# Mathematical models of protein trafficking in neurons

Paul C Bressloff

Department of Mathematics, University of Utah

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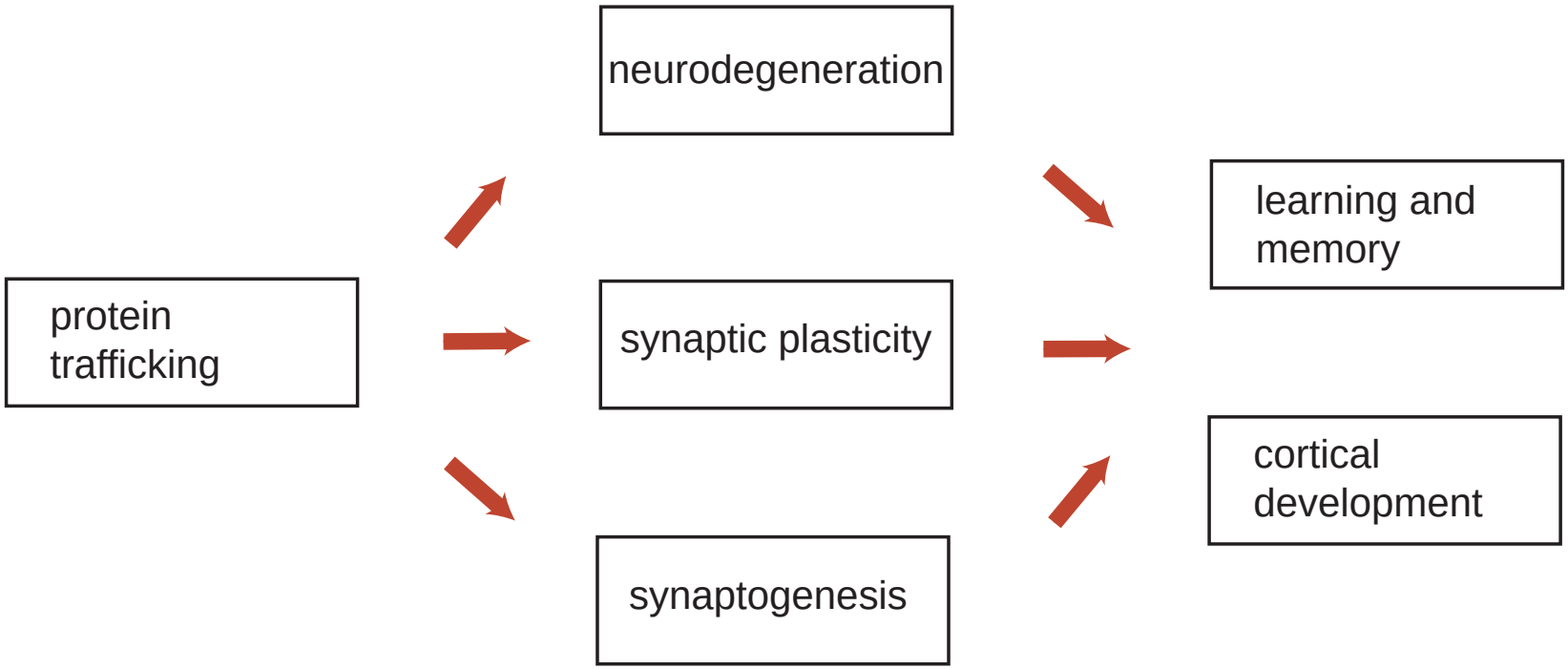
# Protein transport

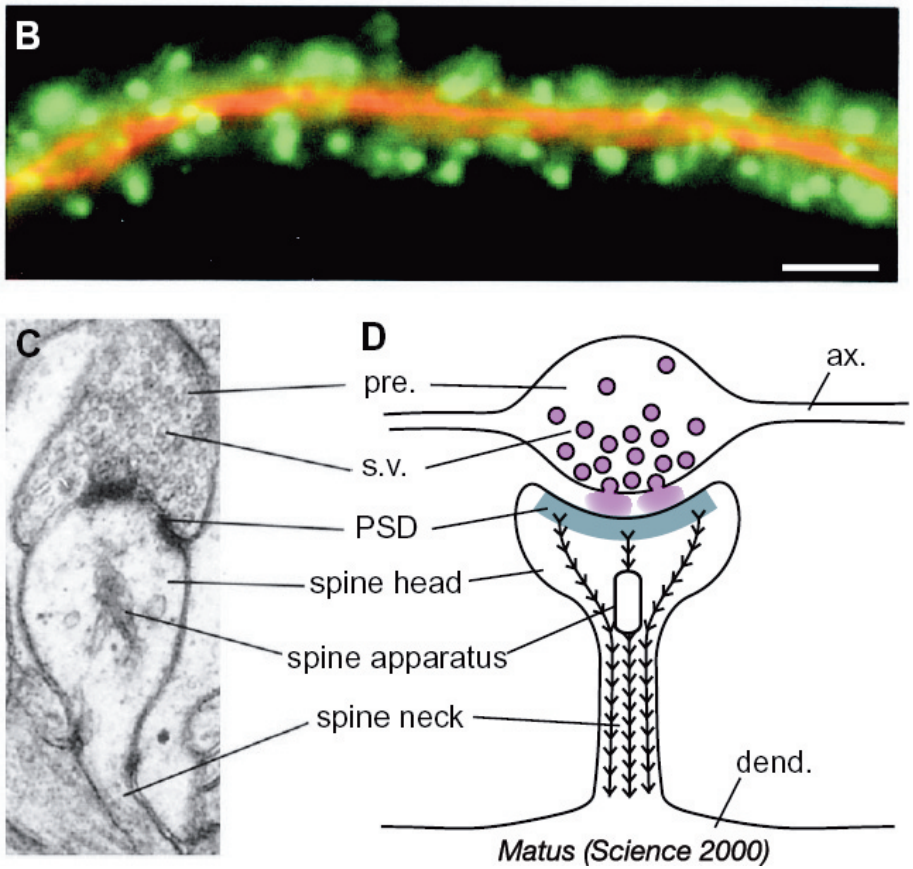



- Proteins must be transported long distances along dendrites and axons
- Protein transport crucial in synapse formation and plasticity
- Certain neurodegenerative diseases involve a breakdown in protein transport

# Outline

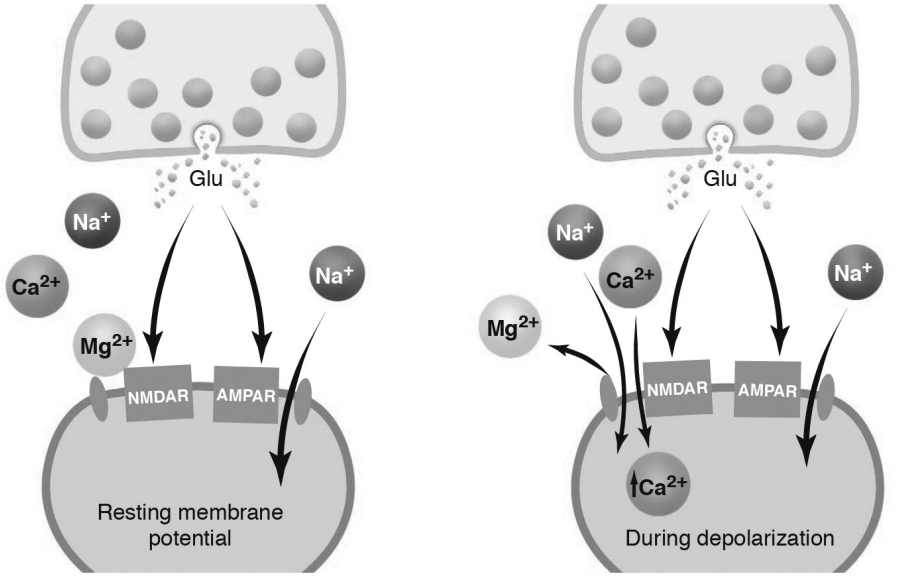
- **Protein receptor trafficking and synaptic plasticity**
- Cable theory of receptor trafficking
- Motor transport of mRNA

# Dendritic spines



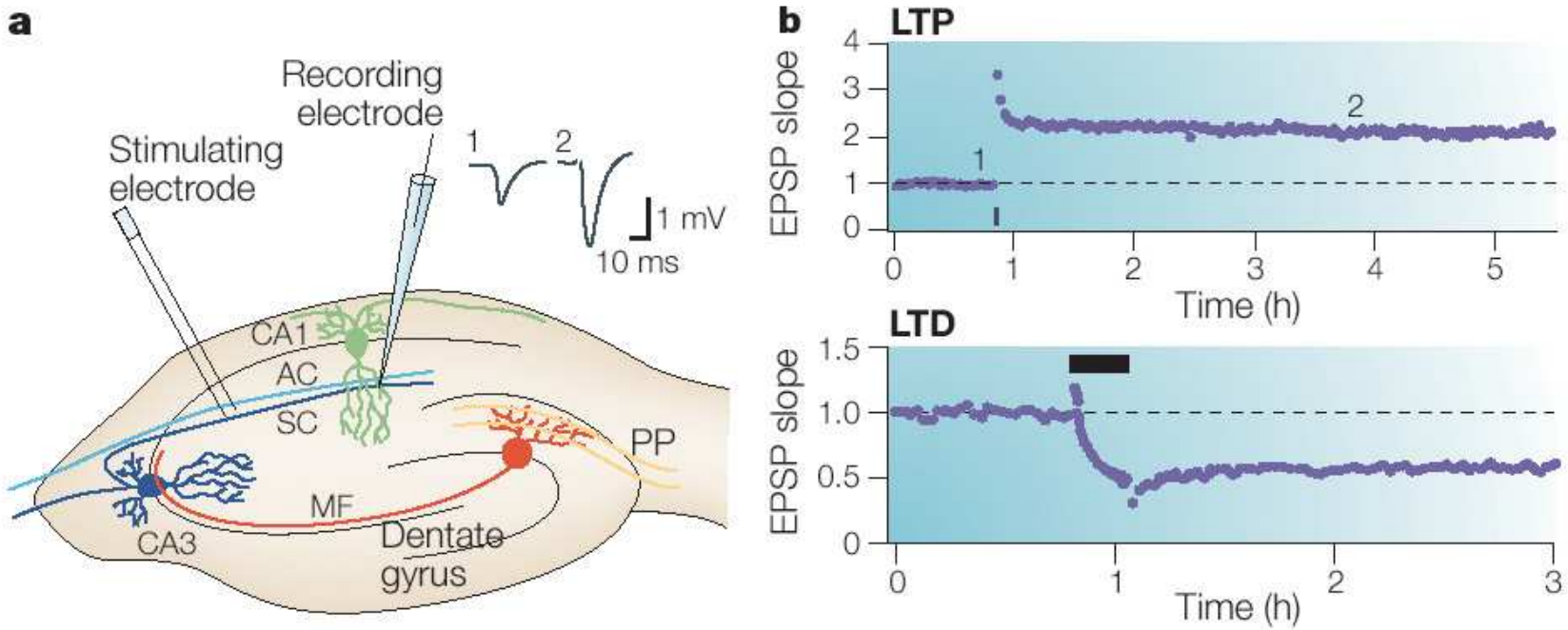

- Most excitatory synapses are located in small mushroom–like appendages called dendritic spines which are rich in actin.
- Associated neurotransmitter is glutamate (Glu).

# Glutamate (Glu) receptors



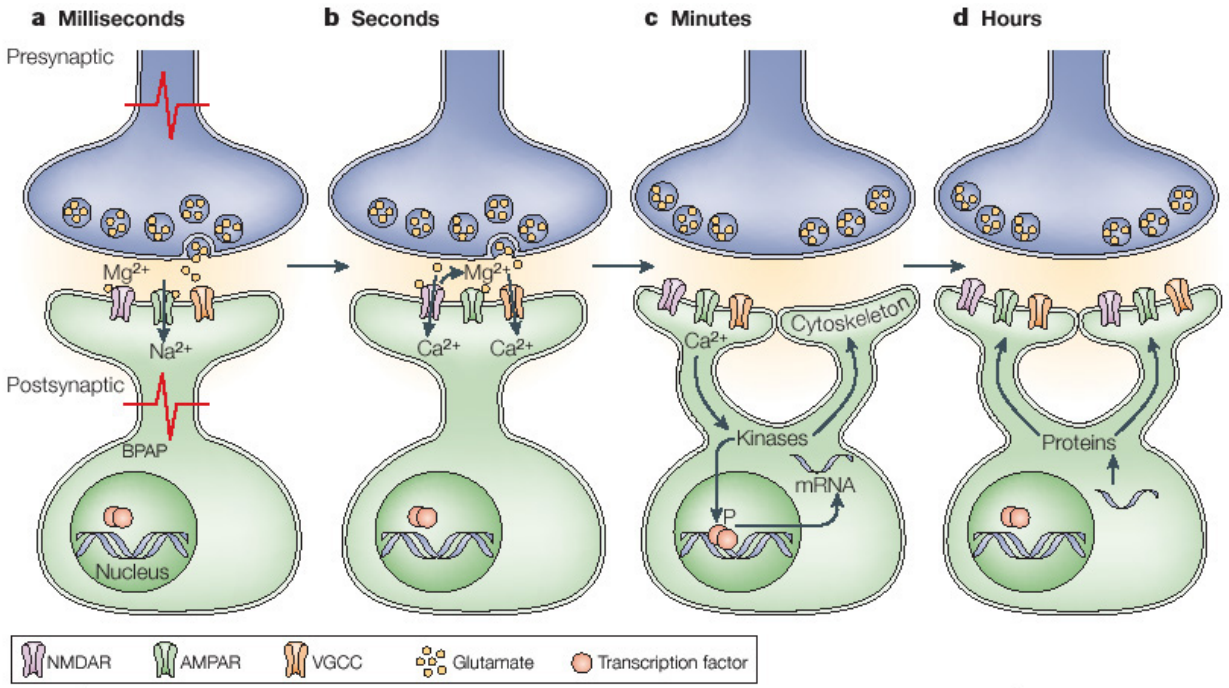

- Two major types of Glu receptor: AMPA and NMDA
- Binding of Glu receptors opens AMPA ion channels leading to depolarization
- Binding of Glu + sufficient depolarization opens NMDA ion channels leading to influx of calcium

# Long-term potentiation/depression



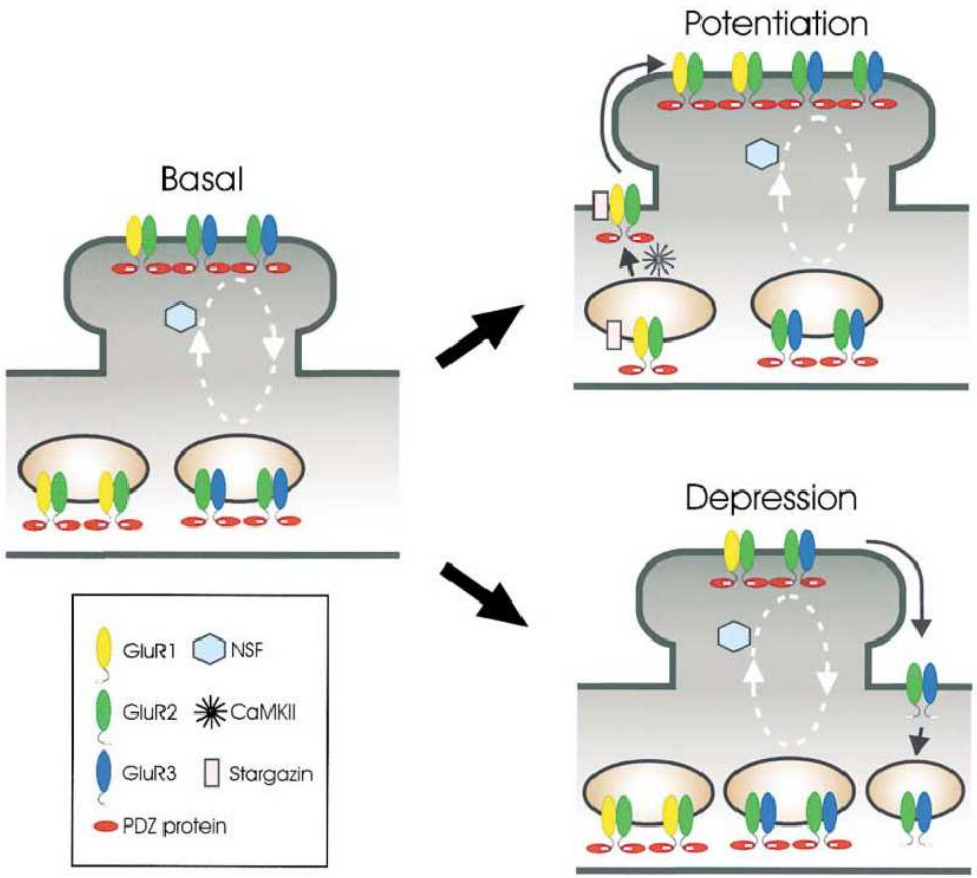

- High frequency (100 Hz) stimulus induces LTP
- Low frequency (1Hz) stimulus induces LTD

# Separation of time-scales



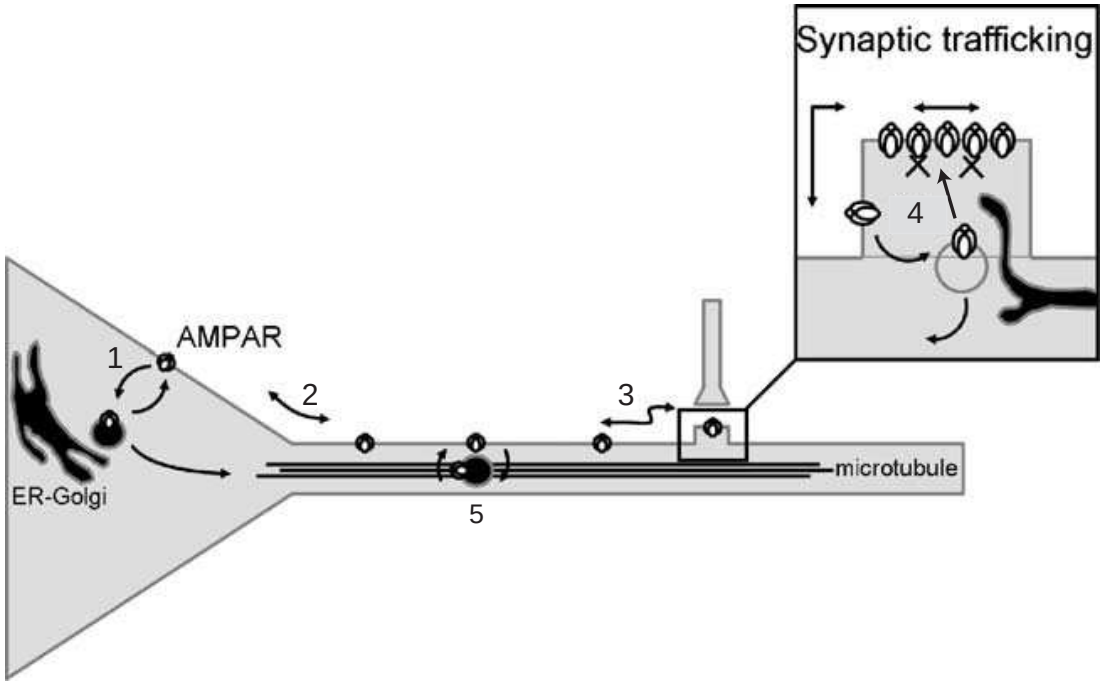

- **Induction**: Calcium signal via NMDA induces action of kinases and phosphotases
- **Expression**: (De)Phosphorylation of AMPAR receptors regulates their trafficking and their conductance state
- **Maintenance**: Persistent changes require protein synthesis

# Regulation of AMPAR trafficking



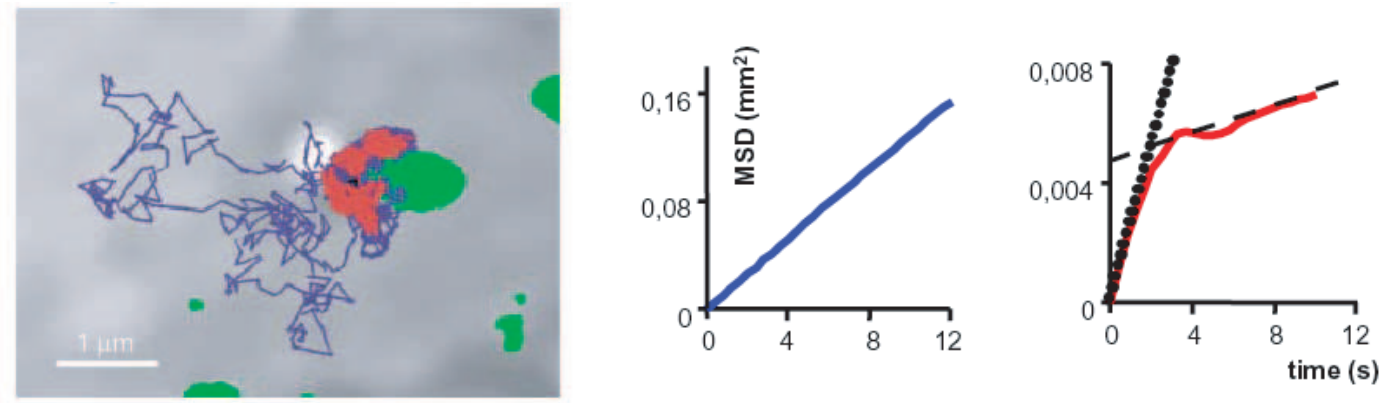

- A major expression mechanism for LTP/LTD is a $Ca^{2+}$-induced change in the number of synaptic AMPARs

# Various mechanisms of receptor trafficking




1. Newly synthesized proteins inserted in cell surface
2. Lateral surface diffusion along dendrite
3. Surface entry into spine
4. Recycling with intracellular pools/binding to scaffolding proteins
5. Motor transport of mRNA and local synthesis of AMPAR

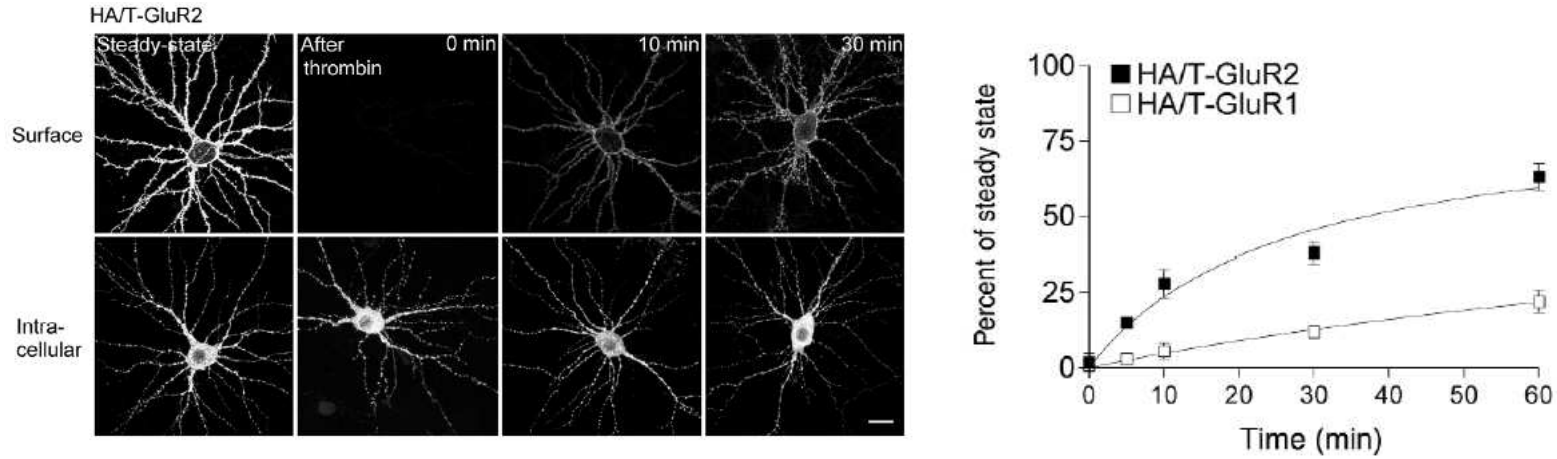
# Single-particle tracking




*(Choquet and Triller, Nat Rev. Neurosci. 2003)*

- Sub-$\mu m$ latex bead is bound to a receptor using ligands (antibodies or scaffolding proteins) and imaged using lasers
- GFP tags reveal regions of high receptor concentration - coincide with confinement domains (red)

# Inactivation and recovery of surface receptors



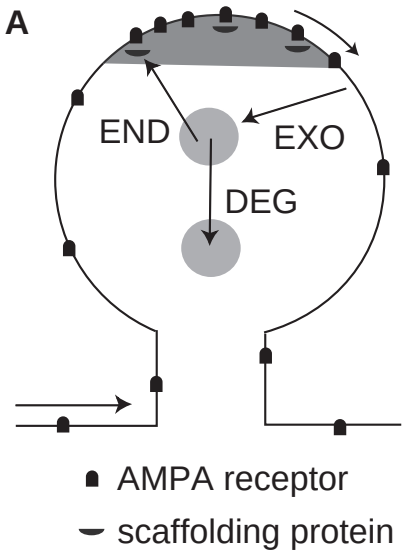

*Passafaro et al (Nature 2001)*

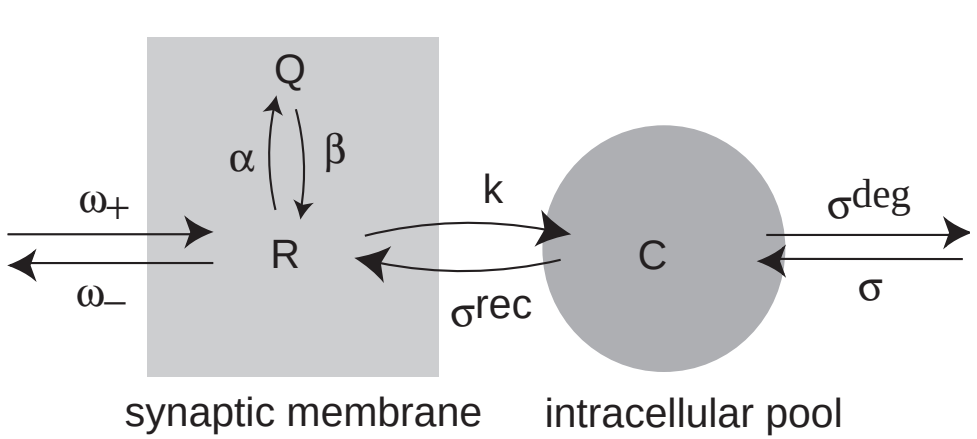
- Transfect AMPAR with an immunoflourescent tag (HA/T)
- Reduce temperature to temporarily stop trafficking
- Treat neuron with thrombin to eliminate surface staining of HA/T
- Washout thrombin and return to normal temperatures: surface expression of HA/T recovers in 30 min.

# Outline

- Protein receptor trafficking and synaptic plasticity
- **Cable theory of receptor trafficking**
- Motor transport of mRNA

# Single–spine model




**R, Q: free and bound receptor concentrations in synapse**

**C: number of intracellular receptors**

**k,** $\sigma^{rec}$, $\sigma^{deg}$, $\sigma$: **rates of endo/exocytosis, deg/syn**

$\omega_{\pm}$: **hopping rates in and out of synapse**

$\alpha$, $\beta$: **rates of binding/unbinding to scaffolding proteins**

- Kinetic equations

$$
\begin{aligned}
a\frac{dR}{dt} &= \omega_+ U - \omega_- R - kR + \sigma^{rec} C - \alpha[Z - Q]R + \beta Q \\
a\frac{dQ}{dt} &= \alpha[Z - Q]R - \beta Q \\
\frac{dC}{dt} &= -\sigma^{rec} C - \sigma^{deg} C + kR + \sigma
\end{aligned}
$$

- $U$ is dendritic receptor concentration at spine boundary
- $Z$ is concentration of scaffolding proteins
- $a$ is area of synapse

- Adiabatic approximation

$$Q(t) = \frac{\alpha Z R(t)}{\alpha R(t) + \beta}$$

- Reduced single-spine model

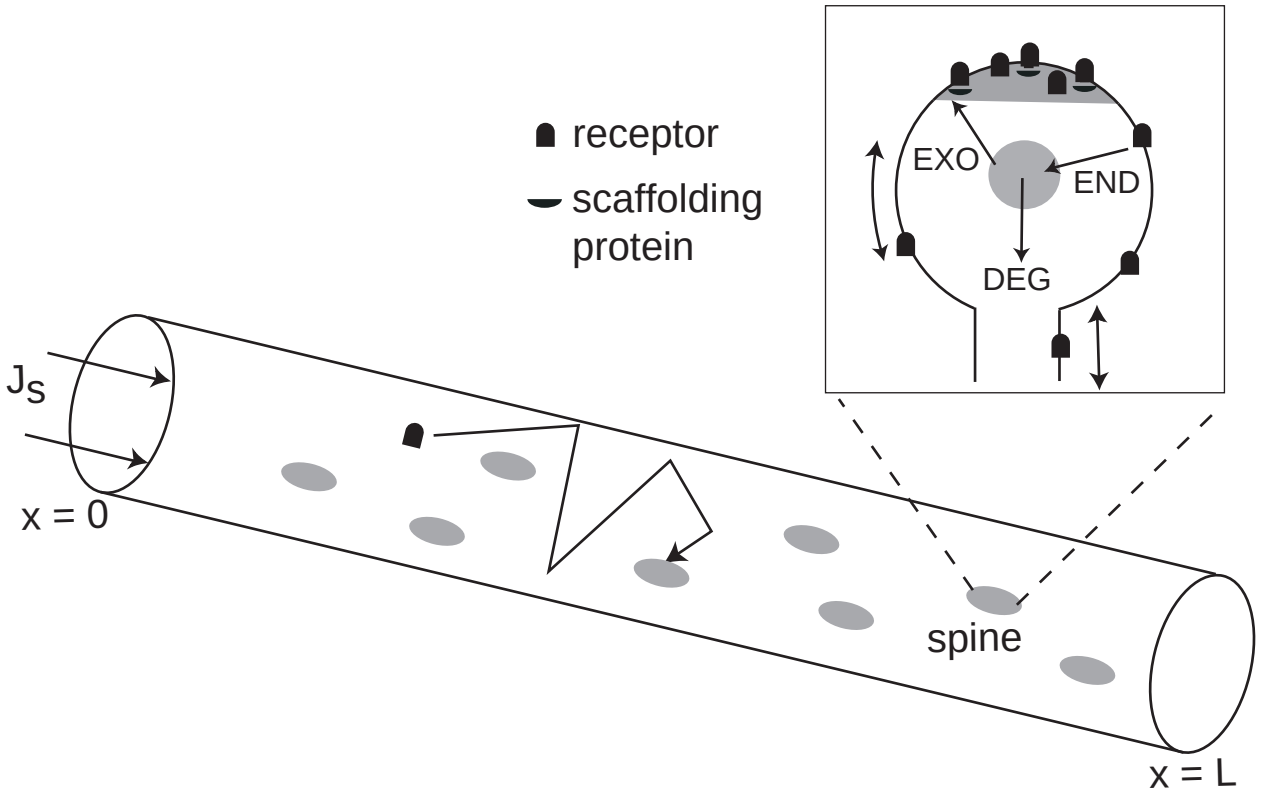
$$a\frac{dR}{dt} = \omega_+ U - \omega_- R - kR + \sigma^{rec} C$$
$$\frac{dC}{dt} = -\sigma^{rec} C - \sigma^{deg} C + kR + \sigma$$

- Strength of a synapse

$$W = a[g_R R + g_Q Q]$$

where $g_R, g_Q$ are conductances of free and bound AMPARs

# Multi-spine diffusion–trapping model[3]




- Consider a dendritic cable of circumference $l$ and length $L$.
- Somatic flux $J_s$ at $x = 0$. Reflecting BC at $x = L$

[3] Bressloff et. al. PRE 2007, SIAM J. Appl. Math. 2008

# 1D Continuum model[4]

- Assume uniform concentration around circumference of cable
- Represent fluxes between spines and cable using Dirac delta functions:

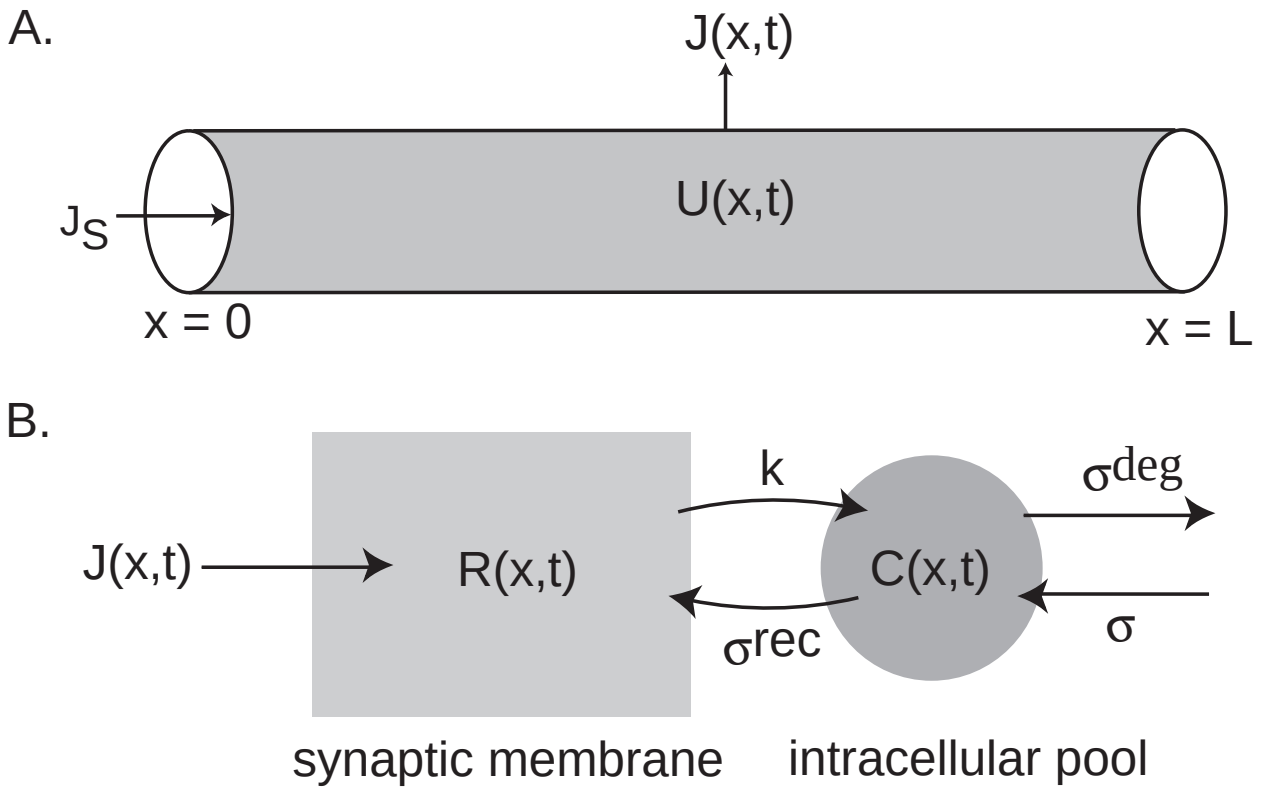
$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \rho(x)[\omega_+ U(x,t) - \omega_- R(x,t)]\,,$$

with

$$\rho(x) = \frac{1}{2\pi l}\sum_{j=1}^{N}\delta(x - x_j)$$

- Continuum approximation: take $\rho(x)$ to be a smooth function so that we obtain a 1D cable equation.

[4] Earnshaw and Bressloff J. Comp Neurosci 2008, Bressloff 2009




- Transverse current

$$J(x,t) = \omega_+ U(x,t) - \omega_- R(x,t)$$

- Basal parameter values

$$k = 10^{-3}\mu m^2 s^{-1}, \sigma^{\text{rec}} = 10^{-3} s^{-1}, \sigma^{\text{rec}} = 10^{-5} s^{-1}, D = 0.1\mu m^2 s^{-1}$$

# Steady–state cable equation

- Uniform spine density $\rho_0 = N/LI$:

$$\frac{d^2U}{dx^2} - \frac{\rho_0\overline{\omega}}{D}[U - \overline{R}] = 0$$

with

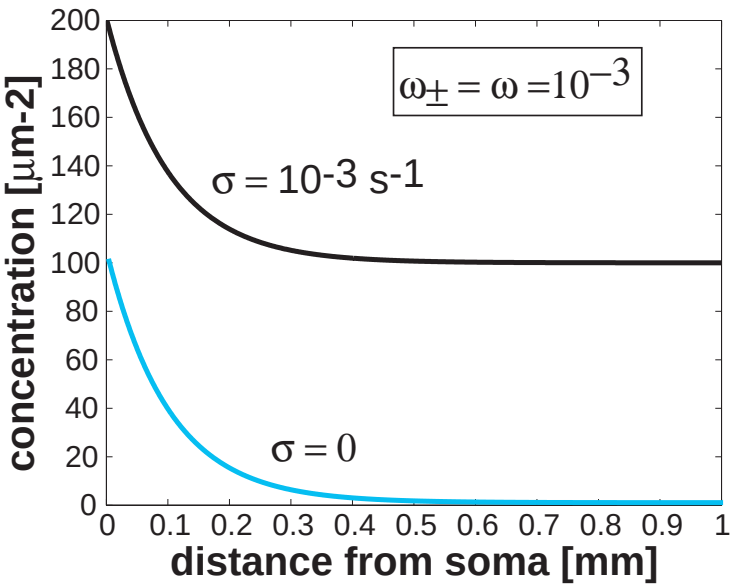
$$\overline{\omega} = \frac{\omega_+ k(1-\Lambda)}{\omega_- + k(1-\Lambda)}, \quad \overline{R} = \frac{\omega_-}{\omega_+}\frac{\Lambda\sigma}{k(1-\Lambda)}, \quad \Lambda = \frac{\sigma^{\rm rec}}{\sigma^{\rm rec}+\sigma^{\rm deg}}.$$

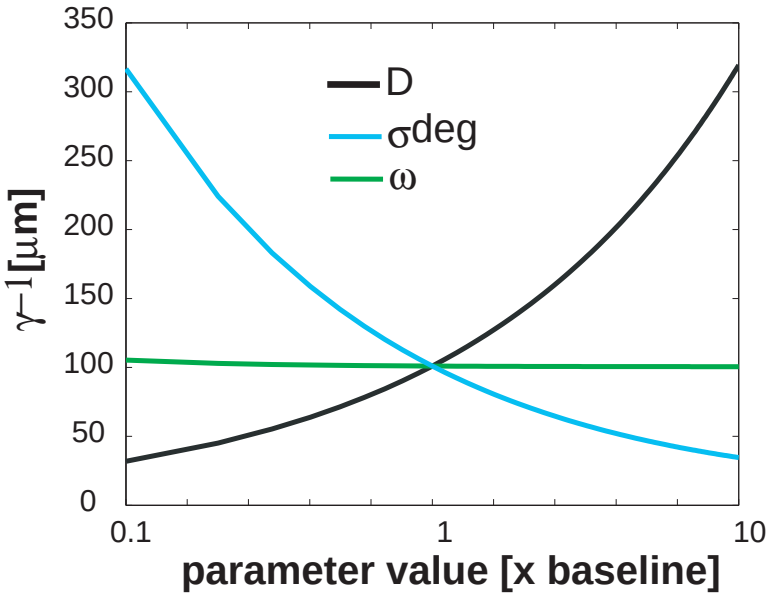
- Solution is

$$U(x) = ZJ_S\frac{\cosh(\gamma[x-L])}{\sinh(\gamma L)} + \overline{R}$$

where $Z$ is characteristic impedance of cable and $\xi \equiv \gamma^{-1}$ is a diffusive space constant:

$$\gamma = \sqrt{\frac{\rho_0\overline{\omega}}{D}}, \quad Z = \frac{1}{ID\gamma}.$$




- Diffusion from soma is insufficient to supply distal synapses with receptors
- Source at soma favors proximal synapses. Synaptic democracy requires non-uniform spines

- Given solution $U(x)$ to cable equation, the free synaptic receptor concentration is

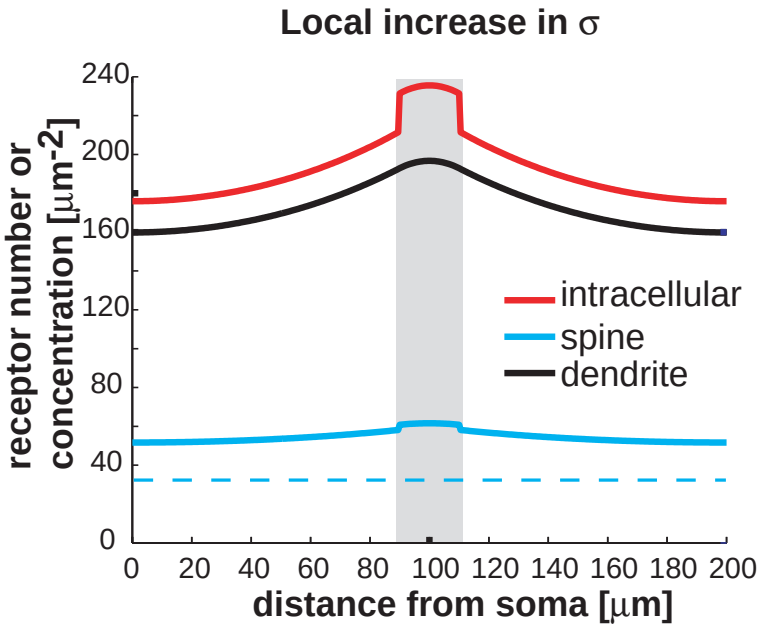
$$R(x) = \frac{\omega_+ U(x) + \Lambda\sigma}{\omega_- + k(1-\Lambda)}$$

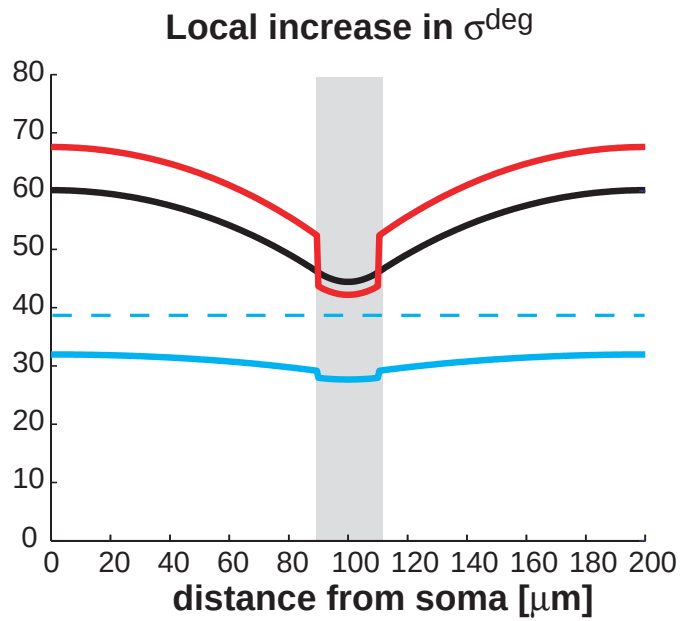
- The steady–state synaptic weight is then

$$W(x) = a(x)\left[g_R R(x) + g_Q \frac{\alpha(x)Z(x)R(x)}{\alpha(x)R(x) + \beta(x)}\right]$$

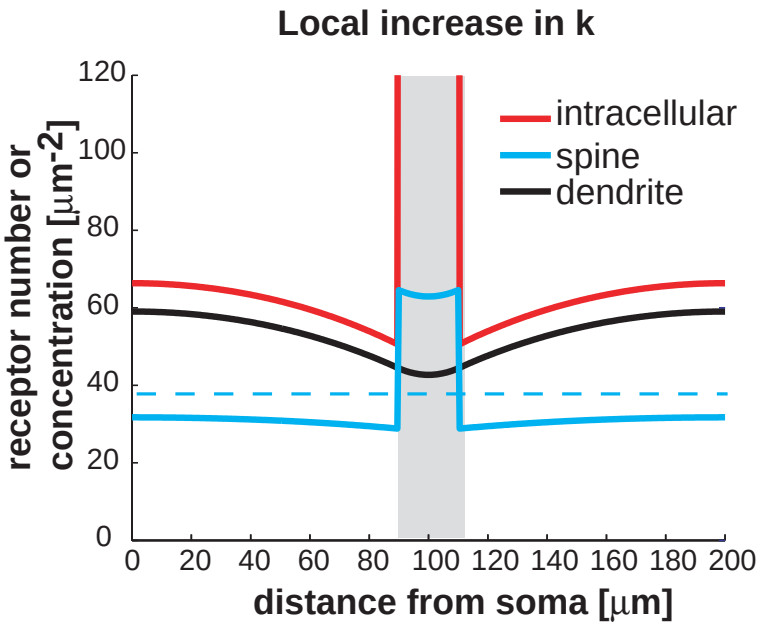
# Heterosynaptic interactions

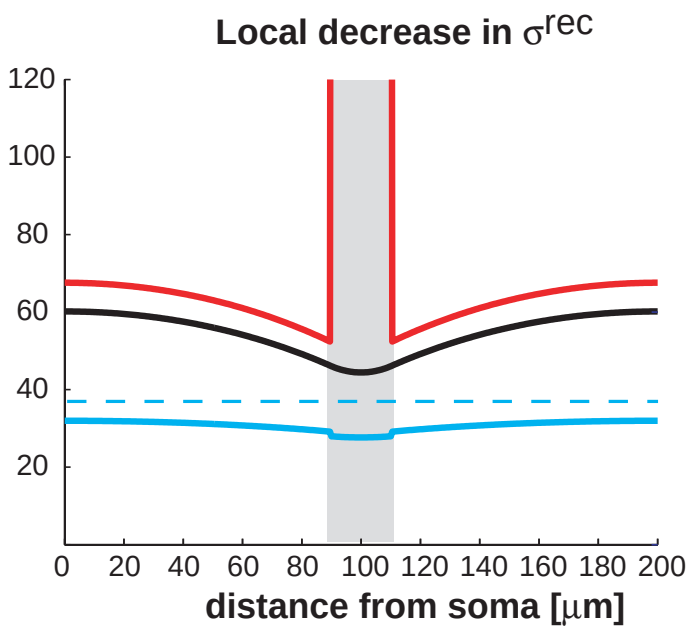
- Spine parameters can be classified according to whether or not they have a nonlocal effect on steady-state receptor numbers mediated by diffusion
- Synaptic parameters are purely local: rates of binding/unbinding, number of binding sites, area of synapse
- Parameters of constitutive recycling are nonlocal: rates of exo/endocytosis, local production and degradation
- If the expression of LTP/LTD involves changes in number of binding sites, then receptor diffusion unlikely to mediate heterosynaptic plasticity




- Increasing local production rate $\sigma$ for spines between $90\mu m$ and $110\mu m$ leads to a global increase in receptor numbers.
- Increasing degradation rate $\sigma^{deg}$ leads to a global reduction in receptor numbers




- Increasing rate of endocytosis $k$ or decreasing rate of recycling $\sigma^{rec}$ for spines between $90\mu m$ and $110\mu m$ leads to a global decrease in receptor numbers.

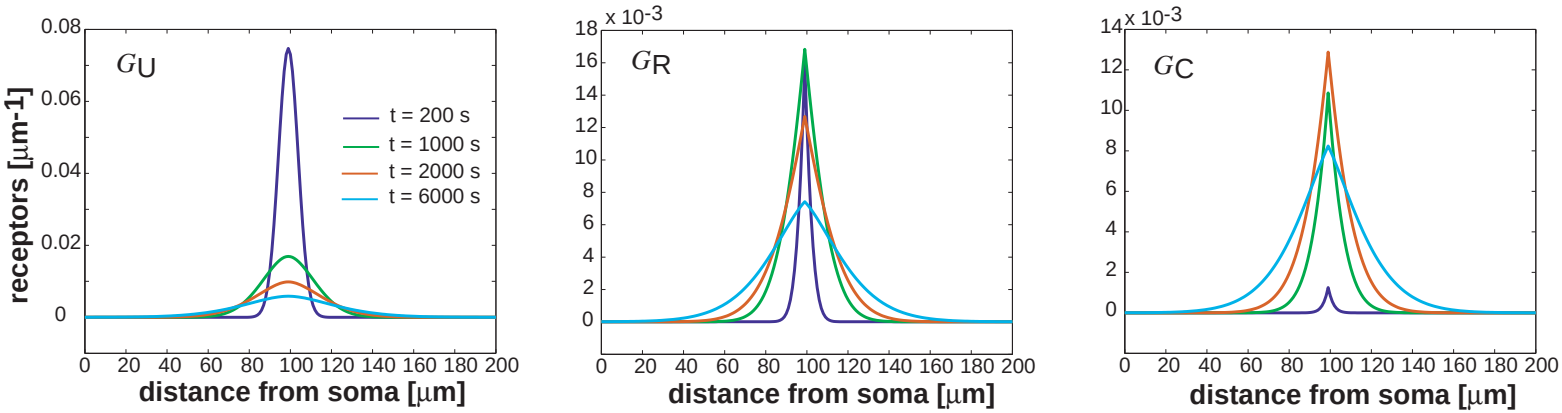
# Green's functions

- Response to a time–dependent surface current source $\mathcal{I}(x,t)$ switched on at $t=0$:

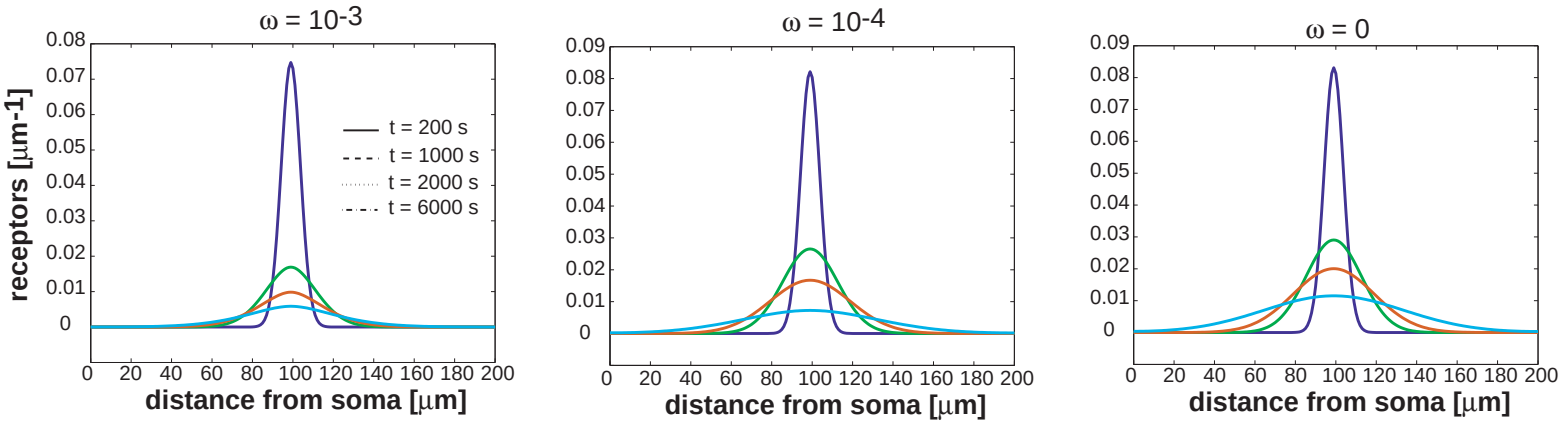
$$A(x,t) = \int_0^t \int_0^L \mathcal{G}_A(x,y;t-t')\mathcal{I}(y,t')dydt'$$

  for $A = U, R, C$ and $A(x,0) = 0$.
- Green's function $\mathcal{G}_A(x,x_0;t)$ is probability density that at time $t$ a single labeled receptor is at position $x$ and in state $A$ given that at $t=0$ it was injected into dendritic surface at $x_0$
- Can be generalized to a time–dependent modification of constitutive recycling induced by synaptic activity.

- Plots of Green's functions for $x_0 = L/2$:

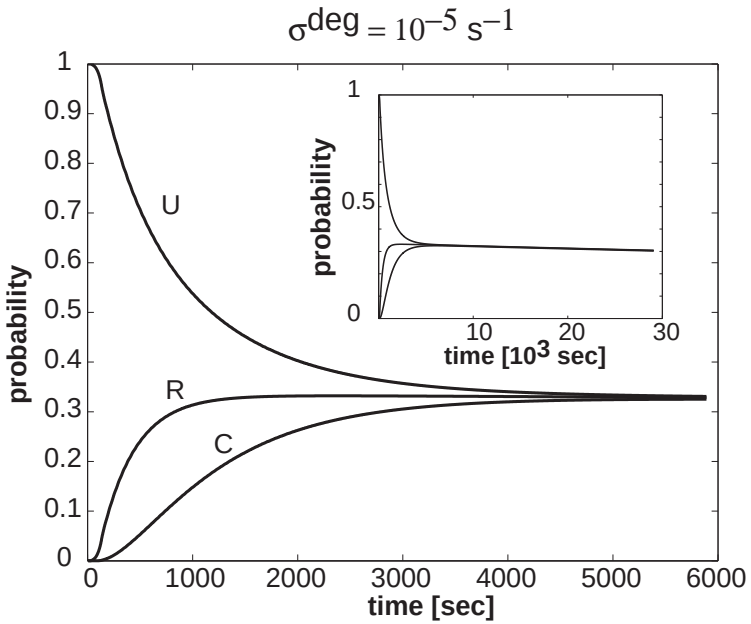


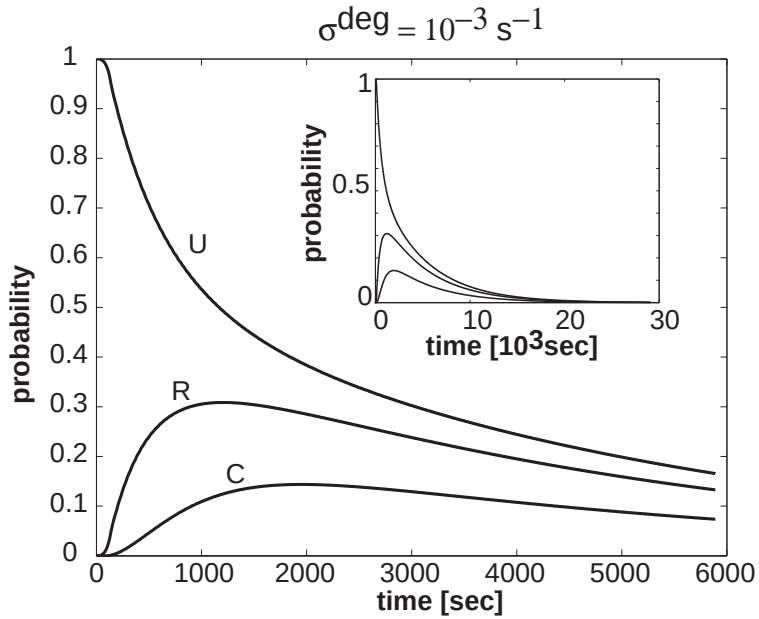

- Dependence of $\mathcal{G}_U$ on diffusive coupling $\omega$.



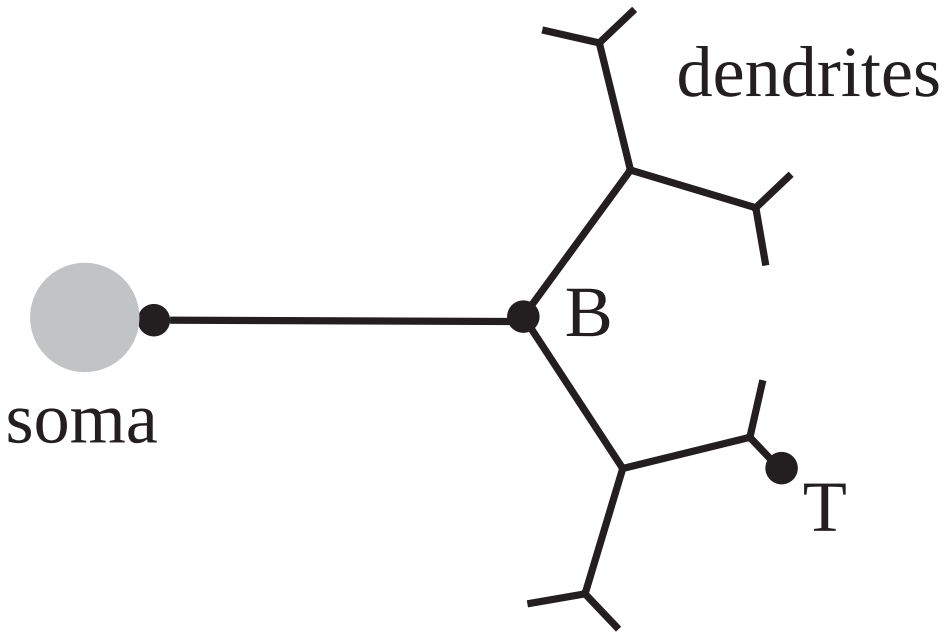
- Let $\mathcal{P}_A(t)$ denote probability to be in state $A$ at time $t$:

$$\mathcal{P}_A(t) = \int_0^L \mathcal{G}_A(x, L/2; t)dx$$



# “Sum–over–trips” on dendritic trees




- Each branch is uniform
- All terminal nodes are closed
- Continuity of receptor concentration at branch nodes
- Conservation of current at branch nodes

- Use Laplace transforms on $j$th branch

$$\frac{d^2\widetilde{U}_j}{dx^2} - \Xi_j(s)\widetilde{U}_j(x,s) = -\frac{\widetilde{\mathcal{I}}_j(x,s)}{D}$$

- Perform the rescalings

$$x \to X = \gamma_j(s)x, \quad L_j \to \mathcal{L}_j(s) = \gamma_j(s)L_j$$

with $\gamma_j(s) = \sqrt{\Xi_j(s)}$ so that

$$\frac{d^2\widetilde{U}_j}{dX^2} - \widetilde{U}_j(X,s) = -\frac{\widetilde{\mathcal{I}}_j(X,s)}{D}$$

- At each branch node

$$\widetilde{U}_i(0,s) = \widetilde{U}_j(0,s)$$

for all pairs $(i,j)$ radiating from the node and

$$\sum_j z_j(s) \left.\frac{\partial \widetilde{U}_j}{\partial X}\right|_{X=0} = 0, \quad z_j(s) = l_j D\gamma_j(s),$$

where the sum is over all branches $j$ connected to the node.

- At all terminal modes

$$\left.\frac{\partial \widetilde{U}_j}{\partial X}\right|_{X=\mathcal{L}_j} = 0.$$

- General solution is of the form

$$\widetilde{U}_i(X,s) = \sum_{j\in\mathcal{T}} \int_0^{\mathcal{L}_j(s)} G_{ij}(X,Y;s)\widetilde{\mathcal{I}}_j(Y,s)dY$$

- The Green's function $G_{ij}(X,Y;s)$ satisfies the homogeneous equation

$$\frac{d^2 G_{ij}(X,Y;s)}{dX^2} - G_{ij}(X,Y;s) = -\frac{1}{D}\delta_{i,j}\delta(X-Y),$$

with the same boundary conditions as $\widetilde{U}_i(X,s)$ for fixed $j, Y$.

- Using the "sum–over–trips" method[5] it can be shown that

$$G_{ij}(X, Y; s) = \sum_{\text{trips}} A_{\text{trip}}(s) G_{\infty}(\mathcal{L}_{\text{trip}}(i, j, X, Y, s)),$$

where $G_{\infty}(X)$ is Green's function for an infinite cable:

$$G_{\infty}(X) = \frac{\mathrm{e}^{-|X|}}{2D},$$

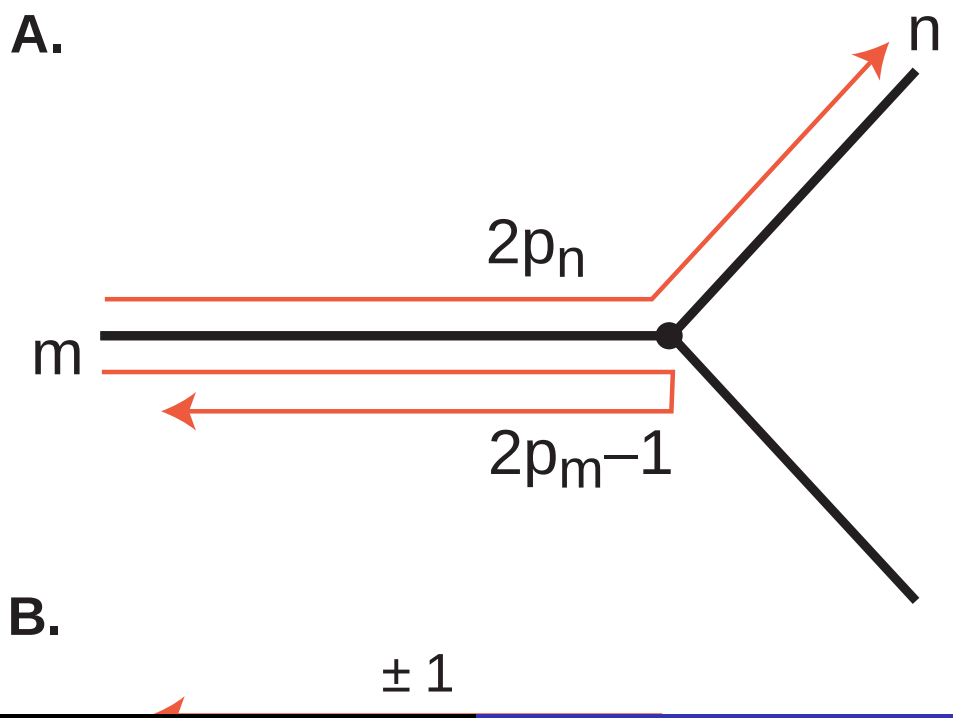
and $\mathcal{L}_{\text{trip}}(i, j, X, Y, s)$ is the length (in rescaled coordinates) of a path along the tree starting at the point $X$ on branch $i$ and ending at the point $Y$ on branch $j$.

- Sum restricted to a special class of paths or *trips*

[5] Abbott et. al. 1991; Bressloff et. al. 1996; Coombes et. al. 2007, Bressloff 2009

## Definition:

A trip from $(X, i)$ to $(Y, j)$ may start out in either direction along branch $i$ but it can subsequently change direction only at a branch or terminal node. A trip is always reflected back at a terminal node, whereas at a branch node it may be transmitted to another branch or reflected back. A trip may pass through the points $(X, i)$ and $(Y, j)$ an arbitrary number of times as long as it starts at $(X, i)$ and ends at $(Y, j)$.



For each trip, the associated amplitude $\mathcal{A}_{\rm trip}$ is calculated according to the following rules:

1. Initially take $\mathcal{A}_{\rm trip}(s) = 1$.
2. For every branch node at which the trip passes from an initial segment $m$ to a different segment $n$, $n \neq m$, multiply $\mathcal{A}_{\rm trip}(s)$ by a factor $2p_n(s)$
3. For every branch node at which the trip is reflected back along the same segment $m$, multiply $\mathcal{A}_{\rm trip}(s)$ by a factor $2p_m(s) - 1$
4. For every closed (open) terminal node, multiply $\mathcal{A}_{\rm trip}(s)$ by a factor $+1$ $(-1)$

The factor $p_m$ is given by

$$p_m(s) = \frac{z_m(s)}{\sum_n z_n(s)},$$

where sum is over all branches $n$ radiating from branch node.

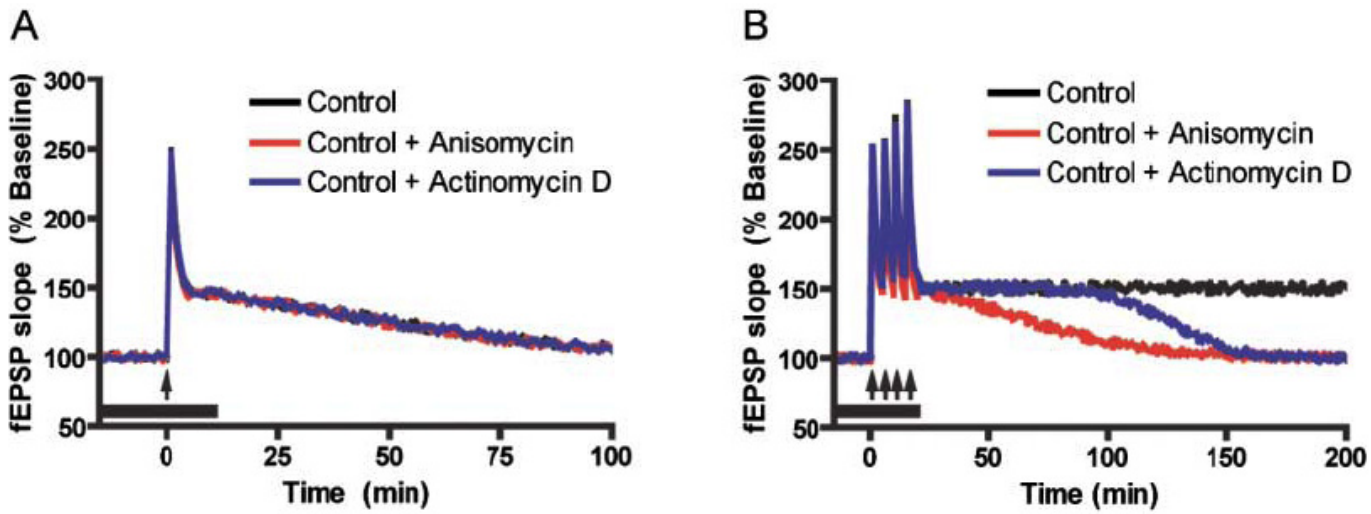
# Future directions

1. How is receptor trafficking **regulated** following the induction of **synaptic plasticity**?
2. How are **stable** synaptic memories maintained given **rapid protein turnover**? Roles of protein synthesis and actin cytoskeleton?
3. What is the effect of **intrinsic noise** (small receptor numbers) on receptor trafficking and plasticity?

# Outline

- Protein receptor trafficking and synaptic plasticity
- Cable theory of receptor trafficking
- **Motor transport of mRNA**

# Protein synthesis required for persistent LTP[6]

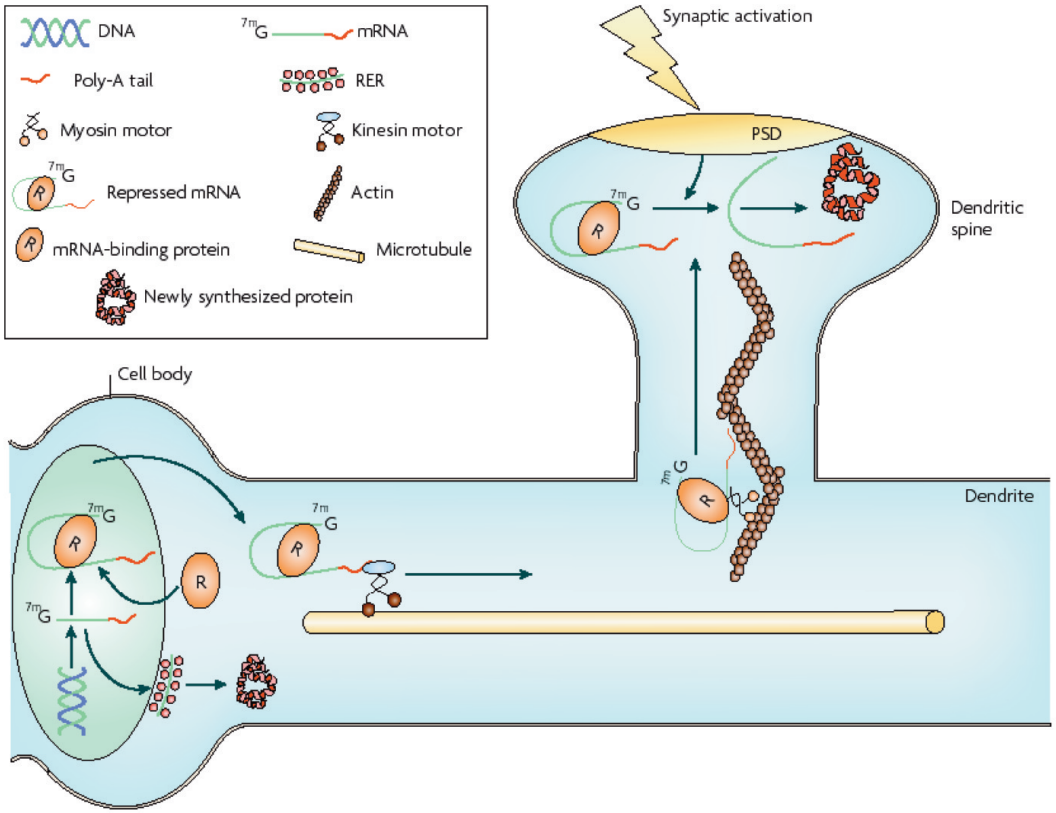



- (A) Single train of tetanic stimulation produces decremental potentiation
- Early-phase LTP insensitive to translational inhibition (anisomycin) and transcriptional inhibition (actinomyosin-D)
- (B) Repeated stimulation induces persistent potentiation that is sensitive to both translational and transcriptional inhibition

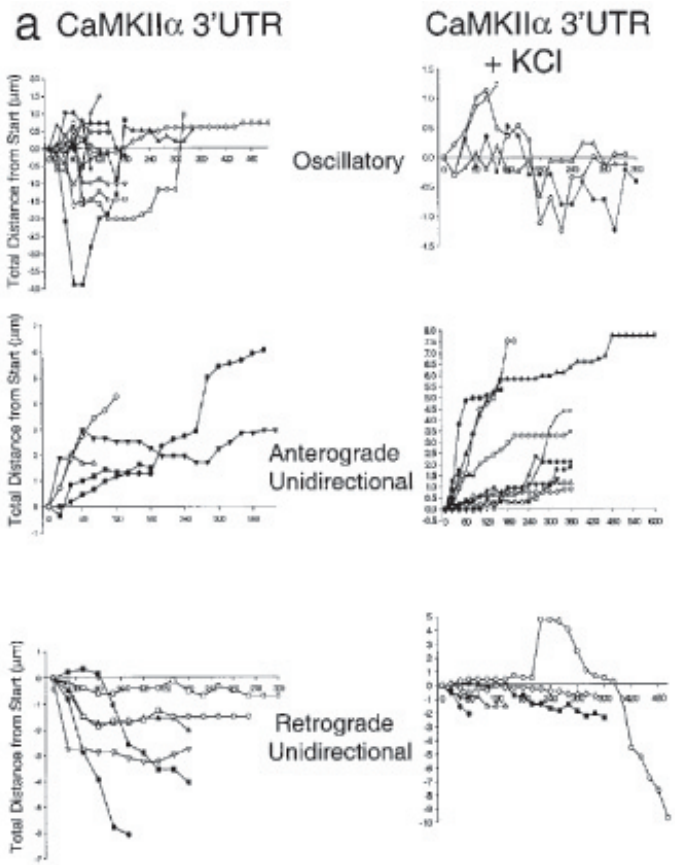
[6] Kelleher et. al. Neuron 2004

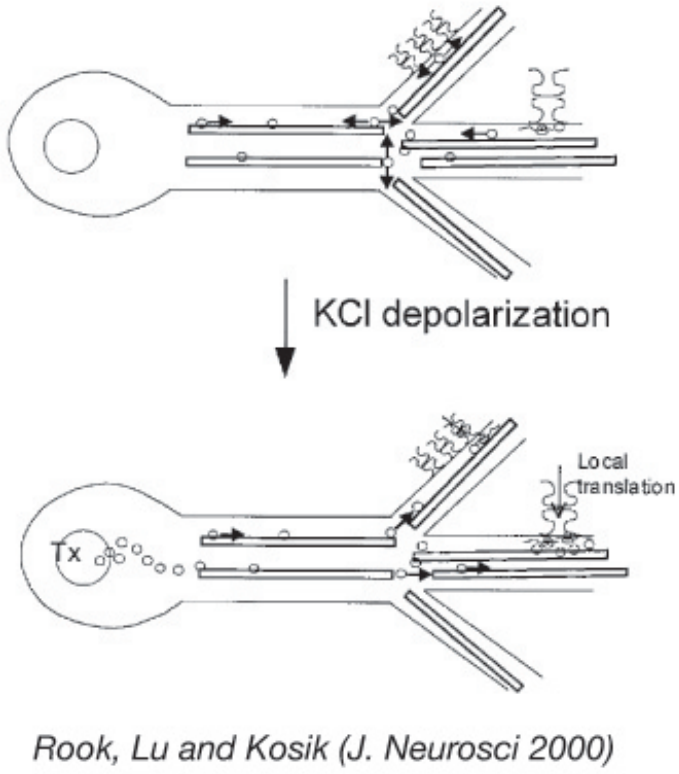
# Motor transport of mRNA[7]

- Newly transcribed mRNA granules are transported into the dendrite by kinesin motors on microtubules.
- Following synaptic activation, mRNA is localized to spines by the actin-based myosin




[7] Bramham and Wells Nat. Rev. Neurosci. 2007

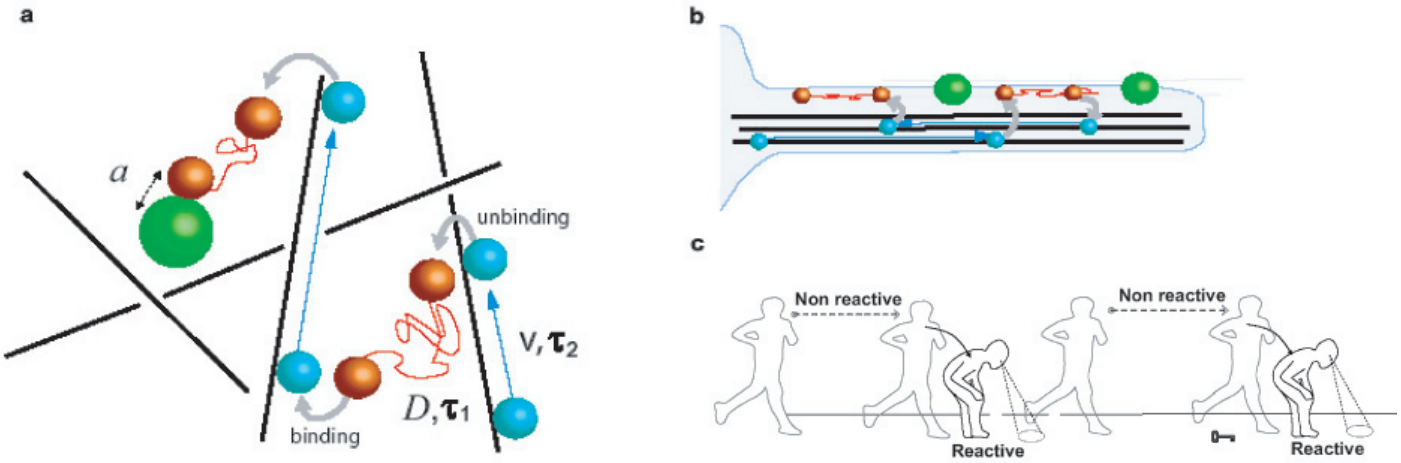



*Rook, Lu and Kosik (J. Neurosci 2000)*

- Motile mRNA particles in cultured hippocampal cells exist in 3 states: oscillatory, anterograde and retrograde
- KCL-induced depolarization increases anterograde motion

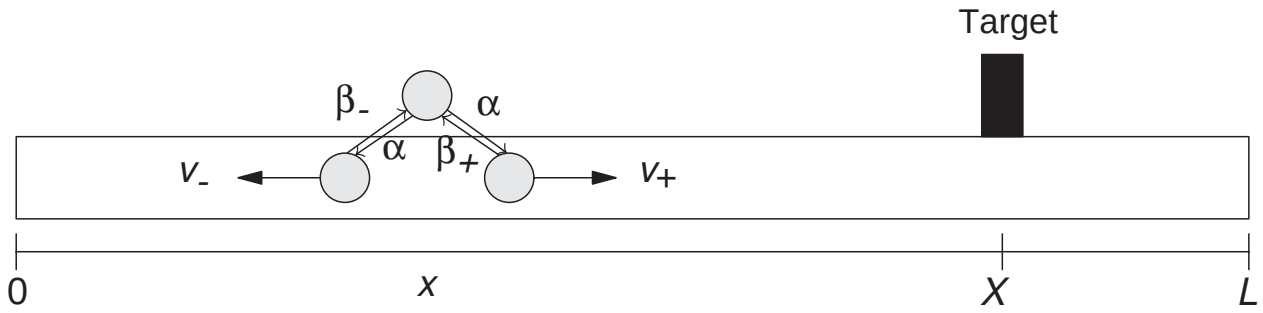
# Intermittent search[8]




- Many problems in nature require search for a randomly hidden target: foraging animals, a protein searching for a specific target site on DNA, microtubular transport of mRNA
- An efficient stochastic search strategy is to alternate between (A) a slow motion (diffusive), intensive search phase and (B) a fast (motor-assisted) ballistic non-search phase

[8] Loverdo et. al. Nat. Phys. 2008

# Stochastic model of directed intermittent search[9]




- Particle injected into dendrite at $x = 0$ and $t = 0$. Fixed hidden target (dendritic spine) at $x = X$.
- Particle exists in 3 states: anterograde with velocity $v_+$, retrograde with velocity $-v_-$, and stationary.
- In stationary state particle can be absorbed at a rate $k$ if within a distance $a$ of target
- Absorbing boundary at $x = L$

[9] Bressloff and Newby 2009

- Let $p_m(x,t)$ denote probability density for anterograde ($m=+$), retrograde ($m=-$) and stationary ($m=0$) states
- Master equation of the form

$$\frac{\partial p_+}{\partial t} = -v_+\frac{\partial p_+}{\partial x} + \alpha p_0 - \beta_+ p_+$$
$$\frac{\partial p_-}{\partial t} = v_-\frac{\partial p_-}{\partial x} + \alpha p_0 - \beta_- p_-$$
$$\frac{\partial p_0}{\partial t} = -2\alpha p_0 + (\beta_+ p_+ + \beta_- p_-) - k\chi(x-X)p_0$$

  where $\chi(x)=1$ if $|x|<a$ and is zero otherwise.
- Initial and boundary conditions:

$$v_- p_-(0,t) = v_+ p_+(0,t), \quad p_-(L,t)=0, \quad p_m(x,0)=\delta(x)\delta_{m,+}$$

- Bias in anterograde direction

$$\beta_+/v_+ < \beta_-/v_-$$

# Optimization problem

- Probability of finding target after time $t$ is

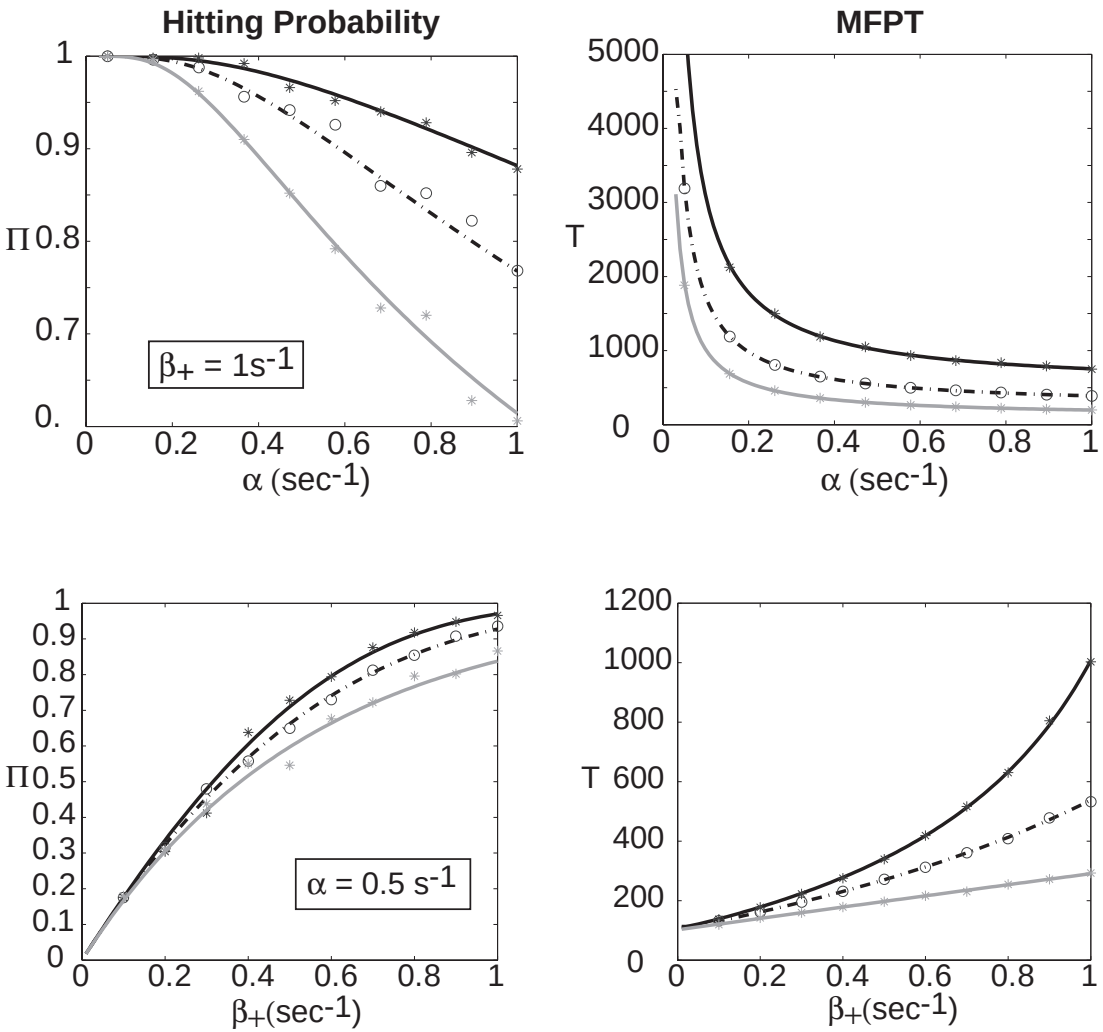
$$\gamma(t) = k \int_t^\infty \int_{X-a}^{X+a} p_0(x, \tau) dx d\tau$$

- Define hitting probability $\Pi$ and conditional MFPT $T$ according to

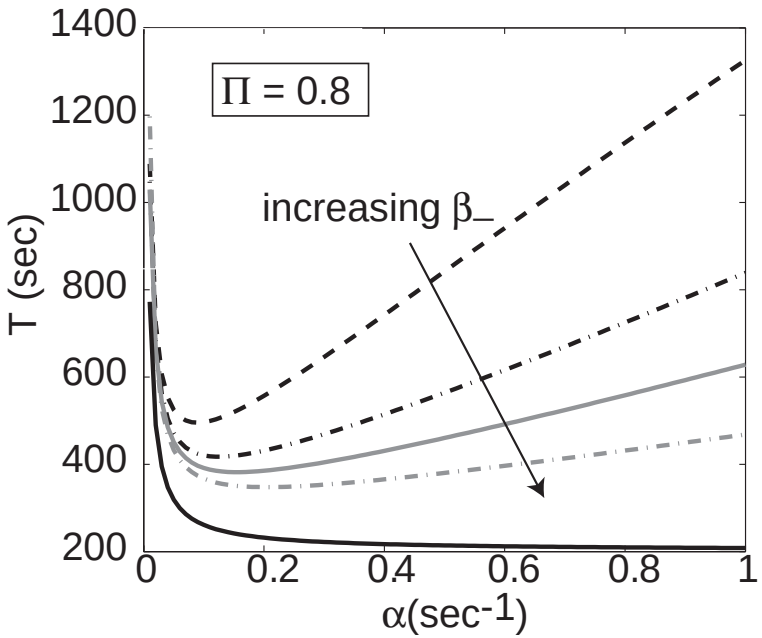
$$\Pi = \gamma(0), \quad T = \int_0^\infty \frac{\gamma(t)}{\gamma(0)} dt$$

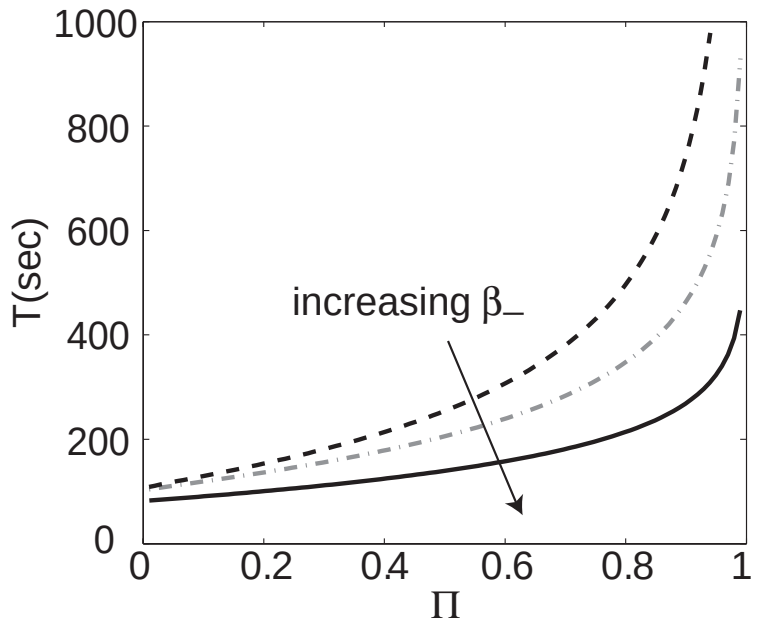
- Determine hitting probability $\Pi$ and MFPT $T$ by solving backwards equation or using Laplace transforms
- Optimization problem: find parameter values that minimize search time and maximize hitting probability?

- Plots of $\Pi$ and $T$ for $\beta_- = 1s^{-1}$ (solid black), $\beta_- = 2.5s^{-1}$ (dashed) and unidirectional (gray)

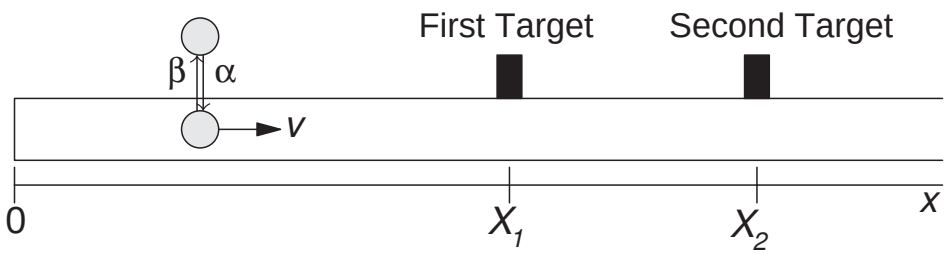


- Determine minimal MFPT for a given hitting probability
- For finite $\beta_-$ (partially biased) there exists a minimum of $T$ as a function of $\alpha$
- Unidirectional transport gives smaller MFPT than bidirectional transport



# Multiple targets




- Unidirectional search and $n+1$ identical targets
- Hitting probability of finding most downstream target is

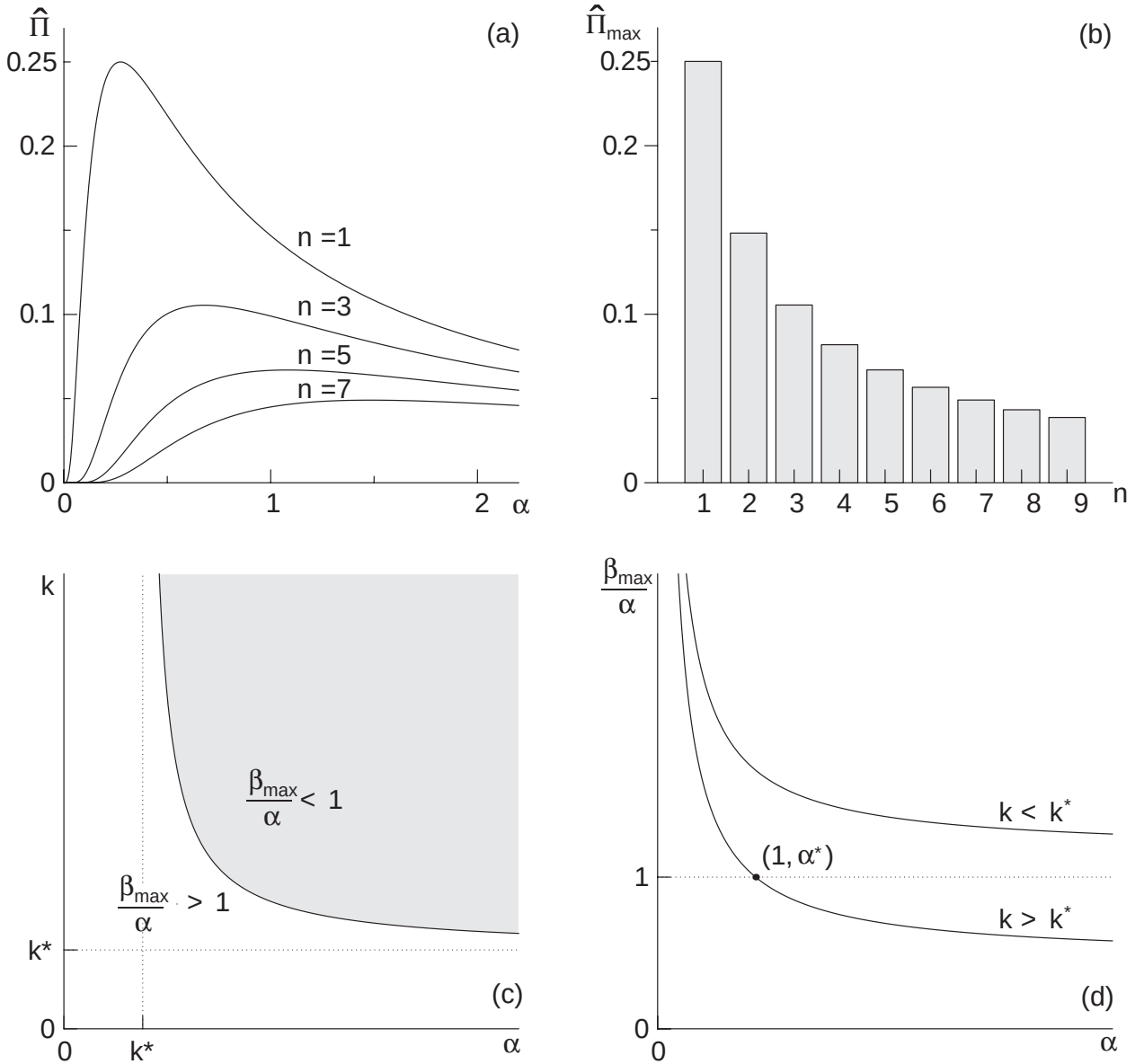
$$\widehat{\Pi} = (1-\Pi)^n \Pi$$

- $\widehat{\Pi}$ is maximized when

$$\beta_{max}(\alpha) = \frac{\ln\left(1+\frac{1}{n}\right) v}{2ka}(\alpha + k).$$

- The maximum hitting probability is

$$\widehat{\Pi}_{max} = \frac{n^n}{(n+1)^{n+1}}.$$


(a)
$\hat{\Pi}$
0.25
0.2
0.1
0
n =1
n =3
n =5
n =7
0
1
2
α
(b)
$\hat{\Pi}_{max}$
0.25
0.2
0.1
0
1 2 3 4 5 6 7 8 9
n
(c)
k
k*
0
k*
α
$\frac{\beta_{max}}{\alpha} < 1$
$\frac{\beta_{max}}{\alpha} > 1$
(d)
$\frac{\beta_{max}}{\alpha}$
1
0
α
$k < k^*$
$(1, \alpha^*)$
$k > k^*$

# Quasi–steady–state approximation

- Fix units of space and time: $x = 1mm$ and $t = 10^4 s$
- Then $v_\pm = \mathcal{O}(1)$ and transition rates $\alpha, \beta_\pm \gg 1$
- Introduce small parameter

$$\varepsilon = \frac{1}{\beta_-} + \frac{1}{\beta_+} + \frac{1}{\alpha}$$

  and set $a = \varepsilon\alpha, b_\pm = \varepsilon\beta_\pm$
- Have linear reaction-hyperbolic system

$$(\partial_t + v_+\partial_x)p_+ = \frac{1}{\epsilon}(-b_+p_+ + ap_0)$$
$$(\partial_t - v_-\partial_x)p_- = \frac{1}{\epsilon}(-b_-p_- + ap_0)$$
$$(\partial_t + k(x))p_0 = \frac{1}{\epsilon}(b_+p_+ + b_-p_- - 2ap_0)$$

- Using projection methods one can show that

$$p_0(x,t) \sim \frac{q(x,t)}{a}, \quad p_\pm(x,t) \sim \frac{q(x,t)}{b_\pm}$$

where $q$ satisfies advection–diffusion equation

$$\frac{\partial q}{\partial t} = -\frac{k(x)}{a} q - v_{\text{eff}} \frac{\partial q}{\partial x} + D_{\text{eff}} \frac{\partial^2 q}{\partial x^2}$$

where

$$v_{\text{eff}} = \gamma_- \equiv \frac{1}{b_+} - \frac{1}{b_-}$$

$$D_{eff} = \epsilon \left( \frac{1-\gamma_-}{b_+^2} + \frac{1+\gamma_-}{b_-^2} \right).$$

- If $k \equiv 0$ then one can write the solution in the form

$$p_m(x,t) = \eta_m Q_\varepsilon \left( \frac{x - vt}{\sqrt{\varepsilon}}, t \right)$$

- Can prove that[10]

$$Q_\varepsilon(s,t) \to q(s,t) \text{ as } \varepsilon \to \infty$$

where $q(s,t)$ is solution of heat equation.

[10] cf. Reed et. al. 1990, Friedman and Hu 2007

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