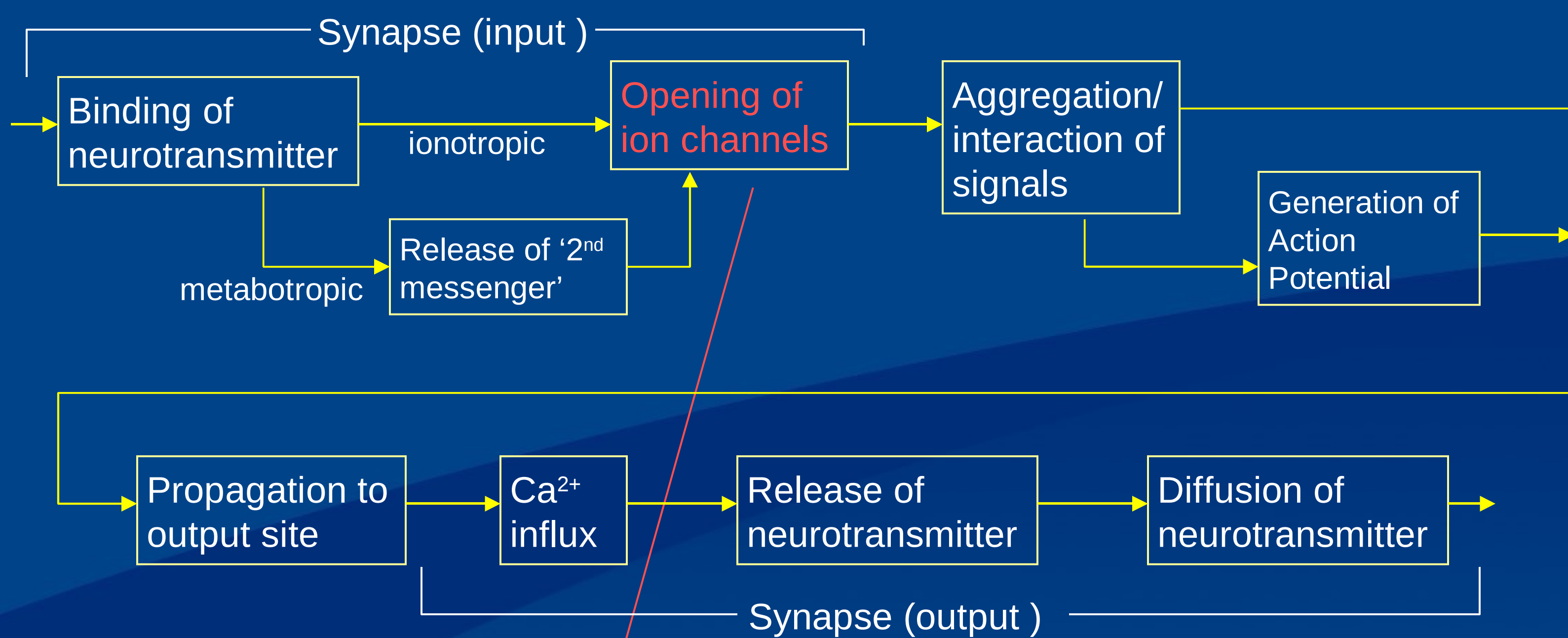
E => ionic reversal potential

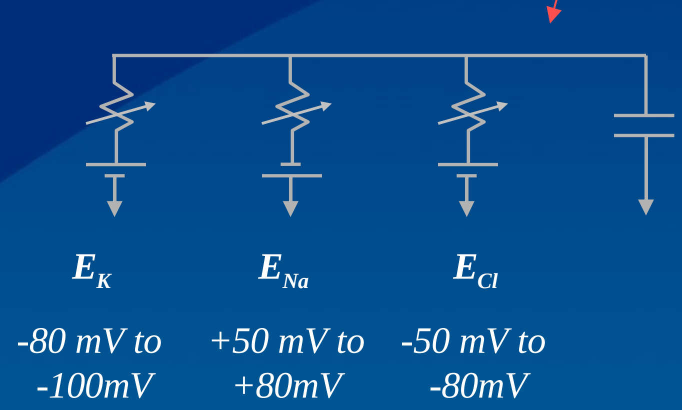
(each specific to ionic species)

Equivalent electrical circuit

Membrane Potential ⇔ State of Neuron

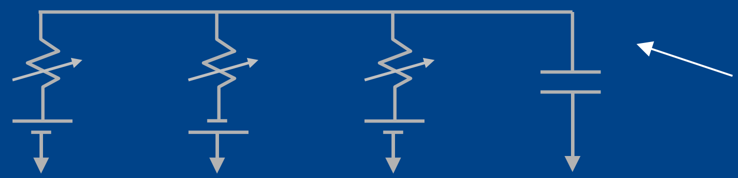
ELECTRICAL SIGNALS / SIGNAL PROCESSING IN NEURONS





- *Excitation* => depolarization (membrane potential ↑, e.g., by ↑ G_{Na})
  - Results in neurotransmitter release
- *Depolarizing Inhibition* (membrane potential ↓, e.g., by ↑ G_K)
- *Shunting Inhibition* => (by ↑ G_{Cl}): Little change in V_m, but ↓ sensitivity to other ΔG

ELECTRICAL SIGNALS / SIGNAL PROCESSING IN NEURONS



E_K E_{Na} E_{Cl}

-80 mV to -100mV *+50 mV to +80mV* *-50 mV to -80mV*

LOOK INITIALLY AT SIMPLE *SINGLE COMPARTMENT* MODEL (NEURON = SINGLE ELECTRICAL NODE)

A FEW NOTES:

Many important classes of ion channels approximately linear (i.e., *ohmic*) over limited range: membrane leakage conductances, & AMPA, kainate, $GABA_A$ synaptic receptors;

Note this implies a *sublinear* relationship between input signal and neuron state!

$$V_m = \frac{G_K E_K + G_{Na} E_{Na} + G_{Cl} E_{Cl}}{G_K + G_{Na} + G_{Cl}}$$

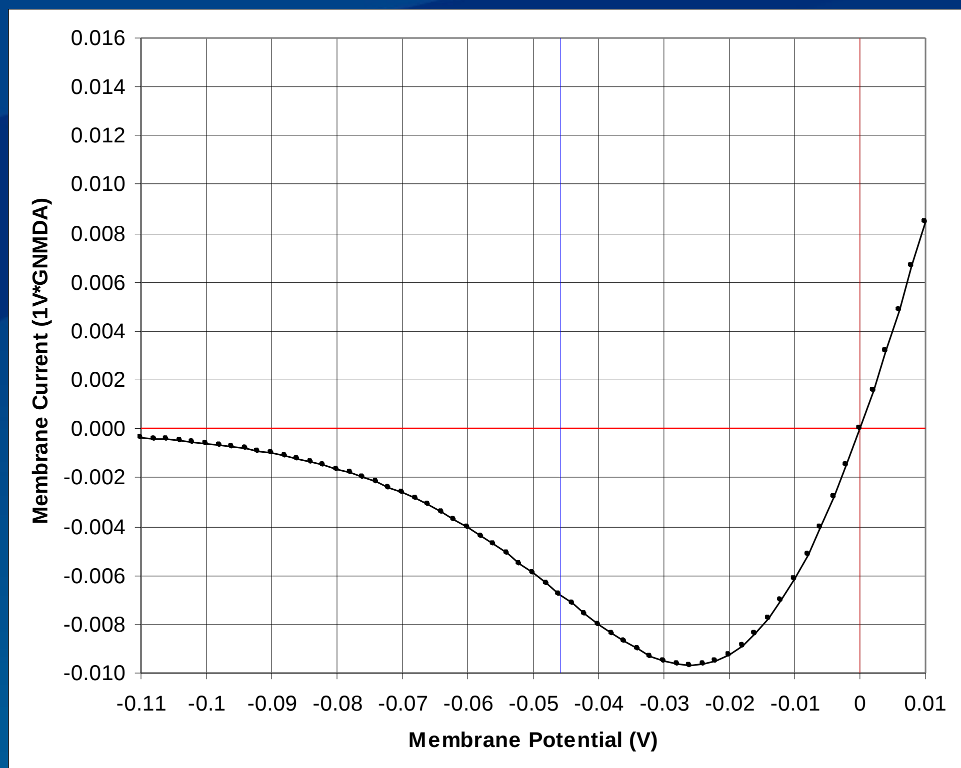
Some channels, however, are significantly non-ohmic under physiological conditions.

Current-voltage relation for NMDA receptor channels is nonlinear / nonmonotonic:

Jahr-Stevens* Model for macroscopic I-V dependence:

$$I_{NMDA} = G_{NMDA} \cdot \underbrace{V_m \Big/ (1 + c \cdot [\,Mg^{2+}\,] \cdot exp(-V_m / v_N))}_{F(V_m)}$$

- Reversal potential near 0V
- Current magnitudes at negative potentials reduced by magnesium blockade



At:

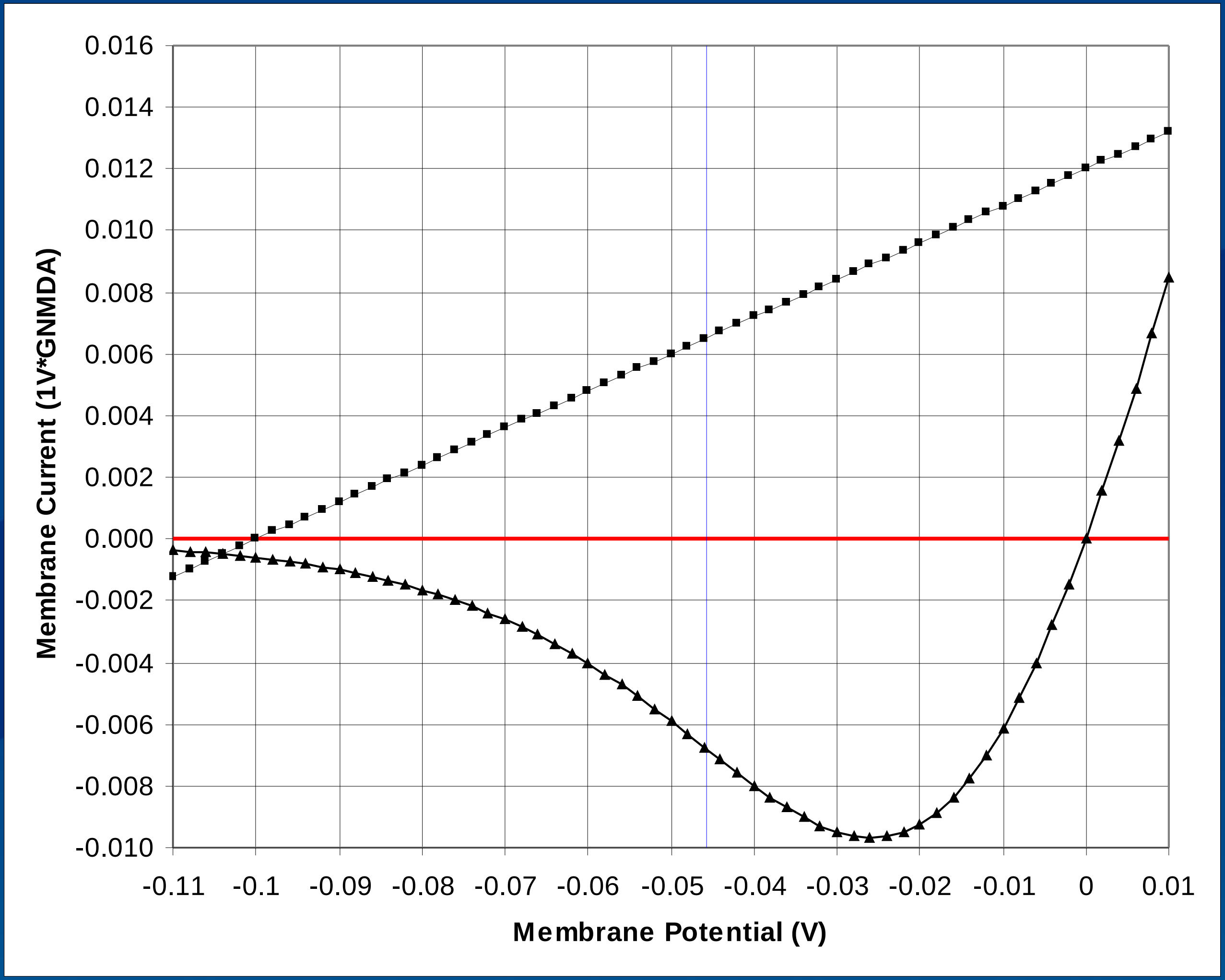
$[Mg^{2+}]$ = 1.2mM

c = 0.28mM^{-1}

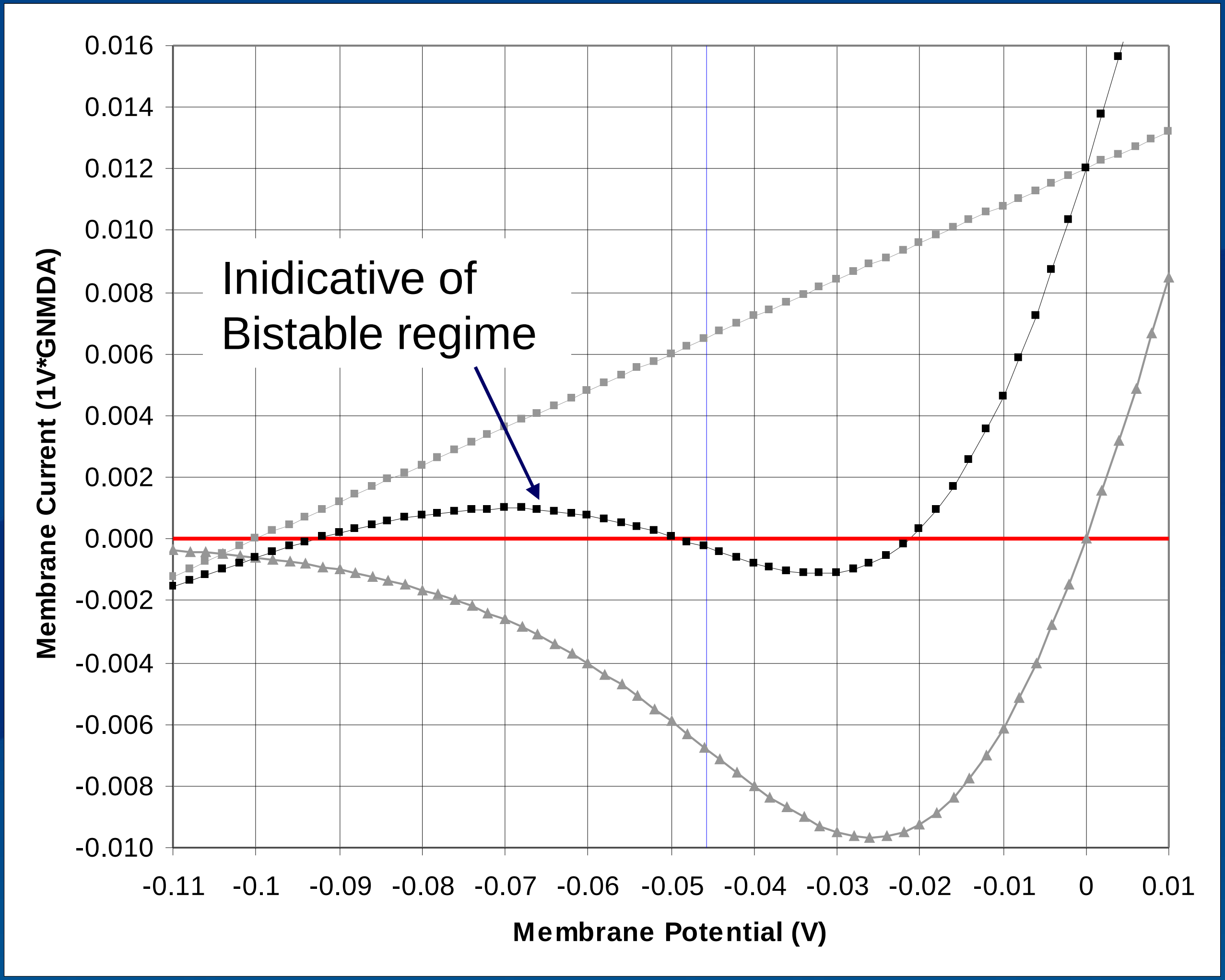
v_N = 16mV

C. Jahr & C. Stevens,
Journal of Neuroscience
10: 3178-3182, 1990

Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



Bistability: Capacity of a system to exist in either of two stable states when at equilibrium

NOTE: The existence of bistable regimes can profoundly affect the behavior of a system when *not* at equilibrium!

Current balance in a single electrical compartment:

$$\underbrace{(\textit{Non-NMDA current}) + G_{NMDA}\cdot F(V_m)}_{=\,0 \text{ at equilibrium}} + C\, dV_m/dt = 0$$

Consider NMDA receptor conductance in combination with ohmic membrane conductances

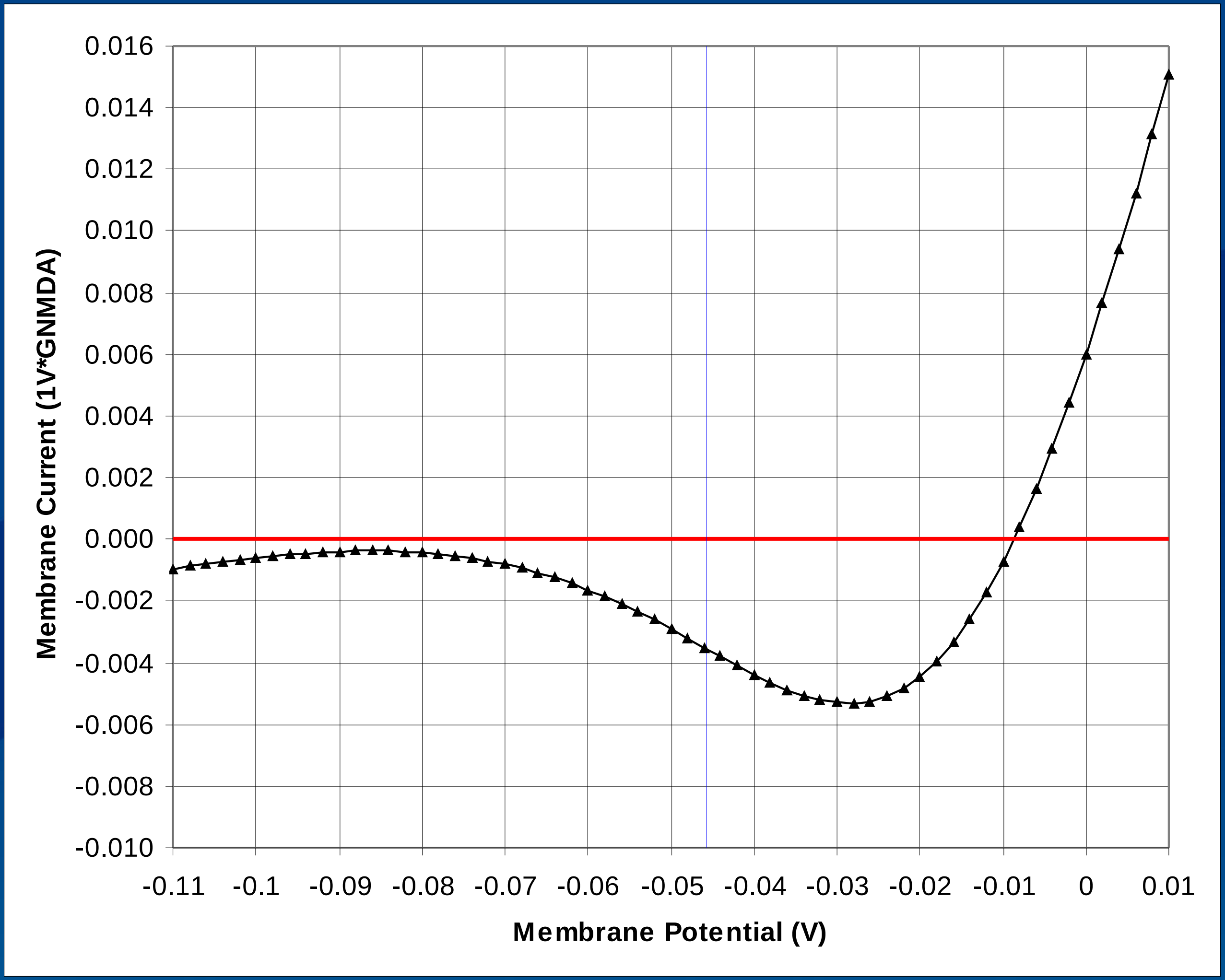
GROUP OHMIC CONDUCTANCES TOGETHER:
Compute total, instantaneous ohmic conductance
and define 'equivalent reversal potential':

$$G_O \equiv \sum_{i=1}^{n} G_i \quad \text{and} \quad V_{rO} \equiv \sum_{i=1}^{n} G_i V_{ri} \Big/ \sum_{i=1}^{n} G_i$$

Current balance in an electrical compartment becomes:

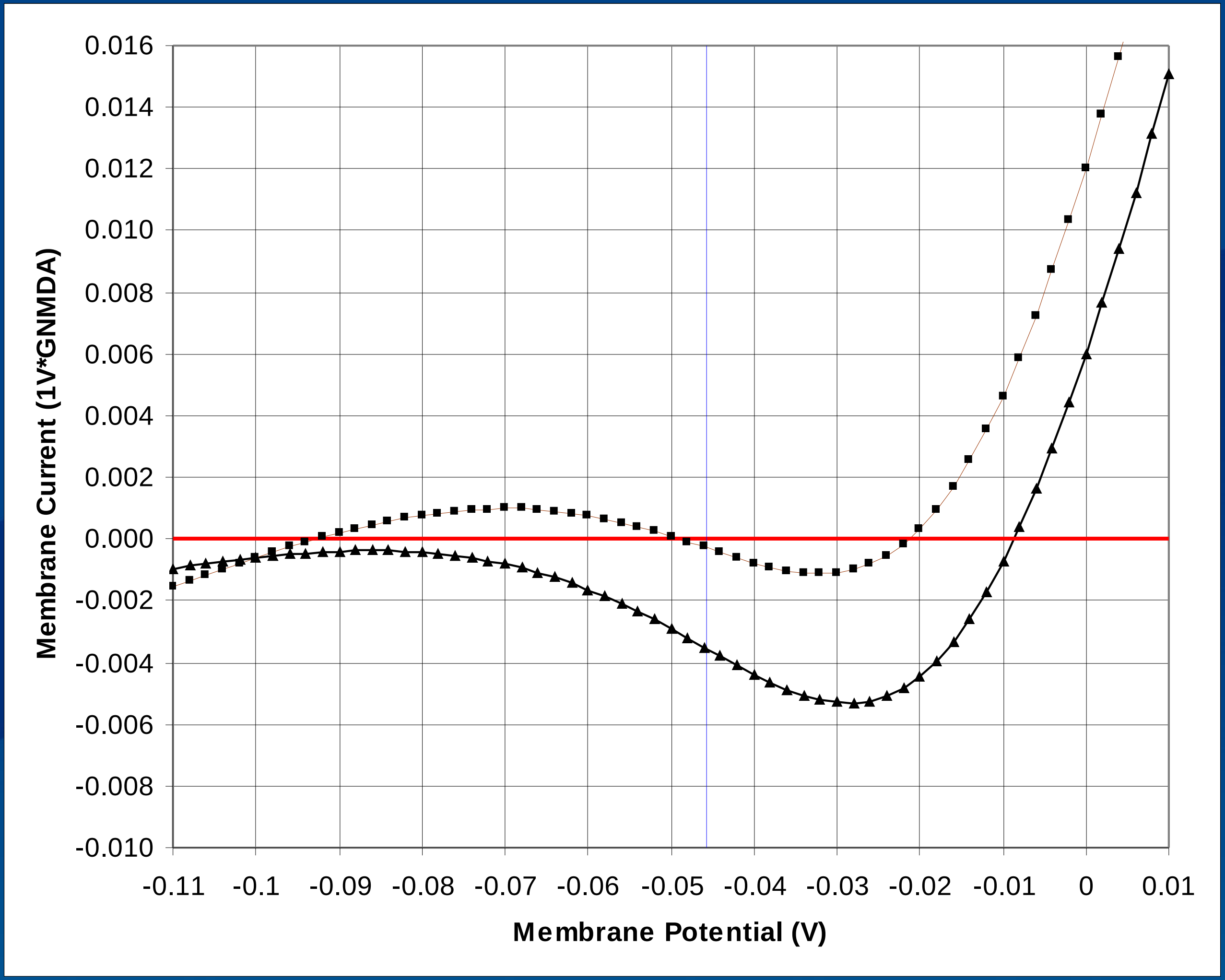
$$\underbrace{G_O(V_m - V_{rO}) + G_{NMDA} F(V_m)}_{= 0 \text{ at equilibrium}} + C\, dV_m / dt = 0$$

Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



(V_{rO} = -100mV; Ohmic conductance increasing)

Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



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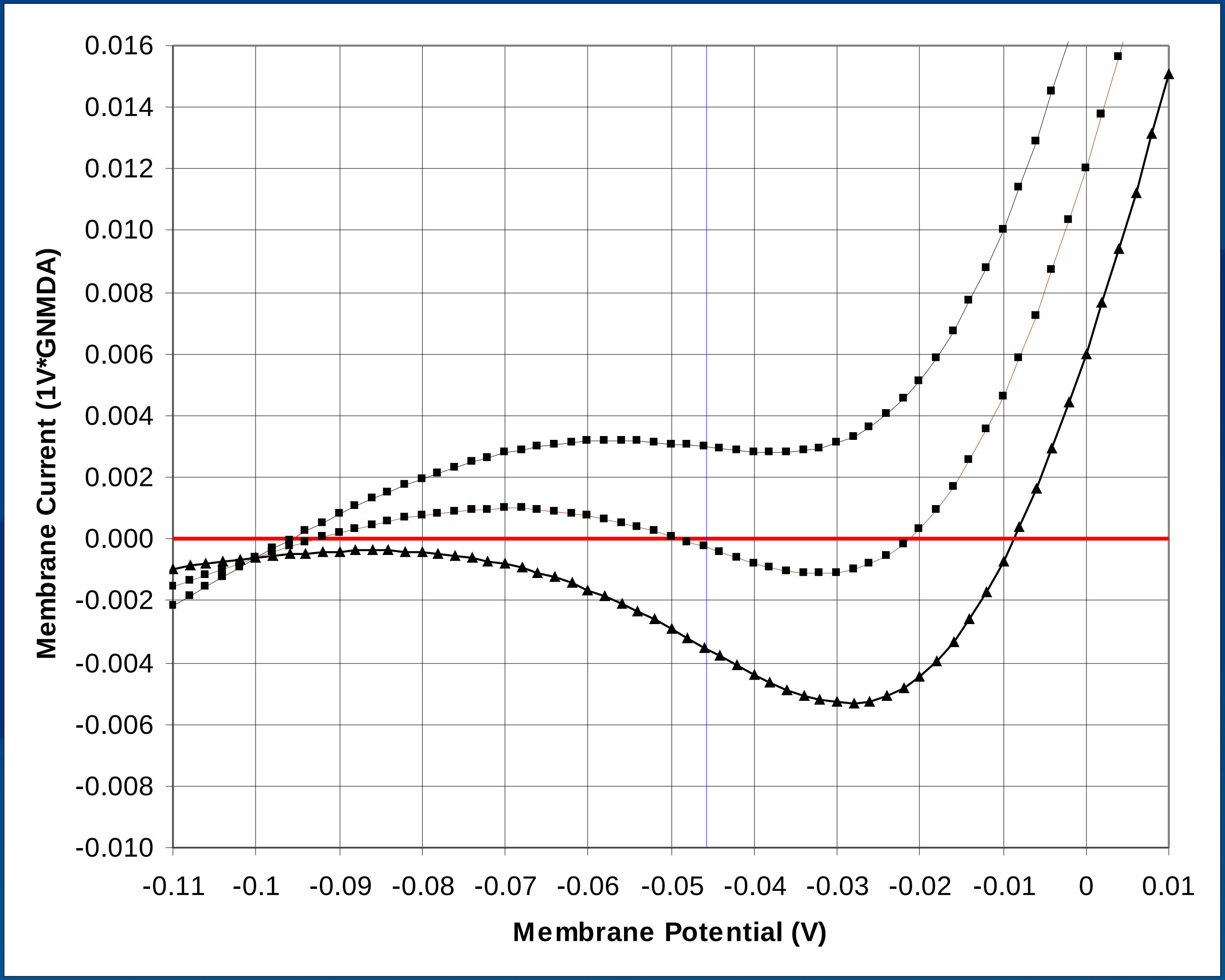

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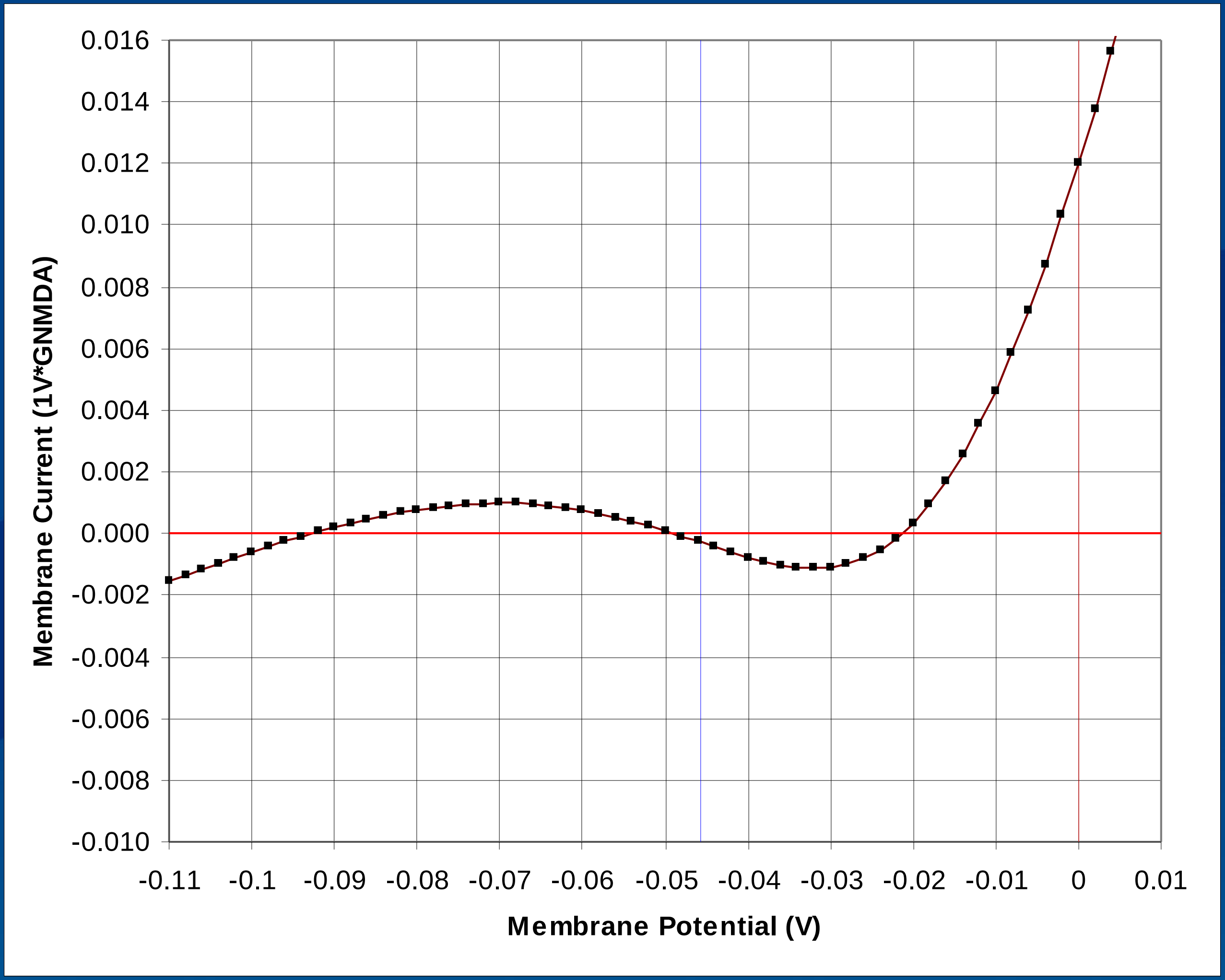
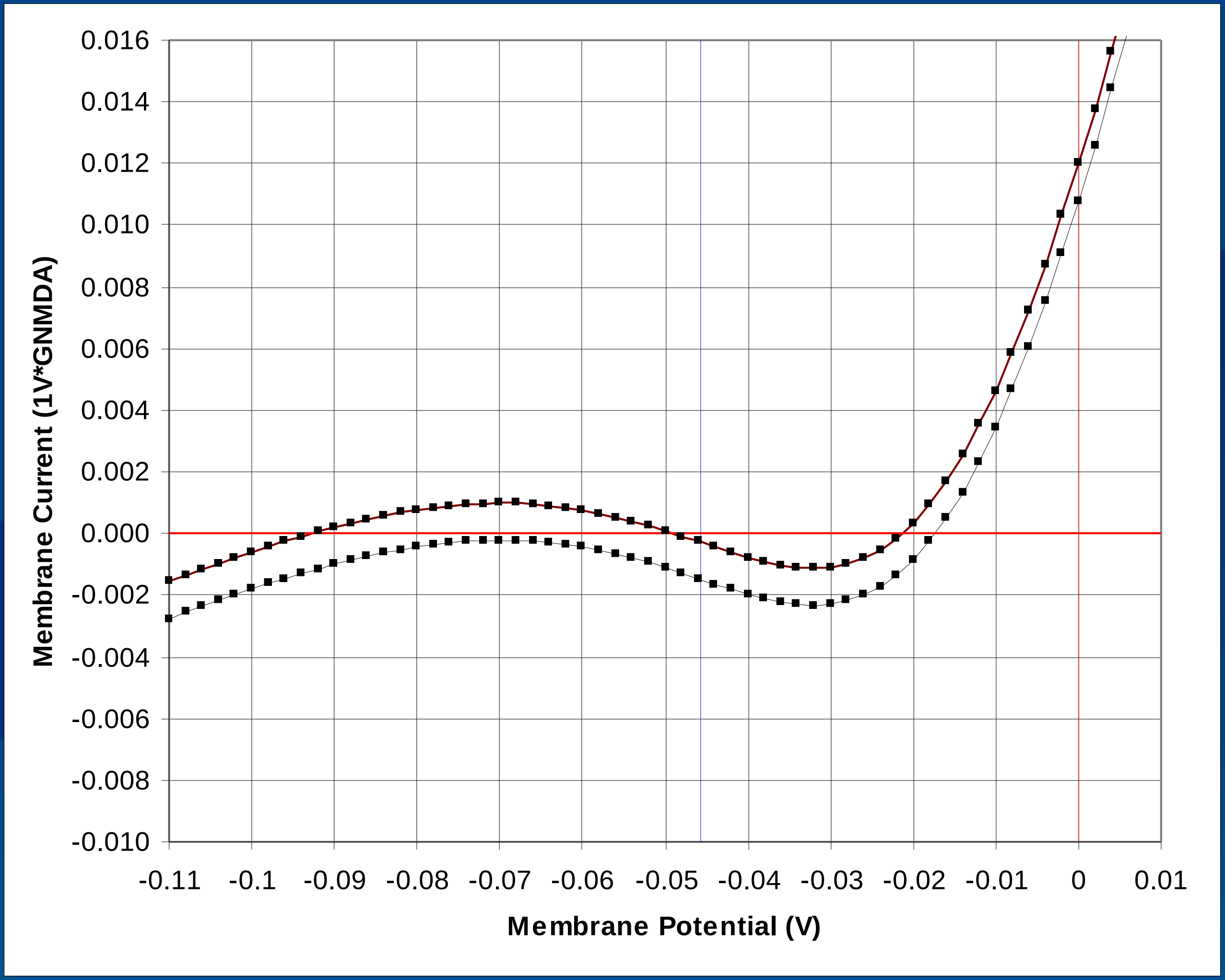


(G_O = 0.12*G_{NMDA}; equivalent reversal potential increasing)

Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



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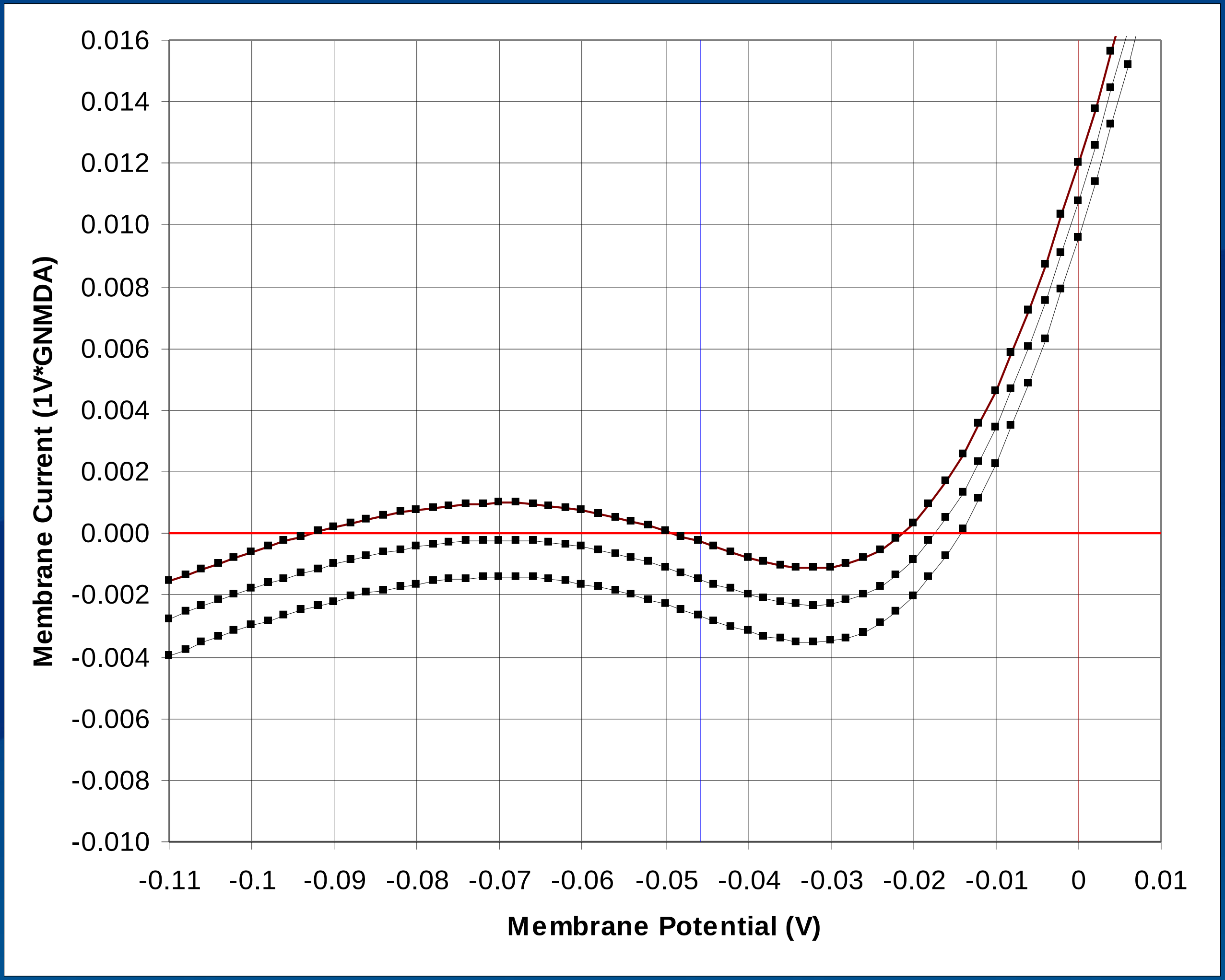
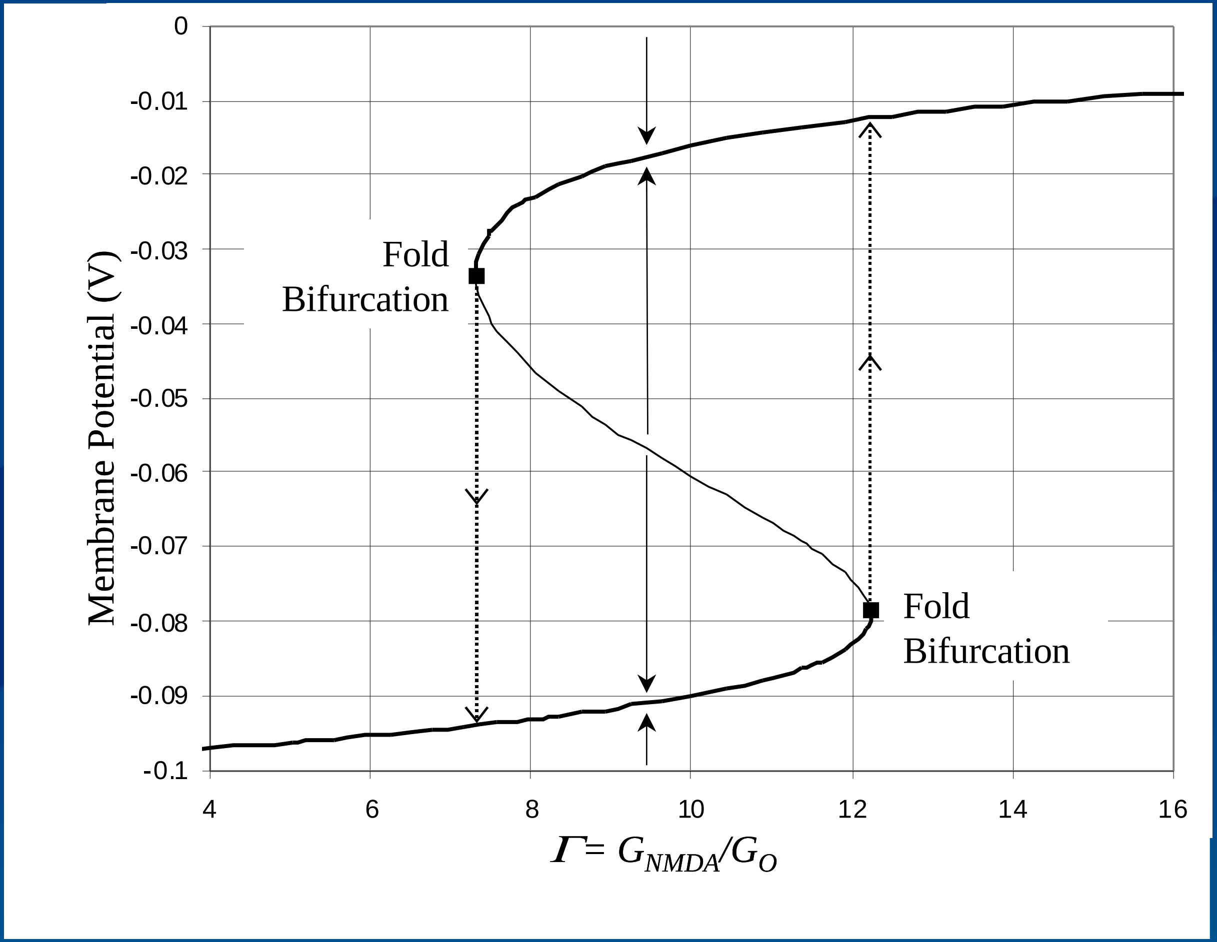
Current-voltage relation for an electrical compartment with NMDA and ohmic membrane conductances



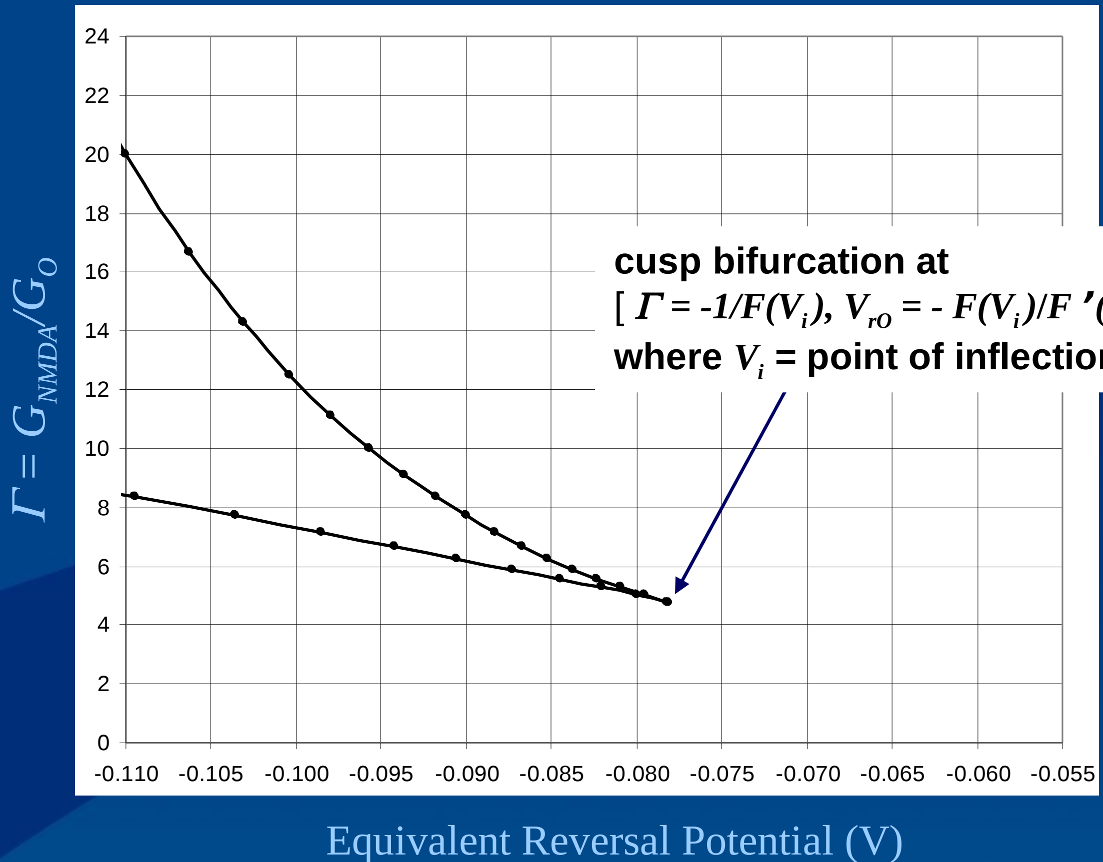
($G_O = 0.12 * G_{NMDA}$; equivalent reversal potential increasing)

Equilibrium Manifold:



(At V_{rO} = -100mV)

Region of bistability in an electrical compartment with NMDA and Ohmic conductances



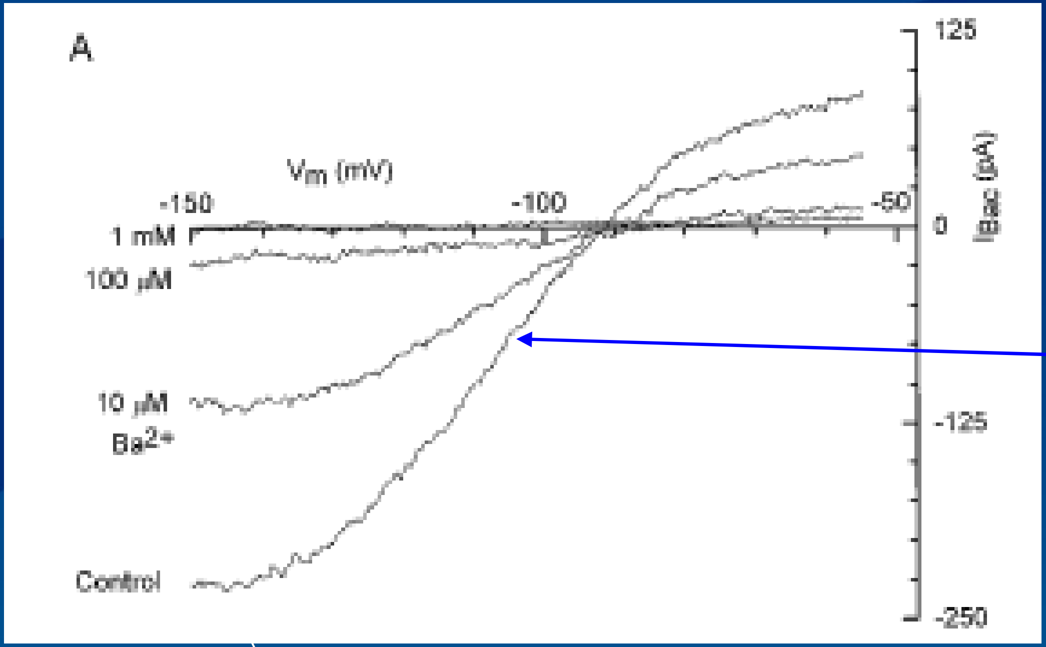
cusp bifurcation at
[$\Gamma = -1/F(V_i)$, $V_{rO} = -F(V_i)/F'(V_i)$],
where V_i = point of inflection of $F(V_m)$

Maximum equivalent reversal potential permitting bistability: ~ -78mV **(varies between -65mV and -80mV for putative physiological 'v_N' values)**

NMDA receptors + Ohmic conductances support bistability in a small region of parameter space, at membrane potentials below typical resting potentials.

Inward-rectifying potassium (Kir) channels :

- Part of resting potassium conductance
- Evidence is accumulating that *$GABA_B$ receptors* activate Kir channels*
  - $GABA_B$ = important class of inhibitory synapses
  - Neurotransmitter = γ-aminobutyric acid
  - Receptors activate ion channels via 'second messenger'



'Control' curve = Kir channel current/voltage relation in hippocampal neurons

*D. Sodickson & B. Bean, *Journal of Neuroscience* 16: 6374-6385, 1996

*T. Tabata et al., *Journal of Physiology* 563.2: 443-457, 2005

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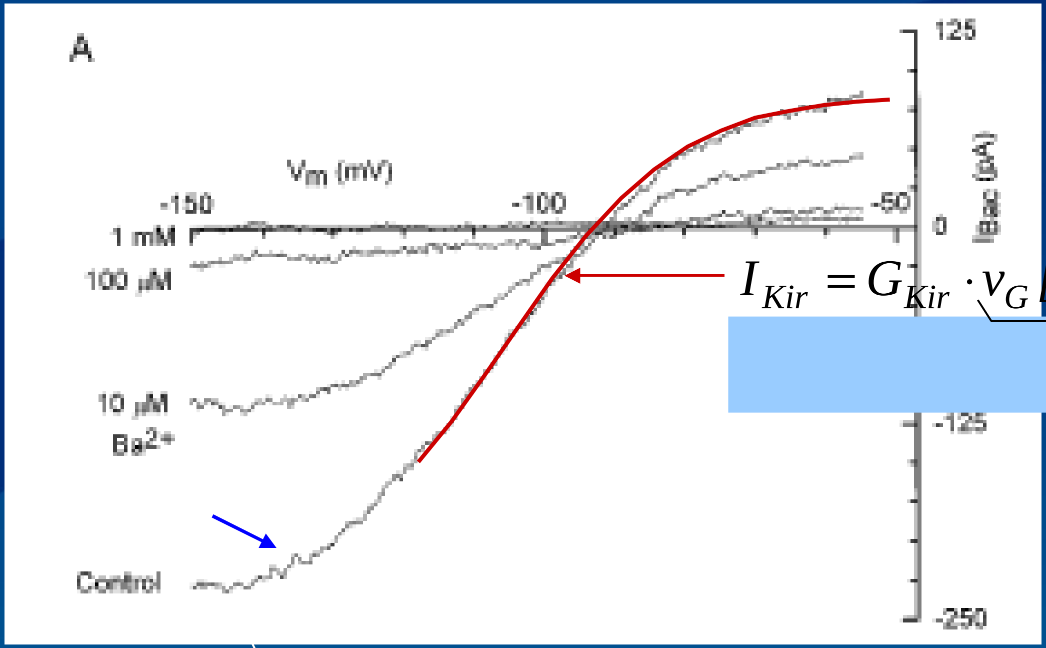


Hand fit with a function:

$$I_{Kir} = G_{Kir} \cdot v_G \underbrace{[\tanh((V_m - b)/v_G) - d]}_{H(V_m)}$$

v_G = 25mV

$b = V_{rK}$ – 13.8mV

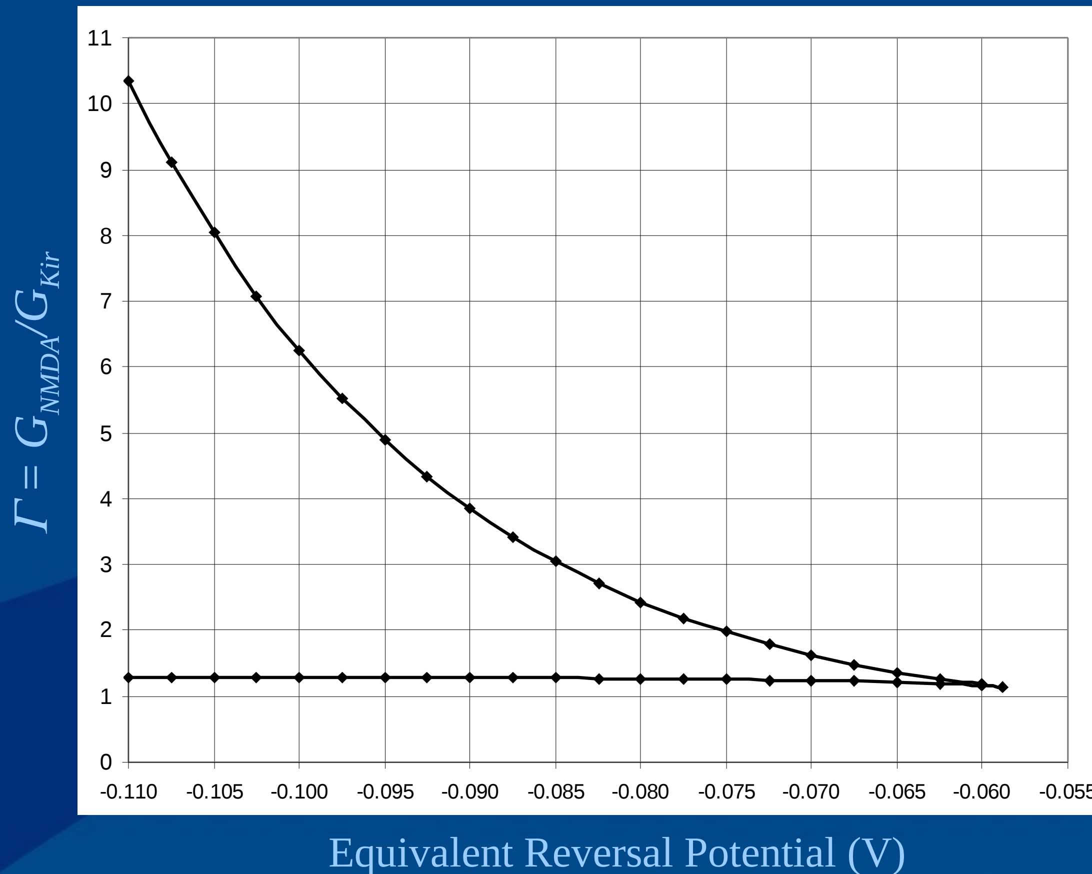
(V_{rK} = rev. potent. K^+
= -93mV in this case)

d = -0.5

*D. Sodickson & B. Bean, *Journal of Neuroscience* 16: 6374-6385, 1996

*T. Tabata *et al*., *Journal of Physiology* 563.2: 443-457, 2005

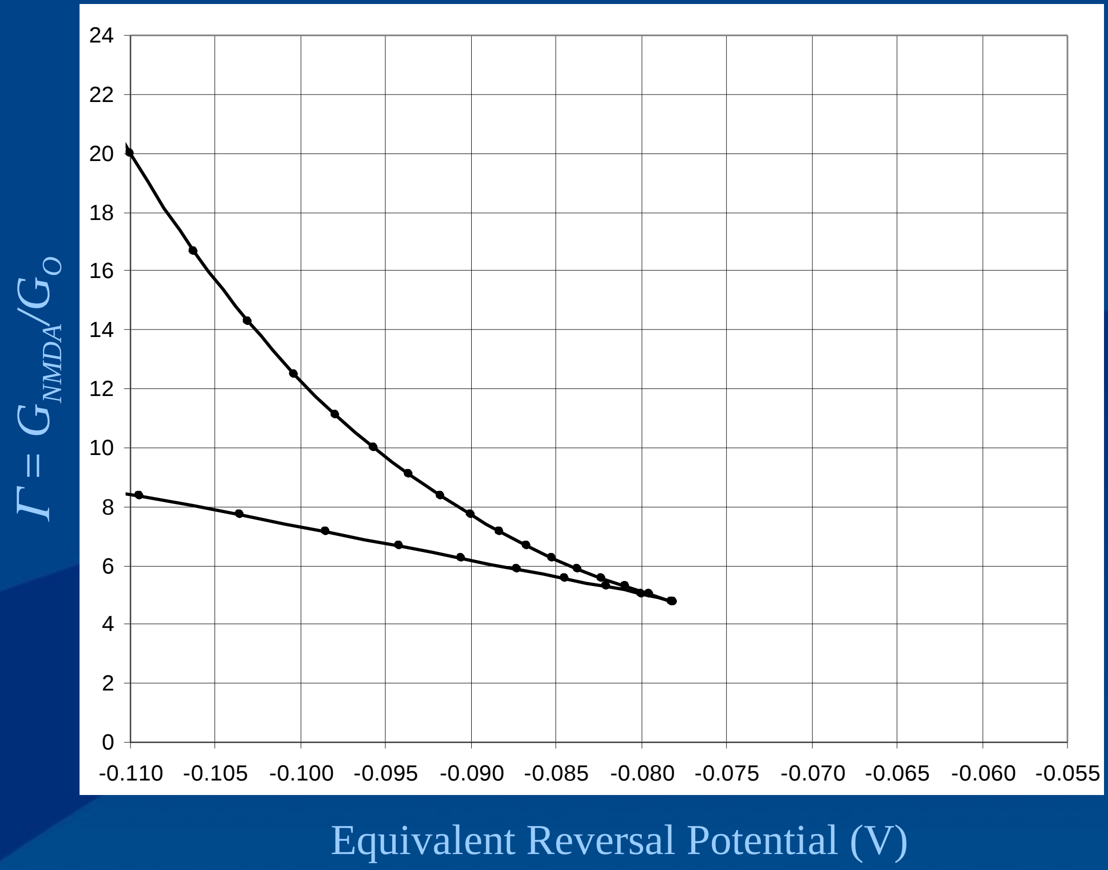
INITIAL RESULTS: Region of bistability in an electrical compartment with NMDA and Kir conductances



Maximum equivalent reversal potential permitting bistability: ~ -58mV

NMDA receptors + inward-rectifying potassium conductance support bistability in a broader region of parameter space, and at membrane potentials around typical resting potentials.

Region of bistability in an electrical compartment with NMDA and Ohmic conductances



Maximum equivalent reversal potential permitting bistability: ~ -78mV (varies between -65mV and -80mV for putative physiological 'v_N' values)

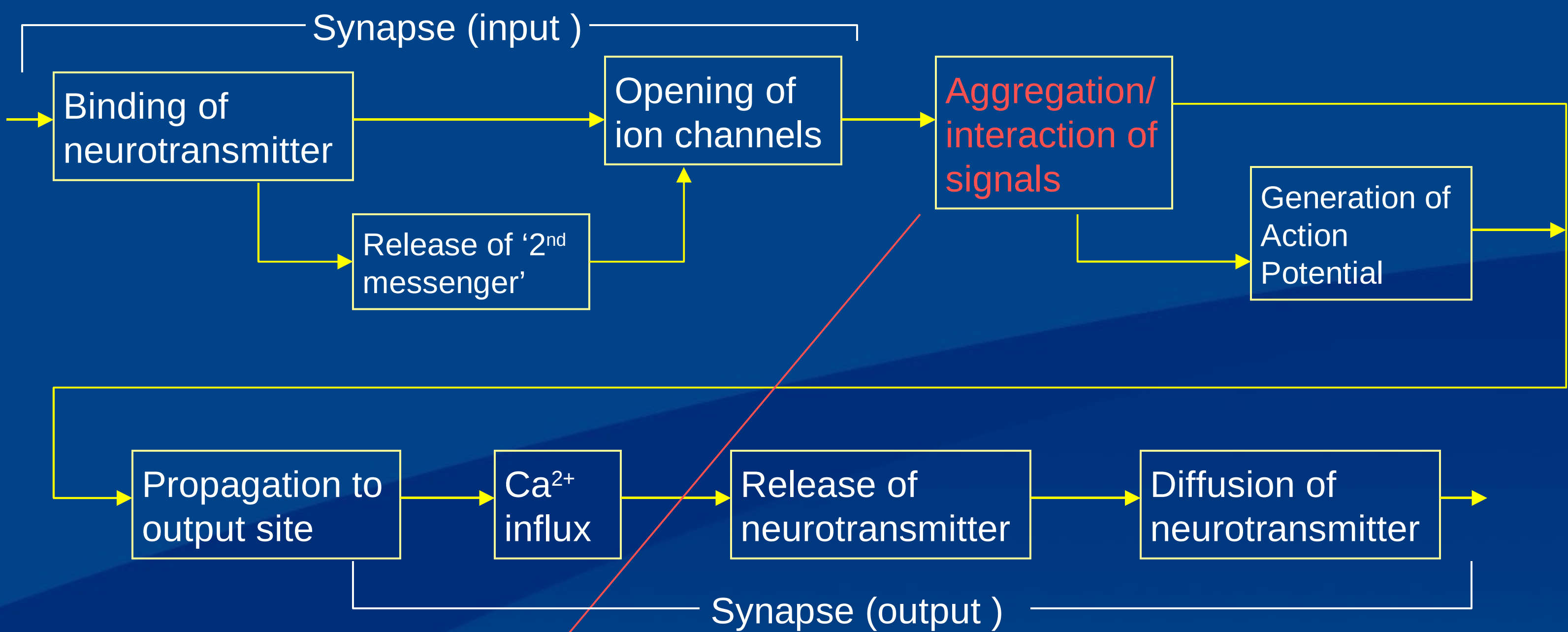
NMDA receptors + Ohmic conductances support bistability in a small region of parameter space, at membrane potentials below typical resting potentials.

INITIAL RESULTS: Region of bistability in an electrical compartment with NMDA and Kir conductances

- **Results from here to end obtained for *ohmic* potassium conductances**

- **Expect similar results to hold (but with broader regions of bistability) for nonlinear Kir conductances**

ELECTRICAL SIGNALS / SIGNAL PROCESSING IN NEURONS



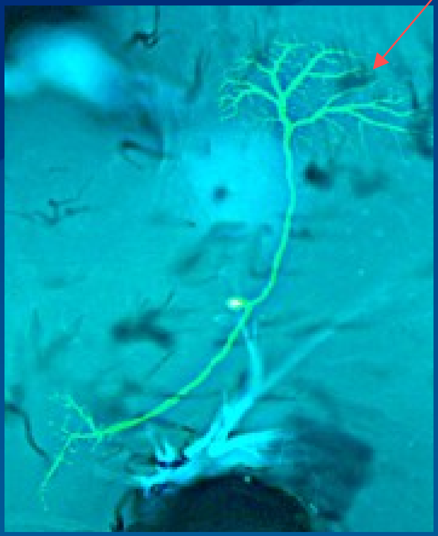


Photo: D. O'Carroll, U. Adelaide

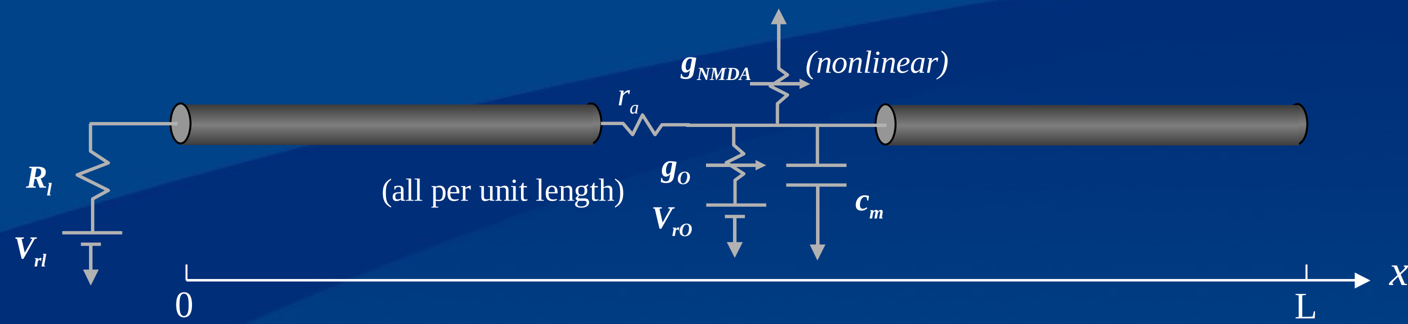
- **Inputs to most neurons occur on tree-like structures, consisting of *dendrites***
- **(Usually) a neuron receives synaptic input from many other cells**
- **Inputs are aggregated at base of tree (usually cell body)**

Bistability in a (cable-like) dendrite:

A dendrite is a *structure*:

- Not normally isopotential
- Axial current flow / voltage drops affect bistability

Load due to soma and/or passive neural process



Governing equation:

$$\partial^2 V_m / \partial x^2 = -r_a \left[g_O (V_m - V_{rO}) + g_{NMDA} F(V_m) + c_m \partial V_m / \partial t \right]$$

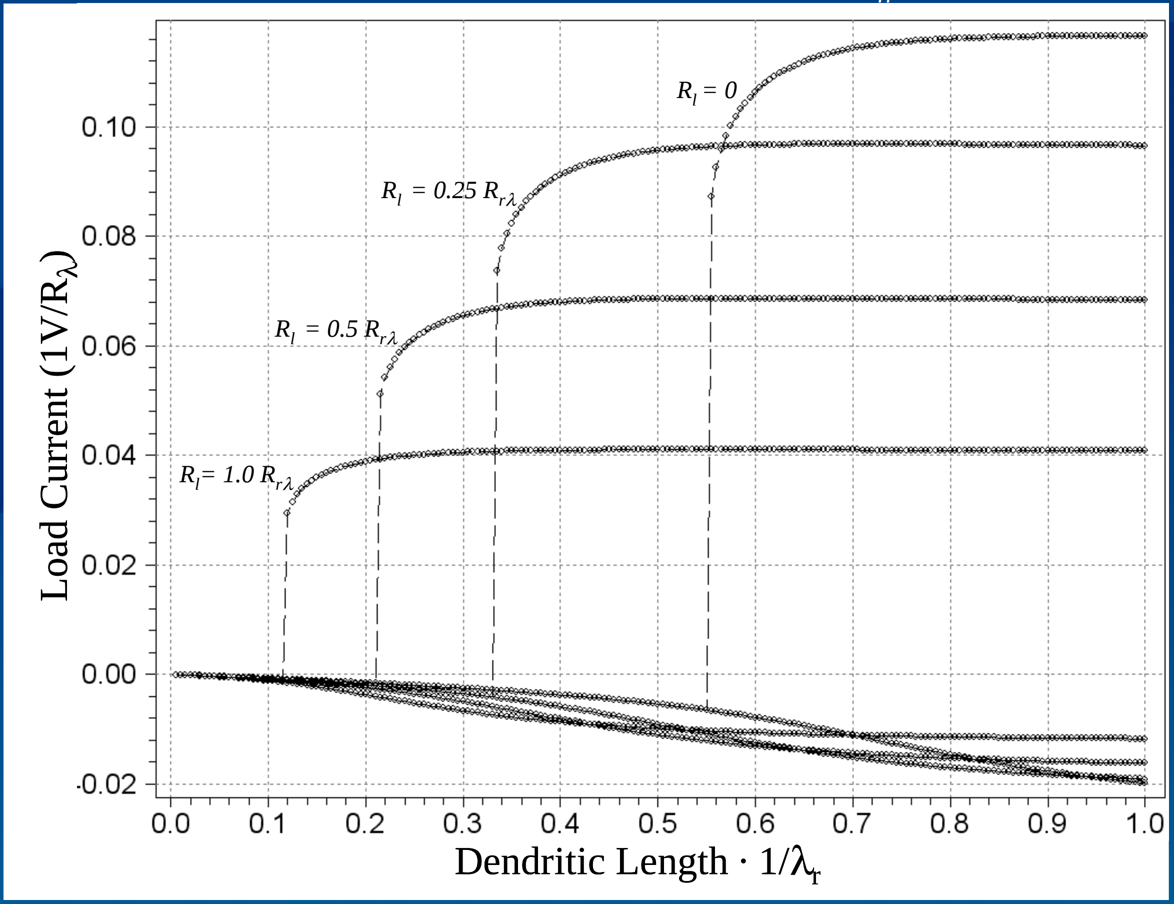
Boundary conditions:

$[(R_l / r_a)(\partial V_m / \partial x) + V_m] |_{x=0} = V_{rl}$ and $\partial V_m / \partial x |_{x=L} = 0$

Bistability in a dendrite with terminal load:

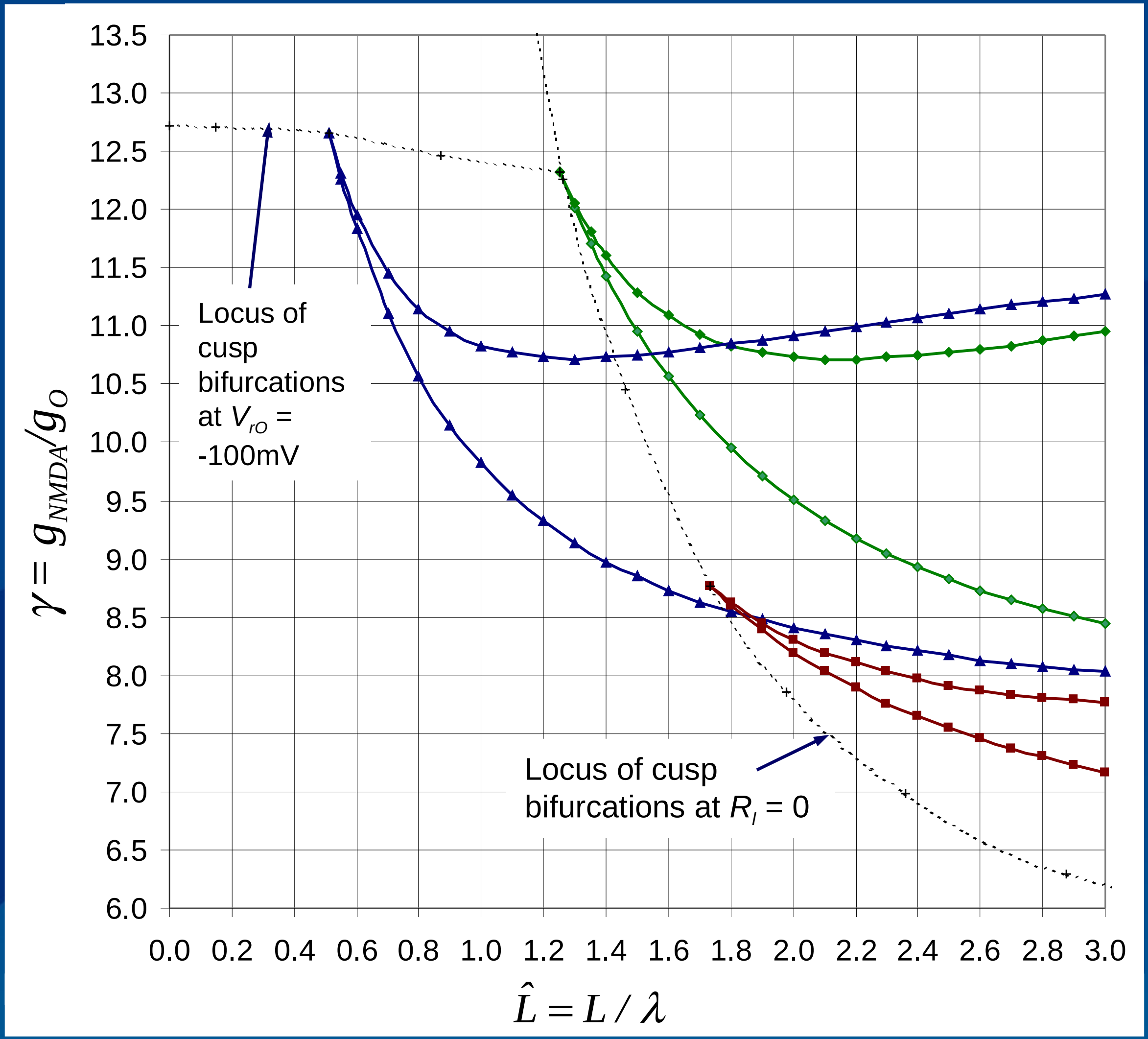
When the conductances in the membrane of a dendrite assume values compatible with bistability, get monostable – bistable bifurcations as its electrical length varies

Bifurcations at various load resistances; V_{rl} = -65mV



Bistable regimes in a cable-like dendrite

(ohmic conductances only)



Load resistance R_l = 0;
Eq. Rev. potential V_{rO} = -100mV

Load resistance R_l = 0;
Eq. Rev. potential V_{rO} = -90mV

Load resistance $R_l = R_{\lambda r}$;
Eq. Rev. potential V_{rO} = -100mV

Receptor conductances constant and uniformly distributed in active region

V_{rl} = -65mV in all cases

$R_{\lambda r}$ = characteristic resistance associated with ohmic conductance (= input resistance of semi-infinite cable)

SO: WHAT IS THE SIGNIFICANCE OF BISTABILITY?

- System in 1 of 2 states, depending upon initial conditions (or other inputs) =>

A MECHANISM FOR (SHORT-TERM) MEMORY

  - Engineering example: the SRAM cell

- However, *this* case not a simple 1- bit storage mechanism:
  - states evolve with time
  - dendritic output magnitude depends on strength of activation
- Important conclusion: individual dendrites may be a locus of memory

NMDA receptors *have* been implicated in ‘working memory’ in neuropsychology*

*C. Adler et al., *Biological Psychiatry* 43: 811–816, 1998

*Wang, X.J., *Journal of Neuroscience* 19: 9587–9603, 1999

Dynamics & Non-Equilibrium States:

- Neurons are rarely in equilibrium!
- Synaptic receptors / channels have dynamics (kinetics)

•NMDA and $GABA_B$ kinetics ‘slow’ relative to membrane time constant, BUT

- Their activations are never static!

IN THE FOLLOWING:

Used the simple kinetic models (impulse response functions) of Destexhe *et al.**)

Assumed inputs are impulsive (arrival of action potentials presynaptically)

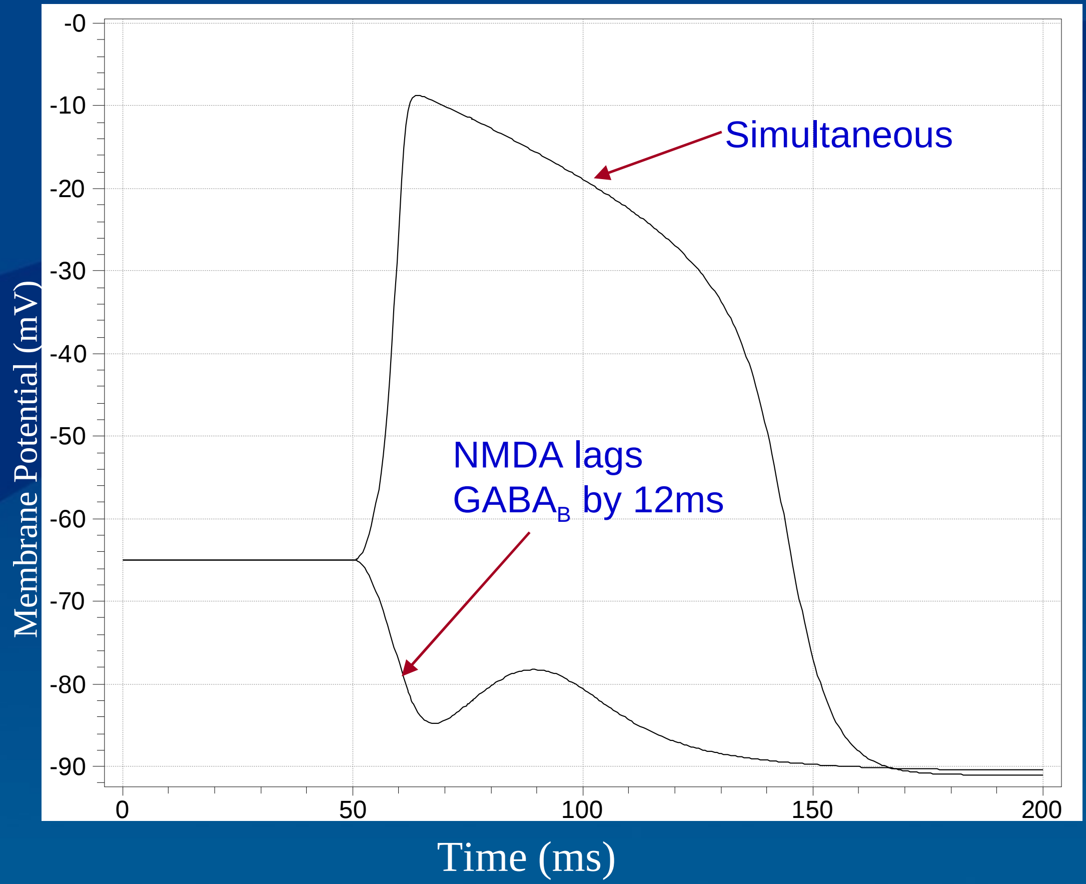
*A. Destexhe et al., Fast kinetic models for simulating AMPA, NMDA, $GABA_A$, and $GABA_B$ receptors, in The Neurobiology of Computation, Bower, ed., Kluwer Academic Press, 1995

Dynamics & Non-Equilibrium States:

When bistable regimes are evoked, subtle differences in:

Timing …

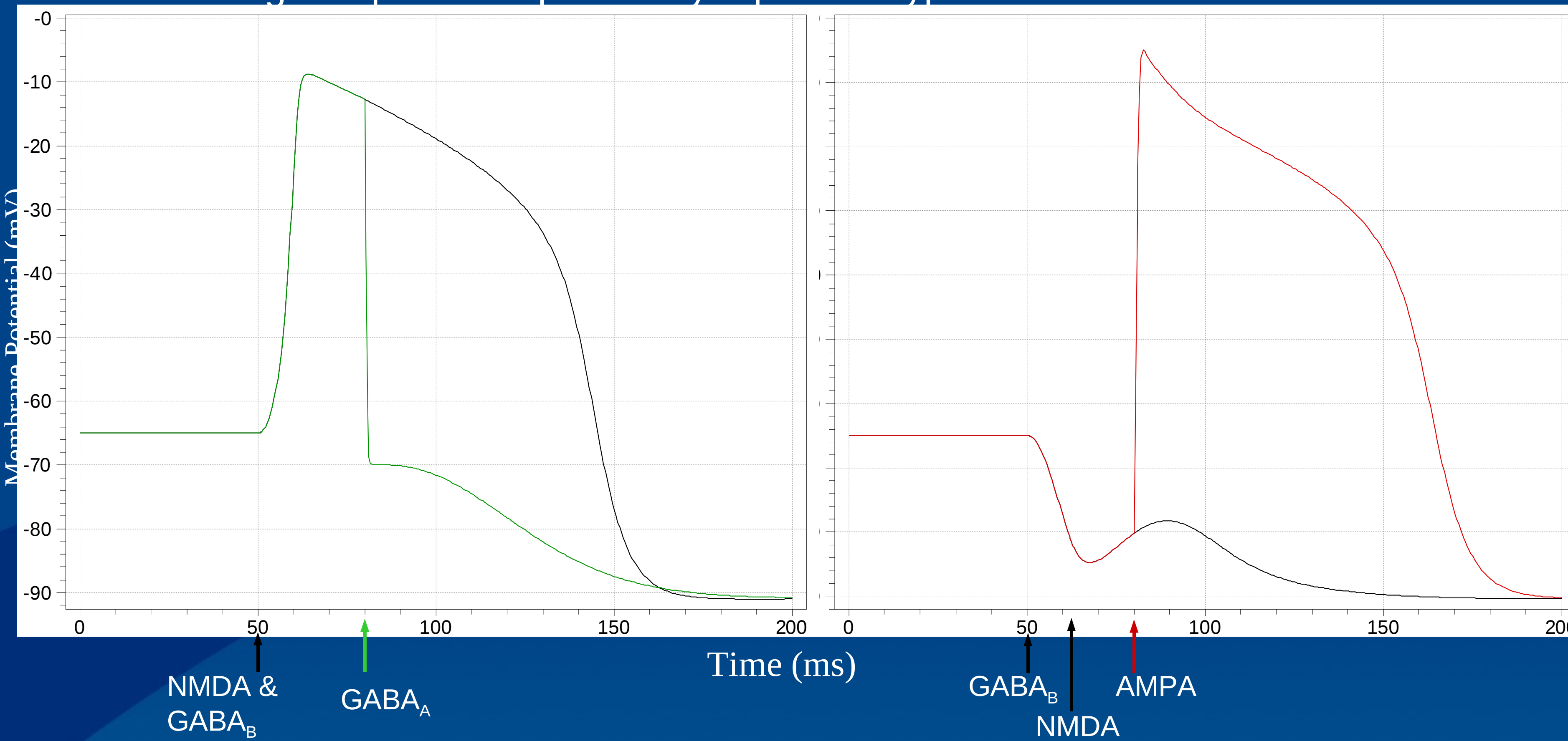
Impulsive coactivation of NMDA and ohmic $GABA_B$ synapses:



(Kinetic channel models of Destexhe *et al*.)

… and other inputs …

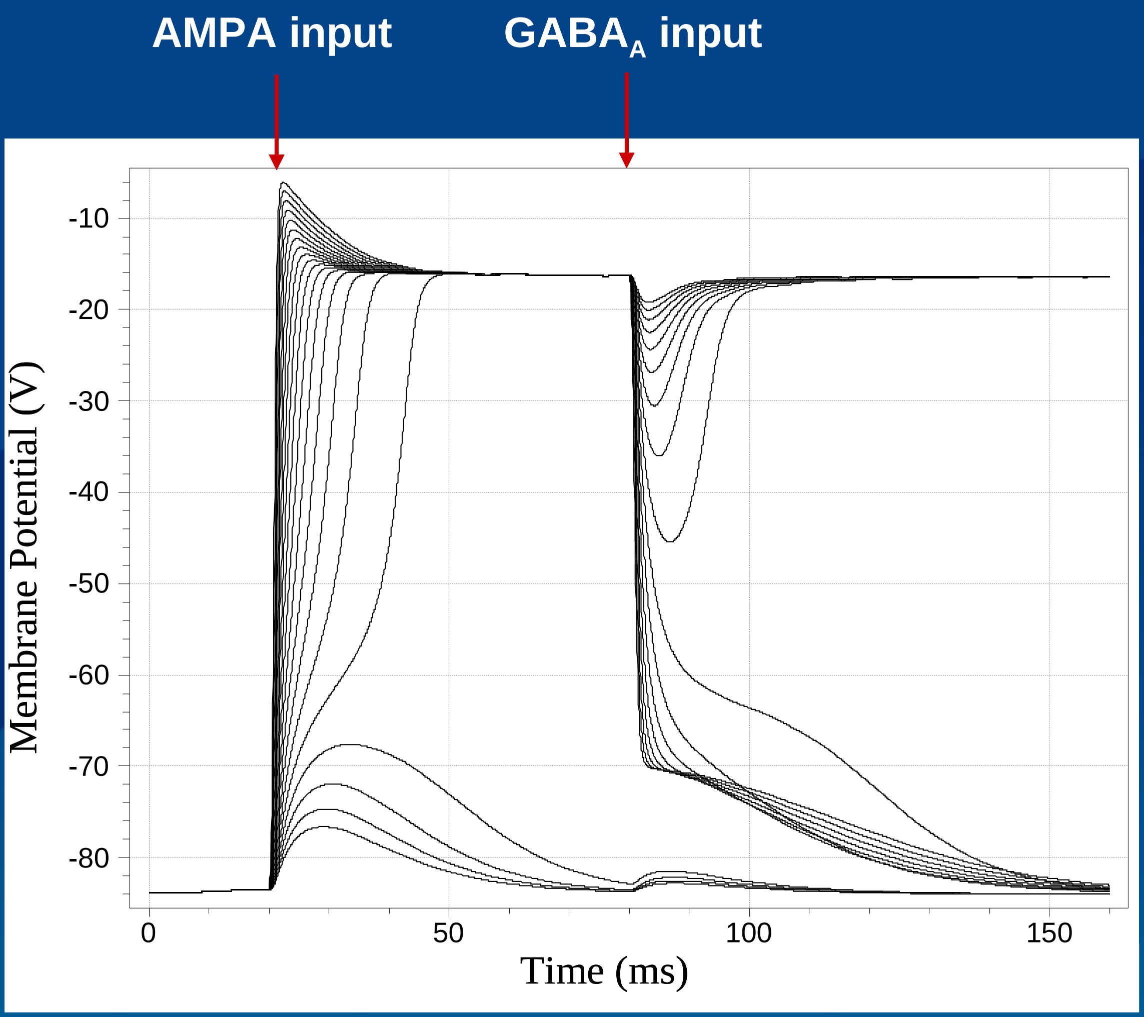
Single impulsive inputs at synapses of types and at times indicated



… can cause radical differences in evolving states, even when stable equilibria are never reached.

Dynamics, cont':

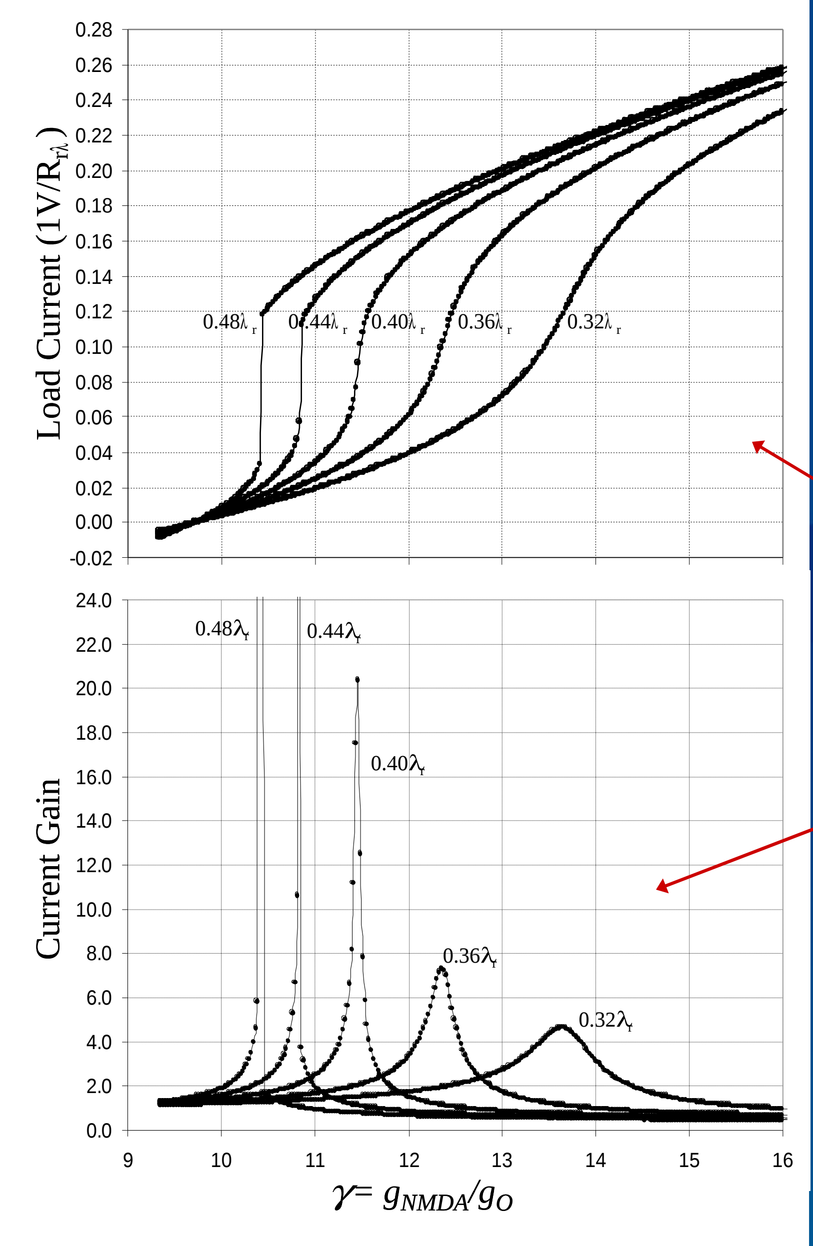
Fast synaptic inputs (AMPA, $GABA_A$) capable of triggering transitions when in a bistable regime



Steady-state NMDA and ohmic K^+ channel conductance;

Impulsive AMPA / $GABA_A$ inputs;

Peak elicited AMPA / $GABA_A$ conductance is parameter



AMPLIFICATION:

Even outside a bistable regime, coactivation of NMDA and inhibitory receptors can enhance *gain*

Current delivered from dendrite to 'somatic load' as function of g_{NMDA}/g_O (length as parameter)

Current gain (in response to uniformly distributed, incremental test current)

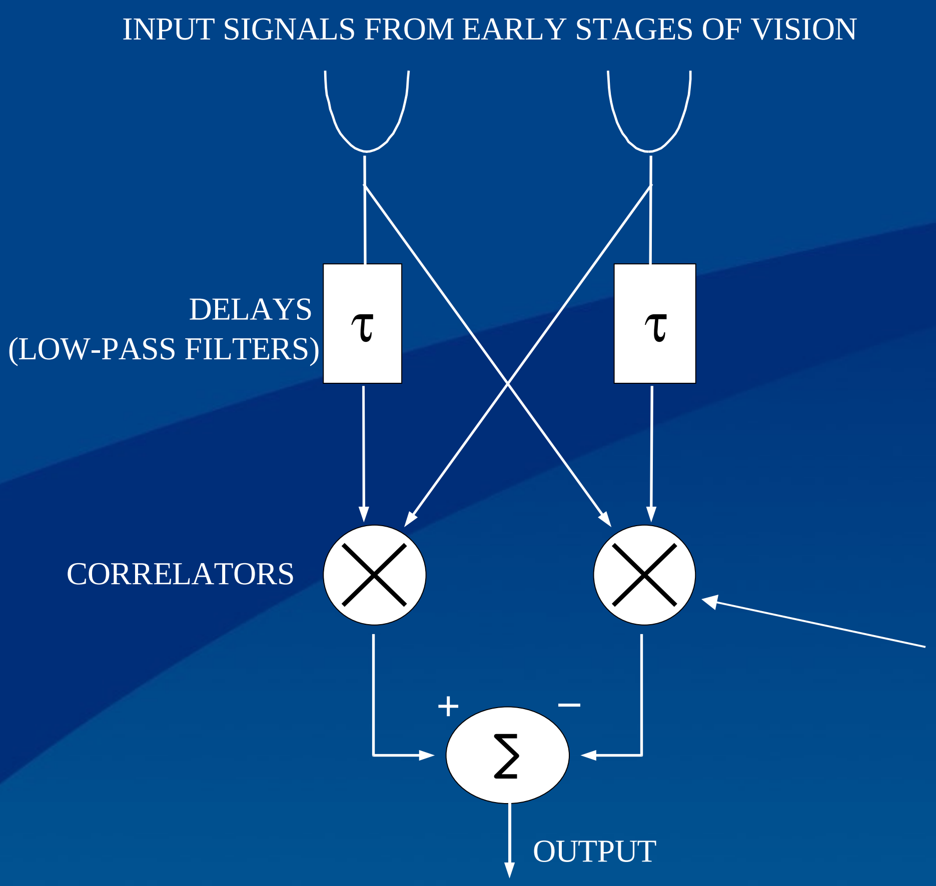
SO WHAT IS THE SIGNIFICANCE OF AMPLIFICATION?

A mechanism for nonlinear facilitation…

Take-Home Points Discussion / Conclusions:

- NMDA receptor conductance (+ other conductances) => bistability & amplification in neurons / dendrites
- Bistable regimes also relevant to nonequilibrium conditions
- Amplification can occur outside of bistable regimes
- Robust bistability: requires additional conductance with hyperpolarizing reversal potential (e.g., to K^+)
  - Coactivation of $GABA_B$ input a likely mechanism for dynamical control
- Individual dendrites can be bistable and in different states
- Possible computational roles are significant
  - Short-term memory
  - Functions requiring memory: spatiotemporal correlation
  - Parametric amplification

VISUAL MOTION (OPTIC FLOW) MUST BE INFERRED FROM SPATIOTEMPORAL PATTERNS OF LUMINANCE



How Is Visual Motion Detection Achieved By Insects?

Primitive functional unit: Hassenstein-Reichardt, or correlational *elementary motion detector* (EMD) model

Could superlinear interaction (correlation) be subserved by bistable/amplifying properties of NMDA synapses?